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Aminoborohydrides. 6. Diastereoselective Reduction of the Carbon-Nitrogen Double Bond in Chiral Imines Using Lithium Diethylaminoborohydride and Lithium Diisopropylaminoborohydride.

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Summary: *Lithium aminoborohydrides (LAB), obtained by the reaction of n-BuLi with amine-boranes, readily reduce imines to the corresponding secondary amines. Lithium diethylaminoborohydride [$Li(Et)_2NBH_3$] and lithium diisopropylaminoborohydride [$Li(i\text{-}Pr)_2NBH_3$] reduce chiral aliphatic and aromatic imines, derived from α-methylbenzylamines, to give the corresponding enantiomerically enriched secondary amines. The yields of secondary amines from this procedure range from very good to essentially quantitative. The diastereomeric induction in the reduction of the carbon-nitrogen double bond with $Li(Et)_2NBH_3$ and $Li(i\text{-}Pr)_2NBH_3$ ranged from moderate to very good.*

The reduction of imines is very important in organic chemistry[2] and has been studied intensively, especially in connection with the syntheses of alkaloids[3] and amino acids.[4] The use of chiral amines as chiral auxiliaries[4-7] and chiral building blocks[8] has extensive applications in modern synthetic chemistry. The most common procedure for the synthesis of chiral amines involves the hydrogenation of prochiral schiff bases.[9] While this method requires the use of a separate chiral auxiliary,[9c] the more successful route has been to hydrogenate or reduce chiral imines synthesized from the corresponding prochiral ketone and a chiral amine.[10] However, these methods suffer from the need of having to use a large excess of hydride, high temperatures over extended periods of time, and the need to rigorously exclude air and water during the reduction.[9e-f] Alternatively, enantiomerically pure primary and secondary amines can be synthesized from chiral organoboranes.[11] Herein, we report the synthesis of enantiomerically enriched secondary amines via the reduction of chiral imines with lithium aminoborohydrides (LAB) to give asymmetric induction as high as 92%.

Recently,[12] we disclosed a new class of reducing agents now known as LAB reagents, comparable in reduction potential to lithium aluminum hydride. LAB reagents are stable to air, are non-pyrophoric, and are thermally stable. LAB reagents can be prepared readily in large scale and in essentially quantitative yield from *n*-BuLi and any amine-borane complex.[12]

We were interested in reducing the imines derived from (*S*)-(-)-α-methylbenzylamine and ketones, such as 2-octanone, pinacolone, cyclohexanone, acetophenone, 2'-acetonapthone and 2-acetylpyridine. These chiral imines were synthesized by the reported procedure[10c] and purified by distillation prior to reduction with LAB. The reductions were carried out by mixing the reactants at 0 °C for 1 h under nitrogen, followed by quenching at 0 °C. Our results are summarized in **Table 1**, and only the major diastereomers are shown. The reduction of chiral imines with either lithium diethylaminoborohydride [$Li(Et)_2NBH_3$] or lithium diisopropylaminoborohydride [$Li(i\text{-}Pr)_2NBH_3$] to the corresponding enantiomerically enriched secondary amines is quite general.[13] Additionally, $Li(Et)_2NBH_3$ efficiently reduced the imine derived from pinacolone and (*S*)-(-)-α-methylbenzylamine, to the corresponding optically active secondary amine in 92 % de (eq. 1).

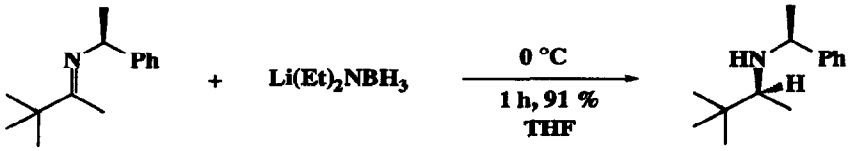
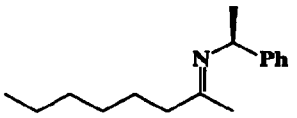
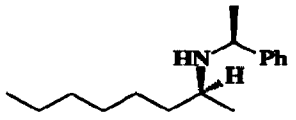
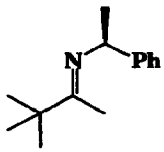
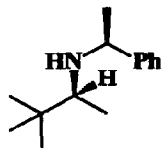
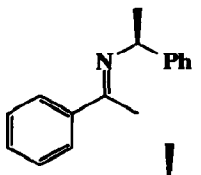
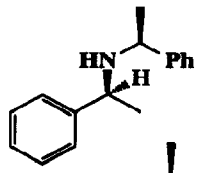
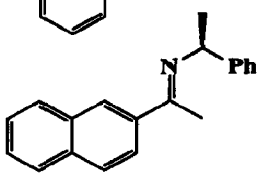
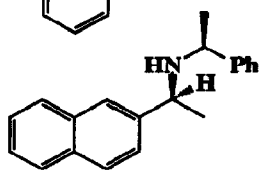
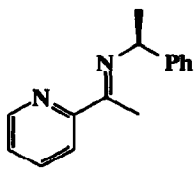
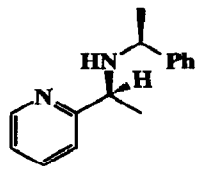


