


Ligands for Copper-Catalyzed C–N Bond Forming Reactions with 1 Mol% CuBr as Catalyst

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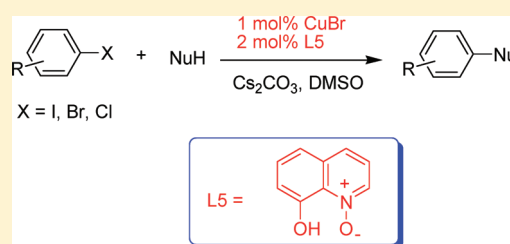
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 Supporting Information

ABSTRACT: Several new ligands were designed to promote copper-catalyzed Ullman C–N coupling reactions. In this group, 8-hydroxyquinolin-*N*-oxide was found to serve as a superior ligand for CuBr-catalyzed coupling reactions of aryl iodides, bromides, and chlorides with aliphatic amines and *N*-heterocycles under a low catalyst loading (1% [Cu] mol). Reactions with the inexpensive catalytic system display a high functional group tolerance as well as excellent chemoselectivity.¹



INTRODUCTION

The copper-catalyzed Ullmann coupling reaction is one of the most important methodologies in modern organic synthesis.^{1,2} During the development of this process, ligand identification has played an important role in improving both the efficiencies and scope of the methodology.^{1,2} Recently, several classes of ligands, including diols,³ diamines,⁴ amino acids,⁵ amino alcohols,⁶ phosphoramidites,⁷ oxime-phosphine oxides,⁸ pyridine *N*-oxide,⁹ and β -diketones and β -keto esters,¹⁰ have been found to promote copper-catalyzed Ullmann C–N bond-forming reactions.^{11–13} However, significant challenges remain to be overcome in this area. For example, it is rare that the process takes place under mild conditions when $\leq 1\%$ [Cu] mol catalyst loading is used. In addition, in order to reduce costs, it is highly desirable to use aryl chlorides in Ullmann C–N coupling reactions.² In the study described below, we observed that 8-hydroxyquinolin-*N*-oxide (L5) serves as an effective ligand for copper-catalyzed C–N bond-forming reactions of aryl iodides, bromides as well as chlorides with aliphatic amines and *N*-heterocyclic substrates that are promoted by using only 1 mol % of CuBr as catalyst.

RESULTS AND DISCUSSION

Ligands that coordinate to the metal center play a key role in governing the efficiencies of catalyst systems employed in Ullmann C–N coupling reactions. An analysis of the results of previous studies showed that the ligands probed thus far contain bidentate chelating centers that have the capability of coordinating with Cu(I) to form five- or six-membered ring structures.¹⁴ On the basis of this consideration, we believed that novel ligands possessing a pyridine and related *N*-oxide ring (L1–L5 in Figure 1) would

promote these copper-catalyzed cross-coupling processes. We reasoned that the *N*-oxide and the carboxyl or hydroxyl oxygen centers in these substances would be capable of participating in formation of six-membered-ring chelates with copper ion.

4-Methyl iodobenzene and benzylamine were selected as model substrates to evaluate the catalytic activity of systems comprised of the designed ligands in room temperature *N*-arylation reactions. Reactions were carried out in DMF with 10 mol % of CuI and Cs₂CO₃ (Table 1, entries 1–6). Importantly, the coupling reaction does not occur when ligands are absent (entry 19). The results showed that the highest yield (67%, entry 5) was obtained when L5 was employed as the ligand. This finding might be a result of the fact that L5 possesses a rigid conformation that enables its strong complexation with copper via a six-membered-ring chelate.

By using L5 as the ligand and DMF as the solvent, reactions employing other bases, including K₂CO₃, K₃PO₄, NaOt-Bu, KOH, and CsOH, were explored. This effort demonstrated that a superior yield is obtained when Cs₂CO₃ is used as the base (Table 1, entries 5 and 7–11). Solvent was also found to play an important role in this process (entries 5 and 12–14). Observations indicate that DMSO is the most favorable solvent for the catalytic reaction (entry 14). In addition, although a variety of copper salts can be utilized in the C–N bond-forming reaction, CuBr was found to promote the highest yielding reactions (92%, entry 18) when 20 mol % of L5 was used. When 1 mol % of CuBr was employed, the reaction at room temperature provided the coupling product in only 46% yield (entry 20). When the temperature was raised to 65 °C, the yield of the process increased

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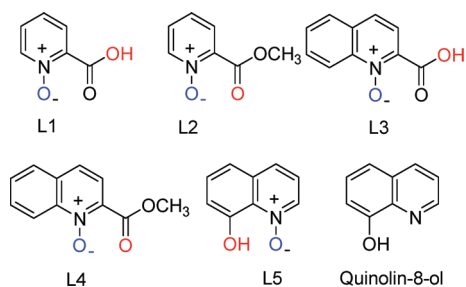
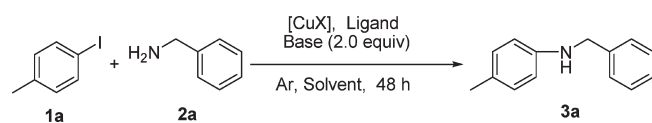


Figure 1. Structures of designed ligands.

Table 1. Designed Ligands for Copper-Catalyzed C–N Coupling Reaction^a

entry	ligand	base	copper source	solvent	yield (%) ^b
1	L1	Cs ₂ CO ₃	CuI	DMF	33
2	L2	Cs ₂ CO ₃	CuI	DMF	31
3	L3	Cs ₂ CO ₃	CuI	DMF	38
4	L4	Cs ₂ CO ₃	CuI	DMF	26
5	L5	Cs ₂ CO ₃	CuI	DMF	67
6	quinolin-8-ol	Cs ₂ CO ₃	CuI	DMF	26
7	L5	K ₂ CO ₃	CuI	DMF	22
8	L5	K ₃ PO ₄	CuI	DMF	57
9	L5	NaOBu ^t	CuI	DMF	20
10	L5	KOH	CuI	DMF	13
11	L5	CsOH	CuI	DMF	20
12	L5	Cs ₂ CO ₃	CuI	toluene	24
13	L5	Cs ₂ CO ₃	CuI	CH ₃ CN	20
14	L5	Cs ₂ CO ₃	CuI	DMSO	88
15	L5	Cs ₂ CO ₃	CuBr ₂	DMSO	36
16	L5	Cs ₂ CO ₃	CuCl ₂	DMSO	9
17	L5	Cs ₂ CO ₃	CuCl	DMSO	91
18	L5	Cs ₂ CO ₃	CuBr	DMSO	92
19	none	Cs ₂ CO ₃	CuI	DMF	0
20 ^c	L5	Cs ₂ CO ₃	CuBr	DMF	46
21 ^d	L5	Cs ₂ CO ₃	CuBr	DMF	86

^a Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), 10 mol % [CuX], 20 mol % ligand, base (2.0 mmol), solvent (2 mL), Ar, 25 °C, 48 h.

