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Graphical Abstract

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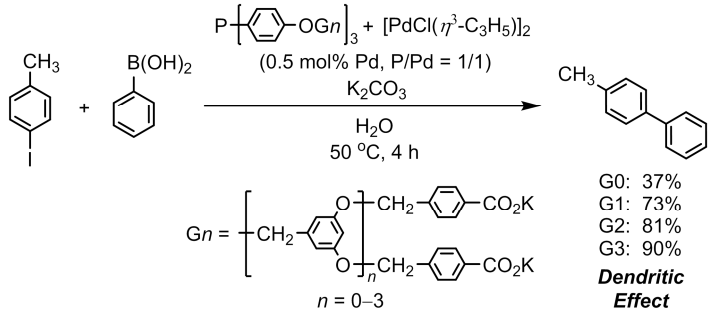

Suzuki–Miyaura reaction catalyzed by a dendritic phosphine–palladium complex

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Keywords:

dendrimer

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Suzuki–Miyaura reaction

Abstract: We prepared several of a new type of a dendritic ligand with a phosphine core by using tris(4-hydroxyphenyl)phosphine oxide and poly(aryl ether) dendron. In particular, when an amphiphilic dendritic phosphine–palladium complex was used as a catalyst, the aqueous media Suzuki–Miyaura reaction proceeded smoothly to provide the corresponding cross-coupling product at 50 ºC. A positive dendritic effect on chemical yields was observed.

1. Introduction

Dendrimers are fascinating man-made macromolecules with their unique physical and chemical properties, and have been widely used as a new class of catalyst supports.[1] Metallodendrimers, which have a catalytic site at their core, have received considerable attention because of their unique selectivity and reactivity, which are caused by a specific reaction field constructed by the dendron.[2] Moreover, their solubilities and physical properties can be altered by peripheral modification.[3] For example, by the introduction of hydrophilic groups to the peripheral layer of a hydrophobic dendritic ligand, the corresponding metal core dendrimers as catalysts can become water-soluble and afford unique catalytic activity.[4]

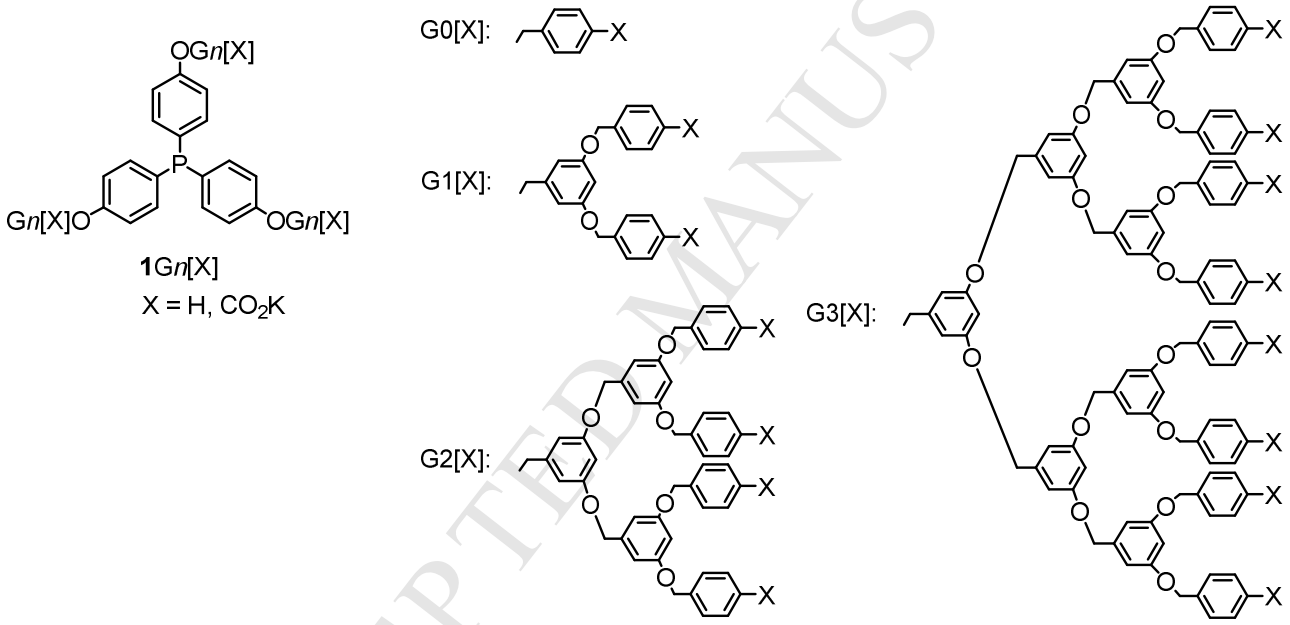


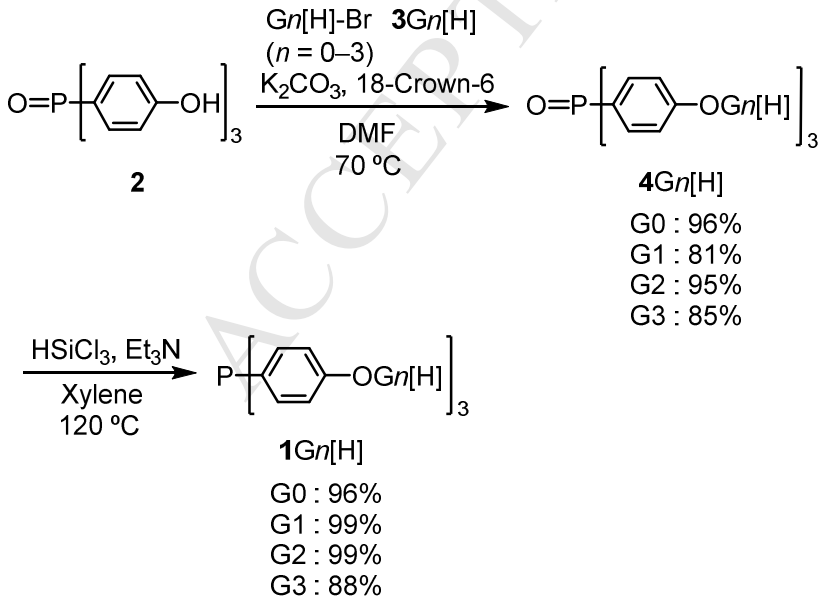
Figure 1 Structural formulas of **1**G*n*[X] and G*n*[X] dendrons (*n* = 0–3)

Recently, several examples of a positive dendritic effect on chemical yields—that is, an enhanced reactivity via an increase in the generation number of the dendrimers—have been reported by us[5] and by other groups.[6] In our previous study, it was found that a hydrophobic dendron was effective as a reaction field in aqueous media organic syntheses.[5a,b] In this paper, we report the synthesis of novel phosphine core dendrimers having poly(benzyl ether) dendrons with the modification of the peripheral layer **1**G*n*[X] (X = H, CO_2K, *n* = 0–3; Figure 1),[7] and their application as phosphine ligands to the Suzuki–Miyaura coupling reaction catalyzed by the phosphine–palladium complex.[8] In particular, by employing amphiphilic dendritic phosphine–palladium complexes having

potassium carboxylate units at the peripheral layer as catalysts, an aqueous media Suzuki–Miyaura reaction proceeded smoothly to provide the corresponding coupling product, and a positive dendritic effect on chemical yields was observed. Suzuki–Miyaura reaction between a boronic acid and an aryl or vinyl halide has become one of the most powerful carbon–carbon coupling methods.[9] This coupling reaction has been widely used in the synthesis of a variety of fine chemicals and pharmaceutical products, as well as in material science. From the perspective of green chemistry, the development of an aqueous media Suzuki–Miyaura reaction is a very attractive field,[10] as water is an environmentally benign solvent.[11]

2. Results and Discussion

Novel phosphine core dendrimers **1**G*n*[H] (*n* = 0–3), 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** and poly(benzyl ether) dendritic bromide **3**G*n*[H] was stirred at 70 ºC in the presence of potassium carbonate and a catalytic amount of 18-crown-6 under an argon atmosphere. The obtained dendritic phosphine oxide **4**G*n*[H] was reduced by trichlorosilane in degassed xylene at 120 ºC to afford the dendritic phosphine **1**G*n*[H]. All transformations were carried out in good chemical yields in all generations.

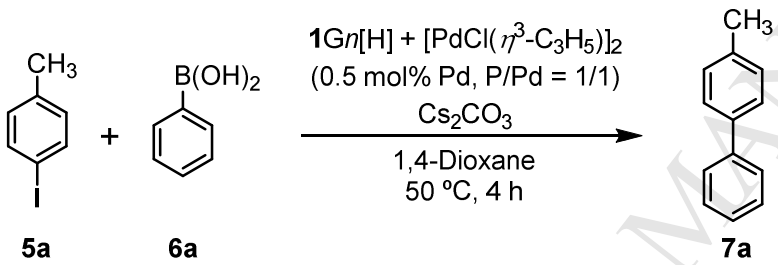


Scheme 1 Preparation of **1**G*n*[H] (*n* = 0–3)

We examined the utility of the dendrimer **1**G*n*[H] (*n* = 0–3) as a phosphine ligand by performing the Suzuki–Miyaura reaction using the corresponding **1**G*n*[H]–palladium catalyst (Table 1).

