COMMUNICATION

Pyridines Bearing Poly(ethylene glycol) Chains: Synthesis and Use as Ligands

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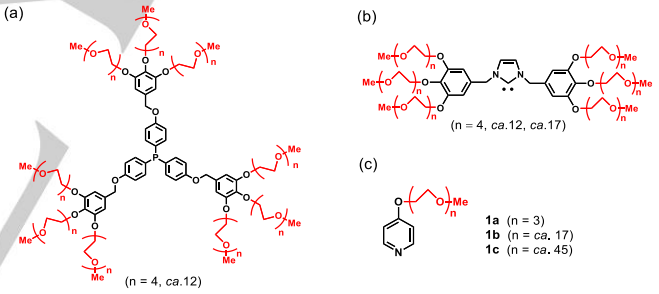
Abstract: A series of pyridine ligands bearing poly(ethylene glycol) (PEG) chains at the *para* position was synthesized and characterized by NMR and ESI-HRMS analysis. ^{1}H NMR analysis showed that pyridines coordinate to $Pd(OAc)_2$ even when a long PEG chain is attached to the pyridine ring. In the Pd-catalyzed oxidation of alcohols, the pyridines bearing longer PEG chains were found to be efficient ligands.

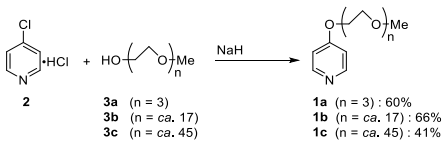
Transition metal-catalyzed reactions are powerful methodologies for synthesizing a diverse range of organic compounds. In these reactions, ligands play important roles in controlling catalytic activity as well as product selectivity.[1] Therefore, the development of new ligands aimed at improving catalyst properties has been intensively studied.[2] Poly(ethylene glycol) (PEG) and its derivatives are polymeric materials composing –CH_2CH_2O– monomer units that are attractive materials owing to their amphiphilicity, low cost, low toxicity, and availability.[3] Although the application of PEG to catalytic systems has been reported, the studies are mainly focused on their use in improving water solubility,[4] controlling solubility for phase separation systems,[5] or catalyst recycling.[6] On the other hand, PEG is a unique functional group for ligands in homogeneous transition metal-catalyzed reactions in organic solvents. For instance, Chen et al. reported Pd- and Ni-catalyzed copolymerization of ethylene and polar monomers with phosphine-sulfonate ligands bearing short PEG ($(CH_2CH_2O)_n$: n = 2) chains.[7] We have focused on the effects of flexible PEG chains on ligands.[8-10] A series of triaryl phosphines and *N*-heterocyclic carbenes bearing PEG ($(CH_2CH_2O)_n$: n = *ca.* 12 or 17) chains at the periphery (Scheme 1a,b) were synthesized and characterized. These ligands were demonstrated to work well in Pd-catalyzed Suzuki–Miyaura coupling reactions using less reactive aryl chlorides as substrates under mild reaction conditions.[8,9]

Pyridines are known to be as efficient ligands in various Pd-catalyzed oxidative reactions since these are stable under the oxidative reaction conditions.[11] We previously reported that a bulky and rigid pyridine ligand was highly effective for the Pd-catalyzed alcohol oxidation reactions.[12] In the reactions, the bulkiness of the ligand successfully suppressed the formation of Pd black. Herein, we report the synthesis of a series of pyridines bearing a flexible PEG chain at the *para* position (**1a**–**b**) in order to reduce steric congestion around the coordination site (Scheme 1c). Regarding PEG-functionalized pyridines, Oberhauser and Frediani reported that a pyridine bearing very long PEG chain (n = *ca.* 116) supported the formation of Pd nanoparticle and the particle worked as heterogeneous catalysts for the oxidation of alcohols in water.[13] In the present study, we found that pyridines bearing PEG chains were effective as ligands in homogeneous Pd-catalyzed oxidation of alcohols in toluene.



Scheme 1. PEG-functionalized ligands in our previous study. (a) Phosphines, (b) N-heterocyclic carbenes, and (c) pyridines (This work).

First, a pyridine bearing a PEG chain (n = 3, **1a**) was synthesized by the reaction of 4-chloropyridine hydrochloride (**2**) with $HO(CH_2CH_2O)_3Me$ (**3a**) in the presence of NaH (Scheme 2) and **1a** was isolated in 60% yield as colorless oil. For **1b** with a longer PEG chain (n = *ca*. 17), the same method used for **1a** was adopted using $HO(CH_2CH_2O)_nMe$ (n = *ca*. 17, **3b**) in place of **3a**, and the desired product **1b** was obtained in 66% yield as a pale yellow oil. Notably, a longer PEG chain was introduced via the method using $HO(CH_2CH_2O)_nMe$ (n = *ca*. 45, **3c**), and **1c** was successfully obtained in 41% yield as pale yellow powder by re-precipitation using Et_2O.



