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# Heck Heterocoupling within a Dendritic Nanoreactor

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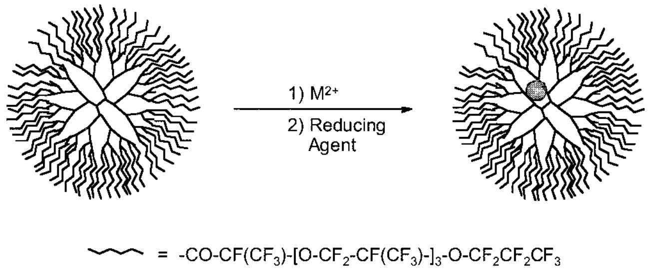
## ABSTRACT

**Palladium nanoparticles (2–3 nm in diameter) have been prepared within covalently functionalized poly(propylene imine) (PPI) dendrimers, and the resulting composite materials are shown to be effective for Heck coupling reactions. Two novel concepts are demonstrated in this report. The first concept involves the incorporation of $Pd^0$ nanoparticles into PPI dendrimers covalently functionalized with perfluorinated polyether chains on their periphery. The second concept involves the first example of a carbon–carbon coupling reaction catalyzed by a dendrimer-templated nanomaterial, specifically, the catalytic heterocoupling between nonactivated aryl halides and *n*-butylacrylate mediated by the dendrimer-encapsulated catalysts. These reactions were carried out in a homogeneous fluorous/organic reaction phase at elevated temperature, and the catalyst was recovered by cooling to room temperature and concomitant phase separation. The catalyst was found to be catalytically active at a reaction temperature of only 90 °C in the absence of toxic phosphines, and it was 100% selective for the production of *n*-butyl-*trans*-formylcinnamate with unoptimized isolated yields up to 70%. The recovered catalysts retained a significant fraction of the original activity, comparable to coordination complex catalysts that use a similar catalyst recovery system.**

We have previously shown that dendrimer-encapsulated metal nanoparticle catalysts (DECs)[1−6] are useful for simple catalytic hydrogenation reactions of alkenes in aqueous,[6] organic,[2] and fluorocarbon[1] solutions. However, until now, the potential scope of these catalytic materials has not been demonstrated. Here, we present the first example of a heterocoupling reaction catalyzed by dendrimer-encapsulated nanoparticles. Specifically, we show that $Pd^0$ nanoparticles sequestered within covalently derivatized poly(propylene imine) (PPI) dendrimers are effective for the coupling of unactivated aryl halides with *n*-butylacrylate at 90 °C in the absence of toxic phosphines. The selectivity is 100% for the production of the *n*-butyl-*trans*-formylcinnamate (**1**) isomer. The results suggest that many other organic reactions can likely be performed using variations of similar dendrimer-based nanoreactors and that the nature of the dendrimer host influences the reaction product distribution. Moreover, the reactions described here were carried out in a fluorocarbon/hydrocarbon solvent mixture, which is an effective system for the recovery and reuse of DECs.

Until now, we have prepared DECs exclusively from poly(amidoamine) (PAMAM) dendrimers. Poly(propylene imine) (PPI) dendrimers, on the other hand, are far more stable at elevated temperatures,[7] and therefore, they are better suited for applications in which long periods of refluxing at high temperatures are necessary, such as for the Heck chemistry reported here. The DECs used in this study were prepared by introducing $Pd^{2+}$ into the interiors of amine-terminated PPI dendrimers, which were previously end-group derivatized (>90%) with perfluorinated polyether chains.[8] In contrast to fluorous-soluble DECs previously prepared by ionic assembly,[1] covalent attachment of the chains to the dendrimer scaffold further enhances the thermal stability of the catalytic ensemble. The resulting dendrimer/$Pd^{2+}$ coordination complex was chemically reduced to yield dendrimer-encapsulated $Pd^0$ nanoparticles (Scheme 1).[9] Both fourth- (PPI-32, where 32 represents the number of amine terminal groups) and fifth-generation (PPI-64) dendrimers were used as templates to investigate the effect of dendrimer generation on the size of the particles and subsequent catalysis while maintaining an identical average Pd concentration.

