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Microwave-enhanced cyanation of aryl halides with a dimeric *ortho*-palladated complex catalyst

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Abstract A new dimeric *ortho*-palladated complex of 2-methoxyphenethylamine was synthesized and characterized and its application as a cyanation catalyst was investigated. The main advantages of this catalyst are its easy preparation, handling, stability, and moisture insensitivity. Thus, $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-}4\text{-}OMe\text{-}5\text{-}\kappa^2\text{-}C,N\}(\mu\text{-}Br)]_2$ showed excellent catalytic activity for the cyanation of aryl iodides and bromides with $K_4[Fe(CN)_6]$, in DMF in the presence of K_2CO_3 under microwave irradiation and conventional heating at 130 °C to give the desired cyanoarene products in good to high yields. The less reactive aryl chlorides also react with $K_4[Fe(CN)_6]$ to give moderate yields of the aromatic nitriles. The effects of various parameters such as solvent, base, and amount of catalyst were studied. The reaction is suitable for a wide variety of substituted aryl halides with different electronic properties. Application of microwave irradiation improved the yields of the reactions and reduced the reaction times from hours to minutes.

Keywords Cyanation reaction · Palladium · $K_4[Fe(CN)_6]$ · Aromatic nitrile · Catalyst

Introduction

Aromatic nitriles find applications as dyes, herbicides, agrochemicals, pharmaceuticals, and natural products [1]. Furthermore, the nitrile group can undergo a wide variety of transformations to give compounds such as benzoic acids, amidines, amides, imidoesters, benzamidines, amines, heterocycles, and aldehydes [2]. Nitriles can also be transformed into a variety of medicinally important groups such as tetrazoles, triazoles, oxazoles, thiazoles, and oxazolidinones [3]. A variety of methods for the introduction of the cyanide functional group into aromatic compounds have been described [4]. The Sandmeyer reaction (involving diazonium salts plus copper(I) cyanide) and Rosenmund–Von Braun reaction, in which aryl halides react with stoichiometric amounts of copper(I) cyanide, provide early examples of the conversion of aryl halides to aryl cyanides [5]. Drawbacks of these reactions are the high temperature required (150–250 °C) and the use of stoichiometric amounts of copper(I) cyanide, which leads to equimolar amounts of heavy metal waste. On an industrial scale, aryl cyanides are mainly produced via ammoxidation of the corresponding toluene derivatives [6]. Since the discovery of transition metal catalyzed cross-coupling reactions, a great deal of interest has been dedicated to the development of a practical catalytic version of this transformation [7]. The first palladium-catalyzed cyanation of aryl halides was introduced in 1973 by Takagi et al., using aryl bromides and iodides with potassium cyanide as cyanating agent [8]. In addition to palladium, transition metal complexes based on nickel [9] and copper have been employed for the coupling of aryl halides with cyanide [10]. The cyanation reaction can also be performed using ligand-free catalysts [11, 12]. However, palladium compounds have some advantages over the other metal complexes, such as less sensitivity to air and humidity

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compared with nickel, more activity than copper and toleration of a wider variety of functional groups [1]. Typical cyanide sources are alkali metal cyanides [10, 13], $Zn(CN)_2$ [14–16], CuCN [17], trimethylsilyl cyanide (TMSCN) [18], and acetone cyanohydrins [19]. These reagents have disadvantages that impede wider applications; for example, alkali metal cyanides are highly poisonous, zinc cyanide leads to heavy metal waste, and both TMSCN and acetone cyanohydrin can easily liberate hydrogen cyanide [20].

In 2004, Beller et al. introduced potassium ferrocyanide, $K_4[Fe(CN)_6]$, as a novel cyanation reagent with lower toxicity and without special precautions for handling [21]. This reagent is used industrially for metal extractions for the fabrication of a range of advanced materials. It is also used in low doses in some food preparations [11] and as an anti-agglutinating auxiliary for NaCl [6].

Microwave-assisted heating under controlled conditions is an alternative to traditional heating, with the possible advantages of reducing the reaction time, increasing the yield, selectivity and purity of the products [22]. This method has been established to be very effective in accelerating cyanation reactions [23].

Herein, following our previous work [24–27], we report the synthesis of a new *ortho*-palladated complex, $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-4-OMe-5-}\kappa^2\text{-}C,N\}(\mu\text{-Br})]_2$ (**3**), from 2-methoxyphenethylamine (**1**) and $Pd(OAc)_2$ using the method reported by Vicente et al. [28], and its application for cyanation of various aryl halides under microwave irradiation and conventional heating using $K_4[Fe(CN)_6]$ as a cyanide source.

