

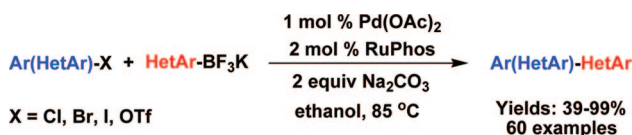
Scope of the Suzuki–Miyaura Cross-Coupling Reactions of Potassium Heteroaryltrifluoroborates

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A wide variety of bench-stable potassium heteroaryltrifluoroborates were prepared, and general reaction conditions were developed for their cross-coupling to aryl and heteroaryl halides. The cross-coupled products were obtained in good to excellent yields. This method represents an efficient and facile installation of heterocyclic building blocks onto preexisting organic substructures.

Introduction

Heterobiaryls are ubiquitous in natural products, pharmacologically active compounds, polymers, and other useful materials. Transition-metal-catalyzed cross-coupling reactions are often utilized for the construction of these compounds because they can directly assemble valuable motifs in a highly convergent fashion. Among the various cross-coupling reactions, the Suzuki–Miyaura reaction is the most extensively used method to prepare these compounds owing to the relatively low toxicity of the boron byproducts, the tolerance of a wide range of functional groups, and the ready availability of organoboron compounds.^{1,2}

Although the cross-coupling of arylboronic acids with aryl and heteroaryl halides has been studied extensively, until recently, the cross-coupling of heteroarylboronic acid counterparts had received less attention, and only isolated examples had been reported. The relative lack of concerted effort in this area might be attributed in part to the difficult preparation and isolation of heteroarylboronic acids.³ Fortunately, remarkable

progress has recently been made by numerous groups in the development of highly active catalyst systems that promote the cross-coupling of a broad range of heteroarylboronic acids with aryl and heteroaryl halides using a single set of reaction conditions.^{4–8} For example, Buchwald and co-workers reported that palladium precatalysts {[Pd₂(dba)₃] and Pd(OAc)₂}, sterically bulky, electron-rich phosphine ligands (SPhos and XPhos),⁹ and K₃PO₄ in *n*-butanol at 100 °C constituted an efficient system to cross-couple a wide range of heteroarylboronic acids with aryl and heteroaryl halides.⁴ Additionally, Fu and co-workers utilized [Pd₂(dba)₃], PCy₃, and K₃PO₄ in dioxane/H₂O at 100 °C to facilitate the cross-coupling of a broad range of nitrogen-containing heterocycles with aryl and heteroaryl halides.⁵ Both of these recent improvements in heteroaryl cross-couplings focused on the development of efficient catalyst

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(9) SPhos, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

systems and employed what is to date the most readily available nucleophilic organoboron reagents (i.e., boronic acids).

Because of their commercial availability, boronic acids are most often utilized in the Suzuki–Miyaura cross-coupling reactions. However, boronic acids are far from ideal, and they exhibit several limitations that make them unattractive nucleophilic coupling partners. Boronic acids are not monomeric materials, but rather exist in equilibrium with dimers and cyclic trimers (boroxines).¹⁰ Consequently, many boronic acids are waxy solids that are difficult to purify. Most importantly, many boronic acids, and especially electron-deficient heteroarylboronic acids, have a short shelf life owing to their tendency to undergo facile protodeboronation. This instability often requires their storage at low temperatures. The tendency to protodeboronate quite often manifests itself during cross-coupling reactions carried out in polar protic solvents.^{7a} The protodeboronation influences the stoichiometry of the reaction, requiring practitioners to use excess boronic acids to ensure that an adequate amount of this nucleophilic partner is available in cross-coupling reactions. *In fact, with a few exceptions,¹¹ virtually every study focusing on heteroarylboronic acid coupling employs excess organoboron reagent (as high as 250%) to achieve satisfactory yields.*

Easily prepared, monomeric organoboron reagents that would be more resistant to protodeboronation would eliminate many of the problems encountered with the cross-coupling of heteroarylboronic acids. Heteroarylboronate esters could partially circumvent the problems associated with heteroarylboronic acids, but they themselves suffer from limitations that make them less appealing alternatives, including a lack of atom economy and problematic purification steps.

In recent years, there has been increased interest in the use of potassium organotrifluoroborates as coupling partners for the Suzuki–Miyaura reaction.¹² Unlike their tricoordinate organoboron counterparts, these tetracoordinate species are less prone to undergo protodeboronation. Consequently, near-stoichiometric amounts of the nucleophilic partner are employed for cross-coupling reactions. The trifluoroborates are easily prepared from a wide variety of organoboron reagents by the addition of inexpensive potassium hydrogen fluoride (KHF₂).¹² The resulting organotrifluoroborates are air and moisture stable and can be stored indefinitely at room temperature without any precaution. Additionally, the vast majority of these salts are easily purified via recrystallization, precipitation, or Soxhlet extraction.

