

Continuous Ligand-Free Suzuki–Miyaura Cross-Coupling Reactions in a Cartridge Flow Reactor Using a Gel-Supported Catalyst

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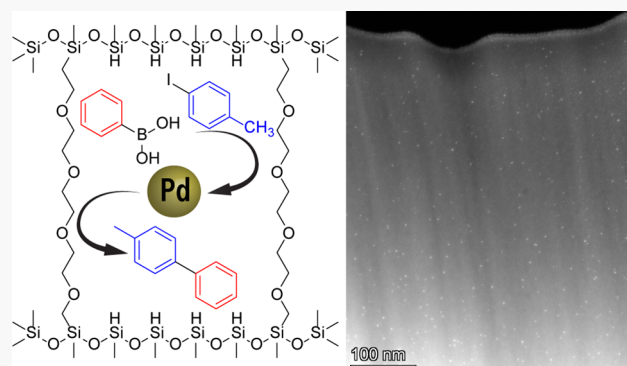


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Supporting Information

ABSTRACT: The Suzuki–Miyaura cross-coupling reaction is one of the most important reactions for pharmaceutical and fine chemical synthesis, performed using both homogeneous and heterogeneous catalysis. In this work, we cross-link poly-(methylhydrosiloxane) (PMHS) with tri(ethylene glycol divinyl ether) to create a versatile and readily accessible gel catalyst support for Suzuki–Miyaura cross-coupling reactions in a pseudoheterogeneous manner. The Si–H units present on the PMHS backbone act dually as the cross-linking site and the reducing agent to anchor and reduce palladium(II) acetate to active palladium(0). The PMHS-supported Pd catalyst is then packed into a stainless-steel flow reactor to create a cartridge-like reactor for the continuous operation of a model Suzuki–Miyaura cross-coupling reaction. We systematically investigate the role of reaction temperature, catalyst loading, cross-linking density, and gel particle size on the transient and steady-state behavior of the cartridge flow reactor through an automated flow chemistry platform. The PMHS-supported catalytic particles demonstrate minimal deactivation and leaching over a continuous (80 h) Suzuki–Miyaura cross-coupling reaction at a 30 min nominal residence time at a relatively high reaction temperature of 95 °C. The developed modular flow chemistry strategy equipped with the cartridge flow reactor enables accelerated studies of the fundamental and applied characteristics of gel-supported catalysts while providing increased safety, higher throughput, and removal of the separation step needed for catalyst recovery compared to homogeneous cross-coupling reactions in batch reactors.



INTRODUCTION

Cross-coupling reactions play a vital role in the modern organic synthesis of fine chemicals and pharmaceuticals due to their robust and selective performance across a broad range of substrate classes.^{1,2} The synthesis of fine chemicals is performed traditionally in a series of batch reactions that possess certain limitations at process scale, including lower transport rates, safety hazards related to large quantities of material, and purification steps that are both labor-intensive and costly.^{3–5} Thus, recent efforts in academia and industry have focused on transitioning the discovery, screening, and optimization of organic reactions from conventional batch formats to rapidly emerging continuous flow strategies.^{5–10} Conducting chemical reactions in flow allows for more consistent results (precise process control), higher efficiency (process intensification), increased safety (small reactor footprint), and higher throughput (continuous synthesis).^{11,12} Furthermore, continuous flow synthesis generally reduces the overall waste generation of a chemical process resulting in a greener chemical manufacturing scheme.^{13–15}

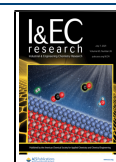
Current methods of performing cross-coupling reactions in continuous flow involve either homogeneous or heterogeneous catalytic systems.¹⁶ Homogeneous catalysis primarily uses expensive air-sensitive ligands that require a costly catalyst recovery step. In contrast, conventional heterogeneous catalysis utilizes complex, multistep catalyst immobilization on a solid substrate. Heterogeneous systems have progressed from materials such as Pd/C¹⁷ and graphene/graphite oxides¹⁸ to dense supports (e.g., silica¹⁹ and magnetic²⁰ particles). Further work has included bulk supports, including metal–organic frameworks (MOFs),²¹ covalent–organic frameworks (COFs),²² and polymer networks²³ (e.g., poly NIPAM,^{7,24} cyclodextrin,^{25,26} and polysiloxanes).^{8,10} A significant amount of research has focused on understanding the role of the Pd species

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in heterogeneous catalysts and the mechanism by which they proceed.^{27,28} The heterogeneous catalysis approach does not require catalyst recovery but has notoriously lower reproducibility, accessibility, and selectivity compared to homogeneous catalysis.^{29–32} These drawbacks of continuous-flow organic synthesis necessitate developing alternative catalytic flow reactors with higher flexibility, modularity, and robustness.

A recent approach in cross-coupling reactions has involved elastomeric polysiloxane networks as a flexible scaffold for loading the active transition metal catalyst.^{26,33–35} Cross-linked polysiloxane polymers are of great commercial importance because of their unique properties and broad technological applications.^{12,29,36–39} Previous studies have demonstrated poly-(methylhydrosiloxane) (PMHS) to be an attractive candidate for the fabrication of gel-supported catalysts.¹⁰ Palladium acetate, Pd(OAc)₂, in the presence of PMHS forms Pd nanoclusters (~40–60 nm) encapsulated in the polysiloxane matrix.⁴⁰ The siloxane backbone serves as a stabilizing agent attached to the Pd nanoclusters. At the same time, it provides dual functionality, allowing for (i) cross-linking via catalytic hydrosilylation with various unsaturated bonds and (ii) *in situ* reduction of the transition metal.⁴¹ This combination enables the entrapment of active metal catalysts in the form of nanoclusters within the bulk, while allowing the transport of reagents to the trapped active sites due to the PMHS network's high free volume, promoting product formation and transport.

