Efficient Ligand-Free, Copper-Catalyzed N-Arylation of Sulfonamides

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Abstract: An efficient and convenient protocol has been developed for the N-arylation of sulfonamides with differently substituted aryl iodides using ligand-free copper iodide to afford the arylated products in good to excellent yields (up to 91%).

Key words: ligand-free, copper, sulfonamides, N-arylation

N-Arylsulfonamides constitute an important class of compound which are prevalent in many pharmaceuticals and bioactive compounds. In particular, they have been reported to possess biological activities associated with class III antiarrhythmic agents,[1] nonpeptidic vasopressin VIa receptor antagonists,[2] translation initiation inhibitors,[3] and HIV-1 protease inhibitors.[4] As such, significant efforts have been channeled to the development of new and sustainable protocols for the preparation of such compounds.

Copper-catalyzed N-arylation of amines[5] (Ullmann condensation) and amides[6] has emerged as powerful methods for the formation of C–N bond. In recent years, these reactions are usually carried out in the presence of a suitable mono- or bidentate ligand such as phosphines,[7] diols,[8] diketone,[9] amino acids,[10] 1,10-phenanthroline derivatives,[11] oxalyldihydrazone,[12] salicylamides,[13] and phosphoramidite[14] to significantly increase the yield of the product, broaden the substrate scope and also to achieve milder reaction conditions. In addition, room-temperature Ullmann arylation reactions have also been documented recently.[15]

Although significant progress has been achieved for the aforementioned reactions, however, the copper-catalyzed, cross-coupling reactions using sulfonamides as nitrogen nucleophiles are limited and still remained as a challenge among the synthetic community. The cross-coupling of sulfonamides with aryl boronic acids was first demonstrated using $Cu(OAc)_2$ as catalyst.[16] He and Wu reported the assembly of *N*-arylsulfonamides through the ligand-free, copper-catalyzed arylation of sulfonamides using microwave heating.[17] This method required the use of microwave heating at 195 °C which limited its practicality. Recently, the N-arylation of sulfonamides with aryl and heteroaryl halides was also achieved using a combination of copper catalysts and assisting ligands under mostly inert conditions.[18]

Based on these precedents, there is still a need to develop economical protocols that provide efficient synthesis of arylated sulfonamide and to widen the substrate scope under practical reaction conditions. As part of our interest in ligand-free, copper catalysis and development of sustainable strategy for the synthesis of *N*-arylsulfonamides, we decided to use copper salts as cheap and readily available catalyst for this reaction. In this paper, we report an efficient cross-coupling of sulfonamides with a wide variety of aryl iodides using air-stable, ligand-free CuI as the catalyst and DMF as the solvent. It is noteworthy that these reactions can be performed without protection from air or moisture.

In our initial study, *p*-toluenesulfonamide and iodobenzene were used as model substrates for optimizing the reaction conditions. The experiments were carried out with 5 mol% of copper salt and Cs_2CO_3 as base in DMF at 130 °C (Table 1). It is interesting to note that several copper salts proved applicable for this coupling reaction furnishing the *N*-phenyltolylsulfonamide in yields ranging from 46–86% with copper(I) iodide being the best catalyst (Table 1, entries 1–6). A control experiment was also carried out to confirm that no product was obtained in the absence of the copper source (Table 1, entry 7). Next, we probed the solvent effect and found out that DMF was the best solvent and proved to be critical for the success of this ligand-free system. Only a trace amount of the products was detected with the use of water, toluene, and acetonitrile as solvents (Table 1, entries 8–10). The influence of bases on the yield of the N-arylated product was also investigated. It was found that Cs_2CO_3 was the most effective base, while the use of other bases such as K_3PO_4, K_2CO_3, and KOH resulted in much lower yields (Table 1, entries 11-13). In summary, the optimal conditions for the N-arylation of *p*-toluenesulfonamide was achieved using a combination of CuI (5 mol%) and Cs_2CO_3 (2 equiv), stirred in DMF at 130 °C for 24 hours.

