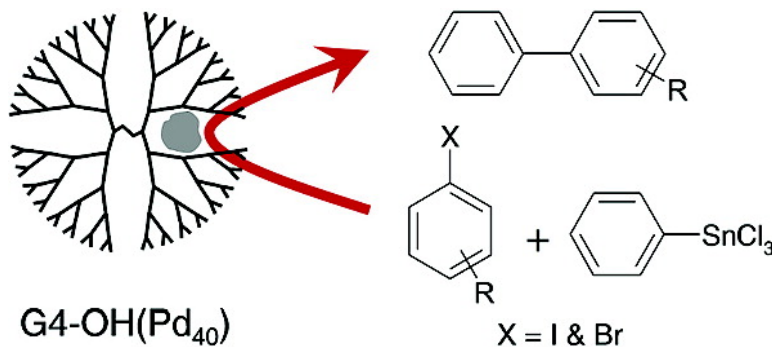


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## Dendrimer-Encapsulated Pd Nanoparticles as Aqueous, Room-Temperature Catalysts for the Stille Reaction

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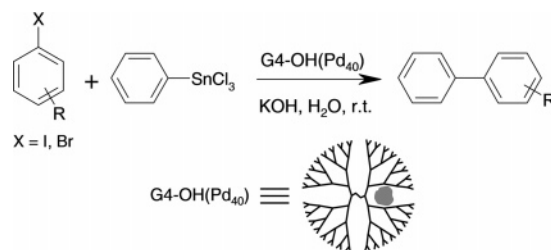
**Abstract:** We report that dendrimer-encapsulated Pd nanoparticles having a diameter of  $\sim 1.7$  nm are effective and general catalysts for coupling aryl halides to organostannanes (the Stille reaction) under mild conditions. The significant results of this study are that the Stille reaction is catalyzed by dendrimer-encapsulated Pd nanoparticles in very good yield, in aqueous solution at 23 °C, and using only 0.100 atom % of Pd as catalyst.

### Introduction

Here we report that dendrimer-encapsulated nanoparticles (DENSs),<sup>1–3</sup> consisting of size-monodisperse Pd nanoparticles within poly(amidoamine) (PAMAM) dendrimers, are effective catalysts for coupling aryl halides to organostannanes (the Stille reaction) in water at room temperature.<sup>4–6</sup> This is a significant result for three reasons. First, it expands the catalytic scope of DENSs for carbon–carbon coupling reactions, which have previously focused exclusively on Heck<sup>7–10</sup> and Suzuki<sup>11–13</sup> reactions. Second, DENSs catalyze the Stille reaction under mild conditions in water, which results in extended catalyst life and reduced likelihood of byproduct formation. Third, the reaction occurs with very good yields in most cases.

Several unique properties of DENSs<sup>1–3</sup> make them attractive for catalytic applications. First, solubility is controlled principally by the chemical composition of the dendrimer periphery.<sup>2</sup> This provides a means for carrying out reactions in green solvents such as water and supercritical CO<sub>2</sub>.<sup>1,2</sup> Second, because the particles are encapsulated within the dendrimer,<sup>1,3</sup> no additional ligands are required for stabilization. Third, their small size means they have a high surface-area-to-volume ratio, which is important for high efficiency.

### Scheme 1



We<sup>7,8,14–19</sup> and others<sup>9–13,20,21</sup> have previously reported the synthesis and characterization of monometallic Pd DENSs and showed they can be used as catalysts for hydrogenations,<sup>14–16,18–20</sup> 4-nitrophenol reduction,<sup>21</sup> Heck-coupling,<sup>7–10</sup> and Suzuki-coupling<sup>11–13</sup> reactions. In all cases where DENSs were previously used for C–C couplings, the reactions were carried out at elevated temperatures ranging from 78 to 140 °C.<sup>7–13</sup> The Stille reaction belongs to the larger family of Pd-catalyzed cross-coupling reactions.<sup>4–6</sup> These reactions are characterized by the coupling of an organostannane derivative with a carbon electrophile in the presence of Pd(0) (Scheme 1).<sup>4–6</sup> The classical conditions for performing the Stille reactions include the use of high reaction temperatures (typically 70–120 °C), organic solvents, a Pd(0) complex (or a Pd(II) salt, which is reduced in situ to Pd(0)), and a phosphine ligand to stabilize the Pd(0) complex. Although there are a few examples in which aqueous<sup>22–24</sup> or room-temperature<sup>25–28</sup> conditions were used for the Stille reaction, there is no precedent in the literature for

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this class of reaction being carried out both in water and at room temperature simultaneously. There are two reports of poly-disperse, polymer-stabilized Pd nanoparticles being used to catalyze the Stille reaction,<sup>29,30</sup> but in both cases the reactions required the use of an organic solvent and a temperature of at least 110 °C.<sup>29,30</sup> Here we report the use of highly monodisperse Pd nanoparticles for catalyzing the Stille reaction in high yield, at room temperature, and in water.

