93362-48-2; **45** (E = CO_2H), 93362-49-3; **45** (E = CHO), 90971-76-9; **45** (E = CH_2OH), 93362-50-6; **45** (E = CH(OH)Ph), 90971-75-8; **45** (E = cyclohexene), 93362-51-7; **45** (E = Ac), 93362-52-8; **46** (E = $C_{18}H_{27}$), 93362-22-2; **46** (E = CO_2H), 931-03-3; **46** (E = CHO), 7126-39-8; **46** (E = Ac), 1072-82-8; **49**, 130408-94-5; **50**, 130408-95-6; **51**, 130408-96-7; **52**, 130408-97-8; **53**, 634-97-9; **54**, 33234-48-9; **56**, 130408-98-9; **57**, 130408-99-0; **58**, 130409-00-6; **59**, 130409-01-7; **60**, 130409-02-8; **61**, 130409-03-9; **62**, 93362-25-5; **63**, 24445-13-4; $(i\text{-}Pr)_3SiCl$, 13154-24-0; n-$C_{18}H_{37}I$, 629-93-6; $H_3CCH_2CH(CH_3)CH_2Br$, 10422-35-2; AcN(OMe)Me, 78191-00-1; pyrrole, 109-97-7; ethyl oxalyl chloride, 4755-77-5; phenylacetyl chloride, 103-80-0; 4-toluenesulfinyl chloride, 10439-23-3; cyclohexanone, 108-94-1.

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

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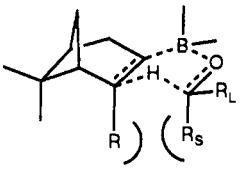
B-(Iso-2-ethylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Eapine-Borane, **7**), and *B*-(Iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Prapine-Borane, **9**), prepared via the hydroboration of 2-ethylapopinene (**6**) or 2-*n*-propylapopinene (**8**), respectively, with 9-borabicyclo[3.3.1]nonane, reduce prochiral α,β-acetylenic ketones and α-keto esters to the corresponding alcohols with significantly higher optical induction than does Alpine-Borane (**1**). (-)-2-*n*-Propylapopinene was synthesized by treating nopyl tosylate with dimethyl cuprate prepared in situ from methyllithium and cuprous iodide. (+)-2-*n*-Propylapopinene was synthesized by Schlosser metalation of (+)-α-pinene followed by treatment with ethyl iodide. 4-Phenyl-3-butyn-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 percent ee for the reduction of α-keto esters. The increase in the percent ee realized is tentatively attributed to the increased steric requirements of the alkyl group at the 2-position of apopinene.

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-deuterio aldehydes,[4] α,β-acetylenic ketones,[5] α-keto esters,[6] and

Scheme I



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

(1) (a) Postdoctoral Research Associate on a Grant from the United States Army Research Office. (b) Postdoctoral Research Associate on a Grant from Dow Chemical Co. (c) Postdoctoral Research Associate on a Grant from the Office of Naval Research.

(2) (a) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, Chapters 2-4. (b) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553.

(3) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.

(4) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(5) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *Ibid.* **1980**, *102*, 867.

(6) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531.

(7) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1983**, *48*, 1784.

(8) Midland, M. M.; Petre, J. E.; Zderic, S. A. *J. Organomet. Chem.* **1979**, *182*, C 53.

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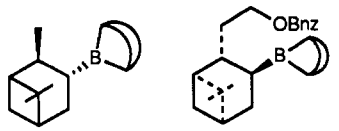
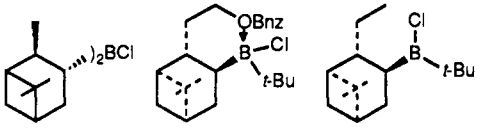
by conducting the reductions under neat conditions which increases the rate of reduction and thus the chiral induction.[9]



1 2

Midland later introduced NB-Enantrane (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 exceses 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 favored transition-state model (Scheme I) 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)[13] was synthesized with the aim of eliminating this internal coordination, while retaining the steric bulk at the 2-position. The rates improved considerably and the chiral inductions were comparable to those obtained with 4.



