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Ligand-free copper(I) catalyzed N- and O-arylation of aryl halides

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Abstract—A simple and industrially viable protocol for C–N and C–O coupling is reported here. Arylation of phenol, benzylamine and imidazole with aryl bromides is achieved using ligand-free Cu(I) halide salts in low catalytic amount (2.5 mol %).

1. Introduction

The formation of aryl-nitrogen and aryl-oxygen bonds via cross-coupling reactions represent a powerful means for the preparation of various compounds that are of biological, pharmaceutical and material interest.[1] Since its discovery, the copper-mediated Ullmann coupling reaction[2] is still the straightforward method to form the requisite carbon–heteroatom bonds. However, the synthetic scope of this reaction is strongly limited by the insolubility of copper(I) salts in organic solvents, the high reaction temperatures required (~200 °C) and the sensitivity of the substituted aryl halide to the harsh reaction conditions applied. Another major drawback of this protocol is the use of stoichiometric amounts of copper or copper salts, which results in the production of large quantities of waste, making this method environmentally unfriendly. Milder reactions using transmetallating agents, such as triarylbismuth,[3] aryllead triacetates,[4] arylboronic acids[5] and hypervalent aryl siloxanes,[6] have been developed but these alternatives are limited since the preparation of highly functionalized substrates usually requires multistep sequences. Important developments have been made on the Ullmann-type coupling reaction, mainly improving the reaction conditions and tolerability of substrates.[7] The key seems to be modification of the catalytic system via addition of a wide range of additives in order to improve the solubility of the copper source, allowing in this way, the use of a catalytic amount of copper and milder reaction conditions. Generally, this goal is reached via in situ formation of a copper-complex by addition of a suitable, often bidentate, chelator such as diamines,[8] amino acids,[9] 1,10-phenanthrolines,[10] diols[11] and other nitrogen- and oxygen-containing ligands.[7,12]

An alternative is the preparation of a chemically well-defined and soluble copper-complex to be employed in the reaction.[13] Recently, for N-[14] and O-[15]arylation reactions soluble aminoarenethiolato-copper(I) complexes (CuSAr)[16] were used. Different disubstituted diaryl ethers and arylamines have been synthesized from aryl bromides, using only 2.5 mol % of the copper(I) complex.

The aminoarenethiolato-copper catalyzed reactions are typically carried out under reaction conditions of 6–16 h at 160 °C, in the presence of 1.1 equiv of inorganic base.[14,15] For mechanistic investigations, tests with catalytic amounts of ligand-free copper halides were undertaken resulting in remarkably high activities. Motivated by these results, several tests on O- and N-arylation reactions with different Cu-halide salts were performed under conventional heating conditions (Tables 1–3).

This Letter contains these preliminary results describing the copper(I)-catalyzed arylation reaction of phenol, benzylamine and imidazole using phenyl iodide and aryl bromides as arylating agents. To the best of our knowledge, protocols using low catalytic amounts of simple, cheap and ligand-free copper(I) salts in the Ullmann-type coupling reaction have not been reported thus far.

2. Results and discussion

Three different Cu(I) halide salts were employed, CuCl, CuBr[17] and CuI, in order to determine the influence of

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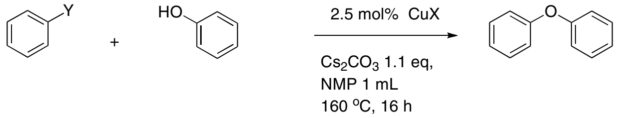
Table 1. O-Arylation reaction of phenol with aryl halides[a]



