Cyanation of Aryl Chlorides with Potassium Hexacyanoferrate(II) Catalyzed by Cyclopalladated Ferrocenylimine Tricyclohexylphosphine Complexes

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Received 9 October 2006

Abstract: Cyanation of aryl chlorides with potassium hexacyanoferrate(II) catalyzed by cyclopalladated ferrocenylimine tricyclohexylphosphine complex has been described. This method is applicable to both activated and deactivated aryl chlorides. The corresponding aryl nitriles were isolated in good to excellent yields

Key words: cyclopalladium, cyanation, aryl chloride, catalysis, coupling

Aryl nitriles are of significant interest in organic chemistry. The versatile transformations of nitrile function make them important intermediates in the synthesis of polyamides, amidines, imidoesters, biologically active molecules.[1,2] Moreover, aryl nitriles themselves are an integral part of herbicides, pesticides, dyes, natural products and pharmaceuticals.[3]

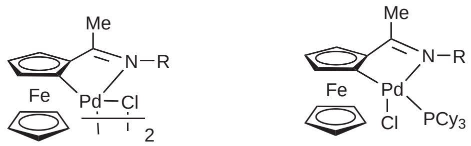
Pd-catalyzed cyanation of aryl halides has been studied extensively. Generally, the cyanide sources used in the cyanation reaction were alkali cyanides (KCN or NaCN), acetone cyanohydrin, TMSCN (trimethylsilylcyanide) and $Zn(CN)_2$.[4,5] Recently, potassium hexacyanoferrate(II) $\{K_4[Fe(CN)_6]\}$ has been used as a cheap and environment-friendly cyanation reagent for catalyzed cyanation of aryl halides. Beller and co-workers reported the first example of palladium-catalyzed cyanation of aryl halides using potassium hexacyanoferrate(II).[6,7] Weissman improved this method and developed a ligand-free cyanation method.[8] Using 1,8-bis(diisopropylphosphino)triptycene as a ligand, Grossman and Gelman developed a mild and air-stable cyanation reaction.[9] Very recently, the palladium-catalyzed cyanation in ionic liquids under microwave irradiation using potassium hexacyanoferrate(II) was reported.[10] The microwave irradiation reduced the reaction time considerably and the catalyst system could be reused several times. Copper-catalyzed cyanation of aryl halides using potassium hexacyanoferrate(II) has also been reported.[11] However, all these methods have been limited to aryl bromides or iodides. Only cyanation of activated aryl chlorides have been reported in these reports. To the best of our knowledge, no efficient method involving potassium hexacyanoferrate(II) has been reported for cyanation of aryl chlorides.

SYNLETT 2007, No. 4, pp 0543–0546
Advanced online publication: 21.02.2007
DOI: 10.1055/s-2007-970741; Art ID: W20806ST

We have focused on the cyclopalladation of ferrocenylimines **1** (Figure 1) and their application in organic synthesis, and found that the dimeric cyclopalladated ferrocenylimines were effective in the Heck reaction[12] and Suzuki reaction of aryl halides.[13] The corresponding tricyclohexylphosphine (PCy_3) complex **2** (Figure 1) showed higher catalytic activities in Suzuki coupling reaction with aryl chlorides.[14]

Here, we would like to report the first efficient catalytic cyanation of inexpensive aryl chlorides[4,9,15,16] with potassium hexacyanoferrate(II) using Pd–PCy_3 complex **2a**.

An initial reaction condition screening was performed on the model cyanation reaction of 4-chlorotoluene with potassium hexacyanoferrate(II). In this study the performance of different cyclopalladium compounds which have been developed in our group, such as **1a**,**b**,[17] their combination with triphenylphosphine and the tricyclohexylphosphine adducts **2a**–**d**[14] were examined. The typical results were listed in Table 1. The dimeric catalysts **1a** and **1b** showed low activities (Table 1 entries 1–3). When 10 mol% triphenylphosphine and 1 mol% **1a** were added to the reaction mixture, the conversion of 4-chlorotoluene was increased dramatically to 84% (Table 1 entry 4).



