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# Mesoscale Flow Chemistry: A Plug-Flow Approach to Reaction Optimisation

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**Abstract:**
**In recent years, chemistry in flowing systems has become more prominent as a method of carrying out chemical transformations, ranging in scale from analytical-scale (microchemistry) through to kilogram-scale synthesis (macrochemistry). The advantages are readily apparent—increased control of conditions leading to greater reproducibility, scaleability, and increased safety/reduced loss—although its acceptance as a viable synthesis technique has been limited due to its drawbacks, primarily precipitation, liquid handling, and diffusion of the reaction within the reactor. Here, we present details of a system which bridges the gap between micro- and macroreactors and has enabled fast reaction optimisation (using small amounts of reagents) and subsequent multigram scale-up using a commercial reactor.**

## Introduction

The development of new pharmaceutical compounds is a lengthy, expensive, and dynamic process.[1] At early stage (gene to candidate), the business driver is to identify a potential drug candidate quickly in order to obtain a strong intellectual property position as soon as possible. Once a candidate is identified and the patent is filed, the focus shifts to getting the drug to market as quickly as possible in order to maximise the revenue generated (i.e., before the patent expires or competitor compounds are marketed). In terms of the chemistry process, the remits for the business units at each end of this spectrum are clearly very different, and the chemical route is certain to undergo numerous changes as the compound progresses from hit generation through to manufacturing.[2] Figure 1 highlights these key processes involved in development of a drug compound and shows clearly how the chemical process is developed and/or optimised within each business unit.

Up until candidate selection, potential drug compounds are usually synthesised on a milligram scale for in vitro and in vivo screening, with lead generation generally occurring via high-throughput methods, and lead optimisation via medicinal chemistry groups. On this scale, where only a few milligrams of the target compound are required for screening, the financial cost benefit from carrying out process optimisation for each chemical transformation is heavily outweighed by the need to obtain as much biological information as quickly as possible. As a result, the synthetic routes identified are not necessarily the cheapest or most efficient as the chemistry is often designed to produce multiple products from common intermediates. However, once a potential candidate is selected, 50−100 g will be required for toxicology studies, and this material will generally be synthesised using the original, nonoptimal route. Once the candidate passes the toxicological studies, the synthetic route is usually transferred to Chemical Development in order to produce 0.5−5 kg material by a Fit For Purpose (FFP) route for First Time in Human (FTIH) studies. Here, the process may be modified in order to increase yields, reduce costs, or remove unattractive steps (e.g., chromatography), although the tight timeframes involved mean that it is preferable to make as few modifications to the original route as possible. Once the compound passes FTIH studies it will progress to Pre-Clinical Development (PCD), where kilograms of material are required for clinical trials. Here, the potential for lowering the cost of goods and the drive for easier, safer production are paramount, and the synthesis may be further modified in order to provide a manufacturing-viable route.

It is clear to see how the chemical route of a drug will undergo many alterations as it is transferred from high-throughput chemistry, through medicinal chemistry and chemical development groups, towards manufacturing. Clearly, a method of streamlining this process to enable seamless transfer of the route from one group to another would offer a potential for large cost- and time savings, resulting in drugs being available to patients as early as possible. Here, flow chemistry is an attractive potential solution as it should allow for rapid early-stage reaction optimisation and direct scale-up.[3] However, it is the area of microchemistry which is currently attracting the most interest. Numerous chemical transformations in microreactors have been demonstrated,[4] but it is the potential to couple this technology to a flow assay in order to provide fully automated, iterative lead generation and optimisation that makes the approach even more attractive.[5]