The coupling reactions were carried out by using 4-iodotoluene **5a** and phenylboronic acid **6a** with 0.5 mol% of various generations of **1**G*n*[H]–palladium catalysts, which were prepared from **1**G*n*[H] and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in situ (P/Pd = 1/1), in 1,4-dioxane at 50 ºC for 4 h. As a result, the corresponding cross-coupling product **7a** was obtained in comparable yields in all generations, contrary to our expectations. In addition, the second-generation **1**G2[H]–palladium catalyst prepared at a P/Pd ratio of 2/1 afforded a slightly lower chemical yield of **7a** than the catalyst prepared at P/Pd = 1/1, as shown in Table 1, column G2.

Table 1 Suzuki–Miyaura reaction in 1,4-dioxane catalyzed by the **1**G*n*[H]–palladium complex[a]



	G0	G1	G2	G3
Yield (%)[b]	78	76	84 (75)[c]	77

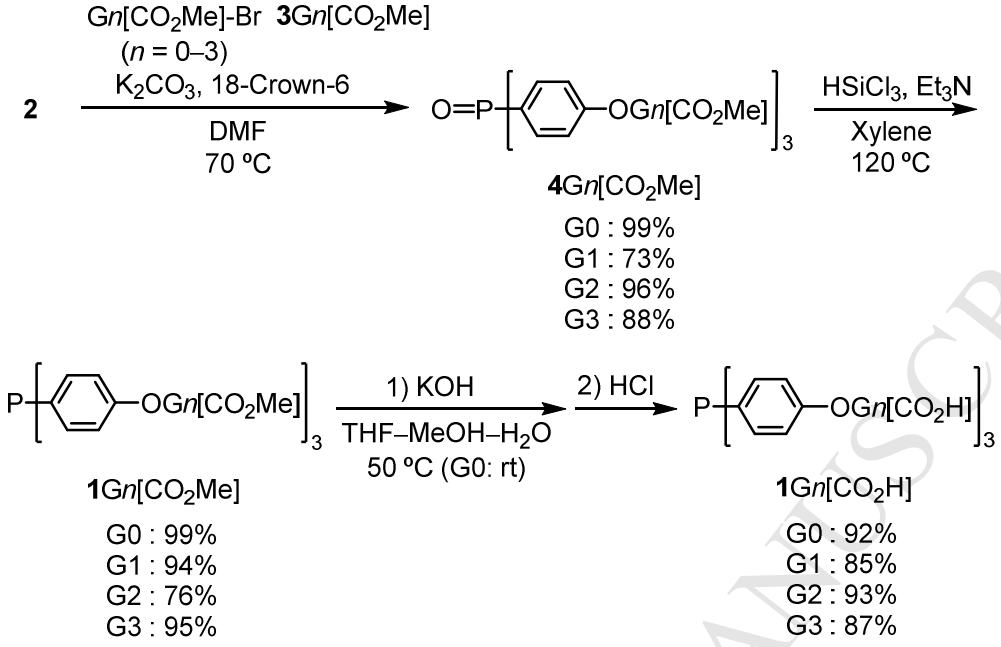
[a] Reaction Conditions: **1**G*n*[H] (0.0055 equiv.), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.0025 equiv., 0.5 mol% Pd), **5a** (1 equiv.), **6a** (1.5 equiv.), Cs_2CO_3 (4.5 equiv.), 1,4-dioxane (0.5 M based on **5a**), carried out at 50 ºC for 4 h.

[b] Isolated yield.

[c] P/Pd = 2/1.

Next, we synthesized the dendritic phosphine having carboxylic groups at the peripheral layer **1**G*n*[CO_2H], which was suitable for an aqueous media Suzuki–Miyaura reaction (Scheme 2). Phosphine core dendrimers **1**G*n*[CO_2Me] were synthesized according to a procedure similar to that used for **1**G*n*[H]. Phosphine core dendrimers having carboxylic groups **1**G*n*[CO_2H] were obtained by hydrolysis of **1**G*n*[CO_2Me] with potassium hydroxide in degassed aqueous solution

(THF–methanol–H_2O) at 50 ºC, followed by protonation of the product with hydrochloric acid. All transformations were carried out in good chemical yields in all generations.[12]



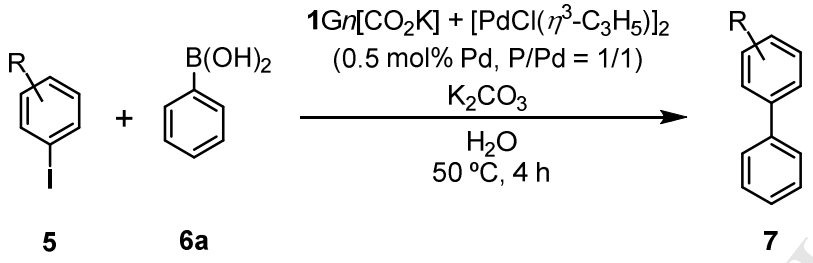
Scheme 2 Preparation of **1**G*n*[CO_2H] (*n* = 0–3)

Then, we examined the utility of the dendrimer **1**G*n*[CO_2H] as a phosphine ligand by performing the Suzuki–Miyaura reaction using the corresponding amphiphilic **1**G*n*[CO_2K]–palladium catalyst (*n* = 0–3) in water (Table 2).

The coupling reactions were carried out by using iodoaryl **5** and phenylboronic acid **6a** with 0.5 mol% of various generations of **1**G*n*[CO_2K]–palladium catalysts (*n* = 0–3) in water at 50 ºC for 4 h. Although the **1**G*n*[CO_2K]–palladium catalysts had micelle-like structures, the reaction mixture was a dispersion mixture.[13] In all cases of 3-iodotoluene, 4-iodotoluene, and 4'-iodoacetophenone, the chemical yield of the coupling product **7** was enhanced by the increase in the generation number of the **1**G*n*[CO_2K]–palladium catalyst.[14] This was especially true when using 4-iodotoluene: the third-generation **1**G3[CO_2K]–palladium catalyst afforded a 90% chemical yield in this case (Table 2, entry 2), which was higher than the yield when a commercially available TPPTS[15]–palladium catalyst was used (76% yield). The relationship between the generation number of the dendritic catalyst and the chemical yields is one of the positive dendritic effects.[5,6,16] On the other hand, by employing the hydrophobic third-generation **1**G3[H]–palladium catalyst in water, the coupling

reaction between 4-iodotoluene and **6a** afforded a poor chemical yield, probably due to the low solubility of the **1**G3[H]–palladium complex in water (16%; Table 2, entry 2, column G3).[17] As a result, we consider that not only the poly(benzyl ether) dendron as a hydrophobic reaction field but also a dispersion formation in a reaction mixture is necessary to catalyze an aqueous media Suzuki–Miyaura reaction.

Table 2 Suzuki–Miyaura reaction in water catalyzed by the **1**G*n*[CO_2K]–palladium complex[a]



Entry	R in **5**	Yield (%)[b]			
		G0	G1	G2	G3
1	3-CH_3	30	42	57	82
2	4-CH_3	37	73	81	90 (16)[c]
3	4-CH_3CO	14	34	50	74

[a] Reaction Conditions: **1**G*n*[CO_2K] (0.0055 equiv.), [PdCl(η^3-C_3H_5)]$_2$ (0.0025 equiv., 0.5 mol% Pd), **5** (1 equiv.), **6a** (1.5 equiv.), K_2CO_3 (4.5 equiv.), H_2O (0.5 M based on **5**), carried out at 50 ºC for 4 h.

[b] Isolated yield.

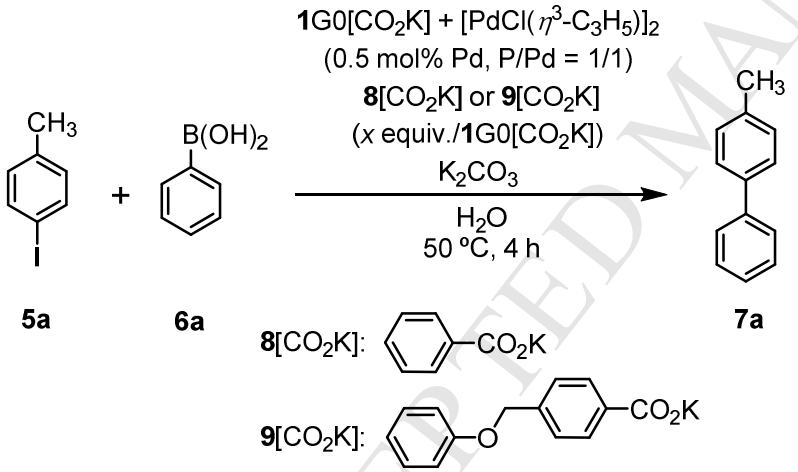
[c] **1**G3[H] was used instead of **1**G3[CO_2K].

