Vesicular Catalyst

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Molecular-Architecture-Based Administration of Catalysis in Water: Self-Assembly of an Amphiphilic Palladium Pincer Complex**

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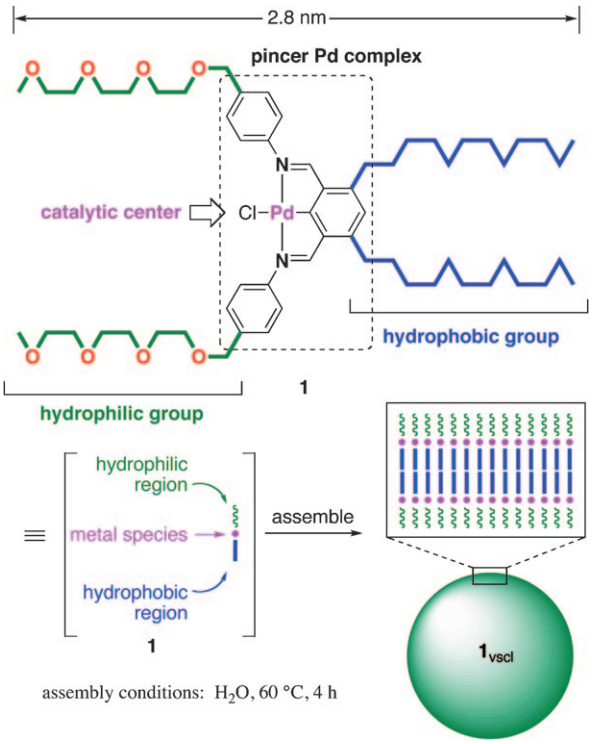
Biological membranes are known to play a key role in controlling life-related molecular functions (e.g., active/passive transport, diffusion, filtration, selective permeation, etc.). Lipid bilayer membrane vesicles (i.e., liposomes) are small assemblies of amphiphilic molecules bearing both hydrophilic and hydrophobic groups and they offer promising prospects for the understanding of biological membranes. If less-catalytically active small molecules can self-assemble to form bilayer vesicles and, in so doing, gain unique catalytic functions for a given molecular transformation, this process could conceivably be used in a catalysis-driven system.[1–3] We report herein the formation of a bilayer membrane vesicle from an amphiphilic palladium complex through self-assembly to realize palladium-catalyzed carbon–carbon bond-forming reactions under ambient conditions (in water, under air, at room temperature), wherein the vesicle architecture is essential for the catalysis. The formation of a catalytically active vesicle and the vesicle-catalyzed organic transformations were both promoted in water by the hydrophobic properties of the substrates and catalysts, as opposed to conventional artificial organic chemical reaction systems (i.e., standard flask reactions) that are often promoted with external driving forces (e.g., heat, pressure, light, etc.).

The pincer palladium complex **1**[4,5] having pairs of hydrophobic dodecyl chains and hydrophilic tri(ethylene glycol) (TEG) chains located opposite to one another on the rigid planar backbone, was designed and prepared for use in the self-assembly formation[6] of vesicles exhibiting catalytic activity in water (Scheme 1; see the Supporting Information). After the complex **1**, which was obtained as an amorphous nanopowder ($\mathbf{1}_{amps}$; Figure 1a), was treated in water at 60 °C for 4 hours, the resulting aqueous mixture was cooled and subjected to a dynamic light scattering (DLS) study (Figure 1c) to demonstrate the formation of the vesicle $\mathbf{1}_{vscl}$ (average diameter = 550 nm).[7] Vesicle $\mathbf{1}_{vscl}$ was isolated by centrifugation and decantation in 10–40% yield based on the recovery of **1** as an amorphous powder from the supernatant. Transmission electron microscopy (TEM) and atomic force microscopy (AFM) images of the isolated vesicle $\mathbf{1}_{vscl}$ are shown in Figures 1b and d, respectively.[8] These microscopic studies revealed that $\mathbf{1}_{vscl}$ was obtained as hard vesicles.[9] Their spherical form was confirmed by AFM (Figure 1d), and the thickness of the vesicle membrane was determined to be 6 nm by TEM methods (Figure 1b). These data are consistent with those of the bilayer membranous structure of $\mathbf{1}_{mono}$ having a monomer length of approximately 2.8 nm in the structure (Scheme 1).[10] The incorporation of the fluorescent reagent, fluorescein, into the $\mathbf{1}_{vscl}$ revealed a hollow structure with an inner hydrophobic region in the exterior membrane.[11] Thus, when the isolated $\mathbf{1}_{vscl}$ was exposed to fluorescein under aqueous conditions, the fluorescent vesicles, $\mathbf{1}_{vscl}$/fluorescein, were isolated after rinsing



