Mild and Efficient Copper-Catalyzed Cyanation of Aryl Iodides and Bromides

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In memory of Dr. Gennady Vasilievich Dolgushin, Head of the Organic Synthesis Laboratory of A. E. Favorsky Irkutsk Institute of Chemistry

Abstract: An efficient copper-catalyzed cyanation of aryl iodides and bromides is reported. Our system combines catalytic amounts of both copper salts and chelating ligands. The latter, which have potential nitrogen- and/or oxygen-binding sites, have never previously been used in this type of reaction. A protocol has been developed that enables the cyanation of aryl bromides through the copper-catalyzed in situ production of the corresponding aryl iodides using catalytic amounts of potassium iodide. Aryl nitriles are obtained in good yields and excellent selectivities in relatively mild conditions (110 °C) compared with the Rosenmund–von Braun cyanation reaction. Furthermore, the reaction is compatible with a wide range of functional groups including nitro and amino substituents. The protocol reported herein involves two main innovations: the use of catalytic amounts of ligands and the use of acetone cyanohydrin as the cyanating agent in copper-mediated cyanation reactions.

Keywords: acetone cyanohydrin · aryl halides · copper · cyanation · homogeneous catalysis

Introduction

Aryl nitriles are stable and valuable intermediates in organic synthesis because of the versatile transformations of the nitrile function.[1] Thus they constitute building blocks for the synthesis of biologically active molecules,[2] polyamides,[3] and metallophthalocyanine precursors.[4] Moreover aryl and heteroaryl nitriles are present in numerous dyes, agrochemicals[5] and pharmaceuticals.[6]

Various methods for the synthesis of aryl nitriles have been reported. One of the most convenient is based on the transition-metal-mediated displacement of aromatic halides by the cyanide ion.[7]

Cassar[8] and Sakakibara[9] and their co-workers used nickel complexes as catalysts in the cyanation of aryl bromides and chlorides with sodium cyanide, potassium cyanide or acetone cyanohydrin. The preparation of aromatic nitriles from aryl halides using nickel salts in conjunction with microwave irradiation has also been recently described.[10] The usefulness of this reaction is however limited because of the high cost and toxicity of the equimolar amounts of nickel derivatives that are required.

Palladium-catalyzed cyanodehalogenation of aryl halides has also been reported.[11] Palladium catalysts are in general more tolerant towards a variety of functional groups than nickel ones but suffer from poor reliability. Sodium and potassium cyanide are generally used as cyano group sources[12] but many variants have been developed: zinc cyanides,[13] trimethylsilyl cyanides,[14] tributyltin cyanides,[15] dialkylcyanoboronates,[16] copper cyanide[17] and potassium hexacyanoferrate(II)[18] can also promote the cyanation of aryl halides to afford the corresponding aryl nitriles. Interestingly, the use of acetone cyanohydrin, already known to be a suitable cyanating agent in the nickel-catalyzed cyanation of aryl halides, has recently been extended to reactions that involve palladium as the catalyst.[19] However, the high cost of this metal and the need to use expensive and toxic phosphines as ligands make the development of methods involving other metals quite attractive.

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Finally, the direct reaction between aryl halides and copper cyanides to give the corresponding aryl nitriles (the Rosenmund–von Braun reaction) has been known for over 80 years since the work of Pongratz.[7,20] This method requires both stoichiometric quantities of CuCN and high reaction temperatures (>150 °C). Furthermore product isolation is complicated by the need to separate the resulting copper halide. Recently aryl cyanides have been obtained at lower temperatures (90–130 °C) in ionic liquids and from aryl iodides in the presence of either two equivalents or catalytic amounts of CuCN.[21] However, the isolated yields are moderate because of the difficulty of isolating the nitriles. Cyanation of aryl halides with an excess or at least stoichiometric amounts of CuCN has also been achieved by microwave-heating in water[22] or in DMSO.[23] The copper-catalyzed cyanation of aryl- and heteroaryl bromides in toluene at around 110–130 °C has also been reported.[24] However, this method requires the use of a ten-fold amount of the rather expensive ligand *N*,*N*′-dimethylethylenediamine relative to the copper salt. This feature is thus less attractive for large-scale applications. As a consequence, the search for more practical methods involving copper catalysis appear necessary to meet the demands of contemporary chemical synthesis, that is, less waste and the use of catalytic processes wherever possible. We report herein our contribution to this search, presenting a method for the copper-catalyzed cyanation of aryl halides which has two main innovations: 1) the use of catalytic amounts of not only the copper precatalyst but also of the ligand and 2) the use of acetone cyanohydrin as the cyanide source. To the best of our knowledge acetone cyanohydrin has until now only been employed in nickel- or palladium-catalyzed cyanation reactions.

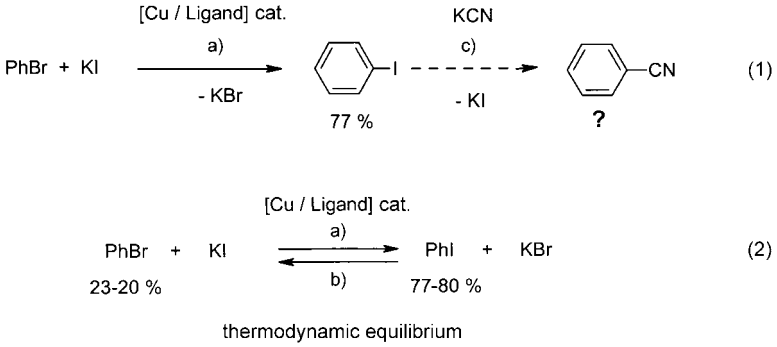
In a previous paper we presented a general and efficient method for the *N*-arylation of pyrazoles with aryl bromides and iodides that involved the use of inexpensive copper-based catalytic systems.[25] We noticed that bi-, tri- or tetradentate ligands with nitrogen and/or oxygen chelating atoms considerably accelerate the copper-catalyzed arylation reactions of pyrazoles. Aryl- or heteroarylpyrazoles were thus obtained with high yields and selectivities under extremely mild conditions. We also reported that phenols,[26] amides, carbamates, nitrogen heterocycles and malonic acid derivatives[27] can be arylated at moderate temperatures with similar catalytic systems.[28] In this report we extend the scope of such catalytic systems to the cyanation of aryl iodides and bromides.

Results and Discussion

Copper-catalyzed cyanation of iodobenzene: In a preliminary set of experiments performed in DMF as solvent, we investigated the cyanation of iodobenzene in the presence of copper(I) catalysts (10 mol% CuI or 5 mol% Cu_2O) and catalytic amounts of a set of bi-, tri- or tetradentate ligands (Figure 1). These additives comprise only nitrogen-binding sites (ligands **1**, **2**, **4**, and **6**) or combine nitrogen- and oxygen-binding sites (ligands **3**, **5**, **7**, and **8**). In all cases, the yields were not affected by the nature of the copper precatalyst, either cuprous iodide or cuprous oxide. In contrast, the nature of the ligand significantly influenced the efficiency of the catalytic system since after 24 h yields of benzonitrile ranged from 48 to 94%. We identified five ligands with various structural features (**1**–**5**) that promote the arylation reaction with yields in excess of 75%. Ligand **1** comprises two pyridine-type binding sites, whereas **2** and **4** combine both pyridine- and imine-type binding sites. Oxime-type ligand **3** and ligand **5** combine nitrogen and oxygen as potential chelating atoms.