In the case of this series of amphiphilic dendritic phosphine ligands **1**G*n*[CO_2K], a non-dendritic **1**G0[CO_2K] has 3, the first-generation **1**G1[CO_2K] has 6, the second-generation **1**G2[CO_2K] has 12, and the third-generation **1**G3[CO_2K] has 24 CO_2K moieties. To confirm the effect of the number of CO_2K groups as surfactants to form dispersions, we carried out the Suzuki–Miyaura reaction of 4-iodotoluene **5a** and phenylboronic acid **6a** by employing a non-dendritic **1**G0[CO_2K]–palladium catalyst having 3 CO_2K moieties and potassium benzoate **8**[CO_2K] or **9**[CO_2K] (*x* equiv./**1**G0[CO_2K]) with the same number of CO_2K moieties of the dendritic ligand **1**G*n*[CO_2K] (*n*

= 1–3) (Table 3). The structure of **8**[CO_2K] is similar to that of the peripheral layer of the dendritic phosphine ligand **1**G*n*[CO_2K]. **9**[CO_2K] has a surfactant-like structure, including a large hydrophobic unit and a CO_2K group.

As a result, the yields of the coupling product **7a** were rather low in all cases, and the chemical yields of **7a** derived using a surfactant-like **9**[CO_2K] were lower than those derived using potassium benzoate **8**[CO_2K] in each generation. Thus the addition of **8**[CO_2K] or **9**[CO_2K] was not effective for increasing the chemical yield of **7a**. Based on these results, it can be concluded that the introduction of hydrophilic groups to the peripheral layer of poly(benzyl ether) dendrons as a hydrophobic reaction field[5a,b] is essential to an efficient aqueous media Suzuki–Miyaura reaction.

Table 3 Suzuki−Miyaura reaction in water catalyzed by the **1**G0[CO_2K]–palladium complex and **8**[CO_2K] or **9**[CO_2K] with the same number of CO_2K moieties of **1**G*n*[CO_2K] (*n* = 1–3)[a]



Entry	**8**[CO_2K] or **9**[CO_2K]	*x* equiv./**1**G0[CO_2K]	Yield (%)[b]
1	**8**[CO_2K]	3	32
2	**8**[CO_2K]	9	25
3	**8**[CO_2K]	21	18
4	**9**[CO_2K]	3	22
5	**9**[CO_2K]	9	21
6	**9**[CO_2K]	21	16

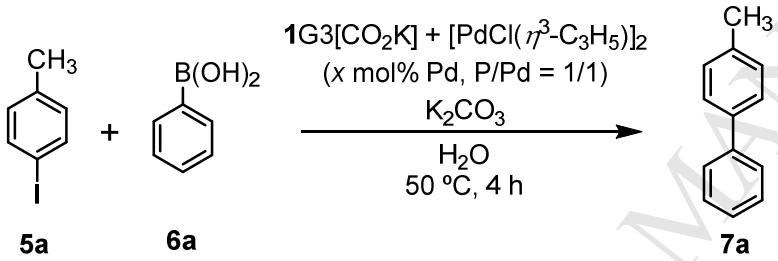
[a] Reaction Conditions: **8**[CO_2K] or **9**[CO_2K] (0.0055*x* equiv.), **1**G0[CO_2K] (0.0055 equiv.), [PdCl(η^3-C_3H_5)]$_2$ (0.0025 equiv., 0.5 mol% Pd), **5a** (1 equiv.), **6a** (1.5 equiv.), K_2CO_3 (4.5 equiv.),

H_2O (0.5 M based on **5a**), carried out at 50 ºC for 4 h.

[b] Isolated yield.

Next, by employing the third-generation **1**G3[CO_2K]–palladium catalyst, which afforded the highest chemical yield in Table 2, we examined the amount of palladium catalyst required for an aqueous media Suzuki–Miyaura reaction, as shown in Table 4. The results showed that a catalytic amount of 0.2 mol% was insufficient to promote an aqueous media Suzuki–Miyaura reaction. 0.5 mol% of **1**G3[CO_2K]–palladium catalyst afforded the coupling product **7a** in the highest chemical yield (90%).

Table 4 Suzuki–Miyaura reaction in water catalyzed by the **1**G3[CO_2K]–palladium complex[a]



5a **6a** **7a**

Pd catalyst (*x* mol%)	0.2	0.5	1
Yield (%)[b]	30	90	83

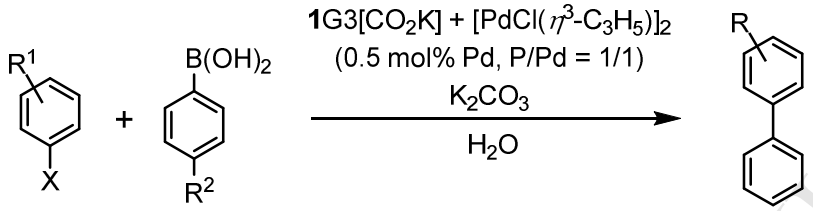
[a] The reaction conditions were the same as those indicated in Table 2.

[b] Isolated yield.

Finally, by employing 0.5 mol% of the third-generation **1**G3[CO_2K]–palladium catalyst, we performed various Suzuki–Miyaura reactions in water until **5** was consumed (Table 5). When iodoarenes were used, by introducing an acetyl group as an electron-withdrawing group to **5**, the reactivity was enhanced and the coupling reaction was completed within 2 h (Table 5, entry 4). In contrast, although the reactivity decreased by the introduction of a methoxy group, the reaction proceeded to afford **7e** for 20 h in a 98% chemical yield (Table 5, entry 5). This tendency in the reactivity of **5** is similar to that previously reported, which is caused by the oxidative addition step of the palladium catalyst to **5** as the rate-determining step.[9d,18] On the other hand, by the introduction of a hydroxyl group to substrate **5**, the corresponding coupling product **7f** was not

obtained (Table 5, entry 6). In the case that 4-bromotoluene was used instead of iodoarenes, even when the coupling reaction was carried out using 1 mol% of the dendritic palladium catalyst for 24 h, the chemical yield of the coupling product **7c** was slightly low (63% yield; Table 5, entry 9). On the other hand, by carrying out the coupling reaction at 100 ºC, **5c** was consumed within 1 h to provide **7c** in a 96% yield (Table 5, entry 11). However, when 4-chlorotoluene was used, the coupling product **7c** was not obtained even at 100 ºC (Table 5, entry 12).

Table 5 Suzuki–Miyaura reaction using the **1**G3[CO_2K]–palladium catalyst in water[a]



5 **6** **7**

Entry	R^1	X	R^2	Temp. (ºC)	Time (h)	Product	Yield (%)[b]
1	2-CH_3	I	H	50	24	**7a**	92
2	3-CH_3	I	H	50	10	**7b**	88
3	4-CH_3	I	H	50	20	**7c**	93
4	4-CH_3CO	I	H	50	2	**7d**	90
5	4-CH_3O	I	H	50	20	**7e**	98
6	4-OH	I	H	50	12	**7f**	0
7	H	I	CH_3CO	50	5	**7d**	85
8	H	I	CH_3O	50	20	**7e**	99
9[c]	4-CH_3	Br	H	50	24	**7c**	63
10	4-CH_3	Br	H	80	4	**7c**	82
11	4-CH_3	Br	H	100	1	**7c**	96
12	4-CH_3	Cl	H	100	24	**7c**	0

[a] The reaction conditions were the same as those indicated in Table 2.

[b] Isolated yield.

[c] 1 mol% of Pd catalyst was used.

3. Conclusion

We prepared several of a new type of a dendritic ligand with a phosphine core. In particular, when an amphiphilic dendritic phosphine–palladium catalyst was used, the aqueous media Suzuki–Miyaura reaction proceeded smoothly to provide the corresponding cross-coupling product. Furthermore, a positive dendritic effect on chemical yields was observed. By employing this new type of an amphiphilic dendritic catalyst, the range of efficient aqueous media organic syntheses could be expanded.

4. Experimental

4.1 General

IR spectra were recorded on a Thermo Electron Nicolet Nexus 470 FT-IR spectrophotometer. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{31}P NMR (202 MHz) spectra were measured with a JEOL LA-500 spectrometer. Chemical shifts of ^{1}H, ^{13}C and ^{31}P NMR were reported as ppm downfield from TMS as an internal standard (^{1}H and ^{13}C NMR) and from phosphoric acid as an external standard (^{31}P NMR) in δ units. Coupling constants (*J*) were given in hertz (Hz). Mass spectra were measured with a JEOL MS 600H (FAB; matrix: 3-nitrobenzyl alcohol) and a Shimadzu AXIMA-CFR (MALDI–TOF; matrix: 2,5-dihydroxybenzoic acid) mass spectrometer. Microanalyses were performed with a CE Instruments EA1110 elemental analyzer.

