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Regioselective Cross-Coupling Reactions of Boronic Acids with Dihalo Heterocycles

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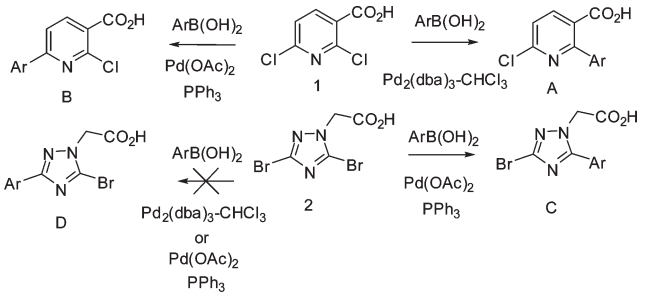
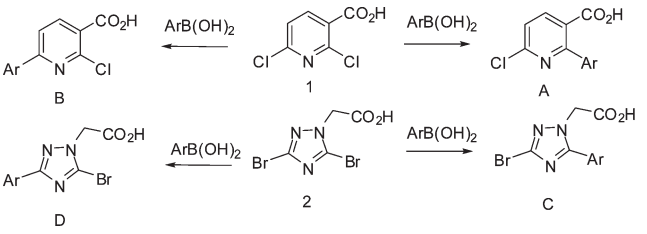


The carboxylic acid anion moiety has been used as a tunable directing group in the cross-coupling reaction of 2,6-dichloronicotinic acid and 2,5-dibromo-1,2,4-triazole derivatives producing selectively the 2- or 6-substituted nicotinic acids, while only the 5-substituted triazoles were obtained under a variety of conditions.

Selective functionalization of core structures to induce structural diversity has long been a goal of synthetic chemists and particularly medicinal chemists.[1] In connection with a Discovery program, we sought to provide such diversifying methodology using our tunable carboxylate-directed cross-coupling reactions of electronically equivalent dihalo aromatics and applying it to two selected key templates involving nicotinic acid **l** and triazoleacetic acid **2** (Scheme 1).[2] In this paper, we describe the successful application of this methodology and the significant differences observed in

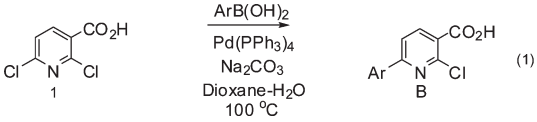
SCHEME 1. Selective Carboxylate-Directed Coupling of 1 and 2



the chemistry of the heterocycles **1** and **2** compared to the carbocyclic analogues.

In contrast to the amide and carbamate[3] functionalities, the directing effect of the carboxylate anion[4] has not been extensively studied, most likely due to its weaker directing "power" in reactions such as *ortho*-metalations or C−H activations.[5] The Yu group recently demonstrated, in an elegant series of studies, the ability of the sodium carboxylate group to effect the site-specific *ortho*-C−H activation of benzoic acid derivatives followed by cross-coupling reactions, halogenations and other useful elaborations.[6] Very recently, they have also used carboxamide derivatives to affect the hitherto unprecedented C−H activation of the pyridine ring followed by cross-coupling with a variety of aryl bromides.[7]

More closely related to our work, Wen and co-workers (eq 1)[8] have achieved regioselective coupling of arylboronic acids with **1** in the presence of $Pd(PPh_3)_4$ in order to prepare 6-substituted chloronicotinic acid derivatives; however, the directing effect of the carboxylate, as the reason for the selectivity observed, was not examined in that work.



In addition, Yang and co-workers have demonstrated the directing effect of the easily deprotonated *secondary* amide function in effecting selective cross-coupling reactions of electronically equivalent 2,6-dichloronicotinamide derivatives. Interesting for our work is the demonstration, by the

(1) Several comprehensive reviews for the synthesis of such pharmacophores are available: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043.

(2) (a) Houpis, I. N.; Huang, C.; Nettekoven, U.; Chen, J. G.; Liu, R.; Canters, M. *Org. Lett.* **2008**, *10*, 5601. (b) Houpis, I. N.; Van Hoeck, J.-P.; Tilstam, U. *Synlett* **2007**, *14*, 2179.