Scheme 2. Synthesis of pyridines **1a**–**1c**.

Each pyridine was characterized by NMR and ESI-HRMS analysis. The ^{1}H and ^{13}C NMR spectra of **1a**–**1c** are consistent with the expected structures. The ESI-HRMS spectrum of **1a** features a peak at *m/z* 242.1384, which is assigned to the mono-protonated adduct of **1a** (*m/z* 242.1392 calcd for $C_{12}H_{20}O_4N$). The mass spectrum of **1b** shows a molecular weight distribution (Figure 1a). A set of peaks separated by *m/z* 44 intervals is observed, where *m/z* 44 corresponds to a $–CH_2CH_2O–$ monomer unit. Therefore, these peaks were attributed to the monovalent ion. A peak at *m/z* 858.5037, as indicated in Figure 1a, is in good agreement with the calculated value for the proton adduct of **1b** (n = 17, *m/z* 858.5062 calcd for $[C_{40}H_{76}O_{18}N]^+$). In addition, the other set of peaks was attributed to the mono-sodium adduct of **1b** (found: *m/z* 880.4856; calcd: *m/z* 880.4881 $[C_{40}H_{75}O_{18}NNa]^+$). On the other hand, **1c** is observed mainly as divalent ions with *m/z* 22 intervals (Figure 1b). The peak at *m/z* 1057.1121, as indicated in Figure 1b, is attributed to the proton-sodium adduct of **1c** where n = 45 (*m/z* 1057.1150 calcd for $[C_{96}H_{188}O_{46}NNa]^{2+}$). In addition, the disodium adducts of **1c** are also observed (found: *m/z* 1068.1028 calcd *m/z* 1068.1060 $[C_{96}H_{187}O_{46}NNa_2]^{2+}$).

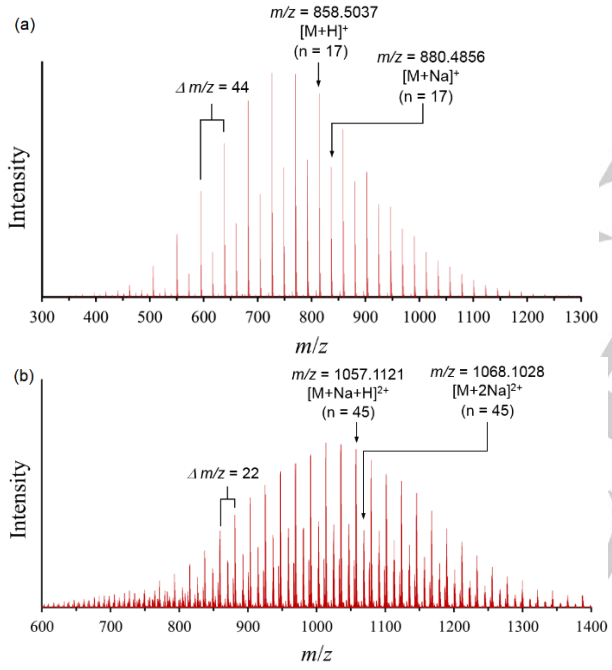


Figure 1. ESI-HRMS spectra of (a) **1b** and (b) **1c** (positive mode).

Coordination ability of the isolated pyridines with $Pd(OAc)_2$ was investigated. The reaction of 4-methoxypyridine (**1**^{OMe}) with $Pd(OAc)_2$ in toluene at 80 °C (Pyridine/Pd = 2:1) afforded $Pd(OAc)_2$(**1**^{OMe})$_2$ that was characterized by single crystal X-ray structure analysis (Figure 2a). The Pd center has a square planar geometry and two pyridine ligands occupy *trans* position. This trans structure is similar to $Pd(OAc)_2(py)_2$.[13] The coordination abilities of pyridine ligands bearing a PEG chain was explored using ^{1}H NMR measurements (Figure 2b,c). The reactions of pyridines with $Pd(OAc)_2$ were carried out in C_6D_6 (pyridine/Pd = 2:1) at room temperature. Employing **1b** as the pyridine, after the addition of $Pd(OAc)_2$, all signals attributed to **1b** disappeared and new signals were observed (Figure 2b). This indicates the formation of $Pd(OAc)_2$(**1b**)$_2$. Notably, the similar change was observed with **1c** bearing a considerably long PEG chain (n = *ca.* 45) (Figure 2c), indicating the length of PEG chains on the pyridines did not affect the coordination to the Pd center.

