22643-67-0; **7f**·DNP, 22643-68-1; **8a**, 70749-11-0; **8a**·DNP, 83586-08-7; **8b**, 83586-09-8; **8b**·DNP, 83586-10-1; **8c**, 83586-11-2; **8c**·DNP, 83586-12-3; **9a**, 70749-10-9; **9c**, 83586-13-4; **9d**, 18174-04-4; **9d**·DNP, 83586-14-5; **9e**, 83586-15-6; **9e**·DNP, 83586-16-7; **9f**, 22645-08-5; **9f**·DNP, 83586-17-8; **10**, 83586-18-9; **10**·DNP, 83586-19-0; **11a**, 70708-57-5; **11a**·DNP, 83586-20-3; **11b**, 59456-40-5; **11b**·DNP, 83586-21-4; **11c**, 83586-22-5; **11c**·DNP, 83586-23-6; **12a**, 70708-57-5; **12a**·DNP, 83586-24-7; **12b**, 83586-25-8; **12c**, 83586-26-9; **12d**, 83586-27-0; **12d**·DNP, 83586-28-1; **12e**, 83586-29-2; **12e**·DNP, 83586-30-5; **12f**, 83586-31-6; **12f**·DNP, 83586-32-7; **15a**, 54812-89-4; **15a**·DNP, 83586-33-8; **15b**, 83586-34-9; **15b**·DNP, 83586-35-0; **15c**, 83586-36-1; **15c**·DNP, 83615-33-2; **16a**, 83648-02-6; **16d**, 83586-37-2; **16d**·DNP, 83586-38-3; **17c**, 83586-39-4; **17c**·DNP, 83586-40-7; **19c**, 83586-41-8; **19c**·DNP, 83586-42-9; **20c**, 83586-43-0; **21**, 83586-44-1; **21**·DNP, 83586-45-2; **22c**, 22643-74-9; **22c**·DNP, 22643-78-3; **23b**, 13025-91-7; **23b**·DNP, 83586-46-3; **23c**, 22647-26-3; **23c**·DNP, 22643-65-8; **24e**, 83586-47-4; **24e**·DNP, 83586-48-5; **24f**, 83586-49-6; **24f**·DNP, 83586-50-9; **25d**, 22645-06-3; **25d**·DNP, 22645-07-4; **25f**, 83586-51-0; **25g**, 83586-52-1; **25g**·DNP, 83586-53-2; **26a**, 83586-54-3; **26a**·DNP, 83586-55-4; **27**, 83586-56-5; **28b**, 83586-57-6; **29b**, 83586-58-7; **29c**, 83586-59-8; **2c**·DNP, 83586-60-1; **29d**, 83586-61-2; **29d**·DNP, 83586-62-3; $AlCl_3$, 7446-70-0.

Hydroboration. 61. Diisopinocampheylborane of High Optical Purity. Improved Preparation and Asymmetric Hydroboration of Representative Cis-Disubstituted Alkenes

Herbert C. Brown,* Manoj C. Desai,[1] and Prabhakar K. Jadhav[1]

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

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The convenient preparation of diisopinocampheylborane of high enantiomeric purity (99.1%) utilizing the commercially available relatively stable borane–methyl sulfide and α-pinene of 92% enantiomeric purity is described. Methyl sulfide liberated in the hydroboration step interferes with the equilibration needed to improve the optical purity of the reagent. However, this difficulty is readily overcome by removal of methyl sulfide under vacuum following hydroboration of the α-pinene. The reagent is then equilibrated in THF with 15% excess α-pinene at 0 °C for 3 days. During this equilibration period, the major isomer becomes incorporated selectively into the reagent. This high optical purity diisopinocampheylborane has been utilized for asymmetric hydroboration of representative cis-disubstituted alkenes such as *cis*-2-butene, *cis*-3-hexene, *cis*-2-pentene, norbornene, norbornadiene, *cis*-4,4-dimethyl-2-pentene, and *cis*-propenylbenzene. Oxidation of the intermediate organoboranes provides the corresponding alcohols in enantiomeric purities of 60–98%.

Diisopinocampheylborane (Ipc_2BH) is perhaps one of the most versatile chiral reagents readily available for laboratory use. It has been applied to the synthesis of many chiral products such as alcohols, halides, amines, ketones, hydrocarbons, and α-amino acids. It has been also applied for the kinetic resolution of alkenes, dienes, and allenes.[2]

In the early exploration of the characteristics of the hydroboration reaction, we were content with the 87% optical purity of 2-butanol realized in the hydroboration of *cis*-2-butene with Ipc_2BH generated from sodium borohydride in situ in diglyme.[3] Disappointingly, a somewhat lower optical purity of 2-butanol (78% ee) was achieved when the hydroboration was carried out with borane in the more convenient solvent tetrahydrofuran (THF). The less gratifying result was attributed to the greater solubility of Ipc_2BH in THF, resulting in a greater dissociation into the less desirable $IpcBH_2$ of the Ipc_2BH present. In diglyme the reagent exists predominantly as the crystalline material, with minimal dissociation.

