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Reinvestigation of Aminomethyltrifluoroborates and Their Application in Suzuki−Miyaura Cross-Coupling Reactions

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Supporting Information

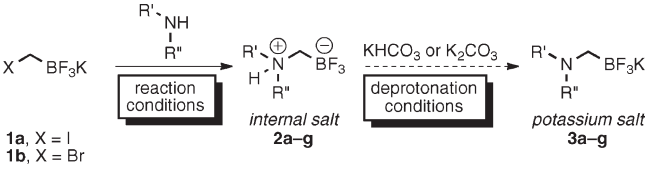
ABSTRACT: A reinvestigation into the chemical composition of potassium aminomethyltrifluoroborates is reported. These trifluoroborato salts have been reassigned as zwitterionic ammoniomethyltrifluoroborates. Minor adjustments to the previously disclosed reaction conditions are reported that permit a similar level of activity as nucleophiles in Suzuki−Miyaura cross-coupling reactions.

INTRODUCTION

Recently, we disclosed a series of reports outlining the synthesis[1] of potassium aminomethyltrifluoroborates and their use as nucleophiles with aryl and heteroaryl bromides[2] and chlorides[3] in Suzuki−Miyaura cross-coupling reactions. Decreased toxicity and simpler purification as compared to those of an analogous, specialized aminomethylstannane[4] provided an impetus for exploiting the dissonant bond-forming connectivity conveyed through the agency of the aminomethyltrifluoroborates. Thus, performing an aminomethylation reaction via a Suzuki−Miyaura cross-coupling reaction between an aminomethyltrifluoroborate and an aryl electrophile is complementary to other commonly utilized routes to these materials, including alkylation of amines with benzylic halides, reductive amination of aromatic aldehydes, and processes initiated from aromatic nitriles. Aminomethylation of aromatic and heteroaromatic halides obviates the need to use lachrymal benzyl halides employed in the amine alkylation approach. Furthermore, the greater commercial availability[5] of aryl and heteroaryl chlorides as compared to the corresponding benzyl halides and aromatic nitriles and aldehydes employed[6] in traditional routes allows inherently less expensive and more rapid access to starting materials and also provides greater structural diversity in targeted aminomethyl compounds.

Because of their utility, we have continued to investigate the reported potassium aminomethyltrifluoroborates and their derivatives.[7] During the course of these investigations and in particular through characterization by ^{1}H NMR and elemental analysis, we discovered that many of the samples assigned as potassium aminomethyltrifluoroborates **3** were instead composed principally of the internal salts **2** and varying amounts of KBr (Scheme 1). Previously, we believed that treatment with either $KHCO_3$ or K_2CO_3 in acetone was sufficient to effect deprotonation, leading to the desired potassium salts, and this belief was supported by several observed changes in the ^{1}H NMR spectra (Figure 1). In addition to the loss of the broad, exchangeable proton assigned to the protonated amine from the piperidine-derived preliminary internal salt, there was a coalescence of peaks, indicating an increase in fluxionality as well as a symmetrization of the axial and equatorial protons, as one might observe concomitant with deprotonation.

Scheme 1. Previously Reported Synthesis of Potassium Aminomethyltrifluoroborates



Although their precise chemical identity and composition was now in question, aminomethyltrifluoroborates prepared in this manner had already proven to be versatile reagents with broad substrate scope and functional group compatibility. Herein, we disclose a reinvestigation of this chemistry and report the synthesis and isolation of ammoniomethyltrifluoroborates in addition to their use as nucleophilic partners in Suzuki−Miyaura cross-coupling reactions.

RESULTS AND DISCUSSION

The first goal was to address whether the observations concerning the nature of the aminomethyltrifluoroborates were the result of a systemic misassignment or represented a case-by-case event. Almost immediately difficulties were encountered in reproducing the previous procedures for the synthesis of the trifluoroborates;[1,2] stirring **2a** with either $KHCO_3$ (20 min) or K_2CO_3 (30 min) in acetone did not lead to a replication of the reported spectra. Finally, after the preliminary product was stirred with K_3PO_4 in acetone overnight, duplication of the observed changes in the ^{1}H NMR spectra considered indicative of a deprotonation to the potassium

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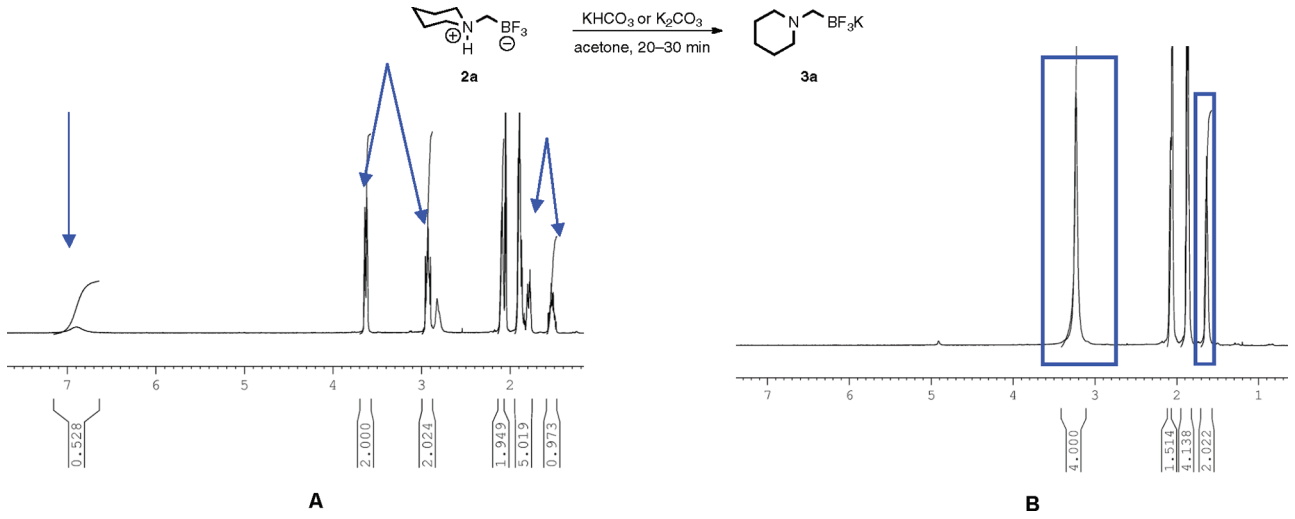

Figure 1. Observed changes in the ^{1}H NMR spectra of **2a** after exposure to base.

