UNIVERSITY OF LEEDS

This is a repository copy of *High-pressure asymmetric hydrogenation in a customized flow reactor and its application in multi-step flow synthesis of chiral drugs*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/173016/

Version: Accepted Version

Article:

Guan, F, Blacker, AJ orcid.org/0000-0003-4898-2712, Hall, B et al. (3 more authors) (2021) High-pressure asymmetric hydrogenation in a customized flow reactor and its application in multi-step flow synthesis of chiral drugs. Journal of Flow Chemistry, 11 (4). pp. 763-772. ISSN 2062-249X

https://doi.org/10.1007/s41981-021-00143-8

©Akadémiai Kiadó 2021. This is an author produced version of an article, published in Journal of Flow Chemistry. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose
university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

COMMUNICATION

A Universal Reactor Platform for Batch and Flow: Application to Homogeneous and Heterogeneous Hydrogenation

Fanfu Guan,[a,c] Nikil Kapur,[b] Louise Sim,[d] Connor J. Taylor,[e] Jialin Wen,[c] Xumu Zhang,[c] and A. John Blacker [a,e]*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

An array of miniature 1.7 mL, 9 bar pressure-rated Continuous Stirred Tank Reactors (CSTRs) have been developed and used to determine optimal hydrogenation conditions in batch, before being reconfigured to carry out the hydrogenation in continuous flow. On-line pressure measurement was used to give direct mass transfer kinetics. The system has been tested using benchmark heterogenous and homogenous reactions in batch and flow. The simplicity of the system enables chemists to overcome problems that are associated with carrying-out pressure hydrogenations.

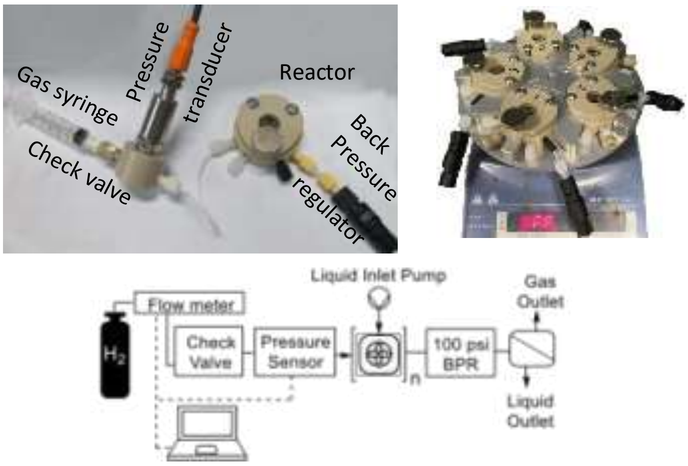


Figure 1. Clockwise. Single batch fReactor with syringe and check valve, for charging hydrogen, back-pressure regulator and pressure transducer; five batch fReactors on hotplate-stirrer; schematic of continuous flow set-up.

Despite the utility of catalytic hydrogenations, the difficulty in using pressurized hydrogen within a laboratory still creates problems in testing reactions.[1] There is need for simple, small-scale pressure hydrogenation equipment that can be easily charged with hydrogen, is well-mixed, and has temperature and pressure control. Furthermore, if the same system could be run in either batch or continuous flow it would increase flexibility and improve operational consistency. For convenience, chemists often use a balloon of hydrogen at near atmospheric pressure attached to a round-bottom flask,[2] though there are limitations of this methodology due to low pressures of hydrogen and poor and variable mixing resulting in slow and varying rates of conversion. Re-sealable glass pressure tubes provide an equipment option,[3] though they lack on-line reaction monitoring, mixing can be poor, and there is no pressure relief, meaning secondary safety measures must be used to control loss of containment. An exothermic catalytic reaction without hydrogen limitation, is controlled by heat loss and hydrogen gas-liquid mass transfer rate.[4,5] The use of hydrogen under pressure requires risk and safety assessment. The outcome of this assessment defines the equipment, the conditions and ultimately the scale of operation. Continuous micro/meso-fluidic reactors have emerged as an important tool to carry out organic synthesis.[6-9] Their small dimensions reduce material requirements and allow precise control of key reaction parameters at steady-state to facilitate process optimization and development.[10] Tubular systems are used widely with homogenous liquid systems, and their unidirectional laminar flow characteristics prevent products over-reacting with starting materials. However, they behave poorly with gas-liquid systems, separating into slugs with small interfaces limiting gas uptake into the liquid.[11] The tube-in-tube reactor overcomes this issue by separating the phases with a gas permeable membrane. This has been used to carry out homogeneous catalytic hydrogenations and, for heterogeneous systems, by pre-saturating the substrate solution with gas before passing over the fixed-bed.[12,13] The H-cube design uses a fixed-bed catalyst to provide static-mixing of the liquid substrate and gaseous hydrogen.[14] In addition to temperature and concentration, the reaction rates in the H-cube depend upon

