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A 5+1 Protic Acid-Assisted *aza*-Pummerer Approach for Synthesis of 4-Chloropiperidines From Homoallylic Amines

Rene Ebule[a], **Sagar Mudshinge**[a], **Michael H. Nantz**[a], **Mark S. Mashuta**[a], **Gerald B. Hammond**[a], and **Bo Xu**[b]

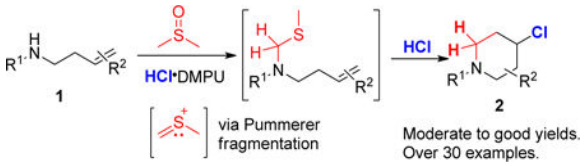
[a]Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States

[b]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai, China

Abstract

We report that HCl•DMPU induces the formation of (thiomethyl)methyl carbenium ion from DMSO under mild conditions. Homoallylic amines react with this electrophile to generate 4-chloropiperidines in good yields. The method applies to both aromatic and aliphatic amines. The use of HCl•DMPU as both non-nucleophilic base and chloride source constitutes an environmentally benign alternative for piperidine formation. The reaction has a broad substrate scope, and the conditions offer good chemical yields with high functional group tolerance and scalability.

Graphical Abstract



Introduction

Functionalized piperidines are ubiquitous in natural products[1] and pharmaceuticals (Figure 1).[2] Despite an extensive literature on piperidine syntheses,[3] there are still demands for more efficient syntheses. The common strategies for the synthesis of piperidine skeletons involve intra-[4], and intermolecular[5] cyclization reactions, ring expansion processes[6] and reduction of pyridines.[7] Cycloaddition is the more effective approach, achieved either by a nucleophilic substitution process (Scheme 1a),[3c, 8] transition metal catalysis (Scheme 1b),[3a, b, 9] or an

Correspondence to: Gerald B. Hammond; Bo Xu.

Corresponding Author gb.hammond@louisville.edu; bo.xu@dhu.edu.cn.

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Copies of ^{1}H and ^{13}C NMR spectra

Notes

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electrophile-or radical-induced cyclization (Scheme 1c).[10] The use of designed or protected substrates and expensive transition metals limit the application of some of these methods. Another important method for obtaining 4-substituted piperidines is through the aza-Prins cyclization method (Scheme 1e).[5a, 11] This method usually requires transition metal or Lewis acid catalysis.

In our search for applications of the newly formulated HCl•DMPU,[12] a highly concentrated, bench stable, readily prepared and easily dispensable anhydrous source of HCl, we observed the activation of DMSO. Activation of dimethyl sulfoxide by electrophiles[13] has been widely reported and has led to the application of DMSO as a viable synthon,[14] as noted by the increased use of DMSO as a one carbon source in the recent literature (Scheme 1d).[15] We describe herein application of our HCl•DMPU-mediated DMSO activation to prepare 4-chloropiperidines.

Despite the tremendous progress made in alkene amino cyclization reactions,[4, 11i, 16] there are still limitations in the substrate scope for intramolecular construction of piperidines. We wanted to avoid the use of toxic formaldehyde as a one carbon synthon. To address these limitations, we surmised one possible solution would be to exploit the formation of (thiomethyl)methyl carbenium ion from DMSO[17] will be trapped by homoallylic amines (Scheme 1f).[18] The thiocarbenium ion generation could arise from a Pummerer fragmentation through the interaction of the sulfoxide with an electrophile. Such activations are common in activated high-molecular weight sulfoxides.[19] However, protic acid activation of DMSO is rare.[20] We envisioned that reaction of the thiocarbenium ion with a homoallylic amine might initiate an intramolecular cyclization to form a piperidine ring. Specifically, tandem electrophilic capture of the DMSO-derived (thiomethyl)methyl carbenium ion by the homoallylic amine followed by intramolecular reaction of the pendant vinyl system with subsequent counterion trapping of the resulting electrophilic center could afford access to 4-substituted piperidines. Such an approach would provide a nice compliment to current halo-piperidation techniques.[5a, 11a, 21]

Results and Discussion

We began our investigation using the homoallylic amine **1a**, HCl•DMPU (2.4 equiv) and DMSO (2.4 equiv) in DCE at 65 °C (Table 1). We were pleased to obtain the desired cyclized product **2a** in decent yield. A solvent screening indicated a better conversion in ethyl acetate (Table 1, entries 1–5). Reaction concentration played an essential role in improving conversion and limiting side product of methylthiolation. (Table 1, entries 6 and 7).

We also investigated other HCl sources. As expected, the lower concentration sources were sluggish (Table 1, entries 8, and 10) while the more concentrated sources gave appreciable conversions with lower desired product ratios thwarted by thiolated side products (Table 1, entries 9 and 11). Use of aqueous HCl gave a dismal outcome; however, the conversions with *in situ* generated HCl Table 1, entries 13 and 14) proceeded with comparable selectivity to the ready-made HCl•DMPU reagent. Encouraged by these results, we examined the

substrate scope of this new cyclization reaction with the optimum condition in hand (Table 2).

We first examined the scope of homoallylic anilines. The study revealed that there was broad tolerance of substituents with various electronic properties on all positions on the aromatic ring giving good to excellent yields. An array of para-substituted anilines containing groups such as methyl (**2b**), halo (**2d, 2e, 2f**), trifluoromethyl (**2j**), methoxy **(2k)**, cyano (**2l**), trifluoromethoxy (**2m**), nitro (**2n**), phenyl (**2r**) and acetyl (**2t**) all proceeded in excellent yields. Single crystal X-ray structure of the 4-nitrophenyl derivative (**2n**), was obtained showing the chlorine atom locked in the axial position (Figure 3). The inclusion of similar substituents at the ortho (**2i**, **2o, 2s**) and meta (**2c, 2g, 2h, 2q**) positions did not affect the yields. The method displayed good functional group tolerance to groups like nitrile (**2l**), ester (**2w**), ethers (**2k, 2m, 2v**) and ketones (**2t, 2u**). Interestingly, homoallylic sulfonamides (**2aa, 2ab, 2ac**) transformed excellent yields. Heteroaromatic amines that contain benzodioxole (**2v**), thiophene (**2w**), pyridine (**2x, 2y**) and pyrazine (**2z**) moieties also gave desired cyclization products in good yields. While meta-polysubstitution (**2p**) was highly selective resulting in a yield of 90%, the trisubstituted substrate (**2ai**) gave an inseparable 3:2 mixture of piperidine and pyrrolidine respectively. Unfortunately, the method was unsuccessful with the hydrazide (**2aj**), hydroxylamine (**2ak**) and indole (**2al**) substrates likely due to substrate intolerance and product instability (Figure 2). We also examined aliphatic amines too. Though strongly basic, we were delighted to observe satisfactory product yields of 51-64%. The reaction conditions tolerated benzyl (**2ag, 2ah**) and longer aliphatic chain (**2ad, 2ae, 2af**) substrates.

Next, we investigated the scope of the alkene chain. Both terminal and internal substituted alkenes afforded desired products (Table 3). The disubstituted alkenes (**3a, 3b, 3c, 3d**) furnished the desired cyclized products (**4a, 4b, 4c, 4d**) in good yields of 81%, 84%, 53% and 65% respectively. The major diastereomer, **4d**, exhibited an anti-stereochemistry. The sterically hindered homoallylic amine derivative of nopol (**3c**) underwent the cyclization in a modest 53% yield. Due to steric demands, the 1,1,2-trisubstituted alkene substrate (**3e**) failed to achieve the desired outcomes. Rather it formed the kinetically favored pyrrolidine product in 64% yield. The mass obtained by GCMS was consistent with that of the pyrrolidine product. Also, the cyclic alkene substrate (**3f**) was unsuccessful probably due to ring strain barrier associated with its formation.

To demonstrate the practicality of the method, we conducted a ten mmol reaction (Scheme 2, eq 1) of **1a** without any further modifications and obtained the desired product **2a** in high yield. To probe the mechanism of the reaction, we carried a deuterium labeling experiment using deuterated DMSO. We observed high deuterium incorporation of over 99% for the resulting piperidine (Scheme 2, eq 2). This result indicates that the extra carbon arises from DMSO. During the preparation of this manuscript, Zhong and co-workers[22] reported that DMSO could serve as a formaldehyde surrogate. Using paraformaldehyde in place of DMSO under similar reaction conditions as ours also yielded the 4-chloropiperidine product (Scheme 2, eq 4). It is, however, inconclusive if that is the only operating mechanism because as earlier referenced, DMSO can equally serve as a one-carbon source. Given the abundance of chloride ion during the reaction, the *in-situ* generation of chloromethyl methyl

sulfide (**IIb**) as an intermediate is possible. Indeed, the reaction of the starting amine with commercially available chloromethyl methyl sulfide led to the formation of **2a** in 64% yield (Scheme 2, eq 3). Finally, to seek insight as to the intermediary of an iminium ion before cyclization, we performed the reaction with tertiary amine **7** and observed no cyclization to give **2a**. Instead, the reaction gave the chlorothiolated product **8**[23] was formed in 67% (Scheme 2, eq 4).

Based on the above results, a plausible mechanism is proposed (Scheme 3). Electrophilic activation of DMSO by HCl generates sulfonium salt **I**, which undergoes base-assisted elimination of water to produce (thiomethyl)methyl carbenium ion **IIa**. Interchangeable formation of chloromethyl methyl sulfide (**IIb**) may also be operative. **IIa/b** reacts with the starting amine to ultimately generate iminium ion **V** from ammonium salt **IV** via proton transfer (P.T.) and elimination of methyl mercaptan. A 6-endo-trig cyclization[24] followed by nucleophilic addition of chloride ion gives the desired product.