^b Isolated yield. ^c **1a** (10.0 mmol), **2a** (15.0 mmol), 1 mol % [CuX], 2 mol % ligand, base (20.0 mmol), solvent (10 mL), Ar, 25 °C, 48 h. ^d 1 mol % [CuBr], at 65 °C.

to 86% (entry 21). The results of the preliminary exploratory investigations described above showed that the optimal conditions for the Ullmann C–N coupling reaction of 4-methyl iodobenzene and benzylamine involves the use of 1 mol % of CuBr, 2 mol % of L5, and 2.0 equiv of Cs₂CO₃ in DMSO at 65 °C.

The scope of the CuBr/L5 catalytic process carried out under the optimized conditions was probed by using a variety of aryl iodides and amines or *N*-heterocyclic substrates. As the results in Table 2 show, coupling reactions with most substrates proceeded at 65 °C in yields ranging from 70% to 87%. Both electron-rich and electron-deficient aryl iodides were observed to display

Table 2. CuBr-Catalyzed Amination of Aryl Iodides^a

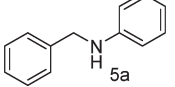
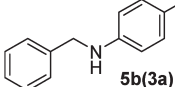
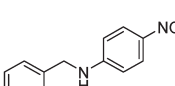
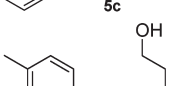
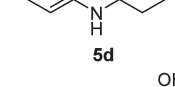
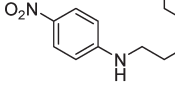
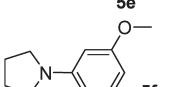
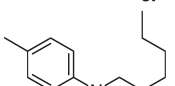
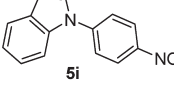
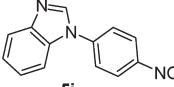
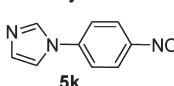
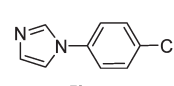

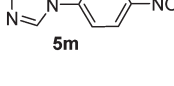
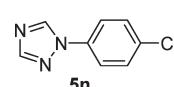
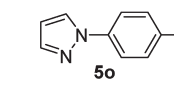
entry	product	time (h)	yield ^b (%)	entry	product	time (h)	yield ^b (%)
1	3a	48	86	8	3h	60	82
2	3b	50	81	9	3i	60	76
3	3c	60	82	10	3j	50	87
4	3d	60	82	11	3k	60	70
5	3e	60	75	12	3l	60	80
6	3f	48	79	13	3m	60	84
7	3g	60	76	14	3n	60	85

^a Reaction conditions: ArI (5.0 mmol), amine (7.5 mmol), Cs₂CO₃ (10.0 mmol), CuBr (0.05 mmol, 1 mol %), and L5 (0.10 mmol, 2 mol %) in 5.0 mL of DMSO at 65 °C under argon. ^b Isolated yield.

similar reactivities. For example, reactions of aryl iodides and primary amines took place in high yields (81–86%) (entries 1–4). Even hindered, cyclic secondary amines, e.g., pyrrolidine, piperidine, and morpholine, react efficiently with aryl iodides (75–76%) (entries 5–7). Interestingly, the catalytic process was highly chemoselective in a case where the amine substrate contains more than one potentially reactive group. This is a highly desirable feature in the context of complex molecule synthesis (entry 8). It is important to note that *N*-arylation reactions of nitrogen-containing heterocycles are often quite sluggish when 1 mol % of Cu catalysts are employed. However, by using the CuBr/L5 catalyst system, coupling reactions of aryl iodides with nitrogen heterocycles, such as pyrazole, pyrrole, imidazole, 1*H*-benzimidazole, and indole, with 1 mol % of CuBr under the optimized conditions developed in this effort smoothly afforded the corresponding products in high yields (entries 9–14).

As pointed out by the results displayed in Table 3, extension of the amination process to aryl bromides was also successful. All the

Table 3. CuBr-Catalyzed Amination of Aryl Bromides^a

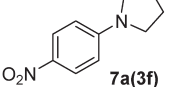
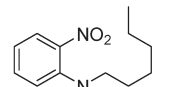
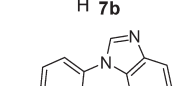
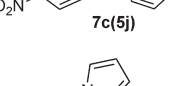
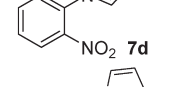
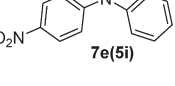
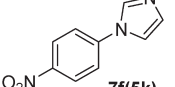
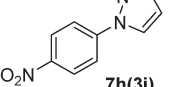
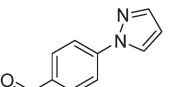
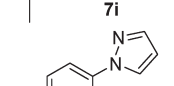
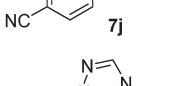
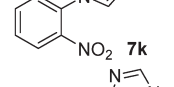
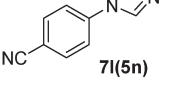
$\text{R}-\text{C}_6\text{H}_4-\text{Br} \quad \text{4} + \quad \text{HNR}_1\text{R}_2 \quad \text{2} \xrightarrow[\text{DMSO, 90 } ^\circ\text{C}]{\substack{1 \text{ mol\% CuBr} \\ 2 \text{ mol\% L5} \\ 2.0 \text{ equiv Cs}_2\text{CO}_3}} \text{R}-\text{C}_6\text{H}_4-\text{NR}_1\text{R}_2 \quad \text{5}$			
Entry	Product	Time (h)	yield (%)
1		48	68
2		48	71
3		24	72
4		60	55
5		24	82
6		60	38
7		60	83 ^c
8		24	78
Entry	Product	Time (h)	yield (%)
9		12	86
10		12	89
11		12	99
12		18	90 ^c
13		12	84
14		20	88 ^c
15		48	60 ^c
16		48	68 ^c

^a Reaction conditions: ArBr (5.0 mmol), amine (7.5 mmol), Cs₂CO₃ (10.0 mmol), CuBr (0.05 mmol, 1 mol %), and L5 (0.10 mmol, 2 mol %) in 5.0 mL of DMSO at 90 °C under argon. ^b Isolated yield. ^c At 110 °C.

aryl bromides examined participate in coupling reactions with primary amines and *N*-heterocycles that occur in good yields at moderate temperatures. The reactions are efficient even in cases of aryl bromides that possess electron-donating groups (entries 2, 7, 15, and 16). In addition, when other potentially reactive functional groups (e.g., hydroxyl) are present, in the amine substrate the arylation occurred chemoselectively at nitrogen (entries 4 and 5).

