

# Application of an Oscillatory Plug Flow Reactor to Enable Scalable and Fast Reactions in Water Using a Biomass-Based Polymeric Additive\*\*

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The utilization of water as a sustainable reaction medium has important advantages over traditional organic solvents. Hydroxypropyl methylcellulose has emerged as a biomass-based polymeric additive that enables organic reactions in water through hydrophobic effects. However, such conditions imply slurries as reaction mixtures, where the efficacy of mass transfer and mixing decreases with increasing vessel size. In order to circumvent this limitation and establish an effectively scalable platform for performing hydroxypropyl methylcellulose-mediated aqueous transformations, we utilized oscillatory plug flow reactors that feature a smart dimensioning design principle

across different scales. Using nucleophilic aromatic substitutions as valuable model reactions, rapid parameter optimization was performed first in a small-scale instrument having an internal channel volume of 5 mL. The optimal conditions were then directly transferred to a 15 mL reactor, achieving a three-fold scale-up without re-optimizing any reaction parameters. By precisely fine-tuning the oscillation parameters, the system achieved optimal homogeneous suspension of solids, preventing settling of particles and clogging of process channels. Ultimately, this resulted in a robust and scalable platform for performing multiphasic reactions under aqueous conditions.

## Introduction

Synthetic processes rely traditionally on organic solvents as reaction medium.<sup>[1]</sup> Unfortunately, the vast majority of solvents used are not recycled, but instead end up as an ever-increasing amount of organic waste. This has led to a renewed interest in the use of water as an environmentally benign alternative to organic solvents.<sup>[2]</sup> However, aqueous chemistries are largely limited by the solubility of typical organic substrates in water. In

order to circumvent the issues of limited solubility and poor reaction rates, aqueous micellar conditions have been suggested to enable organic reactions in water.<sup>[3]</sup> In this manner, surfactants are employed to form micelles as amphiphile nanoreactors, where organic reactions can efficiently take place.<sup>[4]</sup> It was observed that the nature of the amphiphile is crucial in such reactions, and as a result, an array of novel surfactants have been designed that enable diverse transformations to be performed under aqueous micellar conditions.<sup>[5]</sup> Although designer surfactants have numerous desirable properties, they also have some drawbacks. For example, they can be expensive to synthesize and co-solvents are often required to ensure uniform mixing and the achievement of high reaction yields.<sup>[6]</sup>

Recently, hydroxypropyl methylcellulose (HPMC) has also emerged as a surface-active additive that enables organic reactions in water through hydrophobic effects (Scheme 1A).<sup>[7]</sup> HPMC is a semisynthetic polymeric organic compound derived from cellulose. It is available in large quantities, inexpensive and completely harmless.<sup>[8]</sup> HPMC contains both hydrophilic and hydrophobic groups, and its self-aggregation in water leads to the formation of hydrophobic pockets where organic reactions can take place.<sup>[9]</sup> HPMC-mediated conditions have been exploited to enable a variety of reactions in water, such as amide couplings, various reductions, Buchwald-Hartwig aminations and  $S_NAr$  reactions.<sup>[7,9]</sup> In contrast to some of the micelle-mediated chemistries, HPMC-enabled transformations do not require the presence of any co-solvent. However, as a result of self-aggregation, aqueous HPMC solutions suffer temperature dependent gelation during the course of reactions.<sup>[10]</sup> This can result in biphasic mixtures and slurry formation, which lead to

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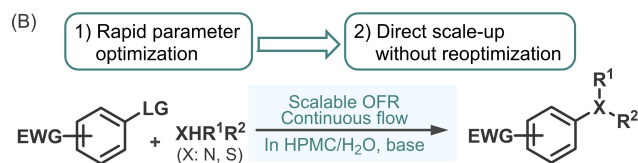
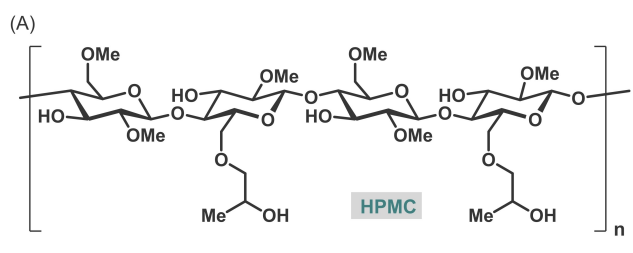
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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cssc.202301149>

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**Scheme 1.** The structure of HPMC (A), and general scheme of the present study (B).

significant limitations on mass transfer and low reaction rates especially at larger scales.

