Simple and Versatile Laboratory Scale CSTR for Multiphasic Continuous-Flow Chemistry and Long Residence Times

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Ⓢ Supporting Information

ABSTRACT: A universal multistage cascade CSTR has been developed that is suitable for a wide range of continuous-flow processes. Coined by our group the "Freactor" (free-to-access reactor), the new reactor integrates the efficiency of pipe-flow processing with the advanced mixing of a CSTR, delivering a general "plug-and-play" reactor platform which is well-suited to multiphasic continuous-flow chemistry. Importantly, the reactor geometry is easily customized to accommodate reactions requiring long residence times (≥3 h tested).

INTRODUCTION

The past two decades have seen far-reaching progress in the development of microfluidic systems for use in chemical synthesis, with the field continuing to mature exponentially.[1−7] On account of their low chemical inventory, continuous-flow systems are highly suited to implement many of the Twelve Principles of Green Chemistry, often producing safer process operating conditions and higher efficiency than can be obtained with traditional batch processing.[8,9] Moreover, the integration of real-time analysis and automation with low-volume flow reactors enables chemists to explore incredibly wide regions of operational parameter space over relatively short periods of time.[10] This paradigm shift from conventional batch chemistry has been employed to efficiently produce numerous pharmaceutical compounds with unmatched environmental footprints, such as Ibuprofen by McQuade,[11] Zyprexa by Kirschning,[12] and Tamoxifen by Ley.[13] In a well-argued publication by Jensen and McMullen, the defacto conditions under which flow chemistry "makes sense" have been condensed to those whereby the rate of chemical reaction surpasses the associated mass transfer of a system.[14] Unfortunately, this regime excludes many multiphasic reaction systems, in which a combination of gas, liquid, or solid comprises the reactants, reagents, catalysts, or (by)products as the reaction proceeds. Frequently met multiphasic examples include enzymatic reactions (organic−aqueous phases), slurries (solid−liquid), or hydrogenation (solid−liquid−gas)—each requiring effective mixing and long residence times. Static mixers built within tubular reactors can offer these conditions, though they require high volumetric flow rates which may not be feasible for slow reactions (e.g., >5 min) (Figure 1).[15]

In 2011, Greiner and colleagues made some headway toward slow continuous-flow processing through use of a nested-pipe reactor.[16] During a 14 day test campaign, the authors demonstrated the potential of this reactor geometry by producing 20 kg of product per day. However, the bespoke
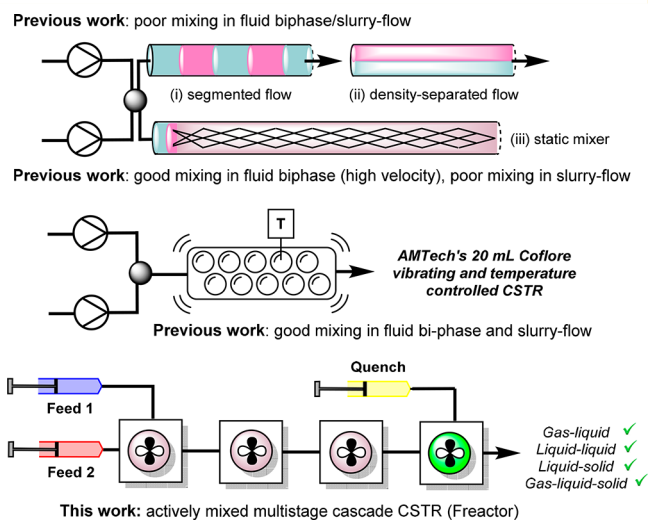
Figure 1. Top: Impact of biphasic flow performance on mixing regime in tubular/static mixed reactors. Middle: Coflore reactor developed by AMTech. Bottom: Well-mixed cascade CSTR reactor reported here.

reactor is not trivial to assemble nor appropriate for small scale processing. Taylor-Couette reactors, in which a rotating cylinder provides mixing, have been employed in slow continuous biological and polymerization processes, though they rely on product extraction against gravity which may become challenging in cases where solid products are formed.[17,18] Consecutive or cascade continuous stirred tank reactors (CSTRs) provide a solution to these problems. However, conventional cascade CSTRs are convoluted, expensive, and oversized where material availability is low—a technological gap which places limitation on the accessibility

and development of continuous-flow chemistry in academia and industry.[19] Thus, miniaturization of CSTRs for synthetic research laboratories represents a significant step toward broadening the range of chemical transformation suitable for continuous mode. AMTech has produced a laboratory and large scale multistage CSTR, the Coflore reactor, consisting of a series of loose-fitting polymer inserts that provide mixing as the entire unit is shaken (Figure 1, middle).[20] Equally, the Jensen group has recently reported a miniature consecutive CSTR which performed comparably to its standard size counterpart in two solid-forming reactions.[21] Likewise, Lapkin and Meadows have also recently published a reactor which closely resembles a sequence of CSTRs linked in a single compact block, comprising no unmixed connections between adjacent chambers, and is suitable for solid-forming processes.[22] Herein, we report our own independent successes in CSTR miniaturization, based on the principles of open-source, inexpensive, and modular reactor design (Figure 1, bottom). The freely accessible cascade CSTRs described here are simple to assemble and modify and provide chemists with a general platform to explore continuous-flow processing with little expertise required. As with other cascade CSTR systems, as the number of reactors in series is increased, the overall performance tends toward that of a well-mixed plug-flow reactor, which ensures uniformity of processing conditions. For example, five 2 mL cascade CSTRs provide greater uniformity of residence time than a single 10 mL CSTR—in general, the greater the number of CSTRs, the closer to ideality the system becomes. The CSTRs have been evaluated against their batch counterparts for a variety of important and challenging multiphasic processes, including enzymatic imine reduction, cycloisomerization, N-chloroamine synthesis, classical resolution of chiral amines, and heterogeneous Pd-catalyzed hydrogenation. Through these examples, we tackle many of the difficulties associated with scale-up of multiphasic phenomena and demonstrate the tunability of our reactor to facilitate reactions requiring long residence times (τ_r, covering a tested range of 2 min to 3 h).

