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

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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.

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] The low solubility of hydrogen in polar solvents and poor mixing limits the reaction rates. The use of hydrogen under pressure requires risk and safety assessment.[3-5] The outcome of this 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] A wide variety of hydrogenator designs have been reported, that include tube-in-tube,[10-13] fixed-bed gas-liquid static mixing,[14] trickle bed,[15] falling thin film,[16] micromesh,[17] and
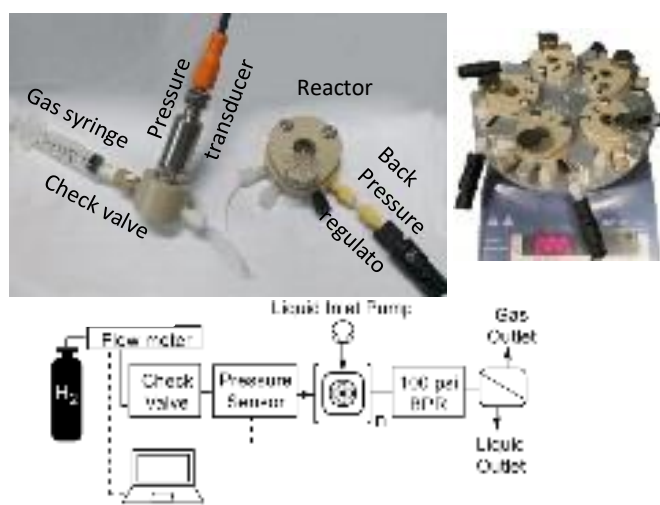

Figure 1 Clockwise. Single batch fReactor with syringe and check valve, for charging hydrogen, back-pressure regulator and pressure transducer; five batch fReactors on hotplate-stirrer; components of single batch fReactor; schematic of set-up in continuous mode.

spinning disc reactors.[18] The Buss-loop hydrogenator is an efficient recirculating batch system widely used in industry, though there is no lab-scale version.[19] The Coflore ACR is a type of lab scale continuous stirred tank reactor (CSTR) and achieves multi-phase mixing with loose disc inserts made to shake in a wider chamber.[20-21] 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

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agitation, thus affecting the rates and conversions. 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, details in ESI 2.[26-28] Destructive testing has shown failure occurs at 50 bar and an operational limit of 9 bar is recommended. The apparatus can be used with a pressure regulated gas supply or more simply by manual pressurisation with a syringe and check-valve (ESI 3.3).[28] To assist with on-line monitoring a PU5404 fast-response pressure transducer (48 measurements/s) was fitted to a bespoke adapter and connected to one of the fReactor ports, Figure 1. Pressure was recorded in real time *via* an Arduino board (ESI 8.0). The addition of the transducer fitting gave an additional 1 ml of volume of gas headspace that was not heated. In each 1.7 ml fReactor, liquid volumes of 1.0 and 0.5 ml were investigated with hydrogen gas providing the balance volume. The hydrogen can be introduced by syringe and 41.6 μmoles.ml^{-1}.bar^{-1} (at 20°C) is available for the reaction, ESI 3.1. With a check-valve, repeat pressurisation with a syringe allows higher pressures (~10bar) to easily be reached. As the reaction proceeds, the pressure falls and the rate can drop. Using pressure to provide a stoichiometric excess 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,[29] 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, substrate to catalyst (S/C)=40 mole/mole) in methanol (0.5 mL, 0.2 M) at 293 K was slurried and charged by syringe. Hydrogen was charged to 8.5 bar with pressure release provided via 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. 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. Hydrogen mass transfer rates have been measured in larger reactors,[30-32] however, the small-scale
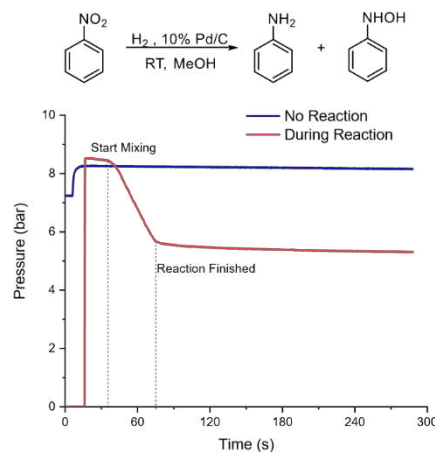

