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A Novel Method for the <u>In Situ</u> Generation of Alkoxydialkylboranes and Their Use in the Selective Preparation of 1,3-<u>Syn</u> Diols

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An <u>in situ</u> method for generating  $\text{Et}_2\text{BOCH}_3$  from triethylborane and methanol without using any other catalysts is described. Using the  $\text{Et}_2\text{BOCH}_3$  thus generated as a chelating agent, <u>syn</u> 1,3-diols are prepared in  $\geq$  98% stereochemical purity by reducing  $\beta$ -hydroxyketones with sodium borohydride.

We have recently reported<sup>1</sup>) a general and efficient method for the synthesis of <u>syn</u> 1,3-diols by NaBH<sub>4</sub> reduction of  $\beta$ -hydroxyketones utilizing alkoxydialkylboranes as chelating agents, with the <u>syn</u> diastereoselection exceeding 98%. These results prompted us to search for methods of <u>in situ</u> generation of alkoxydialkylboranes from the commercially available trialkylboranes. Dialkylborylation of alcohols was hitherto achieved in the literature by treating alcohols with the corresponding trialkylboranes in presence of activating reagents like pivalic acid,<sup>2</sup> air<sup>3</sup> etc.

 $R_{3}B + R'OH \xrightarrow{\text{Activators}} R_{2}BOR'$ 

During our work, we found that the desired alkoxyboranes could be generated by mixing  $Et_3B$  with  $CH_3OH$  in THF in the absence of any further activators.<sup>4</sup>) We established the optimum ratio of  $Et_3B$  and  $CH_3OH$  that is needed for an efficient conversion, by studying the <sup>11</sup>B-NMR spectra<sup>5</sup>) (Table 1) of the reaction mixtures. From these studies (entries 2-5) it is clear that the desired  $Et_2BOCH_3$ could be generated <u>in situ</u> conveniently and quantitatively just by modulating the relative ratios of  $Et_3B$  and  $CH_3OH$ : the higher the ratio of  $CH_3OH/Et_3B$  the faster the rate of formation of  $Et_2BOCH_3$ . The <sup>11</sup>B-NMR spectrum of the sample obtained by mixing  $Et_3B$  (0.25 mmol) with  $CH_3OH$  (0.5 mL) in THF (2 mL) at -78 °C (entry 5) is essentially identical to the one obtained with authentic  $Et_2BOCH_3$  (entry 6).

The probable mechanism for the formation of  $\text{Et}_2\text{BOCH}_3$  from  $\text{Et}_3\text{B}$  and  $\text{CH}_3\text{OH}$  is shown in Scheme 1. The first step in this process is the fast addition of  $\text{CH}_3\text{OH}$ to  $\text{Et}_3\text{B}$  generating an ate complex ( $^{11}\text{B}-\text{NMR}$  & 11.63 ppm) which in principle could protonolyze either in an inter- or intramolecular fashion (route a) forming  $\text{Et}_2\text{BOCH}_3$  ( $^{11}\text{B}-\text{NMR}$  & 35.2 ppm) and ethane. Alternatively, the ate complex, in presence of excess  $\text{CH}_3\text{OH}$ , could equilibrate to borate and methoxonium ions which in turn could generate the  $\text{Et}_2\text{BOCH}_3$  <u>via</u> protonolysis (route b). The latter route may be more likely, as the rate of the formation of  $Et_2BOCH_3$  is proportional to methanol concentration (cf. entries 2-5). At higher  $CH_3OH$  concentrations (entries 4&5), as the <sup>11</sup>B-NMR signal of the ate complex (11.6-11.9 ppm) diminishes due to its conversion to  $Et_2BOCH_3$  (35.2 ppm), the weaker signal of  $EtB(OCH_3)_2$  (12.8 ppm) becomes visible.

			Chemical	shifts <sup>a)</sup> of the	boron signal due to ate complex
Entry No.	Borane	Solvent	Et 3B	Et <sub>2</sub> BOCH <sub>3</sub> (Rel. int.)	and/or EtB(OCH <sub>3</sub> ) <sub>2</sub> (Rel. int.)
1	BEt 3b)	THF	60.06	_	-
2	BEt <sub>3</sub> c) (2 mmol)	THF:CH <sub>3</sub> OH	-	35.27 (20%)	11.63 (80%)
3	BEt <sub>3</sub> c) (1 mmol)	2 mL 0.5 mL "	-	35.23 (29%)	11.90 (71%)
4	BEt <sub>3</sub> c) (0.5 mmol)	н	-	35.23 (57%)	12.81&11.89(43%)
5	BEt <sub>3</sub> C) (0.25 mmol)	"	-	35.23 (93%)	12.89 (7%)
6	Et <sub>2</sub> BOCH <sub>3</sub> d)	THF	-	35.18 (97%)	12.77 (3%)
7	$EtB(OCH_3)_2 e)$	THF	-	-	12.96

Table 1. <sup>11</sup>B-NMR Study of the Interactions of Et<sub>3</sub>B with CH<sub>3</sub>OH

a) Chemical shifts are reported in  $\delta$  ppm with reference to B(OCH<sub>3</sub>)<sub>3</sub> as an external standard, and the NMR spectra are measured using a 10-mm probe. b) Sample obtained from Aldrich. c) The reagents were mixed at -78 °C, and after 30 min at this temperature the NMR spectra were recorded at 22 °C. d) Authentic sample made by following Köster's procedure.<sup>2</sup> e) Sample kindly supplied by Prof. Köster.



