New Nanomagnetic Heterogeneous Cobalt Catalyst for the Synthesis of Aryl Nitriles and Biaryls

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ABSTRACT: Cobalt nanoparticles immobilized on magnetic chitosan (Fe₃O₄@CS-Co) have been prepared. They were identified using various techniques such as Fourier-transform infrared spectroscopy, X-ray diffraction, field emission scanning electron microscopy, energy-dispersive X-ray spectroscopy, transmission electron microscopy, thermogravimetric analysis, vibrating sample magnetometry, X-ray photoelectron spectroscopy, and inductively coupled plasma atomic emission spectroscopy analysis and applied efficiently as a cobalt catalyst in the cyanation and fluoride-/palladium-free Hiyama reactions of different types of aryl halides employing K₄[Fe(CN)₆]·3H₂O and triethoxyphenylsilane, respectively. After each reaction, the catalyst was isolated and reused for the second run. The catalytic activity of the catalyst was not lost apparently even after five runs. No considerable changes in its chemical structure and morphology were observed. It is worth to note that in this paper, the cobalt catalyst has been used for the first time for the cyanation of aryl halides.

1. INTRODUCTION

Aryl nitriles are significant structural units of different biologically active compounds, agrochemicals, dyes, and natural products.¹ Nitriles are important building blocks in the synthesis of heterocycles as they are transformed into a range of functional groups such as amines, carboxylic acids, oximes, amidines, and ketones.² The Rosenmund–von Braun reaction, ammoniation of toluene, and diazotization of anilines, followed by the Sandmeyer reaction are known as the conventional methods for the synthesis of aryl nitriles.³ The reaction of aryl halides with cyanating agents in the presence of transition metals as catalysts are the most powerful protocols for the synthesis of aryl nitriles.⁴ Along this line, cyanation reactions have been reported in the presence of transition metals, such as Pd⁵, Ni,⁶ Rh,⁷ Ir,⁸ and Cu,⁹ using different cyanide reagents such as copper, potassium, sodium, and zinc cyanide, trimethylsilyl cyanide, phenyl cyanates, acetone cyanohydrins, and benzyl thiocyanates.¹⁰ In recent years, potassium hexacyanoferrate(II) trihydrate [K₄[Fe(CN)₆]·3H₂O], which is a nonhygroscopic, commercially accessible, easily handled, and inexpensive cyanide source, has been applied for the cyanation of aryl halides.¹¹ In most cases, a stable cyanide complex with transition metals is formed, and it deactivates the transition-metal catalysts. However, slow in situ generation of cyanide ions from K₄[Fe(CN)₆]·3H₂O improves the efficiency of the metal catalyst.¹²

Biaryl structures are found in numerous physiologically active compounds including natural products, pharmaceuticals, agrochemicals, organic materials, and organocatalysts.¹³ Performing reactions of aryl halides with organometallic reagents in the presence of Pd as a catalyst is the most attractive method for the preparation of biaryl compounds. Organoboron (Suzuki–Miyaura), organomagnesium (Kumada–Corriu), organozinc (Negishi), and organotin (Stille) derivatives are the most general organometallic reagents that are used for this purpose.¹⁴ However, these organometallic compounds have intrinsic drawbacks for practical uses,
including high toxicity, low stability, sensitivity to humidity or water, and poor biocompatibility. In recent years, low toxic, broadly available, low-cost, environmentally benign, and highly stable silicon compounds have received a lot of attention as fascinating reagents for the Hiyama reaction. 15

In particular, the mostly used transition-metal catalysts for the Hiyama cross-coupling and cyanation reactions are Pd catalysts. However, some drawbacks of palladium-based catalysts such as high cost, sensitivity to air, and formation of ineffective palladium cyanide species in the cyanation reactions encouraged the search for the C – C coupling reactions without using palladium catalysts. 16 In this regard, cobalt-based catalytic systems, as a viable alternative to palladium, have gained much interest in organic chemistry because of their low cost and availability. 17 Along this line, a number of methods using cobalt catalysts for improving of Suzuki–Miyaura, Sonogashira, and Heck–Mizoroki cross-coupling reactions have been reported. 18

During the past decades, magnetic nanoparticles (MNPs), which have been extensively studied for different biological and medical applications, have attracted much attention as smart materials for supporting catalysts because of their ease of preparation and functionalization, high surface area, and low cost and toxicity. 19 The most important feature of MNPs is their simple magnetic separation using an external magnet, which is an economic isolation method for industrial applications. Magnetic separation is more valuable than time-consuming filtration, centrifugation, or other workup techniques, as it avoids loss of the nanosized catalysts and increases the product’s purity. However, the catalytic activity of MNPs is decreased by the agglomeration during the catalytic reaction. Therefore, modification of MNPs by a variety of materials such as precious metals, 20 silica, 21 carbon, 22 and biopolymers 23 could prevent them from aggregation. Chitosan as a biopolymer has valuable properties such as hydrophilicity, biocompatibility, and biodegradability. 24 It has several amino and hydroxyl groups, which can be used for further modification with specific components, such as nanoparticles, drugs, and other functional groups. 25 For these reasons, magnetic chitosan has been widely synthesized and applied in catalytic reactions. 26

