Catalysis in Flow Microreactors with Wall Coatings of Acidic Polymer Brushes and Dendrimer-Encapsulated Nanoparticles

Roberto Ricciardi

**CATALYSIS IN FLOW MICROREACTORS
WITH WALL COATINGS OF ACIDIC
POLYMER BRUSHES AND DENDRIMER-
ENCAPSULATED NANOPARTICLES**

Roberto Ricciardi

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UNIVERSITY OF TWENTE.

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CATALYSIS IN FLOW MICROREACTORS WITH WALL COATINGS OF ACIDIC POLYMER BRUSHES AND DENDRIMER- ENCAPSULATED NANOPARTICLES

DISSERTATION

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the degree of doctor at the University of Twente,

on the authority of the rector magnificus

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on account of the decision of the graduation committee,

to be publicly defended

on Friday May 8, 2015 at 14.45 h

by

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"It would be possible to describe everything scientifically, but it would make no sense; it would be without meaning, as if you described a Beethoven symphony as a variation of wave pressure."

Albert Einstein

Alla mia famiglia, con affetto

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Chapter 1

General introduction

Microreactor technology associated with continuous flow processes has brought about a paradigm shift in the way chemical synthesis is perceived and carried out.^{1,2} The main change pertains to the equipment through which a chemical reaction is performed: from conventional batch scale synthesis using round-bottom flasks to meso- and microreactors manufactured for an intended application (Figure 1.1).^{3,4} This has led to an array of new possibilities owing to the properties of microstructured reactors. The miniaturization of the reaction vessel (lateral dimensions in the order of tens to hundreds of micrometers), in fact, offers significant improvements in mixing, heat management, energy efficiency, safety, access to a wide range of reaction conditions, multistep synthesis, reduction of waste generation, and many more.^{5,6} As a consequence, continuous-flow processes performed in microreactors are more effective than standard batch protocols in facilitating the transition towards more sustainable chemical processes.⁷⁻⁹

Figure 1.1 Continuous-flow microreactor (from www.futurechemistry.com).

The development of this technology started as Lab-on-a-Chip research in the early 1990s with the main focus on the miniaturization of the whole reaction system.^{10,11} Nowadays microfluidic reactors are characterized by the quest to enable new functions and open new opportunities in chemistry, the so-called Novel Process Windows defined by Hessel.¹² In particular, flow chemistry exerts its full potential in all those processes that cannot be performed with conventional equipment or require harsh conditions, such as dangerous chemical transformations, flash chemistry, multistep synthesis, and drug discovery, among others.¹³⁻¹⁶

Heterogeneous catalysis is pivotal in numerous transformations in a wide range of applications, especially from an industrial point of view.¹⁷ In a continuous process, the catalyst can be fixed within the microreactor and the reaction mixture can flow over it, combining reaction and separation in a single step.¹⁸ Additionally, the increased surface-to-volume ratio leads to improved contact between reagents and catalysts resulting in high catalytic activities.¹⁹ Heterogeneous catalysis combined with microreactor technology constitutes, therefore, a powerful tool to carry out catalytic reactions under flow conditions, using small amounts of catalysts that can undergo numerous cycles.^{20,21} Solid catalysts can be introduced within a microreactor in several ways: supported in packed-bed reactors, using porous monolithic materials, anchored onto a functionalized inner surface, attached to nanomaterials, etc.²²⁻²⁶ In this way, many organic, metal-based, and enzymatic catalysts have shown their applicability in continuous flow synthesis.²⁷⁻³⁰

Some years ago, Whitesides predicted³¹ that microfluidic technology would constitute a major opportunity in the synthesis and analysis of molecules, as demonstrated by the clear advantages of this technology. He also indicated that the field was still in its infancy and that a lot of effort was needed to establish it outside pure academic research. Almost ten years later, this technology is slowly coming of age, as expressed by deMello,³² at the same time observing that many of the initial

claims were too optimistic. Nevertheless, the recognition of this technology continues to grow as witnessed by the increasing application in industrial processes.

The main aim of this thesis is the development of wall-supported catalysts that can be used heterogeneously in flow microreactors. The large surface-to-volume area created within the microchannel (inner diameter of 150 μm) was exploited for the anchoring of acid- and nanometallic catalysts. In this way, drawbacks associated with packed-bed catalysts (back-pressure building up along the channel and broad residence time distribution) and monoliths (tedious functionalization and swelling) were circumvented. Different strategies for surface modification were employed, such as a single layer of an organic acid catalyst, polymer brushes bearing sulfonic acid groups, and PAMAM dendrimers used for the encapsulation of mono- and bimetallic nanoparticles.

Chapter 2 provides an overview of the use of metallic nanoparticles (NPs) as supported catalysts within microfluidic reactors. Different approaches for the NP formation and stabilization are presented, such as packed-bed reactors, monoliths, wall-catalysts, and NPs supported on different nanomaterials. Their activity is described for several chemical reactions.

In Chapter 3, the use of a perfluorsulfonic acid derivative in different acid-catalyzed reactions is presented. The active catalyst could be obtained by a single step reaction of a cyclic precursor with the glass surface of the microreactor. The activity of this system was investigated in the hydrolysis of acetals, the Friedlander formation of quinolines, and the pseudoionone cyclization as well as its stability and reactivation.

Polymer brushes bearing reactive groups for the functionalization of the surface of a microreactor have already been described in our group.³³⁻³⁶ In Chapter 4, the mixing of sulfonic acid-bearing monomers (3-sulfopropyl methacrylate) and OH-bearing monomers (2-hydroxyethyl methacrylate) is presented. In this way the

influence of the cooperative effect among functional groups created within the highly packed brush architecture could be investigated for a model acid-catalyzed reaction.

Chapter 5 describes the catalytic behavior of different generations of PAMAM dendrimer-encapsulated Pd NPs (Pd DENs) covalently attached to the inner surface of the microreactor. The Suzuki-Miyaura cross-coupling (SMC) of iodobenzene with *p*-tolylboronic acid was used as a model reaction. In addition, a kinetic study using the most active catalyst was carried out to shed light on the NP catalytic mechanism and on the stabilizing effect of the dendrimer template.

Based on those findings, in Chapter 6, we expanded the use of Pd DENs to continuous flow C-C cross-coupling reactions, such as the SMC, the copper-free Sonogashira, and the Mizoroki-Heck reactions. In particular for the SMC, several *para*-substituted aryl halides coupled with arylboronic acid counterparts were used to analyze the substituent effect on the overall reactivity.

Chapter 7 deals with dendrimer-encapsulated Au/Ag alloy NPs (Au/Ag DENs) used for the reduction of 4-nitrophenol in flow microreactors. The aim of the study was to assess the advantage of alloy bimetallic NPs over the single components, and to find the optimal metal alloy composition. Hereto, Au/Ag DENs with different metal ratios were prepared as well as pure Ag and Au DENs, and tested in the model reaction. The most active catalyst was utilized for several consecutive days to assess its stability.

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Chapter 2

Nanocatalysis in flow

This Chapter summarizes the active field of flow nanocatalysis by describing the synthesis, stabilization and catalytic applications of metal nanoparticles (1-50 nm) in combination with microstructured reactors. Different strategies for supporting NPs are presented, namely packed-bed reactors, monolithic flow-through reactors, wall catalysts and a selection of novel approaches (NPs embedded on nanotubes, nanowires, catalytic membranes and magnetic nanoparticles). A number of catalytic reactions, such as hydrogenations, oxidations, cross-coupling reactions, etc., provides a useful guide in order to understand advantages and possible drawbacks to each approach.

2.1 Introduction

Metallic nanoparticles (NPs) supported within microstructured reactors represent an ideal platform for the heterogeneous catalysis of several chemical reactions, especially in terms of high reactivity, selectivity, and ease of separation and reuse. Undoubtedly, the increasing awareness about environmental concerns,¹ the costly procedures to separate and reuse catalysts,² and the strict limits of metal contamination for the final product set by governments³ make the use of heterogeneous catalysts compelling. To date, many studies utilizing metal catalysts make use of homogeneous species which provide excellent activity and selectivity.⁴ Despite their advantages, this approach is undermined by the tedious and expensive separation of the catalyst species from the reaction media. Therefore, a common trend in synthetic chemistry is to transform a homogeneous catalytic process into a heterogeneous one, either by supporting the soluble species on a solid support or by developing new heterogeneous catalysts altogether.⁵⁻¹⁰ In this way, the catalyst is present in a different phase, separated from the reaction stream, thus ensuring easy separation, recovery and usually good reusability, which are striking features in terms of sustainability of the chemical process. However, heterogeneous catalysts usually show lower activity when compared to homogeneous counterparts mainly due to diffusion limits and poor interaction between reagents and catalytic species, especially when present in different phases.

Anchoring solid catalysts inside continuous flow reactors offers the possibility to overcome many of the drawbacks associated with heterogeneous species: the high surface-to-volume ratio deriving from miniaturization of the reactor ensures improved heat and mass transfer and an intimate contact between reagents and catalyst, thus showing much higher activity compared to batch scale reactions.¹¹⁻¹⁴ Moreover, microfluidic devices contribute to rapid catalyst screening and high-throughput catalytic reactions,^{15,16} and provide the possibility to carry out transformations under rather harsh reaction conditions.¹⁷ By and large,

heterogeneous catalysis constitutes an essential integration of microreactor technology and flow chemistry, as witnessed by the already numerous examples of chemical reactions carried out under continuous flow.¹⁸⁻²⁶

Catalysis by nanoparticles, referred to as nanocatalysis,²⁷ is well established in modern chemical synthesis, mainly due to the high reactivity of the nanosized species involved.²⁸⁻³¹ Metallic NPs are formed by atom clusters at the nanometer scale (from 1 to a few tens of nm) with intermediate properties between molecules and bulk metals. This characteristic feature defines new chemical and physical properties advantageous for various applications and particularly for catalysis.^{27,32} In fact, nanocatalysis is commonly regarded as a domain at the interface between homogeneous and heterogeneous catalysis, combining the high reactivity and selectivity of homogeneous species with the ease of separation and reuse of heterogeneous catalysts, thereby meeting the requirements for green catalysts.³³⁻³⁹ The number of metal NP-catalyzed reactions has seen an exponential growth in recent years, as witnessed by the numerous examples found in literature, ranging from hydrogenations,⁴⁰⁻⁴² cross-coupling reactions,⁴³⁻⁴⁷ cycloadditions,⁴⁸ oxidations,^{31,35,49,50} carbonylation,^{51,52} asymmetric synthesis,^{53,54} let alone the increasing importance in industrial applications (refinery, petrochemical, biofuels, pharmaceutical industry, chemical, food processing sectors, etc.).⁵⁵⁻⁵⁷

Anchoring metallic NPs within continuous flow microreactors offers a powerful catalytic system which exploits and enhances the advantages of both nanocatalysis and flow chemistry, the so-called flow nanocatalysis approach.⁵⁸ The rational utilization of such catalysts, however, cannot preclude from answering the question of NP immobilization and stabilization inside the microfluidic device. In fact, the means through which the catalyst is anchored should promote catalytic activity as well as ensuring good stability and recyclability.²¹ Therefore, supporting NPs that are uniform in size, with their surface atoms unpassivated, and good accessibility to

their active sites by the reagents, is of paramount importance for the catalytic process.

In recent years, various approaches have been developed for the stabilization and subsequent anchoring of metal catalysts on solid surfaces and in particular within microstructured reactors. Numerous reviews concern microreactor technology and nanocatalysis. This chapter will, therefore, focus on the different means to support metallic NPs inside continuous flow reactors, covering the conventional packed-bed reactors, monolithic flow-through reactors, and wall catalysts. Furthermore, novel approaches mostly utilizing patterned channels with well-aligned and sizeable porous and fibrous nanostructures (carbon nanotubes, nanowires, nanofibers) as well as catalytic membranes and catalysts supported on magnetic nanoparticles will be discussed. For each category, advantages and possible drawbacks will be analyzed by providing examples of various metal NP-catalyzed reactions. Supported metal complexes lie beyond the scope of the present review and are not included.

2.2 Packed-bed reactors

The easiest way to incorporate a heterogeneous catalyst within a microreactor is to fill the channels with catalyst-supported beads, resins, or polymers.¹³ The advantages of packed-bed reactors derive from the fact that traditional and already optimized catalysts can be easily employed and because of the very high ratio between the active catalyst and substrate/reagents created by an exceptionally high local concentration of catalyst. In a typical procedure, polymer beads grafted with different ligands and coordinated with metals are filled into a column, capillary channel or microreactor, which are attached to a pumping system.⁵⁹ Many studies have been carried out using Pd/C immobilized in replaceable, pre-packed stainless steel cartridges and tested mostly in cross-coupling reactions⁶⁰ and hydrogenations.^{61,62} Another popular choice is represented by the commercially

available polyurea-encapsulated $\text{Pd}(\text{OAc})_2$ developed by Ley *et al.* (commonly known as Pd EnCatTM),⁶³ mostly employed for Suzuki-Miyaura cross-coupling reactions.^{64,65} Despite the preparation of polyurea-microencapsulated palladium nanoparticles (Pd NPs) obtained by reduction of the coordinated $\text{Pd}(\text{OAc})_2$, their application has been restricted to batch reactions.⁶⁶

Silicon dioxide represents an ideal choice to support metal catalysts for their use in flow synthesis, although most of the examples rely on metal complexes stabilized by suitable ligands.^{67,68} Metal complexes have also been supported on ionic liquid phases (SILP),⁶⁹ hyperbranched oligomers,⁷⁰ and spherical siliceous mesocellular foams (MCF).⁷¹ The following sections contain a survey of metallic NPs supported within packed-bed reactors employed in different catalyzed reactions.

2.2.1 Hydrogenations

The most common application of continuous heterogeneous catalysis is in hydrogenation reactions,²³ where the use of a microflow reactor ensures good contact between different phases owing to the high interfacial area, overcoming the usual poor mixing between the gas-liquid-solid phases.⁷² Moreover, the handling and separation of solid precious metals is avoided and the risk of side reactions is reduced. The commercial H-Cube system represents a practical choice to carry out hydrogenations under continuous flow conditions. It is composed of a compact HPLC-like hydrogenator that delivers a small amount of hydrogen in situ obtained from the electrolytic decomposition of water, which is flowed through a pre-packed, replaceable cartridge containing a heterogeneous catalyst.⁷³

The H-Cube system has been largely employed with packed-bed catalysts formed by reduced metal nanoparticles. For example, the use of Fe NPs was demonstrated for the selective hydrogenation of alkenes and alkynes in flow using water as a benign solvent.⁷⁴ The Fe NPs were supported on an amphiphilic polymer

resin composed of polystyrene (PS) beads functionalized with a variety of linkers (LK, Figure 2.1).

Figure 2.1 Schematic representation of hydrogenation reactions using polymer-supported Fe NPs under flow conditions.

To form the active catalyst, two methods were followed: the thermal decomposition of $\text{Fe}(\text{CO})_5$ and the reduction of FeSO_4 using black tea as reducing agent. In the first case, when PS-(PEG)- NH_2 was used as a stabilizer, well-dispersed and monodisperse 5 nm Fe NPs were obtained. Fewer particles were visible when using the tea reduction method, most of them having a size of around 5 nm as well. Other polymers, instead, afforded larger nanoparticles. The polymer-supported Fe NPs were assessed in both flow and batch conditions for the hydrogenation of styrene in ethanol. All iron/polymer systems provided quantitative yields in flow conditions.

The group of Luque⁷⁵ investigated the synthesis of high added-value chemicals such as 2-methyltetrahydrofuran (MTHF) derived from the conversion of levulinic acid (LA) by replacing noble metals with more abundant catalysts under relatively high hydrogen pressures. For this scope, a simple and efficient nanocatalytic Cu-containing silica material was designed (Cu-MINT) as well as a series of metal-containing mesoporous carbonaceous Starbon® materials (Figure 2.2).

Figure 2.2 Reaction pathways for the production of MTHF from LA using Cu-based (top) and other noble metal (bottom) catalytic systems. Bold arrows identify key steps.

Depending on the catalyst, metal nanoparticles with sizes in the range of 2.5-9 nm were observed. Formic acid was used as the hydrogen-donating solvent, which decomposed under microwave heating. Cu-MINT showed excellent activity under batch conditions, providing almost quantitative conversion of LA at 0.51 wt% Cu loading. Comparatively, Starbon®-supported metals provided reduced activities but improved selectivities to MTHF. Furthermore, Cu-MINT and 5% Pd/C commercial catalysts were considered under flow conditions and compared to a commercial Cu/Al₂O₃ catalyst. Despite the good activity, the Cu-MINT catalyst was not stable under flow conditions as demonstrated by leaching studies.

2.2.2 Cross-coupling reactions

Palladium-catalyzed cross-couplings represent some of the most useful and versatile reactions in synthetic chemistry, as witnessed by the increasing importance of these reactions have gained in the pharmaceutical and other industries.⁷⁶⁻⁷⁸ Besides the already mentioned supports for the immobilization of heterogeneous catalysts within microreactors, the use of Pd NPs is under constant investigation to find stable catalysts resistant to leaching, a drawback inherent to cross-coupling reactions and a major issue regarding the utilization of nanoparticle catalysts. This is witnessed by the vibrant debate on whether the catalytic mechanism is ‘purely’ heterogeneous (i.e. happening on the metal surface as for hydrogenation reactions), or, as it seems to be established, it occurs via the formation of charged molecular species leaching out of the metal center.^{79,80} Therefore, in the following analysis of nanoparticle catalysis for cross-coupling reactions under flow conditions, particular attention will be paid to the leaching process.

In most of the examples present in literature, the packed-bed material serves as a support and means of encapsulation for the metal nanoparticles. To this regard, two polymer-encapsulated silica supported Pd NPs catalysts were prepared (**1** and **2**; Figure 2.3).⁸¹ Both catalysts were tested for their activity in the Suzuki coupling reaction between 4-iodoacetophenone and phenylboronic acid under continuous flow conditions. They displayed excellent activities, with catalyst **1** being superior due to the shorter residence time required to reach full conversion. Furthermore, a variety of additional substrates was screened under optimal conditions for Suzuki as well as for Heck coupling. The catalysts were used for over 50 h under continuous operation with no appreciable decrease in activity with Pd residues calculated to be only 1 ppm.

Figure 2.3 Synthesis of supported palladium catalysts.

Pd nano- and microparticles were prepared from Pd(OAc)₂ through a reduction reaction and deposited onto a solid matrix and used to perform the Suzuki cross-coupling reaction of 4-iodotoluene and phenylboronic acid under ultrasonic conditions.⁸² The scaling up of the biaryl synthesis was achieved on a 5 g scale production, owing to the mild conditions ensured by ultrasonication. No significant loss of activity was observed based on the isolated yields. A SEM analysis of the Pd catalyst after 5 runs showed the presence of Pd NPs on the solid support, confirming the good stability and minimum Pd leaching from the solid surface.

With the aim of defining a practical and effective protocol to exploit the features of a solid catalyst for flow chemistry conditions, highly cross-linked imidazolium-based materials were prepared, to be used as support for palladium catalysts.⁸³ Owing to the high imidazolium loading, these materials were able to support a high amount of the metal (10 wt%), constituting Pd NPs with a narrow size distribution (2-4 nm) and uniform dispersion on the polymeric matrix (Figure 2.4).

Figure 2.4 Pd-supported imidazolium-based catalysts.

First, a batch Suzuki reaction was carried out in order to study the catalytic behavior, followed by recycling studies using 0.1 mol% of catalyst. Subsequently, using the flow approach, the sustainability of the protocol was greatly increased as proved by a lower E-factor⁸⁴ as compared to batch operations. Inductively coupled plasma/optical emission spectrometry (ICP-OES) analysis showed the presence of only 0.015 wt% of Pd in the product mixture. This low leaching of palladium was attributed to the ‘release and catch’ mechanism in which the supported palladium catalyst serves as reservoir for active Pd species which are then re-captured at the end of the catalytic cycle.⁸⁵

2.2.3 Oxidations

Oxidation reactions are among the most useful reactions in industrial processes. They are usually accompanied, however, by hazardous processes and deliver a considerable amount of toxic waste.⁸⁶ Therefore, it is not surprising that a lot of attention has been put in recent years on the use of active noble metal nanoparticles, with gold being the metal of choice, in order to improve the process efficiency.³⁵ As evident from the advantages of microreactors in handling hazardous processes and reducing waste production, continuous flow synthesis could be the approach of choice to carry out oxidations using metal nanocatalysts.⁸⁷

Recently, the use of iron oxide NPs was investigated as an alternative to conventional aerobic oxidations with noble metals (e.g. Au).⁸⁸ Fe/Al-SBA-15 (1 wt% Fe) was selected as a catalyst for the selective oxidation of benzyl alcohol to benzaldehyde under continuous flow conditions. The catalyst was prepared using a simple microwave approach in which iron(II) chloride was mixed together with a dispersion of mesoporous Al-SBA-15 silica. In this way, iron oxide nanocrystals of 6-7 nm average size were generated in situ on the silica support through the formation of Al-O-Fe bridges. The catalytic study was conducted using a commercially available stainless-steel flow reactor system (H-Cube) with the installed catalyst cartridge. By tuning the back-pressure, vapor pressure, and reaction conditions (use of TEMPO as co-catalyst) a conversion up to 42% could be obtained in a single pass over the catalyst cartridge. No metal leaching was detected under the reaction conditions in non-polar solvents, supporting the supposed heterogeneity of the reaction mechanism.

The group of Jensen presented platinum-decorated magnetic silica nanoparticles (PMS-NPs) which were further converted into spherical assemblies (PMS-superballs) of micron size. These PMS-superballs were compatible with packed-bed reactors and evaluated in the oxidation of 4-isopropyl benzaldehyde (IBA) as a model reaction.⁸⁹ This study aimed at providing a general platform for the synthesis, assembly, and incorporation of catalytic nanomaterials within microfluidic systems. The three-step approach is presented in Figure 2.5. First, oxide/silica core-shell nanospheres were synthesized in a semi-batch reactor. The iron oxide nanoparticle in the core imparts magnetic properties for the effective recycling of the precious nanocatalyst. Afterwards, a microfluidic reactor was employed to continuously produce and coat Pt NPs of about 2.4 nm onto the surface of the magnetic silica nanospheres. The PMS-NPs, with an average diameter of 85 nm, were aggregated in water using oil emulsions as template to yield PMS-superballs. Without any activation process, the assembled PMS-

superballs were incorporated into a packed-bed reactor and tested in the model oxidation reaction. The thus prepared material showed excellent turnover frequencies (TOFs) and selectivities compared to two commercial noble metal catalysts and could be fully recovered using a magnet.

Figure 2.5 Schematic illustration of the use of multiple microfluidic systems in the synthesis, self-assembly, and catalysis with Pt-decorated magnetic silica (PMS) superballs. a) Continuous synthesis of platinum-decorated magnetic silica nanoparticles (PMS-NPs) starting from silica nanospheres with iron oxide cores in a silicon microreactor. b) Self-assembly of PMS-NPs to form PMS-superballs by employing a monodisperse emulsion produced by a microfluidic drop generator. c) Incorporation of PMS-superballs into a packed-bed microreactor for the characterization of their catalytic properties. After the reactions, all the PMS-superballs could be separated and recovered by application of a magnetic field (© RSC⁸⁹).

