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An Assembled Complex of Palladium and Non-Cross-linked Amphiphilic Polymer: A Highly Active and Recyclable Catalyst for the Suzuki–Miyaura Reaction

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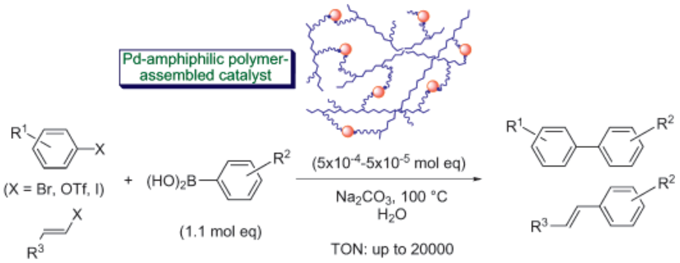
ABSTRACT



An insoluble and assembled catalyst of palladium and a non-cross-linked amphiphilic polymer were developed. In the presence of 50–500 ppm mol equiv of catalyst, the Suzuki–Miyaura reaction proceeded efficiently under organic solvent-free conditions. The catalyst was reused 10 times without any decrease in activity and was recycled without any special treatment.

The Suzuki−Miyaura reaction, the palladium-catalyzed cross-coupling of sp^2-halides or sp^2-triflates with sp^2-boronic acids or their esters, is one of the most important, powerful, and versatile tools for the synthesis of biologically active compounds and liquid crystals.[1] From the standpoint of green chemistry, the development of more environmentally benign conditions for the reaction, the use of water instead of organic solvents, the use of nontoxic reagents, the reduction of hazardous inorganic and organic waste, and a reliance on a minimal amount of reusable catalysts would be desirable.[2] One reaction system employing a highly active immobilized catalyst shows good promise in incorporating these considerations.[3] So far, cross-linked polystyrene resins and silica gels have been utilized as insoluble supports for the catalysts. Unfortunately, they often result in lower catalytic activity compared with their soluble counterparts. In addition, the activity of the recycled catalysts gradually decreases because the palladium species leaches from the supporting polymer or silica gel.[4] To overcome these limitations, a novel

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(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Miley: West Sussex, UK, 2002. (d) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303. (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (f) Tsuji, J. In *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1995.

(2) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998. (b) Tundo, P.; Anastas, P.; Black D. S.; Breen. J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207−1228.

(3) For recent reviews of immobilized palladium catalysts, see: (a) de Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213−4221. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035−1074. (c) Loch, J. A.; Crabtree, R. H. *Pure Appl. Chem.* **2001**, *73*, 119−128. (d) Corain, B.; Kralik, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 99−115. (e) Bergbreiter, D. E. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 736−744.

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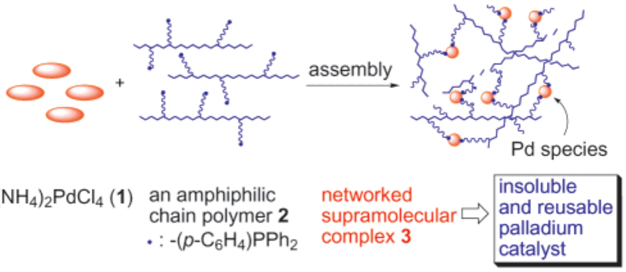
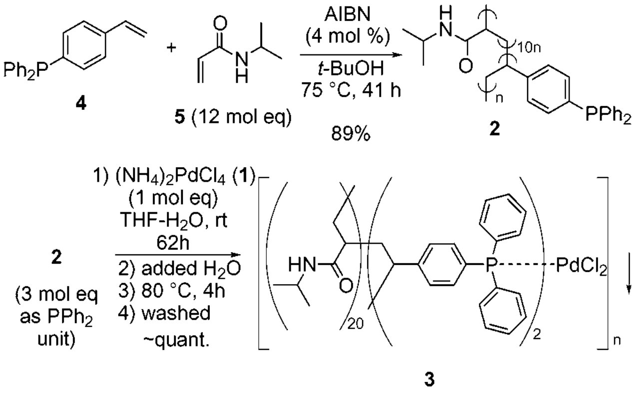
methodology for creating insoluble and highly active catalysts is needed.

