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Efficient ligand-free copper-catalyzed N-arylation of amides with aryl halides in water

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ABSTRACT

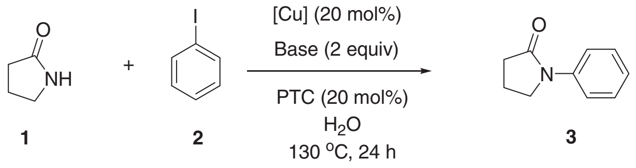
A convenient and efficient protocol has been developed for the cross-coupling of amides and aryl iodides using a ligand-free copper(I) oxide catalyst in water. A variety of amide derivatives afforded the corresponding N-arylated products in moderate to good yields (up to 88%).

N-Arylamides are valuable compounds that are prevalent in numerous compounds of biological, pharmaceutical, and materials interest.[1] Among the various strategies developed to date, the Goldberg-type reaction has proven to be an efficient and versatile method for rapidly accessing N-arylated amides via the copper-catalyzed cross-coupling of amides with aryl halides. In most cases, the presence of an assisting ligand was critical to the success of these protocols.[2] Recently, the use of a ligand-free copper catalytic system to promote the amidation of aryl halides was reported. Guo described the cross-coupling of aryl iodides and amides under ligand-free conditions using copper iodide and K_3PO_4.[3] Wolf demonstrated the amidation of aryl halides using Cu_2O as the catalyst in NMP.[4] Punniyamurthy also developed the cross-coupling of amides with aryl iodides using CuI in tetrabutylammonium bromide (TBAB).[5] However, the majority of these ligand-free catalytic systems developed to date utilize organic solvents as the reaction medium. This creates health and environmental issues due to their toxic and flammable properties.

Catalytic cross-coupling reactions that can be performed in water are of current interest because water is an inexpensive, safe, and environmentally benign medium, and the problems of pollution that arise from organic solvents can be avoided.[6] However, the use of water as a reaction solvent is not always practical for organic reactions since it entails the additional challenges of water tolerance for the catalyst and the associated problems with substrate solubilities and reactivities.[7] Encouraged by our interest in ligand-free copper catalysis and the development of more environmentally friendly approaches and technologies for cross-coupling reactions, we envisaged the application of ligand-free copper catalysts, for the N-arylation of amides using water as the sole reaction medium. Herein, we report an efficient method for the cross-coupling of aryl iodides with a variety of amides using a ligand-free Cu_2O catalytic system in water.

In our initial study, 2-pyrrolidinone **(1)** and iodobenzene **(2)** were chosen as model substrates for the N-arylation reaction. Under ligand-free conditions, the reaction of iodobenzene (1.0 equiv) with 2-pyrrolidinone (1.5 equiv), 20 mol % CuCl as

Table 1
Optimization studies on the ligand-free copper-catalyzed cross-coupling of 2-pyrrolidinone (**1**) and iodobenzene (**2**) in water[a]



1 **2** **3**

Entry	[Cu] source	Base	PTC	Yield[b] (%)
1	CuCl	K_3PO_4	TBAC	62
2	CuI	K_3PO_4	TBAC	63
3	CuBr	K_3PO_4	TBAC	62
4	Cu_2O	K_3PO_4	TBAC	70
5	CuO	K_3PO_4	TBAC	45
6	Cu_2O	KOH	TBAC	Trace
7	Cu_2O	Cs_2CO_3	TBAC	43
8	Cu_2O	K_3PO_4	TBAB	51
9	Cu_2O	K_3PO_4	TPAB	78
10	Cu_2O	K_3PO_4	TPAB	80[c]
11	–	K_3PO_4	TPAB	0

[a] Unless otherwise stated, the reaction was carried out with 2-pyrrolidinone (2.21 mmol), iodobenzene (1.47 mmol), base (2.94 mmol), Cu source (20 mol %), PTC (20 mol %), H_2O (0.75 ml), 130 °C, 24 h.
[b] Isolated yield after column chromatography.
[c] The reaction was performed with Cu_2O (10 mol %) and 0.4 ml of H_2O.

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E-mail address: yongchua.teo@nie.edu.sg (Y.-C. Teo).