Experimental

Melting points were determined in open capillaries with a Gallenkamp instrument and are uncorrected. FT-IR spectra were run on a Jasco-680 spectrophotometer (Japan) as KBr disks or as smears between salt plates. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent at room temperature (TMS was used as an internal standard). A BEIFIN 3420 Gas Chromatograph equipped with a Varian CP SIL 5CB column- 30 m, 0.32 mm, 0.25 µm was used to monitor completion of the reactions. All reagents and solvents used in this study were of reagent grade quality, obtained from commercial suppliers (Acros, Merck, and Aldrich), and used without further purification.

Synthesis of $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-4-OMe-5-}\kappa^2\text{-}C,N\}(\mu\text{-Br})]_2$ (**3**)

A mixture of 258 mg (1.7 mmol) of 2-methoxyphenethylamine and 382 mg (1.7 mmol) of $Pd(OAc)_2$ was heated at 55 °C in acetonitrile (20 mL) for 6 h. After cooling, the resulting suspension was filtered through a plug of $MgSO_4$; the solvent was removed under reduced pressure using a rotary evaporator to give complex **2** as a yellow solid. Solid NaBr (165 mg, 1.6 mmol) was added to a suspension of complex **2** (500 mg, 0.79 mmol) in acetone (30 mL), and the mixture was stirred for 8 h. The solvent was removed, and CH_2Cl_2 (10 mL) was added. The resulting suspension was filtered through a plug of $MgSO_4$, concentrated to 2 mL under reduced pressure using a rotary evaporator and *n*-hexane (15 mL) was added to precipitate a yellow solid, which was filtered off, washed with water and *n*-hexane and air-dried to afford 0.41 mg of complex **3** (77% yield) as a yellow solid, Decomp.: 142 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (t, 1H, C_6H_3), 6.89 (d, 1H, C_6H_3), 6.86 (d, 1H, C_6H_3), 3.82 (s, 3H, OMe), 3.09 (m, 2H, $CH_2\mathbf{CH_2}$), 2.84 (m, 2H, $\mathbf{CH_2}CH_2$), 2.24 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.10$, 129.37, 126.90, 126.79, 119.23, 109.14 (C aromatic), 54.08 (OCH_3), 43.63 ($CH_2\mathbf{CH_2}NH_2$), 35.90 ($\mathbf{CH_2}CH_2NH_2$). IR (KBr, cm^{-1}): ν 3228, 3225, 2936, 1599, 1571, 1494, 1460, 1244, 1031, 754. Anal. Calcd for $C_{18}H_{24}Br_2N_2O_2Pd_2$: C, 32.1; H, 3.6; N, 4.2. Found: C, 32.4, H, 3.5; N, 4.2.

General procedure for the cyanation reactions

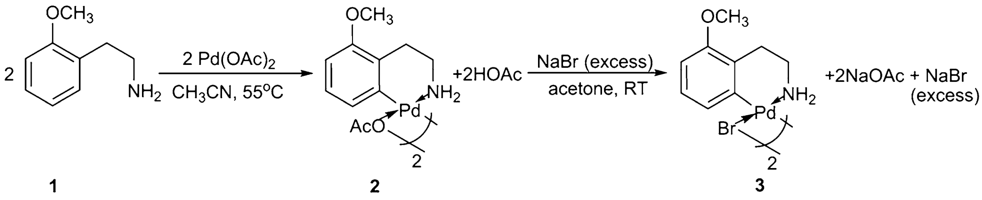
A mixture of the appropriate aryl halide (1 mmol), potassium hexacyanoferrate(II) (0.22 mmol), palladacycle complex **3** (0.4 mol%), and K_2CO_3 (2 mmol) was added to DMF (3 mL) in a round-bottom flask equipped with a condenser and placed into a Milestone Microwave. Initially, the microwave irradiation was set at 500 W, and the temperature was ramped from room temperature to the desired temperature of 130 °C. Once this was reached, the reaction mixture was held at this temperature until the reaction was completed. During this time, the power was modulated automatically to keep the reaction mixture at 130 °C. The mixture was stirred continuously during the reaction. After the reaction was completed, the mixture was cooled to room temperature and diluted with water (20 mL) and *n*-hexane (20 mL). The organic layer was dried over $CaCl_2$, then filtered, and the solvent was evaporated using a rotary evaporator. The residue was purified by recrystallization using ethanol and water.

