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A phase-reversible Pd containing sphere-tobridge-shaped peptide nanostructure for cross-coupling reactions[†]

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A sphere-to-bridge-shaped peptide nanostructure was constructed from a tyrosine-rich peptide (H-YYACAYY-OH) *via* mediating Pd²⁺ ions as well as changing temperature. This novel assembly technique provided a recyclable Pd nano-catalyst with a function of reversible thermal phase transition between the homogeneous and heterogeneous states for cross-coupling reactions.

Natural peptides coordinated with various metal ions *via* amide bonds and functional groups on side chains can form various self-assembled structures.¹ For example, ferritin is a natural intracellular protein which takes a specific conformation through interactions between peptide building blocks and Fe²⁺ ions. Artificial peptides that provide natural or non-natural metal binding sites have been developed to construct metal ion-induced self-assemblies of nanostructures including tubular-, fibre-, vesicle-, spherical-, and rod-coil-type ones.² Such metal coordination can initiate intermolecular self-assembly by bringing two or more peptides into close proximity.³ Furthermore, several metal ions coordinated with peptides have been

involved in a redox reaction to induce irreversible peptide crosslinking *via* covalent bonding *e.g.*, dityrosine formation.⁴⁻⁷ Based on a peptide template, various types of metal-peptide nanostructures have been designed and utilized as electrochemical sensors,⁸ biological scaffolds,^{9,10} and catalysts.¹¹⁻¹³ In

particular, significant effort has been devoted in developing metal nanoparticles (NPs)-incorporated peptide nanostructures which can then be used as catalysts in C–C coupling reaction. To facilitate the reaction, for instant, Knecht group synthesized various shapes of Pd nanostructures with a large surface area by using a self-assembling peptide template composed of R5 peptide.¹⁴ Moreover, peptide amphiphiles possessing both

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hydrophobic carbon-chain and ionic peptide sequences are promising as bio-inspired-templates for growing PdNPsincorporated nanofibers. Recently, several groups have demonstrated nanofiber incorporated with PdNPs using a selfassembled peptide amphiphile. The peptide-templated PdNPs showed high catalytic activity for the Suzuki coupling reaction under environmentally-friendly conditions.^{15,16} Although these peptide-templated PdNPs can afford efficient catalytic activities for the C–C coupling reactions, drawbacks originated from the heterogeneous state limits its broad and practical application of the catalyst.

A recent report has revealed that a tyrosine-rich peptide, YYACAYY (YC₇), can be self-assembled into a two-dimensional peptide nanostructure via interaction of tyrosines and cysteines leading to cross-linking at an air/water interface.17 Based on this finding, we have successfully designed Pd²⁺-ionmediated sphere-to-bridge-shaped peptide nanostructures $(YC_7(a)Pd^{2+})$ through thermally induced phase transition. During the transition, the Pd²⁺ ions have interacted with the YC₇ peptide molecules through coordination, which might be a crucial driving force for leading to a distinctive self-assembled sphere-to-bridge peptide nanostructure. More interestingly, the self-assembled YC7@Pd²⁺ is dissolved into the aqueous solution via thermal transition during cross-coupling process over phase transition temperature and followed by re-assembly under the critical temperature achieving the PdNP-captured astrocyteshaped peptide nanostructures (YC₇@PdNP). This provides a great opportunity to take advantage of YC₇@Pd²⁺ as a versatile and recyclable catalyst, capitalizing both of its homogeneous characteristic over critical temperature and heterogeneous characteristic under the same temperature. Herein, we demonstrate the feasibility of YC7@Pd2+ as a new type of catalyst under environmentally friendly conditions: (a) as a nanocatalyst during C-C coupling reactions; and (b) as a heterogeneous catalyst for separation, especially in Suzuki and

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Sonogashira coupling reactions. $YC_7@Pd^{2+}$, this catalytic system *via* switchable phase enabled reusable catalyst. To the best of our knowledge, this kind of the reassembly process is first demonstrated in this paper.

 YC_7 is a random coil-dominant peptide, which selfassembles in an aqueous phase into a two-dimensional nanostructure.17 From this peptide, we synthesized sphere-to-bridgetype peptide nanostructures (YC₇@Pd²⁺) via thermally controlled Pd²⁺-ion-mediated ionic interactions and (Scheme 1). During heating the peptide up to 90 °C for 1 h, it was allowed to completely dissolve in water. As the peptide solution was gradually cooled to 60 °C, YC₇ underwent a rapid transition into a secondary, α -helix-dominant structure. At this stage, Pd²⁺ ions were injected to induce distinctive Pd-peptide secondary structures via ionic interactions between phenolate anions of tyrosyl residues (or C terminal carboxylate anions) and Pd²⁺ ions. Without Pd²⁺ ions, YC₇ molecules were selfassembled into irregular shaped nanostructures and nanosheets during the thermodynamic transition (90 $^{\circ}C \rightarrow 60 {}^{\circ}C$) *via* interactions between tyrosines and cysteine crosslinking (Fig. S1[†]). However, the YC₇@Pd²⁺, which was self-assembled by interactions with Pd²⁺ ions, was uniform and spherical with an average diameter of 88 \pm 31 nm (count: 100) and further formed linked networks of sphere-to-bridge shapes (Fig. 1a and b). Physicochemical characterization of the nanostructure was performed with several analytical methods. First, the constituent elements of YC7@Pd2+, including Pd, N, O, S and Cl, were analysed by energy-dispersive X-ray microanalysis mapping (Fig. S2^{\dagger}). The results demonstrated that YC₇(a)Pd²⁺ was composed of Pd²⁺ ions, evenly distributed within the YC₇ matrix.

