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Isopinocampheylbromoborane, A New Promising Reagent for the Asymmetric Hydroboration of Prochiral Alkenes

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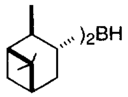
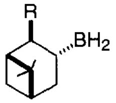
Abstract: A new promising in situ generated hydroborating agent, isopinocampheylbromoborane (IpcBHBr), achieves the asymmetric hydroboration of representative prochiral alkenes in pentane at lower temperatures, even at −78 °C, than has been possible with isopinocampheylborane ($IpcBH_2$) and isopinocampheylchloroborane·EE (IpcBHCl·EE) reagents, usually in higher enantioselectivities than previously achieved. This is first time that the asymmetric hydroboration of prochiral alkenes with an α–pinene-derived borane reagent (IpcBHBr) has been achieved at such low temperature, −78 °C, in a relatively short time, 4-6 h.

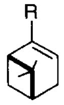
In 1961 the first non-enzymatic asymmetric synthesis in high optical purity was reported *via* a borane reagent incorporating α–pinene as the chiral director.[2] α–Pinene of 92% enantiomeric excess (ee) was converted into diisopinocampheylborane (Ipc_2BH, **1**) and treated with *cis*-2-butene to provide, on oxidation, the chiral 2-butanol in 87% ee.



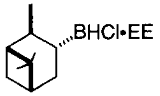
1



2
$RapBH_2$



3a R = Me **3d** R = *i*-Bu
3b R = Et **3e** R = Ph
3c R = Pr **3f** R = *i*-Pr



4a
IpcBHCl•EE

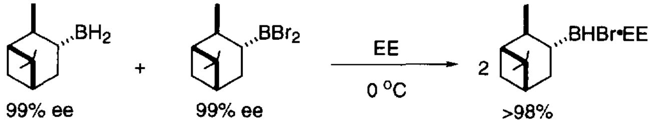
This gratifying achievement led us to synthesize a number of pinene derived borane derivatives which are proving to be convenient, powerful, successful reagents for asymmetric synthesis *via* organoboranes.[3] The hydroboration of pinene can be controlled to provide either the chiral dialkylborane (Ipc_2BH, **1**) or the monoalkylborane ($IpcBH_2$, **2a**),[4] as desired. The former reagent achieves hydroboration of less hindered *cis*-alkenes in high ee,[5] frequently as high as ≥99% ee, but it reacts with moderately hindered alkenes, such as *trans*- and trisubstituted, in a complex manner, with elimination of α–pinene. Moreover, the optical induction in these examples is seriously lowered.[6]

Masamune and coworkers[7] provided a solution to this problem by synthesizing and resolving the C_2 symmetric hydroborating agent, *trans*-2,5-dimethylborolane. This reagent provides excellent enantioselectivities in the chiral hydroboration of the above three classes of olefins. Unfortunately, the synthesis of this reagent is tedious and it has been rarely utilized for asymmetric synthesis.

α–Pinene derived borane reagents, IpcBHX (X = Ipc, H, Cl), are successful in achieving high enantioselectivities in their reactions.[3] It has been demonstrated that the remarkable chiral effectiveness of these reagents must have its origin in the 'Ipc' moiety.[3a] Indeed, the 2-Me group appears to be very important. Moreover, substituents on the boron atom of the reagent also play important roles.[8] As a result, we undertook to modify our terpene-derived reagents to provide structurally varied 2-organylapopinenes (2-R-apopinenes, **3b-f**) in the hope of optimizing the steric fit between the reagent, derived from these chiral auxiliaries, and the substrate in their reactions, thereby improving the enantioselectivities achieved.

IpcBH$_2$ (**2a**) hydroborates trans- and trisubstituted alkenes to provide product alcohols in the range of 53 to ≥99% ee, with higher values realized with phenyl-substituted olefins.[4] EapBH$_2$ (**2b**), derived from **3b**, provides modest improvement.[9a] An important advance in the asymmetric reduction of prochiral ketones was realized utilizing Eap$_2$BCl, as compared to Ipc$_2$BCl.[9b] These highly favorable results prompted us to synthesize 2-phenyl- (**3e**)[10a] and 2-isopropylapopinenes (**3e**)[10b] in the hope that the larger steric requirements of these groups might improve the hydroboration results. Indeed, *i*-PraBH$_2$[10c] derived from **3f** achieved considerable improvement in asymmetric hydroboration. However, to our chagrin, the phenyl derivative, PapBH$_2$,[10a] failed to achieve high enantioselectivity. Possibly, the π–cloud of the phenyl ring is far less effective in exerting major steric influence on the course of the reaction than are the saturated alkyl groups.

