



# A new palladium catalyst system for the cyanation of aryl chlorides<sup>†</sup>

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**Abstract**—The influence of reaction conditions and additives on the palladium-catalyzed cyanation of aryl chlorides with potassium cyanide has been investigated. Successful cyanation of aryl chlorides is observed in the presence of palladium catalysts using potassium cyanide. It is shown that the combination of a 1,5-bis(diphenylphosphino)pentane ligand and the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as a co-catalyst are the key factors in obtaining the corresponding aryl nitriles with improved catalyst productivities and selectivities. © 2001 Elsevier Science Ltd. All rights reserved.

Aryl nitriles are of considerable importance in organic chemistry as integral parts of dyes, herbicides, natural products and pharmaceuticals. In general, aryl nitriles are synthesized from aryl halides and stoichiometric amounts of copper(I) cyanide (Rosenmund–von Braun reaction), from aniline via diazotization and a subsequent Sandmeyer reaction, or on an industrial scale via ammoxidation. Alternatively, aryl nitriles may be synthesized by the transition metal-catalyzed cyanation of aryl halides using inexpensive cyanide salts such as potassium cyanide or sodium cyanide.<sup>1–3</sup> In order to make this reaction attractive for the fine chemical industry it is important to be able to use inexpensive and readily available aryl chlorides<sup>4</sup> instead of aryl iodides or bromides. Unfortunately, the C–Cl bond in aryl chlorides is much more difficult to activate than C–Br or C–I bonds.<sup>1a</sup> In the past comparatively large amounts of nickel catalysts (0.8–10 mol%) were reported to catalyze the cyanation of aryl chlorides with either potassium cyanide or sodium cyanide in the presence of various additives.<sup>2</sup> Palladium catalysts are in general more tolerant than nickel catalysts towards a variety of functional groups and in addition can be more easily tuned for activating aryl–X bonds. There is thus a considerable interest in developing palladium catalysts for this reaction.<sup>3</sup> Unfortunately, the cyana-

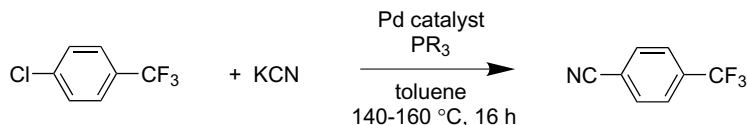
tion of aryl chlorides via palladium catalysis has not been observed until very recently, except in the case of strongly activated C–Cl bonds. A more general procedure was reported last year by Jin and Confalone who discovered that aryl chlorides react with zinc(II) cyanide in the presence of catalytic amounts of Pd<sub>2</sub>(dba)<sub>3</sub>, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and zinc to give the corresponding nitriles.<sup>5</sup> A drawback of this procedure is the use of overstoichiometric amounts (1.2 equiv.) of expensive zinc(II) cyanide, which leads to the formation of stoichiometric amounts of zinc(II) chloride waste. Additional disadvantages of these procedures are the use of 4 mol% palladium-catalyst and the need of zinc as an additive (12 mol%).

*In this paper we report the first procedure for the direct cyanation of activated aryl chlorides using inexpensive potassium cyanide in the presence of catalytic amounts of palladium catalysts.* The cyanation of 4-chlorobenzotrifluoride with potassium cyanide served initially as a model reaction in order to study the influence of critical reaction parameters (solvent, temperature, concentration of starting materials), ligands, and co-catalysts (Fig. 1, Table 1).

In agreement with results from the patent literature<sup>6</sup> we observed a low conversion for the model reaction to give 38% of 4-cyanobenzotrifluoride at 160°C in the presence of 2 mol% Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> and a catalytic amount of a crown ether and base (Table 1, entry 1). As side product ca. 4% benzonitrile is formed due to aryl-aryl-scrambling<sup>7</sup> between the aryl chloride and the

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<sup>†</sup> Palladium-catalyzed reactions for fine chemical synthesis, Part 21; for Part 20, see: Zapf, A.; Beller, M. *Chem. Eur. J.* **2001**, *7*, 2908.



