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Synthesis and Minisci Reactions of Organotrifluoroborato Building Blocks

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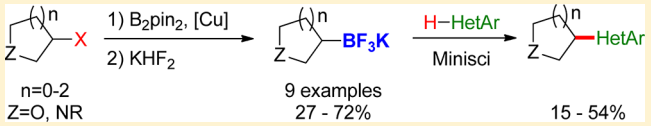
Supporting Information

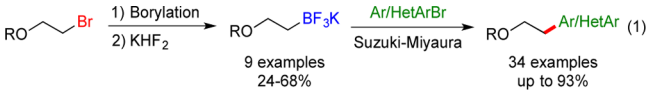
ABSTRACT: Copper-catalyzed borylation of a variety of organic halides with bis(pinacolato)diboron allows the preparation of diverse potassium organotrifluoroborates. The reactions are mild and general, providing access to a variety of interesting, boron-containing building blocks, including those containing piperidine, pyrrole, azetidine, tetrahydropyran, and oxetane substructures. Representative Minisci reactions are reported for select examples.



As a consequence of their successful and, thus, increasing use in a variety of reactions, the demand for new boron-containing building blocks is constantly growing.[1] Among them, organotrifluoroborates have been shown to be a valuable alternative to boronic acids owing to the increased stability conferred by the tetracoordinated boron atom.[2,3] In particular, the efficiency of the organotrifluoroborates in a broad range of reactions has been demonstrated, taking advantage of the reactivity of the boron–carbon bond, as well as reactions where the boron is retained.[4,5]

Aliphatic potassium organotrifluoroborates can be easily obtained by simply treating appropriate organoboron precursors with potassium bifluoride (KHF_2) or KF in the presence of tartaric acid.[6] In general, the requisite organoborons can be accessed by different methods: (1) reaction of an organometallic (organomagnesium or organolithium) reagent with an electrophilic boron species BX_3 (X = Cl, F, OR);[7,8] (2) hydroboration of alkenes;[9,10] or (3) borylation of alkanes by C–H bond activation.[11,12] Recently, much attention has been placed on the use of nucleophilic boron species, and in preference to the highly reactive boryllithiums or NHC-boranes,[13,14] activation of dibora compounds by a nucleophile was found to be a more efficient and useful synthetic protocol.[15,16] More precisely, copper(I)-catalyzed reactions were particularly successful in the case of 1,4-additions to unsaturated carbonyl compounds,[17,18] and after the pioneering work on activated electrophiles by Miyaura,[19] the past year has witnessed the emergence of aliphatic borylation of halogenated substrates. Therefore, primary, secondary, and even tertiary alkylboronates have been prepared by Cu-,[20,21] Ni-,[22,23] or Pd-catalysis,[24] providing access to previously problematic targets.[25] Herein, we report the use of this method for the preparation of a variety of organotrifluoroborate building blocks of potential use as synthons in the development of drug-like compounds.[26]

We recently reported the preparation of potassium β-alkoxyethyltrifluoroborates, using an adaptation of Marder and Liu's conditions,[20] wherein a copper(I)-catalyzed borylation of the corresponding primary bromides was followed by treatment with KHF_2 to afford the target structures. The resulting organotrifluoroborates were subsequently used in Suzuki–Miyaura cross-coupling reactions (eq 1).[27]



Based on the success of this approach, we explored other alkyl halides as substrates for the copper-promoted borylation, and we were particularly interested in saturated heterocycles bearing a secondary halogen, which would provide access to heterocyclic trifluoroborates that are challenging to access by other means. To this end, *N*-Boc-4-bromopiperidine was used as a test substrate under the same conditions used for the β-alkoxyethyl system. The desired transformation proceeded smoothly and afforded, after treatment with potassium bifluoride, the corresponding potassium organotrifluoroborate **1a** in 72% yield (Table 1, entry 1). As was reported previously, the use of polystyrene-supported triphenylphosphine (PS-PPh_3) was found to be crucial to obtain a pure product, avoiding contamination with triphenylphosphine oxide. Moreover, these conditions proved to be general and have been successfully applied to various substrates. Indeed, different protecting groups on the nitrogen atom are tolerated (Table 1, entries 1 and 2) and six-, five-, and even four-membered nitrogen heterocycles provided the desired products in acceptable yields (Table 1, entries 1, 3, and 4, respectively).