We recently reported the creation of micro-packed-bed reactors (μ -PBR) made of spherical PMHS microparticles loaded with active Pd nanoclusters to perform continuous Suzuki–Miyaura cross-coupling reactions.^{8,35} Cross-linker density, chemical composition, and chain length have a strong influence on the catalytic performance of the PMHS-supported Pd catalyst. Increasing the cross-linker density decreases the volume fraction of polysiloxane in the network, resulting in a scaffold with physicochemical properties closer to the cross-linking species. The cross-linker chemical composition plays an essential role in the final performance of the elastomeric scaffold; it regulates the ability of the network to swell in the presence of a reaction solvent media. This characteristic is critical for the start-up delay and network saturation with the reagents in gel-supported μ -PBR. In addition to chemical composition, the cross-linker chain length affects the mechanical properties of the gel-supported catalyst (i.e., modulus and diffusion resistance of the polymer network). In our previous study, 1,5-hexadiene was used as the cross-linking agent for PMHS in the presence of Karstedt's catalyst to form the elastomeric network.^{8,35} Although the hexadiene serves as a convenient cross-linker for PMHS (due to its commercial availability and low cost), its short length and lipophilicity hinders reagent access to the active catalytic sites within the elastomeric network. The reduced reagent access to the active catalytic sites in the case of hexadiene can be attributed to the low degree of gel swelling in the Suzuki–Miyaura reaction media (i.e., ethanol and water). One can hypothesize that the introduction of higher polarity functional groups into the cross-linker chemical structure may enhance the network swelling, enhancing the delivery and access of the cross-coupling reagents to the active transition metal catalyst nanoclusters loaded within the bulk of the elastomeric scaffold.

In this work, we present a highly active cartridge-like PBR to conduct cross-coupling reactions in flow using cross-linked elastomeric particles with tunable network chemistry in the presence of an environmentally friendly solvent mixture of ethanol and water. We utilize a chemical cross-linker containing

hydrophilic groups (i.e., tri(ethylene glycol) divinyl ether (VTEG)) to promote the transport of cross-coupling reagents into the polymeric scaffolds and improve reaction rates and yields through more efficient access to active sites of the gel-supported catalyst. VTEG, owing to its hydrophilic glycol functional groups and the longer chain length than 1,5-hexadiene, will result in a network with a higher affinity for the polar reaction solvent leading to increased swelling as compared to the previously utilized 1,5-hexadiene. The ease of fabrication of the gel-supported catalyst combined with the modularity of the cartridge flow reactor and access to environmentally friendly solvents makes the developed continuous flow chemistry strategy a versatile approach for conducting metal-mediated cross-coupling reactions.

■ EXPERIMENTAL METHODS

Chemicals. Toluene (anhydrous 99.8%), palladium(II) diacetate ($\geq 99.9\%$ trace metals), potassium carbonate, ethanol (EtOH, 100% bioreagent grade), 4-iodotoluene (99%), phenylboronic acid (98%+), naphthalene (99%), 4-phenyltoluene (98%), biphenyl (99%), tri(ethylene glycol) divinyl ether (98%), and poly(methylhydrosiloxane) (average M_n : 1700–3200) were purchased from Sigma-Aldrich. Acetone and 2-propanol (IPA) were purchased from VWR Analytical. Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyl disiloxane (Karstedt's catalyst) (in xylene, Pt-2%) was purchased from Gelest, Inc. All chemicals were used as received.

Packed-Bed Flow Reactor. A range of packed-bed flow reactors was created using gel-supported catalysts to investigate the catalytic performance across PMHS network compositions and process parameter space (Figure S1). PMHS was cross-linked using different concentrations of VTEG (polymer monomer unit to vinyl ratio, R_{PC} , in the range of 3:1–8:1) in the presence of toluene as a cosolvent to produce the bulk polymer gel (Figure 1A and Table S1). After the completion of cross-linking reaction, the PMHS/VTEG gels were mechanically ground and sieved to produce a range of particle sizes between 100 and 500 μm . The 100–500 μm particles result in more compact reactor packing than the $>500 \mu\text{m}$ particles in the flow reactor with lower pressure drop than the $<100 \mu\text{m}$ particles. The size-separated PMHS particles were then swollen in toluene followed by addition of a specific amount of Pd(OAc)₂ salt in toluene (m_c) to incorporate and reduce the Pd nanoclusters into the PMHS network. The reaction was allowed to proceed for 24 h. The Pd-loaded PMHS particles were then washed with water and acetone to remove unreacted Pd(OAc)₂ salt. The particles were dried under vacuum before being packed into a 10 cm long stainless-steel tubing (1/4 in. outer diameter, OD, 3/16 in. inner diameter, ID) for testing (Figure 1B). The cross-coupling reactions were conducted in the presence of deoxygenated solvents and reagents at temperatures ranging from 65 °C–95 °C at 100 psig back pressure to prevent vapor formation within the flow reactor. Before beginning each cross-coupling reaction in flow, the PBR was flushed with deoxygenated reaction solvent mixture (1:2 water/ethanol) to remove any residual unbound surface Pd clusters, the gas in the void spaces, and the oxygen present in the reactor. The cross-coupling reagents (Scheme 1) were then fed continuously into the packed-bed reactor using computer-controlled high-pressure pumps (100DX, Teledyne ISCO). The effluent leaving the PBR was diluted in-line with the reaction solvent and an internal standard (naphthalene), and automatically analyzed using an in-line high-performance liquid

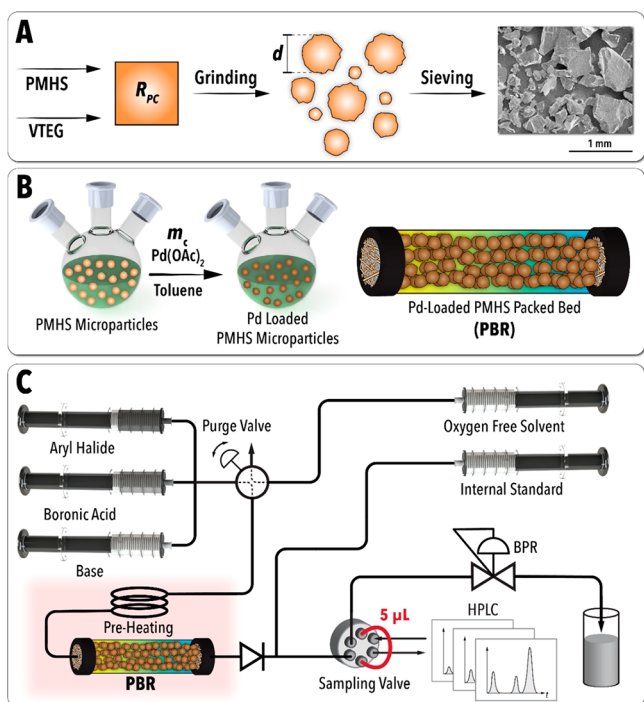


Figure 1. (A) PMHS particle preparation using various cross-linker loadings (R_{PC}). (B) Pd reduction with initial loading m_c and fabrication of cartridge-like PBR for continuous cross-coupling reactions. (C) Schematic of the automated flow chemistry platform with precursor delivery and effluent sampling modules integrated with the PBR loaded with the PMHS-supported Pd catalyst.