RESULTS AND DISCUSSION

Reactor Design. Practicality, simplicity, and versatility to accommodate different reactions were identified as important design principles from the outset. Other key features sought were general chemical resistance, an observation window, simple cleaning, cost effectiveness, and mass production capability. An early decision was made by our team to provide the reactor as an open-source piece of equipment and develop an online user community to share experiences. (The CSTR "Freactors" and stirrer motors were made to the design described in the Supporting Information, with plans to become available from both www.iprd.leeds.ac.uk/Freactors and Asynt Ltd.) The CSTRs and ancillaries are mobile and able to sit alongside standard laboratory equipment (e.g., syringe/peristaltic pumps, glassware, in-line filters, back-pressure regulators, separators, on- or at-line analysis). The reactor reported here is composed of polyacetal plastic, which is inexpensive, compatible with most solvents/reagents (with exception of strong acids/bases), and easily fabricated.[23] This acetal plastic performs well as an insulator, allowing high-temperature reactions to be conducted through feeding hot starting materials directly into the reactor. Over a single CSTR, a flow of water (1 mL min^{-1}) at 50 °C gave a 3.9 °C temperature drop (0.35 W) over the reactor, due to heat loss to

the surroundings with no additional insulation. Conventional machining of a plastic stock rather than 3D printing the reactors[24] (which is entirely feasible for this geometry) brings advantages of high structural integrity of the reactors and the flexibility to change materials (e.g., PTFE to metal). Where 3D printing may become more appropriate, albeit currently at the expense of structural performance, is building additional functionality or flexibility in evaluating designs. The base component of each reactor unit comprises a cylindrical reservoir (2 mL volume) containing a magnetic stir bar for enhanced, low-volume, and uniform mixing (Figure 2, top left).
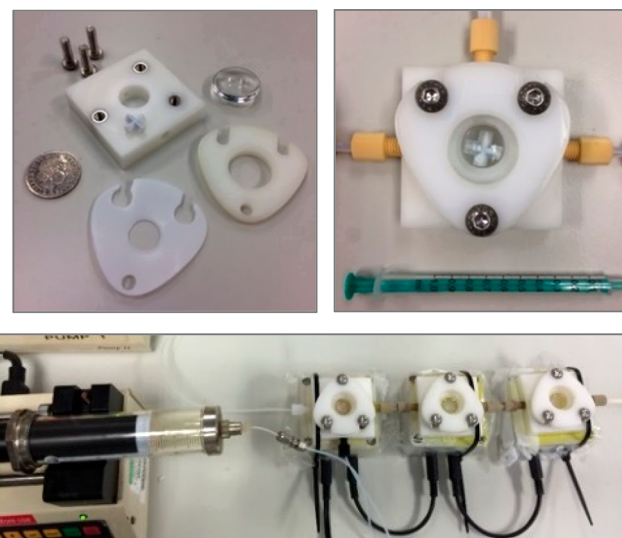
Figure 2. Top left: individual components of the reactor (10 pence for scale). Top right: assembled single reactor unit. Bottom: three-stage cascade of reactors in series.

A convex glass lens is clamped, convex side down, onto a PTFE gasket above the volume element via a triangular lid component with three bolts to provide a robust and simple flow-reactor assembly (Figure 2, top right). The glass window allows physical reaction monitoring and could enable real-time spectroscopic analysis of flow systems or the use of photochemistry by careful choice of glass type and volume depth. Up to five (but generally three) ports are drilled perpendicular to the reaction chamber to allow modular combinations of inlets and outlets. Standard HPLC 1/8 in. o.d. ferrules and tube fittings are sufficient to allow continuous flow of gases, liquids, and solids. The reactor units have been tested up to 6.9 bar using a sequential BPR method (see Supporting Information), with some evidence of leaking beyond this pressure. Importantly, the reactors are stirred magnetically, which is much simpler than use of mechanical agitators or shaker beds (Figure 2, bottom).[25] Both straight and cross-bar PTFE-coated magnetic stir bars (diameter 8−10 mm) were selected to provide a close fit to the walls of the reactor vessel. The rotation rate of the stir bar was assessed using a stroboscope (16 rs^{-1}), comparing favorably with commercial stirrer plates also used within our study (18 rs^{-1}).

Reactor Characterization. Heat transfer capability, residence time distribution (RTD) analysis, and gas−liquid mass transfer efficiency (k_La) were evaluated and are supplied in the Supporting Information.

