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Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate

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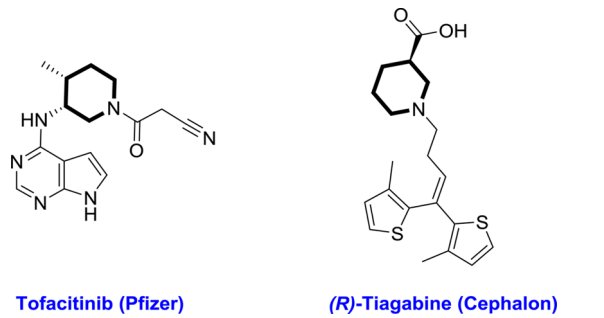
Supporting Information

ABSTRACT: Here we report a process intensification study for the selective, partial, and full hydrogenation of ethyl nicotinate using a trickle bed reactor for meso-flow transformations (HEL FlowCAT). The process achieved a throughput of 1219 g d^{-1} (78 g h^{-1} of product per g of active catalyst) for the partial hydrogenation to ethyl 1,4,5,6-tetrahydropyridine-3-carboxylate, whereas the productivity for the full hydrogenation process reached a 1959 g d^{-1} of throughput (408 g h^{-1} of product per g of active catalyst) on this laboratory-scale flow chemistry platform.

INTRODUCTION

In recent years there has been an increasing demand for new and more efficient chemical processes that cover a wide range of synthetic applications.[1] Correspondingly, many enabling technologies have become available to drive this new agenda.[2,3] However, a particular challenge that has not been fully met is how to move rapidly and safely to scale-up reactions in research laboratories from milligrams to kilograms. It is precisely under these circumstances where new tools can greatly assist the process. Indeed, by definition, process intensification is the "strategy for making dramatic reductions in the size of a chemical plant so as to reach a given production objective".[4] Accordingly, this approach can involve shrinking the size of individual pieces of equipment by cutting the number of unit operations and/or devices involved. Similarly, intensification can occur through using a relevant apparatus to its limits of production, e.g., through the use of high pressure, high temperature, and high substrate concentration. In addition, interests in greater sustainability through more selective processes, often under heterogeneous conditions, have become attractive goals. Nevertheless, working with and scaling up of hydrogen gas reactions brings with it well-recognized issues (i.e., safety assessment, mixing, and H_2 solubility) despite the importance of this reductive process in fine chemical manufacturing. One such process involving precious metal catalyzed hydrogenation of substituted pyridines is of interest due to the importance of the functionalized piperidines products as intermediates in the preparation of many biologically active molecules (Figure 1).[5]

Flow chemistry as an enabling technology has proven useful on a research scale for the continuous catalytic hydrogenation[6−9] of different pyridine derivatives using for example the H-Cube apparatus.[10] Although the latter work covered a useful range of substrates, the throughput of the particular system was limited to around 10 g d^{-1}. Subsequent innovation has led to the development of the H-Cube Midi, which is designed for scale-up reactions up to 500 g d^{-1}, for larger scale work.[11]



Tofacitinib (Pfizer) (*R*)-Tiagabine (Cephalon)

Figure 1. Examples for biologically active molecules containing a piperidine core.

We began our investigation with the aim of safely delivering a throughput in excess of a kilogram per day (kg d^{-1}) in a research laboratory environment. This, we felt, would need considerable process intensification with currently available equipment. We decided to do this by examining the selective hydrogenation, both partial and full, of ethyl nicotinate (**1**) since the products of this process were useful for other programs.

The selective and efficient partial hydrogenation of pyridine derivatives is particularly interesting in order to provide a valuable intermediate for later asymmetric conversion to **3** (Scheme 1).[12,13]

Our approach was to investigate the suitability of the commercially available HEL FlowCAT reactor[14] (Figure 2) for the aforementioned processes and to investigate its suitability for daily production of material using a single charge of catalyst in the trickle bed reactor system.

