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Scalable continuous flow hydrogenations using Pd/Al₂O₃-coated rectangular cross-section 3D-printed static mixers

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Graphical abstract



Catalytic Static Mixer

Highlights

- A continuous flow process for heterogeneously catalyzed hydrogenations is presented
- Specially designed static mixers (SM) are produced by additive manufacturing
- Catalytic Static Mixers (CSM) were obtained by coating SM with a layer of Pd/Al₂O₃
- CSM rectangular cross-section ensured excellent heat transfer and easy scalability
- The performance of CSM was evaluated using an aromatic nitro reduction as model

Abstract

A novel type of catalytic static mixers with rectangular cross-section coated with Pd/Al₂O₃ has been developed. The catalytic mixers, produced by additive manufacturing and coated with the metal oxide catalyst, have shown excellent catalytic performance for continuous flow hydrogenation of nitroaromatics. The heterogeneous catalyst is highly stable. No loss of catalytic performance was observed after long periods of activity and ICP-MS measurements determined that essentially no Pd or Al leaches from the reactor. The rectangular cross-section reactor is readily scalable. The process developed has been showcased for the synthesis of the key intermediate of the medicine tizanidine.

Keywords: catalytic hydrogenation • continuous flow • additive manufacturing • anilines • scale up

1. Introduction

Heterogeneously catalyzed reactions account for the largest share of chemical transformations ranging from petroleum, bulk- and fine chemical, to pharmaceutical industries [1–5]. The prevalence of these transformations typically increases with the production volume of the respective sector, as catalytic reactions are a major strategy to enhance process efficiency and minimize waste generation. This is mainly the result of eliminating the need for stoichiometric reagents or reducing resources required for product isolation, as indicated by the E factor [6-9]. Pursuing the implementation of more sustainable processes for fine chemical and especially pharmaceutical industries, investigations towards catalytic processes are therefore of paramount importance for the synthesis of highly functionalized molecules. In this context, hydrogenation reactions promoted by a heterogeneous catalyst are widely used methods to reduce a variety of functional groups including alkenes, alkynes, imines, nitriles, nitro groups and (hetero-) aromatic moieties [10-12]. Advantages of using heterogeneous catalyst systems for these transformations include increased stability of the catalyst, ease of catalyst separation and recyclability. Among the many metals that are typically employed including nickel, cobalt and other platinum group metals (ruthenium, rhodium, osmium, iridium and platinum), palladium has been recognized as one of the most prominent catalysts for hydrogenation reactions. To increase the active surface area of the metal catalyst, different types of catalyst supports are utilized, including activated carbon, zeolite, BaSO₄, CaCO₃ and Al₂O₃ [5,12].

Utilization of hydrogen gas as reducing agent maximizes atom economy. For the reduction of C-C, C-O or C-N multiple bonds, the reagent is fully incorporated into the product, without any byproduct formation. When functional groups such as nitro groups are reduced by H₂, the only resulting byproduct is water, which can be considered benign in many cases. To optimize the respective

multiphase process between gaseous reagent, liquid substrate (dissolved in a suitable solvent) and solid catalyst (metal immobilized on a high-surface support), different reactors such as agitated tanks, fluidized-, packed-, and trickle beds, slurry systems and microstructured reactors are well established [1,13–17]. The field of microstructured systems has particularly gained attention during the past decades due to their excellent mass and heat transfer properties, high potential for process intensification, and increased safety due to the absence of headspace [18–22].

A common approach to perform a heterogeneously catalyzed multiphase reaction on microstructured scale is to pack a microreactor with commercially available catalyst powders with particle sizes in the order of 10-100 µm [23–26]. Such packed bed systems are commercially available and allow for intensified process conditions up to pressures of 100 bar as well as temperatures up to 100 °C and above [27–32]. Current strategies to intensify hydrogenation reactions using microstructured catalysts include coated walls [33–35], catalytic falling film reactors [36–38], monoliths [39–42], catalytic foams [43–45] and catalytically coated 3D-printed scaffolds [46–50]. These designed porous structure reactors and catalytic static mixers (CSMs) were developed to overcome common limitations associated with packed bed reactors, such as high pressure drops and temperature gradients which can be hard to control. Recently, different coatings including Cu, Ni, Pd, Pt and Au have been immobilized on different 3D-printed base scaffolds by electroplating or cold spray techniques [51].

