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The Impact of Continuous Flow Technology and Collaboration between Academia and Industry

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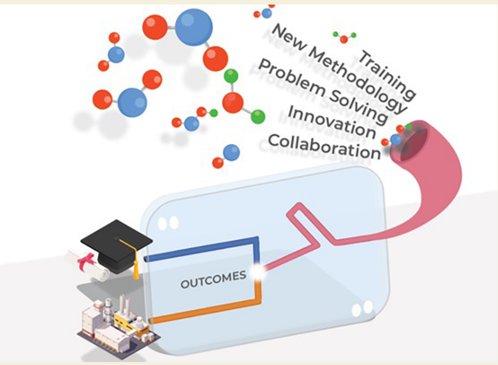
ABSTRACT: Collaboration between researchers is one of the main drivers enabling new discoveries and improved chemical processes. This is especially true in the field of continuous flow technology where synthetic chemists, chemical engineers and data scientists contribute their expertise. This perspective article discusses the impact of such collaborations between academia and industry by highlighting key case studies from the last few years to showcase the continuing need and value of such efforts and provide valuable reference material.



KEYWORDS: *continuous flow chemistry, industrial impact, sustainability, process efficiency, reaction automation, reaction discovery*

INTRODUCTION

Over the past decades advanced synthesis technologies have revolutionized how chemists in both academia and industry use machines to conduct research and produce chemical entities at varying scales.[1] Continuous flow technology is one of the most widely applied tools which continues to impact synthetic chemistry with numerous applications ranging from small molecule synthesis and materials discovery to the manufacture of active pharmaceutical ingredients and agrochemical products.[2−4] Flow chemistry adopts this central position as it combines multiple advantages arising from reactor miniaturization, such as improved heat and mass transfer, its inherent scalability and its ability to streamline reactions *via* reaction telescoping[5−7] and the incorporation of in-line purification[8,9] and analytical tools.[10−13] Development of continuous flow processes requires a fundamental understanding of the chemistry involved which is often achieved *via* batch reaction optimization. However, the translation of these conditions to the final flow process often requires further optimization. Due to the impact of heat and mass transfer in flow the changed kinetics of the reactions can lead to advantages but also setbacks in developing continuous reactions. In addition to enabling chemists to exploit synthetic transformations that safely use *in situ* generated reactive intermediates as well as reaction conditions that would not be deemed feasible in batch mode,[14−16] flow-based processing has also demonstrated new opportunities to minimize the environmental footprint of chemical processes.[17−20] This can be achieved through process intensification whereby increased productivity is paired with reduced reagent, solvent and energy consumption which can positively impact the sustainability of chemical processes under continuous flow conditions.[21] Scaling continuous reactions in flow mode is a further attractive feature as this is primarily a function of time rather than vessel size, and further concepts such as sizing-up and numbering-up allow small footprint set-ups to generate kilogram quantities of products in short periods of time.[22,23] At the same time, flow techniques are appealing for compound library synthesis[24−26] where reaction automation, inline monitoring and scaling-down are critical aspects to facilitate the synthesis of diverse sets of new chemical entities for screening campaigns which can be performed in batch or flow mode. Furthermore, reports over recent years have demonstrated how continuous flow chemistry can be a game changer for innovative transformations employing light, electricity,

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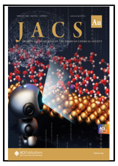
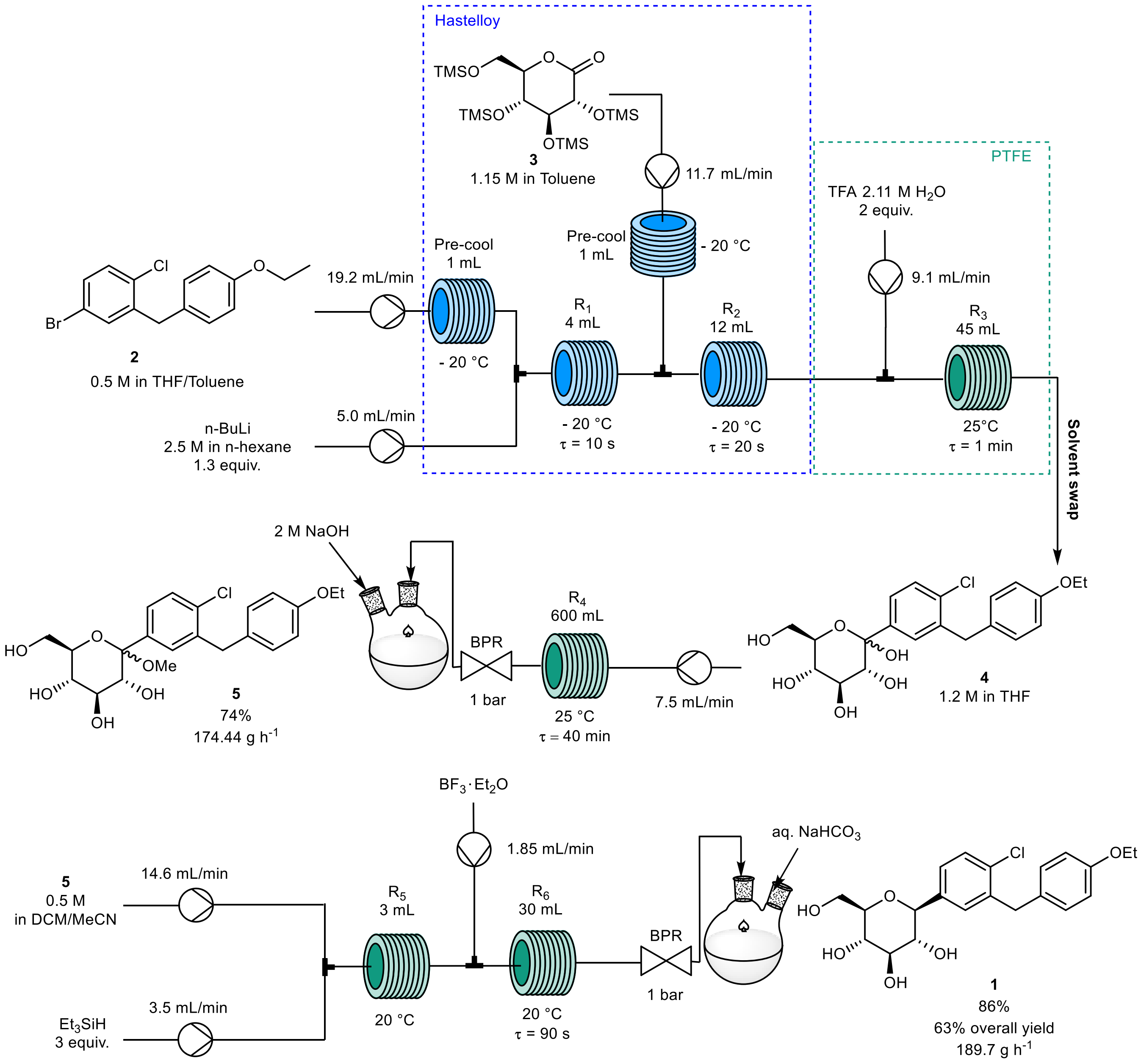