---

[a] Institute of Process Research and Development, School of Chemistry, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.
[b] School of Mechanical Engineering, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.
[c] Department of Chemistry, Southern University of Science and Technology, 1088, Xueyuan Rd., Shenzhen, Guangdong, China.
[d] School of Food Science and Nutrition, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.
[e] School of Chemical and Process Engineering, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK.

the particle properties and flow characteristics. This is also true of trickle-bed reactors that can be used for pressure hydrogenations.[15] The falling thin film,[16] micromesh,[17] and spinning disc reactors,[18] employ either a homogenous or surface supported catalyst, providing high surface area to volumes and in the latter excellent hydrogen mass transfer at short residence times. The Buss-loop reactor is widely used in industry as an efficient hydrogenator, though there is no lab-scale version.[19] A CSTR provides good gas-liquid mixing for carrying-out hydrogenations. The Coflore ACR is a type of CSTR and achieves multi-phase mixing with loose disc inserts made to shake in a wider chamber.[20] In this way a pressure hydrogenation reaction was optimized with better results than in batch.[21] Miniature cascade CSTRs have also been shown to effectively handle a variety of gas-liquid-solid phase combinations in continuous flow.[22-23] Unlike a plug flow reactor that relies on passive mixing, active mixing is used to maintain a high mass transfer efficiency even at low flow rates allowing for long residence times without increasing the reactor volume. Active mixing also ensures the uniform distribution of liquid and solid catalyst, which can be difficult when a solid catalyst is immobile in a fixed-bed reactor. We have previously reported the use of the fReactor platform in multi-point injection of hydrogen in a flowing slurry of Pd/C, at 3 bar pressure.[24]

To transfer a reaction from a batch STR to CSTR, an estimate of the residence time is needed. This can be done by sampling the batch reaction to determine the shortest time to highest conversion. The kinetics enable a suitable flow rate and reactor volume to be determined. A common shortcoming of this method is where reactors have different geometries and agitation, thus affecting the rates and conversions. From our research, few studies have considered use of the same lab-scale reactor for both use in batch and flow.[25,26] In this paper we describe modifications to the fReactor design to allow their safe and convenient use at higher pressure in batch as well as flow and a simple laboratory method to allow charging to several bar of pressure without use of a hydrogen cylinder.

Modifications have been made to the fReactor design to improve the flexibility of the platform and the design now forms the basis of the system available from Asynt Ltd. The material of construction is now PEEK rather than polycarbonate (Delrin) as it has resistance to a wider range of solvents and useful operating temperature of up to 140°C;[27] a more substantial steel construction unit has also been made for use of higher pressures and will be reported separately. A flat glass window replaces the watch glass, and a standard O-ring (Viton in this case) forms a better seal for operating pressurized reactions. Destructive testing has shown failure occurs in the screw fittings at 50 bar and we choose to operate up to a limit of 9 bar. The apparatus can be used with a pressure regulated gas supply or by manual injection by syringe. Each fReactor has a free volume of 1.7 mL, accounting for the volume of the cross-shaped stir bar and when configured in series for flow, an additional volume of 0.24ml per connecting pipe. fReactors with both larger, 7.5 mL, and smaller, 0.4 mL volumes have been produced, though not tested in hydrogenation. The reactors can be operated separately in batch-mode or connected in series with a short length of 1/8" PTFE tubing to give a cascade CSTR, with a multitude of smaller reactors having the advantage of a narrower residence time distribution as compared to a single larger reactor of the same combined volume. The reactor contents are efficiently mixed by a single standard magnetic stirrer on top of which sits up to five reactors located on a close-fitting aluminium plate, itself sat on a standard laboratory hotplate-stirrer, Figure 1.[28] A linear relationship has been determined between the baseplate temperature and the reactor contents, Eq. 1 (ESI 2.0).

$$\text{Reaction Fluid Temperature } {}^{\circ}\text{C} = (0.8 \times \text{Hotplate Temperature } {}^{\circ}\text{C}) + 4.4\ {}^{\circ}\text{C}$$

Equation 1

Standard HPLC fitments to multiple ports (1/4"-28) allow cascading of reactions, sampling or integration of in-line sensors. For the batch reactions, each fReactor was equipped with a one way check valve and a back pressure regulator (BPR). The check valve allows temporary connection of a syringe filled with a starting volume of gas. Once fully depressed, this causes a calculable and reproducible pressure rise in the reactor (details of which are given in ESI 3.1 together with access to an online calculator[29]) and is a convenient way to give high pressures when access to a gas cylinder is not available. Alternatively, hydrogen can be delivered from a regulated gas cylinder. The BPR acts as a safety relief valve, with initial pressures in the reactor selected such that after charging and heating, the maximum pressure is still lower than that required to cause the BPR to discharge pressure (ESI 3.2). The outlet of the BPR is positioned to discharge safely and experiments were carried out in a fume cupboard with a blast shield on the fReactor units. Gas leaks can be detected through either monitoring pressure prior to operation (ESI 7.0), with a fall of 0.01 bar/minute from an initial pressure of 9 bar was deemed satisfactory for reactions taking several hours. Alternatively, joints can be checked with a soap solution.

