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INTRAMOLECULAR CYCLIZATION OF γ-ACETYLENIC ACIDS USING DENDRIMER-ENCAPSULATED Pd^{2+} CATALYSTS

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Abstract – Polyamine dendrimer-encapsulated Pd^{2+} catalysts were prepared by complexation of $PdCl_2$ with internal tertiary amino groups of the dendrimer. The fifth-generation Pd^{2+} dendrimer catalyst showed cooperative catalysis between Pd^{2+} species and the internal nanocavity consisting of regularly arranged tertiary amino groups to promote the intramolecular cyclization of γ-acetylenic acids efficiently.

γ-Alkylidene-γ-butyrolactones are important chemicals as constituent units of a number of natural products and synthetic intermediates of pharmaceuticals.[1] Among the synthetic methods of γ-alkylidene-γ-butyrolactones, intramolecular cyclizations of acetylenic acids have attracted attention because of their 100% atom efficiency.[2-7] To date, various transition metal catalysts, such as Pd,[2] Hg,[3] Pt,[4] Au,[5] Ag,[6] Ir, and Rh,[7] have been reported to promote the cyclization of acetylenic acids. In particular, Pd with base catalyst systems[2] showed higher catalytic activities than other metal ones. Nozaki et al. first reported that $PdCl_2(PhCN)_2$ with triethylamine (TEA) catalyzed the intramolecular cyclization of acetylenic acids.[2a] Hidai et al. exhibited that the combination of a cuboidal $PdMo_3S_4$ cluster and TEA achieved a high catalytic turnover number.[2e] Recently, heterogeneous Pd catalysts were also developed by Michelet et al. through the immobilization of Pd complexes onto basic Zn_2AlNO_3 layered double hydroxide (Pd/LDHs).[2g]

Dedicated to Professor Dr. Ei-ichi Negishi on his 77th birthday.

Dendrimers are well-defined macromolecules with highly branched structures and internal nanocavities composed of a core and branch units.[8] Various guests such as organic molecules, metal ions, and