## Experimental Section

**Chemicals and Materials.** Fourth-generation, hydroxyl-terminated PAMAM dendrimers (G4-OH) having an ethylenediamine core were obtained as 25% aqueous solutions from Dendritech, Inc. (Midland, MI). All aryl halides, organostannanes, deuterated chloroform, KOH, NaBH<sub>4</sub>, and K<sub>2</sub>PdCl<sub>4</sub> were used as received from the Aldrich Chemical Co. (Milwaukee, WI). HCl 35%, HPLC-grade ethyl ether, and dichloromethane were purchased from EMD Chemicals Inc. Milli-Q water (18 MΩ·cm; Millipore, Bedford, MA) was used to prepare aqueous solutions.

**Preparation and Characterization of the Catalyst.** We previously reported the preparation of Pd DENs of the sort used here.<sup>15,18</sup> Nevertheless, a short summary of the basic procedure follows. A 25.0 μL amount of an aqueous 1.00 mM solution of G4-OH was mixed with 0.100 mL of 10.0 mM aqueous K<sub>2</sub>PdCl<sub>4</sub> in a total of 10.0 mL of water. This results in encapsulation of an average of 40 Pd<sup>2+</sup> ions within each dendrimer (G4-OH(Pd<sup>2+</sup>)<sub>40</sub>). Next, this composite was reduced by adding a 10-fold molar excess of NaBH<sub>4</sub> to give a G4-OH(Pd<sub>40</sub>) solution. The spectroscopic properties, size, and size distribution of these DENs were found to be consistent with published results.<sup>7,8,14–19</sup>

**Catalytic Reactions.** The same procedure was used for most of the catalytic reactions, but small deviations were necessary in some cases. These are identified in the appropriate locations in the Results and Discussion section. The reaction conditions used for the coupling of 4-iodobenzoic acid with phenyltin trichloride are presented as an example of the default procedure. A 124 mg (0.50 mmol) amount of 4-iodobenzoic acid and 604 mg (2.00 mmol) of phenyltin trichloride were completely dissolved in 6.00 mL of 3.0 M aqueous KOH and 2.00 mL of deionized water. Next, 5.00 mL of the 2.50 μM G4-OH-(Pd<sub>40</sub>) catalyst solution was added to the reactant mixture. The reaction was carried out for 15 h with stirring, and then it was quenched with 50 mL of 5% aqueous HCl. The aqueous mixture was treated with diethyl ether to extract the organic products, and the organic layer was washed with brine, dried with MgSO<sub>4</sub>, and filtered. After removing the solvent in a rotary evaporator, the product was analyzed (without additional purification) by <sup>1</sup>H NMR and GC-MS.

**Characterization.** UV–vis absorbance spectra were obtained at 23 ± 2 °C using quartz cells and a Hewlett-Packard model 8453 UV–vis spectrometer system (Hewlett-Packard, Wilmington, DE). UV–vis spectra of aqueous 2.50 μM G4-OH-(Pd<sub>40</sub>) solutions were collected using deionized water as the reference.

<sup>1</sup>H NMR spectra were recorded using a 300 MHz Unity p300 spectrometer. Spectra of the crude reaction products were obtained using deuterated chloroform as solvent in a standard 5 mm NMR tube.

MS spectra were obtained using a HP 5970 GC/MS. Because the samples were acidic and thus not compatible with GC, they were converted to trimethylsilyl esters prior to analysis using a standard method.<sup>31–33</sup> Specifically, 5–7 mg of the crude reaction mixture were weighed in a 2 mL vial, and then 200 μL of *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA) was added, resulting in the complete dissolution of the sample. This reaction was allowed to proceed for at least 2 h, and then the sample was diluted in CH<sub>2</sub>Cl<sub>2</sub> and injected to the GC. There was one exception to this procedure: 3-iodobenzoic acid was diluted in THF because it was insoluble in CH<sub>2</sub>Cl<sub>2</sub>.

