Polymer-Incarcerated Palladium with Active Phosphine as Recoverable and Reusable Pd Catalyst for the Amination of Aryl Chlorides

Takeshi Inasaki, Masaharu Ueno, Shinpei Miyamoto, Shū Kobayashi*

Department of Chemistry, School of Science and Graduate School of Pharmaceutical Sciences, The University of Tokyo,
The HFRE Division, ERATO, Japan and Science Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 1130033, Japan
Fax +81(3)56840634; E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp

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Abstract: A new type of polymer-incarcerated (PI) Pd catalyst bearing an active phosphine ligand has been developed. This catalyst was prepared easily according to a conventional PI method (microencapsulation and cross-linking of polymer chains), and TEM images of PI Pd showed the formation of small Pd clusters dispersed on the polymer support without formation of Pd aggregates. The catalyst showed high activity in amination reactions of various aryl chlorides with amines. The reactions proceeded without addition of any external phosphine ligands, and the catalyst was recovered quantitatively by simple filtration and reused at least three times without loss of activity.

Key words: heterogeneous catalysis, polymer, aminations, palladium, aryl chlorides

Palladium-catalyzed coupling reactions are known as one of the most valuable tools for C–C, C–N and C–O bond formation and have been widely used in a variety of transformations in organic synthesis.[1] Recently these systems have attracted a great deal of attention from an economic and environmental point of view and immobilization of Pd catalysts on inorganic solid supports[2] or organic polymers[3] has been widely studied. Among these, heterogeneous catalysts for Suzuki–Miyaura coupling[4] or Heck reaction[3d,5] have been of great interest. On the other hand, to the best of our knowledge, only limited numbers of examples of heterogeneous arylamination reactions have been reported;[6] in particular, investigation of the amination of aryl chlorides using immobilized Pd catalysts is very limited, even though these reactions have found widespread use in many areas of organic synthesis.

In previous papers, we have demonstrated the polymer-incarcerated (PI) method for immobilization of palladium catalysts onto polystyrene-based polymers.[7] The heterogeneous PI palladium catalysts obtained are highly active for hydrogenation and carbon–carbon bond-forming reactions. These catalysts can be recovered quantitatively by simple filtration and reused several times without loss of activity. Among them, phosphinated PI Pd catalysts, whose polymer supports contain diphenylphosphino groups, are highly active for Suzuki–Miyaura coupling reactions without addition of external phosphine ligands.[7c] In this paper, we report a new type of phosphinated PI Pd catalyst that contains more active phosphine ligand, and its application to amination reactions of aryl chlorides.

Within the first generation Pd catalysis of aromatic amination reactions, triarylphosphine-based ligands[8] were often employed for their easy availability and stability towards oxidation. However, the reactions are normally conducted at high temperatures and aryl chlorides are unreactive as substrates, mainly because of retardation due to a slow oxidative addition step. Accordingly, a phosphinated PI Pd on diphenylphosphine basis displayed only low activity with aryl chloride substrates; hence a more active phosphine had to be incorporated.

In general bulky electron-rich phosphines were shown to enable amination reactions of aryl chlorides under mild conditions,[9] with dialkylbiphenylphosphines being among the most versatile due to their air stability[10] and high catalytic activity of their Pd complexes. These ligands have been extensively studied by Buchwald's group, and they showed that amination of aryl chlorides proceeded in high yields by using these ligands under mild homogeneous conditions.[9a–f]

We first prepared copolymer **1**, and PI Pd **2** was prepared from $Pd(OAc)_2$ and **1** according to a conventional PI method (microencapsulation and cross-linking of polymer chains) as reported previously (Scheme 1).[11] ICP analysis showed that palladium was loaded onto the polymer support nearly quantitatively (93%). In a previous report, we have shown that immobilization of palladium onto polymer supports was not successful in the absence of additives such as alkali metal salts.[7d] The fact that these additives were not necessary in the present case indicates that the phosphine moieties incorporated into the polymer support acted as stabilizers for Pd immobilization. In addition, we believe that the phosphine moieties play a role in the reduction of the Pd(II) salt, since some phosphines were observed to be oxidized to the corresponding phosphine oxides during the preparation of the catalyst.

The PI Pd **2**[12] thus prepared was then analyzed by transmission electron microscopy (TEM). Judging from the magnified TEM image of PI Pd **2** (Figure 1), small Pd clusters were dispersed on the polymer support without formation of Pd aggregates (TEM detection limit: ca. 1 nm). The formation of extremely small Pd clusters might be due to a stabilization effect of the polymer and the phosphine moieties.