Enzymatic Biotransformation. *Imine Reductase (IRED).* Imine reductase enzymes are highly efficient biocatalytic

alternatives to chemical (transfer) hydrogenation catalysts in the asymmetric reduction of imines to afford enantioenriched amines.[26,27] The purpose of our study was to evaluate the use of our reactor in improving the productivity of IREDs for imine reduction. A five-stage assembly was connected to two syringe pumps. Feed 1 contained the (R)-IRED and glucose dehydrogenase in aqueous phosphate buffer (pH 7.0). Feed 2 contained a mixture of glucose, NADPH cofactor, and 0.1 M 2-propyl-3,4,5,6-tetrahydropiperidinium hydrochloride (Scheme 1).[28] At an overall flow rate of 0.52 mL min^{-1} (τ_r = 19 min),

Scheme 1. Continuous-Flow Biotransformation of Propyliminium with (R)-IRED in Five-Stage CSTR[a]
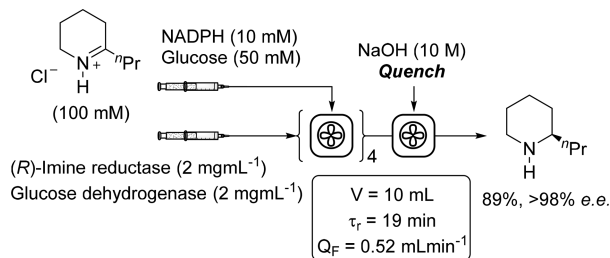
[a]Conversion (%) and ee (%) determined by chiral GC. V = reactor volume, Q$_F$ = final volumetric flow rate.

the process reached steady state after 2.5 reactor volumes (RVs)—noting that the RV is based on the total volume of the cascade.

At this point, 89% conversion of substrate was achieved to produce (R)-amine with 98% ee. The space-time-yield of 17 g L^{-1} h^{-1} compares favorably with the batch reaction (6.4 g L^{-1} h^{-1}), and the improvement is likely due to lack of product accumulation within the system, known to inhibit the catalyst. It is anticipated that this productivity value could be optimized through operating at the optimal temperature of the enzyme, though this is beyond the scope of this version of the reactor.

Chemical Reactions. *Synthesis of N-Chloroamines.* Chlorinated amines represent an electrophilic aminating tool and are useful for a wide number of synthetic reactions.[29] The biphasic liquid synthesis of N-chloroamines from NaOCl and secondary amine in organic solvent may be considered a green reaction, generating only NaCl and NaOH byproducts with high atom efficiency.[30] We have previously reported a continuous-flow synthesis of various N,N-dialkyl-N-chloroamines using either a bespoke mesoscale tubular reactor with static mixers or a 50 mL single-stage CSTR (Table 1, entries 1 and 2, respectively).[31] Taking N-chloro-N-methylbenzylamine as an example, we decided to compare these reactor types to our CSTR (see subsequent entries of Table 1).

Using a two-stage CSTR construct, N-methylbenzylamine (1.0 M in toluene) and NaOCl (1.1 M in water) were fed independently into the reactor at room temperature. Adopting a residence time of 20 min, the chlorinated product was formed in quantitative conversion (entry 3). More productively, a five-stage reactor and residence time of 5 min delivered the product in 94% conversion, leading to a productivity of 0.88 kg L^{-1} h^{-1} at steady state (entry 6). Comparing these with previous studies, a tubular static mixed system produced the N-chloro-N-methylbenzylamine in 89% conversion and a single-stage CSTR in 94% conversion (τ_r = 20 and 25 min, respectively, entries 1 and 2). Interestingly, dibenzylamine substrate partitions preferably into the organic phase, making reactions without a

Table 1. Continuous Liquid Biphase Reaction of NaOCl with Amine in Toluene/Water

entry	no. of CSTRs (n)	reactor volume (mL)	τ_{res} (min)	conversion[a] (%)
1[b]	static mixer	6 (1.6 mixed)	20	89[c]
2[b]	1	50	25	94[c]
3[b]	2	4	20	100
4[b]	3	6	10	83
5[b]	5	10	10	93
6[b]	5	10	5	94
7[d]	1	50	50	40[c]
8[d]	5	10	30	42

[a]Analyzed by ^{1}H NMR spectroscopy. [b]Product N-chloro-N-methylbenzylamine. [c]From ref 31. [d]Product N-chlorodibenzylamine.

phase transfer catalyst even slower and unsuitable for poorly mixed tubular reactors. In the single-stage 50 mL CSTR from previous studies, dibenzylamine chlorinated with 40% conversion in 50 min residence time (entry 7). Pleasingly, using our reactor at 1/5 scale, a comparable conversion was realized in a residence time of 30 min (entry 8), indicating improved mass transfer.

Electrocyclization. Our group recently reported a rapid, NaOH-promoted cycloisomerization reaction of several N-alkynylated 2-aminopyridinium bromides under aqueous conditions.[32] The pyridinium halides are cyclized instantaneously upon contact with base, producing the imidazopyridine products as water-insoluble oils during reaction. While this simplifies product recovery in batch, we speculated that such a rapid reaction would naturally suit a continuous-flow mode to boost space-time-yield. Although the reaction itself appears under diffusive control (i.e., does not require additional mixing nor long residence times), preliminary results have shown the dispersion of product to resist flow through a tubular pipe, complicating process translation. Two options became available to us upon consideration of our reactor for this system: (i) exploit the additional turbulent mixing of the reactor to maintain product dispersion out of the pipe or (ii) input an organic solvent feed to extract the product in situ. To demonstrate the modularity of our design, the latter was selected. Using a four-stage CSTR, aqueous solutions of N-propargyl-2-aminopyridinium bromide (1 M) and NaOH (1.25 M) were fed at equal flow rate into chamber 1. Prior to the mixing zone, a constant stream of DCM solvent was fed at a matched overall flow rate to immediately extract the desired product in continuous flow. At this point, the benefits of our plug-and-play design became evident as the final chamber was linked to a liquid–liquid membrane separator via standard HPLC fixtures, allowing simple in-line purification of the heterocyclic product (Scheme 2).

