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Trimethyl Borate-Catalyzed, Solvent-Free Reductive Amination

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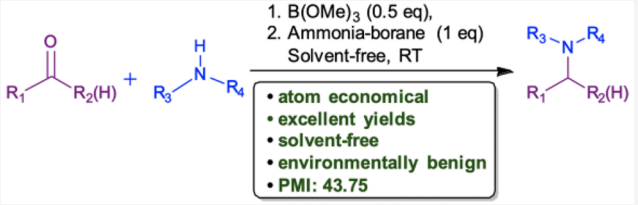
ABSTRACT: Solvent-free reductive amination of aldehydes and ketones with aliphatic and aromatic amines in high-to-excellent yields has been achieved with sub-stoichiometric trimethyl borate as promoter and ammonia borane as reductant.

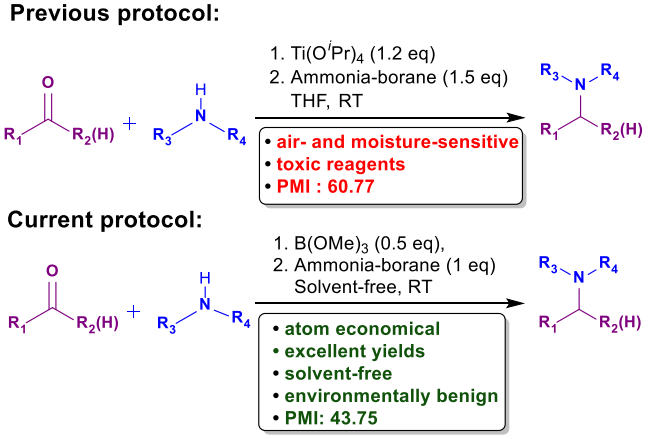


Reductive amination of carbonyls (reductive alkylation of amines), the one-pot reaction of aldehydes or ketones with amines in the presence of a reducing agent, is one of the key reactions in organic chemistry with myriad applications for the synthesis of simple and complex bioactive molecules.[1] Several borohydrides, such as sodium,[2] zinc,[3] or lithium borohydride,[4] tetrabutylammonium[5] or sodium cyanoborohydride ($NaBH_3CN$),[6,7] and sodium triacetoxyborohydride ($NaBH(OAc)_3$),[8] as well as catalytic hydrogenation[9] have been utilized for the reduction step. However, most of these procedures suffer from drawbacks. For example, $NaBH_3CN$ produces toxic and volatile hydrogen cyanide byproducts, $NaBH(OAc)_3$ fails to aminate aromatic ketones,[10] and hydrogenation is not chemoselective.

Another class of reducing agents that is routinely utilized for reductive amination is amine boranes, such as pyridine-borane,[11−13] 2-picoline-borane,[14,15] dimethylamine-borane,[16] *N*-isopropyl-*N*-methyl-*tert*-butylamine-borane,[17] 5-ethyl-2-methylpyridine-borane,[18] and benzylamine-borane.[19] With these reagents, an equivalent of the amine from the reductant remains in the product mixture, necessitating their difficult separation from the desired product amine. This inconvenience was overcome using a protocol involving ammonia borane (AB, **1**) as the reductant, with ammonia as the byproduct, achieving the synthesis of primary-, secondary-, and tertiary-amines.[20] Nevertheless, the use of an equivalent of toxic, air- and moisture-sensitive titanium isopropoxide ($Ti(O\text{-}i\text{-}Pr)_4$)[21] as the Lewis acid made the process still unfavorable. Aiming for a greener protocol, the project was revisited, which resulted in a solvent-free, catalytic, green reductive amination with **1** (Scheme 1). The details follow.

A successful reductive amination relies on a rapid imine formation and selective reduction. Recent reductive amination literature contains numerous protocols examining various Lewis/Bronsted acids for the initial "carbonyl imination" step. For example, acetic acid has been used as the promoter when 2-picoline-borane was used as the reductant[22] and boric acid has been utilized when sodium borohydride was used as

Scheme 1



the reductant.[22] Other Lewis acids employed to promote imination include $Ti(OiPr)_4$,[2,23] $Mg(ClO_4)_2$,[24] $ZnCl_2$,[25] $LiClO_4$,[16,26] $TiCl_4$,[27] Bu_2SnCl_2,[28] etc.

