Inorg. Chem. **2009**, *48*, 4491−4496

Inorganic Chemistry
Article

Dendrimer-Encapsulated Pd Nanoparticles versus Palladium Acetate as Catalytic Precursors in the Stille Reaction in Water

María Bernechea,[†,‡] Ernesto de Jesús,[*,†] Carmen López-Mardomingo,[§] and Pilar Terreros[‡]

Departamento de Química Inorgánica and Departamento de Química Orgánica, Universidad de Alcalá, Campus Universitario, 28871 Alcalá de Henares, Madrid, Spain, and Instituto de Catálisis y Petroleoquímica (CSIC), C/ Marie Curie 2, 28049 Madrid, Spain

Received February 9, 2009

The performance of several palladium precatalysts, namely, palladium(II) acetate, palladium(0) nanoparticles encapsulated into poly(amidoamine) (PAMAM) dendrimers (Pd DENs), and palladium(II)-PAMAM complexes, in the Stille reaction between trichloro(phenyl)stannane and iodoarenes in water is compared. The reactivity of Pd DENs is similar or inferior to that of palladium(II) acetate, although the presence of the dendrimer suppresses the formation of homocoupling products and allows catalyst recycling. It is suggested that the reaction catalyzed by Pd DENs occurs via palladium species which are leached from the nanoparticle but which remain coordinated to the dendritic macromolecule.

Introduction

Palladium is a ubiquitous metal for the formation of carbon−carbon bonds in organic synthesis through transformations which are frequently catalyzed by practically every Pd-containing source.[1] The nature of the real catalyst, which might be quite different from that of the precursor, is, however, a recurring subject of debate. The distinction between homogeneous catalysis by molecular species and "heterogeneous" catalysis by soluble metal nanoparticles[2] is especially relevant in carbon−carbon coupling reactions, which are often performed under conditions favorable for the formation of Pd^0 nanoparticles from molecular precursors. However, key experiments on Heck, Suzuki, Sonogashira, and other coupling reactions support currently that the true catalyst in these reactions consists of monomeric or dimeric palladium complexes;[3] the Pd nanoparticles added as precursors or formed in the catalytic medium are therefore mere reservoirs of palladium from which the metal atoms are leached by oxidative addition of the arylating agent.

Crooks and co-workers have reported[4] the Stille[5] cross-coupling reaction of trichloro(phenyl)stannane with several iodo- and bromoarenes in water using dendrimer-encapsulated palladium nanoparticles (Pd DENs;[6] Scheme 1). The encapsulation of nanoparticles in dendrimers is attractive

---

[*] To whom correspondence should be addressed. E-mail: ernesto.dejesus@uah.es. Phone: +34 918854603. Fax: +34 918854683.

[†] Departamento de Química Inorgánica, Universidad de Alcalá.

[‡] Instituto de Catálisis y Petroleoquímica.

[§] Departamento de Química Orgánica, Universidad de Alcalá.

(1) (a) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: West Sussex, U.K., 2004. (b) *Handbook of Palladium-Catalysed Organic Reactions*; Malleron, J. L., Fiaud, J. C., Legros, J. Y., Eds.; Academic Press: London, U.K., 1997. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002. (d) *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: Berlin/Heidelberg, Germany, 2005.

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

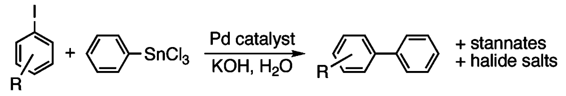
(3) (a) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, H. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288. (b) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559–1563. (c) de Vries, J. G. *Dalton Trans.* **2006**, 421–429. (d) Phan, T. S.; van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (e) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884–1894. (f) Köhler, K.; Kleist, W.; Pröcki, S. S. *Inorg. Chem.* **2007**, *46*, 1876–1883. (g) Consorti, C. S.; Flores, F. R.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 12054–12065. (h) Thathagar, M. B.; Kooyman, P. J.; Boerleider, R.; Jansen, E.; Elsevier, C. J.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 1965–1968. (i) Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2886–2890. (j) Gaikwad, A. V.; Holuigue, A.; Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Chem.−Eur. J.* **2007**, *13*, 6908–6913. (k) Durán Pachón, L.; Rothenberg, G. *Appl. Organomet. Chem.* **2008**, *22*, 288–299. (l) Durand, J.; Teuma, E.; Gómez, M. *Eur. J. Inorg. Chem.* **2008**, 3577–3586. (m) Diéguez, M.; Pàmies, O.; Mata, Y.; Teuma, E.; Gómez, M.; Ribaudo, F.; van Leeuwen, P. W. N. M. *Adv. Synth. Catal.* **2008**, *350*, 2583–2598. (n) Wu, L.; Li, Z.-W.; Zhang, F.; He, Y.-M.; Fan, Q.-H. *Adv. Synth. Catal.* **2008**, *350*, 846–862.