Continuous flow reactors offer unique advantages for improving transport between reacting phases.<sup>[11]</sup> Oscillatory plug flow reactors (OFRs) have proven particularly useful for performing reactions involving solids, as the intense mixing that results from a continuous oscillation superimposed to the net flow of the reaction stream significantly enhances mass transport and ensures stable suspension of solid-liquid mixtures.<sup>[12]</sup> As a result, process intensification and simplification become feasible, and scalability is also more straightforward than under traditional batch conditions.<sup>[13]</sup>

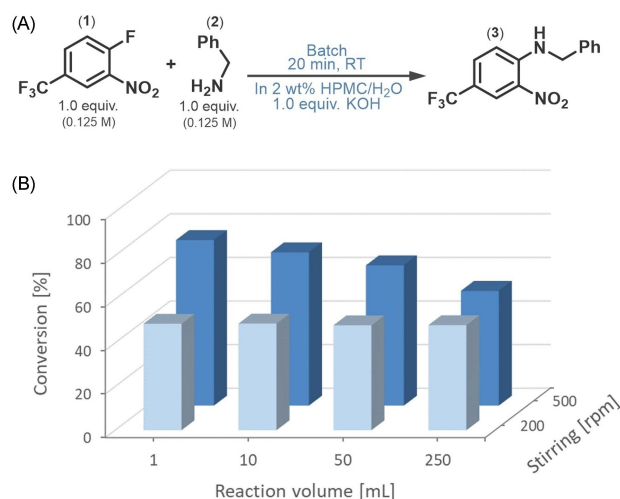
Motivated by the large potential, but also by technical limitations of HPMC-enabled aqueous chemistries, we aimed to develop a novel continuous flow protocol in order to realize organic syntheses involving HPMC-containing slurries as a scalable process. Based on our earlier experiences on processing biphasic reaction mixtures in OFRs, primarily in photocatalytic but more recently also in micelle-enabled aqueous chemistries,<sup>[14]</sup> we selected the commercially available HANU flow reactors (Creaflow) for process development.<sup>[15]</sup> The selection of this particular system was justified by the smart dimensioning approach, which ensures a fixed geometrical layout and thus homogeneous performance across different reactor scales, from lab to manufacturing.<sup>[16]</sup> This allowed us to envision rapid process development using a lab-scale instrument, followed by facile scale-up by directly transferring optimal conditions to a larger-scale reactor without the need for reoptimization of reaction conditions. (Scheme 1B). On the basis of their broad applications in medicinal chemistry as well as in pharmaceutical manufacturing,<sup>[17]</sup> nucleophilic aromatic substitutions ( $S_NAr$  reactions) between various nucleophiles and electrophiles were selected as model reactions. These reactions are typically conducted in classical organic solvents, such as DMSO, DMF, DMAc, 1,4-dioxane, and NMP, and often require heating to temperatures  $>100^\circ\text{C}$  that can result in low chemical selectivity and limited functional group tolerance.<sup>[18]</sup> In a recent report,  $S_NAr$  reactions were achieved under batch conditions using aqueous HPMC solutions as reaction medium

in the presence of KOH as an inexpensive base.<sup>[7a]</sup> These literature findings served as starting point for our investigations.

## Results and Discussion

As concerns physical properties, in particular, the viscosity of aqueous HPMC solutions, the ratio of methoxyl and hydroxypropyl groups on the cellulose backbone play an essential role.<sup>[19]</sup> In order to select a reaction medium that can be processed optimally under flow conditions, our study was initiated by investigating aqueous solutions prepared using different commercially available HPMC types. Mantrocel® E5 and K4M (obtained from Gustav Parmentier GmbH) were explored as 0.2–2 wt% H<sub>2</sub>O solutions (see Table S1 in the Supporting Information). K-type HPMCs can be considered more cellulose-like and thus slightly less swellable in aqueous solutions compared to E-types.<sup>[8]</sup> The viscosity of Mantrocel® E5 solutions at temperatures of 25–60 °C were in the range 1.0–4.0 mPa s, meaning that as reaction medium these can easily be pumped continuously even by using a syringe pump. In contrast, the viscosity of 2 wt% K4M solution was very high (3200 mPa s at 25 °C), preventing any applications as a potential reaction medium. Reducing the K4M concentration to 0.2 wt% lowered the viscosity remarkably, but at higher temperatures, decomposition of the solution occurred suggesting the utilization of Mantrocel® E5 solutions instead as reaction medium in all further experiments.

The  $S_NAr$  reaction of 4-trifluoromethyl-2-nitro-1-fluorobenzene (1) with benzylamine (2) as nucleophile was selected as model reaction using 2 wt% HPMC/H<sub>2</sub>O as reaction medium in the presence of KOH as base (Figure 1A). In order to demonstrate the importance of mass transfer and also to investigate possible limitations in scalability, the reaction was performed



**Figure 1.** The  $S_NAr$  reaction of 4-trifluoromethyl-2-nitro-1-fluorobenzene (1) with benzylamine (2) as nucleophile (A). Effects of the rate of stirring on the batch model reaction at different scales. (Chemical selectivity was  $>95\%$  in all reactions. Conversion and selectivity were determined by HPLC at 215 nm.) (B)

initially in conventionally stirred batch reaction vessels on scales ranging from 1 mL to 250 mL (Figure 1B). The constant and inadequately low conversion (around 50%) at 200 rpm stirring rate can be explained by the accumulation of the insoluble electrophile as a separate phase at the bottom of the reaction vessel regardless of the volume applied. By increasing the stirring rate to 500 rpm, the reaction mixture formed a homogeneous suspension and the conversion reached 75% in the smallest vessel (1 mL volume). However, upon gradual scale-up to 250 mL, conversion decreased rapidly with the batch size to around 50%. This demonstrates a notable mass transfer limitation and implies potential difficulties in case of direct scale-up under batch conditions.