Transmission electron microscopy (TEM) was performed using a JEOL 2010 transmission electron microscope (JEOL USA Inc., Peabody, MA). Samples were prepared by placing one drop of a DEN-containing solution on a holey-carbon-coated Cu grid (EM science, Gibbstown, NJ) and allowing the solvent to evaporate in air.

## Results and Discussion

We previously showed that hydroxyl-terminated PAMAM dendrimers (Gn-OH) can be used as templates for the encapsulation of Pd(0) and Pt(0) nanoparticles in aqueous solution.<sup>1–3,7,8,14–19,34</sup> The size of the entrapped metal nanoparticles can be controlled either by using different dendrimer generations or by manipulating the dendrimer/metal-ion ratio.<sup>1–3</sup> In the present study we investigated the Pd DEN-catalyzed Stille coupling reaction between aryl halides and organostannanes using aqueous KOH as the solvent (Scheme 1). The catalyst was synthesized by mixing a 40:1 molar ratio of PdCl<sub>4</sub><sup>2-</sup> and G4-OH. The product of this reaction is denoted as G4-OH-(Pd<sup>2+</sup>)<sub>40</sub> to indicate that an average of 40 Pd ions are present within each dendrimer. Reduction of G4-OH-(Pd<sup>2+</sup>)<sub>40</sub> with BH<sub>4</sub><sup>-</sup> results in zerovalent Pd DENs containing an average of 40 Pd atoms (G4-OH(Pd<sub>40</sub>)).

The catalyst was initially tested for the Stille reaction using 4-iodobenzoic acid and phenyltin trichloride because both are soluble in basic aqueous solutions. More specifically, 124 mg (0.500 mmol) of 4-iodobenzoic acid and 604 mg (2.00 mmol) of phenyltin trichloride were dissolved in 6.00 mL of 3.0 M aqueous KOH and 2.00 mL of deionized water. Next, 5.00 mL of the G4-OH-(Pd<sub>40</sub>) catalyst solution was added to the reactant solution, which corresponds to 0.100 atom % of the Pd catalyst with respect to 4-iodobenzoic acid. This is significantly lower than the 5–10 atom % of Pd normally used to catalyze the Stille reaction.<sup>4,6</sup> The reaction was carried out for 15 h with stirring, and then it was quenched with 50 mL of 5% aqueous HCl. The aqueous mixture was treated with diethyl ether to extract the organic products, and after removal of the solvent the product was analyzed with no additional purification.

Figure 1a shows the <sup>1</sup>H NMR spectrum of a mixture of 4-iodobenzoic acid and phenyltin trichloride dissolved in CDCl<sub>3</sub> prior to addition of the DEN catalyst. The peaks between 7.87 and 7.78 ppm are attributable to 4-iodobenzoic acid, and they correspond to the AB<sub>q</sub> system with the characteristic coupling constant of 1,4-disubstituted benzene rings (*J* = 8.8 Hz). The multiplet signal between 7.67 and 7.58 ppm is associated with phenyltin trichloride. Figure 1b is the <sup>1</sup>H NMR spectrum of the crude reaction product. Only one compound is represented in the spectrum, and it corresponds to the anticipated Stille coupling

