Progress in the Palladium-Catalyzed Cyanation of Aryl Chlorides

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Abstract: The development of new palladium catalysts for the cyanation of various aryl and heteroaryl chlorides is described. The combination of amine co-catalysts with chelating phosphine ligands, for example, 1,4-bis(diphenylphosphino)butane (dppb) or 1,5-bis(diphenylphosphino)pentane (dpppe), allows an efficient cyanation of chloroarenes with simple potassium cyanide. General palladium-catalyzed cyanation of nonactivated and deactivated chloroarenes is possible for the first time. Studies of the oxidative addition of aryl halides to palladium triphenylphosphine complexes in the presence and absence of amines suggest that the co-catalyst is capable of preventing catalyst deactivation caused by the presence of excess cyanide ions in solution.

Keywords: aryl chlorides · benzonitriles · cyanation · homogeneous catalysis · palladium

Introduction

Palladium-catalyzed coupling reactions of aryl halides have attracted widespread interest for the synthesis of organic building blocks and pharmaceutical and agrochemical derivatives. In addition to small-scale applications (<1 to 100 g), there is increasing awareness of the possible application of this type of reaction for industrial fine chemical synthesis (1 to >100 t per annum).[1] When availability is taken into account, aryl chlorides are economically the most attractive starting materials among the aryl halides. Some time ago, we started a research program to develop palladium-catalyzed coupling reactions of aryl chlorides to a practical level. Initially, the so-called palladacycle was introduced by Herrmann et al. and us as a stable and robust palladium complex.[2] This catalyst gives high turnover numbers for Heck and Suzuki coupling reactions of activated aryl chlorides. However, the catalyst activity is not sufficient to allow an efficient activation of neutral and electron-rich aryl chlorides. Hence, we and other groups developed palladium catalysts based on sterically hindered basic phosphines, which are more active and productive.[3] We were the first to introduce alkyldiadamantylphosphines as ligands for active palladium catalysts. The high activity of these ligands with aryl chlorides as substrates has been demonstrated in Suzuki[4] and Heck[5] reactions, palladium-catalyzed amination,[6] and arylation reactions of ketones.[7] We also demonstrated that basic chelating phosphines based on the ferrocene core allow a general carbonylation of nonactivated chloroarenes.[8] Carbene ligands, as well as electron-rich phosphine ligands, have been demonstrated to generate active palladium catalysts for aryl chloride activation.[9]

Recently we became interested in the cyanation of aryl chlorides also. This transformation offers a simple and elegant approach towards substituted benzonitriles from a number of available aryl and heteroaryl chlorides. The resulting benzonitriles are of considerable industrial importance as integral parts of dyes, herbicides, natural products, agrochemicals, pharmaceuticals, and new active agents. A selection of drugs is shown in Figure 1.[10]

In general, aryl cyanides are synthesized from aryl halides and stoichiometric amounts of copper(I) cyanide (Rosenmund–von Braun reaction), from aniline by diazotization and subsequent Sandmeyer reaction, or on an industrial scale by ammoxidation.[11] Alternatively, benzonitriles may be synthesized by the transition-metal-catalyzed cyanation of aryl halides using inexpensive cyanide salts such as potassium cyanide or sodium cyanide.[12, 13]

In the past, comparatively large amounts of nickel catalysts (up to 10 mol%) were reported to catalyze the cyanation of aryl chlorides with either potassium cyanide or sodium cyanide in the presence of various additives. Apparently, researchers from Bayer have recently improved this method: the nickel-catalyzed cyanation of 4-chlorobenzotrifluoride on a ton scale has been reported.[12d, 14]

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0947-6539/03/0908-1828 $ 20.00+.50/0

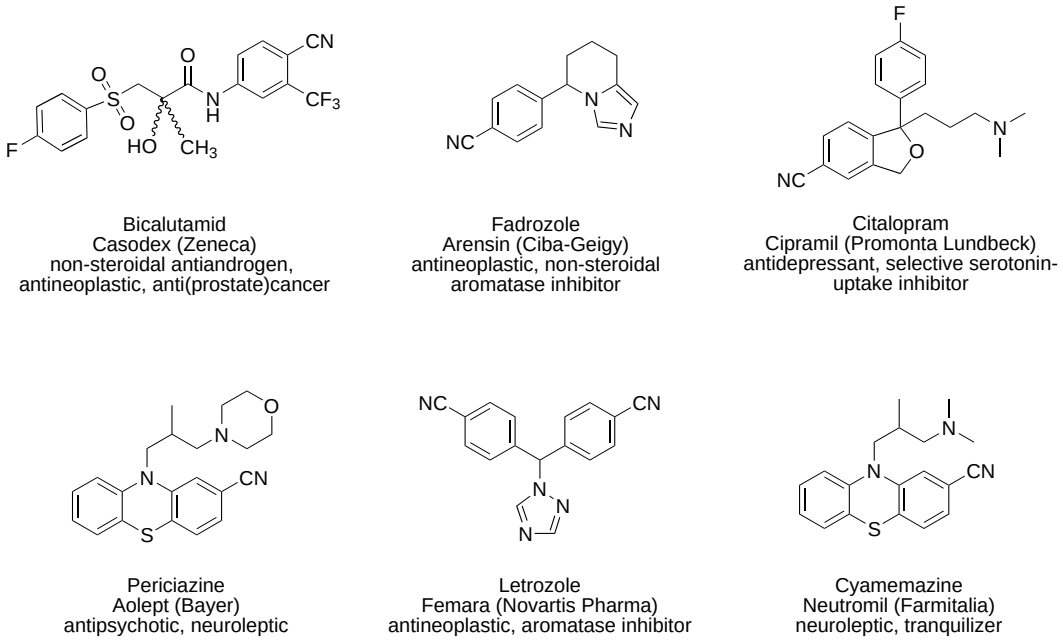
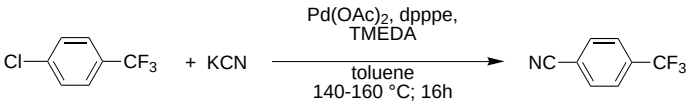


Figure 1. Selected cyano-substituted pharmaceuticals.