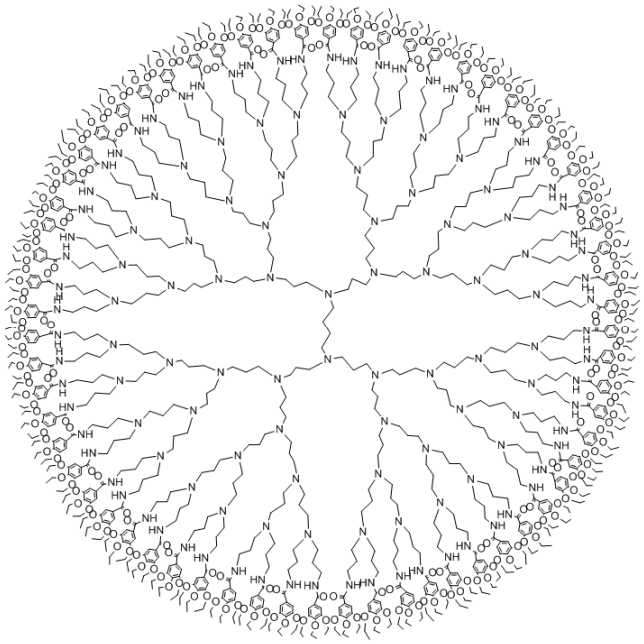


Figure 1. Structure of G_5-TEBA dendrimer

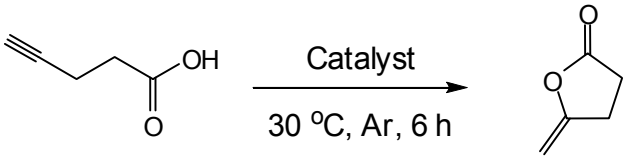
nanoparticles can be accommodated within their nanocavity,[8b-d] giving rise to dendritic catalysis such as site-isolation as well as a high local concentration of the substrate and/or active species.[9] Accordingly, we have demonstrated the unique dendritic catalysis using poly(propylene imine) (PPI) dendrimers encapsulating metal complexes,[9a,d] nanoparticles,[10a] subnano clusters[10b,c] and quaternary ammonium groups.[9e] Very recently, the tertiary amino group within the nanocavities of the PPI dendrimer was also found to act as an efficient organocatalyst, promoting the intramolecular cyclization.[10d] Herein, we report the cooperative effect between Pd^{2+} species and the confined nanocavity of the PPI dendrimers on the catalytic intramolecular cyclization of acetylenic acids. The fifth-generation dendrimer encapsulating Pd^{2+} species was found to act as an efficient catalyst for the cyclization of γ-acetylenic acids.

The triethoxybenzamide terminated-PPI dendrimers (G_x-TEBA, x denotes the generation number of PPI dendrimer, (Figure 1)) were synthesized using the reported procedures.[10a] The PPI dendrimer-encapsulated Pd^{2+} catalysts (G_x-Pd^{2+}_n, n denotes the molar ratio of Pd^{2+} ions to G_x-TEBA) were prepared by treatment of G_x-TEBA with Na_2PdCl_4.[10b,c]

The intramolecular cyclization of 4-pentynoic acid (**1a**) using G_x-Pd^{2+}_n catalysts was examined in THF at 30 °C (Table 1).[11] The ratio of G_5-TEBA to Pd^{2+} (n) strongly affected the catalytic activity of G_5-Pd^{2+}_n (entries 1-6). G_5-Pd^{2+}_8 showed the highest activity to give γ-methylene-γ-butyrolactone (**2a**) in 95% yield

(entry 3). Interestingly, the catalytic activity increased with increasing generation of the dendrimer; the fifth-generation dendrimer catalyst showed the highest activity among G_5-Pd^{2+}_8, G_4-Pd^{2+}_8, and G_3-Pd^{2+}_8 (entries 3, 7, and 8). When the aliphatic tertiary amines comparable in basicity with G_5-TEBA (pK_a =

Table 1. Intramolecular cyclization of 4-pentynoic acid using various Pd^{2+} catalyst systems[a]



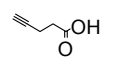
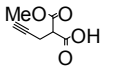
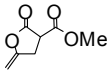
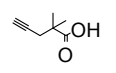
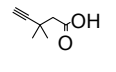
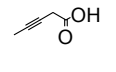
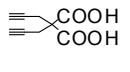
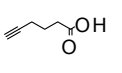
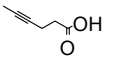
Entry	Catalyst	Additive base[b]	Conv. [%][c]	Yield [%][c]
1	G_5-Pd^{2+}_4	-	55	54
2	G_5-Pd^{2+}_6	-	88	88
3	G_5-Pd^{2+}_8	-	96	95 (89)[d]
4	G_5-Pd^{2+}_{10}	-	81	80
5	G_5-Pd^{2+}_{12}	-	62	60
6	G_5-Pd^{2+}_{16}	-	47	47
7	G_4-Pd^{2+}_8	-	55	55
8	G_3-Pd^{2+}_8	-	27	26
9	$PdCl_2(PhCN)_2$	TEA	15	14
10	$PdCl_2(PhCN)_2$	TMPDA	43	43
11	$PdCl_2(PhCN)_2$	PMDPT	48	45
12	PEI-Pd^{2+}_8	-	17	15

[a] Reaction conditions: 4-pentynoic acid (0.1 mmol), catalyst (Pd: 1 μmol), THF (2 mL). [b] 8 μmol for N atoms. [c] Determined by ^{1}H NMR using an internal standard technique. [d] Isolated yield.