(4) Garcia-Martinez, J. C.; Lezutekong, R.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 5097–5103.

(5) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd, revised ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chap. 3, pp 125−161.

10.1021/ic9002753 CCC: $40.75

Scheme 1. Pd-Catalyzed Stille Reaction of Iodoarenes and Trichloro(phenyl)stannane in Water



because the nanoparticle size is controlled by the dendrimer generation and the amount of metal loading on the dendritic structure, whereas the solubility of the composite material is determined by the chemical nature of the dendritic end-groups.[7−9] The Pd DENs used in the above work consisted of water-soluble, hydroxyl-terminated, fourth-generation poly(amidoamine) (PAMAM) dendrimers loaded with 40 atoms of palladium per molecule (G4-OH(Pd_{40}) (**2**); Figure 1). The reaction conditions (room temperature and 0.1 mol % Pd) contrasted very favorably with those previously reported using $PdCl_2$ complexes of sulfonated[10] or crown-ether-functionalized[11] phosphanes for the activation of aryl iodides (80−100 °C, 0.5−3 mol %),[12,13] although Pd DENs were only tested with haloarenes (acids or phenols) which are soluble in the aqueous KOH solution employed as the reaction medium. Reaction temperatures of up to 60−150 °C are generally required for Mizoroki−Heck[14] or Miyaura−Suzuki[15−17] couplings of aryl iodides using Pd DENs, but Astruc et al. have recently synthesized Pd DENs which are also active at 25 °C in Suzuki reactions.[18]

In the context of the above discussion on the nature of the catalyst, we decided to compare the efficiency of preformed palladium DENs (**2**) and palladium(II) acetate (**1**) under the same reaction conditions. The classical mechanism of the Stille and other cross-coupling reactions starts with the addition of the aryl halide to a palladium(0) complex, although palladium(II) precursors are also efficient because their reduction to Pd^0 takes place under the standard reaction conditions.[19] To understand better the role of the dendrimer in the catalytic reaction, we therefore studied the complexes obtained upon mixing the G4-OH dendrimer and the palladium(II) salts Na_2PdCl_4 (**3**) or $Pd(OAc)_2$ (**4**) in addition to the unreduced palladium(II)-dendrimer.

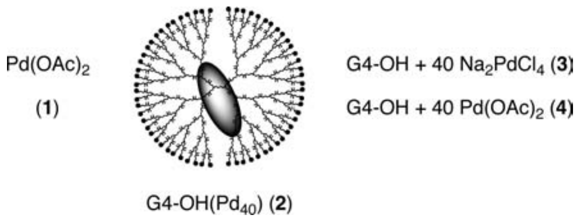


Figure 1. Catalytic precursors: palladium acetate (**1**); palladium nanoparticles encapsulated in fourth-generation hydroxyl-terminated PAMAM dendrimers (**2**); PAMAM dendrimer-palladium(II) complexes (**3** and **4**).

Results and Discussion

Synthesis and Characterization of Catalysts. Pd DENs **2** were obtained in water following the strategy developed by Crooks,[20−22] which involves the coordination of 40 equiv of Na_2PdCl_4 to the inner amine groups of a hydroxyl-terminated G4-PAMAM dendrimer and subsequent reduction of Pd^{II} to Pd^0 with $NaBH_4$. This process results in the formation of water-soluble DENs which nominally contain 40 Pd atoms and which can be separated from the salts present in the solution by dialysis. The nanoparticles were characterized by UV−vis spectroscopy and TEM. The TEM images showed monodisperse, small, and roughly spherical nanoparticles with a narrow size distribution (1.6 ± 0.3 nm), which is consistent with published results.[4,20−22] Quantitative total reflection X-ray fluorescence (TXRF) analyses of two independent samples gave reproducible results of 63 mg/L instead of the theoretical value of 106 mg/L. This loss of metal across the dialysis tubing could be for two reasons: (a) a certain permeability of the membrane to the metal DENs,[23] or (b) leaching of metal fragments from the dendrimer shell during borohydride reduction.[24] Unlike its platinum analogue,[23,25] $PdCl_4^{2-}$ quickly and strongly coordinates to the interior of G4-OH PAMAM dendrimers,[22,26] therefore the metal loss in **2** is not likely to be due to the