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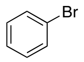
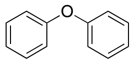
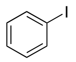
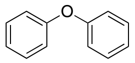
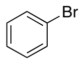
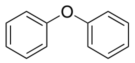
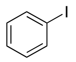
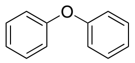
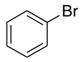
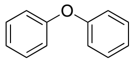
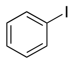
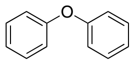
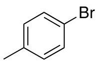
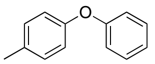
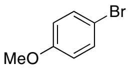
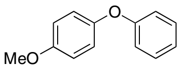
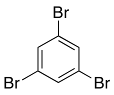
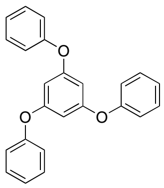
1	CuCl			89
2	CuCl			80[c]
3	CuBr			87[c]
4	CuBr			72
5	CuI			72
6	CuI			42
7	CuBr			89[c]
8	CuBr			78[c]
9	CuI			68[d]

[a] Reaction conditions: aryl halide (5 mmol), phenol (6.5 mmol), Cs_2CO_3 (5.5 mmol), CuX (2.5 mol %), NMP (1 mL), 160 °C, 16 h, under N_2.

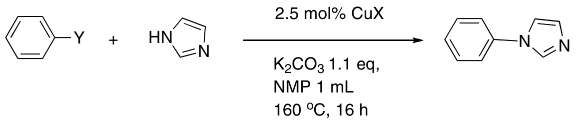
[b] Determined by GC using dihexyl ether as internal standard.

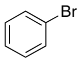
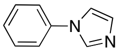
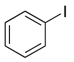
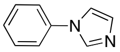
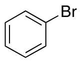
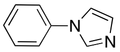
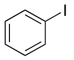
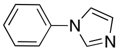
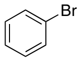
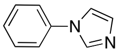
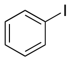
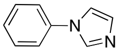
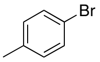
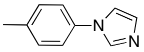
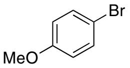
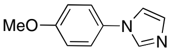
[c] Isolated yield.

[d] 3 equiv of phenol and Cs_2CO_3.

the anion. The solvent (NMP), inorganic base (K_2CO_3 or Cs_2CO_3), temperature (160 °C) and time (16 h) parameters were kept constant to facilitate comparison with data collected previously by us, employing the CuSAr copper catalyst.[14,15] As shown in Tables 1 and 3, the best substrate for these two examples of C–N and C–O coupling reactions was bromobenzene, while in the case of N-arylation with imidazole (Table 2), the arylating agent iodobenzene gave similar results to the bromo compound. The use of chlorobenzene as substrate was not investigated since yields in screening tests were very poor (between 1% and 18%). Moderate to good results were obtained for the O-arylation of bromo and iodobenzene, with yields between 42% and 89%, including an example of tri-substitution of 1,3,5-tribromobenzene with phenol. N-Arylation of imidazole led to the preparation of the desired products in good yields (67–79%) while arylation of benzylamine gave rather poor results (yields between 9% and 50%). As shown in Table 1, *para*-substituted phenyl bromides (entries 7 and 8) were also suitable substrates for the preparation of substituted diaryl ethers. They show a positive influence in the case of the N-arylation of imidazole (Table 2, entries 7 and 8), while in the case of arylation of benzylamine the presence of a substituent on the phenyl ring did not bring about any improvement. These data underline the difference not only between O- and N-nucleophiles in the coupling process, but also between primary and secondary amines. It appears that the nature of the halide anion present in the mixture (derived either from the Cu salt or from the aryl donor) plays a pivotal role in the reaction since the best results were achieved in the presence of bromide anions. A possible explanation could be the presence of iodide ions stabilizing the Cu atom in its +1 oxidation state, rendering the species stable and insoluble,[18] while

Table 2. N-Arylation reaction of imidazole with aryl halides[a]



Entry	CuX	Aryl halide	Product	Yield[b] (%)
1	CuCl			67
2	CuCl			61[c]
3	CuBr			86[c]
4	CuBr			72
5	CuI			70
6	CuI			72[c]
7	CuBr			89
8	CuBr			91

[a] Reaction conditions: aryl halide (5 mmol), imidazole (6.5 mmol), K_2CO_3 (5.5 mmol), CuX (2.5 mol %), NMP (1 mL), 160 °C, 16 h, under N_2.
[b] Determined by GC using dihexyl ether as internal standard.
[c] Isolated yield.

