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Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions of Potassium Aryl- and Heteroaryltrifluoroborates

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An extended study of the reactivity of potassium aryl- and heteroaryltrifluoroborates in Suzuki-Miyaura cross-coupling reactions is presented. The coupling of aryl- and electron-rich heteroaryltrifluoroborates with aryl and activated heteroaryl bromides proceeds readily under ligandless conditions. When deactivated aryl- and heteroaryltrifluoroborates are coupled with aryl and heteroaryl bromides and chlorides, a low loading (0.5−2%) of $PdCl_2(dppf)\cdot CH_2Cl_2$ efficiently catalyzes the reactions. Under either condition, reactions can generally be carried out in an open atmosphere.

Introduction

The synthesis of biaryl and biheteroaryl systems through transition metal catalyzed cross-coupling reactions has been well-studied and developed.[1] Among all the possible organometallics used as nucleophilic partners, tin (Stille coupling)[2] and boron derivatives (Suzuki−Miyaura coupling)[3] and, to a lesser extent, organozinc (Negishi coupling)[4] and Grignard reagents (Kumada coupling),[1] have been the most frequently used for cross-coupling reactions of aryl and heteroaryl compounds. The Suzuki−Miyaura cross-coupling reaction, which involves the coupling of an organoboron compound with an electrophile, possesses notable advantages over the other related techniques. Particularly striking is the array of functionality tolerated in the coupling process. The use of organoboron compounds is also valued because the inorganic byproducts of the reaction are nontoxic and can be readily removed by simple workup procedures, while many tin compounds are toxic, and complete removal of tin-containing byproducts is a well-recognized problem.

From the many parameters that can be changed to ensure success in the Suzuki−Miyaura reaction, the metal/ligand systems that facilitate the cross-coupling with different electrophiles have been the most extensively studied. Combinations that range from Pd(0) (Pd/C, Pd/Al_2O_3, Pd_2dba_3) or Pd(II) [$PdCl_2$, $Pd(OAc)_2$] in the absence of ligands[5] to very elaborate catalyst/ligand systems[6] have been applied. Very recently the successful use of air-stable catalysts has been reported to improve the catalyst turnover, to achieve the coupling with less reactive electrophiles, or to permit coupling with hindered substrates.[7]

One area that has been underdeveloped involves the use of alternative organoboron coupling partners. Although the palladium-catalyzed cross-coupling reaction of arylboronic acids or -esters bearing sp^2-hybridized substituents with electrophiles such as organic halides and triflates generally proceeds readily,[1,3,8] the boronic

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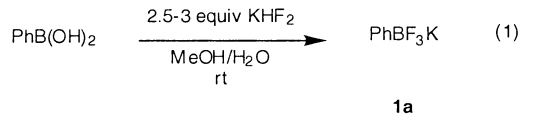
acids are subject to cyclic trimerization, and the resulting uncertainties in stoichiometry require an excess of these compounds in the coupling reactions. The use of boronic esters can partially solve that problem, but this leads to a lack of atom economy and additional (problematic) purification steps, especially when catechol or pinacol are used as the alcohol moiety. Additionally, there are some relatively important compounds (including many heteroaryl derivatives) that do not have an adequate shelf life or cannot be adequately purified. Finally, many arylboronic acids are prone to protodeboronation during the coupling process. This is particularly true for heteroarylboronic acids bearing the boron atom *ortho* to the heteroatom.[9] It is also known that electron-donating groups in the aryl unit increase the rate of protodeboronation, while electron-withdrawing groups decrease the rate.[9] Although the higher reactivity of the former organoboronic acids aids in preventing the protodeboronation from competing with the cross-coupling process, a high percentage of protodeboronated compound can still be produced if the cross-coupling is too slow, and in those cases homocoupling may even become a competing process.[10] On the other hand, electron-poor arylboronic acids have a higher tendency to homocouple.[11] This, combined with lower reactivity in the transmetalation process, leads to lower yields in the cross-coupling, impeding the use of many interesting compounds in the Suzuki reaction. Therefore, the use of a more reactive/more stable organoboron system appears essential.

Among the most promising alternative boron reagents are potassium trifluoroborates. These are easily prepared from organoboronic acids or esters by treatment with an aqueous solution of KHF_2 (eq 1).[12] The potassium organotrifluoroborates are monomeric solids, easily prepared in quantities in excess of 200 g. They are in general indefinitely stable in the air. They can thus be stored on the shelf and/or sold commercially. This not only broadens their availability, but also makes them more useful for employment in combinatorial chemistry and in multistep syntheses in which a Suzuki−Miyaura coupling to a valuable partner comprises a key transformation, or when the organoboron intermediate itself is a very valuable component. In either case, the critical organotrifluoroborate can be isolated and purified, and optimization of the strategic step can be carried out easily and with assurance on small scale. Additionally, the organotrifluoroborates are environmentally friendly. The byproducts of these reactions convert to harmless inorganic salts that are readily separable from the desired products. The trifluoroborates possess a relatively low molecular weight, so that the mass of material required is kept to a minimum. Finally, water may be used as a cosolvent or solvent, minimizing, or in some cases completely eliminating, the need for organic solvent. No protecting groups are needed for organotrifluoroborate substrates bearing ketones, esters, amides, amines, nitriles, nitro groups, halides, alcohols, aldehydes, or carboxylic acids. Finally, the trifluoroborate system appears less subject to protodeboronation than other boron derivatives.



In 1996, Genêt reported the first coupling reactions involving potassium aryl- and alkenyltrifluoroborates with arenediazonium tetrafluoroborates.[13] In 1999, Xia applied this method to carry out the coupling with diaryliodonium salts[14] as the electrophilic partners. These reactions could be performed in the presence of halogen functionalities on the substrates because no base was required, and under these conditions aryl halides do not couple.[8b] Our discovery that added base was required to allow coupling with aryl halides and triflates led us to conduct an exhaustive investigation in the synthesis and application of potassium aryl and heteroaryl trifluoroborates in Suzuki−Miyaura cross-coupling reactions with an array of aryl and heteroaryl halides.

In a previous communication,[15] we reported the efficient ligandless palladium-catalyzed cross-coupling reactions of some potassium aryltrifluoroborates with aryl and heteroaryl bromides. The cross-couplings of several potassium aryltrifluoroborates with simple aryl halides were found to take place efficiently under extremely economical conditions, using a low loading of a ligandless $Pd(OAc)_2$, in alcoholic or aqueous solvents in the air. Thus, these reactions turned out to be highly atom economic, simple to carry out, and insensitive to oxygen. During the course of our investigation, Batey and Quach[16] reported the cross-coupling reactions of tetrabutylammonium organotrifluoroborates, using 5 mol % of $Pd(OAc)_2$ and 5 mol % of dppb as a catalyst in the presence of 2 equiv of Cs_2CO_3 in DME/water (1:1). The reactions usually took between 12 and 24 h. Herein we describe the advances and scope of the coupling process involving a variety of aryl- and heteroaryltrifluoroborates with aryl and heteroaryl halides under conditions with and without ligands.

Results and Discussion

We initiated our study of the Suzuki−Miyaura cross-coupling reaction by optimizing the conditions in terms of catalysts, ligands, bases, and solvents for the reaction between potassium phenyltrifluoroborate (**1a**) and 1-bromonaphthalene (**2a**) (eq 2).

The study was carried out in a reactor block, using 0.25 mmol of each reagent in the presence of 5 mol % of

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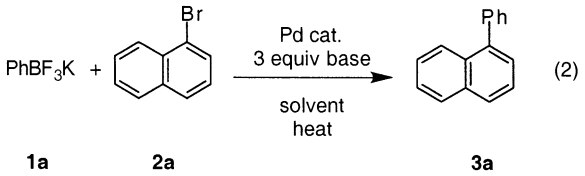

catalyst/ligand, 3 equiv of base, and 2 mL of solvent heating at reflux overnight under a blanket of nitrogen (Table 1). The reactions were analyzed by quantitative gas chromatography, determining the presence of 1-phenylnaphthalene (**3a**), unreacted **2a**, as well as the amount of binaphthyl and biphenyl formed by homocoupling, using the internal standard method (hexadecane used as standard). Naphthalene formed by reduction of **2a** (protodehalogenation) was determined by difference.

Considering commercially available catalysts or those reported in the literature previously determined to be successful in the Suzuki coupling of arylboronic acids, $Pd(OAc)_2$, $Pd_2(dba)_3$, and $PdCl_2(dppf)\cdot CH_2Cl_2$ were chosen and combined with ligands such as 1,1′-bis(diphenylphosphino)ferrocene (dppf) or *t*-Bu_3P. As bases, Et_3N, *i*-Pr_2-NEt (Hünig's base), *t*-$BuNH_2$, K_2CO_3, Cs_2CO_3, KF, and K_3PO_4 were used. Environmentally friendly solvent systems were preferred (water, MeOH, EtOH, *n*-PrOH, *i*-PrOH, dioxane, THF).

