# Copper(I) Oxide/N,N'-Bis[(2-furyl)methyl]oxalamide-Catalyzed Coupling of (Hetero)aryl Halides and Nitrogen Heterocycles at Low Catalytic Loading

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**Abstract:** An easily prepared oxalic diamide is a powerful ligand for the copper-catalyzed coupling of aryl halides with nitrogen heterocycles. Only 1– 2 mol% each of copper(I) oxide and N,N'-bis[(2-furyl)methyl]oxalamide (BFMO) are needed to form *N*-arylation products under mild conditions. More than 10 different types of nitrogen heterocycles are compatible with these conditions, thereby giving the corresponding *N*-arylation products.

**Keywords:** aryl halides; copper salts; coupling; low catalytic loading; nitrogen heterocycles

*N*-Arylated heterocycles are common and important scaffolds in natural products, bioactive compounds and material molecules. Their syntheses have attracted a great deal of attention with the emergence of various excellent methods. Among them, metal-catalyzed C—N bond coupling has become a powerful and efficient tool to create such sophisticated frameworks.<sup>[1]</sup> The most often used metals for this transformation are copper and palladium.<sup>[2,3]</sup> Within the past years, a number of bidentate ligands such as 1,2-diamines,<sup>[4]</sup> phenanthrolines,<sup>[5]</sup> amino acids,<sup>[6]</sup>  $\beta$ -diketones,<sup>[7]</sup> and 8-hydroxyquinolines,<sup>[8]</sup> have proved to be effective ligands to promote copper-catalyzed couplings, making the reaction proceed under increasingly milder conditions.<sup>[9]</sup>

Despite these significant advances it has to be noted that in most cases catalytic loadings are still considerably high (>5 mol% copper salts and ligands),<sup>[4-9]</sup> the established protocols only work for some specific substrates, and generally applicable methods for the wide variety of nitrogen heterocycles are very rare. In order to make this ligand-promoted coupling protocol more synthetically useful, more powerful catalytic systems are still highly desirable.

In this respect, our recent finding of oxalic diamide ligands for copper-catalyzed coupling reactions has significantly expanded the substrate scope and improved the synthetic utility of Cu-catalyzed arylation of N- and O-nucleophiles.<sup>[10]</sup> Encouraged by this success, we proceeded to evaluate whether this catalytic system could also facilitate the coupling of various nitrogen heterocycles with aryl halides in a similar fashion. Our goal in this endeavor was to develop an efficient catalytic process that could be broadly applied to the major classes of nitrogen heterocycles. Central to this objective was the need to identify the best ligand that could effectively facilitate the reactions at low catalyst loadings. Herein, we report that N,N'bis[(2-furyl)methyl]oxalamide (BFMO), a readily prepared amide from very cheap furfurylamine and oxalic chloride, is a powerful ligand for the coppercatalyzed N-arylation of nitrogen heterocycles. The combination of Cu<sub>2</sub>O and BFMO is not only applicable for coupling reactions with more than 10 different types of nitrogen heterocycles, but also work at low catalytic loadings (1-2 mol% catalyst and ligand) that have not been described in previous studies.<sup>[4-9]</sup>

To initiate our studies, 4-bromoanisole (1a) and indole (2b) were selected as model substrates, and 2 mol% Cu<sub>2</sub>O and ligands were used to explore the optimized conditions. As shown in Table 1, we initially tried PMPBO (L1) as the ligand, which has shown excellent ability in our previous studies on coupling with phenols.<sup>[10c]</sup> The desired product could be obtained when the coupling was carried out in DMSO at 120 °C, but yield was only 30% because of poor conversion (entry 1). Two other diaryl-substituted oxalamide ligands L2 and L3 that performed well for coupling with amines,<sup>[10a,b]</sup> gave similar results (entries 2 and 3). Interestingly, modifying the aryl moiety of oxalic diamide ligands with the furfurylamine

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**Table 1.** Cu<sub>2</sub>O-catalyzed coupling of 4-bromoanisole with indole under the assistance of different ligands.<sup>[a]</sup>