For the reasons mentioned above, we decided to focus on a self-assembled process between non-cross-linked amphiphilic copolymer ligands and an inorganic species for the preparation of highly active, insoluble catalysts.[5] For example, a tungsten catalyst was formed from phosphotungstic acid and poly(*N*-isopropylacrylamide) with an ammonium salt.[5a] This catalyst, used in ppm molar equiv, brought about an efficient epoxidation of allylic alcohols. Since this self-assembled catalyst exhibited great potential, we consequently applied the concept to palladium chemistry (Scheme 1). In this letter, we report the development of a new palladium catalyst and its application to the Suzuki−Miyaura reaction. It is noteworthy that the reactions were promoted by only 50−500 ppm mol equiv of the catalyst, which was reused 10 times without any decrease in its activity. Furthermore, the reactions were performed under organic solvent-free conditions.

Scheme 1. Concept for the Preparation of an Assembled Catalyst of Palladium and a Non-Cross-linked Amphiphilic Copolymer



Scheme 2. Preparation of a Recyclable and Assembled Catalyst **3** for the Suzuki−Miyaura Reaction



A novel palladium−polymer catalyst with structure **3** was prepared, as shown in Scheme 2.[6] Random polymerization of 4-diphenylstyrylphosphine (**4**) with 12 mol equiv of *N*-isopropylacrylamide (**5**) in the presence of 4 mol % of AIBN gave **2** in 89% yield.[7] The ratio of the phosphine and the amide units in **2** was 1/10 (determined by ^1H NMR measurements in $CDCl_3$), and the phosphine unit was hardly oxidized in this polymerization (as shown by ^{31}P NMR). Complex **3** was prepared by self-assembly of **2** and $(NH_4)_2PdCl_4$ (**1**) with use of the method for the preparation of $PdCl_2(PPh_3)_2$.[8] All solvents were degassed by ultrasonication and argon substitution prior to use. To a well-stirred solution of **2** (0.36 mmol in phosphine) in THF (72 mL) was added a solution of **1** (0.12 mmol) in H_2O (30 mL), and the mixture was again degassed. After the mixture was stirred for 62 h at room temperature, a yellow precipitate **A** was formed. Water (30 mL) was added to the suspension, and THF was removed at 80 °C for 4 h with Dean−Stark equipment to give a reddish precipitate. This precipitate was stirred at 100 °C successively in H_2O (100 mL) for 12 h, in THF (100 mL) for 3 h, and in H_2O (100 mL) for 12 h to wash the unreacted palladium species and polymers. After drying in vacuo (ca. 0.1 mmHg), a dark red solid **3** was obtained in almost quantitative yield. Complex **3** was insoluble in water and organic solvents such as acetone, CH_3OH, CH_2Cl_2, AcOEt, THF, and hexane, whereas **2** was soluble in organic solvents such as $CHCl_3$, CH_2Cl_2, and THF.

To obtain further information on the structure of the catalyst, we analyzed **3** by gel-phase ^{31}P NMR in $CDCl_3$. The peaks of **2** were observed at −2.9 ppm ($ArPh_2P$) with trace peaks at 32.1 ppm ($ArPh_2P{=}O$) and 27.3 ppm. Catalyst **3** swelled so much in $CDCl_3$ that broad peaks were detected at 32.5 (major) and 26.1 ppm (minor) and assigned as the signals of $ArPh_2P{=}O$ and $PdCl_2(PPh_2Ar)_2$, respectively.[9] This

