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Viral-templated palladium nanocatalysts for Suzuki coupling reaction[†]

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We demonstrate and thoroughly examine tobacco mosaic virus (TMV)-templated palladium (Pd) nanocatalysts for the ligand-free Suzuki coupling reaction under mild conditions. The surface-assembled TMV templates allow for facile catalyst synthesis under mild aqueous conditions that leads to high Pd surface loading and stability. Further, the chip-based format enables simple catalyst separation and reuse as well as facile product recovery. Reaction condition studies demonstrated that the solvent ratio played an important role in the selectivity of the Suzuki reaction, and that a higher water/acetonitrile ratio significantly facilitated the cross-coupling pathway. We envision that our viral template-based bottom-up assembly approach can be readily extended to other biotemplates, metal catalysts and organic reaction systems.

Introduction

Palladium (Pd) is the most versatile and widely applied catalytic metal for a variety of organic reactions including hydrogenation,¹ oxidation,² and C–C coupling reactions.³ For industrial applications, heterogeneous catalysts are the first option due to their inherent advantages of simple separation, stability, and better handling compared to homogeneous catalysts. However, heterogeneous catalysts also face several hurdles, such as harsh preparation conditions, difficulty in uniform metal particle dispersion on supports, uncontrollable particle size distribution, and the unclear influences from the supports on reactivity.

Biological supramolecules have recently gained significant attention as alternative template materials for well-dispersed metal nanoparticle formation, largely *via* electroless deposition.⁴⁻¹⁰ Particularly, tobacco mosaic virus (TMV) has been extensively enlisted for a range of metals in various applications due to the well-defined structure and dimension, along with high stability (a wide range of pH, temperature, and resistance to organic solvents).¹¹ Importantly, the ability to confer precisely spaced functionalities through genetic modification¹²⁻¹⁴ leads to enhanced and readily controllable metal nanoparticle formation,^{7-9,15} increased stability,¹⁶ and tunable high density surface assembly.¹⁷ Despite a few recent studies on the catalytic applications of viral-templated nanoparticles,^{5,6,18-20} there has been no endeavor to harness catalytic activities of such attractive materials

^o there has been no nattractive materials *ring, Tufts University, min.yi@tufts.edu oratory, Argonne, IL,*vailable: Solvent ratio X-ray Photoelectron pled Plasma Optical removal study results. **Fig. 1** Pd-TMV nanocatalyst catalyzed Suzuki reaction. (a) Scheme of Suzuki cross- and homo-coupling reactions catalyzed by nanostructure Pd-TMV complex. (b) Diagram of TMV templated Pd catalyst and simple reaction setup. (c) AFM images of TMV assembled gold chip (i) and Pd formation on assembled TMV (ii).



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for organic synthesis reactions of value-added chemicals and small molecule drugs in order to exploit the unique advantages that these potent nanotubular templates offer.

The Pd-catalyzed Suzuki-Miyaura reaction³ represents one of the most important routes to synthesize biaryl compounds through the cross-coupling of aryl halides with aryl boronic acids, as shown in the general scheme of Fig. 1(a). These reactions are typically carried out with phosphine-based or phosphine-free homogeneous Pd catalysts²¹⁻²³ in organic solvents. In the past few years, a number of ligand-free heterogeneous Pd catalysts on various supports have emerged.²⁴⁻²⁶ While offering simpler catalyst recovery, these ligand-free heterogeneous systems face a number of complications including the need to employ surfactants in aqueous solution^{27,28} or microwave²⁹ to assist phase transfer. Despite the improved conversion and yield, such additives also present obstacles, such as product contamination, more arduous downstream purification, and increased cost.

