Palladium-Catalyzed Cyanation of Aryl Bromides with Malononitrile via Carbon–Nitrile Bond Cleavage Mediated by Copper

Guo-ping Lu, Mei-jie Bu, Chun Cai*

Chemical Engineering College, Nanjing University of Science & Technology, Nanjing, Jiangsu 210094, P. R. of China
E-mail: c.cai@mail.njust.edu.cn

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Abstract: An efficient palladium catalytic system is developed for the cyanation of aryl bromides using malononitrile as a cheap, less toxic, stable and easy-to-handle 'nonmetallic' cyanide source, which proceeds via copper-catalyzed cleavage of carbon–nitrile (C–CN) bonds. The approach provides a novel and alternative route leading to aryl nitriles.

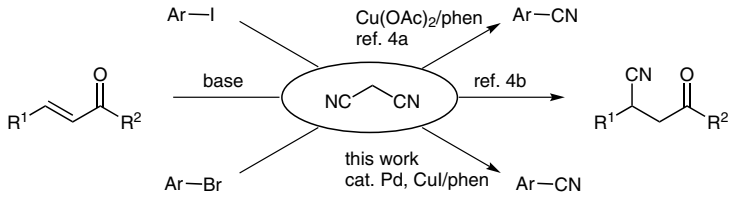
Key words: aryl nitriles, cyanation, malononitrile, aryl bromides, palladium

Procedures for the introduction of a cyano group to aromatic rings for the preparation of aryl nitriles are of significant interest to organic chemists due to the importance of these compounds in chemistry and biology.[1] Typically, aromatic nitriles are prepared efficiently through transition-metal-catalyzed cyanation of aryl (pseudo)halides with metallic cyano-group sources, such as copper(I) cyanide (CuCN), potassium cyanide (KCN), sodium cyanide (NaCN), zinc cyanide [$Zn(CN)_2$], trimethylsilyl cyanide (TMSCN), and potassium hexacyanoferrate(II) {$K_4[Fe(CN)_6]$}.[2] These methods, however, suffer from limitations which include the formation of stoichiometric amounts of metal waste, poisoning of the metal catalysts, or the generation of toxic hydrogen cyanide (HCN) gas. In order to eliminate these problems, a range of 'nonmetallic' organic cyano group sources have been explored for the cyanation of aryl halides and arene C–H bonds.[3]

Compared with commonly employed metallic cyanation reagents, malononitrile as an alternative organic cyanide source has the distinct advantages of being relatively cheap, less toxic, stable and easy-to-handle. Recently, attempts have been made to utilize malononitrile as the source of cyanide in several cyanation reactions (Scheme 1).[4] Zhou and co-workers reported the copper-catalyzed coupling reactions of aryl iodides with malononitrile to form aryl nitriles via cleavage of the C–CN bonds.[4a] Despite the fact that a series of aryl iodides could be employed utilizing this catalytic system, the cyanation of the less reactive aryl bromides and aryl chlorides proved unsuccessful.

The palladium-catalyzed cyanation of aryl halides (especially aryl bromides and aryl chlorides) is a common and powerful tool to obtain substituted benzonitriles.[1c,2b,5] Along these lines, we envisaged the use of palladium catalysts for the synthesis of aryl nitriles employing malononitrile as the cyanide source, such that the cheaper and more widely available aryl bromides and aryl chlorides could be employed in the procedure. Herein, we describe a novel and efficient palladium catalytic system for the cyanation of aryl bromides with malononitrile, which involves a cyano group transfer process from $C(sp^3)$ to $C(sp^2)$ (Scheme 1).

As a representative example, the reaction of bromobenzene (**1a**) and malononitrile was selected to optimize the reaction conditions (Table 1). During the screening of copper sources, copper(I) proved to be a better choice than copper(II), and copper(I) iodide provided the best result (Table 1, entry 6). No reaction took place in the absence of a copper source (Table 1, entry 7). Control experiments indicated the necessity for both sodium *tert*-butoxide and potassium fluoride, and only a trace amount of product was detected in the absence of either of them (Table 1, entries 8–10). Compared with other bases (NaOH, K_2CO_3, Cs_2CO_3, K_3PO_4) and additives (NaF, CsF, KI), the combination of sodium *tert*-butoxide and potassium fluoride was the best selection for this reaction. The use of two equivalents of malononitrile proved to be optimum for the cyanation process (Table 1, entry 11). To further improve the modest yields, different palladium catalysts were employed in the reaction (Table 1, entries 11 and 13–15).



