Selective Reductions. 45. Asymmetric Reduction of Prochiral Ketones by Iso-2-methyl-, Iso-2-ethyl-, and [Iso-2-[2-(benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroboranes. Evidence for a Major Influence of the Steric Requirements of the 2-Substituent on the Efficiency of Asymmetric Reduction[1]

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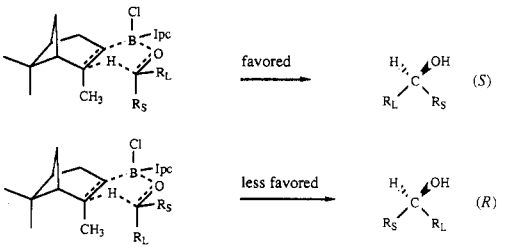
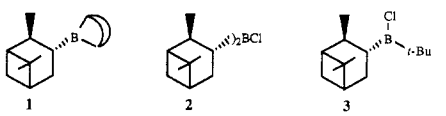
The asymmetric reduction of prochiral aliphatic ketones with chiral organylboranes has not yet given desirable results although considerable success has been achieved for the reduction of prochiral aralkyl and related ketones. We have now developed more efficient chiral reducing agents for aliphatic ketones following a strategy based on a tentative hypothesis that the steric requirements of the substituent at the 2-position of apopinene may be a major factor in achieving successful asymmetric reduction. The adduct of nopol benzyl ether and *tert*-butylchloroborane was prepared and characterized. This compound reduces prochiral ketones to the product alcohols in very high enantiomeric excess. For example, 3-methyl-2-butanone is reduced, in THF, 0.5 M, at room temperature, to the *R* alcohol in 89% ee. Cyclohexyl methyl ketone is reduced to the alcohol in 96% ee. Cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, and cyclopentyl methyl ketone are all reduced to the corresponding *R* alcohols in 85%, 83%, and 81% ee, respectively. 2-Cyclohexen-1-one is reduced to (*S*)-2-cyclohexen-1-ol in 88% ee. Finally, 2-octanone is converted to (*R*)-2-octanol in 40% ee. Unfortunately, these reductions are very slow, requiring 2 to 14 days, or more. The slowness of the reaction is attributed to the coordination of the ether oxygen to the boron atom. The higher optical yields achieved over those realized previously with the related isopinocampheyl-*tert*-butylchloroborane are attributed to the greater steric requirement of the (benzyloxy)ethyl group as compared to the methyl group of the α-pinene unit. On this basis, the corresponding derivative, (iso-2-ethylapopinocampheyl)-*tert*-butylchloroborane was synthesized in the hope that the rates would be higher, because of the absence of a coordinating ether linkage, while the optical yields would be comparable, because of the larger steric requirements of the 2-ethyl substituent. Indeed, the rates are considerably faster and the enantiomeric excesses achieved are almost comparable. 3-Methyl-2-butanone is reduced, in THF, 0.5 M, at room temperature, in 16 h to an alcohol of 84% ee. Cyclohexyl methyl ketone, cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, and cyclopentyl methyl ketone are all reduced to the corresponding *R* alcohols in 90%, 73%, 73%, and 72% ee, respectively. 2-Octanone is reduced to (*R*)-2-octanol in 33% ee. For comparison, the reductions of the same ketones with Ipc-*t*-BuBCl at room temperature and Ipc_2BCl at −25 °C were carried out. ^{d}Ipc-*t*-BuBCl reduces (25 °C) 3-methyl-2-butanone, cyclohexyl methyl ketone, cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, and cyclopentyl methyl ketone to the corresponding *S* alcohols in 37%, 48%, 53%, 50%, and 26% ee, respectively, whereas $^d Ipc_2BCl$ reduces (−25 °C) the same ketones to the corresponding *S* alcohols in 32%, 26%, 23%, 38%, and 45% ee, respectively. This study supports the conclusion that the chiral outcome in reduction with reagents derived from pinanyl derivatives is influenced by the steric requirements of the group at position 2 of apopinene. The X-ray crystal structure of [iso-2-[2-(benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroborane is also presented.

The most convenient method for the preparation of optically pure secondary alcohols is the asymmetric reduction of ketones.[3] Although many reagents are available in the literature[4] that reduce prochiral aromatic ketones to the corresponding alcohols in optical purities approaching 100% ee, chiral reduction of prochiral aliphatic ketones has remained a challenge for the organic chemist. A significant development in chiral reductions was made by M. M. Midland and co-workers who introduced[5] *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane, 1). This is an efficient reducing agent for deuterio aldehydes and α,β-acetylenic ketones, converting them to the corresponding alcohols with very high chirality transfer. However, the reagent is inefficient for the reduction of prochiral aralkyl and aliphatic ketones. Under Midland conditions (0.5 M THF, room temperature), the reductions of these types of ketones are very slow and considerable dehydroboration occurs during this period. This problem was overcome by conducting the reaction under increased concentrations[6] or elevated pressures.[7]

Scheme I



We manipulated the steric and electronic environment of the boron in the pinanylborane derivative and recently reported a highly effective, mild procedure for obtaining *secondary* alcohols in high enantiomeric excess by using (−)-diisopinocampheylchloroborane, $^d Ipc_2BCl$ (**2**).[8] This



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(1) Part of this work was presented at the National Meeting of the American Chemical Society in Denver, CO, ORGN 109, April 7, 1987.
(2) Postdoctoral Research Associate on a grant from the United States Army Research Office (DAAL 03-88-K-0107).
(3) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, Chapters 2, 3, and 4.
(4) For a comparative study of various chiral reducing agents, see: Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(5) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(6) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.
(7) Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.

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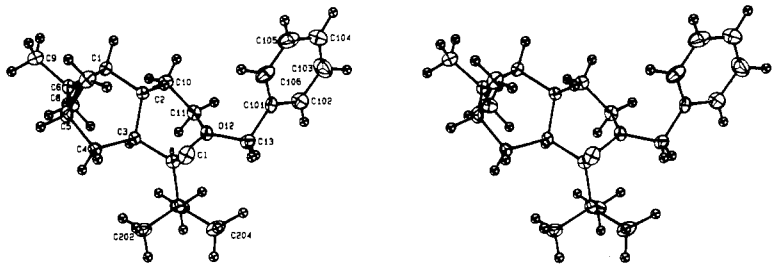
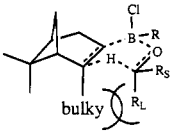


Figure 1. ORTEP stereoview through the B–Cl bond of [iso-2-[2-(benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroborane (**4**) and the numbering scheme.

