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A new palladium catalyst system for the cyanation of aryl chlorides with $K_4[Fe(CN)_6]$

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Abstract—The development of a novel Pd-catalyzed synthesis of (hetero)aromatic nitriles from the corresponding aryl chlorides and potassium hexacyanoferrate(II) is described. This novel protocol avoids the use of highly toxic alkali cyanides and proceeds in the presence of small amounts of palladium catalysts. High yields and selectivities of the corresponding aryl nitriles were achieved applying di(1-adamantyl)-1-butylphosphine (cata*CX*ium® A) as the ligand.

Aromatic nitriles are of considerable importance in organic chemistry as integral part of dyes, herbicides, natural products and pharmaceuticals.[1] Classical methods for the preparation of benzonitriles involve the Rosenmund–von Braun reaction of aryl halides and stoichiometric amounts of copper(I) cyanide,[2] diazotization of anilines and subsequent Sandmeyer reaction,[3] and on an industrial scale the ammoxidation reaction.[4] Since the mid 70s the synthesis of aryl nitriles via transition metal-catalyzed cyanation of aryl halides using inexpensive cyanide salts such as potassium cyanide or sodium cyanide has become more popular.[5–7]

In order to fully exploit the synthetic potential of this reaction it is important that all kinds of aryl and heteroaryl halides can be used as starting materials for this transformation. From an environmental point of view and for applications in the fine chemical industry[8] the efficient activation of inexpensive and readily available aryl bromides and chlorides[9] instead of aryl iodides is desirable. In general, the C–Cl bond in aryl chlorides is more difficult to activate than C–Br or C–I bonds. Nevertheless, the cyanation of aryl chlorides with either potassium cyanide or sodium cyanide in the presence of various additives and comparatively large amounts of nickel catalysts (up to 10 mol %) has been reported previously.[10] Palladium catalysts are in general more tolerant towards a variety of functional groups compared to nickel catalysts, and in addition can be more easily tuned for activating aryl–Cl bonds. Thus, there still exists a considerable interest in developing palladium catalysts for this reaction.[6] The cyanation of aryl chlorides via palladium catalysis has been observed only recently, except in the case of strongly activated C–Cl bonds. The first more general procedure was reported by Jin and Confalone who discovered that aryl chlorides react with zinc(II) cyanide in the presence of catalytic amounts of $Pd_2(dba)_3$, 1,1′-bis(diphenylphosphino)ferrocene (dppf) and zinc to give the corresponding nitriles.[11] A drawback of this procedure is the use of overstoichiometric amounts (1.2 equiv) of expensive and toxic zinc(II) cyanide, which leads to the formation of large amounts of zinc(II) waste. Additional disadvantages of this procedure are the use of 4 mol % palladium catalyst and the need of zinc as an additive (12 mol %). A newer procedure makes use of microwave activation[12] in the presence of 2 mol % palladium and SPhos as the ligand. Again, zinc(II) cyanide is used as cyanide source here. So far the most efficient Pd-catalyzed cyanation of chloroarenes has been described by us dosing acetone cyanohydrin in a controlled manner in the reaction mixture.[13]

More recently, we were able to demonstrate that in the cyanation of aryl bromides highly toxic cyanides can be replaced by potassium hexacyanoferrate(II), which

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is essentially the least toxic cyanide source conceivable. While all known other cyanation sources, for example, KCN (LD_{Lo} (oral, human) = 2.86 mg/kg), are highly poisonous, $K_4[Fe(CN)_6]$ is more or less non-toxic (the LD_{50} of $K_4[Fe(CN)_6]$ is lower than that for NaCl). Our new approach has proven its initial value in both palladium-[14] and copper-catalyzed cyanations[15] of aryl bromides and has been adopted nicely by other groups.[16]

In this Letter we report a new procedure for the direct cyanation of aryl chlorides using inexpensive and non-toxic $K_4[Fe(CN)_6]$ in the presence of less than 1 mol % of commercially available palladium catalysts.

