Copper-Catalyzed Cyanation of Heteroaryl Bromides: A Novel and Versatile Catalyst System Inspired by Nature

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Abstract: An improved copper catalyst system for the cyanation of heteroaryl halides leading to substituted heteroaryl nitriles is described. The catalyst system consists of simple CuI and *N*-alkylimidazoles, and mimics known Cu-containing metalloproteins. It is stable, commercially available, cheap and easily tunable. By using inexpensive and non-toxic $K_4[Fe(CN)_6]$ and the novel Cu catalysts we were able to cyanate both activated and non-activated heteroarenes with high yield and selectivity. The generality of the procedure is demonstrated by a variety of different examples, some of which did not react under other known methods.

Key words: copper, coupling, cyanation, heterocycles, nitriles

Substituted aryl nitriles are of considerable interest for organic synthesis as integral part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.[1] In general, the introduction of cyanide is the most direct and versatile route to prepare functionalized aryl nitriles. For more than a century stoichiometric methods prevailed in the preparation of benzonitriles in laboratory and industry. These include especially the Rosenmund–von Braun reaction of aryl halides,[2] the diazotization of anilines and subsequent Sandmeyer reaction,[3] and the ammoxidation.[4] Due to (over)stoichiometric amounts of metal waste, lack of functional group tolerance, and harsh reaction conditions these methods do not meet the criteria of modern sustainable synthesis. More recently, the introduction of transition-metal-catalyzed C–C coupling processes has revolutionized functionalization reactions of arenes. Nevertheless, there still exist significant challenges in this area. For example, efficient catalysis is often obtained with 'simple' halobenzenes as substrates. More functionalized substrates and especially substituted heteroarenes are more difficult to activate. Moreover, with respect to cyanations the typically used Pd- and Ni-based catalysts suffer from the high affinity towards cyanide. Thus, a fast deactivation of the catalytic system by the formation of stable cyanide complexes is observed and catalysis proceeds in general with low efficiency.[5] We and others have shown that organic, e.g. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA),[6] and inorganic, e.g. Zn and Zn salts,[7] additives as well as slow dosage of the cyanide source[8,9] are beneficial for the reformation of the catalytically active metal center. Other recent developments include microwave activation[10] and the application of new catalyst systems.[11] However, all these developments still have drawbacks such as toxicity of the cyanide source and comparably high catalyst costs.

In 2004, we described for the first time catalytic cyanations with potassium hexacyanoferrate(II) $K_4[Fe(CN)_6]$,[12,13] which has the advantage of being essentially the least toxic cyanide source conceivable. While all known other cyanation sources, e.g. KCN [LD_{Lo} (oral, human) = 2.86 mg/kg], are highly poisonous, $K_4[Fe(CN)_6]$ is essentially non-toxic {the LD_{50} of $K_4[Fe(CN)_6]$ is lower than that for NaCl}. Our new approach has proven its initial value in both palladium- and copper-catalyzed cyanations,[14] and has been adopted nicely by Ozawa, Weissman, and Gelman and co-workers.[11,15]

The first catalytic variant of the Rosenmund–von Braun reaction was reported by Buchwald et al. using *N*,*N*′-dimethylethylenediamine (DMEDA) as ligand.[16] Subsequently, Cristau et al.[17] demonstrated that this reaction also proceeds in the presence of 1,10-phenanthroline as ligand. Both methods still relied upon highly toxic cyanide sources like NaCN or KCN. In addition, a number of potentially interesting substrates, especially heterocycles, could not be converted by any of the known methods so far. This is especially disappointing because with respect to applications probably the most interesting class of substrates for metal-catalyzed coupling reactions are bromoheteroarenes.[18] Thus, in a joint collaboration between industry and academia we set the goal to develop a copper-based catalyst system, which should be industrially feasible and have a broader substrate scope than previously known systems.

Looking for new and improved catalysts for a 'difficult' test reaction, we studied the cyanation of 5-bromopyrimidine in detail. Noteworthy, the resulting product 5-cyanopyrimidine is a versatile intermediate in the fine chemical industry.

At the start of our work, the performance of known copper catalysts was investigated. For example the application of the Cu/DMEDA system failed completely, yielding none of the desired pyrimidine nitrile and a wide spectrum of side products (Table 1, entry 1).

