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Suzuki–Miyaura Coupling Catalyzed by Polymer-Incarcerated Palladium, a Highly Active, Recoverable, and Reusable Pd Catalyst

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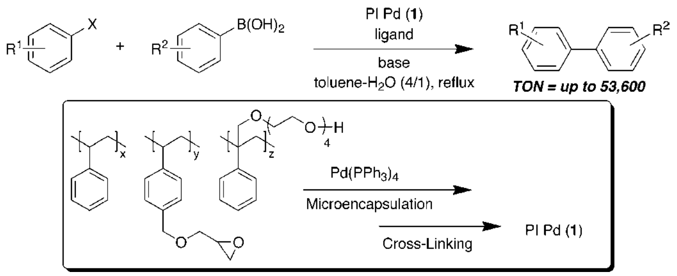
ABSTRACT



Suzuki–Miyaura coupling using a highly efficient and reusable polymer-incarcerated palladium (PI Pd) is described. Various coupling reactions proceeded smoothly using PI Pd with phosphine ligands, and the catalyst could be recovered by simple filtration and reused several times without loss of activity.

Palladium-catalyzed Suzuki−Miyaura coupling has become one of the most important, powerful, and common methods for carbon−carbon bond formation[1] and has been widely used not only in academic laboratories but also in industry. In general, soluble palladium complexes with ligands such as phosphines, amines, or carbenes are used as the catalysts for such couplings, where the choice of the ligands often allows tuning of the catalytic activity and selectivity.[2] However, many of the currently used catalysts are sensitive to air oxidation and cannot be recovered in many cases. Despite many attempts at using palladium metal immobilized on supports, most have lower catalytic activity compared with homogeneous catalysts, and moreover, the recovery and reuse of such catalysts has often not been satisfactory.[3,4] Although

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(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. In *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 49. (d) *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Miley: West Sussex, UK, 2002. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (f) Thompson, L. A.; Ellman, J. A. *Chem Rev.* **1996**, *96*, 555. (g) Tsuji, J. In *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1995. (h) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (e) Bei, X.; Crevier, T.; Guran, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855. (f) Wolfe, J. P.; Singer, R. A.; Yang, B. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (g) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (h) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077. (i) Kataoka, N.; Shelby Q.; Stambuli, J. P.; Hartwig J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(3) For recent reviews, see: (a) de Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035. (c) Loch, J. A.; Crabtree, R. H. *Pure Appl. Chem.* **2001**, *73*, 119. (d) Corain, B.; Kralik, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 99. (e) Bergbreiter, D. E. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 736.

(4) Recently, a highly active hydroxyapatite-supported Pd(II) catalyst has been reported. Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572.

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immobilized palladium catalysts based on polymer-supported phosphines or amines, etc., have been developed,[5] only immobilized ligands can be used because additional external ligands often induce leaching of the metals.

Recently, we developed a method for immobilizing metal catalysts onto polymers: polymer incarceration (PI).[6,7] The method is based on microencapsulation[8] and cross-linking of polymer chains. Using this approach, $Pd(PPh_3)_4$ was successfully immobilized to form polymer-incarcerated palladium (PI Pd, **1**, Figure 1).[9] PI Pd consists of phosphine-free palladium(0) and effectively catalyzes hydrogenations.[6,7] In addition, allylation reactions proceed smoothly using this catalyst in the presence of triphenylphosphine as an external ligand.[6] In this manner, PI Pd has an advantage as a recoverable and reusable catalyst applicable to other reactions by choosing suitable ligands. In this paper, we report a remarkably high activity of PI Pd in Suzuki−Miyaura couplings.

