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Synthesis of Arylethylamines *via* C(sp^3)−C(sp^3) Palladium-Catalyzed Cross-Coupling

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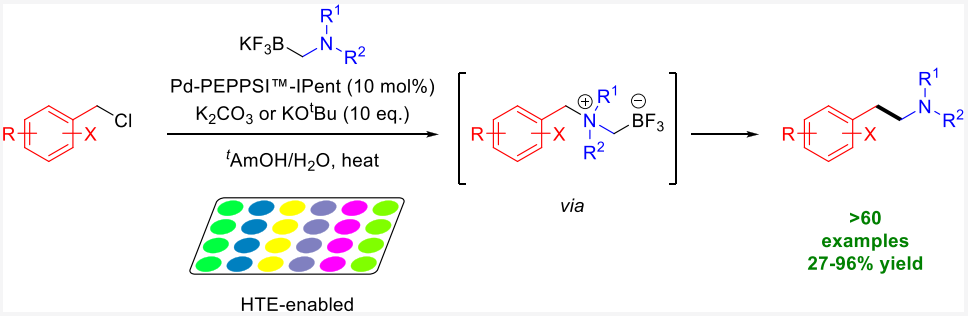

ABSTRACT: Substituted arylethylamines represent a key structural motif in natural, pharmaceutical, and agrochemical compounds. Access to such scaffolds has been the subject of long-standing synthetic interest. Herein, we report the synthesis of such scaffolds *via* a palladium-catalyzed C(sp^3)−C(sp^3) coupling between (chloromethyl)aryls and air-/moisture-stable *N*,*N*-dialkylaminomethyltrifluoroborate salts. Rapid hit identification was achieved using microscale high-throughput experimentation and was followed by millimolar-scale reaction parameter optimization. A range of structurally and electronically varied arylethylamine products were obtained in moderate to excellent yields (27−96%, >60 examples). The reaction mechanism is proposed to proceed *via* formation of a trialkylbenzylammonium species prior to oxidative addition.

INTRODUCTION

Substituted phenethylamines, and structurally related analogues, represent a key pharmacophore found in endogenous and synthetic neurotransmitters, pharmaceutical agents, and agrochemical products (Figure 1).[1−3] This privileged class of compounds plays key pharmacological roles as central nervous system stimulants, nasal decongestants, antidepressants, anti-parkinson agents, and vasopressors among others.

Due to the wide range of biological activities associated with this motif, the scaffold has remained an interesting and challenging problem to synthetic chemists, particularly in the field of alkaloid synthesis. Currently employed methodologies include Heck arylation of *N*-vinyloxazolones,[4] cross-coupling of *β*-aminoalkyl zinc reagents with aryl iodides,[5] and Suzuki−Miyaura cross-coupling of potassium *β*-aminoethyltrifluoroborate salts and aryl halides.[6,7] While effective in selected cases, these methods suffer from forcing conditions, limited reaction scope, and/or air-/moisture-instability of starting materials. Additional olefin reduction steps may also be required to access the fully saturated ethyl linker, compromising functional group tolerance of these methods. Recently, Jui and co-workers reported a metal-free regioselective photocatalytic synthesis of arylethylamines using aryl halides and vinylcarbamates.[8] This methodology tolerated the presence of various functionalities, substitution patterns, and heterocycles with high atom efficiency and generation of nontoxic byproducts. Despite this, a complementary Suzuki−Miyaura-based approach may present an attractive alternative for industrial applications.

N,*N*-Dialkylaminomethyltrifluoroborate salts (which can exist as potassium or internal salts; see Scheme 1), pioneered by Molander and co-workers, offer nontoxic air-/moisture-stable reagents for cross-coupling reactions.[9,10] Such reagents can be easily formed from commercial starting materials and accessed as stable, free-flowing solids upon precipitation/crystallization. The benefits of trifluoroborate salts are well documented.[11,12] Reactions generally benefit from suppression of side reactions such as oxidative homocoupling and protodeboronation, affording high yields and clean reaction profiles.[13,14]

Molander and co-workers exemplified the use of these dialkylaminomethyltrifluoroborate salts in the palladium-catalyzed aminomethylations of various aryl bromides with the scope later being expanded to incorporate other aryl and

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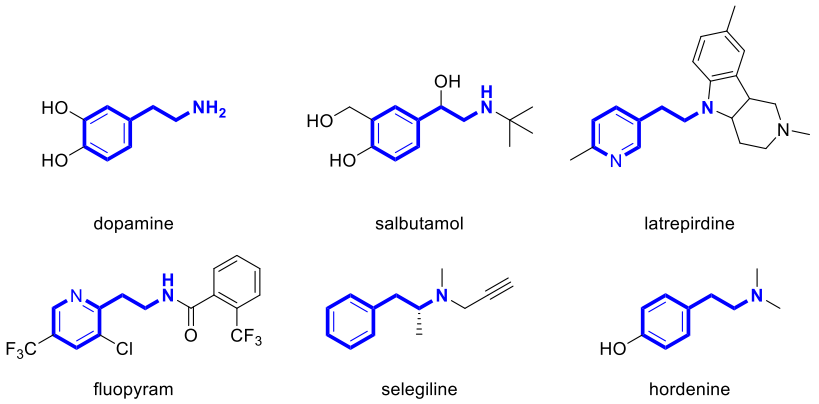
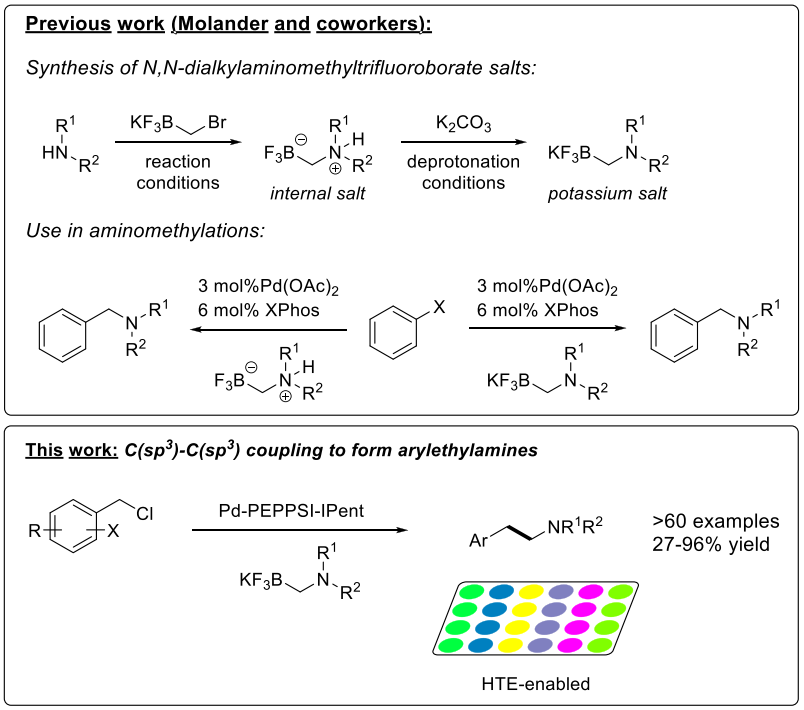


Figure 1. Examples of arylethylamine-containing natural, pharmaceutical, and agrochemical products.

Scheme 1. Previous Aminomethylations Using *N,N*-Dialkylaminomethyltrifluoroborate Salts and C(sp^3)−C(sp^3) Cross-Coupling of These Salts Reported in This Work

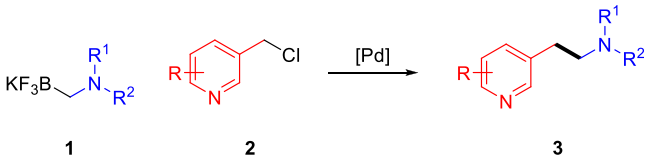


heteroaryl halides.[9,15] Herein, we report the cross-coupling of *N,N*-dialkylaminomethyltrifluoroborate salts with various benzyl chlorides and (chloromethyl)heteroaryls to furnish the coveted arylethylamine scaffold, aided by microscale high-throughput experimentation (HTE) (Scheme 1).

RESULTS AND DISCUSSION

Our interest in accessing such cores arose due to the desire to incorporate the (pyridin-3-yl)ethylamine scaffold **3** in target molecules as part of a medicinal chemistry program. A mild method for the preparation of this motif, compatible with late-stage functionalization, was desired, with, to the best of our knowledge, no general methodology currently existing for this transformation. We hypothesized that the central ethyl linker could be constructed *via* a palladium-catalyzed cross-coupling reaction between potassium aminomethyltrifluoroborate salts **1** and 3-(chloromethyl)pyridine derivatives **2** (Scheme 2). The chloromethyl species **2** was selected over other analogous electrophiles to mitigate risks associated with oligomerization by quaternization of the pyridine nitrogen atom.[16]

Scheme 2. Proposed Synthesis of (Pyridin-3-yl)ethylamine Scaffolds 3 *via* Palladium-Catalyzed Cross-Coupling



The cross-coupling of piperazinotrifluoroborate salt **1a** and 3-picolyl chloride·HCl **2a** was selected as the model reaction for initial investigations, and high-throughput experimentation was used to rapidly identify reaction conditions. A 24-well plate consisting of a variety of Buchwald and trialkylphosphine palladium(0) precatalysts (see the Supporting Information for

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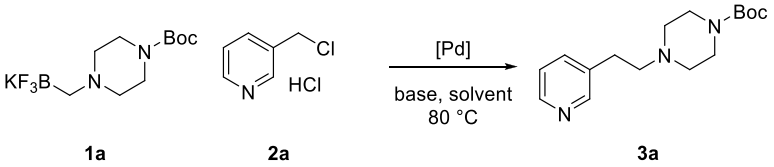
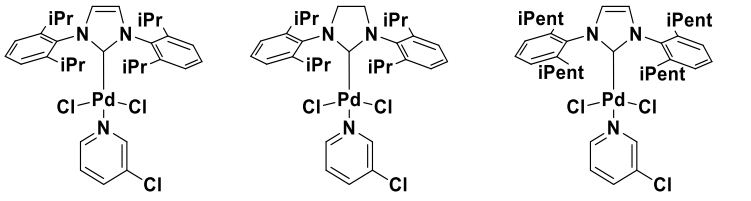
Scheme 3. Conditions Tested for the Formation of Arylethylamine 3a Using HTE. See the Supporting Information (SI) for More Details[a]



		C1	C2	C3	C4	C5	C6
^{t}AmylOH	KO^{t}Bu	0.16	0.36	0.34	0.25	0.14	0
	K_2CO_3	0.18	0.10	0.48	0.15	0	0.10
1,4-Dioxane	KO^{t}Bu	0.20	0.20	0.27	0.11	0.25	0
	K_2CO_3	0.15	0.08	0.26	0.21	0.09	0

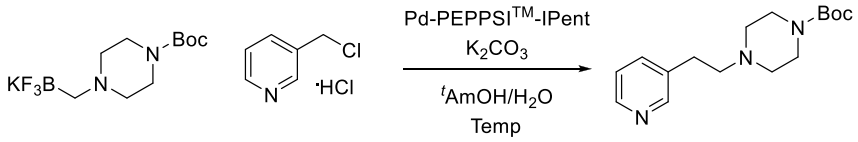


C1 = Pd-PEPPSI^{TM}-IPr C2 = Pd-PEPPSI^{TM}-SIPr C3 = Pd-PEPPSI^{TM}-IPent

C4 = Pd-Allyl-IPr C5 = Pd-Allyl-SIPr C6 = Pd-Allyl-Mes

[a]Reaction performed on 10 μmol of chloride **2a**. Reaction stirred at 80 °C for 24 h. Conditions: pyridine **2a** (1.0 equiv), potassium trifluoroborate **1a** (1.5 equiv), Pd precatalyst (10 mol %), base (4 equiv), solvent:water (4:1), 80 °C, 24 h. Values shown are the ratio of the peak area versus internal standard of triphenylamine as calculated using liquid chromatography-mass spectrometry (LC-MS).

Table 1. Conditions Tested in the Optimization of the Formation of Arylethylamine 3a



entry	^{t}AmOH:H_2O ratio[a]	X equiv of base[b]	time/h	temperature/°C	yield of **3a**[c]/%
1	4:1	4	19	80	13
2	10:1	4	19	80	15
3	10:1	5	21	80	53
4	10:1	10	19	80	84
5	10:1	15	19	80	55
6	4:1	10	19	80	50
7	no H_2O[d]	10	19	80	31
8	10:1	10	19	60	16
9	10:1	10	5	Δ	87
10	10:1	4	15	Δ	61

[a]Reaction performed at 0.1 M concentration. [b]Reactions were performed using 0.70 mmol of pyridine **2a** with 1.5 equiv of salt **1a** and 0.1 equiv of Pd-PEPPSI-IPent. [c]Isolated yield. [d]Karl Fischer titration showed that *tert*-amyl alcohol used contained 0.071 ± 0.005 wt % water.

experimental details) was screened.[17] Of the conditions trialed, only three showed conversion to the desired product **3a**, although this conversion was minimal (≤5%). This was attributed to the inability of the C(sp^3)−Cl bond to undergo

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oxidative addition to the insufficiently electron-rich palladium center.[18] Consequently, a second plate consisting of *N*-heterocyclic carbene (NHC)-based precatalysts was designed and screened (Scheme 3).[19] *tert*-Amyl alcohol and 1,4-dioxane were selected as commonplace protic and aprotic solvents. Potassium *tert*-butoxide was selected due to its frequent use in allyl-NHC precatalyst activation and cross-coupling reactions;[20] potassium carbonate was also chosen as a commonly employed mild base.

The performance of NHC-based precatalysts was far superior to that of the phosphines tested with 20 unique conditions affording the desired product. The combination of Pd-PEPPSI-IPent (**C3**), *tert*-amyl alcohol, and potassium carbonate afforded the greatest conversion to compound **3a**. The high catalytic activity of **C3** is well established and is attributed to the high electron density and "flexible steric bulk" around the palladium center, allowing for efficient oxidative addition and reductive elimination during the catalytic cycle.[21,22]

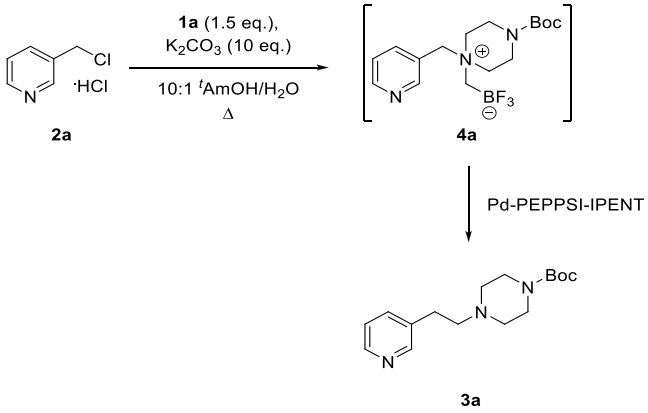
With these conditions identified, precise reaction parameters were then optimized on a millimolar scale (Table 1).

Direct application of the conditions identified by the plate-based screen resulted in a 13% yield of product **3a** (entry 1) with little change upon increasing the solvent:water ratio (entry 2). Increasing the stoichiometry of potassium carbonate was beneficial to the reaction (entries 3 and 4) until a critical point where this became detrimental (entry 5). Deviation from an alcohol:water ratio 10:1 (entries 6 and 7) gave a lower yield. Performing the reaction at a lower temperature (entry 8) afforded a lower yield due to reaction stalling, while conducting the reaction at reflux (entry 9) afforded the greatest yield with a significantly shortened reaction time. Omission of the catalyst, using an unused flask and a stirrer bar, yielded no product, confirming that the process is indeed palladium-catalyzed.[23]

It is proposed that the desiccating property of potassium carbonate (see the SI for Karl Fischer analysis) attenuates the rate of hydrolysis of the trifluoroborate salt.[24] This ensures a suitable rate of hydrolysis, relative to the rates of elementary steps of the catalytic cycle,[14,25] preventing significant accumulation of reactive boronate species, which may be prone to side reactions.[14,26] Monitoring the rate of hydrolysis of aminomethyltrifluoroborate salt **1a** by ^{19}F NMR spectroscopy revealed that under reaction conditions of entry 4 (10 equiv K_2CO_3, 10:1 ^{t}AmOH/H_2O, 80 °C; Table 1), trifluoroborate hydrolysis required ∼8 h, whereas analogous conditions using 4 equiv of potassium carbonate instead of 10 (entry 2, Table 1) allowed for complete hydrolysis within 2 h. Increasing the reaction temperature to refluxing conditions (entry 9, Table 1) engendered rapid hydrolysis (40−50 min), with a complementary increase in the rate of remaining steps of the catalytic cycle inferred by the comparable isolated yields. Use of 4 equiv of potassium carbonate under refluxing conditions (entry 10, Table 1) afforded hydrolysis within 30−40 min, with an accompanying decrease in product yield. Where base loading and subsequent desiccation are too high, excessively slow hydrolysis likely accounts for lower yields (entry 5). Under these conditions (15 equiv K_2CO_3, 10:1 ^{t}AmOH/H_2O, 80 °C), trifluoroborate hydrolysis required >10 h. This slower hydrolysis may result in accumulation of alkyl palladium species, which can undergo undesired side reactions in the absence of an available boronic acid for transmetalation. This is also applicable to low water concentrations (entry 7). Thus, the optimized reaction conditions (entry 9) afford the greatest yield by an optimum balance of reaction rates.

Throughout the optimization process, the rapid formation of an intermediary species was observed by LC-MS prior to product formation (for exemplar LC-MS of reaction mixture for the formation of **3a** after ∼1 h showing betaine **4a** as the major intermediate, see Figure S17 in the SI). Upon isolation and structural elucidation, this intermediate was identified as betaine **4**, formed by S_N2 displacement of the picolyl chloride **2a** by amine **1a** (Scheme 4). The irreversible nature of this

Scheme 4. Formation of Betaine 4a Followed by Addition of Palladium Catalyst, under Optimized Conditions Afforded Full Conversion to Arylethylamine 3a, Suggesting That Oxidative Addition Occurs from Ammonium-Containing 4a



substitution, and its observed formation in the absence of palladium catalyst, prompted the proposal that the mechanism of arylethylamine formation proceeds *via* ammonium-containing betaine formation, and this species is involved the oxidation addition step. Formation of betaine **4** followed by addition of the palladium catalyst afforded full conversion to the desired arylethylamine **3a** in a 75% isolated yield. Cross-couplings of 3-picolyl-derived ammonium salts have been previously reported.[27]

Thus, on the basis of previous reports,[27−29] a plausible mechanism (Scheme 5) involves oxidative addition of betaine **4**, generated *in situ*, to the active Pd(0) catalyst **A**. Upon this oxidative addition to form Pd(II) species **B**, the dialkylaminomethyltrifluoroborate salt may be liberated prior to hydrolysis to the boronic acid **5**, in accordance with mechanisms reported by Lloyd-Jones and co-workers.[13,14] Ligand exchange and transmetalation afford complex **C**, from which reductive elimination furnishes the desired arylethylamine **3**. The precise identity of the "X" ligand is not fully understood; however, computational calculations are ongoing to provide further insight.