**Scheme 1**



$= \text{-CO-CF(CF}_3\text{)-[O-CF}_2\text{-CF(CF}_3\text{)-]}_3\text{-O-CF}_2\text{CF}_2\text{CF}_3$

The perfluorinated polyether-derivatized poly(propylene imine) (PPPI) dendrimers containing $Pd^0$ nanoparticles (PPPI-32/$Pd^0$ and PPPI-64/$Pd^0$) could be dried to a residue and fully

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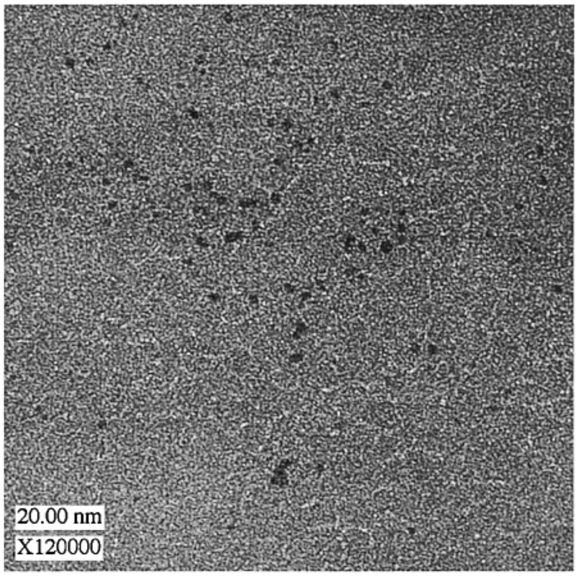


**Figure 1.** High-resolution transmission electron microscopy (HRTEM) image of the PPPI-32/Pd$^0$ nanocomposite prepared on a holey carbon copper grid by evaporation of a dilute fluorocarbon solution of the dendrimer composite.

redissolved in a variety of perfluorinated solvents without detectable agglomeration or precipitation. High-resolution transmission electron microscopy (HRTEM) indicates that the Pd$^0$ nanoparticle diameters are nearly monodisperse (2.2 $\pm$ 0.3 nm for PPPI-32/Pd$^0$ and 2.1 $\pm$ 0.3 nm for PPPI-64/Pd$^0$), although they are not very electron opaque (Figure 1). These observations are consistent with a composite having metallic nanoparticles embedded among the branches of the dendrimers[5] (excluding the covalently attached fluorocarbon-chains, the mean dendrimer diameters are 2.5 and 3.1 nm, respectively).[10] Hence, on the basis of the HRTEM data, we conclude that the average size of the dendrimer-encapsulated nanoparticles is independent of dendrimer generation when the dendrimer/Pd$^{2+}$ ratio is held constant (i.e., the size of the particle depends on the number of metal ions sequestered in the dendrimer template, not necessarily on the size of the template).[6]

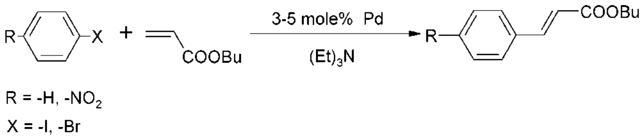
We investigated the DEC-catalyzed coupling of aryl halides with *n*-butylacrylate as an example of the widely useful Heck reaction (Scheme 2 and Table 1)[11,12] using a fluorocarbon/hydrocarbon solvent-based catalyst recovery system,[13−16] which has been shown to be effective for separating a coordination complex Heck catalyst from the reaction products.[17] The coupling takes place with the DECs at 90 °C, in contrast to temperatures in excess of 120 °C used for colloidal Pd$^0$ Heck catalysts[18−24] under homogeneous reaction conditions. Selectivity for the production of the trans isomer of *n*-butyl-formylcinnamate (**1**) has previously been reported to be in the 74-98% range using a fluorous phase-soluble Pd$^0$ complex.[17,25] However, both generations of DECs provide 100% selectivity for (**1**) under all the conditions investigated (Table 1). This finding strongly suggests that the intradendrimer nanoenvironment can be used to impart regio-selectivity in the product distribution. Although we do not at present have a viable model to explain this high level of selectivity, we propose that it may be due to the sterically confined environment within the dendrimer nanoreactor.