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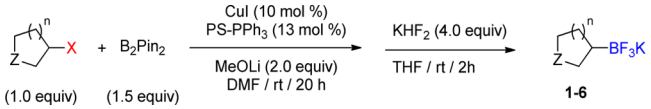
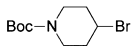
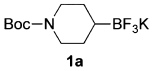
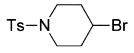
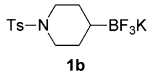
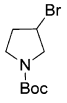
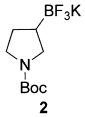
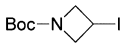
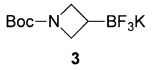
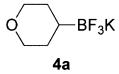
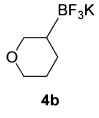
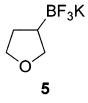
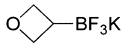
Table 1. Borylation of Various Heterocyclic Halides[a]



entry	alkyl halide	product	yield (%)
1		 **1a**	72
2		 **1b**	51
3		 **2**	59
4		 **3**	54
5		 **4a**	27
6		 **4b**	52
7		 **5**	52
8		 **6**	30

[a]Reaction conditions: Halide (1.0 equiv), B_2pin_2 (1.5 equiv), CuI (10 mol %), PS-PPh_3 (13 mol %), MeOLi (2.0 equiv), DMF ([halide] = 0.2 M), rt, 20 h then sat. aq KHF_2 (4.0 equiv), THF, rt, 2 h.

Additionally, the analogous oxa-heterocyclic trifluoroborates **4**, **5**, and **6** (Table 1, entries 5−8) were obtained under the same conditions in decent yields, thus affording an alternative route to the iridium-catalyzed borylation of cyclic ethers recently reported by Hartwig.[28] It should be noted that these new building blocks were obtained in yields that appear to be reflective of the efficiency of the borylation step. The trifluoroborates synthesized were found to be perfectly stable to air and moisture upon storage.

Owing to the importance of the piperidine moiety in drug discovery, we explored whether this strategy would allow the preparation of other functionalized scaffolds. More precisely, we were particularly interested in the 2-pyridinyl protecting group as it has proven to be efficient in the functionalization of piperidines.[29] Consequently, the desired precursor **9** was obtained in four steps from commercially available reagent **8**: a PEPPSI ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]-(3-chloropyridyl)palladium(II) dichloride)-catalyzed Buchwald−Hartwig amination of 2-chloropyridine **7** provided quantitatively the *N*-arylated intermediate,[30] which, after two steps of deprotection and reduction, was successfully converted to the corresponding brominated compound **9** by heating at reflux in aqueous HBr (43% over four steps).[31] As in the case of other piperidines **1a** and **1b**, the borylation of **9** was easily achieved, providing **1c** in a yield of 60% (Scheme 1).

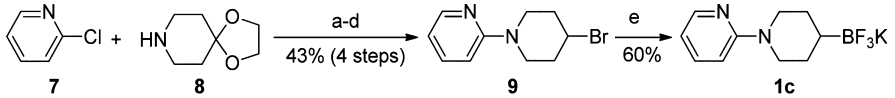
Having synthesized an array of new heterocyclic trifluoroborates, we investigated their behavior in the Minisci reaction with various heteroaromatic compounds. Although conditions previously reported by our laboratory with stoichiometric manganese(III) acetate were only successful in the case of the tetrahydropyran derivative **4a**,[32] slight modifications of the conditions recently developed by Baran proved to be effective for this transformation.[33,34] Indeed, using an increased amount of potassium persulfate and trifluoroacetic acid allowed us to add building blocks **1a**, **3**, and **4a** to lepidine in modest yields (Table 2, compounds **13a−c**). Moreover, pyridazine and quinoxaline (Table 2, compounds **13d** and **13e−f**) were also valuable substrates, opening an alternative route for the preparation of heteroarylazetidines by means of a Minisci reaction.[35]

In conclusion, we have prepared various potassium organotrifluoroborate building blocks by copper-catalyzed borylation of the corresponding halides. This method is general and allows the preparation of useful boron-containing synthons of particular interest to medicinal chemistry in useful yields.[36] Some of these new trifluoroborates have been successfully tested in the Minisci reaction, affording interesting compounds in a straightforward manner with modest yields.

