Hydroboration. 82. Asymmetric Hydroboration of Representative Cis Disubstituted and Heterocyclic Olefins with Dicaranylboranes of High Enantiomeric Purity

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Dicaranylboranes (2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH) are prepared by the reaction of borane–methyl sulfide with (+)-2- and (+)-3-carene, respectively. The reagents readily hydroborate prochiral cis disubstituted olefins to yield the corresponding trialkylboranes, which, upon oxidation, give chiral alcohols of 77–93% ee (2-^{d}Icr$_2$BH) and 36–75% ee (4-^{d}Icr$_2$BH). 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH convert *cis*-alkenes into alcohols of the opposite absolute configurations. The trialkylborane hydroboration products, upon treatment with benzaldehyde, eliminate (+)-2- or (+)-3-carene, providing the corresponding benzyl boronates. Thus, the chiral auxiliary is recovered, and the alcohols can be obtained by oxidation of the benzyl boronates or alternatively by their hydrolysis and oxidation of the boronic acids. Trans disubstituted and trisubstituted olefins are hydroborated by both reagents with partial elimination of (+)-2- or (+)-3-carene and low asymmetric induction. On the other hand, the hydroboration–oxidation of five-membered ring heterocyclic olefins proceeds rapidly to give the corresponding chiral alcohols of 11–85% ee. Convenient procedures for the preparation of high purity (+)-2- and (+)-3-carene are described.

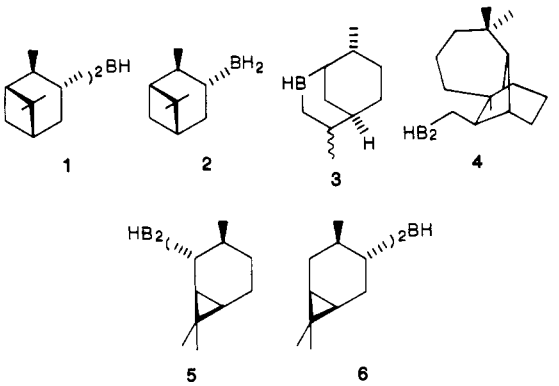
Introduction

Asymmetric hydroboration is one of the most efficient procedures for the synthesis of chiral products. To achieve asymmetric induction, various chiral hydroborating agents, **1–4**, readily prepared from abundantly available low-cost terpenes, e.g., α-pinene, limonene, and longifolene, were developed and used for the hydroboration of prochiral olefins.[3] However, the search for new chiral reagents continues with the growing importance of organoboranes for asymmetric synthesis.

Recently we found that allyldicaranylborane derived from (+)-3-carene is highly enantioselective in the allylboration reaction.[4] Although (+)-2- and (+)-3-carenes are readily available,[5-8] the properties of hydroborating agents derived from these terpenes were not known. Consequently, we decided to prepare and investigate them. This paper describes a systematic study of the hydroboration of cis disubstituted and heterocyclic olefins with [1*S*]-di-2-isocaranylborane (2-^{d}Icr$_2$BH) **5** and [1*S*]-di-4-isocaranylborane (4-^{d}Icr$_2$BH) **6**. (The symbol, ^{d}Icr, is used to indicate that the reagent comes from the (+)-isomer of 2- or 3-carene.)

Results and Discussion

Preparation of Reagents and Purification of Carenes. Both **5** and **6** are conveniently prepared by the hydroboration of (+)-2- and (+)-3-carene with borane–methyl sulfide in tetrahydrofuran, respectively. The reagents crystallize out of solution and are separated by decantation. They can be stored at 0 °C without any appreciable loss of hydride activity or isomerization. Crystallization of **5** from tetrahydrofuran, following a brief warming to dissolve the reagent, is possible. However, **6** is thermally labile and partial isomerization was observed in refluxing tetrahydrofuran with a boron atom moving to C_5. The enantiomeric purity of **5** (>99% ee) was determined by GC analysis of (−)-2-isocaranol derivatized with (−)-menthyl chloroformate and with (+)-MTPA chloride. The alcohol was obtained by methanolysis of **5**, followed by oxidation with hydrogen peroxide. An authentic sample of (+)-2-isocaranol was prepared following the literature procedure.[9] Menthyl formates and MTPA derivatives of (+)- and (−)-2-isocaranol separated well on a 50-m methyl silicon capillary column. The enantiomeric purity of **6** was determined earlier.[10]



(+)-2-Carene (93–95% GC pure), prepared by isomerization of (+)-3-carene and isolated by fractional distillation, was used for the preparation of **5**. Material of 99.5% GC purity can be conveniently prepared by the hydroboration of 1-alkene, e.g., 1-pentene or 1-hexene with **5**, followed by treatment of the trialkylborane formed with 2.5 molar equiv of benzaldehyde at 60 °C. The liberated hydrocarbon is isolated from the reaction mixture by simple vacuum distillation in 90–95% yield.

Although **6** can be prepared from (+)-3-carene ($[\alpha]^{23}_D$ +14.6°), a higher yield (80%) is obtained from material of higher purity ($[\alpha]^{23}_D$ >+17.0°). (+)-3-Carene can be purified by efficient fractional distillation or by the hydroboration–liberation procedure described earlier.[10] However, the latter method requires isolation by prepa-

(1) Postdoctoral research associate on Grant GM 10937-24 from the National Institutes of Health.
(2) Visiting professor on a grant from the Dow Chemical Company.
(3) Brown, H. C.; Jadhav, P. K. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 1.
(4) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1981**, *46*, 2988.
(5) Simonsen, J. L. *The Terpenes*, 2nd ed.; revised by Simonsen, J. L., and Owen, L. N.; Cambridge University Press: Cambridge, England, 1949–1957.
(6) Ohloff, G.; Schulte-Elte, K. H.; Giersch, W. *Helv. Chim. Acta* **1965**, *48*, 1665.
(7) Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc.* **1966**, 41.
(8) Acharya, S. P.; Brown, H. C. *J. Am. Chem. Soc.* **1967**, *89*, 1925.
(9) Brunetti, P.; Fringuelli, F.; Taticchi, A. *Gazz. Chim. Ital.* **1977**, *107*, 433.
(10) Jadhav, P. K.; Vara Prasad, J. V. N.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 3203.