Following 2 RVs, the desired product was formed and separated in 97% yield with a residence time of 2 min (Figure 3), generating a steady-state space-time-yield of 32 g L^{-1} min^{-1}—triple the value obtained in batch (10.9 g L^{-1} min^{-1}).

N-Acetylation of Ethylene Diamine. Selective monofunctionalization of symmetrical materials, such as diamines, is important due to their widespread use as linkers in the pharmaceutical industry. However, two key challenges exist for

Scheme 2. Continuous-Flow Electrocyclization with In-Line Membrane Separation of Product[a]
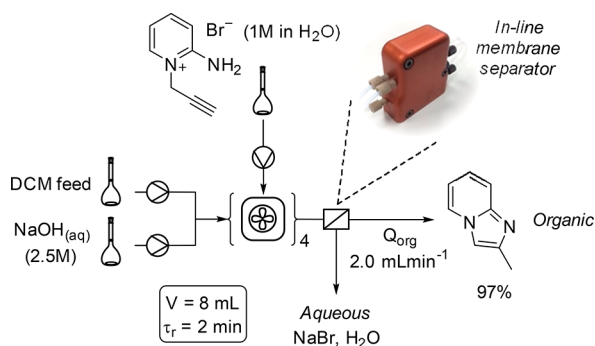
[a]Yield (%) is isolated. Q_{org} = exit flow rate of organic stream.
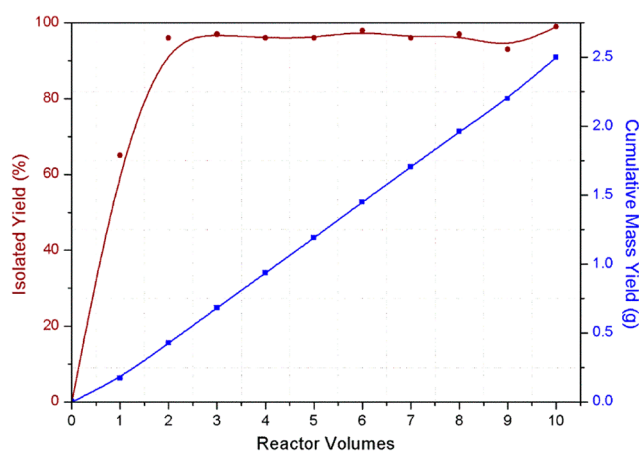

Figure 3. Representative plot of isolated yield (red)/cumulative mass yield (blue) of imidazo[1,2-a]pyridine as a function of reactor volume.

these reactions: (i) suppression of overfunctionalization and (ii) control of phase partitioning, which often leads to low-yielding processes. Maurya and Wille have independently shown the use of continuous plug-flow and microreactor technology to provide high selectivity in making monop-rotected diamines.[33,34] Throughout the reaction, different species partition into separate solvent phases—making mixing crucial to this type of system. Our miniaturized CSTR offers a simple platform to optimize an experimental design (i.e., DOE) for this reaction, allowing for a continuously well-mixed biphase to both minimize difunctionalization and maximize product partitioning. To test this hypothesis, an aqueous feed of ethylene diamine was met with an equimolar toluene solution of acetic anhydride in chamber 1 of the reactor and subsequently flowed through n CSTR stages (Table 2, column 2).

In comparison to batch (entry 1), a six-stage CSTR allowed a 16% increase in conversion of ethylene diamine, with a 7% drop in selectivity to form the desired product (entry 4). Selectivity could be improved by reducing the number of stages in the reactor geometry while maintaining a residence time of 20 min, though this was shown to compromise conversion (entry 2). Employing a five-stage CSTR, with a residence time of 30 min delivered the desired diamine in 83% conversion with 84% selectivity, leading to a productivity value 3.4-fold higher than that obtained in batch mode (entry 5).

Table 2. Batch versus Continuous Liquid Biphase Monoacetylation Reaction

entry	no. of CSTRs (n)	τ_{res} (min)	conversion[a] (%)/ selectivity[a,b] (%)	productivity (g L^{-1} h^{-1})
1	batch	20	69/87	51
2	2	20	53/88	112
3	4	20	83/80	163
4	6	20	85/80	163
5	5	30	83/84	173

[a]Analyzed by ^{1}H NMR spectroscopy at steady state. [b]Selectivity for monoacetylated amine.