A more systematic study of the preparation of Ipc_2BH in THF was carried out more recently.[4] It was found that the reaction of α-pinene with BH_3·THF proceeds rapidly to triisopinocampheyldiborane or monoisopinocampheylborane ($IpcBH_2$), named as the monomer. This species reacts faster than Ipc_2BH with the olefin. It has been established that $IpcBH_2$ on hydroboration–oxidation gives alcohols of configuration opposite[3,6] to that produced by Ipc_2BH. Therefore, a good asymmetric hydroboration cannot be achieved with such a mixture of reagents. In order to suppress the formation of monoisopinocampheylborane, 15% excess α-pinene was used for the preparation of Ipc_2BH. A fortuitous development was the discovery that equilibration of such reaction mixtures at 0 °C for 3 days resulted in the formation of Ipc_2BH, more optically pure than the initial α-pinene. The longer reaction time was accompanied by the selective incorporation of the major isomer of α-pinene into the crystalline reagent, with concurrent accumulation of the minor isomer in the solution. This preparation of Ipc_2BH of high optical purity, however, suffers from a serious limitation. It involves the use of concentrated solutions of borane in THF (2.26 M) and α-pinene of relatively high optical purity (97.4% ee). Neither of these materials is currently available commercially, thereby limiting application of this desirable chiral reagent. Moreover, the high optical purity Ipc_2BH has been applied only for the hydroboration of *cis*-2-butene[4] and *cis*-3-hexene.[6] It appeared desirable to test it more broadly.

In the recent past, borane–methyl sulfide[5] (BMS), because of its several advantages over BH_3·THF or BH_3·DG, has become a key source for the preparation of synthetically useful organoboranes. The present study, therefore, reports the use of commercially available[7] borane–methyl

(1) Postdoctoral research associates on Grant 2 R01 GM 10937-19 from the National Institutes of Health.

(2) For a recent review on "Asymmetric Syntheses via Chiral Organoborane Reagents", see: Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.

(3) (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486. (b) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *Ibid.* **1964**, *86*, 397.

(4) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12.

(5) (a) Braun, L. M.; Braun, R. A.; Crissman, H. R.; Opperman, M.; Adams, R. M. *J. Org. Chem.* **1971**, *36*, 2388. (b) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *Ibid.* **1977**, *42*, 1392.

(6) Mandal, A. K.; Yoon, N. M. *J. Organomet. Chem.* **1978**, *156*, 183.

(7) Borane–methyl sulfide (BMS) and (+)-α-pinene ($[\alpha]^{23}_D$ +47.1° (neat), 92% ee) are available from the Aldrich Chemical Co., Inc.

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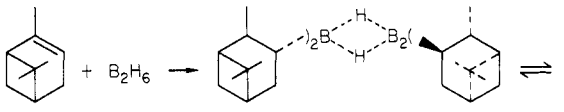
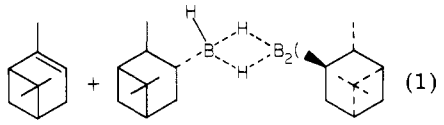
sulfide (BMS) and α-pinene (92% ee) for the preparation of Ipc_2BH of high optical purity (99% ee) and its applications for asymmetric hydroboration of representative symmetrical and unsymmetrical cis-disubstituted olefins.

Results and Discussion

Preparation of Ipc_2BH of High Optical Purity. α-Pinene (1) readily undergoes hydroboration at 0 °C to form *sym*-tetraisopinocampheyldiborane (2).[8,9] Even in the presence of excess α-pinene, the reaction does not proceed further. In the absence of excess α-pinene, there is evidence for a significant dissociation of 2 into α-pinene and triisopinocampheyldiborane[10] (3, eq 1). During the

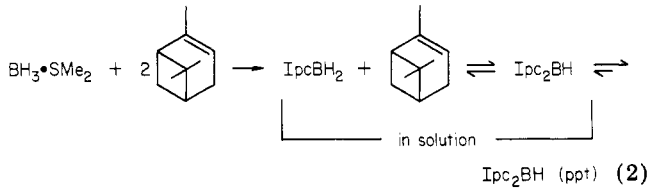


1 2



3 (1)

search for the best conditions for the preparation of high optical purity Ipc_2BH by utilizing commercially available, relatively stable BMS, 15% excess α-pinene was used in all of the experiments for two reasons: (a) to minimize the dissociation of the *sym*-tetraisopinocampheyldiborane (2) and (b) to provide a source of major isomer for incorporation into the reagent (eq 2). The enantiomeric purity

