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Simple and Efficient Recyclable Catalytic System for Performing Copper-Catalysed S-Arylation Reactions in the Presence of Water

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Abstract: A novel protocol for the copper-catalysed S-arylation of thiophenol derivatives with aryl halides leading to diaryl sulfides is reported. The reactions were catalysed by a combination of a copper salt and a 1,2-diamine derivative (acting both as the ligand and as the base) using exclusively water as the solvent. The recovery and successful reutilisation of the aqueous medium containing the active catalyst is described. Furthermore, one example of a "one-pot" process involving Br/I exchange of an aryl bromide and further S-arylation is presented.

Keywords: copper · cross-coupling · heterogeneous catalysis · S-arylation · water chemistry

Introduction

Copper-catalysed coupling reactions were first reported by Ullmann and, since that seminal discovery, have found increasing utility as tools for the construction of carbon–heteroatom bonds.[1] Whereas many such copper-catalysed protocols have been reported over the years to perform C–N and C–O linkages, C–S bond formation leading to diaryl thioethers has received comparatively little attention,[1] despite this framework being present in a great number of pharmaceuticals, biologically active molecules and polymeric materials (Figure 1).[2] Given the industrial importance of diaryl thioethers and that, of the limited number of methods available to make these molecules employing copper catalysts,[3] all involve the use of non-recyclable catalytic systems and strong bases in some cases,[3a,b] the design of a green chemical method for the thiol S-arylation reaction is considered of high practical value.

Indeed, over the last decade there has been an increasing interest in the search for more sustainable chemical processes. In this context, the use of nontoxic chemicals, renewable reagents and environmentally friendly solvents, among which water is the most benign one, is a most valuable feature for the design of a "green" chemical protocol. Thus, in this sense, water has been the solvent of choice to perform a number of organic transformations due to its properties such as non-toxicity, low cost, availability and greater chemoselectivity compared with organic solvents.[4]

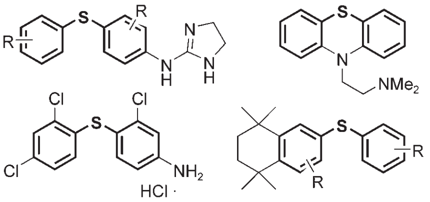

Figure 1. Biologically active molecules comprising the diaryl thioether framework.

Considering our experience in this field with the application of "on-water chemistry" to the synthesis of benzo[*b*]furans through copper-catalysed C–O coupling,[5] we judged it certainly appealing to explore and extend the scope of such advantageous protocol. In this context, we envisaged its application to the C–S bond formation which would allow, in this case, the construction of diaryl thioether derivatives. The aforementioned methodology involves the use of a solution composed of neat water, a catalytic amount of a copper source and a 1,2-diamine reagent which plays a double role: it acts both as the ligand through coordination with the copper and as the base.[5] Hence, we present here a method for the synthesis of diaryl thioethers based on copper-catalysis performed in the presence of water.[6] The reutilization of

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: Literature data for known compounds, selected spectra.

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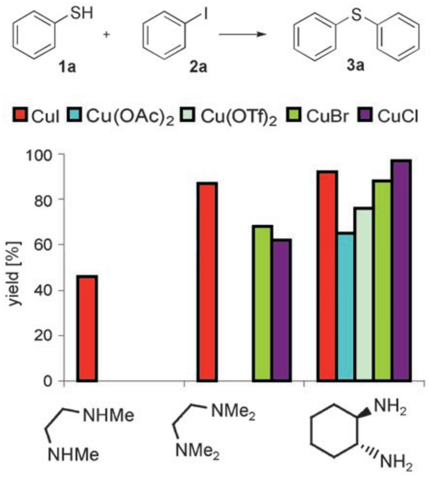
the aqueous medium containing the copper catalysts is also tested.