The generality of this methodology was further extended to the coupling of *p*-toluenesulfonamide with aryl halides. The results are shown in Table 2. The corresponding arylated sulfonamides were obtained in good to excellent yields for substrates with varying types of substitution on the aryl halides. A range of functional groups such as methyl, methoxy, halo (Cl, Br and F), trifluoromethyl, nitro, and ester was tolerated by the system. No significant electronic and steric effects were observed for the *meta*- and

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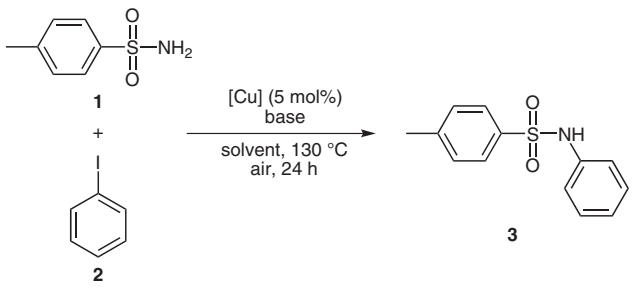
Table 1 Optimization Studies of Ligand-Free Cross-Coupling of *p*-Toluenesulfonamide and Iodobenzene[a]



Entry	[Cu] source	Base	Solvent	Yield (%)[b]
1	Cu	Cs_2CO_3	DMF	52
2	CuO	Cs_2CO_3	DMF	82
3	Cu_2O	Cs_2CO_3	DMF	63
4	CuCl	Cs_2CO_3	DMF	80
5	CuBr	Cs_2CO_3	DMF	46
6	CuI	Cs_2CO_3	DMF	86
7	–	Cs_2CO_3	DMF	0
8	CuI	Cs_2CO_3	MeCN	trace
9	CuI	Cs_2CO_3	toluene	0
10	CuI	Cs_2CO_3	H_2O	trace
11	CuI	K_2CO_3	DMF	36
12	CuI	KOH	DMF	39
13	CuI	K_3PO_4	DMF	58

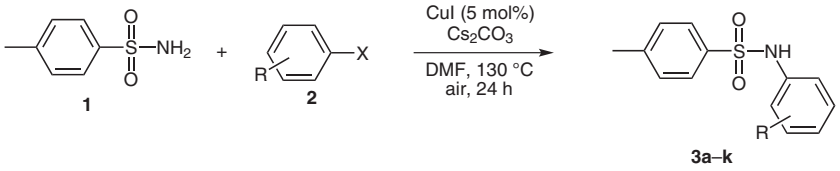
[a] Unless otherwise shown, the reaction was carried out with *p*-toluenesulfonamide (1.47 mmol), iodobenzene (2.21 mmol), base (2.94 mmol), Cu source (5 mol%) in solvent (0.75 mL) at 130 °C for 24 h.
[b] Isolated yield after column chromatography.

para-substituted substrates (Table 2, entries 4–12). However, a steric effect for the *ortho*-substituted aryl iodides was observed for the 2-methoxy group but not with the 2-chloro functionality (Table 2, entries 2 and 3). The protocol was limited only to aryl iodides as evident by the low yields obtained for the bromo counterparts (Table 2, entries 13 and 14).

Next, we tested the scope of this catalytic system by reacting differently substituted sulfonamides with selected aryl iodides. The results are shown in Table 3. In general, the corresponding N-arylated sulfonamides were obtained in good and excellent yields using 10 mol% of catalyst loading (Table 3, entries 1–14). No significant electronic and steric effects were observed for the electron-donating and electron-withdrawing substituted sulfonamides. As expected, neutral and *meta*-substituted electron-rich/electron-deficient aryl iodides were excellent electrophilic counterparts for these coupling reactions.

In summary, we have developed a versatile and operationally simple ligand-free, CuI-catalyzed cross-coupling protocol for the arylation of various sulfonamides with aryl iodides.[19] In most instances, the N-arylated derivatives were obtained in good to excellent yields. The use of ligands for metal-catalyzed reactions very often incur costs both in time and material, with many ligands being more expensive than the metal used. We believe that this ligand-free coupling strategy is an attractive alternative to access various *N*-arylsulfonamides. Exploration into applications of this ligand-free copper catalytic system to other cross-coupling is ongoing.

