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(DPEPhos)Ni(mesityl)Br: An Air-Stable Pre-Catalyst for Challenging Suzuki–Miyaura Cross-Couplings Leading to Unsymmetrical Biheteroaryls

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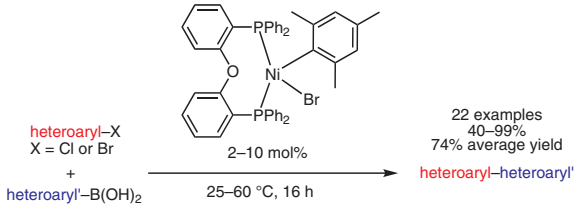

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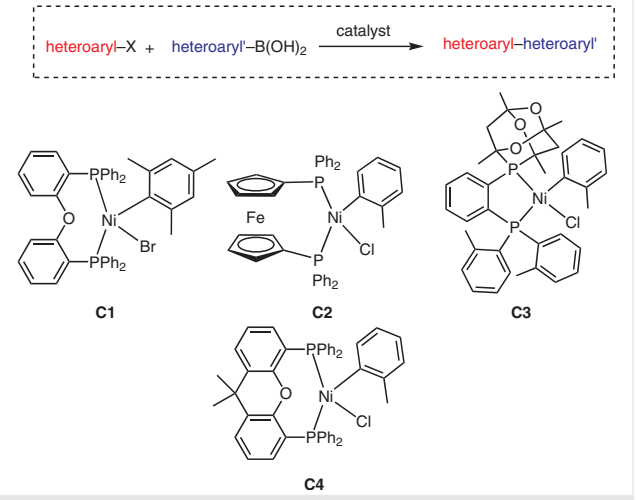
Abstract The successful application of (DPEPhos)Ni(mesityl)Br (C1) as a pre-catalyst in the Suzuki–Miyaura cross-coupling of heteroaryl chlorides or bromides and heteroaryl boronic acids is reported. The use of C1 in this context allows for such reactions to be conducted under mild conditions (2 mol% Ni, 25 °C), including cross-couplings leading to unsymmetrical biheteroaryls. Successful transformations of this type involving problematic pyridinyl boronic acid substrates (10 mol% Ni, 60 °C) are also described.

Key words Suzuki–Miyaura, nickel, biheteroaryls, heteroaryl boronic acids, heteroaryl halides

The broad utility of the palladium-catalyzed cross-coupling of arylboron and aryl (pseudo)halide reagents (i.e., the Suzuki–Miyaura reaction, SM) in the assembly of biaryl-containing pharmaceuticals, natural products, conjugated materials, and fine chemicals was recognized in the awarding of the 2010 Nobel Prize in Chemistry.[1,2] Notwithstanding the now well-established nature of such transformations, important challenges remain with regard to new catalyst development and reaction scope. In an effort to circumvent the use of precious metals and to access new reactivity manifolds, there is significant interest in the establishment of SM catalysts featuring more abundant 3d transition metals. Base-metal catalysts of this type that are capable of effecting cross-couplings of heteroaryl electrophiles and heteroarylboron substrates (Scheme 1) represent particularly attractive targets, given the prevalence of the unsymmetrical biheteroaryl motif in biologically active compounds.[3] However, the synthesis of biheteroaryl compounds by use of SM cross-coupling protocols represents a potential challenge, owing in part to the possibility of catalyst inhibition by the substrate and/or product. Additionally, it has been shown that heteroaryl boronic acids are particularly prone to unwanted protodeborylation at elevated temperatures.[4]



Scheme 1 Targeted unsymmetrical biheteroaryl synthesis, and the precatalysts examined in this study

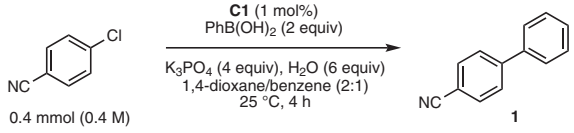
In this context, nickel has emerged as a viable alternative to palladium in challenging SM cross-coupling chemistry,[5] enabling transformations of heteroaryl halides, as well as phenol-derived electrophiles.[6] In a landmark publication by Ge and Hartwig,[7] air-stable (DPPF)Ni(cinnamyl)Cl (DPPF = 1,1′-bis(diphenylphosphino)ferrocene; 0.5 mol% Ni, 50–80 °C) was employed successfully as a pre-catalyst in the first highly effective nickel-catalyzed SM reactions employing heteroaryl chlorides or bromides and five-membered heteroaryl boronic acids, leading to unsymmetrical biheteroaryls. The lack of reactivity of pyridinyl boronic acids under the conditions employed was encountered as a limitation of this synthetic protocol.[7]

