JOC The Journal of Organic Chemistry

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Suzuki-Miyaura Cross-Coupling Reactions of Unprotected Haloimidazoles

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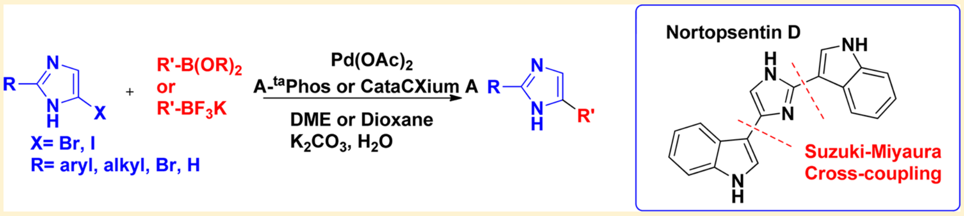
Ⓢ *Supporting Information*



ABSTRACT: An efficient protocol for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of unprotected haloimidazoles is reported. The relatively mild reaction conditions allow for ready access to a wide array of functionalized imidazole derivatives in good to excellent yields. The synthetic utility of this method is demonstrated by the total synthesis of nortopsentin D.

The Suzuki–Miyaura cross-coupling (SMC) reaction is one of the most widely utilized coupling reactions in the pharmaceutical industry due to the mild reaction conditions, functional group compatibility, and accessibility of the organoboron reagents.[1−3] The SMC reaction of heteroaryl halides is particularly useful, as heterocycles are ubiquitous in natural products and active pharmaceutical ingredients;[4,5] however, catalysis is sometimes inefficient due to competitive substrate and/or product inhibition, often requiring laborious protecting group strategies to recover reactivity.[6] In principle, SMC methods that can tolerate the Lewis basic functionality manifest in many heterocyclic motifs would be highly valued in parallel synthesis in endeavors.[4] To this end, our laboratories have been focusing on the development of SMC reactions of heterocyclic moieties.[7]

Imidazoles are an important class of structural motifs in many bioactive natural products and medicines. On the basis of extensive research by medicinal chemists, many imidazole-containing molecules have displayed promising pharmacological activities,[8] which makes them compelling targets for the synthetic community.[1,4,9] For instance, nortopsentin, a bis-indole alkaloid family isolated from the deep sea sponge *Spongosorites ruetzleri*, possesses potent antitumor, antiviral, and antiproliferative activities,[10] whereas the antiviral reagent BMS-790052 is used to treat chronic hepatitis C infections (Figure 1).[11]

Conventionally, imidazole derivatives can be synthesized from suitably functionalized acyclic precursors.[9] While such de novo synthetic strategies are attractive for manufacturing route development, they are suboptimal for fast exploration of structure–activity relationships, where time cycle concerns are paramount.[1,4] With these considerations in mind, we devised an SMC-based strategy where installation of the preconstructed imidazole ring could be accomplished in a single operation. At the onset of this work, only a limited number of examples of SMC reactions with haloimidazoles had been reported, many of which suffered from moderate yields and limited substrate scope and, in most cases, required protection of the imidazole NH group.[7c,12] To date, the unprotected haloimidazoles are recognized as a class of challenging substrates for transition-metal-catalyzed coupling reactions.[13] Undoubtedly, the lack of an efficient Pd-based catalyst has limited the employment of divergent SMC strategies toward functionalized imidazoles.[12] This apparent methodological gap prompted us to search for a more generalized active catalyst. Herein, we report our efforts toward an efficient palladium-catalyzed SMC protocol, which is amenable to unprotected haloimidazoles.

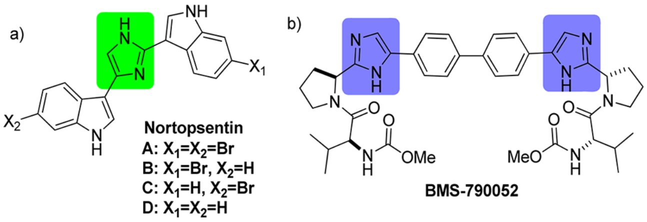


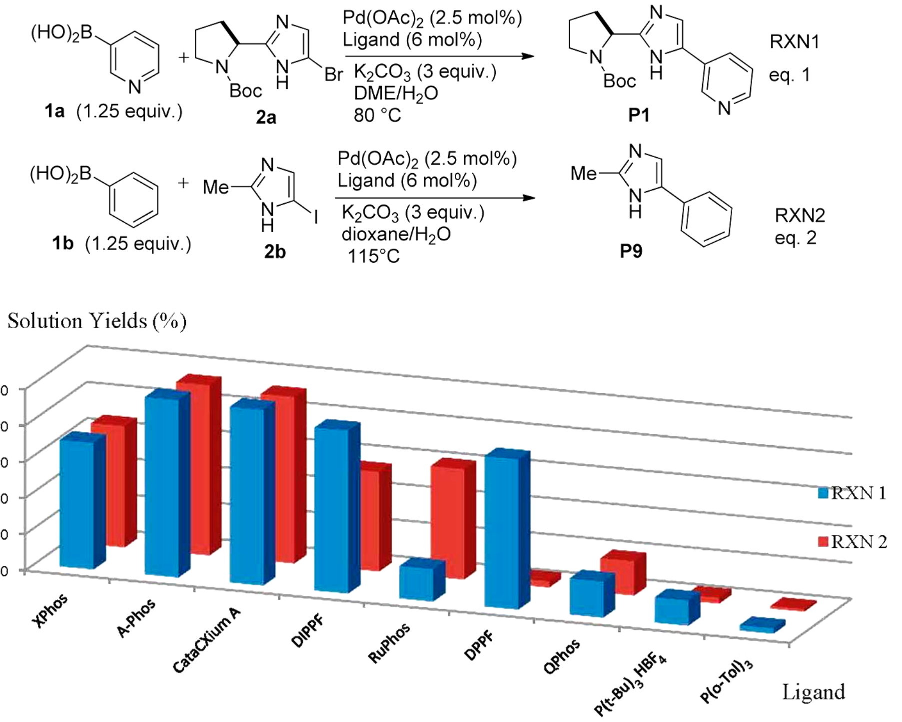
Figure 1. Imidazole-containing bioactive molecules.

