

## A New, Highly Stereoselective Reducing Agent, Lithium (2,3-Dimethyl-2-butyl)-*t*-butoxyborohydride

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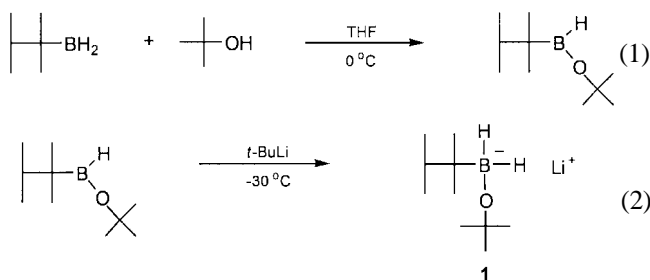
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We have synthesized a new stereoselective reducing agent, lithium (2,3-dimethyl-2-butyl)-*t*-butoxyborohydride (Li Thx'-BuOBH<sub>2</sub>, **1**), and have examined its stereoselectivity toward cyclic ketones. This borohydride reveals an excellent stereoselectivity at 0 and -20 °C, comparable to the results previously achieved with lithium trisiamylborohydride<sup>1</sup> and potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]nonane.<sup>2</sup>

The reagent was prepared by adding a solution of *tert*-butyllithium<sup>3</sup> in *n*-pentane to a solution of hexyl-*t*-butoxyborane (ThxBHO'Bu) in THF at -30 °C (eq. 2). The solution of ThxBHO'Bu was also readily prepared by reacting a solution of hexylborane in THF with *t*-butyl alcohol at 0 °C



(eq. 1).

The reagent readily reduced ketones at 0 or -20 °C and reveals an excellent stereoselectivity with representative cyclic ketones. The results are summarized in Table 1. Its stereoselectivity is comparable to the results previously achieved with lithium trisiamylborohydride (LiSia<sub>3</sub>BH)<sup>1</sup> and potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]nonane (K9-*t*-Bu-9-BBNH),<sup>2</sup> even higher than the selectivity shown by lithium tri-*s*-butylborohydride (Li<sup>*s*</sup>Bu<sub>3</sub>BH) and potassium 9-(2,3-dimethyl-2-butoxy)-9-boratabicyclo[3.3.1]nonane (K9-OThx-9-BBNH)<sup>1b</sup> at 0 °C. The comparable data for the other four reagents are summarized in Table 2.

In recent years, new developments in the area of stereoselective reduction of cyclic ketones have been exceptionally promising.<sup>1,2,5-8</sup> Hindered trisubstituted borohydrides, such as lithium trisiamylborohydride<sup>1a</sup> and potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]nonane,<sup>2</sup> reduce cyclic ketones to the corresponding alcohols of the less stable isomers in the 95-100% range of stereoselectivity. On the other hand, alane and its derivatives, such as aluminum hydride,<sup>7</sup> diisobutylaluminum hydride,<sup>8a</sup> *Al*-isopropoxydiisobutylalane,<sup>8b,c</sup> and 1-pyrrolyldiisobutylalane,<sup>8d</sup> convert cyclic ketones to the

**Table 1.** Stereoselective Reduction of Cyclic Ketones with Lithium (2,3-Dimethyl-2-butyl)-*t*-butoxyborohydride (Li Thx'-BuOBH<sub>2</sub>)<sup>a,b</sup>

Ketone	Reaction temperature (°C)	Reaction time (h)	Conversion (%) <sup>c</sup>	Less Stable isomer	Selectivity (%) <sup>c</sup>
2-Methylcyclopentanone	0	0.5	100	<i>cis</i>	>99.5
	-20	0.5	100		>99.5
2-Methylcyclohexanone	0	0.5	100	<i>cis</i>	>99.5
	-20	0.5	100		>99.9
2- <i>t</i> -Butylcyclohexanone	0	6	100	<i>cis</i>	>99.5
	-20	12	100		>99.9
3-Methylcyclohexanone	0	0.5	100	<i>trans</i>	96
	-20	0.5	100		98
4-Methylcyclohexanone	0	0.5	100	<i>cis</i>	92
	-20	0.5	100		94
4- <i>t</i> -Butylcyclohexanone	0	0.5	100	<i>cis</i>	95
	-20	0.5	100		97
3,3,5-Trimethylcyclohexanone	0	0.5	100	<i>trans</i>	>99.5
	-20	0.5	100		>99.9
Norcamphor	0	0.5	100	<i>endo</i>	98
	-20	0.5	100		99.5
Camphor	0	48	56	<i>exo</i>	>99.5
	25	72	100		>99.5

<sup>a</sup>In a mixed solvent of THF and *n*-pentane. <sup>b</sup>A 2 : 1 ratio for reagent : ketone was utilized. <sup>c</sup>GC yield.

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

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

<sup>a</sup>Data taken from ref 1b. <sup>b</sup>Data taken from ref 4. <sup>c</sup>Data taken from ref 2.

corresponding alcohols of the more stable isomers in the 80 % to 100% range of stereoselectivity. 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 ThxBHO<sup>t</sup>Bu. An oven-dried, 250-mL, round-bottomed flask, equipped with a side arm, a condenser, and an adaptor 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 placed with 160 mL of a 1.25 M solution of ThxBH<sub>2</sub> (200 mmol) in THF. To this was added 15.7 g of *t*-BuOH (210 mmol) dropwise with vigorous stirring. After the hydrogen evolution ceased, the reaction mixture was stirred for additional 1 h at 0 °C to afford a 1.07 M of ThxBHO<sup>t</sup>Bu: <sup>11</sup>B NMR  $\delta$  48.3 ppm (d,  $J_{B-H} = 390$  Hz).

The following procedure served for the preparation of the reagent 1. Into a 100-mL flask was placed 40 mL of the solution of ThxBHO<sup>t</sup>Bu (40.3 mmol) thus prepared above, and the flask was cooled to -30 °C by use of a refrigerating bath circulator. To the flask was added 26 mL of a precooled 1.7 M solution of *t*-butyllithium (44 mmol) in *n*-pentane dropwise with vigorous stirring. After the reaction mixture was stirred for additional 1 h at -30 °C, the flask was brought to 0 °C. The concentration of the reagent was estimated gasometrically by hydrolyzing an aliquot to give 0.60 M of Li Thx<sup>t</sup>BuOBH<sub>2</sub>: <sup>11</sup>B NMR (THF and *n*-pentane)  $\delta$  7.6 ppm (t,  $J_{B-H} = 219$  Hz).<sup>9</sup>

The following procedure was used to explore the stereoselectivity of this reagent. In a 50-mL, round-bottomed flask was placed 5 mL of a 0.60 M solution of the reagent (3.0 mmol). The flask was maintained at 0 °C by use of a refrigerating bath circulator. To the flask was added 1.5 mL of precooled 2-methylcyclohexanone solution in THF (1.0 M in ketone) and the reaction mixture was stirred at 0 °C for 0.5 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>.

GC analysis of the organic layer showed the presence of a quantitative yield of 2-methylcyclohexanol, containing > 99.5% of the *cis* isomer along with a trace of the *trans* isomer.

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- The <sup>11</sup>B NMR spectrum of Li Thx<sup>t</sup>BuOBH<sub>2</sub> at ambient temperature exhibited a clean triplet at  $\delta$  -7.6 ppm along with minor unknown peaks in the range of  $\delta$  45-55 ppm.