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An Amphiphilic Resin-Supported Palladium Catalyst for High-Throughput Cross-Coupling in Water

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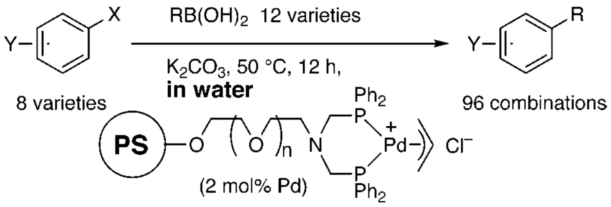
ABSTRACT



The Suzuki–Miyaura coupling of aryl halides (8 varieties) and aryl- or vinylboronic acids (12 varieties) took place in water in the presence of a palladium complex of an amphiphilic polystyrene–poly(ethylene glycol) copolymer resin-supported N-anchored 2-aza-1,3-bis(diphenylphosphino)propane ligand and potassium carbonate to give uniform and quantitative yields of the corresponding biaryls (96 varieties).

High-throughput synthesis by solution-phase catalysis has been recognized as a useful methodology with the advent of efficient methods for compound purification. One approach employs supported catalysts that can be readily removed by filtration.[1] A number of supported palladium complexes, in particular palladium−phosphine complexes, have been designed and prepared to combine the advantages of both homogeneous and heterogeneous catalysts in one system.[2] This class of supported palladium catalysts would solve the basic problems of homogeneous catalysts, namely, the separation and recycling of the catalysts. These palladium complex catalysts also have the advantage of preventing contamination of the ligand residue in the products.

On the other hand, organic reactions in water have recently received much attention, because water is a readily available, safe, and environmentally benign solvent.[3] We have developed amphiphilic resin-supported palladium complexes with a view toward using them for catalytic reactions in water.[4] Thus, for example, π-allylic substitution, carbonylation, and Suzuki−Miyaura cross-coupling have been achieved in water using a palladium complex immobilized by coordination with a triarylphosphine anchored on an amphiphilic polystyrene−poly(ethylene glycol) graft copolymer (PS−PEG-tap) (Figure 1).[5]

Recently, dendrimer- and polymer-supported chelating ligands bearing a 2-aza-1,3-bis(diphenylphosphino)propane moiety were designed, prepared, and complexed to palladium

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[1] For reviews, see: (a) Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 109. (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (c) Burgess, K.; Porte, A. M. *Adv. Catal. Processes* **1997**, *2*, 69. (d) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035.

[2] For reviews, see: (a) Uozumi, Y.; Hayashi, T. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W, Eds.: Wiley-VCH: Weinheim, Germany, 2002; Chapter 19, pp 531−584. (b) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, Germany, 2000.

[3] For reviews, see: (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (b) Grieco, P. A. *Organic Synthesis in Water*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1997.

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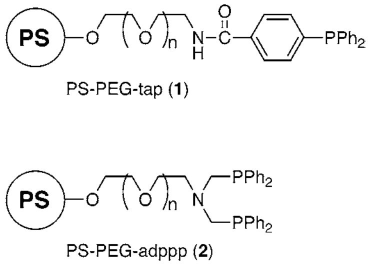


PS-PEG-tap (**1**)

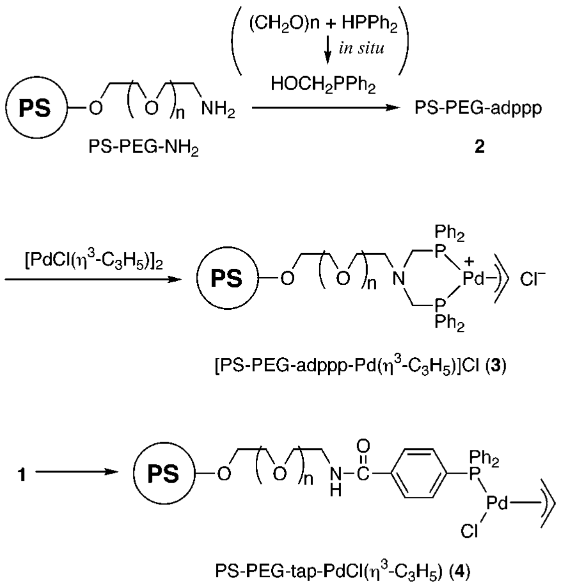
PS-PEG-adppp (**2**)

