pyridine gave 3-*O*-(2-propenyl)-16α-fluoroestradiol 17β-acetate (18): 355 mg (95%); mp 105–108 °C; mass spectrum 372 (M^+); NMR ($CDCl_3$) δ 7.15 (1 H, d, J = 8.5, aromatic 1-H), 6.7 (1 H, dd, J = 8.5, 2.2, aromatic 4-H), 6.62 (1 H, d, J = 2.2, aromatic 4-H), 6.0 (1 H, m, propenyl CH=), 5.25 (2 H, dd, J = 10.5, 1.4, propenyl $=CH_2$), 4.5 (2 H, d, J = 5, propenyl OCH_2), 5.03 (1 H, complex d, J = 50, 16β-H), 4.95 (1 H, s, 17α-H), 2.1 (3 H, s, acetate), 0.87 (3 H, s, 18-CH_3).

Preparation of Fluorine-18 and Reaction with Cyclic Sulfates. [^{18}F]Fluoride was produced by the $^{18}O(p,n)^{18}F$ reaction[16] on [^{18}O]water using 17-MeV protons.[17] After bombardment, the water, containing approximately 10 nmol of ^{18}F-labeled fluoride, was removed from the silver target and added to 10 μmol of tetramethylammonium hydroxide. The water was then evaporated under vacuum (25 cmHg at 120 °C). Three 3-mL portions of dry acetonitrile were then added and evaporated. The sulfate in 3 mL of acetonitrile was then added and refluxed for 10 min. The labeled products were analyzed by HPLC and TLC and then hydrolyzed, except as noted elsewhere, with 3 mL of 1 N HCl at reflux for 10 min–3 h as necessary.

(16) Ruth, T. J.; Wolf, A. P. *Radiochim. Acta* **1979**, *26*, 21–24.
(17) Tewson, T. J.; Berridge, M. S.; Bolomey, L.; Gould, K. L. *Nucl. Med. Biol.* **1988**, *5*, 499–504.

Registry No. 1 (stereoisomer 1), 124535-96-2; 1 (stereoisomer 2), 124536-14-7; 2 (stereoisomer 1), 32644-05-6; 2 (stereoisomer 2), 32644-06-7; 3 (stereoisomer 1), 40811-14-1; 3 (stereoisomer 2), 40811-15-2; 4, 5732-45-6; 5, 124535-97-3; 6, 4426-50-0; 7, 5689-83-8; 8, 5732-44-5; 9, 96092-82-9; 10, 124599-96-8; 11, 3150-15-0; 12, 14187-71-4; 13, 2880-96-8; 14, 124561-57-5; 15, 124535-98-4; 16, 124535-99-5; 17, 92817-10-2; 18, 124536-00-1; $CH_3CH_2CH(OH)CH_2OH$, 584-03-2; $CH_3CH(OH)CH_2CH_2OH$, 107-88-0; KOPh, 100-67-4; $Me_4N^+F^-$, 373-68-2; $CH_3CH_2CH(SO_3K)CH_2OPh$, 124536-01-2; $CH_3CH(SO_3K)(CH_2)_2OPh$, 124536-02-3; $CH_3CH(SO_3K)CH_2OPh$, 124536-03-4; $KO_3S(CH_2)_4OPh$, 124536-04-5; $CH_3CH_2CH(SO_3Na)CH_2F$, 124536-05-6; $CH_3CH(SO_3Na)CH_2CH_2F$, 124536-06-7; $CH_3CH(SO_3Na)CH_2F$, 124536-07-8; $FCH_2(CH_2)_3SO_3Na$, 124536-08-9; $CH_3CHFCH_2SO_3Na$, 124536-09-0; $CH_3CH_2CHFCH_2SO_3Na$, 124536-10-3; $CH_3CHFCH_2CH_2SO_3Na$, 124536-11-4; $FCH_2CH(OH)CH_3$, 430-50-2; $HOCH_2CHFCH_3$, 3824-87-1; $FCH_2CH(OH)CH_2CH_3$, 124536-12-5; $HOCH_2CHFCH_2CH_3$, 4459-24-9; $FCH_2CH_2CH(OH)CH_3$, 18804-31-4; $HOCH_2CH_2CHFCH_3$, 19808-95-8; $F(CH_2)_4OH$, 372-93-0; $HOCH_2CH(OH)CH_3$, 57-55-6; $HO(CH_2)_4OH$, 110-63-4; epiestriol, 547-81-9; allyl bromide, 106-95-6; methyl 4,6-*O*-benzylidene-α-glucopyranoside, 3162-96-7; methyl 4,6-*O*-benzylidene-β-glucopyranoside, 14155-23-8; 3-*O*-acetylepiestriol, 124536-13-6; 3-*O*-(2-propenyl)epiestriol, 5781-42-0.

Hydroboration. 85. Synthesis and Hydroboration of (−)-2-Phenylapopinene. Comparison of Mono(2-phenylapoisopinocampheyl)borane with Its 2-Methyl and 2-Ethyl Analogues for the Chiral Hydroboration of Representative Alkenes

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The dehydration of (+)-2-phenylnopinol with $POCl_3$ provides a new chiral ligand, (−)-2-phenylapopinene (87% ee), with higher steric requirements than those of α-pinene or its 2-ethyl analogue. Hydroboration of (−)-2-phenylapopinene with BH_3·SMe_2 (BMS) (1.2:1 ratio, respectively) provides an equilibrium mixture of the mono(2-phenylapoisopinocampheyl)borane ($PapBH_2$) and the corresponding dialkylborane. Treatment of this mixture with tetramethylethylenediamine (TMEDA) precipitates crystalline $(PapBH_2)_2$·TMEDA. Liberation of the $PapBH_2$ using BF_3·OEt_2 provides the monoalkylborane in ≥99% ee, thus providing the required reagent in significantly higher optical purity than the starting olefin. Hydroboration of a series of representative olefins using $PapBH_2$ at −25 °C, followed by oxidative workup, provides the corresponding chiral alcohols in unexpectedly lower enantiomeric purities than those obtained from the 2-methyl and 2-ethyl analogues under identical conditions. Liberation of the starting auxiliary from the borane reagent provides (−)-2-phenylapopinene of ≥99% ee. The hydroboration of (−)-2-phenylapopinene with 9-borabicyclo[3.3.1]nonane (9-BBN) at 28 °C in THF proceeds at an extremely retarded rate compared to its 2-methyl and 2-ethyl analogues. Fortunately, this lack of reactivity is easily circumvented by reacting $PapBH_2$ with 1,5-cyclooctadiene at room temperature for 1 h, followed by thermal isomerization to provide the desired trialkylborane.

