

Organic & Biomolecular Chemistry

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Dendrimer-encapsulated Pd nanoparticles as catalysts for C-C cross-couplings in flow microreactors

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Roberto Ricciardi, Jurriaan Huskens and Willem Verboom*

The inner walls of glass microreactors were functionalized with dendrimer-encapsulated Pd nanoparticles. The catalysts were efficient for the Heck-Cassar (copper-free Sonogashira) and Suzuki-Miyaura (SMC) cross-coupling reactions. For the Heck-Cassar reaction between iodobenzene and phenylacetylene, the catalytic system exhibited a high turnover frequency (TOF) and on average required milder reaction conditions as compared to other continuous flow cross-couplings. A study of the substituent effect of para-substituted aryl halides revealed a beneficial effect of electron-withdrawing side groups for the SMC. Moreover, a reaction constant (ρ) of 1.5, determined from the Hammett plot, indicated a possible rate-determining step other than the oxidative addition.

Introduction

Carbon-carbon (C-C) cross-couplings are among the most used and studied reactions, especially for their importance in industrial processes.¹ In fact, biaryls and heterobiaryls are intermediates in many pharmaceuticals, natural derivatives, and dyes.² Palladium is the metal of choice for these reactions and several homogeneous catalysts rely on Pd(II) and Pd(0) species, mostly in the form of Pd complexes.³ Depending on the reagent involved, several examples of C-C cross-couplings have been developed since the early 1970s, such as the Suzuki-Miyaura, the Mizoroki-Heck, the Sonogashira, the Stille reactions, etc.⁴ Transition metal nanoparticles (NPs) have gained a lot of interest over the last decade for a variety of applications, with catalysis exerting a central role.⁵ These nanometer species are considered ideal candidates for improving the sustainability of catalytic processes, blending together the advantages of homogeneous and heterogeneous catalysts.⁶ In this respect, Pd NPs are widely utilized as catalyst for C-C cross-coupling reactions, as witnessed by the numerous reviews present in the literature.⁷

A stable heterogeneous catalytic system making use of supported Pd NPs would undoubtedly allow to carry out cross-coupling reactions in continuous flow systems.⁸ In this way, the high local concentration of catalyst, together with the absence

of reagent diffusion limitation, promotes conversion rates that can be much higher than in batch operations.⁹ The use of continuous flow microreactors, however, necessitates stable NPs which can be reused for many cycles. A variety of strategies has already been shown in literature for the stabilization of Pd NPs within microchannels and has been employed mainly in Suzuki-Miyaura and Heck reactions.¹⁰ Examples of continuous-flow Sonogashira,¹¹ Negishi,¹² and Stille¹³ reactions have been based on different Pd catalysts.

The leaching of metal species associated with the use of Pd NPs for C-C cross-couplings under flow conditions represents an important issue. The debate is centered on whether the Pd catalysts act in a heterogeneous or a homogeneous manner.¹⁴ Meanwhile, the accepted mechanism for Pd cross-couplings, independently from the type of catalyst used, involves the formation of Pd²⁺ after the oxidative addition of an aryl halide. These molecular species, even in very small quantities, can catalyze cross-coupling reactions.¹⁵ Usually Pd²⁺ atoms redeposit on the mother NPs at the end of the catalytic cycle, while the application of continuous flow eventually leads to the washing out of dissolved Pd and hence loss of catalyst.¹⁶ To this regard, Kappe *et al.*¹⁷ have conducted a comparative study of some of the most common immobilized diarylphosphine- and triarylphosphine-based Pd catalysts, with particular attention to

the leaching resistance for continuous flow Suzuki-Miyaura and Mizoroki-Heck reactions. Under the reaction conditions used, the SiliaCat DPP-Pd catalyst gave the best results in terms of catalyst efficiency and leaching resistance.¹⁸

Recently, we have presented the synthesis of dendrimer-encapsulated Pd NPs (Pd DENs) anchored onto the inner walls of flow microreactors.¹⁹ The thus formed catalytic platform was successfully used in a test Suzuki-Miyaura cross-coupling (SMC) reaction of iodobenzene with *p*-tolylboronic acid. The choice of this system was motivated by the advantageous feature of dendrimers as a template for NP formation and activity.²⁰ The G3 PAMAM dendrimer exhibited the best activity as compared to higher dendrimer generations. With a turnover frequency (TOF) as high as 11340 h⁻¹, the system outperformed many other flow-supported Pd NP reactors as well as Pd DENs used in batch scale studies. Additionally, dendrimers were demonstrated to have good stabilizing properties towards metal leaching.²¹ In fact, the reactor was run over seven consecutive days showing a minimal Pd leaching (1.2 ppm).¹⁹

