Selective Access to Secondary Amines by a Highly Controlled Reductive Mono-N-Alkylation of Primary Amines

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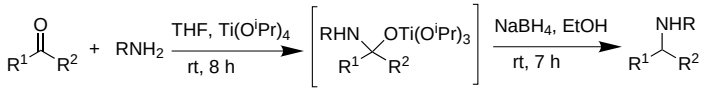
Abstract: A selective and direct access to secondary amines is reported by reductive mono-N-alkylation of primary amines in the presence of Ti(*i*-PrO)$_4$ and $NaBH_4$. Secondary amines are obtained exclusively from a set of carbonyl compounds and primary amines, demonstrating high chemoselectivity toward reductive mono-N-alkylation.

Key Words: mono-N-alkylation, secondary amines, titanium(IV) isopropoxide, sodium borohydride

Development of high-throughput methods for the synthesis of amines remains a topic of paramount importance in view of their versatile biological and medicinal properties. Amines and their carboxamide derivatives are the most prevalent structural moieties found in the comprehensive medicinal chemistry database.[1] Secondary amines are particularly significant as pharmacophores,[2] and versatile building blocks for ligands[3] and library synthesis; as an additional diversity the may easily be added to a secondary amine.[4] Among the various concepts for the synthesis of secondary amines,[5] strategies involving selective mono-N-alkylation of primary amines remain by far the most direct approach. The conventional base-promoted alkylation reactions of primary amines using alkyl halides or sulfates are generally inefficient as they routinely suffer from poor chemoselectivity due to the competing over-alkylation[6] reactions. A mixture of secondary and tertiary amines, along with the corresponding quaternary ammonium salt is usually obtained, imposing a difficult and often impractical purification process. As a result, secondary amine synthesis by N-alkylation of primary amines has been addressed indirectly by using various protecting groups in a multi-step sequence.[7] Moreover; many of the organic halides and sulfates are highly toxic and corrosive to handle.[8]

Another powerful tool for the synthesis of amines is reductive amination[9] of aldehydes and ketones. The synthesis involves the formation of an imine or iminium intermediate upon exposure of a carbonyl compound to ammonia, a primary amine or a secondary amine followed by in situ reduction to an alkylated amine. This approach is highly practiced for rapid access to a diverse set of amines due to the wide choice of starting amines and carbonyl compounds from the available chemical directory. Nevertheless, chemoselectivity in the reductive mono-N-alkylation of primary amines is a major concern with most of the reductive amination techniques. Over-alkylation[9,10] may easily occur resulting in the formation of variable amounts of tertiary amines along with the desired secondary amines. Reductive alkylation reactions using aldehydes are particularly prone to a high degree of overalkylation. In addition, many of the reported protocols are not compatible with otherwise reducible and acid-labile structural moieties. For example, the catalytic hydrogenation protocols[9a] are incompatible with a number of otherwise reducible functional groups such as nitro, cyano and 'C–C' multiple bonds, while the moderately strong acidic reaction conditions using sodium cyanoborohydride[9c] have limitations with acid-labile groups such as acetals, ketals and carbamates. Consequently, finding a robust general protocol for selective mono-N-alkylation of primary amines remains an important objective in organic synthesis, as exemplified in a number of recent publications.[11]

Previously, we reported[12] a versatile reagent system for reductive amination using a combination of Ti(*i*-PrO)$_4$[13] and $NaBH_4$. The protocol works well with a variety of carbonyl compounds including enolizable aldehydes and ketones, and tolerates a variety of potentially acid-labile functional groups such as acetals, acetonides, *N*-Boc group, and silyl ethers.[12,13a,14] In this paper,[15] we report a