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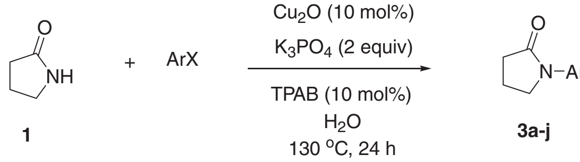
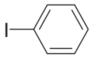
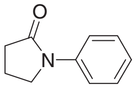
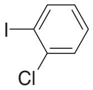
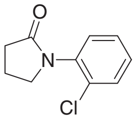
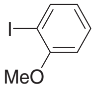
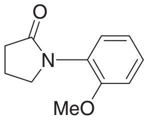
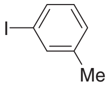
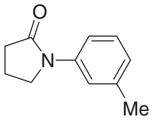
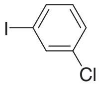
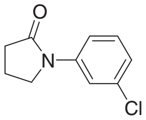
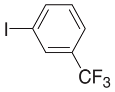
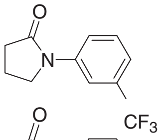
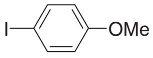
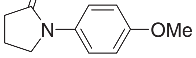
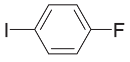
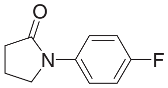
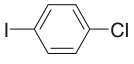
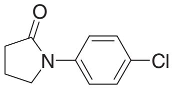
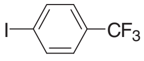
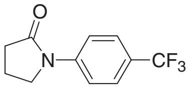
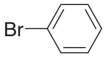
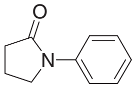
Table 2
N-Arylation of 2-pyrrolidinone with aryl halides catalyzed by ligand-free Cu_2O in water[a]



Entry	ArX	Product		Yield[b] (%)
1			**3a**	80 80[c]
2			**3b**	85
3			**3c**	46 96[c]
4			**3d**	46 60[c]
5			**3e**	73
6			**3f**	74
7			**3g**	70
8			**3h**	85
9			**3i**	88
10			**3j**	74
11			**3a**	31

[a] Unless otherwise stated, the reaction was carried out with 2-pyrrolidinone (2.21 mmol), aryl halide (1.47 mmol), K_3PO_4 (2.94 mmol), Cu_2O (10 mol %), TPAB (10 mol %), H_2O (0.40 ml), 130 °C, 24 h.

[b] Isolated yield after column chromatography.

[c] The reaction was performed with Cu_2O (20 mol %) and TPAB (20 mol %).

catalyst, K_3PO_4 as base and tetrabutylammonium chloride (TBAC) as phase-transfer catalyst (PTC) in water gave a promising yield of 62% (Table 1, entry 1). Encouraged by this result, optimization studies were initiated to evaluate the efficiency of various copper sources for the arylation reaction. Among the copper salts screened (entries 1–5), Cu_2O proved to be the best catalyst (entry 4), affording the N-arylated product in a good yield of 70%. Among the bases studied, K_3PO_4 plays an important role in this coupling reaction; KOH and Cs_2CO_3 were shown to be ineffective (entries 6 and 7). Next, we probed the effect of the PTC on the reaction (entries 8 and 9). TPAB proved to be the PTC of choice giving the product in an excellent yield of 78% under ligand-free conditions (entry 9). Lower yields were obtained in the case of TBAC (entry 4) and TBAB (entry 8). Finally, an attempt to lower the catalyst loading to 10 mol % with reduced solvent volume gave the product in an optimum yield of 80% (entry 10). To rule out the possibility that the catalysis was assisted by other contaminants that might be present in the system, control experiments revealed that no product was obtained in the absence of the copper source (entry 11). The optimized conditions for our ligand-free copper-catalyzed cross-coupling reaction are as follow: Cu_2O[8] (10 mol %), TPAB (10 mol %), and K_3PO_4 (2 equiv) in H_2O (0.40 ml) at 130 °C (entry 10).

To investigate the generality of this protocol, various functionalized aryl halides were coupled with 2-pyrrolidinone under the optimized conditions. The results are summarized in Table 2. In general, good to excellent yields were obtained in most instances (Table 2, entries 1–10). *ortho*-Substituted aryl iodides did not significantly hamper the cross-coupling reaction, affording the expected products in good yields (Table 2, entries 2 and 3), and no significant electronic effects were observed for *meta*- (entries 4–6), and *para*- (entries 7–10) substituted aryl iodides. This proved that aryl iodides were efficient electrophilic coupling partners for this catalytic system. However, this protocol was limited to aryl iodides as the use of bromobenzene as the coupling partner gave only a small amount of the product (entry 11). This difference in reactivity of the halide substituent in the electrophilic counterpart was confirmed by the chemoselective reaction of amide **1** with the iodo functionality of the mixed aryl halides in entries 8 and 9.

