EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201400033

Ligand-Free Ullmann-Type C–Heteroatom Couplings Under Practical Conditions

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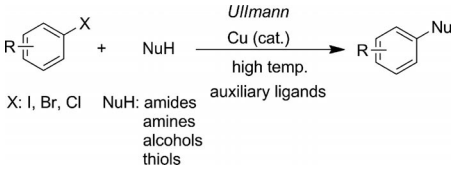
Keywords: Copper / Cross-coupling / Ligand-free catalysis / Ullmann coupling / Dimethyl sulfoxide

A new practical ligand-free protocol for copper-catalyzed C–heteroatom cross-coupling reactions (Ullmann-type) is described. The use of dimethyl sulfoxide (DMSO) as the solvent overcomes the need to use organic auxiliary ligands; thus, DMSO is revealed as a nontoxic and superior solvent for Ullmann-type coupling reactions. This method allows the arylation of a wide range of amides, alcohols, and amines under practical conditions with bromobenzene and iodobenzene derivatives and will likely find direct application in current organic synthesis. The competitive reactivity among different functional groups is reported and rationalized, and the possibility to achieve selective arylation reactions is demonstrated.

Introduction

Diaryl amino and ether moieties are widely present in many compounds with applications in numerous fields, such as life sciences and the chemical, pharmaceutical, and polymer industries, and are also found in natural products and biologically active compounds.[1] The synthesis of these molecules by combining aryl halides and N- or O-nucleophiles has been achieved by two different C–heteroatom coupling methods: (a) copper-catalyzed Ullmann-type coupling reactions[2] and (b) palladium-catalyzed Buchwald–Hartwig couplings.[3] Importantly, the cost and inherent toxicity of palladium catalysts has prompted different research groups to refocus on the copper-mediated Ullmann reactions in the past decade (Scheme 1).[1a,4]



Scheme 1. Copper-mediated Ullmann reaction.

Many approaches and methods have been reported since then, most of which use auxiliary ligands, usually bidentate amine or diketone compounds. These provide a major degree of control over the coordination sphere of the copper center and have also facilitated the investigation of the still-elusive reaction mechanism of Ullmann-type reactions.[4d,5] Nevertheless, more effort is needed to unravel the mechanism and to design better catalysts that work under mild conditions. The latter approach is a long road that needs to be followed, but other methods must be developed to find a compromise between maximum efficiency under mild conditions, which are sought for fully-designed catalysts, and practical, straightforward methods amenable to use in routine organic synthesis.

Cu-catalyzed C–heteroatom coupling reactions are extremely sensitive to experimental conditions, and the operating mechanism can differ among distinct experimental sets. Therefore, the optimization of the different experimental parameters is crucial to achieve good C–heteroatom coupling results, and more efforts in this area are also appreciated.[4c,6] In this sense, a few "ligand-free" procedures have been described in the past decade[7] and, in some cases, represent an enhanced practicality at the expense of mechanistic understanding. In general, the reported ligand-free methods either work with N-based nucleophiles, which can act as ligands for the Cu catalyst, or they use solvents with coordinating abilities such as *N*-methylpyrrolidone (NMP) or *N*,*N*-dimethylformamide (DMF).

Herein, we disclose a simple and practical ligand-free procedure for the copper-catalyzed arylation of different oxygen- and nitrogen-containing nucleophiles. We take advantage of the coordinating ability of dimethyl sulfoxide (DMSO) and describe a new easy-to-use method that is available for regular organic synthesis and is useful for a wide range of substrates. Moreover, DMSO has been lately considered a clean, nontoxic, and superior solvent for many metal-catalyzed transformations,[8] including Ullmann couplings with auxiliary ligands.[9] However, in most reported studies, the evaluation of the reaction outcomes with DMSO in the absence of auxiliary ligands is very scarce.[10]

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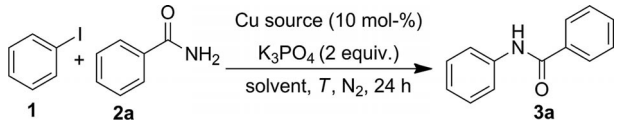
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201400033.

