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Pd/C: A Recyclable Catalyst for Cyanation of Aryl Bromides

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Aryl cyanides have been prepared from the corresponding aryl bromides with potassium hexacyanoferrate(II) using Pd/C as a catalyst. It is shown that the addition of Bu_3N is the key factor in obtaining the corresponding aryl cyanides. Furthermore, the catalyst can be recycled by filtration and washing sequences, making the method also attractive for industrial applications.

Introduction

Aryl cyanides are of considerable interest as integral part of dyes, herbicides, natural products and pharmaceuticals.[1] In addition, cyanides play a crucial role as they can be easily converted into a variety of functional groups such as acids, ketones, oximes and amines.[2]

Various methods for the synthesis of aryl cyanides have been reported. One of the most convenient methods is based on the transition-metal-mediated displacement of aromatic halides by the cyanide ion. Since the discovery of transition-metal-catalyzed cross-coupling reactions, much interest has been devoted to the development of a practical version of this transformation.[3] Until now, a number of successful palladium- and nickel-catalyzed protocols have been reported.[4,5] However, most of the work has concentrated on the inconvenient traditional cyanide sources which have some severe drawbacks. In order to avoid these problems, potassium hexacyanoferrate(II) was rediscovered as a non-toxic cyanide source by Beller.[4f] However, potassium hexacyanoferrate(II) as a cyanide source was only used in homogeneous catalyst system.[4f,4h,4m,4p,4r] Until now, the existing methods employing homogeneous Pd catalyst still suffer from at least one of two drawbacks: quite expensive and hazardous phosphane ligands were generally needed,[4f,4p,4r] recycling of the catalyst was tedious. A good way to overcome these problems would be the use of supported catalysts that are extensively studied for Heck and Suzuki reactions.[6] Nevertheless, only few reports described the cyanation catalyzed by heterogeneous Pd catalysts.[4j,4k] Seki and co-workers have shown that the heterogeneous system (4 mol-% Pd/C + 16 mol-% PPh_3 + 40 mol-% Zn dust + 20 mol-% Br_2) is active for cyanation of aryl bromides.[4j,4k] However, its success remained linked to the use of PPh_3 as ligand.

Quite recently, we chose to investigate a heterogeneous Pd/C (5 wt.-%) catalyst in the cyanation of aryl halides. The reason for using Pd/C is the prospect of attaining much cleaner reactions as palladium can be removed by simple filtration. The "Pd/C" catalyst system for cyanation of aryl bromides using potassium hexacyanoferrate(II)[7] as cyanide source would also be of major interest for both industrial and academic applications.

Results and Discussion

As a starting point for the development of our cyanation system, the reaction of bromobenzene with $K_4[Fe(CN)_6]$ was investigated. The results are recorded in Table 1. At first the reaction of bromobenzene in the presence of 1 mol-% Pd/C (5 wt.-%), 20 mol-% dry $K_4[Fe(CN)_6]$ and 100 mol-% Na_2CO_3 in *N*,*N*-dimethylacetamide (DMAc) at 140 °C for 21 h resulted in poor conversion (Table 1, Entry 1). Increasing the amount of Pd/C only led to a slightly increase in product yield (Table 1, Entries 2, 3). Encouraged by some successful reports of one-pot domino halogen exchange (Halex) coupling reactions,[3b,8] we also tried using this method but found that this had a deleterious effect on the reaction (Table 1, Entry 4).

Since tetrabutylammonium salts have been reported to increase the efficiency by stabilizing palladium nanoparticles,[9] the yield, however, of the desired product decreased when performing the reaction in the presence of phase-transfer catalysts (Table 1, Entries 5, 6).

Then some co-catalysts widely successfully used in coupling reactions to reduce high-valent transition-metal ions to their corresponding low-valent ones, such as Zn,[10] HCOONa,[11] and *i*PrOH,[12] were explored. It was found that the use of Zn as a co-catalyst did not facilitate the

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Table 1. Evaluation of various reaction conditions.[a]

Entry	Pd/C (mol-%)	Additive (mol-%)	Conv. (%)	Yield (%)[b]
1	1	–	40	37
2	3	–	42	38
3	5	–	43	39
4	3	KI (300)	30	27
5	3	TBAB (50)	13	< 2
6	3	PEG-400 (50)	12	< 2
7	1	Zn (50)	43	26
8	1	HCOONa (50)	85	15
9	1	*i*PrOH (50)	60	54
10[c]	1	–	> 99	50
11	1	Bu_3N (50)	92	82
12[d]	1	Bu_3N (50)	> 99	87
13[e]	1	Bu_3N (50)	19	17
14[d,f]	1	Bu_3N (50)	> 99	91
15[d,g]	1	Bu_3N (50)	> 99	81

