Microwave-enhanced synthesis of aryl nitriles using dimeric orthopalladated complex of tribenzylamine and $K_4[Fe(CN)_6]$

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ABSTRACT

The activity of palladacycle $[Pd\{C_6H_4(CH_2N(CH_2Ph)_2)\}(\mu\text{-}Br)]_2$ complex was investigated in the synthesis of benzonitriles under both conventional and microwave irradiation conditions and their results were compared together. This complex is an efficient, stable, and non-sensitive to air and moisture catalyst for the cyanation reaction. The substituted benzonitriles were produced of various aryl halides in excellent yields and short reaction times using a catalytic amount of $[Pd\{C_6H_4(CH_2N(CH_2Ph)_2)\}(\mu\text{-}Br)]_2$ complex and $K_4[Fe(CN)_6]$ in DMF at 130 °C. In comparison to conventional heating conditions, the reactions under microwave irradiation gave higher yields in shorter reaction times.

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The substituted benzonitriles constitute the key components of different commercial compounds, including dyes, herbicides, agrochemicals, pesticides, natural products and pigments, and so on.[1–5] The cyanide functional group serves as an important intermediate for many of the possible transformations into other functional groups such as carboxylic acids and their derivatives, aldehydes, amines, amidines, and heterocycles contain thiazoles, triazoles, tetrazoles, oxadiazoles, and etc.[6–9] So the development of efficient and practical methods for the synthesis of benzonitriles is an attractive subject in organic synthesis. One of the most convenient methods for the synthesis of aryl nitriles is the Rosenmund–von Braun reaction using stoichiometric amounts of CuCN.[10] However the harsh reaction conditions and the use of stoichiometric amounts of copper (I) cyanide lead to the production of equimolar amounts of heavy metal wastes, especially in the case of industrial large-scale synthesis, which is a major drawback of these methods.[11,12] A refined method for the preparation of benzonitriles is the transition-metal-mediated cyanation of aryl halides using inorganic or organic cyanide sources, such as alkali cyanides (KCN and NaCN),[13] $Zn(CN)_2$,[14] CuCN,[15] TMSCN,[16] and acetone cyanohydrins.[17] The toxicity of alkali cyanides, the sensitivity of Me_3SiCN to moisture, the release of HCN, and the production of heavy metal waste, in the case of $Zn(CN)_2$, significantly limit the applications of these reagents. The palladium-catalyzed cyanation of aryl halides using $K_4[Fe(CN)_6]$ as an inexpensive, non-toxic, and efficient source of cyanide is a useful and powerful method to obtain substituted benzonitriles.[18–22] This cyanation agent is also used for metal precipitation in the food industry, in low doses in some food preparation, as an anti-caking agent[23] and anti-agglutinating auxiliary for NaCl.[12]

The use of microwave irradiation in homogeneous transition metal-catalyzed reactions leads to the reduction of reaction times, production of high yields and higher selectivity, the decrease of discarded byproducts from thermal side-reactions, and increased lifetime of the catalyst.[24] Microwave methodology has been reported as a simple, fast and, efficient process for the palladium-catalyzed cyanation of aryl halides.[25–28]

In continuation of our recent investigations on the synthesis and application of the palladacycle catalysts,[29–37] we now wish to report the extension of $[Pd\{C_6H_4(CH_2N(CH_2Ph)_2)\}(\mu\text{-}Br)]_2$ homogeneous complex, as a thermally stable and oxygen insensitive catalyst for the conversion of various aryl halides to aryl nitriles under conventional and microwave irradiations (Scheme 1).
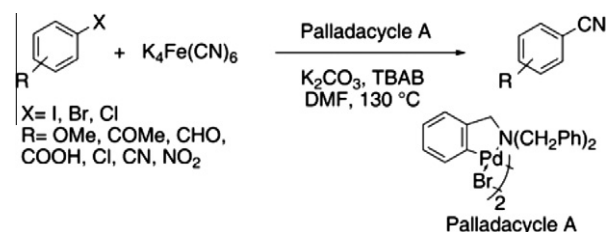
Scheme 1. Cyanation of aryl halides using $K_4[Fe(CN)_6]$.