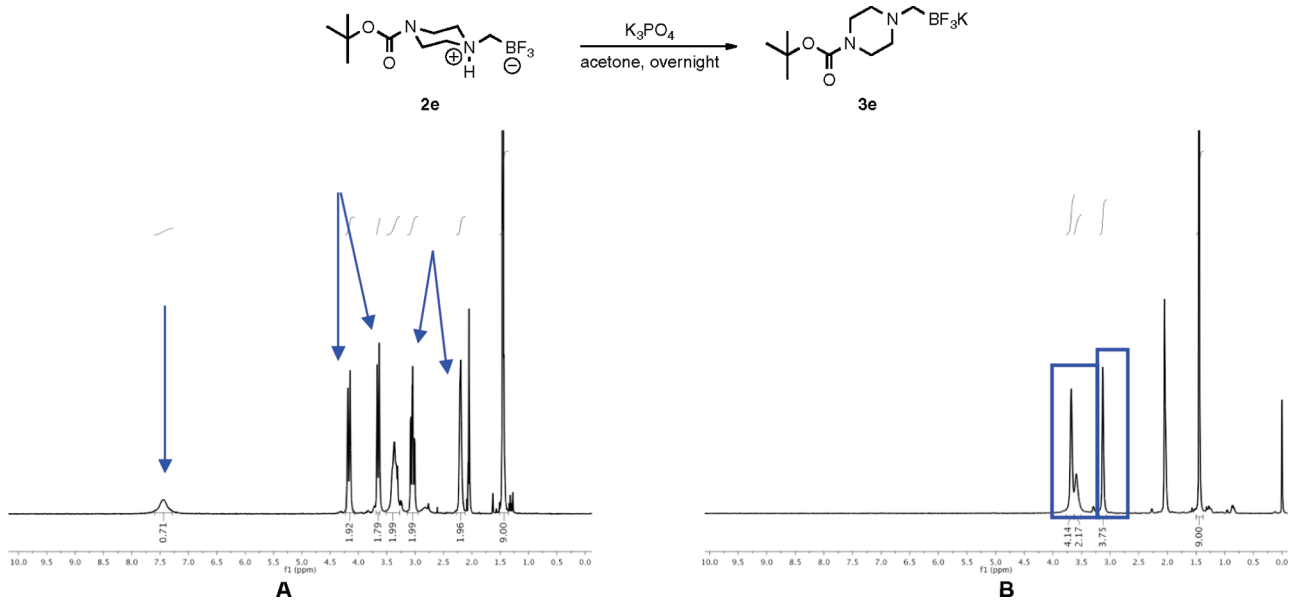

Figure 2. Observed changes in the ^{1}H NMR spectra of **2e** after exposure to base.

aminomethyltrifluoroborate **3a** (Figure 1) was observed, but these results were capricious and not reproducible. It was expected that with compounds presenting the same ^{1}H NMR spectra as previously reported, an X-ray crystal structure of the potassium aminomethyltrifluoroborate could be acquired to confirm the structure, and the purity could be determined by elemental analysis. Although the composition of the internal salt **2a** was confirmed by X-ray analysis (see Figure S1 in the Supporting Information), the structure of the presumed deprotonated potassium aminomethyltrifluoroborate salt **3a** could not be. In agreement with the preliminary elemental analysis results, no potassium ions were detected[8] in crystals formed from compounds having ^{1}H NMR spectra matching those in Figure 1B. Further support of a systemic misassignment came from investigations with internal salt **2e**. Although the same characteristics were exhibited in the ^{1}H NMR of **2e** when it was treated with base, elemental analysis of the resultant product thought to be **3e** (Figure 2B) revealed that this sample could not be the potassium salt because it contained only 3.89% K instead of the expected 12.77% K. Although both analytical techniques convinced us that the deprotonation procedures were inconsistent at best and ineffective at worst, neither addressed the additional possibility of KBr or KI contamination in the final product.

Previously, the aminomethyltrifluoroborates were prepared by alkylation of the desired amine with potassium iodomethyltriflu;oroborate[1] (**1a**) or potassium bromomethyltrifluoroborate[2,3] (**1b**) under neat conditions for inexpensive amines or stoichiometric conditions in THF for the more valuable amines. The resulting crude ammoniomethyltrifluoroborates (**2**) were subjected to treatment with either $KHCO_3$ or K_2CO_3, followed by filtration in hot acetone. To address the probable contamination with KI or KBr in addition to the precise composition of the aminomethyltrifluoroborates, a method was developed to synthesize many of the aminomethyltrifluoroborates from chloromethyltrifluoroborate **1c**. Unexpectedly, in simply replacing bromochloromethane for dibromomethane in our

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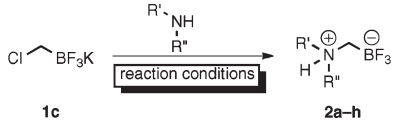
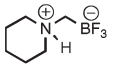
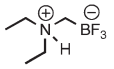
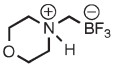
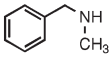
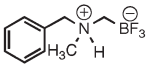
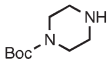
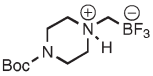
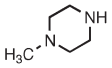
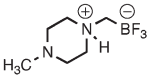
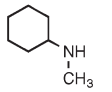
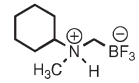
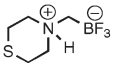
Table 1. Synthesis of Ammoniomethyltrifluoroborates[a]

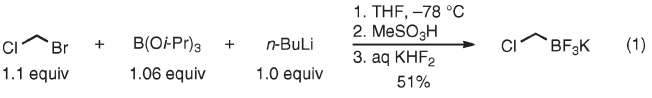


1c 2a–h

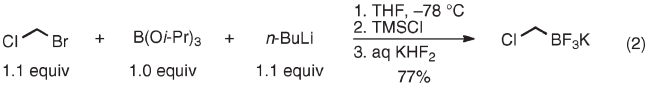
entry	nucleophile	reaction conditions	product		yield (%)[b]
1		A		**2a**	90[c]
2		B		**2b**	62[c]
3		A		**2c**	87
4		A		**2d**	88
5		C		**2e**	80
6		A		**2f**	79
7		A		**2g**	69
8		B		**2h**	75

[a] A 5.00 mmol scale was used unless otherwise noted. Conditions: (A) alkylamine (1.01−2.0 equiv), 3:1 THF:*t*-BuOH (1.0 M), 80 °C, 2−24 h; (B) alkylamine (1.2−2.0 equiv), acetone (0.5 M), 80 °C, 16 h; (C) alkylamine (1.01 equiv), 3:1 CPME:*tert*-amyl alcohol, 110 °C, 6.5 h. [b] Isolated yield. [c] 10.0 mmol scale.

optimized bromomethyltrifluoroborate synthesis (eq 1)[9] the isolated yield of **1c** reached a ceiling of ∼50%. We considered this insufficient as a replacement for such a robust starting material. Adapting Whiting's[10] procedure for the synthesis of pinacol (chloromethyl)boronate by quenching with aqueous KHF_2 instead of ethereal pinacol resulted in a procedure that reliably delivered 70−77% yields of **1c** on scales up to 5 g (eq 2).



