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# The use of catalytic static mixers for continuous flow gas-liquid and transfer hydrogenations in organic synthesis

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## ABSTRACT

Catalytic static mixers were used for the continuous flow hydrogenation of alkenes, alkynes, carbonyls, nitro- and diazo-compounds, nitriles, imines, and halides. This technique relies on tubular reactors fitted with 3D printed static mixers which are coated with a catalytic metal layer, either Pd or Ni. Additive manufacturing of the metal mixer scaffold results in maximum design flexibility and is compatible with deposition methods such as metal cold spraying which allow for mass production and linear process scale up. High to full conversion was achieved for the majority of substrates, demonstrating the flexibility and versatility of the catalytic static mixer technology. In the example of an alkyne reduction, the selectivity of the flow reactor could be directed to either yield an alkene or alkane product by simply changing reactor pressure.

Keywords: flow chemistry, hydrogenation, heterogeneous catalysis, supported catalyst, additive manufacture, static mixer

## Introduction

New solutions combining heterogeneous catalysis with flow chemistry have attracted much interest in the area of organic chemistry over the past years, in large part because they encompass several principles of green chemistry and process intensification.<sup>1–4</sup> The advantages of flow chemistry over classical batch procedures have been demonstrated in numerous publications.<sup>5-10</sup> Compared to their homogeneous liquid phase counterparts, reactors for heterogeneous catalytic reactions are significantly more complex and specialised, hence their implementation in organic synthesis in the laboratory and in industrial production has not been as widespread and straight forward. The majority of flow chemistry devices for heterogeneous catalysis developed to date can be viewed as variations of one of the following three concepts: fixed beds containing porous catalytic particles or beads; porous monoliths with embedded catalyst; porous catalytic layers deposited onto chip- or plate-type structures.<sup>11–19</sup> Compared to these more conventional approaches, our tubular Catalytic Static Mixer (CSM) concept presented herein, has a series of advantages, which we outlined in detail in our previous work.<sup>20</sup> We used additive manufacture to build the mixer scaffold of the CSM, followed by deposition of the catalytic layer via electroplating or cold spraying. Static mixers are classically used to ensure continuous mixing or mixing at the entry of a reactor. Mixer design can vary depending on flow conditions and fluid properties, and the choice of design can have a major impact on the performance of the chemical reaction process. By using additive manufacturing techniques, such as 3D metal printing, limitations of conventional subtractive metal forming methods can be overcome, resulting in an almost complete freedom of design. In 2010 a polymeric flow chemistry concept for heterogeneous catalysis was published<sup>21</sup> which inspired the development our CSM technology. These early polymeric capillary reactor devices were made by polymer melt

extrusion followed by immobilisation of a palladium(0) catalyst on and inside the polymer wall. Due to limited temperature stability of the polymer matrix, these devices could only be used for reactions at temperatures up to 60 °C, while our metal system can be operated at up to 250 °C.

Herein we present a series of hydrogenation reactions, reducing alkenes, alkynes, carbonyls, nitroand diazo-compounds, nitriles, imines, and halides on CSMs containing nickel(0) or palladium(0). The results from these reactions were quantified in terms of turn-over frequency (TOF) and space time yield (STY), to make them easily comparable to other reactor devices. Due to the hierarchical structure (scaffold guiding the fluid flow + porous layer containing the active catalyst), CSM reactors are inherently more adaptable and versatile than many other hydrogenation reactors.

## Experimental

#### **Catalytic Static Mixers**

CSMs are static mixers, coated with a catalytic active layer, which can be fitted inside a tubular reactor geometry, as shown in Figure 1. All CSMs were prepared at CSIRO using a combination of additive manufacturing and metal deposition techniques. Two prototype flow reactors were constructed containing either four or twelve catalytic tube sections, hence one CSM set consists of either four or twelve identical mixers.



Figure 1. CSM fitted inside a stainless steel tube.