In the past few years, we have been making effort in developing heterogeneous nanocatalysts for organic reactions. 27 Recently, we have introduced a heterogeneous cobalt catalytic system (mTEG-CS-Co-Schiff-base) for Hiyama, Mizoroki–Heck, Suzuki, and Hirao cross-coupling processes. 28 We have found that this catalyst was unsuccessful for the cyanation reaction of aryl halides. To improve our ongoing work, in this paper, we introduced cobalt nanoparticles immobilized on magnetic chitosan (Fe3O4@CS-Co) as a new catalyst. This catalyst was identified using a variety of methods such as Fourier-transform infrared (FT-IR) spectroscopy, energy-dispersive X-ray spectroscopy (EDX), field emission scanning electron microscopy (FE-SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), vibrating sample magnetometry (VSM), thermogravimetric analysis (TGA), X-ray photoelectron spectroscopy (XPS), and inductively coupled plasma atomic emission spectroscopy (ICP–AES) analysis and used as a nanomagnetic heterogeneous cobalt catalyst in the cyanation and Hiyama cross-coupling reactions. It is worth to note that here, we report for the first time, the employment of a cobalt catalyst in the cyanation reaction of aryl halides.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Fe3O4@CS-Co. Fe3O4@CS-Co was synthesized as outlined in Scheme 1. The Fe3O4 nanoparticles, which were obtained by chemical coprecipitation protocol, were coated by chitosan to obtain Fe3O4@CS. Cobalt nanoparticles were immobilized on Fe3O4@CS by adsorption of CoCl2 on Fe3O4@CS, followed by reduction with NaBH4. The catalyst was characterized by FT-IR spectroscopy, XRD, FE-SEM, EDX, TEM, TGA, VSM, XPS, and ICP–AES.

The FT-IR spectra of Fe3O4, CS, Fe3O4@CS, and Fe3O4@CS-Co are shown in Figure 1. In the FT-IR spectrum of Fe3O4 NPs, a strong stretching absorbance peak at 573 cm−1 that refers to Fe–O groups is observed (Figure 1a). In the spectrum of chitosan (Figure 1b), a broad peak at 3700–3000 cm−1 can be ascribed to the stretching vibrations of O–H and N–H bonds. The other characteristic peaks appeared at 1661, 1378, 1154, 1073, and 1033 cm−1 that corresponded to N–H (bending), C–H (bending aliphatic), C–O–C bridge, C–O (stretching), and C–N (stretching), respectively. In the FT-IR spectrum of Fe3O4@CS, all characteristic peaks of Fe3O4 NPs and chitosan exist (Figure 1c). These observations indicate that successful coating of Fe3O4 with chitosan was achieved. In
the case of Fe₃O₄@CS-Co, the entrapment of cobalt in the chitosan matrix led to changes in the 1000−1700 cm⁻¹ region of the spectrum (Figure 1d). Slight shifting and changes in the intensity of these bands may account for the interaction of cobalt species with the O and N atoms in chitosan.

The XRD pattern of chitosan and Fe₃O₄@CS-Co are depicted in Figure 2. A broad peak at 21° in the XRD pattern of CS corresponds to the amorphous characteristic of CS (Figure 2a). In the XRD pattern of Fe₃O₄@CS-Co (Figure 2b), strong diffraction peaks at 30.7, 35.75, 43.6, 53.9, 57.5, and 62.9° were related to [2 2 0], [3 1 1], [4 0 0], [4 2 2], [5 1 1], and [4 4 0] planes of the cubic Fe₃O₄ lattice. Diffraction peaks of amorphous CS and Co-NPs appeared at 21 and 75.5°, respectively. The strength of the diffraction peaks of CS decreased in Fe₃O₄@CS-Co because of the attachment of Fe₃O₄ to CS through the amino and hydroxyl groups.

The nanofeature, morphology, and shape of Fe₃O₄@CS-Co were investigated using its TEM and FE-SEM images. The TEM and FE-SEM images (Figure 3a,b) showed that the NPs were spherical in shape. The mean diameter size of the NPs is 18 nm (Figure 3d). On comparison of the TEM image of Fe₃O₄@CS-Co (Figure 3a) with that of Fe₃O₄ (Figure 3c), it was found that Fe₃O₄@CS-Co dispersed considerably. The EDX analysis ensured the existence of Fe, Co, C, N, and O elements in Fe₃O₄@CS-Co (Figure 4). Elemental mapping of Co, N, Fe, C, and O in the Fe₃O₄@CS-Co nanocatalyst (Figure 5) indicated the consistent distribution of these elements on the catalyst surface. According to the ICP−AES analysis, the cobalt content of Fe₃O₄@CS-Co was calculated to be 22.87 wt %.

The TG curve of Fe₃O₄@CS-Co showed a weight loss around 40%, which corresponded to the elimination of absorbed water and thermal decomposition of the chitosan (Figure 6).

