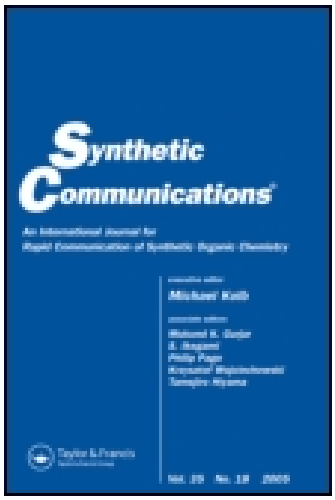

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EFFICIENT PREPARATION OF N-BENZYL SECONDARY AMINES VIA BENZYLAMINE-BORANE MEDIATED REDUCTIVE AMINATION

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EFFICIENT PREPARATION OF *N*-BENZYL SECONDARY AMINES VIA BENZYLAMINE–BORANE MEDIATED REDUCTIVE AMINATION

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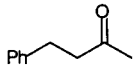
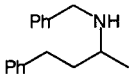
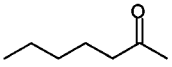
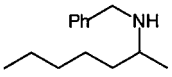
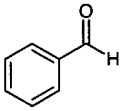
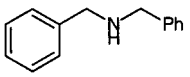
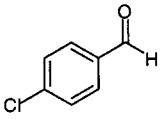
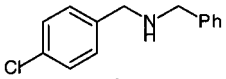
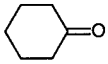
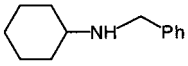
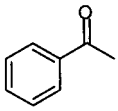
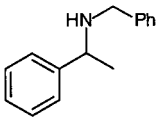
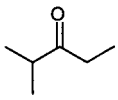
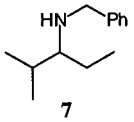
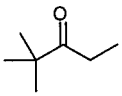
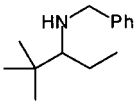
ABSTRACT

An efficient one-pot reductive amination protocol for preparing *N*-benzyl secondary amines is described.

As part of ongoing research, we recently discovered that benzylamine–borane is an effective reductant for *in situ* reductive amination of aldehydes and unhindered ketones. Treatment of the carbonyl compound and benzylamine (1.1 equiv) with benzylamine–borane in the presence of 4 Å molecular sieves gave secondary *N*-benzyl amines in good yields (Table 1). Imines and imminium salts are effectively reduced by a number of hydride reducing agents. However, most of these require pre-formation of the carbon–nitrogen double bond, since reduction of the ketone or aldehyde is a competing reaction. Dimethylamine–borane has been used as a reducing agent for two-step reductive aminations. The reduction is performed in

*Corresponding author.

Table 1. Benzylamine–Borane Promoted Reductive Amination of Selected Ketones and Aldehydes with Benzylamine

Entry	Substrate	Product	Yield (%)[a]
1		 **1**	80[b] 77[c] 75[d]
2		 **2**	75[b] 70[c] 74[d]
3		 **3**	78[b] 82[c] 77[d]
4		 **4**	74[b] 79[c] 73[d]
5		 **5**	54[b] 60[c] 63[d]
6		 **6**	5[b]
7		 **7**	—
8		 **8**	—

[a]Yields refer to isolated product. All compounds gave satisfactory ^{1}H and ^{13}C NMR, and HRMS data. Reaction solvent: [b]THF, [c]CH_2Cl_2, [d]MeOH.

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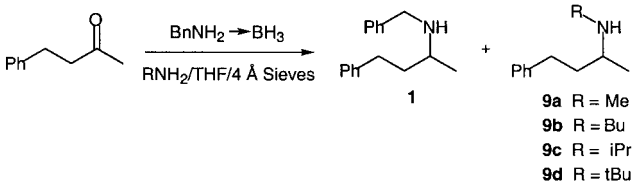
glacial acetic acid and its reported use has been limited to aryl aldimines derived from substituted anilines.[1] Reductants used for *in situ* reductive aminations include pyridine–borane,[2] sodium cyanoborohydride ($NaBH_3CN$),[3] sodium triacetoxy borohydride [$NaBH(OAc)_3$],[4] zinc borohydride–zinc chloride [$ZnBH_4$–$ZnCl_2$],[5] and hydrogen in the presence of transition metal catalysts.[6] While efficient syntheses of *N*-benzyl secondary amines have been achieved with these reagents, they suffer from several significant drawbacks. These include formation of toxic byproducts ($NaBH_3CN$), use of excess amine ($\geq$5 equiv) ($NaBH_3CN$), strongly acidic work-up conditions (1 N HCl) needed to hydrolyze the boron-product complexes (pyridine–borane, $ZnBH_4$–$ZnCl_2$), and acid catalysis (AcOH) for optimum reaction rates [$NaBH(OAc)_3$]. The present method employs stoichiometric amounts of benzylamine under neutral conditions and does not involve production of the toxic byproducts NaCN and HCN. In addition, the boron-product complex is effectively cleaved with refluxing NaOMe/MeOH. Thus, this procedure avoids a number of the drawbacks associated with previous methods and provides a useful alternative for the preparation of secondary *N*-benzyl amines.

We prepared benzylamine–borane by the addition of one molar equivalent of BH_3–THF to benzylamine in THF under N_2. The reagent prepared in this manner could be stored for up to one week at ambient temperature (under air) without noticeable loss in reactivity, and was effective in either protic or aprotic solvents.

