Cross-Coupling *Very Important Paper*

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CuI/Oxalamide Catalyzed Couplings of (Hetero)aryl Chlorides and Phenols for Diaryl Ether Formation

*Mengyang Fan[+], Wei Zhou[+], Yongwen Jiang, and Dawei Ma**

Abstract: *Couplings between (hetero)aryl chlorides and phenols can be effectively promoted by CuI in combination with an N-aryl-N′-alkyl-substituted oxalamide ligand to proceed smoothly at 120°C. For this process, N-aryl-N′-alkyl-substituted oxalamides are more effective ligands than bis(N-aryl)-substituted oxalamides. A wide range of electron-rich and electron-poor aryl and heteroaryl chlorides gave the corresponding coupling products in good yields. Satisfactory conversions were achieved with electron-rich phenols as well as a limited range of electron-poor phenols. Catalyst and ligand loadings as low as 1.5 mol% are sufficient for the scaled-up variants of some of these reactions.*

Diaryl ethers are frequently found structural motifs of natural products and synthetic molecules with various biological functions and properties.[1] The development of useful methods for preparing diaryl ethers has thus received continuous attention from the synthetic community.[2–7] Among the existing methods, metal-catalyzed coupling reactions between aryl halides and phenols represent one of the most reliable approaches and have been intensively applied in both academia and industry.[2] Initially, this transformation required harsh conditions (ca. 200°C) and stoichiometric amounts of copper reagents, and often gave moderate yields with a rather narrow reaction scope.[3] This situation was greatly changed during the past years owing to the discovery of some effective catalytic systems, such as the combination of palladium with sterically demanding phosphines[4] and systems based on copper and bidentate ligands.[5] Although significant progress has been achieved in this area, there remain some limitations. For example, although diaryl ether formation with a Cu/bidentate ligand catalyst system works well for aryl iodides and bromides,[2,5] the less expensive aryl chlorides remain difficult substrates. The only successful example of a Cu/ligand-catalyzed arylation of phenols with aryl chlorides was reported by Xia and Taillefer;[7] 2,2,6,6-tetramethyl-3,5-heptanedione was selected as the ligand, and the reaction took place at 135°C. However, the reaction scope was limited to electron-rich phenols, and a large amount of ligand (0.8 equiv) and relatively expensive Cs_2CO_3 as the base were required for complete conversion. Furthermore, the coupling of pharmaceutically more important (hetero)aryl chlorides has remained unexplored. Therefore, the discovery of more powerful ligands for copper-catalyzed couplings of (hetero)aryl chlorides and phenols is highly warranted.

Building upon our recent success in the development of effective ligands for copper-catalyzed aryl amination reactions with (hetero)aryl chlorides,[8] we discovered that some N-aryl-N′-alkyl-substituted oxalamides could promote copper-catalyzed couplings between (hetero)aryl chlorides and phenols, leading to the formation of a great variety of diaryl ethers at 120°C. Herein, we wish to report our results.

As summarized in Table 1, we selected the coupling of 4-chlorotoluene and phenol as a model reaction to optimize the reaction conditions. Initially, several bis(N-aryl)-substituted oxalamides that led to excellent yields in the amination of (hetero)aryl chlorides were examined. It was found that *N*,*N*′-bis(2,4,6-trimethoxyphenyl)oxalamide (BTMPO, **L1**) could promote this reaction, but only provided about 44% conversion at 120°C after 24 hours (entry 1). The use of oxalamides **L2**–**L4**, which are derived from 2-phenoxy- or 2-phenyl-substituted anilines, gave better results, but incomplete conversion was still observed (entries 2–4). To our surprise, improved conversion was observed when N-aryl-N′-alkyl-substituted oxalamide **L5** was used as the ligand (entry 5), which was inconsistent with the trends observed in our previous studies on aryl amination.[8a]

We next screened several N-aryl-N′-alkyl-substituted oxalamides with different substituents at the 4-position of the aniline moiety. The electronic nature of the aniline group had limited influence on the reaction efficiency (compare entries 5–9 and 11). This phenomenon is also inconsistent with our observations for aryl amination, where the electronic nature of the aniline part exerted a great influence on its efficiency.[8a] The best result was achieved when 4-methyl-2-phenylaniline-derived oxalamide **L9** was employed as the ligand (entry 9). The desired product was isolated in excellent yield when the loading of both CuI and **L9** was reduced to 5 mol% (entry 10). We therefore chose these reaction conditions for further studies.