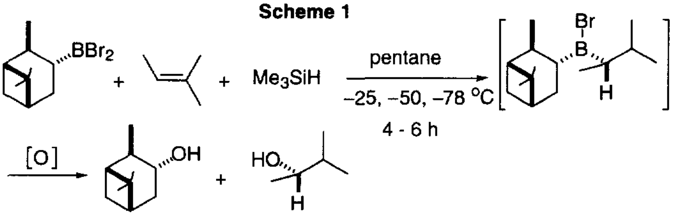
Therefore, to gain a better understanding of the chemistry responsible for achieving high asymmetric induction with the hope of developing improved reagents for asymmetric hydroboration of prochiral alkenes, we undertook to examine the effects of substituting halogen (Cl, Br, and I) in place of one of the hydrides of IpcBH$_2$. Thus, first we made the IpcBHCl (**4a**) reagent and demonstrated its remarkable efficacy for the asymmetric cyclic hydroboration of 1-allyl-1-cyclohexene, providing *trans*-1-decalone in ≥99% ee.[11a] However, IpcBHCl (**4a**) does not achieve much improvement in the chiral hydroboration of representative alkenes.[11b] Consequently, the synthesis and examination of isopinocampheylbromoborane, IpcBHBr, was undertaken (eq 1).



(1)

Thus, reaction of equivalent amounts of IpcBH$_2$ and IpcBBr$_2$ in ethyl ether (EE) at 0 °C provided essentially the desired isopinocampheylbromoborane complexed with EE, IpcBHBr·EE. On the contrary, the corresponding IpcBHCl·EE is always formed as an equilibrium mixture with 6-7% each of IpcBH$_2$ and IpcBCl$_2$.[11b] Thus we had achieved the synthesis of optically pure IpcBHBr·EE in essentially quantitative yield. However, hydroboration of 2-methyl-2-butene with IpcBHBr·EE is relatively slow, requiring 1 h rather than the ~15 min required for IpcBHCl·EE at 0 °C.[11b] The slower rate for the former reagent is attributed to the stronger complexation with EE, thus diminishing the rate of dissociation to the reactive monomeric IpcBHBr species involved in the hydroboration. Therefore, it was decided to investigate the preparation of the reactive monomer, IpcBHBr. We knew that the reduction-hydroboration reaction of IpcBCl$_2$ with Me$_3$SiH in pentane, in the presence of alkene, provides the dialkylchloroborane at 0 and −25 °C in 24 h and 5 days, respectively.[11b] This reaction is very slow. However, we thought that the more reactive IpcBBr$_2$ might cause it to undergo hydridation by Me$_3$SiH in pentane providing more readily the desired monomeric IpcBHBr readily trapped by the alkene already present in the reaction medium. Consequently, this process might be achieved at a lower temperatures in a relatively shorter time than that required for the dissociation of IpcBHCl·EE/THF. However, there is the possibility that the monomeric IpcBHBr thus formed may dimerize to $(IpcBHBr)_2$ instead of hydroborating the alkene present and we had no basis to predict the rate of dissociation of this dimer. To test this possibility, the in situ reduction-hydroboration of equimolar amounts of $IpcBBr_2$ with Me_3SiH in a non-coordinating solvent, such as *pentane*, was performed in the presence of an equimolar amount of 2-methyl-2-butene at 0 °C.[12] The reaction was monitored by ^{11}B NMR of an aliquot quenched with methanol at 0 °C to provide dialkylborinate (^{11}B NMR signal at δ 52-54). Indeed, the reaction was over in less than 5 min to provide the intermediate dialkylbromoborane, which upon oxidative ($NaOH/H_2O_2$) work-up,[9a,11b] provided the desired 3-methyl-2-butanol.

