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A Triarylphosphine Ligand Bearing Dodeca(ethylene glycol) Chains: Enhanced Efficiency in the Palladium-Catalyzed Suzuki−Miyaura Coupling Reaction

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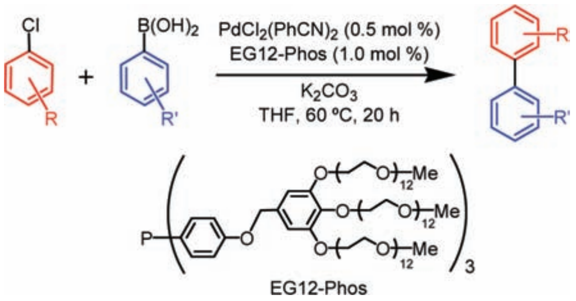
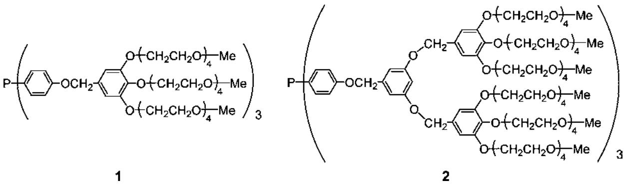
ABSTRACT



A new phosphine bearing dodeca(ethylene glycol) chains has been synthesized and employed as a ligand in the palladium-catalyzed Suzuki−Miyaura coupling reaction. The system was found to be highly effective using unactivated aryl chlorides as the substrate.

Phosphines are one of the most important ligands[1] for homogeneous transition-metal-catalyzed reactions realizing high efficiency.[2] Therefore, a wide variety of phosphines have been designed to realize high catalytic activity and selectivity. Recently, we designed and prepared triarylphosphines (**1** and **2** in Scheme 1), in which tetra(ethylene glycol) (EG4, $M_w = 191$)[3] chains are connected onto the PPh_3 core.[4] Although EG4 moieties are easy to manipulate, the EG4 chain is not long enough and **1** has only limited efficiency as a ligand in the Suzuki−Miyaura coupling reaction[5] of unactivated aryl chlorides.[6] In order to realize highly efficient ligands, EG4 chains must be arranged dendritically at the periphery of the ligand (**2**) via lengthy multistep synthesis.[4] In this paper, we wish to report that a dodeca(ethylene glycol)

Scheme 1



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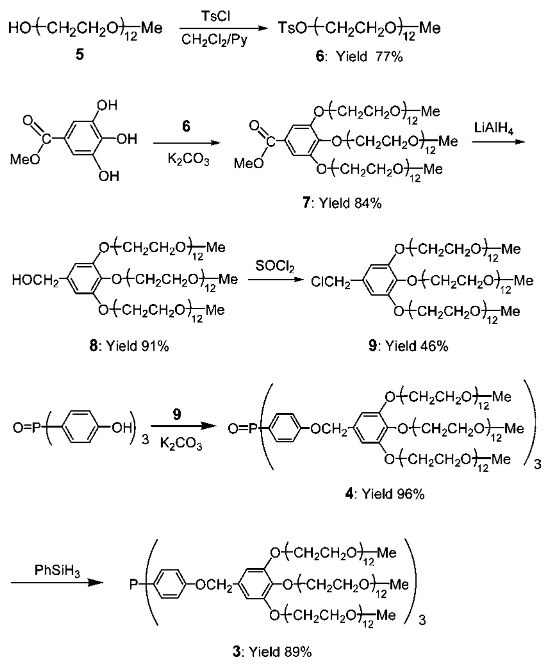
(1) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (c) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904. (d) *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983.

(2) (a) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Applications of Transition Metal Catalysts in Organic Synthesis*; Springer, Berlin, 1999. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principle and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987. (c) *Homogeneous Transition Metal Catalyzed Reaction*; Moser, W. R., Slocum, D. W., Eds.; American Chemical Society: Washington, DC, 1992.

10.1021/ol900578g CCC: $40.75

(EG12, M_w = ca. 540) chain is a suitable moiety to enhance efficiency of the ligand without such an elaborated dendritic structure of **2**. While much longer poly(ethylene glycol) (PEG, mainly $M_w = 2000-6000$) chains are often employed for preparation of water-soluble ligands,[7] we successfully utilized a relatively short EG12 chain to enhance the efficiency of a ligand in an organic solvent.