CSMs for heterogeneous hydrogenation reported so far have utilized circular cross-section channels and, as mentioned above, deposition of thin layers of metal applied by electroplating or cold spray. Importantly, the heat transfer and scalability of tube bundle reactors can be improved using rectangular channels. This is due to their improved heat transfer, which can be more easily maintained when the reactor dimensions are increased [52,53]. For this reason, we hypothesized that the scalability of the CSMs could be further improved by designing mixer templates for rectangular crosssection channels. Moreover, utilization of porous catalyst supports for the coating of the mixers could enhance the contact surface with the reaction mixture. Herein, we present the development, characterization and evaluation of rectangular cross-section CSMs coated with a layer of Pd/Al₂O₃ as active catalyst. The CSMs were designed to fit in a commercially available and scalable reactor system [52–57], and were produced by additive manufacturing. Additive manufacturing features several advantages over conventional machining techniques for the generation of metal parts, such as rapid prototyping and the utilization of lower amounts of materials and energy [58]. The flat rectangular channel structure provided excellent heat transfer (in the order of 10 kW m⁻²K⁻¹ [53]). The system was tested for the reduction of aromatic nitro compounds to the corresponding anilines.

2. Material and methods

2.1. General remarks

Solvents and reagents were obtained from commercial vendors and used without further purification unless noted otherwise. HPLC analysis was performed using a Shimadzu LC20 system with a C-18 column (150 mm × 4.6 mm with a particle size of 5 μ m) at 37 °C. Mobile phases A (water/acetonitrile 9+1 v/v + 0.1% trifluoroacetic acid) and B (acetonitrile + 0.1% trifluoroacetic acid) were pumped with a total flow rate of 1.5 mL/min. The following gradient program was applied: start at 3% solvent B, increase to 5% solvent B until 3 min, increase to 30% solvent B until 7 min and finally increase to 100% solvent B until 10 min. The conversion of 1-nitronaphthalene (**1**) to 1-naphthylamine (**2**) was determined based on the HPLC area at λ 254 nm according to internal calibrations (see Figure A4, Appendix A). NMR spectra were recorded on a Bruker 300 MHz instrument. ¹H and ¹³C spectra were recorded at 300 MHz and 75 MHz, respectively, with a chemical shift (δ) relative to TMS expressed in parts per million. The abbreviations d, dd, and bs are used to indicate doublet, doublet of doublets and broad signals respectively.

2.2. CSM preparation

Additive manufacturing

The rectangular static mixer was designed using SolidWorks CAD design software. The structure allows for high surface area and facilitates multi-phase mixing. The static mixers were manufactured by Conflux Technologies to the design provided by CSIRO [59]. The 3D printing process was performed using selective laser melting and 316L stainless steel powder.

Pre-treatment of the mixers

The 3D-printed static mixers were firstly washed with 3 wt% hydrochloric acid for 1 h to remove oxidized species and then sonicated in deionized water for 20 min, after which they were washed again with acetone for 10 min and finally dried in an oven under 120 °C vacuum. All the static mixers were pretreated with this procedure.

Pd-Alumina coating

Typically, a dip-coating slurry was prepared by adding Pd/Al₂O₃ powder and solvent (water) into a vial and stirring overnight until a uniform slurry was formed.

Uncoated mixers were dipped in the slurry for a few seconds, followed by pressurized air blowing to eliminate excess liquid and prevent channel blockage. The dipped mixers were then horizontally placed in an open container at room temperature for a day so that most of the solvent would evaporate in air. Finally, the mixers were placed in an oven under 120 °C vacuum to eliminate any residual solvent.

This coating and drying process was repeated 2-3 times to gain the desired catalyst layer thickness on the CSMs.

Before and after each coating step, the mass of the mixer was recorded to calculate the loading percentage (typically a total loading 3-5% of Pd/Al_2O_3 is attained). To evaluate the adherence of the catalyst layer, the coated CSMs were subjected to sonication in water for 10 min.

2.3. CSM characterization

Morphological images of CSMs were created using scanning electron microscopy (SEM) via secondary electron (SE)-, and back-scattered electron (BSE) modes at an accelerating voltage of 5 kV, while the elemental mapping was conducted via energy-dispersive X-ray spectroscopy (EDX) mode, by using a Hitachi TM3030Plus tabletop microscope. EDX data was analyzed using an AZtec analysis software.

