Synthesis and Characterization of Carboxylic Acids Bearing Poly(ethylene glycol) Chains

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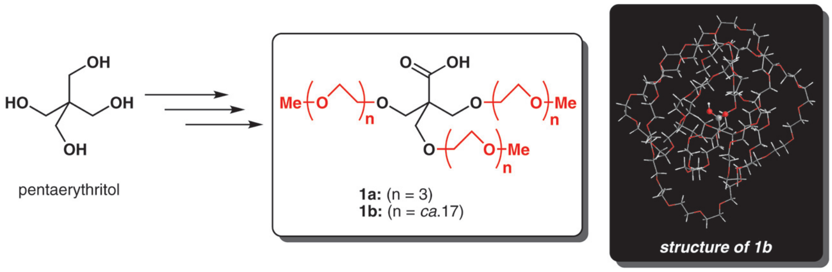

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Abstract Carboxylic acids **1a** and **1b** bearing three poly(ethylene glycol) (PEG) chains and carboxylic acid **1c** bearing one PEG chain were designed and synthesized. The carboxylic acids **1a–c** were fully characterized by NMR and ESI-HRMS analyses. In a Pd-catalyzed aerobic oxidation of 1-phenylethanol, **1a** and **1b** worked well as carboxylate ligands.

Key words carboxylic acids, poly(ethylene) glycol, oxidation, alcohol, palladium

Poly(ethylene glycol) (PEG) derivatives[1] are widely used owing to their low toxicity, high conformational flexibility, and ease of availability. Various PEG materials with different molecular weights and various terminal functionalities are readily and commercially available.

We have been interested in the nature of PEG and developed novel ligands bearing PEGs as modification motifs (Figure 1).[2,3] Triarylphosphines bearing PEG chains on the periphery enhanced the catalytic activity in a Pd-catalyzed Suzuki–Miyaura coupling reaction using less reactive aryl chlorides as substrates (Figure 1, a).[2] Furthermore, we synthesized a series of *N*-heterocyclic carbene (NHC) ligands bearing PEG chains (Figure 1, b).[3] These ligands increased the catalytic activity of Pd-catalyzed Miyaura borylation[3a] and Suzuki–Miyaura coupling reactions.[3a,b]

Herein, we report on the design and synthesis of a series of carboxylic acids **1a–c** bearing PEG chains (Figure 2), because carboxylates are known as common ligands for transition-metal complexes,[4] metalloproteins,[5] and coordination polymers.[6] We found that the carboxylic acids **1a** and **1b** bearing three PEG chains worked well in the Pd-catalyzed aerobic oxidation of 1-phenylethanol.

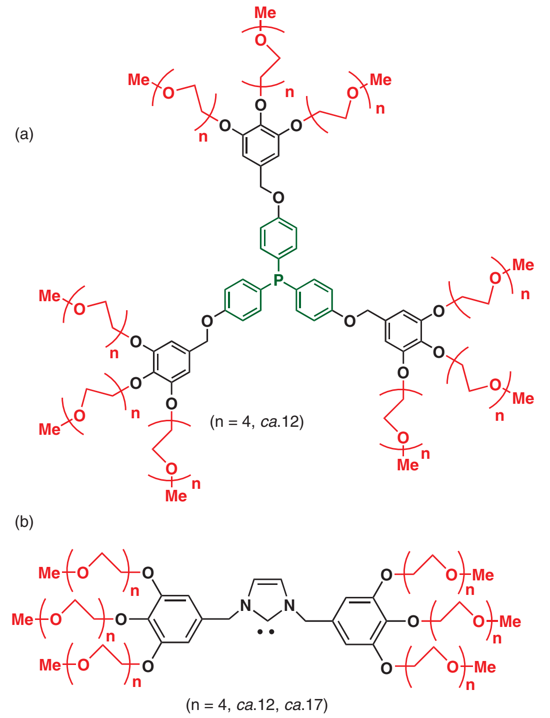
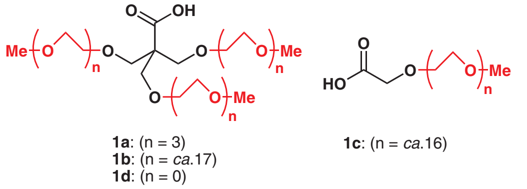


Figure 1 (a) Phosphine ligands bearing PEG chains; (b) *N*-heterocyclic carbene ligands bearing PEG chains.



1a: (n = 3)
1b: (n = *ca.*17)
1d: (n = 0)

1c: (n = *ca.*16)

Figure 2 A series of carboxylic acids bearing PEG chains in this study

First, we synthesized **1a** bearing three PEG chains (n = 3) in the α-position (Scheme 1, a). To synthesize the desired carboxylic acids, inexpensive and easy-to-access pentaerythritol (**2**) was used as a starting material. The monotrityl (CPh_3)-protected compound **3** is a key intermediate for successful introduction of three PEG chains, and it was synthesized according to a published procedure.[7] $MsO(CH_2CH_2O)_3Me$ (**4a**) was prepared from the corresponding commercially available PEG mono-ether, $HO(CH_2CH_2O)_3Me$.