chromatography (HPLC) unit with an automated sampling valve module (Figure 1C). The amount of Pd leaching out during the cross-coupling reaction was monitored using inductively coupled plasma mass spectrometry (ICP-MS) on the reactor effluent of the PBR (Supporting Information section S2, Figure S2). We established that the initial wash of the flow reactor resulted in elevated levels of Pd leachate that rapidly decreased to sub-ppm levels with a brief solvent rinse through the PBR. We determined the experimental flow rates and nominal residence time, t_R , for each PBR based on the reactor void volume calculated using the density of the synthesized catalytic particles (see Supporting Information section S3) and their total mass loaded in the flow reactor.

RESULTS

PMHS Network Characterization. Mechanical and chemical analyses on the cross-linked PMHS network were performed at each R_{PC} and nominal Pd loading, m_c . The swelling studies were performed separately by preparing the PMHS networks within a fluoropolymer tubing (fluorinated ethylene propylene (FEP), 1/8 in. OD, 1/16 in. ID). After PMHS curing,

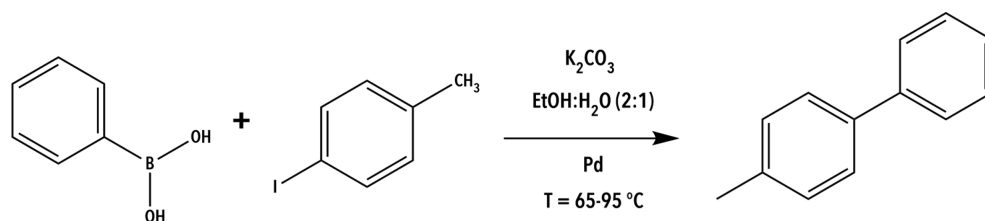
the tubing was cut to approximately 1 cm length, and the cross-linked PMHS cylinders were removed (Figure 2A). After vacuum drying, the PMHS cylinders were imaged to determine the dry diameter of the cylinders, D_d . Next, the dried PMHS cylinders were placed in a vial containing the cross-coupling reaction solvent to swell at room temperature for 1 h, and the swollen PMHS cylinders diameter (D_s) was measured. Volumetric swelling, S , was calculated by measuring the average increase in cylinder diameter (eq 1):

$$S = (D_s/D_d)^2 \quad (1)$$

Swelling measurements were also carried out on cross-linked PMHS cylinders with *in situ* reduced Pd at different nominal catalyst loading. Most swelling occurred in PMHS cylinders without Pd and higher cross-linker content (Figure 2B). Pd salt addition to the cross-linked PMHS and sequential reduction led to a substantial decrease in polymer swelling compared to a Pd-free material. We attribute this observation to the fact that the VTEG cross-linker promotes solvent uptake due to a higher polarity, which increases swelling due to its affinity for the aqueous solvent used in this study. This effect is in contrast to the swelling resistance caused by having a tighter network due to an increased cross-linking degree (R_{PC}). Since silicon hydride (Si–H) bonds in this system act as the cross-linking sites, the cross-link density affects how many Si–H bonds are available for reduction. Figure 2C shows the experimental and theoretical amounts of Si–H remaining in a gel after cross-linking, X_{Si-H} , for each tested R_{PC} composition. The theoretical concentration of the remaining Si–H groups is lower than the amount measured experimentally. This observation reveals that the PMHS network has cross-linker molecules that do not contribute to network formation and remain within the bulk of the gel in the form of dangling chains or are not even attached at all.⁴² This information is critical in understanding the chemical composition of the network since Si–H is also employed as the reducing sites for Pd(II). The remaining amount of Si–H is paramount in determining the amount of Pd that can be reduced and anchored in the polymer network. In the next step, mechanical testing of the cross-linked PMHS gels with and without Pd was used to measure the network storage modulus at different gel compositions (Figure 2D). The storage modulus of the Pd-loaded PMHS particles increases as R_{PC} increases, consistent with the inclusion of fillers and the formation of additional cross-links within the network associated with Pd nanoclusters.^{39,43} We used Fourier transform infrared spectroscopy (FTIR) to analyze the presence of Si–H moieties within the bulk of the PMHS network at various Pd salt loadings (Figure 2E). The consistent Si–H signal across the cross section indicates homogeneous Pd reduction in the bulk polymer at the FTIR resolution.

In Situ Pd Reduction. Transmission electron microscopy (TEM) imaging was used to elucidate the *in situ* reduction

Scheme 1. Reaction Scheme of the Model Suzuki–Miyaura Cross-Coupling Reaction of Phenylboronic Acid and 4-Iodotoluene