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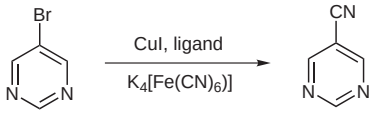
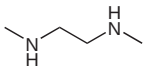
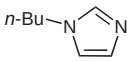
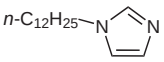
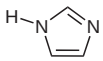
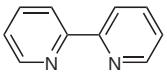
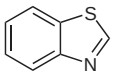
Table 1 Cu-Catalyzed Cyanation of 5-Bromopyrimidine[a]



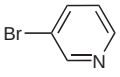
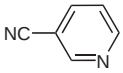
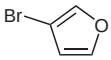
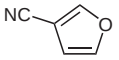
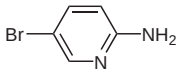
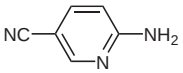
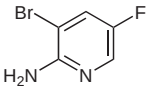
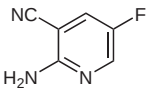
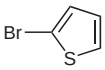
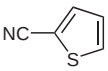
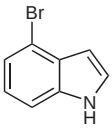
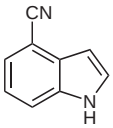
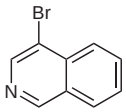
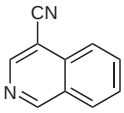
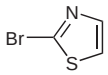
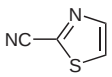
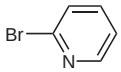
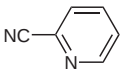
Entry	Ligand	Additive (mol%)	Temp (°C)	Conversion (%)[b]	Yield (%)[b]	Selectivity (%)
1[c,d]		Na_2CO_3 (20), KI (20)	140	87	0	0
2[e]	–	–	140	63	61	97
3		–	160	60	57	94
4		–	160	100	95[f]	95
5		–	160	88	80	91
6		–	160	96	59	61
7		–	160	19	16	83
8[c]		–	160	19	17	92
9		–	160	6	5	77
10		–	160	1	1	–
11		–	160	4	2	45
12[c,g]	dppf (0.2)	$Pd(OAc)_2$ (0.1), Na_2CO_3 (20)	140	5	0	–

[a] Reaction conditions (unless otherwise stated): 2 mmol 5-bromopyrimidine, 20 mol% $K_4[Fe(CN)_6]$, 10 mol% CuI, 200 mol% ligand, 2 mL toluene, 200 μL tetradecane (internal GC standard), 16 h.
[b] Determined by GC.
[c] NMP as solvent.
[d] 100 mol% ligand.
[e] 1-Methylimidazole as solvent.
[f] Isolated yield 55% due to high volatility of the product.
[g] Pd-catalyzed, no CuI added.

Inspired by nature we assumed that imidazoles might be superior ligands to control the stability and selectivity of the copper catalyst. This idea resulted from the fact that the most abundant metal-binding amino acid in nature is histidine. In fact, in most metalloenzymes the actual binding site contains at least one, in some cases up to three histidine units per metal atom.[19] Following this idea, we used in exploratory experiments 1-methylimidazole instead of histidine due to price and availability. To our delight the use of 1-methylimidazole as solvent – to ensure sufficient binding – resulted in a yield of 61% of the desired product (Table 1, entry 2)! Advantageously, the addition of Na_2CO_3, KI or DMEDA, which are necessary in previous protocols, is not necessary here. Further experiments showed that 1-methylimidazole can also be used as an additive in toluene as solvent (Table 1, entry 3). Next, a series of commercially available imidazoles and similar ligands were tested. The more electron-rich and lipophilic 1-butylimidazole performed best, with an almost quantitative yield (95%, Table 1, entry 4). At this point it is interesting to note that to the best of our knowledge 1-alkylimidazoles have not been used as ligands in coupling reactions of aryl halides before.[20] Obviously, imidazoles might be useful ligands for other Cu-catalyzed reactions (amination, ether formation, etc.), too.[21]

Interestingly, even imidazole itself is capable to generate an active catalyst. The decreased product yield (59%) is explained by the lower solubility of imidazole in toluene

