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Copper−Diamine-Catalyzed *N*-Arylation of Pyrroles, Pyrazoles, Indazoles, Imidazoles, and Triazoles

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This paper details the copper-catalyzed *N*-arylation of π-excessive nitrogen heterocycles. The coupling of either aryl iodides or aryl bromides with common nitrogen heterocycles (pyrroles, pyrazoles, indazoles, imidazoles, and triazoles) was successfully performed in good yield with catalysts derived from diamine ligands and CuI. General conditions were found that tolerate functional groups such as aldehydes, ketones, alcohols, primary amines, and nitriles on the aryl halide or heterocycle. Hindered aryl halides or heterocycles were also found to be suitable substrates using the conditions reported herein.

Introduction

Nitrogen-containing heterocycles are subunits found in numerous natural products and in many biologically active pharmaceuticals.[1] It is therefore important that general methods to synthesize or to modify such compounds are developed. One such reaction is the cross-coupling of *N*-H containing heterocycles with aryl halides to form the respective *N*-arylated heterocycle (Ullmann coupling). To date, there have been numerous copper-mediated or copper-catalyzed methods published to allow for such a transformation.[2] However, these reports, while significant contributions, generally suffer from important limitations such as high reaction temperatures (often 140 °C or higher) and poor substrate generality. Another limitation has been that, to date, no single method has found success with each of the major classes of nitrogen heterocycles (imidazoles, pyrroles, pyrazoles, etc.). Recently, the use of C−H bond functionalization via palladium and ruthenium catalysis has been applied to the arylation of several azoles.[3] These methods provide access to a wide range of azole derivatives; however, high temperatures (130−150 °C) are necessary. Palladium-catalyzed cross-coupling of *N*-H heterocycles with aryl halides has been moderately successful, but limitations in terms of generality have lessened the utility of the method.[4] We have previously reported a general method for the *N*-arylation of amides and of nitrogen heterocycles catalyzed by copper−diamine complexes.[5] The use of diamine ligands for copper has resulted in numerous new coupling reactions being developed in our laboratory[6] and in those of others.[7] Herein, we report a general process for the cross-coupling of a variety of nitrogen heterocycles with aryl iodides or aryl bromides. This paper does not present results for the arylation of indoles as our work with this important class of nitrogen hetereocycles was described in detail in an earlier report.[6c]

Results and Discussion

In our initial communication utilizing diamines as ligands for copper catalysis, a number of *N*-H heterocycles were reported to undergo coupling with aryl iodides in dioxane as a solvent.[5] In a subsequent, more detailed exploration of the coupling of aryl halides with indoles,[6c] it became apparent that *N*,*N*′-dimethyl-substituted ligands (**2** and **3**) were superior to the parent ligands (Figure 1). This was at least partly due to the fact that competitive *N*-arylation of the ligand was suppressed because of the increase in steric hindrance at the nitrogen center. It was

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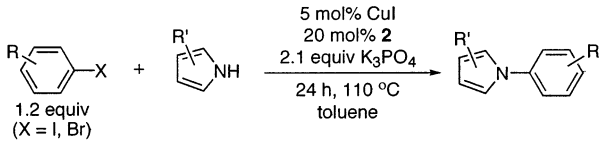
TABLE 1. Copper−Diamine-Catalyzed *N*-Arylation of Pyrroles



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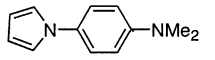
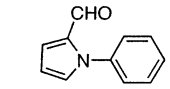
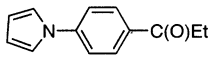
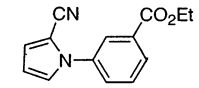
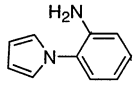
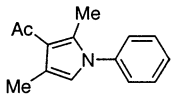
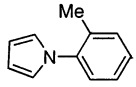
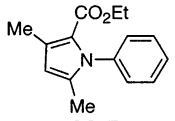
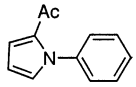
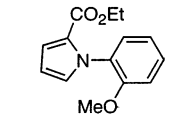
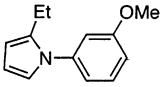
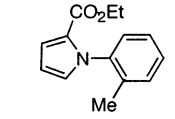
1 (ArBr)		94	7 (ArI)		88
2 (ArBr)		92	8 (ArI)		85
3 (ArBr)		83	9 (ArI)		92[b]
4 (ArBr)		87[a]	10 (ArI)		86[c]
5 (ArI)		96	11 (ArI)		96
6 (ArI)		84	12 (ArI) (K_2CO_3)		89[d]

[a] Reaction performed with 2.0 equiv of ArBr. [b] With 20% ligand **3**. [c] With 20% ligand **3** and neat in aryl iodide (no solvent). [d] Reaction performed neat in aryl iodide (no solvent).

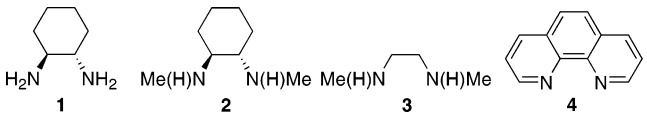


FIGURE 1. Ligands for C−N bond formation.

also found that changing to a less polar solvent like toluene led to improved reaction rates. We have found that these conditions are also applicable, with generality, to the *N*-arylation of pyrroles, pyrazoles, and indazoles. The conditions for the arylation of triazoles required the use of a more polar solvent (DMF), most likely because of the insolubility of the triazoles in toluene. General conditions for the arylation of imidazoles utilizing ligand **2** resulted in a moderate improvement upon our previous publication that utilized 1,10-phenanthroline (**4**) as a ligand to afford such couplings.[8]

The arylation of a wide range of pyrrole substrates utilizing aryl iodides or aryl bromides was accomplished through the application of a general reaction procedure that use[5] K_3PO_4 as a base, 5 mol % CuI, 20 mol % ligand **2**, and toluene as the solvent. Although we have found that ligand **2** is the most effective, these reactions can be conducted with less costly ligands **1** and **3**, albeit with generally lower yields. It is important to note that this represents a general procedure and each individual reaction was not optimized in terms of temperature, quantity of catalyst, nor reaction time. Instead, this procedure is meant to be a starting point or guideline for chemists interested in pursuing the reaction of a new combination of substrates.