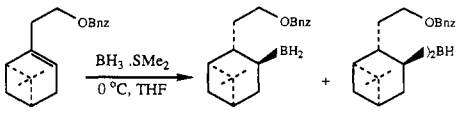
Scheme II



reagent is excellent for the chiral reduction of aralkyl and *α-tertiary* alkyl ketones but is inefficient for achieving high chirality in the reduction of simple dialkyl ketones, viz. 2-butanone, 3-methyl-2-butanone, etc. Consideration of the proposed mechanism for the reduction (Scheme I) indicated that a single pinanyl moiety is probably sufficient to induce asymmetry with the enantiomeric excess of the product alcohols controlled by the methyl group at position 2 in the pinanyl moiety.[8] We then undertook a systematic study of the effect of substituting the second isopinocampheyl moiety in **2** with alkyl groups of different steric requirements. We studied the efficiency of chiral reduction with reagents of the type IpcRBCl when the steric size of R was varied from Me → Et → *i*-Pr → *t*-Bu. This study showed that the enantiomeric excess is controlled by the pinanyl moiety, provided a blocking group of adequate steric requirement is attached to boron.[9] The study also revealed a very fascinating shift in the configuration of the product alcohols achieved by the replacement of other alkyl groups on boron by *tert*-butyl, as in isopinocampheyl-*tert*-butylchloroborane, Ipc-*t*-BuBCl (**3**).

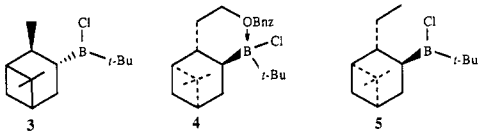
Although the mechanism of the reduction is not yet fully understood, we thought that the current proposed mechanism might provide a basis for a working hypothesis to facilitate the development of superior reagents for chiral reduction. If the mechanism shown in Scheme I were correct, substitution of a bulkier group for the methyl group at the 2-position of the apopinanyl moiety should provide improved optical induction in the product alcohols (Scheme II).

One possible choice for a modified chiral auxiliary would be a derivative of nopol. Accordingly we examined the preparation of the corresponding dialkylchloroborane from commercially available nopol benzyl ether. In this derivative the methyl group of the α-pinene unit would be replaced by $CH_2CH_2OCH_2C_6H_5$, a much larger group. However, our attempts to hydroborate nopol benzyl ether using either the borane–methyl sulfide or the borane–tetrahydrofuran complex yielded only a mixture of mono- and dihydroborated species (eq 1). Fortunately, we have



(1)

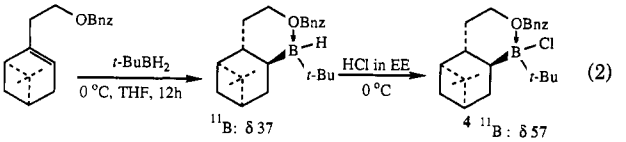
standardized methods for the preparation of monoalkyl boranes and have studied their hydroboration characteristics.[10] Using this methodology, we had prepared various isopinocampheylalkylchloroboranes and had studied their capabilities for chiral reductions.[9] Isopinocampheyl-*tert*-butylchloroborane (**3**) had proven to be especially effective. Consequently, we decided to prepare the cor-



responding *tert*-butylchloroborane **4** from nopol benzyl ether and study its effectiveness for chiral reductions. We succeeded in the preparation of the reagent in very pure form. However, the rate of reaction of the reagent with ketones is extraordinarily slow, much slower than the parent compound, isopinocampheyl-*tert*-butylchloroborane. It appeared probable that this very slow rate is due to internal coordination of the benzylic ether oxygen with the boron atom. An X-ray examination of the crystalline reagent confirmed the presence of a boron–oxygen coordination bond. We then sought to overcome this problem by preparing the reagent using 2-ethylapopinene as the chiral auxiliary. This led us to the preparation of (iso-2-ethylapopinocampheyl)-*tert*-butylchloroborane (**5**). The results of such a strategic development of a chiral reducing agent and its efficiency in chiral reduction as compared to the known corresponding isopinocampheyl-*tert*-butylchloroborane and diisopinocampheylchloroborane are examined in this paper.

Results and Discussion

Addition of 1 equiv of *tert*-butylborane in THF to nopol benzyl ether provided the dialkylborane very cleanly (eq 2). The ^{11}B NMR spectrum of the species (δ 37) shows



(2)

that there must be a strong coordination of the benzyl ether oxygen to the boron atom. Normally a dimeric dialkylborane exhibits a doublet at δ ~28 ppm in the ^{11}B NMR spectrum whereas monomeric dialkylborane shows a doublet at δ ~55–80, depending on the alkyl group (vide infra). The fact that we obtain a doublet at δ 37 shows that the species is monomeric and is internally coordinated, causing the observed upfield shift. Subsequent addition of 1 equiv of HCl in ether liberates 1 equiv of H_2 to provide the reagent **4**. An ^{11}B NMR spectrum of the reagent

(8) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. The superscript *d* indicates that the reagent is derived from (+)-α-pinene.

(9) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.

(10) Cole, T. E.; Bakshi, R. K.; Srebnik, M.; Singaram, B.; Brown, H. C. *Organometallics* **1986**, *5*, 2303.

Table I. Effect of *tert*-Butyl Group on the Boron Atom of the Reagent RR'R''B on the Absolute Configuration of the Product from the Chiral Reduction of Acetophenone

reagent	R	R'	R''	source of chiral auxiliary[a]	confgn of α-phenethanol predctd	confgn of α-phenethanol obsd
1	Ipc	9-BBN		(+)-α-pinene	S	S
2	Ipc	Ipc	Cl	(+)-α-pinene	S	S
3	Ipc	t-Bu	Cl	(+)-α-pinene	S	R
4	(2-BnzO)-Eap	t-Bu	Cl	(−)-β-pinene	R	S
5	Eap	t-Bu	Cl	(−)-β-pinene	R	S

[a] (+)-α-Pinene and (−)-β-pinene and their derived chiral auxiliaries contain apopinene moieties of the opposite absolute configuration.