The current surge of activity in asymmetric synthesis has prompted searches for improved, easily accessible chiral auxiliaries and reagents. Our efforts in the area have centered on chiral, pinene-based borane reagents to perform such asymmetric transformations as the hydroboration of prochiral olefins,[2] reduction of prochiral ketones,[3] asymmetric allyl- and crotylboration,[4] and epoxide ring opening.[5]

The hydroboration of α-pinene can provide either the chiral monoalkylborane ($IpcBH_2$, **1a**) or the dialkylborane (Ipc_2BH, **2**), depending on the reaction conditions. The former reagent has been shown to hydroborate hindered prochiral trans and trisubstituted alkenes with optical

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(2) (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486. (b) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514. (c) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547. (d) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065. (e) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074. (f) 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.
(3) (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(4) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111. (c) Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, *25*, 1215. (d) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (e) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(5) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246.

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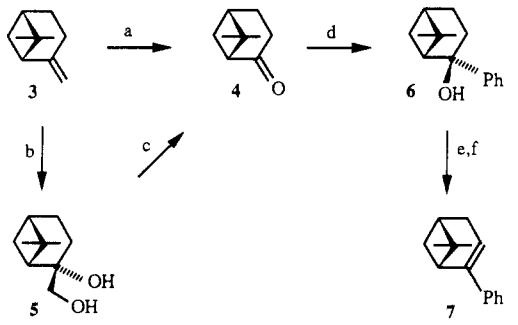
Scheme I[a]



[a] Reagents: (a) O_3, Me_2S (85%); (b) $Me_3NO[H_2O]_2$, catalytic OsO_4 (86%); (c) $Pb(OAc)_4$ (75%); (d) PhLi (73%); (e) $POCl_3$/pyridine (86%); (f) 10 mol % 9-BBN (95% recovery).

inductions ranging from 53 to ≥99% ee, with the higher values obtained with styrene derivatives.[2e] The latter reagent handles *cis*-alkenes well, providing the product alcohols in >90% ee, in most cases.[2c] These results indicate the effectiveness of these two complimentary reagents depends on the steric requirement of the substrate alkene. Whereas the boron reagent of lower steric demand, **1a**, gives optimal results with more crowded olefins, the borane of higher steric demand, **2**, prefers olefins of lower steric requirement.

1a R = Me
1b R = Et

2

This prompted a study where the steric requirements of the reagent were increased in order to optimize the fit between the olefin and the reagent. Introduction of a methyl group at the 10-position of α-pinene provided a new pinene-based auxiliary, 2-ethylapopinene. Employing the monoalkylborane derived from this sterically bulkier apopinene ($EapBH_2$, **1b**) in the hydroboration of a series of representative alkenes provided improved enantiomeric purities of the resulting alcohols than those derived from **1a**.[2f] Additionally, other borane reagents incorporating this ethyl analogue of α-pinene have led to dramatic enhancements in the optical purities of the product alcohols derived from prochiral ketones.[6] Encouraged by these results, we have now modified the apopinene moiety further by introducing a phenyl group at the 2-position. In this paper, we describe the synthesis of 2-phenylapopinene, its hydroboration characteristics, and the results of the asymmetric hydroboration of a series of representative alkenes using the monoalkylborane derived from this new auxiliary, with direct comparison of those results obtained from **1a** and **1b**.

Results and Discussion

The synthesis of (−)-2-phenylapopinene is outlined in Scheme I. (−)-β-Pinene (**3**) [$[\alpha]^{20}_D$ −21° (neat), 92% ee] was treated with ozone at −78 °C, followed by reductive workup with Me_2S[7] to provide pure (+)-nopinone (**4**) [$[\alpha]^{24}_D$ +17.54° (neat), ~92% ee] in 85% isolated yield. Alternatively, since ozonolysis on a large scale can often be tedious and hazardous, we have prepared **4** via two alternative procedures. The first involves the conversion of β-pinene into 2α,10-pinanediol (**5**) using trimethylamine *N*-oxide dihydrate (TMNO) in the presence of a catalytic quantity of OsO_4 (86% yield).[8] *cis*-Hydroxylating reagents, such as OsO_4, are known to preferentially attack the less hindered α-face of the 2,10-double bond of β-pinene to produce the 2α,10-diol, rather than the 2β,10-diol.[9] Subsequent oxidative cleavage of the glycol using lead tetraacetate[10] provided nopinone in 75% yield (65% overall from **3**). A one-pot preparation using $NaIO_4$/TMNO/catalytic OsO_4 provided **4** in 66% yield. If TMNO was not used as a cooxidant here (Lemieux–Johnson reagent),[11] the yield of the one-pot method dropped to 45%. In all cases, no unreacted β-pinene was observed.

(+)-Nopinone was treated with PhLi at 0 °C to provide a 73% isolated yield (81% based on recovered ketone) of the crystalline tertiary alcohol **6**, (+)-2-phenylnopinol. Lower yields of **6** were realized when PhMgBr was employed in place of PhLi. ^{13}C NMR analysis of the isolated product indicated only one epimer was formed. This epimer is tentatively assigned the structure with the phenyl group occupying a position endo (i.e. trans) to the geminal dimethyl groups of the pinane skeleton. Evidence for this assignment is found in the fact that nopinone is almost exclusively attacked by nucleophiles from the less hindered α-face, due to the steric influence exerted by the geminal dimethyl groups which occupy the β-face of the molecule.[9,12] The tertiary alcohol was dehydrated with $POCl_3$/pyridine to provide two products, as evidenced by GC analysis, in a 92:8 ratio. The major product was the desired (−)-2-phenylapopinene (**7**). The minor product, a close-boiling isomer as determined by GC–MS analysis, is presumably a limonene derivative, the result of fission of the acid-sensitive cyclobutane moiety of **7**.[13] Taking advantage of the fact that terminal double bonds, as in the impurity, are known to hydroborate more rapidly with bulky dialkylboranes than a phenyl, trisubstituted double bond,[14] as in **7**, the two compounds were separated by treatment of the mixture with 8–10 mol % of 9-BBN in THF at room temperature. At the end of the reaction period, ^{11}B NMR of the reaction mixture indicated quantitative consumption of the 9-BBN. Short-path distillation provided chemically pure **7** in 87% overall yield from **6**.

Preparation of Mono(2-phenylapoisopinocampheyl)borane ($PapBH_2$, 8). The hydroboration of **7** with BMS in a 1:1 molar ratio in ether at 35 °C generally led to an equilibrium mixture, within 4 h, of unreacted BMS (~6%), monoalkylated species ($PapBH_2$, ~88%), and dialkylated species, Pap_2BH (**9**) (~6%), as determined by ^{11}B NMR of a methanolyzed aliquot. Hydroboration under similar conditions using 2 equiv of the olefin again yielded an undesirable equilibrium mixture of the three aforementioned boranes. Since these results indicated that

(6) Unpublished results.
(7) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, *36*, 4273.
(8) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973. (b) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.
(9) Coxon, J. M.; Dansted, E.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* **1968**, *24*, 1193.
(10) Wolf, F. J.; Weiland, J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 124.
(11) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(12) (a) Hückel, W.; Gelchseimer, E. *Justus Liebigs Ann. Chem.* **1959**, *625*, 12. (b) Gibson, T. W.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771. (c) Hughes, C. R.; MacSweeny, D. F.; Ramage, R. *Tetrahedron* **1971**, *27*, 2247.
(13) Lewis, K. G.; Williams, G. J. *Austr. J. Chem.* **1968**, *21*, 2467.
(14) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.
(15) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.