In the following experiments, we focused our attention on 1,10-phenanthroline (1,10-phen, **1**) and *N*,*N*-dimethyl-*N*′-pyridin-2-ylmethyleneethane-1,2-diamine (Dmeda-Py-Al, **2**), which promote the arylation reaction to give yields of 94 and 83%, respectively. Since benzonitrile can be obtained from iodobenzene in an excellent yield, we decided to extend our methodology to the cyanation of less expensive and more challenging aryl bromides.

Copper-catalyzed cyanation of bromobenzene: The reaction conditions used in the cyanation of iodobenzene were applied to the cyanation of bromobenzene. At first the cross-coupling reaction failed. However we overcame this problem and obtained aryl nitriles through the catalyzed production of iodobenzene from bromobenzene and iodide salts and its subsequent in situ cyanation.[29] We first checked that displacement of the bromide ion by the iodide ion took place under the conditions used in the cyanation of iodobenzene when using 1,10-phen **1** as the ligand (Scheme 1, [Eq. (1)], a)). The rapid formation of iodobenzene was indeed observed, 55% of bromobenzene being converted during the first four hours of the reaction.



Scheme 1. Cyanation of bromobenzene: halide exchange followed by in situ cyanation of iodobenzene. General conditions: a) PhBr (0.5 mmol), KI (0.5 mmol), CuI (0.05 mmol), **1** (0.10 mmol), DMF (300 μL), 48 h, 110 °C; b) PhI (0.5 mmol), KBr (0.5 mmol), CuI (0.05 mmol), **1** (0.10 mmol), DMF (300 μL), 48 h, 110 °C; c) KCN yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

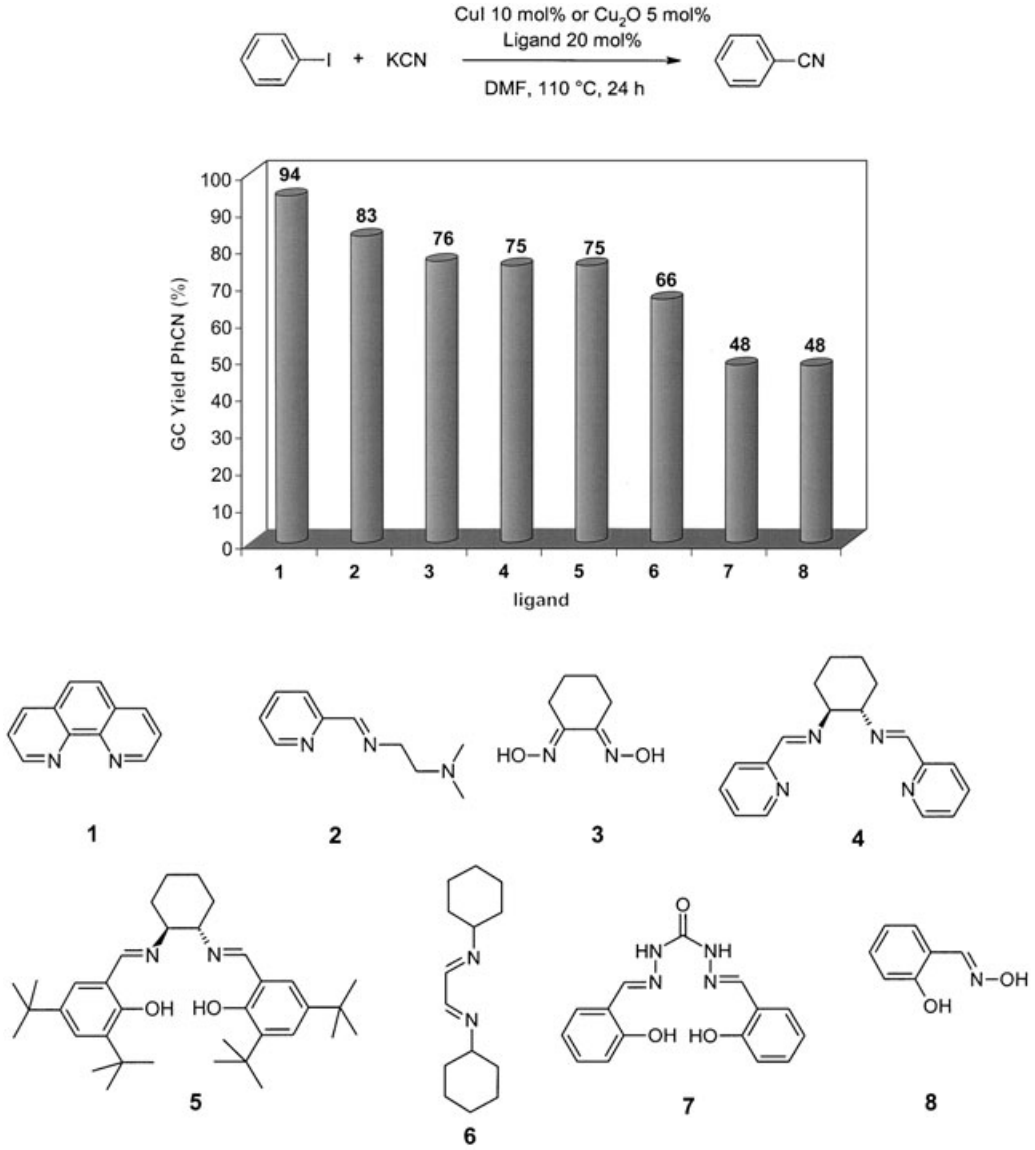
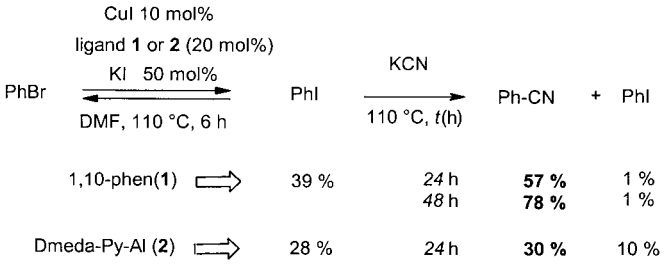


Figure 1. Effect of various ligands on the copper-catalyzed coupling reaction of potassium cyanide and iodobenzene. General conditions: iodobenzene (0.5 mmol), potassium cyanide (0.55 mmol), CuI (0.05 mmol), ligand (0.10 mmol), DMF (300 μL), 24 h, 110 °C. Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

We also demonstrated (Scheme 1, [Eq. (2)]) that the final composition was the same when starting from either an equimolar mixture of bromobenzene and potassium iodide (a) or an equimolar mixture of iodobenzene and potassium bromide (b): the final mixture was composed of about 20% PhBr and 80% PhI. Note that these results are in agreement with the existence of a thermodynamic equilibrium between the two aromatic halides.[30] Therefore it was expected that the addition of cyanide ion, which would trap iodobenzene, would allow the formation of benzonitrile with the simultaneous regeneration of potassium iodide (Scheme 1, [Eq. (1)], c)). As a consequence catalytic amounts of KI might be sufficient to promote the cyanation of PhBr.

