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Isopinocampheylborane Derivatives with >99% ee via the DMAP Complex

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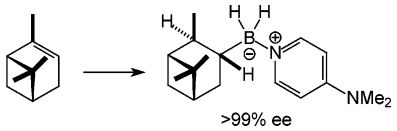
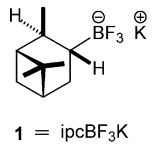


The complex **8** of isopinocampheylborane and *p*-(dimethylamino)pyridine (DMAP) can be obtained with >99% ee starting from α-pinene with 80−90% ee by hydroboration using DMAP·BH_3 (**5**) activated by 5% iodine, or by the conventional hydroboration of α-pinene, followed by addition of DMAP. Purification of the air-stable **8** is readily accomplished by crystallization from methanol. Conversion of **8** into the trifluoroborate adduct **1** using KHF_2 occurs without erosion of ee. Generation of the derived **2** in situ with TMSCl as the fluorophile also occurs with little, if any, loss of ee, as evidenced by the preparation of the salicaldimine complex **11** and the derived amino alcohol **12** with 94% ee overall.

Potassium isopinocampheyltrifluoroborate (**1**) is of interest as a potentially inexpensive precursor of the corresponding chiral Lewis acid **2** (ipcBF_2) and has been prepared from purified α-pinene via conventional hydroboration and treatment with KF.[1,2] However, the higher cost of suitably enriched pinene as compared to that of 80−90% ee material has stimulated the development of methods that upgrade ee at the stage of the alkene or after hydroboration. Brown et al. have described optimized procedures for enantiomeric enrichment of α-pinene via conversion into ipc_2BH (**3**), crystallization, and benzaldehyde-induced elimination of the α-pinene.[3] A second alternative is to generate **3** in solution and to induce cleavage to ipcBH_2 (**4**) in the presence of TMEDA under conditions that afford the crystalline 2:1 adduct of **4** with TMEDA.[4] The adduct can then be treated with BF_3 to release **4** with enantiomeric purity said to approach 100% ee starting from α-pinene with 94% ee (assay based on optical rotation after oxidative cleavage to isopinocampheol). The methodology works well, but there is a "learning curve" with both methods due to the need to crystallize and/or equilibrate air-sensitive boranes. Finally, Bir and Kaufmann have reported that α-pinene (80% ee) can be upgraded to 99% ee by direct crystallization at −130 °C with ca. 30−35% efficiency (360 mL scale).[2]

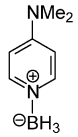


1 = ipcBF_3K

ipcBF_2 **2**

ipc_2BH **3**

ipcBH_2 **4**



5 = DMAP·BH_3

We have encountered a simple laboratory scale preparation of enantiomerically pure **1** starting from scalemic α-pinene during an investigation of catalytic activation of DMAP·BH_3 (**5**) for hydroboration. In our prior study, we had observed that pyridine borane (Py·BH_3) is activated for room-temperature hydroboration of alkenes by conversion to Py·BH_2I upon addition of a stoichiometric amount of iodine.[5] Hydroboration was also observed using catalytic iodine, but the reaction was too slow for most purposes. We have now found that DMAP·BH_3 (**5**)[6] can be activated with 3−5 mol % iodine, resulting in a convenient rate of hydroboration on a time scale of several hours at room temperature. Thus, treatment of a small excess of α-pinene with **5** in the presence of 3 mol % iodine results in consumption of much of the starting alkene after overnight stirring in dichloromethane (Scheme 1). Following the Py·BH_3 analogy, iodine reacts with **5** to generate **6** and hydroboration occurs to give **7**. Hydride transfer from **5** to **7** then takes place to afford **8** and to regenerate the reactive hydroborating agent **6** as required for a catalytic cycle. In contrast to the reaction using stoichiometric iodine, the catalytic process leads to a stable product **8** that can be isolated by simple crystallization. Stability is partly due to the effect of DMAP complexation, but it also reflects the presence of the ipcBH_2 subunit in **8** rather than the solvolytically labile ipcBHI subunit in **7**, the product of stoichiometric activation. It is worth noting that **6** must be a considerably more reactive hydroborating agent as compared to the hindered mono-alkyl analogue **7** in view of the formation of the mono-ipc derivative **8** as the dominant product. This ordering of relative reactivities is consistent with an S_N2-like hydroboration mechanism (alkene acting as the nucleophile to displace iodide), as proposed in the related case of Py·BH_2I.[5]

Crystallization of the air-stable **8** from methanol afforded material with substantially upgraded enantiomeric purity. Starting from commercial α-pinene with 91−2% ee, a single crop of **8** was collected by crystallization from methanol (59% overall yield). Oxidative cleavage of **8** to isopinocampheol using methanolic NaOOH and GLPC assay on chiral support established that this material has 97% ee. A further upgrade of **8** to >99% ee was achieved after a second crystallization (45% overall). No special precautions were needed for the isolation of pure **8**, although crystallizations had to be performed at or below 50 °C to avoid significant decomposition in methanol.