Scheme 2



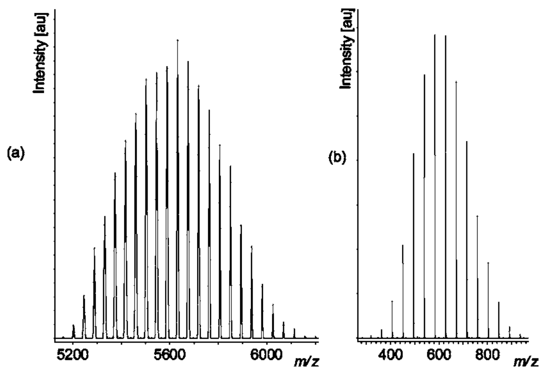
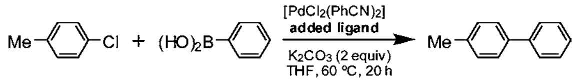


Figure 1. MALDI-TOF mass spectra of (a) **3** and (b) **5**.

The phosphine **3** was prepared straightforwardly in good yields from commercially available EG12 monomethyl ether (**5**, $HO(CH_2CH_2O)_nMe$, $n = 12$ on average) as shown in Scheme 2[4,8] (for details, see Supporting Information). The MALDI-TOF mass spectrum of **3** shows the molecular ion peaks centered at $m/z = 5632$ ([M] + Na^+) with the constant peak interval of 44 (Figure 1a). From the spectrum, the M_w/M_n was calculated to be 1.001, and the value is consistent with the $M_w/M_n = 1.028$ of **5** (Figure 1b). These results clearly indicated that the nine EG12 chains are successfully incorporated onto **3**. $^{31}P\{^1H\}$ NMR spectra of **3** are virtually not affected by a solvent, and ^{31}P resonances appear at −9.22 ppm in $CDCl_3$ and −9.39 ppm in THF-d_8. The basicity of **3** can be evaluated by $^1J_{P-Se}$ coupling constants of the corresponding phosphine selenide $Se{=}PR_3$.[9] The coupling constant (hence basicity) of **3** (715 Hz) is very similar and comparable to those of **1** (714 Hz), **2** (715 Hz),[4] and PPh_3 (730 Hz). Thus, the EG12 chains introduced on the PPh_3 core do not affect the electronic property of the phosphine. These triarylphosphines are much weaker base than $P(t\text{-}Bu)_3$ ($^1J_{P-Se}$ = 686 Hz) and tricyclohexylphosphine ($^1J_{P-Se}$ = 674 Hz).

Table 1. Effect of a Phosphine and Relevant Ligand Systems on the Coupling Reaction[a]



entry	added ligand	yield (%)[b]
1	**1**	53
2	**3**	92(88)
3	PPh_3	0
4	PPh_3 + **5-Me**[c]	0
5	PPh_3 + **7**[d]	0
6	PPh_3 + **4**[e]	0

[a] 4-Chlorotoluene (2.0 mmol), phenylboronic acid (4.0 mmol), $[PdCl_2(PhCN)_2]$ (0.010 mmol, 0.50 mol %), phosphine (0.020 mmol, P/Pd = 2), and K_2CO_3 (4.0 mmol) in THF (1.0 mL) at 60 °C for 20 h. [b] Yield based on the GC internal standard technique. The data in parentheses shows yield of the isolated product. [c] Molar ratio of **5-Me**/PPh_3 = 9. [d] Molar ratio of **7**/PPh_3 = 3. [e] Molar ratio of **4**/PPh_3 = 1.