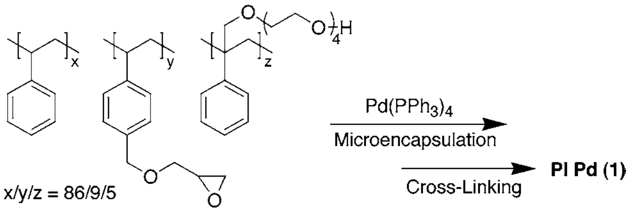
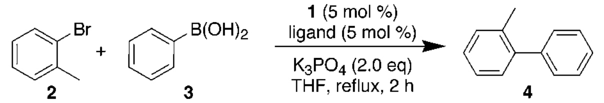
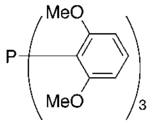
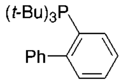
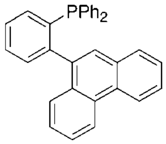
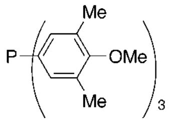


Figure 1. Polymer-incarcerated method.

PI Pd (**1**) was initially examined in the coupling reaction of 2-bromotoluene (**2**) with phenylboronic acid (**3**); several phosphine ligands were tested as additives (Table 1). Triphenylphosphine, tricyclohexylphosphine, and triphenyl phosphite were not effective ligands under these reaction conditions. On the other hand, triarylphosphines having electron-donating groups gave the desired 2-methylbiphenyl (**4**) in high yields. The best result was obtained when tris(*o*-methoxyphenyl)phosphine (**5**) was used as a ligand.

Table 1. Effect of Phosphine Ligands

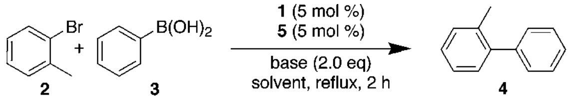


entry	ligand	yield[a] (%)
1	PPh_3	21
2	$P(o\text{-}Tol)_3$	68
3	$P(p\text{-}Tol)_3$	64
4	PCy_3	31
5	$P(p\text{-}MeOC_6H_4)_3$	88
6	$P(o\text{-}MeOC_6H_4)_3$ (**5**)	97
7	$P(OPh)_3$	11
8		3
9		79
10		49
11		93

[a] Isolated yield.

Solvents and bases were next examined, and leaching of the palladium was measured by fluorescence X-ray (XRF) analysis[10] after removal of the catalyst (Table 2). Although leaching of the palladium was observed when THF or toluene was used as a solvent, addition of water was found to decrease the leaching. In a toluene−H_2O (4/1) cosolvent system, no leaching of the palladium was detected. The leaching of the palladium seems to be influenced by a phase separation behavior.

Table 2. Effect of Bases and Solvents



entry	base	solvent	yield[a] (%)	leaching[b] of Pd (%)
1	K_3PO_4	THF	97	33
2	K_3PO_4	toluene	54	44
3	K_2CO_3	THF−H_2O (4/1)	89	15
4	K_2CO_3	toluene−H_2O (4/1)	83	nd
5	K_3PO_4	toluene−H_2O (4/1)	88	nd
6	Na_2CO_3	toluene−H_2O (4/1)	48	nd
7	K_2CO_3	toluene−EtOH (4/1)	86	nd

[a] Isolated yield. [b] Measured by XRF analysis. nd = not detected (<0.94%).

The catalytic activity of PI Pd was compared with that of the homogeneous catalysts palladium acetate and tetrakis(triphenylphosphine)palladium in the coupling reaction of 2-bromotoluene (**2**) with phenylboronic acid (**3**). Judging from the time−yield curves using 5 mol % of the catalysts

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(5) (a) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc*. **1978**, *100*, 7779. (b) Jang, S.-B. *Tetrahedron Lett*. **1997**, *38*, 1793. (c) Fenger, I.; Drian, C. L. *Tetrahedron Lett*. **1998**, *39*, 4287. (d) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem*. **1999**, *64*, 3384. (e) Zecca, M.; Fisera, R.; Palma, G.; Lora, S.; Hronec, M.; Králik, M. *Chem.—Eur. J*. **2000**, *6*, 1980. (f) Li, Y.; Hong, X. M.; Collard, D. M.; Ei-Sayed, M. A. *Org. Lett*. **2000**, *2*, 2385. (g) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 3820. (h) Niu, Y.; Yeung, L. K.; Crooks, R. M. *J. Am. Chem. Soc*. **2001**, *123*, 6840. (i) Mubofu, E. B.; Clark, J. H.; Macquarrie, D. J. *Green Chem*. **2001**, *3*, 23. (j) Cammidge, A. N.; Baines, N. J.; Bellingham, R. K. *Chem. Commun*. **2001**, 2588. (k) Gordon, R. S.; Holmes, A. B. *Chem. Commun*. **2002**, 640. (l) Jansson, A. M.; Grøti, M.; Halkes, K. M.; Meldal, M. *Org. Lett*. **2002**, *4*, 27. (m) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *J. Org. Chem*. **2003**, *68*, 7733.

