

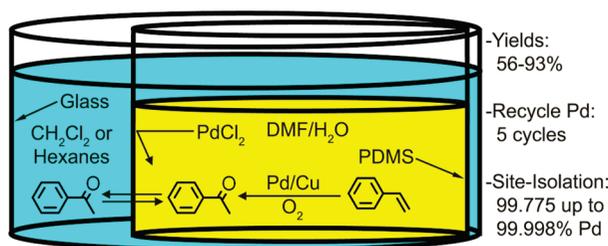
## Site-Isolation and Recycling of PdCl<sub>2</sub> using PDMS Thimbles

A. Lee Miller II and Ned B. Bowden\*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

ned-bowden@uiowa.edu

Received March 17, 2009



Macroscopic thimbles composed of polydimethylsiloxane (PDMS) were used to site-isolate PdCl<sub>2</sub> from the products of Wacker–Tsuji oxidations and Pd-mediated homocouplings. The reactions were completed on the interior of hollow thimbles, and the organic products were isolated by their selective flux to the exterior of the thimbles. Although organic molecules had high flux through the walls of the thimbles, PdCl<sub>2</sub> remained encapsulated as a result of its polar structure that rendered it insoluble in PDMS. In two examples, less than 0.002% of the PdCl<sub>2</sub> added to the interior of the thimble partitioned to the exterior; thus, over 99.998% remained encapsulated on the interior of the thimble. Because it was encapsulated, this catalyst was readily recycled five times for the Wacker–Tsuji oxidation of styrene. A sequential reaction was also completed where *p*-methylstyrene was oxidized to 4'-methyl-acetophenone by PdCl<sub>2</sub> on the interior of a thimble and then fluxed to the exterior to react with phenylmagnesium bromide to yield 1-phenyl-1-*p*-tolyl-ethanol. This method site-isolated PdCl<sub>2</sub> catalysts without requiring them to be rendered heterogeneous, the addition of exogenous ligands, or any modifications to the catalyst. The catalyst was site-isolated by affecting its environment rather than by altering its ligand structure.

### Introduction

Palladium has been called the “magic catalyst” in recognition of the many important and industrially useful reactions it catalyzes.<sup>1</sup> This catalyst is used in the synthesis of C–C, C–O, C–S, and C–N bonds that are challenging, if not impossible, to synthesize with other metals. The importance of these reactions is evident from the large number of pharmaceutical

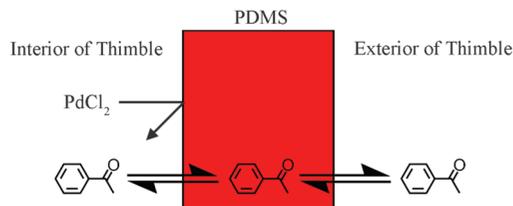
products and bulk chemicals that use Pd catalysts in their synthesis including prosulfuron (a herbicide), 2-ethylhexyl-*p*-methoxycinnamate (a UV-B sunscreen agent), vitamin A, and vitamin B<sub>2</sub>-riboflavin.<sup>2</sup> The synthesis of many of these products would be greatly improved through the expanded use of Pd in industry and academia. Two critical examples of these reactions include the Wacker–Tsuji oxidation that is used in the synthesis of both acetaldehyde and acetone and numerous Pd coupling reactions of aryl halides and boronic acids.<sup>3,4</sup> Despite the tremendous synthetic utility of this catalyst, its high cost and

(1) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 1995; pp 125–527. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (d) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613–632. (e) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547–4554. (f) Lakshman, M. K. *J. Organomet. Chem.* **2002**, *653*, 234–251. (g) Mamane, V. *Targets Heterocycl. Syst.* **2006**, *10*, 197–231. (h) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838–2840. (i) Wuertz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523–1533. (j) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (k) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555–1564. (l) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (m) Hartwig John, F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (n) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (o) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440–1449. (p) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221–229. (q) Zimmer, R.; Dinesh, C. U.; Nandanani, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125.

(2) (a) Balasubramanian, M. *Tetrahedron Org. Chem. Ser.* **2007**, *26*, 587–620. (b) Beller, M.; Zapf, A.; Magerlein, W. *Chem. Eng. Technol.* **2001**, *24*, 575–582. (c) Clement, N. D.; Routaboul, L.; Grotevendt, A.; Jackstell, R.; Beller, M. *Chem.–Eur. J.* **2008**, *14*, 7408–7420. (d) Doucet, H.; Hierso, J.-C. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 672–690. (e) Jackstell, R.; Harkal, S.; Jiao, H.; Spannenberg, A.; Borgmann, C.; Roettger, D.; Nierlich, F.; Elliot, M.; Niven, S.; Cavell, K.; Navarro, O.; Viciu, M. S.; Nolan, S. P.; Beller, M. *Chem.–Eur. J.* **2004**, *10*, 3891–3900. (f) Schils, D.; Stappers, F.; Solberghe, G.; van Heck, R.; Coppens, M.; Van den Heuvel, D.; Van der Donck, P.; Callewaert, T.; Meeussen, F.; De Bie, E.; Eersels, K.; Schouteden, E. *Org. Process Res. Dev.* **2008**, *12*, 530–536. (g) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (h) Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585–604.

