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

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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

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(10) Caspi, E.; Varma, K. R. *J. Org. Chem.* **1968**, *33*, 2181.
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(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.
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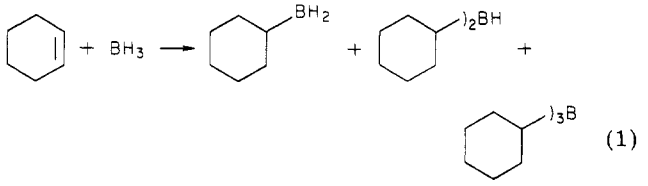
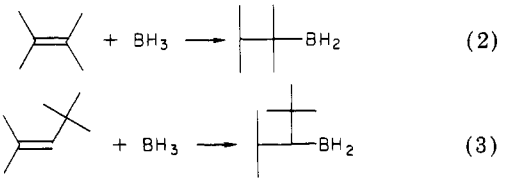
synthesize monoalkylborane by the direct reaction of olefins with borane (eq 1). Only in the case of certain



(1)

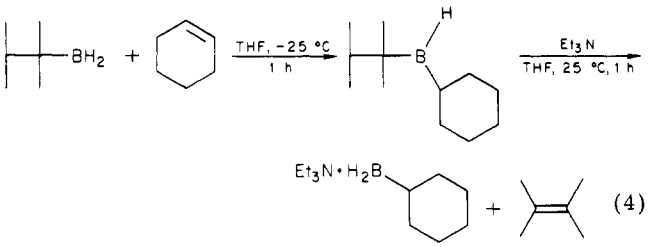
highly hindered olefins such as tetramethylethylene (TME) or 2,4,4-trimethyl-2-pentene (diisobutyl-2-ene ≡ Dib-2) it is possible to control the hydroboration so as to achieve the synthesis of the monoalkylborane $(RBH)_2$.[21,22] In this way, thexylborane ($ThxBH_2$)[23] and diisobutyl-2-eneborane ($DibBH_2$)[24] are readily prepared (eq 2, 3). Fortunately,



(2)

(3)

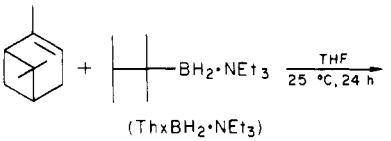
an indirect approach to convert $ThxBH_2$ into monoalkylboranes, as their triethylamine complexes, was discovered, making such monoalkylborane readily available for the first time (eq 4).[25] This procedure thus requires



(4)

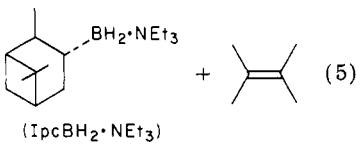
the clean preparation of thexylmonoalkylborane, which in turn yields the desired products. However, in the case of certain hindered olefins, such as α-pinene, hydroboration with $ThxBH_2$ proved to be very slow and does not proceed to thexylmonoisopinocampheylborane cleanly.[25] Therefore, monoisopinocampheylborane–triethylamine ($IpcBH_2{\cdot}NEt_3$) could not be synthesized satisfactorily by this reaction. This difficulty was later circumvented by the discovery that hindered olefins react readily at 25 °C with $ThxBH_2{\cdot}NEt_3$ (1), itself readily obtained from $ThxBH_2$ and Et_3N to displace TME and produce the corresponding $RBH_2{\cdot}NEt_3$.[26] When α-pinene is subjected to this reaction, it cleanly yields $IpcBH_2{\cdot}NEt_3$ (2).[13,26]

Monoisopinocampheylborane–Triethylamine Adduct ($IpcBH_2{\cdot}NEt_3$) (2). $IpcBH_2{\cdot}NEt_3$ (2) was prepared for the first time by the reaction of $ThxBH_2{\cdot}NEt_3$ (1) with α-pinene ($[\alpha]^{25}_D$ +48.0°, 94% ee) at 25 °C for 24 h (eq 5). Following removal of the volatile components (THF, TME), 2 can be obtained as a colorless viscous liquid. Oxidation following methanolysis yielded 97% isopinocampheol ($[\alpha]^{23}_D$ −34.3°, 95% ee) and 3% thexyl alcohol, indicating thereby the formation of 97% of 2. This result also indicates that the displacement has proceeded without



(ThxBH₂·NEt₃)

1



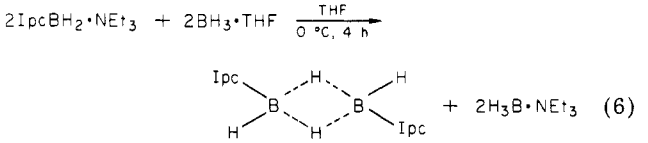
(IpcBH₂·NEt₃)

2

(5)

racemization, and 2 possesses the original optical activity, 95% ee, of the α-pinene used.