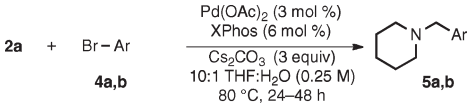
(1)

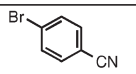
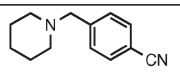
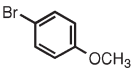
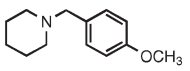


(2)

The synthesis of the ammoniomethyltrifluoroborates was readily accomplished by reacting a variety of amines with **1c** in a cosolvent mixture of THF and *tert*-butyl alcohol. In comparison to the conditions utilized for bromomethyltrifluoroborate (**1b**), increased reaction times were required (Table 1). A few examples (**2b**,**h**) resulted in increased yields by heating in acetone in a sealed tube. After the reactions were judged complete by ^{19}F NMR, the solvent was removed in vacuo. The reaction mixture was subsequently suspended in hot acetone and filtered to remove the KCl byproduct. The internal salts were isolated substantially free from inorganic salt contamination, as KCl is less soluble in acetone than KBr. The procedure used to purify the isolated products (precipitation from hot acetone with diethyl ether) was similar to that commonly used for most potassium organotrifluoroborates. Most importantly, the majority of the ammoniomethyltrifluoroborates retained many of the favorable properties of potassium trifluoroborate salts as easy to manipulate air- and moisture-stable crystalline solids that have proved to be indefinitely bench-stable.

Table 2. Cross-Coupling of Trifluoro(piperidin-1-ium-1-ylmethyl)borate with Aryl Bromides[a]



entry	aryl bromide	product	yield (lit[2], %)[b]	yield (%)[b]
1	 **4a**	 **5a**	83	77
2	 **4b**	 **5b**	80	68

[a] All reactions were carried out using 1.0 mmol of the aryl bromide and 1.3 mmol of the trifluoro(piperidin-1-ium-1-ylmethyl)borate. [b] Isolated yield.

The behavior of the isolated internal salts in Suzuki−Miyaura cross-coupling reactions was next examined, particularly as to how they compared to the previously reported reaction conditions.[2,3] Most of the original research samples were determined[11] to be >90% pure by elemental analysis when reassigned as the internal salt with KBr contamination. Their previous structural misassignment, however, meant that the nucleophilic partner was used in slightly larger excess (<25%) than originally reported.[2] Aryl bromides could be cross-coupled with the ammoniomethyltrifluoroborate under almost identical reaction conditions, after adjusting for the effective molar excess of the trifluoroborate (i.e., 1.3 equiv of trifluoroborate vs the reported 1.1 equiv; Table 2). Under these reaction conditions, we often observed <10% electrophile homocoupling. Isolated yields were decreased in the presence of 1.3 equiv of KBr (54%), were not affected by 1.3 equiv of KCl (80%), and were not improved by the use of 4.0 equiv of Cs_2CO_3 (70%; see Table S1 in the Supporting Information).

Aryl and heteroaryl chlorides also behaved similarly under the previously reported cross-coupling reaction conditions[3] when a few minor modifications were implemented. After adjusting for the effective molar excess of the trifluoroborate (i.e., 1.2 equiv of trifluoroborate vs the reported 1.01 equiv), changing the solvent ratio to 4:1 THF:H_2O, and increasing the reaction time to 45 h, aryl and heteroaryl chlorides remained competent cross-coupling partners for the ammoniomethyltrifluoroborates (Table 3).

The reaction conditions remained general across electron-deficient (Table 3, entry 1) and hindered (Table 3, entries 2 and 3) aryl chlorides, providing moderate to good yields of the desired products. Heteroaryl chlorides were tolerated, including those

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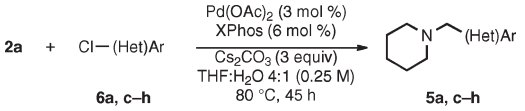
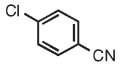
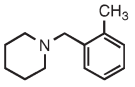
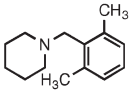
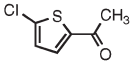
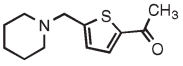
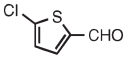
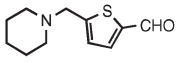
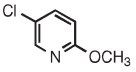
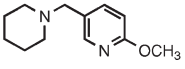
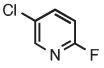
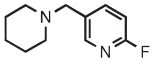
Table 3. Cross-Coupling of Trifluoro(piperidin-1-ium-1-ylmethyl)borate with Aryl Chlorides[a]



entry	aryl chloride	product	yield (lit[3], %)[b]	yield (%)[b]
1	 **6a**	**5a**	92[c]	81
2	 **6c**	 **5c**	63	73
3	 **6d**	 **5d**	66	52
4	 **6e**	 **5e**	93	83
5	 **6f**	 **5f**	78	70
6	 **6g**	 **5g**	87	96
7	 **6h**	 **5h**	n/a	68

[a] All reactions were carried out using 1.0 mmol of the aryl chloride and 1.2 mmol of the trifluoro(piperidin-1-ium-1-ylmethyl)borate. [b] Isolated yield. [c] 10:1 CPME:H_2O (0.25 M) was used as the solvent, 95 °C.

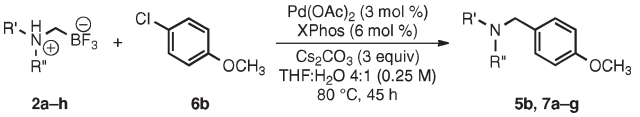
with complementary functional groups, such as aldehydes and ketones (Table 3, entries 4 and 5). 3-Chloropyridines participated in good to excellent yields (Table 3, entries 6 and 7), whereas coupling with heterocycles chlorinated adjacent to nitrogen, such as 2-chloropyridine and 2-chloropyrimidine, remained elusive. Ethanol[12] or cosolvent mixtures, including CH_3CN, *tert*-butyl alcohol, *tert*-amyl alcohol, and *n*-butyl alcohol failed to resolve the challenges of these cross-coupling partners.

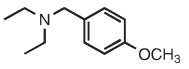
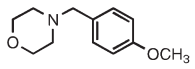
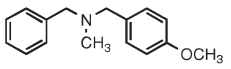
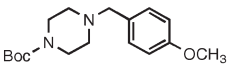
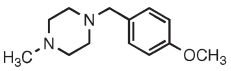
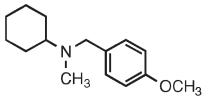
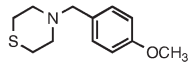
To illustrate the scope of the ammoniomethyltrifluoroborate cross-coupling partner, the breadth of available ammoniomethyltrifluoroborates (Table 1) was cross-coupled with both electron-rich 4-chloroanisole (Table 4) and 3-chloropyridine (Table 5). Most of the ammoniomethyl derivatives participated in the cross-coupling with 4-chloroanisole in good yields, whereas 3-chloropyridine resulted in more moderate yields.