Scheme 1. Continuous Flow Synthesis of Dapagliflozin

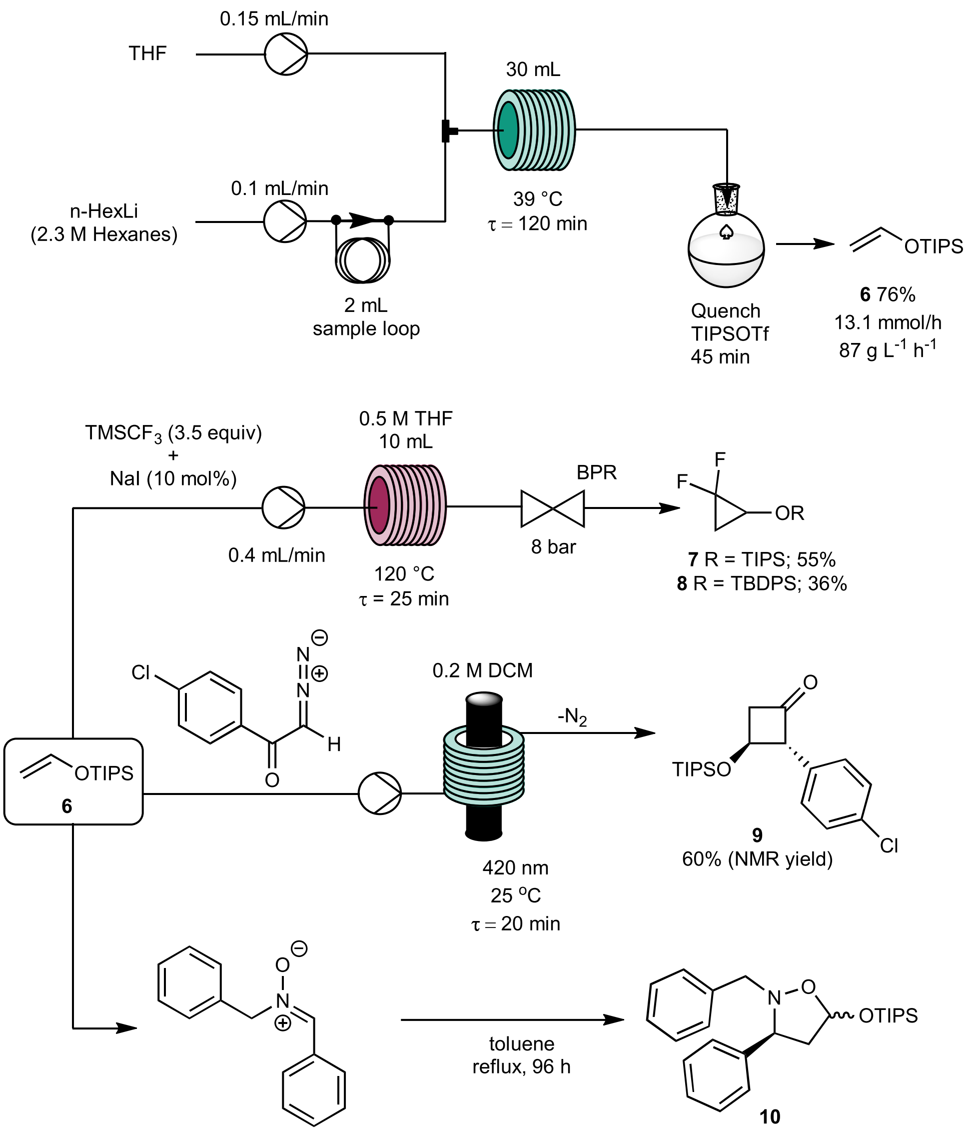


enzymes as well as mechanochemical approaches in view of increasing the sustainability of chemical reactions while expanding the diversity of synthetic methods.[27−31] Together with reaction automation and machine learning techniques, flow processing can today be exploited to autonomously optimize chemical processes providing new opportunities for chemists in academia and industry alike. A critical aspect in such endeavors is the engagement of chemists, chemical engineers as well as data scientists from academia and industry in collaborative efforts. This perspective will investigate the impact of such joint collaborations based on key case studies highlighting a variety of chemical transformations at different process scales and the synergy arising from these vital efforts. In the proceeding sections we will highlight recent collaborative case studies pertaining to the use of temperature-sensitive flow processes, electrochemistry, photochemistry, catalysis, as well as process analytical technologies and automation to assist with reaction scale-up and data capture through which we wish to demonstrate the value of such efforts in advancing the field and impacting training and innovation. Sharing expertise from both academia and industry will not only demonstrate how autonomous end-to-end continuous manufacture and automated high-throughput reaction screening can be achieved in flow mode, but it also highlights new frontiers *via* closed-loop self-optimization and dynamic experimentation for process development enabling the transition of academic research to industrial applications. It is hoped that this account highlights these opportunities to a wide audience while reinforcing the need and value of collaborations across the boundaries of traditional academic and industrial research and development programs.

■ THERMAL CHEMISTRY

Temperature control for chemical reactions is often crucial for a successful outcome. One of the main benefits of continuous flow

Scheme 2. Flow-Based Lithiation Studies of Tetrahydrofuran (THF)

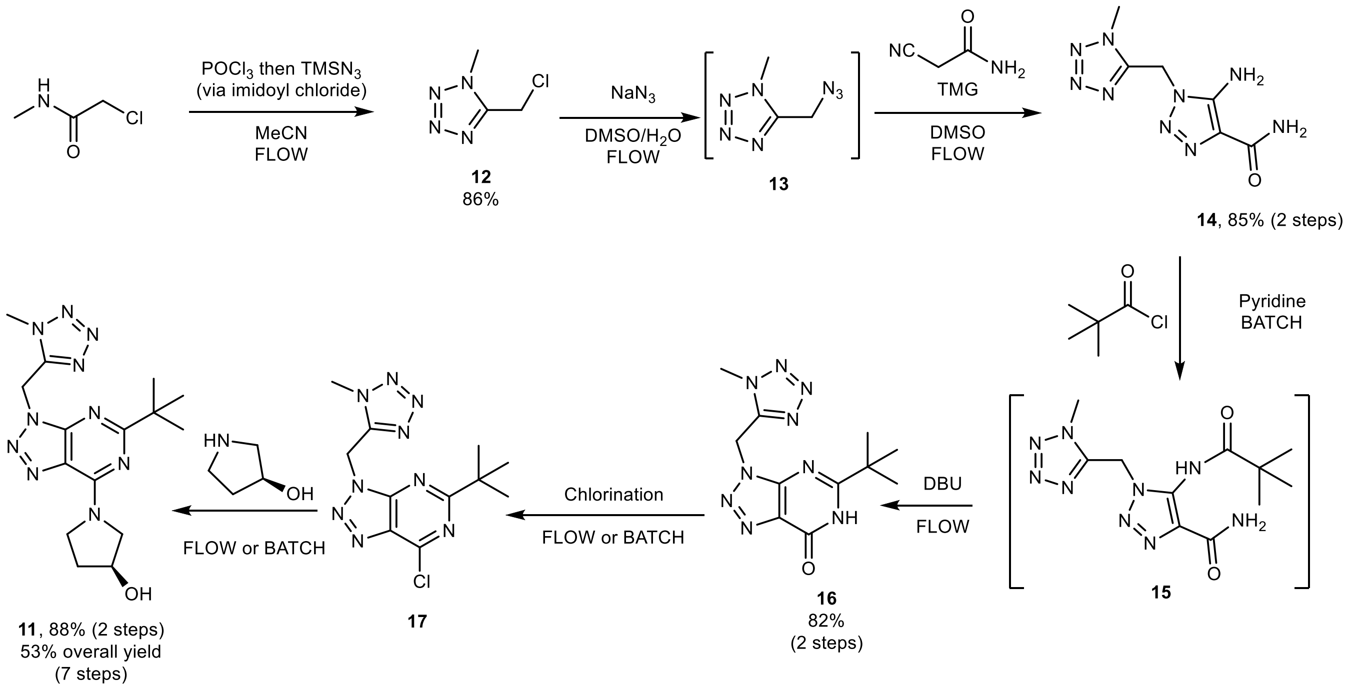


chemistry is its superb heat transfer capabilities.[32,33] Due to the high surface area to volume ratio provided by the reactor channels, superior heat transfer is possible leading to shorter reaction times and fewer impurities.[3,34] This phenomenon was observed by Sun and co-workers from Shenyang Pharmaceutical University when collaborating with the Lunan Pharmaceutical Group. The team developed a continuous flow process for the synthesis of dapagliflozin **1** which is a selective inhibitor of sodium-dependent glucose cotransporter 2 (SGLT2).[35,36] This drug has been used to treat type-2 diabetes, heart failure, and chronic liver disease.[37−39] The traditional batch synthesis requires low temperatures of −78 °C to perform a Br/Li exchange on **2** using *n*-BuLi which is problematic as it adds cost to the process.[40] The group envisioned a fully continuous flow process from commercially available starting materials, aryl bromide **2** and TMS-protected gluconolactone **3**.