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Table I. Physical Constants and GC Purity of (+)-2- and (+)-3-Carenes

olefin	bp, °C (12 Torr)	$[\alpha]^{23}_D$(neat), deg	GC purity, %	lit. $[\alpha]_D$, deg (temp, °C)
(+)-2-carene	58–60	+94.8[a]	99.5	+97.7 (20)
(+)-3-carene	59–60	+17.7	>99.5	+17.7 (23)

[a] Obtained from 2-^{d}Icr$_2$BH of >99% ee. [b] Ohloff, G.; Schulte-Elte, K. H.; Giersch, W. *Helv. Chim. Acta* **1965**, *48*, 179. [c] Jadhav, P. K.; Vara Prasad, J. V. N.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 3203.

rative GC since the liberated product contains a small amount (2–3%) of (−)-4-carene, lowering its rotation. To circumvent this difficulty, we now have developed two simple procedures. Thus, treatment of neat (+)-3-carene ($[\alpha]^{23}_D$ +14.6°) with 10 mol % of 9-BBN dimer at room temperature removes the more reactive impurities. Simple vacuum distillation of the reaction mixture provides material showing $[\alpha]^{23}_D$ +17.3°. Alternatively, (+)-3-carene, similarly to α-pinene,[11] can be crystallized from *n*-pentane at −100 °C to give pure material $[\alpha]^{23}_D$ +17.7°, ~100% ee.

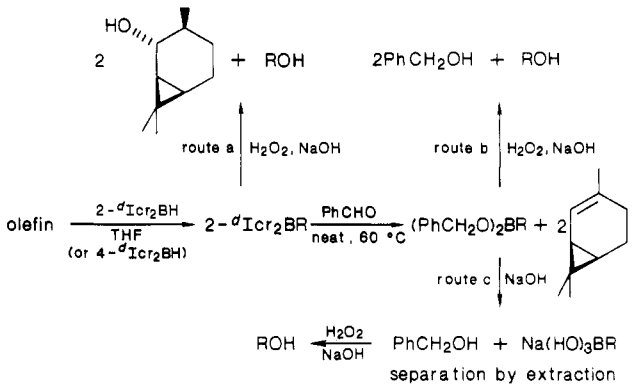
The physical properties of pure (+)-2- and (+)-3-carenes are summarized in Table I.

Hydroboration of Representative Olefins. For the initial exploration of the hydroboration characteristics of 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH, representative terminal, cis, and trans disubstituted and trisubstituted olefins were selected. Unlike Ipc$_2$BH, the dicaranylboranes are not as reactive at −25 °C; hence, the hydroborations were carried out at 0 °C. The reactions were followed by the disappearance of the solid dicaranylboranes and also by quenching aliquots of the reaction mixture in methanol, followed by ^{11}B NMR examination of the sample. The reactivity of the dicaranylboranes toward 1-pentene, 1-hexene, and the alkenes, shown in Table I, decreases with increasing substitution of the double-bond. Hydroboration of the more reactive terminal and cis disubstituted alkenes with 2-^{d}Icr$_2$BH is completed in 2–15 h and with 4-^{d}Icr$_2$BH in 2–120 h, whereas, *trans*-alkenes and trisubstituted olefins react sluggishly with both reagents (Table II).

Asymmetric induction in hydroboration of a terminal prochiral alkene, 2-methyl-1-butene, with the diisocaranylboranes is low, similar to that with diisopinocampheylborane. In contrast, high asymmetric induction is observed in the hydroboration of *cis*-2-butene with 2-^{d}Icr$_2$BH. [*S*]-(+)-2-butanol, obtained by oxidation of the trialkylborane intermediate, showed 93% ee. The hydroboration-oxidation of *cis*-2-butene with 4-^{d}Icr$_2$BH gave [*R*]-(−)-2-butanol of 50% ee. *trans*-2-Butene, 2-methyl-2-butene, and 1-methylcyclopentene react with dicaranylboranes, providing the corresponding alcohols in lower ee (Table II). However, these hydroborations proceed with partial displacement of carenes from the reagents. This is an indication that 2-^{d}Icr$_2$BH or 4-^{d}Icr$_2$BH are not the only hydroborating species involved in these reactions. Since the highest asymmetric induction was realized in the hydroboration of *cis*-2-butene, we applied 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH to other cis disubstituted and cis heterocyclic olefins.

Hydroboration of Representative *cis*-Olefins. The hydroboration–oxidation of *cis*-3-hexene with 2-^{d}Icr$_2$BH gives [*S*]-(+)-3-hexanol (90.5% ee), whereas, 4-^{d}Icr$_2$BH affords [*R*]-(−)-hexanol (36% ee). Similarly, *exo*-norborneols (77% and 75% ee) of opposite absolute configurations are obtained from norbornene with 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH, respectively. High asymmetric inductions are also achieved in the hydroboration of norbornadiene and benzonorbornadiene with 4-^{d}Icr$_2$BH (Table III).

Scheme I



In all of these hydroborations, the chiral auxiliary (2- or 3-carene) can be recovered by the reaction of trialkylborane intermediates with benzaldehyde. The benzyl boronates, which are formed, can be oxidized to the corresponding chiral alcohols. Alternatively, alkaline hydrolysis provides boronic acids which can be separated from benzyl alcohol and then oxidized (Scheme I). The latter procedure (route c) simplifies the isolation of higher boiling alcohols, avoiding their separation from isocaranol (route a) or benzyl alcohol (route b). It should be noted that alkyldicaranylboranes are considerably less reactive toward aldehydes than alkyldiisopinocampheylboranes, e.g., no reaction of *sec*-butyldicaranylboranes with acetaldehyde in THF at room temperature in 12 h is observed. The reaction with benzaldehyde can be accelerated by the addition of boron trifluoride etherate.