Table 2 CuI-Catalyzed N-Arylation of *p*-Toluenesulfonamide with Aryl Halides[a]



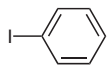
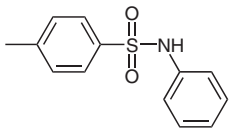
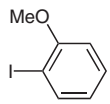
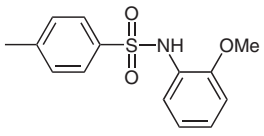
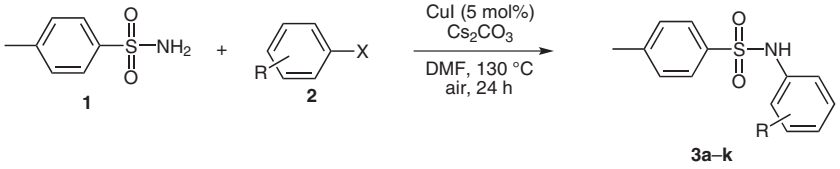
Entry	ArX	Product	Yield (%)[b]
1		 **3a**	86
2		 **3b**	25

Table 2 CuI-Catalyzed N-Arylation of *p*-Toluenesulfonamide with Aryl Halides[a] (continued)



1 2 3a–k

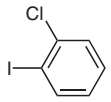
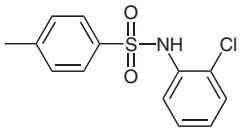
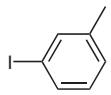
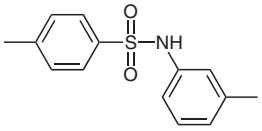
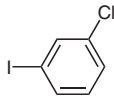
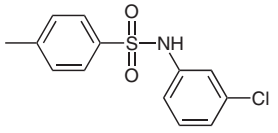
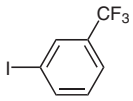
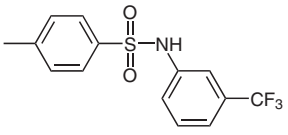
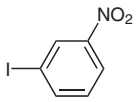
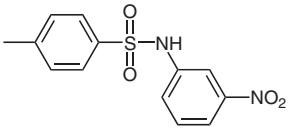
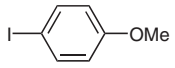
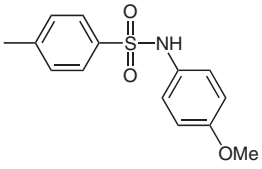
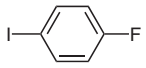
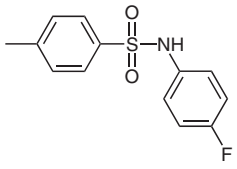
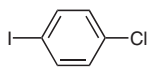
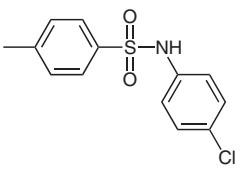
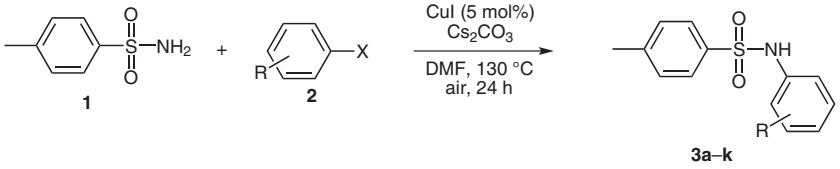
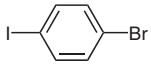
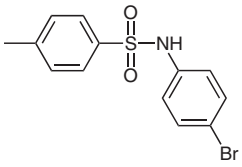
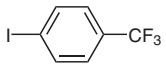
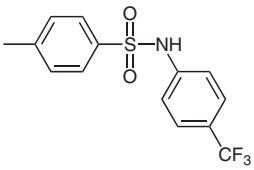
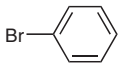
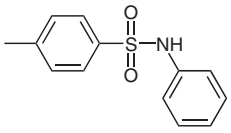
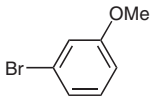
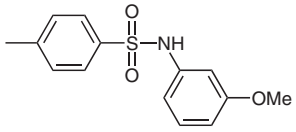
Entry	ArX	Product	Yield (%)[b]
3		 **3c**	72
4		 **3d**	76
5		 **3e**	65
6		 **3f**	73
7		 **3g**	63
8		 **3h**	74
9		 **3i**	80
10		 **3j**	42