---

(6) (a) Zhao, M. Q.; Sun, L.; Crooks, R. M. *J. Am. Chem. Soc.* **1998**, *120*, 4877–4878. (b) Balogh, L.; Tomalia, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 7355–7356.

(7) Selected reviews on dendrimer-encapsulated metal nanoparticles: Crooks, R. M.; Zhao, M. Q.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181–190. Crooks, R. M.; Lemon, B. I.; Sun, L.; Yeung, L. K.; Zhao, M. Q. *Top. Curr. Chem.* **2001**, *212*, 81–135. Niu, Y.; Crooks, R. M. C. R. *Chimia* **2003**, *6*, 1049–1059.

(8) Scott, R. W. J.; Wilson, O. M.; Crooks, R. M. *J. Phys. Chem. B* **2005**, *109*, 692–704.

(9) For a general review on catalysts based on palladium dendrimers, see Andrés, R.; de Jesús, E.; Flores, J. C. *New J. Chem.* **2007**, *31*, 1161–1191.

(10) (a) Roshchin, A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125–128. (b) Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, *36*, 3111–3114.

(11) Fresneda, J.; de Jesús, E.; Gómez-Sal, P.; López-Mardomingo, C. *Eur. J. Inorg. Chem.* **2005**, 1468–1476.

(12) Aryl chlorides have been activated in water at high temperatures (135−140 °C) and Pd loadings (6 mol %) with $PdCl_2$ complexes and hydroxyl-functionalized phosphanes. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551–7554.

(13) Other examples of the Stille reaction in water: Kogan, V.; Aizenshtat, Z.; Popovitz-Biro, R.; Neumann, R. *Org. Lett.* **2002**, *4*, 3529–3532. Ogo, S.; Tabeke, Y.; Uehara, K.; Yamazaki, T.; Nakai, H.; Watanabe, Y.; Fukuzumi, S. *Organometallics* **2006**, *25*, 331–338.

(14) (a) Yeung, L. K.; Crooks, R. M. *Nano. Lett.* **2001**, *1*, 14–17. (b) Yeung, L. K.; Lee, C. T.; Johnston, K. P.; Crooks, R. M. *Chem. Commun.* **2001**, 2290–2291. (c) Rahim, E. H.; Kamounah, F. S.; Frederiksen, J.; Christensen, J. B. *Nano. Lett.* **2001**, *1*, 499–501. (d) Badetti, E.; Caminade, A. M.; Majoral, J.-P.; Moreno-Mañas, M.; Sebastián, R. M. *Langmuir* **2008**, *24*, 2090–2101.

(15) (a) Li, Y.; El-Sayed, M. A. *J. Phys. Chem. B* **2001**, *105*, 8938–8943. (b) Narayanan, R.; El-Sayed, M. A. *J. Phys. Chem. B* **2004**, *108*, 8572–8580.

(16) Pittelkow, M.; Moth-Poulsen, K.; Boas, U.; Christensen, J. B. *Langmuir* **2003**, *19*, 7682–7684.

(17) Lemo, J.; Heuzé, K.; Astruc, D. *Inorg. Chim. Acta* **2006**, *359*, 4909–4911.

(18) (a) Diallo, A. K.; Ornelas, C.; Salmon, L.; Ruiz Aranzaes, J.; Astruc, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 8644–8648. (b) See also Ornelas, C.; Ruiz, J.; Salmon, L.; Astruc, D. *Adv. Synth. Catal.* **2008**, *350*, 837–845.

(19) For a recent review on the mechanisms of the Stille reaction, see Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.

(20) Zhao, M.; Crooks, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 364–366.

(21) Niu, Y.; Yeung, L. K.; Crooks, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 6840–6846.

(22) Scott, R. W. J.; Ye, H. C.; Henriquez, R. R.; Crooks, R. M. *Chem. Mater.* **2003**, *15*, 3873–3878.