For the continuous flow reactions, a reactor setup was established comprising as main components the HANU OFR, two metering pumps for the introduction of reagent streams, and an oscillatory diaphragm pump delivering a tunable pulse superimposed to the net flow of the reaction stream (Figure 2; see also the Experimental Section and Supporting Information for details). The plate-like process channel of HANU reactors is equipped with a series of passive mixers placed within a repeated pattern. The beneficial combination of passive mixing and pulsation-enabled active mixing results in a split-and-recombine mixing phenomena accounting for an improved mass transfer compared with conventionally stirred batch processes. Importantly, the tunable pulse delivered by the oscillator module enables the system to reach optimal homogeneous suspension of solids without settling of particles and thus clogging of process channels. In order to gain a better understanding on the effects of individual oscillation parameters and to assess the mechanisms facilitating mass transfer in aqueous slurries under oscillatory flow conditions, a combined experimental and computational investigation of fluid dynamics and solid transport was performed in parallel.<sup>[20]</sup>

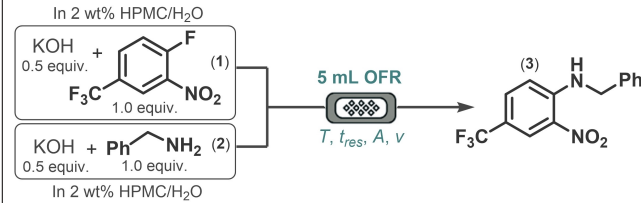
For initial investigations, the HANU 2X 5 OFR with an internal channel volume of 5 mL was selected. This is the smallest HANU reactor available, ideally suited for quick screening of reaction conditions at a small scale.<sup>[15]</sup> By optimization of the pulsation parameters, we anticipated a robust setup for handling the reaction slurry with small axial dispersion and a residence time distribution (RTD) approaching a plug-flow. Experimental investigation of the RTD in the HANU 2X 5 reactor verified that at a given average flow rate, the amplitude of oscillations significantly influenced the distribution curves, whereas oscillation frequency exhibited a lower impact. As expected, higher flow rates diminished the influence of diffusion in the system (Figure S3 in the Supporting Information). To quantify how oscillation impacts the RTD, the Bodenstein (Bo) number was calculated at any combination of flow rates and oscillation parameters experimentally investi-

gated (Table S2 in the Supporting Information). The values of Bo reflected the narrowing of the experimental RTDs and thus confirmed the similarity of RTD characteristics to those observed earlier in the HANU 2X 15 reactor.<sup>[14c-e]</sup> These findings verify that direct scale-up from the HANU 2X 5 to the 2X 15 reactor (with an internal channel volume of 15 mL) can potentially be achieved by adjusting the flow rate, without the need to reoptimize the other reaction parameters.

With a low average flow rate (0.5 mL min<sup>-1</sup>) and oscillation parameters ( $A=0.036$  mL,  $\nu=3.0$  Hz), RTD was compared next in case of HPMC/H<sub>2</sub>O and pure deionized water to investigate any changes in the plug flow character caused by the reaction medium. As detailed in the Supporting Information (see Figure S4 and Table S3), HPMC/H<sub>2</sub>O displayed somewhat better plug flow characteristics than pure water due to its higher viscosity; and increasing the temperature to 60 °C made the RTD profile of the HPMC/H<sub>2</sub>O system even narrower. The calculated Bo values allowed to conclude that the presence of HPMC does not significantly change the fluid dynamic behaviour of pure deionized water, but it improves slightly the plug flow character due its higher viscosity.

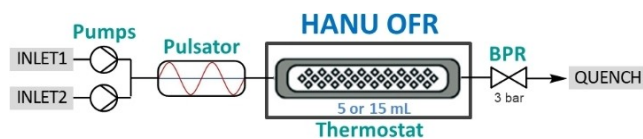
Similar to preliminary batch experiments, parameter optimization in the HANU 2X 5 OFR was performed employing the reaction of electrophile 1 with benzylamine (2) using KOH as base in (Table 1). The effects of substrate concentration, temperature and residence time were explored first utilizing 0.1 wt% or 2 wt% HPMC/H<sub>2</sub>O as reaction medium. Even though we readily managed good conversions and selective trans-

