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Asymmetric oxazaborolidine-catalyzed reduction of prochiral ketones with *N*-*tert*-butyl-*N*-trimethylsilylamine–borane

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Abstract—Employing *N*-*tert*-butyl-*N*-trimethylsilylamine-borane (**1**) as the borane source and 5–10% (*R*)-Me-CBS (**2**), the oxazaborolidine-catalyzed reduction of representative aryl and aliphatic ketones was carried out obtaining the corresponding alcohols (**3**) in 83–89% isolated yields and 69–98% ee. © 2003 Elsevier Science Ltd. All rights reserved.

The oxazaborolidine-catalyzed (CBS) reduction of prochiral ketones with borane provides a convenient access to a wide variety of optically active alcohols, which are valuable chiral building blocks for the synthesis of natural products.[1] Since the initial use of BH_3–THF as the stoichiometric reducing agent in this important asymmetric process,[2] a number of alternative borane reagents have been employed which include: BH_3–SMe_2,[3] BH_3–1,4-thioxane,[4] catecholborane[5] and several phenylamine-BH_3 complexes.[6] These borane reagents however, each suffer from disadvantages such as low concentration, low thermal stability, obnoxious odors and difficulties in separating the borane ligand from the desired alcohol, which often require the use of an acidic or chromatographic workup.[6]

Several years ago, we prepared a series silylamine–borane complexes which proved to be highly useful borane sources for both hydroboration/oxidation and for the efficient synthesis of common mono- and dialkylborane hydroborating agents.[7] In these studies, it was demonstrated that *N*-*tert*-butyl-*N*-trimethylsilylamine-borane (**1**) was the most reactive of these complexes in the hydroboration reaction.[7a] This silylamine–borane complex offered the advantage of easy product isolation through the hydrolysis of the silylamine upon aqueous work-up producing the water-soluble primary *t*-butylamine and volatile silicon by-products.[7a] We envisaged that this unique feature of these reagents could also facilitate the isolation of the alcohol products from a CBS reduction.

The asymmetric oxazaborolidine-catalyzed reduction of some representative aromatic and aliphatic prochiral ketones were examined employing **1** as the borane source and (*R*)-Me-CBS (**2**)[2b] as the catalyst (Eq. (1)). These results are summarized in Table 1.

Employing acetophenone as a model substrate, the effect of reaction temperature, **1**/ketone ratio and the amount of catalyst were briefly explored. Using a 1:1:0.05 ratio of acetophenone/**1**/**2** at room temperature, (1*S*)-phenylethanol was obtained in 84% yield and 97% ee (Table 1, entry 1). By ^{11}B NMR analysis of the reaction mixture taken 20 min after the addition of the ketone, the reaction was complete revealing the presence of the expected dialkoxyborane $(RO)_2BH$ (δ 27), unreacted **1** (δ −20), traces of borate ester $(RO)_3B$ (δ 18) and a triplet centered at 42 ppm which we attribute

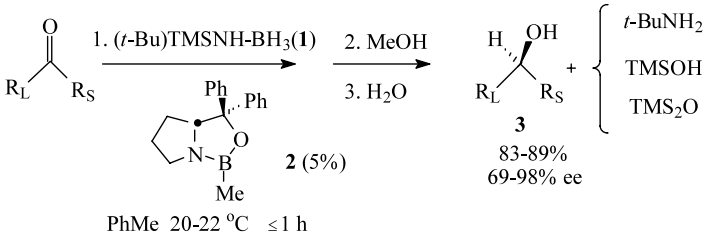

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Table 1. Asymmetric Me-CBS (**2**)-catalyzed reduction of prochiral ketones with **1**

Entry	R_L	R_S	Temperature (°C)	**3** (%)	ee (%)[c]
1	Ph	Me	23	**3a** 84[a]	97[d]
2	Ph	Me	21	**3a** 88[a]	98[e]
3	Ph	Me	23	**3a** 85[a]	90[f]
4	Ph	Me	0	**3a** 83[a]	80[d]
5	Ph	Et	22	**3b** 83[a]	94[d]
6	α-Tetralone		23	**3c** 89[a]	93[d]
7	*c*-Hx	Me	20	**3d** 86[a]	79[d]
8	*i*-Pr	Me	22	**3e** 100[b]	69[d]
9	*t*-Bu	Me	22	**3f** 98[b]	97[d]

[a] Isolated yield of analytically pure material.
[b] GC-yield using internal standard.
[c] % ee Determined by chiral GC with a CDX-B 30 m×0.25 mm column (J and W Scientific) or Mosher Ester.
[d] Ketone/**1**/**2** ratio of 1:1:0.05.
[e] Ketone/**1**/**2** ratio of 1:1:0.1.
[f] Ketone/**1**/**2** ratio of 1.7:1:0.05.

to the alkoxyborane $ROBH_2$ partially complexed to the catalyst. Increasing the catalyst to 10 mol% did not significantly improve the ee in the alcohol product (see entry 2). Lowering the reaction temperature decreased the enantioselectivity (0°C, 80% ee, entry 4). A decrease in the optimal enantioselectivity was also observed when a 1.7:1:0.05 ratio of acetophenone/**1**/**2** was employed (90% ee, entry 3).

