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Pd/CuO nanoparticles as a highly effective catalyst for the cyanation of aryl halides under ligand-free conditions

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ABSTRACT

Copper oxide supported palladium nanoparticles have been used as a separable catalyst for the cyanation of a range of aryl iodides and bromides under ligand-free conditions. The effect of solvent, base, and catalyst loading was investigated. The catalyst can easily be recovered and reused several times without significant loss of catalytic activity.

Aryl nitriles are valuable intermediates in organic chemistry and constitute the key components of a range of pharmaceuticals, herbicides, agrochemicals and dyes.[1] They can also be transformed into other functional groups such as aldehydes, nitrogen-containing heterocycles, carboxylic acids and their derivatives.[2]

Nitriles can be conventionally synthesized by the reaction of aryl halides with stoichiometric amounts of CuCN,[3a–c] the diazotization of anilines and subsequent Sandmeyer reaction or the transition metal-catalyzed cyanation of aryl halides using various cyanide sources which include the alkali-metal cyanides, Me_3SiCN and $Zn(CN)_2$.[3d–g,2d,3h–j] However, in many cases these methods suffer from drawbacks that restrict their use including; long reaction times and use of reagents that are toxic, hazardous, sensitive to moisture or expensive.[3]

Recently, $K_4Fe(CN)_6$ has received attention as an alternative cyanation agent due to favorable properties such as being nonexplosive, nonflammable and inexpensive.[4] Additionally, it is not volatile and is stable in the presence of moisture allowing easy storage. Among the various catalysts examined for the transition metal-catalyzed cyanation of aryl halides using $K_4Fe(CN)_6$, homogeneous catalysts in the presence of various ligands have been widely investigated.[3i,4e–g] However, heterogeneous catalysts proceeding under ligand-free conditions have received significantly less attention.[4] Homogeneous catalysts are more difficult to separate from the reaction mixture and cannot be reused in consecutive reactions.[5] Therefore, the development of a heterogeneous and highly efficient method for the ligand-free synthesis of nitriles is still an interesting research area.

Recently, our laboratory described the cyanation reaction of aryl iodides using carbon supported[4c] and Natrolite zeolite supported copper nanoparticles.[4d] However, the high cost of preparation of these catalysts may restrict their application, especially in large-scale processes. Additionally, this method was limited to the cyanation of aryl iodides.

Catalysis using nanoparticles (NPs) is typically more efficient than their particulate metal counterparts due to the small particle sizes and large surface areas. Therefore, heterogeneous catalysts are increasingly being used in nanoparticle form.[6]

Various methods have been reported for the synthesis of nanoparticles.[7] Recently, we reported the preparation of Pd/CuO nanoparticles using the extract of *Theobroma cacao* L. seed and their catalytic performance in the reduction of 4-nitrophenol and the phosphine-free Heck coupling under aerobic conditions.[8]

Based on our interest in copper, palladium, gold, iron and silver nanoparticle catalyzed reactions,[6] we began to develop an efficient and heterogeneous Pd/CuO catalyst that was air and moisture stable.

Pd/CuO NPs were synthesized according to the literature procedure using *Theobroma cacao* L. seed extract as both reducing and stabilizing agents (Fig. 1). No surfactant, capping agent, and/or template were used in this method for the synthesis of Pd/CuO NPs.[8,9]

In order to examine the feasibility for the cyanation of aryl halides (Scheme 1) and determine the optimum conditions, we examined the reaction of iodobenzene with $K_4Fe(CN)_6$ in the

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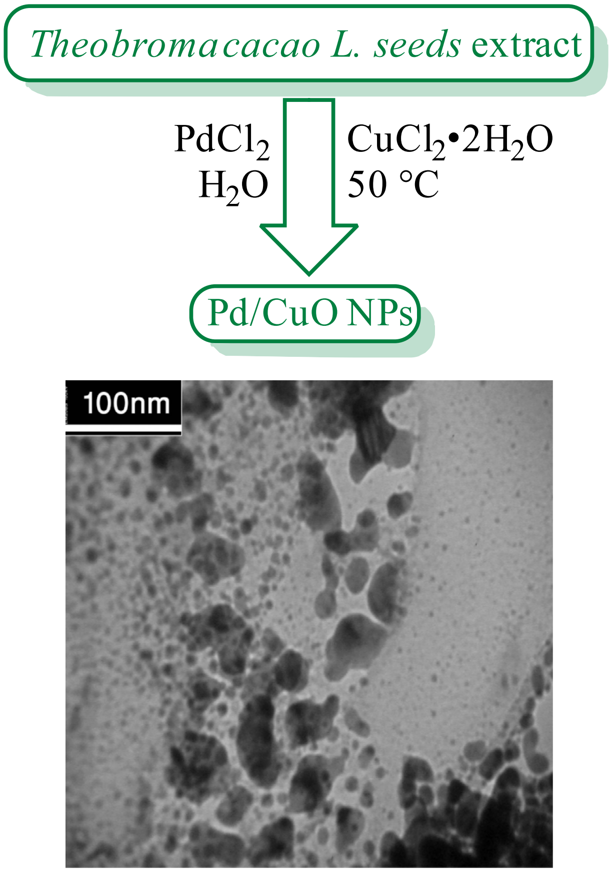
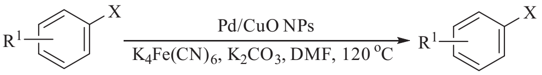
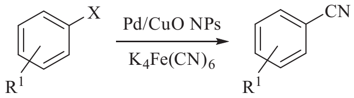


Figure 1. Synthesis of Pd/CuO NPs using Cocoa seed extract.