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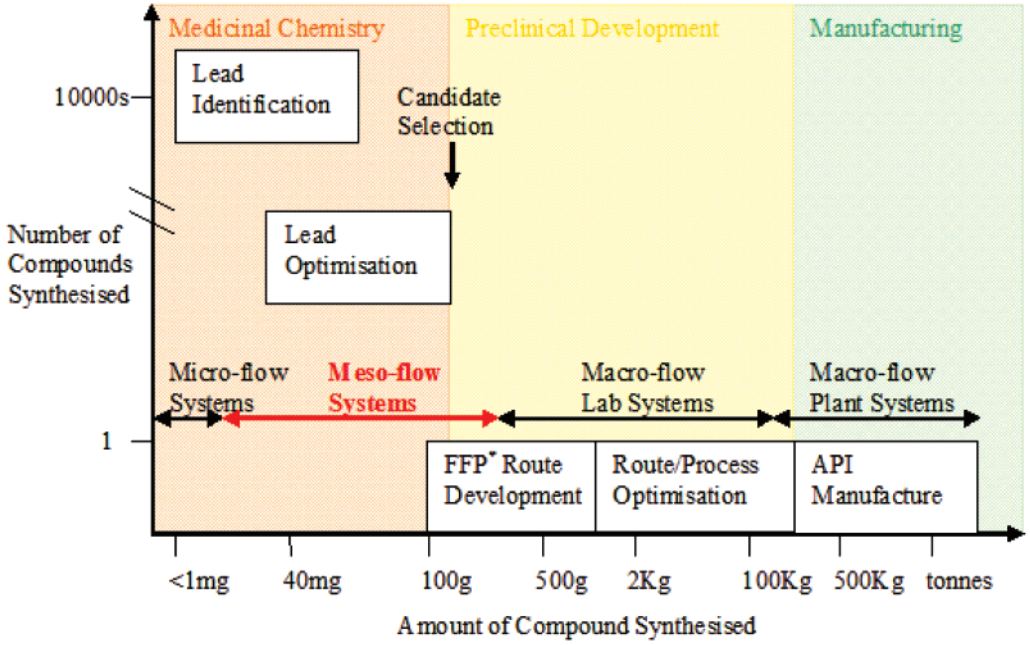


***Figure 1.*** **The chemical activities involved in the development of a drug (*FFP = Fit For Purpose).**

Our group is involved in delivering gram−kilogram quantities of material to support precandidate selection, and we were interested in utilising flow chemistry as a method of performing rapid reaction optimisation and scale-up. Additionally, if we could identify a scalable and efficient synthetic route at an early stage, we would be able to rapidly synthesise sufficient material for early toxicology studies on request. However, scaling up a flow process is not necessarily straightforward, as the physical behaviour of a fluid flowing through a channel varies with its velocity and channel size. A more detailed explanation can be found elsewhere,[6] but the basic premise is that, for common organic solvent solutions, laminar flow will occur in small channels/at low flow rates (e.g., microfluidics) and mixing proceeds purely by diffusion. Indeed, static mixers are often employed in macroscale laminar flow processes to ensure that thorough mixing occurs.[7] In larger channels/at higher flow rates (e.g., macrofluidics), fluid behaviour becomes unpredictable and mixing occurs in a turbulent environment. With this in mind, we felt that a mesoscale microfluidic system offered the most flexibility, as it would allow us to identify a scaleable process using low volumes of reagents. A literature search indicated that two commercial flow systems were available that seemed to meet our requirements, the CYTOS[8] and AFRICA[9] systems, marketed by CPC and Syrris, respectively (Figure 2).

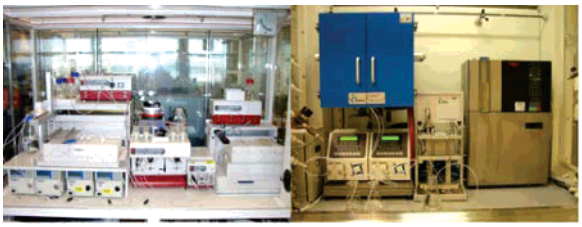

***Figure 2.*** **Commercial flow systems: Syrris AFRICA (left) and CPC CYTOS (right).**

The CYTOS, designed and marketed by CPC (who also market a lower volume model, CYTOS-M), is essentially a stand-alone microreactor which may be connected to any other peripheral device (e.g., pumps, fractioners, etc.). The key advantage of the CYTOS is the complex "splitting" of the reagent inputs into multiple low-volume microchannels, which provides excellent thermodynamic control for the mixing of reagents. Additionally, this facilitates high material throughput via what is essentially a microchemistry process. Syrris's AFRICA system, on the other hand, is a complete flow chemistry system, consisting of pumps and valves to deliver reagents, a temperature-controlled glass reactor chip, and a fraction collector. The low volume of the chip means that the need for a complex mixing approach, such as in the CYTOS, is not required, although the downside is that the throughput is reduced.