Reaction scope was next investigated with respect to the trifluoroborate salt **1** and chloride **2** employed (Scheme 6).

Various dialkylaminomethyltrifluoroborate salts (assigned as the potassium salt due to observations made by ^{1}H NMR spectroscopy) were compatible with the process, rapidly constructing complex scaffolds in moderate to excellent yields. Piperazine derivatives **3a−c** gave excellent yields (76−87%), with good scalability demonstrated by the comparable yields of **3a** obtained on milligram and gram scales. Alternative dialkylaminomethyltrifluoroborate salts coupled in a 36−60% yield with the relatively lower yield of thiomorpholine **3d** potentially due to the metallophilic sulfur atom partially poisoning the catalyst. Protected primary amine **3h** was synthesized in good yield using the potassium Boc-protected

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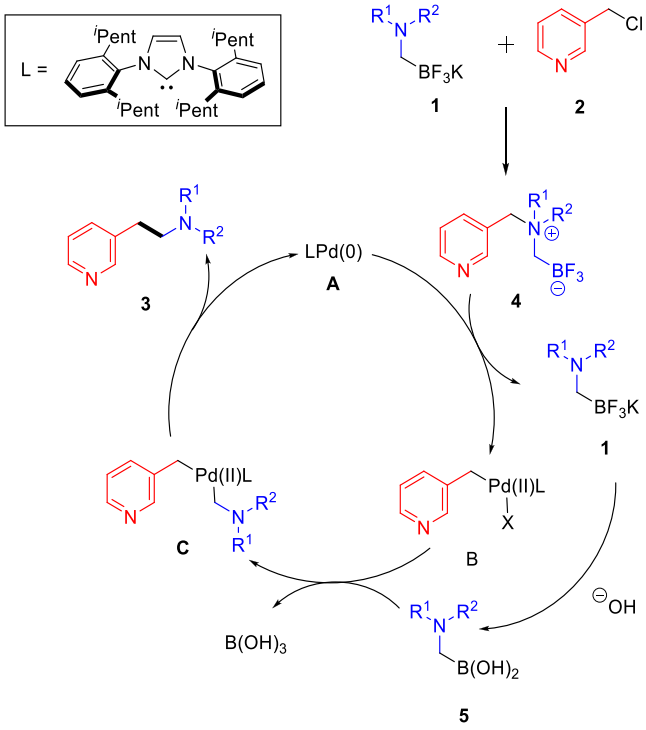
Scheme 5. Proposed Mechanism for the Formation of (Pyridin-3-yl)ethylamines 3 from *N,N*-Dialkylaminomethyltrifluoroborate Salts 1 and 3-(Chloromethyl)pyridine 2 *via* Formation of Ammonium-Containing Betaine 4



aminomethyltrifluoroborate.[30] No evidence of a betaine was seen during the formation of Boc-protected arylethylamine **3h** suggesting that, due to the lower nucleophilicity of carbamate **1h**, the reaction proceeds *via* oxidative addition of 3-(chloromethyl)pyridine to the Pd(0) catalyst, without the formation of an ammonium species. Monoalkylaminotrifluoroborate salt **1i** was incompatible with the reaction, instead forming the arylmethylamine product **3j**. This is likely due to deprotonation of the trialkylammonium ion, formed upon displacement of the picolyl chloride **2a**, affording a tertiary amine that cannot partake in oxidative addition. Hydrolysis and protodeboronation then afford amine **3j**. Attempts to overcome this issue by employing an *N*-benzylamine-derived trifluoroborate salt instead furnished aminomethylpyridine **3l** (as determined by two-dimensional (2D) NMR spectroscopy) as the major product. This result indicates that upon the formation of the corresponding betaine **4b**, insertion of palladium into the benzyl position to generate benzyl palladium species **6** occurs more rapidly than analogous insertion to the pyridyl position, resulting in this scrambling (Scheme 7).

Synthesis of 2- and 4-(chloromethyl)pyridine derivatives **3m** and **3n** could not be achieved by this method. Stable dimers formed by oxidative addition of 2-(chloromethyl)pyridine to Pd(0) have been isolated and characterized previously.[31] Formation of such a complex likely terminates the reaction. Furthermore, the enhanced stability of metalated 2-picoline derivatives has been previously noted, with this stability believed to arise due to lone pair donation from the pyridine nitrogen atom to the palladium center.[32] It has also been noted that functionalization of metalated 4-picolyl derivatives is not facile.[32] All methylpyridine isomers **3o–r** formed in excellent yield (68–87%). The highly electron-donating methoxy group was well tolerated, affording (pyridin-3-yl)ethylamine **3s** in an 86% yield. Electron-withdrawing motifs afforded slightly lower yields but were well tolerated nonetheless. The high yield of 2-fluoropyridine **3v** was particularly pleasing as alternative methods may be limited by the propensity of this moiety to undergo S_NAr-type chemistry in the presence of a nucleophile, which was not an issue in this setting. Groups susceptible to base-catalyzed hydrolysis proved problematic with amide **3x** obtained alongside nitrile **3w**. Highly conjugated heteroatom-rich **3y** and -poor **3z** biaryl-containing (pyridin-3-yl)ethylamines were accessible in high yields (83–94%) using this methodology. Alternative heterocycles such as quinoline **3aa**, unprotected azaindole **3ab**, and pyrimidine **3ac** were all formed in good to excellent yield, particularly the N–H-containing azaindole.

These conditions were also successfully applied to a range of 5-membered heterocycles (Scheme 8). Formation of arylethylamines derived from thiazole **8b**, *N*-methyl imidazole **8c**, and *N*-methyl pyrazole **8e** all proceeded in good to excellent yield, while oxazole **8a** and thiophene **8d** formed in lower, but still synthetically useful, yields. (Chloromethyl)isoxazoles and isothiazoles yielded no desired arylethylamine, potentially due to insertion of palladium into the N–X bond, terminating the reaction.[33,34] Alternative imidazole isomers were also incompatible with the reaction.

When these conditions were applied to benzyl chloride (**9a**), a 52% isolated yield of phenethylamine **10a** was obtained. Given the usefulness of phenethylamines, it was desired to reoptimize conditions for benzyl-derived substrates. Hence, another 24-well plate was designed and tested. A range of solvents (*tert*-amyl alcohol, 1,4-dioxane, iso-propyl alcohol, trifluoroethanol) and inorganic bases (potassium/cesium/sodium carbonate, potassium phosphate, and potassium/sodium *tert*-butoxide) were used in combination with Pd-PEPPSI-IPent C3 (Scheme 9).

1,4-Dioxane, IPA, and *tert*-amyl alcohol all provided successful reaction conditions, while no product **10a** was obtained using any of the screened conditions in trifluoroethanol. The combinations of cesium carbonate/potassium phosphate/potassium *tert*-butoxide in *tert*-amyl alcohol all gave superior conversion to product **10a** than potassium carbonate, with potassium *tert*-butoxide providing the cleanest reaction profile. As such, potassium *tert*-butoxide was selected for further optimization (Table 2).

As with the cross-coupling of pyridine **2a**, the reaction of benzyl chloride **9a** showed a large sensitivity to the amount of base employed. Maintaining a 4:1 solvent:water ratio, a near-3-fold increase in yield was obtained upon moving from 4 equiv of base (entry 1) to 10 (entry 2). Increasing the solvent:water ratio proved detrimental to this reaction (entries 3 and 4), while performing the reaction at reflux gave a near-quantitative yield, in short time (entry 6). As in the case of potassium carbonate, increasing the loading of potassium *tert*-butoxide afforded a decrease in the rate of trifluoroborate hydrolysis, indicating a potential role as a desiccant as well as a base. Under the conditions of Table 3, entry 5 (4 equiv KO^{t}Bu, 4:1 ^{t}AmOH/H_2O, reflux), hydrolysis required 20–30 min; however, under the conditions of Table 3, entry 6 (10 equiv KO^{t}Bu, 4:1 ^{t}AmOH/H_2O, reflux), hydrolysis was slower, requiring 60–80 min. Although the precise reason that these conditions are more effective than the conditions applied to 3-(chloromethyl)-pyridines **3** is not fully understood, this evidence supports the

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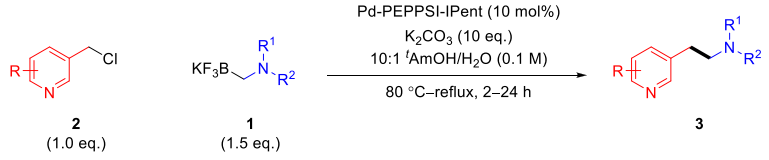
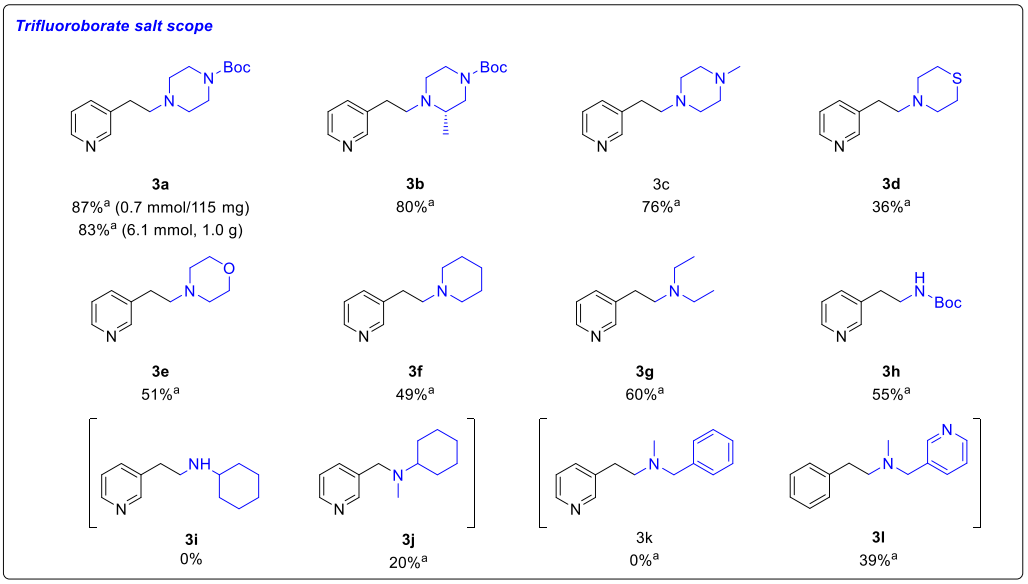
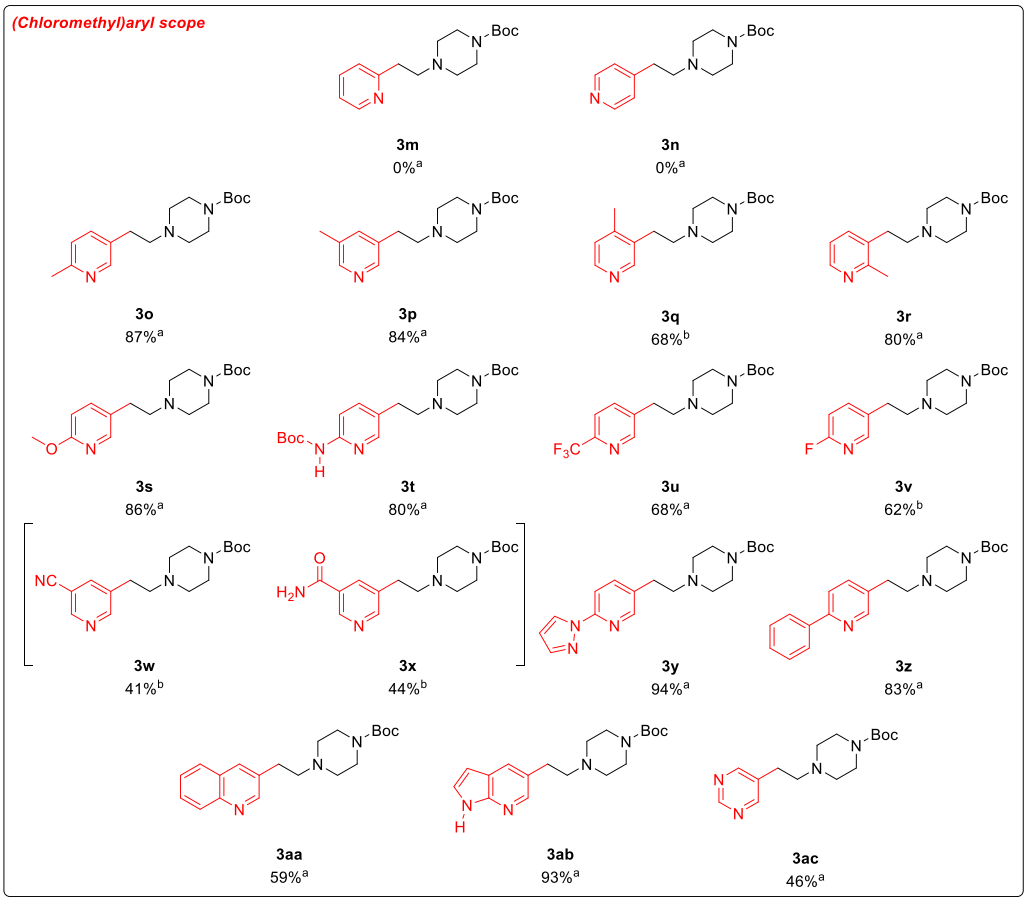
Scheme 6. Reaction Scope and Isolated Yields of the Palladium-Catalyzed Formation of Pyridine-Based Arylethylamines 3[a]







[a]Reactions were performed on 0.70 mmol (1.0 equiv) of chloride **2** unless otherwise stated. Conditions: (a) chloride **2** (1.0 equiv), trifluoroborate salt **1** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), K_2CO_3 (10 equiv), 10:1 ^{t}AmOH/H_2O (0.1 M); reflux; and (b) chloride **2** (1.0 equiv), trifluoroborate salt **1** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), K_2CO_3 (10 equiv), 10:1 ^{t}AmOH/H_2O (0.1 M), 80 °C.

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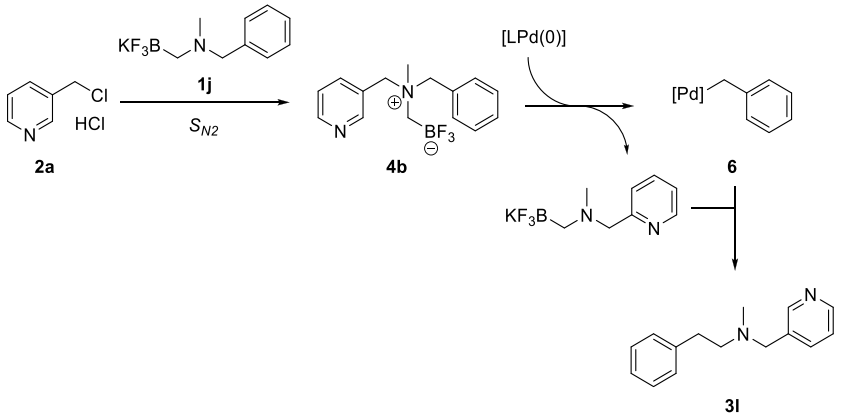
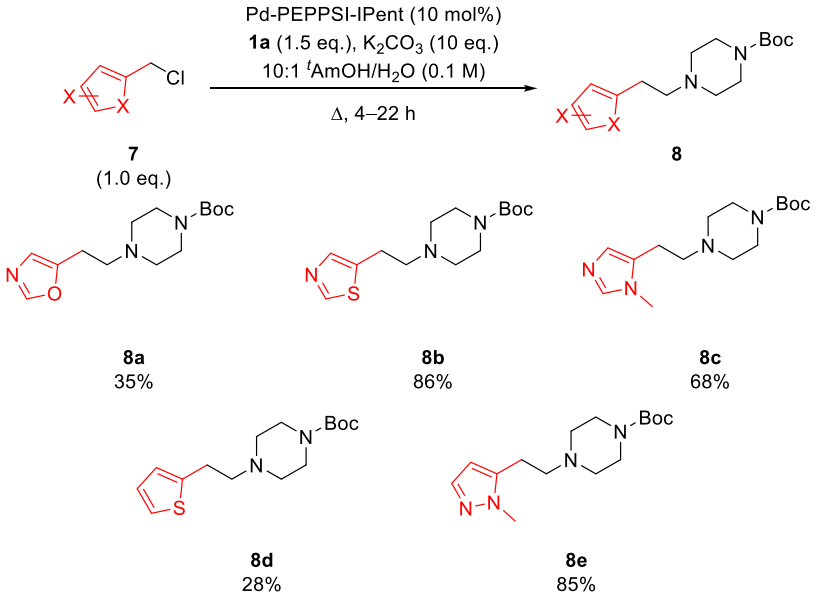
Scheme 7. Proposed Mechanism for the Formation of Aminomethylpyridine 3l from 3-(Chloromethyl)pyridine 2a and Benzylamine-Derived Trifluoroborate Salt 1j



Scheme 8. Reaction Scope and Isolated Yields of the Palladium-Catalyzed Formation of 5-Membered Heterocycle-Based Arylethylamines 8a–e[a]



[a]Reactions were performed on 0.70 mmol of chloride. Conditions: chloride **7** (1.0 equiv), trifluoroborate salt **1a** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), K_2CO_3 (10 equiv), 10:1 $^tAmOH/H_2O$ (0.1 M), reflux.

proposal that obtaining a balance in the rate of hydrolysis and cross-coupling steps is fundamental to reaction success.

