Selective Reduction of Carbonyl Compounds with B-Alkoxydiisopinocampheylborane

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Reaction of carbonyl compounds with *B*-alkoxydiisopinocampheylborane (Ipc_2BOR, R=H, Et, *i*-Pr, *t*-Bu) was investigated in detail in order to establish their usefulness as selective reducing agents. The reagents were extremely mild and reduced only aldehydes effectively under mild conditions. The reagents also reduced α,β-unsaturated aldehydes to the corresponding allylic alcohols without any detectable 1,4-reduction. Furthermore, aldehydes can be reduced in the presence of epoxides and acid chlorides. Consequently, the selective reduction of aldehyde groups in the presence of keto and all other functional groups has been realized with these reagents.

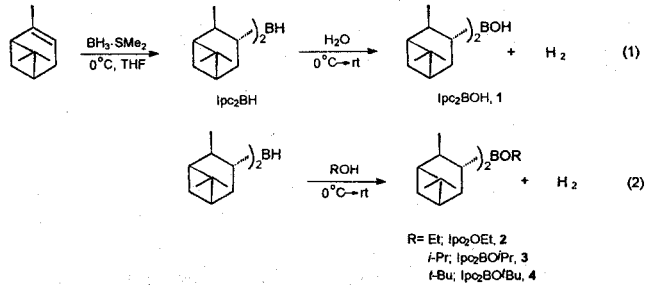
Introduction

Very recently, we reported that *B*-halodiisopinocampheylboranes (Ipc_2BX; X=Cl, Br, I) are extremely efficient chemoselective reducing agents for the reduction of α,β-unsaturated carbonyl compounds to allylic alcohols[1] and for the competitive reduction between carbonyl compounds.[2] Such a high chemoselectivity seems to appear to result from the selective coordination of the reagents to the carbonyl oxygen of compounds followed by the hydride transfer to the carbonyl carbon through dehydroboration *via* a cyclic boatlike transition state. These fascinating results prompted us to examine the alkoxy substituted derivatives of diisopinocampheylborane, *B*-alkoxydiisopinocampheylboranes (Ipc_2BOR). We prepared a series of Ipc_2BOR (R=H, Et, *i*-Pr, *t*-Bu), examined their reactivities toward general organic functional groups, and finally investigated their selectivities in the reduction of aldehydes.

A portion of our results has appeared in the form of preliminary communications.[3,4] We now describe in full the result of our study on the reduction characteristics of *B*-alkoxydiisopinocampheylborane.

Results and Discussion

Ipc_2BOH was prepared from α-pinene by hydroboration followed by treatment with water in THF (Eq. 1). Removal of THF followed by addition of pentane provided a solution of Ipc_2BOH. The other Ipc_2BOR was made by reaction of Ipc_2BH (suspended in pentane) with alcohol (Eq. 2). The ^{11}B NMR spectra of Ipc_2BOR in pentane revealed a singlet at δ 52 ppm for **1**, δ 54 for **2**, δ 54 for **3**, and δ 52 for **4**, relative to $BH_3 \cdot OEt_2$



Reactivities toward Aldehydes and Other Reducible Compounds. The reactivities of Ipc_2BOR toward some representative aldehydes and other reducible compounds were examined, and the results are summarized in Table 1. As shown in Table 1, all the reagents readily reduced a variety of aldehydes at 25 ℃. However, the sterically hindered derivatives, **2**, **3** and **4**, showed a little stronger reactivity than the less hindered one, **1** (Ipc_2BOH). The striking feature observed from the results is that the reagents showed essentially no reactivity toward other functions, such as ketones, epoxides, acid chlorides and esters. These interesting characteristics led us to investigate their chemoselectivites in the reduction of aldehydes in detail.