The use of single-component, air-stable pre-catalysts such as (DPPF)Ni(cinnamyl)Cl, as demonstrated by Ge and Hartwig,[7] provides practical advantages relative to commonly employed protocols employing air-sensitive $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) as the nickel source.[8] Building on this theme, Hazari and co-workers[9] subsequently demonstrated that air-stable (DPPF)Ni(*o*-tolyl)Cl,[10] initially reported by Buchwald and co-workers,[11] can be employed in room temperature cross-couplings of selected heteroaryl chlorides and benzo[*b*]furan-2-yl- or benzo[*b*]thien-2-yl-boronic acid (5 examples, 2.5 mol% Ni). Garg and co-workers[12] have reported on the successful application of $(PCy_3)_2NiCl_2$ as a pre-catalyst for SM cross-couplings of heteroaryl chlorides, bromides, mesylates, or sulfamates with 3-furanyl- or 3-thienyl-boronic acid, as well as 2-methoxy-3-pyridinyl-boronic acid (1–10 mol% Ni, ≥100 °C).[13] The latter transformations, while limited to a single pyridinyl nucleophile, represent the first and only successful nickel-catalyzed SM cross-couplings of pyridinyl boronic acids leading to unsymmetrical biheteroaryls. More recently, Ando et al.[14] documented the utility of Cp(NHC)NiCl (1 mol%)/PPh_3 (20 mol%) catalytic mixtures in the SM cross-coupling of heteroaryl chlorides or bromides with 3-furanyl- or 3-thienyl-boronic acid (90 °C), thus affording unsymmetrical biheteroaryls. The addition of PPh_3 in this catalyst system, while operationally inconvenient, proved crucial in suppressing homocoupling of the heteroaryl boronic acid.

Notwithstanding such progress, the nickel-catalyzed SM cross-coupling of heteroaryl halides and heteroaryl boronic acids remains relatively unexplored. As such, the identification of alternative nickel catalysts that are effective in providing access to unsymmetrical biheteroaryls with broad scope remains an important challenge. In this context, we recently reported on the development of (DPEPhos)Ni(mesityl)Br (**C1**, Scheme 1) for use in the C–N cross-coupling of heteroaryl halides and secondary amines or azoles;[15] notably, **C1** was found to perform competitively versus (DPPF)Ni(*o*-tolyl)Cl[11] (**C2**) in such transformations. On the basis of this finding, and our observation that the effective use of **C1** in C–N cross-couplings required activation with a catalytic amount of phenylboronic acid, we hypothesized that pre-catalyst **C1** would be well-suited to nickel-catalyzed SM cross-couplings. We report herein on the successful application of **C1**in the SM cross-coupling of heteroaryl chlorides or bromides and heteroaryl boronic acids. The use of **C1** in this context allows for a diversity of nickel-catalyzed SM cross-couplings to be achieved under mild conditions (2 mol% Ni, 25 °C), including transformations leading to unsymmetrical biheteroaryls. Successful transformations under more forcing conditions (10 mol% Ni, 60 °C) involving challenging pyridinyl boronic acid substrates are also described.

In an initial effort to probe the potential utility of **C1** in SM chemistry, we examined the room-temperature cross-coupling of 4-chlorobenzonitrile and phenylboronic acid using 1 mol% **C1** as outlined in Table 1. It was found that the use of a 1,4-dioxane:benzene (2:1) solvent mixture, in the presence of K_3PO_4 with added water, afforded high conversion into desired biaryl product **1** after 4 h; the use of alternative solvent media, base, or the exclusion of water afforded inferior results. The beneficial role of added water in this context may arise from the more facile formation of a putative (DPEPhos)Ni(aryl)OH species; such L_nM(aryl)OH complexes (M = Ni, Pd) have been shown to be more reactive towards transmetalation compared to analogous L_nM(aryl)X complexes (X = halide) in SM reactions.[16] Under optimized conditions, use of the DPPF pre-catalyst **C2** in place of **C1** gave only 50% conversion into **1**, showcasing the potential utility of **C1** in room-temperature SM reactions. Pre-catalysts based on PAd-DalPhos (**C3**)[17] or XantPhos (**C4**)[18] afforded no conversion of the substrates. Efforts to employ a reduced amount of base or phenylboronic acid led to inferior results, and the use of related boronic ester or potassium trifluoroborate reagents proved ineffective under these conditions.