Kieselgel 60 F254 (Merck) was used for TLC, and Wakogel C-300 (Wako) was used for silica gel column chromatography. Dendritic bromides **3**G*n*[H] (*n* = 1, 2), methyl 4-(bromomethyl)benzoate **3**G0[CO_2Me], other reagents, and dry solvents were commercially available and were used as received. The third-generation dendritic bromide **3**G3[H][19] and **3**G*n*[CO_2Me] (*n* = 1–3)[20] were prepared by the methods described in the literature. Tris(4-hydroxyphenyl)phosphine oxide **2**[21] and 4-(phenoxymethyl)benzoic acid **9**[CO_2H][22] were also prepared as described previously.

4.2 Synthesis of Dendritic Phosphine Oxide 4G*n*[X] from 2 and 3G*n*[X] (X = H, CO_2Me; Scheme 1 and 2): Typical Procedure

A dry DMF solution (44 mL) of tris(4-hydroxyphenyl)phosphine oxide **2** (216 mg, 0.662 mmol), the third-generation dendritic bromide **3**G3[CO_2Me] (4.50 g, 2.12 mmol), anhydrous potassium carbonate (345 mg, 2.50 mmol), and 18-crown-6 (56.1 mg, 0.212 mmol) was stirred at 70 ºC for 6 h under an argon atmosphere. The reaction mixture was filtered with Celite® to remove inorganic salts,

and the filtrate was evaporated to dryness. The residue was purified with silica gel column chromatography (dichloromethane/acetone = 10/1 as eluent) to obtain **4**G3[CO_2Me] (3.76 g, 0.583 mmol) in an 88% yield.

*4.2.1. Tris(4-benzyloxyphenyl)phosphine Oxide (**4**G0[H]).* White powder; IR (KBr) 3062, 3029, 1595, 1501, 1288, 1250, 1175, 1121, 987, 696, 545 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (dd, *J* = 11.5, 8.8 Hz, 6H, Ar*H*), 7.44–7.30 (m, 15H, Ar*H*), 7.01 (dd, *J* = 8.8, 2.0 Hz, 6H, Ar*H*), 5.08 (s, 6H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 161.6 ($^4J_{C-P}$ = 3 Hz), 136.3, 134.0 ($^2J_{C-P}$ = 12 Hz), 128.7, 128.3, 127.6, 124.9 ($^1J_{C-P}$ = 111 Hz), 114.9 ($^3J_{C-P}$ = 13 Hz), 70.1; ^{31}P NMR ($CDCl_3$) δ = 29.2; FABMS for $C_{39}H_{33}O_4PH$ *m*/*z*: Calcd: 597 [$(M+H)^+$]. Found: 597; Anal. Calcd for $C_{39}H_{33}O_4P$: C, 78.51; H, 5.58%. Found: C, 78.56; H, 5.48%.

*4.2.2. Tris{4-(3,5-dibenzyloxybenzyloxy)phenyl}phosphine Oxide (**4**G1[H]).* Foam; IR (KBr) 3455, 3062, 3030, 2931, 1595, 1499, 1453, 1292, 1248, 1157, 1118, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (dd, *J* = 11.7, 8.7 Hz, 6H, Ar*H*), 7.43–7.27 (m, 30H, Ar*H*), 6.99 (dd, *J* = 8.7, 2.1 Hz, 6H, Ar*H*), 6.65 (d, *J* = 2.1 Hz, 6H, Ar*H*), 6.57 (t, *J* = 2.1 Hz, 3H, Ar*H*), 5.02 (s, 18H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 161.3, 160.12, 160.05, 139.1, 138.6, 136.7, 133.9 ($^2J_{C-P}$ = 12 Hz), 128.6, 128.0, 127.5, 124.8 ($^1J_{C-P}$ = 111 Hz), 114.8 ($^3J_{C-P}$ = 13 Hz), 106.4, 101.6, 101.5, 70.0, 69.96, 69.88; ^{31}P NMR ($CDCl_3$) δ 29.3; FABMS for $C_{81}H_{69}O_{10}P$ *m*/*z*: Calcd: 1232 [M^+]. Found: 1232; Anal. Calcd for $C_{81}H_{69}O_{10}P$: C, 78.88; H, 5.64%. Found: C, 78.60; H, 5.55%.

*4.2.3. Tris[4-{3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy}phenyl]phosphine Oxide (**4**G2[H]).* Foam; IR (KBr) 3031, 2872, 1595, 1452, 1375, 1294, 1156, 1118, 1054, 830, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (dd, *J* = 21.2, 8.6 Hz, 6H, Ar*H*), 7.42–7.27 (m, 60H, Ar*H*), 6.99 (dd, *J* = 8.6, 1.7 Hz, 6H, Ar*H*), 6.66 (d, *J* = 2.2 Hz, 12H, Ar*H*), 6.63 (d, *J* = 2.2 Hz, 6H, Ar*H*), 6.55 (t, *J* = 2.2 Hz, 6H, Ar*H*), 6.54 (t, *J* = 2.2 Hz, 3H, Ar*H*), 5.00 (s, 24H, OCH_2Ar), 4.98 (s, 6H, OCH_2Ar), 4.95 (s, 12H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 161.3($^4J_{C-P}$ = 3 Hz), 160.12, 160.05, 139.1, 138.6, 136.7, 133.9 ($^2J_{C-P}$ = 12 Hz), 128.6, 128.0, 127.5, 124.8 ($^1J_{C-P}$ = 111 Hz), 114.8 ($^3J_{C-P}$ = 13 Hz), 106.4, 106.4, 101.6, 101.5, 70.05, 69.96, 69.9; ^{31}P NMR ($CDCl_3$) δ 29.3; MALDI–TOFMS for $C_{165}H_{141}O_{22}PH$ m/z: Calcd.: 2507.0 [$(M+H)^+$]. Found: 2506.9; Anal. Calcd for $C_{165}H_{141}O_{22}P$: C, 79.05; H, 5.67%. Found: C, 79.08; H, 5.70%.

*4.2.4. Tris(4-[3,5-bis{3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy}benzyloxy]phenyl)phosphine Oxide (**4**G3[H]).* Foam; IR (KBr) 3031, 2871, 1595, 1451, 1374, 1295, 1155, 1051, 830, 735, 696

cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, *J* = 11.3, 8.4 Hz, 6H, Ar*H*), 7.40–7.22 (m, 120H, Ar*H*), 6.95 (d, *J* = 8.4 Hz, 6H, Ar*H*), 6.67–6.59 (m, 42H, Ar*H*), 6.56–6.49 (m, 21H, Ar*H*), 4.95 (s, 48H, OCH_2Ar), 4.94–4.88 (m, 42H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 161.3 ($^{4}J_{C–P}$ = 2 Hz), 160.1, 160.04, 159.99, 139.1, 139.0, 138.6, 136.7, 133.8 ($^{2}J_{C–P}$ = 12 Hz), 128.5, 127.9, 127.5, 124.8 ($^{1}J_{C–P}$ = 110 Hz), 114.7 ($^{3}J_{C–P}$ = 13 Hz), 106.4, 106.3, 101.5, 70.0, 69.9; ^{31}P NMR ($CDCl_3$) δ 29.1; MALDI–TOFMS for $C_{333}H_{285}O_{46}PH$ m/z: Calcd.:5054.5 [$(M+H)^+$]. Found: 5054.1; Anal. Calcd for $C_{333}H_{285}O_{46}P$: C,79.14; H, 5.68%. Found: C,79.34; H, 5.66%.

*4.2.5. Tris[4-{4-(methoxycarbonyl)benzyloxy}phenyl]phosphine Oxide (**4**G0[CO_2Me]).* White powder; IR (KBr) 3421, 2952, 1728, 1595, 1499, 1434, 1384, 1281, 1177, 1120, 1019, 834, 755, 540, 482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 6H, Ar*H*), 7.57 (dd, *J* = 11.5, 7.8 Hz, 6H, Ar*H*), 7.49 (d, *J* = 8.3 Hz, 6H, Ar*H*), 7.02 (dd, *J* = 7.8, 2.0 Hz, 6H, Ar*H*), 5.15 (s, 6H, OCH_2Ar), 3.92 (s, 9H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 161.1 ($^{4}J_{C–P}$ = 2 Hz), 141.3, 133.9 ($^{2}J_{C–P}$ = 11 Hz), 129.90, 129.87, 126.9, 125.0 ($^{1}J_{C–P}$ = 110 Hz), 114.8 ($^{3}J_{C–P}$ = 12 Hz), 69.3, 52.1; ^{31}P NMR ($CDCl_3$) δ 28.3; FABMS for $C_{45}H_{39}O_{10}P$ *m/z*: Calcd: 770 [M^+]. Found: 770; Anal. Calcd for $C_{45}H_{39}O_{10}P$: C, 70.12; H, 5.10%. Found: C, 70.12; H, 5.14%.