Scheme II

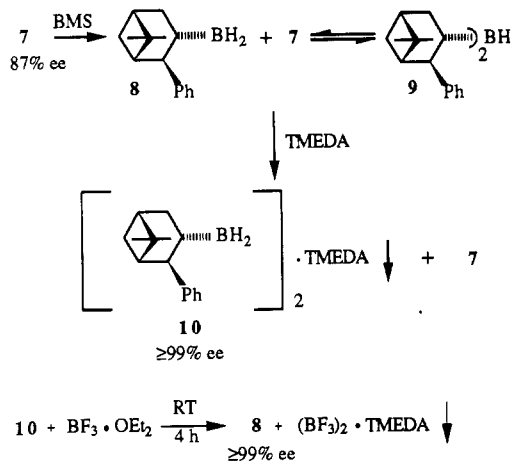


Table I. Asymmetric Hydroboration of Selected Alkenes with Mono(2-phenylapoisopinocampheyl)borane (PapBH$_2$, 8)

olefin	alcohol	% ee	yield, %	configuration
2-methyl-1-butene	2-methyl-1-butanol	1[a]	70	*R*
cis-2-butene	2-butanol	12[b]	71	*R*
trans-2-butene	2-butanol	37[b]	73	*R*
2-methyl-2-butene	3-methyl-2-butanol	31[b]	71	*R*
1-methylcyclopentene	*trans*-2-methylcyclopentanol	20[c]	50	1*R*,2*R*
1-methylcyclohexene	*trans*-2-methylcyclohexanol	51[c]	52	1*R*,2*R*

[a] Determined by comparison with highest reported rotation. [b] Determined by capillary GC as MTPA ester on SPB-5 column. [c] Determined by capillary GC as MCF ester on Supelcowax column.

the hydroboration was difficult to stop cleanly at the desired monoalkyl stage, it was necessary to employ a purification step. Employing a previously devised general method for accomplishing this step,[15] the addition of 0.5 equiv of tetramethylethylenediamine (TMEDA) to a mixture of **8** and **9** produced the expected crystalline adduct, (PapBH$_2$)$_2$·TMEDA (**10**), in 80% isolated yield. The adduct **10** selectively crystallizes from ether solution to provide a compound of ≥99% ee. The desired reagent **8** was liberated from the TMEDA by the addition of BF_3·OEt_2, which precipitated $(BF_3)_2$·TMEDA from ether solution. Filtration of the reaction mixture yielded PapBH$_2$ (≥99% ee) as a solution in ether (Scheme II). The molarity of this solution was conveniently determined by hydride analysis of an aliquot. This TMEDA step not only provided a simple method of obtaining chemically pure **8** but in the process upgraded the *optical* purity of the reagent to nearly 100% having started the synthesis with a chiral auxiliary **7** of only 87% ee.

Asymmetric Hydroboration of Representative Olefins. A study of the asymmetric hydroboration of representative olefins using optically pure PapBH$_2$ was performed. The results are summarized in Table I. In order to allow for direct comparison with **1a** and **1b**, the same olefins were selected for this study as in the previous work,[2e,2f] i.e. representative terminal, cis, trans and trisubstituted alkenes.

The olefins were hydroborated at −25 °C with an equimolar amount of PapBH$_2$ in ethyl ether. The progress of each reaction was monitored periodically by ^{11}B NMR.

Scheme III

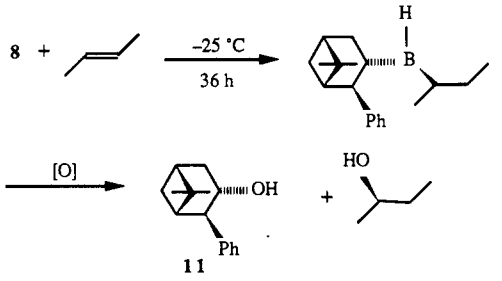


Table II. Comparison of Optical Inductions of Representative Alkenes with IpcBH$_2$,[a] EapBH$_2$,[b] and PapBH$_2$ at −25 °C (in % ee)

olefin	IpcBH$_2$	EapBH$_2$	PapBH$_2$
2-methyl-1-butene	1.5	2	1
cis-2-butene	24	30	12
trans-2-butene	73	76	37
2-methyl-2-butene	53	68	31
1-methylcyclopentene	66	68	20
1-methylcyclohexene	72	78	51

[a] Reference 2e. [b] Reference 2f.

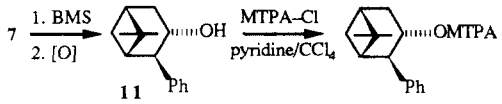
The reaction periods ranged from 24 to 48 h. The intermediate mixed dialkylborane was treated with methanol at −25 °C, followed by oxidative workup (NaOH/H_2O_2) to provide the product alcohol and (+)-2-phenylapoisopinocampheol (**11**). The two alcohols are easily separated by bulb-to-bulb distillation.

Asymmetric induction for the terminal olefin, 2-methyl-1-butene, is poor, providing (+)-2-methyl-1-butanol in only 1% ee. The hydroboration/oxidation of *cis*-2-butene gave (−)-2-butanol in only 12% ee, while *trans*-2-butene was converted into the same alcohol in 37% ee (Scheme III). The three trisubstituted olefins, 2-methyl-2-butene, 1-methylcyclopentene, and 1-methylcyclohexene were converted to the corresponding chiral alcohols in 31% ee, 20% ee, and 51% ee, respectively.

A similar trend emerges here, in that the trans and trisubstituted olefins are asymmetrically hydroborated with improved induction over the cis and 2-methyl-1-alkenes. Surprisingly though, in each instance the optical purities of the product alcohols obtained from PapBH$_2$ were markedly lower than those realized with either **1a** or **1b**. The comparative results are compiled in Table II. Two possible explanations exist for this observed decrease in the optical induction. First, the steric bulk of the phenyl group may be too great, so as to induce the PapBH$_2$ to initiate a preference for stereoselective attack of the olefin from the opposite face than the face preferred by reagents **1a** and **1b**. Alternatively, the π-cloud of the phenyl ring may exert a more powerful and deleterious electronic effect on the chiral induction than the inherent steric effect by perturbing the Lewis acidity of the boron atom.

Synthesis of (−)-2-Phenylapopinene of High Optical Purity. Although the 2-phenylapopinene does not provide improved optical induction in the hydroboration of prochiral olefins using the derived monoalkylborane species, still we were interested in its potential efficacy as a chiral director in other areas of our asymmetric synthesis program. Therefore, we were interested in obtaining optically pure **7** (i.e. ≥99% ee). Treatment of the optically pure PapBH$_2$ with 2.3 equiv of 1-hexene produced quantitative formation of the mixed trialkylborane as determined by ^{11}B NMR (δ 82). Addition of benzaldehyde (1.1 equiv) to the trialkylborane, followed by stirring at 25 °C for 30 min provided nearly quantitative formation of the borinate ester (^{11}B NMR: δ 54) and a 79% isolated yield of the

Scheme IV



eliminated (−)-2-phenylapopinene [$[\alpha]^{23}_D$ −33.12° (*c* 14, MeOH)].