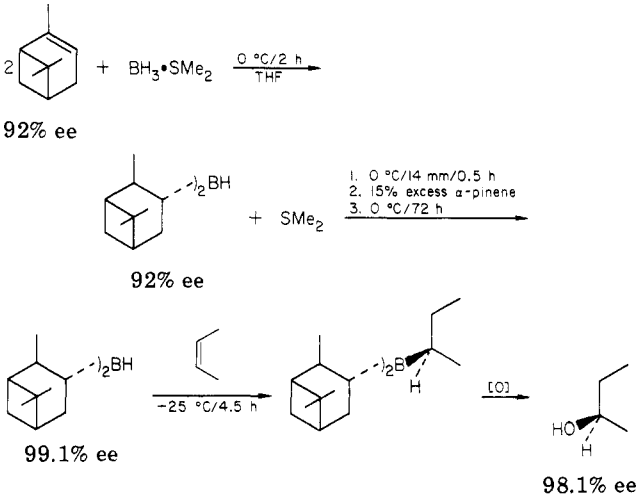


(2)

of the Ipc_2BH after equlibration was determined by measuring the rotation[11] of the isopinocampheol obtained following alkaline hydrogen peroxide oxidation of the reagent. In the early stages of this study Ipc_2BH was prepared by hydroboration of α-pinene (94.9% ee) at 0 °C. After initial stirring at 0 °C for 2 h, the reaction mixture was equilibrated at 0 °C for 2 days. The optical purity of the reagent (95.5% ee) was not satisfactory. An increase in the equilibration time to 3 and 4 days did not achieve significant improvement: 95.8% and 96% ee. It appeared possible that dimethyl sulfide (DMS), generated in the reaction mixture, complexes with the Ipc_2BH, inhibiting the desired equilibration to produce Ipc_2BH of high optical purity. Accordingly, the experimental procedure was modified to remove the inhibitory DMS, prior to the equilibration step.

In the modified procedure, α-pinene was hydroborated with neat BMS (2:1 ratio) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture became a solid mass and could not be stirred further. At this point, DMS was removed under vacuum, and both THF and 15% excess α-pinene were introduced into the flask. The lumps were broken and the contents stirred to provide a mobile slurry. The flask was then stored in the cold room at 0 °C for 3 days. The enantiomeric purity of the Ipc_2BH was found to be 98% ee, a 2% increase over the value found for the preparation in which the DMS had not been removed.

Scheme I



The experimental procedure was then further modified to avoid formation of a solid mass. Instead of neat BMS, BMS in THF was treated with α-pinene (94.9% ee) at 0 °C and further stirred for 2 h at 0 °C. A mixture of DMS and THF was removed under vacuum. The flask was then charged with THF and 15% excess α-pinene. Following equilibration (0 °C/3 days), the optical purity of the Ipc_2BH was 99.1% ee. It is evident that instead of $B\text{-}H_3$·THF, BMS can be used for the preparation of high optical purity Ipc_2BH, provided DMS is removed prior to equilibration.

After establishing the practicality of using BMS for the preparation of Ipc_2BH, we turned our attention to examining the possible use of α-pinene of lower optical purities for the preparation of Ipc_2BH of high optical purity. Thus treatment of α-pinene of 92% ee produced Ipc_2BH of 99.1% ee after the usual equilibration (0 °C/3 days). However, a further decrease in the optical purity of α-pinene to 84% ee did not provide Ipc_2BH of 99.1% ee after equilibration; however, the product did reveal a significant increase in optical purity (from 84% to 92.7% ee). It is probable that a second equilibration would have produced Ipc_2BH of 99.1% purity.

Application of Ipc_2BH of High Optical Purity. Diisopinocampheylborane of 99.1% enantiomeric purity thus prepared was utilized for asymmetric hydroboration of a variety of symmetrical and unsymmetrical cis-disubstituted olefins. Hydroboration of symmetrical unhindered cis olefins such as *cis*-2-butene (Scheme I) and *cis*-3-hexene proceeded rapidly, even at −25 °C, and was complete within 4.5 h in both cases. The progress of the reaction is conveniently followed by the disappearance of the solid Ipc_2BH and confirmed by the formation of trialkylborane (^{11}B NMR δ 87 relative to BF_3·OEt_2). The product alcohols, obtained after oxidation, were isolated by fractional distillation (GC purity >95%), and final purification (GC purity >99.9%) was achieved by preparative gas chromatography. The alcohols 2-butanol and 3-hexanol were obtained in optical purities of 98.1% and 93.1% ee, respectively, by utilizing Ipc_2BH prepared from 92% α-pinene. Such asymmetric induction is remarkable in view of the fact that the enantiomeric excesses of the products are actually higher than that of the starting chiral auxiliary.

Hydroboration followed by oxidation of unsymmetrical *cis*-2-pentene provided a mixture of 2-pentanol and optically inactive 3-pentanol in an isomeric ratio of 59:41. The maximum rotation of 2-pentanol is reported in the

(8) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 2544.
(9) Brown, H. C.; Klender, G. J. *Inorg. Chem.* **1962**, *1*, 204.
(10) Brown, H. C.; Moerikofer, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 1478.
(11) Based on the maximum reported rotation for isopinocampheol, $[\alpha]^{23}_D$ −35.7° (*c* 10, benzene); see ref 4.