In general, optimal conditions were found to involve the use of alcohols as solvents. This can be attributed to the higher solubility of the aryltrifluoroborate salts in methanol and ethanol at refluxing temperatures, which allows a homogeneous reaction. The best system, as for the coupling of alkenyltrifluoroborates,[17] involved the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ and Hünig's base in ethanol as solvent (Table 1, entry 1). Auspiciously, ligandless conditions were found to be quite efficient in the coupling process (Table 1, entry 10).

Surprisingly, the reaction carried out in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ and Cs_2CO_3 in THF/water (entry 9) (used in the coupling of other organotrifluoroborates)[18] led to only 12% yield. A system similar to the one used by Fu[8] to perform the coupling with aryl chlorides [$Pd_2(dba)_3$/(*t*-Bu_3P)] gave only moderate yields (entry 19).

In optimizing the two most efficient conditions [using $PdCl_2(dppf)\cdot CH_2Cl_2$ and $Pd(OAc)_2$] in terms of catalyst loading and reaction time, the advantages of the ligandless condition became evident. The reaction reached completion in shorter reaction times with only a slight decrease in the yield. A reaction scaled up to 15 mmol (entry 13) led to an 80% isolated yield of **3a** and 14% of unreacted 1-bromonaphthalene (**2a**), using 0.2 mol % of catalyst loading after heating at reflux for 9 h. To reduce the cost of the reaction, other amines (Et_3N and *t*-$BuNH_2$) and even K_2CO_3 could be used instead of Hünig's base under ligand-added conditions (entries 4−6) with similar results. *Under both ligand and ligandless conditions, the reactions could be performed in the air without a reduction in the yield of the cross-coupled biaryls.*

A reduction in the amount of base (either amine or K_2CO_3) to 2 equiv lowered the yield substantially, or required longer reaction times to achieve similar yields (compare entries 11 and 14). Different solvent mixtures were also analyzed. The use of 1:1 ethanol/water mixtures led to slightly lower yields under both ligand-added and ligandless conditions (compare entries 3 and 8). Less polar mixtures, such as 20:1 methanol/THF or ethanol/THF (entries 16 and 17), led to even lower yield or cross-coupled product and a higher recovery of unreacted aryl bromide. This reveals a reduced tendency for protodehalogenation under less polar conditions, but a concomitant retardation of the cross-coupling process as well.

Upon choosing the ligandless conditions [0.5 mol % of $Pd(OAc)_2$, 3 equiv of K_2CO_3 in methanol] to perform the cross-coupling reaction, electrophiles incorporating a full palette of functionalities were analyzed in an effort to display compatibility with the process developed. At the outset, the reaction was tested by using aryl bromides possessing electron-withdrawing groups. The results are shown in Table 2.

All of the reactions led to very high yields of cross-coupling product, with reaction times between 45 min and 2 h. The dihaloarene in entry 7 showed reduced yield. This may be ascribed in part to protodehalogenation on both bromine and chlorine positions, because only traces of triphenyl due to double coupling were detected. A variety of functional groups were tolerated, even in the *ortho* position. Interestingly, the reaction involving 4-bromobenzoic acid, **2i** (entry 8), can be performed in water at room temperature and is more efficient in that solvent than methanol. (The reaction in water could be performed at ambient temperature, while that in methanol required heating at reflux. This is perhaps an issue of solubility.[5g])

When coupling potassium 1-phenytrifluoroborate (**1a**) with electron-rich bromides (Table 3), unexpected results were obtained. 4-Bromoanisole (**2j**) reacted very well under ligandless conditions, providing 95% of product after 2 h of reaction (Table 3, entry 1). However, when a second methoxy group was present in the *ortho* position of the aryl halide **2n** (entry 5), both electronic and steric effects conspired to require the presence of a ligand to achieve high yields of the cross-coupling product and minimize the homocoupling of the aryl bromide. The use of a simple ligand such as PPh_3 in a 1:1 ratio with respect to the catalyst proved to be sufficient, providing higher yields than previously reported procedures using more complex ligands.[19,20]

In terms of the preferred solvent for coupling, 4-bromophenol (**2k**) behaved the same as benzoic acid derivative **2i**: in both cases the reaction is more efficient in water than in methanol. However, the difference in yields between methanolic and aqueous conditions was more pronounced. Only under aqueous conditions did the reaction proceed with good yields (Table 3, entry 2).[5g] For halides **2l** and **2m** (entries 3 and 4), the amide or amine themselves may be acting as ligands, presumably lowering the activity of the catalyst in the catalytic cycle.[21] As expected, the *N*-acetyl derivative **2l** was more reactive

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(20) The reaction between the corresponding diazonium salt and phenyltrifluoroborate was performed under ligandless conditions with similar results. See ref 13a.

TABLE 1. Optimal Combinations of Catalyst, Base, and Solvent for the Reaction between Potassium Phenyltrifluoroborate (1a) and 1-Bromonaphthalene (2a)

	reaction conditions[a]				
entry	catalyst/ligand	solvent	time	base	% yield **3a**; % unreacted **2a**[b]
1	5 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$	EtOH	12 h	*i*-Pr_2NEt	97; 0.8
2	(2 mol %)		6 h		95; 0.6
3	(1 mol %)		7 h		99; −
4	(5 mol %)		12 h	Et_3N	90; 8
5	(1 mol %)		12 h	*t*-$BuNH_2$	82; 11
6	(1 mol %)		6 h	K_2CO_3	78; 8
7	(5 mol %)	THF/H_2O 10:1	12 h	*i*-Pr_2NEt	79; 6
8	(1 mol %)	EtOH/H_2O 1:1	6 h	*i*-Pr_2NEt	90; 3
9	(5 mol %)	THF/H_2O 10:1	12 h	Cs_2CO_3	12; 81
10	5 mol % of $Pd(OAc)_2$	MeOH	12 h	K_2CO_3	84; 2
11	(2 mol %)		2 h		90 (88)[c]
12	(0.5 mol %)		2 h		(75)[c]
13	(0.2 mol %)		9 h		80; 14[c,d]
14	(2 mol %)		7 h		80; 15[e]
15	(2 mol %)	EtOH/H_2O 1:1	6 h		85; 13
16	(0.5 mol %)	MeOH/THF 20:1	6 h		78; 13
17	(0.5 mol %)	EtOH/THF 20:1	3 h		70; 29
18	(5 mol %)	H_2O + 1 equiv of $Bu_4N^+Br^-$	12 h	K_2CO_3	79; 12
19	5 mol % of $Pd_2(dba)_3$/(*t*-Bu_3P)[f]	dioxane	12 h	*i*-Pr_2NEt	51; 3

[a] Conditions: 0.25 mmol of aryltrifluoroborate **1a** and aryl bromide **2a** are reacted in the presence of catalyst/ligand, 3 equiv of base and 2 mL of solvent, heating at reflux overnight under nitrogen. [b] The reactions were analyzed by GC with hexadecane as an internal standard. [c] After purification by chromatography on silica gel. [d] Reaction performed on a 15-mmol scale. [e] Two equivalents of base were used. [f] 1.2:1 P:Pd ratio.

than dimethylamine **2m**, leading to higher yields, although incomplete conversion,[22] under ligandless conditions (entry 3). In both cases, the use of water as a solvent proved to be detrimental. For the amine-substituted aryl bromide **2m**, as in the case of **2n**, the addition of PPh_3 was necessary to achieve good yields of product (Table 3, entry 4).[19]

After performing a number of reactions, it became evident that the high yields and the nature of the byproducts allowed very simple workup techniques to be applied. In many cases, after the reactions were cooled and water was added, the products precipitated directly from the aqueous solution (after acidification in the case of acidic substrates). In other cases, the reaction was subjected to a standard aqueous workup. After concentration, the product could be purified either by recrystallization or by being passed through a short pad of silica gel eluting with pentane or pentane−dichloromethane mixtures to obtain the desired product (boronated and catalyst impurities were retained in the silica gel). These two convenient procedures allowed the products to be obtained in most cases with 95% or higher purity.

