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Selective Reductions. 46. Effect of the Steric Requirement at the
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January 17, 1991

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Selective Reductions. 46. Effect of the Steric Bulk at the 2-Position of Apopinene on Chiral Reductions. *B*-Iso-2-ethyl- and *B*-Iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane as Improved Reagents for the Chiral Reduction of α,β -Acetylenic Ketones and α -Keto Esters

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B-Iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonane (Eapine-Borane), and *B*-Iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane (Prapine-Borane), prepared *via* the hydroboration of 2-ethylapopinene or 2-*n*-propylapopinene, respectively, with 9-borabicyclo[3.3.1]nonane, reduce prochiral α,β -acetylenic ketones and α -keto esters to the corresponding alcohols with significantly higher optical induction than does Alpine-Borane. (-)-2-*n*-Propylapopinene was synthesized by treating nopyl tosylate with dimethylcuprate prepared *in situ* from methyl lithium and cuprous iodide. (+)-2-*n*-Propylapopinene was synthesized by Schlosser metallation of (+)- α -pinene followed by treatment with ethyl iodide. 4-Phenyl-3-butyne-2-one was reduced to the corresponding propargylic alcohol in 89% ee and 96% ee by Eapine-Borane and Prapine-Borane, respectively, as compared to 82% ee with Alpine-Borane. Similar improved results were realized in the reduction of other acetylenic ketones by Eapine-Borane and Prapine-Borane. Similar improvements in the optical yields were realized in the reduction of α -keto esters by Eapine-Borane. For example, while Alpine-Borane produced methyl and ethyl lactate in 92% and 91% ee, respectively, Eapine-Borane gave these alcohols in 97% and 96% ee, respectively. Unfortunately, Prapine-Borane shows no improvement in %ee for the reduction of α -keto esters. The increase in the % ee realized is tentatively attributed to the increased steric bulk of the alkyl group at the 2-position of apopinene.

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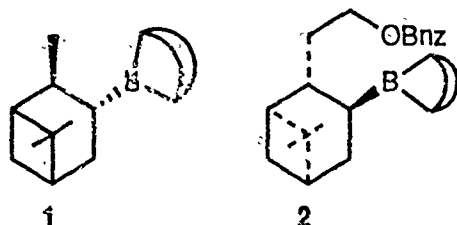
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Introduction

A branch of asymmetric synthesis that has been actively pursued during the last decade is the asymmetric reduction of prochiral ketones.² Various reagents have been developed in the past which provide the product alcohols in good to excellent enantiomeric excess (ee). A compilation of the available literature data showed the absence of a single reagent which is equally effective for all classes of ketones.³ Moreover, no strategic modifications based on observed results have been made. Consequently, we set out to design chiral organoborane reagents based on the knowledge of the behavior of available reducing agents.

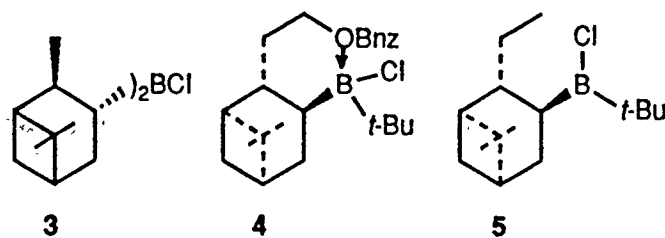
Midland's *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane, **1**), introduced a decade ago, proved very efficient for the chiral reduction of α -deuteroaldehydes,⁴ α,β -acetylenic ketones,⁵ α -keto esters,⁶ and α -halo ketones,⁷ all of which undergo relatively rapid reduction. However, the reagent proved ineffective for the chiral reduction of slower reacting ketones, such as aralkyl and dialkyl ketones. This variation in the chiral inductions of slow versus fast reacting ketones was attributed to the dissociation of the reagent into its components, α -pinene and 9-BBN with the less reactive ketones resulting in achiral reduction.⁸ The dehydroboration is suppressed by conducting the reductions under neat conditions which increases the rate of reduction and thus the chiral induction.⁹



Midland later introduced NB-Enamine (**2**), an efficient chiral reducing agent for the reduction of α,β -acetylenic ketones, as a low-cost alternative to Alpine-Borane prepared from (–)- α -pinene.¹⁰

A comparison of the enantiomeric excesses of the product alcohols obtained from the reduction of prochiral acetylenic ketones shows that **2** achieves slightly higher chiral induction than **1**, though the rates of reduction with **2** are slower. No explanation was provided for the slight increase in the induced chirality achieved by **2**.

To overcome the slow rate of reaction of **1**, we designed a reagent with increased Lewis acidity, *B*-chlorodiisopinocampheylborane (Ipc_2BCl , **3**), a superior reagent for the chiral reduction of aralkyl ketones and α -quaternary alkyl ketones.¹¹ Reagent **3** was then modified by substituting one of the isopinocampheyl moieties with alkyl groups of increasing steric requirement, such as Me, Et, *i*-Pr, *t*-Bu, and Thx.¹² Based on the tentative transition state model for the reductions using **1** and **3**, [iso-2-[2-(benzyloxy)ethyl]apopinocampheyl]-*tert*-butylchloroborane (**4**), was developed.¹³ This reagent reduces ketones to the corresponding alcohols with high induction, but the slow rates of reductions make application of the reagent impractical. The slowness of the rates with **4** were attributed to the internal coordination of the ether oxygen atom to the boron atom of the reagent. Consequently, iso-2-ethylapopinocampheyl-*tert*-butylchloroborane (**5**) was synthesized.¹³ The rates improved considerably and the chiral inductions were comparable to those obtained with **4**.

