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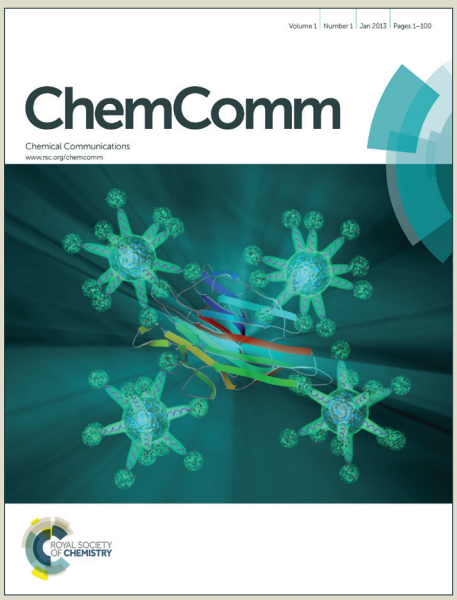

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Cyclization of alkynoic acids in water in the presence of a vesicular self-assembled amphiphilic pincer palladium complex catalyst

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Alkynoic acids were cyclized in the presence of a vesicular palladium-based catalyst and a catalytic amount of triethylamine in water to give the corresponding lactones in moderate-to-good yields. The formation of a vesicular structure was shown to be essential for the promotion of the reaction.

Self-organized nanoarchitectures (micelles, vesicles, nanotubes, etc.), generated by self-assembly of low-molecular-weight molecules by noncovalent interactions, have received much attention from a wide range of chemists.[1] In particular, it has been reported that organic molecules that have rigid planar backbones and both hydrophilic and hydrophobic side chains self-assemble to form bilayer nanoarchitectures.[2] If hydrophilic and hydrophobic side chains are incorporated onto rigid planar metal complexes, the resulting amphiphilic metal complexes should be capable of forming self-assembled architectures that might show catalytic activities.[3,4] On this basis, we designed and synthesized the amphiphilic pincer palladium complexes **1a** and **1b** (Fig. 1).[5] These complexes self-assembled in aqueous solution to form the bilayer vesicles **1a**$_{vscl}$ and **1b**$_{vscl}$, respectively. Vesicles **1b**$_{vscl}$ efficiently catalyzed the ring-opening reaction of vinyl epoxides and the Miyaura–Michael reaction in water; the formation of a vesicular structure was shown to be essential for efficient promotion of both these reactions.[6] The promotion of the reaction through the formation of a vesicular structure is explained in terms of the spontaneous concentration of the organic substrate in the hydrophobic region as a result of hydrophobic interactions, and subsequent approach of the substrate to the catalytic center. The organic transformation proceeds rapidly as a result of the presence of high concentrations of the organic substrate near the catalytic center (Fig. 2). To demonstrate the scope and usability of this concept, we wished to apply the catalytic systems to a cyclization reaction of alkynoic acids.[7] In this communication, we report that self-assembled vesicles **1a**$_{vscl}$ and **1b**$_{vscl}$ of amphiphilic pincer palladium complexes **1a** and **1b** catalyze the cyclization of alkynoic acids in water. The formation of vesicular structure is essential for the promotion of this cyclization reaction.