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Scheme 1

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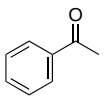
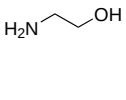
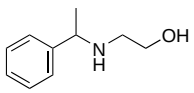
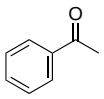
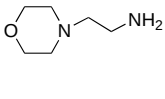
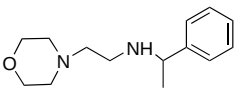
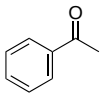
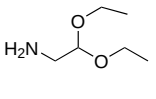
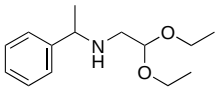
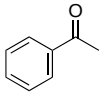
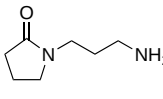
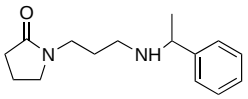
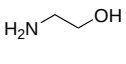
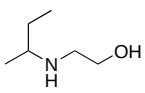
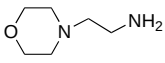
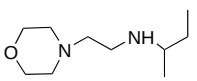
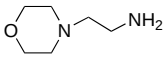
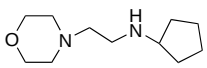
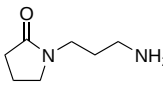
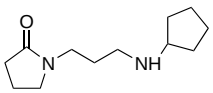
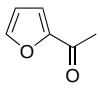
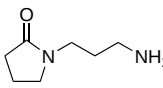
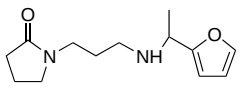
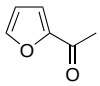
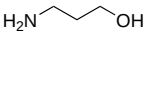
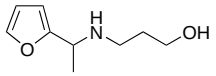
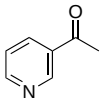
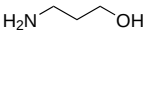
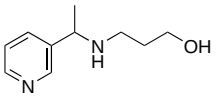
DOI: 10.1055/s-2003-41066; Art ID: M02403SS.pdf

highly chemoselective procedure for reductive mono-N-alkylation of various primary amines using this reagent system, that provides an exclusive, direct access to secondary amines in high yields. The reaction may proceed (Scheme 1) through an intermediate titanium(IV) complex **1**,[13a,14] which is either reduced directly or via equilibration of **1** with a transient iminium species.

The scope of the reaction was assessed using a structurally diverse set of aldehydes and ketones, and primary amines. The carbonyl compounds were allowed to react with the primary amines and Ti(*i*-PrO)$_4$, followed by treatment with $NaBH_4$ under ambient conditions. The reductive aminations required 20% excess of the ketone substrates or 10% excess of the aldehyde substrates in order to drive the reactions towards completion. The reactions were highly chemoselective and afforded only the secondary amines, even in the presence of excess carbonyl compounds. The traditional problem of over-alkylation of the secondary amine product was not observed. The results obtained from a group of ketones and aldehydes are summarized in Tables 1 and 2 respectively. Typically, the intermediate titanium(IV) complex **1** was formed by stirring a mixture of the carbonyl compound, the primary amine and Ti(*i*-PrO)$_4$ in anhydrous THF at ambient temperature for 8 hours. Absolute ethanol was then added followed by $NaBH_4$, and the resulting mixture was stirred for an additional 7 hours at room temperature. The reaction mixture was quenched with aqueous ammonia (2 M) and extracted with Et_2O. In many cases, the product amines were isolated in their pure forms by simple extraction of the organic solution with hydrochloric acid (1 M), thereby separating the non-basic impurities. Subsequent basification of the aqueous layer and extraction with Et_2O afforded the pure secondary amines.

The synthesis worked well for a varied set of ketones with different reactivity profiles that included enolizable ketones and less reactive aromatic ketones. For example, differently substituted primary amines underwent reductive mono-N-alkylation with acetophenone under these conditions. The secondary amine products were isolated in good yield and high purity (Table 1, entries 1–4). Likewise, reactions using heterocyclic systems such as 3-acetylfuran and 3-acetylpyridine with different primary amines afforded the corresponding secondary amines in good yields (Table 1, entries 9–11). Mono-N-alkylation of primary amines with enolizable acyclic and cyclic ketones (Table 1, entries 5–8) also proceeded well under these reaction conditions. Table 2 summarizes the reactions using a set of aldehyde substrates. A number of aliphatic, heterocyclic and aromatic aldehydes were reacted with a range of primary amines to produce the corresponding secondary amines in high yields. As in the case of ketones, these reaction conditions worked well with enolizable aldehydes (Table 2, entries 1, 6 and 7). The chemoselectivity in the reactions using aldehydes is particularly noteworthy, as they are generally prone to high degree of over-alkylation. The reaction conditions tolerated acid-labile functional groups, exemplified by the successful reactions with aminoacetaldehyde diethyl acetals (Table 1, entry 3 and Table 2, entry 1).