The reactions of electron-rich aryltrifluoroborates **1b** and **1c** with 4-bromobenzonitrile (**2e**) (entries 1 and 2, Table 4) proceeded with very good yields. The combination of electron-poor aryl bromide and electron-rich trifluoroborate was the most favorable, and therefore there was no need for special ligands for the coupling. Even the slightly electron-poor 4-fluorophenyltrifluoroborate (**1d**) gave nearly quantitative yields of product under ligandless conditions (Table 4, entry 3). Previously, couplings involving the corresponding boronic acids or esters under ligandless conditions had been performed in the presence of $Bu_4N^+Br^-$ in water,[5k] by applying microwave irradiation,[5j,23] or with aryl iodides to obtain similar yields.[5b,e,g,23]

In applying these conditions to the coupling of other, more electron-deficient trifluoroborates (Table 4, entries 4−8), a high percentage of trifluoroborate homocoupling was observed.[24] The use of the in situ formed catalyst from $Pd(OAc)_2$/(PPh_3) allowed improvement of the yields for the coupling of 4-acetylphenyltrifluoroborate (**1e**) (Table 4, entry 4). However, for the aryltrifluoroborates bearing the 3-nitro, 3,5-bis(trifluoromethyl), and 2,6-difluoro substituents (**1f**, **1g**, and **1h**, respectively), only the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ with triethylamine or K_2CO_3 in ethanol allowed acquisition of the coupling products in high yields (entries 5−7). These results are comparable to those achieved previously with the corresponding arylboronic acids or esters and highly air-sensitive $Pd(PPh_3)_4$, and better than those for 2,6-difluorophenylboronic acid, which has been reported to fail to couple under different conditions.[25]

During the preparation of this paper, Frohn et al.[26] reported the high-yielding coupling of pentafluorophenyltrifluoroborate (**1i**). The conditions developed required the use of 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 in toluene at 100 °C for 3 h, with the addition of 2 equiv of K_2CO_3 and 1.2 equiv of Ag_2O, to afford 76−93% for the reactions with electron-poor aryl iodides. Frohn tested

(21) Ligands containing amine moieties have proved to provide active catalysts for Suzuki couplings when a phosphine group is also present in the molecule: Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051−12052. Other *N*-containing ligands, for example, bis(pyrimidyl)-based palladium complexes, do not show a high efficiency in Suzuki couplings: Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem.* **2001**, *634*, 39−46.

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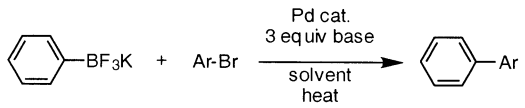
(24) Conditions involving nonpolar solvents, open atmosphere, phosphine or phosphite added, or ligandless $Pd(OAc)_2$ have been used to perform the homocoupling of both electron-poor and electron-rich arylboronic acids. See ref 11.

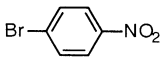
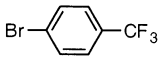
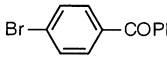
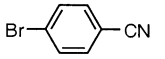
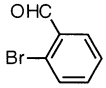
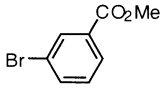
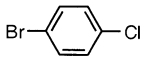
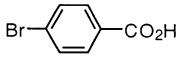
(25) Thiemann, T.; Umeno, K.; Ohira, D.; Inohae, E.; Sawada, T.; Mataka, S. *New J. Chem.* **1999**, *23*, 1067−1070.

(26) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *Tetrahedron Lett.* **2002**, *43*, 8111−8114.

TABLE 2. Cross-Coupling Reactions of Potassium Phenyltrifluoroborate (1a) with Electron-Poor Aryl Halides

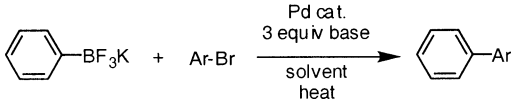


1a 2 3

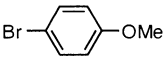
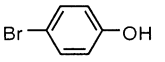
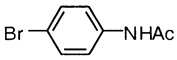
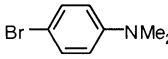
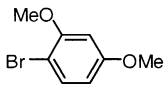
entry	Ar-Br		reaction conditions[a]	% isolated yield
1		**2b**	A, 45 min	**3b**, >99
2		**2c**	A, 1 h	**3c**, 79
3		**2d**	A, 45 min	**3d**, 92
4		**2e**	A, 1 h[b]	**3e**, 87
5		**2f**	A, 1 h	**3f**, 89
6		**2g**	A, 1 h[b]	**3g**, 87
7		**2h**	A, 12 h	**3h**, 75
8		**2i**	A, 2 h B, 2 h[b,c]	**3i**, 96 **3i**, 90; **2i**, 10[d]

[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux, under N_2. Condition B: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), water, 65 °C. [b] Reaction carried out in open atmosphere. [c] Reaction carried out at room temperature. [d] Determined by NMR analysis.

TABLE 3. Cross-Coupling Reactions of Potassium Phenyltrifluoroborate (1a) with Electron-Rich Aryl Halides



1a 2 3

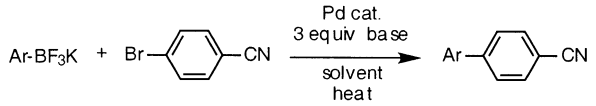
entry	Ar-Br		reaction conditions[a]	% isolated yield
1		**2j**	A, 2 h	**3j**, 95
2		**2k**	A, 1 mol% cat, 36 h B, 2 h	**3k**, 40 **3k**, 82
3		**2l**	A, 18 h B, 2 h	**3l**, 62; **2l**, 24[b] **3l**, 55; **2l**, 41[b]
4		**2m**	A, 24 h C, 1 mol% cat, 14 h	**3m**, traces **3m**, 65
5		**2n**	A, 1 mol% cat, 24 h C, 1 mol% cat, 18 h	**3n**, 50 **3n**, 75

[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition B: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), water, 65 °C. Condition C: $Pd(OAc)_2$ (0.5 mol %), Ph_3P (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. [b] Determined by NMR analysis.

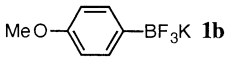
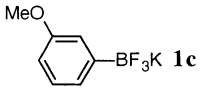
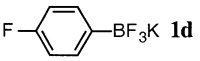
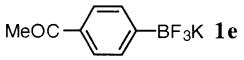
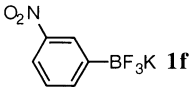
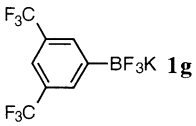
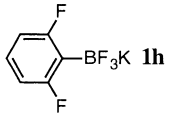
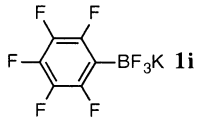
some aryl bromides as well. For example, 4-bromonitrobenzene (**2b**) produced a 62% yield after 24 h. When we performed the coupling of **1i** with 4-bromobenzonitrile (**2e**) under condition D using 3 equiv of K_2CO_3 or Et_3N as base, the reaction led to no product, with a high percentage of homocoupling of the 4-bromobenzonitrile (**2e**) after 36 h. Neither the use of $Pd(PPh_3)_4$ and K_2CO_3 in toluene/ethanol/water 10:10:2 nor aprotic conditions [$PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3, DMF, 90 °C, 24 h] produced the expected product, but rather homocoupling of **2e** and an increased amount of hydrolyzed 4-bromobenzonitrile (under the protic conditions) were observed. When a mixture of methanol/THF 5:1 was used as a solvent in the presence of 5 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ and $(i\text{-}Pr)_2NEt$ as a base, after 36 h 10% of product was detected by GC-MS analysis (entry 8). The crucial role played by solvent was then evident, and the reaction was carried out with dry THF, leading to a 38% yield after 36 h (entry 9). To establish the difference in reactivity between the trifluoroborate salt and the corresponding boronic acid, the reaction involving pentafluorophenylboronic acid was carried out under the same conditions. Analysis by GC-MS after 36 h showed the presence of only traces of product, with a high proportion of unreacted 4-bromobenzonitrile (**2e**). This is the clearest indication yet of the enhanced suitability of the organotrifluoroborate system compared to the corresponding boronic acids in many coupling reactions.