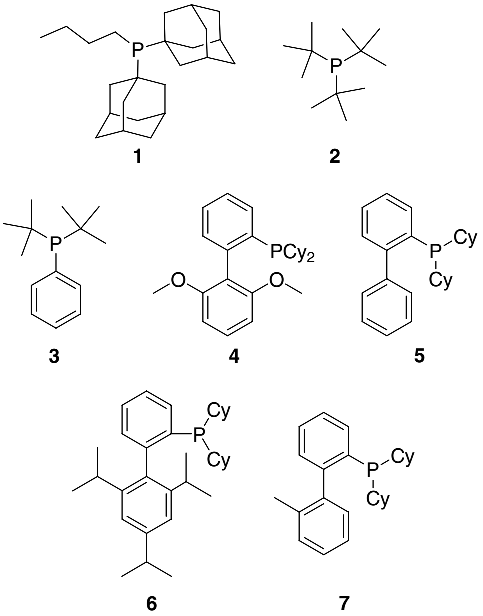
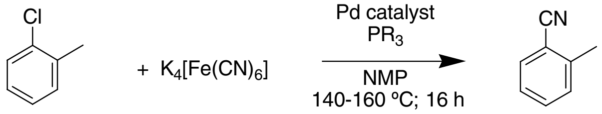


Figure 1. Tested ligands.

The cyanation of 2-chlorotoluene served as a model reaction in order to study the influence of temperature, Pd content, and ligands (Fig. 1; Table 1). Due to its electronic and steric nature, 2-chlorotoluene is a more difficult to activate substrate. According to our previous work a high-boiling polar solvent, temperatures of at least 140 °C and dried potassium hexacyanoferrate(II) were used. As expected exploratory reactions in the presence of aryl phosphines (e.g., PPh_3, P(*o*-tolyl)$_3$) gave no desired 2-methylbenzonitrile. Also carbene ligands, which have proven to form highly active electron rich palladium catalysts for a multitude of similar reactions,[17] showed no activity under these conditions. Therefore we focused on the use of strongly basic and sterically hindered phosphine ligands (Fig. 1). As shown in Table 1 only in the presence of ligand **1** (di(1-adamantyl)-1-butylphosphine; cataCXium® A) yields of more than 50% are observed. The superiority of this ligand for aryl–X activation reactions has already been shown in the formylation of aryl- and heteroaryl bromides.[18] The second best ligand is tri-*tert*-butyl phosphine (**2**; Table 1, entries 5 and 6), while a series of so-called Buchwald's ligands[19] (ligands **4**–**7**) provided yields in the range of 30–50% and below. An interesting feature of the model reaction is the fact that the best result with ligand **1** is obtained with the potassium hexacyanoferrate(II) trihydrate (Table 1, entry 1).

This is in contrast to our previous experiments with aryl bromides as starting materials, where no cyanation reaction took place in the presence of crystal water. However, other groups have not observed a detrimental effect of a water content of 60 mol % in the reaction vessel.[16a] The direct addition of water to a system with dry $K_4[Fe(CN)_6]$, under otherwise the same conditions, led

Table 1. Palladium-catalyzed cyanation of 2-chlorotoluene[a]



Entry	Solvent	Temperature (°C)	Pd precursor (mol % Pd)	Na_2CO_3 (mol %)	Ligand (mol %)	$K_4[Fe(CN)_6]$	Conversion[b] (%)	Yield [b] (%)	Selec. (%)
1	NMP	140	$Pd(OAc)_2$ (0.33)	20	**1** (1)	Hydrate	100	99	99
2	NMP	140	Pd_2dba_3 (0.33)	—	**1** (1)	Hydrate	97	97	>99
3	DMF	140	Pd_2dba_3 (0.33)	20	**1** (1)	Dried	87	78	90
4[c]	NMP	140	Pd_2dba_3 (0.33)	20	**1** (1)	Dried	21	19	88
5	NMP	140	$Pd(OAc)_2$ (0.5)	20	**2** (1)	Dried	54	47	86
6	NMP	160	Pd_2dba_3 (0.5)	5	**2***HBF_4 (1)	Dried	16	9	52
7	NMP	160	Pd_2dba_3 (0.5)	5	**3***HBF_4 (1)	Dried	20	9	40
8	NMP	140	$Pd(OAc)_2$ (0.25)	20	**4** (0.75)	Dried	24	22	95
9	NMP	160	Pd_2dba_3 (0.5)	10	**5** (1)	Dried	45	32	69
10	NMP	160	Pd_2dba_3 (0.5)	—	**6** (1)	Dried	16	4	24
11	NMP	160	Pd_2dba_3 (0.5)	—	**7** (1)	Dried	13	1	12

[a] General reaction conditions: 2 mmol 2-chlorotoluene, 0.4 mmol $K_4[Fe(CN)_6]$, metal precursor and ligand in stock solution in the given solvent, filled up to 2 ml, 200 μl internal standard (tetradecane), 16 h at temperature given, in a pressure tube under argon.

