

Suzuki–Miyaura reaction in water, conducted by employing an amphiphilic dendritic phosphine–palladium catalyst: a positive dendritic effect on chemical yield

Hatsuhiko Hattori, Ken-ichi Fujita,* Takahito Muraki and Ai Sakaba

National Institute of Advanced Industrial Science and Technology (AIST), AIST Tsukuba Central 5, 1-1-1, Higashi, Tsukuba, Ibaraki 305-8565, Japan

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Abstract—A series of amphiphilic dendritic ligands with a phosphine core was synthesized by use of tris(4-hydroxyphenyl)phosphine oxide and poly(benzyl ether) dendron. The corresponding phosphine–palladium core dendrimers were applied as a catalyst to an aqueous-media Suzuki–Miyaura reaction. A positive dendritic effect on chemical yields of cross-coupling products was observed. © 2007 Elsevier Ltd. All rights reserved.

Organic reactions in water without the use of any harmful organic solvents are of great current interest, because water is an easily available, economical, safe, and environmentally friendly solvent.¹ To date, various water-

soluble ligands were prepared, and their applications to aqueous-media organic syntheses were reported. Above all, water-soluble phosphine–transition metal catalysts were widely investigated.²

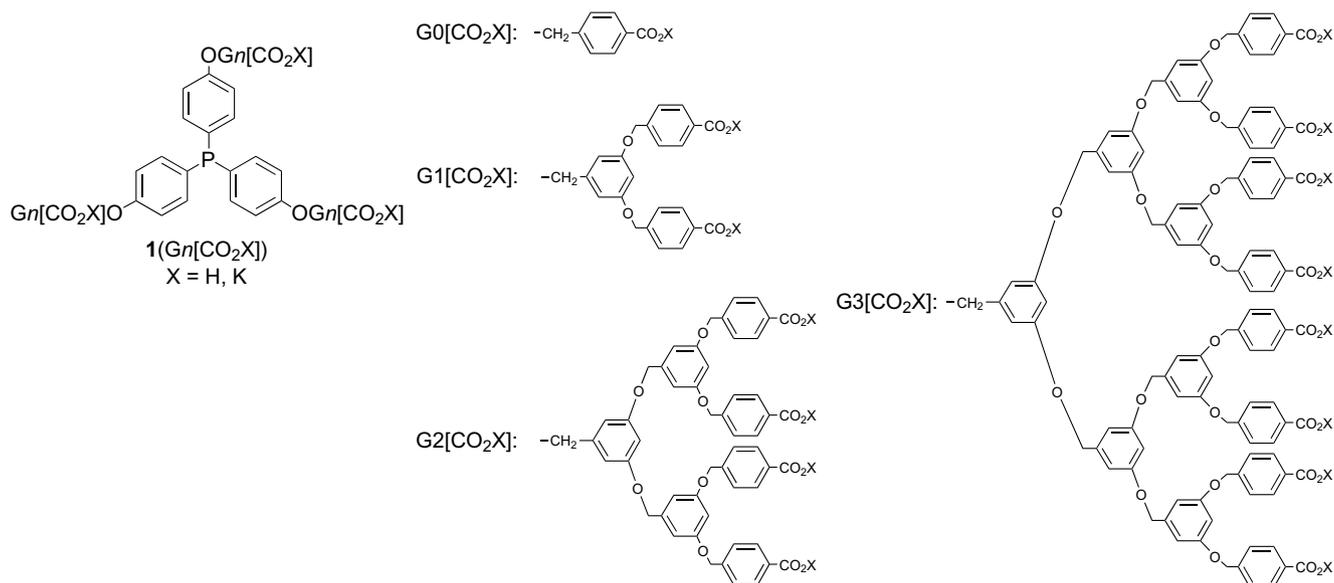


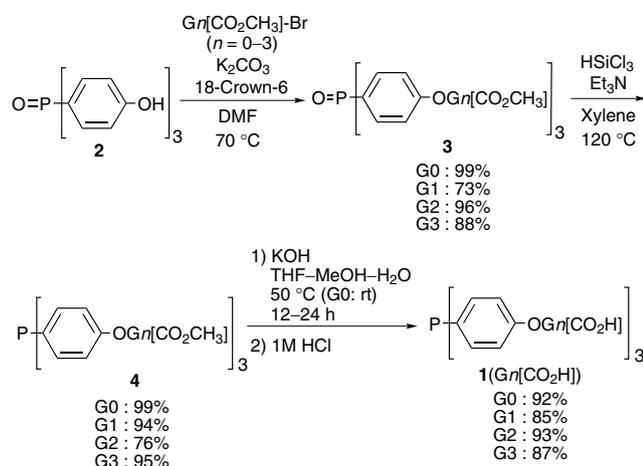
Figure 1. Structural formulas of dendrimer $1(G_n[CO_2X])$ and $G_n[CO_2X]$ dendrons ($n = 0-3$).

