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Suzuki-Miyaura Cross-Coupling Reactions of Primary Alkyltrifluoroborates with Aryl Chlorides

Spencer D. Dreher[†], Siang-Ee Lim[‡], Deidre L. Sandroock[‡], and Gary A. Molander[‡]

[†]Department of Process Research and the Catalytic Reactions Discovery and Development Laboratory, Merck and Co. Inc., Rahway, NJ, USA

[‡]Department of Chemistry, University of Pennsylvania, 231 S. 34th Street, Philadelphia, PA 19104–6323

Abstract

Parallel microscale experimentation was used to develop general conditions for the Suzuki-Miyaura cross-coupling of diversely functionalized primary alkyltrifluoroborates with a variety of aryl chlorides. These conditions were found to be amenable to coupling with aryl bromides, iodides, and triflates as well. The conditions that were previously identified through similar techniques to promote the cross-coupling of secondary alkyltrifluoroborates with aryl chlorides were not optimal for the primary alkyltrifluoroborates, thus demonstrating the value of parallel experimentation to develop novel, substrate specific results.

Introduction

The Suzuki-Miyaura cross-coupling reaction has emerged as one of the most powerful platforms for carbon-carbon bond formation because of its mild reaction conditions and its compatibility with a broad range of functional groups.¹ The organoboron compounds employed in this reaction offer a variety of advantages, including ready accessibility, ease of incorporation of non-transferable boron ligands, and the relative non-toxicity of the byproducts generated upon cross-coupling.

Strategies utilizing the *B*-alkyl Suzuki-Miyaura cross-coupling reaction have emerged in syntheses of various natural products and biologically significant analogues.² Although other alkylmetal cross-coupling reactions have been successfully employed in this context,³ the

E-mail: spencer_dreher@merck.com and E-mail: gmolandr@sas.upenn.edu.

Supporting Information **Available:** Experimental details and spectral data of all compounds synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

advantages associated with the Suzuki-Miyaura reaction often make organoboron reagents the preferred nucleophilic partners.

Trialkylboranes have been most often employed in the Suzuki-Miyaura reaction because they are easily accessed via hydroboration of alkenes with 9-BBN.⁴ Although many effective protocols have been established and optimized for this cross-coupling, the scope of the reactions is limited by the incompatibility of dialkylborane hydroborating agents with a variety of functional groups. The air sensitivity of the trialkylboranes requires them to be prepared and used *in situ*, making optimization on small scale onerous and thus limiting their use in synthetic sequences.

Alkylboronic acids and alkylboronate esters can also be easily prepared and employed as coupling partners in this reaction. However, the cross-coupling of alkylboronic acids is complicated by competitive protodeboronation, and as a result significant excesses of the boronic acids are employed to insure complete consumption of the electrophiles.⁵ The corresponding esters can be employed as the boron reagents, but the use of these compounds leads to low yields unless highly toxic thallium bases (TlOH or Tl₂CO₃) are employed.⁶ A single example demonstrates the cross-coupling of alkylboronate esters in good yields without the use of these toxic bases, but treatment *in situ* with *sec*-butyllithium was required to generate the active lithium *n*-alkylborate reagents.⁷

The first twenty-five years of research devoted to the Suzuki-Miyaura cross-coupling reaction focused largely on optimization of the metal/ligand catalyst systems using the standard set of organoboron reagents outlined above.^{5c,8} Expensive additives were also employed to facilitate product formation.⁹ Although important contributions have been made through these efforts, little consideration had been given to improving the organoboron coupling partner of the reaction, which might also lead to enhancements in the overall process.

Throughout the past decade, organotrifluoroborates have emerged as alternative nucleophilic partners in Suzuki-Miyaura cross-coupling.¹⁰ Fortified by their strong boron-fluorine bonds and tetracoordinate nature, organotrifluoroborates act as protected forms of boronic acids that are readily unmasked under conditions required for cross-coupling. The ease with which alkyltrifluoroborate compounds can be prepared [e.g., via hydroboration of the corresponding alkenes,¹¹ transmetalation from other organometallics,¹² or metalation reactions¹³ followed by treatment with inexpensive potassium hydrogen fluoride (KHF₂)], partnered with their air and moisture stability, reinforce their value as appealing alkylboron reagents for this reaction.