The cyanation was first performed as a one-pot reaction: bromobenzene, potassium cyanide (1.1 equiv), copper iodide (0.1 equiv), ligand (0.2 equiv), potassium iodide (0.5 equiv), and solvent (DMF) were introduced simultaneously. Unfortunately, neither halide exchange nor cyanation took place under these conditions. However, this was not surprising because deactivation of nickel- or palladium-based catalytic systems by an excess of dissolved cyanide is a well-known phenomenon.[9b,12k,13h,14b,19]

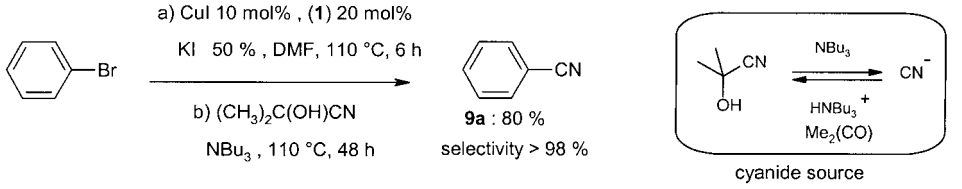
KCN was then introduced into the reaction mixture only once a sufficient quantity of PhI had been generated. During the first stage, bromobenzene was converted into iodobenzene by using potassium iodide (0.5 equiv) in the presence of ligand **1** or **2** (Scheme 2). The composition of both reaction mixtures before the addition of KCN, given in Scheme 2, shows that the halide exchange is quicker with **1** as ligand than with **2**. In the second stage KCN was intro-



Scheme 2. Cyanation of PhBr by using potassium cyanide after halide exchange. General conditions: bromobenzene (0.5 mmol), potassium iodide (0.25 mmol), CuI (0.05 mmol), ligand (0.10 mmol), DMF (300 μL), 6 h, 110 °C and then addition of potassium cyanide (0.55 mmol). Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard. It was arbitrarily decided to add KCN after 6 h and this reaction time has not been optimized.

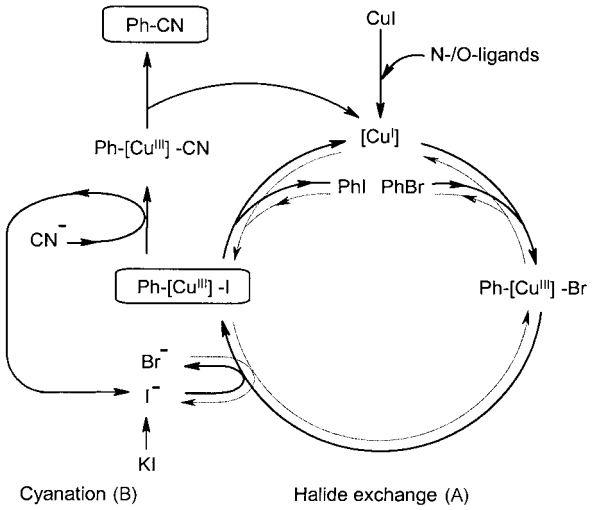
duced to allow cyanation of the iodobenzene previously generated. Note that halide exchange also occurred during the cyanation reaction since the yields of PhCN are higher than the yields of PhI estimated before the addition of KCN. The process being faster in the presence of **1** than with **2**, we therefore focused our attention on 1,10-phen in the following experiments.

Thus, this protocol allows the synthesis of benzonitrile from bromobenzene in a satisfying yield (78%) after 48 h at 110 °C. Moreover, the selectivity was excellent (99%) since the only by-product detected by GC was iodobenzene. However, it is not easy to add KCN, which is a solid that is only slightly soluble in DMF, to the reaction mixture at 110 °C. The use of a liquid cyanation agent, acetone cyanohydrin, was therefore investigated (Scheme 3). This cyanation reagent, used in the presence of a base, is cheap, commercially available on an industrial scale,[19,31] and, to the best of our knowledge, it has never been used in copper-catalyzed cyanation reactions.



Scheme 3. Cyanation of PhBr with acetone cyanohydrin. General conditions: bromobenzene (0.5 mmol), potassium iodide (0.25 mmol), CuI (0.05 mmol), ligand **1** (0.10 mmol), DMF (300 μL), 6 h, 110 °C followed by addition of acetone cyanohydrin (0.55 mmol) and tributylamine (0.6 mmol). Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

As in the case of KCN, the introduction of acetone cyanohydrin and tributylamine to the reaction mixture at the start of the reaction led to deactivation of the catalyst since halide exchange did not occur. This difficulty was once again overcome by delaying the addition of the cyanation reagent (Scheme 3). Benzonitrile was successfully obtained from bromobenzene with a yield of 80% and an excellent selectivity (>98%). A possible mechanism for this reaction is presented in Scheme 4.



Scheme 4. Mechanism proposed for the halide exchange–cyanation process.

Cycle A: This cycle corresponds to the thermodynamic equilibrium between aryl bromide and aryl iodide. The first step involves the oxidative addition of bromobenzene to the catalytically active copper species [Cu^{I}] which is proposed to be a copper(I)–ligand complex.[27] The resulting copper(III) intermediate (Ph–[Cu^{III}]–Br) undergoes nucleophilic substitution of the copper-bound bromide by an iodide ion from potassium iodide to give Ph–[Cu^{III}]–I. The third step involves the reductive elimination of iodobenzene and the subsequent regeneration of the active copper(I) species.

Cycle B: This cycle involves cyanohydrin and describes the synthesis of benzonitrile itself. In the first step the copper(III) intermediate (Ph–[Cu^{III}]–I) is trapped by the cyanide ion, thus displacing the equilibrium between PhBr and PhI in cycle A. The resulting product Ph–[Cu^{III}]–CN then allows, by reductive elimination, the formation of the expected benzonitrile and the regeneration of the active copper species [Cu^{I}]. The cyanide ion is generated in situ from both cyanohydrin and tributylamine and then consumed according to the availability of the intermediate Ph–[Cu^{III}]–I. Another interesting feature of our protocol is the regeneration of the iodide ion (cycle B). Only 0.5 equivalents (based on the bromobenzene) of potassium iodide were used. A lower loading of KI is possible but a decrease in the reaction rate is observed.

As briefly mentioned above, the deactivation of catalysts by an excess of dissolved cyanide ions has already been demonstrated in the nickel- and palladium-mediated cyanation of aryl bromides and chlorides.[9b,12k,13h,14b,19] Several methods to avoid such poisoning have been proposed in the

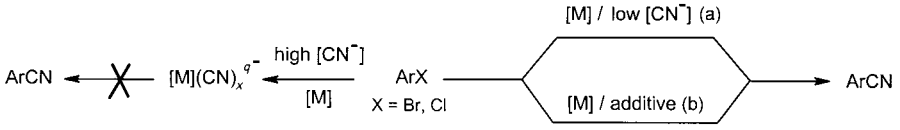
literature (Scheme 5). As with nickel-based catalysts, the use of solvents with lower cyanide solubility permitted the cyanation of heteroaromatic halides to proceed.[9b] In palladium-mediated cyanation reactions, a method involving the continuous addition of the cyanation agent (acetone cyanohydrin[19] or trimethylsilyl cyanide (TMSCN)[14b]) to the reaction mixture was proposed for the cyanodehalogenation of aryl halides. The aim of both of these protocols was to keep the concentration of dissolved cyanide ions low to prevent poisoning of the catalyst. The addition of a further reagent can also prevent inhibition of the active catalyst. For example, the use of zinc acetate allowed the palladium-catalyzed cyanation of aryl bromides; however the role of this additive is not yet clearly understood.[13h] The use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) or 1,1′-methylenedipiperidine (MDP) as co-catalyst has also been reported. These amines should be able to substitute cyanide ions on the palladium center, thus allowing the cyanation of aryl bromides and chlorides.[12k,14b,19] Similarly, the recently reported copper-catalyzed cyanation of aryl bromides seemed to require ten-fold more of the ligand *N*,*N*′-dimethylethylenediamine (DMEDA) than the copper salt.[24] These unusual reaction conditions may be aimed at countering the binding of cyanide ions to copper in order to avoid catalyst deactivation.