[a] Reaction conditions: 3.0 mmol bromobenzene, 1–5 mol-% Pd/C (5 wt.-%), 20 mol-% dry $K_4[Fe(CN)_6]$, 5 mL solvent, 100 mol-% Na_2CO_3, under N_2, 140 °C, 21 h. [b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard. [c] Under H_2. [d] Reaction time 24 h. [e] No Na_2CO_3. [f] Solvent: NMP. [g] Solvent: DMF.

Table 2. Cyanation of bromobenzene in the presence of different amines.[a]

Entry	Amine (mol-%)[b]	Conv. (%)	Yield (%)[c]
1	1,10-phen (50)	15	7
2	bipy (50)	19	16
3	L-proline (50)	44	32
4	TMEDA (50)	56	10
5	Et_3N (50)	94	78
6	DABCO (50)	93	85

[a] 3.0 mmol bromobenzene, 1 mol-% Pd/C (5 wt.-%), 20 mol-% dry $K_4[Fe(CN)_6]$, 5 mL NMP, 100 mol-% Na_2CO_3, under N_2, 140 °C, 24 h. [b] DABCO = 1,4-diazabicyclo[2.2.2]octane, 1,10-phen = 1,10-phenanthroline, bipy = 2,2′-bipyridine, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine. [c] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

reaction (Table 1, Entry 7). HCOONa gave good conversion but lower yield due to dehalogenation (Table 1, Entry 8). Only a slight increase in product yield was observed when *i*PrOH was used (Table 1, Entry 9). When performing the reaction under H_2 excellent conversion could be achieved, but large amounts of dehalogenation product were also obtained (Table 1, Entry 10).

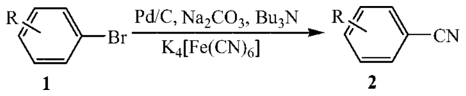
Fortunately, the reactivity of the catalyst system was greatly enhanced in the presence of Bu_3N (Table 1, Entry 11). The synthesis of benzonitrile in an excellent conversion and with a good yield (Table 1, Entry 12) was achieved by an increase of the reaction time. A blank test using Bu_3N as base without Na_2CO_3 afforded benzonitrile only in a poor yield of 17% (Table 1, Entry 13). Addition of Bu_3N was essential to run the reaction effectively and suggested that Bu_3N might play an important role in stabilizing the catalyst in the catalytic cycle. Thus, the combination of Na_2CO_3 with Bu_3N plays a key role in improving the catalytic activity.

The use of other solvents such as NMP, DMF all brought about good yields, and NMP gave the best result (Table 1, Entries 14, 15).

The beneficial effect of Bu_3N as additive prompted us to examine other amines in the cyanation of bromobenzene. The results are shown in Table 2. Interestingly, the presence of 1,10-phen, bipy, L-proline or TMEDA inhibited rather than facilitated the reaction (Table 2, Entries 1–4). Et_3N and DABCO promoted this reaction effectively; nevertheless, they were less effective than Bu_3N (Table 2, Entries 5, 6).

To evaluate the scope and limitations of this procedure, the reactions of a wide variety of aryl halides were examined (Table 3). Very efficient transformation of an array of commercially available β-bromonaphthalene and aryl bromides bearing a variety of electron-withdrawing groups, for example, CH_3CO, F, NO_2, CF_3, CHO for the cyanation. They led to the products in good to excellent yields (Table 3, Entries 1–7). Aryl bromides with electron-donating groups, such as methyl and methoxy, exhibited somewhat diminished yields of the corresponding products and lower selectivity due to the formation of biaryls at prolonged reaction times (Table 3, Entries 9–11). However, the substrate with an amino group was not compatible with the reaction conditions (Table 3, Entry 12). This suggested that the oxidative addition of aryl halide to the Pd catalyst could be the rate-determining step in the reaction. We also attempted to extend the suggested method to a more inexpensive aryl chloride such as 4-chlorobenzotrifluoride. Unfortunately, the corresponding cyanide was obtained in a very low yield (4%) accompanied by a large amount of biaryl (Table 3, Entry 13).