Selective Reduction of α,β-Unsaturated Aldehydes. Selective 1,2-reduction of α,β-unsaturated aldehydes and ketones with metal hydride reducing agents is often difficult due to competing 1,2- *vs.* 1,4- attack by hydride.[5] Among the various reducing systems which have been developed for such purpose, some metal hydride systems have proven to be efficient and convenient.[6] Actually, these reagents are capable of reducing both α,β-unsaturated aldehydes and ketones. To the best of our knowledge only one example has been reported for the selective reduction between α,β-unsaturated aldehydes and ketones: zinc borohydride can achieve the selective reduction of conjugated aldehydes in the presence of conjugated enones at −15 ℃.[7]

As shown in Table 2, α,β-unsaturated aldehydes, such as crotonaldehyde, 2-hexenal and cinnamaldehyde, underwent clean and complete reduction to corresponding allylic alcohols at 25 ℃, whereas under identical reaction conditions α,β-unsaturated ketone, such as 2-cyclohexenone, remained absolutely inert. Only a 10% excess of Ipc_2BOR is good

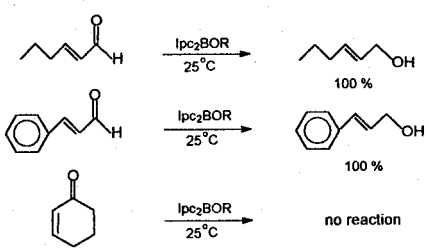


Table 1. Reduction of Aldehyde and Other Functional Groups with *B*-Alkoxydiisopinocampheylborane (Ipc_2BOR) in Pentane at 25 °C[a]

Compound	Reagent[b]	Time, hr	Reduction, %[c]
Butanal	1	1	100 (71)
	2	1	100
	3	1	100
	4	1	100
Hexanal	1	12	100 (73)
	2	6	99
	3	3	97
		6	100
	4	6	100
Benzaldehyde	1	6	94
		12	100
	2	12	100
	3	6	99
	4	6	100
Cyclohexanone	1	48	0
	2	48	0
	3	48	0
	4	48	0
2-Butanone	1	240	32
	3	240	30
	4	240	30
2-Heptanone	1	48	0
	2	48	0
	3	48	0
	4	48	0
Acetophenone	1	48	0
		240	10
	3	48	0
	4	48	0
Norcamphor	1	48	0
	2	144	55[d]
	4	120	85[d]
1,2-Butylene oxide	1	24	0
	4	24	3
Styrene oxide	1	24	0[e]
	4	24	0
Hexanoyl chloride	1	24	0
	4	24	5
Ethyl caproate	1	24	0
	2	24	0
	3	24	0
	4	24	0

[a] Ten % excess reagent was utilized, except where otherwise noted. [b] Ipc_2BOH, **1**; Ipc_2BOEt, **2**; Ipc_2BO^iPr, **3**; Ipc_2BO^tBu, **4**. [c] GC yields with suitable internal standard. The figures in parenthesis are isolated yields. [d] >99.9% endo-norborneol. [e] Ratio of reagent to compound was 2 : 1.

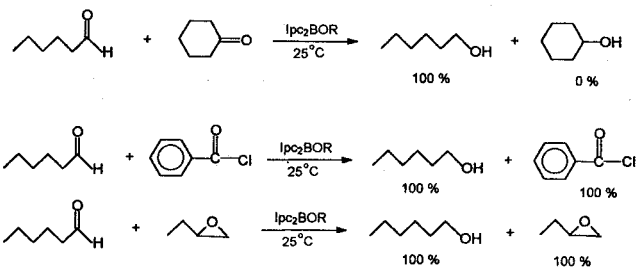
enough for the complete reduction. Even excess reagent did not affect the selectivity.

The present method lacks any limitation. Moreover, the compatibility of these reagents with almost all other reducible functional groups makes them more useful and general than conventional reagents. Particular noteworthy is the selective 1,2-reduction of α,β-unsaturated aldehydes in the presence of α,β-unsaturated ketones, when this is required in a synthetic operation.

Like the case of Ipc_2BCl,[8] the formation of an intermediate alkoxyborane is accompanied by the liberation of α-pinene. The treatment of the reaction mixture with excess acetaldehyde to eliminate the second α-pinene followed by addition of aqueous sodium hydroxide provides the alcohol product.

Selective Reduction of Aldehyde Group in the Presence of Keto and Other Functional Groups. The chemoselective reduction of an aldehyde to a primary alcohol in the presence of keto and other readily reducible groups affords a very useful methodology in organic synthesis. Consequently, in recent years, numerous reagents have been proposed to achieve such objective.[9] However, the ideal reagent has not yet been described. A really clean reduction of aldehydes in the presence of keto and all other reducible functional groups with 100% selectivity had escaped us.