We have demonstrated that high concentrations of cyanide ions did not prevent the copper-catalyzed cyanation of iodobenzene, benzonitrile being quantitatively obtained even though cyanide ions were present from the start of the reaction (Figure 1). Since the cyanation of bromobenzene did not take place under the same reaction conditions, we considered obtaining the corresponding aryl nitrile by the catalyzed production of iodobenzene from bromobenzene and potassium iodide. However, we noticed that introduction of the cyanating agent (potassium cyanide or cyanohydrin) from the beginning of the reaction prevented the halide exchange from taking place. To explain this phenomenon we assumed that copper(I)–cyanide complexes $[Cu](CN)_x^{(1-x)-}$ ($x=1$–4), which should not promote the oxidative addition of bromobenzene, were formed in situ. The affinity of copper(I) for cyanide ions has indeed already been reported.[32] Such complexes would be formed to the detriment of the active copper species [Cu^I] (Scheme 4, cycle A). Thus we overcame the poisoning of our copper-based catalyst by introducing the cyanide source once a sufficient amount of iodobenzene and/or intermediate Ph–[Cu^{III}]–I had been generated in the reaction mixture. As a consequence, the cyanide ions should essentially be used to cyanate the previously formed iodobenzene (Scheme 4, cycle B). The resulting decrease in the concentration of the cyanide ions should thus limit the formation of $[Cu](CN)_x^{(1-x)-}$ complexes, whereas the number of copper species able to afford oxidative addition of bromobenzene to [Cu^I] should increase thus enabling halogen exchange followed by cyanation (Scheme 4). Note that our protocol allowed the cyanide source to be introduced at once without requiring the addition of a further reagent to avoid poisoning.

Copper-catalyzed cyanation of substituted aryl bromides: We were interested in applying our catalytic system to the cyanation of a variety of aryl halides. It has been shown that acetone cyanohydrin can quantitatively convert iodobenzene into benzonitrile in DMF after 48 h at 90 °C. We then focused our attention on more challenging aryl bromides. Thus the cyanation of aryl bromides substituted with different electron-donating and -withdrawing groups was investigated by using acetone cyanohydrin in the presence of catalytic amounts of copper, ligands and potassium iodide (Table 1). Note that to facilitate the isolation of the aryl nitriles, tributylamine can be replaced by a more volatile tertiary amine (diisopropylethylamine, for example), which can be removed more easily from the crude mixture before purification by column chromatography.

The expected aryl nitriles were synthesized whatever the nature of the substituent and the rates of the reactions were not significantly affected by electronic effects. Thus very good yields of aryl nitriles were obtained from the electron-poor *p*-bromobenzotrifluoride, *m*-nitrobromobenzene or *p*-bromoacetophenone (Table 1, entries 2, 5 and 7) and also from the electron-rich *p*-methylbromobenzene and *m*-methoxybromobenzene (Table 1, entries 6 and 8).

In these examples, with the exception of the nitro substituent, cyanation was totally selective with respect to the cyanide ion and almost totally selective with respect to the aryl bromides. Indeed, the only by-products detected by GC

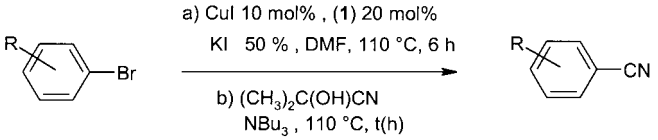


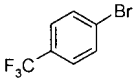
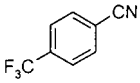
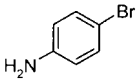
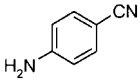
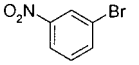
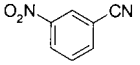
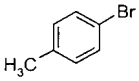
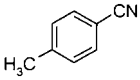
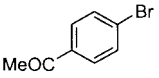
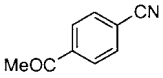
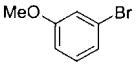
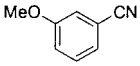
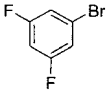
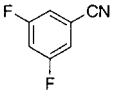
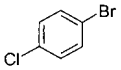
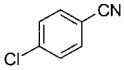
a): - Ni / solvent with low cyanide solubility[9b]
- Pd / continuous addition of cyanohydrin[19] or TMSCN[14b] on ArX in excess

b): - Pd / $Zn(OAc)_2$ (1:15)[13h]
- Pd / TMEDA or MDP (1:10)[12k]
- Cu / DMEDA (1:10)[24]

Scheme 5. Reported methods that avoid the deactivation of catalysts by an excess of dissolved cyanide ions.

Table 1. Cyanation of substituted aryl bromides with acetone cyanohydrin using catalytic amounts of potassium iodide.[a]



Entry	ArX	ArX		Time [h]	Yield [%][b]	Selectivity [%][c]
1			**9a**	48 60	80 90 (88)	98 99
2			**9b**	48 60	85 94 (87)	97 99
3			**9c**	48	100 (98)	100
4			**9d**	48 60	83 98 (70)	97 >99
5			**9e**	48 60	82 81 (75)	88[d] 85[e]
6			**9f**	48 60	74 89 (80)	96 99
7			**9g**	48 60	92 100 (96)	99 100
8			**9h**	48 60 70	62 81 (79) 97	97 97 >99
9			**9i**	48 60	66 98 (94)	99 >99
10			**9j**	48 70	29 43 (40)	99 99
11[f]			**9j**	48[g]	98 (95)	>99
12			**9k**	48 60	86 96 (86)	97 99

[a] General conditions for GC yields: aryl bromide (0.5 mmol), potassium iodide (0.25 mmol), CuI (0.05 mmol), ligand **1** (0.10 mmol), DMF (300 μL), 6 h, 110 °C followed by in situ addition of acetone cyanohydrin (0.55 mmol) and tributylamine (0.6 mmol). General conditions for isolated yields: aryl bromide (5 mmol), potassium iodide (2.5 mmol), CuI (0.5 mmol), ligand **1** (1.0 mmol), DMF (3 mL), 6 h, 110 °C followed by in situ addition of acetone cyanohydrin (5.5 mmol) and diisopropylethylamine (6.0 mmol). [b] Yields refer to GC yields (using 1,3-dimethoxybenzene as internal standard) and yields in parentheses refer to isolated yields; yields are given with respect to aryl bromides. [c] Selectivities are given with respect to aryl bromides. With the exception of entry 5, only negligible amounts of one by-product (the corresponding aryl iodide) are observed. [d] By-products: 3.5 % of $PhNO_2$ and 2.5 % of *p*-$NH_2C_6H_4CN$. [e] By-products: 10.0 % of $PhNO_2$ and 3.5 % of *p*-$NH_2C_6H_4CN$. [f] General conditions: 2-iodotoluene (0.5 mmol), potassium iodide (0.25 mmol), CuI (0.05 mmol), ligand **1** (0.10 mmol), acetone cyanohydrin (0.55 mmol), tributylamine (0.6 mmol) and DMF (300 μL). [g] The reaction time and the temperature were not optimized.

were small amounts of aryl iodides corresponding to the aryl bromides used. Hydrodehalogenation never occurred during the reactions and by-products resulting from biaryl coupling were never observed. In the case of 3-nitrobromobenzene (Table 1, entry 5), small amounts of hydrodehalogenation ($C_6H_5NO_2$) and nitro-reduction ($BrC_6H_4NH_2$) products were detected but the selectivity of 88 % remains acceptable. Our copper-based catalytic system is therefore compatible with the nitro substituent, whereas nickel-catalyzed cyanation of nitro-substituted aryl halides failed.[9a] Note that the presence of an amino substituent also allows the synthesis of the corresponding nitrile in a very good yield and with excellent selectivity (>99 %) (Table 1, entry 4). Indeed the amino group itself is not arylated by aryl bromides under the conditions used.

