

## A New Class of Stereoselective Reducing Agents, Lithium Di(3-methyl-2-butyl)alkoxyborohydrides

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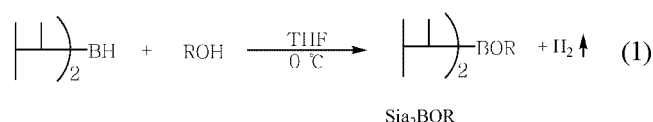
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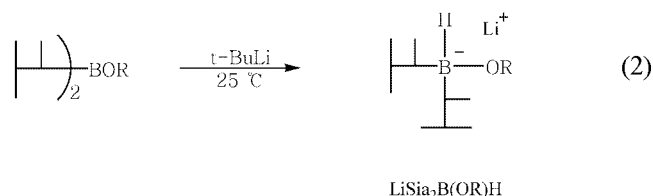
We have synthesized a new class of reducing agents, lithium di(3-methyl-2-butyl)alkoxyborohydrides [LiSia<sub>2</sub>B(OR)H], and have examined its stereoselectivity in the reduction of cyclic ketones. The degree of stereoselectivity exhibits a close correlation with the bulkiness of alkoxy substituent in the reagent. Especially, the *t*-butoxy derivative reveals an excellent stereoselectivity at 0 and -20 °C, comparable to the results previously achieved by lithium trisiamylborohydride,<sup>1</sup> potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]nonane,<sup>2</sup> and lithium (2,3-dimethyl-2-butyl)-*t*-butoxyborohydride.<sup>3</sup>

The reagents were prepared by adding a solution of *tert*-butyllithium<sup>4</sup> in pentane to a solution of di(3-methyl-2-butyl)alkoxy borane (Sia<sub>2</sub>BOR) in THF at 25 °C (eq. 2). The solution of Sia<sub>2</sub>BOR was also readily prepared by reacting a solution of disiamylborane in THF with the corresponding alcohols at 0 °C (eq. 1).



Sia<sub>2</sub>BOR

R = Et, Sia<sub>2</sub>BOEt  
= *i*-Pr, Sia<sub>2</sub>BO<sup>*i*</sup>Pr  
= *t*-Bu, Sia<sub>2</sub>BO<sup>*t*</sup>Bu



LiSia<sub>2</sub>B(OR)H

The stereoselectivity of these new reagents toward representative group of cyclic ketones was examined at 0 and -20 °C, and the results are summarized in Table 1. In general, the degree of stereoselectivity exhibits a close correlation with the bulkiness of alkyl substituent in the reagent. Especially, the stereoselectivity achieved by the *t*-butoxy derivative, lithium di(3-methyl-2-butyl)-*t*-butoxyborohydride [LiSia<sub>2</sub>B(O<sup>*t*</sup>Bu)H], is exceptionally high. As in the comparison data summarized in Table 2, its stereoselectivity performed at 0 °C is comparable to the results

previously achieved with lithium trisiamylborohydride (LiSia<sub>3</sub>BH),<sup>1</sup> potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]nonane (K9-<sup>*t*</sup>Bu-9-BBNH)<sup>2</sup> and lithium(2,3-dimethyl-2-butyl)-*t*-butoxyborohydride (LiThx<sup>*t*</sup>BuOBH<sub>2</sub>),<sup>3</sup> even higher than the selectivity obtained by lithium tri-*s*-butylborohydride (Li<sup>*s*</sup>Bu<sub>3</sub>BH)<sub>3</sub> and potassium 9-(2,3-dimethyl-2-butoxy)-9-boratabicyclo[3.3.1]nonane (K9-OThx-9-BBNH).<sup>1b</sup>

In recent years, new developments in the area of stereoselective reduction of cyclic ketones have been exceptionally promising.<sup>5-8</sup> Substituted borohydrides, such as LiSia<sub>3</sub>BH,<sup>1</sup> K9-<sup>*t*</sup>Bu-9-BBNH<sup>2</sup> and LiThx<sup>*t*</sup>BuOBH<sub>2</sub>,<sup>3</sup> reduce cyclic ketones to the corresponding alcohols of the thermodynamically less stable isomers in the range of 95-100% stereoselectivity. On the other hand, alane and its derivatives, such as aluminum hydride,<sup>5</sup> diisobutylaluminum hydride,<sup>9a</sup> *Al*-isopropoxydiisobutylalane,<sup>9b,c</sup> and 1-pyrrolyldiisobutylalane,<sup>9d</sup> convert cyclic ketones to the corresponding alcohols of the thermodynamically

**Table 1.** Stereoselective Reduction of Cyclic Ketones with Lithium Di(3-methyl-2-butyl)alkoxyborohydrides [LiSia<sub>2</sub>B(OR)H] at 0 and -20 °C<sup>a,b,c</sup>

Ketone	Reaction temperature (°C)	R in LiSia <sub>2</sub> B(OR)H <sup>d</sup>		
		Et	<i>i</i> -Pr	<i>t</i> -Bu
2-Methylcyclopentanone	0	95	98	99.5
	-20	97	99	>99.9
2-Methylcyclohexanone	0	95	98	99.5
	-20	97	99.5	>99.9
3-Methylcyclohexanone	0	92	95	97
	-20	93	96.5	98.5
4-Methylcyclohexanone	0	90	91	92
	-20	92	93	94
4- <i>t</i> -Butylcyclohexanone	0	90	94	96
	-20	92	96	98
3,3,5-Trimethylcyclohexanone	0	95	98	99.5
	-20	96.5	99.5	>99.9
Norcamphor	0	94	98	98
	-20	95.5	99.5	99.5
Camphor	0 <sup>e</sup>	95	98	99

<sup>a</sup>In a mixed solvent of THF and pentane. <sup>b</sup>A ratio for reagent to ketone is 2 : 1. <sup>c</sup>Reaction for 1 h and the alcohol yields are more than 98%, unless otherwise indicated. <sup>d</sup>The figures are ratios in percentage of the thermodynamically less stable isomer alcohols determined by GC analysis. <sup>e</sup>Reacted for 72 h and the alcohol yields are around 90%.