These optimized conditions were successfully applied to a range of aminomethyltrifluoroborate salts **1** and benzyl chlorides **9** (Scheme 10). Formation of dibenzyl **10g** was achieved using the internal salt (as opposed to the potassium salt) as this form proved more amenable to precipitation as a crystalline solid. These conditions could also be applied to the coupling of 3-(chloromethyl)pyridine **2a** with aminomethyltrifluoroborate salts to afford (pyridin-3-yl)ethylamines **3a** and **3e**, albeit in lower yields than under the conditions optimized specifically for this substrate. A variety of substituents around the phenyl ring were tolerated in the reaction. Gratifyingly, the sterically encumbered 2,6-dimethyl **10i** was formed in good yield, while the *para*-methyl **10h** was synthesized in a 92% yield. Arylethylamines derived from naphthalene and quinoline were accessed in 75 and 63% yields, respectively while both aryl sulfones and thioethers were well tolerated. Anisoles **10n–10p** were all obtained in excellent yield (75–93%) with dihydrobenzofuran **10q** obtained in a slightly lower yield, although pleasingly no oxidation to the corresponding benzofuran was seen. Generally, para substitution of mesomeric electron-donating groups resulted in lower yields than ortho- or meta-substituted analogues. This effect was particularly pronounced in the case of *N*,*N*-dimethylanilines **10r–10t**. This may be due to disfavoring the formation of/destabilizing betaine intermediates formed prior to oxidative addition. The same effect was not observed in the case of inductively electron-withdrawing trifluoromethyl substituents. In this case, near-identical yields were obtained for *para* **10x** and *meta* **10y** substitutions, with *ortho* **10z** substitution giving the lowest yield, potentially due to the increased steric encumberment around the reaction center. Reactive vinyl and primary alcohol groups were tolerated but in lower yield, with a degree of oxidation to the corresponding benzaldehyde observed by LC-MS and ^1H NMR spectroscopy during the formation of alcohol **10v**.[35] Carbonyl-containing moieties were applied to the reaction, with acetophenone **10aa** synthesized in good yield despite the presence of acidic α-

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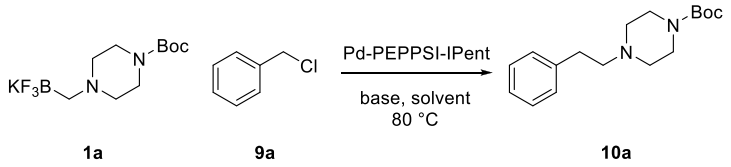
Scheme 9. Conditions Tested for the Formation of Phenethylamine 10a Using HTE[a]

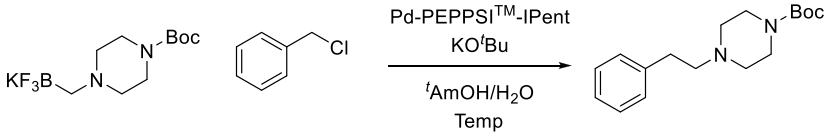


1a 9a 10a

	K_2CO_3	Cs_2CO_3	K_3PO_4	Na_2CO_3	KO^{t}Bu	NaO^{t}Bu
1,4-Dioxane	0.13	0.13	0.13	0.03	0.13	0.10
IPA	0.10	0.13	0.13	0.03	0.01	0.00
^{t}AmOH	0.13	0.17	0.17	0.10	0.17	0.10
TFE	0.00	0.00	0.00	0.00	0.00	0.00

[a]See the Supporting Information (SI) for more details. Conditions: BnCl (**9a**) (1.0 equiv), potassium trifluoroborate **1a** (1.5 equiv), Pd precatalyst (10 mol %), base (4 equiv), solvent:water (4:1), 80 °C, 24 h. Values shown are the ratio of the peak area versus internal standard of triphenylamine as calculated using LC-MS.

Table 2. Conditions Tested in the Optimization of the Formation of Arylethylamine 10a

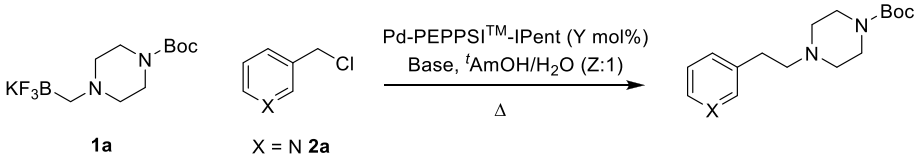


1a 9a 10a

entry	^{t}AmOH:H_2O ratio[a]	X equiv of base[b]	time/h	temperature/°C	yield of **10a**[c]/%
1	4:1	4	19	80	30
2	4:1	10	19	80	87
3	10:1	4	19	80	0
4	10:1	10	19	80	36
5	4:1	4	2	Δ	51
6	4:1	10	2	Δ	96

[a]Reaction performed at 0.1 M concentration. [b]Reactions were performed using 0.86 mmol (0.10 mL) of BnCl **9a** with 1.5 equiv of salt **1a** and 0.1 equiv of Pd-PEPPSI-IPent. [c]Isolated yield.

Table 3. Isolated Yields Obtained for C(sp^3)−C(sp^3) Cross-Coupling Using Lower Catalyst Loadings



1a X = N **2a** X = CH **9a**

starting material	Y/mol %	base	Z	isolated yield/%
2a	5	K_2CO_3	10	84
9a	1	KO^{t}Bu	4	96

protons. Reactions to form ester **10ab** and benzamide **10ac** proceeded smoothly with no hydrolysis, although the less sterically encumbered methyl benzoate fully hydrolyzed to acid **10ad**, which itself could be synthesized from the corresponding (chloromethyl)benzoic acid. Purification of acid **10ad** was achieved by mass-directed high-performance liquid chromatography (HPLC) due to the propensity of the product to exist as a zwitterion.

During investigation of the reaction scope, evidence of the formation of betaines **11**, analogous to intermediate **4**, was seen prior to product formation (for exemplar LC-MS of the reaction mixture for the formation of **10a** after 10 min showing betaine **11a** as the major intermediate, see Figure S18 in the SI), indicating that cross-coupling of aminomethyltrifluoroborate salts with both benzyl chlorides **9** and 3-(chloromethyl)-pyridines **3** proceeds *via* the same mechanism (see Scheme 5). Betaine **11a** was obtained to confirm this by applying the coupling conditions in the absence of palladium catalyst; subsequent reapplication of optimized coupling conditions to betaine **11a** furnished the phenethylamine **10a** in a 90% yield. Furthermore, benzyltriethylammonium chloride (**12**) proved an able electrophile in place of benzyl chloride **9a**, furnishing phenethylamine **10a** in a 91% yield (Scheme 11).

The usefulness of this methodology was exemplified in the synthesis of the pharmaceutical agent darifenacin (**17**) used to treat urinary incontinence.[36] Tosylation of *N*-Boc-hydroxypyr-

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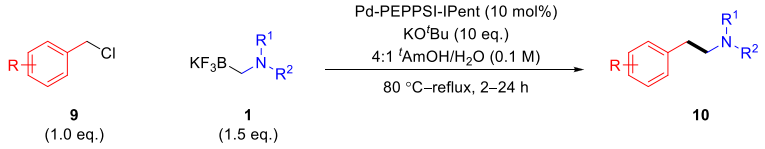
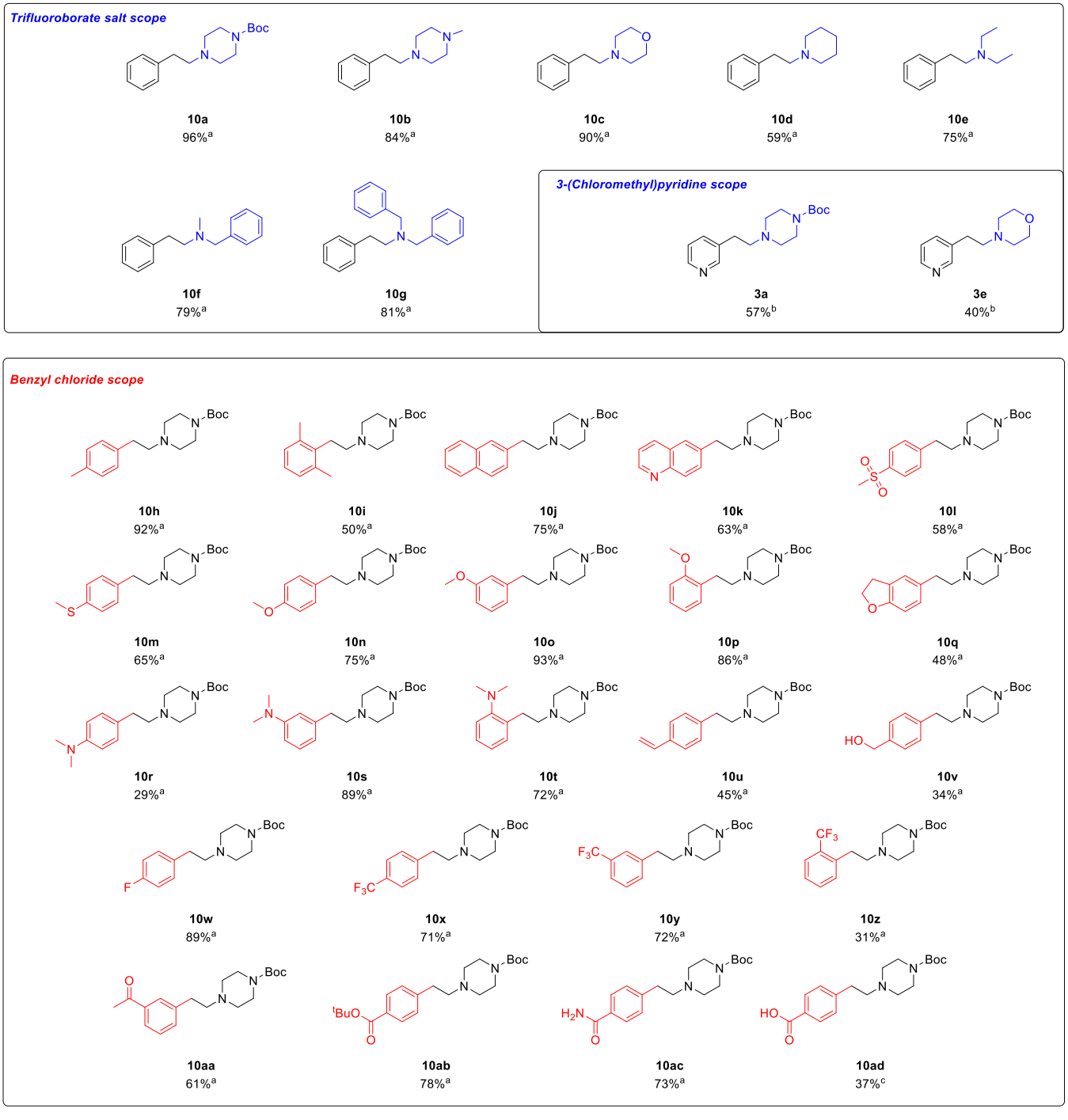
Scheme 10. Reaction Scope and Isolated Yields of the Palladium-Catalyzed Formation of Phenethylamines 10[a]





[a]Conditions: (a) chloride **9** (0.86 mmol, 1.0 equiv), trifluoroborate salt **1** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), KO^{t}Bu (10 equiv), 4:1 ^{t}AmOH/H$_2$O (0.1 M); reflux; (b) chloride **9** (0.70 mmol, 1.0 equiv), trifluoroborate salt **1** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), KO^{t}Bu (10 equiv), 4:1 ^{t}AmOH/H$_2$O (0.1 M), reflux; and (c) chloride **9** (1.00 mmol, 1.0 equiv), trifluoroborate salt **1** (1.5 equiv), Pd-PEPPSI-IPent (10 mol %), KO^{t}Bu (10 equiv), 4:1 ^{t}AmOH/H$_2$O (0.1 M), 80 °C.

rolidine **13** afforded tosyl **14**, which was reacted with the anion of diphenylacetonitrile and deprotected to provide pyrrolidine **15**.[37] Derivatization to the potassium aminomethyltrifluoroborate salt **16** was achieved in good yield under general conditions.[9] Cross-coupling with the requisite chloride followed by hydrolysis using a modification of previously reported

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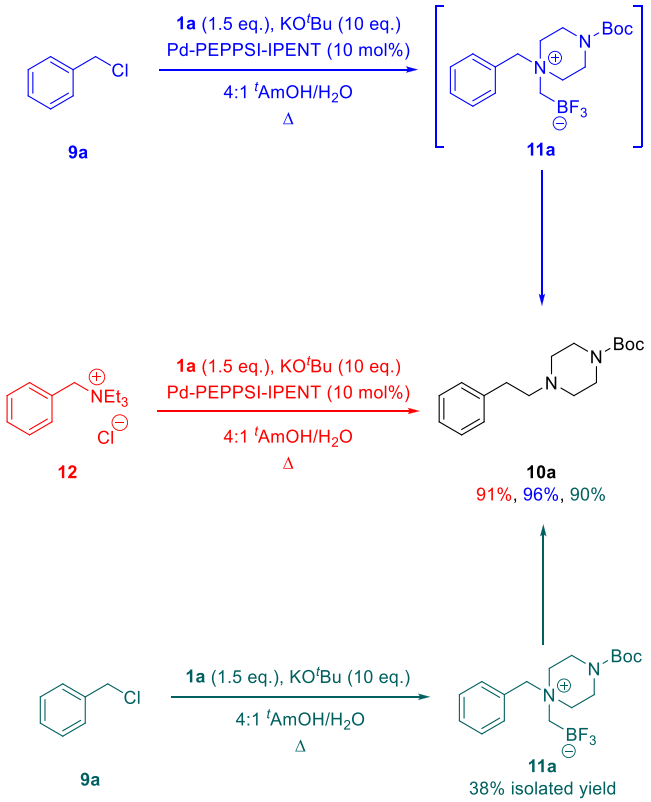
Scheme 11. Proposed Mechanism of the Formation of 10a as Indicated by the Observation, Isolation of Betaine 11a, and Further Reaction to Product (Blue and Teal)[a]



[a]Benzyltriethylammonium chloride (**12**) was also a suitable coupling partner in place of benzyl chloride **9a** (red).

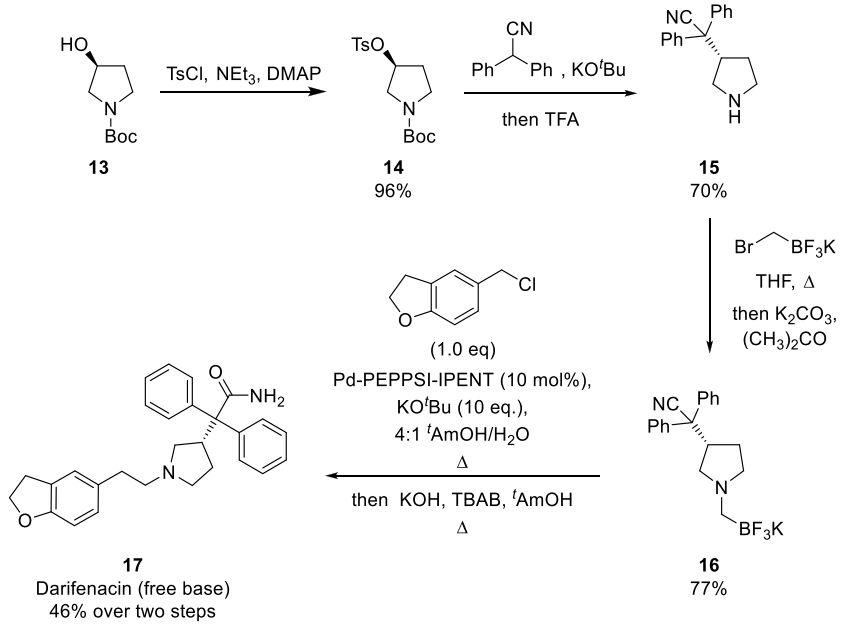
conditions afforded darifenacin (**17**) in a 46% yield (Scheme 12).[38] The yield of the cross-coupling/hydrolysis could likely be improved with further optimization; however, this route does overcome issues pertaining to impurity formation highlighted in the currently employed commercial synthesis.[37]

Finally, with a robust reaction scope established, the possibility of applying lower catalyst loadings was investigated with a view to increasing scalability of this methodology. Pleasingly, cross-coupling of trifluoroborate **1a** with 3-(chloromethyl)pyridine **2a** proceeded in an 84% yield with a 5 mol % catalyst loading, although lower loadings resulted in reaction stalling at betaine **4a**. More pleasing still, the coupling of benzyl chloride **9a** with potassium trifluoroborate **1a** proceeded in a 96% yield with a 1 mol % catalyst loading. It is not presently understood why lower loadings resulted in reaction stalling during the reaction of pyridine **2a**; further investigations are ongoing.

CONCLUSIONS

In conclusion, a novel synthetic procedure for the assembly of arylethylamine scaffolds is reported. Conditions were initially identified using plate-based high-throughput chemistry and were then optimized on mmol scale. This procedure utilizes stable, solid aminomethyltrifluoroborate salts and (chloromethyl)aryls, which can be sourced commercially or easily obtained from the corresponding alcohol. Conditions were initially identified optimized for the synthesis of (pyridin-3-yl)ethylamine derivatives and were found to be suitable for the selection of 5-membered heterocycles as well. A second set of conditions were then reoptimized for the cross-coupling of benzyl chloride derivatives, utilizing the same solvent and catalyst but employing potassium *tert*-butoxide in place of potassium carbonate. Both condition sets utilize 10 equiv of base (versus the limiting chloride), and it is proposed that the desiccating properties of the base employed are key to the reaction success by ensuring that trifluoroborate hydrolysis occurs at an appropriate rate compared to the elementary steps of the Suzuki–Miyaura catalytic cycle. Isolation of ammonium-containing betaines prior to arylethylamine formation indicates that oxidative addition generally occurs with the C–N bond scission and not C–Cl; further mechanistic studies are ongoing.

Scheme 12. Synthesis of Darifenacin (17) Using a C(sp^3)–C(sp^3) Cross-Coupling-Based Approach



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EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers and were used without further purification. Reactions were stirred magnetically and heated using a metal heating block. Air- and moisture-sensitive reactions were performed using standard Schlenk manifold techniques. Column chromatography was performed on disposable normal-phase RediSep Rf columns (12−220 g). Melting points were recorded using a BUCHI Melting Point M-565. Specific rotations were measured using an Anton Paar MCP 150 Modular Compact Polarimeter. Nuclear magnetic resonance spectra were recorded in the solvent stated on Bruker NMR spectrometers (AVIII 400 MHz, AVIIIHD 600 MHz, and AVIII700 MHz). Spectra were referenced to the residual solvent peak. Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and NMR spectroscopy and 0.1 ppm for ^{13}C and ^{19}F NMR spectroscopy. Coupling constants (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz. 2D NMR spectra were obtained to confirm structures where necessary. Multiplicity is quoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet), and br (broad). Infrared spectra were recorded using a Perkin Elmer FTIR spectrometer in the range of 4000−600 cm^{-1}. Liquid chromatography-mass spectra (LC-MS) were recorded as follows: LC conditions: ultrahigh-pressure liquid chromatography (UPLC) analysis was conducted on an Acquity UPLC CSH C18 column (50 mm × 2.1 mm i.d. 1.7 μm packing diameter) at 40 °C using the following methods:

1. 2 min HpH: The solvents employed were A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution, B = acetonitrile. Gradient: 0.0−1.5 min: 0−97% B; 1.5−1.9 min: 97% B; 1.9−2.0 min: 97−0% B.
2. 2 min For: The solvents employed were A = 0.1% v/v solution of formic acid in water adjusted, B = 0.1% v/v solution of formic acid in acetonitrile. Gradient: 0.0−1.5 min: 3−97% B; 1.5−1.9 min: 97% B; 1.9−2.0 min: 97−2% B.
3. 2 min TFA: The solvents employed were A = 0.1% v/v solution of trifluoroacetic acid in water adjusted, B = 0.1% v/v solution of trifluoroacetic acid in acetonitrile. Gradient: 0.0−1.5 min: 5−95% B; 1.5−1.9 min: 95% B; 1.9−2.0 min: 95−5% B.