Table I. Asymmetric Hydroboration of Representative *cis*-Alkenes with High Optical Purity Diisopinocampheylborane (Ipc_2BH)[a,b]

alkene	product alcohols: alcohol	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee	config
cis-2-butene	2-butanol	74	−13.23 (neat)	98.1[c]	*R*
cis-3-hexene	3-hexanol	68	−6.68 (neat)	93.2[d]	*R*
cis-2-pentene	2-pentanol (59%), 3-pentanol (41%)	70	−17.07 (*c* 7.39, Et_2O)	92.3[e]	*R*
norbornene	*exo*-norbornenol	63	−4.2 (*c* 7.5, EtOH)	83[g]	1*S*,2*S*
norbornadiene	*exo*-5-norbornen-2-ol	81	+6.21 (*c* 8.7, $CHCl_3$)	74[g]	1*R*,2*S*
cis-4,4-dimethyl-2-pentene	4,4-dimethyl-2-pentanol (97%), 2,2-dimethyl-3-pentanol (3%)	76	−14.57 (neat)	60[g]	*R*
cis-propenylbenzene	1-phenyl-1-propanol	73	−17.31 (neat)	63.3[f]	*S*

[a] The reagent was prepared from (+)-α-pinene ($[\alpha]^{23}_D$ +47.1° (neat), 92% ee) and BMS. [b] The reactions were carried out on a 50-mmol scale. The percent enantiomeric excess is based on maximum reported rotations (see footnotes *c*–*f*). [c] Leroux, P. J.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 41; $[\alpha]^{25}_D$ −13.5° (neat) for 2-butanol. [d] Kenyon, J.; Poplett, R. *J. Chem. Soc.* **1945**, 273; $[\alpha]^{18}_D$ −7.13° for 3-hexanol. [e] Levene, P. A.; Mikeska, L. A. *J. Biol. Chem.* **1927**, *75*, 587; $[\alpha]^{20}_D$ +18.5° (*c* 7.39, Et_2O). [f] Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1911**, *99*, 45; $[\alpha]^{17}_D$ −27.35° (neat). [g] As determined by 90-MHz NMR with the chiral lanthanide shift reagent $Eu(hfc)_3$.

literature, both as the neat liquid and as a solution in ethyl ether. Since 3-pentanol is inactive, the optical purity of the 2-pentanol in the reaction product was easily determined by measuring the rotation of the mixture under the above conditions and calculating for the contained 2-pentanol (GC analysis). The percent enantiomeric excess of the 2-pentanol was 92.3% ee. These results, therefore, indicate that both symmetrical and unsymmetrical cis olefins are hydroborated with an equally high degree of asymmetric induction.

Similarly, hydroboration of norbornene[3] and norbornadiene[12] proceeded smoothly, without any dehydroboration of the reagent to α-pinene, providing, after oxidation, *exo*-norborneol and *exo*-5-norbornene-2-ol in 83% and 74% ee, respectively. The enantiomeric purities of both alcohols were unambiguously established by the chiral shift reagent tris[(heptafluoroprop-3-yl)hydroxymethylene]-*d*-camphorato]europium(III) [$Eu(hfc)_3$].

Hydroboration of more hindered cis olefins such as *cis*-4,4-dimethyl-2-pentene and *cis*-propenylbenzene was relatively sluggish at −25 °C (48–72 h) and required an additional 24 h at 0 °C to achieve the disappearance of the solid Ipc_2BH. In both cases, although the solid had disappeared after stirring at 0 °C, ^{11}B NMR of the methanolyzed product indicated the presence of Ipc_2BOCH_3 (δ 54), along with the desired trialkylborane (δ 87). Apparently, hydroboration had proceeded in part with displacement[13] of α-pinene from the reagent. The regioselectivity observed in the hydroboration of *cis*-4,4-dimethyl-2-pentene is remarkable and provided 4,4-dimethyl-2-pentanol and 2,2-dimethyl-3-pentanol in an isomeric ratio of 97:3. The enantiomeric purity of the major alcohol was determined to be 60% by the chiral shift reagent $Eu(hfc)_3$. The optical purity of 1-phenyl-1-propanol was found to be 63% by comparison with the maximum reported rotation. The results of our study are summarized in Table I.

Conclusion

Diisopinocampheylborane of very high optical purity is now readily available from commercially available α-pinene (92% ee) and borane–methyl sulfide complex. The reactivity of Ipc_2BH toward cis-disubstituted olefins decreases with the increasing steric requirements of the cis olefins. The enantiomeric purities of the product alcohols increase with increasing reactivity of the cis olefins. Excellent asymmetric inductions are achieved in the cases of unhindered cis olefins. Apparently the steric requirements of unhindered cis olefins are optimum and provide a nearly perfect steric match for Ipc_2BH. Both symmetrical and unsymmetrical unhindered cis olefins are hydroborated with equally high degrees of asymmetric induction. Moderately good asymmetric induction can be achieved, even for hindered cis olefins. The absolute configuration of the new chiral center at the alcohol position is consistently the same in all cases examined.