For measuring the change in pressure, to establish the kinetics, a PU5404 fast-response pressure transducer (48 measurements/s) was screwed into a custom designed probe adapter with the same port threads as the fReactor, and connected to one of the fReactor ports using a pair of flangeless fittings and a short piece of 1/8" tubing, Figure 1. Pressure was recorded on-line in real time *via* an Arduino board (ESI 8.0), although equivalent pressure transducer with a USB outputs are available. The addition of the transducer fitting gave an additional 1ml of volume of gas headspace that was not heated.

For the reported experiments, liquid volumes of 1 ml and 0.5 ml were investigated. 41.6 μmoles ml^{-1} bar^{-1} (at 20°C) of hydrogen is available for the reaction, allowing an appropriate substrate concentration to be determined. As the reaction moves to completion, the pressure falls and the rate drops. Using a stoichiometric excess further enhanced by initially pressurising the reactor, ensures the rate remains high. Alternatively, a properly connected regulated cylinder allows a fixed pressure to be maintained throughout.

For the flow experiments, it is possible to maintain pressure using a pump and BPR, Figure 1. A gas-liquid separator at the exit of the last reactor, prior to the BPR ensures reliable operation of the BPR. A Zaiput continuous separation unit was found effective,[30] however, a simpler solution was to place an additional fReactor on its side to allow the liquid to flow down into a receiver, and the gas upwards out via the BPR (ESI 2.0).

The Pd/C catalysed hydrogenation of nitrobenzene was chosen as a suitable tri-phasic test reaction. Using a single reactor in batch, a degassed solution of nitrobenzene (100 μmol) and Pd/C (10% w/w, 5.6 mg, 2.5 μmol, 50% water content, S/C=40) in methanol (0.5 mL, 0.2 M) at 293 K was slurried and charged by syringe. Hydrogen was charged to 8.5 bar using a 14 bar BPR. Prior to mixing, only a small fall in pressure was observed due to the solubilisation of gas, but as soon as agitation with a frequency of 1500 rpm was started the pressure fell linearly over 45 seconds, then returned to being near isobaric at 5.5 bar, Figure 2.

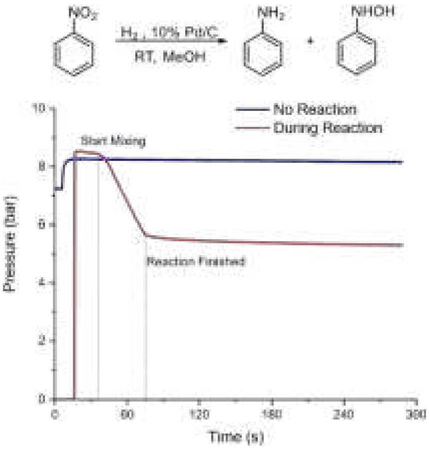


Figure 2. Scheme of nitrobenzene hydrogenation and graph showing the pressure change with time, as a result of stirring.

When the reactor was depressurised and opened, the contents were analysed by ^{1}HNMR, and >99% conversion to aniline was observed, with only a tiny amount of the hydroxylamine. With a pressure drop of 3 bar, and a gas volume in the fRreactor and pressure transducer mount of 2.5 mL, 312 μmoles of gas is consumed which corresponds closely to the theoretical hydrogen requirement of 300 μmoles.

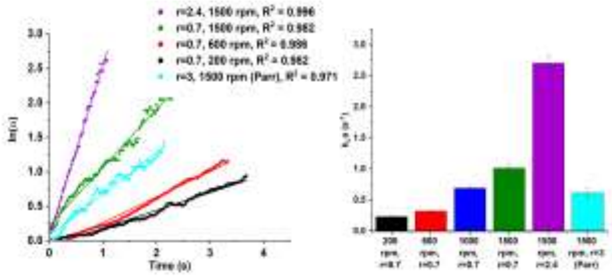


Figure 3. Left, Characterization of gas-liquid mass transfer via batch hydrogen absorption. Right, a bar chart showing the mass transfer coefficient under different conditions.