(23) Ploehn and co-workers have pointed out that benzoylated tubing (1200 Da cutoff) instead of regular dialysis tube (12,400 Da cutoff) must be used to purify G4-OH(Pt_{40}) solutions to prevent loss of PAMAM and Pt. Gu, Y.; Xie, H.; Gao, J.; Liu, D.; Williams, C. T.; Murphy, C. J.; Ploehn, H. J. *Langmuir* **2005**, *21*, 3122–3131.

(24) Hoover, N. N.; Auten, B. J.; Chandler, B. D. *J. Phys. Chem. B.* **2006**, *110*, 8606–8612.

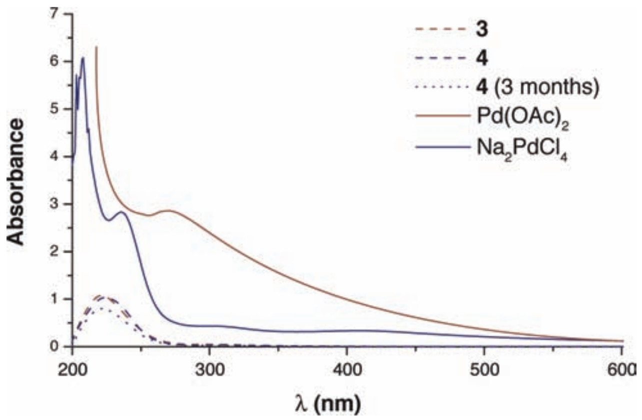


Figure 2. UV−vis absorbance spectra of freshly prepared aqueous solutions of the palladium salts Pd(OAc)$_2$ and Na$_2$PdCl$_4$ (0.50 mM), and the dendrimer-palladium complexes **3** and **4** (0.050 mM in Pd ions, recorded using a G4-OH aqueous solution as the blank). The spectrum of **4** after storing in air for 3 months is also shown.

incomplete coordination of palladium to the PAMAM inner amine groups. The absence of chlorine content in the TXRF analyses confirms the correct elimination of salts during the dialysis process.

The palladium(II)-dendrimer complexes were obtained by stirring a mixture of the G4-OH dendrimer and the palladium salts Na$_2$PdCl$_4$ (**3**) or Pd(OAc)$_2$ (**4**) in water for 30 min. The reduction step applied in the preparation of the Pd DENs **2** was omitted. Coordination of the palladium ions to the interior amino groups of the dendrimer was checked by UV−vis spectroscopy (Figure 2). The absorbance bands of the salt solutions [at approximately 210 and 240 nm for Na$_2$PdCl$_4$ and 270 nm for Pd(OAc)$_2$] disappeared upon addition of G4-OH and a single and identical absorption at around 225 nm was observed for the two precursors.[8,22] This band has previously been assigned to a ligand-to-metal charge transfer (LMCT) transition associated with complexation of the metal ions to the interior tertiary amines of the dendrimer.[20,22] It should be pointed out that the UV−vis spectra of the palladium(II)-dendrimer solutions remained unchanged after 3 months of storage under air, thus suggesting that these species are stable under these conditions for long periods of time.

Catalytic Studies—The Stille Reaction. We first examined the reaction of 4-iodobenzoic acid and phenyltin trichloride, which Crooks and co-workers have reported as being quantitative in 15 h at 23 °C at a loading of 0.1 mol % of Pd atoms in the form of G4-OH(Pd$_{40}$) DENs (**2**).[4] We decided to use reaction times of 24 h, Pd loadings of 0.3 mol % and higher temperatures as standard conditions (Table 1) to allow a better comparison with other less reactive substrates. The activity of Pd(OAc)$_2$ and Pd DENs (**1** and **2**) was similar under these conditions, with both affording complete conversion of iodobenzoic acid and isolated yields close to 100% at 40 °C (Table 1, entries 1 and 2). It should be noted, however, that the yields obtained after 6 h of reaction are 36% for Pd(OAc)$_2$ and 26% for DENs, thus indicating a somewhat superior initial activity for the acetate precatalyst. We were surprised to find that the palladium(II)-dendrimer catalysts were much less active and only afforded quantitative conversions at 80 °C (Table 1, entries 3−6).