*4.2.6. Tris(4-[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]phenyl)phosphine Oxide (**4**G1[CO_2Me]).* White powder; IR (KBr) 3421, 2952, 1728, 1595, 1499, 1434, 1384, 1281, 1177, 1120, 1019, 834, 755, 540, 482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 12H, Ar*H*), 7.57 (dd, *J* = 11.5, 9.0 Hz, 6H, Ar*H*), 7.47 (d, *J* = 8.8 Hz, 12H, Ar*H*), 7.00 (dd, *J* = 9.0, 2.0 Hz, 6H, Ar*H*), 6.66 (d, *J* = 2.0 Hz, 6H, Ar*H*), 6.54 (t, *J* = 2.0 Hz, 3H, Ar*H*), 5.09 (s, 12H, OCH_2Ar), 5.02 (s, 6H, OCH_2Ar), 3.91 (s, 18H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 166.8, 161.4 ($^{4}J_{C–P}$ = 2 Hz), 159.9, 141.8, 138.9, 133.9 ($^{2}J_{C–P}$ = 10 Hz), 129.9, 129.8, 127.0, 124.9 ($^{1}J_{C–P}$ = 110 Hz), 114.9 ($^{3}J_{C–P}$ = 13 Hz), 106.6, 101.7, 69.8, 69.5, 52.2; ^{31}P NMR ($CDCl_3$) δ 28.5; FABMS for $C_{93}H_{81}O_{22}PH$ *m/z*: Calcd: 1581.5 [$(M+H)^+$]. Found: 1581.8; Anal. Calcd for $C_{93}H_{81}O_{22}P$: C, 70.63; H, 5.16%. Found: C, 70.28; H, 5.01%.

*4.2.7. Tris{4-(3,5-bis[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]benzyloxy)phenyl} phosphine Oxide (**4**G2[CO_2Me]).* White powder; IR (KBr) 3421, 2950, 1719, 1596, 1500, 1437, 1375, 1280, 1157, 1109, 1061, 1019, 832, 755, 475 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 24H, Ar*H*), 7.55 (dd, *J* = 11.6, 8.8 Hz, 6H, Ar*H*), 7.45 (d, *J* = 8.2 Hz, 24H, Ar*H*), 6.99 (dd, *J* = 8.8, 2.1 Hz, 6H, Ar*H*), 6.65 (d, *J* = 2.1 Hz, 12H, Ar*H*), 6.62 (d, *J* = 2.1 Hz, 6H, Ar*H*), 6.52 (t, *J* = 2.1 Hz,

6H, Ar*H*), 6.50 (t, *J* = 2.1 Hz, 3H, Ar*H*), 5.06 (s, 24H, OC*H*$_2$Ar), 4.99 (s, 6H, OC*H*$_2$Ar), 4.94 (s, 12H, OC*H*$_2$Ar), 3.89 (s, 36H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 166.7, 161.4, 160.0, 159.9, 141.9, 139.4, 138.7, 133.9 ($^2J_{C–P}$ = 11 Hz), 129.9, 129.7, 127.0, 124.8 ($^1J_{C–P}$ = 110 Hz), 114.9 ($^3J_{C–P}$ = 13 Hz), 106.5, 106.4, 101.6, 69.88, 69.85, 69.4, 52.1; ^{31}P NMR ($CDCl_3$) δ 28.4; MALDI–TOFMS for $C_{189}H_{165}O_{46}PH$ *m/z*: Calcd.: 3204.0 [$(M+H)^+$]. Found: 3204.1; Anal. Calcd for $C_{189}H_{165}O_{46}P$: C, 70.87; H, 5.19%. Found: C, 70.73; H, 5.01%.

*4.2.8. Tris[4-{3,5-bis(3,5-bis[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]benzyloxy) benzyloxy}phenyl]phosphine Oxide (**4**G3[CO$_2$Me]).* White powder; IR (KBr) 3421, 2949, 1720, 1596, 1448, 1436, 1375, 1280, 1157, 1108, 1057, 1019, 835, 755, 473 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 48H, Ar*H*), 7.53 (t, *J* = 8.9 Hz, 6H, Ar*H*), 7.40 (d, *J* = 8.3 Hz, 48H, Ar*H*), 6.95 (d, *J* = 8.9 Hz, 6H, Ar*H*), 6.67–6.56 (m, 42H, Ar*H*), 6.55–6.44 (m, 21H, Ar*H*), 5.01 (s, 48H, OC*H*$_2$Ar), 4.94 (s, 6H, OC*H*$_2$Ar), 4.90 (s, 36H, OC*H*$_2$Ar), 3.86 (s, 72H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 166.7, 161.4, 160.1, 160.0, 159.9, 141.9, 139.4, 139.2, 133.9 ($^2J_{C–P}$ = 11 Hz), 129.8, 129.7, 126.9, 114.8 ($^3J_{C–P}$ = 13 Hz), 106.5, 101.6, 101.5, 70.0, 69.8, 69.4, 52.1; ^{31}P NMR ($CDCl_3$) δ 28.2; MALDI–TOFMS for $C_{381}H_{333}O_{94}PH$ *m/z*: Calcd.: 6447.3 [$(M+H)^+$]. Found 6447.0; Anal. Calcd for $C_{381}H_{333}O_{94}P$: C, 70.98; H, 5.21. Found: C, 70.73; H, 5.13%.

4.3. Synthesis of Dendritic Phosphine 1G*n*[X] from 4G*n*[X] (X = H, CO$_2$Me; Scheme 1 and 2): Typical Procedure

To a solution of the third-generation dendritic phosphine oxide **4**G3[CO$_2$Me] (796 mg, 0.123 mmol) in degassed xylene (12 mL) was added triethylamine (35.0 mg, 0.346 mmol) and trichlorosilane (43.5 mg, 0.321 mmol) at room temperature with stirring. The mixture was stirred at 120 ºC for 20 h under an argon atmosphere. To a reaction mixture was added dichloromethane (20 mL), water (1 mL), and sodium hydrogen carbonate (*ca.* 0.2 g), and the thus obtained mixture was stirred at room temperature for 2 h. After the removal of water by the addition of magnesium sulfate, the mixture was filtered with Celite® to remove inorganic salts, and the filtrate was evaporated to dryness. The residue was purified with silica gel column chromatography (dichloromethane/ethyl acetate = 3/1 as eluent) to obtain **1**G3[CO$_2$Me] (751 mg, 1.17 mmol) in a 95% yield.

*4.3.1. Tris(4-benzyloxyphenyl)phosphine (**1**G0[H]).* White powder; IR (KBr) 3029, 3927, 2868, 1592, 1496, 1243, 1177, 1094, 1001, 830, 739, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44–7.18 (m, 21H, Ar*H*), 6.93 (d, *J* = 8.8 Hz, 6H, Ar*H*), 5.04 (s, 6H, OC*H*$_2$Ar); ^{13}C NMR ($CDCl_3$) δ 159.4, 136.8,

135.0 ($^2J_{C-P}$ = 21 Hz), 129.3 ($^1J_{C-P}$ = 8 Hz), 128.7, 128.1, 127.6, 115.1 ($^3J_{C-P}$ = 7 Hz), 70.0; ^{31}P NMR ($CDCl_3$) δ –9.4; FABMS for $C_{39}H_{33}O_3P$ *m/z*: Calcd: 580 [M^+]. Found: 580; Anal. Calcd for $C_{39}H_{33}O_3P$: C, 80.67; H, 5.73%. Found: C, 80.62; H, 5.53%.

*4.3.2. Tris{4-(3,5-dibenzyloxybenzyloxy)phenyl}phosphine (**1**G1[H]).* Glassy; IR (CH_2Cl_2) 3031, 2872, 1593, 1496, 1453, 1376, 1241, 1159, 1027, 827, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47–7.32 (m, 30H, Ar*H*), 7.29–7.24 (m, 6H, Ar*H*), 6.96 (d, *J* = 8.4 Hz, 6H, Ar*H*), 6.71 (d, *J* = 2.4 Hz, 6H, Ar*H*), 6.62 (d, *J* = 2.2 Hz, 3H, Ar*H*), 5.06 (s, 12H, OCH_2Ar), 5.01 (s, 6H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 160.2, 159.2, 139.3, 136.7, 135.0 ($^2J_{C-P}$ = 20.9 Hz), 129.2 ($^1J_{C-P}$ = 7.5 Hz), 128.6, 128.1, 127.5, 115.1 ($^3J_{C-P}$ = 7.6 Hz), 106.4, 101.6, 70.1, 69.9; ^{31}P NMR ($CDCl_3$) δ –9.4; FABMS for $C_{81}H_{69}O_9P$ *m/z*: Calcd: 1216 [M^+]. Found: 1216; Anal. Calcd for $C_{81}H_{69}O_9P$: C, 79.91; H, 5.71%. Found: C, 80.24; H, 5.82%.

