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The First Example for Cyanation of Arylboronic Acids with Nontoxic and Inexpensive $K_4[Fe(CN)_6]$

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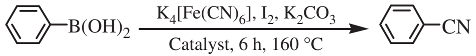
Nontoxic and inexpensive $K_4[Fe(CN)_6]$ is first introduced as a cyanating agent to cyanation of arylboronic acids. The present method is simple, practical, and allowed a wide range of substrates including functionalized phenylboronic acids, 1-naphthylboronic acid as well as heterocyclic boronic acids to be smoothly converted into the corresponding products in moderate to high yields.

Aryl nitriles are an important class of compounds in synthetic chemistry because they not only constitute the key components of a range of pharmaceuticals, agrochemicals, and dyes,[1] but also can be easily converted into various classes of compounds such as nitrogen-containing heterocycles, aldehydes, amines, amidines, acids, and acid derivatives.[2] As a result, their preparation has attracted considerable attention. One of the most convenient methods for the synthesis of aryl nitriles is the direct reaction between aryl halides and CuCN known as Rosenmund–von Braun reaction.[3] However, such a strategy does not meet today's criteria of sustainable synthesis owing to stoichiometric amounts of metal waste, which has prompted chemists to develop some transition-metal-catalyzed methods for the synthesis of benzonitriles including cyanation of aryl halides,[4–8] direct cyanation of heteroarenes,[9] as well as electrophilic cyanation of organolithium, organomagnesium, and organozinc reagents.[10]

Another promising alternative to the synthesis of aryl nitriles is the cyanation of more stable and readily available arylboronic acids with benzyl thiocyanate,[11] $Zn(CN)_2$,[12] *p*-toluenesulfonyl cyanide,[13] CuCN, or TMSCN[14] as the cyanating agent. $K_4[Fe(CN)_6]$ has significant advantages over the above-mentioned cyanide sources from environmental and economic perspectives, and has been widely used as the cyanating agent for the transition-metal-catalyzed direct cyanation of heteroarenes,[15] three-component arylcyanation of internal alkynes,[16] cyanation of benzyl chlorides,[17] and cyanation of aryl halides,[7] whereas previous attempts to introducing such a green agent to the cyanation of arylboronic acids were unsuccessful.[12] Therefore, our attention was drawn to developing a procedure for cyanation of arylboronic acids with nontoxic and inexpensive $K_4[Fe(CN)_6]$ as the cyanating agent, and the results are reported here. It is worth noting that during preparation of this manuscipt, Chang and co-workers reported a copper-mediated method for cyanation of aryl C–B using ammonium iodide and DMF.[18] Their method suffers from at least two drawbacks: the use of as much as 2 equiv copper salt and 2 equiv acetic acid is less attractive for applications, and the use of high-boiling solvent is adverse for the separation and purification of the product.

In our initial study, the cyanation of phenylboronic acid was chosen as a model reaction to demonstrate the catalytic effectiveness of various copper and palladium compounds. As shown in Table 1, the cyanation with 30 mol % $Cu(OAc)_2\cdot H_2O$ as the catalyst gave the desired cyanation product in only 15% yield. Similar results were observed using DMEDA/$Cu(OAc)_2\cdot H_2O$, a typical and effective catalyst system for the cyanation of aryl halides with $K_4[Fe(CN)_6]$.[7f] Both $Pd(OAc)_2$ and PPh_3/$Pd(OAc)_2$ were also less catalytically active. To our delight, a combination of $Pd(OAc)_2$ and $Cu(OAc)_2\cdot H_2O$ improved the cyanation to a satisfactory extent (Table 1, Entry 5). Surprisingly, $Pd(OAc)_2$ in combination with other copper salts including $Cu(NO_3)_2\cdot 3H_2O$, $CuSO_4\cdot 5H_2O$, $CuCl_2\cdot 2H_2O$, CuO, CuCN, CuI, CuBr, and Cu_2O was less effective as the catalysts for the cyanations.

