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

*Michael R. Chapman,[a,c] Maria H. T. Kwan,[c] Georgina King,[c] Katherine E. Jolley,[c] Mariam Hussain,[a] Shahed Hussain,[d] Ibrahim E. Salama,[a,c] Carlos González Niño,[b] Lisa A. Thompson,[c] Mary E. Bayana,[a,c] Adam D. Clayton,[c] Bao N. Nguyen,[a,c] Nicholas J. Turner,[d] Nikil Kapur,[*b,c] and A. John Blacker[*a,c]*

[a] School of Chemical and Process Engineering, University of Leeds, Clarendon Road, Leeds, LS2 9JT, UK.

[b] School of Mechanical Engineering, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.

[c] Institute of Process Research and Development, School of Chemistry, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.

[d] School of Chemistry, University of Manchester, Manchester Institute of Biotechnology, 131 Princess Street, Manchester, M1 7DN, UK.

[*]Corresponding authors. E-mails: *j.blacker@leeds.ac.uk, n.kapur@leeds.ac.uk*

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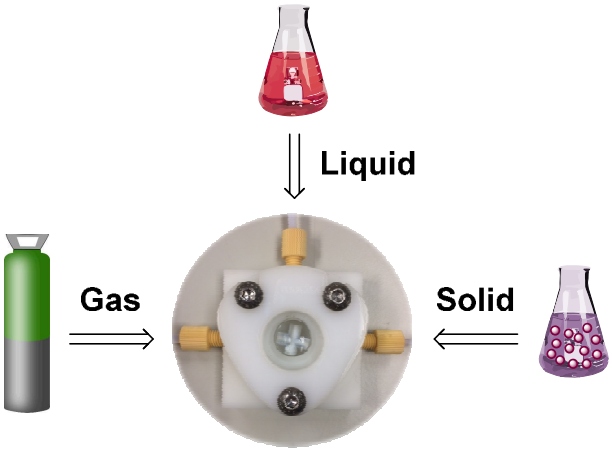


- ✓ Simple, robust cascade CSTR
- ✓ Ideal for multiphasic reactions
- ✓ Residence times up to 3 hours

ABSTRACT: A universal multi-stage cascade CSTR has been developed which 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 hours tested).

KEYWORDS: continuous flow; small continuous stirred tank reactor; multiphase; gas liquid solid; productivity; residence time.

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 *de-facto* 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 require high volumetric flow rates which may not be feasible for slow reactions (*e.g.* > 5 minutes) (Figure 1).[15]

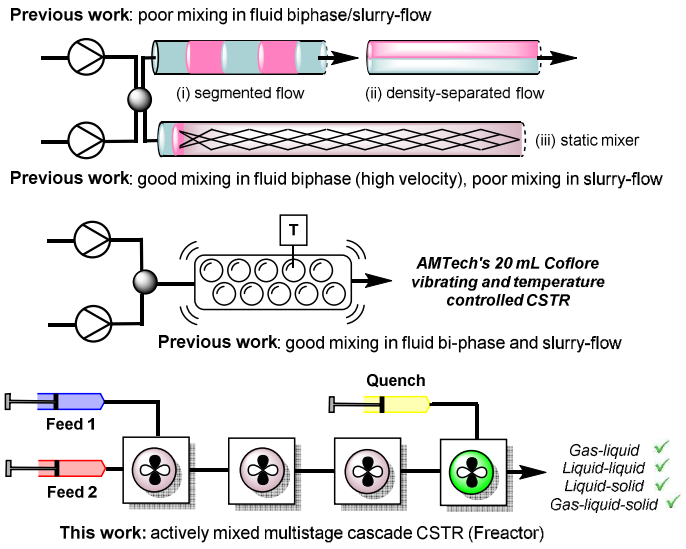


Figure 1. Top: impact of biphasic flow performance on mixing regime in tubular/static mixed reactors. Middle: Coflore™ reactor developed by AMTech. Bottom: well-mixed cascade CSTR reactor reported *here*.

In 2011, Greiner and colleagues made some headway towards 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 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 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 towards

broadening the range of chemical transformation suitable for continuous mode. AMTech have 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 have 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 towards 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 heterogenous 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 minutes to 3 hours).