Palladium catalysts are in general more tolerant towards a variety of functional groups than nickel catalysts, and they can be tuned more easily for activating aryl–X bonds. Hence, there is interest in developing improved palladium catalysts for this reaction. The cyanation of aryl chlorides using palladium catalysis was not observed until very recently, except in the case of strongly activated C–Cl bonds. The most general procedure was reported in 2000 by Jin and Confalone, who discovered that aryl chlorides react with zinc(II) cyanide in the presence of catalytic amounts of $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone), 1,1′-bis(diphenylphosphino)ferrocene (dppf), and zinc to give the corresponding nitriles.[15] A drawback of this procedure is the use of an almost stoichiometric amount (0.6 equiv) of zinc(II) cyanide, which leads to the formation of heavy metal salt waste. Other disadvantages of this procedure are the use of 4 mol% palladium catalyst and the need for zinc as an additive (12 mol%). More recently, we reported on the first procedure for the direct cyanation of activated aryl chlorides using inexpensive potassium cyanide in the presence of catalytic amounts of palladium catalysts.[16] However, nonactivated aryl chlorides such as chlorobenzene and 3-chlorotoluene gave the corresponding nitriles in only low yields (17–33%). Here, we present a full account of our work on catalyst development for the cyanation of aryl chlorides, which has led to a significantly improved procedure for the cyanation of activated, nonactivated and even deactivated aryl chlorides and heteroaryl chlorides, and we offer new insight into the mechanism of the palladium-catalyzed cyanation.

Results and Discussion

Catalysis: In our preliminary communication we reported that the cyanation of 4-chlorobenzotrifluoride proceeds with excellent conversion (97%) and yield (91%) to give 4-cyanobenzotrifluoride in the presence of a combination of $Pd(OAc)_2$, 1,5-bis(diphenylphosphino)pentane (dpppe), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as organic co-catalyst (Scheme 1). We have also shown that these reaction conditions are useful for the cyanation of other activated aryl and heteroaryl chlorides. Less activated or sterically hindered aryl chlorides react only sluggishly under these conditions.



Scheme 1. Palladium-catalyzed cyanation of 4-chlorobenzotrifluoride.

Further studies of our model reaction revealed that the reaction is sensitive to the amount of TMEDA present. As shown in Table 1 (entries 1–4), at least 20 mol% of the amine is necessary to obtain the desired product, 4-cyanobenzotrifluoride, in good yield. Next, we were interested in reducing the amount of catalyst. Early results (Table 1, entries 5, 6) showed that a simple decrease in the amount of palladium complex leads to a breakdown of the catalytic activity. We assumed that cyanide ions might inhibit the palladium catalyst (see the discussion under Mechanistic Studies). If so, at a constant catalyst concentration an increased amount of starting material should be converted successfully, because the ratio of catalyst to dissolved cyanide ions has not changed (Table 1, entries 7–9). Indeed, it is possible to increase the turnover number (TON) by a factor of 2, to approximately 100. However, a further increase is not possible due to the insolubility of potassium cyanide and potassium chloride, which results in a high loading of solids in the reaction mixture.

  0947-6539/03/0908-1829 $ 20.00+.50/0

Table 1. Pd-catalyzed cyanation of 4-chlorobenzotrifluoride.[a]

Entry	4-Chlorobenzotrifluoride [mmol]	$Pd(OAc)_2$ [mol%]	TMEDA [mol%]	Conversion[b] [%]	Yield[b] [%]	Selectivity [%]	TON
1	2	2	10	26	24	92	12
2	2	2	20	97	91	94	46
3	2	2	30	94	88	92	44
4	2	2	40	94	85	91	43
5	2	1	20	3	0	0	0
6	2	1	10	2	1	32	1
7	4	1	20	77	70	90	70
8	8	0.5	20	57	49	90	98
9[c]	20	0.2	20	10	0	1	0

[a] General conditions: 4-chlorobenzotrifluoride, potassium cyanide (1 equiv), dpppe (Pd/P = 1:4), toluene (2 mL), 16 h, 160 °C, in a pressure tube. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] Magnetic stirring breaks down because of the high solids loading.

The beneficial effect of TMEDA as co-catalyst prompted us to investigate the influence of other amines in the palladium-catalyzed cyanation of nonactivated chloroarenes. Here, chlorobenzene is a more suitable model system which does not react efficiently with KCN under standard conditions; for example, benzonitrile is obtained in only 13% yield in the presence of 0.2 equivalents of TMEDA and 2 mol% palladium catalyst. All catalytic experiments using different co-catalysts were performed in ACE pressure tubes with toluene as solvent in the presence of 2 mol% $Pd(OAc)_2$. To ensure reproducibility, each run was performed at least twice. Where observed yield differences were >10%, a third experiment was carried out. In agreement with our previous optimization study, a Pd/dpppe ratio of 1:2 was used. More than 25 primary, secondary, and tertiary amines were tested as co-catalysts (Table 2).

