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An Efficient Ullmann-Type C−O Bond Formation Catalyzed by an Air-Stable Copper(I)−Bipyridyl Complex

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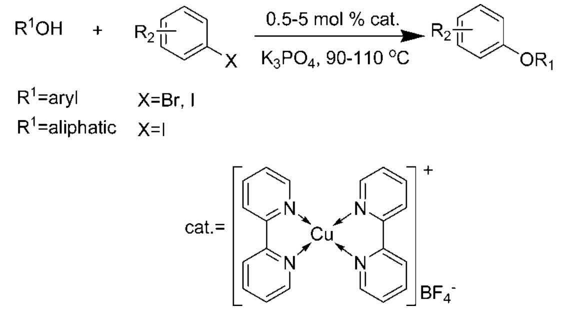

An efficient O-arylation of phenols and aliphatic alcohols with aryl halides was developed that uses an air-stable copper(I) complex as the catalyst. This arylation reaction can be performed in good yield in the absence of Cs_2CO_3. A variety of functional groups are compatible with these reaction conditions with low catalyst loading levels.

Aryl ethers are very important structural motifs of numerous biologically active natural products and important pharmaceutical compounds and polymers in the material science industries.[1,2]

The palladium-catalyzed coupling reaction of aryl halides with phenols or alcohols is one of the two major methods available for aryl ether synthesis.[3] The other one is the copper-mediated Ullmann ether synthesis. However, palladium-based protocols, although successful, have some inherent limitations such as moisture sensitivity, costly metal catalysts, and environmental toxicity. The harsh classical conditions of the Ullmann ether synthesis also have limitations in its application because of the high temperatures required, poor substrate scope, and the use of stoichiometric amounts of copper reagents.[4] During the past few years, some significant modifications have been made for the Ullmann ether synthesis. It has been observed that certain additives, such as 8-hydroxyquinoline,[5a] 1-naphthoic acid,[5b] 2,2,6,6-tetramethylheptane-3,5-dione,[5c] amino acids,[5d−f] Schiff base,[5g] PPAMP,[5h] phosphazene P_4-*t*-Bu base,[5i] β-keto ester,[5j] tripod,[5k] and some copper(I) complexes,[5l,m] can accelerate the rate of these reactions, and therefore, the reactions can be performed under milder conditions. In the coupling of aryl halides and aliphatic alcohols catalyzed by copper systems, both Buchwald and Ma groups reported that using CuI as copper source and adding proper ligand could accomplish the reactions.[6a−d] Even though most of these systems work reasonably well for aryl ether synthesis, the use of moisture-sensitive Cs_2CO_3 is crucial to the success of the reaction.[5b−i,6a−d] Also, there are few reports that copper-based protocols can be used for the synthesis of both diaryl ethers and aryl alkyl ethers.

Herein, we report a very active and air-stable copper(I) complex that can efficiently catalyze the O-arylation of both phenols and aliphatic alcohols with aryl halides by using potassium phosphate as base.

After carefully examining all of the reported ligands used in copper-based Ullmann ether synthesis, it appears that the selection of bidentate nitrogen ligands or triphenylphosphine may be crucial for the success of this type of reaction. Based on this assumption, we prepared three types of copper(I) complexes **1**−**3**.[7] Complex **1** has been reported before,[5h] and **2** is a close analogue of a reported copper complex catalyst.[5i] However, **3**,[8] according to our knowledge, has never been applied in this type C−O formation before and can be easily

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(1) For reviews, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. (b) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065. (c) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345–2347. (d) Thomas, A. W.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.