Magnetic properties of different steps of the catalyst preparation were characterized by VSM. The magnetic curves are shown in Figure 7. These curves showed that the approximate saturation magnetization value of Fe₃O₄@CS is 50 emu g⁻¹. The reduction in the saturation magnetization of this compound compared to that in the pure MNPs (80 emu g⁻¹) is due to the coating of Fe₃O₄ by polymeric layers of CS. An increase in the saturation magnetization of Fe₃O₄@CS-Co was observed, which is a good evidence of successful immobilization of cobalt on Fe₃O₄@CS.

Fe₃O₄@CS-Co was also characterized by XPS spectroscopy (Figure 8). Figure 8a confirms the existence of Co, Fe, O, and C elements in the catalyst. In the C 1s spectrum (Figure 8b), signals of binding energies located at 284.6 (C−C and C−H), 286.03 (C−OH and C−N), and 288.2 (N−C≡O) eV were observed. Figure 8c reveals typical cobalt (0) absorptions at 780.3 and 796.07 eV for 2p₃/2 and 2p₁/2, respectively. The peaks at 782.3 (2p₃/2) and 798.09 eV (2p₁/2) indicated that a little amount of cobalt is in the oxidation state of II. The weak satellite peaks were observed at around 785.8, 788.6, 801.3, and 803.0 eV. These satellite peaks indicated the existence of Co₃O₄ on the surface of the catalyst.

2.2. Cyanation of Aryl Halides Using K₄[Fe(CN)₆]·3H₂O Catalyzed by Fe₃O₄@CS-Co. After the structural characterization of Fe₃O₄@CS-Co, its reactivity as a nanomagnetic heterogeneous cobalt catalyst was investigated in the cyanation reaction of aryl halides. To find the best reaction conditions, some reactions were performed in the presence of Fe₃O₄@CS-Co, using iodobenzene with variation in cyanide sources, temperature, base, solvent, and the amount of the catalyst (Table 1). Based on the results indicated in Table 1, K₄[Fe(CN)₆]·3H₂O, dimethylformamide (DMF), Et₃N, 100 °C, and 5 mol % of the catalyst were chosen as the best conditions. A similar reaction was also investigated using CoCl₂, and it was found that the desired final product was generated in poor yield after 24 h (Table 1, entry 14).

To further investigate the scope and limitations of this protocol, various types of aryl halides were selected and allowed to react using the optimized reaction parameters (Table 2). Different aryl chlorides, bromides, and iodides underwent the cyanation reaction and produced the desired aryl nitriles from good to high yields.
With regard to the recyclability of Fe$_3$O$_4$@CS-Co in the cyanation reaction of iodobenzene using K$_4$[Fe(CN)$_6$]$\cdot$3H$_2$O, after completion of the reaction in the first run, the catalyst was isolated using an external magnet (Figure S1a,b), washed with EtOAc and EtOH (2 × 10 mL), and dried under vacuum. The catalyst was successfully recycled five times. Loss of catalytic activity was not considerably observed for Fe$_3$O$_4$@CS-Co in these reactions (Figure S1c). Comparison of FT-IR spectrum of the reused catalyst (Figure S1d) with that of the freshly prepared one (Figure S1d) indicated that no significant
changes in the chemical structure of the catalyst were observed. Moreover, FE-SEM and TEM images illustrated that the nanoparticles were still spherical in shape even after 5th cycle reuse (Figure S1e,f), and the mean diameter size of the recycled catalyst was 19 nm (Figure S1g).

The heterogeneous character of Fe₃O₄@CS-Co was checked by hot filtration. For this purpose, at half time of the reaction of iodobenzene in the presence of K₄[Fe(CN)₆]·3H₂O (4h approx.), the catalyst was isolated using an external magnetic field from the reaction mixture, and the reaction was then allowed to continue without any catalyst. No additional product formation was observed after 9 h, which clearly indicated the heterogeneous character of Fe₃O₄@CS-Co (Figure 9b). The heterogeneous character of Fe₃O₄@CS-Co was also evaluated after a poisoning test using S₈ as a metal trap. This test was conducted for the aforementioned model reaction in the presence of S₈ (0.05 g). No considerable changes were observed in the progress of the reaction (Figure 8).

Figure 8. XPS deconvolutions of (a) Fe₃O₄@CS-Co, (b) C 1s, and (c) cobalt.

| entry | catalyst (mol %) | source of CN | base | solvent | T (°C) | time (h) | yield (%) |
|-------|-----------------|--------------|------|---------|--------|----------|-----------|
| 1     | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 8        | 85        |
| 2     | 5               | KCN          | Et₃N | DMF     | 100    | 7        | 85        |
| 3     | 5               | Me₃SiCN      | Et₃N | DMF     | 100    | 24       | c         |
| 4     | 5               | Me₃SiCN      | Et₃N | DMF     | 75     | 5        | 50        |
| 5     | 5               | K₄Fe(CN)₆    | Et₃N | EtOH    | b      | 24       | c         |
| 6     | 5               | K₄Fe(CN)₆    | Et₃N | H₂O     | 90     | 3        | 35        |
| 7     | 5               | K₄Fe(CN)₆    | Et₃N | DMSO    | b      | 2        | 30        |
| 8     | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 25     | 7        | 37        |
| 9     | 5               | K₄Fe(CN)₆    | Et₃N | K₂CO₃   | DMF    | 100      | 6         | 42        |
| 10    | 5               | K₄Fe(CN)₆    | Et₃N | NaOEt   | DMF    | 100      | 6.5       | 32        |
| 11    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 9        | 73        |
| 12    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 10       | 64        |
| 13    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 24       | c         |
| 14    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 24       | 20        |

*Reaction conditions: iodobenzene (1 mmol), K₄Fe(CN)₆·3H₂O (1.5 mmol), Et₃N (4 mmol), and DMF (5 mL). Mean ± (1−6%) standard deviation (replicates = 4).