low tolerance levels in pharmaceutical products limit its applications. For instance, the dietary intake of Pd is approximately  $<1.5$  to  $15 \mu\text{g day}^{-1}$ , which translates into typical loadings of less than 10 ppm for active pharmaceutical ingredients that varies based on the amount of drug that is consumed.<sup>5</sup> This requirement imposes extensive cleaning requirements of products to reach these levels and limits the potential uses of Pd.<sup>6</sup>

Most methods to site-isolate Pd catalysts so they may be recycled and not contaminate the product involve transformation of a homogeneous Pd catalyst into a heterogeneous catalyst, incarceration of Pd into polystyrene beads, encapsulation in sol gels, or modification of its structure by attachment to a polymer.<sup>7,8</sup> The key limitation to site-isolating Pd catalysts is that they may be in the homogeneous and colloidal states in the same reaction mixture. For instance, Pd can leach from a heterogeneous surface to form a homogeneous catalyst or fully dissociate from a polymer to form colloidal Pd. Recently, Rothenberg demonstrated that Pd nanoparticles are not the true catalytic species; rather, homogeneous Pd that leached from these particles was the active catalyst.<sup>9</sup> In related work by Weck, the Pd catalyst in Mizoroki–Heck coupling reactions was formed from decomposition of the original Pd species to a catalytically active, soluble Pd(0) catalyst.<sup>8</sup> The fluxional nature of the ligands around Pd and its ability to be present in the colloidal and monomer forms in the same reaction vessel makes



**FIGURE 1.** Pd catalysts remained encapsulated by PDMS thimbles because of their low solubility in PDMS, but organic molecules had high flux through the walls.

site-isolation of these catalysts a challenge and necessitates a different approach that focuses less on the catalyst and more on its environment.

Here, we report a new method for the site-isolation of homogeneous Pd catalysts that does not require modification of their ligand structures and is not adversely affected by the homogeneous/colloid fluxional nature of the catalyst. The focus of this work is not on changing the catalyst; rather, the focus is on its environment and how that environment can be used to site-isolate the catalyst. Commercially available Pd catalysts were used and site-isolated by encapsulation within hollow macroscopic thimbles composed of polydimethylsiloxane (PDMS).<sup>10</sup> These thimbles had widths of 2 cm, heights of 5 cm, and walls that were 100–200  $\mu\text{m}$  thick; dozens of these thimbles could be fabricated in a day. The catalysts used in this study were based on “ligandless” PdCl<sub>2</sub> that are highly polar and soluble only in protic solvents. The catalysts were added to the interiors of the thimbles and did not flux to the exterior, but organic molecules had high flux to the exterior. The reason for the difference in flux was the hydrophobic nature of PDMS; PdCl<sub>2</sub> was simply not soluble in this polymer due to its highly polar structure, but organic molecules were soluble in it (Figure 1). This simple difference in solubility required Pd catalysts to remain encapsulated while organic molecules were free to flux through the walls of the thimble. In this paper, we will describe a method for site-isolation that allowed the Pd catalyst to be recycled at levels up to  $>99.998\%$ , products to be isolated that possess low levels of Pd (less than 2.1 ppm), and otherwise impossible sequential reactions to be developed.

## Results and Discussion

Several examples of the Wacker–Tsuji oxidation of olefins and homocoupling of arylboronic acids were completed on the interior of PDMS thimbles (Table 1). Standard conditions were used with a variety of different solvents to demonstrate that the thimbles were compatible with each of them. Each reaction went to quantitative conversions with lower yields found for the Wacker–Tsuji oxidations than the coupling reactions. These low yields are common for this reaction as a result of byproduct formation and represent limitations of the reaction rather than problems with the thimbles.<sup>4</sup> This method did not place any limitations on the catalysts or reagents. For instance, the homocoupling reactions required the addition of *p*-toluenesulfonyl chloride, and the addition of this reagent was readily accommodated by this method. No concern for the reactive state (homogeneous versus colloidal) of the Pd catalyst was necessary because the reaction was run under standard conditions.

(3) (a) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829. (b) Kabalka, G. W.; Wang, L. *Tetrahedron Lett.* **2002**, *43*, 3067. (c) Pan, C.; Liu, M.; Zhang, L.; Wu, H.; Ding, J.; Cheng, J. *Catal. Commun.* **2008**, *9*, 508. (d) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed.* **1962**, *74*, 93–102. (e) *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; Wiley-Interscience: Hoboken, 2007; pp 309–326. (f) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4321–4323. (g) Thadani Avinash, N.; Rawal Viresh, H. *Org. Lett.* **2002**, *4*, 4321–3. (h) Tietze, L. F.; Kinzel, T. *Pure Appl. Chem.* **2007**, *79*, 629–650.

(4) (a) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907. (b) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903. (c) Trend, R. M.; Ramtohl, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.

(5) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(6) (a) Bullock, K. M.; Mitchell, M. B.; Toczko, J. F. *Org. Process Res. Dev.* **2008**, *12*, 896. (b) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, J. H. H. *Org. Process Res. Dev.* **2007**, *11*, 406. (c) Konigsberger, K.; G.-P., C.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Pepic, O.; Bracklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733.

