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Cross-Coupling of Cyclopropyl- and Cyclobutyltrifluoroborates with Aryl and Heteroaryl Chlorides

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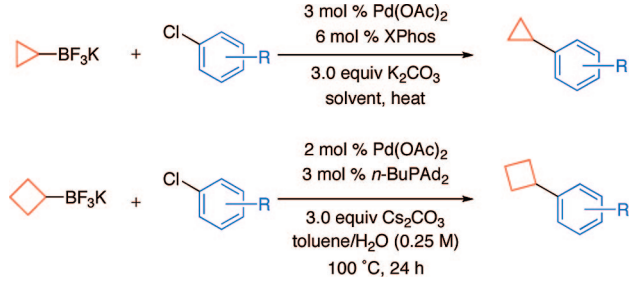

Suitable conditions were found for the Suzuki−Miyaura cross-coupling reaction of potassium cyclopropyl- and cyclobutyltrifluoroborates with aryl chlorides. Both of these secondary alkyl trifluoroborates coupled in moderate to excellent yield with electron-rich, electron-poor, and hindered aryl chlorides to give a variety of substituted aryl cyclopropanes and cyclobutanes.

Introduction

The development of mild methods for the incorporation of the cyclopropyl group into complex molecules is becoming increasingly important as a result of the prevalence of cyclopropanes in natural products[1] as well as in pharmaceutical targets, where the group's distinctive steric and electronic properties create unique opportunities for interrogating biological receptors.[2] The ease of access to cyclopropylborons, combined with the mild reaction conditions and tolerance of diverse functional groups, make the Suzuki−Miyaura cross-coupling[3] an extremely attractive method for the installation of the cyclopropyl group into aromatic and heteroaromatic systems. To date, the majority of investigations employing the Suzuki−Miyaura reaction in this endeavor have focused on the use of cyclopropylboronic acid.[4] Most of these reports feature aryl bromide or iodide electrophiles as opposed to the less expensive and more readily available (albeit less reactive) aryl chlorides. The few examples using aryl chlorides are limited to activated, electron-poor arenes,[4a,5] and although a number of heteroaryl triflates have been successfully cross-coupled with cyclopropylboronic acid,[6] only one example of a heteroaryl chloride exists in the literature.[4a] Furthermore, boronic acids themselves suffer from several notable drawbacks. Most significantly, the propensity of cyclopropylboronic acid to protodeboronate renders it unstable and unsafe upon prolonged storage and requires the use of between 10% and 200% excess[4] in cross-coupling reactions. Consequently, a significant quantity of the key reagent is wasted.

Potassium organotrifluoroborates[7] have proven to be a particularly useful class of boron reagents that are air- and moisture-stable, atom economical, and resistant to protodeboronation,[8] thereby allowing essentially stoichiometric quantities of reagent to be used in cross-coupling protocols. Organotri-

(1) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1648.

(2) (a) *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1987. (b) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabe, F. *J. Am. Chem. Soc.* **2007**, *129*, 44–45.

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(6) Yao, M.-L.; Deng, M.-Z. *New J. Chem.* **2000**, *24*, 425–428.

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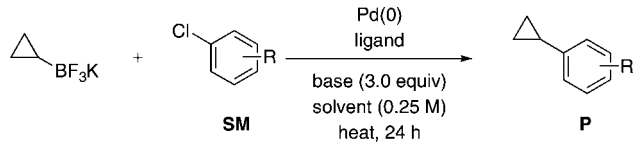
TABLE 1. Optimization of Reaction Conditions for Aryl Chlorides



entry	catalyst/ligand (mol %)	R	base	solvent (°C)	ratio P/SM[a]
1	$PdCl_2(dppf)\cdot CH_2Cl_2$ (3)	4-CN	Cs_2CO_3	THF/H_2O (80)	5/95
2	$Pd(OAc)_2$/XPhos (3/6)	4-CN	Cs_2CO_3	THF/H_2O (80)	99/1
3	**$Pd(OAc)_2$/XPhos (3/6)**	**4-CN**	**K_2CO_3**	**THF/H_2O (80)**	**100/0**
4	$Pd(OAc)_2$/XPhos (3/6)	4-OMe	K_2CO_3	THF/H_2O (80)	78/22
5	$Pd(OAc)_2$/XPhos (3/6)	4-OMe	Cs_2CO_3	THF/H_2O (80)	83/17
6	$Pd(OAc)_2$/1,1,3,3-tetramethylbutylisocyanide (3/6)	4-OMe	Cs_2CO_3	THF/H_2O (80)	4/94
7	**$Pd(OAc)_2$/XPhos (3/6)**	**4-OMe**	**K_2CO_3**	**CPME/H_2O (100)**	**100/0**

[a] Ratio of product/starting material as determined by GC−MS assay.