2.4. Continuous flow setup

The liquid feed was pumped using a Knauer AZURA® P 4.1S HPLC pump. An H-Genie[™] hydrogen generator from ThalesNano Energy was utilized as hydrogen source and introduced into the reactor using a built-in mass flow controller (MFC). The gas and liquid streams were combined in a Y connector made from PEEK immediately before being fed into the Ehrfeld Modular MicroReaction System (MMRS). The hydrogenation reactions were performed in an Ehrfeld Miprowa® Lab reactor (attached to the MMRS) featuring up to 8 channels with a cross section of 1.5 mm × 12 mm and a length of 300 mm each. The channels are connected in series and can be filled individually either with customized CSMs (length 150 mm) or initial herringbone shaped flow baffles (45° angle, strut width 1.0 mm, spacing 2.0 mm, length 300 mm) made of Hastelloy (up to 16 CSMs can be inserted in the reactor). During all experiments, the amount of channels was reduced from 8 to 4 and they were either filled with CSMs or flow baffles to enhance mixing between gas and liquid phase. A Huber CC 304 thermostat, featuring an integrated temperature sensor at the reactor output, was used to adjust the temperature of the Miprowa® Lab reactor. After a stainless steel cooling coil, a Swagelok® KCB series backpressure regulator (BPR) was used to set the pressure inside the flow reactor. The gas/liquid (g/l) mixture was separated by a customized low volume g/l separator at ambient conditions.

2.5. General procedure for continuous flow hydrogenation

In a 250 mL volumetric flask, a 0.2 mol/L solution of 1-nitronaphthalene (**1**) (8.66 g) in absolute EtOH was prepared. Before each experiment, the reactor was purged with a solvent/gas mixture under the reaction conditions (e.g. T = 125 °C, p_{BPR} = 25 bar, Q_L = 1.00 mL/min, Q_G = 50 mL_N/min, with Q_L and Q_G representing the flow rates for the liquid and the gaseous H₂ stream respectively). The reaction was initialized by switching the input of the liquid feed pump from solvent to the substrate solution. Samples were collected at regular intervals at the output of the gas/liquid separator and diluted for HPLC analysis.

2.6. Execution of residence time distribution (RTD) measurements

To determine the RTD under different conditions, a UV/Vis flow cell was connected to the liquid output of the g/l separator. Absorption spectra were recorded using an optical fiber based Avantes AvaSpec-ULS2048 spectrometer and the corresponding AvaLight-DHc light source including both a deuterium and a halogen lamp. A solution of anthracene in EtOH was used as tracer and the absorbance at λ 339 nm, λ 356 nm and λ 375 nm was monitored over time.

2.7. Determination of catalyst leaching by inductively coupled plasma mass spectrometry (ICP-MS) Prior to measurements, the samples were diluted with ultrapure water (Milli-Q) to contain 10 % (v/v) ethanol. The concentrations of Al, Cr, Cu, Fe, Mo, Ni and Pd were determined by ICP-MS (7700x, Agilent Technologies, Waldbronn, Germany). The instrument was equipped with a Micro Mist nebulizer (Glass Expansion, Melbourne, Australia), a Scott type double pass spray chamber, a 2.5 mm ID quartz torch, a sample cone made from copper with nickel tip and a skimmer cone made from nickel. Quantification was done via external calibration. The calibration range was as follows: $0.01-10 \mu g/L$ for Al, Cr, Cu, Fe, Mo, Ni and Pd. The calibration standards include 10% (v/v) of ethanol. Certified reference material (NIST 1640a, Trace Elements in Natural Water) was used to evaluate the trueness of the measurements. The following isotopes were measured: ${}^{27}Al$, ${}^{52}Cr/{}^{53}Cr$, ${}^{56}Fe$, ${}^{60}Ni$, ${}^{65}Cu$, ${}^{98}Mo$, ${}^{105}Pd$.

3. Results and discussion

3.1. Manufacturing and characterization of CSMs



Figure 1. 3D model of rectangular static mixer.

