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Miniaturized Catalysis: Monolithic, Highly Porous, Large Surface Area Capillary Flow Reactors Constructed In-Situ from Polyhedral Oligomeric Silsesquioxanes (POSS)

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A single-step molding utilizing free-radical cross-linking reaction of vinylPOSS in microliter-sized dimensions leads to hierarchically-structured, mechanically robust, porous hybrid structures. Functional variants show excellent performance in Suzuki type coupling reactions. Owing to the small volume, long-term operational robustness, and potential chemical diversity, the materials are promising candidates for catalyst screening applications.

Palladium-based catalytic systems for cross-coupling have been pioneered by Richarf F. Heck, Ei-ichi Negishi and Akira Suzuki.¹ Due to their recognized importance and the inception of a multitude of possibilities emerging therefrom, they have stimulated a great deal of research in academic and industrial communities.² Recent outreach for related carbon-carbon coupling reactions can be found in the development of advanced materials.³

While homogeneous catalytic systems provide high product yields,⁴ their inherent disadvantage is the necessity to separate products from the catalyst.⁵ This situation has spurred developments in heterogeneous catalytic systems with examples reporting packed bed reactors,⁶ monolithic flow-through formats with silica-based materials⁷ and organic (monolithic) polymers.⁸ Notwithstanding, we note that the catalytic reaction is often quasi homogeneous in its nature.⁹

The recent development toward micro-engineering demands utilization of miniaturized formats allowing for reduction in solvent consumption, fast heat and mass transfer, as well as continuous operation with the option of massive parallelization.¹⁰ Such systems allow the use of minute catalyst amounts for screening experiments before up-scaling and producing fine chemicals on a larger scale.

Polyhedral oligomeric silsesquioxanes (POSS) with the formula (RSiO_{1.5})_n are nano-building blocks that have already emerged for creation of advanced porous materials.¹¹ We have demonstrated that vinylPOSS cages can be woven into (bulk) porous monolithic

networks directly via a free-radical initiated in situ reaction in suitable porogenic diluents leading to large specific surface area sorbents.^{11c} Such hybrid porous materials have not yet entered the micro-engineering arena but possess the option for scaling due to the in situ preparation. An important asset is the tailorable amount of tightly tethered vinyl functionality on their internal structure.^{11c}

We herein communicate our first results in a single-step creation of such large surface area hybrid material in 100 μm I.D. fused-silica capillaries covalently anchored to the confining capillary wall. This is followed by straightforward functionalization of their internal porous structure to chelate palladium utilized for Suzuki type coupling reactions.

The internal surface of 100 μm I.D. fused-silica capillaries was first decorated with pendant methacrylate functionality (for details see SI).¹² The porous hybrid monolith precursor mixture was prepared by weighing 20% vinylPOSS as monomer, 51% tetrahydrofuran, and 29% poly(ethylene glycol) 200 as porogenic solvents (all w/w). The precursor mixture additionally contained azobisisobutyronitrile (16 wt% with respect to the vinylPOSS). The homogeneous solution was filled into the capillary mold by means of a syringe. Subsequently, both ends of the capillary were sealed with rubber-stoppers and immersed in a water bath tempered at 60 °C. After monolith formation, the capillary was flushed with tetrahydrofuran to remove porogenic solvents and initiator.

Figure 1 shows example SEM images of the hybrid pristine monolith. It possesses a hierarchical structure of pore space and is covalently attached to the fused-silica capillary inner wall. The dry-state Brunauer-Emmett-Teller (BET) surface area of 898 m² g⁻¹ together with an appreciable dry-state Barrett-Joyner-Halenda (BJH) mesopore volume of 0.4 cm³ g⁻¹ (Fig. S1) of prepared bulk material, clearly support the existence of a large surface area, hierarchical porous structure.

In flow operation, the materials showed a linear increase of backpressure at increased flow rates (Figure S2), indicating their maintained mechanical integrity. A total porosity of 83% was determined with flow experiments of a small hydrophilic tracer (for details see SI). The free-radical initiated linking of vinylPOSS as well results in a multiplicity of pendant vinyl groups (Scheme 1).^{11b} Two in-situ modification strategies were explored for immobilizing the

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desirable phenanthroline ligand to the internal surface of the scaffold, both employing thiol-ene addition as the primary step (Scheme 1).