The phosphine **3** was employed as a ligand in the Suzuki−Miyaura coupling reaction of 4-chlorotoluene with phenylboronic acid in the presence of a catalytic amount of $[PdCl_2(PhCN)_2]$ with K_2CO_3 in THF at 60 °C (Table 1). As reported previously, **1** was not so efficient as a ligand and 4-phenyltoluene was afforded in 36% yield with 0.1 mol % catalyst loading.[4] Even when the amount of catalyst was increased to 0.5 mol %, **1** was still not an efficient ligand (entry 1). In sharp contrast, **3** having EG12 chains was found to be a much more effective ligand, affording the product in

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(3) For ligands with tetra(ethylene glycol) moiety, see: (a) Ohta, H.; Fujihara, T.; Tsuji, Y. *Dalton Trans.* **2008**, *37*, 9–385. (b) Fujita, K.-I.; Kujime, M.; Muraki, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 261–266. (c) Muraki, T.; Fujita, K.-I.; Kujime, M. *J. Org. Chem.* **2007**, *72*, 7863–7870. (d) Muraki, T.; Fujita, K.-I.; Terakado, D. *Synlett* **2006**, *264*, 6–2648. (e) Hoen, R.; Leleu, S.; Botman, P. N. M.; Appelman, V. A. M.; Feringa, B. L.; Hiemstra, H.; Minnaard, A. J.; van Maarseveen, J. H. *Org. Biomol. Chem.* **2006**, *4*, 613–615.

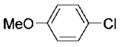
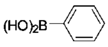
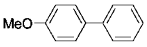
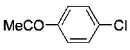
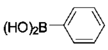
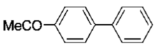
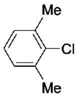
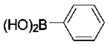
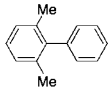
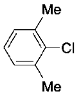
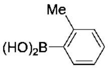
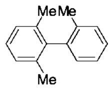
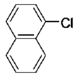
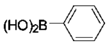
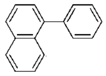
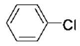
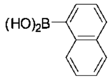
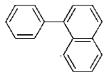
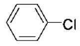
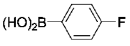
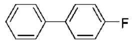
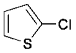
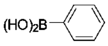
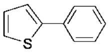
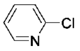
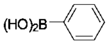
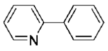
(4) Fujihara, T.; Yoshida, S.; Ohta, H.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8310–8314.

(5) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reaction*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 41−123. (c) Suzuki, A.; Brown, H. C. *Organic Syntheses Via Boranes, Vol. 3, Suzuki Coupling*; Aldrich: Milwaukee, 2003.

(6) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211, and references therein. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

92% yield (entry 2). To clarify the role of the EG12 chains of **3**, some control experiments were carried out with several ligand systems. With PPh_3 (a core part of **3**), no conversion of 4-chlorotoluene was observed (entry 3). The ligand system consisting of a mixture of EG12-dimethyl ether ($MeO(CH_2CH_2O)_{12}Me$, **5-Me**) and PPh_3 in place of **3** did not afford the product at all (entry 4). Furthermore, neither a combination of **7** and PPh_3 (entry 5) nor a mixture of **4** (the oxide of **3**) and PPh_3 (entry 6) afforded the product at all. These results clearly indicate that EG12 moieties must be connected to the phosphine core in order to cause the high efficiency as the ligand. On the other hand, the efficiency of **3** was affected considerably by the reaction conditions such as solvent and base. When entry 2 in Table 1 was carried out in toluene, DMF, DME, 2-propanol, or H_2O as a solvent under otherwise identical reaction conditions, the yield of 4-phenyltoluene decreased to 28%, 46%, 49%, 64%, or 39%, respectively. As for a base, KF, K_3PO_4, Na_2CO_3, Cs_2CO_3, or Li_2CO_3 in place of K_2CO_3 in entry 4 afforded the product in 83%, 90%, 49%, 45%, or 4%, respectively. Thus, **3** works as an efficient ligand in THF with the potassium bases. These observations are very reminiscent of a catalyst system using **2** as the ligand.[4]

Table 2. Reaction of Various Substrates under the Optimum Reaction Conditions[a]

entry	aryl chloride	arylboronic acid	product	yield (%)[b]
1				89
2				99
3				97
4				(49)
5				90
6				89
7				97
8				93
9				(21)

[a] Aryl chloride (2.0 mmol), arylboronic acid (4.0 mmol), $[PdCl_2(PhCN)_2]$ (0.010 mmol, 0.50 mol %), **3** (0.020 mmol), K_2CO_3 (4.0 mmol), and THF (1.0 mL) at 60 °C for 20 h. [b] Yields of the isolated products. The data in the parentheses show yields of the products based on the GC internal standard technique.