Hydrogen mass transfer rates have been measured in larger reactors,[31-33] however, the small-scale of the fReactors makes them useful for kinetic measurement. Using this rapid reaction and fast response pressure transducer, the overall mass transfer coefficient (k_La) could be measured directly by continuously monitoring the pressure drop, Figure 3. This shows the effects of r, and magnetic stir-bar speed, on the k_La in a fReactor (ESI 3.3). The ratio of gas-liquid volume in a reactor is r. With 1 mL of liquid (r=0.7), and a stirrer speed of 200 rpm, the k_La is 0.25 s^{-1}. Increasing the mixing to 1500 rpm the k_La increases to 1s^{-1}. Significantly, as the fReactors sit off-centre from the magnetic stirrer, at high speeds the stir-bars start to bounce around the chamber, which increases the gas-liquid interface and k_La. Changing the gas-liquid ratio from 0.7 to 2.4, gives almost 3 times the rate, because of an increase in gas-liquid surface area. Under the same stirring rate, the fReactor shows a five-fold higher mass transfer rate than the much larger overhead-stirred 600 mL Parr reactor for which individual component mass transfer rates have been previously measured.[33] The power per unit volume in the fReactor is estimated at 200 mW/mL, and compares with a well-mixed hollow-shaft hydrogenator.[32]

A full factorial Design of Experiment (DoE) method was used to optimise the batch hydrogenation of nitrobenzene, so that the starting parameters for continuous flow could be determined. The reactions were conducted under 293 K and 1500 rpm. The variables evaluated were pressure (1 - 4.5 bar), reaction time (2 - 30 minutes) and S/C (200 - 2000) (ESI 4.2). Unsurprisingly, the results show that higher pressures and more catalyst (C) to substrate (S) increase the conversion, however, with little effect on reaction times > 10mins. Below this, the reaction is sensitive to both pressure and S/C, reflecting dependence upon hydrogen mass transfer and catalyst turnover. The DoE data gave an R^2 value of 0.994 which shows the statistical model is described well; the Q^2 value of 0.972, means the model's ability to interpolate and predict the responses from given inputs is accurate. It is predicted that when the S/C is 400 used with 6.3 bar hydrogen pressure, the reaction time to achieve 95% conversion is 9.2 min. These conditions were selected for transferring the reaction to continuous flow mode for lab scale-up. Reconfiguring the reactors, up to four fReactors were used in series with in-reactor filters between each to compartmentalise the solid catalyst, whilst allowing the liquid to flow through. At steady state, each reactor contained solid catalysts and ~0.5 mL of reaction medium (determined by the height of the outflow relative to the base), which was around half the volume in the batch experiments. Hence, half of the catalyst loading (2.8 mg) was used to maintain the same liquid-solid ratio in the reactor. In initial experiments, progressively higher pressures occurred due to the in-line filters becoming partially blocked (ESI 3.4. Therefore, the quantity of catalyst in each reactor was decreased from 2.8 mg to 1.4 mg and 0.5 M nitrobenzene in methanol solution was pumped through to give an S/C ratio of 400.

The experiments in entries 1 and 2 employ two fReactors, with a stirring rate of 1500 rpm, a liquid flow rate of 0.2 mL/min and H$_2$ flow rate of 5 mL/min at 273K and atmospheric pressure (0.78 mL/min at 6.9 bar and 293K), the T_{res} was 4.1 minutes. The yield of aniline, at S/C 80, was 88%, entry 1, and exceeded that predicted, which may be caused by the small pressure increase from 6.3 bar(batch) to 8 bar (flow). However, after 15 reactor volumes (RV) a pressure rise was seen due to in-line filter blockage (ESI 4.3). At S/C 400, entry 2 the average isolated yield of aniline was 70%, so the residence time was increased using four fReactors in series to 8.3 and 9.3 minutes, Entries 3 and 4. At steady state, ~20 minutes, the yield was 88%, Entry 3, and with twice the catalyst was 95%, entry 4. Using continuous flow conditions, the catalyst turnover number (TON) was 2392 and the production rate was up to 4 mmol/h in entry 3. The results show a satisfactory prediction of the flow conditions based upon the optimal parameters established in batch. Using the batch-to-flow protocol reduced the amount of catalyst and starting materials than would have be the case if trying to optimise the reaction entirely in flow. It was seen that with operation over 33 RV, Figure 4 (ESI 4.3), that the conversion declined after 27 RV, partly due to solid catalyst accumulation on the in-line filters, inlets and outlets, and perhaps catalyst poisoning.

Table 1. Pd/C hydrogenation of nitrobenzene in continuous flow.

