

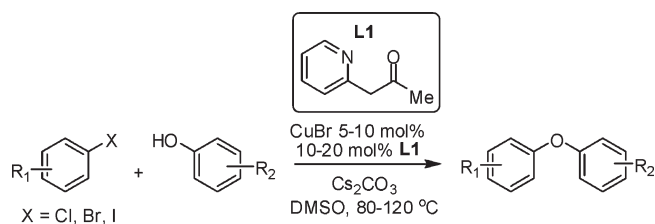
(2-Pyridyl)acetone-Promoted Cu-Catalyzed  
O-Arylation of Phenols with Aryl Iodides, Bromides,  
and Chlorides

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Employing (2-pyridyl)acetone as a new supporting  
ligand, the copper-catalyzed coupling reactions of  
aryl chlorides, aryl bromides, and aryl iodides  
with various phenols successfully proceeded in good  
yields under mild conditions. This reaction displays great  
functional groups compatibility and excellent reactive  
selectivity.

Diaryl ethers represent an important class of intermediates  
for pharmaceuticals, agrochemicals, and polymers.<sup>1,2</sup> Tran-  
sitional metal catalyzed coupling reactions of aryl halides  
and phenols are the most straightforward methods for the

preparations of diaryl ethers.<sup>3–5</sup> Despite the high efficiency  
of the Pd-catalyzed methods, the use of expensive palladium  
and elaborate phosphorated ligands would limit its applica-  
tions to large- or industrial-scale production. The classical  
copper-catalyzed synthesis of diaryl ethers, however, suffers  
from the requirements of high temperature (125–220 °C)  
and stoichiometric amounts of catalysis.<sup>6</sup> In the past years,  
much progress have been achieved for the copper-catalyzed  
synthesis of diaryl ethers. With the carefully selected combi-  
nations of copper sources, bases, and supporting ligands,  
aryl bromides and aryl iodides had been reported to couple  
with phenols with excellent yields under mild conditions.<sup>4</sup>  
Recently, a successful coupling of chlorobenzenes with  
substituted phenols was reported under the catalysis of  
10% CuBr and 80% 2,2,6,6-tetramethyl-3,5-heptanedione  
(TMHD).<sup>5b</sup> In spite of the significant improvements  
achieved, examples for the coupling of aryl chlorides with  
phenols are rare.<sup>1,4i,4n,5b</sup> It is still highly desirable to develop  
new efficient catalytic systems to further improve the effi-  
ciency and generality of the copper-catalyzed coupling of  
phenols with aryl halides.

Recently we identified 2-pyridyl  $\beta$ -ketones as new efficient  
supporting ligands for the copper-catalyzed C–N coupling  
reaction at room temperature.<sup>7</sup> In this paper, we report that  
2-pyridyl acetone (Figure 1, L1), a simple and commercially  
available 2-pyridyl  $\beta$ -ketone analogue, successfully pro-  
motes the copper-catalyzed C–O coupling of substituted  
aryl chlorides, aryl bromides, and aryl iodides with various  
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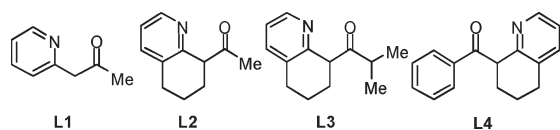
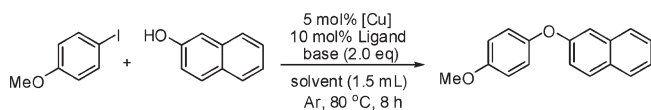


FIGURE 1. Structures of ligands L1–L4.