A tailor-made static mixer design was created to retrofit to the reactor channel geometry of the Ehrfeld Miprowa[®] system. Figure 1 above shows a design drawing of these static mixers. The Miprowa[®] Lab reactor channels have a width of 12 mm, a height of 1.5 mm and a length of 300 mm; we decided to fill one channel with two CSMs of 150 mm length in series. Especially the small channel height of 1.5

mm presented a challenge as most commercial metal printers have a limited resolution, determined by the particle size used for the print, hence design features of < 0.4 mm are not desirable. This minimum design feature of 0.4 mm was adhered to herein, with the thickness of the metal sheet being 0.45 mm and the minor axis of the elongated holes being 0.8 mm. The main design concept here was to achieve a high degree of interfacial contact between liquid and a gas phase, continued break up of bubbles along the pathway of the fluidic channel and to maximize contact of the two mobile phases with the supported catalyst. Secondly, the static mixer was also optimized for a maximum 'coat-able' surface, in order to deposit as much catalyst onto the CSM as possible without obstructing the flow path. The mixer contains triangular ducts above and below the sheet, which are angled towards the side wall of the channel and away from the general flow direction, which is along the length of the CSM. The elongated wholes within the sheet connect the triangular ducts and allow for a cross-flow from the ducts above the sheet to the ducts below and vice versa. This results in a zig-zag type flow pattern over the length of the CSM, changing between flow along the angled ducts and flow crossing the ducts, which in turn is believed to maximize the interfacial contact between liquid phase, hydrogen and solid catalyst mentioned above. The mixing elements were analyzed by scanning electron microscopy before and after the coating process (Figure 2). BSE images showed almost full coverage of the mixer with the Pd/Al₂O₃ and a good catalyst dispersion. Only small spots where the cotaing was detached from the mixing element could be observed by the brighter color of the BSE image (Figure 2c). Additional images and EDX spectra can be found in Figures A1 to A3, Appendix A.



Figure 2. (a,b) Back scattered electron (BSE) images of SM before coating; (c,d) BSE images after coating with Pd/Al₂O₃.

Some of the standard 300 mm herringbone shaped flow baffles of the employed Ehrfeld hydrogenation reactor were replaced by the thus obtained CSMs which fit into the flat rectangular channels (see *Figure 3*). In total 16 CSMs with a length of 150 mm could fit into one reactor.



Figure 3. Opened hydrogenation reactor with up to 8 rectangular channels. The photograph shows two CSMs (top right) compared to the initial herringbone flow baffles (bottom right).

3.2. Reaction parameter optimization using one CSM element

The performance of the Pd/Al₂O₃ CSMs was evaluated using the reduction of nitroaromatics as model. In particular, the conversion of 1-nitronaphthalene (1) to 1-naphthylamine (2) was selected for the study. A series of solvents was initially evaluated, namely methanol, ethanol, ethyl acetate, toluene, tetrahydrofuran and acetonitrile. An important aspect for solvent selection for continuous flow processes is the solubility of both the starting materials and products under the reaction conditions, which needs to be appropriate to avoid clogging of the reactor. Safety, health and environmental score of the solvents were also considered [60]. All tested solvents showed good solubility for amine 2 (> 2 mol/L). The solubility screening for the starting material 1 revealed that the nitroaromatic was readily soluble in ethyl acetate, toluene, tetrahydrofuran and acetonitrile (> 4 mol/L), but it was less soluble in methanol and ethanol (ca. 0.3 mol/L).

Preliminary hydrogenation test runs were carried out at 75 °C in the six solvents (see *Table A1*, Appendix A). The conversions of substrate **1** to amine **2** ranged from 33% in tetrahydrofuran to 53% in ethyl acetate under identical conditions. Considering the results of solubility tests for compounds **1** and **2**, preliminary hydrogenation test runs and CHEM 21 recommendations [59], ethanol and ethyl acetate were identified as most promising solvents. To avoid solubility problems, and consequent precipitate formation, the substrate concentration was set to 0.2 mol/L for all further experiments.

The continuous flow setup was arranged according to *Scheme 1*, including a temperature sensor at the output of the flow reactor (T) and an integrated pressure sensor of the HPLC pump (P). All initial optimization studies were carried out using one CSM, which was inserted at the beginning of the 4th

rectangular reactor channel. To allow better comparison between the different optimization steps, the following conditions were chosen as "standard conditions" for the hydrogenations using one CSM: $Q_L = 1.00 \text{ mL/min}$, $Q_G = 50 \text{ mL}_N/\text{min}$, 125 °C, 25 bar.



