Chemoselective reduction of aldehydes and ketones to alcohols using boron tri-isopropoxide, $B(O\text{-}i\text{-}Pr)_3$ and boron tri-secondary butoxide, $B(O\text{-}s\text{-}Bu)_3$ as catalysts

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Abstract

The reduction of some aldehydes and ketones in the presence of boron *tri*-*iso*-propoxide, $B(O\text{-}i\text{-}Pr)_3$ (BIP) and boron tri-secondary butoxide $B(O\text{-}sec\text{-}Bu)_3$ (BSB) has been studied. The Meerwein-Pondorf-Verley (MPV) reaction is used for reduction of various aldehydes and ketones. BIP and BSB were prepared *in situ* from corresponding alcohols and borane (BH_3.THF) under nitrogen atmosphere at room temperature. The reductions were completed within 6 hours by refluxing in THF. The alcohols that are the reduction product were analyzed by GC-FID and then confirmed by GC-MS. It was found that BIP and BSB catalyze the reduction of aliphatic aldehydes and ketones to alcohols at room temperature. On the other hand, aromatic aldehydes and ketones were not reduced under the same conditions. Moreover, yield of the alcohols were found to be higher with BIP than with BSB. The mechanism proposed involves a six-membered transition state in which both the alcohol and the carbonyl are coordinated to the same boron centre of a boron alkoxide catalyst.

Keywords: Boron tri-*iso*-propoxide, boron tri-*sec*-butoxide, chemoselective reduction, aldehydes and ketones, MPV reduction

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Introduction

Primary and secondary alcohols can be synthesized by reduction of the corresponding carbonyl compounds using a great variety of reagents.[1] Usually, metal *sec*-alkoxides are used as homogeneous catalysts in reductions of the carbonyl compounds.[2] The process is usually termed the Meerwein-Pondorf-Verley (MPV) reduction. This is a mild method for the reduction of aldehydes and ketones in the presence of metal alkoxide catalysts.[3] Generally, a stoichiometric amount of metal alkoxide is required to obtain good yields of the desired alcohols.[4] The chemoselectivity of the reducing agent is very important because reduction of the carbonyl group without affecting the other reducible groups in the molecule is difficult**.** The MPV process provides a highly selective reduction of the carbonyl group in the presence of other reducible sites such as a conjugated double bond, a nitro group or a halogen atom.[5,6]

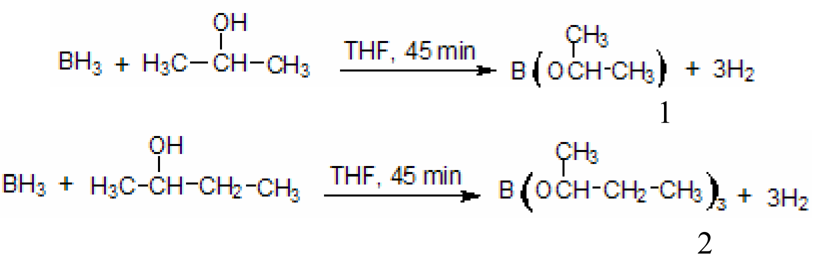
MPV reactions are usually catalyzed homogeneously by metal alkoxides such as aluminum isopropoxide [Al(O-*i*-Pr)$_3$].[7] The catalytic activity of these catalysts is related to their Lewis acidic character in combination with ligand exchangeability.[8] The hydrogen donor is usually a secondary alcohol such as 2-propanol. The reaction proceeds by a hydride transfer to the carbonyl compound from the alcohol, which is coordinated to the metal center as an alkoxide.[9]

Like metal alkoxides, boron alkoxides B(OR)$_3$ are also expected to catalyze MPV reductions. Secondary and tertiary alkyl boron esters are generally more stable than the primary alkyl boron esters. The boron atom in these compounds is in a trigonal coplanar state with sp^2 bond hybridization. A vacant *p*- orbital exists along the threefold axis perpendicular to the BO$_3$ plane. This vacant *p*- orbital readily accepts adjacent unshared electrons, acting electronically in a manner similar to the carbonyl group of an organic ester. Boron alkoxides are very susceptible to hydrolysis in the presence of water or in some cases atmospheric moisture.[10]

Recently, it was shown that boron *tri-iso*-propoxide reduces some aliphatic aldehydes and ketones.[11] This reduction can be considered as an MPV- type reduction.