To evaluate the potential catalytic efficiency of the CuBr/L5 system, coupling reactions of aryl chlorides with amines and *N*-heterocyclic substances were investigated. Owing to the generally low reactivity of aryl chlorides, their participation in copper-catalyzed *N*-arylation is challenging.^{2,10a,11d,12a} We observed that although the coupling reactions of aryl chlorides occur only slowly at room temperature using the CuBr/L5 catalyst, good yields were obtained when the temperature was raised to 110 °C (Table 4). For example, although no product was formed after 24 h when 1-chloro-2-nitrobenzene was reacted with hexylamine at

Table 4. Copper-Catalyzed Amination of Aryl Chlorides^a

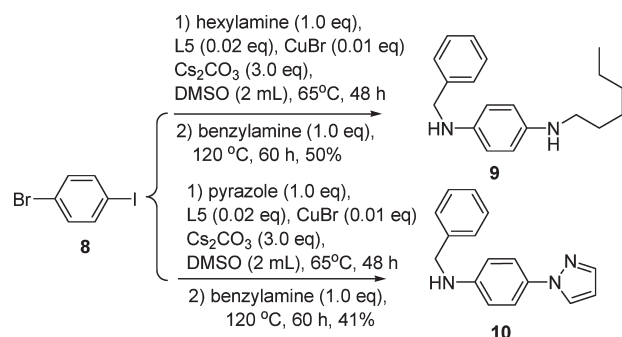
$\text{R}-\text{C}_6\text{H}_4-\text{Cl} \quad \text{6} + \quad \text{HNR}_1\text{R}_2 \quad \text{2} \xrightarrow[\text{DMSO, 110 } ^\circ\text{C}]{\substack{1 \text{ mol\% CuBr} \\ 2 \text{ mol\% L5} \\ 2.0 \text{ equiv Cs}_2\text{CO}_3}} \text{R}-\text{C}_6\text{H}_4-\text{NR}_1\text{R}_2 \quad \text{7}$			
Entry	Product	Time (h)	yield (%)
1		20	81
2		20	85
3		20	88
4		20	76
5		20	80
6		22	89
7		20	90
Entry	Product	Time (h)	yield (%)
8		18	78
9		40	52
10		18	88
11		24	82
12		26	85
13		18	67

^a Reaction conditions: ArCl (5.0 mmol), amine (7.5 mmol), Cs₂CO₃ (10 mmol), CuBr (0.05 mmol, 1 mol %), and L5 (0.10 mmol, 2 mol %) in 5 mL of DMSO at 110 °C under argon. ^b Isolated yield.

room temperature, an 85% yield of the coupling product is generated when the reaction was carried out at 110 °C for 20 h (Table 4, entry 2). Even the sterically more hindered pyrrolidine (entry 1) reacts with this aryl chloride in 81% yield at the elevated temperature. In addition, a good yield (89%) of the coupling product is obtained from reaction of 1-chloro-4-nitrobenzene with imidazole (entry 6), which represents an improvement over other reported reactions of these substrates.¹⁵ As is the case for reactions of the other aryl halides, CuBr/L5 catalyzed Ullman type C–N bond-forming reactions of aryl chlorides display a great functional group tolerance (entries 3–12) and high chemoselectivity when multiple potentially reactive functional groups are present in the amine (entry 13). The results described above demonstrate that the CuBr/L5 catalyst system promotes highly efficient coupling reactions of aryl halides with aliphatic amines and *N*-heterocycles.

Since the efficiencies of intermolecular CuBr/L5 catalyzed amination reactions of aryl iodides, bromides, and chlorides can be controlled by varying temperature, we envisaged that this methodology could be used to carry out a one-pot synthesis of unsymmetrically bis-substituted phenylamine derivatives (Scheme 1). Indeed,

Scheme 1. One-Pot Synthesis of Unsymmetrical *N,N'*-Di-alkylated Phenylenediamines



1-bromo-4-iodobenzene was observed to react independently with hexylamine and pyrazole at 65 °C under the optimized conditions to generate the corresponding *p*-bromophenyl adducts. Without isolation, benzylamine (1.0 equiv) was added to each reaction mixture and the temperature of each was raised to 120 °C, respectively. As anticipated, these processes produced the corresponding *p*-phenylenediamine adducts **9** and **10** in respective yields of 50% and 41%.

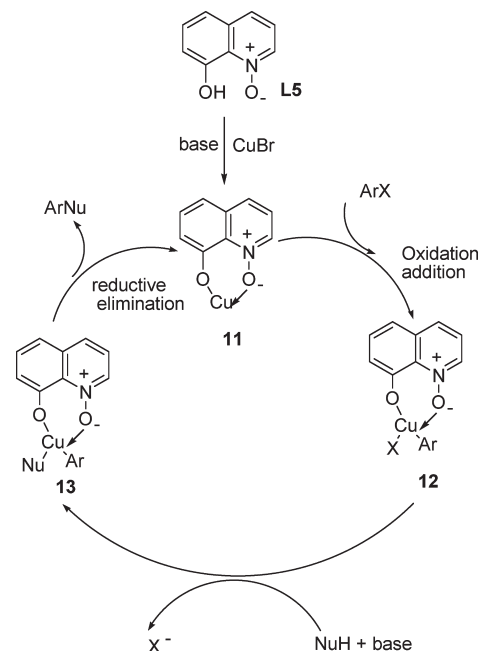
Furthermore, as described in Scheme 2, we have formulated a possible mechanism for the copper-catalyzed *N*-arylation of aliphatic amines or *N*-containing heterocycles that is based on the previously proposed mechanism.¹⁶ Tolman's group and Yamamoto's group have reported reactions of copper(I) or -(II) with *N*-oxides.¹⁷ We proposed that the chelating CuBr with 8-hydroxyquinolin-*N*-oxide (**L5**) formed a six-member reactive species **11**, and the subsequent oxidative addition of the chelating with aryl halides led to the intermediate **12**. In the presence of base, aliphatic amines or *N*-containing heterocycles reacted with intermediate **12** readily to afford intermediate **13**, followed by reductive elimination to provide the desired product and regenerate active Cu(I) species **11**. We inferred that CuBr is the best catalyst for the present reaction by virtue of its insensitivity to light and air.

In summary, this effort has led to the identification of 8-hydroxyquinolin-*N*-oxide as an ideal ligand for promoting copper-catalyzed Ullmann coupling reactions of aryl halides with primary aliphatic amines and their secondary cyclic counterparts, as well as with *N*-heterocyclic substrates. These processes take place with use of a significantly low catalyst loading (1% [Cu] mol) and mild conditions. Significantly, the catalytic system can be used to promote highly efficient C–N bond-forming reactions of inexpensive aryl chlorides. Finally, the protocol we have developed can be used in a one-pot procedure for the synthesis of unsymmetrical *N,N'*-dialkylated or heterocyclic *p*-phenylenediamines derivatives.

