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Guest editor: Matthias Beller

All authors contributed to this issue in honour of the 2010 Nobel Prize in Chemistry winners, Professors Richard F. Heck, Ei-ichi Negishi and Akira Suzuki

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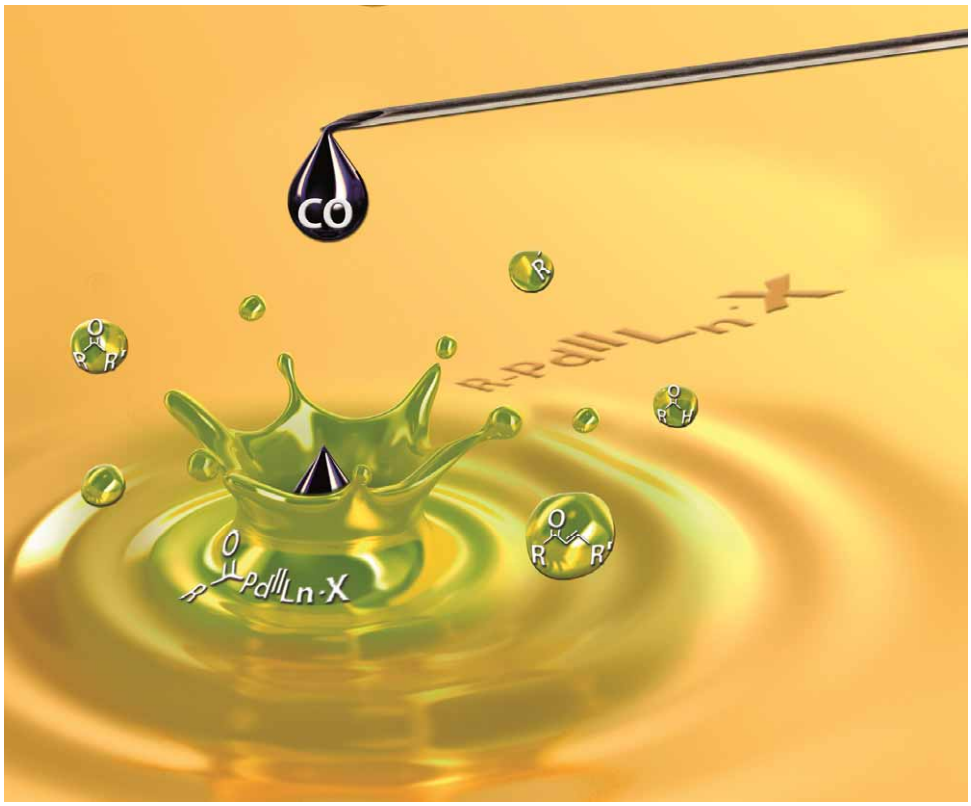

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CRITICAL REVIEW

Recent developments and perspectives in palladium-catalyzed cyanation of aryl halides: synthesis of benzonitriles†

Pazhamalai Anbarasan, Thomas Schareina and Matthias Beller*

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The palladium-catalyzed cyanation of Ar–X (X = I, Br, Cl, OTf, and H) allows for an efficient access towards benzonitriles. After its discovery in 1973 and following significant improvements in recent decades, this methodology has become nowadays the most popular for preparation of substituted aromatic nitriles. In this *critical review*, we summarize the important developments in this area from 2000 until 2010 (151 references).

Introduction

Benzonitriles represent an integral part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products. Moreover, the nitrile group serves as an intermediate for a multitude of transformations into other important functional groups. Some representative reactions are shown in Scheme 1. For example, the synthesis of fluvoxamine, an antidepressant which functions as a selective serotonin reuptake inhibitor, utilizes 4-(trifluoromethyl)benzonitrile as a key intermediate. The latter is readily available from 4-chlorobenzotrifluoride by nickel-catalyzed cyanation on the ton-scale.[1–3]

Benzonitriles themselves are also of significant interest, *e.g.*, as substructures in a number of biologically active agents. In Fig. 1, selected examples of pharmaceuticals containing an aromatic nitrile as an 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 $K^{14}CN$ isotope labeled compounds are easily accessible.[5–9] The resulting products are used in pharmacokinetic studies and investigations on the metabolism of pharmaceuticals.

Obviously, the preparation of benzonitriles can be achieved 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 a subsequent Sandmeyer reaction[20–22] on a laboratory as well as on industrial scale

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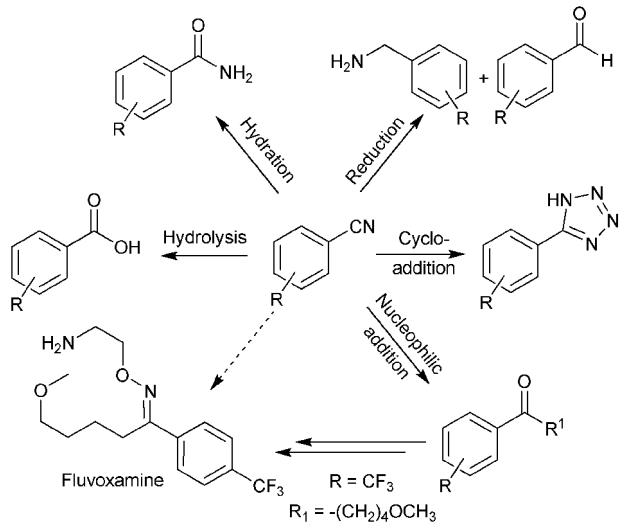
† Part of a themed issue on the topic of palladium-catalysed cross couplings in organic synthesis in honour of the 2010 Nobel Prize winners Professors Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.

Pazhamalai Anbarasan

Pazhamalai Anbarasan was born and raised in Tamil Nadu, India. After completing his masters in chemistry from Madurai Kamaraj University, he obtained his PhD on the enantio-selective synthesis of natural product from Indian Institute of Science, Bangalore with Prof. Kavirayani R. Prasad. Then, he moved to Germany as Alexander von Humboldt fellow to join the group of Prof. Matthias Beller at the Leibniz Institute for Catalysis, where he was involved in the development of methodologies for the synthesis of functionalized arenes. Currently, he is a postdoctoral fellow with Prof. Dean Toste at University of California, Berkeley, USA.

Thomas Schareina

Thomas Schareina received his degree in chemistry and his PhD (1992) at the Ruhr-University of Bochum under the supervision of Günther Snatzke und Peter Welzel. In 1994, he was granted a postdoctoral fellowship at the Institut für Organische Katalyseforschung (IfOK). Currently, he is a staff chemist in the Leibniz-Institute for Catalysis. He is active in developing new and industrially applicable methods in the field of aromatic coupling reactions.



Scheme 1 Representative synthetic applications of benzonitriles.

(Scheme 2). On the 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 (Scheme 2).[23–25]

A drawback of the Rosenmund–von Braun and the Sandmeyer reactions is the use of stoichiometric amounts of copper(I) cyanide as a 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

Matthias Beller

Matthias Beller, born 1962, studied chemistry in Göttingen, Germany, where he completed his PhD thesis in 1989 in the group of Prof. Tietze. Then, he spent one-year in the group of Prof. Sharpless at MIT, USA. From 1991 to 1995, Beller was an employee of Hoechst AG in Frankfurt. In 1996, he moved to the Technical University of Munich as Professor for Inorganic Chemistry. In 1998, he relocated to Rostock to head the Institute for Organic Catalysis (IfOK). Since 2006 Matthias Beller is a director of the Leibniz-Institute for Catalysis. His scientific work has been published in 480 publications and >90 patent applications have been filed in the last decade. Matthias Beller has received numerous awards including the Otto-Roelen Medal, the Leibniz-Price and the German Federal Cross of Merit. In 2010, he received the first "European price for Sustainable Chemistry" and the "Paul-Rylander Award" of the Organic Reaction Catalysis Society, USA. Matthias Beller is a member of the Association for Technical Sciences of the Union of German Academies of Sciences and Humanities, and the German National Academia of Science. He is married to Dr Anja Fischer-Beller and they have two sons.

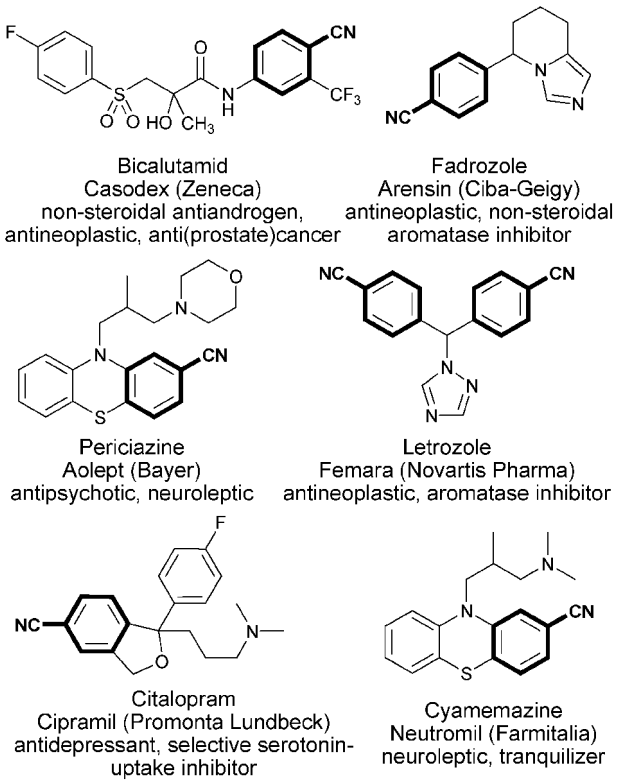
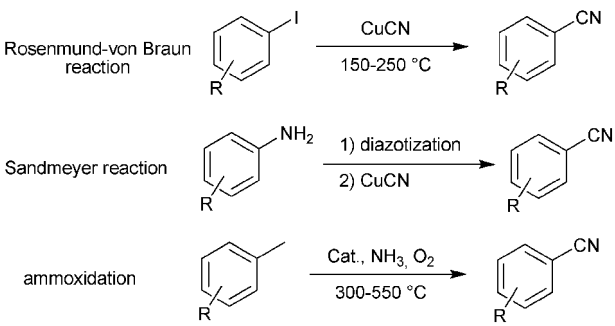


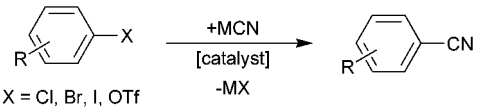
Fig. 1 Examples of pharmaceutically important benzonitriles.



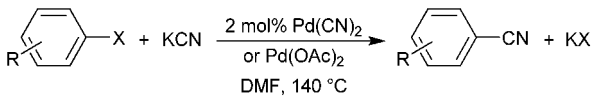
Scheme 2 Traditional methods for the synthesis of benzonitriles.

chlorides and bromides (in general the use of expensive aryl iodides is required). On the other hand, ammoxidations are restricted mostly to non-functionalized substrates because of the high temperature, high pressure, and the large excess of ammonia required. Furthermore, only a limited number of substituted toluenes is available on a larger scale. Hence, this procedure is applied only for products such as benzonitrile, terephthalodinitrile, and chlorobenzonitriles.[26,27]

A useful alternative for the preparation of substituted benzonitriles constitute the transition metal-catalyzed cyanation of aryl–X compounds (X = Cl, Br, I, OTf and H) with cheap and readily available cyanation agents like sodium or potassium cyanide (Scheme 3).[28–31] The order of reactivity of the aryl–X derivatives is opposite to the bond-dissociation energy of the C–X bonds (reactivity: I ≈ OTf > Br > Cl).[32,33] In general, electron-withdrawing substituents on the aryl ring increase the reactivity, while electron-donating substituents decrease the reactivity. Catalysts for coupling of aryl halides or triflates



Scheme 3 Transition metal-catalyzed cyanation of aryl halides.



