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Copper-catalyzed Ullmann coupling under ligand- and additive-free conditions. Part 1: O-Arylation of phenols with aryl halides

Joyce Wei Wei Chang[a], Sheena Chee[a,†], Shiya Mak[a,†], Pongchart Buranaprasertsuk[a,b], Warinthorn Chavasiri[b], Philip Wai Hong Chan[a,*]

[a] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore*

[b] *Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand*

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Abstract

O-Arylation of a wide variety of substituted phenols and aliphatic alcohols with aryl halides catalyzed by copper iodide under mild ligand and additive free conditions (^{n}Bu$_4$NBr, DMF, K$_3$PO$_4$, reflux, 22 h) is accomplished in good to excellent product yields (up to 95%).

The biaryl ether linkage is a common motif found in many natural products and pharmaceutically active compounds.[1] Biaryl ethers also have wide applications in the fine chemicals and polymer industries, and are useful ligands in metal-catalyzed organic transformations.[2] A traditional method for installing this functionality is the copper-catalyzed Ullmann coupling of phenols with aryl halides.[3,4] However, such strategies have often required the use of high reaction temperatures, stoichiometric amounts of the copper catalyst that make scale-up unfeasible and ecologically unfriendly, the use of toxic and air-sensitive aryl coupling reagents that can be difficult to access, and excess phenol starting materials to achieve low to moderate product yields.[4a,5,6] In view of these limitations, strategies to construct the *O*-aryl functionality have been actively pursued. A recent notable achievement has been the Cu-catalyzed O-arylation of phenols with aryl halides in the presence of a variety of P-, N-, and O-based ligands or additives.[7–11] While these procedures have overcome some of the above-mentioned limitations, it remains a challenge to develop analogous O-arylation of phenols which does not require a ligand or additive with aryl halides as the starting materials, which would be desirable from an economical perspective. In this context and in view of recent work in our group showing that the copper iodide-catalyzed N-arylation of a variety of nitrogen heterocycles with an equimolar amount of aryl halide in the presence of ^{n}Bu$_4$NBr as phase transfer catalyst and NaOH as base could be accomplished in good to excellent yields, we wondered whether the same catalytic system could be applied to O-arylation of phenols.[12] Herein, we report the copper iodide-catalyzed O-arylation of a wide variety of phenols with equimolar amounts of aryl halides under ligand and additive free conditions that proceeded in yields up to 95%, being comparable to those reported using ligand and additive promoted strategies (Scheme 1). In the following Letter, we also report the extension of this strategy for the S-arylation of arylthiols.[13]

In preliminary studies with the CuI/NaOH system, the O-arylation of phenol **1a** with iodobenzene **2a** was found to give no reaction. Rationalizing that **1a** could be resistant to deprotonation, we conducted optimization studies with

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[*] Corresponding author. Tel.: +65 6316 8760; fax: +65 6791 1961. *E-mail address:* waihong@ntu.edu.sg (P. W. H. Chan).

[†] Equal contributions to this work.

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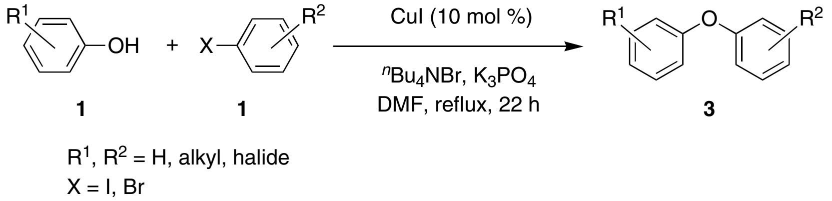
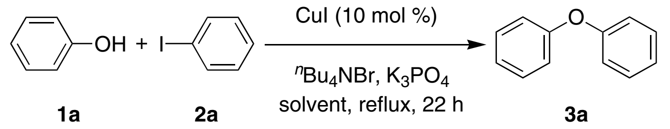


Scheme 1.

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	Yield[b] (%)
1[c]	PhMe	62
2[c,d]	PhMe	51
3	PhMe	82
4	DMSO	72
5	DMF	95
6[e]	DMF	65
7[f]	DMF	42

[a] Unless otherwise stated, all reactions were run for 22 h at reflux with CuI/^{n}Bu$_4$NBr/**1a**/**2a**/K$_3$PO$_4$ ratio of 1:1:10:10:20 in the solvent.

[b] Isolated yield.

[c] Reaction carried out with 5 mol % CuI and ^{n}Bu$_4$NBr.

[d] K$_2$CO$_3$ used in place of K$_3$PO$_4$.

[e] Reaction carried out with C$_6$H$_5$Br **2b** in place of **2a**.

