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A new method for the chemoselective reduction of aldehydes and ketones using boron tri-isopropoxide, $B(O^iPr)_3$: Comparison with boron tri-ethoxide, $B(OEt)_3$

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Abstract. A chemoselective Meerwein–Ponndorf–Verley reduction process of various aliphatic and allylic α,β-unsaturated aldehydes and ketones is described. This chemoselective reduction is catalysed by boron tri-isopropoxide $B(O^iPr)_3$. Kinetics of reduction of aldehydes and ketones to corresponding alcohols were also examined and rate constant of each carbonyl compounds were measured. Rate constant and reduction yield of each carbonyl compounds in the presence of $B(O^iPr)_3$ were compared with those in the presence of $B(OEt)_3$. The alcohols that are the reduction product were analysed by GC-MS. The rate constants and alcohol yields were found to be higher with $B(OEt)_3$ than with $B(O^iPr)_3$. 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-ethoxide; chemoselective reduction; allylic alcohols; Meerwein–Ponndorf–Verley reduction.

1. Introduction

Aldehydes and ketones have long been known to be effectively reduced to corresponding alcohols by metal alkoxides and alcohols. Usually, metal *sec*-alkoxides are used as homogeneous catalysts in reductions of the carbonyl compounds.[1,2] The process is commonly termed the Meerwein–Pondorf–Verley (MPV) reduction. The MPV reduction of carbonyl substrates to primary and secondary alcohols, discovered in 1925,[3–5] is a useful method for the reduction of carbonyl compounds because of its chemoselectivity. 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, so the risk of reducing or oxidizing functions other than the carbonyl group is minimal.[6,7]

The process generally uses inexpensive and environmentally friendly isopropyl alcohol (^{i}PrOH) as a hydride source and aluminum alkoxides as catalysts. The reaction is chemoselective, easy to operate, and readily scalable. These apparent practical advantages make the MPV reduction a particularly attractive green-chemistry approach for reduction of carbonyl compounds.[8]

MPV reactions are usually catalysed homogeneously by metal alkoxides such as aluminum isopropoxide ($Al(O^iPr)_3$).[7] The catalytic activity of these catalysts is related to their Lewis acidic character in combination with their ligand exchange ability.[9] The hydrogen donor is usually a secondary alcohol such as 2-propanol. The classical MPV reduction reaction provides an interesting pathway for the reduction of aldehydes and ketones to alcohols.

Essentially, the reaction proceeds by a hydride transfer to the carbonyl compound from the alcohol, which is coordinated to the metal center as an alkoxide.[10] A ketone (acetone), is formed as a volatile side product, can easily be removed.

This way of reducing C=O bonds is highly attractive on account of its high selectivity towards carbonyl groups. In fact, other reducible functions such as C=C and C–halogen bonds are left untouched.[11]

In addition to the classical ($Al(O^iPr)_3$) catalyst, catalytic applications of other isopropoxides, such as zirconium(IV) isopropoxide[12,13] and lanthanide isopropoxides,[14] in the MPV reaction have been reported.

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In recent years, MPV reduction of carbonyl compounds to the corresponding alcohols has been one of the standard procedures for the selective reduction of unsaturated carbonyls in laboratories and industries.[15–21] Extensive studies have been carried out to expand the potential of the classical MPV reduction.

Heterogenous catalysts for these reductions are superior to homogenous ones from the viewpoint of cost and are utilized for the industrial scale reduction of carbonyls in many applications.[22] However, heterogenous catalysts are poor for the selective reduction of unsaturated carbonyls to unsaturated alcohols.[23]

In a previous study, the effects of the catalytic characteristics of two kinds of boron alkoxides, boron tri-isopropoxide $B(O^iPr)_3$ and boron tri *sec*-butoxide $B(O^sBu)_3$, on the reduction of aliphatic and aromatic aldehydes and ketones were showed.[24] In this paper $B(O^iPr)_3$ and $B(O^sBu)_3$ were prepared *in situ* from corresponding alcohols and borane (BH3.THF). On the other hand, recently, it was shown that $(B(OEt)_3)$ reduces some aliphatic aldehydes and ketones.[25] MPV-type reduction mechanism was proposed for these chemoselective reductions.