The reaction was less effective with hindered ketones (Table 1, Entries 6–8). Tthis is consistent with the increased difficulty of imine formation with hindered ketones.[2a] Reductive aminations of benzylacetone with other primary amines (methylamine, butylamine, isopropylamine, or *tert*-butylamine), with benzylamine–borane as the reducing agent gave mixtures of *N*-benzyl and *N*-alkyl amine products (Scheme 1). This result can be rationalized by borane-amine exchange equilibria that favor the less hindered amines which undergo imine formation more readily than the more hindered amines,[7] and an inverse correlation between the product ratio (**9 : 1**) and the steric bulk of the amine was observed (Table 2).



Scheme 1.

Table 2. Reductive Amination of Benzylacetone with Primary Amines and Benzylamine–Borane[a]

Amine	Product	Yield (%)[b]
CH_3NH_2	**1** (14)	**9a** (71)
$CH_3CH_2CH_2CH_2NH_2$	**1** (32)	**9b** (33)
$(CH_3)_2CHNH_2$	**1** (61)	**9c** (0)
$(CH_3)_3CNH_2$	**1** (52)	**9d** (0)

[a]Reactions were performed in THF.
[b]Yields refer to isolated product.

TYPICAL EXPERIMENTAL

Benzylamine–borane (0.5 M/THF; 4.0 mL), was added to a stirred mixture of the carbonyl compound (2.00 mmol), benzylamine (2.20 mmol), and powdered activated 4 Å sieves (0.400 g) in dried THF (6 mL) and the reaction was stirred overnight at ambient temperature. Volatiles were removed under reduced pressure and the slurry was filtered with Celite (EtOAc wash). The filtrate was evaporated, and the residue was refluxed overnight in NaOMe/MeOH. Chromatography[8] (EtOAc/Hexanes) gave *N*-benzyl secondary amines in >95% purity as determined by ^{1}H NMR.[9] Products gave the expected ^{1}H and ^{13}C NMR spectra and representative data are provided.[10]

Spectroscopic Data

***N*-Benzyl-(1-methyl-3-phenyl)propylamine (1):** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33–7.16 (m, 10H), 3.79 (dd, $J = 12.9$, 21.5 Hz, 2H), 2.79–2.63 (m, 3H), 1.92–1.61 (m, 2H), 1.39 (s, 1H), 1.15 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.4, 140.7, 128.4, 128.3, 128.2, 126.8, 125.6, 51.9, 51.2, 38.6, 32.1, 20.2; MS (CI) m/z 240.1739 (MH^+ [$C_{17}H_{22}N$] = 240.1752).

***N*-Benzyl-(1-methyl)hexylamine (2):** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34–7.24 (m, 5H), 3.79 (dd, $J = 13.2$, 21.8 Hz, 2H), 2.72–2.63 (m, 1H), 1.48–1.21 (m, 9H), 1.08 (d, $J = 6.4$ Hz, 3H); 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.3, 126.8, 126.5, 125.2, 50.8, 49.7, 35.4, 30.4, 24.0, 21.0, 18.6, 12.4; MS (CI) m/z 206.1903 (MH^+ [$C_{14}H_{24}N$] = 206.1909).

Dibenzylamine (3): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.25 (m, 10H), 3.82 (bs, 4H), 1.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.8, 126.9, 126.7, 125.4, 51.5; MS (CI) m/z 198.1277 (MH^+ [$C_{14}H_{16}N$] = 198.1283).

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***N*-Benzyl-(4-chlorophenyl)methylamine (4):** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.26 (m, 9H), 3.79 (s, 2H), 3.77 (s, 2H), 1.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.6, 137.3, 131.0, 127.9, 126.93, 126.88, 126.6, 125.5, 51.5, 50.7; MS (CI) *m*/*z* 232.0901 (MH^+ [$C_{14}H_{15}N^{35}Cl$] = 232.0893).

***N*-Benzylcyclohexylamine (5):** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32–7.23 (m, 5H), 3.88 (d, $J = 2.8$ Hz, 2H), 2.47 (m, 1H), 1.92–1.06 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.4, 126.8, 126.5, 125.1, 54.5, 49.3, 31.8, 24.5, 23.3; MS (CI) *m*/*z* 190.1591 (MH^+ [$C_{13}H_{20}N$] = 190.1591).

***N*-Butyl-(1-methyl-3-phenyl)propylamine (9b):** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.15 (m, 5H), 2.75–2.45 (m, 5H), 1.8–1.6 (m, 2H), 1.57–1.24 (m, 4H), 1.10 (d, $J = 5.6$ Hz, 3H), 0.92 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.5, 128.3, 125.7, 52.7, 46.9, 38.6, 32.5, 32.3, 29.6, 26.0, 20.5, 20.2, 13.9; MS (CI) *m*/*z* 206.1914 (MH^+ [$C_{17}H_{22}N$] = 206.1909).

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10. Melting points for HCl salts of compounds **6** and **9a** were consistent with reported values; **6**: 179–181°C (lit. 178–180°C);[11] **9a**: 95–97°C (lit. 94–96°C; 97–98°C).[12,13]
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