Chiral Synthesis via Organoboranes. 14. Selective Reductions. 41. Diisopinocampheylchloroborane, an Exceptionally Efficient Chiral Reducing Agent

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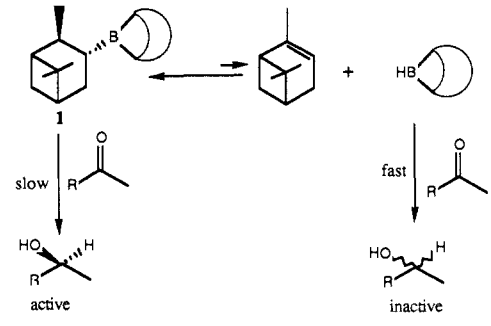
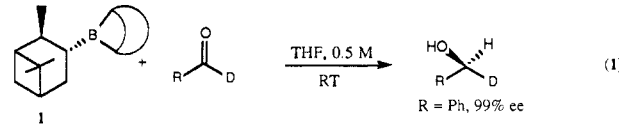
Abstract: Diisopinocampheylchloroborane, readily prepared in both enantiomers in high chemical and optical purities (99% ee) via hydroboration followed by treatment with dry hydrogen chloride in ethyl ether, reduces prochiral ketones at convenient rates in tetrahydrofuran at −25 °C. Reduction of simple dialkyl ketones, 2-butanone, 2-octanone, and 3-methyl-2-butanone, yields the corresponding alcohols with 4%, 7%, and 32% optical induction. On the other hand, aralkyl ketones are reduced with very high asymmetric induction. Thus, acetophenone, propiophenone, butyrophenone, and decanophenone are reduced with 98%, 98%, 98%, and 97% ee, respectively. Branching of the alkyl chain diminishes the induction. Isobutyrophenone and pivalophenone are reduced in 78% and 79% ee, respectively. Functional groups in the aromatic ring are not affected by the reagent and do not appear to influence significantly the optical yield realized. Thus, 2′,5′-dimethoxypropiophenone is reduced in 96% ee. 1-Indanone and α-tetralone are reduced in 98% and 87% ee, respectively. 2′-Acetonaphthone is reduced in 98% ee. Heteroaryl alkyl ketones are also reduced with excellent optical induction. Thus, 3-acetylpyridine and 2-acetylthiophene are reduced in 92% and 91% ee, respectively. The reagent reduces *α-tertiary* aliphatic ketones under neat condition at room temperature with very high optical induction. 3,3-Dimethyl-2-butanone, ethyl 2,2-dimethylacetoacetate, 2,2-dimethylcyclopentanone, 2,2-dimethylcyclohexanone, and spiro[4.4]nonan-1-one are reduced to the corresponding alcohols in 95%, 84%, 98%, 91%, and 95% ee, respectively. Some α,β-unsaturated ketones are reduced with lesser optical induction, such as 4-phenyl-3-butyn-2-one and 2-cyclohexenone, which are reduced to the alcohols in 21 and 36% ee, respectively. On the other hand, *trans*-4-phenyl-3-buten-2-one is reduced to the alcohol in 81% ee. Certain α-keto esters are reduced in 50–70% ee. The mechanism of the reduction is postulated to be via a six-membered cyclic "boatlike" transition state. X-ray crystal structure data for the reagent are presented.

Asymmetric synthesis, in its infancy a decade ago, has come of age today.[2] One of the major areas of research in asymmetric synthesis that has received considerable attention is the reduction of prochiral ketones to optically pure alcohols.[3] Methods to accomplish this include catalytic asymmetric hydrogenation,[4] hydrosilation,[5] enzymatic reduction,[6] and chirally modified metal hydride[7] and alkyl metal reactants[8] to mention a few. Over the past two decades, we have endeavored to illustrate the capabilities of organoborane reagents to prepare many types of chiral functionalities.[9] Asymmetric hydroboration–oxidation has been developed as one of the methodologies for obtaining various classes of optically pure *secondary* alcohols.[10] Diisopinocampheylborane (Ipc_2BH) and monoisopinocampheylborane ($IpcBH_2$) are especially valuable reagents for this purpose. Though Ipc_2BH and $IpcBH_2$ are excellent hydroborating agents, they proved inefficient as chiral reducing agents.[11,12] A significant development in chiral

Scheme I



reductions using an organoborane reagent was made by M. M. Midland and co-workers who discovered that *B*-pinan-3-yl-9-borabicyclo[3.3.1]nonane (Aldrich; Alpine-Borane, **1**) reduces deuterioaldehydes to the corresponding α-deuterio alcohols in tetrahydrofuran (THF) at room temperature (RT) in excellent enantiomeric excess (ee) (eq 1).[13] For example, for R = Ph, 99%



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ee was realized. However, when the reagent was applied to the reduction of ketones, the results were mixed. The relatively unhindered, α,β-acetylenic ketones were reduced reasonably fast to the corresponding acetylenic alcohols with very good optical induction.[14] For example, 4-methyl-1-pentyn-3-one was reduced to the corresponding alcohol in 99% ee. On the other hand, with less reactive ketones, such as acetophenone, the reaction was very

(1) (a) Postdoctoral Research Associate on National Science Foundation Grant CHE 8414171. (b) Postdoctoral Research Associate on U.S. Army Research Office Grant DAAG 29-85-K-0062.
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(3) Reference 2, Vol. 2, Chapters 2–4. We have recently reported a survey on various chiral reducing agents and classified the reagents according to their capability to reduce certain standard classes of ketones: Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406. The percent ee reported here for *trans*-4-phenyl-3-buten-2-one has been corrected to 81% ee from the earlier value of 12%.
(4) Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85.
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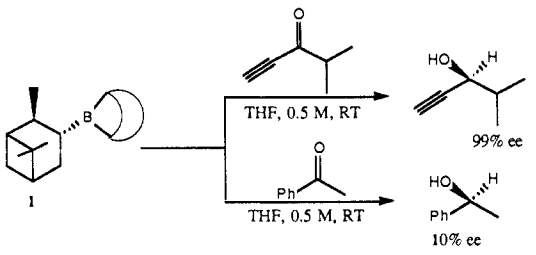
slow and the product showed only 10% ee (eq 2). Enhancing the



(2)

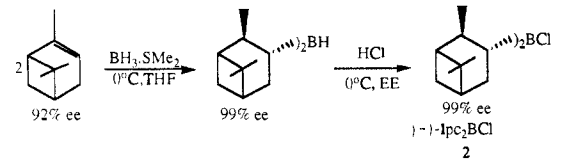
rate of the reaction by increasing the temperature or by increasing the ratio of the reagent to the ketone did not improve the optical induction.

It was diagnosed later that the poor optical induction achieved in the reduction of less reactive ketones was due to a competitive dehydroboration followed by an achiral reduction by 9-BBN (Scheme I).[15] We have shown that conducting the reaction at higher concentration or under neat condition, not only enhances the rate of the reduction but also increases the ee of the alcohols produced by minimizing the dehydroboration component of the overall reaction.[16] Midland has also circumvented the dehydroboration by conducting the reactions at very high hydrostatic pressures.[17]

It occurred to us that a manipulation of the steric and electronic environment of the boron in the pinanylborane derivatives might improve the rate as well as the optical induction in the reduction. We felt that the introduction of a halogen might increase the Lewis acidity of boron and thereby enhance the reaction rate. Consequently, we prepared a series of diisopinocampheylhaloboranes and monoisopinocampheyldihaloboranes (Ipc_2BX and $IpcBX_2$, where X = F, Cl, Br, I) and tested their reduction characteristics by reacting them with a representative aromatic and aliphatic ketone, acetophenone, and 3-methyl-2-butanone, respectively. Preliminary experiments[18] showed the chloro derivative diisopinocampheylchloroborane (Ipc_2BCl, **2**) to be the reagent of choice. Hence, we undertook a detailed study of the reagent and its reducing properties with various ketones, aromatic, heteroaromatic, aliphatic, alicyclic, hindered and unhindered, alkynyl, alkenyl, keto esters, etc. The results are presented in this paper.