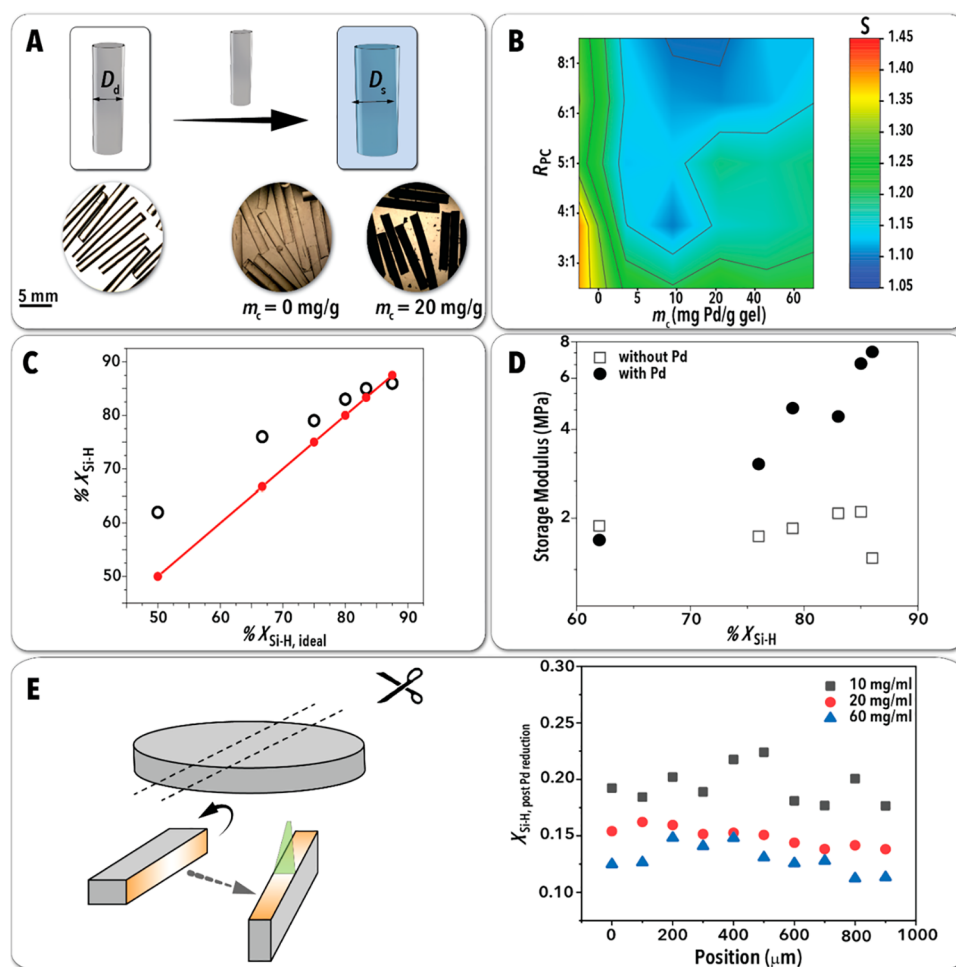


Figure 2. (A) Schematic of swelling experiments. Different cross-linking ratios and nominal Pd loading were tested with a 2:1 (ethanol/water) solvent mixture. (B) Three-dimensional plot showing swelling ratios of gel cylinders at specified cross-link ratios and nominal Pd loading (m_c). (C) FT-IR data showing the percentage of Si–H groups remaining after cross-linking reaction compared to the neat PMHS. (D) Dynamic mechanical analysis results show storage modulus (E') of cross-linked PMHS gels with and without Pd loading. Different Si–H remaining (different cross-linker ratios R_{PC}) are displayed for comparison. (E) Schematic of the preparation of PMHS cross-section for FTIR characterization of Si–H peak across PMHS cross-section.

process and the effect of nominal Pd loading on the catalytic activity of the PMHS-supported Pd catalysts. TEM samples were prepared from microparticles at various nominal Pd loadings using focused ion beam (FIB) lift-out. The prepared samples were then analyzed using TEM to obtain size distributions of the *in situ* formed Pd nanoclusters present within the PMHS network (Figure 3A). From TEM image analysis, Pd nanocluster sizes of 3.3 ± 0.7 nm, 2.4 ± 0.4 nm, and 2.5 ± 0.4 nm were obtained for 10, 20, and 60 mg/g nominal Pd loading, respectively. The size of Pd nanoclusters was found to be independent of the nominal Pd loading for the range tested here. Further characterization with high-resolution TEM (HRTEM) and energy-dispersive X-ray spectroscopy (EDS) (Figures 3B, S3, and S4) validate the presence of crystalline Pd nanoclusters dispersed through the bulk of the reduced PMHS particles. HRTEM images illustrate the lattice fringes of the reduced Pd nanoclusters, thereby supporting the presence of highly crystalline domains. A high-magnification 2D EDS map shows strong localization of Pd in the crystalline domains (Figure 3B). Line-scan EDS was also performed on the cross sections of PMHS:VTEG polymer networks with the reduction conditions of 20 and 60 mg Pd(OAc)₂/g (Figures S3 and S4). A surface region of ~ 100 and ~ 50 μm for the 20 and 60 mg

Pd(OAc)₂/g samples, respectively, exhibited a Pd/Si signal of ~ 1 at the particle surface and decreased toward the bulk value of 0.01 (Figures S3 and S4). The variable width of the surface region indicates a transport-dependent reduction process while still allowing Pd access to the entire bulk of the PMHS network (Supporting Information section S4). We hypothesize that the high nominal loadings of Pd produce a surface transport barrier to both Pd during reduction and reagents during reaction.

Effect of Cross-Linker: VTEG versus Hexadiene.

Following the characterization of the physicochemical characterization of the gel-supported catalyst, we compared the catalytic performance of the PMHS-supported Pd catalyst prepared using a hydrophilic (VTEG) and hydrophobic (1,5-hexadiene)⁸ cross-linker in the cartridge PBR for the model Suzuki–Miyaura cross-coupling reaction shown in Scheme 1. Utilizing the automated flow chemistry platform (Figure 1C), we evaluated the start-up time and steady-state yields for each PBR, shown in Figure 4 (VTEG: Figure 4A; 1,5-hexadiene: Figure 4B). The VTEG-cross-linked catalyst showed increased cross-coupling reaction yield and $>50\%$ reduction in start-up time compared to the hexadiene-cross-linked particles (VTEG: 27% yield, 6 h start-up; hexadiene: 21% yield, 13 h start-up) with the same nominal Pd salt loading. The hydrophilic nature of the