EXPERIMENTAL SECTION

Picolinic acid *N*-oxide (L1**):**^{18a} To a solution of picolinic acid (12.3 g, 0.1 mol) in dry CH₂Cl₂ (150 mL) cooled to 0 °C was added MCPBA (17.3 g, 0.1 mol) in CH₂Cl₂ (50 mL) with efficient stirring in ca. 20 min. After 50 min, the solution was quenched by NaHCO₃ solution (30 mL). The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature, then washed with brine (3 × 20 mL). The organic phase was dried over Na₂SO₄ and concentrated to leave a white solid. Purification by silica gel chromatography afforded picolinic acid *N*-oxide as a white solid (13.5 g, 97%). Mp 162 °C dec; ¹H NMR (400 MHz, CDCl₃) 8.45 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.38 (d, *J* = 6.4

Scheme 2. Proposed Mechanism



Hz, 1H), 7.70 (ddd, *J* = 7.6, 7.6 Hz, *J* = 0.8 Hz, 1H), 7.64 (ddd, *J* = 6.8, 6.0, 2.0 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 160.8, 138.7, 137.3, 130.5, 129.5, 128.9 ppm; MS (EI, *m/z*) 140 (*M*⁺ + 1).

Methyl picolinate *N*-oxide (L2**):**^{18a} To absolute methanol (20 mL) was added thionyl chloride (7.3 mL, 0.1 mol) at 0 °C. Then picolinic acid *N*-oxide (6.96 g, 0.05 mol) was added to the solution. The reaction solution was refluxed for 1 h. Then the solution was evaporated and dissolved with DCM (50 mL), then successively washed with water (3 × 50 mL) and brine (3 × 50 mL). The organic phase was dried over Na₂SO₄ and concentrated to leave a white solid (7.50 g, 98%). Mp 72–73 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.73 (dd, *J* = 4.8, 0.8 Hz, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.83 (m, 1H), 7.46 (m, 1H), 3.99 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 149.7, 147.9, 137.0, 126.9, 125.1, 52.8 ppm.

Quinoline-2-carboxylic acid *N*-oxide (L3**):**^{18b} The procedure was the same as described above for the synthesis of **L1**. Mp 168–170 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.80 (d, *J* = 8.8 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.06 (m, 2H), 7.86 (dd, *J* = 7.2 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 161.8, 139.2, 134.7, 132.6, 131.2, 131.0, 130.1, 128.5, 122.4, 119.7 ppm; MS (EI, *m/z*) 190 (*M*⁺ + 1).

Methyl quinoline-2-carboxylate *N*-oxide (L4**):**^{18c} The procedure was the same as described above for the synthesis of **L2**. Mp 90–91 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 13.2, 8.8 Hz, 1H), 7.60 (m, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 3.99 (s, 3H), ppm; ¹³C NMR (100 MHz, CDCl₃) δ 162.8, 142.6, 137.4, 130.8, 130.7, 129.7, 128.1, 124.3, 121.1, 120.3, 53.1 ppm; MS (EI, *m/z*) 204 (*M*⁺ + 1).

8-Hydroxyquinolin-*N*-oxide (L5**):**^{17b} The procedure was the same as described above for the synthesis of **L1**. Mp 137–138 °C; ¹H NMR (400 MHz, CDCl₃) δ 15.0 (s, 1H), 8.22 (dd, *J* = 5.6, 0.8 Hz, 1H), 7.77 (m, 1H), 7.47 (dd, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 8.0, 6.4 Hz, 2H), 7.04 (dd, *J* = 8.0, 1.2 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 154.0, 134.4, 132.3, 130.6, 129.9, 129.6, 120.4, 116.7, 114.9 ppm; MS (EI, *m/z*) 162 (*M*⁺ + 1).

General Procedure A: Coupling of Aryl Iodides with Amines or *N*-Containing Heterocycles (5.0 mmol scale). A flask was charged with CuBr (7.2 mg, 0.05 mmol, 1 mol %), **L5**

(16 mg, 0.1 mmol, 2 mol %), Cs_2CO_3 (3.25 g, 10.0 mmol), and any remaining solids (amine and/or aryl halide). The flask was evacuated and backfilled with argon. Aryl iodide (5.0 mmol), amine (7.5 mmol) or N-containing heterocycle (7.5 mmol), and DMSO (5 mL) were added to the flask under argon atmosphere. Then the mixture was stirred at 65 °C until complete consumption of starting material, which was monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, then the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate as eluent, to provide the desired product.

N-Benzyl-4-methylbenzenamine (3a):^{5d} Following procedure A, 1-iodo-4-methylbenzene (1.09 g, 5.0 mmol) was allowed to react with benzylamine (805 mg, 7.5 mmol) for 48 h. The crude brown oil was purified by flash chromatography on silica gel to provide 86% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 5H), 7.99 (d, J = 8.0 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 4.32 (m, 2H), 2.25 (s, 3H) ppm.

N-Benzyl-4-nitrobenzenamine (3b):^{5d} Following procedure A, 1-iodo-3-nitrobenzene (1.25 g, 5.0 mmol) was allowed to react with benzylamine (805 mg, 7.5 mmol) for 50 h. The crude brown oil was purified by flash chromatography on silica gel to provide 81% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, J = 2.0, 0.4 Hz, 1H), 7.48 (m, 1H), 7.37–7.25 (m, 6H), 6.87 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 149.7, 148.1, 138.1, 129.8, 128.9, 127.7, 127.5, 118.6, 112.2, 106.8, 48.2 ppm.

N-Allyl-3,5-dimethylbenzenamine (3c): Following procedure A, 1-iodo-3,5-dimethylbenzene (1.16 g, 5.0 mmol) was allowed to react with allylamine (430 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 82% yield of the product as a brown oil. ^1H NMR (400 MHz, CDCl_3) δ 6.42 (s, 1H), 6.30 (s, 2H), 5.95 (m, 1H), 5.31 (dd, J = 16.8, 1.2 Hz, 1H), 5.18 (dd, J = 10.4, 1.2 Hz, 1H), 3.78 (dd, J = 3.8, 1.2 Hz, 2H), 2.27 (d, J = 2.4 Hz, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 148.3, 139.0, 139.9, 119.7, 115.9, 111.2, 110.5, 46.7, 21.5 ppm.