(broad singlet: δ 57) showed it to be very pure and internally coordinated. This reagent was used as such for reductions. However, on removal of the solvent, the reagent was obtained as a solid that could be crystallized from pentane, mp ~30 °C. X-ray crystal structure analysis of reagent **4** (Figure 1) corroborates the fact that the reagent is internally coordinated.[11,12]

The chiral reduction of a ketone presumably involves coordination of the carbonyl oxygen to boron as the initial step.[13] With the boron being internally coordinated with the ether oxygen in the reagent, we expected the reaction of ketones to be relatively slow. The ketone was added to the reagent in THF at −25 °C and the reaction was followed by ^{11}B NMR examination of a methanolyzed aliquot at periodic intervals. Indeed, the reaction was much too slow to be monitored. The reaction mixture was brought to room temperature. The reaction now proceeded, but it required 2 days for a reaction of 3-methyl-2-butanone to be complete. Bulkier ketones needed even longer times. The reaction was worked up by using diethanolamine as reported earlier to remove the boron component[8] and the alcohols obtained were analyzed for their enantiomeric excess by capillary gas chromatography as their (+)-α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA)[14] or (−)-menthyl chloroformate (MCF)[15] derivatives, using a Supelcowax glass capillary column (15 m), a methylsilicone capillary column (50 m), or a SPB-5 capillary column (30 m). In those cases where the reaction was too slow to be followed to completion, acetaldehyde was added after a period of time to quench the reaction (acetaldehyde reacts instantaneously with the reagent at room temperature) and it was then worked up as usual. The distilled mixture of ketone and alcohol was derivatized without further purification and the % ee of the alcohol determined.

The reaction of acetophenone in THF, 0.5 M, with 1.1 equiv of the reagent **4** at room temperature, is 50% complete in 7 days. On working up with diethanolamine after quenching the excess reagent with acetaldehyde, the product α-phenethanol exhibits 71.5% ee (*S*) (eq 3). After correction for the optical purity (89.7% ee) of the nopol benzyl ether[16] used in the reaction, a corrected value of 80% ee for α-phenethanol is obtained. Here also, the presence of the *t*-Bu substituent on the boron atom results in an inversion of configuration of the product phenethanol[9] (Table I). However, the decrease in the % ee for the alcohol as compared to the product from the reduction of acetophenone with **2** (98% ee at −25 °C and 96% ee at 0 °C) or with isopinocampheyl-*tert*-butylchloroborane (**3**) (96% ee at −25 °C and 91% ee at 25 °C) is considerably greater than the effect of increased reaction temperature, 25 °C vs −25 °C. This is noteworthy from the mechanistic point of view, but cannot now be accounted for.

A reaction of 3-methyl-2-butanone under identical conditions is complete in 48 h. The usual workup provides the alcohol in 60% yield and 80% ee in the expected *R* isomer. Correcting for the optical purity of the nopol benzyl ether (89.7% ee), we obtain 89.2% ee for the 3-methyl-2-butanol! (Scheme III.) This is one of the highest values yet realized for the reduction of 3-methyl-2-butanone by a nonenzymatic reagent.[17,18]

Scheme III

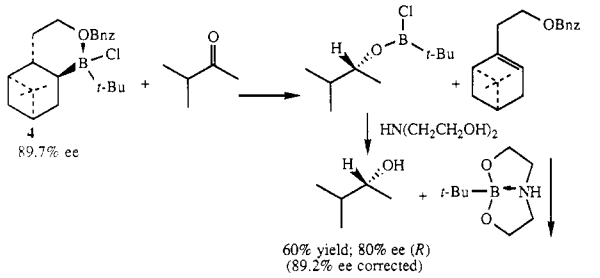
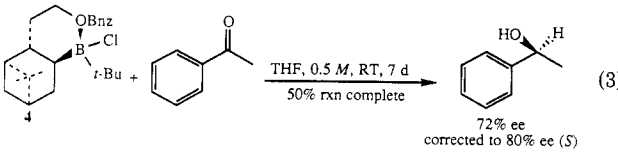


Table II. Reduction of Prochiral Ketones Using 4 in THF, 0.5 M, at Room Temperature

ketone	reactn time	% compltn[a]	% ee[b] obsd	% ee[b] corr	isomer
acetophenone	7 days	50	72	80	S
3-methyl-2-butanone	2 days	100	80	89	R
3-methyl-2-butanone	12 h[c]	100	88		R
cyclohexyl methyl ketone	4 days	60	86	96	R
cyclohexyl ethyl ketone	14 days	30	76	85	R[d]
cyclohexyl *n*-propyl ketone	14 days	25	74	83	R[d]
cyclopentyl methyl ketone	4 days	40	72	81	R[d]
2-cyclohexen-1-one	4 days	50	79	88	S
2-octanone	7 days	30	36	40	R

[a] Determined approximately from ^{11}B NMR peak heights. [b] Determined via MTPA or MCF derivative using a capillary GC. [c] Reaction using crystals under neat condition at room temperature. [d] Based on analogy of cyclohexyl methyl ketone.



(3)

(11) When we prepared the dialkylborane from a reaction of nopol methyl ether and *tert*-butylborane, we obtained the compound that showed a doublet at δ 29 ppm in the ^{11}B NMR, showing a stronger complex. Addition of HCl in EE provided the dialkylchloroborane, which showed a singlet at δ 36 ppm in the ^{11}B NMR spectrum, again suggesting a stronger complex than **4**. This stronger complex was substantiated by a reaction of this dialkylchloroborane with 3-methyl-2-butanone at room temperature, which was only <50% complete even after 2 weeks.

(12) X-ray crystal structure of a related compound, [iso-2-(2-methoxyethyl)apopinocampheyl]chloroborane (**6**), prepared from nopol methyl ether and chloroborane–methyl sulfide was reported by Prof. Shiner and co-workers. Shiner, C. S.; Garner, G. M.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 7167.

(13) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

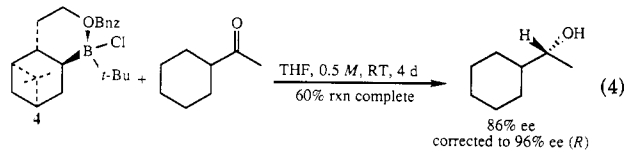
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 1316.

(15) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.

(16) The optical purity of commercialy available nopol benzyl ether, $[\alpha]_D$ = −26.7°, was calculated to be of 89.7% ee based on the maximum rotation of nopol and nopol benzyl ether reported in literature. Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495.

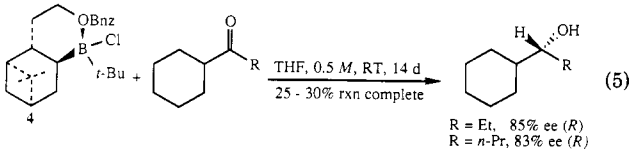
Encouraged by this result, we examined the reaction of a selected series of related ketones with **4**. However, bulkier ketones undergo reaction at a much slower rate. Consequently the reaction mixture was worked up after 4–14 days by adding acetaldehyde to destroy the residual reagent followed by the usual procedure. The extent of completion of the reaction was estimated from the ^{11}B NMR spectrum. The mixture of alcohol and ketone from distillation of the crude reaction product is derivatized as such for the determination of the % ee of the alcohol. The % conversion of the ketones and the % ee obtained for the alcohols produced are summarized in Table II.