Experimental Section

The reaction flask and other glass equipment were dried in an oven and assembled in a stream of dry nitrogen gas. Special experimental techniques used in handling air-sensitive materials are described in detail elsewhere.[14]

Materials. Tetrahydrofuran (THF) was distilled from a small excess of lithium aluminum hydride ($LiAlH_4$) and stored under nitrogen. (−)-α-Pinene of 94.9% ee was prepared by isomerization[15] of (−)-β-pinene. (+)-α-Pinene of 84% ee was received as a gift from Dr. E. Klein of the Dragoco Co., Holzminden, West Germany.[16] $BH_3{\cdot}SMe_2$ and (+)-α-pinene of 92% ee were purchased from Aldrich Chemical Co. All samples of α-pinene were distilled from a small excess of $LiAlH_4$ and stored under nitrogen gas. The alkenes used for this study were commercial products of the highest purity available, and they were purified by distillation over a small quantity of $LiAlH_4$. Norbornene was sublimed before use.

Spectra. ^{11}B NMR spectra were recorded with a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3{\cdot}OEt_2$.

GC analyses were carried out with a Hewlett-Packard 5750 chromatograph using a 6 ft × 0.25 in column packed with 10% Carbowax 20M on Chromosorb W. For preparative GC, a 6 ft × 0.5 in column packed with 10% Carbowax 20M on Chromosorb W was used. GC analyses of 3- and 2-pentanols, 4,4-dimethyl-2-pentanol, and 2,2-dimethyl-3-pentanol was carried out on a Hewlett-Packard 5730A chromatograph using a 50-m capillary column packed with 10% Carbowax 20M.

Preparation of Ipc_2BH. (A) Reaction of $BH_3{\cdot}SMe_2$ in THF and 94.9% ee α-Pinene. Equilibration without Removal of DMS. A 250-mL flask, equipped with a septum inlet, a magnetic stirring bar and a bent tube adaptor, was charged with 5.05 mL of $BH_3{\cdot}SMe_2$ (50 mmol) and 18 mL of THF. It was cooled to 0 °C, and 18.3 mL (115 mmol) of (−)-α-pinene ($[\alpha]^{25}_D$ −48.7° (neat), 94.9% ee) was added dropwise. After the mixture was stirred

(12) Mislow, K.; Berger, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 1956.
(13) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071.
(14) For handling of air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975; p 191.
(15) Brown, C. A. *Synthesis* **1978**, 754.
(16) We are indebted to Dr. E. Klein of the Dragoco Co., Holzminden, West Germany, for a generous gift of (+)-α-pinene.

at 0 °C for 1 h (Ipc_2BH separated as white solid during this time), the flask was stored in a cold room at 0 °C for 2 days. The reaction mixture was methanolyzed with 4.0 mL methanol, followed by treatment with 18.3 mL of 3 *N* NaOH (55 mmol) and careful addition of 20 mL of 30% hydrogen peroxide. The reaction mixture was then maintained at 55 °C for 1 h, cooled, and extracted with three 50-mL portions of ethyl ether. The extract, after being washed with water and brine, was dried over anhydrous $MgSO_4$. Isopinocampheol (13.3 g, 87% yield), obtained after removal of solvents and α-pinene, was crystallized from pentane: mp 55–57 °C; $[\alpha]^{23}_D$ +34.09° (*c* 10, benzene); enantiomeric purity of 95.5%. An additional two experiments, in which the time for equilibration was varied to 3 and 4 days, were carried out under the same conditions. The optical purity of the isopinocampheol, following oxidation, was found to be 95.8% ($[\alpha]^{23}_D$ +34.2° (*c* 10, benzene) and 96% ($[\alpha]^{23}_D$ +34.27 (*c* 10, benzene)), respectively.

(B) Reaction of Neat BH_3·SMe_2 and 94.9% ee α-Pinene. Equilibration in THF after Removal of DMS. A 250-mL flask, equipped with a septum inlet, a magnetic stirring bar, and a distillation condenser, connected to a receiver cooled in a dry ice-acetone bath, was charged with 5.05 mL of BH_3·SMe_2 (50 mmol). It was cooled to 0 °C in an ice bath, and 15.9 mL (100 mmol) of (−)-α-pinene ($[\alpha]^{23}_D$ −48.7° (neat)) was added dropwise with stirring. After the contents were stirred at 0 °C for 0.5 h, Ipc_2BH separated as a solid mass, and the mixture could not be stirred further. It was allowed to stand at 0 °C for an additional 1 h, and the DMS (2.2 g, 70% of the theoretical amount) was removed under vacuum (0 °C/30 mm). The flask was then brought to atmospheric pressure by flushing with N_2 gas. The distillation condenser was quickly replaced by a bent-tube adaptor under a positive pressure of N_2. The flask was then charged with 20 mL of THF and 2.4 mL of (−)-α-pinene (15 mmol), and the contents were vigorously stirred at 0 °C for 2 h until the lumps had been broken to form a mobile slurry. After equilibration at 0 °C for 3 days, the reaction mixture was methanolyzed and oxidized, as described above, to provide isopinocampheol: mp 55–57 °C; $[\alpha]^{23}_D$ +35.03° (*c* 10, benzene); enantiomeric purity of 98.1%.