Table 2. Cyanation Reaction of Various Aryl Halides in the Presence of K₄Fe(CN)₆·3H₂O Catalyzed by Fe₃O₄@CS-Co.

| entry | Ar-X | K₄Fe(CN)₆·3H₂O | Fe₃O₄@CS-Co (5 mol%) | Ar-CN |
|-------|------|----------------|---------------------|-------|
| 1     | Ph   | I              | 8                   | 85    |
| 2     | 4-Cl | I              | 12                  | 72    |
| 3     | 4-(MeO)-C₆H₄ | I              | 10                  | 85    |
| 4     | Ph   | Br             | 9                   | 82    |
| 5     | 4-(NO₂)-C₆H₄ | Br             | 12                  | 73    |
| 6     | 4-(CN)-C₆H₄ | Br             | 12                  | 80    |
| 7     | 4-Me-C₆H₄ | Br             | 13                  | 64    |
| 8     | 4-F-C₆H₄ | Br             | 15                  | 68    |
| 9     | 3-pyridyl | Br             | 11                  | 85    |
| 10    | Cl   | 14             | 76                  |
| 11    | 4-(NO₂)-C₆H₄ | Cl             | 13                  | 65    |
| 12    | 4-(CN)-C₆H₄ | Cl             | 12                  | 71    |
| 13    | 4-Me-C₆H₄ | Cl             | 15                  | 60    |
| 14    | 4-(CHO)-C₆H₄ | Cl             | 24                  | 82    |

*Reaction conditions: 100 °C, iodobenzene (1 mmol), K₄Fe(CN)₆·3H₂O (1.5 mmol), Et₃N (4 mmol), and DMF (5 mL). Mean ± (1−6%) standard deviation (replicates = 4).

Table 1. Optimization of the Reaction Conditions for the Cyanation Reaction of Iodobenzene.

| entry | catalyst (mol %) | source of CN | base | solvent | T (°C) | time (h) | isolated yield (%) |
|-------|-----------------|--------------|------|---------|--------|----------|-------------------|
| 1     | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 8        | 85                |
| 2     | 5               | KCN          | Et₃N | DMF     | 100    | 7        | 85                |
| 3     | 5               | Me₃SiCN      | Et₃N | DMF     | 100    | 24       | c                 |
| 4     | 5               | Me₃SiCN      | Et₃N | DMF     | 75     | 5        | 50                |
| 5     | 5               | K₄Fe(CN)₆    | Et₃N | EtOH    | b      | 24       | c                 |
| 6     | 5               | K₄Fe(CN)₆    | Et₃N | H₂O     | 90     | 3        | 35                |
| 7     | 5               | K₄Fe(CN)₆    | Et₃N | DMSO    | b      | 2        | 30                |
| 8     | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 25     | 7        | 37                |
| 9     | 5               | K₄Fe(CN)₆    | Et₃N | K₂CO₃   | DMF    | 100      | 6                | 42                |
| 10    | 5               | K₄Fe(CN)₆    | Et₃N | NaOEt   | DMF    | 100      | 6.5               | 32                |
| 11    | 3               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 9        | 73                |
| 12    | 1               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 10       | 64                |
| 13    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 24       | c                 |
| 14    | 5               | K₄Fe(CN)₆    | Et₃N | DMF     | 100    | 24       | 20                |

*Reaction conditions: iodobenzene (1 mmol), cyanide source (1.5 mmol), base (4 mmol), and solvent (5 mL). †Under reflux conditions. Trace amount. ‡CoCl₂·4H₂O.
NaF was used as the base, just a trace amount of the product was produced (Table 3, entry 4). During the solvent screening (Table 3, entries 5–8), we found that the best result was obtained in DMF (Table 3, entry 2). The benchmark reaction was performed at different temperatures (Table 3, entries 9, 10), and the best catalytic activity was detected at 100 °C (Table 3, entry 2). The reaction was also studied using different catalyst loadings (Table 3, entries 11 and 12), concluding that the reaction proceeded with 2 mol % of the catalyst (Table 3, entry 12).

The generality of this protocol for the fluoride-free Hiyama reaction of a variety of substituted aryl halides and triethoxyphenylsilane under the optimized reaction conditions was investigated. As depicted in Table 4, various aryl halides (iodides, bromides, and chlorides) having electron-withdrawing groups reacted satisfactorily with triethoxyphenylsilane, and the desired products were obtained in 62–91% yields (Table 4, entries 1–9). Moreover, 1-chloro-4-iodobenzene, 1-bromo-4-chlorobenzene, and 1,4-diiodobenzene chemoselectively furnished 4-chlorobiphenyl and 4-iodobiphenyl as the only products in 74, 85, and 62% yields, respectively (Table 4, entries 10–12).

