

Improving palladium-catalyzed cyanation of aryl halides: development of a state-of-the-art methodology using potassium hexacyanoferrate(II) as cyanating agent

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Abstract

Benzonitriles are easily accessible via palladium-catalyzed cyanation of aryl halides using potassium hexacyanoferrate(II) as cyanide source. This method is applicable on both activated and deactivated aryl and heteroaryl bromides and activated chlorides giving the corresponding benzonitriles in good to excellent yield. Advantageously, the used cyanating agent is non-toxic and cheap. The presented catalyst system is rather simple and it is not necessary to add expensive phosphines, making the novel method also attractive for industrial applications.

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1. Introduction

Benzonitriles are of considerable interest for organic chemistry as integral part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products. The nitrile group also serves as an important intermediate for a multitude of possible transformations into other functional groups. As an example the synthesis of Fluvoxamine is shown in [Scheme 1](#). Here, 4-(trifluoromethyl)benzonitrile, which is available from 4-chlorobenzotrifluoride by nickel-catalyzed cyanation on ton-scale, serves as an intermediate [1–3].

Benzonitriles themselves are also of significant interest, e.g., as substructures in biologically active agents. In [Fig. 1](#) two selected examples of pharmaceuticals containing an aromatic nitrile as part of the molecule are shown along with their names, producers, and effects

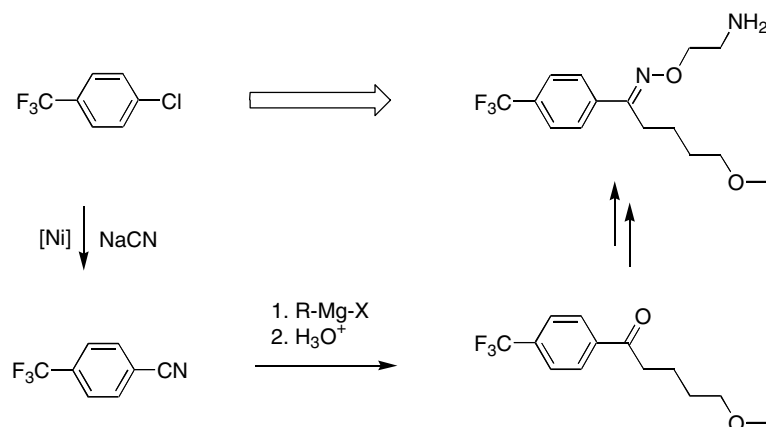
[4]. In case of biologically active benzonitrile derivatives another aspect is worth noting. By applying transition metal-catalyzed cyanation of aryl halides using $K^{11}CN$, $K^{13}CN$ or $K^{14}CN$ isotope labelled compounds are easily accessible [5–9]. The resulting products are used in pharmacokinetic studies and investigations on the metabolism of pharmaceuticals.

Clearly, benzonitriles can be prepared in numerous ways [10–14]. Most often they have been synthesized by the Rosenmund–von Braun reaction [15–19] from aryl halides or diazotization of anilines and subsequent Sandmeyer reaction [20–22] on laboratory as well as on industrial scale. Drawbacks of the Rosenmund–von Braun and the Sandmeyer reaction are the high temperature (150–250 °C) and the use of stoichiometric amounts of copper(I) cyanide as cyanating agent, which leads to equimolar amounts of heavy metal waste.

On ton-scale the method of choice in industry is ammoxidation, whereby the corresponding toluene derivatives are reacted with oxygen and ammonia at 300–550 °C in the presence of heterogeneous fixed-bed

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Scheme 1. 4-(Trifluoromethyl)benzocyanide – a key intermediate in the synthesis of Fluvoxamine.