(C) Reaction of BH_3·SMe_2 in THF and 94.9% ee α-Pinene. Equilibration after Removal of DMS. To a 250-mL flask containing 5.05 mL of BH_3·SMe_2 (50 mmol) and 15 mL of THF, with the experimental setup described above, was added dropwise 15.9 mL of α-pinene (100 mmol) at 0 °C. After the contents were stirred at 0 °C for 3 h, a mixture of DMS and THF (13 mL) was removed under vacuum (0 °/30 mm), and the flask was brought to atmospheric pressure by flushing with N_2 gas and charged with 18 mL of THF and 2.4 mL of α-pinene (15 mmol). It was then stored in the cold room at 0 °C for 3 days to permit equilibration. The isopinocampheol obtained as described above was 99.1% optically pure: mp 55–57 °C; $[\alpha]^{25}_D$ +35.38° (*c* 10, benzene).

(D) Reaction of BH_3·SMe_2 in THF and 92% ee α-Pinene. Equilibration after Removal of DMS. This experiment was carried out exactly as described under C. (+)-α-Pinene ($[\alpha]^{23}_D$ +47.1° (neat), 92% ee) was used for preparation of Ipc_2BH. The isopinocampheol isolated was 99.1% optically pure: mp 55–57 °C; $[\alpha]^{23}_D$ −35.4° (*c* 10, benzene).

(E) Reaction of BH_3·SMe_2 in THF and 84% ee α-Pinene. Equilibration after Removal of DMS. The experimental procedure described under C was followed by using (+)-α-pinene: $[\alpha]^{23}_D$ +43.2° (neat); 84% ee. The optical purity of the isopinocampheol ($[\alpha]^{23}_D$ −33.1° (*c* 10, benzene)) was 92.7%.

Application of Ipc_2BH. (A) Hydroboration of *cis*-2-Butene. Ipc_2BH of 99.1% ee was prepared by following the procedure described under D and was used for the asymmetric hydroboration in all cases. Thus, to a stirred suspension of Ipc_2BH (50 mmol) in THF at −25 °C was added 4.5 mL of *cis*-2-butene. The reaction mixture was stirred at −25 °C for 4.5 h. The solid Ipc_2BH disappeared, and the formation of trialkylborane was complete. The organoborane was treated with 4 mL of methanol, followed by 18.3 mL of 3 N NaOH and careful addition of 20 mL of 30% H_2O_2, maintaining the temperature of the reaction mixture below 40 °C. The reaction mixture was further stirred at 55 °C for 1 h, cooled, and extracted with ether (3 × 50 mL). The extract was washed successively with water (2 × 25 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. The organic layer was carefully fractionated to provide 2-butanol: bp 96–98 °C (740 mm); 2.9 g (73% yield); GC purity >95%. The last traces of impurities (mainly THF) were removed by preparative GC to yield 2-butanol: $[\alpha]^{23}_D$ −13.23° (neat); 98.1% ee.

(B) Hydroboration of *cis*-3-Hexene. To a stirred suspension of Ipc_2BH (50 mmol) in THF at −25 °C was added 6.2 mL (50 mmol) of *cis*-3-hexene. The reaction was complete within 4.5 h (^{11}B NMR) at −25 °C. The trialkylborane was oxidized and worked up as described under the procedure for *cis*-2-butene. The organic extract after fractionation provided 3-hexanol [bp 135–136 °C (745 mm); 3.57 g (68% yield); GC purity >95%] contaminated with an impurity of α-pinene. Preparative GC provided pure 3-hexanol: $[\alpha]^{23}_D$ −6.68° (neat); 93.2% ee.

(C) Hydroboration of *cis*-2-Pentene. To a stirred suspension of Ipc_2BH (50 mmol) in THF at −25 °C was added 5.35 mL (50 mmol) of *cis*-2-pentene. The reaction was complete within 4.5 h at −25 °C (^{11}B NMR). The trialkylborane was oxidized and worked up as described under the *cis*-2-butene procedure. The organic extract on fractionation provided 2- and 3-pentanols: bp 118–120 ° (745 mm); 3.1 g (70% yield); GC purity >95%. It was further purified by preparative GC. Capillary GC analysis established the product to be a mixture of 41% 3-pentanol and 59% 2-pentanol: $[\alpha]^{23}_D$ −12.7° (neat); 92% ee, calculated from the specific rotation of the 2-pentanol in the mixture and the literature value for 100% ee.

(D) Hydroboration of Norbornene. To a stirred suspension of Ipc_2BH (50 mmol) at −25 °C was added 4.7 g (50 mmol) of norbornene in THF (6 mL). The reaction mixture was further stirred at −25 °C for 22 h. The trialkylborane was oxidized and worked up as described for *cis*-2-butene. The residue, after removal of solvent, was distilled to remove α-pinene and provide a mixture of *exo*-norborneol and isopinocampheol. The mixture of alcohols was diluted with 5 mL of *n*-decane and carefully fractionated.[3b] The *exo*-norborneol codistilled with *n*-decane at 158–163 °C. At the end of distillation, an additional 5 mL of *n*-decane was added and distillation continued. In all, five 5-mL fractions were collected, combined, and cooled at −10 °C. At that point, *exo*-norborneol crystallized. The crystalline product was collected: 3.5 g (62% yield); mp 125–126 °C; $[\alpha]^{23}_D$ −4.2° (*c* 7.5, absolute EtOH). The enantiomeric purity was 83% with the chiral shift reagent Eu(hfc)$_3$. A complete resolution of the CH–OH proton was observed in the presence of Eu(hfc)$_3$.