Conclusion

In summary, we have developed a convenient protic acid-catalyzed formation of (thiomethyl)methyl carbenium ion from DMSO under mild conditions. In the presence of homoallylic amines, the *in situ*-generated species reacts in aza-Pummerer fashion to generate an iminium ion intermediate that cyclizes to form 4-chloropiperidines in good yield. The method applies to both aromatic and aliphatic amines. The use of HCl•DMPU as protic acid, non-nucleophilic base and chloride source provides an environmentally benign process for piperidine formation. The reaction has a broad substrate scope and is scalable.

Experimental Section

1. General—^{1}H and ^{13}C (^{1}H) decoupled NMR spectra were recorded either at 400 MHz or 500 MHz, and 101 MHz using $CDCl_3$ or CD_2Cl_2 as a solvent. The chemical shifts are reported in δ (ppm) values (^{1}H and ^{13}C NMR relative to $CHCl_3$, δ 7.26 ppm for 1H NMR and δ 77.0 ppm for ^{13}C NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants (*J*), are reported in Hertz (Hz). The HRMS data was obtained from an Agilent Technologies QTOF spectrometer. All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was developed on silica gel 60 F254 aluminum sheets.

2. General procedures

2.1 Procedure for generation of HCl/DMPU: The reagent HCl•DMPU was prepared as reported in the literature.[12a, b]

2.2 General procedure for the preparation of homoallylic amines, 1 and 3[25].: To a round-bottomed flask equipped with a stirring bar was charged with aryl or alkylamine **1 or 3** (1.2 mmol, 1.2 equiv), K_2CO_3 (2 mmol, 2 equiv) and dry DMF (3 mL). Homoallyl bromide (1 mmol, 1 equiv) was slowly added to the mixture and heated to 110 °C. We monitored the progress of the reaction by GC-MS or TLC. Upon completion, the reaction

mixture was cooled to room temperature and water (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, concentrated and eventually purified silica gel column chromatography with hexanes/ethyl acetate (typically 70/30) or petroleum ether/ethyl acetate (80/20 for **1v**, **1x**, **1y**, **1af**, **1ag**, and **3c**) as eluent.

N-(but-3-en-1-yl)aniline **(1a)** Light yellow oil, 89.8 mg, 61% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.19 (t, *J* = 7.9 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 2H), 5.85–5.79 (m, 1H), 5.21 – 5.07 (m, 2H), 3.63 (s, 1H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.40 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 136.0, 129.4, 117.6, 117.3, 113.1, 43.0, 33.8.

N-(but-3-en-1-yl)-4-methylaniline **(1b)** Colorless oil, 103.2 mg, 64% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.00 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 5.87– 5.78 (m, 1H), 5.17 – 5.10 (m, 2H), 3.52 (s, 1H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.38 (q, *J* = 6.7 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 146.1, 136.0, 129.8, 126.7, 117.1, 113.2, 43.3, 33.8, 20.5.

N-(but-3-en-1-yl)-3-methylaniline **(1c)** Colorless oil, 109.8 mg, 68% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 7.7 Hz, 2H), 5.86 – 5.78 (m, 1H), 5.17 – 5.10 (m, 2H), 3.60 (s, 1H), 3.18 (t, *J* = 6.7 Hz, 2H), 2.42 – 2.32 (m, 2H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.2, 138.9, 135.7, 129.0, 118.2, 116.9, 113.6, 109.9, 42.7, 33.6, 21.5.

N-(but-3-en-1-yl)-4-fluoroaniline **(1d)** Colorless oil, 94.1 mg, 57% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.88 (t, *J* = 8.8 Hz, 2H), 6.54 (dd, *J* = 9.0, 4.4 Hz, 2H), 5.85 – 5.76 (m, 1H), 5.17 – 5.10 (m, 2H), 3.54 (s, 1H), 3.14 (t, *J* = 6.7 Hz, 2H), 2.37 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 156.8, 144.6, 135.7, 117.2, 115.7, 115.6, 113.7, 43.5, 33.6. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −128.35.

N-(but-3-en-1-yl)-4-chloroaniline **(1e)** Colorless oil, 116.2 mg, 63% yield. **1H NMR (500 MHz, $CDCl_3$)** δ 7.11(d, *J* = 7.8, 2H), 6.53 (d, *J* = 7.9, 2H), 5.81 – 5.77 (m, 1H), 5.15 – 5.10 (m, 2H), 3.66 (s, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.37 (q, *J* = 6.7, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.8, 135.5, 129.0, 121.9, 117.3, 113.9, 42.9, 33.5.

4-bromo-N-(but-3-en-1-yl)aniline **(1f)** Colorless oil, 146.9 mg, 65% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 5.97 – 5.88 (m, 1H), 5.29 – 5.23 (m, 2H), 3.80 (s, 1H), 3.27 (t, *J* = 6.7 Hz, 2H), 2.50 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.3, 135.6, 132.0, 117.4, 114.5, 108.9, 42.9, 33.5.

N-(but-3-en-1-yl)-3-iodoaniline **(1g)** Colorless oil, 128.2 mg, 47% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.02 (d, J = 7.7 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.88 (t, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.2, 2.2 Hz, 1H), 5.82 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H), 5.29 – 4.97 (m, 2H), 3.69 (s, 1H), 3.16 (dd, J = 11.9, 6.4 Hz, 2H), 2.39 (dt, J = 7.9, 6.1 Hz, 2H). **^{13}C NMR (126 MHz, CDCl3)** δ 149.4, 135.4, 130.6, 126.1, 121.3, 117.4, 112.2, 95.3, 42.5, 33.4.

3-bromo-N-(but-3-en-1-yl)aniline **(1h)** Colorless oil, 115.3 mg, 51% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.02 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.1 Hz, 1H), 6.75 (d, *J* = 1.7 Hz, 1H),

6.52 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.75–5.63 (m, 1H), 5.15 (t, *J* = 13.2 Hz, 2H), 3.74 (s, 1H), 3.17 (dd, *J* = 12.2, 6.4 Hz, 2H), 2.39 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.5, 135.4, 130.5, 123.3, 120.0, 117.4, 115.3, 111.6, 42.6, 33.4.

N-(but-3-en-1-yl)-2-iodo-4-methylaniline **(1i)** Colorless oil, 206.7 mg, 72 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 1.7 Hz, 1H), 7.02 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.05 (s, 1H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.43 (q, *J* = 6.8 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.9, 139.1, 135.3, 129.8, 127.8, 117.3, 110.5, 85.3, 43.3, 33.3, 19.6.

N-(but-3-en-1-yl)-4-(trifluoromethyl)aniline **(1j)** Colorless oil, 124.7 mg, 58% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 - 7.30 (m, 2H), 6.68 (d, J = 8.3 Hz, 2H), 6.59 (d, J = 8.5 Hz, 2H), 5.81 (dd, J = 17.1, 10.2 Hz, 2H), 5.14 (dd, J = 12.7, 11.0 Hz, 3H), 3.97 (s, 3H), 3.21 (t, J = 6.7 Hz, 3H), 2.39 (d, J = 6.7 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.4, 135.2, 126.6, 126.5, 117.4, 112.0, 42.4, 33.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −61.02.

N-(but-3-en-1-yl)-4-methoxyaniline **(1k)** Colorless oil, 108.1 mg, 61% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.80 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 5.87 – 5.80 (m, 1H), 5.19 – 5.07 (m, 2H), 3.75 (s, 3H), 3.32 (s, 1H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.38 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 152.2, 142.6, 136.0, 117.1, 115.0, 114.3, 55.8, 43.9, 33.8.

4-(but-3-en-1-ylamino)benzonitrile **(1l)** Colorless oil, 86 mg, 50% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.20 – 5.08 (m, 2H), 4.24 (s, 1H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.39 (q, *J* = 6.7, 2H). **13C NMR (100 MHz, $CDCl_3$)** δ 151.2, 135.0, 133.7, 120.5, 117.7, 112.2, 98.6, 42.0, 33.2.

N-(but-3-en-1-yl)-4-(trifluoromethoxy)aniline **(1m)** Colorless oil, 111 mg, 48% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.03 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 9.0 Hz, 2H), 5.87 – 5.78 (m, 1H), 5.25 – 5.14 (m, 2H), 3.78 (s, 1H), 3.21 (t, *J* = 6.7 Hz, 2H), 2.43 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 146.9, 140.3, 135.4, 124.5, 122.3, 121.9, 120.7 (q, *J* = 257 Hz), 119.4, 117.2, 116.8, 112.9, 42.8, 33.4. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −58.31.

N-(but-3-en-1-yl)-4-nitroaniline **(1n)** Yellow solid, 38.4 mg, 20% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 9.2 Hz, 2H), 6.53 (d, *J* = 9.2 Hz, 2H), 5.87– 5.77 (m, 1H), 5.26 –5.11 (m, 2H), 4.50 (s, 1H), 3.29 (dd, *J* = 12.1, 6.6 Hz, 2H), 2.43 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 153.3, 138.2, 134.9, 126.6, 118.2, 111.2, 42.3, 33.3.

N-(but-3-en-1-yl)-2-(trifluoromethyl)aniline **(1o)** Colorless oil, 131.3 mg, 61% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 - 7.19 (m, 2H), 6.95 – 6.62 (m, 2H), 5.92–5.80 (m, 1H), 5.69 – 5.02 (m, 2H), 4.55 (s, 1H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.59 (ddd, *J* = 6.7, 6.2, 1.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.8, 135.2, 133.2, 126.8, 126.7, 124.0, 117.7, 115.9, 111.9, 42.5, 33.4. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −62.44.

N-(but-3-en-1-yl)-3,5-bis(trifluoromethyl)aniline **(1p)** Colorless oil, 113.3 mg, 40% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.04 (s, 1H), 6.83 (s, 2H), 5.72 (td, *J* = 16.8, 6.6 Hz, 1H), 5.16 - 5.03 (m, 2H), 4.01 (s, 1H), 3.14 (dd, *J* = 12.1, 6.3 Hz, 2H), 2.33 (q, *J* = 6.7 Hz, 2H),

1.45 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.3, 134.5, 124.5, 121.8, 117.5, 111.4, 109.7, 41.9, 32.8. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −63.54.