EXPERIMENTAL SECTION

General Considerations. All commercially available reagents including anhydrous solvents were used without purification. CuI (99.999%), PEPPSI-IPr, *N*-Boc-3-bromopyrrolidine, *N*-Boc-3-iodoazetidine, 3-bromotetrahydropyran, and 3-bromotetrahydrofuran were all contained from commercial sources and used as received. *N*-Tosyl-4-bromopiperidine was prepared by the procedure of Gong et al.[37] Reactions under microwave irradiation were performed in a Biotage Initiator system. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography (FC) was performed on a

Scheme 1. Preparation of Potassium *N*-(2-Pyridinyl)-4-trifluoroboratopiperidine 1c[a]



[a]Reaction conditions: (a) **7** (1.0 equiv), **8** (1.2 equiv), PEPPSI-IPr (2 mol %), *t*-BuOK (1.5 equiv), DME, rt, 24 h, quant.; (b) TsOH (20 mol %), H_2O/acetone:1/3, 150 °C (MW), 1 h, 83%; (c) $NaBH_4$ (1.1 equiv), MeOH, rt, 1 h, 90%; (d) HBr (48% in H_2O, 17 equiv), 100 °C, 14 h, 58% (81% brsm); (e) B_2pin_2 (1.5 equiv); CuI (10 mol %), PS-PPh_3 (13 mol %), MeOLi (2.0 equiv), DMF, rt, 20 h then sat. aq KHF_2 (4.0 equiv), THF, rt, 2 h, 60%.

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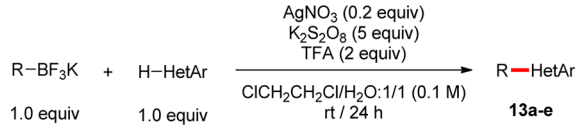
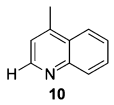
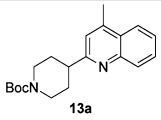
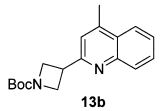
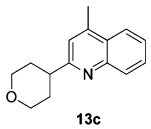
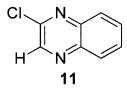
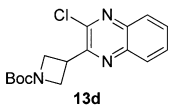
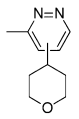
Table 2. Minisci Reaction of Various Heterocyclic Trifluoroborates[a]



entry	RBF_3K	HetArH	product	yield (%)
1	**1a**	 **10**	 **13a**	54
2	**3**	**10**	 **13b**	31
3	**4a**	**10**	 **13c**	38
4	**3**	 **11**	 **13d**	15
5	**4a**	 **12**	 **13e-f** (C4/C5: 40/60)	37

[a]Reaction conditions: Heteroarene (1.0 equiv), potassium organotrifluoroborate (1.1 equiv), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (5.0 equiv), TFA (2.0 equiv), $ClCH_2CH_2Cl/H_2O$, 1:1 ([heteroarene] = 0.1 M), rt, 24 h.

Biotage SP4 base system using GRACE Reveleris columns (silica size 40 μm) of various sizes. Visualization was effected with ultraviolet light and ethanolic $KMnO_4$. NMR spectra were recorded on a 400 MHz or a 360 MHz spectrometer. Chemical shifts are given in ppm. ^{1}H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. The resonance of the carbon center linked to the boron atom was not observed. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). ^{11}B NMR chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (0.0 ppm) with a negative sign indicating an upfield shift. Data are presented as follows: chemical shift δ (ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *br* = broad), coupling constant *J* (Hz), integration. High-resolution mass spectra were obtained by electrospray ionization on a TOF instrument.