There are no available data in literature concerning the kinetics of chemoselective MPV reduction of various aliphatic and allylic α,β-unsaturated aldehydes and ketones with $B(O^iPr)_3$ as catalyst. In this paper, an efficient and selective method for the reduction of aldehydes and ketones such as 1-hexanal, 1-pentanal, 2-pentanone, 2-butanone, cyclopentanone, geranial, neral, 3-methyl-2-butenal, 2-cyclohexen-1-one, 4-Phenyl-3-buten-2-one, cinnamaldehyde using $(B(OPr)_3)$ as the catalyst is described and kinetics of the MPV reduction for these compounds were examined. Also, the rate constant and reduction yield of each carbonyl compounds in the presence of $B(O^iPr)_3$ were compared with case of the presence of $B(OEt)_3$.

2. Experimental

2.1 *General procedure: MPV reduction of 2-cyclohexen-1-one to 2-cyclohexen-1-ol*

The catalytic MPV reduction reaction was conducted in a 50 ml two-mouthed flask with a side stopcock equipped with a 100 cm condenser and it was furnished with a magnetic stirrer. 30 mmol ^{i}PrOH was placed in the flask, and the flask immersed in a water bath. Then, 10 mmol $B(O^iPr)_3$ were added drop-wise to ^{i}PrOH. The solution was stirred for 5 min, then *2-cyclohexen-1-one* (30 mmol, 2.96 ml) were injected into the solution, during the reduction reaction time slow stream of dry nitrogen was passed just over the surface of reaction mixture. In this way, arising acetone was removed by nitrogen flow. Thus the equilibrium reaction was slipped to the right hand.

The resulting solution was stirred for 9 h at room temperature (27°C) as the most suitable reduction time for 2-cyclohexen-1-one was found to be 9 h.

At regular times which last for 1 h, 1 μl of solution was removed and injected into water-isopropanol (1 ml H_2O/1 ml ^{i}PrOH) solution. In this case, boron alkoxide was hydrolysed to boric acid (H_3BO_3) and dissolved in water. For separate water and organic phase, water phase was saturated with K_2CO_3. Thus, yield of alcohol and unreducted ketone remain in organic phase. The rate of reaction was followed by removing aliquots at regular intervals during the course of the reaction and analysing by GC-MS.

Analyses were performed on a Varian CP 3800 gas-chromatograph equipped with a Varian Saturn 2200 MS detector (Walnut Creek, CA, USA) and a VF-5 ms capillary column (30 m length and 0.25 mm I.D., 0.25 μm film thickness) (Palo Alto, CA, USA).

The same procedure was used to reduce all the other aldehydes and the ketones in the presence of $B(O^iPr)_3$. At first, suitable reduction time for each aldehydes and ketones was examined. Then kinetics of each aldehydes and ketones was studied.

All chemicals were purchased from Merck, Fluka or Aldrich, and used as received. All reactions were carried out under a nitrogen atmosphere using modified Schlenk techniques.

3. Results and discussion

Aliphatic and allylic α,β-unsaturated aldehydes and ketones were reduced to the corresponding alcohols using $B(O^iPr)_3$. The rate constant of each carbonyl compound was determined. All aliphatic and allylic α,β-unsaturated aldehydes and ketones exhibited a linear correlation between the natural logarithm of the concentration of the carbonyl group and the reaction time. This suggests that the reaction is first order in the aldehyde concentration and allowed us to calculate the rate constant from the slope of a plot of ln (c_0/c) as a function of time.

$$\ln (c_0/c) = kt,$$

where c_0 is the initial aldehyde concentration, c that at a given time t and k is the rate constant.