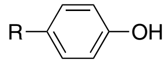
[f] Reaction carried out at 90 °C.

the same starting materials as the model substrates (Table 1). After screening a series of bases, 2 equiv of K$_3$PO$_4$ was determined to be the most effective base and gave diphenyl ether **3a** in 62% yield (entry 1). While replacing K$_3$PO$_4$ with K$_2$CO$_3$ afforded **3a** in a slightly lower yield of 51% (entry 2), the use of other inorganic bases such as NaOAc, Al$_2$O$_3$, and MgO, on the other hand, gave no reaction. Increasing the catalyst loading from 5 to 10 mol % was found to give an improved product yield of 82% (entry 3). Finally, on turning our attention to examining solvent effects, we were pleased to find that DMF as a solvent gave the best result, furnishing **3a** in 95% yield (entry 5).[14] In contrast, the analogous O-arylation of **1a** with bromobenzene **2b** was shown to proceed in a lower product yield of 65% (entry 6). Similarly, a low product yield of 42% was obtained on conducting the reaction at 90 °C (entry 7). The presence of a trace amount of water intrinsically present in the commercially available inorganic bases and ^{n}Bu$_4$NBr phase transfer catalyst was also shown to be essential for the O-arylation reaction. Under our conditions, no reaction occurred in the absence of ^{n}Bu$_4$NBr or when using K$_3$PO$_4$ dried to a constant weight under reduced pressure at 200 °C prior to use. This was consistent with our earlier findings for the analogous N-arylation reactions of nitrogen heteroarenes.[12]

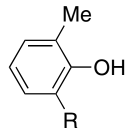
To define the scope of the CuI-catalyzed O-arylation reaction, we applied this process to a variety of phenols **1a**–**e** and aryl iodides **2a**–**h**. As shown in Table 2, O-arylation of **1a** with aryl iodides bearing either electron-withdrawing or electron-donating substituents was shown to give the corresponding products in excellent yields of 80–95% (entries 1–5). Similarly, the coupling of phenols and aryl iodides containing various electron-withdrawing and electron-donating substrate combinations was found to proceed in good to excellent yields, comparable to those obtained for the analogous ligand or additive promoted reactions (entries 7–14).[15] The present procedure was also shown to work well for the O-arylation of phenols and aryl iodides in which either or both starting materials contained a sterically demanding *ortho*-substituent such as a methyl group, with good to excellent product yields being obtained (entries 15–22). Only when both *ortho*-positions of the phenol were substituted with a sterically bulky methyl group as in **1e** was there a pronounced effect on the product yield observed. In these latter reactions, the aryl ethers **3t**–**v** were isolated in moderate yields of 40–41% along with unreacted aryl iodide starting material in yields up to 20% (entries 23–25).

The application of our catalytic system for the O-arylation of aliphatic alcohols was also examined and found to be somewhat intriguing (Table 3). As anticipated, our preliminary studies showed that the reaction of butanol **4f** with **2d** and 10 mol % CuI, 10 mol % ^{n}Bu$_4$NBr and K$_3$PO$_4$ (2 equiv) in DMF at reflux for 22 h gave 1-butoxy-4-chlorobenzene **5a** in 60% yield (entry 1). However, when the same conditions were applied to the reactions of **4g** with either aryl iodide **2d** or **2e**, the corresponding O-arylated products were obtained in low yields of 25% and 26%, respectively. On the other hand, by employing the conditions found suitable for the N-arylation of nitrogen heteroarenes by replacing K$_3$PO$_4$ and DMF with NaOH and toluene, respectively, these latter reactions were shown to proceed to give **5b** and **5c** in good yields (entries 2 and 3). In addition, when the present O-arylation method was applied to **4h**, which contains both an amino and an alcohol functionality, the chemoselective outcome was found to be dependent on the solvent employed. With 1 equiv of **2a** as the aryl iodide coupling partner, the reaction of **4h** in the presence of 10 mol % of CuI, 10 mol % of ^{n}Bu$_4$NBr, K$_3$PO$_4$ (2 equiv) in DMF as solvent at reflux for 22 h proceeded to afford the N-arylated and N,O-diarylated products **5d** and **5e** in yields of 50% and 15%, respectively (entry 4). Conversely, repetition of the same reaction with toluene as the solvent gave a switch in selectivity with **5e** obtained as the major product in 55% yield and the

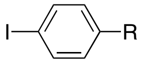
Table 2
CuI-catalyzed O-arylation of phenols **1a–e** with aryl iodides **2a–h**[a]



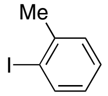
1b, R = Me
1c, R = Cl



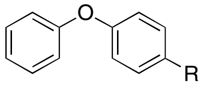
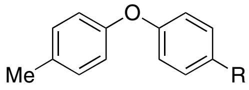
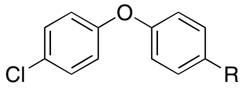
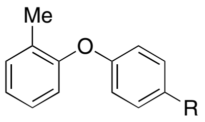
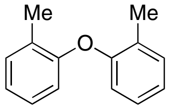
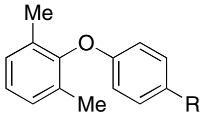
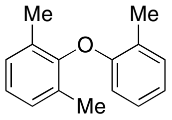
1d, R = H
1e, R = Me



