Chiral Synthesis via Organoboranes. 22. Selective Reductions. 44. The Effect of the Steric Requirements of the Alkyl Substituent in Isopinocampheylalkylchloroboranes for the Asymmetric Reduction of Representative Ketones

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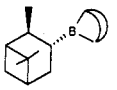
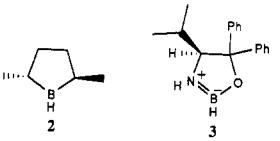
Diisopinocampheylchloroborane, $^{d}Ipc_2BCl$, is an excellent reagent for the chiral reduction of aralkyl ketones and α-*tert*-alkyl ketones. Modifications of this reagent to make new reagents applicable to additional classes of ketones were explored. Reagents with alkyl groups of varying steric requirements, such as ^{d}IpcBRCl, where R = Me, Et, *i*-Pr, Cyp, *t*-Bu, and Thx, were prepared, and their effectiveness in achieving chiral reduction of acetophenone and 3-methyl-2-butanone was examined. Whereas all of the reagents produced (*S*)-3-methyl-2-butanol in a modest range of 22–48% ee, the reagents with R = Me, Et, *i*-Pr, and Cyp produced (*S*)-1-phenethanol in the range of 15–84% ee, while the reagents with R = *t*-Bu and Thx gave (*R*)-1-phenethanol in 96% and 83% ee, respectively. Thus the reagent ^{d}IpcB-*t*-BuCl achieves high asymmetric reduction of acetophenone in the range achieved by $^{d}Ipc_2BCl$, but the product possesses the opposite configuration, *R*, instead of *S*. The general effectiveness of the new reagent, ^{d}IpcB-*t*-BuCl, was explored by reducing the ten standard ketones. ^{d}IpcB-*t*-BuCl reduces acetophenone, 2-chloroacetophenone, and 3-acetylpyridine in 96%, 98%, and 96% ee, respectively, highly enriched in the *R* isomer. Methyl benzoylformate was reduced in 91% ee (*S*). *trans*-4-Phenyl-3-buten-2-one and cyclohexenone were reduced in 84% and 46% ee, respectively, enriched in the *R* isomer. 2,2-Dimethylcyclopentanone and 3-methyl-2-butanone were reduced in 34% ee (*R*) and 44% ee (*S*), respectively. This study clearly demonstrates a major effect of the steric requirements of the R group in the reagents, ^{d}IpcBRCl, both on the effectiveness of the chiral reduction achieved and on the absolute configuration of the product.

The enantioselective reduction of the ubiquitous carbonyl group occupies a position of prominence in asymmetric synthesis.[1] As part of our efforts to develop methods for the synthesis of optically pure compounds via organoboranes,[2] we undertook the development of an effective chiral reducing agent for the reduction of standard classes of prostereogenic ketones. In this regard, many interesting chiral boron reagents, both trigonal and tetrahedral, have been developed in the past, some of them achieving remarkable success for individual classes of ketones. For example, Midland's *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane), **1**, reduces deuterio aldehydes,[3] acetylenic ketones,[4] and α-keto esters[5] with excellent stereogenic transfer; but in the case of prochiral aralkyl and dialkyl ketones, it proved to be less efficient, the reactions being very slow even under neat condition at room temperature.



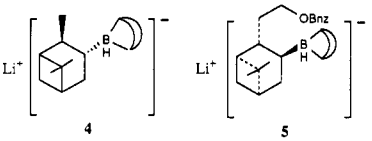
1

Although chiral monoalkyl- and dialkylboranes derived from α-pinene proved inefficient in asymmetric reductions, Masamune recently demonstrated that this is not an inherent property of chiral dialkylboranes. In a long, though elegant synthetic stratagem, the MIT group prepared (*R,R*)-2,5-dimethylborolane (**2**), and found this reagent to be particularly suited for the asymmetric reduction of aromatic ketones.[6] The Itsuno reagent,[7] **3**, derived from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and borane, whose structure has recently been examined by Corey and co-workers,[8] is notable not only for the high levels of enantioselectivity obtained in the reduction of various classes of aromatic and tertiary ketones, but more so for the catalytic nature of the reagent,[8,9] one of the few known catalytic processes involving a boron reagent.



2 **3**

Various reagents have been developed modifying sodium or lithium borohydride with limited success.[10] A decade ago we developed a chiral borohydride reagent, lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride, Alpine-Hydride (**4**). The reagent was not highly effective for asymmetric reductions.[11] However, a similar borohydride reagent developed by Midland, NB-Enantride (**5**), derived from nopol, was relatively efficient for the reduction of straight chain aliphatic ketones.[12]



4 **5**

Recently, we developed in our laboratories a well-defined chiral borohydride reagent, potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K-glucoride, **6**), which is highly effective for

(1) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, Chapters 2–4.
(2) (a) Brown, H. C.; Jadhav, P. K.; Singaram, B. In *Modern Synthetic Methods*; Schefold, R., Ed. Springer-Verlag: Berlin, 1986; Vol. 43, p 307. (b) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9.
(3) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.
(4) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(5) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.
(6) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402.
(7) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. I* **1985**, 2039.
(8) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(9) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395.
(10) (a) Haubenstock, H. *Top. Stereochem.* **1983**, *14*, 231. (b) Kagan, G. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175.
(11) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.
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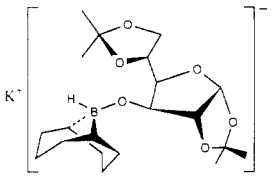
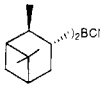
the asymmetric reduction of highly hindered aromatic ketones and α-keto esters.[13]



6

However, the main thrust of our endeavors in asymmetric reductions has been and continues to be centered on reagents derived from monoterpenes in general and α-pinene in particular, both enantiomers of which are readily available in high optical purity. Recently, we reported the development of diisopinocampheylchloroborane, $^{d}Ipc_2BCl$ (the superscript *d* indicates that the reagent is derived from (+)-α-pinene) **7**, an extremely ef-