The first step of the synthesis involves reacting aryl bromide **2** with *n*-BuLi (Scheme 1). To evaluate the possibility of using higher temperatures quenching studies with methanol were performed generating the dehalogenated product. This led to finding that −20 °C was the optimal temperature, with a short residence time of 10 s. A slight excess of base was required (1.3 equiv), achieving a yield of 98%. With this understanding, the next step was to telescope with *C*-arylation reaction by pumping compound **3** (1.4 equiv) into the reactor with a residence time of 20 s followed by a deprotection step to yield compound **4** in a residence time of 1 min. The methoxylation step was performed in flow after a solvent swap to tetrahydrofuran (THF) generating compound **5** in a 74% and throughput of 174.4 g h^{-1}The final reduction step to obtain dapagliflozin **1** was performed in a separate continuous flow reactor with the addition of triethylsilane and boron trifluoride etherate which avoided exposure to moisture and air. Ultimately, a residence time of 90 s and ambient temperature (20 °C) were ideal conditions for this transformation. Including the semibatch crystallization step a throughput of 189.7 g h^{-1} was achieved to produce the active pharmaceutical ingredient (API) in an 86% yield and an overall purity of 99.83%.

In 2025, Pfizer and the Baumann group based in University College Dublin partnered up for the exploration of lithiation based THF fragmentations.[41] This approach was desirable as the availability of THF as a commodity solvent would facilitate its conversion into a synthetically valuable chemical building block. Generation of a lithium enolate from THF and alkyl lithium

Scheme 3. Application of Flow Techniques in the Scale Synthesis of API 11



bases is known as a competitive process even at low temperatures with the evolution of ethylene gas as a byproduct.[42] By elevating the temperature, this lithium enolate is readily formed. Initial batch studies were conducted by reacting THF with lithium bases (*n*-BuLi or *n*-HexLi) and the enolate was trapped with various silicon-based electrophiles. Triisopropylsilyl triflate (TIPSOTf) was the preferred electrophile generating silylenol ether **6** in yields of 66% and 61% when using *n*-BuLi and *n*-HexLi respectively. Due to comparable yields *n*-HexLi was chosen as the base of choice as it is the industrial alternative to *n*-BuLi due to its decomposition product being hexane, rather than butane gas. When transferred to continuous flow, a design of experiment (DoE) study was performed, using MiniTab, to identify the optimal residence time and temperature. The model predicted an optimal residence time of 120 min at a temperature of 39 °C to correspond to a yield of 78%. Under these conditions, the experimental isolated yield of 76% closely matched the predicted yield of **6** (Scheme 2). These conditions produced silylenol ether **6** with throughput of 13.1 mmol h^{-1} which equates to a space-time yield (STY) of 87 g L^{-1} h^{-1}. To demonstrate the robustness of the process, a longer run was performed over a 3-h period leading to a consistent yield of 65–70% at steady state.

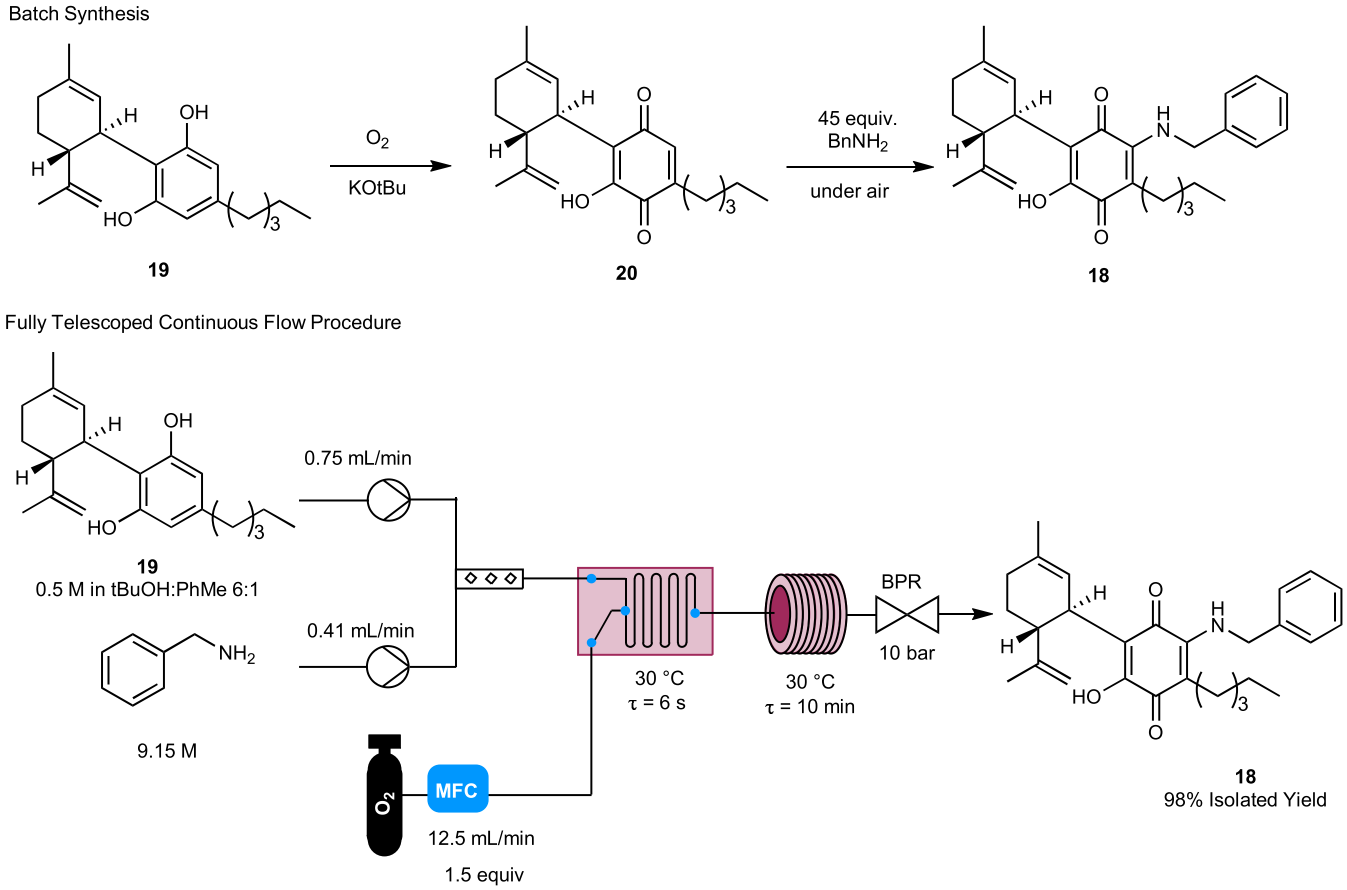
With the continuous flow synthesis of the silylenol ether established, various cycloaddition reactions were trialed to demonstrate the synthetic utility of **6**. A [2 + 1] cycloaddition with various carbenes was performed generating **7** and **8** in acceptable isolated yields, whereas a photochemical [2 + 2] reaction was performed via a ketene intermediate forming cyclobutanone **9** in 60% yield. Finally, a [3 + 2] cycloaddition of a nitrone and silylenol ether **6** formed isoxazolidine **10** in 49% yield.

In the pharmaceutical industry, continuous flow chemistry continues to be explored as a possibility to aid the synthesis of APIs.[43] Many first-generation syntheses are typically performed in batch reactors as the equipment is already available. Involving academic laboratories in the discovery of a second-generation synthesis could be utilized as a crucial step to improve the process. This approach was used by Roche in a collaboration with the Kappe group from the University of Graz.[44,45] The API of choice was a cannabinoid receptor type 2 (CB2) agonist RG7774 (**11**) which is used to treat diabetes. The original procedure involves an 8-step synthesis with the main fault of the synthesis lying with the final step involving an alkylation step leading to poor regioselectivity and an overall yield of 27%.