In previous contributions, the cross-coupling of substituted potassium alkyltrifluoroborates with aryl bromides and triflates has been described.¹⁴ The cross-coupling of several specialized alkyltrifluoroborates (e.g., aminomethyltrifluoroborates,¹⁵ alkoxymethyltrifluoroborates,¹⁶ cyclopropyltrifluoroborates,¹⁷ and β -boratohomoenolates¹⁸) with aryl chlorides has also been communicated. Although these previous contributions represent important developments, a general protocol for the cross-coupling of primary alkyltrifluoroborates with aryl chlorides has yet to be revealed.

Even outside of the alkyltrifluoroborate arena, although numerous publications have appeared outlining the cross-coupling of alkylboron species with aryl chlorides, in all of these examples only straight-chain alkylboronic acids void of embedded functional groups were used. In none of these contributions has there been significant development toward a universal cross-coupling protocol for both aryl and heteroaryl chlorides.^{5d-e,19}

In a recent communication, we disclosed conditions for the cross-coupling of secondary alkyltrifluoroborates with aryl chlorides.²⁰ In that case, the choice of catalyst ligand was dictated by the difficult transmetalation and the interference of β -hydride elimination that are

problematic steps with use of secondary organoborons. These mechanistic issues are minimized for primary alkyltrifluoroborates and indeed, using parallel microscale experimentation, we discovered alternate conditions that are more suitable for primary alkyl trifluoroborates than the conditions used for the secondary reagents.

Results and Discussions

To find optimal cross-coupling conditions for primary alkyltrifluoroborates with both aryl and heteroaryl chlorides, we employed parallel microscale experimentation. We have previously shown in several studies that a toluene/H₂O solvent combination was superior to a THF/H₂O or a CPME (cyclopentyl methyl ether)/H₂O system for the cross-coupling of potassium alkyltrifluoroborates.¹⁵ As a result, toluene/H₂O was employed as a starting point for exploration of the primary alkyltrifluoroborate system. 2-Chloroanisole **2** (electron-rich and sterically hindered) and 3-chloropyridine **3** were chosen as challenging aryl and heteroaryl electrophilic models, respectively, while potassium phenethyltrifluoroborate **1** was selected as the nucleophilic partner (Scheme 1).

The parallel experimentation used in this study was accomplished using a 96-well-plate reactor 1 mL reaction vials [10 μmol of substrate per reaction, 100 μL of solvent, 10 mol % of Pd(OAc)₂, and 20 mol % of ligand]. For each substrate, 72 structurally diverse ligands were screened, and K₂CO₃²¹ was employed as the base. The product from each of the reactions was then analyzed against an internal standard of 4-isopropylbiphenyl using HPLC analysis. Four ligands (SPhos, RuPhos, *n*-BuPAD₂, and DTBPF, Figure 1) emerged as leads for the optimization of this reaction.

To investigate these hits further, an additional set of parallel, microscale experiments was performed, screening both electrophilic species with our model trifluoroborate at lower amounts of catalyst and ligand used [1 and 2 mol % of Pd(OAc)₂]. The reactions were analyzed by HPLC, comparing the ratio of the product generated to the amount of internal standard (4-isopropylbiphenyl) observed (Figure 2). In a direct comparison of catalyst/ligand loadings, an increased loading of 2 mol % of Pd(OAc)₂ and 4 mol % of the ligand provided the highest product ratios. In all cases, SPhos and RuPhos generated the highest ratios of product. However, RuPhos consistently gave slightly better results. Interestingly, the use of Pd(OAc)₂ and *n*-BuPAD₂ as a catalyst system, which proved to be optimally effective for the cross-coupling of secondary alkyltrifluoroborates, did not emerge as the most successful for the primary alkyltrifluoroborates, reinforcing the idea that unique reaction conditions are required for each family of reaction partners.

