Copper Catalysis

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Copper-Catalyzed Cross-Couplings with Part-per-Million Catalyst Loadings**

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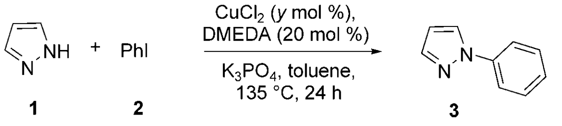
Due to the importance of functionalized arenes as scaffolds in applied organic materials and biologically relevant molecules, metal-catalyzed cross-couplings have gained significant attention in recent years.[1,2] Among them Ullmann type C−X bond formations are particularly attractive because they often allow the use of low-cost starting materials in combination with readily available copper salts.[2] Whereas the initial protocols[3] required high temperatures and over-stoichiometric quantities of metal, recent approaches involving well-chosen and optimized metal–ligand combinations allow for milder reaction conditions and catalytic turnover.[4] Despite these significant advances it has to be noted that commonly in these catalytic Ullmann type reactions both TONs (turnover numbers) as well as TOFs (turnover frequencies) remain rather limited resulting in the requirement of metal salt amounts in the range of 5 to 10 mol %.[5] Lowering the catalyst loading leads to extended reaction times and decreased product yields. Here, we report on Ullmann type reactions with "homeopathic amounts" of copper salts.[6]

During investigations of iron-catalyzed cross-coupling reactions[7,8] it was noted that for some substrate combinations the catalyst activity depended on the metal salt source and its purity.[9] Those observations suggested a closer look into the effects of metal traces under the applied reaction conditions.[10] Taking into account the results by Taillefer and others on Fe/Cu co-catalyses,[11] copper became the prime metal of choice. To our surprise we found that even with catalyst loadings in the 0.01 mol% range of copper(II) salts N-, O-, and S-arylations were possible to provide the corresponding products in yields > 90%. As a representative example, the coupling between pyrazole (**1**) and phenyliodide (**2**, 1.5 equiv) to provide N-arylated product **3** [Eq. (1)] was studied in detail. Further reaction components were *N,N'*-dimethylethylenediamine (DMEDA) as (potential) ligand (20 mol%), $K_3PO_4{\cdot}H_2O$ as base (2 equiv)[12] and toluene as solvent. The reaction mixture was kept under inert atmosphere at 135 °C in a sealed microwave tube for 24 h.



(1)

Figure 1 shows the dependence of the yield of **3** on the amount of copper(II) chloride applied under the conditions described above (as determined by GC using dodecane as internal standard). Catalyst loadings in the range of 0–0.64 mol% were tested, and as the graph reveals even 0.01 mol% of the copper salt led to 88% yield of coupled product **3**. The presence of 0.08 mol% of $CuCl_2$ proved optimal, affording **3** in essentially quantitative (GC) yield. In the absence of both metal and ligand the target arylation did not take place.[13]

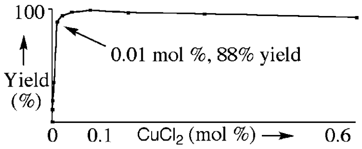


Figure 1. Yield of **3** versus catalyst loading (expressed in mol% of $CuCl_2$); reaction conditions as depicted in Equation (1).

Similar profiles were obtained when sub-mol% amounts of $CuCl_2$ were applied in reactions of phenyliodide (**1**) with benzamide (**4**) or indole (**6**) to give N-arylated products **5** and

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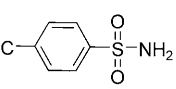

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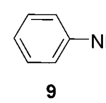

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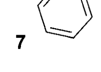

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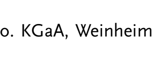

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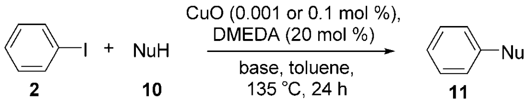
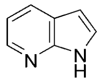
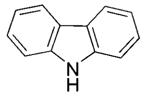
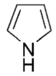
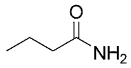
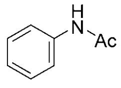
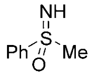
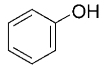
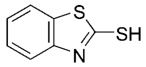
7, respectively. Starting from **1** and **2** use of 0.001 and 0.1 mol% of CuO instead of $CuCl_2$ led to 41 and 94% yield of **3** (isolated after chromatography), respectively. In all cases, it was crucial that the ligand-to-metal ratio was high (with 20 mol% of DMEDA, 0.4 M in toluene, independent of the metal concentration).[14–16]

In order to investigate the scope of the Ullmann type cross-coupling catalyzed by sub-mol% amounts of copper salts, reactions of **2** with various N-, O-, and S-nucleophiles were studied. As metal source CuO was used, and the effects of 0.1 and 0.001 mol% were evaluated. The base was adjusted according to previously optimized protocols. Table 1 summarizes those data.[12,17]

Table 1: Ullmann type couplings of various nucleophiles using sub-mol% amounts of CuO.