The HEL FlowCAT is a compact, benchtop unit which allows screening, optimization, and scale-up of heterogeneous

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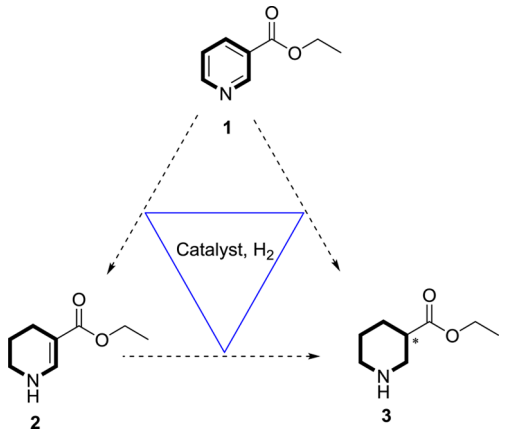
Scheme 1. Products obtained from partial (2) and full (3) reduction of ethyl nicotinate (1)



chemistry and is run under fixed-bed, trickle flow conditions. The system provides a wide range of working pressures and the processing conditions are controlled via software (Supporting Information, SI), which accurately controls parameters such as pressure, temperature, and gas and liquid feed rates (Figure 3).

RESULTS AND DISCUSSION

Partial Hydrogenation Process. The first step towards a full understanding of the advantages of running this transformation in flow was to properly evaluate the constraints of the batch process. For this we used the Chameleon technology[15] as a single unit stirred autoclave (Scheme 2).

We soon recognized that the chemical transformation was difficult under the conditions reported previously,[16] nevertheless using 5% Pd/C as a catalyst under moderately high pressure hydrogen (100 psi) gave us 85% conversion for products **2** and **3** (7:1 average ratio) over 38 h, at room temperature.

Then we examined the H-Cube[7,8] for comparison and quickly found we could reproduce the results described previously by Kappe.[10] However, upon extended reaction time we noticed some variability. Additionally, we were never able to isolate more than 71% of the partial reduced product, owing to engineering constraints such as the hydrogen flow rates and the size of the catalyst cartridges.

In order to deliver material in our target quantities, we identified the HEL FlowCAT reactor as a potentially suitable device for scale up and process intensification studies.[17] Due to the capacity of the trickle bed reactor (reactor column 1, RC1, 6 mm i.d., 3 mL internal volume), it was possible to pack the column with a charge of 2.6 g of catalyst for this particular column configuration.

One practical aspect of major importance, when dealing with this kind of process, is the packing of the reactor column. During our screening we noticed that the performance of the run was highly dependent on catalyst particle size, as too small particles were more amenable to frequent blockages whereas too big particles were associated with channeling and reduced mixing. In our specific case, the use of particles ranging between 0.1 and 0.8 mm was found to be ideal. Notably, the use of smaller particle sizes is possible provided that a "filler material" with bigger particles size is used to "disperse" the smaller particles and create an efficient bed reactor. To avoid any inconvenient issue with blockages, we decided to "dilute" the catalyst particles with inert glass beads with particle sizes

