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Chemoselective reductive alkylation of ammonia with carbonyl compounds: synthesis of primary and symmetrical secondary amines

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Abstract—An efficient, general procedure for highly chemoselective reductive mono-alkylation of ammonia with ketones is reported. Treatment of ketones with ammonia in ethanol and titanium(IV) isopropoxide, followed by in situ sodium borohydride reduction, and a straightforward workup afforded primary amines in good to excellent yields. Reductive alkylation of ammonia with aldehydes, on the other hand, afforded the corresponding symmetrical secondary amines selectively.

1. Introduction

Synthesis of amines is an objective of high priority from the perspective of drug discovery.[1] Amines and their carboxamide derivatives are the most prevalent structural moieties present in the registered drugs globally and constitute more than two thirds of the comprehensive medicinal chemistry database.[2] Reductive amination[3] of carbonyl compounds is a very important and powerful tool for chemists to target the synthesis of structurally diverse primary, secondary and tertiary amines. The sequence proceeds through the formation of an imine or iminium intermediate upon reaction of a carbonyl compound with ammonia, primary amine or secondary amine followed by in situ reduction to an amine of higher order. Catalytic hydrogenation[3a,4] has remained one of the commonly applied methods for carrying out this transformation, which is, however, incompatible with a number of otherwise reducible functional groups such as nitro, cyano and 'C–C' multiple bonds. Among the borohydride reagents, sodium cyanoborohydride[3c,d,5] and sodium triacetoxyborohydride[3e,6] have found significant applications. However, these reagents are not without limitations[3g,6] in terms of functional group tolerance and side reactions. In order to further improve the scope and selectivity in reductive amination reactions, several other reducing systems including pyridine–borane,[7] and variously modified zinc borohydride,[8] sodium borohydride,[9] organosilanes,[10] and organotin hydrides[11] have been described. Apart from hydride-based reagents, development of a Hantzsch dihydropyridine system has been recently reported.[12]

Though many of the reported protocols for reductive amination reactions work well for the preparation of tertiary amines, synthesis of primary and secondary amines is compromised[3,5,6] by over-alkylation reactions in many cases. This is particularly true for reductive alkylation of ammonia with aldehydes and ketones.[13] In this case, the primary amine initially formed continues to undergo further reductive alkylation with the carbonyl compound still present in the reaction mixture. Thus, formation of variable amounts of secondary and tertiary amines along with the desired primary amines is common, thereby making the reaction less useful. A variety of ammonia equivalents such as tritylamine, diallylamine, allylamine and carbamates have been developed[14] to address this problem. However, the reaction sequence routinely involves an additional step to obtain the targeted primary amines in their unprotected form. Development of a direct, chemoselective route for reductive alkylation of ammonia, therefore, remains a challenge.

In the context of our ongoing investigations on titanium(IV) isopropoxide[15,16] mediated reductive amination reactions, we report herein a full account[17] of our efforts on the reductive alkylation of ammonia with carbonyl compounds using the $Ti(O^iPr)_4$–$NaBH_4$ reagent system. In these investigations, primary amines were obtained exclusively from reactions with ketones, and the reaction conditions have been found compatible with various acid-labile groups

Keywords: Reductive amination; Ammonia; Ketones; Aldehydes.
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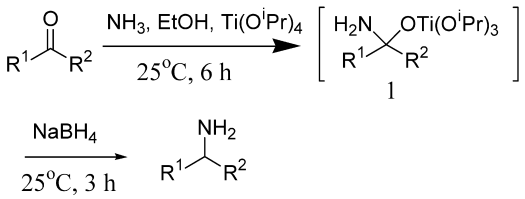


Scheme 1. Primary amines from ketones.

such as N-Boc, carbamate, acetal and ketal. The reactions with aldehydes, on the other hand, afforded a general, chemoselective synthesis of symmetrical secondary amines. To our knowledge, this is the first report for the selective formation of symmetrical secondary amines from reductive amination reactions using highly reactive partners such as ammonia and aldehydes.[18] Syntheses of secondary amines are particularly significant in view of their potential as versatile pharmacophores, ligands and synthetic intermediates.[19]

2. Results and discussion

2.1. Reductive alkylation of ammonia with ketones

The initial experiments for the reductive amination of ketones were performed using a mixture of ammonium chloride and triethylamine in anhydrous ethanol as the source of ammonia. A 2-fold molar excess of ammonium chloride–triethylamine was utilized with respect to the ketones. Though the method avoids the use of gaseous ammonia, the reactions were slow with many ketonic substrates and could not be improved by using up to 5-fold excess of ammonium chloride and triethylamine. There are numerous reports in the literature[3g] that reductive amination reactions using ammonium salts often fail due to their poor solubility in common organic solvents used for such reactions. As an alternative approach, we reasoned that a better transformation might be achieved using a commercially available ethanol solution of ammonia. Treatment of an excess of ammonia–ethanol solution (5 equiv.) with ketones as the limiting reagent in the presence of titanium(IV) isopropoxide, followed by sodium borohydride reduction offered clean conversion at room temperature, affording only the desired primary amines. The primary amines were not contaminated with any secondary and tertiary amine resulting from overalkylation reactions. The reaction may proceed[5c,15,20] through the titanium(IV) complex **1** (Scheme 1) which is either reduced directly or via a transient imine species.