In this paper, we demonstrate and thoroughly examine catalysis of Suzuki coupling reactions by nanostructured Pd nanoparticles templated on TMV, as shown in Fig. 1(b). Specifically, genetically modified TMV templates were assembled on clean gold-coated chip surfaces as shown in the tapping mode atomic force microscopy image of Fig. 1(c)-(i), resulting in dense coverage of TMV that is stable under extensive rinsing processes.9 These TMV-assembled chips are then exposed to Pd precursor solution to form nanoparticles via electroless deposition^{9,19} as shown in Fig. 1(c)-(ii), resulting in highly dense coverage of Pd nanoparticles formed on TMV templates (Pd-TMV) with wellcontrolled particle size.9 These Pd-TMV complexes have shown high chemical stability under acidic environment for catalytic dichromate reduction¹⁹ as well as enhanced thermal stability than Pd particles without TMV templates.¹⁶ These chips (i.e. Pd-TMV chips) were then simply immersed in the reaction mixtures, containing the reactants in various ratios of acetonitrile/water mixtures, in well-sealed vials to carry out the Suzuki reactions, and the catalytic reactivity was then analyzed by High-Performance Liquid Chromatography (HPLC). The results show high selectivity and facile product separation with high water content and complete conversion under mild conditions. Additionally, these catalysts exhibit consistent stability throughout reaction and sample analysis using Atomic Force Microscopy (AFM) and Grazing Incidence Small Angle X-ray Scattering (GISAXS), as well as simple catalyst recovery and reusability rising from surface-assembled chip format. Combined these results demonstrate the facile fabrication of nanostructured viral-metal catalytic systems for ligand-free Suzuki coupling reactions. We believe that our viral-templated bottom-up assembly approach can be readily applied to a wide range of organic synthesis reactions and other noble metal or alloy catalysts where facile catalyst recovery, product separation, and mild reaction conditions are desired.

Experimental

Materials

Gold-coated silicon wafers with 1000 Å thicknesses of Au layer were purchased from Platypus Technologies (Madison, WI). Iodoanisole (IA) (>98%), bromoanisole (99%), chloroanisole (99%), iodophenol (>98%), iodobenzene (>98%), 4-methoxybiphenyl (4-MB) (98%), and sodium carbonate (Na_2CO_3) were purchases from Alfa Aesar (Ward Hill, MA) and used without further purification. Phenylboronic acid (PBA) (>95%), bromobenzene (99%), biphenyl (BP) (99.5%), Sodium tetrachloropalladate (Na_2PdCl_4) (99.998%) and sodium hypophosphite ($NaPH_2O_2$) (>98%) were purchased from Sigma-Aldrich (St. Louis, MO).

Synthesis of TMV-templated Pd catalysts

The Pd-TMV catalyst chips were prepared as previously described¹⁹ with minor modifications. Briefly, clean gold chips (0.7 cm \times 2 cm) were immersed in TMV1cys solution (200 µg/ml) for surface assembly that yielded highly dense and consistent surface loading. These TMV-assembled chips were then exposed to 5 mM Na₂PdCl₄ precursor solution containing 15 mM NaPH₂O₂ reducer for 20 min, which provided reproducible formation of about 13 nm Pd nanoparticles along the TMV tubes.¹⁶ These Pd-TMV chips were then thoroughly rinsed with deionized water, dried, and stored for the reaction studies.

Suzuki reaction studies

The Suzuki reactions between iodoanisole (IA) and phenylboronic acid (PBA) were catalyzed by as-prepared Pd-TMV chips. For this, various amounts of IA, PBA and Na₂CO₃ were dissolved in 5 ml acetonitrile/water (CH₃CN/H₂O) solvent. After the reaction mixture was heated to 50 °C, one Pd-TMV chip was added to start the reaction with stirring at 600 rpm for 24 h.

To study the solvent effect, 0.05 mmol IA (10 mM), 0.05 mmol PBA (10 mM) and 0.15 mmol Na₂CO₃ (30 mM) were dissolved in 5 ml CH₃CN/H₂O mixture with different volume ratio of 3 : 1, 3 : 2, 1 : 1 and 2 : 3. For the reactant ratio study, concentration ratios of IA : PBA : Na₂CO₃ (mM : mM : mM) were varied as 10 : 10 : 30, 10 : 15 : 30, 10 : 20 : 30, 10 : 30 : 30, 10 : 20 : 40, and 10 : 30 : 60 all in a CH₃CN/H₂O (2 : 3) mixture. Reusability studies of Pd-TMV chips were carried out by taking the chips out of the completed reaction mixture, rinsing with deionized water, drying, and then immersing in a fresh reaction mixture for three more reaction cycles without further treatments or activation steps. Suzuki reactions between phenylboronic acid and other aryl halides, including bromoanisole, chloroanisole, iodophenol, iodobenzene, bromobenzene, were carried out under various reaction conditions, as described in Table 1.