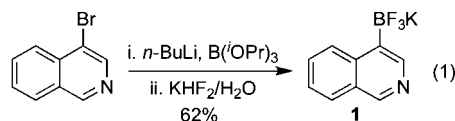
We envisioned that the union of highly active catalyst systems with potassium heteroaryltrifluoroborates as nucleophilic coupling partners would be an ideal platform for the cross-coupling of aryl and heteroaryl systems. Toward this end, we sought unified, general reaction conditions that could be broadly applied to virtually all heterocyclic nucleophiles and a wide range of electrophilic coupling partners. For this study, we specifically employed heteroaryltrifluoroborates for which the corresponding boronic acids were highly problematic. Herein, we describe the

preparation of a wide variety of these bench-stable heteroaryltrifluoroborates and disclose their efficient cross-couplings to a broad range of aryl and heteroaryl halides using a single set of reaction conditions that include near stoichiometric amounts of the nucleophilic coupling partner.

Results and Discussion

In a previous communication, our group disclosed the preparation of a limited number of heteroaryltrifluoroborates and demonstrated their cross-coupling with aryl and heteroaryl halides.¹³ Slightly modifying the previous procedure, a large number of potassium heteroaryltrifluoroborates were prepared, including furanyl-, thiophenyl-, pyrrolyl-, pyrazinyl-, isoxazolyl-, pyridinyl-, pyrimidinyl-, indolyl-, benzothiophenyl-, benzofuran-, and benzopyridinyl derivatives from commercially available heteroarylboronic acids (Table 1). The reactions were monitored by ¹¹B NMR spectroscopy, and in all cases, the transformations were complete in less than 10 min.

The conversion of heteroarylboronic acids to the corresponding heteroaryltrifluoroborates gave the products in yields ranging from 31 to 95% (Table 1). Immediate conversions of commercially received heteroarylboronic acids provided the heteroaryltrifluoroborates in good to excellent yields (Table 1, entries 1, 4, 5, 7, 10–15, 17, 18, 21, and 22). As a testament to their instability, the heteroarylboronic acids that were stored at –28 °C for several weeks and then converted to trifluoroborates gave the products in moderate to low yields (Table 1, entries 2, 3, 6, 8, 9, 16, 19, and 23). Analysis of these commercial samples by ¹¹B NMR spectroscopy revealed that the heteroarylboronic acids had partially protodeboronated (boric acid was observed at δ ~18 ppm). To confirm that the loss of a considerable amount of material was from protodeboronation, we investigated two of the low-yielding trifluoroborates [isoquinolin-4-yltrifluoroborate (**1**) and 4-methylthiophen-2-yltrifluoroborate (**2f**)] more deeply. In the first investigation, **1** was prepared from the corresponding 4-bromoisoquinoline in a sequential process of lithium-halogen exchange, boration using triisopropyl borate and quenching with KHF₂ (eq 1).¹⁴ The one-pot, unoptimized reaction provided the isoquinolin-4-yltrifluoroborate (**1**) in 62% overall yield compared to a 34% yield from the one step procedure using commercially available heteroarylboronic acid (Table 1, entry 23).



In the second study, recrystallization of the commercially obtained 4-methylthiophen-2-ylboronic acid from CHCl₃ and subsequent conversion to the corresponding trifluoroborate afforded the product **2f** in 95% yield compared to a 69% yield achieved from the boronic acid used as received (Table 1, entry 6). Of special note, several heteroaryltrifluoroborates (**2a**, **2i**, **2j**, **2l**) that were stored at ambient temperature for three months displayed tremendous stability, as they showed no sign of protodeboronation over this period of time as determined by ¹¹B NMR spectroscopy.

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(14) See the Supporting Information for the preparation of isoquinolin-4-yltrifluoroborate from the corresponding 4-bromoisoquinoline.