The UV detection was a summed signal from a wavelength of 210−350 nm. MS: Waters QDA; ionization mode: alternate-scan positive and negative electrospray; scan frequency: 5 Hz. High-resolution mass spectra (HRMS) were recorded using an Acquity UPLC CSH C18 column (LC) and Waters XEVO G2-XS QTof (ES+) (MS).

Compound Synthesis and Characterization. *General Procedure A for Preparation of N,N-Dialkylaminotrifluoroborate Salts from Solid Amines.* Potassium (bromomethyl)trifluoroborate (1.00 equiv) was added to a solution of amine (1.00−1.05 equiv) in tetrahydrofuran (THF, 24−50 mL) at rt, heated at 80 °C for 2.5−20 h, and then concentrated *in vacuo*. The residue was dissolved in acetone (120−500 mL), and K_2CO_3 (1.00 equiv) was added. The suspension was stirred for 70 min, filtered through celite to remove the insoluble salts, and concentrated *in vacuo*. The crude solid was dissolved in a minimal amount of hot acetone/Et_2O mixture (2:1), and cyclohexane was added dropwise leading to precipitation of the product. The product was then filtered, collected, and dried overnight *in vacuo* to afford the desired compound.

General Procedure B for Preparation of N,N-Dialkylaminotrifluoroborate Salts from Liquid Amines in THF. Potassium (bromomethyl)trifluoroborate (1.00 equiv) was added to a solution of amine (1.05 equiv) in THF (14−25 mL) at rt, heated at 80 °C for 2−16 h, and then concentrated *in vacuo*. The residue was dissolved in acetone (150 mL), and K_2CO_3 (1.38 g, 10.0 mmol, 1.00 equiv) was added. The suspension was stirred for 1 h, filtered through celite to remove the insoluble salts, and concentrated *in vacuo*. The crude solid was dissolved in a minimal amount of hot acetone, and Et_2O was added dropwise leading to precipitation of the product. The product was then filtered, collected, and dried overnight *in vacuo* to afford the desired compound.

General Procedure C for Preparation of N,N-Dialkylaminotrifluoroborate Salts from Neat Liquid Amines. Potassium (bromomethyl)trifluoroborate (2.00 g, 10.0 mmol, 1.00 equiv) was added to neat amine (24−40 mL) at rt, heated at 80 °C for 0.5−3 h, and then concentrated *in vacuo*. The residue was dissolved in acetone (150 mL), and K_2CO_3 (1.38 g, 10.0 mmol) was added. The suspension was stirred for 1 h, filtered through celite to remove the insoluble salts, and concentrated *in vacuo*. The crude solid was dissolved in a minimal amount of hot acetone, and Et_2O was added dropwise leading to precipitation of the product. The product was then filtered, collected, and dried overnight *in vacuo* to afford the desired compound.

*Potassium 4-Trifluoroboratomethylpiperazine-1-carboxylic Acid tert-Butyl Ester (**1a**).* Prepared according to general procedure A using 1-Boc-piperazine (9.27 g, 49.8 mmol, 1.00 equiv) in THF (40 mL) and stirring at 80 °C for 2.5 h prior to addition of acetone (500 mL) and K_2CO_3 (6.88 g, 49.8 mmol, 1.00 equiv). The title compound was obtained as a white solid (13.8 g, 45.1 mmol, 91% yield). Analytical data are consistent with the literature.[9] Mp: 173−175 °C; IR (neat): 2981, 1646, 1440, 1285, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.47 (br s, 4H), 2.94 (br s, 4H), 1.88 (q, J = 4.9 Hz, 2H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 153.4, 79.6, 53.0, 27.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −137.3; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.3.

*Potassium (S)-((4-(tert-Butoxycarbonyl)-2-methylpiperazin-1-yl)methyl)trifluoroborate (**1b**).* Prepared according to general procedure A using (*S*)-1-Boc-3-methylpiperazine (2.63 g, 13.1 mmol, 1.05 equiv) in THF (24 mL) and stirring at 80 °C for 20 h prior to addition of acetone (120 mL) and K_2CO_3 (1.73 g, 12.5 mmol, 1.00 equiv). The title compound was obtained as a white amorphous solid (2.70 g, 8,43 mmol, 67% yield). Analytical data are consistent with the literature.[39] $[\alpha]_D^{20}$ (c = 10.0 mg/mL, MeOH): −4; IR (neat): 2975, 2935, 1694, 1421, 1054 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (br s, 2H), 3.25 (br s, 4H), 2.83−2.68 (m, 1H), 2.11−1.98 (m, 1H), 1.70 (br s, 1H), 1.40 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 153.5, 79.4, 57.6 (br s), 50.9 (br s), 46.3 (br s), 27.9, 26.3, 13.4 (br s); ^{19}F NMR (376 MHz, DMSO-d_6) δ = −136.8; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.4.

*Potassium 1-Methyl-4-(trifluoroboratomethyl)piperazine (**1c**).* Prepared according to general procedure B using potassium (bromomethyl)trifluoroborate (2.00 g, 10.0 mmol, 1.00 equiv) and 1-methylpiperazine (1.17 mL, 10.5 mmol, 1.05 equiv) in THF (14 mL) and stirring at 80 °C for 4 h. The title compound was obtained as a white solid (1.78 g, 8.09 mmol, 81% yield). Analytical data are consistent with the literature.[15] Mp: 139−142 °C; IR (neat): 2981, 2951, 1460, 1288, 1161, 1055 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ = 3.34 (br s, 4H), 2.70 (br s, 4H), 2.30 (s, 3H), 2.13 (br s, 2H); ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ = 54.9, 52.2, 45.1; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −142.3; ^{11}B NMR (160 MHz, acetone-d_6) δ = 2.0 (q, J = 48.9 Hz).

*Potassium (Thiomorpholin-4-yl-methyl)trifluoroborate (**1d**).* Prepared according to general procedure B using potassium (bromomethyl)trifluoroborate (2.00 g, 10.0 mmol, 1.00 equiv) and thiomorpholine (0.98 mL, 10.5 mmol, 1.05 equiv) in THF (14 mL) and stirring at 80 °C for 16 h. The title compound was obtained as a white solid (1.05 g, 4.71 mmol, 47% yield). Analytical data are consistent with the literature.[40] Mp: 137−140 °C; IR (neat): 2961, 2933, 1455, 1407, 1289, 1061 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.13−3.04 (m, 4H), 2.82−2.74 (m, 4H), 1.81 (q, J = 5.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 55.7, 24.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −136.6; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.4.

*Potassium 4-Trifluoroboratomethyl-morpholine (**1e**).* Prepared according to general procedure C using morpholine (30 mL) and stirring at 80 °C for 30 min. The title compound was obtained as a white amorphous solid (974 mg, 4.70 mmol, 47% yield). Analytical data are consistent with the literature.[9] IR (neat): 2983, 2970, 1459, 1261, 1120, 1053 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.74 (t, J = 4.2 Hz, 4H), 3.05 (br s, 4H), 1.96 (q, J = 5.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 63.4, 53.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −137.4; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.1.

*Potassium 1-(Trifluoroboratomethyl)piperidine (**1f**).* Prepared according to general procedure C using piperidine (24 mL) and stirring at 80 °C for 50 min. The title compound was obtained as a white

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solid (1.33 g, 6.49 mmol, 65% yield). Analytical data are consistent with the literature.[41] Mp: 145−148 °C; IR (neat): 2950, 2866, 1455, 1306, 1130, 1056 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.00 (br s, 4H), 1.91 (q, J = 4.9 Hz, 2H), 1.67 (quin, J = 5.9 Hz, 4H), 1.47 (br s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 54.5, 22.6, 21.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −137.5; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.4 (q, J = 49.9 Hz).

*Potassium N,N-Diethyltrifluoroboratomethylamine (**1g**).* Prepared according to general procedure C using diethylamine (40 mL) and stirring at 80 °C for 3 h. The title compound was obtained as a white solid (1.51 g, 7.82 mmol, 79% yield). Analytical data are consistent with the literature.[9] Mp: 96−99 °C; IR (neat): 2982, 2951, 1471, 1400, 1244, 1065 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 2.99 (q, J = 7.3 Hz, 4H), 1.90 (q, J = 4.9 Hz, 2H), 1.13 (t, J = 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 48.3, 8.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −137.9; ^{11}B NMR (160 MHz, DMSO-d_6) δ = 2.2.

*Potassium (((tert-Butoxycarbonyl)amino)methyl)trifluoroborate (**1h**).* To a stirred solution of 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.53 g, 20.0 mmol, 1.0 equiv) in THF (60 mL) at −78 °C was added KHMDS (1 M in THF) (20.0 mL, 20.0 mmol, 1.0 equiv) slowly over 3 min. The reaction was stirred at −78 °C for 15 min and then at rt for 2 h. The reaction was cooled to 0 °C, and methanol (1.62 mL, 40.0 mmol, 2.0 equiv) was added. After stirring for 1 h, di-*tert*-butyl dicarbonate (9.3 mL, 40.1 mmol, 2.0 equiv) was added in one portion and the reaction was allowed to warm to rt with stirring overnight. The reaction was concentrated *in vacuo*, and the residue was dissolved in methanol (40 mL) and cooled to 0 °C. To this was slowly added a solution of potassium hydrogen fluoride (6.25 g, 80 mmol, 4.0 equiv) in water (20 mL). After stirring vigorously for 30 min, the reaction was concentrated *in vacuo* and further dried *in vacuo* overnight. The crude solid was extracted with acetone (4 × 30 mL), and the combined extracts were concentrated *in vacuo*. Diethyl ether (60 mL) was added to precipitate the product, which was collected by filtration to afford the title compound (1.07 g, 4.51 mmol, 23% yield) as a white solid. Analytical data are consistent with the literature.[30] Mp: 189−192 °C; IR (neat): 3376, 2988, 2895, 1660, 1537, 1169, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.55 (br s, 1H), 1.87−1.77 (m, 2H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 156.3, 76.3, 28.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −142.0; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 3.4.

*Potassium N-Cyclohexyl-aminomethyltrifluoroborate (**1i**).* Prepared according to general procedure C using cyclohexylamine (24 mL) and stirring at 80 °C for 30 min. The title compound was obtained as a white solid (761 mg, 3.47 mmol, 35% yield). Analytical data are consistent with the literature.[41] Mp: 193−195 °C; IR (neat): 3229, 2925, 2856, 1585, 1295, 1067, 1016 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ = 6.73 (br s, 1H), 3.13 (tt, J = 11.5, 3.9 Hz, 1H), 2.31−2.20 (m, 2H), 1.98 (br s, 2H), 1.91−1.80 (m, 2H), 1.73−1.65 (m, 1H), 1.49 (qd, J = 12.2, 3.4 Hz, 2H), 1.37 (qt, J = 12.9, 3.2 Hz, 2H), 1.21 (qt, J = 12.7, 3.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, acetone-d_6) δ = 59.1, 25.5, 24.8; ^{19}F NMR (376 MHz, acetone-d_6) δ = −145.4; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 2.5.

*Potassium N-Benzyltrifluoroboratomethylamine (**1j**).* Prepared according to general procedure B using potassium (bromomethyl)-trifluoroborate (5.02 g, 25.0 mmol, 1.00 equiv) and *N*-benzylmethylamine (3.40 mL, 26.3 mmol, 1.05 equiv) in THF (25 mL) and stirring at 80 °C for 2 h. After filtration of the insoluble salts and concentration *in vacuo*, the residue was triturated with diethyl ether (3 × 40 mL) with sonication and the solid was collected by filtration to afford the title compound (4.61 g, 19.1 mmol, 76% yield) as a white amorphous solid. Analytical data are consistent with the literature.[9] IR (neat): 3187, 2987, 1458, 1318, 1169, 1043 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.50−7.38 (m, 5H), 4.04 (s, 2H), 2.55 (s, 3H), 1.83 (q, J = 5.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 132.1, 130.8, 128.8, 128.5, 61.01 42.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −137.3; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 2.3; LC-MS (HpH): 0.63 min (202) ($[M - K]^-$, 100%).

*((Dibenzylammonio)methyl)trifluoroborate (**1k**).* To a solution of dibenzylamine (3.85 mL, 20.0 mmol, 1.0 equiv) in THF (28 mL) was added potassium (bromomethyl)trifluoroborate (4.02 g, 20.0 mmol, 1.0 equiv) and the mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was dissolved in boiling acetone and filtered to remove KBr. Addition of diethyl ether to the residue and sonication for 5 min precipitated a solid, which was collected by filtration to afford the title compound (4.8 g, 17.20 mmol, 86% yield) as a white solid. Mp: 120−122 °C; IR (neat): 3191, 2988, 2947, 1459, 1405, 1318, 1193, 1054 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 8.90 (br s, 1H), 7.57−7.40 (m, 10H), 4.32−4.05 (m, 4H), 1.88−1.74 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 131.5, 130.6, 129.2, 128.6, 57.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −136.0; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 2.5; LC-MS (HpH): 278 ($[M - H]^-$, 100%); HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{15}H_{21}{}^{11}BF_3N_2^+$ 297.1744; found 297.1751.

*tert-Butyl (5-(Chloromethyl)pyridin-2-yl)carbamate (**2t**).* To a stirred solution of *tert*-butyl (5-(hydroxymethyl)pyridin-2-yl)-carbamate (500 mg, 2.23 mmol, 1.0 equiv) and DIPEA (0.78 mL, 4.47 mmol, 2.0 equiv) in THF (5 mL) at 0 °C was added methanesulfonyl chloride (0.21 mL, 2.70 mmol, 1.2 equiv) dropwise over 1 min. The reaction was stirred for 15 h and then was diluted with ethyl acetate (10 mL), washed with water (2 × 10 mL), passed through a hydrophobic frit, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (10−30% ethyl acetate in petroleum ether) to afford *tert*-butyl (5-(chloromethyl)pyridin-2-yl)carbamate (474 mg, 1.95 mmol, 87% yield) as a white solid. Mp (DCM/cyclohexane): dec. >200 °C; IR (neat): 2982, 1715, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.51 (br s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.71 (dd, J = 8.6, 2.4 Hz, 1H), 4.55 (s, 2H), 1.56 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 152.4, 152.4, 147.7, 138.7, 127.7, 112.2, 81.2, 43.2, 28.3; LC-MS (For): 1.06 min (243) ($[M + H]^+$, 99%); HRMS (ESI) m/z: $[M - CO_2{}^tBu + H]^+$ calcd for $C_6H_8{}^{35}ClN_2^+$ 143.0371; found 143.0376.

General Procedure D for Cross-Coupling of (Chloromethyl)-heteroaryls with Trifluoroborate Salts. A 50 mL round-bottom flask was charged with chloride (if solid) (0.70 mmol, 1.0 equiv), trifluoroborate salt (1.05 mmol, 1.5 equiv), K_2CO_3 (967 mg, 7.00 mmol, 10.0 equiv), and Pd-PEPPSI-IPent catalyst (55 mg, 0.07 mmol, 10 mol %) and was evacuated and back-filled with N_2 (3×). Chloride (if liquid) (0.70 mmol, 1.0 equiv), *tert*-amyl alcohol (6.4 mL), and water (0.6 mL) were added *via* a syringe, and the reaction was stirred at 80 °C/reflux for the stated time. The reaction was cooled to room temperature and filtered through celite eluting with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by automated flash chromatography on silica to afford the desired compound.

*tert-Butyl 4-(2-(Pyridin-3-yl)ethyl)piperazine-1-carboxylate (**3a**).* Prepared according to general procedure D using 3-(chloromethyl)-pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 5 h. Flash chromatography on silica (20−100% acetone in chloroform) afforded the title compound (177 mg, 0.607 mmol, 87% yield) as a white solid. Mp (DCM/cyclohexane): 73−76 °C; IR (neat): 2973, 2937, 2859, 2815, 1690, 1574, 1413, 1243, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.38−8.33 (m, 2H), 7.43 (dt, J = 7.8, 2.0 Hz, 1H), 7.11 (ddd, J = 7.8, 4.9, 1.0 Hz, 1H), 3.35 (t, J = 5.1 Hz, 4H), 2.72−2.66 (m, 2H), 2.53−2.48 (m, 2H), 2.35 (t, J = 5.1 Hz, 4H), 1.36 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.1, 147.7, 136.1, 135.5, 123.3, 79.7, 59.7, 52.9, 43.6 (br. s), 30.6, 28.4; LC-MS (TFA): 0.41 min (292) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_2^+$ 292.2020; found 292.2027.

*tert-Butyl (S)-3-Methyl-4-(2-(pyridin-3-yl)ethyl)piperazine-1-carboxylate (**3b**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium (*S*)-((4-(*tert*-butoxycarbonyl)-2-methylpiperazin-1-yl)-methyl)trifluoroborate (336 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (30−100% acetone in chloroform) afforded the title compound (170 mg, 0.557 mmol, 80% yield) as a colorless gum. $[\alpha]_D^{20}$ (c = 10.0 mg/mL, MeOH): +24; IR (neat): 2974, 2932, 2858, 2809, 1689, 1575, 1423, 1169 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ = 8.48−8.43 (m, 2H), 7.51 (dt, J = 7.7, 1.9

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Hz, 1H), 7.21 (dd, J = 7.7, 4.7 Hz, 1H), 3.81−3.54 (m, 2H), 3.21−3.11 (m, 1H), 2.94−2.69 (m, 5H), 2.60 (ddd, J = 12.9, 9.3, 5.7 Hz, 1H), 2.51−2.43 (m, 1H), 2.40−2.32 (m, 1H), 1.46 (s, 9H), 1.03 (d, J = 5.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ = 154.6, 150.1, 147.6, 136.1, 135.7, 123.2, 79.6, 54.9, 54.2, 51.2−48.9 (m, 2C), 44.8−42.8 (m, 1C), 29.8, 28.4, 14.9 (br s, 1C); LC-MS (HpH): 1.01 min (306) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{28}N_3O_2^+$ 306.2176; found 306.2180.

*1-Methyl-4-(2-(pyridin-3-yl)ethyl)piperazine (**3c**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium 1-methyl-4-(trifluoroboratomethyl)piperazine (231 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (15−100% methanol in acetone) afforded the title compound (109 mg, 0.531 mmol, 76% yield) as a pale yellow oil. IR (neat): 2939, 2876, 2802, 1576, 1459, 1284, 1164, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50−8.40 (m, 2H), 7.51 (dt, J = 7.8, 2.0 Hz, 1H), 7.19 (dd, J = 7.8, 4.9 Hz, 1H), 2.83−2.74 (m, 2H), 2.65−2.39 (m, 10H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 150.1, 147.5, 136.0, 135.7, 123.2, 59.7, 55.1, 53.1, 46.0, 30.7; LC-MS (HpH): 0.58 min (206) ([M + H]$^+$, 99%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}N_3^+$ 206.1652; found 206.1655.