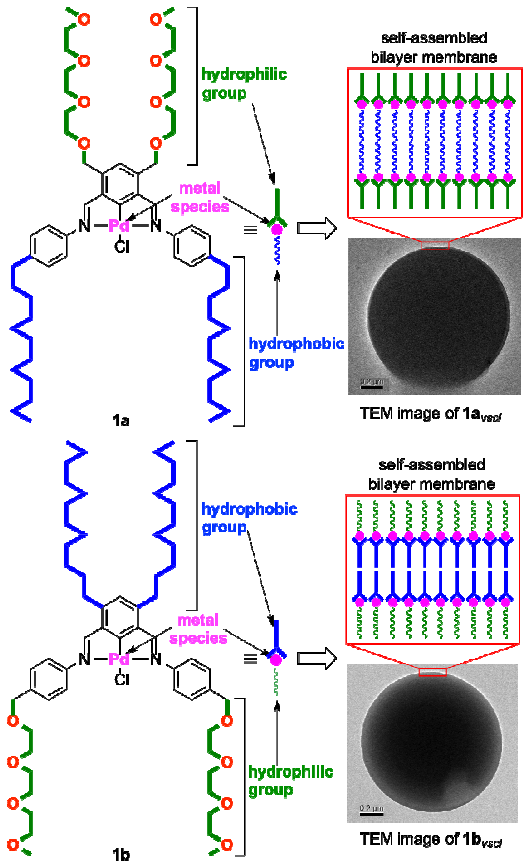


Fig.1 Self-assembly of amphiphilic pincer palladium complexes **1a** and **1b**

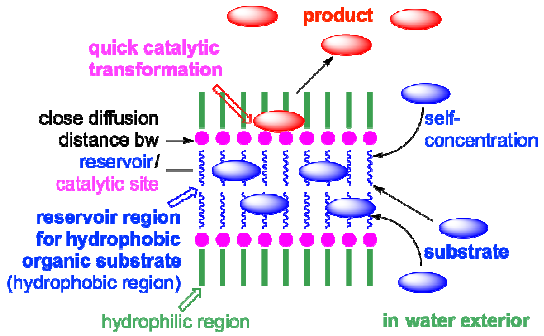
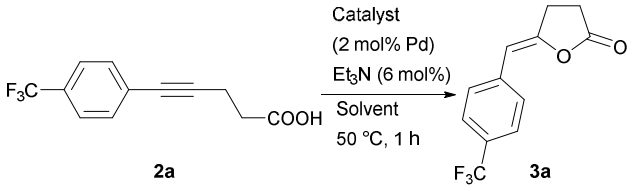


Fig.2 Schematic image of the concept of catalysis within the bilayer membranes of vesicles

We examined the cyclization reaction of 5-[4-(trifluoromethyl)-phenyl]pent-4-ynoic acid (**2a**) with amorphous pincer palladium complexes **1a**$_{amps}$ and **1b**$_{amps}$ and their self-assembled vesicular nanocomposites **1a**$_{vscl}$ and **1b**$_{vscl}$ as catalysts (Table 1). When alkynoic acid **2a** was cyclized in the presence of amorphous amphiphilic NCN pincer palladium complex **1a**$_{amps}$ and triethylamine in water at 50 °C for 1 h, only a 9% yield of the desired γ-lactone **3a** was obtained (Table 1, entry 1). In contrast, the reaction proceeded smoothly in the presence of the self-assembled vesicular **1a**$_{vscl}$, where the potentially reactive Pd-Cl site faces to the hydrophobic inner region (*i.e.* the schematic images of the bilayer membrane of **1a**$_{vscl}$ in Figures 1 (right-top) and 2), to give lactone **3a** in 61% yield (entry 2). The formation of vesicles of the catalyst therefore significantly accelerates the cyclization reaction in water. When the reaction time was prolonged to 2 h, desired lactone **3a** was obtained in 70% yield (parenthesis in entry 2). The amorphous complex **1b**$_{amps}$ and its vesicles **1b**$_{vscl}$ also promoted the reaction and gave γ-lactone **3a** in 10 and 16% yields, respectively (entries 3 and 4). Therefore, self-assembly of complex **1b** resulted in only a slight promotion of the cyclization reaction in water, showing that the position of the hydrophilic and hydrophobic groups on the pincer backbone is critical for efficient promotion of this cyclization reaction. When the reaction was performed in various organic solvents (toluene, 1,2-dichloroethane, tetrahydrofuran, acetonitrile, or methanol), the yield of γ-lactone **3a** was 21% or less, even in when vesicle **1a**$_{vscl}$ was used as the catalyst (entries 5–14). These results indicate that vesicle **1a**$_{vscl}$ disassembled or dissolved to give the catalytically less active monomeric **1a** in organic solvents. Therefore, to acquire the necessary catalytic activity in water, it is essential that amphiphilic pincer complex **1a** forms vesicles. These results are consistent with our proposed concept of a bilayer catalytic system formed by self-assembly of an amphiphilic pincer palladium complex (Fig. 2).

Next, we explored the acceleration effects produced by the formation of a vesicular structure in the cyclization of various pentynoic acids (Table 2). 5-Phenylpent-4-ynoic acid (**2b**) cyclized in the presence of amorphous complex **1a**$_{amps}$ and vesicular **1a**$_{vscl}$ to give the desired γ-lactone **3b** in 8% and 66% yield, respectively (Table 2, entries 1 and 2). An acceleration effect resulting from the formation of a vesicular structure was also observed in the reaction of 5-arylpent-4-ynoic acids substituted with electron-donating or electron-withdrawing groups on the phenyl rings (entries 3–12). The cyclization of the fluorine- and chlorine-containing pentynoic acids **2h** and **2i**, respectively, proceeded in the presence of **1a**$_{amps}$ to give the corresponding γ-lactones **3h** and **3i** in 15 and 26% yield,

Table 1 Effects of catalysts and solvents on the cyclization of 5-[4-(trifluoromethyl)phenyl]pent-4-ynoic acid (**2a**)[a]