The recyclability of the catalyst (Fe$_3$O$_4$@CS-Co) was studied in the reaction of iodobenzene with triethoxyphenylsilane under optimized reaction conditions. After 3 h, the reaction mixture was cooled to ambient temperature, and the catalyst was isolated using an external magnet, washed with EtOAc and EtOH (2 × 10 mL), dried in vacuum, and recycled again. As exhibited in Figure S2, the catalyst was recycled in five consecutive runs without any important loss in activity.

The products in the present work have broad applications as fundamental building blocks in the synthesis of various molecules having different structures in numerous fields of chemistry such as pharmaceuticals and materials sciences. For instance, biaryl segments (products of Hiyama reaction) and aryl nitriles (products of cyanation reaction) are the common scaffold of a number of interesting drugs such as flurbiprofen (inflammatory agent), biphenyl-4-carboxylic acid hydrazide-

Table 4. Hiyama Cross-Coupling Reaction between Various Aryl Halides and Triethoxyphenylsilane Promoted by Fe$_3$O$_4$@CS-Co.

| entry | Ar-X | Ar’-Si(OT)$_3$ | Fe$_3$O$_4$@CS-Co (2 mol %) | Ar-Ar’ | Et$_3$N, 100 °C, DMF |
|-------|------|----------------|-----------------------------|--------|---------------------|
| 1     | Ph   | I              | 1                           | 3      | 91                  |
| 2     | 4-(MeO)-C$_6$H$_4$ | I             | 7                           | 74     |
| 3     | Ph   | Br             | 5                           | 90     |
| 4     | 4-(MeO)-C$_6$H$_4$ | Br           | 6                           | 85     |
| 5     | 4-(NO$_2$)-C$_6$H$_4$ | Br          | 4.5                         | 89     |
| 6     | 4-(CN)-C$_6$H$_4$ | Br           | 5                           | 88     |
| 7     | Ph   | Cl             | 7                           | 85     |
| 8     | 4-(NO$_2$)-C$_6$H$_4$ | Cl          | 6                           | 76     |
| 9     | 4-(CN)-C$_6$H$_4$ | Cl           | 6.5                         | 83     |
| 10    | 4-Cl-C$_6$H$_4$ | I             | 3                           | 74     |
| 11    | 4-Cl-C$_6$H$_4$ | Br           | 4                           | 85     |
| 12    | 4-I-C$_6$H$_4$ | I             | 7                           | 62     |

Reactions conditions: 1-chloro-4-iodobenzene (1.1 mmol), Et$_3$N (2 mmol), DMF (5 mL), and catalyst (2 mol %) at 100 °C. Mean ± (1–6%) standard deviation (number of replicates = 3).

(iodides, bromides, and chlorides) having electron-withdrawing and electron-donating groups reacted satisfactorily with triethoxyphenylsilane, and the desired products were obtained in 62–91% yields (Table 4, entries 1–9). Moreover, 1-chloro-4-iodobenzene, 1-bromo-4-chlorobenzene, and 1,4-diiodobenzene chemoselectively furnished 4-chlorobiphenyl and 4-iodobiphenyl as the only products in 74, 85, and 62% yields, respectively (Table 4, entries 10–12).

The products in the present work have broad applications as fundamental building blocks in the synthesis of various molecules having different structures in numerous fields of chemistry such as pharmaceuticals and materials sciences. For instance, biaryl segments (products of Hiyama reaction) and aryl nitriles (products of cyanation reaction) are the common scaffold of a number of interesting drugs such as flurbiprofen (inflammatory agent), biphenyl-4-carboxylic acid hydrazide-

Table 3. Optimization of the Reaction Conditions for Hiyama Cross-Coupling Reaction of Iodobenzene with Triethoxyphenylsilane

| entry | catalyst (mol %) | base | solvent | T (°C) | time (h) | yield (%) |
|-------|------------------|------|---------|--------|----------|-----------|
| 1     | 1                | NaOH | DMF     | 100    | 8        | 30        |
| 2     | 1                | Et$_3$N | DMF   | 100    | 4.5      | 73        |
| 3     | 1                | K$_2$CO$_3$ | DMF | 100    | 5        | c         |
| 4     | 1                | NaF  | DMF     | 100    | 6        | c         |
| 5     | 1                | Et$_3$N | EtOH | 100    | 4        | 45        |
| 6     | 1                | Et$_3$N | EtOAc | 100    | 5        | 33        |
| 7     | 1                | Et$_3$N | CH$_3$CN | 100   | 24       | c         |
| 8     | 1                | Et$_3$N | H$_2$O | 100    | 4.5      | 47        |
| 9     | 1                | Et$_3$N | DMF   | 50     | 5        | 33        |
| 10    | 1                | Et$_3$N | DMF | 100    | 7        | c         |
| 11    | 0.5              | Et$_3$N | DMF | 100    | 5        | 60        |
| 12    | 2                | Et$_3$N | DMF | 100    | 3        | 91        |