*4-(2-(Pyridin-3-yl)ethyl)thiomorpholine (**3d**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium (thiomorpholin-4-yl-methyl)trifluoroborate (234 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (30−100% acetone in chloroform) afforded the title compound (52 mg, 0.250 mmol, 36% yield) as a pale yellow oil. IR (neat): 2910, 2809, 2769, 1575, 1423, 1282, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48−8.44 (m, 2H), 7.51 (dt, J = 7.7, 2.1 Hz, 1H), 7.21 (ddd, J = 7.7, 4.9, 1.0 Hz, 1H), 2.82−2.75 (m, 6H), 2.72−2.67 (m, 4H), 2.66−2.60 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 150.1, 147.6, 136.1, 135.6, 123.2, 60.4, 54.9, 30.3, 28.0; LC-MS (HpH): 0.78 min (209) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{17}N_2S^+$ 209.1107; found 209.1112.

*4-(2-(Pyridin-3-yl)ethyl)morpholine (**3e**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium (morpholin-4-yl)methyltrifluoroborate (217 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 22 h. Flash chromatography on silica (30−100% acetone in chloroform) afforded the title compound (69 mg, 0.359 mmol, 51% yield) as a colorless oil. IR (neat): 2953, 2854, 2808, 1575, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51−8.44 (m, 2H), 7.54 (dt, J = 7.8, 2.0 Hz, 1H), 7.22 (ddd, J = 7.8, 4.9, 1.0 Hz, 1H), 3.75 (t, J = 4.4 Hz, 4H), 2.86−2.78 (m, 2H), 2.65−2.59 (m, 2H), 2.54 (t, J = 4.4 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 150.1, 147.7, 136.1, 135.4, 123.3, 66.9, 60.0, 53.6, 30.3; LC-MS (HpH): 0.61 min (193) ([M + H]$^+$, 98%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{17}N_2O^+$ 193.1335; found 193.1336.

*3-(2-(Piperidin-1-yl)ethyl)pyridine (**3f**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium 1-(trifluoroboratomethyl)piperidine (215 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 23 h. Flash chromatography on silica (10% methanol in acetone) afforded the title compound (65 mg, 0.342 mmol, 49% yield) as a yellow oil. IR (neat): 2932, 2835, 2780, 2762, 1575, 1423, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48−8.41 (m, 2H), 7.51 (dt, J = 7.8, 2.0 Hz, 1H), 7.19 (dd, J = 7.8, 4.9 Hz, 1H), 2.82−2.75 (m, 2H), 2.58−2.51 (m, 2H), 2.50−2.38 (m, 4H), 1.60 (quin, J = 5.6 Hz, 4H), 1.49−1.41 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 150.1, 147.5, 136.0, 136.0, 123.2, 60.6, 54.5, 30.7, 26.0, 24.4; LC-MS (HpH): 0.85 min (191) ([M + H]$^+$, 95%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{19}N_2^+$ 191.1543; found 191.1550.

*N,N-Diethyl-2-(pyridin-3-yl)ethan-1-amine (**3g**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium *N,N*-diethyltrifluoroboratomethylamine (203 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (15−80% methanol in acetone) afforded the title compound (75 mg, 0.421 mmol, 60% yield) as a pale yellow oil. IR (neat): 2968, 2935, 2873, 2805, 1575, 1478, 1422, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50−8.43 (m, 2H), 7.53 (dt, J = 8.0, 1.9 Hz, 1H), 7.21 (dd, J = 8.0, 5.1 Hz, 1H), 2.80−2.73 (m, 2H), 2.73−2.67 (m, 2H), 2.62 (q, J = 7.1 Hz, 4H), 1.06 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 150.2, 147.4, 136.1, 136.1, 123.2, 54.5, 46.9, 30.9, 11.9; LC-MS (HpH): 0.81 min (179) ([M + H]+, 98%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{19}N_2^+$ 179.1543; found 179.1549.

*tert-Butyl (2-(Pyridin-3-yl)ethyl)carbamate (**3h**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium (((*tert*-butoxycarbonyl)amino)methyl)trifluoroborate (249 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−40% acetone in chloroform) afforded the title compound (85 mg, 0.382 mmol, 55% yield) as a colorless oil. Analytical data are consistent with the literature.[8] IR (neat): 3338, 2976, 2932, 1692, 1525, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46−8.41 (m, 2H), 7.54−7.48 (m, 1H), 7.21 (ddd, J = 7.8, 4.9, 1.0 Hz, 1H), 4.73 (br s, 1H), 3.36 (q, J = 6.6 Hz, 2H), 2.79 (t, J = 7.1 Hz, 2H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.8, 150.1, 147.8, 136.2, 134.4, 123.4, 79.3, 41.4, 33.4, 28.3; LC-MS (HpH): 0.85 min (223) ([M + H]$^+$, 100%).

*N-Methyl-N-(pyridin-3-yl-methyl)cyclohexanamine (**3j**).* Prepared according to general procedure D using 3-(chloromethyl)pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium *N*-cyclohexyl-aminomethyltrifluoroborate (230 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (70−100% EtOAc (+1% NEt_3) in cyclohexane) afforded the title compound (28 mg, 0.137 mmol, 20% yield) as a pale yellow oil. IR (neat): 2932, 2853, 2780, 2762, 1575, 1423, 1114 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.52 (d, J = 1.5 Hz, 1H), 8.50−8.47 (m, 1H), 7.69 (br d, J = 7.3 Hz, 1H), 7.25 (dd, J = 7.7, 4.8 Hz, 1H), 3.58 (s, 2H), 2.49−2.39 (m, 1H), 2.19 (s, 3H), 1.90−1.77 (m, 4H), 1.68−1.57 (m, 1H), 1.37−1.19 (m, 4H), 1.10 (qt, J = 12.6, 3.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ = 150.2, 148.3, 136.5, 135.5 (br s), 123.3, 62.6, 55.0, 37.5, 28.5, 26.3, 25.9; LC-MS (HpH): 1.09 min (205) ([M + H]$^+$, 96%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_{21}N_2^+$ 205.1699; found 205.1706.

*N-Methyl-2-phenyl-N-(pyridin-3-yl-methyl)ethan-1-amine (**3l**).* Prepared according to general procedure D using 3-(chloromethyl)-pyridine hydrochloride (115 mg, 0.70 mmol, 1.0 equiv) and potassium *N*-benzyltrifluoroboratomethylamine (253 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (10−80% acetone in chloroform) afforded the title compound (61 mg, 0.270 mmol, 39% yield) as a pale yellow oil. IR (neat): 2946, 2790, 1576, 1453, 1425, 1122, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54−8.44 (m, 2H), 7.65−7.57 (m, 1H), 7.33−7.15 (m, 6H), 3.57 (s, 2H), 2.87−2.79 (m, 2H), 2.71−2.64 (m, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.27, 148.5, 140.3, 136.5, 134.4, 128.7, 128.3, 126.0, 123.3, 59.4, 59.0, 42.0, 33.9; LC-MS (HpH): 1.07 min (227) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{19}N_2^+$ 227.1543; found 227.1551.

*tert-Butyl 4-(2-(6-Methylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3o**).* Prepared according to general procedure D using 5-(chloromethyl)-2-methylpyridine hydrochloride (125 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (30−100% acetone in chloroform) afforded the title compound (187 mg, 0.612 mmol, 87% yield) as a white solid. Mp (DCM/cyclohexane): 67−70 °C; IR (neat): 2974, 2929, 2809, 1690, 1418, 1244, 1167, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 7.8, 2.3 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 3.40 (t, J = 5.1 Hz, 4H), 2.73−2.67 (m, 2H), 2.55−2.50 (m, 2H), 2.47 (s, 3H), 2.40 (t, J = 5.1 Hz, 4H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.9, 154.6, 149.1, 136.4, 132.2, 122.7, 79.5, 59.7, 52.8, 43.4 (br s), 30.1, 28.3, 23.8; LC-MS (HpH): 1.01 min (306) ([M + H]$^+$, 99%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{28}N_3O_2^+$ 306.2176; found 306.2183.

*tert-Butyl 4-(2-(5-Methylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3p**).* Prepared according to general procedure D using 3-(chloromethyl)-5-methylpyridine hydrochloride (125 mg, 0.70 mmol,

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1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−60% acetone in chloroform) afforded the title compound (180 mg, 0.589 mmol, 84% yield) as a white solid. Mp (DCM/cyclohexane): 66−69 °C; IR (neat): 2975, 2863, 2810, 1693, 1421, 1247, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.35−7.32 (m, 1H), 3.47 (t, J = 4.9 Hz, 4H), 2.82−2.73 (m, 2H), 2.64−2.57 (m, 2H), 2.48 (t, J = 4.9 Hz, 4H), 2.32 (s, 3H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 148.2, 147.3, 136.7, 134.9, 132.7, 79.7, 59.8, 52.9, 43.7 (br s, confirmed by HSQC and HMBC), 30.4, 28.4, 18.3; LC-MS (HpH): 1.04 min (306) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{28}N_3O_2^+$ 306.2176; found 306.2183.

*tert-Butyl 4-(2-(4-Methylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3q**).* Prepared according to general procedure D using 3-(chloromethyl)-5-methylpyridine hydrochloride (125 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at 80 °C for 19 h. Flash chromatography on silica (30−100% acetone in chloroform) afforded the title compound (146 mg, 0.478 mmol, 68% yield) as a pale pink solid. Mp (DCM/cyclohexane): 59−61 °C; IR (neat): 2974, 2933, 2811, 1689, 1595, 1413, 1246, 1667, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 7.05 (d, J = 4.9 Hz, 1H), 3.47 (t, J = 4.9 Hz, 4H), 2.84−2.78 (m, 2H), 2.59−2.52 (m, 2H), 2.49 (t, J = 4.9 Hz, 4H), 2.33 (s, 3H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.2, 147.7, 145.1, 134.0, 125.1, 79.7, 58.7, 53.0, 43.5 (br s), 28.4, 27.9, 18.7; LC-MS (HpH): 1.01 min (306) ($[M + H]^+$, 99%); HRMS (ESI) m/z: calcd for $C_{17}H_{28}N_3O_2^+$ ($[M + H]^+$) 306.2176; found 306.2180.

*tert-Butyl 4-(2-(2-Methylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3r**).* Prepared according to general procedure D using 3-(chloromethyl)-2-methylpyridine hydrochloride (125 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−80% acetone in chloroform) afforded the title compound (172 mg, 0.563 mmol, 80% yield) as a colorless oil. IR (neat): 2974, 2928, 2810, 1693, 1574, 1245, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.36 (dd, J = 4.9, 1.5 Hz, 1H), 7.43 (dd, J = 7.8, 1.5 Hz, 1H), 7.07 (dd, J = 7.8, 4.9 Hz, 1H), 3.48 (t, J = 4.8 Hz, 4H), 2.84−2.78 (m, 2H), 2.60−2.54 (m, 5H), 2.49 (t, J = 4.8 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.7, 154.7, 147.0, 136.8, 133.3, 121.3, 79.7, 58.6, 53.0, 43.6 (br s), 30.2, 28.4, 22.2; LC-MS (HpH): 1.00 min (306) ($[M + H]^+$, 95%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{28}N_3O_2^+$ 306.2176; found 306.2185.

*tert-Butyl 4-(2-(6-Methoxypyridin-3-yl)ethyl)piperazine-1-carboxylate (**3s**).* Prepared according to general procedure D using 5-(chloromethyl)-2-methoxypyridine (110 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 6 h. Flash chromatography on silica (0−60% acetone in chloroform) afforded the title compound (193 mg, 0.600 mmol, 86% yield) as a white solid. Mp (DCM/cyclohexane): 58−60 °C; IR (neat): 2975, 2944, 2863, 2809, 1692, 1609, 1572, 1492, 1247, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 2.5 Hz, 1H), 7.42 (dd, J = 8.3, 2.4 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 3.91 (s, 3H), 3.45 (t, J = 5.1 Hz, 4H), 2.74−2.68 (m, 2H), 2.58−2.52 (m, 2H), 2.45 (t, J = 5.1 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 162.9, 154.7, 146.3, 139.1, 128.1, 110.5, 79.6, 60.1, 53.3, 53.0, 43.5 (br s), 29.6, 28.4; LC-MS (HpH): 1.11 min (322) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{28}N_3O_3^+$ 322.2125; found 322.2130.

*tert-Butyl 4-(2-(6-((tert-Butoxycarbonyl)amino)pyridin-3-yl)ethyl)piperazine-1-carboxylate (**3t**).* Prepared according to general procedure D using *tert*-butyl (5-(chloromethyl)pyridin-2-yl)carbamate (170 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−60% acetone in chloroform) afforded the title compound (229 mg, 0.563 mmol, 80% yield) as a white solid. Mp (DCM/cyclohexane): 191−193 °C; IR (neat): 2979, 2864, 1721, 1673, 1534, 1403, 1251, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.62 (br s, 1H), 7.51 (dd, J = 8.7, 2.4 Hz, 1H), 3.45 (t, J = 4.9 Hz, 4H), 2.78−2.70 (m, 2H), 2.61−2.53 (m, 2H), 2.50−2.40 (m, 4H), 1.54 (s, 9H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 152.6, 150.5, 147.5, 138.4, 130.0, 112.0, 80.8, 79.6, 60.0, 52.9, 43.7 (br s, confirmed by HSQC), 29.9, 28.4, 28.3; LC-MS (HpH): 1.26 min (407) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{35}N_4O_4^+$ 407.2653; found 407.2657.

*tert-Butyl 4-(2-(6-(Trifluoromethyl)pyridin-3-yl)ethyl)piperazine-1-carboxylate (**3u**).* Prepared according to general procedure D using 5-(chloromethyl)-2-(trifluoromethyl)pyridine (162 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 5 h. Flash chromatography on silica (0−50% acetone in chloroform) afforded the title compound (170 mg, 0.473 mmol, 68% yield) as a white solid. Mp: (DCM/cyclohexane): 91−94 °C; IR (neat): 2982, 2859, 2793, 1676, 1420, 1340, 1248, 1164, 1126, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.58 (d, J = 2.0 Hz, 1H), 7.74−7.68 (m, 1H), 7.62−7.57 (m, 1H), 3.43 (t, J = 5.1 Hz, 4H), 2.90−2.83 (m, 2H), 2.65−2.60 (m, 2H), 2.45 (t, J = 5.1 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.3, 146.2 (q, $^2J_{C-F}$ = 34.5 Hz), 139.1, 137.3, 121.7 (q, $^1J_{C-F}$ = 274.1 Hz), 120.0 (q, $^3J_{C-F}$ = 2.9 Hz), 79.7 59.0, 52.9, 43.5 (br s), 30.3, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −67.8; LC-MS (HpH): 1.19 (360) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}F_3N_3O_2^+$ 360.1893; found 360.1900.

*tert-Butyl 4-(2-(6-Fluoropyridin-3-yl)ethyl)piperazine-1-carboxylate (**3v**).* Prepared according to general procedure D using 5-(chloromethyl)-2-fluoropyridine (102 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at 80 °C for 19 h. Flash chromatography on silica (0−40% acetone in chloroform) afforded the title compound (135 mg, 0.436 mmol, 62% yield) as a white solid. Mp (DCM/cyclohexane): 101−102 °C; IR (neat): 2974, 2936, 2864, 2813, 1687, 1594, 1483, 1245, 1168, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.05 (d, J = 2.4 Hz, 1H), 7.63 (td, J = 8.2, 2.4 Hz, 1H), 6.85 (dd, J = 8.2, 2.9 Hz, 1H), 3.44 (t, J = 4.9 Hz, 4H), 2.81−2.73 (m, 2H), 2.61− 2.54 (m, 2H), 2.44 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 162.4 (d, $^1J_{C-F}$ = 237.7 Hz), 154.7, 147.2 (d, $^3J_{C-F}$ = 14.7 Hz), 141.3 (d, $^3J_{C-F}$ = 8.1 Hz), 133.1 (d, $^4J_{C-F}$ = 4.4 Hz), 109.0 (d, $^2J_{C-F}$ = 37.4 Hz), 79.7, 59.6, 52.9, 43.6 (br s), 29.6, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −71.7; LC-MS (HpH): 1.07 min (310) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{25}FN_3O_2^+$ 310.1925; found 310.1927.

*tert-Butyl 4-(2-(5-Cyanopyridin-3-yl)ethyl)piperazine-1-carboxylate **3w** and tert-Butyl 4-(2-(5-Carbamoylpyridin-3-yl)ethyl)-piperazine-1-carboxylate **3x**.* Prepared according to general procedure D using 5-(chloromethyl)nicotinonitrile hydrochloride (132 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at 80 °C for 19 h. Flash chromatography on silica (0−100% acetone in chloroform) afforded **3w** and **3x**.

*tert-Butyl 4-(2-(5-Cyanopyridin-3-yl)ethyl)piperazine-1-carboxylate (**3w**).* Title compound (90 mg, 0.284 mmol, 41% yield) obtained as a white solid. Mp (DCM/cyclohexane): 70−72 °C; IR (neat): 2975, 2931, 2862, 2233, 1686, 1567, 1422, 1243, 1167, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.74 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 3.44 (t, J = 4.9 Hz, 4H), 2.85 (t, J = 7.3 Hz, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.51−2.39 (m, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.6, 153.5, 150.1, 139.1, 136.3, 116.6, 109.6, 79.7, 58.7, 52.8, 43.5 (br s), 30.0, 28.4; LC-MS (HpH): 1.01 min (317) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}N_4O_2^+$ 317.1972; found 317.1975.

*tert-Butyl 4-(2-(5-Carbamoylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3x**).* Title compound (102 mg, 0.305 mmol, 44% yield) obtained as a white solid. Mp (DCM/cyclohexane): 165−167 °C; IR (neat): 3356, 2193, 2974, 2937, 2865, 1667, 1625, 1576, 1166, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.85 (d, J = 2.0 Hz, 1H), 8.61

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(d, J = 2.0 Hz, 1H), 8.05 (t, J = 2.0 Hz, 1H), 6.52−5.80 (m, 2H), 3.44 (t, J = 4.9 Hz, 4H), 2.91−2.82 (m, 2H), 2.69−2.58 (m, 2H), 2.46 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 167.5, 154.7, 153.1, 145.9, 135.9, 135.7, 128.8, 79.7, 59.2, 52.9, 43.6 (br s), 30.3, 28.4; LC-MS (HpH): 0.79 min (335) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{27}N_4O_3^+$ 335.2078; found 335.2084.