We next examined ortho-substituted coupling partners to assess steric effects in the process (Table 5). Under ligandless conditions, 1-naphthyltrifluoroborate (**1j**) produced a 60% yield of product in the reaction with **2e** after 9 h (90% conversion by GC analysis), revealing the increased steric hindrance of the naphthalene ring (Table 5, entry 1). The presence of only one methyl group in the *ortho* position of the trifluoroborate **1k** also permitted the use of ligandless conditions for the couplings (Table 5, entries 2−4), although the reaction with electron-rich 4-bromoanisole (**2j**) or hindered *o*-bromobenzaldehyde (**2f**) required 12−21 h to reach completion. When two methyls were situated *ortho* to the trifluoroborate group [2,6-dimethylphenyltrifluoroborate (**1l**), entries 5 and 6], the reaction required more time and did not reach completion under ligandless conditions. The use of $Pd(OAc)_2/(PPh_3)$

TABLE 4. Cross-Coupling Reactions of Electron-Rich and Electron-Poor Potassium Aryltrifluoroborates with 4-Bromobenzonitrile (2e)



1 2e 3

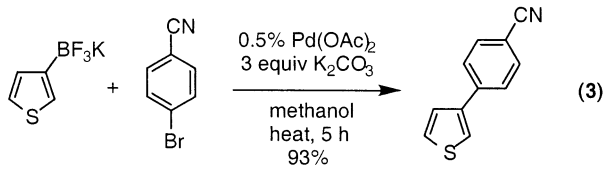
entry	Ar-BF_3K	reaction conditions[a]	% isolated yield
1	 **1b**	A, 1 h	**3o**, 99
2	 **1c**	A, 3 h	**3p**, 91
3	 **1d**	A, 2 h	**3q**, 96
4	 **1e**	C, 8 h	**3r**, 70
5	 **1f**	D, 12 h	**3s**, 89
6	 **1g**	D, 12 h	**3t**, 70
7	 **1h**	D, 1 mol% cat, 6 h	**3u**, 86
8	 **1i**	D, 5 mol% cat, MeOH/THF 5:1, 36 h[c,d]	**3v**, 10[b]
		D, 5 mol% cat, THF, 36 h[c,d]	**3v**, 38

[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition C: $Pd(OAc)_2$ (0.5 mol %), Ph_3P (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.5 mol %), Et_3N (3 equiv), EtOH, reflux. [b] Detected by GC-MS analysis. [c] *i*-Pr_2NEt used as base. [d] Reaction carried out under inert atmosphere.

in 1:1 or 1:2 ratio, which normally allowed an improvement in the oxidative addition of electron-rich aryl bromides, was deleterious in these couplings because it increased the amount of aryl bromide homocoupling. Finally, $PdCl_2(dppf)\cdot CH_2Cl_2$ produced good yields in couplings with 4-bromobenzonitrile (**2e**) after 16 h (entry 5), but only partial conversion for the coupling with 4-bromoanisole (**2j**) after 21 h of reaction (entry 6).

To evaluate the steric hindrance on the halide partner, 2-bromomesitylene (**2o**) was reacted with phenyltrifluoroborate (**1a**) under ligandless conditions. The reaction afforded moderate yields after very long reaction times and high catalyst loading. The use of $PdCl_2(dppf)\cdot CH_2Cl_2$ improved the yields only when used in a mixture of MeOH/THF 5:1, which again suggested the important role of the solvent in the reaction. Because the oxidative addition step was impeded, the use of the more reactive 4-methoxyphenyltrifluoroborate (**1b**) under ligandless conditions did not lead to high yields of product but rather a high proportion of homocoupling of the trifluoroborate after long reaction times. In this case, the use of $Pd(OAc)_2/(PPh_3)$ allowed moderate yields to be achieved (entry 8). Surprisingly, the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ did not improve the yields. Batey and Quach had previously used the tetrabutylammonium salt of the phenyltrifluoroborate in the presence of 5 mol % of $Pd(OAc)_2$(dppb), Cs_2CO_3, and DME/water 1:1 to obtain an 85% yield of **3ac** after 24 h at 50 °C.[16] In that case the Bu_4N^+ cation may not only stabilize the anionic palladium species,[3d,5m,27] but may also act as a phase-transfer catalyst for the solubilization of both reagents in the aqueous−organic medium. We also observed that after similar reaction times, the reactions of **2o** in methanol/THF led to less protodehalogenation of the aryl halide, and consequently higher yields were realized. To achieve good yields in more hindered situations (e.g., steric hindrance in both the trifluoroborate and the bromide) it might be necessary to optimize the reaction further by using other ligands and/or bases under aprotic conditions that have been demonstrated to be efficient in similar situations with arylboronic acids.[6c,8b,28]

Considering the preliminary results obtained in the ligandless couplings of phenyltrifluoroborate (**1a**) with 2-acetyl-5-bromothiophene (**2s**) (Table 6, entry 4) and the coupling between 3-thiophenetrifluoroborate (**1m**) and 4-bromobenzonitrile (**2e**) (eq 3),[15] we intended to determine the scope of the ligandless protocol in couplings involving heteroaryl halides and heteroaryltrifluoroborates, as well as the reactivity of the heteroaryltrifluoroborates in the Suzuki couplings.



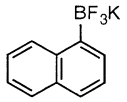
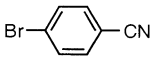
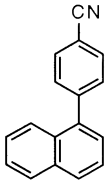
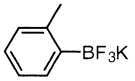
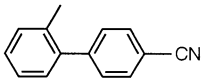
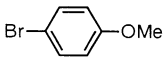
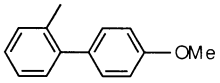
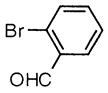
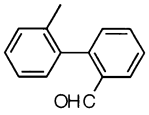
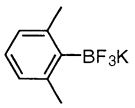
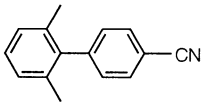
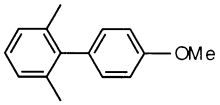
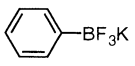
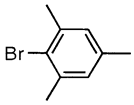
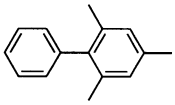
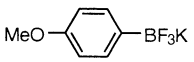
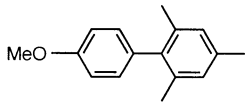
(3)

1m 2e 3ae

Initially, electron-deficient heteroaryl bromides were chosen. When 1-phenyltrifluoroborate (**1a**) was reacted with 2-bromopyridine (**2p**) in the presence of 1 mol % of $Pd(OAc)_2$, the reaction did not reach completion even after 24 h. It was then observed (running a 0.1-mmol reaction in the reactor block) that after 5 h the reaction halted after 90% conversion. Only 70% of product was recovered after workup and purification by chromatography[29] [the reaction was run on a 0.5-mmol scale, with 10% of unreacted bromopyridine (by GC analysis) also present] (Table 6, entry 1). The use of longer reaction times produced the homocoupling product of the remain-

(27) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.
(28) (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210. (b) Castanet, A.-S.; Colobert, F.; Broutin, P.-E.; Obringer, M. *Tetrahedron*: *Asymmetry* **2002**, *13*, 659−665 and references therein.
(29) Colacot, T. J.; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301−3304.

TABLE 5. Cross-Coupling Reactions of Sterically Hindered Potassium Aryltrifluoroborates and Aryl Halides

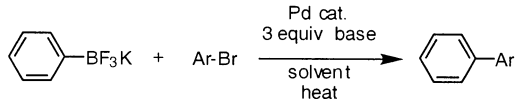
entry	Ar_1-BF_3K	Ar_2-Br	reaction conditions[a]	% isolated yield Ar_1-Ar_2
1	 **1j**	 **2e**	A, 9 h	 **3w**, 60
2	 **1k**	**2e**	A, 5 h	 **3x**, 86
3	**1k**	 **2j**	A, 21 h	 **3y**, 83
4	**1k**	 **2f**	A, 12 h	 **3z**, 84
5	 **1l**	**2e**	D, 16 h	 **3aa**, 82
6	**1l**	**2j**	D, 1 mol % cat, 21 h	 **3ab**, 50
7	 **1a**	 **2o**	A, 5 mol % cat, 36 h D, 1 mol % cat, 15 h THF/MeOH 1:5	 **3ac**, 52 **3ac**, 70
8	 **1b**	**2o**	C, 2 mol % cat, 24 h	 **3ad**, 52

[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition C: $Pd(OAc)_2$ (0.5 mol %), Ph_3P (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.5 mol %), Et_3N (3 equiv), EtOH, reflux.

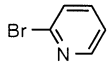
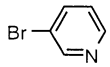
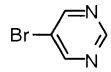
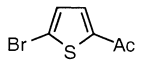
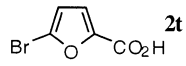
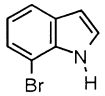
ing 2-bromopyridine. Presumably, the capacity for 2-bromopyridine to complex to the catalyst prevented completion of the coupling.[21] When 3-bromopyridine (**2q**) was used under similar conditions, complete conversion was observed after 2 h, and a 90% yield of product was obtained after workup and purification (Table 6, entry 2). The reaction with 5-bromopyrimidine (**2r**), because it is also an electron-poor heteroaryl bromide, proceeded with very good yields after 5 h under ligandless conditions (Table 6, entry 3).