Table 2 Scope and Limitations of the Copper-Catalyzed Cyanation[a,22]

Entry	Substrate	Product	Method[b]	Conversion (%)[c]	Yield (%)[c]	Selectivity (%)
1			A[d]	87	82	94
2			A[d]	58	49	84
3			B[d]	55	53	96
4			B[e]	100	93	93
5			B[e]	70	67	96
6			A[d]	71	68	96
7			B[e]	63	58	92
8			B[e]	100	>99	99
9			B[e]	100	>99	99

[a] Conditions: 2 mmol substrate, 20 mol% dry $K_4[Fe(CN)_6]$, 10 mol% CuI, 2 mL solvent, 200 μL tetradecane (internal standard for GC), 16 h.
[b] Method A: 200 mol% 1-butylimidazole, toluene as solvent, Method B: 1-methylimidazole as solvent.
[c] Determined by GC; average of two parallel experiments.
[d] At 160 °C.
[e] At 140 °C.

and the increased hydrolysis of the nitrile, which is catalyzed by free imidazole (Table 1, entry 6). Noteworthy, other typical nitrogen ligands like pyridine or 2,2′-bipyridine gave only low yields of 5-cyanopyrimidine (<17%, Table 1, entries 7 and 8). The same holds true for 1-methylpyrazole, *N*-methylpyrrole, and benzothiazole (Table 1, entries 9–11), although they are structurally related to 1-methylimidazole.

The new protocol was also compared to previous state-of-the-art catalytic cyanations (Table 1, entry 12). By means of palladium catalysis the desired product is not obtained. This clearly demonstrates the advantage of the novel catalyst.

To demonstrate the generality, nine different nitrogen-, oxygen-, and sulfur-containing bromoheterocycles were tested in the Cu-catalyzed cyanation applying imidazoles as ligand or solvent (Table 2). It is noteworthy that most of the substrates have not been described previously in metal-catalyzed cyanations. Both electron-poor (e.g. pyridines, thiazoles) and electron-rich (e.g. furans and indoles) substrates gave good to very good yields and high chemoselectivity. Substrates with primary amino groups, which did not react to the corresponding aryl nitriles in the presence of palladium catalysts in our hands, also gave smoothly the desired products (Table 2, entries 3 and 4). The same is true for N-heterocycles with a bromo substituent in 2-position, like 2-bromothiazole and 2-bromopyridine (Table 2, entries 8 and 9).

In summary, we have developed a novel protocol for the cyanation of heteroaryl bromides. Using biomimetic Cu/imidazole catalysts an easy and practical synthesis of the corresponding nitriles is possible. Typically, it is not necessary to exclude moisture or air. This novel procedure seems to be the most environmentally benign and general cyanation protocol for heteroaryl bromides known to date.

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(21) Initial amination reactions of bromobenzenes in the presence of Cu/1-butylimidazole showed that these catalysts are also active for other coupling reactions.
(22) All chemicals are commercially available and were used without further purification. Products were fully characterized after isolation (NMR, IR, MS, EA) or in the case of commercially available products by comparison of GCMS data.
General Procedure: First, $K_4[Fe(CN)_6]\cdot 3H_2O$ is ground to a fine powder and dried in vacuum (ca. 2 mbar) at 80 °C overnight. Then, 0.4 mmol dry $K_4[Fe(CN)_6]$, 0.2 mmol copper precursor, the additive, and 2 mmol aryl halide are placed in a pressure tube under argon. Afterwards, 200 μL tetradecane (internal standard for GC) and 2 mL solvent are added. The pressure tube is sealed and heated for 16 h at the temperature specified in Table 1 and Table 2. After cooling to r.t., 3 mL CH_2Cl_2 are added and the mixture is analyzed by GC. Conversion and yield are calculated as an average of two parallel runs. For isolation of the products the reaction mixture is washed with H_2O and the organic phase is dried over Na_2SO_4. After evaporation of the solvents the residue is subjected to column chromatography (silica, hexane–EtOAc). All prepared nitriles are known compounds and identified by comparison with commercially available materials.
Analytical data of 5-cyanopyrimidine: ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.42 (s, 1 H), 9.04 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 160.5, 159.5, 114.0, 110.2.