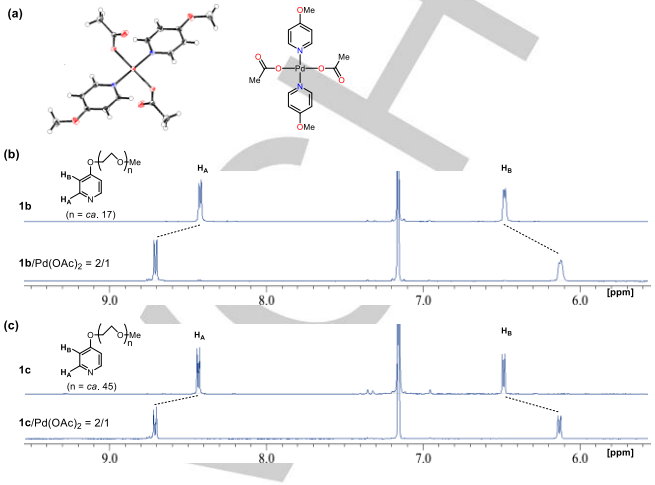
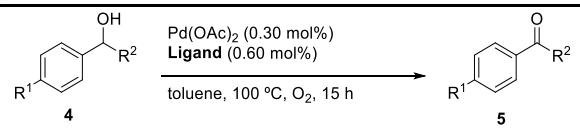


Figure 2. Crystal structure of $Pd(OAc)_2$(**1**^{OMe})$_2$ (a), and ^{1}H NMR spectra of complexation experiment of pyridines with $Pd(OAc)_2$ in C_6D_6: (b) **1b** and (c) **1c**.

Next, the PEG-functionalized pyridines were used as ligands in Pd-catalyzed oxidation of alcohols.[11] The reaction of 1-phenylethanol (**4a**) was performed under low Pd loading conditions (0.30 mol%) in toluene at 100 °C under an oxygen atmosphere (Table 1). Employing pyridine ligands bearing PEG chains at the 4-position (**1**^{OMe}, **1a**, **1b**, and **1c**), the yields of acetophenone (**5a**) increased as the PEG chains extended

Table 1. Effect of pyridines on Pd-catalyzed Oxidation of 1-Phenylethanol under O_2.[a]

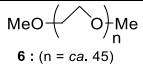


4 5

R^1 = H, R^2 = Me: **4a**
R^1 = Me, R^2 = Me: **4b**
R^1 = H, R^2 = Et: **4c**

Entry	Substrate	Ligand	Yield [%][b]
1	**4a**	**1**^{OMe}	54
2	**4a**	**1a**	65
3	**4a**	**1b**	76
4	**4a**	**1c**	79 (75)[c]
5	**4a**	**1**^{OMe} + **6**[d]	56
6	**4b**	**1c**	70[c]
7	**4c**	**1c**	75[c]

[a] Reaction conditions: 1-phenylethanol (4.0 mmol), $Pd(OAc)_2$ (0.30 mol%), pyridine ligand (0.60 mol%) in toluene (0.60 mL) at 100 °C for 15 h under O_2 (1 atm). [b] Determined by GC analysis. [c] Isolated yield. [d] 0.60 mol% of **6** was added. [c] isolated yield



6 : (n = *ca*. 45)

(entries 1–4). Notably, the highest yield (79% yield) was obtained using the pyridine having the longest PEG chain (**1c**, n = 45, entry 4). From the reaction mixture, **5a** was isolated in 75% yield. Here, a simple mixture of $MeO(CH_2CH_2O)_nMe$ (n = *ca*. 45) (**6**) and $\mathbf{1}^{OMe}$ (0.60 mol%, **6**/$\mathbf{1}^{OMe}$ = 1) instead of **1c** afforded the product in 56% yield, which was comparable to that using $\mathbf{1}^{OMe}$ (entry 5 vs. entry 1). Therefore, these results clearly indicate that PEG chains must be directly connected to the pyridine moiety in order to improve the catalytic activity. From 1-(4-tolyl)ethanol (**4b**) and 1-phenyl-1-propanol (**4c**), the corresponding ketones (**5b** and **5c**) were obtained in 70% and 75% isolated yields, respectively, using **1c** as the ligand under the optimum reaction conditions. The reactions using other alcohols such as 2-octanol, benzyl alcohol, and 1-octanol under the optimum reaction conditions afforded the corresponding products in 16%, 34%, 2% yields, respectively.