Hydroboration of Representative Heterocyclic Olefins. The hydroboration of a simple five-membered ring heterocyclic olefin, 2,3-dihydrofuran, with dicaranylboranes proceeds readily at 0 °C to yield the corresponding trialkylborane intermediate, which, upon further oxidation, affords 3-hydroxytetrahydrofuran. Surprisingly, the trisubstituted double bond of 2-methyl-4,5-dihydrofuran reacts cleanly with both reagents. Oxidation of the trialkylborane intermediate produces *trans*-2-methyl-3-hydroxytetrahydrofuran. The facile hydroboration of this olefin is probably due to the mesomeric effect of the oxygen atom increasing the electron density at the 3-carbon atom. The asymmetric inductions realized in these reactions are in the range of 27–70% ee (Table IV). The hydroboration of a strained rigid system, 7-oxa-1,4-epoxy-1,4-dihydronaphthalene, with 4-^{d}Icr$_2$BH gave 7-oxa-*exo*-2-benzonorborneol of 85% ee.

In contrast to the reactive five-membered ring heterocyclic olefins, the six-membered 3,4-dihydro-2*H*-pyran reacts sluggishly with both reagents. 2-^{d}Icr$_2$BH affords 3-hydroxytetrahydropyran of 60% ee, whereas, 4-^{d}Icr$_2$BH gives product of 11% ee, the reaction proceeding with partial displacement of (+)-3-carene.

General Considerations. The dicaranylboranes are less reactive hydroborating agents as compared to Ipc$_2$BH, the reactivity order being ^{d}Ipc$_2$BH > 2-^{d}Icr$_2$BH ≫ 4-^{d}Icr$_2$BH. At present, Ipc$_2$BH is the best chiral dialkylborane hydroborating agent in terms of reactivity, enantioselectivity and ease of recovery of the chiral auxiliary (α-pinene) from the trialkylborane hydroboration products. 2-^{d}Icr$_2$BH is only slightly poorer, exhibiting comparable enantioselectivity in the hydroboration of *cis*-alkenes, but leading to alcohols of opposite configuration. For more hindered or rigid systems, the dicaranylborane enantio-

(11) Bir, G.; Kaufman, D. *Tetrahedron Lett.* **1987**, *28*, 777.

Table II. Asymmetric Hydroboration of Representative Olefins with 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH of High Enantiomeric Purity (~100%) at 0 °C

olefin	reagent	time, h	product alcohol: alcohol	isolated yield, %	$[\alpha]^{23}_D$(neat), deg	% ee	absolute config
cis-2-butene	2-^{d}Icr$_2$BH	12	2-butanol	63	+12.9	93[h]	*S*
cis-2-butene	4-^{d}Icr$_2$BH	72	2-butanol	58	−6.71	50[i]	*R*
trans-2-butene	2-^{d}Icr$_2$BH	150[a]	2-butanol	69	−4.19	30[i]	*R*
trans-2-butene	4-^{d}Icr$_2$BH	72[b]	2-butanol	62	+5.37	40[i]	*S*
2-methyl-1-butene	2-^{d}Icr$_2$BH	3	2-methyl-1-butanol	61	−0.9	15[j]	*S*
2-methyl-1-butene	4-^{d}Icr$_2$BH	4	2-methyl-1-butanol	72	+0.33	5[j]	*R*
2-methyl-2-butene	2-^{d}Icr$_2$BH	240[c]	3-methyl-2-butanol	61[g]	+1.49	37[k]	*S*
2-methyl-2-butene	4-^{d}Icr$_2$BH	120[d]	3-methyl-2-butanol	75	0	0	
trans-3-hexene	4-^{d}Icr$_2$BH	72[e]	3-hexanol	65	+2.48	32[l]	*S*
1-methylcyclopentene	2-^{d}Icr$_2$BH	240[f]	*trans*-2-methylcyclopentanol	65[g]	−1.4	3[m]	1*R*,2*R*
1-methylcyclopentene	4-^{d}Icr$_2$BH	26[d]	*trans*-2-methylcyclopentanol	72	−1.4	3[m]	1*R*,2*R*

[a] Two molar equivalents of the olefin was used. [b] Reaction not completed. [c] 70% of the reagent reacted. [d] And 4 h at 25 °C. [e] And 16 h at 25 °C. [f] 67% of the reagent reacted. [g] Calculated on the reacted reagent. [h] Derivatized with *N*-TFA-L-prolyl chloride and analyzed by GC on column e. [i] Derivatized with (+)-MTPA chloride and analyzed by GC on column e. [j] Timmermans, J. *Physico-Chemical Constants of Pure Organic Compounds*; Elsevier: New York, 1950; Vol. 1, p 326. $[\alpha]^{23}_D$ −5.9°. [k] Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 4185. α^{27}_D +8.12° (*l* 2, neat). [l] $[\alpha]^{23}_D$ +7.02°, 90.5% ee, Table III. [m] Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797. $[\alpha]^{23}_D$ +46.8° (neat).