#	S/C[1]	Liq. flow[2] rate(mL/min)	Nº of reactors	T_{res}[3] (min)	Conv.[4] (%)	Predicted Conv.[5] (%)
1	80	0.2	2	4.1 [6]	88	82
2	400	0.2	2	4.1 [6]	70	58
3	400	0.2	4	8.3 [7]	88	92
4	200	0.1	4	9.3 [7]	95	>99

[1] Mole ratio PhNO$_2$:Pd in each reactor, eg. for S/C 400 1.4 mg catalyst (0.66 µmol) in each reactor; pro-rata for other loadings. S/C was altered by changing concentration. [2] PhNO$_2$+MeOH@RT and H$_2$ flow rate 5 mL/min STP. [3] T_{res} based on total volume of reactors and tubes (liquid+gas flow rate at 6.9 bar @20°C) and flow rate as combined gas and liquid flow. [4] Average isolated yield of aniline from each RV at steady-state.[5] From DoE model using batch data of 6.3 bar (ESI 4.2). [6] volume (1.70 + 0.12) x 2 = 3.64 mL. [7] volume = (1.70 + 0.12) x 4 = 7.28 mL.

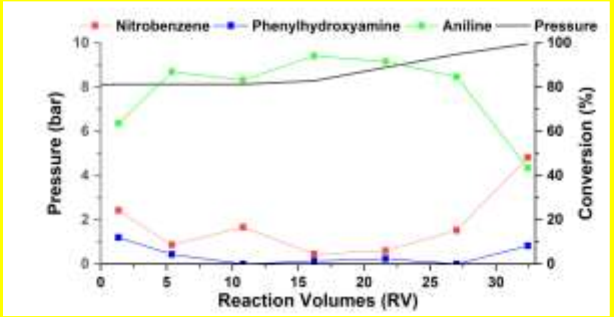
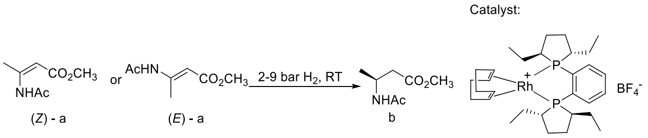


Figure 4. Graph showing continuous flow hydrogenation of nitrobenzene to aniline and phenylhydroxylamine side-product.

A second example using Pd/C in a hydrogenolysis reaction was tested in the fReactors in batch only, due to the scarcity of the starting material, and exemplifies the convenience of this system for testing small-scale pressure reactions. (*S*)-3-benzyl-1-palmitoyl-glycerol (200-450 mg) was dissolved in 0.5 mL dichloromethane (DCM) and charged by syringe to a degassed slurry of 10% Pd/C (5-20 mg) in the same solvent. In three separate experiments the fReactor was pressurised to 9 bar at ambient temperature and mixed at 1500 rpm for 1-1.5 hours. ^{1}HNMR analysis showed in each case >90% loss of the benzyl group (ESI 5).

Having demonstrated the utility of the fReactor in heterogenous hydrogenation, we turned to evaluate an air-sensitive homogenous asymmetric hydrogenation using Rh/(*R*,*R*-Ethyl-DuPHOS) with (*E*)- and (*Z*)-methyl-3-acetamido-2-butenoate to synthesize chiral methyl N-acetamido-β-alanine, Table 2. The catalyst (1 mol%) was prepared in anoxic conditions by in-situ mixing the DuPhos ligand with bis-(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate. The catalyst was transferred by syringe, from the Schlenk into the batch-mode fReactor, containing (*Z*)-enamide in degassed methanol, then pressurised with hydrogen to 9 bar, after 30 minutes the product was produced from the (*Z*)-enamide in 99% conversion and 63% ee, Table 2, entry 1. The product ee was improved to 85% by decreasing the pressure to 6.3 bar, entry 3. Hydrogenation of the (*E*)-enamide was initially conducted at 3.5 bar, however only 24% of the starting material was consumed in 1 hour, entry 5. Increasing the pressure to 6.3, then 9 bar, increased the conversion to 80 and 92% respectively in 30 minutes, entries 6 and 7. From the reaction profiles it was found that the catalyst induction was extended at low pressures e.g. 2 hours at 2 bars, which is likely to be hydrogenation of the precursor diene.[36] Unlike the (*Z*) isomer, the optical activity of the product from the (*E*)-enamide was insensitive to the hydrogen concentration, this probably reflects the known difference in reaction order in the rate limiting step.[36] As before, the fReactor was reconfigured for continuous flow, with initial conditions of those in entry 7: a residence time of 30 minutes, based on a liquid flow rate was 0.05 mL/min, a train of 10 fReactors and 1.2 mL tubes (18.2 mL volume) ~~of which 67% is liquid and 33% gas.~~ This resulted in a steady-state conversion of 93%, where the production rate was 0.56 mmol/h for hydrogenation of (*E*)-a, Figure 5.

Table 2. Reaction conditions and results of asymmetric hydrogenation testing the fReactor in batch and flow.