(7) (a) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412. (b) Kappe, O.; Desai, B. *Top. Curr. Chem.* **2004**, *242*, 177. (c) Schmoger, C.; Szuppa, T.; Tied, A.; Schneider, F.; Stolle, A.; Ondruschka, B. *ChemSusChem* **2008**, *1*, 339. (d) Tucker, C. E.; de Vries, J. G. *Top. Catal.* **2002**, *19*, 111. (e) Papp, A.; Miklos, K.; Forgo, P.; Molnar, A. *J. Mol. Catal. A: Chem.* **2005**, *229*, 107. (f) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375–378. (g) Nishio, R.; Sugiura, M.; Kobayashi, S. *Chem.–Asian J.* **2007**, *2*, 983–995. (h) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871–2873. (i) Heinrichs, B.; Noville, F.; Schoebrechts, J.-P.; Pirard, J.-P. *J. Catal.* **2003**, *220*, 215–225. (j) Polshettiwar, V.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron Lett.* **2007**, *48*, 5363–5366. (k) Talhami, A.; Penn, L.; Jaber, N.; Hamza, K.; Blum, J. *Appl. Catal., A* **2006**, *312*, 115–119. (l) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Karbass, N.; Luis, S. V.; Puzary, A.; Sans, V. *Tetrahedron Lett.* **2006**, *47*, 2311–2314. (m) Bai, L.; Wang, J.-X. *Adv. Synth. Catal.* **2008**, *350*, 315–320. (n) Bolton, K. F.; Cauty, A. J.; Deverell, J. A.; Guijt, R. M.; Hilder, E. F.; Rodemann, T.; Smith, J. A. *Tetrahedron Lett.* **2006**, *47*, 9321–9324. (o) Doherty, S.; Knight, J. G.; Betham, M. *Chem. Commun.* **2006**, 88–90. (p) Hershberger, J. C.; Zhang, L.; Lu, G.; Malinikova, H. C. *J. Org. Chem.* **2006**, *71*, 231–235. (q) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065–12073. (r) Sulman, E.; Matveeva, V.; Doluda, V.; Nicoshvili, L.; Bronstein, L.; Valetsky, P.; Tsvetkova, I. *Top. Catal.* **2006**, *39*, 187–190. (s) Gaikwad, A. V.; Boffa, V.; ten Elshof, J. E.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5407–5410.

(8) (a) Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *46*, 1865. (b) Yu, K.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161.

(9) (a) Gaikwad, A. V.; Holuigue, A.; Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Chem.–Eur. J.* **2007**, *13*, 6908–6913. (b) Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2886–2890.

(10) (a) Miller, A. L., II.; Bowden, N. B. *Adv. Mater.* **2008**, *20*, 4195. (b) Mwangi, M. T.; Runge, M. B.; Hoak, K. M.; Schulz, M. D.; Bowden, N. B. *Chem.–Eur. J.* **2008**, *14*, 6780. (c) Runge, M. B.; Mwangi, M. T.; Miller, A. L., II.; Perring, M.; Bowden, N. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 935.

**TABLE 1. Wacker–Tsujii Oxidations and Homocoupling Reactions with PdCl<sub>2</sub> Catalysts**

$$\text{R}-\text{CH}=\text{CH}_2 \xrightarrow[\text{Solvent}]{\text{PdCl}_2/\text{CuCl}/\text{O}_2} \text{R}-\text{C}(=\text{O})-\text{CH}_3$$

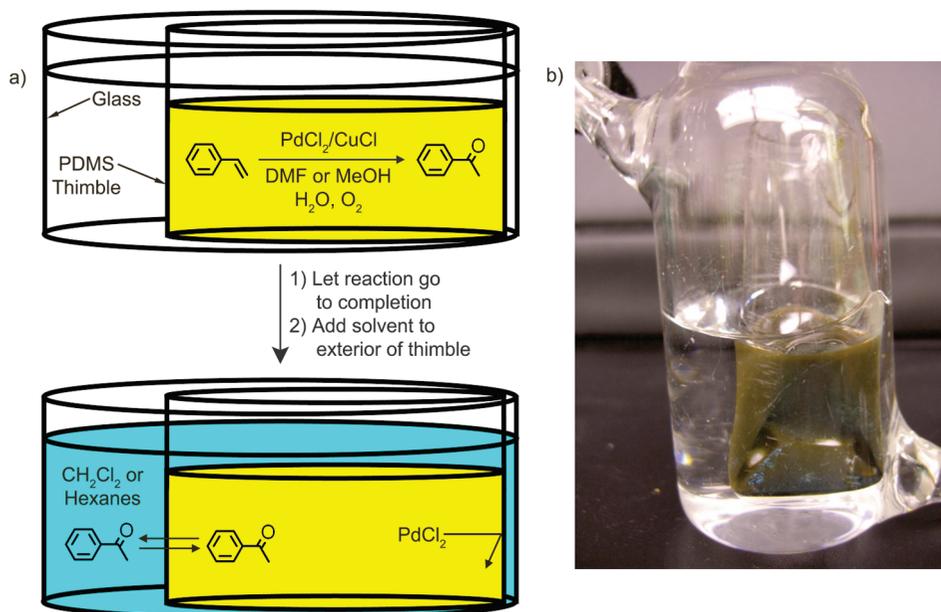
**Wacker–Tsujii Oxidation**

$$\text{R}-\text{C}_6\text{H}_4-\text{B}(\text{OH})_2 \xrightarrow[\text{p-TsCl/Solvent}]{\text{PdCl}_2/\text{Na}_2\text{CO}_3} \text{R}-\left(\text{C}_6\text{H}_4\right)_2$$