It seemed that the 2-phenylaniline moiety of the ligands was important for the high reactivity, as 2-phenoxyaniline-derived oxalamide **L11** gave only 75% conversion (entry 12). Changing the aliphatic amine moiety of the oxalamides also altered their efficiency, as evident from the fact that the cyclohexylamine- and *n*-hexylamine-derived amides **L12** and **L13** led to moderate conversions. Good conversion was retained when the benzylamine group was replaced with (2-furanyl)methylamine (compare entries 9 and 15).

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[*] M. Fan,[+] W. Zhou,[+] Prof. Dr. Y. Jiang, Prof. Dr. D. Ma
State Key Laboratory of Bioorganic & Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (China)
E-mail: madw@mail.sioc.ac.cn

[+] These authors contributed equally to this work.

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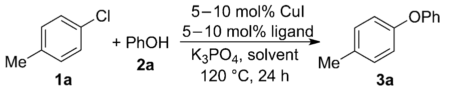
Table 1: CuI catalyzed coupling of 4-chlorotoluene with phenol in the presence of different ligands.[a]



Entry	Ligand	Yield [%][b]	Entry	Ligand	Yield [%][b]
1	**L1**	44	13	**L12**	53
2	**L2**	84	14	**L13**	70
3	**L3**	87	15	**L14**	89
4	**L4**	88	16	**L15**	0
5	**L5**	93	17	**L16**	0
6	**L6**	82	18	**L17**	0
7	**L7**	89	19	**L18**	0
8	**L8**	95	20	**L19**	0
9	**L9**	96	21[d]	**L9**	87
10[c]	**L9**	90	22[e]	**L9**	80
11	**L10**	93	23[f]	**L9**	70
12	**L11**	75	24[g]	**L9**	30

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.3 mmol), CuI (0.1 mmol), ligand (0.1 mmol), K_3PO_4 (1.5 mmol), DMSO (1.0 mL), 120°C, 24 h. [b] Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c] Yield of isolated product obtained with 5 mol% CuI and 5 mol% of the ligand. [d] In DMF. [e] In DMA. [f] In 1,4-dioxane. [g] In MeCN.

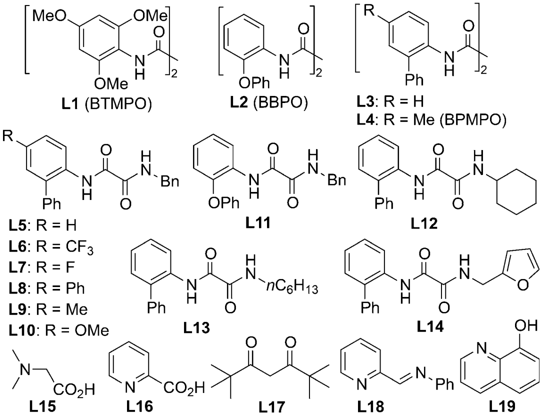
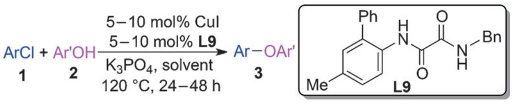
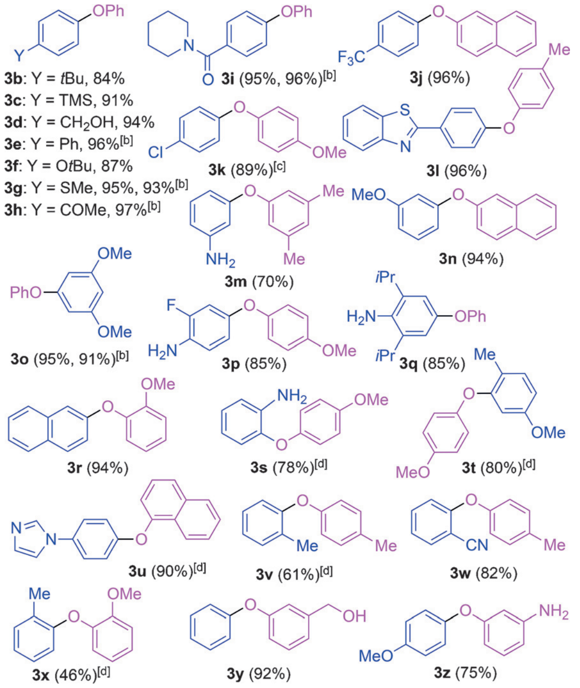