Our studies commenced with the evaluation of the SMC reactions of 3-pyridylboronic acid (**1a**) and phenylboronic acid (**1b**) versus two imidazole halides: viz., (*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**2a**)[12f] (Chart 1, eq 1) and 2-methyl-4-iodoimidazole (**2b**), respectively (Chart 1, eq 2). High-throughput experimentation protocols developed within our catalysis and automation group were used to rapidly evaluate a series of electronically

Received: June 13, 2014
Published: August 20, 2014

dx.doi.org/10.1021/jo501326r

Chart 1. Phosphine Ligand Screen[a–c]



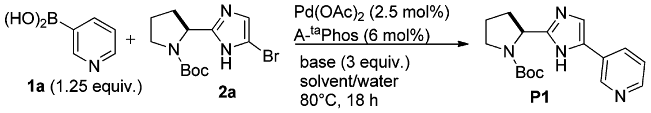
[a]Conditions: **2a**/**2b** (10 μmol), **1a**/**1b** (1.25 equiv), $Pd(OAc)_2$ (2.5 mol %), ligand (6 mol %), biphenyl (internal standard, 0.25 equiv), aqueous K_2CO_3 solution (0.025 mL, 1.2 M), and organic solvent (0.075 mL). [b]Solution yields. [c]Select ligands are shown. For details, see the Supporting Information.

and sterically diverse phosphine ligands.[14] Interestingly, XPhos, a highly efficient and general ligand for the SMC reactions,[2a,d,13a,15] gave moderate yields in both cases. In fact, of the 24 phosphine ligands evaluated,[14] only A-^{ta}Phos[16] and CataCXium A[17] provided the desired coupling products in excellent yields. The ligand 1,1′-bis(diphenylphosphino)-ferrocene (DPPF), which has been reported by Bellina et al. to catalyze the reaction of bromoimidazole exclusively with aromatic boronic acids,[12c] gave a lower yield than A-^{ta}Phos or CataCXium A.

After the most active ligand system was identified for the SMC reaction of haloimidazoles, an extensive survey of solvents and bases was conducted (Table 1). First, the reaction conditions for **1a** and **2a** were validated at the 0.2 mmol scale, giving the desired product **P1** with 95% isolated yield (entry 1). Other solvents, including toluene (PhMe), dimethylformamide (DMF), cyclopentyl methyl ether (CPME), 2-methyltetrahydrofuran (2-MeTHF), and dioxane, were investigated under otherwise identical reaction conditions, with only dioxane offering comparable results (entries 2–6). Evaluation of a series of inorganic bases also failed to further improve the yield (entries 7–9). Notably, when the catalyst loading was reduced to 1.0 mol %, the reaction still performed comparably, providing the desired coupling product in essentially the same yield (entry 10).[14]

A wide range of haloimidazoles and organoboron reagents was then examined to evaluate the scope of the reaction (Table 2). In all reactions of aryl- and vinylboron reagents with **2a**, the coupling products (**P2**–**P5**) were obtained in good yields (Table 2A). It is notable that boronic acids with attenuated nucleophilicity such as **1a** and 4-(ethoxycarbonyl)-phenylboronic acid (**1c**) also provided the coupling products **P1** and **P3** in 97 and 98% yields, respectively. Subjection of Molander's potassium organotrifluoroborates (R-BF_3K) to identical reaction conditions also led to the desired coupling products (**P1**, **P2**, **P5**) in similar yields, highlighting the versatility of this methodology with respect to the nucleophilic component.[18] The utility of this methodology for medicinal chemistry applications was further showcased by the coupling of various heteroaryl boronic acids.[4] Under the optimized reaction conditions, the resultant products (**P6**–**P8**) were all obtained with good yields. Next, 2-methylimidazole bromides

