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Article

Palladium Nanoparticles Supported on β-Cyclodextrin Functionalized Poly(amidoamine)s and Their Application in Suzuki-Miyaura Cross-Coupling Reactions

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Herein, the synthesis, characterization and catalytic application of an organic-inorganic, palladium (Pd)-containing hybrid material, poly(amidoamine)-cyclodextrin (Pd@PAAs-CD), is reported as an efficient catalyst for Suzuki-Miyaura coupling reactions. The structure of Pd@PAAs-CD was confirmed by Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), scanning electron microscopy (SEM), inductively-coupled plasma atomic emission spectroscopy (ICP-AES), and ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Furthermore, an efficient protocol has been developed using Pd@PAAs-CD as the catalyst in a Suzuki-Miyaura cross-coupling reaction in an aqueous medium in high yields. By using cyclodextrin (CD) as the mediator grafted onto PAAs, the Pd nanoparticles (NPs) were dispersed and enhanced the catalytic reaction by promoting host-guest interactions with the CD. In addition, the reusability of the Pd@PAAs-CD hybrid material is demonstrated for use in multiple sequential cross-coupling reactions.

Keywords: β-cyclodextrin, catalysis, palladium nanoparticles, Suzuki-Miyaura cross coupling, poly(amidoamine)

Introduction

Over the past several decades, palladium-catalyzed cross-coupling reactions have become one of the most extensive and universal synthetic tools for the construction of C–C bonds in organic synthesis.[1-7] In particular, palladium-catalyzed Suzuki-Miyaura reactions have several demonstrated advantages, including mild reaction conditions, readily-available organic boron reagents, and tolerance of a variety of functional groups.[8,9] In particular, aryl-aryl Suzuki-Miyaura cross coupling reactions are increasingly employed in the total synthesis of complex natural products[10,11] and certain drug compounds.[12] Macrocyclic supramolecules, such as crown ethers, CD (cyclodextrin), and calixarenes possess unique and size-tunable cavities that exhibit interesting properties. CD is a water-soluble, nontoxic organic macrocycle that is comprised of D-(+)-glucopyranose units (including α-, β-, and γ-CD).[13-15] β-CD is the most widely-used of these macrocyclic compounds since it has a suitable cavity size and economical price.[16-21] In recent years, organic-inorganic hybrid materials have attracted an increasing amount of attention from scientists.[22-26] Organic-inorganic hybrid materials based on CD and noble metal nanoparticles have been widely researched and have shown applications in areas such as catalysis, small-molecule and gas detection, self-assembly, gene delivery, and as photoinitiators.[27-32]

Putta *et al.*[33] reported the use of palladium nanoparticles (Pd NPs)-β-CD-graphene nanosheets (Pd@CD-GNS) as the catalyst for C–C coupling reactions and showed that this material exhibited excellent catalytic activity and dispersibility in water. Kaboudin *et al.*[34] studied the preparation and catalytic activity of a novel Pd^{II}-β-CD complex in Suzuki-Miyaura coupling reactions. In addition, Gruttadauria and co-workers[35] developed synthetic nanoparticle hybrids composed of poly(amidoamine) dendrimers and palladium (SWCNT-PAMAM 3.0-Pd) for the heterogeneous catalysis of Suzuki-Miyaura reactions. Monflier and co-workers[36] designed ruthenium-containing β-cyclodextrin polymer globules that were applied to catalyze the hydrogenation of biomass-derived furanic compounds.

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In this paper, a simple and environmentally-friendly synthetic route is reported for the formation of Pd NPs via the direct reduction of $Pd(OAc)_2$ by poly(amido amine)s-CD (PAAs-CD) and $NaBH_4$ under mild reaction conditions. Since β-CD is a water-soluble macrocycle, the addition of this compound allowed the Pd NPs to be evenly dispersed within the organic-inorganic hybrid materials. The structures of the synthesized Pd@PAAs-CD hybrids were confirmed using FTIR (Fourier transform infrared) spectroscopy, TEM (transmission electron microscopy), SEM (scanning electron microscopy), ICP-AES (inductively coupled plasma atomic emission spectroscopy), and ^{1}H NMR (nuclear magnetic resonance) spectroscopy. The hybrid material Pd@PAAs-CD exhibited excellent catalytic activity for Suzuki-Miyaura cross coupling reactions involving a diverse array of aryl halides in H_2O. Furthermore, selectivity experiments and the reusability of Pd@PAAs-CD were also studied in this paper.

Experimental

Materials

β-CD, palladium diacetate, ethanediamine, phenylboronic acid, and aryl halides were purchased from Adamas (China) and used without further purification. All experiments were carried out under argon atmosphere using standard Schlenk techniques. Solvents were used without further purification, and deionized water was used throughout the experiments.

Procedure for the preparation of PAAs-CD

PAAs based on mecysteine were prepared by the reaction of *N*,*N*-methylene bis(acrylamide) (MBA) and L-cysteine methyl ester hydrochloride (L-cys), by a procedure based on previous work.[37] The polymerization was carried out under argon atmosphere, and a typical procedure is as follows: L-cys (0.25 g, 1.5 mmol) was added to a mixture (6 mL, the volume ratio of water and dimethyl sulfoxide (DMSO) was 1:5) containing MBA (0.45 g, 3.0 mmol). The polymerization was performed at 60 °C with vigorous stirring for 36 h, when an excess of ethanediamine-CD (EDC-CD) 1.2 eq. *per* MBA was added, and the reaction was continued for an additional 36 h. After this time, the solution was concentrated via rotary evaporation, and the resulting residue was precipitated into a 100 mL mixture of cold acetone/ether (5:1, v:v) with stirring. The crude product was further purified by re-precipitation from distilled water and acetone. Then, the product was dialysed (molecular cut off: 3.5 kD) for 48 h (water changed every 12 h). PAAs-CD was obtained by lyophilization and obtained in 87% yield.

EDC-CD

^{1}H NMR (500 MHz, D_2O-d_2) δ 2.74 (s, 2H), 2.79 (s, 2H), 3.50-3.65 (d, 14.3H), 3.90 (d, 28.0H), 5.05 (s, 7.2H).

