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A phase-reversible Pd containing sphere-to-bridge-shaped peptide nanostructure for cross-coupling reactions†

 Seongsu Kim, [‡]^a Hong-Jun Cho, [‡]^b Namhun Lee, ^a Yoon-Sik Lee, ^{*b}
 Dong-Sik Shin ^{*c} and Sang-Myung Lee ^{*a}

A sphere-to-bridge-shaped peptide nanostructure was constructed from a tyrosine-rich peptide (H-YYACAYY-OH) via mediating Pd^{2+} 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 Fe^{2+} 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 cross-linking *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

hydrophobic carbon-chain and ionic peptide sequences are promising as bio-inspired-templates for growing PdNPs-incorporated nanofibers. Recently, several groups have demonstrated nanofiber incorporated with PdNPs using a self-assembled 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 Pd^{2+} -ion-mediated sphere-to-bridge-shaped peptide nanostructures (YC₇@Pd²⁺) through thermally induced phase transition. During the transition, the Pd^{2+} 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 astrocyte-shaped 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

^aDepartment of Chemical Engineering, Kangwon National University, Gangwon-do 24341, Republic of Korea. E-mail: sangmyung@kangwon.ac.kr; Fax: +82 33 251 3658; Tel: +82 33 250 6335

^bSchool of Chemical and Biological Engineering, Seoul National University, Seoul 08826, Republic of Korea. E-mail: yslee@snu.ac.kr; Fax: +82 2 880 1604; Tel: +82 2 880 7073

^cDepartment of Chemical and Biological Engineering, Sookmyung Women's University, Seoul 04310, Republic of Korea. E-mail: dshin@sm.ac.kr; Fax: +82 2 2077 7450; Tel: +82 2 2077 7236

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‡ The authors contributed equally to this work.



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 self-assembles in an aqueous phase into a two-dimensional nanostructure.¹⁷ From this peptide, we synthesized sphere-to-bridge-type peptide nanostructures ($YC_7@Pd^{2+}$) *via* thermally controlled and Pd^{2+} -ion-mediated ionic interactions (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, YC_7 underwent a rapid transition into a secondary, α -helix-dominant structure. At this stage, Pd^{2+} 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 Pd^{2+} ions. Without Pd^{2+} ions, YC_7 molecules were self-assembled into irregular shaped nanostructures and nanosheets during the thermodynamic transition (90 °C → 60 °C) *via* interactions between tyrosines and cysteine crosslinking (Fig. S1†). However, the $YC_7@Pd^{2+}$, which was self-assembled by interactions with Pd^{2+} ions, was uniform and spherical with an average diameter of 88 ± 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 $YC_7@Pd^{2+}$, including Pd, N, O, S and Cl, were analysed by energy-dispersive X-ray microanalysis mapping (Fig. S2†). The results demonstrated that $YC_7@Pd^{2+}$ was composed of Pd^{2+} ions, evenly distributed within the YC_7 matrix.

To analyse the structure of $YC_7@Pd^{2+}$ and the interactions between Pd^{2+} ions and the peptides, it was further characterized by infrared (IR) spectroscopy (Fig. 2). Bands from $\nu(C-O)$, $\nu(CC)$, $\delta(COH)$ of Tyr in YC_7 peptide were observed at $1070-1270\text{ cm}^{-1}$,

