JOC Notes

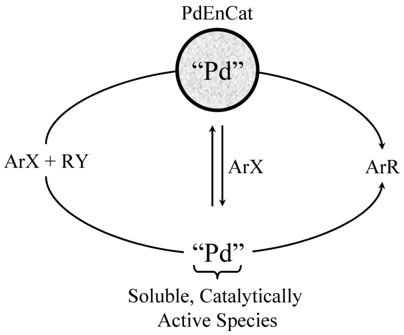
Investigating PdEnCat Catalysis

Steven J. Broadwater and D. Tyler McQuade*

Department of Chemistry and Chemical Biology,
Baker Laboratory, Cornell University,
Ithaca, New York 14853-1301

dtm25@cornell.edu

Received August 25, 2005



The catalytic behavior of three commercially available PdEnCat catalysts was explored. When the three-phase test was used, it was demonstrated that these microencapsulated palladium catalysts act as heterogeneous sources, or reservoirs, for soluble, catalytically active species. In addition, kinetic data coupled with transmission electron microscopy and solvent-dependent investigations were used to support this conclusion.

Immobilized transition metal catalysts offer the promise of easy handling, straightforward separation from reaction mixtures, and decreased product contamination caused by metal leaching.[1−5] Immobilization approaches are varied and include polymer incarceration,[6−12] sol−gels[13−17] and polymer encapsulation,[18−24] and the use of inorganic[2,3,25−27] and polymeric supports.[1,4,28] Our research is focused on designing immobilized catalysts capable of performing multistep one-pot reactions. The benefits of performing multiple reactions simultaneously include lower input and labor costs and decreased waste production. We are interested in a transition metal immobilization approach where the metal is site-isolated within the support throughout the entire reaction. Palladium catalyzes a broad range of carbon−carbon, carbon−oxygen, and carbon−nitrogen bond-forming reactions and is an attractive choice for use in tandem catalysis.[29,30] Palladium, however, may not be compatible with other catalytic materials; therefore, the catalyst must remain site-isolated within the support.

One of the most promising methods of catalyst immobilization is microencapsulation. Ley and co-workers have used microencapsulation techniques to encapsulate $Pd(OAc)_2$ within a polyurea matrix that can include phosphine ligands.[22,31−35] These commercially available PdEnCat catalysts can be used to