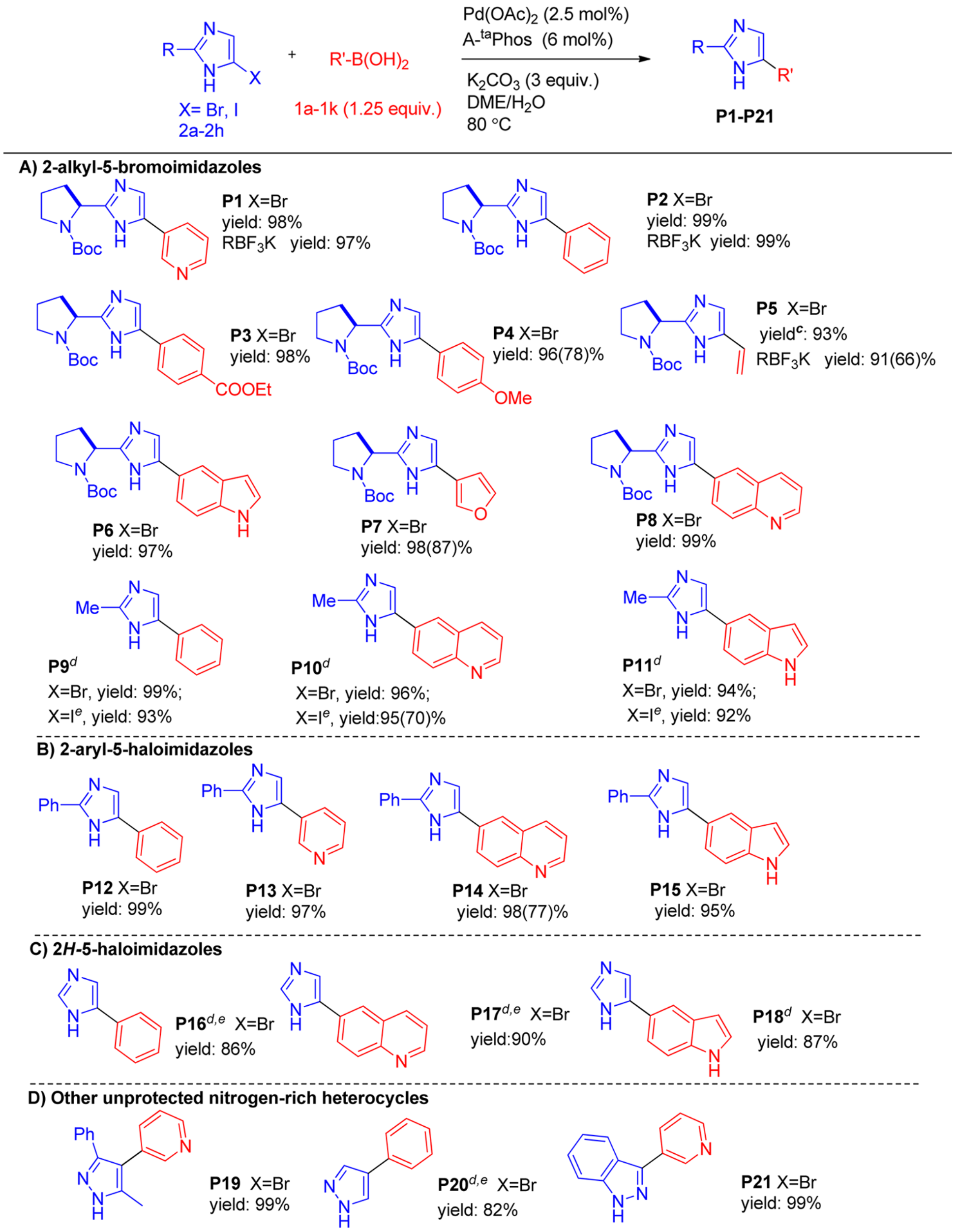
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	base	yield (%)[b]
1	DME	K_2CO_3	98 (95)[c]
2	DMF	K_2CO_3	94
3	PhMe	K_2CO_3	3
4	CPMe	K_2CO_3	21
5	2-MeTHF	K_2CO_3	88
6	dioxane	K_2CO_3	97
7	DME	K_3PO_4	93
8	DME	Na_2CO_3	90
9	DME	Cs_2CO_3	85
10[d]	DME	K_2CO_3	99

[a]Conditions: **2a** (10 μmol), **1a** (1.25 equiv), $Pd(OAc)_2$ (2.5 mol %), A-^{ta}Phos (6 mol %), base (3 equiv), biphenyl (internal standard, 0.25 equiv), aqueous K_2CO_3 (0.025 mL, 1.2 M), and organic solvent (0.075 mL). [b]Solution yields. [c]Yield in parentheses is the isolated yield after column chromatography. [d]Catalyst loading: 1 mol %.

Table 2. Substrate Scope[a,b]



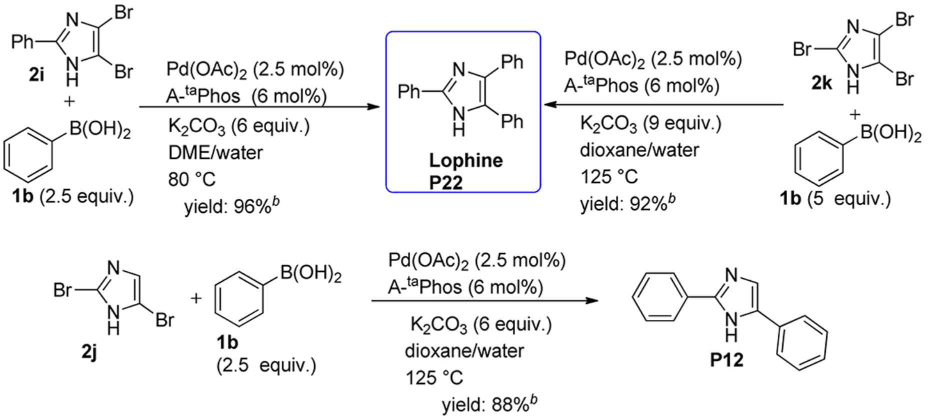
[a] Reaction performed on a 0.2 mmol scale. Yield determined by ^{1}H NMR analysis of unpurified reaction mixture using an IS. [b] Values in parentheses refer to isolated yields after supercritical fluid chromatography. [c] Vinyl MIDA boronate used. [d] Reaction run in dioxane at 115 °C. [e] CataCXium A used instead.

and iodides were both examined with various organoboronic acids, all of which underwent the SMC reaction to afford the desired products (**P9−P11**) in good yields, although a higher reaction temperature was required.[13a]