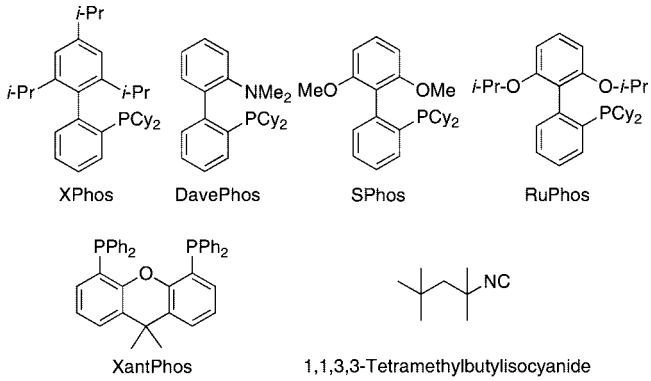


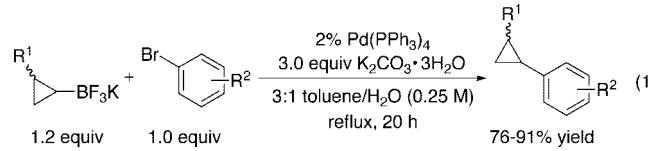
FIGURE 1. Ligands for cross-coupling.

fluoroborates are readily accessible from diverse organoboron precursors, and in accord with this, numerous methods have been developed for their synthesis, including cyclopropanation of alkenylboronic acids or -boronate esters,[9] transmetalation from cyclopropylzinc reagents,[10] and hydroboration of cyclopropenes.[11] Furthermore, the use of chiral boronates[9b] or catalytic asymmetric hydroboration[11] generates enantioenriched cyclopropyl boron reagents that undergo cross-coupling with retention of configuration[9−11] to allow facile, stereospecific incorporation of substituted cyclopropanes into complex molecules. Various cyclopropyltrifluoroborates have been demonstrated to cross-couple stereospecifically to aryl bromides or iodides,[9a,10] but the use of trifluoroborates with aryl chlorides has not been investigated. The current contribution represents an expansion of the utility of the Suzuki−Miyaura reaction for the installation of the cyclopropyl unit into a wide variety of aromatic substrates using potassium organotrifluoroborates, employing both aryl and heteroaryl chlorides.

The increased sp^3 character in the carbon−boron bond of cyclobutyl organometallics, combined with the potential intrusion of a β-hydride elimination from the diorganopalladium intermediate, makes the use of cyclobutyl derivatives in cross-coupling reactions significantly more challenging than that of their cyclopropyl counterparts. In a continued effort to expand the feasibility of secondary alkyl cross-coupling reactions with potassium organotrifluoroborates,[12] we synthesized cyclobutyltrifluoroborate and examined its reaction with various aryl chlorides and report what is, to the best of our knowledge, the first example of a cross-coupling reaction using a cyclobutyl organometallic coupling partner.

Results and Discussion

Our study began with optimization of reaction conditions for the cross-coupling of aryl chlorides with commercially available potassium cyclopropyltrifluoroborate. Previous cross-coupling studies of cyclopropyltrifluoroborates with aryl bromides by Deng and co-workers[9a] utilized traditional catalyst systems such as $PdCl_2(dppf)$ or $Pd(PPh_3)_4$ to good effect (eq 1).



However, the former conditions proved unsuccessful in our case owing to the increased difficulty of oxidative addition to aryl chlorides.[13] Table 1 summarizes our studies toward optimizing reaction conditions for this reaction. Previous success with dialkylbiaryl phosphine ligands in challenging systems[7,13b] led us quickly to examine the Buchwald palette of phosphines. A hindered isonitrile was examined as a unique potential alternative.

