ORGANIC LETTERS
2011
Vol. 13, No. 4
648–651

A Mild and Efficient Palladium-Catalyzed Cyanation of Aryl Chlorides with $K_4[Fe(CN)_6]$

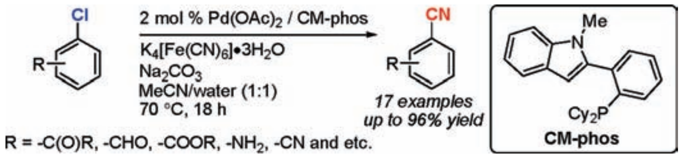
Pui Yee Yeung, Chau Ming So, Chak Po Lau, and Fuk Yee Kwong*

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

bcfyk@inet.polyu.edu.hk

Received November 30, 2010

ABSTRACT



An efficient palladium-catalyzed cyanation of aryl chlorides is established. In the presence of a highly effective Pd/CM-phos catalyst, cyanation of aryl chlorides proceeds at 70 °C in general, which is the mildest reaction temperature achieved so far for this process. Common functional groups such as keto, aldehyde, ester, nitrile and $-NH_2$, and heterocyclic coupling partners including N−H indoles are well tolerated. Moreover, a sterically hindered nonactivated ortho,ortho-disubstituted electrophile is shown to be a feasible coupling partner in cyanation.

Aromatic nitriles are important structural motifs in pharmaceuticals,[1] agrochemicals, dyes, herbicides, and insecticides. In organic synthesis, they are highly valuable because of possible nitrile transformations to benzoic acids/esters, amines, amides, imidoesters, benzamidines, aldehydes, and nitrogen-containing heterocycles.[2] Traditional synthetic methods for the formation of aryl nitriles are the Rosenmund−von Braun[3] and Sandmeyer[4] reactions and the industrially applied ammoxidation.[5] The Rosenmund−von Braun and Sandmeyer reactions convert aryl iodides/bromides and aryl diazonium, respectively, to corresponding nitriles using stoichiometric CuCN at high temperature (e.g., 150−250 °C). Ammoxidation affords aryl nitriles from toluene derivatives in the presence of oxygen and ammonia under harsh reaction conditions (e.g., 220−550 °C, under high pressure) with heterogeneous catalysts.

The relatively limited substrate scope of these reactions drives chemists to explore alternative transition-metal-catalyzed cyanations for the preparation of more diversely substituted aromatic nitriles.[6] Nickel,[7] copper,[8] and palladium complexes are known to be effective catalysts for this

---

(1) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, Germany, 2001; pp 241−242, 488−489, 553, 825−826, 1154, 1598−1599.

(2) (a) Rappoport, Z. *Chemistry of the Cyano Group*; John Wiley & Sons: London, U.K., 1970. (b) Larcok, R. C. *Comprehensive Organic Transformations*; VCH: New York, U.S.A, 1989; Vol. 819.

(3) (a) Rosenmund, K. W.; Struck, E. *Chem. Ber.* **1919**, *52*, 1749. (b) von Braun, J.; Manz, G. *Liebigs Ann. Chem.* **1931**, *488*, 111. For reviews, see:(c) Moury, D. T. *Chem. Rev.* **1948**, *42*, 207. (d) Ellis, G.; Romney-Alexander, T. *Chem. Rev.* **1987**, *87*, 79.

(4) (a) Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 2650. (b) Sandmeyer, T. *Chem. Ber.* **1885**, *18*, 1492.

(5) (a) Stevenson, A. C. *Ind. Eng. Chem.* **1949**, *41*, 1846. (b) Denton, W. I.; Bishop, R. B.; Caldwell, H. P.; Chapman, H. D. *Ind. Eng. Chem.* **1950**, *42*, 796.

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

(7) For selected references on nickel-catalyzed cyanation of aryl halides, see: (a) van Soolingen, J.; Brandsma, L.; Kruse, C. G. EP Patent 613,719, 1993. For microwave-assisted cyanation at 200 °C, see: (b) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122.