As evaluated on a structurally diverse set of ketones, the scope and utility of the protocol proved to be quite general. The results are summarized in Table 1. A mixture of

Table 1. Synthesis of primary amines from ketones

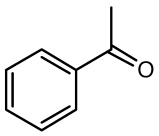
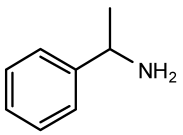
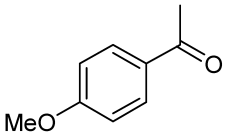
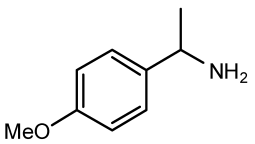
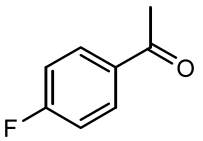
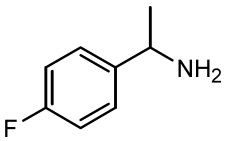
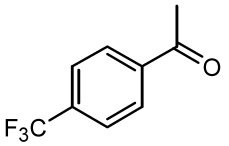
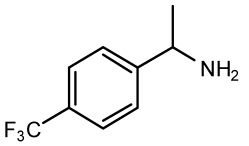
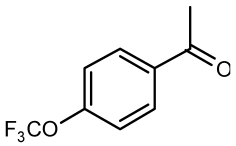
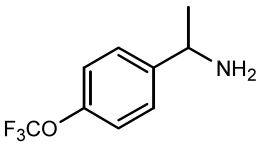
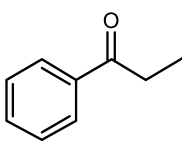
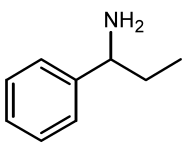
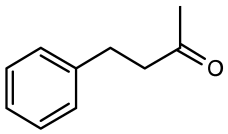
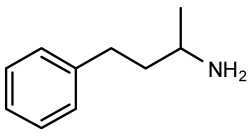
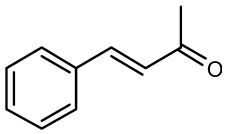
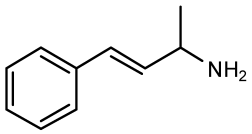
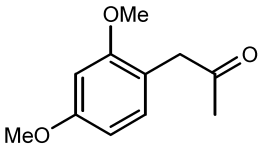
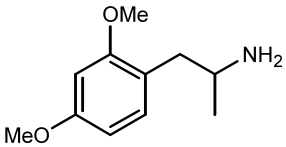
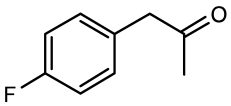
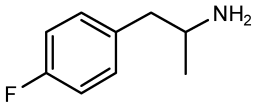
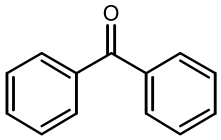
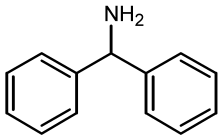
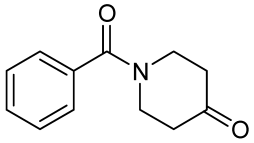
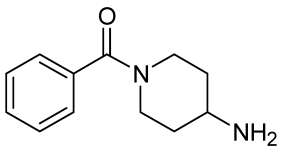
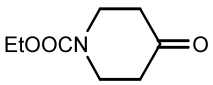
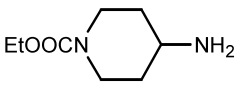
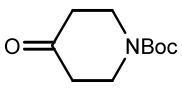
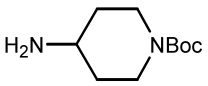
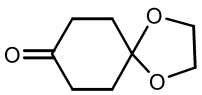
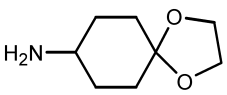
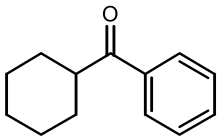
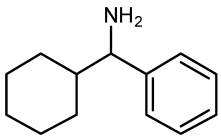
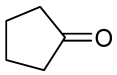
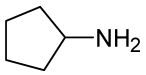
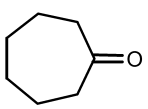
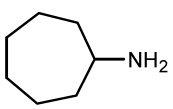
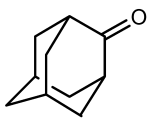
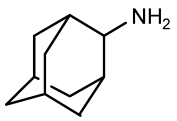
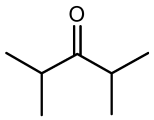
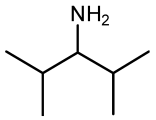
Entry	Starting ketone	Product primary amine	Yield (%)	Purity (%)[a]
1			88	98
2			91	97
3			65	99
4			83	99
5			83	97
6			89	99