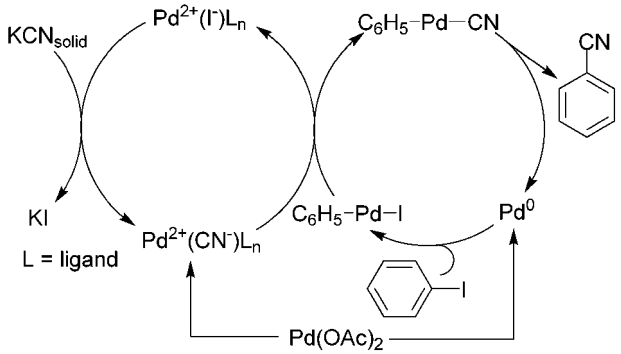
Scheme 4 First palladium-catalyzed cyanation of aryl iodides and bromides.

with cyanide are transition metal complexes of the platinum group, especially palladium or nickel complexes. Particularly, palladium catalysts tolerate a 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 a as cyanating agent (Scheme 4).[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.

Early mechanistic studies by Takagi and co-workers[35] led to the mechanistic proposal shown in Scheme 5. 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 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



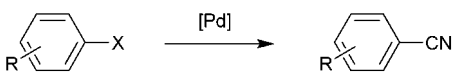
Scheme 5 Proposed mechanism of the palladium-catalyzed cyanation according to Takagi *et al.*

explained by the influence of the cyanide solubility on different reaction media. The higher the solubility of the cyanide salt, the lower the reaction outcome. Another finding of this seminal 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]

Later on, reaction conditions have been optimized and the substrate scope of the method has been considerably enhanced. 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, *n*-Bu_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 few cases the cyanation of chloroarenes was also performed. However, in all these examples highly reactive heteroaryl chlorides were used.

Table 1 demonstrates that palladium-catalyzed cyanations of aryl bromides and iodides work well with different palladium catalysts and cyanide sources. However, the

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



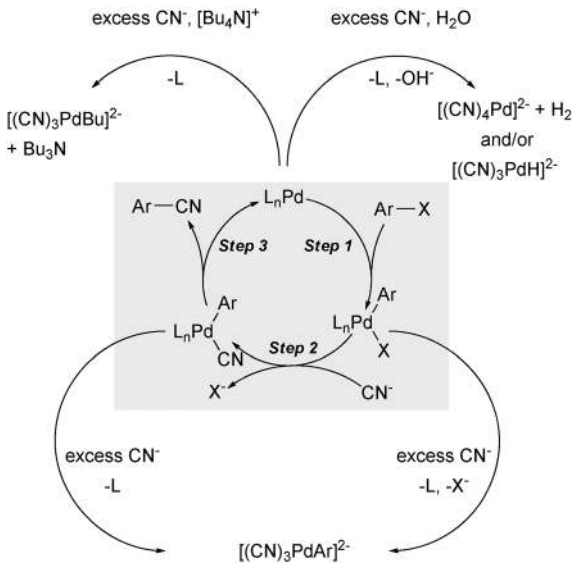
Entry	X	Catalyst (mol%)	Additive (mol%)	Cyanide (equiv.)	Solvent	*T* (°C)/*t* (h)	Ref.
1	I, Br	$Pd(OAc)_2$ (2)	—	KCN (2)	DMF	140/2–12	34
2	I[a]	$Pd(PPh_3)_4$ (20)	—	KCN (1.5)	THF	Reflux/8	38
3	I, Br	$Pd(OAc)_2$ (1.5)	KOH (0.05)/KI (9)	KCN (2)	HMPT	60–90/2–9	39
4	I, Br	$Pd(PPh_3)_4$ (10)	—	NaCN on Al_2O_3 (5)[b]	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[c]	$Pd(PPh_3)_4$ (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[d]	$Pd(PPh_3)_4$ (1.5)	18-C-6 (7.5) CuI (250)	KCN (250)	DMF	Reflux/2	44
10	I[e]	$Pd(PPh_3)_4$ (n.g.)[e]	—	*n*-Bu_3SnCN (n.g.)[f]	DMF	n.g.[f]	45
11	Cl[g]	$PdCl_2(PPh_3)_2$ (2)	—	KCN (2)	DMF	Reflux/2	46
12	I	$Pd_2(dba)_3(CHCl_3)$ (0.5)/dppf[h] (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[g]	$Pd(PPh_3)_4$ (7)	—	$Zn(CN)_2$ (0.6)	NMP	90/20	49

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

described catalyst productivity was always quite low (turnover numbers (TON) were in general in the range of 10–50). Furthermore, many catalyst systems need additives or a special cyanide source to enable good product yields. In the last decade new approaches towards catalyst and methodology development as well as insights into the mechanism of the cyanation reaction have been made by us and other groups which will be discussed below.

Mechanistic considerations

Already early on in the development of the palladium-catalyzed cyanations problems with catalyst deactivation due to the strongly binding cyanide anions were observed. In most cases, an increase in the concentration of the cyanation reagent resulted in a breakdown of the conversion. It was estimated that cyanide complexes of the type $Pd(II)(CN)_x^{(x-2)-}$ (x = 3, 4) are formed, which constitute the "dead end" of the catalysis. As a working hypothesis, the catalytic cycle was assumed to be similar to other standard coupling reactions (Scheme 6, grey box). This assumption is supported by various findings, *e.g.* that the reactivity of aryl halides follows the order ArI > ArBr > ArCl, and electron-rich aromatics react slower than electron-poor ones, which is consistent with the pattern commonly observed in other Pd-catalysed coupling reactions, too. At first, a Pd(0) species undergoes oxidative addition to the aryl halide, resulting in an arylPd(II) halide complex (Scheme 6, step 1). Subsequent anion exchange (Scheme 6, Step 2) results in the corresponding cyano complex, from which the product benzonitriles is formed by reductive elimination (Scheme 6, Step 3) to re-form the active Pd(0) species.



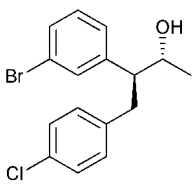
Scheme 6 Catalytic circle of cyanation (grey box), with deactivation pathways (outside of box, see text).

Some initial investigations on the action of additives were performed by our group in 2003.[50] By means of NMR experiments it was shown that bidentate amine ligands, *e.g.* tmeda, are able to prevent the deactivation of $Pd(PPh_3)_4$ even in the presence of an excess of cyanide ions. Later on, Marcantonio *et al.* confirmed that the concentration of cyanide ions in the solution is preeminent for the outcome of the catalytic reaction.[51]

Here, the influence of different additives (NaCl, NaOH, Me_2NH) that enhance the solubility of cyanide ions in DMF was investigated (Table 2). Depending on the addition method and the amount of Pd catalyst the authors showed that for each combination an upper borderline concentration exists.

Buono *et al.* investigated the effects of $ZnBr_2$ and water on the kinetic behaviour of a standard cyanation reaction.[52] The authors demonstrated that both additives influenced

Table 2 Catalytic cyanation reactions in relation to free cyanide ions



Entry	CN (ppm)	Catalyst (mol %)	Method of addition[a]	Conversion[b] (%)
1	505	2	A	100
2	505	1	A	0
3	167	0.5	A	0
4	80	0.5	A	99
5	617	1	A	0
6	617	0.5	B	100
7	617	1	B	100
8	617	0.5	B, fast	0
9	696	1	A	0
10	777	1	B	100
11	1146	1.5	A	0
12	1146	1.5	B	100
13	2000	1	B	0
14	2070	3	B	99

[a] Method A: catalyst added to $Zn(CN)_2$ slurry over 2 min. Method B: $Zn(CN)_2$ slurry added to catalyst over 30 min, except where noted. [b] As determined by HPLC.

mainly the dissolution of cyanide ions from the $Zn(CN)_2$ used. For water exists a threshold value, beyond which the reaction rate decreases.

The most detailed mechanistic investigations were performed by Grushin *et al.*[53,54] In a series of model NMR experiments, the influence of water on the deactivation of the catalyst was determined. Accordingly, water is involved both in the formation of HCN, which is likely to form $Pd(II)(CN)_x^{(x-2)-}$ (x = 3, 4) complexes, and the enhancement of the cyanide solubility in organic solvents. It was further confirmed that the σ-aryl palladium complex (Scheme 6) reacts to ArCN only if no large excess CN^- is present; otherwise, R_3P/CN–ligand exchange competes with the Ar–CN reductive elimination to give catalytically inactive $[(CN)_3PdAr]^{2-}$ complexes. This observation also explains the beneficial effect of zinc,[55] isopropanol[56] or PMHS.[57] The positive effect of these reducing agents is readily explained by catalyst reactivation *via* reduction of $[Pd(CN)_4]^{2-}$, $[(CN)_3PdH]^{2-}$, and $[(CN)_3PdAr]^{2-}$.

The requirement for a cyanide concentration which is low or in the same order of magnitude as the catalyst metal concentration can also be easily achieved by a slow dosage of the cyanide source into the reaction mixture. Since most inorganic cyanide salts are low soluble in the commonly used organic solvents, organic cyanides like acetone cyanohydrin[58] and trimethylsilylcyanide[59] (TMSCN) are better suited for this purpose.

Reactions with potassium and sodium cyanide

The initial examples of metal catalyzed cyanation of aryl halides employed alkali metal cyanides (such as potassium or sodium cyanides) as a cyanation source. Following the first report,[34] the concentration of cyanide ions in the reaction media was controlled by changing solvents and using different additives to achieve improved catalyst turnover numbers. For example, potassium hydroxide in combination with potassium iodide, alumina, 18-crown-6, zinc or copper salts, sodium borohydride, *etc.* were applied as additives (*vide supra*). Furthermore, Okano *et al.*[60] introduced phase-transfer type phosphine ligands and applied these in the palladium-catalyzed cyanation of aryl iodides and bromides. The best ligands in this context are shown in Fig. 2.

Until the late 1990's, in general the substrates used in the cyanation were aryl iodides, bromides and only few activated heteroaryl chlorides. Indeed, the reaction of unactivated chloroarenes with potassium cyanide was unsuccessful even at elevated temperature.[61] In 2001, we described the first general palladium-catalyzed cyanation of aryl chlorides employing potassium cyanide as a readily available and cheap cyanide source, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

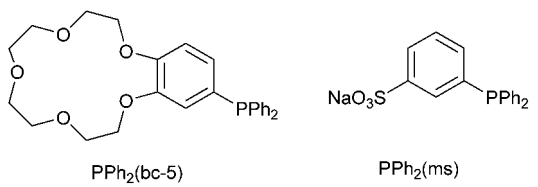
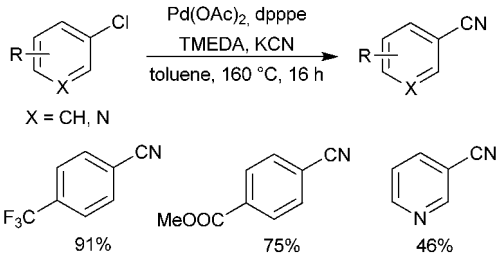


Fig. 2 Ligands with phase transfer catalyst properties.

