Selective Reduction of Carbonyl Compounds with *B*-Acetoxy- and *B*-Trifluoroacetoxydiisopinocampheylboranes

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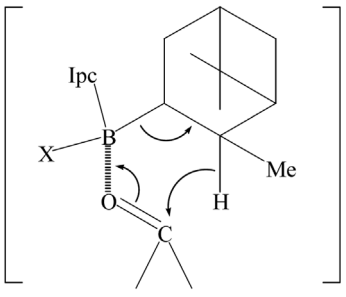
The new MPV-type reagents, ***B***-acetoxydiisopinocampheylborane (Ipc_2BOAc) and ***B***-trifluoroacetoxydiisopinocampheylborane ($Ipc_2BO_2CCF_3$), have been prepared and their reducing characteristics in the reduction of carbonyl compound have been examined in order to find out a new reducing system with unique applicability in organic synthesis. In general, the reactivity of $Ipc_2BO_2CCF_3$ appears to be stronger than that of Ipc_2BOAc, presumably due to the acidity increase by the electron-withdrawing fluorine-substituent. Both reagents show an excellent selectivity in 1,2-reduction of α,β-unsaturatedcarbonyl compounds and in competitive reduction between structurally different carbonyl compounds. In addition, $Ipc_2BO_2CCF_3$ shows interesting features in the stereoreduction of cyclic ketones.

Key Words : Selective reduction, *B*-Acetoxydiisopinocampheylborane, *B*-Trifluoroacetoxydiisopinocampheylborane, MPV type reduction, Carbonyl compounds

Introduction

In the previous report,[1] we came to understand that the Lewis acidity of diisopinocampheylborane derivatives plays a role in part on its reactivity toward the reduction of carbonyl compounds: for instance, the electron-withdrawing effect of phenoxy group made Ipc_2BOPh more reactive than Ipc_2BOC_{hex}. Such a phenomenon strongly suggests that the mechanism can be described by the activation of carbonyl group through its coordination to Lewis acidic boron followed by hydride transfer from isopinocampheyl moiety to the carbonyl acceptor *via* the six-membered transition state **A**, quite similar to the mechanism which is generally accepted in the original Meerwein-Ponndorf-Verley (MPV) reaction using aluminum alkoxides.[2] From the basis of such mechanistic point of view, we designed a new derivative *B*-acetoxydiisopinocampheylborane(Ipc_2BOAc), in which the acetoxy group acts as an electron-withdrawing one. In addition, we prepared the trifluoroacetoxy-substituted derivative, *B*-trifluoroacetoxydiisopinocam-pheylborane ($Ipc_2BO_2CCF_3$). Evidently, trifluoroacetoxy group is a much stronger electron-withdrawing one than acetoxy itself. Hence, it seems to be desirable to characterize the Lewis acidity effect between these two derivatives in such reactions. Accordingly, we examined the reducing characteristics of both derivatives in the reduction of carbonyl compounds and compared their reactivities in order to find out a new reducing system with unique applicability in organic synthesis.[3]



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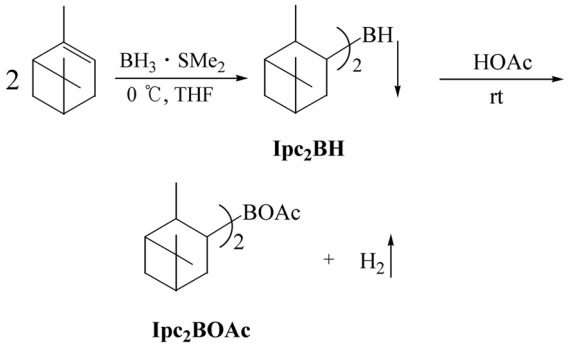
Results and Discussion

Ipc_2BOAc and $Ipc_2BO_2CCF_3$ were prepared by hydroboration of *a*-pinene with borane-methyl sulfide followed by treatment with acetic acid or trifluoroacetic acid, respectively in THF or Et_2O (Eq. 1 and 2).[4]



