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Lithium-*B*-Iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride as an Improved Reagent for Asymmetric Reduction of Unhindered Aliphatic Ketones. Further Evidence for the Improved Enantioselectivity in Reductions by Reagents Containing Increased Steric Requirements at the 2-Position of the Apopinene Structure

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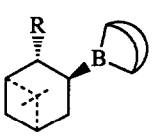
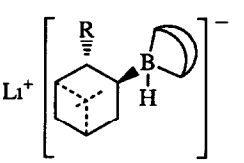
Abstract: Lithium *B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (Eapine-Hydride), prepared by hydroboration of 2-ethylapopinene with 9-borabicyclo[3.3.1]nonane, followed by treatment with *tert*-butyllithium, is as effective as NB-Enantride for the chiral reduction of prochiral ketones. For example Eapine-Hydride reduces 2-octanone, 3-methyl-2-butanone, and acetylcyclohexane in 77% (75%, 79%), 77% (68%), and 80% (80%) ee, respectively, at –100 °C. (Values in parenthesis are for NB-Enantride).

The use of chiral metal hydrides for transforming a prochiral ketone to a chiral alcohol has been the subject of extensive investigations.[1] Chirally modified lithium aluminum hydrides, such as Noyori's Binal-H[2], have given encouraging results.[3] Modifications of lithium and sodium borohydride have been studied by many groups.[4] Our studies of chiral potassium borohydrides as reducing agents led to K-Glucoride, a superior reagent for the chiral reduction of hindered aralkyl ketones and α-ketoesters.[5] Despite these developments, the asymmetric reduction of relatively unhindered aliphatic ketones (such as straight chain) in high ee remains a challenge for organic chemists.

The synthesis of optically active organoboranes by hydroborating optically active terpenes led to borohydrides which achieve asymmetric reduction of prochiral ketones. Our initial effort using this methodology was the synthesis of lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (Aldrich: Alpine-Hydride, **2a**) which achieve a moderate asymmetric reduction of the test ketones (up to 36% ee).[6]



1a R = CH_3
1b R = CH_2CH_2OBnz
1c R = CH_2CH_3
1d R = $CH_2CH_2CH_3$



2a R = CH_3
2b R = CH_2CH_2OBnz
2c R = CH_2CH_3

Subsequently, Midland and Kazubski prepared a similar chiral borohydride, lithium *B*-iso-2-(2-benzyloxy)ethylapopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (NB-Enantride, **2b**),[7] which proved to be especially valuable for the reduction of unhindered aliphatic ketones such as 2-butanone, and 2-octanone (76%

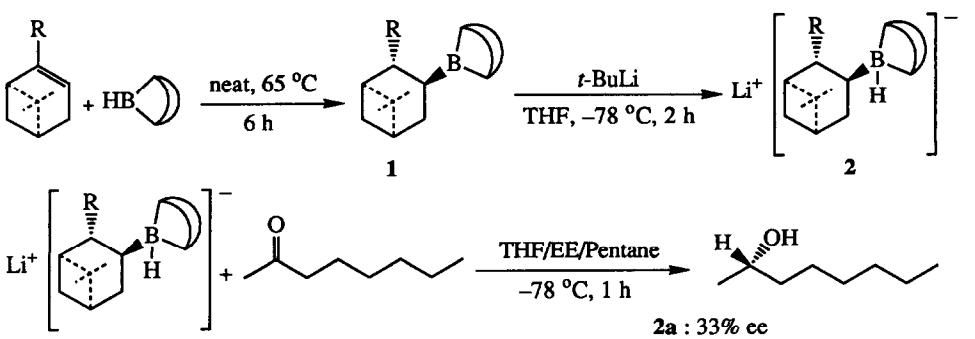
ee and 79% ee, respectively, at –100 °C). This is one of the highest values reported for the reduction of such ketones using a non-enzymatic reagent. The success of this reagent was attributed to the "incorporation of an oxygen into the chiral ligand which provides a fixed coordination site for the lithium and hence a more rigid and thus more sterically demanding transition state".[7] However, lower values were obtained for a similar reagent prepared from myrtenol benzyl ether, which contains one carbon atom less at the 2-position of apopinene .[7]

Recently we postulated that the steric requirement of the substituent at the 2-position of 2-alkylapopinene influences the chiral outcome in reductions using reagents containing that structure.[8] Support for this hypothesis is the higher enantioselectivity realized for the chiral reduction of acetylenic ketones with NB-Enantrane (**1b**), Eapine-Borane (**1c**), and Prapine-Borane (**1d**) as compared to Alpine-Borane (**1a**).[9]

While the exact mode of action of Alpine-Hydride or NB-Enantride is uncertain, we undertook to test our tentative hypothesis to see if it could also be used to explain the high selectivities obtained for the alcohols from unhindered aliphatic ketones using NB-Enantride. If this were true it should be possible to obtain comparable results using a similar reagent prepared from 2-ethylapopinene, a reagent with similar steric properties, but without the special chemical features of the benzyloxy group. The results of the study are presented in this communication.

Reaction of (–)-2-ethylapopinene with 9-BBN under neat conditions at 65 °C for 6 h provides Eapine-Borane.[9] Treatment with *tert*-butyllithium in THF at –78 °C, provided *B*-iso-2-ethylapopinocampheyl-9-borabicyclo[3.3.1]nonylhydride (Eapine-Hydride, **2c**) (^{11}B NMR: δ –6.2 ppm, d, J = 80 Hz). Reaction of 2-octanone with **2c** at –78 °C for 1 h followed by oxidative work up provides an 85% yield of (*S*)-2-octanol, 63.5% ee.[10] Correcting for the optical purity of 2-ethylapopinene used for the preparation of **2c**, the ee becomes 69%. The reaction was repeated using optically pure reagent[11] and the product alcohol obtained in 70% ee. Conducting the reaction at –100 °C with optically pure reagent yields the product alcohol in 77% ee (Scheme I). For a similar reaction of 2-octanone with **2b** at –100 °C, Midland had reported 79% ee for 2-octanol based on Eu-shifted ^{1}H NMR analysis. For direct comparison, we prepared optically pure **2b**[11] and reduced 2-octanone at –78 °C and at –100 °C, achieving 62% ee and 75% ee, respectively.