Since the 2,4(5)-diarylimidazoles had recently been identified as potential human sodium channel inhibitors, we next focused our attention on the SMC reaction of 2-phenyl-5-bromoimidazoles (Table 2B).[19] The reactions proceeded in good yield (**P12−P15**) for both aryl- and heteroarylboronic acids. In addition, 4-bromo-2*H*-imidazoles were coupled with a variety of aryl- and heteroarylboronic acids under the optimized reaction conditions to afford the corresponding SMC adducts **P16−P18** in good yields (Table 2C). Products such as these are suitable for further functionalization at the 2-position via direct arylation,[12c,20] thus providing orthogonal access to the 2,4(5)-disubstituted imidazoles. Although our initial studies focused on the arylation reaction of imidazoles, we next wondered whether other unprotected nitrogen-rich heterocycles would be suitable substrates. In fact, the coupling reactions of bromoindazoles and bromopyrazoles under similar reaction conditions also furnished the resultant products (**P19−P21**) in good yields, increasing the substrate scope of our method (Table 2D).

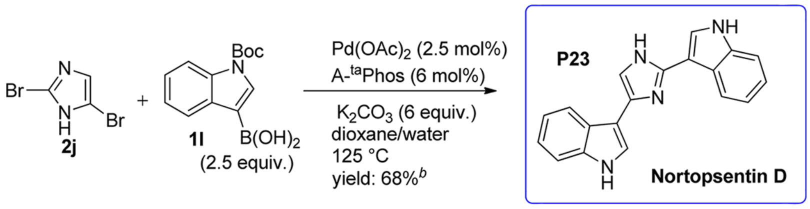
To further demonstrate the synthetic value of this protocol, we next sought to extend the reaction scope to di- and tribromoimidazoles (Scheme 1). To our delight, the double- and triple-SMC reactions proceeded efficiently to give the chemiluminescent molecule lophine **P22** in 96 and 92% yields from 4,5-di- and 2,4,5-tribromoimidazoles, respectively.[21] Next, we investigated the double-SMC reaction of 2,4-dibromoimi-

Scheme 1. SMC Reaction of Di- and Tribromoimidazoles[a]



[a]Reaction performed on a 0.3 mmol scale. [b]Yield determined by ^{1}H NMR of unpurified reaction mixture using an IS.

Scheme 2. Total Synthesis of Nortopsentin D[a]



[a]Reaction performed on a 0.3 mmol scale. [b]Yield determined by ^{1}H NMR of unpurified reaction mixture using an IS.

dazole (**2j**) with **1b**. In this case, a higher reaction temperature was required, resulting in a slightly diminished yield (88% yield) of the desired coupling product **P12**.[22]

Finally, we implemented this methodology in a total synthesis of nortopsentin D (Scheme 2).[23] The desired bis-indole alkaloid **P23** was prepared from commercially available **2j** and *N*-Boc-indole-3-boronic acid **1l**, using the conditions outlined in Scheme 2. A double-SMC reaction followed by in situ thermolysis of the Boc group afforded **P23** in 68% yield.[24] This concise synthesis represents the shortest route to nortopsentin D published to date, further underscoring the synthetic power of our protocol.

In conclusion, we have developed an efficient Pd-catalyzed Suzuki−Miyaura cross-coupling reaction of unprotected haloimidazoles. The broad substrate scope with respect to various aryl- and heteroarylboronic acids together with the mild reaction conditions enabled the rapid synthesis of a wide array of functionalized imidazoles. The synthetic utility of this protocol was demonstrated by synthesizing nortopsentin D from commercially available reagents in a two-step, one-pot process. In comparison to the classical approaches for imidazole synthesis, we anticipate that our methodology will provide an efficient alternative for divergent parallel synthesis efforts.

■ EXPERIMENTAL SECTION

General Methods. All reactions were carried out under a nitrogen atmosphere in a glovebox or using standard Schlenk techniques. The reactions were monitored by either analytical thin-layer chromatography using precoated silica gel plates with F254 indicator or reversed-phase UPLC MS. Visualization was accomplished by UV light (254 nm). The crude product could be purified either using a preparative thin-layer chromatography (TLC) plate or preparative supercritical fluid chromatography (SFC). The SFC conditions are optimized for purity consideration. Room temperature means 20 ± 1 °C. ^{1}H NMR spectra was recorded on a 400/500 MHz spectrometer at ambient temperature. Data are reported as follows: (1) chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm), MeOH-d_4 (3.31 ppm), DMSO-d_6 (2.50 ppm), and acetone-d_6 (2.05 ppm); (2) multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet); (3) coupling constants (Hz). ^{13}C NMR spectra were recorded on a 100/125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.16 ppm), MeOH-d_4 (49.15 ppm), DMSO-d_6 (39.51 ppm), and acetone-d_6 (29.92 ppm). Trifluoroacetic acid (TFA) was occasionally used as the additive for NMR experiments. HRMS data were obtained on a Q-TOF mass spectrometer. All commercial materials were used as received unless otherwise noted.[14]

