Palladium-Catalyzed Cyanation of Aryl Halides: Recent Developments and Perspectives

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The palladium-catalyzed cyanation of aryl halides is an elegant method for the preparation of benzonitriles. Since its discovery in 1973, this reaction has been the topic of several investigations. Nevertheless, the general methodology is still somewhat underdeveloped compared to other palladium-catalyzed coupling reactions. Here, we summarize important developments from 1997 until 2003 in this area. Recent contributions from our group include the development of palladium/phosphane/amine catalyst systems for the cyanation of aryl chlorides, the successful cyanation of aryl halides with acetone cyanohydrin and trimethylsilyl cyanide as cyanation reagents, and a general improvement of catalyst efficiency by using a continuous dosage of cyanide sources.

Introduction

Benzonitriles are of considerable interest for organic chemistry as an integral part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products. The nitrile group also serves as an important intermediate structure 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)-

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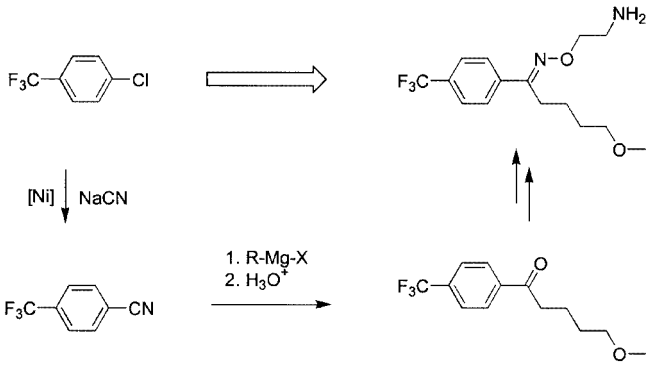
Mark Sundermeier was born in Herford, Germany in 1972. He studied chemistry at the Friedrich-Schiller-University in Jena, where he has done his diploma thesis in 1998 under directions of Prof. R. Beckert on the field of 1,2-dioxetanes and their luminescence. Under the supervision of Prof. M. Beller he started his PhD studies in 1998 on the field of palladium-catalyzed cyanation of aryl−X derivatives at the Leibniz-Institut für Organische Katalyse in Rostock, where he completed his PhD degree in 2002. He focused his research on the cyanation of aryl chlorides and bromides. Since 2003 he is a postdoctoral fellow at the Colorado State University in the group of Prof. T. Rovis working on the field of asymmetric O→C rearrangements.

Alexander Zapf was born in Coburg, Germany, in 1970. After studying chemistry at the Technical University of Munich he worked on his PhD thesis in the area of Heck and Suzuki reactions under the supervision of Prof. M. Beller until 1998. Then he joined the Leibniz-Institut für Organische Katalyse in Rostock, where he became the project leader of "Ar−X activation" in 1999. Pd-catalyzed coupling reactions of aryl chlorides and bromides are the subject of most of the projects, which are mainly worked on in cooperation with industry. Alexander has been a fellow of the Studienstiftung des deutschen Volkes and the Max-Buchner-Forschungsstiftung.

Matthias Beller, born 1962 in Gudensberg, Germany, studied chemistry at the University of Göttingen and obtained his doctorate in 1989 under the guidance of Prof. L. F. Tietze. After postdoctoral studies (1990) with Prof. K. B. Sharpless at Massachussetts Institute of Technology (USA) funded with a Liebig scholarship of the Verband der Chemischen Industrie, he became a research chemist in the Central Research of Hoechst AG in Frankfurt, Germany. In 1993 he became group leader of "Organometallic chemistry - catalysis" and in 1994 project leader of "Homogeneous catalysis" at Hoechst AG. From 1996 to 1998 he was Associate Professor for Inorganic Chemistry at the Technical University of Munich and since June 1998 he is Director of the Leibniz-Institut für Organische Katalyse (IfOK) aligned with a full professorship "Catalysis" at the University of Rostock. His research topics cover the development of a wide range of practical catalytic methodologies. Special attention is given to selective and environmentally benign transformations. More specifically he is interested in palladium-catalyzed coupling reactions, carbonylation reactions, catalytic amination of olefins and oxidations of olefins using air or molecular oxygen as the final oxidant. His scientific work has been published in more than 140 original publications and review articles. In addition 70 patent applications have been filed in the last decade. Together with Prof. Carsten Bolm he has edited a book on the use of "Transition Metals for Organic Synthesis". Matthias Beller is married since 1992 to Dr. Anja Fischer-Beller and they have two sons (Marc-Philipp and Jan-Niclas).

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

benzonitrile, which is available from 4-chloro(trifluoromethyl)benzene by nickel-catalyzed cyanation on ton-scale, serves as an intermediate.[1−3]



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

Benzonitriles themselves are also of significant interest, for example as substructures in biologically active agents. In Figure 1 selected examples of pharmaceuticals containing an aromatic nitrile as integral part of the molecule are shown along with their names, producers, and effects.[4] In the 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 $K^{14}CN$ isotopically labeled 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 are synthesized by the Rosenmund-von Braun reaction[15−19] from aryl halides or diazotization of anilines and subsequent Sandmeyer reaction[20−22] on a laboratory as well as on an industrial scale. On a 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 catalysts.[23−25]

A drawback of the Rosenmund-von Braun and the Sandmeyer reactions is the use of stoichiometric amounts of copper(I) cyanide as cyanating agent, which leads to equimolar amounts of heavy metal waste. Other disadvantages of the Rosenmund-von Braun reaction are the relatively high temperature (150−250 °C) and the low reactivity of aryl chlorides and bromides (in general the use of expensive aryl iodides is required). The ammoxidation is restricted to simpler substrates because of the high temperature, high pressure, and the large excess of ammonia required. Furthermore, only a limited number of toluene derivatives are available on a larger scale. Hence, this procedure is applied for products such as benzonitrile, terephthalodinitrile, and chlorobenzonitriles.[26,27]

A useful alternative for the preparation of substituted benzonitriles is the transition-metal-catalyzed cyanation of aryl−X compounds (X = Cl, Br, I, OTf etc.) with cheap and readily available cyanation agents like sodium or potassium cyanide (Scheme 2).[28−31] The order of reactivity of the aryl−X derivatives is opposite to the bond-dissociation energy of the C−X bond (reactivity: I ≈ OTf > Br > Cl).[32,33] Electron-withdrawing substituents on the aryl ring increase the reactivity, while electron-donating substituents decrease reactivity. Most common catalysts for coupling of aryl halides or triflates with cyanide are transition metal complexes of the platinum group, especially palladium or nickel complexes. Palladium catalysts tolerate a wider vari-