(3) (a) Review: Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, *7*, 949. (b) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fuji, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183. (c) Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 689. (d) Li, L.; Wang, X.; Zhang, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2009**, *11*, 1309.

(4) Reviews: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.

(5) Representative examples of carboxylate-directed processes: Orthometalation reactions: (a) Anctil, E.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Anctil, E. J.-G.; Snieckus, V. In *Metal-Catalyzed Cross Couping Reactions*, 2nd ed.; Diedrich, F., De Meijere, A., Eds.; Wiley: New York, 2004; pp 761−814. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. For initial reports of the carboxylate directing effect see: (d) Maehara, A,; Tsurugi, H,; Satoh, V; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (e) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (f) Tanaka, D.; Stuart, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (g) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (h) Review: Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, *15*, 949. (i) For Cu-catalyzed carboxylate-directed aminations, see: Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270.

(6) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215.

(7) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.

(8) Ma, M.; Li, C.; Li, X.; Wen., K.; Liu, Y. A. *J. Heterocycl. Chem.* **2008**, *45*, 1847.

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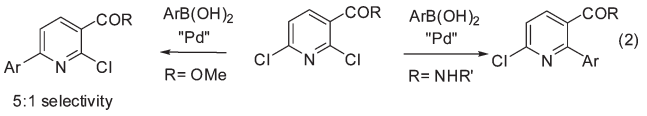
TABLE 1. Initial Screening of Reaction Conditions of 1 with Tolylboronic Acid

entry	catalyst[b]/ligand	solvent, T (°C)	base (equiv)	conc (%)	ratio of **3a**:**3b**:**3c**	HPLC yield[a] (%)	
1	$Pd_2(dba)_3$	NMP-H_2O, 50	LiOH (2.2)	30	17	ND	ND
2	$Pd_2(dba)_3$	NMP-H_2O, 50	Na_2CO_3 (2.2)	31	10	ND	ND
3	$Pd_2(dba)_3$	MeOH, 55	Na_2CO_3 (2.2)	51	33	< 1	2.7
4	$Pd_2(dba)_3$	MeOH, 55	LiOH (2.2)	45	27	3	5
5	$Pd_2(dba)_3$	MeOH, 55	Na_2CO_3 (**3.0**)	72	56	2.5	3.7
6	$Pd_2(dba)_3$	MeOH, 55	K_2CO_3 (**3.0**)	83	74	2	4
7	$Pd_2(dba)_3$	ethylene glycol, 70	K_2CO_3 (**3.0**)	81	69	4	8
8[c]	**$Pd_2(dba)_3$/$CHCl_3$**	**EtOH, 70**	**K_2CO_3 (3.0)**	**98**	**86**	**2**	**6**
9[d]	**$Pd(OAc)_2$/PPh_3**	**MeOH, 55**	**Na_2CO_3 (3.0)**	**99**	**0**	**86**	**2.2**
10	$Pd(OAc)_2$/PPh_3	H_2O, 100	Na_2CO_3 (3.0)	64	11	40	11
11	$Pd(OAc)_2$/PPh_3	MeOH, 55	Na_2CO_3 (4.0)	98	0	69	2.2

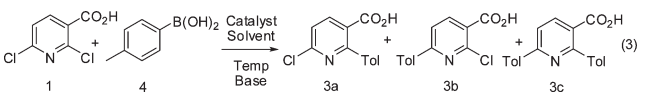
[a]The in situ yield was determined at 220 nm against a standard. [b]Commercial catalyst was used (3 mol %) unless otherwise noted. [c]1.5 mol % of catalyst used. The catalyst was recrystallized from $CHCl_3$; [d]3 mol % of catalyst was used. The Pd/PPh_3 ratio was 1:2.

same researchers, that the ester group exerts a predominantly "*para*-directing" effect (5:1 in favor of the 6-substitued nicotinic ester derivative) under reaction conditions similar to our own (eq 2).[9]



Again, the role of the carboxylate was not explored in determining the observed selectivity; however, the results elegantly corroborate our observations detailed below. Our work began by examining the cross coupling of 2,6-dichloronicotinic acid (**1**) with our model tolylboronic acid **4** (eq 3). Surprisingly, the reaction conditions that were most successful in the dihalobenzoic acid series[2a] proved totally ineffective for the nicotinic acid analogue, with only ca. 30% conversion with both LiOH and Na_2CO_3 (our most successful bases) in NMP−H_2O (our most successful solvent combination). Increasing the equivalents of base (between 2 and 4) or its nature (LiOH or Na_2CO_3) had no beneficial effect (Table 1, entries l and 2). Though the conversion was low in both cases, we were pleased to see that the selectivity was high, exclusively generating the 2-substituted product.