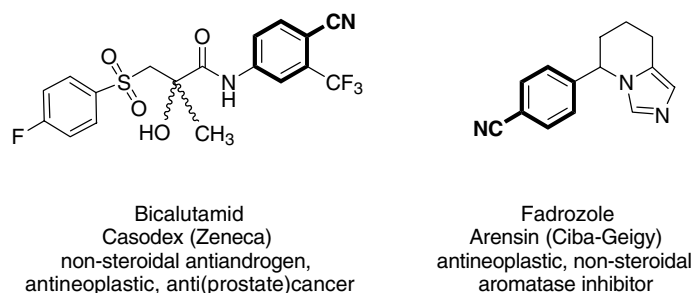
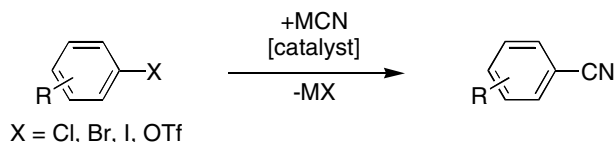


Fig. 1. Examples of pharmaceutically active benzonitriles.

catalysts [23–25]. Unfortunately, the ammoxidation is restricted to products such as benzonitrile, terephthalodinitrile, and chlorobenzonitriles [26,27] because of the high temperature and high pressure needed. In addition, a limited supply of toluene derivatives is available on a larger scale.

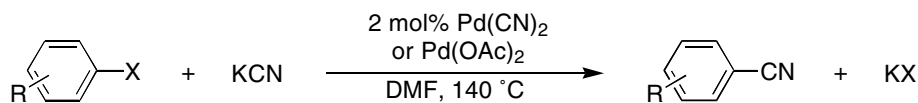
A useful alternative for the preparation of more-substituted benzonitriles is the transition metal-catalyzed cyanation of aryl-X compounds ($X = \text{Cl}, \text{Br}, \text{I}, \text{OTf}$) with cheap and readily available cyanation agents like sodium or potassium cyanide (Scheme 2) [28–32]. The order of reactivity of the aryl-X derivatives is opposite to the bond-dissociation energy of the C–X bond (reactivity: $\text{I} \sim \text{OTf} > \text{Br} > \text{Cl}$) [33,34]. Electron-withdrawing substituents on the aryl ring increase the reactivity, while electron-donating substituents decrease it. Catalysts for coupling of aryl halides or triflates with cyanide are transition metals complexes of the platinum group, especially palladium or nickel complexes. In general, palla-



Scheme 2. Transition metal-catalyzed cyanation of aryl halides.

dium catalysts tolerate a wider variety of functional groups and are less sensitive to air and humidity compared to nickel catalysts. The first palladium-catalyzed cyanation of aryl-X derivatives was introduced in 1973 by Takagi et al. using aryl bromides and iodides with potassium cyanide as cyanating agent (Scheme 3) [35].

Interestingly, palladium(II) cyanide or palladium(II) acetate served as the catalyst without additional ligands present. Typical reaction conditions were: DMF as solvent, 140–150 °C and 2–12 h reaction time. Early studies by Takagi et al. [36] led to a first mechanistic proposal. One especially important point was the fact that an excess of cyanide ions inhibits the catalytic cycle. This deactivation was explained by reaction of cyanide with palladium(II) species, forming inactive palladium(II) cyano compounds, which cannot be reduced to catalytically active palladium(0) species. Potassium tetracyanopalladate(II) and palladium(II) cyanide were shown to be almost inactive in the cyanation reaction, and a dramatic solvent effect was described which can be explained by the influence of the cyanide solubility in different reaction media. The higher the solubility of the cyanide salt, the lower the reaction outcome. Another finding of this work is the positive effect of co-catalysts like potassium hydroxide, sodium ethoxide, potassium carbonate, or sodium phenoxide, which facilitate the reduction of palladium(II) species [37,38].



Scheme 3. First palladium-catalyzed cyanation of aryl bromides and iodides.

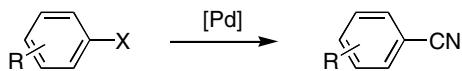
The reaction conditions have subsequently been optimized, various ligated palladium complexes were introduced, and the substrate scope of the method has been considerably enhanced by different groups. In Table 1 the different conditions of palladium-catalyzed cyanation reactions of aryl halides known prior to 2000 are summarized. In general, the cyanation of aryl bromides and iodides has been performed in the presence of an excess of KCN in dipolar aprotic solvents. In addition, NaCN, Me₃SiCN, *n*-Bu₃SnCN and Zn(CN)₂ were employed in selected examples as cyanide sources. Typically, a large amount of catalyst (1.5–20 mol% of Pd) has to be applied in order to obtain significant conversion and yield. Apparently using these catalyst loadings there is no difference in applying palladium(II) or palladium(0) pre-catalysts. In a few cases the cyanation of

chloroarenes was also performed. However, in all these examples highly reactive heteroaryl chlorides were used.