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(4) For recent developments and improvements for heterogeneous catalysis of the Suzuki−Miyaura reaction, see: (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett*. **1994**, *35*, 3277−3280. (b) Jang, S.-B. *Tetrahedron Lett*. **1997**, *38*, 1793−1796. (c) Fenger, I.; Le Drian, C.; *Tetrahedron Lett.* **1998**, *39*, 4287−4290. (d) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem*. **1999**, *64*, 3384−3388. (e) Zhang, T. Y.; Allen. M. J. *Tetrahedron Lett*. **1999**, *40*, 5813−5816. (f) Li, Y.; Hong, X. M.; Collard, D. M.; El-Sayed, M. A. *Org. Lett*. **2000**, *2*, 2385−2388. (g) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 3820−3827. (h) Mubofu, E. B.; Clark, J. H.; Macquarrie, D. J. *Green Chem*. **2001**, *3*, 23−25. (i) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2001**, *40*, 3469−3471. (j) Cammidge, A. N.; Baines, N. J.; Bellingham, R. K. *Chem. Commun*. **2001**, 2588−2589. (k) Barnard, C. F. J.; Griffin, K. G.; Froelich, J.; Ekman, K.; Sundell, M.; Peltonen, R. *Chem. Ind*. **2001**, *82*, 563−571. (l) Bedford, R. B.; Cazin, C. S. J.; Hursthouse, M. B.; Light, M. E.; Pike, K. J.; Wimperis, S. *J. Organomet. Chem*. **2001**, *633*. 173−181. (m) Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem*. **2001**, *634*, 39−46. (n) Kosslick, H.; Mönnich, I.; Paetzold, E.; Fuhrmann, H.; Fricke, R.; Müller, D.; Oehme, G. *Microporous Mesoporous Mater.* **2001**, *44−45*, 537−545. (o) Gordon, R. S.; Holmes, A. B. *Chem. Commun*. **2002**, 640−641. (p) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem*. **2002**, *67*, 2721−2722.

(5) (a) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2001**, *3*, 1837−1841. (b) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2002**, *43*, 3431−3434.

(6) Bergbreiter and co-workers reported excellent homogeneous palladium catalysts prepared from poly(*N*-isopropylacrylamide) copolymers as soluble and thermoresponsive polymers: (a) Bergbreiter, D. E. *Catal. Today* **1998**, *42*, 389−397. (b) Bergbreiter, D. E.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 4250−4251. (c) Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053−6062. For examples of polymer-protected palladium nanoparticles for hydrogenation, see: (d) Chen, C.-W.; Akashi, M. *Polym. Adv. Technol*. **1999**, *10*, 127−133. (e) Chen, C.-W.; Chen, M.-Q.; Serizawa, T.; Akashi, M. *Chem. Commun.* **1998**, 831−832.

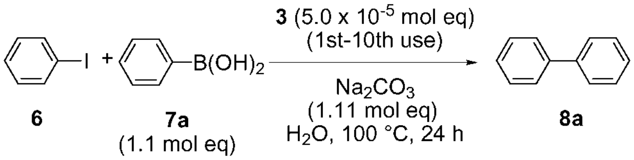
(7) The molecular weight of **2** was wide-ranging (ca. 5000−70000), as checked by gel-permeation chromatography relative to polystyrene standards.

(8) Mann, F. G.; Purdie, D. *J. Chem. Soc*. **1935**, 1549−1563.

result might indicate that the phosphines in **2** interacted with the palladium to form a $PdCl_2(PPh_2Ar)_2$ species in complex **3**, i.e., that the phosphines in **2** were cross-linked by palladium.

To test the potency of complex **3** as a catalyst, we examined the Suzuki–Miyaura reaction of iodobenzene (**6**) with phenylboronic acid (**7a**) (1.1 mol equiv) in the presence of 50 ppm (5×10^{-5}) mol equiv of **3** under organic solvent-free conditions (Table 1).[10] The reaction proceeded efficiently to give biphenyl (**8a**) in 95% yield (entry 1) with the turnover number (TON) of this catalyst reaching approximately 20000.[11]

Table 1. The Suzuki–Miyaura Reaction of Iodobenzene with Phenylboronic Acid Catalyzed by 5×10^{-5} mol equiv of the Recycled Catalyst **3**



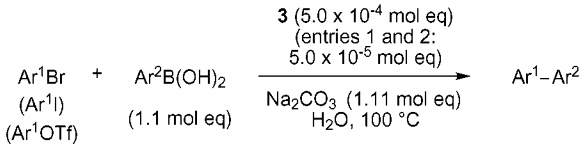
entry	catalyst	yield
1	1st use	95%
2	10th use	93%
3	1st–10th consecutive use	av: 95%

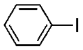
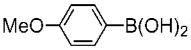
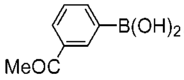
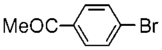
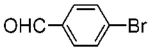
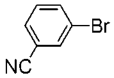
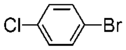
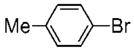
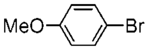
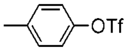
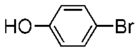
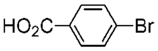
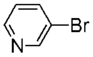
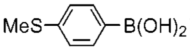
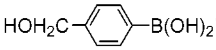
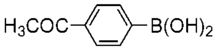
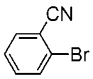
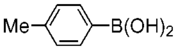
More importantly, the workup of this reaction was performed under organic solvent-free conditions where water was the only solvent used. When the reaction was completed, the reaction mixture was filtered with boiling water under an argon atmosphere. The catalyst **3** was recovered on the filter,[12] and the filtrate was cooled to room temperature to give **8a** as white crystals in high purity.