As mentioned above, the reagents are extremely mild and reduce only aldehydes effectively under mild conditions. Competition experiments carried out by adding one equivalent of Ipc_2BOR to an equimolar mixture of aldehyde and ketone in pentane reveals that Ipc_2BOR is highly selective toward aldehydes (Table 3). Even more remarkable is the chemoselective discrimination between an aldehyde and a more reactive cyclohexanone. A wide variety of aldehydes can be selectively reduced even in the presence of cylohexanone. Also, various representative functional groups, such as ester, lactone, amide, nitrile, alkene, alkyne, anhydride, and carboxylic acid, are not affected by Ipc_2BOR. Futhermore, even epoxides and chlorides are inert to the reagents. Consequently, Ipc_2BOR permits the selective reduction of aldehyde groups in the presence of all other functional groups.



Such a remarkable inertness toward all other functional groups, combinded with a high selectivity for the reduction of aldehydes, has not been realized with any of the reagents previously described. Very recently, *B*-chlorodiisopinocampheylborane (Ipc_2BCl) has been reported to be superior to all of the earlier reagents in its ability to distinguish effectively between aldehyde and ketone.[2~7] However, even Ipc_2BCl shows reactivity toward ketones, epoxides and water.

Conclusion

B-Alkoxydiisopinocampheylborane (Ipc_2BOR, R=H, Et, *i*-Pr, *t*-Bu) is readily prepared by treating water or alcohol with diisopinocampheylborane (Ipc_2BH) in pentane at 0 °C. The reagents are milder than *B*-halodiisopinocampheylborane

Table 2. Reduction of α,β-Unsaturated Aldehydes with Ipc_2BOR in Pentane at 25 °C[a]

Compound	Reagent[b]	Rgt : Compd	Time, hr	Product ratio,[c] 1,2 : 1,4	Yield, %[c]
Crotonaldehyde	**1**	1.1 : 1	3	100 : 0	100
		2 : 1	1	100 : 0	>99.9
	2	2 : 1	1	100 : 0	100
	3	2 : 1	1	100 : 0	100
	4	1.1 : 1	3	100 : 0	100
		2 : 1	1	100 : 0	100 (78)
2-Hexenal	**1**	1.1 : 1	3	100 : 0	95
		1.1 : 1	6	100 : 0	100
		2 : 1	3	100 : 0	>99.9
	2	2 : 1	1	100 : 0	95
		2 : 1	3	100 : 0	100
	3	2 : 1	1	100 : 0	90
		2 : 1	3	100 : 0	100
	4	1.1 : 1	1	100 : 0	90
		1.1 : 1	6	100 : 0	100
		2 : 1	3	100 : 0	100
Cinnamaldehyde	**1**	1.1 : 1	6	100 : 0	85
		1.1 : 1	12	100 : 0	100 (73)
		2 : 1	9	100 : 0	100
	2	2 : 1	3	100 : 0	95
		2 : 1	6	100 : 0	>99.9
	3	2 : 1	24	100 : 0	96
	4	1.1 : 1	6	100 : 0	90
		1.1 : 1	12	100 : 0	>99.9
		2 : 1	6	100 : 0	95
		2 : 1	12	100 : 0	100
2-Cyclohexenone	**1**	1.1 : 1	48		0
	4	1.1 : 1	48		0

[a] Reaction mixtures were *ca.* 1 M in substrates. [b] Ipc_2BOH, **1**; Ipc_2BOEt, **2**; Ipc_2BO^iPr, **3**; Ipc_2BO^tBu, **4**. [c] Determined by GC using suitable internal standard. The figures in parenthesis are isolated yields.

(Ipc_2BX): Ipc_2BOR reduced only aldehydes, effectively at 25 °C, whereas under the identical reaction conditions epoxides and even ketones remains absolutely inert. The reagents reduce α,β-unsaturated aldehydes to the corresponding allylic alcohols with 100% selectivity, resulting from the 1,2-reduction. Ipc_2BOR also achieves the selective reduction of aldehydes in the presence of keto and other readily reducible functional groups. Even acid chlorides are inert to the reagents. Consequently, Ipc_2BOR permits the selective reduction of aldehyde groups in the presence of all other functional groups. These chemoselectivities of the reagents should find wide application in organic synthesis.