**Figure 1.** Pd-catalyzed cyanation of 4-chlorobenzotrifluoride.

**Table 1.** Pd-catalyzed cyanation of 4-chlorobenzotrifluoride<sup>a</sup>

Entry	Na <sub>2</sub> CO <sub>3</sub> (mol%)	18-Crown-6 (mol%)	TMEDA <sup>b</sup> (mol%)	Ligand	Conversion (%) <sup>c</sup>	Yield (%) <sup>c</sup>
1	20	2	0	PPh <sub>3</sub>	42	38
2	20	2	0	Dpppe <sup>d</sup>	63	58
3	20	1	0	Dpppe <sup>d</sup>	50	41
4	20	4	0	Dpppe <sup>d</sup>	50	43
5	0	0	0	Dpppe <sup>d</sup>	15	13
6	20	2	20	Dpppe <sup>d</sup>	56	49
7	20	0	20	Dpppe <sup>d</sup>	28	23
8	0	2	20	Dpppe <sup>d</sup>	10	8
<b>9</b>	<b>0</b>	<b>0</b>	<b>20</b>	<b>Dpppe<sup>d</sup></b>	<b>97</b>	<b>91</b>
10	0	0	20	PPh <sub>3</sub>	10	7
11	0	0	20	PCy <sub>3</sub>	1	0
12	0	0	20	Dppp <sup>e</sup>	4	4
13	0	0	20	Dppb <sup>f</sup>	3	2
14	0	0	20	Dpph <sup>g</sup>	46	42
15	0	0	20	Dppf <sup>h</sup>	23	7

<sup>a</sup> General conditions: 2 mmol 4-chlorobenzotrifluoride, 2 mmol potassium cyanide, 0.04 mmol palladium(II) acetate, molar ratio Pd:P=1:4, 2 ml toluene, 16 h, 160°C, in a pressure tube.

<sup>b</sup> *N,N,N',N'*-Tetramethylethylenediamine.

<sup>c</sup> Conversions and yields were determined by GC using an internal standard (diethyleneglycol di-*n*-butylether).

<sup>d</sup> 1,5-Bis(diphenylphosphino)pentane.

<sup>e</sup> 1,3-Bis(diphenylphosphino)propane.

<sup>f</sup> 1,4-Bis(diphenylphosphino)butane.

<sup>g</sup> 1,6-Bis(diphenylphosphino)hexane.

<sup>h</sup> 1,1'-Bis(diphenylphosphino)ferrocene.

phenyl groups of the phosphine. Hence, we thought the use of sterically more hindered ligands such as tri-*o*-tolylphosphine and tricyclohexylphosphine should improve the catalyst stability. Unfortunately, no better results were obtained in the presence of these and similar ligands. Variation of other phosphines revealed a significant improvement by using chelating ligands. Best yields were obtained in the presence of chelating phosphines forming seven or eight-membered chelate rings. Among the various phosphine ligands tested in the model reaction 1,5-bis(diphenylphosphino)pentane gave best yields of 4-cyanobenzotrifluoride (58%)<sup>8</sup> under the described conditions (Table 1, entry 2).

Since it is known that the concentration of cyanide ions in solution strongly influences the outcome of the palladium-catalyzed cyanation of aryl bromides, we tested different concentrations of 18-crown-6, which enable the solubility of the cyanide ions to be controlled (Table 1, entries 2–5). The best results were obtained by applying sodium carbonate, 18-crown-6 and the palladium catalyst in a molar ratio of 10:1:1 (58% of 4-cyanobenzotrifluoride). Without any base or crown ether added the desired product is obtained in only 13% yield. From a mechanistic standpoint the positive influence of base and crown ether is twofold: on the one hand the concentration of cyanide is controlled, on the

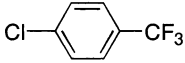

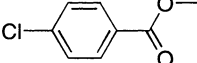
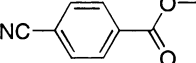
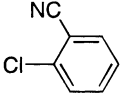
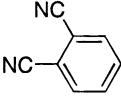
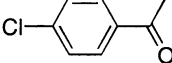
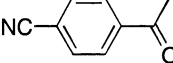
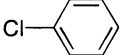
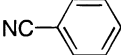
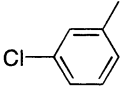
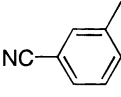
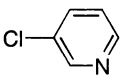
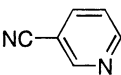
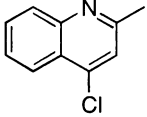
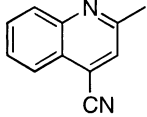
other hand the exchange of cyanide with other ligands is facilitated.<sup>9</sup>