In this study, the effects of the catalytic characteristics of two kinds of boron alkoxides, B(O-*i*-Pr)$_3$ (BIP) and B(O-*s*-Bu)$_3$ (BSB), on the reduction of aliphatic and aromatic aldehydes and ketones were examined. The yields of the alcohol products of reduction were compared. We also discuss why aromatic aldehydes and ketones cannot be reduced with boron alkoxides while aliphatic aldehydes and ketones can.

BIP, **1**, is prepared from borane and 2-propanol (Scheme 1); and BSB, **2**, is prepared from borane and 2-butanol, under nitrogen, at room temperature.



Scheme 1. Preparation of B(O-*i*-Pr)$_3$ and B(O-*s*-Bu)$_3$.

The reaction is normally reversible. However, removal of the H$_2$ gas as it is produced prevents the occurrence of the back- reaction.

Results and Discussion

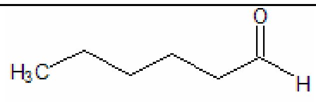
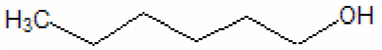
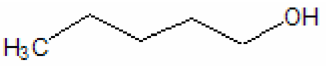
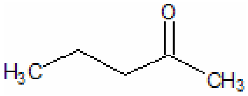
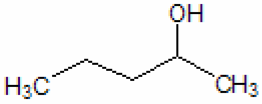
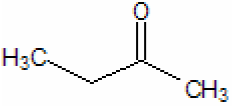
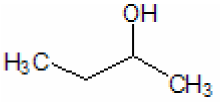
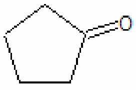
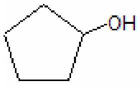
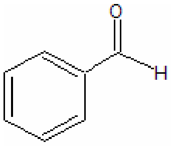
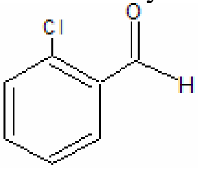
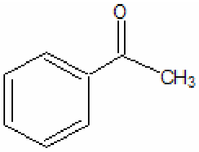
Boron alkoxides such as BIP and BSB are generated *in situ* from borane and the corresponding alcohols in THF using Schlenk techniques at room temperature (~ 27 ^{0}C) within 45 min. The alcohols are used in excess, to take their role in the alkoxide generation reaction and later in the actual reduction.

The reduction reaction of aldehydes and ketones was examined first in the presence of BIP, and then BSB in THF at 27^{o}C under a slow stream of nitrogen. Preliminary experiments showed that the most suitable reduction time was about 6 hours. The alcohols as the reduction product were analyzed by GC-FID and confirmed by GC-MS. It was found that aliphatic aldehydes and ketones can easily be reduced to the corresponding alcohols by the catalytic activity of boron alkoxides in the presence of a secondary alcohol, while aromatic aldehydes and ketones can not be reduced under the same conditions. The selected carbonyl compounds and the yields of the reduction products are summarized in Table 1.

