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PALLADIUM-CATALYZED CYANATION OF ARYL BROMIDES USING PHOSPHINE-FREE PYRIDYL-HYDRAZONE LIGANDS

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Abstract – Palladium-catalyzed cyanation of aryl bromides with potassium hexacyanoferrate(II) trihydrate, $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide source gave benzonitrile derivatives using a catalytic amount of $Pd(OCOCF_3)_2$ in DMF at 110 °C with phosphine-free pyridyl-hydrazone ligand **2c** in good yields.

Benzonitrile derivatives are valuable intermediates in organic synthesis, such as dyes, pharmaceuticals, agrochemicals, and natural products, and can be easily transformed to benzoic acids, benzoic esters, amides, amines, and aldehydes. The traditional method for preparing benzonitriles from corresponding aryl bromides and iodides requires stoichiometric copper(I) cyanide under harsh conditions known as the Rosenmund-von Braun reaction.[1] Therefore, some transition metal catalyzed methods have been developed, such as palladium-, nickel-, and copper-catalyzed methods using KCN,[2] NaCN,[3] $Zn(CN)_2$,[4] and trimethylsilyl cyanide[5] as the cyanide source. However, most work has concentrated on the traditional inconvenient cyanide sources, which have severe drawbacks. To avoid these problems, potassium hexacyanoferrate(II) was rediscovered as a non-toxic cyanide source using $Pd(OAc)_2$/DPPF under a N_2 atmosphere by Beller;[6] the reactions of aryl halides using $Pd(OAc)_2$ with other phosphine ligands were also reported.[7] However, phosphine ligands are often air-sensitive. Although phosphine-free palladium catalytic systems have also been reported,[8] these reactions sometimes require harsh heating conditions or microwave irradiation conditions. And also dried potassium hexacyanoferrate(II) was used sometimes instead of hydrate under the reaction.[8h]

On the other hand, we recently demonstrated air-stable phosphine-free hydrazone as an effective ligand for palladium-catalyzed C-C bond formations.[9] We now report the use of phosphine-free bishydrazone

ligands **1** and pyridyl-hydrazone ligands **2** for a palladium catalyzed cyanation of aryl bromides with potassium hexacyanoferrate(II) trihydrate, $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide source under aerobic conditions at 110 °C.

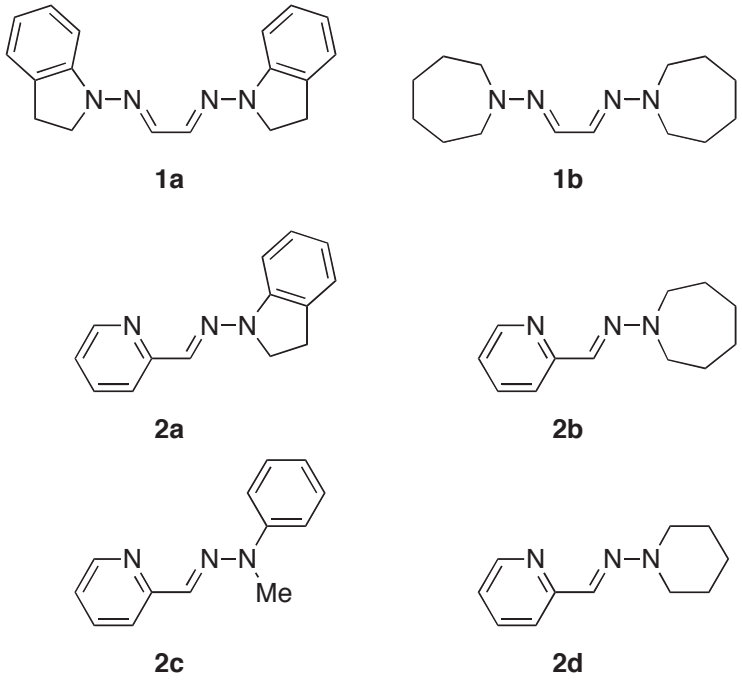
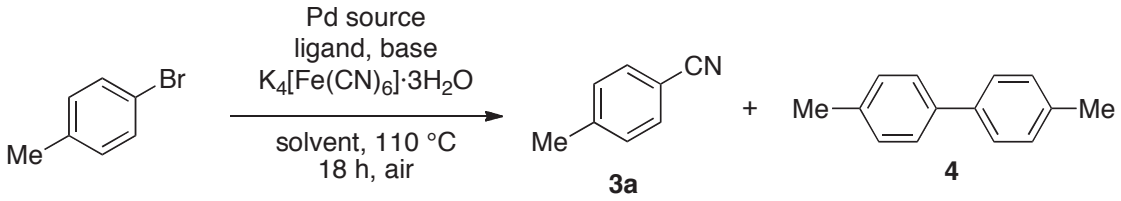