**Pd-Mediated Homocoupling**

Substrate	Reaction Solvent	Extracting Solvent	Product	Product Number	<sup>a</sup> Yield (%)
	MeOH/H <sub>2</sub> O	Hexanes		1	<sup>b</sup> 73
	DMF/H <sub>2</sub> O	Hexanes		2	<sup>c</sup> 56
	H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>		3	<sup>d</sup> 93
	EtOH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>		4	<sup>d</sup> 89
	EtOH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>		5	<sup>d</sup> 93

<sup>a</sup> Isolated yield determined after column chromatography. <sup>b</sup> 0.05 equiv of PdCl<sub>2</sub> used. <sup>c</sup> 0.1 equiv of PdCl<sub>2</sub> used. <sup>d</sup> 0.03 equiv of PdCl<sub>2</sub> used.



**FIGURE 2.** (a) Wacker–Tsujii oxidation inside a PDMS thimble followed by addition of solvent to the exterior to allow the product to flux through the walls of the thimble. (b) Optical micrograph of the thimble with the Pd and Cu catalysts on the interior and solvent on the exterior. The green catalyst on the interior did not flux to the exterior.

To isolate the products on the exterior of the thimbles while keeping the Pd on the interior, 25 mL of solvent was added to the exterior of the thimble after each reaction was complete (Figure 2). The product partitioned to the exterior and was readily isolated, but the Pd catalysts remained on the interior. To ensure complete isolation, the product was extracted from the interior with two to three batches of solvent on the exterior of the thimbles.

It is critically important that Pd catalysts be recycled and site-isolated from the product of a reaction, and our method allowed both of these requirements to be met. In separate experiments, we completed the Wacker–Tsujii oxidation of styrene and the homocoupling of phenylboronic acid on the interior of PDMS

thimbles. The product was extracted from the thimbles by the addition of 25 mL of solvent on the exterior and the amount of Pd on the exterior was measured by inductively coupled plasma-mass spectrometry (ICP-MS; Table 2). ICP-MS measured the concentration of Pd, but the catalyst used in these reactions was PdCl<sub>2</sub>. The values shown in Table 2 reflect the concentrations of Pd (not PdCl<sub>2</sub>) because of the instrument used to find its concentrations and the fluxional nature of the Pd catalysts that result in multiple Pd species present at the same time. To find the ratio of Pd/product, the isolated yields from Table 1 for these reactions were used to find the amount of product on the exterior of the thimbles.

TABLE 2. ICP-MS Data To Demonstrate Site-Isolation of Pd

entry	<sup>a</sup> Method	reaction solvent	extracting solvent	exterior ppm (Pd/ product) <sup>b</sup>	Pd site-isolated (%)
1a	PDMS	DMF/H <sub>2</sub> O	hexanes	<2.1	>99.998
1b	L-L	DMF/H <sub>2</sub> O	hexanes	49.2	99.959
1c	extract	DMF/H <sub>2</sub> O	hexanes	21.0	99.983
2a	PDMS	MeOH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	<2.2	>99.998
2b	L-L	MeOH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	32.3	99.973
2c	extract	MeOH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	416.8	99.655
3a	PDMS	MeOH/H <sub>2</sub> O	hexanes	16.1	99.985
3b	L-L	MeOH/H <sub>2</sub> O	hexanes	28.2	99.977
3c	extract	MeOH/H <sub>2</sub> O	hexanes	32.1	99.973
4a	PDMS	DMF/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	277.7	99.775
4b	L-L	DMF/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	1173	99.026
4c	extract	DMF/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	9099	92.980
5a	<sup>c</sup> PDMS	H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	13.8	99.968
5b	<sup>c</sup> L-L	H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	1685	96.216
5c	<sup>c</sup> extract	H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	1073	97.592
6	PDMS	DMF/H <sub>2</sub> O	DMF/H <sub>2</sub> O	12.5	99.988

<sup>a</sup> Three different extractions methods were indicated and performed by either the addition of solvent to the exterior of the thimble (PDMS), by liquid–liquid extractions from reactions completed in glass vials with added water (L-L), or by extracting directly from the reaction mixture following reactions in glass vials with no additional water (extract).

<sup>b</sup> Based on isolated yields of corresponding product from Table 1.

<sup>c</sup> These entries were measured after the Pd-mediated homocoupling of phenylboronic acid; all other entries are measured after the Wacker–Tsuji oxidation of styrene.

In two sets of control experiments, these reactions were completed under identical conditions but in glass vials in the absence of PDMS thimbles. In the first set of control experiments, the products were isolated by liquid–liquid extractions after the addition of 50 mL of water to fully dissolve the Pd catalyst followed by three extractions with organic solvents as listed in Table 2. In a second set of control experiments, the reactions were completed in glass vessels with the solvents indicated in Table 2, and the products were extracted without the addition of excess water. In both sets of experiments, a variety of solvents were tested to complete the reaction and extract the product.