10.1021/ol1028892

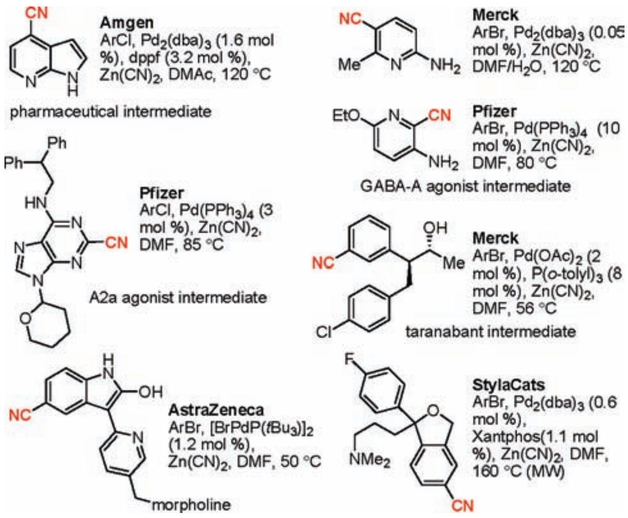


Figure 1. Selected examples of Pd-catalyzed cyanation of aryl halides in pharmaceutical applications.

reaction. However, substoichiometric to stoichiometric nickel complexes are required to drive the reaction.[7b] Copper-catalyzed protocols are currently not applicable for cyanation of aryl chlorides. In 1973, Takagi reported the first palladium-catalyzed cyanation of aryl halides.[9] Since then palladium-based cyanation procedures have attracted a number of applications in pharmaceutical syntheses (Figure 1),[10] because of their favorable features in better functional group tolerance, higher catalyst stability under air/moisture, and superior catalytic activity.

Recent methodology developments in palladium-catalyzed cyanation were focused on relatively reactive aryl iodides and bromides. They were converted to aryl nitriles with the aid of various cyanating agents, for instance, KCN, NaCN,[11] CuCN,[12] $Zn(CN)_2$,[13] TMSCN,[14] and acetone cyanohydrins.[15] In fact, aryl chlorides are superior substrates since they are relatively inexpensive and usually have a wider spectrum of availability when compared to bromoarenes and iodoarenes.[16] In 2000, Jin and Confalone reported the first palladium-catalyzed cyanation of aryl chlorides.[17] This procedure utilized $Zn(CN)_2$ as the cyanating sources and required a high reaction temperature. In 2007, Littke et al. reported mild cyanation conditions (95 °C in general) for aryl chlorides using the Buchwald-type ligand, *rac*-2-di-*tert*-butylphosphino-1,1′-binapththyl.[18] This cyanation used a $Zn(CN)_2$ source which is considerably toxic to humans and the environment.[19] Thus efforts in seeking a more environmental-friendly CN source have emerged. In 2004, Beller and coworkers introduced the Pd-catalyzed cyanation of aryl bromides mediated by $K_4[Fe(CN)_6]$.[20,21] The reaction temperature ranged from 140 to 160 °C. To the best of our knowledge, there has been limited literature report regarding cyanation of aryl chlorides mediated by $K_4[Fe(CN)_6]$ under mild reaction conditions.[22] Herein, we report a general palladium-catalyzed cyanation of aryl chlorides. The reaction temperature of 70 °C is the mildest ever reported in cyanation reactions.

We initially investigated the palladium-catalyzed cyanation using electronically neutral 4-chlorotoluene as the benchmark aryl chloride. A series of commercially

---

(8) For selected references on copper-catalyzed cyanation of aryl halides (ArI and ArBr), see: (a) Ren, Y. L.; Liu, Z. F.; Zhao, S.; Tian, X. Z.; Wang, J. J.; Yin, W. P.; He, S. B. *Catal. Commun.* **2009**, *10*, 768. (b) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem.—Eur. J.* **2007**, *13*, 6249. (c) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2005**, *11*, 2483. (d) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2829.