PAAs-CD

^{1}H NMR (500 MHz, DMSO-d_6) δ 0.74 (s, 4.9H), 1.14 (s, 8.5H), 2.30-2.87 (m, 13.0H), 4.43 (d, 4H), 4.8 (s, 5H), 5.59 (s, 2.4H), 6.20 (d, 2.8H), 8.50-8.68 (d, 3.7H).

Procedure for the preparation of Pd@PAAs-CD

The synthesis of Pd@PAAs-CD is described as follows: 100 mg of PAAs-CD was dispersed into 10 mL DMSO and stirred at 50 °C, and then 60 mg of $Pd(OAc)_2$ was added. The mixture was vigorously stirred, and the $NaBH_4$ solution was added to promote the formation of Pd NPs, with continuous stirring for 18 h. Pd@PAAs-CD precipitated from the solution upon addition of a mixture of acetone/ether (5:1, v:v). Pd@PAAs-CD was obtained via centrifugation (6500 rpm × 3) and was then washed three times with water and then lyophilized for 24 h (80% yield). ICP-AES analysis was performed and showed that the palladium content of Pd@PAAs-CD catalyst was 10.77 wt.%.

Suzuki-Miyaura cross-coupling reaction

A mixture of aryl halide (0.25 mmol), phenylboronic acid (0.3 mmol), Na_2CO_3 (0.25 mmol), PPh_3 (0.025 mmol) and Pd@PAAs-CD (0.5 mg, 0.2 mol% Pd *per* mol of aryl halide) were placed into a 10 mL Schlenck tube with 1 mL H_2O. The reaction mixture was reacted at 80 °C for 18 h, and the reaction progress was monitored via gas chromatography mass spectrometry (GC-MS). The reaction mixture was allowed to cool to room temperature, and then 3 mL water was added, and the product was extracted with ethyl acetate (3 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4 and solvents were evaporated via rotary evaporator. The crude product was purified by column chromatography (200-300 mesh silica) using a mixture of petroleum ether/ethyl acetate (10:1, v:v) as eluent. The structures of the products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopies.

Spectral data for coupling products

Compound **3a**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, 3H, *J* 6.9 Hz, $OCH_2\underline{CH_3}$), 4.01 (q, 2H, *J* 6.9 Hz, $O\underline{CH_2}CH_3$),

7.42 (t, 2H, *J* 7.6 Hz, CH_2), 7.53 (d, 2H, *J* 8.5 Hz, CH_2), 7.56 (m, 5H, Ph–H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.91, 63.55, 114.80, 115.05, 126.73, 128.14, 128.74, 132.10, 132.17, 140.89, 158.54.

Compound **3b**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, 1H, *J* 7.5 Hz, CH), 6.83 (t, 1H, *J* 7.9 Hz, CH), 7.13 (m, 2H, CH_2), 7.35 (m, 1H, CH), 7.45 (m, 4H, CH_2).

Compound **3c**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H, OCH_3), 6.83 (m, 1H, CH), 7.15 (m, 2H, CH_2), 7.27 (m, 2H, CH_2), 7.38 (m, 2H, CH_2), 7.55 (m, 2H, CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.31, 112.69, 112.92, 119.70, 127.21, 127.42, 128.74, 129.75, 141.12, 142.81, 159.96.

Compound **3d**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, 2H, *J* 8.2 Hz, CH_2), 7.18 (m, 1H, CH), 7.34 (m, 4H, CH_2), 7.46 (d, 4H, *J* 7.3 Hz, CH_2).

Compound **3e**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H, Ar), 7.47 (t, 4H, *J* 7.3 Hz, Ar), 7.70-7.66 (d, 4H, *J* 7.5 Hz, Ar), 7.66 (s, 4H, Ar).

Compound **3f**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* 8.2 Hz, Ar), 7.19 (m, 1H, Ar), 7.35 (m, 4H, Ar), 7.47 (d, 4H, *J* 7.3 Hz, Ar).

Compound **3g**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 2H, CH_2), 6.90-6.71 (d, 2H, *J* 7.8 Hz, Ar), 7.16-7.12 (d, 2H, *J* 7.2 Hz, Ar), 7.16-7.17 (m, 1H, Ar), 7.22-7.26 (t, 2H, *J* 7.5 Hz, Ar), 7.30-7.35 (d, 2H, *J* 8.3 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 41.34, 119.98, 126.35, 128.61, 128.90, 130.70, 131.55, 140.14, 140.48.

Compound **3h**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (q, 1H, *J* 7.2 Hz, Ar), 7.50 (t, 2H, *J* 7.4 Hz, Ar), 7.62 (d, 2H, *J* 7.2 Hz, Ar), δ 7.74 (q, 2H, *J* 8.7 Hz, Ar), 8.29 (d, 2H, *J* 8.3 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 124.13, 127.40, 127.80, 128.94, 129.18, 128.68, 138.79, 147.65.

Compound **3i**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, 1H, *J* 7.2 Hz, Ar), 7.41 (m, 4H, Ar), 7.54 (m, 4H, Ar).

Compound **3j**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (q, 1H *J* 7.3 Hz, Ar), 7.48 (t, 2H *J* 7.4 Hz, Ar), 7.58 (d, 2H, *J* 7.3 Hz, Ar), 7.69 (d, 4H *J* 8.4 Hz, Ar), 7.78 (d, 4H *J* 21.6, 8.4 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 110.92, 118.96, 127.25, 127.75, 128.65, 129.13, 132.62, 133.68, 138.54, 139.19, 145.69.

Compound **3l**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 6.99 (d, 2H, *J* 8.5 Hz, Ar), 7.30 (t, 1H, *J* 7.4 Hz, Ar), 7.42 (t, 2H, *J* 7.5 Hz, Ar), 7.56 (t, 4H, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.36, 114.22, 126.67, 126.76, 128.17, 128.73, 133.80, 140.85, 159.16.

Compound **3m**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, 2H, *J* 8.4 Hz, Ar), 7.35 (t, 1H, *J* 7.2 Hz, Ar), 7.44 (t, 2H, *J* 7.4 Hz, Ar), 7.55 (d, 4H, *J* 7.0 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 115.55, 115.72, 127.05, 127.19, 127.28, 128.68, 128.74, 128.84, 137.35, 140.28, 161.51, 163.47.