High-performance liquid chromatography (HPLC) analysis

The reactants and products in the Suzuki reaction mixture were analyzed by HPLC (Waters LC module 1 plus, Milford, MA) equipped with a UV detector at 254 nm. A reversed-phase Nova-Pak C18 column (Waters, 4.6×150 mm, 4μ m) was used with an acetonitrile/water (60 : 40, v/v) mixture as the eluent at a flow rate of 1 ml/min.

Calibration curves, for determining the concentration of all reactants and products, were constructed by plotting the peak area *versus* the concentration of all standard compounds. The solutions were diluted 4 or 8 times to be within the range of calibration curves. The product yields at each time point were calculated based on the original concentration of the aryl halides. For example, the 4-MB yield was calculated by eqn (1).

$$Yield, \% = \frac{[methoybiphenyl]_t}{[iodoanisole]_0} \times 100\%$$
(1)

Catalyst characterization

(1) Atomic force microscopy (AFM). AFM images of Pd-TMV chips before and after Suzuki reactions were acquired using a Dimension 3100 series Scanning Probe Microscope (SPM) (Veeco, Woodbury, NY) in tapping mode with TAP-Al-50 AFM tips (Budget Sensors, Sofia, Bulgaria) and analyzed by NanoScope software.³⁰

(2) Grazing incidence small angle X-ray scattering (GISAXS). GISAXS measurements were conducted at the Advanced Photon Source (Argonne National Lab, Argonne, IL) BESSRC/XOR 12 ID-C beamline as previously described.^{9,19} As shown in Fig. 3(a), the X-ray beam, with energy of 8 keV, was irradiated on the sample at an incident angle (α_i) of 0.1° and the scattered X-rays were collected on a CCD detector (Rayonix, Mar165).

The scattering pattern was analyzed in terms of the scattering vector q_{xy} for all GISAXS measurements.³¹ For a single spherical Pd nanoparticle, the scattered intensity $P(q_{xy})$ can be related to particle radius *R*, volume *v* and density ρ , as given in eqn (2).³¹

$$P(q_{xy}) = \rho^2 v^2 \frac{9(\sin(q_{xy}R) - qR\cos(q_{xy}R))^2}{(q_{xy}R)^6}$$
(2)

and scattering intensity $I(q_{xy})$ of various particles with size distribution, n(R), described by eqn (3).³²

$$I(q_{xy}) = \int n(R)P(q_{xy})dR \tag{3}$$

The size distribution, n(R), was calculated with Irena data fitting software, where the scattering curves were fit using the Maximum Entropy Method.³³

Results and discussion

Effect of solvent ratio on reaction selectivity

We first examine the effect of the solvent ratio between acetonitrile and water (CH₃CN/H₂O) on the selectivity of the Suzuki coupling reaction catalyzed by Pd-TMV chips, as shown in Fig. 2. For this, we prepared Pd-TMV chips, as shown in the schematic diagram of Fig. 1(b), then carried out reactions with 10 mM phenylboronic acid, 10 mM iodoanisole, 30 mM sodium carbonate at 50 °C in well-sealed vials, and analyzed the reactants and products *via* HPLC.

First, Fig. 2(a) shows that the CH₃CN/H₂O ratio is critical to the competition of cross-coupling against the homo-coupling pathway. Specifically, higher water content (*i.e.* CH₃CN/H₂O = 2 : 3) is beneficial for the production of cross-coupling product 4methoxybiphenyl (4-MB), and suppresses the production of homo-coupling product biphenyl (BP). When the CH₃CN/H₂O ratio was changed from 3 : 1 to 2 : 3, the yield of 4-MB increased from 23.3% to 66.9%, while the yield of BP decreased from 20.1% to 14.4% under the reaction conditions studied. This trend clearly shows that water facilitates the cross-coupling pathway while providing mild reaction conditions with less organic solvent. In



Fig. 2 The effect of solvent ratio on reaction selectivity and surface characterization by AFM. Reaction conditions: iodoanisole 10 mM, phenylboronic acid 10 mM, sodium carbonate 30 mM, 5 ml CH₃CN/H₂O mixture, temperature 50 °C. (a) The effect of solvent CH₃CN/H₂O volume ratio on reaction selectivity. (b) Products precipitation at room temperature (c) AFM images of Pd-TMV chip after reaction in CH₃CN/H₂O mixed solvent with volume ratio of 3 : 2 (i) and 2 : 3 (ii).