Table 1 shows that para (entries 1 and 2), meta (entries 6 and 8), or ortho (entries 3, 4 and 11, 12) substitution on the aryl halide is tolerated under these reaction conditions. A variety of functional groups, including esters, primary amines, aldehydes, and ketones can be present on either the pyrrole or aryl halide. Several examples of 2-substituted (entries 5−8, 11, and 12) and trisubstituted pyrroles (entries 9 and 10) were also shown to be good substrates. Particularly noteworthy is the use of the sterically hindered substrate combinations shown in entries 10−12. It was found that in three instances (entries 7, 10, and 12) the use of the aryl iodide (3 equiv) as the solvent was required in order for the reaction to proceed to completion. In two cases, entries 9−10, **3** was shown to be a good ligand for this coupling. In the other examples, diamine **2** gave superior results. It is important to note that both **2** (Strem) and **3** (Aldrich) are commercially available. The method, while more tolerant of steric hindrance than its predecessors, still slows significantly with increased substitution on either substrate. For example, the coupling of 2,5-dimethylpyrrole with iodobenzene only proceeded to 20% conversion of pyrrole even under conditions where the aryl halide was used as the solvent (4 equiv of PhI). Moreover, 2,6-disubstituted aryl iodides were not successfully coupled to pyrrole itself.

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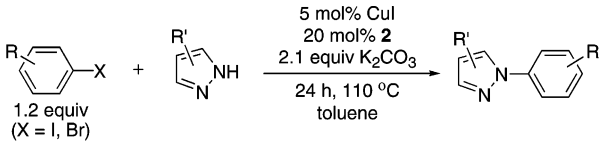
TABLE 2. Copper−Diamine-Catalyzed *N*-Arylation of Pyrazoles



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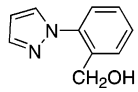
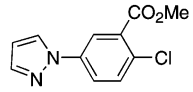
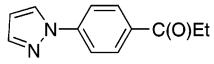
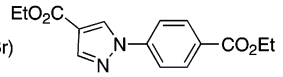
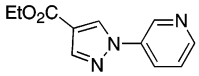
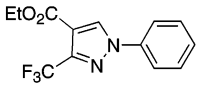
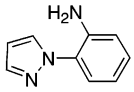
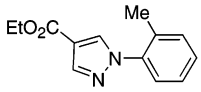
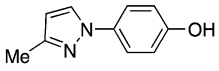
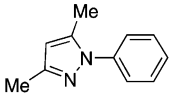
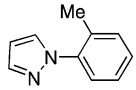
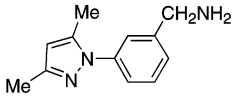
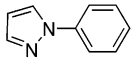
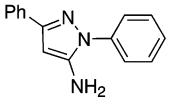
1 (ArBr)		74[a]	8 (ArI)		89
2 (ArBr)		98	9 (ArBr)		79
3 (ArBr)		84	10 (ArI)		77
4 (ArBr)		91	11 (ArBr)		79[b]
5 (ArBr)		78	12 (ArI)		98[b]
6 (ArBr)		92[b]	13 (ArI)		71[b]
7 (ArI)		93[c]	14 (ArI)		88

[a] With 10 mol % of ligand **2**. [b] Reaction run neat in aryl halide (2−4 equiv) with no additional solvent added. [c] Reaction run at 80 °C.

Extending this chemistry to include pyrazoles as substrates proved to be quite successful. It was found that the ideal base for the coupling of pyrazole was K_2CO_3, rather than K_3PO_4. Presumably, this is due to the more acidic pyrazole *N*-H. Again, a number of aryl bromides where found to be quite reactive under the *general* reaction conditions (entries 1−5, 9, and 11 in Table 2) shown below. As with pyrroles, a variety of functional groups were tolerated under the reaction conditions. Hindered substrate combinations (entries 6 and 11−13) required 2−4 equiv of the aryl halide as the solvent to allow for complete conversion of the pyrazole.

Several interesting features are apparent from the results in Table 2. First, the reaction works well with electron−neutral and electron-deficient pyrazoles. Second, the reaction is efficient even for very electron-rich aryl halides (e.g., entries 4 and 5). Third, the reaction of "unsymmetrical" pyrazoles produced products in which the less hindered nitrogen was selectively arylated (entries 5 and 10). This is as would be expected on the basis of literature precedent for alkylation and arylation processes involving substituted pyrazoles.[9]

In our initial studies, we found that the reaction of aryl halides with indazole was readily accomplished using CuI and ligand **1**;[5] excellent regioselectivity for the *N*-1 arylation product was observed (>20/1). It was found that changing the solvent from dioxane to toluene, together with the use of ligand **2**, increased the rate of the reaction. This rate enhancement allowed for the use of aryl bromide substrates. However, a dramatic lowering of regioselectivity was observed when using aryl bromides (compare entries 1−6, Table 3) as substrates. Only in the case of 3-chloroindazole was a high level of regioselectivity for *N*-1 coupling observed with an aryl bromide (entry 7). A possible explanation for this dramatic change in regioselectivity could be due to the fact that oxidative addition with aryl bromides is much slower than that of aryl iodides. We believe that indazole first reacts to form a (diamine)Cu(indazole) intermediate, A1 (Figure 2). Kinetically, A1 is preferred over A2; however, these complexes are in equilibrium. When aryl iodides are employed as substrates, oxidative addition to A1 occurs

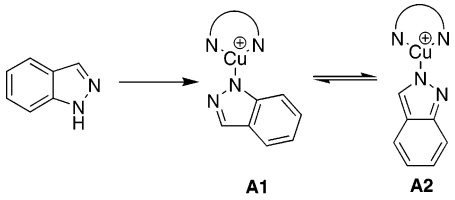
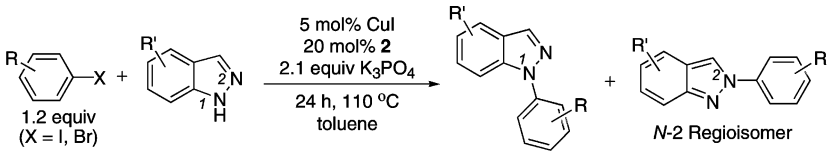


FIGURE 2. Equilibration of the copper−indazole complex.

(9) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*; Blackwell Science Ltd: Oxford, 2000.