Scheme 1 Cyanation reactions using malononitrile as the cyanide source via C–CN bond cleavage

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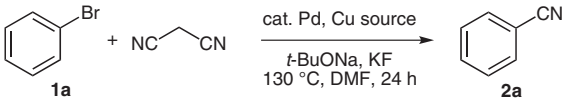
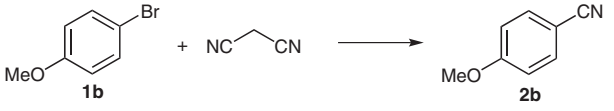
$Pd(Amphos)_2Cl_2$ emerged as the best option for this process (Table 1, entry 11). Additionally, only a trace of product **2a** was obtained without a palladium catalyst (Table 1, entry 16).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Cu source	Yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	9
2	$Pd(PPh_3)_2Cl_2$	Cu	n.r.
3	$Pd(PPh_3)_2Cl_2$	$CuBr_2$	n.r.
4	$Pd(PPh_3)_2Cl_2$	CuBr	25
5	$Pd(PPh_3)_2Cl_2$	CuCl	52
6	$Pd(PPh_3)_2Cl_2$	CuI	54
7	$Pd(PPh_3)_2Cl_2$	–	n.r.
8[c]	$Pd(PPh_3)_2Cl_2$	CuI	12
9[d]	$Pd(PPh_3)_2Cl_2$	CuI	10
10[e]	$Pd(PPh_3)_2Cl_2$	CuI	trace
11	$Pd(Amphos)_2Cl_2$	CuI	76, 56,[f] 74[g]
12[h]	$Pd(Amphos)_2Cl_2$	CuI	73
13	$Pd(dppf)_2Cl_2$	CuI	41
14	$Pd(OAc)_2$	CuI	7
15	$Pd(OAc)_2/2PCy_3$	CuI	68
16	–	CuI	9
17	$Pd(Amphos)_2Cl_2$	CuI/phen[i]	70



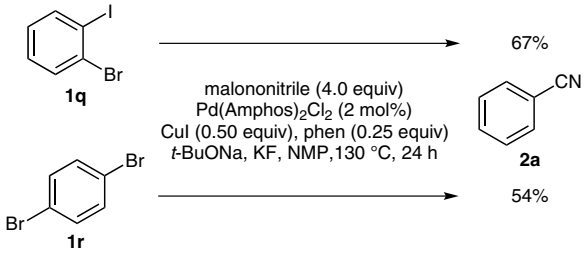
18	$Pd(Amphos)_2Cl_2$	CuI	30
19	$Pd(Amphos)_2Cl_2$	CuCl	28
20	$Pd(Amphos)_2Cl_2$	CuI/phen[j]	71
21	$Pd(Amphos)_2Cl_2$	CuI/phen[i]	75
22	$Pd(Amphos)_2Cl_2$	CuI/phen[k]	36

[a] Reaction conditions: phenyl bromide (0.25 mmol), malononitrile (0.50 mmol), Pd catalyst (2 mol%), Cu source (1.0 equiv), *t*-BuONa (2.0 equiv), KF (2.0 equiv), DMF (1.0 mL), 130 °C, 24 h.
[b] Yields determined by GC; n.r. = no reaction.
[c] No KF was used.
[d] No *t*-BuONa was used.
[e] Neither *t*-BuONa nor KF was used.
[f] Malononitrile (0.25 mmol) was used.
[g] Malononitrile (0.75 mmol) was used.
[h] Reaction under N_2.
[i] CuI (0.50 equiv) and phen (0.25 equiv) were used.
[j] CuI (0.50 equiv) and phen (0.50 equiv) were used.
[k] CuI (0.25 equiv) and phen (0.25 equiv) were used.

A satisfactory 73% yield was obtained when the reaction was carried out under a nitrogen atmosphere, thereby certifying that air did not participate in the protocol (Table 1, entries 11 vs 12). The use of 1,10-phenanthroline (phen) as the ligand in combination with copper failed to improve the results of the model reaction. On the other hand, in the cyanation of 1-bromo-4-methoxybenzene (**1b**) with malononitrile, the yield of product **2b** was enhanced by adding 1,10-phenanthroline as the ligand (Table 1, entries 20 and 21). The amounts of copper(I) iodide and 1,10-phenanthroline were also optimized [CuI (0.50 equiv) and phen (0.25 equiv)] (Table 1, entry 21). Compared with other organic cyanide sources such as ethyl cyanoacetate and 2-cyanoacetic acid, malononitrile was the better cyanide reagent for this catalytic system.

