# Monodisperse Elastomeric Microparticle Scaffolds for Heterogeneous Palladium-Mediated Catalysis

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Metal-mediated cross-coupling reactions offer organic chemists a wide array of stereo- and chemically-selective reactions with broad applications in fine chemical and pharmaceutical synthesis.[1] Current batch-based synthesis methods are beginning to be replaced with flow chemistry strategies to take advantage of the improved consistency and process control methods offered by continuous flow systems.[2,3] Most cross-coupling chemistries still encounter several issues in flow using homogeneous catalysis, including expensive catalyst recovery and air sensitivity due to the chemical nature of the catalyst ligands.[1] To mitigate some of these issues, a ligand-free heterogeneous catalysis reaction was developed using palladium (Pd) loaded into a polymeric network of a silicone elastomer, poly(hydromethylsiloxane) (PHMS), that is not air sensitive and can be used with mild reaction solvents (ethanol and water).[4]

In this work we present a novel method of producing soft catalytic microparticles using a multiphase flow-focusing microreactor and demonstrate their application for continuous Suzuki-Miyaura cross-coupling reactions. The catalytic microparticles are produced in a coaxial glass capillary-based 3D flow-focusing microreactor. The microreactor consists of two precursors, a cross-linking catalyst in toluene and a mixture of the PHMS polymer and a divinyl cross-linker. The dispersed phase containing the polymer, cross-linker, and cross-linking catalyst is continuously mixed and then formed into microdroplets by the continuous phase of water and surfactant (sodium dodecyl sulfate) introduced in a counter-flow configuration. Elastomeric microdroplets with a diameter ranging between 50 to 300 micron are produced at 25 to 250 Hz with a size polydispersity less than 3% in single stream production. The physicochemical properties of the elastomeric microparticles such as particle swelling/softness can be tuned using the ratio of cross-linker to polymer as well as the ratio of polymer mixture to solvent during the particle formation. Swelling in toluene can be tuned up to 400% of the initial particle volume by reducing the concentration of cross-linker in the mixture and increasing the ratio of polymer to solvent during production.[5]

After the particles are produced and collected, they are transferred into toluene containing palladium acetate, allowing the particles to incorporate the palladium into the polymer network and then reduce the palladium to $Pd^0$ with the Si-H functionality present on the PHMS backbones. After the reduction, the Pd-loaded particles can be washed and dried for storage or switched into an ethanol/water solution for loading into a micro-packed bed reactor (μ-PBR) for continuous organic synthesis. The *in-situ* reduction of Pd within the PHMS microparticles was confirmed using energy dispersive X-ray spectroscopy (EDS), X-ray photoelectron spectroscopy (XPS) and focused ion beam-SEM, and TEM techniques.

In the next step, we used the developed μ-PBR to conduct continuous organic synthesis of 4-phenyltoluene by Suzuki-Miyaura cross-coupling of 4-iodotoluene and phenylboronic acid

using potassium carbonate as the base. Catalyst leaching was determined to only occur at sub ppm concentrations even at high solvent flow rates after 24 h of continuous run using inductively coupled plasma mass spectrometry (ICP-MS).

The developed μ-PBR using the elastomeric microparticles is an important initial step towards the development of highly-efficient and green continuous manufacturing technologies in the pharma industry. In addition, the developed elastomeric microparticle synthesis technique can be utilized for the development of a library of other chemically cross-linkable polymer/cross-linker pairs for applications in organic synthesis, targeted drug delivery, cell encapsulation, or biomedical imaging.

**References**


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