With these conditions in hand, the generality of the method was explored with respect to the aryl chloride. To do this, potassium 4-(benzoyloxy)butyltrifluoroborate (**6**) was employed, which was prepared via hydroboration of the corresponding alkene²² followed by addition of aqueous potassium hydrogen fluoride (KHF₂) (eq 1).

(1)

We found that chloroanisole **2** could be cross-coupled with potassium 4-(benzoyloxy) butyltrifluoroborate in 87% yield (Table 1, entry 1). Other electron-rich electrophiles were found to undergo reaction with alkyltrifluoroborate **6**, generating the cross-coupled products in good to excellent yields. Steric hindrance did not affect the reaction, as 1-chloro-2,6-dimethylbenzene cross-coupled in excellent yield (Table 1, entry 5). Additionally, an electron-rich, sterically hindered derivative also cross-coupled very well under the optimized reaction conditions (Table 1, entry 6) providing the product in 92% yield. The reaction conditions also proved to be scalable, providing the cross-coupled product in comparable yield when run on 5 mmol scale (entry 2).

The reaction was not dependent on the electronics of the electrophilic partner (Table 2), as alkyltrifluoroborate **6** cross-coupled in good to excellent yields with electron-neutral (entry 1) and electron-poor (entries 2–8) aryl chlorides. This reaction was found to tolerate a variety of functional groups including ketones, aldehydes, nitriles, and esters. Most notably, the nitro group, which has a propensity to undergo reduction during cross-coupling with alkylborane reagents,²³ survives the current reaction conditions completely intact (entry 3). Potassium 4-(benzoyloxy)butyltrifluoroborate also reacted in excellent yield with a trifluoromethyl-substituted derivative (entry 4).

The coupling conditions were then applied to a variety of heteroaryl chloride substrates (Table 3). The model heteroaryl electrophile, chloropyridine **3**, reacted with potassium 4-(benzoyloxy) butyltrifluoroborate in excellent yield, cleanly generating the cross-coupled product (entry 1). These conditions were amenable to methoxy, fluoro and aldehyde-substituted 3-chloropyridines as well (entries 2–4). A quinoline derivative also cross-coupled in excellent yield (entry 5). In addition to these nitrogen-based heteroaryl systems, a variety of thiophene- and furan derivatives were found to react under the optimized conditions to generate the cross-coupled products in good yields (entries 6–10).

The optimized reaction conditions were amenable to a variety of alkyltrifluoroborates (Table 4). Straight-chain alkyltrifluoroborates (entries 1–2), a trimethylsilyl derivative (entry 3), and substrates with distal ketone, nitrile, and trimethylacetyloxy moieties (entries 4, 6, and 8, respectively) all provided their corresponding cross-coupled products when reacted with 4-chloroanisole. Of note is the tolerance of a silyl ether derivative throughout the overall process (entry 9). Thus, siloxyalkyltrifluoroborate substrate **7** was prepared via iridium-catalyzed hydroboration of the corresponding alkene with pinacolborane, followed by subsequent treatment with saturated aqueous KHF_2 (eq 2). The silyl group not only survives this synthetic process (with exposure to a fluoride source), but also the cross-coupling with a fluoride embedded within the trifluoroborate.

(2)

Potassium isobutyltrifluoroborate **8** was also prepared by the addition of isobutyl magnesium bromide to trimethyl borate, followed by the addition of KHF_2 (eq 3).

(3)

Sterically hindered trifluoroborate substrates (Table 4, entries 3 and 10) also generated the desired products in good yields. However, each of these examples required a slightly longer time to go to completion. Unfortunately, when alkyltrifluoroborates containing alkyl iodides and thioethers were employed, no cross-coupled products were observed.

We also evaluated these conditions for the methylation of aryl chlorides using potassium methyltrifluoroborate. Owing to the low molecular weight and volatility of the corresponding cross-coupled product with use of 4-chloroanisole, 1-(4-chlorophenyl)-1*H*-pyrrole was employed as the electrophilic species in this case. Under the standard conditions, desired product **9** was obtained in 72% yield. (eq 4).