TABLE 1. Preparation of Diverse Potassium Heteroaryltrifluoroborates^a

HetAr-B(OH) ₂ $\xrightarrow[3 \text{ equiv KHF}_2, \text{H}_2\text{O (4.5 M)}]{\text{MeOH (3.5 M)}}$ HetAr-BF ₃ K					
entry	HetAr-BF ₃ K	isolated yield %	entry	HetAr-BF ₃ K	isolated yield %
1		2a 90	13		2m 90
2		2b 59	14		2n 70
3		2c 61	15		2o 74
4		2d 85	16		2p 67
5		2e 95	17		2q 71
6		2f 69(95) ^b	18		2r 79
7		2g 74	19		2s 58
8		2h 31	20		2t 76
9		2i 49	21		2u 73
10		2j 72	22		2v 84
11		2k 94	23		2l 34 (62) ^c
12		2l 71			

^a Commercially available heteroarylboronic acids were used. ^b 4-Methylthiophen-2-ylboronic acid was recrystallized from CHCl₃ immediately prior to use. ^c The isoquinolin-4-yltrifluoroborate was prepared directly from 4-bromoisoquinoline.

With the requisite heteroaryltrifluoroborates in hand, general conditions were sought to accomplish their cross-coupling. The cross-coupling of a few heteroaryltrifluoroborates using conditions reported in the literature gave the cross-coupled products in modest yields,^{13,15} and therefore, additional screening was undertaken to obtain more effective reaction conditions. We chose furan-2-yltrifluoroborate (**2a**) as a model nucleophilic partner because the corresponding furan-2-ylboronic acid is known to protodeboronate rapidly during cross-coupling events.^{4b,7a} After an extensive screening process with 4-bro-

mobenzonitrile as the electrophilic partner, 1 mol % of Pd(OAc)₂, 2 mol % of RuPhos,¹⁶ and 2 equiv of Na₂CO₃ in ethanol at 85 °C were determined to be the most effective coupling conditions.¹⁷

Among the five-membered heterocycles, furan is one of the most extensively studied because numerous natural products, pharmaceutically active compounds, flavors, and fragrances incorporate this motif.¹⁸ Even though the furan moiety is an important scaffold, the low stability¹⁹ of the boronic acid derivatives toward protodeboronation limits their use in Suzuki–Miyaura reactions. Nonetheless, a few research groups have reported the cross-coupling of furanboronic acid derivatives.^{4b,6,7a,20} Recently, Plenio and Fleckstein demonstrated the efficient cross-coupling of furan-3-ylboronic acid with a broad range of activated *N*-heteroaryl chlorides using Na₂PdCl₄ and disulfonated dicyclohexylfluorenylphosphine ligand at elevated temperature (100 °C), but the cross-coupling of furan-2-ylboronic acid was not reported.^{7a}

Using the reaction conditions developed herein, furan-2-yltrifluoroborate (**2a**) was efficiently coupled with a variety of aryl halides. Initially, **2a** was cross-coupled with various aryl bromides (Table 2, entries 1–8). As shown in Table 2, the reaction conditions worked equally well for electron-withdrawing (Table 2, entries 1, 3, 4, 6, and 8), electron-donating (Table 2, entries 2, 5, 7, 9, and 10), and sterically hindered bromides (Table 2, entry 5). Next, attention was turned to other electrophiles, including aryl chlorides, iodides, and triflates. All classes of electrophiles studied provided the products in good yields (Table 2, entry 1). Because aryl chlorides are more readily available and inexpensive compared to other electrophiles, these substrates were examined in some detail with **2a**. As was the case with bromides, electron-withdrawing (Table 2, entries 1 and 3), electron-donating (Table 2, entries 2, 5, and 10), and sterically hindered chlorides (Table 2, entries 5 and 9) all reacted smoothly, affording the products in good to excellent yields. We also demonstrated that the reaction could be scaled to 5 mmol, while at the same time reducing the catalyst/ligand ratio by half [0.5 mol % of Pd(OAc)₂ and 1 mol % of RuPhos, respectively]. In this case the cross-coupled product was isolated in 91% yield (Table 2, entry 1).

To expand the scope of the general reaction conditions further, attention was turned to the cross-coupling of various heteroaryltrifluoroborates with 4-halobenzonitriles.

Five-Membered Ring Heterocycles. As previously mentioned, furan-2-ylboronic acid is a challenging coupling partner,^{4b} and using the protocols developed herein, **2a** was efficiently cross-coupled to aryl bromides and chlorides. The conditions established were utilized to examine the coupling of substituted furan-2-yltrifluoroborate derivatives. Toward this end, 5-methylfuran-2-yltrifluoroborate (**2b**) was coupled with

(16) RuPhos, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl.

(17) Variables changed in coupling optimization included catalyst/ligand ratios (5/10 mol % and 3/6 mol %), solvents (DME, *n*-butanol, *sec*-butanol and *tert*-amyl alcohol), bases (Cs₂CO₃, K₂CO₃, K₃PO₄, and Et₃N), and base equivalents (3, 1, and 0).

