A robust polyfunctional Pd(II)-based magnetic amphiphilic nanocatalyst for the Suzuki–Miyaura coupling reaction

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Herein, a robust Pd(II)-based polyfunctional magnetic amphiphilic artificial metalloenzyme was prepared by anchoring a Pd(2,2'-dipyridylamine)Cl2 bearing hydrophilic monomethyl ether poly(ethylene glycol) (mPEG) chains on the surface of amino-functionalized silica-coated magnetic nanoparticles. The 2,2'-dipyridylamine (dpa) has shown excellent complexation properties for Pd(II) and it could be easily anchored onto functionalized magnetic support by the bridging nitrogen atom. Moreover, the bridging nitrogen atom at the proximity of Pd(II) catalytic center could play an important role in dynamic supramolecular interactions with substrates. The leaching, air and moisture resistant [Pd(dpa)Cl2] complex endow the dynamic and robust structure to the designed artificial enzyme. Moreover, the water dispersibility of designed artificial metalloenzyme raised from mPEG chains and the magnetic nanoparticles core which could function as protein mimics endow it other necessary characters of artificial enzymes. The prepared artificial metalloenzyme displayed remarkable activity in Suzuki–Miyaura cross-coupling reaction employing low-palladium loading under mild conditions, with the exceptionally high turnover frequency, clean reaction profile, easy work-up procedure, good to excellent products yields and short reaction times. The designed air- and moisture-stable artificial metalloenzyme could recycle more than fifteen times with easy separation procedure in aqueous solution under aerobic conditions without any noticeable loss in activity.

Biomimetic chemistry as a rapidly emerging research field in chemical sciences focuses on the simulation of biological function and processes particularly catalysis by purely chemical means1,2. Recently, increasing attention has been given to design and synthesis of artificial enzymes as a very important and exciting branch of biomimetic chemistry3. Given the tremendous progress of nanotechnology, it has been found that, some nanomaterials exhibit unexpected enzyme-like activity4–9. Some individual characteristics of inorganic nanoparticles in terms of size, charge, shape and surface coating with organic functional groups could allow them to function like globular proteins and provide important similarities between them and natural enzymes10. The magnetic nanoparticles were introduced as supported materials with outstanding properties such as their ease of preparation and separation, diverse functionalization, chemical and hydrothermal stability and low cost11. Simple magnetic separation of superparamagnetic nanoparticles is a feature directly relevant to green chemistry goals, which solves the separation and recycling challenges in nanocatalysts and natural enzymes. Such interesting features have attracted the researchers' attention in the field of artificial enzymes.

The design of robust catalysts is important for catalytic systems in the view of green chemistry12. Typically Pd(0) complexes are known as the active catalytic species during cross-coupling reactions, while their inherent
instability to air and moisture compared with Pd(II) complexes has limited their use in such reactions. On the other hand, few instances have employed Pd(II) species as catalytic centers in the Pd(II)/Pd(IV)-based mechanism. It is because the formation of organopalladium(IV) complexes needs to the presence of the strong donor ligands to stabilize them. Despite the fact that the proposal of oxidation mechanism of Pd(II) to Pd(IV) by MeI has been approved with X-ray crystallography as a strong evidence, but few studies have been done in this field. It seems that the question of which of Pd(0)/Pd(II) or Pd(II)/Pd(IV) forms the basis for the oxidative addition/reductive elimination cycle seems to be very complex. In fact, things like the presence of strongly stabilizing ligands or spectator ligands can affect the mechanism. The use of strongly stabilizing ligands may yield catalysts with very high turnover number and high reactivity, but generally only under vigorous conditions which are believed to be associated with slow reduction/dissociation of the precursor complex. Moreover, there is also the issue of the coordination of spectator ligands at Pd, and as a consequence the charge on the catalytic intermediates may vary under different reaction conditions.