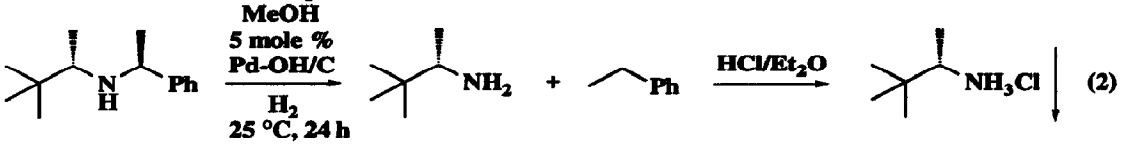
Table 1. Reduction of Chiral Imines with $Li(Et)_2NBH_3$[a] and $Li(i\text{-}Pr)_2NBH_3$[b]

imine	LAB (eq)	product	de[c]	yield, %[d]	BP (Torr)[e]
	1.1[a] 1.1[b]		34 %[a] 34 %[b]	83[a] 88[b]	100-101 (0.4)[a] 89-90 (0.3)[b]
	1.1[a] 1.1[b]		92 %[a] 90 %[b]	91[a] 85[b]	80-81 (0.4)[a] 78-79 (0.3)[b]
	1.1[a] 1.1[b]		66 %[a] 68 %[b]	95[a] 93[b]	113-115 (0.4)[a] 100-101 (0.3)[b]
	1.1[a] 1.1[b]		60 %[a] 58 %[b]	98[a] 97[b]	120-122 (0.4)[a] 120-121 (0.4)[a]
	1.1[a] 1.1[b]		51 %[a,f] 48 %[b,f]	94[a] 92[b]	120-121 (0.3)[a] 120-123 (0.3)[b]

[a,b]See ref. 12. [c]Diastereomeric excess determined by 250 MHz ^1H NMR and capillary GC analysis on a 60 M Methylsilicone column. [d]Isolated yields. [e]Bp/mp are uncorrected. [f]See ref. 10f.

LAB reagents can be used either as solids or as solutions to reduce chiral imines without the need for an inert atmosphere during the reduction reaction. However, it is imperative to cover the reaction vessel with a septa or parafilm to exclude extraneous moisture from the reaction. The crude products obtained in LAB reductions of chiral imines are often of nearly analytical purity. Most of the enantiomerically enriched secondary amines synthesized in our study have not been described before in optically active form and are not commercially available. Consequently, the diastereomeric excess was determined by ^1H NMR and capillary GC analysis.

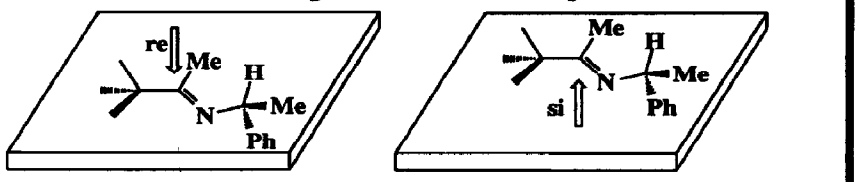
The absolute stereochemistry of the enantiomerically enriched secondary amine derived from the imine of pinacolone and α-methylbenzylamine was determined by catalytic hydrogenation followed by chiroptical comparison of the product 3,3-dimethyl-2-butylamine hydrochloride. Thus, the optically enriched secondary amine (20 mmol, 4.4 g) [**Table 1**, entry #2] in 15 mL of CH_3OH was stirred under 1 atm of H_2 at 25 °C for 24 h in the presence of 5 mole % of Pd-OH/C. The Pd-OH/C was separated by filtration and the filtrate was treated with 1 *M* HCl in Et_2O (20 mL) (eq. 2).



The resulting precipitate was filtered off, and washed with pentane (5 X 20 mL) and dried. This hydrochloride exhibited a rotation $[\alpha]_D = +3.2°$ (*c* 4, MeOH) [Lit.[11] $[\alpha]_D = +2.8°$ (*c* 4, MeOH) for the (*S*)-enantiomer of 96 % ee].

The above result suggested that the approach of $Li(Et)_2NBH_3$ from the pro-*S* face of the carbon-nitrogen bond is favored giving the (*S,S*) diastereomer as shown (Figure 1). Additionally, the chiroptical comparison revealed that reduction of the imine derived from acetophenone and (*S*)-(-)-α-methylbenzylamine also gives the corresponding *S,S* secondary amine. Consequently, based on these results, we propose the (*S,S*) configurations for the major diastereomers formed in our study (**Table 1**).

Figure 1. Models for the approach of $Li(Et)_2NBH_3$ on both the pro-*S* and pro-*R* faces of the carbon nitrogen double bond of the pinacolone imine



Major Diastereomer **Minor Diastereomer**

We are actively exploring the reduction of other compounds containing carbon-nitrogen multiple bonds with LAB reagents.

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(13) The following procedure for the reduction of the chiral imine derived from acetophenone and optically active (*S*)-(-)-α-methylbenzylamine, using $Li(Et)_2NBH_3$, is representative. An oven dried, nitrogen flushed 50-mL round bottom flask equipped with a magnetic stirring bar was charged with 1.0 mL of the chiral imine derived from acetophenone and optically active (*S*)-(-)-α-methylbenzylamine (1.2 g, 5.0 mmol) and 5 mL of distilled tetrahydrofuran (THF). The reaction mixture was then cooled to 0 °C and 5.5 mL of a 1.0 M $Li(Et)_2NBH_3$ solution in THF was added by syringe (5.5 mmol). The reaction mixture was then stirred for 1 h at 0 °C and quenched by the addition of 10 mL of 6 M HCl (60 mmol) [*Caution: Hydrogen evolution*]. The aqueous fraction was layered with diethyl ether (50 mL), and solid sodium hydroxide was added until the reaction mixture was strongly basic to litmus. The ether layer was separated, the aqueous layer extracted with diethyl ether (2 X 25 mL), and the combined ethereal fractions were dried over $MgSO_4$. The solvents were removed in *vacuo* at 60 °C (5 Torr) to yield the corresponding optically enriched secondary amine (95 % isolated yield, BP: 100-101 °C, 0.3 Torr). Capillary GC analysis of the product on a 60 M Methylsilicone column showed a diastereomeric excess of 92 %.

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