The coupling products of 2-bromothiophene (**2v**), 3-bromothiophene (**2w**), and 3-bromofuran (**2x**) with 1-phenyltrifluoroborate (**1a**) sublime at room temperature, which led initially to low recoveries of products from the reaction mixtures, thus providing capricious isolated yields. The progress of the reactions was then monitored by GC and ^1H NMR to determine the relative reactivity of the 2- and 3-halosubstituted substrates. It was observed that 2-bromothiophene led to high conversion (between 70 and 80%, with 5% unreacted **2v** after 6 h), while 3-bromothiophene (**2w**) and 3-bromofuran (**2x**) showed only traces of products under ligandless conditions. In the case of 3-bromothiophene (**2w**), even the use of ligands such as PPh_3, PCy_3, or dppf did not afford more than 50% conversion.[27,30] When the more activated thiophene **2s** and furan **2t** were used, the reactions took place under ligandless conditions in relatively short reaction times (Table 6, entries 4 and 5). Cross-couplings

TABLE 6. Cross-Coupling Reactions of Potassium Phenyltrifluoroborate (1a) and Heteroaryl Halides



1a 2 3

entry	Ar-Br		reaction conditions[a]	% isolated yield
1		**2p**	A, 1 mol% cat, 5 h	**3af**, 70
2		**2q**	A, 1 mol% cat, 2 h	**3ag**, 90
3		**2r**	A, 1 mol% cat, 5 h	**3ah**, 92
4		**2s**	A, 50 min	**3ai**, 93
5		**2t**	A, 8 h B, 6 h	**3aj**, 49 **3aj**, 67
6		**2u**	A, 12 h	**3ak**, 44

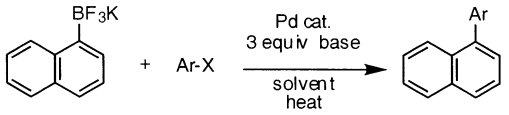
[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition B: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), water, 65 °C.

with thiophene and furan derivatives have been studied by Bussolari and Rehborn[5k] with use of ligandless conditions in water as a solvent. By adding 1 equiv of tetrabutylammonium bromide those reactions could be carried out at room temperature in shorter times. In our studies, only the reaction of **1a** with 5-bromo-2-furoic acid (**2t**) can be carried out in water under ligandless conditions, affording 67% of product **3aj** (Table 6, entry 5), without addition of tetrabutylammonium bromide. As expected, the reaction in methanol furnished only 49% yield after 8 h.

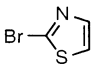
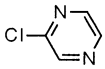
The reaction with the unprotected 7-bromoindole (**2u**) under ligandless conditions produced partial conversion of the heteroaryl bromide. Only 44% of product **3ak** was isolated after purification by column chromatography (Table 6, entry 6). Under the basic conditions the indole may form the nitrogen anion. This not only increases the electron density of the indole ring, but also may increase complexation to the catalyst, thus reducing its activity in the catalytic cycle.[21]

When more sterically hindered 1-naphthyltrifluoroborate (**1j**) was coupled with thiophenes **2v** and **2w**, and 2-bromothiazole (**2y**), only the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ allowed good-to-high conversion to products (Table 7, entries 1, 2, and 4, respectively). The same trend in the reactivity between substitution in the 2- and 3-positions was observed. The reaction with 3-bromofuran (**2x**) had to be carried out in the dark (using an excess of **2x**), due to the tendency of both **2x** and the coupling product **3an** to photodecompose. Under these conditions, a 68% yield of a clear oil was obtained (Table 7, entry 3), which quickly turned yellow even while kept in the dark. In all these reactions, the formation of the homocoupled product from the trifluoroborate, and even from the heteroaryl bromide, was observed, which greatly complicated the purification of the cross-coupling products and reduced the isolated yield to some extent.

TABLE 7. Cross-Coupling Reactions of Potassium 1-Naphthyltrifluoroborate (1j) and Heteroaryl Halides



1j 2 3

entry	Ar-X		reaction conditions[a,b]	% isolated yield
1		**2v**	D, 2 mol% cat, 13 h	**3al**, 83
2		**2w**	D, 2 mol% cat, 13 h	**3am**, 72
3		**2x**	D, 2 mol% cat, 9 h	**3an**, 68
4		**2y**	D, 2 mol% cat, 13 h	**3ao**, 80
5		**2z**	D, 1 mol% cat, 9 h	**3ap**, 85

[a] Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.5 mol %), Et_3N (3 equiv), EtOH, reflux. [b] K_2CO_3 used as a base.

The value of the trifluoroborates to improve the cross-couplings is again exemplified in the reaction with electron-deficient heteroaryl chlorides. When 2-chloropyrazine (**2z**) was reacted with 1-naphthyltrifluoroborate (**1j**), an 85% yield of the desired product **3ap** was obtained after 9 h (Table 7, entry 5). For comparison, the reaction involving a similar arylboronic acid (2-methoxy-1-naphthylboronic acid) and 3,6-dimethyl-2-chloropyrazine requires the use of 3 mol % of $Pd(PPh_3)_4$ in DME (Na_2CO_3 as base) to obtain a 61% yield of product after 48 h (refluxing temperature),[31] and the reaction with the more activated 2-propoxyphenylboronic acid in the presence of 5 mol % of $PdCl_2(dppb)$ in toluene/ethanol/water 4:1:2 requires 24 h at reflux to yield 78% of product.[32]

(30) It has been shown that 3-bromothiophene requires special ligands to afford good yields of coupling products. Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 5659−5662.

(31) McCarthy, M.; Gury, P. J. *Tetrahedron* **1999**, *55*, 3061−3070.

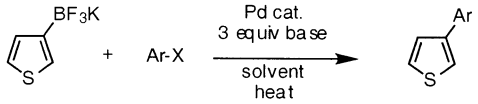
2aa **2ab**

FIGURE 1. Unprotected bromo azoles.

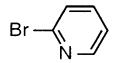
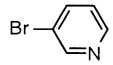
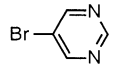
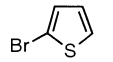
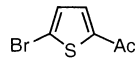
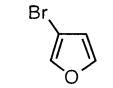
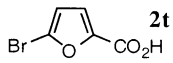
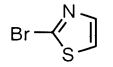
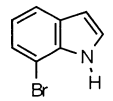
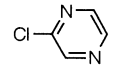
In further studies, potassium 3-thiophenetrifluoroborate (**1m**) was challenged with different heteroaryl halides. Being an electron-rich heteroaromatic compound, **1m** reacted under ligandless conditions with activated (electron deficient) heteroaryl bromides such as pyridines **2p** and **2q** (Table 8, entries 1 and 2). The higher reactivity of the 3-substituted pyridine **2q** was evidenced by the shorter reaction times needed to reach completion. Surprisingly, the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ did not seem to improve the results. Also 5-bromopyrimidine (**2r**)[33] (Table 8, entry 3), and even thiophene **2s** (Table 8, entry 5), can be coupled under ligandless conditions with moderate to high yields. For heteroaryl halide **2r**, partial conversion was observed after 10 h, and the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ provided a slightly higher yield of product, without recovery of starting bromide **2r**, after longer reaction times (Table 8, entry 3). Unfortunately, coupling involving water-soluble heteroaryl halides (such as furan **2t** or some pyridinecarboxylic acids) cannot be performed in water, possibly because of decomposition of the 3-thiophenetrifluoroborate (**1m**) under these conditions. Thus, the reaction with furancarboxylic acid **2t** requires the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ in ethanol to afford 70% yield of product (Table 8, entry 7). Again, the coupling with unactivated thiophene **2v** and thiazole **2y** under ligandless conditions led to low-to-moderate yields, and the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ is required (entries 4 and 8, respectively). For 3-bromofuran (**2x**), because of its lower reactivity, the proportion of trifluoroborate homocoupling is especially high. The tendency of the product to photodecompose and sublime and the impossibility of separation by chromatography forced us to analyze the mixture only by GC-MS and ^{1}H NMR, revealing a poor yield of product **3av** (24%), with 16% of 3,3′-dithiophene (**3aw**).[34] Interestingly, the reaction with the unprotected 7-bromoindole (**2u**) under ligand-added conditions produced a high yield of product (Table 8, entry 9), showing that under basic conditions the unprotected nitrogen cannot compete with the dppf ligand for complexation of the catalyst (compare with Table 6, entry 6). When 2-chloropyrazine (**2z**) was reacted with 3-thiophenetrifluoroborate (**1m**), an 83% yield of the desired product **3ba** was obtained after 12 h (Table 8, entry 10).

The reactions of **1m** with 4-bromo-1*H*-imidazole (**2aa**) and 3,5-dimethyl-4-bromo-1*H*-pyrazole (**2ab**) (Figure 1) led to traces of products detected only by GC-MS analysis.