Among the suite of Buchwald and other ligands examined in initial screens (Figure 1), reaction conditions developed previously in our group for the cross-coupling of aryl chlorides and bromides with aminomethyltrifluoroborates[14] proved the most efficacious for cyclopropyltrifluoroborate (entries 2−5 and 7). Thus, it was determined that 3% $Pd(OAc)_2$ with 6% 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos)[15] as the catalyst system in the presence of a base in a 10:1 mixture of cyclopentyl methyl ether (CMPE) and H_2O (0.25 M) at 100 °C proved suitable for this reaction. In contrast to our previous

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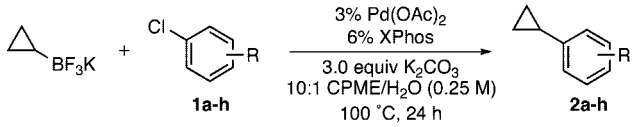
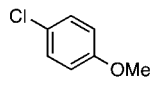
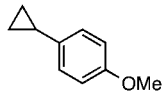
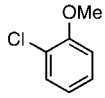
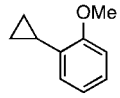
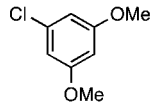
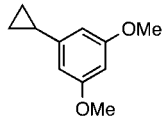
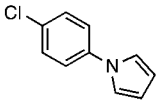
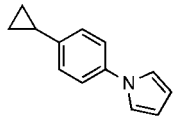
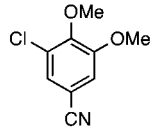
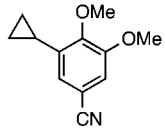
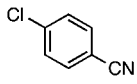
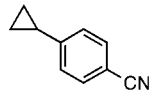
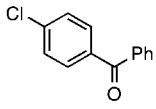
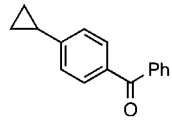
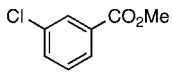
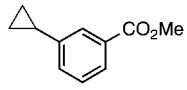
TABLE 2. Cross-Coupling of Potassium Cyclopropyltrifluoroborate with Various Aryl Chlorides[a]

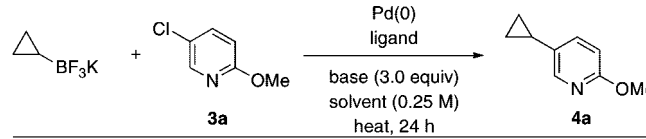


entry	aryl chloride	product	% isolated yield
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	82
3	 **1c**	 **2c**	94
4	 **1d**	 **2d**	90
5	 **1e**	 **2e**	96
6	 **1f**	 **2f**	76[b]
7	 **1g**	 **2g**	80[b]
8	 **1h**	 **2h**	82[c]

[a] All reactions used 0.5 mmol of the aryl chloride and 0.505 mmol of potassium cyclopropyltrifluoroborate. [b] 10:1 THF/H_2O was used as the solvent, 80 °C. [c] Reaction time was 48 h.

reports,[14] which required cesium carbonate to be used as the base, the less expensive potassium carbonate was effective in this case (entries 3 and 7). Using these reaction conditions a 75% yield of the cross-coupled product (**2a**) was obtained from the reaction of potassium cyclopropyltrifluoroborate with 4-chloroanisole.

TABLE 3. Optimization of Reaction Conditions for Heteroaryl Chlorides[a]



entry	catalyst/ligand (mol %)	base	solvent (°C)	ratio **4a/3a**[a]
1	$Pd(OAc)_2$/XPhos (3/6)	K_2CO_3	THF/H_2O (80)	72/28
2	$Pd(OAc)_2$/XPhos (3/6)	K_2CO_3	CPME/H_2O (100)	77/23
3	$Pd(OAc)_2$/RuPhos (3/6)	Cs_2CO_3	THF/H_2O (80)	46/54
4	$Pd(OAc)_2$/DavePhos (3/6)	Cs_2CO_3	THF/H_2O (80)	0/100
5	$Pd(OAc)_2$/SPhos (3/6)	Cs_2CO_3	THF/H_2O (80)	0/100
6	$Pd(OAc)_2$/XantPhos (3/6)	Cs_2CO_3	THF/H_2O (80)	90/10
7	$Pd(OAc)_2$/(*S*)-BINAP (3/6)	Cs_2CO_3	THF/H_2O (80)	0/100
8	$Pd(OAc)_2$/*n*-$BuPAd_2$ (2/3)	Cs_2CO_3	Toluene/ H_2O (100)	100/0

[a] Ratio of product/starting material as determined by GC−MS assay.