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TABLE 2. Cross-Coupling of Potassium Furan-2-yltrifluoroborate with Diverse Aryl Halides^a

$\text{R-C}_6\text{H}_4\text{-X} + \text{KF}_3\text{B-furan} \xrightarrow[\text{ethanol (0.18 M), 85 }^\circ\text{C, 8-36 h}]{\text{1 mol \% Pd(OAc)}_2, \text{2 mol \% RuPhos}, \text{2 equiv Na}_2\text{CO}_3}$			
entry	aryl halide	product	isolated yield %
1			Br = 91 Cl = 84 (86 ^b , 91 ^c) I = 80 OTf = 82
2			Br = 85 Cl = 75
3			Br = 94 Cl = 75
4			Br = 93 Cl = 87
5			Br = 94 Cl = 62
6			Br = 89
7			Br = 91
8			Br = 92
9			Cl = 78
10			Cl = 99

^a All reactions were carried out using 0.25 mmol of aryl halide and 0.26 mmol of furan-2-yltrifluoroborate. ^b 1 mmol scale. ^c 5 mmol scale; reduced catalyst/ligand loading to 0.5 mol % of Pd(OAc)₂ and 1 mol % of RuPhos.

4-bromobenzonitrile, providing the product **4a** in excellent yield (Table 3, entry 1). However, the coupling of **2b** with 4-chlorobenzonitrile afforded the product **4a** in moderate yield (Table 3, entry 1). Additionally, the coupling of 5-formylfuran-2-yltrifluoroborate (**2c**) with 4-bromobenzonitrile gave the desired product **4b** in only 39% yield (Table 3, entry 2).

Thiophenes find extensive use in materials science and in medicinal chemistry.²¹ Although thiophenylboronic acids are more stable than furanylboronic acids,^{7a} they themselves also suffer from protodeboronation under protic conditions, with thiophen-2-ylboronic acid being more prone to protodeborona-

TABLE 3. Cross-Coupling of Five-Membered Potassium Heteroaryltrifluoroborates with 4-Halobenzonitrile^a

$\text{HetAr-BF}_3\text{K} + \text{X-C}_6\text{H}_4\text{-CN} \xrightarrow[\text{ethanol (0.18 M), 85 }^\circ\text{C, 2-12 h}]{\text{1 mol \% Pd(OAc)}_2, \text{2 mol \% RuPhos}, \text{2 equiv Na}_2\text{CO}_3}$			
entry	HetAr-BF ₃ K	product	isolated yield %
1			Br = 95 Cl = 58
2			Br = 39 ^b
3			Br = 93 Cl = 96
4			Br = 98 Cl = 83
5			Cl = 74
6			Br = 90 Cl = 52 ^c
7			Cl = 20 ^d (37) ^e
8			Cl = 26 ^d (84) ^e
9			Cl = 71

^a All reactions were carried out using 0.25 mmol of aryl halide and 0.26 mmol of heteroaryltrifluoroborate. ^b Used 3 mol % of Pd(OAc)₂ and 6 mol % of RuPhos. ^c Recovered 45% of deprotected product. ^d Heated reaction for 48 h. ^e Used 5 mol % of Pd(OAc)₂, 10 mol % of RuPhos, and 3 equiv of Na₂CO₃, 48 h.

tion than thiophen-3-ylboronic acid.²² Until recently, few examples had been reported for the cross-coupling of thiophenylboronic acid derivatives.^{4b,6,7a,20} Doucet and Santelli reported the cross-coupling of thiophen-3- and thiophen-2-ylboronic acids with aryl halides^{6a} and heteroaryl bromides^{6b} using the [Pd(C₃H₅)Cl]₂/Tedicyp²³ catalytic system. These cross-coupling reactions were performed at elevated temperatures (130 °C) using excess boronic acids.

Given the differential sensitivity of isomeric thiophenylboronic acids to protodeboronation, we were pleased that the position of the trifluoroborate moiety (at the 3- or 2-position) did not influence the coupling with 4-bromobenzonitrile, as the desired products **4c,d** were obtained in comparable yields, 93% and 98%, respectively (Table 3, entries 3 and 4). However, for the coupling of 4-chlorobenzonitrile, differences were observed wherein thiophen-3-yltrifluoroborate (**2d**) was coupled in 96% yield, while thiophen-2-yltrifluoroborate (**2e**) coupled in a

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(23) Tedicyp: *cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane.

slightly lower 83% yield. These conditions also proved to be effective for the coupling of 4-methylthiophen-2-yltrifluoroborate (**2f**) with 4-chlorobenzonitrile, affording the product **4e** in 74% yield (Table 3, entry 5).

