

Selective Reduction of Carbonyl Compounds with *B*-Cyclohexoxydiisopinocampheylborane

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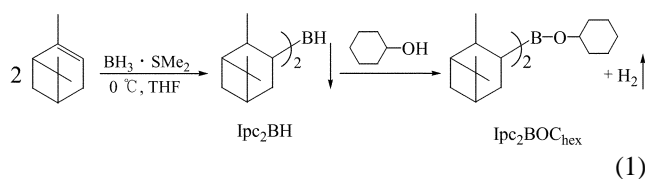
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Since Brown and coworkers developed a new asymmetric reducing agent, diisopinocampheylchloroborane (Ipc₂BCl), for prochiral ketones in 1985,¹ we have investigated extensively the general reducing characteristics of diisopinocampheyl-haloboranes such as Ipc₂BCl, Ipc₂BBr and Ipc₂BI toward organic functional groups. Subsequently, we found that all the reagents possess a very fascinating selectivity in the reduction of carbonyl compounds.² Soon after, we also developed other derivatives such as *Al*-hydroxy- and *Al*-alkoxydiisopinocampheylborane and found that these reagents are one of the mildest reducing agents showing an excellent selectivity in the reduction carbonyl compounds.³ In our continuous effort to develop a new derivative, we prepared *B*-cyclohexoxydiisopinocampheylborane (Ipc₂BOC_{hex}), an alicycloalkoxy derivative, examined its reactivity toward general organic functional groups, and finally investigated its selectivity in the reduction of carbonyl compounds, in the hope of better understanding the nature of the reagent and exploring its role in organic synthesis.

The reagent was prepared from α -pinene by hydroboration followed by treatment with cyclohexanol in THF (Eq. 1).



The reactivity of Ipc₂BOC_{hex} toward some representative organic functional groups was examined⁴ and the results are summarized in Table 1. The reagent can readily reduce a wide variety of aliphatic and aromatic aldehydes to the corresponding alcohols at 25 °C, whereas ketones are absolutely inert even in refluxing THF for at least 3 days. In addition, other general functional groups such as acid chlorides, esters, epoxides and nitriles, are totally inert to the reagent. Such a striking feature observed in this experiment led us investigate its chemoselectivity in the reduction of aldehydes in detail.

The selective reduction of α,β -unsaturated aldehydes with Ipc₂BOC_{hex} to the corresponding allylic alcohols was carried out and the results are summarized in Table 2. Reduction of simple conjugated aldehydes, such as crotonaldehyde, 2-hexenal and cinnamaldehyde, afforded exclusively the corresponding allylic alcohols, resulting only from 1,2-reduction.

Table 1. Reaction of Aldehydes, Ketones and Other Functional Compounds with *B*-Cyclohexoxydiisopinocampheylborane (Ipc₂BOC_{hex}) in Tetrahydrofuran^a

Compound	Time (h)	Reduction (%) ^b	
		0 °C	25 °C
hexanal	1	14	68
	6	24	89
	12	26	98
	24	29	99
cyclohexanecarboxaldehyde	6	21	90
	12	28	100
	24	33	100
crotonaldehyde	3	12	90
	6	33	98
	12	41	99
<i>o</i> -tolualdehyde	1	15	96
	3	16	97
	6	19	99
	12	25	99
<i>p</i> -tolualdehyde	1	25	97
	3	26	98
	6	36	99
	12	42	99
<i>p</i> -chlorobenzaldehyde	1	18	72
	3	19	87
	6	25	98
	12	28	100
<i>m</i> -hydroxybenzaldehyde	24	31	100
	0.5	21	97
	1	29	99
	3	31	99
2-naphthaldehyde	6	38	99
	1	16	74
	3	18	88
	6	19	98
2-heptanone	12	23	99
	24	29	99
	24	0	0 ^c
	72	0	0 ^c
acetophenone	72	0	0 ^c
butyrophenone	72	0	0 ^c
cyclohexanone	24	0	0 ^c
hexanoyl chloride	24	0	0
ethyl acetate	24	0	0 ^c
1,2-butylene oxide	24	0	0
benzointrile	24	0	0

^aTen % excess reagent was utilized. ^bGC yields. ^cReacted both at 25 °C and under reflux.

