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2-Isopropylapoisopinocampheylborane, An Improved Reagent for the Asymmetric Hydroboration of Representative Prochiral Alkenes

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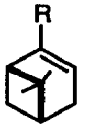
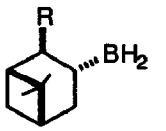
Abstract: *A new hydroborating agent, 2-isopropylapoisopinocampheylborane ($^{i}PraBH_2$, 2f), achieves the asymmetric hydroboration of representative prochiral alkenes in higher optical purities than that achieved by the borane derivatives, 2-organylapoisopinocampheylboranes (R = Me, $IpcBH_2$; R = Et, $EapBH_2$; and R = Ph, $PapBH_2$) previously examined.*

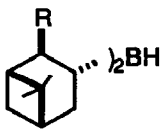
In 1961 the first non-enzymatic asymmetric synthesis in high optical purity was reported.[2] Asymmetric hydroboration of *cis*-2-butene by diisopinocampheylborane, Ipc_2BH (**3a**), from α-pinene of 92% ee, provided the product alcohol in high optical purity (87% ee). Since then, α-pinene and its derived boron derivatives have proven to be convenient, powerful, and successful chiral auxiliaries for asymmetric synthesis *via* organoboranes.[3] Ipc_2BH achieves hydroboration of less hindered olefins (*cis*-alkenes) in ≥99% enantiomeric excess,[4] but it reacts with moderately hindered alkenes such as *trans*- and trisubstituted, in a complex manner, with elimination of α-pinene. As a result, the chiral induction is seriously impaired.[5]



1a R = Me **1d** R = *i*-Bu
1b R = Et **1e** R = Ph
1c R = Pr **1f** R = *i*-Pr



2a-f



3a-f

To handle the more hindered *trans*- and trisubstituted olefins, $IpcBH_2$ (**2a**) was synthesized and tested. A major improvement was achieved, but the results fell short of our goal of ≥99% enantioselectivity.[6] Fortunately, a simple filtration of the boron intermediate did provide products approaching ≥99% ee.[7]

Another solution of this problem was reported by Masamune and coworkers.[8] They synthesized and resolved a new asymmetric hydroborating agent, *trans*-2,5-dimethylborolane. The C_2 symmetry which makes both the faces of the boron atom equivalent is an important feature of this reagent. This reagent provides excellent results for the asymmetric hydroboration of the above three classes of olefins. However, the synthesis of this asymmetric hydroborating reagent requires considerable effort and it has been rarely utilized for asymmetric synthesis.

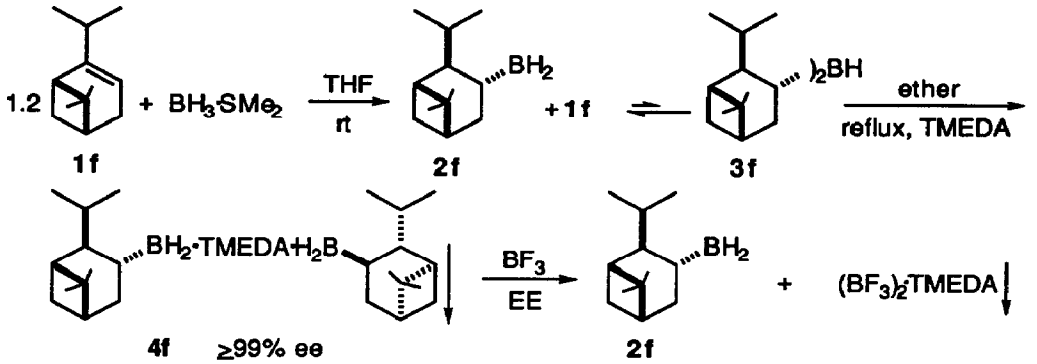
We undertook to improve our terpene-derived reagents. Consideration of the mechanism for asymmetric hydroboration gave us reason to believe that the steric requirements of the methyl group at the 2-position of the

apopinene moiety must be critical for achieving high stereocontrol in such asymmetric hydroborations. This hypothesis is supported by the theoretical calculations reported for the α-pinene-based reagents.[9] Therefore, we launched a program to modify apopinene by introducing more hindered groups at the 2-position.