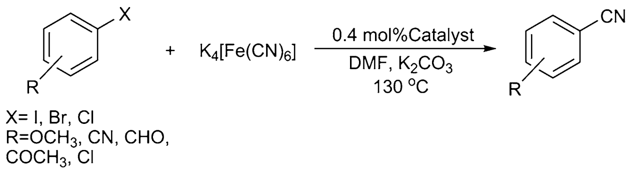
Results and discussion

The reaction of 2-methoxyphenethylamine (**1**) with $Pd(OAc)_2$ in a 1:1 molar ratio in acetonitrile gave the cyclometalated complex $[Pd\{C_6H_3(CH_2CH_2NH_2)\text{-4-OMe-5-}\kappa^2\text{-}C,N\}(\mu\text{-Br})]_2$ (**3**) (Scheme 1).

The application of this complex as a catalyst for the cyanation of various types of aryl halides with $K_4[Fe(CN)_6]$ was examined (Scheme 2).

Scheme 1 The synthesis route for preparation of *ortho*-palladated complex **3**





Scheme 2 Cyanation of aryl halides using $K_4[Fe(CN)_6]$

In order to improve the efficiency of the reaction, the solvent and base were both optimized. Initially, the cyanation reaction conditions were optimized for the reaction of iodobenzene with potassium hexacyanoferrate(II) in the presence of various solvents and bases using 0.5 mol% of catalyst (Table 1). Several organic solvents such as toluene, acetonitrile, *N,N′*-dimethylformamide, *N*-methyl-2-pyrrolidone (NMP), and methanol were examined. According to data given in Table 1, DMF was the most efficient solvent for this reaction (Table 1, entry 2).

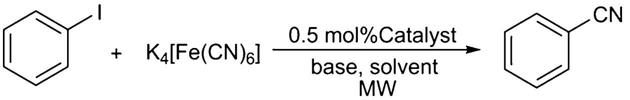
After choosing DMF as the solvent, we examined several different bases. Our experiments showed that the base was necessary for the cyanation reaction (Table 1, entry 11). We found that K_2CO_3 is the best base for this reaction, while Cs_2CO_3, NaOAc, KOH, and Na_2CO_3 led to 97, 90, 80, and 60% conversions to benzonitrile, respectively. NaF was not efficient in this reaction.

We examined the effect of different molar ratios of iodobenzene to $K_4[Fe(CN)_6]$ on the cyanation reaction. A study of the literature suggested that the best results were obtained with 1:0.22 ratio of aryl halide to $K_4[Fe(CN)_6]$ [29]. Using 0.4% palladacycle and a 1:1 molar ratio of iodobenzene to $K_4[Fe(CN)_6]$ led to complete conversion to the benzonitrile product. Furthermore, since each mole of $K_4[Fe(CN)_6]$ contains six cyanide ions, decreasing the ratio of $K_4[Fe(CN)_6]$ to iodobenzene to 0.22:1 did not decrease the reaction yield.

The loading of catalyst was also optimized by employing various amounts of catalyst, and 0.4 mol% gave the best results. (Table 2).

We then used the optimal reaction conditions (aryl halide, 1 mmol; $K_4[Fe(CN)_6]$, 0.22 mmol; K_2CO_3, 2 mmol; and DMF as solvent) for cyanation of different aryl halides under both microwave irradiation and conventional heating conditions, and the results are shown in Tables 3 and 4.

Table 1 Optimization of reaction condition of iodobenzene using palladacycle **3** under microwave irradiation



Entry	Base	Solvent	Temperature (°C)	Time (min)	Conversion[a] (%)
1	K_2CO_3	DMF	130	5	100
2	K_2CO_3	NMP	130	5	90
3	K_2CO_3	MeOH	Reflux	5	0
4	K_2CO_3	CH_3CN	Reflux	5	0
5	K_2CO_3	Toluene	Reflux	5	0
6	Na_2CO_3	DMF	130	5	60
7	Cs_2CO_3	DMF	130	5	97
8	NaOAc	DMF	130	5	90
9	NaF	DMF	130	5	20
10	KOH	DMF	130	5	80
11	–	DMF	130	5	0
12[b]	K_2CO_3	DMF	130	5	100
13[c]	K_2CO_3	DMF	130	5	35

