Selective Reduction of Carbonyl Compounds with *B*-Phenoxydiisopinocampheylborane: Comparison of Its Reactivity to the Cyclohexoxy Derivative

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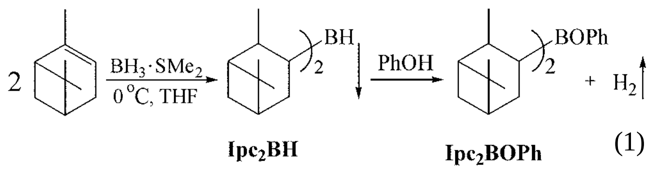
In the previous communication,[1] we reported that *B*-cyclohexoxydiisopinocampheylborane, a new alicyclic derivative of diisopinocampheylborane, is one of the mildest reducing agents, which can reduce only an aldehyde function among the reducible general organic functionalities. The reagent readily reduces a variety of aldehydes at room temperature, but very slowly at 0 °C. It is evident that the reduction proceeds *via* a cyclic boatilike transition state being considered as a Meerwein-Ponndorf-Verley (MPV) type reaction.[2]

In the mechanistic point of view, the key step of such reactions must be the coordination of boron atom of reagent to the carbonyl oxygen of substrate. We believe that the reactivity of diisopino-campheylborane derivatives correlates to their Lewis acidity and steric requirement: stronger the coordination, faster the reduction rate. Accordingly, we decided to examine the reducing characteristics of *B*-phenoxydiisopinocampheylborane (Ipc_2BOPh), an aromatic derivative, and compare its reactivity to that of the cyclohexoxy derivative (Ipc_2BOC_{hex}), in hopes of better understanding the nature of reagent and exploring its role in organic synthesis.

Results and Discussion

Ipc_2BOPh was prepared from α-pinene by hydroboration followed by treatment with phenol in THF (Eq. 1).



(1)

The reactivity of Ipc_2BOPh toward some representative organic functional groups are examined, and the results are summarized and compared with those obtained by Ipc_2BOC_{hex} in Table 1. Ipc_2BOPh readily reduced a wide variety of aldehydes to the corresponding alcohols at 0 °C or room temperature, whereas the other functions including ketones, acid chlorides, esters and nitriles were absolutely inert to this reagent. This chemoselectivity is actually same as that obtained by Ipc_2BOC_{hex}. However, the reactivity of Ipc_2BOPh toward an aldehyde function appeared much

Table 1. Reaction of Aldehydes and Other Functional Compounds with *B*-Phenoxydiiso-pinocampheylborane (Ipc_2BOPh) in Tetrahydrofuran at 25 °C[a]

Compound	Temp (°C)	Time (h)	Yield of alcohol (%)[b]	
			Ipc_2BOPh	Ipc_2BOC_{hex}
hexanal	0	1	94	14
		6	99	24
		12	99.9	26
	25	1	99	68
		3	100	
		6	100	89
		12		98
		24		99
benzaldehyde	0	1	99	13
		3	99	
		6		14
		12		17
		24		19
	25	1	99	81
		3	99	
		6		98
		12		99
o-tolualdehyde	0	1	96	15
		3	98	16
		6	99	19
		12	99	
		24		29
	25	1	97	96
		3	100	97
		6	100	99
		12		99
p-tolualdehyde	0	1	98	25
		3	99	26
		6	99	36
	25	1	98	97
		3	100	98
		6	100	99
		12		99

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Table 1. Continued

Compound	Temp (°C)	Time (h)	Yield of alcohol (%)[b]	
			Ipc_2BOPh	Ipc_2BOC_{hex}
p-chlorobenzaldehyde	0	1	92	18
		3	98	19
		6	99	25
		12	99	28
		24		31
	25	1	93	72
		3	99	87
		6	99	98
		12		100
		24		100
m-hydrobenzaldehyde	0	0.5	98	21
		1	99	29
		3	100	31
		6	100	38
	25	0.5	99	97
		1	100	99
		3	100	99
2-naphthaldehyde	0	1	99	16
		3	100	18
		6		19
		12		23
		24		29
	25	1	99	74
		3	99.9	88
		6	99.9	98
		12		99
		24		99
2-heptanone	0	72	0	0
	25	72	0	0
acetophenone	0	72	0	0
	25	72	0	0
isophorone	0	24	0	0
	25	24	0	0
benzophenone	0	24	0	0
	25	24	0	0
hexanoyl chloride	0	24	0	0
	25	24	0	0
ethyl caproate	0	24	0	0
	24	24	0	0
benzonitrile	0	24	0	0
	25	24	0	0

[a]Ten% excess reagent utilized. [b]GC yield with suitable internal standarde. [c]Data taken from ref.1. [d]Reacted both at 25 °C and under reflux.

stronger than that of Ipc_2BOC_{hex}. Thus, the reaction of aldehydes with Ipc_2BOC_{hex} at 0 °C is very slow, while Ipc_2BOPh can reduce aldehydes readily even at 0 °C. Such a reactivity seems to arise from the Lewis acidity difference between two derivatives: the electron-withdrawing effect of phenoxy group makes the phenoxy derivative more acidic than the cyclohexoxy derivative.