Optimization trials (for summary: see Table S1, Supporting Information) were begun by examining acetic acid and boric acid for the reductive amination of benzaldehyde (**2a**) with benzylamine (**3a**) using **1** in methanol, the common solvent for such reductive aminations.[18] The reaction, monitored by thin layer chromatography (TLC) for the disappearance of **3a**, was complete in 4 h, and the product dibenzylamine (**4aa**)[29] was obtained in 49% (AcOH) and 59% ($B(OH)_3$) yields, respectively. Following the literature,[14] water or a mixture of methanol−water was also verified as solvents. However,

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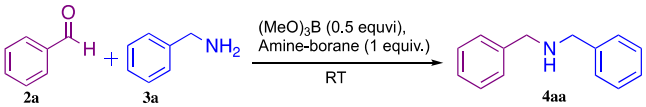
contrary to high yields from a similar solvent system for 2-picoline-borane as the reductant, very low yields (16−39%) were noticed.[14] On the basis of a recent reductive amination using borane and borohydride reagents in "greener" solvents,[30] ethyl acetate was examined, which resulted in no product formation. Having failed to improve the yields, we decided to examine trimethyl borate as a promoter due to its ease of handling compared to boric acid, which has to be ground with the aldehyde.[28] Thus, a reductive amination of **2a** with **3a** was carried out, *under neat conditions*, with an equivalent each of trimethyl borate and **1**, when **4aa** was obtained in 65% yield. Cognizant of the fact that water generated during the imine formation could hydrolyze trimethyl borate to boric acid and methanol, the above reaction was performed in methanol and a similar yield (65%) of **4aa** was obtained. Consequently, the role of trimethyl borate on the reaction was scrutinized under neat conditions. Increasing the measure of trimethyl borate to 2 equiv provided a modest increase in the yield to 68%, and decreasing it to 0.5 equiv provided 73% of **4aa**. A further decrease to 0.2 equiv also gave the increased yield (73%). However, difficulty in stirring of this mixture necessitated the addition of methanol as solvent.

In all of the above reactions, a nontrivial amount (∼10%) of benzyl alcohol was formed as a side product from the competitive reduction of **2a** by **1**. The addition of a slight excess (10%) of **3a** suppressed the carbinol formation and gave the best yield (85%) for **4aa** with negligible reduction product. Under the optimized, solvent-free, reductive amination protocol, **3a** (1.1 mmol) was added to **2a** (1 mmol), at room temperature (RT), followed by the addition of trimethyl borate (0.5 mmol) and **1** (1 mmol). The reaction was stirred to completion (TLC, 4 h) and worked up with dil. HCl, followed by treatment of the aqueous layer with NaOH.

Next, the solvent-free reductive amination was evaluated with other amine-boranes that are commonly used for reductive amination, such as pyridine-borane (**5**), 2-picoline-borane (6), and *t*-butylamine-borane (7) as well as several in-house synthesized[31] amine-boranes, such as triethylamine-borane (**8**), piperidine-borane (**9**), morpholine-borane (**10**), benzylamine-borane (**11**), and cyclohexylamine-borane (**12**). The results summarized in Table 1 reveal very unsatisfactory yields with 2-picoline-borane (entry 3) and *t*-butylamine-borane (entry 4). Triethylamine-borane (entry 5), pyridine-borane (entry 2), piperidine-borane (entry 6), morpholine-borane (entry 7), and benzylamine-borane (entry 8) also gave subpar yields. Only cyclohexylamine-borane (entry 9) gave yields comparable to **1**. Given the benefits, such as low molecular weight, remarkable thermal and hydrolytic stability, convenient handling, and no contamination with byproducts, **1** was adopted as the preferred reductant.