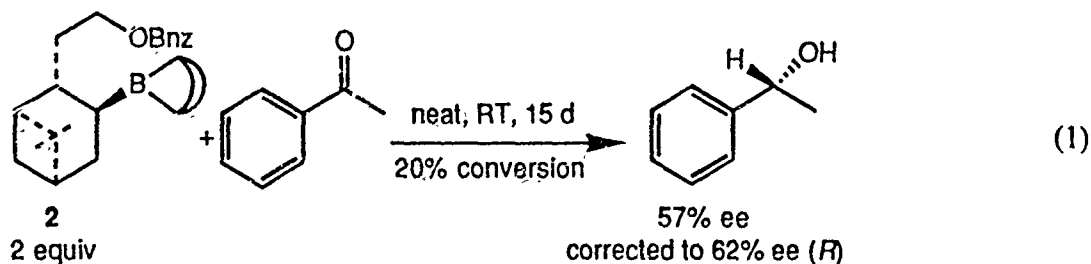


The retarded rate of reduction with **2** can be attributed to the effect of the increased steric bulk of the alkyl group at the 2-position of apopinene, by hindering the coordination of the carbonyl oxygen atom with boron.¹³ Consequently, the increase in the chiral efficiency is achieved at the cost of a decrease in rate. In the present study, reduction of the representative standard ketones³ with **2** was performed, but the reaction rates were too slow to be of any practical use. For example, methyl benzoylformate requires 4 days for 80% reaction, providing alcohol of only 84% ee. Thus NB-Enantrane is a practical reagent only for the reduction of α,β -acetylenic ketones. Earlier results realized with **5** demonstrated that the chiral outcome is comparable to those of **4**, while the rates are considerably faster for the ethyl analogue.¹³ An analogous behavior could be expected for the trialkylborane reagents, i.e. an increase in the steric bulk at the 2-position of the apopinocampheyl moiety in Alpine-Borane should provide better reagents for chiral reduction. To test these, the 9-BBN

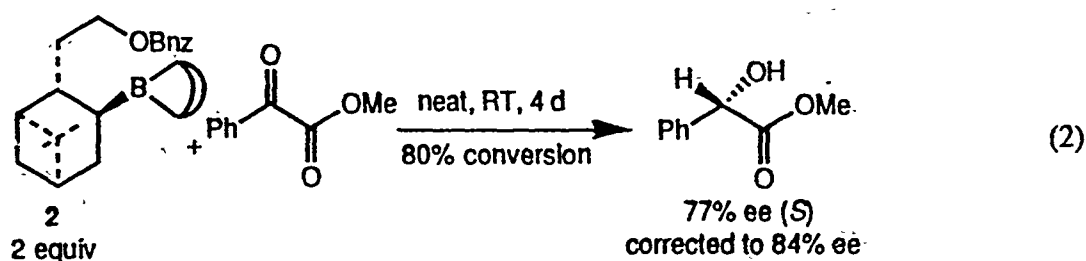
derivatives of 2-ethylapopinene and 2-*n*-propylapopinene were prepared as likely candidates for improved chiral reducing agents.

Results and Discussion

Reductions Using NB-Enantrane. While NB-Enantrane (**2**) is an excellent reagent for the reduction of prochiral α,β -acetylenic ketones, it has not been tested for any other class of ketone to date. In order to fully understand the utility of **2** as a reducing agent, it was screened against our standard series of ketones.³ The reductions were performed under neat conditions at room temperature using two equiv of the reagent and were monitored by ^{11}B NMR spectrum of an aliquot of the reaction mixture dissolved in ethyl ether (EE). Upon completion of the reaction, the excess reagent was destroyed with acetaldehyde and the alcohol isolated using an ethanolamine workup. The liberated alcohol was distilled and analyzed as its α -methoxy- α -(trifluoromethyl)phenylacetate (MTPA)¹⁴ or (-)-menthylchloroformate (MCF)¹⁵ derivative on a capillary GC column. For example, the reduction of acetophenone with **2** proceeded to 20% completion in 15 days to provide (*R*)- α -phenethanol of 62% ee after correcting for the optical purity of the nopol used (92% ee).

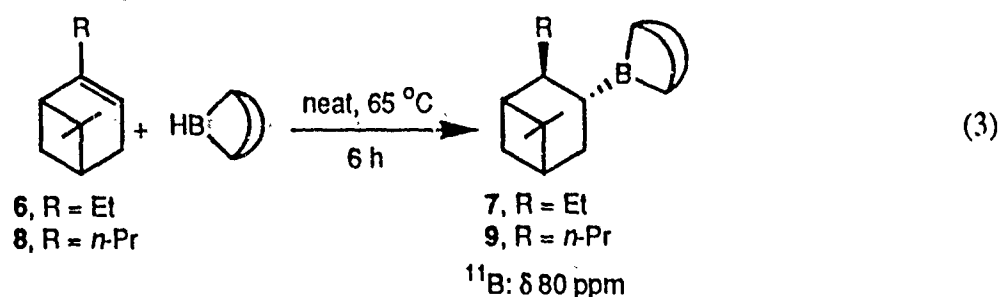


3-Methyl-2-butanone reacted similarly, proceeding to only 30% completion in 15 days; the alcohol produced was 30% ee. 2-Chloroacetophenone was reduced, 50% in 15 days, to the corresponding chlorohydrin of 92% ee. Even methyl benzoylformate required 4 days for 80% reaction giving alcohol of 84% ee (eq 2). Midland had reported 86% ee for the reduction of 4-phenyl-3-butyne-2-one based on $\text{Eu}(\text{hfc})_3$ shifted NMR.¹⁰ We repeated the reaction and obtained a value of 78% ee, corrected to 85% ee. The results are summarized in Table I.