Whilst, the Pd(II)/Pd(IV) cycle is more favorable for the facile reductive elimination and more chemoselective for the oxidative addition. The strong σ-donation assists these steps to develop air- and moisture-stable Pd(II)-based catalysts which are suitable for aerobic conditions in aqueous media. N-donor ligands could maintain proper electron density at metal center. The N,N-type ligands like dipyridyls have shown excellent complexion properties for Pd and they could minimize the Pd leaching in reaction media. The potentially N,N-donor ligand 2,2’-diprydylamine (dpa) belongs to the polydentate nitrogen ligands family. The superior properties of dpa compared with the other N,N-type ligands mainly raised from the bridging nitrogen atom in its structure which could modulate the electronic and steric properties. Such a dpa-based complex in combination with the bridging nitrogen atom as an anchorage point to prepare supported catalysts. Moreover, the bridging nitrogen atom at the proximity of a catalytic center which was coordinated by dipyridyls could play an important role in substrate orientation and activation through hydrogen-bonding in the dpa-based complex. Such dynamic supramolecular interactions which are essential factors in rational design of artificial enzymes persuaded us to design and prepare highly efficient [Pd(dpa)Cl2]-based polyfunctional magnetic amphiphilic artificial metalloenzyme. Considering supramolecular interactions, some artificial enzymes have been designed and synthesized. Some of them designed based on the hydrophobic interactions in their supramolecular structures. In such systems Breslow et al. proposed a supramolecular substrate preorganization strategy with hydrophobic interactions. Moreover, a similar supramolecular substrate preorganization strategy by hydrogen bonding interactions has been developed. The importance of such supramolecular interactions in regioselectivity of reactions, were examined by experiments and DFT calculations. These investigations demonstrated that the undesired product is blocked by host–guest interactions, whereas the desired product is lowered in energy because of the suitable length of the substrate.

The prepared artificial metalloenzyme was employed successfully in Suzuki–Miyaura cross-coupling reaction as one of the most important and versatile transformations in biaryl synthesis. Many of the Suzuki–Miyaura reactions catalyzed by palladium salts or complexes are performed in harmful organic solvents. On the other hand, the major drawback associated with supported catalysts in aqueous reaction media is the poor interaction between active sites of catalysts and organic substrates. Hence, there are many reports on Suzuki–Miyaura reaction promoted by various supported catalysts in harmful organic solvents. Hereupon, some strategies were proposed to solve this problem, such as the development of ionic liquids- or amphiphilic polymers-based supported catalysts. Although these types of catalysts have shown good features, many of them still suffer from hard reaction conditions, higher reaction time or lack of durability/stability of catalysts.

Palladium(0) complexes and palladium nanoparticles were employed widely as the catalysts of the Suzuki–Miyaura reaction. As it was mentioned these catalysts typically have low stability and furthermore, the high activity of palladium nanoparticles reduces their selectivity significantly. In this regard, Cuenca et al. reported a palladium-based artificial metalloenzyme, which was prepared from Candida antarctica B lipase and palladium salt. The prepared palladium nanoparticles enzyme aggregate used for the Suzuki–Miyaura cross-coupling reaction in a mixture of methanol/water (1:1). It was reported that the designed artificial metalloenzyme did not show high yields in 2 to 24 h and it could be recycled 4 times.

To the best of our knowledge, there is no report on the application of supported catalysts based on robust Pd(II) complexes with the evidences to propose more favorable and chemoselective Pd(II)/Pd(IV)-based mechanism in the Suzuki–Miyaura reaction. Hence, it seems that there is still room for developing novel robust Pd(II)-based supported catalysts with special features which were designed directly relevant to green chemistry goals.

In our designed polyfunctional artificial metalloenzyme, amphiphilicity originates from the covalent attachment of the hydrophilic monomethyl ether poly(ethylene glycol) (mPEG) chains to the lipophilic [Pd(dpa)Cl2] complex via cyanoacetic chloride as a cross-linking agent. The unique properties of dpa ligand beside the leaching, air and moisture resistant [Pd(dpa)Cl2] complex endow the dynamic and robust structure to the designed artificial enzyme. Moreover, the water dispersibility of designed artificial metalloenzyme raised from mPEG chains and the magnetic nanoparticles core which could function as protein mimics endow it other necessary characters of artificial enzymes. The prepared artificial metalloenzyme represented good efficiency and selectivity to produce corresponding Suzuki–Miyaura cross-coupling products under mild conditions in aqueous media and no self-coupling of aryl boronic acids were detected.