The second method of preparing the optically pure olefin was to initiate the synthesis of the compound beginning with (−)-β-pinene of ≥99% ee [$[\alpha]^{23}_D$ −22.8° (neat)], obtained in high yield in a two-step, previously described synthesis from commercially available 92% ee (−)-β-pinene.[16] Ozonolysis of the optically pure (−)-β-pinene produced (+)-nopinone, which provided the highest reported rotation for this compound. The values [$[\alpha]^{23}_D$ +19.11° (neat); $[\alpha]^{23}_D$ +40.52° (*c* 4, MeOH)] are in good agreement with the calculated estimates of optically pure material [$[\alpha]^{22}_D$ +39.9° ± 0.3° (*c* 4, MeOH)].[17] The highest reported rotation is $[\alpha]_D$ +39.5° (*c* 4, MeOH).[17] Our own estimates, based on the assumption that no loss of optical activity occurs in the ozonolysis step, are $[\alpha]^{23}_D$ +19.07° (neat) and +39.9° (*c* 4, MeOH). These estimated values are based on the optical rotations obtained from the nopinone obtained from (−)-β-pinene of 92% ee. We also prepared (−)-nopinone using (+)-β-pinene of ≥99% ee[16] [$[\alpha]^{23}_D$ +22.8° (neat)] and obtained optical rotation values of $[\alpha]^{23}_D$ −19.02° (neat) and −40.12° (*c* 4, MeOH). Following the same synthetic approach as above, the optically pure (+)-nopinone was converted into (−)-2-phenylapopinene that had $[\alpha]^{23}_D$ −33.64° (*c* 14, MeOH), which we postulate to represent ≥99% ee (vide infra).

To insure that **10** was in fact ≥99% ee, a batch of the bis TMEDA adduct was prepared using the optically pure (−)-2-phenylapopinene obtained from the (−)-β-pinene of ≥99% ee. Treatment of the bis TMEDA adduct with $BF_3{\cdot}OEt_2$, followed by the above-mentioned liberation reaction, provided (−)-2-phenylapopinene that exhibited $[\alpha]^{23}_D$ −33.53° (*c* 13, MeOH). This confirmed the optical purity of the $PapBH_2$ obtained from (−)-β-pinene of 92% ee. This also implied that the originally derived (−)-2-phenylapopinene possessed an enantiomeric excess of 87%.

Both (+)- and (−)-2-phenylapopinene were hydroborated with BMS and oxidized to provide the corresponding enantiomeric 2-phenylapoisopinocampheols. A racemic mixture of the two enantiomeric alcohols was derivatized with (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl), and the two resulting diastereomers were found to separate cleanly on a SPB-5 capillary GC column (Scheme IV). Thus, we were able to confirm the 87% ee for the (−)-2-phenylapopinene derived from (−)-β-pinene of 92% ee, as well as the ≥99% ee value for the (−)-2-phenylapopinene derived from the liberation of the olefin from $PapBH_2$. The crude **11** obtained as a byproduct during the asymmetric hydroboration/oxidation of the representative alkenes was also derivatized and shown to be ≥99% ee by capillary GC analysis.

Hydroboration of (−)-2-Phenylapopinene with 9-BBN. It was of interest to investigate the reaction of **7** with 9-BBN as a means of producing the corresponding chiral trialkylborane (**12**), potentially useful in the selective asymmetric reduction of acetylenic ketones and α-keto esters. Also, the corresponding lithium trialkylborohydride would produce a sterically bulkier analogue of lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride

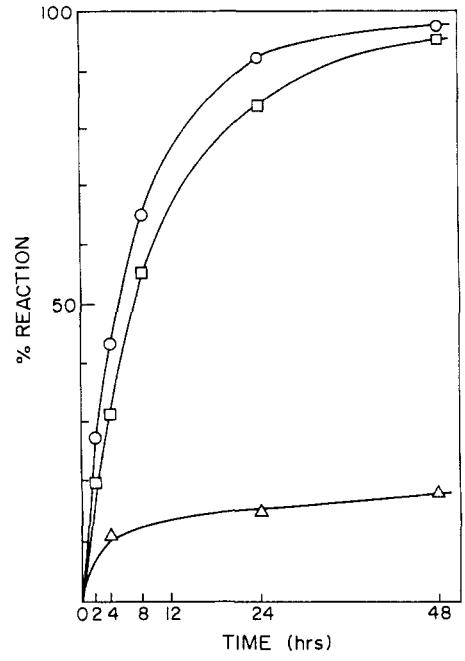


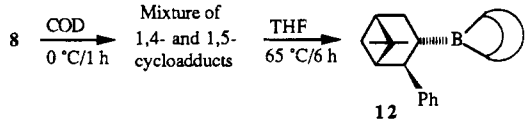
Figure 1. Rate of hydroboration of 9-BBN with α-pinene (○), 2-ethylapopinene (□), and 2-phenylapopinene (△) in THF at 28 °C (1:1 molar ratio) (0.5 M).

(Alpine-Hydride), useful in the asymmetric reduction of prochiral ketones.[18] A comparative study was performed to determine the relative rate of reaction between 9-BBN and three pinene derivatives: α-pinene, 2-ethylapopinene, and 2-phenylapopinene in THF (1:1 molar ratio) (0.5 M) at 28 °C. The results are graphically depicted in Figure 1. The α-pinene and its 2-ethyl analogue both proceed to >90% completion within 48 h. The latter olefin, being more hindered, exhibited a somewhat slower rate than α-pinene as expected. The 2-phenylapopinene exhibited an extremely sluggish rate compared to the other two olefins, proceeding to only ~18% completion after 48 h under identical conditions. Although the 2-phenylapopinene is a more sterically demanding alkene and this is expected to result in a slower rate, it seems more likely that the primary reason for the observed rate is the *electronic* effect of the phenyl group. Previous work has shown that 9-BBN is less sensitive to steric effects of substrate alkenes than other bulky dialkylboranes, such as disiamylborane.[14] This observation has been attributed to the increased electrophilic nature of the boron atom as a result of the steric strain inherent in the 9-borabicyclo[3.3.1]nonane structure. The presence of the phenyl group serves to α-conjugate strongly with electron-deficient centers[19] thus reducing the availability of the π-electrons of the alkene to the borane, resulting in relatively sluggish reactions between styrene derivatives and 9-BBN.[14]

Alternative Synthesis of *B*-(2-Phenylapoisopinocampheyl)-9-borabicyclo[3.3.1]nonane (12). It was evident from the above rate data that the synthesis of **12** was not practical via the reaction of 9-BBN with 2-phenylapopinene. Even under more favorable conditions, such as running the reaction in the absence of solvent with excess olefin at 65 °C for several days, the reaction did not satisfactorally reach completion. Previous work from this laboratory suggested an alternative approach. The cyclic hydroboration of monothexylborane with 1,5-cyclo-

(16) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059.
(17) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50.
(18) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.
(19) Peters, E. N.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 2397.