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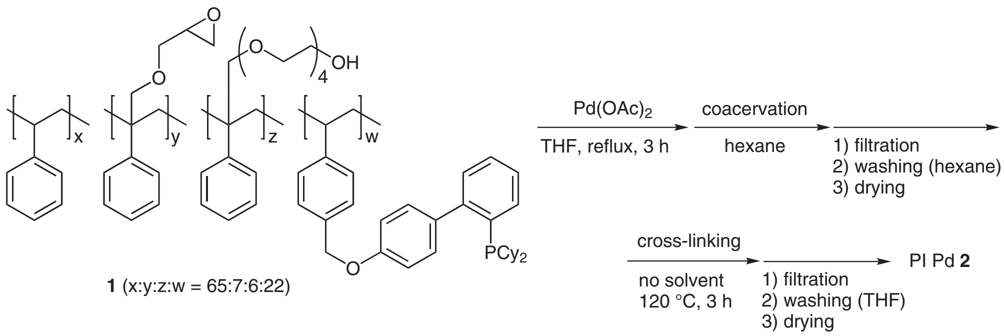


Scheme 1 Preparation of polymer incarcerated palladium (PI Pd **2**) with active phosphine ligands

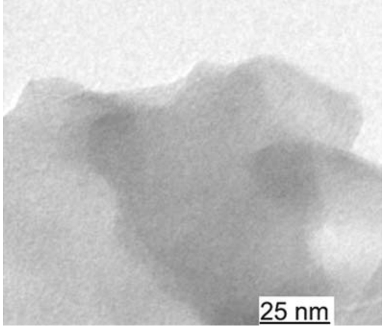
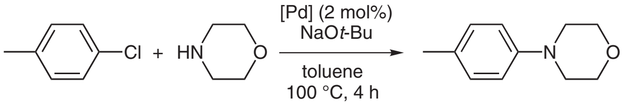
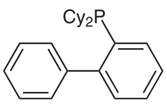


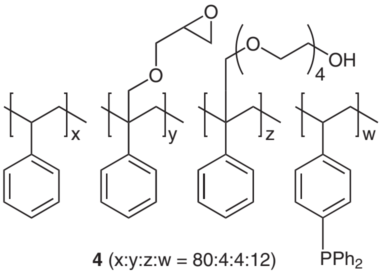
Figure 1 TEM image of PI Pd **2**

Table 1 Comparison of Catalytic Activity



Entry	'Pd'	Additive (4 mol%)	Yield (%)[a]	Leaching (%)[b]
1	Pd/C	–	0	0.03
2	Pd/C		trace[c]	0.23
3	PI Pd **3**[d]	–	0	0.11
4	PI Pd **2**	–	87	0.87

[a] Isolated yield.
[b] Determined by ICP analysis.
[c] Trace < 1%.
[d] PI Pd **3** was prepared from copolymer **4** by the previously reported method.[7c] The loading amount of the palladium was 0.23 mmol/g.



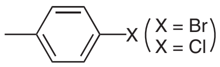
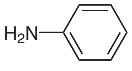
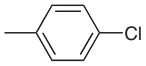
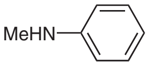
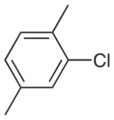
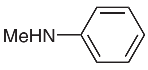
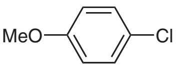
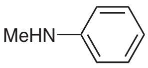
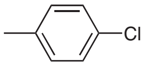
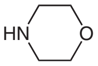
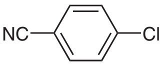
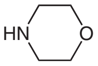
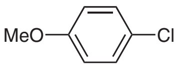
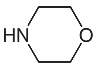
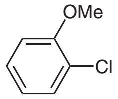
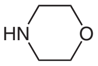
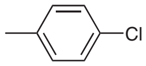
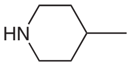
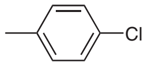
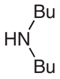
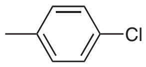
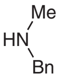
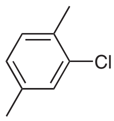
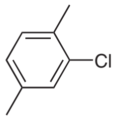
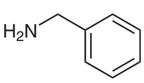
With the catalyst in hand we turned our attention to the investigation of its catalytic activity. First, PI Pd **2** was compared with common heterogeneous catalysts or the previously reported phosphinated PI Pd catalyst[7c] in the coupling reaction of morpholine and 4-chlorotoluene (Table 1). As shown, use of Pd/C, a commonly used heterogeneous palladium catalyst, did not promote the reaction at all (entry 1). Addition of *o*-(dicyclohexylphosphino)biphenyl to Pd/C as an external phosphine ligand resulted in the formation of trace amounts of the desired product (entry 2). As expected, PI Pd **3** with diphenylphosphino groups did not yield Pd catalysts with an appropriate activity for oxidative addition to a chloro–arene bond (entry 3). However on using PI Pd **2**, we were delighted to find that the coupling reaction proceeded in good yield (entry 4). Thus it is noted that the PI method gave a catalyst system that showed high catalytic activity and low Pd leaching in the amination of an aryl chloride.