**Table 1:** Results Obtained from Heck Coupling of *n*-butylacrylate (BA) with Aryl Halides under Various Conditions Using 3−5% Mol Pd PPPI-32/Pd$^0$ and PPPI-64/Pd$^0$ Catalysts[f]

| catalyst | −R | −X (mmol) | base (mmol) | BA (mmol) | % yield |
|---|---|---|---|---|---|
| PPPI-64/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89) | 0.63 | 34 |
| PPPI-64/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 0.63 | 19[a] |
| PPPI-64/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 38[e] |
| PPPI-64/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 27[a, e] |
| PPPI-64/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 70 |
| PPPI-64/Pd$^0$ | H | Br(0.63) | Et$_3$N (1.89)) | 0.63 | 26 |
| PPPI-64/Pd$^0$ | H | Br(0.63) | Et$_3$N (1.89)) | 1.89 | 7[a] |
| PPPI-64/Pd$^0$ | H | Br(0.63) | none | 1.89 | 19 |
| PPPI-64/Pd$^0$ | H | Br(0.63) | none | 0.63 | 0[a] |
| PPPI-64/Pd$^0$ | NO$_2$ | Br(0.63) | Et$_3$N (0.63) | 0.63 | ≈10[b] |
| PPPI-32/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 38 |
| PPPI-32/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 28[c] |
| PPPI-32/Pd$^0$ | H | I (0.63) | Et$_3$N (1.89)) | 1.89 | 37[d] |
| PPPI-32/Pd$^0$ | H | I (0.63) | none | 1.89 | 59 |
| PPPI-32/Pd$^0$ | H | Br(0.63) | Et$_3$N (1.89)) | 0.63 | 10 |
| PPPI-32/Pd$^0$ | NO$_2$ | Br(0.63) | Et$_3$N (1.89)) | 1.89 | ≈11[b] |

[a] These reactions were performed with recovered catalysts. [b] The yields were estimated by NMR. [c] Hydrogen gas was used to reduce the palladium. [d] The DEC was refluxed for 24 h in the solvent mixture before the reactants were added. [e] Palladium acetate was used as the metal source. [f] The −R and −X groups are defined in eq 1.

**Scheme 2**



A number of other interesting conclusions can be drawn from the data in Table 1. Although turnover was observed when a 1:1 ratio of aryl halide to acrylate was used (10−34%), the yields improved significantly with a 3-fold excess of the olefin (28−70%). We also observed that the PPPI-64/Pd$^0$ DEC resulted in a substantially greater yield (70%) than that of the PPPI-32/Pd$^0$ catalyst (38%) under similar reaction conditions and similar Pd loading (3−5 mol %). In these experiments, equal amounts of Pd$^0$ were maintained and the average particle size was the same. Accordingly, in the PPPI-64/Pd$^0$ nanoreactor, the metallic particle is in a less confining space than it is in the PPPI-32 dendrimer. We conclude that the roomier PPPI-64 host allows the reactants easier access to the catalytic particle, which accounts for the greater product yield.

The data in Table 1 also indicate a small decrease in yield upon changing the halide from −I to −Br, but still compares favorably with a previous report utilizing homogeneous colloidal Pd$^0$ particles for the coupling of aryl-bromides and olefins.[18] Unfortunately, aryl chlorides could not be activated with the DEC. In contrast to results from prior Heck studies,[17,26] we observed a large decrease in reactivity when a *para*-nitro activated aryl halide substrate is used. We attribute this finding to the repulsive forces between the electron-rich nitro group and the perfluorinated polyether chains, making penetration of the nitro-functionalized aryl halide through the perfluorinated shell to the nanoparticle surface difficult. This finding again demonstrates that DECs provide an intuitive route to the design of selective catalysis.[2,6] Overall, the yields obtained for unactivated substrates using the novel nanoparticle catalysts (10−70%) falls within the range found when colloidal Pd particles are utilized (2−95%).[18−23]