Since the rates were too slow for any practical use of the reagent, the primary interest in these reaction sequences was to test our hypothesis that chiral reductions using reagents with more sterically bulky substituent at position 2 of the apopinene moiety should result in an increased enantiomeric excess for the product alcohols. Hence we did not attempt any more quantitative establishment of the yield of product alcohols in reductions by this reagent. As can be seen from Table II, the reagent is highly efficient for the reduction of *α-secondary* alkyl ketones. Cyclohexyl methyl ketone is reduced, slowly, 60% in 4 days to the alcohol enriched in the *R* isomer in 96% ee (eq 4). Only



(4)

30% of cyclohexyl ethyl ketone and 25% of cyclohexyl *n*-propyl ketone are reduced in 14 days. The usual workup provides the corresponding *R* alcohols in 85% and 83% ee, respectively (eq 5). The slower rates of reduction of these latter two ketones are not surprizing because even Ipc_2BCl (**2**), which normally reduces ketones within 7 h, requires 36 h for the reduction of cyclohexyl ethyl ketone and 144 h for the reduction of cyclohexyl *n*-propyl ketone (vide infra).

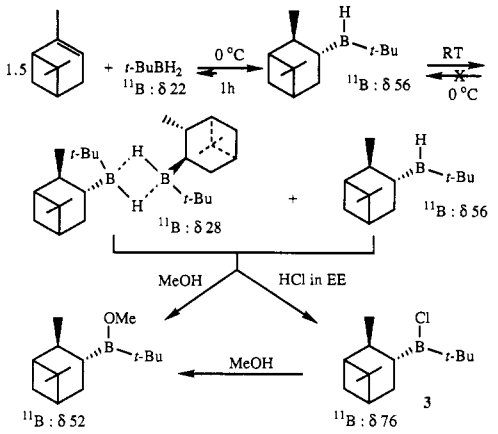


(5)

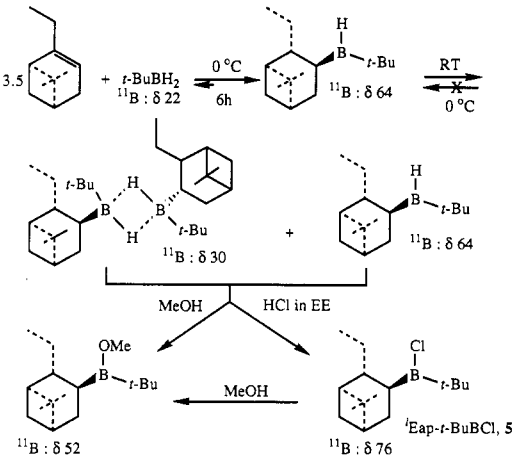
2-Cyclohexen-1-one is reduced to (*S*)-2-cyclohexen-1-ol in 88% ee. As anticipated, from our earlier experience,[9] the alcohol is enriched in the *S* isomer, opposite to that expected for reduction by $^{l}Ipc_2BCl$, the reversal being attributable to the *t*-Bu group on the boron atom. 2-Octanone is reduced, 30%, within 7 days to (*R*)-2-octanol, 40% ee.

We felt that crystallization of the reagent should improve the optical purity of the reagent. Accordingly, a recrystallized sample of the reagent was used for chiral reduction under neat conditions. Reaction of 3-methyl-2-butanone with **4** without solvent at room temperature is complete in 12 h and provides the alcohol in 88.2% ee (eq 6), thus showing that the reagent, on crystallization,

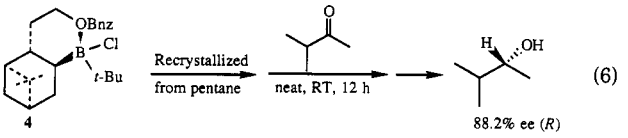
Scheme IV



Scheme V



has been upgraded to 98.9% optical purity, assuming linearity in the relationship between the optical purity of the chiral auxiliary and the product alcohol.[19]



(6)

Thus, although our strategy in developing an efficient chiral reducing agent for aliphatic ketones has been successful, there is a major drawback in the slowness of the reductions. Presumably the coordination of the boron atom to the ether oxygen interferes with the coordination of the carbonyl oxygen to the boron atom of the reagent that is a key step in the reduction mechanism.[13] The reaction rate could be enhanced by carrying out the reactions under neat condition. However, even then the rates are still too slow for practical application of the reagent.

It appeared that an alternate method to improve the rate of the reduction without affecting the high % ee for the alcohols obtained could be effected by preparing a reagent containing a bulky substituent at the 2-position of the apopinanyl moiety, but without an ether oxygen that could coordinate with boron. We selected (−)-2-ethylapopinene,

(17) Enzymatic reductions provide aliphatic alcohols with very high chiral induction. For example, see: Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162.

(18) An example of a nonenzymatic reagent providing high ee for most classes of aliphatic ketones is the dimethylborolane developed by Professor Masamune and co-workers at M.I.T. However, the reagent is prepared with great difficulty and is not readily available. Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, M. *J. Am. Chem. Soc.* **1986**, *108*, 7402.

(19) This reaction provides a method for the upgradation of optical purity of nopol benzyl ether. Addition of 1 equiv of acetaldehyde to **4**, at room temperature, liberated the nopol benzyl ether instantaneously. Unfortunately, we did not check the optical purity of the liberated nopol benzyl ether liberated from a reaction of acetaldehyde with recrystallized **4**.

readily prepared[20] from nopol or α-pinene, as the chiral auxiliary. Hydroboration of (−)-2-ethylapopinene with *tert*-butylborane resulted in an incomplete equilibrium, similar to that for the hydroboration of α-pinene with *tert*-butylborane[9] (Schemes IV and V). In the case of hydroboration of α-pinene using *tert*-butylborane, the equilibrium could be shifted to the product side with a small excess of olefin (1.5 equiv of α-pinene to 1 equiv of *t*-BuBH$_2$). However, hydroboration of 2-ethylapopinene with *tert*-butylborane requires a larger excess of olefin to drive the hydroboration to completion. This is characteristic of the hydroboration of hindered olefins. For example, complete hydroboration of thexylene with thexylborane requires 16 equiv of the olefin to achieve essentially complete formation of dithexylborane.[21]