CONCLUSION

In summary, the products generated after alkylation of amine nucleophiles with chloromethyltrifluoroborate (**1c**) have been identified as ammoniomethyltrifluoroborates, and it has been confirmed that treatment with base is insufficient to transform them to the

Table 4. Cross-Coupling of Various *N,N*-Dialkylammoniomethyltrifluoroborates with 4-Chloroanisole[a]



entry	nucleophile	product	yield (lit[3], %)[b]	yield (%)[b]
1	**2a**	**5b**	94	90
2	**2b**	 **7a**	84	63
3	**2c**	 **7b**	75	85
4	**2d**	 **7c**	95	87
5	**2e**	 **7d**	74	98
6	**2f**	 **7e**	68	76
7	**2g**	 **7f**	75	81
8	**2h**	 **7g**	n/a	60[c]

[a] All reactions were carried out using 1.0 mmol of 4-chloroanisole and 1.2 mmol of the ammoniomethyltrifluoroborate. [b] Isolated yield. [c] Average of three trials.

corresponding potassium aminomethyltrifluoroborates. The described ammoniomethyltrifluoroborates retained many of the favorable characteristics associated with materials previously assigned as potassium trifluoroborate salts. Furthermore, it has been established that minor changes to the previously reported conditions are all that are necessary to achieve a cross-coupling of the isolated and pure ammoniomethyltrifluoroborates with both aryl and heteroaryl bromides and chlorides. Finally, it should be emphasized that the previously reported[1−3] deprotonation procedure with potassium carbonate is required and is sufficient to provide full conversion to the potassium trifluoroborates when a less basic nitrogen has been incorporated within the organoboron substructure (e.g., with pyridyl- and quinolinyltrifluoroborates).

EXPERIMENTAL SECTION

General Considerations. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Acetone, diethyl ether (Et_2O), *tert*-butyl alcohol (*t*-BuOH), $Pd(OAc)_2$, XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), and Cs_2CO_3 were used as received. H_2O was

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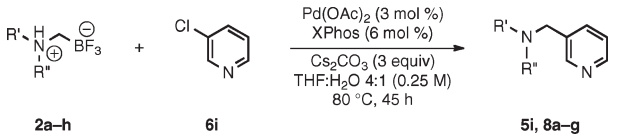
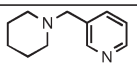
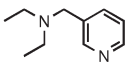
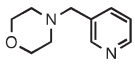
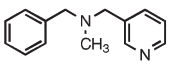
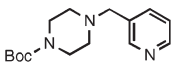
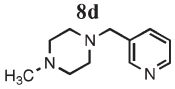
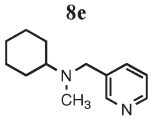
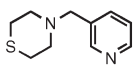
Table 5. Cross-Coupling of Various *N,N*-Dialkylammoniomethyltrifluoroborates with 3-Chloropyridine[a]



2a–h **6i** **5i, 8a–g**

entry	nucleophile	product	yield (lit[3], %)[b]	yield (%)[b]
1	**2a**	 **5i**	77	61
2	**2b**	 **8a**	n/a	30
3	**2c**	 **8b**	n/a	64
4	**2d**	 **8c**	n/a	83
5	**2e**	 **8d**	n/a	quant
6	**2f**	 **8e**	n/a	--[c]
7	**2g**	 **8f**	n/a	75
8	**2h**	 **8g**	n/a	38

[a] All reactions were carried out using 1.0 mmol of 3-chloropyridine and 1.2 mmol of the ammoniomethyltrifluoroborate. [b] Isolated yield. [c] Unable to isolate any desired product.

sparged with nitrogen for at least 20 min prior to use. Standard benchtop techniques were employed for handling air-sensitive reagents.

Amines were fractionally distilled under nitrogen from potassium hydroxide onto activated molecular sieves. All aryl bromides and chlorides were used as received.

Melting points (°C) are uncorrected. NMR spectra were recorded on a 500 or 400 MHz spectrometer. ^{1}H NMR spectra were referenced using residual undeuterated solvent as an internal reference (δ 7.26 for $CDCl_3$; δ 2.50 for DMSO-d_6; δ 2.05 for acetone-d_6; δ 1.94 for CD_3CN). ^{13}C NMR spectra were referenced to either the δ 77.0 resonance of $CDCl_3$, the δ 39.5 resonance of DMSO-d_6, the δ 29.84 resonance of acetone-d_6, or the δ 1.32 resonance of CD_3CN. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). ^{11}B NMR spectra were obtained on a spectrometer equipped with the appropriate decoupling accessories. All ^{11}B NMR chemical shifts were referenced to external $BF_3 \cdot OEt_2$ (0.0 ppm), with a negative sign indicating an upfield shift. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, b = broad), coupling constant J (Hz), and integration. Infrared spectra were recorded on a FT-IR instrument with a horizontal attenuated total reflectance (HATR) device. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Standard flash chromatography procedures were followed using 32−63 μm silica gel. Visualization was effected with ultraviolet light and $KMnO_4$. Reactions conducted in microwave vials were heated conventionally.

*Preparation of Potassium Chloromethyltrifluoroborate (**1c**).* $BrCH_2Cl$ (3.0 mL, 1.991 g/mL, 44.0 mmol) and $B(O\text{-}i\text{-}Pr)_3$ (8.25 mL, 0.912 g/mL, 40.0 mmol) were placed in an oven-dried 250 mL three-neck flask equipped with a stirrer bar and internal thermometer under N_2. Anhydrous THF (39 mL) was added from a syringe. The reaction mixture was cooled to an internal temperature of −50 °C. *n*-BuLi (17.6 mL, 2.5 M in hexanes, 44.0 mmol) was added to an oven-dried 50 mL pear-shaped flask and cooled in a dry ice/acetone bath. The precooled *n*-BuLi was added dropwise at a rate of 1 drop/s, maintaining an internal temperature below −50 °C. After the addition of *n*-BuLi was complete, the reaction mixture was stirred at −50 °C for 30 min before TMSCl (6.1 mL, 0.856 g/mL, 48 mmol) was added dropwise via syringe. After the reaction mixture was stirred for 10 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 24 h. Then, the flask was cooled in an ice−water bath and saturated aqueous KHF_2 (36 mL, ~4.5 M, 160 mmol) was added dropwise. The reaction mixture was stirred for 30 min (and judged complete by ^{11}B NMR) before being concentrated in vacuo. Residual water was removed by azeotroping with toluene before drying in vacuo overnight. The dry, crude mixture was purified by Soxhlet extraction with 250 mL HPLC grade acetone for 10 h. The acetone extracts were concentrated in vacuo to a volume of 50 mL, and Et_2O (5 mL) was added to precipitate the trifluoroborate product. Additional Et_2O (200 mL) was added to assist filtration. Filtration gave a 77% yield of **1c** (4.80 g, 30.7 mmol) as a white powder. Mp: 180−184 °C. IR: ν_{max}(HATR)/cm^{-1} 1418, 1246, 1140, 1112, 1068, 994, 966, 774, 737, 684. ^{1}H NMR (500 MHz): acetone-d_6, δ 2.43 (bs, 2H); DMSO-d_6, δ 2.31 (bs, 2H); CD_3CN, δ 2.44 (bs, 2H). ^{13}C NMR (125 MHz): acetone-d_6, no peaks observed. ^{19}F NMR (470 MHz): acetone-d_6, δ −146.8 (q, J = 51.0 Hz); DMSO-d_6, δ −143.3 (q, J = 50.4 Hz); CD_3CN, δ −146.4 (q, J = 51.0 Hz). ^{11}B NMR (128 MHz): acetone-d_6, δ 1.9 (q, J = 51.4 Hz); DMSO-d_6, δ 2.0−0.2 (m); CD_3CN, δ 1.5 (q, J = 51.2 Hz). Anal. Calcd for CH_2BClF_3K: C, 7.68; H, 1.29; N: 0.0. Found: C, 7.93; H, 1.02; N, <0.02.