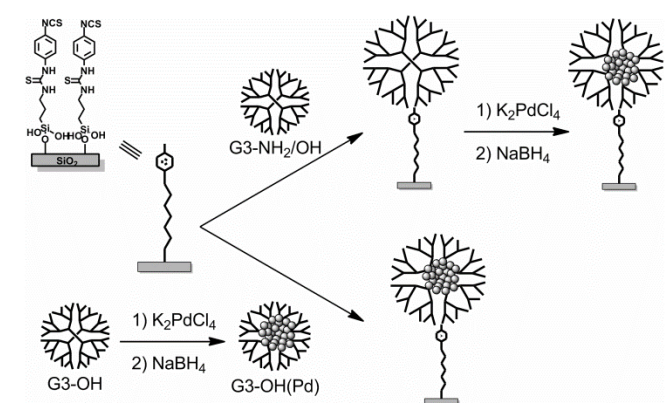
Herein, we expand the scope of Pd DENs as catalysts for cross-coupling reactions under continuous flow. Therefore, the Heck-Cassar coupling (the copper-free Sonogashira) reaction was investigated. Additionally, we studied the influence of *para*-substituted aryl iodides on the overall SMC reactivity. In this way, through a Hammett plot of the aryl iodides substituents, we aimed at gaining insight into some catalytic mechanistic aspects, such the rate-determining step of the reaction.

Results and discussion

Microreactor functionalization

For the functionalization of the microreactor surface we followed the methodology described in a previous publication.¹⁹ Briefly, the inner surface of a glass microreactor was first modified with a reactive monolayer of (3-aminopropyl)triethoxysilane (APTES) followed by *p*-phenylene diisothiocyanate (DITC). In this way the exposed isothiocyanate groups were used for the covalent anchoring of G3-NH₂ and G3-OH PAMAM dendrimers. Two different methodologies for the formation of Pd NPs were employed, as depicted in Scheme 1. In one approach NH₂- and OH-terminated dendrimers were first attached to the monolayer-functionalized surface and thereby Pd NPs were formed *in situ*, using K₂PdCl₄ as a Pd source followed by reduction by NaBH₄. In the other approach, Pd DENs were preformed in solution, based on the procedure developed by Crooks in which Gn-OH dendrimers contained 40-atom Pd NPs,²² and subsequently anchored to the reactive monolayer. The characterization of the Pd DENs was carried out on silicon dioxide surfaces functionalized in the same way as the microchannel interior. Contact angle, UV-vis spectroscopy, X-ray photoelectron spectroscopy (XPS), transmission electron microscopy (TEM), and high-resolution scanning electron microscopy (HRSEM)

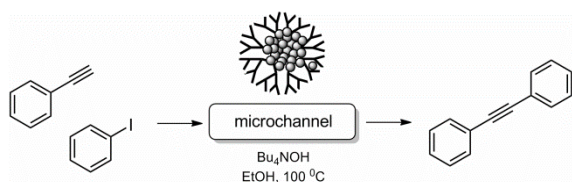
confirmed the formation of homogeneously dispersed 2.4 nm Pd NPs within the dendrimer templates (see supporting information).^{20a} The detailed description of the analytical procedures has been presented elsewhere.¹⁹ The total amount of catalyst within the microreactor was 0.12 μg of Pd metal as measured by total reflection X-ray fluorescence (TXRF). This value indicates the Pd retained by the dendrimer templates attached to the surface of the microreactor. The quantity of metal atoms within the microreactor volume (13 μL) is thus 1.1 nmol.



Scheme 1 Microreactor surface functionalization with dendrimer-encapsulated Pd NPs.

Heck-Cassar coupling (copper-free Sonogashira reaction)

The Sonogashira cross-coupling has become one of the most useful tools for the synthesis of alkyl-aryl- and diaryl-substituted acetylenes.²³ Generally, this reaction is carried out with Pd as the catalyst and a copper salt as a co-catalyst.²⁴ The Cu(I) salt is usually used in the same mixture as the reagents to increase the reactivity through the formation of a copper(I) acetylide with the terminal alkyne.^{23b} However, the addition of copper, although for some aspects beneficial, poses some problems such as avoiding the presence of oxygen that can lead to the formation of alkyne dimers (Glaser-type reactions).²⁵ Moreover, heterogeneous Pd catalysts should ensure a minimal contamination of the final product, another reason to avoid a homogeneous co-catalyst. The solution to address these problems is the use of only a Pd catalyst in the so-called 'copper-free' Sonogashira, or Heck-Cassar coupling, as it is usually referred to.²⁶ However, the Heck-Cassar coupling is more difficult to carry out with Pd NPs than the SMC reaction. The reaction usually requires high temperatures and a large excess of base.²³ Nevertheless, the coupling of iodobenzene and phenylacetylene was efficiently carried out in the Pd DEN-functionalized microreactor (Scheme 2).



Scheme 2 Sonogashira coupling of iodobenzene and phenylacetylene catalyzed by Pd DEN-microreactors.

The catalytic system reached almost quantitative conversion in less than 15 min of residence time (Fig. 1). The temperature was set at 100 °C and tetrabutylammonium hydroxide was used as base. The formation of diphenylacetylene was monitored by GC and no side products were formed in the course of the reaction (Figure S24). Because the two reagents are present in almost stoichiometric amounts, a second order rate constant of $1.3 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ was calculated from the initial rates (see linear fit in Fig. 1).