It is clear that extractions with thimbles were more successful at site-isolating the Pd catalysts than those without thimbles. In fact, for homocoupling reactions approximately 2 orders of magnitude more Pd was found in the product with liquid–liquid extractions rather than with extractions using PDMS thimbles (entries 5a–c). In two examples (entries 1a and 2a), the amount of Pd was below detection limits for the extraction experiments with PDMS thimbles, but they were over a magnitude higher for traditional liquid–liquid extractions. In experiments with PDMS thimbles, up to >99.998% of the Pd was site-isolated on the interior, and even in the worst example of site-isolation 99.775% of the Pd remained on the interior of the thimbles.

To demonstrate that the Pd catalysts did not flux through the thimbles because of the presence of PDMS rather than the difference in solvents used on the interior and exterior of the thimbles, we completed an experiment with DMF/H<sub>2</sub>O (7:1 v/v) on the interior and exterior of the thimbles (entry 6 in Table 2). If the catalyst had a high flux through the PDMS walls, the concentration of Pd would be the same on the interior and exterior of the thimble. Instead, only 0.012% of the Pd originally added to the interior of the thimble diffused to the exterior in 24 h. This result demonstrated that the thimble walls were responsible for the site-isolation.

The reason for the success of these experiments is that the Pd catalysts have low flux through the walls of the thimble but



FIGURE 3. A thimble after the oxidation of styrene in DMF/H<sub>2</sub>O, partitioning of the product to the exterior with 25 mL of hexanes, and decanting of solvent from the interior. The thimble is mostly clear, which reflects the presence of very little Pd on the interior of the PDMS matrix.

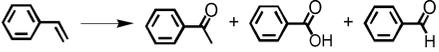
the organic products have high flux. The flux of both PdCl<sub>2</sub> and acetophenone (C<sub>6</sub>H<sub>5</sub>COCH<sub>3</sub>) were measured by their addition to the interior of a thimble containing DMF/water and the addition of hexane to the exterior. The flux of acetophenone (0.158 mmol cm<sup>-2</sup> h<sup>-1</sup>) was nearly 7 orders of magnitude larger than the flux of all forms of Pd (2.38 × 10<sup>-8</sup> mmol cm<sup>-2</sup> h<sup>-1</sup>) as measured by ICP-MS. Flux depends on how well a molecule partitions into a membrane and its rate of diffusion while in a membrane through a set of complex equations that vary on the basis of the geometry of the thimbles.<sup>11</sup> Highly polar molecules have been shown to have low solubilities in PDMS; for instance, ionic liquids do not partition into PDMS and water does not appreciably swell it.<sup>12</sup> In contrast, organic molecules partition well into PDMS and have high flux. The Pd catalysts used in these experiments are soluble in polar, protic solvents but not in apolar solvents such as toluene or PDMS. To demonstrate the low partitioning of Pd catalysts into the matrix of PDMS, a thimble is shown in Figure 3 after oxidation of styrene and extraction of the products with hexanes. The optical micrograph clearly shows that the thimble is mostly clear and that the Pd catalysts do not partition into the matrix of the PDMS but must remain in the solvent on the interior of the thimble. In addition, the amount of Pd dissolved in the solvent on the interior was measured by ICP-MS to be 100% of the Pd that was originally added to the reaction mixture. Clearly, the Pd remained on the interior of the thimble and did not appreciably partition into PDMS.

Efforts to extend this work to other Pd catalysts were not successful. When phosphines were added to the reaction mixture, the solubility of the catalysts greatly increased in organic solvents such that they were also soluble in PDMS. In experiments with Pd catalysts and phosphines on the interior of thimbles, the catalysts were seen to flux to the exterior by eye; the solvent on the exterior became colored. This result is not surprising considering the solubility of these catalysts in apolar solvents such as toluene, and it is a limitation of this work that is being addressed and will be reported in subsequent papers. PdCl<sub>2</sub> is a critically important catalyst such that the relevance of this work is still high even if it is limited to reactions without phosphine ligands. In fact, for many reactions

(11) Crank, J. *The Mathematics of Diffusion*; Clarendon Press: Oxford, 1970.

(12) (a) Lee, J. N.; Park, C.; Whitesides, G. M. *Anal. Chem.* **2003**, *75*, 6544.

(b) Schafer, T.; Di Paolo, R. E.; Franco, R.; Crespo, J. G. *Chem. Commun.* **2005**, 2594.

**TABLE 3.** Recycling of PdCl<sub>2</sub> for Wacker–Tsuji Oxidation of Styrene


cycle	conversion (%) <sup>a</sup>	ketone (%)	acid (%)	aldehyde (%)
1	96	88	9	3
2	94	88	11	1
3	93	88	12	0
4	93	89	11	0
5	96	89	11	0
6	73	95	5	0

<sup>a</sup> Conversion for each cycle determined by <sup>1</sup>H NMR spectroscopy.

the phosphines are more valuable than the Pd metal, so these reactions should focus on the site-isolation of the ligands as well as the Pd.

Because the Pd catalyst remained encapsulated on the interior of the thimbles, it was readily recycled (Table 3). In these experiments, PdCl<sub>2</sub> and CuCl were added to the interior of a thimble with DMF/H<sub>2</sub>O (7:1 v/v) and styrene. The oxidation to acetophenone was allowed to proceed for 24 h, and then the product was extracted from the thimble by the addition of 25 mL of hexanes to the exterior. The hexanes were removed from the reaction vessel, the product was characterized, and additional styrene was added to the interior of the thimble. The average conversion was 94% for five cycles and the selectivity for acetophenone was 88%. These conversions and selectivities are similar to those observed by us and others in single experiments with glass vials and do not reflect limitations with the PDMS thimbles.

