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Development of an aquacatalytic system based on the formation of vesicles of an amphiphilic palladium NNC-pincer complex

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Two amphiphilic palladium NNC-pincer complexes bearing hydrophilic tri(ethylene glycol) chains and hydrophobic dodecyl chains were designed and prepared for the development of a new aquacatalytic system. In water, these amphiphilic complexes self-assembled to form vesicles, the structures which were established by means of a range of physical techniques. When the catalytic activities of the vesicles were investigated in the arylation of terminal alkynes in water, they were found to catalyze the reaction of aryl iodides with terminal alkynes to give good yields of the corresponding internal alkynes. The formation of a vesicular structure was shown to be essential for efficient promotion of this reaction in water.

Introduction

Bilayer vesicles, which are formed by self-assembly of amphiphilic molecules, have received considerable attention as nanomaterials from a wide range of scientists.[1] Several research groups have recently reported that organic molecules that have rigid planar backbones and contain both hydrophilic and hydrophobic groups can self-assemble to form bilayer architectures such as vesicles or nanotubes.[2] If hydrophilic and hydrophobic side chains are incorporated onto rigid planar transition-metal complexes, the resulting amphiphilic complexes can self-assemble to form bilayer vesicles that show catalytic activities.[3,4] On the basis of this concept, we designed and synthesized the amphiphilic palladium NCN-pincer complexes **1a** and **1b** (Figure 1). The prepared complexes **1a** and **1b** self-assembled in aqueous solutions to form bilayer vesicles. These vesicles efficiently catalyzed several organic transformations in water, including ring-opening of vinyl epoxides, the Miyaura–Michael reaction, and the cyclization of alkynoic acids. The formation of bilayer vesicles was shown to be necessary for efficient promotion of these reactions.[5] The promotion of these reactions through the formation of vesicles is explained as follows. The organic substrates are concentrated within the hydrophobic region of the bilayer membrane as a result of hydrophobic interactions, producing high concentrations of the substrate near the catalytic center and, consequently, giving rise to rapid reactions (Figure 2).

On the other hand, palladium-catalyzed arylation of terminal alkynes is one of the most useful synthetic means for making a carbon-carbon bond.[6] To expand the range and usefulness of
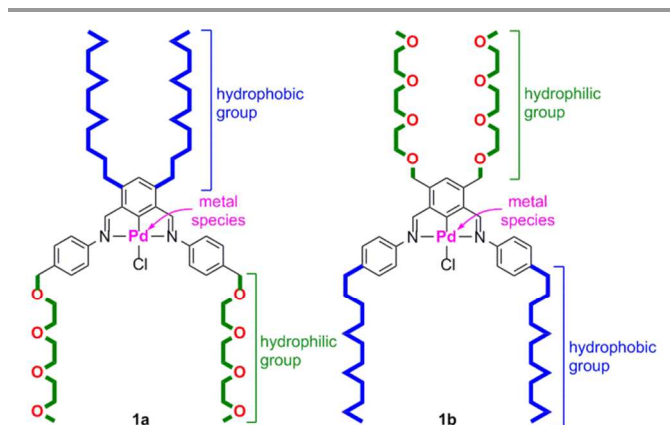

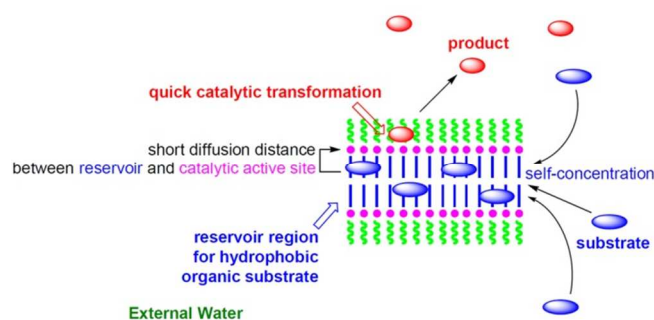**Figure 1** Amphiphilic palladium NCN-pincer complexes **1a** and **1b**.