**Table 1.** Parameter optimization under flow conditions.



| #                 | c <sup>a</sup><br>[M] | T<br>[°C] | A <sup>b</sup><br>[mL] | $\nu^c$<br>[Hz] | t <sub>res</sub> <sup>d</sup><br>[min] | Conv. <sup>e</sup><br>[%] | Sel. <sup>e</sup><br>[%] |
|-------------------|-----------------------|-----------|------------------------|-----------------|--|---------------------------|--------------------------|
| 1 <sup>f,g</sup>  | 0.125                 | RT        | 0.23                   | 1.5             | 7.0                                    | n.d.                      | n.d.                     |
| 2                 | 0.125                 | RT        | 0.23                   | 1.5             | 7.0                                    | 80                        | > 99                     |
| 3 <sup>g</sup>    | 0.25                  | RT        | 0.10                   | 1.5             | 7.0                                    | 92                        | > 99                     |
| 4 <sup>g</sup>    | 0.25                  | RT        | 0.23                   | 1.5             | 7.0                                    | 93                        | > 99                     |
| 5                 | 0.25                  | RT        | 0.26                   | 1.5             | 7.0                                    | 93                        | > 99                     |
| 6                 | 0.25                  | RT        | 0.26                   | 3.0             | 7.0                                    | 88                        | > 99                     |
| 7                 | 0.25                  | RT        | 0.26                   | 3.0             | 3.5                                    | 75                        | > 99                     |
| 8 <sup>g</sup>    | 0.5                   | RT        | 0.26                   | 3.0             | 7.0                                    | 94                        | > 99                     |
| 9                 | 0.25                  | 60        | 0.26                   | 3.0             | 7.0                                    | 94                        | > 99                     |
| 10 <sup>g,h</sup> | 0.25                  | RT        | 0.26                   | 3.0             | 7.0                                    | 59                        | > 99                     |

<sup>a</sup>Concentration of 1 and 2 in the individual substrate feeds. <sup>b</sup>Amplitude of oscillation given in mL displaced per pump stroke. <sup>c</sup>Frequency of oscillation (i.e., the number of strokes per second). <sup>d</sup>Flow rates: 2×1.0 mL min<sup>-1</sup> or 2×0.5 mL min<sup>-1</sup>. <sup>e</sup>Determined by HPLC at 215 nm. <sup>f</sup>Performed in 0.1 wt% HPMC/H<sub>2</sub>O. <sup>g</sup>Product deposition was observed in the reactor plate. <sup>h</sup>Performed in water without any HPMC present.

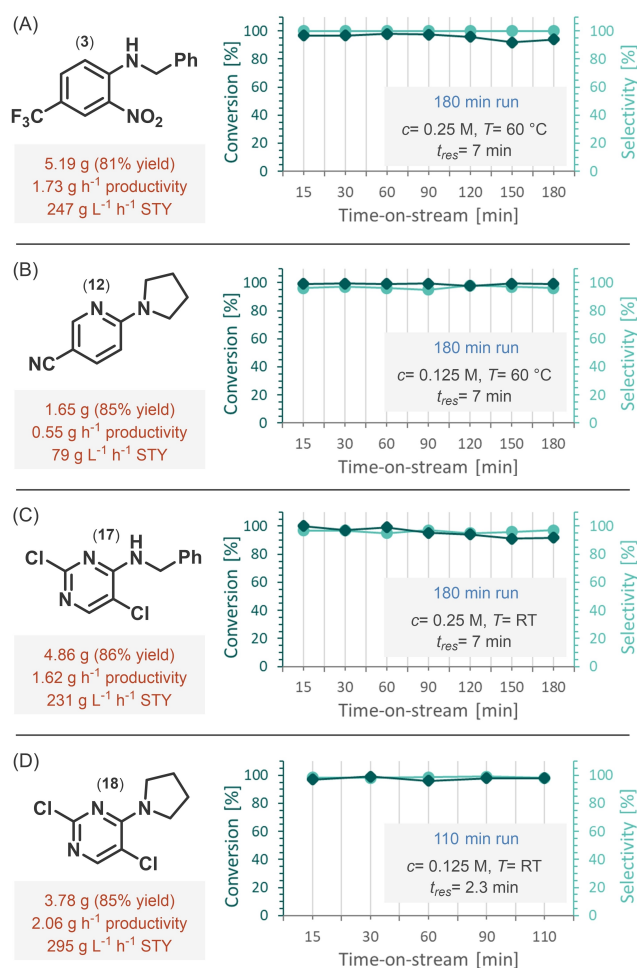


**Figure 2.** Schematic representation of the continuous flow setup.

formations during a set of small-scale runs (entries 1–4), the main challenge of the continuous flow process development was particle deposition and clogging. Gratifyingly, fine-tuning of oscillation frequency and amplitude proved as an effective tool to reach an optimal homogeneous suspension that can be robustly and reproducibly processed (entries 5 and 6). The best results were achieved at 60 °C and 7.0 min residence time using 0.25 M substrate feeds in 2 wt% HPMC/H<sub>2</sub>O, with oscillation parameters amplitude and frequency set to 0.26 mL and 3.0 Hz, respectively (entry 9). Under these conditions, amine **3** was attained with 94% yield without any particle deposition or clogging. Higher substrate concentration or the reduction of the HPMC content resulted in product deposition in the reactor plate and lowering the residence time to 3.5 min implied a considerable drop in yield (entries 1, 7 and 8). In a control experiment performed in pure water as reaction medium without any HPMC present, separation of organic and aqueous phases occurred, and coarse particles of a sticky residue accumulated alongside the reactor plate and the connection tubings (Figure S6 in the Supporting Information). Due to the limited mass transfer under such conditions, conversion decreased notably, and most importantly, significant pressure drops and frequent clogging issues even during shorter runs rendered the application of sole water as reaction medium unfeasible for any further process development.

