Isopinocampheylchloroborane: A Promising New Reagent for Asymmetric Cyclic Hydroboration. A Simple Procedure To Convert 1-Allyl-1-cyclohexene into *trans*-1-Decalone of ≥99% Optical Purity

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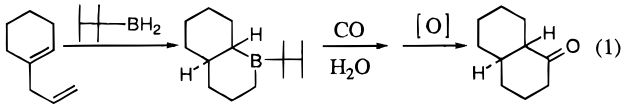
In the past, boron annulation *via* cyclic hydroboration has been studied in considerable detail by our group.[2] This reaction has emerged as an important synthetic tool in the synthesis of natural products.[3,4] A general stereospecific synthesis of *trans*-fused bicyclic ketones of different classes has been reported *via* the cyclic hydroboration−carbonylation protocol of representative dienes with thexylborane ($ThxBH_2$) (eq 1).[2]



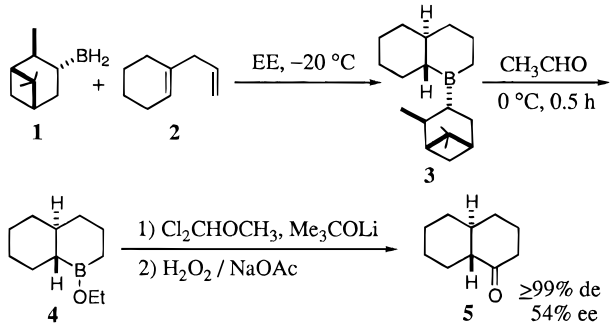
(1)

A large number of natural products possess *trans*-fused polycyclic systems in their structures,[3] and simple, efficient methods to synthesize such ring systems in a high stereo- and enantioselective manner are highly desirable.

It appears that there is no literature precedence for achieving asymmetric cyclic hydroboration as a powerful and convenient synthetic tool for the stereo- and enantioselective production of such synthetically useful *trans*-fused polycyclic systems. Accordingly, we examined the possibility of asymmetric cyclic hydroboration of dienes by replacing the thexyl group of $ThxBH_2$ by the optically pure α-pinene moiety, utilizing the chiral hydroborating agent isopinocampheylborane ($IpcBH_2$, **1**).[5,6] The synthesis of optically active *trans*-1-decalone (**5**) was selected as a trial case to test the practicality of achieving the asymmetric cyclic hydroboration of the diene, 1-allyl-1-cyclohexene (**2**), with $IpcBH_2$. Earlier reports have described tedious routes for the synthesis of *trans*-1-decalone involving resolution procedures,[7,8] emphasizing the value of achieving a general asymmetric synthesis of this versatile synthon.

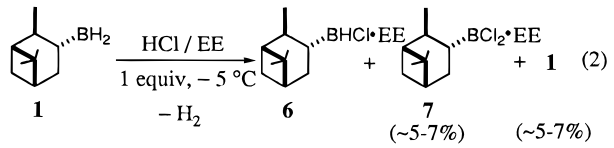
Optically pure isopinocampheylborane (**1**) was conveniently prepared *via* hydroboration of (+)-α-pinene.[6] Cyclic hydroboration of the diene **2** with $^d IpcBH_2$ (**1**) in diethyl ether (EE) at −20 °C formed the corresponding

Scheme 1



cyclic trialkylborane **3**. The trialkylborane on treatment with acetaldehyde[9] underwent a clean, facile elimination of the chiral auxiliary, α-pinene, to form the corresponding cyclic borinate ester **4**. The borinate ester **4** reacted smoothly with α,α-dichloromethyl methyl ether (DCME) in the presence of lithium *tert*-butoxide (the DCME reaction)[10] to yield, after oxidation with buffered hydrogen peroxide, optically active (+)-*trans*-1-decalone in ≥99% de and 54% ee[11] (Scheme 1).

Consequently, the asymmetric induction realized with isopinocampheylborane was only moderate. This result encouraged us to examine modification of the $^d IpcBH_2$ reagent in the hope of achieving improved optical yields. Literature reports[10,11] suggest that the steric and electronic environment around the boron atom in pinene-based reagents must be critical for achieving a high degree of stereoselection in asymmetric hydroboration. Accordingly, we decided to explore the effect of introducing a chlorine atom for one of the hydrogen atoms on the boron atom of the reagent $^d IpcBH_2$. Thus, the reaction of $^d IpcBH_2$ with a stoichiometric amount of ethereal hydrogen chloride provided isopinocampheylchloroborane etherate ($^d IpcBHCl{\cdot}EE$) (**6**) in EE at −5 °C. Systematic investigation of this new reagent showed that $^d IpcBHCl{\cdot}EE$ always exists in equilibrium with small amounts of $IpcBH_2$ and $IpcBCl_2{\cdot}EE$ **7** (∼5−7% each)[14] (eq 2).