$IpcBH_2$ (**2a**) hydroborates hindered and trisubstituted alkenes with optical inductions ranging from 53 to ≥99% ee, with higher values obtained with phenyl-substituted olefins.[6] A modest improvement was realized with the reagent, $EapBH_2$, derived from 2-ethylapopinene (**1b**).[10] An important improvement in asymmetric reduction of ketones was achieved for Eap_2BCl as compared to Ipc_2BCl.[3c] These favorable results led us to synthesize 2-phenylapopinene (**1e**),[11] in the hope that the larger steric requirements of the phenyl group would improve the hydroboration results. Accordingly, **1e** was synthesized and converted into $PapBH_2$ (**2e**).[11] It was a major disappointment to realize less satisfactory hydroboration results,[11] lower than those realized with $IpcBH_2$[6] and $EapBH_2$.[10] Possibly, the π-electrons of the phenyl ring are much less effective than saturated alkyl groups in exerting the desired steric influence in the transition state. We were faced with a major dilemma. Either our working hypothesis was wrong, or the π-cloud of the aromatic ring is far less effective in exerting steric influence on the course of the reaction than saturated alkyl groups. Accordingly, the synthesis of 2-isopropylapopinene (**1f**)[12a] was undertaken to examine the effect of a bulkier alkyl group, isopropyl, at the 2-position of apopinene.

Interestingly, the hydroboration of the sterically bulkier (+)-**1f** (≥91% ee) with BMS in a 1.2 : 1 molar ratio in THF at room temperature, leads to an equilibrium mixture, after 24-36 h, consisting essentially of the monoalkylated species **2f** (>95%), as determined by ^{11}B NMR of a methanolyzed aliquot.[12a,b] However, the hydroboration is difficult to stop cleanly at the desired monoalkyl stage. Fortunately, the addition of 0.5 equiv of tetramethylethylenediamine (TMEDA) to a mixture of **2f** and minor amounts of **3f**, provides the expected crystalline adduct (-)-(**4f**) in 75-77% isolated yield[12b] (Scheme I).

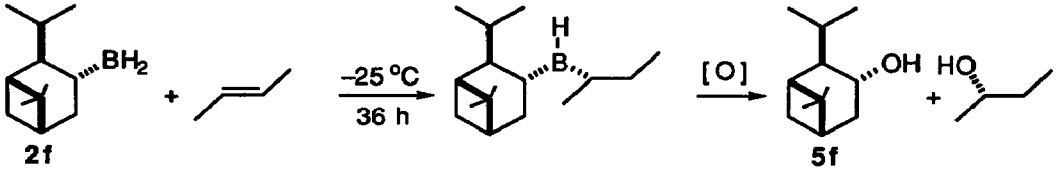
Scheme I



The adduct selectively crystallizes from ethyl ether (EE) solvent to provide a compound of ≥99% ee.[12b] The desired borane reagent **2f**, is liberated in EE by the addition of BF_3·EE, which precipitates the highly insoluble $(BF_3)_2$·TMEDA from the solution. Filtration of the reaction mixture furnishes $^{i}PraBH_2$ (**2f**) (≥99% ee) in ether (Scheme I). The molarity of this solution is conveniently determined by a hydride estimate of an aliquot.[13] To determine the optical purity of $^{i}PraBH_2$, an aliquot was methanolyzed and the corresponding boronate ester was oxidized with alkaline peroxide. The resultant alcohol (**5f**) was isolated and analyzed on capillary GC as its menthyloxycarbonyl derivative[14] indicating an optical purity of ≥99% in comparison with its

1 : 1 diastereomeric mixture. A study of the asymmetric hydroboration of representative olefins using optically pure ^{i}PraBH$_2$ (**2f**) was performed (Scheme II).