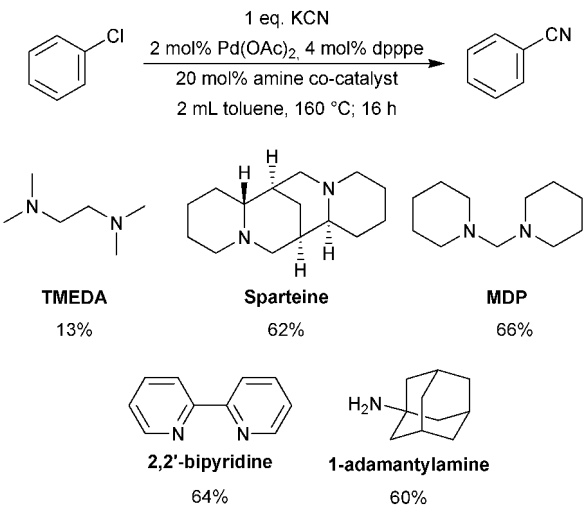


Scheme 7 Palladium-catalyzed cyanation of aryl chlorides with potassium cyanide.

(TMEDA) as an additive and dpppe as a ligand in toluene at 160 °C (Scheme 7).[62] The advantage and success of this protocol are that the use of stoichiometric amounts of zinc or copper metal can be avoided.

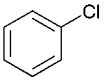
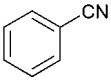
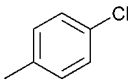
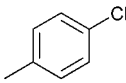
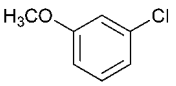
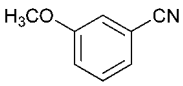
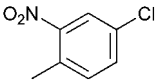
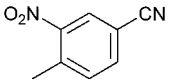
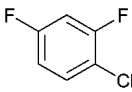
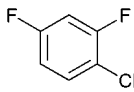
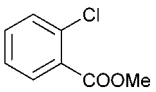
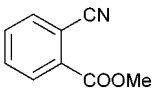
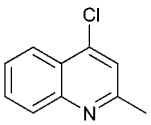
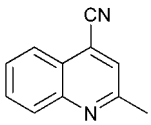
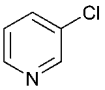
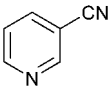
Inspired by the positive effect of TMEDA on the palladium-catalyzed cyanation of aryl chlorides, we further investigated a number of diamines and bulky primary amines as co-catalysts.[63] As shown in Scheme 8, a number of active amine co-catalysts were discovered which work better than TMEDA. The best 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 revealed that there is no obvious connection of catalytic acitivity and structural or electronic properties of the amine (*e.g.* basicity or sterics). On the other hand, it is interesting to note that the amine co-catalysts not only improved the catalytic efficiency, but also the selectivity of the reaction outcome.

Because of the promising results using MDP, the reaction of other non-activated, deactivated, or sterically hindered aryl chlorides and *N*-heteroaryl chlorides was investigated employing MDP as a co-catalyst (Table 3). In most cases we observed considerably improved results with MDP as a co-catalyst compared to TMEDA. Almost all problematic substrates are converted to the desired benzonitriles in good to excellent yields. Following this, in 2004 Yang and Williams from Merck research laboratories utilized a catalytic amount of

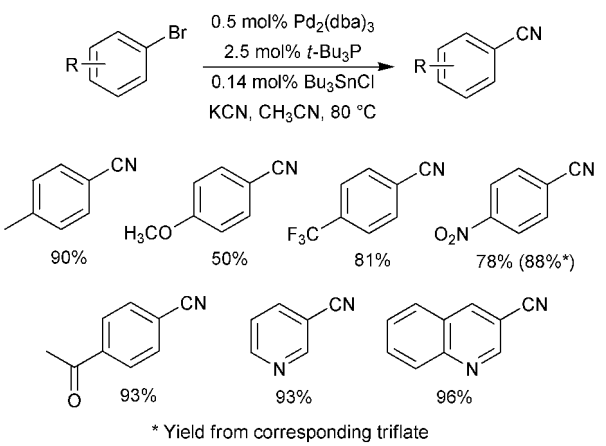


Scheme 8 Variation of the amine co-catalyst in the Pd-catalyzed cyanation of chlorobenzene.

Table 3 Palladium-catalyzed cyanation of various aryl chlorides[a]

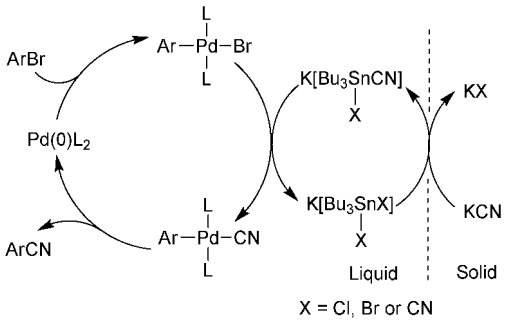
Entry	Substrate	Product	Amine	Yield[b] (%)
1			MDP	66 (84)[c]
2			TMEDA	13
3			MDP	59
4			TMEDA	12
5			MDP	53
6			TMEDA	83
7			MDP	55[d]
8			TMEDA	24
9			MDP	42
10			TMEDA	10
11			MDP	75
12			TMEDA	3
13			MDP	63
14			TMEDA	74
15			MDP	80 (55)[c]
16			TMEDA	46

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



Scheme 9 Palladium-catalyzed cyanation promoted by low level tributyltin chloride by Yang *et al.*

an organotin compound as a co-catalyst for the efficient palladium-catalyzed cyanation of aryl bromides (Scheme 9).[64] In particular, tributyltin chloride was employed at low level and the optimum molar ratio of tributyltin chloride to Pd was about 1 : 3.7, which promotes the palladium-catalyzed cyanation of various activated, unactivated and heteroaryl bromides. In addition, aryl triflates were also converted to the corresponding nitriles.



Scheme 10 Catalytic cycle for Pd-catalyzed cyanation of aryl bromide promoted by tin ate-complex.

Although earlier attempts to use organotin cyanides as a cyanation source in palladium-catalyzed cyanations of aryl halides were unsuccessful,[65] the use of a very low level promoted the reaction to proceed smoothly to yield the desired aryl nitriles. As shown in Scheme 10, tributyltin chloride plays a role similar to a phase transfer catalyst to dose the cyanide in the necessary rate in the reaction media. Based on NMR experiments, it was found that tin ate complexes[66] are formed, which are proposed to be the key to this method. The major drawback of this protocol is the necessity to tune the ratio of ligand and tributyltin chloride to Pd for each substrate independently.

John and co-workers adopted and modified our protocol for the synthesis of aromatic poly-nitrile and oligopyridine ligands, which are used for the synthesis of rare earth metal complexes.[67] Some representative examples are shown in Fig. 3.

In 2009, Li and co-workers developed an efficient one-pot palladium-catalyzed sequential cyanation/N-addition/N-arylation for the construction of the C and D ring in luotonin A (Scheme 11).[68] Thus, luotonin A and its derivatives were synthesized by the combination of two different palladium-catalyzed coupling reactions, cyanation of (hetero)aryl iodide or bromide and intramolecular N-addition of an amide to the CN bond to generate the imidamide followed by N-arylation. Most importantly, both reactions are mainly controlled by the choice of ligands, and allowed the sequential reaction to occur in a one pot manner.

In addition, a palladium-catalyzed cyanation of aryl iodide with labelled [^{14}C]KCN was employed in the synthesis of

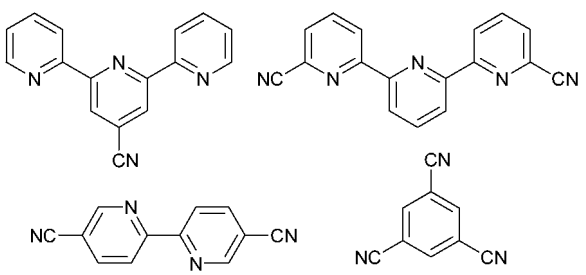
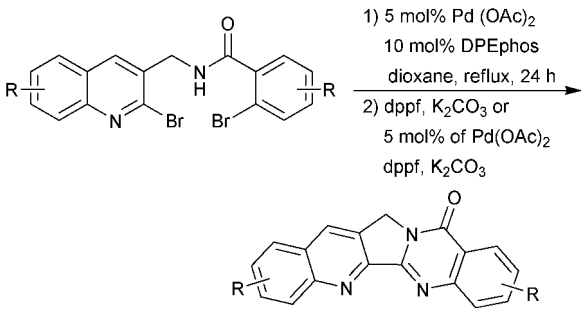
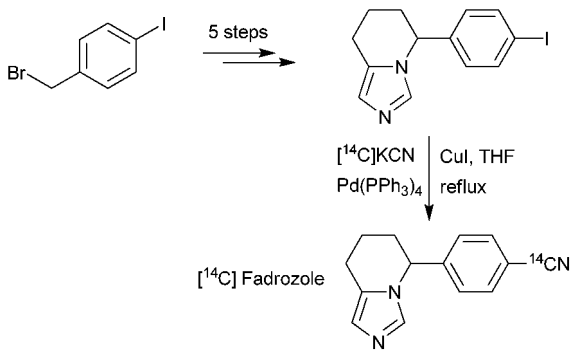


Fig. 3 Poly-nitrile ligands synthesized by John and co-workers.



Scheme 11 One-pot palladium-catalyzed sequential cyanation/N-addition/N-arylation.



Scheme 12 Synthesis of [^{14}C] labelled fadrozole.

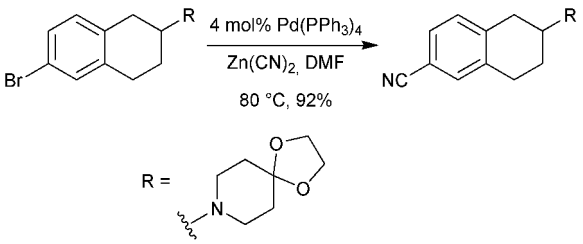
^{14}C-labeled fadrozole, a potent aromatase inhibitor, for metabolism and phamacokinetic studies (Scheme 12).[69]

The synthesis of the key intermediate was achieved in five steps starting from *p*-iodobenzyl bromide. Subsequent cyanation reaction with labelled [^{14}C]KCN in the presence of a catalytic amount of $Pd(PPh_3)_4$, and 10 mol% of copper iodide as a co-catalyst in deoxygenated THF at refluxing conditions afforded the corresponding labelled nitrile in 80% yield.