A revised synthetic route was proposed reducing the procedure to 7 steps, but it contained multiple potentially high-energy intermediates, hence continuous flow technology was considered to minimize the hazards associated with the process.[46,47] The initial step of the synthesis was the formation of tetrazole **12**, which had already been established into a continuous flow process (Scheme 3).[48] The next step was to form azide **13** followed by a *in situ* cycloaddition to generate the highly energetic compound **14**. A combination of a plug flow reactor (PFR) and continuous stirred tank reactor (CSTR) proved to be the most optimal setup, affording compound **14** in a yield of 79% and throughput of 9.5 g h^{-1}. A simulation for a potential scale-up of the three steps shows that this continuous flow process is a viable option producing a yield of 88% and a throughput as high as 8.9 kg h^{-1} of **14**.

The subsequent step in the synthesis involved a *N*-pivaloylation performed in batch due to solubility issues to reach compound **15**, followed by a continuous flow cyclization reaction at 190 °C generating compound **16**. The solvent of choice for this step was MeCN and through the use of a BPR (backpressure regulator) set to 20 bar the solvent could be superheated, allowing the transformation to proceed in a 15 min residence time with a throughput of 9.45 g/h. Compound **16** was chlorinated using $POCl_3$ and in a residence time of 5 min an 86% yield of **17** was achieved with an high STY of 2.68 kg L^{-1} h^{-1}. The final step of the new synthesis was an S_NAr reaction coupling **17** with 3-(*S*)-hydroxypyrroldine. API **11** was isolated in 88% yield and a HPLC assay of 98%. The overall yield over 7 steps was 53% which almost doubled the original value.

Scheme 4. Flow-Based Synthesis of 18 Using Molecular Oxygen Gas



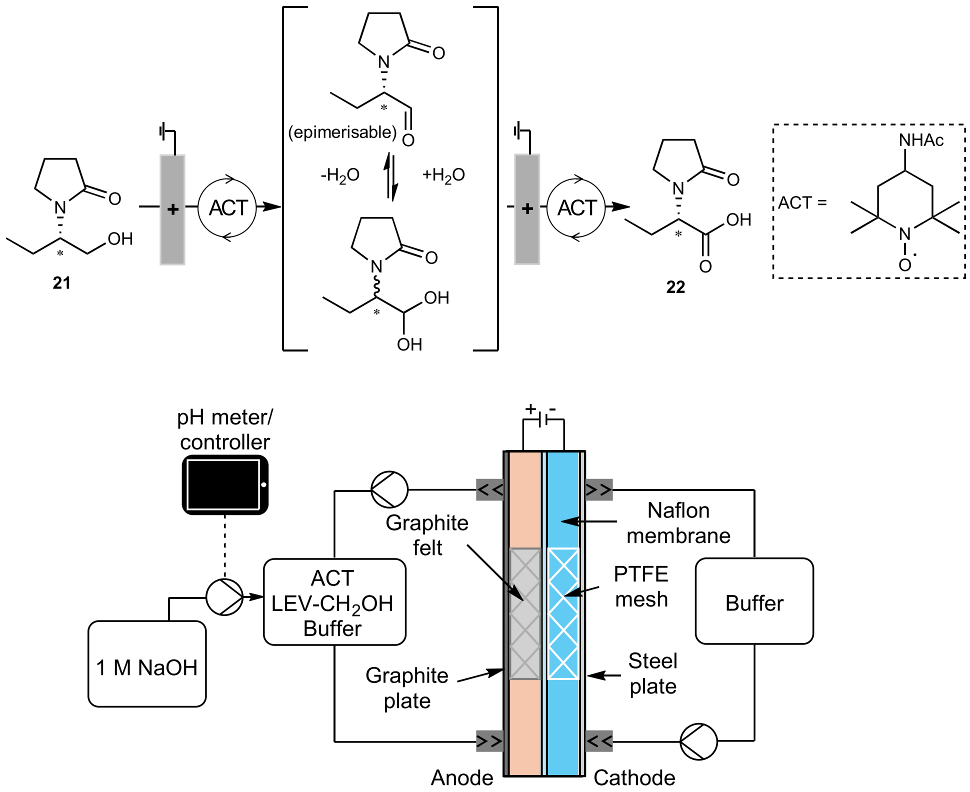
Ultimately, this work highlights the potential of continuous flow processing to enhance yield, safety, and process control in the large-scale manufacture of complex pharmaceutical intermediates.

Oxidation reactions represent another fundamental transformation in the pharmaceutical industry, making up for approximately 30% of all reactions, second to polymerizations.[49] The greenest and most inexpensive oxidant available is molecular oxygen.[50] However, it is underutilized when it comes to API manufacturing due to safety concerns with the risk of explosion or fire to occur.[51] Furthermore, aerobic oxidations using O_2 under batch conditions tend to be mass transfer limited, resulting in long reaction time and poor yields.[52] Continuous flow chemistry can overcome this through enhanced gas−liquid mass transfer enabled by the high surface-to-volume ratio associated with microreactors.[33]

In 2025, the Kappe group partnered up with Lonza AG to perform a continuous flow aerobic oxidation to generate etrinabdione **18** (Scheme 4).[53] Etrinabdione is currently in clinical trials for treatment of peripheral artery disease and can be derived from naturally occurring cannabidiol (CBD) **19**. When CBD is oxidized in the presence of base and air it forms quinone HU-331 **20** which can undergo a nucleophilic addition of benzyl amine to yield the desired API **18**. The original batch protocol, proposed by Muñoz for the synthesis of HU-331 **20** suffers from low reaction concentrations (0.044 M) due to the low solubility of KO*t*Bu in toluene.[54] To establish a more sustainable and industrially applicable procedure, higher concentrations were required to meet product demands. The solvent system was thus altered to mixture of *t*BuOH/PhMe (6:1), which had a higher solubility tolerance for the base allowing the concentration to be increased to 0.5 M when performed in continuous flow. Pure oxygen was utilized to offer the greatest reaction efficiency possible, and this was delivered into the system using a mass flow controller (MFC). Using a Modular MicroReaction System (MMRS) equipped with a FlowPlate Lab reactor, which contained 70 mixing elements (volume = 0.24 mL), the oxidation reaction was completed in a residence time of 6 s achieving 99% isolated yield. An inline quench using HCl (2.5 equiv.) was then incorporated into the setup to achieve 99% isolated yield of **20** and a STY of 43.8 kg L^{-1} h^{-1} (oxidation residence time 4.4 s).

The next step was to develop a continuous flow protocol for the nucleophilic addition of benzyl amine to **20**. The original batch procedure required 45 equiv of benzyl amine and up to 18 h of reaction time. By increasing the reactor volume to 11.6 mL, **18** could be produced in 99% yield in a 10-min residence time. A fully telescoped flow process was then implemented, providing **18** in an overall yield of 98%. The greenness of the flow procedures was compared to the original batch procedure. Close to quantitative yields were achieved for both steps under continuous flow compared to the batch procedure achieving 74 and 56%, respectively. When considering the process mass intensity (PMI), continuous flow drastically outperformed the batch procedure with the first step to synthesize **20** in batch scoring 787 compared to 39 *via* flow. When synthesizing **18**, both flow procedures (nontelescoped and telescoped) outperformed batch scoring 62 and 85 vs 1856, respectively. These results highlight significant reductions in waste generation and process costs, emphasizing the potential of continuous flow

Scheme 5. Electrochemical Oxidation of 21 to 22 (Top)[a]



[a]Schematic of divided flow cell setup (bottom).[55].

strategies for the scalable and sustainable production of pharmaceutical intermediates.

