Cluster Catalysis

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Pd Nanoclusters in C–C Coupling Reactions: Proof of Leaching

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Carbon–carbon coupling reactions are ubiquitous in organic synthesis. Heck,[1,2] Suzuki,[3,4] and Sonogashira couplings[5,6] occupy a special place among such reactions due to their mild reaction conditions. The coupling products are mostly used as intermediates for polymers, natural products, and bioactive compounds.[7,8]

The most common catalyst precursors for these reactions are palladium(II) complexes,[7,9,10] usually with phosphane ligands.[11] However, most of these ligands are air- and moisture-sensitive, involve multistep syntheses, and are difficult to separate from the final product. This makes "ligand-free" Pd catalysis an attractive option.[12–20] Pd^{II} salts form Pd^0 clusters under the reaction conditions, and these can catalyze coupling reactions. However, the "naked" Pd clusters aggregate to inactive Pd black.[15,19,21,22] To prevent this aggregation, stabilized Pd clusters[23] are increasingly being used as C–C coupling catalysts.[20,21,24–32] These clusters may be good catalysts, but we still do not know (in contrast to heterogeneous Pd[33]) whether catalysis occurs on the cluster surface or by leached[34] Pd species.[15,19,22,35,36]

Although much work has been done in this area, there is no single definitive experiment that reveals the detailed mechanism of cluster catalysis in the liquid phase.[35] From studies of cluster-size effects in Heck and Suzuki reactions, it was proposed that catalysis occurs at defect sites on the cluster surface.[27,37,38] Conversely, de Vries et al.[15] suggested an equilibrium between Pd clusters and a monomeric or dimeric moiety which is the actual active species. Recently, using transmission electron microscopy (TEM) and kinetic studies, we[39] and others[26,40] also demonstrated that species leached from the cluster surface are probably responsible for catalysis in these types of reactions. However, the conclusions were based on circumstantial evidence. Here we report the first direct and unambiguous test proving that leached Pd species are the true catalysts in Pd-cluster-catalyzed C–C coupling reactions.

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For this experiment, we built a special U-tube permeation cell[41] membrane reactor (Figure 1, top) consisting of two stainless steel compartments separated by a membrane (henceforth referred to as sides **A** and **B**). The membrane physically separates the Pd clusters and the reaction mixture in the reactor. The concept is simple: the suspension of Pd clusters is placed on one side of the membrane, and the reaction mixture on the other (Figure 1, bottom). The membrane is designed[42] with 5-nm pores that allow the diffusion of leached Pd species, but not of Pd clusters. The clusters cannot pass through the membrane because they are too large (14.5 ± 2.5 nm, see below). Thus, monitoring the reaction over time on both sides gives direct information on the true catalyst.