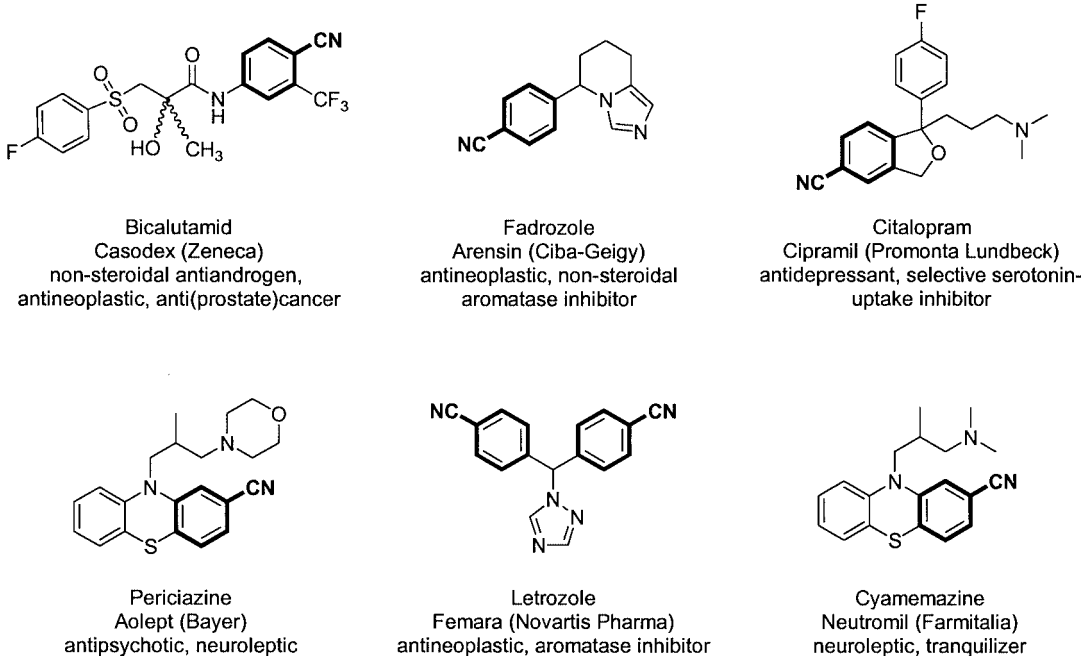
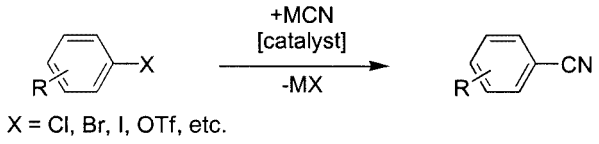


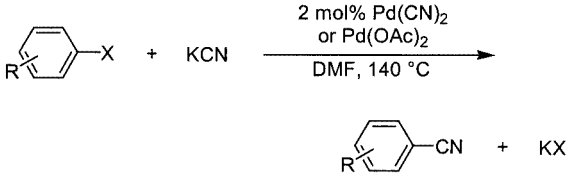
Figure 1. Examples of pharmaceutically active benzonitriles

ety of functional groups and are less sensitive to air and humidity than nickel catalysts.



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

The first palladium-catalyzed cyanation of aryl−X derivatives has been introduced in 1973 by Takagi and co-workers using aryl bromides and iodides with potassium cyanide as the cyanating agent (Scheme 3).[34] 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.



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

Early mechanistic studies by Takagi and co-workers[35] led to the mechanistic proposal shown in Scheme 4. The mechanism consists of two cycles, one representing the typical cycle for a palladium-catalyzed cross-coupling reaction with oxidative addition and reductive elimination, and a second prior cycle, where palladium species act as cyanide carriers. It was pointed out that an excess of cyanide ions inhibits the catalytic cycle. This deactivation was explained by the 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.[36,37]

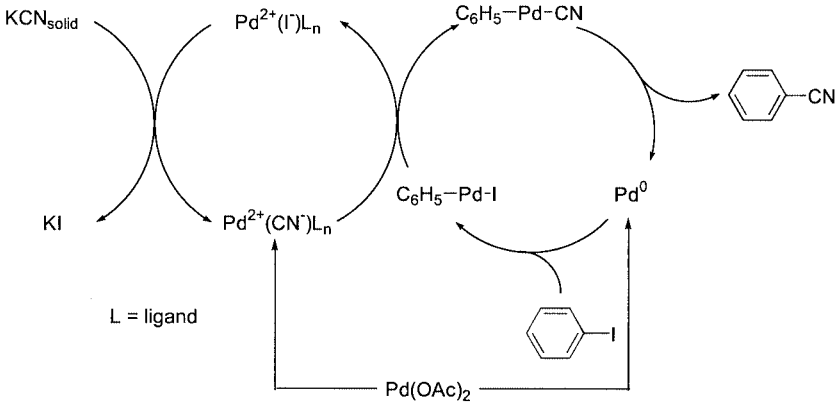
The reaction conditions have subsequently been optimized and the substrate scope of the method has been considerably enhanced by different groups. In Table 1 the different conditions of palladium-catalyzed cyanation reactions of aryl halides known prior to 1997 are summarized. In general the cyanation of aryl bromides and iodides has been performed in the presence of an excess of KCN in dipolar aprotic solvents. In addition, NaCN, Me_3SiCN, nBu_3SnCN and $Zn(CN)_2$ were employed in selected examples as cyanide sources. Apparently 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 have been used.

Table 1 demonstrates that the palladium-catalyzed cyanation of aryl bromides and iodides works with different palladium catalysts and cyanide sources. However, the described catalyst productivity was always quite low (turnover numbers (TON) are in general 10−50). Furthermore, many systems need additives or a special cyanide source to enable good product yields. In the last five years new approaches have been made by us and other groups which will be discussed below.

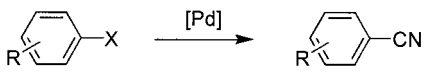
Results and Discussion

Recent Developments in the Palladium-Catalyzed Cyanation of Aryl Bromides and Iodides

Due to the low catalyst efficiency realized with KCN in the palladium-catalyzed cyanation of aryl halides, some recent publications focused on the development of alternative cyanation agents. A somewhat unusual cyanide source are alkyl nitriles, which represent common solvents. In this re-



Scheme 4. Proposed mechanism of the palladium-catalyzed cyanation according to Takagi et al.



Scheme 5. Palladium-catalyzed cyanation of aryl halides

an overstoichiometric amount of zinc powder as additive (4 equiv.). Thus, this protocol might be a viable alternative only for a limited number of benzonitriles. The unusual reaction mechanism is, however, worth mentioning, as it is completely different from the general mechanism for the palladium-catalyzed cyanations. As shown in Scheme 6 the

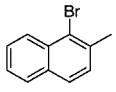
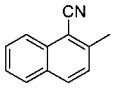
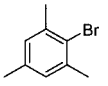
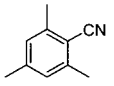
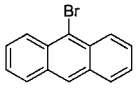
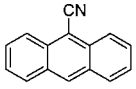
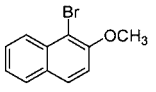
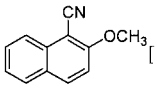
Table 1. Evolution of the palladium-catalyzed cyanation of aryl halides