However, although both of these devices provide an adequate means of performing flow synthesis, they both suffer from three major drawbacks:

(1) Reaction Dispersion. In most flowing systems, it is common practice to first fill the system with an appropriate solvent before making any injections, so that the system may equilibrate and be pressurised. However, the problem with this approach is that, once injected, the reagents/reaction will start to disperse due to the effect of parabolic flow. This gives rise to concentration gradients, and potentially a varying reaction profile across the injected reaction plug. The upshot

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is that the leading and trailing edges of the reaction should ideally not be collected, which means that larger volumes of reagents will be required for reaction optimisation. A common solution to this issue is to introduce air gaps at the start and end of the injected solution, although this is by no means a reliable method as the air may dissolve into the solution, particularly if heat is being applied.

(2) Liquid Handling. CPC's CYTOS is operated by pumping the reagent solutions into the reactor directly through the supplied pumps. Ideally this approach should be avoided, as it requires that the pumps exhibit excellent chemical compatibility over a wide range of reagents and solvents. A further issue is that the pumps must be cleaned out thoroughly in between reactions, which increases both solvent consumption and process time. Syrris avoid this problem in their AFRICA system by introducing the reagents into the system via injection loops, a concept commonly used in HPLC systems. However, the main issue with the AFRICA system is that it uses dual-syringe pumps to provide a constant system flow—this approach clearly limits the flow-rate range, as the maximum flow achievable is governed by the size of the syringes and by the rate at which they can refill without cavitation.

(3) Solid Formation. In all microfluidic devices, the major issue is precipitation within the channels/capillaries, giving rise to system blockages. At best, a light blockage may be relatively easy to clear (e.g., by pumping at higher pressure, sonication, introduction of a different solvent) and provides the user with little more than an inconvenience. At worst, with heavy precipitation, the reactor may become blocked irreversibly and may have to be discarded. Additionally, the system must be equipped with pressure detectors and sufficiently intelligent software to be able to detect when a blockage occurs, thus enabling unattended operation.

## Results and Discussion

In seeking to address the issues outlined above, we became aware of a communication by Song et al.,[10] who demonstrated that a fluorous solvent may be used as a system solvent in order to enable formation of discrete, aqueous, microliter-sized droplets in a flowing system. The group have subsequently demonstrated that the approach is applicable to numerous applications, including protein crystallisation,[11] measurement of reaction kinetics,[12] chemical synthesis[13] and high-throughput screening.[14] In addition to controlling dispersion, this approach enhances mixing within individual plugs, an effect which has been utilised by Ahmed et al.[15] to accelerate biphasic reactions in microreactors.

Although multiphase plug-flow reactions have been demonstrated by other groups, such as Rahman et al., who used a carbon monoxide/ionic liquid flow in the carbonylation aryl halides,[16] we could find no published material which demonstrated monophasic synthesis of drug-like compounds via a plug-flow approach. We realised that this approach would provide a potential solution to our liquid handling and dispersion issues and subsequently developed a plug-flow chemistry system capable of carrying out chemical reactions on a $\mu$L−mL scale, depending on the quantity of material required. A more detailed description of the platform can be found elsewhere (article in press), but in brief, two chemical reagents are loaded into loops using standard HPLC pumps and valves, and these are then injected into a PTFE reactor via a simple "T" junction (Figure 3). Liquid handling is performed by a Kawasaki six-axis robot (Figure 4). The reaction plugs are then tempered, either via conventional or microwave heating, before being collected automatically (reaction plug detection is triggered via the difference in the refractive index between the fluorous and reaction solvents). In this way, optimum reaction conditions can be determined using low volumes of reagents (100 $\mu$L) and then scaled up directly on the same system—a concept we validated on numerous chemical reactions, including nucleophilic aromatic substitution[17] (Scheme 1) and diazo transfer chemistry[18] (Scheme 2). Our perfluorinated solvent of choice was perfluorodecalin (PFD), as it has low solubility in most organic solvents (although it is partially soluble in hexane and diethyl ether), and its high boiling point (142 °C) allowed us to operate at elevated temperatures. Even upon strong heating, we observed that organic reaction plugs appeared to remain intact, and plug flow was still observed at temperatures in excess of 120 °C. An acceptable alternative to PFD is perfluoromethyldecalin (PFMD), which displays physical behaviour similar to that of PFD but has the added advantage that it has a melting point of −40 °C, which offers the potential to perform subambient chemistry. Figure 5 shows a photograph of an organic solvent plug (orange) surrounded by a PFD in a 0.75 mm i.d. PFA tube. In practice, the reaction plugs we injected were much larger than shown (>100 $\mu$L), but the image highlights the low miscibility between the two phases.