Scheme V



12

octadiene (COD) led to two products, the result of 1,4- and 1,5-cycloaddition (4/1 ratio, respectively).[20] Additionally, chiral monoalkylboranes generated in situ from the corresponding lithium borohydride on reaction with trimethylsilyl chloride underwent the same cyclic hydroboration upon reaction with COD. Quantitative isomerization of the less thermodynamically stable 1,4-cycloadduct at 65 °C provided only the 1,5-cycloadduct.[21] This chemistry was successfully applied to the synthesis of **12**. Addition of COD to a 0 °C ether solution of $PapBH_2$ for 1 h, followed by warming to 25 °C, gave quantitative formation of trialkylborane as determined by ^{11}B NMR. Oxidation of an aliquot of the solution showed it to be a 50/50 mixture of 1,4- and 1,5-cyclooctanediols. Heating a THF solution of the initially formed trialkylborane isomers to 65 °C for 6 h, quantitatively converted the 1,4-isomer into the desired 1,5-isomer (Scheme V).

Conclusions

Although the mono(2-phenylapoisopinocampheyl)borane ($PapBH_2$) is not an improved chiral hydroborating reagent, its lack of effectiveness raises the question of whether the phenyl group is primarily exerting a steric or electronic effect, or both. The role of electronic effects in the hydroboration reaction remains unclear. While styrene-based alkenes provide excellent induction in the asymmetric hydroboration with reagents like **1a**, phenyl-based borane reagents give poor inductions in asymmetric hydroboration. Further work, such as placing electron-withdrawing and -donating groups in the meta position of the aromatic ring, is needed to define this effect. The cyclic hydroboration of **8** with COD suggests a simple, new method for making *B*-alkyl-9-BBN derivatives of ≥99% ee from pinene-based alkenes that do not undergo facile hydroboration with 9-BBN.

Experimental Section

All glassware was dried at 140 °C overnight, assembled hot, and cooled to ambient temperature in a stream of nitrogen.[22] All reactions involving air- or moisture-sensitive compounds were performed under a static pressure of dry nitrogen. Reported melting points are uncorrected. ^{11}B NMR were obtained on a Varian FT-80A spectrometer and are referenced relative to $BF_3{\cdot}OEt_2$. ^1H NMR were obtained on a Varian T-60 instrument in $CDCl_3$ solution and recorded relative to internal tetramethylsilane (TMS). ^{13}C NMR were recorded on a GE Gemini 200 instrument in $CDCl_3$ solutions and recorded relative to TMS. Mass spectra were obtained on a Finnigan Model 4000 gas chromatograph/mass spectrometer. GC analyses for chemical purity and rate data were performed on a Hewlett-Packard 5730A chromatograph equipped with columns packed either with 10%-SE 30 on Chromosorb W (100–120 mesh) or 10% Carbowax on Chromosorb W (80–100 mesh). All materials for which optical rotation information is provided were purified by preparative GC on a 6 ft × 0.5 in. column packed with 20% SE-30 on Chromosorb W (60–80 mesh). Optical rotations were measured on a Rudolph Autopol III polarimeter. Capillary GC analyses were performed on a Hewlett-Packard 5890 gas chromatograph equipped with either a Supelcowax (15 M) or a SPB-5 column (30 M).

Materials. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and stored under nitrogen in an air-tight ampule. Borane–dimethyl sulfide complex (BMS), trimethylamine *N*-oxide dihydrate, (−)-β-pinene, lead tetraacetate, and phenyllithium (as a solution in ether/cyclohexane) were purchased from Aldrich and used without further purification. Tetramethylethylenediamine (TMEDA) was distilled over CaH_2 prior to use. Anhydrous diethyl ether (Mallinckrodt) was used without purification.

(1*R*,5*S*)-(+)-Nopinone (4). (−)-β-Pinene (63.2 mL, 398 mmol, 92% ee) was dissolved in methanol (120 mL) and methylene chloride (120 mL). This reaction mixture was exhaustively ozonized at −78 °C. The flask was flushed with nitrogen and treated with excess dimethyl sulfide (150 mL) at −78 °C. The flask was allowed to warm to ambient temperature over a 2-h period and then stirred for an additional 36 h. The volatiles were removed by distillation under reduced pressure. The resulting yellow oil was treated with 50 mL of ether and then 100 mL of a 5% aqueous ferrous sulfate solution and stirred for 15 min. The organic layer was removed, and the aqueous layer was extracted (2 × 50 mL) with ether. The combined organic layers were treated with a saturated sodium bicarbonate solution and stirred for 1 h. The organic layer was removed, dried over sodium sulfate, and concentrated in vacuo. Distillation of the crude material furnished 47.0 g (85%) of (+)-nopinone: bp 92–94 °C (17 mmHg); $[\alpha]^{23}_D$ +17.54° (neat), $[\alpha]^{23}_D$ +36.91° (*c* 4, MeOH) (~92% ee) [lit.[16] $[\alpha]^{22}_D$ +17.4° (neat); $[\alpha]^{22}_D$ + 36.5° (*c* 4, MeOH)]. ^1H NMR spectral data are identical with reported values.[23]

(+)-Nopinone of ≥99% ee was obtained using the above procedure utilizing (−)-β-pinene [$[\alpha]^{23}_D$ −22.8° (neat)] of ≥99% ee. The product exhibited the following: $[\alpha]^{23}_D$ +19.11° (neat), $[\alpha]^{23}_D$ +40.52° (*c* 4, MeOH). Highest reported values are: $[\alpha]_D$ +39.9 ± 0.3° (*c* 4, MeOH) calcd and $[\alpha]^{22}_D$ +39.0° and +39.5° (*c* 4, MeOH).[17] Anal. Calcd for $C_9H_{14}O$: C, 78.20; H, 10.22, Found: C, 78.15; H, 10.53.

(−)-Nopinone of ≥99% ee was obtained using the above procedure utilizing (+)-β-pinene [$[\alpha]^{23}_D$ +22.8° (neat)]. The product exhibited the following: $[\alpha]^{23}_D$ −19.02° (neat), $[\alpha]^{23}_D$ −40.12° (*c* 4, MeOH).