Pyrroles receive significant attention because they are frequently found in natural products and have use in pharmaceuticals, molecular recognition, and materials science.²⁴ Several conditions for the cross-coupling of pyrroleboronic acid derivatives have been reported in the literature.^{4a,b,5,25} The relatively limited number of citations might be attributed to difficulties associated with protodeboronation, as well as the propensity of the boronic acids to homocouple.³ The homocoupling can be avoided by protection of the nitrogen with either *tert*-butoxycarbonyl (Boc), triisopropylsilyl (TIPS), or phenylsulfonyl groups. Buchwald and co-workers recently reported that *N*-protected pyrroleboronate esters serve as a better alternative than the corresponding boronic acids for the cross-coupling reactions.^{4a}

To avoid homocoupling, we examined the couplings of *N*-Boc-pyrrol-2-yltrifluoroborate (**2g**). When 4-bromobenzonitrile was used as the electrophile, the desired product **4f** was isolated in 90% yield (Table 3, entry 6). However, when 4-chlorobenzonitrile was used as the electrophile, the cross-coupled product **4f** was obtained in 52% yield along with the corresponding deprotected product in 45% yield (Table 3, entry 6). The removal of the Boc group under cross-coupling conditions is not unusual and has been previously reported.⁵

Pyrazoles have extensive use in the pharmaceutical²⁶ and agrochemical industries as heterocyclic building blocks. As with the case of pyrroleboronic acid derivatives, the cross-coupling of pyrazoleboronic acid derivatives is also difficult without protecting groups.^{5,27} Fu and co-workers recently attempted the cross-coupling of unprotected 1*H*-pyrazol-4- and 1*H*-pyrazol-5-ylboronic acid, but the products were obtained in <21% yields. Not surprisingly, the protection of pyrazol-4- and pyrazol-5-ylboronic acid improved the yields dramatically.⁵

The cross-coupling of unprotected 1*H*-pyrazol-4- and 1*H*-pyrazol-5-yltrifluoroborate under conditions developed herein provided the desired heterobiaryls **4g,h** in low yields (20% and 26%) after 48 h (Table 3, entries 7 and 8). Upon increasing the catalyst/ligand loading to 5 mol % of Pd(OAc)₂ and 10 mol % of RuPhos using 3 equiv of Na₂CO₃ and heating the reaction for 48 h, the cross-coupling of 1*H*-pyrazol-5-yltrifluoroborate (**2i**) gave the product **4h** in 84% yield (Table 3, entry 8). Disappointingly, the cross-coupling of 1*H*-pyrazol-4-yltrifluoroborate (**2h**) only improved slightly to give the cross-coupled product **4g** in 37% yield (Table 3, entry 7).

Among the five-membered heterocycles, isoxazoles have been studied the least, which is perhaps due to the lack of target compounds containing this structural scaffold.²⁸ Scattered examples have been reported for the cross-coupling of isox-

azoleboronic acid derivatives with aryl bromides, and the couplings typically required 5–10 mol % of catalyst loading.²⁹

The unified conditions developed herein proved to be effective for the coupling of the 3,5-dimethylisoxazol-4-yltrifluoroborate (**2j**) with 4-chlorobenzonitrile, affording the product **4i** in 71% yield (Table 3, entry 9).

Six-Membered-Ring Heterocycles and Benzannulated Heterocycles. Pyridines are prevalent heterocycles found in natural products and bioactive compounds, and therefore, their efficient incorporation onto organic molecules as building blocks is highly desirable.³⁰ However, the installation of pyridyl derivatives via the Suzuki–Miyaura reaction has been challenging owing to their low stability, electron-deficiency, and the resulting reduced nucleophilicity of the organoboron species.³¹ Recently, important progress has been made in the use of pyridinyl derivatives for cross-coupling reactions.^{4,5,7b,13,15a,32}

For the cross-coupling of pyridinyltrifluoroborates, the catalyst/ligand loading was increased to 3 mol % of Pd(OAc)₂ and 6 mol % of RuPhos because the original reaction conditions developed required a longer reaction time (>24 h) for the cross-coupling. The increase in catalyst/ligand loading is not surprising; as mentioned above, pyridinyl derivatives are electron-deficient and less nucleophilic and therefore transmetalate more slowly.³¹