Scheme II



In order to allow for direct comparison of **2f** with **2a,b,e**, the standard set of olefins was examined[6,10,11] i.e. representative terminal, *cis*-, *trans*-, and trisubstituted alkenes. The olefins were hydroborated at –25 °C with an equimolar amount of ^{i}PraBH$_2$ (**2f**) in ether. The progress of each reaction was monitored periodically by ^{11}B NMR. The reaction time ranged from 36-72 h. The intermediate, mixed dialkylborane, is treated with methanol at –25 °C, followed by oxidative workup (NaOH / H_2O_2)[6,10,11] to provide the product alcohol and (-)-isopropylapoisopinocampheol (**5f**). The two alcohols are easily separated by short-path distillation. The results are summarized in Table 1.

Table 1. Asymmetric Hydroboration of Representative Alkenes with 2-Isopropylapoisopinocampheylborane (2f)[a] in EE at –25 °C.

olefins	alcohol	yield (%)	optical purity (% ee)	absolute configuration
2-methyl-1-butene	2-methyl-1-butanol[b]	73	8	*S*
cis-2-butene	2-butanol[c]	76	38	*S*
trans-2-butene	2-butanol[c]	74	76	*S*
2-methyl-2-butene	3-methyl-2-butanol[d]	70	80	*S*
1-methylcyclopentene	*trans*-2-methylcyclopentanol[d]	73	82	*1S,2S*
1-methylcyclohexene	*trans*-2-methylcyclohexanol[d]	62	88	*1S,2S*

[a]Synthesized from (+)-1f. [b]% ee determined by comparison with highest reported rotation.[15] [c]% ee determined by capillary GC as MTPA ester on SPB-5 column. [d]% ee determined by capillary GC as menthyloxycarbonyl derivative on SPB-5 column.

The asymmetric induction achieved for the terminal olefin, 2-methyl-1-butene, is poor, providing (-)-2-methyl-1-butanol in only 8% ee. The hydroboration / oxidation of *cis*-2-butene with ^{i}PraBH$_2$ (**2f**) gives (+)-2-butanol in 38% ee, better than the previously reported chiral 2-R-apoisopinylborane reagents (**2a,b,e**). The *trans*-2-butene is converted into the same alcohol in 76% ee (Scheme II). Significantly better optical yields are realized, *viz.* 80% ee, 82% ee, and 88% ee for the asymmetric hydroboration of the three trisubstituted olefins namely 2-methyl-2-butene, 1-methylcyclopentene, and 1-methylcyclohexene in comparison with the earlier 2-R-apoisopinylborane reagents (**2a,b,e**) examined. The results are summarized in Table 2.

Table 2. Comparison of Optical Induction of Representative Alkenes with $IpcBH_2$,[a] $EapBH_2$,[b] and $PapBH_2$[c] at –25 °C (in % ee).

alkene	$IpcBH_2$ (2a)	$EapBH_2$ (2b)	$PapBH_2$ (2e)	$^{i}PraBH_2$ (2f)
2-methyl-1-butene	1.5	2	1	8
cis-2-butene	24	30	12	38
trans-2-butene	73	76	37	76
2-methyl-2-butene	53	68	31	80
1-methylcyclopentene	66	68	20	82
1-methylcyclohexene	72	78	51	88

[a]Ref 4. [b]Ref 10. [c]Ref 11. Ipc = α-pinene; Eap = 2-ethylapopinene; Pap = 2-phenylapopinene; ^{i}Pra = 2-isopropylapopinene

In conclusion, we have demonstrated that the sterically bulkier chiral borane reagent, $^{i}PraBH_2$, hydroborates prochiral alkenes to achieve significantly better optical induction than those realized by $IpcBH_2$, $EapBH_2$, and $PapBH_2$. These results imply that the steric requirements of saturated alkyl groups at the 2-position of apopinene control the stereoselectivity for asymmetric hydroboration. $^{i}PraBH_2$ is capable of enantioselectively hydroborating trisubstituted alkenes very well, better than any other α-pinene-based reagent available presently. We are planning to extend the study to the more sterically bulky *t*-Bu and CF_3 groups at the 2-position of the apopinene and to the corresponding RapBHX (X = Cl, Br, and I) derivatives. Initial results are quite promising.

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