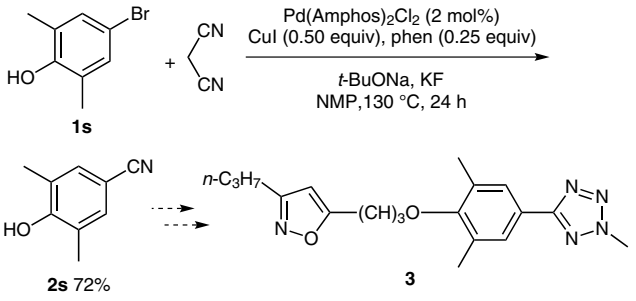
In order to ascertain the scope and generality of the protocol, a series of aryl bromides was employed in the cyanation with malononitrile under the optimized conditions (Table 2). Typically, electron-rich aryl bromides gave moderate to good yields of the desired products. Furthermore, aryl nitriles containing active groups (such as OH and NH_2) could also be prepared from the corresponding aryl bromides via this process, without the need for any protection–deprotection steps (**2i**,**j**,**l**). In some cases, *N*-methyl-2-pyrrolidinone (NMP) proved to be a better solvent than *N*,*N*-dimethylformamide (**2h**–**j**). In contrast, electron-deficient aromatic bromides provided unsatisfactory results (**2m**,**o**,**p**), due to dehalogenation and the formation of undesired side products (aromatic carboxylic acids).[6] Although the cyanation of 2-bromoaniline with malononitrile proceeded smoothly (**2l**), 1-bromo-2-methoxybenzene afforded only a poor yield of the corresponding product **2n**. It can be concluded that the cyanation will be inhibited when the aryl bromide substrate contains a sterically hindered group at the *ortho* position.

Encouraged by these results, we decided to employ the dihalogenated benzenes **1q** and **1r** in this procedure in an attempt to produce the desired dicyanobenzenes. However, instead of the expected dicyanobenzenes, benzonitrile (**2a**) was obtained in these reactions, indicating that both cyanation and dehalogenation occurred in the system (Scheme 2). To further demonstrate the potential of this methodology, aromatic nitrile **2s**, a crucial intermediate en route to the tetrazole analogue **3** related to disoxaril, which displays potent antipicoranvirus activity, was synthesized via the palladium-catalyzed cyanation with



Scheme 2 The cyanation of dihalogenated benzenes using the optimized protocol

malononitrile (Scheme 3). This provides an alternative to the previously reported methods employing toxic metallic cyanide sources.[7]

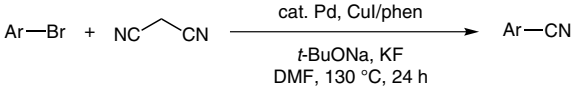


Scheme 3 A potential application of the cyanation to total synthesis

Finally, a proposed mechanism for the reaction is illustrated in Scheme 4. The reaction did not take place in the absence of a copper source, so we believe that copper(I) iodide performs an important role in the cleavage of C–CN bonds,[8] and 1,10-phenanthroline as the ligand has a positive effect on the formation of the coordination complex (CuLCN).[4a] It is more reasonable that cleavage of the C–CN bonds is promoted by sodium *tert*-butoxide and potassium fluoride,[4a,9] rather than an oxidation process, because satisfactory results were also obtained in the absence of an oxidant (Table 1, entries 11 vs 12). Based on the above results, copper(I) iodide may initially chelate to the cyanide triple bonds in malononitrile in the presence of 1,10-phenanthroline. The corresponding carbanion intermediate is formed by deprotonation with the base. Next, the carbon–cyano σ-bond is cleaved to form in situ the cyanide complex, CuLCN. Finally, the aryl nitrile is formed via the typical palladium-catalyzed cyanation mechanism.[3a]