Alternative Syntheses of Nopinone. A. Two-Step Method. (−)-β-Pinene (102.2 g, 750 mmol, 92% ee) was dissolved in 250 mL of water, 1000 mL of *tert*-butyl alcohol, and 50 mL of pyridine. To this vigorously stirred mixture was added trimethylamine *N*-oxide dihydrate (108.3 g, 970 mmol) at room temperature, followed by 20 mL of a 0.09 M aqueous solution of OsO_4. The mixture turns yellow/brown immediately, indicative of osmate ester formation. The solution was heated to reflux (80 °C) for 20 h. The golden yellow solution was cooled to room temperature, and 500 mL of a 20% solution of sodium bisulfite added dropwise. The solution was stirred for 1 h at room temperature, and the solution was concentrated in vacuo at 50 °C for about 6 h to remove the bulk of the alcoholic solvent. To the solution was added 250 mL of saturated brine solution followed by extraction with a 50/50 mixture of THF/ethyl acetate. The organic layers were combined and dried over $MgSO_4$, and the solvents were removed in vacuo. The semisolid residue was dissolved in pentane and stored overnight in a cold room to provide a crystalline mass. The solution was filtered, and the filtrate was cooled to −70 °C in order to precipitate a second crop of compound. Combining the two crops, followed by drying under high vacuum, provided 146.4 g (86%) of (−)-2α,10-pinanediol (**5**): mp 81–82 °C (7/1 pentane/chloroform); $[\alpha]^{23}_D$ −23.2° (*c* 3, EtOH). ^{13}C NMR data are identical with literature values.[24]

The diol (108.3 g, 635 mmol) was dissolved in 600 mL of toluene at 25 °C under N_2, followed by the addition of $Pb(OAc)_4$ (382 g, 862 mmol) in portions over a 30-min period with occasional cooling of the reaction flask by an ice–water bath to control the mildly exothermic reaction. After 8 h at 25 °C, the salts were removed by filtration of the reaction mixture through a sintered-glass

(20) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1972**, *94*, 3567.
(21) Brown, H. C.; Joshi, N. N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 1754.
(22) For handling of air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.
(23) (a) Abraham, R. J.; Bottom, F. H.; Cooper, M. A.; Salmon, J. R.; Whittaker, D. *Org. Magn. Reson.* **1969**, *1*, 51. (b) Boger, D. L.; Mullican, M. D.; Hellberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904.
(24) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1351.

funnel. The solid cake was washed with additional toluene. The combined organics were washed with water and brine, followed by drying over $MgSO_4$. The toluene was distilled at reduced pressure (65 mmHg), and the residue was distilled (48–50 °C, 0.3 mmHg) to provide 65 g of chemically pure (+)-nopinone (75%). ^1H NMR data are identical with reported values.[23]

B. One-Pot Method. (−)-β-Pinene (20.0 g, 147 mmol) was dissolved in 250 mL of *tert*-butyl alcohol and 100 mL of water at 25 °C, followed by the addition of trimethylamine *N*-oxide dihydrate (17.8 g, 161 mmol), 2.5 mL of 0.09 M aqueous solution of OsO_4, and 5 mL of pyridine. With stirring at 25 °C, $NaIO_4$ (109 g, 511 mmol) was added in portions over a 20–30-min period. The solution was stirred at this temperature for 1 h and then heated to reflux (80 °C) for 2 h. The reaction mixture was cooled to room temperature, 100 mL of water was added, and the solution was filtered. The solid was washed with ether repeatedly, and the organic layer was removed. The water layer was extracted with ether. The combined organic layers were washed with 5% aqueous $Na_2S_2O_3 \cdot 5H_2O$ and dried over $MgSO_4$, and the solvent was removed. Distillation of the residue provided 13.3 g (66%) of chemically pure (+)-nopinone. ^1H NMR data are identical with reported values.[23]

(−)-2-Phenylnopinol (6). (+)-Nopinone (102.4 g, 741 mmol, 92% ee), dissolved in 500 mL of dry ether, was added dropwise to a 2.0 M solution of PhLi (555 mL, 1.11 mol) cooled to 0 °C. Once the addition was complete, the solution was allowed to warm to room temperature and stirred for 14 h. The flask was cooled to 0 °C, and sufficient aqueous ammonium chloride solution added dropwise to quench the unreacted PhLi. The aqueous layer was extracted with ether, the organic layers were combined and dried over $MgSO_4$, and the solvents were removed. The crude product, a viscous yellow oil, was crystallized at −70 °C from an ether/pentane mixture to give a white solid. This process was repeated several times using the mother liquor obtained after filtration of a crystallized batch. The crops were combined to give 116.7 g of the tertiary alcohol (**6**) (73% isolated yield, 81% yield based on recovered unreacted nopinone): mp 116–7 °C (pentane); $[\alpha]^{23}_D$ +24.07° (*c* 15, MeOH). The material obtained from ≥99% ee (−)- and (+)-β-pinene exhibited $[\alpha]^{23}_D$ +28.06° (*c* 15, MeOH) and $[\alpha]^{23}_D$ −28.19° (*c* 15, MeOH), respectively. Anal. Calcd for $C_{15}H_{20}O$: C, 83.27; H, 9.33. Found: C, 83.26; H, 9.59. ^{13}C NMR: δ 23.6 (C_9), 25.3 (C_4), 28.0, 28.7 (C_7 or C_8), 32.2 (C_3), 38.4 (C_6), 39.8 (C_5), 52.6 (C_1), 79.0 (C_2), 126.0 (Ph-2 or -3), 127.0 (Ph-4), 128.3 (Ph-2 or -3), 150.6 (Ph-1). ^1H NMR: δ 7.1–7.5 (m, 5 H), 1.7–2.6 (m, 8 H), 1.29 (s, 3 H), 1.21 (s, 3 H), 1.06 (m, 1 H).

(−)-2-Phenylapopinene (7). (−)-2-Phenylnopinol (106.7 g, 493 mmol) was dissolved in 400 mL of dry pyridine and cooled to −5 °C, followed by the dropwise addition of $POCl_3$ (91.9 mL, 986 mmol). The reaction mixture was stirred at 0 °C for 8 h and then at 25 °C overnight. The reaction mixture was slowly poured into stirring ice–water. The water layer was extracted with ether; the organic layers were combined and washed with dilute HCl, water, and aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$, and the volatiles were removed in vacuo to provide a crude yellow liquid. GC analysis of this crude material showed it to be 92–94% pure. Distillation (102 °C, 0.5 mmHg) provided 84.4 g (86%) of (−)-2-phenylapopinene. GC analysis showed the compound to be 92–94% pure. The 6–8% impurity has the same molecular weight as the desired olefin and a similar boiling point, as determined by GC–MS. The mixture of the compounds was dissolved in 300 mL of THF followed by the addition of 9-BBN (5.2 g, 42.6 mmol) and stirred at 25 °C for 20 h. The solvent was removed in vacuo, and the residue was distilled to furnish 74.6 g (~95% recovery; 76% overall from **6**) of (−)-2-phenylapopinene of ≥99% GC purity: $[\alpha]^{23}_D$ −29.02° (*c* 14, MeOH) (87% ee). Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 91.01; H, 9.30. ^{13}C NMR: δ 147.6 (C_2), 141.7 (Ph-1), 128.3 (Ph-2 or -3), 126.5 (Ph-4), 124.9 (Ph-2 or -3), 120.0 (C_3), 45.4 (C_1), 40.8 (C_5), 38.0 (C_6), 32.0 (C_4 or C_7), 31.7, (C_4 or C_7), 26.4 (C_8), 21.0 (C_9). MS (70 eV) *m/e* (relative intensity): 198 (M^+, 5.5), 155 (M^+ − 43, 100). The material obtained from (−)-β-pinene of ≥99% ee exhibited $[\alpha]^{23}_D$ −33.64° (*c* 14, MeOH).