*tert-Butyl 4-(2-(6-(1H-Pyrazol-1-yl)pyridin-3-yl)ethyl)piperazine-1-carboxylate (**3y**).* Prepared according to general procedure D using 5-(chloromethyl)-2-(1*H*-pyrazol-1-yl)pyridine (136 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 15 h. Flash chromatography on silica (0−40% acetone in chloroform) afforded the title compound (234 mg, 0.655 mmol, 94% yield) as a white solid. Mp (DCM/cyclohexane): 121−122 °C; IR (neat): 2973, 2858, 2809, 1687, 1598, 1484, 1394, 1246, 1172, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54−8.51 (m, 1H), 8.28−8.22 (m, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.73−7.69 (m, 1H), 7.65 (dd, J = 8.5, 1.5 Hz, 1H), 6.46−6.43 (m, 1H), 3.45 (t, J = 4.9 Hz, 4H), 2.85−2.77 (m, 2H), 2.65−2.57 (m, 2H), 2.46 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.1, 147.8, 141.7, 138.9, 133.4, 126.8, 112.0, 107.5, 79.6, 59.6, 52.9, 43.6 (br s), 30.0, 28.4; LC-MS (HpH): 1.17 min (358) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{28}N_5O_2^+$ 358.2238; found 358.2243.

*tert-Butyl 4-(2-(6-Phenylpyridin-3-yl)ethyl)piperazine-1-carboxylate (**3z**).* Prepared according to general procedure D using 5-(chloromethyl)-2-phenylpyridine (143 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 15 h. Flash chromatography on silica (0−30% acetone in chloroform) afforded the title compound (213 mg, 0.580 mmol, 83% yield) as a white solid. Mp (DCM/cyclohexane): 128−129 °C; IR (neat): 2975, 2931, 2810, 1689, 1597, 1561, 1244, 1168, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 2.0 Hz, 1H), 8.00−7.95 (m, 2H), 7.68−7.64 (m, 1H), 7.59 (dd, J = 8.3, 2.3 Hz, 1H), 7.50−7.43 (m, 2H), 7.42−7.36 (m, 1H), 3.46 (t, J = 4.9 Hz, 4H), 2.86−2.80 (m, 2H), 2.67−2.61 (m, 2H), 2.48 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.4, 154.7, 149.9, 139.2, 136.9, 134.0, 128.7 (3 C), 126.7, 120.1, 79.6, 59.7, 52.9, 43.6 (br s), 30.3, 28.4; LC-MS (HpH): 1.27 min (368) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{30}N_3O_2^+$ 368.2333; found 368.2335.

*tert-Butyl 4-(2-(Quinolin-3-yl)ethyl)piperazine-1-carboxylate (**3aa**).* Prepared according to general procedure D using 3-(chloromethyl)quinoline hydrochloride (150 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 2 h. Flash chromatography on silica (0−50% acetone in chloroform) afforded the title compound (140 mg, 0.410 mmol, 59% yield) as a pale yellow solid. Mp (DCM/cyclohexane): 95−96 °C; IR (neat): 2975, 2933, 2862, 2810, 1688, 1571, 1419, 1247, 1167, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.76 (dd, J = 8.1, 1.2 Hz, 1H), 7.69−7.64 (m, 1H), 7.56−7.49 (m, 1H), 3.47 (t, J = 4.9 Hz, 4H), 3.02−2.95 (m, 2H), 2.74−2.67 (m, 2H), 2.50 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 152.0, 146.9, 134.6, 132.9, 129.2, 128.7, 128.1, 127.3, 126.6, 79.6, 59.7, 53.0, 43.5 (br s), 30.7, 28.4; LC-MS (HpH): 1.15 min (342) ([M + H]$^+$, 99%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{28}N_3O_2^+$ 342.2176; found 342.2182.

*tert-Butyl 4-(2-(1H-Pyrrolo[2,3-b]pyridin-5-yl)ethyl)piperazine-1-carboxylate **3ab**.* Prepared according to general procedure D using 5-(chloromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine hydrochloride (142 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 2 h. Flash chromatography on silica (0−70% acetone in chloroform) afforded the title compound (215 mg, 0.651 mmol, 93% yield) as a white solid. Mp (DCM/cyclohexane): 189−190 °C; IR (neat): 3190, 2975, 2932, 2864, 2815, 1689, 1423, 1249, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (br s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 3.4, 2.0 Hz, 1H), 6.46 (dd, J = 3.4, 2.0 Hz, 1H), 3.48 (t, J = 5.1 Hz, 4H), 2.96−2.88 (m, 2H), 2.69−2.63 (m, 2H), 2.50 (t, J = 5.1 Hz, 4H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.8, 147.6, 143.7, 128.7, 127.5, 125.1, 120.1, 100.5, 79.6, 61.0, 53.0, 43.7 (br s), 30.8, 28.4; LC-MS (HpH): 1.03 min (331) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{27}N_4O_2^+$ 331.2129; found 331.2142.

*tert-Butyl 4-(2-(Pyrimidin-5-yl)ethyl)piperazine-1-carboxylate (**3ac**).* Prepared according to general procedure D using 5-(chloromethyl)pyrimidine hydrochloride (116 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−80% acetone in chloroform) afforded the title compound (95 mg, 0.325 mmol, 46% yield) as a pale yellow solid. Mp (DCM/cyclohexane): 88−90 °C; IR (neat): 2975, 2932, 2863, 2812, 1687, 1561, 1409, 1244, 1168, 1123 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.07 (s, 1H), 8.60 (s, 2H), 3.42 (t, J = 4.9 Hz, 4H), 2.77 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.44 (t, J = 4.9 Hz, 4H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.9, 154.6, 133.4, 79.7, 58.7, 52.8, 43.5 (br s), 28.4, 27.9; LC-MS (HpH): 0.85 min (293) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{25}N_4O_2^+$ 293.1972; found 293.1978.

*((4-(tert-Butoxycarbonyl)-1-(pyridin-3-yl-methyl)piperazin-1-ium-1-yl)methyl)trifluoroborate (**4a**).* A 50 mL round-bottom flask was charged with 3-(chloromethyl)pyridine hydrochloride (246 mg, 1.50 mmol, 1.0 equiv), potassium 4-trifluoroboratomethylpiperazine-1-carboxylic acid *tert*-butyl ester (689 mg, 2.25 mmol, 1.5 equiv), and potassium carbonate (2.07 g, 15.0 mmol, 10.0 equiv) and was purged with nitrogen. *tert*-Amyl alcohol (13.6 mL) and water (1.4 mL) were added, and the reaction was gradually heated to 110 °C and stirred at this temperature for 60 min. After this time, the reaction mixture was filtered through celite eluting with acetonitrile and the filtrate was concentrated *in vacuo*. The residue was purified by HPLC (Xselect CSH C18 column eluting with 15−55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) and free-dried to afford the title compound (235 mg, 0.654 mmol, 44% yield) as a pale yellow amorphous solid. IR (neat): 2980, 1697, 1596, 1423, 1367, 1250, 1148, 1057 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.75 (d, J = 1.8 Hz, 1H), 8.68 (dd, J = 4.8, 1.8 Hz, 1H), 8.00 (dt, J = 7.9, 1.8 Hz, 1H), 7.54 (dd, J = 7.9, 4.8 Hz, 1H), 4.64 (s, 2H), 3.91−3.80 (m, 2H), 3.50 (br s, 2H), 3.32−3.23 (m, 4H), 2.21 (q, J = 4.4 Hz, 2H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6)* δ = 153.5−153.4 (m), 150.8, 140.7, 124.4, 123.7, 79.8, 62.7, 58.6, 48.7 (br s), 38.1−36.0 (m), 27.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −134.0; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 1.9; LC-MS (HpH): 0.78 min (377) ([M + NH_4]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{26}BF_3N_3O_2^+$ 360.2065; found 360.2063. *Overlapping signal of pyridine ^{13}C−H and ^{13}C═O seen in 2D NMR spectra.

*5-(Chloromethyl)oxazole (**7a**).* To a stirred solution of oxazol-5-ylmethanol (430 mg, 4.34 mmol, 1.0 equiv) in 1:1 DCM/cyclohexane (10 mL) was added thionyl chloride (0.48 mL, 6.51 mmol, 1.5 equiv) dropwise over 5 min. The reaction was stirred at reflux for 3 h and then was neutralized with sat. Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to afford the title compound (448 mg, 3.81 mmol, 88% yield) as a yellow oil, which was used without further purification. Analytical data are consistent with the literature.[42] IR (neat): 2967, 1505, 1273, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (s, 1H), 7.07 (s, 1H), 4.59 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 151.7, 147.7, 125.5, 34.2; LC-MS (HpH): 0.57 min (118) ([M + H]$^+$, 98%).

*5-(Chloromethyl)thiazole (**7b**).* To a stirred solution of thiazol-5-ylmethanol (1.02 g, 8.9 mmol, 1.0 equiv) in DCM (20 mL) was added thionyl chloride (0.776 mL, 10.6 mmol, 1.2 equiv) dropwise over 5 min. The reaction was stirred for 3 h at room temperature and then was poured onto water (30 mL). The phases were separated, and the aqueous phase was basified with sat. $NaHCO_3$ and extracted with ethyl acetate (3 × 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (0−40% ethyl acetate in cyclohexane) to

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afford the title compound (782 mg, 5.9 mmol, 66% yield) as a pale yellow oil. Analytical data are consistent with the literature.[43] IR (neat): 2924, 2854, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.83 (s, 1H), 7.87 (s, 1H), 4.85 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.5, 142.8, 135.5, 37.1; LC-MS (HpH): 0.68 min (134) ($[M + H]^+$, 100%).

*tert-Butyl 4-(2-(Oxazol-5-yl)ethyl)piperazine-1-carboxylate (**8a**).* Prepared according to general procedure D using 5-(chloromethyl)-oxazole (82 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−50% acetone in chloroform) afforded the title compound (69 mg, 0.245 mmol, 35% yield) as an off-white solid. Mp (DCM/cyclohexane): 71−73 °C; IR (neat): 2930, 2975, 2814, 1688, 1419, 1244, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 6.83 (s, 1H), 3.44 (t, J = 4.9 Hz, 4H), 2.92−2.83 (m, 2H), 2.72−2.63 (m, 2H), 2.44 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 151.0, 150.1, 122.6, 79.7, 56.0, 52.8, 43.6 (br s), 28.4, 23.4; LC-MS (HpH): 0.92 min (282) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{24}N_3O_3^+$ 282.1812; found 282.1812.

*tert-Butyl 4-(2-(Thiazol-5-yl)ethyl)piperazine-1-carboxylate (**8b**).* Prepared according to general procedure D using 5-(chloromethyl)-thiazole (94 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 15 h. Flash chromatography on silica (0−40% acetone in chloroform) afforded the title compound (179 mg, 0.602 mmol, 86% yield) as an off-white solid.

Mp (DCM/cyclohexane): 79−81 °C; IR (neat): 2974, 2929, 2810, 1688, 1410, 1242, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.66 (s, 1H), 7.65 (s, 1H), 3.55−3.41 (m, 4H), 3.04 (t, J = 6.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H), 2.55−2.39 (m, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 152.2, 140.7, 136.5 (br s, confirmed by HMBC), 79.7, 58.9, 52.8, 43.6 (br s), 28.4, 24.6; LC-MS (HpH): 1.00 min (298) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{24}N_3O_2S^+$ 298.1584; found 298.1589.

*tert-Butyl 4-(2-(1-Methyl-1H-imidazol-5-yl)ethyl)piperazine-1-carboxylate (**8c**).* Prepared according to general procedure D using 5-(chloromethyl)-1-methyl-1*H*-imidazole hydrochloride (117 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−30% methanol in acetone) afforded the title compound (140 mg, 0.476 mmol, 68% yield) as a white solid. Mp (DCM/cyclohexane): 106−108 °C; IR (neat): 2976, 2816, 1689, 1507, 1423, 1248, 1170, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 6.83 (s, 1H), 3.58 (s, 3H), 3.46 (t, J = 4.9 Hz, 4H), 2.78−2.72 (m, 2H), 2.67−2.60 (m, 2H), 2.47 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 137.5, 130.0, 126.2, 79.7, 57.3, 53.0, 43.5 (br s), 31.4, 28.4, 21.7; LC-MS (HpH): 0.85 min (295) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{27}N_4O_2^+$ 295.2129; found 295.2136.

*tert-Butyl 4-(2-(Thiophen-2-yl)ethyl)piperazine-1-carboxylate (**8d**).* Prepared according to general procedure D using 2-(chloromethyl)thiophene (93 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 22 h. Flash chromatography on silica (0−15% acetone in chloroform) afforded the title compound (58 mg, 0.196 mmol, 28% yield) as an off-white solid. Mp (DCM/cyclohexane): 65−66 °C; IR (neat): 2976, 2935, 2810, 1694, 1422, 1246, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.13 (dd, J = 5.3, 1.0 Hz, 1H), 6.92 (dd, J = 5.3, 3.4 Hz, 1H), 6.83 (dd, J = 3.4, 1.0 Hz, 1H), 3.47 (t, J = 4.9 Hz, 4H), 3.06−2.99 (m, 2H), 2.71−2.65 (m, 2H), 2.48 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 142.5, 126.6, 124.6, 123.5, 79.6, 59.8, 52.8, 43.6 (br s), 28.4, 27.6; LC-MS (HpH): 1.26 min (297) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{25}N_2O_2S^+$ 297.1631; found 297.1641.

*tert-Butyl 4-(2-(1-Methyl-1H-pyrazol-5-yl)ethyl)piperazine-1-carboxylate (**8e**).* Prepared according to general procedure D using 5-(chloromethyl)-1-methyl-1*H*-pyrazole hydrochloride (117 mg, 0.70 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (321 mg, 1.05 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−70% acetone in chloroform) afforded the title compound (175 mg, 0.594 mmol, 85% yield) as a white solid. Mp (DCM/cyclohexane): 45−47 °C; IR (neat): 2974, 2812, 1692, 1421, 1247, 1170, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 2.0 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.46 (t, J = 4.9 Hz, 4H), 2.86−2.77 (m, 2H), 2.69−2.60 (m, 2H), 2.47 (t, J = 4.9 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 140.5, 138.2, 104.3, 79.7, 57.2, 53.0, 43.5 (br s), 36.2, 28.4, 23.4; LC-MS (HpH): 0.93 min (295) ($[M + H]^+$, 100%); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{27}N_4O_2^+$ 295.2129; found 295.2131.

General Procedure E for Cross-Coupling of Benzyl Chlorides with Trifluoroborate Salts. A 50 mL round-bottom flask was charged with chloride (if solid) (0.86 mmol, 1.0 equiv), trifluoroborate salt (1.29 mmol, 1.5 equiv), KO^{t}Bu (965 mg, 8.60 mmol, 10.0 equiv), and Pd-PEPPSI-IPent catalyst (68 mg, 0.086 mmol, 10 mol %) and was evacuated and back-filled with N_2 (3×). Chloride (if liquid) (0.86 mmol, 1 equiv), *tert*-amyl alcohol (6.9 mL), and water (1.7 mL) were added *via* a syringe, and the reaction was stirred at 80 °C/reflux for the stated time. The reaction was cooled to room temperature and filtered through celite eluting with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by automated flash chromatography on silica to afford the desired compound.

*tert-Butyl 4-Phenethylpiperazine-1-carboxylate (**10a**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 2 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (239 mg, 0.823 mmol, 96% yield) as a white solid. Analytical data are consistent with the literature.[44] Mp (DCM/cyclohexane): 64−66 °C; IR (neat): 2974, 2931, 2808, 1692, 1418, 1247, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32−7.26 (m, 2H), 7.23−7.18 (m, 3H), 3.47 (t, J = 5.0 Hz, 4H), 2.85−2.77 (m, 2H), 2.66−2.58 (m, 2H), 2.48 (t, J = 5.0 Hz, 4H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 140.2, 128.7, 128.4, 126.1, 79.6, 60.5, 53.0, 43.6 (br s), 33.5, 28.4; LC-MS (HpH): 1.27 min (291) ($[M + H]^+$, 100%).

*1-Methyl-4-phenethylpiperazine (**10b**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium 1-methyl-4-(trifluoroboratomethyl)piperazine (284 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (0−100% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (147 mg, 0.719 mmol, 84% yield) as a colorless oil. Analytical data are consistent with the literature.[45] IR (neat): 2935, 2792, 1453, 1283, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (m, 5H), 2.86−2.77 (m, 2H), 2.69−2.38 (m, 10H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 140.3, 128.6, 128.3, 126.0, 60.5, 55.2, 53.2, 46.0, 33.6; LC-MS (HpH): 0.87 min (205) ($[M + H]^+$, 100%).

*4-Phenethylmorpholine (**10c**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium 4-trifluoroboratomethyl-morpholine (267 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (0−40% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (148 mg, 0.774 mmol, 90% yield) as a colorless oil. Analytical data are consistent with the literature.[44] IR (neat): 2953, 2853, 2805, 1452, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.27 (m, 2H), 7.24−7.18 (m, 3H), 3.76 (t, J = 4.6 Hz, 4H), 2.85−2.78 (m, 2H), 2.65−2.58 (m, 2H), 2.54 (t, J = 4.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 140.2, 128.7, 128.4, 126.1, 67.0, 60.9, 53.7, 33.4; LC-MS (HpH): 0.94 min (192) ($[M + H]^+$, 100%).

*1-Phenethylpiperidine (**10d**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium 1-(trifluoroboratomethyl)piperidine (265 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (0−40% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (96 mg, 0.507 mmol, 59% yield) as a colorless oil.

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Analytical data are consistent with the literature.[46] IR (neat): 2931, 2854, 2759, 1602, 1452, 1260, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.24−7.15 (m, 3H), 2.86−2.79 (m, 2H), 2.63−2.40 (m, 6H), 1.64 (dt, J = 11.1, 5.7 Hz, 4H), 1.52−1.43 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) = δ 140.7, 128.7, 128.3, 125.9, 61.4, 54.6, 33.7, 26.0, 24.4; LC-MS (HpH): 1.11 min (190) ([M + H]$^+$, 100%).

*N,N-Diethyl-2-phenylethan-1-amine (**10e**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium *N,N*-diethyltrifluoroboratomethylamine (249 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 20 h. Flash chromatography on silica (0−40% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (115 mg, 0.649 mmol, 75% yield) as a colorless oil. Analytical data are consistent with the literature.[47] IR (neat): 2968, 2799, 1453, 1382, 1159, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32−7.26 (m, 2H), 7.24−7.17 (m, 3H), 2.81−2.68 (m, 4H), 2.63 (q, J = 7.2 Hz, 4H), 1.08 (t, J = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 140.8, 128.7, 128.3, 125.9, 55.0, 46.9, 33.5, 11.9; LC-MS (HpH): 1.06 min (178) ([M + H]$^+$, 100%).

*N-Benzyl-N-methyl-2-phenylethan-1-amine (**10f**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and potassium *N*-benzyltrifluoroboratomethylamine (311 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (0−40% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (153 mg, 0.679 mmol, 79% yield) as a colorless oil. Analytical data are consistent with the literature.[48] IR (neat): 2945, 2786, 1494, 1453, 1047, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.20 (m, 13H), 7.17−7.12 (m, 2H), 3.71 (s, 4H), 2.91−2.84 (m, 2H), 2.81−2.75 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.6, 139.1, 129.0, 128.7, 128.3, 128.2, 126.9, 125.9, 62.2, 59.2, 42.2, 34.0; LC-MS (HpH): 1.35 min (226) ([M + H]$^+$, 100%).