10.35)[12] were used instead of G_5-TEBA under similar conditions, these amines such as TEA (pK_a = 10.6),[13] *N*,*N*,*N*',*N*'-tetramethyl-1,3-propanediamine (TMPDA, pK_a = 9.8),[14] and *N*,*N*,*N*',*N*'',*N*''-pentamethyldipropylenetriamine (PMDPT, pK_a = 10.0)[14] resulted in lower yields of **2a** compared to that of G_5-TEBA (entries 9-11).[15] Furthermore, an irregularly branched polyamine of TEBA-modified polyethyleneimine (PEI-TEBA)[16] was tested in the reaction. However, PEI-TEBA was not effective, giving only 15% yield of **2a** (entry 12). These results indicate that the encapsulation of Pd^{2+} species within the nanocavity consisting of regularly arranged tertiary amino groups of G_5-TEBA is necessary to achieve high catalytic efficiency.

Table 2 shows the substrate scope of the G_5-Pd^{2+}_8 catalyst. The cyclization of α-substituted and β-substituted γ-acetylenic acids **1b-d** proceeded efficiently to afford the corresponding γ-methylene-γ-butyrolactones **2b-d** in excellent yields (entries 2-4). β-Acetylenic acid **1e** was also easily converted to the corresponding γ-butyrolactone **2e** (entry 5). The double cyclization of dipropargyl-

Table 2. Intramolecular cyclization of various acetylenic acids using G_5-Pd^{2+}_8 or the $PdCl_2(PhCN)_2$-TEA system

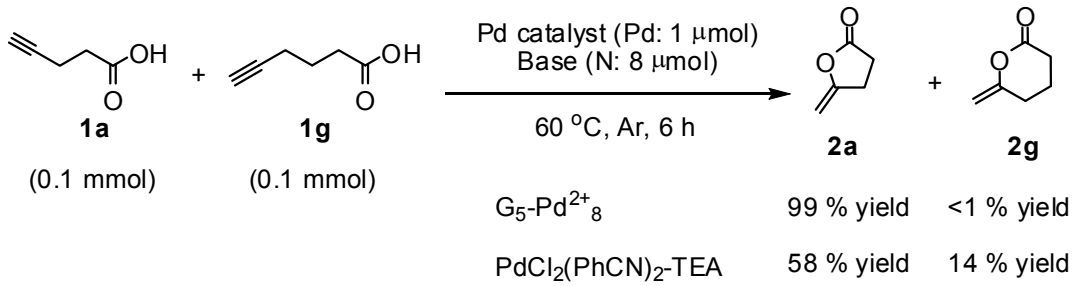
Entry	Substrate		Product		T [°C]	Time [h]	G_5-Pd^{2+}_8[a]		$PdCl_2(PhCN)_2$-TEA[b]	
							Conv. [%][c]	Yield [%][c]	Conv. [%][c]	Yield [%][c]
1		**1a**		**2a**	30	6	96	95	15	14
2		**1b**		**2b**	30	12	99	97	28	26
3		**1c**		**2c**	30	6	98	98	65	64
4		**1d**		**2d**	40	12	98	96	12	9
5		**1e**		**2e**	40	5	>99	97	72	70
6		**1f**		**2f**	40	9	>99	99	35	35
7		**1g**		**2g**	60	12	20	20	65	63
8		**1h**	 	**2ha** **2hb**	60	3	trace	-	38	37 (**2ha**:**2hb** = 82:18)

[a] Reaction conditions: substrate (0.1 mmol), G_5-Pd^{2+}_8 (Pd: 1 μmol), THF (2 mL), Ar. [b] Reaction conditions: substrate (0.1 mmol), $PdCl_2(PhCN)_2$ (Pd: 1 μmol), triethylamine (N: 8 μmol), THF (2 mL), Ar. Determined by GC and ^{1}H NMR using an internal standard technique.

