New Chiral Borohydrides. 2. Preparation of Potassium *B*-Methoxydiisopinocampheylborohydride and Its Asymmetric Reducing Properties[1]

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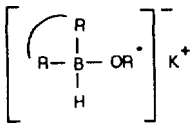
In order to prepare new chiral borohydrides (**4**) possessing chirality on dialkyl moieties, a series of *B*-alkoxydiisopinocampheylborinates (**3**) were synthesized by treatment of diisopinocampheylborane (Ipc_2BH) with alcohols (R in ROH: Me, Et, *i*-Pr, *t*-Bu) and reacted with excess of potassium hydride. Of these chiral borinic esters, only *B*-methoxydiisopinocampheyl borinate (**3a**) was converted into the corresponding dialkylmonoalkoxyborohydride (**4a**). For the other borinic esters, hydride uptake reactions were very slow at room temperature, accompanying disproportionation products at 65℃. The hydride (**4a**) formed is stable at 0℃ and can be stored over potassium hydride for few months. In the asymmetric reduction of the selected ketones, **4a** provided the corresponding alcohols, such as 21% ee for 3-methyl-2-butanone, 11% ee for 2,2-dimethylcyclopentanone, 24% ee for acetophenone, 32% ee for 3-acetylpyridine, 30% for methyl benzoylformate, 31% ee for 4-phenyl-3-butyn-2-one, 39% ee for 3-butyn-2-one, and 34% ee for 3-hexyn-2-one.

Introduction

Recently we have established the synthesis of chiral mixed trisubstituted borohydrides (**1**) consisting of a well defined, single reducing species and investigated their asymmetric reducing properties for the selected ketones.[2] These reagents were generally synthesized by addition of excess of potassium hydride to the corresponding chiral borinic esters bearing cyclic dialkyl moieties.[2a] Asymmetric inducing properties of the chiral hydride reagents of this class could be controlled by introduction of chirality on alkyl groups or alkoxy groups.[2a] Main success of this methodology has been accomplished in chiral dialkylmonoalkoxyborohydrides (**1a**) using 9-borabicyclo[3.3.1]borane(9-BBN) as a cyclic dialkyl group



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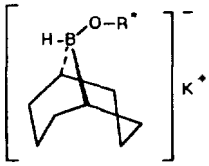
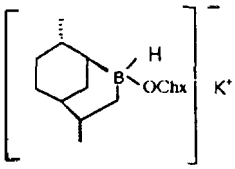


1a



1b

and possessing chirality on alkoxy groups.[2,3] Especially, potassium 9-*O*-(1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicycle[3.3.1]nonane (K glucoride) of this class proved to be one of the highly effective asymmetric reducing agents for ketone reduction.[3] In the case of **1** possessing chirality on alkyl groups, only one example (**1b**) using (+)-limonyl group as a chiral cyclic dialkyl moiety has been reported.[2a] Unfortunately, this reagent afforded very low optical inductions in reduction of the selected ketones.

On the other hand, diisopinocampheylborane (Ipc_2BH, **2**)[4] is currently one of versitile chiral reagents readily available for laboratory use.[5] Numerous applications of this reagent have appeared in the literatures.[6] Since diisopinocampheylborinic esters (**3**) are easily prepared by treatment of **2** with alcohols, it appeared desirable to develop new chiral borohydrides (**4**) possessing chirality on a dialkyl moiety by utilizing **3**. However, no work has been done on exploring the utilities of these chiral borohydrides as asymmetric reducing agents. Therefore, we undertook a study of the synthesis of the chiral hydride reagents (**4**) possessing a diisopinocampheyl moiety as a chiral dialkyl group and their asymmetric reducing characteristics toward the selected ketones.

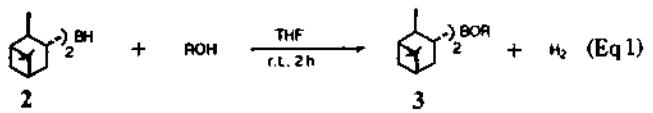
Results and Discussion

Ipc_2BH(**2**) was prepared from the reaction of 2.3 equiv of (+)-α-pinene and borane methyl sulfide (BMS) by the known method.[4] The corresponding borinic esters (**3**) were prepared by treatment of **2** with alcohols (R in ROH: R=Me, Et, *i*-Pr, *t*-Bu) and then was reacted with excess of potassium hydride to obtain the diisopinocampheylborohydrides (**4**). The formation and stability of the resulting borohydrides were examines by ^{11}B-NMR. The stable **4** were characterized by ^{11}B-NMR and IR spectroscopy and by measuring the number of moles of hydrogen evolved by hydrolysis of aliquots of the supernatant solution of **4**. Asymmetric reduction of the selected ketones was carried out with 10% excess of the hydride in THF at −25℃ or 0℃. At the completion of reduction, the reaction mixtures were quenched by addition of methanol. Then the mixtures were oxidized by alkaline hydrogen peroxide, and the products alcohols were worked up following the representative procedure (See experimental section). The optical purities of proucts were determined by capillary GC analyses of MTPA esters[8] or menthyl carbonate derivatives.[9]