The investigation of the reaction mechanism indicated that a more favorable and chemoselective Pd(II) to Pd(IV) route could be a plausible mechanism which was supported by X-ray photoelectron spectroscopy analysis. The designed air- and moisture-stable artificial metalloenzyme could recycle more than fifteen times in aqueous solution under aerobic conditions without any noticeable loss in activity.
Results and discussion

The designed Pd(II)-based polyfunctional magnetic amphiphilic artificial metalloenzyme was synthesized via covalent attachment of the mPEG-anchoring [Pd(dpa)Cl2] complex to amino-functionalized silica-coated magnetic nanoparticles (Fig. 1). The preparation processes were confirmed with NMR and FTIR analyses (ESI, Figure S1-S11). The 1H NMR spectrum of 2-mPEG-4,6-dichloro-1,3,5-triazine confirms successful addition of 2,4,6-trichloro-1,3,5-triazine to mPEG (ESI, Figure S11, A). Disappearance of NH peak in 2-mPEG-4-[Pd(dpa)Cl2]-6-chloro-1,3,5-triazine spectrum in 7.99 ppm comparing with Pd(dpa)Cl2, confirms the covalent linkage of Pd(dpa)Cl2 to 2-mPEG-4,6-dichloro-1,3,5-triazine (ESI, Figure S11, B and C).

The infrared analysis of MNPs@SiO2-NH2@Pd(dpa)Cl2 and all of its precursors is shown in Fig. 2. The Fe–O stretching band as a characteristic peak of magnetite nanoparticles could be observed in Fe3O4 and functionalized Fe3O4 nanoparticles at 580 cm−1 (Fig. 2b–e). The modification of Fe3O4 by tetraethoxysilane (MNPs@SiO2) and its amino-functionalization with (3-aminopropyl)triethoxysilane (MNPs@SiO2-NH2) create strong and broad peaks at 1000–1100 cm–1 associated with Si-(OH) stretching vibration (Fig. 2c–e). The distinct changes of the MNPs@SiO2-NH2 before and after combination with 2-mPEG-4-(Pd(dpa)Cl2)-6-chloro-1,3,5-triazine in the FTIR spectra could be observed in some absorption bands around 770 cm-1 and in the region of 1400–1600 cm−1 which are attributed to the vibrations of pyridyl rings55 and the Pd–N stretching frequencies ranged from 528 to 436 cm−1 (Fig. 2a,e)56. Moreover, the intensity growth of –CH2 – stretching peaks at 2850 and 2917 cm−1 (Fig. 2d, e), which are related to the mPEG is the other evidence that emphasis on the synthesis of MNPs@SiO2-NH2@Pd(dpa)Cl2.