The reaction outcome is influenced significantly by the added amine. Among the various amines tested, the best results were achieved in the presence of 0.2 equivalents of sparteine (Table 2, entry 5: 62% benzonitrile), 1,1′-methylenedipiperidine (Table 2, entry 7: 66%), 2,2′-bipyridine (Table 2, entry 10: 64%), and 1-adamantylamine (Table 2, entry 13: 60%). In the case of 1-adamantylamine a slight increase in the yield of benzonitrile (Table 2, entry 14: 66%) was observed when the amount of additive was reduced to 0.1 equivalents. Interestingly, no palladium-catalyzed amination (Buchwald–Hartwig reaction) was observed in this case. There is no clear trend regarding the product yield and the basicity or steric hindrance of the amine.

As we had better co-catalysts to hand, we also tested the cyanation of chlorobenzene in the presence of phosphines other than dpppe (Table 3). Monodentate basic phosphines, which give good results in other types of coupling reactions, do not catalyze the reaction appreciably. However, the use of 1,4-bis(diphenylphosphino)butane (dppb) leads to some improvement and gives 89% conversion and 84% yield of benzonitrile. To our knowledge, this is the first efficient palladium-catalyzed cyanation of a nonactivated aryl chloride with simple alkali cyanide to be reported. Furthermore, when the variation of the Pd:P ratio was tested again under our new conditions, as expected the best results were obtained with Pd:P = 1/4, as in the case of TMEDA.

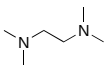
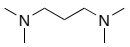
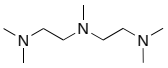
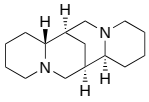
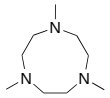
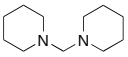
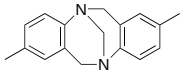
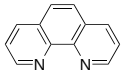
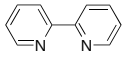
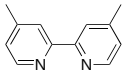
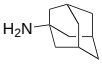
Next, we tested 1,1′-methylenedipiperidine (MDP) in the presence of $Pd(OAc)_2$/2 dpppe or dppb with other chloroarenes to determine the scope and limitations of this new protocol. To compare the new co-catalyst appropriately with the previous catalyst system, reactions were also performed in the presence of TMEDA (Table 4).

Apart from chlorobenzene, we tested 4-chlorotoluene, 3-chloroanisole, and 5-chloroindole as non- or deactivated aryl chlorides. 4-Chlorobenzaldehyde, 2,4-difluorochlorobenzene, and 4-chloro-2-nitrotoluene were used as activated chloroarenes. Activated but sterically more hindered aryl chlorides such as 2-chlorobenzotrifluoride and methyl 2-chlorobenzoate were also employed. We also used 3-chloropyridine, 4-chloroquinaldine, and 2-chloro-6-methoxypyridine as interesting heteroaryl chlorides. Except for 5-chloroindole, the corresponding aryl cyanides were obtained in moderate to excellent yields by using reaction conditions optimized for chlorobenzene and 4-chlorobenzotrifluoride. In general, the use of 0.2 equivalents of MDP as the organic co-catalyst led to significantly improved yields of the corresponding nitriles, compared with the use of TMEDA. Somewhat surprisingly, in the cases of 3-chloroanisole (Table 4, entries 7, 8) and 4-chloroquinaldine (Table 4, entries 20, 21) we observed better results using TMEDA.

Interestingly, the palladium-catalyzed cyanation of 4-chlorobenzaldehyde with KCN gives 4-cyanobenzaldehyde in very good yield (86%) (Table 4, entry 1). In general, cyanide-catalyzed benzoin condensation would be expected to occur in this case. However, the free cyanide ions should be trapped by the palladium; hence, catalytic cyanation is preferred to the classic benzoin condensation. 4-Chloro-2-nitrotoluene (Table 4, entries 9–11) was used as substrate, because the corresponding 4-methyl-3-nitrobenzonitrile and 4-cyanobenzaldehyde represent intermediates in the synthesis of hydroxystilbamide, a potent antiprotozoal agent.[10, 17] Unfortunately, the corresponding nitrile was obtained only in a moderate yield (55%). Remarkably, the cyanation of nonactivated, deactivated, and sterically hindered aryl chlorides proceeded smoothly. 4-Chlorotoluene, 3-chloroanisole, and chlorobenzene (Table 4, entries 2–8) gave the desired nitriles in good yields (59, 82, and 84%, respectively). 5-Chloroindole reacted with KCN in low yields (22%) under our reaction conditions. Sterically hindered aryl chlorides such as 2-chlorobenzotrifluoride (Table 4, entries 16, 17) and methyl 2-chlorobenzoate (Table 4, entries 18, 19) gave the corresponding nitrile in sufficient yield (73–75%). The use of TMEDA as addi-

0947-6539/03/0908-1830 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 8

Table 2. Catalytic cyanation of chlorobenzene in the presence of different co-catalysts.[a]

Entry	Amine	Amine concentration [mol%]	Conversion[b] [%]	Yield[b] [%]
1		20	13	13
2		20	17	16
3		20	23	22
4		20	21	20
5		20	62	62
6		20	35	35
7		20	67	66
8		20	59	59
9		20	30	30
10		20	84	64
11		20	61	58
12	 (*cis*/*trans*)	20	31	30
13		20	61	60
14		10	71	66

[a] General conditions: chlorobenzene (2 mmol), potassium cyanide (2 mmol), palladium(II) acetate (0.04 mmol), dpppe (0.08 mmol), amine, toluene (2 mL), 16 h, 160 °C, in a pressure tube. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether).

tive with these substrates led to very low yields and conversions.