Having established that **2** is effective only for the reduction of α,β -acetylenic ketones, we turned our attention to the preparation and study of *B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonane (**7**), and *B*-iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane (**9**).

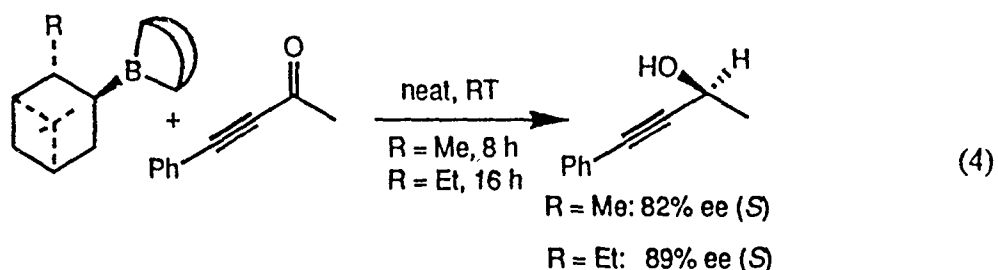
***B*-Iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonane (Eapine-Borane, 7).** The reagent was prepared using the same procedure as for the preparation of Alpine-Borane,⁹ *via* hydroboration of (+)- or (-)-2-ethylapopinene (**6**)¹⁶ with 9-BBN at 65 °C under neat conditions (eq 3). The hydroboration was complete in 6 h as indicated by the ¹¹B NMR spectrum (broad singlet at δ 80 ppm). Treatment of reagent **7** with acetaldehyde liberated the starting olefin **6**, whose spectral properties were identical to an authentic sample, thus indicating that no rearrangement or isomerization occurred under the hydroboration conditions. Also, the iso-2-ethylapopinocampheol derived from the reagent *via* alkaline hydrogen peroxide oxidation showed identical spectral and gas chromatographic characteristics of authentic iso-2-ethylapopinocampheol.



Upon treatment with the standard ketones, reagent **7** reacted at a faster rate than NB-Enantrane as expected, but at a slightly slower rate than Alpine-Borane. For example, acetophenone was reduced in 20 days with 100% excess reagent under neat conditions. The usual work-up provided (*R*)- α -phenethanol of 78% ee. The unexpectedly lower induction observed in the reduction of

acetophenone with **7** as compared to **1** might be accounted for by the slower rate of reduction, thus favoring the dehydroboration mechanism. Dehydroboration might be facilitated by relief of the increased steric interaction of the 2-ethyl group and the cyclobutane portion of the apopinanyl moiety in the reagent.¹⁷ Similar results were realized in the reduction of other standard ketones. 3-Methyl-2-butanone was reduced in 20 days to (*R*)-3-methyl-2-butanol in 37% ee. *trans*-4-Phenyl-3-buten-2-one and cyclohexen-1-one were reduced in 32% ee and 36% ee, respectively. Like **1**, Eapine-Borane reduced α -quaternary alkyl ketones with little or no chirality induced. The results are summarized in Table II.

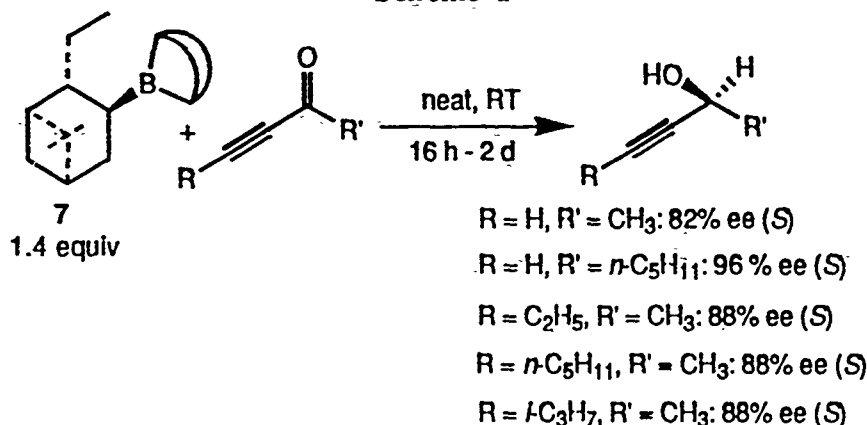
However, the rates of reduction were practical for reactive ketones, such as α,β -acetylenic ketones and α -keto esters. Our standard α,β -acetylenic ketone, 4-phenyl-3-butyne-2-one, was reduced by **7** within 16 h to the corresponding (*S*)-propargylic alcohol in 89% ee (eq 4). By comparison, **1** reduced this ketone in 8-12 h in 82% ee⁹ while **2** required 48 h to provide this alcohol in 85% ee.