The nanoreactors can be fully recovered after each reaction. The fluorous phase retains the dark colored catalyst, and the organic phase remains colorless. There is no detectable precipitation, flocculation, or formation of Pd black on the glassware. Additionally, direct current plasma (DCP) analysis on the recovered organic phase shows that no Pd metal is leached from the nanoreactors ($<$0.01 ppm, detection limited). However, catalytic activity does decrease significantly upon successive recovery/catalysis cycles. Pd coordination complexes with specially synthesized perfluorinated phosphine ligands typically show a difference in yield of 20% upon recycling in a fluorous/organic biphasic reaction medium.[17] In contrast, the DECs show only a difference in yield of 10−15% upon utilization in a second catalytic cycle (Table 1) under similar conditions. Some stabilized Pd$^0$ colloids have shown a tendency toward deactivation upon storage,[22] but DEC solutions show no appreciable change in activity upon storage. More importantly, refluxing the DEC in the reaction solvent system for 24 h prior to addition of the substrates does not significantly change the catalytic activity (Table 1), which also indicates a high level of stability of the DEC nanocomposite. At present, we believe that the observed deactivation of DECs can be explained by changes in the morphology of the Pd nanocluster surface brought about by redox cycling of the Pd atoms, which is a natural consequence of the Heck reaction.[22]

It is interesting to note that most Heck coupling reactions involving palladium complexes require the presence of a base to regenerate the catalyst,[26] however, these DECs are active in the absence of added base. It is possible that the interior tertiary amines of the PPI dendrimer act as the base in this case. Unfortunately, when base is not added, catalytic activity is completely lost after recovery of the catalyst. Efforts are underway to determine the exact cause(s) of DEC deactivation under these conditions.

In conclusion, we have shown that PPI dendrimers having covalently attached perfluorinated polyethers can act as templates for the formation and entrapment of nanoscopic Pd$^0$ particles. Importantly, these dendrimer-based nanoreactors can catalyze the coupling of unactivated aryl halides with butylacrylate in the absence of toxic ligands in a highly selective manner and can do so in an environmentally friendly reaction system. Thus, this represents the first example of an intradendrimer carbon−carbon coupling reaction using DECs. The reaction temperatures are fairly mild compared with other colloidal systems and should be useful when coupling of thermally delicate olefins is desirable. Further refinement of the catalyst and reaction conditions should lead to optimization of yields. We believe this general approach to catalysis will be broadly applicable to many reactions, and that when more is learned about how the dendrimer interior can control selectivity, these materials will be of great use to synthetic organic chemists.

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(9) *Synthesis of PPPI-32/Pd0 and PPPI-64/Pd0.* The preparation of PPPI-32/Pd$^0$ is described below, and it can be easily adapted for the synthesis of PPPI-64/Pd$^0$. All manipulations were performed under ambient laboratory conditions. A 50.0 mg (0.002 mmol) portion of 90% derivatized PPPI-32[8] was dissolved in 5 mL of $C_2F_3Cl_3$ (CFC-113). A 10.4 mg (0.032 mmol) portion of $K_2PdCl_4$ was then dissolved in 5 mL of a 50% ethanol:water solution and added to the fluorocarbon phase with rapid stirring forming an emulsion. Brief sonication induced phase separation. The aqueous-ethanol phase was removed, and the CFC-113 phase was repeatedly washed with deionized water. A solution containing 6.0 mg (0.160 mmol) of $NaBH_4$ in 1 mL of water was added to a stirred solution of the PPPI-32/Pd$^{2+}$ complex. The golden yellow solution immediately turned dark brown. After 10 min, an equal volume of water was added. The dark-colored fluorous phase was removed and washed with an ethanol:water solution (1:5) followed by an equal volume of pure water. This wash cycle was repeated at least 3 times. Following the evaporation of the fluorocarbon solvent, the nanocomposite could be isolated as a tacky residue.

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ether was added to the fluorous phase to ensure total extraction of the product. The organic phases were combined and washed with dilute HCl solution followed by deionized water. Upon removal of the solvent, the product **(1)** was isolated in 19−70% yield, and the purity was confirmed by NMR.
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