Nitrogen-containing heteroaryl chlorides (entries 20–26), for example, 4-chloroquinaldine, 3-chloropyridine, and 2-chloro-6-methoxypyridine, reacted to give the corresponding nitriles in good to excellent yields (74–91%). For 3-chloropyridine we observed higher yields when we used dpppe as ligand instead of dppb. This result contrasted with the reaction of chlorobenzene. Apparently, choice of the best

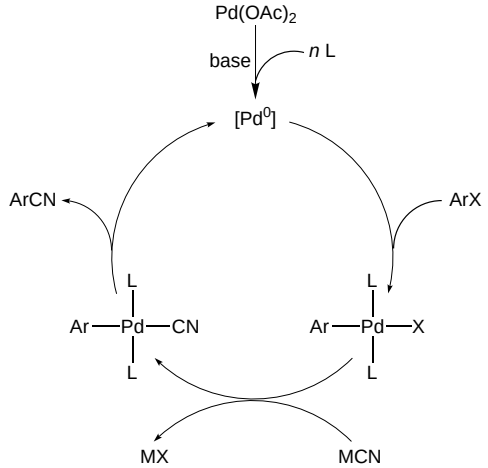
Table 3. Catalytic cyanation of chlorobenzene in the presence of different phosphines.[a]

Entry	Ligand	Conversion[b] [%]	Yield[b] [%]
1	PPh_3	26	18
2	PCy_3	16	8
3	dppb	89	84
4	dpppe	67	66
5	dppf	24	6

[a] General conditions: chlorobenzene (2 mmol), potassium cyanide (2 mmol), palladium(II) acetate (0.04 mmol), Pd/P = 1:4, MDP (0.4 mmol), toluene (2 mL), 16 h, 160 °C, in a pressure tube. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether).

phosphine ligand for the cyanation reaction also depends on the substrate used. Therefore further improvements in some of the reported cases might be possible by changing the phosphine ligand.

Mechanistic studies: The results shown in Table 2 and Table 4 demonstrate that different amines are effective co-catalysts for the cyanation of a variety of aryl chlorides. The question remaining is which elementary steps are influenced by the addition of amine. To understand the effect of the organic co-catalyst in more detail, we performed the palladium-catalyzed C–C coupling in single steps according to the generally accepted mechanism for such reactions[18] (Scheme 2) in the

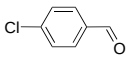
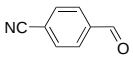
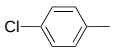
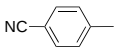
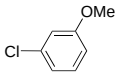
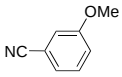
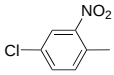
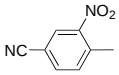
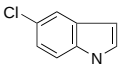
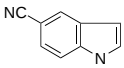
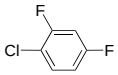
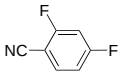
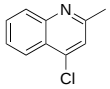
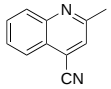
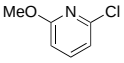
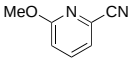


Scheme 2. Proposed mechanism for the palladium-catalyzed cyanation of aryl halides.

presence and absence of TMEDA. The catalytic cycle starts with the oxidative addition of the aryl halide to a Pd° species. For aryl chlorides the activation of the C–X bond is more difficult than for aryl bromides, aryl iodides, or aryl triflates.[19]

The resulting aryl palladium(II) halide complex should undergo an exchange of the halide by cyanide. It is possible that this reaction step is facilitated by base (amine), by in situ formation of the corresponding amine complex. Finally, the aryl palladium(II) cyanide species will reductively eliminate the desired product (benzonitrile) and regenerate the active Pd^0 species. Because of the high temperatures, palladium

Table 4. Catalytic cyanation of various aryl chlorides[a]

Entry	Aryl chloride	Product	Amine	Conversion[b] [%]	Yield[b] [%]
1			TMEDA	99	86
2			MDP	67	66
3[c]			MDP	89	84
4			TMEDA	13	13
5			MDP	71	59
6			TMEDA	22	12
7			MDP	62	53
8			TMEDA	88	82
9			MDP	46	41
10[d]			MDP 66	55	
11			TMEDA	32	24
12			MDP	52	(22)[e]
13			TMEDA	25	trace
14			MDP	67	42
15			TMEDA	11	10
16			MDP	74	73
17			TMEDA	11	11
18			MDP	93	75 (71)[e]
19			TMEDA	12	3
20			MDP	68	63 (58)[e]
21			TMEDA	76	74 (67)[g]
22			MDP	87	80
23[c]			MDP	61	55
24			TMEDA	48	46
25			MDP	95	91
26			TMEDA	86	85 (81)[e]