3 4 5

In the present study, the retarded rate of reduction with 2 was confirmed and found to be too slow to be of any practical use, except for acetylenic ketones. The retarded rate could be due to the steric bulk at the 2-position since no internal coordination was observed in the reagent by ^{11}B NMR (δ 86 ppm).[13] By analogy, it should be possible to improve the asymmetric induction of 1 by increasing the steric requirement of the 2-position of the apopinene skeleton with groups incapable of coordinating to boron. Accordingly, 2-ethyl- and 2-propylapopinene were prepared and a comparative study conducted.

(9) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.
(10) Midland had reported 85% ee for the reduction of 4-phenyl-3-butyn-2-one based on Eu(hfc)$_3$-shifted NMR. We repeated the reaction and obtained a value of 78% ee, corrected to 85% ee. Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814.
(11) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(12) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.
(13) Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 4504.

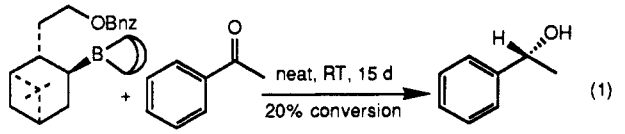
Table I. Reaction of NB-Enantrane, 2, with Representative Ketones at 25 °C

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

[a] Analyzed as the MTPA or MCF derivatives on capillary GC. [b] Percent ee corrected for the optical purity of the chiral auxiliary. [c] From ref 3.

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 2 equiv of the reagent and were monitored by ^{11}B NMR spectrocopy 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. The results, summarized in Table I, show the sluggish nature of the reaction. 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 (92% ee) of the starting material (2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene, Nopol).

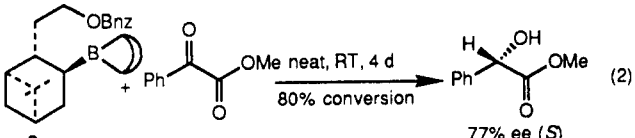


(1)

2
2 equiv

57% ee
corrected to 62% ee (*R*)

Even the usually reactive methyl benzoylformate was only partially reduced by 2 (eq 2). Only the representative aromatic propargylic ketone, 4-phenyl-3-butyn-2-one, was effectively reduced (85% ee/100% conversion/2 days).



(2)

2
2 equiv

77% ee (*S*)
corrected to 84% ee

Since 2 is effective only for the reduction of α,β-acetylenic ketones, 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) was undertaken.

***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

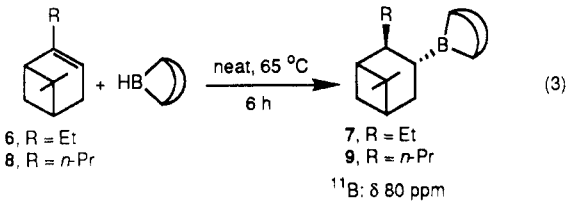
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(15) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.

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 days	38	62
2,2-dimethylcyclopentanone	2	7 days	3	20
acetophenone	2	20 days	78	85
3-acetylpyridine	3	15 days	96	93
2-chloroacetophenone	2	15 days	72	96
methyl benzoylformate	1.4	3 days	90	90
trans-4-phenyl-3-buten-2-one	1.4	15 days	32	56
2-cyclohexenone	2	15 days	36	30
4-phenyl-3-butyn-2-one	1.4	16 h	89	82

[a] Analyzed as the MTPA or MCF derivatives on capillary GC. [b] Percent ee corrected for the optical purity of the chiral auxiliary. [c] From ref 3.

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



(3)

h as indicated by the ^{11}B NMR spectrum (broad singlet at δ 80 ppm). Treatment of reagent **7** with acetaldehyde liberated the starting olefin **6**, whose spectral properties were identical with 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 (Table II). For example, acetophenone was quantitatively reduced to provide (*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] Similarly, while the remaining ketones of the series were quantitatively reduced, albeit at a slower rate, the majority of the product alcohols were of equal or lower enantiomeric purity than those obtained with reagent **1**.

However, the rates of reduction and the induction obtained with **7** for the α,β-acetylenic ketones and α-keto esters were most notable. Our standard α,β-acetylenic ketone, 4-phenyl-3-butyn-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% ee[9] while **2** required 48 h to provide this alcohol in 85% ee.

