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Development of an Open-Air and Robust Method for Large-Scale Palladium-Catalyzed Cyanation of Aryl Halides: The Use of *i*-PrOH to Prevent Catalyst Poisoning by Oxygen

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Abstract:

Palladium-catalyzed cyanation of aryl halides is an often capricious reaction and lacks robustness due to catalyst poisoning by oxygen. In this report, an open-air and robust method for large-scale cyanation was developed and the use of commercially available *i*-propanol as an additive was critical for achieving the open-air, robust and scaleable process. Under the protection by *i*-propanol, the catalyst life was significantly prolonged.

Introduction

Aryl nitriles play an important role in organic synthesis since they not only constitute key components of a range of pharmaceuticals, agrochemicals, dyes, etc.[1] but can also easily be transformed into various classes of compounds such as nitrogen-containing heterocycles, aldehydes, acids, and acid derivatives.[2] One of the most convenient methods for the synthesis of aryl nitriles is the transition metal-catalyzed cyanation of aryl halides such as the palladium-,[3−10] nickel-,[11] and copper-catalyzed methods.[12−14] Of these methods, Pd-catalyzed aryl cyanation has recently attracted the most considerable attention owing to its versatility. Unluckily, the palladium catalysts have often been poisoned by trace amounts of oxygen in the solvent.[15] In order to avoid or suppress the deactivation of the catalysts, it has often been required that the solvent is rigorously degassed and the reaction is run in stringent inert conditions,[15] which restricts the applications of the Pd-catalyzed aryl cyanation.

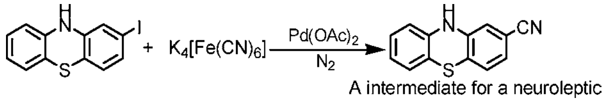

Figure 1. **Application of Weissman's ligand-free procedure for Pd-catalyzed cyanation.**

During the course of applying Weissman's ligand-free procedure to large-scale synthesis of the compound shown in Figure 1,[16] we suffered from unexpected reaction failures, which resulted possibly from the presence of low-level amounts of oxygen either from the solvent or introduced during setup and monitoring. Thus, some inexpensive additives were screened to protect the reaction from being destroyed by oxygen.

Previous studies of palladium-catalyzed cyanation reactions revealed that zinc dust and polymethylhydrosiloxane (PMHS) are able to protect the palladium-catalysts from being poisoned by oxygen.[17] Considering that the use of zinc dust would lead to heavy metal waste, PMHS was chosen to prevent catalyst poisoning. Unluckily, the addition of PMHS into the reaction mixture resulted in the formation of an unacceptable amount of undesired products. To our knowledge, another air-insensitive procedure is Gelman's procedure in which 1,8-bis(diisopropylphosphino)triptycene/Pd(OAc)$_2$ was used as the catalyst,[18] but the use of an expensive ligand compelled us to abandon the application of Gelman's procedure.

Subsequently, we decided to develop a more economical and air-insensitive procedure for large-scale Pd-catalyzed aryl cyanation by improving Weissman's ligand-free procedure.[19] We report our results here.

Results and Discussion

In our initial study, cyanation of iodobenzene was chosen as a model reaction, and PMHS was used as an additive to prevent the Pd-catalyst from being deactivated.[26] Unluckily, the addition of PMHS led to the formation of a considerable amount

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(15) All the reactions of palladium-catalyzed aryl cyanation in refs 12−14 were performed in inert ambiance.

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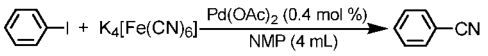
10.1021/op9000725 CCC: $40.75

Table 1. **Cyanation of iodobenzene catalyzed by $Pd(OAc)_2$[a]**



entry	ambiance	*i*-PrOH (vol %)[b]	time (min)	conv. (%)[c]	yield (%)[c]
1	air	–	40	45	44
2	N_2	–	40	86	81
3	N_2	4.6	40	>99	88
4	**air**	**4.8**	**40**	**>99**	**93**
5	air	–	40	44	42
6	air	0.3	40	85	74
7	air	1.2	40	>99	91
8	air	2.4	40	>99	89
9	air	3.3	40	>99	88
10	air	6.9	40	>99	87
11	air	4.7	20	81	69
12[d]	**air**	**4.8**	**20**	**99**	**91**

