A phase-reversible Pd containing sphere-to-bridge-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. 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. Such metal coordination can initiate intermolecular self-assembly by bringing two or more peptides into close proximity. 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.

Based on a peptide template, various types of metal-peptide nanostructures have been designed and utilized as electrochemical sensors, biological scaffolds, and catalysts. 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 Peptide nanostructures with a large surface area by using a self-assembling peptide template composed of R5 peptide. 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. 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. Based on this finding, we have successfully designed Pd2+-ion mediated sphere-to-bridge-shaped peptide nanostructures (YC7@PdNP) 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@PdNP 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@PdNP 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@PdNP as a new type of catalyst under environmentally friendly conditions: (a) as a nano-catalyst during C–C coupling reactions; and (b) as a heterogeneous catalyst for separation, especially in Suzuki and...
Sonogashira coupling reactions. YC7@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.

YC7 is a random coil-dominant peptide, which self-assembles in an aqueous phase into a two-dimensional nanostructure. From this peptide, we synthesized sphere-to-bridge-type peptide nanostructures (YC7@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, YC7 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, YC7 molecules were self-assembled into irregular shaped nanostructures and nano-sheets during the thermodynamic transition (90 °C → 60 °C) via interactions between tyrosines and cysteine crosslinking (Fig. S1†). However, the YC7@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 YC7@Pd^{2+}, including Pd, N, O, S and Cl, were analyzed by energy-dispersive X-ray microanalysis mapping (Fig. S2†). The results demonstrated that YC7@Pd^{2+} was composed of Pd^{2+} ions, evenly distributed within the YC7 matrix.

To analyse the structure of YC7@Pd^{2+} and the interactions between Pd^{2+} 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, 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@Pd^{2+} were compared, YC7@Pd^{2+} 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 Pd^{2+}. These results clearly show that there are strong interactions between Pd^{2+} ions and tyrosine groups of YC7@Pd^{2+}. In addition, a new C=O stretching vibration from the carboxylate of YC7@Pd^{2+} appeared at 1557 cm⁻¹ which corresponds to the asymmetric stretching vibration of metal carboxylates.

Additionally, the X-ray photoelectron spectroscopy (XPS) data of YC7@Pd^{2+} clearly revealed Pd peaks (3d_{3/2} and 3d_{5/2}) at 343.20 and 337.95 eV which corresponded to Pd(II) (Fig. S3†). Taken together, YC7@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 YC7@Pd^{2+} were primarily involved in coordination with Pd^{2+}. 

Scheme 1 Proposed mechanism of YC7@Pd^{2+} synthesis by thermal phase transition of dissolved YC7 and Pd^{2+}-ion-driven self-assembly.
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 YC7@Pd2+ was calculated to be 1.86 mmol Pd per g catalyst.

The X-ray diffraction (XRD) patterns of self-assembled YC7 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 YC7@Pd2+ (Fig. S5†). This result suggests that Pd2+ ions were able to collapse the intrinsic YC7 structure, leading to the irregular shaped peptide arrangement inside the sphere-to-bridge-shaped peptide nanostructure.

We investigated the catalytic activity of the YC7@Pd2+ 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 selected as the best base in the Suzuki and the Sonogashira reactions, respectively (Tables S1 and S2†). However, the catalytic activity of YC7@Pd2+ in the Heck coupling reactions gave unfavourable yields (<2%) even in the presence of cetyl trimethyl ammonium bromide (CTAB) (Table S3†). 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 with Cu+ ion to activate the homocoupling pathway.

Table 1  Suzuki–Miyaura coupling reactions for various aryl iodides in the presence of YC7@Pd2+ catalyst†

| Entry | R        | Time (h) | Yield (%) |
|-------|----------|----------|-----------|
| 1     | COCH3    | 1        | 98.7      |
| 2     | OH       | 3        | 99.6      |
| 3     | OCH3     | 3        | 92.8      |
| 4     | H        | 3/3†     | 88.8/99.9†|
| 5     | CH3      | 6/3†     | 73.8/96.0†|
| 6     | 2-Iodothiophene | 6/3†     | 40.0/91.3†|

† 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. GC yields when 0.5 eq. of CTAB was used. GC yields.

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 YC7@Pd2+ exhibited a high coupling yield with a strong electron-withdrawing substrate (Table S3† 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, YC7@Pd2+ 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 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 YC7@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 YC7@Pd2+, the coupling yields by PdCl2 activation were lower than those of YC7@Pd2+ in same condition (Table S4†).
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). 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@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.

Acknowledgements

This work was supported by the Ministry of Science, ICT & Future Planning and National Research Foundation of Korea through Basic Science Research Program (NRF-2014R1A1A1006711), the Ministry of Trade, Industry & Energy (MOTIE), Korea Institute for Advancement of Technology (KIAT) through the Encouragement Program for The Industries of Economic Cooperation Region (R0004027) and Kangwon National University through 2015 Research Grant (No. 520150081).

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