Table 1. Examination of Amine-Boranes for Reductive Amination of Benzaldehyde with Benzylamine Using Trimethyl Borate Catalyst



entry	amine-borane	time (h)	yield (%)
1	ammonia-borane (**1**)	4	85
2	pyridine-borane (**5**)	7	50
3	2-picoline-borane (**6**)	7	21
4	*t*-butylamine-borane (**7**)	7	22
5	triethylamine-borane (**8**)	12	40
6	piperidine-borane (**9**)	5	53
7	morpholine-borane (**10**)	5.5	58
8	benzylamine-borane (**11**)	5	62
9	cyclohexylamine-borane (**12**)	4	79

The scope of the trimethyl borate-catalyzed reductive amination with **1** was further demonstrated for aldehydes and amines with variable steric and electronic environments as illustrated in Table 2. The effect of amines was examined first by maintaining **2a** as the aldehyde. Electron-rich 4-methoxybenzylamine (**3b**, entry 2) and deactivated 4-chlorobenzylamine (**3c**, entry 3) yielded the corresponding dibenzylamines, **4ab** and **4ac** in 94% and 96% yields, respectively.

Reaction with aniline (**3d**, entry 4) and electron-rich anilines, such as 4-methoxyaniline (**3e**, entry 5) and 2-methoxyaniline (**3f**, entry 6), proceeded without difficulty to produce the corresponding *N*-benzylanilines in 79−85% yields. However, electron deficient 4-nitroaniline (**3g**) gave relatively poor yield (64%, entry 7). In the case of aliphatic 1°- and 2°-alkylamines, this protocol yielded the corresponding *N*-alkylated benzylamines contaminated with a substantial amount of 1°-alcohol from the reduction of the aldehyde. To avoid this undesired product, we modified our protocol with a stepwise reductive amination. Accordingly, the aldehyde or ketone was stirred, at RT, with the amine until complete conversion to the corresponding imine (TLC, ∼4−36 h), followed by the addition of **1** and stirring until the disappearance of the imine (TLC, ∼4 h). This procedural change resulted in a significant decrease of the undesired alcohol and improved amination of **2a**. 1°-Amines, 1-propanamine (**3h**) and 2-propanamine (**3i**) (entries 8 and 9), and a 2°-amine, piperidine (**3j**, entry 10), were benzylated in 62%, 75%, and 71% yields, respectively.

Attention was now turned to the effect of substitution on the aldehydes. Thus, the reaction of activated 4-hydroxybenzaldehyde (**2b**, entry 11) and deactivated 4-nitrobenzaldehyde (**2c**, entry 12) with **3c** proceeded smoothly in 77% and 85% yields, respectively. An aliphatic aldehyde, cyclohexanecarbaldehyde (**2d**), reacted with **3a**, **3c**, and **3d** to produce the corresponding secondary amines in 78−87% yields (entries 13−15). Reductive amination of heteroaraldehydes, such as 1-methylpyrrole-2-carbaldehyde (**2e**, entry 16) and furfural (**2f**, entry 17) with **3b** and **3c**, respectively, gave the appropriate products in excellent yields (97% and 90%, respectively).

Given the facility of the reaction with various aldehydes, the protocol was extended to ketones, which required the two-step protocol for an efficient reaction. Thus, cyclohexanone (**2g**, entry 18), cyclopentanone (**2h**, entry 19) with **3c**, and 3-pentanone (**2i**, entry 20) provided the corresponding amines in yields ranging from 73% to 80%. Similarly, the reaction of acetophenone (**2j**, entry 21) with 4-methoxybenzylamine (**3b**) gave a very good yield (85%) for **4jb**. Indanone (**2k**) reacted with 4-methoxybenzylamine (**3b**, entry 22) and allylamine (**3k**, entry 23) to provide the corresponding secondary amines in 98% and 93% yields, respectively.