Compound **4a**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (t, 3H, *J* 6.9 Hz, $OCH_2\underline{CH_3}$), 4.06 (q, 2H, *J* 6.9 Hz, $O\underline{CH_2}CH_3$), 6.97 (d, 2H, *J* 8.2 Hz, Ar), 7.38 (d, 2H, *J* 8.2 Hz, Ar), 7.46 (d, 4H, *J* 7.8 Hz, Ar).

Compound **4c**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H, *J* 6.9 Hz, OCH_3), 6.92 (m, 1H, Ar), 7.08 (s, 1H, Ar), 7.15 (d, 1H, *J* 7.6 Hz, Ar), 7.37 (t, 1H, *J* 7.9 Hz, Ar), 7.44 (d, 2H, *J* 8.4 Hz, Ar), 7.60 (d, 2H, *J* 8.5 Hz, CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.34, 112.83, 112.93, 119.50, 128.45, 128.90, 128.92, 133.52, 139.54, 141.52, 160.03.

Compound **4d**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (br, 2H, NH_2), 6.68 (d, *J* 8.2 Hz, Ar), 7.29 (t, 4H, *J* 9.2 Hz, Ar), 7.37 (d, 2H, *J* 8.5 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 115.43, 116.74, 127.60, 127.89, 128.78, 130.26, 132.04, 132.17, 139.63, 146.13.

Compound **4f**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 2H, NH_2), 6.68 (d, 2H, *J* 8.2 Hz, Ar), 7.29 (t, 4H, *J* 9.2 Hz, Ar), 7.37 (d, 2H, *J* 8.5 Hz, Ar).

Compound **4i**

White solid; ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.41 (d, 4H, *J* 8.5 Hz, Ar), 7.46 (d, 4H, *J* 8.4 Hz, Ar); ^{13}C NMR

(500 MHz, $CDCl_3$) δ 116.67, 126.23, 129.06, 129.48, 133.76, 128.14.

Compound **4l**

White solid; ^{1}H NMR (500 MHz,$CDCl_3$) δ 3.83 (s, 3H, OCH_3) 6.80-6.95 (t, 2H, *J* 8.5 Hz, Ar), 7.31 (d, 2H, *J* 8.3 Hz, Ar), 7.53 (t, 4H, *J* 8.2 Hz, Ar).

Compound **4p**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 4H, *J* 8.5 Hz, Ar), 7.46 (t, 4H, *J* 8.4 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 116.67, 128.23, 129.06, 129.48, 133.76, 138.44.

Compound **4s**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J* 8.2 Hz, Ar), 7.54 (d, 2H, *J* 8.3 Hz, Ar), 7.61 (t, 1H, *J* 7.7 Hz, Ar), 7.81 (d, 1H, *J* 7.6 Hz, Ar), 7.86 (d, 1H, *J* 8.5 Hz, Ar), 8.06 (s, 1H, Ar), 10.8 (s, 1H, CHO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 116.70, 127.84, 128.40, 129.20, 129.65, 132.86, 134.27, 137.00, 138.14, 140.97, 192.21.

Compound **5b**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (t, 3H, *J* 6.9 Hz, $OCH_2\underline{CH_3}$), 4.07 (t, 2H, *J* 6.9 Hz, $O\underline{CH_2}CH_3$), 6.99 (d, 2H, *J* 8.7 Hz, Ar), 7.51 (d, 2H, *J* 8.7 Hz, Ar), 7.64 (d, 2H, *J* 8.2 Hz, Ar), 7.67 (d, 2H, *J* 8.2 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.81, 63.63, 110.05, 115.08, 119.13, 127.08, 128.33, 132.57, 132.90, 145.28, 159.62.

Compound **5c**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (3, 3H, OCH_3), 6.95-6.87 (m, 1H, Ar), 7.10 (s, 1H, Ar), 7.17 (d, 1H, *J* 8.2 Hz, Ar), 7.17 (t, 1H, *J* 7.9 Hz, Ar), 7.68 (d, 2H, *J* 8.8 Hz, Ar), 7.70 (d, 2H, *J* 7.9 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.40, 113.11, 113.91, 119.68, 127.81, 130.19, 132.58, 140.66, 145.56, 160.15.

Compound **5d**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, 2H, *J* 7.8 Hz, Ar), 7.43 (d, 2H, *J* 7.8 Hz, Ar), 7.62 (d, 2H, *J* 8.2 Hz, Ar), 7.65 (d, 2H, *J* 8.2 Hz, Ar).

Compound **5f**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, 2H, *J* 7.8 Hz, Ar), 7.44 (d, 2H, *J* 7.8 Hz, Ar), 7.64 (d, 2H, *J* 8.2 Hz, Ar), 7.64 (d, 2H, *J* 8.2 Hz, Ar).

Compound **5g**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 1H, Ar), 7.71 (d, 2H, *J* 8.2 Hz, Ar), 7.75 (d, 2H, *J* 8.6 Hz, Ar), 7.84 (d, 1H, J 7.9 Hz, Ar), 7.91 (d, 1H, *J* 7.6 Hz, Ar), 8.10 (s, 1H, Ar), 10.09 (s, 1H, CHO); ^{13}C NMR (500 MHz, $CDCl_3$) δ 111.83, 118.01, 127.83, 127.94, 129.92, 130.12, 132.82, 132.90, 132.98, 137.15, 140.17, 144.15, 191.78.

Compound **5j**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 4H, *J* 8.2 Hz, Ar), 7.77 (d, 4H, *J* 8.2 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 112.46, 116.07, 127.95, 132.59, 143.54.

Compound **5l**

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H, OCH_3), δ 7.01 (d, 2H, *J* 8.8 Hz, Ar), 7.54 (d, 2H, *J* 8.6 Hz, Ar), 7.64 (d, 2H, *J* 8.5 Hz, Ar), 7.68 (d, 2H, *J* 8.5 Hz, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.4, 110.1, 114.5, 119.1, 127.1, 128.3, 131.5, 132.5, 145.2, 160.2.