After significant investigation, we established that performing the reaction in an alcohol in the presence of 3 equiv of a carbonate base (Table 1, entries 3−8) gave high yields; EtOH and K_2CO_3 gave the highest conversion (98%) and isolated yield of **3a** (72%). A small amount of regioisomeric product **3b** also was formed along with 6% of the bis-arylation product (**3c**). Similarly to the observations of Yang et al., the presence of ca. 1−5% of water was essential for the success of the reaction. *The particle size of the carbonate was also crucial, and milled K_2CO_3 must be used for maximum yield*. Interestingly, we have not found any trace of substitution of the halide moieties by EtOH or water at either the 2- or 6-position of **1** as was observed previously.[9]



The reaction appears to have a relatively wide scope (Figure 1), affording good yields and selectivity with phenylboronic acids containing both electron-withdrawing and -donating substituents. However, our single attempt at using a heteroaromatic boronic acid was not successful (Figure 1, **9a**) due to competitive decomposition of the thiopheneboronic acid as observed by quantitative HPLC analysis.

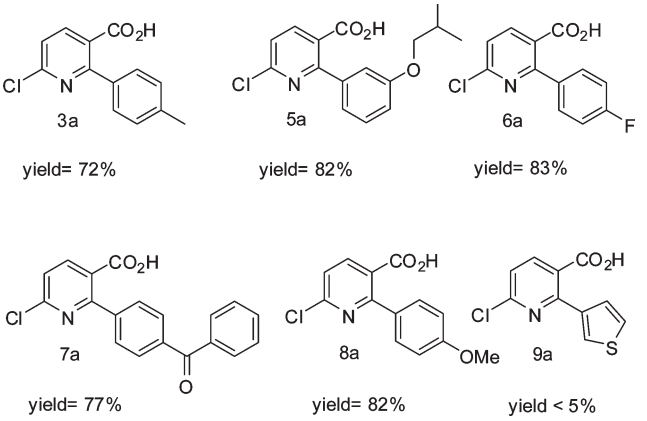


FIGURE 1. Isolated yields of the reaction of **1** with various $ArB(OH)_2$ using 1.5 mol % of $Pd_2(dba)_3/CHCl_3$ as catalyst.

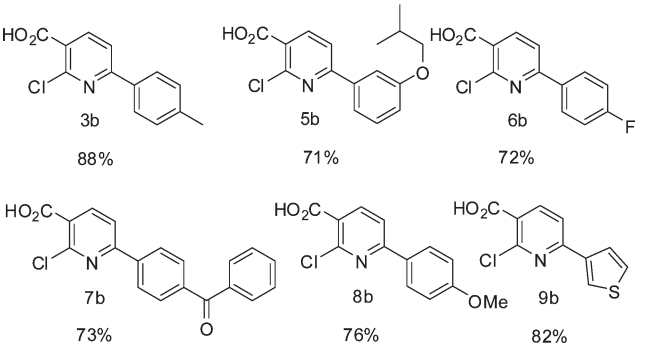


FIGURE 2. Isolated yields of the reaction of **1** with various $ArB(OH)_2$ using 3 mol % of $Pd(OAc)_2/PPh_3$ (1:2 ratio) as catalyst.

As observed in our previous work, employing phosphine ligands with $Pd(OAc)_2$ gave selectively the regioisomeric 6-substituted product **3b** with only traces of the bis-derivative **3c**. Surprisingly, PPh_3 afforded very high selectivity (Table 1, entry 9). This is an unexpected result since in the case of the carbocylic derivative 2,4-dibromobenzoic acid, PPh_3 gave a l:1 mixture of *ortho* to *para* products and DPEphos was required for higher selectivity (*ortho* to *para* = 1:9).[2a]

The mechanistic rationale for this interesting change in selectivity is not yet understood and is under active

(9) Yang, W.; Wang, Y.; Corte, J. R. *Org. Lett.* **2003**, *5*, 3131.

