Continuous-Flow Chemistry

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Stereoselective Catalytic Synthesis of Active Pharmaceutical Ingredients in Homemade 3D-Printed Mesoreactors

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Abstract: *3D-printed flow reactors were designed, fabricated from different materials (PLA, HIPS, nylon), and used for a catalytic stereoselective Henry reaction. The use of readily prepared and tunable 3D-printed reactors enabled the rapid screening of devices with different sizes, shapes, and channel dimensions, aimed at the identification of the best-performing reactor setup. The optimized process afforded the products in high yields, moderate diastereoselectivity, and up to 90% ee. The method was applied to the continuous-flow synthesis of biologically active chiral 1,2-amino alcohols (norephedrine, metaraminol, and methoxamine) through a two-step sequence combining the nitroaldol reaction with a hydrogenation. To highlight potential industrial applications of this method, a multistep continuous synthesis of norephedrine has been realized. The product was isolated without any intermediate purifications or solvent switches.*

The development of 3D-printing devices and technologies has been associated with a new industrial revolution, where "real-life objects" are built in a faster, cheaper, and, most importantly, customized fashion. Instead of producing multiple copies of a single type of object, a single machine creates endless variations of an object with high accuracy.[1] Today, 3D printers based on fused filament fabrication (FFF) technology are accessible at low costs and are commonly available in many stores.[1c] 3D printing has been used in many different fields, from pneumatics to general medical applications. To date, in the chemical sciences, 3D-printed devices have been employed for creating 3D-printed crystallographic models from CIF (crystallographic information framework) data[2] and molecular models for chemical education purposes,[3] but also to build research equipment.[4] 3D printers have found application in the biomedical sciences[5] for the assembly of biodegradable tissue, and for the realization of bone tissue.[6]

The potential of 3D printing technologies has had a significant impact in the field of microfluidic devices.[7] Recently, a commercial microstereolithography 3D printer was used to fabricate conventional polydimethylsiloxane (PDMS) glass lab-on-a-chip devices for glucose concentration diagnostics.[8] 3D-printed flow plates have also been employed for water electrolysis[9] and for continuous-flow organic reactions, such as imine synthesis and reduction.[10] In these pioneering studies, Cronin and co-workers reported the reductive amination of in situ generated benzaldimines in 3D-printed polypropylene (PP) reactors.[11]

Despite the tremendous increase in interest in 3D-printed devices over the last few years, the use of 3D-printed reactors in organic synthesis is still limited to a small number of reactions and, to the best of our knowledge, remains virtually unexplored in catalytic enantioselective transformations. 3D-printed flow reactors are easily tunable devices that are designed and fabricated on demand on very short timescales (Figure 1). Considering the interest of the chemical industries in innovative technologies, their use in sophisticated enantioselective reactions would represent a crucial step towards a new, modern, efficient, and sustainable approach for process chemistry.

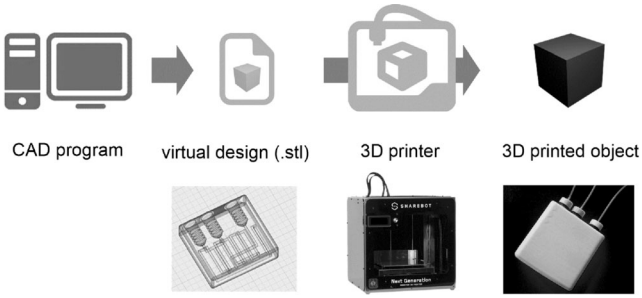

Figure 1. Fabrication of 3D-printed reactors.

We herein describe the development of stereoselective, catalytic continuous-flow reactions in 3D-printed mesoreactors.[12] A copper-catalyzed enantioselective Henry reaction was successfully performed in homemade 3D-printed flow reactors (Figure 1) built of different materials, such as poly(lactic acid) (PLA), high-impact polystyrene (HIPS), and nylon, with different sizes and shapes. This method was applied to the continuous-flow synthesis of biologically active chiral 1,2-amino alcohols (norephedrine, metaraminol, and methoxamine) in a two-step sequence combining a nitroaldol reaction with a hydrogenation (Scheme 1).