Table 1. Cyanation of phenylboronic acid[a]



Entry	Catalyst	Yield/%[b]
1	$Cu(OAc)_2\cdot H_2O$	15
2	$Cu(OAc)_2\cdot H_2O$/DMEDA[c]	8
3	$Pd(OAc)_2$	3
4	$Pd(OAc)_2$/PPh_3[d]	4
5	$Cu(OAc)_2\cdot H_2O$/$Pd(OAc)_2$	78
6	$Cu(NO_3)_2\cdot 3H_2O$/$Pd(OAc)_2$	19
7	$CuSO_4\cdot 5H_2O$/$Pd(OAc)_2$	0
8	$CuCl_2\cdot 2H_2O$/$Pd(OAc)_2$	9
9	CuO/$Pd(OAc)_2$	4
10	CuCN/$Pd(OAc)_2$	0
11	CuI/$Pd(OAc)_2$	4
12	CuBr/$Pd(OAc)_2$	8
13	Cu_2O/$Pd(OAc)_2$	5
14	$Cu(OAc)_2\cdot H_2O$/$Pd(OAc)_2$/DMEDA[c]	31

[a]Reaction conditions: phenylboronic acid (1 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), K_2CO_3 (1 mmol), I_2 (1 mmol), copper salt (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), under N_2, NMP (1.5 mL), 160 °C, 6 h. [b]Determined by GC. [c]0.3 mmol DMEDA. [d]0.02 mmol PPh_3 was used (DMEDA: *N*,*N*′-dimethyl-1,1-ethanediamine). See Supporting Information for details.[22]

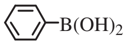
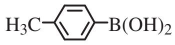
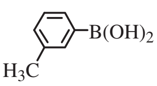
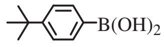
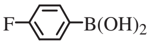
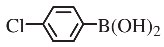
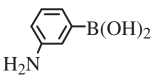
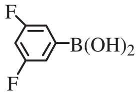
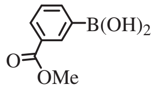
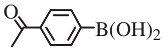
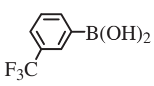
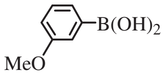
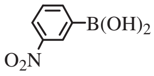
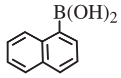
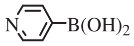
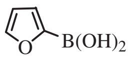
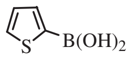
After finding a suitable catalyst system, we optimized other critical parameters such as additive, solvent, reaction time, and temperature. Only 9% yield of benzonitrile was obtained in the absence of inorganic base, suggesting that the use of the base was necessary. Of the screened bases, K_2CO_3 was the most effective one. The effectiveness of Na_2CO_3 was comparable to that of K_2CO_3, whereas other bases such as KF, NaOH, and $K_3PO_4\cdot 3H_2O$ gave the desired product in poor yields. The cyanations were highly dependent on the type of solvent. The experimental results showed that high-boiling and polar solvents including NMP (*N*-methyl-2-pyrrolidone), DMF, and DMSO were optimal in terms of the yield and selectivity of the reactions. Attempts to develop a procedure for the cyanation with environmentally benign water as the solvent were not successful. For instance, only 7% yield of benzyl cyanide was obtained under condition of H_2O as the solvent, 160 °C and 6 h.

We tried to reduce the loading amount of $Cu(OAc)_2 \cdot H_2O$ to 10 mol %, but found that this was not possible without sacrificing product yield even if the reaction time was prolonged to 20 h. The same was true when we tried to decrease the ratio of $K_4[Fe(CN)_6]$ to phenylboronic acid. Changing $K_4[Fe(CN)_6]$ to $K_3[Fe(CN)_6]$ decreased the yield from 89% to 18% under the conditions showed in Entry 1, Table 2. Whether decreasing or increasing the loading amount of I_2 led to a decrease in the yield of the cyanation product, thus 1 equiv of iodine was used in the experiments. The cyanation reactions proceeded in high yields for as short as 2 h, yet the experimental results were less reproducible in such a case, which prompted us to perform the following reactions for 6 h. Our experimental results showed that the presence of oxygen slightly prevented phenylboronic acid from being cyanated. Thus an inert ambience condition was selected to perform the reactions.