TABLE 2. Initial Screening of Reaction Conditions of 2 with Tolylboronic Acid 4

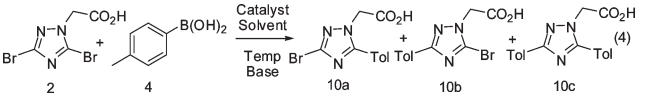
entry	catalyst/ligand	solvent T (°C)	base (equiv)	conc (%)	**10a**:**10b**:**10c** yield[a] (%)		
1[b]	$Pd_2(dba)_3/CHCl_3$	NMP−H_2O, 80	K_2CO_3 (3.2)	0			
2	$PdCl_2/PPh_3$ 1:2	NMP−H_2O, 80	K_2CO_3 (2.0)	96	51	3	4
3	$Pd_2(dba)_3/PPh_3$ (1:2)	NMP-H_2O, 80	K_2CO_3 (2.0)	97	63	4	7
4[c]	$PdCl_2/PPh_3$ 1:2	NMP−H_2O, 80 °C	Na_2CO_3 (2.0)	65	42	2	4
5[d]	$PdCl_2/PPh_3$ 1:4	NMP−H_2O, 80	Na_2CO_3 (3.0)	95	70	5	9
6	$PdCl_2/PPh_3$ 1:2	NMP-H_2O, 80	$NaHCO_3$ (3.0)	92	64	4	8
7	$(ACN)_2PdCl_2/PPh_3$ 1:2	NMP−H_2O, 80	Na_2CO_3 (3.0)	95	72	6	9
8[c]	**$Pd(acac)_2/PPh_3$ 1:2**	**NMP−H_2O, 80**	**Na_2CO_3 (3.0)**	**95**	**73**	**3**	**6**
9[d]	$Pd(acac)_2/PPh_3$ 1:2	NMP−H_2O, 80	Na_2CO_3 (3.0)	95	72	3	8

[a]The in situ yield % was determined at 220 nm against a standard. [b]Commercial catalyst was used (2 mol %) unless otherwise noted. [c]3.0 mol % catalyst was used. The catalyst was recrystallized from $CHCl_3$. [d]1 mol % of catalyst was used.

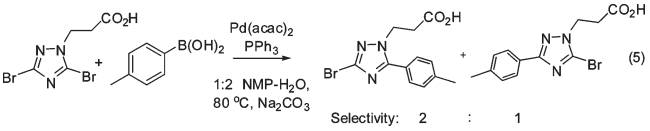
investigation.[10] The reaction is general and affords good yields and excellent selectivity with a variety of electron-rich or electron-poor boronic acids.

Under the conditions of entry 9 (Table 1), even thiopheneboronic acid afforded excellent results (Figure 2). Thus, we have shown that the carboxylic acid moiety serves as a tunable directing group for the preparation of either the 2- or 6- substituted nicotinic acids leaving the other site available for further elaboration.

A different picture emerged when we attempted to expand the scope of this reaction and examined the carboxylate directing effect in the case of the 1,2,4-triazole derivative **2** (eq 4). Reaction of the latter with boronic acid **4**, using Pd_2dba_3 (Table 2, entry 1), gave no product **10a**−**c** under a variety of conditions of solvent, base, or temperature. Intrigued, we evaluated a number of ligands, using robotic parallel experimentation, and we observed that only in the presence of phosphines did the reaction proceed at all. Even more remarkable was the fact that in all these successful "hits" (conversion > 60%) the major product was the C-5-substituted **10a** and not the distal coupling product **10b**, which would be expected in the presence of phosphine ligands based on all our previous experience. All our efforts to reverse the selectivity of this reaction have not been successful to date.[11] Similar results have been observed by Miethchen et al. in the case of 2,5-dihalohalo-4-glycosidyl-1,2,4-triazoles where 5-substituted products were obtained in cross-coupling reactions.[12] Whether this result is due to the intrinsic electron density at C-5 of triazoles or the result of the coordination of the Pd to carboxylate is debatable.[10]



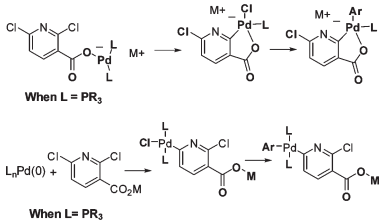
It can be argued that electronic factors predominate, rendering the C-5 position of the triazole electron deficient and thus promoting C-5 substitution, as put forth by Miethchen. However additional, albeit preliminary, results from our laboratory indicate that the carboxylate may have a profound effect on the site-selectivity. For example, the propionic acid derivative, which would have electronic properties similar to those of **2** but would involve a 7-membered palladacycle[10] transition state, only gives a 2:1 ratio of isomers favoring the 5-position (eq 5).