Table III. Asymmetric Hydroboration of Representative Cis Disubstituted Olefins with 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH of High Enantiomeric Purity (~100%) at 0 °C

olefin	reagent	time, h	product alcohol: alcohol	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee	absolute config
cis-2-butene	2-^{d}Icr$_2$BH	12	2-butanol	63	+12.9 (neat)	93[a]	*S*
cis-2-butene	4-^{d}Icr$_2$BH	72	2-butanol	58	−6.71 (neat)	50[b]	*R*
cis-3-hexene	2-^{d}Icr$_2$BH	15	3-hexanol	62	+7.02 (neat)	90.5[a]	*S*
cis-3-hexene	4-^{d}Icr$_2$BH	120	3-hexanol	77	−2.79 (neat)	36	*R*
norbornene	2-^{d}Icr$_2$BH	30	*exo*-norborneol	68	+3.90 (*c* 7.5, EtOH)	77[c,d]	1*R*,2*R*
norbornene	4-^{d}Icr$_2$BH	22	*exo*-norborneol	72	−3.8 (*c* 7.5, EtOH)	75	1*S*,2*S*
norbornadiene	4-^{d}Icr$_2$BH	15	*exo*-norborn-5-en-2-ol	62	+7.75 (*c* 8.7, $CHCl_3$)	80[e]	1*R*,2*S*
benzonorbornadiene	4-^{d}Icr$_2$BH	40	*exo*-2-benzonorborneol	71	+20.97 (*c* 4.2, $CHCl_3$)		1*R*,2*S*

[a] Derivatized with (−)-*N*-TFA-L-prolyl chloride and analyzed by GC on column e. [b] Derivatized with (+)-MTPA chloride and analyzed by GC on column e. [c] Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065. [d] $[\alpha]^{23}_D$ −4.2° (*c* 7.5, EtOH), 83% ee. [e] Brown, H. C.; Singaram, B.; Bakshi, R. K.; Pyun, C., unpublished results: $[\alpha]^{23}_D$ +9.75° (*c* 8.7, $CHCl_3$), 100% ee.

Table IV. Asymmetric Hydroboration of Representative Heterocyclic Olefins with 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH of High Enantiomeric Purity (~100%) at 0 °C

olefin	reagent	time, h	product alcohol: alcohol	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee	absolute config
2,3-dihydrofuran	2-^{d}Icr$_2$BH	3	3-hydroxytetrahydrofuran	53	+8.92 (*c* 2.4, MeOH)	51[a,b]	*S*
2,3-dihydrofuran	4-^{d}Icr$_2$BH	2.5	3-hydroxytetrahydrofuran	78	−6.61 (*c* 2.4, MeOH)	39	*R*
1,4-epoxy-1,4-dihydronaphthalene	4-^{d}Icr$_2$BH	5	7-oxa-*exo*-2-benzonorborneol	72	+25.2 (*c* 2, MeOH)	85[a,c]	1*R*,2*S*,4*R*
3,4-2*H*-dihydropyran	2-^{d}Icr$_2$BH	84[f]	3-hydroxytetrahydropyran	73	−7.66 (neat)	60[a,d]	*S*
3,4-2*H*-dihydropyran	4-^{d}Icr$_2$BH	240[g]	3-hydroxytetrahydropyran	72[h]	+1.35 (neat)	11	*R*
2-methyl-4,5-dihydrofuran	2-^{d}Icr$_2$BH	8	*trans*-2-methyl-3-hydroxytetrahydrofuran	60	+11.7 (*c* 2.5, MeOH)	27	2*R*,3*S*
2-methyl-4,5-dihydrofuran	4-^{d}Icr$_2$BH	8	*trans*-2-methyl-3-hydroxytetrahydrofuran	74	−29.9 (*c* 2.5, MeOH)	70[e]	2*S*,3*R*

[a] Brown, H. C.; Vara Prasad, J. V. N. *J. Am. Chem. Soc.* **1986**, *108*, 2046. [b] $[\alpha]^{23}_D$ −17.3° (*c* 2.4, MeOH), 100% ee. [c] $[\alpha]^{23}_D$ +29.8° (*c* 2, MeOH), 100% ee. [d] $[\alpha]^{23}_D$ +9.8° (neat), 83% ee. [e] Determined by ^{19}F NMR examination of the corresponding Mosher ester on 200-MHz NMR instrument. [f] 50% excess of olefin. [g] 50% excess of olefin, 80% of the reagent reacted. [h] Calculation based on reagent consumed.

selectivities are comparable to that for Ipc$_2$BH, being more selective in specific cases, e.g., 2-methyl-2-butene (2-^{d}Icr$_2$BH 37% ee, ^{d}Ipc$_2$BH 14% ee) or norbornadiene (4-^{d}Icr$_2$BH 80%, ^{d}Ipc$_2$BH 74% ee). The carenes can be recovered from dicaranylalkylboranes by treatment with benzaldehyde at 60 °C but not with acetaldehyde at room temperature, as in the case of trialkylboranes derived from Ipc$_2$BH. This lower tendency to elimination may be useful in potential synthetic applications of dicaranylalkylboranes.

Model Considerations. Long ago we described a model for the asymmetric hydroboration of alkenes with diisopinocampheylborane (^{d}Ipc$_2$BH).[12] The model can also be adapted to the present systems. To account for the change in the absolute configuration of the products from 2-^{d}Icr$_2$BH and 4-^{d}Icr$_2$BH and *cis*-alkenes, we must conclude that the 3-methyl group in these reagents, corresponding to the 2-methyl in ^{d}Ipc$_2$BH, is the large (L) unit.

In both ^{d}Ipc$_2$BH and 4-^{d}Icr$_2$BH, the medium (methylene group) and L units occupy identical positions in the model. However, in 2-^{d}Icr$_2$BH, positions of the medium group (C_1 group) and L are reversed. Hence, in this case, the alkene approaches from the opposite direction as compared to

(12) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.

$^{d}Ipc_2BH$ and 4-$^{d}Icr_2BH$. Consequently, the products obtained are of opposite configuration.

Since the development of models for these reactions has now become so sophisticated in the hands of Houk and his co-workers,[13] we decided there would be no point in providing a more detailed analysis.