[a] General conditions: aryl or heteroaryl chloride (2 mmol), potassium cyanide (2 mmol), palladium(II) acetate (0.04 mmol), dpppe (0.08 mmol), MDP (0.4 mmol), toluene (2 mL), 16 h, 160 °C, in a pressure tube. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] dppb instead of 1,5-bis(diphenylphosphino)pentane. [d] Reaction conditions: aryl or heteroaryl chloride (2 mmol), potassium cyanide (2 mmol), palladium(II) acetate (0.08 mmol), DPPPE(0.16 mmol), MDP (0.4 mmol), toluene (2 mL), 16 h, 160 °C, in a pressure tube. [e] Yields of isolated products in parentheses.

colloids may also be a catalytically active species. It is known that such colloids, or nanoparticles, are formed from unstable palladium phosphine complexes at high temperature and that they show catalytic activity in C–C coupling reactions.[20] However, our reaction mixtures were the pale yellow that is typical of the palladium phosphine complexes discussed here.

Takagi et al. proposed the involvement of some Pd^{II} cyanide complexes as cyanide carriers for the formation of the aryl palladium(II) cyanide.[21] Despite the simplicity of this mechanism and the analogy to similar coupling reactions, there should be some concern about its viability, because so far we know of no report on the isolation of an aryl palladium(II) cyanide complex, and no detailed study on oxidative additions of Pd^0 complexes to aryl halides in cyanation reactions. Therefore we investigated, by ^1H and ^{31}P NMR spectroscopy, the stoichiometric reaction of $[Pd(PPh_3)_4]$ with 4-bromobenzotrifluoride in the presence of different cyanide concentrations. To obtain a controlled amount of cyanide ions in solution, tetra-*n*-butylammonium cyanide was used as the soluble cyanide source. $[Pd(PPh_3)_4]$ was chosen as a model catalyst for two reasons: a) the complex catalyzes the cyanation of aryl chlorides to some extent (as shown in Table 3); and b) the more reactive Pd^0–dpppe and Pd^0–dppb complexes have not been isolated in pure form, because they easily undergo formation of dimeric and oligomeric species, which significantly complicate the interpretation of the NMR data.

The NMR studies were performed in standard NMR tubes. In all experiments tetrakis(triphenylphosphine)palladium(0) and five equivalents of 4-bromobenzotrifluoride were dissolved in $[D_8]$toluene. ^{31}P and ^1H NMR were performed immediately after addition of the respective amount of tetra-

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n-butylammonium cyanide. Then, within minutes, the reaction mixtures were heated from room temperature to 80 °C, at which temperature NMR data were collected every 45 min. The oxidative addition proceeded smoothly at room temperature in the absence of cyanide ions (Figure 2 a).[22] In addition to the signal of $[Pd(PPh_3)_4]$ at $\delta = 13.1$ ppm, a second signal appeared at $\delta = 24.4$ ppm, belonging to the oxidative addition product *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II). Because the liberated triphenylphosphine is in rapid equilibrium with the coordinated triphenylphosphine in the $[Pd(PPh_3)_4]$, two different signals are not observed; only a shift of the $[Pd(PPh_3)_4]$ signal to high fields occurs (the more "free" phosphine is present in the solution, the larger this shift to high fields). Upon heating to 80 °C the reaction was completed and the formation of "free" PPh_3 was observed at $\delta = -3.4$ ppm. In the presence of one equivalent of cyanide (Figure 2 b) no oxidative addition was observed at room temperature. Instead, a significant broadening and shift of the $[Pd(PPh_3)_4]$ signal from $\delta = 13.1$ to 0.7 ppm were observed. This can be explained easily by ligand-exchange reactions of $[Pd(PPh_3)_4]$ with cyanide ions. The increased concentration of PPh_3 accounts for the shift of the signal towards noncoordinated ("free") PPh_3 ($\delta \approx -4$ ppm). When the mixture was heated to 80 °C the formation of *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II) ($\delta = 24$ ppm) and PPh_3 ($\delta = -3.5$ ppm) was observed. Interestingly, GC analysis of the NMR mixture after the reaction revealed the formation of 4-cyanobenzotrifluoride.

In the presence of a fivefold excess of cyanide ions, already at room temperature no signal for $[Pd(PPh_3)_4]$ could be observed. The only clear detectable signal belonged to PPh_3 ($\delta = -3.7$ to -4.9 ppm). If the mixture was heated to 100 °C no formation of the oxidative addition product was observed. GC/MS analysis of the reaction mixture also showed no product formation; only 4-bromobenzotrifluoride and PPh_3 were detected. It is clear that the presence of cyanide ions dramatically decreases the reactivity of palladium(0) complexes towards oxidative addition by replacing PPh_3. In the presence of one equivalent of cyanide (with respect to the palladium complex) the oxidative addition was slowed down, but it still worked at higher temperatures. In the presence of five equivalents no reaction was observed. ^1H NMR inves-

