

Reaction of Aldehydes and Ketones with Boron Triisopropoxide. The Meerwein-Ponndorf-Verley Type Reduction of Boron Alkoxides. 1

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Meerwein-Ponndorf-Verley (MPV) reductions of aldehydes and ketones has been known for a long time.¹ Although its importance has declined due to the introduction of complex metal hydrides, there appear to be several instances where its application is preferable. Extensive studies of the experimental conditions of the reaction have been performed, dealing with the nature of reducing agents^{1d} or of catalysts. The most widely used reducing agents are aluminum alkoxides,^{1a} but *Al*-chloro, *Al*-alkoxy-, *Al*-dialkylamino- and *Al*-pyrrolyldiisobutylalanes have also been reported as new MPV type reducing agents with a high selectivity.²⁻⁵ In addition to that, some other metal alkoxides⁷ such as zirconium alkoxides,⁶ plutonium alkoxide⁷ and some lanthanide alkoxides⁸ have been reported as catalysts in a MPV type reduction of carbonyl compounds.

Nearly twenty years ago, Brown and coworkers developed a new asymmetric reducing agent, diisopinocampheylchloroborane (Ipc₂BCl).⁹ The reaction of prochiral ketones with Ipc₂BH proceeds through a dehydroboration of isopinocampheyl group after the coordination of boron atom to carbonyl oxygen: this seems to be another type of MPV reduction. Since then, we have developed other derivatives such as diisopinocampheylhydroxy- and diisopinocampheylalkoxyboranes and found that these reagents are highly selective MPV type reducing agents in the reduction of carbonyl compounds.^{10,11}

These interesting results led us to examine the reducing characteristics of boron alkoxides, which might serve as a comparative partner of aluminum alkoxides. To our knowledge, the MPV type reduction of boron alkoxides has not appeared yet in a literature. We wish now to report a systematic study on the reducing action of boron triisopropoxide toward a series of representative aldehydes and ketones.

The reaction of aromatic aldehydes examined with the reagent in THF at 25° or in refluxing THF under a slow stream of nitrogen showed actually no reactivity, as shown in Table 1. In contrast to that, aliphatic aldehydes were quite reactive to reduction both at 25° and in refluxing THF, and could be employed for this purpose. However, side reactions are significant¹² and hence yields become lower as the reaction goes on. Therefore, short period of reaction time is required to minimize the undesirable side reaction. Similar side reactions were also found in the MPV reaction of aldehydes with aluminum triisopropoxide.¹

Table 1. Reaction of Aldehydes with Boron Triisopropoxide^a in Tetrahydrofuran under Steam of Nitrogen

Compound	Time (h)	Yield of alcohol (%) ^b	
		25°	reflux
benzaldehyde	72	trace	trace
<i>p</i> -nitrobenzaldehyde	72	trace	trace
<i>p</i> -tolualdehyde	72	trace	trace
<i>p</i> -chlorobenzaldehyde	72	trace	trace
caproaldehyde	1	18	72
	3	47	66
	24	50	54
	72	45	1 ^c
isobutyraldehyde	3	94	92
	6	79	70
	24	80	
trimethylacetaldehyde	3	95	94
	6	92	80
cyclohexanecarboxaldehyde	3	92	90
	6	83	83

^aRatio of reagent to compound is 1 : 1. ^bAnalyzed by GC with a suitable internal standard. ^cAlong with some unidentified condensation products.

On the other hand, the reduction of simple ketones can be carried out very easily, except for aryl alkyl and diaryl ketones. In similar to the case of aldehydes, aromatic ketones were resistant to reduction both at 25° and in refluxing THF, and could not be employed for this purpose. In general, the yields in the reaction of simple ketones range from 75 to 100%. The time required for a reduction varies greatly with the structure of ketones. Practically, the reflux conditions are preferable. Some sterically hindered ketones, such as norcamphor and camphor, are resistant to reduction even in refluxing THF for 72 h.

In the reaction of both aldehydes and ketones, the acetone formed should be removed from the equilibrium mixture by a slow stream of nitrogen: otherwise, the yields are often quite lower.