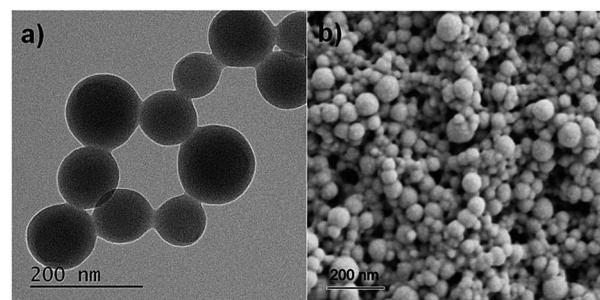
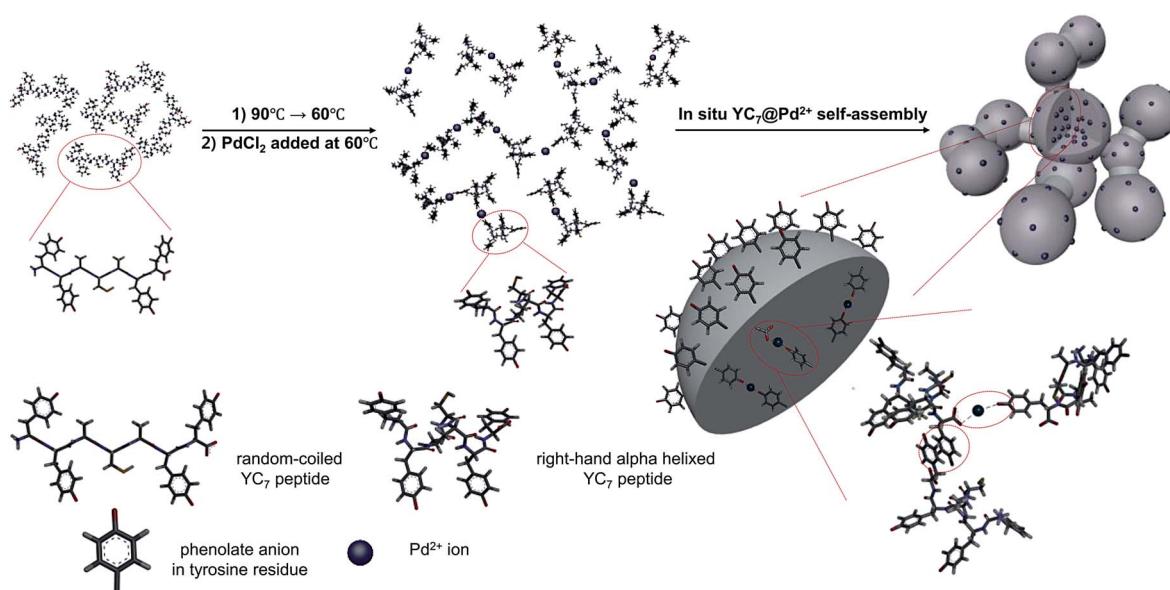


Fig. 1 (a) TEM image and (b) SEM image of $YC_7@Pd^{2+}$ nanostructure.

which exhibited relatively strong intensity due to its polar character (Fig. 2). These peaks are unique in Tyr not in other residues of YC_7 peptide. When the C–O stretching vibration bands of the self-assembled YC_7 and $YC_7@Pd^{2+}$ were compared, $YC_7@Pd^{2+}$ gave strong peaks at 1232 cm^{-1} involving two stretching modes of $\nu(C=C)$ and $\nu(C-O)$ in Tyr–OH, which are attributed to stronger polarity of phenolate (Tyr residue) in the presence of Pd^{2+} .¹⁸⁻²¹ These results clearly show that there are strong interactions between Pd^{2+} ions and tyrosine groups of $YC_7@Pd^{2+}$. In addition, a new C=O stretching vibration from the carboxylate of $YC_7@Pd^{2+}$ appeared at 1557 cm^{-1} which corresponds to the asymmetric stretching vibration of metal carboxylates.²²

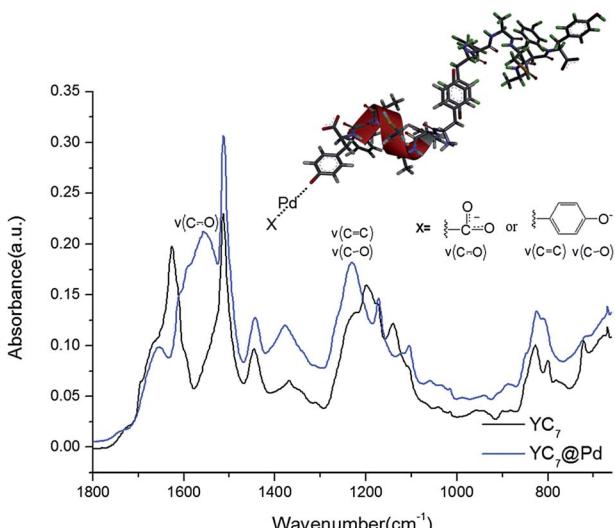
Additionally, the X-ray photoelectron spectroscopy (XPS) data of $YC_7@Pd^{2+}$ clearly revealed Pd peaks ($3d_{2/5}$ and $3d_{3/5}$) at 343.20 and 337.95 eV which corresponded to Pd(II) (Fig. S3†).²³ Taken together, $YC_7@Pd^{2+}$ is a non-crystalline peptide complex coordinated with Pd(II) at tyrosine residues, and has a potential as a Pd catalyst used in C–C coupling reactions. Consequently, Pd^{2+} -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 $YC_7@Pd^{2+}$ synthesis by thermal phase transition of dissolved YC_7 and Pd^{2+} -ion-driven self-assembly.



