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Pd-complex-bound Amino Acid-based Supramolecular Gel Catalyst for Intramolecular Addition–Cyclization of Alkynoic Acids in Water

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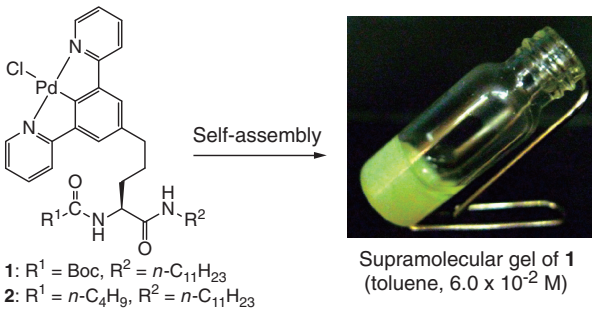
An NCN-pincer Pd-complex-bound norvaline-based supramolecular gel showed efficient catalytic activities for the intramolecular addition–cyclization of alkynoic acid and phenol derivatives in water to afford the corresponding ene-lactones in good to excellent yields.

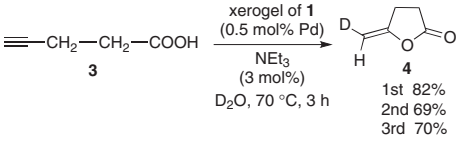
The supramolecular self-assembly of amino acids and peptides has proven to be a useful technique for the fabrication of well-defined nano/microstructures.[1,2] The resulting supramolecular scaffolds with embedded side-chain functional groups have the potential to serve as efficient supramolecular catalytic systems and have attracted considerable attention also in organic synthesis.[3] Recently, we reported the synthesis of a series of Pd-complex-bound amino acids[4] and peptides[5] that showed hydrogen-bonding-induced self-assembly in organic solvents to form a supramolecular gel along with well-organized Pd-arrays. Among these compounds, the NCN-pincer Pd-complex-bound norvaline derivatives **1** and **2** exhibit excellent gelation properties and stability with respect to metal leaching under severe conditions such as high temperature, acidic, and basic conditions (Scheme 1).[4a,6] In this paper, we disclose that a xerogel prepared from the supramolecular gel of **1** shows high catalytic activity for the intramolecular addition of a carboxylic acid or phenol oxygen to a carbon–carbon triple bond. The xerogel catalyzes the reaction in water to afford the corresponding lactones and cyclic ether in high yield and can be reused by a simple filtration/separation procedure.

Pd-complex-based supramolecular gels have been widely recognized as efficient supramolecular catalysts. In particular, coordination polymer gels prepared from Pd complexes and multivalent ligands are highly robust and active heterogeneous catalysts. This is because 1) the stable metal–ligand interaction prevents undesirable metal leaching during the reaction and 2) the porous network structure of these gels enables them to possess efficient substrate binding abilities.[7,8] On the other hand, supramolecular catalysts assembled through weak ligand–ligand interactions such as van der Waals, hydrophobic, π–π stacking, and hydrogen-bonding interactions have remained largely uninvestigated because of a paucity of suitable self-assembling functional units.[9] We envisioned that NCN-pincer Pd-complex-bound norvaline could serve as the assembling unit for the fabrication of supramolecular catalyst based on weak intramolecular interaction through the amino acid moiety. In the resulting supramolecular catalyst, the coordination-free catalytic metal centers would exhibit efficient catalytic activity due to their high accessibility to substrates.



Scheme 1. Supramolecular gel formation of NCN-pincer Pd-complex-bound norvaline derivatives.

To assess the catalytic activity of the supramolecular gel of NCN-pincer Pd-complex-bound norvaline **1**, the cyclization of 4-alkynoic acids was examined as a probe reaction. Because a Pd(II)-catalyzed nonredox mechanism has been proposed and widely accepted,[10] we could exclude the Pd(0)-catalyzed mechanisms which were caused by metal leaching and subsequent reduction of Pd(II). In the case of the pilot reaction expressed by eq 1,



(1)

the cyclization of 4-pentynoic acid (**3**) was carried out in the presence of a xerogel particle of **1** (1.33 mg, 0.5 mol % Pd content)[11] and a catalytic amount of triethylamine (3.0 mol %) in an NMR test tube under D_2O aqueous conditions. Figure 1