(2)

An additional advantage of $IpcBHCl{\cdot}EE$ is that it permits sequential hydroboration. Thus, the hydroboration of 1-allyl-1-cyclohexene (**2**) with $^d IpcBHCl{\cdot}EE$ provides the corresponding isopinocampheylalkylchlo-

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(5) This molecule actually exists in solution as a dimer. However, it is convenient to represent in the monomeric form.

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(11) The optical purity of ketone **5** was determined by analyzing the ketal, which was obtained by the reaction of ketone **5** with optically pure (*S*,*S*)-2,3-butanediol and chlorotrimethylsilane at −10 °C, by capillary GC in comparison with its 1:1 diastereomeric ketals obtained from racemic ketone **5**. Kirk *et al.*[8] have established the absolute configuration of *trans*-1-decalone (**5**). Thus, in accord with the sign of the rotation of the this ketone **5**, obtained by the asymmetric cyclic hydroboration, its absolute configuration should be (9*R*,10*S*).

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(14) Preliminary experiments in asymmetric hydroboration of representative alkenes reveal that $IpcBHCl{\cdot}EE$ is frequently a superior chiral hydroborating reagent compared to $IpcBH_2$. Dhokte, U. P.; Kulkarni. S. V.; Brown, H. C. Research in progress.

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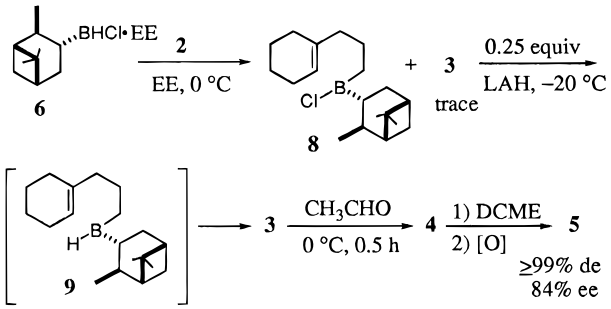
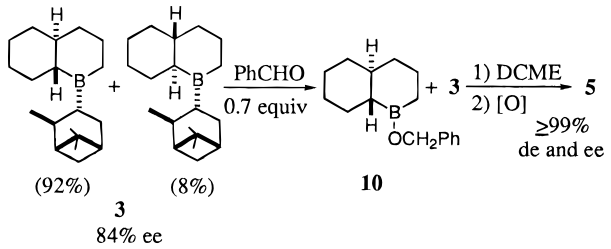
Scheme 2



Scheme 3

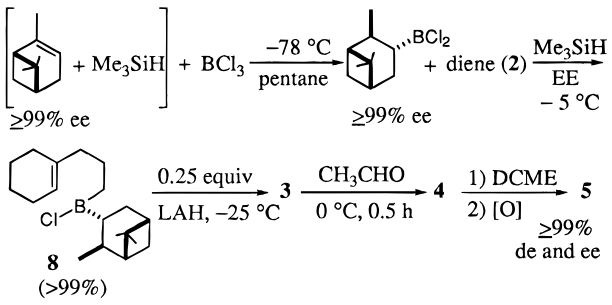


roborane (**8**) predominantly, along with only trace amounts of the trialkylborane **3**. This dialkylchloroborane (**8**) on treatment with 0.25 equiv of $LiAlH_4$ at −20 °C undergoes smooth hydridation[15] with the precipitation of LiCl, forming the corresponding dialkylborane **9** *in situ*, which then undergoes a facile intramolecular cyclic hydroboration to furnish the desired cyclic trialkylborane **3**. Elimination of (+)-α-pinene from **3** by treatment with acetaldehyde, followed by the DCME reaction as described above, affords the (+)-*trans*-1-decalone (**5**) in ≥99% de and 84% ee (Scheme 2).

Thus, the use of preformed ^{d}IpcBHCl·EE improves the optical yield of (+)-*trans*-1-decalone to 84% ee. We had previously established that the controlled treatment of diastereomeric isopinocampheylalkylborinic esters with an aldehyde upgrades the optical purity of the product borinate ester *via* kinetic resolution.[16] Indeed, treatment of the diastereomeric trialkylborane **3** (92:8) with 0.7 equiv of PhCHO, followed by applying the DCME reaction[17] to the resulting borinate ester **10**, provides (+)-*trans*-1-decalone (**5**) in ≥99% ee (Scheme 3).