The addition of nitroalkanes to aldehydes, the so-called Henry reaction, is a powerful and efficient method for the construction of carbon–carbon bonds and results in the formation of β-nitro alcohols, which can be easily converted into 1,2-amino alcohols.[13] Owing to the great importance of these compounds, the catalytic stereoselective procedure to afford enantiomerically enriched products very soon gained particular attention and led to the development of various

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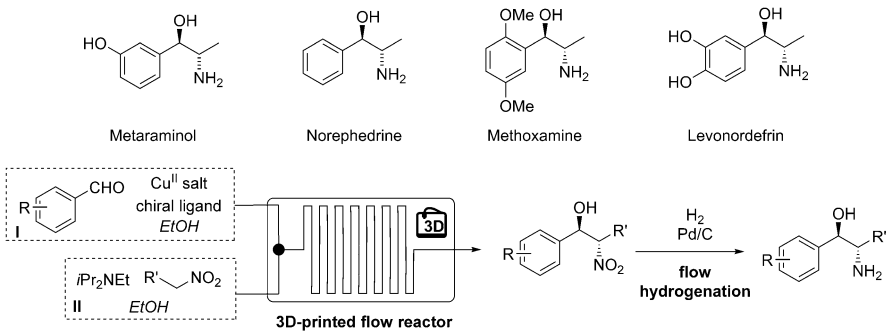
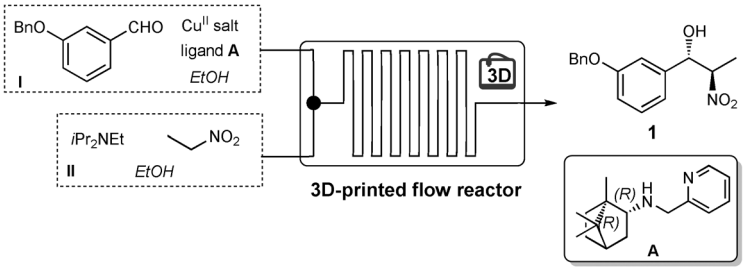


Scheme 1. Enantioselective catalytic synthesis of pharmaceutically active chiral 1,2-amino alcohols in 3D-printed flow reactors.

Running the reaction at 25 °C, a residence time of 5 min resulted in the formation of **1** in 61 % yield as a 60:40 mixture of diastereomers in favor of the *anti* isomer and in 70 % *ee* (Table 1, entry 1). When the reaction temperature was lowered to 0 °C, the stereoselectivity of the process improved (entries 3 and 4). At −20 °C and for a residence time of 10 min, the *anti*-configured nitro alcohol was obtained in 75:25 d.r. and 81 % *ee* (entry 5)., The best results were obtained at −20 °C and with a residence time of 30 min (72 % yield, 73:27 d.r., and 87 % *ee* for the major *anti* isomer with 1*S*,2*R* configuration; entry 6). Using the non-natural camphor-derived chiral ligand with the opposite configuration under the same reaction conditions, the product **1** was also formed with opposite absolute configuration as an immediate precursor of metaraminol, and was isolated in comparable efficiency (75 % yield, 71:29 d.r., 86 % *ee* for the *anti* isomer, 1*R*,2*S* configuration; entry 7).

chiral metal-[14] and non-metal-based[15] catalysts. Compared with the well-developed reaction of aldehydes with nitromethane, Henry reactions with other nitroalkanes are more challenging as they often suffer from low reactivity and poor stereoselectivity. The simultaneous control of the diastereo- and enantioselectivity of the transformation has been a formidable challenge, and only a limited number of suitable asymmetric catalysts have been identified.[16] Moreover, *anti* selectivity is even more difficult to achieve, and only recently, a few efficient catalysts have been developed for this purpose.[16g–n] In this framework, among the metal-based methods, those using copper complexes as catalysts hold a prominent position, in particular owing to their relatively low cost.[17] Therefore, based also on our previous experience,[18] we focused our attention on a readily available and inexpensive chiral copper(II) complex that was generated in situ by mixing copper diacetate and a camphor-derived aminopyridine.[19]



Scheme 2. Enantioselective copper-catalyzed Henry reaction in 3D-printed flow reactors.