2c, R = F
2d, R = Cl
2e, R = Me
2f, R = NO_2
2g, R = OMe



2h

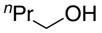
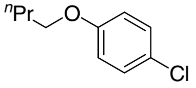
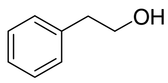
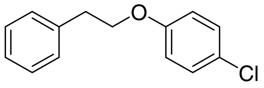
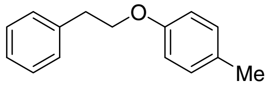
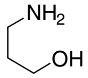
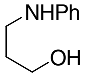
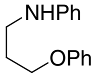
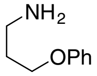
Entry	Substrates	Product		Yield[b] (%)
1	**1a** + **2c**		**3b**, R = F	90
2	**1a** + **2d**		**3c**, R = Cl	90
3	**1a** + **2e**		**3d**, R = Me	89
4	**1a** + **2f**		**3e**, R = NO_2	95
5	**1a** + **2g**		**3f**, R = OMe	80
6	**1b** + **2a**		**3d**, R = H	92
7	**1b** + **2d**		**3h**, R = Cl	82
8	**1b** + **2e**		**3i**, R = Me	87
9	**1b** + **2f**		**3j**, R = NO_2	89
10	**1b** + **2g**		**3k**, R = OMe	48
11	**1c** + **2d**		**3m**, R = Cl	80
12	**1c** + **2e**		**3h**, R = Me	81
13	**1c** + **2f**		**3n**, R = NO_2	80
14	**1c** + **2g**		**3o**, R = OMe	62
15	**1a** + **2h**		**3g**, R = H	74
16	**1b** + **2h**		**3l**, R = Me	81
17	**1d** + **2e**			75
18	**1c** + **2h**		**3p**, R = Cl	52
19	**1d** + **2d**			80
20	**1d** + **2f**		**3q**, R = NO_2	77
21	**1d** + **2g**		**3r**, R = OMe	60
22	**1d** + **2h**		**3s**	87
23	**1e** + **2d**		**3t**, R = Cl	40
24	**1e** + **2e**		**3u**, R = Me	41
25	**1e** + **2h**		**3v**	40

[a] All reactions were performed with CuI/^{n}Bu$_4$NBr/**1**/**2**/K_3PO_4 molar ratio = 1:1:10:10:20 in DMF at reflux for 22 h.
[b] Isolated yield.

O-arylated amine **5f** isolated as the minor product in 20% yield (entry 5).

In summary, we have developed a practical copper-catalyzed procedure for the coupling of a wide variety of phenols and aliphatic alcohols with aryl iodides that proceeded in good to excellent yields. The present protocol is applicable to a variety of phenols and aryl iodides containing electron-withdrawing, electron-donating, and sterically demanding substrate combinations under mild conditions. Further investigation of the scope and applications of this reaction is currently underway and will be reported in due course.

Table 3
CuI-catalyzed O-arylation of alcohols **4f**–**h** with aryl iodides **2a** and **2c**–**d**[a]

Entry	Alcohol	Aryl iodide	Product	Yield[b] (%)
1	 **4f**	**2d**	 **5a**	60
2[c]	 **4g**	**2d**	 **5b**	55
3[c]		**2e**	 **5c**	54
4	 **4h**	**2a**	 **5d**	50
			 **5e**	15
5[d]				55
			 **5f**	20

[a] Unless otherwise stated, all reactions were performed with CuI/^{n}Bu$_4$NBr/**2**/**4**/K$_3$PO$_4$ molar ratio = 1:1:10:10:20 in DMF at reflux for 22 h.

[b] Isolated yield.

[c] Reaction carried out with NaOH as base and PhMe as solvent.

[d] Reaction carried out with PhMe as solvent.

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Gujadhur, R. K.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865–2879; (d) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem. Commun.* **1998**, 2091–2092.

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14. *Typical experimental procedure*: To a round-bottom flask containing alcohol **1** (2 mmol), aryl iodide **2** (2 mmol), CuI (0.2 mmol), $^{n}\text{Bu}_4\text{NBr}$ (0.2 mmol), and base (4 mmol) under a N_2 atmosphere was added solvent (1.3 mL). The reaction mixture was vigorously refluxed for 22 h. On cooling to room temperature, saturated NH_4Cl (20 mL) was added and the organic layer was extracted with Et_2OAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford the title compound.
15. Please refer to Refs. 7d, 8c, 9d, 10, 11b and (a) Wong, K.-T.; Ku, S.-Y.; Yen, F.-W. *Tetrahedron Lett.* **2007**, *48*, 5051–5054; (b) Miao, T.; Wang, L. *Tetrahedron Lett.* **2007**, *48*, 95–98; (c) Sagar, A. D.; Tale, R. H.; Adude, R. N. *Tetrahedron Lett.* **2003**, *44*, 7061–7063.