**Table 1.** Physical properties of CSM sets; catalyst coatings: Ni(0) and Pd(0); deposition methods: electroplating (EP) and cold spraying (CS); scaffold materials: 316L stainless steel; uncoated (non-catalytic) control set: *X-X-4*.

catalyst	no. CSMs	т <sub>сѕм</sub> [g]	m <sub>cat</sub> [g]	V <sub>CSM</sub> [ml]	V <sub>R</sub> [ml]	φ [%]
Pd-EP-1	4	27.0	0.4	3.6	13.4	78.8
Pd-EP-2	12	73.8	1.3	9.2	40.6	81.2
Ni-CS-3	12	96.5	6.0	11.7	38.1	76.3
X-X-4	12	64.7	-	6.2	43.6	87.5

A total of four catalyst sets were prepared for this work (see Table 1). Two different metal catalysts were deposited, namely Pd(0) using electroplating and Ni(0) using cold spraying. The scaffold material chosen for all samples was 316L stainless steel and the design chosen is shown in Figure 1. This mixer design was developed by CSIRO and optimised for mixing, heat transfer and maximum surface area for catalyst deposition. Initial computational fluid dynamics simulations have shown that our design performs well for liquid and liquid-liquid phase flow at low Reynolds numbers of typically below 2300. For baseline comparison, a set of uncoated mixers was prepared, *X-X-4*, which did not contain a catalytic layer. The CSM sets were weighed before and after coating (mass after coating:  $m_{CSM}$ ) in order to determine the amount of catalyst deposited,  $m_{cat}$ . Their combined displacement volume,  $V_{CSM}$ , was determined in order to calculate the remaining reactor volume,  $V_{R}$ , and porosity of the CSM,  $\phi$  (see supporting information).The physical data of the CSM sets is collated in Table 1 and SEM images of some of these mixers coated with Pd (0) or Ni(0) are shown in Figure 2. Several SEM images were taken along the length of the CSMs, conforming the relative uniformity of the catalyst coating.



**Figure 2.** (a+b) SEM images of an electroplated Pd coating on a 3D printed stainless steel scaffold, (c+d) SEM images of a cold sprayed Ni coating on a 3D printed stainless steel scaffold.

## Additive Manufacture of CSM scaffolds

All 3D printed CSMs were manufactured on the Arcam A1 electron beam melting 3D printer using 316L stainless steel powder. The machine process parameters were set by trial for this powder. Arcam Electron Beam Melting (EBM) uses an electron beam to melt and fuse metal powders, layer-by-layer, into three-dimensional parts. The process takes place under vacuum in a powder bed where a rake feeds a layer of powder over a starting plate on a vertically movable table. A typical starting bed temperature for 316L stainless steel is 850 °C. Supports underneath the CSM scaffolds were built ;these are 0.5 mm diameter and 3 mm long support pillars that aid in the melting process to avoid swelling of the part above the plane of the powder layer. A 'net' theme is used for the melting of the mixers due to their fine cross-sections. At the end of the build the unfused powder is removed from the mixer by grit-blasting with the same powder material. Further details of the general 3D printing process of CSMs have been described in previous work.<sup>20</sup>

#### **Catalyst Deposition using Electroplating**

Thin adherent layers of metallic palladium were electroplated onto the static mixers using an axial flow cell and standard galvanostatic (constant current) procedures <sup>22,23</sup>. The electrodes in this flow cell were arranged concentrically with the mixer as the central electrode to ensure an even current

distribution. Prior to electrodeposition, the mixers were thoroughly cleaned and activated using published methods to ensure the deposits were uniform and adherent. The cleaning and activation procedure used for the 316L stainless steel mixers was a simultaneous activation – electroplating process in Watt's Bath (acidic nickel chloride), as described in ASTM B254-92(2014).<sup>24</sup>

#### **Catalyst Deposition using Metal Cold Spraying**

A Plasma Giken PCS-1000 cold spray system, fitted with a water-cooled, one-piece, tungsten carbide nozzle with a 3 mm throat, was used to spray nickel powder (particle size range: 10 to 20  $\mu$ m; d<sub>50</sub> =  $\mu$ m). The conditions described herein produced Ni coatings with high porosity and high metallurgical bonding, which was confirmed by SEM images of the cross-section of the Ni layer. For this work a new custom system was designed and constructed to allow catalysts to be sprayed more efficiently than the method we had previously reported.<sup>20</sup> This system utilized two stepper motors mounted in opposing directions on a common rail. Scaffolds were then held in tension between the shafts of the motors by means of spring couplers and end holding split rods. These types of couplers can be used even with a small amount of misalignment between the motors and/or mixer attachment points. Multiple scaffolds were held between the shafts by concatenating them together with custom-made couplers. To allow this system to grip the scaffolds effectively, the mixers were designed and made with flat tabs on each end. These tabs were made sufficiently strong to not break during spraying but weak enough to be removed after spraying. To prevent any breakage of the scaffolds from the high speed impact of particles and gas from cold spray process, an aluminium backing plate with a semi-circular cross section was mounted and positioned just behind the mounted scaffolds. This backing plate was removed and replaced, as necessary, to prevent fouling of the mixer rotation by excessive overspray coating. A computer program was written in LabVIEW™ to simultaneously rotate the shafts of the motors in opposing directions, i.e., clockwise and anticlockwise as viewed from the shaft. Rotating speeds of up to 300 rpm were used whilst cold spraying the scaffolds. The new method resulted in an increase of productivity and higher surface coverage of catalyst on accessible surfaces of the scaffold. Detailed information on the general cold spraying process and on the specific conditions used in our previous work can be found in Avril et al.<sup>20</sup>