$IpcBH_2{\cdot}NEt_3$ (2) in THF reacts only slowly with olefin at 0 °C or 25 °C. This, therefore, necessitates the removal of triethylamine from 2 to facilitate the reaction. Removal of Et_3N with boron trifluoride in THF is disappointingly slow.[25] However, $BH_3{\cdot}THF$ provided a solution for the removal of Et_3N from 2, producing free $IpcBH_2$ in solution, presumably as the dimer 3, for ready hydroboration of olefins (eq 6). Fortunately, $BH_3{\cdot}NEt_3$ is inert toward

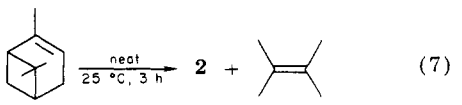


3

(6)

hydroboration, except at elevated temperature, and need not be removed from the reaction product. This procedure, however, suffers from three limitations: (1) it utilizes $BH_3{\cdot}THF$, a less convenient reagent to handle, (2) it requires a relatively long reaction time, and (3) the reaction product, $BH_3{\cdot}NEt_3$, present with 3 in solution in THF, although inert toward hydroboration, interferes in the isolation of the oxidation products, following the chiral hydroboration. Consequently, the alkaline reaction mixture had to be refluxed for 12 h to achieve complete hydrolysis and destruction of $BH_3{\cdot}NEt_3$, prior to isolation of the alcohol products. Such conditions are not desirable in reactions involving asymmetric synthesis. These difficulties were then circumvented by the following procedure.[16]

Improved Synthesis of 2 and 3. This procedure utilizes the convenient reagent, neat $BH_3{\cdot}SMe_2$, for the rapid preparation of neat thexylborane. Removal of methyl sulfide under vacuum and addition of a slight excess (20%) of Et_3N yields 1. This is followed by a fast displacement of TME from 1 by α-pinene at 25 °C to form 2 (eq 7). The volatile components are stripped off under



(7)

vacuum to leave 2 as neat viscous liquid, as before, in 94–95% yield. The removal of Et_3N from 2 is affected by treatment of a pentane solution of 2 with an equivalent amount of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) at 25 °C for 15 min, resulting in the separation of two layers. The lower layer of $BF_3{\cdot}NEt_3$ can be syringed out or else, more conveniently, can be crystallized out of solution at −5 °C. The pentane solution of the product 3 can be removed for hydroboration by simple decantation (eq 8)

Another simple approach to the synthesis of $IpcBH_2{\cdot}NEt_3$ (2) was achieved by the dehydroboration of α-pinene from diisopinocampheylborane by Et_3N. Thus, diiso-

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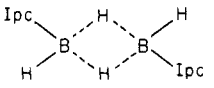
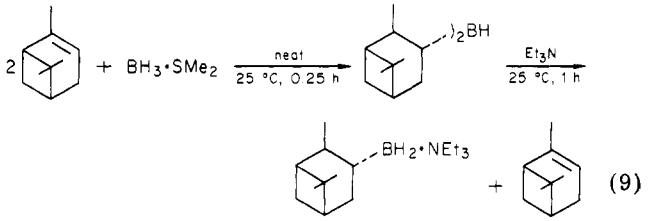
$$2IpcBH_2\cdot NEt_3 + 2BF_3\cdot OEt_2 \xrightarrow[25\ °C,\ 15\ min]{pentane}$$



$$+ 2BF_3\cdot NEt_3\downarrow\ (-5\ °C) \quad (8)$$

3

pinocampheylborane was first prepared neat by the reaction of borane–methyl sulfide with α-pinene. Addition of Et_3N to the product resulted in the formation of 2 in quantitative yield after 1 h at 25 °C (eq 9). The attempted



(9)

2

total removal of the dehydroborated α-pinene under high vacuum (0.05 mm, 3–4 h) at 40 °C proved to be ineffective. It is not clear at this time why all of the α-pinene could not be stripped from **2**.

In any case, in all of these procedures, **2** was obtained as a viscious liquid and could not be readily purified. Therefore, it appeared desirable to explore the possibility of preparing a solid adduct of **3** with some other amine, making it possible to purify it readily by crystallization. *N,N,N′,N′*-Tetramethylethylenediamine (TMED) proved to be suitable for this objective.