Scheme 1. Formation of vesicle $\mathbf{1}_{vscl}$ by self-assembly of the pincer palladium complex **1**.

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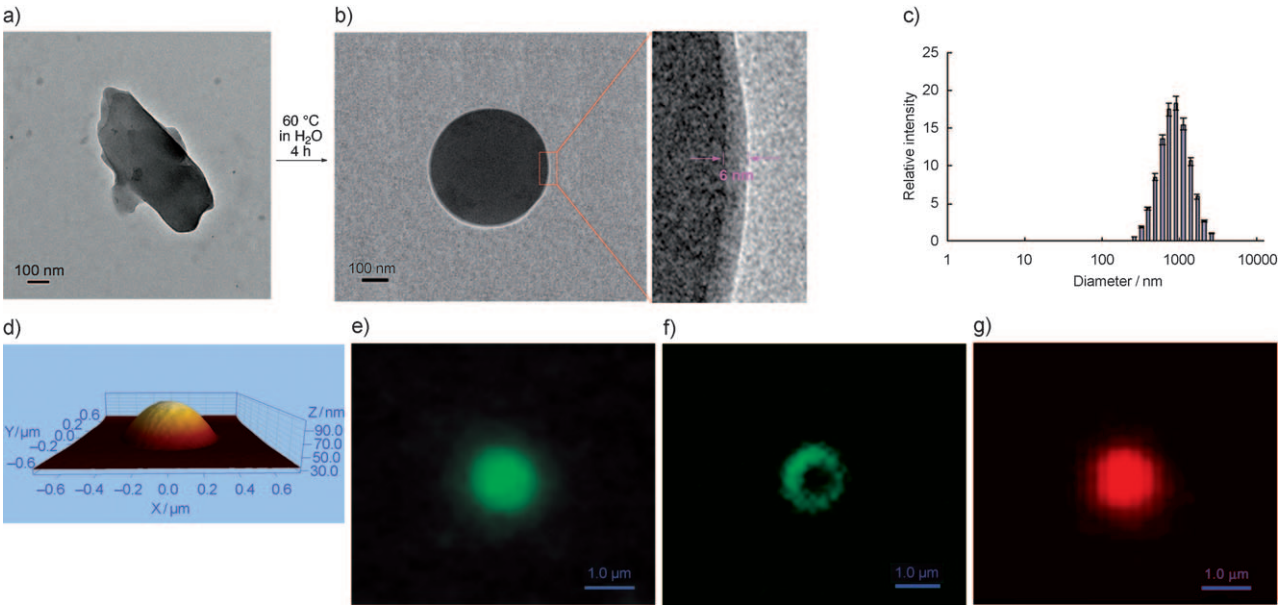


Figure 1. a) TEM image of $\mathbf{1}_{amps}$ (amorphous powder). b) TEM image of $\mathbf{1}_{vscl}$. c) A histogram of the size distribution of $\mathbf{1}_{vscl}$ formed in water as observed by dynamic light scattering. d) AFM image of $\mathbf{1}_{vscl}$. e) Fluorescence microscopic image of $\mathbf{1}_{vscl}$/fluorescein. f) CLSM image of $\mathbf{1}_{vscl}$/fluorescein. g) Fluorescence microscopic image of $\mathbf{1}_{vscl}$/Nile Red.