Figure 2 Concept of organic transformation within a bilayer membrane.

our concept, we examined the design and synthesis of new amphiphilic palladium NNC-pincer complexes **2a** and **2b** bearing both hydrophilic and hydrophobic side chains (Figure 3), their formation of vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$ by self-assembly in water, and their use as catalysts in the arylation reaction of terminal alkynes in water. The formation of a vesicular structure was shown to be essential for efficient catalysis in water.
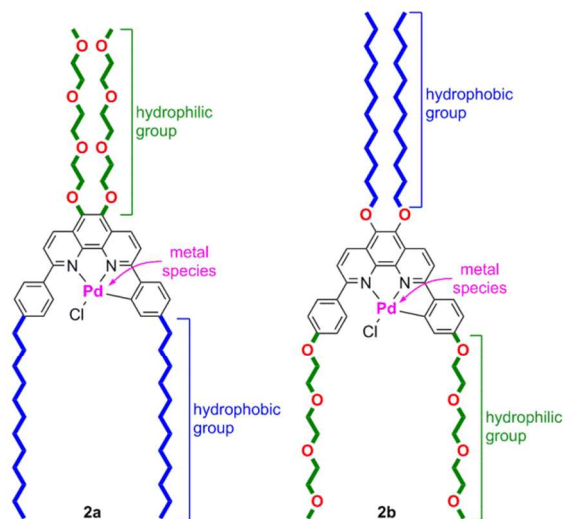

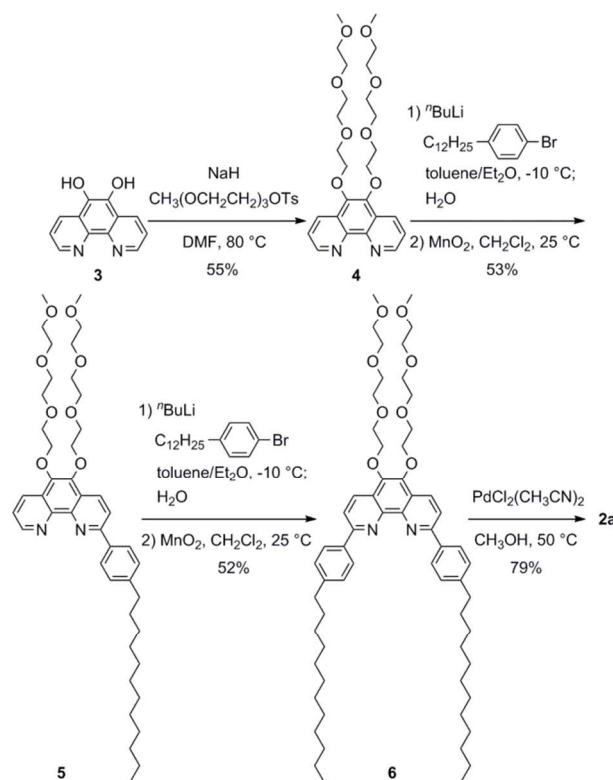**Figure 3** Amphiphilic palladium NNC-pincer complexes **2a** and **2b**.

Results and Discussion

Synthesis of palladium NNC-pincer complexes 2

Amphiphilic palladium NNC-pincer complex **2a** was prepared from 1,10-phenanthroline-5,6-diol (**3**) (Scheme 1).[7] The reaction of 1,10-phenanthroline-5,6-diol (**3**) with CH$_3$(OCH$_2$CH$_2$)$_3$OTs (MeOTEGOTs) gave 5,6-bis(MeOTEGO)-1,10-phenanthroline (**4**) in 55% yield. Monoarylation of hydrophilic phenanthroline **4** was carried out with *p*-dodecylphenyllithium, which was generated in situ by treatment of *p*-bromododecylbenzene with *n*-BuLi at −10 °C, followed by aqueous quenching and subsequent rearomatization with MnO$_2$ to give compound **5** in 53% yield. Monoarylated phenanthroline **5** was converted into diarylated phenanthroline **6** under the similar arylation conditions in 52% yield. Treatment of diarylated phenanthroline **6** with PdCl$_2$(CH$_3$CN)$_2$ in methanol at 50 °C furnished the desired amphiphilic NNC pincer palladium complex **2a** in 79% yield. The ^{1}H NMR spectra of ligand **6** and complex **2a** are shown in Figure 4. Proton signals of **6** and **2a** were assigned by H-H COSY and NOE experiments. Complexation of **6** with PdCl$_2$(CH$_3$CN)$_2$ gave the peaks derived from the unsymmetrical phenanthroline framework (Figure 4, bottom). ESI-MS analysis supported the structure of complex **2a** (Figure 5).

We also synthesized amphiphilic palladium NNC-pincer complex **2b** bearing hydrophilic and hydrophobic chains in the opposite orientation to those of complex **2a** from 1,10-phenanthroline-5,6-diol (**3**) (Scheme 2). Thus, the hydrophobic

dodecyl groups were introduced at the hydroxy groups of **3** to give 5,6-bis(dodecyloxy)-1,10-phenanthroline (**7**) in 72% yield.

Scheme 1 Synthesis of amphiphilic palladium NNC-pincer complex **2a**.