Scheme 1. Continuous flow setup for hydrogenation reaction using CSMs.

When the reaction was performed in EtOAc over a period of 4 h at 125 °C and 25 bar, a decrease of the reaction conversion from 91% to 80% was observed (see *Figure* 4). Notably, the reaction selectivity remained constant (> 99%); HPLC monitoring did not reveal the formation of any side products, but a gradual increase in the amount of unreacted starting material **1**. Using EtOH instead of EtOAc caused less drop in conversion during the first 2 h of operation (from 91% to 87%) and then resulted in a steady conversion within the monitored time. This effect was ascribed to the higher strength of the protic EtOH, capable of eluting with more efficiency amine **2**, which might adhere to the surface of the Al₂O₃ causing a decrease of the active catalyst surface. This phenomenon was temperature dependent. At lower temperatures (e.g. 75 °C) decrease of conversion over time was observed even with EtOH, while above 125 °C the conversion was essentially constant over long periods (vide infra). A 1:1 v/v solvent mixture of EtOH and EtOAc did not provide satisfactory results (Figure 4). Thus, EtOH was selected as solvent for further optimization.



Figure 4. Performance of hydrogenation reaction over 4 h in EtOH, EtOAc and EtOH/EtOAc 1:1. $Q_L = 1.00 \text{ mL/min}$, $Q_G = 50 \text{ mL}_N/\text{min}$, T = 125 °C, $p_{BPR} = 25 \text{ bar}$, c(1) = 0.2 mol/L.

Next, the influence of pressure and temperature were investigated (*Figure 5*). As expected, increase of both parameters had a positive effect on the reaction outcome. A significant increase of conversion was observed from 75 °C to 125 °C (Figure 5a), which then became less pronounced at temperatures up to 163 °C, potentially due to a decreased hydrogen adsorption on the catalyst surface. The reactor pressure was increased up to the limit of the reactor (25 bar) pressure (Figure 5b).



Figure 5. Influence of pressure and temperature $Q_L = 1.00 \text{ mL/min}$, $Q_G = 50 \text{ mL}_N/\text{min}$, c(1) = 0.2 mol/L. (a) Temperature influence at 25 bar. (b) Pressure influence at 125 °C.

The g/l ratio was also investigated. In addition to the hydrogen stoichiometry, this parameter has a profound importance as it may determine the flow regime and the mixing efficiency in the system. Liquid flow rates ranging between 0.50 mL/min and 2.00 mL/min and gas flow rates between 25 mL_N/min and 100 mL_N/min were evaluated (*Figure 6*). Although higher conversions can be achieved at e.g. 163 °C (Figure 5), the experiments were performed at 125 °C to obtain moderate conversions in order to see more clearly the effect of the flow rates. For Q_L = 2.00 mL/min, the gas flow rate was not set below 27 mL_N/min to ensure delivery of 1.00 stoichiometric equivalents of hydrogen. Interestingly, the gas flow rate Q₆ had a negligible effect on the reaction conversion, whereas an almost linear relation between Q_L and the conversion was observed. This effect pointed to a parallel flow regime for the biphasic gas/liquid mixture, in which most likely the liquid stream adheres to the catalyst surface. At low Q₆ values the flow regime would eventually change at the late stage of the reaction, when most of the H₂ has been consumed. This hypothesis was confirmed by determining the residence time distribution in the reactor at a constant value for Q_L = 1 mL and variable gas flow rates (25-100 mL_N/min) under reaction conditions (EtOH, 125 °C, 25 bar). Analogous residence times were obtained in all cases (see *Figure 7*), which would not be the case for a typical segmented plug flow

regime. The conversions determined by HPLC ranged from ca. 71% at Q_L = 2.00 mL/min to 94% at Q_L = 0.50 mL/min.



Figure 6. Relationship between liquid flow rate (Q_L) and gas flow rate (Q_G) for the heterogeneous hydrogenation at 125 °C and 25 bar using one CSM. * At a liquid flow rate of 2.00 mL/min the gas flow rate was increased from 25 mL_N/min to 27 mL_N/min to ensure 1.00 stoichiometric equivalents of hydrogen are delivered.