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

ketone	reagent equiv	reaction time, h	% ee[a,b]	% ee with 1
3-butyn-2-one	1.4	12	82	77
1-octyn-3-one	1.4	48	96	88
3-hexyn-2-one	1.4	36	88	80
3-nonyn-2-one	1.4	72	88	82
5-methyl-3-hexyn-2-one	1.4	72	88	88
4-phenyl-3-butyn-2-one	1.4	16	89	82

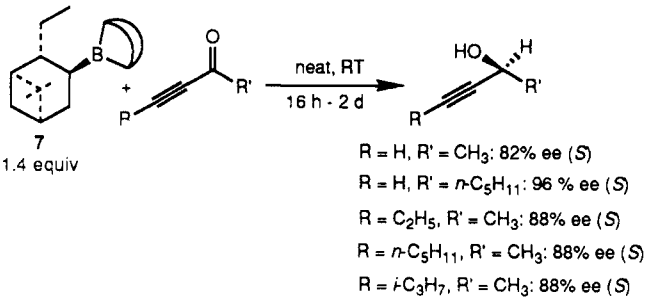
[a] Analyzed as the MTPA derivative on capillary GC. [b] Percent ee corrected for the optical purity of the chiral auxiliary.

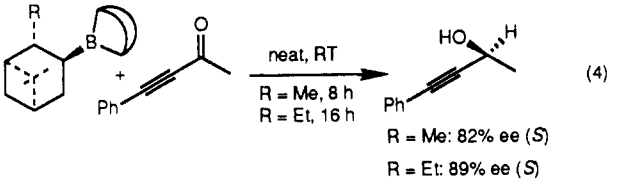
Table IV. Reaction of Eapine-Borane, 7, with α-Keto Esters at 25 °C

ketone	reagent equiv	reaction time	% ee[a,b] (config)	% ee with 1[a,b] (config)
methyl pyruvate	1.4	4 h	97 (*R*)	92 (*S*)
ethyl pyruvate	1.4	4 h	95 (*R*)	91 (*S*)
ethyl 4-methyl-2-oxovalerate	1.4	7 days	82 (*R*)	51 (*S*)
methyl benzoylformate	1.4	3 days	90 (*S*)	90 (*R*)
ethyl benzoylformate	1.4	3 days	89 (*S*)	93 (*R*)

[a] Analyzed as the MTPA derivative on capillary GC. [b] Vales corrected for the optical purity of the chiral auxiliary.

Scheme II



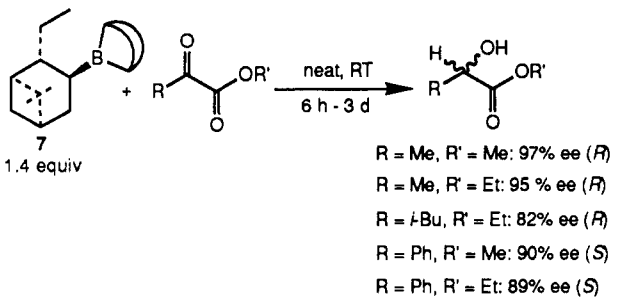


(4)

The preliminary success in the reduction of 4-phenyl-3-butyn-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** (Table III, Scheme II). 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-butyn-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**.

(16) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Weissman, S. A.; Jadhav, P. K.; Perumal, P. T. *J. Org. Chem.* **1988**, *53*, 5513.
(17) (a) Midland, M. M.; Petre, J. E.; Zderic, S. A.; Kazubski, A. *J. Org. Chem.* **1982**, *104*, 528. (b) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. *Organometallics* **1986**, *5*, 2138.

Scheme III



Scheme IV

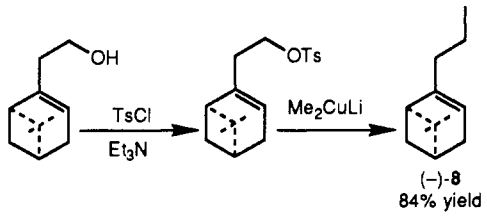


Table V. Reaction of Prapine-Borane, 9, with Representative α,β-Acetylenic Ketones at 25 °C

ketone	reagent equiv	reaction time, h	% ee[a,b] with 9	% ee[a,b] with 7	% ee[a,b] with 1
3-butyn-2-one	1.4	12	82	82	77
1-octyn-3-one	1.4	48	99	96	88
3-hexyn-2-one	1.4	36	88	88	80
3-nonyn-2-one	1.4	72	91	88	82
5-methyl-3-hexyn-2-one	1.4	72	88	88	88
4-phenyl-3-butyn-2-one	1.4	16	96	89	82

[a] Analyzed as the MTPA derivative on capillary GC. [b] Percent ee corrected for the optical purity of the chiral auxiliary.