*4.3.3. Tris[4-{3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy}phenyl]phosphine (**1**G2[H]).* Glassy; IR (CH_2Cl_2) 3032, 2873, 1594, 1496, 1453, 1376, 1241, 1159, 1027, 828, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41–7.18 (m, 66H, Ar*H*), 6.91 (d, *J* = 8.4 Hz, 6H, Ar*H*), 6.66 (d, *J* = 1.6 Hz, 12H, Ar*H*), 6.64 (d, *J* = 2.0 Hz, 6H, Ar*H*), 6.55 (t, *J* = 2.0 Hz, 6H, Ar*H*), 6.53 (t, *J* = 2.0 Hz, 3H, Ar*H*), 5.00 (s, 24H, OCH_2Ar), 4.94 (s, 18H, OCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 160.3, 160.2, 159.4, 139.31, 139.28, 136.9, 135.1 ($^2J_{C-P}$ = 20.5 Hz), 129.3, 128.7, 128.1, 127.7, 115.1 ($^3J_{C-P}$ = 7.6 Hz), 106.5, 101.7, 70.2, 70.1, 69.9, ^{31}P NMR ($CDCl_3$) δ –9.2; MALDI–TOFMS for $C_{165}H_{141}O_{21}PH$ m/z: Calcd.: 2490.99 [$(M+H)^+$]. Found: 2490.83; Anal. Calcd for $C_{165}H_{141}O_{21}P$: C, 79.56; H, 5.71%. Found: C, 79.59; H, 5.83%.

*4.3.4. Tris(4-[3,5-bis{3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy}benzyloxy]phenyl)phosphine (**1**G3[H]).* Foam; IR (KBr) 3030, 2871, 1720, 1596, 1452, 1374, 1295, 1156, 1054, 831, 736, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 120H), 7.18 (dd, *J* = 8.2, 7.5 Hz, 6H), 6.87 (d, *J* = 8.2 Hz, 6H), 6.65–6.61 (m, 42H), 6.53 (t, *J* = 2.0 Hz, 15H), 6.50 (t, *J* = 2.0 Hz, 6H), 4.96 (s, 48H), 4.90 (s, 42H); ^{13}C NMR ($CDCl_3$) δ 160.1, 160.03, 160.00, 159.2, 139.16, 139.12, 136.7, 134.9 ($^2J_{C-P}$ = 21 Hz), 128.5, 129.2 ($^1J_{C-P}$ = 9.1 Hz), 128.0, 127.5, 115.0 ($^3J_{C-P}$ = 7 Hz), 106.4, 106.3, 101.5, 70.0, 69.9, 69.8; ^{31}P NMR ($CDCl_3$) δ –9.34; MALDI–TOFMS for $C_{333}H_{285}O_{45}PH$ m/z: Calcd.:5037.99 [$(M+H)^+$]. Found: 5037.89; Anal. Calcd for $C_{333}H_{285}O_{45}P$: C, 79.39; H, 5.70%. Found: C, 79.28; H, 5.60%.

*4.3.5. Tris[4-{4-(methoxycarbonyl)benzyloxy}phenyl]phosphine (**1**G0[CO_2Me]).* White powder; IR

(KBr) 3422, 2949, 1720, 1592, 1496, 1435, 1281, 1241, 1176, 1108, 1018, 825, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 6H, Ar*H*), 7.48 (d, *J* = 8.3 Hz, 6H, Ar*H*), 7.21 (dd, *J* = 8.8, 7.3 Hz, 6H, Ar*H*), 6.92 (dd, *J* = 8.8, 1.0 Hz, 6H, Ar*H*), 5.11 (s, 6H, OCH_2Ar), 3.92 (s, 9H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 166.8, 159.0, 141.9, 135.0 ($^{2}J_{C-P}$ = 21 Hz), 129.9, 129.7, 129.4 ($^{1}J_{C-P}$ = 9 Hz), 126.9, 115.0 ($^{3}J_{C-P}$ = 7 Hz), 69.2, 52.1; ^{31}P NMR ($CDCl_3$) δ –9.37; FABMS for $C_{45}H_{39}O_9PH$ *m/z*: Calcd: 755 [$(M+H)^+$]. Found: 755; Anal. Calcd for $C_{45}H_{39}O_9P$: C, 71.61; H, 5.21%. Found: C, 71.96; H, 5.19%.

*4.3.6. Tris(4-[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]phenyl)phosphine (**1**G1[CO_2Me]).* White powder; IR (KBr) 3421, 2949, 1719, 1595, 1496, 1436, 1280, 1159, 1107, 1066, 1107, 1066, 1019, 829, 755 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.11 (d, *J* = 8.0 Hz, 12H, Ar*H*), 7.43 (dd, *J* = 8.5, 7.0 Hz, 6H, Ar*H*), 7.15 (d, *J* = 8.0 Hz, 12H, Ar*H*), 6.91 (d, *J* = 8.5 Hz, 6H, Ar*H*), 6.68 (d, *J* = 2.0 Hz, 6H, Ar*H*), 6.56 (t, *J* = 2.0 Hz, 3H, Ar*H*), 4.71 (s, 6H, OCH_2Ar), 4.59 (s, 12H, OCH_2Ar), 3.49 (s, 18H, OCH_3); ^{13}C NMR (C_6D_6) δ 166.4, 160.5, 159.8, 142.2, 140.1, 135.7 ($^{2}J_{C-P}$ = 21 Hz), 130.4, 130.1, 127.3, 115.6 ($^{3}J_{C-P}$ = 7 Hz), 106.9, 102.1, 70.0, 69.4, 51.6; ^{31}P NMR (C_6D_6) δ –9.8; FABMS for $C_{93}H_{81}O_{21}P$ *m/z*: Calcd: 1564 [M^+]. Found: 1564; Anal. Calcd for $C_{93}H_{81}O_{21}P$: C, 71.35; H, 5.22%. Found: C, 71.42; H, 5.14%.

*4.3.7. Tris{4-(3,5-bis[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]benzyloxy)phenyl} phosphine (**1**G2[CO_2Me]).* White powder; IR (KBr) 3421, 2950, 1720, 1596, 1496, 1436, 1280, 1158, 1108, 1060, 1019, 832, 755 cm^{-1}; ^{1}H NMR (THF–d_8) δ 7.97 (d, *J* = 8.2 Hz, 24H, Ar*H*), 7.48 (d, *J* = 8.2 Hz, 24H, Ar*H*), 7.16 (t, *J* = 8.3 Hz, 6H, Ar*H*), 6.92 (d, *J* = 8.3 Hz, 6H, Ar*H*), 6.71 (d, *J* = 1.8 Hz, 12H, Ar*H*), 6.67 (s, 6H, Ar*H*), 6.57 (s, 6H, Ar*H*), 6.55 (s, 3H, Ar*H*), 5.11 (s, 24H, OCH_2Ar), 4.97 (s, 18H, OCH_2Ar), 3.82 (s, 36H, OCH_3); ^{13}C NMR (THF–d_8) δ 166.8, 161.1, 160.9, 160.4, 143.5, 140.9, 140.6, 135.7 ($^{2}J_{C-P}$ = 21 Hz), 130.6, 130.3, 127.7, 115.7 ($^{3}J_{C-P}$ = 7 Hz), 107.1, 107.0, 102.1, 70.5, 70.4, 69.9, 52.1; ^{31}P NMR (THF–d_8) δ –9.6; MALDI–TOFMS for $C_{189}H_{165}O_{45}PH$ *m/z*: Calcd.: 3188.1 [$(M+H)^+$]. Found 3188.0; Anal. Calcd for $C_{189}H_{165}O_{45}P$: C, 71.22; H, 5.22%. Found: C, 71.34; H, 5.35%.

*4.3.8. Tris[4-{3,5-bis(3,5-bis[3,5-bis{4-(methoxycarbonyl)benzyloxy}benzyloxy]benzyloxy) benzyloxy}phenyl]phosphine (**1**G3[CO_2Me]).* White powder; IR (KBr) 3421, 2949, 1720, 1596, 1496, 1436, 1280, 1157, 1108, 1056, 1019, 835, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 48H, Ar*H*), 7.40 (d, *J* = 8.2 Hz, 48H, Ar*H*), 7.17 (dd, *J* = 8.3, 7.3 Hz, 6H, Ar*H*), 6.86 (d, *J* = 8.3 Hz,

6H, Ar*H*), 6.64–6.58 (m, 42H, Ar*H*), 6.53–6.43 (m, 21H, Ar*H*), 5.00 (s, 48H, OCH_2Ar), 4.89 (s, 42H, OCH_2Ar), 3.86 (s, 72H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 160.0, 159.8, 159.1, 141.8, 139.4, 139.23, 139.18, 134.9 ($^2J_{C–P}$ = 22 Hz), 129.8, 129.6, 126.9, 115.0 ($^3J_{C–P}$ = 10 Hz), 106.40, 106.35, 101.5, 101.4, 69.8, 69.7, 69.3, 52.1; ^{31}P NMR ($CDCl_3$) δ –9.43; MALDI–TOFMS for $C_{381}H_{333}O_{93}P$ *m/z*: Calcd.: 6430.3 [M^+]. Found 6430.2; Anal. Calcd for $C_{381}H_{333}O_{93}P$: C, 71.16; H, 5.22%. Found: C, 71.55; H, 5.32%.