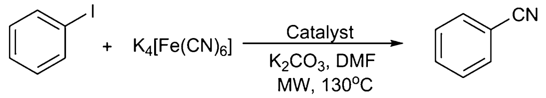
Reactions were carried out with iodobenzene (1 mmol), $K_4[Fe(CN)_6]$ (0.22 mmol), base (2 mmol) in solvent (3 mL)

[a] Determined by GC

[b] $K_4[Fe(CN)_6]$ (1 mmol)

[c] $K_4[Fe(CN)_6]$ (0.16 mmol)

Table 2 Optimization of loading of catalyst in cyanation of iodobenzene with $K_4[Fe(CN)_6]$



Entry	Mol% catalyst	Time (min)	Conversion (%)[a]
1	None	5	0
2	0.2	5	85
3	0.3	5	93
4	0.4	5	98
5	0.5	5	100
6	1	3	100

Reactions were carried out with iodobenzene (1.0 mmol), $K_4[Fe(CN)_6]$ (0.22 mmol), K_2CO_3 (2 mmol), and various concentration of palladacycle **3** in DMF (3 mL)

[a] Determined by GC

As shown in Table 3, full conversions were achieved in all cases except for 4-chloroacetophenone and 2-bromoacetophenone; for these substrates, we were unable to obtain quantitative yields even by prolonging the reaction time (Table 3, entries 12 and 15). This may be due to the lower reactivity of Cl as the leaving group in the former case and steric hindrance in the vicinity of the Br as leaving group in the latter case. In general, however, using these reaction conditions, different types of aryl halides even the less reactive aryl chlorides produced the desired cyanated products (Table 3, entries 3 and 12); these reactions required longer reaction times and their yields were lower than for the other substrates. Also, the aryl iodides reacted more rapidly than similar aryl bromides, reflecting the higher reactivity of I as leaving group. The reaction of 1,4-diiodobenzene as a difunctional aryl halide proceeded quantitatively in a short reaction time using double the amount of other reagents. Reactions were performed with both electron-donating and electron-withdrawing groups, and the results clearly showed that there is no sensitivity to substituents on the aryl ring. The effect of chemoselectivity of the method was investigated using *ortho*-, *meta*-, and *para*-bromochlorobenzene as test substrates. In each case, only Br was substituted, and the chloro-group did not enter into the reactions.

As shown in Tables 3 and 4, the use of homogenous metal catalysts in conjunction with microwave irradiation improved the yields of the reactions and decreased the reaction times in comparison with traditional heating methods.

Concerning the reaction mechanism, we consider that at first Pd(II) changes to Pd(0). Then, the oxidative addition

Table 3 Cyanation of aryl halides with $K_4[Fe(CN)_6]$ using catalyst **3** under microwave irradiation

Entry	Aryl halides	Products	Time (min)	Yield[a] (%)
1	Iodobenzene	Benzonitrile	6	95
2	Bromobenzene	Benzonitrile	7	95
3	Chlorobenzene	Benzonitrile	10	94
4	4-Iodoanisole	4-Methoxybenzonitrile	12	92
5	4-Bromoanisole	4-Methoxybenzonitrile	13	91
6	3-Bromoanisole	3-Methoxybenzonitrile	15	56
7	1-Bromo-4-chlorobenzene	4-Chlorobenzonitrile	4	94
8	1-Bromo-3-chlorobenzene	3-Chlorobenzonitrile	3	93
9	1-Bromo-2-chlorobenzene	2-Chlorobenzonitrile	15	68
10	4-Bromobenzonitrile	1,4-Dicyanobenzene	7	92
11	4-Bromobenzaldehyde	4-Formylbenzonitrile	6	87
12	4-Chloroacetophenone	4-Acetylbenzonitrile	15	40
13	4-Bromoacetophenone	4-Acetylbenzonitrile	7	91
14	4-Iodoacetophenone	4-Acetylbenzonitrile	6	93
15	2-Bromoacetophenone	2-Acetylbenzonitrile	20	30
16	1-Iodo-4-nitrobenzene	4-Nitrobenzonitrile	18	90
17[b]	1,4-Diiodobenzene	1,4-Dicyanobenzene	7	93
18	1-Bromonaphtalene	1-Naphthonitrile	8	89
19	9-Bromophenantrene	Phenanthrene-9-carbonitrile	10	90

Reaction condition: aryl halide (1.0 mmol), $K_4[Fe(CN)_6]$ (0.22 mmol), K_2CO_3 (2 mmol), palladacycle **3** (0.4 mol%), DMF (3 mL), temperature 130 °C