(2) For examples of medicinally important diaryl ethers, see: (a) Zenitani, S.; Tashiro, S.; Shindo, K.; Nagai, K.; Suzuki, K.; Imoto, M. *J. Antibiot.* **2003**, *56*, 617–621. (b) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859–7870. (c) Evans, D. A.; DeVriesK. M. In *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences*; Nagarajan, R., Ed.;Marcel Decker: New York, 1994; pp 63−104. (d) Deshpande, V. E.; Gohkhale, N. J. *Tetrahedron Lett.* **1992**, *33*, 4213–4216. (e) Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797–2800. (f) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909–4913. For examples of agriculturally important diaryl ethers, see: (g) Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1998; p 6265.

(3) For examples of palladium-catalyzed diaryl ethers, see: (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5556. For examples of palladium-catalyzed aryl aliphatic ethers, see: (c) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110. (d) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.

(4) Ullmann, F. *Ber. Dtsch. Chem Ges.* **1903**, *36*, 2382–2384.

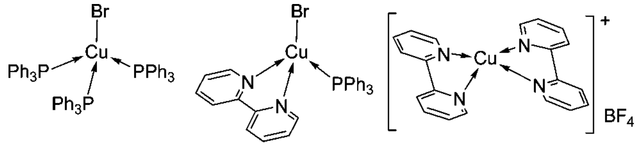
(5) (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051. (b) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. (c) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623–1626. (d) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 3799–3802. (e) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276–1279. (f) Cai, Q.; He, G.; Ma, D. *J. Org. Chem.* **2006**, *71*, 5268–5273. (g) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Tailefer, M. *Org. Lett.* **2004**, *6*, 913–916. (h) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.*−*Eur. J.* **2006**, *12*, 3636–3646. (i) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem. Commun.* **1998**, 2091–2092. (j) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867. (k) Chen, Y.; Chen, H. *Org. Lett.* **2006**, *8*, 5609–5612. (l) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865–2879. (m) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.

(6) (a) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976. (b) Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243–246. (c) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286. (d) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491.

(7) The synthesis details of the three complexes, see the Supporting Information.

(8) Lang, H.; Zoufala, P.; Klaib, S.; Villar, A.; Rheinwald, G. *J. Organomet. Chem.* **2007**, *692*, 4168–4176.

10.1021/jo801002c CCC: $40.75



1 **2** **3**

FIGURE 1. Copper(I) complexes for diaryl ether formation.

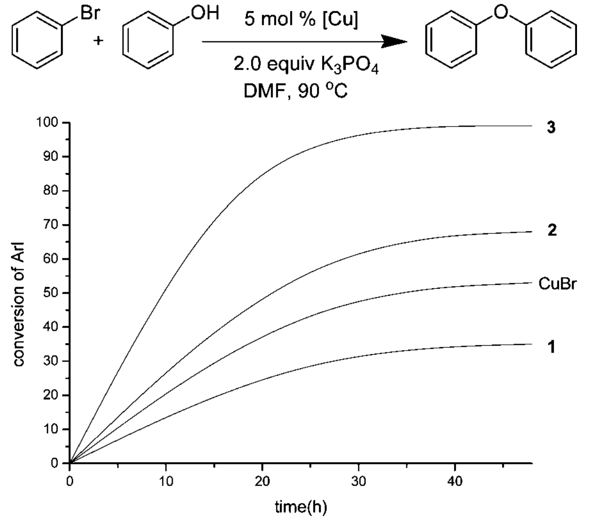
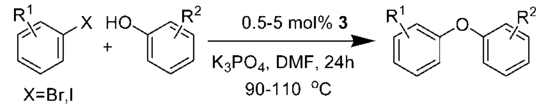


FIGURE 2. Comparison in different copper(I) sources. Reaction conditions: PhBr (1.0 mmol), phenol (1.5 mmol), K_3PO_4 (2 mmol), and 5 mol % of copper(I) were added to a screw-capped test tube followed by the addition of 0.5 mL of anhydrous DMF. The reaction was stirred at 90 °C under argon. Conversion was measured by GC using *p*-methyldiphenyl ether as internal standard.