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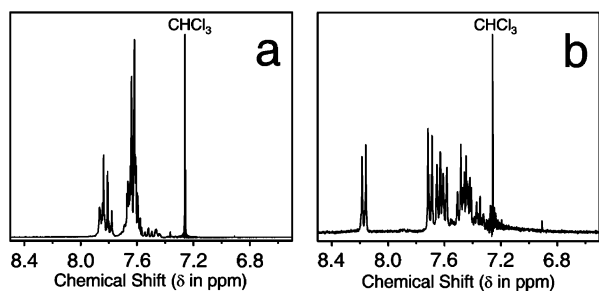
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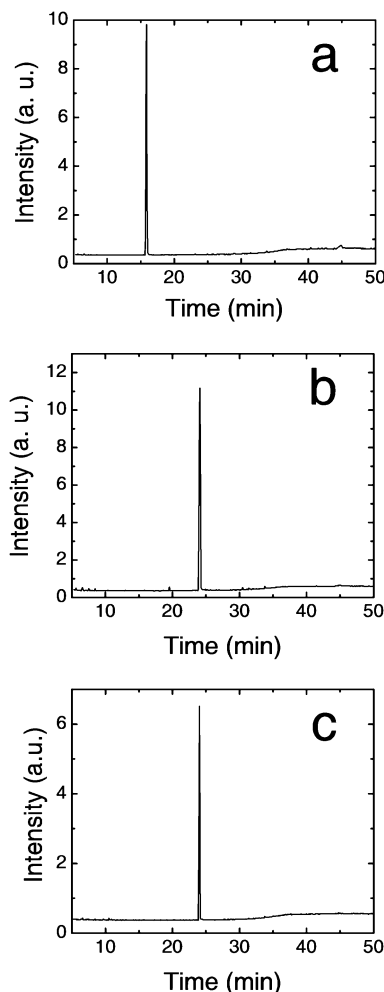
**Figure 1.**  $^1\text{H}$  NMR spectra in  $\text{CDCl}_3$  of (a) a physical mixture of 4-iodobenzoic acid and phenyltin trichloride and (b) the crude product of the Stille reaction. The spectra were recorded on a Unity p300 spectrometer at 300 MHz.

product biphenyl-4-carboxylic acid (Scheme 1). The signal appearing at 8.17 ppm corresponds to one-half of the  $\text{AB}_q$  system with a coupling constant of  $J = 8.8$  Hz. The other half of the  $\text{AB}_q$  system, which has the same coupling constant, is present at 7.70 ppm. This is characteristic of 1,4-disubstituted benzene rings. Between 7.66 and 7.40 ppm there is a multiplet associated with the phenyl moiety. Note that the characteristic peaks of the starting material are absent in Figure 1b.

GC-MS was used to confirm the identity of the final product and estimate the yield of the reaction. Standard methods were used to convert acidic products into the corresponding trimethylsilyl esters before injection into the GC-MS (see Experimental Section for details) to increase their volatility. For example, Figure 2a is a chromatogram of the derivatized 4-iodobenzoic acid starting material, and Figure 2b corresponds to an authentic sample of the anticipated product (biphenyl-4-carboxylic acid) after treatment with MSTFA. The mass spectrum of each peak confirmed that it corresponds to the trimethylsilyl derivatives (See Supporting Information). Figure 2c is a chromatogram of the derivatized crude product resulting from the DEN-catalyzed Stille reaction. The retention time and mass spectrum of the one peak present in this chromatogram match those of the anticipated product: biphenyl-4-carboxylic acid trimethylsilyl ester (Figure 2b). No peaks associated with the starting material or other byproducts were observed. Using 4-*tert*-butylphenol as an internal standard, it was possible to determine the yield of the reaction by  $^1\text{H}$  NMR and GC-MS (Supporting Information). Both methods indicated a yield of 100% for this substrate.

To ensure that the active catalyst in these studies was the Pd DENs, we carried out a number of control experiments. Specifically, reactions performed under identical conditions using G4-OH only (no Pd), the unreduced DEN precursor (G4-OH( $\text{Pd}^{2+}_{40}$ )), and an Au DEN (G4-OH( $\text{Au}_{55}$ ))<sup>35</sup> resulted in no evidence for formation of the Stille cross-coupling product.

In addition to 4-iodobenzoic acid, a number of other aryl halide substrates were tested to evaluate the generality of the DEN-catalyzed Stille reaction. Table 1 lists these reactants and the corresponding yields calculated from NMR and GC-MS data. Because we are primarily interested in using DEN catalysts under aqueous reaction conditions, all the halides selected for evaluation were either acids or phenols. For example, the first three entries in Table 1 are the three iodobenzoic acid isomers. Like 4-iodobenzoic acid, the yield for 3-iodobenzoic acid is



**Figure 2.** GC-MS spectra of (a) 4-iodobenzoic acid trimethylsilyl ester, (b) biphenyl-4-carboxylic acid trimethylsilyl ester, and (c) the crude product of the Stille reaction after derivatization with MSTFA.

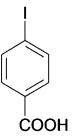
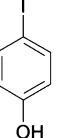
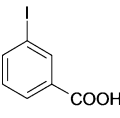
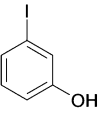
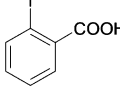

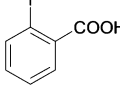
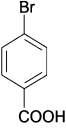
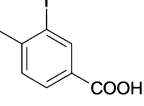
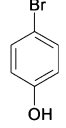
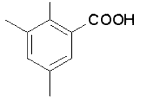
100%. However, the yield dropped to less than 15% for 2-iodobenzoic acid.