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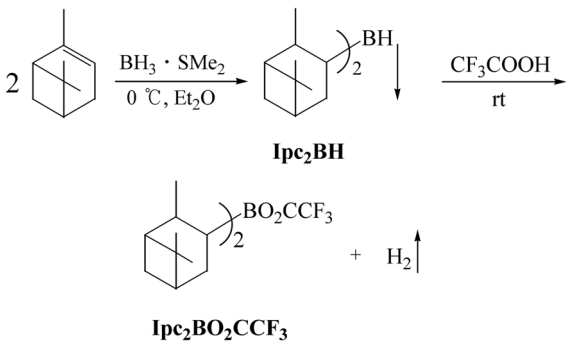

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Table 1. Reaction of Aldehydes, Ketones and Other Functional Compounds with ***B***-Acetoxy- and ***B***-Trifluoroacetoxydiisopinocampheylborane (Ipc_2BOAc and $Ipc_2BO_2CCF_3$) in Tetrahydrofuran[a]

compound	Temp (°C)	Time (h)	Yield of alcohol (%)[b]	
			Ipc_2BOAc[c]	$Ipc_2BO_2CCF_3$[d]
hexanal	0	0.5	98	99
		1	99	99
	25	0.5	99	99
		1	99	100
benzaldehyde	0	0.5	98	99
		1	99	99
	25	0.5	99	99
o-tolualdehyde	0	0.5	81	89
		1	84	95
		3	91	99
		6	99	99
	25	0.5	98	99
		1	98	99.9
		3	99	99.9
		6	99.9	
p-tolualdehyde	0	0.5	95	96
		1	96	97
		3	97	99
		6	99.9	99
	25	0.5	98	99
		1	99	100
p-chloro-benzaldehyde	0	0.5	94	96
		1	96	98
		3	97	99
		6	99	99
	25	0.5	98	99
		1	99	99
m-hydroxy-benzaldehyde	0	0.5	97	98
		1	98	99
		3	99	99
	25	0.5	98	99
		1	99	99.9
2-naphthaldehyde	0	0.5	97	98
		1	98	99
		3	99	99
	25	0.5	99	99
2-heptanone	25	0.5	0	20
		6	2	30
		24	5	43
	reflux	0.5	3	40
		6	7	87
		24	8	98
acetophenone	25	0.5	1	36
		3	2	87
		6	6	89
		24	8	95
		48		99
	reflux	0.5	6	94
		3	13	97
		6	17	99
		24	33	99
butyrophenone	25	0.5	1	34
		3	3	55
		6	8	59
		24	37	61
butyrophenone	reflux	0.5	14	91
		3	28	95
		6	34	99
		24	39	99
isobutyrophenone	25	0.5	0	33
		3		51
		6		59
		24	3	68
	reflux	0.5	1	89
		3		93
		6		95
		24	8	99
benzophenone	25	0.5	1	42
		3		56
		6	11	71
		24	14	79
	reflux	0.5	9	97
		1	11	99
		3	19	99.9
hexanoyl chloride	25	24	0	0
	reflux	6	0	2
ethyl caproate	25	24	0	0
	reflux	6	0	0
benzonitrile	25	24	0	0
	reflux	6	0	0

[a]Ten % excess reagent utilized. [b]GC yield with a suitable internal standard. [c]A clear solution. [d]All the reaction mixtures became glassy, except the reactions under reflux: batch reactions performed in cases where the mixture becomes glassy.

The reactivity of Ipc_2BOAc and $Ipc_2BO_2CCF_3$ toward some representative organic functional compounds in THF was examined, and the results are summarized in Table 1. As shown in the Table, both derivatives readily reduced a wide variety of aldehydes to the corresponding alcohols at 0 or 25 °C: no significant difference in reactivity between Ipc_2BOAc and $Ipc_2BO_2CCF_3$. However, a remarkable reactivity difference appeared when both reagents were applied to the reduction of ketones. Ipc_2BOAc showed very little reactivity toward ketones examined at 25 °C or even under reflux, whereas $Ipc_2BO_2CCF_3$ exhibited a much stronger reactivity under the same reaction conditions. Thus, all the ketones examined were completely reduced by $Ipc_2BO_2CCF_3$ within 24 hr in refluxing THF. These reaults clearly imply that such a reactivity difference was partially dependent on the coordinating ability of the boron reagent to the carbonyl oxygen of bulkier ketones than aldehydes: the electron-withdrawing fluorine-substituent induces $Ipc_2BO_2CCF_3$ more acidic than the acetoxy derivative itself, that in turn made such a reactivity difference. However, both derivatives exhibited no reactivity toward acid chlorides, esters and nitriles, making possible the chemoselective reduction of aldehydes in the presence of such inert compounds (see Table 3).