Monoisopinocampheylborane–*N,N,N′,N′*-Tetramethylethylenediamine Adduct ($IpcBH_2$·TMED, 4). While exploring the usefulness of TMED to stabilize monoalkylboranes (RBH_2) as the RBH_2·TMED adducts, it had been observed[27] that **4** can be obtained by displacement of triethylamine from **2** with TMED (eq 10).

$$\underset{\mathbf{2}}{IpcBH_2\cdot NEt_3} + TMED \xrightarrow[1\ h]{25\ °C} \underset{\mathbf{4}\ (mp\ 113\text{–}115\ °C)}{IpcBH_2\cdot TMED} + Et_3N \quad (10)$$

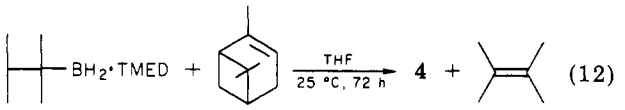
Removal of Et_3N under vacuum yields **4** as a white solid, readily purified by crystallization from pentane; mp 113–115 °C. The compound **4** is air stable and can be stored as such or in THF solution for several weeks at 25 °C without any noticeable hydride loss, isomerization, or disproportionation.

TMED could be readily removed from **4** by treatment of a THF solution of **4** with two equivalent amounts of BF_3·OEt_2 at 25 °C for 0.25 h. $2BF_3$·TMED precipitates out of the THF solution of **3** can be removed by filtration (eq 11).

$$\underset{\mathbf{4}}{IpcBH_2\cdot TMED} + 2Et_2O\cdot BF_3 \xrightarrow[25\ °C,\ 15\ min]{THF} \mathbf{3} + 2BF_3\cdot TMED\downarrow \quad (11)$$

The above procedure, however, requires first of all the preparation of **2**, which is then converted to **4**.

The preparation of **4** is simplified by the treatment of thexylborane–TMED ($ThxBH_2$·TMED, **5**), itself obtained by the reaction of TMED with thexylborane, with α-pinene (3 equiv of olefin is required to facilitate the reaction) for 72 h to yield **4** in 95% yield[28] (eq 12). Removal of volatiles under high vacuum yields **4** as a white solid which can be crystallized from pentane as before.



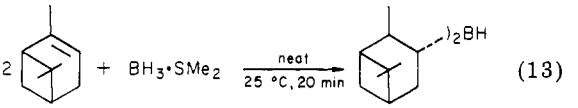
(12)

($ThxBH_2$·TMED)

5

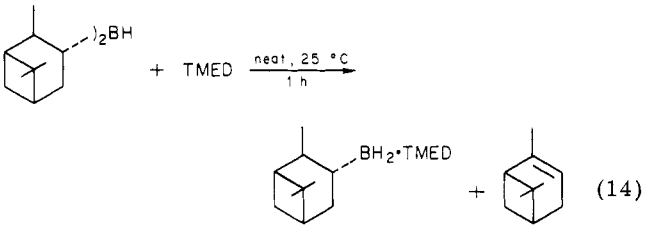
This procedure, however, requires a long reaction time and also utilizes an excess of α-pinene. Therefore, a more simplified procedure was desired. This is outlined below.

This procedure utilizes neat BH_3·SMe_2 for the rapid preparation of diisopinocampheylborane (Ipc_2BH) by the reaction of neat α-pinene with neat BH_3·SMe_2, fast displacement of α-pinene by TMED at 25 °C, and finally, the removal of dehydroborated α-pinene by distillation under high vacuum. With these modifications, the synthesis of **4** becomes a simple, rapid process[29] (eq 13 and 14).



(13)

Ipc_2BH

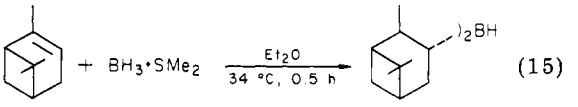


(14)

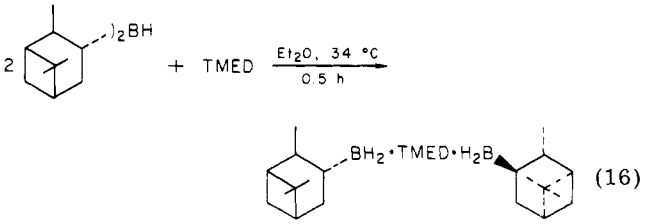
4

TMED could be removed from **4** as before (eq 10) to yield free $IpcBH_2$ (**3**) in quantitative yield. It is to be noted that in all of the procedures discussed so far, **3** is obtained in 95% ee; i.e., it possesses the original activity of the α-pinene.

Bis Adduct of Monoisopinocampheylborane with TMED ($2IpcBH_2$·TMED, 6). The discovery that $IpcBH_2$ forms a crystalline bis adduct with TMED[27] made available the most convenient synthesis of $IpcBH_2$ as $2IpcBH_2$·TMED[17] (**6**). Thus, the present procedure utilizes BH_3·SMe_2 (BMS) in Et_2O for the rapid preparation of Ipc_2BH.[20] A fast displacement of α-pinene by 0.5 equiv of TMED yields **6**: 80% yield; mp 140–141 °C. Finally, TMED could be conveniently removed from **6** to yield **3** in quantitative yield (eq 15–17). Unexpectedly, the bis adduct **6** separates



(15)



(16)