Figure 1. Hydrazone ligands

Initially, we sought the optimal reaction conditions for the palladium-catalyzed cyanation of aryl bromides with potassium hexacyanoferrate(II) trihydrate, $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide source. 4-Bromotoluene was chosen as a model substrate with 2 mol% of Pd catalyst for 18 h under aerobic conditions at 110 °C (Table 1). Using 2 mol% of indoline-derived bishydrazone **1a** as a ligand, we observed that cyanation in the presence of $Pd(OAc)_2$ with 2 equiv. of K_3PO_4 as a base in DMF as a solvent proceeded to give *p*-tolunitrile (**3a**) in 75% yield with a small amount of 4,4'-dimethylbiphenyl (**4**) as a by-product (Table 1, Entry 1). Several commonly used bases were tested (Entries 1-4); K_3PO_4 preferred this reaction (Entry 1). The effect of various solvents was also investigated (Entries 1, and 5-7). The use of DMF as a solvent led to high yield for this reaction (Entry 1). We tested bishydrazone **1b** and pyridyl-hydrazones **2a**-**d** (Entries 9-12) and found that pyridyl-hydrazone **2c** was a very effective ligand for this reaction (Entry 11). The effect of various palladium sources was also investigated (Entries 11, and 13-15). The use of $Pd(OCOCF_3)_2$ led to high yield for this reaction (Entry 15). We found the following optimized conditions; using the $Pd(OCOCF_3)_2$/pyridyl-hydrazone **2c** system, the reaction proceeded with 83% in DMF at 110 °C (Entry 15).

Table 1. Optimization of Reaction Conditions on the Palladium-Catalyzed Cyanation of 4-Bromotoluene[a]



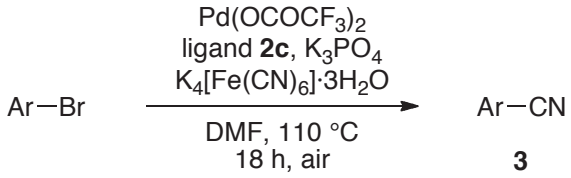
Entry	Base	Solvent	Ligand	Pd source	Yield (%)[b] **3a**/**4**
1	K_3PO_4	DMF	**1a**	$Pd(OAc)_2$	75/5
2	KF	DMF	**1a**	$Pd(OAc)_2$	7/0
3	KOAc	DMF	**1a**	$Pd(OAc)_2$	23/0
4	Na_2CO_3	DMF	**1a**	$Pd(OAc)_2$	6/0
5	K_3PO_4	NMP	**1a**	$Pd(OAc)_2$	11/0
6	K_3PO_4	DMSO	**1a**	$Pd(OAc)_2$	0/0
7	K_3PO_4	PhMe	**1a**	$Pd(OAc)_2$	0/0
8	K_3PO_4	DMF	**1b**	$Pd(OAc)_2$	75/6
9	K_3PO_4	DMF	**2a**	$Pd(OAc)_2$	75/5
10	K_3PO_4	DMF	**2b**	$Pd(OAc)_2$	71/6
11	K_3PO_4	DMF	**2c**	$Pd(OAc)_2$	82/2
12	K_3PO_4	DMF	**2d**	$Pd(OAc)_2$	78/4
13	K_3PO_4	DMF	**2c**	$PdCl_2$	79/3
14	K_3PO_4	DMF	**2c**	$PdCl_2(MeCN)_2$	76/3
15	K_3PO_4	DMF	**2c**	$Pd(OCOCF_3)_2$	83/2

[a] Reaction conditions: 4-Bromotoluene (1.0 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.4 mmol), ligand (2 mol%), Pd source (2 mol%), base (2.0 mmol), solvent (2 mL) at 110 °C for 18 h under an air.
[b] Determined by ^1H NMR or GC using 2-methoxynaphthalene as an internal standard.