Table 2 CuI-Catalyzed N-Arylation of *p*-Toluenesulfonamide with Aryl Halides[a] (continued)

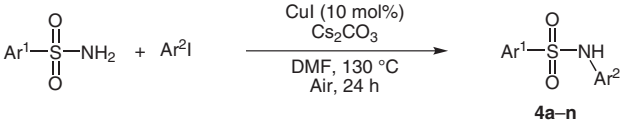


1 2 3a–k

Entry	ArX	Product	Yield (%)[b]
11		 **3k**	52[c]
12		 **3l**	70
13		 **3a**	16
14			14

[a] Reaction conditions: *p*-toluenesulfonamide (1.47 mmol), aryl halides (2.21 mmol), Cs_2CO_3 (2.94 mmol), CuI (5 mol%) in DMF (0.75 ml) at 130 °C for 24 h.
[b] Isolated yield after column chromatography.
[c] Product contains 15% of the regioisomer.

Table 3 CuI-Catalyzed N-Arylation of Sulfonamides with Selected Aryl Halides[a]



4a–n

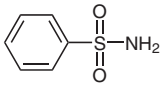
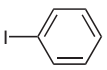
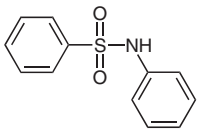
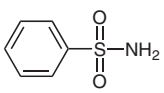
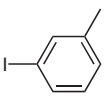
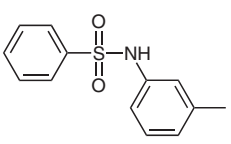
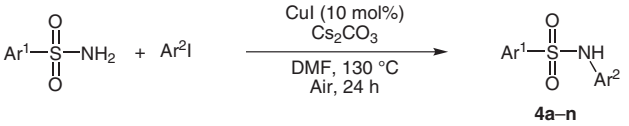
Entry	$Ar^1SO_2NH_2$	Ar^2X	Product	Yield (%)[b]
1			 **4a**	86
2			 **4b**	71

Table 3 CuI-Catalyzed N-Arylation of Sulfonamides with Selected Aryl Halides[a] (continued)