To analyse the structure of YC₇@Pd²⁺ and the interactions between Pd²⁺ ions and the peptides, it was further characterized by infrared (IR) spectroscopy (Fig. 2). Bands from ν (C–O), ν (CC), δ (COH) of Tyr in YC₇ peptide were observed at 1070–1270 cm⁻¹,



Fig. 1 (a) TEM image and (b) SEM image of YC7@Pd²⁺ nanostructure.

which exhibited relatively strong intensity due to its polar character (Fig. 2). These peaks are unique in Tyr not in other residues of YC₇ peptide. When the C–O stretching vibration bands of the self-assembled YC₇ and YC₇@Pd²⁺ were compared, YC₇@Pd²⁺ gave strong peaks at 1232 cm⁻¹ involving two stretching modes of ν (C==C) and ν (C–O) in Tyr–OH, which are attributed to stronger polarity of phenolate (Tyr residue) in the presence of Pd²⁺.^{18–21} These results clearly show that there are strong interactions between Pd²⁺ ions and tyrosine groups of YC₇@Pd²⁺. In addition, a new C==O stretching vibration from the carboxylate of YC₇@Pd²⁺ appeared at 1557 cm⁻¹ which corresponds to the asymmetric stretching vibration of metal carboxylates.²²

Additionally, the X-ray photoelectron spectroscopy (XPS) data of YC₇@Pd²⁺ clearly revealed Pd peaks ($3d_{2/5}$ and $3d_{3/5}$) at 343.20 and 337.95 eV which corresponded to Pd(II) (Fig. S3[†]).²³ Taken together, YC₇@Pd²⁺ is a non-crystalline peptide complex coordinated with Pd(II) at tyrosine residues, and has a potential as a Pd catalyst used in C–C coupling reactions. Consequently, Pd²⁺-ion-mediated peptide self-assembly was well characterized with IR and XPS.

Hence, this proves that the phenolate and carboxylate groups of $YC_7 @Pd^{2+}$ were primarily involved in coordination with Pd^{2+}



Scheme 1 Proposed mechanism of YC₇@Pd²⁺ synthesis by thermal phase transition of dissolved YC₇ and Pd²⁺-ion-driven self-assembly.



Fig. 2 FT-IR spectra of YC₇@Pd²⁺ and YC₇ peptide.

ions leading to the formation of a distinctive Pd-peptide nanostructure. Inductively coupled plasma atomic emission spectroscopy (ICP-OES) analysis revealed that the palladium content of YC_7 @Pd²⁺ was calculated to be 1.86 mmol Pd per g catalyst.

The X-ray diffraction (XRD) patterns of self-assembled YC_7 exhibited distinctive peaks at 10° and 18° originating from the intersheet reflections of peptide sheets, respectively (Fig. S4†). In contrast, peptide sheet-originated regular sharp peaks of face-centered cubic Pd crystals did not appear in the XRD pattern of YC_7 (a)Pd²⁺ (Fig. S5†). This result supports that Pd²⁺ ions were able to collapse the intrinsic YC_7 structure, leading to the irregular shaped peptide arrangement inside the sphere-to-bridge-shaped peptide nanostructure.

We investigated the catalytic activity of the YC₇ $(a)Pd^{2+}$ by evaluating the efficiency of C-C coupling reactions including Suzuki, Heck and Sonogashira coupling reactions.²⁴ Actually, YC₇@Pd²⁺ nanostructures are decomposed into the solution at coupling reaction temperature, and then PdNPs instantly reduced from Pd2+ ions participate in the three kinds of coupling reactions. First, various bases for each coupling reaction were screened in aqueous solution.²⁵ K₂CO₃ and pyrrolidine were selected as the best base in the Suzuki and the Sonogashira reactions, respectively. (Tables S1 and S2[†]). However, the catalytic activity of YC₇(a)Pd²⁺ in the Heck coupling reactions gave unfavourable yields (<2%) even in the presence of cetyl trimethyl ammonium bromide (CTAB) (Table S3[†]).²⁶ Therefore, YC₇@Pd²⁺ was further used as a catalyst for the Suzuki and the Sonogashira coupling reactions of aryl iodides with phenylboronic acid or phenylacetylene in an aqueous solvent system at 80 °C, where YC₇@Pd²⁺ can be transformed into the homogeneous phase.