Results and Discussion

(−)-Diisopinocampheylchloroborane ((−)-Ipc_2BCl, **2**) could be readily prepared from commercially available (+)-α-pinene (92% ee) in high chemical and optical purities (99% ee) by hydroboration followed by treatment with dry hydrogen chloride (HCl) in diethyl ether (EE).[19] Removal of ether and cooling to 0 °C provided solid Ipc_2BCl, which could be recrystallized from pentane, mp 54–56 °C. Alternately, we prepared **2** by suspending Ipc_2BH in EE at 0 °C and bubbling gaseous HCl through the suspension until all of the Ipc_2BH dissolved (eq 3). Removal of EE provided



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2 of 98% chemical purity, as was shown by oxidation with alkaline hydrogen peroxide of Ipc_2BCl to isopinocampheol, followed by GC analysis. The reagent fumes in air and is sensitive to oxygen. Though Ipc_2BCl is unstable in air, it is stable under nitrogen at 0 °C for at least 1 year.[20] The reagent does not complex with

Table I. Complexing Nature (^{11}B NMR) of (−)-Ipc_2BCl in CH_2Cl_2 with 1 Equiv of Tertiary Amines

amine	^{11}B NMR, δ	amine	^{11}B NMR, δ
pyridine	13	diethylmethylamine	76
2-picoline	67	dimethylethylamine	76
2,6-lutidine	76	*N*-methylpyrrolidine	76
triethylamine	76		

Table II. Effect of Solvent and Temperature on the Chiral Induction in the Reductions with Ipc_2BCl

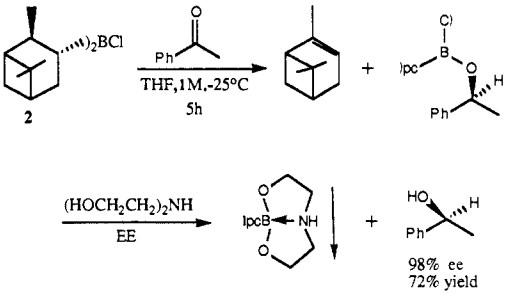
solvent	temp, °C	time, h	% ee[a]
THF	−25	5	97.4
THF	0	3	95.8
EE	−25	5	96.3
CH_2Cl_2	−25	5	95.6
pentane	−25	5	95

[a] Determined via the MTPA ester on a capillary column.

EE, THF, or dimethyl sulfide. The ^{11}B NMR spectrum of the reagent is similar in THF, EE, pentane, and dichloromethane (CH_2Cl_2) (δ 76). It complexes with pyridine, though it does not complex with a series of hindered tertiary amines (Table I).

In general, the reductions were carried out at −25 °C by using a 10% excess of the reagent. The reactions occur at a convenient rate even at that temperature. Conducting the reaction in THF, EE, CH_2Cl_2, and pentane showed that THF is the solvent of choice (Table II). The enantiomeric excess observed was maximum in THF, and the solubility of the reagent was superior in that solvent. The reagent tended to crystallize out from 1 M solutions in CH_2Cl_2 or pentane at −25 °C. Hence, all of the reactions were carried out in THF. The reaction was faster at 0 °C, but the enantiomeric excess of the product alcohol was slightly lower (Table II). In those cases where the reaction was slow, the reaction was conducted under neat conditons at room temperature.[21] On completion of the reduction, as shown by the ^{11}B NMR spectrum of an aliquot after methanolysis, the solvent was removed under aspirator vacuum, and the α-pinene was then removed and collected by distillation at low pressure.

The α-pinene thus collected showed an $[\alpha]_D$ of +52.0° (neat), which equals the maximum reported value in the literature.[22] The isopinocampheol prepared by the hydroboration–oxidation of the liberated α-pinene showed an $[\alpha]_D$ of −35.7°, which again corresponds to the maximum reported value in the literature, thus far.[23] EE was added to the residue, and the phenethyl alcohol was liberated by precipitating the boron components with diethanolamine (eq 4). This nonoxidative workup avaoids the



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formation of isopinocampheol, thus rendering recovery and purification of the active alcohol easier. The products were purified by distillation and/or chromatography. The optical purities of the alcohols were determined by comparison of their rotations with the known maximum rotations reported in the literature and/or by preparing their (+)-α-methoxy-α-(trifluoromethyl)phenyl-

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Table III. Reduction of Representative Prochiral Ketones with (−)-Ipc_2BCl in THF (1 M, −25 °C)

ketone	time, h	% ee[a]	config[a]
2-butanone	5	4	*S*
2-octanone	5	7	*R*
3-methyl-2-butanone	5	32	*S*
acetophenone	5	98	*S*

[a] By comparison with maximum rotation reported in the literature (see the Experimental Section).

Table IV. Reduction of Prochiral Aralkyl Ketones with (−)-Ipc_2BCl in THF (1 M, −25 °C)

ketone	time, h	alcohol yield,[a] %	% ee[b,c]	config[b]
acetophenone	5	72	98 (97.4)	*S*
propiophenone	5	62	98.3 (97.3)	*S*
butyrophenone	5	77	100 (98.2)	*S*
decanophenone	5	75	(95)	(*S*)[d]
isobutyrophenone	24	68	90	*S*
pivalophenone	12 days[e]	*e*	79.3	*R*[f]
1-indanone	15	62	97 (97.4)	*S*
α-tetralone	50	70	85.6 (87.4)	*S*
2′-acetonaphthone	7	90	98.1	*S*
3-acetylpyridine	15[g]	67	91.7 (92.4)	*S*
2-acetylthiophene	15[g]	85	(91.3)	*S*
2′,5′-dimethoxy-propiophenone	1	80	(96)	(*S*)[d]

[a] Isolated yield. [b] Determined by comparison with the literature (see the Experimental Section). [c] Values in parentheses determined by capillary GC via MTPA or MCF derivative. [d] By analogy with other examples. [e] A 60% reaction was complete in 12 days. [f] An artifact of the transition state (see text). [g] A 2-equiv portion of the reagent was used.

acetates[24] (MTPA derivative) or (−)-menthyl chloroformate[25] (MCF) derivative and analyzing them on capillary GC using a Supelcowax glass capillary column (15 m) or a methylsilicone capillary column (50 m). Our results with individual classes of carbonyl compounds are discussed below.

Aryl Alkyl Ketones. Preliminary studies using Ipc_2BCl with 2-butanone, 2-octanone, 3-methyl-2-butanone, and acetophenone (Table III) revealed that Ipc_2BCl has an exceptional capability for reducing aromatic ketones unusually rapidly with excellent induction. Hence, we reduced a representative series of aralkyl ketones, and the results are presented in Table IV. Increasing the chain length of the *n*-alkyl group on one side did not affect the chiral induction. Thus, acetophenone, propiophenone, and butyrophenone were all reduced by Ipc_2BCl to the corresponding alcohols with the same optical purity. Even decanophenone, with an *n*-octyl group on one side of the carbonyl moiety, was reduced to the alcohol in 97% ee. Branching the alkyl group adjacent to the carbonyl group decreases the induction somewhat. Thus, isobutyrophenone is reduced to the alcohol with 90% ee and phenyl *tert*-butyl ketone with 79% ee. 1-Indanone was reduced to 1-indanol with 97% ee, whereas α-tetralone was converted to α-tetralol in 87% ee. Changing the phenyl group of the aromatic side to the naphthyl group had no detrimental effect on the induction. Thus, 2′-acetonaphthone was reduced to 1-(2-naphthalenyl)ethanol with 98% ee. Functional groups in the aromatic ring were unaffected during reduction. Thus, 2′,5′-dimethoxypropiophenone was reduced to the corresponding alcohol in 96% ee. Substituting the aromatic group with a heteroaromatic group resulted in some decrease in the chiral induction, yet the results were remarkable. 3-Acetylpyridine and 2-acetylthiophene were reduced to the corresponding alcohols with 92% and 91% ee, respectively. In the case of heteroaromatic alkyl ketones, 2 equiv of the reagent was used for reduction. Utilizing 1 equiv of the reagent, we observed no reaction in the case of 3-acetylpyridine and a very slow reaction in the case of 2-acetylthiophene. In all of these cases, we obtained *S* alcohol as the major isomer,

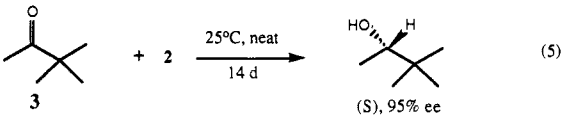
Table V. Reduction of Prochiral α-Tertiary Alkyl Ketones with (−)-Ipc_2BCl (Neat) at 25 °C

ketone	time	isolated yield, %	% ee[a]	config
3,3-dimethyl-2-butanone	12 days	50	93 (95)	*S*
ethyl 2,2-dimethylacetoacetate	12 days	69	(84)	*S*
2,2-dimethylcyclopentanone	12 h	71	(98)	(*S*)[b]
2,2-dimethylcyclohexanone	12 h	60	(91)	(*S*)[b]
spiro[4.4]nonan-1-one	12 h	65	100 (95)	*S*

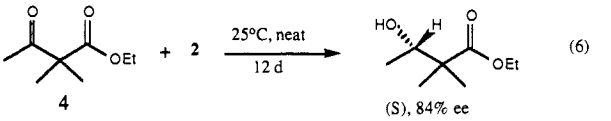
[a] Determined by comparison of maximum rotation reported in the literature. Values in parentheses are by capillary GC analysis (see the Experimental Section). [b] Based on analogy with other examples.

except in the case of pivalophenone where the *R* configuration is in accord with the transition-state model and not an artifact of the priority rule according to the Cahn–Ingold–Prelog[26] convention (vide infra, mechanistic aspects).

