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Copper-Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amides

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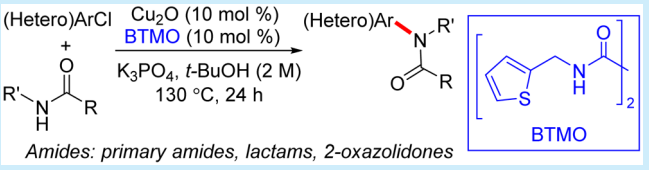
Supporting Information

ABSTRACT: Cu_2O/*N*,*N*′-bis(thiophen-2-ylmethyl)-oxalamide is established to be an effective catalyst system for Goldberg amidation with inferior reactive (hetero)aryl chlorides, which have not been efficiently documented by Cu-catalysis to date. The reaction is well liberalized toward a variety of functionalized (hetero)aryl chlorides and a wide range of aromatic and aliphatic primary amides in good to excellent yields. Furthermore, the arylation of lactams and oxazolidinones is achieved. The present catalytic system also accomplished an intramolecular cross-coupling product.



Transition metal catalyzed *N*-arylation of amides is one of the most proficient and convenient methods for preparing *N*-aryl amides, which play a significant role in pharmaceutical, agrochemical, and material science.[1] The humbled nucleophilicity of amides (electron-withdrawing carbonyl groups) comparable to amines make them challenging partners in metal-catalyzed cross-coupling reactions. In recent decades, a number of Pd-,[2−6] Ni-,[7] and Cu-[8−13] based catalytic systems have been successfully developed for this important transformation. Although less expensive and reactive (hetero)aryl chlorides have been found to be workable under some Pd- and Ni-catalyzed coupling reactions with amides,[5−7] they are still problematic substrates when less expensive copper/ligand catalytic systems were used. In 2001, Buchwald and co-workers[12] for the first time attempted amidation with aryl chlorides under the catalysis of CuI and 1,2-diamine ligands. However, only four examples were demonstrated, in which aryl chlorides (4.0 equiv) were used as both substrates and solvents. Afterward, the same protocols have been followed by Wei et al.[13a] and Cossy et al.[13b] to achieve the amidation of heteroaryl or aryl chlorides. Obviously, the requirement of more excess (hetero)aryl chlorides as both reactants and solvents limits the synthetic usage of these copper-catalytic methods. Thus, discovery of more powerful Cu-based catalytic systems that allow coupling of amides and (hetero)aryl chlorides with good generality and operability is highly desirable.

In 2015, we reported that some biaryl or aryl and alkyl substituted oxalic diamides are effective ligands that enable Cu-catalyzed coupling of (hetero)aryl chlorides with amines, phenols, and hydroxide to proceed under relatively mild conditions.[14] Based on these studies, we envisioned that the use of an appropriate oxalic diamide as the ligand would probably allow us to solve the long-lasting problem in Cu-catalyzed amidation of (hetero)aryl chlorides. Accordingly, exploration of suitable ligands and reaction conditions for this reaction was conducted, and the results are disclosed here.

As indicated in Table 1, using 4-chloroanisole and benzamide as the exemplary substrate combination, we initially screened ligands with 10 mol % CuI as a catalyst, K_3PO_4 as a base in DMSO (2 M) at 130 °C for 24 h. After screening several substituted *N*,*N*′-bisoxalamide symmetrical ligands **L1**−**L4**, which exposed outstanding ability in our previous studies,[14a−d] up to 36% yield was achieved due to poor conversion (Table 1, entries 1−4). Later, we moved to screening unsymmetrical oxalic diamides **L5** and **L6**, but unfortunately the outcome was not considerable (Table 1, entries 5 and 6). Recently, our group discovered that only 1−2 mol % each of Cu_2O and *N*,*N*′-bis[(2-furyl)methyl]oxalamide (BFMO) are enough to synthesize *N*-arylated heterocycles from aryl bromides and iodides.[14e] We then carried out the amidation of 4-chloroanisole and benzamide with 10 mol % CuI/BFMO (**L7**) in DMSO, (Table 1, entry 7) which revealed that the yield of the reaction could be surprisingly increased to 72%; at the same time, we assumed that furyl oxygen might have a crucial role in promoting the reaction. In response to this exciting result, we then customized *N*,*N*′-bis(thiophen-2-ylmethyl)oxalamide (BTMO), **L8**, which is a similar to **L7** containing a sulfur in the aromatic ring, starting from commercially available 2-thiophene-methylamine and performed the coupling reaction. A slight improvement of the yield was observed (Table 1, entry 8). Next, in accordance with our earlier BFMO promoted coupling report, we changed the catalyst from CuI to Cu_2O. It was revealed that a 78% yield was afforded using **L8** whereas **L7** is giving only a 70% yield of our expected amide-coupling product (Table 1, entries 9 and 10). Hence, we considered that

