2010

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## COMMUNICATIONS

# Highly Active Heterogeneous Palladium Nanoparticle Catalysts for Homogeneous Electrophilic Reactions in Solution and the Utilization of a Continuous Flow Reactor

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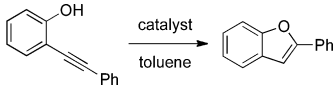
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**Abstract:** A highly active heterogeneous Pd-nanoparticle catalyst for the intramolecular addition of phenols to alkynes was developed and employed in a continuous flow reaction system. Running the reaction in flow mode revealed reaction kinetics, such as the activation energy and catalyst deactivation, and provides many potential practical advantages.

One of the major research directions in the pharmaceutical and fine chemical industries is to convert homogeneous catalytic reactions to heterogeneous versions through immobilization of homogeneous catalysts on polymer or inorganic supports.[1,2] The heterogenized catalysts offer the opportunity of easy catalyst recycling which is particularly important for precious metal catalysts. Additionally, these catalysts may be employed in continuous flow processes, which provides many additional potential advantages, such as improved product quality and yields, facile automation, easy scale-up without substantial further optimization, and improved safety.[3–5] However, in most cases, homogeneous catalysts cannot be simply replaced by a heterogeneous counterpart, due to the well-known problem of lower activity and selectivity.[6] Thus, new catalysis concepts for developing heterogeneous variants of homogeneous catalysts, which avoid these issues, are of paramount importance. Herein, we report the development of a heterogeneous Pd-nanoparticle based catalyst that exhibits superior catalytic activity for $\pi$-bond reaction and its application in a continuous flow reactor.[7]

The Pd nanoparticles were synthesized by using a fourth generation PAMAM dendrimer as the capping agent. The ratio between the palladium salt, $K_2PdCl_4$, and PAMAM dendrimer was 40:1, which resulted in 1 nm diameter nanoparticles.[8] After purification by dialysis, the 40 atom Pd nanoparticles ($Pd_{40}$) were supported on high surface area mesoporous silica, SBA-15.[9] In a recent report, we documented that SBA-15-supported Pt nanoparticles can catalyze a range of $\pi$-bond activation reactions. Prior to this report, they were only known to be catalyzed through homogeneous processes.[10] The analogous $Pd_{40}$ nanoparticles were found to be excellent in catalyzing these reactions, at significantly faster rates.[11] Strikingly, the supported catalyst $Pd_{40}$/SBA-15, using toluene as the solvent and $PhICl_2$ as the oxidizer, showed a much higher activity than all of the homogeneous catalysts surveyed. For example, the hydroalkoxylation of 2-phenylethynylphenol reached completion within 15 h at 20 °C (Table 1, entry 1). Under otherwise identical conditions, $PdBr_2$, known in the literature to catalyze this reaction at room temperature,[11] only gave 6% yield of 2-phenylbenzofuran after

**Table 1.** Heterogeneous and Homogeneous Pd Catalysts for the Hydroalkoxylation of 2-Phenylethynylphenol



| entry | catalyst | loading, mol % | temp, °C | reaction time, h | NMR yield, %[a] |
|---|---|---|---|---|---|
| 1[b] | $Pd_{40}$/SBA-15 | 4 | 20 | 15 | 95 |
| 2 | $PdBr_2$ | 4 | 20 | 15 | 6 |
| 3[c] | $PdBr_2$ | 4 | 20 | 15 | 9 |
| 4 | $PdCl_2$ | 4 | 20 | 15 | 3 |
| 5 | $PdCl_2$ | 4 | 100 | 15 | 25 |
| 6 | $Pd(NCMe)_2Cl_2$ | 4 | 100 | 15 | 7 |
| 7[b] | $Pd(NCMe)_2Cl_2$ | 4 | 100 | 15 | 8 |
| 8 | $[(allyl)PdCl]_2$ | 2 | 100 | 15 | 0 |
| 9 | $Pd(PPh_3)_4$ | 4 | 100 | 15 | 0 |

[a] Determined by using mesitylene as an internal standard. [b] $PhICl_2$ (12 mol %) was added. [c] Dichloromethane was used as solvent.