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We have recently applied dimeric orthopalladate complex $[Pd\{C_6H_4(CH_2N(CH_2Ph)_2)\}$ $(\mu\text{-}Br)]_2$ (A) in the Heck coupling reaction.[35] In this Letter, the efficiency of this catalyst is investigated in the preparation of aryl nitriles under both traditional and microwave irradiation conditions. In order to optimize the reaction conditions, we chose the reaction of 9-bromophenanteren with $K_4[Fe(CN)_6]$ in various solvents and bases (Table 1) using various catalyst concentrations (Table 2) under microwave irradiation. The monitoring system for reaction times, temperature, pressure, and power in the microwave reactor allows for an excellent control of reaction parameters which generally leads to rapid optimization and more reproducible reaction conditions. The direct control of reaction mixture temperature; was carried out with the IR sensors. Among the selected bases, K_2CO_3 acted as the most effective one (Table 1, entries 10–11). Potassium carbonate as a co-catalyst facilitates the reduction of palladium(II) species and has a positive effect on the reaction.[12] A low yield was obtained in the case of no addition of the base. Several different solvents such as toluene, DMF, NMP, DMAc, dioxane, methanol, and ethanol were examined. The best results were obtained in DMF as a microwave absorbing polar aprotic solvent (having the ability to additionally stabilize palladium species by weak coordination) and K_2CO_3 as base (Table 1, entry 11).

Under these conditions and the usage of a 1:1 molar ratio of 9-bromophenanteren to $K_4[Fe(CN)_6]$ in 10 min 9-cyanophenanteren occurred in an 80% yield and 10% 9,9′-biphenanthrene was formed due to the homo coupling reaction of 9-bromophenanteren as the by-product and with a lapse of time the yield of the desired product did not change. The presence of a free cyanide ion in the solution can deactivate the catalyst.[38] $K_4[Fe(CN)_6]$ as a weakly ionizable source due to the inertness of the complex and its large CFSE that causes the release of CN^- to a lesser extent in the reaction media and has more advantages over the other cyanation sources.[18] Moreover, as each mol of $K_4[Fe(CN)_6]$ contains six-fold cyanide ions, we also investigated the 1:0.22 molar ratio of aryl halide to $K_4[Fe(CN)_6]$. The cyano product was obtained in a 60% yield in 10 min and the conversion was completed in 20 min. In order to improve the time and yield reaction, tetrabutylammonium bromide (TBAB) was added into the mixture reaction. By using TBAB as the additive and 0.22 mmol of $K_4[Fe(CN)_6]$ full conversions were

Table 1
Optimization of the reaction conditions for the cyanation reaction under microwave irradiation[a]

Entry	Base	Solvent	Temp (°C)	Time (min)	Conversion[b] (%)
1	K_2CO_3	NMP	130	20	65
2	K_2CO_3	DMAc	130	20	40
3	K_2CO_3	Toluene	120	20	15
4	K_2CO_3	EtOH	70	20	25
5	K_2CO_3	MeOH	55	20	10
6	K_2CO_3	Dioxane	90	20	20
7	K_2CO_3	DMF	130	20	80
8	K_2CO_3	DMF	130	20	80
9[c]	K_2CO_3	DMF	130	10	60
10[c]	K_2CO_3	DMF	130	20	100
11[d]	K_2CO_3	DMF	130	10	100
12	Na_2CO_3	DMF	130	20	58
13	Cs_2CO_3	DMF	130	20	75
14	NaOAc	DMF	130	20	70
15	KOH	DMF	130	20	56
16	CsF	DMF	130	20	23
17	—	DMF	130	20	10

[a] Reaction conditions: 9-bromophenanteren (1 mmol), $K_4[Fe(CN)_6]\cdot3$ H_2O (1 mmol), base (1 mmol), palladacycle catalyst (0.5 mmol %), solvent (3 mL).
[b] Determined by GC.
[c] $K_4[Fe(CN)_6]$ (0.22 mmol).
[d] $K_4[Fe(CN)_6]$ (0.22 mmol), TBAB (1 mmol).

Table 2
Optimization of the catalyst concentration on the cyanation reaction under microwave irradiation[a]

Entry	mmol % catalyst	Time (min)	Conversion[b] (%)
1	None	30	0
2	0.2	20	50
3	0.3	20	68
4	0.4	15	93
5	0.5	10	100
6	1	8	100

[a] Reactions conditions: 9-bromophenanteren (1 mmol), $K_4[Fe(CN)_6]\cdot3$ H_2O (0.22 mmol), K_2CO_3 (1 mmol), TBAB (1 mmol), palladacycle catalyst, DMF (3 mL), 130 °C, 600 W.
[b] Determined by GC.

achieved in 10 min (Table 1, entry 11), and only trace amounts of the homo coupling product were detected.