[a] Reaction conditions are shown in the Experimental Section of this paper (1 mmol iodobenzene was used). [b] Equal to $[V_{i\text{-PrOH}}/(V_{i\text{-PrOH}} + V_{\text{NMP}})] \times 100\%$. [c] Determined by GC with *n*-tetradecane as an internal standard. [d] 5.2 vol % H_2O was used.

of undesired products, which prompted us to use other additives. According to the previous report,[20] some alcohols can be used as the reductants for Pd-catalyzed homocoupling of aryl halides, which implies that oxygen may be eliminated by alcohols in the presence of Pd catalyst. Thus, a variety of alcohols such as MeOH, EtOH, *i*-PrOH, *n*-BuOH, *t*-BuOH, and *t*-AmOH were screened as the additives to eliminate oxygen, and it was found that *i*-propanol had a notable ability to protect the Pd-catalyzed cyanation from being destroyed by oxygen. As shown in Table 1, when cyanation of iodobenzene was performed completely open to the air without degassing of the solvent, the addition of *i*-propanol increased the yield from 44% to 93% (Table 1, entries 1, 4). However, when the reaction was performed under inert conditions the beneficial effect of *i*-propanol was unconspicuous (Table 1, entries 2, 3), which implied that the solvent effect of *i*-propanol was insignificant for the reaction. In conclusion, only under the condition of exposure to air, was the reaction significantly affected by *i*-propanol. This result revealed that *i*-propanol was able to protect the Pd-catalyzed cyanation from being destroyed by oxygen, which was also supported by the fact that the oxidation product of *i*-propanol was detected in our open air reaction. These results were possibly rationalized by assuming that active Pd(0) catalytic species were oxidated to inactive Pd(II) by oxygen, and then *i*-propanol reduced Pd(II) to active Pd(0).

Then our attention was turned to the optimization of the concentration of *i*-propanol. As shown in Table 1 (entries 5−10), all the reactions were performed completely open to the air without stringent degassing of the solvent. The cyanation reaction in the absence of *i*-propanol gave benzonitrile in only 42% yield (Table 1, entry 5). The yield increased from 74% to 91% with the concentration of *i*-propanol increasing from 0.3 vol % to 1.2 vol %, and then remained almost constant with further increase of the concentration of *i*-propanol (Table 1, entries 6−10). These results revealed that more than 1.2 vol % *i*-propanol was preferred for facilitating the open air Pd-catalyzed cyanation. Subsequently, 5.2 vol % H_2O was added into the reaction system to further improve our procedure. As seen from Table 1 (entries 11, 12), the addition of H_2O did accelerate the cyanation reaction, which was possibly attributed to that H_2O played a role of cosolvent to help solubilize $K_4[Fe(CN)_6]$.[21,22] Then our attentions turned to the optimization of concentration of H_2O, and it was found that 4−6 vol % H_2O was preferred for facilitating the Pd-catalyzed cyanation. Cyanation reaction with H_2O as the solvent was also investigated, but the obtained yield was very low, resulting possibly from a poor solubility of iodobenzene in H_2O.

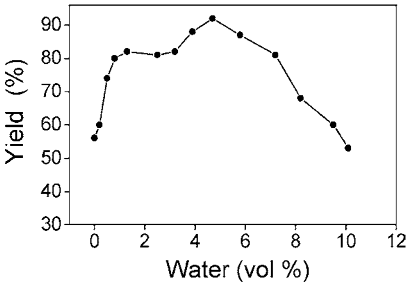


Figure 2. **Effect of concentration of H_2O on the cyanation of bromobenzene (under the reaction conditions as shown in entry 8, Table 2).**

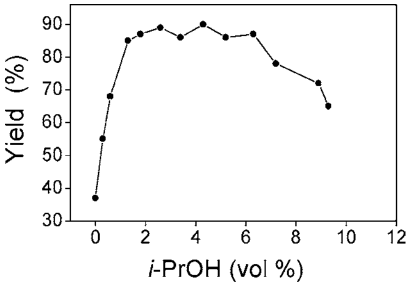


Figure 3. **Effect of concentration of *i*-propanol on the cyanation of bromobenzene (under the reaction conditions as shown in entry 8, Table 2).**

Optimization experiments for the cyanation of bromobenzene included the effect of *i*-propanol, H_2O, reaction time, and temperature. As seen from Figures 2 and 3, about 2−6 vol % *i*-propanol and 4−6 vol % H_2O were optimal for facilitating the reaction. We then tried reducing the reaction time but found that this was not possible without sacrificing product yield. The same was true when we tried to reduce the catalyst loading. We tried eliminating the Na_2CO_3 from the reaction, but such modification resulted in no conversion to product.