4.4. Synthesis of Dendritic Phosphine 1G*n*[CO_2H] from 1G*n*[CO_2Me] (Scheme 2): Typical Procedure

The third-generation dendritic phosphine **1**G3[CO_2Me] (671 mg, 0.104 mmol) and potassium hydroxide (464 mg, 8.27 mmol) in a degassed 1:1 (v/v) mixture (8 mL) of THF and methanol was stirred at 50 ºC under an argon atmosphere. Whenever the precipitation of potassium carboxylate occurred, a small portion of degassed water (total *ca.* 2 mL) was poured into the reaction mixture to dissolve the precipitate. When a precipitation did not form, the hydrolysis was continued by heating at 50 ºC for 24 h. The reaction mixture was evaporated in vacuo to remove organic solvent, and the residue was added dropwise to 1 M hydrochloric acid (36 mL) to protonate the product that was precipitated from solution. The precipitated product was collected by filtration, followed by washing with water and dichloromethane, and was dried at 55 ºC for 24 h to give **1**G3[CO_2H] (553 mg, 0.0907 mmol) in an 87% yield.

*4.4.1. Tris{4-(4-carboxybenzyloxy)phenyl}phosphine (**1**G0[CO_2H]).* White powder; IR (KBr) 3447, 3021, 2664, 2541, 1690, 1592, 1495, 1421, 1283, 1239, 1175, 1094, 1018, 825, 755 cm^{-1}; ^{1}H NMR (DMF–d_7) δ 13.3 (brs, 3H, ArCO_2H), 8.09 (d, *J* = 8.5 Hz, 6H, Ar*H*), 7.67 (d, *J* = 8.5 Hz, 6H, Ar*H*), 7.29 (dd, *J* = 8.5, 7.3 Hz, 6H, Ar*H*), 7.16 (d, *J* = 8.5 Hz, 6H, Ar*H*), 5.30 (s, 6H, OCH_2Ar); ^{13}C NMR (DMF–d_7) δ 166.5, 158.6, 141.6, 134.2 ($^2J_{C–P}$ = 22 Hz), 130.0, 129.0, 128.7 ($^1J_{C–P}$ = 9 Hz), 126.8, 114.6 ($^3J_{C–P}$ = 7 Hz), 68.3; ^{31}P NMR (DMF–d_7) δ –9.85; FABMS for $C_{42}H_{33}O_9PH$ *m*/*z*: Calcd: 713 [$(M+H)^+$]. Found: 713; Anal. Calcd for $C_{42}H_{33}O_9P\cdot 0.1H_2O$: C, 70.60; H, 4.68%. Found: C, 70.36; H, 4.67%.

*4.4.2. Tris[4-{3,5-bis(4-carboxybenzyloxy)benzyloxy}phenyl]phosphine (**1**G1[CO_2H]).* White powder; IR (KBr) 3421, 3018, 2873, 2663, 2537, 1690, 1594, 1495, 1452, 1420, 1375, 1288, 1240, 1156, 1066, 1018, 828, 754 cm^{-1}; ^{1}H NMR (DMF–d_7) δ 11.5 (brs, 3H), 8.09 (d, *J* = 8.5 Hz, 12H, Ar*H*), 7.67 (d, *J* = 8.5 Hz, 12H, Ar*H*), 7.29 (dd, *J* = 8.5, 7.3 Hz, 6H, Ar*H*), 7.13 (d, *J* = 8.5 Hz, 6H,

Ar*H*), 6.88 (brs, 6H, Ar*H*), 6.80 (brs, 3H, Ar*H*), 5.30 (s, 12H, OC*H*$_2$Ar), 5.15 (s, 6H, OC*H*$_2$Ar); ^{13}C NMR (DMF–d_7) δ 167.8, 160.6, 160.1, 143.0, 140.5, 135.4 ($^2J_{C–P}$ = 22 Hz), 131.3, 130.3, 129.9 ($^1J_{C–P}$ = 8 Hz), 128.1, 115.8 ($^3J_{C–P}$ = 7 Hz), 107.5, 101.9, 70.1, 69.8; ^{31}P NMR (DMF–d_7) δ –9.94; FABMS for $C_{87}H_{69}O_{21}P$ *m/z*: Calcd: 1480 [M^+]. Found: 1480; Anal. Calcd. for $C_{87}H_{69}O_{21}P\cdot H_2O$: C, 69.69; H, 4.77%. Found: C, 69.92; H, 4.65%.

*4.4.3. Tris(4-[3,5-bis{3,5-bis(4-carboxybenzyloxy)benzyloxy}benzyloxy]phenyl) phosphine (**1**G2[CO$_2$H]).* Light yellow powder; IR (KBr) 3421, 2925, 2663, 2542, 1691, 1594, 1497, 1449, 1419, 1374, 1281, 1239, 1155, 1059, 1018, 830, 754 cm^{-1}; ^{1}H NMR (DMF–d_7) δ 13.1 (brs, 12H), 8.06 (d, *J* = 8.5 Hz, 24H, Ar*H*), 7.65 (d, *J* = 8.5 Hz, 24H, Ar*H*), 7.27 (dd, *J* = 8.5, 7.3 Hz, 6H, Ar*H*), 7.12 (d, *J* = 8.5 Hz, 6H, Ar*H*), 6.88 (s, 12H, Ar*H*), 6.85 (s, 6H, Ar*H*), 6.78 (brs, 6H, Ar*H*), 6.74 (brs, 3H, Ar*H*), 5.28 (s, 24H, OC*H*$_2$Ar), 5.20 (s, 6H, OC*H*$_2$Ar), 5.15 (s, 12H, OC*H*$_2$Ar); ^{13}C NMR (DMF–d_7) δ 167.8, 160.7, 160.6, 160.1, 143.0, 140.6, 140.4, 135.4 ($^2J_{C–P}$ = 21 Hz), 131.3, 130.3, 129.9 ($^1J_{C–P}$ = 11 Hz), 128.1, 115.9 ($^3J_{C–P}$ = 7 Hz), 107.5, 107.4, 101.9, 70.2, 69.8; ^{31}P NMR (DMF–d_7) δ –9.87; MALDI–TOFMS for $C_{177}H_{141}O_{45}PH$ *m/z*: Calcd.: 3019.86 [$(M+H)^+$]. Found: 3019.81; Anal. Calcd for $C_{177}H_{141}O_{45}P\cdot 2H_2O$: C, 69.59; H, 4.78%. Found: C, 69.57; H, 4.73%.

*4.4.4. Tris{4-(3,5-bis[3,5-bis{3,5-bis(4-carboxybenzyloxy)benzyloxy}benzyloxy]benzyloxy)phenyl} phosphine (**1**G3[CO$_2$H]).* Light yellow powder; IR (KBr) 3422, 3068, 2924, 1692, 1595, 1317, 1153, 1288 cm^{-1}; ^{1}H NMR (DMF–d_7) δ13.3 (brs, 24H, ArCO$_2$*H*), 8.06 (d, *J* = 8.2 Hz, 48H, Ar*H*), 7.62 (d, *J* = 8.2 Hz, 48H, Ar*H*), 7.25 (dd, *J* = 8.2, 7.3 Hz, 6H, Ar*H*), 7.09 (d, *J* = 8.2 Hz, 6H, Ar*H*), 6.89–6.81 (m, 42H, Ar*H*), 6.78–6.70 (m, 21H, Ar*H*), 5.24 (s, 48H, OC*H*$_2$Ar), 5.18–5.06 (m, 42H, OC*H*$_2$Ar); ^{13}C NMR (DMF–d_7) δ 166.5, 159.44, 159.39, 159.3, 141.7, 139.3, 139.2, 139.0, 134.2 ($^2J_{C–P}$ = 21 Hz), 129.9, 129.0, 126.8, 114.6 ($^3J_{C–P}$ = 3 Hz), 106.2, 106.1, 100.6, 100.5, 68.96, 68.95, 68.86, 68.5; ^{31}P NMR (DMF–d_7) δ –9.74; MALDI–TOFMS for $C_{357}H_{285}O_{93}PH$ *m/z*: Calcd.: 6094.64 [$(M+H)^+$]. Found: 6094.67; Anal. Calcd for $C_{357}H_{285}O_{93}P\cdot 3H_2O$: C, 69.74; H, 4.77%. Found: C, 69.80; H, 4.74%.