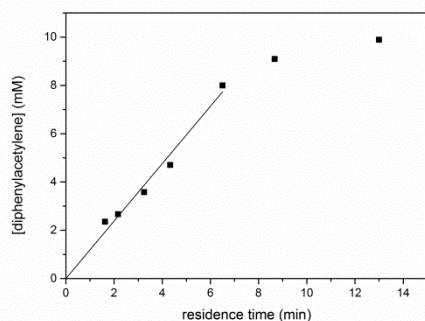


Fig. 1 Diphenylacetylene formation in a G3-NH₂(Pd)-functionalized microreactor. [Iodobenzene] = 10 mM, [phenylacetylene] = 15 mM, [Bu₄NOH] = 20 mM. The line indicates a linear fit through the first data points to estimate the initial rate.

Considering a catalyst loading of 1.1 nmol, the turnover frequency number (TOF) for the continuous flow Pd DEN-catalyzed Sonogashira reaction was 800 h⁻¹. To this regard, Astruc and co-workers²⁷ developed recently a dendritic nanoreactor with hydrophilic triethylene glycol termini and a hydrophobic interior for the stabilization of small Pd NPs. This catalytic system was very efficient for a variety of C-C cross-coupling reactions. The highest TOF obtained for the Sonogashira coupling of iodobenzene and phenylacetylene was 375 h⁻¹, comparable to the value obtained with our catalytic system. In addition, our DEN-functionalized microreactor exhibits a higher TOF as compared to other Pd NP-catalyzed Sonogashira couplings between iodobenzene and phenylacetylene,²⁷ with only a few exceptions.²⁸ The majority of examples of Sonogashira couplings under continuous flow make use of Pd catalysts other than supported NPs.^{8b} Different approaches, ranging from ionic liquids,²⁹ monoliths,³⁰ surface thin layers,^{11b,31} and perovskite catalysts,^{11a} have been used in the coupling of several terminal alkynes with aryl halides. In most of the cases, however, harsher reaction conditions were generally used as compared to our microfluidic reactor, in terms

of temperatures, residence times, and less environmentally friendly solvents such as DMF and NMP.

Substituent effect for the Suzuki-Miyaura cross-coupling reaction

Pd DEN-functionalized microreactors were also used in the SMC, with particular attention to the role of different electron-withdrawing and electron-donating substituents on the aryl halide counterpart. All aryl halides were cross-coupled with a slight excess of phenylboronic acid or *p*-tolylboronic acid in ethanol. Tetrabutylammonium hydroxide was used as a base and the temperature was set at 80 °C (Table 1). The reaction conditions were kept the same for all the experiments to exclude any external influence on the catalytic activity.

Table 1 Suzuki-Miyaura cross-coupling reactions catalyzed by Pd DEN-microreactors.^a

| Entry | Ar-X | R ² | Yield ^b (%) | Conversion ^b (%) |
|-------|------|-----------------|------------------------|-----------------------------|
| 1 | | H | 93 | 96 |
| 2 | | CH ₃ | 91 | 96 |
| 3 | | H | 92 | >99 |
| 4 | | CH ₃ | 91 | >99 |
| 5 | | H | 96 | >99 |
| 6 | | CH ₃ | 96 | >99 |
| 7 | | H | 94 | >99 |
| 8 | | CH ₃ | 95 | >99 |
| 9 | | H | 70 | 74 |
| 10 | | CH ₃ | 65 | 69 |
| 11 | | H | 65 | 70 |
| 12 | | CH ₃ | 60 | 75 |
| 13 | | H | 30 | 33 |
| 14 | | CH ₃ | 28 | 35 |
| 15 | | H | 50 | 54 |
| 16 | | CH ₃ | 40 | 45 |
| 17 | | H | 52 | 55 |
| 18 | | CH ₃ | 10 | 15 |
| 19 | | CH ₃ | 40 | 45 |

^a [Ar-X] = 10 mM; [Ar-B(OH)₂] = 15 mM; [Bu₄NOH] = 20 mM; res. time 13 min. ^b The yield and conversion data were obtained by GC (see Experimental section and Supporting information)

As expected, electron-withdrawing groups enhanced the overall reactivity, with very high yields (92-96%) and conversions > 99% (Table 1, entries 3-8).³² Electron-donating groups, on the other hand, showed a reduced reactivity within the reaction time selected, with yields ranging from 40 to 70% (Table 1, entries 9-17). Aryl bromides are much less reactive as compared to aryl iodides (Table 1, entries 18-19), as is common for SMC reactions. Moreover, little difference in reactivity was observed between phenylboronic- and *p*-tolylboronic acid. The disparity between the yields and the conversions for all entries is due to the presence of some degree of homocoupling and dehalogenated side products (~ 5%).