One difficulty encountered in this reaction was that the

Table 2. Reaction of Aldehydes and Ketones and Other Functional Compounds with ***B***-Trifluoroacetoxydiisopinocampheylborane in in Diethyl Ether at 0 °C[a]

Compound	Time (h)	Yield of Alcohol (%)[b]
hexanal	0.09	100, 78[c]
benzaldehyde	0.09	100, 74[c]
o-tolualdehyde	0.09	99
	0.18	100
p-chlorobenzaldehyde	0.09	100
p-methoxybenzaldehyde	0.09	100
2-butanone	0.5	100
2-heptanone	0.5	61
	6	95
	24	99, 95[d]
	48	99
acetophenone	0.5	97
	1	98
	3	98
benzophenone	0.5	60
	6	75
	24	77
2-methylcyclohexanone	0.5	100[e], 76[c]
norcamphor	0.5	100[f]
hexanoyl chloride	6	0

[a]Ten % excess reagent utilized and clear solution. [b]GC yield with a suitable internal standard otherwise indicated. [c]Isolated yields on distillation. [d]Isolated yield by chromatography. [e]Forty one % of *trans*-2-methylcyclohexanol. [f]Ninety two % of *endo*-norborneol.

solution of $Ipc_2BO_2CCF_3$ in THF was glassy, and the reaction was sometimes heterogeneous. However, fortunately, the solution of $Ipc_2BO_2CCF_3$ in Et_2O was clear and the reactivity toward carbonyl compounds appeared much stronger than that of the reagent in THF. In particular, the reactivity enhancement was apparent in reactions toward ketones (Table 2).

The reactivity difference between Ipc_2BOAc and $Ipc_2BO_2CCF_3$ was also detected in the reaction of α,β-unsaturated aldehydes and ketones, the results being summarized in Table 3. Thus, Ipc_2BOAc reduced α,β-unsaturated aldehydes to the corresponding allyic alcohols at 25 °C, but showed a low reactivity toward α,β-unsaturated ketones under the same reaction condition. However, $Ipc_2BO_2CCF_3$ readily reduced α,β-unsaturated ketones as well as α,β-unsaturated aldehydes cleanly to the coresponding allylic alcohols. The reactivity of $Ipc_2BO_2CCF_3$ was consistently stronger than that of Ipc_2BOAc in these reductions. And also the reactivity of $Ipc_2BO_2CCF_3$ in Et_2O was much stronger than that in THF.

Both reagents also showed an excellent chemoselectivity between aldehyde and the other reducible organic compounds including ketones, acid chlorides, esters and nitriles, as the results summarized in Table 4. In these competitive reactions, Ipc_2BOAc, possessing a lower reactivity rather than $Ipc_2BO_2CCF_3$, exhibited a better result, achieving a complete chemoselectivity. Similarly, $Ipc_2BO_2CCF_3$ in Et_2O is more effective than that in THF.

In comparison with the reactivity of the phenoxy

Table 3. Reaction of α,β-Unsaturated Aldehydes and Ketones with Ipc_2BOAc and $Ipc_2BO_2CCF_3$ in Tetrahydrofuran[a]

Compound	Temp (°C)	Time (h)	Yield of allylic alcohol (%)[b,c]	
			Ipc_2BOAc	$Ipc_2BO_2CCF_3$[d]
crotonaldehyde	0	1	32	78, 100[e]
		3	55	89
		6	59	99
		24	78	99
	25	1	96	97
		3	97	99.9, 74[f]
		6	99	99.9
		24	99	
2-hexenal	0	1	30	76
		3	54	87
		6	60	99.5
		24	76	99.5
	25	1	93	98
		3	95	100, 76[f]
		6	98	100
		24	99.5	
cinnamaldehyde	0	1	39	96, 100[e]
		3	43	98
		6	69	100, 94[g]
		24	88	100
	25	1	98	99.9
		3	99	99.9
		6	99	
isophorone	0	3	8	57
		6	15	71
		24	28	92
	25	3	19	87
		6	20	98
		12		99.9
		24	35	99.9
chalcone	0	3	5	50
		6	9	69
		24	13	89
	25	3	9	88
		6	11	99
		12	15	100
		24	20	100