Results and Discussion

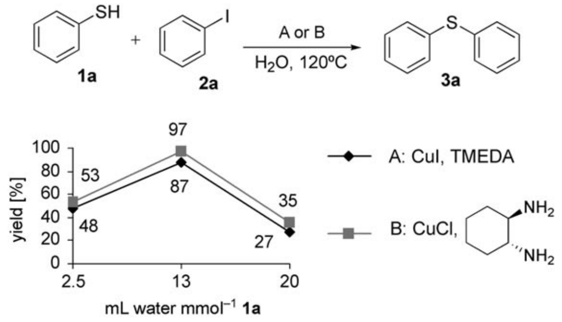
Firstly and with the above precedents in mind,[5] in order to optimise the reaction conditions we chose thiophenol (**1a**) and iodobenzene (**2a**) as the coupling partners for a model system, and the efficiency of several copper(I) and (II) sources and commercially available 1,2-diamine derivatives was then tested, as depicted in Scheme 1.



Scheme 1. Screening of copper sources and 1,2-diamine derivatives for the S-arylation of thiophenol with iodobenzene in water at 120 °C.

Interestingly, both Cu^I and Cu^{II} sources furnished target compound **3a** in comparable yields when *trans*-1,2-diaminocyclohexane was used as the ligand, though Cu^I proved superior. Of the 1,2-diamines tested, the best results were obtained when using the N-substituted tertiary amine TMEDA and the non-substituted *trans*-1,2-diaminocyclohexane. This may suggest that the degree of basicity (pK_b) of the diamine derivatives, despite being the base of the reaction, does not play a key role in the process.[7] Indeed, the reaction outcome may, however, be mainly dependent on the reactivity of the active catalyst, generated in situ from a copper salt and a diamine derivative.[8] The structure of such copper species formed in water solution has not been determined, though it could be inferred from the results shown in Scheme 1, that linear diamines lead to less active catalysts than configurationally fixed ones, such as *trans*-1,2-diaminocyclohexane. Unfortunately, the reason for such catalyst activity enhancement in the S-arylation studied herein remains unknown.

Surprisingly, it was observed that the amount of water present played a critical role in the reaction outcome. Indeed, either a substantial decrease or increase in the volume of water from the optimal value (13 mL mmol^{-1} of **1a**) resulted in much lower yields of **3a** (Scheme 2).[9] These results are in contrast to the conventional understanding that dilution does not influence "on-water" processes, as they take place on the water surface.[4] However, since there are two immiscible phases (aqueous and organic) in the explored S-arylation process, it seems plausible that the reaction occurs through small portions of dissolved solutes in the aqueous–organic interface, and therefore proceeds in a partially homogeneous fashion.[10] At high dilution, the concentration of copper catalyst in the interface would be lower than at the optimised dilution. Therefore, it could be expected that the catalyst amount in contact with the corresponding thiolate and aryl halide molecules in the interface where the reaction takes place is not sufficient to effect the target transformation in a good yield. Conversely, at low dilution, it is anticipated that the amount of copper-catalyst molecules in the aforementioned interface would be greater than at higher dilution. In that situation, the thiolate molecules dissolved in the aqueous phase would encounter and interact more easily with copper atoms, maybe leading to a partial inhibition of the catalyst. These observations are in agreement with research currently developed in our group. Indeed, ongoing investigations dealing with different arylations performed in similar conditions as those reported herein, have shown that when non-sulfur containing substrates are employed, the amount of water can be reduced, that is, no deactivation of the copper catalyst is detected. However, the use of a high amount of water always leads to much lower yields. These results will be fully published elsewhere.



Scheme 2. Dilution screening for the S-arylation of thiophenol with iodobenzene.

On balance then, it was concluded that the optimal reaction conditions for the target S-arylation reaction involved stirring of both substrates **1a** and **2a** in the presence of water at 120 °C, 8.5 mol % CuCl and 3.9 equivalents of *trans*-1,2-diaminocyclohexane (Scheme 1).