6 (mp 140–141 °C)

$$\mathbf{6} + 2BF_3\cdot OEt_2 \xrightarrow[25\ °C,\ 1h]{THF} \mathbf{3} + 2BF_3\cdot TMED\downarrow \quad (17)$$

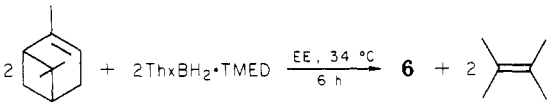
in much higher optical purity (100%) than the (+)-α-

(27) Singaram, B.; Schwier, J. R. *J. Organomet. Chem.* **1978**, *156*, C1.
(28) Unpublished observation with Dr. John R. Schwier.
(29) Unpublished observation with Dr. John R. Schwier, Dr. A. K. Mandal, and Dr. B. Singaram.

pinene used (94% ee) to synthesize Ipc_2BH. This was established by the oxidation of **6** following methanolysis to isopinocampheol; $[\alpha]^{25}_D$ −35.79°, a value which corresponds to 100% ee.[6] Therefore, this procedure achieves the preparation of **6** in exceptionally high optical purity, approaching 100%, from an optically impure substrate.

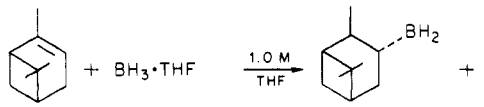
The formation of $2IpcBH_2$·TMED (**6**) of higher optical purity than the purity of the (+)-α-pinene utilized is due to the preferential crystallizatioin of (+),(+)$2IpcBH_2$·TMED over (+),(−)$2IpcBH_2$·TMED. The amount of (−),(−)$2IpcBH_2$·TMED present would be negligible. This hypothesis, however, requires the $2IpcBH_2$·TMED present in solution to have lower optical purity than the crystallized product. Indeed, the isopinocampheol, obtained by oxidation of the $2IpcBH_2$·TMED in solution, has $[\alpha]^{25}_D$ −30.16°, a value which corresponds to 84% ee.

Another convenient method for the preparation of $2IpcBH_2$·TMED of high optical purity is outlined below. We have recently observed[18] that the crystalline bis adducts of monoalkylboranes with TMED ($2RBH_2$·TMED) could be synthesized by the reaction of $2ThxBH_2$·TMED (**7**) with the corresponding olefins in refluxing EE. Thus, the reaction with α-pinene requires 6 h to yield **6**, mp 140–141 °C, in excellent yield (eq 18).

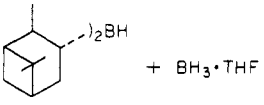


(18)

Direct Synthesis of 3 by the Equilibration of 1:1 α-Pinene and Borane. It has been well established that the reaction of olefin with borane in 1:1 ratio generally yields a mixture of products (eq 1), except in the case of a few hindered olefins, where the reaction proceeds cleanly to the corresponding monoalkylboranes (eq 2 and 3). However, in the course of studies directed to other objectives,[30] we observed that the reaction of α-pinene with BH_3·THF (1.5 M) in a 1:1 ratio at 0 °C for a short time yielded 15% $IpcBH_2$, with 42.5% each of Ipc_2BH and BH_3·THF (eq 19). When the same reaction mixture was



(1) 0 °C, 0.5 h	15%
(2) 0 °C, 0.5 h; 25 °C, 24 h	45%
(3) 0 °C, 0.5 h; 25 °C, 48 h	70%

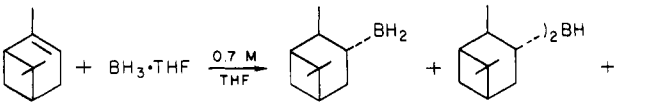


(19)

42.5%	42.5%
27.5%	27.5%
15%	15%

allowed to equilibrate at 25 °C for 24 h, the reaction mixture consisted of 45% $IpcBH_2$ and 27.5% each of Ipc_2BH and BH_3·THF. The above reaction attains equilibrium after 48 h at 25 °C with the following equilibrium distribution: 70% $IpcBH_2$, 15% Ipc_2BH, and 15% BH_3·THF (eq 18). It therefore appeared to us that with the proper reaction conditions, this reaction could give rise to a simple synthesis of $IpcBH_2$.