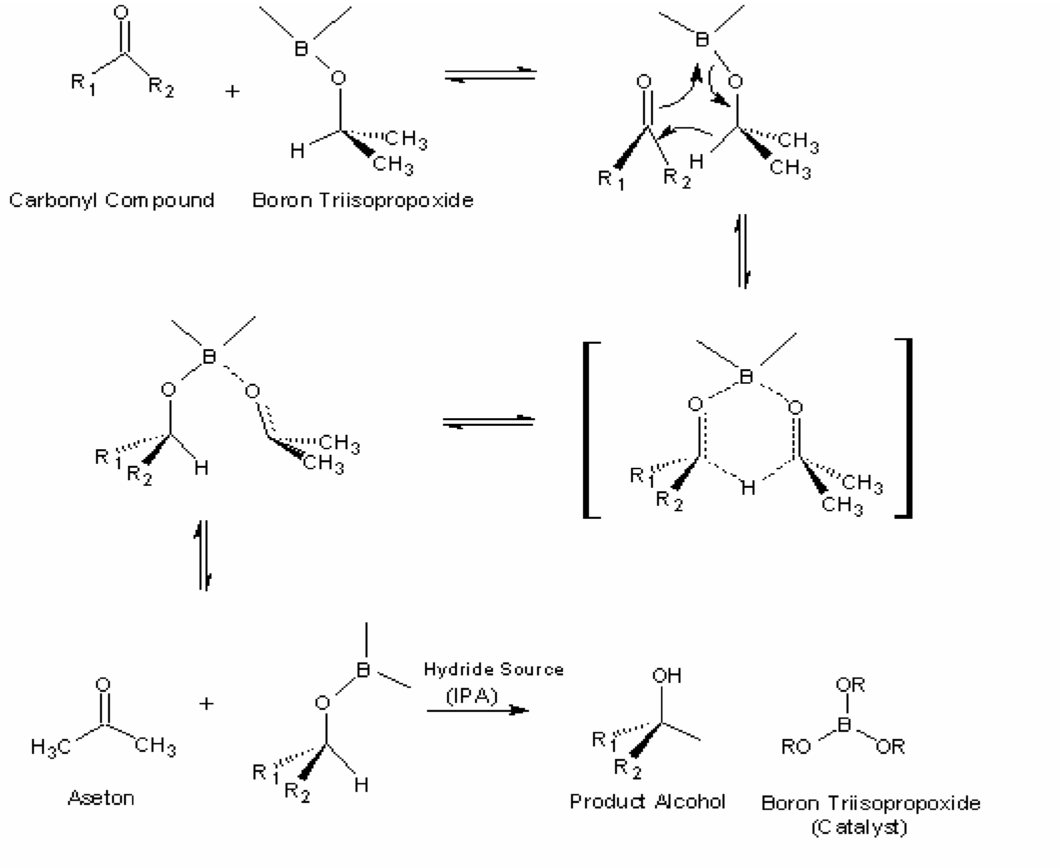
The reaction mechanism for the homogeneous MPV reaction involves a cyclic six-membered transition state.[12] Scheme 2 shows the proposed mechanism for the carbonyl compounds in the presence of BIP. First, the carbonyl compound is coordinated to the boron of the boron alkoxide. The reaction proceeds by hydride- transfer to the carbonyl compound from the *sec*-alcohol, which is bound to the boron center as an alkoxide. Since the reduction is reversible, the acetone was removed from the medium by a slow stream of nitrogen. The removal of the acetone from the reaction solution leads to the progress of reaction to the right hand side. BSB also reduces carbonyl compounds with a similar mechanism; the 2-butanone produced was removed by the same procedure. The removal of 2-butanone (b.p. 81^{0}C) is more difficult than acetone (b.p. 56^{0}C). Therefore, as shown in Tables 1 and 2, the yields of the alcohol products from reduction are greater than those using BSB.