(6) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc*. **2003**, *125*, 3412.

(7) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem*. **2004**, *69* 2871.

(8) (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1998**, *120*, 2985. (b) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org Chem*. **1998**, *63*, 6094. (c) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc*. **1999**, *121*, 11229. (d) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett*. **2001**, *3*, 2649. (e) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2001**, *40*, 3469. (f) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2002**, *41*, 2602.

(9) Experimental details are shown in the Supporting Information.

(10) The lower detection limit is 5 ppm (0.94%).

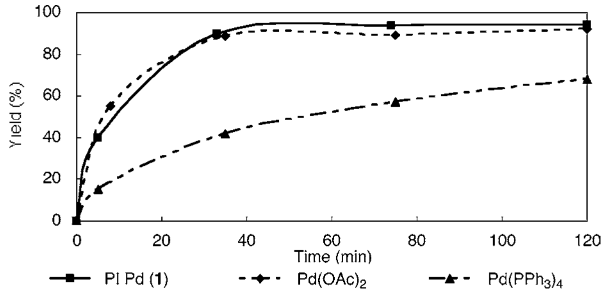


Figure 2. Plot of yield versus time for Suzuki−Miyaura coupling using 5 mol % of catalyst: Yields were determined by GC analysis with internal standard method. Reaction condition: 1.0 equiv of 2-bromotoluene, 1.5 equiv of phenylboronic acid, 2.0 equiv of K_3PO_4, 5 mol % of Pd catalyst, 5 mol % of **5**, toluene−H_2O (4/1), reflux.

(Figure 2), the activity of PI Pd was almost the same as that of palladium acetate and was higher than that of tetrakis(triphenylphosphine)palladium. To compare the activity of PI Pd with that of the homogeneous catalysts more precisely, we conducted the same reaction in the presence of 0.1 mol % of the catalysts (Figure 3). It was exciting to find that PI Pd exhibited higher activity than that of both homogeneous catalysts.

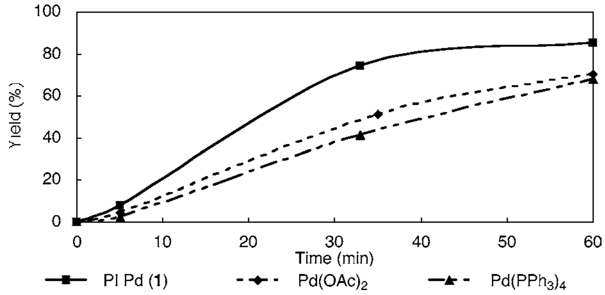


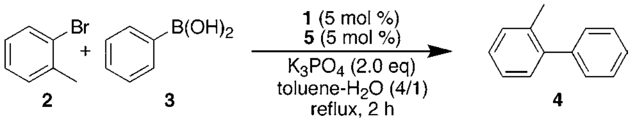
Figure 3. Plot of yield versus time for Suzuki−Miyaura coupling using 0.1 mol % of catalyst: Yields were determined by GC analysis with internal standard method. Reaction conditions 1.0 equiv of 2-bromotoluene, 1.5 equiv of phenylboronic acid, 2.0 equiv of K_3PO_4, 0.1 mol % of Pd catalyst, 0.1 mol % of **5**, toluene−H_2O (4/1), reflux.

Furthermore, PI Pd was recovered by simple filtration and could be reused several times without loss of activity. No leaching of the palladium was detected by XRF analysis in all runs shown in Table 3.