addition, higher or lower water content, beyond the range shown in Fig. 2(a), did not provide adequate solubility of Na_2CO_3 or iodoanisole at 50 °C. Meanwhile, Suzuki reaction of iodoanisol with another boronic acid compound, 4-methoxyphenylboronic acid, was also examined to confirm this selectivity (ESI 1†), and exhibited similar selectivity toward the cross-coupling pathway in higher water content as shown in Table S1†. This further confirms that this effect is not limited to phenylboronic acid, and appears to be general. Furthermore, the homo-coupling reaction between phenylboronic acid in the absence of iodoanisole yielded similar selectivity (*i.e.* suppression of homo-coupling product yield with high water content), as shown in Table S2 (ESI 1†).

There have been limited number of studies with contradictory conclusions on the effect of water on the selectivity of Suzuki reaction.^{25,34} The results shown in Fig. 2(a) demonstrate that a CH₃CN/H₂O mixture with the appropriate ratio is crucial in directing cross- *vs.* homo-coupling pathways, leading to efficient selectivity control. In-depth studies on the mechanism of this striking effect of water content on the selectivity are currently under way.

Importantly, no catalytic conversion was observed for several negative controls (*e.g.* no chip, gold chip and TMV-assembled gold chip) examined under the same reaction conditions (0% conversion for all). This clear difference in conversion demonstrates the catalytic activity of TMV-templated palladium nanoparticles in the Suzuki coupling reaction.

Next, the photograph of Fig. 2(b) shows that both 4-MB and BP products were precipitated as white flocculates while cooling the reaction mixture to room temperature due to their relatively low solubility in CH_3CN/H_2O (2 : 3) mixture. The products can

thus be separated by centrifuge or sedimentation upon completion of the reaction, highlighting an additional advantage of the high water content condition enlisted here. Importantly, this result illustrates the facile and robust nature of our chip-based catalyst format that enables the simple separation of both catalysts and products upon reactions without additional steps such as centrifugation or filtration, as compared to homogeneous Pd catalysts.^{21,23}

Next, to qualitatively evaluate the surface morphology and stability of Pd-TMV chip under the conditions employed, the chips were simply taken out of the reaction mixture and analyzed by AFM, as shown in Fig. 2(c). Compared to the AFM image of the Pd-TMV chip before the catalytic reaction (Fig. 1(c)-(ii)), chips after the reaction in various CH_3CN/H_2O ratios (Fig. 2(c)) show no apparent changes in the Pd loading density or particle size. This preliminary examination indicates that the surface-assembled Pd-TMV complexes were stable under the range of reaction conditions studied. Combined, the results in Fig. 2 show clear reactivity and selectivity, stability of the nanostructured Pd-TMV catalyst chips, along with facile catalysts and products separation for the Suzuki coupling reaction.

Surface characterization by GISAXS

As shown in Fig. 3, we next employed grazing incidence small angle X-ray scattering (GISAXS) to further examine the stability of Pd-TMV chips in the Suzuki reaction. First, the schematic diagram of Fig. 3(a) shows a typical GISAXS setup where the incident X-ray strikes the surface of the Pd-TMV chip and the scattered rays are recorded at low angles (less than 2°) on a 2D CCD detector.³¹ Fig. 3(b) shows scattering images of various samples as a function of the scattering angles 2θ in the horizontal direction and α_f in the vertical direction. First, the TMV1cysassembled gold chip (i) shows strong scattering in the out-ofplane direction (at $2\theta = 0$), characteristic of the rod shaped TMV.35 Second, the Pd-TMV chips before (ii) and after (iii and iv) reactions all show nearly identical isotropic scattering, rising from abundant spherical Pd particles. This result clearly indicates that most Pd particles and Pd-TMV complexes were wellpreserved after completion of the Suzuki reactions under different solvent ratios (CH₃CN/H₂O = 2:3 and 3:2) at 50 °C.