**Table 2.** Comparison of Stereoselectivity in the Reduction of Cyclic Ketones with Representative Reagents at 0 °C

Ketone	Selectivity (%)					
	LiSi <sub>2</sub> B (O <sup>t</sup> Bu)H	LiThx <sup>t</sup> BuOBH <sub>2</sub> <sup>a</sup>	K9-OThx-9- BBNH <sup>b</sup>	Li <sup>t</sup> Bu <sub>3</sub> BH <sup>c</sup>	LiSi <sub>2</sub> BH <sup>d</sup>	K9- <sup>t</sup> Bu-9- BBNH <sup>d</sup>
2-Methylcyclopentanone	99.5	>99.5	98.5	99.3	99.4	99.5
3-Methylcyclohexanone	97	96	90	85	98	96
4-Methylcyclohexanone	92	92	85.5	80.5	93	94
4- <i>t</i> -Butylcyclohexanone	96	95	87	87.5	96.5	98.5
3,3,5-Trimethylcyclohexanone	99.5	>99.5	>99.9	99.8	99	99
Norcamphor	98	98	95	99.6	99	95.5
Camphor	99	>99.5	97.5	99.6	>99.9	99.9

<sup>a</sup>Data taken from ref. 3. <sup>b</sup>Data taken from ref. 1b. <sup>c</sup>Data taken from ref. 5. <sup>d</sup>Data taken from ref. 2.

cally more stable isomers in the 80 to 100% range of stereoselectivity. Similarly, such stereoselectivity can also be obtained by BH<sub>3</sub>-THF.<sup>10</sup> Thus, the reaction of cyclic ketones with borane in refluxing THF gives the thermodynamically more stable alcohols in higher than 98% purity. Therefore, it is worthwhile to emphasize that these are reagents of choice for converting cyclic ketones to the corresponding alcohols of one of two possible isomers.

The following procedure served to prepare Si<sub>2</sub>BOR. The preparation of the *t*-butoxy derivative is representative. An oven-dried, 100-mL, round-bottomed flask, equipped with a side arm, a condenser, and an adapter connected to a mercury bubbler, was cooled to 0 °C by immersion in an ice-water bath under a stream of nitrogen and maintained under a static pressure of nitrogen. The flask was charged with 40 mL of a 1.0 M solution of Si<sub>2</sub>BH (40 mmol) in THF. To this was added 3.1 g of *t*-BuOH (42 mmol) dropwise with stirring. After the hydrogen evolution ceased, the reaction mixture was stirred for additional 1 h at 0 °C to afford a 0.92 M of Si<sub>2</sub>BO<sup>t</sup>Bu. <sup>11</sup>B NMR δ 52 ppm (s) relative to BF<sub>3</sub>·OEt<sub>2</sub>. The <sup>11</sup>B NMR spectra of the other derivatives showed a broad single peak at δ 53 ppm for Si<sub>2</sub>BOEt and at δ 52 ppm for Si<sub>2</sub>BO<sup>i</sup>Pr.

The following procedure served for the preparation of LiSi<sub>2</sub>B(OR)H. The preparation of the *t*-butoxy derivative is illustrative. Into a 100 mL flask was placed 27.2 mL of the solution of Si<sub>2</sub>BO<sup>t</sup>Bu (25 mmol) that prepared above, and the flask was kept at 25 °C by use of a refrigerating bath circulator. To the flask was added 16.2 mL of a 1.7 M solution of *tert*-butyllithium (27.5 mmol) in pentane with vigorous stirring and the reaction mixture was stirred for 12 h at 25 °C. The concentration of the reagent was estimated gasometrically by hydrolyzing an aliquot to give 0.48 M of LiSi<sub>2</sub>B(O<sup>t</sup>Bu)H: <sup>11</sup>B NMR (THF and pentane) δ -3.7 ppm (d, *J*<sub>B-H</sub> = 245.1 Hz). The <sup>11</sup>B NMR spectra of the other derivatives showed a doublet at δ -7.4 ppm (*J*<sub>B-H</sub> = 242.4 Hz) for LiSi<sub>2</sub>B(OEt)H and at δ -3.7 ppm (*J*<sub>B-H</sub> = 251.7 Hz) for LiSi<sub>2</sub>B(O<sup>i</sup>Pr)H.

The following procedure was used to explore the stereoselectivity of the reagents. In a 50-mL, round-bottomed flask

was placed 2 mmole of the reagent. The flask was maintained at 0 °C (or -20 °C) by use of refrigerating bath circulator. To this flask was added 1 mmole of precooled a cyclic ketone solution in THF (2.0 M in ketone) and the reaction mixture was stirred at 0 °C (or -20 °C) for 1 h.

The reaction was then quenched by addition of 2 mL of 3 N NaOH, and the organoborane was oxidized with 30% H<sub>2</sub>O<sub>2</sub>. The aqueous layer was saturated with anhydrous K<sub>2</sub>CO<sub>3</sub>, and the organic layer was analyzed by GC. The ratios of isomer alcohols are summarized in Table 1.

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