4.5. Suzuki–Miyaura Reaction (Table 1–5): General Procedure

1G*n*[CO_2K] was prepared by mixing **1**G*n*[CO_2H] (0.0184 mmol) and potassium hydroxide (1.1 equiv./CO_2H) at room temperature in water (1.5 mL) under an argon atmosphere. By the addition of [PdCl(η^3-C_3H_5)]$_2$ (0.0084 mmol) to **1**G*n*[CO_2K] aqueous solution, the **1**G*n*[CO_2K]–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**G*n*[CO_2K]–palladium aqueous solution at 0 ºC. The resulting mixture was stirred for 4 h at 50 ºC. The reaction mixture was extracted with diethyl ether four times, and the combined organic layers were washed with brine then dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and the residue was purified with silica gel column chromatography to obtain the coupling product **7**.

For the experiment described in Table 1, **1**G*n*[H] and [PdCl(η^3-C_3H_5)]$_2$ were stirred in 1,4-dioxane, and the subsequent Suzuki–Miyaura reaction was also carried out in 1,4-dioxane by use of cesium carbonate stead of potassium carbonate.

For the experiment described in Table 3, potassium hydroxide (1.1 equiv./total CO_2H) was added to a mixture of a non-dendritic **1**G0[CO_2H] and **8**[CO_2H] or **9**[CO_2H] in water. After the reaction mixture was completely dissolved, [PdCl(η^3-C_3H_5)]$_2$ was added to the aqueous mixture.

Cross-coupling products **7a**–**7e** are known compounds, and their NMR spectra are in accordance with those reported in the literature.[23]

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References and Notes

1. (a) He, Y.-M.; Feng, Y.; Fan, Q.-H. *Acc. Chem. Res.* **2014**, *47*, 2894–2906; (b) Caminade, A.-M.; Ouali, A.; Keller, M.; Majoral, J.-P. *Chem. Soc. Rev.* **2012**, *41*, 4113–4125; (c) Astruc, D.; Boisselier, E.; Ornelas, C. *Chem. Rev.* **2010**, *110*, 1857–1959; (d) Hourani, R.; Kakkar, A. *Macromol. Rapid Commun.* **2010**, *31*, 947–974; (e) de Jesus, E.; Flores, J. C. *Ind. Eng. Chem. Res.* **2008**, *47*, 7968–7981.
2. (a) Wang, D.; Astruc, D. *Coord. Chem. Rev.* **2013**, *257*, 2317–2334; (b) Tsuji, Y; Fujihara, T. *Bull. Korean. Chem. Soc.* **2007**, *28*, 1902–1909.
3. (a) Helms, B.; Fréchet, J. M. J. *Adv. Synth. Catal.* **2006**, *348*, 1125–1148; (b) Reek, J. N. H.; Arevalo, S.; van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Adv. Catal.* **2006**, *49*,

71–151; (c) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3867; (d) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991–3023.

4. (a) Fujita, K.; Sato, J.; Inoue, K.; Tsuchimoto, T.; Yasuda, H. *Tetrahedron Lett.* **2014**, *55*, 3013–3016; (b) Fujita, K.; Kujime, M.; Muraki, T. *Bull. Chem. Soc. Jpn.* **2009**, *11*, 2305–2307; (c) Fujihara, T.; Yoshida, S.; Terao, J.; Tsuji, Y. *Org. Lett.* **2009**, *11*, 2121–2124; (d) Fujihara, T.; Yoshida, S.; Ohta, H.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 8310–8314.
5. (a) Muraki, T.; Fujita K.; Kujime, M. *J. Org. Chem.* **2007**, *72*, 7863–7870; (b) Muraki, T.; Fujita K.; Terakado, D. *Synlett* **2006**, 2646–2648; (c) Fujita, K.; Muraki, T.; Hattori, H.; Sakakura, T. *Tetrahedron Lett.* **2006**, *47*, 4831–4834.
6. (a) Caminade, A.-M.; Ouali, A.; Laurent, R.; Turrin, C.-O.; Majoral, J.-P. *Chem. Soc. Rev.* **2015**, *44*, 3890–3899; (b) Servin, P.; Laurent, R.; Gonsalvi, L.; Tristany, M.; Peruzzini, M.; Majoral, J.-P.; Caminade, A.-M. *Dalton Trans.*, **2009**, 4432–4434; (c) Snelders, D. J. M.; van Koten, G.; Gebbink, R. J. M. K. *J. Am. Chem. Soc.* **2009**, *131*, 11407–11416; (d) Wang, Z.-J.; Deng, G.-J.; Li, Y.; He, Y.-M.; Tang, W.-J.; Fan, Q.-H. Org. Lett. **2007**, *9*, 1243–1246; (e) Helms, B.; Liang, C. O.; Hawker, C. J.; Fréchet, J. M. J. *Macromolecules* **2005**, *38*, 5411–5415; (f) Fujihara, T.; Obora, Y.; Tokunaga, M.; Sato, H.; Tsuji, Y. *Chem. Commun.* **2005**, 4526–4528.
7. Previously reported phosphine core dendrimers: (a) Ma, B.; Miao, T.; Sun, Y.; He, Y.; Liu, J.; Feng, Y.; Chen, H.; Fan, Q.-H. *Chem. Eur. J.* **2014**, *20*, 9969–9978 (b) Caminade, A.-M.; Laurent, P. S. R.; Majoral, J.-P. *Chem. Soc. Rev.* **2008**, *37*, 56–67; (c) Wu, L.; Li, B.-L.; Huang, Y.-Y.; Zhou, H.-F.; He, Y.-M.; Fan, Q.-H. *Org. Lett.* **2006**, *8*, 3605–3608; (d) Oosterom, G. E.; Steffens, S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Top. Cat.* **2002**, *19*, 61–73; (e) Balaji, B. S.; Obora, Y.; Ohara, D.; Koide, S.; Tsuji, Y. *Organometallics* **2001**, *20*, 5342–5350.
8. Our preliminary report: Hattori, H.; Fujita, K.; Muraki, T.; Sakaba, A. *Tetrahedron Lett.* **2007**, *48*, 6817–6820.
9. (a) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412–443; (b) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7362–7370; (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59; (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
10. (a) Pinto, J.; Silva, V. L. M.; Silva, A. M. G.; Santos, L. M. N. B. F.; Silva, A. M. S. *J. Org. Chem.* **2015**, *80*, 6649–6659; (b) Handa, S.; Slack, E. D.; Lipshutz, B. H. *Angew. Chem. Int. Ed.*

2015, *54*, 11994–11998; (c) Liu, Y.-S.; Gu, N.-N.; Liu, P.; Ma, X.-W.; Liu, Y.; Xie, J.-W.; Dai, B. *Tetrahedron* **2015**, *71*, 7985–7989.

11. (a) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643–710; (b) Li, C.-J.; Chen, L. *Chem. Soc. Rew*. **2006**, *35*, 68–82; (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165; (d) Cornils, B.; Herrmann, W. A. Eds. *Aqueous-Phase Organometallic Catalysis*; Wiley-VCH: Weinheim, 2004.
12. We confirmed the formation of the **1**G3[CO_2H]–palladium complex by mixing **1**G3[CO_2H] and [PdCl(η^3-C_3H_5)]$_2$ (P/Pd = 1/1) in DMSO-d_6 according to the following ^{31}P NMR spectra; for **1**G3[CO_2H]: –10.68 ppm, for 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.
13. The dispersion system was stable within several minutes. Quick measurement (SEM) of this system indicated that its particle size was 1 μm. Kobayashi et al. have also reported that Lewis acid–surfactant-combined catalyst systems form colloidal dispersions (not micelles). Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202–7207.
14. By employing only [PdCl(η^3-C_3H_5)]$_2$, which was not a dendritic catalyst, the catalytic reaction did not proceed.
15. TPPTS: triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt
16. Previously reported positive dendritic effects on chemical yields caused by the periphery-catalyzed dendrimers: (a) Mansour, A.; Kehat, T.; Portnoy, M. *Org. Biomol. Chem.*, **2008**, *6*, 3382–3387; (b) Dahan, A.; Portnoy, M. *J. Am. Chem. Soc.* **2007**, *129*, 5860–5869; c) Benito, J. M.; de Jesus, E.; de la Mata, F. J.; Flores, J. C.; Gomez, R.; *Chem. Commun.* **2005**, 5217–5219; (d) Delort, E.; Darbre, T.; Reymond, J.-L. *J. Am. Chem. Soc.* **2004**, *126*, 15642–15643.
17. After the preparation of **1**G3[H]–palladium complex in dichloromethane in situ, the Suzuki–Miyaura reaction was carried out, followed by the replacement of dichloromethane by water.
18. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
19. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
20. Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. I* **1993**, 1287–1297.

21. Senear, A. E.; Valient, W.; Wirth, J. *J. Org. Chem.* **1960**, *25*, 2001–2006.

22. Manos-Turvey, A.; Watson, E. E.; Sykes, M. L.; Jones, A. J.; Baell, J. B.; Kaiser, M.; Avery, V. M.; Payne, R. *J. Med. Commun.* **2015**, *6*, 403–406.

23. Yokoyama, N.; Nakayama, Y.; Nara, H.; Sayo, N. *Adv. Synth. Catal.* **2013**, *355*, 2083–2088.