We also optimized the concentration of catalyst, employing various amounts of catalyst for this reaction using K_2CO_3 as base and DMF as solvent. The results were summarized in Table 2.

The low palladium concentration usually led to a long period of reaction as increasing the amount of palladium catalyst shortened the reaction time, but did not increase the yield of 9-cyanophenanteren. The best result was obtained when the cross coupling reaction was carried out with 0.5 mmol % of dimeric complex (Table 2, entry 5).

The optimized reaction conditions were used for the cyanation of a vast range of aryl halides under both conventional heating and microwave irradiation conditions and the results are summarized in Tables 3 and 4. As this catalytic system is not sensitive to oxygen, the reactions were carried out under air atmosphere.

We examined the electronic and steric effects on the resulted yields and conversion times of the reactions. Cyanation reactions were performed using either electron-releasing or electron-withdrawing groups on benzene rings and it was found that these groups did not show any significant effect on yields and reaction times. I and Br substituted aryl halides are most reactive, however Cl analogues are cheaper and more readily available. Aryl chlorides converted to aryl nitriles more slowly and with less yields in comparison to the similar aryl iodides and bromides (Table 3, entries 19–21). The steric hindrance of the procedure was examined using 2-, 3-, and 4-bromoacetophenone as hindered substituted aryls (Table 3, entries 9–11). Increasing the hindrance in the vicinity of the leaving group can cause to decrease the reaction conversion. The chemo-selectivity of the procedure was examined using 2-, 3-, and 4-choloro-bromobenzene. In these reactions Br acted as a better leaving group (Table 3, entries 14–16).

A general proposed mechanism for the cyanation reaction has been presented in Scheme 2. Initially, Pd(II) pre-catalyst converts to Pd(0), followed by the oxidative addition of aryl halide to Pd(0) to form aryl palladium(II) intermediate **1**. After reaction between **1** and $K_4[Fe(CN)_6]$, the intermediate **2** is achieved. Finally, the reductive elimination of intermediate **2** caused the desired cyanated products and the Pd(0) formed in the main catalytic cycle.[12,38]

To evaluate the proposed mechanism of the catalytic system, we carry out the mercury drop test. In the presence of a heterogeneous catalyst, mercury leads to the amalgamation of the surface of the catalyst. In contrast, Hg(0) cannot have a poisoning effect on homogeneous palladium complexes, where the Pd(II) metal centre is tightly bound to the ligand. When a drop of Hg(0) was added to the reaction mixture and heated under the mentioned optimized condition, no aryl nitrile product was obtained and no catalytic activity was observed for the catalyst. The obtained data can confirm the Pd(0):Pd(II) cycle.

Table 3
Cyanation reaction of aryl halides with $K_4[Fe(CN)_6]$ using palladacycle catalyst under microwave irradiation[a]
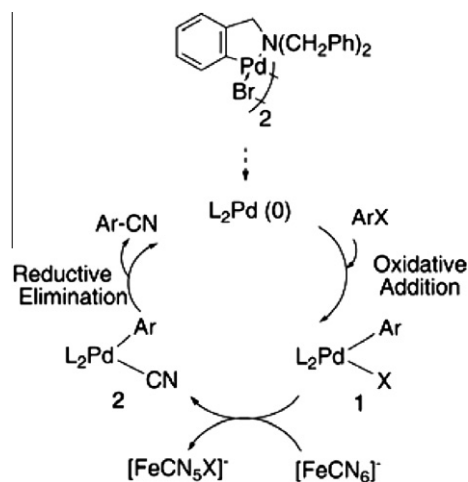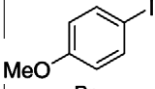
Entry	ArX	Product	Time (min)	Yield[b] (%)
1			5	92
2			7	88
3			7	85
4			10	80
5			6	90
6			7	90
7			7	85
8			8	87
9			8	90
10			10	68
11			20	53
12			8	85
13			8	80
14			5	93
15			5	90
16			10	82
17			8	80
18			10	90
19			10	88

Table 3 (continued)

