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Ligand-Free Copper-Catalyzed *N*-Arylation of Nitrogen Nucleophiles

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Abstract: Versatile, simple and inexpensive ligand-free, copper-catalyzed *N*-arylations of sulfoximines and nitrogen-containing heterocycles have been developed affording *N*-arylated products in high yields.

Keywords: copper catalysis; cross-coupling; ligand-free; nitrogen heterocycles; sulfoximines

Transition metal-catalyzed C–N bond formation by cross-coupling reactions constitutes a powerful strategy for the preparation of important compounds in biological, pharmaceutical and material sciences. Although copper-catalyzed Ullmann-type couplings were discovered more than a century ago,[1] their application in *N*-arylation reactions has remained relatively limited because of the required harsh reaction conditions involving elevated temperatures, highly polar solvents and most of the time over-stoichiometric amounts of copper reagents.[2]

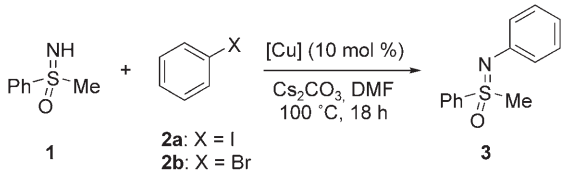
Of particular interest is the *N*-arylation of nitrogen-containing heterocycles, and in a series of papers starting in 1999 Buchwald and co-workers reported the use of various copper-chelating ligands such as 1,10-phenanthroline[3] and vicinal diamines,[4] which now allows us to perform such challenging arylation reactions under comparatively mild reaction conditions. More recently, other bidentate chelates were found to be applicable as well.[5] Despite these successes, *ligand-free* Ullmann-type coupling reactions are rare, and generally they involve chelating substrates (such as amino acids, amino alcohols and *o*-bromobenzoic acids),[6] or they require (over)stoichiometric quantities of copper salts.[7] Consequently, the development of a versatile and experimentally simple, ligand-free catalytic system would still represent a major advance.

Our interest in this area stems from a need for *N*-arylated sulfoximines, which were found to be effective chiral ligands in several catalytic asymmetric reactions.[8] For their synthesis, we utilized various copper-mediated *N*-arylation reactions.[9] To our disappointment, however, the finding of an efficient *catalytic* Ullmann-type coupling employing simple aryl halides and avoiding the use of additional diamine ligands remained an unreached goal. Pleasingly, we have now been able to change this situation. Use of inexpensive and readily available Cu_2O led to the development of an alternative cross-coupling protocol, which is *catalytic* in copper and *ligand-free*.[10–12] Furthermore, it utilizes simple aryl halides (aryl iodides, bromides and chlorides) and can be applied in a wide range of *N*-arylation reactions including those leading to *N*-arylated heterocycles.

For finding the most active ligand-free catalyst system, the metal salt screening involved the *N*-arylation of *S*-methyl-*S*-phenylsulfoximine (**1**) with phenyl iodide (**2a**) as model reaction. Initially, all experiments were carried out with 10 mol% of copper salt and Cs_2CO_3 as base in DMF at 100 °C.[13] To our delight, several copper salts proved applicable furnishing *N*-phenylsulfoximine **3** in yields ranging from 8–95% with copper(I) oxide being the best (Table 1, entry 4). Neither biaryl formation nor reduction of iodobenzene was ever observed. Test reactions with 20 mol% of CuI and 5 mol% of Cu_2O (Table 1, entries 3 and 6, respectively) resulted in lower yields of **3**.[14] With Cu_2O also the less reactive bromobenzene (**2b**) could be used providing *N*-phenylated product **3** in 89% yield (Table 1, entry 7) although, in this case, the reaction required a slightly higher temperature (110 °C) to achieve full conversion. A blank experiment confirmed that in the absence of the metal catalyst no arylated product was formed.

Encouraged by the efficiency of the above-described, ligand-free Ullmann-type coupling and given the fact that the catalytic protocols described so

Table 1. Screening of copper sources for the *N*-arylation of methylphenylsulfoximine.