Table 1 (*continued*)

Entry	Starting ketone	Product primary amine	Yield (%)	Purity (%)[a]
7			88	98
8			89	98
9			87	97
10			78	99
11			78	98
12			96	100
13			93	100
14			88	98
15			91	99
16			72	98
17			90	99
18			88	98
19			93	100
20			85	100

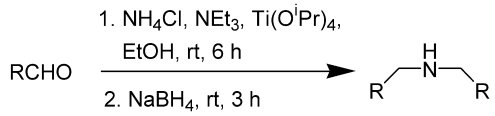
[a] Purity was determined by GC or LC–MS.

ammonia in ethanol, the ketone and titanium(IV) isopropoxide was stirred in a capped flask at ambient temperature to form the intermediate titanium(IV) complex **1**. The progress of the reaction was probed by IR spectral analysis.[5c] In general, the reaction required 6 h for complete formation of the intermediate **1**, as the IR spectrum of the reaction mixture showed no ketone band after 6 h. The reducing agent, sodium borohydride, was then added and the resulting mixture was allowed to stir for a further period of 3 h. Finally, the reaction was quenched with aqueous ammonia. The resulting inorganic precipitate was filtered and the filtrate was extracted with ethyl acetate. The reduction step generally required 3 h for maximum conversion to the primary amine. When reactions were quenched after 1 h, the yields were ca. 40% less. In most of the cases, the product primary amine was isolated in its pure form by simple extraction of the ethyl acetate solution with dilute hydrochloric acid (1 M), basification of the aqueous layer and subsequent extraction with ethyl acetate.

As demonstrated in Table 1, both alkyl and aryl ketones afforded the corresponding primary amines in good yields in most of the cases. In contrast to many acid-mediated reductive amination methods, the present method is equally applicable to substrates containing enolizable carbonyl groups. Aromatic ketones were reported[3,6] to be least reactive in a number of reductive amination protocols. However, under these reaction conditions, acetophenones (Table 1, entries 1–6) afforded the corresponding primary amines in good to excellent yields. Among all the aromatic ketones evaluated, benzophenone and cyclohexyl phenyl ketone were found to be the least reactive (Table 1, entries 11 and 14). In general, aliphatic ketones were more reactive than their aromatic counterparts. Both cyclic and acyclic aliphatic ketones were converted to their primary amines in high to excellent yields. The α,β-unsaturated ketone, 4-phenyl-butenone (Table 1, entry 8) was reductively aminated in high yield with no observable reduction of the C–C double bond. Steric hindrance appeared to play no role in dictating the outcome of the reaction as exemplified by the excellent conversion of 2-adamantanone and diisopropyl ketone to their respective primary amines (Table 1, entries 19 and 20). The reaction conditions were found compatible with acid-labile groups such as ketals, N-Boc and N-COOEt (Table 1, entries 13–15). For example, N-Boc protected 4-piperidone underwent smooth reductive amination under these conditions. Similarly, 1,4-cyclohexanedione monoethylene ketal was successfully converted into the corresponding primary amine in high yield.

2.2. Reductive alkylation of ammonia with aldehydes

Unlike the case of ketones, the reactions with aldehydes could not be controlled at the primary amine stage even by using a 10–20-fold molar excess of ammonia–ethanol solution with respect to the aldehyde substrates. A mixture of primary and symmetrical dialkylamine of varying proportions was obtained with a range of aldehydes. However, the reactions were controlled at the secondary amine stage, formation of any tertiary amine by further alkylation of the secondary amine was not observed. In an effort to survey the reaction conditions for chemoselectivity, we selected benzaldehyde as the test substrate. The initial experiments were performed with 0.5 and 40 equiv. of an ethanol solution of ammonia with respect to benzaldehyde in the presence of $Ti(O^iPr)_4$ and $NaBH_4$, and the crude products analyzed by GC. With 0.5 equiv. of ammonia, the ratio of benzylamine to dibenzylamine was found to be 15:85, while with 40 equiv. of ammonia the ratio was 68:32. The results clearly indicated that even the use of a large excess of ammonia did not favor exclusive formation of the primary amine. However, the high selectivity of dibenzylamine formation was encouraging from the viewpoint of a general synthesis of symmetrical secondary amines. In order to further optimize the reaction conditions, we decided to explore the use of a mixture of ammonium chloride and triethylamine in anhydrous ethanol as the source of ammonia. We surmised that this reagent system would slowly release ammonia due to the low solubility of ammonium chloride in ethanol, and this would allow the initially formed primary amine to react further with the aldehyde present in the reaction mixture to generate symmetrical dialkylamine selectively. Indeed this was the case, as symmetrical secondary amines were isolated in moderate to good yields when aldehydes were reacted with a mixture of ammonium chloride, triethylamine and $Ti(O^iPr)_4$ in ethanol, followed by reduction with $NaBH_4$ (Scheme 2). The scope of dialkylamine synthesis was demonstrated using a variety of aliphatic and aromatic aldehydes. As shown in Table 2, variously substituted aromatic aldehydes containing both electron donating and electron withdrawing groups (Table 2, entries 21–31) were converted to the corresponding dibenzylamines in good yields. The fluorine containing dibenzyl amines (Table 2, entries 26 and 27) were obtained in moderate yields from the corresponding benzaldehydes. An example with a heterocyclic aldehyde included indole-3-aldehyde (Table 2, entry 31). The reductive amination of 3,4-(methylenedioxy)-benzaldehyde afforded the corresponding secondary amine (Table 2, entry 29) in high yield with the acetal group tolerated. The reaction conditions were found equally applicable in the cases of aliphatic aldehydes as exemplified in the entries 32–34 (Table 2).