The reaction of **3** with **4a** produced **5a**. Without thoroughly purifying **5a**, deprotection with trifluoroacetic acid afforded the corresponding alcohol **6a** in 68% yield from **3**. As for oxidation of **6a** to **1a**, Jones oxidation conditions considerably cleaved the PEG chains of **6a**. After several trials, **1a** was successfully obtained in a two-step reaction: Swern oxidation,[8] which afforded **7a**, and Pinnick oxidation,[9] which afforded **1a**, in a high total yield (63% yield from **3**).[10] With regard to **1b** bearing three longer PEG chains (n = *ca.* 17), a method similar to that used for **1a** was adopted, which employed $MsO(CH_2CH_2O)_nMe$ (**4b**, n = *ca.* 17). The corresponding carboxylic acid **1b** was isolated in a total yield of 27% (from **3**) via **5b**, **6b**, and **7b**.[11] Here, these three intermediates (**5b**, **6b**, and **7b**) were not purified and used in the following reactions. Furthermore, **1c** with one PEG chain (n = *ca.* 16) was synthesized by the known[12] oxidation of a commercially available PEG monoether, $HO(CH_2CH_2O)_nMe$ (n = *ca.* 17) (Scheme 1, b). For comparison, carboxylic acid **1d** bearing only three methoxy groups (n = 0, Figure 2) was afforded by the Jones oxidation of **6d**, which was synthesized by trimethylation reaction of **2** (Scheme 1, c).

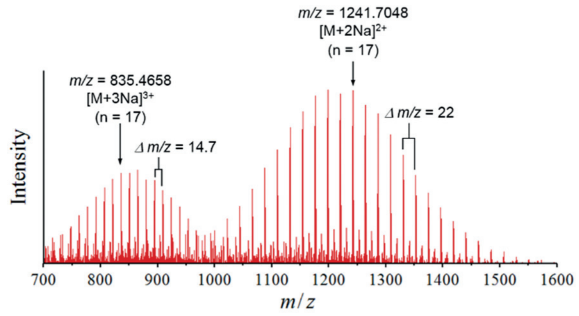
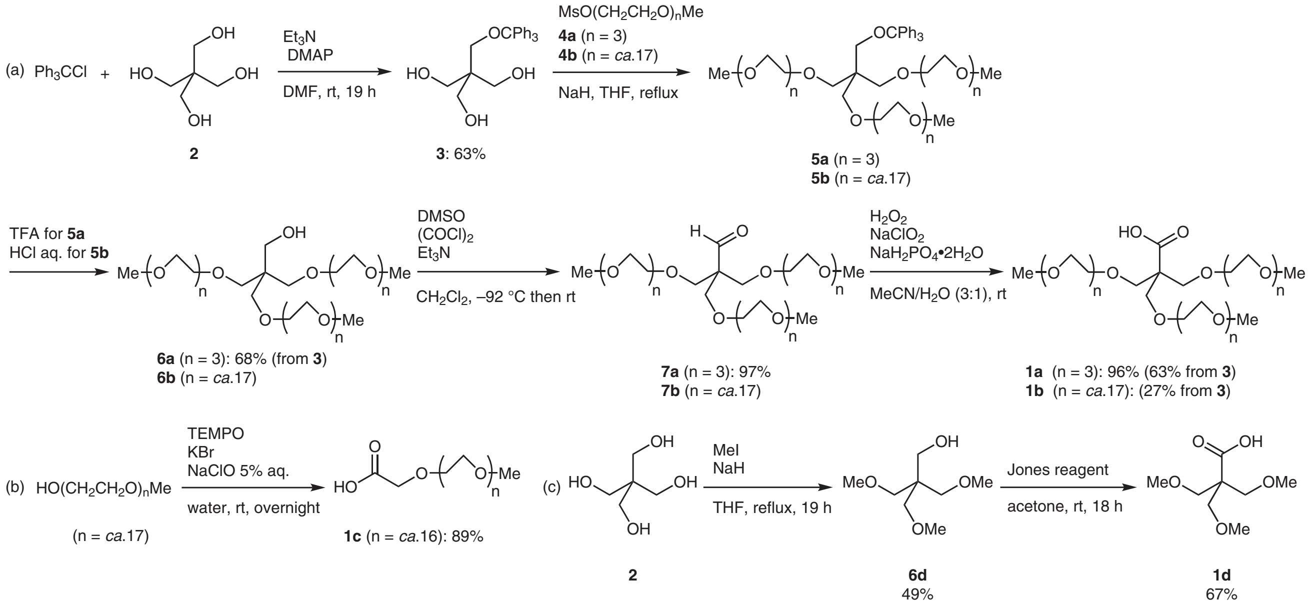