TABLE 1. The Coupling Reaction of Unhindered Aryl Iodides and Aryl Bromides with Phenols Using Catalyst 3[a]



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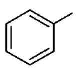
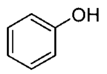
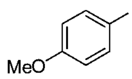
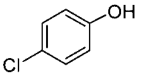
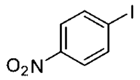
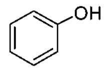
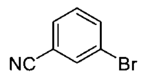
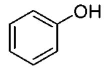
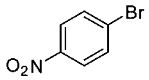
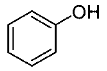
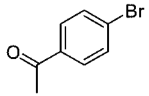
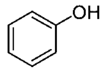
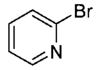
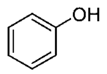
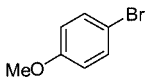
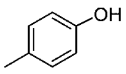
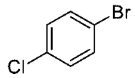
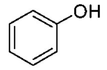
1			5	90	85
2			5	110	81[b]
3			0.5	90	92
4			0.5	90	80
5			0.5	90	92
6			0.5	90	80
7			0.5	90	91
8			3	110	70
9			3	110	88

[a] General reaction conditions: 1.5 mmol of phenol, 1.0 mmol of ArX, 2.0 mmol of K_3PO_4, 0.5 mL of anhydrous DMF. [b] 48 h.

prepared by the addition of 2,2′-bipyridyl to a solution of $Cu(CH_3CN)_4BF_4$ in acetonitrile at room temperature.

The kinetic study was carried out by using four different copper catalysts for the synthesis of Ullmann diaryl ether, bromobenzene, and phenol as model substrates, 5 mol % catalyst loading, potassium phosphate as base, and DMF as solvent (Figures 1 and 2). According to the kinetic profiles shown in Figure 2, CuBr proved to be a better catalyst than complex **1** in the coupling reaction, which suggested that raising the solubility of the copper salt might not always enhance the Ullmann diaryl ether synthesis. One monobipyridyl ligand modified complex, **2**, proved to be superior to the simple copper salt CuBr and the copper complex **1**. The most effective catalyst in this coupling reaction was the bis-bipyridyl ligand modified complex **3**. While the coupling did not approach completion with **1** or **2**, 95% conversion of aryl bromide was achieved after 24 h by using **3**. In our control experiments, both K_2CO_3 and K_3PO_4 were found to be effective bases for the diaryl ether formation. Other bases, including Cs_2CO_3, Na_2CO_3, and some organic bases such as TMG or Et_3N, gave much lower yields.[9] Furthermore, with K_3PO_4 as base, we were able to use a variety of polar aprotic solvents (e.g., EtCN, *n*-PrCN, and NMP).

We expanded our investigation to explore the scope of the complex **3** as a catalyst in the Ullmann diaryl ether synthesis of meta- and para-substituted aryl halides. As shown in Table 1, 5 mol % of **3** was sufficient to effect the coupling reaction. Electron-rich, -neutral, and -deficient aryl halides all provided products in good to excellent yields. Aryl bromides or aryl iodides substituted with electron-withdrawing groups, such as *m*-nitrile, *p*-nitro, and *p*-keto, are particularly good substrates, which could be coupled with phenol at much lower catalyst loadings (**3**, 0.5 mol %) at fairly low temperature (entries 3−6). We were pleased to note that the coupling of two poor substrates, 4-iodoanisole and 4-chlorophenol, with complex **3** (entry 2) gave 63% GC yield after 24 h, and a higher yield (81%) was obtained by prolonging the reaction time to 48 h.

It is known that sterically hindered components are particularly poor substrates for the copper-catalyzed C−O bond formation.[10] With the highly efficient copper catalyst complex **3** in hand, we decided to examine the scope of this coupling reaction further in the reactions of hindered phenols with hindered aryl halides (Table 2). The reaction of ortho-substituted aryl halides was, in some cases, slightly more demanding than that for ortho-substituted phenols; for example, the coupling of 2-iodotoluene with phenol carried out with 5 mol % of **3** for 48 h gave 70% yield of the desired product, but the coupling of 2-methyphenol proceeded more readily (entries 10 and 11).