Preparation of the Bis Adduct of Mono(2-phenylapoisopinocampheyl)borane with TMEDA (10). A dry 500-mL flask, flushed with nitrogen, was charged with BMS (9.73 mL of a 10 M solution, 97.3 mmol) and 70 mL of anhydrous ethyl ether. At 25 °C, with stirring, was added (−)-2-phenylapopinene (19.26 g, 97.3 mmol, 87% ee) dropwise. The reaction mixture was heated to reflux for 4 h. The volatiles were removed in vacuo to remove the liberated dimethyl sulfide. ^{11}B NMR indicated about 20% of the borane remained unreacted. The residue was redissolved in 70 mL of ether, 3.85 g (19.4 mmol) of additional olefin was added at room temperature, and the solution was refluxed for an additional 4 h. Again the volatiles were removed under reduced pressure (16 mmHg) and redissolved in 70 mL of ether. ^{11}B NMR indicated all the BMS had been consumed. TMEDA (7.3 mL, 48.4 mmol) was added dropwise to the refluxing solution. Once the addition was complete, the solution was maintained at reflux for 0.5 h, cooled to ambient temperature, and then placed in the cold room overnight to insure complete crystallization of **10**. The supernatant liquid was removed by a double-ended needle, and the crystals were washed with cold ether and filtered. The solid was dried under vacuum to give 21.0 g (80%) of **10**: mp 148–150 °C (2:1 chloroform/pentane). Anal. Calcd for $C_{36}H_{58}B_2N_2$: C, 79.93; H, 10.82; B, 4.07; N, 5.18. Found: C, 79.66; H, 11.20; B, 3.84; N, 5.38.

Preparation of Mono(2-phenylapoisopinocampheyl)borane (8) from 10. To a dry 250-mL round-bottom flask, flushed with nitrogen, containing **10** (21.0 g, 38.9 mmol) in 125 mL of ether, was added $BF_3 \cdot OEt_2$ (9.3 mL, 75.6 mmol) dropwise at 25 °C, and the mixture was stirred for 4 h. The resulting slurry was transferred with a double-ended needle to a filtration chamber attached to a round-bottom flask flushed with nitrogen. The solid $(BF_3)_2 \cdot$TMEDA was washed with cold ether (2 × 15 mL), and the filtrate was analyzed for hydride content by hydrolyzing an aliquot with a 1:1:1 hydrolyzing mixture of glycerol/water/THF and found to be 0.42 M (152 mL, 84% yield) (^{11}B NMR: δ 24). The solution is best stored under nitrogen at 0 °C.

General Procedure for the Asymmetric Hydroboration of Olefins. The ether solution of the $PapBH_2$ was placed in a round-bottom flask equipped with a septum inlet and a reflux condenser and cooled to −25 °C. An equimolar amount of the alkene was added dropwise to the stirring solution. The solution was stirred at −25 °C for 36–48 h and monitored by ^{11}B NMR. At the end of the reaction period, the solution was treated with a slight excess of methanol at −25 °C and then slowly warmed to room temperature. The solution was then treated with 3 equiv of 3 N NaOH, cooled to 0 °C, and carefully treated with 3 equiv of 30% H_2O_2. Once the addition was complete, the flask was allowed to warm to room temperature and then heated to reflux for 2 h to insure complete oxidation. The organic layer was removed, and the aqueous layer was extracted with ether. The organics were combined dried over magnesium sulfate, and the solvent was carefully removed to provide the crude alcohol. Typical reaction scales were 7–18 mmol.

***(R)*-(+)-2-Methyl-1-butanol.** According to the general procedure, 7.1 mmol of $PapBH_2$ was reacted with 7.1 mmol of 2-methyl-1-butene for 36 h. Usual workup, followed by bulb-to-bulb distillation (64–66 °C, 55 mmHg) provided 0.38 g (70%) of (*R*)-(+)-2-methyl-1-butanol (>98% GC purity). Purification on a preparative GC with a 20% SE-30 column furnished analytically pure material: $[\alpha]^{23}_D$ +0.053° (neat). This indicates 0.9% ee, based on comparison with the highest reported rotation.[25]

***(R)*-(−)-2-Butanol from *cis*-2-Butene.** According to the general procedure, 12.0 mmol of $PapBH_2$ was treated with 12.0 mmol of *cis*-2-butene that had been condensed in a graduated cylinder cooled by a dry ice/acetone bath. The reaction was quenched after 36 h, followed by the usual workup. Distillation (94–96 °C, 740 mmHg) provided 0.63 g (73%) of (*R*)-(+)-2-butanol (>98% GC purity). The alcohol was purified by preparative GC to provide analytically pure material that exhibited $[\alpha]^{23}_D$ −1.67° (neat). This indicates 12% ee, based on the highest reported rotation.[26] Capillary GC analysis of the MTPA ester indicated a value of 11% ee.

***(R)*-(−)-2-Butanol from *trans*-2-Butene.** According to the general procedure, 7.4 mmol of $PapBH_2$ was reacted with 7.4 mmol of *trans*-2-butene that had been condensed in a graduated cylinder cooled by a dry ice/acetone bath. The reaction was quenched after 36 h and oxidative workup, followed by distillation (94–96

(25) Whitmore, F. C.; Olewine, J. H. *J. Am. Chem. Soc.* **1938**, *60*, 2569.
(26) Leroux, P. J.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 41.

°C, 740 mmHg) provided 0.42 g (76%) of (*R*)-(−)-2-butanol (>97% GC purity). The alcohol was purified on preparative GC to furnish material that exhibited $[\alpha]^{23}_D$ −4.86° (neat), indicative of 36% ee based on the highest reported rotation.[26] Capillary GC analysis of the MTPA ester indicated a value of 37% ee.

(*R*)-(−)-3-Methyl-2-butanol. According to the general procedure, 18.0 mmol of $PapBH_2$ was reacted with 18.0 mmol of 2-methyl-2-butene for 48 h. Usual workup, followed by distillation (42 °C, 30 mmHg) gave 1.12 g (71%) of (*R*)-(−)-3-methyl-2-butanol (>98% GC pure). Capillary GC analysis of the alcohol as the MTPA ester indicated 31% ee.

(1*R*,2*R*)-(−)-*trans*-2-Methylcyclopentanol. According to the general procedure, 14.2 mmol of $PapBH_2$ was reacted with 14.2 mmol of 1-methylcyclopentene for 48 h. Usual workup, followed by bulb-to-bulb distillation (65 mmHg) furnished 0.71 g (50%) of >95% GC pure (1*R*,2*R*)-(−)-*trans*-2-methylcyclopentanol. The alcohol was converted into its MCF ester and analyzed by capillary GC which indicated 20% ee.