Isolated yield; reaction conditions: iodobenzene (1 mmol), triethoxyphenylsilane (1.1 mmol), base (2 mmol), and solvent (5 mL). Under reflux conditions. Trace amount of the product was obtained.
hydrazone (antimicrobial), letrozole as an inhibitor for the treatment of hormonally responsive breast cancer, and fadrozole monohydrochloride useful for the treatment of breast cancer (Scheme 2).32

3. CONCLUSIONS

In this paper, we have synthesized Co NPs immobilized on nanomagnetic chitosan (Fe3O4@CS-Co) and identified it using different techniques such as FT-IR, XRD, FE-SEM, EDX, TEM, TGA, VSM, XPS, and ICP–AES analysis. This catalyst was efficiently used as a new nanomagnetic heterogeneous cobalt catalyst in the cyanation reaction and in the fluorde-free Hiyama coupling between various substituted aryl chlorides, bromides, and iodides with K4[Fe(CN)6]·3H2O or triethoxyphenylsilane, respectively. The results of hot filtration and poisoning tests revealed that the catalyst was truly heterogeneous in nature. The catalyst was separated using an external magnet and recycled for at least five times without serious loss in activity. The use of an inexpensive cobalt catalyst instead of a high-cost palladium catalyst, without the employment of toxic ligands or fluoride ions, with K4[Fe(CN)6]·3H2O as an inexpensive cyanide source, the ease of recovery and reusability of the catalyst, and applicability of the method for large-scale usage are the main advantages of this protocol. It is worth to note that, in this paper, the cobalt catalyst has been used for the first time for the cyanation of arylhalides.

4. EXPERIMENTAL SECTION

4.1. General Procedure for the Synthesis of Magnetic Chitosan (Fe3O4@CS).33 A solution of chitosan (1 g) in acetic acid (100 mL, 2%) was sonicated for 0.5 h. Fe3O4 nanoparticles (1.7 g) were added to the sonicated solution and stirred for 1 h. Then, the mixture was neutralized by adding aqueous solution of NaOH (8 mL, 1.66 M) dropwise and stirred for 1 h at ambient temperature. The resulting Fe3O4@CS was separated using an external magnet, washed using H2O and EtOH (3 × 20 mL), and dried under vacuum at 60 °C.

4.2. General Procedure for the Synthesis of Fe3O4@CS-Co. Fe3O4@CS (1 g) was dispersed by sonication in H2O (25 mL). To this mixture, an aqueous solution of K4[Fe(CN)6]·3H2O (1.5 mmol), the aryl halide (1 mmol), and Et3N (2 mmol) in DMF (5 mL) and stirred at 100 °C. After the time indicated in Table 2, the reaction mixture was cooled to ambient temperature, and Fe3O4@CS-Co was isolated using an external magnet, washed with H2O and EtOH (2 × 10 mL), dried in vacuum, and recycled again. The purification of the product was done by column chromatography on silica gel using n-hexane/EtOAc (6:1) as the eluent.

4.4. General Procedure for the Hiyama Cross-Coupling Reaction of Aryl Halides with Triethoxyphenylsilane Catalyzed by Fe3O4@CS-Co. Fe3O4@CS-Co (2 mol %) was added to a mixture containing triethoxyphenylsilane (1.1 mmol), aryl halide (1 mmol), and Et3N (2 mmol) in DMF (5 mL), and the mixture was stirred at 100 °C. After the time indicated in Table 4, the reaction mixture was cooled to ambient temperature, and Fe3O4@CS-Co was isolated using an external magnet, washed with EtOAc and EtOH (2 × 10 mL), dried under vacuum, and recycled again. The purification of the product was done by column chromatography on silica gel using n-hexane/EtOAc (50:1) as the eluent.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01002.

General information on the instruments, analysis of the reused catalyst, and 1H NMR and 13C NMR spectra of the products (PDF)

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Notes

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REFERENCES

(1) (a) Sokolová, R.; Hromadová, M.; Fiedler, J.; Pospíšil, L.; Giannarelli, S.; Valášek, M. Reduction of substituted benzotriazole pesticides. J. Electroanal. Chem. 2008, 622, 211−218. (b) Patel, A. B.; Chikhalia, K. H.; Kumari, P. Facile synthesis of benzotriazole/nicotinitriole based s-triazines as new potential antimycobacterial agents. Eur. J. Med. Chem. 2014, 79, 57−65. (c) Fouda, A. S.; El-Azaly, A. H.; Awad, R. S.; Ahmed, A. M. New benzotriazole azo Dyes as corrosion inhibitors for carbon steel in hydrochloric acid solutions. Int. J. Electrochem. Sci. 2014, 9, 1117−1131. Anbarasan, P.; Neumann, H.; Beller, M. A novel and convenient synthesis of benzotriazoles: electrophilic cyanation of aryl and heteroaryl bromides. Chem. Eur. J. 2011, 17, 4217−4222.

(2) Yan, G.; Zhang, Y.; Wang, J. Recent advances in the synthesis of aryl nitrile compounds. Adv. Synth. Catal. 2017, 359, 4068−4105.