At first, the batch reaction between 3-(benzyloxy)benzaldehyde and nitroethane was studied.[20] Upon screening different reaction conditions, it was found that at −45 °C in ethanol and in the presence of 20 mol % of ligand **A** and $Cu(OAc)_2$, the reaction afforded the nitroaldol product **1** in 91 % yield, 70:30 *anti*/*syn* selectivity, and 92 % *ee* for the major *anti* isomer. We next moved to continuous-flow experiments.[21] A 1 mL 3D-printed reactor made of HIPS (square channel: 1.41 × 1.41 mm^2) was first selected as the continuous-flow reactor. On the basis of preliminary experiments in flow, ethanol was identified as the solvent of choice (Scheme 2).

Syringe **I** was charged with a preformed mixture of 3-(benzyloxy)benzaldehyde (0.25 mmol), ligand **A** (0.0625 mmol), and $Cu(OAc)_2$ (0.05 mmol) in EtOH (1 mL, 0.250 M). Syringe **II** was charged with nitroethane (2.5 mmol), DIPEA (0.25 mmol), and EtOH (750 μL). The two syringes were connected to a syringe pump, and the reagents were injected into the flow reactor at the indicated flow rate and temperature. The output of the reactor was collected in a cooled bath (−78 °C), where the crude product was treated with HCl (10 %) at the end of the process. After extraction with EtOAc, the product was isolated by column chromatography on silica gel. The results of the continuous-flow experiments are reported in Table 1.

Table 1: Screening of reaction conditions.

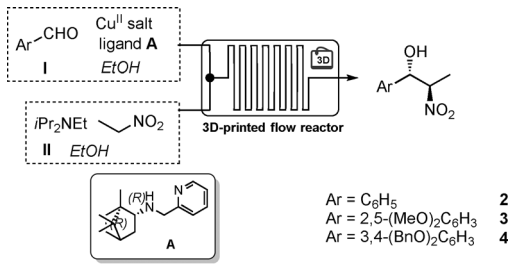
Entry	*T* [°C]	Flow rate [mL min^{-1}]	*t*[a] [min]	Yield[b] [%]	d.r.[b] (*anti*/*syn*)	ee_{anti}[c] [%]
1	25	0.2	5	61	60:40	70
2	25	0.1	10	87	50:50	49
3	0	0.1	10	73	65:35	85
4	0	0.05	20	91	63:37	78
5	−20	0.1	10	20	75:25	81
6	−20	0.033	30	72	73:27	87
7[d]	−20	0.033	30	75	71:29	86[e]

[a] Residence time. [b] Determined by ^1H NMR analysis of the crude product. [c] Determined by HPLC analysis on a chiral stationary phase, value for the 1*S*,2*R* enantiomer. [d] The ligand with the opposite configuration was used. [e] For the 1*R*,2*S* enantiomer.

Having identified the best reaction conditions in terms of the temperature (−20 °C) and residence time (30 min), we explored the use of different types of flow reactors. As HIPS may suffer from some incompatibility problems with organic solvents, the use of 3D-printed reactors made from PLA, which is more robust and less sensitive to decomposition by organic solvents, was investigated. Using a 1 mL 3D-printed

reactor made of PLA (square channel: 1.41×1.41 mm^2), nitro alcohol **1** was obtained in very good yield (87%), 65:35 d.r., and 80% *ee* for the *anti* isomer.

Next, we focused our attention on the preparation of intermediate **2**, a precursor of norephedrine (Scheme 3).



Scheme 3. Stereoselective catalytic reactions in 3D-printed flow reactors.

Table 2: Screening of different 3D-printed flow reactors.