Figure 7. RTD measurement using a step experiment, followed by UV/Vis absorbance. At t = 0 min (step up) a tracer was injected, until t = 30 min (step down) when the tracer was purged from the reactor.

3.3. Process scale up

The process could be readily scaled up by increasing the number of CSMs inserted into the reactor from one to four (arranged in a serial fashion), resulting in a longer catalytically active channel. Thus, the throughput of the hydrogenation could be augmented while maintaining similar contact times with the catalyst surface. Utilizing the flow reactor equipped with 4 CSM units, a new range of flow rates was investigated: Q_L = 4.00 mL/min to 8.00 mL/min and Q_G = 200 mL_N/min to 400 mL_N/min, at 125 °C and 25 bar (Table 1). Compared to the results obtained using one CSM (Figure 6), an impressive increase in conversion to the desired product 2 was observed at higher throughputs. For example, using one CSM at Q_L = 1.00 mL/min and Q_G = 50 mL_N/min, 85% conversion was obtained. With 4 CSMs units and using 4-fold the flow rates (thus matching the contact time with the catalyst) 99% conversion was achieved. This performance increase was ascribed to an improved mass transfer at the higher flow rates utilized, pointing to a diffusion-limited reaction at low flow rates. Even at higher liquid throughputs of 8.00 mL/min, excellent conversions up to 98% to the desired amine 2 could be obtained (Entry i, Table 1). The influence of Q_L on the conversion was much higher than Q_G (similar to the results observed with one CSM, Figure 6). Reactions conducted at $Q_L = 4.00$ mL/min (Entries a-c, Table 1) showed the highest conversion and minimum deviation between the results at different gas flow rates. At $Q_L = 6.00 \text{ mL/min}$ (Entries d-f, *Table 1*) the conversion slightly dropped, but was still above 99%. At Q_L = 8.00 mL/min (Entries g-i, Table 1), the conversion was 96%-98%. The excellent results obtained and the inherent scalability of the reactor utilized using rectangular cross-section channels [57], clearly demonstrate the potential of the concept herein described to develop effective heterogeneous hydrogenation protocols using CSM technology.

	entry	QL	Q_{G}	HPLC conv.
		[mL/min]	[mL _N /min]	[%] ^{a)}
	а	4.00	200	99.9
	b	4.00	300	99.6
	с	4.00	400	99.7
	d	6.00	200	99.0
	e	6.00	300	99.4
	f	6.00	400	99.3
	g	8.00	200	96.7
	h	8.00	300	96.2
	i	8.00	400	98.0

Table 1. Relationship between liquid flow rate (Q $_l$) and gas flow rate (Q $_G$) using a set of four CSMs in the flo	w setup
described in Scheme 1 at 125 °C, 25 bar.	

^{a)} determined at 254 nm

3.4. Synthesis of tizanidine intermediate

A potential practical application of the developed heterogeneous hydrogenation process was showcased with the hydrogenation of 4-chloro-2-nitroaniline (**3**), an intermediate step in the synthesis of the α 2 agonist tizanidine (**5**) (*Scheme 2*) [61,62].



Scheme 2. Synthesis of tizanidine (5), based on the hydrogenation reaction of 3.

The hydrogenation of **3** to 4-chlorobenzene-1,2-diamine (**4**) was conducted using a 0.1 mol/L solution of the nitroaromatic in EtOH abs. as feed solution. The hydrogenation was carried out using 4 CSMs in series. Thus, to achieve full conversion 4 mL/min of liquid feed were injected into the reactor (conditions from entry a in Table 1). The gas flowrate was set to 100 mL_N/min due to the lower concentration of starting material compared to the optimization studies. The reactor (Scheme 1) was set to 125 °C and 25 bar. Gratifyingly, under these conditions full conversion of the nitroarene **3** and excellent selectivity (99%) toward the target amine **4** was observed (GC-FID). The dehalogenation sideproduct o-phenylenediamine was the only impurity detected (typically <1.0%). The hydrogenation process was performed uninterruptedly for 8 h (0.2 mol scale). The product was collected in 4 separate fractions (2 h intervals) under N₂ atmosphere and protected from light. Simple evaporation of the solvent under reduced pressure, without any additional work-up, yielded the target amine **4** with 99% purity (27.3 g, 96% isolated yield). Evaporation of the solvent was carried out for each of the aliquots of the crude reaction mixture (480 mL) as it was collected from the reactor output. The ethanol evaporated during the isolation of **4** was recycled to prepare new starting solution during the course of the long run, allowing to the reduce the solvent consumption for the preparation of the aniline.