Figure 2. Scheme of nitrobenzene hydrogenation and graph showing the pressure change with time, as a result of stirring.
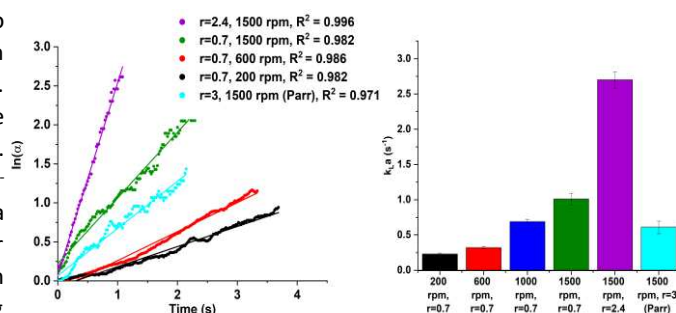

Figure 3. Left, Characterization of gas-liquid mass transfer $\ln(\alpha)$ (for calculation from pressure drop see ESI 3.3) *via* hydrogen uptake in batch. Right, a bar chart showing the mass transfer coefficient (k_La, for calculation see ESI 3.3) under different conditions; r = volume of gas/volume of liquid.

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 the volumetric gas-liquid ratio (r), and magnetic stir-bar speed, on the k_La in a fReactor (ESI 3.3). 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 1 s^{-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.[32] The power per unit volume in the fReactor is estimated at 200 mW/mL, and compares with a well-mixed hollow-shaft hydrogenator.[31] The catalytic hydrogenation of nitrobenzene goes through several intermediates, and previous studies have shown reduction of the hydroxylamine can be rate limiting.[33] We observed small concentrations of this species,

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

Entry	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 @20ºC) 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 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.

that indicates hydrogen transfer is limiting over the reaction timescale, despite efficient mixing. Pressurising the gas can increase the concentration of soluble hydrogen and increase the hydrogenation rate. Whilst the stirring rate is linked to gas-liquid uptake, it can also affect hydrogen and substrate-product adsorption on the solid catalyst and this has been recently evaluated in a similar system.[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. All of the reactions were conducted at 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

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

Catalyst:

Entry#	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]

# indicates the reference number that data is taken from. [1] Yield and ee were determined by Gas Chromatography; reactions were conducted at 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), with flow rate as combined gas and liquid flow, ESI 3.2; [6] Measured at steady-state as an average over 4 RV.
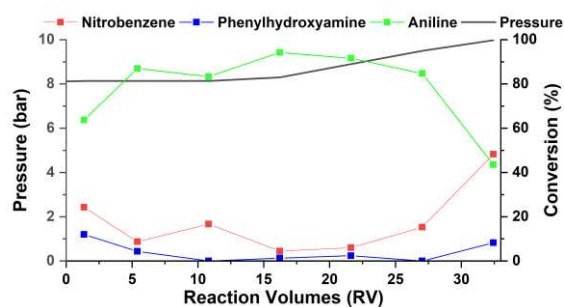
Figure 4. Graph showing continuous flow hydrogenation of nitrobenzene to aniline and phenylhydroxylamine side-product.

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.

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 mixing in-situ 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. This compares well with a similar example in the literature, entry 2.[34] The product was improved to 85% ee by decreasing the pressure to 6.3 bar, but with lower conversion, entry 3. The results using the small scale fReactor compared well to using the larger, 600 mL volume Parr hydrogenator, entry 4. 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, entries 6 and 7, and compares well to the analogous literature reaction, entry 8.[35] 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 (E)-enamide product was insensitive to the hydrogen pressure, this can be attributed to the known difference in reaction order in the rate limiting step with each alkene isomer.[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). 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.
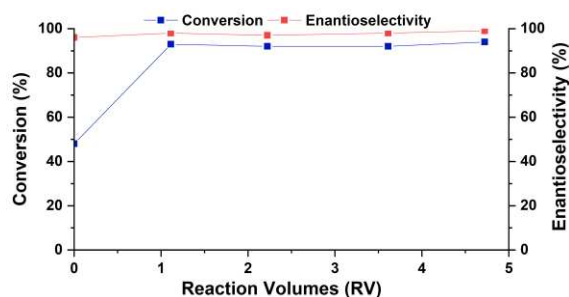

Figure 5. Graph showing conversion and enantiomeric excess with continuous flow hydrogenation of (E)-methyl-3-acetamido-2-butenoate.

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

Entry[#]	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	Rh(MeDuPhos)[2]	10	2	31	0.02
3[37]	H-cube	[Rh(COD)$_4$]/ PTA/ Al$_2$O$_3$ [3]	1/60	1	>99	0.30
4[12]	Tube-in-tube	Iridium catalyst[4]	40	20	>99	3.00

[#] indicates the reference number that data is taken from. [1] 2 mol%; [2] 1 mol%; [3] S/C= 1/360; [4] 2.5 mol% with tri-substituted olefin

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.

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.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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