Conclusions

The hydroboration–oxidation of prochiral *cis*-olefins with 2-$^{d}Icr_2BH$ and 4-$^{d}Icr_2BH$ affords alcohols of opposite configuration. Enantioselectivity in the hydroboration of these alkenes with 2-$^{d}Icr_2BH$ is comparable to that achieved with Ipc_2BH[3] and considerably higher than with 4-$^{d}Icr_2BH$. Both reagents hydroborate more rigid *cis*-olefins, e.g., norbornene, with good asymmetric induction. The hydroboration of norbornadiene with 4-$^{d}Icr_2BH$ provides *exo*-5-norbornen-2-ol of 80% ee—higher than that achieved with Ipc_2BH. The hydroboration of simple heterocyclic five-membered ring olefins with 2-$^{d}Icr_2BH$ and 4-$^{d}Icr_2BH$ is facile and leads to the corresponding chiral alcohols of 27–85% ee. Liberation of (+)-2-carene from the hydroboration product, 2-$^{d}Icr_2BR$, by reaction with benzaldehyde provides a convenient method for its purification. Two simple procedures for the purification of (+)-3-carene have also been developed.

Experimental Section

The reaction flasks and other glass equipment were stored in an oven at 150 °C overnight and assembled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled in a stream of dry nitrogen gas. Special techniques used in handling air-sensitive materials are described in detail elsewhere.[14]

Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3{\cdot}OEt_2$. ^{1}H NMR (90 MHz) and ^{19}F NMR (200 MHz) were recorded on a Perkin-Elmer R-32 and Varian FT-200 instruments, respectively. Optical rotations were measured on a Rudolph polarimeter Autopol III.

GC Analyses. All GC analyses were carried out with a Hewlett-Packard 5750 or a Varian 1200 chromatograph using (a) 12 ft × 0.125 in. column packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh) or (b) 12 ft × 0.125 in. column packed with 10% SE-30 on Chromosorb W (100–200 mesh) were used. For preparative GC, either (c) a 6 ft × 0.5 in. column packed with 20% Carbowax 20M on Chromosorb W (60–80 mesh) or (d) a 6 ft × 0.5 in. column packed with 20% SP-2100 on Chromosorb W (60–80 mesh) was used. For analysis of derivatized alcohols, a 50-m methyl silicon capillary column (e) was used.

Materials. Borane–methyl sulfide (BMS), purchased from the Aldrich Chemical Company, was estimated according to the standard procedure.[14] (+)-2-Carene, $[\alpha]^{23}_D$ +92°, and (+)-3-carene, $[\alpha]^{23}_D$ +14.6° (neat), were distilled from a small excess of LAH. Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. The liquid alkenes were commercial products and were distilled over LAH. 2-Benzonorbornadiene was prepared according to the literature procedure.[15] 4-$^{d}Icr_2BH$ of 100% ee was prepared from BMS and (+)-3-carene according to our previous literature procedure.[10]

Purification of (+)-3-Carene. (a) By Crystallization. (+)-3-Carene, 100 mL, $[\alpha]^{23}_D$ +14.6°, 88% GC pure, was added to 150 mL of *n*-pentane, and the mixture was cooled to −100 °C and kept at this temperature for 4 h. Crystals separated out. The supernatant liquid was decanted, and the crystals were allowed to melt. An equal volume of *n*-pentane was added to the melted material, and the crystallization process was repeated. After two additional crystallizations were carried out in the same way, (+)-3-carene was isolated by distillation: bp 59–60 °C (12 mm), 42 mL, 42%, $[\alpha]^{23}_D$ +17.7°, >99.5% GC pure, [lit.[10] $[\alpha]^{23}_D$ +17.7°, 100% ee].

(b) By Treatment with 9-BBN. (+)-3-Carene, 13.6 g (100 mmol), $[\alpha]^{23}_D$ +14.6°, was added to 1.2 g (10 mmol) of solid 9-BBN dimer, and the mixture was stirred at room temperature for 12 h. The hydrocarbon was recovered from the mixture by distillation (0.5 mm) and collected in a cold trap: 11.6 g, 85%, $[\alpha]^{23}_D$ +17.3°, 97.3% GC pure.

Preparation of [1*S*]-Di-2-isocaranylborane (2-$^{d}Icr_2BH$) of High Optical Purity. A 500-mL flask equipped with a side arm, magnetic stirring bar and gas lead was charged with 250 mL of THF and 12.5 mL (10 M, 125 mmol) of $BH_3{\cdot}SMe_2$ under nitrogen. It was cooled to −10 °C in an ice–salt bath and 37.5 g (275 mmol) of (+)-2-carene, $[\alpha]^{23}_D$ +92° (neat), was added with magnetic stirring over 5 min. The flask was immediately transferred to an ice–water bath and maintained at 0 °C for 24 h without stirring. White needles separated out. The supernatant liquid was decanted by double-ended needle, and the crystals were washed with ice-cold ethyl ether (3 × 30 mL). The solid 2-$^{d}Icr_2BH$ was kept under vacuum (12 mmHg) at room temperature for 1 h to obtain 30.5 g (84%). The solid thus obtained, 14.3 g (50 mmol), was suspended in 30 mL of THF and 2.4 mL (60 mmol) of methanol was added at 0 °C. After evolution of the hydrogen had ceased a clear solution had formed, the reaction mixture was oxidized under nitrogen by using 20 mL of 3 N sodium hydroxide and 12 mL of 30% hydrogen peroxide at 20–30 °C, stirred for 3 h at 30 °C and 1 h at 50 °C, cooled to room temperature, and opened to the atmosphere. It was saturated with anhydrous potassium carbonate and extracted with diethyl ether (3 × 50 mL). The ether extract was washed with water (20 mL) and brine (20 mL) and dried over anhydrous magnesium sulfate. (−)-2-Isocaranol was isolated by distillation: bp 50–52 °C (0.05 mm), 13.1 g (85%), α^{23}_D −31.5° (neat, *l* 1) [lit.[8] bp 85–86 °C (5 mm), α^{26}_D −30.23° (neat, *l* 1)]. GC analysis of its Mosher ester and menthyl formate (prepared by standard procedure)[16,17] using a 50-m methyl silicon capillary column indicated the compound to be >99% ee. A comparison sample of (+)-2-isocaranol for this analysis was prepared by the hydroboration–oxidation of (−)-2-carene, synthesized according to the literature procedure.[9]