Next, we surveyed the substrate scope of PI Pd **2**-catalyzed amination reactions (Table 2). Using PI Pd **2** as a catalyst, aryl chlorides could be successfully utilized as substrates. In the reactions using both electron-rich and electron-deficient aryl chlorides, the corresponding arylamine products were obtained in high yields. It is noteworthy that the detected leaching values of palladium were very low. In addition, the reactions proceeded effectively using lower catalyst loadings (0.4 mol% Pd, entries 3 and 7). As for amine substrates, aromatic primary amines, aromatic secondary amines, aliphatic primary amines and aliphatic secondary amines were all coupled efficiently with various aryl halides in good yields. However, in the cases of reactions of aliphatic primary amines in toluene (entries 14 and 16), the leaching values of palladium were much higher than those with other substrates. We supposed that this was due to a slower reductive elimination reaction in the case of primary amines, which were less bulky than secondary amines, and reasoned that the slower the rate of the reductive elimination, the longer the lifetime of palladium(II) species such as arylpalladium(II) amides. It is thought that PI catalysts were able to stabilize metal species onto their support by electronic interaction between vacant orbitals of metal species and π-electrons of benzene rings. However, unlike palladium(0) species, palladium(II) species are more susceptible to ionic interaction of anionic species like *tert*-butoxide ions, rather than electronic effect of benzene rings. For this reason, it was assumed that palladium(II) species were leached from the support more easily than palladium(0) species under typical basic conditions of arylamination reactions.

For the reason mentioned above, we thought that acceleration of the rate of the reductive elimination would suppress the leaching of palladium. In order to examine the possibility of accelerating the catalytic cycle including the reductive elimination step, we selected another solvent system, *p*-dioxane–*tert*-butyl alcohol, which led to enhanced reaction rates and conversion.[9d] In this way, when the reactions were conducted by method C (Table 2), the reactions proceeded within two hours in good yields, and the leaching values of palladium were greatly reduced compared to those observed with method B.

Finally, we examined the reusability of the PI Pd catalyst. As shown in Table 3, the PI Pd could be recovered quantitatively by simple filtration and reused at least three times. The catalytic activity and the reaction rate were typically unaffected and the reactions were complete within four hours even in the third consecutive reaction. Furthermore, it was confirmed by ICP analysis that palla-

Table 2 Phosphinated PI Pd-Catalyzed Amination Reactions[a,12]

Entry	ArCl	Amine	PI Pd **2** (mol%)	Method[b]	Time (h)	Yield (%)[c]	Pd leaching (%)[d]
1			2	B	8	95	0.96
2			2	B	8	97	0.56
3			0.4	A	24	77	0.84
4			2	B	8	92	0.12
5			2	B	8	89	nd
6			2	A	24	92	0.64
7			0.4	A	24	91	1.10
8			2	A	24	92	0.74
9			2	A	24	84	0.32
10			2	B	8	73	0.19
11			2	B	24	94	0.26
12			2	B	24	73	0.71
13			2	B	24	96	nd
14		$H_2NC_6H_{13}$	2	B	8	92	9.88
15			2	C	2	92	2.79
16			2	B	8	97	8.92
17			2	C	2	89	1.04

[a] Reaction conditions: aryl halide (1.0 equiv), amine (2.0 equiv), *t*-BuONa (2.3 equiv).

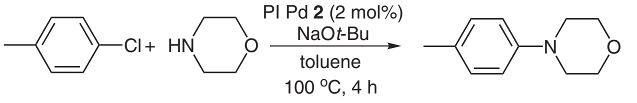
[b] Method A: toluene, 100 °C. Method B: toluene, 110 °C. Method C: *p*-dioxane–*t*-BuOH (3:1), 100 °C.