General Procedures for SMC Reactions in Table 2. In an oven-dried microwave vial were placed heteroaryl halide (0.2 mmol, 1.00 equiv), boronic acid (0.25 mmol, 1.25 equiv), and 1.0 mL of solvent (DME or dioxane) in a glovebox. A premixed solution of palladium(II) acetate (0.0075 mmol, 2.5 mol %) and ligand (A-^{ta}Phos or CataCXium A (0.0018 mmol, 6 mol %)) in 0.50 mL of dioxane or DME was then added followed by the final addition of the aqueous K_2CO_3 solution (0.50 mL, 1.2 M). At this point, the microwave vial was sealed and brought out of the glovebox. The mixture was then heated to a certain reaction temperature and stirred vigorously for 18−24 h. After the UPLC-MS analysis indicated the complete consumption of starting materials, the reaction mixture was then cooled to room temperature and subsequently filtered through a short plug of Celite, the filter cake was washed with ethyl acetate (25 mL), and the combined organic solvents were removed in vacuo. The NMR yield was then determined using 1,3,5-trimethoxybenzene as internal standard (D1 needs to be set as 10 or 30). The crude product could be purified by either preparative SFC (MeOH/CO_2 or MeOH + diethylamine/CO_2) or preparative TLC plates (DCM/MeOH or EtOAc/MeOH). Compounds **P9**, **P12**, **P16**−**P18**, **P20**, and **P21** are known compounds.[14]

General Procedures for Reactions in Schemes 1 and 2. In a microwave vial were placed the heteroaryl halide (0.3 mmol, 1.00 equiv) and boronic acid (0.75 mmol, 2.5 equiv, or 1.5 mmol, 5 equiv) in 1.5 mL of dioxane or DME. A solution of palladium(II) acetate

(0.0075 mmol, 2.5 mol %) and ligand (A-^{ta}Phos or CataCXium A, 0.0018 mmol, 6 mol %) in 0.75 mL of 1,4-dioxane or DME was then added followed by the final addition of an aqueous K_2CO_3 solution (0.75 mL, 2.4 or 4.8 M). The microwave vial was then sealed using a biotag cap equipped with a septum and brought out of the glovebox. The reaction mixture was heated to a certain reaction temperature and stirred vigorously. After the UPLC-MS analysis indicated the complete consumption of starting materials, the reaction mixture was then cooled to room temperature and subsequently filtered through a short plug of Celite, the filter cake was washed with ethyl acetate (25 mL), and the combined organic solvents were removed in vacuo. The NMR yield was then determined using 1,3,5-trimethoxybenzene as internal standard (D1 needs to be set as 10 or 30). The crude products could be purified by either preparative SFC (MeOH/CO_2 or MeOH + diethylamine/CO_2) or preparative TLC plates (DCM/MeOH or EtOAc/MeOH). Compounds **P22** and **P23** are known compounds.[14]

*(S)-tert-Butyl 2-(5-(Pyridin-3-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P1**).* For reaction with boronic acids, 98% yield (62 mg). For reaction with potassium organotrifluoroborates, 97% yield (61 mg). White solid. Mp: 86−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (s, 1H), 8.47 (s, 1H), 8.04 (d, J = 6.8 Hz, 1H), 7.31 (s, 2H) 4.99−4.98 (m, 2H), 3.44−3.43 (m, 1H), 2.99−2.96 (m, 1H), 2.34−1.95 (m, 3H), 1.49−1.37 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 150.2, 147.2, 146.1, 145.1, 132.2, 130.0, 123.7, 115.0, 80.5, 54.2, 47.4, 32.9, 28.5, 28.3, 24.8. MS: calcd for $C_{17}H_{22}N_4O_2$ $[M - H]^+$ 315.1816, found (ES+) 315.1826.

*(S)-tert-Butyl 2-(5-Phenyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P2**).* Yield: 99% (61 mg). Light yellow oil. ^{1}H NMR (400 MHz, MeOH-d_4): 7.67 (d, 7.32 Hz, 2H), 7.36−7.19 (m, 4H), 4.98−4.85 (m, 1H), 3.69−3.65 (m, 1H), 3.52−3.46 (m, 1H), 2.36−1.88 (m, 4H), 1.46−1.22 (m, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 156.6, 156.2, 152.6, 152.1, 139.9, 134.7, 134.4, 129.8, 134.7, 134.4, 129.8, 128.7, 127.9, 125.9, 116.9, 81.3, 57.2, 56.7, 48.4, 47.9, 35.1, 33.8, 28.9, 28.6, 25.3, 24.8. MS: calcd for $C_{18}H_{23}N_3O_2$ $[M - H]^+$ 314.1863, found (ES +) 314.1860.

*(S)-tert-Butyl 2-(5-(4-(Ethoxycarbonyl)phenyl)-1H-imidazol-2-yl)-pyrrolidine-1-carboxylate (**P3**).* NMR yield, 98% (75 mg); isolated yield, 78% (60 mg). Yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): 12.18 (s, 1H), 7.93−7.86 (m, 3H), 7.65 (m, 1H), 4.85−4.79 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.55 (s, 1H), 3.36 (s, 1H), 2.25−2.18 (m, 1H), 1.98−1.84 (m, 3H), 1.39−1.15 (m, 12H). ^{13}C NMR (100 MHz, DMSO): 165.6, 153.8, 153.3, 151.3, 150.6, 138.8, 137.1, 134.2, 129.5, 127.8, 127.0, 123.9, 115.8, 78.6, 78.2, 60.4, 55.1, 54.6, 46.5, 46.3, 33.2, 31.8, 28.1, 27.8, 23.8, 23.1, 14.2. MS: calcd for $C_{21}H_{27}N_3O_4$ $[M - H]^+$ 386.2074, found (ES+) 386.2061.