with water. The fluorescence microscopic image and the confocal laser scanning microscopic (CLSM) image are shown in Figures 1 e and f, respectively.[12]

The fluorescent stain of fluorescein in the membrane observed by CLSM revealed a hydrophobic inner region in the bilayer membrane(Figure 1 f). The fluorescein dye was replaced with another fluorescent dye, Nile Red; the isolated $\mathbf{1}_{vscl}$/fluorescein was exposed to Nile Red in water to give $\mathbf{1}_{vscl}$/Nile Red (Figure 1 g). These experiments demonstrate that a hydrophobic organic molecule can diffuse into the membranous region of $\mathbf{1}_{vscl}$ and be exchanged with another external hydrophobic organic molecule in water.

With the desired vesicles of the palladium-pincer complex in hand, we next explored their catalytic potential for arylating oxirane ring-opening reactions[13] of the vinyl epoxide (**2**) with phenylboronic acid (**3**; Figure 2 a). A mixture of the epoxide **2** and phenylboronic acid **3** (1.2 equiv) was stirred in water with 2 mol% palladium within the vesicle $\mathbf{1}_{vscl}$ for 12 hours. The reaction mixture was extracted with *tert*-butyl methyl ether to give an 84% yield (determined by NMR analysis) of the arylated product **4** along with its regioisomer **5**. The catalyst **1** was recovered from the organic extracts as its amorphous form $\mathbf{1}_{amps}$.[14] However, under similar reaction conditions, the reaction with nano-suspension of the amorphous powder $\mathbf{1}_{amps}$ (Figure 1 a) did not proceed as efficiently. Neither $\mathbf{1}_{vscl}$ nor $\mathbf{1}_{amps}$ catalyzed the arylation in organic solvents, because both the vesicle $\mathbf{1}_{vscl}$ and the amorphous $\mathbf{1}_{amps}$ disassembled/dissolved into the catalytically less active monomer $\mathbf{1}_{mono}$. Thus, vesicle formation is essential for the amphiphilic pincer complex **1** to acquire the necessary catalytic property in water. The organic substrate **2** should be concentrated within the hydrophobic region of the bilayer membrane under aqueous conditions, where the potentially catalytic palladium species is located in

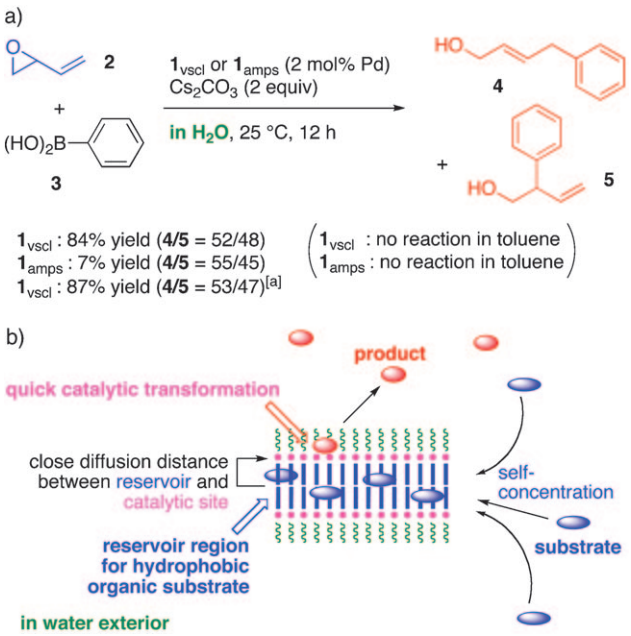
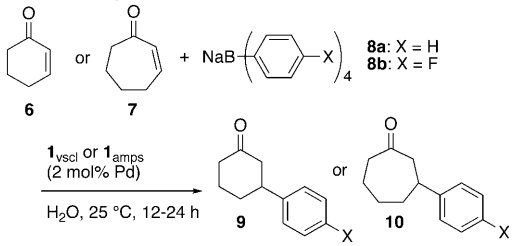


Figure 2. a) Palladium-catalyzed oxirane ring opening with $PhB(OH)_2$. [a] $\mathbf{1}_{vscl}$ was generated in situ without being isolated in water. b) Schematic image of the concept of catalysis within the bilayer membrane of the $\mathbf{1}_{vscl}$.

immediate proximity. This concept is shown schematically in Figure 2 b.