Aliphatic and α-Tertiary Alkyl Ketones. Reduction of straight-chain prochiral aliphatic ketones with Ipc_2BCl did not provide encouraging results. Under the standard conditions (THF, 1 M, −25 °C) the reaction of 2-butanone and 3-methyl-2-butanone provided alcohols that showed an ee of 4% and 32%, respectively, in the *S* isomer (Table III). Reaction of 2-octanone provided alcohol of 7% ee in the *R* isomer. The reason for the change in configuration is not understood presently. Reaction of acetylcyclohexane provided the alcohol in 26% ee. The reaction of 3,3-dimethyl-2-butanone was extremely slow at −25 °C. Hence, we conducted the reaction under neat condition at room temperature. The reaction was complete in 12 days, and workup provided the corresponding alcohol in 95% ee, as determined by both its rotation and MTPA ester analysis! Encouraged by this result, we examined a series of representative α-tertiary alkyl ketones.[21] The results are shown in Table V. The reduction of ethyl 2,2-dimethylacetoacetate (**4**) resembles pinacolone (**3**) in its slow rate of reduction, but the optical yield, 84% ee, is quite good (eq 5 and 6).

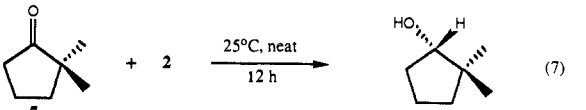


3 (S), 95% ee

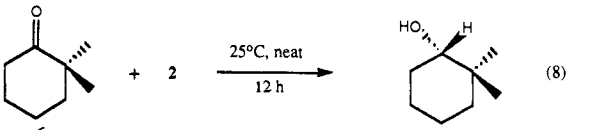


4 (S), 84% ee

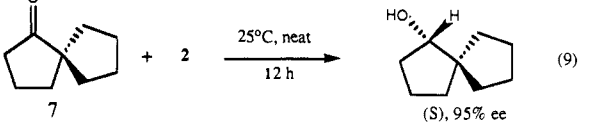
The reduction of hindered alicyclic derivatives is considerably faster, yet the optical yields are excellent. For example, reduction of 2,2-dimethylcyclopentanone (**5**) gives the product alcohol in 98% ee. 2,2-Dimethylcyclohexanone (**6**) yields the corresponding alcohol in 91% ee, and spiro[4.4]nonan-1-one (**7**) provides the alcohol in 95% ee (eq 7–9).



5 (S), 98% ee



6 (S), 91% ee



7 (S), 95% ee

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
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Table VI. Reduction of Prochiral Keto Esters with (−)-Ipc_2BCl

keto ester	reactn condn	time	% ee	config
ethyl pyruvate	THF, 1 M, −25 °C	3 h	45[a]	*S*
methyl benzoylformate	THF, 1 M, −25 °C	1 h	70[b,c]	*R*[d]
ethyl 2,2-dimethyl-acetoacetate	neat, RT	12 days complex reactn	84[b]	*S*
ethyl benzoylacetate	THF, 1 M, −25 °C			

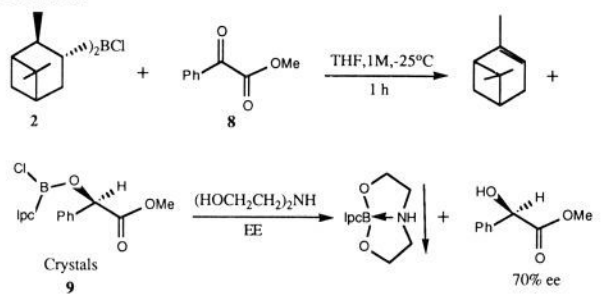
[a] Based on maximum rotation reported in the literature (see the Experimental Section). [b] Determined as the MTPA ester on capillary column. [c] By working up crystalline intermediate (see the Experimental Section). [d] Based on comparison with authentic sample.

Table VII. Reduction of Prochiral α,β-Unsaturated Ketones with (−)-Ipc_2BCl in THF (1 M, −25 °C)

ketone	time, h	yield, %	% ee	config
2-cyclohexenone	7	65	36[a]	*S*
trans-4-phenyl-3-buten-2-one	10	65	81[b]	*S*
4-phenyl-3-butyn-2-one	2	78	21[a]	*R*

[a] Determined as MTPA ester on capillary GC. [b] By comparison of maximum rotation reported in the literature (see the Experimental Section).

Scheme II



Keto Esters. Of the examples given above, the reduction of ethyl 2,2-dimethylacetoacetate showed that Ipc_2BCl can accommodate ester groupings without being affected. This prompted us to study other examples of keto esters (Table VI). When ethyl pyruvate was reduced in THF, 1 M, at −25 °C we obtained ethyl lactate of 45% ee. Reduction of methyl benzoylformate (**8**) showed some interesting features. The reaction was complete within 1 h. The intermediate **9** crystallized out from the reaction medium (Scheme II). We worked up the crystals and the mother liquor separately. The crystals provided the alcohol in 70% ee, whereas the mother liquor provided it in only 50% ee.

β-Keto esters could not be reduced with Ipc_2BCl. The reaction of ethyl benzoylacetate was found to give complex mixtures on analysis of the ^{11}B NMR of the aliquot after methanolysis. The usual workup did not provide any alcohol.

α,β-Unsaturated Ketones. Though Ipc_2BCl, unlike Alpine-Borane, reduces aryl alkyl ketones with extremely good induction, it did not prove to be efficient for α,β-acetylenic ketones even if the unsaturation is conjugated with the phenyl ring (Table VII). However, *trans*-4-phenyl-4-buten-2-one is reduced in 81% ee. 2-Cyclohexenone is reduced in THF, 1 M, at −25 °C within 7 h, providing the alcohol in 36% ee.

Elimination of α-Pinene. The extremely fast rate of reaction of **2** with ketones as compared with Alpine-Borane prompted us to study the rate of the reaction of benzaldehyde with **2**.[27] When we treated **2** in THF, 1 M, with 1 or 2 equiv of benzaldehyde at 0 °C or room temperature, we observed an instantaneous elimination of 1 or 2 mol of α-pinene, respectively. This reaction showed that benzaldehyde could be utilized to eliminate α-pinene from Ipc_2BCl very conveniently. In one experiment, we isolated the α-pinene eliminated by the treatment of benzaldehyde with Ipc_2BCl. It was shown to be of 99.4% ee. Consequently, this procedure now appears to be the most convenient method to upgrade commercial α-pinene, 92% ee, to material of ≥99.4% ee (eq 10).