The utility of our protocol was demonstrated by isolating **4aa** in comparable yield from a mole-scale reaction of **2a** with **3a**. Further, this $(MeO)_3B$-catalyzed protocol was applied for the preparation of racemic Rasagiline[32] (**4kl**) in 92% yield (Scheme 2). The *R*-isomer of this molecule is an irreversible monoamine oxidase-B inhibitor used to treat symptoms in

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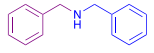
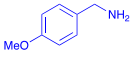
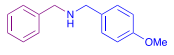
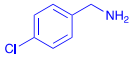
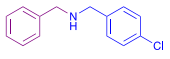
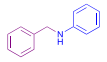
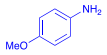
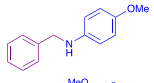
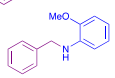
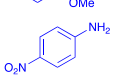
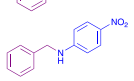
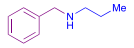
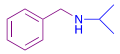
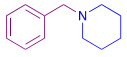
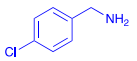
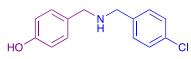
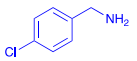
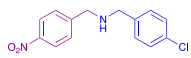
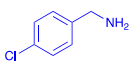
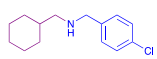
Table 2. Trimethyl Borate-Promoted Reductive Amination of Aldehydes and Ketones with Primary and Secondary Amines

Entry	Carbonyl #	Carbonyl structure	Amine #	Amine structure	Product #	Product structure	Reaction time (h)	Yield (%)[c]
1	2a		3a		4aa		4[a]	84
2	2a		3b		4ab		4[a]	94
3	2a		3c		4ac		4[a]	96
4	2a		3d		4ad		4[a]	85
5	2a		3e		4ae		4[a]	84
6	2a		3f		4af		4[a]	79
7	2a		3g		4ag		24[b]	64
8	2a		3h		4ah		24[b]	62
9	2a		3i		4ai		12[b]	75
10	2a		3j		4aj		32[b]	71
11	2b		3c		4bc		4[a]	77
12	2c		3c		4cc		4[a]	85
13	2d		3c		4dc		12[b]	87
14	2d		3d		4dd		24[b]	78
15	2d		3a		4da		24[b]	83
16	2e		3b		4eb		4[a]	97
17	2f		3c		4fc		4[a]	90
18	2g		3c		4gc		18[b]	80
19	2h		3a		4ha		12[b]	75
20	2i		3b		4ib		36[b]	73
21	2j		3b		4jb		36[b]	85
22	2k		3b		4kb		36[b]	98
23	2k		3k		4kk		12[b]	93

[a]One-pot direct amination protocol has been followed. [b]Indirect reductive amination protocol has been followed. [c]The reactions were carried out using 1:1.1 equiv of benzaldehyde and benzylamine. The yields reported are for isolated product.

early Parkinson's disease or as an adjunct therapy in more advanced cases.[33]

The pharmaceutical industry selected, mass-based green matrix value [Process Mass Intensity (PMI)][34] for this protocol was computed[35] to be 43.7. In comparison, the PMI for our earlier Ti(O-*i*-Pr)$_4$-catalyzed procedure[20] is 60.77, highlighting the low environmental impact of the new reductive amination protocol. This favorably compares with other frequently utilized procedures, such as NaBH(OAc)$_3$- and pyridine-borane-mediated reductive aminations.

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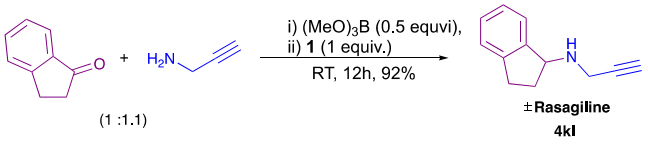
Scheme 2



In conclusion, we have herein reported a facile reductive amination procedure involving trimethyl borate as a catalyst and readily available and inexpensive ammonia borane as reductant, providing 2°- and 3°-amines in good to excellent yields. This convenient, solvent-free, and environmentally benign protocol has a low PMI. The protocol has been applied for a mole-scale reaction and utilized to synthesize Rasagiline in excellent yield.