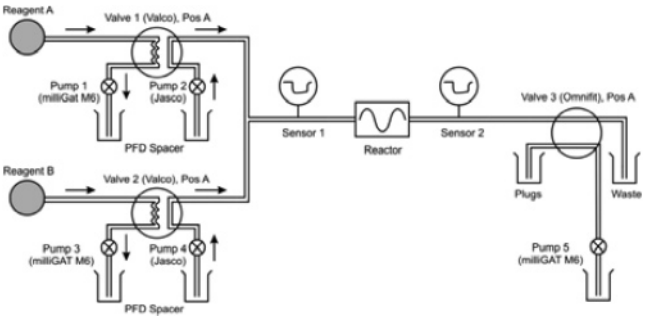


***Figure 3.*** **Schematic of the fluidic connections in the PFR (shows system aspirating reagents).**

After conducting this proof of concept (PoC) work, we next aimed to demonstrate optimisation and scale-up of a

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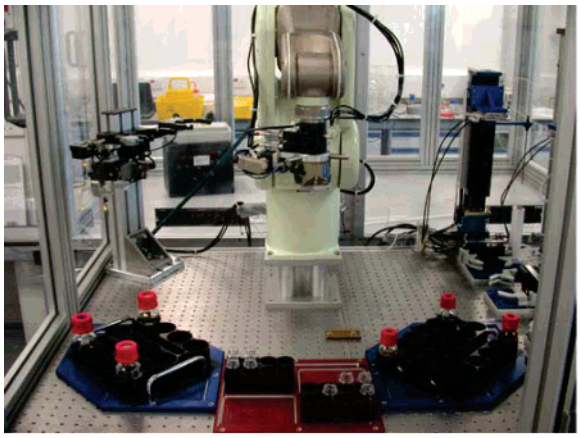
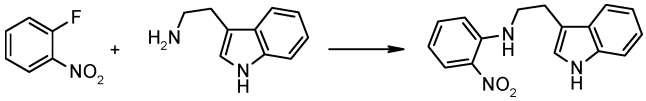
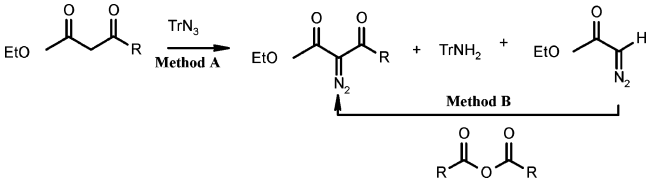


***Figure 4.***
**Automation of the plug-flow reactor concept. Reagent/product solutions are moved to injection/collection stations by a Kawasaki six-axis robot; reactions are then performed as outlined in Figure 3.**

***Scheme 1.*** **Nucleophilic aromatic substitution**



***Scheme 2.*** **α-Diazo-*β*-keto ester synthesis**



multistep process. A three-step synthetic route (Scheme 3) was provided to us by a medicinal chemistry group, with 50 g of compound C being required to support precandidate selection. The chemistry involved oxidation of a secondary alcohol using NMO/TPAP[19] and subsequent trifluoromethylation,[20] followed by a hydrogenation step. Here we aimed to demonstrate that the batch conditions could be optimised in flow using small quantities of reagents, and that these conditions could be scaled up to produce the required 50 g of compound C.