Although aromatic carbonyl compounds are known to be reduced to alcohols by the MPV reaction using 2-propanol and aluminum *iso*-propoxide, they were found to be resistant to MPV reduction using boron alkoxides instead of metal alkoxides. Mixtures of aliphatic and aromatic aldehydes and ketones were also examined for reduction in the present of boron alkoxides. While the aliphatic carbonyl compounds were reduced, the aromatic carbonyl compounds were not. This can be explained on the basis of electronegativity difference between Al (e.n. 1.5) and B (e.n. 2.0). The electron attraction from alkoxy (-OR) groups by the boron in the boron alkoxide is stronger than that by Al in the aluminum alkoxide, and the electron density on the boron atom is higher than on the aluminum. The boron alkoxides are weaker Lewis acids than aluminum alkoxides. The attraction of electrons from the carbonyl groups of aldehydes and ketones is weaker for boron alkoxides than aluminum alkoxides. Aluminum alkoxides reduce most carbonyl compounds, irrespective of structure, as described previously. In the presence of BIP and BSB only aliphatic aldehydes and ketones can be reduced to the corresponding alcohols. This characteristic of boron alkoxides is very important in relation to selective reduction process by the MPV reactions.

Table 1. Selective reduction of ketones and aldehydes using $B(O^iPr)_3$ catalyst*

Entry	Carbonyl Compound	Yield of alcohol (%)		Product
		by BIP	by BSB	
1	 1-hexanal	79	68	 1-hexanol
2	 1-pentanal	91	77	 1-pentanol
3	 2-pentanone	76	72	 2-pentanol
4	 2-butanone	78	-	 2-butanol
5	 cyclopentanone	84	75	 cyclopentanol
6	 benzaldehyde	-	-	
7	 2-chloro benzaldehyde	-	-	
8	 acetophenone	-	-	

*all reactions were carried out under N_2 atmosphere at 27 °C for 6 h.



Scheme 2. A proposed reaction mechanism for the reduction of aliphatic ketones and aldehydes by B(O-*i*-Pr)$_3$.

Conclusions

Two boron alkoxides BIP and BSB are generated *in situ* from the borane in the presence of 2-propanol and 2-butanol, respectively. They catalyze the reduction of aliphatic aldehydes and ketones homogeneously in a good yield. The yields of the alcohols were higher with BIP than with BSB. In the presence of BIP and BSB, aliphatic aldehydes and ketones can be reduced to the corresponding alcohols, but aromatic aldehydes and ketones cannot be reduced. An important finding of this work is that BIP or BSB can catalyze the reduction of aliphatic aldehydes and ketones but are inactive for the reduction of aromatic aldehydes and ketones.

Experimental Section

General Procedures. Chromatographic analysis of the alcohols were performed using an Agilent 6890N series GC-system gas chromatograph, with Flame Ionization Detector (FID) and

DB-WAX capillary column (30m x 0,25µm x 1µm). Mass spectra were obtained on a Varian CP 3800 gas-chromatograph equipped with Varian Saturn 2200 MS detector and VF-5ms capillary column (30m x 0.25mm x 0.25 mm).

All pure alcohol standards, BH_3.THF, benzaldehyde, 2-chlorobenzaldehyde, 2-butanone, 2-pentanone, cyclopentanone and acetophenone were purchased from Aldrich and 1-pentanal and 1-hexanal were obtained from Fluka. All reactions were carried out under a nitrogen atmosphere using modified Schlenk techniques.

General procedure for the chemoselective reduction of aldehydes and ketones: 1-pentanal. The apparatus consisted of a 50 ml two-neck flask with a side stopcock equipped with a 50 cm condenser. A 1.0*M* solution of BH_3 in THF (10 ml, 10mmol) was placed in the flask and the flask immersed in an ice-water bath. 2-Propanol (33mmol, 2.54 ml) was added dropwise to this solution. The solution was stirred for 45 min. After the hydrogen evolution ceased, the solution was removed from the ice-water bath, then stirred until it reached room temperature. 1-Pentanal (10mmol, 1.1 ml) was injected into the solution, with slow stream of dry nitrogen passing just over the surface. The resulting solution was then stirred for 6 h at ambient temperature (27^0 C), then quenched by the addition of water. The aqueous layer was saturated with K_2CO_3 and the organic layer dried over anhydrous $MgSO_4$. The organic layer was analyzed using GC/FID and GC/MS techniques.

The same procedure was used to reduce all the other aldehydes and the ketones in the presence of BIP and BSB.

Acknowledgements

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