4-Chloro-N-hexylbenzenamine (3d):^{12a} Following procedure A, 1-chloro-4-iodobenzene (1.19 g, 5.0 mmol) was allowed to react with *n*-hexylamine (760 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 82% yield of the desired product as a pale purple oil. ^1H NMR (400 MHz, CDCl_3) δ 7.11 (d, J = 6.4 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.55 (brs, NH), 3.08 (s, 2H), 1.63 (m, 2H), 1.44–1.28 (m, 6H), 0.92 (t, J = 6.8 Hz, 3H) ppm.

4-Phenylmorpholine (3e):^{5d} Following procedure A, iodobenzene (1.02 g, 5.0 mmol) was allowed to react with morpholine (655 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 75% yield of the desired product as a white solid. Mp 52–54 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.26 (m, 2H), 6.94–6.87 (m, 3H), 3.87 (t, J = 4.8 Hz, 4H), 3.17 (t, J = 4.8 Hz, 4H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 151.3, 129.2, 120.1, 115.8, 66.9, 49.5 ppm.

1-(4-Nitrophenyl)pyrrolidine (3f):^{19a} Following procedure A, 1-iodo-4-nitrobenzene (1.25 g, 5.0 mmol) was allowed to react with pyrrolidine (535 mg, 7.5 mmol) for 48 h. The crude brown oil was purified by flash chromatography on silica gel to provide 79% yield of the desired product as a yellow solid. Mp 165–167 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, J = 9.2 Hz, 2H), 6.43 (d, J = 9.2 Hz, 2H), 3.38 (t, J = 6.4 Hz, 4H), 2.06 (dt, J = 5.6, 4.0 Hz, 4H) ppm.

1-*p*-Tolylpiperidine (3g):^{5c} Following procedure A, 1-iodo-4-methylbenzene (1.09 g, 5.0 mmol) was allowed to react with piperidine (640 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 76% yield of the desired product as a pale-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.08 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.12 (t, J = 5.6 Hz, 4H), 2.29 (s, 3H), 1.77–1.71 (m, 4H), 1.60–1.56 (m, 2H) ppm.

5-(Phenylamino)pentan-1-ol (3h):^{19b} Following procedure A, iodobenzene (1.02 g, 5.0 mmol) was allowed to react with 5-aminopentan-1-ol (775 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 82% yield of the desired product as a pale-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.17 (m, 2H), 6.69 (m, 1H), 6.60 (dd, J = 8.4, 0.8 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2 H), 3.13 (t, J = 7.2 Hz, 2 H), 1.70–1.59 (m, 4H), 1.53–1.45 (m, 2H) ppm.

1-(3-Chlorophenyl)-1H-pyrazole (3i):^{11j} Following procedure A, 1-chloro-3-iodobenzene (1.19 g, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 60 h. The crude brown oil was purified by flash chromatography on silica gel to provide 76% yield of the desired product as a crude oil. ^1H NMR (400 MHz, CDCl_3) δ 7.73 (dd, J = 8.0, 2.0 Hz, 1H), 7.57 (ddd, J = 8.0, 2.0, 0.8 Hz, 2H), 7.36 (dd, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.0, 2.0, 0.8 Hz, 2H), 6.46 (dd, J = 2.4, 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 141.5, 141.2, 135.3, 130.4, 126.7, 126.3, 119.5, 117.0, 108.0 ppm.

1-(4-Nitrophenyl)-1H-pyrazole (3j):^{11j} Following procedure A, 1-iodo-4-nitrobenzene (1.25 g, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 50 h. The crude brown oil was purified by flash chromatography on silica gel to provide 87% yield of the desired product as a deep yellow solid. Mp 170–172 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.34 (dd, J = 7.2, 2.0 Hz, 2H), 8.04 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 9.6, 2.0 Hz, 2H), 7.80 (d, J = 1.6 Hz, 1H), 6.56 (d, J = 2.4, 1.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 145.4, 144.4, 142.7, 127.0, 125.3, 118.6, 109.3 ppm.

1-(2-Nitrophenyl)-1H-pyrrole (3k):^{19c} Following procedure A, 1-iodo-2-nitrobenzene (1.25 g, 5.0 mmol) was allowed to react with 1H-pyrrole (505 mg, 7.5 mmol) for 60 h at 65 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 70% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (m, 1H), 7.65 (m, 1H), 7.73 (m, 1H), 7.61 (m, 1H), 7.16 (dd, J = 2.0 Hz, 2H), 6.42 (dd, J = 2.0 Hz, 2H) ppm.

1-(4-Methoxyphenyl)-1H-benzo[d]imidazole (3l):^{19d} Following procedure A, 1-iodo-4-methoxybenzene (1.17 g, 5.0 mmol) was allowed to react with 1H-benzo[d]imidazole (885 mg, 7.5 mmol) for 60 h at 65 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 80% yield of the product as a yellow solid. Mp 95–96 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.45 (dd, J = 7.2, 1.6 Hz, 1H), 7.41 (m, 2H), 7.31 (m, 2H), 7.07 (dd, J = 6.8, 2.0 Hz, 2H), 3.89 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 159.3, 143.8, 142.5, 134.2, 129.1, 125.7, 123.5, 122.5, 120.5, 115.1, 110.3, 55.6 ppm.

1-(2-Nitrophenyl)-1H-imidazole (3m):^{19e} Following procedure A, 1-iodo-2-nitrobenzene (1.25 g, 5.0 mmol) was allowed to react with 1H-imidazole (510 mg, 7.5 mmol) for 60 h at 65 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 84% yield of the desired product as a pale-yellow solid. Mp 97–98 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dd, J = 4.0, 1.6 Hz, 1H), 7.74 (ddd, J = 14.0, 4.0, 1.6 Hz, 1H), 7.61 (dd, J = 8.0, 1.2 Hz, 2H), 7.47 (dd, J = 8.0, 1.6 Hz, 1H), 7.22 (s, 1H), 7.07 (dd, J = 1.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 145.5, 137.3, 133.6, 130.7, 130.4, 129.6, 128.6, 125.3, 120.3 ppm.

1-*p*-Tolyl-1H-indole (3n):^{4c} Following procedure A, 1-iodo-4-methylbenzene (1.09 g, 5.0 mmol) was allowed to react with 1H-indole (880 mg, 7.5 mmol) for 60 h at 65 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 85% yield of the desired product as a pale-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.69 (m, 1H), 7.51 (m, 1H), 7.38 (m, 2H), 7.31 (m, 3H), 7.23–7.14 (m, 2H), 6.66 (dd, J = 3.2, 0.8 Hz, 1H), 2.44 (s, 3H) ppm.