An activated aryl iodide (4-iodoacetophenone) was wellconverted to the corresponding biaryl compounds in the Suzuki coupling reaction with over 98% yield in only 1 h with 0.1 mol% of YC₇@Pd²⁺ (Table 1, entry 1). Electron-donating substituents lowered the yields of the corresponding biaryl

Table 1 Suzuki–Miyaura coupling reactions for various aryl iodides in the presence of $YC_7@Pd^{2+}$ catalyst^{*a*}

R	+ -B(OH)2	$\xrightarrow{\text{YC}_7 @Pd^{2*}} R \longrightarrow R$	
Entry	R	Time (h)	Yield ^c (%)
1 2 3	COCH ₃ OH OCH ₃	1 3 3 3	98.7 99.6 92.8
4 5 6	H CH ₃ 2-Iodothiophene	$3/3^{b}$ $6/3^{b}$ $6/3^{b}$	88.8/99.9b 70.8/96.0 ^b 40.0/91.3 ^b

 a Conditions: aryl iodine and heterocyclic halides (0.155 mmol), phenylboronic acid (0.186 mmol), YC₇@Pd²⁺ (0.1 mol%), K₂CO₃ (0.274 mmol) in water (1 mL) at 80 °C. b GC yields when 0.5 eq. of CTAB was used. c GC yields.

compounds (Table 1, entries 2–5). In particular, the oxygencontaining substrates (Table 1, entries 2 (OH) and 3 (OMe)) exhibited more efficient coupling than non-oxygen-containing substrates. These results demonstrated that the hydrogen bonding facilitated the access of YC_7 @Pd²⁺ to the substrate molecules under aqueous conditions providing a compatible coupling environment for the Suzuki coupling reaction. Furthermore, the use of CTAB as a phase-transfer catalyst promoted the interphase transfer of substrates, thereby boosting the coupling yields of the non-oxygen containing substrates (Table 1, entries 4 (H) and 5 (Me)). As a control experiment, compared with the coupling reaction catalyzed by YC_7 @Pd²⁺, the coupling yields by PdCl₂ activation were lower than those of YC_7 @Pd²⁺ in same condition (Table S4†).

Given the successful catalytic activity of YC7@Pd2+ in the Suzuki coupling reactions, we further investigated the catalytic activity of YC₇@Pd²⁺ in the Sonogashira coupling reactions with CuI under aqueous conditions.27 The Sonogashira coupling reaction catalysed by YC_7 (a) Pd^{2+} exhibited a high coupling yield with a strong electron-withdrawing substrate (Table S5,† entry 1). In contrast to the Suzuki coupling reaction, the hydrogen bonding derived from the electron-donating substrates (Table S5,† entries 3 and 6) was not relatively effective on the catalytic activity in the Sonogashira coupling reaction. CTAB strongly suppressed the cross-coupling reaction, and instead, accelerated homo-coupling reaction with activated aryl iodide. The results indicate that CTAB did not afford a compatible crosscoupling environment between the catalyst and the substrates in the Sonogashira coupling reaction, whereas it stabilized phenylacetylene with Cu⁺ ion to activate the homo-coupling pathway.

During the coupling reaction at 80 °C in an aqueous solvent, $YC_7@Pd^{2+}$ disassembled into a soluble Pd-peptide complex, which is reduced into the solubilized PdNP catalyst. After cooling down to room temperature, the PdNP-peptide complex was reassembled and transformed into a nanostructure which is similar with a shape of astrocyte (YC₇@PdNP, Fig. S6b†). This reversible process between homogeneous and heterogeneous

states facilitated easy isolation and reuse of YC₇@PdNP from the reaction mixture. To evaluate the reusability of YC₇@Pd²⁺, the catalyst was recycled in subsequent Suzuki coupling reactions with 4-iodophenol or 4-iodoacetophenone. While the coupling yields of the activated substrates (iodoacetophenone) decreased slightly in the fourth and fifth runs, 4-iodophenol which can form a hydrogen bonding with YC₇@PdNP was converted to the corresponding biaryl compound in excellent yields (yield > 98%) even after 5th use (Fig. S7†).⁹ These results reconfirm that hydrogen bonding enabled the substrates for easy access to the Pd-peptide complex as well as possibly stabilizing the PdNPs for excellent catalytic activity during a series of Suzuki coupling reactions.

In conclusion, we developed a novel method for the construction of Pd²⁺-ion-mediated sphere-to-bridge-shaped peptide nanostructures, YC7@Pd²⁺, of which morphology can be controlled by temperature in an aqueous phase. Characterized by the switchable thermally-reversible phase transition, YC₇@Pd²⁺ acted as a solubilized nano-catalyst during C-C coupling reactions and reassembled into a heterogeneous structure for isolation and reuse after each coupling reaction. YC₇(a)Pd²⁺ showed an excellent activity as a catalyst for the Suzuki and the Sonogashira coupling reactions under aqueous conditions. Especially, in the Suzuki coupling reaction, hydrogen bonding capability of the substrates provided a favourable coupling environment, enhancing the coupling yield and reusability of the catalyst. The morphology controllable self-assembled Pd²⁺-ion-mediated peptide nanostructure can open a new avenue as a reusable catalyst for C-C coupling reactions under environmentally-friendly conditions.

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