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DIASTEREOSELECTIVE REDUCTION OF β-HYDROXYKETONES WITH AMINEBORANES IN THE PRESENCE OF LITHIUM PERCHLORATE

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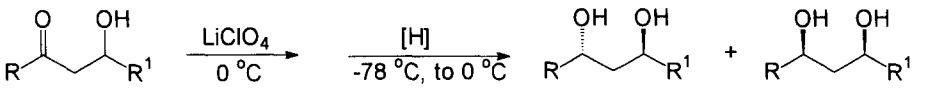
Abstract: The reduction of β-hydroxyketones with amineboranes in the presence of lithium perchlorate produces the corresponding *anti* 1,3-diols as major products. © 1997 Elsevier Science Ltd.

The stereoselective reduction of β-hydroxyketones is an important reaction in organic synthesis. The product *syn* and *anti* 1,3 diols are found in a variety of polyacetate and polypropionate derived natural products.[1] Extensive research has been carried out on the directed reductions of β-hydroxyketones and two generalizations can be made. If the reducing agent can bind to the hydroxy group, an intramolecular transfer of hydride results and the *anti* 1,3 diol is the major product.[2] On the other hand, when an additive (e.g. Et_2BOMe[3], $TiCl_4$[4] or BCl_3[4]) is employed to organize the substrate prior to an intermolecular hydride addition, the *syn* isomer is formed predominantly.

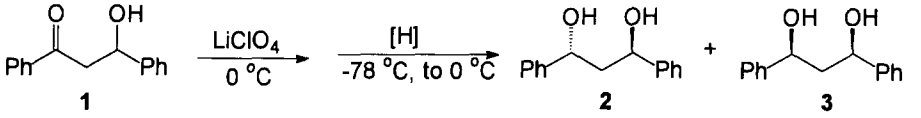
Recently we reported the diastereoselective synthesis of *anti* 1,3-diols via the substrate controlled allylboration of β-hydroxy carbonyl compounds.[5] We now wish to report our preliminary results involving the reduction of β-hydroxyketones with amineboranes in the presence of lithium perchlorate.



1 **2** **3**

The prerequisite β-hydroxyketones were prepared by either the reductive hydrolysis of Δ^2-isoxazolines[6] or crossed aldol reactions.[7] Reductions of β-hydroxyketones with various amineboranes were carried out in the presence of lithium perchlorate and the results are summarized in Table 1. Among the amineboranes utilized, *N,N*-diethylanilineborane (entry 3) and 2,6-lutidineborane (entry 4) gave highest diastereoselectivity. The reactions of various β-hydroxyketones with *N,N*-diethylanilineborane and 2,6-lutidineborane are summarized in Table 2. In control studies, we noted that the diastereoselectivity decreased when the reaction was carried out at 0°. The stereoselectivity also decreased when the β-hydroxy group was replaced by a methoxy group; the reduction of 3-methoxy-1,3-diphenyl-1-propanone with 2,6-lutidineborane in the presence of $LiClO_4$ produced an *anti/syn* ratio of only 60:40.

Table 1.

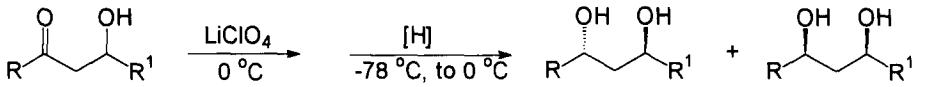


Entry	Reducing Agent	Yield (%)[a,b] (2 + 3)	Diastereoselectivity[c] (2 : 3)
1.	BH_3·THF	92	78:22
2.	Et_3N·BH_3	85	84:16
3.	$PhNEt_2$·BH_3	88	98:2
4.	2,6-lutidine·BH_3	86	99:1[d]
5.	*t*-$BuNH_2$·BH_3	62	92:8
6.	$NaBH_4$ | THF | MeOH	92	25:75

[a] Reaction carried out by mixing $LiClO_4$ and the carbonyl reagent in THF at 0 °C, cooling the mixture to -78 ° C, adding the hydride and then allowing the mixture to warm to 0 °C. [b] Isolated yield of the diastereomeric mixture which gave satisfactory analytical and spectral data. [c] Determined by NMR analysis. [d] In the absence of the $LiClO_4$, the ratio of **2:3** was 85:15.

In a typical procedure $LiClO_4$ (5.0 *M* in Et_2O, 2.5 mmol) is added to the β-hydroxyketone (1.0 mmol) in THF (20 ml) and the mixture stirred at 0°C for 10 min. The ice bath is then replaced by a dry-ice acetone bath (-78°C) and the amineborane (1.2 mmol) is added. The temperature is slowly raised to 0°C (over 2 h) and stirred at that temperature for 1 h. The reaction is quenched with dilute HCl (1 *N*, 10 ml) and the products extracted into ethyl acetate (3 x 25 ml). The combined organic extracts are washed with saturated aqueous $NaHCO_3$, brine and then dried ($MgSO_4$) prior to solvent removal (reduced pressure). The product is purified by column chromatography (silica gel, ethyl acetate-hexanes) and the diastereoselectivity determined by ^1H and ^{13}C NMR.[8]

Table 2.



1 2 3

Entry	R	R^1	Yield (%)[a,b] (2 + 3)	Diastereoselectivity[c] (2 : 3)
1.	Ph[d]	CH_2Ph	84	96:4
2.	Ph[e]	CH_2Ph	88	98:2
3.	Ph[d]	$CH(CH_3)_2$	85	89:11
4.	Ph[e]	$CH(CH_3)_2$	86	99:1
5.	CH_3[d]	Ph	88	54:46
6.	CH_3[e]	Ph	87	89:11
7.	C_2H_5[e]	Ph	88	72:28

[a] Reaction carried out by mixing $LiClO_4$ and the carbonyl reagent in THF at 0 °C, cooling the mixture to -78 °C, adding the hydride and then allowing the mixture to warm to 0 °C. [b]Isolated yield of the diastereomeric mixture which gave satisfactory analytical and spectral data. [c]Determined by NMR analysis. [d] $PhNEt_2 \cdot BH_3$ was used. [e] 2,6-lutidineborane used.

Although the mechanism of the reaction remains to be delineated, the *anti*-selectivity suggests that the boron complexes may be reacting with the β-hydroxy group and then delivering a hydride intramolecularly, the lithium ion presumably increases the diastereoselectivity of the reactions by coordinating with the carbonyl group.[9] The fact that hindered, aromatic amineboranes are hydrolized more readily than their unhindered counterparts[10] would support such a hypothesis along with the observation, noted earlier, that replacement of the β-hydroxy substituent by a methoxy group leads to a dramatic decrease in the *anti/syn* product ratio. The reactions are apparently not proceeding via a cyclic, lithium-chelated intermediate since the *syn* product would have been expected.[11] The *anti*-selective reductions described herein complement the recently reported *syn*-selective reductions which were achieved using various amineboranes in the presence of $TiCl_4$ or BCl_3.[4]

Acknowledgements

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