N-(but-3-en-1-yl)-3-(trifluoromethyl)aniline **(1q)** Colorless oil, 116.2 mg, 54% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 (dd, *J* = 9.2, 6.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.87 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.44 – 4.88 (m, 2H), 3.91 (s, 1H), 3.26 (s, 2H), 2.57 – 2.29 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 135.4, 131.7, 131.4, 129.6, 125.7, 123.0, 117.5, 115.8, 113.7, 113.7, 108.9, 108.9, 42.5, 33.4. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −62.90.

N-(but-3-en-1-yl)-[1,1'-biphenyl]-4-amine **(1r)** Colorless oil, 160.8 mg, 72% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.20 – 7.10 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 5.86 – 5.61 (m, 1H), 5.03 (t, *J* = 14.5 Hz, 2H), 3.63 (s, 1H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.29 (q, *J* = 6.6 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.5, 141.1, 135.6, 130.1, 128.5, 127.8, 126.1, 125.9, 117.0, 113.0, 42.7, 33.5.

N-(but-3-en-1-yl)-[1,1'-biphenyl]-2-amine **(1s)** Colorless oil , 133.9 mg, 60% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 – 7.31 (m, 5H), 7.28 – 7.21 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.73 – 6.68 (m, 1H), 5.94 – 5.50 (m, 1H), 5.00 (dd, *J* = 8.6, 6.5 Hz, 2H), 3.99 (s, 1H), 3.18 (dd, *J* = 11.8, 6.4 Hz, 2H), 2.32 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 145.0, 139.4, 135.6, 130.1, 129.4, 128.8, 128.7, 127.7, 127.1, 117.0, 116.8, 110.4, 42.8, 33.5.

1-(4-(but-3-en-1-ylamino)phenyl)ethanone **(1t)** Colourless oil, 125.1 mg, 66% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 5.78 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.20 – 5.02 (m, 2H), 4.19 (s, 1H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.46 (s, 3H), 2.37 (dtd, *J* = 6.8, 5.5, 1.3 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 196.1, 151.8, 134.9, 130.6, 126.5, 117.4, 111.2, 41.9, 33.1, 25.8.

(3-(but-3-en-1-ylamino)phenyl)(phenyl)methanone **(1u)** Light yellow solid, 158.3 mg, 63% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.06 (d, *J* = 6.5 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.77–5.66 (m, 1H), 5.14 (t, *J* = 13.2 Hz, 2H), 3.81 (s, 1H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.46 - 2.31 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.2, 148.2, 138.6, 137.9, 135.5, 132.2, 130.0, 128.9, 128.1, 119.6, 117.4, 116.9, 113.5, 42.7, 33.5.

N-(but-3-en-1-yl)benzo[d][1,3]dioxol-5-amine **(1v)** Colorless oil, 86.0 mg, 45% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.67 (d, *J* = 8.3 Hz, 1H), 6.26 (s, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 5.97 – 5.74 (m, 3H), 5.10–5.01 (m, 2H), 3.45 (s, 1H), 3.13 (td, *J* = 6.7, 1.4 Hz, 2H), 2.44 - 2.31 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 148.3, 144.1, 139.6, 135.7, 117.1, 108.6, 104.5, 100.5, 96.1, 43.8, 33.6.

methyl 3-(but-3-en-1-ylamino)thiophene-2-carboxylate **(1w)** colorless liquid, 109.8 mg, 52% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.33 (d, *J* = 5.5 Hz, 1H), 6.76 (s, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 5.86 –5.79 (m, 1H), 5.18 – 5.11 (m, 2H), 3.81 (s, 3H), 3.34 (d, *J* = 2.7 Hz,

2H), 2.50 – 2.28 (m, 2H).. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.4, 156.1, 135.1, 132.2, 117.4, 116.2, 98.5, 51.1, 44.4, 34.3.

N-(but-3-en-1-yl)-6-chloropyridin-3-amine **(1x)** Colorless oil, 98.6 mg, 44% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6, 1H), 5.76–5.64 (m, 1H), 5.16 (dd, *J* = 13.3, 6.3 Hz, 2H), 3.74 (s, 1H), 3.18 (dd, *J* = 12.5, 6.4 Hz, 2H), 2.40 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 139.0, 135.0, 134.5, 124.0, 122.2, 117.7, 42.5, 33.3.

N-(but-3-en-1-yl)-4-chloropyridin-2-amine **(1y)** Colorless oil, 122.2 mg, 67% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.03 (s, 1H), 7.36 (d, *J* = 8.8, 1H), 6.33 (d, *J* = 8.9 Hz, 1H), 5.93 – 5.69 (m, 1H), 5.34 – 4.99 (m, 2H), 4.53 (s, 1H), 3.41 – 3.27 (m, 2H), 2.38 (dt, *J* = 6.6, 5.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.4, 138.8, 135.1, 134.5, 124.1, 122.3, 117.7, 42.6, 33.4.

N-(but-3-en-1-yl)-5-chloropyrazin-2-amine **(1z)** Colorless oil, 117.4 mg, 64% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 5.76–5.65 (m, 1H), 5.32 – 4.98 (m, 2H), 4.68 (s, 1H), 3.40 (dd, *J* = 12.4, 6.6 Hz, 2H), 2.40 (q, *J* = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 153.3, 141.2, 136.0, 135.0, 129.9, 117.7, 40.7, 33.4.

N-(but-3-en-1-yl)-4-methylbenzenesulfonamide **(1aa)** white solid, 168.8 mg, 75% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.62 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.04 (t, *J* = 12.6 Hz, 2H), 4.61 (bs, 1H), 3.00 (q, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.19 (q, *J* = 6.8 Hz, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 136.7, 134.0, 129.5, 126.9, 117.9, 77.1, 76.8, 76.5, 41.9, 33.4, 21.3.

N-(but-3-en-1-yl)-4-methoxybenzenesulfonamide **(1ab)** white solid, 173.6 mg, 72% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.72 - 5.39 (m, 1H), 5.13 – 4.78 (m, 2H), 4.65 (d, *J* = 6.0 Hz, 1H), 3.80 (d, *J* = 0.6 Hz, 3H), 3.07 – 2.71 (m, 2H), 2.13 (q, *J* = 6.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.8, 134.1, 131.4, 129.1, 117.9, 114.2, 55.6, 42.0, 33.5.

4-bromo-N-(but-3-en-1-yl)benzenesulfonamide **(1ac)** white solid , 220.4 mg, 76% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 – 7.69 (m, 2H), 7.68 – 7.62 (m, 2H), 5.58–5.46 (m, 1H), 5.16 - 4.95 (m, 2H), 4.90 (s, 1H), 3.03 (dd, *J* = 12.9, 6.7 Hz, 2H), 2.22 (qt, *J* = 6.8, 1.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.0, 133.9, 132.3, 128.6, 127.5, 118.2, 42.1, 33.6.

N-(but-3-en-1-yl)-2-ethylhexan-1-amine **(1ad)** light yellow oil, 69.6 mg, 38% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.78 (m, *J* = 13.7, 10.2, 5.1 Hz, 1H), 5.18 - 4.93 (m, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.49 (d, *J* = 6.2 Hz, 2H), 2.32 - 2.13 (m, 2H), 1.52 – 1.36 (m, 1H), 1.35 - 1.20 (m, 7H), 0.88 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 136.6, 116.1, 53.1, 49.2, 39.4, 34.3, 31.4, 29.0, 24.5, 23.1, 14.1, 10.8.

N-phenethylbut-3-en-1-amine **(1ae)** light yellow oil, 105.2 mg, 60% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 – 7.33 (m, 5H), 5.99 – 5.90 (m, 1H), 5.30 – 5.15 (m, 2H), 3.13 – 3.05 (m, 2H), 3.03 – 2.97 (m, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.44 (q, *J* = 6.9 Hz, 2H), 1.31 (s, 1H)..

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 136.5, 128.8, 128.5, 126.2, 116.4, 51.2, 48.9, 36.5, 34.4.

N-(4-methoxyphenethyl)but-3-en-1-amine **(1af**) light yellow oil, 127.2 mg, 62% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.79 – 5.67 (m, 1H), 5.25 – 4.97 (m, 2H), 3.87 (s, 2H), 2.98 – 2.90 (m, 2H), 2.86 – 2.74 (m, 2H), 2.32 (q, *J* = 6.9 Hz, 2H), 1.83 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.1, 136.4, 132.1, 129.7, 116.4, 113.9, 55.3, 51.3, 48.8, 35.5, 34.3.

N-benzylbut-3-en-1-amine **(1ag)** light yellow oil, 107.9 mg, 67% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.39 – 7.19 (m, 5H), 5.84 – 5.74 (m, 1H), 5.16 – 4.98 (m, 2H), 3.79 (s, 2H), 2.70 (t, *J*=6.8, 2H), 2.28 (dt, *J*=6.9, 6.2, 2H), 1.29 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 140.4, 136.5, 128.4, 128.1, 126.9, 116.3, 53.9, 48.3, 34.3.

(R)-N-(1-phenylethyl)but-3-en-1-amine **(1ah)** light yellow oil, 129.6 mg, 74% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 – 6.33 (m, 5H), 5.69 – 5.58 (m, 1H), 5.31 – 4.69 (m, 2H), 3.76 (q, *J* = 6.6 Hz, 1H), 2.72 – 2.36 (m, 2H), 2.29 – 2.07 (m, 2H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.27 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.7, 136.5, 128.4, 126.8, 126.5, 116.2, 58.2, 46.5, 34.3, 24.3.

N-(3-methylbut-3-en-1-yl)aniline **(3a)** light yellow oil, 106.4 mg, 66% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.19 (t, *J* = 7.6 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 2H), 4.87 (s, 1H), 4.81 (s, 1H), 3.65 (s, 1H), 3.23 (t, *J* = 6.7 Hz, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 1.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.3, 142.9, 129.2, 117.3, 112.8, 112.3, 41.3, 37.4, 21.9.