TABLE 3. Copper−Diamine-Catalyzed *N*-Arylation of Indazoles



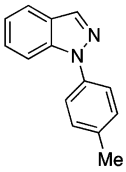
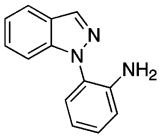
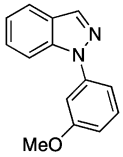
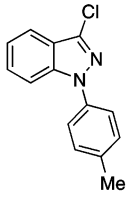
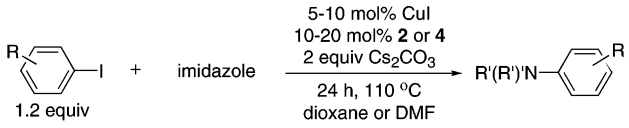
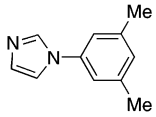
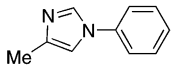
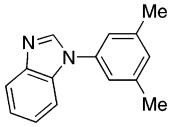
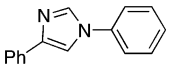
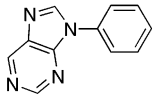
entry	product	% yield	*N*-1/*N*-2	entry	product	% yield	*N*-1/*N*-2
1 (ArI)		**85**	**17 / 1**	**5 (ArI)**		**80**	**20 / 1**
2 (ArBr)		75% conv of indazole	1.8 / 1	6 (ArBr)		70 (mixture)	1.4 / 1
3 (ArI)		**92**	**17 / 1**	**7 (ArBr)**		**86**	**>20 / 1**
4 (ArBr)		74 (mixture)	2 / 1				

TABLE 4. Copper-Catalyzed *N*-Arylation of Imidazoles



entry	product	% yield	entry	product	% yield
1		91[a]	3		74[c,d]
2		91[b]	4		87[c,d]
			5		66[e]

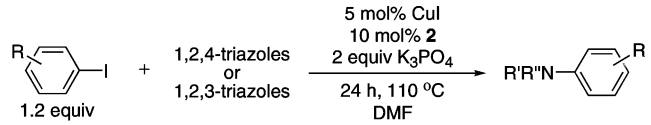
[a] With 5 mol % of CuI, 10 mol % of **4**, and 2 M dioxane. [b] With 10 mol % of CuI, 20 mol % of **4**, and 2 DMF. [c] With 5 mol % of CuI, 20 mol % of **2**, and 2 M DMF. [d] Only one regioisomer was detected as determined by GC/MS on a sample of the crude reaction mixture. [e] With 5 mol % of CuI, 20 mol % of **2**, and 2 M DMF in 70 °C.

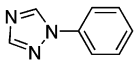
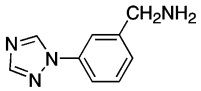
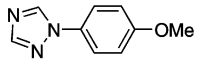
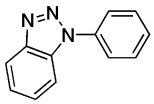
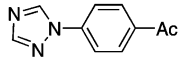
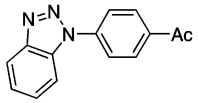
faster than the A1/A2 equilibration, thereby forming predominately the *N*-1 substituted product after reductive elimination. For reactions with aryl bromides, the rate of the A1/A2 equilibration is competitive compared to the rate of oxidative addition and a mixture of products is observed.

It was found to be difficult to improve upon previous conditions for the copper-catalyzed *N*-arylation of imidazoles.[8] Our previous conditions using dioxane, ligand **1**, and Cs_2CO_3 provided a high yield of the arylated imidazole (entries 1−2, Table 4).[5] However, these conditions provided incomplete conversion of starting materials when applied to the arylation of 4-methyl- or 4-phenylimidazole. The copper catalyst derived from **2** provided sufficient activity so that these substrates were reactive (entries 3 and 4). The reaction was found to proceed more efficiently with DMF as a solvent and also required the use of Cs_2CO_3 as the base. Additionally, we were pleased to find that purine could also be arylated using these reaction conditions (entry 5).

Arylation of triazole substrates could also be achieved using copper−diamine catalysts. To optimize this process, a series of experiments were performed that revealed that DMF (solvent) and K_3PO_4 (base) were optimal for obtaining complete conversion of starting materials. The use of other bases such as K_2CO_3 and Cs_2CO_3 was also suitable for reactions of some of the triazoles screened. Both **2** (entries 1−3, 5, and 6, Table 5) and **3** (entry 4)

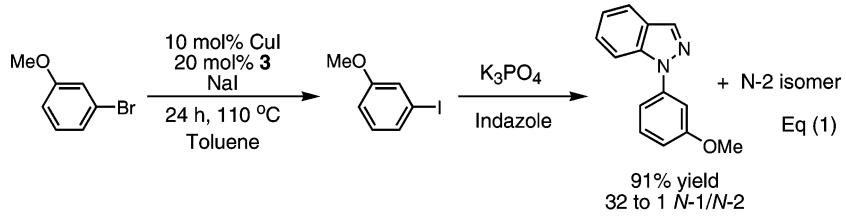
TABLE 5. Copper−Diamine Catalyzed *N*-Arylation of Triazoles



entry	product	% yield	entry	product	% yield
1		89	4		79[a]
2		82	5		93[b]
3		83	6		67[b]

[a] With 10 mol % of ligand **3**. [b] >25:1 Regioselective for the *N*-1 isomer.

SCHEME 1. Halide Exchange/Arylation Sequence



were capable ligands for the arylation of triazoles. The arylation of benzotriazole (entries 5 and 6) occurred almost exclusively at the *N*-1 position; the use of aryl bromides as substrates resulted in low conversion to product. The arylation of 1,2,3-triazole proved to be problematic as competitive *N*-1/*N*-2 arylation resulted, giving mixtures slightly favoring the formation of the *N*-1 isomer.

A general problem encountered in the development of this methodology was the slower rate of reaction with aryl bromides relative to aryl iodides. Another issue that surfaced was the poor regioselectivity found in indazole arylation when using aryl bromides as substrates. These two problems were circumvented by first performing our previously published Cu-catalyzed halide exchange[6b] followed by reaction with the appropriate nitrogen heterocycle in a two-step/one-pot sequence (Scheme 1). Equation 1 shows that, starting from the aryl bromide, one can achieve high regioselectivity for the arylation of indazole. Equation 2 shows that by using this procedure the problem of a particularly slow substrate combination (4-bromotoluene with 2-acetylpyrrole) can be overcome by performing the reaction via the more reactive iodide that can be generated in an in situ fashion.