Catalyst characterizations

^{1}H NMR and ^{13}C NMR (500 MHz) spectra were recorded using a Bruker DMX-500 spectrometer (Switzerland). GC-MS data was obtained using a GC-MS QP2010-SE (Japan). The FTIR spectra were measured with a Nicolet FTIR spectrophotometer (USA) using KBr pellets in the spectral range 4000-400 cm^{-1}. TEM experiments were performed on a JEOL 200CX (Japan), and SEM was measured using a JEOL LTD JSM-7500F (Japan). The Pd content of the samples was determined quantitatively by ICP-AES using a Thermo-Fisher Scientific iCAP 6300 instrument (England). Reagents were used without further purification, and deionized water was used throughout the experiments.

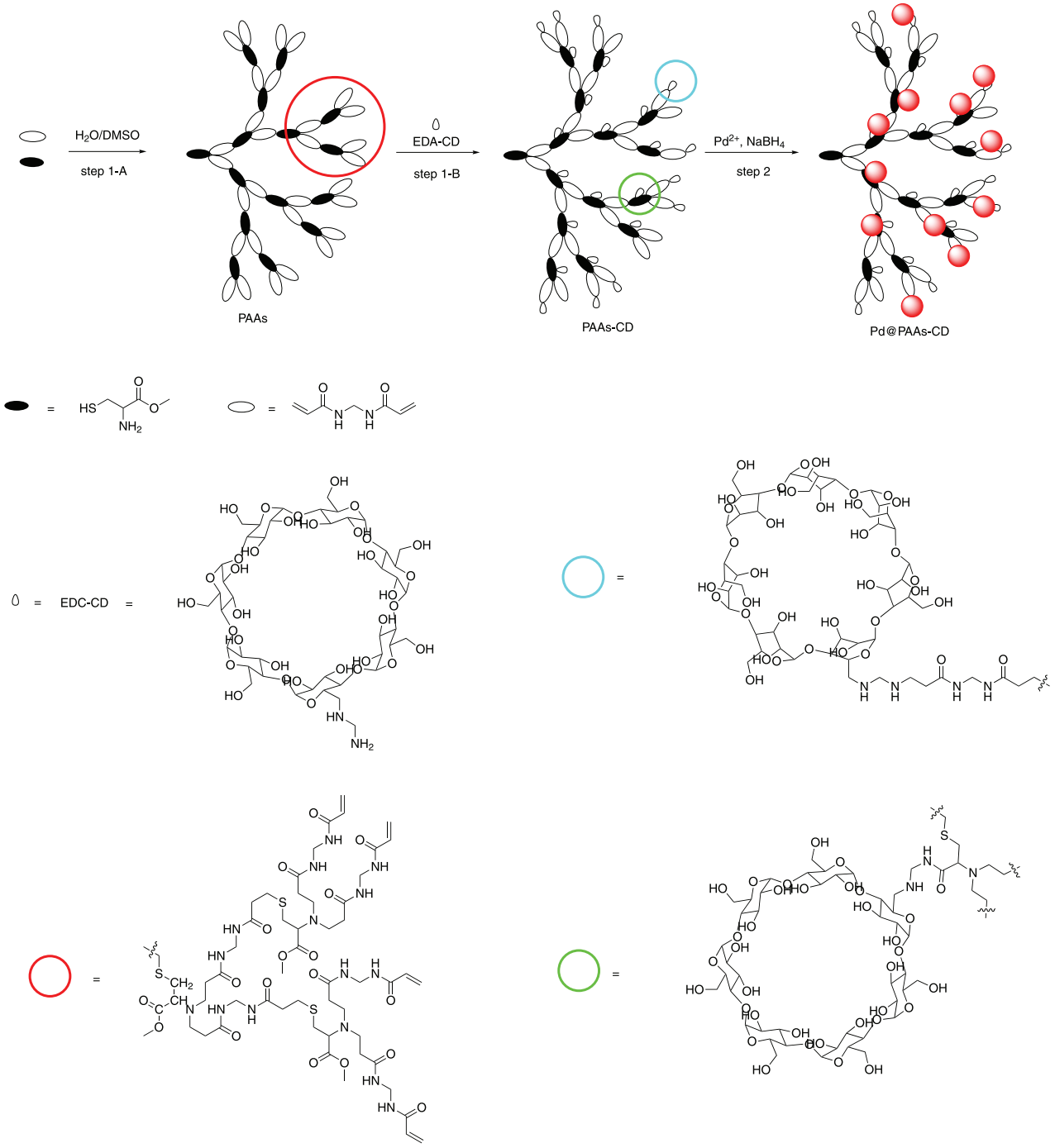
Results and Discussion

Synthesis of Pd@PAAs-CD

The experiment is divided into two parts: step 1 and step 2 (Scheme 1). The first step is a two-step (step 1-A and step 1-B), one-pot reaction. PAAs-CD was prepared via poly-condensation of MBA and L-cys in a 2:1 molar ratio (step 1-A) and then modified with excess ECD-CD (step 1-B). In step 1-A, MBA and L-cys reacted via a Michael polymerization to form branched PAAs, and the intermediate (PAAs) of the first step contained many olefin ends. The red circle is a zoom-in on its basic structure. In step 1-B, ECD-CD was added to aminate the PAAs. In the blue and green circles, the structure of the ECD-CD-loaded PAA is magnified. The CD binds to PAA through both Michael addition and carbonyl substitution. In step 2,

PAAs-CD was dispersed in DMSO, and then $Pd(OAc)_2$ was added. The mixture was continually stirred, and a solution of $NaBH_4$ was added to promote the formation of Pd NPs. A precipitate containing Pd@PAAs-CD formed upon addition of a mixture of acetone and ether, which was then washed with water to give Pd@PAAs-CD. This precipitate was lyophilized to obtain Pd@PAAs-CD.

To verify the structure of the catalyst, a series of characterization experiments was performed. FTIR spectra of the Pd@PAAs-CD catalyst, EDC-CD, and PAAs are shown in Figure 1. In the PAAs sample, the absorption peaks at 3490, 3322, 3180 and 2870 cm^{-1} are due to N–H stretching vibrations from secondary amines, the N–H stretching vibration of acid amides, and the C–H stretching vibrations, respectively. The weak absorption peak located near 2450 cm^{-1} is attributed to the C–S bond. The FTIR data further confirmed the existence of PAAs and CD in the hybrid material Pd@PAAs-CD.