1a R = 4-MeC_6H_4
1b R = 4-$MeOC_6H_4$

2a R = 4-$EtOC_6H_4$
2b R = 4-$MeOC_6H_4$
2c R = 4-MeC_6H_4
2d R = *c*-Hex

Figure 1 Catalysts of cyclopalladated ferrocenylimine

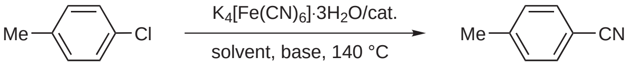
Increasing the loading of **1a** to 2 mol% did not notably improve the conversion (Table 1 entry 5). This result encouraged us to examine the electron-rich tricyclohexylphosphine (PCy_3) as a ligand to facilitate the aryl–Cl bond activation.[18] To our delight, tricyclohexylphosphine complexes showed excellent performance. The cyanation reaction proceeded very well and excellent conversions (98%) were obtained in the presence of 2 mol% of **2a** (Table 1 entry 7). Further examinations revealed that **2b**–**d** had the similar activities. In the presence of 2 mol% **2b**–**d**, respectively, more than 97% 4-chlorotoluene was converted into the corresponding cyanation products

(Table 1 entries 8–10). This indicated that the presence of triphenylphosphine (PPh_3) and tricyclohexylphosphine (PCy_3) facilitated the oxidative addition to C–Cl bond and protected the active palladium center from deactivation in the catalytic cycle. This could be confirmed by the fact that the reaction mixture rapidly changed into black when it was heated without phosphine. Beller and co-workers reported that a decreased amount of catalyst could inhibit agglomeration of molecular palladium complexes to ‘palladium black’ and led to higher yield of cyanation reaction of aryl bromide.[6] But in our reaction, only low conversions were obtained with decreased amount of **2a** (Table 1 entry 19).

Next, we investigated the effect of solvent and base. The combination of DMF/Cs_2CO_3, which had been applied extensively to Suzuki reaction of aryl chloride,[13] was not suitable for our procedure and provided only 35% conversion (Table 1 entry 16). Only moderate conversion was obtained with DMAc/Na_2CO_3, which was used for Pd-catalyzed cyanation of aryl bromides with potassium hexacyanoferrate(II)[8] (Table 1 entries 13 and 14). Both NMP/Na_2CO_3 and DMF/K_3PO_4 were found to be effective. Reactions in NMP/Na_2CO_3 showed higher efficiency (Table 1 entries 6, 7, and 17). Due to high bond energy of C–Cl of aryl chloride,[7,18] a relatively higher reaction temperature (140 °C) was essential for successful conversions.

After optimizing the reaction conditions, we studied the scope and the possible limitations of this reaction. Generally, 2 mol% **2a** and 0.22 equivalents $K_4[Fe(CN)_6]\cdot 3H_2O$ were used. The reaction was conducted in 1 mL NMP combined with 1 equivalent Na_2CO_3 at 140 °C for 16–24 hours.[19] The results are summarized in Table 2. As expected, activated aryl chlorides **3g–k** were smoothly converted into the corresponding **4g–k** in good yields (Table 2 entries 7–9, and 11). Electron-neutral **3a**, mildly

Table 1 Cyanation of 4-Chlorotoluene with $K_4[Fe(CN)_6]$ in the Presence of Cyclopalladium Catalyst[a]