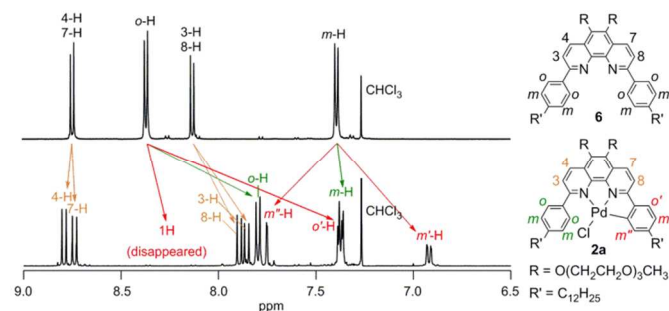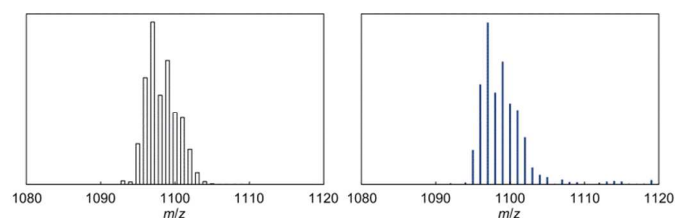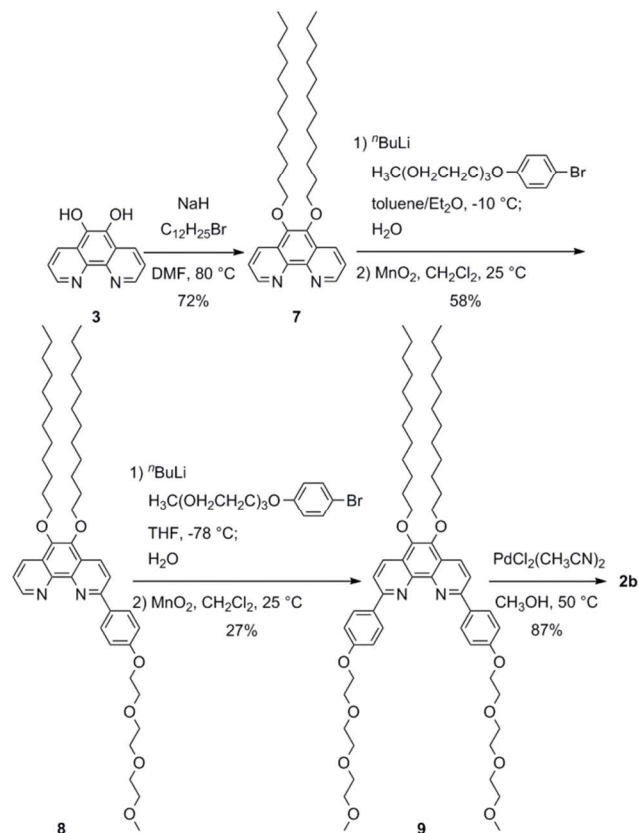**Figure 4** NMR spectra of **6** (top) and **2a** (bottom).

Figure 5 Calculated (left) and observed (right) ESI mass spectra of [**2a**-Cl]$^+$.

The reaction of hydrophobic phenanthroline **7** with *p*-(MeOTEGO)phenyllithium followed by hydrolysis and subsequent rearomatization with MnO$_2$ afforded monoarylated phenanthroline **8**. Diarylated phenanthroline **9** was obtained by

the arylation of monoarylated phenanthroline **8**. Treatment of diarylated phenanthroline **9** with $PdCl_2(CH_3CN)_2$ provided the desired amphiphilic palladium NNC-pincer complex **2b** in 87%

yield. The ^1H NMR spectra of ligand **9** and complex **2b** are shown in Figure 6. After complexation of **9** with $PdCl_2(CH_3CN)_2$, proton signals derived from the unsymmetrical phenanthroline structure were observed (Figure 6, bottom). The structure of complex **2b** was supported by ESI-MS analysis (Figure 7).

Self-assembly of palladium NNC-pincer complexes 2a and 2b

Having prepared the desired complexes **2a** and **2b**, we examined their self-assembly behaviors (Figure 8). After screening of conditions for self-assembly, we found that complexes **2a** and **2b** both self-assembled in water to form the corresponding vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$. Though the correlation between the conditions and the structure (shape and/or size) of the self-assemlage is yet unpredictable,[8] we found the reproducible assembling protocols. Thus, complex **2a** was heated in water at 60 °C for 4 hours without stirring. After standing at 25 °C overnight, the resulting mixture was sonicated for 15 minutes to give a yellow suspension. Complex **2b** was treated in water at 80 °C for 12 hours without stirring.