- <sup>[a]</sup> Reaction conditions: **1a** (5.0 mmol), indole (6.0 mmol), Cu<sub>2</sub>O (0.1 mmol), ligand (0.1 mmol), K<sub>3</sub>PO<sub>4</sub> (10.0 mmol), DMSO (1.5 mL), 36 h.
- <sup>[b]</sup> The yield was determined by <sup>1</sup>H NMR analysis of crude products using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.
- <sup>[c]</sup> DMF as the solvent.
- <sup>[d]</sup> DMA as the solvent.
- <sup>[e]</sup> n-PrCN as the solvent.
- <sup>[f]</sup> Toluene as the solvent.
- <sup>[g]</sup> KOH as the base.
- <sup>[h]</sup>  $K_2CO_3$  as the base.

framework led to the discovery of BFMO (L4) as an excellent ligand (entry 4). Under the same conditions, some reported efficient ligands such as L-proline (L5), *trans-N*,*N*-dimethylcyclohexanediamine (L6) and 1,10-phenanthroline (L7) only afforded **3a** in low yields (entries 5–7), while 4,7-dimethoxy-1,10-phenanthroline (L8) gave a comparable result (entry 8). It is notable that although L4 is much easier to prepare than L8, and therefore it has a significant advantage for further synthetic applications. An evaluation of solvents showed that reaction proceed more efficiently with DMSO or DMA (entry 10) as the solvent, and use of DMF, *n*-PrCN and toluene significantly decreased the yields (entries 9, 11 and 13)

Thus, we concluded that DMSO is the best choice for this transformation, while DMA can also serve as alternative solvent if necessary. The solvent effect could also be observed for ligand **L8**, as evident from the fact that a better yield was obtained when solvent was switched from DMSO to toluene (entries 8 and 14). Investigation of alternative bases revealed that  $K_3PO_4$  was better than  $K_2CO_3$  and KOH (entries 15) and 16). With L4 as a suitable ligand, we also examined the other copper catalysts for this coupling reaction. The use of CuI decreased the reaction yield whereas significantly lower conversion was observed with CuBr. We also attempted the coupling of 2a with 4-chloroanisole; unfortunately only a trace amount of product was detected under the standard conditions. In addition, during optimization studies it was found that the concentration of reactants has a great impact on the transformation, and carrying out the reaction in 3M solution gave the best result (data not showed). Thus, the combination of 2 mol% Cu<sub>2</sub>O,  $2 \mod 8$  BFMO (L4) and  $K_3PO_4$  (2.0 equiv.) in DMSO (1.5 mL) at 120 °C represented the optimal conditions.

We next explored the reaction scope by testing a series of (hetero)aryl halides and nitrogen heterocycles with different substitution patterns. Representative data for this study are shown in Table 2. To our delight, a wide variety of nitrogen heterocycles, which included indole, azaindole, carbazole, indazole, benzimidazole, imidazole, 1H-pyrazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole and pyrrole, participated in this reaction to furnish the desired products. The corresponding products were isolated in 72-99% yield using only 2 mol% catalysts in the majority of cases (3a–3aa). Generally, azoles and pyrroles proved to be more reactive than indoles and carbazoles, as shorter reaction times were required. For the less reactive carbazole, benzimidazole and indazole substrates, a catalytic loading of 3 mol% was required to achieve satisfactory yields (3i, 3j and 3k). Functionalized nitrogen heterocycles are also amenable. For example, the reaction of aryl bromides with some 2-, 3-, and 5substituted indoles smoothly afforded the corresponding products in high yields (3c-3f). Interestingly, this method was also applicable to 2-substituted aryl bromides, as the coupling of 2-bromotoluene with indole, provided the corresponding product 3g in 85% yield. On the other side, a remarkably broad substrate scope of aryl and (hetero)aryl bromides was applicable. Both electron-rich and electron-poor aryl bromides gave the corresponding products in good to excellent yields, regardless of the substitution pattern. The aryl bromides possessing functional groups, such as OH and NH<sub>2</sub>, could also be transformed into the corresponding products in good yields, avoiding the competitive formation of C(aryl)-N and C(aryl)-O bonds (31, 3q and 3r). Several (hetero)aryl bromides bearing pyridine (3b, 3h, 3i, 3n and 3v), quinoline (3m) and benzothiophene (3u and 3w) moieties are applicable for this transformation. Moreover, the possibility for the synthesis of a Nilotinib (anti-cancer drug) intermediate was also evaluated under the stan-