The cross-coupling of pyridin-4-yltrifluoroborate (**2k**) with 4-bromo- and 4-chlorobenzonitrile was examined. The desired product, **5a**, was obtained in excellent yields (Table 4, entry 1). We observed a slight decrease in yields with the coupling of pyridin-3-yltrifluoroborate (**2l**) with 4-bromo- and 4-chlorobenzonitrile (Table 4, entry 2). Next, we examined the coupling of substituted pyridyl derivatives, 2-fluoropyridin-3- and 6-fluoropyridin-3-yltrifluoroborate (Table 4, entries 3 and 4). The coupling of 2-fluoropyridin-3-yltrifluoroborate (**2m**) with 4-bromobenzonitrile afforded the product **5c** in 73% yield, while the coupling with 4-chlorobenzonitrile afforded the product **5c** in only 49% yield (Table 4, entry 3). Surprisingly, for the cross-coupling of 6-fluoropyridin-3-yltrifluoroborate (**2n**), the opposite trend was observed, wherein the coupling with 4-chlorobenzonitrile provided the product **5d** in a higher yield than 4-bromobenzonitrile (Table 4, entry 4). Of particular note, the coupling of pyridin-2-yltrifluoroborate with 4-chlorobenzonitrile was attempted, but unfortunately none of the cross-coupled product was obtained.

Pyrimidine derivatives, including the nucleobase uracil, have extensive use in the pharmaceutical industry.³³ In particular,

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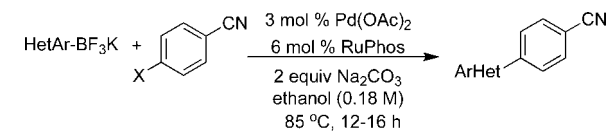
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TABLE 4. Cross-Coupling of Six-Membered Potassium Heteroaryltrifluoroborates with 4-Halobenzonitrile^a

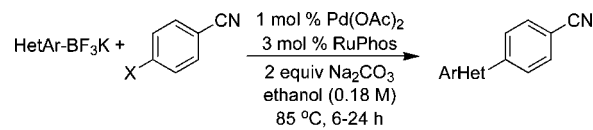
entry	HetAr-BF ₃ K	product	isolated yield %
1			Br = 90 Cl = 96
2			Br = 75 Cl = 78
3			Br = 73 Cl = 49
4			Br = 61 Cl = 77
5			Br = 88 Cl = 86
6			Cl = 96

^a All reactions were carried out using 0.25 mmol of aryl halide and 0.26 mmol of heteroaryltrifluoroborate.

5-substituted uracil derivatives are potential antiviral agents, and one possible method for their preparation is by Suzuki–Miyaura cross-coupling followed by a reduction.³⁴ In 2005, Seley and co-workers reported the preparation of a 5-substituted uracil derivative via cross-coupling of 2,4-dibenzyloxypyrimidin-5-ylboronic acid with an appropriate electrophile in the presence of 5.5 mol % of Pd(PPh₃)₄, followed by a reduction with ammonia in butanol. The desired product was isolated in 78% yield over two steps.³⁵

Using the conditions developed herein, the efficient cross-coupling of 2,4-dimethoxypyrimidin-5-yltrifluoroborate (**2o**) was demonstrated with 4-bromo- and 4-chlorobenzonitrile in 88% and 86% yields, respectively (Table 4, entry 5). Additionally, 2-methoxypyrimidin-4-yltrifluoroborate (**2p**) was successfully coupled to 4-chlorobenzonitrile in excellent yield (Table 4, entry 6).

Indoles are among the most important heterocycles because they are found in myriad natural products, pharmaceutical agents, and polymers.³⁶ Because they are highly desirable targets, numerous methods to incorporate this heterocyclic core

TABLE 5. Cross-Coupling of Benzannulated Potassium Heteroaryltrifluoroborates with 4-Halobenzonitrile^a

entry	HetAr-BF ₃ K	product	isolated yield %
1			Br = 96 Cl = 83
2			Cl = 98
3			Cl = 81
4			Cl = 82
5			Cl = 92
6			Br = 88 ^b Cl = 86 ^b
7			Cl = 85 ^b

^a All reactions were carried out using 0.25 mmol of aryl halide and 0.26 mmol of heteroaryltrifluoroborate. ^b Used 3 mol % of Pd(OAc)₂ and 6 mol % of RuPhos.

into organic molecules have been developed. As with pyrrolyl- and pyrazinylboronic acid derivatives, indolylboronic acid derivatives usually necessitate protection for an efficient cross-coupling. The Suzuki–Miyaura cross-coupling of substituted indolylboronic acid derivatives with aryl and heteroaryl halides has been reported in the literature.^{4a,b,5,7b,37} Recently, indolyltrifluoroborates have been shown to be better nucleophilic partners for the cross-coupling reactions, as they provided the products in higher yields.^{15c,38}

To expand the utility of the general reaction conditions to indoles, we cross-coupled 1*H*-indol-6- and 1*H*-indol-5-yltrifluoroborate, obtaining the products **6a,b** in excellent yields (Table 5, entries 1 and 2). During the cross-coupling of *N*-Boc-indol-2-yltrifluoroborate (**2s**), the Boc group was cleaved under the reaction conditions, and the deprotected product **6c** was obtained in 81% yield (Table 5, entry 3).