For Catalyst 1, the hybrid monolith was functionalized with 3-chloro-1-propanethiol via thiol-ene addition. Then, 5-amino-1,10-phenanthroline was bound via nucleophilic substitution under

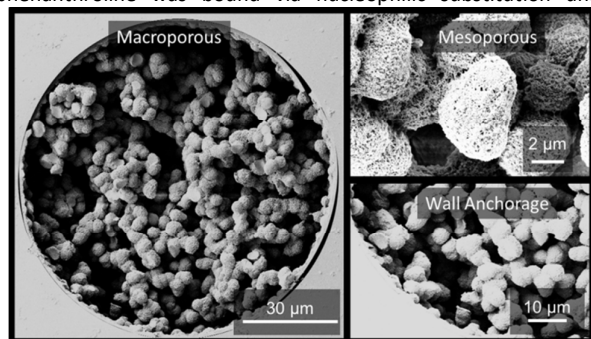
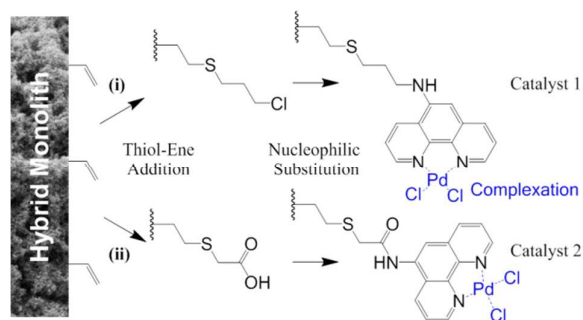


Figure 1. Scanning electron microscopy (SEM) images of the large surface area vinylPOSS hybrid pristine polymer. Cross-section of monolithic hybrid polymer incorporated in 100 µm I.D. fused silica capillaries clearly showing the macroporous structure and indication of an appreciable amount of nanopores (<50 nm) further supported by nitrogen adsorption/desorption measurements of bulk material (Fig. S1). As well seen is the anchorage to the fused-silica capillary wall.

secondary amine formation (Scheme 1, Route (i)). For Catalyst 2, the hybrid monolith was modified with thioglycolic acid via thiol-ene addition. The acid was then activated to an acyl chloride and 5-amino-1,10-phenanthroline was immobilized via amide bond formation (Scheme 1, Route (ii)). Both phenanthroline pendant scaffolds were subsequently provided with chelated palladium species by flushing solutions of Pd(MeCN)₂Cl₂ complex in acetonitrile through the reactors. Further details are provided in the supporting information.

To indicate existence of chelated palladium on the internal structure of the highly porous material according to Scheme 1, the as-prepared and washed reactors were analyzed by energy-dispersive X-ray spectroscopy (EDX) on their cross-sections. The results in Figures 2 clearly confirm existence of sulfur, indicating successful thiol-ene addition, as well as Pd and Cl functionalities indicating successful Pd chelation for Catalysts 1 and 2 (Scheme 1). These signals are totally absent for the pristine material.

The reaction of iodobenzene and *p*-tolylboronic acid in 75/25 acetonitrile/water (% v/v) was used as a model to judge on reactor



Scheme 1. In-situ functionalization of hybrid porous polymer via thiol-ene addition as the primary step with either (i) 3-chloro-1-propane-thiol, or (ii) thioglycolic acid. Following nucleophilic substitution leads to linkage of the 5-amino-1,10-phenanthroline as chelating functionality for palladium.

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performance under typical conditions, i.e. at a temperature of $T = 80\text{ }^{\circ}\text{C}$ and continuous flow. Figure 3a compares the respective yields

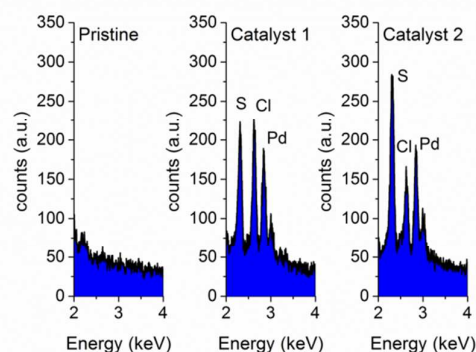


Figure 2. Energy-dispersive X-ray spectroscopy (EDX) analysis of cross-sections of porous materials with the pristine and reactor variants