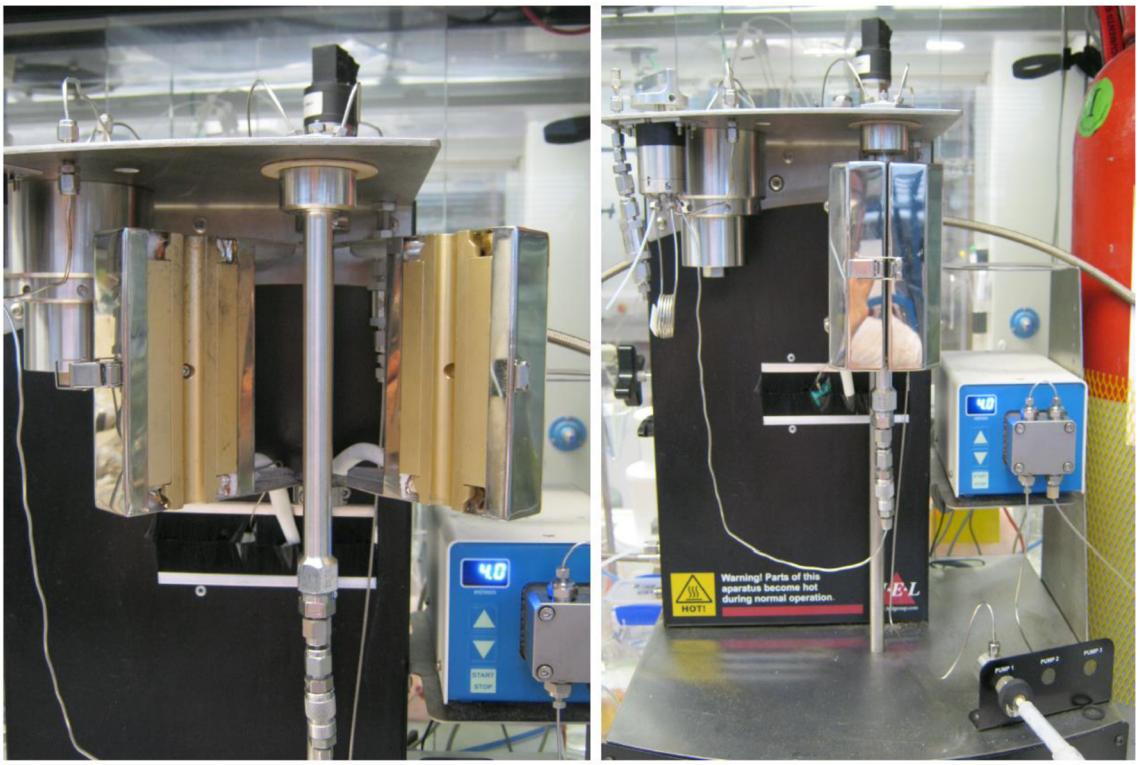


Figure 2. Picture of the trickle bed reactor (HEL FlowCAT reactor) used for the heterogeneous hydrogenation (left: column reactor; right: whole system).

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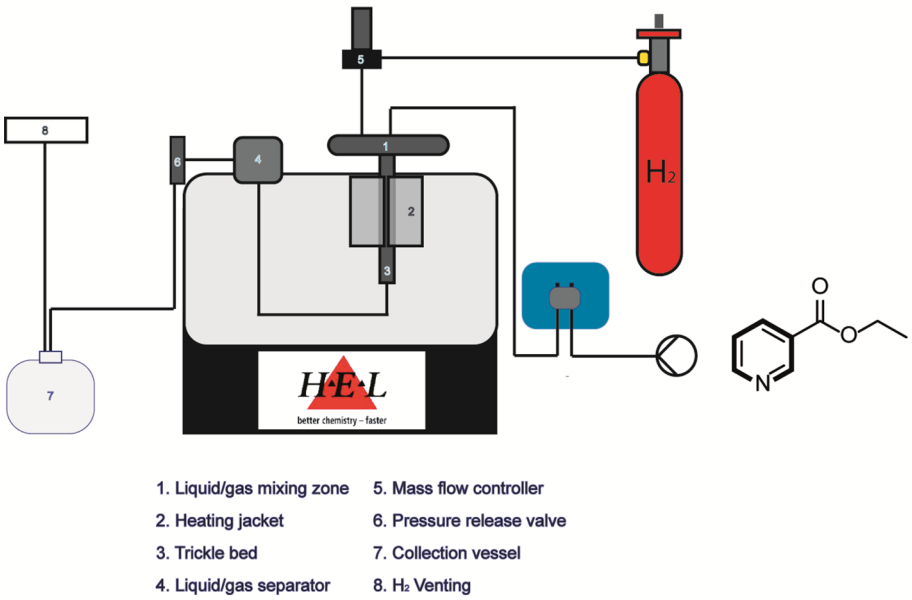
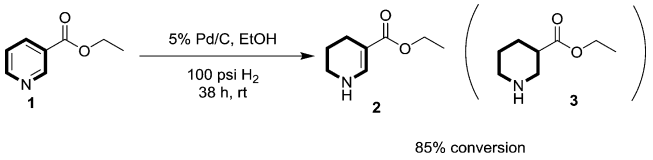


Figure 3. Schematic view of the HEL FlowCAT.