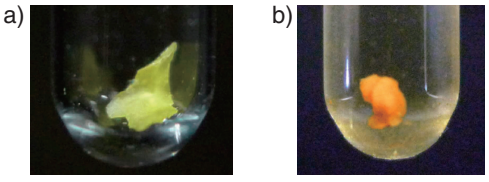
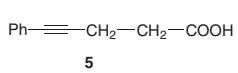
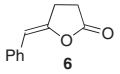
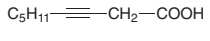
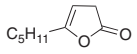
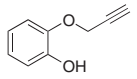
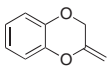
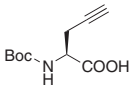
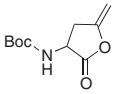
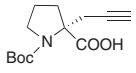
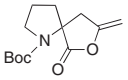
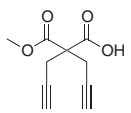
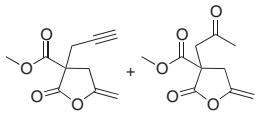


Figure 1. a) Xerogel catalyst **1** before addition of **3** and b) swollen gel catalyst **1** after addition of **3** in an NMR test tube (D_2O).

Table 1. Supramolecular xerogel **1**-catalyzed cyclization reaction of alkynoic acid derivatives[a]

Entry	Substrate	Product	Yield/%[b](Time/h)
1	 **5**	 **6**	72 (6)
2	 **7**	 **8**	>99[c] (3)
3	 **9**	 **10**	82 (10)
4	 **11** $[\alpha]_D^{25} = +7.0$ (*c* 0.11, $CHCl_3$)	 **12** $[\alpha]_D^{25} = -4.3$ (*c* 0.030, $CHCl_3$)	>99[c] (3)
5	 **13** $[\alpha]_D^{25} = +5.8$ (*c* 0.15, $CHCl_3$)	 **14** $[\alpha]_D^{25} = +1.6$ (*c* 0.18, $CHCl_3$)	84 (3)
6	 **15**	 **16** 14 (6) **17** 20 (6)	

[a]Reactions were carried out with substrate (0.5 mmol), xerogel **1** (0.5 mol % Pd content), and NEt_3 (3 mol %) in H_2O at 70 °C. [b]Isolated yield. [c]NMR yield.

shows the change in the xerogel catalyst **1** upon the occurrence of the reaction. When substrate **3** was added to the xerogel particle in D_2O, the lemon yellow xerogel (Figure 1a) promptly swelled through the absorption of **3** to afford an orange gel (Figure 1b). Upon heating the reaction mixture, the corresponding five-membered ring-cyclization product (*E*)-5-(2-deuteriummethylene)-γ-butyrolactone (**4**) was obtained in 82% yield. The water-insoluble gel catalyst can be recovered by filtration and reused at least three times, without significant loss of catalytic activity; this catalyst afforded **4** in 69% and 70% yields when it was reused the second and the third time, respectively. The residual palladium catalyst in the product **4** was found to be very low content (23 ppm), which was determined by ICP-MS analysis. Table 1 summarizes the supramolecular gel-catalyzed cyclization with various substrates. 5-Phenyl-4-pentynoic acid (**5**), having an internal C–C triple bond also underwent 5-exo cyclization to give (*Z*)-γ-benzylidene-γ-butyrolactone (**6**) exclusively (Entry 1). The stereochemistry of **6** was confirmed by ^{1}H NMR analysis in comparison with the literature data.[12] In the case of the cyclization of 3-alkynoic acid **7**, 5-endo cyclization proceeded to afford 5-*n*-pentyl-2,3-dihydro-2-furanone (**8**)[13] with an excellent yield (Entry 2). Upon treatment of the 2-propynyl ether of catechol **9** with the xerogel catalyst **1**, 6-exo cyclization of the phenolic hydroxy group onto the alkyne moiety occurred to yield 1,4-benzodioxene derivative **10**,[14] which is an important precursor of potential drug candidates for asthma and arthritis therapy[15] (Entry 3). The α-(2-propynyl)-substituted amino acids such as Boc-α-(2-propynyl)-L-glycine **11** and Boc-α-(2-propynyl)-L-proline **13** underwent 5-exo cyclization to form 3-substituted-5-methylene-γ-butyrolactone **12**[16] and **14**, respectively (Entries 4 and 5). Di(2-propynyl) substrate, 2-(methoxycarbonyl)-2-(2-propynyl)-4-pentynoic acid (**15**) was cyclized to yield the corresponding acetylene lactone, methyl tetrahydro-5-methylene-2-oxo-3-(2-propynyl)furan-3-carboxylate (**16**) along with a hydrolysis product of methyl tetrahydro-5-methylene-2-oxo-3-(2-oxopropyl)furan-3-carboxylate (**17**) (Entry 6). Although notable chiral induction was not observed in the reaction, we are currently studying the application of the supramolecular gel catalysts to asymmetric synthesis.