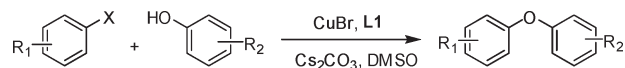
TABLE 1. Copper-Catalyzed O-Arylation of 2-Naphthol with 4-Iodoanisole: Optimization of the Reaction Conditions<sup>a</sup>

entry	[Cu]	ligand	base	solvent	yield (%)
1	CuI	L2	Cs <sub>2</sub> CO <sub>3</sub>	DMF	71
2	CuI	L3	Cs <sub>2</sub> CO <sub>3</sub>	DMF	66
3	CuI	L4	Cs <sub>2</sub> CO <sub>3</sub>	DMF	60
4	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMF	82
5	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMF	23
6	CuI	L1	K <sub>2</sub> CO <sub>3</sub>	DMF	44
7	CuI	L1	K <sub>3</sub> PO <sub>4</sub>	DMF	42
8	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	73
9	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	89
10	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	toluene	30
11	CuI	L1	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	80
12	CuBr	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	89
13	CuCl	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	84
14	Cu(acac) <sub>2</sub>	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	80
15	Cu <sub>2</sub> O	L1	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	63
16			Cs <sub>2</sub> CO <sub>3</sub>	DMSO	0

<sup>a</sup>Reaction conditions: CuBr (0.05 mmol), ligand (0.10 mmol), aryl-I (1.0 mmol), phenol (1.2 mmol), bases (2.0 mmol), solvents (1.5 mL), 80 °C.

The investigation was initiated by using the coupling of 4-iodoanisole and 2-naphthol as a model reaction. Since the conformation-constrained 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanones displayed great activity to promote CuI-catalyzed C–N bond formation,<sup>7</sup> we first evaluated the catalytic efficiency of these compounds (L2–L4) for the O-arylation of 2-naphthol. As shown in Table 1, these ligands showed moderate potency for the copper-catalyzed coupling of 4-iodoanisole and 2-naphthol. For instance, a 71% yield was obtained when the coupling was performed under the combination of 5% CuI, 10% L2 (1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone), and 200% cesium carbonate in DMF at 80 °C (Table 1, entry 1). Interestingly, 2-pyridyl acetone (L1), one of the simplest and commercially available 2-pyridyl β-ketone analogues, displayed the best catalytic efficiency (Table 1, entry 4). Further conditional optimization revealed that Cs<sub>2</sub>CO<sub>3</sub><sup>8</sup> and DMSO were the optimal base and solvent, respectively (Table 1, entries 6–11). The potential catalytic efficiency of several other copper salts was also evaluated. As shown in Table 1 (entries 12–15), almost all the copper salts displayed good catalytic activity except for the fact that Cu<sub>2</sub>O was less active (entry 15). Therefore, the combination of less expensive CuBr (5%), 10% 2-pyridylacetone (L1), and 200% Cs<sub>2</sub>CO<sub>3</sub> in DMSO at 80 °C was chosen as the optimal conditions for further exploration.

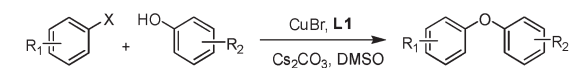
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TABLE 2. Cu-Catalyzed Coupling Reaction of Aryl Iodides or Aryl Bromides with Phenols<sup>a</sup>

entry	Ar-X	Ar-OH	time (h)	yield (%)
1			8	95 <sup>b</sup>
2			7	97 <sup>b</sup>
3			6	97 <sup>b</sup>
4			20	96 <sup>b</sup>
5			18	71
6			18	80
7			24	88
8			18	92
9			20	87
10			20	91
11			18	90
12			18	97 89 <sup>c</sup>
13			20	91
14			24	93
15			24	91
16			24	85
17			18	71
18			18	65
19			18	79
20			24	0
21			17	52
22			24	50
23			24	70

<sup>a</sup>Reaction conditions: CuBr (0.10 mmol), L1 (0.20 mmol), aryl-I (1.0 mmol), phenol (1.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol), DMSO (1.5 mL), 90 °C. <sup>b</sup>CuBr (0.05 mmol), L1 (0.10 mmol), 80 °C. <sup>c</sup>The reaction was carried out in the absence of CuBr and L1.