Scheme 1. Cyanation of aryl halides with $K_4Fe(CN)_6$ in the presence of Pd/CuO NPs.

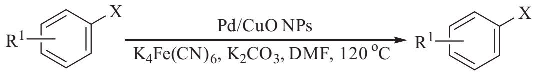
Table 1
Optimization of the reaction conditions for the cyanation of iodobenzene with $K_4Fe(CN)_6$[a]

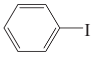
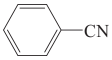
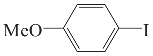
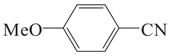
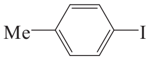
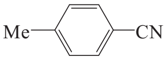
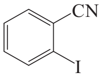
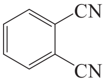
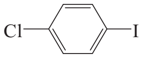
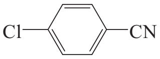
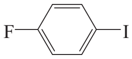
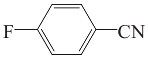
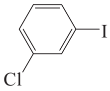
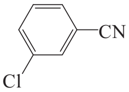
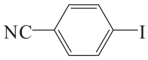
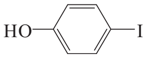
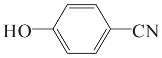
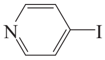
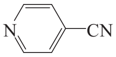
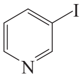
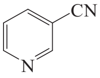
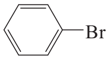
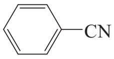
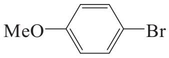
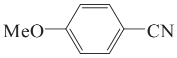
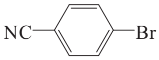
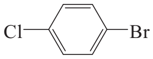
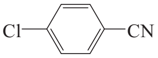


Entry	Pd/CuO NPs (mol %)	Solvent	Base	Yield[b] (%)
1	0.024	DMF	K_2CO_3	86
2	0.024	DMSO	K_2CO_3	82
3	0.024	Toluene	K_2CO_3	14
4	0.024	H_2O	K_2CO_3	13
5	0.024	NMP	K_2CO_3	25
6	0.024	DMF	Na_2CO_3	58
7	0.024	DMF	Et_3N	17
8	0.024	DMF	NaF	22
9	0.024	DMF	KOAc	75
10	0.015	DMF	K_2CO_3	60
11	0.06	DMF	K_2CO_3	86

[a] Reaction conditions: iodobenzene (1.0 mmol), $K_4Fe(CN)_6$ (0.17 mmol), base (1.0 mmol), DMF (5.0 mL), 120 °C, 12 h.
[b] Isolated yield.

Table 2
Cyanation of aryl halides with $K_4Fe(CN)_6$[a]



Entry	Aryl halide	Product	Time (h)	Yield[b] (%)
1			12	86 (86, 86, 85, 84, 83)[c]
2			15	88
3			15	89
4			12	91
5			12	92
6			12	93
7			13	88
8			12	93
9			12	92
10			12	92
11			12	93
12			15	85
13			15	88
14			15	91
15			15	90

[a] Reaction conditions: Pd/CuO NPs (0.024 mol %), aryl halide (1.0 mmol), $K_4Fe(CN)_6$ (0.17 mmol), K_2CO_3 (1.0 mmol), DMF (5 mL), 120 °C.
[b] Isolated yield.
[c] Yields from five subsequent runs using the same recovered catalyst.

presence of Pd/CuO NPs, various solvents and bases (Table 1). The reaction was significantly influenced by the solvent employed and the highest yield was obtained in DMF (Table 1, entry 1). Examination of several bases showed that K_2CO_3 gave the highest yield (Table 1, entry 1). It was found that it was not necessary to use an excess of $K_4Fe(CN)_6$, as each mole of $K_4Fe(CN)_6$ contained six cyanide ions. Therefore, the ratio of $K_4Fe(CN)_6$ to aryl halide was 0.17:1. Finally, the effect of catalyst loading was probed. The best result was obtained with Pd/CuO NPs (0.024 mol %) which gave the product in a good yield of 86%. Increasing the catalyst loading showed no substantial improvement in yield.