The cyanation of *o*-bromotoluene was more troublesome and sluggish (40 % yield after 70 h at 110 °C, Table 1, entry 10). This lack of reactivity could be due to steric hindrance in the substrate. However, *o*-tolunitrile can be obtained in a quantitative yield from *o*-iodotoluene at 110 °C (Table 1, entry 11). The cyanation reaction has also been extended to heteroaryl bromides, for example, 2-bromopyridine is quantitatively and selectively converted into 2-cyanopyridine (Table 1, entry 3). Finally, differences in the reactivity of aryl halides in the oxidative addition to copper(I) active species can be exploited to obtain a monosubstituted product from reactions involving di- or trihalobenzenes (Table 1, entries 9 and 12). The cyanation of 4-chlorobromobenzene (Table 1, entry 12) and 3,5-difluorobromobenzene (Table 1, entry 12) took place exclusively at the bromine position.

Conclusions

To conclude, herein we propose a high-yielding, copper-catalyzed method for the cyanation of aryl iodides and bromides. Our catalytic system involves not only the use of catalytic amounts of copper salts but also catalytic amounts of ligands. Aryl nitriles were obtained from aryl bromides through the copper-catalyzed in situ production of the corresponding aryl iodides by using catalytic amounts of potassium iodide. Furthermore, we have shown

that acetone cyanohydrin can be used as a cyanating agent. To the best of our knowledge, copper-catalyzed cyanation with cyanohydrin has not been previously reported. This method avoids deactivation of the catalyst by cyanide ions. Finally, this protocol is practical on the laboratory scale and can easily be adapted to an industrial scale.[28d,31] We are currently working to extend the scope of our cyanation method to other aromatic compounds such as aryl triflates and especially aryl chlorides and the results will be reported in due course.

Experimental Section

General: Column chromatography was performed with SDS 60 A C.C silica gel (35–70 μm). Thin-layer chromatography was carried out with Merck silica gel 60 F_{254} plates. All products were characterized by analysis of their NMR, GC-MS and IR spectra. NMR spectra were recorded at 20 °C on Bruker AC 200, DRX-250 and DRX-400 spectrometers working respectively at 200.13, 250.13, and 400.13 MHz for ^{1}H, at 50.32, 62.90, and 100.61 MHz for ^{13}C and at 188.31, 236.36, and 376.50 for ^{19}F NMR spectroscopy. $CDCl_3$ was used as solvent unless otherwise stated. Coupling constants are reported in Hz and chemical shifts in ppm [relative to TMS for ^{1}H and $\{^1H\}^{13}C$ ($\delta = 77.00$ ppm for the *C*DCl_3 signal) and to $CFCl_3$ for $\{^1H\}^{19}F$]. The first-order peak patterns are indicated as s (singlet), d (doublet), t (triplet) and q (quadruplet). Complex non-first-order signals are indicated as m (multiplet) and broad signals as br. ^{13}C NMR signals were assigned by using HMQC and HMBC sequences. Gas chromatography-mass spectra (GC-MS) were recorded using an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and a HP5-MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm). GC-MS method: initial temperature, 45 °C; initial time, 2 min; ramp, 10 °C min^{-1}; final temperature, 250 °C; final time, 10 min. IR spectra were recorded with a Nicolet 210 FTIR instrument (neat, thin film for liquid products and KBr pellet or in carbon tetrachloride solution for solid products). FAB+ mass spectra were recorded with a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a *m*-nitrobenzyl alcohol matrix. Melting points were determined by using a Büchi B-540 apparatus and are uncorrected.

Materials

Caution: *Safety precautions must be taken with potassium cyanide and acetone cyanohydrin*. All reactions were carried out in 35 mL Schlenk tubes or in Carousel "reaction stations RR98030" Radley tubes under pure and dry nitrogen. DMF was distilled under vacuum from $MgSO_4$ and stored, protected from light, on 4 Å activated molecular sieves under nitrogen. KI (SDS) and KCN (Fluka) were ground to a fine powder. The former was stored under vacuum at 100 °C in the presence of P_4O_{10}. The latter was dried in vacuo and stored under nitrogen. All other solid materials were stored in the presence of P_4O_{10} in a bench-top desiccator under vacuum at room temperature and weighed in air. Copper(I) iodide was purified according to literature procedures[33] and stored protected from light. 1,10-Phenanthroline (ligand **1**) and salicylaldoxime (ligand **8**) were purchased from commercial sources. The latter was recrystallized in petroleum ether prior to use. The following ligands were synthesized according to or by adapting literature procedures: **3**,[34,35] **6**[36] and **7**.[37] The stereochemistry of oxime-type ligands **3** and **8** has not been determined. The syntheses of ligands **2** and **4** are reported below. All aryl halides, acetone cyanohydrin and amines (tributylamine or diisopropylethylamine) were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). Solids were recrystallized in an appropriate solvent[38] while liquids were distilled under vacuum and stored under nitrogen. Special care was taken with liquid aryl iodides: the samples were regularly distilled and stored protected from light. Amines were distilled from potassium hydroxide.

General procedure for the cyanation of aryl bromides (5 mmol scale): After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar was charged with CuI (95.2 mg, 0.5 mmol), 1,10-phenanthroline (181.2 mg, 1.0 mmol), KI (415.0 mg, 2.5 mmol) and the aryl bromide (5.0 mmol), if a solid. The tube was evacuated and back-filled with nitrogen. If a liquid, the aryl bromide was added by syringe under a stream of nitrogen at room temperature, followed by anhydrous and degassed DMF (3 mL). The tube was sealed under a positive pressure of nitrogen, and stirred and heated at 110 °C for six hours. Acetone cyanohydrin (502 μL, 5.5 mmol) and diisopropylethylamine (1.05 mL, 6.0 mmol) were then added by syringe at 110 °C and the reaction mixture was stirred for 60 h at this temperature. After cooling to room temperature, the mixture was diluted with diethyl ether (~50 mL) and filtered through a plug of Celite, the filter cake being further washed with diethyl ether (~10 mL). The filtrate was washed twice with water (2 × ~30 mL). The aqueous phases were combined and extracted twice with diethyl ether (~30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a brown oil. Excess of diisopropylethylamine was then distilled and the crude product obtained was purified by silica gel chromatography with hexanes and ethyl acetate as eluent.

General procedure for reactivity comparisons or screening of reaction conditions (0.5 mmol scale):

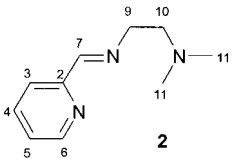
Cyanation of aryl bromides with acetone cyanohydrin: The above procedure was applied on a 0.5 mmol scale and by using tributylamine (143 μL, 0.6 mmol) instead of diisopropylethylamine. After heating for the required period of time, the reaction mixture was allowed to cool to room temperature and was diluted with diethyl ether (5 mL). 1,3-Dimethoxybenzene (65 μL) was then added as an internal standard. A small sample of the reaction mixture was taken and filtered through a plug of Celite, the filter cake being further washed with diethyl ether. The filtrate was washed three times with water and analyzed by gas chromatography. The GC yields were determined by obtaining correction factors using authentic samples of the expected products.