* Corresponding author. Fax: +81 29 861 4577; e-mail: k.fujita@aist.go.jp

Dendrimers are fascinating molecules due to their unique physical and chemical properties caused by their well-defined hyperbranched frameworks.³ Metallo-dendrimers with a functional or catalytic site at their core have received considerable attention. Their solubility and physical properties can be altered by peripheral modification.⁴ For example, by the introduction of hydrophilic groups to the peripheral layer of a hydrophobic dendron, water-soluble dendritic unimolecular micelles can be prepared.⁵ However, there are few examples of their use as catalysts.^{5d,f}

Recently, several examples of a positive dendritic effect on chemical yields, which means that the reactivity is enhanced by increasing the generation number of the dendrimer, have been reported by us⁶ and by other groups.⁷ In our previous study, it was found that a hydrophobic dendron was effective as a reaction field in aqueous-media organic syntheses.^{6b,c} We wish to report herein the synthesis of novel amphiphilic dendritic ligands with a phosphine core,⁸ utilizing a Suzuki–Miyaura coupling reaction in water, conducted by employing the corresponding amphiphilic phosphine–palladium catalyst, and the positive dendritic effect on chemical yields of the coupling products.

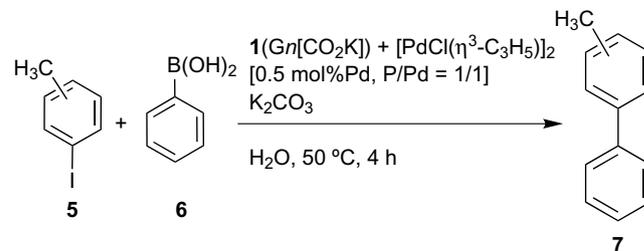
Novel phosphine core dendrimers **1**(*Gn*[CO₂H]), which are shown in Figure 1, were synthesized as follows (Scheme 1). An *N,N*-dimethylformamide (DMF) solution of tris(4-hydroxyphenyl)phosphine oxide **2**⁹ and poly(benzyl ether) dendritic bromide *Gn*[CO₂CH₃]-Br^{5g} was stirred at 70 °C in the presence of potassium carbonate and a catalytic amount of 18-crown-6 for 6 h under an argon atmosphere. The obtained dendritic phosphine oxide **3** was reduced by trichlorosilane in degassed xylene at 120 °C for 12 h to afford dendritic phosphine **4**. **1**(*Gn*[CO₂H]) was obtained by hydrolysis of **4** with potassium hydroxide in degassed aqueous solution (THF–methanol–H₂O) at 50 °C, followed by protonation of the product with hydrochloric acid. All transformations were carried out in fair yields in all generations.^{10,11}



Scheme 1. Synthesis of dendrimer **1**(*Gn*[CO₂H]).

We examined the utility of dendrimer **1**(*Gn*[CO₂H]) as a dendritic ligand by performing Suzuki–Miyaura coupling reaction using the corresponding amphiphilic **1**(*Gn*[CO₂K])–palladium catalyst in water (Table 1).

Table 1. Dendritic effect on chemical yields^a



Entry	CH ₃ in 5	Yield ^b (%)			
		G0	G1	G2	G3
1	3-CH ₃	30	42	57	82
2	4-CH ₃	37	73	81	90

^a Reaction conditions: **1**(*Gn*[CO₂K]) (0.0055 equiv), [PdCl(η³-C₃H₅)₂] (0.0025 equiv, 0.5 mol % Pd), **5** (1 equiv), **6** (1.5 equiv), K₂CO₃ (4.5 equiv), H₂O (0.5 M based on **5**), carried out at 50 °C for 4 h.