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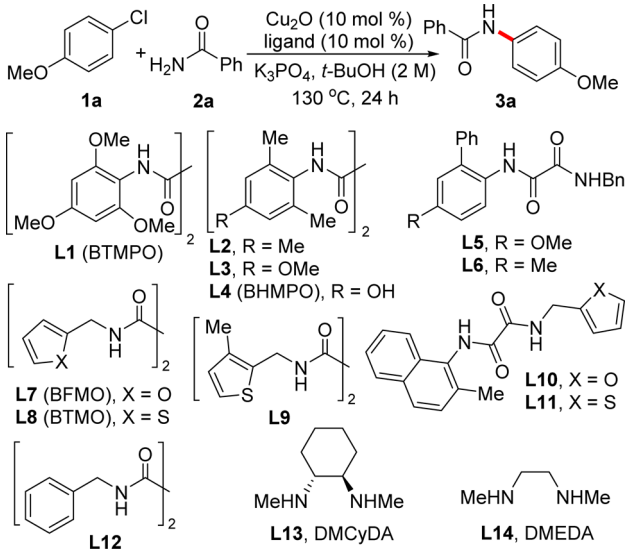
Table 1. Cu_2O-Catalyzed Coupling of 4-Chloroanisole with Benzamide under the Assistance of Different Ligands[a]



entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1[c]	**L1**	14	20	**L10**	82
2[c]	**L2**	23	21	**L11**	23
3[c]	**L3**	36	22	**L12**	35
4[c]	**L4**	20	23	no	0
5[c]	**L5**	5	24[c]	**L8**	38
6[c]	**L6**	8	25[d]	**L8**	35
7[c]	**L7**	72	26[e]	**L8**	33
8[c]	**L8**	75	27[f]	**L8**	44
9	**L7**	70	28[g]	**L8**	45
10	**L8**	78	29[h]	**L8**	50
11	**L7**	47	30[i]	**L8**	15
12	**L8**	87	31[j]	**L8**	21
13	**L1**	11	32[k]	**L8**	39
14	**L2**	25	33[l]	**L8**	52
15	**L3**	15	34[m]	**L8**	53
16	**L4**	21	35[n]	**L8**	67
17	**L5**	trace	36	**L13**	5
18	**L6**	9	37	**L14**	13
19	**L9**	79			

[a]General conditions: **1a** (1 mmol), benzamide (1.5 mmol), Cu_2O (0.1 mmol), ligand (0.1 mmol), K_3PO_4 (2.0 mmol), DMSO (0.5 mL, for entries 1−10), or *t*-BuOH (0.5 mL, for entries 11−26, 31−37). [b]The yield was determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c]CuI as the catalyst. [d]CuBr as the catalyst. [e]$Cu(OAc)_2$ as the catalyst. [f]DMF as the solvent. [g]DMA as the solvent. [h]NMP as the solvent. [i]Neat conditions. [j]K_2CO_3 as the base. [k]Cs_2CO_3 as the base. [l]KOH as the base. [m]Cu_2O (5 mol %), ligand (5 mol %). [n]The reaction was conducted at 120 °C.

Cu_2O/**L8** might be the better choice for further studies. Encouraged by this result, we decided to change the solvent from DMSO to *t*-BuOH and conducted the coupling reaction at 130 °C (Table 1, entries 11 and 12). To our delight, it was observed that **L8** gave an 87% yield of our anticipated product **3a** (Table 1, entry 12).

With these conditions, we then tried to screen other oxalamide ligands (**L1** to **L6**), but no momentous improvement in conversion was observed (Table 1, entries 13−18). We also modified the ligand structure and synthesized symmetrical **L9** and unsymmetrical **L10** and **L11** from 2-thiophenemethylamine and furfurylamine. Under the same conditions, **L10** afforded the coupling product in 82% yield, while other modified ligands are not effective for this coupling reaction (Table 1, entries 19−21). To check the ligand efficiency we carried out a reaction with **L12**, which contained no heteroatom in the phenyl ring. The reaction became sluggish, and the yield sharply decreased to 35% (Table 1, entry 22). This result demonstrated that the heteroatom in the aromatic ring must have a great impact to coordinate and further stabilize the Cu-complexes in the catalytic cycle.

Later, to verify the role of ligands, we performed a coupling reaction without the aid of any ligand (Table 1, entry 23), and it was determined that the ligand greatly impacts this coupling reaction. Subsequently, considering **L8** as suitable ligands, we tested the reaction using different Cu-catalysts in *t*-BuOH solvent, but yields sharply decreased (Table 1, entries 24−26). By studying various solvents and bases (Table 1, entries 27−33), and even under neat conditions (Table 1, entry 30), *t*-BuOH and K_3PO_4 were found to be the best combination for this coupling reaction.