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 to 80%.

The utility of 7 was also demonstrated for the reduction of α-keto esters (Table IV). 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% ee[18] 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 III).[18] Reagent 7 offers no advantage for the reduction of aromatic α-keto esters.

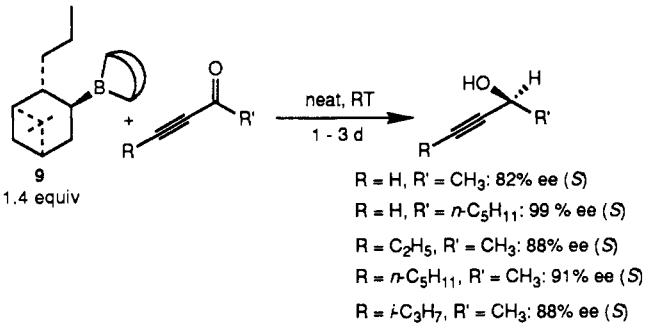
***B*-(Iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (Prapine-Borane, 9).** The succes in chiral reduction achieved by changing the substituent from methyl to ethyl at the 2-position of apopinene prompted the study of the next higher homologue, *B*-(iso-2-*n*-propylapopinocampheyl)-9-borabicyclo[3.3.1]nonane (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 dimethyl cuprate prepared in situ[19] from methyllithium and cuprous iodide (Scheme IV). Reagent **9** was prepared using the same procedure for the preparation of 1 and 7 (eq 3). The

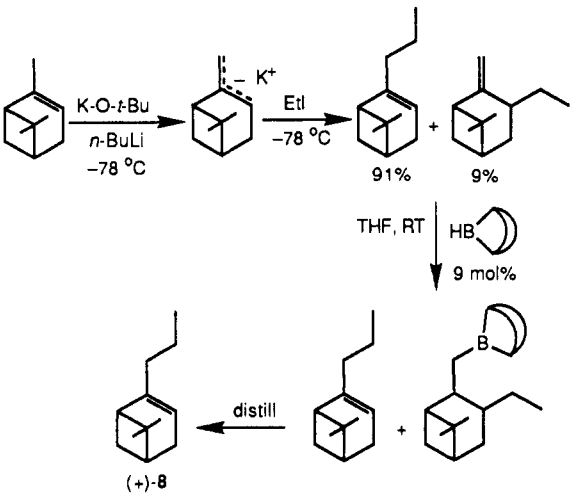
(18) We had reported 83% ee for methyl lactate and 86% ee for ethyl lactate produced by a reaction of 1 based on optical rotation measurements: ref 9.

(19) Johnson, C. R.; Dutra, C. R. *J. Am. Chem. Soc.* **1973**, *95*, 7777.

Scheme V

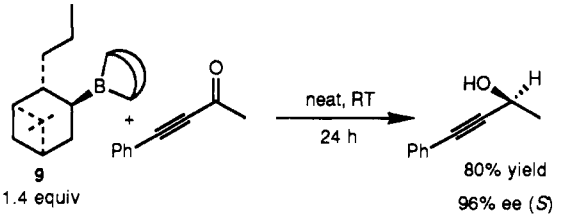


Scheme VI



elimination of 8 from reagent **9** was performed as before to ensure the lack of isomerization or rearrangement during the hydroboration reaction.

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 (Table V, Scheme V). Under the standard conditions, **9** reduces 4-phenyl-3-butyn-2-one in 24 h to provide the corresponding (*S*)-propargylic alcohol in 96% ee (eq 5).



(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.

Terpenic olefin (+)-8 was prepared in 78% yield via the Schlosser metallation of (+)-α-pinene[16] followed by treatment with ethyl iodide (Scheme VI). Reaction of the 9-BBN adduct derived from (+)-8 with 4-phenyl-3-butyn-2-one provided the (*R*)-propargylic alcohol in 96% ee.