15 h (entry 2–3). A homogeneous catalyt potentially related to the present $Pd_{40}$/SBA-15/$PhICl_2$ system, $PdCl_2$, only resulted in 3% of the desired product (entry 4). The diminished yields associated with $PdBr_2$ and $PdCl_2$ were most likely due to their minute solubility in toluene at room temperature. However, increasing the reaction temperature to 100 °C only caused a moderate improvement of the yield (entry 5). A few other Pd complexes were surveyed, including $Pd(NCMe)_2Cl_2$, $[(allyl)PdCl]_2$, and $Pd(PPh_3)_4$, but the product was not formed to any significant extent (entries 6–9). Notably, the combination of $Pd(NCMe)_2Cl_2$ and $PhICl_2$ did not prove beneficial (entry 7). The low conversion observed at 100 °C using homogeneous catalysts was presumably the consequence of rapid catalyst decomposition.

$PtCl_2$, $Rh(CO)_2(acac)$, and cationic Ir hydride complexes are also known as competent catalysts for this transformation, but they typically require elevated temperatures to be efficient.[13–15] For example, with 5 mol % loading of $PtCl_2$, 97% yield was achieved within 1.5 h at 80 °C.[15] Moreover, Zhang et al. reported that, with a homogeneous Au catalytic system, $(Ph_3P)AuCl/AgOTf$, a 95% yield of benzo[b]furan could be obtained at room temperature in 0.5 h;[16] however, the heterogeneous $Pd_{40}$/SBA-15 catalysts reported herein can be easily separated, recycled, and applied in a continuous flow reactor.

Catalyst leaching is one of the major obstacles in heterogenizing homogeneous catalytic reactions, in which case the reaction is actually catalyzed by the leached active species presented in solution. Therefore, having demonstrated the superior activity of
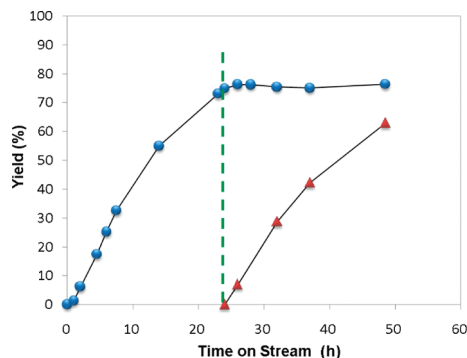
**Figure 1.** Pd$_{40}$ nanoparticles supported on silica mesoporous pellet were used as the catalyst for the hydroalkoxylation of 2-phenylethynylphenol. The reaction reached 75% yield after 24 h. Reaction solution was then removed from the reaction vessel under anaerobic conditions. A new solution with starting material was recharged (indicated by the green dashed line). In the removed solution, the reaction ceased (blue dots after green dashed line), which indicates that no active homogeneous catalysts leached into the solution. In the recharged solution, the reaction progressed (red triangles) at almost the same rate as the first run.

the Pd$_{40}$/SBA-15 catalytic system, it was necessary to exclude the possibility that the supported Pd$_{40}$/SBA-15 exhibits its catalytic function homogeneously by leached active Pd species. Pd$_{40}$ nanoparticles were supported on pelletized mesoporous silica.[10] The pelletized catalyst does not form a fine suspension under the reaction conditions; thus the solution phase of the reaction medium can be easily and cleanly separated from the solid component without any filtration, which involves exposure to air and may cause the deactivation of the active catalyst.[6] As shown in Figure 1, the conversion stopped after the solution was removed from the reaction vessel (blue dots after the green dashed line), indicating that Pd$_{40}$/SBA-15 did not leach out any homogeneous active species in solution. Moreover, the reaction occurred at the same rate when we added a fresh substrate solution to the reactor containing the pellet catalyst (red triangles in Figure 1). Elemental analysis was also conducted, which showed no evidence of Pd leaching (see Supporting Information).