Cyanation of iodobenzene by KCN: After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar was charged with CuI (9.5 mg, 0.05 mmol), ligand (0.1 mmol) and KCN (35.6 mg, 0.55 mmol). The tube was evacuated and back-filled with nitrogen. Iodobenzene was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMF (300 μL). The tube was sealed under a positive pressure of nitrogen and stirred and heated at 110 °C for 24 h. The reaction mixture was allowed to cool to room temperature and was diluted with diethyl ether (5 mL). 1,3-Dimethoxybenzene (65 μL) was added as an internal standard. A small sample of the reaction mixture was taken and filtered through a plug of Celite, the filter cake being further washed with diethyl ether. The filtrate was washed three times with water and analyzed by gas chromatography. The GC yields were determined by obtaining the correction factor using an authentic sample of benzonitrile.

Cyanation of iodobenzene by acetone cyanohydrin: After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar was charged with CuI (9.5 mg, 0.05 mmol) and 1,10-phen (18.0 mg, 0.1 mmol). The tube was evacuated and back-filled with nitrogen. Iodobenzene (56 μL, 0.5 mmol), acetone cyanohydrin (50 μL, 0.55 mmol) and triethylamine (84 μL, 0.6 mmol) were added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMF (300 μL). The tube was sealed under a positive pressure of nitrogen, and stirred and heated at 90 °C for 48 h. The reaction mixture was allowed to cool to room temperature and was then diluted with diethyl ether (5 mL). 1,3-Dimethoxybenzene (65 μL) was added as an internal standard. A small sample of the reaction mixture was taken and filtered through a plug of Celite, the filter cake being further washed with diethyl ether. The filtrate was washed three times with water and analyzed by gas chromatography. The quantitative GC yield

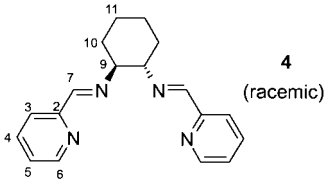
was determined by obtaining the correction factor using an authentic sample of benzonitrile.

Synthesis of ligands 2 and 4:



2

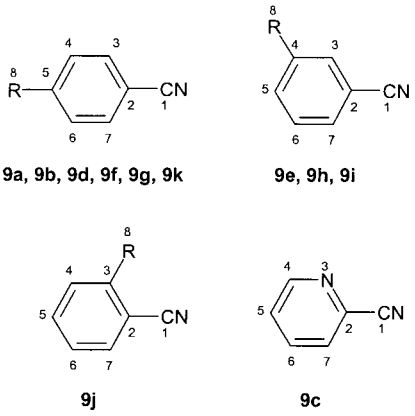
*N,N-Dimethyl-N′-(pyridin-2-ylmethylene)ethane-1,2-diamine (Dmeda-Py-Al) (**2**)*: Anhydrous magnesium sulfate (3.6 g, 30.0 mmol) and *rac-trans*-1,2-diaminocyclohexane (2.15 mL, 20.0 mmol) were successively added to a solution of 2-pyridinecarboxaldehyde (1.90 mL, 20.0 mmol) in absolute ethanol (20 mL). The mixture was stirred for 72 h at room temperature and filtered through a frit. The solid was discarded and the filtrate was concentrated in vacuo. The desired product (2.8 g, 78%) was obtained as a brown oil. ^{1}H NMR: $\delta = 8.54$ (ddd, $^3J_{H5,H6} = 4.9$ Hz, $^4J_{H4,H6} = 1.7$ Hz, $^5J_{H3,H6} = 1.0$ Hz, H-1), 8.35 (t, $^4J_{H7,H9} = 1.5$ Hz, H-7), 7.92 (ddd, $^3J_{H3,H4} = 8.0$ Hz, $^4J_{H3,H5} = 1.2$ Hz, $^5J_{H3,H6} = 1.0$ Hz, 1H, H-3), 7.92 (ddd, $^3J_{H3,H4} = 8.0$ Hz, $^3J_{H4,H5} = 7.6$ Hz, $^4J_{H4,H6} = 1.7$ Hz, 1H, H-4), 7.25 (ddd, $^3J_{H4,H5} = 7.6$ Hz, $^3J_{H5,H6} = 4.9$ Hz, $^4J_{H3,H5} = 1.2$ Hz, H-5), 3.74 (td, $^3J_{H9,H10} = 7.1$ Hz, $^4J_{H7,H9} = 1.5$ Hz, 2H, H-9), 2.61 (t, $^3J_{H9,H10} = 7.1$ Hz, 2H, H-10), 2.36 ppm (s, 6H, H-11); ^{13}C NMR: $\delta = 162.29$ (C-7), 159.96 (C-2), 149.60 (C-6), 136.10 (C-4), 124.29 (C-5), 120.56 (C-3), 61.77 (C-9), 59.79 (C-10), 45.60 ppm (C-11); IR (CCl_4): $\nu = 3338$, 3055, 2973, 2933, 2853, 2822, 2765, 2364, 2336, 1675, 1650, 1583, 1563, 1465, 1431, 1044, 989, 776, 744, 618 cm^{-1}: GC-MS: retention time, rt = 16.44 min, *m*/*z*: 177



4 (racemic)

*trans-1,2-Bis(2′-pyridylideneamino)cyclohexane (Chxn-Py-Al) (**4**)*: Anhydrous magnesium sulfate (12.65 g, 105.1 mmol) and *rac-trans*-1,2-diaminocyclohexane (4.2 mL, 35.0 mmol) were successively added to a solution of 2-pyridinecarboxaldehyde (6.66 mL, 70.0 mmol) in absolute ethanol (50 mL). The mixture was stirred for 20 h at room temperature, refluxed for 2.5 h and filtered through a frit while still hot. The solid was discarded and the filtrate was concentrated in vacuo. The residue was recrystallized in ethanol to provide 8.2 g (80% yield) of the desired product as pale yellow crystals. M.p. 140–141 °C (EtOH); ^{1}H NMR: $\delta = 8.54$ (ddd, $^3J_{H5,H6} = 4.9$ Hz, $^4J_{H4,H6} = 1.7$ Hz, $^5J_{H3,H6} = 1.0$ Hz, 2H, H-6), 8.30 (brs, 2H, H-7), 7.87 (ddd, $^3J_{H3,H4} = 7.9$ Hz, $^4J_{H3,H5} = 1.5$ Hz, $^5J_{H3,H6} = 1.0$ Hz, 2H, H-3), 7.63 (dddd, $^3J_{H,H} = 7.9$ Hz, $^3J_{H3,H4} = 7.5$ Hz, $^4J_{H4,H5} = 1.7$ Hz, $^5J_{H4,H6} = 0.6$ Hz, 2H, H-4), 7.22 (ddd, $^3J_{H4,H5} = 7.5$ Hz, $^3J_{H5,H6} = 4.9$ Hz, $^4J_{H3,H5} = 1.5$ Hz, 2H, H-5), 3.50 (m, 2H, H-9), 1.83 (m, 6H, H-10ax, H-11), 1.40–1.55 ppm (m, 2H, H-10eq); ^{13}C NMR: $\delta = 161.4$ (C-7), 154.6 (C-2), 149.2 (C-6), 136.4 (C-4), 124.4 (C-5), 121.3 (C-3), 73.5 (C-9), 32.7 (C-10), 24.3 ppm (C-11); IR (KBr): $\nu = 3273$, 3071, 3055, 3050, 2941, 2934, 2925, 2865, 2857, 2850, 1644, 1586, 1566, 1467, 1449, 1433, 1372, 1338, 991, 934, 867, 839, 771, 743 cm^{-1}; MS (FAB+, NBA): *m*/*z* (%): 293 (100) [M^++H], 107 (52), 92 (38), 119 (25), 294 (23) [M^++2H], 204 (22), 79 (21), 187 (20), 585 (!) [2M^++H].