The effectiveness of **3** as the ligand was further confirmed using various aryl chlorides and arylboronic acids under the optimum reaction conditions in THF with K_2CO_3 (Table 2). The electron-rich and -poor aryl chlorides were smoothly converted to the corresponding biphenyl compounds in high yields (entries 1 and 2). In the more sterically demanding coupling reaction of 2-chloro-1,3-dimethylbenzene with phenylboronic acid or 2-methylphenylboronic acid, the products were obtained in high or moderate yields (entries 3 and 4). 1-Phenylnaphthalene was obtained either from 1-chloronaphthalene or chlorobenzene in high yields (entries 5 and 6). 4-Fluorophenylboronic acid afforded the product in 97% yield (entry 7). From 2-chloro-thiophene and phenylboronic acid, the desired product was obtained in 93% yield (entry 8), while 2-chloropyridine was converted to the corresponding compound in low yield, possibly as a result of the coordination of the pyridine moiety to a catalyst center (entry 9). When **1** instead of **3** was used as the ligand in entries 1 and 6, the yields of the products decreased to 47% and 50%, respectively, showing efficacy of longer EG12 chains of **3**.

Figure 2 shows an optimized structure of **3** calculated by the ONIOM[10] (B3LYP/LANL2DZ-UFF) method, in which

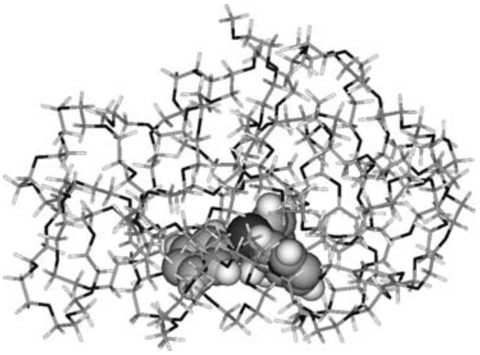


Figure 2. Optimized structure of **3** by ONIOM (B3LYP/LANL2DZ: UFF) method. The space-filling diagram shows the triphenylphosphine core.

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(7) For recent papers on PEG-functionalized ligands in water, see: (a) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508–3509. (b) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577–2580. (c) Adidou, O.; Goux-Henry, C.; Safi, M.; Soufiaoui, M.; Framery, E. *Tetrahedron Lett.* **2008**, *49*, 7217–7219. (d) Leyva, A.; García, H.; Corma, A. *Tetrahedron* **2007**, *63*, 7097–7111. (e) Corma, A.; García, H.; Leyva, A. *J. Catal.* **2006**, *240*, 87–99. (f) Wang, X.; Yin, L.; Yang, T.; Wang, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 108–114.

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long EG12 chains are folded around the PPh_3 core. The calculation shows that the structure in Figure 2 is far more stable than one with *straight* EG12 chains (Figure S1 in Supporting Information) by 68 kcal mol^{-1}. Thus, **3** has a particular gigantic shape: the Connolly solvent-excluded volumes[11] of the optimized **3**, **2**, and PPh_3 were 6720, 5830, and 230 Å^3, respectively. The catalytic behavior using **3** as the ligand was very reminiscent of one using **2** (vide supra). The high efficiency of **2** as the ligand has been attributed to the particular bulky structure with folded EG4 chains with the dendritic arrangement.[4] In the case of **3**, the same mechanism would be operative to enhance the catalytic activity, i.e., the phosphine of the massive shape (Figure 2) might exclude other same phosphines (**3**) in the coordination sphere to generate a highly unsaturated[12] and hence extremely active catalyst species.

In summary, a new phosphine (**3**) bearing EG12 chains was designed and synthesized. In the palladium-catalyzed Suzuki−Miyaura coupling reaction of unactivated aryl chlorides, **3** was a highly effective ligand without the elaborated dendritic structures such as in **2**. Further application of the unique phosphines with flexible long chains in catalysis is currently under investigation.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (“Chemistry of Concerto Catalysis” and “Synergy of Elements”) from Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures including the synthesis of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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