Entry	Aryl halide	Cu source	Yield of **3** [%][a]
1	**2a**	Cu	32
2	**2a**	CuI	26
3	**2a**[b]	CuI	56
4	**2a**	CuO	8
5	**2a**	Cu_2O	95
6	**2a**[c]	Cu_2O	76
7	**2a**	CuBr	76
8	**2a**	$Cu(acac)_2$	77
9	**2b**[d]	Cu_2O	89

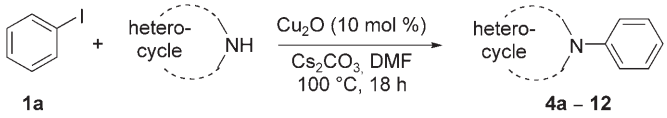
[a] Yield of isolated product after flash chromatography.
[b] Use of 20 mol % of CuI.
[c] Use of 5 mol % of Cu_2O.
[d] The reaction was carried out at 110 °C.

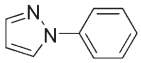
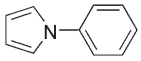
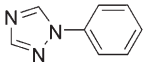
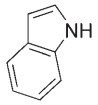
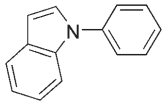
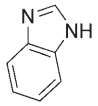
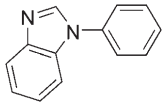
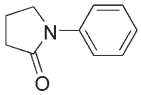
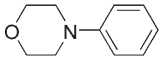
far for the *N*-arylation of heterocycles mostly involve the use of bidentate chelating ligands,[2–5] we decided to investigate the substrate scope. As shown in Table 2, the Cu_2O-catalyzed coupling reaction also worked for *N*-arylations of heterocycles such as pyrazole, pyrrole, triazole, indole and benzimidazole.[15] In all of these cases the couplings with phenyl iodide (**1a**) led to the corresponding *N*-phenyl heterocycles **4a–8** in good to excellent yields (76–98 %, Table 2, entries 1–5). Furthermore, *N*-arylation of 2-pyrrolidinone afforded the corresponding cyclic *N*-arylamide in 64 % yield (entry 6). Alkyl and aromatic amines proved to be unsuitable substrates (entries 7–9).

In order to evaluate the scope of the process with respect to the aryl halide, a variety of substituted aryl iodides, bromides and chlorides were tested under the optimized reaction conditions using pyrazole as model substrate.[10] Hence, both aryl iodides and aryl bromides, independent of the nature of their substituents, afforded the corresponding coupling products **4a–h** in excellent yields (93–99 %, Table 3, entries 1–8). Noteworthy is also that *ortho*-substituents did not hamper the *N*-arylation reaction (entries 2, 5 and 6) and that even a heteroaryl bromide (2-bromothiophene) proved to be a highly efficient coupling partner (entry 8). Interestingly, although attempts to use chlorobenzene as aryl source failed, the employment of an activated aryl chloride led to the corresponding coupling product in excellent yield (98 % yield, entry 9) comparable to the ones obtained with the iodide and bromide derivatives.

In summary, we have developed a versatile and simple, ligand-free, copper-catalyzed coupling protocol for the *N*-arylation of various nitrogen nucleophiles with differently substituted aryl iodides, bromides and chlorides. The commercial availability and experimental simplicity of the presented catalytic system is expected to be useful for a variety of synthetic chemists.

Table 2. Scope of the optimized Cu_2O-catalyzed *N*-arylation.



Entry	*N*-Heterocycle	Product		Yield [%][a]
1			**4a**	98
2			**5**	93
3			**6**	76
4			**7**	95
5			**8**	86
6			**9**	64
7			**10**	0
8	$PhNH_2$	PhNHPh	**11**	0
9	$BnNH_2$	BnNHPh	**12**	0

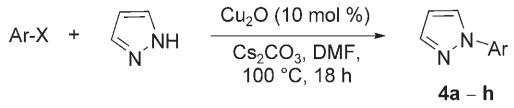
[a] Yield of isolated product after flash chromatography.