We next demonstrated the substrate scope of this method. Table 2 shows the reaction of potassium cyclopropyltrifluoroborate with various aryl chlorides. Electron-rich, electron-poor, and hindered aryl chlorides proved amenable to the reaction conditions, which tolerated numerous functional groups such as ketones, nitriles, and esters. However, reduction of the nitro group to the corresponding aniline resulted when 4-chloro-1-nitrobenzene was used. This phenomenon has been observed previously in cross-coupling of organoborons with nitro-containing aryl halides.[16] Highlighting the advantages of organotrifluoroborates over boronic acids and their derivatives,[4] only 1% excess of the trifluoroborate was used in all cases.

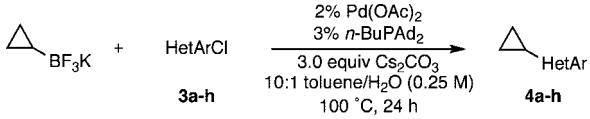
We next extended the method to heteroaryl chlorides, a class of electrophiles only minimally explored for the Suzuki−Miyaura reaction of cyclopropylborons.[4a] Unfortunately, the reaction conditions used for aryl chlorides and several other catalyst systems (Table 3, entries 1−7) failed to afford the cross-coupled product in useful yields.

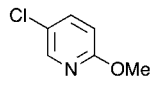
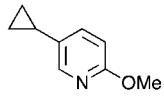
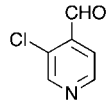
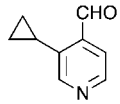
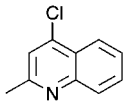
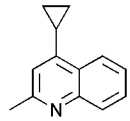
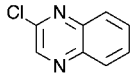
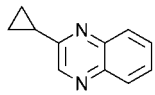
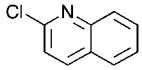
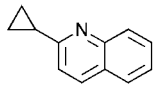
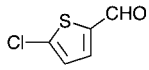
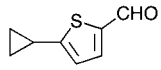
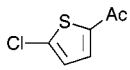
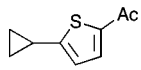
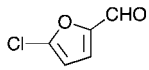
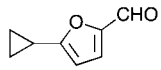
Simultaneously in our group, reaction conditions for the cross-coupling of secondary alkyltrifluoroborates, such as cyclopentyltrifluoroborate, were developed (entry 8).[12] Using these conditions [2% $Pd(OAc)_2$, 3% *n*-$BuPAd_2$, 3.0 equiv of Cs_2CO_3 in 10:1 toluene/H_2O at 100 °C], an 85% yield of 5-cyclopropyl-2-methoxypyridine (**4a**) was obtained from the reaction of 5-chloro-2-methoxypyridine with potassium cyclopropyltrifluoroborate. The scope of this reaction proved to be quite broad with respect to a wide variety of heteroaryl chlorides (Table 4).

Various substitution patterns and functional groups were well tolerated. Of particular interest are the 2-substituted nitrogen heterocycles, such as 2-chloroquinoline (**4e**) and 2-chloroquinoxaline (**4d**), which are sometimes difficult to couple owing to catalyst deactivation via complexation to the palladium catalyst[17] but are nevertheless desirable as substructures embedded within pharmacologically active materials.[18] Notably, 4-chlorobenzonitrile and 3-chloro-4,5-dimethoxybenzonitrile failed to react and afforded only starting material after 48 h by GC−MS analysis. We postulate that some interaction between the nitrile and the metal center causes the catalysts to be inactivated because the effect seems to be ligand dependent.

(16) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221–223.
(17) Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem.* **2001**, *634*, 39–46.
(18) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

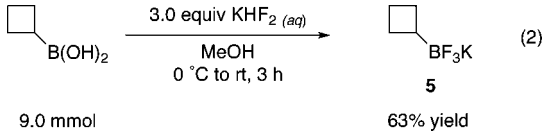
TABLE 4. Cross-Coupling of Potassium Cyclopropyltrifluoroborate with Various Heteroaryl Chlorides[a]



entry	heteroaryl chloride	product	% isolated yield
1	 **3a**	 **4a**	85
2	 **3b**	 **4b**	52
3	 **3c**	 **4c**	95
4	 **3d**	 **4d**	79
5	 **3e**	 **4e**	70
6	 **3f**	 **4f**	99
7	 **3g**	 **4g**	90
8	 **3h**	 **4h**	78

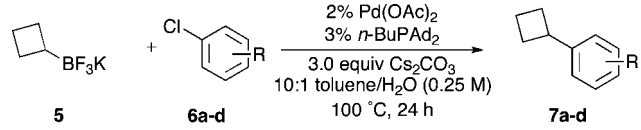
[a] All reactions used 0.5 mmol of the heteroaryl chloride and 0.505 mmol of potassium cyclopropyltrifluoroborate.