[a]Ten % excess reagent utilized. [b]The purity of all allylic alcohol products was absolutely 100%, determined by GC. [c]GC yields otherwise indicated. [d]Glassy reaction mixture: batch reaction. [e]Reaction for 10 min in Et_2O at 0 °C; a clear solution. [f]Isolated yields on distillation. [g]Isolated yield by chromatography.

derivative (Ipc_2BOPh) toward carbonyl compounds,[1] these acetoxy derivatives (Ipc_2BOAc and $Ipc_2BO_2CCF_3$) showed a slightly different reactivity. Thus, Ipc_2BOPh can reduce only aldehyde function among reducible organic functional groups; Ipc_2BOAc reduces aldehydes in a much faster rate than Ipc_2BOPh, whereas $Ipc_2BO_2CCF_3$ readily reduces both aldehydes and ketones. However, all these derivatives achieved almost perfect chemoselectivity in the competitive reaction and in the reduction of α,β-unsaturated aldehydes or/and ketones. With organic research undertaking the synthesis of structures of increasing complexity, there was an evident and growing need for reagents possessing a high

Table 4. Competitive Reduction of Aldehydes in the Presence of Other Functional Compounds with Ipc_2BOAc or $Ipc_2BO_2CCF_3$ in Tetrahydrofuran[a]

Starting mixture	Temp (°C)	Time (h)	Ratio of reduction products[b]	
			Ipc_2BOAc	$Ipc_2BO_2CCF_3$
hexanal / 2-heptanone	0	3	100 : 0	100 : 0
	25	1	100 : 0	99 : 1
hexanal / acetophenone	0	3	100 : 0	100 : 0
	25	1	100 : 0	100 : 0
hexanal / benzophenone	0	3	100 : 0	100 : 0
	25	3	100 : 0	99 : 1
hexanal / hexanoyl chloride	25	1	100 : 0	100 : 0
hexanal / ethyl caproate	25	1	100 : 0	100 : 0
hexanal / benzonitrile	25	1	100 : 0	100 : 0
benzaldehyde /	0	3	100 : 0	100 : 0
2-heptanone	25	3	100 : 0	99 : 1
benzaldehyde/	0	3	100 : 0	100 : 0
acetophenone	25	3	100 : 0	100 : 0
o-tolualdehyde /	0	24	100 : 0	100 : 0
2-heptanone	25	6	100 : 0	98 : 2

[a]Ten % excess reagent (1.1 equiv) was utilized for an equimolar mixture of two compounds. [b]Determined by GC with an appropriate internal standard; the total yields of product alcohol were 99.5%.

degree of selectivity. Therefore, such a slight reactivity difference would have the organic chemist available a more complete spectrum of reagents for selective reductions.

Finally, we applied $Ipc_2BO_2CCF_3$ in THF to the reduction of representative cyclic ketones and examined its stereochemistry. As shown in Table 5, the reagent readily reduced all the cyclic ketones examined at 25 °C only except for 2-*t*-butylcyclohexanone. Particularly, the distinct rate difference between 2-methyl- and 2-*t*-butylcyclohexanone is remarkable: 2-methylcyclohexanone was readily reduced, but 2-*t*-butylcyclohexanone was completely inert to this reagent at 25 °C. These results clearly indicate that the steric requirement around the coordination sphere is also an important factor upon the reduction rate. However, the stereochemistry achieved by the reagent does not correlate well with the steric surroundings on cyclic and bicyclic ketones, showing an insignificant stereoselectivity. Again, the reagent in Et_2O showed a much stronger reactivity than that in THF in these cyclic ketone reductions. However, the stereochemistry appeared in both solvents was essentially same.