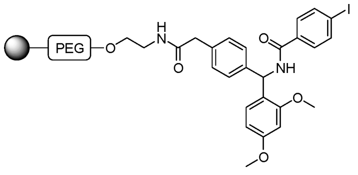
---

(1) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217−3273.
(2) Wight, A. P.; Davis, M. E. *Chem. Rev.* **2002**, *102*, 3589−3613.
(3) De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615−3640.
(4) Uozumi, Y. *Immobilized Catalysts*; Springer-Verlag: Berlin, 2004; Vol. 242, pp 77−112.
(5) Horn, J.; Michalek, F.; Tzschucke, C. C.; Bannwarth, W. *Immobilized Catalysts*; Springer-Verlag: Berlin, 2004; Vol. 242, pp 43−75.
(6) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094−6095.
(7) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412−3413.
(8) Kobayashi, S.; Akiyama, R. *Chem. Commun.* **2003**, 449−460.
(9) Akiyama, R.; Sagae, T.; Sugiura, M.; Kobayashi, S. *J. Organomet. Chem.* **2004**, *689*, 3806−3809.
(10) Hagio, H.; Sugiura, M.; Kobayashi, S. *Synlett* **2005**, 813−816.
(11) Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* **2004**, *6*, 1987−1990.
(12) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871−2873.
(13) Blum, J.; Gelman, F.; Abu-Reziq, R.; Miloslavski, I.; Schumann, H.; Avnir, D. *Polyhedron* **2000**, *19*, 509−512.
(14) Sarussi, L.; Blum, J.; Avnir, D. *J. Sol.-Gel Sci. Technol.* **2000**, *19*, 17−22.
(15) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2002**, *124*, 14460−14463.
(16) Gelman, F.; Blum, J.; Avnir, D. *New J. Chem.* **2003**, *27*, 205−207.
(17) Gelman, F.; Blum, J.; Schumann, H.; Avnir, D. *J. Sol.-Gel Sci. Technol.* **2003**, *26*, 43−46.
(18) Price, K. E.; McQuade, D. T. *Chem. Commun.* **2005**, 1714−1716.
(19) Jung, H. M.; Price, K. E.; McQuade, D. T. *J. Am. Chem. Soc.* **2003**, *125*, 5351−5355.
(20) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195.
(21) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573−586.
(22) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134−1135.
(23) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J. Q.; Zhou, W. Z. *Org. Lett.* **2003**, *5*, 4665−4668.
(24) Ley, S. V.; Ramarao, C.; Lee, A. L.; Ostergaard, N.; Smith, S. C.; Shirley, I. M. *Org. Lett.* **2003**, *5*, 185−187.
(25) Bhanage, B. M.; Arai, M. *Catal. Rev.* **2001**, *43*, 315−344.
(26) Smith, M. D.; Stepan, A. F.; Ramarao, C.; Brennan, P. E.; Ley, S. V. *Chem. Commun.* **2003**, 2652−2653.
(27) Thomas, J. M.; Raja, R. *J. Organomet. Chem.* **2004**, *689*, 4110−4124.
(28) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637−4662.
(29) Heck, R. F. *Palladium reagents in organic synthesis*; Academic Press: Orlando, FL, 1985.
(30) Tsuji, J. *Palladium reagents and catalysts: Innovations in organic synthesis*; Wiley & Sons: New York, 1995.
(31) Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. *Synlett* **2002**, 1843−1844.
(32) Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmeida, N. *Chem. Commun.* **2002**, 1132−1133.
(33) Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C.; Tapolczay, D. J. Microencapsulated Catalyst Methods of Preparation and Methods of Use Thereof. U.S. Patent Application. US20040254066, 2004.
(34) Holmes, A. B.; Ley, S. V.; Gordon, R. S.; Ramarao, C.; Early, T. R. Use of Microencapsulated Transition Metal Reagents For Reactions in Supercritical Fluids. U.S. Patent Application. US20050010068, 2005.
(35) Pears, D. A.; Treacher, K. E.; Nisar, M. Microencapsulated Catalyst-Ligand System, Methods of Preparation and Methods of Use Thereof. World Patent Application. WO2005016510, 2005.

10.1021/jo0517904 CCC: $33.50

catalyze a wide variety of reactions, including cross-couplings, carbonylations, and hydrogenations.

PdEnCats are attractive for tandem catalysis because of their wide substrate scope, high activity, low leaching, and strong recycling capability. Active catalyst escape from PdEnCats, however, has not been critically examined. Many reports indicate that heterogeneous catalysts often serve as reservoirs for soluble, catalytically active species.[36−43] Prior to using these catalysts in a multistep, one-pot synthesis, we investigated if an active palladium catalyst leaches from the PdEnCat core under standard reaction conditions.



1

Site isolation is our major requirement for an immobilized catalyst; therefore, we determined that the three-phase test is the most definitive indicator of active catalyst escape, Figure 1.[37,44−48] In the three-phase test, an immobilized catalyst is exposed to soluble reagents and reagents bound to a solid support. As depicted in Figure 1, if an active catalyst leaches from the immobilized media, it will result in conversion of the resin-bound reagent.

Following the general method of Davies and co-workers,[37] the base-stable Tenta-Gel Macrobead-supported aryl iodide (**1**) was prepared. The three-phase test was performed using three commercially available PdEnCats: 30, TPP30, and TOTP30. PdEnCat 30 consists of palladium(II) ligated by the urea encapsulation matrix, whereas PdEnCat TPP30 contains triphenylphosphine and PdEnCat TOTP30 contains tri-*o*-tolylphosphine as catalyst modifiers. Heck and Suzuki reactions were run to assess whether leaching was reaction dependent. When performing the three-phase test on a palladium catalyst, it is necessary to run the homogeneous reaction and the solid phase reaction simultaneously in the same vessel.[49−51] This is because the leaching species is hypothesized to be a Pd(II) intermediate formed after oxidative addition occurs.[37,52]