(9) (a) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, *5*, 471. (b) Takagi, K.; Okamoto, T.; Yasumasa, S.; Ohno, A.; Oka, S.; Hayama, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298.

(10) (a) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021. (b) Challenger, S.; Dessi, Y.; Fox, D. E.; Hesmondhalgh, L. C.; Pascal, P.; Pettman, A. J.; Smith, J. D. *Org. Process Res. Dev.* **2008**, *12*, 575. (c) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (d) Beaudin, J.; Bourassa, D. E.; Bowles, P.; Castaldi, M. J.; Clay, R.; Couturier, M. A.; Karrick, G.; Makowski, T. W.; McDermott, R. E.; Meltz, C. N.; Meltz, M.; Phillips, J. E.; Ragan, J. A.; Brown Ripin, D. H.; Singer, R. A.; Tucker, J. L.; Wei, L. *Org. Process Res. Dev.* **2003**, *7*, 873. (e) Wallace, D. J.; Campos, K. R.; Schultz, C. S.; Klapars, A.; Zewge, D.; Crump, B. R.; Phenix, B. D.; McWilliams, J. C.; Krska, S.; Sun, Y.; Chen, C.-Y.; Spindler, F. *Org. Process Res. Dev.* **2009**, *13*, 84. (f) Ryberg, P. *Org. Process Res. Dev.* **2008**, *12*, 540. (g) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705.

(11) For selected references, see: (a) Sakakibara, Y.; Sasaki, K.; Okuda, F.; Hokimoto, A.; Ueda, T.; Sakai, M.; Takai, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1013. (b) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707.

(12) For selected references, see: (a) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (b) Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119. (c) Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908.

(13) For selected references, see: (a) Tshaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (b) Marcantonio, K.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C.-Y. *Org. Lett.* **2004**, *6*, 3723. (c) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441. (d) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, *46*, 8645. (e) Chobanian, H. R.; Fors, B. P.; Lin, L. S. *Tetrahedron Lett.* **2006**, *47*, 3303. (f) Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008**, *10*, 5325. (g) see ref 10.

(14) For selected references, see: (a) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *41*, 2911. (b) Nakamura, H.; Shibata, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 2911.

(15) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.

(16) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(17) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271.

(18) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711.

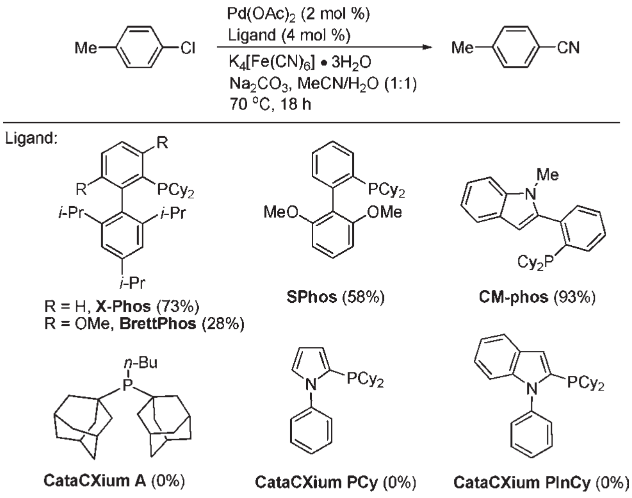
(19) $Zn(CN)_2$ [LD_{50} (oral, rat) = 54 mg/kg]; KCN [LD_{50} (oral, rat) = 5 mg/kg]. Toxicity data taken from corresponding Material Safety Data Sheet (MSDS) from Acros Organics, http://www.acros.com. KCN [LD_{50} (oral, human) = 2.86 mg/kg]; the LD_{50} of $K_4[Fe(CN)_6]$ is even lower than that for NaCl. Toxicity data taken from corresponding MSDS from Merck KGA, http://www.merck-chemicals.de.