Scheme 2. Hydrogenation of 1 under batch mode conditions using the Chameleon technology (description within the SI)



around 0.2 mm (description of the packing is reported within the SI).[18]

For the initial study, we used a Pd/C catalyst (Table 1).[19,20] We started to screen our system at room temperature with 10% Pd/C. Using a H_2 feed of 0.2 L min^{-1} and system pressure of 20 bar, we were able to selectively obtain 78% conversion to **2** (liquid flow rate 2.0 mL min^{-1}) (Table 1, entry 1). Increasing the temperature to 60 °C and the flow rate to 5.0 mL min^{-1} (system pressure of 20 bar and gas feed of 0.2 L min^{-1}) gave a throughput of 54.78 g d^{-1} with the disadvantage of reducing the 2/3 selectivity (Table 1, entry 5). The best result was achieved using 5% Pd/C[20] (Table 1, entry 6), although this arrangement gave a lower product output (21.6 g d^{-1} throughput). We recognized that the concentration of the starting material was a limiting parameter under these conditions and any attempt to increase the molarity of the solution above 0.05 M failed, resulting in incomplete consumption of the starting material.

We decided therefore to screen different supported forms of Pd catalyst and found that Pd/Al_2O_3[21,22] exerted a beneficial catalytic activity in terms of both productivity and selectivity.[23]

In this particular case, the catalyst particle size was of extreme importance, with particles ranging between 0.1 and 0.25 mm being the most efficient. As shown in Table 2, running the reaction at 60 °C and a liquid flow rate of 3.0 mL min^{-1} delivered an improved productivity of over 260 g d^{-1} (entry 7). Also of importance was that under those conditions considerably higher concentrations of the material feedstock are tolerated (up to 0.4 M).

The robustness of the system was evaluated by conducting an experiment for 22.5 h, following the conditions reported in entry 7 (Table 2), without noticing any decrease in either selectivity or catalytic performance of the system while producing a throughput of over 240 g of material overall (see SI).

Although this productivity was more than 25-fold the throughput obtained with the H-Cube, we believed further

Table 1. Partial reduction of ethyl nicotinate with Pd/C using HEL FlowCAT reactor RC1

							ratio (%)[a]			
eun	catalyst	conc. of **1** (M)	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	H_2 flow (L min^{-1})	**1**	**2**	**3**	throughput of **1** (g min^{-1})
1	10% Pd/C[b]	0.05	2.0	25	20	0.1	22.0	78.0	N.D.	0.015
2	10% Pd/C[b]	0.05	2.0	40	20	0.1	1.1	84.2	14.7	0.015
3	10% Pd/C[b]	0.05	2.0	25	40	0.1	15.2	71.3	13.5	0.015
4	10% Pd/C[b]	0.05	4.0	60	20	0.2	1.1	78.8	20.1	0.030
5	10% Pd/C[b]	0.05	5.0	60	20	0.2	4.8	75.1	20.1	0.038 (54.78 g d^{-1})
6	5% Pd/C[c]	0.05	2.0	40	20	0.1	1.0	90.7	8.3	0.015 (21.60 g d^{-1})
7	5% Pd/C[c]	0.05	4.0	60	20	0.2	1.8	78.4	19.8	0.030

[a]Ratios are based on crude ^{1}H NMR data. [b]Particle size 0.40−0.80 mm.[19] [c]Particle size 0.30−0.85 mm.[20]