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[a] General conditions: 1 (5.0 mmol), 2 (6.0 mmol for 3a-3i, 7.5 mmol for 3j-3aa), Cu<sub>2</sub>O (0.10 mmol), BFMO (0.10 mmol), K<sub>3</sub>PO<sub>4</sub> (10 mmol), DMSO (1.5 mL), 120 °C, 36 h for 3a-3h, 24 h for 3k-3aa, isolated yieldd.

<sup>[b]</sup> The reaction was conducted with 3.0 mol% Cu<sub>2</sub>O and 3.0 mol% BFMO at 120 °C for 48 h.

dard conditions.<sup>[11]</sup> This was found to work well with 4-methylimidazole to generate desired product 3aa in 89% yield, with a regioisomeric ratio (4:1) similar to that previously observed.

Extending this catalytic system to include aryl iodides as coupling partners proved to be quite successful. It was found, under the catalysis of 1 mol% Cu<sub>2</sub>O and 1 mol% BFMO (L4), after 24 h at 80 °C, to deliver **3a** in 65% yield (Table 3, entry 1). In an effort to further improve the method, we next examined the influence of the solvent. The use of DMF and toluene slightly decreased the yields (entries 2 and 5), whereas significantly lower conversions were observed with DMA and dioxane (entries 3 and 4).

The best result was observed when MeCN was used as a solvent (entry 6). As expected, a significantly reduced activity of the catalytic system was observed when L-proline (L5), trans-N,N-dimethyl-cyclohexanediamine (L6) and 1,10-phenanthroline (L6) ligands were used (entries 7-10). Thus, we found that the optimal conditions for coupling with aryl iodides were to use 1 mol% Cu<sub>2</sub>O as the catalyst, 1 mol% BFMO (L4) as the ligand, and carry out the reaction in MeCN at 80°C. These conditions were examined by varying both coupling partners and the results are summarized in Table 4. Delightfully, we were able to couple various nitrogen heterocycles with a range of aryl iodides that contain functionalized groups. It is notable that the coupling of 2-methylindole with 2-iodopyridine worked well, affording the desired product in 99% yield at 80°C (3ac). The azaindole, carbazole, indazole and benzimidazole substrates were found to be relatively difficult coupling partners, and their coupling reactions were only completed after increasing the catalytic loadings and prolonging the reaction times (3ae, 3h, 3ah, 3j and 3k). We further looked into sterically hindered substrates, and were pleased that ortho-substituted aryl iodides could be employed

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**Table 3.** Cu<sub>2</sub>O-catalyzed coupling of 4-iodoanisole with indole under the assistance of different ligands.<sup>[a]</sup>



| Entry            | Ligand | Yield [%] <sup>[b]</sup> | Entry            | Ligand | Yield [%] <sup>[b]</sup> |
|------------------|--------|--------------------------|------------------|--------|--------------------------|
| 1 <sup>[c]</sup> | L4     | 64                       | 6 <sup>[h]</sup> | L4     | 85                       |
| 2 <sup>[d]</sup> | L4     | 52                       | 7 <sup>[d]</sup> | L5     | trace                    |
| 3 <sup>[e]</sup> | L4     | 18                       | 8 <sup>[e]</sup> | L6     | 42                       |
| 4 <sup>[f]</sup> | L4     | trace                    | 9 <sup>[e]</sup> | L6     | 24                       |
| 5 <sup>[g]</sup> | L4     | trace                    | $10^{[f]}$       | L7     | trace                    |