The preliminary success in the reduction of 4-phenyl-3-butyne-2-one prompted an examination of the reduction of a series of α,β -acetylenic ketones with **7** and the results were compared with those realized with **1**. Previously, the optical induction reported for the reduction of α,β -acetylenic ketones and α -keto esters with **1** had been determined by comparing the observed optical rotations with those reported in the literature,⁹ or by Eu(hfc)₃ shifted NMR spectroscopy.⁴ To make a direct comparison possible, all the reductions employing **1** reported herein were repeated under neat conditions and the asymmetric induction determined by capillary GC analysis of appropriate diastereomeric esters. While **1** reduced the parent acetylenic ketone, 3-butyne-2-one, in 77% ee, **7** induced 82% ee. 1-Octyn-3-one was reduced in 88% and 96% ee, respectively by reagents **1** and **7**. Indeed, similar improvements were observed for all of the acetylenic ketones studied. In all the cases studied, the

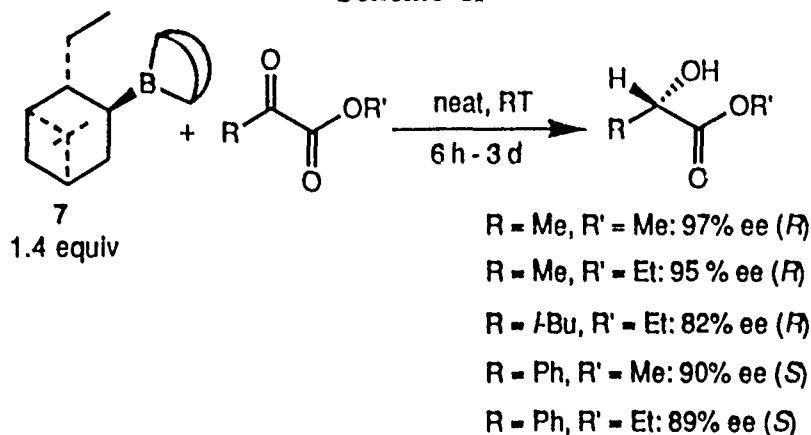
isolated yield of product alcohols ranged from 72-80%. The comparative results of the reduction of acetylenic ketones using **1** and **7** are presented in Table III (Scheme I).

Scheme I



The utility of **7** was also demonstrated for the reduction of α -keto esters. For example, ethyl pyruvate was reduced in 6 h with 1.4 equiv of **7** under neat conditions at room temperature to ethyl lactate in 95% ee as compared to the 91% ee¹⁸ obtained for the reduction of ethyl pyruvate with **1** under the same conditions. The reduction of methyl pyruvate to methyl lactate also showed a similar increase in the induced chirality, 97% ee vs. 92% ee obtained with **1** (Scheme II).¹⁸ However, the reduction of a representative aromatic keto ester, methyl benzoylformate, did not show any improvement in the optical purity achieved (90% ee in both cases). In the reduction of ethyl benzoylformate, a slightly lower value (89%) was obtained in comparison to **1** (93%). The results are summarized in Table IV.

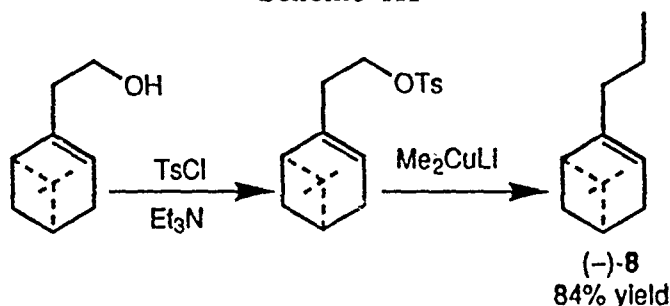
Scheme II



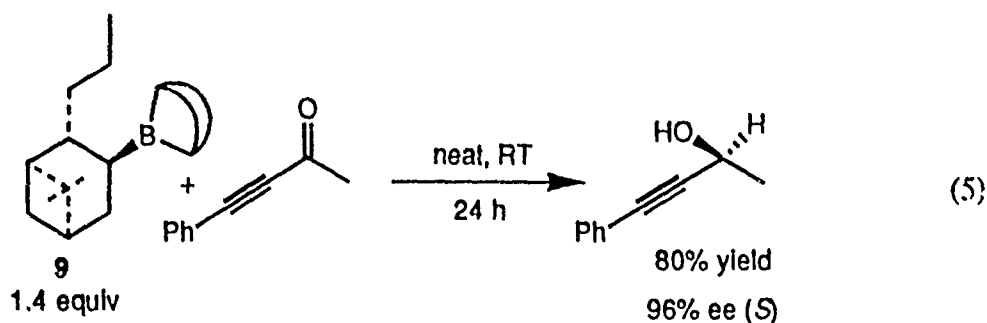
***B*-Iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane** (Prapine-Borane, **9**). The success in chiral reduction achieved by changing the substituent from methyl to ethyl at the 2-position of apopinene prompted the study of the next higher homolog, *B*-iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane, (Prapine-Borane, **9**). Based upon the previous results, **9** was studied for the reduction of only two classes of ketones, α,β -acetylenic ketones and α -keto esters.

(-)-2-*n*-Propylapopinene ((-)-**8**) was prepared in 84% yield from nopyl tosylate by treatment with dimethylcuprate prepared *in situ*¹⁹ from methyl lithium and cuprous iodide (Scheme III). Reagent **9** was prepared using the same procedure for the preparation of **1** and **7** (eq 3). The elimination of **8** from reagent **9** was performed as before to ensure the lack of isomerization or rearrangement during the hydroboration reaction.