Under these optimistic conditions, we achieved 53% and 67% yields when the reaction was executed using 5 mol % Cu_2O/**L8** at 130 °C and 10 mol % Cu_2O/**L8** at 120 °C, respectively (Table 1, entry 34 and 35). The conversion was very poor in the case of *N*,*N*′-dimethyl-1,2-cyclohexanediamine (DMCyDA) and *N*,*N*′-dimethylethylenediamine (DMEDA) as the ligands (Table 1, entries 36 and 37).

With reliable and optimal conditions in hand, we then examined the substrate scope using a variety of (hetero)aryl chlorides with different amides, as encapsulated in Scheme 1. A series of benzanilides (**3b−f**), along with a few bioactive small benzanilides,[1e] were synthesized in 74−92% isolated yields. In order to exhibit advantages of this catalytic system, we accomplished reactions where we could probe the electronic and steric nature of the aryl chlorides. Noticeably, 3-thiophenyl and 2-pyridinyl chlorides underwent smooth reactions to afford products **3g−i** in up to 81% yield. Changing amides from benzamide to other aromatic amides and aliphatic amides was also possible, leading the formation of substituted benzamides **3j−o** in good to excellent yields. In order to make our strategy practically viable, two reactions were conducted with 4 mmol scales under our standard conditions, which afforded **3d** and **3m** in 72% and 71% yields, respectively. Notably, coupling of 1,2-dichlorobenzene and benzamide selectively gave mono-amidation coupling product **3n** in 73% yield. Our catalytic system is also well tolerated in the coupling of nicotinamide and 2-thiophenecarboxamide, providing the corresponding products **3p** and **3q** in 83% and 79% yields, respectively. When aliphatic amides were used, a broad range of *N*-arylated secondary amides, including N-arylated cyclopropanecarboxamide (**3r**), cyclopentanecarboxamide (**3s**), thiopheneacetamide (**3t**), 2-phenylacetamide (**3u**), acetamide (**3v**), trifluoroacetamide (**3w**), and propionamides (**3x** and **3y**), could be obtained. However, to our disappointment, using this particular optimized set of conditions, the amidation reaction of acyclic secondary amides with aryl chlorides was not successful, probably due to the larger steric hindrance of acyclic secondary amides compared to primary amides.

Next, we explored the possibility for coupling (hetero)aryl chlorides with lactams and oxazolidinones because various substituted *N*-arylated lactams and oxazolidinones have shown important biological activities. As depicted in Scheme 2, under the standard conditions, a series of *para*-substituted aryl chlorides containing either electron-releasing or electron-

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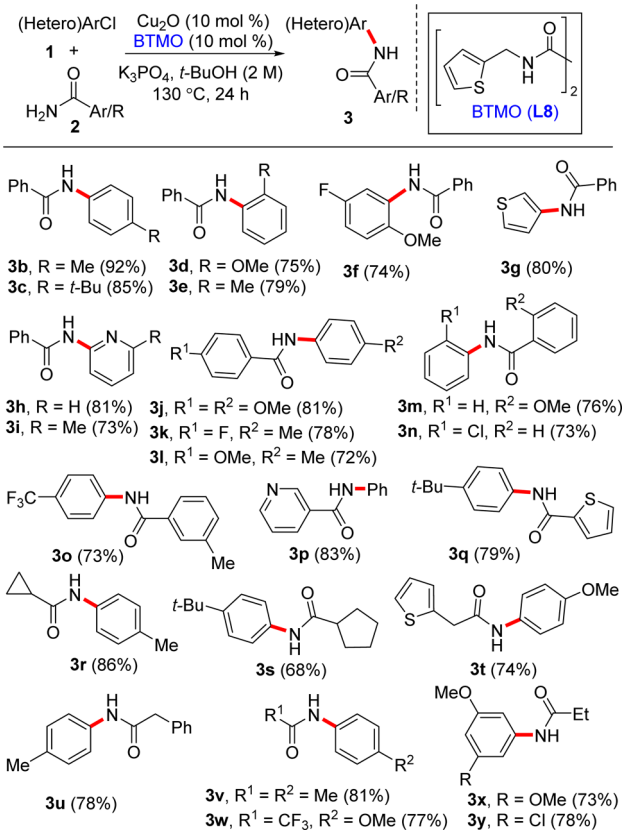
Scheme 1. Scope of Cu_2O/BTMO Catalyzed Coupling Reaction of (Hetero)aryl Chlorides with Amides[a]