*N,N-Dibenzyl-2-phenylethan-1-amine (**10g**).* Prepared according to general procedure E using benzyl chloride (0.10 mL, 0.86 mmol, 1.0 equiv) and ((dibenzylammonio)methyl)trifluoroborate (360 mg, 1.29 mmol. 1.5 equiv) and stirring at reflux for 15 h. Flash chromatography on silica (0−5% ethyl acetate (+1% NEt_3) in cyclohexane) afforded the title compound (210 mg, 0.697 mmol, 81% yield) as a colorless oil. Analytical data are consistent with the literature.[49] IR (neat): 3025, 2929, 2794, 1602, 1494, 1452, 1365, 1118, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.11 (m, 13H), 7.09−7.02 (m, 2H), 3.62 (s, 4H), 2.82−2.74 (m, 2H), 2.73−2.66 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.6, 139.7, 128.8, 128.7, 128.2, 128.1, 126.8, 125.8, 58.2, 55.1, 33.5; LC-MS (HpH): 1.65 min (302) ([M + H]$^+$, 100%).

*tert-Butyl 4-(4-Methylphenethyl)piperazine-1-carboxylate (**10h**).* Prepared according to general procedure E using 4-methylbenzyl-chloride (114 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (240 mg, 0.788 mmol, 92% yield) as a white solid. Mp (cyclohexane): 44−45 °C; IR (neat): 2975, 2925, 2861, 1687, 1405, 1364, 1246, 1168, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.10 (s, 4H), 3.47 (t, J = 5.0 Hz, 4H), 2.81−2.74 (m, 2H), 2.62−2.56 (m, 2H), 2.47 (t, J = 5.0 Hz, 4H), 2.33 (s, 3H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 137.0, 135.5, 129.1, 128.5, 79.6, 60.6, 53.0, 43.6 (br s), 33.1, 28.4, 21.0; LC-MS (HpH): 1.35 min (305) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_2^+$ 305.2224; found 305.2224.

*tert-Butyl 4-(2,6-Dimethylphenethyl)piperazine-1-carboxylate (**10i**).* Prepared according to general procedure E using 2-(chloromethyl)-1,3-dimethylbenzene (133 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (138 mg, 0.433 mmol, 50% yield) as a white solid. Mp (DCM/cyclohexane): 74−75 °C; IR (neat): 2974, 2811, 1685, 1423, 1249, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.07−6.97 (m, 3H), 3.50 (t, J = 4.9 Hz, 4H), 2.91−2.81 (m, 2H), 2.56−2.42 (m, 6H), 2.35 (s, 6H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, CHLOROFORM-d) δ = 154.7, 136.4, 136.3, 128.2, 126.0, 79.6, 57.4, 53.0, 44.4−42.8 (m), 28.4, 27.0, 19.8; LC-MS (HpH): 1.39 min (319) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{31}N_2O_2^+$ 319.2380; found 319.2387.

*tert-Butyl 4-(2-(Naphthalen-2-yl)ethyl)piperazine-1-carboxylate (**10j**).* Prepared according to general procedure E using 2-(chloromethyl)naphthalene (152 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−30% ethyl acetate in cyclohexane) afforded the title compound (218 mg, 0.640 mmol, 75% yield) as an off-white solid. Mp (DCM/cyclohexane): 94−95 °C; IR (neat): 2974, 2937, 2865, 1693, 1456, 1422, 1248, 1172, 1033 cm^{-1};^1H NMR (600 MHz, $CDCl_3$) δ = 7.83−7.77 (m, 3H), 7.65 (s, 1H), 7.49− 7.41 (m, 2H), 7.35 (dd, J = 8.4, 1.7 Hz, 1H), 3.49 (t, J = 5.0 Hz, 4H), 3.01−2.95 (m, 2H), 2.74−2.69 (m, 2H), 2.55−2.46 (m, 4H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ = 154.7, 137.7, 133.6, 132.1, 127.9, 127.6, 127.4, 127.4, 126.8, 126.0, 125.3, 79.6, 60.3, 53.0, 46.7−42.7 (m), 33.7, 28.4; LC-MS (HpH): 1.41 min (341) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{29}N_2O_2^+$ 341.2224; found 341.2234.

*tert-Butyl 4-(2-(Quinolin-6-yl)ethyl)piperazine-1-carboxylate (**10k**).* Prepared according to general procedure E using 6-(chloromethyl)quinoline (153 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−50% acetone in chloroform) afforded the title compound (185 mg, 0.542 mmol, 63% yield) as a colorless gum. IR (neat): 2974, 2863, 1687, 1594, 1571, 1419, 1365, 1246, 1168, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.87 (dd, J = 4.2, 1.7 Hz, 1H), 8.12−8.07 (m, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.63−7.60 (m, 1H), 7.58 (dd, J = 8.6, 2.0 Hz, 1H), 7.37 (dd, J = 8.2, 4.3 Hz, 1H), 3.47 (t, J = 5.1 Hz, 4H), 3.03−2.96 (m, 2H), 2.74−2.68 (m, 2H), 2.50 (t, J = 5.1 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 149.8, 147.2, 138.7, 135.5, 131.0, 129.4, 128.3, 126.6, 121.1, 79.6, 60.1, 53.0, 43.7 (br s), 33.5, 28.4; LC-MS (HpH): 1.11 min (342) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{28}N_3O_2^+$ 342.2176; found 342.2172.

*tert-Butyl 4-(4-(Methylsulfonyl)phenethyl)piperazine-1-carboxylate (**10l**).* Prepared according to general procedure E using 1-(chloromethyl)-4-(methylsulfonyl)benzene (176 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−50% acetone in chloroform) afforded the title compound (183 mg, 0.497 mmol, 58% yield) as a white solid. Mp (DCM/cyclohexane): 118−119 °C; IR (neat): 2973, 2936, 2867, 1668, 1422, 1249, 1150, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.88−7.83 (m, 2H), 7.44−7.36 (m, 2H), 3.45 (t, J = 5.0 Hz, 4H), 3.04 (s, 3H), 2.92−2.85 (m, 2H), 2.66−2.60 (m, 2H), 2.45 (t, J = 5.0 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 146.9, 138.4, 129.6, 127.5, 79.7, 59.5, 52.9, 44.5, 43.4 (br s), 33.4, 28.4; LC-MS (HpH): 1.03 min (369) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_4S^+$ 369.1843; found 369.1848.

*tert-Butyl 4-(4-(Methylthio)phenethyl)piperazine-1-carboxylate (**10m**).* Prepared according to general procedure E using 1-(chloromethyl)-4-methylthiobenzene (148 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (188 mg, 0.559 mmol, 65% yield) as an off-white solid. Mp (DCM/cyclohexane): 73−74 °C; IR (neat): 2974, 2923, 2862, 2809, 1692, 1419, 1247, 1169, 1124, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23−7.18 (m, 2H), 7.15−7.11 (m, 2H), 3.46 (t, J = 5.1 Hz, 4H), 2.80−2.73 (m, 2H), 2.61−2.55 (m, 2H), 2.49−2.43 (m, 7H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 137.3, 135.7, 129.2, 127.2, 79.6, 60.3, 53.0, 43.6 (br s), 33.0, 28.4, 16.3; LC-MS (HpH): 1.34 min (337) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_2S^+$ 337.1944; found 337.1946.

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*tert-Butyl 4-(4-Methoxyphenethyl)piperazine-1-carboxylate (**10n**).* Prepared according to general procedure E using 1-(chloromethyl)-4-methoxybenzene (117 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 24 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (206 mg, 0.643 mmol, 75% yield) as a white solid. Mp (DCM/cyclohexane): 50−52 °C; IR (neat): 2932, 2807, 1691, 1512, 1243, 1169, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.15−7.09 (m, 2H), 6.86−6.81 (m, 2H), 3.79 (s, 3H), 3.46 (t, J = 4.9 Hz, 4H), 2.79−2.71 (m, 2H), 2.61−2.54 (m, 2H), 2.46 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 158.0, 154.7, 132.2, 129.5, 113.8, 79.6, 60.7, 55.2, 53.0, 43.6 (br s), 32.6, 28.4; LC-MS (HpH): 1.25 min (321) ([M + H]$^+$, 100%); HRMS (ESI) m/z: calcd for $C_{18}H_{29}N_2O_3^+$ ([M + H]$^+$) 321.2173; found 321.2176.

*tert-Butyl 4-(3-Methoxyphenethyl)piperazine-1-carboxylate (**10o**).* Prepared according to general procedure E using 1-(chloromethyl)-3-methoxybenzene (117 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux overnight. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (256 mg, 0.799 mmol, 93% yield) as a colorless oil. IR (neat): 2934, 2808, 1690, 1418, 1246, 1121 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ = 7.24−7.17 (m, 1H), 6.82−6.73 (m, 3H), 3.80 (s, 3H), 3.47 (t, J = 5.1 Hz, 4H), 2.83−2.75 (m, 2H), 2.65−2.58 (m, 2H), 2.47 (t, J = 5.0 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 159.7, 154.7, 141.8, 129.4, 121.1, 114.5, 111.3, 79.6, 60.3, 55.1, 53.0, 43.7 (br s), 33.6, 28.4; LC-MS (HpH): 1.26 min (321) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_3^+$ 321.2173; found 321.2178.

*tert-Butyl 4-(2-Methoxyphenethyl)piperazine-1-carboxylate (**10p**).* Prepared according to general procedure E using 1-(chloromethyl)-2-methoxybenzene (117 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (236 mg, 0.737 mmol, 86% yield) as a colorless oil. IR (neat): 2932, 2806, 1691, 1418, 1241, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23−7.12 (m, 2H), 6.92−6.83 (m, 2H), 3.82 (s, 3H), 3.47 (t, J = 4.9 Hz, 4H), 2.87−2.79 (m, 2H), 2.61−2.55 (m, 2H), 2.49 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 157.5, 154.7, 130.2, 128.5, 127.4, 120.4, 110.3, 79.5, 58.8, 55.2, 52.9, 43.6 (br s), 28.4, 27.8; LC-MS (HpH): 1.29 min (321) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_3^+$ 321.2173; found 321.2173.

*tert-Butyl 4-(2-(2,3-Dihydrobenzofuran-5-yl)ethyl)piperazine-1-carboxylate (**10q**).* Prepared according to general procedure E using 5-(chloromethyl)-2,3-dihydrobenzofuran (145 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−100% ethyl acetate in cyclohexane) afforded the title compound (136 mg, 0.409 mmol, 48% yield) as a white solid. Mp (DCM/cyclohexane): 75−77 °C; IR (neat): 2974, 2935, 1690, 1491, 1365, 1243, 1168, 1123, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.04−7.00 (m, 1H), 6.95−6.88 (m, 1H), 6.69 (d, J = 8.1 Hz, 1H), 4.53 (t, J = 8.7 Hz, 2H), 3.46 (t, J = 5.0 Hz, 4H), 3.17 (t, J = 8.7 Hz, 2H), 2.75−2.69 (m, 2H), 2.58−2.52 (m, 2H), 2.45 (t, J = 5.0 Hz, 4H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 158.4, 154.7, 131.9, 128.0, 127.0, 125.1, 109.0, 79.5, 71.1, 61.0, 53.0, 43.6 (br s), 32.9, 29.7, 28.4; LC-MS (HpH): 1.24 min (333) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{29}N_2O_3^+$ 333.2173; found 333.2163.

*tert-Butyl 4-(4-(Dimethylamino)phenethyl)piperazine-1-carboxylate (**10r**).* Prepared according to general procedure E using 4-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride (177 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−50% ethyl acetate in cyclohexane) afforded the title compound (84 mg, 0.252 mmol, 29% yield) as an off-white solid. Mp (DCM/cyclohexane): 92−94 °C; IR (neat): 2973, 2859, 2796, 1688, 1615, 1518, 1410, 1286, 1169, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.12−7.05 (m, 2H), 6.73−6.67 (m, 2H), 3.47 (t, J = 5.1 Hz, 4H), 2.92 (s, 6H), 2.76−2.69 (m, 2H), 2.61−2.54 (m, 2H), 2.47 (t, J = 5.1 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.7, 149.2, 129.2, 128.1, 113.0, 79.5, 60.9, 53.0, 43.6 (br s), 40.8, 32.4, 28.4; LC-MS (HpH): 1.30 min (334) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{32}N_3O_2^+$ 334.2489; found 334.2486.

*tert-Butyl 4-(3-(Dimethylamino)phenethyl)piperazine-1-carboxylate (**10s**).* Prepared according to general procedure E using 3-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride (177 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−50% ethyl acetate in cyclohexane) afforded the title compound (255 mg, 0.765 mmol, 89% yield) as a colorless oil. IR (neat): 2931, 2806, 1689, 1602, 1581, 1499, 1420, 1365, 1289, 1169, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.19−7.12 (m, 1H), 6.63−6.55 (m, 3H), 3.47 (t, J = 5.1 Hz, 4H), 2.94 (s, 6H), 2.81−2.74 (m, 2H), 2.67−2.60 (m, 2H), 2.48 (t, J = 5.1 Hz, 4H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.8, 141.0, 129.0, 117.0, 113.0, 110.5, 79.5, 60.6, 53.0, 43.6 (br s), 40.6, 34.0, 28.4; LC-MS (HpH): 1.31 (334) ([M + H]$^+$, 99%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{32}N_3O_2^+$ 334.2489; found 334.2486.

*tert-Butyl 4-(2-(Dimethylamino)phenethyl)piperazine-1-carboxylate (**10t**).* Prepared according to general procedure E using 2-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride (177 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 16 h. Flash chromatography on silica (0−50% ethyl acetate in cyclohexane) afforded the title compound (205 mg, 0.615 mmol, 72% yield) as a colorless oil. IR (neat): 2974, 2858, 2821, 1693, 1597,1418, 1364, 1246, 1169, 1122, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.22−7.10 (m, 3H), 7.01 (td, J = 7.3, 1.6 Hz, 1H), 3.48 (t, J = 5.1 Hz, 4H), 2.95−2.88 (m, 2H), 2.70−2.61 (m, 8H), 2.50 (t, J = 5.1 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.8, 153.1, 135.3, 129.9, 126.9, 123.5, 119.8, 79.5, 59.7, 53.0, 45.3, 43.7 (br s), 28.5, 28.1; LC-MS (HpH): 1.35 min (334) ([M + H]$^+$, 100%); HRMS (ESI) m/z: calcd for $C_{19}H_{32}N_3O_2^+$ ([M + H]$^+$) 334.2489; found 334.2480.

*tert-Butyl 4-(4-Vinylphenethyl)piperazine-1-carboxylate (**10u**).* Prepared according to general procedure E using 1-(chloromethyl)-4-vinylbenzene (121 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 19 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (123 mg, 0.389 mmol, 45% yield) as an off-white solid. Mp (DCM/cyclohexane): 53−55 °C; IR (neat): 2977, 2806, 1697, 1421, 1248, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.70 (dd, J = 17.6, 10.8 Hz, 1H), 5.71 (dd, J = 17.6, 1.0 Hz, 1H), 5.21 (dd, J = 10.8, 1.0 Hz, 1H), 3.47 (t, J = 4.9 Hz, 4H), 2.84−2.75 (m, 2H), 2.65−2.57 (m, 2H), 2.47 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 154.7, 139.8, 136.6, 135.6, 128.8, 126.3, 113.2, 79.6, 60.3, 53.0, 43.7 (br s), 33.2, 28.4; LC-MS (HpH): 1.38 min (317) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{29}N_2O_2^+$ 317.2224; found 317.2223.

*tert-Butyl 4-(4-(Hydroxymethyl)phenethyl)piperazine-1-carboxylate (**10v**).* Prepared according to general procedure E using (4-(chloromethyl)phenyl)methanol (135 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 20 h. Flash chromatography on silica (0−80% ethyl acetate in cyclohexane) afforded the title compound (93 mg, 0.290 mmol, 34% yield) as a white solid. Mp (DCM/cyclohexane): 125−126 °C; IR (neat): 3407, 2975, 2932, 2815, 1694, 1421, 1249, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 4.67 (s, 2H), 3.46 (t, J = 5.1 Hz, 4H), 2.85−2.76 (m, 2H), 2.64−2.56 (m, 2H), 2.46 (t, J = 5.0 Hz, 4H), 1.84 (br s, 1H), 1.47 (s, 9H); $^{13}C\{^1H\}$ NMR

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(101 MHz, $CDCl_3$) δ = 154.7, 139.6, 138.8, 128.9, 127.2, 79.6, 65.1, 60.4, 53.0, 43.6 (br s), 33.2, 28.4; LC-MS (HpH): 1.01 (321) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_3^+$ 321.2173; found 321.2173.

*tert-Butyl 4-(4-Fluorophenethyl)piperazine-1-carboxylate (**10w**).* Prepared according to general procedure E using 1-(chloromethyl)-4-fluorobenzene (103 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 6 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (236 mg, 0.765 mmol, 89% yield) as a white solid. Analytical data are consistent with the literature.[50] Mp (DCM/cyclohexane): 70−72 °C; IR (neat): 2983, 2928, 2864, 1683, 1510, 1407, 1367, 1247, 1219, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19−7.11 (m, 2H), 7.02−6.91 (m, 2H), 3.46 (t, J = 5.0 Hz, 4H), 2.81−2.74 (m, 2H), 2.61−2.54 (m, 2H), 2.45 (t, J = 5.0 Hz, 4H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 161.4 (d, $^1J_{C-F}$ = 243.6 Hz), 154.7, 135.8 (d, $^4J_{C-F}$ = 2.9 Hz), 130.0 (d, $^3J_{C-F}$ = 7.3 Hz), 115.1 (d, $^2J_{C-F}$ = 21.3 Hz), 79.6, 60.4, 53.0, 43.6 (br s), 32.7, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −117.3; LC-MS (HpH): 1.28 min ([M + H]$^+$, 100%).

*tert-Butyl 4-(4-(Trifluoromethyl)phenethyl)piperazine-1-carboxylate (**10x**).* Prepared according to general procedure E using 1-(chloromethyl)-4-(trifluoromethyl)benzene (127 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−40% ethyl acetate in cyclohexane) afforded the title compound (218 mg, 0.608 mmol, 71% yield) as a white solid. Mp (DCM/cyclohexane): 111−113 °C; IR (neat): 2978, 2934, 2810, 1691, 1323, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 3.46 (t, J = 4.9 Hz, 4H), 2.91−2.82 (m, 2H), 2.67−2.59 (m, 2H), 2.47 (t, J = 4.9 Hz, 4H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ = 154.7, 144.3, 129.0, 128.5 (q, $^2J_{C-F}$ = 32.4 Hz), 125.3 (q, $^3J_{C-F}$ = 3.6 Hz), 124.3 (q, $^1J_{C-F}$ = 271.5 Hz), 79.7, 59.8, 53.0, 44.6−42.6 (m), 33.3, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −62.4; LC-MS (HpH): 1.39 min (359) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{26}F_3N_2O_2^+$ 359.1941; found 359.1939.