Although synthesis of *trans*-1-decalone in ≥99% ee had been achieved by this upgradation procedure, we decided to investigate the formation of pure IpcBHCl. Since the preformed IpcBHCl·EE (≥99% ee, 85−90% pure, eq 2) reagent, produced as an equilibrium mixture, provides ketone **5** in only 84% ee, it was thought that the decreased ee might be due to the ~5−7% $IpcBH_2$ present in the equilibrium mixture. Therefore, we undertook the modification of the synthesis of IpcBHCl·EE to provide this reagent without the presence of $IpcBH_2$. In that case the asymmetric hydroboration of 1-allyl-1-cyclohexene might provide the optically pure *trans*-1-decalone. Stable, optically pure isopinocampheyldichloroborane[18] (^{d}$IpcBCl_2$, ≥99% ee) was prepared by the reaction of boron trichloride (BCl_3), trimethylsilane, and (+)-α-pinene (≥99% ee).[19] *In situ* reduction of ^{d}$IpcBCl_2$ with trimethylsilane

Scheme 4



provides the intermediate IpcBHCl which immediately hydroborates diene **2**, present in the reaction, in EE at −5 °C, to provide the dialkylchloroborane **8** exclusively, without contamination with trialkylborane **3** (Scheme 4).[20]

The pure dialkylchloroborane intermediate (**8**, ≥99%) is subjected to hydridation with 0.25 equiv of LAH at −25 °C in EE for 4 h to provide the trialkylborane **3**. This trialkylborane **3**, following the same reaction sequence shown in Schemes 2 and 3, provides (+)-*trans*-1-decalone (**5**) in ≥99% de and ee.[20] Consequently, we had achieved the synthesis of (+)-*trans*-1-decalone in essentially ≥99% ee from the *in situ* generated ^{d}IpcBHCl produced from the reaction of $IpcBCl_2$·EE with trimethylsilane in EE in the presence of 1-allyl-1-cyclohexene. Therefore, asymmetric cyclic hydroboration now provides a highly efficient, simple, and promising synthetic route to *trans*-fused bicyclic systems in high enantiomeric purity. We are currently testing the applicability of this synthesis to other dienes previously cyclized, in our earlier achiral cyclic hydroboration, to provide optically pure *trans*-fused bicylic ketones.[2]

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(17) The DCME reaction−oxidation process transforms borinate esters **10** into ketones and trialkylboranes into a tertiary alcohols.

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(20) The typical procedure for *in situ* generated IpcBHCl·EE, obtained from the reduction of $IpcBCl_2$ with trimethylsilane (TMS) in EE, and its hydroboration with 1-allyl-1-cyclohexene: Neat $IpcBCl_2$ (2.19 g, 10 mmol) was placed in a flask and cooled to −5 °C, and cold (0 °C) EE (9.0 mL) was added. To this resulting $IpcBCl_2$·EE was added diene **2** (1.34 g, 11 mmol), followed by liquid trimethylsilane (0.74 g, 10 mmol, collected at −78 °C). The reaction mixture was stirred for 10 min and brought to ambient temperature. ^{11}B NMR showed the formation of dialkylchloroborane (δ 76−77) exclusively. Volatiles of the reaction mixture were removed by applying aspirator vacuum, and dry EE (9 mL) was introduced in the flask and cooled to −25 °C. LAH in EE (1.0 M, 2.5 mL) was added from the side of the flask. The reaction mixture was stirred for 4 h and warmed to ambient temperature; ^{11}B NMR showed clean formation of trialkylborane (δ 84). Acetaldehyde (20 mmol) was added at 0 °C, and the mixture was stirred for 30 min; ^{11}B NMR indicated the formation of borinate ester (δ 52). Volatiles were removed by applying aspirator vacuum. The borinate ester was taken in EE (10 mL), and the clear EE solution containing the borinate ester was transferred into another flask and cooled to 0 °C. α,α-Dichloromethyl methyl ester (1.72 g, 15 mmol) was added followed by the dropwise addition of lithium *tert*-butoxide (22 mmol) in *n*-hexane, obtained from *tert*-butanol and *n*-butyllithium, with stirring. The mixture was stirred at 0 °C for 30 min and then at 25 °C for 2 h. The reaction mixture was washed with water (4 × 20 mL) to make it neutral and subjected to oxidation with 3 M NaOAc (4.5 mL) and 30% H_2O_2 (4.5 mL) at 0 °C for 15 min, followed by heating under reflux for 2 h. The mixture was diluted with EE (40 mL), washed with water (4 × 10 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was removed and the residue distilled (64−66 °C, 0.5 mmHg) to afford (+)-*trans*-1-decalone (1.13 g, 74% yield) and a small amount of crude material further purified by preparative GC: mp 41−2 °C (lit.[8] mp 43 °C); $[\alpha]^{23}_D$ +10.2 (*c* 0.53, EtOH) (lit.[8] $[\alpha]^{23}_D$ −10 ± 1 (*c* 0.55, EtOH)).