Next, a Guinier analysis^{9,31,32} was employed to further examine the average Pd particle diameters. For this, scattering curves were first created by making a horizontal line-cut of intensity (shown by the red line in Fig. 3(b)-(ii)) and plotting intensity vs. the scattering vector, q_{xy} . The table in Fig. 3(c) shows that the average Pd particle diameter did not change significantly under all the reaction conditions examined, with slight variations rising from different Pd-TMV chips for the *ex-situ* GISAXS analysis.

Finally, normalized particle volume distributions of Pd-TMV chips before and after reactions under different reaction conditions were examined by simulating size distributions from the scattering curves using Irena software. The Irena software utilizes the Maximum Entropy Method (MEM) with a 15% error allowance to simulate particle size distributions.³³ As shown in Fig. 3(d), the average Pd particle size remained nearly identical upon completion of the reactions in all three solvent ratios examined, which further confirms the results in Fig. 3(c) acquired from Guinier analysis and the preliminary observation *via* AFM



Fig. 3 Pd particle size distribution of Pd-TMV catalyst examined by GISAXS. (a) Schematic diagram of GISAXS. (b) Scattering patterns of TMV-gold chip (i), Pd-TMV chip before reaction (ii), Pd-TMV after reaction in CH_3CN/H_2O solvent with ratio of 2 : 3 (iii) and 3 : 2 (iv). (c) Summary of average Pd particle size on Pd-TMV chip before and after reaction. (d) Pd particle size distribution of Pd-TMV chips before and after reactions. Y-axis represents normalized number density of Pd nanoparticles n(R).

shown in Fig. 2(c). While the particle size distribution for all three samples appears to broaden upon reaction, we note that the ex-situ GISAXS measurements without direct comparison to the same pre-reaction chips may not provide reliable means to examine the change in particle size distribution. The reaction mechanism of the Suzuki reaction is generally considered to occur by a small number of molecular Pd species that leach out into the bulk solution, which then re-deposit rapidly onto supports.³⁶ Our consistent particle size retention results in Fig. 3 show no apparent disappearance of the original particles or increase of larger size particles (through Ostwald ripening) that may lead to different size distributions and larger average particle sizes. Given the potential of GISAXS for the statistically meaningful in situ examination of dynamic yet subtle changes at nanoscale,^{16,37,38} further in situ GISAXS studies are currently under way to gain deeper understanding.

Meanwhile, in-depth X-ray Photoelectron Spectroscopy (XPS) analysis revealed further information on the elemental composition and chemical states of the Pd-TMV chips before and after reactions as shown in Fig. S1 (ESI 2†). Briefly, the spectra show full coverage of Pd nanoparticles on the TMV-assembled chips, either before or after reaction, confirming the AFM-based observations made in Fig. 1 and 2. The relative metallic Pd content over the overall Pd species, Pd/(Pd + PdO), were determined to be $60.9 \pm 2.7\%$. Importantly, only minimal change in chemical states upon reactions was observed, as shown in Fig. S1.†

In summary, the GISAXS-based in-depth analysis (Fig. 3) and XPS surface characterization (Fig. S1[†]) clearly demonstrate the dimensional, structural and chemical stability of Pd-TMV chips for Suzuki reaction, and further corroborate the enhanced thermostability¹⁶ of Pd-TMV complexes under the catalytic reaction conditions employed in this study.

Batch reaction profile

Fig. 4 shows the reactants conversion and products yield curves at 50 °C. For this, Suzuki reaction of 10 mM iodoanisole with 15 mM phenylboronic acid was carried out in the presence of Pd-TMV chips in 5 ml CH₃CN/H₂O (2 : 3) mixture for 24 h. Samples were taken at certain intervals and analyzed with HPLC as described above.

The concentration of both reactants (iodoanisole and phenylboronic acid) decreased rapidly in the first 2 h, and then decreased slowly until the end of the reaction. Meanwhile, the target product 4-MB started forming rapidly in the first 0.5 h and kept increasing steadily until the 4th hour. After 5 h, the 4-MB concentration reached the maximum value of 8.2 mM and didn't change significantly until the end of the reaction. A similar trend was observed for the formation of BP. The curves show that the majority of both products (4-MB and BP) were formed within the first 5 h, which is sufficient for near-complete conversion of IA at 50 °C. In addition, the reaction time didn't affect the reaction selectivity. Meanwhile, further in-depth Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) experiments (ESI 3[†]) revealed the total Pd amount per chip to be 8.3 µg, which leads to the Pd catalyst ratio of 0.15 mol% based on iodoanisole (0.05 mmol per batch). Furthermore, the "apparent" reaction rate within the first 5 h was determined to be 0.0165 mol/



Fig. 4 Concentration of reactants and products vs. reaction time Reaction condition: iodoanisole 10 mM, phenylboronic acid 15 mM, sodium carbonate 30 mM, 5 ml CH₃CN/H₂O mixture solvent with ratio of 2 : 3, temperature 50 °C.