Table 1 Optimization of Conditions and Pre-Catalyst Screening



0.4 mmol (0.4 M)

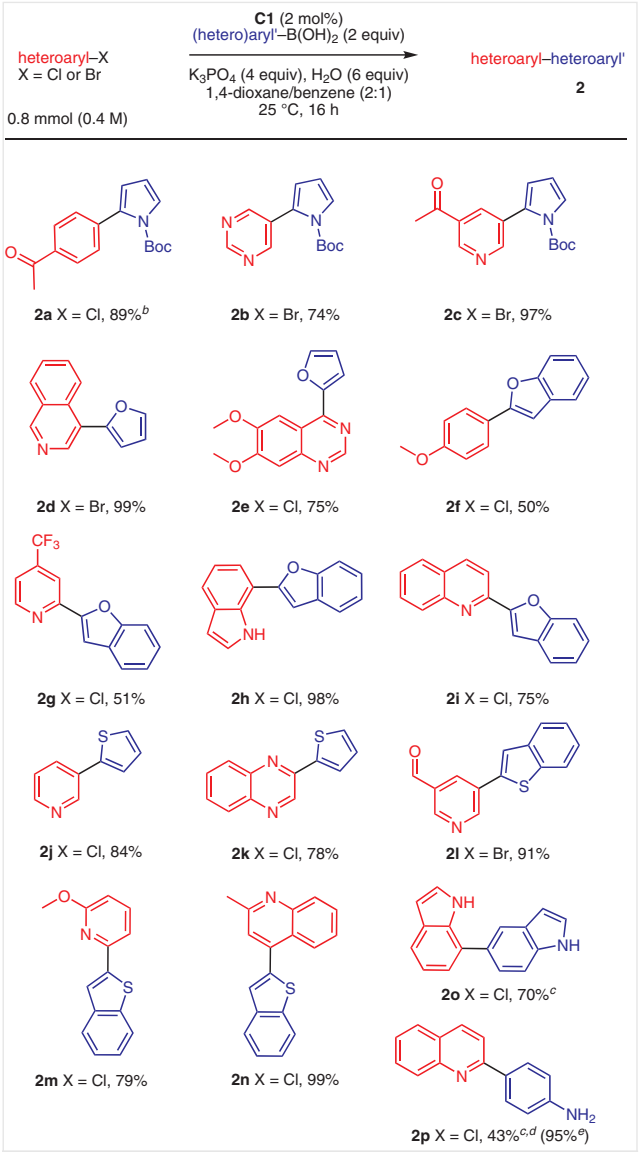
Deviation from above	Conversion into **1** (%)[a]
none	>90
1,4-dioxane	10
toluene	70
water, 50 °C	60
no water	80
THF	nd
MeCN, K_2CO_3	nd
C2	50
C3	nd
C4	nd
1.1 equiv $PhB(OH)_2$	80
2 equiv K_3PO_4	40
PhBpin	nd
PhBneopent	nd
$PhBF_3K$	nd

[a] Estimated conversion into **1** on the basis of calibrated GC data; nd = not detected.