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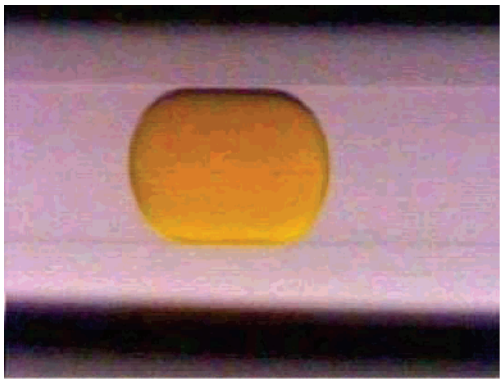

***Figure 5.*** **Formation of an organic reaction plug (orange solution) in a perfluorinated solvent system in 0.75 mm i.d. PFA tubing.**

***Scheme 3.*** **Synthetic route to key intermediate C**

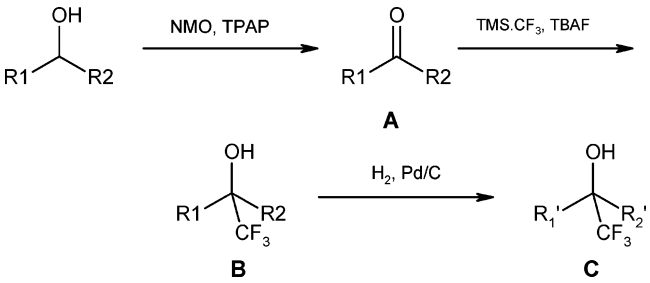

***Table 1.*** **Effect of plug size on the reactivity of the nucleophilic substitution of 2-nitrofluorobenzene with tryptamine (Scheme 1)**

| run | plug size | % conversion |
|---|---|---|
| 1 | 0.2 | 78 |
| 2 | 0.5 | 78 |
| 3 | 1.0 | 76 |
| 4 | 2.0 | 75 |
| 5 | 5.0 | 75 |

In carrying out the initial PoC work, we wanted to determine whether reactions carried out in plug format observed the same reaction profile regardless of plug volume. To this end, we studied the nucleophilic aromatic substitution of 2-nitrofluorobenzene with tryptamine. Reaction plugs of various volumes were formed and passed through a reactor for 6.5 min at 80 °C. One drop of each reaction was collected, diluted with acetonitrile, and analysed by LC/MS (Table 1). The results show that a consistent reaction profile is observed for all plugs, and this suggests that reactions may be optimised on a 200 $\mu$L scale and then scaled up to provide the quantity of material required.

With successful PoC in hand, we next wanted to assess how effectively we could apply optimal reaction conditions to different substrates. An internal chemistry project required 2 g each of the α-diazo-*β*-keto ester, as shown in Scheme 2. The suggested procedure involved diazo transfer onto the *β*-keto ester using trisyl azide (method A, Scheme 2), and in studying this chemistry for R = Me, we found that a 15 min reaction at room temperature gave the desired product in approximately 100% conversion (LC/MS). These conditions were successfully scaled up (via injecting multiple reaction plugs) to give the diazoester in 85% yield, after

***Table 2.*** **Yields for the formation of α-diazo-*β*-keto esters**

| R group | % yield | |
|---|---|---|
| | method A | method B |
| Me | 85 | 0 |
| $CHF_2$ | 34 | 82 |
| $CF_3$ | 6 | 88 |

chromatography. However, upon transferring these conditions to R = $CHF_2$/$CF_3$ we were unable to obtain the same result due to the labile nature of the ketone group, and under these conditions we obtained predominantly ethyldiazoacetate. A recent article[21] suggested that we should be able to convert ethyldiazoacetate back to the desired product by reacting it with the appropriate anhydride under basic conditions (method B, Scheme 2). This approach proved to be more successful, and excellent yields were observed for the fluorinated substrates, although no reactivity was observed with acetic anhydride (summarised in Table 2).

Our next project involved scaling up an existing medicinal chemistry process in order to produce 50 g of compound C (Scheme 3). The route and conditions were provided to us from medicinal chemistry and we noted that the first two steps required slow, controlled mixing of the reagents and purification via flash column chromatography. The final step involved hydrogenation, and although the product was obtained in good yield, the reaction required handling large volumes of hydrogen gas and removal of the catalyst via filtration—a process which is unattractive on a large scale.