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 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 is 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 $mLmin^{-1}$) 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). 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 $^{1}/_{8}$" 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 ESI), 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 (dia. 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}).

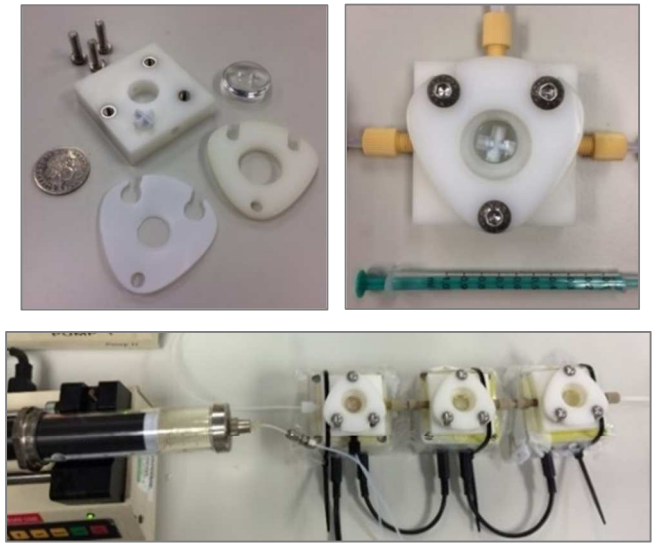


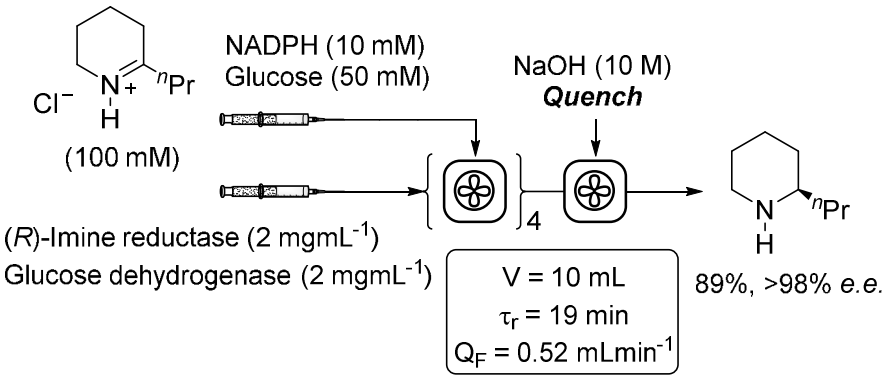
Figure 2. Top left: individual components of the reactor (10 pence for scale). Top right: assembled single reactor unit. Bottom: 3-stage cascade of reactors in series.

Reactor characterization. Heat transfer capability, residence time distribution (RTD) analysis and gas-liquid mass transfer efficiency ($k_L a$) were evaluated and are supplied in the ESI.

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 5-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 0.1M 2-propyl-3,4,5,6-*tetra*hydro piperidinium hydrochloride (Scheme 1).[28] At an overall flow-rate of 0.52 mLmin^{-1} (τ_r = 19 min), the process reached steady-state after 2.5 reactor volumes (RVs) – noting that the RV is based on the total volume of the cascade.

Scheme 1. Continuous-flow biotransformation of propyl iminium with (*R*)-IRED in 5-stage CSTR.



Conversion (%) and *e.e.* (%) determined by chiral GC. V = reactor volume, Q_F = final volumetric flow-rate.

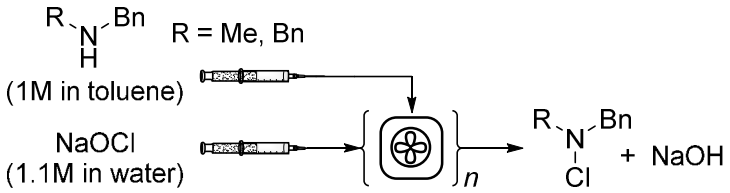
At this point, 89% conversion of substrate was achieved to produce (*R*)-amine with 98% *e.e.*. The space-time-yield of 17 gL^{-1}h^{-1} compares favorably with the batch reaction (6.4 gL^{-1}h^{-1}), the

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 which 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 meso-scale 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, it was decided to compare these reactor types to our CSTR (see subsequent entries of Table 1).