To understand these results we performed a few key control experiments. For example, we have previously shown that the dendrimer surrounding the encapsulated catalyst can lead to selectivity enhancements for substrates that are only slightly different from one another.<sup>15</sup> Accordingly, the reaction was carried out using the ortho isomer under the conditions described previously, but in this case the Pd catalyst was prepared in the absence of dendrimer (Table 1, Entry 4). No product was observed under these conditions, suggesting that the dendrimer is not responsible for the low conversion of the ortho isomer of iodobenzoic acid. Next, to determine if the low yield for 2-iodobenzoic acid is a consequence of steric hindrance between the two functional groups, the yield for 3-iodo-4-methylbenzoic acid (Table 1, Entry 5) was determined. This compound has a methyl group ortho to the iodine, which should be able to sterically hinder the approach of the substrate to the catalyst to more or less the same extent as an acid group. However, the corresponding Stille coupling product was found to be formed in quantitative yield. The most likely remaining possibility for the low yield of 2-iodobenzoic acid relates to unfavorable electronic interactions between the closely spaced iodine and carboxylic acid groups. To test this idea the reaction was carried out in the presence of 2-iodo-3,5-dimethylbenzoic acid (Table

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Table 1. Reaction Yields for the Stille Reaction Calculated by <sup>1</sup>H NMR and GC-MS

#	Ar-X	Yield NMR (%)	Yield GC-MS (%)	#	Ar-X	Yield NMR (%)	Yield GC-MS (%)
1		100	100	7		80	73 (26) <sup>a</sup>
2		100	100	8		75	77 (21) <sup>a</sup>
3		10	14	9		71	69 (10) <sup>a</sup>
4		0 <sup>b</sup>	0 <sup>b</sup>	10		100	100
5		100	100	11		79	76 (5) <sup>a</sup>
6		0	0				

<sup>a</sup> Values within parentheses correspond to the yield of the homocoupling byproduct when it was observed. <sup>b</sup> This reaction was carried out in the absence of dendrimer (Pd only). See text for details.

1, Entry 6). In this case no product was formed, which suggests that there is some generality to the observation of the ortho carboxylic acid isomers being less reactive than the others independent of the identity of the catalyst. Finally, an equimolar mixture of 4-iodobenzoic acid and 2-iodobenzoic acid was placed in the reaction vial simultaneously. This resulted in a biphenyl-4-carboxylic acid yield of <15%. This experiment clearly indicates that 2-iodobenzoic acid irreversibly passivates the catalyst, probably by adsorption onto the surface of the encapsulated Pd nanoparticle.

The experiments thus far described provide a basis for constructing a model to explain the poor turn over of 2-iodobenzoic acid compared to the other two isomers. It is accepted that the first step in this sort of catalytic carbon-carbon coupling reaction involves oxidative addition of the halide to the zerovalent metal catalyst.<sup>4,6</sup> It seems likely that the close proximity of the iodine and acid groups allows both of them to interact with the Pd nanoparticle (part b of Scheme 2). This bidentate interaction results in irreversible attachment of the substrate to the catalyst, thereby poisoning it. This same explanation has previously been used in other cross-coupling reactions to account for the reduced reactivity of 2-iodobenzoic acid in the presence of a homogeneous Pd catalyst.<sup>36,37</sup>

The effectiveness of the Pd DEN catalyst was also tested against substrates functionalized with Br rather than I and with phenols rather than acids. For example, entries 7–9 in Table 1 indicate that the yields for I-functionalized phenols is about 25% lower than those for the corresponding acids (entries 1 and 2 in Table 1). This is a consequence of formation of the homocoupling byproduct instead of the expected Stille compound. Specifically, the homocoupling byproduct of 4-iodophenol is [1,1'-biphenyl]-4,4'-diol, and its yield was about 25%. This homocoupling byproduct has been observed previously, but its origin is still uncertain.<sup>4,6</sup> Homocoupling has not been observed for acid derivatives.