Table 1 demonstrates that the palladium-catalyzed cyanation of aryl bromides and iodides works with different palladium catalysts and cyanide sources (Scheme 4). Clearly, drawbacks of these procedures are the described catalyst productivity, which is always quite low (turnover numbers (TON) are in general 10–50), furthermore, many systems need additives or a special cyanide source (e.g. Zn(CN)₂) to enable good product yields.

In the last years new approaches have been made by us and other groups in order to overcome the limitations and drawbacks of the shown reactions, which will be discussed below.

Regarding costs and availability aryl chlorides are favorable substrates for catalytic refinement of aryl-X derivatives [54–57]. So far the most versatile and practical procedure for the palladium-catalyzed cyanation of aryl chlorides using potassium cyanide was published by our group [58,59]. Here, as a catalyst system 2 mol% Pd(OAc)₂, 1,5-bis(diphenylphosphino)pentane as ligand and 20 mol% of *N,N,N',N'*-tetramethylethylene-



Scheme 4. Palladium-catalyzed cyanation of aryl halides.

Table 1
Evolution of the palladium-catalyzed cyanation of aryl halides

Entry	X	Catalyst (mol%)	Additive (mol%)	Cyanide (equiv.)	Solvent	T (°C)/t (h)	Ref.
1	I, Br	Pd(OAc) ₂ (2)	–	KCN (2)	DMF	140/2–12	[35]
2	I	Pd(PPh ₃) ₄ (20)	–	KCN (1.5)	THF	reflux/8	[39]
3	I, Br	Pd(OAc) ₂ (1.5)	KOH (0.05) KI (9)	KCN (2)	HMPT	60–90/2–9	[40]
4	I, Br	Pd(PPh ₃) ₄ (10)	–	NaCN on Al ₂ O ₃ (5) ^a	Toluene	80–100/2–40	[41]
5	I, Br	Pd(PPh ₃) ₄ (10)	Al ₂ O ₃	NaCN (5)	Toluene	80–100/2–40	[41]
6	Cl ^b	Pd(PPh ₃) ₄ (5)	–	KCN (1.5)	DMF	reflux/2.5	[42]
7	Br	Pd(PPh ₃) ₄ (20)	18-C-6 (40)	KCN (1)	Benzene	100/65	[43]
8	I	Pd(PPh ₃) ₄ (2)	–	Me ₃ SiCN (1.5)	Et ₃ N	reflux/0.17–0.5	[44]
9	Br ^c	Pd(PPh ₃) ₄ (1.5)	18-C-6 (7.5) CuI (250)	KCN (250)	DMF	reflux/2	[45]
10	I ^d	Pd(PPh ₃) ₄ (n.g.) ^e	–	<i>n</i> -Bu ₃ SnCN (n.g.)	DMF	n.g. ^e	[46]
11	Cl ^f	PdCl ₂ (PPh ₃) ₂ (2)	–	KCN (2)	DMF	reflux/2	[47]
12	I	Pd ₂ (dba) ₃ (CHCl ₃) (0.5) dppf ^g (2)	–	KCN (2)	NMP	60–80/1–8	[48]
13	I, Br	Pd(PPh ₃) ₄ (2–6)	–	Zn(CN) ₂ (0.6)	DMF	80/0.5–7	[49]
14	Cl ^f	Pd(PPh ₃) ₄ (7)	–	Zn(CN) ₂ (0.6)	NMP	90/20	[50]
15	I, Br ^h , OTf	Pd(PPh ₃) ₄ (5)	CuI (10)	NaCN (2)	RCN ⁱ	reflux/1–6	[51]
16	Br	Pd ₂ (dba) ₃ (0.05–1), dppf	–	Zn(CN) ₂ (0.6)	DMF (wet)	120/20	[52]
17	Cl	Pd ₂ (dba) ₃ (2)	Zn (12)	Zn(CN) ₂ (0.6)	DMA	120/1–12	[53]

^a 5 mmol NaCN per g Al₂O₃.