[c] Isolated yield.

[d] Determined by ICP analysis; nd = not determined (<0.07%).

dium leaching was low in each case. In addition, it was noted that the leaching values decreased gradually in each successive reaction, and in particular the leaching after the third reaction approached the limit of determination (0.07%).

Table 3 Recovery and Reuse of PI Pd **2**



Run	First	Second	Third
Yield (%)[a]	87	89	95
Pd leaching (%)[b]	1.50	0.42	0.09

[a] Isolated yield.

[b] Determined by ICP analysis.

In summary, we have developed a new type of PI Pd catalyst that contains active phosphine ligands. This catalyst showed high activity in amination reactions of various aryl chlorides with amines. The reactions proceeded without addition of any external phosphine ligands, and the catalyst could be recovered quantitatively by simple filtration and reused at least three times without loss of activity. We believe that this report has shown the first efficient amination of aryl chlorides using an immobilized Pd catalyst based on the PI method.

References and Notes

(1) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, **1995**. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley and Sons: New York, **2002**. (c) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.

(2) (a) Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (b) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077. (c) Kim, N.; Kwon, M. S.; Park, C. M.; Park, J. *Tetrahedron Lett.* **2004**, *45*, 7057. (d) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.

(3) (a) Lin, C.-A.; Luo, F.-T. *Tetrahedron Lett.* **2003**, *44*, 7565. (b) Luo, F.-T.; Xue, C.; Ko, S.-L.; Shao, Y.-D.; Wu, C.-J.; Kuo, Y.-M. *Tetrahedron* **2005**, *61*, 6040. (c) Chauhan, B. P.; Rathore, J. S.; Chauhan, M.; Krawicz, A. *J. Am. Chem. Soc.* **2003**, *125*, 2876. (d) Biffs, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 249.

(4) (a) Tsang, C.-W.; Baharloo, B.; Riendl, D.; Yam, M.; Gates, D. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 5682. (b) Li, J.-H.; Hu, X.-C.; Xie, Y.-X. *Tetrahedron Lett.* **2006**, *47*, 9239. (c) He, H. S.; Yan, J. J.; Shen, R.; Zhuo, S.; Toy, P. H. *Synlett* **2006**, 563. (d) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2003**, *44*, 2379.

(5) (a) Yamada, Y. M. A.; Tabata, H.; Takahashi, H.; Ikegami, S. *Synlett* **2002**, 2031. (b) Zhang, Z.; Wang, Z. *J. Org. Chem.* **2006**, *71*, 7485. (c) Singh, G.; Bali, S.; Singh, A. K. *Polyhedron* **2006**, *26*, 897. (d) Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990.

(6) (a) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820. (b) Guinó, M.; Hii, K. K. *Tetrahedron Lett.* **2005**, *46*, 7363. (c) Leyva, A.; García, H.; Corma, A. *Tetrahedron* **2007**, *63*, 7097. (d) Nishio, R.; Sugiura, M.; Kobayashi, S. *Chem. Asian J.* **2007**, *2*, 983. (e) To the best of our knowledge reports on the amination of aryl chlorides using immobilized Pd catalysts have been very limited, and in no case, except in ref. 6d, was information relating to Pd leaching reported. On the other hand, Lipshutz et al. reported Ni/C catalysis for the amination: Lipshutz, B. H.; Ueda, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 4492. (f) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem.* **2003**, *68*, 1177. (g) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190.

(7) Polymer incarcerated catalysts: (a) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412. (b) Takeuchi, M.; Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 13096. (c) Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4831. (d) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375. (e) Okamoto, K.; Akiyama, R.; Yoshida, H.; Yoshida, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 2125. (f) Kobayashi, S.; Miyamura, H.; Akiyama, R.; Ishida, T. *J. Am. Chem. Soc.* **2005**, *127*, 9251.

(8) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(9) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (e) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413. (f) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (g) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (h) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (i) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371. (j) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028.

(10) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096.

(11) Microencapsulated catalysts: (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.

