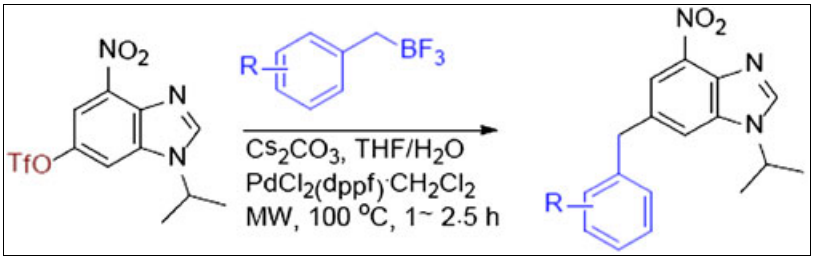
Suzuki–Miyaura Cross-Coupling of Potassium Organoborates with 6-Sulfonate Benzimidazoles Using Microwave Irradiation

Prashi Jain, Shuyan Yi, and Patrick Thomas Flaherty*

School of Pharmacy, Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States
*E-mail: flahertyp@duq.edu

Received September 2, 2010
DOI 10.1002/jhet.1109
Published online 18 April 2013 in Wiley Online Library (wileyonlinelibrary.com).



This article focuses on the utility of organotrifluoroborate salts as coupling partners for Suzuki–Miyaura cross-coupling with 4-nitro-6-triflyl benzimidazoles using microwave irradiation. The C–C bond formation at the 6-position of the electron-rich 1-,4-,6-trisubstituted benzimidazole core is challenging and was not achievable via Kumada, Negishi, Stille, or Heck coupling strategies. Yields of 37–70% could be obtained via palladium coupling strategies utilizing potassium benzyl trifluoroborates as the organometallic coupling partner.

J Heterocyclic Chem., **50**, E166 (2013).

INTRODUCTION

Palladium-catalyzed carbon–carbon bond forming reactions are a central tenet of modern synthetic organic chemistry. Various methods currently exist for palladium-catalyzed formation of C–C bonds [1,2]. The Suzuki–Miyaura cross-coupling reaction[3] has numerous advantages including mild reaction conditions, functional group tolerance, low toxicity, and the ready availability of organoboron compounds [1]. Boronic acid, boronate esters, and organoboranes have been employed as coupling partners for Suzuki–Miyaura cross-coupling reactions. However, limitations still exist such as difficulty in purification, indeterminate stoichiometry, air and moisture instability of boronic acids, and cost [4].

In contrast, potassium trifluoroborate salts are air-stable and moisture-stable crystalline solids. Potassium organotrifluoroborates show greater nucleophilicity than their corresponding organoboranes or boronic acid derivatives [4,5]. They are less prone to protodeboronate during cross-coupling reactions even at elevated temperatures. NMR studies established that fluoride/hydroxyl exchange on the organotrifluoroborates existed. This discovery resulted in cross-coupling reaction protocols, where water and a base were used as essential components for the success of the reaction. Trifluoroborate can be viewed as a protected boronic acid, producing intermediates analogous to those generated by traditional boronic acid precursors in a palladium-coupling reactions [6]. Potassium trifluoroborate salts can be easily prepared by boration of a substituted benzyl bromide or by transmetallation from an organomagnesium species in one pot [7]. Reviews on the utility of potassium trifluoroborate salts are available [1,5,6,8,9].

The benzimidazole nucleus is an important heterocycle because of its broad range of pharmacological activities and high thermal stability [10]. It is a component of several antifungal, antiulcer, and antibacterial agents and has recently been reported as a scaffold for kinase inhibitors [11–13]. Although the benzimidazole core has demonstrated both utility and future potential, functionalization on the benzimidazole scaffold is challenging. Functionalization at the 1-, 2-, and 3-positions are reported and structurally tractable [14,10]. Functionalization at the 5-position or 6-position of benzimidazole is less fully explored [15]. There is need for organometallic couplings on the benzimidazole core. As a part of our continuing interest in 6-hydroxy-derived 1,4-disubstituted benzimidazoles [16], we sought efficient ways to functionalize the 6-hydroxy substituent of the benzimidazole core to the corresponding 6-carbon analogues. Carbon–carbon bond forming reactions of sp^3-hybridized organoboranes with sp^2 or aromatic hybridized triflates or bromides have been reported previously by the Molander group [17]. There are no reported methods for the cross-coupling of benzimidazoles at the 6-position. The electrophilicity of a trisubstituted benzimidazole core is significantly reduced because of the electron-rich nature of the imidazole moiety that makes coupling at the 6-position difficult. The presence of a nitro group at 4-position of a benzimidazole scaffold was anticipated to reduce the electron-rich nature of the imidazole ring and the known greater nucleophilicity of the potassium trifluoroborate compared with the

corresponding boronic acid, suggested the potential utility of this strategy, and provided a point for structural elaboration found to be relevant to kinase inhibition [16]. Novel functionalization of 1-,4-,6-trisubstituted benzimidazoles at 6-position using Suzuki–Miyaura cross-coupling conditions is presented.

RESULTS AND DISCUSSION

We have reported aryl hetero bond formation at 6-position of benzimidazole in the development of CDK5 [18] and MEK5 [16] inhibitors. To complete our structure activity relationship studies of these series, we wanted to explore carbon analogues at the 6-position. There is no reported literature method for the C–C bond formation of benzimidazoles at the 6-position. Synthesis of common intermediate **1** was previously described and proceeded well [19]. Compound **1** was subjected to demethylation in 48% HBr at 120°C for 2.5 h with microwave irradiation. Compound **2** was then treated with 4-nitrophenyl trifluoromethanesulfonate and potassium carbonate at room temperature to generate the triflate **3** in 87% yield. This synthetic route is presented in Scheme 1. Attempted triflate ester formation utilizing triflic anhydride and pyridine resulted in lower yield and lower purity. Other sulfonyl-leaving groups have also been prepared and examined, but triflates were the only reactive members of the sulfonyl family identified. Early attempts to couple triflate **3** with different nucleophiles are summarized in Table 1.