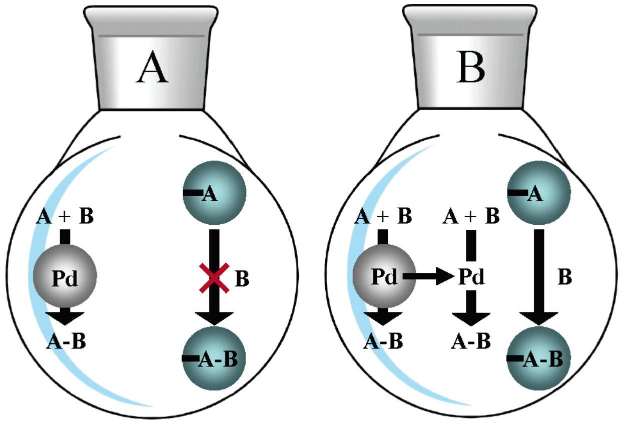
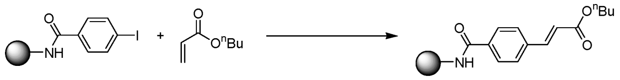
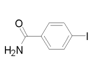
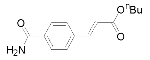


FIGURE 1. Representation of the three-phase test. A: The palladium catalyst remains site-isolated, allowing only solution-phase reagents to participate in the reaction; the resin-bound reagent does not react. B: The palladium catalyst leaches out of the heterogeneous support, allowing both the solution-phase and the resin-bound reagents to react.

TABLE 1. Three-Phase Test Results of Heck Coupling[a,b]



Catalyst		
PdEnCat 30	8%	92%
PdEnCat TPP30	<1%	>99%
PdEnCat TOTP30	<1%	>99%

[a] Reagents and conditions: resin-bound Ar−I, PdEnCat (2.5 mol %), 4-bromoacetophenone (1.0 equiv), *n*-butyl acrylate (1.5 equiv), *n*-Bu_4NOAc (3.0 equiv), isopropyl alcohol, 90 °C, 24 h. [b] Yields determined by GC.

The three-phase test was used to examine the Heck coupling of 4-bromoacetophenone and *n*-butyl acrylate, performed under the optimized conditions of Ley et al., Table 1. We observed high conversion of **1** to the corresponding cinnamate derivative for all three PdEnCat catalysts after 24 h at 90 °C, indicating that an active palladium catalyst leached out of the polyurea matrix during the reaction. The homogeneous reaction also ran to completion within the same period, indicating that the same species may catalyze the reaction on and off the solid support.

We also used the three-phase test to study the Suzuki coupling of 4-bromoacetophenone and phenylboronic acid. We found that all three PdEnCat catalysts converted the resin-bound aryl iodide to the biphenyl derivative in high yield, Table 2. In addition, control experiments demonstrated that **1** was not functionalized under Heck or Suzuki reaction conditions when the palladium

---

(36) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(37) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139−10140.

(38) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055−4082.

(39) Yu, K. Q.; Sommer, W.; Weck, M.; Jones, C. W. *J. Catal.* **2004**, *226*, 101−110.

(40) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *Adv. Synth. Catal.* **2005**, *347*, 172−184.

(41) Hagen, C. M.; Widegren, J. A.; Maitlis, P. M.; Finke, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 4423−4432.

(42) Wen, F.; Bonnemann, H.; Jiang, J. Y.; Lu, D. M.; Wang, Y. H.; Jin, Z. L. *Appl. Organomet. Chem.* **2005**, *19*, 81−89.

(43) Yu, K. Q.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161−171.

(44) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112−7114.

(45) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454−455.

(46) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1975**, *97*, 1591−1592.

(47) Rebek, J. *Tetrahedron* **1979**, *35*, 723−731.

(48) Kagan, H. B.; Peyronel, J. F.; Yamagishi, T. *Advances in Chemistry Series: Inorganic Compounds with Unusual Properties-II;* American Chemical Society: Washington, D.C., 1979; Vol. 173, pp 50−66. For examples of the three-phase test being performed without all reagents present in solution, see refs 49−51. All three of these examples report catalysts that pass the three-phase test.

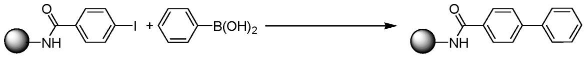
(49) Okamoto, K.; Akiyama, R.; Yoshida, H.; Yoshida, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 2125−2135.