The Thermogravimetric (TG) and derivative thermogravimetric (DTG) curves of MNPs@SiO2-NH2@Pd(dpa)Cl2 artificial metalloenzyme and MNPs@SiO2-NH2 before functionalization with 2-mPEG-4-(Pd(dpa)Cl2)-6-chloro-1,3,5-triazine are represented in Figure S12. The thermal decomposition profile of MNPs@SiO2-NH2@Pd(dpa)Cl2 represented three distinct steps of weight losses upon heating from room temperature to 800 °C under airflow (Figure S12 c and d). The first and second weight loss steps at 83 and 299 °C are due to the removal of solvents adsorbed on the surface as well as structural water molecules within amorphous SiO2 layers. The third weight loss at 605 °C indicated the cleavage of 2-mPEG-4-(Pd(dpa)Cl2)-6-chloro-1,3,5-triazine moiety of the MNPs@SiO2-NH2@Pd(dpa)Cl2 structure. This weight loss step revealed that the weight percentage of 2-mPEG-4-(Pd(dpa)Cl2)-6-chloro-1,3,5-triazine moiety was about 15% and the Pd(II) percentage was about 1% consequently which is corresponded well to the inductively coupled plasma mass spectroscopy (ICP-MS; 1.05% Pd). Microscopic properties of MNPs@SiO2-NH2@Pd(dpa)Cl2 nanoparticles were characterized by scanning electron microscope (SEM) and field emission transmission electron microscopy combined with an energy-dispersive X-ray spectroscopy (FE-TEM/EDS) analyses (Fig. 3a,b and Figure S17, S18 and Table S2).
analysis revealed their spherical and uniform particle structures. The (FE-TEM/EDS) employed to provide the morphological characteristics of chemical composition of MNPs@SiO₂-NH₂-Pd(dpa)Cl₂. Electron diffraction data which were obtained on single MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ nanoparticles indicated that the large black spots in Fig. 3b contained a large amounts of Fe which could represent magnetic nanoparticles, and small dark gray spots seen on a light gray halo around large black spots indicate the presence of palladium located on the polymer chains around magnetic nanoparticles. The average particle diameter of about 20 nm was obtained for MNPs@SiO₂-NH₂-Pd(dpa)Cl₂. Moreover, the EDS represented the C, N, O, Si, Fe and Pd signals as the principal elements of MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ nanocatalyst (Fig. 3c).

The magnetic hysteresis loops for the MNPs@SiO₂-NH₂ and MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ nanoparticles were recorded at room temperature. Figure S13 shows that the MNPs@SiO₂-NH₂ and MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ nanoparticles exhibit superparamagnetic behavior at room temperature. The saturated mass magnetization of the MNPs@SiO₂-NH₂ and MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ are about 61.3 and 53 emu g⁻¹ respectively. These values show their high permeability and consequently indicate simple magnetic recoverability of MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ nanocatalyst from the reaction media.

The X-ray diffraction (XRD) pattern of prepared MNPs@SiO₂-NH₂-Pd(dpa)Cl₂ represented strong and sharp peaks that can be ascribed to the pure phase of magnetite in its structure (Figure S14). Additionally, the
diffraction peaks of nanostructured palladium complex can be observed over the MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ sample. According to the Scherrer equation $D = \frac{K\lambda}{\beta \cos \theta}$ the crystallite size of MNPs and nanostructured palladium complex at their highest diffraction lines (35.61° and 38.08°) were 15 and 30 nm respectively.

The X-ray photoelectron spectroscopy (XPS) of the fresh and recycled MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme was investigated in order to verify its action mechanism in the Suzuki–Miyaura cross-coupling reaction (Figure S20). The XPS of the fresh MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme indicated PdCl₂ species (Fig. 4a); however, after reaction cycles, small shoulder peak in addition to main peak was observed which is assigned to PdO (Fig. 4b). It could be interpreted that the nitrogen-based ligands take a hydrogen ion from a water molecule in reaction media to produce hydroxide ions. Then the chloride ions in PdCl₂ species could slowly replace with hydroxide ions and produce PdO after the removal of a molecule of water. It should be notice that the XPS spectra of fresh and recycled catalyst did not show any Pd(0) signals, which have been observed simply in reactions based on Pd(0)/Pd(II) mechanisms after catalytic cycles. It could be a good evidence to confirm the Pd(II)/Pd(IV) mechanism in our designed artificial metalloenzyme-based Suzuki–Miyaura cross-coupling reaction.

On the other hand, in SEM–EDS spectra of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanoparticles (Figure S18), we can see Pd and Cl elements at the same position. The XPS peak was observed at 338.39 eV, being assigned to PdCl₂ (Fig. 4a). This assignment is supported by SEM–EDS result.

The Suzuki–Miyaura coupling reaction based on Pd(II)/Pd(IV) catalytic cycle involves some fundamental steps as demonstrated in Fig. 5. At the first step oxidative addition of aryl halides to Pd(II) complex gives cis intermediate (1), a Pd(IV) species. Since the more stable form of the oxidative addition product is the trans form then, the cis product can isomerise to a more stable trans intermediate (2). At the transmetalation step the organoborane compound reacts with trans intermediate (2) to afford trans intermediate (3). Then the second isomerization occurs and the cis intermediate (4) is produced which is subject to reductive elimination to give the desired coupling product and regenerate the original Pd(II) species.