Entry	Flow reactor	Conv.[a] [%]	d.r.[a] (*anti*/*syn*)	ee_{anti}[b] [%]
1	1 mL PTFE coiled tube (circular channel, id = 1.69 mm)	92	65:35	80
2	1 mL 3D-printed PLA (square channel, 1.41×1.41 mm^2)	96	67:33	80
3	1 mL 3D-printed nylon (square channel, 1.41×1.41 mm^2)	97	68:32	81
4	1 mL 3D-printed PLA (circular channel, id = 1.59 mm)	98	67:33	84
5	1 mL 3D-printed PLA (square channel, 1.0×1.0 mm^2)	98	67:33	85
6	10 mL 3D-printed PLA (square channel, 2.65×2.65 mm^2)	96 (80)[c]	74:26	90

[a] Determined by ^{1}H NMR analysis of the crude product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Yield of isolated product given in parentheses. id = inner diameter.

Employing the previously described experimental setup and optimized reaction conditions (−20 °C in ethanol, 30 min residence time), the use of flow reactors made of different materials was studied (Table 2). The use of 1 mL 3D-printed reactors made of PLA (square channel: 1.41×1.41 mm^2) or nylon (square channel: 1.41×1.41 mm^2) for the copper-catalyzed stereoselective Henry reaction gave similar results (entries 2 and 3). Changing the size or the shape of the 3D-printed PLA reactors did not have a significant effect on the outcome of the reaction; intermediate **2** was obtained in very good conversions, reasonable d.r., and good *ee* (entries 4 and 5).[22] Finally, the reaction was scaled up by using a 10 mL 3D-printed reactor (square channel: 2.65×2.65 mm^2) made from PLA; pleasingly, nitroaldol **2** was obtained in very good yield, 74:26 d.r., and 90% *ee*. For the sake of comparison, a 1 mL coiled tube made of PTFE (circular channel; inner diameter: 1.69 mm) was also employed as a continuous-flow reactor; the product was then isolated in slightly lower yield and enantioselectivity (entry 1).

However, it should be noted that 3D-printed reactors are extremely cheap and can be designed and modified ad hoc by the operator (see the Supporting Information for a series of 3D-printed reactors of different geometries and shapes prepared by our group). To further demonstrate the versatility and advantages that easily customizable 3D-printed reactors may offer over other flow reactors, the performance of PLA reactors with different geometries, sizes, and shapes was investigated, including new devices with zigzag flow channels. Nitroaldol reactions with benzaldehyde and 3-(benzyloxy)benzaldehyde were then run in these microreactors at −20 °C with short residence times (3 and 5 min; see Table 3 for selected results). The reactor design indeed influenced the conversion and, to a smaller extent, also the stereoselectivity of the reaction (in some cases, the 3D-printed devices afforded better results than traditional PTFE tubings of similar dimensions).

Analogous results were obtained in the synthesis of nitro alcohol **3**, a precursor of methoxamine. Using a 1 mL 3D-printed PLA reactor, the product was isolated in 90% yield, 73:27 d.r., and 87% *ee* for the *anti* isomer, which compares well with the results of the batch reaction (72% yield, 70:30 d.r., 91% *ee*). Similarly, the stereoselective Henry reaction between 3,4-bis(benzyloxy)benzaldehyde and nitroethane in a mixture of EtOH/THF as the solvent at −20 °C afforded the corresponding product **4** in 67% yield, 65:35 d.r., and 80% *ee*.

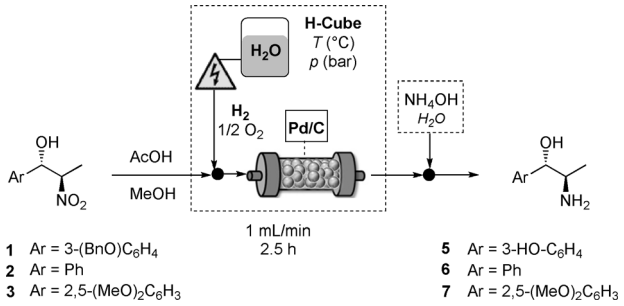
To obtain the desired chiral amino alcohols, the nitroaldol products **1**–**3** were subjected to a continuous-flow hydrogenation in a ThalesNano H-Cube Mini device equipped with a cartridge of Pd/C (10 wt%) as the catalyst (Scheme 4). A rapid screening of reaction conditions was performed using nitro alcohol **2** (see the Supporting Information, Table S3).