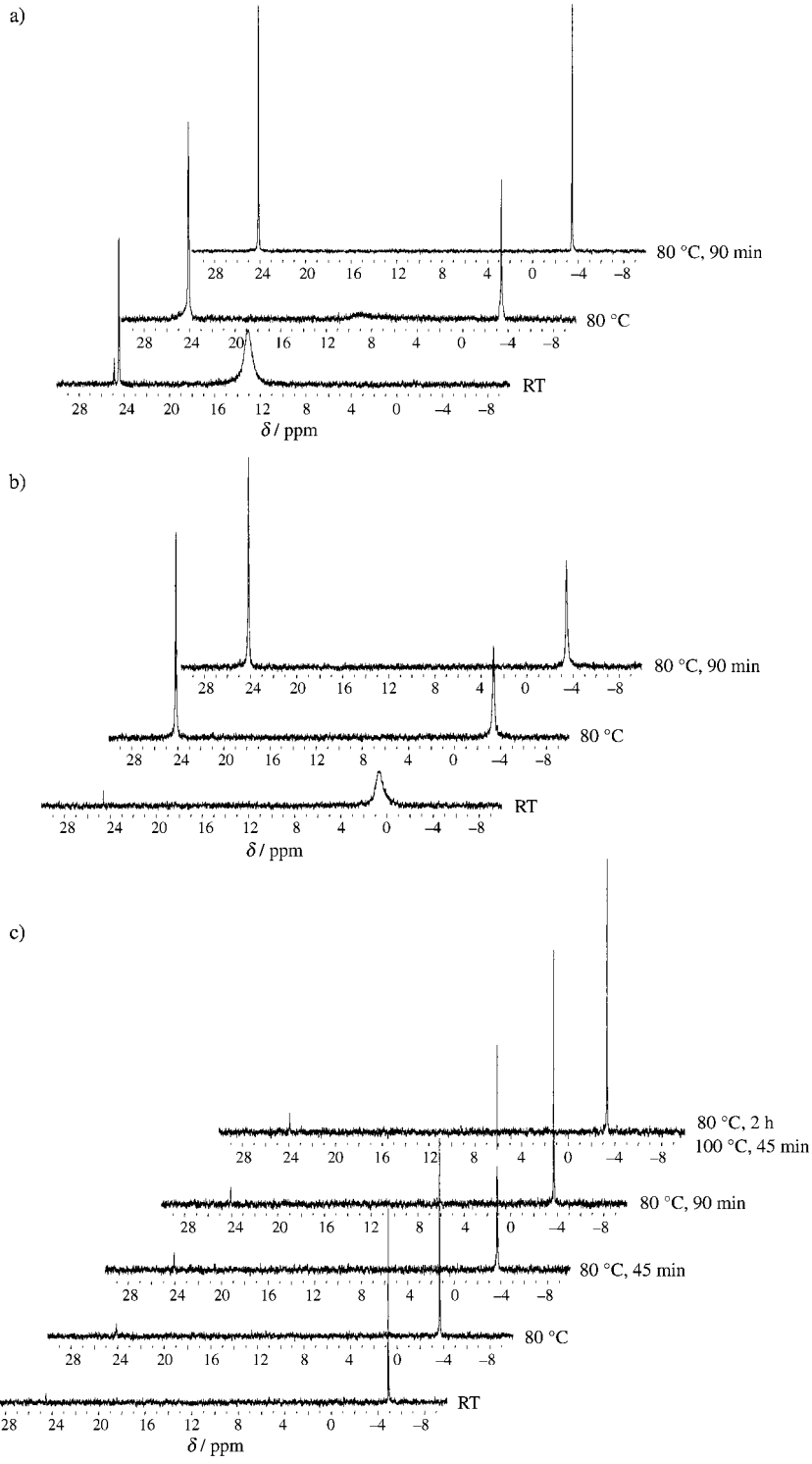


Figure 2. ^{31}P NMR spectra of the oxidative addition of $[Pd(PPh_3)_4]$ to 4-bromobenzotrifluoride in the presence of different amounts of nBu_4NCN: a) without added cyanide; b) in the presence of one equivalent of cyanide; c) in the presence of five equivalents of cyanide.

tigations of the oxidative addition reaction at different cyanide concentrations produced similar results. Different palladium(0) cyanide complexes were most probably formed, which were in equilibrium with each other. Therefore no defined signal was observed.

As we showed, the use of TMEDA as co-catalyst leads to improved yields of 4-cyanobenzotrifluoride in the palladium-catalyzed cyanation of 4-chlorobenzotrifluoride.[16] Therefore, we performed the same NMR studies of the model reaction in the presence of a 10-fold excess of TMEDA; this resembles the conditions of the catalytic reactions. Somewhat disappointingly, no difference was seen in the ^{31}P NMR and ^{1}H NMR spectra. Whereas in the presence of one equivalent of cyanide the signal of the arylpalladium(II) complex appeared again at $\delta = 24$ ppm, no signal of the oxidative addition product was observed in the presence of five equivalents of cyanide ions. Apparently, the addition of TMEDA had no effect on the oxidative addition. However, a closer GC/MS examination of the NMR mixture after the reaction detected, surprisingly, in addition to 4-bromobenzotrifluoride and PPh_3, the desired product (4-cyanobenzotrifluoride) in 45% yield! The addition of TMEDA doubtless prevents deactivation of the palladium(0) complex. We assume that the amine is capable of substituting cyanide ions on the palladium center, thereby regenerating an active palladium catalyst. Moreover, it is evident that the arylpalladium(II) halide complex formed in situ reacts immediately with cyanide to give the corresponding benzonitrile and a palladium(0) complex. Hence, the second and third elementary steps in the catalytic cycle, transmetalation and reductive elimination, must be much faster than the oxidative addition. It should be kept in mind that these are model studies, as the actual catalysis takes place at 160 °C. To prove whether TMEDA also has a beneficial effect on one of these latter steps of the catalytic cycle, we studied the reaction of *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)-palladium(II) with an excess of tetra-*n*-butylammonium cyanide in toluene (Scheme 3).