Continuous Crystallization. Solid-forming reactions are notoriously challenging to process in continuous flow due to reactor fouling and blockage, often at small gauge tubing connectors or sharp turns in reactor channeling. These problems have been tackled by (i) introduction of a solubilizing agent, (ii) use of ultrasonication/pulsed agitation, or (iii) use of specifically engineered reactors to facilitate the transport of a slurry.[35−39] With these in mind, we became interested in the ability to manage the flow of particulate suspensions, as a general alternative to those listed above. The classical resolution of *rac*-salsolidine **1**, via diastereomeric crystallization with (S)-mandelic acid **2**(S), was investigated (Scheme 3). Employing a

Scheme 3. Slurry-Flow Diastereomeric Crystallization of Salsolidine and (S)-Mandelic Acid in a Five-Stage Reactor[a]
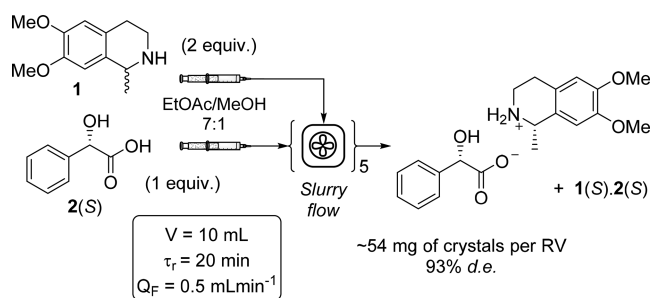
[a]Weight of crystals are dry, and de (%) is determined by ^{1}H NMR spectroscopy. V = reactor volume, Q_F = final volumetric flow rate.

five-stage CSTR, EtOAc/MeOH (7:1) solutions of each were pumped into chamber 1—immediately producing a crystalline slurry upon contact (0.7 wt % at steady state). Following a residence time of 20 min, crystals of **1**(R)·**2**(S) from the output stream were collected by filtration and analyzed by ^{1}H NMR spectroscopy to show a de of 91% at steady state.

Each RV consistently delivered crystals of **1**(R)·**2**(S) in 1.8% isolated yield, which, albeit relatively low, produced a cumulative yield of 24% over 13 RVs (Figure 4). These findings compare favorably with the analogous batch system, affording lower quality crystals in 30% yield with 83% de (see the Supporting Information). Ongoing research from our group has shown semibatch recirculation of the mother liquor through the reactor to be a useful method of achieving full resolution (i.e., 50% yield).
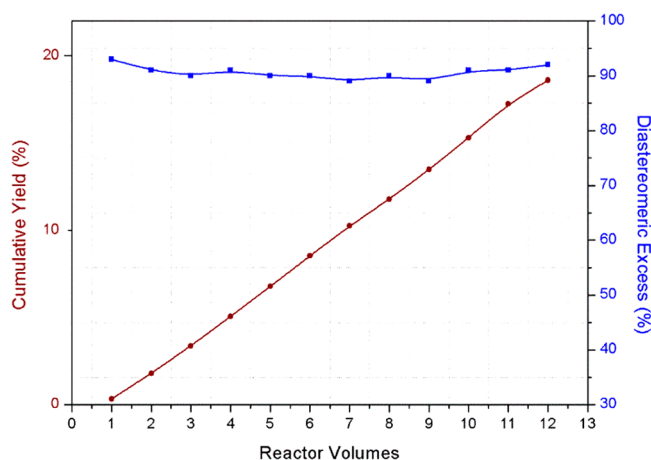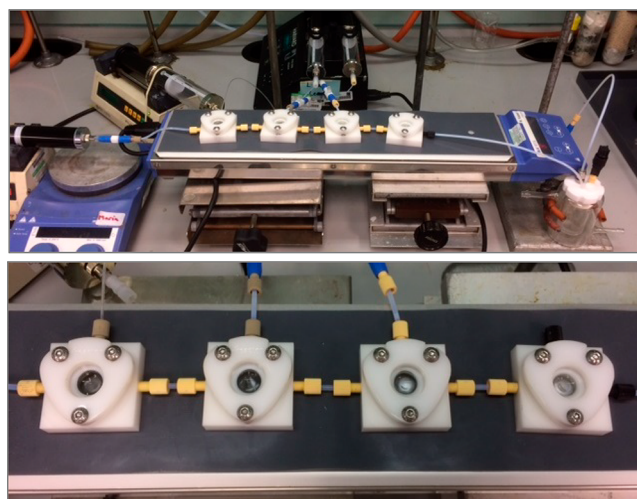
Figure 4. Representative plot of cumulative yield (red)/diastereomeric excess (blue) of **1**(R)·**2**(S) as a function of reactor volume. Cumulative yield is calculated based on 1.8% yield per RV, ceasing at a maximum value of 50%.

Three-Phase Catalytic Hydrogenation. Hydrogenation of organic compounds in the presence of a suitable heterogeneous metal catalyst is of great importance to both academic and industrial laboratories. Small scale batch hydrogenations pose an operational hazard in the use of hydrogen gas, requiring dedicated high-pressure resistant reactors and autoclave conditions.[40] Moreover, small batch vessels at the industrial scale become impractical, as reduced plant size incurs the penalty of multiple fill/empty cycles. Our low-volume reactor offers a combination of better heat transfer and mixing than typical batch reactors—ideal for S/L/G-phase reactions such as hydrogenation which are both exothermic and mass transfer limited (for heat capacity studies, see the Supporting Information). A benchmark reduction reaction comprising a solid catalyst (Pd/C), liquid reagent feed (nitrobenzene), and hydrogen gas was employed to assess the feasibility of this idea. A methanolic slurry of 5% Pd/C and nitrobenzene (500 mM) was fed into chamber 1 of a four-stage CSTR, meeting three separate streams of hydrogen gas in the mixing zones of chambers 1, 2, and 3 (Scheme 4 and Figure 5).