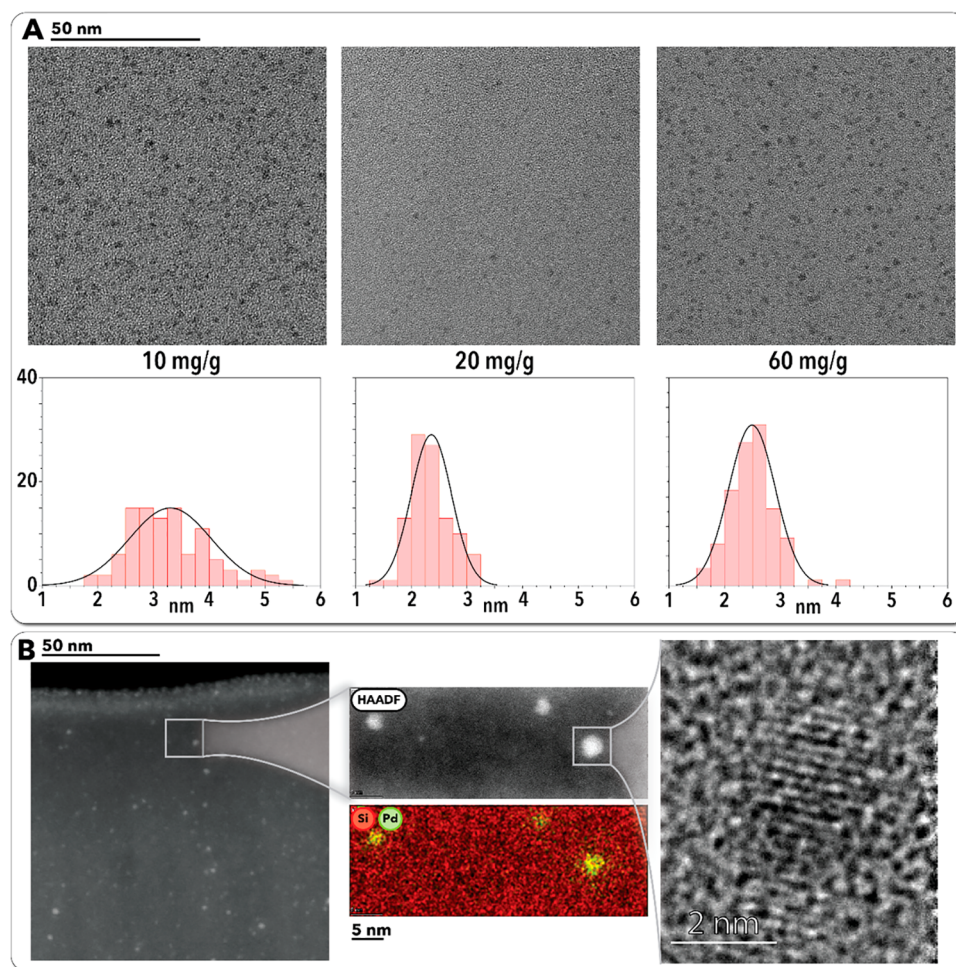


Figure 3. (A) TEM Images of samples prepared from cross-linked and reduced microparticles with various nominal Pd loadings (left to right, 10, 20, and 60 mg/g). Pd nanocluster size histogram extracted from TEM images. (B) Dark-field TEM and 2D EDS map showing localization of Pd inside the nanoclusters with HRTEM image of Pd nanocluster lattice fringes indicating crystallinity.

VTEG-cross-linked network promotes the uptake of the cross-coupling precursors (4-iodotoluene and phenylboronic acid) in the presence of the polar solvent while simultaneously favoring the release of the nonpolar product (4-phenyl toluene) from the bulk of the Pd-loaded PMHS particle back into the reaction mixture (i.e., faster start-up time).

Pd Loading Characterization. In the first set of cartridge PBR screening experiments with VTEG as the cross-linker, we investigated the effect of nominal Pd loading with R_{PC} of 4:1 on the continuous Suzuki–Miyaura cross-coupling reaction (Scheme 1). For each PBR tested, the effluent was automatically sampled and analyzed using an in-line HPLC at every residence time. The results were analyzed for both the start-up and steady-state periods of operation. The steady-state yield was calculated by averaging the cross-coupling reaction yields obtained from the in-line HPLC unit after the start-up stage (i.e., particle saturation period). The highest average steady-state reaction yields were obtained with the nominal Pd loadings of 20 and 40 mg/g beds, while PBRs with 10 and 60 mg/g loadings showed lower activity (Figure 5). A few competing effects define the optimum in the nominal Pd loading. The total concentration of Pd nanoclusters in the network directly affects the overall catalytic performance, as an increase in the number of accessible reaction sites per unit volume of the catalyst leads to a rise in the reaction rate. It competes with a limiting amount of Pd that is

capable of being supported by the elastomeric network, with excess reduced Pd in the 60 mg/g sample depositing out of solution onto the surface of PMHS particles, forming a metallic barrier for diffusion into the network matrix. To reduce the formation of surface-bound Pd layers, we selected PBRs with the nominal Pd loading of 20 mg/g instead of 40 mg/g Pd loading for the subsequent reaction studies, as it produces nearly equivalent yield to 40 mg/g, while using half of the Pd during the reduction step.

Polymer Network Density Characterization. In the next set of screening experiments, we investigated the effect of R_{PC} on the catalytic performance of the PMHS-supported Pd catalyst at the nominal Pd loading of 20 mg/g. The R_{PC} ratio of 2:1 was not considered, as the polymer network precursors were not miscible without further addition of a significant amount of solvent, which would affect the cross-linking density. Additionally, PMHS gels with R_{PC} values higher than 8:1 become softer and more difficult to handle in a PBR. In the high limit of R_{PC} (~ 25 , less than two cross-links per polymer chain on average), the polymer network is unable to solidify into a gel and remains a liquid. We obtained the highest Suzuki–Miyaura cross-coupling yield with the R_{PC} ratio of 4:1 (Figure 6). As R_{PC} increases, (i) the amount of remaining Si–H sites to reduce and stabilize active Pd species increases, (ii) the network mesh size increases, and (iii) the bulk hydrophilicity of the PMHS network

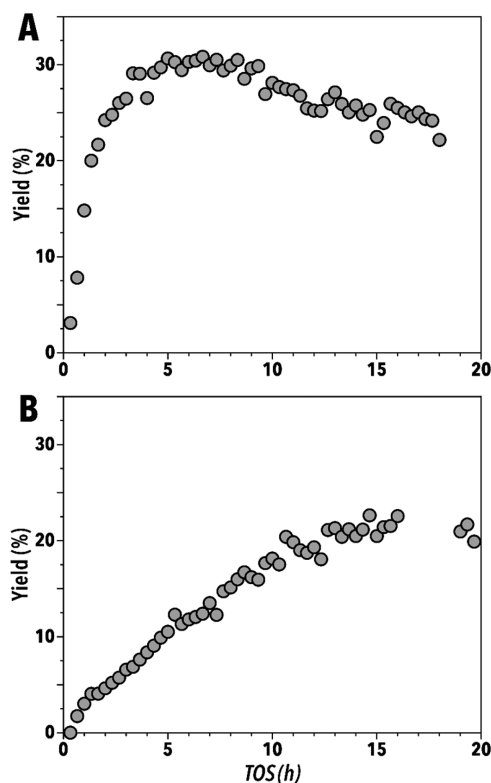


Figure 4. Exemplary start-up plot for 16 h continuous time on stream (TOS) of Suzuki–Miyaura cross-coupling reactions shown in Scheme 1 for (A) 5:1 PMHS/VTEG and (B) PMHS/hexadiene. $T = 65\text{ }^{\circ}\text{C}$, $t_R = 10\text{ min}$.