(4)

Finally, we investigated the compatibility of the optimized cross-coupling conditions with a variety of electrophilic species (Table 5). The aryl bromide and triflate both cross-coupled under the reaction conditions (86% and 75%, respectively) albeit in lower yield than that of the corresponding chloride. The aryl iodide was transformed in 80% yield; however, the reaction required Cs₂CO₃ as the base to go to completion.

Conclusion

Using parallel microscale experimentation for reaction optimization, reaction conditions were identified to accommodate the cross-coupling of both aryl and heteroaryl chlorides with primary alkyltrifluoroborates. These results represent an important extension to methods described in the literature for aryl bromides and triflates, because less expensive aryl chlorides can now be employed in this cross-coupling reaction. These conditions have also proved to be compatible with a variety of electrophilic partners, providing a metal/catalyst system capable of cross-coupling primary alkyltrifluoroborates with aryl iodides, bromides, and triflates. Importantly, the ligand choice was found to be different than that used for secondary alkyltrifluoroborates, demonstrating the utility of parallel microscale experimentation to find substrate specific cross-coupling conditions rapidly.

Experimental Section

Procedures for Preparation of Primary Potassium Alkyltrifluoroborates

Potassium 4-(Benzoyloxy)butyltrifluoroborate 6—A reaction flask was fitted with a reflux condenser and to it was added but-3-enyl benzoate (7.0 g, 40 mmol) in CH_2Cl_2 (20 mL). $^{22}\text{HBBBr}_2\text{-SMe}_2$ (40 mL, 1 M in CH_2Cl_2 , 40 mmol) was added slowly, and the mixture was heated to reflux for 4 h. The reaction was allowed to cool to rt and then cooled to 0 °C at which point it was added via a double ended needle to a 0 °C solution of H_2O (6 mL) in Et_2O (20 mL). The resulting mixture was stirred for 30 min and then the organic layer was separated. The aqueous layer was extracted with Et_2O (2×50 mL). The organic extracts were combined and washed with H_2O (50 mL). The resulting crude boronic acid was then dissolved in MeOH (100 mL) and cooled to 0 °C. To it was added saturated aqueous KHF_2 (36 mL, 4.5 M) dropwise, and then the reaction mixture was allowed to warm to rt. After 30 min, the solution was concentrated *in vacuo*. The resulting white solid was then subjected to high vacuum overnight. The dried solids were triturated with hot acetone (3×20 mL) and filtered to remove inorganic salts. The resulting solution was concentrated until the trifluoroborate was minimally soluble in acetone. Et_2O (~30 mL) was added to precipitate the product. The pure compound was filtered and dried *in vacuo* and obtained as a white crystalline solid in 80% yield (9.01 g, 31.7 mmol). mp = 187–189 °C. ^1H NMR (500 MHz, acetone- d_6): 8.01–8.03 (d, J = 7.4 Hz, 2H), 7.59–7.63 (t, J = 7.4 Hz, 1H), 7.48–7.51 (t, J = 7.4 Hz, 2H), 4.25–4.28 (t, J = 6.9 Hz, 2H), 1.70–1.74 (m, 2H), 1.39–1.43 (m, 2H), 0.18–0.22 (m, 2H). ^{13}C NMR (125.8 MHz, acetone- d_6): 166.9, 133.6, 131.8, 130.1, 129.3, 66.4, 33.0, 22.8. ^{19}F NMR (470.8 MHz, acetone- d_6): –141.6. ^{11}B NMR (128.4 MHz, acetone- d_6): 5.93. IR (KBr) 3061, 2924, 2858, 1712, 1453, 1278, 1117, 1075 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{13}\text{BF}_3\text{O}_2$ $[\text{M-K}]^-$ 245.0961, found 245.0950.