Leitner *et al.*⁹⁰ developed a catalytic system for the selective aerobic oxidation of alcohols based on highly dispersed Pd NPs in a poly(ethylene glycol) (PEG) matrix using supercritical carbon dioxide (scCO₂) as the substrate and product phase. The PEG matrix proved to be effective in stabilizing and immobilizing the catalytically active particles (3.6 nm average size), while scCO₂ allowed continuous processing due to its unique solubility and mass-transfer properties. The catalytic material reached a single-pass conversion of around 50% when the CO₂ pressure was slightly reduced as compared to batch experiments.

2.2.4 Other catalytic reactions

The number of catalytic reactions carried out within microreactors spans over a vast range.⁹¹ Synchrotron-based microspectroscopy has been used by Somorjai *et al.* for the *in situ* kinetic mapping of complex organic transformations.⁹² Au nanoclusters (2 nm size) loaded on a mesoporous SiO₂ support and subsequently packed in a flow microreactor were employed as catalysts for the formation of a dihydropyran derivative (**5**; Figure 2.6). This reaction is particularly suitable for microspectroscopy mapping because each of the reactants and products shows distinguishable IR signatures. Au clusters were synthesized within a fourth-generation poly(amidoamine) PAMAM dendrimer and loaded on SBA-15 (Au-G4OH/SBA-15), thus ensuring catalyst stability under liquid flow reaction conditions. Afterwards, the Au-G4OH/SBA-15 catalyst was packed in a fixed-bed stainless-steel plug flow microreactor. In this way, the kinetic evolution of the organic transformation and the role of the primary product as an intermediate were analyzed via *in situ* IR microspectroscopy, revealing the correlation between catalytically active areas along the flow reactor and the local high concentration of catalytically active species (Au³⁺). A wide applicability of this methodology is foreseen for many organic reactions, fulfilling a major challenge in flow chemistry.¹⁹

Figure 2.6 Dihydropyran (**5**) derivative formation within a flow reactor and kinetic mapping along the channel.

The same catalytic system (Au-G4OH/SBA-15) was used to study olefin cyclopropanation reactions, exemplified in the reaction of propargyl pivalate (**6**) and styrene (**7**; Scheme 2.1). This study aimed at gaining control over the selectivity in heterogeneous catalysis.⁹³ In fact, by replacing homogeneous AuCl_3 with the dendrimer-encapsulated Au NPs, the diastereoselectivity of Au-catalyzed cyclopropanation reactions could be enhanced significantly, with a 5-fold increase in the *cis:trans* ratio of **8**.

Scheme 2.1 Cyclopropane derivative (**8**) synthesis catalyzed by Au-G4OH/SBA-15.

The dendrimer-encapsulated Au NPs presented a narrow size distribution (2 ± 0.3 nm)^{94,95} and were deposited on the mesoporous support via formation of hydrogen bonding with the silica surface. Importantly, the high reactivity and diastereoselectivity of the catalyst was maintained when employed in the fixed-bed system for the flow experiments (58% yield and 18:1 *cis:trans* ratio of **8**). Despite initial deactivation (after 6 h), the catalyst could be reactivated by re-oxidation using PhICl_2 showing even a higher reactivity and longer lifetime (90% yield and 9 h of use). Moreover, a highlight of using the catalyst in a fixed-bed flow reactor was the control of the catalytic reactivity and product selectivity of secondary reactions simply by tuning the residence time of the reactants, an advantage unattainable in a batch reaction mode as well as in traditional homogeneous catalysis.

PAMAM dendrimers were also employed for the synthesis of Pd NPs which then catalyzed the intramolecular addition of phenols to alkynes.⁹⁶ The dendrimer-encapsulated Pd NPs had an average diameter of 1 nm and were subsequently

supported on SBA-15. First, the catalyst was investigated in the batch hydroalkoxylation reaction of 2-phenylethynylphenol, showing a much higher activity than all the homogeneous catalysts surveyed. Since no leaching of catalytically active species was detected from the Pd/SBA-15 catalyst, the same was applied in a fixed bed plug flow reactor. The catalyst remained stable and highly active for more than 10 h at room temperature by the addition of PhICl_2 to the reaction media. Moreover, the flow catalysis proved useful to study the deactivation kinetics of the catalyst under steady reagent feeding.

The use of a versatile low-loaded iron oxide nanocatalyst was demonstrated for the alkylation of toluene with benzyl chloride.⁹⁷ The supported iron oxide NPs were prepared using a mechanochemical protocol based on the grinding of the metal precursor ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$) and the pre-formed aluminosilicate SBA-15 support. This protocol yielded small Fe_2O_3 NPs (2-3 nm in size) accounting for an iron content of about 0.25 wt%. The catalytic reactions were carried out using a commercially available stainless-steel flow reactor system (X-Cube) under similar conditions to those optimized with microwave heating at lab scale. Good to excellent yields were achieved for the alkylated products, promoted by the good accessibility to the Lewis and Brønsted acid sites of the Fe-containing materials, as compared to the parent support. Importantly, minimum leaching into solution was detected (0.02 wt% Fe) even after several hours of reaction.

A three-step synthesis of pyridine derivatives was investigated using a combined micro-flow through system having two different heterogeneous catalyst assemblies (Scheme 2.2).⁹⁸ For the initial condensation reaction, montmorillonite was investigated as a heterogeneous catalyst, while the subsequent oxidation reaction steps were catalyzed by different types of nanoparticles impregnated on alumina. The nanoparticles were prepared by a simple impregnation procedure, i.e. reduction of an ethanolic solution of noble metal salts to yield Cu, Ag, and Au nanoparticles of different sizes (1.4 nm Au, 28 nm Ag, μm size Cu due to

precipitation). Best results for the cyclization/aromatization (step 2) were obtained with Au NPs, reaching full conversion within 20 s of residence time using a 1.3-fold stoichiometric excess of oxygen.

Scheme 2.2 Reaction sequence yielding α -substituted pyridines.

2.3 Monolithic flow-through reactors

The continuous flow processes described so far utilize reactors with randomly packed beads, which commonly results in uncontrolled fluid dynamics, hot-spot formation, broad residence time distribution, low selectivity and, overall, low process efficiency.^{59,99} Among the possible alternatives, the use of macroporous monoliths in flow-through processes is a convenient approach to overcome the above mentioned drawbacks.¹⁰⁰ Monolithic structures have a high void volume and a large geometric surface area, thus resulting in a small pressure drop along the microchannel whilst maintaining a large contact area of the reagent or the catalyst with the fluid.¹⁰¹ The most commonly used monolithic families for application in catalysis under continuous flow conditions consist of polymers, hybrid polymer/glass composites, and inorganic matrices (silica, zeolites) exhibiting macropores ranging between 2 to 10 μm . Metallic nanoparticles can be anchored to the polymer functionalities or loaded onto the pores of silica or other materials.¹¹

2.3.1 Hydrogenations

One of the early pioneers of the use of monolithic materials in flow-through processes is Kirschning, who developed the so-called PASSflow (polymer-assisted

solution-phase synthesis) reactor.¹⁰² The monolithic system contains a highly porous polymer/glass composite. Specifically, poly(vinylchlorobenzene) cross-linked with 2-20% of divinylbenzene was prepared by precipitation polymerization in the pore volume of highly porous glass rods to achieve a polymeric matrix inside the rod. In this way, the swelling of the polymer was confined within the rod pore volume, leaving the outer dimension stable. By sequentially incorporating this material in a solvent-resistant tube and in a pressure-resistant epoxy resin, whereby the termini were equipped with HPLC fittings, the system could be used in continuous flow processes. Some of the first applications of this system were transfer-hydrogenation and cross-coupling reactions.¹⁰³ To this end, the vinylbenzyl chloride-based polymer was transformed into a quaternary ammonium ion-exchange resin. Therefore, an aqueous solution of sodium tetrachloropalladate and subsequent reduction by means of a borohydride solution yielded Pd NPs (with an estimated diameter less than 10 nm; Scheme 2.3).

Scheme 2.3 Immobilization of Pd NPs onto the monolithic phase inside a microreactor.

A study of the influence of the flow rate on the palladium particle size showed that borohydride reduction under flow conditions yielded smaller Pd clusters with a narrower particle size distribution and better dispersion in the polymer matrix as compared to reduction under diffusion control.¹⁰⁴ The nature of the polymer composition also influenced the Pd particle size, with an increase in the degree of cross-linking leading to a decrease in the particle size. The catalysts were tested both under conventional and microwave heating using the transfer hydrogenation of ethyl cinnamate (**10**) as a model reaction (Scheme 2.4). The reactivity of the catalyst under microwave heating was improved for bigger NPs with the opposite

behavior for smaller NPs. This result was ascribed to the presence of a site dilution effect. Under conventional heating, the site dilution produces a decrease in the nanoparticle size leading to a higher surface area and thus higher catalytic activity. For microwave irradiation the same dilution produces a decrease in the Pd content leading to a small rate enhancement by a hot spot effect due to low microwave energy absorption and dissipation. Nevertheless, microwave heated samples showed no decrease in catalytic activity.

Scheme 2.4 Transfer hydrogenation of ethyl cinnamate (**10**).

Despite the practical solution of constraining the polymeric monolith within a porous glass material as in the PASSflow system, polymeric monoliths usually suffer from unpredictable changes in volume and porosity due to swelling and poor thermal, chemical, and mechanical stability.¹⁰⁵ To overcome the swelling problems of such monoliths, the use of novel unconventional monolithic inorganic (silica) microreactors was proposed (MonoSil).¹⁰⁶ Formed by an interconnected and homogeneous system of macropores (2-4 μm) and adjustable mesopores (3-40 nm), they present high chemical and physical stabilities due to a high condensation state of silica, which can be readily functionalized by several catalytic active species. This pore-flow-through silica monolith microreactor was employed in a triphasic gas/liquid/solid selective hydrogenation reaction catalyzed by Pd NPs immobilized onto the silica network.¹⁰⁷ A straightforward Pd NP functionalization was carried out by impregnation of the monolith with an aqueous solution of $\text{Pd}(\text{NH}_3)_4(\text{NO}_3)_2$, thus exchanging the protons on the silica with $\text{Pd}(\text{NH}_3)_4^{2+}$ cations. Reduction with H_2 gave well-dispersed Pd NPs of 6-7 nm size formed within the mesopores of the

silica monolith. The efficiency of Pd-MonoSil was tested in the hydrogenation of 1,5-cyclooctadiene (COD, **12**) and 3-hexyn-1-ol (**15**) at room temperature under low H_2 pressure (Scheme 2.5).

Scheme 2.5 Reduction of 1,5-cyclooctadiene (**12**) and 3-hexyn-1-ol (**15**) using Pd-MonoSil catalyst.

The COD (**12**) hydrogenation showed a conversion of 95% and a selectivity of 90% in monohydrogenated product (**13**), which remained constant over a period of 70 h. In the latter hydrogenation a conversion of 85% and a selectivity of 80% for the *cis* isomer (**16**) were obtained over a period of 7 h, with a higher overall productivity than a Lindlar catalyst used in batch conditions.

Titania monoliths present a well-defined hierarchical porosity onto which metal nanoparticles can be supported.¹⁰⁸ The choice of titania as support is motivated by its chemical resistance, the positive influence on the activity of immobilized catalysts, and the contribution in reducing Pd NPs sintering. Therefore, after monolith preparation, Pd NPs of 5 nm size with a narrow size distribution were formed by simple flow of a Pd salt followed by reduction under H_2 flow. The prepared Pd@TiO₂ was employed as catalyst in continuous flow hydrogenation reactions of unsaturated C-C bonds using a homemade microreactor. The catalyst showed long-term stability as it retained 99% of its starting activity after three days of continuous reactants stream and it could be reused without any reactivation treatment. Moreover, no Pd leaching was detected by ICP-OES.

A recently developed macroporous polymeric monolith, called MonoBor, is constituted of cation-exchange tetraphenylborate anions incorporated in a highly cross-linked styrene-divinylbenzene matrix.¹⁰⁹ The advantageous feature of this material is its reproducible isotropic microstructure, possessing flow-through pores of 10 μm size, which guarantees a very low flow resistance and a high mechanical stability. Pd NPs were immobilized onto the monolithic material (Pd@MonoBor) and used in the catalytic, partial hydrogenation of alkynes under continuous flow.¹¹⁰ The catalysts were generated in a one-pot synthesis using a Pd salt followed by reduction yielding well-dispersed, spheroidal Pd NPs of 2.5 nm average diameter (Figure 2.7).

Figure 2.7 Synthetic procedure (top) and images of MonoBor (a), $\text{Pd}(\text{NO}_3)_2$ impregnated MonoBor (b) and Pd@MonoBor (c) monolithic columns (© Elsevier¹¹⁰).

Various substrates were chosen to test the efficiency of the catalyst for productivity and selectivity in semi-hydrogenations, including terminal and internal alkynols, diols, alkyne-esters, and unsubstituted alkynes. Excellent activities were

observed in terms of productivity, selectivity, and catalyst durability (in all cases, no palladium was detected in solution by ICP-OES).

The same monolithic material was used to generate Rh NPs for catalytic liquid-phase hydrogenations.¹¹¹ The metal NPs were grown using the same procedure as described above, by flowing a solution of $[\text{Rh}(\text{NBD})_2]\text{BF}_4$ through a preformed MonoBor monolith, followed by H_2 reduction yielding 3.9 nm Rh NPs. The hydrogenation of cyclohexene was used to evaluate the activity of a homemade flow reactor. Excellent conversions under mild conditions (1 bar H_2 and rt) were obtained, with a selectivity towards cyclohexane of 99.9%. Leaching of Rh could not be detected by ICP-OES. Furthermore, the hydrogenation of carbonyl compounds was investigated using Rh@MonoBor and Pd@MonoBor catalysts as well as the hydrogenation of substrates derived from natural terpenoids. In some instances, Pd performed slightly better than Rh, both in terms of activity and selectivity, attributed to a different adsorption mechanism on the metal surface.

2.3.2 Cross-coupling reactions

Pd NPs were loaded on polyionic polymers and employed in various continuous flow C-C cross-coupling reactions.¹¹² A Merrifield-type resin was functionalized as shown in Scheme 2.3 and then incorporated inside megaporous glass-shaped Raschig-rings, subsequently integrated inside a flow microreactor (Figure 2.8). By using an optimized composite material (5.3% cross-linker, Pd NPs with 7-10 nm average size), the Suzuki-Miyaura cross-coupling of 4-bromoacetophenone and phenylboronic acid was studied as a model reaction. The Pd NPs inside the flow reactor showed excellent stability without loss of activity after ten runs, although it was noted that most likely these polyionic gels serve as reservoirs of Pd nanoclusters that are released into solution at very low concentration (Pd leaching was determined to be 0.7 ppm). The catalytic system was also active for the Heck-Mizoroki reaction.

Figure 2.8 Reactor with functionalized Raschig-rings (© Beilstein¹¹²).

A polymer monolith derivatized with Pd NPs was applied by Ley and co-workers to perform ligand-free Heck cross-coupling reactions.¹¹³ They used a rigid macroporous organic monolith (Frechet type¹¹⁴) in which vinylbenzyl chloride was co-polymerized with divinylbenzene using azobisisobutyronitrile (AIBN) as radical initiator and a suitable porogen. After quaternarization of the material, an aqueous solution of a Pd salt was passed through the monolith and then reduced with a borohydride solution yielding Pd NPs in the range of 5 to 50 nm. A variety of aryl halides and alkenes were used to examine the effectiveness of the monolithic reactor to carry out the Heck cross-coupling (Scheme 2.6). The yields were generally high (>80%), and the reaction time shorter than its corresponding batch equivalent. The catalyst showed good activity and stability and it could be reused at least 25 times without regeneration, although an average metal content of 270 ppm was detected in solution. This problem was tackled by inserting a second column containing the metal scavenger resin Quadrapure TU directly after the nanoparticulate Pd reactor column, resulting in Pd levels below 5 ppm.

Scheme 2.6 Heck cross-coupling of aryl halides and alkenes using Pd NPs.

A Pd-supported silica-based monolith reactor coupled with microwave heating was developed to carry out Suzuki-Miyaura reactions.¹¹⁵ Silica monoliths having two different diameters, 3.2 and 6.4 mm, were synthesized from poly(ethylene oxide; PEO), tetraethoxysilane, and nitric acid. Using the reaction of bromobenzene with phenylboronic acid as a model reaction, the influence of different Pd precursors on the catalytic activity was investigated. Despite the fact that all the Pd-monoliths containing the same amount of palladium, their catalytic activities differed significantly, with the Na_2PdCl_4 precursor giving the best activity. Furthermore, the scaling-up strategy did not encounter any processing problems, with the amount of product obtained with the Pd-monolith-6.4 being four times greater than that obtained with the Pd-monolith-3.2 under similar conditions. Finally, the amount of palladium present in the product sample was <100 ppb, suggesting the presence of a highly specific and strong interaction between the impregnated metal NPs and the monolith support surface.

2.3.3 Monolith-supported alloy nanoparticles

In a study about monolith-supported metal alloy nanoparticles, hierarchically porous hydrogen silsesquioxane (HSQ, $\text{HSiO}_{1.5}$) monoliths were used bearing well-defined macro- and mesopores and exhibiting a high surface redox activity owing to the presence of abundant Si-H groups.¹¹⁶ Therefore, bi-, tri- and tetrametallic nanoparticles were synthesized with controlled composition and loadings and tested for their catalytic activity in the reduction of 4-nitrophenol. The supported alloy metal nanoparticles were also used in continuous flow reactors.

Initially, the simultaneous reduction of an equimolar mixture of Au^{3+} and Pd^{2+} was conducted on the HSQ monolith (Figure 2.9). A homogeneous distribution of both elements in each Au-Pd nanoparticle was found, and although the NPs showed a broad size distribution ranging from 2 to 35 nm, most of the particles were <10 nm.

Figure 2.9 Preparation of HSQ monoliths and controlled on-site reduction for the formation of metal alloy nanoparticles (© RSC¹¹⁶).

The applicability of this methodology was confirmed by co-reduction of different pairs of metal ions such as Au^{3+} - Pt^{4+} , Pt^{4+} - Rh^{3+} , and Pd^{2+} - Rh^{3+} . In all cases, quantitative reduction and simultaneous immobilization of the alloy NPs were obtained, and the NP composition could be tuned by changing the ratio of the metal ions. Most of the NPs had an average size <5 nm. It was even possible to synthesize multimetallic nanoparticles with three (Au^{3+} , Pd^{2+} , and Pt^{4+}) and four (Au^{3+} , Pd^{2+} , Pt^{4+} , and Rh^{3+}) elements. Satisfyingly, a homogeneous mixture was achieved, reflected by the formation of a single lattice that did not correspond to any monometallic lattice. All the supported mono-, bi-, tri- and tetrametallic NPs synthesized with an identical loading (4 mol%) were tested in the catalytic reduction of 4-nitrophenol with NaBH_4 . In particular, different Au_xPt_y catalysts exhibited favorable rate constants and turnover frequency (TOF) values, with an optimum composition of Au_1Pd_3 (Figure 2.10).

Figure 2.10 a) Reaction rates and b) TOF values of the reduction of 4-nitrophenol with NaBH_4 through a HSQ monolith (© RSC¹¹⁶).

The other bimetallic alloy catalytic systems exhibited similar catalytic activities with very high TOF values (around 4000 h^{-1}). However, lower TOF values were found for tri- and tetrametallic NPs-embedded monoliths (2400 h^{-1}). Finally, the Pd_1Rh_4 -monolith, which showed a high catalytic activity and acceptable reusability in batch experiments, was investigated in a continuous flow reactor retaining high conversion and, thus, demonstrating the applicability of metal alloy NPs-supported monoliths as efficient flow-through catalysts.

2.4 Wall-functionalized microreactors

As the high surface-to-volume ratio is arguably a very striking feature,²⁶ catalyst functionalization of the huge surface available should be central in the planning of a heterogeneously catalyzed reaction conducted in flow-through microreactors, especially in the case of multi-phase reactions involving interface interactions.¹⁹ Moreover, this approach generally solves the issues of back-pressure build-up along the microreactor and poor control over residence time distribution experienced with packed-bed reactors and, eventually, also with polymeric monolithic flow-through reactors.¹⁰⁶

In general, the bare surface of the microchannel is not sufficiently active to effectively carry out catalytic reactions, although its role in enhancing the reactivity for certain reactions has been demonstrated.¹¹⁷ Therefore, it is necessary to increase the specific surface area by chemical treatment of the channel walls or by applying porous coatings, which can be catalytically active or serve as support for a catalytic phase.¹¹⁸⁻¹²⁰ Metal catalysts can be deposited on the interior wall by a variety of techniques including thin-film deposition or liquid preparation techniques.¹²¹ In addition, they should fulfill certain prerequisites, such as high mechanical stability, adequate thickness to the chemical process being carried out, optimum porosity, and high activity and selectivity.¹⁴ The following sections will focus on the anchoring and stabilization of metallic nanoparticles directly on the inner walls of continuous flow microreactors and their application in different heterogeneously catalyzed reactions.

2.4.1 Hydrogenations

Reactor miniaturization has undoubtedly exerted its full potential in hydrogenation reactions, which usually require a gas/liquid/solid interaction and are thus favored by an increase of available surface area and its functionalization with metal catalysts.^{23,122,123} Hydrogenations using Pd NPs grown on the walls of a microstructured reactor have seen their first important contribution in the work of Kobayashi.¹²⁴ Exploiting the high interfacial area of a micro-device having a channel of 200 μm in width, 100 μm in depth, and 45 cm in length, a solid catalyst was immobilized on the microreactor walls. By flowing the liquid and gas phases into the channel, and achieving good control over the flow, the gas was forced through the center and the liquid along the inner surface of the channel, resulting in an excellent interaction between the three phases. Microencapsulated (MC) Pd was used as metal source and anchored onto an amino-functionalized surface as outlined in Scheme 2.7.¹²⁵ The hydrogenation of benzalacetone was carried out as

catalytic test reaction. When the flow rate of hydrogen was relatively slow, alternating slugs of the liquid and gas were observed resulting in insufficient yield. By increasing the hydrogen flow rate, however, a quantitative conversion was observed (residence time of 2 min). Additionally, reduction of other olefins and alkynes was successfully examined as well as the removal of a benzyl ether and of a carbamate group. In most cases, Pd was not detected in the product solution by ICP analysis and the microreactor could be used several times without loss of activity.

Scheme 2.7 Synthesis and immobilization of MC Pd catalyst.