In both reactions 4-cyanobenzotrifluoride was obtained in good yield (70–72% with respect to the complex used). The yield of the product was not changed, but the selectivity of the reaction was influenced significantly by the presence of the amine co-catalyst. Without TMEDA, 70% benzonitrile (with respect to the complex used) was produced, demonstrating the low stability of triphenylphosphine towards ligand degradation (aryl–aryl scrambling).[23] In the presence of TMEDA this side reaction was reduced significantly. Thus, only 18% of benzonitrile was observed. Again, this unexpected result might be explained by ligand exchange reactions of TMEDA. Here, a substitution of triphenylphosphine by TMEDA is possible. This beneficial effect of TMEDA might be useful for other types of palladium-catalyzed coupling reactions, too.

Conclusion

These results demonstrate that the palladium-catalyzed cyanation of nonactivated and activated aryl chlorides with KCN is possible in good yields and selectivities in the presence of chelating phosphine ligands and new amine co-catalysts. This procedure for the first time allows the use of simple alkali cyanides for a general palladium-catalyzed cyanation of chloroarenes. Thus, it represents an important advance in this area. On the basis of NMR studies we conclude that the amine co-catalyst prevents deactivation of Pd^0 complexes caused by cyanide ions and increases the stability of the phosphine ligand. In addition, we observed that aryl palladium cyanide formation and reductive elimination were significantly faster than the oxidative addition. Owing to the importance of the concentration of cyanide in solution, caution should be exercised regarding the crystallite size of the cyanide source and the purity of the solvents.[24]

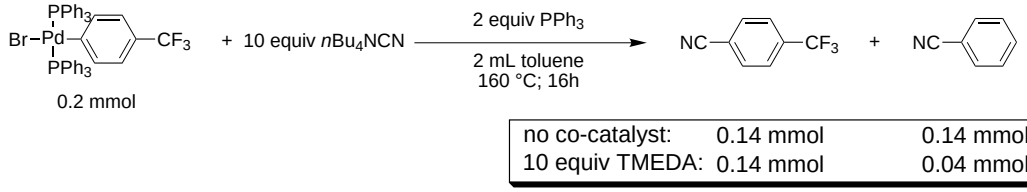
Experimental Section

General: All chemicals were commercially available and used without further purification. Potassium cyanide (Fluka) was dried in vacuo and stored under argon. The KCN crystallites used measured 120 nm.

General procedure: In an ACE pressure tube (Aldrich) aryl chloride (2 mmol), potassium cyanide (2 mmol), TMEDA (0.4 mmol), palladium(II) acetate (0.04 mmol), dppe (0.08 mmol), and toluene (2 mL) were stirred under argon at 160 °C for 16 h. After cooling, the internal standard (diethylene glycol di-*n*-butyl ether) was added, and the mixture was diluted with dichloromethane (2 mL) and washed with water (2 mL). The organic layer was dried over sodium sulfate and analyzed by gas chromatography. Products were isolated by column chromatography.

NMR experiments: In a 5 mm NMR tube containing $[Pd(PPh_3)_4]$ (29 mg, 0.025 mmol) and tetra-*n*-butylammonium cyanide (1st experiment: 0 mg; 2nd experiment: 6.7 mg, 0.025 mmol; 3rd experiment: 33.5 mg, 0.125 mmol), 4-bromobenzotrifluoride (17.5 μL, 0.125 mmol), and $[D_8]$toluene (1 mL) were added under argon. After the mixture was heated from room temperature to 80 °C/100 °C, ^{1}H and ^{31}P NMR spectra were measured every 45 min. Finally, the reaction mixture was analyzed by GC/MS.

Stoichiometric reaction of *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II): In an ACE pressure tube (Aldrich) *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II) (171 mg, 0.20 mmol), triphenylphosphine (105 mg, 0.40 mmol), TMEDA (1st experiment: 0 μL; 2nd experiment: 302 μL, 2.0 mmol), tetra-*n*-butylammonium cyanide (536 mg, 2.0 mmol), and toluene (2 mL) were stirred under argon at 160 °C for 16 h. After the mixture had been cooled, the internal standard (diethylene glycol di-*n*-butyl ether) was added, then the mixture was diluted with dichloromethane (1 mL) and washed with



no co-catalyst:	0.14 mmol	0.14 mmol
10 equiv TMEDA:	0.14 mmol	0.04 mmol

Scheme 3. Stoichiometric reaction of *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II) with tetra-*n*-butylammonium cyanide.

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water (3 mL). The organic layer was dried over sodium sulfate and analyzed by gas chromatography.

Analytical data

4-Cyanoquinaldine: ^{1}H NMR (400 MHz, $CDCl_3$, 297 K): δ = 8.07 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 0.8 Hz, 1H), 8.04 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.77 (dt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.4 Hz, 1H), 7.63 (dt, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.0 Hz, 1H), 7.56 (s, 1H), 2.75 ppm (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 297 K): δ = 158.8, 148.2, 131.5, 129.9, 128.6, 126.2, 125.1, 124.3, 119.2, 116.1, 25.6 ppm; MS (70 eV, EI): *m/z*: 168 [M^+], 153 [$M^+ - CH_3$], 140; IR (KBr): $\tilde{\nu}$ = 3067, 2230, 1594, 1560, 1503, 1408, 1383, 1323, 894, 756 cm^{-1}; elemental analysis (%) calcd for $C_{11}H_8N_2$: C 78.55, H 4.79, N 16.66; found: C 78.77, H 4.87, N 16.61.