3.5. CSM stability, Pd leaching and coating characteristics

One of the most important characteristics of immobilized catalysts is their stability over long periods. In this context, it should be noted that all optimizations in this study were performed using the same CSM over two months and with a net reaction time well beyond 50 h. During that time very high reproducibility was observed for the experiments carried out under standard conditions (T = 125 °C, $p_{BPR} = 25$ bar, $Q_L = 1.00$ mL/min, $Q_G = 50$ mL_N/min). Moreover, the weight of the CSM element was

completely stable during that time (7.458 g before the first hydrogenation, compared to 7.462 g after two months of operation).

To investigate the stability of the CSMs further, the amount of Pd leaching was determined by ICP-MS, together with other metal constituents of the CSMs and the reactor, such as Al, Cr, Fe, Ni, Cu and Mo. All analyzed samples (see *Table A2*) show a Pd concentration below 0.5 ppb and an Al concentration below 50 ppb, indicating very high stability of the Pd/Al_2O_3 coating under the employed reaction conditions. No difference was observed between a used mixer and new mixers, which were used for the first time during the hydrogenation reactions. The concentration of other metals contained in the stainless steel scaffold, such as Cr, Fe, Ni, Cu and Mo was below the limit of quantification (1 to 10 ppb depending on the metal analyzed), except one sample from a hydrogenation reaction at 125 °C, which showed a Ni content of 19 ± 2 ppb.

When a set of four new CSMs was used for the hydrogenation reaction, the concentration of product eluted from the reactor was monitored by regular HPLC sampling. The flow rates were adapted accordingly to $Q_L = 4.00 \text{ mL/min}$ and $Q_G = 200 \text{ mL}_N/\text{min}$. During the first run, the concentration of amine **2** increased steadily over the monitored duration of 1 h, despite quantitative conversion (see *Figure A6*). During the second run, the concentration of eluted product **2** reached a constant plateau within 5 - 10 min. We assume this observed effect is based on the retention of compounds by the highly porous Al₂O₃ support.

4. Conclusions

We have developed a continuous hydrogenation process using a heterogeneous palladium catalyst immobilized on static mixing elements in a highly porous Al₂O₃ support. The presented catalytic static mixers are very stable under intensified reaction conditions (> 100 °C, 25 bar), indicated by high catalytic activity over time, constant weight and essentially no metal leaching (confirmed by ICP-MS measurements). During the optimization process, the influence of pressure, temperature and flow rates of both the gas and the liquid flow rates were investigated using the hydrogenation of 1-nitronaphthalene (1) to 1-naphthylamine (2) as model. Only a minor influence of the hydrogen flow rate was observed within the investigated range, pointing to a parallel flow regime in the reactor. When the amount of CSMs in the reactor was increased from 1 to 4 units, the corresponding increase in the liquid flow rate resulted in excellent conversions > 99%. This effect was ascribed to the increased mass transfer at elevated liquid throughputs. To demonstrate the applicability of the developed process using CSMs for sustainable hydrogenations in pharmaceutical industry, 4-chloro-2-nitroaniline (3) was reduced to 4-chlorobenzene-1,2-diamine (4), a key intermediate in the synthesis of the drug

tizanidine. The process was operated for 8 h, yielding 96% of the desired product after simple removal of the solvent.

The lab-scale continuous flow reactor utilized, featuring rectangular cross-section reaction channels, has the advantage of a very fast transfer to pilot and to production scales with minimal re-optimization of the reaction conditions. This is achieved by the 'smart dimensioning' concept of the reactor design, and the excellent heat transfer than can be achieved in rectangular cross-section channels, typically superior to e.g. circular cross-section channels [52,53]. This scale up concept has already been demonstrated for a very exotermic g/l alkoxylation reaction involving ethylene oxide, in which improved product quality, yield and safety were achieved by transferring the process from batch to flow on ultimately 10.000 t/a scale [57].

Author credt statement

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https:/doi.org/10.1016/j.cattod.xxxxxx

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