The architecture-based catalysis was also performed in one pot without isolation of the catalytically active vesicle $\mathbf{1}_{vscl}$. Thus, a mixture of $\mathbf{1}_{amps}$ of in water was preheated at 100 °C for 4 hours prior to being used in the catalysis. During this time, the vesicles $\mathbf{1}_{vscl}$ should have formed in situ. After the mixture was cooled, the oxirane **2** and phenylboronic acid

Table 1: Miyaura–Michael reaction of α,β-unsaturated ketones **6** and **7** with sodium tetraarylborates **8**.[a]



Entry	Catalyst	Product	Conv. [%][b]	Yield [%][b]	Selectivity [%]
1	$\mathbf{1}_{vscl}$	**9a** (X = H)	85	83	98
2	$\mathbf{1}_{amps}$	**9a** (X = H)	23	7	30
3	$\mathbf{1}_{vscl}$	**9b** (X = F)	66	63	95
4	$\mathbf{1}_{amps}$	**9b** (X = F)	3	< 1	n.a.
5	$\mathbf{1}_{vscl}$	**10a** (X = H)	39	39	> 99
6	$\mathbf{1}_{amps}$	**10a** (X = H)	18	3	17
7	$\mathbf{1}_{vscl}$	**10b** (X = F)	17	14	82
8	$\mathbf{1}_{amps}$	**10b** (X = F)	7	5	71

[a] Reaction conditions: cycloalkenone (**6** or **7**; 1 equiv), sodium tetraarylborate (**8**; 1.5 equiv), water, palladium (2 mol%) using either $\mathbf{1}_{vscl}$ or $\mathbf{1}_{amps}$, 25 °C, 12–24 h. [b] Determined by ^{1}H NMR analysis using an internal standard ($Cl_2CHCHCl_2$).

3 were added to the aqueous mixture at ambient temperature (25 °C, 12 h) to give **4**/**5** in 87% yield (**4**/**5** = 53:47). However, the $\mathbf{1}_{amps}$ did not promote the ring-opening reaction without preheating.

The architecture-based production of catalysts, wherein the self-assembly for vesicle formation, self-concentration of the substrate inside the bilayer membrane, and the catalytic transformation of the substrate with the palladium species took place sequentially, was demonstrated in the Miyaura–Michael reaction (Table 1).[15] Thus, the vesicle $\mathbf{1}_{vscl}$ (2 mol% Pd) catalyzed the Miyaura–Michael reaction of cyclohexenone (**6**) with sodium tetraphenylborate (**8a**, 1.5 equiv) in water to give the desired arylated product **9a** in 83% yield with 98% reaction selectivity after 12 hours (entry 1), whereas the amorphous $\mathbf{1}_{amps}$ afforded only a 7% yield of **9a** with much lower selectivity (entry 2). The reaction of cyclohexenone (**6**) with sodium tetrakis(4-fluorophenyl)borate (**8b**) also proceeded to afford **9b** in 63% yield and 95% selectivity, whereas $\mathbf{1}_{amps}$ did not promote the reaction (entries 3 and 4). Significant acceleration of the reaction with the vesicle $\mathbf{1}_{vscl}$ was also observed in the reaction of cycloheptenone (**7**) with sodium tetraarylborates (**8a**, **8b**; entries 5–8).

In conclusion, we have developed an architecture-based system of transition-metal catalysis using an amphiphilic pincer palladium complex **1** bearing hydrophilic and hydrophobic chains. This system involves 1) the self-assembly of bilayer vesicles of **1**, 2) the self-concentration of organic substrates within the hydrophobic region of the bilayer membrane, and 3) the catalytic transformation of the substrate with the palladium species located within close diffusion proximity, all of which occur sequentially in water. Various types of catalysis are being developed using this approach in our laboratory and will be reported in due course.

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