#[Ref]	Mode	Substrate	Pressure (bar)	Time (h)	Conv.[1] (%)	ee[1] (%)
1	Batch	(*Z*)-a	9	0.5	>99	63
2[34]	Batch	(*Z*)-a	9[2]	0.67[2]	>99	47
3	Batch	(*Z*)-a	6.3	0.5	73	85
4	Batch	(*Z*)-a (Parr Reactor)	9	0.5	85	60
5	Batch	(*E*)-a	3.5	1	24	96
6	Batch	(*E*)-a	6.3	0.5	80	96
7	Batch	(*E*)-a	9	0.5	92	96
8[35]	Batch	(*E*)-a	2.7	0.45	>99	94
9	Flow	(*Z*)-a[3]	6.9 [4]	0.5 [5]	80 [6]	80 [6]
10	Flow	(*E*)-a[3]	6.9[4]	0.5[5]	93[6]	98[6]

1. Yield and ee were determined by Gas Chromatography. The reactions were conducted under 293 K and a stirring rate of 1500 rpm. [2] published data 30 bar 0.2h, data normalised to compare with entry 1. [3] S/C=50; [4] With gas flow rate 4 mL/min (sccm). [5] T_{res} based on 0.05 mL/min, 10 fReactors and 2.4 mL tube (18.2 mL) ~~and 67% gas volume~~ with flow rate as combined gas and liquid flow, ESI3.2; [6] Measured at steady-state as an average over 4 RV.

This productivity can be compared with other continuous flow reactor designs for similar catalytic asymmetric hydrogenation reactions, albeit under different conditions that are partly defined by the reactor, Table 3. The micromesh reactor, requiring inserts impregnated with the catalyst, was 25-times less productive Entry 2,[17] and this may reflect its lower hydrogen gas to liquid transfer rate. The H-cube used 140 mg of a solid-supported catalyst in fixed bed to give a high conversion to the racemic product with comparable productivity of 0.3 mmol/h, entry 3.[37] Lastly, a tube-in-tube system using an iridium catalyst is reported with a high productivity, 3 mmol/h at 20 bar hydrogen, that indicates high hydrogen mass transfer rates, entry 4.[12] This is achieved by two tube-in-tube reactors in parallel, two 10 mL tubular reactors and a mixer chip.

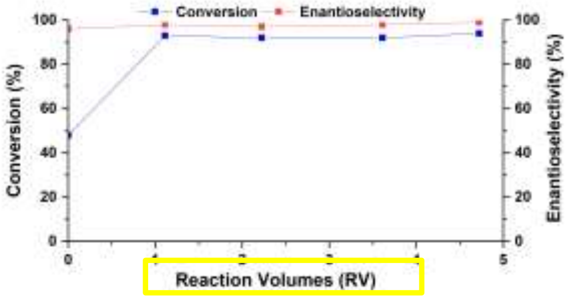


Figure 5. Graph showing conversion and enantiomeric excess with continuous flow hydrogenation of *(E)*-methyl-3-acetamido-2-butenoate.

In conclusion, the fReactor shows great potential for assessing small scale heterogeneous and air-sensitive homogeneous hydrogenations in both batch and continuous flow. The batch experimental design data provided the basis for choosing a residence time for continuous flow operation; the benefit of using the same reactors and mixing regime is that the mass transfer coefficients are identical. The limitations of most pressure hydrogenators are their size and complexity required to ensure good mixing and safety. Many chemists avoid this by using hydrogen-filled balloons that are restricted to pressures only marginally above atmospheric. The fReactor provides a simple, small-scale, low cost solution to batch and rapid translation to continuous flow and lab scale-up. The ability to charge hydrogen manually by syringe via a non-return valve up to ~10 bar pressure makes hydrogenations practical, and parallel reactors enable different conditions to be tested. Active mixing gives high gas-liquid mass transfer rates that can be monitored directly using an on-line pressure sensor. In a benchmark Pd/C catalysed hydrogenation of nitrobenzene, fast reactions and high conversions were achieved using high stirrer speeds and gas to liquid ratios. The fReactor exceeded the mass transfer rates of a 600 mL mechanically-stirred Parr hydrogenator. A further benchmark reaction of a homogenous asymmetric hydrogenation showed the use of an air-sensitive catalyst in both batch and flow. Using the fReactor, the hydrogenation of the (*E*)-isomer gave similar conversions and optical activities to those reported in literature. Furthermore, the known dependency of the ee on hydrogen pressure was reconfirmed, whilst the (*E*)-isomer was shown insensitive to this. Adopting a standard and easy-to-use hydrogenation platform constructed with good engineering design supports robust batch and flow experimentation and reporting of results.