Despite the excellent performance of the Pd-microstructured reactor, the problem of scaling up such a system was addressed, especially from a practical and spatial point of view. In this regard, capillary column reactors (i.d. 200 μm) were used instead, suitable for large-scale production, and the immobilization of Pd catalysts was conducted with the same procedure described above.¹²⁶ In this way, nine Pd-immobilized capillaries were assembled and connected in parallel. The hydrogenation of 1-phenyl-1-cyclohexene (**18**) was chosen as a model reaction,

with the product (**19**) obtained in quantitative yield in 17 min (Scheme 2.8). Noteworthy, the productivity was about 280 times that of the previous microchannel system. Again, Pd leaching was measured to be only minimal (0.20 μg).

Scheme 2.8 Hydrogenation reaction using assembled Pd-immobilized capillaries.

A further development of this methodology consisted of the use of scCO_2 as reaction medium to carry out hydrogenation reactions.¹²⁷ The same procedure presented above was used for the immobilization of Pd on the wall of a microchannel reactor (Scheme 2.7). In this case, hydrogen was first dissolved in scCO_2 by means of an autoclave kept at 50 °C and then the mixture was flowed through the channel. During the reaction, CO_2 was supplied continuously at a constant flow rate. A variety of substrates were converted to the desired products in nearly quantitative yields with reaction times estimated to be less than 1 s. Compared to the previous system,¹²⁴ the productivity revealed an increase from 0.01 mmol h^{-1} to 0.1 mmol h^{-1} per channel, attributed to the increased solubility of hydrogen in scCO_2 .

More recently, Kobayashi presented a new method for the immobilization of Pd catalysts on the channel wall of a capillary.¹²⁸ Polysilane was used as anchoring medium due to its double function as backbone for the immobilized catalyst and as connecting material between the surface of a glass wall and catalysts via silicon-oxygen networks. The polysilane-supported palladium catalyst (Pd/PSi) was prepared according to a procedure summarized in Scheme 2.9.

Scheme 2.9 Typical procedure for the preparation of Pd/PSi-MO_x immobilized capillaries.

Without the addition of a metal oxide (MO_x) to the Pd/PSi catalyst, the capillary was not very effective for the hydrogenation of 2,4-diphenyl-4-methyl-1-pentene (**20**; Scheme 2.10). Aluminum oxide and titanium oxide used as additives gave good conversions. Subsequently titanium oxide was also employed in smaller particles to increase the catalyst surface area. The thus formed Pd/PSi-TiO₂ was tested for the reduction of several substrates to afford, in most cases, good to excellent conversions. The purity of the products was 99% (analyzed by gas chromatography) without any additional purification. No leaching of Pd was detected after the reaction in each case and the system could be reused at least 15 times without loss of activity.

Scheme 2.10 Hydrogenation using the Pd/PSi-MO_x immobilized capillary.

Pd NPs embedded in a polysiloxane matrix grown in a capillary reactor were also employed for the high-throughput screening of catalysts.¹²⁹ Both for hydrogenations over the Pd NPs as well as for the ring-closing metathesis over a Grubbs second generation catalyst, it was demonstrated that combining catalysis and separation allows high-throughput reaction rate measurements of substrate libraries. The Pd NPs for the three-phase hydrogenations were prepared by

embedding the catalysts in polysiloxanes, which act both as solvent and as stationary separation phase (Figure 2.11).

Figure 2.11 Preparation of Pd NPs embedded in a polysiloxane matrix used for hydrogenation reactions in a microcapillary reactor.

Pd ions were coordinated by the vinyl groups of the copolymer and subsequently reduced by the addition of hydridomethylsiloxane-dimethylsiloxane copolymer to yield spherical, crystalline nanoparticles of around 3.2 nm in size. On-column catalysis was carried out by coupling the microcapillary, functionalized with Pd NPs, between a pre-separation capillary (1 m) and a separation column (25 m). The chemoselectivity of compound libraries was studied by simultaneously injecting 22 unsaturated compounds (alkenes, alkynes, aromatic hydrocarbons). All hydrogenations went to completion within a very short residence time (within 1 s) at low reaction temperatures (60 °C). The high activity of the Pd NPs was sustained by the calculated activation parameters, notably the low activation enthalpies and negative activation entropies. Systematic TEM investigations elucidated that the size and morphology of the Pd NPs depended on the ratio of stabilizing polysiloxane, the activation temperature to immobilize the stationary phase on the surface of the capillary, and the loading of Pd precursor.¹³⁰ This dependency was explained by kinetic effects, with the reduction of Pd²⁺ to Pd⁰ being as fast as the hydrosilylation leading to cross-linking and NPs stabilization.

Thin films of inorganic mesoporous materials represent an excellent carrier for the deposition of metallic nanoparticles to the walls of reactor channels, thereby increasing the surface area of the catalytic coatings.^{131,132} The group of Schouten

used continuous-flow capillary microreactors functionalized with mesoporous titania thin films as support for several metallic nanoparticles of different compositions (Ni-Pd, Fe-Pd, Mg-Pd, Pd, and Pt).¹³³ The NPs showed an approximately 2.5 nm mean diameter and were synthesized using a polyol reduction method.¹³⁴ The confinement within the mesopores of the inorganic matrix stabilized the particles and prevented agglomeration, even after calcination at 300 °C used to adhere titania layers (around 100 nm thick) on the walls of fused silica capillaries (i.d. 250 μm). The capillary system was tested as microreactor in selective hydrogenations under different flow and temperature conditions. The semi-hydrogenation of phenylacetylene showed a TOF value of 2 s⁻¹ comparable to that reported for the same NP-catalyzed reaction in homogeneous phase. Moreover, the same activity and selectivity was maintained during more than one month of continuous use.

The versatility of the capillary system was exploited to embed Pd and bimetallic Pd₂₅Zn₇₅ nanoparticles for the hydrogenation of 2-methyl-3-butynol (**22**) as model reaction (Scheme 2.11).¹³⁵ The Pd/TiO₂ catalyst demonstrated an order of magnitude higher hydrogenation reaction rate than the commercial Lindlar catalyst and gave an alkene (**23**) selectivity of 89% at 3 bar hydrogen pressure in the presence of pyridine. Using the Pd₂₅Zn₇₅/TiO₂ catalyst the selectivity reached 97%, although the reaction rate dropped by a factor of 16 compared to that of the Pd/TiO₂ catalyst.

Scheme 2.11 Hydrogenation of 2-methyl-3-butynol (**22**) using a Pd₂₅Zn₇₅ bimetallic catalyst.

More recently, platinum nanoparticles were immobilized onto thin films of mesoporous silica, mesoporous titania, and titania, all used as support layers to coat the microreactor walls, and employed for the hydrogenation of nitrobenzene.¹³⁶ SEM was used to evaluate the NPs adsorption on the different support layers (Figure 2.12). Results showed that the interaction between Pt NPs and the naked borosilicate microreactor wall was weak, while the Pt immobilization on the mesoporous silica layer (MPS) was uneven. Therefore, TiO_2 and mesoporous titania (MPT) were subsequently used, showing uniform NP adsorption and retention of their size (ca 3 nm). During the course of the hydrogenation of nitrobenzene, the catalysts were progressively deactivated, but they could be easily regenerated by supplying diluted H_2O_2 . The catalytic activity was 5.5 and 2.7 times greater than that in batch experiments conducted using Pt NPs on TiO_2 powder and Pt/C catalysts, respectively.

Figure 2.12 SEM images of Pt nanoparticles inside the microreactors with support layers of (a) No Coat, (b) MPS, (c) TiO_2 , and (d) MPT (scale bar: 100 nm; © Elsevier¹³⁶).

Kreutzer *et al.* proposed the use of wall-catalyzed segmented flow to better control the catalyst-reagents interaction and to enhance the contact between different phases.¹³⁷ They used commercially available fused-silica capillaries

coated with a 6 μm thick layer of high surface area $\gamma\text{-Al}_2\text{O}_3$ impregnated with Pd NPs (5 nm average size). Segmented flow ensured optimal yields due to the extremely fast mass transfer to the catalytic wall. Moreover, the conversion was monitored visually, thus facilitating the control over the activity and the deactivation of the catalyst. Exploiting the advantages of segmented flow, the reduction of 3-azidopropyl benzene to give 3-phenylpropyl amine was carried out (Figure 2.13).

Figure 2.13 Continuous capillary microreactor with a Pd catalyst immobilized on the inner wall operated in segmented gas–liquid flow used for the reduction of 3-azidopropyl benzene (© Wiley¹³⁷).

Ley and co-workers functionalized the inner surface of multi-channelled polymer devices in order to carry out palladium-promoted hydrogenations.¹³⁸ This approach enables the easy ‘numbering-up’ or ‘scale-out’ of optimized reaction conditions by assembling several microcapillaries running in parallel. The disc-shaped microreactors were fabricated from a flat polymer film of ethylene-vinyl

alcohol (EVOH) in which arrays of parallel capillaries were molded. The EVOH capillaries (i.d. 146 μm) were stable against water and alcohols and possessed an overall good resistance to many organic solvents. The surface functionalization was carried out in four subsequent steps: 1) washing of the inner surface with a NaOH solution to expose the hydroxy groups; 2) treatment with *N*-trimethoxysilylpropyl-*N,N,N*-trimethylammonium chloride; 3) Pd was introduced as an aqueous solution of Na_2PdCl_4 and the Pd^{2+} ions exchanged with the quaternized silyl linker; and 4) final reduction with NaBH_4 yielded the Pd NPs (it was not possible to determine their size, but from the uniform channel wall surface after coating and the absence of large metallic deposits it was suggested that the particles were in the nanometer range; Scheme 2.12).

Scheme 2.12 Wall surface functionalization of microcapillaries inside EVOH-MFDs (MFDs = microcapillary flow discs).

The thus formed Pd-functionalized capillary reactor was employed in transfer hydrogenation reactions using triethylsilane as the hydrogen donor. Upon introduction of the substrate into the microcapillaries, the formation of small gas bubbles, which evolved in a steady gas-liquid slug flow, was considered beneficial because of the better mixing and interaction with the catalytic wall. A series of reduction reactions was successfully carried out, including carbonyl groups to alcohols, imines and nitro groups to amines, as well as C-C double and triple

bonds. Leaching of Pd was minimal (below the detection limit for the reaction scale) and the disc could be used several times without loss of catalytic activity.

Another example of chemical surface modification for the *in situ* anchoring of Pd NPs involves the use of a PDMS microfluidic reactor.¹³⁹ Its surface was functionalized with biotin and 3-aminopropyltrimethoxysilane (APTMS) in order to introduce binding moieties for the formation of Pd NPs with a narrow distribution size (2-4 nm; Scheme 2.13). Biotin was used as ligand because of its thioether moiety that can be used to stabilize soft metals like Pd. The device was evaluated in the hydrogenation of 6-bromo-1-hexene at room temperature and one atmosphere of hydrogen pressure. The flow rates of the liquid and the gas were controlled to ensure that the liquid traveled along the walls of the channels, with the gas in the center to maximize the three-phase interaction. A decrease in conversion was noted after a few cycles due to possible detachment of immobilized catalyst or fouling of the catalyst surface.

Scheme 2.13 Immobilization of biotinylated Pd NPs onto an amino-functionalized surface.

The same procedure was used to introduce different types of metal nanocatalysts, such as Pd, Pt, and Ru, for high-throughput assessments of their intrinsic catalytic activity, using the same model hydrogenation reaction described above.¹⁴⁰ The metal NPs were stabilized by n-dodecyl sulfide (NDS) and attached to amino-functionalized PDMS microreactors. NDS proved to be effective in the formation of stable and uniform NPs (average diameters: Pd 3.0 nm, Pt 3.3 nm, and Ru 3.5 nm). All reactions showed 100% selectivity and various degrees of

conversion with TOF values hundreds of times higher than in analogous batch reactions.

2.4.2 Redox reactions

Oxidations using molecular oxygen could take advantage of heterogeneous catalysts attached to the inner wall of microfluidic reactors, as already demonstrated for hydrogenations, due to the high interfacial area created within microstructures for the optimal interaction of gas/liquid/solid phases. Kobayashi *c.s.* used a catalytic system similar to that employed for hydrogenation reactions, namely a gold-immobilized microchannel, for the oxidation of alcohols with molecular oxygen.¹⁴¹ A capillary column (250 μm inner diameter) was coated with polysiloxane containing 50% phenyl and 50% *n*-cyanopropyl groups on silicon atoms (film thickness: 250 nm). Microencapsulated gold (MC-Au) prepared from chlorotriphenylphosphine gold and copolymer was used as gold source (Figure 2.14).

Figure 2.14 Immobilization of the gold catalyst. a) Reduction of the cyano group to an amine. b) Preparation of microencapsulated gold (MC-Au). c) Immobilization of the gold catalyst.

Gold nanoparticles were also immobilized on a fused silica capillary surface by a simple surface chemical modification.^{142,143} A microfluidic setup was developed for the production of homodispersed 1-2 nm Au NPs, by controlling reaction parameters such as reagent flows, concentration, temperature and reaction time. Au NPs of 15 nm, prepared following the Turkevich protocol,¹⁴⁴ were incorporated within a fused silica capillary of 100 μm internal diameter following two grafting procedures: surface (2D) or volume (3D). In the former approach, the Au NPs were attached to an APTES-functionalized inner surface. In the 3D approach, instead, the Au NPs were trapped inside the complete volume of the microcapillary by anchoring the particles on an amino-functionalized monolith generated *in situ*.¹⁴²

The 2D strategy was further extended by the immobilization of different types of polymer-stabilized Au NPs. Their catalytic activities were screened in the oxidation of benzyl alcohol in the presence of hydrogen peroxide.¹⁴³ Two different linkers were used: APTES and MPTES, exploiting electrostatic affinity and strong interaction of thiols with gold, respectively (Scheme 2.14). Depending on the linker used, slight differences in terms of conversion were observed for the oxidation of benzyl alcohol, with MPTES showing a higher efficiency.

Scheme 2.14 Gold nanoparticle immobilization with APTES and MPTES anchoring agents.

In our group, a versatile strategy was developed to form metallic NPs in a brush-gel structure grown directly from the inner surface of glass microreactors.¹⁴⁵ Pd and Ag NPs were synthesized and tested in the reduction of 4-nitrophenol and the Heck reaction of iodobenzene and ethyl acrylate. A polymer brush made of hydroxyethyl methacrylate (HEMA) co-polymerized with tetraethylene glycol dimethacrylate (TEGDMA) was grown via ATRP (Atom Transfer Radical Polymerization), achieving good control over the polymer thickness and thus the catalyst loading, as shown for other brush-supported catalysts.^{146,147} Moreover, the NP size could be tuned by varying the amount of cross-linker. By this method, Ag NPs (20 nm) and Pd NPs (30 nm) were formed within the brush-gel structure (< 100 nm thick; Figure 2.15).

Figure 2.15 General scheme for initiator immobilization, surface initiated polymerization of HEMA-TEGDMA, and in situ formation of Ag and Pd NPs (© Wiley¹⁴⁵).

Glass microreactors with channel dimensions of 110 μm in width and 50 μm in height were coated with the brush/Ag NPs catalytic layer and used for the reduction of 4-nitrophenol using NaBH₄. In all the experiments, the reaction was complete within a few seconds. Interestingly, experiments carried out in

microreactors with different brush/NP hybrid layer thicknesses showed a correlation with the catalytic activity. Also the brush/Pd catalytic system was used in the reduction of 4-nitrophenol under the same conditions, showing even a higher activity than the Ag counterpart.

In another study, polymer brushes were adopted to functionalize the inner walls of nanoporous anodic aluminum oxide (AAO) for the grafting of Au NPs.¹⁴⁸ The flow-through system consisted of a parallel array of AAO nanochannel membranes assembled in a sandwich configuration enabling the formation of a nanoreactor. ATRP was used to grow polymer brushes of methacryloethyltrimethyl ammonium chloride (METAC). By subsequent exchange of the Cl^- anion in the polymer brush with AuCl_4^- and reduction with NaBH_4 , Au NPs with a particle size of around 6-8 nm were generated *in situ* (Figure 2.16). The nanoreactor showed a high catalytic activity and instantaneous separation of products for the reduction of 4-nitrophenol with NaBH_4 .

Figure 2.16 Schematic representation of (i) anchoring initiators within the nanochannels of an AAO membrane, (ii) surface initiated polymerization of PMETAC brushes, and (iii) *in situ* immobilization of Au NPs (© RSC¹⁴⁸).

2.4.3 Other catalytic reactions

Undoubtedly, cross-coupling reactions carried out in continuous flow fashion benefit from an increased catalyst loading, prerogative of packed-bed reactors and monolithic flow-through systems, especially due to the usual harsh reaction

conditions they require. The so-called microwave-assisted organic synthesis combined with flow techniques (MACOS) can improve the performance of C-C cross coupling reactions, among others.¹⁴⁹ To this respect, Organ *et al.* suggested the immobilization of reagents and catalysts on surfaces as a way to foster this research area.¹⁵⁰ Pd nanoclusters were deposited on the inner surface of capillaries and the resulting thin metal film was used as a catalyst in Suzuki and Heck reactions under MACOS conditions. The preparation of the Pd films was based on methods for the preparation of Pd particles and sols by thermal decomposition of organometallic compounds. In this way a film made of small grains of Pd in the range of 60 to 140 nm in diameter was obtained. The catalytic activity of the capillary was compared to a conventionally heated batch experiment for both the Suzuki and Heck reactions: whereas the reaction under flow conditions gave quantitative conversion after a few seconds, the batch reaction barely proceeded. Moreover, no Pd was detected upon completion of the continuous flow reaction.

Microreactor technology shows its full advantage in the handling of hazardous reactions, such as the formation of hydrogen peroxide from H₂ and O₂. Therefore, Jaenicke and co-workers immobilized Pd NPs within a polymer coating on the microreactor walls,¹⁵¹ using the polymer-micelle incarceration (PMI) technique.¹⁵² The Pd clusters were well distributed throughout the polymer support showing a uniform size of around 2.5-3.6 nm. The developed catalytic system was suitable for the *in situ* generation of hydrogen peroxide under mild conditions, *i.e.* room temperature and atmospheric pressure. Despite the corrosive conditions, the PMI-immobilized catalyst showed little leaching and could be used continuously for 11 days.

Carbamoylation of aniline (**25**) by dimethyl carbonate (**26**; Scheme 2.15) was performed under continuous flow using a microreactor (10 μ m microchannels) the surface of which was covered by nanoparticulated ceria (CeO₂, 5 nm average size) and Au NPs supported on nanoparticulate ceria (3-4 nm in size).¹⁵³ The two

catalysts were selected because of their complete selectivity for carbamoylation of aromatic amines in batch experiments. Although the conversion level was moderate (around 35 %), the addition of gold increased the space velocity of the experiment and stabilized the system (no decay in the activity) compared to CeO₂.

Scheme 2.15 Carbamoylation of aniline by dimethyl carbonate.

2.5 Other approaches

Different strategies have been devised to introduce metal nanoparticles within continuous flow microreactors apart from the conventional methods so far described. The use of functionalized magnetic nanoparticles to support metal NPs is promising due to the ease of separation, by simple application of a magnet, and the possibility to use inductive heating as an energy source. Catalytic membranes display catalytic activity and separation both in the same system. Finally, nanomaterials, such as carbon nanotubes, carbon nanofibers, nanowires, *etc.*, offer the possibility to greatly increase the active surface area as well as achieve a good control over fluid dynamics and thus flow rate and residence time.

2.5.1 Metal catalysts supported by magnetic nanoparticles

Magnetic nanoparticles are of great interest in diverse fields of application, including catalysis.¹⁵⁴ By coating the nanoparticles with SiO₂, metal oxides, gold or carbon, they can be used as supports for the anchoring of catalysts, which can then be separated from the reaction medium by simple application of a magnet.

Kirschning used silica-coated magnetic NPs in a microfluidic fixed-bed reactor to perform a variety of catalytic transformations by using inductive heating, such as

transesterifications, condensations, Claisen rearrangements, etc.^{155,156} Due to the silica coating, the surface of the magnetic NPs could be functionalized with Pd particles obtained by reductive precipitation of ammonium-bound Pd salts (Scheme 2.16).

Scheme 2.16 Preparation of magnetic nanoparticles functionalized with Pd NPs.

The particles, employed in various Pd-catalyzed cross-coupling reactions, showed little leaching (34 ppm for Suzuki-Miyaura reactions and 100 ppm for Heck reactions). The catalyst could be reused more than three times without a decrease in activity.

2.5.2 Catalytic membranes

Porous membranes provide an alternative support for nanoparticle immobilization and are especially attractive for heterogeneous catalysis because of the membrane geometry that allows flow-through reactions without the need to separate the catalyst.¹⁵⁷ Alumina and polymeric membranes were modified with metal nanoparticles and the resulting systems tested in the reduction of 4-nitrophenol.¹⁵⁸ The layer-by-layer approach was used to adsorb citrate-stabilized gold NPs onto alumina (Figure 2.17). Modification of alumina membranes occurred through the sequential flow of polyacrylic acid, water, protonated poly(allylamine), water, gold NPs (12 nm), and water. The functionalized membranes showed remarkable conversions of 4-nitro- to 4-aminophenol at high

flow rates. The number of Au NPs could be increased by increasing the number of adsorbed layers.

Figure 2.17 Schematic diagram showing the modification of a pore of an alumina membrane by adsorption of two polyelectrolytes and gold nanoparticles (© ACS¹⁵⁸).

A new type of free-standing membrane was displayed consisting of highly uniform and active carbonaceous nanofibers (CNFs) whose surfaces allow for easy loading of various nanoparticles.¹⁵⁹ In this way, CNFs-Fe₃O₄, CNFs-TiO₂, CNFs-Ag, and CNFs-Au were prepared and applied to magnetic actuation, antibiofouling filtration, and continuous flow catalysis. CNFs-Au composite fibrous membranes were selected for the continuous flow reduction of 4-nitrophenol using NaBH₄. The catalytic membrane reactors thus combine conversion efficiency (catalysts) and separation (membrane) in a single unit and display a huge active catalytic surface due to the uniform dispersion of Au NPs on the surface of the CNF matrix. Interestingly, the membrane could maintain >99% conversion of 4-nitrophenol for more than 10000 membrane volumes, indicating its long-term catalytic activity.

A variety of membrane polymeric palladium catalysts were immobilized at the laminar flow interface of the channels of a microchannel reactor, based on the concept of molecular convolution.¹⁶⁰⁻¹⁶² Herein, a soluble, linear polymer with multiple ligands is convoluted with transition metals by means of coordinative or ionic complexation, to achieve the one step preparation of the insoluble polymeric

metal composite (Figure 2.18). The resulting microflow devices were successfully applied to the Suzuki-Miyaura and allylic arylation reactions.^{160,162} Reduction of the polymeric Pd complexes resulted in polymeric Pd NP-containing membranes installed in microflow devices, which were applied in instantaneous, mild, and safe hydrodehalogenations, achieving instantaneous, quantitative conversion to dehalogenated products at 50-90 °C within a residence time of only 2-8 s.¹⁶¹ TEM images indicated that Pd NPs had formed in the membrane, with diameters between 6 and 12 nm.