Conclusion

In summary, we have shown that the Cu-catalyzed *N*-arylation of common nitrogen heterocycles, taken with our previous work on indole arylation, is a broadly applicable method. A general reaction protocol for each class of heterocycles was determined, and represents a good starting point for future studies with particular substrates of interest. This work should find wide application among synthetic and medicinal chemists in industry and academics. While we have made considerable inroads, future work is needed to further generalize this type of heterocycle arylation. In particular, the development of new catalysts that allow for C−N bond formation to take place with more highly hindered substrate combinations is desirable.

Experimental Section

General Considerations. All reactions were carried out in resealable Schlenk or test tubes and run under an atmosphere of dry argon or nitrogen. Toluene was purchased from J. T. Baker in CYCLE-TAINER solvent delivery kegs, was vigorously purged with argon for 2 h, and was further purified

by passing through two packed columns of neutral alumina and copper(II) oxide under argon pressure. K_3PO_4 was purchased from Fluka and used without further purification. It is important that the base is powdered and free-flowing. Copper(I) iodide was purchased from Strem (98% purity, off-white) and was a fine powder. Aryl halides and nitrogen heterocycles were purchased from commercial sources and used without further purification. *trans-N,N′*-Dimethyl-1,2-cyclohexanediamine was prepared as previously described[6c] and is commercially available. Flash column chromatography was performed using Merck silica gel (230−400 mesh). IR spectra were recorded for all previously unknown compounds (neat, thin film). ^{1}H NMR and ^{13}C NMR was recorded at 400 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS). Gas chromatographic analysis was performed on an instrument with an FID or MS detector using a capillary column. All yields reported represent an average of at least two independent runs. Previously unknown compounds were synthesized, purified, and analyzed from a single run; yields are the average yield of the two experiments. Unknown compounds were characterized by ^{1}H and ^{13}C NMR, IR, and GC. They were further characterized by elemental analysis. For compounds that did not return a satisfactory elemental analysis, 1-(3′-Pyridinyl)ethyl-4-pyrazolecarboxylate, 3,5-dimethyl-1-phenylpyrazole, 1-(3′-aminomethylphenyl)-2,4-triazole), and (1-(4′-methylphenyl)-2-acetylpyrrole, copies of their ^{1}H and ^{13}C NMR spectra are included in the Supporting Information. Compounds described in the literature were characterized by comparing their ^{1}H NMR, melting point (mp), and GC/MS to the previously reported data; their purity was confirmed by GC and ^{1}H NMR.

See the Supporting Information for a general procedure for the *N*-arylation of nitrogen heterocycles.

1-(4-Dimethylamino)pyrrole (Entry 1). Following the general procedure, pyrrole (69 μL, 1.0 mmol) was coupled with 4-bromo-*N,N′*-dimethylaminoaniline (0.240 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (5:1 hexanes/ethyl acetate) provided 0.175 g (94% yield) of the title compound as a white solid, mp 152−153 °C (chloroform) [lit.[10] 150−151 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[10]

1-(4-Propiophenone)pyrrole (Entry 2). Following the general procedure, pyrrole (69 μL, 1.0 mmol) was coupled with 4′-bromopropiophenone (0.277 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (3:1 hexanes/ethyl acetate) provided 0.180 g (90% yield) of the title compound as a white solid. Mp: 123−125 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 2H, J = 8.7 Hz), 7.45 (d, 2H, J = 8.7 Hz), 6.17 (t, 2H, J = 2.2 Hz), 6.38 (t, 2H, J = 2.2 Hz), 3.01 (q, 2H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 143.8, 133.7, 129.7, 119.3, 119.0, 111.5, 31.6, 8.2. IR (neat, cm^{-1}): 3140, 1686, 1607, 1333, 1194, 843, 796, 737, 608. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.57. Found: C, 78.25; H, 6.59.

1-(2-Aminophenyl)pyrrole (Entry 3). Following the general procedure, pyrrole (69 μL, 1.0 mmol) was coupled with 2-bromoaniline (0.206 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.130 g (82% yield) of the title compound as a white solid, mp 96−97 °C (chloroform) [lit.[11] 96−98 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[11]

1-(2-Methylphenyl)pyrrole (Entry 4). Following the general procedure, pyrrole (69 μL, 1.0 mmol) was coupled with 2-bromotoluene (240 μL, 2.00 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (50:1 hexanes/ethyl acetate) provided 0.140 g (89% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[12]

2-Acetyl-1-phenylpyrrole (Entry 5). Following the general procedure, 2-acetylpyrrole (0.109 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in toluene (1 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.176 g (95% yield) of the title compound as a colorless oil that solidified upon standing at 4 °C to give a white solid, mp 52−54 °C (chloroform) [lit.[13] 52−53 °C (pet. ether)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[13]

1-(3-Methoxyphenyl)-2-ethylpyrrole (Entry 6). Following the general procedure, 2-ethylpyrrole (0.106 g, 1.0 mmol, based on 90% tech material) was coupled with 3-iodoanisole (143 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (50:1 hexanes/ethyl acetate) provided 0.172 g (85% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, 1H, J = 8.0 Hz), 6.85 (m, 3H), 6.73 (m, 1H), 6.21 (t, 1H, J = 3.1 Hz), 6.06 (m, 1H), 3.77 (s, 3H), 2.56 (q, 2H, J = 7.6 Hz), 1.15 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 141.4, 135.4, 130.0, 129.6, 121.3, 118.2, 112.5, 111.7, 111.0, 107.8, 106.0, 55.2, 20.0, 13.2. IR (neat, cm^{-1}): 2968, 1606, 1495, 1336, 1241, 1221, 1047, 843, 780, 698. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.82; H, 7.44.