(20) For initial development by the Beller group, see: (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, *12*, 1388. (b) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576.

(21) For investigations from other research groups, see: (c) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (d) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189. (e) Li, L.-H.; Pan, Z.-L.; Duan, X.-H.; Liang, Y.-M. *Synlett* **2006**, 2094. (f) Ren, Y.; Liu, Z.; He, S.; Zhao, S.; Wang, J.; Niu, R.; Yin, W. *Org. Process Res. Dev.* **2009**, *13*, 764. (g) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918. (h) Štěpnička, P.; Schulz, J.; Klemann, T.; Siemeling, U.; Císařová, I. *Organometallics* **2010**, *29*, 3187. (i) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052.

(22) Schareina, T.; Jackstell, R.; Schulz, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 643.

Scheme 1. Ligand Screening in Palladium-Catalyzed Cyanation of Aryl Chloride[a]



[a] Reaction conditions: 4-Chlorotoluene (1.0 mmol), $K_4[Fe(CN)_6]\bullet 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol), Pd/Ligand (1:2), Na_2CO_3 (0.125 mmol) in MeCN/water (1:1, 2 mL total) at 70 °C for 18 h. Calibrated GC yields were reported using dodecane as the internal standard.

available ligands were tested for their efficacy in this reaction (Scheme 1).

CM-phos[23] gave the best conversion (93% yield) of aryl chloride when compared to XPhos,[24] SPhos,[25] and BrettPhos[26] (Scheme 1). The CataCXium[27] ligand series did not promote the cyanation reaction. Further experiments were conducted for optimization of the cyanation process (Table 1). Inorganic bases were found to be important to promote this cyanation (entries 1−4). Na_2CO_3 afforded the best result (entry 1). The stoichiometry of Na_2CO_3 used also affected the substrate conversion (entries 1, 5−8). Acetonitrile/water mixtures were the best solvent medium of choice for this reaction (entry 7 vs 9−10). It should be noted that a no substrate conversion was observed when acetonitrile solvent was used alone (entry 11). We were intrigued that this inferior result may be due to the poor solubility of $K_4[Fe(CN)_6]\bullet 3H_2O$ in acetonitrile. Therefore, we attempted to add water in the reaction system in order to enhance the solubility of hydrated $K_4[Fe(CN)_6]$. The effect of water added to the cyanation reaction is summerized in Figure 2. Neither water nor acetonitrile alone provided substrate conversion. The best solvent mixtures ranged from 30 to 50% water in acetonitrile.

Table 1. Effect of Base and Solvent on the Cyantaion of 4-Chlorotoluene[a]

entry	base (mmol)	solvent (ratio)	yield (%)[b]
1	Na_2CO_3 (0.25)	$MeCN/H_2O$ (1:1)	91
2	K_2CO_3 (0.25)	$MeCN/H_2O$ (1:1)	81
3	Na_3PO_4 (0.25)	$MeCN/H_2O$ (1:1)	80
4	K_3PO_4 (0.25)	$MeCN/H_2O$ (1:1)	69
5	Na_2CO_3 (1.0)	$MeCN/H_2O$ (1:1)	57
6	Na_2CO_3 (0.5)	$MeCN/H_2O$ (1:1)	65
7	Na_2CO_3 (0.125)	$MeCN/H_2O$ (1:1)	96
8	Na_2CO_3 (0.063)	$MeCN/H_2O$ (1:1)	92
9	Na_2CO_3 (0.125)	*t*BuOH/H_2O (1:1)	22
10	Na_2CO_3 (0.125)	dioxane/H_2O (1:1)	50
11	Na_2CO_3 (0.125)	MeCN	0
12[c]	Na_2CO_3 (0.125)	$MeCN/H_2O$ (1:1)	66