Entry	NuH	Base	Yield of **11** with CuO (0.001 mol%)	Yield of **11** with CuO (0.1 mol%)
1		$K_3PO_4\cdot H_2O$	86	n.p.[a]
2		$K_3PO_4\cdot H_2O$	8	25
3		$K_3PO_4\cdot H_2O$	0	11
4		K_2CO_3	33	56
5		Cs_2CO_3	0	38
6[b]		K_2CO_3	51	89
7[c]		Cs_2CO_3	87	n.p.[a]
8		NaO*t*Bu	24	76

[a] n.p. = Not performed. [b] Use of 40 mol% of DMEDA. [c] Use of 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) instead of DMEDA and DMF instead of toluene.

As revealed by the data in Table 1 several substrates could be arylated under the catalysis of CuO in sub-mol% quantities. Even with 0.001 mol% of the copper salt high yields (86 and 87%) were achieved in the N- and O-arylation of azaindole and phenole, respectively (Table 1, entries 1 and 7). Other substrates proved less active, and only the use of 0.1 mol% of CuO led to moderate to good yields. Noteworthy is, however, that these catalyst loadings are still much lower than those commonly applied for conversions of the same substrates. Only tolylsulfonamide (**8**) and aniline (**9**) proved unreactive under the attempted arylations with sub-mol% amounts of CuO.

At the present stage, no complete mechanistic rational can be provided for explaining the high activity of the reported system.[18] It is apparent that individual substrate characteristics demand an adjustment and fine-tuning of both the catalyst system itself (types of ligand and base, for example) and the general reaction parameters (e.g. solvent and concentration). Two factors, however, appear to be dominant in this case: the ligand quantity and the temperature. Without a high concentration of the ligand or at too low temperature, the cross-couplings do not take place at all or require larger metal quantities. We suspect that the ligand shifts equilibria away from favorable low-coordinated copper species which otherwise would be deactivated by aggregation. The importance of keeping low metal concentrations is well described for (ligand-free) palladium catalyses.[6,16b] Further studies appear inevitable to fully shed light on this scientifically stimulating and synthetically relevant phenomena.

Experimental Section

Procedure for the $CuCl_2$-catalyzed reactions between **1** and **2** using sub-mol% amounts of metal salts (see Equation (1): Into twelve microwave vials was added pyrazole (136 mg, 2 mmol, 1 equiv) and K_3PO_4 (849 mg, 4 mmol, 2 equiv). The vials were sealed and a $CuCl_2$ solution (0 to 2560 µL, 5 mM in THF) was added into each of them. The THF was removed by three cycles of vacuum followed by nitrogen, whereupon toluene (2 mL), DMEDA (43 µL, 0.4 mmol, 20 mol%), iodobenzene (334 µL, 3 mmol, 1.5 equiv), and dodecane (50 µL, 0.22 mmol) were added. The closed vials were heated to 135 °C for 24 h. Samples (100 µL) were collected, filtered through a small silica plug and analyzed by GC. The (GC) yield was determined using dodecane as internal standard.

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Keywords: copper · cross-coupling · homogeneous catalysis · N-arylation · Ullmann reaction

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[12] In our initial Communication (ref. [7a]) we had reported the use of K_3PO_4. Later we found out that $K_3PO_4 \cdot H_2O$ had been applied. Control experiments indicated that in most cases the yields were superior with the latter.

[13] Due to the sensitivity of the reaction towards metal traces it was necessary to either use new equipment (glassware, stir-bar etc.) each time or to wash used vials with KOH/isopropyl alcohol followed by rinsing with distilled water and drying overnight at 150 °C in order to entirely suppress the formation of **3** by metal traces from previous reactions.

[14] According to Buchwald's protocol (ref. [3b]) the standard condition of the copper-catalyzed pyrazole arylation with phenyliodide involves 5 mol% of CuI (98% purity, Strem), 20 mol% of DMEDA and 2.1 equivalents of K_2CO_3 in toluene at 80 °C.

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