To determine the scope of the presented coupling reaction we decided to apply this protocol to a range of commercially available thiophenols **1** and aryl iodides **2**. The methodology proved suitable for the synthesis of the corresponding diaryl sulfides **3** in good to excellent yields as shown in Table 1. It must be pointed out that the reaction worked well even when either the thiophenol derivative or the aryl iodide were substituted with free amino and hydroxy moieties, known to readily couple with aryl halides in the presence of

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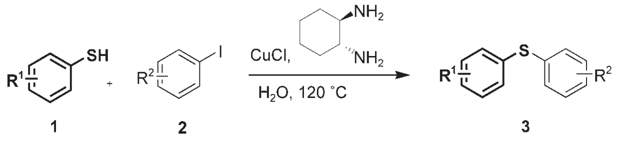
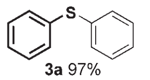
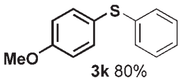
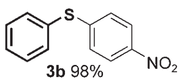
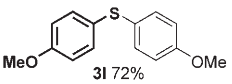
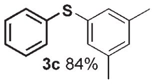
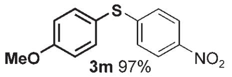
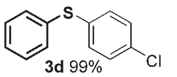
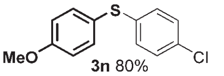
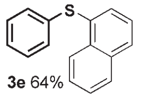
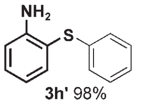
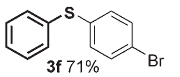
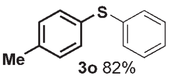
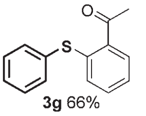
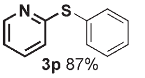
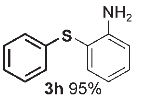
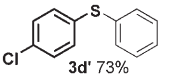
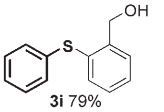
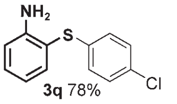
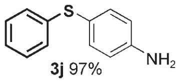
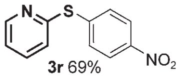
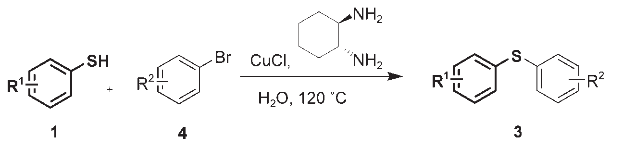
Table 1. S-arylation of thiophenol derivatives **1** with aryl iodides **2**.

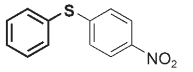
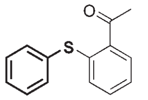
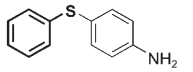
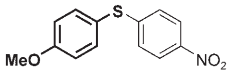
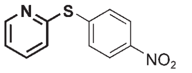
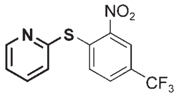
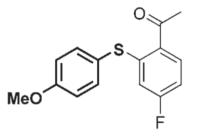
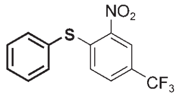
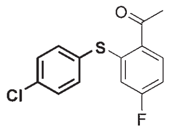


Entry	3[a]	Entry	3[a]
1	 **3a** 97%	11	 **3k** 80%
2	 **3b** 98%	12	 **3l** 72%
3	 **3c** 84%	13	 **3m** 97%
4	 **3d** 99%	14	 **3n** 80%
5	 **3e** 64%	15	 **3h'** 98%
6	 **3f** 71%	16	 **3o** 82%
7	 **3g** 66%	17	 **3p** 87%
8	 **3h** 95%	18	 **3d'** 73%
9	 **3i** 79%	19	 **3q** 78%
10	 **3j** 97%	20	 **3r** 69%

[a] Isolated yields.

Table 2. S-arylation of thiophenol derivatives **1** with aryl bromides **4**.