Scheme 1. Synthesis of Pd@PAAs-CD.

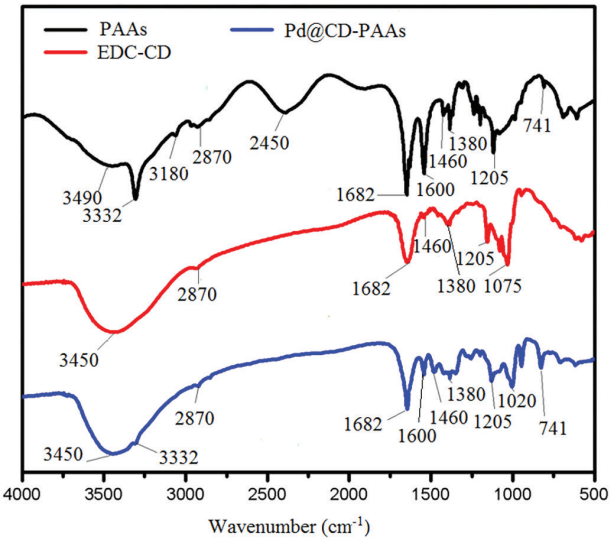


Figure 1. FTIR spectra of (a) PAAs (black) and (b) EDC-CD (red), (c) Pd@PAAs-CD (blue).

Figure 2a shows the TEM image of CD-PAAs before Pd NPs loading, and Figure 2b shows the TEM image of Pd@PAAs-CD that demonstrates the even dispersion of the Pd NPs onto the 10-15 nm PAAs-CD. The SEM image of Pd@PAAs-CD is shown in Figure 2c, which shows that the morphology of the Pd NPs has a globular radius of 10 nm, indicating that the Pd NPs were uniformly dispersed onto the PAAs-CD.

Pd@PAAs-CD exhibited good dispersion and stability in water because of the introduction of CD, which also improved the uniformity of the Pd NPs. The catalyst showed excellent catalytic activity in C–C coupling reactions, likely due to the dispersibility of the Pd@PAAs-CD, which contained a variety of functional groups with lower catalyst loadings (Pd 0.2 mol%) (Table 1, entries 1-10). After screening different bases, it was found that Na_2CO_3 gave the best yield (92%), with Cs_2CO_3 giving a yield of 44%, while K_3PO_4 resulted in a yield of 78% (Table 1, entries 1, 5, 10). The reaction between 4-bromophenetole and phenylboronic acid afforded the product in 86% isolated yield with Na_2CO_3 (Table 1, entry 10). The temperature of 80 °C was determined to be the most suitable temperature for this reaction (Table 1, entries 11-14). When PAAs-CD was used as catalyst, no product was furnished (Table 1, entry 15), regardless of how much catalyst was added (Table 1, entries 16-17). A comparative experiment with the catalyst was also performed, but the yield was not ideal (Table 1, entry 18). These control experiments indicated the important role of CD in catalysis, which showed that using only $Pd(OAc)_2$ under the same conditions was not ideal (Table 1, entry 19). After the catalytic cycle, the trivalent phosphine ligand was transformed into triphenyl phosphine oxide.

The selectivity of Pd@PAAs-CD was also investigated (Table 2), and the results show that the Pd/C loaded with the same amount of palladium displays no catalytic activity (Table 2, entry 4). When the amount of Pd/C was doubled, product yield was significantly improved, but by-products (mainly self-coupling products and raw materials) were also formed (Table 2, entry 5). When the amount of Pd/C was tripled, the yield reached 87% (Table 2, entry 6). When compared to Pd/C, the Pd@PAAs-CD exhibited a much higher catalytic efficiency, and in order to confirm that this increase in catalytic activity was due to addition of CD, a series of control experiments was performed. To the best of our knowledge, the binding of CD to amantadine has been widely reported.[38-41] When amantadine was added to the solution of Pd@PAAs-CD, the catalytic effect was effectively inhibited (Table 2, entry 2), and no catalytic activity was observed even when the amount of catalyst was doubled (Table 2, entry 3). This was attributed to the fact that amantadine filled the cavity of CD, which hindered the contact of guest molecules with Pd NPs and thus inhibited the activity of Pd@PAAs-CD. However, when amantadine was added to the solution of Pd/C, this compound still retained general activity (Table 2, entry 7). These

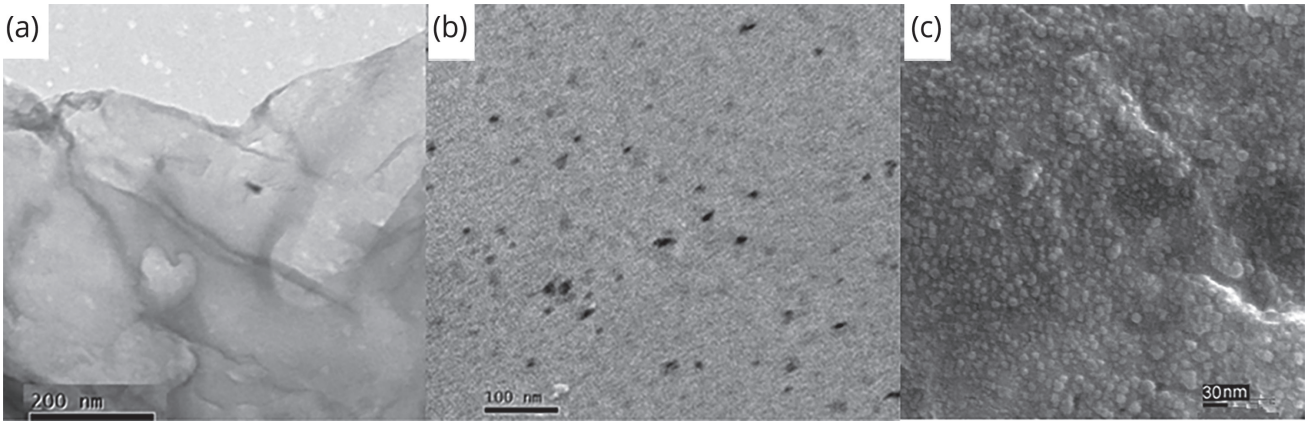
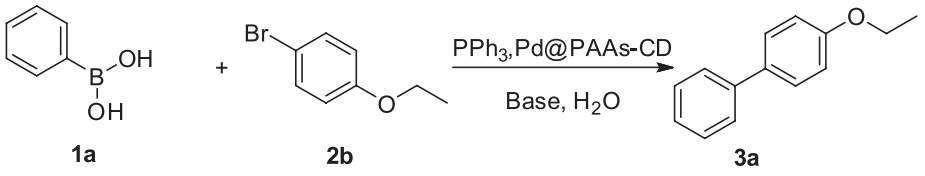


Figure 2. (a) TEM image of the PAAs-CD; (b) TEM image of the Pd@PAAs-CD; (c) SEM micrographs of Pd@PAAs-CD.