Results and Discussion

To develop a practical Ullmann-type coupling procedure, our initial study consisted of a set of experiments with iodobenzene (**1**) as a model substrate and benzamide (**2a**) as a N-nucleophile. Firstly, CuI (5–10 mol-%) was chosen as the copper(I) source, and K_3PO_4 (1–2 equiv.) was chosen as the inorganic base. DMSO was the solvent of choice, and the reaction outcome was screened at different temperatures under a N_2 atmosphere (Table 1, Entries 1–7). Yields were obtained as the average of at least two runs and were determined by GC, unless otherwise stated, because the isolated yields for different coupling products were similar to those obtained by GC (see Tables 1, 2, and 4). The optimized combination of 90 °C, CuI (10 mol-%), and K_3PO_4 (2 equiv.) afforded the coupling product benzanilide (**3a**) in 97% yield. Subsequently, we explored other copper sources such as $Cu^{II}(OTf)_2$ (OTf = trifluoromethanesulfonate), but much longer reaction times were required to reach quantitative yields (Table S1, Entries 1–5); this suggests the existence of a reduction step when a copper(II) source is used and clearly indicates the involvement of Cu^{I} species in the catalytic cycle. This was further confirmed by the observation of an almost complete quench of the reaction under an O_2 atmosphere, which precluded the in situ reduction of Cu^{II} to Cu^{I} species (Table S1, Entry 5). The latter can be explained by the presence of the DMSO solvent, which has been previously reported to act as a reducing reagent in other reaction systems.[11] The preoptimization results in terms of the nature of the inorganic base and of the final concentration of the catalytic reaction are included in the Supporting Information (Table S2). The most efficient results were obtained with K_3PO_4 and with a concentration of **1** of 1.25 M. With minor CuI catalyst loadings (5 mol-%), the yields of **3a** dropped to 74% (Table 1, Entry 6). Additionally, $[Cu(CH_3CN)_4][CF_3SO_3]$ was also tested as the copper(I) source, and very similar results as those for CuI were obtained (Table 1, Entry 10 and Table S1). If no copper salt is added as catalyst, the reaction does not occur (Table 1, Entry 9).

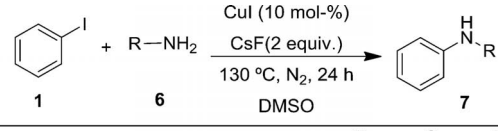
Table 1. Arylation of benzamide (**2**) with iodobenzene (**1**) under different conditions.



Entry[a]	Cu source [mol-%]	Solvent	Temp. [°C]	Conv. [%]	Yield [%][b]
1	CuI (10)	DMSO	50	46	46
2	CuI (10)	DMSO	60	53	53
3	CuI (10)	DMSO	70	78	77
4	CuI (10)	DMSO	90	97	97
5	CuI (10)	DMSO	90	82	82[c]
6	CuI (5)	DMSO	90	74	74
7	CuI (10)	DMSO	90	90	88[d]
8	$Cu(OTf)_2$ (10)	DMSO	90	45	43
9	–	DMSO	90	0	0
10	CuOTf[e] (10)	DMSO	90	93	93
11	CuOTf (10)	ACN	90	90	90
12	CuOTf (10)	THF	90	57	43
13	CuOTf (10)	THF/DMSO(9:1)	90	77	77
14	CuOTf (10)	THF/DMSO(2:1)	90	81	81
15	CuI (10)	DPSO	90	17	16
16	CuI (10)	MPSO	90	70	70

[a] Reaction conditions: **1** (1.75 mmol, 1.25 M), **2a** (3.5 mmol), copper salt (0.2 mmol), and K_3PO_4 (3.5 mmol). [b] Yield was determined by GC. [c] Scaled-up reaction (1 mL of iodobenzene). GC yield 82%, isolated yield 76%. [d] 1.2 equiv. of K_3PO_4. [e] CuOTf is $[Cu(CH_3CN)_4][CF_3SO_3]$.

Table 2. Ligand-free *N*-arylation of amides with iodobenzene.



Entry[a]	Amides	Product	Temp. (°C)	Conv. (%)	Yield (%)[b]
1	2a	3a	90	100	97
2	2b	3b	110	100	94
3[c]	2c	3c	130	67	41
4	2d	3d	130	85	84
5	2e	3e	130	79[d]	39
6	2f	3f	110	96	90
7	2g	3g	130 130	100[e] 99[g]	74[f] 82[h]
8	2h	3h	130	84	66[i]
9	2i*	3i	130	15	4
10	2j	3j	130	67	23

[a] Reaction conditions: **1** (1.75 mmol, 1.25 M), **2** (3.5 mmol). [b] Yield was determined by GC. [c] 2.2 mmol of amide was used instead of 3.5 mmol. [d] 30% isolated yield of **3e**, 5% GC yield and 4% isolated yield of *p*-phenoxybenzamide (**5i**), and 6% GC yield and 5% isolated yield of *p*-phenoxybenzamide-*N*-benzanilide (**3e′**) were obtained (also see Scheme 2). With 1 mL of iodobenzene (scale-up reaction), the same results were obtained. [e] 8% yield of *N*,*N*-diphenylacetamide (**3g′**). [f] Isolated yield: 64%. [g] Scaled-up reaction (1 mL of iodobenzene); 6% yield of *N*,*N*-diphenylacetamide (**3g′**). [h] Isolated yield: 76%. [i] Isolated yield: 52%; * **2i** = **3a**, now used as substrate.