**Figure 3.** Schematic diagram of the cold spray set-up for coating nickel onto a 3D printed metal scaffold; highlighted in light blue is the location of the CSM scaffolds.

#### **Reactor Design**

The continuous flow reactor set-up was designed and built by CSIRO. The set-up could either be run with a rectangular reactor module, housing four CSMs (Mk 1, built by Cambridge Reactor Design to CSIRO's specifications, see also previous work<sup>20</sup>) or a cylindrical reactor module housing twelve CSMs (Mk 2, built by CSIRO). Figure 4 shows a process flow diagram of the reactor set-up and Figure 5 shows photographs of the Mk 1 and Mk 2 reactor modules. The Mk 2 module was used herein for reactions using gaseous hydrogen and the Mk 1 module was used for transfer hydrogenations using ammonium formate. The Mk 2 module with its cylindrical body and two endplates presents an improvement over our previous Mk 1 design, as it holds three times as many CSMs, equating to three times the reaction volume on a similar reactor foot print. Changeover time between catalyst sets was also shortened by using the Mk 2 design. The Mk 2 module is heated electrically using a heating mantle and is shielded and insulated by a stainless steel box. A detailed description of the Mk 1 reactor was previously reported in our earlier work.<sup>20</sup> Further details on the Mk 2 reactor configuration and a comparison between the Mk1 and Mk2 reactors for the hydrogenation of vinyl acetate can be found in the supporting information.



**Figure 4.** Process flow diagram of the tubular flow reactor set-up for continuous flow hydrogenations with gaseous  $H_2$  (Mk 2) or for continuous flow transfer hydrogenations (Mk 1); the gas line, highlighted in red, was only used for reactions with gaseous  $H_2$  (Mk 2 configuration).



**Figure 5.** Photographs of the two continuous flow hydrogenation reactors; Mk 1 reactor configuration housing four CSMs was used for transfer hydrogenations using a liquid line only; Mk 2 reactor configuration housing 12 CSMs was used for hydrogenations with a gaseous H<sub>2</sub> line and a liquid substrate line.

#### Continuous flow hydrogenation reactions using gaseous H<sub>2</sub> (Mk 2 configuration)

A series of continuous flow experiments with hydrogen gas were conducted on the Mk 2 configuration, investigating the hydrogenation of several substrates, containing C-C double and triple bonds, carbonyl-, nitro-, nitrile-, imine-, and halide-groups. A typical hydrogenation of vinyl acetate (VAc) using the Mk 2 reactor configuration was conducted as follows:

First the CSMs inside the reactor (*Pd-EP-2*) were activated by flowing hydrogen over them at 16 bar, 120 °C and a gas flow rate of 67.9 mL<sub>N</sub>/min. The activation was conducted for 60 min. After activation the reactor was flushed with solvent, ethanol (EtOH), using the liquid reagent pump. The substrate, VAc, was dissolved in EtOH to a concentration of 2 mol/L. Upon start-up of the reactor system, hydrogen gas was introduced, together with the washing solvent to prime the reactor, and the parameters for the reaction were adjusted to the following: reactor pressure,  $p_R = 16$  bar, liquid flow rate,  $\dot{V}_L = 1$  mL/min, gas flow rate inside the reactor at reaction pressure,  $\dot{V}_{G,R} = 5$  mL/min, normal gas flow rate measured by the hydrogen mass flow controller,  $\dot{V}_{G,N} = 67.9$  mL<sub>N</sub>/min, gas to liquid ratio, G/L = 5, reactor temperature,  $T_R = 120$  °C. Once pressure and temperature had stabilised, the liquid feed was changed from solvent to stock solution, thus starting the reaction. The clear product, ethyl acetate in the solvent, was collected at the outlet of the reactor in several fractions, which were then analysed by <sup>1</sup>H-NMR and GC. Further details on analysis methods and reagents can be found in the supporting information.