EXPERIMENTAL SECTION

General Information. All reactions were performed open to air. All chemicals were purchased from Sigma-Aldrich and used without further purification, unless otherwise noted. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded in $CDCl_3$ on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe, and chemical shifts (δ) are given in ppm relative to TMS. Flash chromatography was performed using 40−63 μm, 60 Å silica gel.

General Experimental Procedure. One-pot direct reductive amination of carbonyls: To the carbonyl compound (5 mmol, 1 equiv) was added the amine (5.5 mmol), followed by the addition of $(MeO)_3B$ 2.5 mmol) and ammonia borane (5 mmol). The reaction mixture was stirred for about 4 h at RT. Upon completion of the reaction, as revealed by TLC, the resulting mixture was treated with HCl (15 mL, 6 M), diluted with water (30 mL), and extracted with diethyl ether (3 × 15 mL). The aqueous layer was then treated with NaOH (6 M) until pH 10−12 and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (1 × 45 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain the crude product, which was purified by silica gel flash chromatography to obtain the desired product.

Indirect reductive amination of carbonyls: To the solution of the carbonyl (5 mmol), the amine (5.5 mmol) was added $(MeO)_3B$ (2.5 mmol) and stirred at RT, followed by TLC until complete conversion to the corresponding imine. Subsequently, ammonia borane (5 mmol) was added and further stirred at the same temperature until the disappearance of the imine. The resulting mixture was treated with HCl (15 mL, 6 M), diluted with water (30 mL), and extracted with diethyl ether (3 × 15 mL). The aqueous layer was then treated with NaOH (6 M) until pH 10−12 and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (1 × 45 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain the crude product, which was purified by silica gel flash chromatography to obtain the desired product.

*Dibenzyl Amine (**4aa**).* The product was isolated in 84% yield (0.828 g, 4.2 mmol) as a colorless liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[36] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42−7.25 (m, 10H), 3.85 (s, 4H), 2.09 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 140.0, 128.4, 128.2, 127.0, 53.1.

*N-Benzyl-1-(4-methoxyphenyl)methanamine (**4ab**).* The product was isolated in 94% yield (1.067 g, 4.7 mmol) as a pale yellow liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36−7.27 (m, 8H), 6.89 (d, J = 8.6 Hz, 2H), 3.81 (s, 4H), 3.76 (s, 3H) 2.29 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) 158.7, 139.2, 131.2, 129.6, 128.4, 128.3, 127.1, 113.8, 55.3, 52.6, 52.2.

*N-Benzyl-1-(4-cholorophenyl)methanamine (**4ac**).* The product was isolated in 96% yield (1.108 g, 4.8 mmol) as a colorless liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37−7.25 (m, 10H), 3.79 (dd, J = 5.4, 0.9 Hz, 4H), 1.90 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 139.8, 138.5, 132.6, 129.5, 128.4, 128.4, 128.1, 127.0, 53.1, 52.4.

*N-Benzylaniline (**4ad**).* The product was isolated in 85% yield (0.777 g, 4.25 mmol) as a colorless liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42−7.14 (m, 8H), 6.81−6.66 (m, 2H), 4.34 (s, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 146.9, 129.2, 128.6, 127.7, 127.3, 118.4, 113.7, 49.0.

*N-Benzyl-4-nitroaniline (**4ag**).* The product was isolated in 64% yield (0.729 g, 3.2 mmol) as an orange solid after purification via column chromatography on silica gel using hexane/EtOAc (9:1) as an eluent. The spectral data matched with those reported in the literature.[37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.13−8.06 (m, 2H), 7.43−7.29 (m, 5H), 6.63 (d, J = 9.1 Hz, 2H), 4.44 (s, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 152.9, 138.2, 137.3, 128.9, 127.8, 127.3, 126.3, 111.29, 47.7.

*N-Benzyl-4-methoxyaniline (**4ae**).* The product was isolated in 84% yield (0.894 g, 4.2 mmol) as a pale yellow solid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40−7.25 (m, 5H), 6.83−6.75 (m, 2H), 6.71−6.64 (m, 2H), 4.29 (s, 2H), 3.75 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 152.2, 142.6, 139.9, 128.7, 127.6, 127.2, 115.0, 114.2, 55.9, 49.3.