To gain insight into structure of **1c** (n = 45), conformational analysis was performed by using CONFLEX[15] (MMFF94 force field). During the conformational search, a large number of conformers with small energy differences were found around an energy-minimized conformer. This indicates that the PEG chain is highly flexible. Then, the energy-minimized structure was further optimized by DFT calculations (B3LYP/6-31G(d)). Figure 3a shows the optimized structure of **1c**, wherein a flexible PEG chain is folded and forms a bulky structure. Under catalytic reaction conditions with L/Pd = 2 (L = **1b** or **1c**), $Pd(OAc)_2(L)_2$ must be initially generated. Thus, structures of $Pd(OAc)_2(\mathbf{1b})_2$ was optimized by ONIOM[16] (B3PW91/LANL2DZ-UFF) calculation. In the structure of $Pd(OAc)_2(\mathbf{1b})_2$, a folded PEG chains covers the rear side of the pyridine ring (Figure 3b). The structure would suppress the aggregation of Pd species owing to its long-range flexible steric bulk.

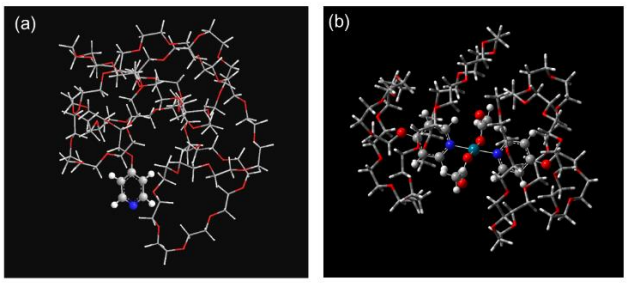


Figure 3. Optimized structures of PEG-functionalized pyridines. (a) **1c** (n = 45). The pyridine ring moiety is shown as a ball and stick model. (b) $Pd(OAc)_2(\mathbf{1b})_2$ (n = 17). The $Pd(OAc)_2(py)_2$ core is shown as a ball and stick model.

In summary, we designed and prepared a series of pyridine ligands bearing PEG chains (**1a**–**c**) by straightforward methods using a commercially available 4-chloropyridine and PEG derivatives as starting materials. These pyridines were characterized by NMR and ESI-HRMS analyses. The pyridine ligands bearing longer PEG chains were efficient in the Pd-catalyzed oxidation of alcohols. Conformational analysis and DFT calculations indicated that **1c** has a unique and bulky structure that could suppress the aggregation of Pd catalysts in alcohol oxidation. Further studies on the position effect of the pyridine ring and application to other reactions are currently underway.

Experimental Section

Preparation of 1a: In a dried two-neck 300-mL round-bottomed flask, **3a** (4.9 g, 30 mmol, 1.0 equiv) was dissolved in THF (120 mL) and the solution was stirred at 0 ºC. To this solution, NaH (3.4 g as a 60% dispersion, 84 mmol, 2.8 equiv) was added portion wise and the mixture was stirred for 40 min at 0 ºC. After stirring, 4-chloropyridine hydrochloride (**2**, 5.4 g, 36 mmol, 1.2 equiv) was added and the mixture was stirred for 23 h under reflux. The progress of the reaction was monitored by ^{1}H NMR measurements, and in order to ensure completion of the reaction, the additional **2** (5.4 g, 36 mmol) and NaH (1.4 g as 60% dispersion, 36 mmol) were added to the reaction mixture and the mixture was further stirred for 3 h under reflux. After the reaction was completed, water (10 mL) was added and THF was evaporated. The resulting mixture was passed through a pad of celite. The water (150 mL) was added to the resulting solution and the aqueous solution was washed with hexane (150 mL × 5). The resulting aqueous layer was extracted with CH_2Cl_2 (80 mL × 4) and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was evaporated to dryness and the resulting oil was purified by silica gel column chromatography using $CHCl_3$/MeOH (30:1, v/v) as an eluent. After removal of all volatiles, **1a** was obtained in 60% yield (4.4 g, 18 mmol) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44-8.40 (m, 2H), 6.85-6.81 (m, 2H), 4.20-4.16 (m, 2H), 3.90-3.86 (m, 2H), 3.76-3.71 (m, 2H), 3.70-3.63 (m, 4H), 3.57-3.53 (m, 2H), 3.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 150.9, 110.3, 71.8, 70.8, 70.6, 70.5, 69.2, 67.1, 58.9. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{20}O_4N$, 242.1387; found, 242.1384.

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Keywords: alcohol • oxidation • palladium • poly(ethylene glycol) • pyridine

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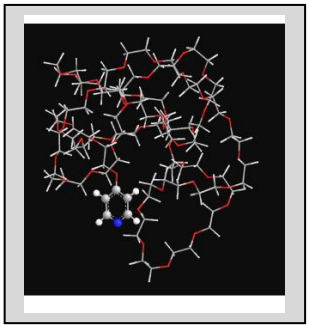

A series of pyridine ligands bearing poly(ethylene glycol) (PEG) chains at the *para* positions were synthesized and characterized by NMR and ESI-HRMS analyses. In the Pd-catalyzed oxidation o.f alcohols, the pyridines bearing longer PEG chains were efficient.