Scheme 4. Triphasic Hydrogenation of Nitrobenzene in a Four-Stage Heated Reactor
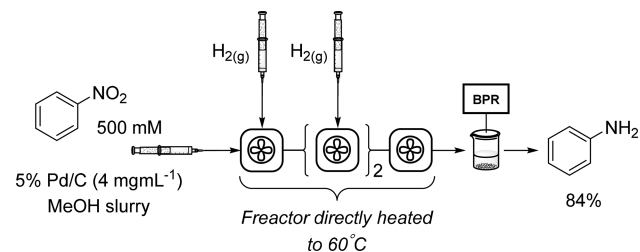
The full, noninsulated reactor was simply heated using a multiposition stirrer hot plate, generating a reaction mixture temperature of 60 °C after 2 min heating time (Figure 5). After a long residence time of 3 h was employed and following 1 RV, the aromatic nitro group was reduced to afford aniline in 84% conversion at steady state (Figure 6). In our hands, the analogous batch protocol required 16 h to reach 92% conversion (see the Supporting Information).

Figure 5. Top: Experimental configuration, centered around a multiposition stirrer hot plate at 80 °C. Bottom: Well-mixed triphasic reaction mixtures in cascade CSTRs.
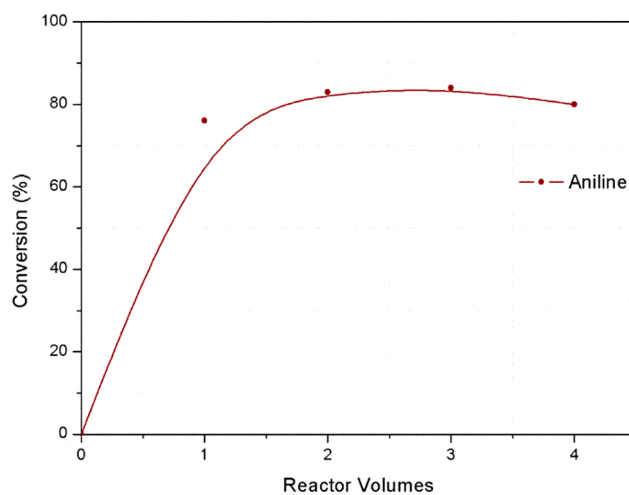
Figure 6. Representative plot of conversion of nitrobenzene to aniline over 4 RVs, as determined by GC analysis.

This final study demonstrates the (i) modularity, (ii) enhanced mixing over long residence time, and (iii) simple heating capability of the reactor, opening up a broad array of continuous-flow chemistry to this reactor type.

■ CONCLUSIONS

A new, free-to-access multistage continuous stirred tank reactor has been designed, constructed, and implemented in a variety of multiphasic chemical processes. The reactor has been conceived to enable chemists to explore continuous-flow methodology with little to no expertise required. The design is simple, versatile, and inexpensive to produce, with 60 reactors and stirrer motors currently in operation from our laboratory. The small volume of each reactor is well-suited to laboratory scale experiments where materials are typically precious and not commercially available. Moreover, these plug-and-play units are equipped with universal HPLC fixtures and fittings—ideal for deployment among common laboratory equipment (as demonstrated within). Through this report, we have provided examples of processes involving combinations of solid, liquid, and gas reagents/products and the potential for our reactor

design to accommodate each (see Table 3 for a summary). In all but one of the cases, productivities were improved by

Table 3. Summary of Multiphasic Reactions Evaluated within This Study

				productivity (g L^{-1} h^{-1})	
entry	type of reaction	phase (G, L, S)	τ_{res} (min)	batch	flow
1	IRED	L	19	6.4	17
2	*N*-chloroamine	L/L	5–50	198[a]	826[b]
3	monoacetylation	L/L	30	51	173
4	heterocyclization	L → L/L	2	660[c]	1920
5	crystallization	L → L/S	20	8.2	31
6	hydrogenation	G/L/S	180	3.5[d]	0.12

[a]Using static mixer; see ref 31. [b]τ_{res} = 5 min. [c]See ref 32. [d]92% yield at 16 h.

process translation from batch to flow. The current model shows some limitation where solid−liquid reactions are concerned (0.7 wt % demonstrated here), though a recent study from our group (not reported here) has shown a slurry of Cs$_2$CO$_3$ in DMF to flow comfortably through the reactor without blockage; research remains ongoing to improve these systems. Nevertheless, our straightforward design requires only removal of one bolt to fully disassemble the reactor for easy clean-out of reaction debris. The ability to join low-volume CSTR units in cascade provides a means of tailoring reactor volume, and therefore residence time, to suit markedly different reaction types. On each end of this spectrum, we have performed a rapid, room temperature heterocyclization reaction (τ_r = 120 s) alongside a much slower, high-temperature triphasic catalytic hydrogenation (τ_r = 3 h)—both being feasible with the same reactor geometry, which is unprecedented. It is anticipated that these simple yet robust, freely accessible reactors will open new avenues for flow chemistry and help lift the current barriers associated with process translation for the modern chemist.

■ EXPERIMENTAL SECTION

General Remarks. Standard 1/8 or 1/6 in. o.d. PTFE tubing and fittings were used as purchased from commercial HPLC suppliers. PTFE-coated magnetic cross (10 mm dia.) and straight stir bars (8 × 3 mm) were obtained from VWR Ltd. All reactor cascades were linked using 1/8 in. PTFE tubing. All reactions were carried out under an atmosphere of air. Propargylpyridinium bromide was prepared as previously reported.[32] Deuterated CDCl$_3$ and D$_2$O were used as supplied. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DPX300 (300/75 MHz) spectrometer or a Bruker AV3-400 (400/100 MHz) spectrometer using the residual solvent as an internal standard. The values of chemical shifts are reported in parts per million (ppm) with the multiplicities of the spectra reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br); values for coupling constants (*J*) are assigned in hertz.