The catalytic activity of the prepared MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme was evaluated in Suzuki–Miyaura coupling reaction. Amphiphilic structure of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanoparticles (Figure S18) could provide a suitable interaction between the water-soluble boronic acids and hydrophobic aryl halides and thereby could improve the efficiency of Suzuki reaction in aqueous media. The dispersibility of magnetic nanoparticles in solvents depends on the suitable choice of their size, precursors, pH, surfactants/coating agents, as well as functionalizing agents.

It has been indicated that the surface charge on colloids, their dispersibility and affinity are well correlated with dielectric constant of the solvents. This is reflected in increase in our examined Suzuki–Miyaura reaction rate employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanocatalyst in H₂O:EtOH mixture (1:1) compared with EtOH which is raised from better dispersion of nanocatalyst particles in the reaction media (ESI, Table S1). Water as a “greener” solvent, being more polar, involves in hydrogen bonding. In high polarity index of dispersed medium, a strong electrical double layer forms around the colloidal particles. Then, the zeta potential of nanoparticles increases, and the particles are prevented from aggregation by repelling each other and as a result a good dispersion of nanoparticles could be expected.

The reaction of bromobenzene and phenyl boronic acid was used for initial studies and after optimization of solvent, catalyst amount and temperature (ESI, Table S1) the best result was obtained after 12 min at 60 °C using MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ catalyst (Pd, 0.01 mol%) and K₂CO₃ as a base. The presence of organic co-solvent (EtOH) was necessary to ensure the full dissolution of reactants in aqueous medium of dispersed nanocatalyst.

Figure 4. XPS analysis of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme before (a), and after (b), reaction cycles.
Figure 5. Proposed mechanism of the Suzuki–Miyaura cross-coupling reaction employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂.

Table 1. Suzuki–Miyaura coupling of aryl halides with aryl boronic acids employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme. Reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.2 mmol), K₂CO₃ (1.5 mmol), MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ (Pd, 0.01 mol% with respect to aryl halide), H₂O/EtOH (1:1) (2.0 mL). *Isolated yield. †The reaction was performed without any base.
Having optimized the reaction conditions, we examined the scope and limitation of the designed MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme in the Suzuki–Miyaura cross-coupling reaction of various types of iodo-, bromo-, and chloroaryl derivatives and arylboronic acids (Table 1). Generally, all of the products were obtained in good to excellent yields employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ (Pd, 0.01 mol%) and K₂CO₃ as a base during the 5–150 min in H₂O:EtOH (1:1) under aerobic conditions. As expected, aryl iodides were rapidly converted to the respective products even without any base (Table 1, entries 1, 5, 10, 13 and 17). Moreover, bromoaryl derivatives were reacted with boronic acids in high yields, whilst K₂CO₃ is necessary for the reactions’ progress. It is worth mentioning that the electron-rich aryl halides, which are known as highly challenging coupling partners, selectively produced the corresponding products and no self-coupling of aryl boronic acids were detected.

Encouraged by these results, we focused our investigation on the use of more challenging chloroarenes for this reaction employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂, which could afford the corresponding products at longer reaction times (Table 1, entries 3 and 9).

As a case study, the turnover frequency for the MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ was calculated according to the time-dependent ¹H NMR spectrum of the reaction mixture of α-naphthalenoboronic acid and 4-bromotoluene under optimized reaction conditions. Accordingly, a high turnover frequency of 1.8 × 10⁵ h⁻¹ was observed.

The stability of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ suspension in water was evaluated by dynamic light scattering (DLS) analysis. The presence of hydrophilic mPEG chains in the surface of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ provides a stable suspension after its dispersion in water (Figure S15 a).