Table 1. Rate constants and yields obtained in the MPV reduction of carbonyl compounds using $B(O^iPr)_3$.

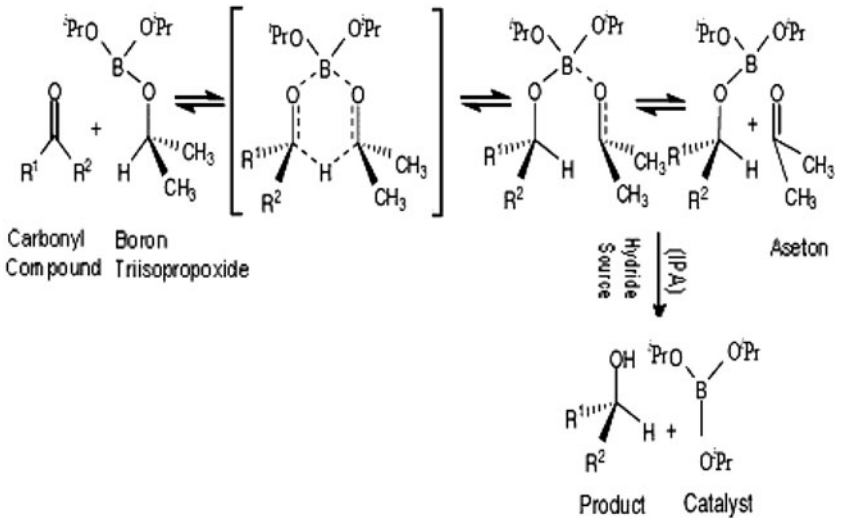
Entry	Compound	Yield of alcohol(%)		Reaction time (h)		$kx10^{-3}$ $(min^{-1})^a$		Product
		by $B(O^iPr)_3$	by $B(OEt)_3$	by $B(O^iPr)_3$	by $B(Et)_3$	by $B(O^iPr)_3$	by $B(OEt)_3$	
1.	1-Hexanal	87.7	88.8	9	8	4.163	4.378	1-hexanol
2.	1-Pentanal	87.8	89	9	8	4.02	4.128	1-pentanol
3.	2-Pentanone	85.1	86.6	9	8	3.53	3.713	2-pentanol
4.	2-Butanone	86.5	87.1	9	8	3.748	3.858	2-butanol
5.	Cyclopentanone	89.5	90	9	8	4.47	4.563	cyclopentanol
6.	Geranial[a]	84.3	86.6	20	20	2.052	2.470	geraniol (*trans*)
7.	Neral[b]	83.1	85.2	20	20	1.948	2.280	nerol (*cis*)
8.	3-methyl-2-butenal	87.9	88.3	15	15	2.478	2.54	3-Methyl-2-butenol
9.	2-cyclohexen-1-one	88.7	89.5	9	9	4.155	4.278	2-cyclohexen-1-ol
10.	4Phenyl-3buten-2one	86.5	87	14	14	2.258	2.318	4Phenyl-3buten-2ol
11.	Cinnamaldehyde	86.8	87.9	13	13	2.43	2.487	cinnamalcohol

a) *trans*-citral; *b*) *cis*-citral

The selected carbonyl compounds, the yields of the reduction products, and the rate constants of various aldehydes and ketones are summarized in table 1. As it can be seen from table 1, some differences were observed in reduction yields, rate constants and reduction times. Smaller rate constant for cinnamaldehyde, 3-methyl-2-butenal, 4-phenyl-3-buten-2-one (benzalacetone) and citral (3,7-dimethyl 2,6-octadienal) can be attributed to their steric hindrance and to the presence of a double bond conjugated to the carbonyl group. Ruiz and co-workers reported that the presence of a double bond conjugated with the carbonyl group substantially reduced the reaction rate.[26]