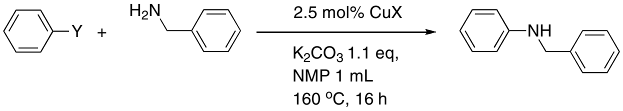
the bromide ion would permit a change in oxidation state, allowing a possible catalytic cycle. In this regard, four mechanisms are proposed in the literature that can be classified into two main categories: those in which the oxidation state of copper changes throughout the mechanistic cycle and those in which the oxidation state remains constant. The four different alternatives involve: (a) oxidative addition/reductive elimination of ArX on copper(I); (b) aryl radical intermediates; (c) σ-bond metathesis through a four-centred intermediate and (d) π-complexation of copper(I) on ArX.[7] Therefore, the positive influence of bromide ions observed in the above-mentioned reactions seems to corroborate with mechanism (a) or (b), which presumes a change of the Cu formal oxidation state during the C–X coupling reaction. Further investigations regarding mechanistic aspects of the copper-catalyzed aromatic nucleophilic substitutions are currently in progress.

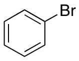
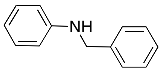
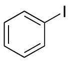
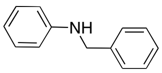
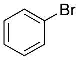
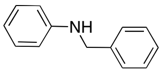
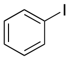
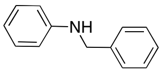
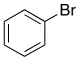
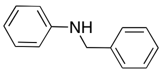
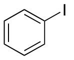
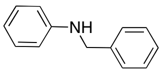
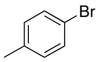
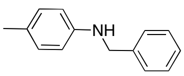
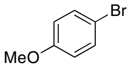
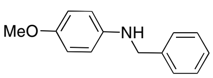
In summary, this Letter describes a simple method for the preparation of diaryl ethers and *N*-arylated benzylamines and imidazoles. The catalytic system adopted is simple and cheap, starting from commercially available compounds and employing only a catalytic amount (2.5 mol %) of the Cu(I) halide salt. This protocol avoids the otherwise time-consuming and sometimes expensive preparation of external ligands and activated substrates.

3. Experimental

General procedure for catalytic test reactions: The catalytic tests were performed using standard Schlenk techniques. In a general procedure, a Schlenk tube containing N_2 was charged with inorganic base (5.5 mmol) and solid substrate. Liquid reagents (aryl halide: 5 mmol; amine/phenol: 6.5 mmol) and solvent (NMP, 1 mL) were then added and finally the copper(I) salt was added. The reaction was kept under an inert atmosphere[19] and placed in a preheated oil bath at 160 °C for 16 h. Subsequently, the reaction was allowed to cool to room temperature and quenched by adding acetonitrile (5 mL) and dihexyl ether (100 μl, 0.425 mmol) as external standard. All samples were analyzed by gas chromatography. For the etherification reaction, the reaction mixture was filtered through a plug of Celite and the solvent removed in vacuo to yield the crude product, which was purified by silica gel chromatography (eluent: hexane). In the case of the amination reaction, the reaction mixture was washed with 4 M NaOH and the organic layer was dried over

Table 3. N-Arylation reaction of benzylamine with aryl halides[a]



Entry	CuX	Aryl halide	Product	Yield[b] (%)
1	CuCl			32[c]
2	CuCl			11
3	CuBr			15
4	CuBr			10
5	CuI			50
6	CuI			9
7	CuI			35
8	CuI			25

[a] Reaction conditions: aryl halide (5 mmol), benzylamine (6.5 mmol), K_2CO_3 (5.5 mmol), CuX (2.5 mol %), NMP (1 mL), 160 °C, 16 h, under N_2.

[b] Determined by GC using dihexyl ether as internal standard.

[c] Isolated yield.

$MgSO_4$, filtered and evaporated in vacuo to yield the crude product, which was purified by silica gel column chromatography (eluent: EtOAc/hexane).

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