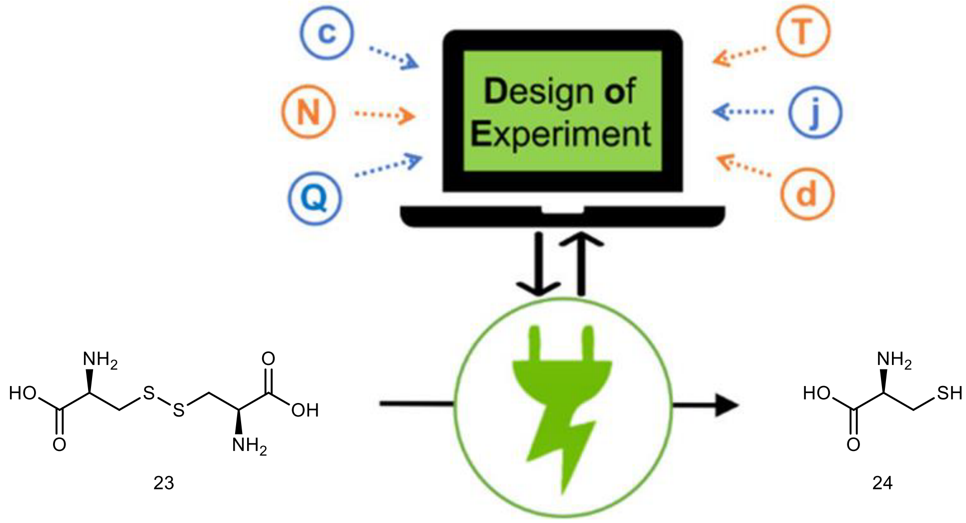
■ ELECTROCHEMICAL REACTIONS

Work from the Stahl group at the University of Wisconsin, in collaboration with AbbVie, investigated the use of continuous flow electrochemistry for the synthesis of Levetiracetam (LEV).[55] LEV is a globally used antiepileptic drug.[56] To address the challenge of maintaining enantiopurity, the group developed an electrochemical method for the oxidation of LEV-CH_2OH **21** to LEV-CO_2H **22** using 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxyl (ACT) as a catalytic redox mediator.[57] However, batch reactions suffered from low reaction rates and drops in enantiomeric purity on larger scales, prompting the group to translate the process to continuous flow. The slow flow rates under single-pass operation were insufficient for the catalytic ACT system.[58] To overcome this, the group explored a recirculation approach for flow-based electrolysis (Scheme 5).

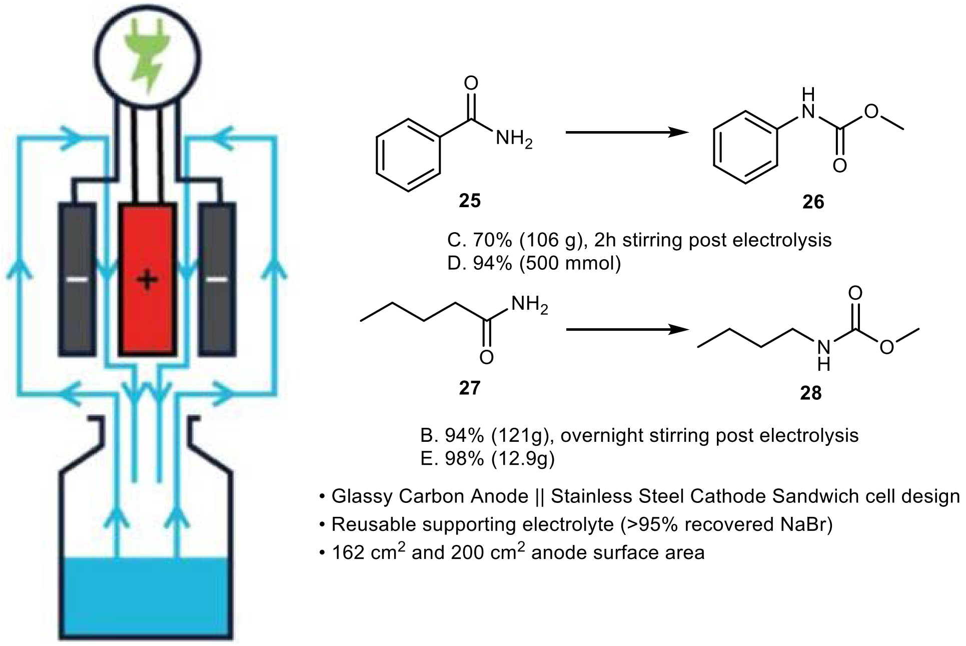
A commercially available parallel-plate electrolysis cell was used, featuring a porous graphite felt (GF) anode, a stainless-steel plate cathode, and a PTFE spacer to construct an undivided flow cell (UDFC). The initial batch reaction required 11 h and resulted an enantiomeric retention of 92% in the LEV-CO_2H product **22**. Initial flow experiments with the UDFC achieved complete conversion in just 1.2 h and a significant improvement in enantiomeric retention 97%. Lowering the reaction pH to 8 further improved enantiomeric retention to 98% but yielding only 50% product in the same 1.2 h period. The group also investigated a divided flow cell (DFC) configuration, using a Nafion 324 membrane. However, the DFC initially showed poor performance due to acidification. By maintaining the pH with titration, the group optimized the DFC setup, achieving a 92% yield in just 0.6 h with >99% enantiomeric retention. Further studies compared the performance of batch, UDFC, and DFC configurations under identical electrode sizes and conditions. The DFC achieved a current density of 250 mA at a constant potential of 0.8 V vs Ag/AgCl—twice that of the UDFC and twenty times higher than batch. This improvement is attributed to the forced flow of anolyte through the graphite felt anode in the DFC, compared to the UDFC, where only half the solution passes by the anode, and batch, where interaction is even lower. Both UDFC and DFC showed significantly improved *ee* retention over batch, with virtually no loss of enantiopurity at pH 8−9, due to faster reaction rates reducing the time available for epimerization.Through in-depth investigation of reaction conditions, the group successfully scaled the process to 200 g of LEV-CH_2OH **21** using the Electro MP Cell, which accommodates a GF electrode area of 100 cm^2. The oxidation was conducted at a constant current density of 300 mA cm^{-2}, resulted in enantiomeric LEV-CO_2H **22** in 91% isolated yield with 97.3% ee retention over 4.5 h. The DFC reactor achieved a throughput of 44.5 g h^{-1}, a substantial improvement over the previously reported batch throughput of 1.4 g h^{-1} on a 40 g scale.

L-Cysteine **24** is a widely used amino acid with diverse applications however, its commercial production presents numerous challenges, particularly in purifying complex reaction mixtures.[59] One promising alternative is the electrochemical synthesis of L-Cysteine **24** via the reductive cleavage of its dimer, L-Cystine **23**, which itself can be obtained through bacterial fermentation.[60] Building on earlier work by Walsh and coworkers,[61] and Fritz-Langhals,[62] the Waldvogel group in collaboration with Wacker Chemie, employed a design of experiment (DoE) approach to optimize and scale up the electrochemical reduction of L-Cystine **23** to L-Cysteine **24**

Scheme 6. Utilizing DoE to Optimize the Electrochemical Synthesis of L-Cysteine 24, Adapted from Ref [63].



Scheme 7. Electrochemical Hoffmann Rearrangement Using Sandwich Flow Cell[67]