[a] Isolated yield

[b] Reaction condition: aryl halide (1.0 mmol), $K_4[Fe(CN)_6]$ (0.44 mmol), K_2CO_3 (4 mmol), palladacycle **3** (0.8 mol%), DMF (3 mL), temperature 130 °C

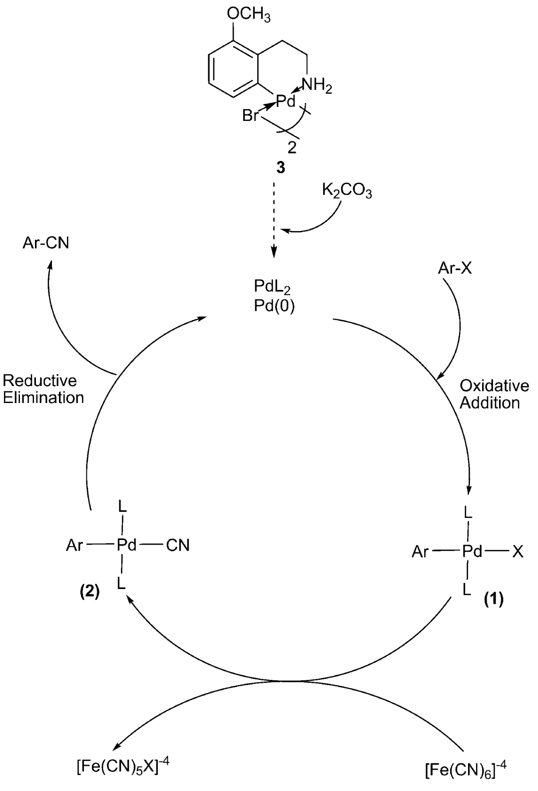
Table 4 Cyanation of aryl halides with $K_4[Fe(CN)_6]$ using catalyst **3** under conventional heating conditions using an oil bath

Entry	Aryl halides	Products	Time (h:min)	Yield[a] (%)
1	Iodobenzene	Benzonitrile	1:15	93
2	Bromobenzene	Benzonitrile	1:45	92
3	4-Iodoanisole	4-Methoxybenzonitrile	2:30	90
4	1-Bromo-4-chlorobenzene	4-Chlorobenzonitrile	1	92
5	1-Bromo-3-chlorobenzene	3-Chlorobenzonitrile	0:45	91
6	4-Bromobenzonitrile	1,4-Dicyanobenzene	2:15	90
7	4-Bromobenzaldehyde	4-Formylbenzonitrile	1:30	84
8	9-Bromophenantrene	Phenanthrene-9-carbonitrile	2	87

Reaction condition: aryl halide (1.0 mmol), $K_4[Fe(CN)_6]$ (0.22 mmol), K_2CO_3 (2 mmol), palladacycle **3** (0.4 mol%), DMF (3 mL), temperature 130 °C

[a] Isolated yield

of aryl halides to Pd(0) forms the aryl palladium(II) intermediate **1**. After reaction between **1** and $K_4[Fe(CN)_6]$, the intermediate **2** is produced. To test the proposed mechanism, the mercury drop test was carried out. In the presence of a heterogeneous catalyst, mercury leads to amalgamation on the surface. In contrast, Hg(0) cannot have a poisoning effect on homogeneous palladium complexes, where the Pd(II) metal centre remains tightly bound to the ligand. When a drop of Hg(0) was added to the reaction mixture with iodobenzene under the optimized conditions and heated, the complex **3** lost its catalytic activity (Scheme 3). The data obtained can be rationalized in terms of a Pd(0):Pd(II) cycle. We suggest that 2-methoxyphenethylamine prevents the fast agglomeration of Pd(0) species.



Scheme 3 Proposed mechanism for cyanation reaction

All the aromatic nitriles in this paper have been reported previously and characterized by comparison with their reported data [30–32].

Conclusion

A novel palladium-based catalyst was successfully applied for the cyanation of aryl halides using $K_4[Fe(CN)_6]$ as a nontoxic cyanating agent under both microwave irradiation and conventional heating. Catalytic amounts of this complex converted different aryl bromides and iodides to the corresponding arenenitriles in high yields and short reaction times, but aryl chlorides were changed to benzonitriles with moderate yields. The results showed that under microwave irradiation conditions, the reaction times can be reduced from hours to minutes.

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