As already mentioned, ipcBH_2 (**4**) can be upgraded via the crystalline 2:1 adduct that is obtained when TMEDA is added

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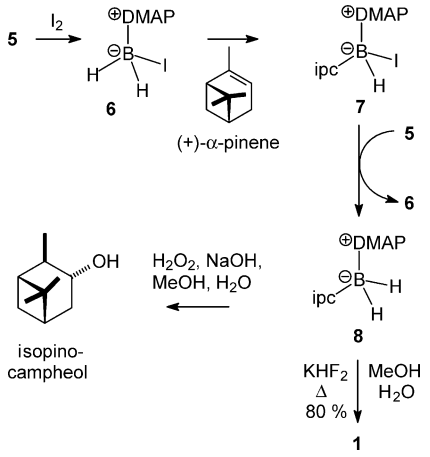
SCHEME 1



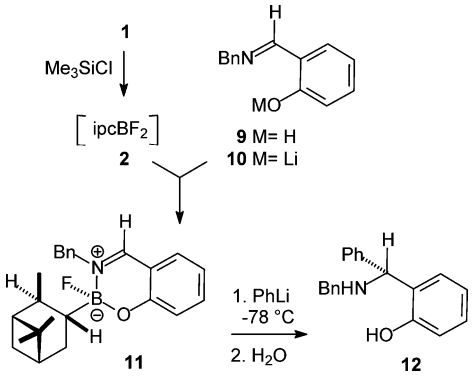
to ipc_2BH (**3**) at 35 °C. However, the 1:1 adduct of **4** and TMEDA is also known and crystallizes without upgrading enantiomeric purity under somewhat different conditions.[4b] To our knowledge, the DMAP complex **8** is the only 1:1 Lewis base:Lewis acid adduct of **4** that has been crystallized to >99% enantiomeric purity.

In view of the excellent crystallinity of **8**, the conventional hydroboration of α-pinene (92% ee) with THF·BH_3 was performed as described by Pelter et al.,[7] but the workup was modified by the addition of DMAP to afford the air-stable **8** via complexation of the initially formed $ipcBH_2$. After crystallization from methanol, **8** was obtained in 60% yield (one crop), 98.6% ee (35 mmol scale). This may be a more practical synthesis of **8** as compared to the catalytic hydroboration method using DMAP·BH_3 (**5**) because the latter reagent is not currently available from commercial sources, but the THF·BH_3 method does require maintaining inert atmosphere conditions for 4 days to equilibrate the kinetic mixture of ipc_2BH and $ipcBH_2$.[7] If desired, either the conventional or the catalytic procedure can be performed using the inexpensive grade of α-pinene, labeled as >80% ee, but this results in somewhat lower yields. Initial experiments with THF·BH_3 on 1.3 mmol scale followed by DMAP addition and crystallization gave **8** with 85−89% ee. However, **8** was isolated with 97% ee (48% obtained as the first crop) if the hydroboration and crystallization were conducted on 14 mmol scale, and recrystallization gave material with >99% ee. In view of the low cost of 80% ee α-pinene, no effort was made to recover **8** from the mother liquors in any of the hydroborations.

For the conversion to **1**, a methanolic solution of **8** (99% ee) was refluxed with aqueous KHF_2 (3 h).[8] The starting **8** was consumed and nonaqueous workup gave the desired potassium trifluoroborate salt **1** in 80% yield as a colorless powder. Attempts to recrystallize this material were not successful, thereby underscoring the importance of ee upgrade by crystallization at the stage of the relatively more soluble **8.** Oxidation of **1** with basic hydrogen peroxide provided isopinocampheol with 99% ee, confirming that the sequence from **8** to **1** occurs without compromising enantiomeric purity.