The ^{11}B NMR spectrum of the dialkylborane also exhibited the characteristics previously shown by isopinocampheyl-*tert*-butylborane. At the hydroboration temperature, i.e., at 0 °C, the dialkylborane exists predominantly as the monomeric species. Like Ipc-*t*-BuBH, which exhibits a doulbet at δ 56, Eap-*t*-BuBH provides a doublet at δ 64 ppm. On warming to room temperature, Ipc-*t*-BuBH shows a doublet at δ 56 as well as at δ 28 ppm. The δ 28 peak corresponds to the dimeric dialkylborane. Eap-*t*-BuBH shows corresponding peaks at δ 64 and δ 30 ppm on warming to room temperature. On methanolyis of the above species, a singlet at δ 52 ppm corresponding to the dialkylborinate is obtained. Apparently, both the dissociation of the dimer and the association of the monomer are not instantaneous, probably involving a significant energy of activation. For example, once the species is partially transformed to the dimeric species at room temperature, it does not revert back to the monomeric species on being cooled back to 0 °C.

A similar equilibrium is not observed in the hydroboration of nopol benzyl ether because the oxygen of the ether linkage is coordinated to the boron atom in the product and this probably serves as a stabilizing step that drives the reaction to completion.

Addition of 1 equiv of ethereal hydrogen chloride to the dialkylborane liberates 1 equiv of hydrogen and provides the reagent ^{t}Eap-*t*-BuBCl (**5**) quite cleanly. The ^{11}B NMR spectrum of **5** shows the expected singlet at δ 76 ppm, unlike the shifted δ 57 ppm exhibited by **4** attributed to internal coordination. ^{11}B NMR examination of a methanolyzed sample of **5** shows a singlet at δ 52 ppm. The reagent is used as such for reductions. In an earlier case, we had shown that excess olefin (α-pinene) did not affect the chiral outcome.[9] Here also the excess olefin present does not affect the yields of the product alcohols obtained. The reaction of acetophenone with **5** is much faster than that of **4**, being complete in 16 h. Workup using diethanolamine provides the alcohol along with the 2-ethylapopinene liberated during the reaction and the excess 2-ethylapopinene used to shift the equilibrium during hydroboration. Chromatography of the crude mixture provides the chiral auxiliary and the product alcohol, α-phenethyl alcohol, in 70% yield, 74.5% ee, corrected to 81% ee. The decreased % ee for this alcohol as compared to that obtained for reductions using Ipc$_2$BCl (**2**) (98% at −25 °C and 96% at 0 °C) and Ipc-*t*-BuBCl (**3**) (96% at −25 °C and 91% at room temperature) corresponds to the 80% ee realized for the reduction of acetophenone with **4** at room temperature.

(20) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Weissman, S. A.; Jadhav, P. K.; Perumal, P. T. *J. Org. Chem.* **1988**, *53*, 5513.
(21) Negishi, E.; Katz, J. J.; Brown, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 4025.

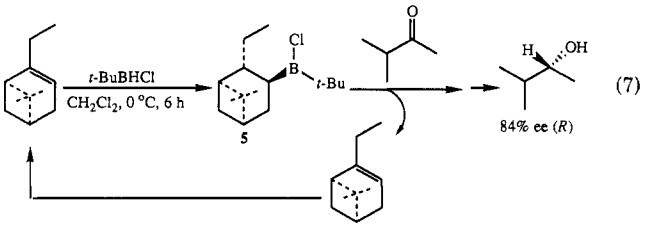
Table III. Reduction of Prochiral Ketones Using ^{t}Eap-*t*-BuBCl (5) in THF, 0.5 M, at Room Temperature

ketone	reactn time	% yield, isolated	% ee[a] obsd	% ee[a] corr	isomer
acetophenone	24 h	70	75	81	*S*
3-methyl-2-butanone	16 h	65	77	84	*R*
cyclohexyl methyl ketone	2 days	65	83	90	*R*
cyclohexyl ethyl ketone	6 days	62	67	73	*R*
cyclohexyl *n*-propyl ketone	10 days	60	67	73	*R*
cyclopentyl methyl ketone	2 days	65	66	72	*R*
2-cyclohexen-1-one	3 days	55	46	50	*S*
2-octanone	24 h	70	30	33	*R*

[a] Determined via MTPA or MCF derivative using capillary GC.

It should be recalled that **2** and **3** are prepared from (+)-α-pinene, while **4** and **5** are prepared from nopol of opposite configuration (via (−)-β-pinene). It might have been anticipated that the phenethanol produced by the reduction of acetophenone by **2** and **3** would have the *S* configuration, whereas **4** and **5** would give an alcohol with the *R* configuration. But the effect of the *tert*-butyl group in reversing the expected configuration for reduction by **3** is also observed in reductions by the other *tert*-butyl derivatives **4** and **5** (Table I). (**2** → *S*; **3** → *R*; **4** → *S*; **5** → *S*).

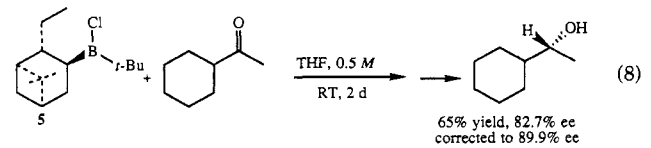
We then prepared **5** via a direct hydroboration using *tert*-butylchloroborane[9] (eq 7). The hydroboration was complete in 6 h and the reagent was obtained in ~95% chemical purity. This reagent was then utilized for further reductions.



(7)

Reaction of reagent **5** with 3-methyl-2-butanone under identical conditions, room temperature, THF, 0.5 M, is also complete within 16 h and the product alcohol, 65% yield, on analysis as its MCF derivative on capillary GC shows an ee of 77.4% corrected to 84.1% in the *R* isomer (eq 7). Again, the 84% ee obtained for the 3-methyl-2-butanol is considerably higher than that obtained for reduction by ^{d}Ipc$_2$BCl (**2**) or ^{d}Ipc-*t*-BuBCl (**3**), 32% and 37% ee, respectively.

Gratified by the improved rate of reduction and the relatively high % ee of the alcohols produced, we examined the reduction, with **5**, of the same series of *α-secondary* alkyl ketones previously reduced with **4**. The results are summarized in Table III. The reaction of cyclohexyl methyl ketone is complete in 2 days under identical reaction conditions and the usual workup provided (*R*)-1-cyclohexylethanol, 65% yield and 82.7% ee, corrected to 89.9% ee (eq 8). The reductions of cyclohexyl ethyl ketone and cyclohexyl *n*-propyl ketone are slower, but could be completed within 6 days and 10 days, respectively.