General Procedure A for the Preparation of Compounds 1–6. In air, B_2pin_2 (1.5 equiv), LiOMe (2.0 equiv), PS-PPh_3 (13 mol %), and CuI (10 mol %) were weighed in a round-bottomed flask equipped with a stir bar. The flask was closed with a septum, evacuated, and backfilled with N_2. DMF (5 mL) and the halide (1.0 mmol, 1.0 equiv) were successively added by syringes (or, if the halide was solid, it was added as a solution in DMF), and the reaction was vigorously stirred at rt for 20 h. Then, the reaction was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and rinsed with CH_2Cl_2 (20 mL). The resulting solution was concentrated, poured into sat. aq NH_4Cl (20 mL), and extracted three times with Et_2O (20 mL). The combined organic layers were washed successively with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was solubilized in THF (5 mL) in a round-bottomed flask equipped with a stir bar, and sat. aq KHF_2 (4.5 M, 0.9 mL, 4.0 equiv) was added. The flask was closed with a septum, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was evaporated to dryness, and the resulting salt was extracted several times with hot acetone. The filtrate was concentrated to ~5 mL, and precipitation was achieved by dropwise addition of the filtrate to Et_2O (100 mL) at 0 °C. The resulting product was collected by gravity filtration on a fritted funnel and dried to afford the corresponding potassium heterocyclic trifluoroborate as a white solid.

Potassium N-Boc-4-(Trifluoroborato)piperidine ***1a.*** Following general procedure A, the reaction performed with *N*-Boc-4-bromopiperidine (0.94 g, 3.55 mmol) afforded 741 mg (72%) of the title compound as a white solid. Mp 213–215 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 3.97 (br, 2H), 2.52 (br, 2H), 1.49 (dd, *J* = 13, 3 Hz, 2H), 1.41 (s, 9H), 1.26 - 1.10 (m, 2H), 0.28 (m, 1H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 155.3 (C), 78.4 (C), 46.6 (2 CH_2), 29.1 (2 CH_2), 28.8 (3 CH_3). ^{11}B NMR (acetone-d^6, 128 MHz): δ 4.84 (br). ^{19}F NMR (acetone-d^6, 377 MHz): δ −148.4. HRMS (ESI) *m/z*: $(M - K)^-$ Calcd for $C_{10}H_{18}BF_3NO_2$ 252.1388; Found 252.1380.

Potassium N-Tosyl-4-(trifluoroborato)piperidine ***1b.*** Following general procedure A, the reaction performed with *N*-tosyl-4-bromopiperidine (596 mg, 1.87 mmol) afforded 330 mg (51%) of the title compound as a white solid. Mp 217–220 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 7.56 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H), 3.51–3.49 (m, 2H), 2.40 (s, 3H), 1.99–1.93 (m, 2H), 1.46 (dd, *J* = 13, 2 Hz, 2H), 1.27–1.10 (m, 2H), −0.16 (br, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 142.9 (C), 132.9 (C), 129.5 (2 CH), 127.3 (2 CH), 47.9 (2 CH_2), 27.4 (2 CH_2), 20.9 (CH_3). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.71 (br). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −144.6. HRMS (ESI) *m/z*: $(M - K)^-$ Calcd for $C_{12}H_{16}BF_3NO_2S$ 306.0952; Found 306.0950.

Potassium N-Boc-3-(Trifluoroborato)pyrrolidine ***2.*** Following general procedure A, the reaction performed with *N*-Boc-3-bromopyrrolidine (625 mg, 2.50 mmol) afforded 408 mg (59%) of the title compound as a white solid. Mp 195–199 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 3.35–3.22 (m, 2H), 3.05–2.91 (m, 2H), 1.69 (dt, *J* = 12, 6 Hz, 1H), 1.63–1.50 (m, 1H), 1.41 (s, 9H), 0.94 (br, 1H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 155.2 (C), 77.8 (C), 50.9 (CH_2), 50.5 (CH_2), 48.3 (CH_2), 28.9 (3 CH_3). ^{11}B NMR (acetone-d^6, 128 MHz): δ 4.55 (br). ^{19}F NMR (acetone-d^6, 377 MHz): δ −146.2. HRMS (ESI) *m/z*: $(M - K)^-$ Calcd for $C_9H_{16}BF_3NO_2$ 238.1232; Found 238.1223.

Potassium N-Boc-3-(Trifluoroborato)azetidine ***3.*** Following general procedure A, the reaction performed with *N*-Boc-3-iodoazetidine (1.63 g, 5.75 mmol) afforded 826 mg (54%) of the title compound as a white solid. Mp 182–185 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 3.57 (br, 4H), 1.34 (s, 9H), 1.31 (br, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 155.6 (C), 77.1 (C), 51.9 (CH_2), 50.7 (CH_2), 28.2 (3 CH_3). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.11 (br). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −145.2. HRMS (ESI) *m/z*: $(M - K)^-$ Calcd for $C_8H_{14}BF_3NO_2$ 224.1075; Found 224.1067.