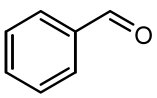
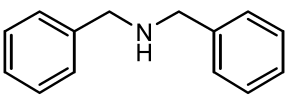
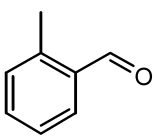
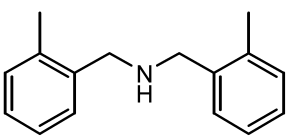
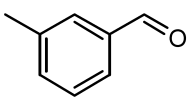
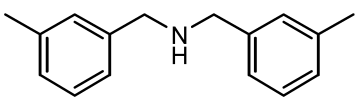
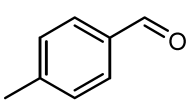
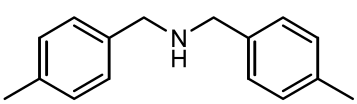
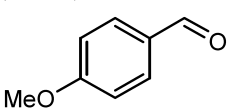
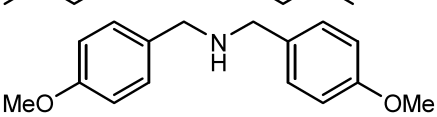
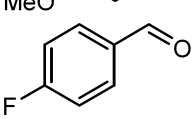
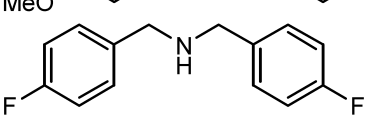
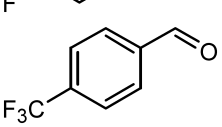
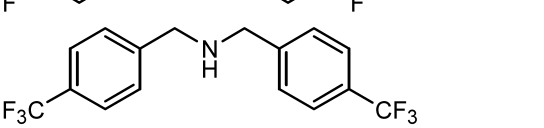
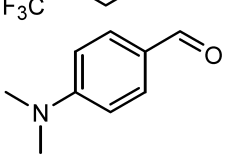
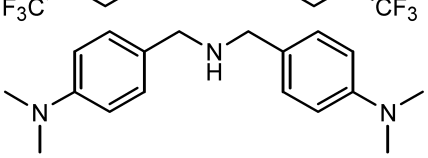
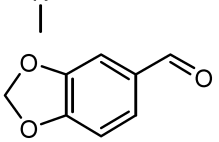
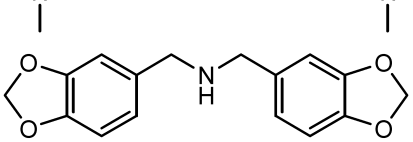
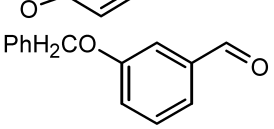
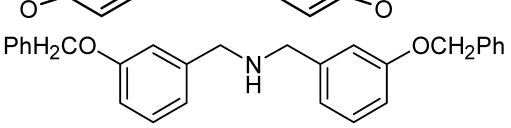
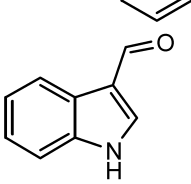
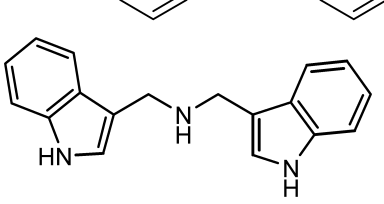
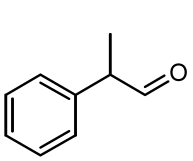
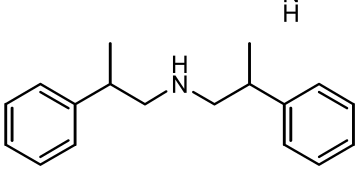
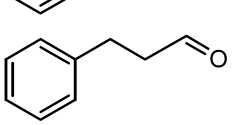
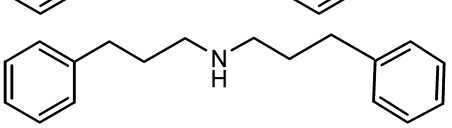
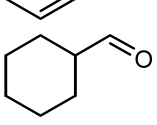
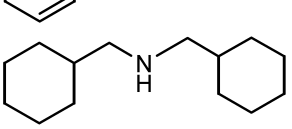


Scheme 2. Symmetrical secondary amines from aldehydes.