General Experimental Procedure for Suzuki-Miyaura Cross-Coupling Reaction of Aryl- and Heteroaryl Electrophiles with Potassium 4-(Benzoyloxy)butyltrifluoroborate. Preparation of 4-(2-Methoxyphenyl)butyl Benzoate

4-(2-Methoxyphenyl)butyl Benzoate—A Biotage microwave vial was charged with Pd (OAc) $_2$ (2.3 mg, 0.01 mmol), RuPhos (9.3 mg, 0.02 mmol) 2-chloroanisole (71.3 mg, 0.50 mmol), potassium 4-(benzoyloxy)butyltrifluoroborate (142 mg, 0.50 mmol) and K_2CO_3 (207 mg, 1.5 mmol). The test tube was sealed with a cap lined with a disposable Teflon septum, evacuated and purged with N_2 ($\times 3$). To the vial was added toluene (2.5 mL) and H_2O (0.25 mL), and then the reaction was heated to 80 °C for 24 h. The reaction mixture was allowed to cool to rt and GC/MS analysis showed complete conversion of the aryl chloride. The organic layer was separated, and the aqueous layer was washed with EtOAc (3×1 mL). The resulting light yellow solution was concentrated and purified by silica gel column chromatography (elution with hexane/EtOAc 99:1) to yield the product as a clear, colorless oil in 87% yield (124 mg, 0.44 mmol). ^1H NMR (500 MHz, CDCl_3): 7.98–7.99 (d, J = 7.6 Hz, 2H), 7.48–7.50 (t, J = 7.6 Hz, 1H), 7.36–7.39 (t, J = 7.8 Hz, 2H), 7.08–7.12 (m, 2H), 6.78–6.83 (m, 2H), 4.28–4.31 (t, J = 6.4 Hz, 2H), 3.75 (s, 3H), 2.62–2.65 (t, J = 7.4 Hz, 2H), 1.68–1.78 (m, 4H); ^{13}C NMR (125.8 MHz, CDCl_3): = 166.7, 132.7, 130.6, 130.5, 129.8, 129.5, 128.3, 127.0, 120.4, 110.3, 64.9, 55.2, 29.8, 28.5, 26.2; IR (neat) 3062, 2996, 2950, 2834, 1716, 1600, 1586, 1493, 1464, 1452, 1314, 1272, 1243, 1115 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{20}\text{NaO}_3$ $[\text{M+Na}]^+$ 307.1310, found 307.1306.

4-(Pyridin-3-yl)butyl Benzoate—According to the general procedure described above using 3-chloropyridine on a 0.50 mmol scale the title compound was isolated in 93% yield (119 mg, 0.47 mmol) as a clear, colorless oil after silica gel column chromatography (elution with hexane/EtOAc 3:2). ^1H NMR (500 MHz, CDCl_3): 8.41–8.44 (m, 2H), 7.99–8.01 (d, J = 7.6 Hz, 2H), 7.49–7.53 (t, J = 7.6 Hz, 1H), 7.46–7.48 (d, J = 7.8 Hz, 1H), 7.38–7.41 (t, J = 7.6

Hz, 2H), 7.16–7.18 (m, 1H), 4.30–4.33 (t, $J = 6.1$ Hz, 2H), 2.64–2.67 (t, $J = 7.0$ Hz, 2H), 1.71–1.82 (m, 4H); ^{13}C -NMR (125.8 MHz, CDCl_3): 166.6, 150.0, 147.5, 137.2, 135.9, 133.0, 130.4, 129.6, 128.4, 123.4, 64.6, 32.6, 28.3, 27.6; IR (neat) 3028, 2941, 2860, 1717, 1274, 1116 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 256.1338, found 256.1327.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

SPhos

RuPhos

n-BuPAd₂

DTBPF

FIGURE 1.
Lead Ligands from Parallel Microscale Experimentation Study

Figure 2.
Optimization of Conditions for Suzuki-Miyaura Cross-Coupling of Potassium Alkyltrifluoroborates with Aryl and Heteroaryl Chlorides

Table 1

Suzuki-Miyaura Cross-Coupling of Potassium 4-(Benzoyloxy)butyltrifluoroborate with Various Electron-Rich Aryl Chlorides^a