To show that **1** can serve as an in situ source of **2** with retention of enantiomeric purity, we have briefly investigated

SCHEME 2



the sequence from salicaldimine **9** to the chiral complex **11** and the subsequent reaction with phenyllithium (Scheme 2). It was necessary to activate both components to achieve the conversion to **11**. This was accomplished by deprotonation of **9** with *n*BuLi to **10**, and by treatment of **1** with 1 equiv of trimethylchlorosilane as the fluorophile to release the reactive difluoroborane **2** in situ.[9,10] Trituration of crude **11** with hexane afforded a pale yellow powder that was characterized by NMR analysis at −10 °C as a single isomer. The spectrum remained unchanged at 0 °C for up to 30 min, but signals of a second isomer appeared upon warming to room temperature, resulting in a 3:1 equilibrium ratio within an hour. These observations are consistent with crystallization-induced asymmetric transformation via reversible epimerization at boron during the isolation of **11**, as observed in analogous systems.[9] The relative configuration of the crystalline isomer obtained starting from (1*R*)-α-pinene was established by X-ray crystallography as (R_B)-2-fluoro-2-isopinocampheyl-3-benzyl-2*H*-benzo[*e*]-1,3,2-oxaza-boratane (**11**).

Addition of phenyllithium to **11** provided the known chiral amine **12** in 65% yield and 94% ee according to HPLC assay on chiral support. The configuration of **12** was deduced from comparison of the sign of optical rotation with a literature report[11,12] and corresponds to least hindered attack of PhLi away from the ipc substituent at boron in **11**.

In summary, the formation of the isolable DMAP complex **8** via conventional or catalytic hydroboration provides convenient access to >99% enantiomerically pure derivatives of $ipcBH_2$ on laboratory scale. The catalytic procedure is especially easy and involves minimal handling of trivalent boranes. The sequence from **8** to **1** to derivatives such as **2** and **12** can be carried out with retention of absolute configuration.

Experimental Section

Isopinocampheylborane-4-(dimethylamino)pyridine Complex 8 (DMAPBH_2·ipc). Method A (from (*R*)-(+)-α-Pinene, Sold as 91%+ ee, Using BH_3·THF). Using the method of Pelter et al.,[7] BH_3·THF, 1 M in THF (35.0 mL, 35.0 mmol) was added dropwise by syringe at 0 °C to a stirred solution of (*R*)-(+)-α-pinene (91%+ ee, 5.55 mL, 35.0 mmol) in THF (9.45 mL) under a static nitrogen

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(9) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

(10) If **1** was activated with 2 equiv of trimethylsilyl chloride, a cyclic difluoroborate complex derived from **10** was obtained (78%), perhaps resulting from **2** via retro-hydroboration.

(11) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361.

(12) The optical rotation of **12** with 94% ee was $[\alpha]_D = -141.0$, while ref 11 reports $[\alpha]_D = -34.9$ for material of unstated purity, obtained by classical resolution.

atmosphere to make the solution 0.7 M in both reagents. After gentle nitrogen flush, nitrogen lines were removed, the septa were secured with wire and wrapped with Parafilm, and the borane solution was equilibrated by stirring at room temperature for 96 h. The septum was then removed while flushing under a slow nitrogen flow, and DMAP (4.27 g, 35.0 mmol) was added as a solid in several portions. After the exotherm had subsided, stirring was continued for 3 h at room temperature. The solvent was then removed (rotary evaporator) until the product had crystallized to give a thick slurry. The mixture was then filtered under vacuum to collect the solid product, using minimal cold THF to rinse the flask; analytical TLC on K6F silica gel 60A, 1:1 hexane/EtOAc, $R_f = 0.33$. Pure material was obtained by recrystallization from methanol (260 mL, ~7.5 mL/mmol), dissolution by warming at 50 °C, followed by crystallization overnight in the freezer (**Caution**: Temperatures above 50 °C result in decomposition of **8** by methanolysis). The crystalline product was collected by vacuum filtration, rinsed with 10−20 mL of cold (0 °C) methanol, and air-dried to give 5.73 g (60%) of **8** as colorless needles, mp 129.5−131.5 °C, dec; electrospray ESMS for $C_{17}H_{29}N_2BNa$ (M + Na), $m/z = 295.2325$, error 1 ppm; IR (neat, cm^{-1}) 2300, B−H; 2285, B−H; 400 MHz NMR ($CDCl_3$, ppm) δ 8.13 (2H, d, $J = 7.3$ Hz), 6.50 (2H, d, $J = 7.3$ Hz), 3.10 (6H, s), 2.90−2.10 (2H, br), 2.17−2.10 (1H, m), 1.88−1.72 (3H, m), 1.70−1.65 (1H, m), 1.56−1.48 (1H, m), 1.13 (3H, s), 1.06 (3H, s), 0.86−0.72 (1H, br), 0.79 (3H, d, $J = 7.3$ Hz), 0.75 (1H, d, $J = 9.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.8, 146.4, 106.1, 49.3, 42.7, 41.8, 39.4, 39.4, 33.4, 29.4 br, 28.4, 23.0, 22.8; ^{11}B NMR (115.5 MHz, $CDCl_3$, ppm) δ −2.3 (br, $W_{1/2} = 340$ Hz). Oxidative cleavage of a sample of the crystallized material as described below gave isopinocampheol with 98.6% ee.