Initial $Fe(acac)_3$ catalyzed cross-coupling with EtMgBr as the organometallic coupling partner [20] did not proceed. Ni(0)-catalyzed Kumada coupling [21] utilizing Ni(dppp) Cl_2 and $PhCH_2MgBr$ as the organometallic coupling partner also failed. Attempts at Stille coupling [22] with tributyl(3-Me-2-butenyl)tin as the organometallic coupling partner also failed. Negishi [23] cross-coupling with $PhCH_2ZnBr$ as the organometallic coupling partner with a variety of palladium ligands gave a complicated mixture with inseparable products. Heck coupling [24] with ethyl methacrylate at 120°C using microwave irradiation also did not provide any conversion to the product.

Failure of the aforementioned methods prompted us to explore a Suzuki–Miyaura cross-coupling strategy employing the very nucleophillic potassium benzyltrifluoroborates. It is established [17,25,26] that potassium benzyltrifluoroborates can react with aryl triflates generating a C–C bond. Previously electron-rich aryl triflates were identified as giving poor or no conversion. Thus, Suzuki–Miyaura cross-coupling on the electron-rich benzimidazole core was conceivable (Scheme 2) but had not yet been reduced to the level of practical utility.

Under established conditions [17], when triflate **3** and the commercially available potassium benzyl trifluoroborate salt **4a** were treated with cesium carbonate, THF, water, and palladium catalyst at reflux (68°C) for 24 h, the reaction did not proceed to completion and the coupled product could not be isolated. When the reaction was heated using microwave irradiation at 100°C for 20 min, the reaction proceeded and the product **5a** was isolated in 20% yield. Unreacted starting material **3** was recovered with 50% efficiency. Optimization of the reaction time and temperature under microwave irradiation provided improved yield with substituted benzyl analogues. The utility of microwave heating in facilitating palladium coupling reactions is believed to result from achieving higher internal temperatures (110°C for microwave compared with 66°C on the bench top) and a resultant acceleration of the rate of reaction.

Non-commercially available potassium benzyl trifluoroborates **4b–e** were synthesized from the corresponding halides **6b–d** in acceptable yield. A one-pot procedure was pursued to permit isolation of the more stable benzyl trifluoroborate salt rather than utilizing the unstable trivalent organoboron species. The precursor halides were treated with Mg metal in dry diethylether under argon to yield the Grignard reagent, followed directly by boron exchange with trimethoxyborane to give the intermediate trivalent organoboron species, and followed by final treatment with KHF_2 to produce the stable substituted potassium benzyl trifluoroborates **4b–e** [27]. Conversion to the Grignard species **7b–d** was assayed with anhydrous diphenyl acetic acid as a titrant and 1,10-phenanthroline as an indicator [28]. Grignard reagent **7e** was commercially available. Electron-withdrawing groups on the benzyl ring provide moderate to good yield with this three-step reaction sequence (24%), whereas electron-donating groups such as 4-OMe give a lower yield (20%). The synthesis of the substituted potassium benzyl trifluoroborates examined is presented in Scheme 3.

All substituted potassium benzyl trifluoroborate salts were subjected to Suzuki–Miyaura cross-coupling using microwave irradiation with the common intermediate **3** to generate compounds **5a–e** in 50–70% isolated yield. The

Scheme 1. Preparation of common intermediates.

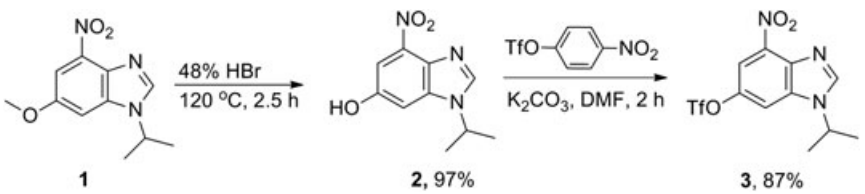


Table 1

Attempted coupling strategies with **3**.

Organometallic coupling partner	Catalyst/ligand	Solvent	Temperature (°C)/time (h)	Result
$(CH_3)_2CHCH_2MgBr$	$Fe(acac)_3$	THF/NMP	23, 2	NR
CH_3CH_2MgBr	Fe[Salen] complex	THF	23, 3	NR
$PhCH_2MgBr$	$Ni(dppp)Cl_2$	THF	23, 20	NR
Tributyl(3-Me-2-butenyl)tin	$Pd(PPh_3)_4$, LiCl	Dioxane	101, 7	CM
$PhCH_2ZnBr$	Pd_2dba_3	THF	68, 20	CM
	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	THF	68, 20	CM
	$Pd(PPh_3)_4$	THF	68, 20	CM
	$Pd(OAc)_2$ and Xantphos	THF	68, 20	CM
	$Pd(OAc)_2$ and DPEphos	THF	68, 20	CM
Ethyl methacrylate	$(PPh_3)_2{\cdot}PdCl_2$ $NaHCO_3$	DMF	120, 2	NR

NR = no reaction, CM = complicated mixture, no clear evidence of product

2-F substituted benzyl analogue **4c** generated a lower yield due to electron-withdrawing effects or perhaps due to steric hindrance (Table 2).