Investigation established that the reaction of α-pinene with BH_3·THF in 1:1 ratio in 0.7 M THF at 25 °C attained equilibrium after 96 h, and the equilibrium mixture consisted of 91% $IpcBH_2$ and 4.5% each of Ipc_2BH and BH_3·THF (eq 19).[31] Alternatively, the reaction mixture was found to attain equilibrium at 50 °C after 3.5–4 h, with the equilibrium mixture containing 86% $IpcBH_2$ and 7% each of Ipc_2BH and BH_3·THF (eq 20). The components

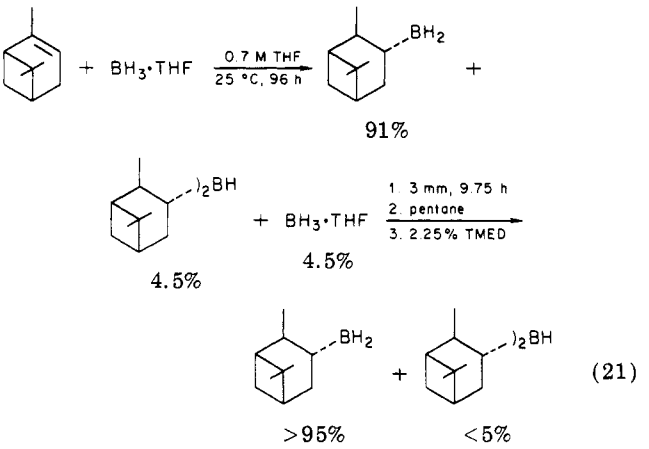


25 °C, 96 h	91%	4.5%
50 °C, 4 h	86%	7%

(20)

4.5%
7%

of the equilibrium mixture were analyzed by low-temperature methanolysis of aliquots followed by ^1H and ^{11}B NMR determination of Ipc_2BOMe, $Ipc(OMe)_2$, and $B(OMe)_3$. After the equilibrium had been attained, THF was removed under vacuum and replaced by pentane. Addition of an appropriate amount of TMED equivalent to the BH_3·THF present led to the precipitation of $2BH_3$·TMED which, if desired, could be removed by filtration. However, $2BH_3$·TMED is very inert toward hydroboration, and if direct hydroboration is envisaged, it need not be removed from the supernatant liquid, which contains >95% of $IpcBH_2$ for the 25 °C equilibration and 92.5% $IpcBH_2$ for the 50 °C equilibration (eq 21).



(21)

Therefore, it has been shown that the reaction of α-pinene with BH_3·THF in a 1:1 ratio gives rise to $IpcBH_2$ in >95% yield.

This procedure suffers from one limitation. It utilizes the less convenient BH_3·THF. Therefore, we undertook to establish whether the reaction of α-pinene with BH_3·SMe_2 in a 1:1 ratio would yield $IpcBH_2$. However, the above reaction in 0.7 M THF attained equilibrium only after ~6 days with the equilibrium mixture containing ~70% $IpcBH_2$ and 15% each of Ipc_2BH and BH_3·SMe_2.

Conclusion

Monoisopinocampheylborane ($IpcBH_2$) has emerged as a useful reagent for the asymmetric hydroboration of trans-disubstituted and trisubstituted olefins to provide the corresponding alcohols in high optical purities (50–100%). It also offers promise for asymmetric reduction and coordination. Consequently, a simple synthesis of the reagent was desired. The present paper described the synthetic approaches that were taken to achieve this

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(31) Pelter, A.; Ryder, D. J.; Sheppard, J. H.; Subrahmanyam, C.; Brown, H. C.; Mandal, A. K. *Tetrahedron Lett.* **1979**, 4777.

objective. The most convenient method now appears to be the preparation of $IpcBH_2$ as $2IpcBH_2$·TMED by the reaction of 0.5 equiv of TMED with diisopinocampheylborane, followed by the removal and precipitation of TMED by BF_3·OEt_2. This procedure is simple, yet it yields, $IpcBH_2$ of 100% optical purity.

Experimental Section

Materials. All operations were carried out under nitrogen. The solvents were purified by standard procedures.[19] Borane in THF was prepared from $NaBH_4$ and BF_3·OEt_2.[19] BMS was obtained from the Aldrich Chemical Co. TME (Aldrich) and (+)-α-pinene (Dragoco Co.) were distilled from $LiAlH_4$ and stored under nitrogen. (+)-α-Pinene showed an optical rotation of $[\alpha]^{25}_D$ +48.03° (94% ee). The optical rotations were measured by using a Rudolph polarimeter. Melting points are uncorrected and were obtained in sealed capillary tubes.

Preparation of Monoisopinocampheylborane–Triethylamine Adduct (2). A 2.0 M solution of thexylborane in THF was prepared by adding 6.6 mL (55 mmol) of TME to 20.9 mL of a 2.63 M (55 mmol) solution of BH_3·THF at 0 °C and following the standard procedure.[19,25] To this solution was added 8.4 mL (60 mmol, 10% excess) of NEt_3. A 1.5 M solution of $ThxBH_2$·NEt_3 in THF was obtained. To this was added 8.8 mL (55 mmol) of (+)-α-pinene, and the reaction mixture was stirred at 25 °C for 24 h. TME and THF were removed under aspirator vacuum (15 mm), providing $IpcBH_2$·NEt_3 (**2**, 55 mmol) as a viscous liquid. A portion of **2** (5 mmol) was methanolyzed with 0.8 mL of methanol. Oxidation with alkaline hydrogen peroxide yielded isopinocampheol: $[\alpha]^{25}_D$ −34.3° (*c* 5, benzene), 95% ee.