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	[34]
2	I	$[Pd(PPh_3)_4]$ (20)	–	KCN (1.5)	THF	reflux/8	[38]
3	I, Br	$Pd(OAc)_2$ (1.5)	KOH (0.05) KI (9)	KCN (2)	HMPT	60–90/2–9	[39]
4	I, Br	$[Pd(PPh_3)_4]$ (10)	–	NaCN on Al_2O_3 (5)[a]	Toluene	80–100/2–40	[40]
5	I, Br	$[Pd(PPh_3)_4]$ (10)	Al_2O_3	NaCN (5)	Toluene	80–100/2–40	[40]
6	Cl[b]	$[Pd(PPh_3)_4]$ (5)	–	KCN (1.5)	DMF	reflux/2.5	[41]
7	Br	$[Pd(PPh_3)_4]$ (20)	18-C-6 (40)	KCN (1)	Benzene	100/65	[42]
8	I	$[Pd(PPh_3)_4]$ (2)	–	Me_3SiCN (1.5)	Et_3N	reflux/0.17–0.5	[43]
9	Br[c]	$[Pd(PPh_3)_4]$ (1.5)	18-C-6 (7.5) CuI (250)	KCN (250)	DMF	reflux/2	[44]
10	I[d]	$[Pd(PPh_3)_4]$ (n.g.)[e]	–	nBu_3SnCN (n.g.)[e]	DMF	n.g.[e]	[45]
11	Cl[f]	$[PdCl_2(PPh_3)_2]$ (2)	–	KCN (2)	DMF	reflux/2	[46]
12	I	$[Pd_2(dba)_3(CHCl_3)]$·0.5dppf[g] (2)	–	KCN (2)	NMP	60–80/1–8	[47]
13	I, Br	$[Pd(PPh_3)_4]$ (2–6)	–	$Zn(CN)_2$ (0.6)	DMF	80/0.5–7	[48]
14	Cl[f]	$[Pd(PPh_3)_4]$ (7)	–	$Zn(CN)_2$ (0.6)	NMP	90/20	[49]

[a] 5 mmol NaCN per g Al_2O_3. [b] Only chloropyrazines. [c] Only bromopyrazines. [d] Only 2-iodoadenosine. [e] Not given. [f] Only chloropurines. [g] 1,1′-Bis(diphenylphosphanyl)ferrocene.

gard it is interesting to note that Luo et al. have shown that a transfer of the nitrile function from acetonitrile to aryl halides is possible at high temperature (160 °C).[50] Table 2 presents a summary of the obtained results. In contrast to most other cyanation protocols good yields of 2-substituted benzonitriles and even 2,6-disubstituted benzonitriles are obtained.

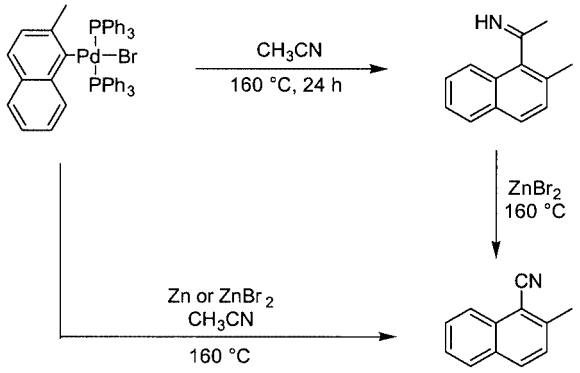
Table 2. Acetonitrile as solvent and cyanide source

Entry	Substrate	Product[a]	Catalyst	Yield [%][b]
1			$[PdCl_2(PBu_3)_2]$	81
2			$[PdCl_2(PPh_3)_2]$/8 PPh_3	76 (69)[c]
3			$[PdCl_2(dppp)_2]$	90
4			$[PdCl_2(PBu_3)_2]$	100
5			$[PdCl_2(PPh_3)_2]$/8 PPh_3	94 (76)[c]
6			$[PdCl_2(PBu_3)_2]$	(70)[c]
7			$[PdCl_2(PBu_3)_2]$	32
8			$[PdCl_2(PPh_3)_2]$/8 PPh_3	30 (28)[c]

[a] General conditions: 5 mmol aryl bromide, 10 mol % Pd-catalyst, 4 equiv. Zn-powder, 30 mL acetonitrile, 160 °C, 24 h.[b] Yields determined by ^1H NMR using $HCONEt_2$ as internal standard.[c] Isolated yield in parentheses.

Unfortunately, this transformation requires high catalyst concentration (10 mol %), high temperature (160 °C) and

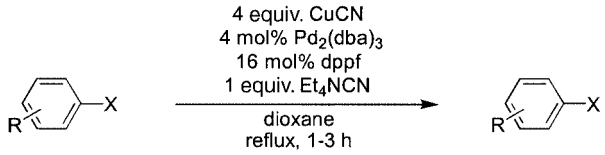
oxidative addition product of the aryl halide and palladium(0) first gives the corresponding imine, which is then degraded by Lewis acid catalysis to the desired nitrile. Stoichiometric amounts of zinc(II) salts are formed during the reaction.



Scheme 6. Mechanism of the palladium-catalyzed cyanation using acetonitrile as cyanating agent

Surprisingly, copper(I) cyanide, the typical cyanating agent in the Rosenmund-von Braun and the Sandmeyer reaction, was not described as a cyanide source in palladium-catalyzed reactions of aryl halides until recently. Hence, the first palladium-catalyzed Rosenmund-von Braun reaction was developed by Sakamoto and Ohsawa in 1999 (Scheme 7).[51]

This protocol is useful for the transformation of electron-rich and electron-poor aryl bromides. Also *N*-heteroaryl iodides and bromides [e.g., *N*-(phenylsulfonyl)indoles, pyrrols, quinolines] give the corresponding nitriles in good

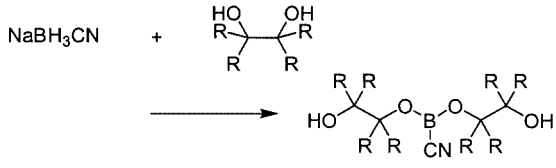


R	X = I	X = Br
4-OMe	82 %	91 %
4-CO_2Me	88 %	89 %
4-NO_2	65 %	56 %
2-OMe	94 %	76 %
2-CO_2Me	88 %	83 %
2-NO_2	67 %	23 %

Scheme 7. Palladium-catalyzed Rosenmund-von Braun reaction

yield. A comparison of the palladium-catalyzed variant and the noncatalytic reaction shows that the palladium catalyst leads to higher yields. Nevertheless, the use of copper(I) cyanide leads to no improvement of the palladium catalyst efficiency compared to other cyanating agents. A comparatively high catalyst concentration (8 mol % Pd), an overstoichiometric amount of copper(I) cyanide (4 equiv.) and a stoichiometric amount of an additive (Et_4NCN) are still required for successful reactions.

Based on the knowledge of the well-established palladium-catalyzed cross-coupling of aryl halides with organoboron compounds (Suzuki reaction), Jiang et al. used dialkyl cyanoboronates as the cyanide source.[52] Dialkyl cyanoboronates are easily prepared by the reaction of sodium cyanoborohydride and 1,2-diols (Scheme 8). As shown in Table 3, the cyanation of aryl bromides, iodides and strongly activated chlorides is possible under these conditions.

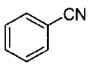
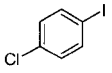
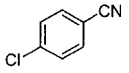
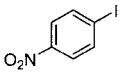
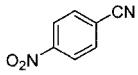
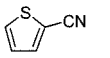
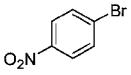
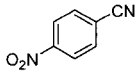
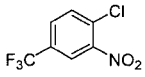
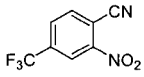
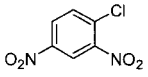
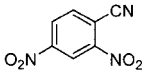


Scheme 8. Dialkyl cyanoboronates — new cyanating agents

Apart from variations of the cyanide source the optimization of co-catalysts and ligands was studied in order to improve the palladium-catalyzed cyanation of aryl halides in efficiency and scope. For example Okano et al. introduced a new class of phase-transfer-type phosphane ligands for this reaction. Here, the known positive effect of a phase-transfer catalyst (PTC) was introduced in the phosphane ligand in order to control the reactivity of the palladium catalyst. Several ligands, containing crown ether, sulfonic acid, carbonic acid or ammonium salts, or similar substructures were tested (Figure 2).[53,54] The best results were obtained in the presence of PPh_2(bc-5) and PPh_2(ms) as ligand (Table 4 and 5).