Liberation of (+)-2-Carene. The solid 2-$^{d}Icr_2BH$, 14.3 g (50 mmol), was suspended in 25 mL of THF, and 3.6 g (52 mmol) of 1-pentene was added at 0 °C with stirring. After 2 h, a clear solution formed and ^{11}B NMR indicated trialkylborane, δ 82. The solvent was removed under vacuum at room temperature, and 15.9 g (125 mmol) of benzaldehyde was added. The mixture was kept at 60 °C for 10 h. The liberated (+)-2-carene and excess benzaldehyde were removed by vacuum distillation (0.5 mm, bath temperature, 60–70 °C) and collected in a cold trap. The distillate was washed with 3 × 50 mL of 10% sodium bisulfite solution, dried over $MgSO_4$ and distilled from lithium aluminum hydride: bp 58–60 °C (12 mm), 12.4 g, 91%, GC purity 99.5% (50-m methyl silicon capillary column), $[\alpha]^{23}_D$ +94.8° [lit.[6] $[\alpha]^{20}_D$ +97.7°].

Hydroboration–Oxidation of Olefins with 2-$^{d}Icr_2BH$. General Procedure. Olefin (55 mmol) was added to a stirred suspension of 2-$^{d}Icr_2BH$ (50 mmol) in 30 mL of THF at 0 °C. The mixture was kept at this temperature with stirring until a clear solution was obtained. ^{11}B NMR analysis indicated a trialkylborane. The mixture was oxidized by using 20 mL of 3 N sodium hydroxide and 20 mL of 30% hydrogen peroxide at 20–30 °C. It was further stirred for 3 h at this temperature and for 1 h at 50 °C. After cooling to room temperature, it was saturated with potassium carbonate. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic solutions were washed with brine (2 × 10 mL) and dried over $MgSO_4$. The product was isolated by fractional distillation using a short Widmer column. The final GC purification from small amounts of THF, 2-carene, and (−)-2-isocaranol was carried out on columns c and d. In cases when the hydro-

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boration was not 100% complete (indicated in the tables), the unreacted 2-^{d}Icr$_2$BH was methanolyzed before oxidation.

Hydroboration of Olefins with 2-^{d}Icr$_2$BH. The Synthesis of Chiral Alcohols via Oxidation of Boronic Acids. A Typical Procedure. Norbornene, 2.6 g (27.5 mmol), was added to a suspension of 7.2 g (25 mmol) of 2-^{d}Icr$_2$BH in 15 mL of THF at 0 °C under nitrogen. The mixture was stirred at this temperature for 30 h. A clear solution formed, and ^{11}B NMR analysis indicated the complete formation of trialkylborane (δ 84.2). The solvent was removed under vacuum, 6.6 g (62.5 mmol) of benzaldehyde was added, and the mixture was kept at 60 °C for 10 h. The liberated (+)-2-carene and excess benzaldehyde were removed by distillation. The distillation flask containing benzyl boronate (^{11}B NMR, δ 31.2) was cooled, and 25 mL of *n*-pentane was added, followed by 15 mL of 3 M sodium hydroxide. The mixture was vigorously stirred for 0.5 h. The aqueous layer was separated and the pentane layer was extracted with 2 × 15 mL of 3 M sodium hydroxide. The alkaline solutions were combined, 20 mL of THF was added, and the mixture was oxidized with 5 mL of 30% hydrogen peroxide at 20–30 °C. It was further stirred for 3 h at this temperature and for 1 h at 50 °C, cooled, opened to the atmosphere, and saturated with anhydrous potassium carbonate. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic solutions were combined, washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated to give [1*R*,2*R*]-(+)-*exo*-norborneol, mp 115–120 °C, 1.9 g, 68%. After GC purification (column d), mp 125–126 °C [lit.[14] mp 126–127], $[\alpha]^{23}_D$ +3.90° (*c* 7.5, EtOH), 78% ee.

Hydroboration of *cis*-2-Butene with 4-^{d}Icr$_2$BH. *cis*-2-Butene (50 mmol, 4.6 mL) was added to 4-^{d}Icr$_2$BH (50 mmol, 14.3 g) in 31.1 mL of THF at 0 °C with stirring. The trialkylborane (^{11}B NMR δ 85.5) was formed within 72 h. The reaction mixture was oxidized with 18.4 mL of 3 N NaOH and careful addition of 20 mL of 30% H_2O_2, maintaining the reaction temperature below 40 °C. The reaction mixture was further stirred at 55 °C for 1 h, cooled, and extracted with 3 × 25 mL of ether and dried over anhydrous $MgSO_4$. The organic layer was fractionated to obtain 2.07 g of [*R*]-(−)-2-butanol (58% yield), bp 96–98 °C (740 mm). The sample was further purified by preparative GC using columns c and d to furnish GC-pure material: α^{23}_D −2.713° (neat, *l* 0.5), 50% ee.

Hydroboration of *trans*-2-Butene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (50 mmol, 14.3 g) in 31.1 mL of THF was added 4.6 mL (50 mmol) of *trans*-2-butene at 0 °C. The reaction mixture was stirred at 0 °C for 72 h and methanolyzed and oxidized as described for *cis*-2-butene. The organic layer was carefully fractionated to afford 2.2 g (62% yield) of [*S*]-(+)-2-butanol, which was further purified by preparative GC: α^{23}_D +2.17° (neat, *l* 0.5), 40% ee.