Aryl nitriles: The following numbering system differs from the conventional one to allow convenient comparison of chemical shifts.



9a, 9b, 9d, 9f, 9g, 9k **9e, 9h, 9i**

9j **9c**

R = H, CF_3, NH_2, NO_2, CH_3, $COCH_3$, OCH_3, F, Cl

*Aryl nitrile (**9a**)*: The cyanation of bromobenzene (539 μL, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel to provide 452 mg (88% yield) of the desired product as a colourless oil. ^{1}H NMR: $\delta = 7.71$–7.47 ppm (m, H-3, H-4, H-5, H-6, H-7); ^{13}C NMR: $\delta = 132.30$ (C-5), 131.51 (C-3, C-7), 128.65 (C-4, C-6), 118.27 (C-1), 111.77 ppm (C-2); GC-MS (EI): rt = 9.10 min, *m*/*z*: 103; $R_f = 0.31$ (hexanes/AcOEt, 95:5).

*Aryl nitrile (**9b**)*: The cyanation of 4-bromobenzotrifluoride (700 μL, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel to provide 745 mg (87% yield) of the desired product as a white powder. M.p. 38–39 °C (hexanes/AcOEt) [lit.[39]: 36–37 °C (hexanes)]; ^{1}H NMR: $\delta = 7.84$ (m, H-5, H-7), 7.78 ppm (m, H-4, H-6); ^{13}C NMR: $\delta = 134.43$ (q, $^2J_{C,F} = 32.7$ Hz, C-5), 132.62 (s, C-3, C-7), 126.09 (q, $^3J_{C,F} = 3.7$ Hz, C-4, C-6), 123.00 (q, $^1J_{C,F} = 273.0$ Hz, C-8), 117.36 (s, C-1), 115.99 ppm (q, $^5J_{C,F} = 1.5$ Hz, C-2); ^{19}F NMR: $\delta = (-)63.99$ ppm (s, F-8, CF_3); GC-MS (EI): rt = 18.50 min, *m*/*z*: 171; $R_f = 0.45$ (hexanes/AcOEt, 90:10).

*Aryl nitrile (**9c**)*: The cyanation of 2-bromopyridine (477 μL, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 80:20) to provide 510 mg (98% yield) of the desired product as a white powder. M.p. 26–27 °C (hexanes/AcOEt) (lit.:[40] 26–28 °C); ^{1}H NMR: $\delta = 8.75$ (ddd, $^3J_{H4,H5} = 4.8$ Hz, $^4J_{H4,H6} = 1.7$ Hz, $^5J_{H4,H7} = 1.0$ Hz, H-4), 7.88 (ddd, $^3J_{H6,H7} = 7.8$ Hz, $^3J_{H5,H6} = 7.7$ Hz, $^4J_{H4,H6} = 1.7$ Hz, 1H, H-6), 7.73 (ddd, $^3J_{H6,H7} = 7.8$ Hz, $^3J_{H5,H7} = 1.3$ Hz, $^5J_{H4,H7} = 1.0$ Hz, H-7), 7.57 ppm (ddd, $^3J_{H5,H6} = 7.7$ Hz, $^3J_{H4,H5} = 4.8$ Hz, $^4J_{H5,H7} = 1.3$ Hz, H-5); ^{13}C NMR: $\delta = 150.93$ (C-4), 136.99 (C-6), 133.64 (C-2), 128.39 (C-7), 126.88 (C-5), 117.04 ppm (C-1); GC-MS (EI): rt = 10.56 min, *m*/*z*: 104; $R_f = 0.21$ (hexanes/AcOEt, 80:20).

*Aryl nitrile (**9d**)*: The cyanation of 4-bromoaniline (860.0 mg, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 70:30) to provide 413 mg (70% yield) of the desired product as a white solid. M.p. 84–85 °C (hexanes/AcOEt) [lit.:[41] 86 °C (petroleum ether)]; ^{1}H NMR: $\delta = 7.43$ (m, H-3, H-7), 6.67 (m, H-4, H-6), 4.21 ppm (brs, H-8, NH_2); ^{13}C NMR: $\delta = 150.49$ (C-5), 133.67 (C-3, C-7), 120.16 (C-1), 114.32 (C-4, C-6), 99.77 ppm (C-2); GC-MS (EI): rt = 16.33 min, *m*/*z*: 118; $R_f = 0.21$ (hexanes/AcOEt, 70:30).

*Aryl nitrile (**9e**)*: The cyanation of 3-nitrobromobenzene (1.01 g, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 555 mg (75% yield) of the desired product as a white solid. M.p. 115–116 °C (hexanes/AcOEt) (lit.:[42] 115–117 °C); ^{1}H NMR: $\delta = 8.57$ (ddd, $^4J_{H3,H5} = 2.3$ Hz, $^4J_{H3,H7} = 1.5$ Hz, $^5J_{H3,H6} = 0.6$ Hz, H-3), 8.51 (ddd, $^3J_{H5,H6} = 8.3$ Hz, $^4J_{H3,H5} = 2.3$ Hz, $^4J_{H5,H7} = 1.1$ Hz, H-5), 8.03 (ddd, $^3J_{H6,H7} = 7.8$ Hz, $^4J_{H3,H7} = 1.5$ Hz, $^4J_{H5,H7} = 1.1$ Hz, H-7), 7.77 ppm (ddd, $^3J_{H5,H6} = 8.3$ Hz, $^3J_{H6,H7} = 7.8$ Hz, $^5J_{H3,H6} = 0.6$ Hz, H-6); ^{13}C NMR: $\delta = 148.19$ (C-4), 137.57 (C-7), 130.64 (C-6),

127.45 (C-5) 127.20 (C-3), 116.50 (C-2), 114.10 ppm (C-1); GC-MS (EI): rt = 15.19 min, *m/z*: 148; R_f = 0.25 (hexanes/AcOEt, 75:25).

*Aryl nitrile (**9f**)*: The cyanation of 4-bromotoluene (855.2 mg, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 470 mg (80% yield) of the desired product as a white solid. M.p. 27–28°C (hexanes/AcOEt) (lit.:[43] 28°C); ^{1}H NMR: δ = 7.56 (m, H-3, H-7), 7.29 (m, H-4, H-6), 2.36 ppm (s, 3H, H-8, CH_3); ^{13}C NMR: δ = 143.54 (C-5), 131.81 (C-3, C-7), 129.66 (C-4, C-6), 118.96 (C-1), 109.06 (C-2), 21.62 ppm (C-8); GC-MS (EI): rt = 11.34 min, *m/z*: 117; R_f = 0.36 (hexanes/AcOEt, 90:10).

*Aryl nitrile (**9g**)*: The cyanation of 4-acetylbromobenzene (995.3 mg, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 80:20) to provide 698 mg (96% yield) of the desired product as a pale yellow solid. M.p. 57–58°C (hexanes/AcOEt) [lit.:[44] 58–59°C (aqueous ethanol)]; ^{1}H NMR: δ = 8.07 (m, H-4, H-6), 7.80 (m, H-3, H-7), 2.67 ppm (s, 3H, H-9, CH_3); ^{13}C NMR: δ = 196.48 (C-8), 139.82 (C-5), 132.42 (C-4, C-6), 128.61 (C-3, C-7), 117.83 (C-1), 116.28 (C-2), 26.67 ppm (C-9); GC-MS (EI): rt = 15.13 min, *m/z*: 145; R_f = 0.21 (hexanes/AcOEt, 80:20).