Figure 2.18 Illustration of a Y-junction microchannel reactor with two inlets and one outlet (top). Concept for the preparation of catalytic membranes at the interface of a laminar flow inside a microchannel reactor (bottom; © Wiley¹⁶⁰).

2.5.3 Nanomaterial-supported catalysts

Carbon nanotubes (CNTs) are a promising catalyst support material, mainly due to their high surface area, ease of chemical modification, and high mechanical stability.¹⁶³ Therefore, a new type of microreactor was fabricated containing

incorporated Pt-supported aligned carbon nanotubes.¹⁶⁴ Compared to conventional wall-functionalized microreactors, the main advantages are: the CNTs are fixed inside the channel and do not require solvents, large surface area between reactants and catalysts, and separation after the reaction is not needed. The CNTs were aligned in the reaction zone of a microreactor (2.5 mm width, 170 μm height, 200 mm length) and afterwards Pt NPs were introduced following two methods: impregnation of a Pt salt and direct deposition of Pt NPs (Figure 2.19). The nanoparticle size was measured to be on average in the range of 1 to 10 nm.

Figure 2.19 Schematic illustration of (a) a conventional microreactor using a Pt film deposited on the walls of the flow channel and (b) a microreactor with Pt-modified aligned nanotubes in the flow channel (adapted with permission from ref. 164).

The hydrosilylation of olefins was used as a model reaction. Equal amounts of 1-octene (**28**) and dimethylphenylsilane (**29**; Scheme 2.17) were introduced in the Pt-CNT-functionalized reactor resulting in an increase in conversion and catalyst lifetime compared to traditional microreactors having either thin films of Pt or colloidal Pt NPs deposited directly on the channel walls.

Scheme 2.17 Hydrosilylation of 1-octene (**28**) with dimethylphenylsilane (**29**) in a Pt-CNTs-functionalized reactor.

Following the same strategy to build nanostructures that hold catalysts within microchannels, the fabrication of vertically aligned peptide/Pd hybrid nanowires (NWs) was reported, showing good stability and applicability to soft polymeric substrates.¹⁶⁵ Specifically, in the reaction zone of a polyvinylsilazane microreactor (width 500 μm , height 50 μm , length 3 cm) diphenylalanine (Phe-Phe) peptide NWs were grown on the polymer surface in a self-assembled manner using polydopamine (PDA) as an adhesion promoter. Afterwards, the Phe-Phe peptide nanowires were incubated in a Pd precursor solution to grow Pd NPs along the Phe-Phe peptide NWs (NPs in the range 4-20 nm; Figure 2.20).

Figure 2.20 Schematic representation of peptide/Pd nanowires built-in microfluidic system for heterogeneous catalytic hydrogenation and Suzuki coupling reactions (© RSC¹⁶⁵).

Calculations revealed that an array of Phe-Phe peptide NWs (300 nm in diameter and 10 μm long) would give a surface area around 10^2 times larger than that of a flat surface, thus increasing the amount of immobilized Pd NPs. The system was investigated both in hydrogenation and Suzuki coupling reactions and compared with unfunctionalized microreactors. The results for both type of reactions showed higher yields by using the Phe-Phe peptide/Pd hybrid NWs microreactor, which exhibited also good resistance towards strongly swelling solvents such as THF/water. For example, the hydrogenation of 1-phenyl-1-cyclohexene resulted in a 62% yield compared to no conversion in a plain microreactor under the same reaction conditions.

As a logical extension, three-dimensionally (3D) ordered macroporous materials with mechanical and chemical robustness were introduced within microfluidic channels.¹⁶⁶ The fabrication process consisted of a series of packing sacrificial polystyrene (PS) beads onto a substrate coated with a non-adhesive fluoropolymer, then UV curing and wet-etching the structure, which led to a macroporous polymeric structure. Afterwards, Pd NPs were implanted on the inner surface of the porous acrylated perfluoropolyether (PFPE) microstructure (around 5 nm in size; Figure 2.21a).

Figure 2.21 Procedure for fabrication of (a) 3D ordered macroporous PFPE patterns, (b) SU-8 microchannel with built-in 3D ordered porous PFPE patterns (© RSC¹⁶⁶).

In addition, a conventional photolithographic process was employed to fabricate the built-in macroporous microstructure in a microfluidic channel (Figure 2.21b). The catalytic system was tested in a Suzuki coupling reaction exhibiting higher performance than a plain microchannel containing Pd NPs, especially at high flow rates where the increased surface area and catalyst loading exerted their optimal

effect. For example, at a flow rate of 5 ml min^{-1} of reactants, the built-in microreactor resulted in 40% product yield, while nearly no conversion was observed in the plain microreactor at the same flow rate.

Silver micro-nanostructures, called silver microflower arrays (SMAs), were fabricated inside a microfluidic channel (width $100 \text{ }\mu\text{m}$, height $30 \text{ }\mu\text{m}$).¹⁶⁷ By a two-photon absorption-induced photoreduction of a silver precursor, 4×50 SMAs were deposited at the bottom of a microchannel with an average diameter of $9 \text{ }\mu\text{m}$ (Figure 2.22). Each microflower was made of upright nanoplates embedded with silver nanoclusters. The reduction of 4-nitrophenol was chosen to test the catalytic activity of the system as well as to carry out *in situ* surface-enhanced Raman spectroscopy (SERS) detection. The SMAs showed both high catalytic activity reaching full conversion at 1 mL h^{-1} , and high SERS enhancement for the monitoring of the reaction.

Figure 2.22 Laser fabrication of silver microflower arrays (SMAs) inside a microfluidic channel (© RSC¹⁶⁷).

As already mentioned, porous and fibrous nanostructures as catalyst support have gained a great deal of attention, mainly for their large surface area, but also for the possibility to gain good control over the flow rate, thanks to the sizeable pores of these structures. Recently, vertical Au nanowires (AuNWs) were grown on glass fibers to greatly improve catalyst loading and the flow rate due to the large

pores in the support.¹⁶⁸ In a typical synthesis, glass fibers were functionalized with 3-aminopropyltrimethoxysilane to adsorb small Au seeds (3-5 nm). SEM images of the glass fibers confirmed the presence of a dense layer of vertical AuNWs. The catalytic fibers could be loosely packed into a simple column and their activity was tested for the conversion of 4-nitro- to 4-aminophenol. By studying the flow rate profiles, it was concluded that in a fixed-bed system, the flow rate depends on the crevices among the support particles, usually silica or polystyrene microspheres. Hence the more support material used, the slower the flow rate, whereas the crevices inside a loose column of glass fibers can be much larger. Within the glass fiber approaches, there are two ways to load a catalyst, either by directly adsorbing 3-5 nm Au NPs on the surface or by growing vertical AuNWs ($d = 5$ nm, length = $1\text{ }\mu\text{m}$) on the support. The latter method presents a 200 times higher surface area than the Au NPs deposited directly on the surface (Figure 2.23).

Figure 2.23 Schematic representation illustrating the difference of pores among (a) loosely packed silica spheres and (b) glass fibers, and the difference in terms of available catalytic surface for (c) AuNPs, and (d) AuNWs loaded on a support surface. With a same surface density, AuNWs would have 200 times the catalytic surface area of AuNPs (© Wiley¹⁶⁸).

2.6 Conclusions and outlook

Nanocatalysis and continuous flow synthesis (flow nanocatalysis) march hand in hand to fulfill the requirements of modern green chemistry.⁵⁸ Metallic nanoparticles bring about enhanced catalytic activity and selectivity, at the intersection between homogeneous and heterogeneous catalysis. Anchoring these nanospecies within a microfluidic reactor dramatically increases the reagent/catalyst interaction, avoiding the diffusion limit experienced with round-bottom flasks and stirred tanks, especially for multiphase reactions, such as hydrogenations, oxidations, etc.^{23,87}

This Chapter deals with the already numerous examples of nanocatalysts used in combination with continuous flow microreactors to carry out hydrogenations, oxidations, cross-coupling reductions, etc. The technical and operational challenges of this approach lie in the immobilization of the metal species inside the microchannels, specifically the means of stabilization should ensure, and possibly maximize, the catalytic activity and stability of the heterogeneous catalyst (high TOF and TON values). With the premise that a general method to incorporate nanoparticles into microfluidic devices has not been developed yet, there are, however, different strategies for the nanoparticle anchoring and stabilization. Packed-bed reactors provide an increased active surface for the catalyst to be loaded on inorganic or polymeric supports. Monolithic flow-through systems improve the permeability along the channel and the control over the residence time. Wall catalysts are particularly suited for multiphase reactions such as hydrogenations. The use of nanomaterials for supporting nanoparticles (nanotubes, nanowire, membranes) could bridge the gap between the traditional approaches just mentioned, namely high catalyst loading as well as ordered catalyst packing to avoid a broad residence time distribution.

In addition, researchers should address the issues of quantitative loading of catalysts, controllable positioning of catalysts, uniform dispersion of catalytically

active sites, and stability.¹² Most likely the solutions lie in the manufacturing of *ad hoc* nanoparticle-functionalized devices, taking into account the catalytic process and the nanomaterial used. For example, microreactors with a stable, uniform distribution, and shape control of wall-deposited metal particles are good candidates for hydrogenation reactions. In addition, a homogeneous metal pre-catalyst coupled with a separation setup would be more suited for C-C cross-coupling reactions, as recently proposed by Kappe *c.s.*, to overcome the ‘leaching issue’ related to these transformations.⁷⁹

Future research should inevitably focus on the sustainability of the processes, by developing cheaper, less toxic, low loaded catalytic systems as well as investigate green chemical syntheses. To this regard, although only a few examples describe the application in continuous flow devices, bimetallic nanocatalysts can bring significant advantages, provided that a good tuning of the structure is achieved.

2.7 References

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Chapter 3

Heterogeneous acid catalysis using a perfluorosulfonic acid monolayer- functionalized microreactor*

The inner walls of a glass microreactor were functionalized in a one-step procedure with a single layer of a strong perfluoroalkylsulfonic acid. The applicability of the catalytic device was demonstrated in the successful hydrolysis of benzaldehyde dimethyl acetal in acetonitrile, achieving quantitative conversion within a residence time of only 60 s. Furthermore, the catalytic system showed high conversion for the Friedlander quinoline synthesis between 2-aminobenzophenone and ethyl acetoacetate. The cyclization of pseudoionone in methylcyclohexane proved the wide applicability of the acid-functionalized microreactor also for reactions carried out in apolar media. The platform showed activity for 6 hours to 2 days, depending on the solvent, and was reactivated by simple treatment with the catalyst precursor.

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3.1 Introduction

In recent years, several examples of flow-through syntheses have been reported utilizing immobilized catalysts. The most used approach is by filling the microstructured reactor with packed columns, usually constituted of a functionalized solid support,¹⁻⁴ or by using flow-through materials, especially monoliths.⁵⁻⁸ Although these strategies offer advantages such as increased active surface and a wide choice of supports and catalysts, the randomly packed catalytic beds may lead to uncontrolled fluid dynamics, broad residence time distributions, and low selectivity. However, microstructured reactors with a wall catalyst rather than conventional reactors with catalyst pellets offer good control over the reaction conditions.⁹ In fact, wall-coated systems have gained increasing attention, with several examples ranging from Au-films,¹⁰ enzymes,¹¹ to polymer brushes.¹²⁻¹⁵ Another approach involves the use of a nanoparticle-containing catalytic membrane at the laminar flow interface of a microflow reactor.¹⁶

Acid-catalyzed reactions are of great interest in organic synthesis, with widespread application in industry. These reactions are mostly performed using strong mineral acids, such as sulfuric acid or hydrogen chloride, which are deployed in a homogeneous fashion and hence as single use reagents. However, the increasing concerns of environment protection and safety issues, have stimulated the development of stable, reusable and highly active solid acid catalysts.^{17,18} Therefore efforts have been made to transform a successful homogeneous catalyst into a heterogeneous catalytic system, i.e. an acid catalyst immobilized on some form of support, especially by functionalization of ordered mesostructured silica^{19,20} or polymer-based materials.^{21,22} Although characterized by high acid loadings and activity, these procedures mostly suffer from a tedious multi-step preparation process and incomplete functionalization. In contrast, Corma *et al.*^{23,24} reported a single step anchoring of a perfluoroalkanesulfonic acid group onto mesoporous MCM-41 and SBA-15. The resulting material showed a significant

enhancement in catalytic activity for the esterification of carboxylic acids and Friedel-Crafts acylations. The same strategy was followed by Jones *et al.*²⁵ who tethered the fluorinated sultone precursor to SBA-15. The hybrid organic/inorganic material was used as co-catalyst/support for the activation of various zirconocenes for the production of polyethylene. The group of Fierro used amorphous silica gel as support for the covalent anchoring of β -sultone to the hydroxylic groups on the silica surface. The hybrid organic/inorganic system was tested in the esterification reaction of acetic acid with methanol.²⁶ So far, these procedures have not been implemented in microfluidic devices, in which acid catalysts have been introduced mostly through packed-bed supports.^{5,27}

In this chapter the functionalization of a glass microreactor is reported by single-step anchoring of a perfluoroalkylsulfonic acid, from a precursor β -sultone, to the inner walls. This simple procedure allows the formation of a single layer of a strong organic acid catalyst, in contrast to other studies where films or brushes, containing multiple catalytic sites, are required to give a reasonable catalytic activity (*vide supra*). A large advantage of this process is that it obviates an activation step as the acid is formed by the surface coupling reaction. Its high activity and versatility is demonstrated in the hydrolysis of benzaldehyde dimethyl acetal, the Friedlander annulation to give quinolines, and the cyclization of pseudoionone. These examples confirmed the enhancing effect of the microstructured system on these reactions as compared to lab scale conditions.

3.2 Results and discussion

3.2.1 Catalytic monolayer preparation

The construction of a catalytic acid layer was first performed on an activated flat silicon dioxide surface in order to be able to characterize the immobilized catalyst. The anchoring was carried out by single-step ring opening via reaction of 1,2,2-trifluoro-2-hydroxy-1-trifluoromethylethane sulfonic acid β -sultone

(hereafter β -sultone, **1**) with the surface OH groups of the silicon oxide surface (Scheme 3.1), in an analogous procedure as reported in literature.²³

Scheme 3.1 Functionalization of flat silicon dioxide surface and glass microreactor by β -sultone (**1**).

The introduction of the sultone moiety on the silica surface was proven by X-ray photoelectron spectroscopy (XPS), clearly showing the presence of the terminal sulfur and the fluorine atoms. Yet, it also revealed the presence of a 1.4 nm thick carbonaceous layer on top of the β -sultone layer, probably from contamination from the air. The observed F/C ratio (2.4), when taking into account only the carbon fraction bound to F atoms, is close to the theoretical value of 2, while the S/C ratio was 0.14 (expected 0.3). These values are in agreement with those observed by Fierro *et al.*,²⁶ where the β -sultone moiety was used for the functionalization of amorphous silica gel.

With FT-IR analysis the single layer of organic acid was not detectable. The thickness of the flat surface was measured by ellipsometry to give an average value of 2.3 nm. The result is in agreement with the expected thickness of a single layer of β -sultone together with the deposited carbon layer. Additionally, an XPS simulation of the attenuated carbon signal indicated a 0.8 nm β -sultone layer underneath the adventitious carbon.

The same procedure was applied for the functionalization of a glass microreactor. A solution of β -sultone (**1**) in dry toluene was flowed through the microstructured reactor and allowed to react for 4 h at 75 °C. This simple

procedure allowed the functionalization of the inner surface of the microreactor by a single layer of perfluorinated sulfonic acid. The unreacted reagent was washed away by extensive rinsing with toluene. The microreactor used consisted of a two inlets Y-shaped mixing portion and an outlet for the collection of the sample. Two reactors were used, differing in the internal volume (13 μL and 0.3 μL , Figure 3.1). The thus obtained platform was applied in different continuous flow acid-catalyzed reactions.

Figure 3.1 Schematic representation of the glass microreactors used and their specifications.

3.2.2 Sulfonic acid-catalyzed reactions

The sulfonic acid-functionalized microreactor was tested in the deprotection reaction of benzaldehyde dimethyl acetal (BDMA **2**, Scheme 3.2).²⁸ BDMA and water were dissolved in acetonitrile and flowed through the 0.3 μL device at room temperature. This microreactor gave rise to short residence times (4-72 s) using flow rates ranging from 4 to 0.250 $\mu\text{L min}^{-1}$. The conversion of the reaction at different residence times was followed by GC, checking the formation of benzaldehyde (**3**), which was the only product formed.

Scheme 3.2 Deprotection of benzaldehyde dimethyl acetal (**2**).

The conversion profile for the formation of benzaldehyde (**3**) is shown in Figure 3.2. The system turned out to be highly active in the deprotection reaction, reaching already full conversion in about 60 seconds of residence time. Assuming a full coverage of the inner surface of the microreactor by β -sultone, a catalyst loading of 0.01 w/w% was calculated. A first order fitting of the experimental data gave a rate constant of $(6.3 \pm 0.7) \times 10^{-2} s^{-1}$. Gill *et al.*²⁹ investigated the use of four different sulfonic acid-functionalized silica nanoparticles in the hydrolysis of BDMA. Best results were obtained when a perfluorosulfonic acid catalyst was employed, reaching full conversion within 5 minutes. Our results demonstrate the enhanced activity provided by the use of a sulfonic acid monolayer-functionalized microfluidic platform.

Figure 3.2 Formation of benzaldehyde (**3**) by hydrolysis of BDMA (**2**, $5 \times 10^{-3} M$) in a β -sultone-functionalized microreactor at different residence times at room temperature.

When a bare microreactor was used without functionalization, a negligible conversion (< 5%) was detected using the same reaction conditions, confirming that the perfluorosulfonic acid groups are responsible for the catalytic activity.

Furthermore, the Friedlander annulation of 2-aminobenzophenone (**4**) and ethyl acetoacetate (**5**) to give quinoline derivative **6** was tested under continuous flow conditions using the acid-functionalized microreactor (Scheme 3.3).³⁰

Scheme 3.3 Friedlander synthesis between 2-aminobenzophenone (**4**) and ethyl acetoacetate (**5**).

2-Aminobenzophenone (**4**) was flowed through the 13 μL microreactor with a twofold excess of ethyl acetoacetate (**5**) in acetonitrile at 70 °C, in order to have residence times of 2-13 min (flow rates in the range of 1-5 $\mu\text{L min}^{-1}$). The course of the reaction was monitored by on-line UV spectroscopy following the disappearing of the absorbance of compound **4** at a wavelength of 374 nm (Figure 3.3). The formation of quinoline derivative **6** was unequivocally proven using GC analysis excluding the possibility that the decrease of absorbance originates from an acid-base reaction. Assuming a full coverage of the inner surface of the microreactor with the β -sultone moiety, a loading of 15 w/w% of catalyst was calculated.

Figure 3.3 Conversion of 2-aminobenzophenone (**4**; 3×10^{-5} M) in a β -sultone-functionalized microreactor at different residence times ($T = 70$ °C).

Many literature examples of the acid-catalyzed Friedlander synthesis using 2-aminobenzophenone (**4**) and ethyl acetoacetate (**5**) give yields up to 90% for longer reaction times (13 min vs 2.5 h), using about 100-fold higher concentrations, mostly at higher temperatures, and at a comparable amount of catalyst employed.³¹ No conversion was detected when a bare microreactor was used, thus again confirming the catalytic role of the perfluorinated sulfonic acid moiety.

In order to prove the wider applicability of our catalytic platform, the sulfonic acid-functionalized microreactor was tested in the acid-catalyzed cyclization of pseudoionone (**7**) in the apolar methylcyclohexane to give α - (**8**) and β -ionone (**9**; Scheme 3.4). α -Ionone is widely used in the synthesis of perfumes and cosmetics, whereas β -ionone is a precursor in the synthesis of vitamin A and β -carotene.³²

Scheme 3.4 Cyclization of pseudoionone (**7**).

A solution of the starting reagent **7** in methylcyclohexane was introduced in the 13 μL microreactor and allowed to react at different reaction times (flow rates between 1 and 15 $\mu\text{L min}^{-1}$) at 80 $^{\circ}\text{C}$. The reaction was followed by on-line UV detection by monitoring the disappearing of the reagent absorbance at $\lambda = 282 \text{ nm}$. As confirmed in a separate lab scale experiment, the α -isomer (rac-**8**) is the main reaction product while the β -isomer (**9**) is formed in $< 2\%$.³³ The conversion profile of pseudoionone (**7**) in the acid-functionalized device is shown in Figure 3.4.

Figure 3.4 Conversion of pseudoionone (**7**; 10^{-5} M) in a β -sultone-functionalized microreactor at different residence times ($T = 80 \text{ }^{\circ}\text{C}$).

The experimental data gave rise to a first order rate constant of $(3.5 \pm 1.0) \times 10^{-1} \text{ min}^{-1}$ showing a conversion of pseudoionone (**7**) up to 60% in less than 15 min residence time (catalyst loading of 40 w/w%). The use of a macroreticular sulfonic-perfluorinated polystyrene ion-exchange resin by Lin *et al.*³⁴ displayed a conversion of 70% in a reaction time of 30 minutes using 0.2 M pseudoionone (**7**). Therefore, the β -sultone-functionalized device again confirmed its excellent properties under the reaction conditions used. No conversion was observed when the reaction was carried out in a bare microreactor under the same conditions.

The microfluidic catalytic platform could be used continuously for several runs maintaining its activity. However, in the deprotection of BDMA (Scheme 3.2) a decrease in activity after 6-7 h of continuous utilization was observed. This gradual deactivation over time may be due to the possible hydrolysis of the Si-O-C bond under the conditions used.²³ Gill *et al.*²⁹ claim that the presence of water may be responsible for this hydrolysis, while some of the activity could be due to the formed free sulfonic acid. Preliminary experiments to block the possible residual free silanol groups by reaction with *n*-dodecyldimethylmethoxy silane or the introduction of an extra C-3 spacer between the surface and the sulfonic acid did not affect the stability of the layer. Despite the decrease in activity over time, simple treatment of the microreactor with a fresh solution of β -sultone (**1**) ensured the recovery of the initial activity and its use for several consecutive runs. The use of apolar media, as in the cyclization of pseudoionone (Scheme 3.4), showed a markedly slow decrease in activity, and the reaction could be run for at least two consecutive days without loss of activity.

3.3 Conclusions

In this chapter a simple procedure was presented to functionalize the inner walls of a glass microreactor with strong perfluorosulfonic acid groups via single-step anchoring of β -sultone (**1**). Although there is only a catalytic monolayer present, the system turned out to be highly active in different acid-catalyzed reactions. In other examples¹²⁻¹⁵ the inner walls had to be coated, via a rather laborious procedure, with polymer brushes containing many catalytic sites to induce a reasonable catalytic activity. The combination of heterogeneous acid catalysis with continuous flow syntheses follows the lines of the growing environmental protection and green chemistry issues. The easy introduction of a catalytic monolayer on the inner wall microreactor is very promising for other types of catalysts to study a variety of reactions in a simple way.