Larger differences between the reactivity of palladium acetate and DENs were found in the case of the less water-soluble substrates. Thus, activated 4-iodoacetophenone reacted almost quantitatively in the presence of palladium acetate (**1**) at 40 °C (Table 1, entry 7) whereas the temperature had to be raised to 80 °C when using Pd DENs (**2**) or Pd^{II}-dendrimer complexes (**3**, **4**) to achieve yields close to 70% (Table 1, entries 8−11).[27] A similar trend was observed in the case of 3-iodopyridine or inactivated 4-iodoanisole, for which DENs were of little use and palladium acetate afforded moderate yields only at 80 °C (Table 1, entries 12−19). It can therefore be concluded that the general order of activity of the compared (pre)catalysts is Pd(OAc)$_2$ (**1**) > Pd DENs (**2**) ≫ dendrimer-palladium(II) complexes (**3**, **4**).

The presence of the dendrimer in catalysts **2**−**4** nevertheless has a positive impact on the reaction's selectivity, with these catalysts affording exclusively the cross-coupling product **5** with all substrates tested except for iodoanisole[28] (Table 1, entries 13−15). In contrast, 5−10% of homocoupling product **6** is systematically observed in all reactions with the dendrimer-free Pd(OAc)$_2$ catalyst.

These results might suggest that the simplest catalyst [Pd(OAc)$_2$] is the most efficient of the Pd catalysts compared here for the Stille reaction in water. However, this conclusion must be qualified when the viability of catalyst reuse is considered in this analysis. 4-Iodoacetophenone was selected for testing recyclability because all the catalysts afforded good yields at 80 °C with this substrate and the products could be extracted from the aqueous solution with diethyl ether once the reaction had finished. The aqueous solution was then recharged with a new load of reactants, and a new reaction cycle was started. The yields obtained in each cycle are compared in Table 2 for catalysts **1**−**4**.

It should be noted that the dendrimer-free Pd(OAc)$_2$ solution **1** was found to be completely inactive after the first reaction cycle whereas all the dendrimer-containing solutions conserved some degree of activity for at least four recovery cycles. The product yields decrease slowly but steadily for preformed Pd DENs (**2**), which is in contrast with the marked reduction found between the first and second cycles for the mixtures of dendrimer and palladium salts **3** and **4**. The amount of palladium remaining in solution after the first catalytic cycle provides a reasonable explanation for these results. The values measured quantitatively by ICP-MS are 7.011 (**1**), 141.42 (**2**), 74.81 (**3**), and 45.93 μg (**4**), which means that the amount of Pd remaining in solution after the

---

(25) Pellechia, P. J.; Gao, J.; Gu, Y.; Ploehn, H. J.; Murphy, C. J. *Inorg. Chem.* **2004**, *43*, 1421–1428.

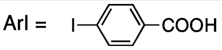
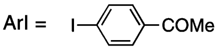
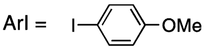
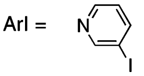
(26) Ooe, M.; Murata, M.; Mizugati, T.; Ebitani, K.; Kaneda, K. *Nano Lett.* **2002**, *2*, 999–1002.

(27) Pd DENs are more prone to aggregate at elevated temperature (>50 °C) and this should be taking into account when considering the results obtained at 80 °C here reported. See ref 4.

(28) It has been reported that the organometallic reagent employed for C−C coupling can react with palladium to give homocoupling products if the substrate reacts slowly with palladium. Chen, J.-S.; Vasiliev, A. N.; Panarello, A. P.; Khinast, J. G. *Appl. Catal., A* **2007**, *325*, 76–86.

Table 1. Cross-Coupling Reactions of Trichloro(phenyl)tin with Aryl Iodides in Water[a]

$$\text{Ar–I} + \text{PhSnCl}_3 \xrightarrow[\text{KOH / H}_2\text{O, 24 h}]{\text{0.3 mol\% [Pd]}} \underset{\mathbf{5}}{\text{Ph–Ar}} + \underset{\mathbf{6}}{\text{Ar–Ar}}$$