N-(3-bromobut-3-en-1-yl)aniline **(3b)** light yellow oil, 144.6 mg, 64% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 – 7.17 (m, 2H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 - 6.58 (m, 2H), 5.75 – 5.63 (m, 1H), 5.55 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 147.6, 131.3, 129.3, 118.9, 117.7, 113.0, 41.6, 40.9.

N-(2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)aniline **(3c)** colorless liquid, 139.9 mg, 58% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 – 7.11 (m, 2H), 6.72 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.65 – 6.55 (m, 2H), 5.37 (dt, *J* = 4.2, 1.3 Hz, 1H), 3.66 (s, 1H), 3.27 – 2.93 (m, 2H), 2.41 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.36 – 2.24 (m, 4H), 2.17 – 1.99 (m, 2H), 1.41 – 1.22 (m, 5H), 0.93 – 0.81 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 145.6, 129.2, 118.7, 117.2, 112.9, 45.4, 41.2, 40.8, 38.0, 36.5, 31.8, 31.4, 26.3, 22.7, 21.2, 14.2.

(E)-N-(pent-3-en-1-yl)aniline **(3d**) light yellow liquid, 111.2 mg, 69% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.18 (t, *J* = 7.9 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 5.54–5.44 (m, 1H), 5.50 – 5.37 (m, 1H), 3.65 (s, 1H), 3.13 (t, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 6.7 Hz, 2H), 1.70 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 129.2, 128.2, 127.7, 117.2, 112.8, 43.3, 32.4, 18.0.

N-(4-methylpent-3-en-1-yl)aniline **(3e)** light yellow oil, 114 mg, 65% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 (t, *J* = 7.7 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H),

5.28 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.44 (d, *J* = 7.0 Hz, 2H), 1.86 (s, 3H), 1.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.5, 134.4, 129.3, 121.4, 117.3, 113.0, 43.9, 28.2, 25.9, 18.0.

2.3 Procedure for the synthesis of 4-chloropiperidines, 2 and 4.: A glass vial equipped with a screw cap and a stirring bar was charged with alkene **1** (0.5 mmol). Then ethyl acetate was added (2.5 mL) followed by DMSO (2.4 mmol) and HCl/DMPU (102 μL, 2.4 mmol). We stirred the reaction mixture at 65 °C and monitored the progress of the reaction by GC-MS or TLC. Upon completion, the reaction mixture was quenched with water and extracted with DCM. The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated. We purified the crude product by silica gel column chromatography (hexanes/ethyl acetate typically 97/3).

4-chloro-1-phenylpiperidine **(2a)** Colorless oil, 92.6 mg, 95% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.23 (t, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 4.25 – 4.14 (m, 1H), 3.54 – 3.45 (m, 2H), 3.07 – 2.97 (m, 2H), 2.25 – 2.15 (m, 2H), 2.03 – 1.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.1, 129.2, 119.8, 116.6, 57.2, 47.5, 35.1. **HRMS (EI+)** calcd. for [$C_{11}H_{14}NCl$] (MH+) 196.1044; found 196.1041.

4-chloro-1-(p-tolyl)piperidine **(2b)** Colorless oil, 89.1 mg, 85% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.05 (d, *J*=7.7, 2H), 6.83 (d, *J*=7.5, 2H), 4.16 (*bs*, 1H), 3.42 – 3.44 (m, 2H), 2.99 – 2.95 (m, 2H), 2.29 – 2.12 (m, 5H), 2.00 – 1.98 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.0, 129.6, 129.3, 116.9, 57.1, 48.1, 35.2, 20.4. **HRMS (EI+)** calcd. for [C H NCl] (MH^+) 210.1044; found 210.1042.

4-chloro-1-(m-tolyl)piperidine **(2c)** Colorless oil, 97.5 mg, 93% yield. **1H NMR (400 MHz, $CDCl_3$)** δ 7.16 (t, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 7.4 Hz, 1H), 4.23 – 4.17 (m, 1H), 3.55 – 3.47 (m, 2H), 3.09 – 2.99 (m, 2H), 2.32 (s, 3H), 2.26 – 2.17 (m, 2H), 2.06 – 1.95 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.1, 138.9, 129.0, 120.8, 117.5, 113.7, 57.2, 47.7, 35.1, 21.8. **HRMS (EI+)** calcd. for [$C_{12}H_{17}NCl$] (MH+) 210.1044; found 210.1042.

4-chloro-1-(4-fluorophenyl)piperidine **(2d)** Colorless oil, 89.5 mg, 84% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.01 – 6.84 (m, 4H), 4.19 (tt, *J* = 8.0, 3.9 Hz, 1H), 3.45 – 3.31 (m, 2H), 3.02 – 2.93 (m, 2H), 2.22 (dtd, *J* = 10.4, 7.0, 3.6 Hz, 2H), 2.09 – 1.95 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.3, 155.9, 147.7, 118.4, 115.5, 115.3, 56.7, 48.3, 35.0. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −124.31 (s, 1H). **HRMS (EI+)** calcd. for [$C_{11}H_{13}ClFN$] (M^+) 213.0719; found 213.0714.

4-chloro-1-(4-chlorophenyl)piperidine **(2e)** Colorless oil, 104.7 mg, 91 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.21 (tt, *J* = 7.6, 3.7 Hz, 1H), 3.52 – 3.35 (m, 2H), 3.13 – 2.97 (m, 2H), 2.27 – 2.11 (m, 2H), 2.06 – 1.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.6, 129.0, 124.6, 117.7, 56.8, 47.4, 34.8. **HRMS (EI+)** calcd. for [$C_{11}H_{14}NCl_2$] (MH^+) 230.0498; found 230.0496.

1-(4-bromophenyl)-4-chloropiperidine **(2f)** Colorless oil, 109.9 mg, 80% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.21 (tt, *J* = 7.8, 3.9 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.12 – 2.94 (m, 2H), 2.20 (dtd, *J* = 10.5, 7.0, 3.6 Hz, 2H), 2.06 – 1.94 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.0, 131.9, 129.1, 118.1, 56.8, 47.2, 34.7. **HRMS (EI+)** calcd. for [$C_{11}H_{14}NBrCl$] (MH^+) 273.9993; found 273.9989.

4-chloro-1-(3-iodophenyl)piperidine **(2g)** Colorless oil, 112.3 mg, 70% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 – 7.23 (m, 1H), 7.18 – 7.13 (m, 1H), 6.98 – 6.93 (m, 1H), 6.87 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 4.21 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.12 – 3.01 (m, 2H), 2.18 (ddd, *J* = 13.1, 6.8, 3.3 Hz, 2H), 2.03 – 1.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$** δ 152.1, 130.5, 128.4, 125.2, 115.6, 95.2, 56.8, 46.9, 34.7. **HRMS (EI+)** calcd. for [$C_{11}H_{13}ClIN$] (M^+) 320.9781; found 320.9775.

1-(3-bromophenyl)-4-chloropiperidine **(2h)** Colorless oil, 137 mg, 86% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.11 (t, *J*=8.1, 1H), 7.05 (t, *J*=2.1, 1H), 6.96 (ddd, *J*=7.8, 1.8, 0.8, 1H), 6.87 – 6.81 (m, 1H), 4.22 (tt, *J*=7.8, 3.8, 1H), 3.57 – 3.45 (m, 2H), 3.15 – 3.04 (m, 2H), 2.25 – 2.15 (m, 2H), 2.05 – 1.93 (m,2H). **^{13}C NMR (100 MHz $CDCl_3$)** δ 152.2, 130.4, 123.2, 122.2, 119.1, 114.8, 56.8, 46.8, 34.6. **HRMS (EI+)** calcd. For [$C_8H_{14}NBrClF_2$] (MH^+) 275.9970; found 275.9969.

4-chloro-1-(2-iodo-4-methylphenyl)piperidine **(2i)** Colorless oil, 106.5 mg, 81% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.28 – 4.28 (m, 1H), 3.64 – 3.53 (m, 2H), 3.25 – 3.15 (m, 2H), 2.23 – 2.17 (m, 2H), 2.04 – 1.91 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 152.7, 129.0, 126.4, 125.9, 125.6, 123.2, 120.5, 114.8, 58.6, 45.9, 34.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −61.35. **HRMS (EI+)** calcd. for [C H ClF N] (M^+) 263.0691; found 263.0686.

4-chloro-1-(4-(trifluoromethyl)phenyl)piperidine **(2j)** Colorless oil, 106.5 mg, 81% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.28 – 4.28 (m, 1H), 3.64 – 3.53 (m, 2H), 3.25 – 3.15 (m, 2H), 2.23 – 2.17 (m, 2H), 2.04 – 1.91 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 152.7, 129.0, 126.4, 125.9, 125.6, 123.2, 120.5, 114.8, 58.6, 45.9, 34.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −61.35. **HRMS (EI+)** calcd. for [$C_{12}H_{13}ClF_3N$] (M^+) 263.0691; found 263.0686.

4-chloro-1-(4-methoxyphenyl)piperidine **(2k)** Colorless oil, 101.5 mg, 90% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 6.93 (d, *J*=9.0, 2H), 6.85 (d, *J*=8.9, 2H), 4.24 – 4.12 (m, 1H), 3.79 (s, 3H), 3.46 – 3.34 (m, 2H), 3.00 – 2.90 (m, 2H), 2.22 (s, 2H), 2.12 – 2.00 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 153.9, 145.6, 118.8, 114.4, 57.1, 55.5, 49.1, 35.4. **HRMS (EI +)** calcd. for [$C_{12}H_{17}ONCl$] (MH+) 226.0993; found 226.0990.