Several examples of PI Pd-catalyzed Suzuki−Miyaura coupling of aryl halides with arylboronic acids are summarized in Table 4. Both electron-rich and electron-deficient arylhalides are reactive, and the desired coupling adducts are obtained in good yields without any leaching of the palladium.

Sterically hindered substrates have also been examined (Table 5). When tris(*o*-methoxyphenyl)phosphine (**5**) was used as a ligand, yields were lower and some leaching of palladium was observed. Recently, Buchwald et al. have

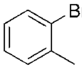
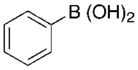
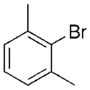
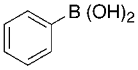
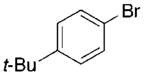
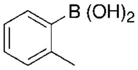
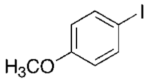
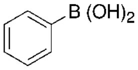
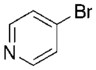
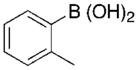
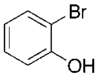
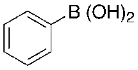
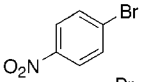
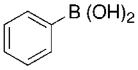
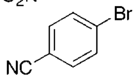
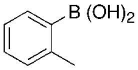
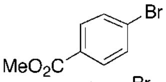
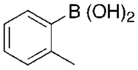
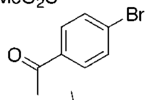
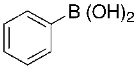
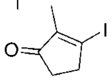
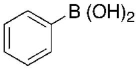
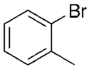
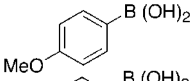
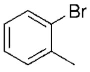
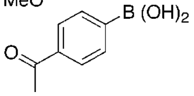
Table 3. Reuse of PI Pd[a]



run	1	2	3	4	5
yield[b] (%)	83	88	85	85	83
leaching of Pd[c]	nd	nd	nd	nd	nd

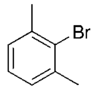
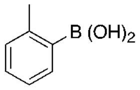
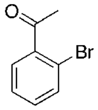
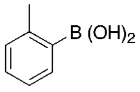
[a] After the reaction, the mixture was diluted with hexane and the catalysts was filtered off. The catalyst was reused after washing with THF, H_2O, and MeOH, successively, and dried. [b] Isolated yield. [c] Measured by XRF analysis. nd = not detected (<0.94%).

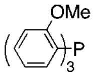
Table 4. PI Pd-Catalyzed Couplings of Various Substrates[a]

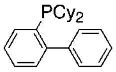
entry	arylhalide	boronic acid	yield (%)[b]	leaching[c] of Pd
1			88	nd
2			83	nd
3			97	nd
4			89	nd
5			88	nd
6			92	nd
7			86	nd
8			92	nd
9			quant	nd
10			99	nd
11			98	nd
12			75	nd
13			92	nd

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, 5 mol % of **1** (0.15 mmol/g), 5 mol % of **5**, toluene−H_2O (4/1), reflux, 2 h. Workup conditions: Reaction mixture was diluted with hexane, and the catalyst was filtered off and then washed with THF and MeOH. [b] Isolated yield. [c] Measured by XRF analysis. nd = not detected (<0.94%).

Table 5. PI Pd-Catalyzed Couplings of Hindered Substrates[a]

entry	arylbromide	boronic acid	ligand	yield[b] (%)	leaching[c] of Pd (%)
1			**5**	57	13
2			**6**	71	nd
3			**5**	59	11
4			**6**	quant	nd

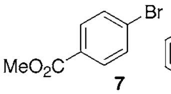
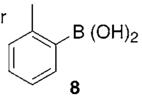
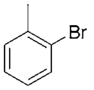
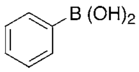
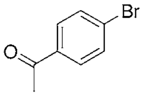
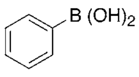
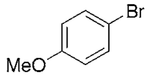
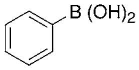
5: 

6: 