Table 3. Pd/C-catalyzed cyanation of various aryl halides.[a]



Entry	Ar-X	Ar-CN	Time (h)	Conv. (%)	Yield (%)[b]
1	β-bromonaphthalene	**2a**	2	100	95
2	*p*-$CH_3COC_6H_4Br$	**2b**	2	100	92
3	*p*-FC_6H_4Br	**2c**	2	100	94
4	*p*-$O_2NC_6H_4Br$	**2d**	2	> 99	88
5	*p*-$CF_3C_6H_4Br$	**2e**	2	> 99	89
6	*m*-$CF_3C_6H_4Br$	**2f**	2	> 99	87
7	*m*-$CHOC_6H_4Br$	**2g**	2	100	88
8	C_6H_5Br	**2h**	24	> 99	91
9[c]	*p*-$CH_3C_6H_4Br$	**2i**	36	91	80
10[d]	*p*-$CH_3OC_6H_4Br$	**2j**	36	> 99	50
11[d]	*o*-$CH_3OC_6H_4Br$	**2k**	36	95	40
12[d]	*p*-$H_2NC_6H_4Br$	**2l**	36	–	–
13[d]	*p*-$CF_3C_6H_4Cl$	**2m**	36	63	4

[a] Reaction conditions: 3.0 mmol aryl halide, 20 mol-% dry $K_4[Fe(CN)_6]$, 1 mol-% Pd/C (5 wt.-%), 5 mL NMP, 100 mol-% Na_2CO_3, 50 mol-% Bu_3N, under N_2, 140 °C. [b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard. [c] 2 mol-% Pd/C was used. [d] 3 mol-% Pd/C was used.

In order to illustrate the recycling of the catalyst, 4-bromobenzotrifluoride was cyanated under Pd/C, with Bu_3N as additive, NMP as solvent and Na_2CO_3 as base. After filtering off the product, Pd/C was washed with deionized water and CH_2Cl_2, and dried in air at room temperature. The dried catalyst was then reused directly in the next reaction. The same procedure was repeated for all further cycles. In addition, the amount of palladium of the crude product was determined by ICP-AES. The Pd content was found to be 0.45 ppm. On the other hand, the Pd content for using the same, but homogeneous catalyst system [0.1 mol-% $Pd(OAc)_2$] was 1.76 ppm which is higher than that for the Pd/C catalyst system. This catalytic system has the advantages of homogeneous catalysis to some extent. Although, the catalytic activity was gradually diminished, the yield was still 80% even in the third reuse (Table 4). Therefore, it is easy for the catalyst to be reused, and it has a potential application on an industrial scale.

Table 4. Recycling of the catalyst (without addition of fresh catalyst).[a]

Entry	Pd/C	Yield (%)[b]
1	fresh	88
2	first reuse	87
3	second reuse	84
4	third reuse	80

[a] Reaction conditions: 3.0 mmol p-$CF_3C_6H_4Br$, 20 mol-% dry $K_4[Fe(CN)_6]$, 5 mL NMP, 100 mol-% Na_2CO_3, 50 mol-% Bu_3N, 140 °C, 2 h. 1 mol-% Pd/C (5 wt.-%) was used in the first run, then the recovered catalyst was used directly in the next runs. [b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

Conclusions

We propose a Pd/C-catalyzed method for the cyanation of aryl bromides using potassium hexacyanoferrate(II) which is non-toxic and inexpensive. This protocol avoids the use of expensive and/or air-sensitive ligands. High catalytic activity was obtained using Na_2CO_3 with Bu_3N. A variety of aryl halides gave the corresponding benzonitriles in good to excellent yields. Furthermore, Pd/C can be recycled by simple filtration and washing sequences, even in the third reuse.

Experimental Section

General Procedure for the Cyanation of Aryl Halides: After standard cycles of evacuation and filling with dry and pure nitrogen, an oven-dried tube was charged with aryl halide (3 mmol), $K_4[Fe(CN)_6]$ (221 mg, 20 mol-%), Pd/C (5 wt.-%, 64 mg, 1 mol-%), Bu_3N (278 mg, 50 mol-%), Na_2CO_3 (318 mg, 3 mmol), and NMP (5 mL). The tube was evacuated and filled with nitrogen. Then the tube was sealed and the mixture was stirred at 140 °C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered. Then 1,3-dimethoxybenzene (800 μL) was added as the internal standard and the mixture was analyzed by GC. For isolating the products, the filtrate was washed with water (2 × 15 mL) and 5% NH_4OH (1 × 15 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product obtained was purified by silica gel chromatography with hexane and ethyl acetate as eluent. All prepared benzonitriles are known compounds and identified by GC-MS.

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