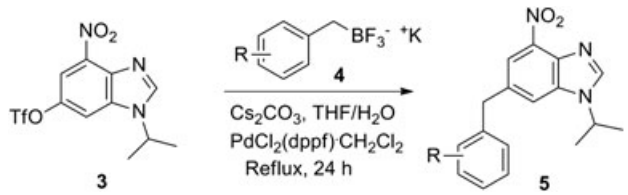
Another common intermediate **8** was also explored. Compound **9** was treated with hydrobromic acid for 2.5 h at 120°C in microwave to yield **10** in 86% yield. Triflate **8** was prepared from **10** with 4-nitrophenyl trifluoromethanesulfonate at 23°C in 87% over 4 h. Triflate **8** underwent Suzuki–Miyaura cross-coupling with potassium trifluoroborate salt **4a** to afford **11** in 17% yields. Yields were consistent with the isopropyl variant (Schemes 4 and 5).

An attempt [29] to prepare the 6-benzimidazolyl organoboron reagent **12** and then couple with an electrophile [30] to generate **5a** is shown in Scheme 6. This strategy was not successful. A rationale for this lack of reactivity is that the generated aryl organoborane lacks sufficient nucleophilicity to couple with a normally very reactive electrophile and establishes the practical necessity for use of the potassium trifluoroborate in Suzuki–Miyaura couplings with this system.

CONCLUSIONS

Palladium-catalyzed cross-coupling reaction of potassium aryltrifluoroborates with less reactive benzimidazole triflates is achievable with microwave irradiation. The advantage of the microwave irradiation method includes shorter reaction time, fewer side reactions, and higher product yield, when contrasted against conventionally heated Suzuki–Miyaura cross-coupling reactions.

Scheme 2. Suzuki–Miyaura cross-coupling using potassium trifluoroborate salts.



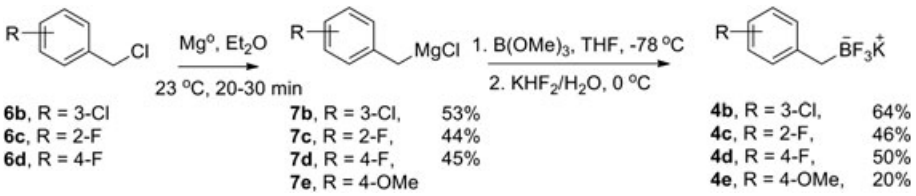
EXPERIMENTAL

All solvents and reagents were used as received unless noted otherwise. Tetrahydrofuran (THF) was distilled from Na-benzophenone ketyl radical under a blanket of argon prior to use. All reactions were conducted in dry glassware and under an atmosphere of argon unless otherwise noted. Microwave reactions were conducted in sealed tube and utilized a multimode Milestone Start apparatus for irradiation with power and control parameters as noted. Melting points were determined on a MelTemp apparatus and are uncorrected. All proton NMR spectra were obtained with 500 or 400 MHz Oxford spectrospin cryostat, controlled by a Bruker Avance system, and were acquired using Bruker Topspin 2.0 acquisition software. Acquired FIDs were analyzed using MestReC 3.2. Elemental analyses were conducted by Atlantic Microlabs and are ±0.4 of theoretical. All HRMS mass spectral analyses were conducted at Duquesne University with a nano ESI chip cube TOF HRMS and are ±0.004 of theoretical. All ^1H NMR spectra were taken in $CDCl_3$ unless otherwise noted and are reported as parts per million relative to TMS as an internal standard. Coupling values are reported in hertz.

***1-Isopropyl-4-nitro-1H*-benzo[*d*]imidazol-6-ol (2).** 1-Isopropyl-6-methoxy-4-nitro-1*H*-benzo[*d*]imidazole (1.00 g, 4.25 mmol) and 48% HBr (20 mL) were added to a 50 mL microwave tube. The mixture was subjected to microwave irradiation (350 W) to maintain 120°C for 2.5 h. After cooling, solvent was removed on the rotavap. The resulting yellow solid was dissolved in minimum amount of water. Saturated $NaHCO_3$ (aq) was added until pH = 6. The mixture was filtered and the yellow solid was collected and washed with water then dried under high vacuum (150 μm) to afford 0.92 g (97%) of the desired compound **2**. R_f 0.36 (CH_2Cl_2/MeOH/NH_4OH 100 : 10 : 0.1). mp 206–207°C. ^1H NMR (DMSO-d_6): δ 10.16 (s, 1H), 8.45 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 4.68–4.75 (m, 1H), 1.50 (d, J = 6.8 Hz, 6H). *Anal*. Calcd. for $C_{10}H_{11}N_3O_3$: 0.131 HBr: C, 51.81; H, 4.84; N, 18.12; O, 21.70. Found: C, 51.84; H, 4.73; N, 18.07.

1-Isopropyl-4-nitro-1H-benzo[d]imidazol-6-yl trifluoromethanesulfonate (3). Solid K_2CO_3 (608.1 mg, 4.4 mmol) was added to a solution of 1-isopropyl-4-nitro-1*H*-benzo[*d*]imidazol-6-ol (486.7 mg, 2.2 mmol) and 4-nitrophenyl trifluoromethanesulfonate (656.5 mg, 2.42 mmol) in 11 mL of DMF. This suspension was stirred at 23°C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (250 mL) and then filtered. The filtrate was washed with water (100 mL × 4) and brine and dried over sodium sulfate. Evaporation of the solvent gave a yellow oil, which was then subjected to silica gel column

Scheme 3. Synthesis of substituted potassium benzyltrifluoroborates.