*(S)-tert-Butyl 2-(5-(4-Methoxyphenyl)-1H-imidazol-2-yl)-pyrrolidine-1-carboxylate (**P4**).* Yield: 98% (67 mg). Yellow oil. ^{1}H NMR (400 MHz, MeOH-d_4): 7.59 (d, J = 8.2 Hz, 2H), 7.16−7.12 (m, 1H), 6.92 (d, J = 8.6 Hz, 2H), 4.86−4.83 (m, 1H), 3.79 (s, 1H), 3.70−3.64 (m, 1H), 3.52−3.46 (m, 1H), 2.37−2.27 (m, 1H), 2.02−1.88 (m, 3H), 1.46−1.23 (m, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 160.3, 156.6, 156.2, 152.2, 151.7, 127.2, 115.2, 81.3, 57.2, 56.7, 55.8, 48.4, 47.9, 35.1, 33.8, 28.9, 28.6, 25.3, 24.8. MS: calcd for $C_{19}H_{25}N_3O_3$ $[M - H]^+$ 344.1969, found (ES+) 344.1970.

*(S)-tert-Butyl 2-(5-Vinyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P5**).* For reaction with organoboronate, yield: 93% (49 mg). For reaction with potassium organotrifluoroborates, NMR yield: 91% (48 mg); isolated yield: 66% (35 mg). Light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): 9.59 (s, 1H), 7.02−6.89 (m 1H), 6.55 (dd, J = 17.6, 11.2 Hz, 1H), 5.52 (d, J = 17.6 Hz, 1H), 5.10 (d, J = 11.2 Hz, 1H), 4.95−4.94 (m, 1H), 3.58−3.36 (m, 2H), 3.81 (m, 1H), 2.17−1.92 (m, 3H), 1.48−1.36 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 156.3, 149.4, 133.8, 125.9, 120.3, 111.8, 80.5, 54.0, 47.3, 32.7, 28.4, 24.8. MS: calcd for $C_{14}H_{21}N_3O_2$ $[M - H]^+$ 264.1707, found (ES+) 264.1696.

*(S)-tert-Butyl 2-(5-(1H-Indol-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P6**).* Yield: 97% (68 mg). Yellow amorphous solid. ^{1}H NMR (400 MHz, MeOH-d_4): 7.85 (s, 1H), 7.44−7.37 (m, 2H), 7.21−7.13 (m, 2H), 6.45 (d, J = 2.9 Hz, 2H), 4.98−4.83 (m, 1H), 3.70−3.64 (m, 1H), 3.49−3.41 (m, 1H), 2.31−2.22 (m, 1H), 2.05−1.85 (m, 3H), 1.44−1.21 (m, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 156.7, 156.3, 151.8, 151.2, 139.3, 137.1, 129.9, 126.4, 125.0, 120.4, 117.6, 117.0, 112.5, 102.7, 81.3, 57.2, 56.6, 48.3, 47.9, 35.1, 33.6, 28.9, 28.7, 25.3, 24.8. MS: calcd for $C_{20}H_{24}N_4O_2$ $[M - H]^+$ 353.1972, found (ES+) 353.1975.

*(S)-tert-Butyl 2-(5-(Furan-3-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P7**).* NMR yield, 98% (59 mg); isolated yield, 87% (52 mg). Yellow oil. ^{1}H NMR (400 MHz, MeOH-d_4): 7.79 (s, 1H), 7.49 (s, 1H), 7.09−7.06 (m, 1H), 6.69 (s, 1H), 4.84−4.81 (m, 1H), 3.69−3.64 (m, 1H), 3.52−3.46 (m, 1H), 2.37−2.27 (m, 1H), 2.05−1.90 (m, 3H), 1.46−1.23 (m, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 156.6, 156.2, 152.3, 151.7, 144.7, 139.3, 120.5, 109.7, 81.3, 57.2, 56.7, 48.4, 47.9, 35.1, 33.8, 28.9, 28.6, 25.3, 24.8. MS: calcd for $C_{16}H_{21}N_3O_3$ $[M - H]^+$ 304.1656, found (ES+) 304.1664.

*(S)-tert-Butyl 2-(5-(Quinolin-6-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**P8**).* Yield: 99% (72 mg). White solid. Mp: 158−160 °C. ^{1}H NMR (400 MHz, MeOH-d_4): 8.73 (s, 1H), 8.31−7.95 (m, 4H), 7.55−7.46 (m, 2H), 5.01−4.91 (m, 2H), 3.68 (s, 1H), 3.52−3.48 (m, 1H), 2.37−2.31 (m, 1H), 2.04−1.93 (m, 3H), 1.45−1.23 (m, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 156.6, 156.1, 153.4, 152.9, 150.6, 148.0, 138.3, 134.5, 130.4, 129.5, 129.1, 123.5, 123.0, 114.7, 81.3, 57.3, 56.8, 48.4, 48.0, 35.1, 33.8, 28.9, 28.6, 27.5, 25.4, 24.8. MS: calcd for $C_{21}H_{24}N_4O_2$ $[M - H]^+$ 365.1972, found (ES+) 365.1973.

*6-(2-Methyl-1H-imidazol-5-yl)quinoline (**P10**).* For bromoimidazole: yield 96% (40 mg). For iodoimidazole: NMR yield, 95% (40 mg); isolated yield, 70% (29 mg). Yellow oil. ^{1}H NMR (500 MHz, MeOH-d_4): 8.74 (d, J = 4.5 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.49−7.47 (m, 2H), 2.44 (s, 1H). ^{13}C NMR (125 MHz, MeOH-d_4 + TFA): 151.0, 148.1, 147.5, 138.4, 137.5, 131.9, 130.3, 129.7, 128.7, 123.8, 123.2, 117.2, 13.2. MS: calcd for $C_{13}H_{11}N_3$ $[M - H]^+$ 210.1026, found (ES+) 210.1027.