Figure 1. PS−PEG resin-supported triarylphosphine (PS−PEG-tap, above) and the resin-supported 2-aza-1,3-bis(diphenylphosphino)propane (PS−PEG-adppp, below).

or rhodium species to form P−P chelate complexes that were found to be effective as catalysts in hydrogenation, olefin hydroformylation, the Heck reaction, and π-allylic substitution.[6] These results prompted us to prepare a PS−PEG resin-supported P−P chelate palladium complex of the N-anchored 2-aza-1,3-bis(diphenylphosphino)propane ligand, PS−PEG-adppp (Figure 1), which would be effective in water-based transition metal catalysis and provide high recyclability, owing to the amphiphilic property of the PS−PEG support and the stability of the chelate coordination. We report here the preparation of PS−PEG-adppp and its use for the palladium-catalyzed Suzuki−Miyaura coupling of various combinations of aryl halides with arylboronic acids in water.

PS−PEG-adppp was readily prepared by treatment of PS−PEG-NH$_2$[7] with diphenylphosphinomethanol (Scheme 1). Thus, a mixture of PS−PEG-NH$_2$ (loading value = 0.37 mmol/g) and an excess amount of diphenylphosphinomethanol generated in situ by mixing paraformaldehyde and diphenylphosphine was agitated in toluene−MeOH at 25 °C for 3 h to give PS−PEG-adppp (loading value = 0.32 mmol/g) quantitatively. Gel-phase ^{31}P MAS NMR studies demonstrated complete consumption of the starting amino resin and exclusive formation of the desired bisphosphine residue.[8] Formation of a palladium complex of the bisphosphine ligand PS−PEG-adppp was performed by mixing [PdCl(η^3-C_3H_5)]$_2$ in toluene at 25 °C for 15 min to give [PS−PEG-adppp-Pd-(η^3-C_3H_5)]Cl in quantitative yield.

Scheme 1



PS-PEG-NH$_2$

2

[PS-PEG-adppp-Pd(η^3-C_3H_5)]Cl (**3**)

PS-PEG-tap-PdCl(η^3-C_3H_5) (**4**)

The catalytic utility of the amphiphilic resin-supported P−P chelate complex **3** in water was examined for the palladium-catalyzed cross-coupling of aryl halides with arylboronic acids, the so-called Suzuki−Miyaura coupling, which has been recognized as one of the most versatile carbon−carbon bond-forming reactions.[9] The coupling of iodobenzene (**5a**) with 1.2 equiv of phenylboronic acid (**6A**) took place smoothly in the presence of 2 mol % palladium of the PS−PEG-adppp-Pd complex **3** in a 1.5 M aqueous solution of potassium hydroxide at 25 °C to give, after 12 h, biphenyl **7aA** in 97% yield (Table 1, entry 1). Under similar conditions, the reaction with the palladium complexes of PS−PEG-tap (**4** in Scheme 1) and that of sodium triphenylphosphine trisulfonate (TPPTS)[10] for 24 h afforded biphenyl **7aA** in 88 and 59% yields, respectively (entries 2 and 3), demonstrating the high catalytic activity of complex **3**. After surveying reaction variables (temperature, time, base, etc.), a reaction system exhibiting quantitative chemical

Table 1. Suzuki−Miyaura Coupling of PhI (**5a**) with PhB(OH)$_2$ (**6A**) in Water[a]

$$\mathrm{PhI}\ (\mathbf{5a}) + \mathrm{PhB(OH)_2}\ (\mathbf{6A}) \xrightarrow[\text{in water}]{\text{[Pd](cat), base}} \mathrm{Ph{-}Ph}\ (\mathbf{7aA})$$

entry	cat	base	temp (°C)	yield (%) of **7aA**
1	**3**	KOH	25	97
2[b]	**4**	KOH	25	88
3[b]	Pd/TPPTS	KOH	25	59
4	**3**	K_2CO_3	50	>99
5	**3** (second use)	K_2CO_3	50	>99
6	**3** (third use)	K_2CO_3	50	>99

[a] All reactions were carried out in water with shaking for 12 h. The ratio of **5a** (mol)/**6A** (mol)/[Pd]/base (equiv)/H$_2$O (L) = 1.0/1.2/0.02/5.0/3.3. [b] Reaction time = 24 h (ref 4(b)).