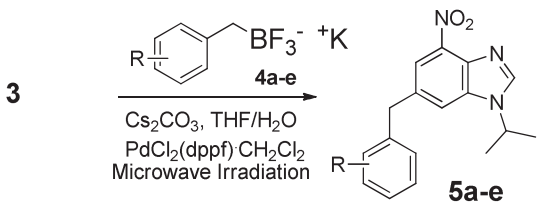
6b, R = 3-Cl
6c, R = 2-F
6d, R = 4-F

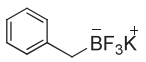
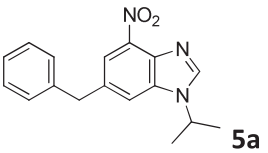
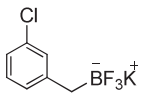
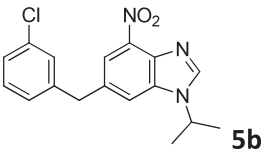
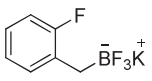
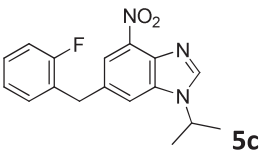
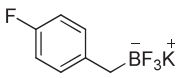
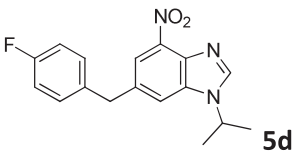
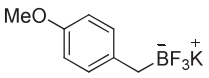
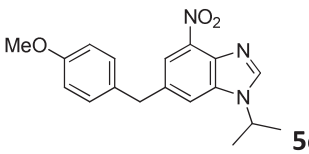
7b, R = 3-Cl, 53%
7c, R = 2-F, 44%
7d, R = 4-F, 45%
7e, R = 4-OMe

4b, R = 3-Cl, 64%
4c, R = 2-F, 46%
4d, R = 4-F, 50%
4e, R = 4-OMe, 20%

Table 2

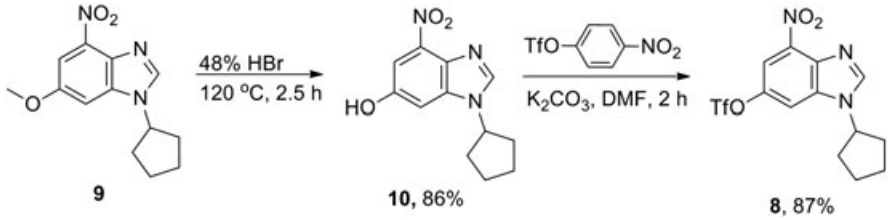
Synthetic route for compounds **5a–e**.



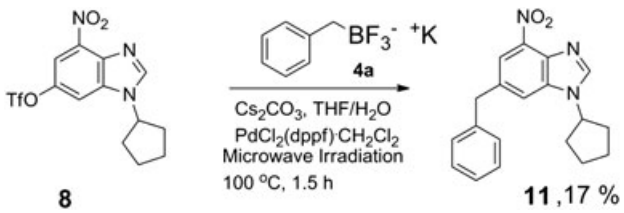
Triflate	R-BF_3K	Product	Isolated yield (%)
3	 **4a**	 **5a**	37[a]
3	 **4b**	 **5b**	70[b]
3	 **4c**	 **5c**	38[b]
3	 **4d**	 **5d**	58[b]
3	 **4e**	 **5e**	50[b]

[a]1.1 equiv R-BF_3K, 1.5 equiv Cs_2CO_3, THF/H_2O (1/0.1), 0.1 equiv $PdCl_2$(dppf)•CH_2Cl_2, MW, 100°C, 1 ~ 2.5 h.
[b]3.0 equiv Cs_2CO_3.

Scheme 4. *N*-1-Cyclopentyl benzimidazole analogues.



Scheme 5. Synthetic strategies for *N*-1-cyclopentyl benzimidazole analogues.



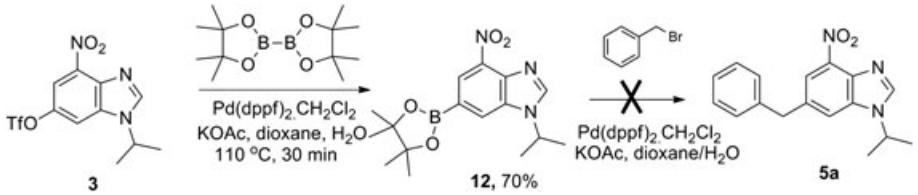
chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 673.0 mg of the triflate **3** (87%). R_f 0.42 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 129.5–130.5°C. ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 4.71 (m, J = 6.71 Hz, 1H), 1.70 (d, J = 6.77 Hz, 6H). *Anal*. Calcd. for $C_{11}H_{10}F_3N_3O_5S$: C, 37.40; H, 2.85; N, 11.89. Found: C, 37.43; H, 2.79; N, 11.84.

6-Benzyl-1-isopropyl-4-nitro-1H-benzo[d]imidazole (5a). A dry microwave tube with a stir bar was charged with 1-isopropyl-4-nitro-1H-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (353.0 mg, 1.0 mmol), potassium benzyltrifluoroborate (198.0 mg, 1.0 mmol), Cs_2CO_3 (488.7 mg, 1.50 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (81.66 mg, 0.1 mmol). The microwave tube was capped with a rubber septum and underwent three vacuum/N_2 purge cycles. Degassed deionized water (0.7 mL) and THF (7 mL) were added via syringe. The rubber septum was quickly removed and replaced with the microwave tube cap. The mixture was subjected to microwave irradiation at 250 W to maintain 110°C for 1.5 h. After cooling to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with 5 mL brine and dried over magnesium sulfate. Filtration then evaporation of the solvent under reduced pressure gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 70.0 mg of the desired product in **5a** (32%). R_f 0.4 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 106–106.5°C. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 8.05 (d, J = 1.26 Hz 1H), 7.52 (d, J = 0.93 Hz, 1H), 7.34 (m, 2H), 7.27 (m, 1H), 7.22 (d, J = 7.16 Hz, 2H), 4.64 (m, J = 6.75 Hz, 1H), 4.21 (s, 2H), 1.63 (d, J = 6.75 Hz, 6H). *Anal*. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.97; H, 5.80; N, 14.23.