Table 2. Reduction of α,β -Unsaturated Aldehydes and Ketones with $\text{Ipc}_2\text{BOC}_{\text{hex}}$ in Tetrahydrofuran^a

Compound	Temperature (°C)	Time (h)	Product ratio ^b	Yield
			1,2 : 1,4	(%) ^b
crotonaldehyde	0	6	100 : 0	33
		24	100 : 0	49
	25	3	100 : 0	90
		6	100 : 0	98
		12	100 : 0	99
2-hexenal	0	6	100 : 0	29
		24	100 : 0	46
	25	6	100 : 0	96
		12	100 : 0	100
		24	100 : 0	100
cinnamaldehyde	0	6	100 : 0	33
		24	100 : 0	43
	25	3	100 : 0	97
		6	100 : 0	99
		24	100 : 0	99
isophorone	25	24		0
chalcone	25	24		0

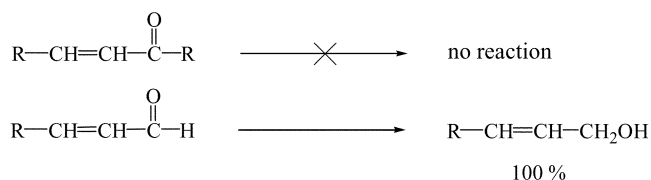
^aTen % excess reagent utilized. ^bDetermined by GC using calibrated internal standard.

Table 3. Competitive Reduction between Aldehydes and Ketones or Other Functional Compounds with $\text{Ipc}_2\text{BOC}_{\text{hex}}$ in Tetrahydrofuran at 25 °C^a

Starting mixture	Time (h)	Ratio of reduction products ^b
hexanal / 2-heptanone	24	100 : 0
hexanal / acetophenone	24	100 : 0
hexanal / benzophenone	24	100 : 0
hexanal / benzonitrile	24	100 : 0
hexanal / hexanoyl chloride	24	100 : 0
hexanal / ethyl benzoate	24	100 : 0
benzaldehyde / 2-heptanone	24	100 : 0
benzaldehyde / acetophenone	24	100 : 0
<i>o</i> -tolualdehyde / 2-heptanone	24	100 : 0

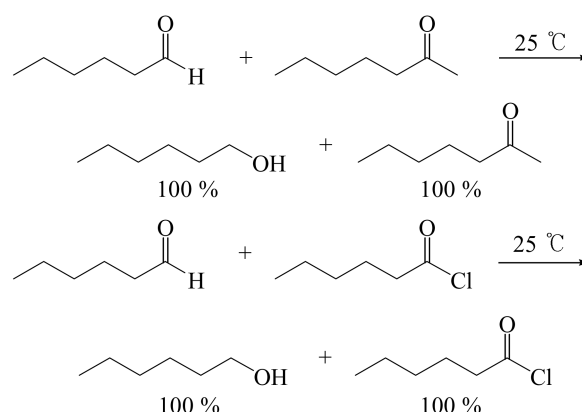
^aTen % excess reagent (1.1 equiv) was utilized for the competitive reaction of equimolar mixture of two compounds. ^bNormalized ratio determined by GC with appropriate internal standard; the total yields of product alcohols were $\geq 99.5\%$.

The selectivity reaches 100%. However, α,β -unsaturated ketones are absolutely inert to this reagent.



As shown in Table 1 and 2, the reagent is only reactive to aldehydes among reducible organic functional groups. Such a reactivity allows the chemoselective reduction of aldehyde function in the presence of the other functions such as ketone, acid chloride, epoxide and ester, as summarized in Table 3. The reagent reduces only aldehydes completely to

alcohols within 24 h at room temperature in the presence of other functional compounds.⁵



$\text{Ipc}_2\text{BOC}_{\text{hex}}$ appears one of the Meerwein-Ponndorf-Verley (MPV) type reducing agents, which reacts only with aldehyde function. This unique reactivity of the reagent affords the possibility for achieving a selective reduction of aldehyde function in a complex molecule.

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References and Notes

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- All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a steam of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out using standard techniques for handling air-sensitive materials. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled. All liquid materials were transferred by using hypodermic syringes.
- The following competitive reduction between hexanal and 2-heptanone is representative. In a 50-mL, round-bottomed flask was placed 5.0 mmol each compound solution (2.0 M) in THF, followed by 0.60 mL of *n*-tridecane as an internal standard. The flask was kept at 25 °C in a water bath. To this flask was added 6.0 mL of a 1.0 M solution of $\text{Ipc}_2\text{BOC}_{\text{hex}}$ in THF (6.0 mmol) with vigorous stirring. The reaction mixture was stirred at 25 °C for 24 h. It was then hydrolyzed with 2 mL of 2 N NaOH, and then the organoborane was oxidized with 1 mL of 30% H₂O₂ for 2 h at room temperature with stirring. After oxidation, the aqueous layer was saturated with K₂CO₃ and the separated organic layer was dried over anhydrous MgSO₄. GC analysis of the THF layer showed a 100% yield of 1-hexanol and a 100% yield of recovered 2-heptanone, indicating no presence of 2-heptanol.