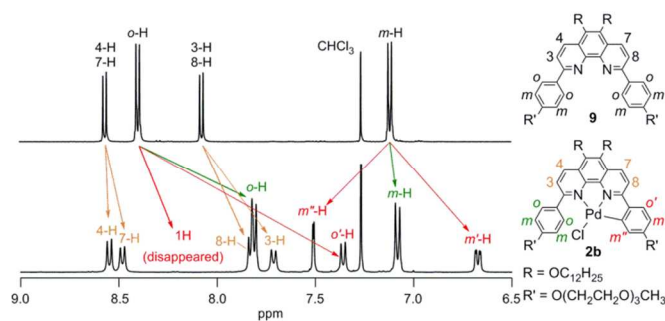**Scheme 2** Synthesis of amphiphilic palladium NNC-pincer complex **2b**.

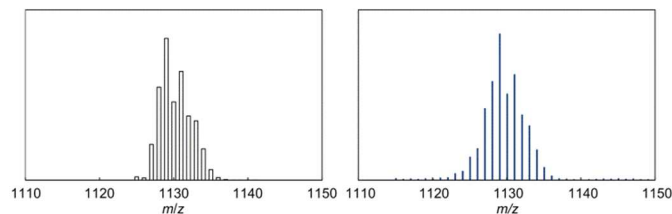**Figure 6** NMR spectra of **9** (top) and **2b** (bottom).

Figure 7 Calculated (left) and observed (right) ESI mass spectra of [**2b**-Cl]$^+$.
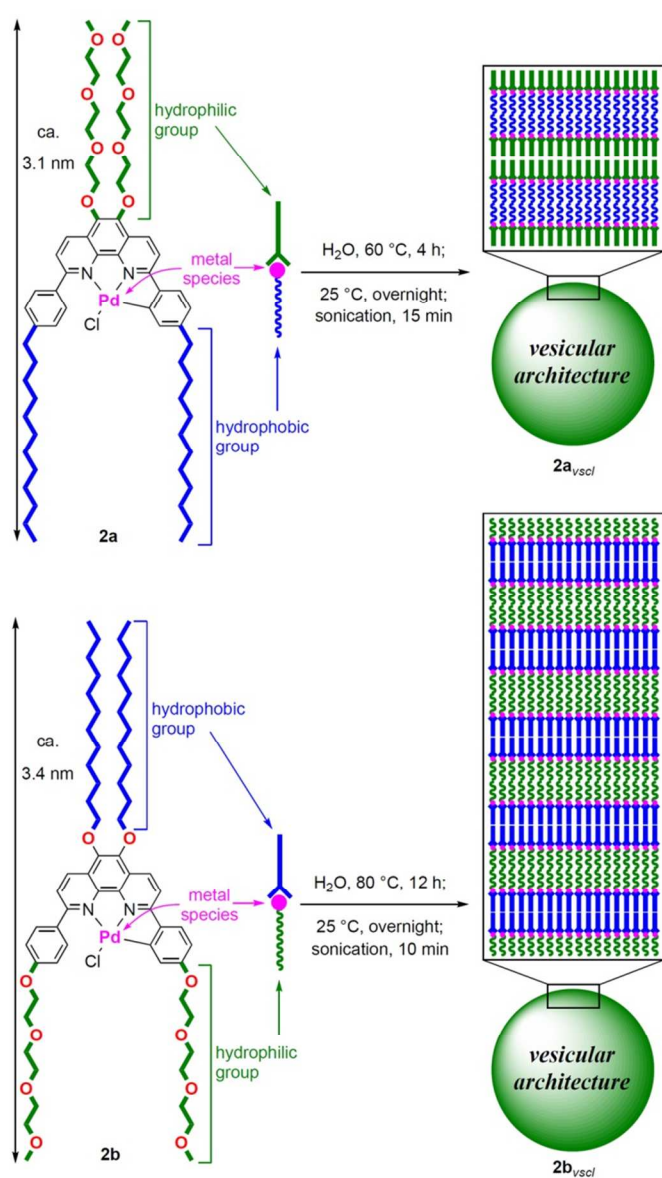
Figure 8 Self-assembly of amphiphilic palladium NNC-pincer complexes **2**.

Figure 9 (a) A histogram of the size distribution of **2a**$_{vscl}$ in water. (b) AFM image of **2a**$_{vscl}$. (c) TEM image of **2a**$_{vscl}$. (d) Fluorescence micrograph of **2a**$_{vscl}$. (e) CLSM image of **2a**$_{vscl}$.