To assess the electronic substituent effects in a quantitative manner, the apparent rate constants, k_{obs} , for a variety of substituted aryl iodides were calculated by using a large excess of phenylboronic acid. In this way pseudo-first-order conditions were obtained and the k_{obs} values were calculated from the corresponding kinetic curves (two examples for electron-withdrawing and electron-donating *para*-substituents are shown in Fig. 2). The logarithms of the thus obtained k_{obs} values were plotted against the Hammett parameter σ (Fig. 3).³³ Although it is problematic to obtain relevant mechanistic information from this analysis whenever multistep reactions are involved, it is possible to gain useful information, especially about the electronic state of the transition state of the rate-determining step.³⁴ The catalytic cycle of transition-metal-catalyzed cross-coupling reactions, including the SMC, consists of three steps: oxidative addition, transmetalation, and reductive elimination.³⁴ In most cases, the oxidative addition represents the rate-determining step of the catalytic cycle for the SMC.³² In our study, a linear Hammett plot was obtained with a positive reaction constant ($\rho = 1.5$). This result indicates the presence of a negative charge at the reaction center in the transition state of the rate-determining step, with electron-withdrawing substituents at aryl iodides that increase the reaction rate.³⁵ Usually, the SMC reactions of substituted aryl bromides and aryl tosylates show low, positive ρ values (for ArBr: 0.48, 0.66,³⁶ 0.18,³⁷ and 1;³⁸ for ArOTs: 0.80³⁹), suggesting that the aryl halide oxidative addition is not the rate-determining step in this process, but possibly the transmetalation or the reductive elimination. In contrast, higher ρ values were obtained for the oxidative addition of aryl chlorides to Pd(0) complexes (5.2,⁴⁰ and 2.3⁴¹).

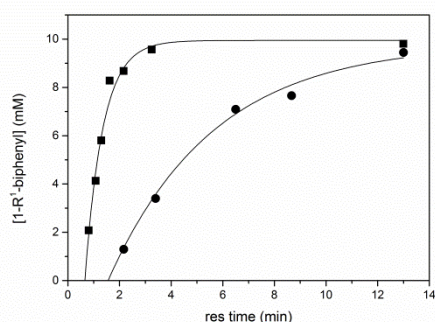


Fig. 2 Formation of 1-R¹-biphenyls using Pd DENs-functionalized microreactors. R¹ = (■) COCH₃; (●) OCH₃. [4-R¹-iodobenzene] = 10 mM, [phenylboronic acid] = 150 mM, [Bu₄NOH] = 160 mM.

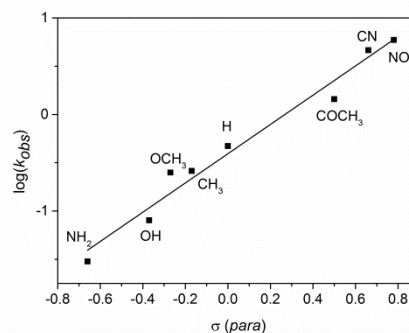


Fig. 3 Hammett plot for Suzuki-Miyaura cross-couplings using Pd DEN-functionalized microreactors showing the effect of *para*-substituted iodobenzenes on the reaction rate.

Conclusions

Continuous-flow microreactors functionalized using small dendrimer-encapsulated Pd NPs were employed in the catalysis of C-C cross-coupling reactions. This same approach has been presented in a recent study for the efficient catalysis of a model Suzuki-Miyaura cross-coupling (SMC) reaction,¹⁹ demonstrating also the influence of dendrimers in the stabilization of the Pd NPs with low metal leaching. Here, the reaction scope of the Pd DEN microreactors was expanded, including the Sonogashira coupling of iodobenzene and phenylacetylene, carried out in the absence of a copper co-catalyst (Heck-Cassar coupling) and at milder reaction conditions than other Pd catalysts used in flow. The calculated TOF of 800 h⁻¹ was comparatively higher than many other Pd DEN platforms used for the batch scale Sonogashira synthesis. Furthermore, the beneficial effect of electron-withdrawing groups was proved for the SMC of substituted aryl iodides. The Hammett plot analysis confirmed the influence of the substituent on the kinetics and thus on the transition state of the rate-determining step, which is most likely not represented by the oxidative addition as common, but possibly the transmetalation or reductive elimination steps.

Further work is needed to extend the applicability of the Pd DENs microreactors to other C-C cross-couplings, such as the Mizoroki-Heck and the Stille reactions. Nevertheless, the anchoring of DENs within microreactors would allow the easy screening of several mono- and bimetallic nanoparticles for a variety of catalytic reactions.