Imine Reductase Bioreaction. Batch procedure: a previously reported protocol (Turner et al.) was followed to obtain (*R*)-2-propylpiperidine with >98% conversion and >98% ee after 24 h.[27] Product analyzed by chiral GC: $t_{R(imine)}$ = 14.92, $t_{R(S)\text{-amine}}$ = 15.57, $t_{R(R)\text{-amine}}$ = 15.80 min. Flow procedure: a five-stage CSTR was connected to two 50 mL automated syringes. Syringe 1: (*R*)-IRED enzyme (2 mgmL^{-1}), glucose dehydro-

genase CDX-901 Codexis (2 mgmL^{-1}) in 50 mL of NaPi buffer (100 mM, pH 7.0). Syringe 2: 2-propyl-3,4,5,6-tetrahydropiperidinium hydrochloride (100 mM), NADPH (10 mM), glucose (50 mM) in 50 mL of NaPi buffer (100 mM, pH 7.0). Each syringe was fed at 0.26 mL min^{-1} (τ_{res} = 19 min), and the reactor eluent was collected in RV fractions containing NaOH (10 M, aqueous) to immediately quench the output phase. Under steady-state conditions, the reaction achieved 89% conversion and 98% ee, as determined by the same chiral GC method above.

Synthesis of *N*-Chloroamines. Two syringe pumps equipped with 50 mL syringes were connected to a reactor of *n* chambers in series. Syringe 1: *N*-methylbenzylamine/*N*,*N*-dibenzylamine (1 M in toluene). Syringe 2: NaOCl (1.1 M in water). Each syringe was fed at equal flow rate to provide the desired τ_{res} over *n* CSTRs (see Table 1). The reactor eluent was collected in RV fractions and the organic phase separated immediately to prevent further reaction. The organic phase was concentrated in vacuo and analyzed by ^{1}H NMR spectroscopy to determine crude conversion (see below).

N-Chloro-N-methylbenzylamine. Two-stage CSTR, τ_{res} = 20 min, quantitative conversion. ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H (ppm) 7.35−7.31 (m, 5H, C*H*Ar), 4.05 (s, 2H, C*H*$_2$), 2.94 (s, 3H, C*H*$_3$).

N-Chloro-N,N-dibenzylamine. Five-stage CSTR, τ_{res} = 30 min, 42% conversion. ^{1}H NMR (CDCl$_3$, 300 MHz) δ_H (ppm) 7.39−7.30 (m, 20H, C*H*Ar amine and chloramine), 4.14 (s, 4H, 2 × NClC*H*$_2$ chloramine), 3.81 (s, 4H, 2 × NHC*H*$_2$ amine). All data are consistent with those reported in the literature.[31]

Electrocyclization Reaction. A four-stage CSTR was connected to two input feeds. Feed 1: a biphasic (binary) mixture of aqueous NaOH (1.25 M) and DCM (blank). Feed 2: aqueous *N*-propargylpyridinium bromide (1 M). Each feed was pumped at 2.0 mL min^{-1} (τ_{res} = 2 min) through the reactor, and a commercially available membrane-based liquid/liquid separator (Zaiput) was utilized to segment the organic and aqueous phases in continuous flow.[41] The organic partition was collected in reactor volume fractions (4 mL, based on full L−L separation) and the solvent allowed to evaporate. The residue was analyzed by ^{1}H NMR spectroscopy to assess purity and weighed to determine isolated yield. Under steady-state conditions, the imidazopyridine product was formed in 97% isolated yield.

2-Methylimidazo[1,2-a]pyridine. ^{1}H NMR (300 MHz, CDCl$_3$) δ_H (ppm) 8.24 (dt, *J* = 6.6, 2.1, 0.9 Hz, 1H, py*H*), 7.58 (d, *J* = 9.0 Hz, 1H, py*H*), 7.49 (s, 1H, im*H*), 7.20 (m, 1H, py*H*), 6.80 (td, *J* = 9.0, 6.6, 0.9 Hz, 1H, py*H*), 2.41 (d, *J* = 0.9 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ_C (ppm) 143.2, 140.2, 126.5, 126.1, 115.2, 113.3, 110.2, 13.1. All data are consistent with those reported in the literature.[32]

Amine Monoacetylation Reaction. Batch procedure: ethylene diamine (60 mg, 1 mmol) and DI water (0.63 mL) were added to a round-bottomed flask. Acetic anhydride (102 mg, 1 mmol) in toluene (0.63 mL) was added dropwise, and the reaction continued for 20 min. The aqueous phase was separated, and water was removed to leave a crude product residue. The oil composition was analyzed by ^{1}H NMR spectroscopy.

Flow procedure: two syringe pumps equipped with 50 mL syringes were connected to a reactor of *n* chambers in series. Syringe 1: ethylene diamine (1.6M) in NaOAc/AcOH (2M, buffered to pH 5). Syringe 2: acetic anhydride (1.6M) in toluene. Each syringe was fed at equal flow rate to provide the

desired τ_{res} over n CSTRs (see Table 2). The biphasic reactor eluent was collected in RV fractions, and the aqueous phase was separated immediately to prevent further reaction. Water was removed in vacuo to leave the crude product mixture as an oily residue, which was analyzed by ^{1}H NMR spectroscopy to determine crude composition (see below).