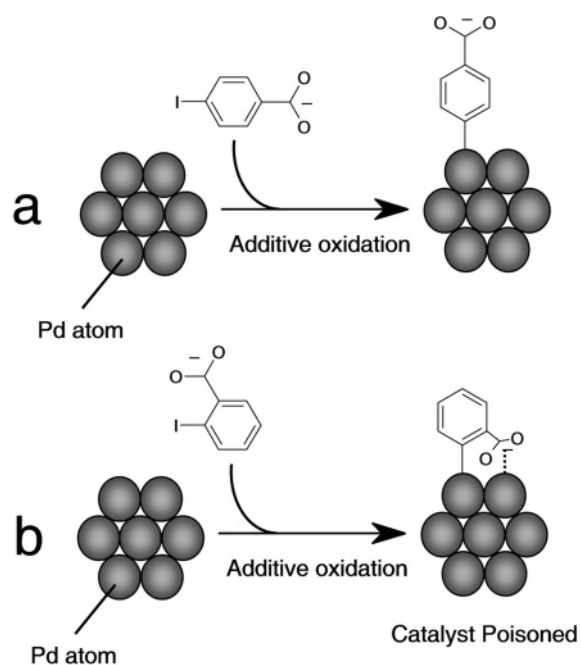
Bromide derivatives of the acid and phenol (Table 1, entries 10 and 11, respectively) also undergo Pd DEN-catalyzed Stille reactions. However, a higher concentration of the G4-OH(Pd<sub>40</sub>) catalyst was required to couple the bromides compared to the iodides (25.0 versus 2.50 μM, respectively) because of the lower reactivity of the bromide.<sup>4,6</sup> The reaction yields are good in both cases, but there is a significant contribution (5%) from the homocoupling byproduct for the phenol.

In addition to phenyltin trichloride, divinylidichlorotin, which is also soluble in aqueous base, was found to be active for the

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Scheme 2



Stille reaction. Specifically, divinylchlorotin and 4-iodobenzoic acid react in 40% yield to form 4-vinylbenzoic acid under the same catalytic conditions used for the analogous reaction with phenyltin trichloride. This reaction was not optimized, which may account for the low yield, but the main point is that Pd DEN is an effective Stille catalyst for at least two organostannanes.

The turnover frequency (TOF) for the Stille reaction was determined by  $^1\text{H}$  NMR to compare the efficiency of the catalyst for different substrates. For example, the TOF for the reaction between 4-iodobenzoic acid and phenyltin trichloride to yield biphenyl-4-carboxylic acid was determined for the G4-OH(Pd<sub>40</sub>) catalyst. This experiment was carried out by preparing 24.0 mL of a KOH solution containing 1.00 mmol of 4-iodobenzoic acid, 4.00 mmol of phenyltin trichloride, and 1.00 mmol of 4-*tert*-butylphenol as an internal reference. Next, 2.00 mL of a 2.50  $\mu\text{M}$  G4-OH(Pd<sub>40</sub>) catalyst solution was added to this mixture with stirring. Periodically, 2.00 mL aliquots were removed from the reaction mixture, the reaction in this aliquot was quenched with 1 mL of concentrated HCl, and the organic products present on the mixture were extracted with diethyl ether. Following evaporation of the organic layer, the  $^1\text{H}$  NMR spectrum was obtained for each aliquot, and the amount of final product was estimated by comparison of the integral of the product peaks with that of the 4-*tert*-butylphenol internal standard (Supporting Information). Figure 3a shows the result of this experiment. The reaction progresses more or less exponentially as a function of time and after 30 min reaches 50% completion. The TOF was determined using the linear part of the data at short times (times < 0.35 h) (Figure 3b). This results in a TOF of 2000 mol product $\cdot$ mol Pd<sup>-1</sup> $\cdot$ h<sup>-1</sup> for 4-iodobenzoic acid.

Table 2 summarizes the TOF values for a total of five Stille substrates. These values were all calculated from data like that shown in Figure 3a, and in all cases only the linear part of the curve was used to extract the TOF. To estimate the reproducibility of the TOF data, the reaction for two of the substrates, 4-iodobenzoic acid and 4-iodophenol, was repeated five times