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Table 2. Partial reduction of ethyl nicotinate with Pd/Al_2O_3 using HEL FlowCAT reactor RC1

run	catalyst	conc. of **1** (M)	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a] **1**	**2**	**3**	throughput of **1** (g min^{-1})
1	5% Pd/Al_2O_3[b]	0.1	2.5	40	24	0.2	ND	88.5	11.5	0.038
2	5% Pd/Al_2O_3[b]	0.2	2.5	50	23	0.2	6.4	83.3	10.3	0.076
3	5% Pd/Al_2O_3[b]	0.2	3.0	60	24	0.2	2.4	86.5	11.1	0.091
4	5% Pd/Al_2O_3[c]	0.2	4.0	50	20	0.2	1.8	83.2	15.0	0.121
5	5% Pd/Al_2O_3[c]	0.2	4.0	50	20	0.1	11.0	76.7	12.2	0.121
6	5% Pd/Al_2O_3[c]	0.4	2.0	50	20	0.2	3.2	80.1	16.7	0.121
7	5% Pd/Al_2O_3[c]	0.4	3.0	60	20	0.2	0.9	84.0	15.1	0.181 (260.64 g d^{-1})

[a]Ratios are based on crude ^{1}H NMR data. [b]Particle size 0.25−0. 50 mm.[21] [c]Particle size 0.10−0.25 mm.[22]

process intensification was possible. For this the reactor column was increased to 12 mL of internal volume (RC2, Figure 4).

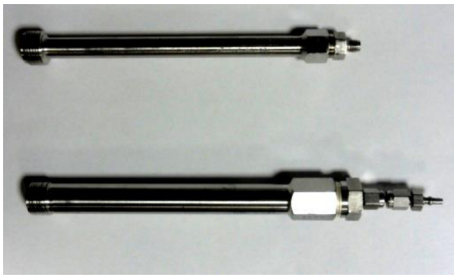

Figure 4. Picture of RC1, top, and RC2, bottom.

The new reactor column accommodated a larger quantity of catalyst (13 g), hence a corresponding increase in productivity was anticipated.

After screening different parameters (Table 3) using RC2, the concentration could be increased to 0.8 M and the flow rate adjusted to 7.0 mL min^{-1} to obtain a throughput of 1219 g d^{-1} with complete consumption of the starting material, with slightly reduced selectivity (Table 3, entry 7).

Compound **2** could be isolated in 73% yield (purity >99%) just via concentration under vacuo, followed by dissolution of the material collected in CH_2Cl_2 and then washing away the byproduct **3** with citric acid 10% solution.[10] The reaction was run for 10 h under the optimized conditions, processing 507 g of starting material (entry 7). Additionally, negligible leaching of Pd catalyst (below 9.5 ppb) was detected by inductively coupled plasma-mass spectrometry (ICP-MS) analyses.

Full Hydrogenation Process. To achieve the full hydrogenation of **1** to **3**, we followed a similar optimization approach. Kappe and co-workers[10] had reported that "full hydrogenation of pyridine to **3** was unsuccessful using the EtOH/Pd/C conditions" and the transformation was conducted by using Pt/C and acetic acid (AcOH) as solvent at 100 °C to provide 92% of the final ethylpiperidine 3-carboxylate (**3**). However, the use of Pt/C would be more expensive on scale than a Pd catalyst, and also AcOH is not a preferred solvent for larger scale reactions.[24]

We started screening different solvents in the H-Cube apparatus using available Pd catalysts (Table 4). Noteworthy here is that even with 10% Pd/C, which was previously reported to provide only 50% yield, and by using ethyl acetate (AcOEt) as solvent, this resulted in a 69.4% yield of material at 100 °C, with a calculated throughput of only just over 5 g d^{-1}. Interestingly, 10% Pd/Al_2O_3 gave us almost full conversion to the desired product **3**, with very good selectivity and no by-product observed (Table 4, entry 7).

The hydrogenation process was then transferred to the HEL platform using the RC1 trickle bed reactor. Given the results obtained with Pd/Al_2O_3[22] as catalyst, we decided to use this material to perform the full hydrogenation. After very few experiments, it was easily found that by running the reaction at 100 bar hydrogen, 160 °C, and 3 mL min^{-1}, with a hydrogen feed equating to 0.2 L min^{-1} and a 0.8 M solution of **1**, we could obtain pure product **3** free from partially hydrogenated by-product (**2**). This system successfully delivered a throughput of 522 g d^{-1} of compound (**3**) (Scheme 3).