Potassium 4-(Trifluoroborato)tetrahydropyran ***4a.*** Following general procedure A, the reaction performed with 4-bromotetrahydropyran (0.5 g, 3.0 mmol) afforded 155 mg (27%) of the title compound as a white solid. Mp >250 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 3.74 (d, *J* = 10 Hz, 2H), 3.12 (td, *J* = 10, 3 Hz, 2H), 1.32–1.13 (m, 4H), 0.21–0.19 (m, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 69.3 (2 CH_2), 28.9 (2 CH_2). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.39 (q, *J* = 58 Hz). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −145.0. HRMS (ESI) *m/z*: $(M - K)^-$ Calcd for $C_5H_9BF_3O$ 153.0704; Found 153.0697. Analytical data are consistent with those previously reported.[32]

Potassium 3-(Trifluoroborato)tetrahydropyran ***4b.*** Following general procedure A, the reaction performed with 3-bromotetrahydropyran (0.5 g, 3.0 mmol) afforded 304 mg (52%) of the title compound as a white solid. Mp 204–207 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 3.73–3.64 (m, 2H), 3.03–3.17 (m, 2H), 1.57–1.53 (m,

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1H), 1.37−1.31 (m, 2H), 1.20−1.07 (m, 1H), 0.40 (br, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 72.3 (CH_2), 67.7 (CH_2), 28.0 (CH_2), 25.7 (CH_2). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 3.80 (br). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −143.2. HRMS (ESI) m/z: $(M - K)^-$ Calcd for $C_5H_9BF_3O$ 153.0704; Found 153.0697.

Potassium 3-(Trifluoroborato)tetrahydrofuran ***5***. Following general procedure A, the reaction performed with 3-bromotetrahydrofuran (0.5 g, 3.3 mmol) afforded 307 mg (52%) of the title compound as a white solid. Mp 169−171 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 3.63 (t, J = 8 Hz, 1H), 3.53 (td, J = 8, 3 Hz, 1H), 3.41−3.35 (m, 1H), 3.23 (dd, J = 10, 8 Hz, 1H), 1.68−1.57 (m, 1H), 1.46 (t, J = 10 Hz, 1H), 0.78 (br, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 71.8 (CH_2), 67.6 (CH_2), 29.5 (CH_2). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.32 (q, J = 59 Hz). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −141.0. HRMS (ESI) m/z: $(M - K)^-$ Calcd for $C_4H_7BF_3O$ 139.0548; Found 139.0538. Analytical data are consistent with those previously reported.[28]

Potassium 3-(Trifluoroborato)oxetane ***6***. Following general procedure A, the reaction performed with 3-iodooxetane (2.14 g, 11.63 mmol) afforded 580 mg (30%) of the title compound as a white solid. Mp 211−213 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 4.44−4.42 (br, 4H), 1.93 (br, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 74.7 (2 CH_2). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 3.97 (q, J = 59 Hz). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −144.2. HRMS (ESI) m/z: $(M - K)^-$ Calcd for $C_3H_5BF_3O$ 125.0391; Found 125.0381.

Potassium N-(2-Pyridinyl)-4-trifluoroboratopiperidine ***1c***. *N-(2-Pyridinyl)-4-piperidinone Ethylene Ketal*. In air, KO*t*-Bu (9.0 g, 79.86 mmol, 1.5 equiv) and PEPPSI-IPr (702 mg, 1.06 mmol, 2 mol %) were weighed in a 250 mL round-bottom flask equipped with a stir bar. The flask was closed with a septum, evacuated, and backfilled with N_2. DME (50 mL), 2-chloropyridine (6.04 g, 53.24 mmol, 1.0 equiv), and 4-piperidinone ethylene ketal (9.16 g, 63.89 mmol, 1.2 equiv) were successively added by syringes. The reaction was stirred for 24 h. Then, the reaction mixture was filtered through a pad of Celite (rinsed with 100 mL of EtOAc), and the filtrate was evaporated to afford the crude product. Purification by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/EtOAc, 1:1) afforded 11.8 g (quant) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.22−8.12 (m, 1H), 7.52−7.38 (m, 1H), 6.75−6.63 (m, 1H), 6.63−6.50 (m, 1H), 3.99 (s, 4H), 3.74−3.63 (m, 4H), 1.81−1.72 (m, 4H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 158.8 (C), 147.9 (CH), 137.4 (CH), 112.7 (CH), 107.5 (C), 107.0 (CH), 64.3 (2 CH_2), 43.4 (2 CH_2), 34.3 (2 CH_2). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{12}H_{17}N_2O_2$ 221.1290; Found 221.1279. Analytical data are consistent with those previously reported.[29]