Experimental Section

All glassware used in this study was predried at 140 °C for at least 9 hours, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions were performed under a dry N_2 atmosphere. All chemicals used were commercial products of the highest purity available, which were further purified by standard methods before use. THF and Et_2O were distilled from sodium-benzophenone ketyl prior to use. Gas chromatographic analyses were carried out with a Varian 3300 chromatograph using a 10% Carbowax 20 M capillary column (30 m).

Preparation of *B*-Acetoxy- and *B*-Trifluoroacetoxy-diisopinocampheylborane (Ipc_2BOAc and $Ipc_2BO_2CCF_3$). To an oven-dried, 100 mL flask with a sidearm and a reflux condenser leading to a mercury bubbler were added 2.5 mL

Table 5. Stereochemistry in the Reduction of Representative Cyclic Ketone with $Ipc_2BO_2CCF_3$ [a,b]

Compound	Time (h)	0 °C (in Et_2O)		25 °C (in THF)[d]		Reflux (in THF)	
		Total yield of alcohol (%)	Yield of stable isomer (%)	Total yield of alcohol (%)	Yield of stable isomer (%)[e]	Total yield of alcohol (%)	Yield of stable isomer (%)[e]
2-methylcyclohexanone	1	100	41[f]	98	60[f]	99	59[f]
	3			99	60	100	59
3-methylcyclohexanone	0.5	100	36[g]	100	40[g]	100	43[g]
4-methylcyclohexanone	1	100	47[f]	99	46[f]	100	49[f]
	3			99	46	100	50
3,3,5-	0.5	100	8[g]	91	5[g]	100	14[g]
trimethylcyclohexanone	1			99	6	100	14
2-*t*-butyl-cyclohexanone	0.5			0		99	12[f]
	6			0		99	12
4-*t*-butylcyclohexanone	0.5	100	51[f]	80	47[f]	100	47[f]
	1			84	47	100	47
	3			100	55		
camphor	1	100	8[h]	56	4[h]	81	15[h]
	6			79	5	87	17
	24			99	4	100	17
norcamphor	0.5			92	91[i]	100	96[i]
	1	52	99.9[i]	100	93	100	96
	72	72	99.9				
	120	99.9	99.9				

[a]Ten % excess reagent utilized. [b]Determined by GC. [c]Clear solution. [d]Classy mixture. [e]Normalized yield. [f]*Trans* isomer. [g]*Cis* isomer. [h]*Exo* isomer. [i]*Endo* isomer.

of BMS (10 M, 25 mmol) and 2 mL of THF. It was cooled to 0 °C, and 8.5 mL (52.5 mmol) of α-pinene was added dropwise with stirring. After the complete addition of α-pinene, the stirring was stopped and the flask was stored at 0 °C for 6 hrs. The supernatant solution was decanted by using a double-ended needle. The crystalline lumps of Ipc_2BH was suspended in THF (or Et_2O) (10 mL), and to this was added 5.5 mL of a 5.0 M solution of acetic acid (or trifluoroacetic acid) (27.5 mmol) dropwise with stirring. An equivalent of hydrogen gas was evolved immediately.[3] Then the solution was diluted with THF (or Et_2O) to be 1.0 M. The ^{11}B NMR spectra of the solution showed a broad singlet at δ 46 (Ipc_2BOAc) and δ 52 ppm ($Ipc_2BO_2CCF_3$) relative to $BF_3{\cdot}OEt_2$.

General Reduction of Carbonyl Compounds with Ipc_2BOAc or $Ipc_2BO_2CCF_3$. The reaction of hexanal with Ipc_2BOAc in illustrative. 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 2.0 M solution of hexanal (5 mmol) in THF (or Et_2O) and dodecane as an internal standard. The solution was maintained in a circulating bath at either 0 or 25 °C. To this was added 5.5 mL of a stock solution of Ipc_2BOAc (5.5 mmol) in THF with stirring. At the appropriate time intervals, an aliquot (*ca.* 1 mL) was withdrawn, and the mixture was stirred for 6 hrs. After the addition of NaOH (6 N, 5 mL), The aqueous layer was saturated with K_2CO_3 and the organic layer was dried over anhydrous $MgSO_4$. The organic layer was then subjected to gas chromatographic analysis.