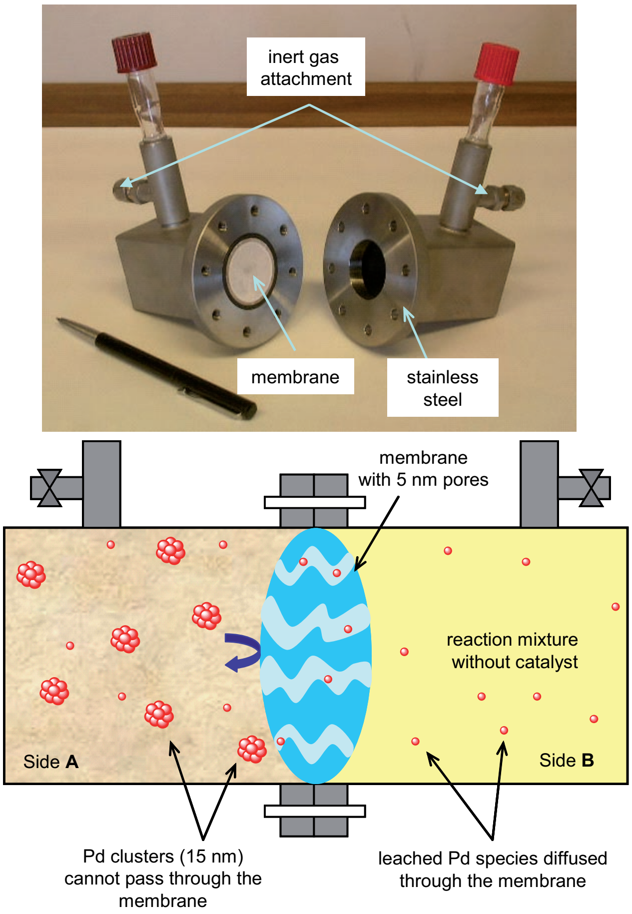


Figure 1. Photograph (top) and schematic (bottom) of the two-compartment membrane reactor and the cluster-exclusion concept.

The Pd clusters were synthesized by reducing $Pd(NO_3)_2$ with tetraoctylammonium glycolate (TOAG), used both as reducing and stabilizing agent.[43] This method gives clusters with an average size of 14.5 nm and a narrow particle size distribution (Figure 2). An α-alumina-supported nanoporous γ-alumina membrane was synthesized according to the reported procedure.[42] The pore size distribution of the membrane was determined by permporometry.[44,45] Most of the pores were around 4.9 nm and few pores were larger than 5 nm, with a maximum size of 11 nm. The minimum Pd cluster size was 12 nm. Moreover, due to the amorphous structure of the membrane, all the paths through it are tortuous worm-holes, and no path consists of only maximum-size pores. Thus, this membrane also retains particles smaller than 11 nm.

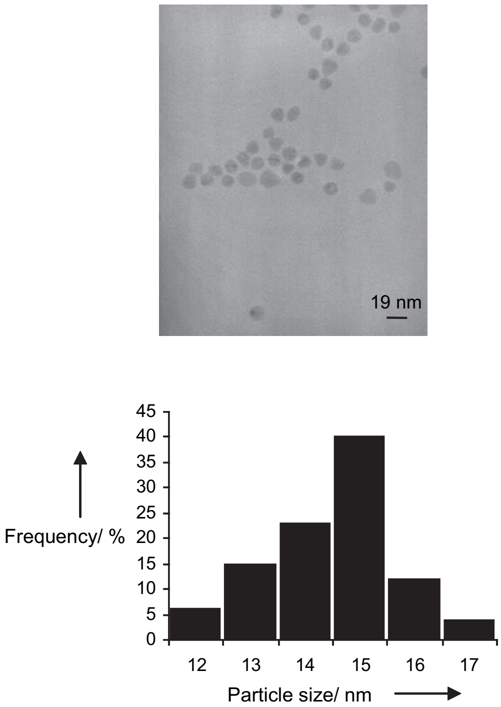
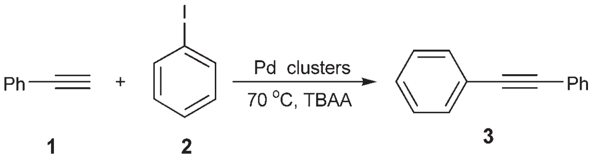


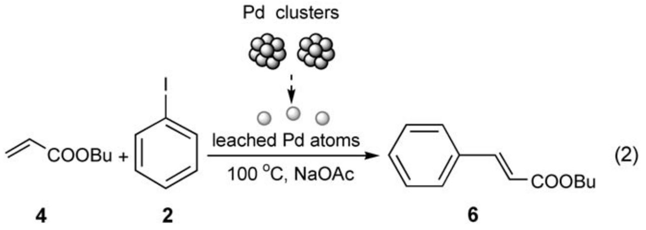
Figure 2. Transmission electron micrograph (top) and corresponding size distribution of the Pd clusters (bottom, based on 85 particles counted).