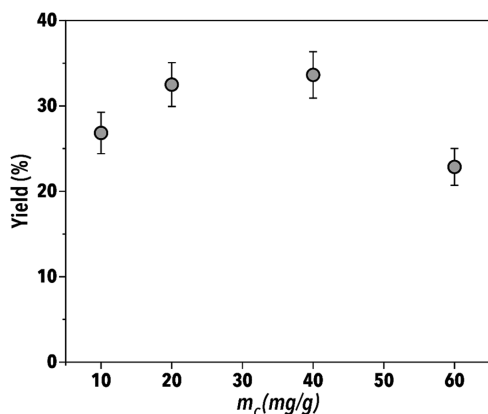


Figure 5. Observed continuous steady-state cross-coupling reaction yields for different nominal Pd loadings using 4:1 PMHS/VTEG particles. $T = 65\text{ }^{\circ}\text{C}$, $t_R = 10\text{ min}$.

decreases. One expects that the increased amount of reduced Pd species due to the extra available Si–H sites and increased network size would improve the catalytic activity. However, this increased catalytic activity is mitigated by the decreased affinity of the aryl halide substrate for the PMHS network as the fraction of VTEG units is decreased. Thus, the R_{PC} ratio of 4:1 was selected as the optimal value for the temperature and residence time screening experiments.

Palladium Reduction Characterization. Following the PMHS network composition screening experiments, we investigated the nature of surface- versus bulk-based catalysis of the PMHS-supported Pd catalyst by comparing three

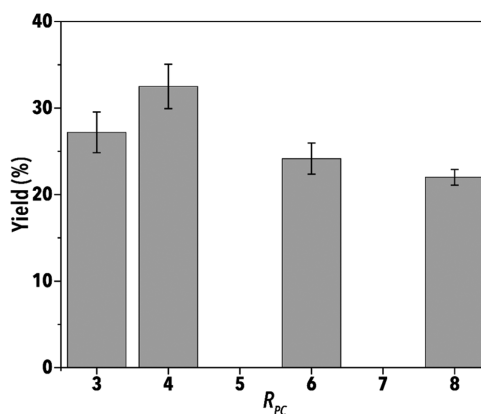


Figure 6. Continuous steady-state yields for different cross-link densities (R_{PC}) at 20 mg/g Pd loading. $T = 65\text{ }^{\circ}\text{C}$, $t_R = 10\text{ min}$.

reduction methods for three sets of catalytic particles (R_{PC} of 4:1, 10, 20, and 60 mg/g). In methods 1 and 2, Pd was reduced in $>500\text{ }\mu\text{m}$ particles and 100–500 μm , respectively. In method 3, Pd was initially reduced in $>500\text{ }\mu\text{m}$ particles, and then the particles were crushed to obtain 100–500 μm particles. For the same total mass of PMHS, particles in method 1 have a lower surface area available for Pd reduction than those in method 2. Particles in method 3 have a size similar to those in method 1 but have a lower initial surface area with reduced Pd. Particles in sets 2 and 3 have the same packing characteristics inside the PBR. Both the trends of the increased surface area of Pd reduction and increased transport rate enhance the carbon–carbon cross-coupling reaction yield (Figure 7), indicating that there is both a

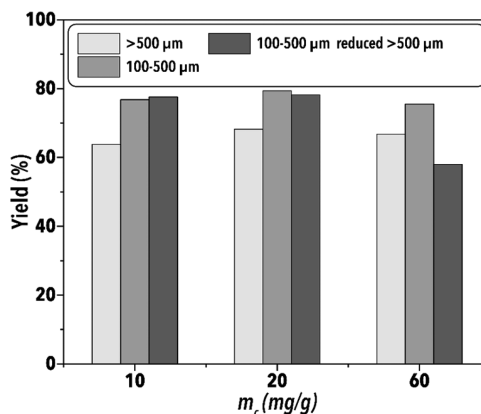


Figure 7. Steady-state reaction yields of PBRs loaded with particles of $R_{PC} = 4:1$ and $m_C = 10\text{--}60\text{ mg/g}$ with Pd loading reduction performed at different particle sizes. Reduced at $>500\text{ }\mu\text{m}$, 100–500 μm , and $>500\text{ }\mu\text{m}$ followed by crushed to 100–500 μm .

surface and bulk component to the PMHS-supported Pd catalyst activity. The surface reaction effect can be observed by comparing the particles reduced at 100–500 μm (set 2) with the particles reduced at $>500\text{ }\mu\text{m}$ (set 1). The former has a significantly increased surface area during the Pd reduction. The bulk reaction effect is evident when comparing the Pd-reduced $>500\text{ }\mu\text{m}$ particles (set 1) and particles crushed to 100–500 μm after Pd reduction (set 3). The particle surface that was initially reduced with Pd remains the same, while set 3 has a lower average particle size and characteristic diffusion length scale with the interior of particles exposed after crushing the original catalytic particles. Crushed particles of the high-concentration

nominal Pd loading of 60 mg/g underperformed compared to the large particles. The high initial concentration of Pd during the reduction resulted in rapid deposition onto the surface of the gel particles, creating a shell-like barrier, making it difficult for Pd salt to diffuse into the particles for further reduction. At these higher nominal Pd loading concentrations, exposing the internal parts of the particle via crushing decreases the efficacy due to the lower availability of active Pd nanoclusters inside the catalytic particles.

In a separate set of experiments, we investigated the effect of the initial $\text{Pd}(\text{OAc})_2$ solution concentration used for the Pd reduction at the same nominal Pd loading on the catalytic performance of the PMHS-supported Pd catalyst (Figure 8).