The scope of the copper-catalyzed C–O bond formation was explored by using a variety of aryl iodides or aryl bromides with substituted phenols under the optimized conditions. As shown in Table 2, the coupling reactions were performed well for all the aryl iodides examined with

**TABLE 3.** Cu-Catalyzed Coupling Reaction of Heteroaromatic Halides with Phenols<sup>a</sup>

entry	Ar-X	Ar-OH	time (h)	yield (%)
1			10	97 <sup>b</sup>
2			9	96 <sup>b</sup>
3			15	90
4			15	98
5			20	72
6			20	95
7			18	83

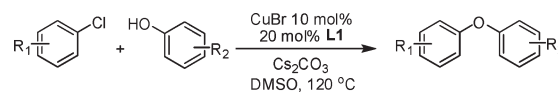
<sup>a</sup>Reaction conditions: CuBr (0.10 mmol), **L1** (0.20 mmol), aryl-Br (1.0 mmol), phenol (1.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol), DMSO (1.5 mL), 90 °C. <sup>b</sup>CuBr (0.05 mmol), **L1** (0.10 mmol), 80 °C.

excellent yields (Table 2, entries 1–4). Less active aryl bromides were also successfully coupled with phenols under the catalysis of 10% CuBr and 20% **L1** (Table 2, entries 5–23). More importantly, the CuBr/**L1** combination was able to be recycled at least 3 times without significantly losing the catalytic efficiency (Supporting Information).<sup>9</sup>

The results revealed that an electron-withdrawing group in the aryl bromide favored the coupling reactions (Table 2, entries 9–13). For example, 1-bromo-4-nitrobenzene successfully coupled with 4-methoxyphenol with an excellent yield without the presence of copper catalyst and supporting ligand, which might be due to a nucleophilic aromatic substitution mechanism (Table 2, entry 12).<sup>4m,5b</sup> The results also clearly showed that the CuBr/**L1** combination significantly improved the reaction efficiency in most cases (Supporting Information).<sup>9</sup> The coupling of electron-deficient phenols with aryl bromides also proceeded smoothly in good yields (Table 2, entries 16–19) with the exception of *p*-nitrophenol, which led to a total failure for the coupling reaction (Table 2, entry 20). This might be due to the stronger decreased nucleophilicity of phenols induced by the nitro group.<sup>4d,h,10</sup> The results also indicated that steric hindrance had a huge influence on the coupling reaction (Table 2, entries 22 and 23). For instance, only 50% yield was obtained when 2-methylphenyl bromide coupled with the corresponding phenol (Table 2, entry 22). It was noteworthy that 2-acetylphenyl bromide, a problematic substrate in a previous report for the Pd-catalyzed synthesis of diaryl ether,<sup>31</sup> coupled with the corresponding phenol in an acceptable yield (52%) (Table 2, entry 21), which highlighted the high catalytic efficiency of the CuBr/**L1** combination. In addition,

(9) For details about the coupling of the other electron-deficient aromatic halides with phenols in the absence of Cu and ligand, see the Supporting Information.

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**TABLE 4.** Cu-Catalyzed Coupling Reaction of Aryl Chlorides with Phenols<sup>a</sup>

entry	Ar-Cl	Ar-OH	time (h)	yield (%)
1			23	52 <sup>b</sup> 71
2			18	97
3			24	52 <sup>c</sup>
4			24	81
5			24	70
6			24	61
7			24	72
8			24	79
9			24	88
10			24	45 65 <sup>d</sup> 11 <sup>e</sup>
11			24	37 60 <sup>d</sup>
12			24	31 70 <sup>d</sup>
13			24	19 34 <sup>d</sup>
14			23	43 51 <sup>d</sup>
15			22	21 46 <sup>d</sup>
16			24	20 33 <sup>d</sup>
17			24	32 60 <sup>d</sup>

<sup>a</sup>Reaction conditions: CuBr (0.10 mmol), **L1** (0.20 mmol), aryl-Cl (1.0 mmol), phenol (1.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol), DMSO (1.5 mL), 120 °C. <sup>b</sup>At 90 °C. <sup>c</sup>Product of diether/polyether: 42:10. <sup>d</sup>CuBr (0.1 mmol), **L1** (0.2 mmol), aryl-Cl (2.0 mL), phenol (1.0 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol), 150 °C. <sup>e</sup>CuBr (0.1 mmol), *N*-methylglycine (0.2 mmol), aryl-Cl (2.0 mL), phenol (1.0 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol), 150 °C.