entry	catalyst	temp. (°C)	yield[b] (%)	selectivity[b] (**5**/**6**)
	ArI = 			
1	$Pd(OAc)_2$ (**1**)	40	87[c]	95/5
2	G4-OH(Pd_{40}) (**2**)	40	100[c]	100/--
3	G4-OH + 40 Na_2PdCl_4 (**3**)	40	18	100/--
4		80	81[c]	100/--
5	G4-OH + 40 $Pd(OAc)_2$ (**4**)	40	46	100/--
6		80	91[c]	100/--
	ArI = 			
7	$Pd(OAc)_2$ (**1**)	40	91[c]	90/10
8	G4-OH(Pd_{40}) (**2**)	40	17	100/--
9		80	66	100/--
10	G4-OH + 40 Na_2PdCl_4 (**3**)	80	66	100/--
11	G4-OH + 40 $Pd(OAc)_2$ (**4**)	80	68	100/--
	ArI = 			
12	$Pd(OAc)_2$ (**1**)	80	44	95/5
13	G4-OH(Pd_{40}) (**2**)	80	15	96/4
14	G4-OH + 40 Na_2PdCl_4 (**3**)	80	6	70/30
15	G4-OH + 40 $Pd(OAc)_2$ (**4**)	80	4	70/30
	ArI = 			
16	$Pd(OAc)_2$ (**1**)	80	60	95/5
17	G4-OH(Pd_{40}) (**2**)	80	3	100/--
18	G4-OH + 40 Na_2PdCl_4 (**3**)	80	traces	
19	G4-OH + 40 $Pd(OAc)_2$ (**4**)	80	traces	

[a] In a typical experiment, 2.0 mmol of $PhSnCl_3$, 0.50 equiv of the ArI, and 0.3 mol % of Pd catalyst were stirred for 24 h in 6.0 mL of a 3.0 M KOH/H_2O solution at the temperature given. [b] Isolated yields and selectivities determined by ^1H NMR integration. [c] 100% conversion based on ArI.

Table 2. Catalyst Recycling Experiments for the Reaction of Trichloro(phenyl)tin with 4-Iodoacetophenone in Water[a]

	yield (%)[b]			
cycle	$Pd(OAc)_2$ (**1**)	G4-OH(Pd_{40}) (**2**)	G4-OH +40 Na_2PdCl_4 (**3**)	G4-OH +40 $Pd(OAc)_2$ (**4**)
1	91	75	66	68
2	0[c]	62	22	26
3		55	25	17
4		42	26	20

[a] Each cycle was run for 24 h at 80 °C. See footnote *a* in Table 1 or the Experimental Section for other general conditions. [b] Yields and selectivities determined by ^1H NMR integration. [c] 4-Iodoacetophenone was recovered unreacted.

first cycle (initial palladium loading of 160 μg) ranges from 4% for dendrimer-free $Pd(OAc)_2$ (**1**) to 88% for the dendrimer-encapsulated nanoparticles (**2**). The recycling experiments therefore reflect the ability of the dendrimer to retain the palladium species in the aqueous phase, probably by preventing the aggregation of palladium(0) and its precipitation as palladium black (precipitation of palladium black is observed in all the reactions carried out with dendrimer-free $Pd(OAc)_2$) and also by enhancing the water-solubility of the encapsulated Pd species, thereby avoiding their migration into the organic solvent employed for extraction. It is worth noting that reduction of the dendrimer-encapsulated palladium(II) salts in situ affords composites which are less efficient than preformed DENs at retaining Pd in the reaction medium, at least after the first catalytic cycle.

The size of the preformed palladium nanoparticles **2**, as measured by TEM, after the fourth recycling run was 2.3 ±

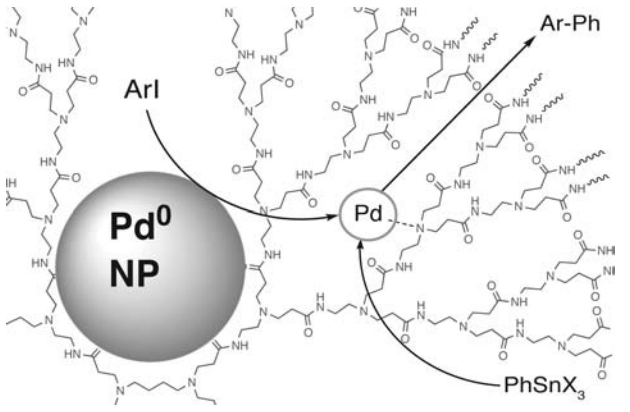


Figure 3. Suggested mechanism for the Stille reaction in water using the Pd DEN precatalyst **2**. The reaction is catalyzed by palladium species leached from the nanoparticle and coordinated to the dendritic interior.