7

ficient reagent for the reduction of aralkyl ketones and α-hindered aliphatic ketones.[14] We demonstrated the utility of this reagent for the synthesis of some important pharmaceuticals.[15] The superiority of this reagent over Alpine-Borane is apparently due to the changed electronic and steric environment attained by attachment of the chlorine atom to boron. To gain a better understanding of the factor(s) responsible for asymmetric induction and with the hope of developing improved reagents, we undertook a systematic study of the effect of substituting one of the isopinocampheyl, Ipc, moieties of $^{d}Ipc_2BCl$ with alkyl groups of varying steric requirements. Earlier a study of the reagents prepared by changing the halogen atom failed to provide improved reagents.[16]

Results and Discussion

A number of recent developments in our laboratory enabled us to approach the synthesis of the title compounds in a direct and unambiguous manner. We discovered that certain esters of boronic acids undergo a facile displacement reaction with $LiAlH_4$ to afford lithium alkylborohydrides cleanly (eq 1).[17]

$$RB(OR')_2 + LiAlH_4 \rightarrow LiRBH_3 + HAl(OR')_2 \quad (1)$$

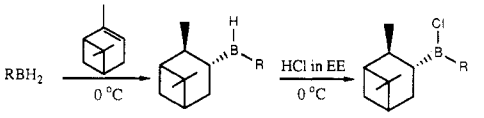
Investigation of the chemistry of these monoalkylborohydrides revealed some interesting properties. For instance, treatment of these alkylborohydrides with, inter alia, anhydrous ethereal hydrogen chloride liberated the corresponding monoalkylboranes in isomerically pure form (eq 2).[18]

$$LiRBH_3 + HCl \rightarrow RBH_2 + H_2 + LiCl \quad (2)$$

These monoalkylboranes could hydroborate a large variety of olefins to afford exclusively products of monohydroboration (eq 3).[19]

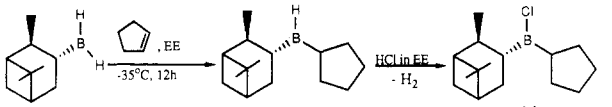
$$RBH_2 + \text{alkene} \rightarrow RR'BH \quad (3)$$

This property was exploited in hydroborating α-pinene to provide isopinocampheylalkylboranes, which were converted to the corresponding chloroboranes by treatment with anhydrous hydrogen chloride in ethyl ether (eq 4).



(4)

However, isopinocampheylcyclopentylchloroborane was prepared by an alternative synthesis, direct hydroboration of cyclopentene with monoisopinocampheylborane, $IpcBH_2$,[20] followed by treatment with dry ethereal hydrogen chloride (eq 5).



(5)

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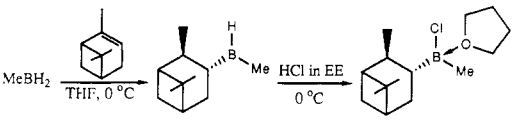
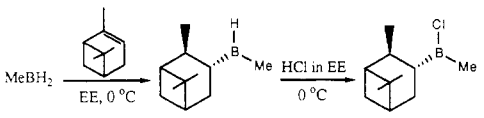
Isopinocampheylmethylchloroborane ($^{d}IpcBMeCl$, 8). Hydroboration of (+)-α-pinene of 99% ee with methylborane in THF at 0 °C for 10–15 min provided the corresponding isopinocampheylmethylborane, which, when treated in situ with anhydrous ethereal hydrogen chloride, furnished $^{d}IpcBMeCl$ (**8**) as the THF complex (eq 6).



(6)

However, the THF complex does not reduce ketones at reasonable rates. Attempted distillation of the $^{d}IpcBMeCl$·THF to obtain the reagent free of THF resulted in the decomposition of the compound. We overcame this problem by hydroborating α-pinene by using ethyl ether as the solvent followed by treatment with dry HCl in EE (eq 7). Removal of the solvent provided **8** as an oil.



(7)

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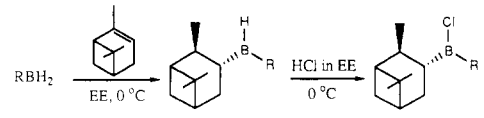
Isopinocampheylethylchloroborane ($^{d}IpcBEtCl$, 9) and Isopinocampheylisopropylchloroborane ($^{d}IpcB$-*i*-PrCl, 10). Both of these reagents **9** and **10** were prepared, in a manner similar to the preparation of $^{d}IpcBMeCl$, by the hydroboration of α-pinene with an ethereal solution of the corresponding boranes, followed by treatment with HCl in EE (eq 8).



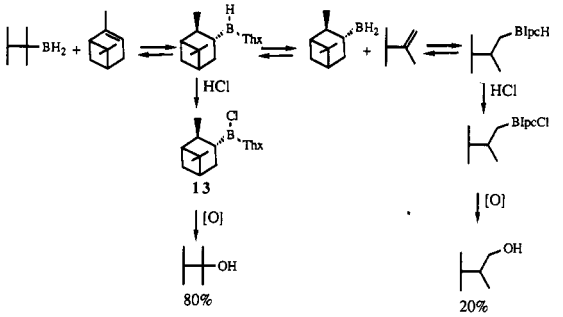
(8)

9 R = Et
10 R = *i*-Pr

However, unlike **8**, $^{d}IpcBEtCl$ coordinates reversibly with THF and can be obtained in the free state from a solution of THF by removal of the solvent under reduced pressure. By way of contrast, the isopropyl analogue does not coordinate with THF to any appreciable extent and hence can be prepared directly in this solvent.

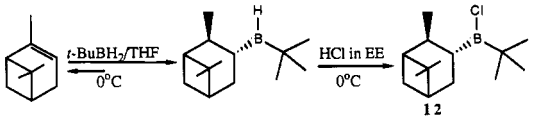
(13) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231.
(14) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(15) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916.
(16) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. Unpublished work.
(17) Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 774.
(18) Cole, T. E.; Bakshi, R. K.; Srebnik, M.; Singaram, B.; Brown, H. C. *Organometallics* **1986**, *5*, 2303.
(19) For instance, see: Srebnik, M.; Cole, T. E.; Brown, H. C. *Tetrahedron Lett.* **1987**, *33*, 3771.
(20) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.

