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

Motoi Satou, Arata Kiyooka, Yasushi Tsuji and Tetsuaki Fujihara*

Dedication (please delete if not required)

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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 composed – CH$_2$CH$_2$O– 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,$^{[4,5]}$ controlling solubility for phase separation systems,$^{[6]}$ or catalyst recycling.$^{[7]}$ 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$_2$)$_n$CH$_2$O)$_n$, $n = 2$) chains.$^{[8]}$ We have focused on the effects of flexible PEG chains on ligands.$^{[9,10]}$ A series of triaryl phosphines and N-Heterocyclic carbenes bearing PEG (CH$_2$CH$_2$O)$_n$, $n = 12$ 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.$^{[9,10]}$

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 ($n = 116$) 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.

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**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$_2$CH$_2$O)$_3$Me (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 ($n = 17$), the same method used for 1a was adopted using HO(CH$_2$CH$_2$O)$_7$Me ($n = 17$, 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$_2$CH$_2$O)$_7$Me ($n = ca. 45$, 3c), and 1c was successfully obtained in 41% yield as pale yellow powder by re-precipitation using EtO.
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 calcld for \(\text{C}_9\text{H}_7\text{O}_{11}\text{N}\)). 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 \(-\text{CH}_2\text{CH}_2\text{O}-\) 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 calcld for [\(\text{C}_{46}\text{H}_{37}\text{O}_{15}\text{N}\)]). In addition, the other set of peaks was attributed to the mono-sodium adduct of 1b (found: \(m/z\) 880.4856; calcld: \(m/z\) 880.4881 [\(\text{C}_{46}\text{H}_{37}\text{O}_{15}\text{NNa}\)]). 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 calcld for [\(\text{C}_{220}\text{H}_{187}\text{O}_{66}\text{NNa}\)]). In addition, the disodium adducts of 1c are also observed (found: \(m/z\) 1068.1028 calcld \(m/z\) 1068.1060 [\(\text{C}_{220}\text{H}_{187}\text{O}_{66}\text{NNa}_2\)]).

![Figure 1. ESI-HRMS spectra of (a) 1b and (b) 1c (positive mode).](image)

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 (\(^1\)OMs, 1a, 1b, and 1c), the yields of acetophenone (5a) increased as the PEG chains extended.

![Figure 2. Crystal structure of Pd(OAc)\(_2\)(1OMs)\(_2\) (a), and \(^1\)H NMR spectra of complexation experiment of pyridines with Pd(OAc)\(_2\) in \(\text{C}_6\text{D}_6\) (b) 1b and (c) 1c.](image)

**Table 1. Effect of pyridines on Pd-catalyzed Oxidation of 1-Phenylethanol under \(\text{O}_2\).**

| Entry | Substrate | Ligand | Yield [%]| |
|-------|-----------|--------|----------|
| 1     | 4a        | \(^1\)OMs | 54       |
| 2     | 4a        | 1a     | 65       |
| 3     | 4a        | 1b     | 76       |
| 4     | 4a        | 1c     | 79 (75)  |
| 5     | 4a        | \(^1\)OMs + 6\[\dagger\] | 56       |
| 6     | 4b        | 1c     | 70\[\dagger\] |
| 7     | 4c        | 1c     | 75\[\dagger\] |

[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 \(\text{O}_2\) (1 atm). [b] Determined by GC analysis. [c] Isolated yield. [d] 0.60 mol% of 6 was added. [\dagger] Isolated yield.
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 °C. 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 °C. 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 1H 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$_2$Cl$_2$ (80 mL × 4) and the organic layer was washed 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. 1H 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). 13C 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$_2$N, 242.1387; found, 242.1384.

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

**References**

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[4] For the selected examples of PEG-functionalized ligands in water, see:


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