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Although benzothiophenes and benzofurans are less common heterocycles than indoles, they still have use in the pharmaceutical industry.³⁹ The cross-coupling of benzothiophenyl- and benzofuranylboronic acid derivatives has been reported, generally with aryl bromides.⁴⁰ We demonstrated that 4-chlorobenzonitrile smoothly cross-coupled to benzothiophen-2-yltrifluoroborate (**2t**) and benzofuran-2-yltrifluoroborate (**2u**) in 82% and 92% yields, respectively (Table 5, entries 4 and 5).


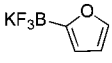

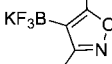

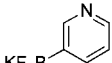

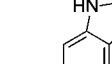

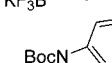

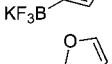

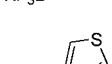

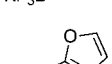

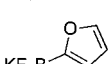

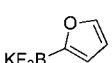
Benzopyridine derivatives, including quinoline and isoquinoline, are most often found in naturally occurring alkaloids and other pharmacologically active compounds. Even though the first synthesis of quinolin-3-ylboronic acid dates back to 1959,³ only a few examples have been reported in the literature of their incorporation into an organic molecule by means of the Suzuki–Miyaura cross-coupling reaction.^{11a,41}

The cross-coupling of quinolin-3-yltrifluoroborate (**2v**) with 4-bromo- and 4-chlorobenzonitrile afforded the heterobiaryl product **6f** in comparable yields (Table 5, entry 6). The cross-coupling of isoquinolin-4-yltrifluoroborate (**1**) with 4-chlorobenzonitrile provided the product **6g** in 85% yield (Table 5, entry 7).

Heterobiaryls. One of the biggest challenges in cross-coupling reactions occurs when both coupling partners are heterocycles. Until recently, no general conditions had been developed to enable this useful C–C bond formation.^{4a,5,6b,7} To expand the scope of the general reaction conditions further, attention was turned to the coupling of heterobiaryls. Because these are difficult couplings, 3 mol % of Pd(OAc)₂ and 6 mol % of RuPhos were employed. Initially, we examined the cross-coupling of 2-chloropyridine with **2a**, because both are known to be demanding coupling partners.^{7a} We were able to achieve coupling, albeit in modest yield (Table 6, entry 1). Subsequently, the coupling of 2-chloropyridine with **2j** and **2l** was successful, affording the desired coupled products **7b,c** in 95% and 82% yield, respectively (Table 6, entries 2 and 3). The coupling of 3-chloropyridine with **2q** afforded the product **7d** in excellent yield (Table 6, entry 4), but the coupling of **2s** provided the deprotected product **7e** in only moderate yield (Table 6, entry 5). Additionally, **2a** coupled to 2-chloropyrimidine, 2-acetyl-5-chlorothiophene, 2-formyl-5-chlorothiophene, and 2-formyl-5-chlorofuran in moderate to excellent yields (Table 6, entries 6–10).

In conclusion, over twenty structurally diverse five-membered, six-membered, and benzannulated heteroaryltrifluoroborate derivatives were prepared from commercially available boronic acids. We determined that these organotrifluoroborates are much less prone to protodeboronation when compared to their heteroarylboronic acid counterparts, and thus they can be stored indefinitely at ambient temperatures. By combining the electron-rich, monodentate ligand, RuPhos, with heteroaryltrifluoroborates as the nucleophilic coupling partners, general, mild, and efficient reaction conditions for cross-coupling were developed. Of note, essentially stoichiometric ratios of the heteroaryltrifluoroborates can be employed in these reactions, which take

TABLE 6. Cross-Coupling of Various Potassium Heteroaryltrifluoroborates with Various Heteroaryl Chlorides^a

$\text{HetAr-Cl} + \text{HetAr-BF}_3\text{K} \xrightarrow[\text{ethanol (0.18 M), 85 }^\circ\text{C, 12-28 h}]{\text{3 mol \% Pd(OAc)}_2, \text{ 6 mol \% RuPhos}, \text{ 2 equiv Na}_2\text{CO}_3} \text{HetAr-HetAr}$				
entry	HetAr-Cl	HetAr-BF ₃ K		isolated yield %
1			2a	67 (7a)
2			2j	95 (7b)
3			2l	82 (7c)
4			2q	93 (7d)
5			2s	57 ^b (7e)
6			2a	92 (7f)
7			2a	52 (7g)
8			2a	77 (7h)
9			2a	64 (7i)
10			2a	81 (7j)