We also examined the reuse of the catalyst. In general, the continuous recycle of resin-supported palladium catalysts is difficult owing to leaching of the palladium species from the polymer supports, which often reduces their activity within a five-recycle run. However, when the reaction of **6** and **7a** was performed even with only 50 ppm mol equiv of **3**, the catalyst could be recycled 10 times without any loss of activity. The reaction promoted by the 10th recycled catalyst gave **8a** in 93% yield (Table 1, entry 2). The average yield of **8a** in consecutive reactions promoted by the 1st through the 10th recycled catalysts was 95% (entry 3). All the reactions catalyzed by recycled catalyst **3** could be worked up under organic solvent-free conditions as mentioned above.

With these results in hand, we next examined aryl iodides, aryl bromides, and an aryl triflate with arylboronic acids as substrates (Table 2).[13] The reaction of **6** with the electron-rich (**7b**) or the electron-deficient (**7c**) arylboronic acids catalyzed by 50 ppm (5×10^{-5}) mol equiv of **3** afforded the corresponding biaryls **8b** and **8c** in almost quantitative yields (entries 1 and 2). The reaction of electron-deficient aryl bromides **9a–d** with **7a** proceeded smoothly in the presence of 500 ppm (5×10^{-4}) mol equiv of **3** to give the

Table 2. The Suzuki–Miyaura Reaction of Aryl Iodides, Bromides, and Triflate with Arylboronic Acids Catalyzed by **3**



Entry	Ar^1Br (Ar^1OTf)	$Ar^2B(OH)_2$	Time	Yield
1	 **6**	 **7b**	24 h	**8b**: 97%
2	**6**	 **7c**	24 h	**8c**: 98%
3	 **9a**	**7a**	24 h	**8d**: 98%
4	 **9b**	**7a**	9 h	**8e**: 97%
5	 **9c**	**7a**	9 h	**8f**: 98%
6	 **9d**	**7a**	12 h	**8g**: 94%
7	 **9e**	**7a**	9 h	**8h**: 95%
8	 **9f**	**7a**	24 h	**8b**: 87%
9	 **9g**	**7a**	9 h	**8h**: 93%
10	 **9h**	**7a**	4 h (24 h at rt)	**8i**: 91% (80% at rt)
11	 **9i**	**7a**	4 h	**8j**: 95%
12	 **9j**	**7a**	9 h	**8k**: 99%
13	**9e**	**7b**	9 h	**8l**: 91%
14	**9e**	 **7d**	9 h	**8m**: 95%
15	**9e**	 **7e**	9 h	**8n**: 87%
16	**9e**	 **7f**	9 h	**8o**: 84%
17	 **9k**	 **7g**	24 h	**8p**: 93%

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[9] The signal of $PdCl_2(PPh_3)_2$ was observed at 26.5 ppm in $CDCl_3$ solution. The peaks of **A** were also detected at 32.0 (minor) and 26.0 ppm (major) in gel-phase $CDCl_3$ and were similar to those of **3** except for the difference in integrated intensity.

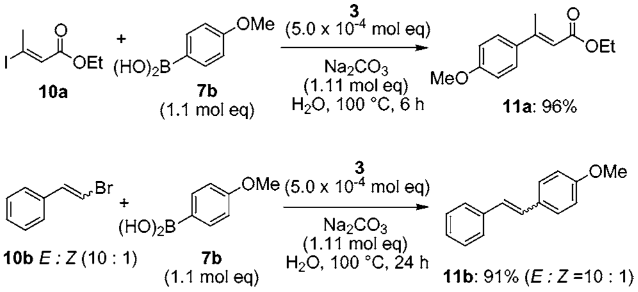
[10] The reaction was carried out in a reaction vessel equipped with a glass filter under an argon atmosphere.