The DLS analysis indicated that the size and size distribution of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanoparticles suspension remain almost constant even for several days without any precipitation (ESI, Figure S16). The recyclability of the MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme was examined upon the Suzuki–Miyaura cross-coupling reaction of iodobenzene and phenylboronic acid under the optimized conditions. The results indicated that the MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ was reused up to 15 cycles without noticeable loss in its catalytic activity (Figure S19 and S21). Moreover, the ICP results before and after catalytic cycles revealed that no appreciable metal leaching was observed in designed MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme (ICP-MS: 1.05% Pd before and 1.01% Pd after catalytic cycles). This result confirms the robust structure of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial metalloenzyme after repeated cycles under aerobic conditions in aqueous media.

Methods

Synthesis of the [Pd(dpa)Cl₂] complex. A solution of 1.00 g (5.64 mmol) PdCl₂ in 57 ml distilled water was added to a solution of 0.968 g (5.65 mmol) 2,2′-dipyridylamine (dpa) in 58 ml of distilled water. The mixture was stirred at 60 °C for 24 h. The resulting brown precipitate was filtered off, and washed three times with 20 ml cold water and dried under vacuum at room temperature. The yield was 70%.

[Pd(dpa)Cl₂] (MW:348.52): IR (KBr) (cm⁻¹): 3416, 2925, 1660, 1604, 1525, 1437, 1032, 770; ¹H NMR (250.13 MHz, CDCl₃, 25 °C, TMS): 8.27 (br, 2H), 7.99 (s, 1H), 7.53–7.59 (m, 4H), 6.84 (t, J = 5.25, 2H), 4.59 (br, 2H), 3.80 (br, 2H), 3.59 (br, 176H), 3.33 (s, 3H).
Functionalization of MNPs with tetraethoxysilane (MNPs@SiO₂). The MNPs were functionalized with tetraethoxysilane through a modified Stober method. In a typical procedure, prepared Fe₃O₄ particles (1.5 g) were dispersed in a mixture of ethanol (105 ml), deionized water (30 ml), and tetraethoxysilane (TEOS) (0.75 ml) in an ultrasonic bath. Afterward, 6 ml of ammonia solution (25%) was added dropwise. After being stirring for 8 h at room temperature, the MNPs@SiO₂ were collected by magnetic separation and washed with ethanol and deionized water five times and then dried at 60 °C under vacuum oven (yield: 90%).

Functionalization of MNPs@SiO₂ with (3-aminopropyl)triethoxysilane (MNPs@SiO₂-NH₂). In order to functionalization of MNPs@SiO₂ with (3-aminopropyl)triethoxysilane, the synthesized MNPs@SiO₂ (1.00 g) was dispersed in ethanol (300 ml) via sonication for 15 min. Then (3-aminopropyl)triethoxysilane (4 ml, 8.58 mmol) was added dropwise under mechanical stirring and nitrogen atmosphere at room temperature. Then deionized water (4 ml) was added to increase the hydrolysis rate of (3-aminopropyl)triethoxysilane. The reaction mixture was stirred for 8 h and the obtained amine-functionalized magnetite nanoparticles (MNPs@SiO₂-NH₂) was separated by external magnetic field and was washed five times with deionized water and ethanol and dried under vacuum for 24 h at room temperature (yield: 91%).

Functionalization of MNPs@SiO₂-NH₂ with 2-mPEG-4-(Pd(dpa)Cl₂)-6-chloro-1,3,5-triazine (MNPs@SiO₂-NH₂@Pd(dpa)Cl₂). In order to functionalization of MNPs@SiO₂-NH₂ with 2-mPEG-4-(Pd(dpa)Cl₂)-6-chloro-1,3,5-triazine, the synthesized MNPs@SiO₂-NH₂ (0.85 g) was dispersed in acetonitrile (25 ml) via sonication for 10 min. Then 2-mPEG-4-(Pd(dpa)Cl₂)-6-chloro-1,3,5-triazine (1.27 g) was added under mechanical stirring and nitrogen atmosphere at 80 °C. The reaction mixture was stirred for 48 h and the obtained MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ was separated by external magnetic field and was washed five times with deionized water and ethanol and dried under vacuum for 24 h at room temperature (yield: 80%).