Table 1. Continuous liquid biphase reaction of NaOCl with amine in toluene/water.



Entry	No. 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

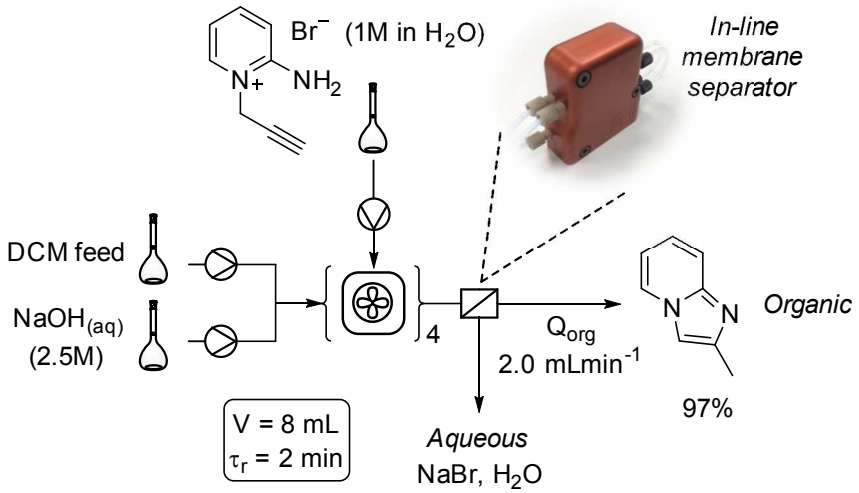
[a]Analyzed by ^{1}H NMR spectroscopy, [b]product *N*-chloro-*N*-methylbenzylamine, [c]ref.[31], [d]product *N*-chlorodibenzylamine.

Using a 2-stage CSTR construct, *N*-methylbenzylamine (1.0M in toluene) and NaOCl (1.1M in water) were fed independently into the reactor at room temperature. Adopting a residence time of 20 minutes, the chlorinated product was formed in quantitative conversion (entry 3). More productively, a 5-stage reactor and residence time of 5 minutes delivered the product in 94% conversion, leading to a productivity of 0.88 $kgL^{-1}h^{-1}$ 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 minutes, respectively – entries 1 and 2). Interestingly, dibenzylamine substrate partitions preferably into the organic phase, making reactions without a 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 minutes' residence time (entry 7). Pleasingly, using our reactor at $^1/_5{}^{th}$ the scale, a comparable conversion was realized in a residence time of 30 minutes (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. Whilst 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 4-stage CSTR, aqueous solutions of *N*-propargyl-2-aminopyridinium bromide (1M) and NaOH (1.25M) 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).

Scheme 2. Continuous-flow electrocyclization, with in-line membrane separation of product.



Yield (%) is isolated. Q_{org} = exit flow-rate of organic stream.

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

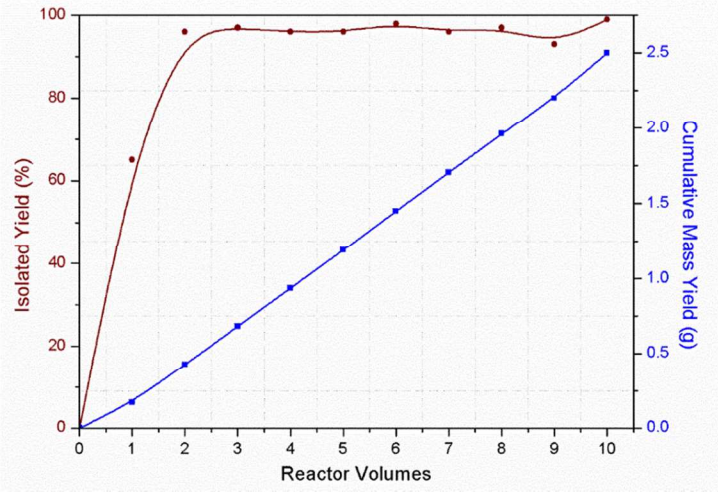
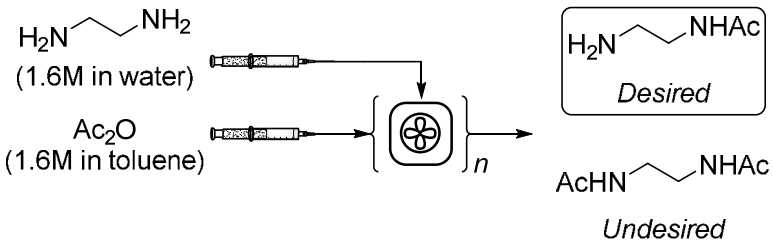