General Experimental Procedure for the Preparation of Ammoniomethyltrifluoroborates. *Reaction Conditions A. Preparation of Trifluoro(piperidin-1-ium-1-ylmethyl)borate (**2a**).* An oven-dried 10−20 mL microwave vial equipped with a stirrer bar was charged with **1c** (1.56 g, 10.0 mmol) and sealed with a cap lined with a disposable PTFE septum. The vial was then evacuated under vacuum and purged with N_2 (3×). Anhydrous THF (5.5 mL), *t*-BuOH (2.5 mL), and piperidine (2.0 mL, 8.62 g/mL, 20.0 mmol) were added via syringes (solid amines were added with **1c**). The reaction mixture was stirred and heated to 80 °C for 2 h and judged complete by ^{19}F NMR. At this point the reaction mixture was transferred to a 100 mL round-bottom flask, and the volatiles were removed in vacuo. The crude solid was dried under high vacuum overnight before being dissolved in a solution of hot HPLC acetone and the solution filtered to remove KCl. The filtrate was concentrated in vacuo, dissolved in a minimal amount of hot acetone (20 mL), and precipitated by the dropwise addition of Et_2O (5 mL). Additional Et_2O (150 mL) was added to facilitate filtering. Filtration and drying overnight in vacuo over P_2O_5 afforded **2a** (1.51 g, 90%, 9.04 mmol) as a white powder: mp 147−150 °C; IR ν(HATR)/cm^{-1} 3405 (bs, R_3NH^+), 3176, 2950, 1458, 1307, 1058, 980, 956; ^{1}H NMR (500 MHz, CD_3CN) δ 6.04 (s, 1H), 3.47 (d, J = 12.4 Hz, 2H), 2.80 (t, J = 12.1 Hz, 2H), 2.07 (s, 2H), 1.81 (s, 2H), 1.71 (s, 3H), 1.41 (d, J = 10.9 Hz, 1H); ^{13}C NMR (126 MHz, CD_3CN) δ 56.5, 23.9, 22.3; ^{19}F NMR (471 MHz, CD_3CN) δ −141.9 (q, J = 49.7 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 2.3 (q, J = 51.4 Hz). Anal. Calcd for $C_6H_{13}BF_3N$: C, 43.16; H, 7.85; N, 8.39. Found: C, 42.95; H, 7.84; N, 8.39.

*Reaction Conditions B. Preparation of [(Diethylammonio)methyl]trifluoroborate (**2b**).* An oven-dried 10−20 mL microwave vial equipped with a stirrer bar was charged with **1c** (1.56 g, 10.0 mmol) and sealed with a

cap lined with a disposable PTFE septum. The vial was then evacuated under vacuum and then purged with N_2 (3×). Acetone (20 mL) and Et_2NH (2.0 mL, 0.707 g/mL, 20.0 mmol) were added via syringe. The reaction mixture was heated to 80 °C for 24 h and judged complete by ^{19}F NMR. At this point the reaction mixture was transferred to a 100 mL round-bottom flask, and the volatiles were removed in vacuo. The crude solid was dried under high vacuum overnight before being dissolved in a solution of hot HPLC acetone and the solution filtered to remove KCl. The filtrate was concentrated in vacuo, dissolved in a minimal amount of hot acetone (20 mL), and precipitated by the dropwise addition of Et_2O (100 mL). Filtration and drying overnight in vacuo over P_2O_5 afforded **2b** (0.895 g, 57%, 5.77 mmol) as an off-white powder: mp 108−111 °C; IR ν(HATR)/cm^{-1} 3592 (bs, R_3NH^+), 3188, 1470, 1019, 988; ^1H NMR (500 MHz, CD_3CN) δ 6.25−5.87 (m, 1H), 3.23−3.02 (m, 4H), 2.08 (s, 2H), 1.23 (q, J = 7.5 Hz, 6H); ^{13}C NMR (126 MHz, CD_3CN) δ 50.4, 9.3; ^{19}F NMR (471 MHz, CD_3CN) δ −142.4 (q, J = 49.9 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 2.0 (q, J = 51.3 Hz); Anal. Calcd for $C_5H_{13}BF_3N$: C, 38.75; H, 8.46; N, 9.04. Found: C, 38.14 (low); H, 8.34 (low); N, 8.79 (low). HRMS (ESI-TOF): calcd for $C_5H_{12}BF_3N^-$ $[M - H]^-$ 154.1015, found 154.1016.

*Trifluoro(morpholin-4-iummethyl)borate (**2c**).* Using general reaction conditions A with morpholine (0.87 mL, 0.996 g/mL, 10.0 mmol) and **1c** (0.782 g, 5.0 mmol) for 1.5 h, **2c** was obtained (0.739 g, 87%, 4.37 mmol) as a pale yellow powder: mp 170−172 °C; IR ν(HATR)/cm^{-1} 3537, 3112, 1638, 1442, 1262, 1122, 1079, 1054, 1028, 960; ^1H NMR (500 MHz, CD_3CN) δ 6.57 (s, 1H), 3.93 (d, J = 13.0 Hz, 2H), 3.73 (dd, J = 18.1, 6.7 Hz, 2H), 3.43 (d, J = 13.5 Hz, 2H), 3.06−2.92 (m, 2H), 2.15 (s, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 64.7, 55.3; ^{19}F NMR (471 MHz, CD_3CN) δ −141.8 (q, J = 50.2 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 2.9−1.0 (m). Anal. Calcd. for $C_5H_{11}BF_3NO$: C, 35.54; H, 6.56; N, 8.29. Found: C, 34.44 (low); H, 6.74 (high); N, 7.92 (low). HRMS (ESI-TOF): calcd for $C_5H_{10}BF_3NO^-$ $[M - H]^-$ 168.0808, found 168.0809.

*{[Benzyl(methyl)ammonio]methyl}trifluoroborate (**2d**).* Using general reaction conditions A with *N*-benzylmethylamine (0.65 mL, 0.939 g/mL, 5.05 mmol) and **1c** (0.782 g, 5.0 mmol) for 16 h, **2d** was obtained (0.895 g, 88%, 4.40 mmol) as an off-white powder: mp 109−112 °C; IR ν(HATR)/cm^{-1} 3188, 1458, 1318, 1045, 1003, 934, 780, 748, 700; ^1H NMR (500 MHz, CD_3CN) δ 7.47 (s, 5H), 6.56 (bs, 1H), 4.30 (d, J = 13.0 Hz, 1H), 4.08 (d, J = 13.0 Hz, 1H), 2.71 (s, 3H), 2.17 (bs, 1H), 2.03 (bs, 1H); ^{13}C NMR (126 MHz, CD_3CN) δ 132.0, 131.5, 130.7, 130.0, 62.3, 43.3; ^{19}F NMR (471 MHz, CD_3CN) δ −141.94 (q, J = 47.4 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 2.0 (q, J = 50.7 Hz). Anal. Calcd for $C_9H_{13}BF_3N$: C, 53.25; H, 6.45; N, 6.90. Found: C, 52.05 (low); H, 5.98 (low); N, 6.68. HRMS (ESI-TOF): calcd for $C_9H_{13}BF_3N^-$ $[M - H]^-$ 202.1015, found 202.1018.