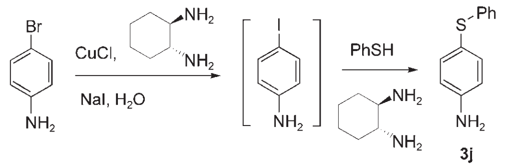
Entry	3[a]	
1[b]		**3b** 87 (98)
2[b]		**3g** 79 (66)
3[b,c]		**3j** 84 (97)
4[b]		**3m** 95 (97)
5[b]		**3r** 71 (69)
6		**3s** 99.9
7		**3t** 87
8		**3u** 75
9		**3v** 73

[a] Isolated yields. [b] The value in parentheses refers to the yield obtained for the same product **3** but using the corresponding aryl iodide. [c] The reaction took place through a "one-pot" halide exchange process. See the text below.

a copper catalyst (Table 1, entries 8–10, 15 and 19). Fortunately, the chemoselectivity of the protocol, based on the nucleophilicity of thiolates, resulted in no competitive N- or O-arylation processes being detected.

Interestingly, the methodology described herein was not limited to the use of aryl iodides. Indeed, it also proved suitable for the coupling of aryl bromides **4** with thiophenols **1**, affording the corresponding diaryl sulfides in good to excellent yields, which were comparable and even better than those obtained when using aryl iodides in some cases (Table 2, entries 1–2, 4 and 5). Furthermore, the reaction outcome was not affected by the steric hindrance derived from the presence of *ortho*-substituents on both partners of the reaction, furnishing target diaryl thioethers **3** in good yields (Table 1, entries 8–9, 15 and 19; Table 2, entries 2, 6–9). In addition, the coupling reactions between a pyridinyl thiol and both aryl iodide and bromide derivatives were successfully performed, delivering the corresponding heteroaromatic sulfides in good yields (Table 1, entries 17 and 20; Table 2, entries 5 and 8).

Unfortunately, the use of bromide derivatives **4** was mainly restricted to those bearing electron-withdrawing substituents. In an effort to overcome this limitation, we considered performing such couplings via an in situ halogen exchange (based on the work of Buchwald's group[11]), and subsequent S-arylation reactions using the same catalytic system to effect both transformations in a "one-pot" process. Thus, as depicted in Scheme 3, an aqueous solution of CuCl and *trans*-1,2-diaminocyclohexane (both in catalytic amount) containing *p*-bromoaniline and NaI was stirred at 120 °C for 24 h to effect the Br/I exchange. Subsequently, the thiophenol and more diamine derivative were added to



Scheme 3. Br/I exchange and subsequent S-arylation reaction.

perform the S-arylation reaction, which successfully rendered the corresponding sulfide in 84 % yield (Table 2, entry 3) in addition to a certain amount of unexchanged aryl bromide. Although this is a preliminary result and the halogen exchange under the above conditions remains to be optimised prior to its application to other aryl bromides, this one-pot protocol is a valuable complement to the coupling reported here so that it could effectively broaden the range of substrates available for S-arylation.

Finally, the recovery and reutilisation of the violet aqueous solution containing the copper complex was tested using the formation of compounds **3d** and **k** as model reactions. Thus, after each reaction, the latter compounds were isolated by extraction of the crude mixtures and the recovered aqueous solutions were used again to accomplish each respective transformation up to four times. As shown in Figure 2, it is possible to use the water solutions containing the copper complexes three times with hardly any variation in the yields of the target compounds. However, after the third use a change of colour in the water solutions from the original violet to brown was observed, and the utilisation of such brown aqueous solution to perform the fourth run of each reaction resulted in a clear decrease in the yields of both sulfides **3d** and **k**.[13]

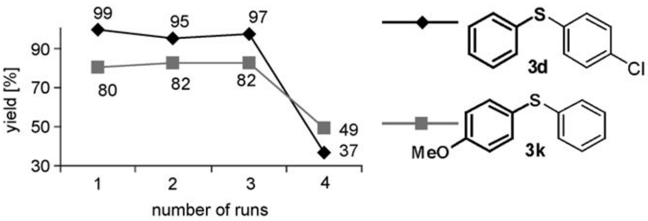


Figure 2. Reutilisation of the aqueous solutions containing the copper complexes.