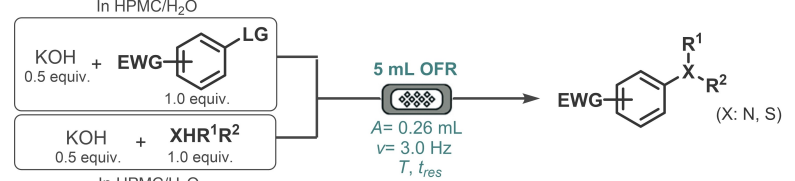
With sufficient amount of data on the effects of reaction conditions, we next investigated the reaction scope using the HANU 2X 5 OFR (Table 2). A series of electrophiles (**1**, **10**, **16**) were explored in combination with benzylamine (**2**), piperidine (**4**), piperidin-4-ol (**6**) and pyrrolidine (**11**) as *N*-nucleophiles, or with naphthalene-2-thiol (**8**) as *S*-nucleophile, utilizing the previously optimized values of the oscillation parameters ( $A = 0.26$  mL and  $\nu = 3.0$  Hz). Similar to benzylamine (**2**, entry 1), *N*-nucleophiles **4** and **6** were reacted smoothly with electrophile **1** within 3.5–14 min residence times (entries 2–6). These reactions furnished selective transformations and conversions up to >99% employing substrate concentrations of 0.25 M or 0.5 M at room temperature. To our delight, *S*-nucleophile **8** was also tolerated well by the flow process (entry 7); however, substrate concentration had to be decreased to 0.125 M to eliminate clogging issues. Flow reactions of 6-fluoronicotinonitrile (**10**) with nucleophiles **11**, **4**, **6** and **8** produced the desired adducts with conversions of 87–97% and with chemical selectivities up to >99% (entries 8–13). For these experiments, residence times around 7 min, a gentle heating at 60 °C, and substrate concentrations of 0.125 M or 0.25 M were found optimal. Notably, in reactions of piperidin-4-ol (**6**), containing both amine and alcohol functional groups, very high chemoselectivity was observed (>99% or 96%, entries 6 and 12) thereby eliminating the need for the application of protecting groups. 2,4,5-Trichloropyrimidine (**16**), exhibiting chloride as a leaving group, furnished excellent results in combination with nucleophiles **2** and **11** within residence times as low as 2.3 min or 3.5 min (entries 14–17). The conversions and chemical selectivities achieved in investigating the reaction scope compare well with the literature batch data.<sup>[7a]</sup>

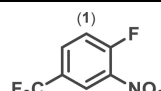

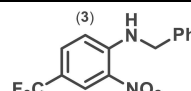
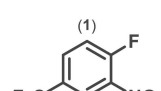

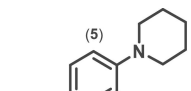
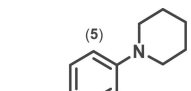
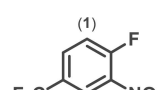

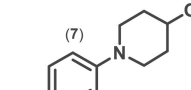
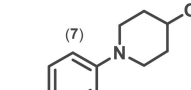
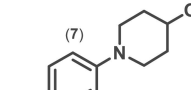
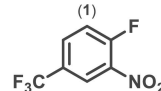

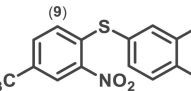
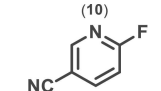

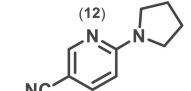
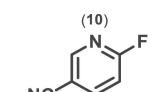

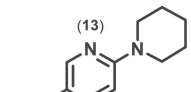
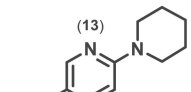
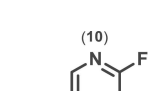

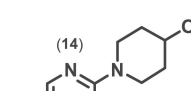
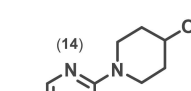
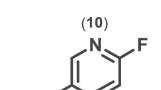

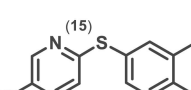
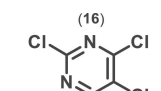

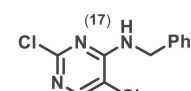
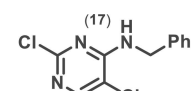
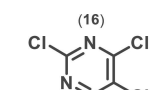

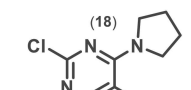
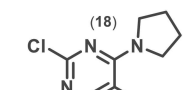
In order to explore the stability as well as the preparative capabilities of the flow process in the HANU 2X 5 OFR, long-run experiments were performed for some representative examples (Figure 3). Substrate concentration, temperature, residence time and oscillation parameters were set to the same values used during initial small-scale trials shown in Table 2, but all experiments were run continuously for 110–180 min under steady state conditions. Samples were taken for HPLC analysis at regular intervals to determine conversion and chemoselectivity. All four experiments were accomplished exhibiting stable conversion and selectivity values observed during the explored process times and, importantly, without any detectable particle deposition or clogging. Since conversion and selectivity was  $\geq 90\%$  in all fractions collected, sufficiently pure products were obtained after simple extractive work-up. As a result of the preparative runs, multigram quantities (1.65–5.19 g) of pure isolated material were produced (81–85% isolated yield), correlating to space-time-yields (STY) up to 295 g L<sup>-1</sup> h<sup>-1</sup> and productivities up to 2.06 g h<sup>-1</sup>.