*N-Benzyl-2-methoxyaniline (**4af**).* The product was isolated in 79% yield (0.841 g, 3.95 mmol) as a yellow solid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[38] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42−7.26 (m, 5H), 6.88−6.62 (m, 4H), 4.37 (s, 2H), 3.86 (s, 3H). ^{13}C{1H} NMR (75 MHz, CDCl3) δ 146.7, 139.4, 128.5, 127.5, 127.1, 121.2, 116.7, 110.2, 109.3, 55.5, 48.1.

*N-Benzylpropan-1-amine (**4ah**).* The product was isolated in 62% yield (0.461 g, 3.1 mmol) as a yellow liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[39] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 (d, J = 6.6 Hz, 2H), 7.43−7.40 (m, 2H), 7.36−7.32 (m, 1H), 3.67 (s, 2H), 2.68−2.34 (m, 2H), 1.87−1.42 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 140.1, 128.8, 128.2, 126.7, 58.5, 55.6, 20.4, 12.1.

*N-Benzylpropan-2-amine (**4ai**).* The product was isolated in 75% yield (0.558 g, 3.75 mmol) as a yellow liquid after purification via column chromatography on silica gel using hexane as an eluent. The spectral data matched with those reported in the literature.[40] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38−7.20 (m, 5H), 3.79 (s, 2H), 2.86 (p, J = 6.2 Hz, 1H), 1.69 (s, 1H), 1.11 (d, J = 6.2 Hz, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 134.9, 129.3, 128.6, 128.0, 49.3, 48.1, 20.6.

*Benzylpiperidine (**4aj**).* The product was isolated in 71% yield (0.621 g, 3.55 mmol) as a clear yellow liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[41] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40−7.23 (m, 5H), 3.51 (s, 2H), 2.42 (t, J = 5.3 Hz, 4H), 1.71−1.58 (m, 4H), 1.48 (td, J = 6.1, 3.2 Hz, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 138.6, 129.2, 128.0, 126.8, 64.0, 54.6, 26.2, 24.6.

*(((4-Chlorobenzyl)amino)methyl)phenol (**4bc**).* The product was isolated in 77% yield (0.950 g, 3.85 mmol) as a yellow oil after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}ClNO$ 248.0842, found 248.0840. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41−7.22 (m, 4H), 7.22−7.03 (m, 2H), 6.83−6.47 (m, 2H), 3.74 (d, J = 23.6 Hz, 4H). ^{13}C{1H} NMR (75 MHz,

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$CDCl_3$) δ 156.0, 138.6, 132.1, 130.3, 129.4, 129.2, 128.2, 115.3, 52.4, 52.0.

N-(4-Chlorobenzyl)-1-(4-nitrophenyl)methanamine (**4cc**). The product was isolated in 85% yield (1.176 g, 4.25 mmol) as a pale yellow solid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. Mp. (92−93 °C). HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}ClN_2O_2$ 277.0744; found 277.0740. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.26−8.10 (m, 2H), 7.60−7.49 (m, 2H), 7.40−7.18 (m, 4H), 3.84 (d, *J* = 33.7 Hz, 4H), 2.26 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 152.0, 142.3, 139.5, 128.5, 127.4, 127.1, 114.8, 114.0, 55.8, 49.3.

N-(4-Chlorobenzyl)-1-cyclohexylmethanamine (**4dc**). The product was isolated in 87% yield (1.030 g, 4.35 mmol) as a yellow oil after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{21}ClN$ 238.1362; found 238.1356. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 (m, *J* = 4.8 Hz, 4H), 3.65 (d, *J* = 5.2 Hz, 2H), 2.37 (dd, *J* = 6.7, 4.3 Hz, 2H), 1.68 (dt, *J* = 13.6, 6.8 Hz, 4H), 1.41 (ddd, *J* = 11.0, 7.1, 3.6 Hz, 1H), 1.16 (dq, *J* = 14.3, 10.9, 10.5 Hz, 4H), 1.00−0.67 (m, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 139.2, 132.2, 129.2, 128.2, 56.2, 53.4, 38.2, 31.6, 26.8, 26.2.