Experimental section

Materials and equipment

The chemicals and solvents were purchased from Sigma Aldrich unless otherwise stated and were used without purification unless specified. Single-side-polished silicon

wafers were purchased from OKMETIC with (100) orientation. Methanol and ethanol (VWR, analytical reagent grade) were used without further purification, water was purified with the Milli-Q pulse (millipore, $R = 18.2 \text{ M}\Omega \text{ cm}$) ultrapure water system, toluene was purified through a solvent purification system dispensing ultra dry solvents (MBraun, MB-SPS-800). Contact angles were measured on a Krüss G10 contact angle measuring instrument, equipped with a CCD camera. Gas chromatography (GC) experiments were performed with an Agilent DB-5MS UI column ($30 \text{ m} \times 0.32 \text{ mm i.d.}$, $25 \mu\text{m}$ film thickness) with a constant pressure of 11.9 psi. GC samples were prepared by collecting $50 \mu\text{L}$ of reaction mixture. The oven temperature was held at $50 \text{ }^\circ\text{C}$ for 1 min and increased linearly at a rate of $30 \text{ }^\circ\text{C min}^{-1}$ to $290 \text{ }^\circ\text{C}$ with a final hold of 1 min. The conversions were determined from the area under the curve of the peaks corresponding to reagents, products and possible side products. The peaks were identified by injecting the corresponding reaction products which were commercially available. The yields were calculated with reference to calibration curves calculated injecting the commercially available compounds at three different concentrations (5 mM, 10 mM, and 15 mM). For all the experiments Bu_4NOH was used as internal standard because the area under its peak remained constant during the course of the reaction, unless specified otherwise. For X-ray photoelectron spectroscopy (XPS) a Quantera Scanning X-ray Multiprobe instrument was used, equipped with a monochromatic Al $K\alpha$ X-ray source producing approximately 25 W of X-ray power. XPS-data were collected from a surface area of $1000 \times 300 \mu\text{m}$ with a pass energy of 224 eV and a step energy of 0.8 eV for survey scan and 0.4 for high resolution scans. For quantitative analysis, high resolution scans were used. Absorption spectra were recorded on a Perkin Elmer Lambda 850 UV-vis spectrophotometer. The optical path length was 10 mm, and deionized water was used as reference. For high resolution scanning electron microscopy (HRSEM) characterization a Zeiss 1550 FE-SEM was used. Transmission electron microscopy (TEM) was performed using a Philips CM300 microscope operating at 300 kV. Samples for imaging were deposited onto a 200 mesh copper grid and the liquid was allowed to dry in air at room temperature. The nanoparticle dimensions were obtained from TEM images with ImageJ software, for each sample at least 50 particles were measured. Total reflection X-ray fluorescence (TXRF) measurements were carried out on a S2-PICOFOX™ (Bruker AXS, Karlsruhe, Germany) system with a low power X-ray tube by means of a Mo source and an energy-dispersive, 50 Peltier-cooled silicon drift detector (SDD, XFlash™). The software SPECTRA version 6.1.5.0 (Bruker AXS, Karlsruhe, Germany) was used for data evaluation.⁴²

Flow apparatus

In all microreactor experiments, the sample solutions were mobilized by means of a PHD 22/2000 series syringe pump (Harvard Apparatus, United Kingdom) equipped with $500 \mu\text{L}$ flat tip syringes (Hamilton). Syringes were connected to fused silica capillaries ($100 \mu\text{m i.d.}$, $362 \mu\text{m o.d.}$, Polymicro

Technologies) by means of Upchurch Nanoport™ assembly parts (i.e., Nano-Tight™ unions and fittings, Upchurch Scientific Inc. USA). During the experiments, the microreactor was placed in a home-built chip holder designed for fitting fused silica fibers into the inlet/outlet chip reservoirs by means of commercially available Upchurch Nanoport™ assembly parts. Glass microreactors with a residual volume of $13 \mu\text{L}$ (dimensions: $150 \mu\text{m}$ width and $150 \mu\text{m}$ depth) were purchased from Micronit Microfluidics.

Dendrimer-encapsulated Pd NP functionalization of flat surfaces and microreactors

Deposition of a monolayer of APTES and DITC. Both the SiO_2 surface and the microreactor channels were cleaned with a Piranha solution ($\text{H}_2\text{SO}_4:\text{H}_2\text{O}_2$ 3:1) and then copiously rinsed with water and dried with a stream of nitrogen. (CAUTION: Piranha solution is a very strong oxidant and reacts violently with many organic materials). The clean surface was functionalized with a monolayer of (3-aminopropyl)triethoxysilane (APTES) and *p*-phenylene diisothiocyanate (DITC, Acros Organics) following a slightly modified literature procedure.⁴³ First, the silicon surface was soaked in a 10 mM solution of APTES in dry toluene for 15 h. For functionalization in the device the same solution was flowed for 15 h at a flow rate of $0.05 \mu\text{L min}^{-1}$. Silicon wafers and microchannels were rinsed with dry toluene and ethanol to remove the unreacted reagent and dried with a stream of nitrogen. Subsequently, the APTES-modified flat surface was reacted with a 50 mM solution of DITC in dry toluene for 5 h. The same solution was flowed within the microreactor for 5 h at $0.05 \mu\text{L min}^{-1}$. Silicon wafers and microchannels were rinsed with dry toluene and ethanol to remove the unreacted reagent and dried with a stream of nitrogen.