3.4 Experimental

3.4.1 Materials and equipment

The chemicals and solvents were purchased from Sigma Aldrich unless otherwise stated and were used without purification unless specified. 1,2,2-Trifluoro-2-hydroxy-1-trifluoromethylethanesulphonic acid sultone (95%) (**1**) was purchased from ABCR chemicals. Water was purified with the Milli-Q pulse (Millipore, R = 18.2 M Ω cm) ultra pure water system. Acetonitrile and toluene were purified through a solvent purification system dispensing ultra dry solvents (MBraun, MB-SPS-800).

Gas chromatography (GC). GC experiments were performed with an Agilent DB-5MS UI column (30 m $\times$ 0.32 mm i.d., 25 μ m film thickness) with a constant pressure of 11.9 psi.

In-line UV. These experiments were carried out using a micro HPLC flow-through cell (ZEUTECH opto-elektronik, Germany), with a spectral UV/VIS/NIR range of 250-2500 nm, an optical path length of 10 mm, and an internal volume of 2 μ L. The flow cell is connected, via 2 optical fibers (SR 600 nm, Ocean optics Inc., The Netherlands), to a miniature deuterium halogen light source (DT-Mini-2-GS, Mikropack GmbH, Germany) and to a high-resolution miniature fiber optic spectrometer (HR4000, Ocean optics Inc., The Netherlands).

Ellipsometry. These measurements were performed with a plasmon ellipsometer (λ = 632.8 nm) assuming a refractive index of 1.5 for the organic compound.

XPS. For X-ray photoelectron spectroscopy (XPS) a Quantera Scanning X-ray Multiprobe instrument was used, equipped with a monochromatic Al K α X-ray source producing approximately 25 W of X-ray power. XPS-data were collected from a surface area of 1000 $\times$ 300 μ 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.

FT-IR. This analysis was performed using a Nicolet 6700 instrument (Thermo Scientific) in transmission mode.

3.4.2 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 μ L flat tip syringes (Hamilton). Syringes were connected to fused silica capillaries (100 μ m i.d., 362 μ 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. The temperature in the microreactor was controlled by interfacing a thermoelectric module with a heat sink to the microreactor. The temperature variation on the glass surface of the microreactor measured with a thermocouple was $< \pm 0.1$ °C. A glass microreactor with a residual volume of 13 μ L (dimensions: 150 μ m width and 150 μ m depth) and one with a residual volume of 0.3 μ L (dimensions: 150 μ m width and 20 μ m depth) were purchased from Micronit Microfluidics.

3.4.3 Functionalization of flat silicon dioxide surface and microreactor

1,2,2-Trifluoro-2-hydroxy-1-trifluoromethylethanesulphonic acid sultone (β -sultone; **1**) was grafted on a flat silicon dioxide surface and within a glass microreactor in an analogous procedure as reported in literature.²³ Both the silicon surface and the microreactor 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 cleaned silicon wafers were soaked in a 0.1 M solution of β -sultone (**1**) in dry toluene and kept for 4 h at 75 °C. For functionalization in the device the same solution was flowed for 4 h at a flow rate of 0.05 $\mu\text{L min}^{-1}$ at 75 °C. Silicon wafers and microchannels were rinsed with dry toluene to remove the unreacted reagent and dried with a stream of nitrogen.

3.4.4 Catalytic studies inside the microreactor

Benzaldehyde dimethyl acetal (**2**; BDMA, 5 mM) and water (10 mM) were dissolved in dry acetonitrile and passed through a 0.3 μL internal volume microreactor kept at room temperature at flow rates from 4 $\mu\text{L min}^{-1}$ to 0.250 $\mu\text{L min}^{-1}$. The reaction products were collected and analyzed off-line by GC.

2-Aminobenzophenone (**4**; 30 μM) and ethyl acetoacetate (**5**; 60 μM) in dry acetonitrile were passed through a 13 μL internal volume microreactor kept at 70 °C at flow rates varying from 15 $\mu\text{L min}^{-1}$ to 1 $\mu\text{L min}^{-1}$. The reaction was monitored by on-line UV, with the outlet of the device connected to the UV flow cell through a back pressure regulator. The conversion curve was obtained by monitoring the disappearing of the 2-aminobenzophenone (**4**) absorption at a wavelength of 374 nm. The consumption of the reagent corresponds to the formation of quinoline **6**, with no side products being formed.

A 15 μM solution of pseudoionone (**7**) in methylcyclohexane was passed through a 13 μL internal volume reactor at 80 °C at flow rates varying from 15 $\mu\text{L min}^{-1}$ to 1 $\mu\text{L min}^{-1}$. The reaction profile was monitored by on-line UV connecting the outlet of the device to a UV flow cell through a back pressure regulator. The conversion profile was determined by disappearance of the reagent absorption at 282 nm.

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Chapter 4

Improved catalytic activity and stability using mixed sulfonic acid and hydroxy-bearing polymer brushes in microreactors*

Sulfonic acid-bearing polymer brushes were grown on the inner walls of continuous flow glass microreactors and tested in the acid-catalyzed hydrolysis of benzaldehyde dimethyl acetal. Randomly 1:1 mixed polymer brushes of poly-3-sulfopropyl methacrylate (PSPM) and poly-2-hydroxyethyl methacrylate (PHEMA) showed a 6-fold increase in the turnover frequency (TOF) compared to the solely PSPM-containing microreactor. This remarkable improvement is attributed to the cooperative stabilizing effect of proximal OH groups on the active sulfonic acid moieties within the brush architecture. In fact, the rational mixing of SPM with methyl methacrylate (MMA) as an OH-free comonomer caused a drop in the activity of the resulting catalytic platform. A 5-fold increase of the turnover number (TON) of the 1:1 PSPM-PHEMA versus the PSPM homopolymer brush systems additionally demonstrates the substantial increase of the stability of the mixed brush catalytic platform, which could be continuously run over 7 days without significant loss of activity. The 1:1 PSPM-PHEMA mixed brush catalytic system also showed good activity in the deprotection of 2-benzyl tetrahydropyranyl ether.

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4.1 Introduction

Catalysts anchored within a microstructured reactor offer the possibility of easy product separation, reuse of the catalyst, and less waste, all of which play a central role in modern organic synthesis in adherence to the so-called ‘green parameters’.^{1,2} However, despite the numerous examples of chemical reactions in microfluidic devices,³ less effort has been put towards the development of on-chip catalysis.⁴ Within the field of supported catalysis, many studies have made use of packed-bed microreactors, in which the catalyst is anchored to different supports and therefore ‘packed’ within the chip.⁵⁻⁸ Despite the increased active surface for catalyst anchoring, this approach suffers from high back-pressure developed along the channel, a random bead distribution, and a broad residence time. By using microreactors with wall catalysts, good control over the reaction conditions can be achieved⁹ as demonstrated for several examples.¹⁰⁻¹²

Polymer brushes offer a versatile method for surface functionalization.¹³ They consist of polymeric structures tethered at one end to a solid substrate, and the distance between neighboring chains influences the architecture of the brush.¹⁴ The great interest for polymer brushes arises from the possibility of tuning the surface properties of a material by growing chains with the desired functionalities. With respect to this, polymer brushes bearing catalytic moieties have gained considerable attention, combining a high local concentration of catalyst to the versatility of supported active sites.¹⁵⁻¹⁸ Recently, our group has developed a new strategy for the anchoring of polymer brushes within microfluidic reactors bearing a wide range of catalysts, such as organic,¹¹ metallic,¹⁹ enzymatic,²⁰ and Lewis-acidic.²¹ Interestingly, this approach combines continuous flow-supported catalysis and the possibility to fine-tune the type of active catalytic sites employed as well as their loading.²²

Acid catalysis plays a central role in organic synthesis, especially in industry. However, the use of mineral acids in a homogeneous fashion is still predominant.

Nevertheless, the transition from homogeneous to heterogeneous acid catalysis is an active research field,²³ with sulfonic acid moieties supported onto ion-exchange resins,²⁴ ordered mesoporous materials,²⁵⁻²⁷ and amorphous carbon.²⁸ To this regard, the use of solid acid catalysis using polymer brushes grown onto silica,²⁹ mesoporous polymers,³⁰ and particles³¹ is well documented.

At present, heterogeneous acid catalysis in continuous flow reactors is mostly carried out using packed-bed reactors of supported acids.^{32,33} In Chapter 3 a single step functionalization of the inner walls of glass microreactors by a strong perfluorosulfonic acid has been described and its activity in different acid-catalyzed reactions was shown.³⁴

This chapter aims to study the grafting of sulfonic acid-bearing polymer brushes onto the walls of microreactors and investigate their catalytic activity in a model reaction, the hydrolysis of benzaldehyde dimethyl acetal. Mixed brushes grown from a 1:1 mixture of 3-sulfopropyl methacrylate (SPM) and 2-hydroxyethyl methacrylate (HEMA) are compared to homopolymer brushes of SPM to study the effect of an OH group-bearing comonomer on the catalytic activity and stability that could be expected from a proximity effect created within the brush architecture. A kinetic study using the model reaction is performed to assess the activity and stability of the two catalytic microreactors. To investigate the influence of the OH groups, SPM was also copolymerized with an OH-free monomer, *i.e.* methyl methacrylate (MMA), as a control. In addition, the reaction scope of the 1:1 PSPM-PHEMA catalytic brush system was extended to the deprotection of 2-benzyl tetrahydropyranyl ether.

4.2 Results and discussion

4.2.1 Flat surface and microreactor functionalization

The growth and characterization of sulfonic acid-bearing polymer brushes were first performed on a flat silicon dioxide surface. First, a self-assembled monolayer

(SAM) of an atom transfer radical polymerization (ATRP) initiator (**1**) was deposited according to a literature procedure.³⁵ Afterwards, different mixtures of methacrylate monomers (**2**) were grown via ATRP yielding homopolymer brushes of PSPM and mixed brushes of PSPM-PHEMA and PSPM-PMMA (Figure 4.1).

Figure 4.1 General procedure for the functionalization of a flat silicon dioxide surface and glass microreactors by poly-3-sulfopropyl methacrylate (PSPM), mixed brushes of PSPM with poly-2-hydroxyethyl methacrylate (PHEMA), and mixed brushes of PSPM with poly-(methylmethacrylate) (PMMA).

PSPM was grafted following a procedure reported in literature, where 3-sulfopropyl methacrylate potassium salt monomer (SPM) was dissolved in a degassed methanol/water solvent mixture with bipyridyl and copper salts.³⁶ The mixed brushes were synthesized using 1:1, 2:1, and 1:2 molar ratios of the two monomers, SPM-HEMA and a 1:1 molar ratio for SPM-MMA, which were dissolved in a degassed methanol/water (3:1 v/v) mixture containing bipyridyl and copper salts. Finally, all the polymer brush-functionalized surfaces were treated with a 2 M HCl solution to obtain the catalytic SO_3H active sites.

Water contact angle measurements of the initiator-functionalized samples showed a static contact angle value of 85° . Upon polymerization the value

decreased considerably to below 30° , due to the high hydrophilicity of the brushes, also in the case of the mixed PSPM-PMMA. The value of the contact angle stayed below 30° after activation of the sulfonic acid groups by HCl.

Transmission FT-IR of the PSPM homopolymer (Figure 4.2) indicated successful surface functionalization as demonstrated by the stretching of the carbonyl peak at around 1720 cm^{-1} , CH_2 bending vibrations around 1450 cm^{-1} , the asymmetric sulfonate stretching around 1200 cm^{-1} , and the symmetric sulfonate stretching around 1045 cm^{-1} .³⁶ The strong band at around 1100 cm^{-1} belongs to the Si-O-Si stretching of the silicon substrate. Upon treatment with HCl, the intensity of the carbonyl absorbance remained the same, indicating no substantial hydrolysis or polymer detachment from the surface, whereas both the asymmetric and the symmetric sulfonate stretching decreased. The FT-IR spectrum of the PSPM-PHEMA mixed brushes displayed the same peaks as PSPM as well as a broad band around 3500 cm^{-1} belonging to the HEMA OH groups (not shown).

Figure 4.2 Transmission FT-IR spectrum of a PSPM-functionalized flat SiO_2 surface.

X-ray photoelectron spectroscopy (XPS) was performed after HCl treatment for the brush-functionalized surfaces. The experimental data reported in Table 4.1 supports the expected random (co)polymerization for the (mixed) brushes, the

experimental values being in excellent agreement with the theoretical atomic ratios. The sulfur content in the PSPM-PMMA brush was around 20% higher than the theoretical value for a 50:50 monomer mixture, suggesting a SPM:MMA 60:40 ratio. Potassium was not detected, thus confirming the sulfonic acid activation, supported by the sulfur S_{2p} spectra that showed a binding energy fitting the $C-SO_3$ bond. In all cases the thickness of the brush layers exceeded 20 nm (*vide infra* for the exact values), thereby the interference of the silicon substrate and of the SAM of the initiator could be excluded from the analysis.

Table 4.1 XPS data of PSPM, PSPM-PHEMA, and PSPM-PMMA-functionalized silicon dioxide surfaces.

Atomic ratio	PSPM		PSPM-PHEMA						PSPM-PMMA	
			1:1		2:1		1:2		1:1	
	Theor	Exp	Theor	Exp	Theor	Exp	Theor	Exp	Theor	Exp
C/S	7	7.1	13	12.6	10	9.0	19	17.0	12	9.8
C/O	1.4	1.4	1.6	1.8	1.5	1.5	1.7	1.7	1.7	1.6

The thickness of the different polymer brushes on flat surfaces was determined by ellipsometry (Table 4.2). Using the same polymerization times in flow, the film thicknesses in the microreactors were estimated to have the same values, as proven in a previous study.¹¹

Table 4.2 Polymerization times and correspondent ellipsometric thicknesses for PSPM, PSPM-PHEMA, and PSPM-PMMA polymer brushes on flat silicon dioxide surfaces.

System	Polymer. time (min)	Thickness (nm)
PSPM	45	92
PSPM-PHEMA (1:1)	40	55
PSPM-PMMA	50	83

The same procedures described for the flat surfaces were followed for the functionalization of several glass microreactors (Figure 4.1). After the activation of the inner surface, the solution of the ATRP initiator (**1**) in toluene was flowed through the channel overnight. The initiator-functionalized chip was subsequently reacted with the monomer mixtures (**2**) for the aforementioned polymerization times. A 2 M solution of HCl was finally flowed through the channel for 2 hours to activate the sulfonate groups.

4.2.2 Catalytic activity

To prove the validity of the catalytic systems, the hydrolysis of benzaldehyde dimethyl acetal (**3**, BDMA) was chosen as a model reaction (Scheme 4.1).³⁷ A mixture of BDMA (**3**) and water in acetonitrile was flowed continuously through the brush-functionalized microreactors at room temperature. The formation of benzaldehyde (**4**) was followed by GC, confirming that there are no side products forming during the course of the reaction.

Scheme 4.1 Acid-catalyzed hydrolysis of benzaldehyde dimethyl acetal (**3**).

At first, the catalytic activity of the sulfonic acid-bearing polymer brushes of the PSPM homopolymer was investigated. Exploiting the high local concentration of catalyst created in the brush film, the system turned out to be highly active in the acid-catalyzed test reaction reaching conversions up to 90% within a few minutes of residence time. To perform a kinetic study for the hydrolysis of BDMA (**3**), its concentration was varied in the range from 10-30 mM using an excess of water to achieve pseudo-first-order kinetics (Figure 4.3). For each BDMA concentration a

pseudo-first-order rate constant was calculated, specifically 0.45 min^{-1} at 10 mM, 0.34 min^{-1} at 20 mM, and 0.22 min^{-1} at 30 mM. The amount of catalyst loaded in the microreactor was calculated based on the volume that the brush architecture occupies, considering the internal surface available for functionalization ($3.47 \times 10^{14} \text{ nm}^2$) and a polymer thickness of 92 nm as measured on a flat surface using the same experimental conditions. Assuming a brush density close to that of the bulk material (1 g mL^{-1}) results in a loading of 130 nmol. For all substrate concentrations a turnover frequency (TOF) value of around $1.0 \times 10^{-2} \text{ s}^{-1}$ was calculated, demonstrating that the amount of catalyst controls the rate of the reaction.

Figure 4.3 Formation of benzaldehyde (**4**) within a PSPM-functionalized microreactor at different BDMA (**3**) concentrations: (●) 10 mM, (◆) 20 mM, (■) 30 mM. [Water] = 100 mM.

A control experiment was carried out to assess that the observed activity is due to the anchored brush. First, the microreactor was ‘deactivated’ by an ion-exchange reaction with a 1 M aqueous K_2CO_3 solution to obtain an inactive salt form of the brushes. Afterwards, the test reaction was repeated under the same conditions showing a marginal conversion ($< 5\%$) for a residence time up to 7 min.

Subsequently, the chip was reactivated with a 2 M solution of HCl and the pristine activity could be restored, thus confirming the role of the sulfonic acid moieties as active catalysts.

To study the effect of temperature on the stability of the polymeric architecture, the brush-functionalized microreactors were kept at 80 °C in acetonitrile for at least 6 h. Afterwards, the hydrolysis of BDMA (**3**) was carried out under the standard conditions retaining the pristine activity, thus excluding any alteration of the catalytic active sites.

For potential applications, the long term stability of the catalytic platform is of importance. To this respect, stability studies carried out with the PSPM-functionalized microreactor at a fixed residence time (3.25 min) showed that the system could be run for 3 days with a marginal decrease in activity for the test reaction. After this term, however, progressive deactivation of the catalytic active sites required reactivation by means of a fresh HCl solution, which restored the pristine activity. The reason for the deactivation may be found in the replacement of the active SO_3H proton with contaminant cations present.

To improve the activity of the brush catalysts, the use of mixed brushes was considered. In this approach an appropriate monomer was introduced to stabilize the catalytically active sites, exploiting the proximity effect created in the brush environment.³⁸ This was verified by introducing OH group-bearing polymer brushes in the polymeric system, using the HEMA monomer. Therefore, a kinetic study of the catalytic test reaction (Scheme 4.1) was repeated with the 1:1 PSPM-PHEMA-functionalized microreactor under the same experimental conditions as used with the PSPM homopolymer (Figure 4.4).

Figure 4.4 Formation of benzaldehyde (**4**) within a 1:1 PSPM-PHEMA-functionalized microreactor at different BDMA (**3**) concentrations: (●) 10 mM, (◆) 20 mM, (■) 30 mM. [Water] = 100 mM.

In this case, pseudo-first-order rate constants of 1.17 min^{-1} , 0.77 min^{-1} , and 0.51 min^{-1} were calculated for 10, 20, and 30 mM BDMA (**3**) concentrations, respectively. The amount of active sites was determined to be 51 nmol of catalyst, calculated based on the same assumptions as described for the homopolymeric system, taking into account the thickness measured on an equivalent flat surface (55 nm) and the presence of half of the sulfonic acid moieties (50:50 monomer ratio). TOF values for the different concentrations of **3** are presented in Table 4.3, showing an average of $6.0 \times 10^{-2} \text{ s}^{-1}$.

Comparing the TOFs of the two catalytic systems highlights a remarkable six times larger value for the 1:1 PSPM-PHEMA mixed brushes, compared with the use of PSPM (Table 4.3). These results clearly show the influence of the proximal OH groups of PHEMA on the sulfonic acid moieties, most probably *via* hydrogen bonding. In fact, in a recent work by Kass *et al.* it has been demonstrated that hydrogen bonds can improve the catalytic activity and enhance Brønsted acidities, especially through stabilization of the conjugate bases.³⁹ In a similar way, enzyme

active sites make use of hydrogen bonds to stabilize transition-state structures by delocalizing negatively charged centers.⁴⁰

Table 4.3 TOF values for the hydrolysis of BDMA (**3**) in PSPM and 1:1 PSPM-PHEMA-functionalized microreactors at different concentrations of BDMA (**3**).

[3] (mM)	TOF (10^{-2} s^{-1})		
	PSPM	PSPM-PHEMA	Ratio
10	0.8	5.0	6.3
20	1.1	6.5	5.9
30	1.1	6.5	5.9

In a similar way as described for the homobrushes, the 1:1 PSPM-PHEMA brushes could be deactivated and reactivated by treatment with a 1 M aqueous K_2CO_3 solution and 2 M HCl, respectively. The two brush systems showed similar behavior, also when a much lower concentration of 20 μM K_2CO_3 was used. This means that the OH groups do not affect the blocking by cations.

In order to further study the influence of the number of OH groups on the activity of the system, 2:1 PSPM-PHEMA and 1:2 PSPM-PHEMA mixed brushes were prepared, having 33% less and more OH groups, respectively, compared with the standard 1:1 mixed polymer. XPS data confirmed that the two monomers, SPM and HEMA, mix randomly and follow the ratio used in the feeding solution (Table 4.1). For both catalytic systems the TOF values of the model reaction were determined (Table 4.4). Clearly, the best activity was obtained with the 1:1 mixed system. The TOF value for the 2:1 PSPM-PHEMA system was considerably lower than that of the 1:1 mixed system. Apparently, the presence of fewer OH groups gives rise to a decrease in the activity. The 1:2 PSPM-PHEMA mixed system showed a higher activity than the 2:1 PSPM-PHEMA mixed system, where the OH groups play their stabilizing role, however, with fewer active sites.

Table 4.4 TOF values for the hydrolysis of BDMA (**3**, 10 mM) for different PSPM-PHEMA-functionalized microreactors.

PSPM-PHEMA	TOF (10^{-2} s^{-1})
1:1	5.0
2:1	0.1
1:2	1.2

Interestingly, PSPM-PHEMA mixed brushes turned out to improve also the stability of the catalytic platform. As evident from Figure 4.5, the mixed brush-functionalized microreactor could be run for at least seven consecutive days maintaining a substantial activity in the catalytic test reaction. Strikingly, direct comparison with the PSPM homopolymer highlights the stabilizing effect of the HEMA moieties. However, in case of a PSPM-PMMA mixed brush microreactor containing OH-free methyl methacrylate (MMA), the overall activity for 3.25 min residence time was only around 30%, while the reusability was limited to two days of continuous use (Figure 4.5).

Figure 4.5 Hydrolysis of BDMA (**3**) in a PSPM, 1:1 PSPM-PHEMA, and PSPM-PMMA-functionalized microreactor. [**3**] = 10 mM; [water] = 100 mM; residence time = 3.25 min.

A TON of 470 was calculated for the PSPM catalytic system, while that for the mixed PSPM-PHEMA brush system was of 2200, involving an approximately 5-fold increase. The TON for the PSPM-PMMA microreactor was only 82. This unequivocally assesses the improved catalytic activity and stability of the PSPM-PHEMA mixed brush system.