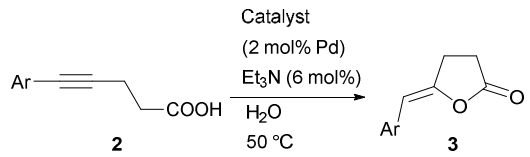


2a **3a**

Entry	Catalyst	Solvent	Yield[b] (%)
1	**1a**$_{amps}$	H_2O	9
2	**1a**$_{vscl}$	H_2O	61 (70)[c]
3	**1b**$_{amps}$	H_2O	10
4	**1b**$_{vscl}$	H_2O	16
5	**1a**$_{amps}$	toluene	<1
6	**1a**$_{vscl}$	toluene	2
7	**1a**$_{amps}$	1,2-DCE	5
8	**1a**$_{vscl}$	1,2-DCE	8
9	**1a**$_{amps}$	THF	1
10	**1a**$_{vscl}$	THF	4
11	**1a**$_{amps}$	MeCN	6
12	**1a**$_{vscl}$	MeCN	14
13	**1a**$_{amps}$	MeOH	8
14	**1a**$_{vscl}$	MeOH	21

[a] *Reaction conditions:* **2a** (0.12 mmol), catalyst (2.4×10^{-3} mmol), Et_3N (7.2×10^{-3} mmol), solvent (1 mL); [b] Isolated yield; [c] Run for 2 h.

Table 2 Scope for the lactonization of 5-(het)arylpent-4-ynoic acids[a]

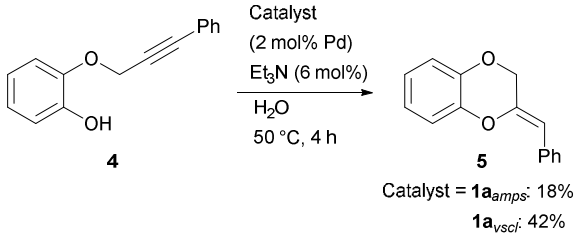


Entry	Catalyst	Time (h)	Product	Yield[b] (%)
1	**1a**$_{amps}$	4	**3b** (Ar = Ph)	8
2	**1a**$_{vscl}$	4	**3b** (Ar = Ph)	66 (88)[c]
3	**1a**$_{amps}$	8	**3c** (Ar = 4-MeC_6H_4)	15
4	**1a**$_{vscl}$	8	**3c** (Ar = 4-MeC_6H_4)	39
5	**1a**$_{amps}$	3	**3d** (Ar = 4-MeOC_6H_4)	13
6	**1a**$_{vscl}$	3	**3d** (Ar = 4-MeOC_6H_4)	82 (94)[d]
7	**1a**$_{amps}$	1	**3e** (Ar = 4-^{t}BuC_6H_4)	11
8	**1a**$_{vscl}$	1	**3e** (Ar = 4-^{t}BuC_6H_4)	42 (78)[e]
9	**1a**$_{amps}$	3	**3f** (Ar = 4-PhC_6H_4)	8
10	**1a**$_{vscl}$	3	**3f** (Ar = 4-PhC_6H_4)	62 (90)[c]
11	**1a**$_{amps}$	4	**3g** (Ar = 4-$O_2NC_6H_4$)	21
12	**1a**$_{vscl}$	4	**3g** (Ar = 4-$O_2NC_6H_4$)	42
13	**1a**$_{amps}$	4	**3h** (Ar = 4-FC_6H_4)	15
14	**1a**$_{vscl}$	4	**3h** (Ar = 4-FC_6H_4)	38
15	**1a**$_{amps}$	4	**3i** (Ar = 4-ClC_6H_4)	26
16	**1a**$_{vscl}$	4	**3i** (Ar = 4-ClC_6H_4)	49
17	**1a**$_{amps}$	8	**3j** (Ar = 2-MeC_6H_4)	4
18	**1a**$_{vscl}$	8	**3j** (Ar = 2-MeC_6H_4)	49
19	**1a**$_{amps}$	8	**3k** (Ar = 1-naphthyl)	10
20	**1a**$_{vscl}$	8	**3k** (Ar = 1-naphthyl)	82
21	**1a**$_{amps}$	2	**3l** (Ar = 2-thienyl)	16
22	**1a**$_{vscl}$	2	**3l** (Ar = 2-thienyl)	42 (74)[d]

[a] *Reaction conditions*: **2** (0.12 mmol), catalyst (2.4 × 10^{-3} mmol), Et_3N (7.2 × 10^{-3} mmol), H_2O (1 mL); [b] Isolated yield; [c] Run for 6 h; [d] Run for 4 h; [e] Run for 2 h.