Because the Pd catalyst and solvent remained site-isolated on the interior of the thimbles, they allowed for otherwise incompatible reactions to be completed on the exterior of the thimbles. For instance, we completed the Wacker–Tsuji oxidation of *p*-methylstyrene and then extracted the product to the exterior with hexane (Figure 4). Phenylmagnesium bromide was

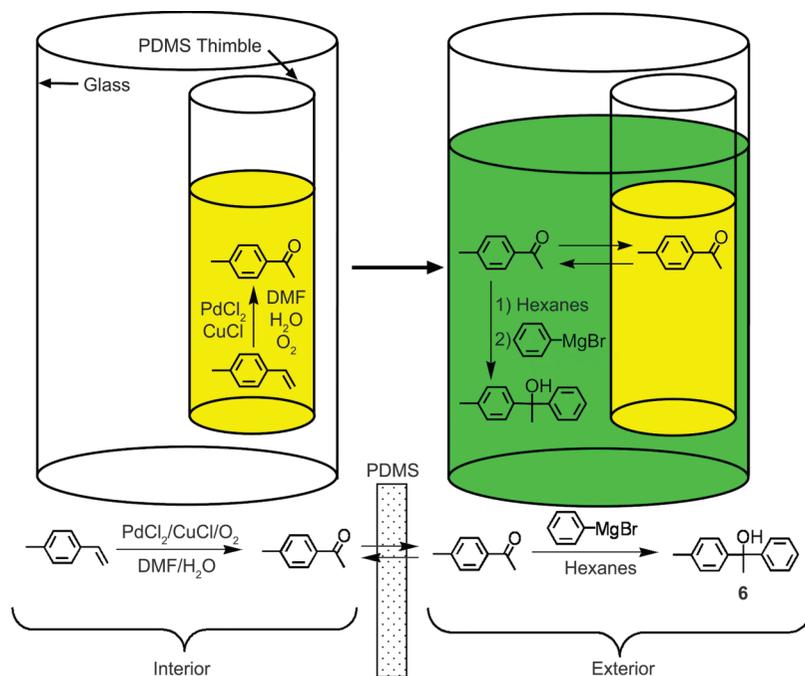
added to the exterior to react with the ketone despite the presence of water/DMF on the interior of the thimble that would, if allowed to flux through the PDMS walls, quench the entire Grignard reagent. Because of the differential flux of the ketone versus water and DMF, the reaction was successful and an isolated yield of 62% was found for the two-step sequential reaction.

## Conclusions

We report a new method to site-isolate a Pd catalyst that focuses on the materials properties of thimbles rather than the structure of the Pd catalyst. PdCl<sub>2</sub> is site-isolated within a PDMS thimble and products of reactions with this catalyst can be isolated with very low levels of Pd. Organic molecules readily flux through the walls of the thimbles, but PdCl<sub>2</sub> remains encapsulated due to its lack of solubility in PDMS. Importantly, catalysts in these reactions could be recycled without any alterations to their structure or by requiring them to be heterogeneous. Commercially available PdCl<sub>2</sub> was used without concern for whether the active catalyst was colloidal or single site Pd; well-established reactions were readily integrated with this approach. This work represents a new approach to the site-isolation of homogeneous Pd catalysts that relies on the materials properties of thimbles rather than the development of new ligands.

## Experimental Section

**Fabrication of PDMS Thimbles.** Screw thread glass vials (19 mm × 65 mm) were placed in a desiccator with 3 drops of trichloro(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silane and placed under a static vacuum for 12 h to allow for easy removal of the thimbles after fabrication. Commercially available PDMS was mixed as two components (elastomer and curing agent) in a 10:1 ratio (by mass) and degassed for approximately 2 h. The glass vials were dipped into the PDMS mixture, turned upside down, and placed in a 65



**FIGURE 4.** Sequential reaction diagram where the first reaction takes place inside a PDMS thimble. Upon completion of the first reaction, hexanes is added to the exterior of the thimble to allow the product to flux through the PDMS. A Grignard reagent is then added to the exterior of the thimble to form the alcohol.

°C oven for approximately 1 h. Then the vials were redipped into the PDMS mixture for a second coat, turned upside down, and placed in a 65 °C oven overnight to cross-link. Following the curing process, the tops of the vials were cut around the cap with a razor blade and placed in hexanes to delaminate the thimbles from the vials for 2 h. The hexanes were decanted and the thimbles were soaked twice in CH<sub>2</sub>Cl<sub>2</sub> for 2 h each time. The thimbles were dried in a 125 °C oven. The average size of PDMS thimbles was 5 cm tall by 2 cm wide with 100–200 μm thick walls.