Preparation of Monoisopinocampheylborane (3). The above product (2 × 50 mmol) was dissolved in 20 mL of THF and 25.0 mL of 2.0 M BH_3·THF (50 mmol) added. After 4 h at 0 °C, the formation of BH_3·NEt_3 is complete, and the solution now contained free monoisopinocampheylborane, presumably as the dimer **3**.

Improved Synthesis of 2 and 3. With the usual experimental setup,[19] the reaction was carried out in a 200-mL flask. The flask was charged with BH_3·SMe_2 (10.0 mL, 100 mmol). TME (12.0 mL, 100 mmol) was added to it dropwise, keeping the flask in a water bath at 25 °C. After 20 min, dimethyl sulfide was removed under aspirator vacuum (14 mm) for 10–15 min, thereby yielding neat thexylborane (100 mmol). To this product was added triethylamine (16.8 mL, 120 mmol) at 25 °C, forming the addition compound, $ThxBH_2$·NEt_3. (+)-α-Pinene (16.0 mL, 100 mmol) was then added to the stirred reaction mixture. After the reaction mixture was stirred for 3 h at 25 °C, TME and excess Et_3N were removed under aspirator vacuum (14 mm) for 3–4 h, providing **2** (~100 mmol) as a viscous liquid. The product was then dissolved in pentane.

To **2** in pentane (12.8 mL of 1.56 M solution, 20 mmol) there was added at 25 °C BF_3·OEt_2 (2.5 mL, 20 mmol). The reaction mixture was stirred at 25 °C for 15 min. Two layers separated. when the reaction flask was cooled to −5 °C, the lower layer of BF_3·NEt_3 crystallized. The free product **3** in pentane was then decanted off to another flask by using a double-ended needle. The crystalline BF_3·NEt_3 was thoroughly washed with pentane (15 mL), and the pentane washings were transferred to the main solution. The free borane **3** thus obtained could be utilized for hydroboration.

Preparation of 2 by Dehydroboration of α-Pinene from Ipc_2BH. To a stirred solution of neat borane–methyl sulfide (2.0 mL, 20 mmol) at room temperature there was added dropwise 7.36 mL (46 mmol) of (+)-α-pinene (94% ee) over a period of 5 min. The precipitate of Ipc_2BH appeared after 5 min. After 10 min, the reaction mixture could not be stirred. To it was added 3.36 mL (24 mmol) of triethylamine, and the lumps were broken with a needle. After 45 min, the reaction mixture became homogeneous. The dehydroboration of α-pinene to form **2** is complete after 1 h at 25 °C, as is evidenced by (1) the oxidation of an aliquot, followed by GC analysis for α-pinene, and by (2) the ^{11}B NMR spectrum. The reaction mixture was put under high vacuum (0.05 mm) for 4 h. An aliquot was oxidized, and it was found to contain ~50% of α-pinene. ^1H NMR also indicated the presence of ~53% of α-pinene.

Preparation of $IpcBH_2$·TMED (4) from $IpcBH_2$·NEt_3 (2). To neat $IpcBH_2$·NEt_3 (5 mmol), prepared as before, was added at 25 °C 0.75 mL (5 mmol) of TMED at 25 °C, and the mixture was stirred for 1.5 h. The heavy white precipitate of $IpcBH_2$·TMED was collected by centrifugation, washed with cold pentane, and dried. There was obtained 1.01 g (75%) of **4**, mp 113–115 °C (recrystallized from pentane).

Preparation of 4 from $ThxBH_2$·TMED (5). To a stirred solution of 10.0 mL (10 mmol) of $ThxBH_2$·TMED in THF, prepared by adding 1.5 mL (10 mmol) of TMED to 8.5 mL (10 mmol) of $ThxBH_2$, was added at 25 °C 4.76 mL (30 mmol) of (+)-α-pinene over 5–10 min. Stirring was continued for 72 h at 25 °C to give a 95% yield of **4**. Following evaporation of THF and TME under aspirator vacuum (12 mm) for 2 h and then α-pinene at 0.05 mm for 4 h, **4** could be isolated in >90% yield as a white solid. Recrystallization from *n*-pentane yielded pure **4**, mp 113–115 °C.

The excess α-pinene could be recovered in pure form in ca. 90% yield by trapping the evaporated olefin at −78 °C.