Fig. 5 Effect of reactants ratios on product yields. Reactions were carried out with Pd-TMV chips at solvent ratio of $CH_3CN/H_2O = 2:3$ and temperature 50 °C.

 $(\min \cdot g)$ based on this amount of Pd employed for each batch reaction (ESI 3[†]).

Meanwhile, Suzuki reactions at lower reaction temperatures (25 and 40 °C) were also examined and yielded much slower reaction rates (data not shown). Therefore, a moderately high temperature clearly facilitated the Pd-TMV catalyzed Suzuki reaction.

Effect of reactant ratio on the reaction conversion

To further investigate the effect of reactant ratio (iodoanisole (IA):phenylboronic acid (PBA):base) on the product yields, we carried out Suzuki reactions with different reactant concentrations in CH₃CN/H₂O (2 : 3) mixture, as shown in Fig. 5.

We first studied the influence of PBA amount on the product yields by keeping IA and base concentration constant (Entries 1–4). In Entry 1, equivalent amount of two reactants IA and PBA

(both 10 mM) resulted in only 68.6% yield of 4-MB. When PBA concentration was increased from 10 mM to 20 mM from Entry 1 to 3, both 4-methoxybiphenyl (4-MB) and biphenyl (BP) yields increased simultaneously. Entry 3 shows that two-fold higher concentration of PSB than IA leads to 100% yield of 4-MB and 29.6% of BP. Meanwhile, further addition of PBA up to 30 mM (Entry 4) didn't have a significant influence on either reaction conversion or selectivity. The mass balance analysis based on HPLC quantification indicated that all BP was formed from the homo-coupling of PBA. These results indicate that more PBA content than IA is needed to complete the cross-coupling reaction, since a certain amount of PBA follows the homo-coupling pathway catalyzed by Pd^{39,40} or Au⁴¹ as previously reported.

Next, the effect of base (Na₂CO₃) amount was investigated (Entries 5 and 6). Compared to Entry 3, 33% higher base concentration (Entry 5) yielded similar final product amounts. A two-fold higher base amount (Entry 6, 60 mM) yielded 8% more byproduct (BP) than Entry 4, showing relatively lower reaction selectivity. It is well known that base could activate phenylboronic acid in the Suzuki coupling reaction;⁴² the results shown here indicate that excess base may lead to more homo-coupling byproducts while certain amount of base is required to complete the cross-coupling reaction. Overall, the results in Fig. 5 demonstrate that proper reactant ratio plays an important role on both reaction conversion and selectivity.

Reusability of Pd-TMV catalysts

As shown in Fig. 6, we further conducted recycle reaction studies to examine the reusability of our Pd-TMV catalysts based on the clear stability shown *via* GISAXS in Fig. 3 and XPS in Fig. S1[†]. For this, Pd-TMV chips were thoroughly rinsed with deionized water and applied to three more batch reaction cycles without any regeneration treatments. The reactions were carried out in the optimized conditions as described above, with 10 mM IA, 20 mM PBA and 30 mM base in CH₃CN/H₂O (2 : 3) solvent at 50 °C for 24 h. The results in Fig. 6 show a small decrease in the catalytic activity of Pd-TMV chip in the second cycle: the yield of 4-MB decreased from 100% (first run) to 91.7% (second run) and BP decreased from 29.6% to 28.8%. However, the third and



Fig. 6 Recycling test of Pd-TMV chip catalyzed Suzuki reaction of iodoanisole with phenylboronic acid.

fourth batches did not show a further decrease in activity, as shown in the fourth reuse of catalysts: the yield of 4-MB was maintained at 91.4%. These results are consistent with our previous findings in the dichromate reduction reaction,^{19,20} and clearly demonstrate the stability and reusability of Pd-TMV catalysts for the Suzuki reaction under the conditions studied. More importantly, the surface-assembled TMV-templated format enables the significantly simpler recovery and repeated use of the catalysts (*i.e.* mechanical removal of the chip from the reaction mixture) with minimal loss of catalytic activity without arduous separation and/or regeneration procedures.