Table 1. Screening of reaction conditions[a]



1a **2b** **3a**

entry	Catalyst	Base	Solvent	Temperature / °C	Yield[b] / %
1	Pd@PAAs-CD	Cs_2CO_3	H_2O	80	44
2	Pd@PAAs-CD	K_2CO_3	H_2O	80	40
3	Pd@PAAs-CD	Li_2CO_3	H_2O	80	75
4	Pd@PAAs-CD	NaH_2PO_4	H_2O	80	trace
5	Pd@PAAs-CD	K_3PO_4	H_2O	80	78
6	Pd@PAAs-CD	$NaHCO_3$	H_2O	80	80
7	Pd@PAAs-CD	Na_3PO_4	H_2O	80	70
8	Pd@PAAs-CD	K_2HPO_4	H_2O	80	50
9	Pd@PAAs-CD	triethylamine	H_2O	80	77
10	Pd@PAAs-CD	Na_2CO_3	H_2O	80	92 (86%)[c]
11	Pd@PAAs-CD	Na_2CO_3	H_2O	r.t.	5
12	Pd@PAAs-CD	Na_2CO_3	H_2O	50	45
13	Pd@PAAs-CD	Na_2CO_3	H_2O	100	84
14	Pd@PAAs-CD	*t*-BuOLi	H_2O	100	85
15	PAAs-CD	Na_2CO_3	H_2O	80	trace
16	Pd@PAAs-CD	Na_2CO_3	H_2O	80	92[d]
17	Pd@PAAs-CD	Na_2CO_3	H_2O	80	92[e]
18	Pd@PAAs[f]	Na_2CO_3	H_2O	80	65
19	$Pd(OAc)_2$[g]	Na_2CO_3	H_2O	80	6

[a]Reaction conditions: aryl halide (0.25 mmol), phenylboronic acid (0.30 mmol), PPh_3 (0.025 mmol), base (0.25 mmol), Pd@PAAs-CD (0.5 mg, 0.2 mol% Pd *per* mol of aryl halide) and H_2O (1 mL), under air, heated at 80 °C for 18 h; [b] yield based on alkyl bromide and determined by GC-MS; [c]isolated yield; [d]Pd@PAAs-CD (1 mg); [e]Pd@ PAAs-CD (2 mg); [f]Pd@PAAs (0.2 mol% Pd *per* mol of aryl halide); [g]$Pd(OAc)_2$ (0.2 mol% Pd *per* mol of aryl halide). PAA: poly(amido amine); CD: cyclodextrin; r.t.: room temperature.

Table 2. Selective experiments of catalysts[a]

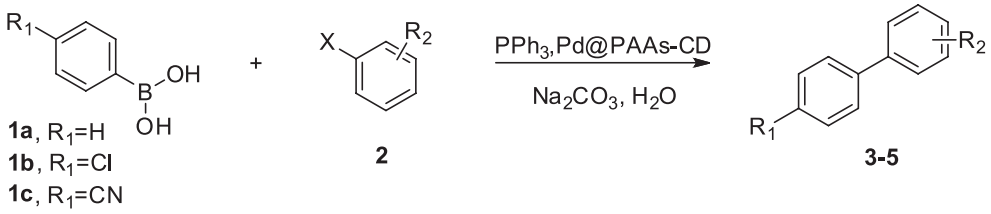
entry	Catalyst	Additive[b]	Yield[c] / %
1	Pd@PAAs-CD (Pd 0.2 mol%)	–	90
2	Pd@PAAs-CD (Pd 0.2 mol%)	amantadine	trace
3	Pd@PAAs-CD (Pd 0.6 mol%)	amantadine	trace
4	Pd/C (Pd 0.2 mol%)	–	trace
5	Pd/C (Pd 0.4 mol%)	–	55
6	Pd/C (Pd 0.6 mol%)	–	87
7	Pd/C (Pd 0.6 mol%)	amantadine	35

[a]Reaction conditions: aryl halide (0.25 mmol), phenylboronic acid (0.30 mmol), PPh_3 (0.025 mmol), Na_2CO_3 (0.25 mmol), Pd@PAAs-CD/(Pd/C)/PAAs-CD and H_2O (1 mL), under air, heated at 80 °C for 18 h; [b]the quality of amantadine is 10 times that of Pd@PAAs-CD/(Pd/C); [c]yield based on alkyl halide and determined by GC-MS. PAA: poly(amido amine); CD: cyclodextrin.

experiments show that using CD as the supramolecule could potentially improve the catalytic efficiency of Pd@PAAs-CD through host-guest interactions.

Reactions between phenylboronic acid and a variety of aryl halides were performed (Table 3), and the products were obtained in average to excellent yields. Even sterically-hindered aryl bromides substituted at the *ortho*- and *meta*- positions afforded 87 and 92% isolated yields when the reactions were run in pure water (**3b** and **3c**). The reaction with *p*-chloroaniline also achieved an average yield (**3f**). Notably, aryl halides with electron-donating amino, benzyl, bromomethyl, chloro, and methoxy substituents (**3d**, **3e**, **3f**, **3g**, **3i**, **3l**, and **3m**) gave the desired products in 80-90% yield. Electron-withdrawing groups, such as nitro, cyanide, and fluoro substituents (**3h**, **3j**, and **3m**) yielded products in 80-90%. In addition, 2,4,6-trimethyliodobenzene with large amounts of steric hindrance (**3k**) gave products with a 44% yield. Unfortunately, aromatic alkanes and secondary aromatic bromides failed to give products in good yields using this catalyst system.