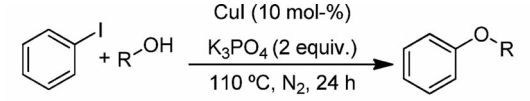
Next, we examined the effect of substituting DMSO by other solvents. For example, if acetonitrile (ACN) is used, yields decrease significantly at 50 and 70 °C, albeit yields of 90% of **3a** were obtained at 90 °C (Table 1, Entry 11 and

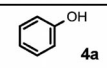
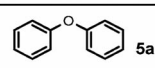
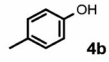
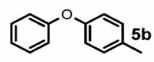
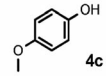
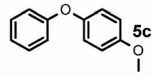
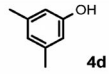
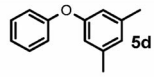
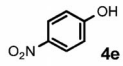
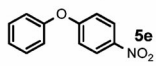
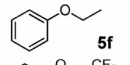
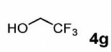
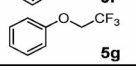
Table S1, Entries 9–11). The use of tetrahydrofuran (THF) also resulted in decreased yields, whereas mixtures of THF and DMSO afforded good yields at higher DMSO ratios (Table 1, Entries 12–14). Furthermore, the substitution of one or two methyl groups of the sulfoxide for a phenyl group [methylphenylsulfoxide (MPSO) and diphenylsulfoxide (DPSO), Table 1, Entries 15 and 16] had a strong effect on the reaction outcome and gave moderate and low yields, respectively. In general, the solvent screening shows that (a) highly polar aprotic solvents are beneficial for this reaction and enhance the solubility of the base and (b) the presence of the phenyl group affords poorer yields, most likely because of increased steric hindrance and the reduction of the electron-donating ability of the sulfoxide moiety as a ligand.

To examine the scope of this reaction, iodobenzene was subjected to N-arylation with various primary and secondary amides (Table 2). Aromatic primary amides analogous to benzylamide (**2a**) such as 2-hydroxybenzamide (**2d**) and nicotinamide (**2f**) afforded good-to-excellent yields, albeit at higher reaction temperatures (130 °C; Table 2, Entries 1, 4, and 6). The present method also tolerates aliphatic primary amides such as acetamide (**2g**) and affords an 82% yield of *N*-phenylacetamide (**3g**) in a gram-scale reaction (Table 2, Entry 7). This reaction seemed to be sensitive to the steric hindrance of the nucleophile, because although cyclic aliphatic secondary amides such as pyrrolidin-2-one (**2b**) afforded excellent yields of the coupling product **3b** under the optimized reaction conditions, the acyclic ones such as *N*-methylacetamide (**2h**) and *N*-ethylacetamide (**2j**) afforded moderate and low yields, respectively (Table 2, Entries 2, 8, and 10). In any case, the 66% yield of **3h** should be highlighted as acyclic secondary amides are usually poor counterparts in arylation cross-coupling reactions. A copper-free blank experiment was performed for **2b**, and the reaction did not proceed (0% conversion, Table S3, Entry 1). In contrast, aromatic secondary amides were less prone to arylation, and low or very low yields were obtained for **2c** and **2i** as nucleophiles (Table 2, Entries 3 and 9). The generally low reactivity of secondary amides explains the high selectivity encountered with primary amides. An exception for these reactivity trends was found for 4-hydroxybenzamide (**2e**), which gave the desired product in only 39% yield owing to the formation of side products (Table 2, Entry 5 and Scheme 2, E). In contrast, the *ortho*-substituted benzanilide **3d** did not afford byproducts related to the arylation of the alcohol group, probably because of steric hindrance (Table 2, Entry 4).

After screening the amide family of N-nucleophiles under optimized conditions, we then turned our attention to O-nucleophiles. Various substituted phenols and aliphatic alcohols were treated with iodobenzene (see Tables 3 and S3) at different temperatures; 110 °C is the optimal temperature for phenol derivatives. The copper-free reaction was tested for **4c**, and the reaction did not occur (0% conversion; Table S3, Entry 2). The electronic properties of the substituents played a crucial role in governing the product yield. Whereas the presence of electron-donating groups at the *para* and *meta* positions of phenols (Table 3, Entries 2–4) increased the yields compared with those of the nonsubstituted phenol (Table 3, Entry 1), the formation of product was almost quenched with electron-withdrawing groups at the *para* position (Table 3, Entry 5). For aliphatic alcohols, it was much more difficult to obtain the desired product in moderate yields owing to the formation of several side products (Table S4, Entries 4 and 5). When CsF was used as the base instead of K_3PO_4, the final products formed without the presence of byproducts (Table 3, Entries 6–7) but in low or moderate-to-good yields. Trifluoroethanol (**4g**) affords much better yields than ethanol (**4f**), and this suggests that the deprotonation step has a clear role in the reaction (see below).