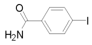
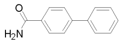
(50) Steel, P. G.; Teasdale, C. W. T. *Tetrahedron Lett.* **2004**, *45*, 8977−8980.

(51) User Guide-PdEnCat. http://www.reaxa.co.uk/technology.htm.

(52) Biffis, A.; Zecca, M.; Basato, M. *Eur. J. Inorg. Chem.* **2001**, 1131−1133.

TABLE 2. Three-Phase Test Results of Suzuki Coupling[a,b]



Catalyst		
PdEnCat 30	2%	98%
PdEnCat TPP30	<1%	>99%
PdEnCat TOTP30	<1%	>99%

[a] Reagents and conditions: resin-bound Ar−I, PdEnCat (5.0 mol %), 4-bromoacetophenone (1.0 equiv), phenylboronic acid (1.5 equiv), n-Bu$_4$NOAc (3.0 equiv), isopropyl alcohol, 90 °C, 24 h. [b] Yields determined by GC.

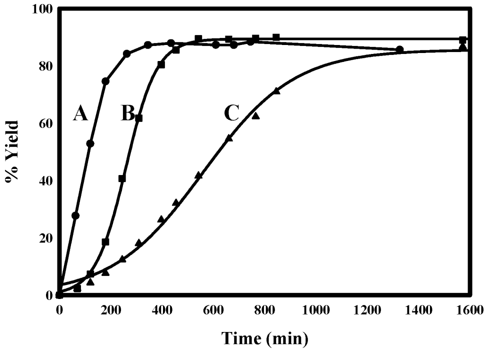


FIGURE 2. Plot of yield vs reaction time for the Heck reaction of 4-bromoacetophenone with n-butyl acrylate at 90 °C in isopropyl alcohol; base, n-Bu$_4$NOAc; catalyst, (A) PdEnCat 30, (B) PdEnCat TOTP30, and (C) PdEnCat TPP30.

source was excluded. The observation that both the Heck and Suzuki reactions fail the three-phase test is strong evidence that the PdEnCat serves as a reservoir or precatalyst.[53] We chose to examine reaction kinetics coupled with transmission electron microscopy (TEM) and catalyst decomposition as further means to support this hypothesis.

Monitoring product formation via GC yielded sigmoidal kinetic profiles for TPP30 and TOTP30, which is consistent with previous findings, Figure 2.[51] The observation of a sigmoidal conversion plot is indicative of in situ maturation of a precatalyst into an active catalyst.[54] The induction period may be related to the additional phosphine ligands retarding the rate of oxidative addition of the aryl halide.

To further characterize the nature of the catalytic species that caused the failure of the three-phase test, TEM was used to analyze the supernatant from the Heck reaction catalyzed by PdEnCat 30. The reaction mixture was sampled at 85% conversion, hot filtered, and deposited on a TEM grid. Palladium nanoparticles in the size range of 5−10 nm were observed, and the identity of the metal was confirmed using X-ray analysis and energy filtration imaging, Figure 3.

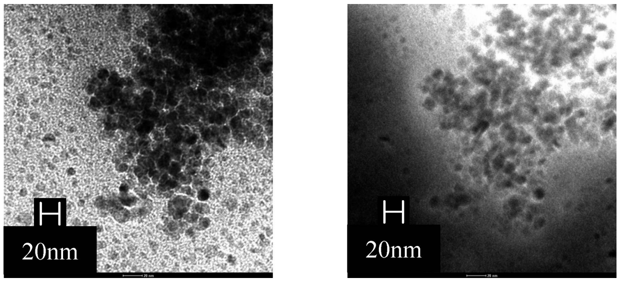
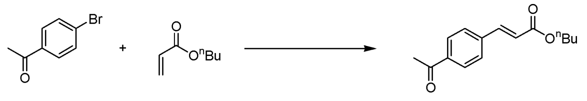


FIGURE 3. (A) TEM image of Heck reaction supernatant catalyzed by PdEnCat 30 in isopropyl alcohol. (B) TEM image of the same sample using energy filtration specific for Pd.