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[6] (a) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1526. (b) Alper, H.; Arya, P.; Bourque, S. C.; Jefferson, G. R.; Manzer, L. E. *Can. J. Chem.* **2000**, *78*, 920. (c) Arya, P.; Panda, N.; Rao, V.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Am. Chem. Soc.* G. **2001**, *123*, 2889. (d) Eggeling, E. B.; Hovestad, N. J.; Jastrzebski, J. T. B. H.; Vogt, D.; van Koten, G. *J. Org. Chem.* **2000**, *65*, 8857−8865. (e) Mizugaki, T.; Murata, M.; Ooe, M.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2002**, 52.

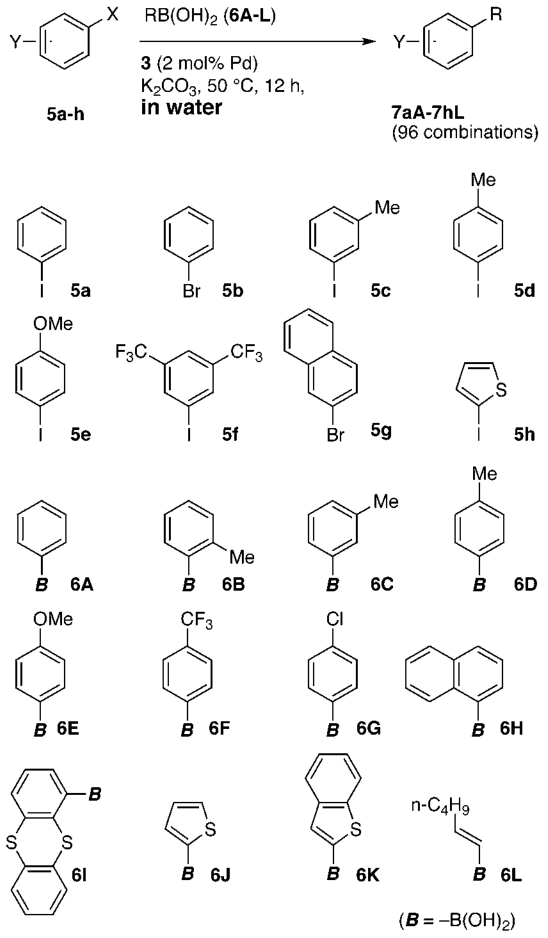
[7] ArgoGel NH$_2$ (loading of amino residue = 0.37 mmol/g) (1% DVB cross-linked) was used.

[8] Compound **2**: ^{31}P NMR (CDCl$_3$) δ −28.7. Compound **3**: ^{31}P NMR (CDCl$_3$) δ 2.20.

[9] For reviews, see: (a) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[10] (a) Kuntz, E. G. German Patent 2627354, 1976. (b) Sinou, D. *Bull. Soc. Chim. Fr.* **1987**, *3*, 480.

Scheme 2



yields under noncorrosive mild aqueous alkaline conditions was identified. Thus, the present coupling was carried out in aqueous potassium carbonate at 50 °C for 12 h. The reaction mixture was filtered, and the resin catalyst was rinsed with a small portion of water and ether (five times). The combined organic washings were dried and concentrated in vacuo to give a quantitative yield of **7aA** (entry 4) as an analytically pure sample.[11] No loss of catalytic activity was observed in the second and third use of the recovered catalyst for the coupling forming **7aA** under the same reaction conditions (entries 5 and 6).