During further process intensification studies, it was anticipated that the use of the larger reactor RC2 should be able to increase the throughput to >1000 g d^{-1}. Accordingly, with the 12 mL reactor (RC2), we were pleased to generate the equivalent of 1524 g d^{-1}, using a 1.0 M solution of the starting material. In one long run experiment a quantity of 242 g (isolated yield 99%, purity >99%) of material was collected over just 3 h and 45 min simply via removal of AcOEt by

Table 3. Partial reduction of ethyl nicotinate using HEL FlowCAT reactor RC2

run	catalyst[b]	conc. of **1** (M)	flow rate (mL min^{-1})	temp.[c] (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a] **1**	**2**	**3**	throughput of **1** (g min^{-1})
1	5% Pd/Al_2O_3	0.5	10.0	65	20	0.6	0.6	74.4	25.0	0.756 (1088.35 g d^{-1})
2	5% Pd/Al_2O_3	0.8	6.0	45	20	0.6	1.2	78.7	20.1	0.726 (1044.82 g d^{-1})
3	5% Pd/Al_2O_3	0.8	6.0	65	12	0.6	ND	62.9	37.1	0.726
4	5% Pd/Al_2O_3	0.8	6.0	65	20	0.6	ND	61.3	38.7	0.726
5	5% Pd/Al_2O_3	0.8	8.0	65	20	0.6	ND	69.9	30.1	0.967 (1393.09 g d^{-1})
6	5% Pd/Al_2O_3	0.8	8.0	55	20	0.4	19.2	67.5	13.3	0.967 (1393.09 g d^{-1})
7[d]	5% Pd/Al_2O_3	0.8	7.0	55	20	0.6	trace	75.8	24.2	0.846 (1218.95 g d^{-1})

[a]Ratios are based on crude ^{1}H NMR data. [b]Particle size 0.10−0.25 mm.[22] [c]Temperature of the external heating jacket. [d]10 h run.

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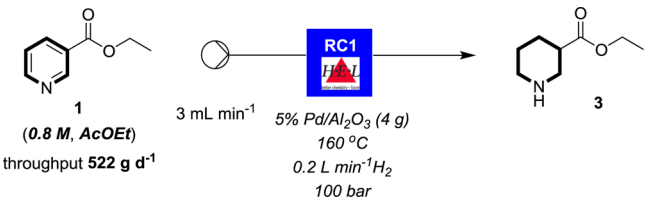
Table 4. Solvent and catalyst optimization study for the full hydrogenation of ethyl nicotinate 1 with different Pd catalysts, using the H-Cube apparatus

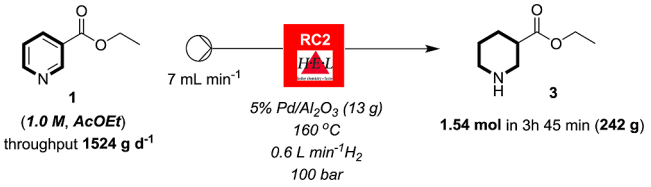
			ratio (%)[c]			
entry[a,b]	catalyst	solvent	1	2	3	throughput of 3 (g min^{-1})
1	10% Pd/C	EtOH	N.D.	39.4	60.4	0.00375
2	10% Pd/C	THF	N.D.	32.4	67.6	0.00375
3	10% Pd/C	toluene	N.D.	41.7	58.3	0.00375
4	10% Pd/C	AcOEt	N.D.	30.6	69.4	0.00375
5	5% Pd/C	AcOEt	N.D.	73.0	27.0	0.00375
6	10% Pd/Al_2O_3	EtOH	N.D.	50.5	49.5	0.00375
7	10% Pd/Al_2O_3	AcOEt	N.D.	9.3	90.7	0.00375

[a]The data reported are only related to representative examples. [b]Conditions: full hydrogen mode, 100 °C, 0.5 mL min^{-1}. [c]Ratios are based on crude ^{1}H NMR.

