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CuI/1,10-phenanthroline: An efficient catalyst system for the cyanation of aryl halides

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Aryl nitriles have been prepared in good yields from the corresponding aryl halides with potassium hexacyanoferrate(II) using CuI/1,10-phenanthroline as the catalyst system. Furthermore, the reaction is compatible with a wide range of functional groups including nitro and carbonyl substituents.

Keywords: copper(I) catalysis, 1,10-phenanthroline, cyanation, potassium hexacyanoferrate(II), aryl nitrile

Aryl nitriles are of considerable interest as an integral part of pharmaceuticals, herbicides, natural products and dyes.[1] In addition, nitriles play a crucial role as they can be easily converted into a variety of functional groups such as acids, ketones, oximes and amines.[2]

In general, the most common and direct method for the introduction of the cyano group is via cyanation of the parent aryl halides. Since the discovery of transition metal catalysed cross-coupling reactions, a great deal of interest has been devoted to the development of a practical version of this transformation.[3] Until now, a number of successful palladium- and nickel-catalysed protocols have been reported.[4,5] However, the major disadvantages associated with the broad application of currently known palladium- and nickel-catalysed protocols are the high cost of these metals and the need for using expensive and toxic phosphines as ligands. This makes the development of methods using Cu catalysts quite attractive.

Until now, most of the work has concentrated on the inconvenient traditional cyanide sources such as alkali cyanides,[2b] zinc cyanide, trimethylsilyl cyanide, and acetone cyanohydrin. However, these cyanide sources all have some severe drawbacks. In order to avoid these problems, potassium hexacyanoferrate(II) was rediscovered as a non-toxic cyanide source by Beller.[4g] Nevertheless, only two reports described the cyanation catalysed by Cu catalysts using potassium hexacyanoferrate(II) as cyanide source.[6,7] Although applying $Cu(BF_4)_2{\cdot}6H_2O$ and *N*,*N*'-dimethyl ethylenediamine (DMEDA) as the catalyst system was reported, the process used KI as additive to make the cyanation work effectively.[6] Subsequently, Beller and co-workers demonstrated CuI/*N*-alkylimidazole as the catalyst system for the cyanation of heteroaryl halides without the use of KI as additive.[7] However, two equivalents of ligand (*N*-alkylimidazole) was needed in the reaction. Very recently, 1,10-phenanthroline and its derivatives as ligands have been successfully used in copper-catalysed coupling reactions.[8] To further expand easier and safer methods for cyanation reactions, nontoxic copper(I)-catalysed cyanation can still attract current interest. Herein, our efforts have shown that the cyanation of aryl halides with $K_4[Fe(CN)_6]$ can be efficiently catalysed by CuI in the presence of 1,10-phenanthroline.

As a starting point for the development of our cyanation system, the reaction of bromobenzene with $K_4[Fe(CN)_6]$[9] was investigated. Variation of reaction conditions on this model reaction is shown in Table 1. The reaction was first attempted using 3 mmol bromobenzene, 40 mol% dry $K_4[Fe(CN)_6]$, 1.0 equivalent of Na_2CO_3, 10 mol% CuI, 20 mol% KI, 0.8 equivalent of 2,2'-bipyridine (BIPY) as the ligand in DMAc. A moderate yield of 50% of benzonitrile was obtained (entry 1). Using 1,10-phenanthroline (1,10-phen) as ligand led to a similar effect (entry 2). Other ligands, such as *N*,*N*,*N*',*N*'-tetramethyl ethylenediamine (TMEDA) and 1,4-diazabicyclo[2.2.2]octane (DABCO) have also been employed in this reaction and none of them gave a higher yield than BIPY and 1,10-phen (entries 3 and 4). A blank test without ligand afforded benzonitrile only in a poor yield of 11% (entry 5), which suggested that the ligand was the key factor in obtaining the corresponding aryl nitriles. When 20 mol% of CuI was used, a good yield of 75% of benzonitrile was obtained (entry 6). Attempts to add PEG-400 decreased the product yield (entries 7 and 8). To our surprise, cyanation without additive also gave a similar yield to the cyanation using 20 mol% KI as additive (entry 9). This catalyst system was unlike previously reported