Figure 3. Representative plot of isolated yield (red)/cumulative mass yield (blue) of imidazo[1,2-*a*]pyridine as a function of reactor volume.

***N*-Acetylation of ethylene diamine**. Selective *mono*-functionalization 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 these reactions: (i) suppression of over-functionalization, 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 *mono*-protected 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 di-functionalization 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).

Table 2. Batch *versus* continuous liquid biphase *mono*-acetylation reaction.



Entry	No. CSTRs (n)	τ_{res} (min)	Conversion (%)[a]/ Selectivity (%)[a,b]	Productivity ($gL^{-1}h^{-1}$)
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

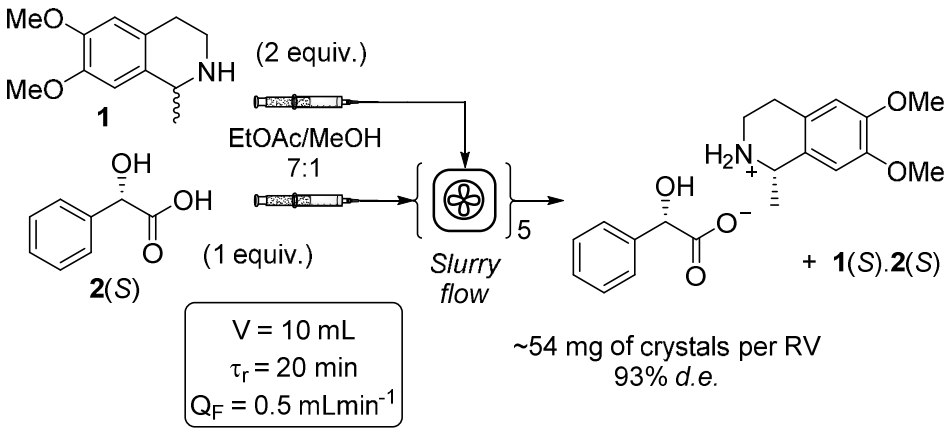
[a]Analyzed by ^{1}H NMR spectroscopy at steady-state, [b]selectivity for *mono*-acetylated amine.

In comparison to batch (entry 1), a 6-stage CSTR allowed a 16% increase in conversion of ethylene diamine, with 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 whilst maintaining a residence time of 20 minutes, though this was shown to compromise conversion (entry 2). Employing a 5-stage CSTR, with a residence time of 30 minutes delivered the desired diamine in 83% conversion with 84% selectivity, leading to a 3.4-fold higher productivity value than obtained in batch mode (entry 5).

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 5-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 minutes, crystals of **1**(*R*).**2**(*S*) from the output stream were collected by filtration and analyzed by ^{1}H NMR spectroscopy to show a *d.e.* of 91% at steady-state.

Scheme 3. Slurry-flow diastereomeric crystallization of salsolidine and (*S*)-mandelic acid in a 5-stage reactor.



Weight of crystals are dry, and *d.e.* (%) is determined by ^{1}H NMR spectroscopy. V = reactor volume, Q_F = final volumetric flow-rate.

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% *d.e.* (see ESI). Ongoing research from our group has shown semi-batch

recirculation of the mother liquor through the reactor to be a useful method of achieving full resolution (*i.e.* 50% yield).