3. Conclusion

In summary, we have described an efficient, chemoselective method for the synthesis of primary amines by reductive amination of ketones with ammonia in the presence of titanium(IV) isopropoxide and sodium borohydride. The scope of the reaction has been demonstrated with aliphatic, aromatic, cyclic and acyclic ketones. Because this method allows easy access to structurally diverse primary amines, it should find wide application. Reductive alkylation of ammonia with aldehydes, on the other hand, has afforded symmetrical secondary amines as the only isolated products. Notable advantages of the present method include: mild, neutral reaction conditions that can tolerate a variety of acid-sensitive functional groups such as acetal, ketal, N-Boc and carbamate, and simple workup.

Table 2. Synthesis of symmetrical secondary amines from aldehydes

Entry	Starting aldehyde	Product secondary amine	Yield (%)	Purity (%)[a]
21			76	99
22			70	99
23			71	99
24			78	98
25			50	98
26			75	98
27			70	100
28			62	100
29			77	97
30			67	97
31			65	98
32			58	98
33			75	100
34			68	98

[a] Purity was determined by GC or LC–MS.

4. Experimental

The starting aldehydes and ketones, reagents and solvents were used as obtained from their respective suppliers without further purification. Two molar solutions of ammonia in ethanol are commercially available and were obtained from Aldrich Chemical Company, USA. IR spectra were recorded with $CHCl_3$ as solvent (Bruker Vector 33 FTIR). ^1H NMR spectra were run in $CDCl_3$ at 400 MHz on a Bruker AM 400 spectrometer. Chemical shifts are reported in ppm referenced to TMS. Liquid chromatography and electrospray ionization mass spectrometry (EIMS) were performed with a Waters 2690 Separation Module HPLC system and a Waters/Micromass ZQ 2000 mass spectrometer in the positive ion detection mode. Components were resolved using a Waters Symmetry C18 5 mm HPLC column (2.1×50 mm). Flash chromatography was performed on silica gel (200–400 mesh, Natland). 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 ^1H NMR, IR and mass spectral data; identities of known compounds were established by comparison of their NMR spectral data with the values reported in the literature. The purities of the product primary and secondary amines were determined by using GC or LC–MS analysis.

4.1. General procedure for the synthesis of primary amines from ketones

A mixture of the ketone (10 mmol), titanium(IV) isopropoxide (6.0 mL, 20 mmol) and ammonia in ethyl alcohol (2 M, 25 mL, 50 mmol) was stirred under argon in a capped flask at ambient temperature for 6 h. Sodium borohydride (0.6 g, 15 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 3 h. The reaction was then quenched by pouring into ammonium hydroxide (2 M, 25 mL), the resulting inorganic precipitate was filtered off, and washed with ethyl acetate (25 mL×2). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (25 mL×2).

The combined organic solution was next extracted with hydrochloric acid (1 M, 30 mL) to separate the neutral materials. The acidic aqueous extracts were washed with ethyl acetate (50 mL), then treated with aqueous sodium hydroxide (2 M) to pH 10–12, and extracted with ethyl acetate (50 mL×3). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the corresponding primary amine.

The data below correspond to the entries in Table 1.

4.1.1. 1-Phenylethylamine[21a] (1). Yield 88%; IR: 3359, 3062, 3028, 2968, 2640, 1640, 1570, 1453, 1359, 1093, 1028, 890, 770, 703, 531 cm^{-1}; ^1H NMR: δ 7.34–7.22 (m, 5H), 4.15–4.08 (q, J=6.6 Hz, 1H), 1.4–1.38 (d, J=6.6 Hz, 3H); EIMS: 122.0 (M+H, calcd for $C_8H_{11}N$, 122.19).

4.1.2. 1-(4′-Methoxyphenyl)ethylamine[21b] (2). Yield 91%; IR: 2998, 2934, 2834, 1611, 1511, 1463, 1246, 1175, 1034, 822, 517 cm^{-1}; ^1H NMR: δ 7.28–7.25 (m, 2H), 6.87–6.85 (m, 2H), 4.10–4.06 (q, J=6.6 Hz, 1H), 3.8 (s, 3H), 1.37–1.36 (d, J=6.5 Hz, 3H).

4.1.3. 1-(4′-Fluorophenyl)ethylamine[21c] (3). Yield 65%; IR: 3370, 2971, 1604, 1510, 1456, 1375, 1224, 1159, 1014, 836, 544 cm^{-1}; ^1H NMR: δ 7.32–7.26 (m, 2H), 7.02–6.97 (m, 2H), 4.13–4.08 (q, J=6.6 Hz, 1H), 1.37–1.35 (d, J=6.6 Hz, 3H); EIMS:140.0 (M+H, calcd for $C_8H_{10}FN$, 140.18).

4.1.4. 1-(4′-Trifluoromethylphenyl)ethylamine[21d] (4). Yield 83%; ^1H NMR: δ 7.59–7.57 (d, J=8.2 Hz, 2H), 7.48–7.46 (d, J=8.2 Hz, 2H), 4.21–4.17 (q, J=6.6 Hz, 1H), 1.40–1.38 (d, J=6.6 Hz, 3H).