Table 3. Suzuki-Miyaura cross coupling reactions between aryl halides and phenylboronic acid[a,b]



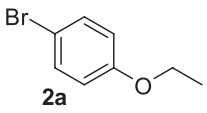
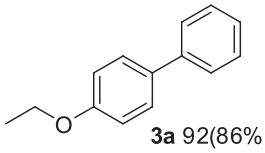
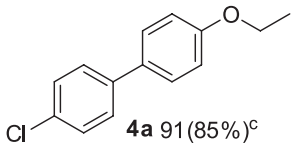
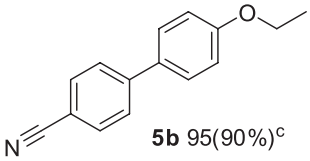
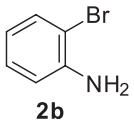
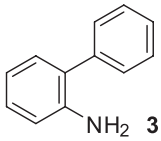
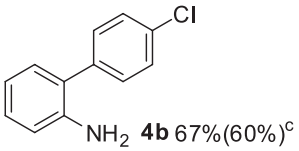
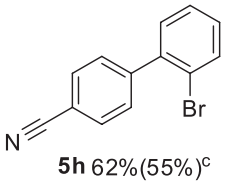
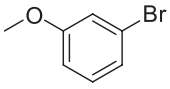
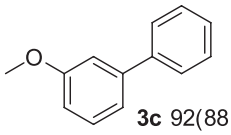
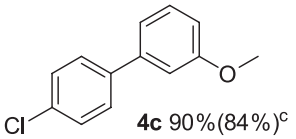
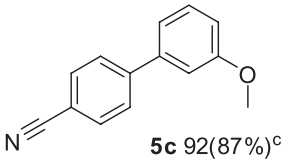
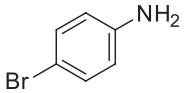
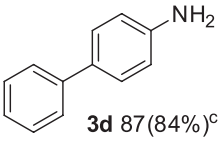
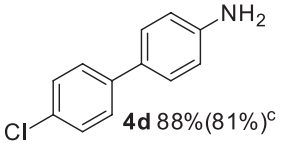
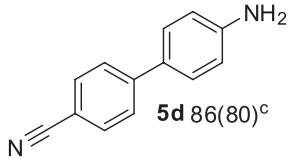
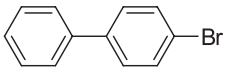
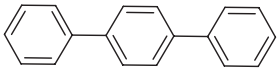
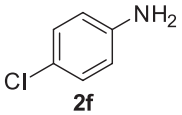
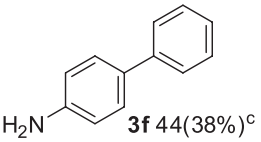
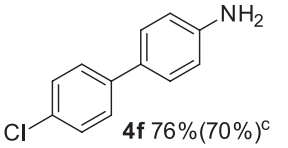
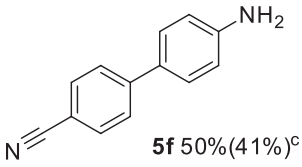
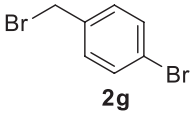
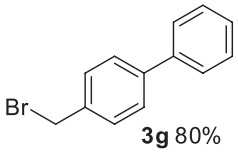
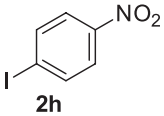
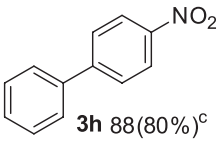
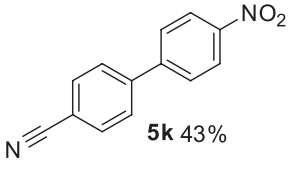
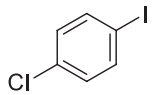
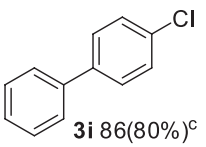
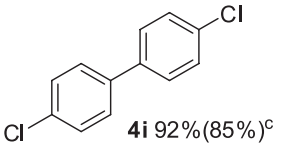
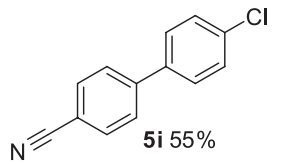
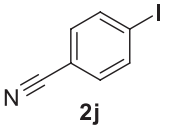
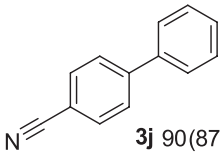
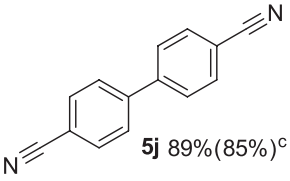
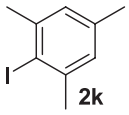
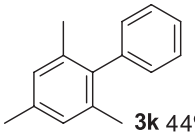
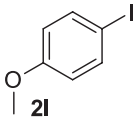
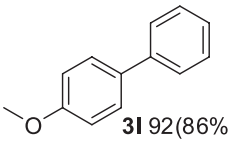
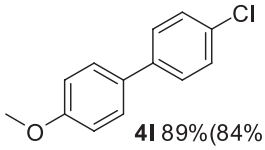
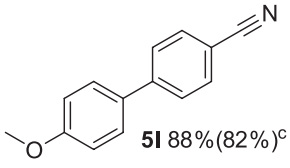
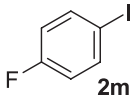
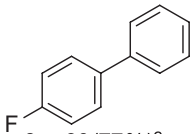
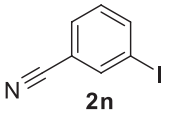
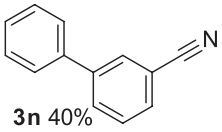
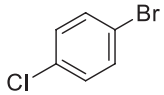
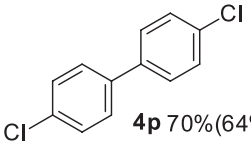
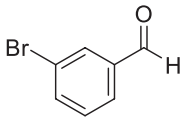
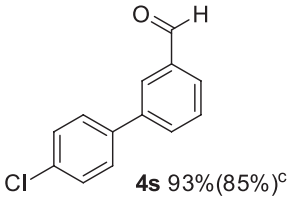
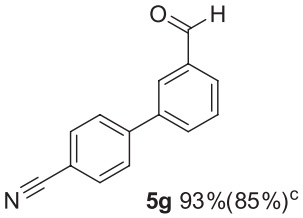
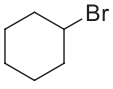
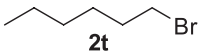
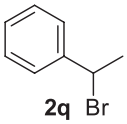
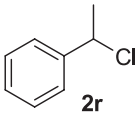
entry	Aryl halides	1a	1b	1c
1	 **2a**	 **3a** 92(86%)[c]	 **4a** 91(85%)[c]	 **5b** 95(90%)[c]
2	 **2b**	 **3b** 87(85%)[c]	 **4b** 67%(60%)[c]	 **5h** 62%(55%)[c]
3	 **2c**	 **3c** 92(88%)[c]	 **4c** 90%(84%)[c]	 **5c** 92(87%)[c]
4	 **2d**	 **3d** 87(84%)[c]	 **4d** 88%(81%)[c]	 **5d** 86(80)[c]
5	 **2e**	 **3e** 80%	–	–
6	 **2f**	 **3f** 44(38%)[c]	 **4f** 76%(70%)[c]	 **5f** 50%(41%)[c]
7	 **2g**	 **3g** 80%	–	–
8	 **2h**	 **3h** 88(80%)[c]	–	 **5k** 43%
9	 **2i**	 **3i** 86(80%)[c]	 **4i** 92%(85%)[c]	 **5i** 55%