Table 3. Ligand-free *O*-arylation of phenols with iodobenzene.



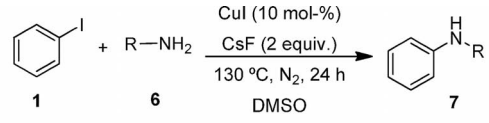
Entry[a]	Alcohols	Product	Conv. (%)	Yield (%)[b]
1	 4a	 5a	72	56
2	 4b	 5b	89	88
3[c]	 4c	 5c	98	96
4	 4d	 5d	84	84
5	 4e	 5e	14	3[c]
6	 4f	 5f	17	17[c,d]
7	 4g	 5g	72	59[c,d,e]

[a] Reaction conditions: **1** (1.75 mmol, 1.25 M), **4** (3.5 mmol). [b] Yield was determined by GC. [c] Reaction temperature of 130 °C. [d] CsF used as base. [e] Yield was determined by ^{1}H NMR spectroscopy.

We also wanted to test the N-arylation with primary and secondary amines as nucleophiles. We observed that the final products were obtained in modest yields under the same optimized conditions (Table S5). As fluoride salts can accelerate some transition-metal-catalyzed coupling reactions,[12] we used CsF as a stronger base to replace the generally used K_3PO_4 and were very pleased to find higher yields and reduced side reactions after 24 h (Table 4). We also tested the use of Cs_2CO_3 as a base for the reactions with **6a**, **6b**, and **6d** nucleophiles and obtained similar or lower yields compared to those with CsF.

Aromatic primary amines could be introduced in moderate-to-excellent yields. The presence of an aromatic ring decreased the reactivity, and aniline (**6a**) was less reactive (Table 4, Entry 1). The introduction of *para* substituents also had a strong influence. In this case, the electron-de-

Table 4. Ligand-free *N*-arylation of amines with iodobenzene.



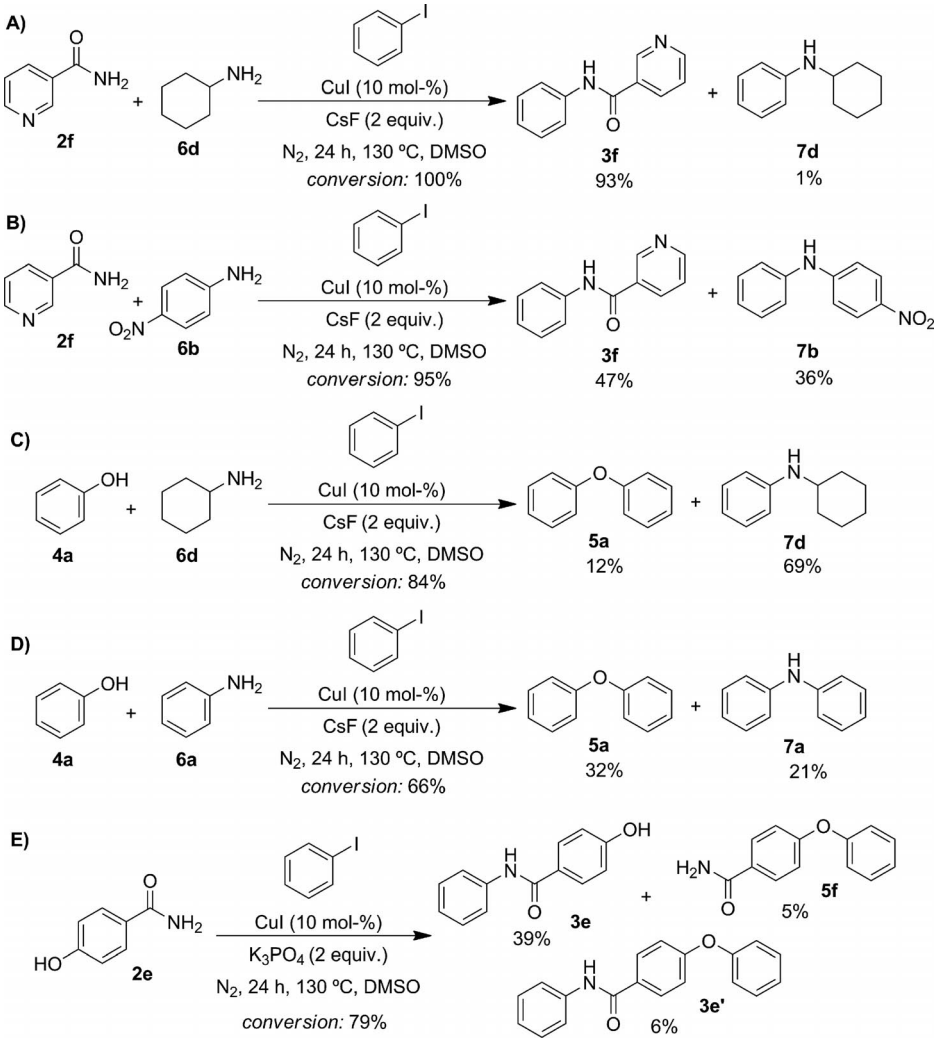
Entry[a]	Amines	Product	Conv. (%)	Yield (%)[b]
1	6a	7a	73[c]	39
2	6b	7b	97	79
3	6c	7c	53[d]	37
4	6d	7d	92	91[e]
5	6e	7e	<15	–
6	6f	7f	2	–[f]
7	6g	7g	24	4
8	6h	7h	64	57[g]
9	6i	7i	98	89[h,i]
10	6j	7j	91	84[h,j]
11	6k	7k'	99	70[k,l,m]
12	7k	7k'	93	92[k,l,n]
13	6l	7l'	98	94[k,o]
14	6m	7m'	95	70[k,l,p]