Table 2: Coupling of aryl chlorides with phenols.[a,b]





[a] Reaction conditions: **1** (1 mmol), **2** (1.3 mmol), CuI (0.05 mmol), ligand (0.05 mmol), K_3PO_4 (1.5 mmol), DMSO (1.0 mL), 120°C, 24 h. Yields of isolated products are given. [b] In DMF. [c] Aryl chloride (2 mmol) and phenol (1 mmol). [d] Yield of isolated product with 10 mol% CuI and 10 mol% of the ligand; reaction time: 48 h. TMS = trimethylsilyl.

Several bidentate ligands that led to excellent efficiencies in CuI catalyzed couplings of phenols with aryl iodides and bromides (such as *N*,*N*-dimethylglycine (**L15**),[5d] picolinic acid (**L16**),[5m] 2,2,6,6-tetramethyl-3,5-heptanedione (**L17**),[5c] Schiff base ligand **L18**,[5e] and 8-hydroxyquinoline (**L19**))[5b] were also tested under the present reaction conditions. However, none of them led to the formation of **3a** from 4-chlorotoluene, indicating that the use of N-aryl-N′-alkyl-substituted oxalamides as the ligands was essential.

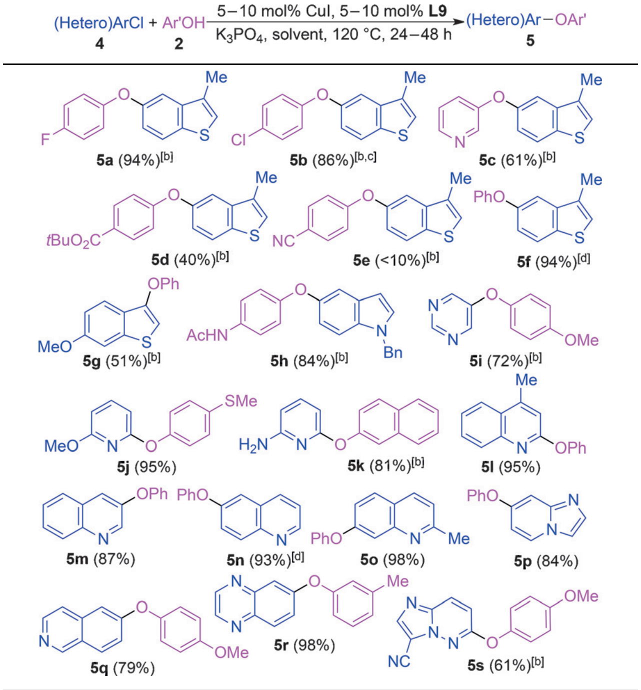
With **L9** as a suitable ligand, we examined the solvent effects of this coupling reaction. The use of DMF and DMA slightly decreased the yields whereas significantly lower conversions were observed with 1,4-dioxane and MeCN as the solvents. Thus we concluded that DMSO is the best solvent for this process while DMF and DMA can serve as alternative solvents if necessary for practical reasons.