In the first test reactions, we carried out Sonogashira coupling of phenylacetylene (**1**) with iodobenzene (**2**) [Eq. (1)]. We placed the Pd cluster suspension on side **A**, and **1, 2**, and tetrabutylammonium acetate (TBAA) as base on side **B**. The experiments were performed in DMF at 70 °C. Note that the base is soluble in this case. After 3 days, we observed 72 % yield of coupling product **3** on side **B**, where there was originally no catalyst. However, as the reactants and base were not evenly distributed on both sides, they may have diffused from side **B** to the lower concentration on side **A**. It cannot be excluded that the reaction occurred in compartment **A** and the product then diffused from side **A** to side **B**. We did observe 9 % yield of **3** on side **A**, which could be attributed to the product coming from side **B** or forming on side **A**. Consequently, this experiment did not give a clear answer to our question.



(1)

To reveal the actual catalytic species, it was necessary to prevent diffusion of the reactants through the membrane and to use an insoluble base. We therefore investigated the Heck reaction in the presence of NaOAc, which is insoluble in DMF. The coupling of *n*-butyl acrylate (**4**) with iodobenzene (**2**) to give *n*-butyl cinnamate (**6**) was used as a model reaction [Eq. (2)].



(2)

Before performing the coupling reaction, we examined the time-dependent transport of **4, 2**, and **6** through the membrane. Pure **4, 2**, and **6** in DMF were placed on side **B**, and only DMF on side **A**. Figure 3 shows that indeed all three compounds were transported from side **B** to side **A**. Note that no pressure was applied to the system; transport was purely due to concentration gradients. The transport rate was size-dependent: **4** > **2** > **6**. After 100 h, 10.5 mol % of **4**, 6.5 mol % of **2**, and 4.5 mol % of **6** were transported to side **A**. This blank experiment gives a measure of the background diffusion of these specific compounds through the membrane. Similar transport behavior can be expected during the reaction.

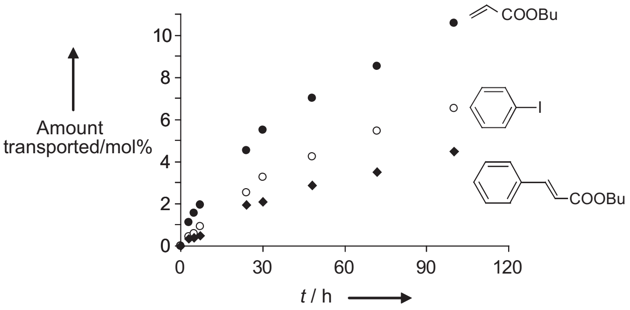


Figure 3. Time-dependent transport of molecules through the membrane from side **B** to side **A**.

We then ran the Heck reaction using 1.5:1 molar mixtures of **4** and **2** on both sides of the membrane to avoid concentration gradients. NaOAc (1.5 equiv) was then added to side **B**, and the suspension of Pd clusters (0.01 equiv) was introduced into side **A** at 100 °C. Note that the base is necessary for closing the catalytic cycle. As there is no base on side **A**, no product can form there. Thus, any product observed on side **A** must come from **B**.[46]

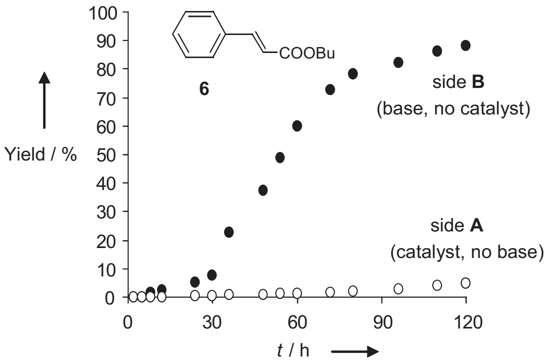


Figure 4. Time-resolved profile for the yield of **6**. The product observed on side **A** has diffused from side **B**.

Figure 4 shows the yield of *n*-butyl cinnamate (**6**) versus time. No reaction was observed for the first 5 h because the released Pd species from side **A** must first diffuse through the nanoporous membrane to initiate the catalytic cycle on side **B**. When the leached Pd species reach side **B** the reaction rate increases and then slows as **2** is consumed. After 120 h, the yield of **6** on side **B** was 88 %. We did not observe any diffused product **6** during the first 12 h on side **A**. However, after 120 h 4.9 % of the product was observed that may have diffused from side **B**. Duplicate experiments showed good reproducibility. No aggregation was observed after the reaction on either side of the reactor.