Scheme I



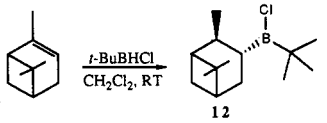
Isopinocampheylcyclopentylchloroborane (^{d}IpcBCypCl, 11). Unlike the above series of monoisopinocampheylalkylchloroboranes, the cyclopentyl analog was prepared by the hydroboration of cyclopentene with monoisopinocampheylborane at -35 °C followed by treatment with dry HCl in EE (eq 5). This preparation has an advantage that the optical purity of the chiral auxiliary is upgraded during the preparation of ^{d}IpcBH$_2$ and thus avoids a need for optically pure α-pinene. The reagent is a liquid at room temperature and is stable under inert conditions.

Isopinocampheyl-*tert*-butylchloroborane (^{d}IpcB-*t*-BuCl, 12). Hydroboration of α-pinene with *tert*-butylborane proceeds readily at 0 °C in EE or THF. Analysis of the reaction mixture by ^{11}B NMR spectroscopy, however, indicates that the reaction proceeds only to 80% completion. Apparently, this is due to a facile elimination of α-pinene to establish an equilibrium. The reaction can be brought to essential completion by using a modest excess of α-pinene. Addition of dry ethereal HCl and removal of solvents provides the reagent **12** (eq 9). The excess α-pinene neither interferes with the synthesis nor with the subsequent reduction.



(9)

A more direct method, which circumvents the need for excess olefin, makes use of *tert*-butylchloroborane, *t*-BuBHCl, readily prepared from the corresponding borohydride and 2 equiv of HCl. Hydroboration of α-pinene at room temperature with a solution of *t*-BuBHCl in EE or CH_2Cl_2 but not THF (the latter is cleaved by the reagent) affords ^{d}IpcB-*t*-BuCl, **12** (eq 10).



(10)

The reagent, like **10**, does not complex with THF. The reagent is a viscous liquid and is stable under an inert atmosphere.

Isopinocampheylthexylchloroborane (^{d}IpcBThxCl, 13). Preparation of this compound by hydroboration of α-pinene with thexylborane, ThxBH$_2$,[21] followed by treatment with HCl, provides a reagent, which although pure by ^{11}B NMR (δ 78), nevertheless gave erratic results in the reduction of ketones. Apparently, this is due to a facile dehydroboration/hydroboration reaction that affords a mixture of the desired compound and the rearranged isomer (Scheme I).

(21) Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77.

Table I. ^{11}B NMR Spectral Data for Isopinocampheylalkylchloroboranes, ^{d}IpcBRCl[a]

R	^{11}B NMR, δ	isol yield, %	complexing nature with ethers: EE	complexing nature with ethers: THF
Me	75.6 (19)[b]	93	–	+
Et	76.3	99	–	±[c]
i-Pr	76.1	98	–	–
Cyp	76	73	–	–
Ipc	76	75	–	–
t-Bu	76.7[d]	95	–	–
Thx	78.3[e]	99	–	–

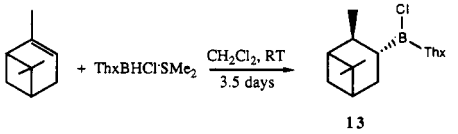
[a] Spectra were run in EE unless otherwise indicated. The superscript *d* indicates that the reagent was derived from (+)-α-pinene. [b] THF complex. [c] The reagent forms a loose complex that can be removed by removing the solvent in vacuum. [d] In THF. [e] In CH_2Cl_2. In all cases methanolysis of the chloroboranes yielded a single peak, which absorbed at ~54 ppm.

Table II. Reduction of Acetophenone with Isopinocampheylalkylchloroboranes, ^{d}IpcBRCl[a]

R	solvent	time, h	temp, °C	%ee of alcohol[b]	abs config
Me	EE	12	−25	14.8	*S*
Et	EE	12	−25	33.2	*S*
i-Pr	EE	12	−25	81.1	*S*
Cyp	EE	24	−25	84	*S*
Ipc	THF	7	−25	98	*S*
t-Bu	THF	24	−25	96	*R*
Thx	CH_2Cl_2	66	25	83	*R*

[a] The superscript *d* indicates that the reagent was derived from (+)-α-pinene. [b] Determined as the (+)-MTPA ester and analysis on a Supelcowax glass capillary column (15 m).

That this indeed occurred was readily demonstrated by analyzing for the isomeric alcohols obtained following an alkaline oxidation of the reaction mixture. Approximately 20% of 2,3-dimethylbutan-1-ol was produced, indicating that rearrangement had occurred to a similar degree. Fortunately, the problem could be avoided by preparing the reagent by direct hydroboration of α-pinene using thexylchloroborane–methyl sulfide complex, ThxBHCl·SMe$_2$[22] in CH_2Cl_2. The reacion proceeds readily at room temperature in 3.5 days (eq 11). Subsequent isolation and purification provides ^{d}IpcBThxCl as a very viscous oil in 99% yield.



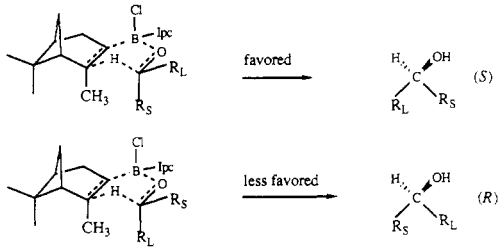
(11)

The ^{11}B NMR data and complexing nature with EE and THF of all of the reagents prepared are summarized in Table I.

Asymmetric Reduction of Representative Ketones. Two representative ketones, acetophenone and 3-methyl-2-butanone, were selected to test the reactivities and enantioselectivities in the asymmetric reduction with these new reagents. We have the information that the nature of the halogen atom in ^{d}Ipc$_2$BX (X = F, Cl, Br, I) does not significantly influence the chiral outcome.[16] Consequently, we anticipated, in view of the mechanism for asymmetric reduction postulated earlier,[14,23] that all of the above reagents (**8**–**13**) would behave similarly, providing alcohols of essentially the same % ee. But the facts proved otherwise. The effect of the structure of the alkyl

(22) Brown, H. C.; Sikorski, J. A. *Organometallics* **1982**, *1*, 28.
(23) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316.