C. 70% (106 g), 2h stirring post electrolysis
D. 94% (500 mmol)

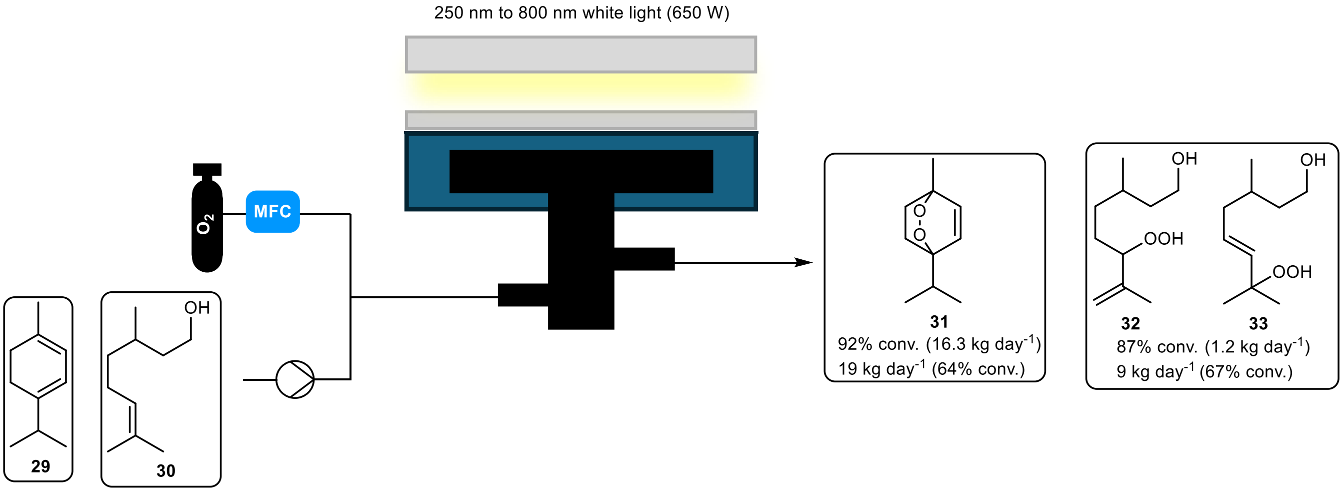
B. 94% (121g), overnight stirring post electrolysis
E. 98% (12.9g)

- Glassy Carbon Anode || Stainless Steel Cathode Sandwich cell design
- Reusable supporting electrolyte (>95% recovered NaBr)
- 162 cm^2 and 200 cm^2 anode surface area

(Scheme 6).[63] A preliminary screening of cathode materials, in batch, was first conducted to identify the most suitable electrode. Among the materials tested, zinc, tin, and lead exhibited the best performance, with zinc and tin providing the highest yields at lower current densities. However, due to severe corrosion observed with zinc and tin during electrolysis, lead was selected as the cathode material for further optimization. The DoE optimization was carried out in a divided flow cell equipped with a lead cathode, a Nafion 424 membrane separator, and a mixed metal oxide (IrO_2–RuO_2/Ti) anode. The reactor design permitted adjustment of the interelectrode gap. Using a two-level fractional factorial design, the parameters evaluated for statistical significance included current density, applied charge, temperature, L-Cystine **23** concentration, and interelectrode gap. Initial single-pass experiments resulted in a significant drop in product yield, attributed to mass-transfer limitations inherent in the slow flow rates of single-pass operation. Among the tested parameters, current density, applied charge, and interelectrode gap significantly affected the yield, whereas temperature and substrate concentration showed little influence.

Given the limitations of single-pass operation, the group implemented a recirculation mode to improve performance. In this configuration, the key variables—current density, applied charge, and number of cycles—were optimized while maintaining the smallest possible interelectrode gap 1.5 mm and an L-Cystine **23** concentration of 225 g/L. Through this approach, the yield improved from 75% in single-pass operation to approximately 92.5%. However, as L-Cystine **23** was consumed, HER (hydrogen evolution reaction) became increasingly dominant because of the high current density. To address this, a multiple-response optimization was performed to determine the applied charge that provided the best tradeoff between yield and Faradaic efficiency (FE, a measure of electrical charge efficiency: theoretical charge required with respect to total experimental charge.). A value of 2.3 F was determined to offer the most favorable balance. Operating at a current density of 100

Scheme 8. Photochemical Oxidation of 29 and 30 Using the pRS SDR[71]



mA/cm^2 until 2.3 F of charge had passed, followed by a step-down to 10 mA/cm^2, yielded a 99% product yield after a total of 2.65 F. In contrast, applying 100 mA/cm^2 for the entire 2.65 F resulted in only a 96% yield and required up to 4 F to reach full conversion. Using the DoE approach, the optimized conditions achieved a 99% yield with a 75% FE. This significantly outperformed comparable studies reporting yields of 96% and FE values of 64%. The optimized process exhibited a low electrical consumption of 0.6 kWh/kg product, compared to 3.3 kWh/kg product previously reported for the batch-based L-Cystine **23** reduction by Walsh and co-workers. Furthermore, the group successfully scaled up the process from 10 to 100 cm^2 electrode area, maintaining excellent yield and energy efficiency at larger scale. The authors additionally found that increasing the flow cell area from 10 to 100 cm^2 resulted in a decrease in Pb contamination of 45−140 to 1−13 ppm respectively, longer use of the Pb cathode further decreased the levels of contamination. Using DoE, six reaction parameters were effectively evaluated and optimized across only 34 experimental runs. The study not only demonstrated the efficiency of continuous flow electrochemical systems for fine chemical synthesis but also highlighted the value of computer-assisted optimization strategies such as DoE for both industrial and academic chemical process development.

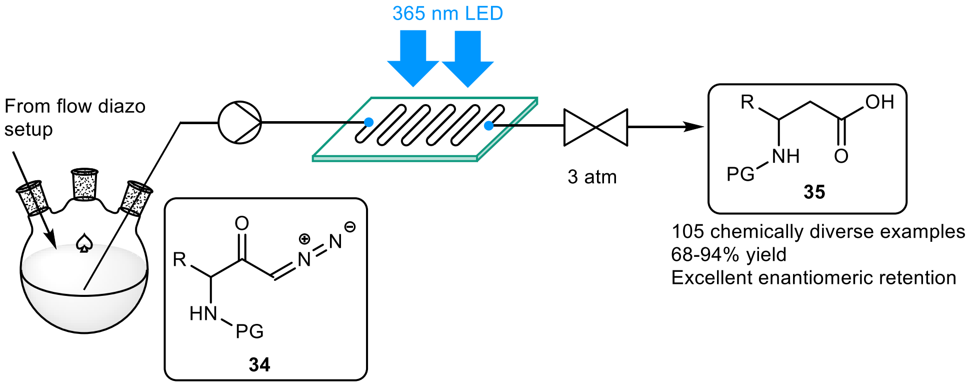
The Hofmann rearrangement is a widely used reaction in the synthesis of drug-like molecules and their intermediates. One of the first significant demonstration of this electrochemical Hofmann rearrangement was reported by the Zhang group in 2018, who showed that the method could be applied with more than 30 examples using a batch setup.[64] Subsequent developments were made by the Waldvogel group (2024)[65] and the Kappe group (2023),[66] who both adapted the reaction for continuous flow operation (Scheme 7). The Waldvogel group presented over 20 examples with good to excellent yields, while the Kappe group used an in-house created spinning electrode reactor that addressed the mass-transfer limitations inherent in single-pass systems. Building on these advancements, the Waldvogel group, in collaboration with Boehringer Ingelheim Pharma, recently developed an electrochemical method for the hectogram-scale synthesis of carbamates.[67] The reactor, known as the Condias SZ100 Sandwich Cell, consisted of two undivided but separate compartments, with both sides of the anode functioning as the center. This configuration effectively doubled the usable anode surface area. The cell incorporated a single glassy carbon anode (81 cm^2) positioned between two stainless-steel cathodes, resulting in a total anode surface area of 162 cm^2.

Using this reactor configuration (initially operating with only one side of the anode, 81 cm^2), the team applied their previously established conditions for the electrochemical rearrangement of benzamide. The reaction yielded methyl *N*-phenylcarbamate **26** in 62% isolated yield—approximately two-thirds of the yield obtained in the earlier study using a smaller 12 cm^2 anode. Consequently, the reaction parameters were reoptimized for the new reactor to achieve both high-yielding and high-productivity conditions for the conversion of benzamide **25** and valeramide **27**.

For the transformation of benzamide **25** to methyl *N*-phenylcarbamate **26**, two optimized methods were developed, designated as Method **A** and Method **C**. Method **A**, designed for maximal product yield, achieved 88% isolated yield with a productivity of 26 mmol/h. Method **C**, optimized for throughput, afforded a slightly lower yield of 81% but doubled productivity to 52 mmol/h. For valeramide **27** conversion to methyl *N*-butylcarbamate **28**, a single method (Method **B**) was developed and optimized for yield. Under these conditions, the reaction delivered a 98% yield and a productivity of 46 mmol h^{-1}. In all cases, reactions were followed by a 2-h post electrolysis stirring period to ensure completion. Both reactions were subsequently scaled to the hectogram scale (1 mol scale), utilizing the full 162 cm^2 anode area. Under Method **C**, methyl *N*-phenylcarbamate **26** was obtained in 70% isolated yield (106 g) after a 2-h poststirring period, while Method B afforded methyl *N*-butylcarbamate **28** in 94% yield (121 g) following overnight stirring. In both cases, bromide salt recovery exceeded 95%.