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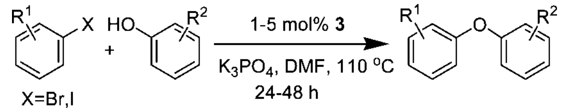
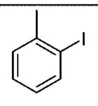
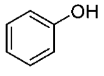
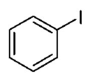
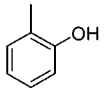
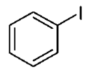
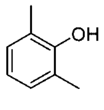
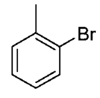
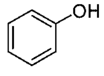
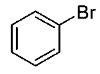
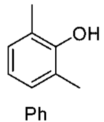
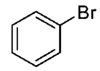
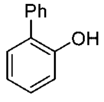
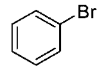
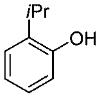
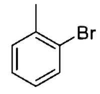
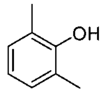
(9) GC yield of the desired product after 24 h for the reactions using another base: K_2CO_3 (74%), Na_2CO_3 (5%), Cs_2CO_3 (20%), TMG, and Et_3N (no more than 10%).

(10) (a) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643–646. (b) Mederski, W. W. K. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757–12770. (c) Lam, Y. S. P.; Clark, C. G.; Sauber, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674–676.

TABLE 2. Coupling Reaction of Hindered Phenol−Aryl Halide Combinations under Catalysis of 3[a]



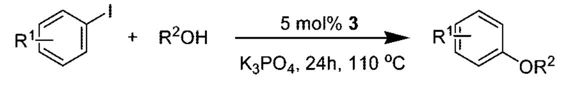
entry	ArX	Phenol	3, mol%	Time, h	yield, %
1			5	48	70
2			3	24	88
3			3	24	92
4			5	48	80
5			3	24	90
6			3	24	90
7			1	24	89
8			3	48	42

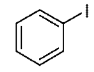
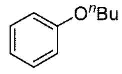
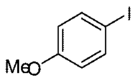
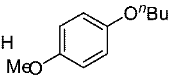
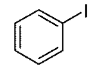
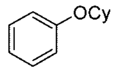
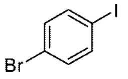
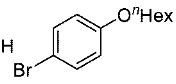
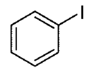
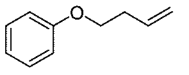
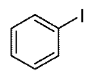
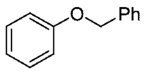
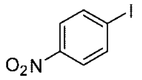
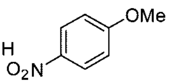
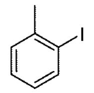
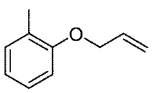
[a] General reaction conditions: 1.5 mmol of phenol, 1.0 mmol of ArX, 2.0 mmol of K_3PO_4, 0.5 mL of anhydrous DMF.

The same trend was also observed in entries 13 and 14. More sterically hindered phenols such as 2-isopropylphenol and 2-phenylphenol were almost quantitatively coupled with bromobeneze by using this catalytic system (entries 15 and 16). The synthesis of *o*,*o*,*o*′-trimethyl-substituted diaryl ether represents a great challenge. Upon loading with 3 mol % of **3**, the coupling of 2,6-dimethylphenol and 2-bromotoluene can be accomplished in 48 h with 42% yield (entry 17).

Using the copper complex **3**−potassium phosphate−alcohol procedure, we examined the C−O coupling reaction between aryl iodides and aliphatic alcohols (Table 3). In a preliminary survey, a variety of different reaction conditions were examined. Our standard conditions, 5 mol % complex loading, potassium phosphate as base, and alcohol as solvent, proved to be the best. It was found that primary alcohols such as butanol could be successfully coupled with different aryl iodides in excellent yield. It was not successful when we tried to couple aryl bromides and aliphatic alcohols, which may be due to the intrinsic reactivity differences of aryl halides in Cu-catalyzed reactions (I > Br ≫ Cl > F).[1,11] We were able to exploit this point to couple iodide selectively rather than bromide with an −OH group (entry 4). The system was also compatible with alkenyl alcohol; 85% product was obtained after 24 h with no coupled side products (entry 5).