In order to demonstrate further the effectiveness of *i*-propanol in this process, Gas chromatography was used to monitor the cyanation of iodobenzene. As seen from Figure 4, the open air reaction in the presence of *i*-propanol proceeded at essentially the same rate as the reaction performed in inert ambiance, while the same open air reaction in the absence of *i*-propanol stalled after only 25 min (up to 47% yield was obtained). These results revealed that the effectiveness of *i*-propanol was significant to protect Pd-catalyzed cyanation from being destroyed by oxygen. When the aforementioned reactions proceeded for 60 min,

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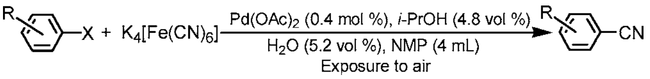
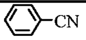
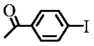
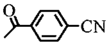
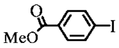
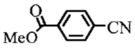
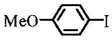
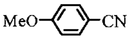
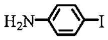
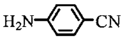
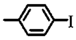
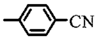
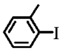
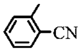
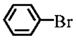
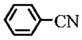
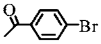
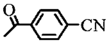
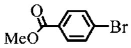
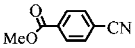
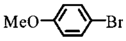
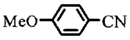
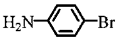
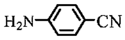
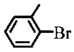
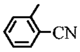
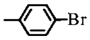
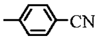
Table 2. **Cyanation of various aryl halides catalyzed by $Pd(OAc)_2$[a]**



Entry	Substrate	Product[b]	Time (h)	Conv. (%)[c]	Yield (%)[c]
1			0.4	99	89
2			0.4	> 99	91
3			0.5	98[d]	90[d]
4			0.6	95	86
5			0.7	84[d]	72[d]
6			0.4	> 99	98
7			2	81	69
8			5	98	90
9			5	95	83
10			3	> 99[d]	78[d]
11			4	98	91
12			5	91[d]	74[d]
13			5	95	88
14			5	> 99	95

[a] Reaction conditions are shown in the Experimental Section of this paper (1 mmol aryl halide was used). [b] Characterized by comparison of ^1H NMR and ^{13}C NMR data with that in the literature. [c] Determined by GC with *n*-tetradecane as an internal standard. [d] Isolated yield.

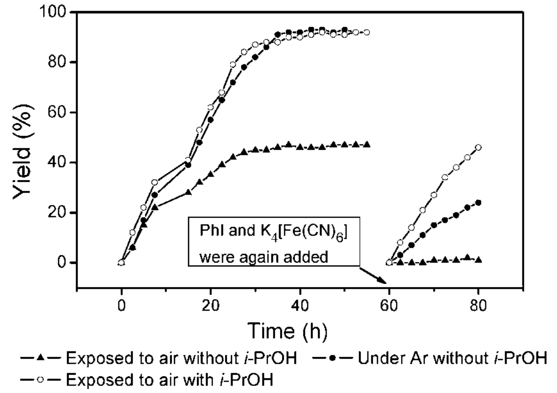


Figure 4. **Palladium-catalyzed cyanation of iodobenzene (under the reaction conditions as shown in entry 4, Table 1).**

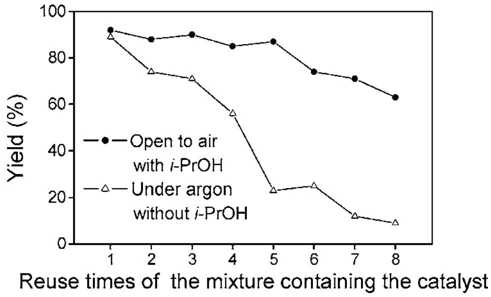


Figure 5. **Reuse of the mixture containing the catalyst for cyanation of iodobenzene without separation of the product. Besides the reaction time (60 min), other reaction conditions are shown in entry 4, Table 1.**

iodobenzene and $K_4[Fe(CN)_6]$ were again added into the reaction system to reuse the catalyst without separation of the product. As shown in Figure 4, in the case of reusing the catalyst, the rate of the open air reaction in the presence of *i*-propanol far exceeded the rate of the reaction performed in inert ambiance, which also implied that *i*-propanol was of ability to protect the catalyst from inactivation and thus prolong the catalyst life. This conclusion was supported by the following experimental results (Figure 5): without separation of the product, the mixture containing the catalyst could be reused five times with no significant loss of activity in the case of both the presence of *i*-propanol and exposing the reaction to air, while the catalyst showed a complete deactivation after being reused only one time in the case of both the absence of *i*-propanol and protecting the reaction with argon.