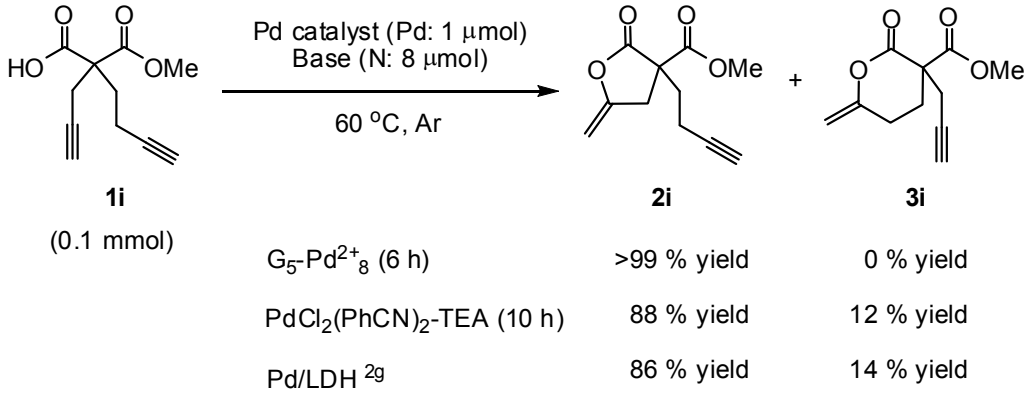
malonic acid **1f** gave the spiro lactone product **2f** quantitatively (entry 6). However, the cyclization of δ-acetylenic acid such as 5-hexynoic acid **1g** did not proceed smoothly (entry 7). A γ-acetylenic acid with an internal alkyne **1h** was intact (entry 8)[17]. In contrast, the $PdCl_2(PhCN)_2$-TEA system showed good to moderate catalytic activities for the cyclizations of **1g** and **1h** (entries 7 and 8).

The high activity of G_5-Pd^{2+}_8 for the formation of γ-butyrolactones was further exemplified in the competitive reaction between γ-acetylenic acid and δ-one. In the *intermolecular* competitive reaction between **1a** and **1g**, **1a** was converted to **2a** quantitatively without formation of **2g** (Scheme 1). In comparison, the $PdCl_2(PhCN)_2$-TEA system afforded a mixture of **2a** and **2g**. The *intramolecular*

competitive cyclization of **1i** proceeded exclusively to give the 5-membered lactone **2i** (Scheme 2) while the reaction of **1i** using the $PdCl_2(PhCN)_2$-TEA system resulted in the formation of a mixture of **2i** and the 6-membered lactone **3i**. It has also been reported that the Pd/LDH catalyst converts **1i** to a mixture of **2i** and **3i** in 86% and 14% selectivity, respectively.[2g] These results clearly show that G_5-$Pd^{2+}{}_8$ exhibits the specific activity for the cyclization of γ-acetylenic acids compared to δ-one.



Scheme 1. Intermolecular competitive cyclization between γ-acetylenic acid and δ-acetylenic acid



Scheme 2. Intramolecular competitive cyclization between γ-acetylenic acid and δ-acetylenic acid

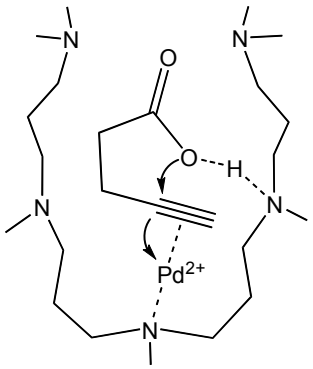


Figure 2. Proposed reaction intermediate

The Pd-catalyzed cyclization of acetylenic acids generally involves the intramolecular nucleophilic attack of a carboxylate anion to the acetylenic bond coordinated to a Pd center, followed by the protonolysis of

the resulting vinylpalladium species.[2a,g] In the case of the G_5-Pd^{2+}_8 catalyst, Pd^{2+} species and the regularly arranged tertiary amino groups would cooperatively function within the sterically confined nanocavity; a carboxyl group of the substrate is oriented toward an acetylenic bond on the Pd species by the steric effect of the nanocavity of G_5-Pd^{2+}_8, resulting in facile intramolecular nucleophilic attack of the carboxyl group activated by regularly arranged tertiary amino groups (Figure 2). The specific activity of G_5-Pd^{2+}_8 for the cyclization of γ-acetylenic acids may be attributable to the steric congestion around the Pd species within the internal nanocavity of the G_5-TEBA dendrimer.[18]

In conclusion, the PPI dendrimer-encapsulated Pd^{2+} catalysts synthesized by the complexation of $PdCl_2$ with internal tertiary amino groups can be applied to the intramolecular cyclization of acetylenic acids. The fifth-generation dendrimer catalyst, G_5-Pd^{2+}_8, specifically and efficiently promoted the cyclization of γ-acetylenic acids due to the cooperative catalysis between the Pd^{2+} species and the internal nanocavity consisting of regularly arranged tertiary amino groups of G_5-TEBA.