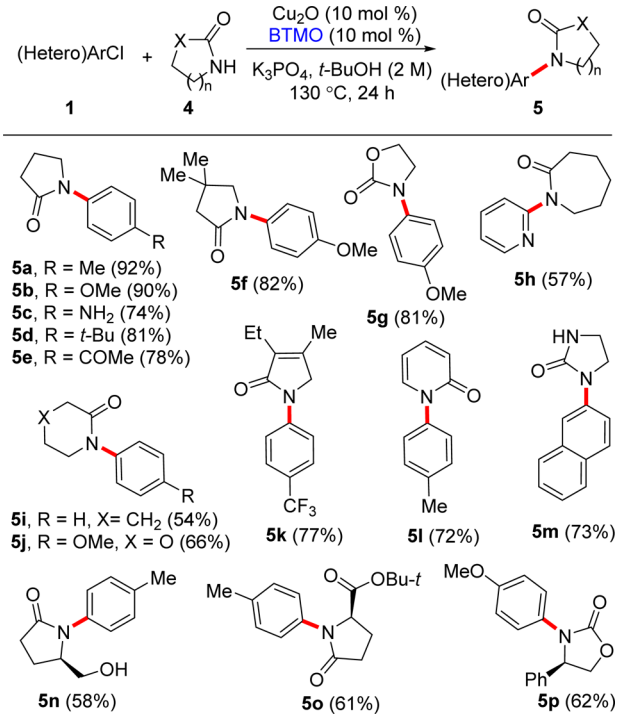
[a]General reaction conditions: **1** (1 mmol), amide **2** (1.5 mmol), Cu_2O (0.1 mmol), BTMO (0.1 mmol), K_3PO_4 (2.0 mmol), *t*-BuOH (0.5 mL), 130 °C, 24 h.

withdrawing groups afforded complete conversion in coupling with 2-pyrrolidinones and 2-oxazolidinone (**5a**–**g**). When more bulky six- and seven-membered lactams were used, the coupling became sluggish and decreased yields were observed (**5h**–**j**). A polysubstituted 2-pyrrolidinone also provided us with a satisfactory outcome with a 77% isolated yield (**5k**). Remarkably, under the optimized conditions, 2-hydroxypyridine selectively delivered *N*-arylated product **5l** with 4-chlorotoluene; no *O*-arylated product was observed.[15] The monoarylated product **5m** could be obtained in 73% yield when 2-imidazolidone was used. Some enantioenriched 2-pyrrolidinones and oxazolidinone were also applicable, delivering the related amidation products **5n**–**p** in moderate yields.

To show the versatility of this catalytic system, an intramolecular version of the N-arylation protocol was investigated (Scheme 3). Delightfully, we observed that 2-(2-chlorophenyl)acetamide **6** afforded 2-oxindole **7** in 75% yield.

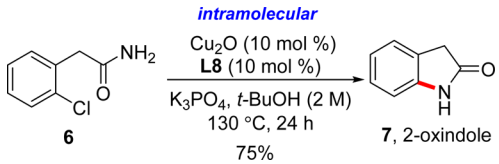
A tentatively proposed mechanism for the present coupling reaction is shown in Scheme 4. We thought that, with treatment of K_3PO_4, Cu_2O might react with BTMO to afford Cu(I) complex **A**, in which the strong electron-donating ability of the ligand could make this complex very active toward the oxidative addition with an aryl chloride. The oxidation addition product, Cu(III) complex **B**, might undergo a ligand exchange with an anion generated from the amide to provide complex **C**. Reductive elimination of **C** would deliver the aryl amide and regenerate the catalytic species **A**.

Scheme 2. Scope of Cu_2O/BTMO Catalyzed Coupling Reaction of (Hetero)aryl Chlorides with Lactams and Oxazolidinones[a]

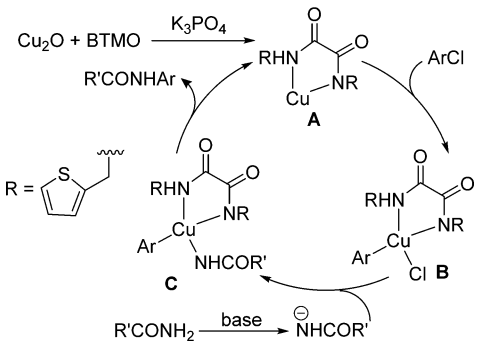


[a]General conditions: **1** (1 mmol), **4** (1.5 mmol), Cu_2O (0.1 mmol), BTMO (0.1 mmol), K_3PO_4 (2.0 mmol), *t*-BuOH (0.5 mL), 130 °C, 24 h.

Scheme 3. Cu-Catalyzed Intramolecular Amidation of Aryl Chloride



Scheme 4. Possible Mechanism



In conclusion, we have demonstrated that *N*,*N*′-bis-(thiophen-2-ylmethyl)oxalamide (BTMO) is a powerful promoter for Cu-catalyzed Goldberg-amidation coupling with (hetero)aryl chlorides. Utilizing our catalytic system, we were able to synthesize a wide variety of N-arylated amides, lactams, and oxazolidinones. Further exploration of this strategy and mechanistic studies are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, spectra data, and copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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