^b Only chloropyrazines.

^c Only bromopyrazines.

^d Only 2-iodoadenosine.

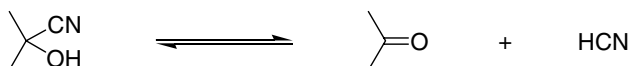
^e Not given.

^f Only chloropurines.

^g 1,1'-Bis(diphenylphosphino)ferrocene.

^h One example of a vinyl bromide.

ⁱ R = Me for iodides and triflates, R = Et for bromides.



Scheme 5. Acetone cyanohydrin, a useful HCN equivalent.

diamine (TMEDA) as additive work for most aryl chlorides, either activated or deactivated.

As discussed above various palladium species (palladium(0) as well as palladium(II) species) are deactivated by cyanide ions in solution. To overcome this problem and to improve catalyst productivity (TON) it is necessary to control the concentration of cyanide at a defined low level, which allows the reductive coupling to proceed efficiently, but prevents catalyst deactivation at the same time. An elegant and promising approach is the defined dosage of a liquid cyanide source to the reaction mixture using a syringe pump. One of the simplest soluble cyanide sources for such reactions is acetone cyanohydrin, which is commercially available on large scale (Scheme 5).

The cyanation of aryl bromides with acetone cyanohydrin is possible in a very efficient manner [60]. Remarkable are the convenient reaction conditions, the excellent nitrile selectivity and the low catalyst concentration. Until very recently, the highest turnover number for palladium-catalyzed cyanation of aryl halides known has been reported by applying acetone cyanohydrin as cyanating agent (TON = 129900). Similarly, trimethylsilylcyanide (TMSCN) can be used to control the concentration of cyanide ions in solution [61].

Recent efforts by other groups which have been pursued to further improve the reaction scope are mainly based on the use of zinc salts. For example, a room temperature aryl bromide cyanation with 2.5 mol% Pd₂(dba)₃, tri-*t*-butylphosphine as ligand, 1.8 equiv. Zn(CN)₂ as the cyanide source and 0.12 equiv. Zn as activating agent in DMF was presented by Maddaford et al. [62]. Zinc was also used as activating agent, together with Zn(OAc)₂, in a procedure by Chidambaram [63]. The advantage of this method is a relatively low Pd

loading of 0.1 mol% and the tolerance of low amounts of oxygen, so that reagent grade solvent DMF without special pre-treatment can be used.

2. Results

In continuation of our own work on the cyanation reaction we have discovered earlier this year that slow liberation of cyanide ions is also guaranteed by using the extremely stable potassium hexacyanoferrate(II) as cyanide source, with Pd(OAc)₂ as catalyst and dppf (1,1'-bis(diphenylphosphino)ferrocene) as ligand [64]. An advantageous side effect of this procedure was the high catalyst productivity achievable. Hence, a TON of 9700 was reached for the cyanation of bromobenzene. Keeping safety aspects in mind, the use of K₄[Fe(CN)₆] is significantly preferable compared to other highly toxic cyanide sources. While KCN is extremely toxic (LD₅₀ (oral, human) = 2.86 mg/kg) and develops HCN on contact with acidic water, K₄[Fe(CN)₆] is non-toxic and even used in food industry for metal precipitation. It has also been used as anti-agglutinating auxiliary for NaCl (table salt) [65]. It is soluble in water without decomposition, even on addition of hydrochloric acid HCN is developed only by boiling. Other previously known cyanating agents such as NaCN, Zn(CN)₂ and CuCN are comparably toxic to KCN. In addition, K₄[Fe(CN)₆] is commercially available on ton-scale and comparably in price to KCN [66].