*{[4-(tert-Butoxycarbonyl)piperazin-1-ium-1-yl]methyl}trifluoroborate (**2e**).* Using general reaction conditions A with *tert*-butyl piperazine-1-carboxylate (0.940 g, 5.05 mmol) and **1c** (0.782 g, 5.0 mmol) for 6.5 h in 3/1 CPME/*tert*-amyl alcohol, **2e** was obtained (1.07 g, 80%, 3.99 mmol) as an off-white powder: mp 185 °C dec; IR ν(HATR)/cm^{-1} 3177, 1697, 1646 (C═O), 1421, 1284, 1170, 1143, 1034, 959; ^1H NMR (360 MHz, acetone-d_6) δ 7.43 (s, 1H), 4.17 (d, J = 14.6 Hz, 2H), 3.65 (d, J = 13.1 Hz, 2H), 3.47−3.27 (m, 2H), 3.05 (td, J = 12.6, 3.5 Hz, 2H), 2.20 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, acetone-d_6) δ 154.6, 80.8, 55.0, 41.4, 28.4; ^{19}F NMR (339 MHz, acetone-d_6) δ −142.1 (q, J = 43.7 Hz); ^{11}B NMR (128 MHz, acetone-d_6) δ 2.2 (q, J = 49.5 Hz). Anal. Calcd for $C_{10}H_{20}BF_3N_2O_2$: C, 44.80; H, 7.52; N, 10.45. Found: C, 44.52; H, 7.52; N, 10.40.

*Trifluoro[(4-methylpiperazin-1-ium-1-yl)methyl]borate (**2f**).* Using general reaction conditions A with 1-methylpiperazine (0.61 mL, 0.903 g/mL, 5.50 mmol) and **1c** (0.782 g, 5.0 mmol) for 4 h, **2f** was obtained (0.722 g, 79%, 3.96 mmol) as a white powder: mp 73−78 °C; IR ν(HATR)/cm^{-1} 3601, 3168, 2808, 1455, 1068, 1040, 966; ^1H NMR (500 MHz, CD_3CN) δ 6.16 (s, 1H), 3.44 (d, J = 12.3 Hz, 2H), 2.96 (t, J = 11.0 Hz, 2H), 2.82 (d, J = 12.5 Hz, 2H), 2.31 (t, J = 11.4 Hz, 2H), 2.25 (d, J = 4.0 Hz, 3H), 2.11 (s, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 55.4, 52.6, 45.6; ^{19}F NMR (471 MHz, CD_3CN) δ −141.9 (q, J = 47.7 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 2.0 (q, J = 50.7 Hz). Anal. Calcd for $C_6H_{14}BF_3N_2$: C, 39.60; H, 7.75; N, 15.39. Found: C, 38.05 (low); H, 7.66 (low); N, 14.44 (low). HRMS (ESI-TOF): calcd for $C_6H_{13}BF_3N_2^-$ $[M - H]^-$ 181.1124, found 181.1120.

*{[Cyclohexyl(methyl)ammonio]methyl}trifluoroborate (**2g**).* Using general reaction conditions A with *N*-methylcyclohexylamine (0.72 mL, 0.868 g/mL, 5.50 mmol) and **1c** (0.782 g, 5.0 mmol) for 24 h, **2g** was obtained (0.671 g, 69%, 3.44) as a white powder: mp 105−108 °C; IR ν(HATR)/cm^{-1} 3182, 2942, 2863 1293, 1061, 1024, 985, 944; ^1H NMR (500 MHz, DMSO-d_6) δ 8.38−7.84 (m, 1H), 2.95 (s, 1H), 2.57 (s, 3H), 2.07−1.50 (m, 7H), 1.37−0.99 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 64.5, 38.8, 25.9, 25.7, 24.8, 24.5; ^{19}F NMR (471 MHz, DMSO-d_6) δ −138.2; ^{11}B NMR (128 MHz, DMSO-d_6) δ 1.9. Anal. Calcd for $C_8H_{17}BF_3N$: C, 49.27; H, 8.79; N, 7.18. Found: C, 48.04 (low); H, 8.04 (low); N, 6.84. HRMS (ESI-TOF): calcd for $C_8H_{16}BF_3N^-$ $[M - H]^-$: 194.1330, found 194.1328.

*Trifluoro(thiomorpholino-4-iummethyl)borate (**2h**).* Using general reaction conditions B and reaction with thiomorpholine (0.57 mL, 1.026 g/mL, 6.0 mmol) and **1c** (0.782 g, 5.0 mmol) for 16 h, **2h** was obtained (0.693 g, 75%, 3.74 mmol) as an off-white powder after trituration with cold acetone: mp 188−189 °C; IR ν(HATR)/cm^{-1} 3178, 1736, 1408, 1075, 1028, 967, 952, 925; ^1H NMR (500 MHz, CD_3CN) δ 6.26 (s, 1H), 3.72 (d, J = 12.0, 2H), 3.2−2.92 (m, 4H), 2.77 (d, J = 14.0, 2H), 2.14 (s, 2H);^{13}C NMR (126 MHz, CD_3CN) δ 57.0, 25.4; ^{19}F NMR (471 MHz, CD_3CN) δ −141.6 (q, J = 49.3 Hz); ^{11}B NMR (128 MHz, CD_3CN) δ 1.6 (q, J = 51.1 Hz). Anal. Calcd for $C_5H_{11}BF_3NS$: C, 32.46; H, 5.99; N, 7.57; S, 17.33. Found: C, 32.39; H, 5.86; N, 7.36; S, 17.14.