#### Continuous flow transfer hydrogenation reactions (Mk 1 configuration)

A series of continuous flow transfer hydrogenation experiments were conducted on the Mk 1 reactor configuration, investigating the reduction of several substrates, containing nitro- and halidegroups. A typical hydrogenation of *p*-nitroanisole using this set-up was conducted as follows:

Ammonium formate in methanol (MeOH) in the presence of a palladium coated static mixer was used to effect the transfer hydrogenation. This procedure was based on previous work by Ram and Ehrenkaufer<sup>25</sup> and Barret and Spilling.<sup>26</sup> A solution of *p*-nitroanisole (153 mg, 1 mmol), and ammonium formate (315 mg, 4.6 mmol) in MeOH (3 mL) was passed through the Mk 1 reactor, fitted with the CSM set *Pd-EP-1*, and heated at 130 °C at 12 bar, at a flow rate of 1 mL/min. The eluent was collected and the solvent was evaporated to give *p*-methoxyaniline which was then analysed by <sup>1</sup>H-NMR (see Table 3 vide infra). This continuous flow transfer hydrogenation procedure was adopted from earlier work using a palladium(0) catalyst immobilised on a polymeric continuous flow capillary reactor and triethylsilane as the hydrogen source.<sup>21</sup>

## **Results and discussion**

#### Hydrogenation of alkenes, alkynes, halides, carbonyls and organic nitrogen compounds

The two rector configurations described above were used for a series of continuous flow hydrogenations using the Pd or Ni CSM sets described in Table 1. A series of model substrates containing alkene, alkyne, nitrile, imine, nitro, diazo, halide and carbonyl groups were reduced. Table 2 shows all examples reacted on the Mk 2 set-up using gaseous H<sub>2</sub>; table 3 shows all examples reacted on the Mk 1 set-up using the transfer hydrogenation approach. This presents the first demonstration of a transfer hydrogenation reaction inside a CSM reactor. A series of other flow chemistry reactor procedures for transfer hydrogenations have previously been described in the literature, <sup>21,27–29</sup> but none of them use a combination of additive manufacture and supported catalyst. For most of our examples in the tables below only one hydrogenation product was detected; where there were more than one, details are given in the table or in the text below. The reactive groups reduced during operation are highlighted in red for each example.

**Table 2.** Substrates (reactive groups reduced during process are highlighted in red), reaction conditions (substrate concentration in the liquid feed, reactor pressure, liquid flow rate and gas flow rate at reactor pressure) and results (conversion, TOF, and STY) from hydrogenation experiments using Ni and Pd catalysts in the Mk 2 reactor. All reactions were conducted at 120 °C. For entries 2.1, 2.2, 2.4, 2.5, 2.7, 2.8, 2.9 and 2.10, EtOH was used as solvent, for all others EtOAc was used.

Entry	Substrate	Conc. [M]	Catalyst	p [bar]	Ů <sub>L</sub> [mL min <sup>-1</sup> ]	Ÿ <sub>G,R</sub> [mL min <sup>−1</sup> ]	Conv. [%]	TOF [h⁻¹]	STY [g L <sup>-1</sup> h <sup>-1</sup> ]
2.1	O	2	Pd-EP-2	20	1	5	100	7.26	254
2.2		2	Ni-CS-3	20	1	5	97	1.15	264
2.3		0.5	Pd-EP-2	20	1	4	75	1.36	65
2.4		1	Pd-EP-2	24	1	5	54	1.96	96
2.5		2	Ni-CS-3	24	1	5	6	0.07	22
2.6ª		0.5	Pd-EP-2	20	1	4	100 <sup>ª</sup>	1.80	75
2.7 <sup>ª</sup>		2	Ni-CS-3	16	1	5	100 <sup>ª</sup>	1.18	322
2.8 <sup>b</sup>	CN	1	Pd-EP-2	20	2	8	68 <sup>b</sup>	4.96	237
2.9 <sup>b</sup>	CN	1	Pd-EP-2	24	1	8	86 <sup>b</sup>	3.13	149
2.10 <sup>b</sup>	CN	0.5	Ni-CS-3	24	0.5	5	48 <sup>b</sup>	0.07	22
2.11 <sup>c</sup>	0	1	Pd-EP-2	24	2	8	100 <sup>c</sup>	3.27	176
2.12 <sup>d</sup>	CI	0.5	Pd-EP-2	20	1	4	65 <sup>d</sup>	1.07	66
2.13	NO <sub>2</sub>	1	Pd-EP-2	24	2	8	98	7.11	397
2.14	NO <sub>2</sub>	0.5	Pd-EP-2	20	1	4	99	1.80	112
2.15	NO <sub>2</sub>	1	Pd-EP-2	20	2	8	78	5.66	353
2.16	NO <sub>2</sub>	1	Pd-EP-2	20	2	8	87	6.31	393
2.17	NO <sub>2</sub>	1	Pd-EP-2	20	2	8	30	2.18	136