- <sup>[a]</sup> General conditions: **3a** (5.0 mmol), indole (6.0 mmol), Cu<sub>2</sub>O (0.05 mmol), ligand (0.05 mmol), K<sub>3</sub>PO<sub>4</sub> (10.0 mmol), solvent (1.5 mL).
- <sup>[b]</sup> The yield was determined by <sup>1</sup>H NMR analysis of crude products using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.
- <sup>[c]</sup> DMSO as the solvent.
- <sup>[d]</sup> DMF as the solvent.
- <sup>[e]</sup> DMA as the solvent.
- <sup>[f]</sup> Dioxane as the solvent.
- <sup>[g]</sup> Toluene as the solvent.
- <sup>[h]</sup> MeCN as the solvent.

to prepare the corresponding *N*-arylated products in good to excellent yields (**3af**, **3ag** and **3ap**). The reaction of an unsymmetrical imidazole with aryl iodides was also evaluated under the standard conditions, which resulted in the formation of regioisomeric products (1.1:1) in a 94% combined yield (**3aq**). Overall, no significant electronic effects were observed for substituted aryl halides (X = Br, I) as well as nitrogen heterocycles; the rates and yields of the reactions were comparable. It is worth mentioning that Cu<sub>2</sub>O/BFMO-catalyzed couplings were generally clean and contained only coupling product and unreacted starting material.

In conclusion, we have demonstrated a general and practical Cu(I)/oxalic diamide-catalyzed methodology for the synthesis of valuable *N*-arylated heterocycles, including indoles, pyrroles and various azoles, which could be used for the further preparation of industrially and pharmaceutically important compounds. Both aryl halides and heterocycles performed very well at low catalytic loadings under the standard conditions, delivering the corresponding products efficiently. The broad substrate scope, low cost for preparation of the ligand, operational simplicity, and multigram scale synthetic ability are important features of this reaction in terms of practical applications. Further investigations on the substrate scope and synthet-

Table 4. Scope of the Cu<sub>2</sub>O/BFMO-catalyzed coupling reaction of (hetero)aryl iodides with nitrogen heterocycles.<sup>[a]</sup>



[a] General conditions: 4 (5.0 mmol), 2 (6.0 mmol for indole, azaindole, benzimidazole and carbazole, 7.5 mmol for pyrrole and azoles), Cu<sub>2</sub>O (0.05 mmol), BFMO (0.05 mmol), K<sub>3</sub>PO<sub>4</sub> (10.0 mmol), MeCN (1.5 mL), 80 °C, 24 h, isolated yield.
 [b] The reaction was conducted with 2.0 mol% Cu O and 2.0 mol% BFMO at 80 °C for 36, 48 h

The reaction was conducted with 2.0 mol% Cu<sub>2</sub>O and 2.0 mol% BFMO at 80°C for 36–48 h.
 The reaction was conducted with 3.0 mol% Cu<sub>2</sub>O and 3.0 mol% BFMO at 80°C for 48 h.

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ic applications of this transformation are currently in progress in our laboratory.

## **Experimental Section**

#### **Typical Experimental Procedure**

The (hetero)aryl bromide or iodide (5.0 mmol), nitrogen heterocycle (7.5 mmol) [NB: for indole, azaindole and carbazole (6.0 mmol)], Cu<sub>2</sub>O (1-2 mol%), K<sub>3</sub>PO<sub>4</sub> (10.0 mmol, 2.12 g) and ligand L4 (1–2 mol%) were placed into a Schlenk tube (10 mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon three times, and DMSO (1.5 mL) was added afterwards (NB: for liquid substrates, they were added after the tube was backfilled with argon). The reaction mixture was heated at 80-120 °C for 24-36 h under vigorous stirring. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, and dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The residue was purified by column chromatography (eluting with ethyl acetate/hexanes or dichloromethane/methanol) on silica gel to afford the corresponding products.

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 $X = I, 1 \mod Cu_2O \& BFMO, K_3PO_4, MeCN, 80 °C$   $X = Br, 2 \mod Cu_2O \& BFMO, K_3PO_4, DMSO, 120 °C$ More than 10 different types of nitrogen heterocycles worked well

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