The resulting aqueous mixture was cooled to 25 °C and then sonicated for 10 minutes to give a yellow slurry. Dynamic light-scattering (DLS) analyses showed that the average diameters of vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$ were 554 and 985 nm, respectively (Figures 9a and 10a).[8] To investigate the morphologies of the vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$, the self-assembled architectures were characterized by means of various

(b)

(c)

200 nm

32 nm

(d)

1.0 μm

(e)

1.0 μm
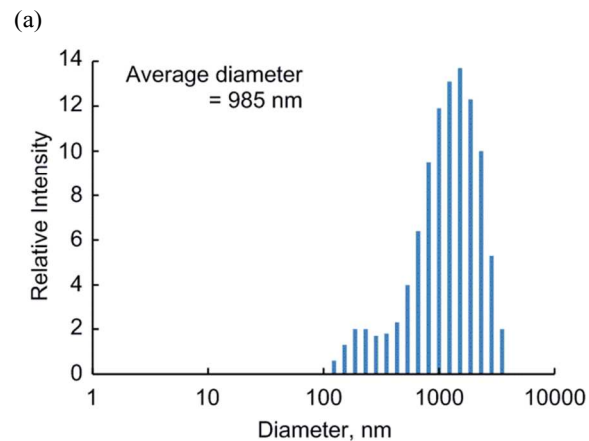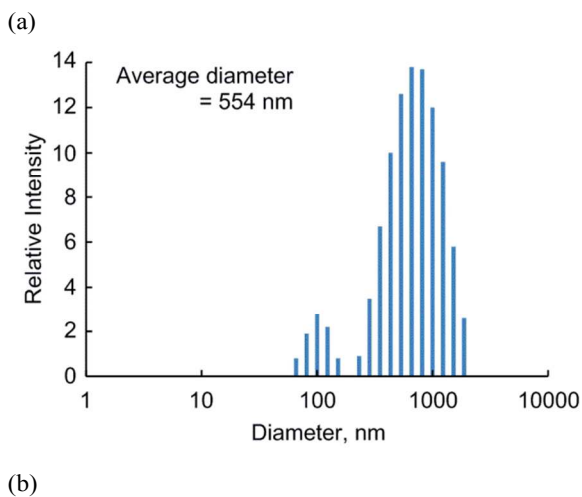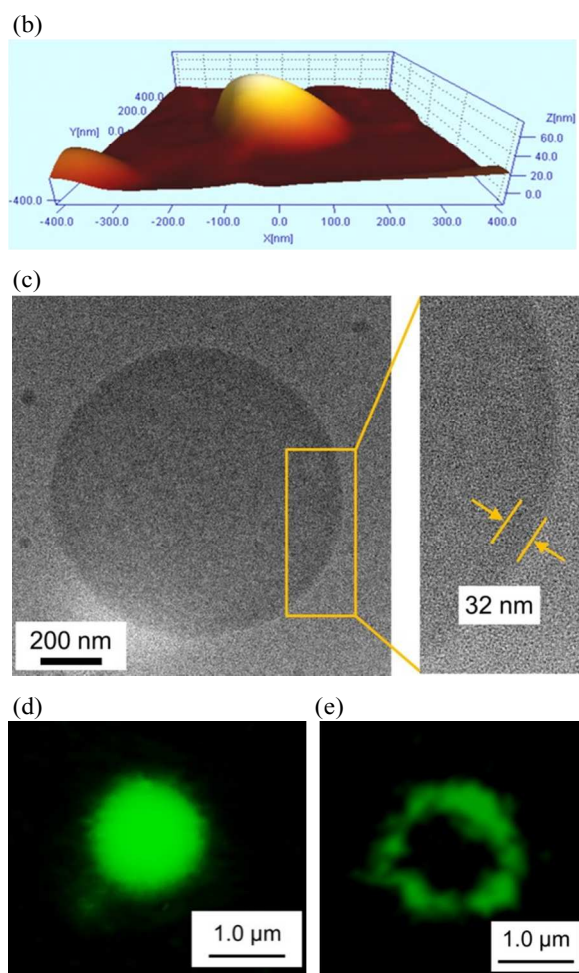
Figure 10 (a) A histogram of the size distribution of **2b**$_{vscl}$ in water. (b) AFM image of **2b**$_{vscl}$. (c) TEM image of **2b**$_{vscl}$. (d) Fluorescence micrograph of **2b**$_{vscl}$. (e) CLSM image of **2b**$_{vscl}$.