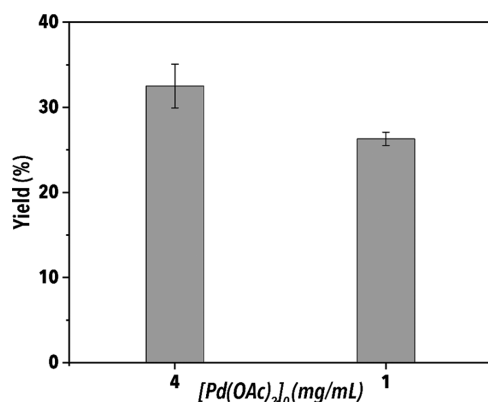


Figure 8. Steady-state reaction yields for PBRs loaded with particles reduced from concentrated (4 mg $\text{Pd}(\text{OAc})_2$ /mL toluene) versus dilute (1 mg $\text{Pd}(\text{OAc})_2$ /mL toluene) $\text{Pd}(\text{OAc})_2$ solutions. $T = 65^\circ\text{C}$, $t_R = 10$ min.

Higher concentration reduction of Pd (4 mg of $\text{Pd}(\text{OAc})_2$ per 1 mL of toluene) resulted in a higher steady-state cross-coupling reaction yield than the lower concentration Pd solution (1 mg of $\text{Pd}(\text{OAc})_2$ per 1 mL of toluene). We attribute the higher reaction yield observed with a higher initial concentration of $\text{Pd}(\text{OAc})_2$ to the fact that the higher concentration Pd solution forms a larger amount of Pd(0) close to the particle surface (Supporting Information sections S3 and S4). In contrast, the lower concentration of Pd solution results in Pd(0) being dispersed more uniformly throughout the PMHS particles due to the reduced rate of reduction as compared with diffusion. At high nominal loading concentrations of $\text{Pd}(\text{OAc})_2$, Pd(0) forms promptly at the surface of the particles, and this layer reduces the diffusion rate of $\text{Pd}(\text{OAc})_2$ inside the particle. Most of the catalytic activity occurs in the near-surface region of the particles.

Cross-Coupling Reaction Condition Screening. Following the studies of the PMHS composition and nominal Pd loading on the catalytic performance of the PMHS-supported Pd catalyst, we investigated the effect of reaction temperature and nominal residence time (t_R) on the model Suzuki–Miyaura cross-coupling reaction (Scheme 1) using a set of cartridge PBRs prepared with R_{PC} ratio of 4:1 and nominal Pd loading of 20 mg/g. Suzuki–Miyaura cross-coupling reactions have previously exhibited higher reaction yields at temperatures between 75 and 95°C in batch reactors.^{25,44} For reaction temperature screening experiments, we evaluated the catalytic performance of the PMHS-supported Pd catalyst in the cartridge PBR at temperatures in the range of 65 – 95°C and at a nominal residence time of 10 min (Figure 9). The measured increase in reaction yield

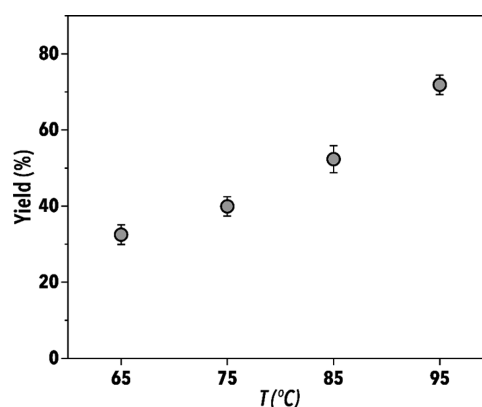


Figure 9. Steady-state reaction yields of the model Suzuki–Miyaura cross-coupling reaction (Scheme 1) at temperatures from 65 to 95°C with $R_{\text{PC}} = 4:1$, $m_c = 20$ mg/g, and $t_R = 10$ min.

with increased temperature follows the reaction trends expected for the Suzuki–Miyaura cross-coupling mechanism.⁴⁵ Still, our findings highlight the advantage of a continuous flow synthesis system that allows for an increased range of reaction temperatures to be accessed for a gel-supported catalyst due to the presence of a back-pressure regulator (at atmospheric pressure, the solvent mixture would evaporate at temperatures $>70^\circ\text{C}$).

Residence time in a PBR describes the average length of time chemical species spend within the flow reactor. A common strategy to maximize the reaction yield in catalysis is to increase the reaction time, thereby giving each reagent molecule a higher probability of completing the catalytic cycle using the active catalyst species.³⁰ As shown in Figure 10, a 75% reaction yield

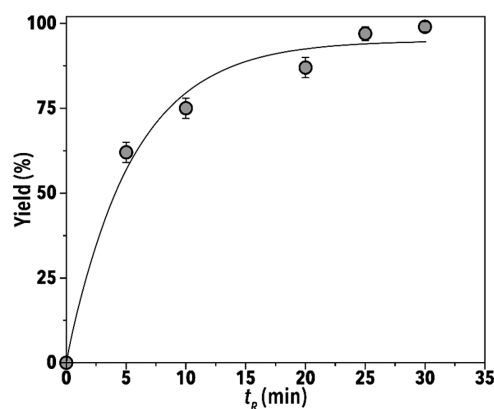


Figure 10. Steady-state reaction yields of the model Suzuki–Miyaura cross-coupling reaction (Scheme 1) at different nominal residence times at $T = 95^\circ\text{C}$ with $R_{\text{PC}} = 4:1$ and $m_c = 20$ mg/g.

for the model Suzuki–Miyaura cross-coupling reaction (4-iodotoluene and phenylboronic acid) was obtained with a 10 min nominal residence time at 95°C . Increasing the residence time to 25 min resulted in 97% yield (Figure 10). Increasing the nominal residence time in a fixed-length PBR has the obvious trade-off of decreasing the reaction throughput with increased reaction yield.