Such a phenomenon was also detected in the reaction of α,β-unsaturated aldehydes and ketones, the results being summarized in Table 2. Ipc_2BOPh reduced α,β-unsaturated

Table 2. Reaction of α,β-Unsaturated Aldehydes and Ketone with Ipc_2BOPh in Tetrahydrofuran[a]

Compound	Temp (°C)	Time (h)	Product ratio [b,c] 1,2 : 1,4	Yield of allyic alcohol(%)	
				Ipc_2BOPh	Ipc_2BOC_{hex}[d]
crotonaldehyde	0	1	100:0	19	9
		3	100:0	33	12
		6	100:0	53	33
		12	100:0	60	
		24	100:0	70	49
		72	100:0	88	52
	25	1	100:0	88	81
		3	100:0	92	90
		6	100:0	100	98
		12	100:0	100	99
		24	100:0		99
2-hexenal	0	3	100:0		
		6	100:0		
		12	100:0		
	25	3	100:0		
		6	100:0		
		12	100:0		
cinnamaldehyde	0	1	100:0	93	3
		3	100:0	95	6
		6	100:0	99	33
		24	100:0	99	43
	25	1	100:0	99	86
		3	100:0	99.9	97
		6	100:0	99.9	99
		12	100:0		99
isophorone	0	24		0	0
	25	24		0	0
chalcone	0	24		0	0
	25	24		0	0
benzalacetone	0	24		0	0
	25	24		0	0

[a]Ten % excess reagent utilized. [b]Determined by GC using calibrated internal standard. [c]Normalized product ratio. [d]Data taken from ref. 1.

Table 3. Competitive Reduction of Aldehydes in the presence of Other Functional Compounds with Ipc_2BOPh in Tetrahydrofuran at 25 °C[a]

Starting mixture	Time (h)	Ratio of reduction products[b]
hexanal / 2-heptanone	12	100:0
hexanal / acetophenone	12	100:0
hexanal / benzophenone	12	100:0
hexanal / hexanoyl chloride	12	100:0
hexanal / benzonitrile	12	100:0
hexanal / ethyl benzoate	12	100:0
benzaldehyde / hexanal	1	96:0
	3	97:3(98:2)[c]
benzaldehyde / 2-heptanone	1	100:0
benzaldehyde / acetophenone	3	99:0
o-tolualdehyde / 2-heptanone	3	100:0

[a]Ten % excess reagent (1.1 equiv) was utilized for the competitive reaction of equimolar mixture of two compounds. [b]Determined by GC with appropriate internal standard; the total yield of product alcohol were 99.5%. [c]At 0 °C.

aldehydes cleanly to the corresponding allylic alcohols, but did not attack α,β-unsaturarted ketones at all, being exactly same results obtained by Ipc_2BOC_{hex}. However, the reactivity of Ipc_2BOPh is still stronger than that of Ipc_2BC_{hex} in these reductions.

The reagent also showed an excellent chemoselectivity between aldehydes and the other reducible organic compounds including ketones, acid chlorides, esters and nitriles, and the results are summarized in Table 3. As seen in the Table, the complete discrimination between aldehydes and ketones are remarkable. Especially, the chemoselectivity between benzaldehyde and hexanal is noteworthy (93 : 7 at 25° and 98 : 2 at 0°): the results is quite comparable to that achieved by Ipc_2BOC_{hex} (98 : 2 at 25°).

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 reaction 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 was distilled from sodium-benzophenone ketyl prior to use. Gas chromatographic analyses were cavried out with a Varian 3300 chromatograph using a 10% Carbowax 20M capillary column (30 m).

Preparation of *B*-Phenoxydiisopinocampheylborane (Ipc_2BOPh). To an oven-dried, 200 mL flask with a sidearm and a reflux condenser loading to a mercury bubbler were added 5 mL of BMS (10 M, 50 mmol) and 4 mL of THF. It was cooled to 0 °C, and 17 mL (105 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 h. The supernatant solution was decanted by using a double-ended needle. The crystalline lumps of Ipc_2BH was suspended in THF (20 mL), and to this was added a 5.0 M solution of phenol in THF (55 mmol) dropwise with stirring. The solid was disappeared as hydrogen evolved. The solution was diluted with THF to be 1.0 M. The ^{11}B NMR spectrum of the solution showed a broad singlet at δ 54 ppm.

General Reduction of Aldehydes with Ipc_2BOPh. 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 aldehyde solution (5 mmol) in THF 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_2BOPh (5.5 mmol) in THF with stirring. At the appropriate time intervals, an aliquot (*ca*. 1 mL) was withdrawn, and the mixture was quenched by addition of acetaldehyde (0.39 mL, 7 mmol) and the mixture was stirred for 6 h. 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.

Competitive Reduction. The following procedure for the competitive reaction between hexanal and 2-heptanone with Ipc_2BOPh 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 25 °C in a water bath and 4.4 mL of a 1.0 M solution of Ipc_2BOPh (4.4 mmol) in THF was added rapidly with stirring. The reaction mixture was stirred for 12 hrs and the mixture was quenched with 3 N NaOH (2 mL) and dodecane was added (2 mmol) 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 in a total yield of 99.5%.

References and Notes

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