Potassium (3-chlorobenzyl)trifluoroborate (4b). A dry single-neck round bottom flask with a nitrogen inlet was charged with trimethoxyborate (780.0 mg, 7.5 mmol) and in 10 mL of THF. The solution was cooled to −78 °C, and (3-chlorobenzyl)magnesium chloride 0.85 *M* in THF (5.9 mL, 5 mmol) was added dropwise over 15 min. The mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature over 1 h. The resulting white slurry was cooled to 0°C, and MeOH (5 mL) was added dropwise over 5 min. Then the nitrogen inlet was removed and a 4.5 *M* aqueous solution of KHF_2 (6.5 mL, 30 mmol) was added dropwise at 0°C. After the addition, the mixture was stirred at 0°C for 1 h. The mixture was concentrated and azeotroped with toluene three times at 60°C on the rotavap to remove residual water and then dried under high vacuum overnight to afford a white solid. This solid was broken into a fine powder with a spatula and suspended in 10 mL of acetone on rotavap with rotation at atmosphere pressure for 5 min at 40°C. The suspension was filtered through Celite. Acetone (5 mL) was added to the remaining solid in the flask, and the procedure was repeated two more times. The combined filtrates were concentrated under vacuum. The solid obtained was suspended in 4 mL of Et_2O and filtered, and the collected solid was washed with an additional 4 mL of aliquots of Et_2O, then dried under high vacuum to afford 747.0 mg of the desired salt (64%). ^{1}H NMR (DMSO-d_6): δ 7.05(t, J = 27.6 Hz 1H), 6.96 (s, 1H), 6.89–6.92 (m, 2H), 1.44 (br, 2H).

6-(3-Chlorobenzyl)-1-isopropyl-4-nitro-1H-benzo[d]imidazole (5b). A 10 mL dry microwave reactor tube with a stir bar was charged with 1-isopropyl-4-nitro-1*H*-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (176.6 mg, 0.50 mmol), potassium (3-chlorobenzyl)trifluoroborate (137.5 mg, 0.59 mmol), Cs_2CO_3 (485.7 mg, 1.50 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (41.0 mg, 0.05 mmol). The microwave reactor tube was capped with a rubber septum, evacuated and underwent three vacuum/N_2 purge cycles. Degassed deionized water (0.5 mL) and THF (5 mL) were added via syringe. The rubber septum was quickly removed and replaced with the microwave reactor tube cap,

Scheme 6. Alternate Suzuki–Miyaura cross-coupling strategy.



and the mixture was subjected to microwave irradiation at 100°C for 2.5 h. After cooling to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with brine and dried over magnesium sulfate. Filtration and then evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 673.0 mg of **5b** (70%). R_f 0.37 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 136.7–137.1°C. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 8.01 (s, 1H), 7.49 (s, 1H), 7.23 (m, 2H), 7.18 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 4.61–4.67 (m, 1H), 4.16 (s, 2H), 1.63 (d, J = 7.0 Hz, 6H). *Anal*. Calcd. for $C_{17}H_{16}ClN_3O_2$: C, 61.91; H, 4.89; Cl, 10.75; N, 12.74; O, 9.70. Found: C, 62.20; H, 4.91; N, 12.59.

Potassium (2-fluorobenzyl)trifluoroborate (4c). A dry single-neck round bottom flask with a nitrogen inlet was charged with trimethoxyborate (780 mg, 7.5 mmol) and 10 mL of THF. The solution was cooled to −78°C, and (2-fluorobenzyl) magnesium chloride 0.74 *M* in THF (6.8 mL, 5 mmol) was added dropwise over 15 min. The mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature over 1 h. The resulting white slurry was cooled to 0°C, and methanol (5 mL) was added dropwise over 5 min. Then the nitrogen inlet was removed, and a 4.5 *M* aqueous solution of KHF_2 (6.5 mL, 30 mmol) was added over 5 min at 0°C. After addition, the mixture was stirred at 0°C for 1 h. The mixture was concentrated and azeotroped with toluene three times at 60°C on the rotavap to remove residual water and then dried under high vacuum overnight to afford a white solid. The solid was broken into a fine powder with a spatula and suspended in 10 mL acetone on rotavap with rotation at atmosphere pressure for 5 min at 40°C. The suspension was filtered through Celite. Acetone (5 mL) was added to the remaining solid in the flask, and the procedure was repeated two more times. Combined filtrates were concentrated on vacuum. The solid obtained was dissolved into minimal amount of hot acetone (4 mL), and Et_2O (5 mL) was added dropwise to precipitate the white solid. The mixture was slowly cooled to room temperature, placed in ice bath for 1 h and then in the refrigerator for another 2 h. The mixture was filtered, and the white solid was collected and dried under vacuum to afford 498 mg (46%) of the desired product (**4c**).