Scheme II



group on the asymmetric reduction of aromatic ketones was large. The % ee obtained for the product alcohols is summarized in Table II.

In general, reductions were carried out in tetrahydrofuran (THF), ethyl ether (EE), or dichloromethane (CH_2Cl_2) at −25 °C by using a 10% excess of the reagent. Whenever the reactions were slow, the temperature was raised to 0 °C or room temperature and, if needed, the reactions were conducted without solvent. The reactions were followed by ^{11}B NMR examination of a methanolyzed aliquot. On completion of the reaction, the reaction mixture was stripped of solvent and the α-pinene generated during the reaction removed under reduced pressure. EE was added to the residue followed by 2.2 equiv of diethanolamine, which precipitated the boron components as a complex and liberated the alcohol. The alcohol was purified by distillation and/or chromatography. The optical purity of the alcohols was determined by preparing their (+)-α-(methoxy)-α-(trifluoromethyl)phenylacetate (MTPA)[24] or (−)-menthyl chloroformate (MCF)[25] derivatives, followed by analysis on a Supelcowax glass capillary column (15 m) or a methylsilicone capillary column (50 m). Whenever analysis was not possible by capillary GC, the % ee was determined by comparison of the optical rotation with the known maximum rotation reported in the literature. Our results with the reagents 8–13 are discussed below.

When the R group in ^{d}IpcBRCl was methyl, the reduction of acetophenone resulted in poor optical induction (15% ee). This result clearly suggests that the effects of substitution on boron should also be taken into consideration when postulating the transition state and indicates that the model in Scheme II may need modification. When we reduced acetophenone with the reagent containing R = Et, a slight improvement in ee was obtained (33%). Increasing the bulk of the R group to a *sec*-alkyl group, such as isopropyl, resulted in a sharp increase in the optical induction obtained, 81% ee. That we obtained such a high ee for α-phenethanol was confirmed by preparing the reagent with the related alkyl group, cyclopentyl, and reducing acetophenone. ^{d}IpcBCypCl gave α-phenethanol of 84% ee. In fact, the reagent of choice for aralkyl ketones, ^{d}Ipc_2BCl also bears a *sec*-alkyl group, Ipc, for R in ^{d}IpcBRCl. Thus, it seems that a *sec*-alkyl group provides the necessary steric fit to provide good ee in aralkyl ketone reduction. From the results realized for R = Ipc, this group must provide a nearly ideal fit. This must also be true for Alpine–Borane, where the 9-BBN moiety can be considered to contain two *sec*-alkyl fragments attached to the boron.

Upon increasing the bulk of the alkyl group further, i.e., for R = *t*-Bu in ^{d}IpcBRCl, the results realized were totally unexpected. For reductions using ^{d}IpcB-*t*-BuCl, the phenethanol from acetophenone revealed an *R* absolute configuration in contrast to the *S* configuration realized with the reagents containing R = Me, Et, *i*-Pr, and Ipc.

Thus, the pattern revealed by changes in the steric requirement of the substituent R becomes clear. As we increase the bulk from Me to Et to *i*-Pr (Cyp, Ipc), we observe a steady increase in % ee with formation of the *S* isomer favored. But a further increase in the steric requirements, isopropyl to *tert*-butyl, results in the preferred formation of the *R* isomer. Perhaps even more suprising is the fact that the *R* alcohol is formed in very high ee. The model in Scheme II does not predict this. The steric effect of the *tert*-butyl group was further substantiated by substituting a thexyl group for the *tert*-butyl. A similar effect was observed. The reaction of ^{d}IpcBThxCl with ketone was very low at −25 °C and 0 °C, and so was conducted at room temperature. The product 1-phenethanol from acetophenone showed an ee of 83% in the *R* isomer. The diminished ee may be due either to the higher temperature at which the reaction was conducted or to a partial dissociation of the highly strained reagent during the reaction.

On the other hand, the reduction of a representative dialkyl ketone, 3-methyl-2-butanone, did not show any suprises. ^{d}Ipc_2BCl reduces the above ketone at −25 °C to provide the corresponding alcohol in 32% ee (*S*). When we examined the asymmetric induction capabilities of 8–13 with this ketone, we observed only modest effects of steric size. The results are summarized in Table III. Unlike the behavior for acetophenone, the reduction of 3-methyl-2-butanone by ^{d}IpcBMeCl gave most favorable induction (48% ee), decreasing with increasing steric requirement of R: ^{d}IpcBEtCl, 36%; ^{d}IpcB*i*-PrCl, 25%; ^{d}IpcBCypCl, 22%.

Another interesting aspect is the fact that unlike the behavior of the aralkyl ketone, the reduction of 3-methyl-2-butanone by ^{d}IpcB-*t*-BuCl did not give alcohol of opposite (*R*) configuration. 3-Methyl-2-butanol was obtained in 44% (*S*), similar to the *S* configuration realized with ^{d}IpcBMeCl, as well as with R = Et, and *i*-Pr. ^{d}IpcBThxCl also gave 3-methyl-2-butanol with the *S* configuration, but in lower ee, only 18%.

Reduction of Representative Classes of Ketones Using ^{d}IpcB-*t*-BuCl. The results of the reduction of representative aromatic and aliphatic ketones using the reagents 8–13 (Tables II and III) showed that the reagent **12**, ^{d}IpcB-*t*-BuCl, could be very promising. Though **12** did not give good ee for the reduction of the aliphatic ketone, the reduction of the aromatic ketone was especially interesting. The very high ee (96%) for 1-phenethanol, coupled with the fact that the alcohol has a configuration opposite to that obtained from reduction with ^{d}Ipc_2BCl, makes this reagent very promising. If this reagent behaves like **7** in the efficiency of its asymmetric reduction of aralkyl ketones, yet provides alcohols of the opposite con-

Table III. Reduction of 3-Methyl-2-butanone with Isopinocampheylalkylchloroboranes, ^{d}IpcBRCl[a]

R	solvent	reactn time, h	reactn temp, °C	% ee[b] of alcohol	abs config
Me	EE	12	−25	47.9	*S*
Et	EE	12	−25	35.9	*S*
i-Pr	EE	12	−25	24.9	*S*
Cyp	EE	24	−25	28	*S*
Ipc	THF	7	−25	32	*S*
t-Bu	THF	24	−25	43.5	*S*
Thx	CH_2Cl_2	66	25	18	*S*

[a] See footnotes of Table II. [b] Determined on a methylsilicone column (50 m) as the MCF derivative.