X-ray photoelectron spectroscopy was performed on the membrane after the reaction to determine whether Pd enters the pores (see Supporting Information for details). There were no significant differences between the elemental compositions of the surface and subsurface layers. Traces of Pd were found on all spots on or below the membrane surface, but the concentration was in all cases within the range of 0.02–0.07 atom %. As the specific surface area[47] of this γ-alumina is about 285 $m^2 g^{-1}$, this is equivalent to a surface concentration of roughly one Pd atom per 20 nm^2.

The above results prove that the reaction involves leached Pd species, for which the nanosized Pd clusters act as reservoirs. We still do not know whether these species are Pd^0 atoms released from the defect sites or soluble Pd^{II} species formed after oxidative addition of PhI.[36,39] In theory, the Pd^0 and Pd^{II} species could "recluster" on the other side of the membrane, but in practice there is no stabilizer or reducing agent, both of which are crucial for cluster formation, so this option is extremely unlikely. In any event, these experiments prove the hypothesis of de Vries et al. regarding ligand-free Pd catalysts in Heck reactions.[15,48]

In summary, using a simple approach based on physical exclusion, we prove here that the Pd-cluster-catalyzed Heck reaction between *n*-butyl acrylate and iodobenzene (and probably also other Heck and Sonogashira reactions)[39] involves soluble Pd species released from the surface of the clusters. Moreover, the general new technique we described here permits the testing of many individual reactions. Further investigations into the mechanism of other cross-coupling reactions will be the subject of future research.

Experimental Section

Membrane preparation: The alumina membrane consists of a macroporous α-alumina support and a thin nanoporous γ-alumina layer. The α-alumina supports were made by colloidal filtration of well-dispersed 0.3-μm α-alumina particles (AKP-30, Sumitomo) in demineralized water. The 50-wt % dispersion was stabilized by peptizing with 0.02 M HNO_3. After drying at 25 °C for 24 h, the filter compact was sintered at 1100 °C in air for 2 h. Flat disks (∅ 39 mm, 2.0 mm thickness) were obtained by machining and polishing. The final porosity of these supports is about 30 %, and the average pore size 80–120 nm.[49] The nanoporous γ-alumina layer was prepared by dip-coating the α-alumina supports in a boehmite-based dip sol. The boehmite sol was prepared by heating 70.0 mol of double-distilled water to 95 °C, and then adding 0.50 mol of $Al(OsBu)_3$ (97 % purity, Acros) dropwise under a nitrogen flow to avoid premature hydrolysis. The mixture was stirred vigorously throughout the synthesis. After all the $Al(OsBu)_3$ was added, the mixture was kept at 95 °C for 3 h to evaporate the butanol. The mixture was cooled to 60 °C, peptized with HNO_3 (65 %, Merck) to pH 2.5, and then heated at reflux at 90 °C for 20 h (pH increases to 3.5) to yield a homogeneous and stable 0.5 M boehmite sol. The dip sol was prepared by mixing 30 mL of the boehmite sol with 20.0 mL of a solution of poly(vinyl alcohol) (PVA, Fluka, 98 % purity, $M = 72\,000\ \text{g mol}^{-1}$) made by adding 150 g of 0.05 M HNO_3 in water to 4.5 g of PVA and stirring for 2 h at 80 °C. The α-alumina supports were dip-coated with the γ-alumina sol under class 1000 clean-room conditions at a dip-coating speed of $1.1\ \text{cm s}^{-1}$. The coated supports were dried for 3 h (25 °C, relative humidity 40 %), and then calcined for 1 h (600 °C, air, heating/cooling rates $0.5\ ^{\circ}\text{C min}^{-1}$). The deposition/calcination cycle was repeated. This resulted in a flat nanoporous γ-alumina layer with a layer thickness of about 3 μm.