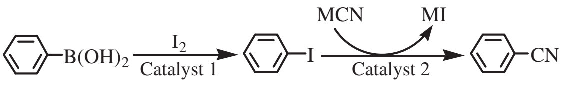
In some cases, a small amount of biphenyl from dimerization of phenylboronic acid was obtained.[19] In addition, a by-product from iodination of phenyl cycle by cleaving the C–H bonds was observed.[20] Another iodination by-product was from cleavage of the $B(OH)_2$ group, revealing that the role of iodine was to be reacted with phenylboronic acid to afford iodobenzene, and the cyanation was a stepwise reaction where conversion of phenylboronic acid into iodobenzene was followed by the cyanation of the resulting iodobenzene to yield the desired product (Scheme 1). In accord with this hypothesis, the iodination product was obtained in moderate yield in the absence of $K_4[Fe(CN)_6]$ (Scheme 2). Copper-catalyzed iodination of phenylboronic acid is known,[21] and our experimental results showed that the Pd/Cu system was effective for the formation of iodobenzene (Scheme 2). Thus the catalyst for the iodination step may be the mixture of copper salts and palladium salts. Copper- or palladium-catalyzed cyanation of iodobenzene is also well known,[7] and the catalytic activity of palladium is often higher than that of copper salts.[7] In fact, Pd/Cu system-mediated cross-coupling has been reported,[15] and our experimental results showed that the cyanation of iodobenzene in the presence of Pd/Cu system did occur. Based on these results, the catalyst for the cyanation step may be the mixture of copper salts and palladium salts. In addition, the CN in the product turns out to be from $K_4[Fe(CN)_6]$,[7] so MCN represents $K_4[Fe(CN)_6]$ in Scheme 1.

With the above results in mind, we decided to examine the scope and limitations of the cyanation protocol by testing a variety of representative arylboronic acids, and the results are shown in Table 2. Several phenylboronic acids with alkyl substituents in the benzene ring were converted into the desired products in excellent yields (Table 2, Entries 1–8). Fluorinated and trifluoromethylated phenylboronic acids were also suitable substrates, and their cyanation gave the pharmaceutically interesting products in high yields even at temperatures as low as 120 °C (Table 2, Entries 10 and 21). Moreover, more challenging functionalized phenylboronic acids were also compatible with the present cyanation conditions (Table 2, Entries 13, 17, 18, and 25). The cyanation of 1-naphthylboronic acid required higher reaction temperature and catalyst loading

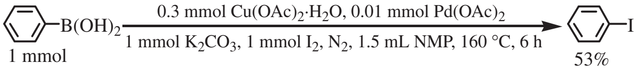
Table 2. Cyanation of various arylboronic acids catalyzed by $Cu(OAc)_2 \cdot H_2O/Pd(OAc)_2$[a]

Entry	Substrate	Temperature /°C	Time /h	Yield/%[b]
1[d]		160	6	89
2		140	6	70
3		120	24	16
4[d]		160	6	74
5		160	6	76
6[d]		160	6	90
7		140	6	76
8[d]		120	24	69
9		160	6	82
10		120	10	86
11		100	24	37
12		160	10	77
13		140	6	12
14[d]		160	6	89
15		140	6	88
16		120	24	62
17		140	6	35
18		160	6	44
19		160	6	86
20		140	6	90
21		120	24	82
22		100	24	46
23		160	12	58
24		140	10	45
25		140	6	46
26[c,d]		180	6	76
27		160	12	48
28		160	6	28
29		140	6	37
30		160	6	45
31		120	24	52
32		160	6	36
33		140	6	35

[a] Reaction conditions: arylboronic acid (1 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), K_2CO_3 (1 mmol), I_2 (1 mmol), under N_2, DMSO (1.5 mL). [b] Determined by GC. [c] 0.5 mmol of $Cu(OAc)_2 \cdot H_2O$ was used. [d] Isolated yield is respectively 60% (Entry 1), 62% (Entry 4), 75% (Entry 6), 71% (Entry 8), 63% (Entry 14), and 71% (Entry 26).



Scheme 1. Proposed pathway for the cyanation.



Scheme 2. Iodination of phenylboronic acid.

for a satisfactory yield (Table 2, Entry 26). A moderate yield was obtained in the case of electron-rich phenylboronic acid with a methoxy group in the meta-position of the boronic acid group (Table 2, Entry 23).

In conclusion, nontoxic and inexpensive $K_4[Fe(CN)_6]$ was demonstrated to be an effective cyanating agent for the cyanation of arylboronic acids with $Pd(OAc)_2/Cu(OAc)_2 \cdot H_2O$ as the catalyst. The experimental results showed that high-boiling and polar solvents including NMP, DMF, and DMSO were optimal in terms of the yield and selectivity of the reactions, and the use of the inorganic base was necessary. A wide range of substrates including fluorinated, trifluoromethylated, alkylated, chlorinated, methoxylated, and acylated phenylboronic acids and 1-naphthaleneboronic acid, as well as heteroarylboronic acids were smoothly converted into the corresponding products in moderate to high yields in the case of 100–180 °C and 6–24 h.

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