4.1.5. 1-(4′-Trifluoromethoxyphenyl)ethylamine[21e] (5). Yield 83%; ^1H NMR: δ 7.38–7.36 (d, J=8.6 Hz, 2H), 7.18–7.16 (d, J=8.4 Hz, 2H), 4.17–4.12 (q, J=6.6 Hz, 1H), 1.38–1.36 (d, J=6.6 Hz, 3H).

4.1.6. 1-Phenylpropylamine[21f] (6). Yield 89%; oil; IR: 3361, 3028, 2964, 1628, 1577, 1454, 1376, 906, 701, 545 cm^{-1}; ^1H NMR: δ 7.35–7.22 (m, 5H), 3.82–3.78 (t, J=6.8 Hz, 1H), 1.74–1.68 (m, 2H), 0.89–0.85 (t, J=7.4 Hz, 3H); EIMS: 136.0 (M+H, calcd for $C_9H_{13}N$, 136.21).

4.1.7. 1-Methyl-3-phenylpropylamine[21g] (7). Yield 88%; IR: 2961, 1647, 1495, 1455, 1378, 1065, 764, 699, 594 cm^{-1}; ^1H NMR: δ 7.3–7.16 (m, 5H), 2.97–2.9 (m, 1H), 2.8–2.5 (m, 2H), 1.7–1.64 (m, 2H), 1.13–1.12 (d, J=6.4 Hz, 3H); EIMS: 150.3 (M+H, calcd for $C_{10}H_{15}N$, 150.24).

4.1.8. 1-Methyl-3-phenylallylamine[21h] (8). Yield 89%; IR: 3026, 2970, 1638, 1559, 1493, 1450, 1374, 1072, 968, 749, 694 cm^{-1}; ^1H NMR: δ 7.38–7.21 (m, 5H), 6.48–6.44 (d, J=16 Hz, 1H), 6.23–6.18 (dd, J=6.6, 16 Hz, 1H), 3.68–3.65 (m, 1H), 1.26–1.25 (d, J=6.5 Hz, 3H).

4.1.9. 2-(2′,4′-Dimethoxyphenyl)-1-methylethylamine[21i] (9). Yield 87%; IR: 3358, 2960, 2837, 1612, 1508, 1464, 1288, 1261, 1157, 1036, 923, 833, 635 cm^{-1}; ^1H NMR: δ 7.02–7.0 (d, J=8 Hz, 1H), 6.45–6.4 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.17–3.08 (m, 1H), 2.68–2.63 (dd, J=5.4, 7.9 Hz, 1H), 2.47–2.42 (dd, J=5.3, 7.8 Hz, 1H), 1.09–1.07 (d, J=6 Hz, 3H); EIMS: 196.2 (M+H, calcd for $C_{11}H_{17}NO_2$, 196.26).

4.1.10. 2-(4′-Fluorophenyl)-1-methylethylamine[21j] (10). Yield 78%; IR: 3359, 2966, 1602, 1509, 1457, 1376, 1222, 1158, 811, 765, 551, 503 cm^{-1}; ^1H NMR: δ 7.14–7.11 (m, 2H), 6.99–6.95 (m, 2H), 3.15–3.1 (m, 1H), 2.68–2.63 (dd, J=5.4, 8 Hz, 1H), 2.51–2.46 (dd, J=8, 5.4 Hz, 1H), 1.1–1.09 (d, J=6.3 Hz, 3H); EIMS: 154.1 (M+H, calcd for $C_9H_{12}NF$, 154.2).

4.1.11. Diphenylmethylamine[21k] (11). Yield 78%; IR: 3369, 3060, 3026, 1600, 1492, 1452, 1277, 1190, 1027, 903, 742, 699, 552 cm^{-1}; ^1H NMR: δ 7.42–7.22 (m, 10H), 5.23 (s, 1H).

4.1.12. *N*-Benzoyl-4-aminopiperidine[21l] (12). Yield 96%; IR: 3349, 2935, 1616, 1448, 1281, 1029, 789, 711,

636 cm^{-1}; ^1H NMR: δ 7.54–7.48 (m, 5H), 4.6 (br s, 1H), 3.74 (br s, 1H), 3.11–3.04 (m, 3H), 2.14–1.92 (m, 4H), 1.62–1.21 (m, 2H); EIMS: 205.5 (M+H, calcd for $C_{12}H_{16}N_2O$, 205.27).

4.1.13. 4-Aminopiperidine-1-carboxylic acid ethyl ester (13). Yield 93%; IR: 3352, 2934, 1689, 1594, 1436, 1385, 1235, 1173, 1100, 1031, 769, 571 cm^{-1}; ^1H NMR: δ 4.12–4.06 (m, 4H), 2.83–2.77 (m, 3H), 1.78–1.75 (m, 2H), 1.24–1.17 (m, 5H); EIMS: 173.1 (M+H, calcd for $C_8H_{16}N_2O_2$, 173.23).