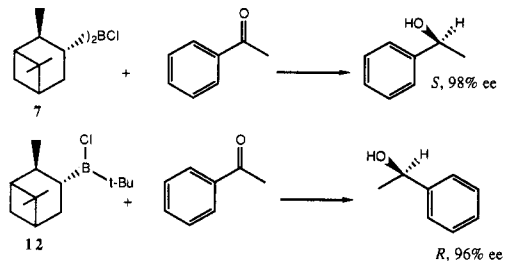
(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(25) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.

Table IV. Reduction of Representative Classes of Ketones Using ^{d}IpcB-*t*-BuCl in THF (1 M, -25 °C)

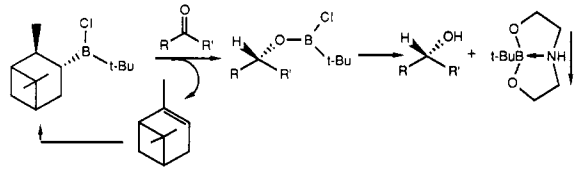
ketone	reactn time, h	isol yield, %	% ee[a] of alcohol	abs config	% ee for Ipc_2BCl[b] (abs config)
3-methyl-2-butanone	24	60	44	*S*	32 (*S*)
2,2-dimethylcyclopentanone	24[c]	65	34	*R*	98 (*S*)
acetophenone	24	68	96	*R*	98 (*S*)
3-acetylpyridine	7 days	62	96	*R*	92 (*S*)
2-chloroacetophenone	24	68	98	*S*	95 (*R*)
2-cyclohexenone	24	60	46	*R*	36 (*S*)
trans-4-phenyl-3-buten-2-one	24	72	85[d]	*R*	81 (*S*)
4-phenyl-3-butyn-2-one	5	70	21	*S*	21 (*R*)
methyl benzoylformate	1	70	91	*S*	70 (*R*)
ethyl benzoyl acetate	no redn				no redn

[a] Determined as MTPA ester or MCF derivative on a capillary column. [b] Ref. 14. [c] Reaction conducted at room temperature. [d] Based on optical rotation and comparison with maximum rotation reported. Ref. 29.

Scheme III



Scheme IV



figuration, it could very well be complimentary to **7** for the reduction of such ketones, making it possible to produce alcohols of either *R* or *S* absolute configuration with the more economical (+)-α-pinene (Scheme III). Another promising feature of reagent **12** is that, unlike **7**, the chiral auxiliary can be recovered completely during workup (Scheme IV). Hence, we felt it desirable to examine the behavior of **12** for the reduction of our standard ten classes of ketones[26] and to compare the results with the results obtained for the reduction of these ten ketones with ^{d}Ipc_2BCl. The results are summarized in Table IV.

From Table IV, it is clear that the reagent is very effective in reducing five of the ten classes of ketones. As discussed earlier, acetophenone is reduced in THF, 1 M, at -25 °C, to (*R*)-α-phenethyl alcohol in 96% ee. Ipc_2BCl gives (*S*)-α-phenethyl alcohol in 98% ee under identical conditions. 3-Methyl-2-butanol is produced in 44% ee (*S*) by **12** as compared to the 32% ee (*S*) given by **7**. Whereas ^{d}Ipc_2BCl reduced 2,2-dimethylcyclopentanone to the corresponding alcohol in 98% ee, **12** reduced this ketone to the *R* alcohol only in 34% ee. Again, the steric bulk of the *tert*-butyl group must play some significant role, not evident from the current mechanism for such reductions (Scheme II).

However, 3-acetylpyridine, 2-chloroacetophenone, and methyl benzoyl formate were all reduced by **12** in high ee: 96% (*R*), 98% (*R*), and 91% ee (*S*), respectively. The value obtained for the α-keto ester methyl benzoylformate (91%) is considerably higher than that obtained for the reduction using ^{d}Ipc_2BCl (70%). In all three cases, we obtained alcohols of the opposite configuration, compared with those produced in reductions with ^{d}Ipc_2BCl.

The β-keto ester could not be reduced by **12**.

The enones *trans*-4-phenyl-3-buten-2-one and 2-cyclohexenone were reduced in 85% ee and 46% ee, respectively. In both of these cases we also obtained alcohols with a configuration opposite to that produced by ^{d}Ipc_2BCl, with a modest improvement in the % ee. ^{d}IpcB-*t*-BuCl appears to be a better reagent for certain enone reductions, providing alcohols that could be important intermediates in prostaglandin syntheses.

As with ^{d}Ipc_2BCl, **12** reduces the acetylenic ketone, 4-phenyl-3-butyn-2-one, with poor ee. However, here also the configuration of the product alcohol was reversed.

Conclusion

In conclusion, we have synthesized and examined a series of isopinocampheylalkylchloroborane reagents for chiral reductions in order to understand the influence of the alkyl substituent on the chiral outcome. A better understanding of the sensitivity of the chiral reduction to the structure of the reagent has been achieved. This should be helpful in future modifications of these reagents. Of the reagents prepared, ^{d}IpcB-*t*-BuCl holds promise as reagent complimentary to ^{d}Ipc_2BCl. The fact that the chiral auxiliary α-pinene is available in both optical forms and can be recovered completely after the reaction makes this reagent especially attractive. This reagent is superior to ^{d}Ipc_2BCl both for enone reductions and for the reduction of α-keto esters. These valuable applications of the reagent are being explored further.

Based on the insight provided by this study as to the major effect of steric influences on the effectiveness of this chiral reductions, we are currently investigating other modified reagents for the reduction of all classes of ketones. Preliminary results are exceptionally promising.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[27] Spectroscopic (^{1}H and ^{11}B NMR and 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 methylsilicone capillary column (50 m) at appropriate

(26) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.