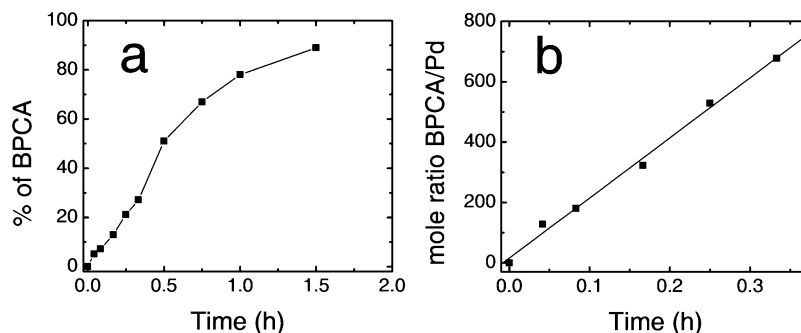
each (Table 2, entries 1 and 3). The TOF values reported for these two substrates correspond to the average of these five measurements, and the precision ( $\pm 200$  mol product $\cdot$ mol Pd<sup>-1</sup> $\cdot$ h<sup>-1</sup>) is represented by the standard deviation.

To better understand how the presence of the dendrimer affects the reaction, we compared the TOF for the G4-OH(Pd<sub>40</sub>)-catalyzed reaction between 4-iodobenzoic acid and phenyltin trichloride (Table 2, entry 1) with the identical reaction carried out in the absence of dendrimer (Table 2, entry 2). The latter reaction was performed with the same concentrations of substrates and the same amount of Pd. However, in this case the catalyst was prepared by reducing a 100  $\mu\text{M}$  aqueous K<sub>2</sub>PdCl<sub>4</sub> solution with a 10-fold molar excess of NaBH<sub>4</sub>. Because the Pd was reduced in the absence of the dendrimer template in this experiment, the catalyst was highly size polydisperse. In the absence of dendrimer, the TOF is a little lower. This is an important result because we have previously shown that dendrimers can hinder access of the substrate to the encapsulated nanoparticles. The extent of this barrier to mass transport depends on the size of the dendrimer, the size of the functional groups present on the periphery of the dendrimer, and the size of the reactants.<sup>3,15</sup> The higher TOF for the DEN-catalyzed Stille reaction implies that the higher surface area of the DENs offsets this barrier to mass transfer and results in a slightly more efficient catalyst.

Table 2 shows that the TOF for the DEN-catalyzed Stille reaction depends on the isomer used for the reaction. Specifically,  $\sim 20$ – $30\%$  lower TOFs were found for the meta compounds compared to the para derivatives. This similar trend has been reported for Stille reactions carried out using catalysts other than DENs.<sup>4,6</sup> Similarly, TOF values were lower by  $\sim 20$ – $30\%$  for the phenol compounds compared to the analogous acid derivatives. This finding is probably attributable to the lower solubility of the phenols in aqueous solutions or, as discussed earlier, to the competition of side reactions that result in the formation of homocoupled byproducts. The slight difference in the TOFs for the trisubstituted acid compared to the analogous disubstituted compound (Table 2, entries 6 and 4, respectively) could perhaps be attributed to the slight difference in size of these two compounds,<sup>15</sup> but confirmation of this speculation would require testing of substrates having a range of sizes.

The DEN catalysts were evaluated by transmission electron microscopy (TEM) before and after the Stille reaction (Supporting Information). Prior to reaction the metal core of the G4-OH(Pd<sub>40</sub>) catalyst had an average diameter of  $1.7 \pm 0.4$  nm, which is in accord with previous results obtained for similarly prepared materials.<sup>15,16,18</sup> After reaction the average diameter increased to  $2.7 \pm 1.1$  nm, indicating a modest amount of aggregation. To confirm that this aggregation was a consequence of the catalytic reaction, rather than just exposure to the solvent, a G4-OH(Pd<sub>40</sub>) solution identical to that used for the catalytic reaction was stirred overnight. The particle size before and after exposure to only the solvent resulted in a change in the particle diameter from  $1.7 \pm 0.4$  to  $1.9 \pm 0.6$  nm.

When the Stille reaction was carried out for 4-iodobenzoic acid and phenyltin trichloride in the presence of Pd DENs at elevated temperature (50, 70, and 90  $^{\circ}\text{C}$ ), aggregation was more pronounced and the product yield decreased (to 90%, 85%, and 82%, respectively). For example, after reaction at temperatures  $> 50$   $^{\circ}\text{C}$ , the solution was colorless rather than brown and a



**Figure 3.** (a) Plot of the percentage of biphenyl-4-carboxylic acid (BPCA) formed as a function of time. (b) Plot of the mole ratio of BPCA to Pd as a function of time. The solid line corresponds to the best linear fit of the data, and the slope represents the TOF value.