*General Experimental Procedure for the Suzuki−Miyaura Cross-Coupling Reactions of Aryl Bromides. Preparation of 4-(Piperidin-1-ylmethyl)benzonitrile (**5a**).* A 2−5 mL microwave vial equipped with a stirrer bar was charged with **2a** (0.217 g, 1.3 mmol), Cs_2CO_3 (0.977 g, 3.0 mmol), **4a** (0.182 g, 1.0 mmol), $Pd(OAc)_2$ (0.067 g, 0.03 mmol), and XPhos[13] (0.029 g, 0.06 mmol) and then sealed with a cap lined with a disposable PTFE septum. The vial was then evacuated under vacuum and purged with N_2 (3×). Anhydrous THF (3.63 mL) and H_2O (0.36 mL) were added by syringe (aryl bromides that were liquids at room temperature were added by syringe), and the reaction mixture was stirred and heated at 80 °C for 24 h and then cooled to room temperature and diluted with H_2O (1 mL). The reaction mixture was extracted with EtOAc (3 × 3 mL). The combined organics were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo. Purification by flash column chromatography, with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent, afforded **5a** (0.156 g, 78%, 0.78 mmol) as a yellow oil: R_f = 0.08 (silica gel, hexanes/EtOAc 7/1 with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

*1-(4-Methoxybenzyl)piperidine (**5b**).* Using the general procedure with **4b** (0.187 g, 1.0 mmol) for 44 h, **5b** was obtained in 68% yield (0.140 g, 0.68 mmol) as a yellow oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.05 (7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

*General Experimental Procedure for the Suzuki−Miyaura Cross-Coupling Reactions of Aryl and Heteroaryl Chlorides. Preparation of 4-(Piperidin-1-ylmethyl)benzonitrile (**5a**).* A 2−5 mL microwave vial equipped with a stirrer bar was charged with **2a** (0.200 g, 1.2 mmol), Cs_2CO_3 (0.977 g, 3.0 mmol), **6a** (0.138 g, 1.0 mmol), $Pd(OAc)_2$ (0.067 g, 0.03 mmol), and XPhos (0.029 g, 0.06 mmol) and then sealed with a cap lined with a disposable PTFE septum. The vial was then evacuated under vacuum and purged with N_2 (3×). Anhydrous THF (3.2 mL) and H_2O (0.80 mL) were added by syringe (aryl and heteroaryl chlorides that were liquids at room temperature were added by syringe), and the reaction mixture was stirred and heated at 80 °C for 45 h and then cooled

to room temperature and diluted with H_2O (1 mL). The reaction mixture was extracted with EtOAc (3 × 3 mL). The combined organics were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo. Purification by flash column chromatography, with 7/1 hexanes/EtOAc with 0.2% Et_3N to 4/1 hexanes/EtOAc with 0.2% Et_3N as eluent, afforded **5a** (0.163 g, 81%) as a yellow oil: R_f = 0.06 (silica gel, hexanes/EtOAc 7/1 with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

1-(2-Methylbenzyl)piperidine (***5c***). Using the general procedure with **6c** (0.126 g, 1.0 mmol), **5c** was obtained in 73% yield (0.138 g, 0.73 mmol) as a pale yellow oil after silica gel column chromatography (with 9/1 hexanes/EtOAc with 0.2% Et_3N to 7/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.2 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

1-(2,6-Dimethylbenzyl)piperidine (***5d***). Using the general procedure with **6d** (0.145 g, 1.0 mmol), **5d** was obtained in 53% yield (0.107 g, 0.53 mmol) as a yellow solid after silica gel column chromatography (with 99/1 hexanes/EtOAc to 9/1 hexanes/EtOAc as eluent): R_f = 0.5 (silica gel, 9/1 hexanes/EtOAc); mp 25−26 °C. ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

1-[5-(Piperidin-1-ylmethyl)thiophen-2-yl]ethanone (***5e***). Using the general procedure with **6e** (0.161 g, 1.0 mmol), **5e** was obtained in 83% yield (0.184 g, 0.82 mmol) as a yellow solid after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 100% EtOAc as eluent): R_f = 0.08 (silica gel, 8/2 $CHCl_3$/EtOAc); mp 50−52 °C. NMR spectra are comparable to those reported in the literature.[3]

5-(Piperidin-1-ylmethyl)thiophene-2-carbaldehyde (***5f***). Using the general procedure with **6f** (0.147 g, 1.0 mmol), **5f** was obtained in 70% yield (0.147 g, 0.70 mmol) as an orange oil after silica gel column chromatography (with 9/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 1% Et_3N as eluent): R_f = 0.2 (silica gel, 8/2 $CHCl_3$/EtOAc). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

2-Methoxy-5-(piperidin-1-ylmethyl)pyridine (***5g***). Using the general procedure with **6g** (0.144 g, 1.0 mmol), **5g** was obtained in 96% yield (0.197 g, 0.96 mmol) as a yellow oil after silica gel column chromatography (with 8/2 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.1 (silica gel, 8/2 $CHCl_3$/EtOAc). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

2-Fluoro-5-(piperidin-1-ylmethyl)pyridine (***5h***). Using the general procedure with **6h** (0.132 g, 1.0 mmol), **5h** was obtained in 68% yield (0.132 g, 0.68 mmol) as a yellow oil after silica gel column chromatography (with 8/2 $CHCl_3$/EtOAc to 99/1 EtOAc/Et_3N as eluent): R_f = 0.04 (silica gel, 8/2 $CHCl_3$/EtOAc); IR ν(HATR)/cm^{-1} 2937, 1598, 1483, 1245, 1114, 908, 858, 832, 755, 733; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.78 (t, J = 8.1 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 3.44 (s, 2H), 2.36 (bs, 4H), 1.61−1.49 (m, 4H), 1.48−1.38 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 (d, J = 237.9 Hz), 147.8 (d, J = 14.5 Hz), 142.1 (d, J = 7.9 Hz), 132.0 (d, J = 4.4 Hz), 109.2 (d, J = 37.4 Hz) 60.1, 54.5, 26.0, 24.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −70.8; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{16}FN_2^+$ $[M + H]^+$ 195.1298, found 195.1293.

1-(4-Methoxybenzyl)piperidine (***5b***). Using the general procedure with **6b** (0.142 g, 1.0 mmol), **5b** was obtained in 90% yield (0.185 g, 0.90 mmol) as a yellow oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.05 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

N-Ethyl-N-(4-methoxybenzyl)ethanamine (***7a***). Using the general procedure with **2b** (0.186 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7a** was obtained in 63% yield (0.122 g, 0.63 mmol) as a yellow oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.08 (silica gel, hexanes/EtOAc 7/1 with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

4-(4-Methoxybenzyl)morpholine (***7b***). Using the general procedure with **2c** (0.203 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7b** was obtained in 85% yield (0.176 g, 0.85 mmol) as a yellow oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.05 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

N-Benzyl-1-(4-methoxyphenyl)-N-methylmethanamine (***7c***). Using the general procedure with **2d** (0.244 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7c** was obtained in 87% yield (0.211 g, 0.87 mmol) as a clear, colorless oil after silica gel column chromatography (with 9/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.4 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

tert-Butyl-4-(4-methoxybenzyl)piperazine-1-carboxylate (***7d***). Using the general procedure and reaction with **2e** (0.322 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7d** was obtained in 98% yield (0.302 g, 0.98 mmol) as a white solid after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.09 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N); mp 55−57 °C. ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

1-(4-Methoxybenzyl)-4-methylpiperazine (***7e***). Using the general procedure and reaction with **2f** (0.218 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7e** was obtained in 76% yield (0.168 g, 0.76 mmol) as a dark yellow oil after silica gel column chromatography (with 8/2 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.4 (silica gel, EtOAc/Et_3N 99/1). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