Table 3 Comparison of different continuous hydrogenators used for asymmetric hydrogenation of (*Z*)-a.

#[Ref]	Reactor	Catalyst	T_{res} (min)	Pressure (bar)	Conv. (%)	Productivity (mmol/h)
1	fReactor	Rh (MeDuPhos)[1]	27	6.9	93	0.56
2[17]	Micro-mesh Reactor	Rh (MeDuPhos)[2]	10	2	31	0.02
3[37]	H-cube Reactor	$[Rh(COD)_4]$/ PTA/ Al_2O_3 [3]	1/60	1	>99	0.30
4[12]	Tube-in-tube	Iridium catalyst[4]	40	20	>99	3.00

[1] 2 mol%; [2] 1 mol%; [3] S/C=1/360~~, 0.28 mol%~~; [4] 2.5 mol% with tri-substituted olefin

Conflicts of interest

In accordance with our policy on Conflicts of interest please ensure that a conflicts of interest statement is included in your manuscript here. Please note that this statement is required for all submitted manuscripts. If no conflicts exist, please state that "There are no conflicts to declare".

Acknowledgements

We would like to thank the kind support of: SUSTech and University of Leeds for FG; Nestle UK Ltd and BBSRC (Award BB/N504294/1) for LS; AstraZeneca Ltd and EPSRC for CJT (Award EP/R513258/1).

References

1. T. Chandra and J. P. Zebrowski, Hazards associated with laboratory scale hydrogenations, *J. Chemical Health and Safety*, 2016, **23**, 16-25.
2. For example: J. R. Gillard, P. L. Beaulieu, *Org. Synth.* 2012, **89**, 131.
3. P. Z. Anthony, A simplified apparatus for pressure reactions, *J. Chem. Ed*., 1959, **36**, 489.
4. C. De Bellefon (2002) Mass Transfer Limitations: A Bottleneck for High Throughput Screening in Multiphase Catalysis. In: Derouane E.G., Parmon V., Lemos F., Ribeiro F.R. (eds) Principles and Methods for Accelerated Catalyst Design and Testing. NATO Science Series (Series II: Mathematics, Physics and Chemistry), vol 69. Springer, Dordrecht.
5. U. K. Singh and M. A. Vannice, Kinetics of liquid-phase hydrogenation reactions over supported metal catalysts — a review, *Appl. Catalysis A: General* 2001, **213**, 1–24.
6. K. Geyer, J. D. C. Codée and P. H. Seeberger, Microreactors as Tools for Synthetic Chemists. The Chemists' Round-Bottomed Flask of the 21st Century? *Chem. Eur. J.*, 2006, **12**, 8434–8442.
7. M. B. Plutschack, B. Pieber, K.Gilmore, and P. H. Seeberger. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.*, 2017, **117**, 11796–11893.
8. F. M. Akwi and P. Watts, Continuous flow chemistry: where are we now? Recent applications, challenges and limitations. *Chem. Com.*, 2018, **54**, 13894-13928.

9. P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey and C. P. Gordon. The expanding utility of continuous flow hydrogenation. *Org. Biomol. Chem*., 2015, **13**, 7119-7130.

10. C. Mateos, M. J. Nieves-Remacha and J. A. Rincón, Automated platforms for reaction self-optimization in flow, *React. Chem. Eng*., 2019, **4**, 1536-1544

11. J. F. Davies and K. R. Wilson, (2018), Physical Chemistry of Gas-Liquid Interfaces: Chapter 13 - Heterogeneous Reactions in Aerosol, pp 403-433, Elsevier Inc.

12. S. Newton, S. V. Ley, E. C. Arc and D. M. Grainger. Asymmetric Homogeneous Hydrogenation in Flow using a Tube-in-Tube Reactor. *Adv. Synth. Catal.*, 2012, **354**, 1805-1812.

13. M. O'Brien, N. T., A. Polyzos, I. R. Baxendale and S. V. Ley. Hydrogenation in flow: Homogeneous and heterogeneous catalysis using Teflon AF-2400 to effect gas–liquid contact at elevated pressure. *Chem. Sci.*, 2011, **2**, 1250-1257.

14. R. V. Jones, L. Godorhazy, N. Varga, D. Szalay, L. Urge and F. Darvas, Continuous-Flow High Pressure Hydrogenation Reactor for Optimization and High-Throughput Synthesis. *J. Comb. Chem.*, 2005, **8**, 110-116.

15. S. G. Newman and K. F. Jensen. The role of flow in green chemistry and engineering. *Green Chemistry*, 2013, **15**, 1456-1472

16. C. d. Bellefon, T. Lamouille, N. Pestre, F. Bornette, H. Pennemann, F. Neumann and V. Hessel. Asymmetric catalytic hydrogenations at micro-litre scale in a helicoidal single channel falling film micro-reactor. *Catalysis Today*, 2005, **110**, 179-187.