[11] It was confirmed that the filtrate separated from the reaction mixture had no catalytic activity. This result indicated that the catalytic activity observed was due to the heterogeneous component of the system.

[12] Catalyst **3** was able to be reused without further treatment.

biaryl **8d**−**g** in 94−98% yield (entries 3−6). This catalyst was applicable to the electron-rich aryl bromides **9e**−**f** (entries 7 and 8) and an aryl triflate **9g** (entry 9). 4-Bromophenol (**9h**), 4-bromobenzoic acid (**9i**), and 3-bromopyridine (**9j**) also proved to be suitable substrates (entries 10−12). The reactions of **9h** and **9i**, which were soluble in water, were almost complete in 4 h to give **8i** and **8j** in 91% and 95% yield, respectively. The reaction in entry 10 can be performed at room temperature to afford **8i** in 80% yield. Substituted arylboronic acids can be used as reactants (entries 13−16). The reaction of the sulfur-containing boronic acid **7d** also proceeded smoothly to afford **8m** in 95% yield (entry 14). In general, when the reaction of electron-deficient arylboronic acid is performed in the presence of Na_2CO_3 as base, a critical hydrolysis of arylboronic acid occurs to decrease the yield of the corresponding biaryl.[14] However, it was found that the reaction of 1.1 mol equiv of the electron-deficient arylboronic acid **7f** gave the biaryl **8o** in 84% yield (entry 16). Furthermore, the product **8p** that is the intermediate in the synthesis of the angiotensin II antagonists[15] can be prepared by the reaction of 2-bromobenzonitrile (**9k**) with *p*-tolylboronic acid (**7g**) (entry 17); **8p** was obtained in 93% yield.

Scheme 3. The Suzuki−Miyaura Reaction of Alkenyl Halides



This catalyst **3** was also effective in the reactions of alkenyl halides, as shown in Scheme 3. These reactions can likewise be performed in the presence of 5×10^{-4} mol equiv of **3**. Ethyl *cis*-3-iodomethacrylate **10a** was converted to the corresponding coupling product **11a** in 96% yield. When β-bromostyrene (**10b**) ($E/Z = 10/1$) was reacted with **7b**, isomerization did not take place and **11b** was produced in 91% yield ($E/Z = 10/1$).

In conclusion, we have developed a new insoluble and reusable catalyst prepared from a self-assembly of $(NH_4)_2PdCl_4$ (**1**) and the non-cross-linked amphiphilic phosphine copolymer **2**. The Suzuki−Miyaura reaction using catalyst **3** afforded the desired products in high yields. This catalyst was also applied to reactions of aryl halides, alkenyl halides, and an aryl triflate with arylboronic acids. Using only 50 ppm mol equiv, catalyst **3** could be reused up to 10 times while still retaining its activity. Since the reaction system itself exhibited great potential and could be promoted by ppm mol equiv of the catalyst, applications to other reactions catalyzed by the palladium catalyst are currently under study.

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[13] **General Procedure for the Suzuki−Miyaura Reactions Catalyzed by 3 (Normal Method).** The reactions, except entry 1, were worked up with organic solvents as follows: The mixture of aryl halides (or an aryl triflate) **6** (22.5 mmol) or **9** (2.25 mmol), arylboronic acid **7** (in **6**, 24.8 mmol; in **9**, 2.48 mmol), Na_2CO_3 (in **6**, 25.0 mmol; in **9**, 2.50 mmol), and **3** (1.13 μmol) in water (in **6**, 75 mL; in **9**, 7.5 mL) was stirred at 100 °C under an argon atmosphere. After the reaction was complete and cooled to room temperature, AcOEt was added. The mixture was filtered through a glass filter, and the filtrate was separated. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, dried in vacuo, and purified by column chromatography to give the corresponding product **8**.

[14] Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210.

[15] (a) For the synthesis of candesartan, see: Kubo, K.; Kohara, Y.; Imamiya, E.; Sugiura, Y.; Inada, Y.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem*. **1993**, *36*, 2182−2195. (b) For the synthesis of losartan, see: Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem*. **1991**, *34*, 2525−2547. (c) For the synthesis of L-158809, see: Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem*. **1991**, *34*, 2919−2922.