Table 1 Evaluation of various reaction conditions[a]

Entry	Cu/mol%	Ligand[b]	Additive/mol%	Yield/%[c]
1	CuI(10)	BIPY	KI(20)	50
2	CuI(10)	1,10-phen	KI(20)	51
3	CuI(10)	TMEDA	KI(20)	7
4	CuI(10)	DABCO	KI(20)	Trace
5	CuI(10)	–	KI(20)	11
6	CuI(20)	1,10-phen	KI(20)	75
7	CuI(20)	1,10-phen	PEG-400(20)	55
8	CuI(20)	1,10-phen	PEG400(20), KI(20)	35
9	CuI(20)	1,10-phen	–	75
10	CuI(20)	BIPY	–	54
11[d]	CuI(20)	1,10-phen	–	85
12[d]	CuCl(20)	1,10-phen	–	26
13[d]	CuBr(20)	1,10-phen	–	39
14[d]	Cu_2O(10)	1,10-phen	–	41
15[d]	Cu (20)	1,10-phen	–	40

[a] Reaction conditions: 3.0 mmol bromobenzene, 40 mol% dry $K_4[Fe(CN)_6]$, 5 ml DMAc, 100 mol% Na_2CO_3, 140°C, 24 h.

[b] 80 mol%; BIPY = 2,2'-bipyridine, 1,10-phen = 1,10-phenanthroline, TMEDA = N,N,N',N'-tetramethyl ethylenediamine, DABCO = 1,4-diazabicyclo[2.2.2]octane.

[c] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

[d] 60 mol% dry $K_4[Fe(CN)_6]$ was used.

Table 2 Cyanation of bromobenzene in the presence of different bases and solvents[a]

Entry	Base	Solvent	Yield/%[b]
1	Na_2CO_3	DMAc	85
2	K_2CO_3	DMAc	51
3	KOH	DMAc	13
4	CH_3COONa	DMAc	41
5	CH_3CH_2ONa	DMAc	Trace
6	*t*-BuOK	DMAc	12
7	HCOONa	DMAc	13
8	$K_3PO_4{\cdot}3H_2O$	DMAc	30
9	KF	DMAc	55
10	Na_2CO_3	DMF	67
11	Na_2CO_3	NMP	63

[a] Reaction conditions: 3.0 mmol bromobenzene, 60 mol% dry $K_4[Fe(CN)_6]$, 20 mol% CuI, 5 ml solvent, 100 mol% base, 80 mol% 1,10-phen, 140°C, 24 h.

[b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

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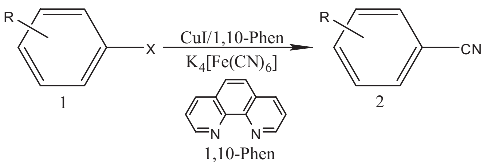
Table 3 Copper-catalysed cyanation of various aryl halides[a]



Entry	Ar-X **1**	Yield/%[b] of **2**
1	β-bromonaphthalene	83 (78)
2	*p*-$CH_3COC_6H_4Br$	85 (81)
3	*p*-FC_6H_4Br	81
4	*p*-$O_2NC_6H_4Br$	80 (72)
5	*p*-$CF_3C_6H_4Br$	81 (75)
6	*m*-$CF_3C_6H_4Br$	83
7	*p*-$CH_3C_6H_4Br$	78
8	*p*-$CH_3OC_6H_4Br$	61 (53)
9	*o*-$CH_3OC_6H_4Br$	52
10	*p*-$H_2NC_6H_4Br$	47
11	C_6H_5I	99
12	*o*-$CH_3C_6H_4I$	99 (92)
13	*m*-$CH_3C_6H_4I$	96
14	*p*-$CH_3C_6H_4I$	99 (93)
15	*o*-$O_2NC_6H_4I$	84
16	*p*-$O_2NC_6H_4I$	87 (76)
17[c]	*p*-$CF_3C_6H_4Cl$	Trace

[a]Reaction conditions: 3.0 mmol aryl halide, 20 mol% CuI, 60 mol% dry $K_4[Fe(CN)_6]$, 5 ml DMAc, 100 mol% Na_2CO_3, 80 mol% 1,10-phen, 140°C, 24 h.