4-(4-chloropiperidin-1-yl)benzonitrile **(2l)** Colorless oil, 79.4 mg, 72% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.31 – 4.26 (m, 1H), 3.69 – 3.57 (m, 2H), 3.32 – 3.26 (m, 2H), 2.21 – 2.14 (m, 2H), 2.00 – 1.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 152.7, 133.4, 119.8, 114.3, 100.0, 56.3, 44.9, 34.1. **HRMS (EI+)** calcd. for [$C_{12}H_{14}N_2Cl$] (MH^+) 221.0840; found 221.0837.

4-chloro-1-(4-(trifluoromethoxy)phenyl)piperidine **(2m)** Colorless oil, 126 mg, 90 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.11 (d, *J*=8.7, 2H), 6.90 (d, *J*=8.9, 2H), 4.22 (dt, *J*=11.7, 3.8, 1H), 3.53 – 3.44 (m, 2H), 3.13 – 3.03 (m, 2H), 2.21 (dd, *J*=14.6, 11.6, 2H), 2.06 – 1.96 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.7, 141.9, 124.2, 121.8, 121.6, 119.2, 117.1, 116.8, 114.4, 56.6, 47.3, 34.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ = −58.32. **HRMS (EI+)** calcd. for [$C_{12}H_{14}ONClF_3$] (MH+) 280.0711; found 280.0708.

4-chloro-1-(4-nitrophenyl)piperidine **(2n)** Yellow solid, 72.0 mg, 60% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 9.4 Hz, 2H), 6.82 (d, *J* = 9.4 Hz, 2H), 4.32 (dq, *J* = 10.8, 3.7 Hz, 1H), 3.78 – 3.65 (m, 2H), 3.40 (ddd, *J* = 11.5, 7.3, 3.6 Hz, 2H), 2.26 – 2.11 (m, 2H), 2.01 – 1.93 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.4, 138.4, 126.1, 112.9, 56.3, 44.9, 34.3. **HRMS (EI+)** calcd. for [$C_{11}H_{13}ClN_2O_2$] (M+) 240.0669; found 240.0664.

4-chloro-1-(2-(trifluoromethyl)phenyl)piperidine **(2o)** Colorless oil, 105.4 mg, 80% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 4.23 (bs, 1H), 3.21 – 3.02 (m, 2H), 2.81 (ddd, *J* = 11.2, 7.7, 3.2 Hz, 2H), 2.21 (ddd, *J* = 13.5, 6.9, 3.4 Hz, 2H), 2.09 – 1.97 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 152.8, 132.9, 128.2, 127.3, 125.5, 125.0, 124.2, 122.8, 120.1, 57.4, 51.4, 35.9. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −60.5, −62.21 (side product). **HRMS (EI+)** calcd. for [$C_{12}H_{14}NClF_3$] (MH+) 264.0761; found 264.0758.

1-(3,5-bis(trifluoromethyl)phenyl)-4-chloropiperidine **(2p)** Colorless oil, 149.2 mg, 90% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 –7.21 (m, 3H), 4.28 (tt, *J*=7.4, 3.7, 1H), 3.64 – 3.55 (m, 2H), 3.29 – 3.19 (m, 2H), 2.22 (ddt, *J*=14.3, 7.4, 3.6, 2H), 2.06 – 1.96 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.3, 132.8, 132.5, 132.2, 131.8, 127.5, 124.8, 122.1, 119.4, 115.0, 112.0, 56.0, 46.0, 34.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ = - 63.10. **HRMS (EI+)** calcd. for [$C_{13}H_{13}NClF_6$] (MH+) 332.0635; found 332.0632.

4-chloro-1-(3-(trifluoromethyl)phenyl)piperidine **(2q)** Colorless oil, 95 mg, 72% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (t, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.24 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.60 – 3.48 (m, 2H), 3.20 – 3.08 (m, 2H), 2.29 – 2.15 (m, 2H), 2.07 – 1.94 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.1, 131.9, 131.6, 131.3, 131.0, 130.0, 125.6, 122.9, 119.2, 115.8, 112.6, 56.6, 46.8, 34.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ −62.83. **HRMS (EI+)** calcd. for [$C_{12}H_{14}NClF_3$] (MH+) 264.0761; found 264.0760.

1-([1,1'-biphenyl]-4-yl)-4-chloropiperidine **(2r)** White solid, 111.4 mg, 82% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 14.7, 7.2 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.16 – 4.10 (m, 1H), 3.51 – 3.43 (m, 2H), 3.08 – 2.97 (m, 2H), 2.19 – 2.08 (m, 2H), 1.99 – 1.87 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.1, 140.7, 132.2, 128.6, 127.7, 126.4, 126.4, 116.5, 57.0, 47.3, 34.8. **HRMS (EI+)** calcd. for [$C_{17}H_{19}NCl$] (MH+) 272.1201; found 272.1200.

1-([1,1'-biphenyl]-2-yl)-4-chloropiperidine **(2s)** Colorless oil, 114.1 mg, 84% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.60 (m, 2H), 7.42 (dd, *J*=10.5, 4.7, 2H), 7.34 – 7.24 (m, 3H), 7.08 (ddd, *J*=11.9, 9.2, 4.6, 2H), 4.13 – 3.97 (m, 1H), 3.18 – 3.07 (m, 2H), 2.70 (ddd, *J*=11.8, 8.8, 2.9, 2H), 2.01 – 1.93 (m, 2H), 1.86 – 1.71 (m, 2H**). ^{13}C NMR (100 MHz,**

$CDCl_3$) δ 150.2, 141.0, 135.1, 131.3, 128.6, 128.1, 126.7, 122.7, 118.5, 57.3, 49.4, 35.6. **HRMS (EI+)** calcd. for [$C_{17}H_{19}NCl$] (MH+) 272.1201; found 272.1199.

1-(4-(4-chloropiperidin-1-yl)phenyl)ethanone **(2t)** Colorless oil, 97.4 mg, 82% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J*=9.0, 2H), 6.87 (d, *J*=9.0, 2H), 4.28 (tt, *J*=7.6, 3.8, 1H), 3.68 (ddd, *J*=12.8, 7.3, 3.6, 2H), 3.29 (ddd, *J*=13.2, 7.8, 3.5, 2H), 2.52 (s, 3H), 2.05-1.95 (m, 2H), 1.96 (dtd, *J*=11.3, 7.7, 3.6, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.4, 153.6, 130.4, 127.5, 113.6, 56.7, 45.3, 34.4, 26.1. **HRMS (EI+)** calcd. For [$C_{13}H_{17}ONCl$] (MH+) 238.0993; found 238.0991.

(3-(4-chloropiperidin-1-yl)phenyl)(phenyl)methanone **(2u)** Colorless liquid, 111 mg, 74 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (s, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 14.1, 7.7 Hz, 2H), 4.23 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.19 – 3.09 (m, 2H), 2.21 (bs, 2H), 2.07 – 1.96 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.9, 150.8, 138.4, 137.6, 132.3, 130.0, 128.8, 128.1, 121.7, 120.4, 117.1, 56.7, 47.0, 34.7. **HRMS (EI+)** calcd. for [$C_{18}H_{19}ONCl$] (MH+) 300.1150; found 300.1150.

1-(benzo[d][1,3]dioxol-5-yl)-4-chloropiperidine **(2v)** Yellow liquid, 81.3 mg, 68 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.90 (s, 2H), 4.17 (td, *J* = 8.0, 4.0 Hz, 1H), 3.40 – 3.27 (m, 2H), 2.92 (ddd, *J* = 12.0, 8.4, 3.4 Hz, 2H), 2.20 (dd, *J* = 16.4, 3.5 Hz, 2H), 2.08 – 1.94 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 110.0, 109.7, 108.1, 100.9, 100.5, 84.4, 57.0, 49.2, 35.3. **HRMS (EI +)** calcd. for [$C_{12}H_{14}O_2NCl$] (MH+) 239.0713; found 239.0707.

methyl 3-(4-chloropiperidin-1-yl)thiophene-2-carboxylate **(2w)** Pale yellow oil, 80.3 mg, 62 % yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 5.4 Hz, 1H), 6.84 (d, *J* = 5.4 Hz, 1H), 4.37 – 4.19 (m, 1H), 3.84 (s, 3H), 3.57 – 3.45 (m, 2H), 3.23 – 3.11 (m, 2H), 2.28 (ddd, *J* = 13.9, 7.4, 3.9 Hz, 2H), 2.12 – 1.98 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.1, 157.6, 156.7, 131.1, 121.0, 56.9, 51.6, 49.8, 35.2. **HRMS (EI+)** calcd. for [$C_{11}H_{14}O_2NClS$] (M+) 259.0434; found 259.0430.

2-chloro-5-(4-chloropiperidin-1-yl)pyridine **(2x)** Yellow liquid, 91.3 mg, 79 % yield. **1H NMR (400 MHz, $CDCl_3$)** δ 8.15 – 8.03 (m, 1H), 7.41 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 4.27 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.87 (ddd, *J* = 13.0, 7.1, 3.7 Hz, 2H), 3.41 (ddd, *J* = 13.3, 8.1, 3.5 Hz, 2H), 2.20 – 2.08 (m, 2H), 1.96 – 1.82 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.3, 146.3, 137.2, 120.0, 107.8, 57.2, 43.2, 34.4. **HRMS (EI+)** calcd. for [$C_{10}H_{13}N_2Cl_2$] (MH+) 231.0450; found 231.0447.

4-chloro-2-(4-chloropiperidin-1-yl)pyridine **(2y)** Colorless oil, 87.4 mg, 76% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (d, *J*=1.5, 1H), 7.31 (s, 1H), 7.25 – 7.19 (m, 1H), 4.29 (tt, *J*=7.5, 3.8, 1H), 3.58 – 3.47 (m, 2H), 3.23 – 3.12 (m, 2H), 2.26 (ddt, *J*=14.2, 7.3, 3.6, 2H), 2.11 – 2.00 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 146.0, 141.3, 137.9, 126.2, 124.0, 56.2, 46.5, 34.4. **HRMS (EI+)** calcd. for [$C_{10}H_{12}Cl_2N_2$] (M+) 230.0382; found 230.0378.