In the meantime, preliminary reaction mechanism was studied through chip removal experiments along with ICP-OES analysis (ESI 4†). The results suggest that the Suzuki reactions may be catalyzed largely by trace amounts of Pd species (1–90 ppb) in the reaction solution under the conditions employed in our study. The Pd nanoparticles formed on TMVs in this study can thus be considered as a reservoir, or "pre-catalysts" of the catalytically active Pd species in the reaction solution.^{36,43,44} In addition, the simplicity of this chip removal experiment (*i.e.* mechanical removal of the entire chip from the reaction solution) further supports the advantage of our surface-assembled catalyst format toward facile mechanistic studies. Further *in situ* SAXS studies to understand the molecular mechanisms are currently underway.

Catalytic Suzuki reaction of other aryl halides with phenylboronic acid

Finally, we further examined the conversion and selectivity of the Pd-TMV catalyzed Suzuki reaction for a range of aryl halides as summarized in Table 1. Entries 1 and 2 show that Pd-TMV catalysts are active for the cross-coupling of PBA with bromoanisole, but not chloroanisole. This result is consistent with previous reports, where the relative cross-coupling reactivity decreased in the order of I > Br \gg C1.^{3,36} Next, Entries 3–6 show the Suzuki reaction of 4-iodophenol with PBA, where the solvent ratio also played a significant role on the reactivity. Higher water content (Entry 3 vs. 4) produced more of the cross-coupling product 4-phenylphenol (80%) and less biphenyl (14%), which is consistent with the trend shown in Fig. 2 for iodoanisole. Contrary to other reports,²⁴ iodophenol is only slightly soluble in water, thus no product was observed in aqueous solution (Entry 6). Meanwhile, the commonly used dimethylacetamide (DMA)/ water (1:1) mixture^{25,34} (Entry 5) did not yield significant conversion for this catalytic reaction. Next, Suzuki reactions using benzene halides were also studied (Entries 7 and 8). The reaction with iodobenzene (Entry 7) led to 133.7% yield (vs. initial iodobenzene) of biphenyl, most likely from both the crosscoupling (between iodobenzene and PBA) and the homocoupling reactions (between two moles of PBA). The reaction with bromobenzene in Entry 8 showed a much lower conversion, as expected from the lower reactivity of bromides.

Considering the unoptimized reaction conditions for each reactant case shown in Table 1, higher product yields could be expected upon further examination of parameters (*e.g.* solvent ratio, base addition amount, reactants ratio). Overall, these studies show that our TMV-templated Pd catalysts are active with several different reactants examined, further confirming the general catalytic activity for Suzuki coupling reactions.

Table 1 Pd-TMV chip catalyzed Suzuki reaction of aryl halides with phenylboronic acid



^{*a*} Solvent ratios are all based on volume ratio. ^{*b*} The yield of Ar-C₆H₅ is calculated from the conversion of IC₆H₄OH on a basis of mass balance. ^{*c*} Byproduct from homo-coupling of C₆H₅B(OH)₂ is the same as cross-coupling product, so the yield of biphenyl based on iodobenzene is higher than 100%.

Conclusions

In this paper, we demonstrated and thoroughly examined, for the first time, the catalytic activity of TMV-templated Pd nanoparticles for the Suzuki coupling reaction toward value-added chemical synthesis. The surface-assembled chip based format allowed for simple catalyst and product separation as well as simple catalysts recycling for several reaction batches. Over 90% of the initial catalytic activity was retained for four reaction cycles. In depth reaction condition studies indicated that the solvent ratio played an important role in the selectivity of the Suzuki reaction, and that a higher water content is beneficial for the cross-coupling pathway. Importantly, these results suggest that the viral template-based bottom-up assembly approach may lead to facile catalyst synthesis and separation. We envision that our TMV-templated Pd catalysis strategy can be readily extended to other biotemplates, catalysts and reaction systems.

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