Heck coupling: Identical 1.5:1 mixtures of **4** (3.0 mmol, 0.38 g) and **2** (2.0 mmol, 0.40 g) in 50 mL of DMF were placed on both sides of the membrane reactor. NaOAc (3.0 mmol, 0.41 g) was then added to side **B**, and the Pd cluster suspension (3 mL, 10 mM, 1.0 mol %) was added to side **A**. The reactor was heated to 100 °C, and samples were taken from both compartments and analyzed by GC (pentadecane internal standard). After each experiment, the membrane was washed with acetone (4 × 10 mL) and extracted for 24 h with EtOH.

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[1] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
[2] V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553.
[3] N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.
[4] F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419.
[5] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
[6] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2633.
[7] *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1997**.
[8] *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals* (Ed.: M. Beller), Wiley-VCH, Weinheim, **2004**.
[9] A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101.
[10] R. B. Bedford, C. S. J. Cazin, D. Holder, *Coord. Chem. Rev.* **2004**, *248*, 2283.
[11] D. H. Valentine, J. H. Hillhouse, *Synthesis* **2003**, 2437.
[12] Q. W. Yao, E. P. Kinney, Z. Yang, *J. Org. Chem.* **2003**, *68*, 7528.
[13] Y. Mori, M. Seki, *J. Org. Chem.* **2003**, *68*, 1571.
[14] A. Alimardanov, L. Schmieder-van de Vondervoort, A. H. M. de Vries, J. G. de Vries, *Adv. Synth. Catal.* **2004**, *346*, 1812.
[15] A. H. M. de Vries, J. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285.
[16] A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. M. Walet, J. G. de Vries, *Adv. Synth. Catal.* **2002**, *344*, 996.
[17] B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, *124*, 14127.
[18] M. B. Thathagar, J. Beckers, G. Rothenberg, *Green Chem.* **2004**, *6*, 215.
[19] M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559.
[20] M. T. Reetz, E. Westermann, *Angew. Chem.* **2000**, *112*, 170; *Angew. Chem. Int. Ed.* **2000**, *39*, 165.
[21] M. B. Thathagar, J. Beckers, G. Rothenberg, *Adv. Synth. Catal.* **2003**, *345*, 979.
[22] A. Biffis, M. Zecca, M. Basato, *J. Mol. Catal. A* **2001**, *173*, 249.
[23] For a general overview on metal nanoclusters and their applications in catalysis, see: a) J. D. Aiken III, R. G. Finke, *J. Mol. Catal. A* **1999**, *145*, 1; b) J. S. Bradley, E. Hill, M. E. Leonowicz, H. Witzke, *J. Mol. Catal.* **1987**, *41*, 59; c) H. Bönnemann, R. M. Richards, *Eur. J. Org. Chem.* **2001**, 2455.
[24] For a recent review on the application of metal nanoclusters in C–C bond-formation reactions, see: M. Moreno-Mañas, R. Pleixats, *Acc. Chem. Res.* **2003**, *36*, 638.
[25] M. B. Thathagar, J. Beckers, G. Rothenberg, *J. Am. Chem. Soc.* **2002**, *124*, 11858.
[26] A. Gniewek, A. M. Trzeciak, J. J. Ziolkowski, L. Kepinski, J. Wrzyszcz, W. Tylus, *J. Catal.* **2005**, *229*, 332.
[27] R. Narayanan, M. A. El-Sayed, *Langmuir* **2005**, *21*, 2027.
[28] M. Beller, H. Fischer, K. Kuhlein, C. P. Reisinger, W. A. Herrmann, *J. Organomet. Chem.* **1996**, *520*, 257.
[29] M. T. Reetz, G. Lohmer, *Chem. Commun.* **1996**, 1921.
[30] M. T. Reetz, R. Breinbauer, K. Wanninger, *Tetrahedron Lett.* **1996**, *37*, 4499.
[31] Y. Li, X. M. Hong, D. M. Collard, M. A. El-Sayed, *Org. Lett.* **2000**, *2*, 2385.
[32] A. R. Gholap, K. Venkatesan, R. Pasricha, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Org. Chem.* **2005**, *70*, 4869.
[33] a) F. Y. Zhao, B. M. Bhanage, M. Shirai, M. Arai, *Chem. Eur. J.* **2000**, *6*, 843; b) R. L. Augustine, S. T. Oleary, *J. Mol. Catal. A* **1995**, *95*, 277; c) A. Biffis, M. Zecca, M. Basato, *J. Mol. Catal. A* **2001**, *173*, 249; d) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, *124*, 14127; e) S. S. Prockl, W. Kleist, M. A. Gruber, K. Köhler, *Angew. Chem.* **2004**, *116*, 1917; *Angew. Chem. Int. Ed.* **2004**, *43*, 1881; f) K. Köhler, R. G. Heidenreich, J. G. E. Krauter, M. Pietsch, *Chem. Eur. J.* **2002**, *8*, 622.
[34] For clarity, we use here the term "leaching", which is common in this context. In practice, oxidative addition is most likely the first event leading to detachment of Pd^{II} ions from the cluster.
[35] J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317.
[36] A. Biffis, M. Zecca, M. Basato, *Eur. J. Inorg. Chem.* **2001**, 1131.
[37] Y. Li, E. Boone, M. A. El-Sayed, *Langmuir* **2002**, *18*, 4921.
[38] J. Le Bars, U. Specht, J. S. Bradley, D. G. Blackmond, *Langmuir* **1999**, *15*, 7621.
[39] M. B. Thathagar, P. J. Kooyman, R. Boerleider, E. Jansen, C. J. Elsevier, G. Rothenberg, *Adv. Synth. Catal.* **2005**, *347*, 1965.
[40] C. C. Cassol, A. P. Umpierre, G. Machado, S. I. Wolke, J. Dupont, *J. Am. Chem. Soc.* **2005**, *127*, 3298.
[41] K. B. Jirage, J. C. Hulteen, C. R. Martin, *Science* **1997**, *278*, 655.
[42] S. R. Chowdhury, J. E. ten Elshof, N. E. Benes, K. Keizer, *Desalination* **2002**, *144*, 41.
[43] J. S. Bradley, B. Tesche, W. Busser, M. Maase, M. T. Reetz, *J. Am. Chem. Soc.* **2000**, *122*, 4631.
[44] Permporometry is a characterization technique for determining pore size distributions in membranes. It is based on the controlled blocking of the pores by capillary condensation and the simultaneous measurement of the inert-gas diffusion flux through the remaining open pores. When a condensable vapor (e.g., cyclohexane) is introduced at low vapor pressure, first a molecular adsorption layer (the t layer) is formed on the inner surface of the pores. The pore size (d [nm]) is defined by $d = 2(r_K + t)$, where r_K is the Kelvin radius, and t the layer thickness