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

temperatures and integrated by using 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 (98% ee) were obtained from the Aldrich Chemical Co. The ketones were obtained from the Aldrich Chemical Co. or Wiley Organics and were used as received. MTPA was obtained from the Aldrich Chemical Co. and converted to the acid chloride by using the literature procedure.[24] MCF was obtained from the Aldrich Chemical Co. Anhydrous etheral hydrogen chloride (~3 M) was prepared by using a Brown automatic gasimeter from hydrochloric acid and sulfuric acid.[28]

Preparation of the Reagents. General Procedure. An over-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. $LiRBH_3$ (5 mmol) was transferred to the flask via a syringe and cooled to 0 °C. HCl in EE (5 mmol) was added dropwise, to liberate the RBH_2. (+)-α-Pinene (5.5 mmol) was added and stirred until the hydroboration was complete (^{11}B NMR). A second equivalent of HCl in EE (5 mmol) was then added. An instantaneous evolution of 1 equiv of hydrogen was observed with a concurrent formation of the reagent. ^{11}B NMR of **8–13** are given in Table I. The reagents were used as such for further reactions.

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. The reagent (5.5 mmol) was transferred to the flask via a syringe and appropriate solvent (THF, EE, or CH_2Cl_2) was added. The solution was cooled to the appropriate temperature and the ketone (5 mmol) was added. The reaction was followed by ^{11}B NMR after aliquots were methanolyzed at the reaction temperature at periodic intervals. When the reaction was complete, the mixture was raised to room temperature and the solvent was removed at aspirator vacuum. α-Pinene liberated during the reaction was collected in a cold trap using a high vacuum pump. The residue was dissolved in EE (20 mL), diethanolamine (2.2 equiv) was added, and the mixture was stirred for 2 h. The separated solid was filtered off and washed with pentane. The combined filtrates were concentrated and the residue was distilled to obtain the alcohol in >95% purity. The MTPA ester or the MCF derivative of the alcohol was prepared by standard procedures.[24,25] Analysis of the derivative was performed on a capillary GC to obtain the enantiomeric excess. Preparation of the individual reagent and their reactions are given below.

Preparation of Isopinocampheylmethylchloroborane (^{d}IpcBMeCl, 8) in THF. A 100-mL round-bottom flask equipped with a side arm and stirring bar was charged with 20 mL of a 1 M solution of $LiMeBH_3$ in THF and cooled to 0 °C. Ethereal HCl (6.0 mL, 3.34 M) was added followed by (+)-α-pinene of 98% ee (3.5 mL, 22 mmol). The reaction was stirred for 15 min, when an additional portion of ethereal HCl (6.0 mL, 3.34 M) was added. The solution was diluted with pentane (20 mL) and filtered and all volatiles were removed under aspirator pressure to afford ^{d}Ipc(Me)BCl·THF as a viscous oil. Yield: 5.03 g, 18.5 mmol, 93%. ^{11}B NMR: δ 19. Attempted distillation resulted in the decomposition of the material.

In Ethyl Ether. The compound was prepared in the same manner and proportions as described for the preparation in THF, using a stock solution of $LiMeBH_3$ in EE. Yield: 3.69 g, 18.6 mmol, 93%. ^{d}IpcBMeCl is a light oil at ambient temperature with a tendency to discolor. However, the discoloration disappears in solution. ^{11}B NMR showed a peak at δ 75.6. Methanolysis yields a single peak at δ 53.

Reduction of Acetophenone. The reaction was performed on a 5-mmol scale (5.5 mmol reagent) in EE at −25 °C for 12 h. Workup as described in the general procedure yielded (*S*)-1-phenethanol. Yield: 0.48 g, 3.9 mmol, 78%. The enantiomeric excess was determined on Supelcowax (15 m) of the (+)-MTPA derivative: 42.6% *R* and 57.4% *S* = 14.8% *S*.

Reduction of 3-Methyl-2-butanone. The reaction was run under identical conditions and proportions as described for the reduction of acetophenone. Yield: 0.31 g, 3.5 mmol, 70%. The ee was determined on a methylsilicone column (50 m) on the MCF derivative: *R* 26.05% and *S* 73.95% = 47.9% *S*.

Preparation of Isopinocampheylethylchloroborane (^{d}IpcBEtCl, 9). The reagent **9** was prepared from a stock solution of $LiEtBH_3$ in EE in the same manner and proportions as described for the methyl derivative. Yield: 4.21 g, 19.8 mmol, 99% as a clear white oil. ^{11}B NMR: δ 76.3, which upon methanolysis shifted to δ 54.

Reduction of Acetophenone. Acetophenone (0.59 mL, 5 mmol) was added at −25 °C to a solution of **9** (5.5 mmol) in EE prepared as described above. After 12 h the usual workup gave (*S*)-1-phenethanol, 0.46 g, 3.75 mmol, 75%. Analysis of the (+)-MTPA derivative on a Supelcowax column (15 m) showed a peak ratio of 33.4% *R* and 66.6% *S*, i.e., 33.2% *S*.

Reduction of 3-Methyl-2-butanone. The reduction was performed on a 5-mmol scale as described for acetophenone at −25 °C for 12 h in EE. Workup and bulb-to-bulb distillation afforded the alcohol. Yield: 0.31 g, 3.5 mmol, 70%. Analysis on a methylsilicone column (50 m) showed a peak ratio of 32.1% *R* and 68% *S*, i.e., 35.9% *S*.

Preparation of Isopinocampheylisopropylchloroborane (^{d}IpcB-*i*-PrCl, 10). The reagent was prepared from a stock solution of Li-*i*-$PrBH_3$ in EE and (+)-α-pinene as described for the preparation of the methyl derivative, but the reaction was stirred for 1.5 h at 0 °C prior to adding the second portion of HCl. The usual workup furnished **10**, 4.4 g, 19.6 mmol 98% as a viscous oil. ^{11}B NMR showed a peak at δ 76.1, which after methanolysis shifted to δ 53.5.