[a] Reaction conditions: **1** (1.75 mmol, 1.25 M), **6** (3.5 mmol). [b] Yield was determined by GC. [c] 12% yield of side product *N*,*N*-diphenylaniline. [d] 15% yield of side product 4-methoxy-*N*,*N*-diphenylaniline. [e] Isolated yield: 87%. [f] Product not detected by GC–MS. [g] Yield was determined by ^{1}H NMR spectroscopy. [h] Reaction temperature of 90 °C. [i] Isolated yield: 84%. [j] Isolated yield: 81%. [k] K_3PO_4 used as base. [l] Reaction temperature of 110 °C. [m] 28% yield of side product *N*-phenylpyridin-2-amine (**7k**). [n] 8 h reaction time. [o] 6 h at room temperature, traces of monoarylated product **7l** were found. [p] 15% yield of *N*-phenylpyridazin-3-amine (**7m**).

ficient arylamine **6b** is more reactive than the electron-rich **6c**, as the yield increased from moderate to excellent. The aliphatic cyclohexanamine (**6d**) afforded very good arylation yields (**7d**; Table 4, Entry 4). Cyclic and acyclic secondary amines proved to be much more difficult nucleophiles for the C–N coupling catalysis. The acyclic ones did not react or afforded poor yields (<5%; Table 4, Entries 5–7), and the cyclic aliphatic piperidine (**6h**) afforded moderate yields of the arylated product **7h** (Table 4, Entry 8). In contrast, conjugated N-heterocyclic secondary amines were highly reactive and gave the desired products in excellent yields even at 90 °C (Table 4, Entries 9 and 10). The reaction time needed with our method is much shorter and the results are comparable to those of previously reported ligand-free[10b] and non-ligand-free reactions.[13] Similarly, heteroaromatic amines were highly reactive, as the corresponding biaryl products were obtained as the major products (Table 4, Entries 11–14). Pyridin-2-amine (**6k**) afforded full conversion of the double arylated product **7k′** (70% with respect to iodobenzene) at 110 °C, together with minor amounts of the monoarylated one (**7k**, 28% yield). As expected, if **7k** is used as the nucleophile, the reaction afforded almost quantitative formation of **7k′** (92%, Table 4, Entry 12). For quinolin-8-amine (**6l**; Table 4, Entry 13), excellent yields (94% with respect to iodobenzene) of the biaryl coupling product **7l′** were obtained at room temperature and within 6 h (Table 4, Entry 13). Thus, the possible chelating ability of this nucleophile allows the reaction to occur smoothly under very mild conditions. Finally, pyridazine-3-amine (**6m**; Table 4, Entry 14) was also tested and afforded 70% yield (with respect to iodobenzene) of the biarylated product **7m′** at 110 °C. The reaction is fully copper-dependent, as copper-free blank reactions afforded 0% conversion (Table S3, Entry 3).