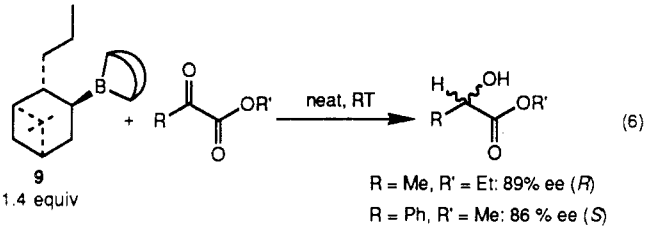
Table VI. Reaction of Prapine-Borane, 9, with α-Keto Esters at 25 °C

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 days	86 (*S*)	90 (*S*)

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

Thus, we can readily synthesize both enantiomers of this and other propargylic alcohols in very high ee.

Reagent 9 failed to provide improved inductions in the reduction of α-keto esters, as compared to 1 (eq 6, Table VI).



9
1.4 equiv

R = Me, R' = Et: 89% ee (*R*)
R = Ph, R' = Me: 86 % ee (*S*)

(6)

Conclusions

Based on the proposed theory that the steric requirement 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 further increased steric requirement at the 2-position of apopinene.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[21] Spectroscopic measurements (^{1}H 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, $^1/_8$ in. × 12 ft, 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), a 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*-butyllithium, nopol, ethanolamine, menthyl chloroformate (MCF) were all obtained from Aldrich Chemical Co. (-)- and (+)-2-Ethylapopinene were prepared according to 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 was removed under vacuum, and the ketone (5 mmol) was 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 room temperature before the precipitated boron components were removed, and the filtrate was 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 glovebag. 2-Ethylapopinene, $[\alpha]^{24}_D$ -42° (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 an aqueous NaOH removed the boron components, and the ethylapopinene was extracted into ether, dried ($MgSO_4$), concentrated, and distilled. Gas chromatographic analysis was identical with 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-butyn-2-one is representative. To a 50-mL round-bottomed flask fitted as usual[21] was added 14 mmol of the reagent, followed by 4-phenyl-3-butyn-2-one (1.46 mL, 10 mmol) and the mixture stirred at room temperature. The reaction was followed by ^{11}B NMR spectroscopy 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 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, poured into a chilled saturated aqueous NH_4Cl solution, and stirred for 15

(20) Optically pure propargylic alcohols are utilized as synthons in the synthesis of alkaloids: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851. Pheromones: Midland, M. M.; Nguyen, N. H. *J. Org. Chem.* **1981**, *46*, 4107. Prostaglandins: Fried, J.; Lin, C. H. *J. Med. Chem.* **1973**, *16*, 429. Steroids: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512. Vitamins: Chan, K.; Specian Jr., A. C.; Saucy, G. *J. Org. Chem.* **1978**, *43*, 3435. Utilization of α-hydroxy esters have been made in many syntheses. For references, see the references cited in Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1986**, *51*, 3396.

min. The organic layer was removed, and the aqueous layer was extracted with ether. The combined organics were washed with brine and water and dried over $MgSO_4$. Evaporation of the volatiles, followed by distillation over LAH, provided 14.9 g (84%) of GC pure material. ^1H NMR ($CDCl_3$): δ 5.16 (m, 1 H), 2.28–2.4 (m, 1 H), 2.21 (br, 2 H), 1.85–2.15 (m, 4 H), 1.45–1.29 (m, 2 H), 1.26 (s, 3 H), 1.14 (d, 1 H, J = 8 Hz), 0.88 (t, 2 H, J = 7 Hz), 0.83 (s, 3 H). ^{13}C NMR: δ 149.00 (C_2), 116.05 (C_3), 46.04 (C_1), 41.14 (C_5), 39.35 (C_{10}), 38.07 (C_6), 31.81 (C_7), 31.43 (C_4), 26.51 (C_8), 21.29 (C_9), 20.51 (C_{11}), 14.08 (C_{12}). MS (70 eV): m/e 164 (M^+), 79 (C_6H_7, 100). Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.73; H, 12.59. $[\alpha]^{25}_D$ −32.69° (neat) (density: 0.862); $[\alpha]^{26}_D$ −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 ($[\alpha]^{25}_D$ +47.1° (neat); 92% ee) over a 0.5-h period. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The resulting potassium salt was dissolved in 100 mL of THF, cooled to −78 °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 room temperature, and poured into ice water. The organic layer was separated, and the aqueous layer was 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 two 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 room temperature for 12 h. The solvent was evaporated in vacuo, and the residue was distilled (94 °C (28 mmHg)) to provide 22.8 g of GC pure 2-*n*-propylapopinene (78% overall yield): $[\alpha]^{24}_D$ +31.36° (neat, d = 0.862); $[\alpha]^{25}_D$ +35.61° (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 hydroborate (^{11}B NMR: δ 80 ppm).