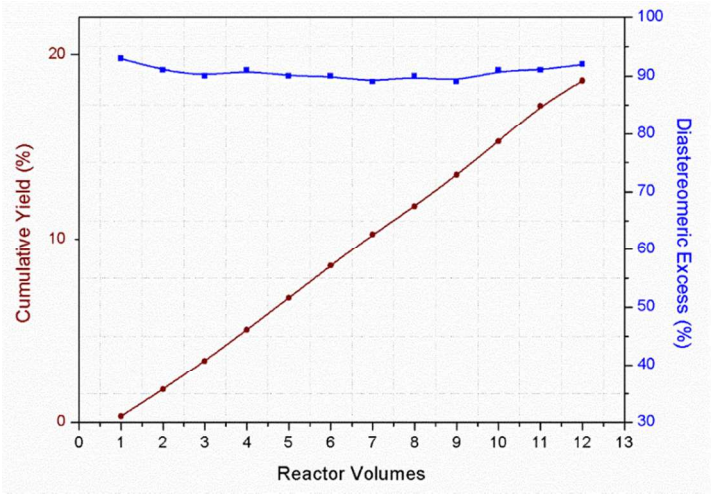
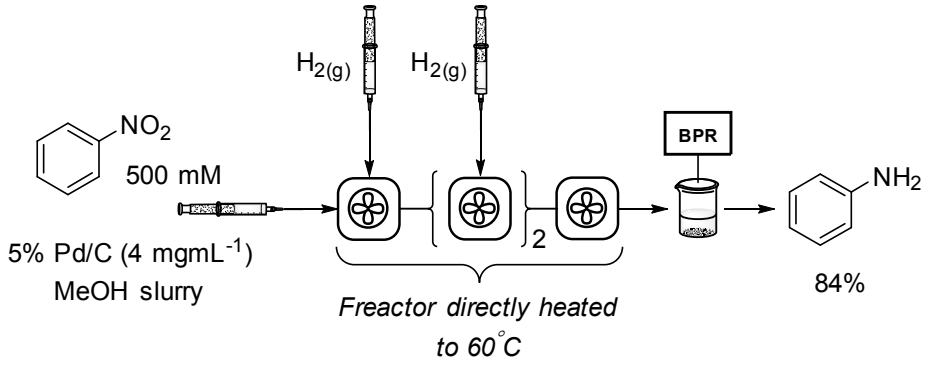


Figure 4. Representative plot of cumulative yield (red)/diastereomeric excess (blue) of **1**(*R*).**2**(*S*) as a function of reactor volume. Cumulative yield is calculated based on 1.8% yield per RV, ceasing at a maximum value of 50%.

Three-phase catalytic hydrogenation. Hydrogenation of organic compounds in the presence of a suitable heterogenous 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 ESI). 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) were fed into chamber 1 of a 4-stage

CSTR, meeting 3 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 4-stage heated reactor.