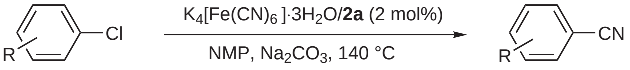


Entry	Solvent	Base	Catalyst	Catalyst loading (Pd mol%)	Conversion (%)[b]
1	NMP[c]	Na_2CO_3	**1a**	1	5
2	NMP	Na_2CO_3	**1a**	2	9
3	NMP	Na_2CO_3	**1b**	2	3
4	NMP	Na_2CO_3	**1a** + PPh_3 (10%)	1	84
5	NMP	Na_2CO_3	**1a** + PPh_3 (10%)	2	87
6	NMP	Na_2CO_3	**2a**	1	89
7	NMP	Na_2CO_3	**2a**	2	98
8	NMP	Na_2CO_3	**2b**	2	97
9	NMP	Na_2CO_3	**2c**	2	97
10	NMP	Na_2CO_3	**2d**	2	97
11	NMP	K_2CO_3	**2a**	2	85
12	NMP	*t*-BuOK	**2a**	2	62
13	DMAc[d]	Na_2CO_3	**2a**	2	75
14	DMAc	K_2CO_3	**2a**	2	72
15	DMF	Na_2CO_3	**2a**	2	71
16	DMF	Cs_2CO_3	**2a**	2	35
17	DMF	K_3PO_4	**2a**	2	89
18	NMP	Na_2CO_3	**2a**	0.5	82
19	NMP	Na_2CO_3	**2a**	0.1	32

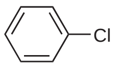
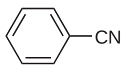
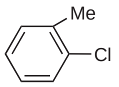
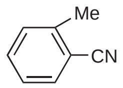
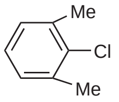
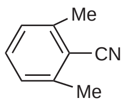
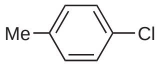
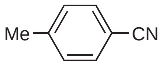
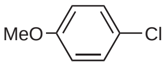
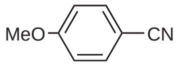
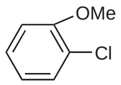
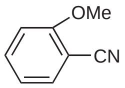
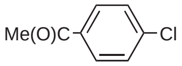
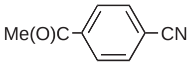
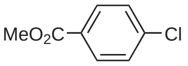
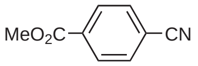
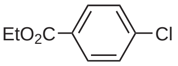
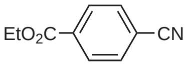
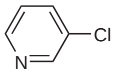
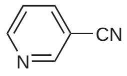
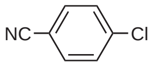
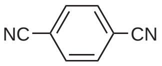
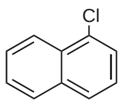
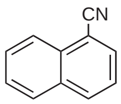
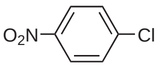
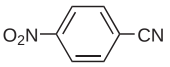
[a] Reaction conditions: 1 mmol 4-chlorotoluene, 0.22 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$, 1 mL solvent, 1 mmol base, 140 °C for 18 h.
[b] Conversion is determined by GC using *n*-undecane as an internal standard.
[c] NMP: *N*-methyl-2-pyrrolidone.
[d] DMAc: *N*,*N*-dimethylacetamide.

electron-rich **3b** and **3d** worked well and moderate to good yields were obtained (Table 2 entries 1, 2, and 4). Remarkably, even electron-rich **3f** also showed good reactivity, the corresponding **4f** could be isolated in 66% yield (Table 2 entry 6). Though only 47% yield was obtained for 4-chloroanisole (**3e**) under the optimized conditions, the result could be improved to 72% when DMAc/K_2CO_3 system was used (Table 2 entry 5). 3-Chloropyridine (**3j**) also exhibited satisfactory reactivity and **4j** was isolated in 82% yield (Table 2 entry 10). Further investigation revealed that the steric hindrance of substrates had little effect on this cyanation reaction. 2-Chlorotoluene (**3b**), 2,6-dimethylchlorobenzene (**3c**) and 1-chloronaphthalene (**3l**) afforded products in good to excellent yields (Table 2 entries 2, 3, and 12). Surprisingly, although a nitro group can activate the C–Cl bond of chloride-substituted nitrobenzene in most Pd-catalyzed C–C, C–N coupling reactions,[14,20,21] however, 4-nitrochlorobenzene (**3m**) did not give any desired product in this cyanation reaction.