(ca. 0.3 nm). For more details, see: a) A. Mey-Marom, M. G. Katz, *J. Memb. Sci.* **1986**, *27*, 119; b) M. G. Katz, G. Baruch, *Desalination* **1986**, *58*, 199.

[45] N. Benes, A. Nijmeijer, H. Verweij in *Recent Advances in Gas Separation by Microporous Ceramic Membranes* (Ed.: N. K. Kanellopoulos), Elsevier, Amsterdam, **2000**.

[46] One can quantify the number of moles of diffused **6** on the clusters side by comparing the diffusion rates. However, very small amounts of **6** form since in the initial stage of the Heck reaction the concentration gradient is very low. This results in lower diffusion rates of **6** (3.5 mol% after 100 h) compared to those observed in the control experiments with pure **6** (4.5 mol% after 100 h, see Figure 3).

[47] S. R. Chowdhury, K. Keizer, J. E. ten Elshof, D. H. A. Blank, *Langmuir* **2004**, *20*, 4548.

[48] J. G. de Vries, *Dalton Trans.* **2006**, 421.

[49] For a detailed overview of this type of synthesis, see: N. Benes, A. Nijmeijer, H. Verweij in *Recent Advances in Gas Separation by Microporous Ceramic Membranes* (Ed.: N. K. Kanellopoulos), Elsevier, Amsterdam, **2000**, pp. 335–372.