When the reaction was performed in MeOH at 30 °C and 15 bar H_2 pressure, complete conversion of the starting material into amino alcohol **6** was observed. Considering a possible multistep process, we also investigated the use of ethanol as the reaction medium. When **2** was used as a 0.1 M solution in EtOH, it was reduced with a conversion of 80% after 2.5 hours under the same reaction conditions. To increase the reaction conversion from 80% to 98%, it was

Table 3: Reactions in 3D-printed flow reactors of different geometries and designs.[a]

Entry	ArCHO	Flow reactor	Conv.[b] [%]	d.r.[b] (*anti*/*syn*)
1	PhCHO	1 mL PTFE coiled tube (circ. channel, id = 1.69 mm)	8	74:26
2	PhCHO	1 mL 3D-printed PLA (rect. zigzag channel, 1.1×1.7 mm^2)	15	80:20
3	3-(BnO)C_6H_4CHO	1 mL 3D-printed PLA (circ. channel, id = 1.59 mm)	10	61:39
4	3-(BnO)C_6H_4CHO	1 mL 3D-printed PLA (rect. zigzag channel, 1.1×1.7 mm^2)	21	71:29
5	3-(BnO)C_6H_4CHO	1 mL 3D-printed PLA (circ. zigzag channel, id = 1.59 mm)	18	60:40

[a] Residence times of 5 min. [b] Determined by ^{1}H NMR analysis of the crude product.



Scheme 4. Continuous-flow hydrogenation of chiral nitro alcohols **1**–**3**.

necessary to dilute the reaction mixture from 0.1 to 0.03 M. Amino alcohol **6** was obtained in its neutral form after a simple treatment with NH_4OH with no need for further purification. In all cases, no erosion of the stereochemical integrity of the process was observed (the *ee* was determined after derivatization of norephedrine into its O,N-bisacetylated form). Analogously, the continuous-flow hydrogenation of **3** proceeded with complete conversion into amino alcohol **7**.

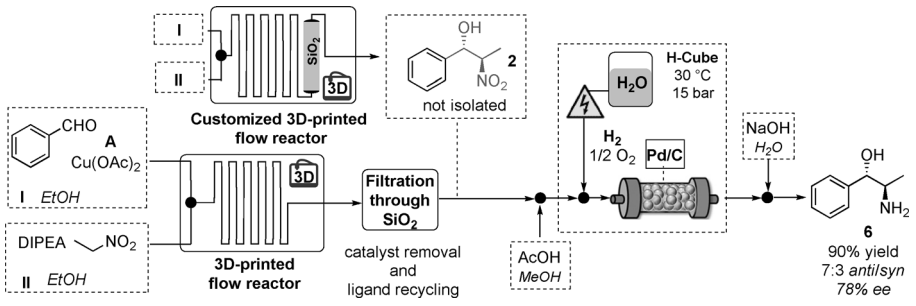
To obtain metaraminol, nitro alcohol **1** was subjected to both nitro group reduction and O-debenzylation. After 2.5 h of recirculation at 50 °C and under 50 bar of H_2, amino alcohol **5** (as its acetate salt) was obtained with complete conversion and without any erosion of its stereochemical purity.

Having confirmed the feasibility of a two-step sequence for the synthesis of chiral 1,2-amino alcohols, we explored the possibility of simulating a continuous-flow multistep process without the need for isolation and purification of the nitro alcohol intermediate or solvent switching (Scheme 5). This procedure would be appealing for the synthesis of chiral 1,2-amino alcohols on a preparative scale.