Reactions with zinc cyanide [$Zn(CN)_2$]

Zinc cyanide is the second most used cyanide source till date. Although it produces at least stoichiometric amounts of heavy metal waste, there are advantages associated with its use. For example, the toxicity of zinc cyanide is comparably lower compared to other alternative cyanide sources. It has a low solubility in most organic solvents[70] and both cyanide ions from zinc cyanide can be transformed to the product. In addition, it has been demonstrated that $Zn(CN)_2$ afforded higher yields in several cyanation reactions than KCN or NaCN as a result of the lower concentration of cyanide ions (due to the highly covalent nature of the zinc cyanide bond) in the catalytic reaction mixture. Hence, it allows for lower level catalyst loading by decreasing the catalyst poisoning.[48] Besides these, $Zn(CN)_2$ can also facilitate the transmetallation of cyanide to the arylpalladium halide species, a similar phenomenon is precedent in the field of Negishi coupling.[71]

Tschaen *et al.* have used zinc cyanide for the first time in palladium-catalyzed cyanations of aryl bromides and iodides.[48] During their synthesis of MK-0499, a potent potassium channel blocker which mediates repolarization of



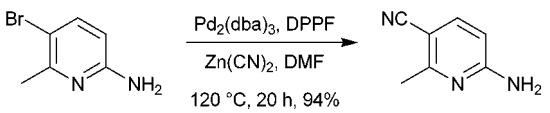
Scheme 13 First palladium-catalyzed cyanation with zinc cyanide.

cardiac tissue, they were in need of mild reaction conditions for the cyanation of the respective aryl bromide. As a result, a tetrakis(triphenyl-phosphine)palladium-catalyzed cyanation of aryl bromides and iodides with $Zn(CN)_2$ evolved (Scheme 13). Following this development, Selnick *et al.*[72] utilized similar conditions for the synthesis of 6-cyano-1,2,3,4-tetrahydroisoquinoline from the corresponding aryl triflate.

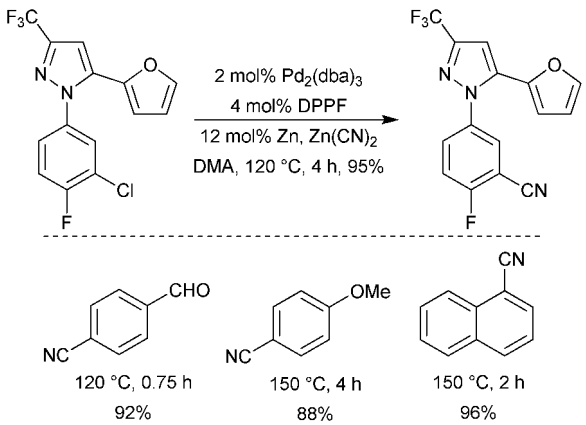
Next, the catalytic cyanation of chloropurines was achieved by Gundersen in 1996.[49] Furthermore, Rice and co-workers developed the cyanation of 2-methoxyphenyl triflate, a hindered and electron-rich triflate utilizing a similar strategy.[73]

For the first time Maligres *et al.* studied the effect of different ligands on the palladium-catalyzed cyanation of aryl bromides with zinc cyanide (Scheme 14).[74] It was discovered that dppf performed best among the different ligands tested. The resultant catalytic system worked well for simple as well as hindered electron-rich substrates.

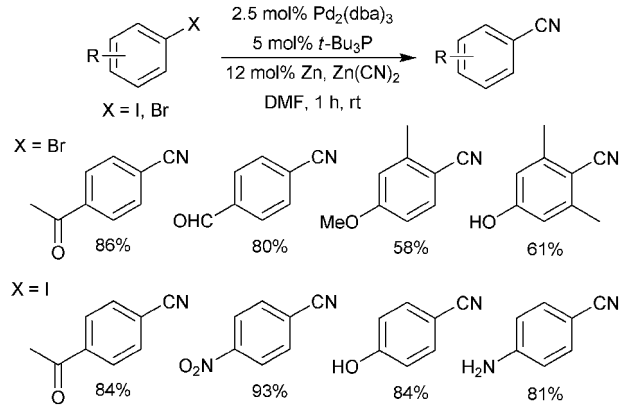
In 2000, during their studies on the cyanation of a pyrazole-substituted chloroarene Jin *et al.* developed a palladium-catalyzed cyanation of aryl chlorides with zinc cyanide (Scheme 15).[55] The catalytic system consisting of $Pd_2(dba)_3$ and dppf cyanated electron-rich and electron-deficient aryl chlorides, employing $Zn(CN)_2$ and a catalytic amount of zinc (12–24 mol%) to avoid cyanide-induced catalyst deactivation. With respect to the substrate scope, electron-deficient



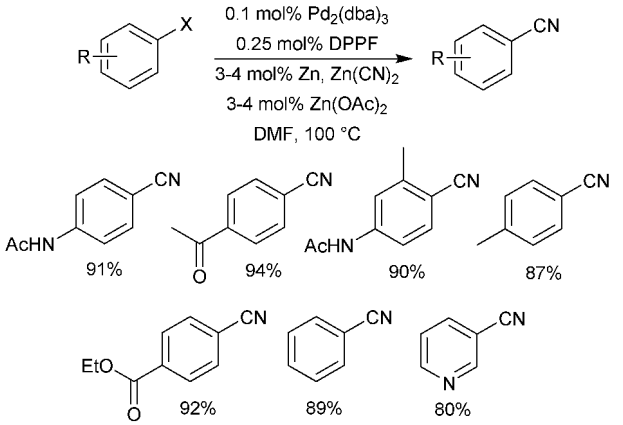
Scheme 14 Palladium-catalyzed cyanation by Maligres *et al.*



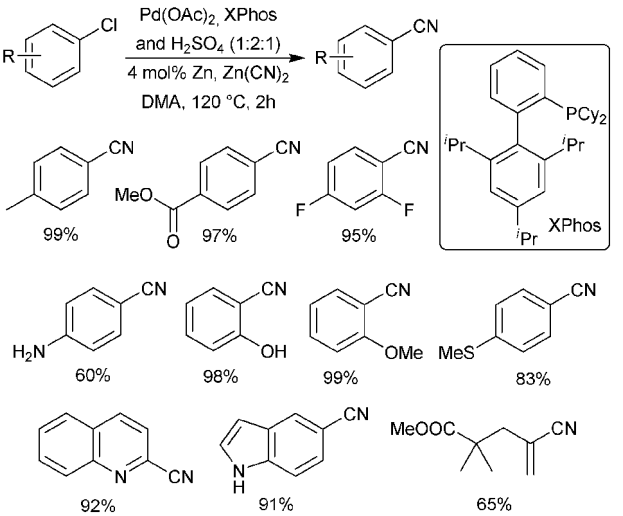
Scheme 15 Palladium-catalyzed cyanation of aryl chlorides by Jin *et al.*



Scheme 16 Room temperature palladium-catalyzed cyanation of aryl bromide/iodide by Maddaford and co-workers.



Scheme 17 Cyanation of aryl bromides in the presence of zinc acetate.



Scheme 18 Cyanation of aryl chloride in the presence of sulfuric acid. Yields estimated by HPLC.

chloroarenes underwent cyanation at 120 °C in shorter reaction times, while electron-rich and neutral aryl chlorides needed a higher loading of catalyst, elevated temperature (150 °C) and longer reaction times to achieve comparable yields. This protocol was further applied in the synthesis of a number of thiophene nitriles in moderate to good yields by Erker and Nemec in 2004.[75]

Maddaford and co-workers realized that the right choice of ligand allows for palladium-catalyzed cyanations of aryl bromides and iodides even at room temperature (Scheme 16).[76] For this purpose, they screened various ligands, such as tri-*tert*-butylphosphine, triphenylphosphine, dppf, Xanthphos, and 2′-dicyclohexylphosphinobiphenyl under reaction conditions similar to that reported by Jin *et al.*[55] and found that the bulky and basic tri-*tert*-butylphosphine was the best ligand.

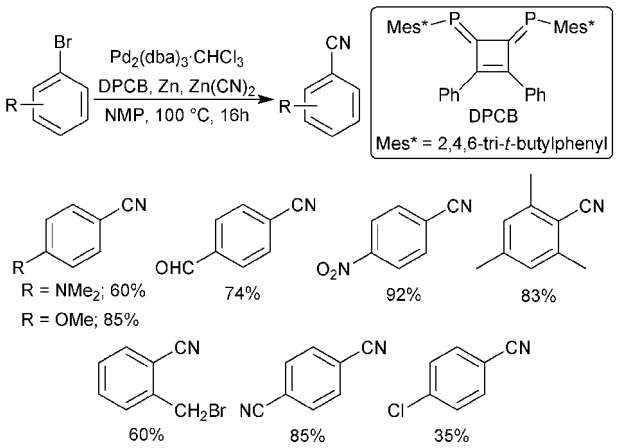
An important point to note in this protocol is the palladium to ligand ratio, which should be always 1 : 1. While electron-deficient and *ortho*-substituted electron-rich aryl bromides afforded the corresponding cyanoarenes in moderate to good yield, both electron-deficient and electron-rich aryl iodides, irrespective of *ortho*-substitution, gave the cyanoarenes in excellent yields.

Next, Chidambaram developed a robust palladium-catalyzed cyanation of aryl bromides that entail the use of zinc dust to keep the Pd in the zero oxidation state and zinc acetate to ensure higher catalytic activity,[77] following the protocol of Maligres *et al.*[74] and Jin and Confalone.[55] The use of zinc acetate was based upon the finding of a positive effect of acetic acid on the catalysis. Since acetic acid could potentially produce highly toxic hydrogen cyanide upon reaction with $Zn(CN)_2$, alternative additives were examined and zinc acetate was found to be the best. The author suggested that zinc acetate presumably keeps the catalyst 'alive' in the catalytic cycle long enough to complete the cyanation. Also this catalytic system was successfully applied in the synthesis of various aryl nitriles (Scheme 17).

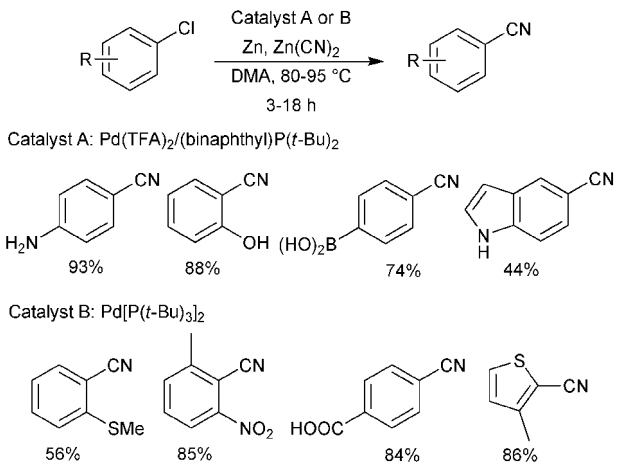
Most recently, Shevlin introduced sulfate additives (particularly sulfuric acid) for an active and robust catalytic system for the cyanation of aryl chlorides (Scheme 18),[78] similar to the report of Chidambaram. Although there was no clear explanation of the effect of the additive, sulfate activation leads to highly active catalysts with various ligands. This catalytic system also proved to be efficient in the synthesis of various aryl and alkenyl nitriles.

A unique bidentate phosphorus ligand (DPCB) was introduced by Yoshifuji and co-workers for the catalytic cyanation of aryl halides (Scheme 19).[79] They have found an interesting class of ligands bearing extremely low-lying π* orbitals mainly located around the phosphorus, which have the marked tendency to engage in metal-to-phosphorous π-back bonding. This feature is expected to stabilize low-valent metal species with high electron density and to facilitate the reduction of transition metal complexes. Hence, this ligand allowed for the palladium-catalyzed cyanation of various aryl halides with $Zn(CN)_2$ in moderate to very good yields.