2-chloro-5-(4-chloropiperidin-1-yl)pyrazine **(2z)** Brown oil, 91.7 mg, 79% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (s, 1H), 7.88 (s, 1H), 4.34 – 4.28 (m, 1H), 3.89 – 3.81 (m, 2H),

3.55 – 3.47 (m, 2H), 2.18 – 2.11 (m, 2H), 1.97 – 1.89 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 153.4, 141.0, 136.0, 129.2, 56.6, 42.4, 34.2. **HRMS (EI+)** calcd. for [$C_9H_{12}N_3Cl_2$] (MH+) 232.0403; found 232.0400.

4-chloro-1-tosylpiperidine **(2aa)** White solid. 89.1 mg, 85% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.16 – 4.09 (m, 1H), 3.21 – 3.07 (m, 4H), 2.44 (s, 3H), 2.16 – 2.09 (m, 2H), 1.98 – 1.89 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.5, 132.8, 129.6, 127.4, 55.2, 42.7, 33.8, 21.4. **HRMS (EI+)** calcd. for [$C_{12}H_{17}O_2NClS$] (MH+) 274.0663; found 274.0660.

4-chloro-1-((4-methoxyphenyl)sulfonyl)piperidine **(2ab)** White solid, 113 mg, 78 % yield. **^{1}H NMR (400 MHz, ($CDCl_3$)** δ 7.60 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.07 – 3.97 (m, 1H), 3.78 (s, 3H), 3.11 – 3.05 (m, 2H), 3.03 – 2.95 (m, 2H), 2.10 – 1.97 (m, 2H), 1.88 – 1.80 (m, 2H). **^{13}C NMR (100 MHz, ($CDCl_3$)** δ 162.9, 129.5, 127.6, 114.1, 55.5, 55.2, 42.7, 33.9. **HRMS (EI+)** calcd. for [$C_{12}H_{17}O_3NClS$] (MH+) 290.0612; found 290.0610.

1-((4-bromophenyl)sulfonyl)-4-chloropiperidine **(2ac)** White solid, 120.2mg, 71 % yield. **^{1}H NMR (400 MHz, $CDCl_3$)** 7.68 (d, *J* = 8.6, 2H), 7.62 (d, *J* = 8.6, 2H), 4.17 – 4.13 (m, 1H), 3.15 (t, *J* = 5.4 Hz, 4H), 2.17 – 2.10 (m, 2H), 1.97 – 1.91 (m, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 135.4, 132.6, 129.2, 128.2, 55.2, 42.9, 34.1. **HRMS (EI+)** calcd. for [$C_{11}H_{13}O_2NBrClNaS$] (M+Na) 359.9431; found 359.9429.

4-chloro-1-(2-ethylhexyl)piperidine **(2ad)** Colorless oil, 64.4 mg, 54% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 4.01 (bs, 1H), 2.71 (bs, 2H), 2.13 (dd, *J* = 6.6, 4.4 Hz, 5H), 1.98 – 1.81 (m, 3H), 1.44 (bs, 2H), 1.29 – 1.23 (m, 7H), 0.88 (dt, *J* = 14.9, 7.1 Hz, 7H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 62.7, 58.0, 52.2, 36.5, 35.8, 31.5, 28.9, 24.7, 23.1, 14.1, 10.8. **HRMS (EI +)** calcd. for [$C_{13}H_{26}ClN$] (M+) 231.1756; found 231.1751.

4-chloro-1-(4-methoxyphenethyl)piperidine **(2ae)** Colorless oil, 56.9 mg, 51% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.10 (m, 5H), 4.01 (s, 1H), 2.78 – 2.72 (m, 4H), 2.54 (dd, *J*=9.7, 6.5, 2H), 2.27 (bs, 2H), 2.07 (d, *J*=12.4, 2H), 1.94 – 1.80 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 140.2, 128.6, 128.3, 125.9, 60.3, 57.3, 51.2, 35.5, 33.7. **HRMS (EI+)** calcd. for [$C_{13}H_{18}ClN$] (M+) 223.1232; found 223.1228.

4-chloro-1-(4-methoxyphenethyl)piperidine **(2af)** Colorless oil, 73.4 mg, 58% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.12 – 4.00 (m, 1H), 3.79 (s, 3H), 2.88 – 2.79 (m, 2H), 2.78 – 2.67 (m, 3H), 2.61 – 2.52 (m, 2H), 2.38 – 2.25 (m, 2H), 2.18 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.0, 132.3, 129.6, 113.8, 60.6, 57.4, 55.3, 51.3, 35.6, 32.9. **HRMS (EI+)** calcd. for [$C_{14}H_{20}ClNO$] (M+) 253.1232; found 253.1228.

1-benzyl-4-chloropiperidine **(2ag)** Colorless oil, 64 mg, 61% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 – 7.12 (m, 5H), 4.03 (bs, 1H), 3.49 (bs, 2H), 2.80 – 2.67 (m, 2H), 2.23 (s, 2H), 2.13 – 2.02 (m, 2H), 1.96 – 1.84 (m, 2H**). ^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.3, 129.0, 128.2, 127.0, 62.8, 57.5, 51.3, 35.6. **HRMS (EI+)** calcd. for [$C_{12}H_{16}ClN$] (M+) 209.0973; found 209.0967.

4-chloro-1-(1-phenylethyl)piperidine **(2ah)** Colorless liquid, 72.7 mg, 65% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.21 (m, 5H), 3.98 (bs, 1H), 3.44 (q, *J*=6.7, 1H), 2.86 (bs, 1H), 2.78 – 2.66 (m, 1H), 2.29 – 2.12 (m, 2H), 2.14 – 1.99 (m, 2H), 1.97 – 1.80 (m, 2H), 1.37 (d, *J*=6.7, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.8, 128.2, 127.5, 126.9, 64.4, 57.8, 48.6, 35.9, 19.4. **HRMS (EI+)** calcd. for [C_{13} H_{19}NCl] (MH+) 224.1201; found 224.1197.

4-chloro-4-methyl-1-phenylpiperidine **(4a)** Colorless liquid, 84.9 mg, 81% yield.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.22 (m, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.85 (t, *J* = 7.0 Hz, 1H), 3.51 (d, *J* = 12.8 Hz, 2H), 3.25 – 3.12 (m, 2H), 1.95 (ddd, *J* = 22.6, 18.0, 8.3 Hz, 4H), 1.68 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 151.1, 129.1, 119.5, 116.4, 69.5, 46.0, 40.3, 33.2. **HRMS (EI+)** calcd. for [$C_{12}H_{17}$NCl] (MH+) 210.1044; found 210.1040.

4-bromo-4-chloro-1-phenylpiperidine **(4b)** Colorless liquid, 114.7 mg, 84% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.45 – 3.28 (m, 4H), 2.68 (ddd, *J* = 13.7, 7.1, 3.7 Hz, 2H), 2.55 (ddd, *J* = 13.7, 7.0, 3.7 Hz, 2H). **^{13}C NMR (100 MHz $CDCl_3$)** δ 150.2, 129.1, 120.0, 116.4, 78.9, 47.5, 46.4. **HRMS (EI+)** calcd. for [$C_{11}H_{13}$BrClN] (M+) 272.9917; found 272.9912.

4a-chloro-6,6-dimethyl-2-phenyldecahydro-5,7-methanoisoquinoline **(4c)** Colorless oil, 76.62 mg, 53% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.23 (d, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 3.70 – 3.60 (m, 3H), 2.79 (td, *J* = 12.6, 3.0 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.23 (td, *J* = 12.1, 6.4 Hz, 1H), 2.10 (td, *J* = 12.8, 4.5 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.79 (d, *J* = 10.7 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.35 (d, *J* = 11.2 Hz, 1H), 1.08 (s, 3H), 1.01 (s, 3H), 0.92 (dt, *J* = 13.0, 4.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 151.1, 129.0, 118.9, 116.3, 77.7, 55.2, 51.8, 47.5, 47.3, 39.4, 34.8, 30.5, 30.4, 29.9, 27.7, 23.2. **HRMS (EI+)** calcd. for [$C_{18}H_{24}$ClN] (M+) 289.1595; found 289.1590.

4-chloro-3-methyl-1-phenylpiperidine **(4d)** Colorless oil, 68.1 mg, 65% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** Major (anti-) diastereomer: δ 7.31 – 7.22 (m, 2H), 6.96 – 6.90 (m, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 3.73 – 3.57 (m, 3H), 2.80 (td, *J* = 12.5, 2.7 Hz, 1H), 2.50 (dd, *J* = 12.9, 10.6 Hz, 1H), 2.31 – 2.21 (m, 1H), 2.14 – 1.95 (m, 2H), 1.14 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.7, 129.1, 119.7, 116.5, 64.7, 56.4, 49.4, 39.5, 35.8, 16.9. **HRMS (EI+)** calcd. for [$C_{12}H_{17}$NCl] (MH+) 210.1044; found 210.1042.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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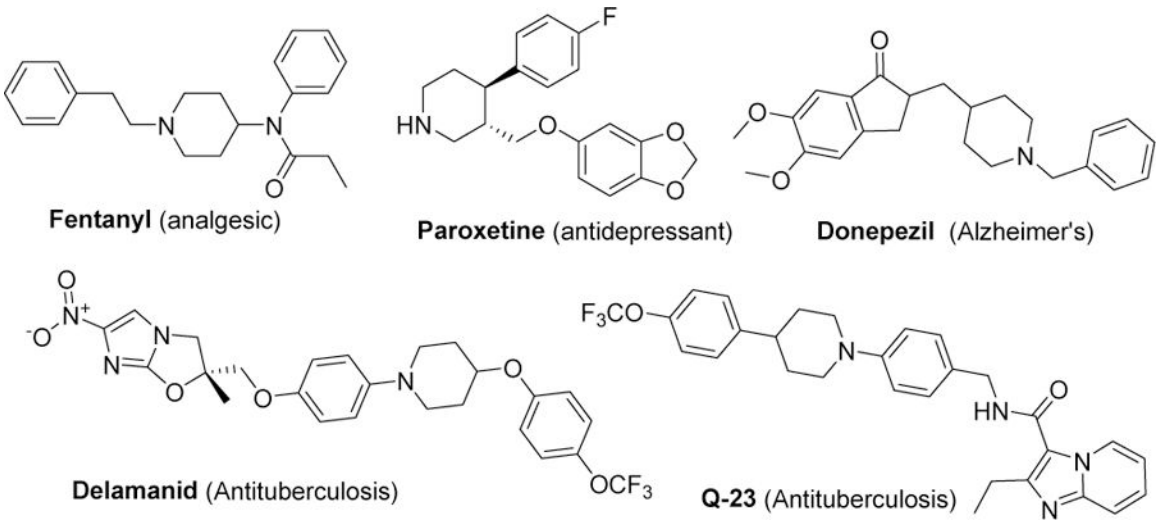


Figure 1.
Examples of piperidine-containing natural products and drug molecules.