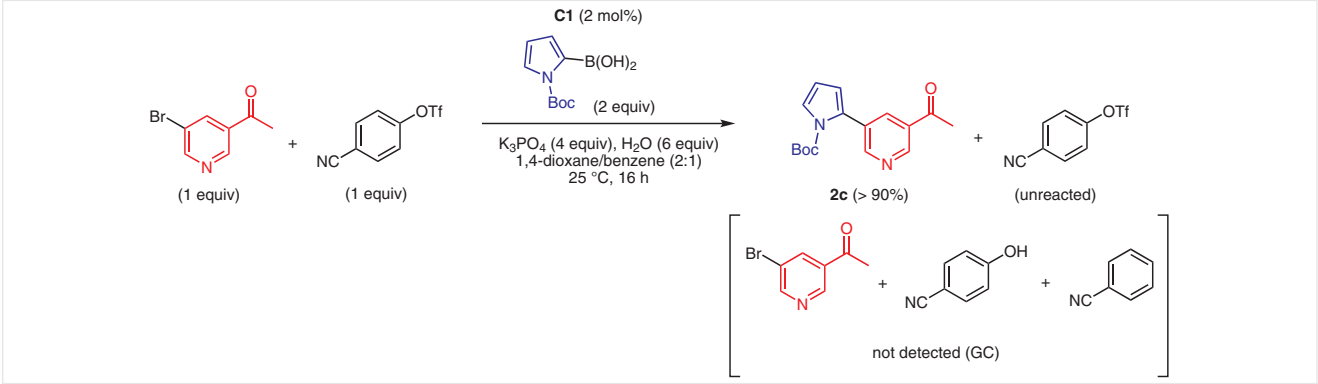
With optimized conditions in hand, we set out to examine the scope of room-temperature SM cross-couplings using **C1**, including for the construction of unsymmetrical biheteroaryls (Scheme 2). To facilitate more challenging transformations of this type, we typically opted to employ higher catalyst loading (2 mol% **C1**) and longer reaction times (16 h) to ensure optimal conversion. A selection of five-membered heteroaryl boronic acids in combination with heteroaryl chlorides and bromides were employed successfully in this chemistry (**2a**–**p**), with isolated yields that are generally comparable to those achieved by use of DPPF-based nickel pre-catalysts.[7,9] In the context of SM reactions employing **C1** leading to unsymmetrical biheteroaryls, *N*-Boc pyrrole, (benzo)furan, (benzo)thiophene, and unprotected NH-indole structures proved compatible in the boronic acid substrate, as did pyridine, pyrimidine, (iso)quinoline, quinaldine, quinazoline, quinoxaline, and unprotected NH-indole frameworks in the heteroaryl electrophile reaction partner. The tolerance of trifluoromethyl, ketone, aldehyde, and ether groups was also demonstrated. Despite the established ability of **C1** in C–N cross-coupling chemistry,[15] under the conditions employed formation of the SM cross-coupling product **2p** is favored over *N*-arylation of the primary aniline moiety within the boronic acid substrate.

Some limitations were encountered in this chemistry. Application of **C1** as a pre-catalyst for SM cross-couplings with sterically hindered electrophiles such as 2-chloro-*m*-xylene proved problematic, with negligible turnover observed. As well, electron-rich aryl chlorides presented a challenge, as evidenced by the moderate yield (50%) obtained for **2f**. While heteroaryl chlorides and bromides were found to be effective in these SM cross-couplings using **C1** (Scheme 2), sulfonate electrophiles (e.g., mesylates, tosylates, and triflates) failed to react. Intrigued by this observation, we sought to assess whether sulfonate electrophiles were inert or gave rise to catalyst deactivation in this reaction setting, by examining the progress of the otherwise successful SM cross-coupling leading to the unsymmetrical biheteroaryl **2c** by use of **C1**, in the presence of an added aryl triflate (Scheme 3). Gas chromatographic analysis of the reaction mixture revealed the clean formation of **2c**, with the aryl tosylate remaining unconsumed; neither the derived phenol nor aryl triflate reduction byproducts were detected, thereby confirming the inert nature of sulfonate electrophiles in this catalytic system.

The nickel-catalyzed SM cross-coupling of pyridinyl boronic acids and heteroaryl halides leading to unsymmetrical biheteroaryls is limited to a report by Garg and co-workers,[12] whereby the cross-coupling of 2-methoxy-3-pyridinylboronic acid with 3-chloropyridine or 5-bromopyrimidine by use of $(PCy_3)_2NiCl_2$ as a pre-catalyst is described. Our initial efforts to employ pyridinyl boronic acids as cross-coupling partners with **C1** under the conditions outlined in Scheme 2 were unsuccessful; no conversion of the starting materials was observed on the basis of gas chromatographic analysis. However, in employing modified conditions described by Watson and co-workers[19] for the nickel-catalyzed sp^3–sp^2 cross-coupling of pyridinyl boronic acids and alkylpyridinium electrophiles, the successful cross-coupling of 4-chloro-2-fluorotoluene and 3-pyridinyl-boronic acid by use of **C1** was achieved (Table 2). While high conversion of the test substrates was noted under these conditions, the isolated yield of the target product **3a** was found to be 61%, with 2-fluorotoluene being the major byproduct. Increasing the reaction temperature from 60 °C to



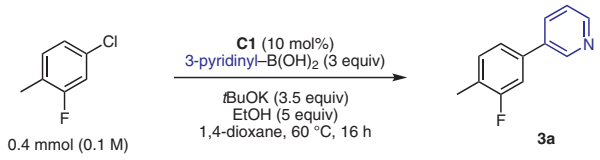
Scheme 2 Suzuki–Miyaura cross-couplings using **C1**. [a] Unless stated, isolated yields reported. [b] 1 mol% **C1**. [c] 50 °C. [d] **2p** was found to decompose partially under the chromatographic conditions employed. [e] NMR yield relative to 1,4-di-*tert*-butylbenzene.