After the initial stereoselective Henry reaction in a 3D-printed flow reactor, the key step was the removal of the copper catalyst and the chiral ligand to avoid possible interference with the continuous-flow palladium-catalyzed hydrogenation. The reaction between benzaldehyde and nitroethane was selected to develop a multistep flow process for the synthesis of 1,2-amino alcohol **6**. Filtration through a short pad of silica followed by elution with EtOH was identified to be a valid approach to remove the copper ligand complex for the Henry reaction from the crude reaction mixture. According to this strategy, no solvent switching is necessary; additionally, the precious chiral ligand can be easily recycled by simple treatment of the silica gel with ethanolic HCl solution.

In the experimental setup, the two syringes were connected to a syringe pump, and the reagents were injected into the 3D-printed flow reactor at −20 °C for a residence time of 30 min. The output of the reactor (dark blue solution, 3 mL) was filtered over a short pad of silica ($h = 1$ cm, $d = 2$ cm) by elution with EtOH (6 mL). To the resulting mixture (light yellow), 30 equiv of AcOH were added, and the resulting mixture was subjected to continuous-flow hydrogenation with H-Cube ($T = 30$ °C, $p = 1$ bar, flow rate $= 1$ mL min^{-1}, $t =$ 2.5 h). The solvent was then evaporated, and the resulting mixture was treated with 33 % aqueous NH_4OH and extracted five times with EtOAc. Amino alcohol **6** was obtained in 90 % yield (over 2 steps), 70:30 d.r., and 81 % *ee* as a pure white solid. Taking advantage of the powerful possibility offered by 3D printing to easily and quickly modify the reactor design, it was also possible to fabricate a customized reactor containing the flow channels and the short column of silica in a single device (Scheme 5). The nitroaldol intermediate was then obtained in 96 % yield, 65:35 d.r., and 83 % *ee* (see the Supporting Information for details).

In conclusion, a two-step continuous-flow process for the stereoselective catalytic synthesis of chiral 1,2-amino alcohols, aimed at the preparation of biologically active targets (norephedrine, metaraminol, and methoxamine), has been developed. For the first time, homemade 3D-printed reactors have been used in catalytic enantioselective reactions, and reactor channels of different materials, geometries, sizes, and shapes have been studied. The use of a 10 mL 3D-printed reactor for a scaled-up version of the process has also been demonstrated. Furthermore, a multistep continuous-flow process for the synthesis of norephedrine through a Henry reaction and nitro group reduction has been developed. Under the optimized reaction conditions, the final product was isolated without any intermediate purifications or solvent switching, thus opening the way to a fully automated continuous-flow process for the synthesis of enantiopure 1,2-amino alcohols. The unprecedented demonstration of the possibility to use highly tunable, customizable 3D-printed reactors in stereoselective catalytic reactions represents a key step towards the widespread use of 3D-printed devices in organic synthesis, even for the assembly of highly functionalized chiral molecules. Customized 3D printing of reactors is already a reality; the use of other 3D-printed devices in combination with reactors, including homemade printed syringe pumps,[23] and the possibility to optimize the final design to further reduce costs and printing times are other feasible working plans for the future.



Scheme 5. Multistep in-flow synthesis of pharmaceutically valuable chiral 1,2-amino alcohols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 3D printing · amino alcohols · flow reactors · nitroaldol reactions · stereoselective catalysis

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Communications

Continuous-Flow Chemistry

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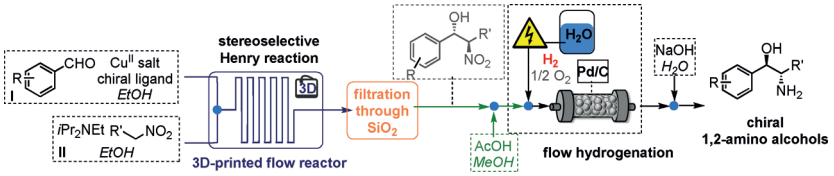
Stereoselective Catalytic Synthesis of Active Pharmaceutical Ingredients in Homemade 3D-Printed Mesoreactors



Homemade reactors: Stereoselective catalytic reactions were conducted in tunable homemade 3D-printed mesoreactors. This method was applied to the continuous-flow synthesis of biologically active chiral 1,2-amino alcohols in a two-step sequencing combining a nitroaldol reaction and hydrogenation.