As shown in Table 4, when using PPh_2(bc-5) as ligand the cyanation of bromo- and iodoarenes is possible in the presence of a comparatively low catalyst concentration (0.33 mol %). Here, no further additives are necessary, but

Table 3. Dialkyl cyanoboronates in the palladium-catalyzed cyanation of aryl halides

Entry	Substrate	Product[a]	t [h]	Conversion (yield) [%][b]
1			24	80 (78)
2			17	67 (37)
3			48	58 (50)
4			10	72 (69)
5			24	83 (75)
6			144	97 (89)
7			24	87 (72)
8			24	40 (19)
9			12	58 (50)

[a] General conditions: 0.5 mmol aryl bromide, 5 mol % $[Pd(PPh_3)_4]$, 1.2 equiv. cyanoboronate ester, 1.5 equiv. K_3PO_4, 5 mL THF, 50 °C. [b] Conversions determined by GC-MS, isolated yield in parentheses.

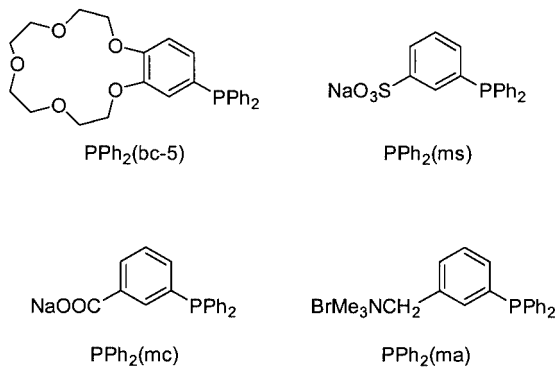
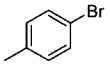
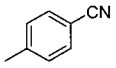
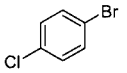
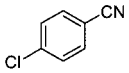
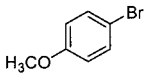
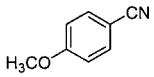
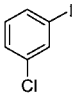
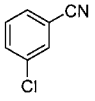


Figure 2. Ligands with phase-transfer catalyst properties

PPh_2(ms) as ligand requires the addition of $ZnCl_2$ and $NaBH_4$ in order to obtain satisfactory results (Table 5).

Unfortunately, using PPh_2(ms) as ligand just aryl iodides and electron-deficient aryl bromides can be cyanated in good yield, whereas bromobenzene is hardly converted. Without sodium borohydride, no catalytic activity at all is observed. The authors state that the hydride is needed for reduction of the catalyst precursor $[PdCl_2\{PPh_2(ms)\}_4]$,

Table 4. PPh_2(bc-5) as new ligand in the palladium-catalyzed cyanation

Entry	Substrate	Product[a]	Yield [%][b]
1			92 (77)
2			93 (81)
3			86
4			91
5			87

[a] General conditions: 7.5 mmol aryl bromide, 3 equiv. NaCN, 0.33 mol % *trans*-[PhPdBr{PPh_2(bc-5)$_2$}], 0.66 mol % PPh_2(bc-5), 5 mL dioxane, reflux, 20 h. [b] Yields determined by GC-MS, isolated yield in parentheses.

however the reduction of catalytically nonactive cyanopalladium species, which result from catalyst deactivation processes in the presence of an excess of cyanide ions, has to be considered, too.

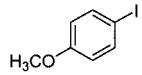
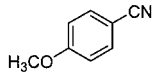
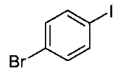
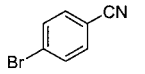
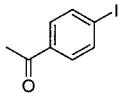
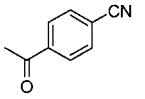
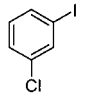
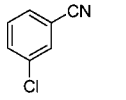
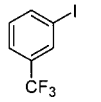
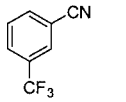
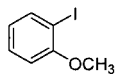
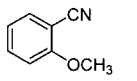
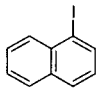
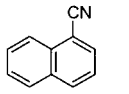
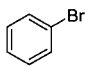
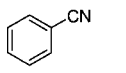
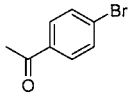
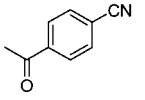
Anderson et al. studied the influence of solvent, cyanide source, co-catalysts, and the palladium source on the palladium-catalyzed cyanation of aryl halides.[55] Depending on the reaction conditions, potassium and sodium cyanide both gave satisfactory results. The choice of the right cyanide source is mainly influenced by the solvent. While KCN gives better results in THF, NaCN is preferable in ethyl acetate or acetonitrile. Furthermore, the authors discovered that copper salts were effective additives for the cyanation of 1-iodonaphthalene (Scheme 9, Table 6). In addition, aryl bromides and triflates can be coupled to the corresponding nitriles in good to very good yields.

Another new procedure has been described by Maligres et al.[56] They combined the palladium catalyst system introduced by Takagi ($Pd_2(dba)_3$/dppf)[47] with the use of zinc(II) cyanide as the cyanating agent (introduced by Tschaen et al.)[48] to get an efficient system for the palladium-catalyzed cyanation of aryl bromides (Scheme 10). Besides dppf several other phosphane ligands have also been tested, but with little success.

Palladium-Catalyzed Cyanation of Aryl Chlorides

Regarding costs and availability aryl chlorides are favorable substrates for catalytic refinement of aryl−X derivatives.[57−60] Because of their low reactivity, the cyanation of chloroarenes has been known prior to 2000 only with nickel catalysts[29,61−68] or with palladium catalysts for activated (hetero)aryl chlorides (e.g., pyrazines,[44] purines[46,49]). In 2000, Jin and Confalone reported the first general method for the palladium-catalyzed cyanation of aryl chlorides (Scheme 11).[69]

Table 5. Palladium-catalyzed cyanation of aryl halides using PPh_2(ms) as ligand

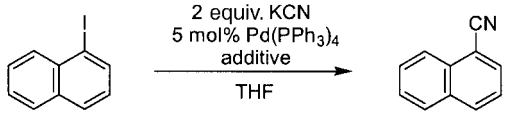
Entry	Substrate	Product[a]	*t* [h]	Yield [%][b]
1			7	98
2			3	82[c]
3			1	97 (91)
4			3	98
5			3	98 (93)
6			24	78
7			7	97 (89)
8			5	8
9			10	95

[a] General conditions: 10 mmol aryl halide, 1.3 equiv. NaCN, 1 mol % [$PdCl_2$[{Ph_2(ms)}$_4$], 50 mol % $ZnCl_2$, 20 mol % $NaBH_4$, 10 mL heptane, 10 mL water, reflux. [b] Yields determined by GC-MS, isolated yield in parentheses. [c] 13% Terephthalonitrile detected.