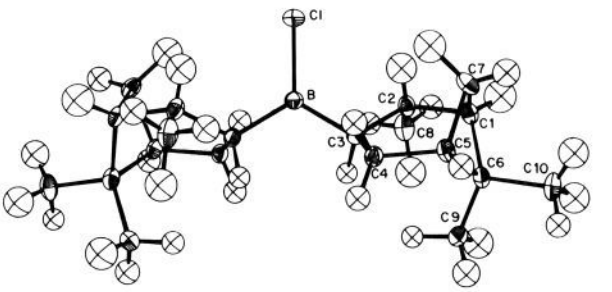
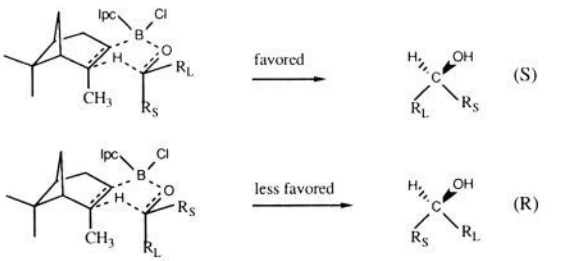
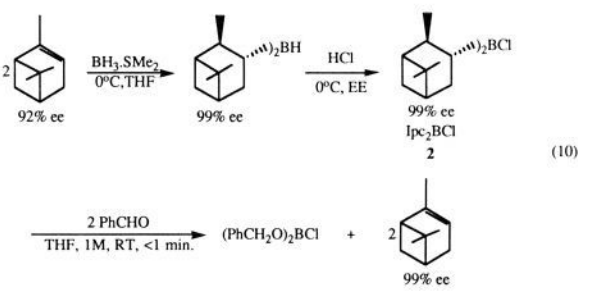


Figure 1. X-ray crystal structure and numbering scheme of Ipc_2BCl—an ORTEP nonstereoview.

Scheme III. Transition-State Model for Asymmetric Reduction with (−)-Ipc_2BCl





Reaction of 2 Equiv of Acetophenone with Ipc_2BCl. All our experiments with various classes of ketone thus far mentioned used only 1 equiv of ketone for 1 mol of Ipc_2BCl. In theory, it should be possible to reduce 2 equiv of the ketone with 1 mol of Ipc_2BCl. But, when we utilized 2 equiv of acetophenone for 1 mol of **2**, we saw that only 1 mol of acetophenone was reduced in a reasonable time, with the second mole reacting at a rate that was immeasurably slow.

(+)-Ipc_2BCl. In order to show that we could obtain the opposite enantiomer of alcohols with (+)-Ipc_2BCl for reductions, we prepared (+)-Ipc_2BCl, from (−)-α-pinene, using the procedure followed for (−)-Ipc_2BCl. Reduction of acetophenone with the reagent produced (*R*)-phenethyl alcohol in 97.2% ee.

Mechanistic Aspects. All of the reductions with **2** gave predominantly the *S* configuration in the product alcohols. The mechanism of reduction with **2**, we believe, is similar to that proposed by Midland for Alpine-Borane reductions[28] via a six-membered, cyclic, "boatlike" transition state. The eliminating boron moiety and the β-hydrogen are cis, probably resulting in a syn elimination. In the preferred transition state, only the smaller alkyl group (R_S) has to face the syn axial methyl interaction, while the bulky alkyl group (R_L) assumes an equatorial-like orientation. This explains the formation of the *S* isomer of the alcohols predominantly. The *R* configuration for the alcohol produced in the reduction of pivalophenone arises from the fact that the bulky *tert*-butyl group occupies the equatorial position in the transition state (Scheme III).

(27) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. *Organometallics* **1986**, *5*, 2138.

(28) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.

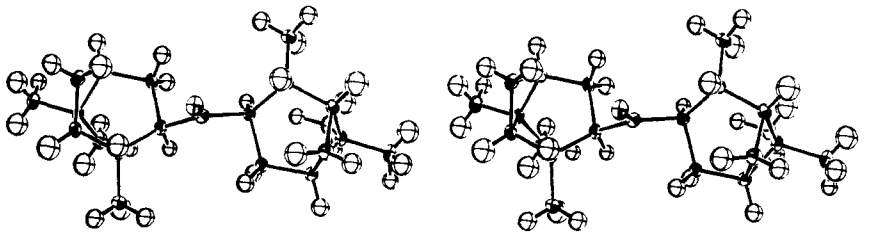


Figure 2. ORTEP stereoview through the B–Cl bond of Ipc_2BCl.

Table VIII. Bond Distances (Å) for Ipc_2BCl[a]

atom 1	atom 2	distance	atom 1	atom 2	distance
Cl	B	1.7748 (9)	C5	C6	1.556 (2)
Cl	B	1.7748 (9)	C5	C7	1.542 (2)
B	C3	1.561 (2)	C5	H5	1.01 (2)
B	C3	1.561 (2)	C6	C9	1.522 (2)
C1	C2	1.528 (2)	C6	C10	1.526 (2)
C1	C6	1.565 (2)	C7	H7-1	0.88 (2)
C1	C7	1.552 (2)	C7	H7-2	1.14 (3)
C1	H1	1.02 (3)	C8	H8-1	0.94 (2)
C2	C3	1.551 (2)	C8	H8-2	1.05 (3)
C2	C8	1.522 (2)	C8	H8-3	0.93 (2)
C2	H2	0.85 (3)	C9	H9-1	0.97 (3)
C3	C4	1.578 (3)	C9	H9-2	1.01 (2)
C3	H3	0.98 (2)	C9	H9-3	0.91 (3)
C4	C5	1.523 (2)	C10	H10-1	0.93 (3)
C4	H4-1	1.05 (2)	C10	H10-2	1.05 (2)
C4	H4-2	0.94 (2)	C10	H10-3	0.92 (2)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

X-ray Crystal Structure. Single-crystal X-ray diffraction analysis of **2** was performed as described in the Experimental Section. This is the first crystal structure determination of a diisopinocampheylborane system.[29] An ORTEP nonstereoview of the structure and the numbering scheme are shown in Figure 1. Figure 2 shows the stereoview through the B–Cl bond. Table VIII gives the bond lengths, and Table IX gives the bond angles. Details of the crystal diffraction data are presented in Table X (supplementary material).

It can be seen from Figures 1 and 2 that **2** exists with the six-membered ring attached to the boron in a nonchair conformation. The C_3–B bond and the C_2–H bond are at a dihedral angle of 24°. The C_2–H and C_3–B are both in the equatorial orientation. Although these data provide no clue regarding the nature of the transition state in solution, it must be noted that for the idealized transition state, as depicted above, the H–C_2–C_3–B dihedral angle must become 0°. It is probable that in reality the picture may be close to, if not exactly as, the model proposed.

Conclusions

In conclusion, (–)- and (+)-diisopinocampheylchloroborane, a readily available reagent,[30] has been proven to be extremely efficient for the chiral reduction of aralkyl ketones. Many functional groups are compatible with the reagent.[31] Since both the enantiomers of the reagent are commercially available, either isomer of the alcohol can be synthesized at will. The ready availability, simple reaction conditions, and easy workup procedure make the reagent very attractive. We have used this reagent for the synthesis of very important pharmaceuticals.[32] The mechanism of the reaction is explained via a cyclic boatlike transition state, and this gives pointers for the synthesis of more efficient chiral reducing agents. On the basis of this , we are currently investigating effective chiral reducing agents for the reduction of aliphatic ketones. Preliminary results are highly promising.[33]

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[34] Spectroscopic (^1H and ^{11}B NMR, IR) and polarimetric measurements were made with standard instruments. GC analysis was done on a Varian Aerograph Series 1200 gas chromatograph having a flame ionization detector, integrated with a Hewlett-Packard 3380 S 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 methyl silicone capillary column (50 m) at appropriate temperatures and integrated with a Hewlett-Packard 3390 A integrator.

Materials. THF was distilled from benzophenone ketyl and stored under nitrogen in an ampule. Borane–methyl sulfide (BMS) and α-pinene (92% ee) were obtained from Aldrich Chemical Co. The ketones were obtained from Aldrich or Wiley Organics and were used as received. The ketones synthesized by literature procedures are reported at appropriate subsections in this section. MTPA was obtained from Aldrich and converted to the acid chloride by the literature procedure.[24] MCF was obtained from Aldrich. Anhydrous ethereal hydrogen chloride (~3 M) was prepared with a Brown automatic gasimeter from hydrochloric acid and sulfuric acid.[35]

Preparation of (–)-Diisopinocampheylchloroborane ((–)-Ipc_2BCl). Method A. Diisopinocampheylborane, prepared from (+)-α-pinene (230 mmol) and BH_3·SMe_2 (100 mmol) in THF (96 mL) at 0 °C by the reported procedure,[36] was suspended in diethyl ether (EE; 50 mL) in a 250-mL round-bottom flask containing a magnetic stirring bar and fitted with a septum-capped side arm and a connecting tube. Dry HCl in EE[36] (1 equiv, calculated for the amount of Ipc_2BH) was added. After being stirred for 15 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred at that temperature until all of the solid dissolved and gas evolution ceased (2 h). ^{11}B NMR showed a singlet at δ 74. The product on methanolysis showed a singlet at δ 54 in ^{11}B NMR. Upon removal of the ether solvent and cooling, IPC_2BCl solidified: mp 54–56 °C after crystallization from pentane; $[\alpha]_D$ −67.07° (*c* 13.5 CH_2Cl_2); yield, 75% based on BH_3·SMe_2. Ipc_2BCl need not be crystallized and can be used as such for reactions. Ipc_2BCl is sensitive to the atmosphere and should be handled under nitrogen.