Scheme 3. Full reduction of ethyl nicotinate with Pd/Al_2O_3 using HEL FlowCAT reactor (RC1)



Scheme 4. Full reduction of ethyl nicotinate with Pd/Al_2O_3 using HEL FlowCAT reactor (RC2)



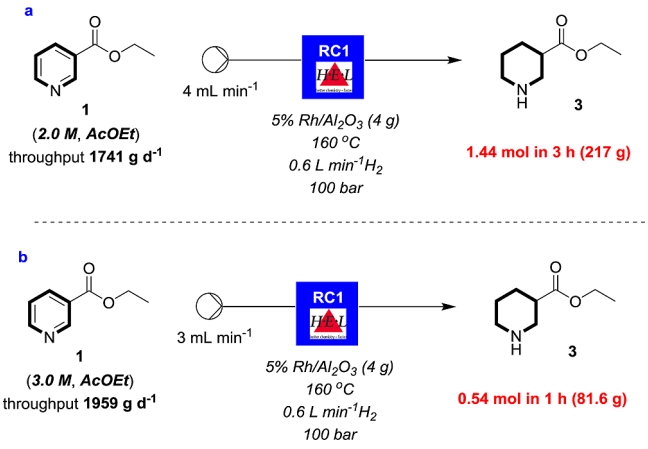
concentration (Scheme 4). As in many other fixed bed reactor processes, here the use of continuous flow represents a huge advantage as it enables the removal of troublesome operations (i.e., filtration of catalyst, washing procedure).

Nonetheless, we wanted to check the suitability of the system for higher productivity. After a more careful screening of different catalysts, we realized that the use of a 0.05 M solution of **1** in AcOEt could be fully hydrogenated with Rh/Al_2O_3 catalyst, using the H-Cube platform. However, the daily throughput could not be increased under these conditions on this equipment.

The use of the FlowCAT system with RC1 and Rh/Al_2O_3[25] catalyst gave an outstanding 1741 g d^{-1} throughput which was seen as genuine improvement over previously reported procedures (Scheme 5a). We also were very pleased to find out that the system could tolerate even higher concentrations of starting material as we could process a 3 M solution of ethyl nicotinate successfully (Scheme 5b).

Under the optimized conditions, we were able to continuously produce 81.6 g of material in just 1 h (99% purity), and the total amount of material processed over five different experiments was 530 g using the same catalyst bed (overall 6.5 h), which equates to 1959 g d^{-1} throughput of material. An examination to the gas stoichiometry for b (Scheme 5) shows that the ratio of hydrogen to substrate is represented as follows:

Scheme 5. (a and b) Full reduction of ethyl nicotinate with Rh/Al_2O_3 using HEL FlowCAT reactor RC1



$$[(0.6\ \text{L min}^{-1})/22.4\ \text{L mol}^{-1})]/[(3.0\ \text{mol L}^{-1})\ (0.003\ \text{L min}^{-1})] = 2.98\ \text{mol H}_2/\text{mol ethyl nicotinate}$$

This calculation suggests we are working at the current limit of the gas feed to the RC1.[26]

Pleasingly, ICP-MS analyses showed that leaching of Rh catalysts is very low with all values detected below 10 ppb.

CONCLUSIONS

In conclusion, we reported a study for a specific process intensification program for hydrogenation reactions that can be carried out in a research laboratory environment. The use of flow technologies allowed operating at high pressure and temperature which enabled the use of high substrate concentrations and high flow rates. Under the agreements of departmental safety protocols (University of Cambridge) with appropriate excess hydrogen venting (operating under parameters within the safety criteria of the equipment), this provided very high throughput from a benchtop reactor, with potential throughput to multikilogram scale through extended run times. Studies on catalyst degradation are ongoing and our future plans involve the engineering improvements of the flow machinery in order to increase the throughput of material using even larger column reactors.

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■ ASSOCIATED CONTENT

Supporting Information

Characterization of compounds, analytical data, and technical information on the catalysts used. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

RC1, reactor column 1; RC2, reactor column 2

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