To clarify further the roles of *i*-propanol in this process, $Pd(OAc)_2$-catalyzed cyanation of iodobenzene was purposefully

Table 3. **Large-scale cyanation of bromobenzene**[a]

entry	order of addition of the reagents	yield[b]
1	*i*-PrOH, Na_2CO_3, $Pd(OAc)_2$, $K_4[Fe(CN)_6]\cdot 3H_2O$, and bromobenzene were mixed with NMP, whereafter the mixture was heated to 140 °C	56
2	*i*-PrOH, Na_2CO_3, $Pd(OAc)_2$, and bromobenzene were heated to 140 °C in NMP, whereafter $K_4[Fe(CN)_6]\cdot 3H_2O$ were added.	90
3	Na_2CO_3, $Pd(OAc)_2$ and bromobenzene were heated to 140 °C in NMP, whereafter $K_4[Fe(CN)_6]\cdot 3H_2O$ and *i*-PrOH were added.	35

[a] Reaction time is 5 h, other reaction conditions are shown in the Experimental Section of this paper. [b] Isolated yield.

stalled by exposure to air prior to the addition of *i*-propanol, and the result showed that the addition of *i*-propanol failed to restart the stalled reaction, revealing that *i*-propanol could not reactivate the catalyst that has been deactivated.

A series of aryl iodides were then screened to determine the scope and limitation of the suggested large-scale protocol. As shown in Table 2, the cyanation reactions were able to tolerate a wide range of functional groups such as ketone, carbonyl, ester, and methoxy groups. The primary amino group was even well tolerated and did not suffer from *N*-arylation (Table 2, entry 5), which possibly resulted from the high affinity of the cyanide nucleophile toward the palladium catalyst.[23] The electronic effect of the substrate seemed to be unpredictable under our conditions. Both electron-poor and electron-rich aryl iodides gave moderate to high yields under similar conditions (Table 2, entries 2−7). 4-Iodotoluene gave a yield of 98% in 0.4 h, while 2-iodotoluene gave a lower yield of 69% in a longer reaction time (Table 2, entries 6, 7). These results indicated that the substituent in ortho-position lowered the reaction rate. Considering that aryl bromides are less expensive than corresponding aryl iodides, we applied the present open-air protocol to the cyanation of aryl bromides. Although the cyanation of aryl bromides was slower, moderate to high yields of the aromatic nitriles could still be obtained in a longer reaction time (Table 2, entries 8−14).

Subsequently, the suggested protocol was applied to the large-scale cyanation of bromobenzene, and a yield of 56% was obtained (Table 3, entry 1). In an attempt to optimize the conditions for the large-scale reaction, several experiments were conducted where different orders of addition of the reagents were evaluated. As seen from Table 3, the addition of $K_4[Fe(CN)_6]\cdot 3H_2O$ to a preheated mixture of other reactants was critical for achieving a robust and scaleable process (Table 3, entry 2). The addition of *i*-PrOH prior to the heating operation had also positive effect on the scaleable reaction.

The isolation of the products was difficult in the case of using NMP as the solvent, prompting us to use DMF having a lower boiling point than the solvent. Luckily, the reaction also proceeded smoothly in DMF. After the reaction proceeded to completeness, the fractionation of the mixture afforded the desired product in high purity (>95%). Whereafter, we focused on the safety issues of the scaleable reaction. Considering that volatilization of the solvent was dangerous to the environment in the case of exposing the reaction to air, we performed the scaleable reaction in a closed vessel without the protection of inert gas. Several aryl bromides were tested to determine the scope and limitation of this protocol for the large-scale reaction. As shown in Table 4, all the tested aryl halides proceeded efficiently with 0.4 mol % catalyst on a 2.5 mol scale.

Conclusions

In conclusion, an open-air and robust method for the large-scale palladium-catalyzed cyanation of aryl halides was developed, and the use of *i*-propanol as an additive was critical for achieving the open-air, robust and scaleable process. Under the protection by *i*-propanol, the catalyst life was significantly prolonged. The suggested protocol allowed the cyanation of aryl halides to be smoothly completed within 0.5−7 h on a 2.5 mol scale.