**Figure 3.** Results of preparative long-run experiments in a HANU 2X 5 OFR. Reactions were performed in 2 wt% HPMC/H<sub>2</sub>O. For all the experiments, the corresponding electrophile and nucleophile was pumped as separate streams along with 0.5 equiv. of KOH as base in both mixtures (see also the reaction scheme in Table 2). In all runs, amplitude was set to 0.26 mL and oscillation frequency to 3.0 Hz. (Yields shown are isolated yields. Conversion and selectivity were determined by HPLC at 215 nm.)



**Table 2.** Substrate scope of the HPMC-mediated  $S_NAr$  reaction under continuous flow conditions.


| #               | Electrophile  | Nucleophile   | Product   | HPMC [wt%] | $c^a$ [M] | $T$ [°C] | $t_{res}^b$ [min] | Conv. <sup>c</sup> [%] | Sel. <sup>c</sup> [%] |
|-----------------|---|---|---|------------|-----------|----------|-------------------|------------------------|-----------------------|
| 1               |    |    |    | 2          | 0.25      | 60       | 7                 | 94                     | > 99                  |
| 2 <sup>d</sup>  |    |    |    | 2          | 0.25      | RT       | 3.5               | 93                     | > 99                  |
| 3               |   |   |    | 0.1        | 0.25      | RT       | 3.5               | 97                     | > 99                  |
| 4               |    |    |    | 2          | 0.25      | RT       | 7                 | 93                     | > 99                  |
| 5 <sup>d</sup>  |   |   |    | 2          | 0.5       | RT       | 14                | > 99                   | > 99                  |
| 6               |   |   |    | 0.1        | 0.5       | RT       | 14                | > 99                   | > 99                  |
| 7               |    |    |    | 2          | 0.125     | 60       | 7                 | 92                     | > 99                  |
| 8               |   |   |   | 2          | 0.125     | 60       | 7                 | 98                     | 96                    |
| 9               |  |  |  | 0.1        | 0.125     | RT       | 3.5               | 89                     | 71                    |
| 10              |   |   |  | 0.1        | 0.125     | RT       | 7                 | 95                     | 69                    |
| 11              |  |  |  | 2          | 0.125     | 60       | 7                 | 79                     | 96                    |
| 12              |   |   |  | 2          | 0.25      | 60       | 14                | 97                     | 96                    |
| 13              |  |  |  | 2          | 0.125     | 60       | 7                 | 87                     | > 99                  |
| 14              |  |  |  | 2          | 0.25      | RT       | 3.5               | 75                     | 97                    |
| 15              |   |   |  | 2          | 0.25      | RT       | 7                 | 99                     | 93                    |
| 16 <sup>d</sup> |  |  |  | 2          | 0.25      | RT       | 3.5               | > 99                   | 99                    |
| 17              |   |   |  | 2          | 0.25      | RT       | 2.3               | > 99                   | 99                    |

<sup>a</sup>Concentration of the electrophile and the nucleophile in the individual substrate feeds. <sup>b</sup>Flow rates:  $2 \times 1.5 \text{ mL min}^{-1}$ ,  $2 \times 1.0 \text{ mL min}^{-1}$  or  $2 \times 0.5 \text{ mL min}^{-1}$ .

<sup>c</sup>Determined by HPLC at 215 nm. <sup>d</sup>Product deposition was observed in the reactor plate.

Finally, we wanted to perform the three-fold scale-up of selected  $S_NAr$  reactions using the HANU 2X 15 flow reactor. The geometrical layout of the reactor channels of the HANU 2X 5 and HANU 2X 15 OFRs is identical, the only difference is the length and thus the internal volume (5 mL vs 15 mL).<sup>15</sup> The so-

called smart dimensioning design strategy ensures the homogeneity of performance at different scales.<sup>[16]</sup> Practically, this means that the residence time and mass transfer characteristics are kept consistent, whilst throughput is easily increased with the flow rate enabling direct scale-up without the re-optimiza-

tion of the reaction parameters. This feature is of crucial importance regarding technical difficulties related to the processing of biphasic reaction mixtures. The aqueous HPMC-mediated synthesis of compounds **3** and **18** was selected for the scale-up study (Figure 4). In order to match the increased reactor volume with the residence time values previously studied in the small-scale reactor, flow rates were tripled for scale-up, but all other reaction conditions were unchanged. In this manner, the 15 mL OFR ensured productivities of around  $5.6 \text{ g h}^{-1}$ , which is roughly three times what was obtained using the 5 mL reactor. Similar to what was measured in the HANU 2X 5 OFR, STYs were around  $270 \text{ g L h}^{-1}$  indicating consistent performance at the scales explored. Both large-scale experiments were run continuously for 180 min without any technical difficulties and resulted around 17 g of pure isolated material after extractive work-up.<sup>[21]</sup> Importantly, only low amounts of waste were generated as indicated by E-factors of 1.3 and 2.7 determined for the synthesis of **3** and **18**, respectively.