Scheme III

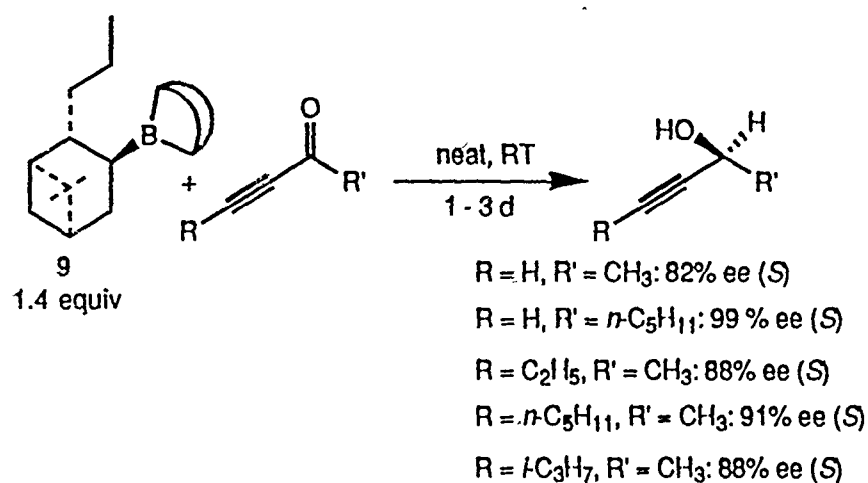


In general, the rate of reduction of a given ketone with **9** is slightly slower than with **7**, but this factor is superceded by the improved chiral inductions. Under the standard conditions, **9** reduces 4-phenyl-3-butyne-2-one in 24 h to provide the corresponding (*S*)-propargylic alcohol in 96% ee (eq 5).



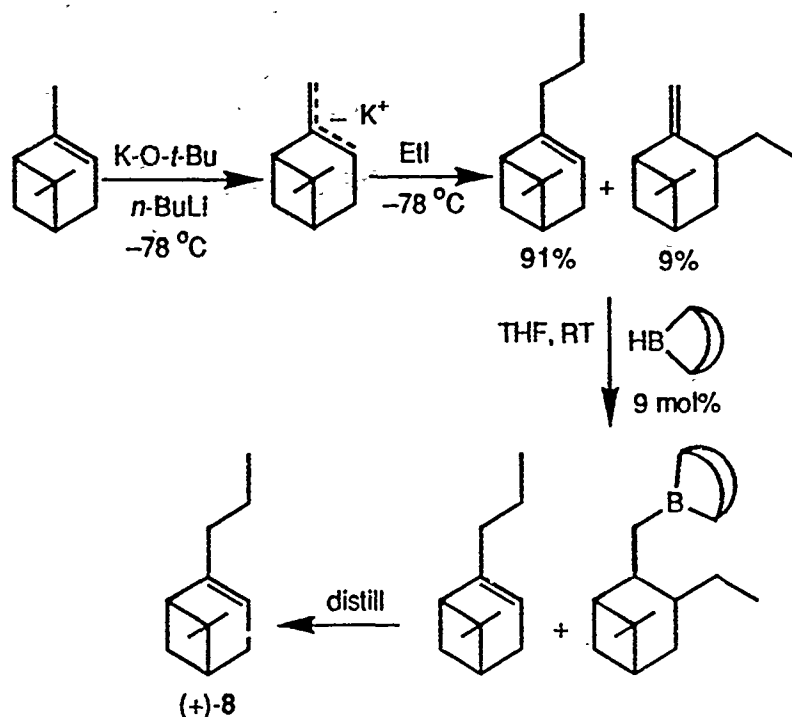
A similar increase in optical inductions was observed for the reduction of 1-octyn-3-one which provided the alcohol in 99% ee. 3-Nonyn-2-one was reduced to the corresponding alcohol in 91% ee by **9** whereas **1** provided the alcohol in 82% ee and **7** provided the same alcohol in 88% ee. These results support the assumption that increases in the steric bulk of the alkyl group at the 2-position of apopinene improve the chiral induction in these product alcohols. However, the other acetylenic ketones studied with **9** gave the same asymmetric induction as realized with **7** which indicates that other factors may be exerting minor influences. The results are summarized in Table V (Scheme IV).

Scheme IV

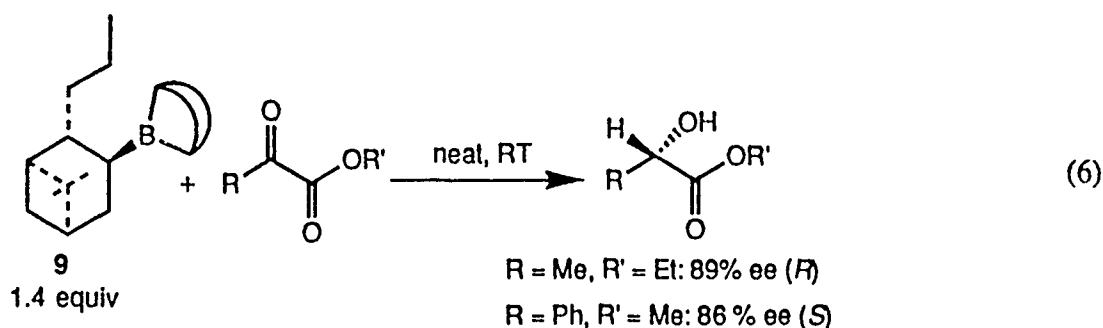


Terpenic olefin (+)-**8** was prepared in 78% yield *via* the Schlosser metallation of (+)- α -pinene¹⁶ followed by treatment with ethyl iodide (Scheme V). Reaction of the 9-BBN adduct derived from (+)-**8** with 4-phenyl-3-butyne-2-one provided the (*R*)-propargylic alcohol in 96% ee. Thus, we can readily synthesize both enantiomers of this and other propargylic alcohols in very high ee.