To further improve performance at larger scale, the group transitioned from the commercial parallel-plate reactor to a custom-built electrochemical cell featuring a 100 cm^2 glassy carbon anode and a total anode surface area of 200 cm^2 (Method **D** and **E**). Using this system, the reaction achieved yields of 94% for methyl *N*-phenylcarbamate **26** and 98% for methyl *N*-butylcarbamate **28**, with no poststirring required. Productivities increased substantially to 160 and 182 mmol/h, respectively, highlighting the effectiveness of the optimized reactor design for high throughput Hofmann rearrangements.

Scheme 9. Simplified Schematic of Photochemical Wolff Rearrangement Setup, Adapted From Ref 73



PHOTOCHEMICAL REACTIONS

The use of gaseous reagents in chemical transformations, including photochemical processes, is often desirable because of the inherently high atom economy. Scaling up such systems often requires one phase to be used in large excess to maintain adequate interfacial contact.[68] To address these challenges, the Noël group developed the rotor-stator spinning disc reactor (RS SDR). By integrating a quartz glass window, photochemical operation for gas−liquid and gas−liquid−solid reactions was possible.[69,70] Using this photochemical rotor-stator spinning disc reactor (pRS SDR), the team demonstrated efficient photochemical oxidation of α-terpinene to ascaridole with a productivity of 1.1 kg day^{-1}.[70] This study revealed that light intensity was a limiting factor for further productivity. To overcome this, the group collaborated with Signify to develop a custom high-power light source specifically matched to the reactor system.[71] This light source developed by Signify delivers a maximum optical output of 652 W (from a 1750 W electrical input) across a 250−800 nm white light spectrum. With a circular illuminated area of 176.6 cm^2 (Scheme 8).

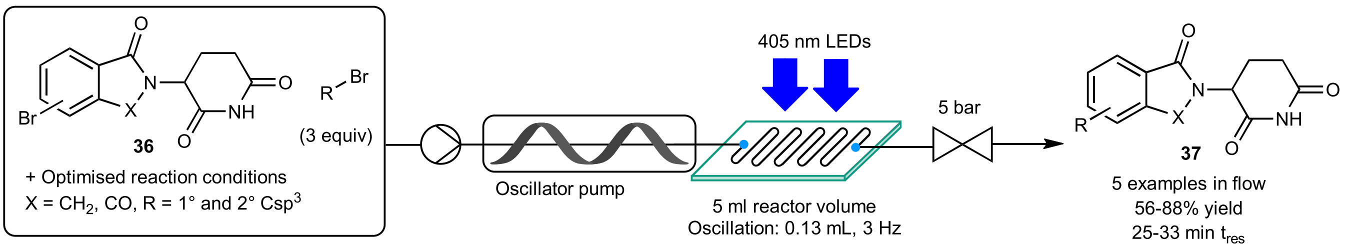
To assess the capabilities of the pRS SDR combined with the new light source, two benchmark gas−liquid photooxygenation reactions were chosen: (1) the [4 + 2]-cycloaddition of α-terpinene **29** with singlet oxygen to form ascaridole **31**, and (2) the Schenk-ene reaction of β-citronellol **30** with singlet oxygen to yield two allylic hydroperoxides **32** and **33**. Both transformations are commonly used as model reactions for evaluating the efficiency of photochemical reactors and rely on Rose Bengal as the photosensitizer. In studying the [4 + 2]-cycloaddition, the group found that under optimized conditions, a conversion of 92% and a productivity of 16.3 kg day^{-1}. Operating at a higher flow rate (25 mL s^{-1}) increased productivity to 19 kg day^{-1} but lowered conversion to 64%. For the Schenk-ene reaction of β-citronellol **30** the overall conversion was lower than that observed for α-terpinene **29** oxidation. Increased light intensity and rotor speed had little effect on yield, suggesting an additional kinetic limitation beyond photon flux and mass transfer. Only when reducing the flow rate to 5 mL s^{-1}, thereby increasing residence time, did conversion rise to 71%. This behavior suggests that the Schenk-ene mechanism involves a higher energy transition state. Under optimized parameters, the group achieved an 87% conversion and 1.2 kg day^{-1} productivity. Productivity could again be increased to 9 kg day^{-1}, though with a lower conversion of 67%.

Overall, this collaborative effort between the Noël group and Signify demonstrates an impressive advance in photochemical gas−liquid reactor design and performance. The pRS SDR effectively overcomes mass transfer limitations inherent to gas−liquid systems, and integration with a high power, custom light source further enhanced productivity from 1.1 to 19 kg day^{-1}. This combination highlights the potential of engineering-driven photochemistry for efficient, scalable oxidative transformations.

The Volochnyuk group, in collaboration with Enamine Ltd., developed an upscaled pseudotelescopic Arndt−Eistert α-amino acid homologation process for the synthesis of β-amino acids. β-Amino acids represent an important class of compounds with significant biological potential, where their incorporation can strongly influence pharmacological activity.[72] These compounds can be accessed from natural α-amino acids through the Arndt−Eistert synthesis, *via* the generation of diazoketone intermediates that undergo a Wolff rearrangement to yield the corresponding β-amino acid analogues.[73]

The group aimed to address several long-standing challenges associated with this transformation namely safety concerns, limited substrate scope, and inefficiencies by employing continuous flow technology. Their work focused on the photochemically induced Wolff rearrangement step. While the Kappe group had previously reported a fully telescoped Arndt−Eistert synthesis on the laboratory scale, the Volochnyuk team encountered difficulties when translating the process to pilot scale. Specifically, the formation of the diazoketone intermediate required an additional batch step, prompting the development of a pseudotelescopic approach that combined batch preparation of the diazoketone with continuous flow photo Wolff rearrangement (Scheme 9). To establish baseline performance, the researchers first utilized the UOSlab Test Flow Photoreactor to optimize reaction parameters on small scale. They achieved over 90% conversion of a model substrate with minimal side product formation. The process was then transferred to a pilot scale UOSlab FlowReactor UF365/450, where further optimization was performed to account for larger scale flow dynamics. Using a 0.1 M solution in THF containing 10 equiv of water and phenylalanine diazoketone **34** as the model substrate, the group examined the effects of flow rate, temperature, and irradiation intensity. The optimized conditions were then applied to explore the reaction scope, affording 105 examples of structurally diverse β-amino acids across a 50−1000 g scale, with isolated yields ranging from 68 to 94%. The method displayed broad functional group tolerance and succeeded even with substrates traditionally considered challenging for the Wolff rearrangement. Notably, several weakly reactive or unstable intermediates that typically fail under silver nitrate mediated thermal Wolff conditions performed well under the photochemical flow setup. Although a fully telescoped pilot scale

Scheme 10. Csp3−Csp2 Reductive Cross-Coupling to Form 37 Using Oscillatory Flow Setup[74]



Arndt−Eistert synthesis could not be realized due to limitations in the diazoketone formation step, the work nonetheless represents a major achievement in scaling the photochemical Wolff rearrangement.