It should be pointed out that in most of the examples of catalyst reutilisation reported, the metal complex has to be separated from the reaction medium and often requires reactivation prior to reuse.[14] However, in our case we recycle not only the copper complex, but also the aqueous reaction medium itself (containing the active catalyst).

Conclusion

To sum up, we have developed an environmentally friendly access to diaryl sulfides through a copper-catalysed S-arylation novel protocol in neat water. The advantages derived from the use of such a benign solvent as water are clear in terms of safety, cost and innocuousness. Furthermore, the methodology is applicable to a wide range of thiophenol derivatives, aryl iodides and bromides. The latter halides, when necessary, could be converted into their iodide analogues through halogen exchange with NaI under the same reaction conditions as those employed to effect S-arylation, although such exchange process still requires further optimisation. In addition, recycling of the aqueous reaction medium containing the copper complex can be effected up to three times without a significant variation in the yield of the reaction, providing thereby environmental and economic advantages over previously reported protocols and rendering this methodology highly suitable for industrial application.

Experimental Section

All reagents were purchased and used without further purification. Redistilled water was employed for the copper-catalysed reactions. TLC was carried out on silica gel (silica gel 60 F_{254}, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). Drying of organic extracts after work-up of reactions was performed over anhydrous Na_2SO_4. ^1H and ^{13}C spectra were recorded in $CDCl_3$ solution in a Bruker AC-300 and chemical shifts are reported in ppm downfield (δ) from Me_4Si. Low and high resolution mass spectra were performed by the Mass Spectroscopy Section of the University of the Basque Country (UPV/EHU). For the new compounds, IR spectra were recorded on a Perkin–Elmer 1600-FT infrared spectrophotometer and melting points were determined in a capillary tube and are uncorrected. All the reactions were carried out under argon. Literature data of known compounds are given in the Supporting Information.

Typical procedure for the coupling of thiols with aryl iodides (Table 1)

Diphenyl sulfide (3a):[14] A Schlenk flask was charged with CuCl (4.8 mg, 0.048 mmol), iodobenzene (0.12 mL, 1.05 mmol), *trans*-1,2-diaminocyclohexane (0.26 mL, 2.21 mmol), water (6.3 mL) and thiophenol (0.06 mL, 0.57 mmol). The flask was sealed under a positive pressure of argon and the resulting violet solution was heated overnight at 120 °C. The product was extracted from the aqueous layer with dichloromethane, dried and concentrated in vacuo. The crude mixture was then purified by flash chromatography (10 % CH_2Cl_2/hexane) to give sulfide **3a** (102.1 mg, 97 %) as a colourless liquid.

Typical procedure for the recycling of the aqueous solution containing the catalyst

4-Chlorophenyl phenyl sulfide (3d):[15] The typical procedure was followed starting from the corresponding aryl iodide (227.2 mg, 0.94 mmol) and thiol (0.05 mL, 0.47 mmol) to afford sulfide **3d** (102.7 mg, 99 %) as a colourless liquid.

Recycling of the aqueous solution containing the catalyst: After extraction with CH_2Cl_2, the recovered aqueous layer was placed in a Schlenk flask under argon, and aryl iodide (227.2 mg, 0.94 mmol), *trans*-diaminocyclohexane (0.17 mL, 1.42 mmol) and thiol (0.05 mL, 0.47 mmol) were added. The resulting mixture was heated at 120 °C overnight and the isolation of the product was accomplished as described before. This procedure, employing identical amounts for each reactant, was repeated three times.

Typical procedure for the coupling of thiols with aryl bromides (Table 2)

4-Nitrophenyl phenyl sulfide (3b):[14] A Schlenk flask was charged with CuCl (4.0 mg, 0.04 mmol), 4-nitrobromophenyl (215.6 mg, 0.94 mmol), *trans*-1,2-diaminocyclohexane (0.22 mL, 1.84 mmol), water (6.1 mL) and thiophenol (0.05 mL, 0.47 mmol). The flask was sealed under a positive pressure of argon and the resulting violet solution was heated overnight at 120 °C. The product was extracted from the aqueous layer with dichloromethane, dried and concentrated in vacuo. The crude mixture was then purified by flash chromatography (35 % CH_2Cl_2/hexane) to give sulfide **3b** (94.9 mg, 87 %) as a yellow solid.