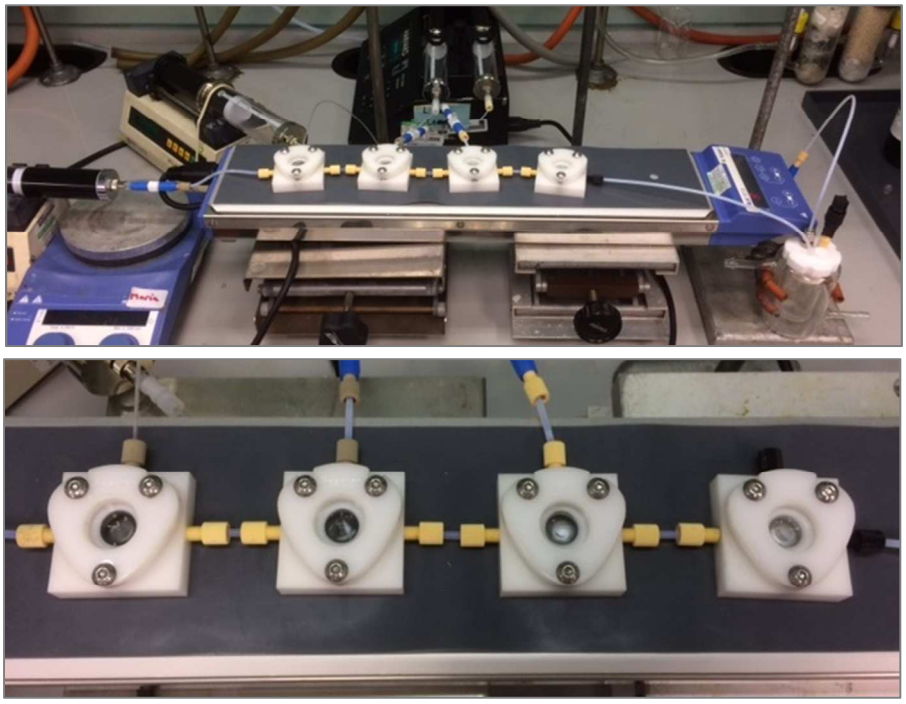


Figure 5. Top: experimental configuration, centered around a multi-position stirrer hotplate at 80°C. Bottom: well-mixed triphasic reaction mixtures in cascade CSTRs.

The full, non-insulated reactor was simply heated using a multi-position stirrer hotplate, generating a reaction mixture temperature of 60°C after 2 minutes heating time (Figure 5). Employing a long residence time of 3 hours 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 hours to reach 92% conversion (see ESI).

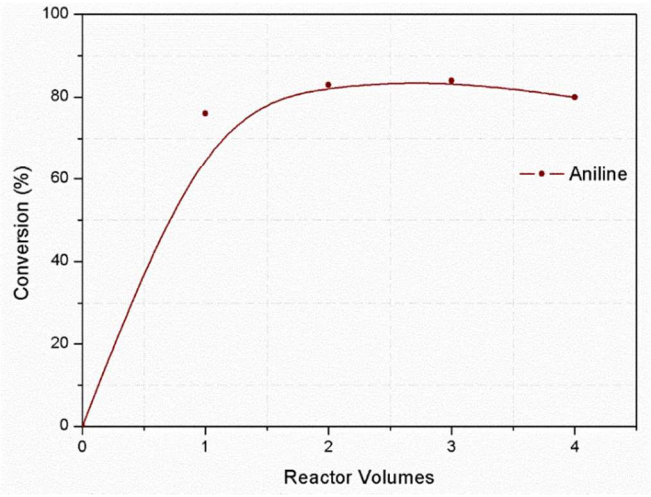


Figure 6. Representative plot of conversion of nitrobenzene to aniline over 4 RVs, as determined by GC analysis.

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 multi-stage 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 amongst 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 cases, productivities were improved by 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_2CO_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 heterocyclisation reaction (τ_r = 120 seconds) alongside a much slower, high temperature triphasic catalytic hydrogenation (τ_r = 3 hours) – 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.

Table 3. Summary of multiphasic reactions evaluated within this study.

Entry	Type of Reaction	Phase	τ_{res}	Productivity ($gL^{-1}h^{-1}$)	
		(G, L, S)	(min)	Batch	Flow
1	IRED	L	19	6.4	17
2	*N*-Chloroamine	L/L	5-50	198[a]	826[b]
3	*Mono*-acetylation	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 minutes. [c]See ref. [32]. [d]92% yield at 16 hours.

EXPERIMENTAL

General remarks. Standard $^1/_8$" or $^1/_{16}$" 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 $^1/_8$" PTFE tubing. All reactions were carried out under an atmosphere of air. Propargyl pyridinium bromide was prepared as previously reported.[32] Deuterated $CDCl_3$ and D_2O 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 Hz.

Imine reductase bioreaction. Batch procedure: a previously reported protocol (Turner *et al*.) was followed to obtain (*R*)-2-propylpiperidine with >98% conversion and >98% *e.e*. after 24 hours.[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 minutes. Flow procedure: a 5-stage CSTR was connected to two 50 mL automated syringes. Syringe 1: (*R*)-IRED enzyme (2 mgmL^{-1}), glucose dehydrogenase 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-*tetra*hydropiperidinium 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 mLmin^{-1} (τ_{res} = 19 minutes), and the reactor eluent was collected in RV fractions containing NaOH (10M, aqueous) to immediately quench the output phase. Under steady-state conditions, the reaction achieved 89% conversion and 98% *e.e.*, 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 (1M in toluene). Syringe 2: NaOCl (1.1M 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. 2-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, CH_2), 2.94 (s, 3H, CH_3).