Scheme 1.

The above method of <u>in situ</u> generation of alkoxydialkylboranes was found to be generally applicable to substrates such as triethyl- and tributylboranes in combination with simple alcohols like methanol, ethanol, allyl alcohol etc. The details of these results will be published in due course of time.

In order to check the applicability of this method to the diastereoselective reduction of  $\beta$ -hydroxyketones with NaBH<sub>4</sub>, we compared the results obtained with

the <u>in situ</u> reagent with those obtained with authentic<sup>1</sup>)  $\text{Et}_2\text{BOCH}_3$ . In all cases thus far examined, the <u>syn</u> diastereoselectivity<sup>6</sup>) was found to be  $\geq 98$ % (Table 2). The details of the reaction conditions for the <u>in situ</u> method are described in the general procedure below.

Example	e Reactant	Product	syn/ %	Yield /%
1.			>99	95
2.	OH O g	OH OH gr CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	>99	80
3.	OH O CO2CH3	OH OH CO2CH3	>99	90
4.	F CO <sub>2</sub> CH <sub>3</sub> H <sub>3</sub> C <sup>-/</sup> CH <sub>3</sub> OH O	$ \begin{array}{c} F \\ \hline N \\ H_3C \\ \hline CH_3 \\ C$	>98	70
5.	OH O $\mathcal{B}$ O CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> $\mathcal{B}$	OH OH B' CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	>99	75
6.			>99	70

Table 2.	Diastereoselective	Reductions	of	$\beta$ -hydroxyketones	with	NaBH 4	in	the	Presence
		of Et 2BOCH	3 (i	n situ Method)					

With the intention of monitoring the transformations that take place around boron nucleus during the reduction process (Scheme 2), the <sup>11</sup>B-NMR spectra of the reduction mixture with example 4 were measured at different intervals. The signal at  $\delta$  35 ppm essentially remained unchanged during the whole course of the reduction presumably due to the fact that solvation, present from the beginning of the experiment, has a similar effect on the <sup>11</sup>B-NMR shift as does chelation. Therefore, we could not further prove the presence of the six-membered chelate intermediate,<sup>1</sup>,<sup>3</sup>) the model for explaining the <u>syn</u> diastereoselectivity.

The high degree of diastereoselectivity observed in the reduction of  $\beta$ -hydroxyketones with sodium borohydride by using alkoxydialkyl boranes as chelating agents and the fact that these reagents in turn can be quantitatively generated <u>in situ</u> from the commercially available trialkylboranes, make the above method for the preparation of <u>syn</u> 1,3-diols unique. These results complement well the recently reported <u>anti</u>-selective reductions.<sup>7</sup>)

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A solution of  $\text{Et}_3\text{B}$  (1.1 mL of 1 M solution in THF) was added to a mixture of dry THF (8 mL) and methanol (2 mL) at room temperature under argon. After stirring for one hour, the mixture was cooled to -70 °C followed by the addition of a  $\beta$ -hydroxyketone (1 mmol), and the stirring was continued for 30 min. Then sodium borohydride (1.1 mmol) was added, and the mixture was stirred for 3-5 h, depending on the substrate used. The reaction mixture was diluted with ethyl acetate, quenched with aqueous ammonium chloride solution, and the organic phase was dried and evaporated to dryness. The residue was azeotroped a few times with methanol until boron-containing compounds were removed, then chromatographed on silica gel using ethyl acetate/hexane as eluent to give 1,3-diols.

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- 4) The possibility that traces of air or peroxide impurities could be responsible for the results was ruled out by carrying out experiments in degassed solvents as well as in the presence of Galvinoxyl,<sup>8</sup> a radical inhibitor. The results were always consistent and reproducible.
- 5) Trialkyl, dialkyl monooxygenated and monoalkyl dioxygenated boranes can be readily differentiated by <sup>11</sup>B-NMR as the boron chemical shifts of these compounds are widely separated and very characteristic.
- 6) The <u>syn/anti</u> ratios were calculated on the basis of the relative intensity of the two sets of  $^{13}$ C-NMR signals of the two stereogenic carbons.<sup>1</sup>)
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