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Ligand-Free Palladium-Catalyzed Cyanation of Aryl Halides

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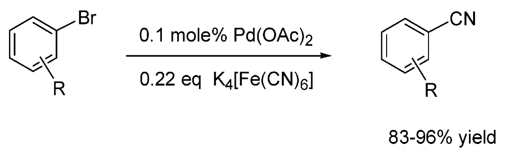

A practical, *ligand-free* cyanation of aryl bromides that utilizes as little as 0.1 mol % Pd(OAc)$_2$ in combination with a nontoxic cyanide source, M$_4$[Fe(CN)$_6$] (M = K, Na), is described. The reactions are performed in DMAC at 120 °C and provide the corresponding aryl nitrile in 83−96% yield, typically in less than 5 h. TON values of up to 7100 were attained.

Aromatic nitriles constitute a key component of numerous commercial compounds, including pharmaceuticals, agrochemicals (herbicides, pesticides), and pigments and dyes.[1] Their utility also stems from the myriad of possible nitrile transformations, including the synthesis of benzoic acids/esters, amidines, amides, imidoesters, benzamidines, amines, heterocycles, and aldehydes.[2] The traditional method for preparing aromatic nitriles from the corresponding aryl bromides/iodides, Rosemund−Von Braun reaction,[3] requires stoichiometric copper(I) cyanide at elevated temperatures, often with complicated workups. In 1973, Takagi described the first metal-catalyzed cyanation of aryl halides that also happened to be a ligand-free system.[4] This methodology employed KCN and 2 mol % Pd(CN)$_2$ (for the aryl bromides substrates) with conversions ranging from 64 to 91% at ≥140 °C. A subsequent modification using catalytic KOH and KI in conjunction with 1.5 mol % Pd(OAc)$_2$ at 90 °C was also reported by that group.[5] Since then, palladium-based methods[6] have garnered most of the attention due to their functional group tolerance, air stability, and high catalytic activity, but none of these methods offered the ligand-free advantage. One constraint of these procedures, which typically utilize M−CN (M = Na, K, TMS, Cu) as the nucleophile, is the high level of dissolved cyanide in the reaction that inhibits the catalytic cycle, namely, the oxidative insertion, due to formation of unreactive palladium(II) cyano species. This has led to the use of additives such as zinc acetate,[7] diamines,[8] zinc dust,[9] and Me$_3$SnCl[10] to enhance the catalytic turnover. Controlling the CN concentration via defined dosing of the cyanide has also been used toward this end,[11] as has the use of less soluble cyanide reagents such as zinc cyanide[12] and potassium ferrocyanide(II) (K$_4$[Fe(CN)$_6$]).[13] The latter reagent, recently rediscovered[14] as a cyanide source by Beller, is particularly intriguing because all six CN are available for reaction and it is inexpensive, easily handled, and nontoxic.[15] The use of ligands was thought to improve the catalytic activity and allowed for milder reaction conditions and the inclusion of typically unreactive aryl chlorides. The phosphine ligands though are often air/moisture-sensitive, more costly than the palladium species, and difficult to remove from the product and to recover. This has led to a reexamination of the role of ligands in Pd-catalyzed aromatic substitution reactions, as evidenced by recent work describing ligand-free Heck,[16] Suzuki,[17] and Sonogashira[18] reactions. Those results suggest that at low Pd(0) concentrations, the rate of oxidative addition exceeds that of the catalyst aggregation.[14a] As noted by Beletskaya,[19] "the inherent reactivity of unligated palladium is sufficient for oxidative addition to most kinds of C−X bonds." This prompted

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[1] For example, *The Merck Index* (13th ed.; O'Neil, M. J., Ed.; Merck: 2001) lists 22 compounds that incorporate this functionality: Monograph nos. 926, 1098, 1204, 1426, 1446, 1477, 2185, 2283, 2299, 2342, 2712, 2720, 3068, 3958, 5469, 5481, 5576, 6690, 7242, 9615.

[2] *Chemistry of the Cyano Group*; Rappoport, Z., Ed.; John Wiley & Sons: London 1970.

[3] (a) For a review, see: Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189−283. (b) For improved conditions, see: Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522−2524.

[4] Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, *5*, 471−4.

[5] Takagi, K.; Okamoto, T.; Yasumasa, S.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298−3301.

[6] For reviews, see: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513−3526. (b) Takagi, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis;* Negishi, E., Ed.; J. Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 657−672.

[7] Chidambaram, R. *Tetrahedron Lett.* **2004**, 1441−1444.

[8] Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828−1836.

[9] Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, 243−244.

[10] Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837−2840.

[11] TMS−CN: Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50−55. Acetone cyanohydrin: Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661−1664.

[12] Use of zinc cyanide in this capacity was introduced by: Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887−890.