N-(2-Pyridinyl)-4-piperidinone. In air, a solution of *N*-(2-pyridinyl)-4-piperidinone ethylene ketal (9.8 g, 44.4 mmol, 1.0 equiv) and *p*-TsOH monohydrate (846 mg, 4.45 mmol, 10 mol %) in acetone (36 mL) and H_2O (12 mL) was split equally in four 10−20 mL microwave vials equipped with a stir bar. The tubes were sealed, and each of them was irradiated at 150 °C for 30 min. The tops were removed, and another portion of *p*-TsOH (10 mol %) was added. The tubes were sealed, and each of them was irradiated at 150 °C for 30 min. The tops were removed, and the reaction mixtures were combined and concentrated to afford the crude product. Purification by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/MeOH, 98:2) afforded 6.5 g (83%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.22−8.15 (m, 1H), 7.56−7.46 (m, 1H), 6.73 (d, J = 8 Hz, 1H), 6.65 (dd, J = 7, 5 Hz, 1H), 3.89 (d, J = 12 Hz, 4H), 2.48 (d, J = 12 Hz, 4H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 208.4 (C), 157.7 (C), 148.1 (CH), 137.7 (CH), 113.5 (CH), 106.8 (CH), 44.6 (2 CH_2), 40.5 (2 CH_2). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{10}H_{13}N_2O$ 177.1028; Found 177.1008.

N-(2-Pyridinyl)-4-hydroxypiperidine. In air, *N*-(2-pyridinyl)-4-piperidinone (6.2 g, 35.3 mmol, 1.0 equiv) was solubilized in MeOH (150 mL) in a 250 mL round-bottom flask equipped with a stir bar. The flask was closed with a septum and cooled to 0 °C. $NaBH_4$ (1.5 g, 38.8 mmol, 1.1 equiv) was added portionwise. The reaction was stirred at rt for 1 h. Then, the reaction mixture was poured into saturated aq NH_4Cl (200 mL), and the resulting solution was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and evaporated to afford the crude product. Purification by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/MeOH, 95:5) afforded 5.7 g (90%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.16 (dd, J = 5, 1 Hz, 1H), 7.51−7.40 (m, 1H), 6.73−6.62 (m, 1H), 6.58 (dd, J = 7, 5 Hz, 1H), 4.05 (ddd, J = 9, 8, 4 Hz, 2H), 3.90 (tt, J = 9, 4 Hz, 1H), 3.20−3.04 (m, 2H), 2.13 (br, 1H), 2.03−1.87 (m, 2H), 1.57 (dtd, J = 13, 9, 4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 159.2 (C), 147.9 (CH), 137.5 (CH), 112.8 (CH), 107.2 (CH), 68.1 (CH), 43.1 (2 CH_2), 33.8 (2 CH_2). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{10}H_{15}N_2O$ 179.1184; Found 179.1155.