Littke *et al.* have developed two different palladium catalytic systems consisting of $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$ (catalyst A) and $Pd[P(t\text{-}Bu)_3]_2$ (catalyst B), respectively, for mild cyanations of aryl and heteroaryl chlorides (Scheme 20).[80] In general, catalyst A worked well with electron-rich and neutral aryl chlorides, but for electron-deficient and sulfur-containing aryl chlorides (2-chlorothioanisole) catalyst B gave better results. Although this methodology can be carried out at relatively low temperature (80–95 °C), it suffers from the use



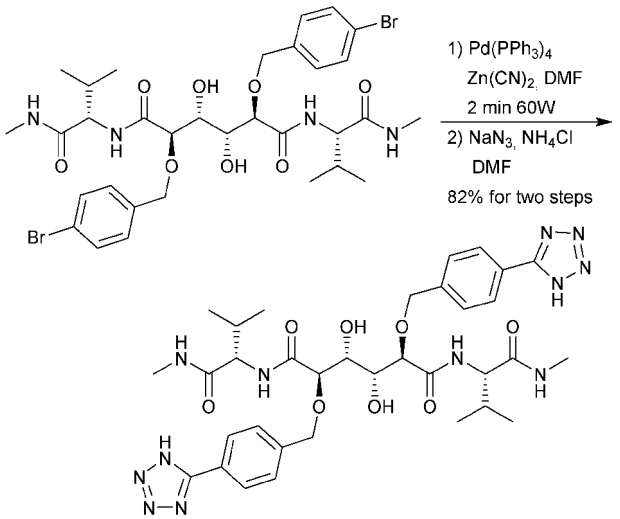
Scheme 19 Palladium-catalyzed cyanation of aryl halides with $Zn(CN)_2$ using the DPCB ligand.



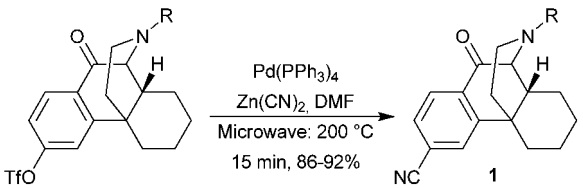
Scheme 20 Cyanation of aryl chlorides by Littke *et al.*

of around 5 mol% of palladium catalyst and 20 mol% of zinc. Employing similar conditions with higher loading of catalyst [10 mol% $Pd(OAc)_2$, 10 mol% (binaphthyl)$P(t\text{-}Bu)_2$] and higher temperature (110 °C), Wang and co-workers reported the cyanation of aryl chlorides and bromides in good yields.[81] Furthermore, in 2007 Martin *et al.* reported the open air palladium-catalyzed cyanation of aryl bromides with $Zn(CN)_2$ by changing the commonly used zinc to polymethylhydrosiloxane (PMHS) as a reductant, which generates a robust catalyst system, allowing the reaction to be performed in open air.[57]

Microwave irradiation enables the heating of a reaction mixture very rapidly, directly and uniformly. Hence, this methodology has been exploited in numerous reactions as a heating source.[82] For the first time Hallberg and Alterman developed a microwave-assisted palladium-catalyzed cyanation of aryl bromides with zinc cyanide, which took place in ~2–2.5 min.[83] Furthermore, they have combined this process with a cycloaddition reaction of sodium azide for the generation of tetrazoles, the most commonly used bioisostere of the carboxyl group. Finally, the synthesis of a HIV-1 protease inhibitor[84] was achieved in one pot, employing the microwave-assisted cyanation and cycloaddition reactions (Scheme 21).



Scheme 21 Microwave-assisted palladium-catalyzed cyanation for the synthesis of a HIV-1 protease inhibitor.

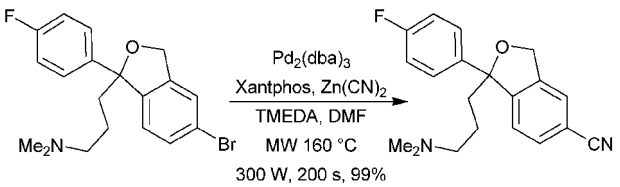


Scheme 22 Microwave-assisted cyanation reaction with aryl triflate.

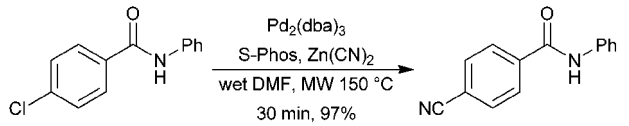
In 2003, Zhang and Neumeyer reported the first microwave-assisted Pd-catalyzed cyanation of aryl triflates, particularly for the synthesis of nitrile **1**, a key intermediate for a series of κ opioid receptor selective agonists/antagonists (Scheme 22).[85] An important limitation in this strategy is the need for *para*-keto substitution in the aryl triflate, or else it affords poor yields of the corresponding nitriles.

Pitts *et al.* have also studied the effect of ligands and additives in the microwave-assisted cyanation of aryl bromides at low catalyst loading (0.5 mol%), during their improvement of the last step in the synthesis of citalopram (Scheme 23).[86] In contrast to dppf as a ligand and Zn as an additive, used in many cases, they found optimum conditions applying xanthphos and TMEDA as a ligand and additive, respectively.

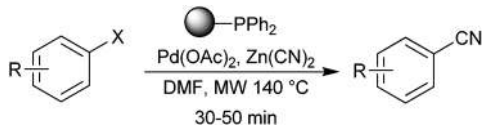
Modifying the protocol of Jin and Confalone,[55] Chobanian and co-workers accomplished the microwave-assisted Pd-catalyzed cyanation of aryl chlorides in wet DMF (Scheme 24).[87] A simple change from dppf to S-Phos as ligand gave an excellent yield of aryl nitriles. In addition, it also avoids the use of metallic zinc as an additive.



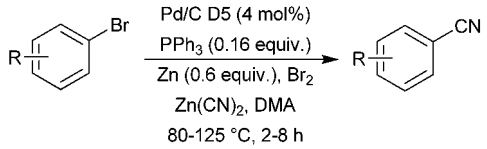
Scheme 23 Microwave-assisted synthesis of citalopram.



Scheme 24 Microwave-assisted Pd/S-Phos-catalyzed cyanation of aryl chlorides.



Scheme 25 Polymer-supported Pd-catalyzed cyanation of aryl halides(triflates) under microwave irradiation.



Scheme 26 Cyanation of aryl bromides with $Zn(CN)_2$ in the presence of heterogeneous Pd/C.

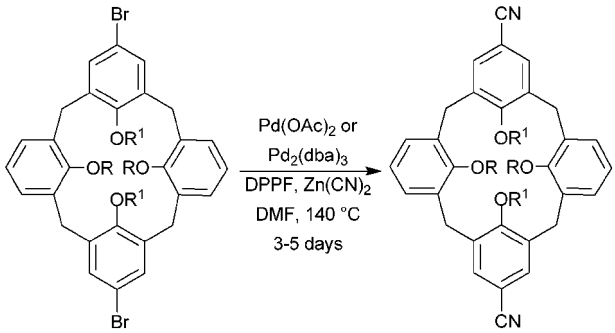
Srivastava and co-workers described the cyanation of aryl halides and triflates applying the combination of microwave irradiation and polymer-supported triphenylphosphine as ligand (Scheme 25).[88,89] This method allows the cyanation to occur at shorter reaction times and in a purification-free manner, which is often required under homogenous conditions. In their strategy, premixing of polymer-supported triphenylphosphine, $Pd(OAc)_2$ in DMF and stirring for 2 h are essential to get the desired products in high purity.

To recover the expensive metal catalyst, Seki and co-workers used Pd/C for cyanation with $Zn(CN)_2$ (Scheme 26).[90,91] For generating a reproducible catalyst both the use of Pd/C of an oxidic and thickshell type with a Pd distribution of 200–500 nm on the surface as well as prior addition of bromine to zinc dust as an additive, resulting in the *in situ* formation of zinc bromide, are important to obtain high catalyst activity.[92]

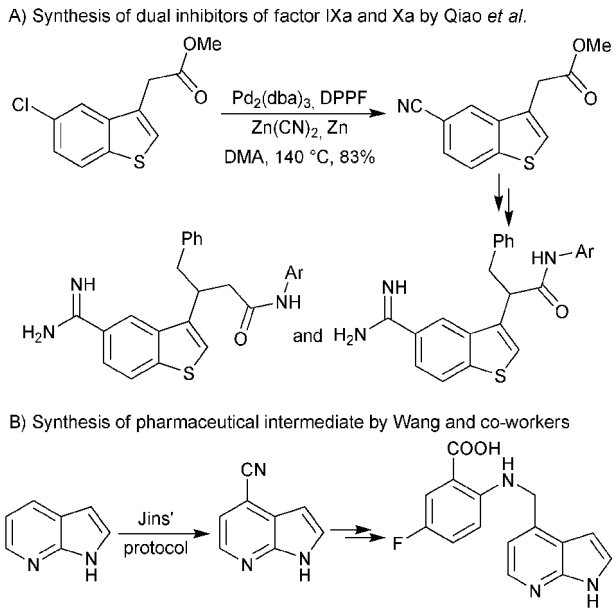
Using a statistical experimental design approach (DOE),[93] Santagostino and co-workers found room temperature conditions for the cyanation of aryl bromides with $Pd_2(dba)_3 \cdot CHCl_3$, $[(t\text{-}Bu)_3PH]BF_4$, $Zn(CN)_2$ and Zn in wet NMP,[94] similar to the report of Maddaford and co-workers.[76] On the other hand, Ryberg introduced a mild (50 °C) and robust cyanation of 5-bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indol-2-ol on a multigram scale.[95] The success of this method was depending on the mode of addition of reagents.

Parallel to methodological developments, $Zn(CN)_2$ was applied as a cyanation source for various purposes. Some examples follow below: In 2001, Hioki *et al.* modified the protocol of Maligres and co-workers[74] for the synthesis of cyano-substituted calixarenes, useful intermediates for the construction of calixarene-based host molecules (Scheme 27).[96]

As shown in Scheme 28, Jin's protocol[55] was employed as one of the key steps in the synthesis of number of 5-aminobenzo[*b*]thiophenes, dual inhibitors of factor IXa and Xa, by Qiao *et al.*[97] Interestingly, these inhibitors showed greater selectivity toward factor IXa relative to factor Xa. In addition,



Scheme 27 Palladium-catalyzed cyanation of calix[4]arenes possessing various groups at the lower rim.



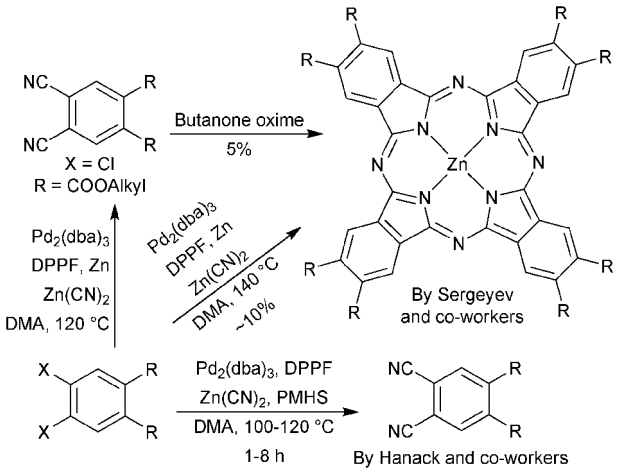
Scheme 28 Application of Jin's protocol in the synthesis of pharmaceutical intermediates.

Wang and co-workers also applied Jin's protocol for the introduction of a dimethylamino group in the synthesis of 2-((1*H*-pyrrolo[2,3-*b*]pyridine-4-yl)methylamino)-5-fluoronicotinic acid (Scheme 28).[98]

Sergeyev and co-workers employed the palladium-catalyzed cyanation of 1,2-dichlorobenzene-3,4-dicarboxylate with zinc cyanide for the synthesis of phthalocyanines (Scheme 29).[99] Phthalocyanines found a number of applications in industry as dyes and pigments, due to their bright colour combined with extraordinary thermal and photochemical stability.[100] Alternatively, zinc phthalocyanines were obtained in low yield directly from the dichloro-precursor at 140 °C.