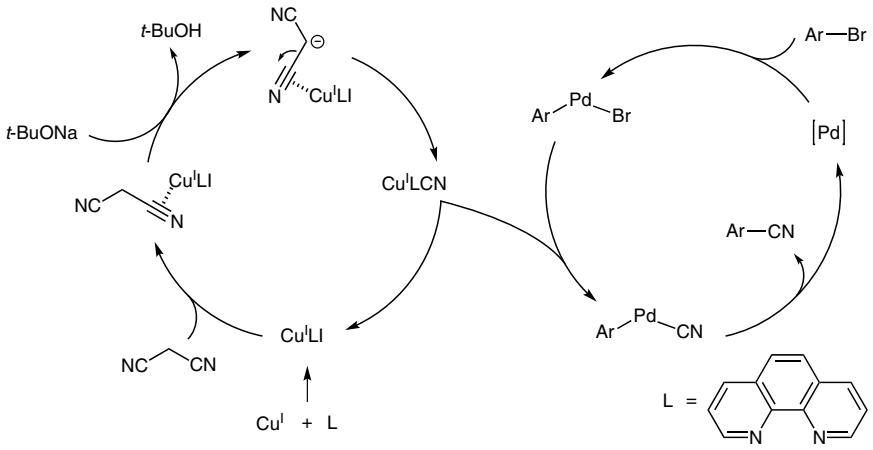
In conclusion, the cyanation of aryl bromides with malononitrile was achieved via a C(sp^3) to C(sp^2) cyano group transfer process in the presence of copper(I) iodide/1,10-phenanthroline, sodium *tert*-butoxide and potassium fluoride.[10] The use of palladium as the catalyst resulted in considerable enhancement of the cyanation of aryl bromides.

Table 2 Cyanation of Aryl Bromides with Malononitrile Catalyzed by Palladium[a]



Entry	Product	Ar	Yield (%)[b]
1	**2a**	Ph	68[c]
2	**2b**	4-MeOC$_6$H$_4$	70
3	**2c**	4-F$_3$CC$_6$H$_4$	73
4	**2d**	4-MeC$_6$H$_4$	78
5	**2e**	2-naphthyl	75
6	**2f**	1-naphthyl	60
7	**2g**	4-PhC$_6$H$_4$	70
8	**2h**	3,4-(MeO)$_2$C$_6$H$_4$	65[d]
9	**2i**	4-HOC$_6$H$_4$	79[d]
10	**2j**	4-H$_2$NC$_6$H$_4$	76[e]
11	**2k**	4-Me$_2$NC$_6$H$_4$	61
12	**2l**	2-H$_2$NC$_6$H$_4$	72
13	**2m**	4-O$_2$NC$_6$H$_4$	40
14	**2n**	2-MeOC$_6$H$_4$	21[f]
15	**2o**	4-AcC$_6$H$_4$	trace
16	**2p**	2-pyridyl	n.r.

[a] Reaction conditions: aryl bromide (0.25 mmol), malononitrile (0.50 mmol), Pd(Amphos)$_2$Cl$_2$ (2 mol%), CuI (0.5 equiv), phen (0.25 equiv), *t*-BuONa (2.0 equiv), KF (2.0 equiv), DMF (1.0 mL), 130 °C, 24 h.
[b] Yields are those of isolated products. NR = no reaction.
[c] Reaction conditions: Pd(Amphos)$_2$Cl$_2$ (2 mol%), CuI (1.0 equiv), *t*-BuONa (2.0 equiv), KF (2.0 equiv), DMF (1.0 mL), 130 °C, 24 h.
[d] NMP was used as the solvent.
[e] The reaction was performed in NMP at 150 °C.
[f] Yield determined by GC.



Scheme 4 A proposed mechanism for the palladium-catalyzed cyanation of aryl bromides with malononitrile

The protocol avoids the use of a highly toxic cyanide source, thereby offering considerable potential for applications in organic synthesis. Further investigations on the synthesis of aryl nitriles using 'nonmetallic' cyano-group sources are ongoing in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **Palladium-Catalyzed Cyanation, General Procedure**
A mixture of aryl bromide (0.250 mmol), malononitrile (0.500 mmol), Pd catalyst (0.005 mmol), CuI (0.125 mmol), 1,10-phenanthroline (0.063 mmol), *t*-BuONa (0.500 mmol) and KF (0.500 mmol) in DMF or NMP (1 mL) was stirred at 130 °C for 24 h. Upon completion of the reaction, the mixture was diluted with EtOAc (4.0 mL), and filtered through a bed of silica gel layered over Celite. The volatiles were removed in vacuo to afford the crude product. The extent of conversion was determined by GC. Further purification by column chromatography on silica gel afforded the desired product.
All products are known compounds, which are identified by ^{1}H NMR, ^{13}C NMR and MS, and compared with previously reported data.