Figure 3 ESI-HRMS spectrum of **1b** (positive mode)

Each carboxylic acid was identified by NMR analysis and mass spectrometry. ^1H NMR and ^{13}C NMR spectra of **1a–d** confirmed the structures (see Supporting Information for details). The ESI-HRMS spectrum of **1a** exhibited a peak at *m*/*z* 611.3237, which was assigned as a sodium adduct of **1a** (*m*/*z* 611.3249 calcd for $C_{26}H_{52}O_{14}Na$). In contrast, the mass spectrum of **1b** showed molecular-weight distributions comprising two sets of molecular ion peaks (Figure 3). The former set of peaks was observed with *m*/*z* 14.7 intervals, which corresponds to the one-third of 44 ($–CH_2CH_2O–$ monomer unit). Therefore, these peaks were attributed to the trivalent ion. A peak at *m*/*z* 835.4658, as indicated in Figure 3, was in good agreement with the calculated value for the trisodium adduct of **1b** whose n = 17 (*m*/*z* 835.4681 calcd for $[C_{110}H_{222}O_{55}Na_3]^{3+}$). In the latter set, the peaks appeared with *m*/*z* 22 intervals (i.e., half of 44) and were therefore determined as divalent ions. The *m*/*z* value of the peak indicated in Figure 3 (*m*/*z* 1241.7048) is assigned to a



Scheme 1 Synthesis of carboxylic acids **1a–d**

disodium adduct of **1b** whose n = 17 (*m/z* 1241.7076 calcd for $[C_{110}H_{222}O_{55}Na_2]^{2+}$).

To gain insight into the structures of carboxylic acids bearing PEG chains, conformational analysis of **1b** was performed using CONFLEX[13] (MMFF94s force field[14]). Figure 4 (a) shows the most stable structure of **1b** (n = 17), wherein long PEG chains have a folded structure and wrap-up the carboxylic acid center. The folded structure in Figure 4 (a) is much more stable by 80.6 kcal/mol (energy calculations by B3LYP/6-31g(d)) than the all-*trans* and extended structures shown in Figure 4 (b). From a conformational calculation, multiple conformers with small energy differences were found around the most stable structure. Thus, PEG chains are considerably flexible due to C–C and C–O bond rotation. We envisioned that such flexible and bulky structures of **1b** might function well as ligands in transition-metal-catalyzed reactions.

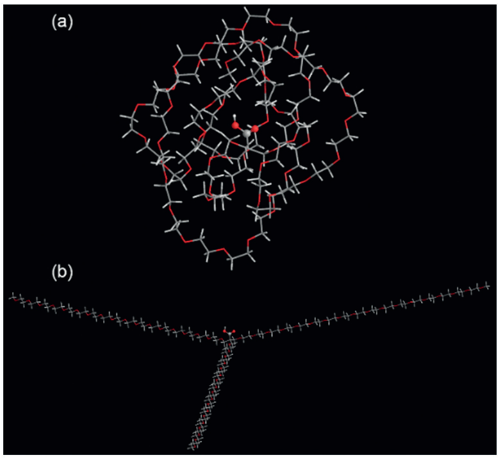
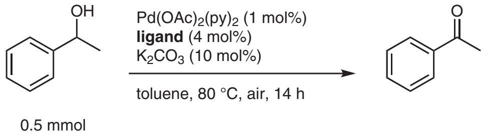


Figure 4 Structures of **1b** (n = 17). (a) The most stable structure by CONFLEX (MMFF94s) and (b) all-*trans*-extended structure. The carboxy group is represented by the ball and stick model, and the other parts are indicated by the stick model.

Previously, we reported that a pyridine ligand bearing a rigid and bulky dendrimer moiety was highly effective in the Pd-catalyzed aerobic oxidation of alcohols.[15] The bulkiness of the pyridine ligand successfully suppressed Pd black formation. On the other hand, carboxylate ligands also play an important role in oxidation reactions.[16] Therefore, we used **1a–d** as ligands in the Pd-catalyzed aerobic oxidation of 1-phenylethanol.[17]