Experimental Section

Techniques for handling air-sensitive compounds have been previously described.[10] All glassware used in this study was oven-dried, assembled hot and cooled to room temperature in a stream of nitrogen. All reactions involving air- and moisture- sensitive materials were carried out under a static pressure of nitrogen. The liquids were transferred with syringes or double-ended needles. ^{11}B NMR spectra were recorded on a Bruker AMX-300 spectrometer relative to $BF_3 \cdot OEt_2$. ^1H NMR spectra were obtained on a Varian EM-360A instrument relative to TMS. Analyses of the product alcohols were performed on a Donam DS6200 FID gas chromatograph equipped with a Youngin D520B computing integrator using a 10% Carbowax 20 M capillary column (25 m).

All chemicals were commercial products of the highest purity which were further purified by standard methods before use. Pentane was bubbled with dry nitrogen, dried over 4 Å molecular sieves and distilled. Borane-methyl sulfide (BMS) and α-pinene were purchased from Aldrich Chemical Co. Anhydrous ethereal hydrogen chloride and hydrogen bromide were prepared from hydrochloric acid-sulfuric acid and hydrobromic acid-phosphorus tribromide in ethyl acetate, respectively, using a Brown apparatus.

Preparation of *B*-Alkoxydiisopinocampheylborane (Ipc_2BOR)

B-Hydroxydiisopinocampheylborane (Ipc_2BOH, 1) in Pentane. To an oven-dried, 250 mL flask with a sidearm and a reflux condenser leading to a mercury bubbler were added 10 mL of BMS (10 M, 100 mmol) and 96 mL

Table 3. Selective Reduction of Aldehydes Groups in the Presence of Keto and Other Functional Groups with Ipc_2BOR in Pentane at 25 ℃[a]

Starting mixture	Reagent	Time, hr	Ratio of redn products[b]
Butanal/	**1**	1	100 : 0
Cyclohexanone	**2**	1	>99.9 : 0
	3	1	100 : 0
	4	1	100 : 0
Hexanal/	**1**	12	100 : 0
Cyclohexanone	**2**	6	95 : 0
		12	100 : 0
	3	6	97 : 0
		12	100 : 0
	4	6	100 : 0
Hexanal/	**1**	12	100 : 0
2-Heptanone	**2**	12	90 : 10
	3	6	95 : 5
	4	6	100 : 0
Hexanal/	**1**	24	100 : 0
Acetophenone	**2**	24	>99.9 : 0
	3	6	>99.9 : 0
	4	6	100 : 0
Hexanal/	**1**	24	100 : 0
Benzophenone	**2**	24	100 : 0
	3	6	>99.9 : 0
	4	6	100 : 0
Benzaldehyde/	**1**	12	100 : 0
Cyclohexanone	**2**	12	100 : 0
	3	6	100 : 0
	4	6	100 : 0
p-Anisaldehyde/	**1**	24	85 : 15
Cyclohexanone		48[c]	95 : 5
	2	24	90 : 10
	3	12	95 : 5
	4	6	>99.9 : trace
Hexanal/	**1**	12	100 : 0
Hexanoyl chloride	**2**	12	100 : 0
	3	6	100 : 0
	4	6	100 : 0
Hexanal/	**1**	12	100 : 0
Benzoyl chloride	**2**	12	100 : 0
	3	6	100 : 0
	4	6	100 : 0
Hexanal/	**1**	12	100 : 0
1,2-Butylene oxide	**2**	12	100 : 0
	3	6	100 : 0
	4	6	100 : 0
Hexanal/	**1**	12	100 : 0
Ethyl benzoate	**2**	12	100 : 0
	3	6	100 : 0
	4	6	100 : 0

[a]Reaction mixture were *ca.* 1 M in substrates. One equivalent of reagent was utilized for competitive reduction of equimolar mixture of two carbonyl compounds. [b]GC yields with appropriate internal standard. [c]At 0 ℃.

of THF. It was cooled to 0 ℃, and 33.5 mL (210 mmol) of α-pinene was added dropwise with stirring. After the addition of α-pinene, the stirring was stopped and the flask was stored at 0 ℃ for 6 h.[11] The supernatant solution was decanted by using a double-ended needle. The crystalline lumps of Ipc_2BH were broken and washed with diethyl ether (3×12 mL).