**Wacker–Tsuiji Oxidation of Styrene in a PDMS Thimble.** A PDMS thimble containing PdCl<sub>2</sub> (0.025 g, 0.141 mmol) and CuCl (0.282 g, 2.82 mmol) was placed in a two-necked Schlenk flask with a stir bar. MeOH (1.98 mL) and H<sub>2</sub>O (0.28 mL) were added to the inside of the PDMS thimble, and the flask was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. Styrene (0.323 mL, 2.82 mmol) was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The PDMS thimble was swelled with hexane (2 × 25 mL) for 12 h with a stir bar on the exterior of the PDMS thimble. The hexane extracts were combined, and the solvent was removed in vacuo. A <sup>1</sup>H NMR spectrograph was recorded in CDCl<sub>3</sub> to determine quantitative conversion of the styrene to the following products: 89% ketone, 1% aldehyde, 8% acetal, and 2% ketal. Acetophenone (0.249 g, 73% yield) was isolated as a clear liquid by column chromatography using hexanes/EtOAc (95/5). NMR spectra matched those reported in the literature.<sup>13</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 7.94 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 2.58 (s, 3H). <sup>13</sup>C NMR (75.48 MHz; CDCl<sub>3</sub>, δ): 197.9, 137.0, 132.9, 128.4, 128.1 and 26.4.

**Wacker–Tsuiji Oxidation of (1,1,5-Trimethyl-hept-6-enyloxy-methyl)benzene in a PDMS Thimble.** A PDMS thimble containing PdCl<sub>2</sub> (0.100 g, 0.564 mmol) and CuCl (0.564 g, 5.64 mmol) was placed in a two-necked Schlenk flask with a stir bar. DMF (3.96 mL) and H<sub>2</sub>O (0.56 mL) were added to the inside of the PDMS thimble, and the flask was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. The olefin starting material, 1,1,5-trimethyl-hept-6-enyloxymethyl)benzene (1.39 g, 5.64 mmol), was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The PDMS thimble was swelled with hexane (2 × 25 mL) for 12 h with a stir bar on the exterior of the PDMS thimble. The hexane extracts were combined, and the solvent was removed in vacuo. A <sup>1</sup>H NMR spectrograph was recorded in CDCl<sub>3</sub> to determine quantitative conversion of the starting material to the ketone product. 7-Benzyloxy-3,7-dimethyl-octan-2-one (0.828 g, 56% yield) was isolated as a clear liquid by column chromatography using hexanes/EtOAc (95/5). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 7.24 (m, 5H), 4.39 (s, 2H), 2.51 (m, 1H), 2.11 (s, 3H), 1.66–1.34 (m, 6H), 1.23 (s, 6H), 1.07 (d, J = 5.4 Hz, 3H). <sup>13</sup>C NMR (75.48 MHz; CDCl<sub>3</sub>, δ): 212.6, 139.7, 128.1, 127.2, 126.9, 74.9, 63.5, 47.0, 40.5, 33.2, 27.9, 25.5, 21.5, 16.1. HRMS calcd for C<sub>7</sub>H<sub>13</sub>O 113.0966, found 113.0973; calcd for C<sub>10</sub>H<sub>13</sub>O 149.0966, found 149.0973.

**Pd-Mediated Homocoupling of 4-Bromophenylboronic Acid.** A PDMS thimble containing 4-bromophenylboronic acid (0.402 g, 2.00 mmol), *p*-toluenesulfonyl chloride (0.191 g, 1.00 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.424 g, 4.00 mmol) and PdCl<sub>2</sub> (0.011 g, 0.06 mmol) was placed in a two-necked Schlenk flask with a stir bar. H<sub>2</sub>O (2.5 mL) and EtOH (2.5 mL) were added to the inside of the PDMS thimble, the flask was capped, and the reaction was stirred overnight for 12 h under air. The PDMS thimble was swelled with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL) for 2 h with a stir bar added to the exterior of the PDMS thimble. The CH<sub>2</sub>Cl<sub>2</sub> extracts were combined, and the solvent was removed in vacuo. A <sup>1</sup>H NMR spectrograph was recorded in CDCl<sub>3</sub> to determine quantitative conversion of the 4-bromophenylboronic acid to the 4,4'-dibromobiphenyl product. 4,4'-Dibromobiphenyl (0.291 g, 93% yield) was isolated as a white solid by column chromatography using hexanes/EtOAc (10/1). NMR spectra matched

those reported in the literature.<sup>14</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 7.55 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H). <sup>13</sup>C NMR (75.48 MHz; CDCl<sub>3</sub>, δ): 138.9, 132.0, 128.5, 121.9.

**ICP-MS Sample Preparation.** Three different approaches were followed to gather ICP-MS data for Table 2. The three methods are labeled as PDMS, Liquid–Liquid (L-L), and Extract. Each of these approaches is described in detail once; the same method was followed for each sample.

**Wacker–Tsuiji Oxidation in PDMS Thimbles Followed by Extraction of the Product with Hexanes (PDMS Method).** A PDMS thimble containing PdCl<sub>2</sub> (0.050 g, 0.282 mmol) and CuCl (0.282 g, 2.82 mmol) was placed in a two-necked Schlenk flask with a stir bar. DMF (1.98 mL) and H<sub>2</sub>O (0.28 mL) were added to the inside of the PDMS thimble, and the flask was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. Styrene (0.323 mL, 2.82 mmol) was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The PDMS thimble was swelled with hexanes (25 mL) for 24 h with a stir bar added to the exterior of the PDMS thimble. The PDMS thimble was removed, and the interior contents and exterior contents were subjected to ICP-MS measurements by the University of Iowa Hygiene Laboratory.