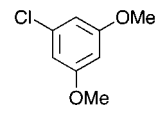
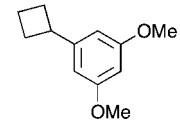
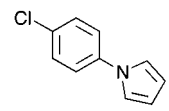
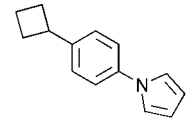
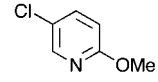
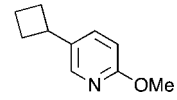
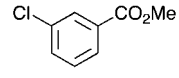
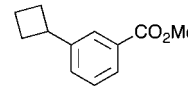
Finally, in an effort to expand the utility of this method for the installation of small rings into complex molecules, we synthesized cyclobutyltrifluoroborate (**5**) (eq 2) and subjected it to our optimized reaction conditions for cross-coupling with heteroaryl chlorides (Table 5).



The reaction proved to be somewhat substrate dependent; however, it afforded aryl cyclobutanes in moderate to good yields. Unfortunately, the reaction failed to reach completion with several substrates (4-chlorobenzophenone, 5-chloro-2-thiophenecarboxaldehyde and 1-chloro-4-methoxy-2,6-dimethylbenzene). The similar physicochemical characteristics of the aryl chloride and cross-coupled products in these particular cases made effective separation by silica gel column chromatography difficult, and the desired products could not be readily isolated in pure form.

TABLE 5. Cross-Coupling of Potassium Cyclobutyltrifluoroborate with Various Aryl and Heteroaryl Chlorides[a]



entry	chloride	product	% isolated yield
1	 **6a**	 **7a**	82
2	 **6b**	 **7b**	74
3	 **6c**	 **7c**	45
4	 **6d**	 **7d**	63

[a] All reactions used 0.5 mmol of the aryl or heteroaryl chloride and 0.505 mmol of potassium cyclobutyltrifluoroborate.

Conclusion

We have demonstrated that the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction can be effectively applied to the cyclopropanation of aryl chlorides. The reaction accommodates aryl as well as heteroaryl chlorides with diverse functional groups (esters, ketones, aldehydes, nitriles) and substitution patterns. This method, in conjunction with previously developed methods for the syntheses of stereodefined cyclopropyltrifluoroborates, should find utility for the installation of cyclopropanes into a variety of functionalized aryl and heteroaryl target molecules. Finally, suitable conditions were found for the cross-coupling of potassium cyclobutyltrifluoroborate with aryl chlorides, representing an unprecedented mode of cross-coupling reactivity.

Experimental Section

General Experimental Procedure for the Suzuki–Miyaura Cross-Coupling Reactions of Cyclopropyltrifluoroborate with Aryl Chlorides. Preparation of 1-Cyclopropyl-4-methoxyben-

zene (2a). A Biotage microwave vial was charged with $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), XPhos (14.3 mg, 0.03 mmol), potassium cyclopropyltrifluoroborate (74.7 mg, 0.505 mmol), and K_2CO_3 (210 mg, 1.5 mmol). The tube was sealed with a cap lined with a disposable Teflon septum, evacuated under vacuum, and purged with N_2 three times. 4-Chloroanisole (71.3 mg, 0.5 mmol) and CPME/H_2O (10:1) (2 mL) were added by syringe, and the reaction was stirred at 100 °C for 24 h, cooled to room temperature, and diluted with H_2O (1.5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (elution with hexane/EtOAc 99:1; R_f 0.31) to yield the product as a light yellow oil in 75% yield (55.7 mg, 0.37 mmol). The spectral data match those reported in the literature.[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.01 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 1.82−1.86 (m, 1H), 0.86−0.89 (m, 2H), 0.60−0.62 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 157.9, 136.1, 127.1, 114.0, 55.5, 14.8, 8.6.