4-Aminophenyl phenyl sulfide (3j) (Br/I exchange and subsequent S-arylation):[16] A Schlenk flask was charged with CuCl (4.0 mg, 0.04 mmol), 4-bromoaniline (167.3 mg, 0.94 mmol), *trans*-1,2-diaminocyclohexane (20 μL, 0.17 mmol), NaI (284.2, 1.89 mmol) and water (6.3 mL). Then, the flask was sealed under a positive pressure of argon and the resulting violet solution was heated at 120 °C. After 24 h, the mixture was allowed to reach room temperature under argon; subsequently *trans*-1,2-diaminocyclohexane (0.20 mL, 1.67 mmol) and thiophenol (0.05 mL, 0.47 mmol) were added and the solution was heated overnight at 120 °C The product was isolated following the typical procedure to give sulfide **3j** (79.6 mg, 84 %) as a white solid.

2-Nitro-4-trifluoromethylphenyl phenyl sulfide (3s):[17] The typical procedure was followed starting from the corresponding aryl bromide (0.15 mL, 0.96 mmol) and thiol (0.06 mL, 0.57 mmol) to afford sulfide **3s** (169.2 mg, 99.9 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 7.61–7.49 (m, 6 H), 6.97 ppm (d, J = 8.60 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 144.1, 135.9, 130.7, 130.4, 129.6, 129.4 (q, J = 3.34 Hz), 128.8, 127.3 (q, J = 34.40 Hz), 123.0 (q, J = 3.99 Hz), 122.9 ppm (q, J = 272.08 Hz); MS (70 eV, EI): m/z (%): 299 (9) $[M]^+$, 254 (16), 235 (100), 216 (39), 202 (28), 185 (95), 166 (74), 152 (27), 139 (41), 97 (37), 85 (43), 77 (40); HRMS (EI): m/z: calcd for $C_{13}H_8NO_2SF_3$: 299.0228; found: 299.0230 $[M]^+$.

2-Acetyl-5-fluorophenyl 4-methoxyphenyl sulfide (3t): The typical procedure was followed starting from the corresponding aryl bromide (265 mg, 0.96 mmol) and thiol (0.06 mL, 0.48 mmol) to afford sulfide **3t** (115.1 mg, 87 %) as a white solid. M.p. 138–140 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, J = 7.93, 6.15 Hz, 1 H), 7.45 (d, J = 8.16 Hz, 2 H), 6.97 (d, J = 8.21 Hz, 2 H), 6.78 (t, J = 7.68 Hz, 1 H), 6.43 (d, J = 10.47 Hz, 1 H), 3.84 (s, 3 H), 2.62 ppm (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 164.8 (d, J = 254.84 Hz), 160.8, 148.5 (d, J = 8.58 Hz), 137.4, 133.3 (d, J = 9.90 Hz), 129.2 (d, J = 2.55 Hz), 122.4, 115.5, 113.6 (d, J = 25.86 Hz), 110.8 (d, J = 22.45 Hz), 55.3, 27.8 ppm; IR (film): $\tilde{\nu}$ = 2837.8, 1666.8, 1590.4, 1484.6 cm^{-1}; MS (70 eV, EI): m/z (%): 276 (100) $[M]^+$, 261 (46), 218 (51), 189 (33), 139 (19), 124 (24), 122 (17), 94 (19); HRMS (EI): m/z: calcd for $C_{15}H_{13}O_2SF$: 276.0620; found: 276.0630 $[M]^+$.