General Procedure B: Coupling of Aryl Bromides with Amines or N-Containing Heterocycles (5.0 mmol scale). An oven-dried Schlenk tube equipped with a Teflon valve (Kontes) was charged with a magnetic stir bar, CuBr (7.2 mg, 0.05 mmol, 1 mol %), the

L5 (16 mg, 0.1 mmol, 2 mol %), and Cs_2CO_3 (3.25 g, 10.0 mmol). Any remaining solids (amine and/or aryl bromide) were added at this point. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine (7.5 mmol) (if liquid), aryl bromide (5.0 mmol) (if liquid), and DMSO (5.0 mL) were added by syringe. Finally, the tube was sealed and the mixture was heated at the indicated temperature (90–110 °C) for the indicated period of time. Upon completion of the reaction, the mixture was allowed to cool to room temperature and then was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, then the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under vacuum for at least 1 h.

N-Benzylbenzenamine (5a):^{5d} Following procedure B, bromobenzene (785 mg, 5.0 mmol) was allowed to react with benzylamine (805 mg, 7.5 mmol) for 48 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 68% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.35 (m, 4H), 7.32–7.30 (m, 1H), 7.20 (dd, J = 8.0 Hz, 2H), 6.75 (dd, J = 7.2 Hz, 1H), 6.66 (d, J = 8.0 Hz, 2H), 4.36 (s, 2H), 4.04 (br s, 1H) ppm.

N-Benzyl-4-methylbenzenamine (5b/3a):^{5d} Following procedure B, 1-bromo-4-methylbenzene (855 mg, 5.0 mmol) was allowed to react with benzylamine (805 mg, 7.5 mmol) for 48 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 71% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.26 (m, 5H), 6.99 (d, J = 8.0 Hz, 2H), 6.57 (d, J = 8.0 Hz, 2H), 4.32 (s, 2H), 2.25 (s, 3H) ppm.

N-Benzyl-4-nitrobenzenamine (5c):^{20a} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with benzylamine (805 mg, 7.5 mmol) for 24 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 72% yield of the desired product as a yellow solid. Mp 146–148 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (ddd, J = 9.2, 2.4, 2.0 Hz, 2H), 7.40–7.32 (m, 5H), 6.57 (ddd, J = 9.2, 2.4, 2.0 Hz, 2H), 4.91 (br s, 1H), 4.43 (d, J = 5.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 153.1, 138.6, 137.4, 128.9, 127.9, 127.3, 126.3, 111.4, 47.7 ppm.

5-(*p*-Toluidino)pentan-1-ol (5d):^{20b} Following procedure B, 1-bromo-4-methylbenzene (855 mg, 5.0 mmol) was allowed to react with 5-aminopentan-1-ol (775 mg, 7.5 mmol) for 60 h at 50 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 55% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, J = 8.0 Hz, 2H), 6.54 (dd, J = 6.4, 1.6 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 2.24 (s, 3H), 1.66–1.56 (m, 4H), 1.52–1.45 (m, 2H) ppm.

5-(4-Nitrophenylamino)pentan-1-ol (5e):^{20b} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with 5-aminopentan-1-ol (775 mg, 7.5 mmol) for 24 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 82% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, J = 9.2 Hz, 2H), 6.49 (d, J = 9.2, 2H), 3.64 (t, J = 6.2 Hz, 2H), 3.18 (t, J = 6.2 Hz, 2H), 2.02 (br s, 2H), 1.69–1.58 (m, 4H), 1.48 (m, 2H) ppm.

1-(3-Methoxyphenyl)pyrrolidine (5f):^{5c} Following procedure B, 1-bromo-3-methoxybenzene (935 mg, 5.0 mmol) was allowed to react with pyrrolidine (535 mg, 7.5 mmol) for 60 h at 50 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 38% yield of the desired product as a crude oil. ^1H NMR (400 MHz, CDCl_3) δ 7.14 (dd, J = 8.0 Hz, 1H), 6.26–6.19 (m, 2H), 6.12 (dd, J = 2.4 Hz, 1H), 3.81 (s, 3H), 3.29–3.26 (m, 4H), 2.01–1.98 (m, 4H) ppm.

N-Hexyl-2,4-dimethylbenzenamine (5g):^{20c} Following procedure B, 1-bromo-2,4-dimethylbenzene (925 mg, 5.0 mmol) was allowed to react with *n*-hexylamine (760 mg, 7.5 mmol) for 60 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 83% yield of the desired product as a pale-yellow oil. ^1H NMR

(400 MHz, CDCl_3) δ 6.44 (s, 1H), 6.32 (s, 2H), 3.54 (br s, 1H), 3.15 (t, J = 7.2 Hz, 2H), 2.32 (s, 6H), 1.71–1.64 (m, 2H), 1.49–1.41 (m, 6H), 1.01–0.98 (m, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 148.8, 138.8, 119.2, 110.8, 44.2, 31.7, 29.8, 26.9, 22.6, 21.5, 13.9 ppm.

N-Hexyl-4-nitrobenzenamine (5h):^{20c} Following procedure B, 1-bromo-3-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with *n*-hexylamine (760 mg, 7.5 mmol) for 24 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 78% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.03–7.99 (m, 2H), 6.51–6.47 (m, 2H), 4.89 (s, 1H), 3.18–3.13 (m, 2H), 1.64–1.57 (m, 2H), 1.38–1.25 (m, 6H), 0.87–0.84 (m, 3H) ppm.

1-(4-Nitrophenyl)-1*H*-indole (5i):^{20d} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with 1*H*-indole (880 mg, 7.5 mmol) for 12 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 86% yield of the desired product as a yellow solid. Mp 130–132 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.40 (dt, J = 9.2, 2.8 Hz, 2H), 7.73–7.65 (m, 4H), 7.38 (d, J = 3.6 Hz, 1H), 7.33–7.29 (m, 1H), 7.27–7.23 (m, 1H), 6.78 (dd, J = 3.4, 0.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 145.2, 145.0, 135.2, 130.1, 127.1, 125.5, 123.4, 123.3, 121.6, 121.5, 110.4, 106.1 ppm.

1-(4-Nitrophenyl)-1*H*-benzo[*d*]imidazole (5j):^{20d} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with 1*H*-benzo[*d*]imidazole (885 mg, 7.5 mmol) for 12 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 89% yield of the desired product as a yellow solid. Mp 180–182 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.48 (dt, J = 9.2, 2.8 Hz, 2H), 8.18 (s, 1H), 7.91–7.89 (m, 1H), 7.73 (dt, J = 9.2, 2.8 Hz, 2H), 7.62–7.59 (m, 1H), 7.42–7.38 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 146.5, 144.4, 141.6, 141.5, 132.7, 125.8, 124.5, 123.7, 123.6, 121.1, 110.2 ppm.

1-(4-Nitrophenyl)-1*H*-imidazole (5k):^{19c} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with 1*H*-imidazole (510 mg, 7.5 mmol) for 15 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 99% yield of the desired product as a pale-yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.23 (dt, J = 9.2, 2.8 Hz, 2H), 7.91 (s, 1H), 7.50 (dt, J = 8.8, 3.2 Hz, 2H), 7.31 (s, 1H), 7.12 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 145.9, 141.7, 135.2, 131.3, 125.4, 120.7, 117.4 ppm.