As shown in Table 7 the corresponding benzonitriles were obtained in good to very good yields by using 4 mol % of a palladium complex generated in situ from [tris(dibenzylideneacetone)dipalladium(0)] and [1,1′-bis(diphenylphosphanyl)ferrocene] (dppf). The use of zinc(II) cyanide as cyanide source and catalytic amounts of zinc powder to reduce palladium(II), which is formed to some extent in side reactions, is important for successful cyanation.

Despite its usefulness the procedure has some drawbacks such as the need for a comparatively high amount of catalyst (4 mol % palladium) and the use of zinc(II) cyanide as cyanide source, which leads to significant amounts of metal waste.

In a joint project with SKW Trostberg AG (now Degussa AG) we became interested in this topic in 1998. Based on our catalyst developments for Heck,[70−73] Suzuki[74−77] and amination[78,79] reactions of aryl chlorides, we were primarily attracted in finding more productive palladium catalyst

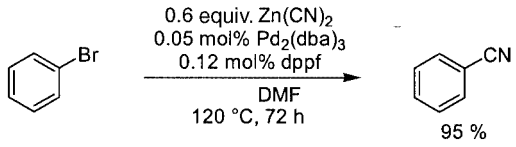


Scheme 9. Additive effects on the Pd-catalyzed cyanation of 1-iodonaphthalene

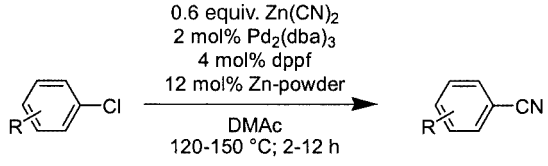
Table 6. Effect of additives on the palladium-catalyzed cyanation of 1-iodonaphthalene

Entry	Additive[a]	*t* [h]	Conversion [%][b]
1	–	6	7
2	5 mol % CuI	2	100
3	10 mol % CuCN	2	100
4	10 mol % CuOTf	4	94
5	10 mol % $Cu(OTf)_2$	3	57
6	10 mol % CuBr	3	100
7	10 mol % ZnI_2	2.5	100
8	10 mol % TMSCN	3.5	> 98
9	10 mol % BPh_3	2	100

[a] General conditions: 0.4 M 1-iodonaphthalene in THF, 2 equiv. KCN, 5 mol % $[Pd(PPh_3)_4]$. [b] Determined by HPLC.



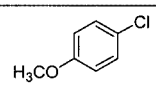
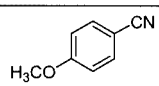
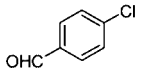
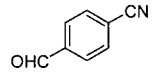
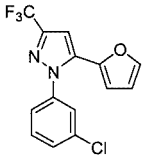
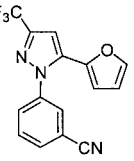
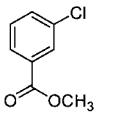
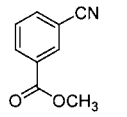
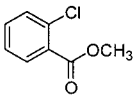
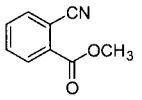
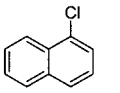
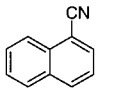
Scheme 10. Palladium-catalyzed cyanation of aryl bromides according to Maligres et al.



Scheme 11. Palladium-catalyzed cyanation of aryl chlorides according to Jin et al.

systems for the cyanation of aryl chlorides, which work in the presence of a cheap and readily available cyanide source (e.g., sodium or potassium cyanide). Initially, we studied the relation of various positive additives described for cyanations of aryl bromides using 4-chloro(trifluoromethyl)benzene as a model substrate. For example, we combined the known positive effect of crown ethers[53,54] with the use of inorganic bases like sodium carbonate or potassium hydroxide as co-catalysts.[39] Surprisingly, this combination of additives has never been tested before. As shown in Table 8 (Entries 1–3) a significant improvement of the product yield can be realized under these conditions.[80] Apart from additives the right choice of phosphane ligand is also important in order to obtain good results. Similar to carbonylation reactions of aryl chlorides,[81–85] the best results are observed in the presence of chelating phosphane ligands such as dppb and dpppe.

Table 7. Palladium-catalyzed cyanation of aryl chlorides by Jin and Confalone

Entry	Substrate	Product[a]	*T* [°C]	*t* [h]	Yield [%][b]
1[c]			150	4	88
2			120	0.75	92
3			150	10	91
4			120	10	91
5			120	2	93
6			150	2	96

[a] General conditions: 3 mmol aryl chloride, 0.6 equiv. $Zn(CN)_2$, 2 mol % $[Pd_2(dba)_3]$, 4 mol % dppf, 12 mol % Zn, 6 mL DMAc. [b] Isolated yield. [c] 4 Mol % $[Pd_2(dba)_3]$, 8 mol % dppf, 24 mol % Zn.

Table 8. Palladium-catalyzed cyanation of 4-chloro(trifluoromethyl)benzene with different co-catalysts

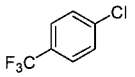
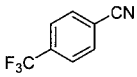
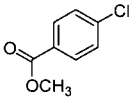
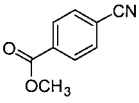
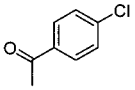
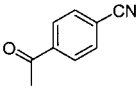
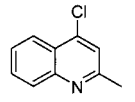
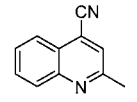
Entry[a]	Na_2CO_3 [mol %]	18-Crown-6 [mol %]	TMEDA [mol %]	Conv. [%][b]	Yield [%][b]
1	–	–	–	15	13
2	20	–	–	37	18
3	20	2	–	63	58
4[c]	20	2	–	42	38
5	20	2	20	56	49
6	20	–	20	50	43
7	–	2	20	10	8
8	–	–	20	97	91

[a] General conditions: 2 mmol 4-chloro(trifluoromethyl)benzene, 1 equiv. potassium cyanide, 2 mol % palladium(II) acetate, 4 mol % 1,5-bis(diphenylphosphanyl)pentane, 2 mL toluene, 16 h, 160 °C. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] Triphenylphosphane instead of 1,5-bis(diphenylphosphanyl)pentane.

As the combination of base and crown ether led to better results in the cyanation reaction, the question arose as to whether both properties could be combined into one single additive. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) is a typical candidate for the desired type of substances. Therefore, we tried the cyanation reaction in the presence of various amounts of TMEDA. To our delight,

the addition of 20 mol % of TMEDA as co-catalyst (Table 8, Entries 5−8) gave excellent yield (91%) and selectivity (94%) of 4-trifluoromethylbenzonitrile. Somewhat surprisingly, the combination of TMEDA with sodium carbonate and 18-crown-6 gave lower yields than with TMEDA alone. In the presence of TMEDA and 18-crown-6 a disappointingly low yield (8%) of the desired nitrile was observed. The dramatic influence of these additives on selectivity and yield of the desired benzonitrile is explained by their effect on the cyanide concentration in solution. While a high concentration of cyanide ions leads to immediate catalyst deactivation, a low concentration of CN^- retards the reductive coupling of the aryl group and cyanide ions (see mechanistic discussion below). The general applicability of the new protocol is shown in Table 9.