N-Chloro-N,N-dibenzylamine. 5-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 × NClCH_2 chloramine), 3.81 (s, 4H, 2 × NHCH_2 amine). All data are consistent with those reported in the literature.[31]

Electrocyclization reaction. A 4-stage CSTR was connected to two input feeds. Feed 1: a biphasic (binary) mixture of aqueous NaOH (1.25M) and DCM (blank). Feed 2: aqueous *N*-propargyl pyridinium bromide (1M). Each feed was pumped at 2.0 mLmin^{-1} (τ_{res} = 2 minutes) through the reactor, and a commercially available membrane-based liquid/liquid separator (Zaiput) was utilised 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 analysed 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, CH_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]

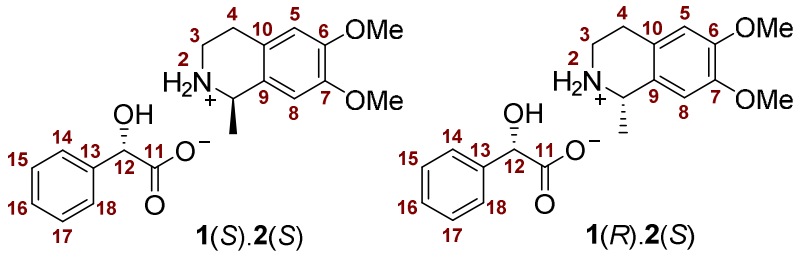
Amine *mono*-acetylation reaction. Batch procedure: ethylene diamine (60 mg, 1 mmol) and D.I. water (0.63 mL) were added to a round-bottomed flask. Acetic anhydride (102 mg, 1 mmol) in toluene (0.63 mL) was added dropwise, and the reaction continued for 20 minutes. The aqueous phase was separated, and water 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 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).

Mono-acetylated amine. ^{1}H NMR (500 MHz, D_2O) δ_H 3.42 (t, J = 5.8 Hz, 2H, AcHNCH_2), 3.07 (t, J = 5.8 Hz, 2H, H_2NCH_2) 1.95 (s, 3H, CH_3). All data are consistent with those reported in the literature.[42]

Di-acetylated amine. ^{1}H NMR (500 MHz, D_2O) 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 5-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 $mLmin^{-1}$ (τ_{res} = 20 minutes) and the reactor output collected in RV fractions. Each fraction was filtered, dried and weighed to assess isolated yield (the sum of which provides cumulative yield). The *d.e.* of each RV was determined by ^{1}H NMR spectroscopy, relative to each pure diastereoisomeric salt (see below).



1(*S*).**2**(*S*) **1**(*R*).**2**(*S*)

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 (O*C*H_3), 56.0 (O*C*H_3), 50.3 (C1), 38.9 (C3), 25.3 (C4), 19.6 (*C*H_3).

Catalytic hydrogenation reaction. Stage 1 of a 4-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 $mLmin^{-1}$. Feed 2: a gas-tight glass syringe containing hydrogen gas (100 mL), fed at 0.2 $mLmin^{-1}$. 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 multi-position stirrer hotplate 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 hours' process time), filtered over Celite, diluted with an internal standard and analyzed by gas chromatography to assess conversion: $t_{R(ArNO2)}$ = 3.10, $t_{R(ArNH2)}$ = 1.81, $t_{R(ISTD)}$ = 11.10 minutes. Under steady-state conditions, the reaction achieved 84% conversion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information document provides reactor design and characterization information and supplementary reaction information. This file (.PDF) is available free of charge.

Author Contributions

The manuscript was written through contributions from A.J.B., N.K., M.B. and M.R.C.. All authors have given approval to the final version of the manuscript.

Notes

† The CSTR 'Freactors' and stirrer motors were made to the design described in the ESI, with plans to become available from both www.iprd.leeds.ac.uk/Freactors and Asynt Ltd..

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