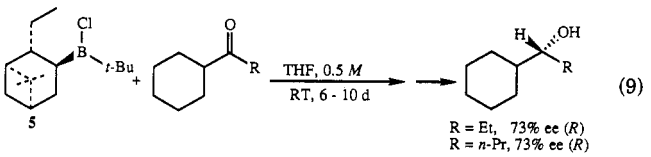
(8)

Table IV. Reduction of Prochiral Ketones Using ^{d}Ipc-*t*-BuBCl (3) in THF, 0.5 M, at Room Temperature

ketone	reactn time	% yield, isolated	% ee[a]	isomer obtained
acetophenone	12 h	68	91 (96)[b]	*R*
3-methyl-2-butanone	12 h	60	37 (48)[b]	*S*
cyclohexyl methyl ketone	12 h	65	48	*S*
cyclohexyl ethyl ketone	72 h	65	53	*S*
cyclohexyl *n*-propyl ketone	7 days	59	50	*S*
cyclopentyl methyl ketone	12 h	62	26	*S*
2-cyclohexen-1-one	24 h	60	46[b]	*R*
2-octanone	12 h	71	18	*S*

[a] Determined via MTPA or MCF derivative using capillary GC. [b] For a reaction at −25 °C from ref 9.

Workup provides both of the alcohols in 62% and 60% yields, respectively, in 73% ee (eq 9). Cyclopentyl methyl



(9)

ketone is reduced in 2 days to the corresponding alcohol in 65% yield and in 72% ee. 2-Cyclohexen-1-one is reduced to 2-cyclohexen-1-ol in 50% ee. 2-Octanone is converted to 2-octanol in 33% ee. Thus the % ee realized for the chiral reduction of these ketones with **5** are almost equal to the values with **4**, while the rates of reduction with **5** are considerably greater than those with **4**.

To further test our conclusion that the % ee realized in the chiral reduction of prochiral ketones with a reagent having a bulkier group at position 2 of apopinene is considerably higher than that obtained with the isopinocampheyl analogue, we carried out the reduction of the same series of ketones with isopinocampheyl-*tert*-butylchloroborane (**3**). The reductions are carried out according to our reported procedure,[9] but at room temperature instead of the reported −25 °C to permit direct comparison of the results. The data are summarized in Table IV. The results confirm that the % ee values realized for the product alcohols are consistently higher than those obtained for the reduction of the same ketones with ^{d}Ipc$_2$BCl (**2**) (vide infra). This is expected from our earlier results.[9] However, the values of % ee are considerably lower than those realized for the same alcohols from reductions with **4** or **5**, thus supporting our hypothesis that the steric bulk of substituents at position 2 of apopinene can influence the chiral outcome in such asymmetric reductions.

To complete the study, we examined the reduction of the same ketones with Ipc$_2$BCl (**2**) under our standard conditions of our original study,[8] −25 °C. The results are summarized in Table V. We had observed that **2** reduces most prochiral ketones in ≤7 h. However, the reduction of cyclohexyl ethyl ketone is complete only in 36 h and the reduction of cyclohexyl *n*-propyl ketone takes even longer (144 h) for completion. Yet the % ee realized were in the same ranges as attained for the other dialkyl ketones with **2**. This shows that the rate of the reductions does not control the chiral outcome of the reductions.

The % ee obtained for the reduction of the above series of ketones with the reagents **2**, **3**, **4**, and **5** are summarized and compared in Table VI.

X-ray Crystal Structure of 4

Single-crystal X-ray diffraction analysis of **4** was performed by using standard procedures. An ORTEP stereoview of the structure and numbering scheme are shown in

Table V. Reduction of Prochiral Ketones Using ^{d}Ipc$_2$BCl (2) in THF, 1 M, at −25 °C

ketone	reactn time, h	% yield, isolated	% ee[a]	isomer obtained
acetophenone	5	72	98[b]	*S*
3-methyl-2-butanone	5	72	32[b]	*S*
cyclohexyl methyl ketone	5	68	26[b]	*S*
cyclohexyl ethyl ketone	36	66	23	*S*[c]
cyclohexyl *n*-propyl ketone	144	65	38	*S*[c]
cyclopentyl methyl ketone	5	70	45	*S*[c]
2-cyclohexen-1-one	7	65	36[b]	*S*
2-octanone	5	62	6	*R*

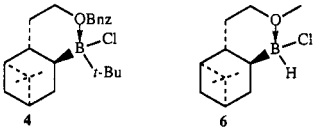
[a] Determined via MTPA or MCF derivative using capillary GC. [b] From ref 8. [c] Based on analogy of cyclohexyl methyl ketone.

Table VI. Comparison of % ee of Alcohols Obtained from Chiral Reduction of Prochiral Ketones Using Reagents 2, 3, 4, and 5

ketone	% ee with 2, −25 °C	with 4, rt[b]	with 3, rt[b]	with 5, rt[b]
acetophenone	98	80	91	81
3-methyl-2-butanone	32	89	37	84
cyclohexyl methyl ketone	26	96	48	90
cyclohexyl ethyl ketone	23	85	53	73
cyclohexyl *n*-propyl ketone	38	83	53	73
cyclopentyl methyl ketone	45	81	26	72
2-cyclohexen-1-one	36	88	46[a]	50
2-octanone	6	40	18	33

[a] For a reaction at −25 °C from ref 9. [b] rt = room temperature.

Figure 1. The crystal structure provides clear evidence for the internal coordination between the boron and the oxygen (B–O bond length 1.67 Å) as supported by the ^{11}B NMR chemical shift. The crystal structure of **4** stands in



sharp contrast to the X-ray structure of iso-2-(2-methoxyethyl)apopinocampheyl]chloroborane (**6**) reported by Shiner and co-workers.[12] Whereas in Shiner's compound the six-membered heterocyclic ring exists in a chair conformation, the heterocyclic ring in **4** exists in a twist-boat form with the C(10) and B atoms near the least-square plane, the oxygen and C(2) atoms above the plane, and the C(3) and C(11) atoms below the plane. We believe that the change in the conformation of the heterocyclic ring is caused by the bulky *tert*-butyl group on the boron atom of **4**. Details of the X-ray crystal structure will be discussed elsewhere.[22]