(1*R*,2*R*)-(−)-*trans*-2-Methylcyclohexanol. According to the general procedure, 14.4 mmol of $PapBH_2$ was treated with 14.4 mmol of 1-methylcyclohexene and reacted for 48 h. Usual workup, followed by bulb-to-bulb distillation (70 mmHg), gave 0.83 g (52%) of (1*R*,2*R*)-(−)-*trans*-2-methylcyclohexanol (>95% GC pure). The alcohol was converted into the MCF ester. Capillary GC analysis indicated 51% ee.

Liberation of (−)-2-Phenylapopinene of High Optical Purity. At 0 °C, 1-hexene (1.8 mL, 14.4 mmol) was added dropwise to a 0.42 M solution of $PapBH_2$ in ether (15.0 mL, 6.4 mmol). The reaction mixture was warmed to 25 °C and stirred for 30 min. ^{11}B NMR indicated quantitative formation of the mixed trialkylborane (δ 82). Benzaldehyde (0.70 mL, 6.9 mmol) was added, and the mixture was stirred for 30 min at 25 °C. ^{11}B NMR indicated quantitative formation of the corresponding borinate ester (δ 54). Ethanolamine (0.8 mL, 13.3 mmol) was added to the reaction mixture at 25 °C. After 30 min, the solvents were removed, and the resulting oil was dissolved in pentane (25 mL). The organic layer was washed with aqueous sodium bisulfite, water, 3 N NaOH, and brine. The organic layer was dried over sodium sulfate, and the volatiles were removed. Distillation of the residue (80–82 °C, 0.1 mmHg) gave 0.99 g (79%) of (−)-2-phenylapopinene (≥99% GC pure). Analytically pure material exhibited $[\alpha]^{23}_D$ −33.12° (*c* 14, MeOH), indicative of material of ≥99% ee. The (−)-2-phenylapopinene obtained from the above-mentioned two-step sequence (BF_3·OEt_2, then benzaldehyde) using bis TMEDA adduct **10**, that was originally prepared using ≥99% ee (−)-2-phenylapopinene, exhibited $[\alpha]^{23}_D$ −33.53° (*c* 13, MeOH).

Rate Studies for the Reaction of α-Pinene and Its 2-Ethyl and 2-Phenyl Analogues with 9-BBN. The reactions were carried out in the presence of an internal standard (*n*-octane or *n*-dodecane) on a 10-mmol scale as follows: 1.0 equiv of solid 9-BBN was dissolved in sufficient THF to yield a 0.50 M solution and maintained at 28 °C. The appropriate olefin (1.0 equiv) was added dropwise. At appropriate intervals, a 1-mL aliquot was removed, dissolved in 4–5 mL of THF, and oxidized (NaOH/H_2O_2). GC analysis of the unreacted amount of olefin was measured against the internal standard, whose response factors had been calculated. These results are graphically depicted in Figure 1.

Synthesis of (+)-2-Phenylapoisopinocampheol (11). A round-bottom flask was charged with BMS (0.5 mL of a 10 M solution, 5 mmol) and 5 mL of ether and cooled to 0 °C. To the stirred solution was added (−)-2-phenylapopinene (1.19 g, 6 mmol, 87% ee). The flask was warmed to room temperature and then heated to reflux for 8 h. The organoboranes were oxidized by adding 6 mL of 3 N NaOH at room temperature and then 6 mL of 30% H_2O_2 at 0 °C to the reaction flask. The contents were then heated to reflux for 3 h to insure complete oxidation. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and saturated brine solution and dried over magnesium sulfate. Evaporation of the solvents provided the crude alcohol which was crystallized from pentane to give 0.84 g (78%) of pure **11**: mp 108–109 °C; $[\alpha]^{24}_D$ +23.38° (*c* 10, MeOH). Capillary GC analysis of **11** as its MTPA ester indicates 87% ee. Anal. Calcd for $C_{15}H_{20}O$: C, 83.27; H, 9.33. Found: C, 83.22; H, 9.49. ^1H NMR: δ 0.78 (s, 3 H), 1.32 (br s, 4 H), 1.6–2.8 (br, 6 H), 3.21 (br d, 1 H), 4.47 (m, 1 H), 7.04–7.5 (br, 5 H). The alcohol obtained from optically pure (−)-2-phenylapopinene exhibited $[\alpha]^{24}_D$ +27.04° (*c* 10, MeOH). Capillary GC analysis indicates ≥99% ee.

Synthesis of *B*-(2-phenylapoisopinocampheyl)-9-borabicyclo[3.3.1]nonane (12) from 8. An ether solution of $PapBH_2$ (**8**) (10.0 mL of a 0.70 M solution, 7.0 mmol) was cooled to 0 °C, followed by the dropwise addition of 1,5-cyclooctadiene (0.98 mL, 8.0 mmol). The solution was stirred at this temperature for 1 h and allowed to warm to 25 °C. ^{11}B NMR showed quantitative consumption of **8** as evidenced by a single peak at δ 83. Oxidation (NaOH/H_2O_2) of an aliquot of this solution indicated a 50/50 mixture of *cis*-1,4-cyclooctanediol and *cis*-1,5-cyclooctanediol, as determined by capillary GC analysis (SPB-5 column) of the silylated diols. The ether was evaporated from the original reaction flask (16 mmHg), 7 mL of THF was added, and the solution was refluxed for 6 h. Oxidation of an aliquot at this time showed only the presence of the 1,5-diol, as determined by analysis of the silylated diol on capillary GC, indicative of complete thermal isomerization to provide pure **12**. The diols were silylated with bis(trimethylsilyl)acetamide (BTSA)/pyridine in THF at 25 °C for 4 h.

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Registry No. (+)-**3**, 19902-08-0; (−)-**3**, 18172-67-3; (+)-**4**, 38651-65-9; (−)-**4**, 77982-63-9; **5**, 124439-19-6; (+)-**6**, 124355-70-0; (−)-**6**, 124379-62-0; (−)-**7**, 124355-71-1; **8**, 124355-72-2; **9**, 124355-73-3; **10**, 124355-74-4; **11**, 124355-75-5; **12**, 124355-76-6; 1,5-COD, 111-78-4; 2-methyl-1-butene, 563-46-2; (*R*)-(+)-2-methyl-1-butanol, 616-16-0; *cis*-2-butene, 590-18-1; (*R*)-(−)-2-butanol, 14898-79-4; *trans*-2-butene, 624-64-6; 2-methyl-2-butene, 513-35-9; (*R*)-(−)-3-methyl-2-butanol, 1572-93-6; 1-methylcyclopentene, 693-89-0; (1*R*,2*R*)-*trans*-(−)-2-methylcyclopentanol, 39947-47-2; 1-methylcyclohexene, 591-49-1; (1*R*,2*R*)-*trans*-(−)-2-methylcyclohexanol, 19043-03-9.