Entry	ArX	Product	Time (min)	Yield[b] (%)
20			20	58
21			20	50

[a] Reaction conditions: aryl halide (1 mmol), $K_4[Fe(CN)_6] \cdot 3\ H_2O$ (0.22 mmol), K_2CO_3 (1 mmol), TBAB (1 mmol), palladacycle catalyst (0.5 mmol %), DMF (3 ml), 130 °C, 600 W.
[b] Isolated yield.
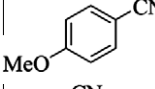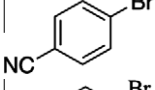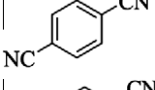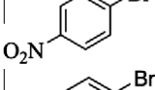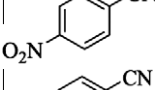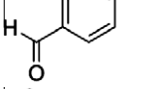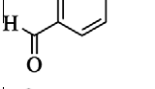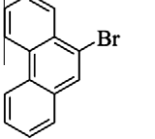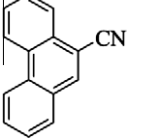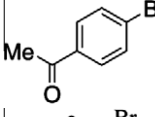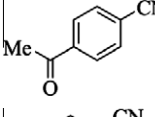
Scheme 2. General mechanism for cyanation reaction.

The results summarized in Table 4 showed that the use of homogenous metal catalysts in conjunction with microwave irradiation improved the yields of the reactions and decreased the reaction times in comparison to the traditional heating methods. The dramatic rate enhancement is due to the rapid and uniform heating of the reaction mixture and increased catalyst lifetime by the elimination of wall effects in microwave versus oil-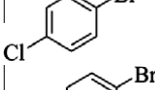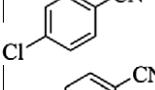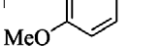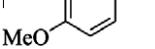bath heating.[24] Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first.[39]

General procedure for cyanation reaction of aryl halides with $K_4[Fe(CN)_6]$ under microwave irradiation

A mixture of the aryl halide (1 mmol), $K_4[Fe(CN)_6] \cdot 3\ H_2O$ (0.22 mmol, 92.9 mg), TBAB (1 mmol, 322.4 mg), palladacycle catalyst (0.5 mmol %, 4.7 mg), and K_2CO_3 (1 mmol, 138.2 mg) was added to DMF (3 mL) in a round-bottomed flask equipped with a condenser and placed into the Milestone microwave. Initially using a microwave power of 600 W the temperature was ramped from room temperature to 130 °C, this taking approximately 1 min, and then 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 using an appropriate magnet during the reaction. After the reaction was completed, the mixture was cooled to room

Table 4
Cyanation reaction of aryl halides using palladacycle under conventional heating conditions using an oil bath[a]

Entry	ArX	Product	Time (h)	Yield[b] (%)
1	iodobenzene	benzonitrile	2	88
2	4-iodoanisole (MeO)	4-methoxybenzonitrile (MeO–CN)	3	85
3	bromobenzene	benzonitrile	2.5	85
4	4-bromobenzonitrile (NC)	terephthalonitrile (NC–CN)	4	80
5	4-bromonitrobenzene (O_2N)	4-nitrobenzonitrile (O_2N–CN)	3	80
6	4-bromobenzaldehyde (CHO)	4-formylbenzonitrile (CHO–CN)	3.5	78
7	9-bromophenanthrene	9-cyanophenanthrene	4	84
8	4-bromoacetophenone (Me–CO)	4-acetylbenzonitrile (Me–CO–CN)	3	80
9	4-bromochlorobenzene (Cl)	4-chlorobenzonitrile (Cl–CN)	2	84
10	4-bromoanisole (MeO)	4-methoxybenzonitrile (MeO–CN)	3	80

[a] Reaction conditions: aryl halide (1 mmol), $K_4[Fe(CN)_6]\cdot3\ H_2O$ (0.22 mmol), K_2CO_3 (1 mmol), TBAB (1 mmol), palladacycle catalyst (0.5 mmol %), DMF (3 ml), 130 °C.
[b] Isolated yield.

temperature and diluted with water (30 ml) and ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated using rotary evaporator. The residue was purified by silica gel column chromatography or by recrystallization using ethanol and water. The products were characterized by comparing their mp, IR, ^1H, ^{13}C NMR spectra with those found in the literature.[19,20]

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