1-Phenylpyrrole-2-carboxaldehyde (Entry 7). Following the general procedure, pyrrole-2-carboxaldehyde (0.095 g, 1.0 mmol) was coupled with iodobenzene (336 μL, 3.00 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.154 g (89% yield) of the title compound as a yellow oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[14]

1-(3-Carboxymethyl)-2-cyanopyrrole (Entry 8). Following the general procedure, pyrrole-2-carbonitrile (85 μL, 1.0 mmol) was coupled with ethyl-3-iodobenzoate (293 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (5:1 hexanes/ethyl acetate) provided 0.204 g (85% yield) of the title compound as a colorless oil that solidified to give a white solid upon drying. Mp: 69−70 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.67 (m, 1H), 7.58 (t, 1H, J = 8.1 Hz), 7.12 (dd, 1H, J = 1.6, 2.6 Hz), 7.00 (dd, 1H, J = 1.5, 3.9 Hz), 6.37 (dd, 1H, J = 2.9, 3.9 Hz), 4.41 (q, 2H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 138.1, 132.1, 129.6, 129.1, 128.1, 126.9, 125.0, 122.3, 113.3, 110.8, 104.0, 61.3, 14.1. IR (neat, cm^{-1}): 3124, 2983, 2219, 1721, 1590, 1492, 1460, 1262, 1174, 757, 689. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03. Found: C, 70.21; H, 5.10.

3-Acetyl-2,4-dimethyl-1-phenylpyrrole (Entry 9). Following the general procedure, 3-acetyl-2,4-dimethylpyrrole (0.137 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **3** (22 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (5:1 hexanes/ethyl acetate) provided 0.202 g (95% yield) of the title compound as a white solid. Mp: 80−81 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.39 (m, 1H), 7.23 (m, 2H), 6.47 (s, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 138.8, 135.9, 129.1, 127.8, 126.2, 122.4, 120.7,

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(11) Aldrich Chemical Spectra, FT-NMR **1**(3), 4B.
(12) Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271.
(13) Cheeseman, G. W. H.; Hawi, A. A. *J. Heterocycl. Chem.* **1983**, *20*, 585.
(14) Ewen, J. A.; Elder, M. J.; Jones, R. L.; Rheingold, A. L.; Liable-Sands, L. M.; Sommer, R. D. *J. Am. Chem. Soc.* **2001**, *123*, 4763.

119.7, 31.1, 13.4, 12.8. IR (neat, cm^{-1}): 3050, 2946, 1638, 1495, 1413, 1210, 944, 773, 750, 702. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.66; H, 7.04.

2,4-Dimethyl-1-phenyl-3-carboxyethylpyrrole (Entry 10). Following the general procedure, 2,4-dimethyl-5-carboxyethylpyrrole (0.167 g, 1.00 mmol) was coupled with iodobenzene (336 μL, 3.00 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **3** (22 μL, 0.20 mmol, 20 mol %) with no additional solvent. Column chromatography (19:1 hexanes/ethyl acetate) provided 0.215 g (89% yield) of the title compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 3H), 7.16 (m, 2H), 5.91 (s, 1H), 4.03 (q, 2H, J = 7.1 Hz), 2.38 (s, 3H), 1.95 (s, 3H), 1.04 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 140.2, 135.9, 130.1, 128.5, 127.7, 127.6, 120.5, 111.0, 59.0, 13.9, 13.7, 12.7. IR (neat, cm^{-1}): 3065, 2980, 2927, 1950, 1882, 1698, 1498, 1273, 1182, 1090, 762, 698, 637. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04. Found: C, 74.14; H, 7.16.

1-(2′-Methoxyphenyl)ethylpyrrole-2-carboxylate (Entry 11). Following the general procedure, ethylpyrrole-2-carboxylate (0.139 g, 1.00 mmol) was coupled with 2-iodoanisole (156 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). The crude reaction mixture was dissolved in ethyl acetate (~3 mL), and 15 mL of hexanes was added to this solution. The resulting turbid solution was placed in a freezer at −20 °C for 16 h. Filtration and concentration under reduced pressure provided 0.243 g (99%) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (td, 1H, J = 1.7, 8.0 Hz), 7.19 (dd, 1H, J = 1.7, 7.6 Hz), 7.07 (dd, 1H, J = 1.8, 3.9 Hz), 6.95 (m, 2H), 6.81 (dd, 1H, J = 1.9, 2.4 Hz), 6.27 (dd, 1H, J = 2.6, 3.9 Hz), 4.11 (q, 2H, J = 7.1 Hz), 3.68 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 160.2, 154.5, 129.6, 128.9, 127.4, 124.2, 120.0, 117.3, 111.2, 108.6, 59.4, 55.3, 13.9. IR (neat, cm^{-1}): 2980, 2839, 1711, 1508, 1417, 1268, 1109, 1025, 751. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.45; H, 6.27.

1-(2′-Methylphenyl)ethylpyrrole-2-carboxylate (Entry 12). Following the general procedure, ethyl pyrrole-2-carboxylate (0.139 g, 1.00 mmol) was coupled with 2-iodotoluene (510 μL, 4.00 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with no additional solvent. Column chromatography (19:1 hexanes/ethyl acetate) provided 0.202 g (88% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H), 7.18 (m, 1H), 7.10 (m, 1H), 6.79 (dd, 1H, J = 1.8, 2.5 Hz), 6.25 (m, 1H), 4.02 (dq, 2H, J = 1.8, 7.1 Hz), 2.00 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 140.0, 135.5, 130.1, 128.8, 128.3, 127.1, 126.0, 123.9, 117.6, 108.9, 59.6, 17.0, 14.0. IR (neat, cm^{-1}): 2981, 1712, 1499, 1417, 1266, 1324, 1111, 1023, 741. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.08; H, 6.57.

1-(Phenyl-2-methanol)pyrazole (Entry 1). Following the general procedure, pyrazole (0.068 g, 1.0 mmol) was coupled with 2-bromobenzyl alcohol (0.187 g, 1.00 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in toluene (0.5 mL). Column chromatography (3:1 hexanes:ethyl acetate) provided 0.132 g (76% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (m, 1H), 7.69 (m, 1H), 7.48 (m, 1H), 7.30 (m, 3H), 6.46 (m, 1H), 5.33 (t, 1H, J = 7.0 Hz), 4.40 (d, 2H, J = 7.00 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 139.4, 135.2, 131.4, 130.0, 128.6, 128.0, 123.6, 106.9, 62.2. IR (neat, cm^{-1}): 3364, 2878, 1519, 1456, 1397, 1329, 1203, 1051, 1022, 943, 761. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 68.59; H, 5.81.