General procedure for the Suzuki–Miyaura cross-coupling reaction using MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ artificial enzyme. The Suzuki–Miyaura reaction was performed in a 5 ml round bottomed flask. Accordingly, aryl halide (1.0 mmol), arylboronic acid (1.2 mmol) and K₂CO₃ (1.5 mmol) were mixed under optimized reaction conditions in a dispersed suspension of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ (Pd, 0.01 mol% with respect to aryl halide) in H₂O:EtOH (1:1) (2.0 ml) at 60 °C (ESI, Table S1). The dispersibility of magnetic nanoparticles in solvents depends on the suitable choice of their size, precursors, pH, surfactants/coating agents, as well as functionalizing agents.

It has been indicated that the surface charge on colloids, their dispersibility and affinity are well correlated with dielectric constant of the solvents. This is reflected in increase in our examined Suzuki–Miyaura reaction rate employing MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanocatalyst in H₂O:EtOH mixture (1:1) compared with EtOH which is raised from better dispersion of nanopalladium particles in the reaction media. Water as a “greener” solvent, being more polar, involves in hydrogen bonding. In high polarity index of dispersed medium, a strong electrical double layer forms around the colloidal particles. Then, the zeta potential of nanoparticles increases, and the particles are prevented from aggregation by repelling each other and as a result a good dispersion of nanoparticles could be expected.

The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. Then the MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ nanocatalyst was completely separated from the aqueous media using an external magnetic field (Figure S15c). The resulting biaryl was extracted with addition of 2 ml n-hexane. The n-hexane phase was dried with MgSO₄ and the solvent was then removed under reduced pressure to get the product without need to further purification. All the products were characterized by FT-IR and NMR techniques.

The recycling experiments were performed according to the water dispersibility of synthesized MNPs@SiO₂-NH₂@Pd(dpa)Cl₂. The presence of hydrophilic mPEG chains in the surface of MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ provides a means of its complete dispersion into the aqueous phase, and it had no affinity to the n-hexane phase. Accordingly, after the first use of the catalyst and vacuum concentration of reaction the product was simply extracted with n-hexane while the magnetic nanocatalyst remained in the aqueous phase (Figure S15b). In the next catalytic cycle, ethanol is added to the aqueous phase containing catalyst and it was recharged with reactants and K₂CO₃ for the next cycle without any catalyst washing.

Conclusions

In conclusion, a novel designed robust Pd(II)-based polyfunctional magnetic amphiphilic artificial metalloenzyme was developed. In the designed polyfunctional artificial nanozyme, amphiphilicity originates from the attachment of the mPEG to the lipophilic [Pd(dpa)Cl₂] complex via cyanuric chloride cross-linker. Moreover, its water dispersibility raised from mPEG chains and the nanomagnetic core as protein mimics endow it other necessary characters of artificial enzymes.

The designed metalloenzyme was efficiently employed for the Suzuki–Miyaura coupling reaction according to an operationally convenient green protocol to afford the desired products in high yields under aerobic conditions in aqueous media. Furthermore, the prepared air and moisture stable artificial metalloenzyme shows excellent reusabilities over at least 15 reaction cycles. Moreover, the artificial metalloenzyme can be easily separated using an external magnetic field without employing inefficient filtration methods. Interestingly, recovery studies indicated that the metal content of recovered MNPs@SiO₂-NH₂@Pd(dpa)Cl₂ did not alter significantly. According to the XPS analysis the Pd(II)/Pd(IV)-based mechanism is the more likely pathway because of the presence of dpa as a strong donor ligand in the designed metalloenzyme that could stabilize organopalladium(IV) complexes in Pd(II)/Pd(IV) mechanism.
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Author contributions

A.R. and S.J.T.R. conceived the idea; H.A. designed the experiments, analyzed the experimental data and wrote the manuscript; M.S. synthesized the catalyst and carried out the experiments and N.A. assisted him in data collection; H.Y. and M.M. performed the XPS and TEM analysis and interpreted their results; all the authors contributed to discussions.

Competing interests

The authors declare no competing interests.

Additional information

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