[a] Reaction conditions: 4-Chlorotoluene (1.0 mmol), $K_4[Fe(CN)_6]\bullet 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol), Pd/CM-phos (1:2, precomplexation/preactivation of the catalyst was achieved by stirring Pd/CM-phos with Et_3N in CH_2Cl_2; see Supporting Information for details), base (as indicated), solvent (2 mL total) at 70 °C for 18 h. [b] Calibrated GC yields were reported using dodecane as the internal standard. [c] Pd_2dba_3 (0.01 mmol) was used instead of $Pd(OAc)_2$ (0.02 mmol).

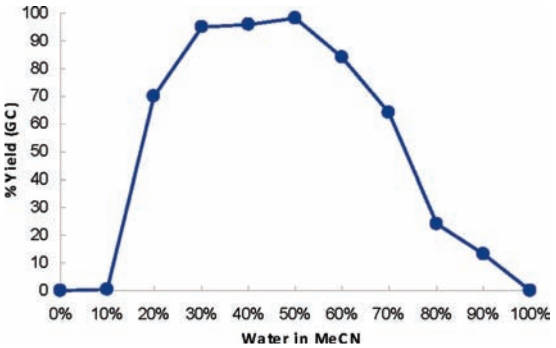


Figure 2. Effect of cosolvent (water) added to the benchmark conditions. Reaction conditions: 4-Chlorotoluene (1.0 mmol), $K_4[Fe(CN)_6]\bullet 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol), Pd/CM-phos (1:2), Na_2CO_3 (0.125 mmol), mixed solvent (2 mL total) at 70 °C for 18 h. Calibrated GC yields were reported using dodecane as the internal standard.

With the optimized reaction conditions in hand, we next tested the scope of this cyanation (Table 2). Common functional groups, such as aldehydo, keto, ester, nitrile, and free amino groups were well tolerated under these reaction conditions (entries 3, 5−9, 15). A deactivated aryl chloride also afforded a good yield (entry 2). The cyanation of benzothiazolyl and quinolyl chlorides furnished the corresponding products in satisfactory yields (entries 11−13). Notably, the cyanation of an unprotected indole gave the nitrile product in 91% yield (entry 14). The cyanation proceeded smoothly for sterically congested aryl chloride (entry 16).

---

(23) For our initial developments of CM-phos, see: (a) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402. (b) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. (c) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731.

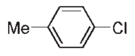
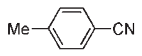
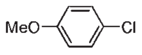
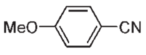
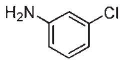
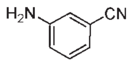
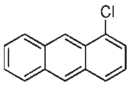
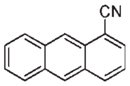
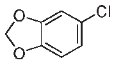
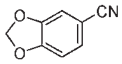
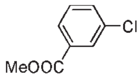
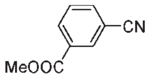
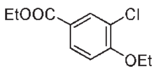
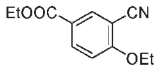
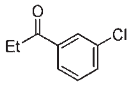
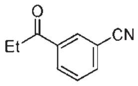
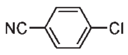
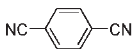
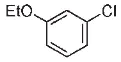
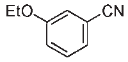
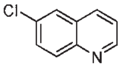
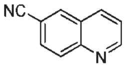
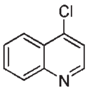
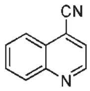
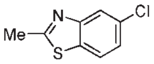
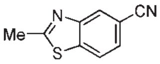
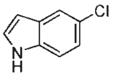
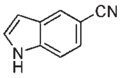
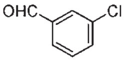
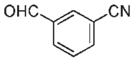
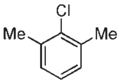
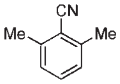
(24) For Buchwald's X-Phos in C−C coupling reactions, see: Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(25) For SPhos, see: Barder, T. E.; Walker, S. D.; Marinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(26) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

(27) For CataCXium A, see: (a) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. For CataCXium PCy, see:(b) Zapf, A.; Beller, M. *Chem Commun.* **2005**, 431. For CataCXium PInCy, see: (c) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983.