a) multiple products identified, see Scheme 1 and Figure 6, conversion is based on total consumption of substrate; b) multiple products identified, see Scheme S1 and Figure S1 in supporting information, conversion is based on total consumption of substrate; c) multiple products identified, see Scheme 2 and Figure 7, conversion is based on total consumption of substrate; d) multiple products identified: 59%  $\beta$ -methylstyrene, 2% propylbenzene, 4% allylbenzene, conversion is based on total consumption of substrate; e) control experiment with an uncoated mixer set.

**Table 3.** Substrates (reactive groups reduced during process are highlighted in red), reactor pressure, conversion, TOF and STY, from transfer hydrogenation experiments using ammonium formate and the Pd catalyst *Pd-EP-1* in the Mk 1 reactor. All reactions were conducted at 130 °C with a liquid flow rate of 1 ml/min. All substrates were used at concentration of 0.33 M in MeOH.

Entry	Substrate	p [bar]	Conv. [%]	TOF [h <sup>-1</sup> ]	STY [g L <sup>-1</sup> h <sup>-1</sup> ]
3.1	NO <sub>2</sub>	12	31	1.48	56
3.2	NO <sub>2</sub>	20	36	1.72	65
3.3	NO <sub>2</sub>	20	87	4.17	176
3.4	HO NO <sub>2</sub>	20	17	0.81	35
3.5	NO <sub>2</sub>	12	10	0.48	23
3.6	NO <sub>2</sub>	12	20	0.96	45
3.7	NO <sub>2</sub>	12	100	4.76	225
3.8	Br	12	65	3.11	191

High catalytic activity was observed throughout both experimental sets presented in tables 2 and 3. The hydrogenation reactions using a gaseous H<sub>2</sub> feed reached high conversions of >75 % for the majority of examples and full or close to full conversion in several cases; for the transfer hydrogenations conversions were generally lower, but for some entries conversions >75% were achieved. Turn-over frequencies and space time yields of the H<sub>2</sub> gas experiments were higher than for the transfer hydrogenations (max TOF: 7.3 vs 4.8 h<sup>-1</sup>; max STY: ~400 vs ~200 g L<sup>-1</sup> h<sup>-1</sup>), demonstrating that the H<sub>2</sub> gas operation is the more efficient process. While the H<sub>2</sub> gas hydrogenations were more efficient and used a much cheaper hydrogen source, the transfer hydrogenations are more convenient, especially on small laboratory scale, as no gas handling upstream of the reactor is required. The control experiment using an uncoated mixer set, *X-X-4*, listed as entry 2.26, resulted in no conversion of the VAc starting material.

#### Selectivity of the CSM hydrogenation reactor

In the process of evaluating the CSM reactor for the above mentioned examples, a series of interesting selectivity effects were observed. In some cases these selective hydrogenations could be influenced by changing the operation parameters of the reactor, meaning that for the same catalyst and substrate combination a different product could be formed depending on the reactor pressure and flow rates used. In most heterogeneous catalytic applications, selectivity is influenced by a number of factors, and most commonly selectivity towards a desired product is adjusted by the choice of catalyst, rather than the operation parameters.<sup>30</sup> This means that a CSM reactor can be operated in a much more flexible setting than systems that require a catalyst change over to control selectivity. In the following, a few of the entries from Table 2, for which we observed an interesting selectivity effect, are singled out and discussed in further detail.

 The hydrogenation of phenyl acetylene (entries 2.6 and 2.7) can progress through the unsaturated styrene intermediate to the fully hydrogenated ethyl benzene, as shown in Scheme 1. Using a Ni CSM set, we could influence selectivity either towards styrene or ethylbenzene, by simply changing the process conditions, reactor pressure and G/L (see Fig. 5). Using mild conditions (16 bar, G/L = 5, c = 2 mol/L, we achieved full conversion of starting material with a ratio of 9:1 of styrene to ethylbenzene in the product. When using forcing conditions (24 bar, G/L = 10, c = 1 mol/L), we achieved full conversion of starting material to ethylbenzene; no presence of styrene was detected in the product. This demonstrates how selectivity of the CSM reactor was changed from partial reduction to full reduction of the alkyne by simply changing process parameters. This makes this reactor system tuneable to yield different products without the need to change catalyst. In comparison, most examples in the literature are concerned with the influence of the catalyst on the selectivity of the catalytic process; e.g. Bianchini *et al.*<sup>31</sup> and Duca *et al.*<sup>32</sup> describe the selective hydrogenation of phenyl acetylene on supported Pd catalysts or ruthenium complexes and Jia et al.<sup>33</sup> and Kang et al.<sup>34</sup> describe the selective hydrogenation of acetylene over Au/Al<sub>2</sub>O<sub>3</sub> or TiO<sub>2</sub>-added Pd catalysts.