2-Nitro-4-trifluoromethylphenyl 2-pyridinyl sulfide (3u): The typical procedure was followed starting from the corresponding aryl bromide (0.15 mL, 0.96 mmol) and thiol (53.6 mg, 0.482 mmol) to afford sulfide **3u** (109.1 mg, 75 %) as a yellow solid. M.p. 90–92 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, J = 3.71 Hz, 1 H), 8.41 (s, 1 H), 7.78 (dt, J = 7.67, 1.72 Hz, 1 H), 7.61 (d, J = 7.84 Hz, 2 H), 7.37–7.33 ppm (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 151.3, 146.1, 139.9, 138.1, 131.1, 129.2 (q, J = 3.27 Hz), 128.9, 128.6 (q, J = 34.50 Hz), 123.8, 122.8 (q, J = 3.91 Hz), 122.7 ppm (q, J = 272.85 Hz); IR (film): $\tilde{\nu}$ = 1525.7, 1320.1, 1132.0 cm^{-1}; MS (70 eV, EI): m/z (%) 300 (1) $[M]^+$, 254 (100), 184 (29), 78 (61); HRMS (EI): m/z: calcd for $C_{12}H_7N_2O_2SF_3$: 300.0180; found: 300.0178 $[M]^+$.

2-Acetyl-5-fluorophenyl 4-chlorophenyl sulfide (3v): The typical procedure was followed starting from the corresponding aryl bromide (208.9 mg, 0.93 mmol) and thiol (67.0 mg, 0.46 mmol) to afford sulfide **3v** (94.6 mg, 73 %) as a white solid. M.p. 104–106 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, J = 8.63, 5.88 Hz, 1 H), 7.47 (d, J = 8.48 Hz, 2 H), 7.41 (d, J = 8.49 Hz, 2 H), 6.83 (dt, J = 8.67, 2.38 Hz, 1 H), 6.45 (dd, J = 10.40, 2.34 Hz, 1 H), 2.63 ppm (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 164.7 (d, J = 258.03 Hz), 146.5 (d, J = 8.75 Hz), 136.9, 136.0, 133.3 (d, J = 9.92 Hz), 130.5, 130.2, 129.7 (d, J = 2.66 Hz), 114.0 (d, J = 25.79 Hz), 111.4 (d, J = 22.28 Hz), 27.7 ppm; IR (film): $\tilde{\nu}$ = 1660.9, 1566.9, 1467.0, 1384.7, 1249.6 cm^{-1}; MS (70 eV, EI): m/z (%): 282 (31) $[M+2]^+$, 280 (72) $[M]^+$, 267 (30), 230 (91), 202 (100), 170 (30), 157 (48), 111 (37), 94 (41); HRMS (EI): m/z: calcd for $C_{14}H_{10}OSClF$: 280.0125; found: 280.0130 $[M]^+$.

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[7] This observation is in contrast with the results obtained in our previously reported protocol for the synthesis of benzo[*b*]furans. In that case, the basicity of the diamine was more relevant and TMEDA provided better yields for the target compounds than *trans*-1,2-diaminecyclohexane. See ref. [5].

[8] It is assumed that the oxidation state for in situ generated copper complexes in this type of reactions is +1 and +3, see ref. [1b]. Nevertheless, it is also known that copper(I) could dissociate to copper(0) and (II). However, no evidence of copper(0) precipitation has been observed while performing the target reaction.

[9] Subsequent experiments have shown that this optimal value of 13 $mL\,mmol^{-1}$ is actually approximate. Indeed, the reaction outcome has proved to be very similar when using from approximately 12 to 14 $mL\,mmol^{-1}$. Lower yields were observed when using other dilution values.

[10] To understand better the process it should be borne in mind that the species that dissolve in the aqueous phase are probably not the starting materials as such, but ionic species derived from them. For

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instance, in the case of the thiol, the soluble specie would be the corresponding thiolate. For the aryl halide, however, it is plausible that the water-soluble copper catalyst may also be soluble in the organic phase so that the oxidative addition step of the aryl halide may take place in the organic layer. Thus, if so, the species prone to dissolve in the water phase would be a copper complex holding the corresponding aryl fragment, but not directly the aryl halide. However, there are no experimental evidences to support these hypotheses.

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