General Experimental Procedure for the Suzuki−Miyaura Cross-Coupling Reactions of Heteroaryl Chlorides with Potassium Cyclopropyltrifluoroborate. Preparation of 5-Cyclopropyl-2-methoxypyridine (4a). In the glovebox, a Biotage microwave vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), *n*-$BuPAd_2$ (5.3 mg, 0.015 mmol), potassium cyclopropyltrifluoroborate (74.7 mg, 0.505 mmol), and Cs_2CO_3 (480 mg, 1.5 mmol). The tube was sealed with a cap lined with a disposable Teflon septum and removed from the glove box. 5-Chloro-2-methoxypyridine (71.7 mg, 0.5 mmol) and toluene/H_2O (10:1) (2 mL) were added by syringe, and the reaction was stirred at 100 °C for 24 h, cooled to room temperature, and diluted with H_2O (1.5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (elution with hexane/EtOAc 99:1; R_f 0.22) to yield the product as a light yellow oil in 85% yield (65.3 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.24 (dd, J = 8.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 1.81−1.85 (m, 1H), 0.90−0.93 (m, 2H), 0.59−0.63 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 162.8, 145.1, 136.6, 131.8, 110.5, 53.5, 12.4, 8.0. IR (neat) = 3006, 1608, 1495, 1286, 1025 cm^{-1}. HRMS (CI) calcd for $C_9H_{12}NO$ (MH^+) 150.0919, found 150.0926.

Preparation of Potassium Cyclobutyltrifluoroborate (5). Cyclobutylboronic acid (909 mg, 9.1 mmol) was dissolved in methanol (20 mL) at room temperature, and the solution was cooled to 0 °C in an ice bath. A saturated aqueous solution of KHF_2 (11.1 mL) was added to the stirring solution dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for an additional 3 h. The solvent was removed in vacuo and dried under vacuum overnight. The resulting crude solid was extracted three times by sonicating for 15 min and stirring for an additional 15 min in dry acetonitrile. The solvent was removed in vacuo. A minimal amount of hot acetonitrile (∼50 mL) was added to dissolve the crude product, and Et_2O (∼150 mL) was added, leading to precipitation of the product in 63% yield as a white crystalline solid (929 mg, 5.7 mmol), which was collected by vacuum filtration and dried under vacuum. Mp 200 °C (dec). ^{1}H NMR (500 MHz, acetone-d_6) δ: 1.77−1.84 (m, 6H), 1.38 (br s, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 23.7, 12.4. ^{19}F NMR (471 MHz, DMSO-d_6) δ: −144.64. ^{11}B NMR (128.37 MHz, acetone-d_6) δ: 4.28. IR (KBr) = 2967, 1316, 1121, 924 cm^{-1}.

General Experimental Procedure for the Suzuki−Miyaura Cross-Coupling Reactions of Aryl and Heteroaryl Chlorides with Potassium Cyclobutyltrifluoroborate. Preparation of 1-Cyclobutyl-3,5-dimethoxybenzene (7a). In the glovebox, a Biotage microwave vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), *n*-$BuPAd_2$ (5.3 mg, 0.015 mmol), potassium cyclobutyltrifluoroborate (81.8 mg, 0.505 mmol), and Cs_2CO_3 (480 mg, 1.5 mmol). The tube was sealed with a cap lined with a disposable Teflon septum and removed from the glove box. 5-Chloro-1,3-dimethoxybenzene (86.3 mg, 0.5 mmol) and toluene/H_2O (10:1) (2 mL) were added by syringe, and the reaction was stirred at 100 °C for 24 h, cooled to room temperature, and diluted with H_2O (1.5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (elution with hexane/EtOAc 99:1; R_f 0.48) to yield the product as a light yellow oil in 82% yield (81.0 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.28−6.51 (m, 3H), 3.78 (s, 6H), 3.46−3.50 (m, 1H), 2.29−2.33 (m, 2H), 2.10−2.15 (m, 2H), 1.97−1.99 (m, 1H), 1.84 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 161.0, 149.0, 107.2, 104.6, 99.5, 97.9, 55.7, 55.4, 40.8, 29.8, 18.3. IR (neat) = 2958, 1595, 1458, 1154 cm^{-1}. HRMS (TOF) calcd for $C_{12}H_{17}O_2$ (MH^+) 193.1229, found 193.1235.

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Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at http://pubs.acs.org.

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