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

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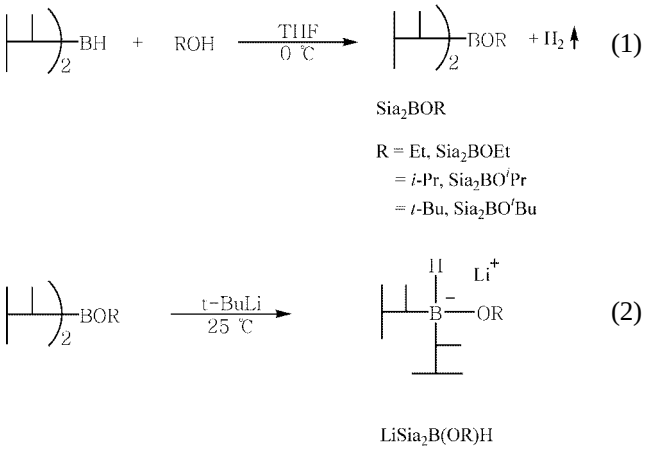
We have synthesized a new class of reducing agents, lithium di(3-methyl-2-buthyl)alkoxyborohydrides [$LiSia_2B(OR)H$], and have examined its stereoselectivity in the reduction of cyclic ketones. The degree of stereoselcetivity exhibits a close correlation with the bulkiness of alkoxy substituent in the reagent. Especially, the *t*-butoxy derivative reveals an excellent stereoselectivity at 0 and -20 °C, comparable to the results previously achieved by lithium trisiamylborohydride,[1] potassium 9-*t*-butyl-9-boratabicyclo-[3.3.1]nonane,[2] and lithium (2,3-dimethyl-2-butyl)-*t*-butoxy-borohydride.[3]

The reagents were prepared by adding a solution of *tert*-butyllithium[4] in pentane to a solution of di(3-methyl-2-butyl)alkoxy borane(Sia_2BOR) in THF at 25 °C (eq. 2). The solution of Sia_2BOR was also readily prepared by reacting a solution of disiamylborane in THF with the corresponding alcohols at 0 °C (eq. 1).



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*-butoxy-boro hydride [$LiSia_2B(O^tBu)H$], 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 ($LiSia_3BH$),[1] potassium 9-*t*-butyl-9-boratabicyclo[3.3.1]-nonane (K9-^{t}Bu-9-BBNH)[2] and lithium(2,3-dimethyl-2-butyl)-*t*-butoxyborohydride ($LiThx^tBuOBH_2$),[3] even higher than the selectivity obtained by lithium tri-*s*-butylborohydride (Li^sBu_3BH)$_5$and potassium 9-(2,3-dimethyl-2-butoxy)-9-boratabicyclo[3.3.1]nonane (K9-OThx-9-BBNH).[1b]

In recent years, new developments in the area of stereoselective reduction of cyclic ketones have been exceptionally promising.[5~8] Substituted borohydrides, such as $LiSia_3BH$,[1] K9-^{t}Bu-9-BBNH[2] and $LiThx^tBuOBH_2$[3] reduce cyclic ketones to the corresponding alcohols of the thermodynamically less stable isomers in the range of 95-100% stereoselctivity. On the other hand, alane and its derivatives, such as aluminum hydride,[8] diisobutylaluminum hydride,[9a] A*l*-isopropoxydiisobutylalane,[9b,c] and 1-pyrrolyldiisobutyalane,[9d] convert cyclic ketones to the corresponding alcohols of the thermodynami-

Table 1. Stereoselective Reduction of Cyclic Ketones with Lithium Di(3-methyl-2-butyl)alkoxyborohydrides[$LiSia_2B(OR)H$] at 0 and -20 °C[a,b,c]

Ketone	Reaction temperaure (°C)	R in $LiSia_2B(OR)H$[d]		
		Et	*i*-Pr	*t*-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-*t*-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[e]	95	98	99

[a]In a mixed solvent of THF and pentane. [b]A ratio for reagent to ketone is 2 : 1. [c]Reaction for 1 h and the alcohol yields are more than 98%, unless otherwise indicated. [d]The figures are ratios in percentage of the thermodynamically less stable isomer alcohols determined by GC analysis. [e]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 (%)					
	$LiSia_2B(O^tBu)H$	$LiThx^tBuOBH_2$[a]	K9-OThx-9-BBNH[b]	Li^sBu_3BH[c]	$LiSia_3BH$[b]	K9-^{t}Bu-9-BBNH[d]
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-*t*-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

[a]Data taken from ref. 3. [b]Data taken from ref. 1b. [c]Data taken from ref. 5. [d]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_3-THF.[10] Thus, the reaction of cyclic ketones with borane in refluxing THF gives the 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 Sia_2BOR. 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 Sia_2BH (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 Sia_2BO^tBu: ^{11}B NMR δ 52 ppm (s) relative to $BF_3{\cdot}OEt_2$. The ^{11}B NMR spectra of the other derivatives showed a broad single peak at δ 53 ppm for Sia_2BOEt and at δ 52 ppm for Sia_2BO^iPr.

The following procedure served for the preparation of $LiSia_2B(OR)H$. The preparation of the *t*-butoxy derivative is illustrative. Into a 100 mL flask was placed 27.2 mL of the solution of Sia_2BO^tBu (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 $LiSia_2B(O^tBu)H$: ^{11}B NMR (THF and pentane) δ -3.7 ppm (d, $J_{B\text{-}H}$ = 245.1 Hz). The ^{11}B NMR spectra of the other derivatives showed a doublet at δ -7.4 ppm ($J_{B\text{-}H}$ = 242.4 Hz) for $LiSia_2B(OEt)H$ and at δ -3.7 ppm ($J_{B\text{-}H}$ = 251.7 Hz) for $LiSia_2B(O^iPr)H$.

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_2O_2. The aqueous layer was saturated with anhydrous K_2CO_3, and the organic layer was analyzed by GC. The ratios of isomer alcohols are summarized in Table 1.

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