In the same year, Drechsler and Hanack reported the combination of their own protocol[101] and that of Martin for the synthesis of phthalonitriles (Scheme 29).[102] In 2006, Lautens and co-workers applied the cyanation strategy as a termination step in their novel tandem reaction, consisting of C–H activation, intra- and intermolecular alkylation and cyanation (Scheme 30).[103]

Moreover, zinc cyanide [as $Zn(^{14}CN)_2$] was used in the synthesis of ^{14}C-labelled benzonitriles and their corresponding acids.[104,105]



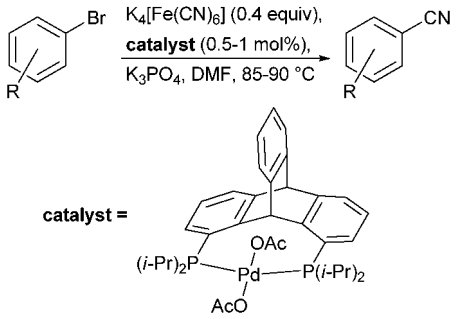
Scheme 29 Synthesis of phthalonitriles and zinc phthalocyanines.

Scheme 30 Synthesis of polycyclic benzonitriles by Lautens.

Reactions with potassium ferrocyanide $K_4[Fe(CN)_6]$

Potassium ferrocyanide has been introduced as a cyanation reagent for Pd-catalyzed coupling reactions by our group in 2004.[106,107] $K_4[Fe(CN)_6]$ has significant benefits both in the handling and in the chemical application. The main advantage in handling is its non- or low toxicity.[108] Potassium ferrocyanide is used in the food industry as a table salt additive[109] and for the removal of metal salts from wine.[110] Compared to the toxic cyanides otherwise used for the cyanation reaction it is much easier to handle both on a laboratory as well as industrial scale. Additionally, it is not very hygroscopic, and its price is in the same region as that of NaCN and acetone cyanohydrin. In the first synthetic application, already significantly higher catalyst turnover numbers compared to previously known procedures were achieved. Some authors have suspected the high stability/low dissociation of the ferrocyanide ion, covalent bonding of Fe and cyanide ions, the low solubility of the fourfold charged anion in organic solvents or a reducing activity of the ferrocyanide Fe(II) to be responsible for the success of the reagent. None of these assumptions has been supported by mechanistic investigations as far as the literature is known.

In addition to our group,[111] Weissman *et al.*[112] were able to show that this coupling reaction worked even without expensive phosphine ligands for a list of standard aryl bromide substrates. A recent improvement showed that the reproducibility and the easiness of handling of the procedure can be further enhanced by the addition of isopropanol to the reaction mixture. In that case there is no need for an inert atmosphere and dry solvents.[113]



Scheme 31 Cyanations according to Gelmann *et al.*

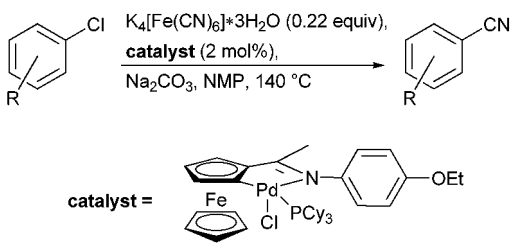
A number of useful extensions of the initial protocol were made since then; *e.g.* development of novel catalyst systems, conversion of challenging substrates like aryl chlorides, tosylates and mesylates, introduction of heterogenized catalysts and alternative solvent systems.

For example, Grossman and Gelman showed the use of a new type of Pd complex with wide bite angle ligands for the cyanation of aryl bromides (Scheme 31).[114] An advantage of this system is its insensitivity against air. Most model compounds were converted to the corresponding aryl nitriles in yields greater than 80% at comparably mild reaction temperatures (85–90 °C), 4-bromoanisole gave a yield of 69% (GC). However, a reactive aryl chloride (methyl 4-chlorobenzoate) yielded only 21% (GC) of product.

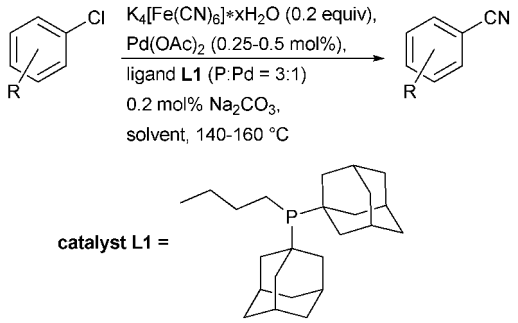
A first procedure for the transformation of aryl chlorides used a cyclopalladated ferrocenylimine as a catalytic system (Scheme 32).[115] Most standard model compounds were converted with 2 mol% of the catalyst at 140 °C in yields between 66% (2-chloroanisole) and 97% (1-chloronaphthalene).

Schareina *et al.* used the commercially available sterically hindered and electron-rich ligand *CatAXcium A* (**L1**) in combination with only 0.25–0.5 mmol $Pd(OAc)_2$ as a catalyst system for the cyanation of standard aryl halides (Scheme 33).[116] Notably, electron-rich, electron-poor, heterocyclic and sterically hindered substrates were transformed in up to quantitative yields. For optimum results, slight modifications of the reaction conditions were necessary depending on the respective substrate.

More recently, our group extended the scope of the aryl chloride cyanation to substrates containing challenging amino- and hydroxy-substituents (Fig. 4).[117] For this purpose a list of partially new ligands was tested under various conditions. An all-purpose "best" ligand could not be identified, and almost each substrate needed another ligand and slightly varying conditions.



Scheme 32 Cyanation of aryl chlorides with cyclopalladated ferrocenylimine.



Scheme 33 Cyanation of aryl chlorides by Schareina *et al.*

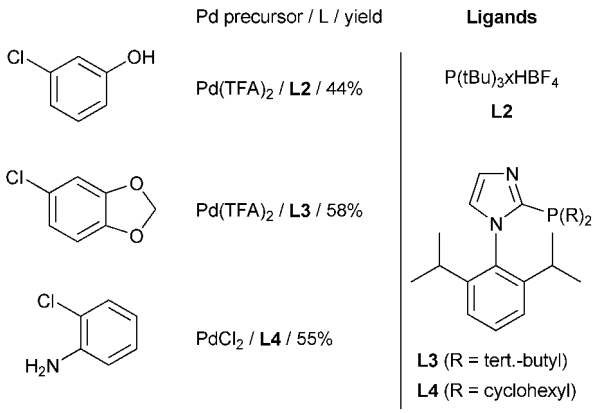
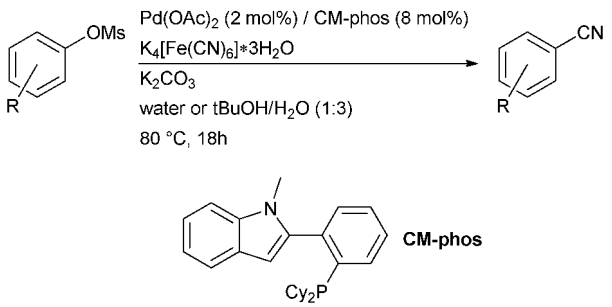


Fig. 4 Ligands for the cyanation of "difficult" aryl chlorides.

Reactions of aromatic *O*-sulfonates extend coupling methodologies towards the conversion of phenolic OH groups into the corresponding benzonitriles. While trifluoromethylsulfonates (triflates) have been used as substrates in a number of cyanation reactions before, the first report using $K_4[Fe(CN)_6]$ as a cyanide source was published by Zhu and Cai.[118] The conditions are similar to the ones in ref. 106, although a high catalyst load (5 mol% $Pd(OAc)_2$) is needed for good yields. Perfluorooctylsulfonates are somewhat more active. Hence, in most cases 1–2 mol% of $Pd(OAc)_2$ in the presence of PPh_3 were sufficient.[119]

Very recently, the group of Kwong applied the CM-phos ligand (8 mol%) together with 2 mol% of $Pd(OAc)_2$ and potassium ferrocyanide for the cyanation of easily accessible aryl mesylates (Scheme 34).[120] Interestingly, coupling proceeded in aqueous solvent at low reaction temperature (80 °C). This methodology represents an interesting breakthrough



Scheme 34 Cyanation of aryl mesylates using the CM-phos ligand.

concerning the substrate scope of this ArX coupling reaction. The same catalyst system has been applied by the same group for the hitherto mildest cyanation of aryl chlorides.[121]

The direct activation of aromatic C–H bonds has gained increasing interest in organometallic chemistry in recent years. In this respect, the direct non-chelated cyanation of indoles[122] has been performed with $K_4[Fe(CN)_6]$. Notably, also chelation-directed cascade bromination/cyanations of 2-arylpyridines with $K_3[Fe(CN)_6]$[123] and chelation-assisted direct cyanations of 2-arylpyridines with CuCN[124] have been described.

Aryl iodides and non-activated aryl bromides were converted in good yields using 0.5 mol% of palladacycle **L5** (Fig. 5) using microwave heating, while most aryl chlorides were less reactive.[125]

However, using another type of palladacycle catalyst **L6** (Fig. 6) results for aryl chlorides could be improved, *e.g.* chlorobenzene yielded 85% of benzonitrile.[126]

Ligands XPhos and Xphos–SO_3Na (Fig. 7) were used in an aqueous system (water/dioxane 1 : 1) at temperatures of 140 °C for the cyanation of aryl chlorides, aryl tosylates and aryl benzenesulfonates.[127] Despite its low solubility in the aqueous phase, XPhos gave better yields in the case of naphthyl tosylates.

The good results are explained by the solubility of $K_4[Fe(CN)_6]$ in water and its activation by the base K_2CO_3. This method significantly enhanced the substrate scope for the cyanation. A minor drawback is the need of 1.5 mol% of $Pd(OAc)_2$ and 3 mol% of ligand. Heterocyclic substrates were not tested.

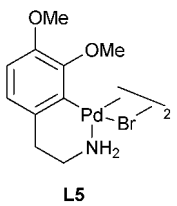


Fig. 5 Palladacycle **L5**.

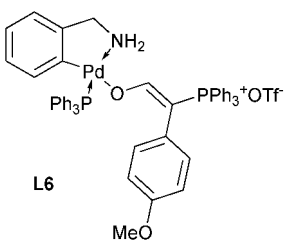


Fig. 6 Palladacycle **L6**.

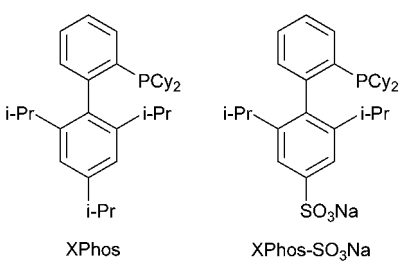


Fig. 7 XPhos and sulfonated XPhos.