The 1:1 PSPM-PHEMA catalytic system was employed in another acid-catalyzed reaction to study its wider applicability. Preliminary results showed a good activity for the deprotection of tetrahydropyranyl (THP) ethers. THP is one of the most common and useful protecting groups for alcohols and phenols.⁴¹ A variety of deprotection methods of THP groups in the presence of other functional groups were carried out using acidic, neutral, and reductive media. However, most of these methods involve tedious work-up, heating, highly toxic reagents, quantitative amounts of reagents, and formation of numerous side products. The use of a continuous flow solid acid catalyst may be beneficial to overcome these drawbacks. The deprotection of 2-benzyl-THP (**5**) to give benzyl alcohol (**6**) was chosen as test reaction (Scheme 4.2). This reaction performed in the 1:1 PSPM-PHEMA catalytic system reached 70% conversion at a residence time of 6.5 min. No side products were detected during the course of the reaction, confirming the advantage of the mixed-brush catalytic system.

Scheme 4.2 Acid-catalyzed deprotection of benzyl-THP (**5**).

4.3 Conclusions

The effective use of sulfonic acid-bearing polymer brushes (PSPM) in continuous flow microreactors for the hydrolysis of benzaldehyde dimethyl acetal has been described. The grafting of a 1:1 mixed PSPM-PHEMA brush system resulted in a remarkable increase in catalytic activity and stability, evident from a 6-fold increase of the TOF and 5-fold increase of the TON. This behavior was attributed to the cooperative effect of the OH groups in stabilizing the sulfonic acid moieties, due to the environment created within the brush architecture. In fact, when PMMA was used as co-monomer, *i.e.* in the absence of OH groups, the activity of the catalytic system dropped considerably. By using mixed-brush systems with different percentages of HEMA monomer, thus by varying the number of OH groups present, it turned out that the best catalytic activity was obtained for a presence of about 50% OH groups. Moreover, the 1:1 PSPM-PHEMA mixed system effectively catalyzed the deprotection of 2-benzyl tetrahydropyranyl ether (benzyl-THP).

This approach will be promising to study a wide range of acid-catalyzed reactions in a continuous flow microreactor since both the number of the active sites and the activity and stability of the catalytic system can be fine-tuned.

4.4 Experimental

4.4.1 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. 3-(5'-Trichlorosilylpentyl) 2-bromo-2-methylpropionate was synthesized following a literature procedure.³⁵ CuBr was purified by washing with glacial acetic acid and, after filtration, by rinsing with ethanol and acetone, it was stored in a vacuum

desiccator. Methanol and ethanol (VWR, analytical reagent grade) were used without further purification, water was purified with the Milli-Q pulse (millipore, R = 18.2 M Ω cm) ultrapure water system, acetonitrile and toluene were purified through a solvent purification system dispensing ultra dry solvents (MBraun, MB-SPS-800).

Contact angle. Contact angles were measured on a Krüss G10 contact angle measuring instrument, equipped with a CCD camera.

GC, ellipsometry, XPS, and FT-IR. See Chapter 3.

4.4.2 Flow apparatus

For all microreactor experiments the same set up described in Chapter 3 was used. Glass microreactors with a residual volume of 13 μ L (dimensions: 150 μ m width and 150 μ m depth) were purchased from Micronit Microfluidics (see Figure 4.1).

4.4.3 Polymer brush functionalization of flat silicon dioxide surface and microreactor

Poly-3-sulfopropyl methacrylate. Immobilization of the trichlorosilane initiator and the PSPM brushes was carried out following literature procedures.³⁶ A solution of 3-sulfopropyl methacrylate sodium salt (4.0 g, 16.2 mmol), 2,2'-bipyridyl (156 mg, 1 mmol), and CuBr₂ (5 mg, 0.02 mmol) in a 2:1 mixture of methanol and water (9 mL) was degassed using the freeze-pump-thaw method (in a sealed Schlenk vessel). This solution was transferred in a degassed flask containing CuBr (60 mg, 0.42 mmol) and stirred for 30 min to ensure the complete dissolution of the solid. Afterwards an initiator coated silicon wafer was placed in a Schlenk tube and the flask sealed with a septum. The tube was filled with argon and the monomer solution was syringed inside. For the polymerization in the device, the same solution was syringed through the microchannel until the device was completely

filled. The solution was kept in contact with the silicon wafer and with the microchannel at a flow rate of $0.1 \mu\text{L min}^{-1}$ for 45 min. After the polymerization, the silicon wafer and the microchannel were rinsed with water and methanol, and dried with a stream of nitrogen. In the next step the silicon wafers were soaked in a 2 M solution of HCl. The same solution was flowed with a flow rate of $0.1 \mu\text{L min}^{-1}$ through the microreactor. After 2 h they were rinsed with water, acetone, and acetonitrile, and subsequently dried with a stream of nitrogen.

Mixed brushes of poly-2-hydroxyethyl methacrylate and poly-3-sulfopropyl methacrylate. A 1:1 molar ratio of the two monomers 2-hydroxyethyl methacrylate (1.95 g, 15 mmol) and 3-sulfopropyl methacrylate potassium salt (3.69 g, 15 mmol) were dissolved in a 3:1 solvent mixture of methanol and water (12 mL). To this solution were added 2,2'-bipyridyl (281 mg, 1.8 mmol) and CuBr_2 (8.4 mg, 0.04 mmol). The resulting mixture was degassed using the freeze-pump-thaw method (in a sealed Schlenk vessel). This solution was transferred in a degassed flask containing CuBr (107 mg, 0.75 mmol) and stirred for 30 min to ensure the complete dissolution of the solid. Afterwards an initiator coated silicon wafer was placed in a Schlenk tube and the flask sealed with a septum. The tube was filled with argon and the monomers solution was syringed inside. For the polymerization in the device, the same solution was syringed through the microchannel until the device was completely filled. The solution was kept in contact with the silicon wafer and with the microchannel at a flow rate of $0.1 \mu\text{L min}^{-1}$ for 40 min. After the polymerization, the silicon wafer and the microchannel were rinsed with water and methanol, and dried with a stream of nitrogen. In the next step the silicon wafers were soaked in a 2 M solution of HCl. The same solution was flowed with a flow rate of $0.1 \mu\text{L min}^{-1}$ through the microreactor. After 2 h they were rinsed with water, acetone, and acetonitrile, and subsequently dried with a stream of nitrogen.

The same procedure was followed for the growth of the 2:1 PSPM-PHEMA (20 mmol SPM, 10 mmol HEMA) and 1:2 PSPM-PHEMA (10 mmol SPM, 20 mmol HEMA) brush systems.

Mixed brushes of poly(methyl methacrylate) and poly-3-sulfopropyl methacrylate. These mixed polymer brushes were prepared using a 1:1 monomer molar ratio and following the same procedure as described for the PSPM-PHEMA mixed brushes.

4.4.4 Catalytic reactions inside the microreactor

Benzaldehyde dimethyl acetal (**3**; BDMA, 10 mM) and water (100 mM) were dissolved in dry acetonitrile and passed through a 13 μL internal volume microreactor kept at room temperature at flow rates varying from 10 $\mu\text{L min}^{-1}$ to 1 $\mu\text{L min}^{-1}$. The reaction products were collected and analyzed off-line by GC. For the kinetic study within a PSPM and PSPM-PHEMA-functionalized microreactors, the concentration of BDMA was varied in the range of 10-30 mM and the concentration of water was kept constant at 100 mM. Flow rates from 13 $\mu\text{L min}^{-1}$ to 2 $\mu\text{L min}^{-1}$ were used. The experimental error in these measurements is $\pm 4\%$.

2-Benzyl tetrahydropyranyl ether (**5**) was synthesized according to a literature procedure.⁴² A 10 mM solution of **5** in dry acetonitrile was passed through the 1:1 PSPM-PHEMA-functionalized microreactor at room temperature at a flow rate of 1 $\mu\text{L min}^{-1}$. The reaction product was collected and analyzed off-line by GC.

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4.6 References

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Chapter 5

Dendrimer-encapsulated Pd nanoparticles for continuous-flow Suzuki-Miyaura cross-coupling reaction*

Generation 3, 4, and 5 PAMAM dendrimers were used for the encapsulation of palladium nanoparticles (Pd NPs) and their covalent anchoring within glass microreactors. G3-encapsulated Pd NPs showed the highest activity for a model Suzuki-Miyaura cross-coupling (SMC) reaction, as compared to G4 and G5. A kinetic study indicated a role of the nanoparticle as a pro-catalyst from which molecular species are formed with an induction time of around one minute. The dendrimer-nanoparticle catalytic platform exhibited excellent reactivity (high turnover frequencies and numbers) as compared to other Pd NP flow reactors and dendrimer-encapsulated Pd NPs at batch scale. Moreover, the Pd microreactor exhibited a good stability, as witnessed by running the SMC reaction for more than seven days with a low Pd leaching of 1.2 ppm. The covalently attached dendrimers may play a crucial role in stabilizing the Pd NPs, a critical feature in flow SMC reactions.

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5.1 Introduction

Combining continuous flow microreactor technology and supported metal nanocatalysts improves the efficiency of several catalyzed organic reactions as well as their sustainability.¹ Metal nanoparticles show unique properties at the frontier between the bulk solid and the molecular state.^{2,3} Due to their small size (from one to a few tens of nanometers) and thus increased active surface, they show high chemical activity and specificity of interaction, all attractive features in catalysis, especially from an industrial point of view.^{4,5} Moreover, the possibility to support metallic nanoparticles onto a solid support makes them suitable for heterogeneous catalysis. In particular, they have been considered ideal candidates for the blend between homogeneous and heterogeneous catalysis.⁶⁻⁹ Anchoring the nanoparticles within continuous-flow reactors paves the way for chemistry to follow the so-called ‘green chemistry’ principles, designed to reduce or eliminate the negative environmental impact of chemical processes.¹⁰⁻¹³

Palladium is one of the most versatile metals in catalysis. In addition to hydrogenation reactions, it is being used in a number of C-C cross-coupling reactions.^{14,15} Among them, the Suzuki-Miyaura coupling (SMC) is one of the most used for the synthesis of a variety of biaryl derivatives, useful building blocks for active natural and pharmaceutical compounds.¹⁶⁻¹⁸ Although this reaction is typically catalyzed in a homogeneous manner, the use of palladium nanoparticles in a heterogeneous fashion is gaining increasing interest, especially for continuous-flow operation.¹⁹⁻²² The accepted mechanism for the Pd-catalyzed SMC involves the formation of Pd²⁺ species upon the oxidative addition of organic halides.¹⁵ In this regard, strong experimental evidence suggests that supported NPs may only act as a ‘reservoir’ for Pd²⁺, while these molecular species are responsible for the so-called (quasi)homogeneous catalytic mechanism.²³⁻²⁶ This aspect becomes even more stringent in continuous-flow operations, in which case the leached Pd is eventually ‘washed out’ of the reactor, as underlined in a recent review by Cantillo

and Kappe.²⁷ Inevitably, great focus is directed at the support for NP synthesis and stabilization within microreactors, to possibly reduce the leaching of molecular species. Numerous examples are already present in literature, ranging from silica-supported Pd NPs packed within the reactor channel,^{28,29} monoliths,^{30,31} surface thin films,³² magnetic nanoparticles,³³ and polymer brushes.³⁴

Dendrimers used for the encapsulation and stabilization of metal nanoparticles are attractive in catalysis owing to their favorable characteristics.^{35,36} Dendrimer-encapsulated NPs (DENs) show uniform size distribution in the range of 1-3 nm, while remaining protected from agglomeration. Moreover, the dendrimer periphery can act as a nanofilter (depending on the generation) and can be tailored to direct the anchoring to a solid support.^{37,38} Despite the great number of studies dealing with DENs in solution,³⁵ starting from the pioneering works of Crooks³⁹ and Tomalia,⁴⁰ there are only a few examples of their use in continuous flow microreactors, in which they are usually adsorbed on porous materials, such as SBA-15.^{41,42}

This chapter describes the use of covalently-anchored dendrimer-encapsulated Pd nanoparticles (Pd DENs) on the inner walls of glass microreactors. The thus formed catalytic system was tested in a continuous-flow SMC reaction between iodobenzene and *p*-tolylboronic acid. The influence of the dendrimer generation on the catalytic activity was investigated by using different PAMAM amino- and hydroxy-terminated dendrimers (Gn-NH₂ and Gn-OH, n = 3, 4, and 5). Despite the low amount of catalyst present, the system turned out to be very active for the test SMC reaction. A kinetic study of this reaction was used to gain information about the NP-mediated catalytic mechanism under continuous flow conditions. The influence of the dendrimer template on Pd leaching was assessed during a stability study using the same catalytic reaction.

5.2 Results and discussion

5.2.1 Functionalization of flat surfaces and microreactor channel walls

Pd DENs were anchored within glass microreactors and on flat silicon dioxide surfaces, the latter was used for characterization. First, the surface was functionalized with a suitable reactive monolayer, consisting of (3-aminopropyl)triethoxysilane (APTES) and *p*-phenylene diisothiocyanate (DITC), used for the attachment of PAMAM dendrimers.⁴³ In this way, amino- (Gn-NH₂) and hydroxy-terminated (Gn-OH) dendrimers were covalently attached to the monolayer through the formation of thiourea and *O*-thiocarbamate bonds, respectively.

Two different methodologies for the formation of Pd NPs within microreactors were employed, as depicted in Scheme 5.1. In one approach, Gn-NH₂ 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. This procedure could also be adopted for Gn-OH dendrimers. 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.⁴⁴ To this end, K₂PdCl₄ was added to an aqueous dendrimer solution so that Pd ions could be bound by the dendrimer and coordinated to its internal tertiary amino groups. Afterwards, NaBH₄ was added to yield Gn-OH(Pd) NPs. The thus formed catalysts were flowed within the microchannel and hence covalently attached to the monolayer-functionalized surface. Amino-terminated dendrimers could not be used in solution, most probably because the addition of a Pd salt results in immediate agglomeration and formation of a precipitate due to cross-linking of the dendrimers by Pd²⁺ ions.⁴⁵

Scheme 5.1 Formation of Pd DENs onto a flat silicon dioxide surface and within a glass microreactor.

Water contact angle measurements on flat surfaces showed the changes of the surface wettability upon each functionalization step. The values for the monolayer of APTES (55°) and DITC (70°) were similar to values reported in the literature.⁴⁶ The subsequent attachment of amino- or hydroxyl-terminated dendrimers was confirmed by contact angle measurements, giving values of 60° for NH_2 -terminated dendrimers and 50° for OH-terminated dendrimers.

UV-vis spectroscopy is a useful tool for analyzing the formation of DENs (Figure 5.1). The peak at about 230 nm for the oxidized Pd corresponds to a strong ligand-to-metal charge transfer (LMCT) band due to the complexation of Pd^{2+} with interior tertiary amino groups of the dendrimer. After reduction, the LMCT band disappears and is replaced by an exponential decay curve at lower energy, typical of NP formation. The small peak at around 290 nm may be due to a surface plasmon band of oxidized Pd species. This analysis was conducted using Gn-OH(Pd) , confirming the formation of encapsulated NPs according to previous studies of Crooks.^{47,48}

Figure 5.1 UV-vis spectra of 5 μM solutions of $\text{G3-OH(Pd}^{2+})$ and $\text{G3-OH(Pd}^0)$.

X-ray photoelectron spectroscopy (XPS) analysis revealed the presence of C, N, O, and Pd at the $\text{G3-NH}_2(\text{Pd})$ -functionalized silicon surface. An organic/metal layer of around 5 nm in thickness could be detected, calculated with respect to the Si_{2p} peak. This value is in good agreement with the expected thickness of a single layer of APTES-DITC-G3-NH₂, considering an average diameter for G3 PAMAM of 3.6 nm.⁴⁹ Moreover, the survey spectrum and the binding energies for Pd confirm its presence in the zerovalent state, with only a small percentage in the oxidized state, presumably due to exposure of the sample to air.

Transmission electron microscopy (TEM) was used to determine the size of the Pd NPs. Spherical particles with an average diameter of 2.4 ± 0.5 nm were found for G3-OH(Pd) NPs preformed in solution (Figure 5.2), in agreement with the expected 1-3 nm size for Pd NPs formed within dendrimer templates.⁴⁷

Figure 5.2 TEM image of G3-OH(Pd) NPs (left; scale bar 10 nm) and nanoparticle size distribution (right).

High-resolution scanning electron microscopy (HRSEM) performed onto a G3-NH₂(Pd)-functionalized surface showed a homogeneous NP distribution (Figure 5.3). The NPs on this surface were introduced following the *in situ* procedure. Prior to the SEM analysis, the surface was thoroughly rinsed with water in addition to ultrasonication to ensure removal of non-specifically bound Pd.

Figure 5.3 HRSEM of a G3-NH₂(Pd)-functionalized SiO₂ surface (scale bar 20 nm).

The same procedures were followed for the functionalization of several glass microreactors. First a solution of APTES in toluene was flowed through the microreactor for 15 h and subsequently reacted with a DITC solution in toluene. Different Gn-NH₂/OH dendrimers ($n = 3, 4, 5$) were anchored within the

monolayer-functionalized microreactor and palladium was introduced as aqueous solution of K_2PdCl_4 , and subsequently reduced by $NaBH_4$ to yield $Gn-NH_2(Pd)$ -functionalized microreactors. In addition, $Gn-OH(Pd)$ NPs ($n = 3, 4, 5$) were prepared in solution according to the procedure described above, and subsequently attached within the monolayer-functionalized microchannel.

5.2.2 Catalytic activity

The Pd DEN-functionalized microreactors were tested for their catalytic activity in a model Suzuki-Miyaura cross-coupling (SMC) reaction. To this end, a 1:1.5 mixture of iodobenzene (**1**) and *p*-tolylboronic acid (**2**) in ethanol was flowed continuously through the dendrimer-functionalized microreactors at different flow rates. Tetrabutylammonium hydroxide was used as a base and the temperature was set at 80 °C (Scheme 5.2).

Scheme 5.2 Suzuki-Miyaura cross-coupling reaction.

The microreactor system turned out to be highly active in the model SMC reaction, reaching high conversions within 10 min of residence time (Figure 5.4). The conversion was calculated by monitoring the formation of the biphenyl product (**3**) with GC. The side products of homocoupling and dehalogenation were also formed in the course of the reaction and accounted for less than 5% of the final product.²²

Figure 5.4 Formation of 4-phenyltoluene (**3**) in a G3-NH₂(Pd)-functionalized microreactor. [**1**] = 10 mM, [**2**] = 15 mM, [Bu₄NOH] = 20 mM.

To study the influence of the dendrimer generation on the catalytic activity of the encapsulated NPs, we selected G3, G4 and G5 PAMAM dendrimers. The choice of these dendrimer generations was based on the fact that only starting from generation 3, a real encapsulation effect is asserted by the dendrimer template.^{50,51} In fact, lower dendrimer generations mostly act as stabilizing agents, meaning that the NP is not located within the voids of a single dendrimer, but rather stabilized by peripheral groups of the dendrimer. For the model SMC reaction, the generation 3 PAMAM dendrimer gave rise to the highest activity compared to generations 4 and 5, as verified by the rate constants for the catalytic test reaction measured using hydroxy- and amino-terminated dendrimers (Table 5.1). In addition, the data confirms the similar reactivity of Gn-OH and Gn-NH₂ introduced within the microreactor following the different anchoring procedures described in Scheme 5.1.

Table 5.1 Apparent rate constant, k_{app} , for the reaction between iodobenzene (**1**) and *p*-tolylboronic acid (**2**) using Gn-NH₂/OH(Pd)-functionalized microreactors. [**1**] 10-30 mM [**2**] = 150 mM; [Bu₄NOH] = 160 mM; ethanol, 80 °C.

DENs	k_{app} (10 ⁻³ s ⁻¹)		
	G3	G4	G5
Gn-OH	13.8	2.3	4.3
Gn-NH ₂	10.5	4.7	5.1

The same trend was also found in batch scale reactions.⁵² The explanation for this behavior must be found in the dendrimer periphery. In fact, the higher the dendrimer generation, the more crowded its periphery, thus the dendrimer can act as a size-selective nanofilter to control the access of small molecules to its interior. Accordingly, an increase of the dendrimer generation is associated with a decrease in catalytic activity, explained by a higher resistance to mass transfer and/or passivation of the catalyst surface by functional groups for higher dendrimer generations.³⁶ For example, El-Sayed *et al.*⁵⁰ showed that the G4 dendrimer provided an effective protection of Pd particles, but the strong encapsulation within the dendrimers resulted in a loss of catalytic activity.

Having assessed that G3 dendrimers provide the highest activity, the focus was put on the catalytic role of the nanoparticles for the model SMC reaction, in terms of activity and stability. The reaction kinetics is a powerful tool to gain more insight into the catalytic mechanism. Despite the considerable attention paid to the optimization of the catalytic process and to the investigation of the active species involved, some aspects of the SMC reaction are not clear yet.^{25,53} Particularly active is the debate on whether the catalysis follows a completely homogeneous pathway, with the release of molecular species responsible for the catalytic activity,^{25,26,54} or occurs on the metal surface, especially at defects, edges, and corners.^{24,55}

Here, an excess of *p*-tolylboronic acid (**2**) was used to ensure pseudo-first order reaction conditions. The concentration of iodobenzene (**1**) was varied in the range from 10 to 30 mM and for each iodobenzene concentration, the flow rates were adjusted in order to ensure complete conversion (Figure 5.5). The pseudo-first order rate constants for the different concentrations of **1** are shown in Table 5.2. The fact that the overall yield is not affected by the iodobenzene concentration may be an indication of an overall first order reaction. Moreover, the sigmoidal shape observed for the conversion profile (Figure 5.4) suggests the occurrence of an induction period, which is typical for the presence or formation of a pro-catalyst.^{56,57} An induction time of about 1 min was deduced from the curves in Figure 5.5. Interestingly, the same induction period was observed for all substrate concentrations, thus providing evidence for the presence of leached molecular species responsible for the catalytic process, either in the form of a pro-catalyst or as dissolved ‘pool’ of active catalyst.

Figure 5.5 Formation of 4-phenyltoluene (**3**) in a G3-NH₂(Pd)-functionalized microreactor at different concentrations of **1**: ■ 10 mM, ● 20 mM, ▲ 30 mM; [**2**] = 150 mM; [Bu₄NOH] = 160 mM.

The total amount of catalyst within the microreactor was 0.12 μg as measured by total reflection X-ray fluorescence (TXRF). The catalyst mol% with respect to

the reagent concentration and the corresponding turnover frequency (TOF) values are shown in Table 5.2. Although a direct comparison is not straightforward due to the influence of the reagents on the overall SMC activity, the measured TOFs confirm the high reactivity of the described catalytic platform. In fact, the TOF values are considerably higher compared to SMC reactions catalyzed by other Pd NP systems in continuous flow operations^{29,58,59} as well as by using Pd DENs in batch scale synthesis.⁶⁰⁻⁶³

Table 5.2 Apparent rate constant, k_{app} , catalyst amount, and TOF for the SMC of iodobenzene (**1**) and *p*-tolylboronic acid (**2**) in a G3-NH₂(Pd)-functionalized microreactor at different concentrations of **1**. [**2**] = 150 mM; [Bu₄NOH] = 160 mM; ethanol, 80 °C.