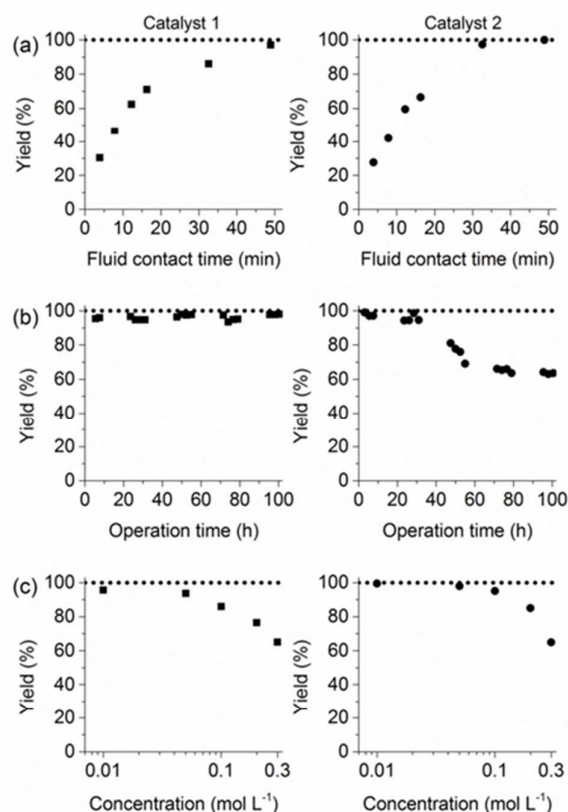
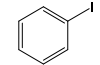
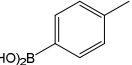
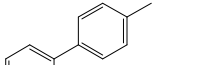
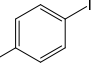
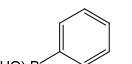
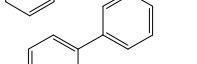
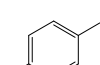
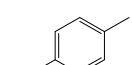
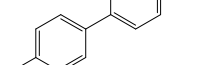
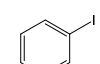
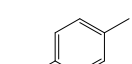
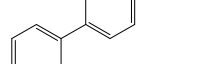
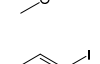

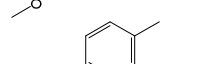
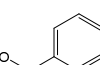
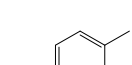
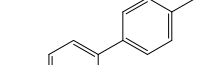
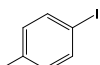
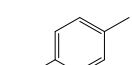
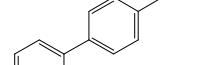


Figure 3. (a) Impact of fluid contact time in the reactors on yield obtained for the reaction of 0.1 mol L^{-1} iodobenzene and 0.125 mol L^{-1} *p*-tolylboronic acid (entry 1, Table 1). (b) Long term stability of the reactors in steady-state at a fluid contact time of 49 min. (c) Yield achieved from flow-through catalysis of the reaction of iodobenzene with *p*-tolylboronic acid keeping a stoichiometric ratio of 1:1.25 but varying concentration at a fluid contact time of 32.6 min. The reactors had the same length of 30 cm. Other conditions: Fluid phase of 75/25 acetonitrile/water (% v/v) and 2 eq. triethylamine (to that of the iodobenzene) as the base. Reactions were performed at a constant reactor temperature of $T = 80\text{ }^{\circ}\text{C}$.

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of the flow reactor systems originating from the same pristine material. The materials with chelated palladium functionality (Catalysts **1** and **2**, Scheme 1) approach larger than 85% quantitative yield after a mere of 30 min fluid contact time (Figure 3a). The shape of the yield-fluid contact time curves of Catalysts **1** and **2** is similar. The performance of both reactors with chelated palladium is better than homogeneous “control” variants in batch experiments and an open tube implementation both with pristine palladium complex Pd(MeCN)₂Cl₂ as catalyst of 1 mol% (with respect to the iodobenzene) in the same fluid phase (Fig. S4). Yet, we calculated an overall catalyst concentrations of 10 mmol⁻¹ (Catalyst **1**) and 4 mmol⁻¹ (Catalyst **2**) in the monolithic reactors (see SI). This qualitatively indicates that at a concentration of 0.1 mol L⁻¹ of the reactants in the fluid phase of one reactor volume 10 mol% of palladium sites are present for Catalyst **1**. Eventually, not all of the palladium sites in the material are catalytically active, which may originate from the limited accessibility of the very small pores providing diffusional resistance and significantly contributing to the large dry-state surface areas (Fig. S1).