(3) (a) Rapolu, C. R.; Panja, K. R. Highly selective V-P-O/Al₂O₃ catalysts in the ammoniation of toluene to benzonitrile. J. Chem. Soc., Chem. Commun. 1993, 1157−1158. (b) Koelsch, C. F.; Whitney, A. G. The Rosenmund-von Braun nitrile synthesis. J. Org. Chem. 1941, 06, 795−803. (c) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovski, P. V. Catalytic Sandmeyer cyanation as a synthetic pathway to aryl nitriles. J. Organomet. Chem. 2004, 689, 3810−3812.

(4) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. A mild and efficient palladium-catalyzed cyanation of aryl chlorides with K₄[Fe(CN)₆] catalyzed by encapsulated palladium nanoparticles in polyurethane nanosponge (Pd-CD-PU-NS): An efficient catalyst for Hiyama reaction in fluoride-free condition. Tetrahedron Lett. 2015, 56, 175−178.

(5) (a) Khajeh Dangolani, S.; Sharifat, S.; Panahi, F.; Khalafi-Nezhad, A. Immobilized palladium nanoparticles on a cyclodextrin−catalyzed cyanide-free cyanation of aryl halide by using formamide as a cyanide source. Tetrahedron Lett. 2015, 56, 175−178. (b) Nakamura, Y.; Kawamura, T.; Uehara, T.; Matsuda, M. An efficient palladium-catalyzed cyanation of aryl chlorides with K₄[Fe(CN)₆]− catalyzed by encapsulated palladium nanoparticles in bioguanidine-chitosan matrix as core-shell recyclable heterogeneous nanocatalyst. Polycrystal 2019, 159, 212−216. (b) Karimi, B.; Vafaeezadeh, M.; Akhavan, P. F. Heterocyclic Carbene-Pd Polymers as Reusable Precatalysts for Cyanation and Ullmann Homocoupling of Aryl Halides: The Role of Solvent in Product Distribution. ChemCatChem 2015, 7, 2248−2254. (12) Ganapathy, D.; Ratha, S. S.; Sekar, G. Stable palladium nanoparticles catalyzed synthesis of benzotriazoles K₄[Fe(CN)₆] catalyzed by encapsulated palladium nanoparticles in acetonitrile via C−N bond cleavage assisted by 1,4-bis(trimethylsilyl)−2,3,5,6-tetramethyl−1,4-dihydropryrazine. J. Chem. Soc., Chem. Commun. 1999, 648−651.

(6) (a) Khajeh Dangolani, S.; Sharifat, S.; Panahi, F.; Khalafi-Nezhad, A. Immobilized palladium nanoparticles on a cyclodextrin−catalyzed cyanide-free cyanation of aryl halide by using formamide as a cyanide source. Tetrahedron Lett. 2015, 56, 175−178. (b) Nakamura, Y.; Kawamura, T.; Uehara, T.; Matsuda, M. An efficient palladium-catalyzed cyanation of aryl chlorides with K₄[Fe(CN)₆]− catalyzed by encapsulated palladium nanoparticles in bioguanidine-chitosan matrix as core-shell recyclable heterogeneous nanocatalyst. Polycrystal 2019, 159, 212−216. (b) Karimi, B.; Vafaeezadeh, M.; Akhavan, P. F. Heterocyclic Carbene-Pd Polymers as Reusable Precatalysts for Cyanation and Ullmann Homocoupling of Aryl Halides: The Role of Solvent in Product Distribution. ChemCatChem 2015, 7, 2248−2254. (12) Ganapathy, D.; Ratha, S. S.; Sekar, G. Stable palladium nanoparticles catalyzed synthesis of benzotriazoles K₄[Fe(CN)₆] catalyzed by encapsulated palladium nanoparticles in acetonitrile via C−N bond cleavage assisted by 1,4-bis(trimethylsilyl)−2,3,5,6-tetramethyl−1,4-dihydropryrazine. J. Chem. Soc., Chem. Commun. 1999, 648−651.
Fakhri, A. Heterogeneous Fe\textsubscript{3}O\textsubscript{4}@chitosan-Schiff base Pd nanocatalyst for the Suzuki-Miyaura and Heck-Mizoroki cross-coupling reactions. \textit{Green Chem.} 2017, 19, 5625–5641.

(19) (a) Nasir Baig, R. B.; Varma, R. S. Organic synthesis via magnetic attraction: benign and sustainable protocols using magnetic nanoferrites. \textit{Green Chem.} 2013, 15, 398–417. (b) Hudson, R.; Feng, Y.; Varma, R. S.; Moores, A. Bare magnetic nanoparticles: sustainable synthesis and applications in catalytic organic transformations. \textit{Green Chem.} 2014, 16, 4493–4505. (c) Reddy, L. H.; Arias, J. I.; Nicolas, J.; Couvreur, P. Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications. \textit{Chem. Rev.} 2012, 112, 5818–5878. (d) Laurent, S.; Forge, D.; Port, M.; Roch, A.; Kobic, C.; Vander Elst, L.; Muller, R. N. Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications. \textit{Chem. Rev.} 2008, 108, 2064–2110.