4.1.14. 4-Aminopiperidine-1-carboxylic acid *tert* butyl ester (14). Yield 88%; ^1H NMR: δ 4.05 (br s, 2H), 2.85–2.70 (m, 3H), 1.8–1.7 (m, 4H), 1.43 (s, 9H), 1.3–1.2 (m, 2H); EIMS: 201.4 (M+H, calcd for $C_{10}H_{20}N_2O_2$, 201.15).

4.1.15. 4-Aminocyclohexanone ethylene ketal (15). Yield 91%; ^1H NMR: δ 3.95 (s, 4H), 2.91–2.75 (m, 1H), 2.07 (br s, 2H), 1.89–1.74 (m, 4H), 1.63–1.45 (m, 4H); EIMS: 158.3 (M+H, calcd for $C_8H_{15}NO_2$, 158.11).

4.1.16. Cyclohexylphenylmethylamine[21m] (16). Yield 72%; ^1H NMR: δ 7.35–7.3 (m, 5H), 3.87–3.85 (d, J=8 Hz, 1H), 2.02–1.99 (d, J=12 Hz, 1H), 1.91 (broad, 1H), 1.77–1.73 (d, J=12 Hz, 1H), 1.6–0.85 (m, 10H); EIMS: 190.2 (M+H, calcd for $C_{13}H_{19}N$, 190.3).

4.1.17. Cyclopentylamine[21n] (17). Yield 90%; IR: 3359, 2927, 2853, 2672, 1646, 1595, 1450, 1374, 1106, 1048, 955, 886, 708 cm^{-1}; ^1H NMR: δ 2.59 (m, 1H), 1.81–1.77 (m, 4H), 1.7–1.55 (m, 4H); EIMS: 86.0 (M+H, calcd for $C_5H_{11}N$, 86.21).

4.1.18. Cycloheptylamine[21o] (18). Yield 88%; IR: 2925, 2855, 1560, 1459, 1117, 1023, 961, 812, 653 cm^{-1}; ^1H NMR: δ 2.93–2.88 (m, 1H). 1.6–1.33 (m, 12H); EIMS: 114.0 (M+H, calcd for $C_7H_{15}N$, 114.21.

4.1.19. Adamantan-2-ylamine[21p] (19). Yield 93%; ^1H NMR: δ 2.99 (s, 1H), 1.99–1.96 (d, J=13 Hz, 2H), 1.86–1.79 (m, 4H), 1.74–1.7 (m, 8H), 1.54–1.51 (d, J=7.8 Hz, 2H); EIMS: 152.3 (M+H, calcd for $C_{10}H_{17}N$, 152.25).

4.1.20. 3-Amino-2,4-dimethylpentane[21q] (20). Yield 85%; IR: 2938, 2875, 1647, 1541, 1457, 1061, 617 cm^{-1}; ^1H NMR: δ 2.42 (broad, 1H), 1.7–1.66 (m, 2H), 0.98–0.94 (d, J=6 Hz, 12H); EIMS: 116.0 (M+H, calcd for $C_7H_{17}N$, 116.22).

4.2. General procedure for the synthesis of symmetrical secondary amines from aldehydes

A slurry of the aldehyde (10 mmol), titanium(IV) isopropoxide (6.0 mL, 20 mmol), ammonium chloride (1.1 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol) in absolute ethanol (20 mL) was stirred under argon in a capped flask at ambient temperature for 6 h. Sodium borohydride (0.6 g, 15 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 3 h. The reaction was then quenched by pouring into ammonium hydroxide (2 M, 25 mL), the resulting inorganic precipitate was filtered off, and washed with ethyl acetate (25 mL×2). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (25 mL×2). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified over silica gel by flash chromatography using hexanes/ethyl acetate to afford the corresponding symmetrical secondary amines.

The data below correspond to the entries in Table 2.

4.2.1. Dibenzylamine[22a] (21). Yield 76%; IR: 3339, 3062, 2815, 1603, 1495, 1453, 1198, 1027, 734, 697 cm^{-1}; ^1H NMR: δ 7.36–7.26 (m, 10H), 3.83 (s, 4H); EIMS: 198.2 (M+H, calcd for $C_{14}H_{15}N$, 198.2).