The crystalline Ipc_2BH (90 mmol) was suspended in THF (40 mL) and cooled to 0 ℃. To this was added 1.7 mL (95 mmol) of water dropwise with stirring. The solid was disappeared as hydrogen evolved. After the addition of water, the mixture was warmed to room temperature and stirred for 1 h. The volatile materials were evaporated. The viscous Ipc_2BOH was diluted with pentane to be 2 M. The ^{11}B NMR spectrum of the solution showed broad singlet at δ 52 ppm.

***B*-Alkoxydiisopinocampheylborane (Ipc_2BOEt, 2; Ipc_2BOiPr, 3; Ipc_2B^tBu 4) in Pentane.** To Ipc_2BH (90 mmol) suspended in pentane (40 mL) at 0 ℃ was added the alcohol (100 mmol) dropwise with stirring. The solid was disappeared as hydrogen evolved. After the addition of alcohol, the mixture was warmed to room temperature and stirred for 1 h. The ^{11}B NMR spectra of **2**, **3** and **4** in pentane showed a broad singlet δ 54, δ 54 and δ 52 ppm, respectively.

Reduction of Butanal with 1

An oven-dried, 50 mL flask, fitted with a sidearm and a bent adapter connected to a mercury bubbler, was charged with 2.5 mL of a 2 M butanal solution (5 mmol) in pentane and dodecane as an internal standard. The solution was maintained at 25 ℃ in a water bath. To this solution was added 2.75 mL of a 2 M 1 solution (5.5 mmol) in pentane with stirring, and the reaction mixture was stirred for 1 h at 25 ℃. Acetaldehyde (0.39 mL, 7 mmol) was added dropwise and the mixture was stirred for 6 h. Sodium hydroxide (6 N, 5 mL) was added to the mixture. The aqueous layer was then saturated with potassium carbonate and thoroughly extracted into pentane. The combined pentane extract was dried over magnesium sulfate. Gas chromatographic analysis showed 100% 1-butanol.

In a larger scale of reaction, butanal (30 mmol) was treated with **1** (33 mmol) for 1 h at 25 ℃. Workup as described above, followed by distillation provided 1-butanol in 73% yield: bp 117-119 ℃/761 mmHg. GC analysis showed >99% purity and ^1H NMR spectrum was identical to that of an authentic sample.

Reduction of Crotonaldehyde with 4

Crotonaldehyde (40 mmol) was reduced with 4 (80 mmol) in pentane at 25 ℃ as described above. The reaction was complete in 1 h. GC analysis of the reaction mixture after the standard workup indicated the presence of crotyl alcohol as a sole product in 100% yield. The distillation provided crotyl alcohol in 78% yield: bp 120-122 ℃/759 mmHg.

Competitive Reduction

The following procedure for the competitive reaction between hexanal and cyclohexanone with 1 is representative. A 50 mL flask was charged with equimolar mixture of hexanal (4 mmol) and cyclohexanone (4 mmol) in 4 mL of pentane. The solution was maintained at 25 ℃ in a water bath and 2.0 mL of a 2 M solution of 1 (4 mmol) in pentane

was added rapidly with vigorous stirring. The reaction mixture was stirred for 12 hrs at 25 ℃ and the mixture was then quenched with 3 N aqueous sodium hydroxide (2 mL) and dodecane was added as an internal standard. The organoborane derivative was oxidized by the addition of a buffer solution (pH 7.0, 2 mL)[12] and 30% hydrogen peroxide (0.8 mL). The aqueous layer was then saturated with potassium carbonate and thoroughly extracted into pentane. The combined pentane extract was dried over magnesium sulfate and subjected to GC analysis to show the presence of 100% 1-hexanol and 100% cyclohexanone in a total yield of 99%.

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11. In the literature (Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945), 230 mmol of α-pinene (15% excess) was used and the resulting slurry (Ipc_2BH) was kept for 3 days at 0 ℃ in order to achieve optical upgradation of Ipc_2BH was needed. Therefore, a simple hydroboration procedure is enough for preparing Ipc_2BH which is necessary for our purpose.
12. In the case of aldehyde-ketone pairs, a buffer solution (pH 7.0) was added before the oxidation step in order to avoid possible oxidation of starting aldehyde unreacted.