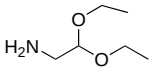
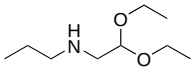
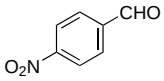
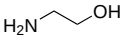
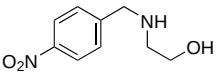
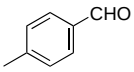
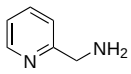
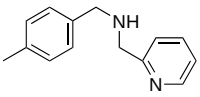
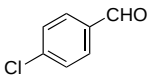
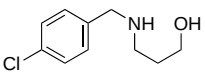
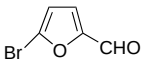
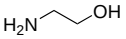
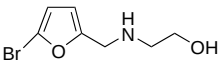
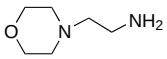
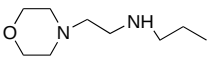
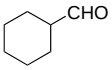
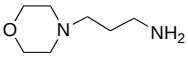
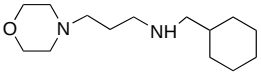
Table 1 Reductive Mono-N-Alkylation of Primary Amines with Ketones

Entry	Starting Ketone	Starting Amine	Product Amine	Yield (%)
1				75
2				72
3				75
4				70
5				80
6				75
7				84
8				82
9				72
10				75
11				77

In summary, we have described a highly chemoselective synthesis of secondary amines by reductive mono-N-alkylation of primary amines. Because this method allows selective, direct access to secondary amines, it should find widespread application in the synthesis of diverse secondary amines and their derivatives.

Starting materials were used as received from their respective suppliers. ^{1}H NMR spectra were obtained at 300 MHz on a Bruker AM 300 spectrometer, using $CDCl_3$ with TMS as the internal reference. Elemental analyses were performed by Galbraith Laboratories Inc., 2323 Sycamore Drive, Knoxville, TN 37921, USA. Analytical TLC was performed on pre-coated silica gel plates with fluorescent indicators using purified solvents, followed by iodine visualization, as necessary. All products were characterized by their ^{1}H NMR spec-

Table 2 Reductive Mono-N-Alkylation of Primary Amines with Aldehydes

Entry	Starting Aldehyde	Starting Amine	Product Amine	Yield (%)
1	CH_3CH_2CHO			85
2				82
3				78
4				75
5				80
6	CH_3CH_2CHO			84
7				88

tral data and elemental analyses; identities of known compounds were established by comparison of their NMR spectral data with the values reported in the literature.

Secondary Amines from Ketones and Primary Amines; General Procedure

A mixture of the ketone (6 mmol), Ti(*i*-PrO)$_4$ (3.0 mL, 10 mmol) and the primary amine (5 mmol) in anhyd THF (15 mL) was allowed to stir for 8 h at r.t. under N_2. $NaBH_4$ (0.57 g, 15 mmol) and absolute EtOH (5 mL) were then added, and the resulting mixture was stirred for an additional 8 h at r.t. The mixture was then poured into aq ammonia (2 M, 20 mL), the resulting inorganic precipitate was filtered and washed with Et_2O (50 mL). The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (30 mL). The combined organic layers were next extracted with 1 M HCl (20 mL) to separate the neutral materials. The acidic aqueous solution was washed once with Et_2O (20 mL) to separate the non-basic impurities, then treated with aq 2 M NaOH to pH 10–12, and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the solvent was removed to afford the secondary amine in good to excellent yield (Table 1). In many cases, the products were typically 90–95% pure by NMR and TLC analyses after simple work-up. Preparative TLC or column chromatography (Et_2O–MeOH, 9:1) was, however, employed for analytical samples. In the case of the reaction of acetophenone with acid-sensitive aminoacetaldehyde diethyl acetal (Table 1, entry 3), the product isolation did not involve any extraction with aq HCl. Instead, the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel (Et_2O–MeOH, 9: 1) to afford the secondary amine in 75% yield. The data below correspond to the entries in Table 1.

Entry 1

^{1}H NMR: δ = 1.48 (3 H, d, *J* = 6.9 Hz), 2.55–2.7 (2 H, m), 3.00 (2 H, br s), 3.55–3.70 (2 H, m), 3.99 (1 H, q, *J* = 6.9 Hz), 7.20–7.38 (5 H, m).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.40; H, 9.43; N, 8.61.

Entry 2

^{1}H NMR: δ = 1.37 (3 H, d, *J* = 6.6 Hz), 2.10 (1 H, br s), 2.35 (4 H, t, *J* = 4.8 Hz), 2.38–2.60 (4 H, m), 3.65 (4 H, t, *J* = 4.8 Hz), 3.72 (1 H, q, *J* = 6.6 Hz), 7.15–7.35 (5 H, m).

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.45; H, 9.78; N, 11.67.

Entry 3

^{1}H NMR: δ = 1.18 (3 H, t, *J* = 6.8 Hz), 1.22 (3 H, t, *J* = 6.8 Hz), 1.37 (3 H, d, *J* = 6.6 Hz), 1.65 (1 H, br s), 2.55–2.7 (2 H, m), 3.46–3.82 (5 H, m), 4.61 (1 H, t, *J* = 5.5 Hz), 7.20–7.50 (5 H, m).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.50; H, 10.08; N, 5.90.