^a All reactions were carried out using 0.25 mmol of heteroaryl halide and 0.26 mmol of heteroaryltrifluoroborate. ^b Yield of Boc-deprotected cross-coupled product.

place at lower temperatures than previously developed protocols when using comparable catalyst loading (as low as 0.5 mol %). Using a unified set of reaction conditions, a broad range of aryl and heteroaryl halides were cross-coupled in good to excellent yields. Furthermore, the reaction conditions developed are scalable and economically viable because inexpensive aryl chlorides, Na₂CO₃, and ethanol are utilized in the cross-coupling reactions.

Experimental Section

General Experimental Procedure for the Preparation of Potassium Heteroaryltrifluoroborates. Preparation of Potassium Furan-2-yltrifluoroborate (2a**).**⁴² To a solution of furan-2-ylboronic acid (1.0 g, 8.93 mmol) in MeOH (2.6 mL, 3.5 M or enough MeOH to give a free flowing suspension) under N₂ was added KHF₂ (2.09 g, 26.8 mmol) in one portion at 0 °C. To the suspension was added H₂O dropwise (5.95 mL, 4.5M) at 0 °C. The ice–water bath was

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removed, and the reaction was stirred at rt until ^{11}B NMR indicated completion of the reaction (~ 2 min). The crude mixture was concentrated and dried overnight in vacuo. The crude solid was purified using continuous Soxhlet extraction (4 h) with acetone (60 mL) (unless otherwise specified). The collected solvent was concentrated and then redissolved in a minimal amount of acetone (5 mL). The addition of ether (30 mL) led to the precipitation of the product. The product was filtered, concentrated, and dried in vacuo to afford the pure compound in 90% yield (1.08 g, 8.03 mmol) as a light orange solid: mp > 200 $^{\circ}\text{C}$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.40 (m, 1H), 6.18 (m, 1H), 6.06 (d, 1H, $J = 2.6$ Hz); ^{13}C NMR (125.8 MHz, $\text{DMSO}-d_6$) δ 141.0, 110.2, 108.5; ^{19}F NMR (470.8 MHz, $\text{DMSO}-d_6$) δ -139.1 ; ^{11}B NMR (128.4 MHz, $\text{DMSO}-d_6$) δ 0.3; FT-IR (KBr) 3428, 3022, 2921, 2822, 1496, 1126, 1088, 1066, 1002 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_4\text{H}_3\text{BF}_3\text{O}$ ($M - \text{K}$) 135.0235, found 135.0234.

General Experimental Procedure for Suzuki–Miyaura Cross-Coupling Reaction of Aryl and Heteroaryl Electrophiles with Heteroaryltrifluoroborates. Preparation of 4-(Furan-2-yl)benzonitrile (3a).⁴³ A Biotage microwave vial was charged with $\text{Pd}(\text{OAc})_2$ (3.4 mg, 0.015 mmol), RuPhos (14 mg, 0.03 mmol), 4-bromobenzonitrile (46.0 mg, 0.25 mmol), potassium furan-2-yltrifluoroborate (46.0 mg, 0.26 mmol), and Na_2CO_3 (53.0 mg, 0.5 mmol). The test tube was sealed with a cap lined with a disposable Teflon septum,

evacuated, and purged with nitrogen ($\times 3$). Ethanol (0.18 M, 1.4 mL) was added via syringe, and the reaction was heated at 85 $^{\circ}\text{C}$ for 12 h. The reaction mixture was allowed to cool to rt and filtered through a thin pad of silica gel (elution with 25% methanol in EtOAc). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (elution with hexane/EtOAc 7:1) to yield the pure product in 91% yield (38.49 mg, 0.23 mmol) as a white solid: ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, 1H, $J = 8.5$ Hz), 7.63 (d, 1H, $J = 8.5$ Hz), 7.52 (m, 1H), 6.80 (d, 1H, $J = 3.5$ Hz), 6.52 (dd, 1H, $J = 1.8, 3.4$ Hz); ^{13}C NMR (125.8 MHz, CDCl_3) δ 152.1, 143.8, 134.8, 132.7, 124.1, 119.0, 112.3, 110.4, 108.3.

Acknowledgment. This work was generously supported by the National Institutes of Health (General Medical Sciences) and Merck Research Laboratories. We also acknowledge Aldrich, BoroChem, and Frontier Scientific for their donation of the heteroarylboronic acids.

Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^1H , ^{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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