4a–n

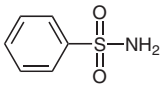
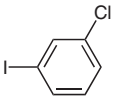
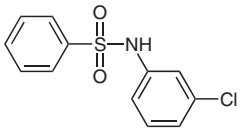
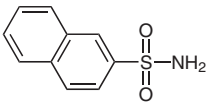
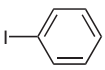
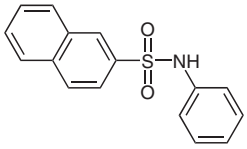
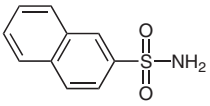
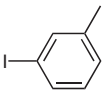
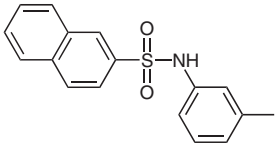
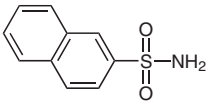
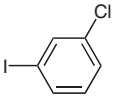
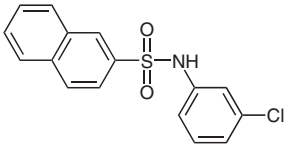
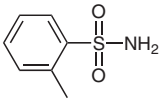
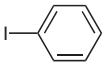
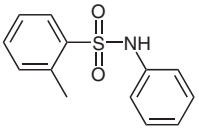
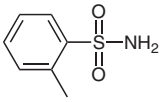
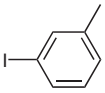
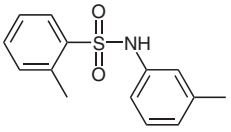
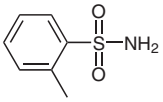
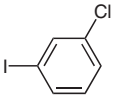
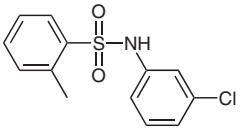
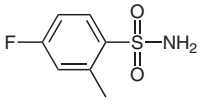
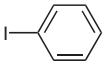
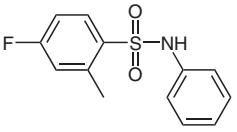
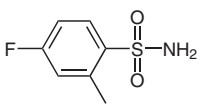
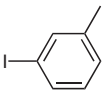
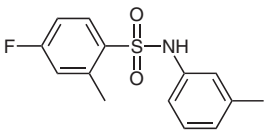
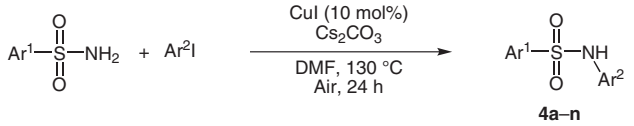
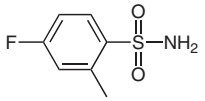
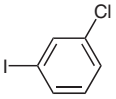
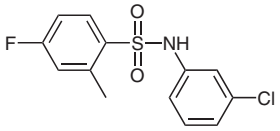
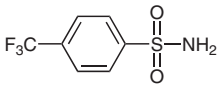
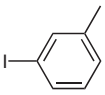
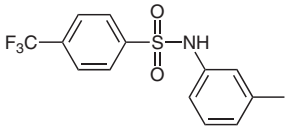
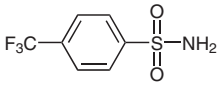
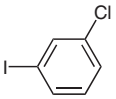
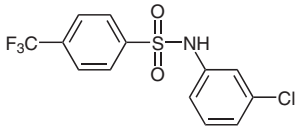
Entry	$Ar^1SO_2NH_2$	Ar^2X	Product	Yield (%)[b]
3			 **4c**	82
4			 **4d**	91 77[c]
5			 **4e**	84
6			 **4f**	86
7			 **4g**	76
8			 **4h**	80
9			 **4i**	88
10			 **4j**	73
11			 **4k**	83

Table 3 CuI-Catalyzed N-Arylation of Sulfonamides with Selected Aryl Halides[a] (continued)



4a–n

Entry	$Ar^1SO_2NH_2$	Ar^2X	Product	Yield (%)[b]
12			 **4l**	80
13			 **4m**	71
14			 **4n**	82

[a] Unless otherwise shown, the reaction was carried out with *p*-toluenesulfonamide (1.47 mmol), aryl iodides (2.21 mmol), Cs_2CO_3 (2.94 mmol), CuI (10 mol%) in DMF (0.75 mL) at 130 °C for 24 h.
[b] Isolated yield after column chromatography.
[c] The reaction was performed with CuI (5 mol%).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(19) **Representative Procedure for N-Arylation of Sulfonamides**

A mixture of CuI (Sigma-Aldrich, 99.99%, 0.0735 mmol) and Cs_2CO_3 (2.94 mmol) was dissolved in DMF (0.75 mL). Then, aryl halide (2.21 mmol) and sulfonamide (1.47 mmol) were added to this reaction vial, and a screw cap was fitted to it. The reaction mixture was stirred under air in a closed system at 135 °C for 24 h, then the heterogeneous mixture was cooled to r.t. and diluted with CH_2Cl_2. The resulting solution was directly filtered through a pad of Celite. The combined organic extracts were dried with anhyd Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the N-arylated product. The identity and purity of the products was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Following the general procedure using *p*-toluenesulfonamide (1.47 mmol) and iodobenzene (2.94 mmol) provided 314 mg (86%) of the coupling product **3a** as a yellowish solid after purification by flash chromatography (hexane–EtOAc, 85:15) of the crude oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.3 Hz, 2 H), 7.22–7.18 (m, 4 H), 7.11–7.06 (m, 3 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 136.7, 136.0, 129.6, 129.2, 127.3, 125.1, 121.3, 21.5. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; S, 12.97. Found: C, 62.68; H, 5.29; N, 5.53; S, 12.72.