The ligand-free method described so far proved to be very efficient for primary amides and amines, whereas reactions with secondary amides and amines were much more difficult. The new procedure described here also proved efficient for phenols (except those with strong electron-withdrawing groups) and acidic aliphatic alcohols. Bearing in mind the necessity to discriminate between functional groups within a multifunctionalized compound, we conducted competitive experiments among pairs of amides and amines and also pairs of phenol and amines (Scheme 2). The competitive reactions were performed under unified optimized conditions: 130 °C, CsF as base, and iodobenzene as the limiting reagent. The competition between nicotinamide (**2f**) and cyclohexanamine (**6d**) clearly showed a much enhanced reactivity of the amide **2f** to arylation (Scheme 2, A; Table S7, Entry 1). This result indicates that this method is orthogonal and clearly discriminates in favor of primary amides with primary aliphatic amines unreacted.

When the competition is done between **2f** and the most reactive *para*-nitro-substituted aniline (**6b**; Table 4), the arylation of the amide occurred with a slight preference over the amine (1.4:1; Scheme 2, B). On the other hand, the competition between phenol (**4a**) and cyclohexanamine (**6d**)



Scheme 2. Competitive cross-coupling studies among different nucleophiles.

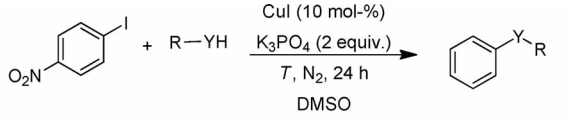
clearly showed an enhanced selectivity (7:1) for the arylation of the aliphatic primary amine (Scheme 2, C; Table S7, Entry 2). On the contrary, when the competition is between phenol (**4a**) and aniline (**6a**), only a slight preference for the formation of the diphenyl ether (**5a**) is observed (3:2; Scheme 2, D). As shown in Scheme 2, part E, the reactivity with 4-hydroxybenzamide (**2e**) is a showcase for the comparison of the reactivity between two functional groups (phenol and benzamide moieties) in the same molecule. Again, the enhanced reactivity of the amide moiety over other functional groups (in this case the phenol moiety) was clearly observed.

With these good results in hand and to substantiate the generality of this new method, we increased the substrate scope to other aryl halides. We selected two new aryl iodide derivatives *p*-nitroiodobenzene and *p*-iodotoluene to check the effect of electron-withdrawing and electron-donating substituents and selected bromobenzene and chlorobenzene to study the reactivity of different halides (Tables 5, 6, and 7). For these reactions, we used the N- and O-nucleophiles that gave the best results with iodobenzene (**2a**, **2b**, **4a**, **4c**, **4d**, **6b**, and **6d**). On one hand, the presence of electron-withdrawing or electron-donating groups at the *para* position of the iodobenzene ring did not result in an important effect on the reactivity at high temperatures, although better results were obtained for the *para*-nitro derivative at lower reaction temperatures (Tables 5 and 6).

On the other hand, we were delighted to observe that bromobenzene is a good electrophilic partner in these cross-coupling reactions when aromatic alcohol and amine nucleophiles are used; however, it fails for amide nucleophiles (Table 7). Excellent results were obtained for phenol derivatives, and remarkable yields were obtained for amines (up to 62% for *p*-nitroaniline). With chlorobenzene, the reactivity was almost completely suppressed for all nucleophiles tested (Table 8).

Regarding the possible reaction mechanism in the examples reported, the deprotonation of the nucleophile is not relevant for amides (Table 2), as the yield of the reaction is not affected over a wide range of pK_a values (values in DMSO), that is, between 18.5 (indolin-2-one, **2c**) to 25.5 (acetamide, **2g**). On the contrary, phenol substrates bearing electron-donating substituents (p$K_a \approx 18$–19) afforded better yields than those with strong electron-withdrawing

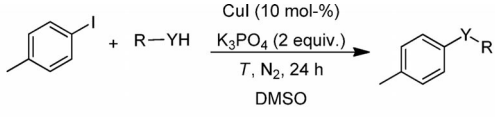
Table 5. Ligand-free *N*- and *O*-arylation with *p*-iodonitrobenzene.



Entry[a]	Nucleophile	Product	Temp. (°C)	Conv. (%)	Yield (%)[b]
1	2b	3k	90	100	70
2	2a	3l	90	98	80
3	4c	5h	90	100	92
4	4a	5e	90	100	88
5[c,d]	6d	7m	90	62	61[e]

[a] Reaction conditions: *p*-iodonitrobenzene (1.75 mmol, 1.25 M), nucleophile (3.5 mmol). [b] Yield was determined by GC. [c] CsF used as base. [d] Yield was determined by ^{1}H NMR spectroscopy. [e] At 130 °C, lower yields of **7k** were obtained owing to side reactions.

Table 6. Ligand-free *N*- and *O*-arylation with *p*-iodotoluene.