## Conclusions

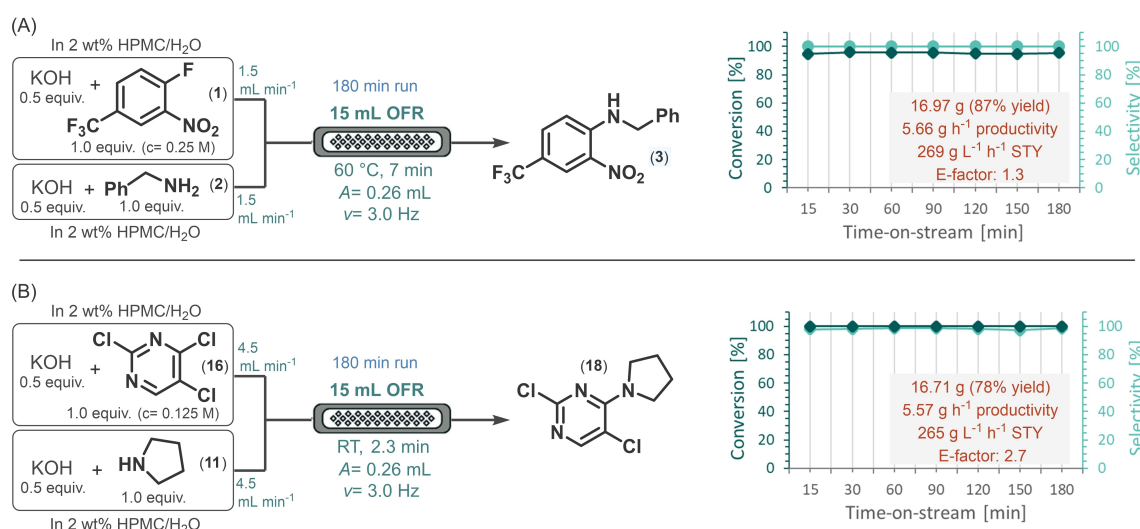
In the present study, we exploited the benefits of OFRs in combination with smart dimensioning to realize HPMC-mediated aqueous reactions as a directly scalable continuous process.  $S_NAr$  reactions between various nucleophiles and electrophiles were selected as model for this proof-of-concept study. The flow reactors utilized herein ensured a beneficial combination of active and passive mixing and enabled a significantly improved mass transfer compared to batch conditions. Initially, rapid parameter optimization was performed by using a lab-scale instrument having an internal channel volume of 5 mL. Fine-tuning of oscillation parameters, such as frequency and amplitude, proved particularly useful in reaching an optimal homogeneous suspension that can be robustly and reproducibly processed. In this manner, we were able to

perform a rapid parameter optimization, and also push the lab-scale reactor to its limits and realize selected  $S_NAr$  reactions on multigram scales by performing multiple long-run experiments without any detectable particle deposition or clogging. Ultimately, the optimal conditions from the small-scale experiments were directly transferred to a 15 mL OFR, achieving a three-fold scale-up. Because the residence time and mass transfer characteristics were kept consistent, direct scale-up was readily achieved without re-optimizing the reaction parameters. This protocol ensured the production of approx. 5.6 g of pure product per hour, which translates to around 130 grams per day using a small-footprint reactor system and water as a sustainable reaction medium. Further utilization of the smart dimensioning-based design strategy using a 150 mL reactor can improve throughput to production scales without changing process characteristics.<sup>[22]</sup>

## Experimental Section

### Continuous flow reactor setup

Flow reactions were performed using a commercially available system containing a HANU 2X 5 or HANU 2X 15 OFR made of Hastelloy as central element (Creaflow).<sup>15</sup> Both reactors comprise a linear plate-like process channel equipped with a series of cubic static mixing elements ( $2 \times 2 \times 2 \text{ mm}$ ) placed within a repeated pattern. The internal geometry (i.e., the pattern of the static mixers and the channel cross sections) as well as the width and height of the two reactor plates are identical, the only difference is their length and internal volume (HANU 2X 5: outer dimensions  $20 \times 9 \times 7 \text{ cm}$ , internal channel volume 5 mL; HANU 2X 15: outer dimensions  $56 \times 9 \times 7 \text{ cm}$ , internal channel volume 15 mL). The system also contained a pulsator module (Creaflow, Beta/5 pump with a Hastelloy pump head and PTFE membrane) that generates pulsation superimposed to the net flow of the reaction stream to facilitate mass transfer. The pulsator can deliver a tunable amplitude in the range approx.  $0.035\text{--}0.44 \text{ mL}$  per stroke, and adjustable frequency in the range of  $0.3\text{--}3.0 \text{ Hz}$ . The reagent feeds were introduced via two separate streams using Vapourtec SF-10