(E) Hydroboration of Norbornadiene. To a stirred suspension of Ipc_2BH (50 mmol) at −25 °C was added 4.6 g (50 mmol) of norbornadiene in THF (6 mL). The reaction mixture was further stirred at −25 °C for 6 h. The trialkylborane was oxidized and worked up as described in the procedure for *cis*-2-butene. The residue, after removal of solvent, was distilled to remove α-pinene and provide a mixture of *exo*-5-norbornen-2-ol and isopinocampheol (17 g, ~81% yield). The mixture of alcohols were converted into their acetates and separated by fractional distillation by following the reported procedure[12] to provide pure *exo*-5-norbornene-2-yl acetate: α^{23}_D +26.7° (neat, *l* = 1 dm) [lit. α^{25}_D +22.9° (neat, *l* = 1 dm)[12]]. At this point, the enantiomeric excess of the acetate was determined by NMR with the chiral shift reagent Eu(hfc)$_3$. A complete resolution of the $CHOCOCH_3$ proton was observed (74% ee). Lithium aluminum hydride (0.91 M, 3 mL) reduction of 0.353 g of 5-norbornene-2-yl acetate in refluxing ethyl ether (0.5 h), followed by the usual workup, provided *exo*-5-norbornen-2-ol. It was purified by sublimation: mp 84–90 °C; $[\alpha]^{23}_D$ +6.2° (*c* 8.7, $CHCl_3$) [lit. $[\alpha]_D$ +5.8° (*c* 8.7, $CHCl_3$)[12]].

(F) Hydroboration of *cis*-4,4-Dimethyl-2-pentene. To a stirred suspension of Ipc_2BH (50 mmol) in THF at −25 °C was added 7.1 mL of *cis*-4,4-dimethyl-2-pentene. The reaction mixture was stirred at −25 °C for 48 h and then at 0 °C for 24 h. It was oxidized and worked up as usual. The organic extract was carefully fractionated to provide 4.6 g (76% yield) of 4,4-dimethyl-2-pentanol: bp 74 °C (100 mm); GC purity >96%. It was further purified by preparative GC, $[\alpha]^{23}_D$ −14.57° (neat). Analysis on capillary GC showed it to be a mixture of 97% 4,4-dimethyl-2-pentanol and 3% 2,2-dimethyl-3-pentanol. The percent of the major isomer was determined to be 60% by NMR with Eu(hfc)$_3$.

(G) Hydroboration of *cis*-Propenylbenzene. To a stirred suspension of Ipc_2BH (50 mmol) in THF was added 6.5 mL (50 mmol) of *cis*-propenylbenzene. The reaction mixture was further stirred at −25 °C for 72 h and then at 0 °C for 24 h. The resulting

organoborane was oxidized and worked up as usual. The organic extract, after removal of solvent, was fractionated to provide a mixture of 1-phenyl-1-propanol and isopinocampheol, bp 80 °C (2 mm) (17.1 g). A portion (2.3 g) of the mixture was separated by "flash chromatography": fraction I, 10% Et_2O in pentane (4 × 25 mL), 0.363 g of pure 1-phenyl-1-propanol; fraction II, 10% Et_2O in pentane (6 × 25 mL), 0.320 g of 90% pure 1-phenyl-1-propanol (fractions I and II combined yield, 73%); fraction III 10% Et_2O in pentane (5 × 250 mL), 1.6 g of pure isopinocampheol. Fraction I was distilled to yield pure 1-phenyl-1-propanol, $[\alpha]^{23}_D$ −17.31° (neat), 63.3% ee.

Registry No. Ipc_2BH, 21947-87-5; $BH_3{\cdot}SMe_2$, 13292-87-0; (+)-α-pinene, 7785-70-8; isopinocampheol, 27779-29-9; (*R*)-(−)-2-butanol, 14898-79-4; (*R*)-(−)-3-hexanol, 13471-42-6; (*R*)-(−)-2-pentanol, 31087-44-2; 3-pentanol, 584-02-1; (1*S*,2*S*)-(−)-*exo*-bornenol, 61277-93-8; (1*R*,2*S*)-(+)-*exo*-5-norbornen-2-ol, 71030-15-4; (*R*)-(−)-4,4-dimethyl-2-pentanol, 83615-50-3; 2,2-dimethyl-3-pentanol, 3970-62-5; (*S*)-(−)-1-phenyl-1-propanol, 613-87-6; *cis*-2-butene, 590-18-1; *cis*-3-hexene, 7642-09-3; *cis*-2-pentene, 627-20-3; norbornene, 498-66-8; norbornadiene, 121-46-0; *cis*-4,4-dimethyl-2-pentene, 762-63-0; *cis*-propenylbenzene, 766-90-5; (1*R*,2*S*)-(+)-*exo*-5-norbornen-2-ol acetate, 83679-37-2.