microscopic techniques. Atomic-force microscopy (AFM) confirmed that vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$ were spherical in shape (Figures 9b and 10b). Transmission electron microscopy (TEM) showed that vesicles **2a**$_{vs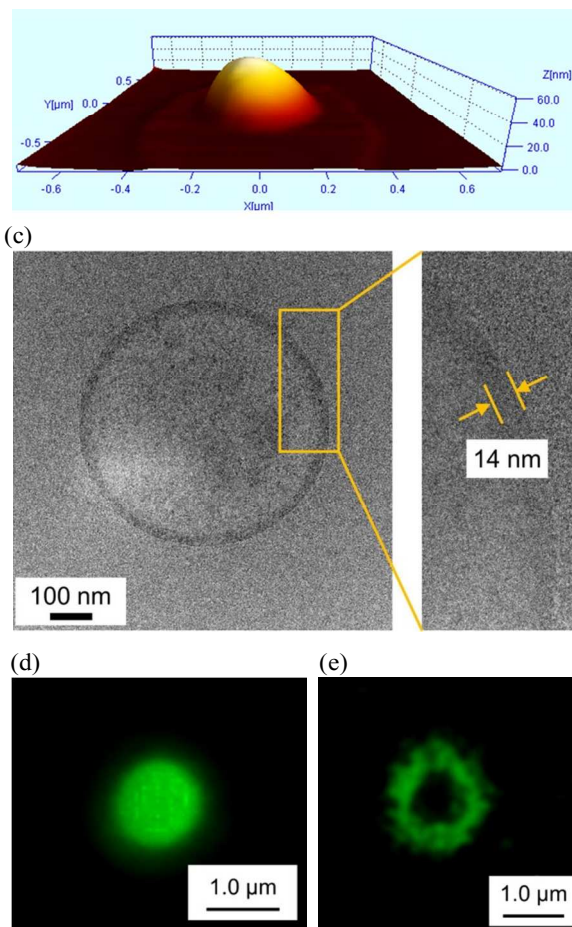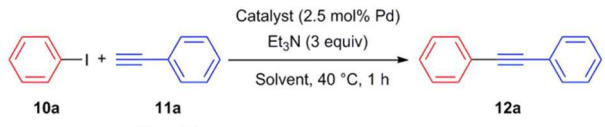cl}$ and **2b**$_{vscl}$ had hollow structures (Figures 9c and 10c); TEM also showed that the thicknesses of the membranes of the observed vesicles were 14 and 32 nm, respectively. These observations suggested that membranes of **2a**$_{vesl}$ and **2b**$_{vscl}$ consisted of tetralayer structure of **2a** having a monomer length of approximately 3.1 nm (Figure 8, top) and decalayer structure of **2b** having a monomer length of approximately 3.4 nm (Figure 8, bottom), respectively.[9] The addition of fluorescein as a fluorophore to aqueous suspensions of vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$ gave the corresponding fluorescent vesicles **2a**$_{vscl}$/fluorescein and **2b**$_{vscl}$/fluorescein. The incorporation of fluorescein into these vesicles was confirmed by means of fluorescence microscopy (Figures 9d and 10d). Furthermore, confocal laser-scanning microscopy (CLSM) showed the presence of hollow structures with membranes containing fluorescein (Figures 9e and 10e). These observations revealed the presence of an inner hydrophobic region within the exterior membranes of vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$. After heating

of **2a**$_{vscl}$ and **2b**$_{vscl}$ at 100 °C in water for 1 hour, structural integrity was observed for both vesicles through TEM observation (see Electronic Supplementary Information).
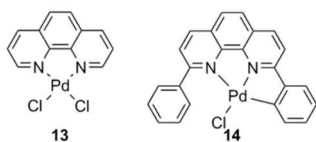
Arylation of terminal alkynes in water