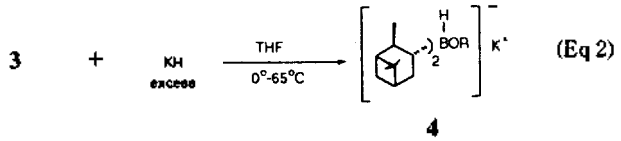
Synthesis of Chiral Borinic Esters. Ipc_2BH was treated with 1.2 equiv of methanol, ethanol, isopropanol, and *tert*-butanol, respectively. The reactions proceeded smoothly in THF at 25℃ with evolution of 1 equiv of hydrogen within 2 h (Eq 1). The ^{11}B-NMR spectra of the resulting solution

revealed appearance of only the desired borinc esters (δ 52-56 ppm). As the solvent was pumped off in *vacuo* at room temperature, the products were obtained almost quantitatively. This borinic esters appear to be thermally unstable.

Formation and Stability of Chiral *B*-Alkoxydiisopinocampheylborohydrids (4). To obtain **4**, the chiral borinic esters (**3**) were reacted with a slight excess of potassium hydride in THF (Eq 2). Among the chiral borinic esters examined, only *B*-methoxydiisopinocampheylborane (**3a**) ta-



^{11}B-NMR (δ, ppm)
a: 53.9, **b**: 53.7, **c**: 51.6, **d**:54.9



where ROH; **a**=MeOH, **b**=EtOH, **c**−*i*-PrOH, **d**=*tert*-BuOH.

kes up hydride readily, slightly exothermically, to form the corresponding borohydride (**4a**) within 2 h at 25℃. The course of the reaction was monitored by withdrawing aliquots of the mixture at appropriate time intervals and observing their ^{11}B-NMR spectra. Chemical shift of the borinic ester (**3a**) in ^{11}B-NMR showed at δ 53.9 ppm, whereas the corresponding borohydride (**4a**) exhibited a signal at δ 3.68 ppm (d, $J_{B\text{-}H}$=58.5 Hz). Consequently, the reactions could be easily followed by the disappearance of the borinic ester signal with the concurrent of the borohydride signal.

IR spectra of solution of **3a** in THF displayed charateristically strong absorption around 2015 cm^{-1} attributed to B-H stretching vibration. The ^{11}B-NMR spectra of the solution (*ca.* 0.2 M) of this borohydride exhibits doublet in the region slightly downfield from the $BF_3 \cdot OEt_2$. However, when the concentration of the compound is relatively high (>0.5 M), the solution exhibits a broad singlet, probably due to the relatively high viscosity of this solution. This phenomenon is similar to that previously observed for K 9-alkoxy-9-BBNH.[2,3,7]

Stoichiometric ratio of K : B : H in **4a** was defined as 1 : 1 : 1 by determining as moles of hydrogen and potassium hydroxide following hydrolysis and GC analysis of isopinocampheyl alcohol following oxidation with alkaline hydrogen peroxide of the supernatant solution of **4a**, respectively.

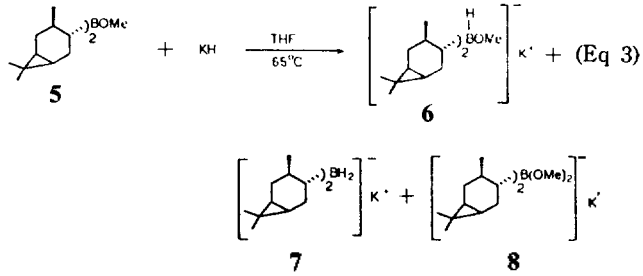
The stability of **4a** was examined by utilizing the ^{11}B-NMR spectra and measuring the number of moles of hydrogen evolved by hydrolysis of aliquots of the supernatant solution at appropriate time intervals. Thus, we found that the hydride solution of **4a** could be stored over excess of potassium hydride under a positive pressure of nitrogen at 0℃ for at least 2 months without disproportionation and loss of hydride activity. When **4a** was allowed to stand at 25℃ for 3 days, disproportionation products of **4a** were observed. However, to our knowledge, this hydride **4a** is the first example of chiral dialkylmonoalkoxyborohydride obtained from noncyclic borinic esters possessing chirality on dialkyl moieties.[10]