Scheme V



Reagent **9** failed to provide improved inductions in the reduction of α -keto esters, as compared to **1**. For example methyl benzoylformate was reduced by **9** in 4 days to methyl mandelate in 86% ee and ethyl lactate was produced in 89% ee (eq 6, Table VI). Since these two keto esters were obtained with lower ee, **9** was not studied further.



Conclusions

Based on the proposed theory that the steric bulk of the alkyl group at the 2-position of apopinene influences the extent of asymmetric reduction, *B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonane (**7**), and *B*-iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane (**9**), have been developed as improved reagents for the chiral reduction of α,β -acetylenic ketones.

Efficient methods for the preparation of both enantiomers of the chiral auxiliary **8** have been presented. The availability of both enantiomers of α -pinene in quantity makes **7** and **9** readily accessible, adding to their convenience, as does the ability to recover the chiral auxiliary following the reduction.

In addition, **7** is an efficient reagent for the reduction of alkyl α -keto esters of appreciable steric difference between the two groups on both sides of the carbonyl group. Reduction of these two classes of ketones constitutes a key step in several syntheses.²⁰ These factors make the search for an ideal reagent for chiral reductions very desirable. Consequently, we are extending our studies to other reagents with modified bulk at the 2-position of apopinene.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.²¹ Spectroscopic measurements (^1H and ^{11}B NMR and IR) were made with standard instruments. GC analyses were done on a Varian Aerograph Series 1200 gas chromatograph having a flame ionization detector and integrated with a Hewlett-Packard 3380 S integrator. GC columns, 1/8"x12', were packed with 10% SP-2100 on Chromosorb W (80-100 mesh) or 5% Carbowax 1540 on Chromosorb W (80-100 mesh). Analyses of the MTPA esters or MCF derivatives were performed on a Hewlett-Packard 5890A gas chromatograph using a Supelcowax glass capillary column (15 m), methylsilicone capillary column (50 m) or a SPB-5 capillary column (30 m), at appropriate temperatures, and integrated using a Hewlett-Packard 3390A integrator.

Materials. THF was distilled from sodium benzophenone ketyl and stored under nitrogen in an ampule. 9-BBN, NB-Enantrane, *tert*-butyl lithium, nopol, ethanolamine, menthyl chloroformate (MCF) were all obtained from Aldrich Chemical Co. (-)- and (+)-2-Ethylapopinene were prepared according to our published procedures.¹⁶ The ketones were obtained from Aldrich Chemical Co. or Wiley Organics and were used as received. Most of the acetylenic ketones were prepared from the corresponding alcohols by Jones oxidation. α -Methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using the literature procedure.¹⁴

Reaction of Ketones with NB-Enantrane. NB-Enantrane (20 mL of a 0.5 M solution in THF, 10 mmol) was transferred to a 50-mL round bottom flask, the THF removed under vacuum and the ketone (5 mmol) added. The reaction was followed by ^{11}B NMR spectrum of a diluted (EE) aliquot and quenched using excess acetaldehyde (0.5 mL) at 0 °C. EE (10 mL) was added to the reaction mixture followed by ethanolamine (0.6 mL, 10 mmol). The reaction mixture was stirred for 30 min at RT before the precipitated boron components were removed and the filtrate concentrated. The mixture of ketone and alcohol was distilled, with the pot residue consisting mainly of the chiral auxiliary, nopol benzyl ether. The distillate was derivatized as such using MTPA-Cl or MCF and analyzed by a capillary gas chromatograph. The extent of reaction for each ketone, the corresponding reaction time and the % ee obtained in each case are reported in Table I.

Preparation of *B*-Iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]-nonane (Eapine-Borane, 7). Solid 9-BBN (12.5 g, 100 mmol) was transferred under nitrogen to a 100-mL round bottom flask using a glove bag. 2-Ethylapopinene, $[\alpha]_{\text{D}}^{24} -42^\circ$ (neat) (92% ee), (16.5 g, 110 mmol) was syringed into the flask. The flask was heated in an oil bath at 65 °C for 6 h to complete the hydroboration (^{11}B NMR: δ 80 ppm).

A measured aliquot of the reagent was treated with one equiv of acetaldehyde at 0 °C (exothermic reaction!) to liberate 2-ethylapopinene. Treatment with aq. NaOH removed the boron components and the ethylapopinene was extracted into ether, dried (MgSO_4), concentrated and distilled. Gas chromatographic analysis was identical to an authentic sample, thus indicating no isomerization occurred during the preparation of the reagent.

The reagent was used as such for further reductions.

Reduction of Ketones with Eapine-Borane. The reduction of 4-phenyl-3-butyne-2-one is representative. To a 50-mL round-bottomed flask fitted as usual,²¹ 14 mmol of the reagent was added, followed by 4-phenyl-3-butyne-2-one (1.46 mL, 10 mmol) and the mixture stirred at RT. The reaction was followed by ^{11}B NMR of an aliquot dissolved in EE. When the reaction was complete (16 h), acetaldehyde (0.28 mL, 5 mmol) was added at 0 °C and stirred for 30 min. The 2-ethylapopinene liberated during the reaction was collected using a high vacuum pump (0.01 Torr, 6 h). EE (20 mL) was then added to the reaction mixture followed by ethanolamine (0.84 mL) and

stirring continued for 1 h during which time the boron components precipitated. The product alcohol was separated by filtering the precipitate and washing with pentane. 4-Phenyl-3-butyn-2-ol was distilled using a Kugelrohr apparatus at high vacuum. Yield: 1.17 g (80%). MTPA ester was prepared and analyzed on an SPB-5 (30 m) capillary GC column (15 m) which indicated 82% ee of the *S*-isomer, corrected to 89% ee.