		$\text{BzO(CH}_2\text{)}_3\text{BF}_3\text{K} + \text{Cl-C}_6\text{H}_4\text{-R}'$	Pd(OAc)_2 RuPhos 3 eq 10:1 to 24
entry	ArCl		
1
2

entry

ArCl

entry

ArCl

4

entry

ArCl

5

entry

ArCl

6

7

^a General conditions: Pd(OAc)₂ (2 mol %), RuPhos (4 mol %), RBF₃K (1.0 equiv), electrophile (1.0 equiv), K₂CO₃ (3.0 equiv), and 10:1 toluene/H₂O (0.25 M), 24 h, 80 °C, 0.5 mmol scale.

^b Reaction scaled to 5 mmol.

Table 2

Suzuki-Miyaura Cross-Coupling of Potassium 4-(Benzoyloxy)butyltrifluoroborate with Various Electron-Poor and Electron-Neutral Aryl Chlorides^a

entry	Ar-Cl	

1

entry

Ar-Cl

2

3

entry

Ar-Cl

4

5

6

entry

Ar-Cl

7

8

^a General conditions: Pd(OAc)₂ (2 mol %), RuPhos (4 mol %), RBF₃K (1.0 equiv), electrophile (1.0 equiv), K₂CO₃ (3.0 equiv), and 10:1 toluene/H₂O (0.25 M), 24 h, 80 °C, 0.5 mmol scale.

Table 3Suzuki-Miyaura Cross-Coupling of Potassium 4-(Benzoyloxy)butyltrifluoroborate with Various Heteroaryl Chlorides^a

		$\text{BzOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{BF}_3\text{K} + \text{HetArCl}$	$\xrightarrow[10:1 \text{ to } 24]{\text{Pd(OAc)}_2, \text{RuPhos}, 3 \text{ eq}}$
entry	HetAr-Cl		
1
2

entry

HetAr-Cl

entry

HetAr-Cl

entry

HetAr-Cl

5

entry

HetAr-Cl

6

7

entry

HetAr-Cl

8

entry

HetAr-Cl

entry

HetAr-Cl

10

^aGeneral conditions: Pd(OAc)₂ (2 mol %), RuPhos (4 mol %), RBF₃K (1.0 equiv), electrophile (1.0 equiv), K₂CO₃ (3.0 equiv), and 10:1 toluene/H₂O (0.25 M), 24 h, 80 °C, 0.5 mmol scale.

Table 4Cross-Coupling of Various Primary Alkyl Trifluoroborates with 4-Chloroanisole^a

entry	RBF ₃ K
1	
2	
3	
4

entry	RBF_3K
5	$\text{BzO}-(\text{CH}_2)_5\text{BF}_3\text{K}$
6	$\text{NC}-(\text{CH}_2)_4\text{BF}_3\text{K}$
7	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{BF}_3\text{K}$

entry

 RBF_3K

8

9

10

11

entry

 RBF_3K

12

^a General conditions: Pd(OAc)_2 (2 mol %), RuPhos (4 mol %), RBF_3K (1.0 equiv), electrophile (1.0 equiv), K_2CO_3 (3.0 equiv), and 10:1 toluene/ H_2O (0.25 M), 24 h, 80 $^\circ\text{C}$, 0.5 mmol scale.

^b Reaction required 36 h to go to completion.

Table 5

Electrophile Compatibility in the Cross-Coupling of Potassium 4-(Benzoyloxy)butyltrifluoroborate

entry	aryl electrophile	bas
1		K ₂ CO ₃
2		K ₂ CO ₃
3		Cs ₂ CO ₃

entry	aryl electrophile	base
4		K_2CO_3

^aGeneral conditions: Pd(OAc)_2 (2 mol %), RuPhos (4 mol %), RBF_3K (1.0 equiv), electrophile (1.0 equiv), K_2CO_3 or Cs_2CO_3 (3.0 equiv), and 10:1 toluene/ H_2O (0.25 M), 24 h, 80 $^\circ\text{C}$, 0.5 mmol scale.