[b] Conversions and yields were determined by GC, average of 2 experiments.

[c] 50 μl water were added.

to a reduced yield of the product (Table 1, entry 4). Obviously, there is no significant difference between Pd(II)- and Pd(0)-pre-catalysts (Table 1, entries 1 and 2).

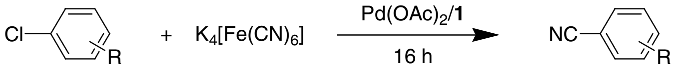
After realization of the successful cyanation of 2-chlorotoluene, we were interested in exploring the scope and limitations of this new protocol.[20] Hence, a number of different chloroarenes were reacted under standard conditions. It turned out that the conditions, which have been optimized for 2-chlorotoluene, were not fully satisfactory for other substrates. Especially the use of potassium hexacyanoferrate(II) trihydrate is preferable only for one more starting material, 1-chloro-2-(trifluoromethyl)benzene (Table 2, entry 2). In all other cases an improved yield is obtained under water-free conditions. Notably, applying catalyst loadings below 0.1 mol % Pd resulted in less reproducible experiments.

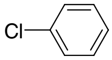
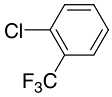
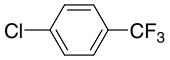
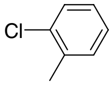
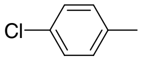
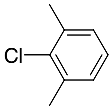
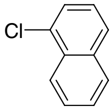
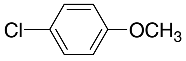
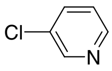
As shown in Table 2 both activated and non-activated aryl chlorides gave the desired benzonitriles in good to excellent yields, although with a slight variation of the catalyst amount. Remarkably, the sterically hindered 2-chloro-1,3-dimethylbenzene yielded 2,6-dimethylbenzonitrile with as little as 0.33 mol % palladium in 87% yield (Table 2, entry 5). It is well-known that palladium-catalyzed cyanations with sterically hindered substrates are much more difficult to perform. Accordingly, mono-*ortho*-substituted chloroarenes such as 1-chloro-2-(trifluoromethyl)benzene and *o*-chlorotoluene resulted in yields of 82% and 99%, respectively (Table 2, entries 2 and 4).

As an example for an electron-poor nitrogen heterocycle 3-chloropyridine was cyanated in 88% yield (Table 2, entry 9).

In summary, we have developed a general protocol for the palladium-catalyzed cyanation of electron-rich and -poor aryl chlorides utilizing non-toxic potassium hexacyanoferrate(II) as the cyanide source. This procedure is complementary to our previous protocols applying aryl bromides. Noteworthy, the cyanation proceeds in a high yield and selectivity using catalyst amounts of 0.2–0.5 mol %. Further applications of this chemistry towards the use of Cu catalysts are under way in our laboratory.

Table 2. Scope and limitations of the palladium-catalyzed cyanation of aryl and heteroaryl chlorides[a]



Entry	Substrate	Solvent	T (°C)	$Pd(OAc)_2$ (mol %)	$K_4[Fe(CN)_6]$	Conversion[b] (%)	Yield[b] (%)	Selectivity (%)
1		NMP	140	0.25	Dried	94	75	80
2		DMAc	160	0.25	Hydrate	85	82	97
3		NMP	160	0.5	Dried	99	74	74
4		NMP	140	0.33	Hydrate	100	99	99
5		NMP	160	0.5	Dried	96	91	95
6		NMP	140	0.33	Dried	89	87	97
7		NMP	160	0.5	Dried	92	73	79
8		NMP	160	0.5	Dried	83	82	98
9		NMP	160	0.5	Dried	100	88	88

[a] General conditions: 2 mmol aryl or heteroaryl chloride, 0.4 mmol Na_2CO_3, 0.4 mmol $K_4[Fe(CN)_6]$, metal precursor and ligand **1** (P:Pd = 3:1) in stock solution in the given solvent, filled up to 2 ml, 200 μl internal standard (tetradecane), 16 h at temperature given, in a pressure tube under argon.

[b] Conversions and yields were determined by GC, average of 2 experiments.