4.2.2. Bis-(2-methylbenzyl)amine[22b] (22). Yield 70%; IR: 3328, 3018, 2819, 1604, 1492, 1460, 1377, 1182, 1092, 743 cm^{-1}; ^1H NMR: δ 7.36–7.35 (m, 2H), 7.21–7.18 (m, 6H), 3.85 (s, 4H), 2.36 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.3. Bis-(3-methylbenzyl)amine[22c] (23). Yield 71%; IR: 3324, 3023, 2820, 1608, 1487, 1453, 1357, 1158, 1090, 839, 778, 696 cm^{-1}; ^1H NMR: δ 7.26–7.07 (m, 8H), 3.80 (s, 4H), 2.36 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.4. Bis-(4-methylbenzyl)amine[22d] (24). Yield 78%; IR: 3390, 2919, 2793, 1637, 1456, 1396, 1261, 1092, 1021, 801 cm^{-1}; ^1H NMR: δ 7.26–7.22 (m, 4H), 7.16–7.14 (m, 4H), 3.78 (s, 4H), 2.35 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.5. Bis-(4-methoxybenzyl)amine[22e] (25). Yield 50%; IR: 2999, 2834, 1612, 1511, 1463, 1301, 1246, 1035, 822, 560 cm^{-1}; ^1H NMR: δ 7.26–7.24 (d, J=8.3 Hz, 4H), 6.88–6.86 (d, J=8.6 Hz, 4H), 3.8 (s, 6H), 3.73 (s, 4H); EIMS: 258.3 (M+H, calcd for $C_{16}H_{19}NO_2$, 258.34).

4.2.6. Bis-(4-fluorobenzyl)amine[22f] (26). Yield 75%; IR: 3328, 3041, 2826, 1603, 1509, 1452, 1221, 1155, 1093, 825, 501 cm^{-1}; ^1H NMR: δ 7.32–7.26 (m, 4H), 7.04–6.99 (m, 4H), 3.76 (s, 4H); EIMS: 234.2 (M+H, calcd for $C_{14}H_{13}NF_2$, 234.26).

4.2.7. Bis-(4-trifluoromethylbenzyl)amine[22f] (27). Yield 70%; IR: 2989, 1636, 1325, 1160, 1107, 1068, 664 cm^{-1}; ^1H NMR: δ 7.39–7.35 (m, 4H), 7.2–7.17 (m, 4H), 3.3 (s, 4H); EIMS: 334.1 (M+H, calcd for $C_{16}H_{13}NF_6$, 334.28).

4.2.8. Bis-(4-*N*,*N*-dimethylaminobenzyl)amine (28). Yield 62%; IR: 3328, 2996, 2800, 1615, 1522, 1444, 1345, 1224, 1186, 1163, 947, 806 cm^{-1}; ^1H NMR: δ 7.22–7.20 (d, J=8.5 Hz, 4H), 6.74–6.72 (d, J=8.5 Hz, 4H), 3.71 (s, 4H), 2.94 (s, 12H); EIMS: 284.2 (M+H, calcd for $C_{18}H_{25}N_3$, 284.42).

4.2.9. Bis-(benzo-1,3-dioxol-5-ylmethyl)amine[22g] (29). Yield 77%; ^1H NMR: δ 6.85 (s, 2H), 6.76 (s, 4H), 5.94 (s, 4H), 3.69 (s, 4H); EIMS: 286.4 (M+H, calcd for $C_{16}H_{15}NO_4$, 286.31).

4.2.10. Bis-(3-benzyloxybenzyl)amine (30). Yield 67%; ^1H NMR: δ 7.46–7.24 (m, 12H), 7.01–6.93 (m, 6H), 5.08 (s,

4H), 3.79 (s, 4H); EIMS: 410.6 (M+H, calcd for $C_{28}H_{27}NO_2$, 410.53).

4.2.11. Bis-(indol-3-ylmethyl)amine[22h] (31). Yield 65%; IR: 3409, 3054, 2794, 1556, 1456, 1421, 1338, 125, 1092, 1009, 741 cm^{-1}; ^1H NMR: δ 10.85 (s, 2H), 7.49–7.47 (d, J=8 Hz, 2H), 7.32–7.30 (d, J=8 Hz, 2H), 7.26 (s, 2H), 7.1–6.9 (m, 2H), 6.88–6.85 (m, 2H), 3.67 (s, 4H); EIMS: 276.3 (M+H, calcd for $C_{18}H_{17}N_3$, 276.35).

4.2.12. Bis-(2-phenylpropyl)amine[22i] (32). Yield 58%; IR: 3297, 3027, 2961, 1601, 1493, 1452, 1228, 1129, 761, 700 cm^{-1}; ^1H NMR: δ 7.35–7.09 (m, 10H), 2.9–2.86 (m, 2H), 2.82–2.67 (m, 4H), 1.2–1.18 (2d, J=4 Hz, 6H); EIMS: 254.3 (M+H, calcd for $C_{18}H_{23}N$, 254.39.

4.2.13. Bis-(3-phenylpropyl)amine[22i] (33). Yield 75%; ^1H NMR: δ 7.38–7.06 (m, 10H), 3.5 (t, 1H, J=6.0 Hz), 3.0–2.3 (m, 6H), 2.2–1.5 (m, 6H); EIMS: 254.5 (M+H, calcd for $C_{18}H_{23}N$, 254.39.

4.2.14. Bis-(cyclohexylmethyl)amine (34). Yield 68%; ^1H NMR: δ 2.43 (d, 4H, J=6.0 Hz), 1.85–1.62 (m, 11H), 1.55–1.4 (m, 4H), 1.35–1.1 (m, 8H); EIMS: 211.5 (M+H, calcd for $C_{14}H_{27}N$, 210.37.

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