Next we considered using organic bases as co-catalysts. Especially chelating amines should also influence the solubility and ligand exchange reactions of cyanide with palladium. Unfortunately, different combinations of TMEDA with sodium carbonate and 18-crown-6 resulted in significantly lower yields of the desired product as shown in Table 1 (entries 6–8). However, the addition of 0.2 equiv. of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) alone led to a conversion of 97% and a yield of 91% of 4-cyano-benzotrifluoride (Table 1, entry 9).

Among the various ligands tested in the presence of the TMEDA co-catalyst, only 1,5-bis(diphenylphosphino)pentane and 1,6-bis(diphenylphosphino)hexane showed significant conversion. In agreement with our initial ligand study the use of dpppe as the ligand gives the best yields of the corresponding aryl nitrile (Table 1, entries 9–15).

After realization of the successful cyanation of 4-chlorobenzotrifluoride we were interested in exploring the scope and limitations of this new protocol.<sup>10</sup> As shown in Table 2 activated aryl chlorides (methyl 4-

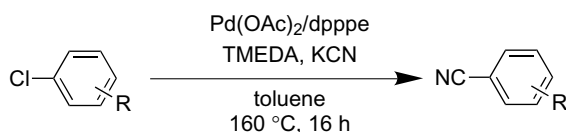
**Table 2.** Scope and limitations of the Pd-catalyzed cyanation of aryl and heteroaryl chlorides<sup>a</sup>

Entry	Aryl chloride	Product	Conversion (%) <sup>b</sup>	Yield (%) <sup>b</sup>
1			97	91
2			85	75
3			96	91
4			99	96
5 <sup>c</sup>			33	33
6 <sup>c</sup>			23	17
7			48	46
8			76	74 (67) <sup>d</sup>

<sup>a</sup> General conditions: 2 mmol aryl or heteroaryl chloride, 2 mmol potassium cyanide, 0.04 mmol palladium(II) acetate, 0.08 mmol 1,5-bis(diphenylphosphino)pentane, 0.4 mmol *N,N,N',N'*-tetramethylethylenediamine, 2 ml toluene, 16 h, 160 °C, in a pressure tube. <sup>b</sup> Conversions and yields were determined by GC using an internal standard (diethyleneglycol di-*n*-butyl ether). <sup>c</sup> Reaction conditions: 2 mmol aryl chloride, 2 mmol potassium cyanide, 0.06 mmol palladium(II) acetate, 0.12 mmol 1,5-bis(diphenylphosphino)pentane, 0.6 mmol *N,N,N',N'*-tetramethylethylenediamine, 2 ml toluene, 16 h, 160 °C in a pressure tube. <sup>d</sup> Isolated yield in parenthesis.

chlorobenzoate, 2-chlorobenzonitrile, 4-chloroacetophenone) yield the corresponding nitriles in good to excellent yields (75–96%) and very good selectivities. Non-activated aryl chlorides (chlorobenzene and 3-chlorotoluene) give the desired products in lower yields (17–33%), while *N*-heteroaryl chlorides provide the corresponding nitriles in moderate to good yields (46–74%).

In summary, we have shown that the palladium-catalyzed cyanation of activated aryl chlorides (Fig. 2) can be performed using simple KCN as cyanide source. The use of stoichiometric amounts of zinc or copper metal or salts can be avoided. Therefore no stoichiometric amounts of environmentally harmful transition metal chlorides are formed during the reaction.

**Figure 2.** Pd-catalyzed cyanation of aryl chlorides.

Crucial to the success of the reaction is the use of catalytic amounts of TMEDA. It is clear that despite the development of the reported procedure for the practical application further improvements have to be made (reduction of catalyst amount; increasing catalyst activity). Nevertheless the unexplored potential of the new co-catalysts makes us confident that the use of other chelating bases will lead to even better catalyst systems in future. Also, the combination of chelating amines with palladium catalysts may improve catalyst productivity (activity) for the cyanation of aryl bromides.

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