Scheme 1. Consecutive hydrogenation of phenyl acetylene to styrene and ethyl benzene.



Figure 7. Hydrogenation of cinnamaldehyde (CAL) to hydrocinnamaldehyde (HCAL), cinnamyl alcohol (COH) and hydrocinnamyl alcohol (HCOH) using PD-EP-2 and the Mk-2 configuration.

CAL HCAL COH HCOH

8 bar 12 bar 16 bar 20 bar 24 bar

The hydrogenation of benzyl cyanide (entries 2.8 to 2.10) resulted in high selectivity towards the primary amine, and only showed minor amounts of the undesired dimeric side product between 3 and 9% (see Scheme S1 and Figure S1 in the supporting information). The conversions were medium to good with values as high as 86%. The reduction of nitriles is a frequently occurring industrial operation in the pharmaceuticals and food supplements area, and unwanted formation of secondary amine dimers are a known problem<sup>35</sup>.



**Scheme 2.** Hydrogenation pathway of cinnamaldehyde (CAL), yielding cinnamyl alcohol (COH), hydrocinnamaldehyde (HCAL) and hydrocinnamyl alcohol (HCOH).

The hydrogenation of cinnamaldehyde (entry 2.11 and Scheme 2), a substrate containing a carbonyl group and a C-C double bond, was performed on Pd. At 24 bar full conversion of the starting material was achieved, whereby the majority, 60%, was hydrogenated to the corresponding saturated aldehyde hydrocinnamaldehyde (HCAL); 37% of the fully hydrogenated hydrocinnamyl alcohol (HCOH) and 3% of the unsaturated alcohol, cinnamyl alcohol (COH) made up the remaining product. This trend was also observed at lower reactor pressures which yielded lower conversions (see Figure 7). These results show that the Pd catalyst was more selective towards the reduction of the double bond than the aldehyde. This is in contrast to our previous work where a Pt CSM was used, favouring the reduction of the aldehyde.<sup>20</sup> Similar to the case of phenyl acetylene, the product composition and hence selectivity of the hydrogenation process could be influenced by the chosen reactor pressure. In contrast, most literature is concerned with the influence of the catalyst on the selectivity of the hydrogenation of cinnamaldehyde, rather than the influence of the process parameters (see for example work by Tessonnier *et al.*,<sup>36</sup> Vu *et al.*<sup>37</sup> and Zhang *et al.*<sup>38</sup>).

Analogously, the reduction of cinnamyl chloride (entry 2.12) was expected to result in two intermediates and a fully hydrogenated product. Here the following products were observed: 59%  $\beta$ -methylstyrene, 2% propylbenzene, 4% allylbenzene.



**Figure 8.** Hydrogenation of ortho-, meta- and para-substituted nitro benzenes to the corresponding anilines using *Pd-EP-2* and the Mk-2 configuration.

 Furthermore the influence of different substituents on the benzene ring for the hydrogenation of nitro benzenes was investigated. The entries 2.15 to 2.20 and the graph in Figure 8 show reactions conducted under comparable conditions on the Mk 2 reactor using *Pd-EP-2*. Here, ortho-, meta- and para-substituted methoxy nitro benzenes and chloro nitro benzenes were hydrogenated to the corresponding anilines. It can be seen from Figure 8 that the meta-substituted nitro benzenes showed the highest reactivity, closely followed by the ortho-substituted isomers. The para-substituted isomers showed significantly lower reactivity than the other two.