Conclusion

The present investigation was undertaken to test our hypothesis that the steric requirements of the substituent at the 2-position of apopinene may be a major factor in achieving successful asymmetric induction in reagents containing that structural feature. Our results clearly support our hypothesis. We synthesized two new reagents, [iso-2-[(2-benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroborane (**4**) and (iso-2-ethylapopinocampheyl)-*tert*-butylchloroborane, (**5**), and compared them with diisopinocampheylchloroborane (**2**) and isopinocampheyl-*tert*-butylchloroborane (**3**) for the chiral reduction of aliphatic ketones. **4** and **5** were very effective in transferring chirality into the reduction products, although the rates

(22) Ramachandran, P. V.; Fanwick, P. E. Manuscript in preparation.

of reductions were slow. Much of the very slow rate of reduction using **4** was overcome by removing the ether linkage, which coordinates with the boron atom of the reagent. The optical induction achieved was, however, comparable. Although the proposed mechanism for chiral reductions using Ipc_2BCl (Scheme I) has not answered many questions posed during a systematic study,[9] it has served in the present study as a good working model to direct further improvements in the reagent. As a result we have been led to considerably improved reagents, both of the diisopinocampheylchloroborane type[8] and the Alpine-Hydride type.[23] These new reagents are currently being subjected to detailed study to be described at their completion. To our knowledge, this is the first time that it has been possible to proceed to the development of improved enantioselective reducing agents on the basis of a theoretical, rather than an empirical, approach.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[24] Spectroscopic (^1H and ^{11}B NMR and IR) and polarimetric measurements were made with standard instruments. GC analyses were 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). Analyses of the MTPA esters or MCF derivatives were performed on a Hewlett-Packard 5890 A gas chromatograph using a Supelcowax glass capillary column (15 m), methylsilicone capillary column (50 m), or a SPB-5 capillary column (30 m) at appropriate temperatures and integrated on a Hewlett-Packard 3390 A integrator.

Materials. THF was distilled from benzophenone ketyl and stored under nitrogen in an ampule. Borane–methyl sulfide (BMS), nopol, nopol benzyl ether, *tert*-butylmagnesium chloride, trimethylborate, and *B*-chlorodiisopinocampheylborane were all obtained from Aldrich Chemical Co. 2-Ethylapopinene,[20] Li-*t*-$BuBH_3$,[9] and Ipc-*t*-BuBCl[9] were prepared according to the literature procedure. The ketones were obtained from Aldrich Chemical Co. or Wiley Organics and were used as received. MTPA was obtained from Aldrich Chemical Co. and converted to the acid chloride by using the literature procedure.[14] MCF was obtained from Aldrich Chemical Co. Anhydrous ethereal hydrogen chloride (~3 M) was prepared by using a Brown automatic gasimeter from hydrochloric acid and sulfuric acid.[25]

Preparation of [Iso-2-[2-(benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroborane (4). An oven-dried, 50-mL round-bottom flask equipped with a septum-capped side arm, magnetic stirring bar, and connecting tube was cooled to room temperature in a stream of nitrogen. Li-*t*-$BuBH_3$ (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 *t*-$BuBH_2$. Nopol benzyl ether, $[\alpha]_D = -26.7°$ (neat) (89.7% ee) (5.5 mmol), was added and the solution was stirred until the hydroboration was complete (^{11}B NMR: δ 37 ppm, doublet). 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 **4**. An ^{11}B NMR spectrum of the reagent showed a singlet at δ 57 ppm, which was shifted to δ 52 ppm on methanolysis. The reagent was used as such for further reactions. Removal of solvents provided **4** as a low melting solid. Recrystallization of the solid from pentane provided needle-shaped crystals, mp ~30 °C.

Reduction of Carbonyl Compounds. A Representative Procedure. Under nitrogen and with stirring, to 5.5 mmol of the reagent prepared as above was added, at room temperature, 3-methyl-2-butanone (0.54 mL, 0.43 g, 5 mmol). The reaction was followed by ^{11}B NMR of a methanolyzed aliquot and was found to be complete in 48 h. The solvents were removed under aspirator vacuum. The residue was dissolved in ether (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 3-methyl-2-butanol, bp 112 °C, in 65% yield (0.3 g, 3.25 mmol). The higher boiling nopol benzyl ether was left as pot residue. The MCF derivative of the alcohol was prepared and analyzed on a methylsilicone (50 m) capillary column by using HP-5890 A gas chromatograph. Analysis showed a composition of 90% *R* isomer and 10% *S* isomer, i.e., 80% ee in the *R* isomer. Correcting for the optical purity (89.7%) of the nopol benzyl ether used to prepare the reagent, we obtain an ee of 89.2% in the *R* isomer for 3-methyl-2-butanol.

A similar reaction using the crystals of the reagent under neat condition at room temperature was complete in 12 h and the usual workup provided 3-methyl-2-butanol in 88.2% ee.

Reduction of other ketones such as acetophenone, cyclohexyl methyl ketone, cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, cyclopentyl methyl ketone, 2-cyclohexen-1-one, and 2-octanone was very slow and excess acetaldehyde was added to the reaction mixture after 4–14 days and worked up as usual. The mixture of ketone and alcohol obtained on distillation was derivatized as such and analyzed for the % ee. The % conversion and the % ee are presented in Table II.

Preparation of (Iso-2-ethylapopinocampheyl)-*tert*-butylchlorobrane (^{i}Eap-*t*-BuBCl, 5). Method A. An oven-dried, 50-mL round-bottom flask equipped with a septum-capped side arm, magnetic stirring bar, and connecting tube was cooled to room temperature in a stream of nitrogen. Li-*t*-$BuBH_3$ (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 *t*-$BuBH_2$. (–)-2-Ethylapopinene, $[\alpha]_D = -42.78°$ (neat) (92.2% ee) (2.6 g, 17.5 mmol), was added and the solution was stirred for 6 h when the hydroboration was complete. An ^{11}B NMR spectrum of the species showed a doublet at δ 30 immediately after syringing out the aliquot for ^{11}B NMR analysis. On warming up to room temperature, it showed a doublet at δ 64 ppm (major) and δ 30 ppm (minor). This is due to the mixture of monomeric and dimeric Eap-*t*-BuBH. Methanolysis of this species provided Eap-*t*-BuBOMe with its characteristic ^{11}B NMR peak at δ 52 ppm. Addition of a second equivalent of HCl in EE (1.5 mL, 3.3 M, 5 mmol) caused a liberation of a second equivalent of hydrogen with a simultaneous formation of the reagent **5** as characterized by the ^{11}B NMR (δ 76 ppm). This reagent with the excess olefin 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 equipped with a septum-capped side arm, magnetic stirring bar, and connecting tube. THF was substituted with CH_2Cl_2. 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. (–)-2-Ethylapopinene, $[\alpha]_D = -42.78°$ (92.2% ee) (0.83 g, 5.5 mmol), was added to the flask and the solution was left stirring at 0 °C. The hydroboration was complete in 6 h as shown by ^{11}B NMR spectroscopy (δ 76 ppm). There was a little (~5%) impurity, a peak at δ 42 ppm corresponding to ether cleaved product, probably caused by cleavage of EE by *t*-BuBHCl. However, this reagent **5** was used as such for further reductions.