**Table 2.** Turnover Frequency (TOF) Values Estimated from  $^1\text{H}$  NMR

Entry	R-Ph-X	TOF <sup>a</sup> ( $10^3$ )	Entry	R-Ph-X	TOF <sup>a</sup> ( $10^3$ )
1		$2.0 \pm 0.2^b$	4		1.6
2		$1.8^c$	5		1.0
3		$1.6 \pm 0.2^b$	6		1.5

<sup>a</sup> The units for turnover frequency (TOF) are  $\text{mol product} \cdot \text{mol Pd}^{-1} \cdot \text{h}^{-1}$ . <sup>b</sup> These reactions were repeated five times each to estimate the reproducibility of the TOF data. The TOF values reported correspond to the average of these five measurements, and the estimated precision corresponds to one standard deviation from the average. <sup>c</sup> This reaction was carried out in the absence of dendrimer (Pd only). See text for details.

black precipitate was observed in the bottom of the flask. However, at temperatures  $< 50^\circ\text{C}$ , the color of the solution did not change after reaction and no precipitate was observed, indicating that the catalyst remains water soluble and thus encapsulated within the dendrimer. The instability of the catalyst at higher temperatures is likely attributable to dendrimer decomposition.<sup>1</sup>

When the G4-OH(Pd<sub>40</sub>) catalyst is used at room temperature, it remains active even after a reaction is taken to completion. This was demonstrated by running two sequential Stille reactions as follows. A 110 mg (0.500 mmol) amount of 4-iodophenol was placed in one 30 mL vial, and 124 mg (0.500 mmol) of 4-iodobenzoic acid was placed in another. A 604 mg (2.00 mmol) amount of phenyltin trichloride was added to each of the two vials, and the mixtures were dissolved in 6.00 mL of 3.0 M aqueous KOH and 2.00 mL of deionized water. Next, 5.00 mL of the G4-OH(Pd<sub>40</sub>) catalyst solution was added to the vial containing 4-iodophenol, and the reaction was allowed to proceed for 15 h. After this first reaction the solution in the second vial containing 4-iodobenzoic acid was added to the just-completed reaction mixture in the first vial. If the DEN catalyst was still active, then we expected that conversion of 4-iodobenzoic acid to biphenyl-4-carboxylic acid would proceed just as if the reaction with 4-iodophenol had not preceded it. After

15 h the second reaction was quenched and the catalyst and organic products were extracted in diethyl ether. Analysis of this mixture by GC-MS revealed the presence of the product of the first reaction (4-phenylphenol) in 73% yield and the presence of the second reaction (biphenyl-4-carboxylic acid) in 80% yield. This result indicates that the catalyst remains active after the first catalytic cycle.

## Summary and Conclusions

To summarize, we have shown that Pd nanoparticles encapsulated within the interior of PAMAM dendrimers are catalytically active for the Stille reaction. The main result of this study is that the Stille reaction is catalyzed by Pd DENs for many different substrates. Moreover, the reaction takes place under very mild conditions (water, room temperature) and with good yields. Finally, the Stille reaction is the third class of carbon-coupling reactions that DENs have been demonstrated to catalyze,<sup>7-9,11-13</sup> and therefore, there is a reason to believe these catalysts are generally useful for organic transformations. This is interesting because it is somewhat surprising that two such large reactants (Scheme 1) could find their way into the restricted volume of the dendrimer interior, encounter the catalyst, and react.

We have previously shown that the dendrimer portion of DEN catalysts is often not a passive component but that it can be used to impart substrate and product selectivity to intrinsically nonselective metal nanoparticles.<sup>3,15</sup> Looking to the future, therefore, it may eventually be possible to design dendrimers that result in formation of unusual Stille coupling products.<sup>8</sup> We have also recently shown that well-defined bimetallic nanoparticles can be prepared within DENs,<sup>38</sup> and therefore, it should be possible to study TOFs and product yields for carbon-coupling reactions as a function of catalyst size, structure, and composition using the approach described in this report.

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**Supporting Information Available:** UV–vis absorbance spectra of G4-OH(Pd<sub>40</sub>), experimental conditions used for the Stille reaction, determination of the reaction yield by <sup>1</sup>H NMR and GC-MS using an internal standard, and HRTEM micrographs of G4-OH(Pd<sub>40</sub>) before and after catalytic reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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