Reduction of all other ketones was performed using an identical procedure. The results are summarized in Tables II-IV.

Preparation of *B*-Iso-2-*n*-Propylapopinocampheyl-9-borabicyclo[3.3.1]nonane, (Prapine-Borane, 9).

(-)-2-*n*-Propylapopinene ((-)-8): Methyllithium (330 mL of a 1.3 *M* solution in hexane, 0.43 mol) was added to a suspension of CuI (40.8 g, 0.214 mol) in 100 mL EE at -10 °C and stirred for 2 h, followed by the dropwise addition of a 1 *M* EE solution of nopyl tosylate (34.3 g, 0.107 mol) over a 1 h period. The reaction mixture was maintained at -10 °C for 1 h, warmed to 0 °C and poured into a chilled saturated aqueous NH₄Cl solution and stirred for 15 min. The organic layer was removed and the aqueous layer extracted with ether. The combined organics were washed with brine and water and dried over MgSO₄. Evaporation of the volatiles, followed by distillation over LAH provided 14.9 g (84%) of GC pure material. ¹H NMR (CDCl₃): δ 5.16 (m, 1H); 2.28-2.4 (m, 1H); 2.21 (br, 2H); 1.85-2.15 (m, 4H); 1.45-1.29 (m, 2H); 1.26 (s, 3H); 1.14 (d, 1H, *J* = 8 Hz); 0.88 (t, 2H, *J* = 7 Hz); 0.83 (s, 3H). ¹³C NMR: δ 149.00 (C₂), 116.05 (C₃), 46.04 (C₁), 41.14 (C₅), 39.35 (C₁₀), 38.07 (C₆), 31.81 (C₇), 31.43 (C₄), 26.51 (C₈), 21.29 (C₉), 20.51 (C₁₁), 14.08 (C₁₂). MS: 70 eV *M/e* 164 (*M*⁺); 79 (C₆H₇, 100%). Anal. Calcd for C₁₂H₂₀: C 87.73; H 12.27; Found: C 87.73; H 12.59. [α]_D²⁵ -32.69° (neat) (density: 0.862); [α]_D²⁶ -36.0° (c 20, MeOH)

(+)-2-*n*-Propylapopinene ((+)-8): *t*-BuOK (25.0 g, 223 mmol) was dissolved in 75 mL of *n*-hexane and cooled to -78 °C. The solution was treated dropwise with *n*-BuLi (106 mL, 2.1 *M* solution in hexanes, 223 mmol), followed by the addition of 24.2 g (180 mmol) of (+)- α -pinene, ([α]_D²⁵ +47.1° (neat); 92% ee) over a 0.5 h period. The reaction mixture was allowed to warm to RT and stirred for 48 h. The resulting potassium salt was dissolved in 100 mL THF, cooled to -78

$^{\circ}\text{C}$, and ethyl iodide (55.8 g, 358 mmol) was added slowly over a 20 min period. The solution was stirred at -78°C for an additional 45 min, warmed to RT, and poured into ice water. The organic layer was separated and the aqueous layer extracted with ether. The combined organics were washed with water and brine and dried over MgSO_4 . Evaporation of the volatiles, followed by distillation from LAH provided 25.2 g (86%) of material, GC analysis of which indicated the presence of 2 components in a 91:9 ratio. The impurity, presumably 3-ethyl- β -pinene, was removed by dissolving the mixture in 80 mL of THF followed by treatment with 9-BBN (0.18 g, 1.5 mmol) at RT for 12 h. The solvent was evaporated *in vacuo* and the residue distilled ($94^{\circ}\text{C}/28\text{ mmHg}$) to provide 22.8 g of GC pure 2-*n*-propylapopinene (78% overall yield). $[\alpha]_{\text{D}}^{24} +31.36^{\circ}$ (neat, $d = 0.862$); $[\alpha]_{\text{D}}^{25} +35.61^{\circ}$ ($c\ 21$, MeOH).

***B*-Iso-2-*n*-propylapopinocampheyl-9-borabicyclo[3.3.1]nonane (Prapine-Borane, 9).** An oven-dried 100-mL round-bottom flask equipped as before was charged with solid 9-BBN (12.5 g, 100 mmol) followed by the addition of 2-*n*-propylapopinene (18.1 g, 110 mmol). A static pressure of nitrogen was maintained. The flask was heated in an oil bath at 65°C for 6 h to complete the hydroboration (^{11}B NMR: $\delta\ 80\text{ ppm}$).

A measured aliquot of the reagent was treated with one equiv of acetaldehyde at 0°C for 0.5 h (exothermic reaction!) to liberate 2-*n*-propylapopinene. Treatment with aq. NaOH removed the boron components and the ethylapopinene was extracted into ether, dried (MgSO_4), concentrated and distilled. Gas chromatographic analysis was identical to an authentic sample, indicating no isomerization occurred during the preparation of the reagent.

The reagent was used as such for further reductions.