[b]Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard. Numbers in parentheses show isolated yields. All prepared benzonitriles are commercially available.

[c]The nitrile was not observed even after 36 h (150°C).

procedures where KI was needed to make the cyanation work effectively.[3b,6,8a] However, using BIPY as a ligand we could not obtain a higher yield under the same conditions (entry 10). Increasing the amount of $K_4[Fe(CN)_6]$ to 60 mol% led to benzonitrile in up to 85% yield (entry 11). While several Cu catalysts were screened for the cyanation (entries 12–15) CuI was confirmed to be the most effective catalyst for this cyanation.

The influences of bases and solvents on the cyanation of bromobenzene were also investigated (Table 2). It was found that the base played an important role in the reaction. Na_2CO_3 proved to be the most efficient (entry 1). Other bases such as K_2CO_3, KOH, CH_3COONa, CH_3CH_2ONa, *t*-BuOK, HCOONa, $K_3PO_4{\cdot}3H_2O$, and KF, were less effective (entries 2–9). In addition, a switch in the solvent to DMF or NMP did not bring about better results (entries 10, 11).

To expand the scope of the copper-catalysed cyanation system, a variety of aryl halides were used under the optimised condition (Table 3). Very efficient transformation of *β*-bromonaphthalene (entry 1) and aryl bromides with electron-withdrawing groups (entries 2–6) was observed under the reaction conditions. Substrates with electron-donating groups such as methyl, amino, and methoxy exhibited somewhat diminished yields of the corresponding products (entries 7–10).

Then aryl iodides were also used to carry out this copper-catalysed cyanation. Aryl iodides all provided products in good to excellent yields (entries 11–16). However, substrates with a nitro group substituent gave lower yields due to the dehalogenation of aromatic iodides.

Inspired by these results, we attempted to extend the method to a less reactive aryl chloride. Unfortunately, the reactivity of this copper-catalysed system was insufficient to drive the reaction to occur even at higher reaction temperature and prolonged reaction time (entry 17).

To conclude, we report a copper(I)-catalysed method for the cyanation of aryl bromides and iodides using potassium hexacyanoferrate(II). The cyanide source is non-toxic and inexpensive. Furthermore, this protocol is palladium-free and avoids the use of expensive and/or air-sensitive ligands. A variety of aryl halides give the corresponding benzonitriles in good to excellent yields.

Experimental

General procedure for the cyanation of aryl halides: After standard cycles of evacuation and filling with dry and pure nitrogen, an oven-dried tube was charged with CuI (0.6 mmol), 1,10-phenanthroline (2.4 mmol), Na_2CO_3 (3 mmol), aryl halide (3 mmol) and DMAc (5 ml). The tube was evacuated and filled with nitrogen. Then the tube was sealed and the mixture was stirred at 140°C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 ml) and filtered. Then 1,3-dimethoxybenzene (400 µl) was added as the internal standard for chromatography. The filtrate was washed with water (3 × 15 ml) and analysed by gas chromatography. The GC yields were determined by obtaining correction factors using authentic samples of the expected products.

For isolating the products: After the reaction was completed, the mixture was diluted with ethyl acetate (30 ml) and filtered. The filtrate was washed with water (3 × 15 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Finally, the product was isolated by flash chromatography on silica gel with EtOAc–petroleum ether as the eluent. All prepared benzonitriles are known commercial compounds and were identified by GC–MS.

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9 $K_4[Fe(CN)_6]{\cdot}3H_2O$ is ground to a fine powder and dried under a high vacuum at 80°C overnight.