6-(2-Fluorobenzyl)-1-isopropyl-4-nitro-1H-benzo[d]imidazole (5c). A dry microwave reactor tube with a stir bar was charged with 1-isopropyl-4-nitro-1*H*-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (212.0 mg, 0.60 mmol), potassium (2-fluorobenzyl)trifluoroborate (155.4 mg, 0.72 mmol), Cs_2CO_3 (586.4 mg, 1.80 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (50.0 mg, 0.06 mmol). The microwave reactor tube was capped with a rubber septum and subjected to three vacuum/N_2 purge cycles. Degassed deionized water (0.6 mL) and THF (6 mL) were added via syringe. The rubber septum was quickly removed and replaced with the microwave reactor tube cap, and the mixture was subjected to microwave irradiation at 250 W to maintain a temperature of 100°C for 1.5 h. After cooling to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 72.0 mg of **5c** (38%). R_f 0.36 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 124.8–125.1°C. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 8.03 (s, 1H), 7.58 (s, 1H), 7.18–1.25 (m, 2H), 7.04–7.11 (m, 2H), 4.62–4.68 (m, 1H), 4.19 (s, 2H), 1.63 (d, J = 6.8 Hz, 6H). *Anal*. Calcd. for $C_{17}H_{16}FN_3O_2$: C, 65.17; H, 5.15; F, 6.06; N, 13.41; O, 10.21 Found: C, 64.98; H, 5.16; N, 13.33.

Potassium (4-fluorobenzyl)trifluoroborate (4d). A dry single-neck round bottom flask with a nitrogen inlet was charged with trimethoxyborate (780.0 mg, 7.5 mmol) and 10 mL of THF. The solution was cooled to −78°C, and (4-fluorobenzyl) magnesium chloride 0.75 *M* in THF (6.7 mL, 5 mmol) was added dropwise over 15 min. The mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature over 1 h. The resulting white slurry was cooled to 0°C, and MeOH (5 mL) was added dropwise over 5 min. Then the nitrogen inlet was removed, and 4.5 *M* aqueous solution of KHF_2 (6.5 mL, 30 mmol) was added dropwise at 0°C. After addition, the mixture was stirred at 0°C for 1 h. The mixture was concentrated and azeotroped with toluene three times at 60°C on the rotavap to remove residual water and then dried under high vacuum overnight to afford a white solid. The solid was broken into a fine powder with a spatula and then suspended in 10 mL acetone on rotavap with rotation at atmosphere pressure for 5 min at 40°C. The suspension was filtered through Celite. Acetone (5 mL) was added to the remaining solid in the flask, and the procedure was repeated two more times. The combined filtrate was concentrated under vacuum. The solid obtained was suspended in 10 mL of Et_2O, then filtered, and the collected solid was washed with 10 mL of Et_2O and dried under high vacuum to afford 399.6 mg of **4d** (37%). ^{1}H NMR (DMSO-d_6): δ 6.94–6.97 (m, 2H), 6.81–6.84 (m, 2H), 1.41 (br, 2H).

6-(4-Fluorobenzyl)-1-isopropyl-4-nitro-1H-benzo[d]imidazole (5d). A dry microwave tube with a stir bar was charged with 1-isopropyl-4-nitro-1*H*-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (176.6 mg, 0.50 mmol), potassium (2-fluorobenzyl)trifluoroborate (129.6 mg, 0.60 mmol), Cs_2CO_3 (485.7 mg, 1.50 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (41.0 mg, 0.05 mmol). The microwave tube was capped with a rubber septum and subjected to three vacuum/N_2 purge cycles. Degassed deionized water (0.5 mL) and THF (5 mL) were added via syringe. The rubber septum was quickly removed and replaced with the microwave tube cap, and the mixture was subjected to microwave irradiation at 250 W to maintain a temperature of 100°C for 3 h. After cooling down to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with brine and then dried over magnesium sulfate. Filtration then evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 91.0 mg of **5d** (58%). R_f 0.42 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.58 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.15–7.18 (m, 2H), 6.98–7.03 (m, 2H), 4.62–4.68 (m, 1H), 4.17 (s, 2H), 1.63 (d, J = 8.5 Hz, 6H). HRMS (EI) Calcd. for $C_{17}H_{16}FN_3O_2$: 314.1260. Found 314.1311 [M═H^+].

Potassium (4-methoxybenzyl)trifluoroborate (4e). A dry single-neck round bottom flask with a nitrogen inlet was charged with trimethoxyborate (0.74 mL, 6.5 mmol) and 10 mL of THF. The solution was cooled to −78°C, and (2-fluorobenzyl) magnesium chloride 0.217 *M* in THF (20 mL, 4.34 mmol) was added dropwise over 15 min. The mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature over 1 h. The resultant white slurry was cooled to 0°C, and methanol (5 mL) was added dropwise over 5 min. The nitrogen inlet was

removed, and a 4.5 *M* aqueous solution of KHF_2 (5.78 mL, 26 mmol) was added at 0°C. After addition, the mixture was stirred at 0°C for 1 h. The mixture was concentrated and azeotroped with toluene three times at 60°C on the rotavap to remove residual water and dried under high vacuum overnight to afford a white solid. The solid was broken into fine powder with a spatula and then suspended in 10 mL acetone on rotavap with rotation at atmosphere pressure for 5 min at 40°C. The suspension was filtered through Celite. Acetone (5 mL) was added to the remaining solid in the flask and the procedure was repeated two more times. The combined filtrates were concentrated under vacuum. The solid obtained was dissolved in minimum amount of hot acetone (4 mL), and Et_2O (5 mL) was added to precipitate a white solid. The mixture was slowly cooled to room temperature, placed in ice bath for 1 h and in refrigerator for another 2 h. The mixture was filtered, and the white solid was collected and then dried under vacuum to afford 135.0 mg (14%) of the desired product **4e**. ^{1}H NMR (DMSO-d_6): δ 6.89–6.90 (m, 2H), 6.62–6.64 (m, 2H), 3.65 (s, 3H), 1.37 (br, 2H).