the reaction also displayed a great tolerance to multiple functional groups such as ketone, nitrile, nitro, carboxylic ester, and free amido or hydroxyl groups. To the best of our knowledge, the examples for Pd- or Cu-catalyzed diaryl ether synthesis with substrates bearing a free amido or hydroxyl substituents were relatively rare.<sup>3,4b,11</sup>

The catalytic efficiency of the CuBr/**L1** combination for the coupling of heteroaromatic iodides or bromides

(11) For examples, see: (a) Thomas, S.; Alexander, Z.; Alain, C.; Nikolaus, M.; Matthias, B. *Tetrahedron Lett.* **2008**, *49*, 1851–1855. (b) Thomas, S.; Alexander, Z.; Alain, C.; Nikolaus, M.; Matthias, B. *Org. Process Res. Dev.* **2008**, *12*, 537–539. (c) Ghosh, R.; Samuelson, A. G. *New J. Chem.* **2004**, *28*, 1390–1393.

with the corresponding phenols was also evaluated. As shown in Table 3, various heteroaromatic halides, including pyridine, quinoline, and benzothiazole bromides, successfully coupled with phenols in good-to-excellent yields (Table 3).

Because of their low cost and ready availability, aryl chlorides are much more attractive substrates for the industrial production and laboratory preparation of diaryl ethers.<sup>1,5b</sup> We further investigated the potential catalytic efficiency of the CuBr/L1 system for the coupling between aryl chlorides and phenols. As summarized in Table 4, CuBr/L1 combination successfully promoted the coupling reaction with good or moderate yields for most of the substrates examined. For example, a 52% yield was obtained when 1-(4-chlorophenyl)ethanone was reacted with phenol at 90 °C. The yield was improved to 71% when the reaction was carried out at 120 °C (Table 4, entry 1). The other electron-deficient aromatic chlorides tested also gave good yields (61–97%) under the catalysis of CuBr/L1 at 120 °C (Table 4, entries 2–6). It is noteworthy that significantly lower yields were obtained for the coupling of aryl chlorides with phenols when the copper catalyst and ligand were absent (Supporting Information).<sup>9</sup> The cross-coupling of chloropyridines and chloroquinoline with phenols also took place smoothly with satisfactory yields (Table 4, entries 7–9). Furthermore, acceptable yields were also obtained for the substrates with electron-donating groups when excessive aryl chlorides were applied (Table 4, entries 10–17).

In summary, an efficient Cu-catalyzed synthesis of diaryl ethers from various aromatic or heteroaromatic iodides, bromides, and chlorides was developed by using (2-pyridyl)acetone (L1) as the ligand. The Cu/L1 catalytic system displays excellent functional group compatibility and high chemical selectivity in the presence of a broad range of functional groups at moderate temperature. Our report provides an attractive addition to the strategies for the synthesis of diaryl ether derivatives.

## Experimental Section

**General Procedure for the Coupling of Aryl Halides with Phenols.** A test tube equipped with a Teflon valve was charged with a magnetic stir bar, CuBr (5–10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (650 mg, 2 mmol), and any remaining solid phenols (1.2 mmol) and aryl halides (1.0 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, 1.2 mmol of phenols (if liquid), 1 mmol of aryl halides (if liquid), DMSO (1.5 mL), and L1 (10–20 mol %) were added by syringe. The tube was evacuated and backfilled with argon again (this procedure was repeated three times) and sealed. The reaction mixture was heated to the indicated temperature (80–120 °C) for the required time period. After cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) then passed through a fritted glass filter to remove the inorganic salts and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 1 h.

**N-(4-phenoxyphenyl)acetamide (Table 2, entry 8):** white solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.34 (1H, s), 7.46 (2H, d, *J* = 7.2 Hz), 7.30–7.32 (2H, m), 7.05 (1H, t, *J* = 7.6 Hz), 6.93 (4H, t, *J* = 8.4 Hz), 2.15 (3H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.1, 157.5, 153.5, 133.5, 129.8, 123.1, 122.0, 119.5, 118.5, 24.2; GC/MS *rt* = 8.99 min, *m/z* 227.

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**Supporting Information Available:** Typical experimental procedure, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all of the coupling products with additional HRMS spectra for the unknown compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.