The reaction was performed in the presence of a catalytic amount of $Pd(OAc)_2(py)_2$, **1a–d**, and K_2CO_3 in toluene at 80 °C under air (Table 1).[18] Employing **1a** bearing three PEG chains (n = 3) as the ligand, acetophenone was obtained in 68% yield (Table 1, entry 1). In addition, **1b** with three longer PEG chains (n = *ca.* 17) afforded the product in 67% yield (Table 1, entry 2). In contrast, **1c** bearing one PEG chain (n = *ca.* 16) did not work well (Table 1, entry 3). An addition of **1d** without any PEG chains was not effective (27% yield, Table 1, entry 4). When acetic acid was added, the product was obtained in moderate yield (Table 1, entry 5). In the absence of carboxylic acid, acetophenone was obtained in low yield (21% yield, Table 1, entry 6). In place of **1a**, a simple mixture of $MeO(CH_2CH_2O)_3Me$ (**8**) and **1d** (12 mol% and 4.0 mol%, respectively, **8**/**1d** = 3) as a ligand afforded the product in only 8% yield (Table 1, entry 7). Therefore, these results clearly indicate that PEG chains must be connected to the carboxylic acid moiety in order to expedite the catalytic activity. As a Pd precursor, $PdCl_2(py)_2$ was also applicable (Table 1, entry 8). When the reaction using **1a** as the carboxylic acid was carried out in mesitylene, DMSO, 4-methyltetrahydropyran, water, *n*-octane, and 1,2-dichloroethane, the product was obtained in 45%, 30%, 18%, 9%, 8% and 4% yields, respectively. The bulky and wrapped-up structure as shown Figure 4 (a) might suppress the aggregation of the Pd center and prevent Pd black formation.[19]

Table 1 Effect of Carboxylic Acids on Pd-Catalyzed Aerobic Oxidation of 1-Phenylethanol[a]



Entry	Ligand system	Yield (%)[b]
1	**1a**	68
2	**1b**	67
3	**1c**	20
4	**1d**	27
5	AcOH	46
6	none	21
7	**1d** + **8**[c]	8
8[d]	**1a**	66

[a] Reaction conditions: 1-phenylethanol (0.50 mmol), $Pd(OAc)_2(py)_2$(1.0 mol%), carboxylic acid (4.0 mol%), K_2CO_3 (10 mol%) in toluene (1.25 mL) at 80 °C for 14 h.
[b] Determined by GC analysis using tridecane as an internal standard. The yields were the average of 2 runs.
[c] $MeO(CH_2CH_2O)_3Me$ (**8**) (12 mol%, 0.060 mmol) was added.
[d] $PdCl_2(py)_2$ (1.0 mol%) was used as a Pd precursor instead of $Pd(OAc)_2(py)_2$.

In summary, we designed carboxylic acids with PEG chains, and the desired carboxylic acids **1a** and **1b** were efficiently synthesized using pentaerythritol as a starting material. In the Pd-catalyzed aerobic oxidation of 1-phenylethanol, **1a** and **1b** functioned as ligands to prevent catalyst deactivation. Further research on the application of these carboxylic acids in other catalytic reactions is under way.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591840.

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(10) **1a** was obtained as colorless oil (1.8 g, 63% yield from **3**).
Spectroscopic Data of 1a
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.68 (s, 6 H), 3.67–3.60 (m, 30 H, signals of CH_2 protons were overlapped), 3.58–3.56 (m, 6 H) 3.39 (s, 9 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.5, 71.3, 70.5, 69.82, 69.78, 69.6, 69.5, 68.2, 58.0, 52.5. ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{52}O_{14}Na$: 611.3249; found: 611.3237.

(11) **1b** was obtained as colorless oil (0.36 g, 27% yield from **3**).
Spectroscopic Data of 1b
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73–3.58 (m, 211 H, signals of CH_2 protons were overlapped), 3.57–3.53 (m, 6 H), 3.38 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.3, 71.9, 71.0, 70.6 (signals of CH_2 carbons were overlapped), 70.0, 69.1, 59.0, 53.1. ESI-HRMS: *m*/*z* $[M + 2Na]^{2+}$ calcd for $C_{110}H_{220}O_{56}Na_2$: 1241.7076; found: 1241.7048.

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(18) **General Procedure for the Pd-Catalyzed Aerobic Oxidation of 1-Phenylethanol**
A 20 mL Schlenk flask was first charged with a CH_2Cl_2 solution (*ca.* 1 mL) of carboxylic acid (in case it is liquid or sticky solid, 4 mol%). Then, CH_2Cl_2 was removed by gentle heating under vacuum. The flask was further charged with a carboxylic acid (in case it is a solid, 4 mol%), $Pd(OAc)_2(py)_2$ (1.9 mg, 5.0 μmol, 1.0 mol%), K_2CO_3 (6.9 mg, 50 μmol, 10 mol%), toluene (1.25 mL), and Teflon-coated stirring bar under air. The resulting mixture was stirred under air at room temperature for 1 min, and further at 80 °C for 3 min. Next, 1-phenylethanol (61 mg, 0.50 mmol) was added at 80 °C, and the reaction was carried out at the same temperature for 14 h under air. After the reaction, the mixture was diluted with ethyl acetate (4 mL), and the solution was passed through a pad of Celite. The yield of acetophenone was determined by GC analysis relative to an internal standard (tridecane).

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