Table 2 Cyanation of Aryl Chlorides Catalyzed by Cyclopalladium Compound **2a**[a]



3 **4**

Entry	Aryl chloride		Time (h)	Product		Yield (%)[b]
1		**3a**	18		**4a**	81
2		**3b**	18		**4b**	79
3		**3c**	18		**4c**	80
4		**3d**	18		**4d**	71
5		**3e**	24		**4e**	47 (72)[c]
6		**3f**	24		**4f**	66
7		**3g**	16		**4g**	81
8		**3h**	16		**4h**	80
9		**3i**	16		**4i**	88
10		**3j**	18		**4j**	82
11		**3k**	16		**4k**	73
12		**3l**	16		**4l**	97
13		**3m**	24		**4m**	0

[a] Reaction conditions: 1 mmol substrate, 0.22 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$, 2 mol% catalyst, 1 mmol Na_2CO_3 and 1 mL NMP, 140 °C reaction temperature.

[b] Isolated yield.

[c] Yield with DMAc/K_2CO_3 is given in parentheses.

In summary, we developed an efficient method for cyanation of less costly aryl chloride with environmentally benign cyanide source – potassium hexacyanoferrate(II). A variety of activated or deactivated aryl chlorides can be successfully converted into corresponding cyanides.

Acknowledgment

We thank the National Natural Science Foundation of China (No. 20472074) and the Innovation Fund for Outstanding Scholar of Henan Province (No. 0621001100) for financial support. We thank Dr. Weiguo Zhu, Mr. Janxun Kang for their excellent analytical support and Prof. Junfang Gong, Xiuling Cui, Dr. Chen Xu for their help.

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(19) **General Procedure.**
A reaction vessel was charged with 1 mmol Na_2CO_3, 0.22 mmol $K_4[Fe(CN)_6]\cdot 3H_2O$ and 2% mol catalyst **2a**. The vessel was then evacuated and backfilled with N_2 four times. Then, 1 mmol aryl chloride in 1 mL NMP was added to the vessel. The mixture was heated at 140 °C for 16–24 h. The suspension was cooled down to r.t., diluted with 5 mL CH_2Cl_2 and washed with 5 mL H_2O. The aqueous layer was extracted twice with CH_2Cl_2 (3 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvents the residue was subjected to TLC (hexane–EtOAc). All prepared compounds were known and identified by ^1H NMR, ^{13}C NMR and MS.
Selected Data.
Compound **4c**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.53$ (s, 6 H), 7.11 (d, $J = 7.7$ Hz, 2 H), 7.34 (dd, $J = 7.7$ Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.8$, 113.3, 117.3, 127.3, 132.1, 142.1 ppm. MS (ESI): $m/z = 154.1$ $[M + Na]^+$.
Compound **4e**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.87$ (s, 3 H), 6.95 (d, $J = 8.9$ Hz, 2 H), 7.58 (d, $J = 8.9$ Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 103.7, 114.5, 119.0, 133.7, 162.6 ppm. MS (ESI): $m/z = 156.0$ $[M + Na]^+$.
Compound **4i**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3 H), 4.42 (q, $J = 7.1$ Hz, 2 H), 7.74 (d, $J = 8.3$ Hz, 2 H), 8.14 (d, $J = 8.3$ Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 61.6, 116.0, 117.8, 129.8, 131.9, 134.1, 164.7 ppm. MS (ESI): $m/z = 197.8$ $[M + Na]^+$.
Compound **4j**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (m, 1 H), 7.98 (m, 1 H), 8.83 (m, 1 H), 8.91 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 110.3$, 116.5, 123.6, 139.3, 152.5, 153.0 ppm. MS (ESI): $m/z = 105.0$ $[M + H]^+$.

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