Reduction of Acetophenone. The reduction was carried out on a 5-mmol scale exactly as with the previous reagents. Yield: 0.48 g, 3.9 mmol, 78%. GC analysis was done on a Supelcowax column (15 m) on the (+)-MTPA derivative: 9.5% *R* and 90.6% *S* = 81.1% *S*.

Reduction of 3-Methyl-2-butanone. A reaction of the ketone (5 mmol) with **10** (5.5 mmol) in EE at −25 °C yielded 0.31 g, 3.5 mmol, 70% of the alcohol. The enantiomeric excess was determined on a methylsilicone column (50 m) as the MCF derivative: *R* 37.6% and *S* 62.5%, i.e., 24.9% *S*.

Preparation of Isopinocampheylcyclopentylchloroborane (^{d}IpcBCypCl, 11). To a solution of $IpcBH_2$ in EE[20] (10 mmol) at −35 °C was added cyclopentene (0.88 mL, 10 mmol). After 1 h, a solid separated. The reaction mixture was left overnight at −35 °C. The solid was filtered and washed with ice-cold dry ether. This was then suspended in EE at −78 °C and treated with a stoichiometric amount of HCl in EE. On warming to 0 °C, the solid dissolved with the liberation of 1 equiv of H_2. ^{11}B NMR indicated a peak at δ 76 ppm. An aliquot upon methanolysis showed a peak at δ 54 ppm in the ^{11}B NMR spectrum. Removal of the solvent provided **11** as an oil in 73% yield.

Reduction of Acetophenone. Acetophenone (0.59 mL, 5 mmol) was added to **11** in EE at −25 °C. The reaction was complete in 24 h and workup gave 75% of the alcohol, which when analyzed as its MTPA ester showed an ee of 84% in the *S* isomer.

Reduction of 3-Methyl-2-butanone. The ketone (0.54 mL, 5 mmol) was added to **11**, in EE at −25 °C, and the reaction was complete in 24 h. Workup gave 0.23 g of the alcohol, which was analyzed as its MCF derivative on a methylsilicone capillary column to be of 22% ee in the *S* isomer.

Preparation of Isopinocampheyl-*tert*-butylchloroborane (^{d}IpcB-*t*-BuCl, 12). Method A. 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. Li-*t*-$BuBH_3$ (5.95 mL, 0.84 M in THF, 5 mmol) was transferred to the flask via a syringe and cooled to 0 °C. HCl in EE (1.5 mL of 3.34 M, 5 mmol) was added dropwise, to liberate the *t*-$BuBH_2$. α-Pinene (1.2 mL, 7.5 mmol) was added and the solution was stirred for 2 h when the hydroboration was complete (^{11}B NMR: δ 57). A second equivalent of HCl in EE (1.5 mL of 3.34 M, 5 mmol) was then added when an instantaneous evolution of hydrogen with a concurrent formation of **12**. ^{11}B NMR of **12** showed a singlet at δ 76, and a methanolyzed aliquot showed a singlet at δ 54. Removal of the solvent provided **12** as an oil. The reagent was used as such for further reactions.

Method B. Under nitrogen, Li-*t*-$BuBH_3$ (5.95 mL, 0.84 M in THF, 5 mmol) was transferred to a 50-mL round-bottom flask

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

equipped with a septum capped side arm, magnetic stirring bar, and a connecting tube. The flask was cooled to 0 °C and under stirring, HCl in EE (3 mL of 3.34 M, 10 mmol) was added, dropwise, when 2 equiv of H_2 was liberated with concurrent formation of t-BuBHCl·OEt$_2$. ^{11}B NMR showed a doublet at δ 14.3. Methanolysis of an aliquot shifted the peak to δ 32 in ^{11}B NMR. α-Pinene (0.79 mL, 5 mmol) was added to the flask, and the solution was stirred until the hydroboration was complete (0.5 h, ^{11}B NMR: δ 76). The reagent was used as such for further reactions.

Reduction of Acetophenone. Acetophenone (0.59 mL, 5 mmol) was added at −25 °C, to a solution of **12** (5.5 mmol) prepared as above. The reaction was complete in 24 h. Workup using diethanolamine and distillation (98 °C/20 mmHg) provided (*R*)-1-phenethanol (0.41 g, 68% yield). GC analysis of its MTPA ester on Supelcowax glass capillary column (15 m) showed a composition of 98% *R* and 2% *S*, i.e., 96% ee in *R* isomer.

Reduction of 3-Methyl-2-butanone. The ketone (0.54 mL, 5 mmol) was added at −25 °C to a solution of **12** (5.5 mmol) prepared as above and the reaction was followed by ^{11}B NMR spectroscopy. On completion of the reaction (24 h), the usual workup and distillation gave 0.26 g (60%) of the alcohol, bp 112–114 °C. Analysis of the MCF derivative on methylsilicone capillary column (50 m) showed a composition of 72% *S* and 28% *R*, i.e., an ee of 44% in the *S* alcohol.

Reduction of 3-Acetylpyridine. 3-Acetylpyridine (0.6 g, 0.55 mL, 5 mmol) was added, at 0 °C, to a solution of **12** (11 mmol) prepared as above. The reaction was too slow to be followed. The reaction mixture was warmed to room temperature and the reaction was complete in 7 days. Water 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 and the solution became turbid. The organic phase was extracted with dichloromethane, washed with water, and dried ($MgSO_4$). Removal of solvent and distillation (80 °C/1.5 mmHg) provided 0.38 g (62%) of the alcohol. Analysis of the MTPA ester on a Supelcowax glass capillary column showed an ee of 96% in the *R* isomer.

Reduction of 4-Phenyl-3-butyn-2-one. The ketone (0.72 g, 0.73 mL, 5 mmol) was added at −25 °C to a solution of **12** (5.5 mmol) prepared as above. The reaction was complete in 5 h. The usual workup and distillation gave 0.51 g (70%) of the alcohol, bp 100 °C/0.8 mmHg. Analysis of the MTPA ester on a methylsilicone capillary column (50 m, 200 °C) revealed an ee of 21% in the *S* isomer.