In order to expand the scope of this ligand-free Cu_2O-catalyzed amidation, the method was tested using a series of amide derivatives. The arylation of a representative cyclic secondary amide, δ-valerolactam, and heterocyclic amide, thiophene-2-carboxamide gave the respective arylated products in good yields (Table 3, entries 1–8). Moreover, the aromatic amide 4-methoxybenzamide gave the corresponding N-arylated product in moderate yield under the influence of ligand-free Cu_2O catalysis (entries 9–12). No significant electronic effects were observed for the cross-coupling of the amide derivatives with the selected *meta*-substituted aryl iodides. Currently, this catalytic system is not effective when aliphatic amides are employed, as only trace amounts of products are observed.

In summary, a simple and practical strategy was developed for the N-arylation of various amides with substituted aryl iodides using a ligand-free Cu_2O catalyst in water. In most cases, the N-arylated derivative was obtained in good to excellent yield. This ligand-free catalytic system which utilizes inexpensive and commercially available cuprous oxide as the catalyst, and water is expected to be particularly useful in industrial applications. Adaptation of this ligand-free Cu catalytic system to other cross-coupling reactions is ongoing in our laboratory.

Acknowledgments

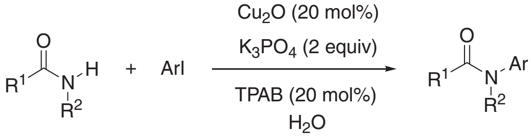
We thank the National Institute of Education and Nanyang Technological University for their generous support.

Supplementary data

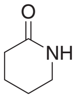
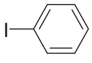
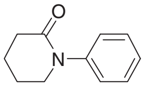
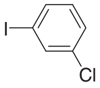
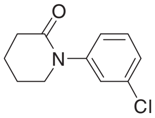
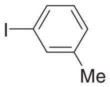
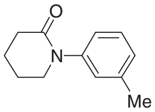
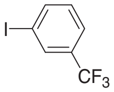
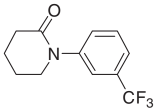
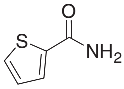
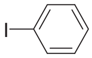
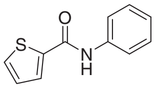
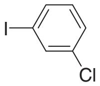
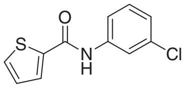
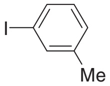
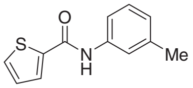
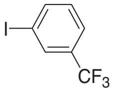
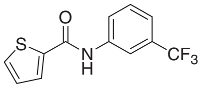
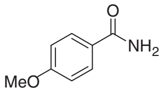
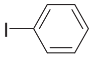
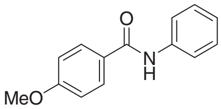
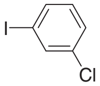
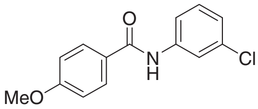
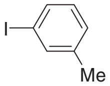
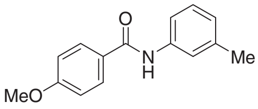
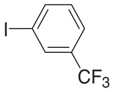
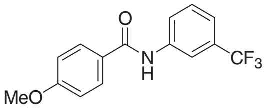
Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.003.

Table 3

N-Arylation of various amides with selected aryl iodides catalyzed by ligand-free Cu_2O in water[a]



4a-l

Entry	Amide	ArX	Product		Yield[b] (%)
1				**4a**	60
2				**4b**	63
3				**4c**	65
4				**4d**	58
5				**4e**	64
6				**4f**	76
7				**4g**	60
8				**4h**	63
9				**4i**	41
10				**4j**	50
11				**4k**	40
12				**4l**	44

[a] Unless otherwise stated, the reaction was carried out with amide (2.21 mmol), aryl iodide (1.47 mmol), K_3PO_4 (2.94 mmol), Cu_2O (10 mol %), TPAB (10 mol %), H_2O (0.40 ml), 130 °C, 24 h.

[b] Isolated yield after column chromatography.

References and notes

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8. Cu_2O (99.99% purity) was purchased from Sigma–Aldrich.