[13] Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, *12*, 1388−1389. We observed no need to dehydrate (3 equiv of water present) this reagent as was described by the authors in this reference. The reagent particle size is critical, as material obtained from Alfa/Aesar performed well (mean particle size 312 μm; 90% <509 μm), while material from Acros (mean particle size 464 μm; 90% <822 μm) showed only 5% conversion to benzonitrile after 10 h at 120 °C. The latter material performed typically (99% conversion/1 h) after pulverization to values of 184 and 374 μm, respectively.

[14] First use of potassium ferrocyanide in this capacity (uncatalyzed reaction): Merz, V.; Weith, W. *Ber.* **1877**, *10*, 746−765.

[15] K$_4$[Fe(CN)$_6$] (aka yellow prussiate of potash) is used as a food additive in table salt to prevent "caking" and in wine production to precipitate metals. The lower toxicity is attributed to the tight bond between the iron center and the CN groups.

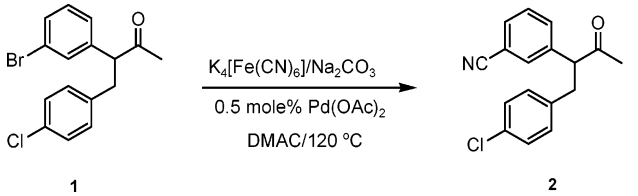
[16] (a) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288. (b) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559−1563.

[17] de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799−811.

[18] Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752−5755.

[19] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

10.1021/jo0481250 CCC: $30.25



1 **2**

FIGURE 1. Ligand-free cyanation of bromoketone **1**.

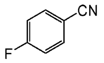
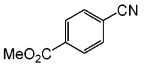
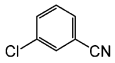
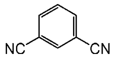
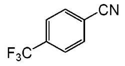
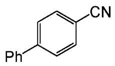
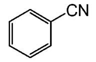
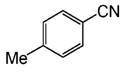
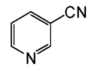
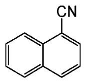
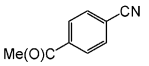
a study into the potential for similar reactivity with the aromatic cyanation reaction. *Herein, we describe a practical, ligand-free cyanation of aryl bromides using homeopathic amounts of palladium.*[20]

We required a practical procedure to convert bromoketone **1** into cyanoketone **2** (Figure 1). Application of the Beller protocol ($K_4[Fe(CN)_6]/Pd(OAc)_2$/dppf) in DMF with sodium carbonate gave an 86% assay yield of **2** within 4 h at 120 °C (>99% conversion). A recent result describing the use of 1,4-diazabicyclo-[2.2.2]octane (DABCO) as a palladium ligand in the Suzuki coupling[21] led us to try a similar tactic in the aryl cyanation reaction. By replacing the dppf with 2 mol % DABCO, in conjunction with 1 mol % $Pd(OAc)_2$ and 22 mol % $K_4[Fe(CN)_6]\cdot 3\ H_2O$ in DMF, a 90% assay yield of nitrile **2** was obtained within 4 h at 120 °C; no bis cyanide was observed. A control reaction in DMF in the absence of DABCO showed only 23% conversion after 5 h at 120 °C

This result suggests that in DMF, the DABCO acts as a ligand to accelerate the reaction. The role of sodium carbonate is essential, as only 3% conversion was observed after 3 h at 120 °C in its absence. Subsequently, the use of dimethylacetamide (DMAC) solvent was preferred, as it led to more robust and faster reactions (2 h). The fact that DMF is known to thermally degrade to dimethylamine (DMA) could be a contributing factor, as recent work from these laboratories has demonstrated[22] that DMA enhances cyanide solubility in the case of $ZnCN_2$. *When a control reaction using 0.5 mol % $Pd(OAc)_2$ in DMAC was performed in the absence of the DABCO (i.e., ligand-free), surprisingly an 87% assay yield was obtained within 2 h.*

This result led to a study into the scope and limitations of this new aryl cyanation methodology.[23] A series of aryl halides were reacted under standard conditions,[24] and the results are displayed in Table 1. Rapid (≤5 h) and complete reactions were observed for activated aryl bromides (i.e., electron-withdrawing group present) as would be expected (entries 2−6). Even electron−neutral systems (entries 7, 8, 11) and a mildly electron-rich arene, *p*-bromotoluene (run 9), were completely reacted within 5 h with assay yields >90%. The cyanation of an *N*-heteroaryl bromide (entry 10) gave an 86% assay yield after 8 h at 120 °C. High selectivity was observed for 3-bromochlorobenzene (entry 4). In this example, the $K_4[Fe(CN)_6]$ charge was reduced to 0.18 equiv (1.07 equiv CN). After 1.5 h at 120 °C, the reaction showed >98% conversion and a 22:1 A% ratio of mono:bis cyanation. The trace amount of cyanation of the aryl chloride led us to investigate extending this methodology to aryl chlorides.