TABLE 8. Cross-Coupling Reactions of Potassium 3-Thiophenetrifluoroborate (1m) and Heteroaryl Halides



1m **2** **3**

entry	Ar-X		reaction conditions[a]	% isolated yield
1		**2p**	A, 1 mol% cat, 15 h	**3aq**, 60
2		**2q**	A, 7 h	**3ar**, 68
3		**2r**	A, 7 h D, 18 h	**3as**, 64; **2r**, 30[b] **3as**, 75
4		**2v**	D, 13 h	**3at**, 63
5		**2s**	A, 2 mol% cat, 10 h	**3au**, 84
6		**2x**	D, 1 mol% cat, 10 h	**3av**, 24
7		**2t**	D, 1 mol% cat, 10 h[c]	**3ax**, 70
8		**2y**	D, 2 mol% cat, 14 h	**3ay**, 67
9		**2u**	D, 1 mol% cat, 10 h	**3az**, 77
10		**2z**	D, 1 mol% cat, 12 h[c]	**3ba**, 83

[a] Condition A: $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.5 mol %), Et_3N (3 equiv), EtOH, reflux. [b] Determined by NMR analysis. [c] K_2CO_3 used as a base.

In the case of these azoles not only complexation of the nitrogen anion under the basic conditions[35] but also the more electron-rich nucleus may conspire to decrease the rate of the oxidative addition. Protection of the nitrogen with electron-withdrawing groups may allow the desired coupling products to be accessed.

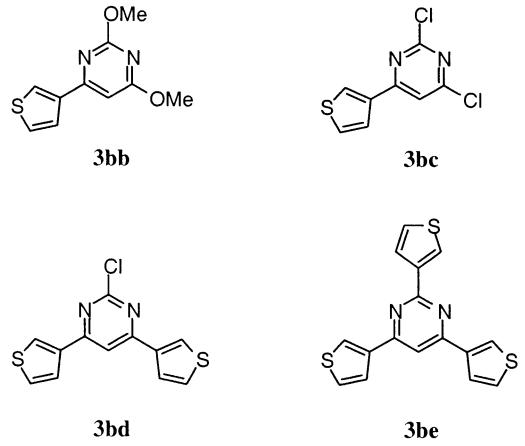
The selectivity in the cross-coupling between 3-thiophenetrifluoroborate (**1m**) and 2,4,6-trichloropyrimidine (**2ac**) (Figure 2) was analyzed under different conditions (Table 9). Assuming that the higher reactivity of the heteroaryl

(32) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117−8126.

(33) The coupling with 3-thiopheneboronic acid has been performed in the presence of 3 mol % of $Pd(PPh_3)_4$, Na_2CO_3, in DME−water, affording 72% yield of product after heating at reflux overnight. Gronowitz, S.; Hoernfeldt, A. B.; Kristjansson, V.; Musil, T. *Chem. Scr.* **1986**, *26*, 305−309.

(34) The cross-coupling and homocoupling products are highly sensitive to light and sublime at room temperature, accounting for the low recovery of product.

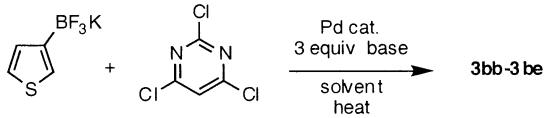
(35) Different pyrazoles have been employed as nonchelating and chelating ligands. Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem.* **2002**, *67*, 9200−9209.



3bb **3bc** **3bd** **3be**

FIGURE 2. Products of coupling between potassium 3-thiophenyltrifluoroborate **1m** and 2,4,6-trichloropyrimidine **2ac** in Table 9.

TABLE 9. Cross-Coupling Reactions of Potassium 3-Thiophenetrifluoroborate (1m) and 2,4,6-Trichloropyrimidine (2ac)



1m **2ac**

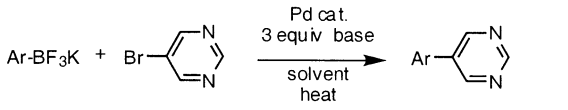
entry	quantity of **1m**	reaction conditions[a]	% isolated yield of **3**
1	1 equiv	3 equiv base A, 12 h	**3bb,** 40[b]
2	1 equiv	3 equiv base D, 9 h	**3bc,** 70; **3bd**, 10
3	2 equiv	6 equiv base D, 9 h	**3bd**, 50, **3be,** 25
4	3 equiv	9 equiv base D, 9 h	**3bd,** 5; **3be**, 65

[a] Condition A: $Pd(OAc)_2$ (2 mol %), K_2CO_3 (3 equiv), MeOH, reflux. Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (1 mol %), Et_3N (3 equiv), EtOH, reflux. [b] Determined by GC-MS analysis.

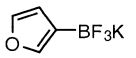
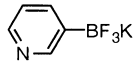
halide would allow us to perform the reaction under ligandless conditions, the coupling was carried out with 1 equiv of trifluoroborate and 3 equiv of K_2CO_3 in the presence of 2 mol % of $Pd(OAc)_2$. Surprisingly, the crude reaction mixture showed a mixture of products arising from mono-, di-, and trisubstitution of the chlorine with methoxy groups,[36] along with a high percentage of disubstituted and monocoupled product **3bb** (Table 9, entry 1).

When the reaction was performed in the presence of 1 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$, 70% of monocoupled product **3bc** was obtained, along with 10% of bicoupled pyrimidine **3bd** (Table 9, entry 2). The reaction with 2 equiv of trifluoroborate **1m** and 6 equiv of base allowed the isolation of 50% of the bicoupled product **3bd** and 25% of tricoupled pyrimidine **3be** (Table 9, entry 3), and with 3 equiv of **1m** and 9 equiv of base, the tricoupled product **3be** was accessed in 65%, with only 5% of bicoupled product **3bd** (Table 9, entry 4).[37] It is thus possible to couple a heteroaryl or aryl moiety selectively to the trichloropyrimidine **2ac** in the 4-position with use of just 1 equiv of trifluoroborate. The selectivity might be enhanced by the use of a less reactive trifluoroborate, as well as a lower catalyst loading. These results are in agreement with those reported by Schomaker and Delia[38] in the coupling of phenylboronic acid and 2,4,6-trichloropyrimidine in the presence of 5 mol % of $Pd(OAc)_2$-$(PPh_3)_2$, using Na_2CO_3 as a base after 18 h in boiling DME/water. It is also evident from comparison that the heteroaryltrifluoroborate system has a higher reactivity than phenylboronic acid, because it undergoes the coupling process with a lower loading of catalyst in shorter reaction times.

TABLE 10. Cross-Coupling Reactions of Potassium Heteroaryltrifluoroborates and 5-Bromopyrimidine (2r)



1 **2r** **3**

entry	Ar-BF_3K		reaction conditions[a]	% isolated yield
1		**1n**	D, 18 h	**3bf**, 72
2		**1o**	D, 18 h	**3bg**, 64

[a] Condition D: $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.5 mol %), Et_3N (3 equiv), EtOH, reflux.

For the reactions of other heteroaryltrifluoroborates, 5-bromopyrimidine (**2r**) was chosen as the coupling partner (Table 10). Unlike cross-couplings with the thiophenetrifluoroborate **1m**, reactions involving the furantrifluoroborate **1n** and pyridinetrifluoroborate **1o** did not afford good yields of products under ligandless conditions. In the case of **1n**, the reaction in the presence of $Pd(OAc)_2$ led to incomplete conversion (23%) while for **1o**, the reaction did not proceed at all. On the other hand, the reaction with $PdCl_2(dppf)\cdot CH_2Cl_2$ led to 72% yield of product (Table 10, entry 1) for electron-rich trifluorobo-

(36) Trichloropyrimidine is known to undergo nucleophilic substitution by phenolate ions. Delia, T. J.; Nagarajan, A. *J. Heterocycl. Chem.* **1998**, *35*, 269−273. Whether the palladium catalyst plays a role in favoring this reaction under our conditions is not known.

(37) Several byproducts arising from substitution of the chlorine atoms by ethoxy groups and/or coupling with the aryltrifluoroborates were detected by GC-MS analysis, in trace levels, which accounts for the conversion of the remaining 20−30% of halide **2ac**, for entries 2−4, Table 9.

(38) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125−7128.