Next, to examine the stability of the PMHS-based Pd catalyst, we conducted a continuous 80 h time on stream run of the model Suzuki–Miyaura cross-coupling reaction between 4-iodotoluene and phenylboronic acid in a cartridge PBR with R_{PC} of 4:1 and m_c of 20 mg/g at a nominal residence time of 30 min

(combined precursor flow rate of 25 $\mu\text{L}/\text{min}$) and reaction temperature of 95 $^{\circ}\text{C}$ (Figure 11). Even with operation over

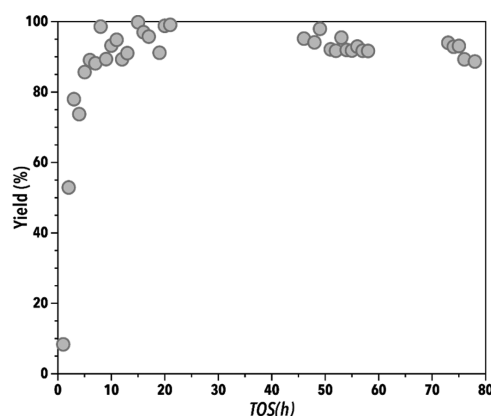


Figure 11. Continuous operation (80 h) of the PBR for the model Suzuki–Miyaura cross-coupling reaction at $t_R = 30$ min, $T = 95$ $^{\circ}\text{C}$, $R_{PC} = 4:1$, and $m_c = 20$ mg/g.

extended periods at extreme reaction conditions (i.e., 95 $^{\circ}\text{C}$), only a mild reduction in catalyst yield (99% peak yield to 92% yield after 80 h) was observed, indicating good catalyst stability.

CONCLUSIONS

In this work, we designed and developed a modular flow chemistry strategy to rapidly investigate the fundamental and applied characteristics of gel-supported catalysts in a plug-and-play cartridge-like packed-bed flow reactor. Utilizing the robust flow chemistry platform, we explored the design space of a readily synthesizable network-supported Pd catalyst and investigated the critical parameters of polymer catalyst synthesis controlling the catalyst performance in a model Suzuki–Miyaura cross-coupling reaction. We systematically explored the effects of intrinsic (e.g., polymer network composition) and extrinsic (e.g., reaction temperature, residence time) process parameters on the start-up and steady-state yield of the model carbon–carbon cross-coupling reaction. The automated in-line reaction monitoring of the developed flow chemistry platform enabled rapid exploration of the complex chemical interactions during synthesis and reaction of the PMHS-supported Pd catalyst. The automated in-line reaction sampling enabled the collection of up to 144 HPLC chromatograms per day during continuous operation. This approach allowed us to examine the start-up and steady-state behavior of the gel-supported Pd catalyst during cross-coupling reaction in a way that would be prohibitively labor-intensive for manual sampling techniques. The accessible design space of possible catalyst systems in the “cross-link-able” polymer is vast, not to mention the possible functionalization or postsynthetic modifications. With such a large parameter space, the developed cartridge PBR integrated within the automated flow chemistry workflow makes it possible to rapidly identify an optimal combination of intrinsic and extrinsic parameters for a specific metal-mediated catalytic reaction using the gel-supported catalyst approach.

The parameters investigated here also lead to further questions addressing a deeper fundamental understanding of the metal interactions with the polymer network support and the microstructure of these nanoparticle-filled networks. Further research should focus on designing new mechanisms for catalyst

immobilization and polymer networks interaction with the reduced catalytic nanoclusters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.1c01531>.

Experimental procedures, catalyst leaching characterization, void volume verification, EDS characterization and analysis, XPS characterization and analysis (PDF)

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Notes

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Bradley A. Davis was born in Bluefield, West Virginia, but grew up in Reidsville, North Carolina. He received his B.S. degree in Polymer Chemistry from the University of North Carolina at Chapel Hill in 2018 and conducted post-polymerization modification research under Dr. Frank Leibfarth. He received his M.S. in Chemical Engineering in 2020 and is conducting graduate research to obtain his PhD in Chemical Engineering from North Carolina State University. Bradley's graduate research primarily involves designing polymeric supports for catalysts and adapting them to continuous flow. His research is conducted under the supervision of Dr. Milad Abolhasani and Dr. Jan Genzer.



Mahdi Ramezani received his Ph.D. in mechanical engineering with a minor in chemical engineering from Iowa State University in 2016. He gained plenty of experience in design, scale up, and testing of various multiphase flow reactors during his PhD. He then joined the Abolhasani Lab at North Carolina State University as a postdoctoral research scholar with a focus on small molecule organic chemistry using fully automated continuous flow chemistry platforms. Throughout his academic career, he was involved with highly interdisciplinary research taking advantage of his background in mechanical, chemical, electrical, and software engineering to serve several state-, government-, and industry-funded projects.



Jan Genzer holds a Dipl-Ing (University of Chemistry & Technology, Prague, Czech Republic, 1989) in chemical and materials engineering and a Ph.D. (University of Pennsylvania, 1996) in materials science & engineering. After two post-doctoral stints at Cornell University (1996-1997) and at the University of California at Santa Barbara (1997-1998), Genzer joined the faculty of chemical engineering at NC State University as an Assistant Professor in fall 1998. He is the S. Frank and Doris Culberson Distinguished Professor in the Department of Chemical and Biomolecular Engineering at NC State University. Genzer and his group study the behavior of polymers at surfaces, interfaces, and in confined geometries.



Kirill Efimenko received an M.Sc. degree in physics of semiconducting materials from Belarusian State University in 1996 (Minsk, Belarus) and a Ph.D. in Material Science and Technology from the Institute of Chemical Technology in Prague, Czech Republic in 1999. Shortly after that, he joined the Department of Chemical Engineering at North Carolina State University as Postdoctoral Fellow. In 2012 he was appointed to the position of Research Associate Professor in the Department of Chemical and Biomolecular Engineering. His research interests include stimuli-responsive polymer materials, functionalized siloxanes, processes of self- and directed assembly, and biofouling.



Milad Abolhasani is an Assistant Professor and a University Faculty Scholar in the Department of Chemical and Biomolecular Engineering at NC State University. He received his Ph.D. degree (2014) from the Department of Mechanical and Industrial Engineering in collaboration with the Department of Chemistry at the University of Toronto. Prior to joining NC State University, he was an NSERC postdoctoral fellow in the Department of Chemical Engineering at Massachusetts Institute of Technology. Dr. Abolhasani leads a diverse research group that studies flow chemistry strategies tailored towards accelerated development and manufacturing of fine chemicals and functional nanomaterials using autonomous robotic experimentation.

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