Scheme I



2a : 33% ee
2b : 62% ee (75% ee at –100 °C)
2c : 70% ee (77% ee at –100 °C)

A reaction of 2-octanone with **2a** at –78 °C provides 2-octanol of only 33% ee.[12] Such a drastic increase in selectivity: 33% to 70% for the product 2-octanol by increasing the steric requirement of the substituent at the 2-position of apopinene in the reagent supports our hypothesis.

To further substantiate the point, our standard set of representative ketones[13] were reduced using **2a**, **2b**, and **2c** and the results compared (Table I). A reaction of 3-methyl-2-butanone with **2** at –100 °C provides the corresponding alcohol in 68% ee whereas **2c** provides the alcohol in 77% ee. Alpine-Hydride provides this alcohol in only 36% ee at –78 °C.[5] Acetylcyclohexane is reduced by both **2b** and **2c** in 80% ee at –100 °C. Acetophenone is reduced at –78 °C by **2a**, **2b**, and 2c in 20%, 63% and 56% ee, respectively. At –100 °C, **2b** provides α-phenethanol in 70% ee whereas **2c** induces only 61% ee. Similar effects are observed for the reduction of 2-chloroacetophenone. None of the above reagents could induce significant asymmetry in the reduction of sterically hindered ketones, such as 2,2-dimethylcyclopentanone, or acetylenic ketones, such as 4-phenyl-3-butyn-2-one. 2-Cyclohexenone undergoes 1,4-addition with these reagents at –78 °C.[13] Consequently, we did not try the reaction at –100 °C. In all other cases, the reductions are complete within 1 h at –78 °C and 3 h at –100 °C with yields of 75-80% for the isolated alcohols. All the alcohols produced in the reductions are of the (*S*)-configuration[10] except the product from the reduction of 2-chloroacetophenone where (*R*)-alcohol is obtained (an artifact of the Cahn-Ingold-Prelog rules).[14]

Table I. Reduction of Representative Ketones with Chiral Trialkylborohydrides.

class of ketone[a]	ketone	%ee				
		Alpine-Hydride, **2a** –78 °C	NB-Enantride, **2b** –78 °C	–100 °C	Eapine-Hydride, **2c** –78 °C	–100 °C
I	2-octanone	33	62	75 (79)[b]	70	77
I	3-methyl-2-butanone*	36		68[b]		77
I	acetylcyclohexane	27	65[c]	80	70[c]	80
II	2,2-dimethylcyclopentanone*	1	0.5		7	
III	acetophenone*	20	63[c]	70[b]	56[c]	61
V	2-chloroacetophenone*	4	41[c]		48[c]	
X	4-phenyl-3-butyn-2-one*	5		10[b]	5[c]	

[a]Ref. 13. Those marked with asterisks are the selected representatives of the class indicated. [b]Ref. 7. [c]Corrected for the optical purity of the reagent (92% ee).

In conclusion, we have synthesized a new chiral borohydride, Eapine-Hydride and reduced prochiral ketones to test the hypothesis that the steric requirement at the 2-position of 2-alkylapopinene controls the stereoselectivity for reductions using reagents containing that structure. Eapine-Hydride is as effective as the 2-(2-benzyloxy)ethyl analog, NB-Enantride. Of the ten classes of our standard ketones,[13] Eapine-Hydride is capable of chirally reducing unhindered class I ketones i.e. acyclic aliphatic ketones, very well, better than any other reagent available presently. We are currently studying reagents with even larger steric bulk at the 2-position of apopinene and the initial results are very promising.

The following experiment is typical: Procedures for handling air- sensitive materials are described elsewhere.[15] Solid 9-BBN (1.25g, 10mmol) was transferred under nitrogen to a 100mL round bottomed flask using a glove bag. 2-Ethylapopinene $[\alpha]_D^{23}$ –45.65 (neat), (≥99% ee) (1.65 g, 11 mmol) was syringed into the flask and heated for 6 h to form **1c**.[9] This was dissolved in THF (10 mL) and cooled to –78 °C. *tert*-Butyllithium (6.5 mL of 1.7 *M* in hexanes, 11 mmol) was added dropwise and stirred at –78 °C for 2 h and warmed to 25 °C to form Eapine-Hydride (^{11}B NMR: δ –6.2 ppm, d, J = 80 Hz). The reagent was standardized by hydride estimation.[15] A 5 mmol aliquot of this reagent was diluted with 5 mL of THF and 5 mL of EE and cooled to –100 °C [petroleum ether (30-60 °C)/2-propanol/acetone (4:1:1)/liquid nitrogen bath].[16] 2-Octanone (0.7 mL, 4.5 mmol) in 10 mL of THF/pentane/EE 4:1:1 was cooled to –100 °C in another flask and added dropwise to the reagent at –100 °C by using a double-ended needle. The reaction mixture was stirred for 3 h and quenched with cold (–100 °C) ethanol (1 mL) and subjected to the usual alkaline H_2O_2 workup. Extraction of the product in ether and distillation provided 0.47 g (80%yield) of 2-octanol. Analysis of the MTPA ester using an SPB-5 (30 m) capillary column showed a composition of 88.5% *S* isomer and 11.5% of *R* isomer i.e. an ee of 77%.

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