Formation and anchoring of Pd DENs. In situ procedure. A methanolic solution of $150 \mu\text{M}$ G3 PAMAM dendrimer (ethylenediamine core) was reacted with the APTES-DITC-functionalized silicon surface for 10 h at room temperature. After rinsing with methanol and water, the surface was soaked in a 5 mM solution of K_2PdCl_4 for 2 h after which it was rinsed with water. Afterwards, the reduction of Pd particles was obtained by reaction with a 20 mM aqueous solution of NaBH_4 (20 min). The same procedure was followed for the microreactor functionalization by flowing the dendrimer, palladium salt, and reducing agent solutions at $0.05 \mu\text{L min}^{-1}$ for the respective times.

Preformed in solution procedure. The formation of Pd DENs in solution was accomplished by following a slightly modified literature procedure.²² First, a $150 \mu\text{M}$ aqueous solution of G3 PAMAM-OH dendrimers was prepared and stirred for 30 min. A 40-fold excess of palladium was introduced by means of K_2PdCl_4 and the mixture was left for 2 h at room temperature. Pd NPs were obtained by reduction with a 10-fold excess of NaBH_4 . The so-formed G3-OH(Pd) NPs were anchored onto the APTES-DITC-functionalized silicon surface by dipping the wafer into the dendrimer solution for 15 h and subsequently rinsing it with water and ethanol. The same solution was flowed

within the microchannel for 15 h at 0.05 $\mu\text{L min}^{-1}$ followed by thorough rinsing with water and ethanol.

Continuous flow Sonogashira (Heck-Cassar) cross-coupling reaction

Iodobenzene (0.10 mmol) was reacted with phenylacetylene (0.15 mmol) in ethanol (10 mL) at 80 °C using tetrabutylammonium hydroxide as base (0.20 mmol, 1.0 M solution in methanol). This solution was passed through the catalytic microreactor at different flow rates and the reaction product was collected and analyzed off-line by GC (Fig. S24). The second order rate constant was determined from the initial rate according to the equation: initial rate = $k \cdot [\text{iodobenzene}]_0 \cdot [\text{phenylacetylene}]_0$. The turnover frequency (TOF) was calculated based on the moles of product per unit time per moles of catalyst within the microreactor volume (13 μL). The moles of catalyst are based on the total amount of metal atoms (1.1 nmol of Pd).

Continuous flow Suzuki-Miyaura cross-coupling reactions

For all the experiments described aryl halides (0.10 mmol) were reacted with *p*-tolylboronic acid or phenylboronic acid (0.15 mmol) in ethanol (10 mL) at 80 °C using tetrabutylammonium hydroxide as base (0.20 mmol, 1.0 M solution in methanol). All solutions were passed through the catalytic microreactor at different flow rates and the reaction products were collected and analyzed off-line by GC (see Supporting Information, Figs. S5-S23). For the Hammett plot analysis, the apparent rate constants for the different substrates were calculated using a large excess of phenylboronic acid to achieve pseudo-first order conditions. Therefore, 10 mM solutions of *p*-substituted aryl iodides were reacted with a 150 mM solution of phenylboronic acid. The Bu_4NOH concentration was 160 mM.

Acknowledgements

We gratefully acknowledge the Netherlands Organization for Scientific Research (NWO) for financial support (project ECHO.09.TD.024). Michael Holtkamp and Uwe Karst (University of Münster, Germany) are gratefully thanked for the TXRF measurements.

Notes and references

Laboratory of Molecular Nanofabrication, MESA+ Institute for Nanotechnology, University of Twente.
P.O. Box 217, 7500 AE Enschede, The Netherlands
E-mail: w.verboom@utwente.nl.

Electronic Supplementary Information (ESI) available: UV-Vis, XPS, TEM, HRSEM data of the catalytic layer, GC chromatograms of Suzuki-Miyaura and Heck-Cassar couplings. See DOI: 10.1039/b000000x/