Table 4 Heterogeneous and heterogenized palladium catalysts for the cyanation of aryl halides

Entry	X[a]	Catalyst (mol% Pd)	Additive (equiv.)	$K_4[Fe(CN)_6]$ [equiv.]	Solvent	T (°C)	Ref.
1	I, activated Br	Pd/C (1–3)	Bu_3N (0.5)	0.20	NMP	140	131
2	I, Br	Pd/C (1)	Bu_3N (0.5)	0.20	H_2O, PEG	130–160 (mw)	132
3	I	Polymer-bound Pd (0.5–1)	Et_3N (1.33)	0.67	DMF	110	133
4	Br	Polymer-bound Pd (1)	—	0.22	DMF	120–140	134
5	I	Pd/CuO (1)	—	0.17	DMF	120	135
6	I	Pd on pyridine-modified silica (10)	Et_3N (2)	0.7	DMF	155	136

[a] Type of aryl halide.

A practical system (easy workup, solvent and catalyst recovery) was developed based on the ionic liquid [BMIm]BF_4.[128] With 2.5 mol% $PdCl_2$ and *N*,*N*-dimethylethylendiamine as an additive, activated and simple aryl bromides were cyanated; however, deactivated substrates gave no conversion. Under essentially the same conditions β-bromostyrenes gave the corresponding cinnamic acid nitriles. Yields were in between 76% ((*E*)-1-(2-bromovinyl)-naphthalene) and 31% ((*E*)-1-(2-bromovinyl)-2-chlorobenzene). The stereoselectivity was not in all cases preserved. ArI and activated ArBr, but no ArCl, yielded benzonitriles in another generic combination of microwave heating and aqueous solvent.[129]

A considerable amount of research work has been devoted to the development of heterogenized and recyclable Pd catalyst systems. However, in most cases the recyclability was proven only with reactive aryl iodides. These results are summarized in Table 4. Zhu and Cai[131] demonstrated the use of Pd on charcoal as a recyclable catalyst for the cyanation reaction with $K_4[Fe(CN)_6]$ as a cyanide source (Table 4, entry 1). Aryl iodides and activated bromides gave high yields, while non-activated and deactivated aryl bromides were less efficiently converted. Tri-*n*-butylamine was necessary to stabilize the palladium in the homogeneous phase. In recycling experiments, the activity of the catalyst system started to decrease after the third cycle.

ArI and ArBr were cyanated in good yields with microwave heating in aqueous PEG applying 1 mol% of a heterogeneous Pd catalyst (5 wt% Pd/C) in the presence of 50 mol% of Bu_3N as a stabilizer.[132] In 2010, Islam and co-workers published a row of papers where polymer-bound Pd catalysts with similar structural motifs (see Fig. 9) were used for various coupling reactions, including the cyanation of aryl halides using $K_4[Fe(CN)_6]$.[133] Generally, 1 mol% of Pd was used in the catalytic tests, only aryl iodides were sufficiently reactive to yield the corresponding benzonitrile products.

A polyimidazole-based ligand (Fig. 8), copolymerized with a caprolactame monomer, was also used as a support for $PdCl_2$ in cyanation reactions.[134] All types of aryl bromides were converted in good yield using 1 mol% of palladium. However, again the system did not work for aryl chlorides. In recycling experiments deterioration began only after the 10th cycle.

Besides Suzuki coupling reactions, cyanation with $K_4[Fe(CN)_6]$ was used as a test application for copper-oxide supported Pd catalysts.[135] Here, only aryl iodides were converted under the conditions used and a recycling of the catalyst was not possible. A similar reactivity was shown for palladium salts fixed on pyridine-modified silica (Fig. 10).[136] Once more, only aryl iodides were cyanated. However, the catalyst could be re-used.

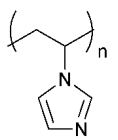


Fig. 8 Polymerized ligand for Pd-catalyzed cyanation.

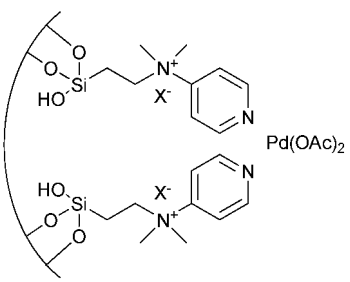


Fig. 10 Pyridine-type silica-grafted Pd complex by Polshettiwar.

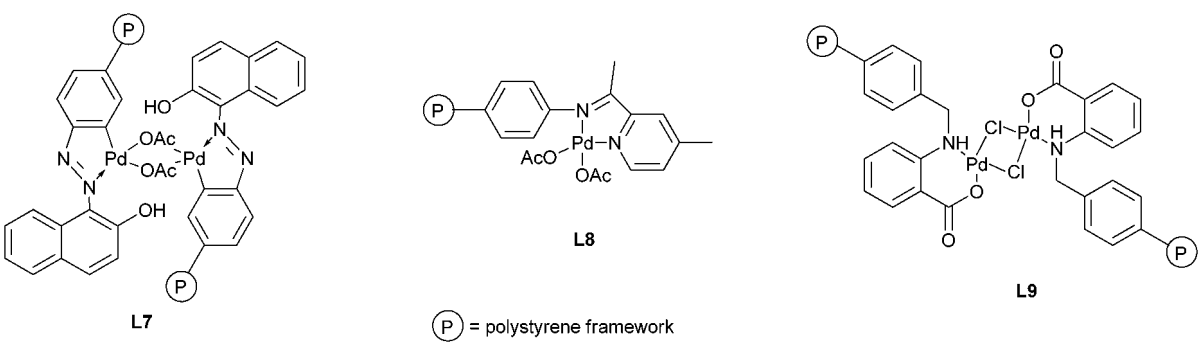
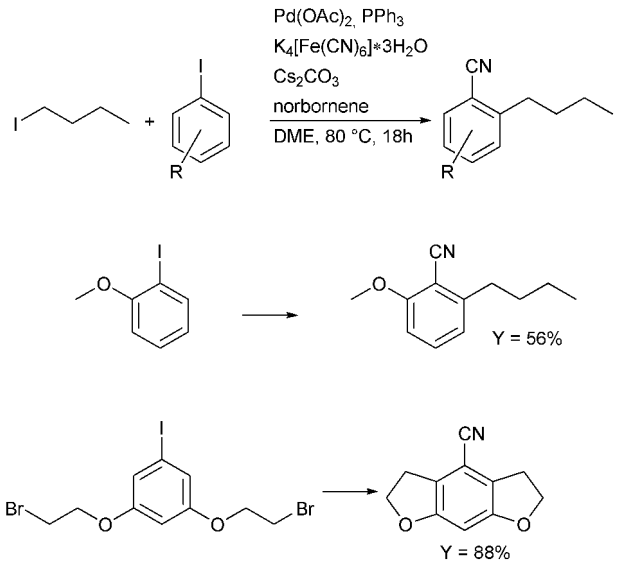
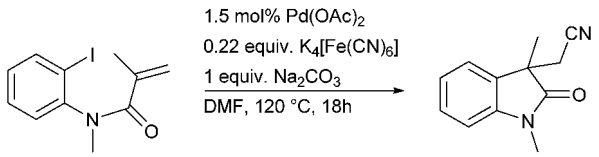


Fig. 9 Heterogenized ligands developed by the Islam group.



Scheme 35 Pd-catalyzed Catellani reaction with cyanide trapping by Mariampillai *et al.*



Scheme 36 Domino-Heck-cyanation sequence.

The combination of different coupling reactions in a one pot manner allows for the efficient construction of polycyclic arenes. In this respect, several domino reactions make use of $K_4[Fe(CN)_6]$ as a final scavenging reagent. For example, Mariampillai *et al.* performed a palladium-catalyzed Catellani reaction and applied cyanation as the final step (Scheme 35).[130] $K_4[Fe(CN)_6]$ was advantageous compared to other cyanide donors because of its slow reaction, leading to a lower amount of side products.

Another example is shown in Scheme 36.[137] Although this reaction represents no aromatic cyanation, it shows the application of $K_4[Fe(CN)_6]$ as a cyanide source. A similar kind of cascade reaction resulting in vinylogous aromatic cyanation was shown by other groups, too (Scheme 37).[138] More examples for different domino reaction sequences with the common element of cyanide transfer from potassium ferrocyanide are just briefly mentioned here.[139,140]

In a single-substrate application, Franz *et al.* demonstrated that potassium ferrocyanide not only works as a cyanation agent but also as a reductant.[141] In this example the electron-rich dibromo diphenothiazine is partially oligomerized, resulting in novel materials with special optical and electronical properties (Scheme 38).

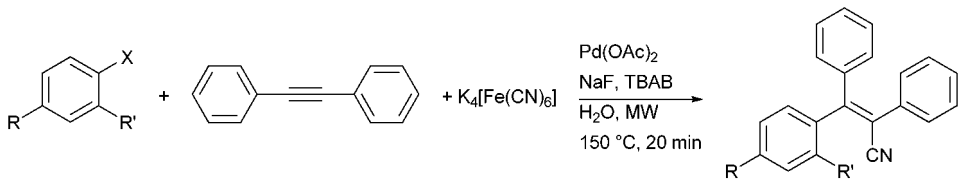
Reactions with cyanohydrines

Early 2000, the major concern in palladium-catalyzed cyanations was the cyanide poisoning of catalyst due to the presence of an excess of cyanide (*vide supra*), which led to lower catalyst turnover numbers (TON) compared to other metal catalyzed coupling reactions. At that time the use of cyanohydrines,[142] as an equivalent of HCN, was unknown in this field.[143] In 2003, for the first time we came up with the different strategy to control cyanide ion concentration in the reaction mixture by slow addition of a liquid cyanation source, such as acetone cyanohydrin, with the aid of a syringe pump technique.[58] As shown in Table 5, high TON up to 1900 were achieved, the highest TON reported until that date.

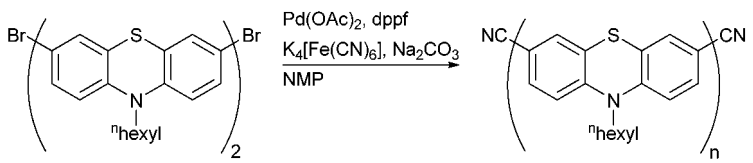
In addition to the model reaction shown in Table 5, a variety of functionalized aryl halides have been cyanated with acetone cyanohydrin. Most recently, also cyclohexanone cyanohydrin was employed as a cyanation source by Taran and co-workers in the palladium-catalyzed decarboxylative cyanation of *ortho*-substituted arene carboxylic acids. In this reaction other typical cyanation reagents (KCN, CuCN, $K_4[Fe(CN)_6]$, *etc.*) showed unsatisfactory results (Scheme 39).[144]

Reactions with trimethylsilyl cyanide (TMSCN)

Trimethylsilyl cyanide (TMSCN) has been used as an alternative to the traditional metal cyanides for a number of synthetic applications.[145] The first application of this reagent

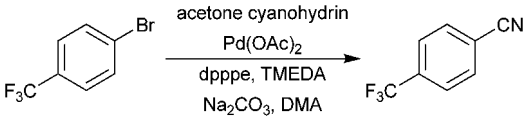


Scheme 37 Pd-catalyzed Sonogashira-cyanation sequence.



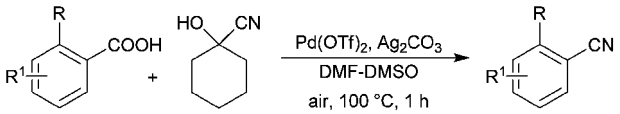
Scheme 38 Partial oligomerization of phenothiazines.