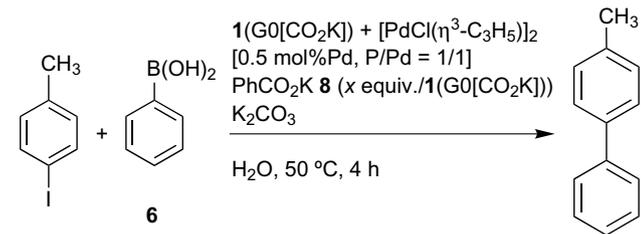
^b Isolated yield.

The coupling reactions were carried out by use of iodotoluene **5** and phenylboronic acid **6** with 0.5 mol % of various generation **1**(*Gn*[CO₂K])–palladium catalysts, which were prepared from **1**(*Gn*[CO₂K]) and [PdCl(η³-C₃H₅)₂] in situ (P/Pd = 1/1), in water at 50 °C for 4 h.¹² Although **1**(*Gn*[CO₂K])–palladium catalysts had micelle-like structures, the reaction mixture was a dispersion mixture.¹³ In both cases of 3-iodotoluene and 4-iodotoluene, the chemical yield of the coupling product **7** was enhanced by increasing the generation number of **1**(*Gn*[CO₂K])–palladium catalyst.¹⁴ Especially, in the case of using 4-iodotoluene, the third-generation **1**(G3[CO₂K])–palladium catalyst afforded 90% yield, which was higher than that in the case of using commercially available TPPTS¹⁵–palladium catalyst (76% yield). The relationship between the generation number of the dendritic catalyst and the chemical yields is one of the positive dendritic effects.^{6,7,16}

In the case of this series of dendritic phosphine ligands **1**(*Gn*[CO₂K]), **1**(G0[CO₂K]) has 3 –CO₂K moieties, **1**(G1[CO₂K]) has 6, **1**(G2[CO₂K]) has 12, and **1**(G3[CO₂K]) has 24 –CO₂K moieties. To confirm the effect of the number of –CO₂K groups as surfactants to form dispersions, we have carried out a Suzuki–Miyaura reaction of 4-iodotoluene and **6** by employing non-dendritic **1**(G0[CO₂K])–palladium catalyst having 3 –CO₂K moieties and potassium benzoate **8** (*x* equiv/**1**(G0[CO₂K])) with the same amount of –CO₂K moieties of **1**(*Gn*[CO₂K]) (*n* = 1–3) (Table 2).

As a result, the yields of the coupling products were rather low in all cases, thus the addition of **8** was therefore not effective in increasing the chemical yield. Based on these results, it can be concluded that the introduction of hydrophilic groups to the peripheral layer of poly(benzyl ether) dendron as a hydrophobic reaction

Table 2. Suzuki–Miyaura reaction in water by employing **1**(G0[CO₂K])–palladium catalyst and **8** with the same amount of –CO₂K moieties of **1**(G_{*n*}[CO₂K]) (*n* = 1–3)



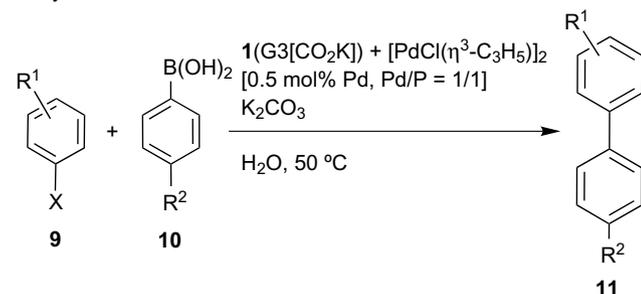
Entry	<i>x</i> equiv of 8	Yield ^a (%)
1	3	32
2	9	25
3	21	18

^a Isolated yield.

field^{6b,c} is essential to an efficient aqueous-media Suzuki–Miyaura coupling reaction.

Next, by employing 0.5 mol% of the third-generation **1**(G3[CO₂K])–palladium catalyst, which afforded the highest chemical yield in Table 1, we performed various Suzuki–Miyaura coupling reactions in water, which were carried out until **9** was consumed (Table 3). In the case of using iodoarenes, by the introduction of an acetyl group, which is an electron-withdrawing group, to substrates **9** or **10**, the reactivity was enhanced to complete the coupling reactions within several hours (entries 4 and 6). In contrast, although the reactivity was decreased by the introduction of a methoxy group, reactions proceeded to afford **11** in excellent yields (entries 5 and 7, 98% and 99% yield). In the case of using 4-bromotoluene instead of iodoarenes, by carrying out the coupling reaction at 80 °C, it proceeded to provide **11** in 82% yield (entry 8).