5-Cyanoindole: ^{1}H NMR (400 MHz, $CDCl_3$, 297 K): δ = 8.99 (bs, 1H), 7.98 (d, ^4J(H,H) = 1.6 Hz, 1H), 7.48 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.37 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.6 Hz, 1H), 7.32 (d, ^3J(H,H) = 3.5 Hz, 1H), 6.59 ppm (d, ^3J(H,H) = 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 297 K): δ = 137.6, 127.6, 126.7, 126.3, 124.6, 121.1, 112.14, 103.1, 102.2 ppm; MS (70 eV, EI): *m/z*: 142 [M^+], 115 [M^+ – HCN]; elemental analysis (%) calcd for $C_9H_6N_2$: C 76.04, H 4.25, N 19.71; found: C 76.45, H 4.47, N 19.26.

2-Cyano-6-methoxypyridine: ^{1}H NMR (400 MHz, CD_2Cl_2, 297 K): δ = 7.68 (dd, ^3J(H,H) = 7.3 Hz and 8.5 Hz, 1H), 7.31 (dd, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 0.8 Hz, 1H), 6.98 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 0.8 Hz, 1H), 3.94 ppm (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2, 297 K): δ = 164.7, 139.5, 130.6, 122.6, 117.7, 116.4, 54.3 ppm; MS (70 eV, EI): *m/z*: 134 [M^+], 133, 104 [$M^+ - CH_2O$], 77 [$M^+ - CH_2O - HCN$], 40; IR (KBr): $\tilde{\nu}$ = 3002, 2949, 2915, 2853, 2225, 1603, 1465, 1131, 1028 cm^{-1}; elemental analysis (%) calcd for $C_7H_6N_2O$: C 62.68, H 4.51, N 20.88; found: C 62.29, H 4.57, N 20.48.

Methyl 2-cyanobenzoate: ^{1}H NMR (400 MHz, $CDCl_3$, 297 K): δ = 8.09–8.14 (m, 1H), 7.76–7.81 (m, 1H), 7.61–7.68 (m, 2H), 3.97 ppm (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 297 K): δ = 164.4, 134.8, 132.7, 132.4, 132.3, 131.1, 117.5, 112.9, 52.8 ppm; MS (70 eV, EI) *m/z*: 161 [M^+], 130, 102 [$M^+ - COOCH_3$], 89, 77 [$C_6H_5^+$], 51 [$C_4H_3^+$]; elemental analysis (%) calcd for $C_9H_7NO_2$: C 67.07, H 4.38, N 8.69; found: C 67.14, H 4.31, N 8.97.

All other cyanation products are commercially available. In these cases reaction products were identified by comparison with authentic samples using GC/MS methods.

***trans*-Bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II)**: [Pd(PPh_3)$_4$] (5.8 g, 5 mmol) was suspended in toluene (20 mL) and 4-bromobenzotrifluoride (2.8 mL, 20 mmol) was added under argon. The mixture was stirred for 4 h at 80 °C and, after cooling to room temperature, evaporated under reduced pressure. The crude reaction product was purified by washing with diethyl ether and crystallization from dichloromethane/*n*-pentane. ^{1}H NMR (400 MHz, CD_2Cl_2, 297 K): δ = 7.50–7.53 (m, 12H), 7.36–7.40 (m, 6H), 7.26–7.31 (m, 12H), 6.76 (d, ^3J(H,H) = 8.1 Hz, 2H), 6.41 ppm (d, ^3J(H,H) = 8.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2, 297 K): δ = 136.3, 135.0, 131.4, 130.4, 128.3, 123.6 ppm; ^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2, 297 K): δ = 24.24 ppm; MS (NBA, FAB): *m/z*: 855 [$M^+ - 1$], 775 [$M^+ - 1 - Br$], 630 [$M^+ - 1 - Br - PhCF_3$], 407 [$PPh_3(C_6H_4CF_3)^+$], 339 [PPh_4^+], 262 [PPh_3^+]; IR (Nujol): $\tilde{\nu}$ = 3054, 1586, 1480, 1437, 1322, 1158, 1111, 1096, 1069, 1010, 817, 745, 726, 693, 519, 495 cm^{-1}; elemental analysis (%) calcd for $C_{43}H_{34}BrF_3P_2Pd$: C 60.34, H 4.00, Br 9.33, P 7.24, Pd 12.43; found: C 60.01, H 4.27, Br 9.71, P 7.25, Pd 12.12.

Acknowledgement

The authors thank Dr. A. Spannenberg (X-ray of *trans*-bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphine)palladium(II); IfOK), Mrs. H. Baudisch (GC/MS; IfOK), and Dr. A. Köckritz (KCN crystallite measurement; ACA Berlin) for analytical support. Dr. H.-P. Krimmer and Dr. M. Gómez Andreu (Degussa AG) are thanked for general discussions. Generous support of this project from Degussa AG (formerly SKW Trostberg AG), the State of Mecklenburg-Western Pomerania, the Fonds der Chemischen Industrie, and the Bundesministerium für Bildung und Forschung (BMBF) is gratefully acknowledged. OMG is thanked for generous gifts of palladium compounds.

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Received: October 18, 2002
Revised: December 18, 2002 [F4515]