Table 5 Palladium-catalyzed cyanation using acetone cyanohydrin

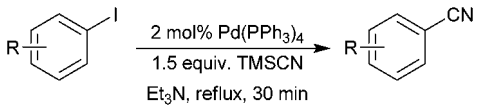


Entry	$Pd(OAc)_2$ (mol%)	Pd/P	TMEDA (mol%)	Dosage rate/mmol h^{-1}	Time/h	Temp. (°C)	Yield[a] (%)	TON
1	2	1 : 4	20	0.1	21	80	≥ 99	49.5
2	1	1 : 4	20	0.1	21	100	≥ 99	99
3	0.5	1 : 4	10	0.1	21	100	≥ 99	198
4	0.1	1 : 4	10	0.1	21	120	0	0
5	0.1	1 : 8	10	0.05	42	120	80	800
6	0.05	1 : 16	10	0.05	42	140	95	1900

[a] Yields are determined by GC using diethyleneglycol di-*n*-butyl ether as an internal standard.



Scheme 39 Synthesis of aryl nitriles *via* decarboxylative cyanation of arene carboxylic acids.



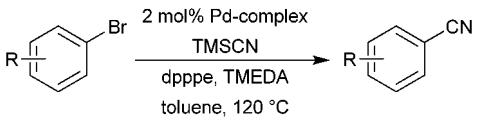
Scheme 40 Pd-catalyzed cyanation of aryl iodides with TMSCN by Chatani *et al.*

Scheme 41 Stoichiometric reaction of Pd(II) bromo complex with TMSCN.

in palladium-catalyzed cyanations took place in 1986 by Chatani and Hanafusa.[43] As shown in Scheme 40, they described the cyanation of various aryl iodides in the presence of $Pd(PPh_3)_4$ in good to excellent yields. The choice of the solvent was very important and the use of Et_3N gave the best results compared to other typical polar and non-polar solvents. Unfortunately, this catalytic system failed to convert aryl bromides and chlorides.

In 2003, we came up with an efficient catalytic system for the cyanation of aryl bromides with TMSCN.[59] During our investigation on the insights into the mechanism of the cyanation of aryl halides, we attempted to prepare an aryl-palladium(II) cyano complex from *trans*-bromo[4-(trifluoromethyl)phenyl]bis-(triphenylphosphine)palladium(II) and TMSCN (Scheme 41). Gratifyingly, during the treatment of the palladium complex with TMSCN formation of the corresponding benzonitrile was observed in 95% yield with excellent selectivity, even below 0 °C.

Based on this observation and our earlier success with a slow dosage of acetone cyanohydrin, we developed an efficient protocol applying dpppe as a ligand and TMEDA as an additive for aryl bromides (Scheme 42).



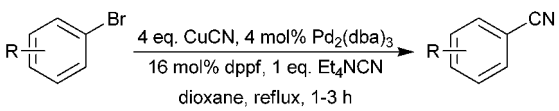
Scheme 42 Palladium-catalyzed cyanation of aryl bromides with TMSCN.

Miscellaneous cyanations

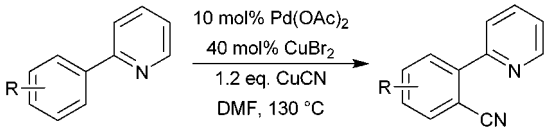
Apart from the classified cyanation sources (mentioned above), there are also other cyanation sources employed in palladium-catalyzed cyanations. One of the cyanation sources, copper(I) cyanide, the typical cyanating agent in the Rosenmund–von Braun and the Sandmeyer reaction, was first described in palladium-catalyzed reactions of aryl halides by Sakamoto and Ohsawa in 1999 (Scheme 43).[146]

This protocol was useful for the transformation of electron-rich and -poor aryl bromides. Also *N*-heteroaryl iodides and bromides gave the corresponding nitriles in good yield. A comparison of the palladium-catalyzed variant and the non-catalytic reaction showed that the palladium-catalyzed variant leads to higher yields. However, the use of copper(I) cyanide is not advantageous compared to other cyanating agents. Still, comparatively high catalyst-concentration (8 mol% Pd), overstoichiometric amount of copper(I) cyanide (4 eq.) and a stoichiometric amount of an additive (Et_4NCN) are required for successful reactions. Thus, this protocol was not further explored.

Most recently, Jia and co-workers utilized copper cyanide as a cyanation source in the palladium-catalyzed direct cyanation of 2-arylpyridines *via* C–H functionalization reactions (Scheme 44).[124] Thus, chelation-assisted cyanation of various 2-aryl nitrogen heterocycles (pyridine, pyrazole, *etc.*) occurred in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol%), copper(I) cyanide as a cyanide source, and copper(II) bromide as an oxidation transfer reagent with oxygen being the terminal oxidant in DMF at 130 °C.



Scheme 43 Palladium-catalyzed Rosenmund–von Braun reaction.



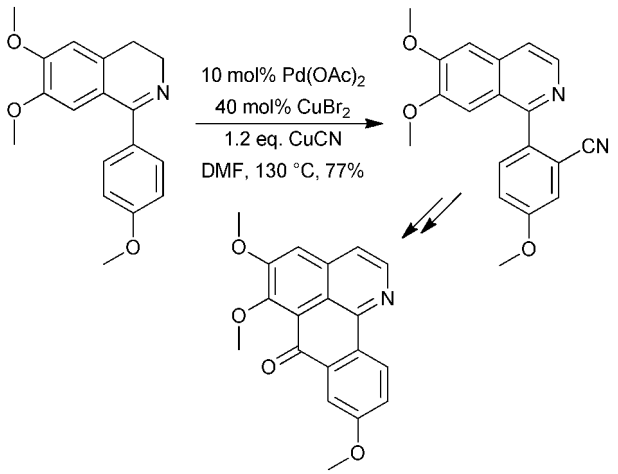
Scheme 44 Palladium-catalyzed cyanation of 2-arylpyridines.

The authors demonstrated the efficiency of their protocol by the synthesis of a key intermediate for the synthesis of 5,6,9-trimethoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one, a base from *Menispermum dauricum* DC (Scheme 45).[147]

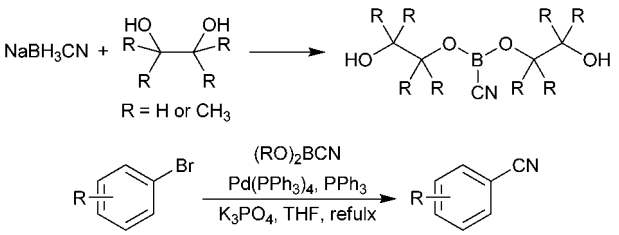
In 2001, Jiang *et al.* used dialkyl cyanoboronates for cyanation of aryl bromides, iodides and strongly activated chlorides (Scheme 46).[148] The required cyanation reagents are easily prepared by the reaction of sodium cyanoborohydride and 1,2-diols (Scheme 46).

Suda and co-workers introduced cyanoethylzinc bromide for the catalytic cyanation of phorphyrins to yield various cyanated Zn(II)–porphyrins (Scheme 47).[149] Here, generation of free cyanide ions are expected to occur *via* Boord-type fragmentation. Hence, ethylene is produced as a side-product. Most recently, Trapp and co-workers observed a similar kind of cyanation of aryl iodides with a nitrile group contained in the stationary phase (cyano-ethylmethyl-phenylmethyl-siloxane). More specifically, they applied a micro-capillary column reactor and used palladium nanoparticles as catalysts.[150] Although the yields were low (around 35%), the reaction can be tuned by the flow rate.

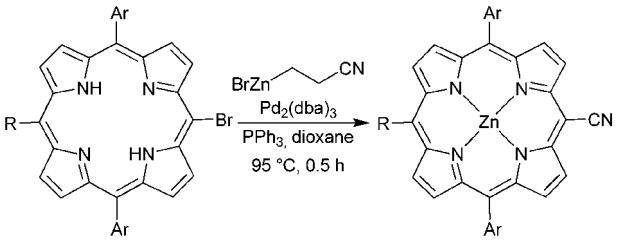
Accidentally, a novel direct cyanation was discovered when ammonia was tested in DMF for the amination of aryl C–H



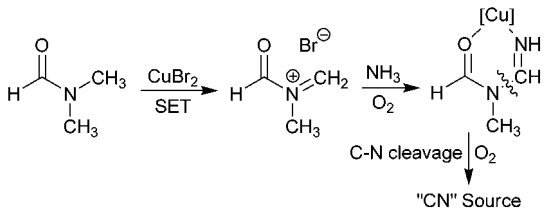
Scheme 45 Synthesis of 5,6,9-trimethoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one.



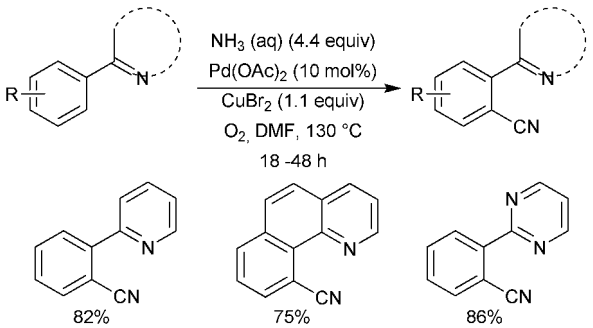
Scheme 46 Synthesis and application of dialkyl cyanoboronates by Jiang *et al.*



Scheme 47 Palladium-catalyzed cyanation of porphyrins with cyanoethylzinc bromide.



Scheme 48 Mechanistic proposal for CN formation by Chang and co-workers.



Scheme 49 Palladium-catalyzed cyanation with NH_3(aq) and DMF.

bonds by Chang and co-workers.[151] Surprisingly, they observed the formation of cyanoarene rather than aniline derivates. It was found that the following reagents and conditions are essential: palladium, copper(II) bromide, DMF and oxygen. Various labelling experiments showed that the carbon and nitrogen of the "CN" unit comes from DMF and ammonia, respectively. Hence, they have proposed the mechanism as copper mediated single electron transfer to give an imine species, followed by attack of ammonia to provide an amidine intermediate. C–N bond cleavage in this intermediate under aerobic conditions was expected to give the "CN" unit (Scheme 48).

Although the mechanism is not fully clear yet, the cyanation protocol is valuable. As shown in Scheme 49, the chelation-assisted cyanation of a number of other substrates yielded the corresponding products in good yield and high selectivity. Moreover, this methodology allowed for the formation of a doubly labeled nitrile for the first time.

Conclusions

The ongoing success of palladium-catalyzed cross-coupling methodologies in the last decade is also documented by the increased use of related cyanation reactions. There is no doubt

that palladium-catalyzed cyanations have become best practices for the synthesis of functionalized benzonitriles on a laboratory scale. Nevertheless, like every type of chemical transformation, this cross-coupling methodology has disadvantages, too, which offer opportunities for future improvements. Although an extensive know-how in catalyst optimization strategies has emerged during the last two decades, still the cost for the precious metal palladium and sometimes ligands is relatively high because most cyanations have to be performed with comparably high catalyst loadings. In this respect, especially reactions with potassium ferrocyanide offer the possibility to perform cost efficient cyanations.

In addition, the reaction produces at least one equivalent of inorganic salts as waste. Even though there are useful ways of recycling, especially for bromide salts, this is a significant drawback for ton-scale applications. Despite these drawbacks, it is most likely that the recent advancements in this area will also result in first commercial applications.

Furthermore, we anticipate more applications of catalytic cyanations in organic synthesis. In particular in the area of domino and tandem reactions novel interesting reaction sequences wait to be discovered.

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