Thus, we believe that the coordination of the carboxylate determines the site of the initial oxidative addition. This conclusion is also supported by the results of Yang (eq 2), where substitution of the carboxylate by an ester, thus diminishing the coordination effects compared to a carboxylate ion, led to substitution at the distal C-6 position due to the steric effect we propose. Of course, the observed results can be due to a combination of electronic and coordinative effects to direct the oxidative addition and subsequent cross-coupling to C-5.

Being unable to tune the site of the coupling, we set out to optimize the reaction. From our screens, PPh_3 emerged as the most effective and inexpensive ligand, while NMP−H_2O (1:1) proved to be the best solvent combination. The optimization of the metal precursor, Pd/PPh_3 ratio, and base are shown in Table 2. Thus, $Pd(acac)_2$ (3 mol %) was a marginally superior Pd precursor (Table 2, entry 8), although most catalyst precursors performed well. Carbonate bases were somewhat more effective than hydroxide. The counterion was of little significance, although the equivalents of base are important (Table 2, entries 4 vs 8). Finally, it was determined that 80 °C was the best temperature to achieve reasonable reaction rates (reactions required ca. 18 h for completion).

(10) Our initial observations would tend to support that the selectivity is determined by the coordinating effect of the CO_2^- in the absence of phosphine ligands, while in the presence of phosphines the oxidative addition takes place in the less sterically encumbered position. As shown by us (eq 3) and Yang et al.,[9] under conditions where the formation of the palladacycle is not advantageous, the selectivity for the proximal reaction site is significantly reduced.



(11) A number of phosphines such as $H(PCy_3)BF_4$, *n*-$BuAd_2$, $BnPAd_2$, S-Phos, PPh_3, $(4\text{-MeO-}3,4\text{-Me-Ph})_3P$, $H(P\text{-}t\text{-}Bu_3)BF_4$, X-Phos, Xantphos, iPrPh-Im-Cl, and commercially available PEPPSI were investigated. The metal precursors were $Pd_2(dba)_3$, $Pd(OAc)_2$. Bases were chosen from K_2CO_3, K_3PO_4, KF, and Cs_2CO_3. Solvents included EtOH, MeOH, dioxane/H_2O, DMF/H_2O, and DMA/H_2O. Some product could be observed in all cases except in the case of the imidazolinium carbene ligands where no reaction was observed. In all cases, **10a** was formed predominantly in varying ratios with PPh_3 affording the best results.

(12) Wille, S.; Hein, M.; Miethchen, R. *Tetrahedron* **2006**, *62*, 3301.

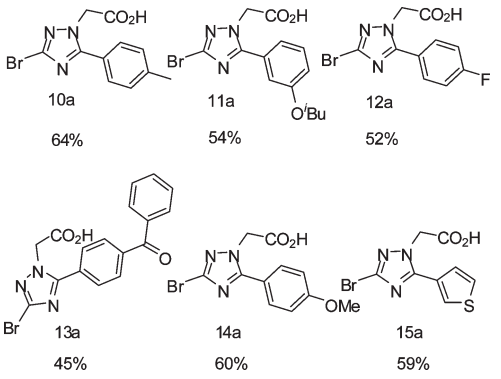


FIGURE 3. Isolated yields of the reaction of **2** with various ArB(OH)$_2$ using 3 mol % of Pd(OAc)$_2$/PPh$_3$ (1:2 ratio).

Combining these observations produced the most successful reaction (Table 2, entry 8) that afforded ca. 73% in situ yield of **10a**, while 3% and 6% of **10b** and **10c** were produced, respectively. The catalyst load can be decreased to 1 mol %, but significantly lower reaction rates were observed.