(12) **Preparation of Copolymer 1**: Styrene (2.24 g, 21.6 mmol), 2-[(2-phenylallyloxy)methyl]oxirane (630 mg, 3.32 mmol), tetraethyleneglycol mono-2-phenyl-2-propenyl ether (1.03 g, 3.32 mmol), dicyclohexyl-2-[4′-(4-styrylmethoxy)phenyl]phenylphosphine (2.40 g, 4.97 mmol) and 2,2′-azobis(isobutyronitrile) (54.4 mg, 0.332 mmol) were mixed in $CHCl_3$ (4.2 mL). The mixture was stirred at reflux for 27 h under argon and was then cooled to r.t. The resulting polymer solution was poured slowly into hot deoxygenated hexane and the precipitated polymer was collected by filtration and washed with hexane. The polymer so obtained was dissolved in $CHCl_3$, and the resulting solution was poured slowly into MeCN. The precipitated polymer was filtered and washed with MeCN several times and dried in

vacuo to afford the desired copolymer **1** (3.67 g, 58%). The molar ratio of the monomer was determined by ^{1}H NMR analysis {styrene–2-[(2-phenylallyloxy)methyl]oxirane–tetraethyleneglycol mono-2-phenyl-2-propenyl ether–dicyclohexyl-2-[4′-(4-styrylmethoxy)phenyl]phenylphosphine = 65:7:6:22}. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –12.9, 48.5. Mw: 11520, Mn: 8470, Mw/Mn = 1.36 (GPC).

Preparation of PI Pd 2: Copolymer **1** (3.66 g) was dissolved in THF (20 mL) and the solution was refluxed under argon. A solution of palladium acetate (177 mg, 0.79 mmol) in THF (20 mL) was added dropwise to the polymer solution, and the reaction mixture was refluxed under argon for 3 h, and then cooled to r.t. Hexane (80 mL) was then slowly added to the mixture. The mixture was left to stand at r.t. for 1 h, and the precipitated catalyst capsules were washed with hexane several times and dried at r.t. in vacuo. Next, the catalyst capsules were stirred at 120 °C for 4 h under reduced pressure to cross-link the microencapsulated palladium. The cross-linked solid was then washed with THF, toluene and hexane, and then dried in vacuo to give the polymer incarcerated palladium (PI Pd **2**, 3.54 g); loading value of palladium metal: 0.19 mmol/g; the ratio of phosphorus atoms in the polymer to palladium atoms (P/Pd): 5.71.

Typical Experimental Procedure for Phosphinated PI Pd-Catalyzed Amination (Table 2, entry 2): 4-Chlorotoluene (76.0 mg, 0.6 mmol), aniline (111.8 mg, 1.2 mmol), PI Pd **2** (63.5 mg, 0.012 mmol, 2 mol%), and *t*-BuONa (132.6 mg, 1.38 mmol) were combined in toluene (2 mL) under argon. The mixture was stirred for 8 h at reflux. After cooling to r.t., the mixture was diluted with hexane (6 mL), filtered and rinsed with hexane and toluene. The combined organic layers were concentrated in vacuo, and the volume of the residue was adjusted to 50 mL using hexane. The solution was then divided into two halves.

One portion was placed in a 50-mL test tube and the solvent was removed by evaporation. To this mixture was added sulfuric acid (1.0 mL), and the mixture was heated at 180 °C. Then nitric acid (0.5 mL) was added dropwise to decompose the organic residue. After cooling to r.t., the solution was adjusted to 25 mL by H_2O and then the amount of palladium metal was measured by ICP analysis to determine the leaching of palladium.

The other portion of the reaction mixture was taken, and the solvents were removed by evaporation. The residual crude product was purified by preparative TLC on silica gel (hexane–EtOAc, 10:1) to afford *N*-(4-methylphenyl)aniline (53.3 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 5.58 (s, 1 H), 6.87 (t, J = 7.6 Hz, 1 H), 6.99–7.02 (m, 4 H), 7.08 (d, J = 8.0 Hz, 1 H), 7.24 (dd, J = 7.6, 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 116.9, 118.9, 120.3, 129.3, 129.9, 130.9, 140.3, 143.9.

Typical Recycling Procedures: 4-Chlorotoluene (144.4 mg, 1.14 mmol), morpholine (197.6 mg, 2.27 mmol), PI Pd **2** (120.4 mg, 0.023 mmol, 2 mol%), and *t*-BuONa (250.6 mg, 2.61 mmol) were combined in toluene (3.8 mL) under argon. The mixture was stirred for 4 h at 100 °C. After cooling to r.t., the mixture was diluted with hexane (10 mL) and filtered. The collected catalyst was further washed with hexane and toluene, and then filtered. The combined organic washing solutions were subjected to the procedures described above for product isolation and detection of palladium leaching. The catalyst was rinsed with H_2O and MeOH and was then dried in vacuo. The catalyst was reused without any other purification step.