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References and notes

1. (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989, 819; (b) Grundmann, C. In *Houben-Weyl: Methoden der organischen Chemie*, 4th ed.; Falbe, J., Ed.; Georg Thieme: Stuttgart, 1985; Vol. E5, p 1313.
2. Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
3. For a recent catalytic variant of the Sandmeyer reaction see: Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2004**, *689*, 3810.
4. Hagedorn, F.; Gelbke, H.-P. In *Ullmanns Encyklopädie der technischen Chemie*, 4th ed.; Bartholomé, E., Biekert, E., Hellmann, H., Ley, H., Weigert, W. M., Weise, E., Eds.; Verlag Chemie: Weinheim, 1979; Vol. 17, p 333.
5. For reviews see: (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779; (b) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.
6. For the palladium-catalyzed cyanation of aryl bromides and iodides see: (a) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224; (b) Anderson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1395; (c) Akita, Y.; Shimazaki, M.; Ohta, A. *Synthesis* **1981**, 974; (d) Dalton, J. R.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 4443; (e) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3177; (f) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298; (g) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471.
7. For the copper-catalyzed cyanation of aryl halides see: (a) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2005**, *11*, 2483; (b) Zanon, J.; Klapars, A.; Buchwald, S. *J. Am. Chem. Soc.* **2003**, *125*, 2890; (c) Wu, J. X.; Beck, B.; Ren, R. X. *Tetrahedron Lett.* **2002**, *43*, 387.
8. (a) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101; (b) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086; (c) Blaser, H.-U.; Studer, M. *Appl. Catal. A: Gen.* **1999**, *189*, 191.
9. For reviews on the use of aryl chlorides in Pd-catalyzed coupling reactions see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem.* **2002**, *114*, 4350; Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed* **2002**, *41*, 4176; (b) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283; for a personal account see: (c) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.
10. (a) Rock, M.-H.; Merhold, A. WO Patent 98/37058, **1998**; (b) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776; (c) Sakakibara, Y.; Okuda, F.; Shimoyabashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985; (d) Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G. P. *J. Organomet. Chem.* **1979**, *173*, 335.
11. Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271.
12. Chobanian, H. R.; Fors, B. P.; Lin, L. S. *Tetrahedron Lett.* **2006**, *47*, 3303.
13. (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem.* **2003**, *115*, 1700; *Angew. Chem., Int. Ed.* **2003**, *42*, 1661; for other cyanations of aryl chlorides see: (b) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707; (c) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828.
14. (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388; (b) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576.
15. Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585.
16. (a) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508; (b) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, *46*, 8645; (c) Grossmann, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189.
17. (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69; (b) Herrmann, W. A. *Angew. Chem.* **2002**, *114*, 1342; *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
18. (a) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W. R.; Rossen, K.; Beller, M. *Angew. Chem.* **2006**, *118*, 161; *Angew. Chem., Int. Ed.* **2006**, *45*, 154; for some other applications of this ligand in coupling reactions see: (b) Michalik, D.; Kumar, K.; Zapf, A.; Tillack, A.; Arlt, M.; Heinrich, T.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 2057; (c) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Synthesis* **2004**, 935; (d) Datta, A.; Ebert, K.; Plenio, H. *Organometallics* **2003**, *22*, 4685; (e) Datta, A.; Plenio, H. *Chem. Commun.* **2003**, 1504; (f) Benedi, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claver, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073; (g) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209; (h) Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346; (i) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem.* **2000**, *112*, 4315; Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153; (j) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589.
19. (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem.* **1999**, *111*, 2570; Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413; (b) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360; (c) Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (d) Nguyen, H. N.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818; (e) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
20. *Standard reaction procedure*: Potassium hexacyanoferrate(II) (0.4 mmol) (either powdered $K_4[Fe(CN)_6]^*3H_2O$ or dry $K_4[Fe(CN)_6]$, which is yielded by grinding $K_4[Fe(CN)_6]^*3H_2O$ to a fine powder and drying in vacuum (ca. 2 mbar) at 80 °C overnight), 2 mmol aryl chloride, 0.4 mmol Na_2CO_3, metal precursor and ligand (in a stock solution in the given solvent) are mixed in a pressure tube under argon. Then the solvent (filled up to 2 ml) and 200 μl of internal standard (tetradecane) are added and the mixture is stirred for 16 h at the given temperature. After cooling to room temperature, 3 ml of dichloromethane are added and the reaction mixture is analyzed by GC. Conversion and yield are calculated as average of 2 parallel runs. The products can be isolated by column chromatography (SiO_2, ethyl acetate/hexane) after washing the organic phase with water, drying over sodium sulfate and distilling the solvents.