The solution of $Ipc_2BO_2CCF_3$ is too viscous to withdraw an aliquot with a hyperdermic syringe. Therefore, we adopted a batch reaction method: each measurement at an appropriate time interval was done separately on a 1-mmol scale and by quenching the reaction mixture in a reaction flask.

Isolation of Alcohols. The following procedure is representative for isolation of product alcohols on distillation. In the assembly previously described was placed 3.37 g of 2-methylcyclohexanone (30 mmol) in 15 mL of Et_2O and the solution was maintained in a circulating bath at 0 °C. Into the solution was injected 33 mL of a stock solution of $Ipc_2BO_2CCF_3$ (33 mmol) in Et_2O with stirring, and the reaction mixture was stirred for 0.5 h. The mixture was then quenched with 3 N NaOH (16 mL) and the organoborane derivative was oxidized by addition of 30% H_2O_2 (8 mL). The aqueous layer was saturated with NaCl. The separated organic layer was dried over anhydrous K_2CO_3. The soluent was evaporated under reduced pressure and a careful fractional distillation gave 2.6 g (76% yield) of essentially pure 2-methylcyclohexanol, bp 162-167 °C (758 mm). GC examination revealed the presence of 59% of *cis*- and 49% of *trans*-2-methylcyclohexanol.

The following procedure is illustrative for isolation of product alcohols by column chromatography. In the assembly was placed 0.57 g of 2-heptanone (5 mmol) in 2 mL of Et_2O and the flask was maintained in a circulating bath at 0 °C. Into the flask was injected 5.5 mL of a stock solution of $Ipc_2BO_2CCF_3$ (5.5 mmol) in Et_2O with stirring, and the reaction mixture was stirred for 24 h. The mixture was then quenched with 3 N NaOH (2 mL) and the organoborane was oxidized by addition of 30% H_2O_2 (1.5 mL). The solvent was removed under reduced pressure and the product was chromatographed on a column of silica gel using a mixture of hexane : ethyl acetate (10 : 1) as eluent to afford 0.55 g of 2-heptanol (96%). The product was characterized by proton NMR.

Competitive Reduction. The following procedure for the competitive reaction between hexanal and 2-heptanone with Ipc_2BOAc is representative. A 50 mL flask was charged with equimolar mixture of hexanal (4 mmol) and 2-heptanone (4 mmol) in 4 mL of THF. The solution was maintained at either 0 or 25 °C in a circulating bath and 4.4 mL of a 1.0 M solution of Ipc_2BOAc (4.4 mmol) in THF was added rapidly with stirring. The reaction mixture was stirred for 1 or 3 h depending upon the reaction temperature and the reaction mixture was quenched with 3 N NaOH (2 mL) and dodecane (2 mmol) was added as an internal standard. The organoborane derivative was oxidized by the addition of buffer solution (pH 7.0, 2 mL) and 30% H_2O_2 (0.8 mL). The aqueous layer was then saturated with K_2CO_3 and dried over anhydrous $MgSO_4$. GC analysis showed only the reduced product hexanol and unreacted 2-heptanone.

Reduction of Cyclic Ketones. The following procedure was used to explore the stereoselectivity of $Ipc_2BO_2CCF_3$. In the usual setup, the flask containing 4.4 mmol of $Ipc_2BO_2CCF_3$ was charged with 2 mL of ketone solution in THF (or Et_2O) (2.0 M in ketone). The reaction mixture was stirred at 25 °C or under reflux. After the appropriate time intervals, the mixture was quenched with 3 N NaOH (2 mL) and the organoborane derivative was oxidized by addition of 30% H_2O_2 (0.8 mL). The aqueous was then saturated with K_2CO_3 and dried over anhydrous $MgSO_4$. The isomeric ratios of alcohol products analyzed by GC using a capillary column are listed in Table 4.

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4. The solution of Ipc_2BOAc in THF was clear, whereas the solution of $Ipc_2BO_2CCF_3$ in THF becames viscous as the hydrogen gas evolved. However, the solution of $Ipc_2BO_2CF_3$ in Et_2O was clear.