Reduction of Carbonyl Compounds. A Representative Procedure. Under nitrogen and with stirring, to 5.5 mmol of the reagent prepared as above was added, at room temperature, THF (5 mL), followed by 3-methyl-2-butanone (0.43 g, 0.54 mL, 5 mmol). The reaction was followed by ^{11}B NMR of a methanolyzed aliquot. The reaction was found to be complete within 16 h. The solvents were removed under aspirator vacuum. The residue was dissolved in ether (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 filterates were concentrated and the residue was chromatographed over silica gel. The chiral auxiliary ethylapopinene was eluted with pentane, followed by the alcohol, which was eluted with ether. Removal of ether and distillation provided 0.28 g (62%) of 3-methyl-2-butanol. Analysis of its MCF derivative on a methyl-

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

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

silicone (50 m) capillary column using HP-5890 A gas chromatograph showed a composition of 88.72% *R* and 11.28% *S* isomer, i.e., 77.44% ee in the *R* isomer. Correcting for the optical purity (92% ee) of the ethylapopinene used to prepare the reagent, we obtain an ee of 84.2% in the *R* isomer for the 3-methyl-2-butanol produced in the reaction.

Reduction of other ketones was done under identical conditions. Different ketones had different reaction times, which are summarized in Table III. Workups were as in the case of 3-methyl-2-butanol and analyses were done as MTPA or MCF derivatives on a methylsilicone (50 m), Supelcowax (15 m), or SPB-5 (30 m) capillary column. The % ee obtained for each alcohol is summarized in Table III.

Reduction of Carbonyl Compounds Using ^{d}Ipc-*t*-BuBCl (3). The reductions of cyclohexyl methyl ketone, cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, cyclopentyl methyl ketone, and 2-octanone were conducted at room temperature with ^{d}Ipc-*t*-BuBCl prepared from optically pure (+)-α-pinene by using the procedure reported earlier.[9] For an accurate comparison, the reactions of acetophenone and 3-methyl-2-butanone were repeated at room temperature. Analyses of the alcohols were done as their MTPA esters or MCF derivative on a capillary column. The results are summarized in Table IV.

Reduction of Carbonyl Compounds Using ^{d}Ipc$_2$BCl (2). For a comparative study, the reductions of cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, and cyclopentyl methyl ketone were carried out in THF at −25 °C by using commercially available ^{d}Ipc$_2$BCl. The reactions were carried out by using the procedure reported earlier.[8] The reaction of cyclopentyl methyl ketone took 5 h for completion, whereas, unexpectedly, the reaction of cyclohexyl ethyl ketone took 36 h and the reaction of cyclohexyl *n*-propyl ketone took 144 h for completion. There was no correlation between the rate of the reduction and the % ee realized. Analyses of the alcohols for the % ee were done as their MTPA esters on a methylsilicone (50 m), Supelcowax (15 m), or SPB-5 (30 m) capillary column. The values of % ee for the reduction of acetophenone, 3-methyl-2-butanone, cyclohexyl methyl ketone, 2-cyclohexenone, and 2-octanone were from what we have reported earlier.[8] The results are summarized in Table V.

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New and Effective Routes to Fluoro Analogues of Aliphatic and Aromatic Amino Acids

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New and efficient syntheses of 4,4,4-trifluorovaline (**1**), 5,5,5-trifluoronorvaline (**2**), 5,5,5-trifluoroleucine (**5**), 6,6,6-trifluoronorleucine (**6**), 4,5,6,7-tetrafluorotryptophan (**25**), and α-(trifluoromethyl)-β-alanine are studied. Trifluorovaline (**1**) and trifluoronorvaline (**2**) are synthesized through amidocarbonylation of 2-(trifluoromethyl)propanal (2-TFMPA) and 3-(trifluoromethyl)propanal (3-TFMPA), respectively, followed by hydrolysis. Trifluoroleucine (**5**) and trifluoronorleucine (**6**) are synthesized by using modified Erlenmeyer's azlactone method from 2-TFMPA and 3-TFMPA, respectively. (*S*)- and (*R*)-trifluoronorvalines ((*S*)-**2** and (*R*)-**2**) and trifluoronorleucines ((*S*)-**6** and (*R*)-**6**) with high enantiomeric purities (95–100% ee) are obtained through enzymatic optical resolution of *N*-acetyltrifluoronorvaline (**4**) and *N*-acetyltrifluoronorleucine (**17**) with the use of a porcine kidney acylase I. Optically active trifluoronorleucine ((*S*)-**6**, 87–89% ee) is also obtained via the asymmetric hydrogenation of (*Z*)-*N*-benzoyldehydrotrifluoroleucine ethyl ester (**10a-Z**) with a chiral rhodium catalyst, [Rh(diPAMP)(NBD)]ClO$_4$, followed by hydrolysis. Unexpectedly high diastereoselectivities (80–87% ee) are observed in the hydrogenation of (*Z*)-*N*-benzoyldehydrotrifluoroleucine ethyl ester (**11b**) and (*Z*)-*N*-benzoyl-4-(pentafluorophenyl)dehydronorvaline (**14-Z**) over palladium/carbon. 4,5,6,7-Tetrafluorotryptophan (**25**) and 4,5,6,7-tetrahydrotryptamine (**30**) are synthesized from 3-formyl-4,5,6,7-tetrafluoroindole (**22a**) in 51% (four steps) and 83% (two steps) overall yields, respectively. 4,5,6,7-Tetrafluoroindoleacetic acid (**28**) is obtained from 1-acetyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (**23a**) in four steps in 65% overall yield. The 3-formyl- and 1-acetyl-3-(acetoxymethyl)tetrafluoroindoles (**22a**, **23a**) are prepared through selenium dioxide oxidation of 1-acyl-3-methyl-4,5,6,7-tetrafluoroindole (**21**), which is obtained via the cyclization of a Schiff base of 2-(pentafluorophenyl)propanal (2-PFPPA), in good yields.

Introduction

It has been shown that fluorinated analogues of naturally occurring biologically active compounds often exhibit unique physiological activities.[3,4] Recently, there has been an increasing interest in the incorporation of fluoro amino acids into peptides.[5] Accordingly, it is important to de-

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