Entry 4

^{1}H NMR: δ = 1.33 (3 H, d, *J* = 6.6 Hz), 1.63 (2 H, quintet, *J* = 6.9 Hz), 1.95 (2 H, quintet, *J* = 6.9 Hz), 2.13 (1 H, s), 2.34 (2 H, t, *J* = 6.9 Hz), 2.38–2.50 (2 H, m), 3.27 (2 H, t, *J* = 6.7 Hz), 3.29 (2 H, t, *J* = 6.7 Hz), 3.60 (1 H, q, *J* = 6.6 Hz), 7.18–7.35 (5 H, s).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.0; N, 11.37. Found: C, 73.53; H, 9.31; N, 11.13.

Entry 5

^{1}H NMR: δ = 0.88 (3 H, t, *J* = 7.4 Hz), 1.03 (3 H, d, *J* = 6.3 Hz), 1.25–1.38 (1 H, m), 1.40–1.58 (1 H, m), 2.48–2.62 (2 H, m), 2.64–2.82 (3 H, m), 3.62 (2 H, t, *J* = 5.1 Hz).

Anal. Calcd for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.24; H, 13.00; N, 11.60.

Entry 6

^{1}H NMR: δ = 0.81 (3 H, t, *J* = 7.4 Hz), 0.92 (3 H, d, *J* = 6.3 Hz), 1.22 (1 H, quintet, *J* = 7.4 Hz), 1.38 (1 H, quintet, *J* = 7.4 Hz), 2.3–2.48 (7 H, m), 2.5–2.75 (3 H, m), 3.59 (4 H, t, *J* = 4.7 Hz).

Anal. Calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.34; H, 11.70; N, 15.25.

Entry 7
^{1}H NMR: δ = 1.05–1.25 (2 H, m), 1.30–1.45 (2 H, m), 1.47–1.6 (2 H, m), 1.62–1.78 (2 H, m), 1.9 (1 H, br s), 2.28 (3 H, t, *J* = 4.6 Hz), 2.32 (3 H, t, *J* = 6.2 Hz), 2.54 (2 H, t, *J* = 6.0 Hz), 2.88 (1 H, quint, *J* = 6.7 Hz), 3.52 (4 H, t, *J* = 4.7 Hz).

Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.34; H, 11.29; N, 14.65.

Entry 8
^{1}H NMR: δ = 1.15–1.30 (2 H, m), 1.38–1.48 (2 H, m), 1.52–1.70 (3 H, m), 1.70–1.84 (2 H, m), 1.97 (4 H, quintet, *J* = 4.0 Hz), 2.30 (2 H, t, *J* = 4.2 Hz), 2.50 (2 H, t, *J* = 7.0 Hz), 2.95 (1 H, quint, *J* = 6.9 Hz), 3.28 (4 H, quintet, *J* = 6.0 Hz).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.63; H, 10.85; N, 13.15.

Entry 9
^{1}H NMR: δ = 1.12 (3 H, d, *J* = 3.4 Hz), 1.58–1.65 (2 H, m), 1.88–1.96 (2 H, m), 2.22 (2 H, t, *J* = 4.4 Hz), 2.50 (2 H, t, *J* = 6.9 Hz), 3.16–3.26 (4 H, m), 3.90 (1 H, q, *J* = 3.4 Hz), 6.00 (1 H, d, *J* = 3.1 Hz), 6.30 (1 H, d, *J* = 3.1 Hz), 7.20 (1 H, d, *J* = 1.8 Hz).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.03; H, 8.85; N, 11.68.

Entry 10
^{1}H NMR: δ = 1.41 (3 H, d, *J* = 4.2 Hz), 1.62–1.73 (2 H, m), 2.70 (2 H, t, *J* = 6.8 Hz), 2.78 (2 H, br s), 3.70 (1 H, t, *J* = 4.2 Hz), 3.88 (2 H, q, *J* = 6.8 Hz), 6.30 (1 H, d, *J* = 3.1 Hz), 6.40 (1 H, dd, *J* = 1.8, 3.1 Hz), 7.60 (1 H, d, *J* = 1.8 Hz).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.73; H, 8.95; N, 8.26.