Scheme 3 Electrophile selectivity in Suzuki–Miyaura cross-couplings using **C1**

110 °C resulted in high substrate conversion but negligible production of **3a**, whereas no substrate conversion was achieved at 25 °C. Diminished conversion and yield of **3a** occurred when using lower loadings of **C1**. No substrate conversion was achieved under our otherwise optimal conditions when ethanol was excluded, underscoring the importance of this additive in the successful formation of **3a**. The addition of 18-crown-6 was tested given our observation that a large amount of insoluble material, potentially including potassium borate species, was observed in these cross-coupling reactions; however, this addition had no effect on the outcome of the reaction.

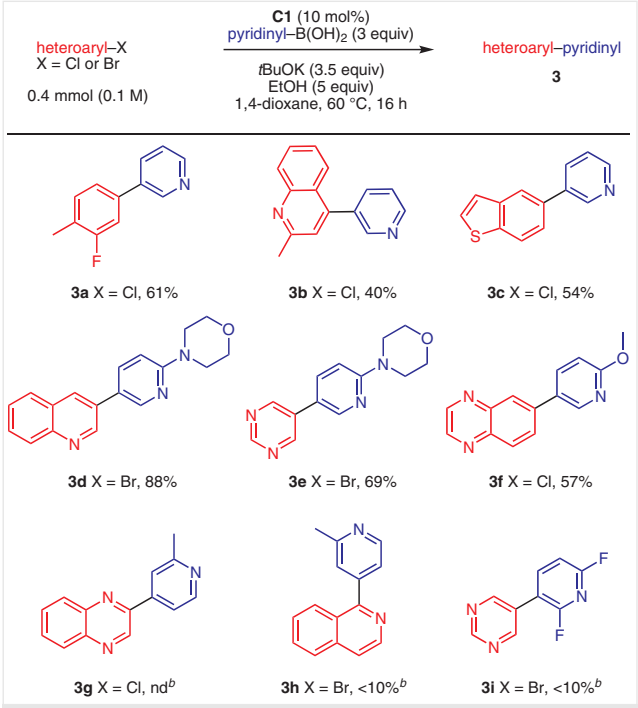
Table 2 Optimization of Conditions for Pyridinyl Boronic Acids Using **C1**



Deviation from above	Conversion of ArCl (%)[a]
none	>90 (61[b])
110 °C	>90 (nd)
25 °C	nd
5 mol% **C1**	50
no EtOH	nd
3 equiv 18-crown-6	>90 (63[b])

[a] Estimated conversion of aryl chloride on the basis of calibrated GC data; nd = not detected.
[b] Isolated yield of **3a**.

Having identified suitable conditions for SM cross-couplings of pyridinyl boronic acids and heteroaryl halides employing **C1** (Table 2), we set out to explore the scope of such transformations, including in the context of the synthesis of unsymmetrical biheteroaryls (Scheme 4). Several successful cross-couplings of this type were achieved by using either 3-pyridinyl-boronic acid or *ortho*-substituted variants, affording the target products **3a–f** in synthetically useful isolated yields (40–88%); in all cases, no heteroaryl halide remained at the end of the reaction, in keeping with competing side reactivity including electrophile hydrodehalogenation. The success of the cross-coupling was found to be sensitive to the structure of the pyridine nucleophile, with 2-methyl-4-pyridinyl-boronic acid and an electron-poor 3-pyridinyl-boronic acid failing to react (**3g–i**) under conditions whereby other 3-pyridinyl-boronic acids worked well. Notwithstanding these limitations, the successful cross-couplings leading to the new compounds **3a–f** represent the most di-



Scheme 4 Suzuki–Miyaura cross-couplings of pyridinyl boronic acids using **C1**. [a] Unless stated, isolated yields reported. [b] Estimated conversion into **3** on the basis of calibrated GC data; nd = not detected.

verse collection of such nickel-catalyzed transformations reported thus far in the literature, thereby underscoring the utility of pre-catalyst **C1**.