Table 1. Catalytic reactions performed in the 100 μm ID fused silica capillaries containing Catalyst **1** operated with 75/25 acetonitrile/water (% v/v). Concentration of each aryl halide was 0.1 mol L⁻¹ and of each boronic acid 0.125 mol L⁻¹ with 2 eq. of triethylamine (to that of the aryl halide) as the base. The reactions were performed at T = 80 °C with a reactor fluid contact time of 32.6 min.

Arylhalide	Boronic Acid	Main Product	%Yield ^a
			85
			95
			95
			97
			17
			10
			58

^aConversion of the arylhalide was found equivalent to the yield of main product, yield of homocoupling of the boronic acid was < 1% in all cases.

Notwithstanding, the performance of the reactors could be deduced to a good distribution of flow and significant interactive contact area with chelated palladium functionality. We further found stability and robustness of the reactors over prolonged periods of time demonstrated for this example reaction using Catalyst **1** for more than 125 reactor volumes and more than 100 hours of continuous operation (Figure 3b). In contrast, Catalyst **2** lost performance at longer times of operation, though initial steady-state reactor performance under these conditions is readily similar for both. These results strongly indicate the lower stability of Catalyst **2** associated to the ligand linking strategy (Scheme 1). It is worth noting that the here demonstrated fluid contact times are smaller, and obtained yields larger, than that reported in the literature.^{8b,c} Stability of the microscale reactor containing Catalyst **1** as well is demonstrated for a timescale twice larger than that of a recently reported larger scale packed bed reactor.^{6d} Varying reactant concentration over more than an order of magnitude for both reactor systems showed an expected, though decent, loss of quantitative yield at increased reactant concentration until the reactant solubility limit in the fluid phase is reached (Figure 3c).

The catalytic system worked for other reactants as well and was studied for more stable Catalyst **1**. The determined conversion and yields are summarized in Table 1. High selectivity for the catalyzed reaction with an exclusive absence of homocoupling of the aryl halide together with small concentrations of the boronic acid homocoupling product is observed (Table 1). The coupling reactions with that of electron-donating methoxy groups on the aryl halide improved yields, except for the methoxy group in ortho position. This may be explained by sterical effects. We found electron-withdrawing groups such as esters to decrease respective yields. In comparison, the amine substituent in para position shows a good yield under otherwise same reactions conditions. This brief study indicates systematic insight for catalytic implementations involving varying reaction partners, made possible with the microscale reactors.

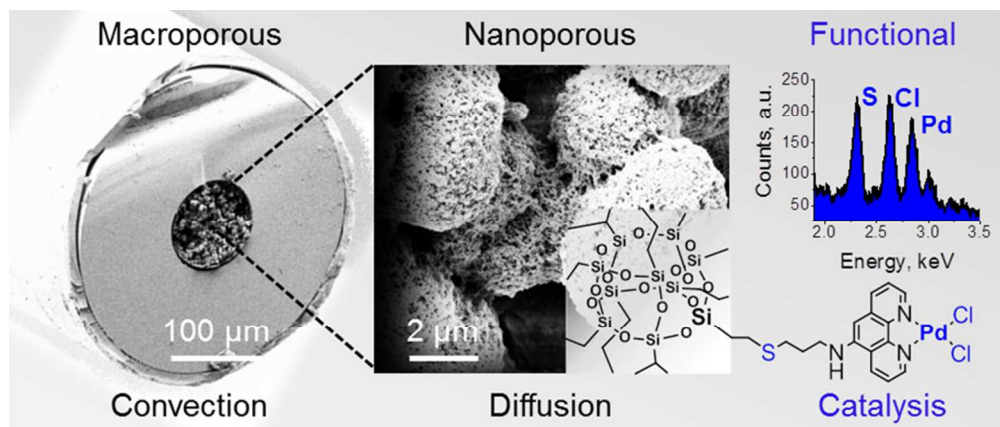
In conclusion, results presented in this preliminary account clearly demonstrate the possibility for the preparation of highly efficient and robust capillary flow reactors based on a large surface area, hierarchically-structured porous hybrid material constructed in situ from vinylPOSS. The excellent integration ability of this material and in situ modification demonstrated here for the generation of a catalytically active chelated palladium functionality used for Suzuki, carbon-carbon cross-coupling reactions is only one implementation these materials may find use in. Further tailoring of porous, hydrodynamic, and in particular chemical properties of the here described pristine porous hybrid polymer may enable further exploration of diversity and associated performance. The materials may pave the way for a family of catalyst systems which allow for independent tailoring of porous and hydrodynamic properties as well as internal chemistry, both building a pivotal role for catalytic implementations.

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