Table 3. Suzuki–Miyaura reaction using **1**(G3[CO₂K])–palladium catalyst in water



Entry	R ¹	X	R ²	Time (h)	Yield ^a (%)
1	2-CH ₃	I	H	24	92
2	3-CH ₃	I	H	10	88
3	4-CH ₃	I	H	20	93
4	4-Ac	I	H	2	90
5	4-CH ₃ O	I	H	20	98
6	H	I	Ac	5	85
7	H	I	CH ₃ O	20	99
8 ^b	4-CH ₃	Br	H	4	82

^a Isolated yield.

^b Carried out at 80 °C.

In summary, by performing an aqueous-media Suzuki–Miyaura reaction using a novel amphiphilic dendritic phosphine–palladium catalyst, a positive dendritic effect on chemical yields was observed. By employing this new type of water-soluble dendritic catalyst, the range of more efficient aqueous-media organic syntheses may be expanded.

Acknowledgment

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Supplementary data

Supplementary data (typical procedure for hydrolysis of **4** and characterization data of **1**(G_{*n*}[CO₂H])) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.062.

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10. *Selected data*: **1**(G3[CO₂H]). Light yellow powder; IR (KBr) 3422, 3068, 2924, 1692, 1595, 1317, 1153, 1288 cm⁻¹; ¹H NMR (500 MHz; DMF-*d*₇) δ = 13.3 (br s, 24H), 8.06 (d, *J* = 8.2 Hz, 48H), 7.62 (d, *J* = 8.2 Hz, 48H), 7.25 (dd, *J* = 8.2, 7.3 Hz, 6H), 7.09 (d, *J* = 8.2 Hz, 6H), 6.89–6.81 (m, 42H), 6.78–6.70 (m, 21H), 5.24 (s, 48H), 5.18–5.06 (m, 42H); ¹³C NMR (125 MHz; DMF-*d*₇) δ = 166.5, 159.44, 159.39, 159.3, 141.7, 139.3, 139.2, 139.0, 134.2 (²*J*_{C-P} = 21 Hz), 129.9, 129.0, 126.8, 114.6 (³*J*_{C-P} = 3 Hz), 106.2, 106.1, 100.6, 100.5, 68.96, 68.95, 68.86, 68.5; ³¹P NMR (202 MHz; DMF-*d*₇) δ = -9.74; MALDI-TOF-MS for C₃₅₇H₂₈₅O₉₃PH *m/z*: Calcd.: 6094.64 [(M+H)⁺]. Found: 6094.67; Anal. Calcd for C₃₅₇H₂₈₅O₉₃P·3H₂O: C, 69.74; H, 4.77. Found: C, 69.80; H, 4.74.
11. We have confirmed the formation of **1**(G3[CO₂H])–palladium complex by the mixing of **1**(G3[CO₂H]) and [PdCl(η³-C₃H₅)₂] (P/Pd = 1/1) in DMSO-*d*₆ according to ³¹P NMR; **1**(G3[CO₂H]): -10.68 ppm, palladium complex: 19.35 ppm. This downfield shift is similar to that reported in the literature: Iwasawa, T.; Komano, T.; Tajima, A.; Tokunaga, M.; Obora, Y.; Fujihara, T.; Tsuji, Y. *Organometallics* **2006**, *25*, 4665–4669.
12. *General procedure*: **1**(Gn[CO₂K]) was prepared by the mixing of **1**(Gn[CO₂H]) (0.0184 mmol) and potassium hydroxide (1.1 equiv/CO₂H) at room temperature in water (1.5 mL) under an argon atmosphere. By the addition of [PdCl(η³-C₃H₅)₂] (0.0084 mmol) to **1**(Gn[CO₂K]) aqueous solution, the **1**(Gn[CO₂K])–palladium catalyst was prepared with stirring for 15 min. To a mixture of **5** (3.34 mmol), **6** (5.01 mmol), and potassium carbonate (15.0 mmol) in water (5.2 mL) was added the above-prepared **1**(Gn[CO₂K])–palladium aqueous solution at 0 °C. The resulting mixture was stirred for 4 h at 50 °C. The reaction mixture was subjected to the usual extractive workup with diethyl ether. The residual oil obtained after evaporation of diethyl ether, which was dried over magnesium sulfate, was purified by column chromatography on silica gel to give the coupling product **7**.
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