Experimental Section

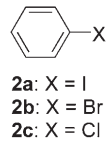
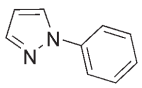
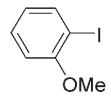
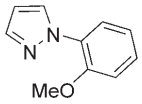
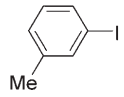
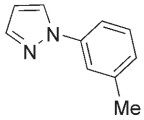
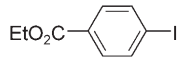
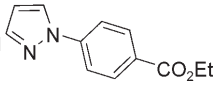
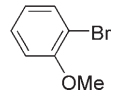
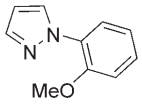
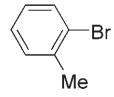
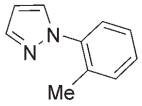
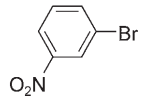
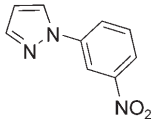
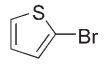
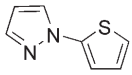
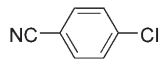
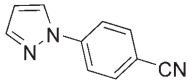
General Procedure for *N*-Arylation of Nitrogen Nucleophiles

An oven-dried tube was charged with *S*-methyl-*S*-phenylsulfoximine (**1**, 100 mg, 0.64 mmol), Cu_2O (9.5 mg, 0.064 mmol) and Cs_2CO_3 (417 mg, 1.28 mmol). Under an argon atmosphere iodobenzene (**2a**, 0.11 mL, 0.97 mmol) or bromobenzene (**2b**, 0.10 mL, 0.97 mmol) was added followed by dry DMF (1 mL). The tube was sealed under argon, and the mixture was heated to 100 °C. After stirring at this temperature for 18 h, the heterogeneous mixture was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica gel and concentrated to yield the product, which was purified by silica gel chromatography (1:1 pentane/ethyl acetate) to yield *N*-phenyl-S-methyl-S-phenylsulfoximine (**3**) as white solid; yield: 140 mg (95 %). The identity and purity of

Table 3. Cu_2O-catalyzed *N*-arylation of pyrazole with different aryl halides.



4a – h

Entry	ArX	Product		Yield [%][a]
1	 **2a**: X = I **2b**: X = Br **2c**: X = Cl		**4a**	98 (X = I) 93 (X = Br) 0 (X = Cl)
2			**4b**	94
3			**4c**	98
4			**4d**	99
5			**4b**	99[b]
6			**4e**	91[b]
7			**4f**	98[b]
8			**4g**	95[b]
9			**4h**	98[b]

[a] Yield of isolated product by flash chromatography.
[b] The reaction was carried out at 110 °C.

the product was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, see Supporting Information for full details.

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[9] a) J. Sedelmeier, C. Bolm, *J. Org. Chem.* **2005**, *70*, 6904; b) G. Y. Cho, P. Rémy, J. Jansson, C. Moessner, C. Bolm, *Org. Lett.* **2004**, *6*, 3293; c) C. Moessner, C. Bolm, *Org. Lett.* **2005**, *7*, 2667.

[10] Related approaches have only been reported in the patent literature, but they have largely been uncited. For *N*-arylations of azoles with aryl iodides employing catalytic systems based on copper(I) iodide, see: a) U. Yasutsugu, N. Mayumi, (Koei Chem. Co. Ltd.), Japanese Patent Application JP 2006–342127, **2006**; b) M. Taillefer, H. J. Cristau, P. P. Cellier, J.-F. Spindler, (Rhodia Chimie, Fr.), French Patent Application 2859205 A1 20050304, **2005**.

[11] While this work was in progress, an alternative *N*-arylation of aryl iodides using catalytic amounts of CuI was reported. There, the reaction was performed in toluene under reflux in the presence of NaOH and Bu_4NBr. In contrast to the Cu_2O catalysis described here, aryl halides other than bromides showed a very low reactivity: J. W. W. Chang, X. Xu, P. W. H. Chan, *Tetrahedron Lett.* **2007**, *48*, 245.

[12] For a ligand-free bimetallic system using Fe and Cu combinations in *N*-arylations, see: M. Taillefer, N. Xia, A. Oualli, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934.

[13] Use of toluene, dioxane or water in combination with other inorganic bases such as Na_2CO_3, K_2CO_3 or K_3PO_4 led to lower yields in the *N*-arylation reactions. Whether DMF is acting as ligand cannot be judged.

[14] From these two results we conclude that the active catalyst is not copper(I) iodide, which is formed during the course of the reaction.

[15] For the use of a catalytic amount of Cu_2O in the *N*-arylation of ammonia with a 2-bromopyridine derivative performed in ethylene glycol, see: F. Lang, D. Zewge, I. N. Houpis, R. P. Volante, *Tetrahedron Lett.* **2001**, *42*, 3251.