1p **1q**

FIGURE 3. Potassium α-heteroaryltrifluoroborates.

rate **1n**. The yield in this case again may be reduced because of sublimation during the workup process. For the electron-deficient 3-pyridyl derivative **1o**, the reaction afforded 64% of the desired product (entry 2). Previous coupling reactions of the corresponding heteroarylboronic acids or esters have been performed in general under more severe conditions, such as using $Pd(PPh_3)_4$ with moderate yields[39] or with $Pd(OAc)_2$(dppf) or $Pd(OAc)_2$[P(*o*-tolyl$_3$)]$_2$ in DMF at 100 °C.[40]

Unfortunately, when the trifluoroborate group is α to the heteroatom in the furans and pyridines (Figure 3), the tendency for protodeboronation is higher than that for the electron-poor aryltrifluoroborates previously analyzed and even for the corresponding boronic acids. Furthermore, the synthesis of the corresponding trifluoroborates (**1p** and **1q**) is complicated by solubility issues and the fact that the products do not show an adequate (extended) shelf life. Therefore, under protic conditions the reactions of **1p** and **1q** led to no coupling products. Furthermore, an extensive analysis of diverse combinations of bases (Et_3N, K_2CO_3, K_3PO_4, KOTf, CsF, NaOMe), protic (methanol, ethanol/water, toluene/ethanol, DME/water) and aprotic solvents (ethyl acetate, THF, dioxane), and even different catalysts [$Pd(OAc)_2$, $PdCl_2$(dppf)·CH_2Cl_2, $Pd(PPh_3)_4$] for the reaction between 2-pyridyltrifluoroborate (**1q**) and 4-bromobenzonitrile (**2e**) or 5-bromopyrimidine (**2r**) led to no success. No high-yielding cross-coupling reactions have been reported with 2-pyridylboronic acid. The only successful reported reaction of this type involved the coupling between the corresponding dimethyl boronic ester (5 equiv) and 1,4-dibromobenzene in the presence of 7 mol % of $Pd(PPh_3)_4$ in dry DME, and this combination produced 64% of bicoupled product after 20 h.[41] Careful examination of the experimental procedure for the preparation of this boron compound[42] shows that the actual species may be the "ate" complex, because no acidic workup was applied after the lithium−boron transmetalation step. Under these conditions (having a preformed "ate" complex), no base would be required for the coupling, and the transmetalation step could be accelerated, with a decreased tendency to protodeboronate owing to the use of dry DME as solvent.

Mechanistic Studies

In analyzing the optimal amount of base necessary to carry out the coupling process, we observed that the use of only 2 equiv of amine or K_2CO_3 for the ligand-added and ligandless conditions, respectively, forced us to apply longer reaction times to achieve similar yields. To understand the role of the amount of base required, and considering that a tetracoordinate species was involved in the transmetalation step,[13,43] several experiments were performed. We conducted experiments heating $PhBF_3K$ in methanol at reflux with the addition of 0, 1, 2, and 3 equiv of base. After 2 h, all of the reaction mixtures were filtered, equal amounts of deuterated acetone was added to each one, and the resulting solutions were then analyzed by using ^{11}B and ^{19}F NMR. The results are summarized in Table 11.

The addition of 3 equiv of K_2CO_3 led to the gradual displacement of fluoride from the trifluoroborate salt, eventually leading to a different "ate" complex containing no fluorine substituents (Table 11, entry 4, 5.47 ppm compared to entry 5, 28.48 ppm of the boronic acid, by ^{11}B NMR; the signal at −149.29 ppm in the ^{19}F NMR is a sharp singlet, which corresponds to a fluorinated species with no boron attached). On the basis of the shift in the ^{11}B NMR (4.35 ppm in entry 1 to 5.47 ppm in entry 4), the formation of a tetracoordinate species could be postulated wherein all of the fluorides have been displaced for less electron withdrawing groups. It has been claimed that water as a cosolvent is necessary for the cross-coupling reaction to proceed, and that one or more hydroxyl groups in this case would be attached to the boron.[42] Because we found that water, methanol, or ethanol in the presence of a base could be used in the coupling process, the tetracoordinate species may arise from the substitution of fluoride by either hydroxy, alkoxy, or HCO_3^- groups. Two additional experiments were then carried out: $PhBF_3K$ and $PhB(OH)_2$ were heated separately at reflux in wet deuterated methanol in the presence of 3 equiv of base (entries 6 and 7). After 45 min, both reactions were analyzed by ^1H, ^{13}C, ^{19}F, and ^{11}B NMR. The experiment involving **1a** by ^1H and ^{13}C NMR showed the presence of a single species, which by ^{19}F NMR showed the absence of fluorine attached to the boron derivative (Table 11, entry 6), and by ^{11}B NMR corresponded to an "ate" complex. In no case was the signal of the phenylboronic acid detected. It is then possible to conclude that under our ligandless conditions, the use of 3 equiv of base provides an "ate" complex from the corresponding potassium organotrifluoroborate with complete substitution of the fluoride by hydroxyl groups. This species is the most predominant in the reaction, although it does not exclude the possibility that mono-, di-, or trifluorinated species could also be involved in the catalytic cycle. Thus, the fluoride, which has been shown to have a beneficial effect on some coupling processes,[8b] plays a complicated role in these reactions.[25] The fluoride may be part of the counterion sphere, stabilizing various catalytic intermediates, in addition to serving as a ligand on the "ate" complex. Surprisingly, the experiment involving phenylboronic acid showed the presence of the same single species by ^1H, ^{13}C, and ^{11}B NMR (Table 11, entry 7). It therefore appears that both boronated reagents undergo the formation of the same "ate" complex.

By contrast, the feasibility of performing the cross-coupling reaction of potassium pentafluorophenyltrifluo-

(39) Gronowitz, S.; Peters, D. *Heterocycles* **1990**, *30*, 645−58.

(40) Under these conditions, the reactions with the more electron deficient methyl 5-bromonicotinate afford high yields of products after 2−6 h. (a) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237−5243. (b) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052−2055.

(41) Sindkhedkar, M. D.; Mulla, H. R.; Wurth, M. A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991−2996.

(42) Bromopyridine in dry diethyl ether at −78 °C was treated with 1 equiv of *n*-BuLi, then with 2 equiv of $B(OMe)_3$, and then allowed to warm to room temperature overnight. The solvent was evaporated, and volatile impurities were removed as an azeotrope with dry MeOH.

(43) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461−470.

TABLE 11. Effect of the Addition of Base to Potassium Phenyltrifluoroborate (1a)

entry	experiment	^{19}F NMR	^{11}B NMR
1	**1a** + 0 equiv of K_2CO_3 in methanol/acetone-d_6[a]	−143.58 (q) −151.51 (q)	4.35 (q)
2	**1a** + 1 equiv of K_2CO_3 in methanol/acetone-d_6	−148.72 (br s) −150.82 (q)	5.74 (br s)
3	**1a** + 2 equiv of K_2CO_3 in methanol/acetone-d_6	−147.9 (br s) −150.38 (q)	5.59 (br s)
4	**1a** + 3 equiv of K_2CO_3 in methanol/acetone-d_6	−149.29 (s)	5.47 (br s)
5	phenylboronic acid in methanol/acetone-d_6		28.48 (br s)
6	**1a** + 3 equiv of K_2CO_3 in methyl-d_3 alcohol-d	−150.21(s)	4.98 (br s)
7	phenylboronic acid + 3 equiv of K_2CO_3 in methyl-d_3 alcohol-d		4.83 (br s)

[a] After the reaction was cooled, a precipitate was formed that dissolved in acetone-d_6.

roborate (**1i**) under aprotic conditions (dry THF as solvent, dry *i*-Pr_2NEt as base) suggests that fluorinated species can be the key intermediates in the catalytic process. To assess this possibility and the different reactivity of **1i** and its boronic acid analogue, two additional experiments were carried out with these reagents in dry THF, adding 3 equiv of Hünig's base, and heating to reflux during 12 h. Both crude reactions were then analyzed by ^{19}F and ^{11}B NMR after deuterated acetone was added. Surprisingly, the pentafluorophenylboronic acid showed no signal of the boronic acid in ^{11}B NMR, and the presence of at least 5 different signals in the ^{19}F NMR spectrum. Trifluoroborate **1i** remained as a single "ate" complex (quartet at 3.72 ppm in ^{11}B NMR, which suggests the presence of BF_3^-), with four signals still present in ^{19}F NMR. These preliminary results suggest that if, as observed for phenyltrifluoroborate (**1a**), partial or completely fluorinated intermediates are not predominant in the catalytic cycle, the trifluoroborates could still be involved in the cross-coupling process. A more exhaustive analysis must be done to determine the actual species involved in the catalytic cycle, as well as the degree of protodeboronation and homocoupling of the aryltrifluoroborate that compete with the cross-coupling reaction.