The reaction appears to be general with both electron-withdrawing and -donating benzeneboronic acids giving good in situ yields (>70%) of **l0a**−**l5a**, although the isolation of each product has not yet been optimized (Figure 3).

In conclusion, we have managed to extend our previously developed methodology, wherein the carboxylic acid moiety serves as a tunable directing group for the regioselective preparation of these pharmaceutically interesting 2- or 6-substituted heteroaromatic systems, with good control of the regiochemistry in the case of nicotinic acids.

In addition, we have developed conditions for effective cross-couplings involving 3,5-dibromo-1*H*-1,2,4-triazole-1-acetic acid and a variety of aromatic boronic acids to produce C-5 substituted 1,2,4-triazoleacetic acid derivatives.

Experimental Section

Representative experimental procedures for the preparation of compounds **3a**−**9a**:

3a. 2,6-Dichloronicotinic acid (0.57 g, 3 mmol), toluneboronic acid (3.3 mmol), and K_2CO_3 (1.24 g, 9 mmol) in EtOH (15 mL) were stirred under nitrogen. $Pd_2(dba)_3 \cdot CHCl_3$ (0.077 g, 0.075 mmol) was added, and the mixture was heated to 70 °C for 18 h until HPLC analysis indicated complete consumption of nicotinic acid (conversion >95%). The reaction mixture was cooled to 25 °C and filtered to remove the solids, and the filtrate was concentrated under vacuum and partitioned between a solution of CH_2Cl_2 (20 mL) and NaOH (1 M, 30 mL). The aqueous layer was acidified to pH = 2−3 by using citric acid (1 M) followed by extraction with EtOAc (2 × 20 mL). The combined EtOAc layers were dried over $MgSO_4$, filtered, and concentrated to give an off-white or yellowish residue which was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH (v/v 10/1) as eluent: ^{1}H NMR (DMSO, 400 MHz) 2.32 (3H, s, CH_3), 7.15 (2H, d, J = 8 Hz, Ar), 7.27 (1H, d, J = 8 Hz, Ar), 7.65 (1H, d, J = 8 Hz, Ar), 7.69 (2H, d, J = 8 Hz, Ar); ^{13}C NMR (DMSO, 400 MHz) 20.8, 121.9, 128.4, 136.5, 137.5, 137.8, 138.7, 146.1, 153.5, 171.1; HRMS calcd for $C_{13}H_{11}ClNO_2$ $[M + H]^+$ 248.0473, found 248.0467.

Representative experimental procedures for the preparation of compounds **3b**−**9b**:

3b. 2,6-Dichloronicotinic acid (1.92 g, 10 mmol), toluneboronic acid (11 mmol), Na_2CO_3 (3.18 g, 30 mmol), and PPh_3 (0.157 g, 0.6 mmol) in MeOH (40 mL) were stirred under nitrogen. Pd(OAc)$_2$ (0.067 g, 0.3 mmol) was added, and the mixture was heated to 55 °C for 18 h until HPLC indicated complete consumption of nicotinic acid (conversion >95%). The reaction mixture was cooled to 25 °C and filtered to remove the solid, and the filtrate was concentrated under vacuum. The residue was slurried in CH_2Cl_2 for 12 h and filtered to give an off-white or yellowish solid. This solid compound was dissolved in H_2O (200 mL) and then was acidified to pH = 2−3 by using citric acid (1 M) to form a precipitate. The precipitate was filtered, washed with 100 mL of water twice, and dried in the oven for 12 h to give white solid product: ^{1}H NMR (DMSO, 400 MHz) 2.35 (3H, s, CH_3), 7.32 (2H, d, J = 8 Hz, Ar), 8.0 (2H, d, J = 8 Hz, Ar), 8.03 (1H, d, J = 8 Hz, Ar), 8.26 (1H, d, J = 8 Hz, Ar); ^{13}C NMR (DMSO, 400 MHz) 21.3, 119.0, 125.9, 130.1, 133.7, 140.9, 141.9, 148.5, 158.7, 166.0; HRMS calcd for $C_{13}H_{11}ClNO_2$ $[M + H]^+$ 248.0473, found 248.0471.

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Supporting Information Available: Compound characterization data and copies of spectra supporting the structural assignments. This material is available free of charge via the Internet at http://pubs.acs.org.