1-(4′-Propiophenone)pyrazole (Entry 2). Following the general procedure, pyrazole (0.068 g, 1.00 mmol) was coupled with 4′-bromopropiophenone (0.277 g, 1.20 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with toluene (1 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.196 g (98% yield) of the title compound as a white solid. Mp: 90−91 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (m, 2H), 8.02 (d, 1H, J = 2.3 Hz), 7.79 (m, 3H), 6.51 (s, 1H), 3.02 (q, 2H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 143.0, 141.9, 134.4, 129.6, 126.8, 118.3, 108.5, 31.7, 8.2. IR (neat, cm^{-1}): 3132, 2972, 1681, 1604, 1413, 1201, 1047, 932, 850, 801, 747. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 71.83; H, 6.11.

1-(3′-Pyridine)ethyl-4-pyrazolecarboxylate (Entry 3). Following the general procedure, ethyl-4-pyrazolecarboxylate (0.140 g, 1.00 mmol) was coupled with 3-bromopyridine (116 μL, 1.20 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (1:1 hexanes/ethyl acetate for two rows and then ethyl acetate to elute) provided 0.186 g (86% yield) of the title compound as a white solid. Mp: 87−89 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.62 (d, 1H, J = 4.3 Hz), 8.52 (s, 1H), 8.15 (s, 1H), 8.08 (d, 1H, J = 8.1 Hz), 7.45 (dd, 1H, J = 4.7, 8.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 1.38 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 148.4, 142.6, 140.7, 135.6, 130.0, 126.7, 123.8, 117.5, 60.4, 14.17. IR (neat, cm^{-1}): 3123, 2978, 1706, 1561, 1275, 1258, 1140, 949, 766.

1-(2′-Aminophenyl)pyrazole (Entry 4). Following the general procedure, pyrazole (0.068 g, 1.0 mmol) was coupled with 2-bromoaniline (0.206 g, 1.20 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.144 g (90% yield) of the title compound as a yellow oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[15]

1-(4′-Hydroxyphenyl)-3-methylpyrazole (Entry 5). Following the general procedure, 3-methylpyrazole (81 μL, 1.00 mmol) was coupled with 4-bromophenol (0.208 g, 1.20 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (3:1 hexanes/ethyl acetate) provided 0.138 g (79% yield) of the title compound as a white solid. Mp: 92−93 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 1H, J = 2.3 Hz), 7.42 (m, 2H), 6.85 (m, 2H), 6.23 (d, 1H, J = 2.3 Hz), 4.99 (bs, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 151.2, 134.2, 130.1, 122.5, 117.0, 108.0, 13.5. IR (neat, cm^{-1}): 3423, 1642, 1455, 1374, 1275, 1237, 1053, 833, 768. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 68.59; H, 5.78.

1-(2′-Methylphenyl)pyrazole (Entry 6). Following the general procedure, pyrazole (0.068 g, 1.0 mmol) was coupled with 2-bromotoluene (1 mL, 8.31 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with no additional solvent. Column chromatography (19:1 hexanes/ethyl acetate and then 4:1 hexanes/ethyl acetate to elute product) provided 0.142 g (90% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[16]

1-Phenylpyrazole (Entry 7). Following the general procedure, pyrazole (0.068 g, 1.0 mmol) was coupled with iodobenzene (134 μL, 8.31 mmol) using K_2CO_3 (0.290 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL) at 80 °C for 24 h. Column chromatography (19:1 hexanes/ethyl acetate) provided 0.134 g (93% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[17]

1-(4″-Chloro-3′-carboxymethylphenyl)pyrazole (Entry 8). Following the general procedure, pyrazole (0.034 g, 0.50 mmol) was coupled with 3-carboxymethyl-4-choloro-1-iodobenzene (0.178 g, 0.0600 mmol) using K_2CO_3 (0.145 g, 1.05

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mmol), CuI (0.0048 g, 0.025 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in toluene (0.5 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.104 g (88% yield) of the title compound as a white solid. Mp: 101−102 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 1H, J = 2.7 Hz), 7.94 (d, 1H, J = 2.5 Hz), 7.75 (m, 2H), 7.50 (d, 1H, J = 8.7 Hz), 6.48 (m, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 141.6, 138.4, 132.0, 131.0, 130.5, 126.6, 122.5, 121.3, 108.3, 52.6. IR (neat, cm^{-1}): 3131, 3147, 2955, 1724, 1582, 1481, 1345, 1233, 1058, 944, 828, 742. Anal. Calcd for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83. Found: C, 56.04; H, 3.93.

1-(Ethyl-4′-benzoate)ethylpyrazole-4-carboxylate (Entry 9). Following the general procedure, ethyl 4-pyrazolecarboxylate (0.140 g, 1.00 mmol) was coupled with ethyl 4-bromobenzoate (196 μL, 1.20 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.226 g (78% yield) of the title compound as a white solid. Mp: 135−136 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.15 (m, 3H), 7.81 (d, 2H, J = 8.7 Hz), 4.38 (m, 4H), 1.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.4, 142.6, 142.3, 131.1, 130.0, 129.1, 118.7, 117.5, 61.2, 60.5, 14.3, 14.2. IR (neat, cm^{-1}): 3135, 2981, 1715, 1610, 1563, 1413, 1283, 1107, 1030, 949, 858, 767. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59. Found: C, 62.73; H, 5.68.

1-Phenyl-3-(trifluoromethyl)ethylpyrazole-4-carboxylate (Entry 10). Following the general procedure, ethyl-3-(triflouromethyl)-pyrazole-4-carboxylate (0.208 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (9:1 hexanes/ethyl acetate) provided 0.223 g (78% yield) of the title compound as a white solid. Mp: 91−93 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.70 (m, 2H), 7.48 (m, 2H), 7.40 (m, 1H), 4.35 (q, 2H, J = 7.1 Hz), 1.37 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 138.5, 132.8, 129.7, 128.4, 121.7, 119.9, 119.0, 114.7, 61.0, 14.0. IR (neat, cm^{-1}): 3136, 2992, 1732, 1551, 1490, 1303, 1220, 1148, 1068, 1049, 909, 743. Anal. Calcd for $C_{13}H_{11}N_2O_2F_3$: C, 54.93; H, 3.90. Found: C, 55.02; H, 3.89. The regiochemistry of the product (i.e., arylation at *N*-1 vs *N*-2) was determined via X-ray crystallography. See the Supporting Information for details.