Table 1. Asymmetric Reduction of the Selected Ketones with **4a** in THF at −25℃[a]

Ketones	Time	Yield (%)[b]	% ee[c]	Abs. config.[f]
3-methyl-2-butanone	16 h	95	21(14)[g]	R
2,2-dimethylcyclopentanone	4 d[d]	90	11[e]	S
Acetophenone	20 h	93	24(3)[g]	R
3-acetylpyridine	24 h	94	32	R
Methyl benzoylformate	20 h	97	30	S
4-phenyl-3-butyn-2-one	20 h	95	31	R
3-butyn-2-one	18 h	98	39	R
3-hexyn-2-one	18 h	96	34	R

[a] [Hydride/ketones]=1.1, [reaction mixture]=0.25 M. [b] Determined by Gc analysis. [c] Determined by capilary Gc analysis of MTPA eaters.[8] [d] At 0℃. [e] Determined by capillary Gc analysis of (−)-menthyl carbonate.[9] [f] By elution order of MTPA esters or menthyl carbonate compared with those of the optically active compounds with the known absoulte configurations. [g] The figures in parentheses indicated date given by **1b**; ref. 2a.

In contrast, the hydridation reactions of the other chiral borinic esters (**3b-3d**) with potassium hydride were unsuccessful. The reactions underwent very slowly to give incomplete hydridation even at 65℃, accompanying disproportionation products.



With the same methodology, we also investigated the synthesis of chiral *B*-methoxy-4-dicarenylborohydride (**6**) by treatment of the corresponding borinic ester (**5**)[11] with potassium hydride. However, in contrast to **3a**, the hydridation reaction proceeded very slowly at room temperature. At 65℃, ^{11}B-NMR spectra indicated that the reaction provided the corresponding hydride (**6**, δ, 5.26 ppm, br. s) and dispropotionation products (**7**, δ −10.85 ppm, t, $J_{B\text{-}H}$=75 Hz and **8**, δ 53.9 ppm), simultaneously (Eq 3).

Asymmetric Reduction of Representative Ketones. As representative ketones, the different classes of ketones, such as 3-methyl-2-butanone, 2,2-dimethylcyclopentanone, acetophenone, 3-acetylpyridine, methylbenzoylformate, 4-phenly-3-butyn-2-one, 3-butyn-2-one, and 3-hexyn-2-one were selected to examine the reactivities and the effectiveness of asymmetric reduction by **4a**. All of the reduction with the exception of 2,2-dimethylcyclopentanone proceeded to give the corresponding alcohols in the yields of >90% within 24 h in THF at −25℃.[12] As shown in Table 1, the reductions of the selected ketones examined provied 21% ee for 3-me-

thyl-2-butanone, 24% ee for acetophenone, 32% ee for 3-acetylpyridine, 34% ee for methyl benzoylformate, 31% ee for 4-phenyl-3-butyn-2-one, 39% ee for 3-butyn-2-one, and 34% ee for 3-hexyn-2-one. The alcohols obtained afforded the enantiomers produced by addition of *si* face of the hydride. In contrast, the reduction of 2,2-dimethylcyclopentanone underwent very slow to require 4 days at 0℃ for 90% yield, providing 11% ee of optical induction enriched in S enantiomer produced by addition of *re* face of the hydride. The results indicated that **4a** afforded better optical inductions in contrast to those obtained by the same class of borohydride, **1a**, which gave 14% ee for 3-methyl-2-butanone and 3% ee for acetophenone.

Conclusion

The synthesis of chiral dialkylmonoalkoxyborohydrides possessing chirality on dialkyl moieties was investigated by reacting chiral borinic esters (3) derived from readly available chiral dialkylborane, Ipc_2BH with potassium hydride. In this study, we discovered a new, stable chiral dialkylmonoalkoxyborohydride, *B*-methoxydiisopinocampheylborohydride (**4a**) consisting of a well defined, single reducing species. The hydride is the first example of chiral dialkylborohydride obtained from noncyclic borinic esters possessing chirality on dialkyl moieties. This reagent provides optical inductions of 11-39% ee for the selected ketones.