Having prepared and characterized vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$, we next explored their catalytic activities in the coupling reaction of iodobenzene (**10a**) with ethynylbenzene (**11a**) in water (Table 1).[10–12] Vesicles **2a**$_{vscl}$ promoted the reaction of iodobenzene (**10a**) with ethynylbenzene (**11a**) in water at 40 °C for 1 h in the presence of triethylamine to give 1,1'-ethyne-1,2-diyldibenzene (**12a**) in 92% yield (Table 1, entry 1).[13] In contrast, when the amorphous complex **2a**$_{amps}$ (non-assembled nanopowder of complex **2a**)[14] was used as the catalyst, only a 14% yield of the desired product **12a** was obtained (Table 1, entry 2). The formation of a vesicular structure therefore significantly accelerated the coupling reaction of iodobenzene (**10a**) with ethynylbenzene (**11a**) in water.[15] In the presence of vesicles **2b**$_{vscl}$ and the amorphous complex **2b**$_{amps}$ (non-assembled nanopowder of complex **2b**)[14], the reaction of iodobenzene (**10a**) with ethynylbenzene (**11a**) gave **12a** in yields of 32 and 30%, respectively (entries 3 and 4). The formation of vesicles from **2b** did not, therefore, improve its catalytic activity in this reaction. The catalytic activity of vesicles **2a**$_{vscl}$ bearing hydrophobic dodecyl chains near the palladium center was greater than that of vesicles **2b**$_{vscl}$, which bore hydrophilic tri(ethylene glycol) chains near the palladium center (entries 1 and 3). The difference in the catalytic activities of **2a**$_{vscl}$ and **2b**$_{vscl}$ might be explicable as follows: when vesicles **2a**$_{vscl}$ are used as the catalyst, the organic substrates (aryl iodides and alkynes) are present near the catalytic centers because the palladium atoms are directed to the hydrophobic regions; consequently, the coupling reaction proceeds smoothly. On the other hand, when vesicles **2b**$_{vscl}$ are used as the catalyst, the approach of the organic substrates to the palladium is hindered because the palladium is present in a hydrophilic region and, consequently, the reaction does not proceed efficiently. The directions of the hydrophilic chains and the hydrophobic chains attached to the phenanthroline backbone therefore influence the catalytic activity. The simple palladium phenanthroline complexes **13** and **14** did not efficiently promote the reaction (entries 5 and 6). We also examined the catalytic activities of **2a**$_{vscl}$ and **2a**$_{amps}$ in organic solvents. In the presence of vesicles **2a**$_{vscl}$ or the amorphous complex **2a**$_{amps}$, the reaction did not proceed in toluene, dichloromethane, or tetrahydrofuran (THF) (entries 7–12). When acetonitrile or methanol was used as the solvent, the reaction gave only 3–11% yields of **12a** (entries 13–16). These results indicate that vesicles **2a**$_{vscl}$ disassembled or dissolved in the organic solvents to give the catalytically less-active monomeric complex **2a**.

Table 1 The reaction of iodobenzene (**10a**) with ethynylbenzene (**11a**)[a]

Entry	Catalyst	Solvent	Yield (%)[b]
1	**2a**$_{vscl}$	H_2O	92
2	**2a**$_{amps}$	H_2O	14
3	**2b**$_{vscl}$	H_2O	30
4	**2b**$_{amps}$	H_2O	32
5	**13**	H_2O	0
6	**14**	H_2O	5
7	**2a**$_{vscl}$	Toluene	0
8	**2a**$_{amps}$	Toluene	0
9	**2a**$_{vscl}$	CH_2Cl_2	0
10	**2a**$_{amps}$	CH_2Cl_2	0
11	**2a**$_{vscl}$	THF	0
12	**2a**$_{amps}$	THF	0
13	**2a**$_{vscl}$	CH_3CN	3
14	**2a**$_{amps}$	CH_3CN	3
15	**2a**$_{vscl}$	CH_3OH	11
16	**2a**$_{amps}$	CH_3OH	7

[a] *Reaction conditions*: **10a** (0.034 mmol), **11a** (0.068 mmol), catalyst $(8.5 \times 10^{-4}$ mmol), Et_3N (0.10 mmol), solvent (1.0 mL), 40 °C. [b] Isolated yield.

To investigate the scope of the acceleration effect resulting from the formation of vesicles **2a**$_{vscl}$ in the arylation of terminal alkynes, reactions of various aryl iodides **10** with a range of alkynes **11** were carried out in the presence of vesicles **2a**$_{vscl}$ or the amorphous complex **2a**$_{amps}$ in water (Scheme 3). Vesicles **2a**$_{vscl}$ promoted the reactions of 1-iodo-4-(trifluoromethyl)benzene (**10b**) or 1-iodo-4-methoxybenzene (**10c**) with ethynylbenzene (**11a**) in water to give desired internal alkynes **12b** and **12c** in yields of 63 and 85%, respectively. In contrast, the amorphous complex **2a**$_{amps}$ gave **12b** and **12c** in only 19 and 18% yields, respectively. A similar acceleration effect resulting from the formation of the vesicular structure was also observed in the reaction of 1-iodo-3-methylbenzene (**10d**) or sterically hindered aryl iodides such as 1-iodo-2-methylbenzene (**10e**) or 1-iodonaphthalene (**10f**) with ethynylbenzene (**11a**). Vesicles **2a**$_{vscl}$ also catalyzed the reaction of 2-iodothiophene (**10g**) with ethynylbenzene (**11a**) to give the desired product **12g** in 75% yield, whereas the amorphous complex **2a**$_{amps}$ gave only a 24% yield of **12g**. The reaction of iodobenzene (**10a**) with 1-ethynylcyclohexene (**11b**)
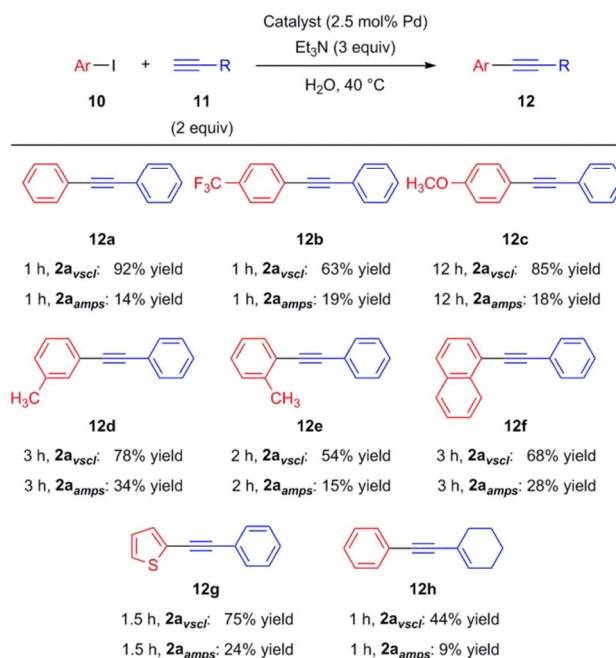
Scheme 3 The reactions of various aryl iodides and alkynes. *Reaction conditions*: **10** (0.034 mmol), **11** (0.068 mmol), catalyst (8.5×10^{-4} mmol), Et_3N (0.10 mmol), water (1.0 mL), 40 °C. The yields refer to isolated products.