Entry 11
^{1}H NMR: δ = 1.19 (3 H, d, *J* = 6.6 Hz), 1.49 (2 H, quintet, *J* = 6.3 Hz), 2.40–2.60 (2 H, m), 3.10 (2 H, br s), 3.52–3.62 (2 H, m), 3.68 (1 H, q, *J* = 6.6 Hz), 6.98 (1 H, ddd, *J* = 8.4, 4.5, 0.9 Hz), 7.08 (1 H, d, *J* = 8.0 Hz), 7.47 (1 H, dd, *J* = 7.9, 1.8 Hz), 8.36 (1 H, d, *J* = 4.5 Hz).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.51; H, 8.99; N, 15.27.

Secondary Amines from Aldehydes and Primary Amines; General Procedure
A mixture of the aldehyde (5.5 mmol), Ti(*i*-PrO)$_4$ (3.0 mL, 10 mmol) and the primary amine (5 mmol) in anhyd THF (15 mL) was allowed to stir for 8 h at r.t. under N_2. $NaBH_4$ (0.57 g, 15 mmol) and absolute EtOH (5 mL) were then added, and the resulting mixture was stirred for an additional 7 h at r.t. The reaction mixture was then quenched and worked up as described above for the reductive amination of ketones. For the reaction involving aminoacetaldehyde diethyl acetal (Table 2, entry 1), the work-up and purification procedures were same as described above in the case of entry 3, Table 1. The data below correspond to the entries in Table 2.

Entry 1
^{1}H NMR: δ = 0.93 (3 H, t, *J* = 7.2 Hz), 1.21 (6 H, t, *J* = 7.0 Hz), 1.42–1.65 (2 H, m), 2.04 (2 H, q, *J* = 7.3 Hz), 2.57–2.75 (2 H, m), 3.13 (1 H, br s) 3.67 (4 H, q, *J* = 7.0 Hz), 4.60 (1 H, t, *J* = 5.6 Hz).

Anal. Calcd for $C_9H_{21}NO_2$: C, 61.67; H, 12.08; N, 7.99. Found: C, 61.41; H, 11.95; N, 7.72.

Entry 2
^{1}H NMR: δ = 2.19 (2 H, br s), 2.80 (2 H, t, *J* = 5.1 Hz), 3.60 (2 H, t, *J* = 5.1 Hz), 3.90 (2 H, s), 7.50 (2 H, d, *J* = 8 Hz), 8.26 (2 H, d, *J* = 8 Hz).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.81; H, 6.43; N, 14.42.

Entry 3
^{1}H NMR: δ = 2.30 (3 H, s), 3.75 (2 H, s), 3.90 (2 H, s), 7.06–7.32 (6 H, m), 7.56-7.64 (1 H, m), 8.50 (1 H, d, *J* = 8 Hz).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.05; H, 7.73; N, 13.51.

Entry 4
^{1}H NMR: δ = 1.75 (2 H, quintet, *J* = 6.1 Hz), 2.23 (1 H, br s), 2.65 (2 H, t, *J* = 6.1 Hz), 2.89 (1 H, br s), 3.50 (2 H, s), 3.78 (2 H, t, *J* = 6.0 Hz), 7.15–7.25 (4 H, m).

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.35; H, 7.13; N, 7.03.

Entry 5
^{1}H NMR: δ = 2.29 (2 H, s), 2.75 (2 H, t, *J* = 5.0 Hz), 3.50 (2 H, t, *J* = 5.0 Hz), 3.76 (2 H, s), 6.18 (1 H, d, *J* = 3.2 Hz), 6.23 (1 H, d, *J* = 3.2 Hz).

Anal. Calcd for $C_7H_{10}BrNO_2$: C, 38.20; H, 4.58; N, 6.36. Found: C, 37.92; H, 4.71; N, 6.36.

Entry 6
^{1}H NMR: δ = 0.90 (t, 3 H, *J* = 7.2 Hz), 1.50 (q, 2 H, *J* = 7.2 Hz), 2.10 (1 H, br s), 2.30–2.80 (m, 10 H), 3.50–3.80 (m, 4 H).

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.39; H, 11.43; N, 16.42.

Entry 7
^{1}H NMR: δ = 0.72–0.95 (2 H, m), 1.04–1.28 (3 H, m), 1.32–1.48 (1 H, m), 1.54–1.76 (7 H, m), 2.24–2.46 (8 H, m), 2.58 (2 H, t, *J* = 7.0 Hz), 3.62 (4 H, t, *J* = 6.0 Hz).

Anal. Calcd for $C_{14}H_{28}N_2O$: C, 69.95; H, 11.74; N, 11.65. Found: C, 69.61; H, 11.93; N, 11.32.

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