A measured aliquot of the reagent was treated with 1 equiv of acetaldehyde at 0 °C for 0.5 h (exothermic reaction!) to liberate 2-*n*-propylapopinene. Treatment with aqueuous NaOH removed the boron components, and the ethylapopinene was extracted into ether, dried ($MgSO_4$), concentrated, and distilled. Gas chromatographic analysis was identical with 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-butyn-2-one is representative. To a 50-mL round-bottom 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-butyn-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 was 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-butyn-2-ol was 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.

Acknowledgment. Financial assistances from the United States Army Research Office (Grant No. DAAL 03-88-K-0107), Dow Chemical Co. (Grant No. 1247670), and the Office of Naval Research (Grant No. N00014-89-J-1128) are gratefully acknowledged. The efforts of Drs. R. S. Randad and U. P. Dhokte are also acknowledged.

Registry No. (*N*)-6, 38359-49-8; (1*S*)-7, 129364-65-4; (+)-8, 129444-04-8; (−)-8, 129364-67-6; (1*S*)-9, 129364-66-5; 9-BBN, 280-64-8; 3-methyl-2-butanone, 563-80-4; (*R*)-3-methyl-2-butanol, 1572-93-6; acetophenone, 98-86-2; (*R*)-α-phenethanol, 1517-69-7; 2-chloroacetophenone, 532-27-4; (*S*)-α-(chloromethyl)benzyl alcohol, 70111-05-6; 4-phenyl-3-butyn-2-one, 1817-57-8; (*S*)-4-phenyl-3-butyn-2-ol, 81555-86-4; methyl benzoylformate, 15206-55-0; methyl (*S*)-mandelate, 21210-43-5; 2,2-dimethylcyclopentanone, 4541-32-6; (*R*)-2,2-dimethylcyclopentanol, 109530-56-5; 3-acetylpyridine, 350-03-8; (*R*)-1-(3-pyridyl)ethanol, 7606-26-0; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; (*R*)-*trans*-4-phenyl-3-buten-2-ol, 62413-47-2; 2-cyclohexenone, 930-68-7; 2-cyclohexenol, 822-67-3; 3-butyn-2-one, 1423-60-5; (*S*)-3-butyn-2-ol, 2914-69-4; 1-octyn-3-one, 27593-19-7; (*S*)-1-octyn-3-ol, 32556-71-1; 3-hexyn-2-one, 1679-36-3; (*S*)-3-hexyn-2-ol, 129364-62-1; 3-nonyn-2-one, 27259-09-2; (*S*)-3-nonyn-2-ol, 129364-63-2; 5-methyl-3-hexyn-2-one, 51686-95-4; (*S*)-5-methyl-3-hexyn-2-ol, 129364-64-3; methyl pyruvate, 600-22-6; methyl (*R*)-lactate, 17392-83-5; methyl (*S*)-lactate, 27871-49-4; ethyl pyruvate, 617-35-6; ethyl (*R*)-lactate, 7699-00-5; ethyl (*S*)-lactate, 687-47-8; ethyl 4-methyl-2-oxovalerate, 26073-09-6; ethyl (*R*)-2-hydroxy-4-methylvalerate, 60856-83-9; ethyl (*S*)-2-hydroxy-4-methylvalerate, 60856-85-1; methyl (*R*)-mandelate, 20698-91-3; ethyl benzoylformate, 1603-79-8; ethyl (*S*)-mendelate, 13704-09-1; ethyl (*R*)-mandelate, 10606-72-1; nopol tosylate, 81600-63-7.

(21) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.