1-(2′-Bromophenyl)ethylpyrazole-4-carboxylate (Entry 11). Following the general procedure, ethylpyrazole-4-carboxylate (0.140 g, 1.00 mmol) was coupled with 2-bromotoluene (361 μL, 3.00 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with no added solvent. Column chromatography (9:1 hexanes/ethyl acetate) provided 0.180 g (78% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 2H, J = 6.6 Hz), 7.30 (m, 4H), 4.33 (q, 2H, J = 7.1 Hz), 2.24 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 141.5, 139.0, 133.7, 133.6, 131.3, 129.0, 126.6, 125.9, 115.8, 60.2, 17.8, 14.3. IR (neat, cm^{-1}): 3129, 2981, 1717, 1556, 1505, 1406, 1247, 1140, 1030, 955, 764. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.76; H, 6.18.

3,5-Dimethyl-1-phenylpyrazole (Entry 12). Following the general procedure, 3,5-dimethylpyrazole (0.096 g, 1.0 mmol) was coupled with iodobenzene (225 μL, 2.00 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with no added solvent. Column chromatography (3:1 hexanes/ethyl acetate) provided 0.171 g (91% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 4H), 7.31 (m, 1H), 5.98 (s, 1H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 139.7, 139.1, 128.8, 127.0, 124.5, 106.7, 13.3, 12.2. IR (neat, cm^{-1}): 2922, 1598, 1557, 1504, 1419, 1381, 1366, 1132, 1026, 779, 755, 696.

3,5-Dimethyl-1-(3′-aminomethylphenyl)pyrazole (Entry 13). Following the general procedure, 3,5-dimethylpyrazole (0.096 g, 1.0 mmol) was coupled with 3-iodobenzylamine (266 μL, 2.00 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) with no added solvent. Column chromatography (50:1 CH_2Cl_2/MeOH solution saturated with ammonia) provided 0.137 g (68% yield) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 2H), 7.27 (m, 2H), 5.97 (s, 1H), 3.89 (s, 2H), 2.61 (s, 2H), 2.28 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 144.3, 139.9, 139.1, 128.7, 125.6, 123.3, 122.6, 106.7, 45.9, 13.2, 12.1. IR (neat, cm^{-1}): 3362, 2924, 1593, 1557, 1495, 1367, 1323, 1133, 1025, 979, 906, 794, 701. Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51. Found: C, 71.51; H, 7.23.

2,5-Diphenyl-3-aminopyrazole (Entry 14). Following the general procedure, 3-amino-5-phenylpyrazole (0.159 g, 1.00 mmol) was coupled with iodobenzene (112 μL, 1.00 mmol) using K_2CO_3 (0.290 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (0.5 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.212 g (90% yield) of the title compound as a pale brown solid. Mp: 129−130 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.59 (m, 2H), 7.47 (m, 2H), 7.35 (m, 4H), 5.88 (s, 1H), 3.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 145.8, 138.5, 133.4, 129.4, 128.4, 127.7, 127.4, 125.5, 124.0, 88.0. IR (neat, cm^{-1}): 3060, 1624, 1598, 1561, 1480, 1505, 1456, 1070, 954, 758, 698, 653. Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57. Found: C, 76.48; H, 5.54. The regiochemistry of the product (i.e., arylation at *N*-1 vs *N*-2) was determined via NOE difference experiments. See the Supporting Information for details.

1-(4′-Methylphenyl)indazole (Entry 1). Following the general procedure, indazole (0.118 g, 1.00 mmol) was coupled with 4-iodotoluene (0.262 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (19:1 hexanes/ethyl acetate) provided 0.178 g (85% yield) of the title compound as a white solid. Mp: 62−64 °C (chloroform) [lit.[18] mp 63−65 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[18]

1-(3′-Methoxyphenyl)indazole (Entry 3): Following the general procedure, indazole (0.118 g, 1.00 mmol) was coupled with 3-iodoanisole (0.281, 1.20 mmol) using K_3PO_4 (0.446 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (19:1 hexanes/ethyl acetate) provided 0.204 g (91% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.77 (m, 2H), 7.41 (m, 2H), 7.30 (m, 2H), 7.21 (m, 1H), 6.88 (m, 1H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 141.2, 138.6, 135.3, 130.0, 127.1, 125.2, 121.5, 121.2, 114.6, 112.5, 110.5, 108.2, 55.4. IR (neat, cm^{-1}): 3063, 2960, 2836, 1607, 1497, 1419, 1244, 1163, 909, 844, 744, 691. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found: C, 74.83; H, 5.55.

1-(2′-Aminophenyl)indazole (Entry 5). Following the general procedure, indazole (0.118 g, 1.00 mmol) was coupled with 2-iodoaniline (0.263 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (5:1 hexanes/ethyl acetate) provided 0.180 g (80% yield) of the title compound as an orange oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[19]

3-Chloro-1-(4′-methylphenyl)-ndazole (Entry 7). Following the general procedure, 3-chloroindazole (0.153 g, 1.00 mmol) was coupled with 4-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in toluene (1 mL). Column chromatography (50:1 hexanes/ethyl acetate) provided 0.206 g (85% yield) of the title compound as a white solid. Mp: 51−52 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H,

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J = 8.2 Hz), 7.62 (d, 1H, J = 8.6 Hz), 7.52 (m, 2H), 7.41 (m, 1H), 7.28 (d, 2H, J = 8.2 Hz), 7.22 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 137.0, 136.8, 135.4, 130.0, 128.1, 122.5, 122.1, 121.9, 119.9, 110.7, 21.0. IR (neat, cm^{-1}): 3040, 2922, 1613, 1517, 1465, 1337, 1213, 1040, 819, 743. Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57. Found: C, 69.50; H, 4.73.

1-(3,5-Dimethylphenyl)imidazole (Entry 1). Prepared as previously described.[5] Column chromatography provided 0.158 g (92% yield) of the title compound as a white solid. The ^{1}H NMR spectrum was in accord with that reported in the literature.[5]

1-(3,5-Dimethylphenyl)benzimidazole (Entry 2). Prepared as previously described.[5] Column chromatography (1:1 hexanes/ethyl acetate) provided 0.205 g (92% yield) of the title compound as a white solid. The ^{1}H NMR spectrum was in accord with that reported in the literature.[5]

1-Phenyl-4-methylimidazole (Entry 3). Following the general procedure, 4-methylimidazole (0.082 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using Cs_2CO_3 (0.684 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in DMF (0.5 mL). Column chromatography (10:1 hexanes/ethyl acetate) provided 0.122 g (77% yield) of the title compound as a white solid. Mp: 61−63 °C (chloroform) [lit.[20] mp 59.5−60.5 °C (ether)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[20] Only one regioisomer was detected by GC/MS from the crude reaction mixture.