(20) Wang, L.; Park, H.-Y.; Lim, S.-I.; Schadt, M. J.; Mott, D.; Luo, J.; Wang, X.; Zhong, C.-J. Core@shell nanomaterials: Gold-coated magnetic oxide nanoparticles. \textit{J. Mater. Chem.} 2008, 18, 2629–2635.

(21) Stjern Dahl, M.; Andersson, M.; Hall, H. E.; Pajerowski, D. M.; Meisel, M. W.; Duran, R. S. Superparamagnetic Fe\textsubscript{3}O\textsubscript{4}/SiO\textsubscript{2} nanocomposites: Enabling the tuning of both the iron oxide load and the size of the nanoparticles. \textit{Langmuir} 2008, 24, 3532–3536.

(22) Xu, L.; Zhang, W.; Ding, Y.; Peng, Y.; Zhang, S.; Yu, W.; Qian, Y. Formation, characterization and magnetic properties of Fe\textsubscript{3}O\textsubscript{4} nanowires encapsulated in carbon microtubes. \textit{J. Phys. Chem. B} 2004, 108, 10859–10862.

(23) Berry, C. C.; Wells, S.; Charles, S.; Curtis, A. S. G. Dextran and albumin derivatised iron oxide nanoparticles: influence on fibroblasts in vitro. \textit{Biomaterials} 2003, 24, 4551–4557.

(24) (a) Guo, T.-Y.; Xia, Y.-Q.; Wang, J.; Song, M.-D.; Zhang, B.-H. Chitosan beads as molecularly imprinted polymer matrix for selective separation of proteins. \textit{Biomaterials} 2005, 26, 5737–5745. (b) Baran, T.; Mentes, A. Microwave assisted synthesis of biaryl by C-C coupling reactions with a new chitosan supported Pd (II) catalyst. \textit{J. Mol. Struct.} 2006, 1122, 111–116.

(25) (a) Liang, Y.-Y.; Zhang, L.-M. Bioconjugation of papain on superparamagnetic nanoparticles decorated with carboxymethylated chitosan. \textit{Biomacromolecules} 2007, 8, 1480–1486. (b) Sinha, V. R.; Singha, A. K.; Wadhawan, S.; Kaushik, R.; Kumria, R.; Bansal, K.; Dhawan, S. Chitosan microspheres as a potential carrier for drugs. \textit{Int. J. Pharm.} 2004, 274, 1–33.

(26) (a) Ayati, A.; Heravi, M. M.; Daraei, M.; Tanhaei, B.; Bamoharram, F. F.; Sillanpaa, M. H.PMo\textsubscript{12}O\textsubscript{40} immobilized chitosan/Fe\textsubscript{3}O\textsubscript{4} as a novel efficient, green and recyclable nanocatalyst in the synthesis of pyrano-pyrazole derivatives. \textit{J. Iran. Chem. Soc.} 2016, 13, 2301–2308. (b) Shaabani, A.; Borjani Boroujeni, M.; Laeini, M. S. Copper(II) supported on magnetic chitosan: a green nanocatalyst for the synthesis of 2,4,6-triaryl pyridines by C-N bond cleavage of benzylamines. \textit{RSC Adv.} 2016, 6, 27706–27713. (c) Naghipour, A.; Fakhri, A. Heterogeneous Fe\textsubscript{3}O\textsubscript{4}/chitosan-Schiff base Pd nano-catalyst: Fabrication, characterization and application as highly efficient and magnetically-recoverable catalyst for Suzuki-Miyaura and Heck-Mizoroki C-C coupling reactions. \textit{Catal. Commun.} 2016, 73, 39–45. (d) Hajipour, A. R.; Tavangar-Rizi, Z. Methionine-functionalized chitosan-Pd(0) complex: A novel magnetically separable catalyst for Heck reaction of aryl iodide and aryl bromides at room temperature in water as only solvent. \textit{Appl. Organomet. Chem.} 2017, 31, e3638–e3645. (e) Chetta, M.; Ali, A. A.; Bhuyan, D.; Saikia, L.; Sarma, D. Magnetically recoverable chitosan-stabilised copper-iron oxide nanocomposite material as an efficient heterogeneous catalyst for azide-alkyne cycloaddition reactions. \textit{New J. Chem.} 2015, 39, 5902–5907.

(27) (a) Sobhani, S.; Vahidi, Z.; Zeraatkar, Z.; Khodadadi, S. A pd complex of a NNN pincer ligand supported on γ-Fe\textsubscript{3}O\textsubscript{4}/SiO\textsubscript{2} as the first magnetically recoverable heterogeneous catalyst for C-P bond forming reactions. \textit{RSC Adv.} 2015, 5, 36552–36559. (b) Sobhani, S.; Habibollahi, A.; Zeraatkar, Z. A novel water-dispersible/magnetically recyclable Pd catalyst for C-C cross-coupling reactions in pure water. \textit{Org. Process Res. Dev.} 2019, 23, 1321–1332. (c) Sobhani, S.; Chakhrami, F. O.; Sansano, J. M. A new bifunctional heterogeneous nanocatalyst for one-pot reduction-Schiff base condensation and reduction-carbonylation of nitroarenes. \textit{RSC Adv.} 2019, 9, 1362–1372.