0.6 nm (initial value: 1.6 ± 0.3 nm). A similar increase in the average particle size and size distribution of Pd DENs as a result of a catalytic reaction has been observed previously in this and related processes.[4,15] The TEM images taken from the $Pd(OAc)_2$-catalyzed reaction medium with 4-iodobenzoic acid at 80 °C show no nanoparticle formation after 15 min of reaction, whereas a few nanoparticles as big as 50 nm are detected after 2 h.[29]

Catalysis Inside/Outside Dendrimers. The above experiments shed some light on the nature of the catalytic process and, especially, on the role of the dendritic templates. On the basis of the results published in the literature and referred to in the introduction, we assume the existence of a dynamic equilibrium between the Pd nanoparticles and molecular palladium species during the catalytic process. The molecular species are most likely responsible for the observed activity and, in this sense, the comparison made in this work with molecular precursors such as palladium acetate is relevant. The leaching of palladium atoms from DENs is possibly produced after addition of ArI to the nanoparticle surface (Figure 3). A fraction of palladium(II) might then migrate from the dendritic interior to the solution, which explains the loss of palladium and the size increase of DENs observed during the recycling experiments. Pd^{II} species leached from the nanoparticle surface should, however, remain predominantly coordinated to the dendrimer during the catalytic process to explain the recurrent selectivity differences observed in the presence and absence of dendrimer. In this case, the lower yields obtained with the Pd^{II}-dendrimer complexes **3** and **4** with respect to those obtained with the Pd DENs **2** can only be ascribed to a poor efficiency of the initial Pd^{II} to Pd^0 reduction in the dendritic interior. On the other hand, it is foreseeable that this initial reduction is accompanied by partial decoordination of Pd from the dendrimer, thus explaining the loss of activity and palladium content after the first (and only after the first) catalytic cycle.

Conclusions

We have shown that palladium acetate affords excellent yields in the Stille reaction in an aqueous medium with some substrates and that this simple catalyst performs somewhat better than dendrimer-encapsulated palladium nanoparticles, whose excellent reported activities are apparently limited to water-soluble substrates. From a practical point of view, however, it is important to highlight that DENs can easily be recovered by liquid−liquid extraction and reused in several catalytic runs. The presence of the dendrimer suppresses the homocoupling side reaction, which is also important from a conceptual point of view because it implies that the catalysis occurs under the influence of the dendrimer. Finally, we would like to stress the importance of comparative studies between dendritic and non-dendritic catalysts to understand the exact role of dendrimers in catalysis.

Experimental Section

Chemicals and Materials. All the reactions were performed using standard Schlenk techniques under an argon atmosphere. Deionized water (type II quality) was obtained with a Millipore Elix 10 UV Water Purification System. Diethyl ether (HPLC grade) was dried and deoxygenated with purifier columns and collected under an argon atmosphere using an MBraun Solvent Purification System. Reagents and catalysts were used as received from commercial sources (Na_2PdCl_4 from Johnson Matthey, and $PhSnCl_3$, $NaBH_4$, $Pd(OAc)_2$ and aryl iodides from Aldrich). The fourth-generation, hydroxyl-terminated PAMAM dendrimer (G4-OH) with an ethylenediamine core was obtained as a 17.72% (w/w) solution in methanol from Dendritech. The solvent was removed under vacuum (3 h) and replaced by water prior to use.

G4-OH(Pd_{40}^{2+}) and G4-OH(Pd_{40}) were prepared according to previously reported methods[4,21,22] from PAMAM G4-OH dendrimer and Na_2PdCl_4, and were stored under argon.[30] Pd DENs were reduced using a 10-fold molar excess of $NaBH_4$ and the resulting solution was dialyzed against water using a regular cellulose membrane (cutoff of 12,400 Da, supplied by Aldrich). The final solution had a nominal Pd concentration of 1 mM (106 mg/L), although TXRF analyses of two independent samples gave reproducible results of 62.75 mg/L.