Reduction of Methyl Benzoylformate. The α-keto ester (0.82 g, 0.71 mL, 5 mmol) was added at −25 °C to a solution of **12** (5.5 mmol) prepared as above. The reaction was complete in 1 h. Usual workup using diethanolamine and distillation provided 0.59 g (70%) of the alcohol. MTPA ester analysis on a Supelcowax glass capillary column (15 m, 200 °C) showed an ee of 91% in the *S* isomer.

Reduction of Ethyl Benzoylacetate. The β-keto ester (0.96 g, 0.87 mL, 5 mmol) was added to a solution of **12** (5.5 mmol) at −25 °C. The reaction was followed by ^{11}B NMR spectroscopy, which showed a complex mixture that remained the same with time. The usual workup did not yield any alcohol.

Reduction of 2,2-Dimethylcyclopentanone. 2,2-Dimethylcyclopentanone (0.56 g, 5 mmol) was added to a solution of **12** at −25 °C. The reaction was very slow at −25 °C and even at room temperature, but was found to be complete in 24 h under neat condition. The usual workup provided 0.37 g (65% yield) of the alcohol. MCF derivative of the alcohol showed an ee of 34% in the *R* isomer.

Reduction of *trans*-4-Phenyl-3-buten-2-one. The ketone (0.73 g, 5 mmol) was added to **12** at −25 °C and the reaction was complete in 24 h. Usual workup provided the crude alcohol, which was chromatographed over silica gel (60–200 mesh), and elution with hexane/ethyl acetate (90/10) gave 0.52 g (70%) of the product alcohol, $[\alpha]_D$ = +33.5° (c = 4.3, $CHCl_3$), which corresponds to an ee of 84.5% in the *R* isomer based on the maximum rotation reported in the literature.[29]

Reduction of 2-Chloroacetophenone. The chloro ketone (0.78 g, 5 mmol) was added to **12** at −25 °C, and the reaction that was complete in 24 h was worked up as usual to provide 0.57 g (72%) of the alcohol. Analysis of the MTPA ester on a Supelcowax glass capillary column showed an ee of 98% in the *S* isomer.

Reduction of 2-Cyclohexenone. 2-Cyclohexenone (0.49 mL, 5 mmol) was added to **12** at −25 °C, and the reaction that was complete in 24 h was worked up as usual to provide 0.34 g (70%) of the alcohol. Analysis of the MCF derivative on a methyl silicone capillary column showed an ee of 46% in the *R* isomer.

Preparation of Isopinocampheylthexylchloroborane (^{d}IpcBThxCl, 13). To an ice-cold solution of ThxBHCl·SMe$_2$ (Aldrich, 15 mmol) in CH_2Cl_2 (15 mL) was added neat (+)-α-pinene (15 mmol), and the reaction was left standing at 25 °C for 3.5 days after which ^{11}B NMR analysis indicated that the reaction had proceeded to >99% conversion. Pentane was added and the solution was filtered. Volatiles were removed under reduced pressure (first aspirator, then at 0.01 mmHg) to yield a very viscous oil, 4.0 g, 14.9 mmol, 99%. ^{11}B NMR δ 78.3. Anal. Calcd for $C_{16}H_{30}BCl$: B, 4.1; Cl, 13.2. Found: B, 4.02; Cl, 12.3.

In another experiment the above reagent (10 mmol) was oxidized in the presence of two internal standards, *n*-octane and *n*-undecane. GC analysis (SP-2100, 5%, 10 ft) indicated that 10.1 mmol of thexyl alcohol and <0.01 mmol of 2,3-dimethylbutanol had been formed, indicating that no significant redistribution had taken place.

Reduction of Acetophenone. The reaction was run in CH_2Cl_2 at 25 °C for 3.5 days on a 5-mmol scale. The usual workup procedure provided (*R*)-1-phenethanol, 0.46 g, 3.75 mmol (75%), enriched in the *R* isomer, 83% ee.

Reduction of 3-Methyl-2-butanone. The reaction was run in CH_2Cl_2 as described for acetophenone. Yield: 0.31 g, 3.5 mmol, 70%, enriched in the *S* isomer, 18% ee.

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Registry No. 8, 118476-75-8; 9, 118494-33-0; 10, 118494-34-1; 11, 118476-76-9; 12, 118476-77-0; 13, 118476-78-1; LiMeBH$_3$, 52950-75-1; ^{d}Ipc(Me)BCl·THF, 118494-35-2; Li·*i*-PrBH$_3$, 84280-38-6; ^{d}IpcBH$_2$, 64234-27-1; ^{d}IpcBH(c-C$_5$H$_9$), 118476-79-2; Li·*t*-BuBH$_3$, 76826-51-2; *t*-BuBHCl·OEt$_2$, 118494-36-3; ThxBHCl·SMe$_2$, 75067-06-0; (+)-α-pinene, 7785-70-8; acetophenone, 98-86-2; (*R*)-1-phenethanol, 1517-69-7; (*S*)-1-phenethanol, 1445-91-6; 3-methyl-2-butanone, 563-80-4; (*R*)-3-methyl-2-butanol, 1572-93-6; (*S*)-3-methyl-2-butanol, 1517-66-4; cyclopentene, 142-29-0; 3-acetylpyridine, 350-03-8; (*R*)-3-(1-hydroxyethyl)pyridine, 7606-26-0; 4-phenyl-3-butyn-2-one, 1817-57-8; (*R*)-4-phenyl-3-butyn-2-ol, 73922-81-3; (*S*)-4-phenyl-3-butyn-2-ol, 81555-86-4; methyl benzoylformate, 15206-55-0; methyl (*S*)-hydroxyphenylacetate, 21210-43-5; ethyl benzoylacetate, 94-02-0; 2,2-dimethylcyclopentanone, 4541-32-6; (*R*)-2,2-dimethylcyclopentanol, 109530-56-5; (*S*)-2,2-dimethylcyclopentanol, 103532-77-0; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; (*R*)-*trans*-4-phenyl-3-buten-2-ol, 62413-47-2; 2-chloroacetophenone, 532-27-4; (*S*)-2-chloro-1-phenylethanol, 70111-05-6; 2-cyclohexenone, 930-68-7; (*R*)-2-cyclohexenol, 3413-44-3; (*S*)-2-cyclohexenol, 6426-26-2.

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