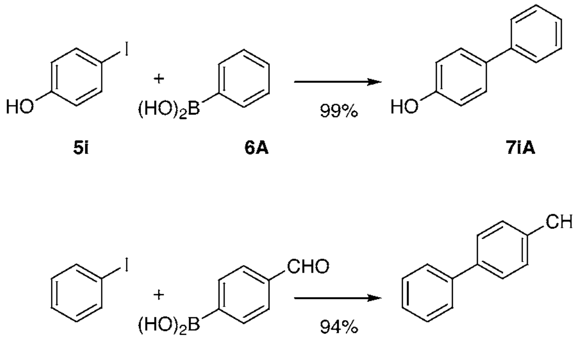
With a practical and safe catalytic protocol for the Suzuki–Miyaura coupling in hand, we next examined the combinatorial coupling of a variety of aromatic halides and arylboronic acids in water. Thus, 96 combinations of 8 varieties of aromatic halides and 12 varieties of aryl- or vinylboronic acids were subjected to the coupling in aqueous potassium carbonate at 50 °C for 12 h in the presence of 2 mol % palladium of the PS–PEG-adppp complex **3** (Scheme 2). The reaction mixture was filtered, and the catalyst resin was rinsed with a small portion of ether to give a crude coupling product. The chemical yields and purities of the coupling products **7** were determined by GC analysis using an appropriate internal standard, and the chemical identification of the products was carried out using GC-MS spectra of the NIST mass database library, showing good (>95%) similarity with authentic data. The results are shown in Table 2. All combinations of **5a**–**h** and **6A**–**L** afforded quantitative yields of the coupling products **7aA**–**hL** under the given conditions. The cross-coupling reactions using aryl iodide **5i** and the boronic acid **6M**, which have a phenolic hydroxyl group and an aldehyde group, respectively, proceeded smoothly under the same reaction conditions to exhibit wide functional group tolerance of this reaction system (Scheme 3). Thus, iodophenol **5i** reacted with phenylboronic acid (**6A**) in water in the presence of 2 mol % palladium of PS–PEG-adppp-Pd complex **3** at 50 °C to give 99% yield of

Table 2. Yields (%) of Combinatorial Couplings of **5** and **6** Forming **7**[a]

6\5	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
A	99	>99	97	94	>99	>99	>99	>99
B	>99	>99	98	99	>99	>99	>99	>99
C	97	>99	98	>99	>99	>99	>99	>99
D	>99	97	99	99	>99	>99	>99	>99
E	99	>99	98	99	>99	>99	>99	>99
F	97	97	99	99	>99	>99	>99	>99
G	>99	>99	96	99	>99	>99	>99	>99
H	>99	>99	>99	98	>99	>99	>99	>99
I	>99	>99	99	97	96	>99	>99	>99
J	>99	>99	98	99	>99	>99	>99	>99
K	>99	>99	97	>99	>99	>99	>99	>99
L	>99	>99	>99	>99	>99	>99	>99	>99

[a] All reactions were carried out in water in the presence of **3** (2 mol % Pd) and K$_2$CO$_3$ at 50 °C for 12 h. All yields are GC yields based on an internal standard. All products **7aA**–**hL** are >95% pure by GC analysis.

Scheme 3



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[11] A typical procedure is given for the reaction of iodobenzene (**5a**) and phenylboronic acid (**6A**) (Table 1, entry 4). A Baker Disposable Filtration Column was charged with iodobenzene (102 mg, 0.5 mmol), phenylboronic acid (73 mg, 0.6 mmol), K$_2$CO$_3$ (346 mg, 2.5 mmol), water (1.65 mL), and Pd-PS–PEG-adppp complex **3** (33 mg, 10 μmol Pd), and the mixture was shaken on a LibraKit at 50 °C for 12 h. The reaction mixture was filtered, rinsed with water (4 mL × 5) and diethyl ether (5 mL × 5). The organic layer was separated, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was filtered through a silica gel pad (eluent, hexane) to give **7aA** (76 mg, 99% yield).

hydroxybiphenyl **7iA**. The aldehyde **6M** also underwent the reaction with **5a** to give biphenylaldehyde **7aM** in 94% yield. Taking into account the safe and simple manipulation as well as the uniformly excellent results, the Suzuki–Miyaura coupling with PS–PEG-adppp-Pd complex (**3**) in water would be one of the best protocols for combinatorial high-throughput preparation of substituted aromatics.

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Supporting Information Available: Experimental procedure for the preparation of **2** and **3** and a general procedure for Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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