Hydroboration of 2-Methyl-2-butene with 4-^{d}Icr$_2$BH. 2-Methyl-2-butene (2.65 mL, 25 mmol) was addd to 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 14.7 mL of THF at 0 °C with stirring. It was stirred at 0 °C for 120 h, followed by 25 °C for 4 h. The reaction mixture was oxidized and worked up as described in the *cis*-2-butene experiment to furnish 1.65 g of 3-methyl-2-butanol (75% yield). It was purified by using column d to provide a GC-pure sample: $[\alpha]^{23}_D$ 0°.

Hydroboration of 2-Methyl-1-butene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (7.2 g, 25 mmol) was added 2.7 mL (25 mmol) of 2-methyl-1-butene at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was oxidized as described in the *cis*-2-butene experiment to obtain 1.6 g of (+)-2-methyl-1-butanol, further purified by column d to obtain GC-pure material: $[\alpha]^{23}_D$ +0.33°; 5% ee.

Hydroboration of *cis*-3-Hexene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in THF (14.7 mL) was added 3.1 mL (25 mmol) of *cis*-3-hexene at 0 °C. The reaction mixture was stirred at 0 °C for 120 h. The solid disappeared and the formation of trialkylborane (^{11}B NMR δ 86.4) was complete. The reaction mixture was oxidized with 9.2 mL of 3 N NaOH and 10 mL of 30% H_2O_2, maintaining the reaction temperature below 40 °C during the addition and then stirred at 55 °C for 1 h. It was cooled, extracted with 3 × 25 mL of ether, and dried over $MgSO_4$. The organic layer was fractionated, providing 2.02 g of 3-hexanol, bp 135–136 °C (745 mm); 77% isolated yield. The sample was further purified by preparative GC using column c to furnish GC-pure material: $[\alpha]^{23}_D$ −2.79° (neat), 36% ee.

Hydroboration of *trans*-3-Hexene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in THF (14.7 mL) was added 3.1 mL (25 mmol) of *trans*-3-hexene at 0 °C. The reaction mixture was stirred at 0 °C for 72 h and then at 25 °C for 16 h, whereby, a clear solution was obtained. The reaction was methanolyzed, oxidized, and worked up as above to afford crude 3-hexanol. It was filtered through silica gel. The pentane eluents removed (+)-3-carene, whereas, ether eluents afforded alcohols. It was distilled to afford 1.7 g of 3-hexanol. The GC-pure material, obtained after preparative GC, showed $[\alpha]^{23}_D$ +2.48° (neat), 32% ee.

Hydroboration of 1-Methylcyclopentene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 15.1 mL of THF was added 2.7 mL (25 mmol) of 1-methylcyclopentene at 0 °C. The reaction mixture was stirred at 0 °C for 26 h and then at 25 °C for 4 h. The reaction mixture was worked up as described under the procedure for *trans*-3-hexene to afford 1.8 g of *trans*-2-methylcyclopentanol, bp 72 °C (15 mm); 72% isolated yield. It was purified by using column d to furnish GC-pure material: $[\alpha]^{23}_D$ −1.4° (neat), 3% ee.

Hydroboration of Norbornene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 10.4 mL of THF was added 2.4 g (25 mmol) of norbornene in 5 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 22 h to afford the trialkylborane (^{11}B NMR δ 86). The solvent was pumped off at 25 °C. The neat trialkylborane was treated with 5.1 mL (50 mmol) of benzaldehyde. The reaction mixture was kept at 100 °C for 2 h. To the boronate (^{11}B NMR δ 31.4) was added 25 mL of pentane and extracted with 3 × 15 mL of 3 M sodium hydroxide. To the alkali extracts 20 mL of THF was added and oxidized with 5 mL of 30% hydrogen peroxide. The reaction mixture was further stirred at 55 °C for 1 h and worked up as described for *cis*-3-hexene. *exo*-Norborneol, 2 g (72% isolated yield), was further purified on column d to afford GC-pure sample: mp 126 °C; $[\alpha]^{23}_D$ −3.8° (*c* 7.5, absolute EtOH); 75% ee.

Hydroboration of Norbornadiene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 15.1 mL of THF was added 2.7 mL (25 mmol) of norbornadiene at 0 °C. The trialkylborane (^{11}B NMR δ 82.8) was formed within 15 h at 0 °C. Transformation into the corresponding boronate (^{11}B NMR δ 34.6) and further oxidation was done as described above under the procedure for norbornene. Thus, 1.7 g of *exo*-norborn-5-en-2-ol was isolated (62% yield) and further purified by preparative GC on column d to afford GC-pure sample: mp 86–90 °C; $[\alpha]^{23}_D$ +7.75° (*c* 8.7, $CHCl_3$), 80% ee.

Hydroboration of 2-Benzonorbornadiene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 14.2 mL of THF was added 3.6 g (25 mmol) of 2-benzonorbornadiene at 0 °C. The reaction mixture was stirred at 0 °C for 40 h to afford trialkylborane (^{11}B NMR δ 86.8). The reaction was worked up as described under norbornene to yield 2.8 g of *exo*-2-benzonorborneol (71% isolated yield). It was further purified by preparative GC using column d: mp 62–66 °C, $[\alpha]^{23}_D$ +20.97° (*c* 4.2, chloroform).

Hydroboration of 2,3-Dihydrofuran with 4-^{d}Icr$_2$BH. The reaction was done (25 mmol scale) as described under *cis*-3-hexene at 0 °C for 2.5 h. The trialkylborane (3 h, ^{11}B NMR δ 87.8) obtained was oxidized and worked up as described under *cis*-3-hexene to yield 1.7 g of 3-hydroxytetrahydrofuran (78% isolated yield), bp 80 °C (15 mm). It was further purified by preparative GC using column c to furnish GC-pure material: $[\alpha]^{23}_D$ −6.61° (*c* 2.4, MeOH); 39% ee.