N-(2-Pyridinyl)-4-bromopiperidine ***9***. In air, *N*-(2-pyridinyl)-4-hydroxypiperidine (4.5 g, 25.5 mmol, 1.0 equiv) was solubilized in HBr, 48% in H_2O (50 mL, 17 equiv) in a 250 mL round-bottom flask equipped with a stir bar, and the flask was equipped with a condenser. The reaction was heated at 120 °C (oil bath temperature) for 14 h. Then, the reaction mixture was cooled to rt, and 1 M aq NaOH was added until pH > 12. The resulting solution was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to afford the crude product. Purification by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/MeOH, 95:5) afforded 3.6 g (58%) of the title compound as a yellow oil (and 1.24 g of recovered starting material). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.24−8.12 (m, 1H), 7.55−7.42 (m, 1H), 6.74−6.53 (m, 2H), 4.42 (dt, J = 8, 4 Hz, 1H), 4.02−3.84 (m, 2H), 3.52−3.33 (m, 2H), 2.26−2.17 (m, 2H), 2.14−1.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 159.0 (C), 148.0 (CH), 137.5 (CH), 113.1 (CH), 107.1 (CH), 50.2 (CH), 44.1 (2 CH_2), 35.4 (2 CH_2). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{10}H_{14}BrN_2$ 241.0340; Found 241.0369.

Potassium N-(2-Pyridinyl)-4-(trifluoroborato)piperidine ***1c***. Following general procedure A, the reaction performed with *N*-(2-pyridinyl)-4-bromopiperidine **9** (3.4 g, 14.1 mmol) afforded 2.27 g (60%) of the title compound as a white solid. Mp 215−217 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 8.06−7.98 (m, 1H), 7.41 (ddd, J = 9, 7, 2 Hz, 1H), 6.67 (d, J = 9 Hz, 1H), 6.51−6.42 (m, 1H), 4.19−4.16 (m, 2H), 2.61−2.56 (m, 2H), 1.49−1.45 (m, 2H), 1.20−1.09 (m, 2H), 0.23−0.18 (m, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 159.3 (C), 147.4 (CH), 137.1 (CH), 111.2 (CH), 106.6 (CH), 47.2 (2 CH_2), 27.6 (2 CH_2). ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.47 (br). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −144.5. HRMS (ESI) m/z: $(M - K)^-$ Calcd for $C_{10}H_{13}BF_3N_2$ 229.1129; Found 229.1122.

General Procedure B for the Minisci Reactions. In air, potassium organotrifluoroborate (1.1 equiv), $AgNO_3$ (0.2 equiv) and $K_2S_2O_8$ (5.0 equiv) were weighed in a reaction tube equipped with a stir bar. $ClCH_2CH_2Cl$ (2.5 mL), H_2O (2.5 mL), heteroarene (0.5 mmol, 1.0 equiv), and TFA (2.0 equiv) were successively added, and the tube was sealed. The reaction was vigorously stirred at rt for 24 h. Then, the reaction mixture was poured into 20 mL of a 1/1 v/v mixture of sat. aq $NaHCO_3$ and 5% aq NaS_2O_3, and the resulting solution was extracted three times with CH_2Cl_2 (30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the crude product. Purification by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/MeOH, 95:5) afforded the desired product.

2-(N-Boc-4-Piperidinyl)lepidine ***13a***. Following general procedure B, the reaction performed with **1a** (160 mg, 0.55 mmol) and **10** (72 mg, 0.50 mmol) afforded 88 mg (54%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.04 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 7.73−7.64 (m, 1H), 7.57−7.47 (m, 1H), 7.15 (s, 1H), 4.29 (br, 2H), 3.09−2.96 (m, 1 H), 2.89 (br, 2H), 2.69 (s, 3H), 2.04−1.92 (m, 2H), 1.92−1.75 (m, 2H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 164.3 (C), 154.8 (C), 147.6 (C), 144.6 (C), 129.5 (CH), 129.1 (CH), 127.1 (C), 125.6 (CH), 123.6 (CH), 120.0 (CH), 79.4 (C), 45.5 (CH), 43.6 (2 CH_2), 31.6 (2 CH_2), 28.5 (3 CH_3), 18.8 (CH_3). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{20}H_{27}N_2O_2$ 327.2072; Found 327.2059.