TABLE 1. Ligand-free Cyanation of Aryl Bromides[a]

Entry	Product	Yield[b] (%)	Time (h)	Conv (A%)
1	**2**	87	2	>99
2		96	1	>99
3		83	5	>99
4[c]		81	3	>98
5[d]		90	5	>99
6		90	2	>99
7		91	1	>99
8		92	1.5	>99
9		90	2	>99
10		86	8	>99
11		92	1.5	>99
12		86	5	95

[a] Reaction conditions: 1.0 equiv of aryl bromide (4−6 mmols), 0.22 equiv of $K_4[Fe(CN)_6]$, 1.0 equiv of Na_2CO_3, 0.1−0.5 mol % $Pd(OAc)_2$, DMAC (0.6 M), 120 °C. [b] Assay yield determined by LC vs authentic standard. [c] Performed with 0.18 equiv of $K_4[Fe(CN)_6]$. [d] Starting material was 3-bromobenzonitrile.

When 0.44 equiv of $K_4[Fe(CN)_6]$ was used with 3-bromochlorobenzene, the reaction stalled at a 63:37 ratio (bis:mono cyanation) after 4 h at 120 °C.[25] This result suggested that aryl chlorides are partially reacted under these conditions. Similarly, the cyanation of 3-chlorobenzonitrile stalled after 51% conversion. Lower yields and/or incomplete reactions were observed with 4-bromo-

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(20) Term "homeopathic quantity" refers to low loadings of ligand-free palladium (generally 0.1 mol % or lower). See ref 18.

(21) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809−2811. Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449−8452.

(22) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D.; Chen, C. *Org. Lett.* **2004**, *6*, 3723−3725.

(23) Sodium ferrocyanide ($Na_4[Fe(CN)_6]\cdot 10\ H_2O$), also known as yellow prussiate of soda, also can be used as the cyanide source with equal performance.

(24) Standard conditions: 0.1−0.5 mol % $Pd(OAc)_2$/22 mol % $K_4[Fe(CN)_6]$/1.0 equiv Na_2CO_3 in DMAC (0.6−0.7 M) at 120 °C.

(25) Increasing the temperature to 130 °C had no effect on further conversion.

benzaldehyde (61% assay yield), 4-bromoanisole (11% conversion), and 3-bromothiophene.

The cyanation reactions proceeded efficiently with as little as 0.1 mol % catalyst, corresponding to a catalyst turnover number (TON) approaching 1000. An attempt to reduce the charge to 0.01 mol % with 4-trifluoromethyl-bromobenzene stalled at 71% conversion (TON = 7100). The reaction temperature can be reduced to 100 °C, as evidenced by the >99% conversion attained within 3 h for 4-trifluoromethyl-bromobenzene (entry 6) with 0.1 mol % $Pd(OAc)_2$. Elimination of the base gave minimal reaction (3% conversion) and suggests that the base might play a role in reducing the $Pd(II)(OAc)_2$ to the active Pd(0) species.[26] Inherently, there is no need for base, as several aryl cyanation methodologies use none at all. The reaction does not proceed in the absence of the palladium.[27]

We have developed a practical, ligand-free aryl cyanation methodology utilizing inexpensive, easy-to handle, and nontoxic reagents. This procedure gives high yields for a respectable variety of aryl bromides and is amenable to large-scale work, as the reactions are rapid and require only a modest catalyst charge. This result adds to the growing list of metal-catalyzed reactions that can be performed ligand-free.

Experimental Section

General Procedure. A 25 mL flask was charged with the aryl bromide (6 mmols), DMAC (10 mL), $K_4[Fe(CN)_6]\cdot 3\,H_2O$ (557 mg; 1.32 mmols; 0.22 equiv), sodium carbonate (636 mg; 6 mmols; 1.0 equiv), and $Pd(OAc)_2$ (0.1−0.5 mol %; either as a solid or as a 1 mg/mL solution in DMAC). The flask was evacuated and filled with nitrogen (two times) and heated to 120 °C. Reaction conversion was monitored by HPLC. Upon completion, the reaction mixture was cooled to rt and diluted with 20 mL of EtOAc. The resulting slurry was filtered and the filtrate assayed for content. The product can be isolated by washing the filtrate with water (2 × 15 mL) and 5% NH_4OH (1 × 15 mL). The organic layer was dried over Na_2SO_4, and the volatiles were removed in vacuo to provide the product.

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Note Added in Revision. During the review process, a paper appeared in print by Professor Beller and coworkers on this topic (*J. Organomet. Chem.* **2004**, *689* (24), 4576−4583).

Supporting Information Available: Experimental details and characterization of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] Thermal decomposition of $Pd(OAc)_2$ to Pd(0) in propylene carbonate at 100 °C has been observed and might be a factor in this system as well. See: Reetz, M.; Lohmer, G. *Chem. Commun.* **1996**, 1921−1922.

[27] Use of 0.5 mol % Pd_2dba_3 also provides a nearly equivalent outcome for bromoketone **1**.