To evaluate the scope and limitations of this procedure, the reactions of various aryl bromides were investigated (Table 2). Using 1-bromo-4-alkylbenzenes and *p*-bromobiphenyl led to good yields of corresponding benzonitriles (Entries 1-4) including such fragrance compounds as *p*-isopropylbenzonitrile (cumin nitrile) (**3b**). Moreover, aryl bromides with methoxy and phenoxy groups at the *para*-position also led to good yields (Entries 5 and 6). On the other hand, aryl bromides with electron-withdrawing groups, such as *p*-bromobenzophenone and 1-bromo-4-chlorobenzene, led to moderate yields (Entries 7 and 8). We also investigated the reaction of 3-substituted and 2-substituted aryl bromides (Entries 9-13). Although the reaction with *o*-bromoanisole gave a small amount of homocoupling product instead of corresponding product (Entry 13), the other reactions gave corresponding products in moderate to good yields. Using 1-bromonaphthalene also led to good yield of the corresponding nitrile (Entry 14).

In conclusion, we found that the palladium-catalyzed cyanation of aryl bromides with potassium hexacyanoferrate(II) trihydrate, $K_4[Fe(CN)_6]\cdot 3H_2O$ as the cyanide source gave benzonitrile derivatives using a catalytic amount of $Pd(OCOCF_3)_2$ in DMF at 110 °C under aerobic conditions with phosphine-free pyridyl-hydrazone ligand **2c** in good yields.

Table 2. Palladium-Catalyzed Cyanation of Aryl Bromides with Pyridyl-Hydrazone Ligand **2c**[a]



Entry	Ar	Product	Yield (%)[b]
1	4-MeC_6H_4	**3a**	73
2	4-$^{i}PrC_6H_4$	**3b**	71
3	4-$^{t}BuC_6H_4$	**3c**	72
4	4-PhC_6H_4	**3d**	70
5	4-$MeOC_6H_4$	**3e**	84
6	4-$PhOC_6H_4$	**3f**	75
7	4-BzC_6H_4	**3g**	47
8	4-ClC_6H_4	**3h**	34
9	3-MeC_6H_4	**3i**	64
10	3-$MeOC_6H_4$	**3j**	65
11	3,5-diMeC_6H_3	**3k**	77
12	2-MeC_6H_4	**3l**	64
13	2-$MeOC_6H_4$	**3m**	0[c]
14	1-Naphthyl	**3n**	77

[a] Reaction conditions: Aryl bromide (1.0 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.4 mmol), ligand **2c** (2 mol%), $Pd(OCOCF_3)_2$ (2 mol%), K_3PO_4 (2.0 mmol), DMF (2 mL) at 110 °C for 18 h under an air.
[b] Isolated yields.
[c] Homocoupling product was obtained in 4% yield.

EXPERIMENTAL

General

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard. Infrared (IR) spectra were obtained using a JASCO FT/IR 230 spectrophotometer. Mass spectra were recorded on a GCMS-QP 5050. Hydrazone ligands **1**[9c,d] and **2**[9b,c,d,e] were prepared according to the literature methods.

General procedure of palladium-catalyzed cyanation of aryl bromides.

To a mixture of $K_4[Fe(CN)_6]\cdot 3H_2O$ (169.5 mg, 0.4 mmol), K_3PO_4 (424 mg, 2.0 mmol), $Pd(OCOCF_3)_2$ (6.69 mg, 20 μmol), and ligand **2c** (4.26 mg, 20 μmol) in DMF (2.0 mL) was added aryl bromide (1.0 mmol) at room temperature under an air. The mixture was stirred at 110 °C. After 18 h, the mixture was diluted with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane or hexane/EtOAc = 20-100/1).

p-Tolunitrile (**3a**)[2a]: 73% as a white solid; mp 25-26 °C; ^1H NMR ($CDCl_3$) δ: 2.42 (s, 3H), 7.27 (d, J = 8.0

Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.8, 109.3, 119.1, 129.8, 132.0, 143.6; IR (KBr): (CN) 2226 cm^{-1}; EI-MS *m/z* (rel intensity): 117 (M^+, 100).

p-Isopropylbenzonitrile (**3b**)[10]: 71% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 1.26 (d, *J* = 6.9 Hz, 6H), 2.88-3.07 (m,1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 23.5, 34.4, 109.6, 119.2, 127.3, 132.2, 154.3; IR (neat): (CN) 2227 cm^{-1}; EI-MS *m/z* (rel intensity): 145 (M^+, 24).

p-tert-Butylbenzonitrile (**3c**)[7c]: 72% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 1.33 (s, 9H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 30.9, 35.3, 109.3, 119.1, 126.1, 132.0, 156.6; IR (neat): (CN) 2227 cm^{-1}; EI-MS *m/z* (rel intensity): 159 (M^+, 21).