Experimental Section

General Procedures. All glassware was dried at 140℃ overnight, assembled hot, and cooled to room temperature in a stream of nitrogen. The experimental techniques used in handling air-sensitive materials are described elsewhere.[14] ^{11}B-NMR spectra were recorded on a Varian FT-80 spectrometer and all ^{11}B chemical shifts were in δ (ppm) relative to $BF_3 \cdot OEt_2$. ^{1}H-NMR spectra were scanned on a Varian T-60A spectrometer with Me_4Si as an internal standard, all of the chemical shifts were reported in δ (ppm) relative to Me_4Si. IR measurements were conducted on a Shimadzu IR-435 equipped with a Shimadzu DRR-1 data station. Gas chromatographic analyses are carried out with a Shimadzu 7A instrument attached with a Shimadzu CR-1B intergrator/plotter using 2 m×3 mm column of 10% carbowax 20 M on Chromosorb W and an internal standard. Optical purities (% ee) were determined by capillary Gc analysis using a Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 3390 intergrator/plotter and a 50 m methyl silicon capillary column.

Materials. Tetrahydrofuran(THF) was distilled from sodium benzophenone ketyl prior to use. Anhydrous ethyl ether was purchased from Mallinckrodt, Inc. and used directly. (+)-α pinene, (+)-3-carene were purchased from Aldrich Chemical Company and distilled over small amount excess of $LiAlH_4$. Borane methyl sulfide(BMS) and (−)-menthylchloroformate were purchased from Aldrich Chemical Company and used without further purification. Commercially available prochiral ketones were used without purification. (R)-MTPA (Aldrich) was converted to the acid chloride[8] and distilled. Potassium hydride (Aldrich) was used in oil-free form.

Preparation of *B*-Alkoxydiisopinocampheylborinates (3). The preparation of *B*-methoxydiisopinocampheylborinate (**3a**) is described as representative. An oven-dried, 100 m*l*, round-bottom flask with a side arm, magnetic stirring bar, and stopcock adaptor was cooled to room temperature under a stream of nitrogen. To a suspension of crystalline Ipc_2BH[4] (2, 50 mmol) in THF (50 m*l*), anhydrous methanol (60 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, allowing hydrogen evolution (a separate small-scale experiment exhibited evolution of 1 equiv of H_2). ^{11}B-NMR spectra indicated that the reaction was complete to form the desired borinic ester. After solvent was evaporated under reduced pressure (12 mmhg, 25℃, then 0.1 mmHg, 25℃, 3 h), the product **3a** was obtained as a syrup: yield, 17.98 g, 98%; ^{11}B-NMR δ 53.9 (s) (THF). Attempted distillation resulted in the decomposition of the material. With the same procedure, **3b**, **3c**, and **3d** were obtained almost quantitavely.

Preparation of *B*-Methoxydiisopinocampheylborohydrides (4a). Experimental set-up is the same as above. To the flask was transferred potassium hydride as oil suspension by using a double-ended needle. Then the potassium hydride was washed with n-pentane (3×50 m*l*). After evaporation of n-pentane, THF was added to the oil-free potassium hydride. To this suspension of oil-free potassium hydride (2.1 g, 52 mmol) in THF (40 m*l*) was added a THF solution (40 m*l*) of **3a** (12.65 g, 40 mmol) *via* a double-ended needle with vigorous stirring at 0℃. After 1 h, the reaction mixture was warmed up to room temperature. The reaction was monitored both by hydrolysis of centrifuged aliqouts and ^{11}B-NMR. It was complete within 2 h, producing the addition compound **4a**. The excess potassium hydride was allowed to settle. Then an aliquot of the supernatant clear solution was hydrolyzed in a THF-glycerol-2 N HCl (1 : 1 : 1) solution, and the hydrogen evolved was measured. The concentration of **4a** was founded to be 0.47 M (94% yield): ^{11}B-NMR: δ 3.68 ppm (d, J_{B-H}=58.5 Hz at ca. 0.2 M): IR ν_{B-H} 2015 cm^{-1}. The content of potassium was measured as KOH following hydrolysis, indicating $[K^+]$=0.468 M by titration of standard acid. The concentration of boron was estimated Gc analysis of isopinocampheol following oxidation of an aliquot with alkaline hydrogen peroxide, indicating [B]=0.467 M. Therefore, a stoichiometry of K : B :H as 1.0 : 1.0 : 1.0 was established. The hydride solution of **4a** in THF can be stored over excess potassium hydride under positive nitrogen pressure at 0℃ for at least 2 months without any disproportionation or loss of hydride activity. When this was stored at room temperature for 3 days, disproportionation product were observed. The formation of **4b-4b** by hydridation reaction of the other borinates (**3b-3d**) with potassium hydride was unsucessful to give undesired reaction products.