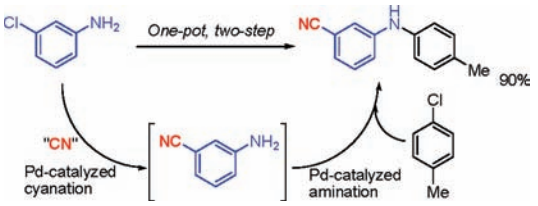
Table 2. Palladium-Catalyzed Cyanation of Aryl Chlorides[a]

entry	ArCl	ArCN	yield (%)[b]
1			90
2			85
3			95
4			86
5			90
6			78
7			74
8			94
9			75
10			90
11			96
12[c]			81
13[d]			97
14[d]			91
15[d]			71
16[e]			85

[a] Reaction conditions: ArCl (1.0 mmol), $K_4[Fe(CN)_6]•3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol, 2 mol %), Pd/CM-phos (1:2), K_2CO_3 (0.125 mmol), MeCN/water (1:1, total 2 mL), 70 °C, 18 h (reaction time was not optimized for each substrate). [b] Isolated yields. [c] 3 mol % $Pd(OAc)_2$. [d] 4 mol % $Pd(OAc)_2$. [e] 5 mol % $Pd(OAc)_2$.

A facile assembly of modular organic molecules using cross-coupling protocols is highly attractive.[28] To our delight, under our reaction conditions for cyanation, common functional groups are well tolerated. Thus, it is possible to perform sequential coupling reactions to access multifunctional molecules. To demonstrate the feasibility of this approach, a one-pot sequential synthesis was attempted (Scheme 2). 3-Chloroaniline was cyanated to give 3-aminobenzonitrile. Without further addition of catalyst, the *N*-aryl aminobenzonitrile was obtained in good yield after the addition of 4-chlorotoluene (Scheme 2).

Scheme 2. One-Pot Sequential Cyanation−Amination Reaction[a]



[a] Reaction conditions: (*Cyanation*) same as that in Table 2, entry 3; (*Amination*) 4-chlorotoluene (0.6 mmol), Cs_2CO_3 (3.0 mmol), toluene (2 mL, additional) were added and stirred at 110 °C for 24 h (see Supporting Information for detailed procedures).

In summary, we have reported a general and efficient palladium-catalyzed cyanation of aryl chlorides. The reaction temperature of 70 °C is the mildest condition reported so far for such reactions. Particularly noteworthy is that water is found necessary as cosolvent to facilitate the cyanation. This key finding may be useful for future cyanation investigations using $K_4[Fe(CN)_6]•3H_2O$ as the cyanide source. The mild palladium system described here exhibits excellent functional group compatibility. Nitrile, ester, keto, aldehyde, free amine, and heterocyclic groups remain intact during the course of the reaction. The one-pot cyanation−amination sequence shows the potential of this catalyst system for further functional group manipulation of a synthetic devise, yet without isolation of the intermediate or addition of extra catalyst.

Acknowledgment. Dedicated to Professor Albert S. C. Chan on the occasion of his 60th birthday. We thank the Research Grants Council of Hong Kong (PolyU 5008/08P), PolyU Internal Competitive Research Grant (A-PG13), and the University Grants Committee Areas of Excellence Scheme (AoE/P-10/01) for financial support.

Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of aryl nitriles. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(28) For reviews concerning the application of cross-coupling sequences for the preparation of pharmaceutically useful intermediates, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) King, A. O.; Yasuda, N. In *Organometallics in Process Chemistry*; Larsen, R. D., Ed.; Springer: Berlin, Germany, 2004; pp 205−246.