*Aryl nitrile (**9h**)*: The cyanation of 3-methoxybromobenzene (633 μL, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 524 mg (79% yield) of the desired product as a colourless oil. ^{1}H NMR:[45] δ = 7.38 (m, $^3J_{H5,H6}$ = 8.4 Hz, $^3J_{H6,H7}$ = 7.6 Hz, $^5J_{H3,H6}$ = 0.7 Hz, H-6), 7.24 (m, $^3J_{H6,H7}$ = 7.6 Hz, $^4J_{H3,H7}$ = 1.4, $^4J_{H5,H7}$ = 1.0 Hz, H-7), 7.14 (m, $^4J_{H3,H5}$ = 2.6 Hz, $^4J_{H3,H7}$ = 1.4 Hz, $^5J_{H3,H6}$ = 0.7 Hz, H-3), 7.14 (m, $^3J_{H5,H6}$ = 8.4 Hz, $^4J_{H3,H5}$ = 2.6 Hz, $^4J_{H3,H7}$ = 1.0 Hz, H-5), 3.83 ppm (s, 3H, H-9, CH_3); ^{13}C NMR: δ = 159.43 (C-4), 129.86 (C-6), 124.22 (C-7), 119.33 (C-5), 118.71 (C-1), 116.37 (C-3), 111.98 (C-2), 55.32 ppm (C-8); GC-MS (EI): rt = 13.27 min, *m/z*: 133; R_f = 0.33 (hexanes/AcOEt, 90:10).

*Aryl nitrile (**9i**)*: The cyanation of 3,5-difluorobromobenzene (576 μL, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 653 mg (94% yield) of the desired product as white needles. M.p. 85–86°C (hexanes/AcOEt) [lit.:[45] 83–85°C (hexanes)]; ^{1}H NMR:[45] δ = 7.23 (m, $^4J_{H3,H7}$ = 8.5 Hz, $^3J_{H,F}$ = 7.7 Hz, $^4J_{H5,H3}$ = $^4J_{H5,H7}$ = 2.3 Hz, $^5J_{H,F}$ = 1.1 Hz, H-3, H-7), 7.12 ppm (m, $^3J_{H5,F4}$ = $^3J_{H5,F6}$ = 8.7 Hz, $^4J_{H5,H3}$ = $^4J_{H5,H7}$ = 2.3 Hz, H-5); ^{13}C NMR:[45] δ = 162.83 (dd, $^1J_{C,F}$ = 252.2 Hz, $^3J_{C,F}$ = 12.6 Hz, C-4, C-6), 116.45 (t, $^4J_{C,F}$ = 3.4 Hz, C-1), 115.61 (m, $^2J_{C,F}$ = 20.3 Hz, $^4J_{C,F}$ = 8.6 Hz, C-3, C-7), 114.30 (t, $^3J_{C,F}$ = 11.6 Hz, C-2), 109.39 ppm (t, $^2J_{C,F}$ = 24.9 Hz, C-5); ^{19}F NMR:[45] δ = 105.69 ppm (m, $^3J_{H,F}$ = 8.7 Hz, $^3J_{H,F}$ = 7.7 Hz, $^4J_{F,F}$ = 1.3 Hz , $^5J_{H,F}$ = 1.1 Hz, F-4, F-6); GC-MS (EI): rt = 7.16 min, *m/z*: 139; R_f = 0.41 (hexanes/AcOEt, 90:10).

*Aryl nitrile (**9k**)*: The cyanation of 4-chlorobromobenzene (957.3 mg, 5.0 mmol) was achieved by following the general procedure. The resulting crude oily residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 588 mg (86% yield) of the desired product as white needles. M.p. 91–92°C (hexanes/AcOEt) (lit.:[46] 94°C); ^{1}H NMR: δ = 7.64 (m, H-3, H-7), 7.50 ppm (m, H-4, H-6); ^{13}C NMR: δ = 139.39 (C-5), 133.26 (C-3, C-7), 129.56 (C-4, C-6), 117.82 (C-1), 110.66 ppm (C-2); GC-MS (EI): rt = 12.06 min, *m/z*: 137; R_f = 0.43 (hexanes/AcOEt, 90:10).

*Aryl nitrile (**9j**)*: After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar was charged with CuI (95.2 mg, 0.5 mmol) and 1,10-phenanthroline (181.2 mg, 1.0 mmol). The tube was evacuated and back-filled with nitrogen. 2-Iodotoluene (636 μL, 5.0 mmol), acetone cyanohydrin (502 μL, 5.5 mmol) and diisopropylethylamine (1.05 mL, 6.0 mmol) were added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMF (3 mL). The tube was sealed under a positive pressure of nitrogen, and stirred and heated at 110°C for 48 h. After cooling to room temperature, the mixture was diluted with diethyl ether (~50 mL) and filtered through a plug of Celite, the filter cake being further washed with diethyl ether (~10 mL). The filtrate was washed twice with water (~30 mL × 2). The combined aqueous phases were twice extracted with diethyl ether (2 × ~30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a brown oil. Diisopropylethylamine was then distilled and the crude product obtained was purified on silica gel (eluent: hexanes/ethyl acetate, 90:10) to provide 554 mg (95% yield) of the desired product as a colourless oil. ^{1}H NMR: δ = 7.60 (ddd, $^3J_{H6,H7}$ = 7.6 Hz, $^4J_{H5,H7}$ = 1.4 Hz, $^5J_{H4,H7}$ = 0.6 Hz, H-7), 7.50 (td, $^3J_{H4,H5}$ = $^3J_{H5,H6}$ = 7.6 Hz, $^4J_{H5,H7}$ = 1.4 Hz, H-5), 7.33 (ddd, $^3J_{H4,H5}$ = 7.6 Hz, $^4J_{H4,H6}$ = 1.3 Hz, $^4J_{H4,H7}$ = 0.6 Hz, H-4), 7.28 (td, $^3J_{H6,H7}$ = $^3J_{H5,H6}$ = 7.6 Hz, $^4J_{H4,H6}$ = 1.3 Hz, H-6), 2.56 ppm (s, 3H, H-8, CH_3); ^{13}C NMR: δ = 141.69 (C-3), 132.48 (C-5), 132.27 (C-7), 130.06 (C-4), 126.06 (C-6), 117.92 (C-1), 112.54 (C-2), 20.23 ppm (C-8); GC-MS (EI): rt = 10.68 min, *m/z*: 117; R_f = 0.57 (hexanes/AcOEt, 90:10).

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[28] Note that these results, including those presented in this article, have already been published as patents: Rights to the commercial use of the catalytic systems presented in this work are held by Rhodia Recherches under the following patents: a) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, FR 2833947, **2003**; [*Chem. Abstr.* **2003**, *139*, 69290]; b) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, WO 03/050885, **2003**; c) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, FR 2840303, **2003**; [*Chem. Abstr.* **2004**, *140*, 16744]; d) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, A. Ouali, WO 03/101966, **2003**; e) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler, Patent priority number FR 03 10253, **2004**.

[29] We developed this strategy more than two years ago and published the results as a patent (see ref. [28d]). A copper-catalyzed halide exchange-cyanation of aryl bromides has been described but this procedure involved stoichiometric amounts of ligand with respect to the aryl bromide (see ref. [24]).

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