Fig. 2 FT-IR spectra of $\text{YC}_7\text{@Pd}^{2+}$ and YC_7 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 $\text{YC}_7\text{@Pd}^{2+}$ 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 $\text{YC}_7\text{@Pd}^{2+}$ (Fig. S5†). This result supports that Pd^{2+} 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 $\text{YC}_7\text{@Pd}^{2+}$ by evaluating the efficiency of C-C coupling reactions including Suzuki, Heck and Sonogashira coupling reactions.²⁴ Actually, $\text{YC}_7\text{@Pd}^{2+}$ nanostructures are decomposed into the solution at coupling reaction temperature, and then PdNPs instantly reduced from Pd^{2+} ions participate in the three kinds of coupling reactions. First, various bases for each coupling reaction were screened in aqueous solution.²⁵ K_2CO_3 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 $\text{YC}_7\text{@Pd}^{2+}$ in the Heck coupling reactions gave unfavourable yields (<2%) even in the presence of cetyl trimethyl ammonium bromide (CTAB) (Table S3†).²⁶ Therefore, $\text{YC}_7\text{@Pd}^{2+}$ 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 $\text{YC}_7\text{@Pd}^{2+}$ can be transformed into the homogeneous phase.

An activated aryl iodide (4-iodoacetophenone) was well-converted to the corresponding biaryl compounds in the Suzuki coupling reaction with over 98% yield in only 1 h with 0.1 mol% of $\text{YC}_7\text{@Pd}^{2+}$ (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 $\text{YC}_7\text{@Pd}^{2+}$ catalyst^a

		$\text{R}-\text{C}_6\text{H}_4-\text{I} + \text{C}_6\text{H}_5\text{B(OH)}_2 \xrightarrow[\text{K}_2\text{CO}_3, \text{H}_2\text{O}, 80^\circ\text{C}]{\text{YC}_7\text{@Pd}^{2+}}$	
Entry	R	Time (h)	Yield ^c (%)
1	COCH_3	1	98.7
2	OH	3	99.6
3	OCH_3	3	92.8
4	H	3/3 ^b	88.8/99.9 ^b
5	CH_3	6/3 ^b	70.8/96.0 ^b
6	2-Iodothiophene	6/3 ^b	40.0/91.3 ^b

^a Conditions: aryl iodine and heterocyclic halides (0.155 mmol), phenylboronic acid (0.186 mmol), $\text{YC}_7\text{@Pd}^{2+}$ (0.1 mol%), K_2CO_3 (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 oxygen-containing 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 $\text{YC}_7\text{@Pd}^{2+}$ 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 $\text{YC}_7\text{@Pd}^{2+}$, the coupling yields by PdCl_2 activation were lower than those of $\text{YC}_7\text{@Pd}^{2+}$ in same condition (Table S4†).

Given the successful catalytic activity of $\text{YC}_7\text{@Pd}^{2+}$ in the Suzuki coupling reactions, we further investigated the catalytic activity of $\text{YC}_7\text{@Pd}^{2+}$ in the Sonogashira coupling reactions with CuI under aqueous conditions.²⁷ The Sonogashira coupling reaction catalysed by $\text{YC}_7\text{@Pd}^{2+}$ 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 cross-coupling 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, $\text{YC}_7\text{@Pd}^{2+}$ 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 ($\text{YC}_7\text{@PdNP}$, Fig. S6b†). This reversible process between homogeneous and heterogeneous



states facilitated easy isolation and reuse of $\text{YC}_7@\text{PdNP}$ from the reaction mixture. To evaluate the reusability of $\text{YC}_7@\text{Pd}^{2+}$, 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 $\text{YC}_7@\text{PdNP}$ 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 Pd^{2+} -ion-mediated sphere-to-bridge-shaped peptide nanostructures, $\text{YC}_7@\text{Pd}^{2+}$, of which morphology can be controlled by temperature in an aqueous phase. Characterized by the switchable thermally-reversible phase transition, $\text{YC}_7@\text{Pd}^{2+}$ 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. $\text{YC}_7@\text{Pd}^{2+}$ 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 Pd^{2+} -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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