*5-(2-Methyl-1H-imidazol-4-yl)-1H-indole (**P11**).* For bromoimidazole, yield 94% (37 mg). For iodoimidazole, yield 92% (36 mg). White solid. Mp: 111−114 °C. ^{1}H NMR (400 MHz, MeOH-d_4): 7.832−7.827 (dd, J = 2.4, 0.7 Hz 1H), 7.43−7.37 (m, 2H), 7.23 (d, J = 4.0 Hz, 1H), 7.12 (s, 1H), 6.46 (dd, J = 4.0, 0.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4 + TFA): 146.0, 139.2, 137.1, 129.9, 126.3, 125.0, 120.2, 117.3, 116.7, 112.5, 102.7, 13.2. MS: calcd for $C_{12}H_{11}N_3$ $[M - H]^+$ 198.1026, found (ES+) 198.1025.

*3-(2-Phenyl-1H-imidazol-5-yl)pyridine (**P13**).* Yield: 97% (43 mg). Yellow solid. Mp: 146−148 °C. ^{1}H NMR (500 MHz, MeOH-d_4): 8.98 (s, 1H), 8.41 (d, J = 4.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.93 (t, J = 7.0 Hz, 2H), 7.70 (s, 1H), 7.48−7.39 (m, 4H). ^{13}C NMR (100 MHz, MeOH-d_4 + TFA): 149.3, 147.5, 145.7, 136.5, 136.0, 131.3, 130.8, 130.4, 129.4, 127.3, 126.1, 118.8. MS: calcd for $C_{14}H_{11}N_3$ $[M - H]^+$ 222.1026, found (ES+) 222.1031.

*6-(2-Phenyl-1H-imidazol-5-yl)quinoline (**P14**).* NMR yield, 98% (53 mg); isolated yield, 77% (42 mg). Yellow amorphous solid. ^{1}H NMR (400 MHz, MeOH-d_4): 8.73 (dd, J = 4.3, 2.0 Hz, 1H), 8.32−8.27 (m, 2H), 8.16 (dd, J = 8.8, 1.9 Hz, 1H), 8.00−7.94 (m, 3H), 7.65 (s, 1H), 7.48−7.45 (m, 3H), 7.42−7.39 (m, 1H). ^{13}C NMR (100 MHz, MeOH-d_4 + TFA): 151.0, 148.8, 147.8, 138.9, 138.3, 131.5, 131.0, 130.4, 130.2, 129.5, 129.1, 128.8, 127.4, 124.7, 123.3, 119.2. MS: calcd for $C_{18}H_{13}N_3$ $[M - H]^+$ 272.1182, found (ES+) 272.1186.

*5-(2-Phenyl-1H-imidazol-5-yl)-1H-indole (**P15**).* Yield: 95% (49 mg). Colorless oil. ^{1}H NMR (400 MHz, MeOH-d_4): 7.96−7.94 (m, 3H), 7.52−7.50 (m, 13H), 7.47−7.34 (m, 5H), 7.24 (d, J = 3.1 Hz, 1H), 6.49 (dd, J = 3.2, 0.6 Hz, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): 148.2, 140.6, 137.3, 131.8, 130.0, 129.9, 129.7, 126.7, 126.5, 124.5, 120.7, 119.8, 118.1, 112.6, 102.8. MS: calcd for $C_{17}H_{13}N_3$ $[M - H]^+$ 260.1182, found (ES+) 260.1191.

*3-(5-Methyl-3-phenyl-1H-pyrazol-4-yl)pyridine (**P19**).* Yield: 99% (46 mg). Brown oil. ^{1}H NMR (500 MHz, MeOH-d_4): 8.42 (dd, J = 4.8, 1.0 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 7.67−7.65 (dt, J = 7.9, 1.9 Hz,1H); 7.40 (dd, J = 7.9, 4.7 Hz, 1H), 7.300−7.297 (m, 4H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4 + TFA): 148.5, 145.8, 143.8, 142.2, 133.3, 129.9, 129.6, 129.5, 126.4, 114.1, 10.9. MS: calcd for $C_{15}H_{13}N_3$ $[M - H]^+$ 236.1182, found (ES+) 236.1177.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving optimization details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.T. is grateful to the Merck Postdoctoral Research Fellows Program for financial support and the MRL Catalysis and Automation Group for making available the use of the instrumentation for this study. We thank Dr. Matthew Tudge for advices on manuscript preparation, Rong-Sheng Yang for obtaining HRMS data, and Dr. Dan DiRocco and Dr. Peter Dormer for assistance with LCMS and NMR experiments, respectively.

■ REFERENCES

(1) (a) *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*; Molnár, A., Ed.; Wiley-VCH: Weinheim, Germany, 2013. (b) *Applications of Transition Metal Catalysis in Drug Discovery and Development*; Crawley, M. L.; Trost, B. M., Eds.; Wiley: New York. 2012. (c) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027.

(2) (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314. (c) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (e) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (f) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(3) (a) Wong, S. M.; So, C. M.; Kwong, F. Y. *Synlett* **2012**, 1132. (b) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J.-L. *Chem. Soc. Rev.* **2011**, *40*, 3895. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

(4) (a) *Heterocyclic Chemistry in Drug Discovery*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2013. (b) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208. (c) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (d) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *Adv. Biol. Res.* **2011**, *5*, 120. (e) Broughton, H. B.; Watson, I. A. *J. Mol. Graph. Mod.* **2004**, *23*, 51. (f) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ocariz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869.