N-(Cyclohexylmethyl)aniline (**4dd**). The product was isolated in 78% yield (0.621 g, 3.55 mmol) as a clear yellow liquid after purification via column chromatography on silica gel using hexane as an eluent. The spectral data matched with those reported in the literature.[41] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22−7.09 (m, 2H), 6.76−6.63 (m, 3H), 3.11 (s, 2H), 1.71−1.45 (m, 9H), 1.40−1.26 (m, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 148.7, 129.2, 117.6, 113.2, 71.5, 54.3, 35.9, 26.0, 22.1.

N-Benzyl-1-cyclohexylmethanamine (**4da**). The product was isolated in 83% yield (0.791 g, 3.9 mmol) as a pale yellow liquid after purification via column chromatography on silica gel using hexane as an eluent. The spectral data matched with those reported in the literature.[42] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 (dd, *J* = 23.7, 4.5 Hz, 5H), 3.80 (s, 2H), 2.50 (d, *J* = 6.7 Hz, 2H), 1.89−1.63 (m, 4H), 1.62−1.46 (m, 1H), 1.42−1.09 (m, 4H), 0.97 (td, *J* = 11.7, 2.9 Hz, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 140.6, 128.3, 128.1, 128.0, 126.8, 56.3, 54.3, 38.1, 31.9, 31.6, 26.9, 26.3.

N-(4-Methoxybenzyl)-1-(1-methyl-1H-pyrrol-2-yl)methanamine (**4eb**). The product was isolated in 97% yield (1.115 g, 4.85 mmol) as a dark brown liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$ 231.1497; found 231.1493. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.60 (t, *J* = 2.1 Hz, 1H), 6.06 (d, *J* = 2.6 Hz, 2H), 3.89−3.70 (m, 7H), 3.64 (s, 3H), 1.94 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 158.6, 132.6, 131.1, 129.3, 122.4, 113.8, 108.0, 106.5, 1, 55.3, 52.8, 44.9.

N-(4-Chlorobenzyl)-1-(furan-2-yl)methanamine (**4fc**). The product was isolated in 90% yield (0.994 g, 4.50 mmol) as a brown oil after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{13}ClNO$ 222.0685; found 222.0682. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50−7.05 (m, 5H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 3.74 (d, *J* = 6.5 Hz, 4H), 1.98−1.70 (m, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 153.4, 141.8, 138.2, 132.6, 129.5, 129.5, 110.1, 107.2, 52.0, 45.3.

N-(4-Chlorobenzyl)cyclohexanamine (**4gc**). The product was isolated in 80% yield (0.892 g, 4.00 mmol) as a yellow liquid after purification via column chromatography on silica gel using hexane as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{19}ClN$ 224.1206; found 224.1203. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52−7.09 (m, 4H), 3.77 (s, 2H), 2.45 (tt, *J* = 10.1, 3.7 Hz, 1H), 1.89 (dd, *J* = 11.8, 3.8 Hz, 2H), 1.81−1.69 (m, 2H), 1.66−1.54 (m, 1H), 1.38−0.87 (m, 5H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 139.4, 132.3, 129.3, 128.3, 56.1, 50.3, 33.6, 26.2, 25.1.

N-Benzylcyclopentanamine (**4ha**). The product was isolated in 75% yield (0.791 g, 3.9 mmol) as a yellow oil after purification via column chromatography on silica gel using hexane/EtOAc (9:1) as an eluent. The spectral data matched with those reported in the literature.[43] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.9 Hz, 5H), 3.72 (d, *J* = 9.4 Hz, 2H), 3.06 (p, *J* = 6.6 Hz, 1H), 1.95−1.20 (m, 8H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 140.3, 128.3, 128.2, 126.8, 59.1, 52.7, 33.2, 24.2.