Table 9. Scope and limitations of the palladium-catalyzed cyanation of aryl and heteroaryl chlorides in the presence of TMEDA

Entry	Substrate	Product[a]	Conversion [%][b]	Yield [%][b]
1			97	91
2			85	75
3			96	91
4			99	96
5[c]			33	33
6[c]			23	17
7			48	46
8			76	74 (67)[d]

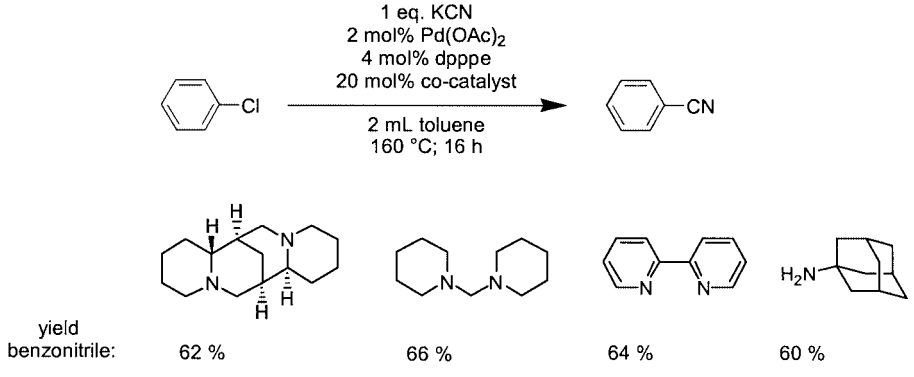
[a] General conditions: 2 mmol aryl or heteroaryl chloride, 1 equiv. potassium cyanide, 2 mol % palladium(II) acetate, 4 mol % 1,5-bis(diphenylphosphanyl)pentane, 20 mol % TMEDA, 2 mL toluene, 16 h, 160 °C. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] Reaction conditions: 2 mmol aryl chloride, 1 equiv. potassium cyanide, 3 mol % palladium(II) acetate, 6 mol % 1,5-bis(diphenylphosphanyl)pentane, 30 mol % TMEDA, 2 mL toluene, 16 h, 160 °C. [d] Isolated yield in parentheses.

The catalyst system is applicable to activated aryl chlorides, which react with KCN to give the corresponding benzonitriles in high yields. Also *N*-heteroaryl chlorides such as 3-chloropyridine and 4-chloroquinaldine give the desired product in moderate to good yield. Unfortunately, deactivated and nonactivated aryl chlorides like chlorobenzene and 3-chlorotoluene lead to poor results under these conditions (Table 9, Entries 5−6).

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 was used as a more suitable model system, which does not react efficiently with KCN under standard conditions, i.e., benzonitrile is obtained only in 13% in the presence of 0.2 equiv. of TMEDA and 2 mol % palladium catalyst. Selected examples of successful co-catalysts are shown in Scheme 12.[86]

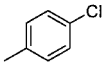
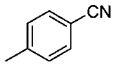
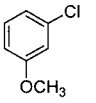
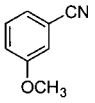
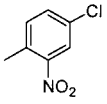
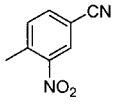
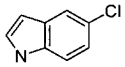
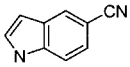
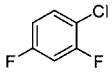
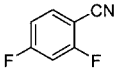
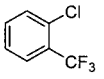
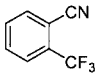
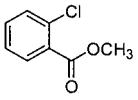
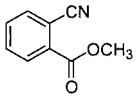
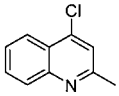
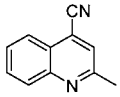
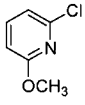
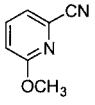
Clearly, the reaction outcome is significantly influenced by the added amine. Among the various amines tested the best results were obtained in the presence of sparteine, 1,1′-methylenedipiperidine (MDP), 2,2′-bipyridine, and 1-adamantylamine. A closer look at the catalysis results reveals that there is no obvious connection of catalytic activity and any structural property of the amine (e.g., basicity or sterics). Because of the promising results using MDP, the reaction of other nonactivated, deactivated, or sterically hindered aryl chlorides and *N*-heteroaryl chlorides was investigated with this additive (Table 10).

In most cases we observed considerably improved results with MDP as co-catalyst compared to TMEDA. Almost all problematic substrates are converted into the desired benzonitriles in good to very good yields. This procedure



Scheme 12. Variation of the co-catalyst in the palladium-catalyzed cyanation of chlorobenzene

Table 10. Catalytic cyanation of various aryl chlorides

Entry	Substrate	Product[a]	Conv. [%][b]	Yield [%][b]
1			67	66
2[c]			89	84
3			71	59
4			62	53
5			46	41
6[d]			66	55
7			52	(22)[e]
8			67	42
9			74	73
10			93	75 (71)[e]
11			68	63 (58)[e]
12			87	80
13[c]			61	55
14			95	91

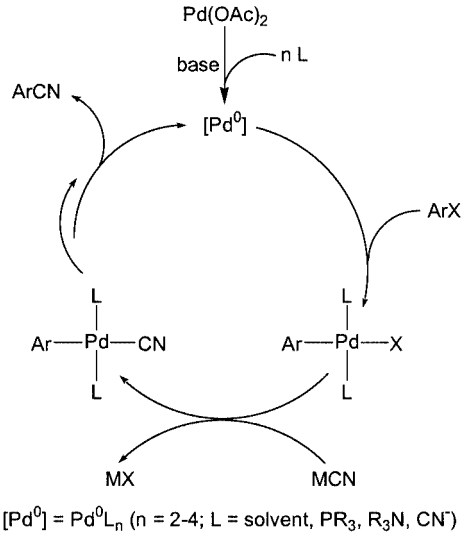
[a] General conditions: 2 mmol aryl or heteroaryl chloride, 1 equiv. potassium cyanide, 2 mol % palladium(II) acetate, 4 mol % 1,5-bis(diphenylphosphanyl)pentane, 20 mol % MDP, 2 mL toluene, 16 h, 160 °C. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] 1,4-Bis(diphenylphosphanyl)butane instead of 1,5-bis(diphenylphosphanyl)pentane. [d] 4 Mol % palladium(II) acetate, 8 mol % 1,5-bis(diphenylphosphanyl)pentane. [e] Isolated yield in parentheses.

with either TMEDA or MDP as co-catalyst is until today the most efficient and widely applicable method for the palladium-catalyzed cyanation of aryl chlorides with readily available and cheap KCN.

Mechanistic Investigations into the Palladium-Catalyzed Cyanation of Aryl Halides

The catalysis results discussed above show that different amines have a positive effect on the palladium-catalyzed cyanation reaction. The question remains, however, which elementary steps are influenced by the addition of amine. Because of the high temperatures palladium colloids also have to be considered as potential catalysts. It is known that such colloids, or nanoparticles, are formed from unstable palladium phosphane complexes at high temperature and that they show catalytic activity in C−C coupling reactions.[87,88] However, the color of the reaction mixtures (typically pale yellow for palladium phosphane complexes) makes this unlikely.