Experimental Section

General Details. All chemicals were of reagent grade quality, obtained from commercial sources, and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$. GC analysis was performed on Varian CP-3800 gas chromatograph with a capillary column (CP-WAX 57CB 25 mm × 0.32 mm).

General Experimental Procedure for Small-Scale Cyanation of Aryl Halides. *i*-PrOH (4.8 vol %), Na_2CO_3 (159 mg, 1.5 mmol) and $Pd(OAc)_2$ (1.4 mg, 0.006 mmol) were ordinally added into a 10 mL tube equipped with 2 mL of *N*-methyl-2-pyrrolidone (NMP). In order to give a homogeneous solution as soon as possible, the mixture was stirred at room temperature for about 5 min. Then aryl halides (1.5 mmol) and NMP (2 mL) were added. After the tube was sealed with a 50 mL balloon that was fully filled with air, the reaction mixture was heated to 140 °C. $K_4[Fe(CN)_6]$ (221 mg, 0.6 mmol) was then added. The final mixture was stirred for corresponding reaction times given in Tables 1 and 2 at 140 °C. Filtration was followed by the GC analysis of the corresponding products. The desired products were purified by column chromatography and characterized by comparison of ^1H NMR and ^{13}C NMR data with those in the literature.

Typical Experimental Procedure for Large-Scale Cyanation of Aryl Halides. *i*-PrOH (4.8 vol %), Na_2CO_3 (265 g, 2.5 mol), $Pd(OAc)_2$ (2.3 g, 0.01 mol), and aryl halides (2.5 mol) were mixed with DMF (2.5 L). After the reaction mixture was heated to 140 °C, $K_4[Fe(CN)_6]\cdot 3H_2O$ (317 g, 0.75 mol) was added. Then the vessel was sealed, and the final mixture was stirred for corresponding reaction times given in Tables 3 and 4 at 140 °C. After the product was analyzed by GC with *n*-tetradecane as an internal standard, the reaction mixture was filtered, and the filter cake was washed with DMF (0.1 L). Fractionation of the filtrate afforded the desired product in high purity (>95%), and the product was characterized by comparison of ^1H NMR and ^{13}C NMR data with those in the literature.

All compounds are known, and their characterization data are as follows. Benzonitrile: ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.57−7.61 (m, 2H), 7.55−7.56 (m, 1H), 7.39−7.45 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 132.8, 132.1, 129.1, 118.8, 112.3. 4-Acetylbenzonitrile: ^1H NMR (400 MHz,

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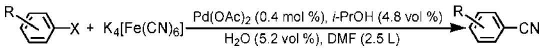
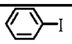
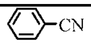
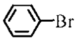
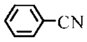
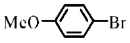
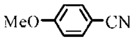
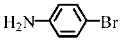
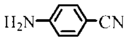
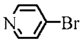
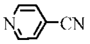
(23) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890–2891.

Table 4. **Large-scale cyanation of various aryl halides**[a]



1			0.5	92	83
2			5	76	81
3			5	83	92
4			5	91	75
5			8	89	70

[a] Reaction conditions were shown in the Experimental Section of this paper (2.5 mol aryl halide was used).

$CDCl_3$) δ (ppm) = 8.04−8.07 (m, 2H), 7.78−7.80 (m, 2H), 2.66 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 196.5, 139.9, 132.5, 128.7, 117.9, 116.4, 26.8. Methyl-4-cyanobenzoate: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.12−8.14 (m, 2H), 7.73−7.75 (m, 2H), 3.95 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 165.4, 133.9, 132.2, 130.1, 117.9, 116.4, 52.7. 4-Methoxybenzonitrile: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.57−7.61 (m, 2H), 6.94−6.97 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 162.8, 134.0, 119.2, 114.7, 103.9, 55.5. 4-Aminobenzonitrile: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.40−7.43 (m, 2H), 6.64−6.67 (m, 2H), 4.23 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 150.5, 133.8, 120.2, 114.4, 99.9. 4-Methylbenzonitrile: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.52−7.55 (m, 2H), 7.25−7.27 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 143.7, 132.0, 129.8, 119.2, 109.3, 21.8. 2-Methylbenzonitrile: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.39−7.44 (m, 1H), 7.35−7.37 (m, 1H), 7.14−7.20 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) = 141.6, 132.6, 132.3, 130.1, 126.2, 117.9, 112.5, 20.2.

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Supporting Information Available

Typical experimental procedure, characterization data, and copies of ^1H and ^{13}C NMR spectra for all cyanation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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