Method B. Ipc_2BH prepared as in the above procedure was suspended in EE at 0 °C, and HCl gas was passed through the solution from a lecture bottle until all of the solid dissolved. Removal of the solvent provided the reagent as a white powder, mp 54–55 °C.

Reduction of Carbonyl Compounds. General Procedure. An oven-dried, 50-mL round-bottom flask equipped with a septum-capped side-arm, magnetic stirring bar, and a connecting tube was cooled to room temperature in a stream of nitrogen. (–)-Ipc_2BCl (9.0 g, 28 mmol) was transferred to the flask in a glovebag and dissolved in THF (20 mL). The solution was cooled to −25 °C, and the ketone (25 mmol) was added. The reaction was followed by ^{11}B NMR after aliquots were methanolyzed at −25 °C at periodic intervals. When the reaction was complete, the mixture was raised to room temperature and THF was removed at aspirator vacuum. α-Pinene liberated during the reaction was collected in

(29) For a paper on a related compound from nopol methyl ether and monochloroborane, see: Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 7167.

(30) Diisopinocampheylchloroborane is now commercially available from Aldrich Chemical Co.

(31) We have subsequently studied Ipc_2BCl with various multifunctional ketones and found it to be compatible with all of them. Srebnik, M.; Ramachandran, P. V.; Brown, H. C. Presented at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 7, 1987; paper ORGN 110.

(32) Srebnik, M., Ramachandran, P. V.; Brown, H. C., manuscript in preparation. Oberlander, R. A.; Nichols, D. E.; Ramachandran, P. V.; Srebnik, M. *J. Pharm. Pharmacol.*, in press.

(33) Brown, H. C.; Ramachandran, P. V.; Srebnik, M. Presented at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 7, 1987; paper ORGN 109.

(34) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

(35) Brown, H. C.; Rei, M.-H. *J. Org. Chem.* **1966**, *31*, 1090.

(36) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

Table IX. Bond Angles (degrees) for Ipc_2BCl

atom 1	atom 2	atom 3	angle	atom 1	atom 2	atom 3	angle
Cl	B	C3	120.27 (8)	C7	C5	H5	118 (1)
Cl	B	C3	120.27 (8)	C1	C6	C5	85.3 (1)
C3	B	C3	119.5 (1)	C1	C6	C9	122.4 (1)
C2	C1	C6	114.9 (1)	C1	C6	C10	110.7 (1)
C2	C1	C7	106.7 (1)	C5	C6	C9	118.5 (1)
C2	C1	H1	108 (2)	C5	C6	C10	111.1 (1)
C6	C1	C7	87.5 (1)	C9	C6	C10	107.4 (1)
C6	C1	H1	120 (2)	C1	C7	C5	86.2 (1)
C7	C1	H1	118 (2)	C1	C7	H7-1	114 (2)
C1	C2	C3	111.8 (1)	C1	C7	H7-2	120 (1)
C1	C2	C8	112.9 (1)	C5	C7	H7-1	112 (2)
C1	C2	H2	102 (2)	C5	C7	H7-2	110 (2)
C3	C2	C8	111.5 (1)	H7-1	C7	H7-2	113 (2)
C3	C2	H2	105 (2)	C2	C8	H8-1	112 (1)
C8	C2	H2	113 (2)	C2	C8	H8-2	112 (1)
B	C3	C2	120.0 (1)	C2	C8	H8-3	114 (1)
B	C3	C4	101.3 (2)	H8-1	C8	H8-2	112 (2)
B	C3	H3	110 (1)	H8-1	C8	H8-3	106 (2)
C2	C3	C4	114.7 (1)	H8-2	C8	H8-3	101 (3)
C2	C3	H3	103 (1)	C6	C9	H9-1	110 (2)
C4	C3	H3	109 (1)	C6	C9	H9-2	114 (1)
C3	C4	C5	112.8 (1)	C6	C9	H9-3	110 (2)
C3	C4	H4-1	109 (1)	H9-1	C9	H9-2	107 (3)
C3	C4	H4-2	107 (1)	H9-1	C9	H9-3	107 (2)
C5	C4	H4-1	104 (1)	H9-2	C9	H9-3	108 (3)
C5	C4	H4-2	113 (2)	C6	C10	H10-1	115 (2)
H4-1	C4	H4-2	114 (2)	C6	C10	H10-7	107 (1)
C4	C5	C6	111.4 (1)	C6	C10	H10-3	114 (2)
C4	C5	C7	108.4 (1)	H10-1	C10	H10-2	103 (2)
C4	C5	H5	113 (1)	H10-1	C10	H10-3	110 (2)
C6	C5	C7	88.2 (1)	H10-2	C10	H10-3	107 (2)
C6	C5	H5	117 (1)				

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

a cold trap by a high vacuum pump (0.1 mmHg, 8 h). The residue was dissolved in EE (100 mL), diethanolamine (2.2 equiv) was added, and the mixture stirred for 2 h. The separated solid was filtered off and washed with pentane (2 × 20 mL). The combined filtrates were concentrated. The residue was distilled to obtain the alcohol in >95% purity. This was further purified by preparative gas chromatography with appropriate columns (SP-2100 or Carbowax 20M). The rotation was measured. The MTPA ester[24] of the alcohol or the MCF carbonate[25] was prepared by standard procedures. Analysis of the derivative was performed, on a capillary GC, to obtain the enantiomeric excess.

Reduction of Acetophenone. Acetophenone (3.05 mL, 26 mmol) was treated with (-)-Ipc_2BCl, (**2**; 9.0 g, 28 mmol) in THF (20 mL) at -25 °C. Workup using diethanolamine and distillation (98 °C (20 mmHg) provided (*S*)-1-phenethanol (2.3 g (72% yield); $[\alpha]^{20}_D$ -42.6° (neat)) after purification by preparative gas chromatography on a 20% Carbowax 20M column at 120 °C; 98% ee based on $[\alpha]_D^{20}$ -43.5° for maximum rotation reported.[37] GC analysis of its MTPA ester on Supelcowax glass capillary column (15 m) showed a composition of 98.7% *S* and 1.3% *R*, i.e., 97.4% ee, in good agreement with the optical rotation measurement.

α-Pinene from the above experiment was distilled over lithium aluminum hydride and purified by preparative gas chromatography on a 10% SP-2100 column (80 °C). It showed $[\alpha]_D$ +52.0°, 100% ee based on maximum rotation reported.[22] This α-pinene was converted into the isopinocampheol by hydroboration–oxidation and purified by preparative gas chromatography (20% Carbowax 20M, 125 °C), and the alcohol showed $[\alpha]_D$ -35.7° (*c* 1, benzene), ~100% based on the literature rotation.[23]

Reduction of Propiophenone. Propiophenone (2.8 mL, 21 mmol) was added to a solution of **2** (7.4 g, 23.13 mmol) in THF (18 mL) at -25 °C. The reaction was complete in 5 h when it was worked up by the standard procedure to obtain 1.77 g (62%) of 1-phenylpropanol: bp 122–124 °C (15 mmHg). The product was further purified by preparative gas chromatography (Carbowax 20M, 20%, 140 °C). The alcohol showed a rotation of $[\alpha]_D$ -28.61° (neat), which corresponds to 98.3% ee based on maximum rotation ($[\alpha]_D$ - 29.1°(neat)) reported in the literature.[37] MTPA ester analysis by Supelcowax glass capillary column (15 m, 200 °C) showed a composition of 98.66% *S* isomer and 1.34% *R* isomer, i.e., 97.3% ee.

Reduction of Butyrophenone. Butyrophenone (2.96 g, 20 mmol) was added to a solution of **2** (7.3 g, 22.8 mmol) in THF (18 mL) at -25 °C, and the reaction was followed by ^{11}B NMR. After the reaction was complete (5 h), the usual workup provided 2.3 g (77%) of 1-phenylbutanol: bp 134–136 °C (22 mmHg). The liquid solidified on disturbance. Further purification by preparative gas chromatography on 20% Carbowax 20M (140 °C) provided pure solid: mp 46–47 °C; $[\alpha]_D$ -45.64° (*c* 4.59, benzene); 100% optically pure based on the literature value of -45.2°.[38] MTPA ester analysis on Supelcowax glass capillary column (15 m, 200 °C) showed an ee of 98.2%.