Since the conditions employed in entry 1 gave the best results for this substrate, these conditions were selected for the other prochiral ketones examined. All of the reductions were complete in $\leq$1 h. As indicated in Table 1 acetophenone, propiophenone, α-tetralone and pinacolone were reduced to the corresponding alcohols in excellent enantioselectivities which are comparable to those reported using other borane reagents.[1b] As expected, lower enantioselectivities were obtained for the isopropyl (69%) and cyclohexyl (79%) methyl ketones, consistent with the results from other borane sources. These less Lewis acidic aliphatic ketones are thought to possibly undergo a non-catalyzed borane reduction.[1b,8] However, we view this as simply a sterically based *syn* versus *anti* **2**/ketone complexation problem which disappears for the isotropically bulkier pinacolone (98% ee).

All of the nonvolatile chiral alcohols were isolated in excellent yields (83–89%) (entries 1–7)[9] and GC analysis showed quantitative conversion for the pinacolone and isopropyl methyl ketone cases (entries 8–9). As in the hydroboration–oxidation process, the isolation of the alcohols does not require acidic extractions, as is the case when *N*,*N*-diethylaniline-borane or other 3°-amines are employed as stoichiometric reagents.[6a,10] GC and NMR analysis of the crude non-volatile alcohols prior to purification by vacuum distillation revealed only trace amounts of hexamethyldisiloxane (TMS_2O) and toluene.

In summary, *N*-*tert*-butyl(trimethylsilyl)amine-borane (**1**) acts as an efficient borane source in the oxazaborolidine-catalyzed asymmetric reduction of representative aryl and alkyl ketones. The corresponding chiral alcohols were isolated in excellent yields with enantiomeric excesses comparable to those reported employing other combinations of borane reagents with the attractive feature that an acidic workup is not required. The fact that the *N*-*tert*-butyl-*N*-trimethylsilylamine ligand undergoes hydrolysis during the neutral aqueous workup step to give volatile and/or water-soluble products also greatly facilitates the isolation of the CBS reduction product when compared to bulky 3°-amine–borane complexes.[6]

Acknowledgements

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8. The non-catalyzed reduction of acetophenone at room temperature with **1** was carried out employing a 2:1 ketone/silylamine–borane stoichiometry. The reaction was completed after 4 h. This reaction time was considerably less than that reported for BACH-EL™ and *N-tert*-butyl-*N*-methyl-isopropylamine–borane (18 h).[10]
9. **General procedure**: A dry 100 mL thee-necked round-bottomed flask equipped with an addition funnel, magnetic stirring bar, thermocouple and septum inlet was charged with **1** (1.59 g, 10.0 mmol) inside a glove box. The vessel was charged with 10 mL of dry toluene and a 1.0 M solution of **2** in toluene (1.0 mL, 1.0 mmol). The flask was immersed in a water bath to moderate the temperature. Acetophenone (1.20 g, 10.0 mmol) in 5 mL of toluene was placed in the addition funnel and slowly added to the reaction flask over 1 h (four drops/min). The temperature was maintained between 20 and 22°C during the course of the addition. After the addition of the ketone was complete, stirring was continued for an additional 1 h. The reaction mixture was quenched with methanol (5 mL), heated at reflux for 0.5 h, and allowed to reach room temperature. A short path distillation apparatus was connected to the flask and the contents were distilled to remove most of the volatiles. To the remaining oil residue was added water (10 mL) and the aqueous layer was washed with ether (3×10 mL). The combined organic portions were washed with water (3×10 mL) and brine (10 mL). The organic layer was analyzed for the optical purity by GC with a CDX-B 30 m×0.25 mm column (J and W Scientific) and found to be 98% ee (*S*)-*sec*-phenethyl alcohol. The ether was distilled off under atmospheric pressure and the crude *sec*-phenethyl alcohol was distilled under reduced pressure to obtain 1.07 g (88%) of pure product. The enantiomeric purity and absolute configuration of the alcohol was also corroborated by its optical rotation ($[\alpha]_D^{23}$ −40.5 (neat), lit.[11] −41.3 (neat).
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