1,4-Diphenylimidazole (Entry 4). Following the general procedure, 4-phenylimidazole (0.144 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using Cs_2CO_3 (0.652 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in DMF (0.5 mL). Column chromatography (2:1 hexanes/ethyl acetate) provided 0.194 g (88% yield) of the title compound as a white solid. Mp: 98−99 °C (chloroform) [lit.[21] mp 96−98 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[21] Only one regioisomer was detected by GC/MS from the crude reaction mixture.

9-Phenylpurine (Entry 5). Following the general procedure, purine (0.120 g, 1.00 mmol) was coupled with iodobenzene (2225 μL, 2.00 mmol) using Cs_2CO_3 (0.684 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (32 μL, 0.20 mmol, 20 mol %) in DMF (0.5 mL). Column chromatography (1:2 hexanes/ethyl acetate) provided 0.136 g (69% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[22]

1-Phenyl-2,4-triazole (Entry 1). Following the general procedure, 1,2,4-triazole (0.069 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.425 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (3:1 hexanes/ethyl acetate) provided 0.135 g (93% yield) of the title compound as a colorless oil that solidified to a light yellow solid after drying under vacuum. Mp: 44−44.5 °C (chloroform) (lit.[23] mp 44−45 °C). The ^{1}H NMR spectrum was in accord with that reported in the literature.[23]

1-(4′-Methoxyphenyl)-2,4-triazole (Entry 2). Following the general procedure, 1,2,4-triazole (0.069 g, 1.00 mmol) was coupled with 4-iodoanisole (0.281 g, 1.20 mmol) using K_3PO_4 (0.425 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.138 g (79% yield) of the title compound as a white solid. Mp: 96−97 °C (chloroform) [lit.[24] mp 95−96 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[24]

1-(4′-Acetylphenyl)-2,4-triazole (Entry 3). Following the general procedure, 1,2,4-triazole (0.069 g, 1.00 mmol) was coupled with 4′-iodoacetophenone (0.295 g, 1.20 mmol) using K_3PO_4 (0.425 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.147 g (79% yield) of the title compound as a white solid. Mp: 151.5−152.5 °C (chloroform) [lit.[25] mp 150−151 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[25]

1-(3′-Aminomethylphenyl)-2,4-triazole (Entry 4). Following the general procedure, 1,2,4-triazole (0.069 g, 1.00 mmol) was coupled with 3-iodobenzylamine (133 μL, 1.00 mmol) using K_3PO_4 (0.425 g, 2.10 mmol), CuI (0.0095 g, 0.050 mmol), and **3** (11 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (100:1 CH_2Cl_2/MeOH solution saturated with ammonia, then 25:1 to elute product) provided 0.138 g (79% yield) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.07 (s, 1H), 7.67 (s, 1H), 7.50 (m, 3H), 3.94 (s, 2H), 1.57 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 145.0, 140.5, 136.7, 129.4, 126.4, 118.3, 117.8, 45.7. IR (neat, cm^{-1}): 3348, 3098, 2917, 1594, 1510, 1279, 1145, 994, 790, 674.

1-Phenylbenzotriazole (Entry 5). Following the general procedure, benzotriazole (0.119 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.425 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.175 g (90% yield) of the title compound as a white solid. Mp: 85−87 °C (chloroform) (lit.[26] mp 85−86 °C). The ^{1}H NMR spectrum was in accord with that reported in the literature.[26]

1-(4′-Acetylphenyl)benzotriazole (Entry 6). Following the general procedure, benzotriazole (0.119 g, 1.00 mmol) was coupled with 4′-iodoacetophenone (0.295 g, 1.20 mmol) using K_3PO_4 (0.425 g, 2.0 mmol), CuI (0.0095 g, 0.050 mmol), and **2** (16 μL, 0.10 mmol, 10 mol %) in DMF (1 mL). Column chromatography (1:1 hexanes/ethyl acetate) provided 0.149 g (63% yield) of the title compound as a white solid. Mp: 151−152 °C (chloroform) [lit.[27] mp 152−153 °C (no solvent given)]. The ^{1}H NMR spectrum was in accord with that reported in the literature.[27]

General Procedure for Halide Exchange/Arylation Sequence and Characterization of Products. 1-(4′-Methylphenyl)-2-acetylpyrrole. To a screw cap resealable test tube with stir bar were added CuI (0.019 g, 0.10 mmol) and NaI (0.300 g, 2.00 mmol). A rubber septum was attached, and the tube was evacuated and then back-filled with argon and repeated. To this tube was then added 4-bromotoluene (123 μL, 1.20 mmol), **3** (22 μL, 0.20 mmol, 20 mol %), and toluene (1 mL) by syringe. A screw cap was fitted, and the tube was immerged into a preheated oil bath (caution: build-up of pressure possible; use a safety shield) at 110 °C for 24 h with magnetic stirring. The tube was temporarily removed from the oil bath and cooled at ambient temperature for 15 min, and then 2-acetylpyrrole (0.109 g, 1.00 mmol) and K_3PO_4 (0.446 g, 2.10 mmol) were quickly added and the tube was re-capped and again placed in the oil bath for an additional 24 h. The reaction mixture was removed from heating, allowed to attain ambient temperature, diluted with ethyl acetate (2−3 mL), filtered through a plug of silica gel, and eluted with additional ethyl acetate (10−20 mL). The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (2 × 25 cm of silica, 9:1 hexanes/ethyl

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acetate) to provided 0.147 g (74% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (m, 2H), 7.12 (m, 2H), 7.09 (m, 1H), 6.89 (m, 1H), 6.23 (m, 1H), 2.37 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 138.1, 137.2, 131.3, 130.9, 129.0, 125.6, 120.1, 108.8, 27.0, 20.9. IR (neat, cm^{-1}): 3034, 2923, 1664, 1516, 1408, 1347, 1268, 1111, 935, 821, 741.

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Supporting Information Available: Required ^{1}H and ^{13}C NMR spectra for unknown compounds, X-ray crystallography data, and NOE difference spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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