[1] (mM)	k_{app} (10 ⁻² s ⁻¹)	Catalyst mol%	TOF (h ⁻¹)
10	0.6	1	2220
20	1.1	0.5	7680
30	1.1	0.3	11340

The use of supported Pd NPs under continuous flow conditions for SMC reactions poses the need to consider the stability of the metallic species against leaching (*vide supra*). In this regard, the G3-NH₂(Pd)-functionalized microreactor was run continuously over seven days showing little decrease of the catalytic activity for the model SMC reaction (Figure 5.6). TXRF measurements revealed a Pd leaching of 1.2 ppm under the conditions used. Although the leached Pd was little, it accounts for almost 10% of the whole catalyst loading in this time course. This confirms the ‘homogeneous pathway’ for the catalytic SMC reaction under continuous flow conditions, in which the NPs act as a source of homogeneous, probably ionic, catalytic Pd species. Nevertheless, the exceedingly high turnover number (TON) of 39560 for the catalytic system is a clear indication of the dendrimeric stabilizing effect,⁶⁴ especially compared to other Pd NP systems used for continuous flow SMC reactions.^{29,58} To this end, Kato *et al.*^{65,66} claim that the

isolated Pd species remain to a great extent coordinated to the dendrimer ligands, hence facilitating the return of Pd atoms to the mother NP as final step in the catalytic cycle.^{64,66}

Figure 5.6 Formation of 4-phenyltoluene (**3**) in a G3-OH(Pd)-functionalized microreactor under continuous use. [**1**] = 10 mM, [**2**] = 15 mM; [Bu₄NOH] = 20 mM; residence time: 13 min.

5.3 Conclusions

Small dendrimer-encapsulated Pd NPs (2.4 nm) were attached to the reactive monolayer-functionalized inner walls of glass microreactors. PAMAM generation 3 dendrimers gave rise to the highest activity of the Pd NPs in a model SMC of iodobenzene (**1**) and *p*-tolylboronic acid (**2**) as compared to generations 4 and 5, presumably due to the less crowded dendrimer periphery of G3 dendrimers. A kinetic study conducted for the SMC model reaction suggested the formation of Pd molecular species responsible for the catalytic activity within one minute of induction time. The high reactivity of the Pd DEN-functionalized reactor was confirmed by the TOFs measured at different concentrations of **1**. In fact, with a TOF as high as 11340, the system performed comparatively better than other SMC reactions catalyzed by Pd NPs in flow or by DENs at batch scale. The system could

be run for at least seven consecutive days exhibiting a satisfyingly high TON (39560). A little Pd leaching of around 1.2 ppm was measured under the conditions used.

Despite the inevitable leaching of Pd²⁺ species during cross-coupling reactions, especially under continuous flow operations,²⁷ the use of covalently-attached dendrimers as NP templates enables a prolonged activity.^{64,65} Moreover, DENs are versatile templates for a variety of metal species either as monometallic or bimetallic nanocomposites. Optimization of the reaction conditions to further decrease the metal leaching could be achieved by fine-tuning the different polarities of the catalyst material and solvent, as suggested recently by Somorjai *et al.*⁶⁷

5.4 Experimental

5.4.1 Materials and equipment

All chemicals and solvents were purchased from Sigma Aldrich and used without purification unless otherwise stated. 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 MΩ cm) ultrapure water system, toluene was purified through a solvent purification system dispensing ultra dry solvents (MBraun, MB-SPS-800).

GC, and XPS. See Chapter 3.

Contact angle. See Chapter 4.

UV-vis. 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.

HRSEM. For high resolution scanning electron microscopy (HRSEM) characterization a Zeiss 1550 FE-SEM was used.

TEM. 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 are obtained from TEM images with ImageJ software: for each sample at least 50 particles were measured.

TXRF. Total reflection X-ray fluorescence (TXRF) measurements were performed at the University of Münster using a S2-PICOFOXTM (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, XFlashTM). The software SPECTRA version 6.1.5.0 (Bruker AXS, Karlsruhe, Germany) was used for data evaluation.

5.4.2 Flow apparatus

See Chapter 3.

5.4.3 Dendrimer-encapsulated Pd NP functionalization of flat surfaces and microreactors

Deposition of a monolayer of APTES and DITC. Both the SiO₂ surface and the microreactor channels were cleaned with a Piranha solution (H₂SO₄:H₂O₂ 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.^{43,46} 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. Methanolic solutions of $150\ \mu\text{M}$ amino-terminated PAMAM dendrimer (ethylenediamine core) of different generations (3.0, 4.0, 5.0) were 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.⁴⁴ First, $150\ \mu\text{M}$ aqueous solutions of different PAMAM-OH dendrimers (generation 3.0, 4.0, 5.0) were 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 Gn-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.

5.4.4 Continuous flow Suzuki-Miyaura cross-coupling reaction

Iodobenzene (**1**, 0.10 mmol) was reacted with *p*-tolylboronic acid (**2**, 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. For the kinetic study, the concentration of **1** was varied in the range of 10-30 mM and the concentration of **2** was kept constant at 150 mM (base 160 mM). Flow rates in the range of 4-0.5 $\mu\text{L min}^{-1}$ were used. The experimental error in these measurements is $\pm 5\%$.

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Chapter 6

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

The inner walls of glass microreactors were functionalized with dendrimer-encapsulated Pd nanoparticles. The catalysts were efficient for the Suzuki-Miyaura (SMC) and the copper-free Sonogashira cross-coupling reactions. In the case of the Mizoroki-Heck reaction of aryl iodides with acrylates and styrene only conversions of < 10% were obtained under the conditions used. For the Sonogashira 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 was determined from the Hammett plot, indicating a possible rate-determining step other than the oxidative addition.

6.1 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.^{3,4} Depending on the reagent involved, several examples of C-C cross-couplings have been developed since the early 1970s (Figure 6.1).⁵

Figure 6.1 Pd-catalyzed C-C cross-coupling reactions.

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 (see Chapters 2 and 5).⁶ These nanometer species are considered ideal candidates for improving the sustainability of catalytic processes, blending together the advantages of homogeneous and heterogeneous catalysts.⁷⁻¹⁰ 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.¹¹⁻¹⁴ A stable heterogeneous catalytic system making use of supported Pd NPs would undoubtedly allow to carry out

cross-coupling reactions in continuous flow systems.¹⁵ 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.¹⁶

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.¹⁷⁻²¹ Examples of continuous-flow Sonogashira,^{22,23} Negishi,²⁴ and Stille²⁵ reactions have been based on different Pd catalysts.

In Chapter 5, the synthesis of dendrimer-encapsulated Pd NPs (Pd DENs) anchored onto the inner walls of flow microreactors was described. 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.²⁶⁻²⁸ 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, our 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.²⁹⁻³¹ In fact, the reactor was run over seven consecutive days showing a minimal Pd leaching.

In this chapter, the scope of Pd DENs as catalysts for cross-coupling reactions under continuous flow is expanded. Besides the SMC reaction described in the previous chapter, the copper-free Sonogashira and the Mizoroki-Heck reactions were investigated. Additionally, the influence of *para*-substituted aryl iodides on the overall SMC reactivity was studied. In this way, a Hammett plot of the aryl iodides substituents provides useful insight into some catalytic mechanistic aspects, such as the rate-determining step of the reaction.

6.2 Results and discussion

6.2.1 Microreactor functionalization

For the functionalization of the microreactor surface the methodology described in Chapter 5 was followed (Scheme 6.1). Accordingly, G3-NH₂ PAMAM dendrimers were employed for the formation of Pd DENs.

The characterization of the Pd DENs was carried out on silicon dioxide surfaces functionalized in the same way as the microchannel interior. For the description of the analytical procedures, we direct the reader to the discussion presented in Chapter 5. It is worth mentioning here, however, the NP size of about 2.5 nm, in agreement with the encapsulation within dendrimers.²⁶

Scheme 6.1 Microreactor surface functionalization with dendrimer-encapsulated Pd NPs.

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.

6.2.2 Reaction scope of Pd DEN-microreactors

The Sonogashira cross-coupling has become one of the most useful tools for the synthesis of alkyl-aryl- and diaryl-substituted acetylenes.³² Generally, this reaction is carried out with Pd as the catalyst and a copper salt as a co-catalyst.³³ Since the Cu(I) salt is usually used in the same mixture as the reagents, it is not surprising that great attention is put on the elimination of the copper co-catalyst whenever heterogeneous Pd catalysts are used (Glaser-type reactions).^{34,35} However, the copper-free Sonogashira 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.³² Nevertheless, the copper-free Sonogashira coupling of iodobenzene and phenylacetylene was carried out in the Pd DEN-functionalized microreactor (Scheme 6.2).

Scheme 6.2 Sonogashira coupling catalyzed by Pd DEN-microreactors.

The catalytic system reached almost quantitative conversion in less than 15 min of residence time (Figure 6.2). The temperature was set at $100\text{ }^\circ\text{C}$ 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 6.2 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.

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 Figure 6.2). 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} (see section 6.4.4). To this regard, Astruc and co-workers³⁶ developed recently a dendritic nanoreactor with hydrophilic triethylene glycol termini and a hydrophobic interior for the stabilization of small Pd NPs. This catalytic system is 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 the catalytic system described here. In addition, our DEN-functionalized microreactor exhibits a higher TOF as compared to other Pd NP-catalyzed Sonogashira couplings between iodobenzene and phenylacetylene,³⁶ with only a few exceptions.^{37,38}

The majority of examples of Sonogashira couplings under continuous flow make use of Pd catalysts other than supported NPs.¹⁶ Different approaches, ranging from ionic liquids,³⁹ monoliths,^{40,41} surface thin layers,^{23,42} and perovskite

catalysts,²² 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.

The Pd-catalyzed Mizoroki-Heck reaction is the most useful approach for the vinylation of aryl halides or triflates.^{43,44} Along with the SMC, the Heck reaction is one of the most studied C-C bond formation reaction, both in batch and in flow.^{14,16,45} Here, the coupling of iodobenzenes with a few acrylates, namely methyl, ethyl, and butyl acrylate and with styrene, were performed (Scheme 6.3). The product formation was measured with in-line UV-vis spectroscopy by monitoring the product bands occurring in the range 280-300 nm.

Scheme 6.3 Mizoroki-Heck couplings catalyzed by Pd DEN-microreactors.

At first the reaction conditions were kept similar to those of the SMC, i.e., using ethanol as the solvent and Bu_4NOH as the base (the temperature was raised to 100 °C). For all examples, conversions $\leq 10\%$ were measured. The efforts in optimizing the reaction conditions (use of DMF as the solvent and triethylamine as the base) led to a little improvement of the overall reactivity. The stereoselective control of the Mizoroki-Heck reaction is of importance in the synthesis of many active compounds. The use of Pd NPs supported within a microreactor can help

reducing the environmental impact of this synthesis, as witnessed by the similar overall reactivity when a relatively benign solvent (ethanol) is employed.

6.2.3 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 6.1). The reaction conditions were kept the same for all the experiments to exclude any external influence on the catalytic activity.

As expected, electron-withdrawing groups enhanced the overall reactivity, with very high yields (92-96%) and conversions > 99% (Table 6.1, entries 3-8).⁴⁶ Electron-donating groups, on the other hand, showed a reduced reactivity within the reaction time selected, with yields ranging from 40 to 70% (Table 6.1, entries 9-17). Aryl bromides are much less reactive as compared to aryl iodides (Table 6.1, 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%).

Table 6.1 Suzuki-Miyaura cross-coupling reactions catalyzed by Pd DEN-microreactors.^a

entry	Ar-X	R ²	Yield (%)	Conversion (%)
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	65
13		H	30	33
14		CH ₃	38	42
15		H	50	54
16		CH ₃	40	45
17		H	52	55
18		CH ₃	55	62
19		CH ₃	10	12

^a [Ar-X] = 10 mM; [Ar-B(OH)₂] = 15 mM; [Bu₄NOH] = 20 mM; res. time 13 min.

To assess the electronic substituent effects in a quantitative manner, the apparent rate constants, k_{obs} , for a variety of 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 Figure 6.3).

Figure 6.3 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.

The logarithms of the thus obtained k_{obs} values were plotted against the Hammett parameter σ (Figure 6.5).⁴⁷ 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.⁴⁸ The catalytic cycle of transition-metal-catalyzed cross-coupling reactions, including the SMC, consists of three steps: oxidative addition, transmetalation, and reductive elimination (Figure 6.4).³ In most cases, the oxidative addition represents the rate-determining step of the catalytic cycle for the SMC.⁴⁶

Figure 6.4 Suzuki-Miyaura catalytic cycle using Pd NPs.

Here, 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.^{49,50} Usually, the SMC reactions of substituted aryl bromides and aryl tosylates show low, positive ρ values (for ArBr: 0.48, 0.66,⁵¹ 0.18,⁵² and 1;⁵³ for ArOTs: 0.80⁵⁴), 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 (5.2,⁵⁵ and 2.3⁵⁶). In our case, a ρ value of 1.5 confirms the influence of the substituents on the reactivity of the aryl iodides, and most probably the rate-determining step is represented by the transmetalation process.^{50,53,54}

Figure 6.5 Hammett plot for Suzuki-Miyaura cross-couplings using Pd DEN-functionalized microreactors showing the effect of *para*-substituted iodobenzenes on the reaction rate.

6.3 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 Chapter 5 for the efficient catalysis of a model Suzuki-Miyaura cross-coupling (SMC) reaction. Moreover, the influence of dendrimers in the stabilization of the Pd NPs has been demonstrated in the same study. Here, the reaction scope of the Pd DEN microreactors was expanded, including the Sonogashira and Mizoroki-Heck cross-couplings. In particular, the Sonogashira coupling of iodobenzene and phenylacetylene was carried out in the absence of a copper co-catalyst and at milder reaction conditions than other Pd catalysts used in flow. Moreover, 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 proven 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 represented by the transmetalation process.

Despite the efficiency of the Pd DEN-functionalized microreactor for the continuous flow SMC and Sonogashira reactions, further work is needed to extend its applicability to other C-C cross-couplings, such as the Mizoroki-Heck and the Stille reactions, just to name a few.

6.4 Experimental

6.4.1 Materials and equipment

All chemicals and solvents were purchased from Sigma Aldrich and used without purification unless otherwise stated. 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).

GC, in-line UV, and XPS. See Chapter 3.

Contact angle. See Chapter 4.

UV-vis, HRSEM, TEM, and TXRF. See Chapter 5.

6.4.2 Flow apparatus

See Chapter 3.

6.4.3 Dendrimer-encapsulated Pd NP functionalization of flat surfaces and microreactors

Deposition of a monolayer of APTES and DITC. The same procedure described in Chapter 5 was followed for the functionalization of SiO_2 surfaces and microreactor inner walls.

Formation and anchoring of Pd DENs. The same procedures described in Chapter 5 were followed for the synthesis of Pd DENs within the microreactors and on SiO₂ surfaces

6.4.4 Continuous flow Sonogashira 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. 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).

6.4.5 Continuous flow Mizoroki-Heck couplings

Iodobenzene and 4-iodoacetophenone (0.30 μmol) were reacted with methyl-, ethyl, butylacrylate, styrene (0.45 μmol) in ethanol or DMF (10 mL) using tetrabutylammonium hydroxide and triethylamine (0.60 μmol) as bases, respectively. These solutions were analyzed in-line by UV-vis spectroscopy by controlling the product bands at around $\lambda = 280 \text{ nm}$.

6.4.6 Continuous flow Suzuki-Miyaura cross-coupling reactions

For all the experiments described in this chapter 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 the solutions were passed through the catalytic

microreactor at different flow rates and the reaction products were collected and analyzed off-line by GC. All the compounds synthesized have already been characterized. 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 Bu₄NOH concentration was 160 mM.

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Chapter 7

Influence of the Au/Ag ratio on the catalytic activity of dendrimer-encapsulated bimetallic nanoparticles in microreactors

Generation 4 amino-terminated dendrimers were covalently attached to a monolayer-functionalized inner surface of glass microreactors. Au/Ag alloy nanoparticles (NPs) were formed by co-complexation of the two metal salts within the dendrimer template. Additionally, dendrimer-encapsulated Au/Ag NPs were preformed in solution and subsequently attached to the reactive monolayer. The influence of the bimetallic alloy structure and of the different metal ratios was investigated for the reduction of 4-nitrophenol using NaBH_4 . Remarkably, the Au/Ag-dendrimer nanocomposite with a 1:1 Au/Ag metal ratio showed the highest activity as compared to other metal ratios and to pure Ag and Au. The catalytic system performed comparatively better than other bimetallic catalysts for the reduction of 4-nitrophenol both in batch and in flow. The dendrimer template exerted a stabilizing effect as demonstrated by a stability study, in which the flow reactor was run for six consecutive days with almost no decrease in conversion.

7.1 Introduction

Bimetallic nanoparticles (NPs) are receiving increasing attention because of the advantageous features of combining two or more metals in the same heterocomposite structure, with widespread application in the biomedical, electronic, and catalytic areas.¹⁻⁴ Following the increasing importance of nanotechnology in catalysis,⁵⁻⁸ bimetallic particles in the range of a few nanometers are one of the major candidates in heterogeneous catalysis, in agreement with the modern challenge to lower the environmental impact of chemical reactions.^{9,10}

Due to synergistic effects, the physical and chemical behavior of a bimetallic system is considerably different from the mere combination of the two metal constituents. There is a general consensus that the differences in catalytic performance between a bimetallic and a monometallic catalyst are due to electronic or geometric effects, or a combination thereof.⁴ Therefore, the catalytic activity can be tailored by combining two or more metals in the same nanocomposite structure.¹¹ Depending on the mixing compositions, there are three main types of structures: core/shell, intermetallic, and alloys.^{12,13}

The interplay between geometry and electronic structure for bimetallic systems has been recently investigated in detail for the reduction of 4-nitrophenol.¹⁴ Using a combined experimental-computational approach, different alloy NPs were synthesized (Pt/Cu, Pd/Cu, Pd/Au, Pt/Au, and Au/Cu) and evaluated for their catalytic activity, considering the binding energy of the 4-nitrophenol molecule onto the nanoparticle surface which in turn influences the reaction rate constant. The results show that the catalytic activity of the heterometallic systems depends on the lattice parameters of the two metals, which differ from a linear combination of the properties of the two metals.

Undoubtedly, the surface properties of these catalysts rely on the morphology, size, and distribution of the nanoparticles. To this end, dendrimers offer the opportunity to synthesize well-defined metallic NPs, and to combine the

advantages of homogeneous and heterogeneous catalysis.¹⁵⁻¹⁷ The synthesis of bimetallic dendrimer-encapsulated NPs (DENs) usually follows one of three main approaches: co-complexation, sequential loading, and partial displacement.^{18,19} Bimetallic alloys are usually formed *via* the co-complexation route, where the two metal salts are added at the same time and upon metal ion-dendrimer complexation, a strong reducing agent (usually NaBH_4) yields well-mixed alloy NPs.²⁰⁻²⁵

Despite the increasing importance of nanocatalysis within continuous flow microreactors,²⁶⁻³⁰ there are relatively few examples of supported bimetallic nanocatalysts in combination with microfluidic reactors.³¹⁻³³ Nevertheless, the large surface-to-volume ratio and the improved heat and mixing efficiency ensured by microstructured reactors is expected to be beneficial to fully exploit the synergistic properties of supported bimetallic NPs.³⁴⁻³⁸

In this chapter the influence of the metal composition of Au/Ag alloy NPs as catalysts for the reduction of 4-nitrophenol under continuous flow conditions was investigated. First, the inner surface of glass microreactors was functionalized by means of dendrimer-encapsulated bimetallic NPs (Au/Ag DENs). The formation of alloy NPs was analyzed by XPS, UV-vis spectroscopy, HRTEM, and EDX techniques. Bimetallic NPs of different Au/Ag ratios were prepared as well as monometallic Ag and Au NPs. The most active microreactor was run over several consecutive days to verify the reusability and the stability against leaching of the Au/Ag DENs.

7.2 Results and discussion

7.2.1 Flat surface and microreactor functionalization

Gold/silver alloy DENs were formed by encapsulation within the generation 4 PAMAM dendrimer (G4-NH_2) following the co-complexation approach. These DENs were attached to the inner walls of flow microreactors (Scheme 7.1). To this end, 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, see Chapter 5). In this way the exposed isothiocyanate groups were used for the covalent anchoring of G4-NH₂ dendrimers *via* formation of thiourea bonds (Scheme 7.1, Route A).³⁹ Different mixtures of HAuCl₄ and AgNO₃ salts with G4-NH₂ dendrimers were prepared, followed by NaBH₄ reduction. NH₂-terminated dendrimers were preferred over OH-terminated dendrimers because the peripheral hydroxy groups have shown to reduce Au³⁺ ions to zerovalent Au, resulting in agglomeration of gold.⁴⁰ Alternatively, dendrimer-encapsulated Au/Ag alloy NPs were preformed in solution²⁴ and subsequently anchored to the APTES-DITC monolayer (Scheme 7.1, Route B). For both methods, the two metal salts were mixed in different ratios, namely Au/Ag 1:0, 3:1, 1:1, 1:3, and 0:1.⁴¹

Scheme 7.1 Microreactor surface functionalization with dendrimer-encapsulated Au/Ag NPs.

X-ray photoelectron spectroscopy (XPS) provided information about the metal composition. The analysis was performed on a silicon dioxide surface functionalized in the same way as the glass microchannel surface. Of particular interest was the correlation between the Au/Ag ratio and the feed ratios of the two metal salts. Table 7.1 summarizes the relationship between Ag_{3d} and Au_{4f} peaks for $\text{G4-NH}_2(\text{Au}_x\text{Ag}_y)$ -functionalized surfaces, prepared according to the two approaches depicted in Scheme 7.1. It can be noted that the synthesis of Au/Ag NPs in solution (Route B) gave rise to a metal composition close to the nominal feeding ratio. The results of the *in situ* approach (Route A), however, diverge to a greater extent from the theoretical metal composition. Such behavior may be explained by the presence of non-specifically bound metal at the outside of the dendrimer template.

Table 7.1. XPS analysis of the Ag_{3d} and Au_{4f} peaks for a $\text{G4-NH}_2(\text{Au}_x\text{Ag}_y)$ -functionalized silicon dioxide surface.