respectively (entries 13 and 15), whereas vesicular **1a**$_{vscl}$ catalyzed these the cyclization reactions to give **3h** and **3i** in 38 and 49% yield, respectively. For these substrates, therefore, moderate acceleration of the reaction through formation of vesicles was observed. When the sterically hindered substrate **2j** was subjected to cyclization, catalysts **1a**$_{amps}$ and **1a**$_{vscl}$ gave the desired γ–lactone **3j** in 4 and 49% yield, respectively (entries 17 and 18). The naphthyl- and-thienyl substituted alkynoic acids **2k** and **2l** also underwent a cyclization that was accelerated by the formation of a vesicular structure (entries 19–22). When the reaction time was prolonged in the presence of vesicular **1a**$_{vscl}$, the yields of the desired lactones were increased (parentheses in entries 2, 6, 8, 10 and 22).

We also examined the cyclization reaction of 2-[(3-phenylprop-2-yn-1-yl)oxy]phenol (**4**; Scheme 2).[8] The cyclization reaction of alkynol **4** proceeded in the presence of **1a**$_{amps}$ and triethylamine in water at 50 °C for 4 h to give the dihydrobenzodioxine **5** in 18% yield. In contrast, when vesicular **1a**$_{vscl}$ was used as the catalyst, dihydrobenzodioxine **5** was obtained in 42% yield, showing that and acceleration effect through formation of vesicles also occurs with phenolic substrates.



Scheme 1. Cyclization of 2-[(3-phenylprop-2-yn-1-yl)oxy]phenol (**4**)

In summary, 5-(het)arylpent-4-ynoic acids were cyclized in water by the vesicular catalyst **1a**$_{vscl}$ to give the corresponding γ-lactones. In addition, 2-[(phenylethynyl)oxy]phenol was similarly cyclized also to afford the corresponding dihydrobenzodioxine. The formation of a vesicular structure is essential for efficient promotion of the cyclization reaction. Other catalytic applications of the vesicular catalysts **1a**$_{vscl}$ and **1b**$_{vscl}$ are currently under investigation in our laboratory and will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic data for all compounds. See DOI: 10.1039/b000000x/

1 J. W. Steed and J. L. Atwood, *Supramolecular Chemistry 2-nd ed.*, Wiely, Chichester, 2009.
2 (a) J. P. Hill, A. Kosaka, T. Fukushima, H. Ichihara, T. Shimomura, K. Ito, T. Hashizume, N. Ishii and T. Aida, T. *Science*, 2004, **304**, 1481. (b) X. Zhang, Z. Chen and F. J. Würthner, *J. Am. Chem. Soc.* 2007, **129**, 4886. (c) K. V. Rao and S. J. George, *Org. Lett.* 2010, **12**, 2656.
3 For a review on self-assembled architectures serving as nanoreactors for catalytic molecular transformations, see: D. M. Vriezema, M. C. Aragonès, A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev.* 2005, **105**, 1445.
4 Selected examples of catalytic application of self-assembled architectures in water, see (a) M. S. Goedheijt, B. E. Hanson, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* 2000, **122**, 1650. (b) M. Ferreira, H. Bricout, N. Azaroual, C. Gaillard, D. Landy, S. Tilloy and E. Monflier, *Adv. Synth. Catal.* 2010, **352**, 1193. (c) J. P. Patterson, P. Cotanda, E. Z. Kelley, A. O. Moughton, A. Lu, T. H. Epps, III and R. K. O'Reilly, *Polym. Chem.* 2013, **4**, 2033. (d) M. C. M. van Oers, L. K. E. A. Abdelmohsen, F. P. J. Rutjes and J. C. M. van Hest, *Chem. Commun*., 2014, **50**, 4040.
5 K. Takenaka, M. Minakawa and Y. Uozumi, *J. Am. Chem. Soc.* 2005, **127**, 12273.
6 (a) G. Hamasaka, T. Muto and Y. Uozumi, *Angew. Chem. Int. Ed.* 2011, **50**, 4876. (b) G. Hamasaka, T. Muto and Y. Uozumi, *Dalton. Trans.* 2011, **40**, 8859.

7 Selected examples of Pd-catalyzed the cyclization of alkynoic acids, see (a) C. Lambert, K. Utimoto and H. Nozaki, *Tetrahedron Lett.* 1984, **25**, 5323. (b) K. Ogata, D. Sasano, T. Yokoi, K. Isozaki, H. Seike, H. Takaya and M. Nakamura, *Chem. Lett.* 2012, **41**, 498.
8 M. Yamamoto, *J. Chem. Soc., Perkin Trans 1* 1979, 3161.