Reduction of Decanophenone. Decanophenone (1.16 g, 5 mmol) was added to a solution of **2** (1.76 g, 5.5 mmol) in THF (4 mL) at -25 °C, and the reaction was followed by ^{11}B NMR. When the reaction was complete (5 h), the usual workup and distillation (pot temperature 160 °C (0.5 mmHg)) provided 0.88 g (75%) of 1-phenyldecanol. Analysis of the MTPA ester of the alcohol on a Supelcowax glass capillary column 15 m) showed it to be of 97% ee.

Reduction of 2',5'-Dimethoxypropiophenone. The ketone was prepared from *p*-dimethoxybenzene and propionyl chloride by a literature procedure.[39] The ketone (7.42 g, 38.2 mmol) was added to **2** (14.09 g, 44 mol) in THF (40 mL) at -25 °C. The reaction was complete in 1 h. The usual workup provided 6.00 g (80%) of the alcohol, bp 108–110 °C (0.2 mmHg). Analysis as the MCF derivative on a methyl silicone capillary column (50 m, 200 °C) showed an ee of 96%.

Reduction of Isobutyrophenone. Isobutyrophenone (3.85 g, 26 mmol) was added to a solution of **2** (9.3 g, 29 mmol) in THF (22 mL) at -25 °C. The reaction was complete in 24 h. The reaction mixture was worked up as usual to obtain, on distillation (120–140 °C (10 mmHg)), 2.66 g (68%) of 2-methyl-1-phenylpropanol, which was further purified by preparative gas chromatography (20% Carbowax 20M, 125 °C) $[\alpha]_D$ -19.7° (neat), which corresponds to 78% ee based on the maximum rotation reported in the literature.[40] Analysis of the MTPA ester on the Supelcowax capillary column (15 m, 180 °C) showed an ee of 90%.

Reduction of Pivalophenone. Pivalophenone was prepared by the reaction of phenylmagnesium bromide with pivalonitrile.[41] To **2** (3.68 g, 11.5 mmol) was added 1.68 mL (10 mmol) of pivalophenone at room temperature. Sufficient THF was added to make a homogeneous solution

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(39) Shulgin, A. T.; Dyer, D. C. *J. Med. Chem.* **1975**, *18*, 1201.

(40) Nasipuri, D.; Sarkar, G. J. *J. Indian. Chem. Soc.* **1967**, *44*, 165.

(41) Pearson, D. E. *J. Am. Chem. Soc.* **1950**, *72*, 4169.

(2 mL), and the mixture was stirred at room temperature. The reaction was ~60% complete in 12 days, when it was worked up as usual. Distillation gave a mixture of alcohol and ketone. Purification by preparative gas chromatography (20% Carbowax 20M, 150 °C) gave pure 2,2-dimethyl-1-phenylpropanol, $[\alpha]_D$ +20.53° (*c*, 1.98 benzene), i.e., 79.3% ee in the *R* isomer based on the literature value of +25.9° (*c* 2.2, benzene).[42]

Reduction of 1-Indanone. 1-Indanone (3.25 g, 24.6 mmol) was dissolved in THF (2 mL) and added to **2** (8.9 g, 27.8 mmol) in THF (20 mL) at −25 °C. The reaction was complete in 15 h. THF was pumped off and the residue worked up as usual. The indanol (2.15 g, 62% yield) was purified by column chromatography (eluent, benzene) and further purified by preparative gas chromatography (20% Carbowax 20M, 150 °C), mp 72 °C, $[\alpha]^{22}_D$ +32.98° (*c* 3, $CHCl_3$), which corresponds to an ee of 97% based on literature rotation.[43] MTPA ester analysis on a methyl silicone column (50 m, 190 °C) showed an ee of 97.4% in the *S* isomer.

Reduction of α-Tetralone. α-Tetralone (3.72 mL, 28 mmol) was added to **2** (9.52 g, 29.75 mmol) in THF (18 mL) at −25 °C. The reaction was complete in 50 h. THF was pumped off at aspirator vacuum and the residue worked up as usual and distilled (140 °C (17 mmHg) to obtain 2.87 g (70%) of α-tetralol, which was further purified by preparative gas chromatography (20% Carbowax 20M, 150 °C), $[a]_D$ +27.98° (*c* 3.86, $CHCl_3$), which corresponds to an ee of 85.6%.[44] MTPA ester analysis on a methyl silicone column (50 m, 190 °C) showed an ee of 87.4%.

Reduction of 2′-Acetonaphthone. 2′-Acetonaphthone (3.74 g, 22 mmol) in THF (2 mL) was added to **2** (7.64 g, 23.9 mmol) in THF (18 mL) at −25 °C. The reaction was complete in 7 h, when it was worked up as usual to obtain 3.4 g (90% yield) of 2′-naphthylethanol. Attempts to purify the alcohol by preparative GC (20% Carbowax 20M, 180 °C) failed because the compound decomposed on the column. Hence, the alcohol was recrystallized from hexane, mp 70–72 °C, $[\alpha]_D$ −41.1° (*c* 6.03, ethanol), which corresponds to 98.1% ee based on −41.5 (*c* 4.92, ethanol).[45]

Reduction of 3-Acetylpyridine. 3-Acetylpyridine (3.63 g, 3.3 mL, 30 mmol) was added to **2** (21.1 g, 66 mmol) in THF (25 mL) at −25 °C. The reaction was complete in 15 h. Water (10 mL) was added to the mixture, and the organic layer was extracted off with ether. Saturated sodium bicarbonate was added to the aqueous layer until the effervescence ceased when it became turbid. The organic phase was extracted with ether (2 × 20 mL), washed with water (2 × 20 mL), and dried ($MgSO_4$). On pumping off the ether and distilling, 2.46 g (67%) of the alcohol was obtained, bp 80 °C (1.5 mmHg). The alcohol was 99.7% GC pure. Further purification by preparative GC on an SP-2100 column (125 °C) provided the pure alcohol, $[\alpha]_D$ − 43.23° (neat), which corresponds to 91.65% ee.[46] MTPA ester analysis on a Supelcowax glass capillary column (15 m, 200 °C) showed an ee of 92.4% in the *S* isomer.

Reduction of 2-Acetylthiophene. (a) With 1 Equiv of the Reagent. 2-Acetylthiophene (3.53 g, 3 mL, 28 mmol) was added to **2** (9.92 g, 31 mmol) in THF (20 mL) at −25 °C. The reaction was complete in 52 h. Workup using the standard procedure yielded 2.0 g (56%) of the alcohol, bp 55 °C (1 mmHg). Preparative chromatography (20% Carbowax 20M, 125 °C) afforded the pure alcohol, $[\alpha]^{22}$ −12.2° (neat). Analysis of its MTPA ester (methyl silicone 50 m, 140°) showed the alcohol to be 85.1% enantiomerically pure.

(b) With 2 Equiv of the Reagent. 2-Acetylthiophene (2.48 mL, 23 mmol) was added to **2** (16.24 g, 50.75 mmol) in THF (20 mL) at −25 °C. The reaction was complete in 15 h. Acetaldehyde (1.22 g, 1.55 mL, 28 mmol) was added at −25 °C to destroy the excess reagent and the resultant mixture was left stirring overnight at that temperature. Workup as usual provided, on distillation, 2.5 g (85%) of the alcohol. Purification by preparative gas chromatography afforded the pure alcohol $[\alpha]^{22}$ −12.65° (neat), $[\alpha]^{22}_D$ −22.5° (*c* 4.41, benzene); 91.3% optically pure by capillary GC analysis (methyl silicone 50 m, 140 °C).

Reduction of 4-Phenyl-3-butyn-2-one. The ketone (1.0 g, 1.03 mL, 7 mmol) was added to **2** (2.47 g, 7.7 mmol) in THF (5 mL) at −25 °C. The reaction was complete in 2 h. The usual workup gave 0.8 g (78%) of the alcohol, bp 100 °C (0.8 mmHg). Analysis of the MTPA ester on a methyl silicone column (50 m, 200 °C) revealed an ee of 21%.