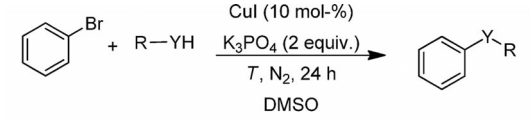


Entry[a]	Nucleophile	Product	Temp. (°C)	Conv. (%)	Yield (%)[b]
1	2b	3m	90	89	69
2			110	100	92
3	2a	3n	90	57	56
4			110	100	>99
5	4c	5i	90	48	45
6			110	100	>99
7	4a	5b	90	20	20
8			110	97	93
9[c,d]	6d	7o	90	68	68
10[c,d]			130	75	75

[a] Reaction conditions: *p*-iodotoluene (1.75 mmol, 1.25 M), nucleophile (3.5 mmol). [b] Yield was determined by GC. [c] CsF used as base. [d] Yield was determined by ^{1}H NMR spectroscopy.

groups (*p*-NO_2-phenol, pK_a = 10.8). The latter suggests that the mechanism of action for phenols (and probably for amides) does not involve a rate-limiting deprotonation step, but mostly indicates that the stabilization of a high oxidation state copper center (as a putative aryl–Cu^{III}–nucleophile intermediate) is mandatory for the reaction to proceed.[4d] On the other hand, *p*-NO_2-aniline (**6b**, pK_a = 20.9) showed exactly the opposite effect and afforded the best yield compared to the other anilines (**6a**, pK_a = 30.6 and **6c**, pK_a > 30). The latter suggest that the rate-limiting step has now switched to the deprotonation of the nucleophile

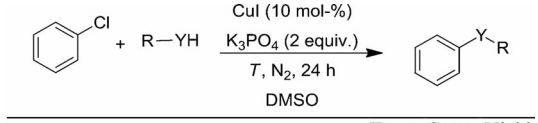
Table 7. Ligand-free *N*- and *O*-arylation with bromobenzene.



Entry[a]	Nucleophile	Product	Temp. (°C)	Conv. (%)	Yield (%)[b]
1	2a	3a	130	12	3
2	2b	3b	130	9	1
3	4a	5a	130	96	87
4	4c	5c	130	96	96
5	4d	5d	130	98	98
6[c]	6b	7b	130	63	62
7[c]	6d	7d	130	43	41

[a] Reaction conditions: bromobenzene (1.75 mmol, 1.25 M), nucleophile (3.5 mmol). [b] Yield was determined by GC. [c] CsF was used as the base.

Table 8. Ligand-free *N*- and *O*-arylation with chlorobenzene.



Entry[a]	Nucleophile	Product	Temp. (°C)	Conv. (%)	Yield (%)[b]
1	2a	3a	130	2	0
2	4a	5a	130	3	3
3	4c	5c	130	2	2
4	4d	5d	130	3	2
5[c]	6b	7b	130	2	2
6[c]	6d	7d	130	0	0

[a] Reaction conditions: **1** (1.75 mmol, 1.25 M), nucleophile (3.5 mmol). [b] Yield was determined by GC. [c] CsF used as base.

within the aromatic amines. The same effect is observed for ethanol (**4f**, pK_a = 29.8) and trifluoroethanol (**4g**, pK_a = 23.5), as the yield of **5g** is much higher than that of **5f**.

The determination of the precise nature of the active copper species that accounts for the catalytic coupling reactions reported here is extremely difficult to achieve. The combination of DMSO with a base at high temperatures generates the dimsyl anion in the reaction mixture.[14] High resolution mass spectrometry studies allowed us to propose the forma-

tion of the reactive dimsyl anion ($CH_3SOCH_2^-$) under the experimental conditions used and it might have a relevant role in all catalytic reactions. After 2 h of heating a suspension of K_3PO_4 in DMSO at 130 °C, an aliquot of the brown solution was filtered and injected into the HRMS spectrometer, and a clear peak at m/z = 94.9791 corresponds to methanesulfonate species ($CH_3SO_3^-$; see Figure S1), which is one of the thermal decomposition products of the dimsyl anion.[15] Similar brownish mixtures were observed for most catalytic reactions. Therefore, on the basis of the clear positive effect of DMSO on our catalysis, we favor that the dimsyl anion is produced in situ and can act as the actual base for the deprotonation of the nucleophiles and as the reducing agent in the experiment with Cu^{II} salts instead of Cu^{I} salts; we also cannot exclude the possibility that it participates as an anionic ligand for the catalytically active copper(I) species, together with neutral DMSO molecules and deprotonated nucleophiles.