Reduction of Ketones by Prapine-Borane. The reduction of 4-phenyl-3-butyne-2-one is representative. To a 50-mL round-bottomed flask fitted as usual,²¹ 14 mmol of the reagent was added, followed by 1.44 g (1.46 mL, 10 mmol) of 4-phenyl-3-butyne-2-one and stirred at room temperature. The reaction was followed by ^{11}B NMR of an aliquot dissolved in EE. When the reaction was complete (24 h), acetaldehyde (0.28 mL, 5 mmol) was added to the reaction mixture at 0°C and stirred for 30 min. EE (20 mL) was then added to the reaction mixture followed by ethanolamine (0.84 mL) and stirring continued for 1 h during which time the boron components

precipitated. Filtration of this precipitate followed by washing with pentane gave a mixture of 2-*n*-propylapopinene and the product alcohol. The chiral auxiliary was separated on a silica gel column (pentane eluent) and the 4-phenyl-3-butyne-2-ol eluted with ether, concentrated and distilled using a Kugelrohr apparatus at high vacuum. Yield: 1.08 g (74%). The MTPA ester was prepared and analyzed on an SPB-5 (30 m) capillary column (15 m) which showed an ee of 88% in the *S*-isomer, corrected to 96% ee.

Reduction of all other ketones was done using an identical procedure. The results are summarized in Tables V and VI.

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Table I. Reaction of NB-Enantrane, 2 with Representative Ketones at 25 °C.

ketone	reagent equiv	reaction time (% conversion)	% ee ^{a,b}	% ee with 1 ^c
3-methyl-2-butanone	2	15 d (30)	30	62
acetophenone	2	15 d (20)	62	85
2-chloroacetophenone	2	15 d (50)	92	96
4-phenyl-3-butyne-2-one	2	2 d (100)	85	82
methyl benzoylformate	2	4 d (80)	84	90

^a Analyzed as the MTPA or MCF derivatives on capillary GC. ^b % ee corrected for the optical purity of the chiral auxiliary. ^c From Ref. 3

Table II. Reaction of Eapine-Borane, 7 with Representative Ketones at 25 °C

ketone	reagent equiv	reaction time	% ee ^{a,b}	% ee with 1 ^c
3-methyl-2-butanone	2	20 d	38	62
2,2-dimethylcyclopentanone	2	7 d	3	20
acetophenone	2	20 d	78	85
3-acetylpyridine	3	15 d	96	93
2-chloroacetophenone	2	15 d	72	96
methyl benzoylformate	1.4	3 d	90	90
<i>trans</i> -4-phenyl-3-buten-2-one	1.4	15 d	32	56
2-cyclohexenone	2	15 d	36	30
4-phenyl-3-butyne-2-one	1.4	16 h	89	82

^a Analyzed as the MTPA or MCF derivatives on capillary GC. ^b % ee corrected for the optical purity of the chiral auxiliary. ^c From Ref. 3.

Table III. Reaction of Eapine-Borane, 7 with Representative α,β -Acetylenic Ketones at 25 °C

ketone	reagent equiv	reaction time	% ee ^{a,b}	% ee with 1
3-butyne-2-one	1.4	12 h	82	77
1-octyne-3-one	1.4	48 h	96	88
3-hexyne-2-one	1.4	36 h	88	80
3-nonyne-2-one	1.4	72 h	88	82
5-methyl-3-hexyne-2-one	1.4	72 h	88	88
4-phenyl-3-butyne-2-one	1.4	16 h	89	82

^a Analyzed as the MTPA derivative on capillary GC. ^b % ee corrected for the optical purity of the chiral auxiliary.

Table IV. Reaction of Eapine-Borane, 7 with α -keto esters at 25 °C.

ketone	reagent equiv	reaction time	% ee ^{a,b} (config)	% ee with 1 ^{a,b} (config)
methyl pyruvate	1.4	4 h	97 (<i>R</i>)	92 (<i>S</i>)
ethyl pyruvate	1.4	4 h	95 (<i>R</i>)	91 (<i>S</i>)
ethyl 4-methyl-2-oxovalerate	1.4	7 d	82 (<i>R</i>)	51 (<i>S</i>)
methyl benzoylformate	1.4	3 d	90 (<i>S</i>)	90 (<i>R</i>)
ethyl benzoylformate	1.4	3 d	89 (<i>S</i>)	93 (<i>R</i>)

^a Analyzed as the MTPA derivative on capillary GC. ^b Values corrected for the optical purity of the chiral auxiliary.

Table V. Reaction of Prapine-Borane, 9 with Representative α,β -Acetylenic Ketones at 25 °C

ketone	reagent equiv	reaction time	% ee ^{a,b}		
			with 9	with 7	with 1
3-butyne-2-one	1.4	12 h	82	82	77
1-octyne-3-one	1.4	48 h	99	96	88
3-hexyne-2-one	1.4	36 h	88	88	80
3-nonyne-2-one	1.4	72 h	91	88	82
5-methyl-3-hexyne-2-one	1.4	72 h	88	88	88
4-phenyl-3-butyne-2-one	1.4	16 h	96	89	82

^a Analyzed as the MTPA derivative on capillary GC. ^b % ee corrected for the optical purity of the chiral auxiliary.

Table VI. Reaction of Prapine-Borane, 9 with α -keto esters at 25 °C.

ketone	reagent equiv	reaction time	% ee ^{a,b} (config)	% ee with 7 (config)
ethyl pyruvate	1.4	4 h	89 (R)	95 (R)
methyl benzoylformate	1.4	3 d	86 (S)	90 (S)

^a Analyzed as the MTPA derivative on capillary GC. ^b Values corrected for the optical purity of the chiral auxiliary.