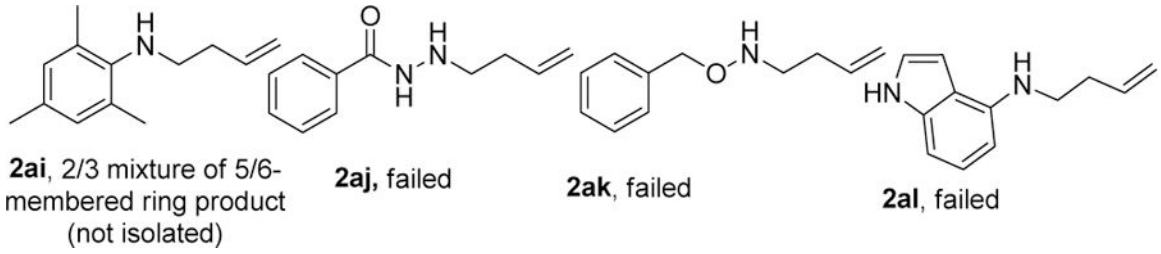


Figure 2.
Failed substrates.

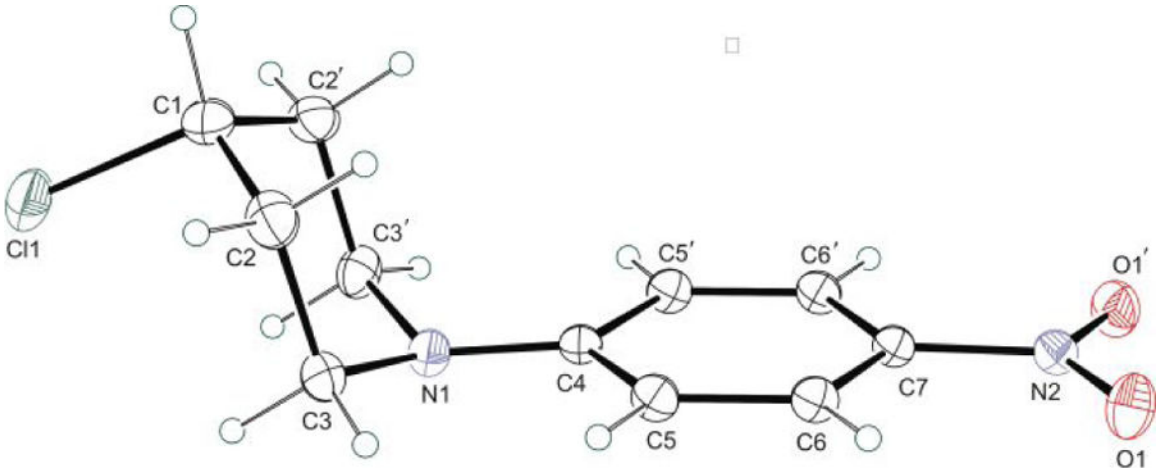
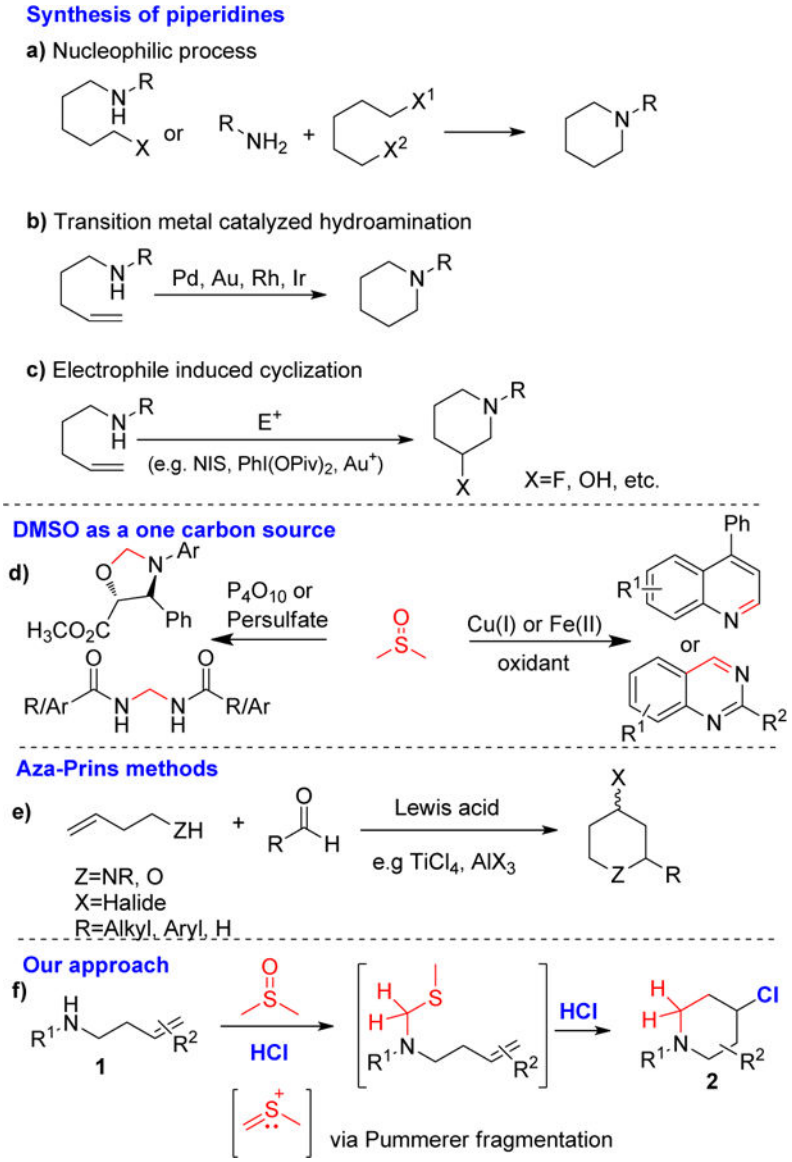
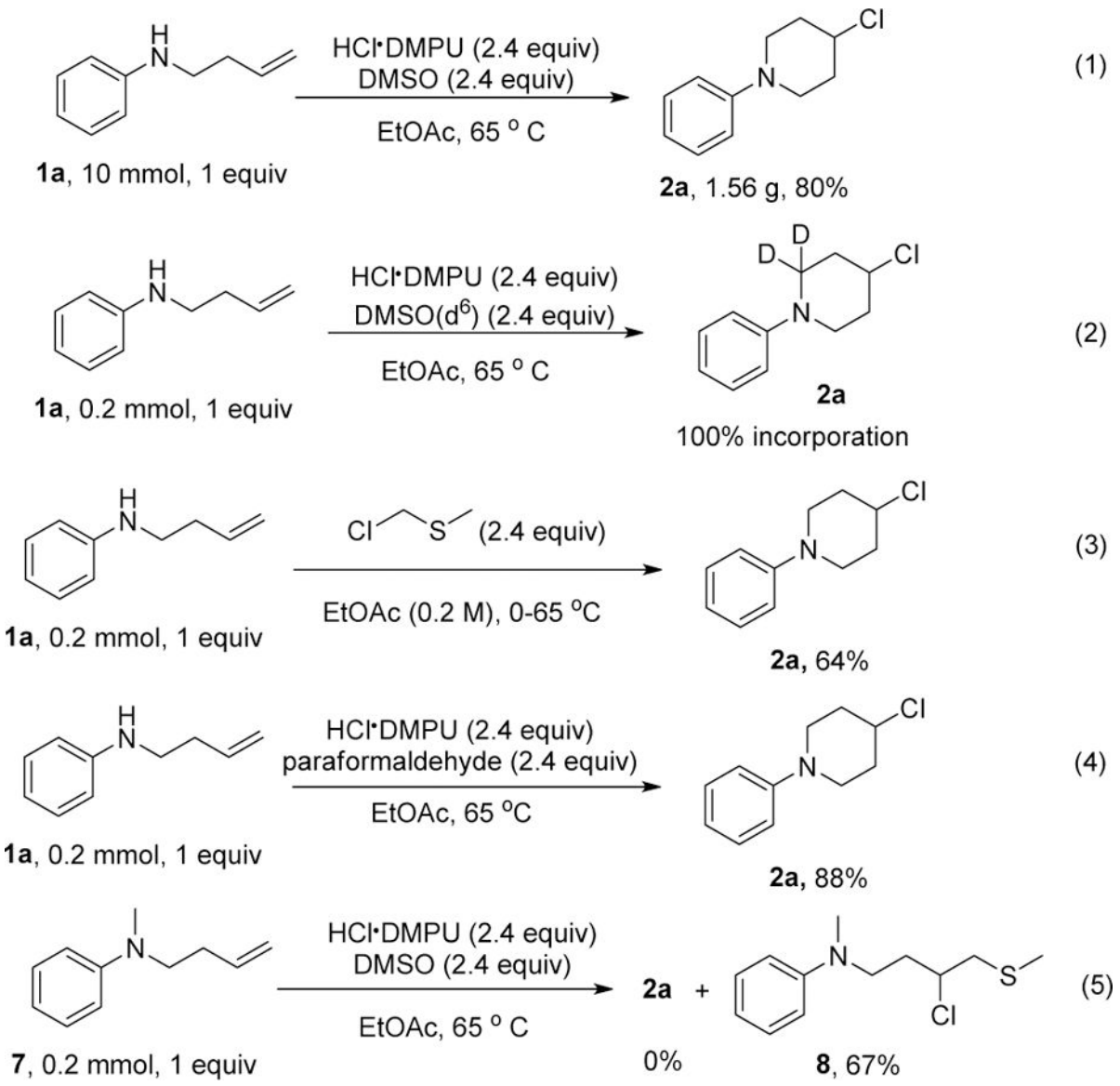