Asymmetric Reduction of Prochiral Ketones with 4a. The reductions of the following compounds are representative. The results on asymmetric reduction are summarized in Table 1. The absolute configurations of the products alcohols obtained were determined by the comparison of their elution orders of MTPA esters or menthyl carbonates of the corresponding optically active alcohols with the known absolute configurations.[3a]

3-Methyl-2-butanone. An oven-dried, long necked round bottom flask equipped with a side arm, a magnetic stirring bar and a stopcock adaptor was cooled under nitro-

gen atmosphere. To the flask was added **4a** in THF (5.5 mmol, 0.47 M, 11.7 m*l*) and cooled to −25℃. To this was added a THF solution of 3-methyl-2-butanone (5 m*l*, 8.3 m*l*) procooled to −25℃ *via* double-ended needle. The reaction was carried out for 16 h at −25℃. Then unreacted hydride was destroyed by addition of 1 m*l* of anhydrous methanol at −25℃, and solvent was evaporated under reduced pressure. The residue was dissolved in ethyl ether (15 m*l*) and oxidized with 4 m*l* of 3 N NaOH and 2 m*l* of 30% hydrogen peroxide (4 h, 25℃). The aqueous layer was saturated with potassium carbonate and extracted with ethyl ether (2×10 m*l*). The combined extract was dried over anhydrous magnesium sulfate. Gc analysis indicated the presence of 95% of 3-methyl-2-butanol in ether solution. The product alcohol was isolated by fractional distillation using a Widmer column, and derivertized to the MTPA ester.[8] Capillary Gc analysis of the MTPA ester using a 50 m methylsilicon capillary column (130℃, isothermal) revealed 21% ee, R.

3-Acetylpyridine. Following the same procedure as described above, 3 mmol of 3-acetylpyridine was treated with 3.3 mmol of **4a** in THF at −25℃. After 24 h, the mixture was quenched by addition of anhydrous HCl in ethyl ether pecooled to −25℃ and then solvent was evaporated under reduced pressure. The residue was dissolved in chloroform, treated with 3 N HCl for 1 h, and finally basified with 6 N NaOH. The chloform layer was separated and water layer was extracted with chloform (2×15 m*l*). The combines organic layer was dried over anhydrous magnesium sulfate. Gc analysis revealed the formation of 94% of product alcohol. After evaporation of solvent, the product was isolated by bulb-to-bulb distillation and derivatized with MTPA acid chloride to the MTPA ester. Capillary Gc analysis of the ester using a 50 m methylsilicon column (210℃, isothermal) provided 32% ee, R.

Methyl Benzoylformate. The reduction was carried out with the same experimental setups and procedures. Methyl benzoylformate (3 mmol) was reacted with **4a** (3.3 mmol) in THF at −25℃ for 24 h. After unreacted hydride was destroyed by addition of anhydrous methanol, the solvent was pumped off in *vacuo*. The residue was dissolved in ethyl ether (10 m*l*). To this was added pH 7 buffer solution (2 m*l*) and the mixture was oxidized with 30% hydrogen peroxide (1.5 m*l*) for at 0℃. Gc analysis showed the presence of the product alcohol in 97% yield. The distilled alcohol isolated by bulb-to-bulb distillation was directly derivatzed to the MTPA ester. Capillary analysis of the ester using a 50 m methylsilicon capillary column (215℃, isothermal) revealed 30% ee enriched with S enantiomer.

4-Phenyl-3-butyn-2-one. The reaction was carried out with the same procedure described in the reduction of 3-methyl-2-butanone. The ketone (3 mmol) was treated with **4a** (3.3 mmol) in THF at −25℃. After the usual work-up following alkaline hydrogen oxidation, Gc analysis indicated the formation of 95% of product alcohol. Capillary Gc analysis of MTPA ester of the distilled product using a 50 m methylsilicon capillary column (210℃, isothermal) showed 31% ee, R.

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10. It is realized that dialkylmonoalkoxyborohydrides (1) are generally stable toward disproportionation, when the corresponding borine esters possess cyclic alkyl moieties, such as 9-BBN: ref. 7.
11. The borinate **5** was obtained almost quantitatively from the reaction of (+)-(4)-dicarenylborane[13] and methanol. Its signal in ^{11}B-NMR exhibits at δ 55.2 ppm.
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