### **Catalyst leaching**

In order to investigate catalyst leaching, a series of dedicated steady state operations were performed on the Mk 2 reactor over several days, using the catalyst sets *Pd-EP-2* and *Ni-CS-3* for the hydrogenation of VAc. A total of 1 L of product solution was processed during these reactions on each CSM set. The reactor performance was checked frequently by NMR showing that no significant drop in conversion was observed over the entire period of operation. The combined product solutions were then concentrated and a total of four samples were submitted for ICP-OES. The product stream from these steady state experiments contained on average 140 ppb Ni, 553 ppb Fe and 30 ppb Cr for *Ni-CS-3* and >1 ppb Pd, 266 ppb Ni, 568 ppb Fe and 218 ppb Cr for *Pd-EP-2*. These results show that both the Pd and the Ni catalysts are very well bound to the substrate, and that the majority of the soluble metal was Fe, which is a contamination that can be attributed to the stainless steel reactor tubing and/or the CSM substrate. This data is consistent with previous findings.<sup>20</sup>

## Conclusion

In this work we present a series of hydrogenation reactions performed on a novel continuous flow reactor system, using 3D printed catalytic static mixers. The CSMs were designed and printed in house, and the catalyst was deposited using either cold spraying or electroplating. The cost of manufacture of our 3D printed mixers are estimated to be lower by a factor of 10 to 100 compared to commercial metallic static mixers of similar dimensions, as labour intensive welding or other joining steps can be avoided when building the mixers in one print. This new approach has a series of interesting improvements over current state of the art chemical reactor systems for heterogeneous catalysis: a) tubular reactor technology is simple, well understood and it offers excellent control over the chemical reaction when using IDs between 3 and 10 mm; b) 3D printing allows for rapid design and manufacture of tailored mixer solutions for many different liquid and gas flow applications; c) the potential to mass manufacture CSMs using techniques such as cold spraying is a major benefit over existing complex multicomponent catalyst systems; d) changeover of catalyst is straight forward, leading to a versatile and easy to maintain continuous flow reactor system which creates the potential to greatly reduce downtime of industrial operations during maintenance and changeover cycles; e) scale-up from laboratory to production can be achieved in fewer and less time and labour intensive steps than classical batch scale-up. The reaction examples presented herein, which include the reduction of alkenes, alkynes, carbonyls, nitro- and diazo-compounds, nitriles, imines, and halides represent many different classes of industrial hydrogenations used in the manufacture of pharmaceuticals, fine chemicals, food products, polymers, agrochemicals and others. In one example, the reduction of an alkyne, it was possible to change selectivity simply by adjusting process parameters such as reactor pressure in order to either yield an alkene or an alkane product. This work showcases the versatility, efficiency and robustness of the CSM technology for different heterogeneous catalytic reductions and its great potential for use in R&D laboratories and as a scale-up tool for fine chemical and pharmaceutical production.

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## **Supporting Information**

The supplementary material contains information on used reagents, analysis procedures, reactor design and operation, calculation of CSM porosity, mean residence times and gas flow rates inside the reactor, a comparison between the Mk1 and Mk2 reactors for the hydrogenation of vinyl acetate and experiments on the hydrogenation of benzyl cyanide and cinnamaldehyde in ethanol.

## References

- 1 P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2009, **39**, 301–312.
- 2 S. G. Newman and K. F. Jensen, Green Chem., 2013, 15, 1456–1472.
- 3 A. J. Blacker, J. R. Breen, R. A. Bourne and C. A. Hone, in *Chapter 12:The Growing Impact* of Continuous Flow Methods on the Twelve Principles of Green Chemistry, 2016, pp. 140–155.
- 4 A. P. Harvey, M. R. Mackley and T. Seliger, *J. Chem. Technol. Biotechnol.*, 2003, **78**, 338–341.
- 5 T. Glasnov, *Continuous-Flow Chemistry in the Research Laboratory*, Springer New York, Dordrecht, Heidelberg, London, 2016.
- 6 B. Gutmann, D. Cantillo and C. O. Kappe, Angew. Chem. Int. Ed., 2015, 54, 6688–6728.
- 7 S. V. Ley, D. E. Fitzpatrick, R. J. Ingham and R. M. Myers, *Angew. Chem.*, 2015, **127**, 3514–3530.
- 8 R. M. Myers, D. E. Fitzpatrick, R. M. Turner and S. V. Ley, *Chem. Eur. J.*, 2014, **20**, 12348–12366.
- 9 V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *ChemSusChem*, 2013, **6**, 746–789.
- 10V. Hessel, S. Hardt and H. Löwe, *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, 2004.
- 11S. V. Ley, A. G. Leach and R. I. Storer, J. Chem. Soc. [Perkin 1], 2001, 358–361.
- 12G. Eigenberger and W. Ruppel, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- 13 M. Herskowitz and J. M. Smith, *AIChE J.*, 1983, **29**, 1–18.
- 14A. Sachse, A. Galarneau, B. Coq and F. Fajula, New J. Chem., 2011, 35, 259–264.
- 15P. He, S. J. Haswell, P. D. I. Fletcher, S. M. Kelly and A. Mansfield, *Beilstein J. Org. Chem.*, 2011, **7**, 1150–1157.
- 16N. Nikbin, M. Ladlow and S. V. Ley, Org. Process Res. Dev., 2007, 11, 458–462.
- 17G. M. Whitesides, *Nature*, 2006, **442**, 368–373.
- 18L. Kiwi-Minsker and A. Renken, *Catal. Today*, 2005, **110**, 2–14.