Method B (from (*R*)-(+)-α-Pinene, Sold as 80%+ ee, Using BH_3·THF). A 1 M solution of BH_3 in THF (14.0 mL, 14.0 mmol) was added dropwise by syringe at 0 °C to a stirred solution of (*R*)-(+)-α-pinene (80%+ ee, 2.22 mL, 14.0 mmol) in THF (3.8 mL) in a nitrogen-flushed flask equipped with a condenser topped with a septum and vented to a nitrogen bypass line. After 30 min, the solution of hydroboration products was equilibrated by warming to 50 °C for 4 h, and was then cooled to 0 °C. Solid DMAP (1.71 g) was added in several portions to the stirred mixture as described under Method A. After the initial exotherm had subsided, the solution was allowed to warm to room temperature and was stirred overnight. Isolation of the crude product was performed as described under Method A. The resulting solid product was stirred with methanol (40 mL) and warmed to 50 °C. More methanol was slowly added (ca. 35 mL) until the solids dissolved. After being cooled in the freezer, a first crop of crystals was collected and rinsed with ca. 10 mL of cold methanol to give **8** (1.84 g, 48%), identical by NMR spectroscopy to material obtained according to method A. Oxidative cleavage and ee assay of the isopinocampheol product as described below indicated 97% ee.

Preparation of 8 by Hydroboration of α-Pinene Using DMAP·BH_3 (5) and Catalytic Iodine. DMAP·BH_3 (**5**) was prepared by complexation of DMAP and BH_3·THF in toluene or THF, followed by evaporation of the solvent to dryness.[6] Recrystallization of **5** from methanol/chloroform provided colorless plates of high purity, but it was not necessary to recrystallize **5** for the pinene hydroborations if freshly prepared reagent was used. Thus, iodine (83.5 mg, 0.33 mmol) was added to a solution of **5**[6] (1.49 g, 11 mmol) in dichloromethane (30 mL). After the gas evolution had ceased, (*R*)-(+)-α-pinene (sold as 91%+ ee, 2.09 mL, 13.2 mmol) was added. After 15 h, the reaction was poured into saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with DCM (2 × 30 mL), and the extracts were dried through a column of Na_2SO_4 (4 × 2 cm) and concentrated (aspirator). Pure **8** was obtained as before by crystallization from methanol (80 mL) to give 1.75 g (59%) of product. Oxidative cleavage of a sample of the crystallized material as described below gave isopinocampheol with 97% ee.

Determination of Optical Purity of 8. The isolated DMAP·BH_2ipc, **8** (20 mg), was dissolved in MeOH (4 mL) and treated successively with NaOH (15% aq, 0.2 mL) and H_2O_2 (30% aq, 0.2 mL). A colorless granular precipitate formed over 1 h. After 14 h, the MeOH was removed by a stream of N_2. The residue was diluted with water (6 mL), acidified with HCl (2 N, 1 mL), and extracted with DCM (3 × 6 mL). The extracts were dried through a column of Na_2SO_4 (2 × 2 cm) and concentrated (aspirator) to provide crude isopinocampheol (~90%). GLC analysis on chiral support indicated >99% ee: Supelco Alpha Dex 120 Capillary column; 30 m × 0.25 mm; isothermal 90 °C; 2 mL/min; t_R (minor) = 19.1 min; t_R (major) = 19.8 min.