2-(N-Boc-3-Azetidinyl)lepidine ***13b***. Following general procedure B, the reaction performed with **3** (145 mg, 0.55 mmol) and **10** (72 mg, 0.50 mmol) afforded 47 mg (31%) of the title compound as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dd, J = 9, 1 Hz, 1H), 7.96 (dd, J = 8, 1.0 Hz, 1H), 7.69 (ddd, J = 8, 7, 1 Hz, 1H), 7.53 (ddd, J = 8, 7, 1 Hz, 1H), 7.25 (s, 1H), 4.43−4.34 (m, 2H), 4.32−4.24 (m, 2H),

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4.07−3.95 (m, 1H), 2.70 (d, J = 1 Hz, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8 (C), 156.5 (C), 147.4 (C), 145.1 (C), 129.6 (CH), 129.3 (CH), 127.1 (C), 126.0 (CH), 123.6 (CH), 119.9 (CH), 79.4 (C), 54.5 (2 CH_2), 35.7 (CH), 28.4 (3 CH_3), 18.7 (CH_3). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{18}H_{23}N_2O_2$ 299.1759; Found 299.1789. Analytical data are consistent with those previously reported.[35]

2-(4-Tetrahydropyranyl)lepidine ***13c.*** Following general procedure B, the reaction performed with **4a** (106 mg, 0.55 mmol) and **10** (72 mg, 0.50 mmol) afforded 44 mg (38%) of the title compound as a white solid. Mp 108 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, J = 8, 1 Hz, 1H), 7.93 (dd, J = 8, 1 Hz, 1H), 7.66 (ddd, J = 8, 7, 1 Hz, 1H), 7.49 (ddd, J = 8, 7, 1 Hz, 1H), 7.16 (s, 1H), 4.16−4.07 (m, 2 H), 3.58 (td, J = 12, 2 Hz, 2H), 3.11 (tt, J = 11.9, 4.0 Hz, 1H), 2.65−2.70 (m, 3H), 2.09−1.95 (m, 2H), 1.95−1.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1 (C), 147.5 (C), 144.8 (C), 129.4 (CH), 129.0 (CH), 127.0 (C), 125.5 (CH), 123.5 (CH), 119.8 (CH), 68.0 (2 CH_2), 44.2 (CH), 32.2 (2 CH_2), 18.7 (CH_3). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{15}H_{18}NO$ 228.1388; Found 228.1386. Analytical data are consistent with those previously reported.[32]

2-Chloro-3-(N-Boc-3-azetidinyl)quinoxaline ***13d.*** Following general procedure B, the reaction performed with **3** (66 mg, 0.25 mmol) and **11** (41 mg, 0.25 mmol) afforded 12 mg (15%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14−8.12 (*m*, 1H), 8.03−8.01 (*m*, 1H), 7.82−7.78 (*m*, 2H), 4.46 (*br*, 2H), 4,41 (*t*, J = 8.0 Hz, 2H), 4.36−4.33 (*m*, 1H), 1.47 (*s*, 9H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 156.3 (C), 153.1 (C), 146.8 (C), 141.0 (C), 140.5 (C), 130.6 (CH), 130.3 (CH), 128.9 (CH), 128.0 (CH), 79.6 (C), 38.8 (2 CH_2), 32.9 (CH), 28.3 (3 CH_3). HRMS (ESI) m/z: $(M_2 + H)^+$ Calcd for $C_{32}H_{37}N_6O_4Cl_2$ 639.2253; Found 639.2231.

3-Methyl-4-(4-tetrahydropyranyl)pyridazine ***13e*** *and 3-Methyl-5-(4-tetrahydropyranyl)pyridazine* ***13f.*** Following general procedure B, the reaction performed with **4a** (106 mg, 0.55 mmol) and **12** (47 mg, 0.50 mmol) afforded 33 mg (37%) of **13e** and **13f** (C^4 and C^5 regioisomers, respectively) as a 40:60 mixture as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (d, J = 5 Hz, 1H), 8.89 (d, J = 2 Hz, 1H), 7.21 (d, J = 5 Hz, 1H), 7.11 (d, J = 2 Hz, 1H), 4.12−4.01 (m, 4H), 3.58−3.44 (m, 4H), 2.73−2.92 (m, 2H), 2.72 (s, 3H), 2.66 (s, 3H), 1.68−1.79 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7 (C), 158.8 (C), 150.0 (CH), 149.2 (CH), 144.1 (C), 143.0 (C), 124.3 (CH), 122.9 (CH), 67.8 (2 CH_2), 67.6 (2 CH_2), 38.3 (CH), 36.4 (CH), 32.2 (2 CH_2), 31.7 (2 CH_2), 22.2 (CH_3), 19.8 (CH_3). HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{10}H_{15}N_2O$ 179.1184; Found 179.1202.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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