Preparation of 4 by the Dehydroboration of α-Pinene from Ipc_2BH with TMED. With the usual experimental setup, the reaction was carried out in a 100-mL flask. The flask was then charged with 5.0 mL (50 mmol) of borane–methyl sulfide (BMS). To it was added dropwise 18.4 mL (115 mmol) of (+)-α-pinene, keeping the flask in a water bath at 25 °C. After 20 min, the formation of diisopinocampheylborane (Ipc_2BH) as a white solid was complete. To this product was added 7.6 mL (50 mmol) of TMED at 25 °C, forming $IpcBH_2$·TMED within 1 h by the displacement of α-pinene. After 1 h at 25 °C, the α-pinene and methyl sulfide were stripped off under aspirator vacuum (12 mm) for 3–4 h, providing $IpcBH_2$·TMED (**4**) as a white solid, mp 113–115 °C (recrystallization from pentane).

Preparation of 3 from 4. To 10.0 mL of $IpcBH_2$·TMED (**4**) in 2.0 M THF (20 mmol) there was added at 25 °C 5.0 mL (40 mmol) of BF_3·OEt_2. The reaction mixture was stirred for 15 min, during which time a heavy white precipitate of $2BF_3$·TMED formed. The solution containing free $IpcBH_2$ was then removed from the slurry of $2BF_3$·TMED by filtration under nitrogen through a filter chamber.[32] The solid $2BF_3$·TMED was then washed thoroughly with portions (2 × 5 mL) of THF, and the washings were transferred to the main solution. Thus a solution of **3** in THF was obtained. Reaction with 3.2 mL (80 mmol, 100% excess) of methanol evolved 36 mmol of hydrogen. Oxidation with alkaline hydrogen peroxide yielded isopinocampheol: $[\alpha]^{25}_D$ −34.1° (*c* 1.35, benzene), 95% ee.

Preparation of $2IpcBH_2$·TMED (6) of High Optical Purity. With the usual experimental setup, the reaction was carried out in a 200-mL flask. The flask was charged with 10.0 mL (100 mmol) of BH_3·SMe_2 and 65 mL of Et_2O. While the solution was stirred at room temperature, 36.8 mL (230 mmol) of (+)-α-pinene ($[\alpha]_D$ +48.05°, 94% ee) was added dropwise at such a rate that the reaction mixture refluxed gently. Following addition of α-pinene, the reaction mixture was allowed to reflux for an additional 0.5 h during which time the preparation of Ipc_2BH was complete. TMED (7.54 mL, 50 mmol) was then added, and the reaction mixture was refluxed for 0.5 h. Seedlings of $2IpcBH_2$·TMED (**6**) were then introduced into the flask by the withdrawal of an aliquot from the reaction mixture by means of a hypodermic syringe and then pushing it back into the solution (two or three times).[33] When the mixture cooled to room temperature, **6** started crystallizing out of the solution. To ensure complete crystallization, the reaction mixture was kept at 0 °C overnight. The supernatant liquid was then removed from the solid by means of a double-ended needle. The crystalline **6** was washed with pentane (3 × 25 mL), and the washings were added to the supernatant liquid. The solid was then dried under vacuum (1 h at 15 mm and 2 h at 1 mm) to yield 16.4 g (~79%) of 100% optically pure $2IpcBH_2$·TMED (**6**): mp 140.5–141.5 °C; $[\alpha]^{23}_D$ +69.03° (*c* 9.33, THF). A portion of **6** (5 mmol) in THF was methanolyzed with excess methanol and then oxidized with alkaline hydrogen peroxide to afford isopinocampheol with $[\alpha]^{27}_D$ −35.79° (*c* 0.9,

(32) The description of the filtration chamber is given on page 224 of ref 19.

(33) Seedlings of $2IpcBH_2$·TMED are needed for crystallization. The product does not crystallize out of the solution even if it is kept at 0 °C for 3 days.

benzene), a value which corresponds to ~100% ee.

The combined washings were collected, and excess methanol was added. Oxidation as before yielded isopinocampheol with $[\alpha]^{25}_D$ −30.2° (c 1.2, benzene), a value which corresponds to 84.6% ee. This result therefore indicates that the minor isomer has accumulated in the solution.

In another reaction, 2IpcBH$_2$·TMED was prepared on a 250-mmol scale, and the dehydroborated α-pinene was recovered from the washings as shown below. The volatiles (Et_2O and pentane) were removed, and the residue was then steam distilled. α-Pinene (49.5 mL, 95%) was collected. This was further purified by distillation over $LiAlH_4$ to yield 45.8 mL (88%) of pure α-pinene: $[\alpha]^{23}_D$ +47.6° (neat), ~93% ee.

Preparation of 3 from 6. For liberation of the free borane **3**, 14.6 g of **6** (35 mmol) was dissolved in 50 mL of THF, and 8.6 mL (70 mmol) of BF_3·OEt_2 was added with constant stirring. After 1.25 h at 25 °C, the precipitation of 2BF_3·TMED was complete. The solution containing free borane **3** was removed from the slurry of 2BF_3·TMED by filtration as before. The solid 2BF_3·TMED was washed with dry, ice-cold THF (3 × 9 mL), and the washings were transferred to the main solution. The filtrate was analyzed for IpcBH$_2$ by hydrolysis. The recovery of IpcBH$_2$ is 80–84%.