With optimized reaction conditions in hand, we next explored the substrate scope and functional-group tolerance of the reaction by coupling a variety of (hetero)aryl chlorides with phenols. As summarized in Table 2, a range of *para*-substituted aryl chlorides bearing either electron-donating or -withdrawing groups were suitable coupling partners and enabled the formation of diaryl ethers **3b**–**3l** in 84 to 97% yield. With 1,4-dichlorobenzene as the coupling partner, the reaction could be stopped at the monoarylation stage, and the desired product **3k** was isolated in 89% yield when 2 equiv of 1,4-dichlorobenzene were used. Five *meta*-substituted aryl chlorides were all suitable, providing **3m**–**3q** in good to excellent yields. We further looked into sterically hindered substrates, and were pleased that both *ortho*-substituted aryl chlorides and phenols could be employed for preparing the corresponding diaryl ethers **3r**–**3x**. However, most of these reactions were relatively sluggish, and increased catalyst loadings and prolonged reaction times were often required to ensure complete conversion. Interestingly, the electronic nature of the aryl chloride turned out to be significant for the coupling reaction. With 5 mol% of CuI and **L9**, **3w** was obtained in 84% yield, whereas **3v** was formed with incomplete conversion even at higher catalyst loadings. Furthermore, the successful formation of **3y** and **3z** indicated that free aliphatic alcohols and primary anilines have no influence on the reaction course.

Next, the coupling of 3-methyl-5-chlorobenzothiophene with several electron-deficient phenols was studied. As predicted, they were less reactive than electron-rich phenols.

For 4-fluorophenol and 4-chlorophenol, the coupling reaction reached completion after 48 hours in the presence of 10 mol% CuI and 10 mol% **L9**, delivering the diaryl ethers **5a** and **5b** in 94 and 86% yield, respectively (Table 3). Under the same conditions, 3-hydroxypyridine also produced the desired product **5c** in reasonable yield. However, poor conversions were observed with 4-(*tert*-butoxycarbonyl)phenol and 4-cyanophenol as the substrates (into **5d** and **5e**). Further studies are required to solve this problem.

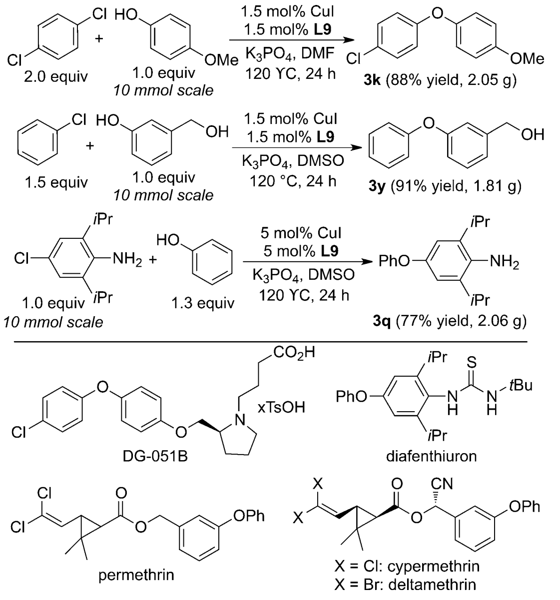
Table 3: Coupling of heteroaryl chlorides with phenols.[a,b]



[a] Reaction conditions: **4** (1 mmol), **2** (1.3 mmol), CuI (0.05 mmol), ligand (0.05 mmol), K_3PO_4 (1.5 mmol), DMSO (1.0 mL), 120°C, 24 h. Yields of isolated products are given. [b] CuI (10 mol%), **L9** (10 mol%), 48 h. [c] 3-Methyl-5-chlorobenzothiophene (3 mmol), 4-chlorophenol (1 mmol). [d] In DMF.

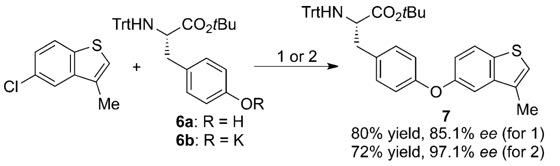
Aside from chlorobenzothiophene, other heteroaryl chlorides could also be smoothly coupled with phenols under similar reaction conditions to deliver the heterocycle-containing diaryl ethers **5g**–**5s** in yields of 61–98%. These heterocycles include indole (**5h**), pyrimidine (**5i**), pyridine (**5j** and **5k**), quinoline (**5l**–**5o**), imidazopyridine (**5p**), isoquinoline (**5q**), quinoxaline (**5r**) and imidazo[1,2-*b*]pyridazine (**5s**). Generally, electron-poor heteroaryl chlorides were more reactive than electron-rich ones (compare **5a**–**5h** with **5j**–**5r**), which is consistent with the observation for the coupling of aryl chlorides.