ACKNOWLEDGEMENTS

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11. A typical cyclization reaction of acetylenic acid was carried out in a Schlenk glass tube. The glass tube was charged with acetylenic acid (0.1 mmol), THF (2 mL), and G_5-$Pd^{2+}{}_8$ (Pd: 1 μmol). The reaction mixture was vigorously stirred at 30 ^{o}C. After the reaction, the reaction mixture was analyzed by GC and ^{1}H NMR using an internal standard technique.
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14. R. von Rometsch, A. Marxer, and K. Miescher, *Helv*. *Chim*. *Acta*, 1951, **34**, 1611.
15. The ratio of tertiary amino groups to Pd^{2+} in the $PdCl_2(PhCN)_2$-aliphatic tertiary amine systems was adjusted to that in G_5-$Pd^{2+}{}_8$ catalyst.
16. TEBA-modified polyethyleneimine (PEI-TEBA) was synthesized as follows: to a THF solution (100 mL) of polyethyleneimine (0.50 g, 3.15, 3.15, and 2.7 mmol for primary, secondary, and tertiary amine, respectively) and TEA (3.07 g, 30.4 mmol) was added a THF solution (20 mL) of 3,4,5-triethoxybenzoyl chloride dropwise (2.39 g, 8.8 mmol) at 30 °C for 5 min. The mixture was stirred at 40 °C for 48 h, then concentrated under reduced pressure. The residue was washed with 1 M NaOH aqueous solution (3 x 200 mL) and water (5 x 200 mL), and dried under vacuum for 24 h to give PEI-TEBA as a brownish solid (1.48 g). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 50 °C), δ 0.66-1.47 (1512H, br, C*H*$_3$CH$_2$O-), 2.01-2.95 (444H, br, (C*H*$_2$)$_3$N), 2.96-4.55 (1512H, br, (C*H*$_2$)$_2$NCOAr + C*H*$_2$NHCOAr + CH$_3$C*H*$_2$O-), 6.08-6.70 (168H, br, (CH$_2$)$_2$NCO*Ar*), 6.78-7.18 (168H, br, CH$_2$NHCO*Ar*), 7.50-8.29 (84H, br, CH$_2$N*H*COAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$. TMS, 50 °C), 14.9, 15.6, 38.4, 53.5, 64.8, 68.8, 106.5, 129.3, 131.2, 139.2, 141.2, 152.8, 167.6, 171.8. IR (KBr, cm^{-1}), 3329 (N-H stretch), 3016 (Aromatic C-H stretch), 1629 (C=O stretch), 1580 (N-H vend), 1215 (C-N stretch), 1030 (Ar-O-CH$_2$ stretch), 755 (Aromatic C-H vend), 668 (-NH vibration). Anal. Calcd for $C_{2664}H_{3888}N_{240}O_{672}$: C, 63.95; H, 7.83; N, 6.71. Found: C, 63.56; H, 8.01; N, 6.59. PEI-$Pd^{2+}{}_8$ was prepared in a similar way by treatment of PEI-TEBA with Na_2PdCl_4 aqueous solution. See refs 10a and 10b.
17. The low reactivity of **1h** might be due to the steric hindrance of the methyl group which inhibits the coordination of the alkyne group to Pd^{2+}.
18. Several transition metal complex catalysts having bulky ligands were reported to show extremely lower catalytic activity for the cyclization of 5-hexynoic acid than that of 4-pentynoic acid. See refs 2e, 7b, and 7d.