In order to understand the effect of the organic co-catalyst in more detail, single steps of the generally accepted mechanism for such types of palladium-catalyzed C−C coupling reactions[89−92] were performed in the presence and absence of TMEDA. As shown in Scheme 13 the catalytic cycle starts with the oxidative addition of the aryl halide to a Pd^0 species. In case of aryl chlorides the activation of the C−X bond is more difficult than with aryl bromides, aryl iodides or aryl triflates.[93]



Scheme 13. Proposed mechanism of the palladium-catalyzed cyanation of aryl−X

Despite the simplicity and analogy to similar coupling reactions there should be some concern about the viability of the proposed mechanism, because so far there is no report known about the isolation of an arylpalladium(II) cyanide complex. Recent ^1H and ^{31}P NMR experiments concerning the oxidative addition of 4-bromo(trifluoromethyl)-benzene to $[Pd(PPh_3)_4]$ at different cyanide concentrations showed that excess cyanide ions not only deactivate palladium(II), but also turn off the activity of palladium(0) complexes.[86] It was suggested that only 1−2 equivalents of cyanide ions with respect to palladium are tolerated by the catalyst system.

In the presence of TMEDA deactivation of the palladium(0) complex is prevented, even in the presence of an overstoichiometric amount of cyanide (five equivalents). It was assumed that the amine is capable of substituting cyanide ions at the palladium center, thereby regenerating an active palladium catalyst. Interestingly, the in situ formed arylpalladium(II) halide complex reacts immediately with cyanide to give the corresponding benzonitrile and a pal-

ladium(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. In stoichiometric oxidative addition reactions of 4-bromo(trifluoromethyl)benzene and Pd^0 it has also been shown that TMEDA increases the stability of the phosphane ligand towards ligand degradation (aryl-aryl scrambling[94−96]).

Improved Efficiency by Dosage of the Cyanide Source as a Result of the Mechanistic Studies

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 it is necessary to control the concentration of cyanide at a predefined low level, which allows the reductive coupling to proceed efficiently but prevents catalyst deactivation at the same time. In the past, this was done by careful selection of a solvent, in which the solubility of the cyanide is low and can be increased by means of a phase-transfer catalyst (crown ether, amine, etc.). However, it is clear that the CN^- concentration is difficult to control and that reproducibility problems might arise.

A more elegant and promising approach is the defined dosage of cyanide to the reaction mixture. Unfortunately, dosage of a solid cyanide source like potassium or sodium cyanide is difficult. However, the continuous addition of a liquid cyanide source using a syringe pump is easy. One of the simplest soluble cyanide sources for such reactions is acetone cyanohydrin, which is cheap and commercially available on a large scale (Scheme 14).[97−99]

Scheme 14. Acetone cyanohydrin, a useful HCN equivalent

As shown in Table 11, the cyanation of 4-bromo(trifluoromethyl)benzene with acetone cyanohydrin is possible in a very efficient manner.[100] The convenient reaction conditions, the excellent nitrile selectivity and the low catalyst concentration (Table 11, Entry 10) are remarkable. So far the highest turnover number for palladium-catalyzed cyanation of aryl halides known has been reported by applying acetone cyanohydrin as cyanating agent (TON 1900).

The generality of this approach is shown in Table 12. Activated, nonactivated, and deactivated aryl bromides give very good results in the cyanation, as do heteroaryl bromides. Electron-deficient aryl chlorides also react under these conditions (Table 12, Entries 13−15). However, conversion of *ortho*-substituted aryl halides to their corresponding benzonitriles is not satisfactory.

Another useful liquid cyanating agent is trimethylsilyl cyanide (TMSCN).[101] It has been described for the palladium-catalyzed cyanation of aryl iodides, whereas conversion of aryl bromides and chlorides was not possible in the past.[43] Apparently, catalyst deactivation takes place. Recently, we observed that *trans*-bromo[4-(trifluoromethyl)-phenyl]bis(triphenylphosphane)palladium(II) (**1**) reacts readily with TMSCN yielding the corresponding benzonitrile even at 0 °C (Scheme 15).[102]

So it was not surprising that continuous dosage of TMSCN works well for aryl bromides. By using the corresponding oxidative addition product with additional phosphane ligand as catalyst system the cyanation reactions exhibited excellent yield and selectivity (Scheme 16).[102]

As outlined in Table 13, a plethora of aryl bromides can easily be transformed into the corresponding benzonitriles. Less-reactive aryl chlorides can be coupled only with moderate success under these conditions (Table 13, Entry 14). However, utilization of an autoclave with dosage equipment, which allows to work at temperatures significantly above the boiling point of TMSCN and the solvent, should provide a possibility to overcome this problem.

Microwave-Assisted Palladium-Catalyzed Cyanation of Aryl Bromides

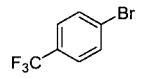
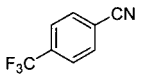
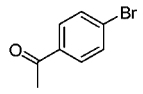
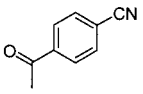
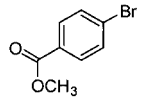
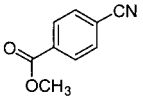
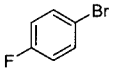
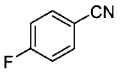
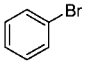
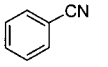
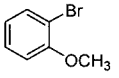
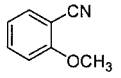
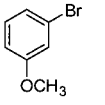
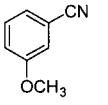
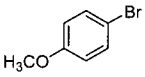
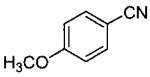
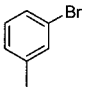
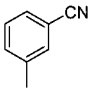
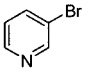
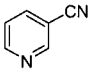
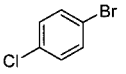
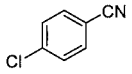
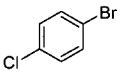
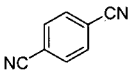
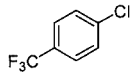
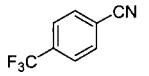
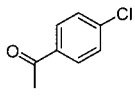
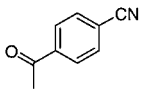
For many reactions it is possible to enhance the reaction rate by applying microwaves. This holds also true for the palladium-catalyzed cyanation of aryl halides. Alterman

Table 11. Acetone cyanohydrin as cyanating agent in the Pd-catalyzed cyanation of 4-bromo(trifluoromethyl)benzene

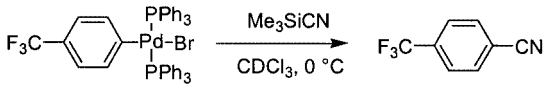
Entry[a]	$Pd(OAc)_2$ [mol %]	Pd:P	TMEDA [mol %]	Dosage rate [mmol/h]	*t* [h]	*T* [°C]	Conversion [%][b]	Yield [%][b]
1	2	1:4	20	0.1	21	120	100	≥ 99
2	2	1:4	20	0.1	21	100	100	≥ 99
3	2	1:4	20	0.1	21	80	100	≥ 99
4	2	1:4	20	0.1	21	60		1
5	1	1:4	20	0.1	21	100	100	≥ 99
6	0.5	1:4	10	0.1	21	100	100	≥ 99
7	0.1	1:4	10	0.1	21	120	0	0
8	0.1	1:8	10	0.05	42	120	81	80
9	0.1	1:8	–	0.05	42	120	8	0
10	0.05	1:16	10	0.05	42	140	97	95

[a] General conditions: 2 mmol 4-bromo(trifluoromethyl)benzene, 2.1 mL acetone cyanohydrin solution (1 M in DMAc), 1,5-bis(diphenylphosphanyl)pentane, 2.1 mmol sodium carbonate, 2 mL DMAc. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether).