Scheme 1



Encouraged by this success, we carried out this reaction in pentane at −25 −50 and −78 °C to provide the alcohol, 3-methyl-2-butanol, in 65%, 70%, and 76% ee, respectively (Scheme 1). In all these cases, the reaction was over in ~4-6 h. In order to justify our conclusion that the reactive monomeric IpcBHBr is really responsible for the asymmetric hydroboration at the lower temperatures, monomeric IpcBHBr was generated in situ by reacting preformed $IpcBHBr{\cdot}SMe_2$[12a] with an equivalent amount of BBr_3[12b] in the presence of 2-methyl-2-butene in pentane at −25 and −50 °C. The results of these experiments were similar to those for the in situ generation of IpcBHBr at those temperatures. These results are summarized in Table 1. Consequently, this is the first time that we had achieved the asymmetric hydroboration of prochiral alkene at temperatures lower than −25 °C. Next we carried out the asymmetric hydroboration of representative prochiral alkenes, i.e. cis, trans, and trisubstituted alkenes with the in situ generated IpcBHBr in pentane at −25, −50 and −78 °C, and compared the results of these reactions with those realized with IpcBHCl and $IpcBH_2$ (Scheme 1).

Significantly higher enantioselectivity was observed in the hydroboration of 2-methyl-2-butene and *cis*-2-butene with IpcBHBr at −50 and −78 °C in comparison with IpcBHX (X = H and Cl). Also, the hydroboration of *trans*-2-butene and 1-methyl-1-cyclohexene with in situ generated IpcBHBr in pentane at −78 °C provided higher ee's than those realized with IpcBHCl. However, IpcBHBr provided almost same ee for *trans*-2-butene at −78 °C as that realized with $IpcBH_2$. Surprisingly, asymmetric hydroboration of 1-methyl-1-cyclopentene with IpcBHBr provided poorer enantioselectivity than that realized with the IpcBHCl reagent.[11b] These results are summarized in Table 1.

Thus, we have demonstrated that, in situ reduction-hydroboration using $IpcBBr_2$, Me_3SiH and prochiral alkenes can be achieved in pentane at −78 °C in a relatively short time (~4-6 h). In some cases, significantly improved enantioselectivities are achieved for this reaction than those realized with the IpcBHCl·EE reagent. These results imply that the halo substituent on the boron atom of the IpcBHX reagent can influences enantioselectivity. Currently, we are exploring the possibility of achieving higher enantioselectivity for the asymmetric hydroboration of prochiral alkenes with other higher 2-organylapoisopinocampheylchloro- and -bromoborane reagents at lower temperatures.

Table 1. Asymmetric Hydroboration of Representative Alkenes with Optically Pure IpcBHBr at Lower Temperatures (−25°, −50° and −78 °C) and Its Comparison with the Results Realized with $IpcBH_2$ and IpcBHCl at −25 °C.

		enantiomeric excess (%)				
		IpcBHBr[a]			IpcBHCl[c,d]	$IpcBH_2$[d]
alkene	alcohol[b]	−25 °	−50 °	−78 °C	−25 °	−25 °C
cis-2-butene	2-butanol[e]	56-57	60-61	73	44	24
trans-2-butene	2-butanol[e]	60-63	69-70	73-74	64-65	73
2-methyl-2-butene	3-methyl-2-butanol[f]	64-65[g]	70-71[h]	65-67	65-67	53
1-methyl-1-cyclopentene	*trans*-2-methylcyclopentanol[f]	18-19			44	66
1-methyl-1-cyclohexene	*trans*-2-methylcyclohexanol[f]	75-77	80-81	86[i]	79	72

[a] Synthesized from (+)-α-pinene and obtained in situ from the reduction of $IpcBBr_2$ with Me_3SiH in pentane. [b] *S*-configuration for product alcohols obtained in 40-75% isolated yields. [c] Results from either preformed IpcBHCl·EE or IpcBHCl obtained from in situ reduction of $IpcBCl_2$ with Me_3SiH. [d] Reaction in EE. [e] Percent ee determined by capillary GC as the MTPA-ester on an SPB-5 column. [f] Percent ee determined by capillary GC as the menthyl carbonate derivative on an SPB-5 column. [g] 65% ee was obtained from the hydroboration with preformed $IpcBHBr{\cdot}SMe_2$ in the presence of 1.0 equiv of BBr_3. [h] 69% ee was obtained from the hydroboration with preformed $IpcBHBr{\cdot}SMe_2$ in the presence of 1.0 equiv of BBr_3. [i] Reaction was 65% complete after 6 h by ^{11}B NMR after methanolysis.

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