Since no leaching of catalytically active species was detected from the Pd$_{40}$/SBA-15 catalyst, this catalyst was applied in a fixed bed plug flow reactor to catalyze the reaction in a continuous flow mode (see Supporting Information), the purpose of which being to avoid the necessity of separating the catalyst from reaction medium. Furthermore, as long as a highly active heterogeneous catalyst can achieve a full conversion of reactants to products, any further purification of the product is obviated, since the reaction stream coming out from the flow reactor will only contain pure product. Since the heterogeneous Pd$_{40}$/SBA-15 catalyst is very active for the hydroalkoxylation reaction, it would be possible to achieve 100% conversion of 2-phenylethynylphenol in a continuous flow reactor with reasonable catalyst loading and acceptable reactant concentration and flow rate. As shown by the blue dots in Figure 2, Pd$_{40}$/SBA-15 pretreated with PhICl$_2$ was initially able to convert 2-phenylethynylphenol to 2-phenylbenzofuran completely at room temperature. However, the catalytic activity quickly deteriorated to less than 5% conversion after 15 h. However, when the reaction solution contained 5 mM of PhICl$_2$, the activity was restored. A complete conversion to 2-phenylbenzofuran was observed for more than 10 h. Note that, in the latter case, the oxidation agent constantly flowed through the catalyst bed.

The dependence of product yield on time shown by the flow reactor indicates that the catalyst is deactivated faster if no oxidation
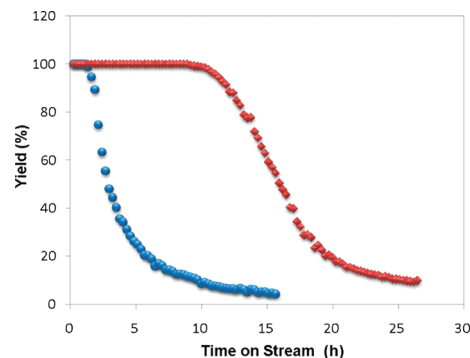


**Figure 2.** Time on stream of product yield of the hydroalkoxylation of 2-phenylethynylphenol catalyzed by Pd$_{40}$/SBA-15. In the presence of 5 mM PhICl$_2$ in the reaction stream (a 50 mM solution of 2-phenylethynylphenol in toluene), the catalyst was more stable and was deactivated relatively slowly (red diamonds), compared to the case when only reactant was flowed through the reactor (blue dots). The flow rate was 0.6 mL/h.
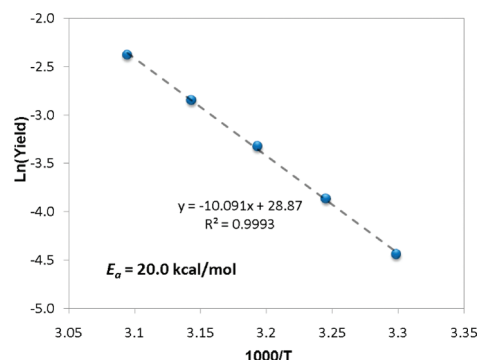


**Figure 3.** Activation energy determination of hydroalkoxylation of 2-phenylethynylphenol catalyzed by Pd$_{40}$/SBA-15 using a continuous flow reactor.

agent is present in the reactant solution. If the oxidation agent is introduced to the catalyst bed together with the reactant, the deactivated catalysts can be reactivated *in situ*. However, after 10 h of 100% conversion, the catalyst was eventually deactivated. The deactivated catalysts can be nevertheless regenerated with H$_2$ reduction at 100 °C followed by the PhICl$_2$ oxidation at 20 °C, which suggests that the oxidant alone is not sufficient to maintain Pd$_{40}$/SBA-15 in its active state at room temperature. Several factors, such as the catalyst loading, concentration of the reactant and oxidant, reaction temperature, flow rate, and catalyst support, are considered to play major roles in the deactivation of the catalyst. The mechanism of catalyst deactivation is currently under investigation. Nevertheless, the deactivation kinetics of catalyst under steady reactant feeding conditions cannot be investigated in a batch reactor because the concentrations of reactant and product keep changing during a batch mode reaction. With the continuous supply of the fresh reactant and removal of the product, catalyst deactivation induced by product poisoning could be diminished or eliminated.[17]

Additionally, the continuous flow mode reaction can also be a useful and convenient tool in probing other kinetic parameters of a given reaction, such as the activation energy. Figure 3 shows the activation energy of this reaction measured after the catalytic turnover reached its steady state. In a flow reactor, the activity of Pd$_{40}$/SBA-15 at different reaction temperatures could be conveniently measured, from which the apparent activation

energy was determined to be 20.0 kcal/mol. Activation energy is an important reaction parameter that can help to gain a deeper understanding of reaction mechanisms. To measure the activation energy in a batch mode, multiple reactions must be repeated at different temperatures. As a result, any operational error in these reactions will generate inaccuracy in the activation energy. Using a flow reactor, all reaction parameters can be controlled precisely and reproduced easily, while the only variable is temperature.