General Method for the Cross-Coupling Reactions. A mixture of trichloro(phenyl)stannane (0.33 mL, 2.0 mmol) and a 3.0 M aqueous solution of potassium hydroxide in water (6.0 mL, 18.0 mmol) was stirred at room temperature for 5 min. The corresponding iodoarene (0.50 mmol) and a 3.0×10^{-4} M solution (based on Pd atoms) of the corresponding catalyst (5.0 mL, 1.5 μmol, 0.3 mol % of Pd relative to the iodoarene) were subsequently added, and the reaction mixture was heated in an oil bath at 40 and 80 °C and stirred for 24 h. It was then allowed to cool to room temperature and extracted with diethyl ether (3 × 20 mL). In the case of the reaction with 4-iodobenzoic acid, the mixture was filtered prior to the extraction and acidified with aqueous 5% HCl. The combined ethereal layers were dried over $MgSO_4$ and the solvent eliminated in vacuo. The final yields were determined by ^1H NMR spectroscopy using hexamethyldisiloxane as an internal standard, and the spectroscopic data of the final products reported elsewhere (biphenyl-4-carboxylic acid in ref 4, and 4-acetylbiphenyl, 3-phenylpy-

---

(29) The observation of NPs might be obscured by the heterogeneity of the reaction media and, in fact, the TEM grids presented a great quantity of solid on the surface. In cross-coupling reactions carried out under similar conditions but using silanes as the organometallic reagent, we have observed the formation of Pd NPs even at room temperature. Gordillo, A.; de Jesús, E.; López-Mardomingo, C. *J. Am. Chem. Soc.* **2009**, doi: 10.1021/ja900333x.

(30) After 4 month of storage under air, we observed changes in the UV−vis spectra of the solutions that suggest oxidation of the metal. See ref 22.

ridine, and 4-methoxybiphenyl in ref 31). All the catalytic tests were repeated at least twice.

Catalyst Recycling. The first cycle was run as described above at 80 °C and using 4-iodoacetophenone as substrate. After extraction of the products with diethyl ether, the aqueous solution was separated and an additional 3 mL of the 3 M KOH solution was added to maintain a basic pH during the reactions. The aqueous solution was then recharged with trichloro(phenyl)silane (0.33 mL, 2.0 mmol) and 4-iodoacetophenone (0.126 g, 0.50 mmol). An additional amount of deionized water was subsequently added (2 mL), and the reaction continued at 80 °C for 24 h, as described above.

Characterization. ^{1}H NMR spectra were recorded with Varian Mercury 300, Unity 300, or Unity 500 Plus spectrometers. UV−vis absorbance spectra were recorded using quartz cells on a Perkin-Elmer Lambda 18 UV−vis spectrometer. The SIDI laboratories of the Universidad Autónoma de Madrid performed TXRF analysis with an 8030 C spectrometer (FEI COMPANY, Munich, Germany), equipped with two X-ray fine focus lines, Mo and W anodes, and a Si(Li) detector with an active area of 80 mm^2 and a resolution of 148 eV at 5.895 keV (Mn Kα). The same laboratories performed the ICP-MS analysis of the aqueous samples, which were diluted with 1% HNO_3 and then analyzed with an ELAN-6000 unit (Perkin-Elmer Sciex, Ontario, Canada) under the following instrumental conditions: RF power of 1200 W, nebulizer gas flow of 0.8 L/min, lens setting as auto lens, cross-flow nebulizer, and nickel cones. The ICP-MS acquisition settings were as follows: dwell time of 50 ms, number of sweeps equal to 30, 5 replicates, peak hopping scan mode, 1 MCA channels per peak, and a dual detector mode. All the samples were analyzed under the same instrumental conditions.

TEM images were obtained by the Microscopy Centre “Luis Bru” of the Universidad Complutense de Madrid using a JEOL 2000FX microscope operating at an accelerating voltage of 200 kV. Samples were prepared by placing two drops of the aqueous solutions on a holey-carbon-coated grid and allowing the solvent to evaporate in air. The average diameter was calculated by measuring the diameters of no less than 100 randomly selected metal particles from the non-aggregated areas in at least two micrographs of each sample.

Acknowledgment. We gratefully acknowledge financial support from the Spanish Ministerio de Educación y Ciencia (project CTQ2005-00795/BQU) and the Comunidad de Madrid (project S-0505/PPQ/0328-03 and a postdoctoral contract to M.B.).

Supporting Information Available: TEM images and size distribution histograms of the initial G4-OH(Pd_{40}) DENs and the same DENs after the four recycling runs with the 4-iodoacetophenone substrate. This material is available free of charge via the Internet at http://pubs.acs.org.

IC9002753

---

(31) Gordillo, A.; de Jesús, E.; López-Mardomingo, C. *Org. Lett.* **2006**, *8*, 3517–3520.