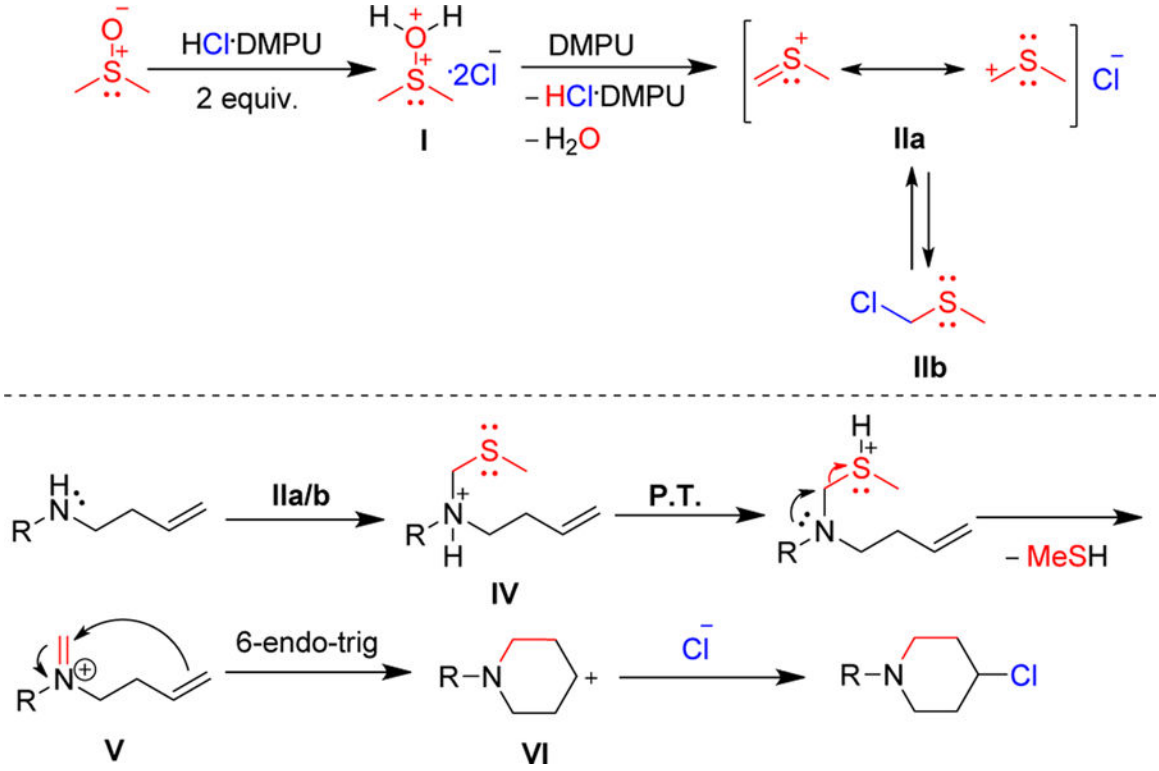
Figure 3.
ORTEP representation of (2n) with thermal ellipsoids shown at the 50% probability level.



Scheme 1.
Literature background.



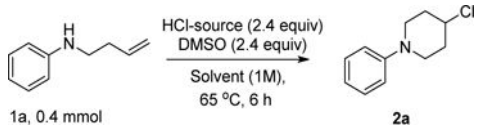
Scheme 2.
Gram scale reaction and mechanistic study.



Scheme 3.
Proposed mechanism.

Table 1.

Reaction optimization.[a]



Entry	Solvent	HCl source	Conc.	Conv./%[a]
1	DCE	HCl•DMPU	1.0	64
2	CH_3CN	HCl•DMPU	1.0	22
3	CH_3NO_3	HCl•DMPU	1.0	30
4	EtOAc	HCl•DMPU	1.0	90
5	DMSO	HCl•DMPU	1.0	18
6	EtOAc	HCl•DMPU	0.5	89
7	**EtOAc**	**HCl•DMPU**	0.2	**99**
8	EtOAc	HCl, Et_2O	0.2	32 (98)[b]
9	EtOAc	HCl, 2-propanol	0.2	99[c]
10	EtOAc	HCl, dioxane	0.2	65 (94)[b]
11	EtOAc	HCl, AcOH	0.2	99[c]
12	EtOAc	HCl, H_2O	0.2	29 (65)[b]
13	EtOAc	CH_3COCl/EtOH	0.2	99
14	EtOAc	TMSCl/MeOH	0.2	95

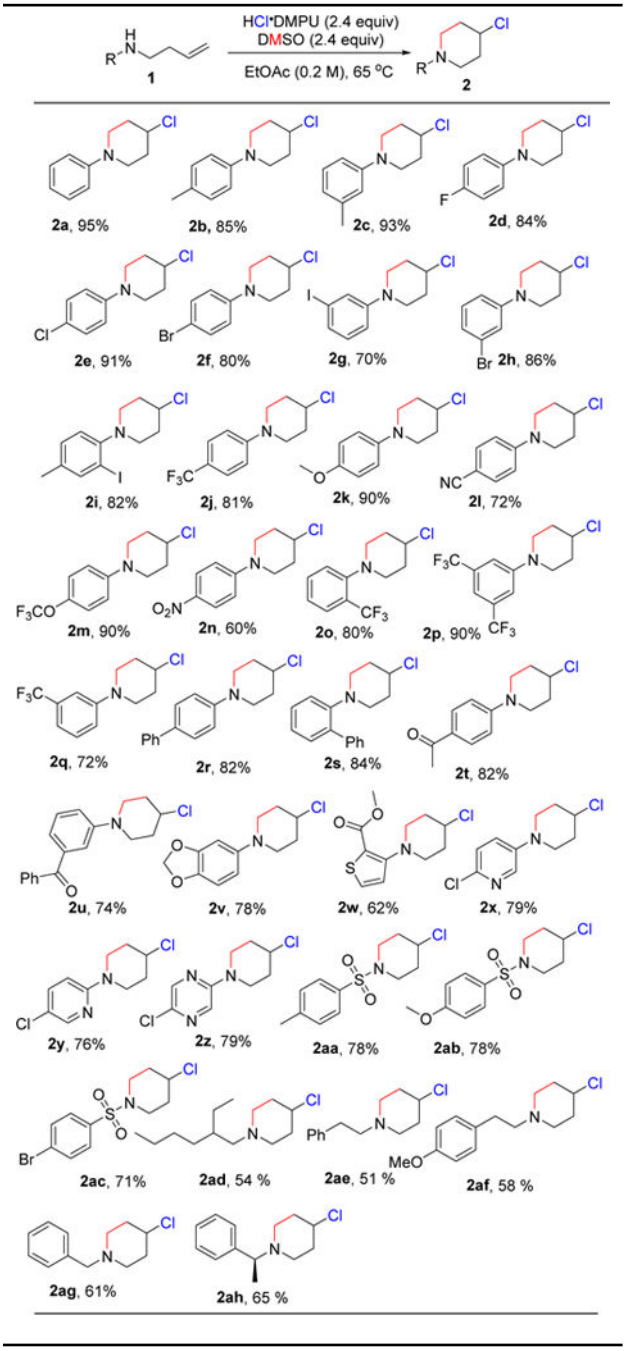
[a]Determined by GC-MS with dodecane as the internal standard.

[b]24 h

[c]combined with thiolated side product.

Table 2.

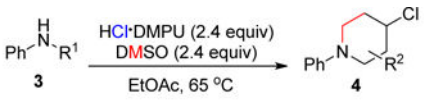
Substrate scope for the synthesis of 4-chloropiperidines.[a]

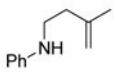
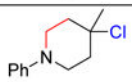
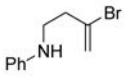
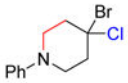
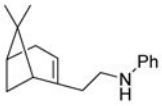
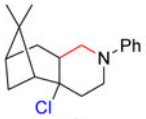
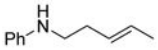
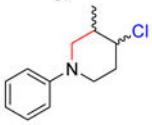
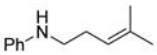
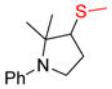
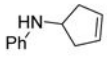
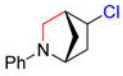


[a] **1** (0.2 mmol), HCl•DMPU (2.4 equiv), DMSO (2.4 equiv), 65 °C, 9–24 h. All yields are isolated yields.

Table 3.

Scope for the synthesis of 4-chloropiperidines.[a]



entry	3	4	Yield[a]
1			**4a**, 81%
2			**4b**, 84%
3			**4c**, 53%
4			**4d,** 65%, 3:1 dr
5			**4e**, 64%[b]
6			**4f**, unsuccessful

[a] **3** (0.2 mmol), HCl DMPU (2.4 equiv), DMSO (2.4 equiv), 65 °C, 9–18 h, isolated yields, [b] ^{1}H NMR with CH_2Br_2 as internal standard.