***6-(4-Methoxy benzyl)-1-isopropyl-4-nitro-1H*-benzo[*d*]imidazole (5e).** A dry microwave tube with a stir bar was charged with 1-isopropyl-4-nitro-1*H*-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (176.5 mg, 0.50 mmol), potassium (4-methoxybenzyl)trifluoroborate (135.0 mg, 0.60 mmol), Cs_2CO_3 (488.73 mg, 1.5 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (40.83 mg, 0.05 mmol). The microwave tube was capped with a rubber septum and subjected to vacuum/N_2 purge cycles three times. Degassed deionized water (0.5 mL) and THF (5 mL) were added via syringe. The rubber septum was quickly removed and replaced with the microwave tube cap, and the mixture was subjected to microwave irradiation at 250 W to maintain a temperature of 110°C for 2.5 h. After cooling down to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with brine and dried over magnesium sulfate. Filtration and then evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 80.0 mg of **5e** (50%). R_f 0.4 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 8.01 (d, J = 1.38 Hz, 1H), 7.50 (d, J = 1.36 Hz, 1H), 7.13 (d, J = 8.74 Hz, 2H), 6.87 (d, J = 8.71 Hz, 2H), 4.63 (m, 1H), 4.14 (s, 2H), 1.63 (d, J = 6.75 Hz, 6H). HRMS (EI) Calcd. for $C_{18}H_{19}N_3O_3$: 326.1499 [M + H^+]. Found 326.1500 [M + H^+], 348.1317 [M + Na^+].

***1-Cyclopentyl-6-methoxy-4-nitro-1H*-benzo[*d*]imidazole (9).** A 500 mL one-neck flask was charged with 5-methoxy-3-nitrobenzene-1,2-diamine (3.67 g, 20.0 mmol), $NaBH(OAc)_3$ (12.71 g, 60.0 mmol), THF (60 mL), cyclopentanone (8.948 mL, 100.0 mmol), and formic acid (2.26 mL, 60.0 mmol). The mixture was stirred overnight. The solvent was removed *in vacuo*, and the dark red residue was dissolved in formic acid (60 mL). Butylated hydroxytoluene (20 mg) was added, and the mixture was cooled to 0°C. Concentrated HCl (80 mL) was added, and the mixture was heated to reflux with a heating mantle. After maintaining reflux for 25 min, most of the solvent was removed *in vacuo* at 80°C. The aqueous solution was neutralized with saturated potassium carbonate solution to pH 8 and extracted with EA (50 mL × 4). The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA 1 : 1) to afford 2.1 g (40%) of **9** as a yellow solid (40%). R_f 0.32 (CH_2Cl_2/MeOH/NH_4OH 100 : 10 : 0.1). mp 107–108°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.79 (d, J = 2.32 Hz, 1H), 7.23(d, J = 2.3 Hz, 1H), 4.68–4.75 (m, 1H), 3.95 (s, 3H), 2.35–2.30 (m, 2H), 1.83–2.05 (m, 6H). *Anal*. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08; O, 18.37. Found: C,59.88; H, 5.84; N, 16.27.

1-Cyclopentyl-4-nitro-1H-benzo[d]imidazol-6-ol hydrobromide (10). A 50 mL microwave reactor tube was charged with 1-cyclopentyl-6-methoxy-4-nitro-1*H*-benzo[*d*]imidazole (0.75 g, 2.87 mmol) and 48% HBr (10 mL) and subjected to microwave irradiation at 250 W to maintain a temperature of 120°C for 2.5 h. The solvent was removed *in vacuo*. The resultant yellow solid was dissolved in a minimum amount of water. Solid Na_2CO_3 was added in small portions until the pH was 6. The mixture was filtered, and the yellow solid was collected then washed with water and dried under high vacuum pump to afford 0.6 g (85.7%) of **10**. R_f 0.36 (CH_2Cl_2/MeOH/NH_4OH 100 : 10 : 0.1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 2.17 Hz, 1H), 7.38 (d, J = 2.21 Hz, 1H), 4.81–4.87 (m, 1H), 2.15–2.21 (m, 2H), 1.70–1.96 (m, 6H). *Anal*. Calcd. for $C_{12}H_{13}N_3O_3$: 1.175. HBr: C, 42.09; H, 4.17; N, 12.27. Found: C, 42.13; H, 4.33; N, 12.12.

1-Cyclopentyl-4-nitro-1H-benzo[d]imidazol-6-yl trifluoromethanesulfonate (8). Solid K_2CO_3 (246.0 mg, 1.78 mmol) was added to a solution of 1-cyclopentyl-4-nitro-1*H*-benzo[*d*]imidazol-6-ol (220.0 mg, 0.89 mmol) and 4-nitrophenyl trifluoromethanesulfonate (265.5 mg, 0.979 mmol) in 5 mL of DMF. The suspension was stirred at room temperature for 4 h. Then the reaction mixture was diluted with EA (30 mL) and filtered. The filtrate was washed with water (20 mL × 5) and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent gave a yellow oil, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 290.0 mg of triflate **8** (86%). R_f 0.5 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 124–125°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.10 (d, J = 2.26 Hz, 1H), 7.74 (d, J = 2.27 Hz, 1H), 4.78–4.83 (m, 1H), 2.42–2.36 (m, 2H), 1.91–2.05 (m, 6H). *Anal*. Calcd. for $C_{13}H_{12}F_3N_3O_5S$: C, 41.16; H, 3.19; F, 15.03; N, 11.08; O, 21.09; S, 8.45. Found: C, 41.21; H, 3.15; N, 11.08.