**Figure 4.** Direct scale-up of HPMC-mediated  $S_NAr$  reactions in a HANU 2X 15 OFR. (Yields shown are isolated yields. Conversion and selectivity were determined by HPLC at 215 nm.)

peristaltic pumps upstream the pulsator. To avoid entering air bubbles from the reactor outlet during backward pulsation, pressure was applied by using an adjustable backpressure regulator (BPR) from Vapourtec. Thermal regulation was achieved by using a Huber CC304 thermostat (transfer fluid: diethylene glycol). Parts of the setup were connected using PTFE or PFA tubes (1/16" OD, 0.8 mm ID for the HANU 2X 5 reactor and 1/8" OD, 1.6 mm ID for the HANU 2X 15 reactor) along with PEEK or stainless-steel fittings.

### Representative procedures for the flow experiments

Parameter optimization and reaction scope investigation were performed using the HANU 2X 5 flow reactor. A Duran bottle was charged with the corresponding electrophile (1.0 equiv, 0.125 M, 0.25 M or 0.5 M) and KOH (0.5 equiv.) as base in 2 wt% or 0.1 wt% HPMC/H<sub>2</sub>O as reaction medium. Similarly, in another Duran bottle a mixture containing the selected nucleophile (1.0 equiv) and KOH (0.5 equiv.) in 2 wt% or 0.1 wt% HPMC/H<sub>2</sub>O was prepared. While being stirred vigorously using a magnetic stirrer, the mixtures were pumped continuously using peristaltic pumps. The combined stream was passed through the pulsator and then the OFR at the selected flow rate, amplitude and frequency while maintaining 3 bar pressure. The reactions were performed either at RT or at 60 °C. The product mixture was collected for a duration equivalent to three times the average residence time under steady-state conditions into a stirred flask containing EtOAc to quench the reaction. After removal of the organic phase, the aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. No further purification steps were performed. Conversion and chemical selectivity were determined by analytical HPLC after calibration.

Preparative long-runs were performed using the HANU 2X 5 flow reactor under optimized reaction conditions in similar manner than described above for smaller scale experiments. Reagent feeds (both in 2 wt% HPMC/H<sub>2</sub>O) were pumped at identical flow rates of 0.5 mL min<sup>-1</sup> or 1.5 mL min<sup>-1</sup>. The combined stream was passed through the pulsator and then the OFR while maintaining 0.26 mL oscillation amplitude, 3.0 Hz frequency and 3 bar pressure. The reactions were performed either at RT or at 60 °C. The product mixture was collected for 180 min or 110 min under steady state conditions into a stirred flask containing EtOAc to quench the reaction. Work-up and product analysis were performed similarly as discussed above for smaller scale runs. Isolated compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Purity of products was determined by GC-FID.

Direct scale-up was performed using the HANU 2X 15 flow reactor under conditions previously optimized in the HANU 2X 5 system using 2 wt% HPMC/H<sub>2</sub>O as reaction medium. In order to match the increased reactor volume with residence times previously established, the flow rates utilized were tripled (reagent streams were pumped at identical flow rates of 1.5 mL min<sup>-1</sup> or 4.5 mL min<sup>-1</sup>), but all other reaction parameters (amplitude, frequency and temperature) were set to the previously optimized values. The product mixture was collected for 180 min under steady state conditions into a stirred flask containing EtOAc to quench the reaction. Work-up, product analysis and characterization were performed similarly as discussed above for experiments in the HANU 2X 5 OFR. See also the Supporting Information for more experimental details as well as photographs on the setups employed.

## Supporting Information

Synthetic procedures, additional reaction data, compound characterization data and copies of NMR spectra are provided in the Supporting Information. The authors cited additional references within the Supporting Information.<sup>[23]</sup>

## Acknowledgements

The Research Center Pharmaceutical Engineering (RCPE) is funded within the framework of COMET – Competence Centers for Excellent Technologies by BMK, BMDW, Land Steiermark and SFG. The COMET program is managed by the FFG. The authors acknowledge the financial support by the University of Graz. We also acknowledge the financial support of the European Union and the Italian Ministry of University and Research (MUR) received through resources from the National Operational Program (PON) Research and Innovation 2014–2020 (CCI 2014IT16M2OP005). We would like to thank Creaflo for the generous loan of the HANU reactor used in this study. We also thank Gustav Parmentier GmbH (Frankfurt, Germany) for providing HPMC samples (Mantrocel® E5 or K4M). We are grateful to Prof. Anton Huber and Mrs. Helga Reischl for their support in the viscosity measurements.

## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Continuous flow · Hydroxypropyl methylcellulose · Oscillatory plug flow reactor · Scale-up · Nucleophilic substitution · Water chemistry

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Manuscript received: August 3, 2023

Revised manuscript received: September 21, 2023

Accepted manuscript online: September 22, 2023

Version of record online: November 22, 2023