4-(1*H*-Imidazole-1-yl)benzonitrile (5l):^{5c} Following procedure B, 4-bromobenzonitrile (910 mg, 5.0 mmol) was allowed to react with 1*H*-imidazole (510 mg, 7.5 mmol) for 18 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 90% yield of the desired product as a white solid. Mp 152–154 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.77 (m, 2H), 7.51 (m, 2H), 7.32 (s, 1H), 7.23 (s, 1H) ppm; ^{13}C NMR (400 MHz, CDCl_3) δ 140.5, 135.3, 134.1, 131.5, 121.4, 117.7, 117.5, 111.2 ppm.

1-(4-Nitrophenyl)-1*H*-1,2,4-triazole (5m):^{20e} Following procedure B, 1-bromo-4-nitrobenzene (1.01 g, 5.0 mmol) was allowed to react with 1*H*-1,2,4-triazole (517.5 mg, 7.5 mmol) for 12 h at 90 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 84% yield of the desired product as a pale-yellow solid. Mp 190–192 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 8.40 (dt, J = 9.2, 2.8 Hz, 2H), 8.17 (s, 1H), 7.92 (dt, J = 8.8, 2.8 Hz, 2H) ppm.

4-(1*H*-1,2,4-Triazol-1-yl)benzonitrile (5n):^{20e} Following procedure B, 4-bromobenzonitrile (910 mg, 5.0 mmol) was allowed to react with 1*H*-1,2,4-triazole (517.5 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 88% yield of the desired product as a white solid. Mp 167–169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 8.12 (s, 1H), 7.86–7.79 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 153.3, 141.1, 139.9, 133.9, 120.0, 117.6, 111.9 ppm.

1-*p*-Tolyl-1*H*-pyrazole (5o):^{11j} Following procedure B, 1-bromo-4-methylbenzene (855 mg, 5.0 mmol) was allowed to react with 1*H*-pyrazole (510 mg, 7.5 mmol) for 48 h at 110 °C. The crude brown oil

was purified by flash chromatography on silica gel to provide 60% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.57 (dt, J = 8.4, 2.4 Hz, 2H), 7.24 (m, 2H), 6.44 (dd, J = 2.0 Hz, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 140.7, 138.1, 136.2, 129.9, 126.6, 119.2, 107.2, 20.8 ppm.

1-(4-Methoxyphenyl)-1H-pyrazole (5p):^{11j} Following procedure B, 1-bromo-4-methoxybenzene (935 mg, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 48 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 68% yield of the desired product as a brown oil. ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.57 (dd, J = 6.8, 2.0 Hz, 2H), 6.95 (dd, J = 6.8, 2.0 Hz, 2H), 6.42 (t, J = 2.4 Hz, 1H), 3.81 (s, 3H) ppm.

General Procedure C: Coupling of Aryl Chlorides with Amines or N-Containing Heterocycles (5.0 mmol scale). An oven-dried Schlenk tube equipped with a Teflon valve (Kontes) was charged with a magnetic stir bar, CuBr (7.2 mg, 0.05 mmol, 1 mol %), the L5 (16 mg, 0.1 mmol, 2 mol %), and Cs_2CO_3 (3.25 g, 10.0 mmol). Any remaining solids (amine and/or aryl chloride) were added at this point. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine (7.5 mmol) (if liquid), aryl chloride (5.0 mmol) (if liquid), and DMSO (5.0 mL) were added by syringe. Finally, the tube was sealed and the mixture was heated at the indicated temperature (110 °C) for the indicated period of time. Upon completion of the reaction, the mixture was allowed to cool to room temperature and then was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, then solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under vacuum for at least 1 h.

1-(4-Nitrophenyl)pyrrolidine (7a/3f):^{19a} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with pyrrolidine (535 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 81% yield of the desired product as a yellow solid. Mp 165–167 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, J = 9.2 Hz, 2H), 6.43 (d, J = 9.2 Hz, 2H), 3.38 (t, J = 6.4 Hz, 4H), 2.06 (dt, J = 5.6, 4.0 Hz, 4H) ppm.

N-Hexyl-2-nitrobenzenamine (7b): Following procedure C, 1-chloro-2-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with *n*-hexylamine (760 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 85% yield of the desired product as a yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 1.6 Hz, 1H), 8.05 (s, 1H), 7.42 (m, 1H), 6.84 (dd, J = 8.4, 1.2 Hz, 1H), 6.62 (m, 1H), 3.29 (dt, J = 9.2, 5.2 Hz, 2H), 1.73 (m, 2H), 1.44 (m, 2H), 1.37–1.32 (m, 4H), 0.91 (m, 3H) ppm.

1-(4-Nitrophenyl)-1H-benzo[d]imidazole (7c/5j):^{20d} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-benzo[d]imidazole (885 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 88% yield of the desired product as a yellow solid. Mp 180–182 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (m, 2H), 8.19 (s, 1H), 7.91 (m, 1H), 7.74 (ddd, J = 8.8, 4.8, 2.8 Hz, 2H), 7.60 (m, 1H), 7.40 (m, 2H) ppm.

1-(2-Nitrophenyl)-1H-pyrrole (7d):^{19c} Following procedure C, 1-chloro-2-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-pyrrole (505 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 76% yield of the desired product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (m, 1H), 7.65 (m, 1H), 7.47 (m, 2H), 6.80 (dd, J = 2.0 Hz, 2H), 6.37 (dd, J = 2.0 Hz, 2H) ppm.

1-(4-Nitrophenyl)-1H-indole (7e/5i):^{20d} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-indole (880 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown

oil was purified by flash chromatography on silica gel to provide 80% yield of the desired product as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.40 (dd, J = 9.2, 2.4 Hz, 2H), 7.67 (m, 4H), 7.38 (d, J = 3.2 Hz, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 6.78 (d, J = 3.2 Hz, 1H) ppm.

1-(4-Nitrophenyl)-1H-imidazole (7f/5k):^{19e} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-imidazole (510 mg, 7.5 mmol) for 22 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 89% yield of the desired product as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.38 (dd, J = 8.8, 5.2, 3.2 Hz, 2H), 7.98 (s, 1H), 7.58 (ddd, J = 9.2, 4.8, 2.8 Hz, 2H), 7.38 (s, 1H), 7.27 (s, 1H) ppm.

4-(1H-Imidazole-1-yl)benzonitrile (7g/5l):^{5c} Following procedure C, 4-chlorobenzonitrile (690 mg, 5.0 mmol) was allowed to react with 1H-imidazole (510 mg, 7.5 mmol) for 20 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 90% yield of the desired product as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.82 (m, 2H), 7.55 (m, 2H), 7.35 (d, J = 1.2 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H) ppm.