N-(4-Methoxybenzyl)pentan-3-amine (**4ib**). The product was isolated in 73% yield (0.755 g, 3.65 mmol) as a yellow liquid after purification via column chromatography on silica gel using hexane/EtOAc (9:1) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{22}NO$ 208.1696; found 208.1701. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34−7.17 (m, 2H), 6.91−6.73 (m, 2H), 3.79 (s, 3H), 3.69 (s, 2H), 2.43 (p, *J* = 5.9 Hz, 1H), 1.46 (qdd, *J* = 7.3, 5.9, 1.8 Hz, 4H), 1.25 (d, *J* = 13.0 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 158.4, 133.2, 113.6, 59.2, 55.2, 50.5, 25.7, 9.8.

N-(4-Methoxybenzyl)-1-phenylethan-1-amine (**4jb**). The product was isolated in 85% yield (1.024 g, 4.25 mmol) as a light yellow liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{20}NO$ 242.1545; found 242.1541. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53−7.07 (m, 7H), 7.01−6.75 (m, 2H), 3.82 (d, *J* = 8.1 Hz, 5H), 3.59 (d, *J* = 8.2 Hz, 1H), 1.61 (s, 1H), 1.39 (d, *J* = 6.6 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 158.4, 145.5, 132.7, 129.2, 128.4, 126.6, 113.7, 57.4, 55.3, 51.1, 24.6.

N-(4-Methoxybenzyl)-2,3-dihydro-1H-inden-1-amine (**4kb**). The product was isolated in 98% yield (1.239 g, 4.90 mmol) as a dark brown liquid after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}NO$ 254.1545; found 254.1544. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49−7.13 (m, 6H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 1H), 3.81 (d, *J* = 15.4 Hz, 5H), 3.12−2.95 (m, 1H), 2.82 (dt, *J* = 15.8, 7.6 Hz, 1H), 2.52−2.32 (m, 1H), 2.03−1.82 (m, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 158.4, 145.2, 143.5, 132.6, 129.2, 127.3, 126.1, 124.6, 124.0, 113.7, 62.6, 55.3, 50.8, 33.7, 30.5.

N-Allyl-2,3-dihydro-1H-inden-1-amine (**4kk**). The product was isolated in 93% yield (0.804 g, 4.65 mmol) as a brown oil after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. HRMS (CI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{16}N$ 174.1282; found 174.1280. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45−7.33 (m, 1H), 7.22 (dd, *J* = 8.6, 3.1 Hz, 3H), 6.09−5.92 (m, 1H), 5.31−5.09 (m, 2H), 4.32−4.25 (m, 1H), 3.39 (ddd, *J* = 6.1, 3.3, 1.5 Hz, 2H), 3.03 (ddd, *J* = 13.6, 8.5, 5.0 Hz, 1H), 2.83 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.43 (dddd, *J* = 12.0, 8.2, 6.5, 5.0 Hz, 1H), 1.74 (m, 2H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 145.0, 143.6, 136.9, 127.4, 126.2, 124.7, 124.1, 115.9, 62.7, 50.0, 33.7, 30.5.

Rasagiline (**4kl**). The product was isolated in 92% yield (0.786 g, 4.6 mmol) as a solid, mp = 148 °C, after purification via column chromatography on silica gel using hexane/EtOAc (95:5) as an eluent. The spectral data matched with those reported in the literature.[44] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47−7.10 (m, 4H), 4.43 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.53 (dd, *J* = 2.5, 1.5 Hz, 2H), 3.07 (ddd, *J* = 16.1, 8.3, 5.7 Hz, 1H), 2.84 (ddd, *J* = 15.3, 8.3, 6.2 Hz, 1H), 2.41 (ddddd, *J* = 12.6, 8.0, 6.8, 5.7, 1.0 Hz, 2H), 1.97−1.78 (m, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 144.4, 143.7, 127.5, 126.2, 124.8, 124.2, 82.6, 71.6, 61.9, 36.2, 33.5, 30.6

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02143.

Optimization summary, PMI calculation, and copies of PMR and CMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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