Table 3. Suzuki-Miyaura cross coupling reactions between aryl halides and phenylboronic acid[a,b] (cont.)

entry	Aryl halides	1a	1b	1c
10	 **2j**	 **3j** 90(87%)[c]	–	 **5j** 89%(85%)[c]
11	 **2k**	 **3k** 44%	–	–
12	 **2l**	 **3l** 92(86%)[c]	 **4l** 89%(84%)[c]	 **5l** 88%(82%)[c]
13	 **2m**	 **3m** 80(77%)[c]	–	–
14	 **2n**	 **3n** 40%	–	–
15	 **2p**	–	 **4p** 70%(64%)[c]	–
16	 **2s**	–	 **4s** 93%(85%)[c]	 **5g** 93%(85%)[c]
17	 **2o**	trace	–	–
18	 **2t**	trace	–	–
19	 **2q**	trace	–	–
20	 **2r**	trace	–	–

[a]Reaction conditions: aryl halide (**2**) (0.25 mmol), phenylboronic acid (**1a-1c**) (0.30 mmol), PPh_3 (0.025 mmol), Na_2CO_3 (0.25 mmol), Pd@PAAs-CD (0.5 mg, 0.2 mol% Pd *per* mol of aryl halide) and H_2O (1 mL), under air, heated at 80 °C for 18 h; [b]yield based on alkyl halide and determined by GC-MS; [c]isolated yield.

Table 4. Reusability of Pd@PAAs-CD[a]

No. of cycles	1	2	3	4	5	6
Reaction conversion[b] / %	90	87	85	82	81	79
time / h	18	18	18	18	18	18

[a]Reaction conditions: *p*-bromoethylbenzene (0.25 mmol), phenylboronic acid (0.30 mmol), PPh_3 (0.025 mmol), Na_2CO_3 (0.25 mmol), Pd@PAAs-CD (0.5 mg, 0.2 mol% Pd *per* mol of aryl halide) and H_2O (1 mL), under air, heated at 80 °C; [b]yield based on alkyl halide and determined by GC-MS.

The coupling reactions of other phenylboronic acid aryl compounds (**1b** and **1c**) with aryl halides were also studied using optimized reaction conditions. As shown in Table 3, substrates possessing electron-donating substituents worked well, returning the desired products in 91 and 89% yields (**4a** and **4l**). Substrates containing varying amounts of steric hindrance furnished the corresponding coupling products in 67 and 90% yields (**4b** and **4c**). Substrates with electron-withdrawing substituents gave 85% isolated yields (**4s**). However, neither 4-chlorophenylboronic acid nor 4-cyanophenyl boronic acid reacted with nitro-substituted substrates. Furthermore, the reactions between **1c** and aryl halides were also investigated under identical conditions. **1c** was similar to **1b**, highlighting the fact that most substituted alkyl bromides containing ether, amino, and nitrile groups are all well tolerated under these optimized reaction conditions, furnishing products in 95 and 86% yields (**5b** and **5d**). Aryl halides also gave desired products in 62-92% yields without any interference from steric hindrance (**5c**, **5g**, and **5h**), but 4-cyanophenyl boronic acid still failed to produce product in reasonable yields.

In addition, the catalytic performance of recycled Pd@PAAs-CD was studied, and the reusability of the catalyst system is attributed to the presence of β-CD, which protects the catalytic activity of Pd@PAAs-CD. The use of cyclodextrin and PAAs also made it easy to separate the product from the reaction mixture by simple extraction due to the heterogeneous nature of the catalyst system. Conversions demonstrating the recyclability of Pd@PAAs-CD in cross-coupling reactions are shown in Table 4, where Pd@PAAs-CD still retains high catalytic activity even after six successive reaction cycles with a conversion rate of 79%.

Conclusions

In this paper, Pd NPs modified with PAAs-CD have been successfully synthesized via a facile method. It has been shown that Pd@PAAs-CD can act as an efficient and recyclable catalyst for Suzuki-Miyaura cross-coupling reactions in water with high yields and tolerate of a wide variety of functional groups. The source of this excellent catalytic activity is attributed to the special structure and properties of CD which is hydrophobic on its interior and hydrophilic on its exterior, which helps promote the catalytic activity of Pd@PAAs-CD through host-guest interactions. In addition, it was also demonstrated that Pd@PAAs-CD could be recycled and reused in cross-coupling reactions and showed only a minimal decrease in catalytic activity, even after six reaction cycles. The catalyst developed here can be applied to heterogeneous green chemical reactions and further studies of the applications of this hybrid material in selective catalysis are currently underway.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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