^{1}H NMR time-course-dependent analysis was performed on the cyclization of **3** in order to compare the catalytic activity of the xerogel of **1** with that of the parent complex of [PdCl(dpb)]. The catalytic activities were estimated by the initial NMR yield of the cyclization product **4** from 0 to 0.5 h. The yield **4** of 88% for the gel catalyst **1** and 55% for [PdCl(dpb)] indicated slightly yet apparently enhanced activity of the supramolecular gel catalysts. It can be attributed to the amphiphilicity of alkynoic acid, which presumably facilitates substrate transportation from the aqueous phase to the organic gel phase. Unfortunately, the heterogeneous gel-phase reaction and the homogeneous solution-phase reaction could not be accurately compared. Because this cyclization–addition reaction was quite sluggish under the homogeneous conditions in aprotic solvents such as toluene, THF, and $CHCl_3$ in which the xerogel of **1** showed excellent solubility, affording a solution of **1** instantly, the observed solvent effect demonstrates that poor solvents for **1** are essential for the success of the present reaction. Protonolysis would be crucial to complete the catalytic cycle, and hence, the reaction was accelerated in water (vide infra).

The proposed catalytic cycle of the NCN-pincer Pd-complex-bound norvaline-catalyzed cyclization of alkynoic acids is illustrated in Figure 2. This reaction can be rationalized by assuming the carbophilic Pd(II) cationic intermediate **B**, which was formed via Cl ligand exchange on catalyst **A** by the substrate alkyne. The intramolecular addition of carboxylate oxygen to the activated C–C triple bond proceeded to afford the vinyl Pd(II) species **C**. The observed 5-exo cyclization as shown in Table 1 supports the formation of **C**. Subsequent protonolysis of **C** in conjunction with ligand recombination afford the cyclization product and the catalyst **A** to complete the catalytic cycle. The formation of deuterio product in the cyclization of 4-pentynoic acid definitely corroborates the proposed protonolysis step. The Pd(II) catalytic cycle was confirmed by Pd K-edge XANES spectra of gel catalyst **1**.[17,18] The spectra showed no significant change between the states before and after the cyclization of 4-pentynoic acid in water with the divalent [PdCl(dpb)] complex.

In summary, the efficiency of an amino-acid-based supramolecular gel catalyst was shown by using NCN-pincer Pd-complex-bound norvaline **1**. The incorporated, highly assembled Pd-complex array in the supramolecular gel of **1** catalyzed the cyclization reaction of alkynoic acids to yield the corresponding lactones. The robustness of the hydrogen-bonding-based supra-

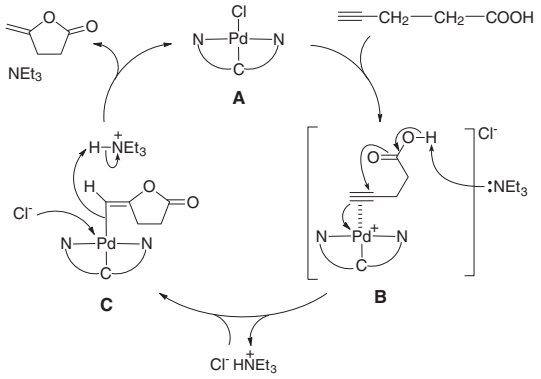


Figure 2. Proposed mechanism of cyclization reaction of alkynoic acid.

molecular gel catalyst was proven by the reusability of the supramolecular gel catalyst **1**.

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17 For XANES spectra, See SI, Figure S7.[18]

18 Supporting Information is available electronically on the CSJ-Journal Web site at http://www.csj.jp/journals/chem-lett/index.html.