In summary, air-stable (DPEPhos)Ni(mesityl)Br (**C1**) is shown to be an effective pre-catalyst for Suzuki–Miyaura (SM) cross-couplings of heteroaryl chlorides or bromides and heteroaryl boronic acids, including rather challenging transformations leading to unsymmetrical biheteroaryls for which few competent nickel-based catalysts are known.[20–23] A diverse collection of reaction partners were accommodated in this chemistry, in many cases at room temperature (2 mol% **C1**). In keeping with previous literature reports, SM cross-couplings involving pyridinyl boronic acids and heteroaryl electrophiles proved difficult and required more forcing reaction conditions (10 mol% **C1**, 60 °C). Nonetheless, the modest established substrate scope achieved by use of **C1** exceeds that previously reported for nickel-catalyzed SM cross-couplings leading to unsymmetrical biheteroaryls. Future work will focus on applying **C1** in other challenging nickel-catalyzed transformations, as well as on the rational development of ancillary ligands for such synthetic applications.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591523.

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(20) **General Procedure for Cross-coupling (GP1)**
Unless otherwise specified, under an inert atmosphere **C1** (12.7 mg, 0.016 mmol, 2 mol %), aryl halide (0.8 mmol), boronic acid (1.6 mmol), and K_3PO_4 (679 mg, 3.2 mmol) were added to an oven-dried 4 dram vial containing a magnetic stir bar. 1,4-Dioxane (1.3 mL) and benzene (700 µL) were added, the vial was sealed with a screwcap featuring a PTFE/silicone septum and was removed from the glovebox. Degassed water (86 µL) was added via a gas-tight syringe. The reaction mixture was magnetically stirred for 16 h at room temperature. Note: On several occasions the base became clumpy and stuck to the bottom of the reaction vial; in these cases it was noted that reactions were more successful if efficient stirring was maintained. After 16 h, the reaction mixture was taken up in EtOAc (ca. 10 mL) and extracted with distilled water (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated with the aid of a rotary evaporator.
(21) **General Procedure for Cross-Coupling Using Pyridinyl Boronic Acids (GP2)**
Unless otherwise specified, under an inert atmosphere **C1** (31.9 mg, 0.04 mmol, 10 mol %), aryl halide (0.4 mmol), boronic acid (1.2 mmol), and KO*t*Bu (157.1 mg, 1.4 mmol), were added to an oven-dried 4 dram vial containing a magnetic stir bar. 1,4-Dioxane (4 mL) and EtOH (101.7 µL) were added. The vial was sealed with a screwcap featuring a PTFE/silicone septum and was removed from the glovebox. The reaction mixture was magnetically stirred for 16 h in a temperature-controlled aluminum heating block set to 60 °C. After 16 h, the reaction mixture was cooled to room temperature, taken up in EtOAc (ca. 10 mL), and extracted with distilled water (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated with the aid of a rotary evaporator.
(22) **Representative Synthesis A: Preparation of 2b**
Following **GP1** (aryl halide 127.2 mg, boronic acid 337.6 mg), the title product was obtained via flash chromatography using silica and 30% EtOAc in hexanes. The product was isolated as white solid (74%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.76 (s, 2 H), 7.49–7.48 (m, 1 H), 6.36–6.32 (m, 2 H), 1.46 (s, 9 H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ = 156.9, 156.3, 148.7, 128.6, 127.5, 124.1, 116.5, 111.2, 84.7, 27.7. HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{15}N_3NaO_2$: 268.1056; found: 268.1067 [M + Na]$^+$.
(23) **Representative Synthesis B: Preparation of 3d**
Following **GP2** (aryl halide 54.4 mg, boronic acid 249.6 mg), the title product was obtained via flash chromatography using silica and 70% EtOAc in hexanes. The product was isolated as a white solid (88%). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 9.16 (d, *J* = 2.2 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 8.25 (d, *J* = 2.1 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 7.91–7.89 (m, 2 H), 7.75–7.72 (m, 1 H), 7.62–7.59 (m, 1 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 3.89 (t, *J* = 4.7 Hz, 4 H), 3.64 (t, *J* = 5.0 Hz, 4 H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ = 159.0, 149.2, 147.1, 146.5, 136.2, 131.7, 131.1, 129.2, 129.1, 128.1, 127.7, 127.0, 123.3, 106.8, 66.7, 45.5; HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{18}N_3O$: 292.1444; found: 292.1443 [M + H]$^+$.