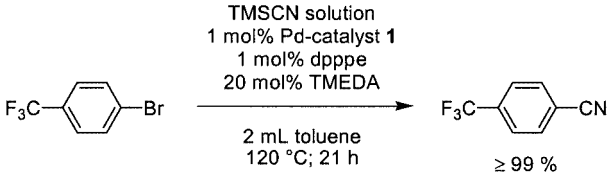
Table 12. Scope of the palladium-catalyzed cyanation using acetone cyanohydrine

Entry	Substrate	Product[a]	T [°C]	Conversion [%][b]	Yield [%][b]
1			100	100	≥ 99
2			100	100	≥ 99
3			100	100	95
4			120	98	96
5			120	96	96
6			140	27	21
7			120	99	99
8			120	98	98
9			120	100	≥ 99
10			100	82	82
12			100	82	82
13[c]			120	100	≥ 99
14[d]			140	78	77
15[d]			140	90	89

[a] General conditions: 2 mmol aryl or heteroaryl bromide, 2.1 mL acetone cyanohydrine solution (1 M), dosage rate 0.1 mL/h, 0.5 mol % palladium(II) acetate, 1 mol % 1,5-bis(diphenylphosphanyl)-pentane, 10 mol % TMEDA, 1.05 equiv. sodium carbonate, 2 mL DMAc, 21 h. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] 4.2 mL acetone cyanohydrin solution (1 M), dosage rate 0.1 mL/h, 2.1 equiv. sodium carbonate, 42 h. [d] 1 mol % palladium(II) acetate, 2 mol % 1,5-bis(diphenylphosphanyl)pentane.



Scheme 15. Stoichiometric reaction of the oxidative addition product **1** with TMSCN



Scheme 16. Use of TMSCN in the palladium-catalyzed cyanation of 4-bromo(trifluoromethyl)benzene

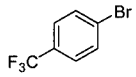
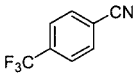
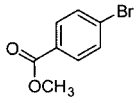
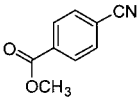
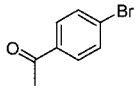
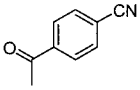
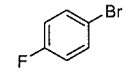
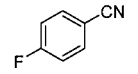
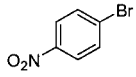
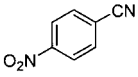
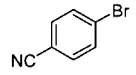
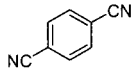
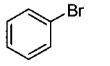
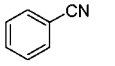
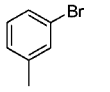
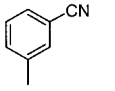
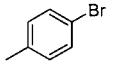
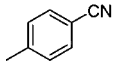
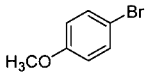
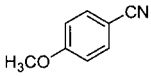
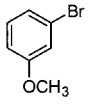
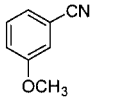
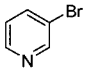
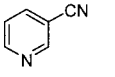
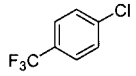
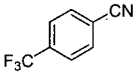
and Halberg have shown that microwave irradiation accelerates the rate of cyanation considerably. Reaction times could be reduced from hours to a few minutes in the case of aryl bromides. The corresponding benzonitriles were obtained in high yield and selectivity. Some examples of this methodology are given in Table 14.[103]

Conclusion

Significant progress with regard to substrate compatibility and catalyst efficiency has been achieved in the palladium-catalyzed cyanation of aryl halides. Hence, industrial realizations of this methodology in the area of fine chemical syntheses seem to be feasible in the near future. Based on mechanistic investigations it became clear that catalyst deactivation by excess cyanide ions is one of the main reasons for the low productivity and activity of palladium catalysts in the cyanation reaction of aryl halides when compared to other C−C-coupling reactions.[104−113] Hence, an important factor for further development of this reaction is the control of the concentration of cyanide ions in solution. One way to achieve this is the continuous dosage of cyanide to the reaction mixture. Another possibility is to apply a two-phase system (liquid-liquid or liquid-solid) and to control the cyanide concentration by use of phase transfer catalysts or by adjusting the solubility by choosing an appropriate solvent.

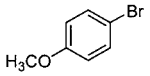
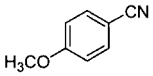
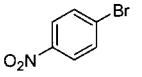
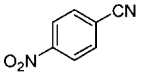
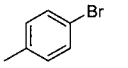
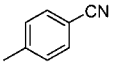
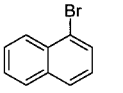
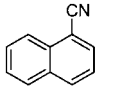
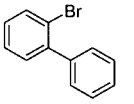
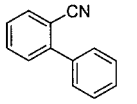
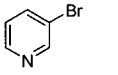
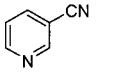
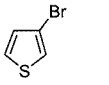
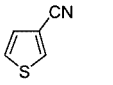
Because of the relatively mild reaction conditions and the broad scope, the palladium-catalyzed cyanation of aryl halides has become an interesting tool for the total synthesis of natural products and pharmaceuticals. Since the first total synthesis using this methodology (the synthesis of (+)-estradiol[114]), numerous biologically active substances have been synthesized including a palladium-catalyzed cyanation step (Fadrozol, Robalzotan, etc.).[5−7,45,115−118] In addition to active agents, other more complicated organic products, for example special calixarenes,[119] have also been synthesized by palladium-catalyzed cyanations. Obviously, further catalyst improvements will increase the usage of this methodology in organic synthesis.

Table 13. Scope of the palladium-catalyzed cyanation using TMSCN

Entry	Substrate	Product[a]	Catalyst	Conversion [%][b]	Yield [%][b]
1			**1**[c]	100	≥ 99
2			**2**[d]	100	98
3			**2**	87	82
4			**2**	71	56
5			**2**	83	76
6			**2**	67	53
7			**2**	100	63
8			**2**	100	≥ 99
9[e]			**2**	100	92
10			**2**	99	96
11			**2**	70	62
12			**2**	90	89
13			**2**	75	68
14[f]			**1**	50	39

[a] General conditions: 2 mmol aryl or heteroaryl bromide, 2.1 mL trimethylsilyl cyanide solution (1 M in toluene), dosage rate 0.1 mL/h, 2 mol % palladium-catalyst, 2 mol % 1,5-bis(diphenylphosphanyl)pentane, 20 mol % TMEDA, 2 mL toluene, reflux, 21 h. [b] Conversions and yields were determined by GC using an internal standard (diethylene glycol di-*n*-butyl ether). [c] *trans*-Bromo[4-(trifluoromethyl)phenyl]bis(triphenylphosphane)palladium(II). [d] *trans*-Bromo[3-tolyl]bis(triphenylphosphane)palladium(II). [e] 1 Mol % palladium catalyst, 2 mol % 1,5-bis(diphenylphosphanyl)-pentane. [f] Xylene (mixture of isomers) instead of toluene, 140 °C.

Table 14. Palladium-catalyzed cyanation of aryl bromides promoted by microwave irradiation

Entry	Substrate	Product[a]	*t* [min]	Power [W]	Yield [%][b]
1			2	60	81
2			2	60	78
3			2	60	90
4			2	60	90
5			2	60	95
6			2	60	88
7			2.5	60	80

[a] General conditions: 0.2 mmol aryl or heteroaryl bromide, 0.2 mmol $Zn(CN)_2$, 3 mol % $Pd(PPh_3)_4$, 1 mL DMF. [b] Isolated yields.

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