Preparation of 6 from 2ThxBH$_2$·TMED. Neat ThxBH$_2$ was prepared as before by adding 1.2 mL (10 mmol) of TME to 1.0 mL of 10 M (10 mmol) BH_3·SMe_2 at 25 °C for 0.5 h. To this reaction mixture was added 0.75 mL (5 mmol) of TMED followed by the addition of 2.0 mL of Et_2O, thus providing a 1.0 M solution of 2ThxBH$_2$·TMED in Et_2O. The Et_2O solvent was refluxed, and 1.6 mL (10 mmol) of (+)-α-pinene was added. The reaction mixture was refluxed for 6 h. The volatiles were then removed under aspirator vacuum (12 mm) to yield **6** in 95% isolated yield. This is then crystallized from Et_2O to yield pure **6**, mp 140–141 °C.

Preparation of 3 by the Equilibration of 1:1 α-Pinene and BH_3·THF. The reaction was carried out in a 100-mL flask. The flask was charged with 22.03 mL of 2.27 M (50 mmol) BH_3·THF and 41.4 mL of THF to make the resulting reaction mixture 0.7 M with respect to borane. (+)-α-Pinene (8.0 mL) was then added, and the reaction mixture was stirred for ~96 h at 25 °C. During this time the reaction attained equilibrium, and the equilibrium mixture contained 91% IpcBH$_2$ and 4.5% each of Ipc$_2$BH and BH_3·THF. THF was removed under vacuum and replaced by 30 mL of pentane. Addition of 0.17 mL (1.1 mmol) of TMED precipitated BH_3 as 2BH_3·TMED in 0.75 h, which was removed from the supernatant solution by filtration as before. The 2BH_3·TMED was washed with portions (2 × 5 mL) of cold pentane, and the washings were added to the main solution. Thus a solution of IpcBH$_2$ (>95%) in THF was obtained.

Acknowledgment. This investigation was supported by Grant 2 R01 GM 10937-9 from the National Institutes of Health. We are deeply indebted to Dr. E. Klein of the Dragoco Co., Holzminden, West Germany, for a generous gift of high-purity α-pinene.

Registry No. 1, 56118-59-3; 2, 64234-28-2; 3, 64234-27-1; 4, 67826-91-9; 5, 67826-89-5; 6, 67826-92-0; TMED, 110-18-9; BH_3·THF, 14044-65-6; BH_3·SMe_2, 13292-87-0; Ipc$_2$BH, 21947-87-5; 2ThxBH$_2$·TMED, 67826-90-8; (+)-α-pinene, 7785-70-8; thexylborane, 3688-24-2; isopinocampheol, 27779-29-9.

Hydroboration. 62. Monoisopinocampheylborane, an Excellent Chiral Hydroborating Agent for Trans-Disubstituted and Trisubstituted Alkenes. Evidence for a Strong Steric Dependence in Such Asymmetric Hydroborations

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Monoisopinocampheylborane (IpcBH$_2$), the first monoalkylborane chiral hydroborating agent, is capable of reacting with olefins of varying structural and steric requirements to produce, in most cases, clean dialkylboranes. IpcBH$_2$ achieves the asymmetric hydroboration of trans-disubstituted and trisubstituted olefins with exceptionally high asymmetric induction. The product alcohols, produced by oxidation of the intermediate organoboranes, exhibit enantiomeric purities in the range of 53–100% ee and reveal the same absolute configuration. Enantiomeric purities of the products increase with increasing steric requirements of the alkyl or phenyl substituent in the trans-disubstituted or trisubstituted alkene.

Organoboranes are clearly one of the most versatile organometallic intermediates for organic synthesis.[1] The stereospecificity and regioselectivity provided by monoalkyl- and dialkylboranes in the hydroboration of olefins is remarkable. This property, coupled with an asymmetric attack on the enantiotopic face of prochiral olefin by a chiral hydroborating agent makes this reaction a most valuable one for asymmetric synthesis. In fact, in 1961, the chiral hydroborating agent diisopinocampheylborane (Ipc$_2$BH, 1) marked the beginning of a practical, nonenzymatic asymmetric synthesis.[2] Prior to this time, asymmetric syntheses had been very inefficient, with the excess of one enantiomer over the other produced in the known asymmetric syntheses being generally quite small and hardly of practical utility.

Diisopinocampheylborane is currently one of the most versatile chiral reagents readily available for laboratory use.[3] It is readily prepared by the hydroboration of α-pinene with diborane,[4] BH_3·THF,[5] or BH_3·SMe_2.[6] The

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