In conclusion, we synthesized a highly active catalyst for the hydroalkoxylation of 2-phenylethynylphenol by supporting $Pd_{40}$ nanoparticles encapsulated by the PAMAM dendrimer on SBA-15. Uniquely, when employed in conjunction with $PhICl_2$, $Pd_{40}$/SBA-15 catalyzes the hydroxylalkoxylation reaction more efficiently than homogeneous catalysts. To take advantage of the heightened reactivity and heterogeneous nature of this catalyst, a fixed bed plug flow reactor system filled with $Pd_{40}$/SBA-15 was developed. Impressively, in this flow reactor, the catalyst remained stable and highly active for more than 10 h at room temperature by the addition of $PhICl_2$ to the reaction stream. The deactivation kinetics of the catalyst under steady reactant feeding conditions was also measured, which cannot be achieved in a batch reactor because the concentrations of reactant and product change continuously. By conducting this reaction in a flow mode, the activation energy of the reaction was easily measured. A more in-depth investigation of the mechanistic aspects of this catalytic system is currently underway and will be reported in due course.

**Supporting Information Available:** Experimental procedures and elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

### References

(1) Ikegami, S.; Hamamoto, H. *Chem. Rev.* **2009**, *109*, 583–593.
(2) Mennecke, K.; Cecilia, R.; Glasnov, T. N.; Gruhl, S.; Vogt, C.; Feldhoff, A.; Vargas, M. A. L.; Kappe, C. O.; Kunz, U.; Kirschning, A. *Adv. Synth. Catal.* **2008**, *350*, 717–730.
(3) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367–1390.
(4) Jas, G. In *Immobilized Catalysts: Solid Phases, Immobilization and Applications*; Kirschning, A., Ed.; Topics in Current Chemistry; Springer: Berlin, London, 2004; Vol. 242, pp 209−239.
(5) (a) Jas, G.; Kirschning, A. *Chem.—Eur. J.* **2003**, *9*, 5708–5723. (b) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.—Eur. J.* **2006**, *12*, 5972–5990.
(6) Anderson, N. G. *Org. Process Res. Dev.* **2001**, *5*, 613–621.
(7) For examples of palladium nanoparticles as catalysts in continuous flow processes, see: (a) Hou, Z.; Theyssen, N.; Brinkmann, A.; Leitner, W. *Angew. Chem., Int. Ed.* **2005**, *44*, 1346–1349. (b) Nikbin, N.; Ladlow, M.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 458–462.
(8) Zhao, M. Q.; Crooks, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 364–366.
(9) Huang, W. Y.; Kuhn, J. N.; Tsung, C.-K.; Zhang, Y.; Habas, S. E.; Yang, P.; Somorjai, G. A. *Nano Lett.* **2008**, *8*, 2027–2034.
(10) Witham, C. A.; Huang, W. Y.; Tsung, C. K.; Kuhn, J. N.; Somorjai, G. A.; Toste, F. D. *Nat. Chem.* **2010**, *2*, 36–41.
(11) The hydroalkoxylation of 2-phenylethynylphenol catalyzed by $Pd_{40}$/SBA-15 in toluene at 100 °C was completed within 30 min, whereas approximately 50 h were necessary for $Pd_{40}$/SBA-15 under otherwise identical conditions (cf. ref 10).
(12) Liang, Y.; Tang, S.; Zhang, X. D.; Mao, L. Q.; Xie, Y. X.; Li, J. H. *Org. Lett.* **2006**, *8*, 3017–3020.
(13) Li, X. W.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437–5440.
(14) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329–1331.
(15) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025.
(16) Zhang, Y.; Xin, Z. J.; Xue, J. J.; Li, Y. *Chin. J. Chem.* **2008**, *26*, 1461–1464.
(17) Our preliminary results show that the TOF in a continuous flow reactor decreases more slowly than that in a batch mode reactor.

JA108898T