We decided to use the batch conditions as a starting point and transferred the first two steps to our Automated Plug Flow Synthesis (APFS) system. We observed that each step could be driven to completion within 15 min via careful tweaking of the reaction conditions. Purities were also greatly increased, and the purifications were simplified. (Although chromatography was still employed, we simply aimed to remove baseline impurities, and as a result we were able to massively overload the silica). However, even though we successfully demonstrated that transfer of the process to a flow setup would offer us considerable advantages, we realised that we were limited by the APFS's throughput—the projected time to carry out the 50 g synthesis of the first two steps in this way (excluding purification) would be approximately 52 h, compared with 40 in batch. A potential solution to this issue could be to replace the 6-port valves with 8- or 10-port valves, providing a dual-loop/continuous-feed system, although the throughput would still be restricted by the low reactor volume. In order to accomplish the goal of 50 g synthesis, we turned to CPC's CYTOS, which is designed for continual flow applications. Due to the complex reactor design, which involves splitting the main flow into multiple, parallel microchannels, we were unable to successfully transfer the plug-flow setup to this system as the injected plugs emerged from the reactor heavily fragmented. As a result, we elected to attempt the scale-up in the CYTOS under non-plug-flow conditions, as we felt that any differences in reactivity at the leading/trailing edges of the reaction would be minimised by the relatively large scale of the reaction. Additionally, as the reaction volume for both the oxidation and trifluoromethylation reactions exceeded the volume of the reactor, the concept of a discreet reaction plug became obsolete.

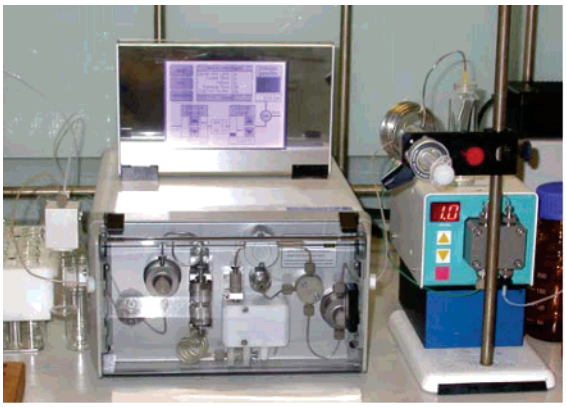

***Figure 6.*** **Thales H-Cube.**

As predicted, the chemistry transferred smoothly, and the process time for the synthesis of compound B was reduced to approximately 13 h, including a purification step at each stage. For the liquid handling of reagents on this scale, we elected to pump the reagent solutions directly into the system via HPLC pumps—not our preferred approach, but one which allowed us to validate that the chemistry could be successfully transferred between systems.

The final step was carried out on the H-cube[22] (Figure 6), a system which provides the means to carry out safe and scaleable hydrogenation reactions. The optimum conditions were found to be a 0.27 M solution flowing over a 10% Pd/C cartridge (CatCart 70) at 1.3 mL/min, and we successfully synthesised 50 g of compound C in this manner (synthesised via three ∼16 g batches, as the processing time for each batch was approximately 5 h). In performing the synthesis, we collected the output in fractions to ensure that the catalyst remained active throughout the course of the run. Towards the end of the second batch, we observed that the reactivity began to fall away, and the catalyst had to be replaced. The partially reacted material was mixed with the remaining unreacted solution, and passed back through the hydrogenator a second time, giving the desired compound in 100% conversion. For the third and final batch, a new CatCart was used, and all 16 g was successfully processed in one run.

Overall, the yield for the synthesis of compound C was increased from 52% in batch to 71% using our optimised flow approach, and the process time (including purification) was reduced by approximately 25 h (a further reduction could have been achieved if hydrogenation could have been paralleled out to increase the throughput). A summary comparing the batch and flow processes is given in Table 3.