Reduction of *trans*-4-Phenyl-3-buten-2-one. The ketone (3.06 g, 21 mmol) was added to **2** (7.68 g, 23.75 mmol) in THF (20 mL) at −25 °C. The reaction was complete in 10 h. The usual workup provided 2.02 g (65%) of the alcohol, which was further provided by preparative gas chromatography (20% Carbowax 20M, 120 °C), $[\alpha]_D$ −32.16° (*c* 5, $CHCl_3$), which is 81% ee based on the maximum reported rotation in the literature.[47]

Reduction of 2-Cyclohexenone. 2-Cyclohexenone (0.9 g, 0.9 mL, 9.4 mmol) was added to **2** (3.3 g, 10.31 mmol) in THF at −25 °C. The reaction was complete within 7 h. Usual workup and distillation (bp 65° (15 mmHg)) provided 0.6 g (65%) of the alcohol. Analysis of the MTPA ester on a Supelcowax glass capillary column showed an ee of 36%.

Reduction of Ethyl Pyruvate. Ethyl pyruvate (2.9 g, 25 mmol) was added to Ipc_2BCl (8.8 g, 27.5 mmol) in THF (20 mL) at −25 °C, and the reaction was followed by ^{11}B NMR. On completion of the reaction (3 h), the usual workup provided 1.68 g (57%) of the hydroxy ester (70 °C (21 mmHg)), which was purified by preparative gas chromatography (20% Carbowax 20M, 85 °C) providing ethyl lactate, $[\alpha]^{22}_D$ −5.15°, which corresponds to 44.7% ee based on $[\alpha]^{22}_D$ −11.5° reported in the literature.[48]

Reduction of Methyl Benzoylformate. The α-keto ester (1.35 g, 1.17 mL, 8.25 mmol) was added to **2** (2.9 g, 9.07 mmol) in THF (6 mL) at −25 °C. The reaction was complete in 1 h. The intermediate crystallized out at this stage. The crystals were separated at −25 °C, EE was added, and the reaction was worked up as usual. On distillation 0.3 g (22%) of the alcohol was obtained. MTPA ester analysis (Supelcowax, 15 m, 200 °C) revealed an ee of 70%.

The filtrate was stripped off the solvent and worked up as usual to obtain 0.65 g (47.5%) of the alcohol. MTPA analysis showed an ee of 50%.

Reduction of Ethyl Benzoylacetate. The β-keto ester (2.66 g, 2.38 mL, 14 mmol) was added to **2** (4.88 g, 15.25 mmol) in THF (10 mL) at −25 °C. The reaction was followed by ^{11}B NMR. The reaction mixture on methanolysis after 1 h showed three peaks at δ 55, 32, and 16, which remain the same even after a week. The usual workup did not yield any alcohol.

Reduction of 2-Butanone. 2-Butanone (1.8 g, 25 mmol) was added to **2** (8.8 g, 27.5 mmol) in THF at −25 °C. The reaction was complete in 7 h. The usual workup gave 1.3 g of the alcohol, a yield of 72%. The product was further purified by preparative gas chromatography (10% SP-2100, 50 °C), $[\alpha]_D$ +0.57° (neat), corresponding to 4.2% ee, based on the maximum rotation of $[\alpha]_D$ +13.5° reported in the literature.[49]

Reduction of 2-Octanone. To **2** (9.07 g, 28.3 mmol) in THF (20 mL) at −25 °C was added 2-octanone (3.91 mL, 25 mmol). The reaction was complete in 3 h. The usual workup provided 2.02 g (62%) of the alcohol. Further purification by preparative gas chromatography (20% Carbowax 20M, 90 °C) gave a pure sample, $[\alpha]_D$ −0.66° (neat), i.e., 7% ee, based on $[\alpha]_D$ +9.57°, the maximum rotation reported[50] for the *S* alcohol.

Reduction of 3-Methyl-2-butanone. The ketone (1.98 g, 23 mmol) was added to **2** (8.0 g, 25 mmol) in THF (20 mL) at −25 °C. The reaction was complete in 5 h. Workup by the standard procedure gave 1.4 g (72%) of the alcohol, bp 112–114 °C, which was purified by preparative gas chromatography (10% SP-2100, 55 °C): $[\alpha]_D$ +1.67° (neat); 31.27% ee based on $[\alpha]_D$ +5.34° for 100% ee.[51]

Reduction of Acetylcyclohexane. Cyclohexyl methyl ketone (0.63 g, 0.69 mL, 5 mmol) was added to **2** (1.76 g, 5.5 mmol) in THF (4 mL) at −25 °C. The reaction was complete within 5 h, as was shown by the ^{11}B NMR of the methanolyzed aliquot of the reaction mixture. The usual workup and distillation (bp 92–95 °C (20 mm Hg)) provided 0.41 g (68% yield) of the alcohol. Analysis of the MTPA ester of the alcohol on a methyl silicone capillary column, 50 m, 180 °C) showed the alcohol to be of 26% ee.

Reduction of 3,3-Dimethyl-2-butanone. Pinacolone (3.13 mL, 25 mmol) was added, neat, to **2** (8.8 g, 27.5 mmol) at room temperature. Ipc_2BCl goes into solution within a few hours. The reaction was followed by ^{11}B NMR spectroscopy and was found to be complete in 12 d. α-Pinene was pumped off at high vacuum. Workup by the standard procedure yields 1.28 g (50%) of the alcohol, further purified by preparative gas chromatography (10% SP-2100, 50 °C), $[\alpha]_D$ +7.53° (neat), i.e., 93% ee, based on $[\alpha]_D$ +8.1° for maximum rotation reported.[52] Analysis by MTPA ester on a capillary GC (Supelcowax 15 m, 120 °C) showed an ee of 95%.

Reduction of 2,2-Dimethylcyclopentanone. 2,2-Dimethylcyclopentanone (2.54 g, 23 mmol) was added, neat, to **2** (8.0 g, 25 mmol) at room temperature. Ipc_2BCl goes into solution within 2 h. The reaction was complete in 12 h. The usual workup provides 1.84 g (71%) of the

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alcohol, bp 79–80 °C (60 mmHg). Purification by preparative GC (20% Carbowax 20M, 70 °C) gave the pure alcohol: α + 24.2° (neat), $[\alpha]_D$ +1.37° (*c* 5.64, benzene). Analysis of its MCF derivative showed an ee of 98%.

In THF (1 M), the reaction was complete in 70 h, in contrast to the 12 h required for the neat condition.

Reduction of 2,2-Dimethylcyclohexanone. 2,2-Dimethylcyclohexanone was prepared by a literature procedure.[53] To **2** (3.52 g, 11 mmol) was added, neat, at room temperature, 2,2-dimethylcyclohexanone (1.4 mL, 10 mmol), and the resultant mixture was stirred at room temperature. The reaction was complete in 12 h. After the usual workup, the alcohol was obtained in 60% yield (0.85 g). Analysis of the MCF derivative on a methyl silicone capillary column (50 m, 160 °C) showed an ee of 91%.

Reduction of Spiro[4.4]nonan-1-one. The ketone was prepared by the procedure reported in the literature.[54] The spirononanone (2.76 g, 20 mmol) was added to Ipc_2BCl (7.6 g, 22 mmol), and the reaction was conducted without any solvent. The reaction, followed by ^{11}B NMR, was found to be complete in 12 h. The usual workup provided the alcohol: 1.8 g (65%); bp 98–100 °C (16 mmHg). Purification of the alcohol by preparative gas chromatography (20% Carbowax 20M, 125 °C) provided the alcohol, $[\alpha]^{22}_D$ +40.33° (*c* 0.6, benzene), corresponding to 95% ee as shown by capillary GC analysis (methyl silicone, 50 m, 200 °C) of the menthyl chloroformate derivative. Maximum rotation reported in the literature[55] is $[\alpha]^{22}_D$ +39.8°.

Reduction of Ethyl 2,2-Dimethylacetoacetate. The keto ester was synthesized as follows: Ethyl 2-methylacetoacetate (14.42 g, 14.15 mL, 100 mmol) was added dropwise, with stirring, to a 500-mL round-bottom flask containing 2.88 g (120 mmol) of sodium hydride in THF (100 mL) at 0 °C. An immediate formation of solid was observed. The mixture was stirred at room temperature for an additional 1 h and cooled once again to 0 °C, followed by the addition of methyl iodide (7.8 mL, 125 mmol). The solid then dissolves. The mixture was stirred at room temperature for 2 h and solid sodium iodide separated. The reaction was worked up by dissolving the sodium iodide in a minimum amount of water, removing the solvent under aspirator vacuum, dissolving the residue in water, and extracting with EE. The ether extract was washed with dilute HCl, water, and brine and dried over anhydrous magnesium sulfate. Removal of EE and distillation (bp 72–75 °C (14 mmHg) (lit.[56] bp 72–73 °C (14 mmHg)) provided 12 g (76%) of ethyl 2,2-dimethylacetoacetate.