Monoacetylated Amine. ^{1}H NMR (500 MHz, D$_2$O) δ_H 3.42 (t, J = 5.8 Hz, 2H, AcHNCH_2), 3.07 (t, J = 5.8 Hz, 2H, H$_2$NCH_2) 1.95 (s, 3H, CH_3). All data are consistent with those reported in the literature.[42]

Diacetylated Amine. ^{1}H NMR (500 MHz, D$_2$O) δ_H 3.22 (s, 4H, 2 × CH_2), 1.90 (s, 6H, 2 × CH_3). All data are consistent with those reported in the literature.[43]

Continuous Crystallization Reaction. A five-stage CSTR was connected to two syringe pumps equipped with 60 mL syringes. Syringe 1: *rac*-salsolidine (0.35 g, 16.8 mmol, 0.28M) in EtOAc/MeOH (7:1) (60 mL). Syringe 2: (S)-mandelic acid (1.3 g, 8.4 mmol, 0.14M) in uniform solvent. Each syringe was fed at 0.25 mL min^{-1} (τ_{res} = 20 min), and the reactor output was collected in RV fractions. Each fraction was filtered, dried, and weighed to assess isolated yield (the sum of which provides cumulative yield). The de of each RV was determined by ^{1}H NMR spectroscopy, relative to each pure diastereoisomeric salt (see below).
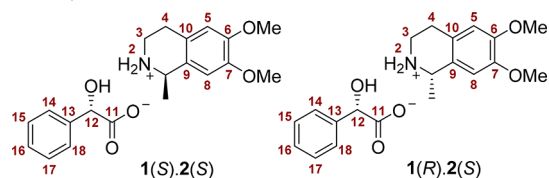
1(S)·2(S). $[\alpha]_D^{23}$ = +39.6 (c 1.10, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H (ppm) 7.31 (d, J = 7.0 Hz, 2H, H^{14} and H^{18}), 7.19 (m, 3H, H^{15}, H^{16} and H^{17}), 6.53 (s, 1H, H^8), 6.47 (s, 1H, H^5), 4.77 (s, 1H, H^{12}), 3.98 (q, J = 6.6 Hz, 1H, H^1), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.16 (m, 1H, H^3), 2.98 (m, 1H, H^3), 2.72 (m, 2H, H^3 and H^4), 1.45 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ_C (ppm) 178.8 (C11), 148.6 (C7), 148.3 (C6), 142.2 (C13), 128.0 (C15 and C17), 127.0 (C16), 126.5 (C14 and C18), 125.6 (C9), 123.6 (C10), 111.3 (C8), 108.7 (C5), 74.4 (C12), 56.1 (OCH$_3$), 55.9 (OCH$_3$), 50.3 (C1), 39.0 (C3), 25.2 (C4), 19.8 (CH$_3$).

1(R)·2(S). $[\alpha]_D^{23}$ = +66.3 (c 1.10, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H (ppm) 7.27 (m, 2H, H^{14} and H^{18}), 7.15 (m, 3H, H^{15}, H^{16} and H^{17}), 6.55 (s, 1H, H^8), 6.48 (s, 1H, H^5), 4.74 (s, 1H, H^{12}), 4.17 (q, J = 6.6 Hz, 1H, H^1), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.19 (m, 1H, H^3), 2.89 (m, 2H, H^3 and H^4), 2.74 (m, 1H, H^4), 1.41 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ_C (ppm) 178.8 (C11), 148.6 (C7), 148.3 (C6), 142.1 (C13), 127.9 (C15 and C17), 127.0 (C16), 126.4 (C14 and C18), 125.7 (C9), 123.6 (C10), 111.3 (C8), 108.7 (C5), 74.4 (C12), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 50.3 (C1), 38.9 (C3), 25.3 (C4), 19.6 (CH$_3$).

Catalytic Hydrogenation Reaction. Stage 1 of a four-stage CSTR was connected to two input feeds. Feed 1: a 50 mL glass syringe containing a microstir bar charged with nitrobenzene (500 mM), 5% Pd/C (4 mgmL^{-1}), and methanol (50 mL). The syringe contents were stirred throughout the reaction to allow pumping of a uniform suspension, at 0.04 mL min^{-1}. Feed 2: a gastight glass syringe containing hydrogen gas (100 mL), fed at 0.2 mL min^{-1}. Stages 2 and 3 were each linked to hydrogen gas feeds in an analogous manner. The entire reactor was placed directly onto a commercially available multiposition

stirrer hot plate maintained at 80 °C, generating an internal solvent temperature of 60 °C. The output of stage 4 was flowed directly into a sealed container housing a back-pressure regulator (20 psi) exit valve to provide controlled multiphasic flow. The reactor eluent was collected in RV fractions (4 × RVs over 12 h process time), filtered over Celite, diluted with an internal standard, and analyzed by gas chromatography to assess conversion: $t_{R(ArNO_2)}$ = 3.10, $t_{R(ArNH_2)}$ = 1.81, $t_{R(ISTD)}$ = 11.10 min. Under steady-state conditions, the reaction achieved 84% conversion.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00173.

    Reactor design and characterization information and supplementary reaction information (PDF)

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Notes
The authors declare no competing financial interest.

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