Here, we report for the first time that palladium-catalyzed cyanations using K₄[Fe(CN)₆] also work highly efficiently with simple palladium salts as catalyst! In general there is no necessity to add an expensive phosphine ligand, making this procedure highly attractive for applications.

In Table 2 selected examples of catalyst variations for our model reaction are shown. Initially, we discovered that Pd/dppf gives excellent results in this reaction (Table 2, entry 1). To our surprise in the presence of other ligands such as PPh₃, PCy₃, bpephos and even carbenes

Table 2
Variation of reaction conditions for the cyanation of bromobenzene

Entry	Solvent	Pd(OAc) ₂ [mol%]	Ligand [mol%]	Conv. [%]	Yield [%]	TON
1	NMP	0.01	dppf (0.02)	100	97	9700
2	NMP	1	PPh ₃ (4)	64	54	54
3	NMP	1	PCy ₃ (4)	84	70	70
4	NMP	1	bpephos (2) ^a	73	59	59
5	NMP	0.01 ^b	–	100	98	9800
6	NMP	1	–	17	11	11
7	NMP	0.05	–	97	89	1800
8	NMP	0.01	–	95	92	9200

Conditions: 2 mmol bromobenzene, 0.5 mmol dry K₄[Fe(CN)₆], 2 mmol Na₂CO₃, 2 ml NMP, Pd(OAc)₂, 120 °C, 16 h.

^a 2,2'-bis(diphenylphosphino)diphenylether.

^b Pd(IMes)(dvds) = 1,3-dimesitylimidazole-2-ylidene-palladium(0)-η²,η²-1,1,3,3-tetramethyl-1,3-divinyldisiloxane [67].

Table 3
Cyanation of various aryl halides [68]

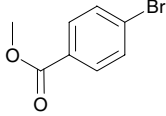
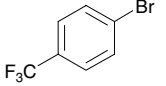
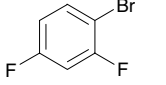
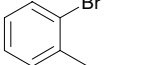
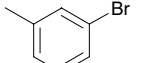
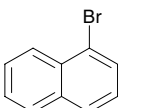
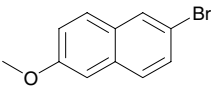
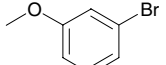
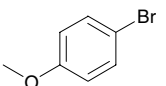
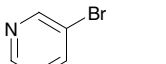
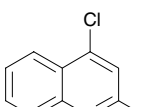
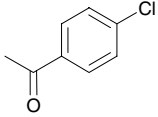
Entry	Aryl halide	Temp. [°C]	Pd(OAc) ₂ [mol%]	Conv. [%]	Yield [%]	TON
1		140	0.025	100	69	2760
2		140	0.025	100	98	3920
3		140	0.1	97	75	750
4		140	0.025	100	92	3680
5		140	0.025	92	90	3600
6		140	0.005 ^a	100	91	18,200
7		140	0.01 ^a	100	98	9800
8		140	0.025	100	95	3800
9		140	0.025	100	92	3680
10		140	0.1	100	>99	1000
11		140	0.1	99	84	840

Table 3 (continued)

Entry	Aryl halide	Temp. [°C]	Pd(OAc) ₂ [mol%]	Conv. [%]	Yield [%]	TON
12		120	0.1	85	77	770

^a 20 mol% Na₂CO₃.

also a high yield of benzonitrile at relatively low catalyst concentration was obtained (Table 2, entries 2–5). Because of the comparably low influence of the nature of the ligand, next reactions without ligand were performed. A blind test at 1 mol% Pd without phosphine ligand shows only a low yield of the product benzonitrile (Table 2, entry 6).

Nevertheless, reactions performed at lower Pd loading resulted in activities comparable to the highest ones achieved in the presence of phosphine ligands (Table 2, entries 7–8). Due to the often high price of phosphine ligands and the simplified process without any ligands present this is an interesting feature worth further examination. Therefore, the new protocol was then applied to the cyanation of various aryl halides (Table 3).