The ketone (3.95 g, 25 mmol) was added to the reagent (8.8 g, 27.5 mmol), and the reaction was conducted under neat conditions. The reaction, as was shown by the ^{11}B NMR, was complete in 12 days. The usual workup provided the alcohol (bp 90–92 °C (20 mmHg), 2.36 g (68.5% yield)), which was further purified by preparative gas chromatography (20% Carbowax 20M, 100 °C), $[\alpha]^{22}$ +3.43° (neat, *l* 0.5).[57] Analysis of the MTPA ester on a Supelcowax glass capillary column (15 m, 160 °C) showed the alcohol to be of 83.7% ee.

High-Purity α-Pinene. To a solution of (−)-Ipc_2BCl (8 g, 25 mmol) in THF (20 mL) was added benzaldehyde (5.11 mL, 50 mmol) at room temperature. α-Pinene was eliminated instantaneously, as shown by the ^{11}B NMR of a methanolyzed aliquot (δ +18), and was collected in a cold trap with a high-vacuum pump. Distillation over lithium aluminum hydride provided 6.1 g (90%) of α-pinene (>99% GC pure), $[\alpha]^{22}_D$ +51.3° (neat, *l* 0.5), which corresponds to 99.4% ee.

Preparation of (+)-Diisopinocampheylchloroborane and Reduction of Acetophenone. (+)-Ipc_2BCl was prepared from (−)-α-pinene by a procedure similar to that used for the preparation of (−)-Ipc_2BCl. Reaction of (+)-Ipc_2BCl with acetophenone under identical conditions and workup provided, on purification, (*R*)-α-phenethyl alcohol, which was shown to be of 97.2% ee by capillary GC analysis.

X-ray Analysis. The details of the data collection and structure determination are given in Table X (supplementary material). The crystal used was cut from a larger chunk (which was grown in pentane) and mounted on a glass fiber with epoxy resin in a glovebag under nitrogen and then quickly transferred to the low-temperature nitrogen stream. The unique systematic absences (001: $l = 2n + 1$; *h*00: $h = 2n + 1$) and Patterson map were indicative for the enantiomeric space groups $P4_12_12$ (No. 92) and $P4_32_12$ (No. 96). The positions of the chlorine atoms were located from subsequent difference Fourier maps after least-squares refinement. After final refinement in $P4_12_12$, the other enantiomer was tested in $P4_32_12$. The original refinement resulted in slightly lower (though not statistically significant) values for the *R* factors, and it is this result that is reported.

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Registry No. 2, 85116-37-6; **3**, 75-97-8; **4**, 597-04-6; **5**, 4541-32-6; **6**, 1193-47-1; **7**, 14727-58-3; **8**, 15206-55-0; MTPA, 20445-31-2; MCF, 112321-33-2; (−)-Ipc2BH, 21947-87-5; (+)-Ipc2BCl, 112246-73-8; (+)-Ipc2BH, 21932-54-7; (−)-Ipc2B(py)Cl, 112347-71-4; $BH_3{\cdot}SMe_2$, 13292-87-0; (+)-α-pinene, 7785-70-8; (−)-α-pinene, 7785-26-4; acetophenone, 98-86-2; (*S*)-1-phenethanol, 1445-91-6; (*S*)-1-phenethanol (MTP ester), 61184-95-0; propiophenone, 93-55-0; (*S*)-1-phenylpropanol, 613-87-6; (*S*)-1-phenylpropanol (MTPA ester), 61217-69-4; butyrophenone, 495-40-9; (*S*)-1-phenylbutanol, 22135-49-5; (*S*)-1-phenylbutanol (MTP ester), 61184-96-1; decanophenone, 6048-82-4; (*S*)-1-phenyldecanol, 112419-76-8; (*S*)-1-phenyldecanol (MTP ester), 112321-34-3; 2′,5′-dimethoxypropiophenone, 5803-30-5; (*S*)-1-(2,5-dimethoxyphenyl)propanol, 112321-32-1; (*S*)-1-(2,5-dimethoxyphenyl)-propanol (MCF derivative), 112321-35-4; isobutryophenone, 611-70-1; (*S*)-2-methyl-1-phenylpropanol, 34857-28-8; pivalophenone, 938-16-9; (*R*)-2,2-dimethyl-1-phenylpropanol, 23439-91-0; 1-indanone, 83-33-0; (*S*)-1-indanol, 25501-32-0; (*S*)-1-indanol (MTPA ester), 112321-36-5; α-tetralone, 529-34-0; (*S*)-α-tetralol, 53732-47-1; (*S*)-α-tetralol (MTPA ester), 61184-82-5; 2′-acetonaphthone, 93-08-3; (*S*)-2′-naphthylethanol, 27544-18-9; 3-acetylpyridine, 350-03-8; (*S*)-3′-pyridylethanol, 5096-11-7; (*S*)-3′-pyridylethanol (MTPA ester), 112321-37-6; 2-acetylthiophene, 88-15-3; (*S*)-2′-thiophenylethanol, 27948-39-6; (*S*)-2′-thiophenylethanol (MTPA ester), 112321-38-7; 4-phenyl-3-butyn-2-one, 1817-57-8; (*R*)-4-phenyl-3-butyn-2-ol, 73922-81-3; (*R*)-4-phenyl-3-butyn-2-ol (MTPA ester), 112321-39-8; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; (*S*)-*trans*-4-phenyl-3-buten-2-ol, 81176-43-4; 2-cyclohexenone, 930-68-7; (*S*)-2-cyclohexenol, 6426-26-2; (*S*)-2-cyclohexenol (MTPA ester), 112347-35-0; ethyl pyruvate, 617-35-6; ethyl (*S*)-2-hydroxypropanoate, 687-47-8; methyl (*R*)-α-hydroxybenzeneacetate, 20698-91-3; methyl (*R*)-α-hydroxybenzeneacetate(MTPA ester), 20455-47-4; ethyl benzoylacetate, 94-02-0; 2-butanone, 78-93-3; (*S*)-2-butanol, 4221-99-2; 2-octanone, 111-13-7; (*R*)-2-octanol, 5978-70-1; 3-methyl-2-butanone, 563-80-4; (*S*)-3-methyl-2-butanol, 1517-66-4; acetylcyclohexane, 823-76-7; (*S*)-1-cyclohexylethanol, 3113-98-2; (*S*)-1-cyclohexylethanol (MTPA ester), 112321-40-1; (*S*)-3,3-dimethyl-2-butanol, 1517-67-5; (*S*)-3,3-dimethyl-2-butanol (MTPA ester), 20445-12-9; (*S*)-2,2-dimethylcyclopentanol, 103532-77-0; (*S*)-2,2-dimethylcyclopentanol (MCF derivative), 112321-41-2; (*S*)-2,2-dimethylcyclohexanol, 103532-78-1; (*S*)-2,2-dimethylcyclohexanol (MCF derivative), 112321-42-3; (*S*)-spiro[4.4]nonan-1-ol, 21945-22-2; (*S*)-spiro[4.4]nonan-1-ol (MCF derivative), 112321-43-4; ethyl (*S*)-2,2-dimethyl-3-hydroxybutanoate, 79634-82-5; ethyl (*S*)-2,2-dimethyl-3-hydroxybutanoate (MTPA ester), 112321-44-5; ethyl 2-methylacetoacetate, 609-14-3; benzaldehyde, 100-52-7; (*R*)-α-phenethyl alcohol, 1517-69-7; dichloromethane, 75-09-2; pentane, 109-66-0; 2-picoline, 109-06-8; 2,6-lutidine, 108-48-5; triethylamine, 121-44-8; diethylmethylamine, 616-39-7; dimethylethylamine, 598-56-1; *N*-methylpyrrolidine, 120-94-5.

Supplementary Material Available: Tables of crystal data and data collection parameters for Ipc_2BCl (Table X), anisotropic thermal parameters, and positional parameters and their estimated standard deviations (4 pages). Ordering information is given on any current masthead page.

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