TABLE 3. Coupling Reaction of Aryl Iodides with Aliphatic Alcohols under Catalysis of 3[a]



entry	aryl iodide	R²OH	Product	yield,%
1		*n*BuOH		80
2		*n*BuOH		61
3		cyclohexanol		81[b]
4		*n*HexOH		72
5		3-buten-1-ol		85
6		benzyl alcohol		91
7		MeOH		80[c]
8		allyl alcohol		82[d]

[a] General reaction conditions: 1.0 mmol of ArX, 1 mL of R^2OH, 2.0 mmol of K_3PO_4 under argon in a sealed test tube. [b] 48 h. [c] Reaction temperature of 80 °C. [d] Cs_2CO_3 as base.

In conclusion, we have described the use of a new air-stable copper(I)−bipyridyl catalyst for the O-arylation of phenols and alcohols, which displays increased reactivity, requires lower levels of catalyst loading, and does not require the use of more expensive and moisture-sensitive bases such as Cs_2CO_3. This catalytic system is not only capable of coupling hindered substrate combinations but also tolerates a broad range of a series of functional groups.

Experimental Section

General Procedure for the O-Arylation of Phenols under Catalysis of 3. Compound **3** (0.5−5 mol %), phenol (1.5 mmol), aryl halide (if solid, 1 mmol), and K_3PO_4 (425 mg, 2.0 mmol) were added to a screw-capped Schlenk tube under argon. The tube was then evacuated and backfilled with argon (three cycles). Aryl halide (if liquid, 1.0 mmol) and dry DMF (0.5 mL) were added by syringe at room temperature. The reaction mixture was stirred at needed temperature (90 or 110 °C) for 24 h. The reaction mixture was allowed to reach room temperature and then diluted with dichloromethane (10 mL). The slurry was filtered, and filter cake was washed with 10 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to afford the desired product.

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(11) For examples of Cu-catalyzed amination reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337–2364. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.

General Procedure for the O-Arylation of Aliphatic Alcohols under Catalysis of 3. Compound **3** (5 mol %), aryl halide (if solid, 1 mmol), and K_3PO_4 (425 mg, 2.0 mmol) were added to a screw-capped Schlenk tube under argon. The tube was then evacuated and backfilled with argon (three cycles). Aryl halide (if liquid, 1.0 mmol) and alcohol (1 mL) were added by syringe at room temperature. The reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was allowed to reach room temperature and then diluted with dichloromethane (10 mL). The slurry was filtered, and filter cake was washed with 10 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to afford the desired product.

Diaryl Ether (Table 1, Entry 1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32−7.35 (m, 4H) 7.10 (t, $J = 7.2$ Hz, 2H), 7.01 (dd, $J = 9.0$, 1.2 Hz, 4H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 157.2, 129.7, 123.2, 118.9. MS *m/z* 170 (M^+), 141, 77, 65, 51, 39. Anal. Calcd for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.56; H, 5.90.

4-Chloro-4′-methoxydiphenyl Ether (Table 1, Entry 2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23−7.25 (m, 2H), 6.95−6.97 (m, 2H), 6.86−6.89 (m, 4H), 3.80 (s, 3H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 157.2, 156.1, 149.8, 129.5, 127.3, 120.8, 118.7, 114.9, 55.6. MS *m/z* 236, 234 (M^+), 221, 219, 140, 111, 95, 75, 63, 50. Anal. Calcd for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.72. Found: C, 66.49; H, 4.85.

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Supporting Information Available: Crystallographic information files. NMR spectra of coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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