Compared to reactions with phosphine ligands present, a slightly higher temperature of 140 °C has to be used to obtain optimum results. In most cases the yields of benzonitriles are higher or considerably less Pd is needed, when performing the experiments without additional phosphine ligand. Moreover, we found that 1.2 equiv. of cyanide (20 mol% K₄[Fe(CN)₆]) is sufficient to ensure a complete reaction at high rate.

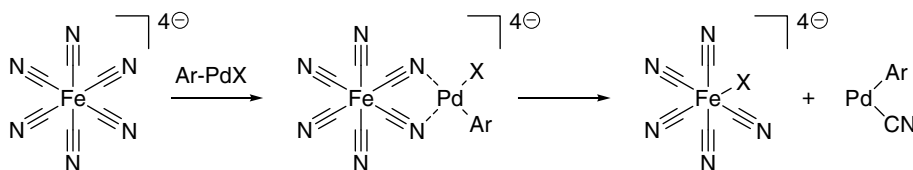
3. Discussion

In general, we obtain good to excellent results for all types of aryl bromides present in this reaction. Uniformly, electron poor (Table 3, entries 1–3) and electron rich (Table 3, entries 4, 5, 7–9) bromoarenes give high yields (69 to >99%) at low catalyst loadings (0.005–0.1 mol%). Ortho substituents such as fluoro or methyl groups are well tolerated. Furthermore, heteroaryl bromides, e.g., 3-bromopyridine (Table 3, entry 10) can be

cyanated under these conditions. Some aryl chlorides, for instance 4-chloroquinoline (Table 3, entry 11) and 4-chloroacetophenone (Table 3, entry 12), are sufficiently activated to react, while more electron rich ones, like 4-chloroanisole, give so far only low conversion (<10%). Most outstanding is the TON of >18,000 for 1-bromonaphthalene, which is an unprecedented high productivity for a metal-catalyzed cyanation of aryl halides.

What are the reasons for the high catalyst stability and activity without phosphine ligands present? It is well documented in literature that palladium catalysts used in coupling reactions of aryl halides might be stabilized by anions (halides, carboxylates) or even solvents. In this context it is interesting to note that “naked” metal catalysts can be sufficiently stable to perform a desired reaction more efficiently than a ligand-modified catalyst [69–73]. Even for some reactions with metal/ligand systems it is assumed that the “real” catalysts are ligand free, solvent stabilized metal ions, clusters or colloids [74]. Often, the defined ligand coordinated complexes are considered merely as a storage pool for the metal in a low oxidation state.

Regarding the dramatic increase of product yield at lower catalyst concentration (compare Table 2, entries 6–8), we explain the observation by a decrease of agglomeration of molecular palladium complexes to palladium black. A similar effect has been described by de Vries et al. [73,75] for Heck olefinations of aryl iodides. NMP and cyanide anions are well enough suited as ligands to stabilize the intermediate Pd(0) and Pd(II) species. Furthermore, stabilization of active Pd species by binding to hexacyanoferrate(II) ions might occur, which is in agreement to a mechanism proposed by Prasad [76] for the Hg(II)-catalyzed ligand exchange in hexacyanoferrate(II) (Scheme 6).



Scheme 6. Proposed Pd-catalyzed transfer of cyanide.

Another important factor for the high productivity of our system may be contributed by the reductive properties of the reagent hexacyanoferrate(II). As has been stated originally by Takagi, catalyst deactivation is based on the fact that palladium(II) tetracyano compounds cannot be reduced to catalytically active palladium(0) species. Hexacyanoferrate(II) might be able to perform this reduction and, moreover, reduce also traces of oxygen and other impurities from the reaction mixture.

4. Conclusion

We have developed an improved protocol for the cyanation of aryl halides. Our procedure relies on the use of non-poisonous potassium hexacyanoferrate(II) and, compared to our previous report, omits the necessity of adding phosphines such as dppf, while keeping the catalyst productivity and product yield at least constant and in some cases even improving them. Using the described catalyst system the best turnover number (>18,000) for a transition metal-catalyzed cyanation of aryl halides has been obtained. Combining the advantages of the cyanide source and the simplicity of the catalyst system we believe that the new procedure constitutes the current state-of-the-art cyanation technology for aryl halides.

Acknowledgments

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