When some coupling reactions (**3k** and **3y**) were scaled up to 10 mmol, complete conversion could be achieved even with only 1.5 mol% of CuI and the ligand (Scheme 1). For an electron-rich aryl chloride, a catalyst loading of 5 mol% (for both CuI and **L9**) was still necessary to obtain coupling product **3q** in good yield. These three products are important building blocks for assembling bioactive molecules that have been prepared on large scale by employing different coupling methods.[9–12] For example, diaryl ether **3k** is the key intermediate for synthesizing DG-051B, which has entered phase II clinical evaluation for the treatment of myocardial infarction and stroke.[1e,9] Diaryl ether **3q** has been used for manufacturing the insecticide diafenthiuron,[10] and diaryl ether **3y** is a common building block for manufacturing insecticidal pyrethroids, such as permethrin, cypermethrin, and deltamethrin.[1e,11] The currently adopted synthetic approaches require the use of more expensive aryl bromides as the coupling partners (for **3k**[9] and **3q**),**[10]** or higher reaction temperatures (150–170°C for **3y**).[11] Our coupling method has clear advantages over previously reported ones and will probably find practical usage for preparing these diaryl ethers.



Scheme 1. Scaled-up coupling reactions.

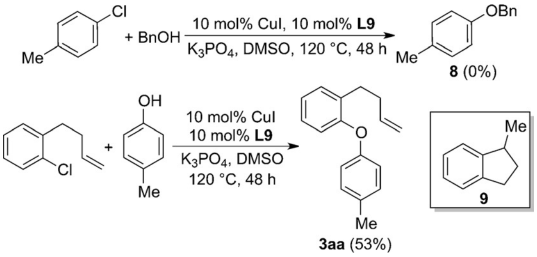
Under our standard conditions, the coupling of 3-methyl-5-chlorobenzothiophene with tyrosine derivative **6a** took place to afford diaryl ether **7** in 80% yield (Scheme 2). However, the *ee* of the product was 85.1%, indicating that partial racemization had occurred. We envisioned that K_3PO_4 might be too basic and that the phenolic salt **6b** might also be a suitable coupling partner. Pleasingly, the coupling then proceeded in the absence of K_3PO_4, providing **7** in 72% yield and 97.1% *ee*, indicating minimum racemization. This method should be valuable for assembling synthetically



Scheme 2. Reagents and conditions: 1) **6a** (1.3 equiv), CuI (5 mol%), **L9** (5 mol%), K_3PO_4 (1.3 equiv), DMSO, 120°C, 24 h. 2) **6b** (1.3 equiv), CuI (5 mol%), **L9** (5 mol%), DMSO, 120°C, 24 h. Trt = triphenylmethyl.

important tyrosine-containing diaryl ethers[1a,5g] from (hetero)aryl chlorides.

When benzyl alcohol was used, the desired coupling did not take place to give ether **8** (Scheme 3), indicating that aliphatic alcohols are not suitable coupling partners under the present reaction conditions. Furthermore, the coupling of 4-(2-chlorophenyl)-1-butene gave **3aa** as the only product, while compound **9** was not detected by GC-MS analysis. This result illustrates that this coupling reaction might not proceed through a radical mechanism.[13]



Scheme 3. Using benzyl alcohol or 4-(2-chlorophenyl)-1-butene as the coupling partner.

In summary, we have shown that N-aryl-N′-alkyl-substituted oxalamides are powerful ligands for CuI catalyzed coupling reactions of (hetero)aryl chlorides and phenols, providing diaryl ethers in good to excellent yields under mild reaction conditions. A broad range of functional groups, including amines, alcohols, amides, halides, esters, ketones, and nitriles, as well as a number of heterocycles were tolerated. The broad substrate scope, together with the low costs associated with both the catalysts and ligands, renders this coupling reaction particularly attractive for the large-scale synthesis of diaryl ethers. Furthermore, the identification of different structure–activity relationships for ligands in diaryl ether formation and aryl amination should be of benefit for further ligand design.

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Keywords: biaryl ethers · copper · cross-coupling · (hetero)aryl chlorides · ligand screen

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