p-Phenylbenzonitrile (**3d**)[2b]: 70% as a white solid; mp 81-82 °C; ^{1}H NMR ($CDCl_3$) δ: 7.39-7.53 (m, 3H), 7.56-7.62 (m, 2H), 7.66-7.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 110.8, 118.9, 127.2. 127.7, 128.6, 129.1, 132.6, 139.1, 145.6; IR (KBr): (CN) 2225 cm^{-1}; EI-MS *m/z* (rel intensity): 179 (M^+, 100).

p-Methoxybenzonitrile (**3e**)[2b]: 84% as a white solid; mp 52-53 °C; ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 3H), 6.92-6.99 (m, 2H), 7.64-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 55.5, 104.0, 114.7, 119.2, 134.0, 162.8; IR (KBr): (CN) 2217 cm^{-1}; EI-MS *m/z* (rel intensity): 133 (M^+, 100).

p-Phenoxybenzonitrile (**3f**)[11]: 75% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 6.98-7.08 (m, 4H), 7.20-7.27 (m, 1H), 7.38-7.44 (m, 2H), 7.58-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 105.7, 117.8, 118.8, 120.4, 125.1, 130.2, 134.1, 154.7, 161.6; IR (neat): (CN) 2225 cm^{-1}; EI-MS *m/z* (rel intensity): 195 (M^+, 100).

4-Cyanobenzophenone (**3g**)[12]: 47% as a white solid; mp 104-105 °C; ^{1}H NMR ($CDCl_3$) δ: 7.52 (t, *J* = 7.8 Hz, 2H), 7.62-7.68 (m, 1H), 7.78-7.81 (m, 4H), 7.87-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 115.6, 118.0, 128.6, 130.0, 130.2, 132.1, 133.3, 136.3, 141.2, 195.0; IR (KBr): (CN) 2227 cm^{-1}, (CO) 1647 cm^{-1}; EI-MS *m/z* (rel intensity): 207 (M^+, 44).

p-Chlorobenzonitrile (**3h**)[2a]: 34% as a white solid; mp 87-88 °C; ^{1}H NMR ($CDCl_3$) δ: 7.45-7.49 (m, 2H), 7.59-7.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 110.7, 118.0, 129.7, 133.4, 139.5; IR (neat): (CN) 2225 cm^{-1}; EI-MS *m/z* (rel intensity): 137 (M^+, 100).

m-Tolunitrile (**3i**)[4b]: 64% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 7.32-7.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 21.1, 112.2, 119.0, 129.0, 129.3, 132.5, 133.6, 139.2; IR (neat): (CN) 2229 cm^{-1}; EI-MS *m/z* (rel intensity): 117 (M^+, 100).

m-Methoxybenzonitrile (**3j**)[2a]: 65% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 3H), 7.11-7.17 (m, 2H), 7.22-7.25 (m, 1H), 7.34-7.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 55.5, 113.1, 116.8, 118.7, 119.3, 124.5, 130.3, 159.6; IR (neat): (CN) 2230 cm^{-1}; EI-MS *m/z* (rel intensity): 133 (M^+, 100).

3,5-Dimethylbenzonitrile (**3k**)[7c]: 77% as a white solid; mp 42-43 °C; ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 6H), 7.22 (s, 1H), 7.26 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.0, 112.0, 119.2, 129.6, 134.6, 139.0; IR (KBr): (CN) 2230 cm^{-1}; EI-MS *m/z* (rel intensity): 131 (M^+, 63).

o-Tolunitrile (**3l**)[7c]: 64% as a colorless liquid; ^{1}H NMR ($CDCl_3$) δ: 2.56 (s, 3H), 7.23-7.37 (m, 2H),

7.44-7.53 (m, 1H), 7.57-7.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 20.4, 112.7, 118.1, 126.2, 130.2, 132.5, 132.6, 141.9; IR (neat): (CN) 2225 cm^{-1}; EI-MS *m/z* (rel intensity): 117 (M^+, 100).

1-Cyanonaphthalene (**3n**)[7c]: 77% as a brown solid; mp 30-31 °C; ^{1}H NMR ($CDCl_3$) δ: 7.50-7.73 (m, 3H), 7.91-7.95 (m, 2H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 110.2, 117.8, 124.9, 125.1, 127.5, 128.58, 128.63, 132.3, 132.6, 132.9, 133.3; IR (KBr): (CN) 2218 cm^{-1}; EI-MS *m/z* (rel intensity): 153 (M^+, 100).

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