G4-NH_2	Au:Ag	Theoretical	Experimental ^a	Au content (%)
Route A	3:1	3	0.67	40
	1:1	1	0.42	30
	1:3	0.33	0.30	23
Route B	3:1	3	2.50	70
	1:1	1	0.83	45
	1:3	0.33	0.30	23

^a Average numbers based on 3 measurements

Figure 7.1 shows the UV-vis spectra of 10 μM aqueous solutions of different G4-NH_2 bimetallic nanocomposites. The presence of only one surface plasmon resonance (SPR) band in the region between 400 and 500 nm suggests the formation of alloy NPs. In fact, previous studies have shown that Au/Ag alloys

exhibit a single peak in their absorption spectra, the position of which shifts gradually from that of pure Ag at around 400 nm to that of pure Au at around 500 nm (Figure 7.1, right).^{24,41,42} This observation indicates that the NPs are alloys rather than core/shell particles or mixtures of monometallic NPs, in which case the UV-vis spectrum would show two different peaks corresponding to Ag and Au.^{24,43} The identification of the $\lambda_{\max}$ for pure Ag DENs was impeded by the presence of a broad band at around 400 nm. Nevertheless, the extrapolation of the trendline in Figure 7.1, right, to 0% Au indicates a value at about 415 nm, in agreement with the values reported in literature for Ag NPs.²⁴

Figure 7.1 UV-vis spectra of G4-NH₂ Au/Ag NPs for different metal ratios (left); location of the SPR band *versus* the amount of gold (right).

Transmission electron microscopy (TEM) images of a 1:1 Au/Ag alloy NPs sample (formed *via* route B) showed uniform spherical NPs with an average diameter of 3.2 ± 0.8 nm (Figure 7.2). The obtained average size is in agreement with the study of Endo *et al.*⁴¹ for Au/Ag DEN nanocomposites. While pure gold NPs exhibit a similar size as the bimetallic ones, pure silver NPs have been shown to display a bigger diameter (around 10 nm).^{41,43} Therefore, the formation of quite monodispersed NPs supports alloy formation.⁴⁴

Figure 7.2 TEM image of G4-NH₂ Au/Ag 1:1 NPs (left; scale bar 40 nm) and nanoparticle size distribution (right) formed *via* Route B.

Figure 7.3 (left) shows a high-resolution TEM (HRTEM) image of the alloy nanoparticles and their electron diffraction patterns. A basal spacing of 2.3 Å was calculated, indicating the (111) lattice plane. This value is almost identical to the one of monometallic Ag and Au, which have similar lattice constants, namely 4.079 and 4.0765 Å, respectively,^{45,46} thus not allowing a clear distinction between alloy and single metal NPs. Nevertheless, the image shows an excellent atomic alignment within the particle, with no lattice distortion as expected for a homogeneous mixing of Ag and Au. Additionally, energy-dispersive X-ray spectroscopy (EDX) provides powerful information to assess the NP atomic composition. Therefore several dendrimer-Au/Ag 1:1 nanocomposites preformed in solution (route B) were analyzed by EDX. Noteworthy, the values obtained for individual particles match very closely with the feeding atomic composition, the experimental values for Au and Ag being 45.6% and 54.4%, respectively (within a 7% error margin; Figure 7.3, right).

Figure 7.3 HRTEM image of a single crystal of a DEN Au/Ag 1:1 nanocomposite (route B) and a Fourier transformed image indicating the electron diffraction pattern in the inset (scale bar 10 nm, left). EDX spectrum of the DEN Au/Ag 1:1 nanocomposite (right).

The catalyst loading of a G4-NH₂ 1:1 Au/Ag-functionalized microreactor as prepared by Route B was calculated by total reflection X-ray fluorescence (TXRF). In particular, the amount of both metals retained by the dendrimer templates attached to the microreactor surface was measured, namely 22 ng (0.11 nmol) of Au and 20 ng (0.18 nmol) of Ag. This confirms the equal loading efficiencies of these metals from a 1:1 feed.

7.2.2 Influence of metal ratio on the catalytic reduction of 4-nitrophenol

The reduction of 4-nitrophenol to 4-aminophenol using NaBH₄ was chosen as a model reaction to study the catalytic performance of Au/Ag DEN-functionalized microreactors (Scheme 7.2). Arguably, the reduction of 4-nitrophenol is one of the most studied reactions for investigating the catalytic activity of metallic NPs, and therefore constitutes an optimal benchmark for evaluating the activities of mono- and bimetallic NPs and the efficiencies of their preparation methods.^{21,47,48}

Scheme 7.2 Reduction of 4-nitrophenol to 4-aminophenol in Au/Ag DEN-functionalized microreactors.

The continuous reaction process was monitored by in-line UV-vis spectroscopy because of the strong absorbance of 4-nitrophenol at 400 nm. The progress of the reaction was characterized by a decrease of the absorbance at 400 nm and a concomitant (small) increase of the absorbance at about 300 nm due to formation of 4-aminophenol (Figure 7.4).^{49,50} Furthermore, the overall reaction rate for this reaction appeared to be pseudo-first order when the reducing agent was used in large excess.

Figure 7.4 In line UV-vis spectra for the reduction of 4-nitrophenol to 4-aminophenol with NaBH_4 in a G4-NH₂ Au/Ag 3:1 microreactor functionalized following the route A.

For this reason, a kinetic study was performed for Au/Ag DENs with different metal ratios as well as pure Au and Ag. For this study, the catalysts were

introduced *in situ* inside glass microreactors (Route A, Scheme 7.1). An excess of NaBH_4 was used to achieve pseudo-first order conditions. The kinetic curves shown in Figure 7.5 represent the activities of the Au:Ag metal ratios employed, namely 1:0 3:1, 1:1, and 1:3 expressed in terms of nominal Au content (%). For all metal ratios, an induction time of about 15 s could be extrapolated from the kinetic curves. Pure Ag NPs exhibited much longer induction and residence times and their kinetic profile has not been included in Figure 7.5.

Figure 7.5 Formation of 4-aminophenol *versus* residence time in G4-NH₂ Au/Ag- and G4-NH₂ Au-functionalized microreactors (Route A) for different gold contents in the metal feed (%). [4-nitrophenol] = 0.1 mM, [NaBH₄] = 2 mM, water, rt.

In order to quantify the differences in reactivity, the observed rate constants (k_{obs}) were extrapolated from the kinetic curves and plotted *versus* the amount of gold in the heterometallic NPs (Figure 7.6). Strikingly, Au/Ag 1:1 bimetallic nanocomposites gave rise to the highest activity, being remarkably superior to that of other bimetallic feed ratios and to the one of pure gold, which accounts for most of the activity for this reaction. In fact, as demonstrated by Endo *et al.*,⁴¹ the Au/Ag ratio of DEN bimetallic NPs influences the reaction rate, in which case the apparent rate constant appeared to be directly proportional to the gold content. The authors speculated that the enhanced catalytic activity that is observed for

core/shell and alloy particles is due to an ensemble effect at the surface atoms, although in their study the maximum of activity was observed for the Au/Ag 3:1 ratio 75%.^{41,51}

Figure 7.6 Observed rate constants *versus* nominal Au content for the reduction of 4-nitrophenol using G4-NH₂ Au/Ag-functionalized microreactors (Route A). [4-nitrophenol] = 0.1 mM, [NaBH₄] = 2 mM, water, rt (the error bars represent standard deviations of multiple measurements).

The k_{obs} for the G4-NH₂ Au/Ag 1:1-functionalized microreactor was 0.18 s⁻¹, hence exhibiting a turnover frequency (TOF) of 2850 h⁻¹ (calculated as moles of product per unit time per moles of catalyst present inside the chip; moles of catalyst are based on the total amount of metal atoms). Other Au NP catalysts have shown TOFs up to 1028 h⁻¹, with only Pd NPs stabilized by a dendritic nanoreactor reaching a value as high as 22500 h⁻¹.⁵² With respect to Au/Ag bimetallic NP catalysts, k_{obs} values of about 0.015 s⁻¹ and 0.005 s⁻¹ were found in literature, thus confirming the high activity of our catalytic system.^{41,53,54} Only a G6-OH(Pd₁Cu₁) catalyst showed a similar k_{obs} (0.12 s⁻¹).¹⁴ There are only few examples of metal NPs supported within microfluidic reactors for the reduction of 4-nitrophenol. For instance, the k_{obs} of Ag and Pd NPs entrapped in a brush-functionalized microreactor was 0.03 s⁻¹,³⁰ which is lower than our Au/Ag DEN-microreactor.

As described by Ballauff *et al.*,⁴⁷ another important feature of the reduction of 4-nitrophenol catalyzed by metallic NPs is the presence of an induction time, after which the reaction starts. This induction time has been explained to occur due to the restructuring of the surface by mostly 4-nitrophenol, and usually it takes up to several minutes.^{47,55-57} As already mentioned, the kinetic analysis conducted using different bimetallic ratios gave rise to an induction time of only 15 s for the Au/Ag DENs. In one of the examples present in the literature,⁴⁷ however, the induction time using Au NPs at similar reagents concentrations, was about 50 s. The fact that silver exhibited a much longer induction time (around 5 min), may suggest a predominant role of gold in the surface restructuring upon reaction, and/or the generally larger particle size and thus lower surface area of Ag NPs.

To attribute the improved catalytic efficiency of alloy NPs to surface electronic or geometric effects, the influence of the capping agent on the catalytic activity should be excluded. To this regard, Esumi *et al.*⁵⁸ investigated the catalytic activity of several dendrimer-stabilized NPs for the reduction of 4-nitrophenol. They concluded that the reaction is diffusion controlled, and that the rate constants decrease with increasing dendrimer concentration, probably due to the coverage of the dendrimer on the metal particle surface. In our case, the use of a microfluidic reactor may reduce the diffusion limitation. Moreover, only a single dendrimer layer is anchored on the surface, thus not only maintaining a constant dendrimer concentration throughout the channel, but also avoiding any interdendrimer interaction.

Therefore, the enhanced activity for bimetallic Au/Ag must be found in a combination of structural and electronic effects. In particular, the latter aspect may arise from the fact that electrons could transfer from Ag to Au, leading to an increase in the electron density on the surface of the bimetallic heterocomposites.^{53,59,60} This effect is particularly advantageous for the model reaction under investigation where BH_4^- ions are formed, which in turn interact

with the 4-nitrophenol molecule. The Langmuir-Hinshelwood (LH) model,⁶¹ which assumes the adsorption of both reagents on the metal surface, may explain the favorable effect of an enhanced electron density on the catalytic activity. The hydrogens liberated by the interaction of the borohydride with the surface react with the 4-nitrophenol molecule adsorbed onto a vacant site of the surface. The reduction process constitutes the rate-determining step, whereas the adsorption/desorption of the reagents/products is fast (Figure 7.7).^{47,60,62}

Figure 7.7 Langmuir-Hinshelwood mechanism of the reduction of 4-NP by borohydride on the surface of metallic nanoparticles (adapted from ref. 47).

At last, a continuous flow investigation was conducted to assess the durability of the catalytic system. Accordingly, a stability study was carried out utilizing the most active catalyst, *i.e.* the G4-NH₂ Au/Ag 1:1-functionalized microreactor through *in situ* catalyst loading (Route A, Scheme 7.1). Satisfyingly, the model reaction could be run for several consecutive days, with only a little decrease of activity upon the 6th day of utilization (Figure 7.8). The turnover number (TON) for this investigation was 5050 (considering 4 h of continuous process for each day of use). More importantly, the amount of metal leached out of the microreactor in the course of the investigation was of only 2 ng as measured by TXRF (corresponding to less than 5% of the total catalyst amount). Interestingly, only Ag was detected, with no trace of Au in the product solution. This can be ascribed to the stabilizing effect exerted by the dendrimer template on the metallic nanocomposites, as demonstrated in Chapter 5 for Pd DENs and witnessed by recent studies of Somorjai and co-workers.^{63,64}

Figure 7.8 Conversion vs reaction time for the reduction of 4-nitrophenol in a G4-NH₂ Au/Ag 1:1-functionalized microreactor (Route A). [4-nitrophenol] = 0.1 mM, [NaBH₄] = 2 mM, water, rt, residence time: 78 s.

7.3 Conclusions

Alloy Au/Ag DENs were covalently attached to the inner walls of glass microreactors functionalized by means of a reactive monolayer. The bimetallic NPs were formed by co-complexation of the two metal salts using G4 PAMAM dendrimers as template. A variety of analyses confirmed the formation of homogeneously mixed alloy nanocomposites of about 3 nm in size. The thus formed catalytic flow microreactors highlight the enhanced activity of bimetallic NPs over the corresponding monometallic metals. The reduction of 4-nitrophenol was chosen as model reaction allowing a kinetic study of different Au/Ag metal ratios. Noteworthy, the Au/Ag 1:1 nanocomposite (TOF of 2850 h⁻¹) performed indisputably better than the other alloy NPs and pure Au, which is the most active metal for the model reaction. The enhanced activity of the alloy/DEN nanocomposites may be found in a combination of geometric and electronic effects. The latter can be explained by the possible increase of electronic density upon formation of Au/Ag alloy NPs.^{59,60} Moreover, the use of a microfluidic reactor may reduce diffusion limitations and improve the reagent/metal interaction,

as witnessed by the short induction time for the reaction to occur. Finally, the dendrimer template improves the stability of the bimetallic catalyst, as demonstrated by at least six consecutive days of use and minimal metal leaching (5% of the total catalyst amount).

Bimetallic NPs have not yet been fully explored in flow microreactors, with just a few examples in the literature. However, this discipline could be of increasing importance for applications in catalysis, sensing, and electronics, just to name a few. Mechanistic studies of the influence of the type of metals employed and their interaction in alloy or core/shell nanocomposites are needed to further establish this promising research field.

7.4 Experimental

7.4.1 Materials and equipment

All chemicals and solvents were purchased from Sigma Aldrich and used without purification unless otherwise stated. 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).

XPS and in-line UV. See Chapter 3.

Contact angle. See Chapter 4.

UV-vis, TEM, and TXRF. See Chapter 5.

EDX. Energy-dispersive X-ray spectroscopy (EDX) was performed by a Noran System Six EDX analyzer Nanotrace detector.

7.4.2 Flow apparatus

See Chapter 3.

7.4.3 Functionalization of flat silicon dioxide surfaces and microreactor inner walls by dendrimer-encapsulated Au/Ag alloy NPs

Deposition of a monolayer of APTES and DITC. The same procedure described in Chapter 5 was followed for the functionalization of SiO₂ surfaces and microreactor inner walls.

Formation and anchoring of G4-NH₂(Au_xAg_y), G4-NH₂(Au), and G4-NH₂(Ag).

Route A. A methanolic solution of 150 μ M G4-NH₂ 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 2 mM aqueous solutions of HAuCl₄ (Acros Organics) and AgNO₃ for 30 min at room temperature. G4-NH₂-encapsulated Au/Ag alloy NPs were prepared in the following Au/Ag ratios (in 1 mL of water): 1:1 (1×10^{-3} mmol of HAuCl₄ and AgNO₃), 3:1 (1.5×10^{-3} mmol of HAuCl₄ and 0.5×10^{-3} mmol of AgNO₃), 1:3 (0.5×10^{-3} mmol of HAuCl₄ and 1.5×10^{-3} mmol of AgNO₃). For pure Au and Ag NPs, 2×10^{-3} mmol of HAuCl₄ and AgNO₃ were added to 1 mL of water, respectively. Afterwards, the reduction of the metallic particles was obtained by reaction with a 20 mM aqueous solution of NaBH₄ (20 min). The same procedure was followed for the microreactor functionalization by flowing the dendrimer, gold and silver salts, and reducing agent solutions at 0.05 μ L min⁻¹ for the respective times.

Route B. The formation of G4-NH₂(Au_xAg_y), G4-NH₂(Au), and G4-NH₂(Ag) in solution was accomplished by following a slightly modified literature procedure.²⁴ First, 150 μ M aqueous solutions of PAMAM dendrimers (generation 4.0) were prepared and stirred for 30 min. A 40-fold excess of gold and silver salts were introduced by means of HAuCl₄ and AgNO₃, respectively, according to the metal ratios described above for the alloy NPs and pure Au and Ag NPs. The mixtures were left for 15 min at room temperature. NPs were obtained by reduction with a 10-fold excess of NaBH₄. The so-formed G4-NH₂-encapsulated NPs were

anchored onto 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.

7.4.4 Continuous flow reduction of 4-nitrophenol

4-Nitrophenol (0.1 mM) was mixed with a freshly prepared solution of NaBH_4 (2 mM) in water. This solution was passed through the catalytic microreactors at different flow rates and the reaction was monitored by in-line UV-vis spectroscopy. The decrease of the 4-nitrophenol absorbance at 400 nm was used to calculate the pseudo-first order rate constants for the different DEN-functionalized microreactors. The turnover frequency (TOF) for the G4- NH_2 1:1 Au/Ag-functionalized microreactor was calculated based on the moles of product per unit time per moles of catalyst within the microreactor volume ($13 \mu\text{L}$). The moles of catalyst are based on the total amount of metal atoms (0.11 nmol of Au and 0.18 nmol of Ag). The observed rate constant was used in the calculation according to the formula: $(k_{\text{obs}} * M_{\text{product}} * V_{\text{microreactor}}) / (mol_{\text{cat}} * 3600)$.

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7.6 References

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Summary

Continuous-flow microreactors are an invaluable tool to carry out organic reactions owing to their numerous advantages with respect to batch scale synthesis. In particular, supported catalysts enable heterogeneous catalysis to be conducted in an efficient way. In this thesis, the development and activity of different organic and nanometallic catalysts supported in different ways on the inner walls of glass microreactors, has been presented. Their catalytic activity is proven in a variety of acid-catalyzed reactions, C-C cross-couplings, and reductions.

Chapter 2 presents a literature overview about the state-of-the-art of nanoparticle catalysis in microfluidic reactors. Different strategies for supporting and stabilizing metallic nanoparticles (NPs) have been presented, such as packed-bed reactors, monolithic supports, wall-catalysts, and nanomaterials. Flow hydrogenations, oxidations, C-C cross-couplings, and other reactions demonstrate the applicability and advantages of the supported NPs.

Chapters 3 and 4 show two strategies for the introduction of sulfonic acid groups within microreactors. The first example (Chapter 3) makes use of a cyclic precursor (β -sultone) which directly gives the active catalyst upon reaction with the microreactor surface. The acidity of the organic catalyst was enhanced by the presence of fluorine groups in its proximity and thus efficiently catalyzed the hydrolysis of benzaldehyde dimethylacetal, the Friedlander formation of a quinoline derivative, and the cyclization of pseudoionone. In the second example (Chapter 4), sulfonic acid-bearing polymer brushes were grown on the inner wall of a microreactor. Mixed brushes of 3-sulfopropyl methacrylate (SPM) and 2-hydroxyethyl methacrylate (HEMA) improved the activity and stability of the active groups as compared to the homopolymer of SPM. The mixed PSPM-PHEMA brushes exhibited a 6-fold and 5-fold higher turnover frequency (TOF)

and turnover number (TON), respectively, for the hydrolysis of benzaldehyde dimethylacetal, which was chosen as a model reaction.

The second part of this thesis deals with the use of dendrimer-encapsulated metallic nanoparticles (M DENs) covalently attached to the inner surface of a microreactor. In Chapter 5, generation 3 PAMAM dendrimers (G3) imparted the highest catalytic activity to the encapsulated Pd NPs for the model Suzuki-Miyaura cross-coupling (SMC) of iodobenzene and *p*-tolylboronic acid. In addition, a kinetic study revealed the high performance of the G3 Pd DEN-functionalized microreactors as witnessed by a higher TOF compared to those of other Pd NP-catalyzed SMC reactions. Noteworthy, the dendrimer template stabilized the Pd NPs over seven days of consecutive use with minimal leaching. The reaction scope of Pd DENs was extended to other C-C cross-coupling reactions such as the Sonogashira and the Mizoroki-Heck reactions (Chapter 6). In particular, the copper-free Sonogashira reaction turned out to be quite efficient under mild reaction conditions. Moreover, electron-withdrawing substituents on the aryl halide counterpart improved the overall reactivity of the SMC reaction. A study of the substituent effect, using a Hammett plot, indicated the occurrence of a rate-limiting step other than the oxidative addition, most likely the transmetalation. Chapter 7 shows the beneficial influence of the metal ratio of alloy bimetallic Au/Ag DENs on the reduction of 4-nitrophenol. Remarkably, the Au/Ag 1:1 nanocomposite exhibited the highest activity as compared to other metal ratios and pure Au and Ag NPs as well as compared to other mono- and bimetallic NP catalysts for the model reaction.

In summary, the results presented in this thesis highlight the advantages of using supported catalysts within continuous-flow microreactors for heterogeneous catalysis. Functionalization of the large inner surface of microreactors was achieved by using a single layer of an organic acid catalyst, by catalyst-bearing polymer brushes and by dendrimer-encapsulated nanoparticles. The vast portfolio

of supported catalysts together with the safety and the efficiency of carrying out many organic reactions will undoubtedly establish microfluidic reactors as a core technology in chemical synthesis and analysis.

Samenvatting

Continue doorstroomde microreactoren zijn zeer waardevol om organische reacties uit te voeren doordat ze verscheidene voordelen hebben ten opzichte van batch reacties. In dit proefschrift wordt de ontwikkeling en activiteit beschreven van verschillende organische en nano-metallische katalysatoren die op verschillende manieren op de binnenwand van een glazen microreactor aangebracht zijn.

Hoofdstuk 2 geeft een literatuuroverzicht van de katalyse van nanodeeltjes in microreactoren. De hoofdstukken 3 en 4 beschrijven twee methoden om sulfonzuur-groepen in microreactoren te introduceren en de toepassing in zuur-gekatalyseerde reacties. Het tweede deel van dit proefschrift gaat in op het gebruik van metallische nanodeeltjes, ingekapseld in dendrimeren aan de binnenwand van de microreactor, voor de katalyse van verschillende zgn. ‘cross-coupling’ reacties.

Samenvattend tonen de resultaten die in dit proefschrift gepresenteerd worden de voordelen van het gebruik van geïmmobiliseerde katalysatoren in continue doorstroomde microreactoren voor heterogene katalyse. Door de uitgebreide portfolio aan dit type katalysatoren, samen met de veiligheid en efficiëntie van microreactoren, kan de beschreven methodologie een belangrijke plaats innemen bij de efficiënte bestudering van gekatalyseerde reacties. Meer details zijn te vinden in de Engelse versie van de samenvatting.

Samenvatting

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About the author

Roberto Ricciardi was born in Santeramo in Colle (Bari), Italy, on 1st of May 1986. He studied Pharmaceutical Chemistry and Tecnology (CTF) at the University of Bari, Italy, where he received his degree on July 2010 (*summa cum laude*). During his undergraduate training period he worked on the synthesis of arylossazolic derivatives for the diagnosis by PET of the neurodegenerative diseases of CNS at the farmaco-chimico department of the University of Bari under the direction of Prof. N. A. Colabufo.

On January 2011 he started his PhD project in the MnF group of Prof. J. Huskens and the supervision of Dr. Verboom at the University of Twente, The Netherlands. The aim of his project was to develop different methodologies to immobilize organic and metallic catalysts in continuous-flow microreactors. The results of this research are described in this thesis.

Since March 2015 he is a post doc in the MnF group of Prof. J. Huskens working on the Nanopill 2.0 project for the development of a cancer detection kit in collaboration with other groups at the University of Twente.

List of publications

- **R. Ricciardi**, J. Huskens, W. Verboom, Nanocatalysis in flow, *Angew. Chem. Int. Ed.* **2015**, submitted.
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