N-(4-Methoxybenzyl)-N-methylcyclohexanamine (***7f***). Using the general procedure with **2g** (0.234 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7f** was obtained in 81% yield (0.189 g, 0.81 mmol) as a clear orange oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.08 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[3]

4-(4-Methoxybenzyl)thiomorpholine (***7g***). Using the general procedure with **2h** (0.222 g, 1.2 mmol) and **6b** (0.142 g, 1.0 mmol), **7g** was obtained in 72% yield (0.160 g, 0.72 mmol) as a yellow oil after silica gel column chromatography (with 7/1 hexanes/EtOAc with 0.2% Et_3N to 1/1 hexanes/EtOAc with 0.2% Et_3N as eluent): R_f = 0.4 (silica gel, 7/1 hexanes/EtOAc with 0.2% Et_3N); IR ν(HATR)/cm^{-1} 2908, 2803, 1611, 1511, 1242, 1035, 957, 823; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 3.45 (s, 2H), 2.74−2.61 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 130.3, 130.1, 113.7, 63.2, 55.3, 54.9, 28.1; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{18}NOS^+$ $[M + H]^+$ 224.1109, found 224.1103.

3-(Piperidin-1-ylmethyl)pyridine (***5i***). Using the general procedure with **6i** (0.114 g, 1.0 mmol), **5i** was obtained in 61% yield (0.107 g, 0.61 mmol) as an orange oil after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.4 (silica gel, 99/1 EtOAc/Et_3N). ^1H and ^{13}C NMR spectra are comparable to those reported in the literature.[2]

N-Ethyl-N-(pyridin-3-ylmethyl)ethanamine (***8a***). Using the general procedure with **2b** (0.186 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8a** was obtained in 30% yield (0.050 g, 0.30 mmol) as an orange oil after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.4 (silica gel, 99/1 EtOAc/Et_3N); IR ν(HATR)/cm^{-1} 3029, 2966, 2935, 2806, 1576, 1424, 1201, 714; ^1H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 1.5 Hz, 1H), 8.48 (dd, J = 4.7, 1.3 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 7.7, 4.8 Hz, 1H), 3.57 (s, 2H), 2.52 (q, J = 7.1 Hz, 4H), 1.04 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 148.4, 136.6, 135.5, 123.4, 55.0, 46.9, 11.9; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{17}N_2^+$ $[M + H]^+$ 165.1392, found 165.1389.

*4-(Pyridin-3-ylmethyl)morpholine (**8b**).* Using the general procedure with **2c** (0.203 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8b** was obtained in 64% yield (0.113 g, 0.63 mmol) as an orange oil after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.06 (silica gel, 8/2 $CHCl_3$/EtOAc); IR ν(HATR)/cm^{-1} 3416, 2809, 1115, 1007, 865, 715; ^1H NMR (500 MHz, CD_3CN) δ 8.54−8.39 (m, 2H), 7.69 (s, 1H), 7.30 (s, 1H), 3.61 (s, 4H), 3.49 (s, 2H), 2.39 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 148.9, 136.9, 133.4, 123.5, 67.1, 60.7, 53.7; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O^+$ $[M + H]^+$ 179.1184, found 179.1183.

*N-Benzyl-N-methyl-1-(pyridin-3-yl)methanamine (**8c**).* Using the general procedure with **2d** (0.244 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8c** was obtained in 83% yield (0.178 g, 0.83 mmol) as a pale yellow oil after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 100% EtOAc as eluent): R_f = 0.2 (silica gel, 8/2 $CHCl_3$/EtOAc); IR ν(HATR)/cm^{-1} 3028, 2788, 1576, 1453, 1425, 1367, 1023, 788, 740, 714, 699; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.49 (dd, J = 4.7, 1.4 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.40−7.28 (m, 4H), 7.28−7.20 (m, 2H), 3.53 (s, 2H), 3.50 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 148.6, 139.0, 136.5, 134.8, 128.9, 128.4, 127.2, 123.4, 62.0, 58.9, 42.2; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{17}N_2^+$ $[M + H]^+$ 213.1392, found 213.1386.

*tert-Butyl-4-(pyridin-3-ylmethyl)piperazine-1-carboxylate (**8d**).* Using the general procedure with **2e** (0.322 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8d** was obtained in 99% yield (0.274 g, 0.99 mmol) as a yellow solid after silica gel column chromatography (with 8/2 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.1 (silica gel, 8/2 $CHCl_3$/EtOAc); mp 93 °C dec; IR ν(HATR)/cm^{-1} 2975, 2950, 2809, 1679 (C═O), 1426, 1240, 1163, 1129, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.52−8.48 (m, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.27−7.23 (m, 1H), 3.51 (s, 2H), 3.45−3.38 (m, 4H), 2.42−2.34 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 150.6, 148.9, 136.7, 133.5, 123.4, 79.7, 60.3, 52.9, 44.2, 43.3, 28.5; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{24}N_3O_2^+$ $[M + H]^+$ 278.1869, found 278.1860.

*N-Methyl-N-(pyridin-3-ylmethyl)cyclohexanamine (**8f**).* Using the general procedure with **2g** (0.234 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8f** was obtained in 75% yield (0.154 g, 0.75 mmol) as a clear, yellow oil after silica gel column chromatography (with 9/1 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.2 (silica gel, 8/2 $CHCl_3$/EtOAc); IR ν(HATR)/cm^{-1} 3030, 2928, 2853, 1450, 1426, 1026, 793, 714; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.48 (d, J = 4.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.23 (dd, J = 7.7, 4.9 Hz, 1H), 3.57 (s, 2H), 2.48−2.37 (m, 1H), 2.18 (s, 3H), 1.91−1.76 (m, 4H), 1.68−1.58 (m, 1H), 1.37−1.16 (m, 4H), 1.17−1.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 148.4, 136.5, 136.0, 123.4, 62.8, 55.3, 37.7, 28.8, 26.5, 26.1; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{21}N_2^+$ $[M + H]^+$ 205.1705, found 205.1706.

*4-(Pyridin-3-ylmethyl)thiomorpholine (**8g**).* Using the general procedure with **2h** (0.222 g, 1.2 mmol) and **6i** (0.114 g, 1.0 mmol), **8g** was obtained in 39% yield (0.075 g, 0.39 mmol) as a dark orange oil after silica gel column chromatography (with 8/2 $CHCl_3$/EtOAc to 98/2 EtOAc/Et_3N as eluent): R_f = 0.10 (silica gel, 8/2 $CHCl_3$/EtOAc); IR ν(HATR)/cm^{-1} 3025, 2925, 2806, 1457, 1424, 1286, 1101, 1006, 955, 801, 708; ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.47 (d, J = 3.7 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.22 (dd, J = 7.6 Hz, 4.9, 1H), 3.49 (s, 2H), 2.72−2.59 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 148.8, 136.7, 133.7, 123.5, 61.0, 55.0, 28.1; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2S^+$ $[M + H]^+$ 195.0956, found 195.0959.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Text, tables, figures, and a CIF file giving full experimental details and NMR spectra for all compounds and X-ray crystal structure data for compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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