proceeded in the presence of vesicles **2a**$_{vscl}$ to give alkyne **12h** in 44% yield, whereas only a 9% yield of **12h** was obtained when **2a**$_{amps}$ was used as the catalyst. The formation of vesicles therefore enhances the activity of the catalyst in the reactions of various aryl iodides with a range of alkynes.[16]

Conclusions

In summary, we have designed and synthesized two amphiphilic palladium NNC-pincer complexes **2a** and **2b** bearing both hydrophilic and hydrophobic chains for the development of new aquacatalytic systems. These complexes self-assembled in water to form vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$, which were characterized by means of DLS, TEM, AFM, fluorescence microscopy, and CLSM. In the arylation of terminal alkynes in water, vesicles **2a**$_{vscl}$ showed a superior catalytic activity to that of the amorphous complex **2a**$_{amps}$. The formation of a vesicular structure is essential for efficient promotion of this reaction. On the other hand, when vesicles **2b**$_{vscl}$ and amorphous complex **2b**$_{amps}$ were used as catalysts, the formation of vesicles **2b**$_{vscl}$ did not improve the catalytic activity for the reaction. The directions of the hydrophilic chains and the hydrophobic chains attached to the phenanthroline backbone therefore influence the catalytic activity. We are currently examining further applications of the aquacatalytic system based on the formation of vesicles **2a**$_{vscl}$ and **2b**$_{vscl}$ to a range of aqueous reaction systems, and these will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, additional TEM images and spectroscopic data for all products. See DOI: 10.1039/b000000x/

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11 *Typical procedure for the arylation of terminal alkynes*: To a vial equipped with a screw cap, 1 mL aqueous suspension of **2a**$_{vscl}$ (1.0 mg, 8.5×10^{-4} mmol), triethylamine (10.3 mg, 0.10 mmol), ethynylbenzene (**11a**) (7.0 mg, 0.068 mmol), and iodobenzene (**10a**) (6.9 mg, 0.034 mmol) were added. The reaction mixture was agitated with shaking at 40 °C for 1 h and allowed to cool to 25 °C. The reaction mixture was extracted with *tert*-butyl-methyl ether (1.0 mL, 5 times). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (eluent: hexane) to give 1,1'-ethyne-1,2-diyldibenzene **12a** (11.5 mg, 0.063 mmol, 92%) as white solids.

12 We also tested the coupling reaction of **10a** with **11a** in the presence of **1a**$_{vscl}$, **1a**$_{amps}$, **1b**$_{vscl}$, and **1b**$_{amps}$ in water under the similar reaction conditions for Table 1 to give **12a** in 34, 29, 23, and 27% yield, respectively. The formation of vesicles from **1a** and **1b** did not accelerate the reaction.

13 After the reaction, TEM analysis showed that the vesicular structure of **2a**$_{vscl}$ was maintained (see Electric Supplementary Information).

14 For TEM images of **2a**$_{amps}$ and **2b**$_{amps}$, see Electronic Supplementary Information.

15 The reaction of bromobenzene with ethynylbenzene (**11a**) with **2a**$_{vscl}$ (40 °C for 24 h in water) gave 1,1'-ethyne-1,2-diyldibenzene (**12a**) in 21% yield.

16 The reaction of iodobenzene (**10a**) with 1-*n*-heptyne with **2a**$_{vscl}$ (40 °C for 24 h in water) gave 1-heptyn-1-yl-benzene in only 22% yield.