Having determined the optimal reaction conditions for the cyanation of aryl halides we next examined the reaction scope (Table 2). The catalyst exhibited excellent activity for the cyanation of aryl halides containing electron-donating (entries 2, 3 and 13) or electron-withdrawing groups (entries 4–8, 14 and 15).[10] Additionally, the reaction tolerated functional groups such as methoxy,

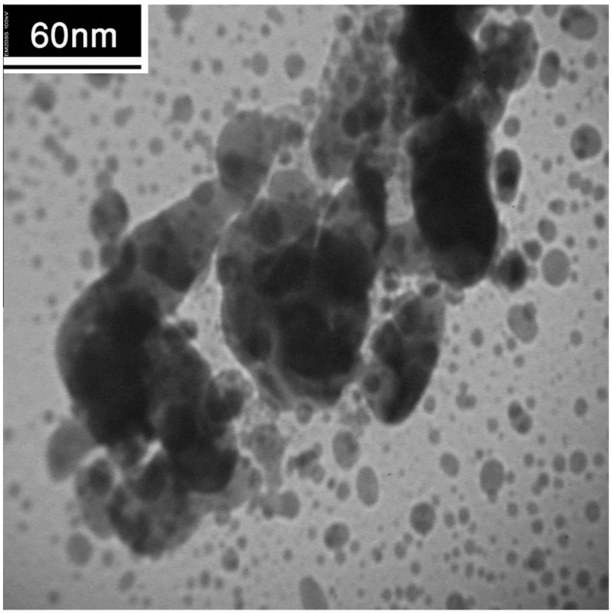


Figure 2. TEM image of recycled Pd/CuO NPs.

nitrile and hydroxy groups. In all cases, this protocol afforded the desired products in good to excellent yields. In addition, steric hindrance of the substituent did not influence the yield (Table 2, entry 4). The reaction of electron-poor nitrogen heterocycles, 4-iodopyridine and 3-iodopyridine proceeded in good yield (Table 2, entries 10 and 11). Aryl bromides were equally reactive while aryl chlorides were unreactive allowing selective reactions for 1-chloro-4-iodobenzene (Table 2, entry 5) and 1-bromo-4-chlorobenzene (Table 2, entry 15). In each case the products were characterized by comparison of their spectroscopic data (IR, NMR) and melting points with the literature.[11]

Finally, the reusability of the catalyst was examined in the cyanation reaction of iodobenzene with $K_4Fe(CN)_6$ (Table 2, entry 1). After reaction completion, the catalyst was separated from the reaction mixture using a centrifuge. The catalyst was washed several times with water and ethyl acetate, dried in an oven at 100 °C for 2 h and employed for the next reaction. The catalytic behavior of the Pd/CuO NPs was found to be unchanged over five consecutive cycles confirming the recyclability of the catalyst.

A TEM image of the recycled Pd/CuO NPs (Fig. 2) showed that the Pd particles were identical in shape and size even after the fifth run.

Previously reported methods for the cyanation of aryl halides[11] typically utilize homogeneous catalysts and/or ligands which cannot be easily recovered and recycled. In some cases, these methods are only limited to the cyanation of aryl iodides and require the use of KI for the conversion of aryl bromides into the more reactive aryl iodides. In contrast our method offers several notable features, compared to other reported reactions. For example the Pd/CuO NPs were prepared using mild reaction conditions using a simple procedure, are recoverable and react with aryl bromides. These advantages make the present method a convenient alternative method for the cyanation of aryl halides.

In conclusion, we have developed an efficient and simple procedure for the cyanation of aryl halides in good to excellent yields using Pd/CuO NPs under ligand-free conditions. The advantages of this protocol include a simple reaction setup, easy work-up, catalyst recyclability and elimination of toxic and expensive reagents.

Acknowledgements

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9. *Preparation of Pd/CuO NPs*: in a typical synthesis of Pd/CuO NPs, Cocoa seed aqueous extract (15 mL) was added dropwise to a well-mixed solution of $PdCl_2$/$CuCl_2 \cdot 2H_2O$ (40 mL, 0.2 mM/1.0 mM) with constant stirring at 50 °C for 2 h. After 7 min the color of the solution turned dark indicating the formation of Pd/CuO NPs. The colored solution was centrifuged at 7000 rpm for 30 min to complete precipitation of the Pd/CuO NPs. The obtained precipitate was washed three times with chloroform (10 mL) and ethanol (10 mL), respectively.[8]
10. *General procedure for the cyanation of aryl halides*: a mixture of aryl halide (1.0 mmol), $K_4Fe(CN)_6$ (0.17 mmol), K_2CO_3 (1.0 mmol) and Pd/CuO NPs (0.024 mol %) in DMF (5.0 mL) was heated at 120 °C for the appropriate time. After completion of the reaction, the mixture was cooled to room temperature and the catalyst separated from the reaction mixture using centrifuge. The resultant solution was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product. The residue was purified by recrystallization using ethanol and water. The purity of the compounds was confirmed by ^{1}H NMR. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature.[1,11]
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