6-Benzyl-1-cyclopentyl-4-nitro-1H-benzo[d]imidazole (11). A dry microwave tube with a stir bar was charged with 1-cyclopentyl-4-nitro-1*H*-benzo[*d*]imidazol-6-yl trifluoromethanesulfonate (500.0 mg, 1.31 mmol), potassium benzyltrifluoroborate (259.41 mg, 1.31 mmol), Cs_2CO_3 (640.23 mg, 1.965 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (106.98 mg, 0.131 mmol). The microwave tube was capped with a rubber septum and subjected to three vacuum/N_2 purge cycles. Degassed deionized water (0.8 mL) and THF (8 mL) were added via syringe. The rubber septum was quickly replaced with the microwave tube cap, and the mixture was subjected to microwave irradiation at 250 W to maintain 110°C for 1.8 h. After cooling down to room temperature, the mixture was filtered through Celite. The filtrate was extracted with EA. The combined extracts were washed with brine and dried over magnesium sulfate. Filtration then evaporation of the solvent gave a brown solid, which was subjected to silica gel column chromatography (Hex/EA/TEA 1 : 1 : 0.005) to afford 70.0 mg of the desired product (17%). R_f 0.45 (CH_2Cl_2/MeOH/NH_4OH 100 : 5 : 0.1). mp 145–147°C. ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H), 8.06 (d, J = 1.41 Hz 1H), 7.55(d, J = 1.46 Hz, 1H), 7.36 (m, 2H), 7.28 (m, 1H), 7.23 (dd, J = 1.41 Hz, J = 8.1 Hz, 2H), 4.75 (m,1H), 4.22 (s, 2H), 2.29–2.36 (m, 2H), 1.85–2.02 (m, 6H). *Anal*. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; O, 9.96. Found: C, 70.83; H, 5.88; N, 13.10.

Acknowledgments. The authors would like to thank Tim Fahrenholz for acquisition and analysis of high resolution mass spectral analysis and NIH (NINDS): 1R15NS057772 and NSF equipment grant for the NMR (NMR: CHE 0614785).

REFERENCES AND NOTES

[1] Molander, G. A.; Ham, J.; Seapy, D. G. Tetrahedron 2007, 63, 768.
[2] Fu, G. C. Acc Chem Res 2008, 41, 1555.
[3] Miyaura, N.; Suzuki, A. Chem Rev 1995, 95, 2457.
[4] Molander, G. A.; Figueroa, R. Aldrichimica Acta 2005, 38, 49.
[5] Darses, S.; Genet, J.-P. Chem Rev, 2008, 108, 288.
[6] Molander, G. A.; Ellis, N. Acc Chem Res 2007, 40, 275.
[7] Darses, S.; Genet, J.-P. Eur J Org Chem 2003, 4313.
[8] Molander, G. A.; Canturk, B. Angew Chem Int Ed 2009, 48, 9240.
[9] Doucet, H. Eur J Org Chem 2008, 12, 2013.
[10] Grimmett, M. R. Sci Synth 2002, 12, 529.
[11] Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. J Org Chem 2010, 75, 980.
[12] Iwahi, T.; Satoh, H.; Nakao, M.; Iwasaki, T.; Yamazaki, T.; Kubo, K.; Tamura, T.; Imada, A. Antimicrob Agents Chemother 1991, 35, 490.
[13] Lacey, E. Parasitol Today 1990, 6, 112.
[14] Brown, R. D.; Heffernan, M. L. J Chem Soc 1956, 540, 4288.
[15] Cheung, M.; Emmitte, K. A.; Salovich, J. M. US33683,2007030361 2007, (Smithkline Beecham Corp., USA), USA, 107.
[16] Flaherty, P. T.; Chopra, I.; Jain, P.; Yi, S.; Allen, E.; Cavanaugh, J. Bioorg Med Chem Lett 2010, 20, 2892.
[17] Molander, G. A.; Ito, T. Org Lett 2001, 3, 393.
[18] Flaherty, P. T.; Jain, P.; Yi, S.; Chopra, I.; Bleasdell, G.; Lipay, J.; Ferandin, Y.; Meijer, L.; Madura, J.D. Bioorg Med Chem 2011, 19, 359.
[19] Moore, M. D.; Jain, P.; Flaherty, P. T.; Wildfong, P. L. D. Acta Crystallogr Sect E: Struct Rep Online 2008 E64, o1336.
[20] Fuerstner, A.; Leitner, A. Angew Chem Int Ed 2002, 41, 609.
[21] Limmert, M. E.; Roy, A. H.; Hartwig, J. F. J Org Chem 2005, 70, 9364.
[22] Echavarren, A. M.; Stille, J. K. J Am Chem Soc 1987, 109, 5478.
[23] Zhou, J.; Fu, G. C. J Am Chem Soc 2003, 125, 12527.
[24] Takahashi, H.; Fukami, T.; Kojima, H.; Yamakawa, T.; Takahashi, H.; Sakamoto, T.; Nishimura, T.; Nakamura, M.; Yosizumi, T.; Niiyama, K.; Ohtake, N.; Hayama, T. Tetrahedron 2005, 61, 3473.
[25] Molander, G. A.; Sandrock, D. L. Org Lett 2007, 9, 1597.
[26] Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. J Org Chem 2003, 68, 5534.
[27] Molander, G. A.; Petrillo, D. E. Org Synth 2007, 84, 317.
[28] Wakefield, B. J.. Organomagnesium Methods in Organic Chemistry (Best Synthetic Methods); Academic Press: New York, 1995.
[29] Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. Synthesis Tetrahedron Lett 1997, 38, 3447.
[30] Gonzalez-Bobes, F.; Fu, G. C. J Am Chem Soc 2006, 128, 5360.