**Wacker–Tsuiji Oxidation in Glass Vials Followed by Liquid–Liquid Extraction with Hexanes (L-L Method).** PdCl<sub>2</sub> (0.050 g, 0.282 mmol) and CuCl (0.282 g, 2.82 mmol) were placed in a glass vial with a stir bar. DMF (1.98 mL) and H<sub>2</sub>O (0.28 mL) were added to the vial, and the vial was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. Styrene (0.323 mL, 2.82 mmol) was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The reaction mixture was transferred to a separatory funnel with 50 mL of H<sub>2</sub>O and extracted with hexanes (3 × 50 mL). The hexanes was concentrated in vacuo and subjected to ICP-MS measurements by the University of Iowa Hygiene Laboratory.

**Wacker–Tsuiji Oxidation in Glass Vials Followed by Extraction with Hexanes and No Added Water (Extract Method).** PdCl<sub>2</sub> (0.050 g, 0.282 mmol) and CuCl (0.282 g, 2.82 mmol) were placed in a glass vial with a stir bar. DMF (1.98 mL) and H<sub>2</sub>O (0.28 mL) were added to the vial, and the vial was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. Styrene (0.323 mL, 2.82 mmol) was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The reaction mixture was transferred to a separatory funnel, and 25 mL of hexanes was added. The hexanes layer was separated, concentrated in vacuo, and subjected to ICP-MS measurements by the University of Iowa Hygiene Laboratory.

**Sequential Reaction of a Wacker–Tsuiji Oxidation Followed by Grignard Reduction.** A PDMS thimble containing PdCl<sub>2</sub> (0.100 g, 0.564 mmol) and CuCl (0.564 g, 5.64 mmol) was placed in a two-necked Schlenk flask with a stir bar. DMF (3.96 mL) and H<sub>2</sub>O (0.56 mL) were added to the inside of the PDMS thimble, and the flask was capped with a rubber septum. A balloon filled with O<sub>2</sub> was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. *p*-Methylstyrene (0.742 mL, 5.64 mmol) was added to the reaction mixture and allowed to stir under an O<sub>2</sub> atmosphere for 24 h. The PDMS thimble was swelled with hexanes (30 mL) for 0.5 h with a stir bar added to the exterior of the PDMS thimble. Phenylmagnesium bromide (3 M in Et<sub>2</sub>O, 18.8 mL, 56.4 mmol) was added to the exterior of the thimble and stirred under N<sub>2</sub> for 12 h. The exterior solvent was removed, and the PDMS thimble was swelled with Et<sub>2</sub>O (4 × 50 mL). The combined solvents were transferred to a separatory funnel, and 3 N HCl (200 mL) was added. 3 N HCl (200 mL) was used two more times to extract

(13) Tsuiji, J. *Synthesis* **1984**, 5, 369–384.

(14) Amatore, C.; Cammoun, C.; Jutand, A. *Eur. J. Org. Chem.* **2008**, 27, 4567–4570.

from the organic layer, and then the organic layer was dried over  $\text{Na}_2\text{SO}_4$  and filtered. The organic solvents were concentrated in vacuo. 1-Phenyl-1-*p*-tolyl-ethanol (0.737 g, 62% yield) was isolated by column chromatography using hexanes/EtOAc (95/5). NMR spectra agree with those reported in the literature.<sup>15</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.33 (d,  $J = 8.1$  Hz, 2H), 7.17 (m, 5H), 7.03 (d,  $J = 8.1$  Hz, 2H), 2.62 (s, 1H), 2.25 (s, 3H), 1.81 (s, 3H).  $^{13}\text{C}$  NMR (75.48 MHz;  $\text{CDCl}_3$ ,  $\delta$ ): 148.1, 145.0, 136.2, 128.6, 127.9, 126.6, 125.7, 125.6, 75.8, 30.6, 20.8.

**Recycling of Pd Catalysts in the Wacker–Tsuji Oxidation Reaction.** A PDMS thimble containing  $\text{PdCl}_2$  (0.050 g, 0.282 mmol) and  $\text{CuCl}$  (0.282 g, 2.82 mmol) was placed in a two-necked Schlenk flask with a stir bar. DMF (1.98 mL) and  $\text{H}_2\text{O}$  (0.28 mL) were added to the interior of the PDMS thimble, and the flask was capped with a rubber septum. A balloon filled with  $\text{O}_2$  was affixed to the septum, and the reaction mixture was stirred at room temperature for 1 h. Styrene (0.323 mL, 2.82 mmol) was added to the reaction

mixture and allowed to stir under an  $\text{O}_2$  atmosphere for 24 h. The PDMS thimble was swelled with hexanes (25 mL) for 24 h with a stir bar added to the exterior of the PDMS thimble. The hexanes was removed. One equivalent of styrene (0.323 mL, 2.82 mmol) was added to the interior of the PDMS thimble and allowed to react for 24 h. The procedure was repeated for 6 cycles, and the hexanes from each cycle was concentrated in vacuo. Conversions and product distributions were determined by  $^1\text{H}$  NMR spectroscopy.

**Acknowledgment.** We thank the Carver Charitable Trust and the Research Corporation for financial support of this research. We would also like to thank Brian Wels and Steve Bernholtz for collecting the ICP-MS data.

**Supporting Information Available:** Full characterization and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(15) Antunes, A. C. S.; Beitti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 3884–3891.

JO900570Y