- 1 A. Dumrath, C. Lübke and M. Beller, in *Palladium-Catalyzed Coupling Reactions*, ed. A. Molnár, Wiley-VCH, Weinheim, 2013, ch. 12, p. 445-489.
- 2 M. C. Kozłowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193-3207.
- 3 (a) K. Köhler, K. Wussow and A. S. Wirth, in *Palladium-Catalyzed Coupling Reactions*, ed. A. Molnár, 2013, Wiley-VCH, Weinheim, 2013, ch. 1, p. 1-30; (b) A. Molnár, *Chem. Rev.*, 2011, **111**, 2251-2320.
- 4 X.-F. Wu, P. Anbarasan, H. Neuman and M. Beller, *Angew. Chem. Int. Ed.*, 2010, **49**, 9047-9050.
- 5 K. Na, Q. Zhang, and G. A. Somorjai, *J. Clust. Sci.*, 2014, **25**, 83-114.
- 6 (a) F. Zaera, *Chem. Soc. Rev.*, 2013, **42**, 2746-2762; (b) K. Philippot and P. Serp, in *Nanomaterials in Catalysis*, eds. K. Philippot and P. Serp, Wiley-VCH, Weinheim, 2013, ch. 1, p. 1-54; (c) V. Polshettiwar, J.-M. Basset and D. Astruc, *ChemSusChem*, 2012, **5**, 6-8; (d) S. B. Kalidindi and B. R. Jagirdar, *ChemSusChem*, 2012, **5**, 65-75.
- 7 (a) P. Taladriz-Blanco, P. Hervés and J. Pérez-Juste, *Top. Catal.*, 2013, **56**, 1154-1170; (b) A. Fihri, M. Bouhrara, B. Nekoueshahraki, J.-M. Basset and V. Polshettiwar, *Chem. Soc. Rev.*, 2011, **40**, 5181-5203; (c) S. K. Beaumont, *J. Chem. Technol. Biotechnol.*, 2012, **87**, 595-600; (d) A. Balanta, C. Godard and C. Claver, *Chem. Soc. Rev.*, 2011, **40**, 4973-4985.
- 8 (a) W. R. Reynolds and C. G. Frost, in *Palladium-Catalyzed Coupling Reactions*, ed. A. Molnár, Wiley-VCH, Weinheim, 2013, ch. 11, p. 409-443; (b) T. Noël and S. L. Buchwald, *Chem. Soc. Rev.*, 2011, **40**, 5010-5029.
- 9 For some recent reviews about catalysis in microreactors see: (a) R. Munirathinam, J. Huskens and W. Verboom, *Adv. Synth. Catal.*, 2015, DOI: 10.1002/adsc.201401001; (b) C. Wiles and P. Watts, *Green Chem.*, 2014, **16**, 55-62; (c) Y. Su, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Eur. J.*, 2014, **20**, 10562-10589; (d) B.-B. Xu, Y.-L. Zhang, S. Wei, H. Ding and H.-B. Sun, *ChemCatChem*, 2013, **5**, 2091-2099; (e) T. Noël, X. Wang and V. Hessel, *Chim. Oggi*, 2013, **31**, 10-14; (f) S. G. Newman and K. F. Jensen, *Green Chem.*, 2012, **15**, 1456-1472; (g) T. Chinnusamy, S. Yudha S, M. Hager, P. Kreitmeier and O. Reiser, *ChemSusChem*, 2012, **5**, 247-255; (h) J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.*, 2012, **354**, 17-57.
- 10 (a) W. R. Reynolds, P. Plucinski and C. G. Frost, *Catal. Sci. Technol.*, 2014, **4**, 948-954; (b) C. Pavia, E. Ballerini, L. A. Bivona, F. Giacalone, C. Aprile, L. Vaccaro and M. Gruttadauria, *Adv. Synth. Catal.*, 2013, **355**, 2007-2018; (c) A. K. Shil, N. R. Guha, D. Sharma and P. Das, *RSC Adv.*, 2013, **3**, 13671-13676; (d) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2011, **50**, 5943-5946; (e) K. Mennecke and A. Kirschning, *Beilstein J. Org. Chem.*, 2009, **5**, No 21, DOI: 10.3762/bjoc.5.21.
- 11 (a) C. Battilocchio, B. N. Bhawal, R. Chorghade, B. J. Deadman, J. M. Hawkins and S. V. Ley, *Isr. J. Chem.*, 2014, **54**, 371-380; (b) L.-M. Tan, Z.-Y. Sem, W.-Y. Chong, X. Liu, Hendra; W. L. Kwan and C.-L. K. Lee, *Org. Lett.*, 2012, **15**, 65-67.
- 12 B. Egle, J. Muñoz, N. Alonso, W. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *J. Flow Chem.*, 2014, **4**, 22-25.
- 13 G. Shi, F. Hong, Q. Liang, H. Fang, S. Nelson and S. G. Weber, *Anal. Chem.*, 2006, **78**, 1972-1979.
- 14 (a) M. Pagliaro, V. Pandarus, R. Ciriminna, F. Béland and P. Demma Carà, *ChemCatChem*, 2012, **4**, 432-445; (b) M. Pérez-Lorenzo, *J. Phys. Chem. Lett.*, 2011, **3**, 167-174.