Conclusions

It has been demonstrated that there are inherent advantages in utilizing organotrifluoroborates for Suzuki coupling reactions. In general, they are more robust, more easily purified, easier to handle, and less prone to protodeboronation. A wide array of electron-withdrawing and electron-donating groups in both coupling partners is tolerated under the ligandless and ligand-added protocols.

Generally, the trifluoroborate coupling system proved to be more reactive than the corresponding boronic acids or esters under standard reaction conditions. Despite several reports applying ligandless conditions to the reactions of arylboronic acids or esters,[5] there is no single contribution accounting for as many successful couplings of reagents bearing such a variety of functional groups as is reported herein. In general a lower loading of catalyst, lower temperatures, and shorter reaction times can be utilized to match the yields obtained in previously reported couplings involving aryl- and heteroarylboronic acids, even when $PdCl_2(dppf)\cdot CH_2Cl_2$ was required as catalyst. Most importantly, in all of the examples shown, the reactions can be carried out in air with no attenuation in the yields.

It is important to point out the use of $PdCl_2(dppf)\cdot CH_2Cl_2$ instead of $Pd(PPh_3)_4$ in the reactions involving electron-poor aryltrifluoroborates as well as heteroaryltrifluoroborates, which permits reactions to be carried out in an open atmosphere and with a lower loading of catalyst. The ability to utilize electron-deficient arylborons routinely is another hallmark advantage of the trifluoroborate technology over that of boronic acid-based methods.

Unfortunately, the same factors that contribute to the higher reactivity of these trifluoroborates (e.g., the higher electron-withdrawing strength of the trifluoroborate group and the preformed "ate" complex) leads to facile protodeboronation for some of the α-heteroaryltrifluoroborates examined. This may be considered one of the few disadvantages in the use of these boron reagents.

Biaryls are found in many compounds of pharmaceutical interest, and many recently reported drug candidates and analogues have been synthesized via Suzuki coupling reactions. What remains then is a study to demonstrate the applicability of the trifluoroborate syntheses and reactions for valuable intermediates in the natural product synthesis. These studies currently are being undertaken in our group.

Experimental Section

General Procedure for Potassium Aryl- and Heteroaryltrifluoroborate Synthesis. Preparation of Potassium 3-Thiophenyltrifluoroborate (1m). 3-Thiophenylboronic acid (26.2 mmol, 4.9757 g) and potassium hydrogen fluoride (65.8 mmol, 5.1419 g) were placed in a 100-mL Nalgene container and were vigorously stirred in a mixture of methanol (7.5 mL) and water (14 mL) for 2 h. The resulting amber solid was allowed to stand for 2 h at 4 °C and was then filtered and washed with a minimum amount of cold methanol. The solid was then taken up in hot acetone and filtered again. The filtrate was cooled to room temperature and ethyl ether was added in portions, with stirring, until no cloudiness was observed in the supernatant. The mixture was allowed to stand for 1 h at 4 °C to complete crystallization. The solid was filtered and washed with cold ethyl ether until white crystals were obtained. The crystalline solid was dried on a high-vacuum Schlenk line to give 4.6793 g (94%) of the desired material. The spectral data obtained were in accordance with those described in the literature.[11c] mp >260 °C dec. ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.20 (s, 1 H), 7.14 (m, 2 H). ^{13}C NMR (acetone-d_6, 125 MHz) δ 131.8, 125.2, 122.3. ^{11}B NMR (acetone-d_6, 64.2 MHz) δ 4.91 (br s). ^{19}F NMR (acetone-d_6, 470.5 MHz) δ −139.5 (d, J = 75 Hz). Anal. Calcd for $C_4H_3BF_3KS$: C, 25.28, H, 1.59. Found: C, 25.36, H, 1.66.

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions under Condition A. Preparation of 1-Phenylnaphthalene (3a). To a suspension of potassium

phenyltrifluoroborate (**1a**) (0.0923 g, 0.50 mmol), 1-bromonaphthalene (**2a**) (0.1035 g, 0.50 mmol), and K_2CO_3 (0.2045 g, 1.5 mmol) in 0.75 mL of methanol was added 1.25 mL of a 2×10^{-3} M solution of $Pd(OAc)_2$ in methanol (0.5 mol %), and the reaction mixture was stirred and heated at reflux for 2 h, then cooled to room temperature and diluted with water. The aqueous phase was then extracted with dichloromethane. The organic solution was washed with 1 N HCl and brine and dried over $MgSO_4$. The solvent was removed under vacuum. Purification by chromatography on silica gel (elution with hexane) yielded 1-phenylnaphthalene (**3a**) (0.0761 mg, 0.37 mmol, 75%). The product was identical with authentic material by ^1H NMR, ^{13}C NMR, and GC retention time.

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions under Condition B. Preparation of 4-Hydroxybiphenyl (3k). To a mixture of potassium phenyltrifluoroborate (**1a**) (0.1834 g, 1 mmol), 4-bromophenol (**2k**) (0.1764 g, 1 mmol), K_2CO_3 (0.4153 g, 3 mmol), and $Pd(OAc)_2$ (0.0011 g, 5×10^{-3} mmol, 0.5 mol %) was added water (4 mL). The reaction was heated at 65 °C with stirring for 2 h. The reaction mixture was then cooled to room temperature and treated with 1 N HCl until it was acidic to litmus. The precipitate was filtered off, washed with water, dissolved with dichloromethane, and filtered again to eliminate the palladium black formed during the reaction. The organic solution was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the product **3k** was analyzed by NMR after recrystallization from dichloromethane/hexane (82% yield). The spectral data obtained were in accordance with those described in the literature.[44]

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions under Condition C. Preparation of 2,4-Dimethoxybiphenyl (3n). A mixture of 0.0088 g of $Pd(OAc)_2$ and 0.0263 g of Ph_3P was stirred in 10 mL of methanol for 30 min to obtain a 4×10^{-3} M solution of $Pd(OAc)_2/(Ph_3P)$. Then 1.25 mL of the solution (5×10^{-3} mmol, 1 mol %) was added to a mixture of potassium phenyltrifluoroborate (**1a**) (0.0925 g, 0.5 mmol), 2,4-dimethoxy-1-bromobenzene (**2n**) (0.1080 g, 0.5 mmol), and K_2CO_3 (0.2127 g, 1.5 mmol) in 0.75 mL of methanol. The reaction mixture was stirred and heated at reflux in an open atmosphere for 18 h, then cooled to room temperature and diluted with water. The aqueous phase was then extracted with dichloromethane. The organic solution was washed with brine and dried over $MgSO_4$. The solution was then filtered through a short pad of silica gel, using a sequence of pentane (to eliminate any nonpolar byproducts) and pentane/dichloromethane (to elute the product). Further addition of pure dichloromethane eluted polar byproducts and the catalyst residue. The solvent was then removed under vacuum to yield **3n** as a colorless oil (0.0809 g, 75%). The spectral data obtained were in accordance with those described in the literature.[11b]

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions under Condition D. Preparation of 3′-Nitrobiphenyl-4-carbonitrile (3s). To a mixture of potassium 3-nitrophenyltrifluoroborate (**1f**) (0.1150 g, 0.5 mmol), 4-bromobenzonitrile (**2e**) (0.0912 g, 0.5 mmol), Et_3N (0.21 mL, 1.5 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.0020 g, 5×10^{-3} mmol, 0.5 mol %) was added ethanol (2 mL). The reaction was heated at reflux with stirring in an open atmosphere for 12 h, then cooled to room temperature. Upon addition of water, a precipitate was formed. The precipitate was filtered off, thoroughly washed with water, dissolved in dichloromethane, and dried over $MgSO_4$. The solution was then filtered through a short pad of silica gel, using a sequence of pentane (to eliminate nonpolar byproducts) and pentane/dichloromethane (to elute the product). The solvent was removed under vacuum and the crude material was purified by recrystallization with dichloromethane/hexane, to yield **3s** as a white solid (0.0999 g, 89%). mp 162−164. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.46 (t, J = 1.9 Hz, 1 H), 8.29 (dd, J = 8.1, 1.3 Hz, 1 H), 7.93 (dd, J = 7.8, 1.3 Hz, 1 H), 7.81 (dd, J = 6.7, 1.7 Hz, 2 H), 7.75 (dd, J = 8.4, 1.9 Hz, 2 H), 7.69 (t, J = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0, 140.8, 133.0, 132.9, 130.2, 127.9, 123.3, 122.1, 118.3, 112.4. HRMS (ESI): m/z calcd for $C_{13}H_8N_2O_2$ (M^+) 224.0586, found 224.0579.

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Supporting Information Available: Full experimental details and copies of all NMR spectra (^1H, ^{13}C, ^{19}F, and ^{11}B). This material is available free of charge via the Internet at http://pubs.acs.org.

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