## Conclusion

In summary, we have developed a system capable of performing chemical reactions on a microliter scale in order

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***Table 3.*** **Summary of the processes involved with the synthesis of alcohol C**

| step | conditions | purification | process time (h) | yield (%) |
|---|---|---|---|---|
| | | Batch | | |
| 1 | slow addition of TPAP to a DCM solution of the alcohol/NMO, keeping temperature below 25 °C. Stir overnight | evaporate then flash chromatography (14 gsilica/1 g crude) | 24 | 69 |
| 2 | slow addition of TBAF to a THF solution of the ketone/silane at 0 °C; stir overnight | acidify (2 N HCl) and extract with ether, followed by flash chromatography (19 g silica/1 g crude) | 24 | 82 |
| 3 | mix reagents and stir under $H_2$ for 5 h | filter catalyst through celite and concentrate solution | 6 | 92 |
| | | Flow | | |
| 1 | 15 min reaction, throughput of 3.14 mL/min | wash with water and then pour directly onto a silica column (1 g silica to 1 g crude) to remove baseline peaks | 9 | 86 |
| 2 | 5 min reaction, throughput of 3.4 mL/min | acidify (2 N HCl) and extract with ether, followed by flash chromatography (2 g silica/1 g crude) | 4 | 84 |
| 3 | 1.5 min reaction time (approximately), throughput of 1.3 mL/min | concentrate collected solution | 16 | 98 |

to provide optimal and scaleable reaction conditions. As the conditions are readily transferable to other flowing systems, throughput is increased, and processing times are shortened from traditional batch processes. This system bridges the gap between micro- and macroflow systems and offers the first step towards a seamless chemical process in drug discovery.

## Experimental Section

All reagents and solvents were of analytical grade and were used without further purification. NMR spectra were recorded on a Bruker Avance Ultrashield 400 using tetramethylsilane (TMS) as an internal standard. LC/MS analyses were carried out on an Agilent series 1100 HPLC coupled to a Waters Micromass ZQ mass spectrometer. Chromatography was performed using an ISCO Combiflash system, or with IST Isolute Flash Si cartridges.

**Generic Flow Setup (APFS).** The equipment was set up as outlined in the schematic in Figure 4. Two reagent solutions (A and B) were prepared and then aspirated into loops (20′, 0.03″ i.d. PFA tubing) on a Vici six-port valve using Milligat M6 pumps. The reaction plugs were then formed by using Jasco PU2080 HPLC pumps to drive the two reagents back out of the loops, where they met at a PEEK Y-junction (0.75 mm i.d., Anachem). Once formed, the plug was then flowed through a reactor—a coil of 0.75 mm i.d. PFA tubing (6.75 mL internal volume), which was incubated by wrapping around a metal cylinder which had been designed to fit on top of a hotplate/stirrer. The reaction time was then defined by altering the flow rates of the pumps accordingly (reaction time = reactor volume/total flow rate).

**Generic Flow Setup (CPC Cytos).** The system was configured so that it consisted of a mixer unit (2 mL internal volume) and 1−3 reactor units (15 mL internal volume each), and the reagent solutions were pumped through the reactor using Jasco PU2080 HPLC pumps. The reaction time was defined by altering the flow rates of the pumps accordingly (reaction time = total reactor volume/total flow rate).

***N*-[2-(1*H*-Indol-3-yl)ethyl]-2-nitroaniline.** APFS system is used. Solution A = 2-nitrofluorobenzene (1.41 g, 10 mmol), DMF (15 mL); solution B = tryptamine (1.60 g, 10 mmol), DMF (15 mL). Reaction plugs were formed (1:1 stoichiometry, v/v) and injected into a reactor, which had been preheated to 80 °C, at a total flow rate of 0.3 mL/min, giving a reaction time of 6.5 min. One drop of each reaction was collected (from approximately the middle of the plug) into 1.5 mL water for LC/MS analysis.