- 15 A. V. Gaikwad, A. Holuigue, M. B. Thathagar, J. E. ten Elshof and G. Rothenberg, *Chem. Eur. J.*, 2007, **13**, 6908-6913.
- 16 D. Cantillo and C. O. Kappe, *ChemCatChem*, 2014, **6**, 3286-3305.
- 17 R. Greco, W. Goessler, D. Cantillo and C. O. Kappe, *ACS Catal.*, 2015, **5**, 1303-1312.
- 18 (a) J. de M. Muñoz, J. Alcázar, A. de la Hoz and A. Díaz-Ortiz, *Adv. Synth. Cat.*, 2012, **354**, 3456-3460; (b) B. Egle, J. de M. Muñoz, N. Alonso, W. M. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *J. Flow Chem.*, 2014, **4**, 22-25; (c) V. Pandarus, G. Gingras, F. Béland, R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2014, **18**, 1550-1555.
- 19 R. Ricciardi, J. Huskens, M. Holtkamp, U. Karst and W. Verboom, *ChemCatChem*, 2015, **7**, 936-942.
- 20 (a) V. S. Myers, M. G. Weir, E. V. Carino, D. F. Yancey, S. Pande and R. M. Crooks, *Chem. Sci.*, 2011, **2**, 1632-1646; (b) L. M. Bronstein and Z. B. Shifrina, *Chem. Rev.*, 2011, **111**, 5301-5344; (c) D. Astruc, A. Diallo and C. Ornelas, in *Nanomaterials in Catalysis*, eds. K. Philippot and P. Serp, Wiley-VCH, Weinheim, 2013, ch. 3, p. 97-122.
- 21 (a) S. Ogasawara and S. Kato, *J. Am. Chem. Soc.*, 2010, **132**, 4608-4613; (b) Y. Li, J. H.-C. Liu, J. C. A. Witham, W. Huang, M. A. Marcus, S. C. Fakra, P. Alayoglu, Z. Zhu, C. M. Thompson, A. Arjun, K. Lee, E. Gross, F. D. Toste and G. A. Somorjai, *J. Am. Chem. Soc.*, 2011, **133**, 13527-13533; (c) Y. Yang, S. Ogasawara, G. Li and S. Kato, *J. Phys. Chem. C*, 2014, **118**, 5872-5880.
- 22 R. W. J. Scott, H. Ye, R. R. Henriquez and R. M. Crooks, *Chem. Mat.*, 2003, **15**, 3873-3878.
- 23 (a) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874-922; (b) R. Chinchilla and C. Najera, *Chem. Soc. Rev.*, 2011, **40**, 5084-5121.
- 24 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467-4470.
- 25 (a) P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem. Int. Ed.*, 2000, **39**, 2632-2657; (b) L. Djakovitch and P. Rollet, *Adv. Synth. Cat.*, 2004, **346**, 1782-1792.
- 26 (a) H. A. Dieck and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259-263; (b) L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253-257.
- 27 C. Deraedt, L. Salmon and D. Astruc, *Adv. Synth. Cat.*, 2014, **356**, 2525-2538.
- 28 (a) P. Veerakumar, M. Velayudham, K.-L. Lu and S. Rajagopal, *Appl. Catal., A*, 2013, **455**, 247-260; (b) S. Moussa, A. R. Siamaki, B. F. Gupton and M. S. El-Shall, *ACS Catal.*, 2011, **2**, 145-154.
- 29 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691-1694.
- 30 (a) A. Gömann, J. A. Deverell, K. F. Munting, R. C. Jones, T. Rodemann, A. J. Canty, J. A. Smith and R. M. Guijt, *Tetrahedron*, 2009, **65**, 1450-1454; (b) W. Solodenko, H. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schönfeld, U. Kunz and A. Kirschning, *Eur. J. Org. Chem.*, 2004, 3601-3610.
- 31 R. Javid, H. Kawanami, M. Chatterjee, T. Ishizaka, A. Suzuki and T. M. Suzuki, *Chem. Eng. J.*, 2011, **167**, 431-435.
- 32 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483.
- 33 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165-195.
- 34 V. P. W. Böhm and W. A. Herrmann, *Chem. Eur. J.*, 2001, **7**, 4191-4197.
- 35 (a) Y.-T. Hung, M.-T. Chen, M.-H. Huang, T.-Y. Kao, Y.-S. Liu and L.-C. Liang, *Inorg. Chem. Front.*, 2014, **1**, 405-413; (b) C. He, J. Ke, H. Xu and A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 1527-1530.
- 36 L.-C. Liang, P.-S. Chien and M.-H. Huang, *Organometallics*, 2004, **24**, 353-357.
- 37 S. Proch, Y. Mei, J. M. R. Villanueva, Y. Lu, A. Karpov, M. Ballauff and R. Kempe, *Adv. Synth. Cat.*, 2008, **350**, 493-500.
- 38 H. Weissman and D. Milstein, *Chem. Commun.*, 1999, 1901-1902.
- 39 D. Zim, V. R. Lando, J. Dupont and A. L. Monteiro, *Org. Lett.*, 2001, **3**, 3049-3051.
- 40 M. Portnoy and D. Milstein, *Organometallics*, 1993, **12**, 1665-1673.
- 41 M. R. Biscoe, B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 6686-6687.
- 42 M. Holtkamp, C. A. Wehe, F. Blaske, C. Holtschulte, M. Sperling and U. Karst, *J. Anal. Atomic Spectrom.*, 2012, **27**, 1799-1802.
- 43 M. J. W. Ludden, X. Y. Ling, T. Gang, W. P. Bula, H. J. G. E. Gardeniers, D. N. Reinhoudt and J. Huskens, *Chem. Eur. J.*, 2008, **14**, 136-142.

Table of Contents

Dendrimer-encapsulated Pd nanoparticles anchored within continuous flow microreactors are efficient for C-C cross-coupling reactions. This is witnessed by the good catalytic performance for the Heck-Cassar coupling reaction of iodobenzene and phenylacetylene. Electron-withdrawing para-substituted aryl halides improve the reactivity of Suzuki-Miyaura couplings.