(5) (a) *Heterocycles from Transition Metal Catalysis: Formation and Functionalization*; Kotschy, A., Timári, T., Eds.; Springer: Dordrecht, The Netherlands, 2005. (b) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (c) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(6) (a) Knochel, P.; Schade, M. A.; Bernhardt, S.; Manolikakes, G.; Metzger, A.; Piller, F. M.; Rohbogner, C. J.; Mosrin, M. *Beilstein J. Org. Chem.* **2011**, *7*, 1261. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Oberli, M. A.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 4606. (d) Billingsley, K.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484. (e) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

(7) (a) Dai, X.; Chen, Y. G.; Garrell, S.; Liu, H.; Zhang, L.-K.; Palani, A.; Hughes, G.; Nargund, R. *J. Org. Chem.* **2013**, *78*, 7758. (b) Schmink, J. R.; Tudge, M. T. *Tetrahedron Lett.* **2013**, *54*, 15. (c) Strotman, N. A.; Chobanian, H. R.; He, J.; Guo, Y.; Dormer, P. G.; Jones, C. M.; Steves, J. E. *J. Org. Chem.* **2010**, *75*, 1733. (d) Kuethe, J. T.; Childers, K. G. *Adv. Synth. Catal.* **2008**, *350*, 1577. (e) Cai, C.; Chung, J. Y. L.; McWilliams, J. C.; Sun, Y.; Shultz, C. S.; Palucki, M. *Org. Process Res. Dev.* **2007**, *11*, 328. (f) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875. (g) Chen, C.-Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633. (h) Yasuda, N. *J. Organomet. Chem.* **2002**, *653*, 279 and references therein.

(8) (a) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143. (b) Shalini, K.; Sharma, P. K.; Jumar, N. *Chem. Sin.* **2010**, *1*, 36. (c) Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. *Pharm. Sin.* **2010**, *1*, 172. (d) De, L. L. *Curr. Med. Chem.* **2006**, *13*, 1. (e) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931.

(9) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic: San Diego, CA, 1997.

(10) (a) Carbone, A.; Pennati, M.; Parrino, B.; Lopergolo, A.; Barraja, P.; Montalbano, A.; Spanò, V.; Sbarra, S.; Doldi, V.; De Cesare, M.; Cirrincione, G.; Diana, P.; Zaffaroni, N. *J. Med. Chem.* **2013**, *56*, 7060. (b) Carbone, A.; Parrino, B.; Spanò, V.; Barraja, P.; Cirrincione, G.; Diana, P.; Maier, A.; Kelter, G.; Fiebig, H.-H. *Mar. Drugs* **2013**, *11*, 643. (c) Diana, P.; Carbone, A.; Barraja, P.; Kelter, H. H.; Fiebig, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2010**, *18*, 4524.

(11) Fridell, R. A.; Qiu, D.; Valera, L.; Wang, C. F.; Rose, R. E.; Gao, M. *J. Virol.* **2011**, *85*, 7312.

(12) (a) Sandtorv, A. H.; Bjørsvik, H. *Adv. Synth. Catal.* **2013**, *355*, 3231. (b) Bellina, F.; Cauteruccio, S.; Fiore, A. D.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436. (c) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543. (d) Langhammer, I.; Erker, T. *Heterocycles* **2005**, *65*, 1975. (e) Zhong, Y.-L.; Lee, J.; Reamer, R. A.; Askin, D. *Org. Lett.* **2004**, *6*, 929. (f) Mangion, I. K.; Chen, C.-Y.; Li, H. M.; Maligres, P.; Chen, Y. G.; Christensen, M.; Cohen, R.; Jeon, I.; Klapars, A.; Krska, S.; Nguyen, H.; Reamer, R. A.; Sherry, B.; Zavialov, I. *Org. Lett.* **2014**, *16*, 2310.

(13) (a) Düfert, M. A.; Billingsley, K. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 12877. (b) Yang, Y.; Oldenhius, N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 615. (c) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57. (d) Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

(14) For details, see the Supporting Information.

(15) (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(16) (a) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787. (b) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104.

(17) (a) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (b) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056.

(18) (a) Molander, G. A.; Jean-Gérard, L. *Org. React.* **2013**, *79*, 1. (b) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240 and references therein.

(19) (a) Fantini, M.; Rivara, M.; Zuliani, V.; Kalmar, C. L.; Vacondio, F.; Silva, C.; Baheti, A. R.; Singh, N.; Merrick, E. C.; Katari, R. S.; Cocconcelli, G.; Ghiron, C.; Patel, M. K. *Bioorg. Med. Chem.* **2009**, *17*, 3642. (b) Rivara, M.; Baheti, A. R.; Fantini, M.; Cocconcelli, G.; Ghiron, C.; Kalmar, C. L.; Singh, N.; Merrick, E. C.; Patel, M. K.; Zuliani, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5460.

(20) (a) Joo, J. M.; Tourré, B. B.; Sames, D. *J. Org. Chem.* **2010**, *75*, 4911. (b) Yang, X.-D.; Li, L.; Zhang, H.-B. *Helv. Chim. Acta* **2008**, *91*, 1435.

(21) White, E. H.; Harding, M. J. C. *J. Am. Chem. Soc.* **1964**, *86*, 5686.

(22) The major byproducts were from homocoupling reactions. For reference, see: Cliff, M. D.; Pyne, S. G. *Synthesis* **1994**, 681.

(23) (a) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121. (b) Kaswasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085. (c) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1994**, *44*, 1831.

(24) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.