[a] Reaction conditions: 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, 5 mol % of **1** (0.15 mmol/g), 5 mol % of ligand, toluene−H_2O (4/1), reflux, 2 h. Workup conditions: Reaction mixture was diluted with hexane, and the catalyst was filtered off and then washed with THF and MeOH. [b] Isolated yield. [c] Measured by XRF analysis. nd = not detected (< 0.94%).

reported that 2-(dicyclohexylphosphino)biphenyl (**6**) is an effective ligand for the Suzuki−Miyaura coupling of hindered substrates.[2f] We tested this ligand and confirmed that **6** was also effective for the coupling reactions with the hindered substrates of our system. It is noteworthy that not only were the yields improved but also the leaching of the palladium was suppressed using the new phosphine ligand. We assumed at this stage that the palladium might leach out as palladium(II) intermediates from PI Pd when regeneration of palladium(0) was prevented in a catalytic cycle. In general, the character of palladium are strongly dependent on the ligands selected. It should be noted from these results that one advantage of PI Pd over other polymer-supported palladium catalysts is that various ligands can be selected in each reaction.

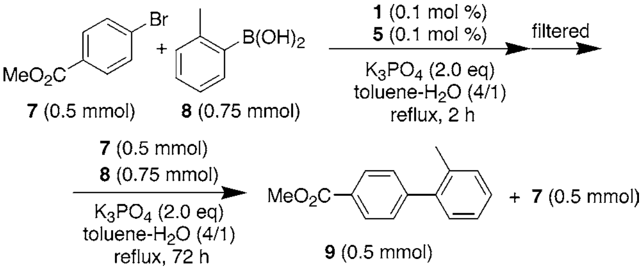
Table 6. The Minimum Amount of the Catalyst[a]

entry	arylbromide	boronic acid	PI Pd (mol %)	time (h)	yield[b] (%)	TON
1	 **7**	 **8**	5	2	quant	20
2			0.1	2	quant	1 000
3			0.01	24	quant	10 000
4			0.002	72	80	40 080
5			0.001	72	54	53 600
6			5	2	88 (94[c])	19
7			0.1	8	85 (90[c])	900
8			0.01	72	73	7 330
9			0.005	72	52	10 430
10			0.001	72	10	10 000
11			5	2	99	20
12			0.01	72	95	9 480
13			0.005	72	83	16 600
14			0.001	72	21	21 000
15			5	2	85	17
16			0.01	72	68	6 780
17			0.005	72	49	9 800
18			0.001	72	11	11 000

[a] Reaction conditions: 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, **1**/**5** = 1, toluene−H_2O (4/1), reflux. [b] Isolated yield. [c] GC yield.

Finally, we evaluated the minimum amount of catalyst that could be used to mediate several coupling reactions (Table 6). Reactions that use very small amounts of the catalyst also afford the desired coupling products with high turnover numbers (TONs). The maximum TON reached 53 600 (entry 5). In this system, we carefully looked for any catalytic effect for the filtrate (Scheme 1). Thus, after coupling **7** (0.5 mmol) with **8** (0.75 mmol) using 0.1 mol % each of PI Pd and ligand (**5**) and potassium phosphate (1.0 mmol), the PI Pd was removed by simple filtration, and to the filtrate were added **7** (0.5 mmol), **8** (0.75 mmol), and potassium phosphate (1.0 mmol). The mixture was refluxed for 72 h, but no additional formation of **9** was observed. This result showed that dissolved active palladium species did not exist in the solution phase of the reaction mixture.

Scheme 1. Filtrate Test in Suzuki−Miyaura Coupling Using PI Pd



In summary, we have revealed that PI Pd is a highly efficient reusable catalyst for Suzuki−Miyaura coupling. Various coupling reactions proceeded smoothly by using PI Pd. PI Pd was recovered by simple filtration and reused several times without loss of activity, and no leaching of the palladium was detected under all optimized conditions. It is noted that the activity of PI Pd is even higher than that of homogeneous palladium catalysts. One characteristic feature of PI Pd as an immobilized catalyst is that the activity of the catalyst is remarkably improved by changing the external phosphine ligands. Further investigations on other PI Pd-catalyzed coupling reactions are now in progress.

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Supporting Information Available: Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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