Potassium Isopinocampheyltrifluoroborate (KipcBF$_3$) (1). Using the published method,[8] a solution of potassium hydrogen fluoride (KHF_2, 3.87 g, 49.5 mmol) in water (10 mL) was added to a slurry of DMAP·BH_2ipc (**8**) (3.37 g, 12.4 mmol) in MeOH (120 mL). Gas was liberated and a thick sludge formed. The reaction was heated to reflux for 3 h over which time the sludge dissolved. The reaction was cooled to room temperature and concentrated (aspirator). The solid residue was slurried in $CHCl_3$ (100 mL) and filtered through a glass frit. The solids were washed with $CHCl_3$ (100 mL) and benzene (2 × 100 mL) to remove the DMAP. The product salt was washed from the frit with CH_3CN (2 × 100 mL). Evaporation of the CH_3CN solution to dryness provided 2.39 g (79%) of pure KipcBF$_3$ (**1**) as a colorless powder. The NMR data were consistent with the literature.[1]

(R_B)-2-Fluoro-2-isopinocampheyl-3-benzyl-2*H*-benzo[*e*]-1,3,2-oxazaboratane (11). Trimethylsilyl chloride (245 μL, 1.93 mmol) was added to a solution of potassium isopinocampheyltrifluoroborate (**1**) (471 mg, 1.93 mmol) in THF (5 mL), and the solution turned cloudy. In a separate flask, *n*-butyllithium (1.51 M in hexanes, 1.41 mL, 2.12 mmol) was added at 0 °C to a solution of aldimine **8** (448 mg, 2.12 mmol) in THF (5 mL). The red solution was then added via a cannula to the cloudy solution of ipcBF$_2$, which turned yellow in color. After 1 h, the reaction was quenched with water (15 mL) and extracted with DCM (3 × 15 mL). The extracts were dried through a column of Na_2SO_4 (2 × 2 cm) and concentrated (aspirator) to give 840 mg of a thick yellow gum. Pure material was obtained by trituration with hexane to give 332 mg of aldimine borane complex (**11**) (46%), mp 148.5−150 °C, pale yellow powder. EIMS for $C_{24}H_{30}BFNO$ (M + 1), $m/z = 378.2397$, error = 2 ppm; IR (neat, cm^{-1}) 1648, C=N; 400 MHz NMR (−10 °C, $CDCl_3$, ppm) δ 7.76 (1H, s), 7.50−7.42 (4H, m), 7.39−7.35 (2H, m), 7.08 (1H, dd, $J = 7.7$, 1.5 Hz), 6.97 (1H, d, $J = 8.4$ Hz), 6.79−6.73 (1H, m), 5.00 (1H, d, $J = 15.8$ Hz), 4.76 (1H, d, $J = 15.8$ Hz), 2.45−2.36 (1H, m), 2.20−2.10 (1H, m), 1.82−1.68 (4H, m), 1.40−1.33 (1H, m), 1.21−1.12 (6H, m), 1.07 (3H, s), 0.97 (1H, d, $J = 9.2$ Hz); ^{13}C NMR (100 MHz, −10 °C, $CDCl_3$, ppm) δ 162.1, 160.2, 137.9, 132.7, 131.5, 130.5, 129.4, 129.1, 119.0, 118.4, 115.1, 55.5, 48.2, 41.2, 38.9, 36.7, 32.3, 28.1, 28.4, 26.7, 23.8, 22.8; ^{19}F NMR (362 MHz, −10 °C, $CDCl_3$, ppm) δ −147.4 (br).

Amine 12 by Phenyllithium Addition to 11. THF (2.5 mL) was cooled to −78 °C and transferred via a cold cannula to a cold (−78 °C) flask containing aldimine−borane complex (**11**) (40.7 mg, 0.108 mmol). Phenyllithium (1.27 M in cyclohexane/ether, 0.170 mL, 0.216 mmol) was diluted with THF (1 mL), cooled to −78 °C, and then transferred via a cold cannula to the solution of borane complex. A bright pink color developed. After 30 min, the reaction was quenched with water (6 mL) and extracted with DCM (3 × 8 mL). The extracts were dried through a column of Na_2SO_4 (2 × 2 cm). After removal of the solvent (aspirator), the residue was purified by PLC on silica 60A (20 × 20 × 0.1 cm), 4:1 hexane/EtOAc eluent to provide 20.4 mg (65%) of **12**; analytical TLC on K6F silica gel 60A, 4:1 hexane/EtOAc, $R_f = 0.51$. The NMR data were consistent with those published in the literature,[11] but $[\alpha]_D = -141.0$ ($c = 1.23$, $CHCl_3$) was higher than reported; lit. for (*R*) $[\alpha]_D = -34.9$ ($c = 2.3$, $CHCl_3$), obtained by classical resolution.

Analysis of **12** by HPLC on a chiral stationary phase (Chiralpak AD column; 3% IPA in hexane eluent; 1 mL min^{-1}) indicated 94% ee; t_R (minor) = 17.2 min, t_R (major) = 18.1 min.

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Supporting Information Available: NMR spectra of new compounds; HPLC assay data for **12**; ORTEP and X-ray structure data for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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