1	
2	
3	19E. V. Rebrov, G. B. F. Seijger, H. P. A. Calis, M. H. J. M. de Croon, C. M. van den Bleek and J.
4	C. Schouten, Appl. Catal. Gen., 2001, <b>206</b> , 125–143.
5	20A Avril C H Hornung A Urban D Fraser M Horne L-P Veder L Tsanaktsidis T
6	Podenoulos C Honry and D. P. Gunasogaram Paget Cham Eng
7	Rouopoulos, C. Helli y allu D. R. Gullasegaralli, <i>Reuct. Chelli. Lity.</i> , ,
8	DOI:10.1039/C6RE00188B.
9	21C. H. Hornung, B. Hallmark, M. R. Mackley, I. R. Baxendale and S. V. Ley, Adv. Synth.
10	Catal., 2010, <b>352</b> , 1736–1745.
11	22Y. D. Gamburg and G. Zangari, Theory and Practice of Metal Electrodeposition, Springer
12	New York, Dordrecht, Heidelberg, London, 2011.
13	23C. R. K. Rao and D. C. Trivedi, <i>Coord. Chem. Rev.</i> , 2005, <b>249</b> , 613–631.
14	24 ASTM B481 - 68(2013) Standard Practice for Prenaration of Titanium and Titanium Alloys
16	for Electronizing ACTM P491 69(2012) Standard Practice for Droppration of Titanium
17	Tor Electropiating, ASTW B401 - 00(2015) Standard Practice for Preparation of Intallum
18	and litanium Alloys for Electroplating, https://www.astm.org/Standards/B481.htm,
19	(accessed July 11, 2016).
20	25S. Ram and R. E. Ehrenkaufer, <i>Tetrahedron Lett.</i> , 1984, <b>25</b> , 3415–3418.
21	26A. G. M. Barrett and C. D. Spilling, <i>Tetrahedron Lett.</i> , 1988, <b>29</b> , 5733–5734.
22	27J. Sedelmeier, S. V. Ley and I. R. Baxendale, <i>Green Chem.</i> , 2009, <b>11</b> , 683–685.
23	28C. Battilocchio, J. M. Hawkins and S. V. Lev. Org. Lett., 2014, 16, 1060–1063.
24	29M Hutchings and T Wirth Svalett 2016 <b>27</b> 1832–1835
25	20 P. Gallezot and D. Richard. Catal. Rev. 1998 10 81-126
26	30F. Gallezot and D. Kichard, Catal. Nev., 1998, 40, 81–120.
27	31C. Bianchini, C. Bohanna, M. A. Esteruelas, P. Frediani, A. Meli, L. A. Oro and M. Peruzzini,
28	Organometallics, 1992, <b>11</b> , 3837–3844.
29	32 D. Duca, L. F. Liotta and G. Deganello, <i>J. Catal.</i> , 1995, <b>154</b> , 69–79.
30	33J. Jia, K. Haraki, J. N. Kondo, K. Domen and K. Tamaru, J. Phys. Chem. B, 2000, 104, 11153–
31	11156.
3Z 22	34J. H. Kang, E. W. Shin, W. J. Kim, J. D. Park and S. H. Moon, <i>J. Catal.</i> , 2002, <b>208</b> , 310–320.
24	35.J. Barrault and Y. Pouilloux. <i>Catal. Today.</i> 1997. <b>37</b> , 137–153.
35	361-P Tessonnier I Pesant G Ehret M I Ledoux and C Pham-Huu Anni Catal Gen
36	2005 <b>288</b> 202_210
37	2003, <b>200</b> , 203-210.
38	37 H. VU, F. GONÇAIVES, K. PHIIIPPE, E. LAMOUROUX, IVI. COMAS, Y. KIMI, D. PIEE, P. KAICK AND P.
39	Serp, J. Catal., 2006, <b>240</b> , 18–22.
40	38Y. Zhang, S. Liao, Y. Xu and D. Yu, <i>Appl. Catal. Gen.</i> , 2000, <b>192</b> , 247–251.
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