As shown in Table 2, the remarkable difference in rates in the reduction by boron triisopropoxide between aliphatic ketones and aromatic ketones suggests the possibility of achieving the selective reduction of a carbonyl group attached to aliphatic moieties in the presence of a carbonyl group attached to aromatic moieties. This possibility was tested in

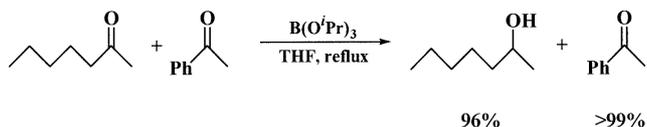
Table 2. Reaction of Ketones with Boron Triisopropoxide^a in Tetrahydrofuran under Stream of Nitrogen

Compound	Time (h)	Yield of alcohol (%) ^b	
		25°	reflux
acetophenone	72	trace	trace
butyrophenone	72	trace	trace
benzophenone	72	0	0
2-butanone	24	75	99
2-heptanone	3	13	18
	6	18	25
	24	56	97
	72	97	98
cyclohexanone	6	90	99
2-methylcyclohexanone	6	86	100 ^c
3-methylcyclohexanone	6	82	98 ^d
4-methylcyclohexanone	6	81	99 ^e
4- <i>t</i> -butylcyclohexanone	24	80	100 ^f
3,3,5-trimethylcyclohexanone	24	75	101 ^g
norcamphor	72		0
camphor	72		0

^aRatio of compound to reagent is 1 : 1. ^bAnalyzed by GC with a suitable internal standard. ^c68% of *trans*-isomer. ^d76% of *cis*-isomer. ^e80% of *trans*-isomer. ^f75% *trans*-isomer. ^g60% of *cis*-isomer.

the following manner. A mixture of equimolar amounts of 2-heptanone and acetophenone was treated with 1 mmol equiv of boron triisopropoxide. After 24-h reaction in refluxing THF, GC analysis of the product revealed a 96% yield of 2-heptanol, with only traces of 1-phenylethanol.

In general, the reaction with boron triisopropoxide is much



milder than that with aluminum triisopropoxide. Boron triisopropoxide only can reduce aliphatic aldehydes and ketones among the carbonyl compounds, whereas the aluminum reagent reduces most carbonyl compounds irrespective of its structure.^{1d} In addition to that, a preliminary experiment revealed that boron triisopropoxide does not affect other groups such as carboxylic acids, esters, nitriles, amides and acid chlorides, except for epoxides. Therefore, we will explore in more detail the possibility achieving a selective reduction of particular organic functional groups.

The following procedure was illustrative for reduction of carbonyl compounds with boron triisopropoxide. The apparatus consists of a 50 mL flask with a side-arm, equipped with a 50 cm Vigreux column, the upper end of which is connected to a downward-directed, water-cooled condenser leading to a mercury bubbler.^{13,14} Into the flask 5 mL of a 1.0 M solution of BH₃ in THF (5 mmol) was placed and the flask was immersed into an ice-water bath. To this 1.0 g of isopropyl alcohol (16.5 mmol) was added dropwise. After the hydrogen evolution ceased, the mixture was stirred for an additional 30 min at room temperature.¹⁵ Into this

solution of boron triisopropoxide in THF 0.57 g of 2-heptanone (5 mmol) was injected, and allow to flow a slow stream of dry nitrogen just over the surface of reaction mixture using a 6-inch needle with stirring at 25°. After 72 h at that temperature, tridecane (5 mmol) was added as an internal standard and mixture was quenched by addition of water. The aqueous layer was saturated with K₂CO₃ and the organic layer was dried over anhydrous MgSO₄. GC analysis of the organic layer indicated the presence of 2-heptanol in a yield of 97%. The other results in appropriate time interval were listed in Table 2.

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- Aldol condensations often are possible not only between two molecules of the aldehyde but also between the aldehyde and acetone formed.^{1d}
- All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reaction and manipulations of air- and moisture-sensitive materials were carried out using standard techniques for handling air-sensitive materials.¹⁴ Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled. All liquid materials were transferred by using hypodermic syringes.
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- ¹¹B NMR spectrum of a solution of boron triisopropoxide in THF showed a sharp singlet centered at δ 18 ppm relative to BF₃·OEt.