**Diazoester Synthesis.** *Method A. Ethyl 2-Diazo-3-oxobutanoate.* APFS system is used. Solution A = ethylacetoacetate (3.2 mL, 25 mmol), acetonitrile (25 mL); solution B = DABCO (5.5 g, 49 mmol), acetonitrile (35 mL); 11 × 5 mL reaction plugs (1:1 stoichiometry, v/v) were injected sequentially into a reactor at ambient temperature, with a total flow rate of 0.45 mL/min, giving a reaction time of 15 min. The combined reaction plugs were quenched into a stirred flask of water (100 mL), which was subsequently extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to an oil. Hexane was added and the mixture cooled in an ice bath to induce precipitation of $TrNH_2$, which was removed by filtration, and the filtrate was purified by flash column chromatography (DCM) to afford the diazoester (3.31 g, 85% yield). $^1$H NMR ($CDCl_3$) $\delta$ 4.28−4.34 (2H, q, $J$ = 7.2 Hz), 2.48 (3H, s), 1.32−1.36 (3H, t, $J$ = 7.2 Hz).

*Method B. Ethyl 2-Diazo-4,4,4-trifluoro-3-oxobutanoate.* APFS system is used. Solution A = ethyldiazoacetate (2.1 mL, 20 mmol), pyridine (1.8 mL, 22 mmol), DCM (20 mL); solution B = trifluoroacetic anhydride (3.5 mL, 30 mmol), DCM (20 mL); 5 × 5 mL reaction plugs (1:1 stoichiometry, v/v) were injected sequentially into a reactor at 38 °C, with a total flow rate of 0.45 mL/min, giving a reaction time of 15 min. The combined reaction plugs were quenched into water (50 mL), which was subsequently extracted with DCM (2 × 35 mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to an oil, the diazoester by $^1$H NMR analysis (3.76 g, 88% yield). $^1$H NMR ($CDCl_3$) $\delta$ 4.34−4.39 (2H, q, $J$ = 7.2 Hz), 1.34−1.37 (3H, t, $J$ = 7.2 Hz).

**Ethyl 2-diazo-4,4-difluoro-3-oxobutanoate:** method B followed, 82% yield. $^1$H NMR ($CDCl_3$) $\delta$ 6.47−6.74 (1H, t, $J$ = 53 Hz), 4.33−4.39 (2H, q, $J$ = 7.2 Hz), 1.34−1.38 (3H, t, $J$ = 7.2 Hz).

**Ketone A.** CPC CYTOS is used with three reactor units, giving an internal volume of 47 mL. Solution A = alcohol

(80 g, 294 mmol) + acetonitrile (580 mL); solution B = TPAP (5.16 g, 14.7 mmol) + NMO (58.5 g, 500 mmol) + acetonitrile (580 mL). The two solutions were pumped into the CYTOS at a flow rate of 1.57 mL/min each, giving a reaction time of 15 min. The output of the reactor was concentrated in vacuo, diluted with DCM (30 mL), and split into three batches to simplify the purification. Each batch was poured onto a silica column (50 g), and the column was then washed with DCM (180 mL). The eluent was then concentrated in vacuo to afford the clean ketone **A** (68.25 g, 86%).

**Alcohol B.** CPC CYTOS is configured with one reactor unit, giving an internal volume of 17 mL. Solution A = ketone (32.5 g, 120 mmol) + TMS·$CF_3$ (40.4 g, 284 mmol) + THF (52 mL); solution B = TBAF (5.16 g, 14.7 mmol) + THF (65 mL). The two solutions were pumped into the CYTOS at a flow rate of 1.7 mL/min each, giving a reaction time of 5 min. The temperature was maintained at 25 °C. The reactor output was directed over stirred, 2 M aqueous hydrochloric acid (250 mL), which was subsequently extracted with ether (2 × 100 mL). The combined ethereal extracts were washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude title compound. The crude was then dissolved in DCM (10 mL) and poured onto two silica columns (50 g); each column was then eluted with DCM (60 mL fractions). The fractions which contained the product by TLC were combined and concentrated in vacuo to give clean alcohol **B** (34.3 g, 84%).

**Alcohol C.** The H-Cube was fitted with a CatCart 70 10% Pd/C cartridge and the system purged with ethanol. The hydrogen flow was then activated using "full $H_2$" mode at a temperature of 80 °C. A solution of the alcohol (34.2 g, 100 mmol) in ethanol (340 mL) was then flowed through the system at 1.3 mL/min, and the system was washed through with a further 10 mL ethanol before the hydrogen flow was stopped. The collected material was concentrated in vacuo to give the hydrogenated compound **C** (16.61 g, 104% yield).

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