TABLE 3. ICP Analysis of Heck Reaction Filtrates



catalyst	solvent	% Pd leached
PdEnCat 30	toluene	37
PdEnCat 30	isopropyl alcohol	0.5
PdEnCat 30	DMF	46
PdEnCat TOTP30	toluene	42
PdEnCat TOTP30	isopropyl alcohol	9
PdEnCat TOTP30	DMF	52

To determine if leaching is a solvent-dependent process, we ran the same Heck reaction using either toluene or DMF as solvent. These reactions yielded dark red solutions upon heating, which indicate palladium leaching and subsequent formation of nanoparticles.[55] Reactions performed in these solvents are sluggish when aryl bromides are used as substrates, suggesting that the formed palladium species are not very active. Inductively coupled plasma (ICP) analysis of the reaction filtrates indicated that both of these solvents caused substantially higher levels of palladium leaching compared to that of isopropyl alcohol, Table 3. It is plausible to conclude that increased palladium leaching favors deactivation pathways (e.g., palladium-black formation), resulting in lower activity.[56,57] Also, it is worth mentioning that PdEnCat TOTP30 leached significantly more in isopropyl alcohol than PdEnCat 30, suggesting that the co-encapsulated phosphine ligand promotes palladium escape.

It has been demonstrated that the powerful and versatile PdEnCat systems behave as heterogeneous sources for soluble, catalytically active species during the course of Heck and Suzuki couplings. This is not to say that catalysis is occurring only in solution, but there is a solution-phase contribution that one must be aware of when using these materials. This conclusion is supported by kinetic behavior displayed by these catalysts, the observation of nanoparticles by TEM, and the solvent dependence of reactivity and leaching. Although these catalysts are highly useful, caution must be exercised when considering these materials, as well as other heterogeneous catalysts, for use in systems where site isolation is required.

Experimental Section

General Method for Carrying out the Three-Phase Test: Heck Reaction. Following the method of Ley et al.,[22] 4-bromoacetophenone (0.050 g, 0.25 mmol), n-Bu$_4$NOAc (0.23 g, 0.75

---

(53) Functionalization of resin-bound reagents occurred at roughly the same rate as with soluble reagents.

(54) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317−341.

(55) Yeung, L. K.; Crooks, R. M. *Nano Lett.* **2001**, *1*, 14−17.

(56) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288.

(57) Alimardanov, A.; Schmieder-van de Vondervoort, L.; de Vries, A. H. M.; de Vries, J. G. *Adv. Synth. Catal.* **2004**, *346*, 1812−1817.

mmol), PdEnCat (15.7 mg, 0.00625 mmol), mesitylene (0.050 mL, internal standard), Tenta-Gel MB-supported aryl iodide (1; 0.025 g, 0.010−0.015 mmol loading), and isopropyl alcohol (1.25 mL) were added to a screw-cap vial equipped with a septum. *n*-Butyl acrylate (0.054 mL, 0.375 mmol) was added, and the reaction mixture was warmed to 90 °C. The solution-phase reaction was monitored via GC. After 24 h, the reaction mixture was transferred to a syringe equipped with a frit. The insoluble material was washed thoroughly with H_2O (3 × 2 mL), MeOH (3 × 2 mL), EtOAc (3 × 2 mL), THF (3 × 2 mL), and CH_2Cl_2 (3 × 2 mL). The resin-bound material was liberated by treatment with 20% v/v TFA in CH_2Cl_2 (2.5 mL) and agitated for 30 min. The cleavage solution was removed, and the resin was washed with CH_2Cl_2 (3 × 2 mL), EtOAc (3 × 2 mL), and THF (3 × 2 mL). The combined filtrates were evaporated, redissolved in THF, and analyzed by GC.

Acknowledgment. We thank John Grazul for help with TEM analysis, Christopher Simoneau for discussion, and the ARO DAAD19-02-1-0275 Macromolecular Architecture for Performance, the Cornell Center for Materials Research (CCMR, DMR-0079992), Cornell University, the Dreyfus Foundation, NSF (SENSORS), and NYSTAR for support.

Supporting Information Available: Representative reaction conditions, experimental details for the three-phase test, ICP analysis, and TEM characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0517904