17. R. Abdallah, V. Meille, J. Shaw, D. Wenn and C. de Bellefon, Gas–liquid and gas–liquid–solid catalysis in a mesh microreactor. *Chem. Commun*., 2004, **4**, 372-373

18. M. Meeuwse, J. van der Schaaf, B. F. M. Kuster and J. C. Schouten, Mass Transfer in a Rotor−Stator Spinning Disk Reactor with Cofeeding of Gas and Liquid, *Chem. Eng. Sci.* 2010, **65**, 466-471.

19.http://www.buss-ct.com/up/files/PDFs_RT/Brochure_RT_Advanced_Loop_Reactor_operating_principle.pdf [last accessed 24/12/19].

20. D. L. Browne, B. J. Deadman, R. Ashe, I. R. Baxendale and S. V. Ley, Continuous Flow Processing of Slurries: Evaluation of an Agitated Cell Reactor, *Org. Process Res. Dev.*, 2011, **15**, 693–697.

21.http://cyberfrogdesign.uk/test/amtech/hydrogenation-batch-to-continuous/ [last accessed 25/11/19]

22. Y. Mo and K. F. Jensen, A miniature CSTR cascade for continuous flow of reactions containing solids, *React. Chem. Eng.*, 2016, **1**, 501–507.

23. Y. Mo, H. Lin and K. F. Jensen, High-performance miniature CSTR for biphasic C–C bond-forming reactions. *Chem. Eng. J.*, 2018, **335**, 936-94426.

24. M. R. Chapman, M. H. T. Kwan, G. King, K. E. Jolley, M. Hussain, S. Hussain, C. G. Niño, L. A. Thompson, M. E. Bayana, A. D. Clayton, B. N. Nguyen, N. J. Turner, N. Kapur and A. J. Blacker, Simple and Versatile Laboratory Scale CSTR for Multiphasic Continuous-Flow Chemistry and Long Residence Times, *Org. Process Res. Dev.*, 2017, **21**, 1294-1301.

25. D. Thoenes, (1998) Chemical Reactor Development: from Laboratory Synthesis to Industrial Production, Springer-Science+Business Media, BV, Dordrecht.

26. www.cambridgereactordesign.com/reactor-technology.html [last accessed 12/02/20].

27. Material Properties Data: Polyetheretherketone (PEEK) www.makeitfrom.com [last accessed 12/02/20].

28. Commercially available from www.asynt.com/product/freactor-complete-kit/ [last accessed 12/02/20]

29. www.freactor.com [last accessed 12/02/20]

30. www.zaiput.com [last accessed 12/02/20]

31. E. Dietrich, C. Mathieu, H. Delmas and J. Jenck, Raney-Nickel Catalyzed Hydrogenations: Gas-Liquid Mass Transfer In Gas-Induced Stirred Slurry Reactors, *Chem. Eng. Sci.* **47**, (13/14), 3597-3604

32. M. D. Johnson, S. A. May, B. Haeberle, G. R. Lambertus, S. R. Pulley and J. R. Stout, Design and Comparison of Tubular and Pipes-in-Series Continuous Reactors for Direct Asymmetric Reductive Amination, *Org. Proc. Res. Dev* 2016, **20**, 1305–1320

33. I. K. Stamatiou and F. L. Muller, Determination of Mass Transfer Resistances of Fast Reactions in Three-Phase Mechanically Agitated Slurry Reactors. *AIChE Journal*, 2017, **63**(1), 273-282

34. D. Heller, J. Holz, H. J. Drexler, J. Lang, K. Drauz, H. P. Krimmer and A. Börner, Pressure Dependent Highly Enantioselective Hydrogenation of Unsaturated β-Amino Acid Precursors. *J. Org. Chem.,* 2001, **66**, 6816-6817.

35. G. Zhu, Z. Chen and X. Zhang, Highly efficient asymmetric synthesis of β-amino acid derivatives via rhodium-catalyzed hydrogenation of β-(Acylamino) acrylates. *J. Org. Chem*., 1999, **64**, 6907-6910.

36. D. Heller, J. Holz, S. Borns, A. Spannenberg, R. Kempe, U. Schmidt, A. Börner, Influence of a remote hydroxy group in the ligand on the reactivity of a chiral hydrogenation catalyst, *Tetrahedron: Asymmetry* 1997, **8**, 213-222

37. S. Balogh, G. Farkas, J. Madarász, Á. Szöllősy, J. Kovács, F. Darvas and J. Bakos, L. Asymmetric hydrogenation of C=C double bonds using Rh-complex under homogeneous, heterogeneous and continuous mode conditions. *Green Chemistry*, 2012, **14**, 1146-1151.