It is apparent that from table 1, the simple ($B(O^iPr)_3$) catalyst show lower activity than previously reported ($B(OEt)_3$) catalyst. In addition, ($B(O^iPr)_3$) catalyst demonstrates the same chemoselectivity for hydride transfer reaction of various aliphatic and allylic α,β-unsaturated aldehydes and ketones. The reduction yield of carbonyl compounds with these two boron alkoxide catalysts is higher than the previously reported aluminium alkoxide catalysts.[27]

The MPV reduction in the presence of boron alkoxide catalysts showed good chemoselectivity for allylic α,β-unsaturated aldehydes and ketones. 3-methyl-2-butenal, 2-cyclohexen-1-one, benzalacetone, cinnamaldehyde and citral are important allylic α,β-unsaturated aldehydes and ketones. These important carbonyl compounds possess conjugated C=C and C=O bonds. The C=C bonds are more readily hydrogenated than the C=O bonds in most usual techniques.[28] Although reduction of the C=O bonds without affecting



Scheme 1. A proposed reaction mechanism for the reduction of aliphatic and allylic α,β-unsaturated aldehydes and ketones by $B(O^iPr)_3$.

the C=C bonds is highly difficult, C=O bond of these compounds were reduced using $B(O^iPr)_3$ catalyst in this study (table 1).

Conversions of citral to nerol and geraniol above 85% within 20 h of reaction were achieved. The preferential formation of geraniol as compared to nerol can be explained by steric hindrance of the bulky chain.[29] The carbonyl group of the geranial is *trans* to the bulky chain of the molecule, minimizing any steric hindrance for the binding of C=O to the boron center. Hence, the rate of reaction for geranial is faster than for neral.

The reaction mechanism for the MPV reduction in the homogeneous phase involves a cyclic six-membered transition state.[15] Scheme 1 shows the proposed mechanism for the carbonyl compounds in the presence of $B(O^iPr)_3$. 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 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 the reaction to the right hand side (see scheme 1). The alcohol yields using $B(OEt)_3$ catalysts were found greater than those using $B(O^iPr)_3$ because of the removal of methanal are easier than acetone.

Catalysis in the perfumery industry is one of the new research fields using hydrogenation catalysts. There are numerous hydrogenation processes both in gas and liquid phases, but most of them are not selective to target α,β-unsaturated alcohols. Selective hydrogenation of α,β-unsaturated aldehydes and ketones such as crotonaldehyde, cinnamaldehyde, citral, 2-cyclohexen-1-one, benzalacetone (*trans*-4-fenil-3-buten-2-on) to their corresponding α,β-unsaturated alcohols is highly desirable due to the corresponding allylic alcohols are useful as intermediates, pharmaceuticals, and as flavour chemicals.[30–32] But the bond energy of C=C bond is smaller (615 kcal/mol) than that of C=O bond (715 kcal/mol), so which makes the hydrogenation of C=O bond difficult.[28] In this instance, the selective reduction of C=O bond using boron alkoxides as catalyst will be promising process for perfumery industry.

4. Conclusion

Catalytic MPV reduction was successfully carried out using $B(O^iPr)_3$ as catalyst. In the presence of $B(O^iPr)_3$, various aliphatic and allylic α,β-unsaturated aldehydes and ketones were reduced to the corresponding alcohols, without reducing the C=C double bonds. The rate of the reduction of aliphatic and allylic α,β-unsaturated aldehydes and ketones to the corresponding alcohols is first order. Also in these reaction conditions, $B(O^iPr)_3$ at room temperature, *trans*- and *cis*-citral are selectively reducted to the corresponding alcohols (geraniol and nerol, respectively). Since steric hindrance of the bulky chain, the reaction rate is faster for geranial than for neral in the presence of boron alkoxide catalysts. We conclude that $B(OEt)_3$ is a slightly good chemoselective catalyst than the $B(O^iPr)_3$ for the MPV reduction and both of the boron alkoxide catalysts facilitate the chemoselective reduction of a variety of unsaturated ketones and aldehydes to allylic alcohols.

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