Hydroboration of 1,4-Epoxy-1,4-dihydronaphthalene with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 9.2 mL of THF was added 3.6 g (25 mmol) of 1,4-epoxy-1,4-dihydronaphthalene in 5 mL of THF at 0 °C. The trialkylborane (^{11}B NMR δ 86) formation was observed within 5 h at 0 °C. The reaction mixture was oxidized and worked up as described under *cis*-3-hexene. The crude reaction mixture was subjected to flash chromatography over silica gel; 40% ether in pentane eluents removes (−)-4-isocaranol, whereas, ether eluents gave the pure alcohol. Later on, crystallization from pentane afforded 3.1 g of crystalline GC-pure material: mp 102–104 °C,

72% isolated yield; $[\alpha]^{23}_D$ +25.2° (c 2, MeOH); 85% ee.

Hydroboration of 2-Methyl-4,5-dihydrofuran with 4-^{d}Icr$_2$BH. The reaction (25-mmol scale) was done as described under *cis*-3-hexene at 0 °C for 8 h. The trialkylborane (^{11}B NMR δ 86.4) was oxidized and the reaction mixture worked as described above to afford 1.9 g of *trans*-2-methyl-3-hydroxytetrahydrofuran, (74% isolated yield): bp 91–92 °C (15 mm); $[\alpha]^{23}_D$ −29.91° (c 2.5, MeOH); 70% ee.

Hydroboration of 3,4-Dihydro-2*H*-pyran with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 15.5 mL of THF was added 4.6 mL (50 mmol) of 3,4-2*H*-dihydropyran at 0 °C. The reaction mixture was stirred for 240 h at 0 °C, methanolyzed (80% of 4-^{d}Icr$_2$BH reacted), oxidized, and worked up as described under *trans*-3-hexene to afford 1.47 g of 3-hydroxytetrahydropyran (58% isolated yield), bp 90 °C (20 mm). Preparative GC was done using columns c and d to furnish GC-pure material: $[\alpha]^{23}_D$ +1.35° (neat), 11% ee.

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Chiral Synthesis via Organoboranes. 18. Selective Reductions. 43. Diisopinocampheylchloroborane as an Excellent Chiral Reducing Reagent for the Synthesis of Halo Alcohols of High Enantiomeric Purity. A Highly Enantioselective Synthesis of Both Optical Isomers of Tomoxetine, Fluoxetine, and Nisoxetine

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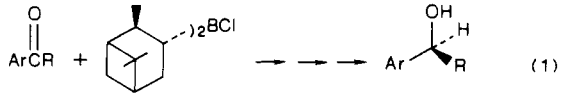
Diisopinocampheylchloroborane, ^{d}Ipc$_2$BCl, reduces ring and chain substituted haloaralkyl ketones to the corresponding halo alcohols in excellent enantiomeric excess. In certain cases these alcohols can be upgraded by simple methods to essentially 100% ee. For instance, (+)- or (−)-3-chloro-1-phenyl-1-propanol is initially obtained in 97% ee. Simple recrystallization then furnishes the pure enantiomers. These chiral halo alcohols are highly versatile intermediates. They can be readily cyclized to oxiranes and 2-substituted tetrahydrofurans with retention of chirality. Utilizing this methodology, we have developed an efficient, highly enantioselective synthesis of both optical isomers of the antidepressant drugs, Tomoxetine, Fluoxetine, and Nisoxetine, from the common intermediates (+)- or (−)-3-chloro-1-phenyl-1-propanol.

We[3-5] and others[6] have recently demonstrated the utility of chirally modified tri- and tetragonal boron compounds for the asymmetric reduction of prochiral ketones. In particular, we have shown that diisopinocampheylchloroborane, ^{d}Ipc$_2$BCl, (the symbol *d* indicates that the reagent is derived from (+)-α-pinene), enantioselectively reduces prochiral aralkyl ketones to the corresponding alcohols[3] (eq 1). We have further discovered that certain α-*tert*-



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alkyl ketones can be similarly chirally reduced.[4] In these initial investigations we restricted ourselves to relatively simple ketones. However, difunctional chiral alcohols would be more valuable for the elaboration of complex compounds. With this in mind, we turned our attention to more suitably functionalized ketones, in particular, to various halo ketones.

Table I. Asymmetric Reductions of Haloaralkyl Ketones with ^{d}Ipc$_2$BCl in THF at −25 °C

	halo alcohol product[a]		cyclized product % ee
	% ee[b]	abs config	
2-chloroacetophenone	96	*R*[d]	96
2-bromoacetophenone	86[c]	*R*[d]	86
2-iodoacetophenone	67[c]	*R*	67
2′-bromoacetophenone	99	(*S*)[e]	
4′-bromoacetophenone	97	(*S*)[e]	
3-chloropropiophenone	97	(*S*)[e]	
4-chloropropiophenone	98	(*S*)[e]	
2,2′,4′-trichloroacetophenone	93	(*R*)[d,f]	
1-(4-bromophenyl)-4-chlorobutyrophenone	98	(*S*)[e]	98[f]

[a] Chemical yields of the alcohols were all in the 70–85% range. [b] Determined by capillary GC analysis of [*R*]-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate. [c] Determined by conversion to the epoxide and measuring the rotation. [d] See ref 9. [e] By analogy to the reduction of acetophenone and propiophenone: ref 3. [f] By analogy to the cyclization of 2-chloroacetophenone.

Results and Discussion

It has been demonstrated that the chiral reduction of 2-haloacetophenones with chirally modified boron reagents

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