1-(4-Nitrophenyl)-1H-pyrazole (7h/3j):^{11j} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 18 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 78% yield of the desired product as a deep yellow solid. Mp 170–172 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.34 (dd, J = 7.2, 2.0 Hz, 2H), 8.04 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 9.6, 2.0 Hz, 2H), 7.80 (d, J = 1.6 Hz, 1H), 6.56 (d, J = 2.4, 1.6 Hz, 1H) ppm.

1-(4-(1H-Pyrazol-1-yl)phenyl)ethanone (7i):^{11j} Following procedure C, 1-(4-chlorophenyl)ethanone (772.5 mg, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 40 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 52% yield of the desired product as a white solid. Mp 107–109 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (ddd, J = 16.8, 6.8, 2.4 Hz, 2H), 8.01 (d, J = 2.8 Hz, 1H), 7.81 (ddd, J = 16.8, 6.8, 2.4 Hz, 2H), 7.76 (d, J = 1.2 Hz, 1H), 6.51 (dd, J = 2.4, 2.0 Hz, 1H), 2.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 196.5, 143.4, 142.0, 135.0, 130.0, 126.8, 118.4, 108.4, 26.4 ppm.

4-(1H-Pyrazol-1-yl)benzonitrile (7j):^{11j} Following procedure C, 4-chlorobenzonitrile (690 mg, 5.0 mmol) was allowed to react with 1H-pyrazole (510 mg, 7.5 mmol) for 18 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 88% yield of the desired product as a white solid. Mp 87–89 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 2.8 Hz, 1H), 7.84 (ddd, J = 9.2, 4.0, 2.0 Hz, 2H), 7.75 (m, 3H), 7.53 (dd, J = 2.4, 1.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 143.0, 142.4, 133.6, 126.8, 119.0, 118.4, 109.6, 109.0 ppm.

1-(2-Nitrophenyl)-1H-1,2,4-triazole (7k):^{20e} Following procedure C, 1-chloro-2-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 1H-1,2,4-triazole (517.5 mg, 7.5 mmol) for 24 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 82% yield of the desired product as a yellow solid. Mp 113–115 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 8.12 (s, 1H), 8.02 (dd, J = 8.0, 1.2 Hz, 1H), 7.77 (ddd, J = 14.0, 7.6, 1.6 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.59 (ddd, J = 6.4, 4.0, 1.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 153.1, 144.6, 143.8, 133.7, 130.3, 130.2, 127.4, 125.5 ppm.

4-(1H-1,2,4-Triazol-1-yl)benzonitrile (7l/5n):^{20e} Following procedure C, 4-chlorobenzonitrile (690 mg, 5.0 mmol) was allowed to react with 1H-1,2,4-triazole (517.5 mg, 7.5 mmol) for 26 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 85% yield of the desired product as a white solid. Mp 167–169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 8.14 (s, 1H), 7.84 (m, 4H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 153.2, 141.1, 139.9, 133.9, 112.0, 117.7, 111.8 ppm.

5-(4-Nitrophenylamino)pentan-1-ol (7m/5e):^{20b} Following procedure C, 1-chloro-4-nitrobenzene (790 mg, 5.0 mmol) was allowed to react with 5-aminopentan-1-ol (775 mg, 7.5 mmol) for 18 h at 110 °C. The crude brown oil was purified by flash chromatography on silica gel to provide 67% yield of the desired product as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 9.2 Hz, 2H), 6.49 (d, *J* = 9.2 Hz, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 3.18 (t, *J* = 6.2 Hz, 2H), 1.69–1.58 (m, 4H), 1.48 (m, 2H) ppm.

N¹-Benzyl-N⁴-pentylbenzene-1,4-diamine (9): A flask was charged with CuBr (14 mg, 0.1 mmol, 1 mol %), L5 (32 mg, 0.2 mmol, 2 mol %), Cs₂CO₃ (9.75 g, 30.0 mmol), and 1-bromo-4-iodobenzene (2.82 g, 10.0 mmol). The flask was evacuated and backfilled with argon. Hexan-1-amine (1.01 g, 10 mmol) and DMSO (10 mL) were added to the flask under argon atmosphere. Then the mixture was stirred for 48 h at 65 °C. Then benzylamine (1.07 g, 10.0 mmol) was added subsequently. The mixture was heated at 120 °C for 60 h. The mixture was allowed to cool to room temperature and then was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, then the solvent was removed with the aid of a rotary evaporator. The residue was purified by flash chromatography on silica gel to provide the product as a yellow oil (1.41 g, 50% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.31 (m, 4H), 7.26 (m, 1H), 6.57 (m, 4H), 4.26 (s, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 1.58 (m, 2H), 1.42–1.24 (m, 6H), 0.91–0.84 (m, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 128.5, 127.6, 127.1, 114.8, 49.6, 45.4, 31.7, 29.7, 26.9, 22.6, 14.0 ppm; MS (EI, *m/z*) 283 (*M*⁺ + 1); HRMS (ESI) C₁₉H₂₇N₂ calcd [*M* + H]⁺ 283.2174, found 283.2173.

N-Benzyl-4-(1H-pyrazol-1-yl)benzenamine (10): A flask was charged with CuBr (14 mg, 0.1 mmol, 1 mol %), L5 (32 mg, 0.2 mmol, 2 mol %), Cs₂CO₃ (9.75 g, 30.0 mmol), 1-bromo-4-iodobenzene (2.82 g, 10.0 mmol), and 1H-pyrazole (680 mg, 10.0 mmol). The flask was evacuated and backfilled with argon. DMSO (10 mL) was added to the flask under argon atmosphere. Then the mixture was stirred for 48 h at 65 °C. Then benzylamine (1.07 g, 10.0 mmol) was added subsequently. The mixture was heated at 120 °C for 60 h. The mixture was allowed to cool to room temperature and then was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, then the solvent was removed with the aid of a rotary evaporator. The residue was purified by flash chromatography on silica gel to provide the product as a yellow solid (1.03 g, 41% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 2.4 Hz, 1H), 7.67 (m, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.36 (m, 4H), 7.28 (m, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.40 (dd, *J* = 8.8 Hz, 1H), 4.37 (s, 2H), 4.17 (brs, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 147.0, 140.1, 139.1, 131.8, 128.7, 127.4, 127.3, 126.6, 121.2, 113.2, 106.6, 48.5 ppm; MS (EI, *m/z*) 250 (*M*⁺ + 1); HRMS (ESI) C₁₆H₁₆N₃ calcd [*M* + H]⁺ 250.1344, found 250.1343.

■ ASSOCIATED CONTENT

S Supporting Information. ¹H NMR and ¹³C NMR spectra of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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