*tert-Butyl 4-(3-(Trifluoromethyl)phenethyl)piperazine-1-carboxylate (**10y**).* Prepared according to general procedure E using 1-(chloromethyl)-3-(trifluoromethyl)benzene (127 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−50% ethyl acetate in cyclohexane) afforded the title compound (223 mg, 0.622 mmol, 72% yield) as a colorless oil. IR (neat): 2933, 2810, 1691, 1419, 1330, 1247, 1161, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49−7.35 (m, 4H), 3.45 (t, J = 5.1 Hz, 4H), 2.88−2.82 (m, 2H), 2.64−2.58 (m, 2H), 2.46 (t, J = 5.1 Hz, 4H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 154.7, 141.1, 132.1, 130.7 (q, $^2J_{C-F}$ = 31.5 Hz), 128.8, 125.4 (q, $^3J_{C-F}$ = 3.7 Hz), 124.2 (q, $^1J_{C-F}$ = 272.2 Hz), 123.0 (q, $^3J_{C-F}$ = 3.7 Hz), 79.6, 59.9, 53.0, 43.6 (br s), 33.3, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −62.6; LC-MS (HpH): 1.37 min (359) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{26}F_3N_2O_2^+$ 359.1941; found 359.1941.

*tert-Butyl 4-(2-(Trifluoromethyl)phenethyl)piperazine-1-carboxylate (**10z**).* Prepared according to general procedure E using 1-(chloromethyl)-2-(trifluoromethyl)benzene (127 μL, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−50% ethyl acetate in cyclohexane) afforded the title compound (95 mg, 0.262 mmol, 31% yield) as a colorless oil. IR (neat): 2976, 2811, 1692, 1455, 1419, 1365, 1248, 1164, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.1 Hz, 1H), 7.49−7.41 (m, 1H), 7.37−7.23 (m, 2H), 3.46 (t, J = 5.1 Hz, 4H), 3.01−2.93 (m, 2H), 2.65−2.56 (m, 2H), 2.47 (t, J = 5.1 Hz, 4H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 154.7, 138.69, 131.7, 131.5, 128.6 (q, $^2J_{C-F}$ = 29.6 Hz), 126.1, 125.9 (q, $^3J_{C-F}$ = 5.9 Hz), 124.5 (q, $^1J_{C-F}$ = 272.9 Hz), 79.5, 60.1, 52.8, 43.6 (br s), 30.0, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −59.6; LC-MS (HpH): 1.39 min (359) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{26}F_3N_2O_2^+$ 359.1941; found 359.1937.

*tert-Butyl 4-(3-Acetylphenethyl)piperazine-1-carboxylate (**10aa**).* Prepared according to general procedure E using 1-(3-(chloromethyl)-phenyl)ethan-1-one (145 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 4 h. Flash chromatography on silica (0−60% ethyl acetate in cyclohexane) afforded the title compound (175 mg, 0.526 mmol, 61% yield) as a colorless gum. IR (neat): 2975, 2931, 2809, 1686, 1603, 1585, 1421, 1364, 1248, 1171, 1004 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83−7.76 (m, 2H), 7.44−7.35 (m, 2H), 3.46 (t, J = 5.1 Hz, 4H), 2.89−2.84 (m, 2H), 2.66−2.59 (m, 5H), 2.47 (t, J = 5.1 Hz, 4H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 198.2, 154.7, 140.8, 137.3, 133.5, 128.6, 128.4, 126.3, 79.6, 60.1, 53.0, 43.6 (br s), 33.3, 28.4, 26.6; LC-MS (HpH): 1.17 min (333) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{29}N_2O_3^+$ 333.2173; found 333.2171.

*tert-Butyl 4-(4-(tert-Butoxycarbonyl)phenethyl)piperazine-1-carboxylate (**10ab**).* Prepared according to general procedure E using *tert*-butyl 4-(chloromethyl)benzoate (195mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 2 h. Flash chromatography on silica (0−30% ethyl acetate in cyclohexane) afforded the title compound (261 mg, 0.688 mmol, 78% yield) as a white solid. Mp (DCM/cyclohexane): 74−75 °C; IR (neat): 2975, 2808, 1694, 1611, 1410, 1289, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93−7.88 (m, 2H), 7.26−7.21 (m, 2H), 3.45 (t, J = 4.9 Hz, 4H), 2.88−2.81 (m, 2H), 2.64−2.58 (m, 2H), 2.45 (t, J = 4.9 Hz, 4H), 1.59 (s, 9H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 165.7, 154.7, 145.1, 130.0, 129.5, 128.5, 80.8, 79.6, 59.9, 52.9, 43.6 (br s), 33.5, 28.4, 28.2; LC-MS (HpH): 1.46 min (391) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{35}N_2O_4^+$ 391.2591; found 391.2596.

*tert-Butyl 4-(4-Carbamoylphenethyl)piperazine-1-carboxylate (**10ac**).* Prepared according to general procedure E using *tert*-butyl 4-(chloromethyl)benzamide (146 mg, 0.86 mmol, 1.0 equiv) and potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (395 mg, 1.29 mmol, 1.5 equiv) and stirring at reflux for 3 h. Flash chromatography on silica (0−30% ethyl acetate in cyclohexane) afforded the title compound (208 mg, 0.624 mmol, 73% yield) as a white solid. Mp (DCM/cyclohexane): 191−193 °C; IR (neat): 3395, 3169, 2979, 1693, 1651, 1614, 1567, 1416, 1244, 1171, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77−7.72 (m, 2H), 7.31−7.27 (m, 2H), 6.19−5.64 (m, 2H), 3.45 (t, J = 5.0 Hz, 4H), 2.89−2.82 (m, 2H), 2.65−2.59 (m, 2H), 2.46 (t, J = 5.0 Hz, 4H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 169.1, 154.7, 144.7, 131.2, 128.9, 127.5, 79.7, 59.9, 53.0, 43.6 (br s), 33.4, 28.4; LC-MS (HpH): 0.91 min (334) ([M + H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{28}N_3O_3^+$ 334.2125; found 334.2136.

*4-(2-(4-(tert-Butoxycarbonyl)piperazin-1-yl)ethyl)benzoic Acid (**10ad**).* A 50 mL round-bottom flask was charged with 4-(chloromethyl)benzoic acid (171 mg, 1.0 mmol, 1.0 equiv), potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (459 mg, 1.5 mmol, 1.5 equiv), KO^{t}Bu (1.12 g, 10.0 mmol, 10.0 equiv), and Pd-PEPPSI-IPent catalyst (79 mg, 0.01 mmol, 10 mol %) and was evacuated and back-filled with N_2 (×3). *tert*-Amyl alcohol (8.0 mL) and water (2.0 mL) were added *via* a syringe, and the reaction was stirred at 80 °C overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was suspended in 1:1 MeOH/DMSO (6 mL), passed through a 0.45 μm syringe filter, and purified by mass-directed HPLC (Xbridge C18 column eluting with 15−55% acetonitrile in water with a 10 mM ammonium bicarbonate modifier) to afford the title compound (122 mg, 0.365 mmol, 37% yield) as a colorless gum. IR (neat): 3430, 2978, 2933, 2872, 1692, 1611, 1419, 1251, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.33 (br s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 3.70−3.57 (m, 4H), 3.05−2.90 (m, 4H), 2.87−2.76 (m, 4H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 169.9, 154.4, 143.4, 130.3, 129.6, 128.6, 80.4, 58.8, 52.3, 42.0 (br s), 31.8, 28.3; LC-MS (HpH): 0.69 min (335) ([M

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+ H]$^+$, 100%); HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{27}N_2O_4^+$ 335.1965; found 335.1972.

*((1-Benzyl-4-(tert-butoxycarbonyl)piperazin-1-ium-1-yl)methyl)-trifluoroborate (**11a**).* A flask was charged with potassium 4-(trifluoroboratomethyl)piperazine-1-carboxylic acid *tert*-butyl ester (919 mg, 3.0 mmol, 1.5 equiv) and potassium *tert*-butoxide (2.24 g, 20.0 mmol, 10 equiv) and was purged with N_2 (3×). Benzyl chloride (0.23 mL, 2.0 mmol), *tert*-amyl alcohol (16.000 mL), and water (4.00 mL) were added sequentially, and the reaction was gradually heated to 110 °C and was stirred at this temperature for 80 min. After this time, the reaction mixture was filtered through celite eluting with acetonitrile and the filtrate was concentrated *in vacuo*. The residue was triturated with diethyl ether and filtered to afford a solid. The solid was collected and further triturated with ∼1:1:1 MeCN/H_2O/MeOH (∼5 mL). The solid was collected by filtration and dried *in vacuo* to give the title compound (273 mg, 0.76 mmol, 38% yield) as a white solid. Mp: 199−200 °C; IR (neat): 2973, 1696, 1471, 1396, 1141, 1054 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.63−7.56 (m, 2H), 7.52−7.45 (m, 3H), 4.59 (s, 2H), 3.85 (dt, J = 14.7, 3.3 Hz, 2H), 3.50 (br s, 2H), 3.29−3.22 (m, 4H), 2.24 (q, J = 4.4 Hz, 2H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 153.4, 133.3, 129.9, 128.6, 128.2, 79.7, 65.3, 58.3, 48.8 (br s), 38.3−36.3 (m), 27; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −134.1; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 2.0; LC-MS (HpH): 0.99 min (376) ([M + NH_4]$^+$, 100%); HRMS (ESI) m/z: [M + NH_4]$^+$ calcd for $C_{17}H_{30}{}^{11}BF_3N_3O_2^+$ 376.2378; found 376.2376.

*tert-Butyl (S)-3-(Tosyloxy)pyrrolidine-1-carboxylate (**14**).* To a stirred solution of *tert*-butyl (*S*)-3-hydroxypyrrolidine-1-carboxylate (20.0 g, 107 mmol, 1.0 equiv), DMAP (1.31 g, 10.7 mmol, 10 mol %), and triethylamine (44.7 mL, 320 mmol, 3.0 equiv) in DCM (200 mL) at 0 °C was added tosyl chloride (30.5 g, 160 mmol, 1.5 equiv) portionwise over 3 min. The reaction was allowed to warm to rt with stirring over 23 h and then sat. $NaHCO_3$ (200 mL) was added, and the mixture was stirred vigorously for 15 min. The phases were separated, and the aqueous phase was extracted with DCM (2 × 150 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by flash chromatography (0−40% ethyl acetate in cyclohexane) to afford the title compound (34.9 g, 102 mmol, 96% yield) as a viscous yellow oil. Analytical data are consistent with the literature.[37] $[\alpha]_D^{20}$ (c = 1.0, MeOH): +22; IR (neat): 2978, 2884, 1696, 1407, 1365, 1175, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.97 (br s, 1H), 3.48−3.27 (m, 4H), 2.37 (s, 3H), 2.13−1.83 (m, 2H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)* δ = 153.8, 144.8, 133.8−133.4 (m), 129.8, 127.4, 80.8−79.7 (m), 79.4, 51.9−50.8 (m), 43.7−42.7 (m), 32.3−30.9 (m, 1C), 28.2, 21.4; LC-MS (HpH): 1.22 min (359) ([M + NH_4]$^+$, 100%). *Room-temperature ^{13}C{^{1}H} NMR spectrum shows evidence of rotamers.

*(S)-2,2-Diphenyl-2-(pyrrolidin-3-yl)acetonitrile (**15**).* To a stirred solution of 2,2-diphenylacetonitrile (21.3 g, 110 mmol, 1.1 equiv) in 1:1 THF/DMF (200 mL) at 0 °C was added potassium *tert*-butoxide (16.9 g, 151 mmol, 1.5 equiv) portionwise over 5 min. After stirring for 1 h, a solution of *tert*-butyl (*S*)-3-(tosyloxy)pyrrolidine-1-carboxylate **14** (34.2 g, 100 mmol, 1.0 equiv) in 1:1 THF/DMF (200 mL) was added *via* cannular. The reaction was heated gradually to 60 °C and was stirred at this temperature for 15 h. After this time, the THF was removed *in vacuo* and the residue was diluted with 5% LiCl (200 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organics were passed through a hydrophobic frit, concentrated *in vacuo*, and the residue was coevaporated with toluene (2 × 100 mL). The residue was dissolved in DCM (50 mL) and to this was added TFA (70 mL, 909 mmol, 9.1 equiv) and the reaction was stirred at rt for 1 h and then at 50 °C for 90 min. The mixture was concentrated *in vacuo*, diluted with water (200 mL), and extracted with DCM (200 mL). The aqueous phase was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2 × 200 mL). The combined DCM and $CHCl_3$ layers were passed through a hydrophobic frit, concentrated *in vacuo*, and purified by flash chromatography on silica (99:1 EtOAc/NEt_3) to afford the title compound (18.3 g, 69.8 mmol, 70% yield) as a viscous yellow oil. Analytical data are consistent with the literature.[37] $[\alpha]_D^{20}$ (c = 1.0, MeOH): +19; IR (neat): 3408, 2966, 2237, 1597, 1494, 1450, 1201 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51−7.43 (m, 4H), 7.40−7.33 (m, 4H), 7.32−7.26 (m, 2H), 5.46 (br s, 1H), 3.50 (quin, J = 8.3 Hz, 1H), 3.30−3.22 (m, 1H), 3.21−3.08 (m, 2H), 2.99 (dd, J = 12.0, 8.8 Hz, 1H), 2.09−1.96 (m, 1H), 1.95−1.82 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 139.4, 139.2, 129.2, 129.1, 128.2, 128.1, 126.6, 126.5, 120.8, 56.3, 49.5, 46.4, 45.9, 29.4; LC-MS (HpH): 1.03 min (263) ([M + H]$^+$, 100%).

*Potassium (S)-((3-(Cyanodiphenylmethyl)pyrrolidin-1-yl)-methyl)trifluoroborate (**16**).* To a solution of (*S*)-2,2-diphenyl-2-(pyrrolidin-3-yl)acetonitrile **15** (3.65 g, 13.9 mmol, 1.0 equiv) in THF (28 mL) was added potassium (bromomethyl)trifluoroborate (2.79 g, 13.9 mmol, 1.0 equiv) and the mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to rt and then concentrated *in vacuo*. Acetone (100 mL) and potassium carbonate (1.92 g, 13.9 mmol, 1.0 equiv) were added, and the reaction was stirred for 30 min. The insoluble salts were filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in a minimum volume of acetone, and diethyl ether was added dropwise to afford the title compound (4.10 g, 10.7 mmol, 77% yield) as a pale pink amorphous solid, which was collected by filtration. $[\alpha]_D^{20}$ (c = 1.0, MeOH): +18; IR (neat): 3100−2684, 2234, 1598, 1493, 1445, 1202, 1001 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.58−7.40 (m, 8H), 7.39−7.29 (m, 2H), 3.96 (quin, J = 8.7 Hz, 1H), 3.43−3.14 (m, 4H), 2.89 (t, J = 11.0 Hz, 1H), 2.10−1.95 (m, 3H), 1.80 (dq, J = 13.4, 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 138.8, 138.6, 129.4, 129.3, 128.4, 128.2, 126.2, 126.1, 120.3, 57.1, 55.8, 55.8, 49.4 (br s, confirmed by HSQC), 42.5, 27.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −139.0; ^{11}B NMR (128 MHz, DMSO-d_6) δ = 2.2; LC-MS (HpH): 0.97 min (343) ([M − K]$^-$, 100%); HRMS (ESI) m/z: [M − K + H + NH_4]$^+$ calcd for $C_{19}H_{24}{}^{11}BF_3N_3^+$ 362.2010; found 362.2007.

*(S)-2-(1-(2-(2,3-Dihydrobenzofuran-5-yl)ethyl)pyrrolidin-3-yl)-2,2-diphenylacetamide (**17**).* A flask was charged with 5-(chloromethyl)-2,3-dihydrobenzofuran (169 mg, 1.0 mmol, 1.0 equiv), potassium (*S*)-((3-(cyanodiphenylmethyl)pyrrolidin-1-yl)methyl)-trifluoroborate **16** (573 mg, 1.5 mmol, 1.5 equiv), Pd-PEPPSI-iPent (79 mg, 0.10 mmol, 10 mol %), and potassium *tert*-butoxide (1.12 g, 10.0 mmol, 10.0 equiv) and was purged with N_2. *tert*-Amyl alcohol (8.0 mL) and water (2.0 mL) were added, and the reaction was stirred at 110 °C for 20 h. After this time, the reaction mixture was cooled to rt and filtered through celite eluting with *tert*−butyl methyl ether (TBME) and the filtrate was concentrated *in vacuo*. The residue was dissolved in *tert*-amyl alcohol (8.0 mL), and potassium hydroxide (1.68 g, 30.0 mmol, 30.0 equiv) and tetrabutylammonium bromide (32.2 mg, 0.10 mmol, 10 mol %) were added and the reaction was stirred at 110 °C for 24 h. After this time, the reaction was cooled to rt and diluted with water (15 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organics were passed through a hydrophobic frit. The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica (0−10% MeOH in DCM) to afford the title compound (194 mg, 0.46 mmol, 46% yield) as a pale yellow viscous gum. Analytical data are consistent with the literature.[51] $[\alpha]_D^{20}$ (c = 1.0, MeOH): −26; IR (neat): 3476, 2958, 2799, 1676, 1598, 1492, 1243, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (br s, 1H), 7.45−7.39 (m, 2H), 7.35−7.20 (m, 8H), 6.99−6.96 (m, 1H), 6.87 (dd, J = 8.1, 2.0 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.45 (br s, 1H), 4.54 (t, J = 8.7 Hz, 2H), 3.49−3.39 (m, 1H), 3.16 (t, J = 8.7 Hz, 2H), 2.87 (dd, J = 9.9, 5.3 Hz, 1H), 2.79−2.55 (m, 6H), 2.43 (q, J = 8.3 Hz, 1H), 2.02−1.87 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 175.4, 158.4, 144.7, 143.8, 132.1, 129.3, 129.3, 127.9, 127.9, 127.8, 126.9, 126.8, 126.5, 125.0, 108.9, 71.1, 64.5, 57.7, 57.2, 53.9, 44.4, 34.3, 29.7, 28.9; LC-MS (HpH): 1.24 min (427) ([M + H]$^+$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02958.

Detailed procedures for high-throughput experimentation, preparation, and characterization of compounds; and ^{1}H and ^{13}C{^{1}H} NMR spectra of compounds and

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procedures for monitoring of trifluoroborate salt hydrolysis rates (PDF)

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Notes

The authors declare the following competing financial interest(s): Authors TB and DB are shareholders in GSK.

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DEDICATION

Dedicated to Professor Ilhyong Ryu on the occasion of his 70th birthday.

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