In comparison to other methods reported, our procedure avoids the use of a large excess of strong bases such as KOH and, thus, tolerates functional groups sensitive to basic hydrolysis (Table S2). This is exemplified by the shorter reaction times and higher yields for the arylation of benzamide. In general, the ligand- and metal-free procedure reported by Yus and co-workers does not require the use of copper catalyst, but 48–96 h reaction times are required and the efficacy of their method for the arylation of amides is not documented (with the exception of benzamide, 68% yield, 72 h at 120 °C).[10b] On the other hand, the method used by Nageswar and co-workers combines KOH as base, DMSO as solvent, and CuO supported on alumina as the catalyst and affords the arylation of phenols in good yields with reaction times below 24 h, but the nucleophile scope reported is limited to phenols.[10a]

Conclusions

We have developed an effective, general, and straightforward Cu^{I}-catalyzed ligand-free method for the arylation of a wide range of amides, alcohols, and amines at moderate temperatures with *para*-substituted iodobenzene derivatives. Furthermore, bromobenzene is also tolerated for cross-coupling with phenols and amines. Moreover, we disclosed the possibility to discriminate between these functional groups in a rational way. As no auxiliary ligands are required and CuI is cheap and widely available, this practical method will likely find direct application in current organic synthesis. More mechanistic investigations are underway in our laboratory to fully understand these copper-catalyzed couplings.

Experimental Section

General Methods: The reagents and solvents used were commercially available reagent quality unless indicated otherwise. Solvents were purchased from SDS and were purified and dried by passing them through an activated alumina purification system (MBraun SPS-800). The preparation and handling of air-sensitive materials were performed in a N_2 drybox (Jacomex-GP-Concept-II-P) with O_2 and H_2O concentrations of <1 ppm. ^1H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz or Bruker 300 MHz NMR spectrometer. Chemical shifts (δ) are reported in ppm and were directly referenced to the solvent signal. GC product analyses were performed with an Agilent 7820A gas chromatograph equipped with an HP-5 capillary column (30 m × 0.32 mm × 0.25 μm) and a flame ionization detector. GC–MS analyses were performed with an Agilent 7890A gas chromatograph equipped with an HP-5 capillary column interfaced with an Agilent 5975C mass spectrometer. The electron ionization (EI) source was set at 70 eV. High resolution mass spectra (HRMS) were recorded with a Bruker MicrOTOF-Q IITM instrument with ESI or Cryospray ionization sources at the Serveis Tècnics de Recerca of the University of Girona. Samples were introduced into the mass spectrometer ion source by direct injection through a syringe pump and were externally calibrated by using sodium formate.

General Procedure for Catalytic Experiments: A vial was loaded with the base (3.5 mmol) and the solid nucleophile (3.5 mmol). Then, in an inert-atmosphere glovebox, copper(I) (10 mol-%) in DMSO and the aryl iodide (1.8 mmol) were added. Liquid nucleophiles were added after the aryl iodide. The vial was sealed, and the reaction mixture was kept under an inert atmosphere and placed in a preheated oil bath at the required temperature. After the reaction mixture was stirred for 24 h, 1,3,5-trimethoxybenzene (400 μL, 1.5 M in DMSO) as internal standard was added. Subsequently, the reaction was quenched by the addition of AcOEt (10 mL). The workup consisted of the filtration of 400 μL of the crude product through silica gel with AcOEt as eluent. All samples were analyzed by gas chromatography. The GC yields were obtained through calibration curves obtained with authentic sample of all products with 1,3,5-trimethoxybenzene as the internal standard. ^1H NMR spectroscopic yields were obtained for very volatile products, also with 1,3,5-trimethoxybenzene as the internal standard.

Supporting Information (see footnote on the first page of this article): Catalysis optimization tables and full characterization data for all compounds.

Acknowledgments

The authors acknowledge financial support from the European Research Council for Starting Grant Project (ERC-2011-StG-277801), from the Spanish Ministerio de Economía y Competitividad (Consolider-Ingenio CSD2010-00065, INNPLANTA project INP-2011-0059-PCT-420000-ACT1) and from the Generalitat de Catalunya (2009SGR637). X. R. also thanks the Institució Catalana de Recerca i Estudis Avançats (ICREA) for an ICREA-Acadèmia award.

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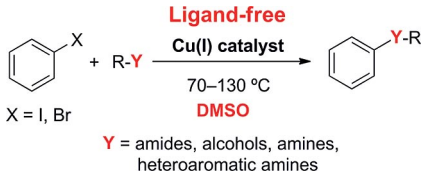
Received: January 8, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Cross-Coupling

We describe a new easy-to-use method for the ligand-free copper-catalyzed arylation of amides, alcohols, and amines that affords good cross-coupling product yields for a wide range of substrates (bromobenzene and iodobenzene derivatives) and nucleophiles.



Keywords: Copper / Cross-coupling / Ligand-free catalysis / Ullmann coupling / Dimethyl sulfoxide