Organoboranes. 27. Exploration of Synthetic Procedures for the Preparation of Monoisopinocampheylborane

Herbert C. Brown,* Arun K. Mandal, Nung Min Yoon, Bakthan Singaram, John R. Schwier, and Prabhakar K. Jadhav

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

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Monoisopinocampheylborane ($IpcBH_2$) has emerged as a useful chiral hydroborating agent for hindered olefins. This was prepared for the first time as the triethylamine–monoisopinocampheylborane adduct ($IpcBH_2{\cdot}NEt_3$) by the reaction of the triethylamine–thexylborane adduct $ThxBH_2{\cdot}NEt_3$ with α-pinene. The free borane can then be liberated by treatment with borane in tetrahydrofuran (THF) or boron trifluoride etherate. The adduct is a viscous liquid and could not be purified readily. A solid derivative of $IpcBH_2$, the $IpcBH_2{\cdot}$TMED adduct, can be readily prepared with *N,N,N′,N′*-tetramethylethylenediamine (TMED). This adduct can be purified readily by crystallization. However, $IpcBH_2$ thus obtained retains only the original optical purity of the α-pinene used to synthesize the reagent. $IpcBH_2$ of high optical purity (~100% ee) can be obtained from optically impure α-pinene via the $2IpcBH_2{\cdot}$TMED adduct, either by the reaction of diisopinocampheylborane with 0.5 equiv of TMED or by the reaction of $2ThxBH_2{\cdot}$TMED with α-pinene. The free borane in THF is then obtained by the removal of TMED with 2 equiv of $BF_3{\cdot}OEt_2$. It has also been observed that the direct synthesis of $IpcBH_2$ could be achieved by the equilibration reaction of 1:1 α-pinene and $BH_3{\cdot}$THF.

The introduction of chirality in a molecule by means of an optically active reagent is an important transformation in organic synthesis. Several reagents have been developed to effect this transformation.[1] However, in recent years, chiral organoboranes have emerged as a valuable means to achieve such asymmetric syntheses.[1,2] One of the most versatile chiral reagents available for such laboratory application is diisopinocampheylborane (Ipc_2BH). This reagent is an excellent hydroborating agent for cis olefins.[3-5] Indeed, it has recently achieved the conversion of *cis*-2-butene into 2-butanol in 98.4% ee.[6] The reagent also permits the partial resolution of racemic olefins.[3,7] Another useful application of the reagent has been the asymmetric reduction of prochiral ketones to optically active alcohols.[8-11] Unfortunately, the reactions of this reagent with hindered olefins such as 1-methylcyclopentene, 1-methylcyclohexene, *trans*-2-butene, etc. are slow and mechanistically complicated, proceeding with partial displacement of α-pinene from the reagent. In such cases, the product alcohols reveal much lower enantiomeric purities, in the range of 14–22% ee.[12] Therefore, it appeared desirable to develop a less hindered optically active hydroborating agent which could be effectively used with trisubstituted and other relatively hindered types. Recent studies in our laboratory led to the discovery of monoisopinocampheylborane ($IpcBH_2$), a less hindered optically active hydroborating agent for such hindered olefins. It has been observed that this reagent hydroborates both trans-disubstituted and trisubstituted olefins smoothly to yield, after oxidation, the corresponding alcohols in high enantiomeric purities (50–100% ee).[13-15] A detailed account of these applications of $IpcBH_2$ for chiral hydroboration are discussed in the succeeding paper. In this paper we discuss our exploration of convenient synthetic routes to isopinocampheylborane, $IpcBH_2$.[13,16-18]

Results and Discussion

Hydroboration of olefins with $BH_3{\cdot}$THF or $BH_3{\cdot}SMe_2$ generally proceeds rapidly past the monoalkylborane stage.[19,20] Consequently, it is generally not possible to

(1) Morrison, J. D.; Mosher, H. R. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffts, NJ, 1971.
(2) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.
(3) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.
(4) Sandman, D. J.; Mislow, K.; Gidding, W. P.; Dirlam, J.; Henson, G. C. *J. Am. Chem. Soc.* **1968**, *90*, 4877.
(5) Partridge, J. J.; Chadda, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.
(6) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12.
(7) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1962**, *84*, 1341.
(8) (a) Brown, H. C.; Bigley, D. B. *J. Am. Chem. Soc.* **1961**, *83*, 3166. (b) Brown, H. C.; Mandal, A. K. *J. Org. Chem.* **1977**, *42*, 2996.
(9) Varma, K. R.; Caspi, E. *Tetrahedron* **1968**, *24*, 6365.
(10) Caspi, E.; Varma, K. R. *J. Org. Chem.* **1968**, *33*, 2181.
(11) Wolfe, S.; Rank, A. *Can. J. Chem.* **1966**, *44*, 2591.
(12) Brown, H. C.; Ayyanger, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071.
(13) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514.
(14) Mandal, A. K.; Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3543.
(15) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1981**, *46*, 5047.
(16) Brown, H. C.; Mandal, A. K. *Synthesis* **1978**, 146.
(17) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.
(18) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1979**, *44*, 465.
(19) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.

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