Flow chemistry provides additional advantages for photochemical transformations, including enhanced light penetration, improved heat transfer, and scalability. Motivated by these benefits, the Kappe group, in collaboration with Merck, for the synthesis of thalidomide analogues as potential Proteolysis-targeting chimeras (PROTACs) building blocks.[74] PROTACs are an important class of molecules capable of selectively targeting and degrading proteins of interest.[75] One of the most widely used ligands in PROTAC design is the thalidomide moiety, which binds to the E3 ligase cereblon (CRBN). However, the synthesis of thalidomide derivatives is often step- and yield-inefficient.[76] Cross-coupling reactions represent an attractive strategy for such functionalization, yet conventional reductive couplings typically require stoichiometric amounts of reducing agents, limiting their scalability. A promising alternative is the nickel−photoredox C(sp^3)−C(sp^2) cross-coupling developed by the MacMillan group in 2016, which uses silyl radicals as reductants.[77]

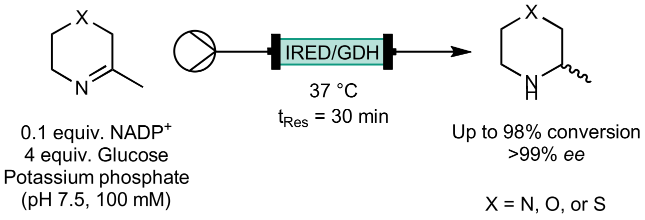
While metallaphotoredox reductive couplings had previously been demonstrated, most examples were limited by the handling of solid reagents and the formation of insoluble byproducts. To address these challenges, the Kappe group utilized an oscillatory flow reactor (Creaflow HANU 2X 5) designed to manage slurry reactions—through imposing a periodic back-and-forth motion the reactor creates intense mixing within a more compact reactor design (Scheme 10). The study began by optimizing the cross-coupling reaction under batch conditions. Four thalidomide-derived ligands were investigated, all reaching full conversion after 5 h of irradiation. Using one substrate as a model, the reaction was then adapted for continuous flow. However, the initial attempts resulted in severe sedimentation, forming a thick paste that obstructed flow through the reactor. To prevent this, additional optimization was carried out in batch mode. These studies revealed that the addition of 10% DMA to DME as cosolvent and the reduction of Na$_2$CO$_3$ particle size improved both yield and dispersion stability, rendering the reaction more amenable to flow. With these adjustments, the flow process ran smoothly without sediment formation, enabling stable, continuous operation. Process optimization targeted photocatalyst loading, temperature, and residence time. Increasing the photocatalyst loading from 0.1 to 1 mol % significantly improved yield from 40 to 75%. Although raising the reaction temperature enhanced conversion, it decreased selectivity. Extending the residence time from 25 to 33 min further improved the yield to 88%. To evaluate process robustness, a continuous 5.5-h run was performed under steady-state conditions. The product yield remained consistent, fluctuating by only ± 3%, furnishing 1.48 g (81%) of the product as its HCl salt. The optimized conditions were next applied to four additional thalidomide analogues on a 2 mmol scale, affording products in 56−75% yield with residence times of 25−33 min. Through careful optimization and the strategic use of an oscillatory flow reactor, the Kappe group successfully developed a continuous nickel−photoredox C(sp^3)−C(sp^2) cross-coupling protocol compatible with thalidomide derivatives. The process overcomes long-standing issues related to solid formation and base sensitivity, achieving high yields and stable operation under extended flow conditions. This work highlights the potential of metallaphotoredox catalysis in scalable PROTAC synthesis and establishes a valuable framework for future ligand diversification.

BIOCATALYSIS AND METAL CATALYSIS IN FLOW

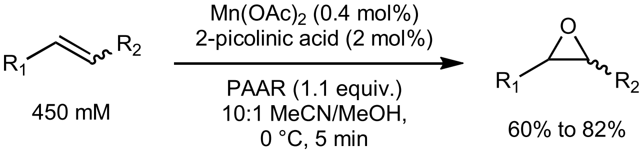
The synthesis of products using enzymes (fungal or bacterial) is known as biocatalysis and is an area of research that has received tremendous attention in recent years across both academic and industrial disciplines.[78] The combination of continuous flow and biocatalysis is a natural progression due to the unique advantages that flow has to offer, such as increased scalability relative to batch processes.[79] Continuous flow biocatalysis typically involves the immobilization of an enzyme onto a solid support and loading into packed-bed reactors (PBR).[20,80] Once immobilized, the enzymes experience increased stability, recyclability, and reusability compared to the soluble enzyme.[81] Immobilized enzymes used in batch mode often see a deleterious effect on enzyme activity due to mass-transfer limitations.[82] In flow, this issue can be overcome, as the relationship between the enzyme and substrate is effectively reversed, resulting in a constant excess of biocatalyst relative to the substrate passing over it.[83] The following section will discuss cases where academic and industrial partnerships have developed continuous biocatalytic as well as metal-catalyzed flow processes.

Heterocyclic chiral amines are highly sought-after products due to their applications in pharmaceuticals and fine chemicals. However, current methods, which traditionally rely on metal-locatalysts or high-loading organocatalysts, often require harsh conditions, generate significant waste, and have a high environmental impact, making them unsuitable for industry seeking to meet sustainability criteria.[84] The Paradisi group, in collaboration with inSEIT AG and Boehringer Ingelheim, developed a continuous flow process that uses immobilized IREDs for the synthesis of chiral amine heterocycles (Scheme 11).[85] Initial work focused on screening six IREDs against a panel of model substrates to evaluate those with the highest activity. Immobilization strategies were then pursued. Notably, bioinformatic analysis tools were used to streamline this process and demonstrate the potential cost reduction for campaigns. Investigations into immobilization yield, activity, efficiency, and reusability were conducted to determine the optimal platform that could be adopted by industry. Upon finding the best setup,

Scheme 11. Continuous Flow Biocatalytic Reduction of Heterocyclic Imines to the Corresponding Amines



Scheme 12. Batch Investigations for the Epoxidation of Various Alkenes Using $Mn(OAc)_2$, 2-Picolinic Acid, and Resin-Synthesized Peracetic Acid/10 wt % KOH/AcOH (PAA_R)



batch experiments with immobilized enzymes under optimal conditions provided one of the model substrates in over 90% conversion across ten cycles. Furthermore, no leaching of the IREDs was observed. Translation to continuous flow was achieved by evaluating the best ratio of primary to auxiliary recycling enzyme. At a substrate concentration of 10 mM, yields of up to 98% were achieved; at higher substrate concentrations of 100 mM, conversions of up to 61% were realized. Even at lower conversions, the space-time yields were high (up to 20.7 g L^{-1} h^{-1}), with high stability of the biocatalyst (up to 20 column volumes). Stereochemical purity of the generated chiral amines was found to be greater than 99% *ee* for both (*S*)- and (*R*)-selective IREDs. Finally, sustainability parameters such as *E*-factor were considered, and the process was found to be viable by industrial standards (if water was omitted from the calculation) based on the simple *E*-factor.[86]

Epoxides are versatile functional handles that frequently appear as intermediates in drug syntheses. Their tendency to undergo hydrolysis and nucleophilic addition is well-established.[87] Alkenes are obvious precursors for epoxide formation, but traditional epoxidation methods typically rely on stoichiometric oxidants such as 3-chloroperoxybenzoic acid. Such reagents pose stability and safety challenges, particularly during scale-up.[88] Catalytic epoxidation methods using manganese and iron offer new routes which better align with industrial sustainability requirements. Notably, the Stack Group at Stanford University reported a homogeneous manganese-catalyzed epoxidation of alkenes employing low loadings of manganese triflate (0.4 mol %), pyridine-2-carboxylic acid as a ligand, and a base-modified peracetic acid oxidant.[89] This method affords rapid epoxide formation in as little as 5 min. However, large-scale application is limited by significant exotherms (ΔH_{rxn} = −40 to −50 kcal mol^{-1}). To overcome this limitation, researchers at Queen's University Belfast, in collaboration with Almac Pharmaceuticals, applied continuous-flow chemistry to improve the scalability and safety of this process.[90] Continuous-flow reactors handle low volumes of reactive material at any given time, mitigating risk, and allowing more effective control of exothermic reactions.

Batch studies successfully reproduced the literature precedent, and encouragingly, the less expensive $Mn(OAc)_2$ and $MnCl_2$ catalysts were also effective (Scheme 12). Differential scanning calorimetry (DSC) analysis indicated an adiabatic temperature rise of 60.5 °C, confirming that slow addition was crucial to prevent a potential runaway reaction. These findings suggested that the controlled and *in situ* generation of peracetic acid would be feasible in a flow process.

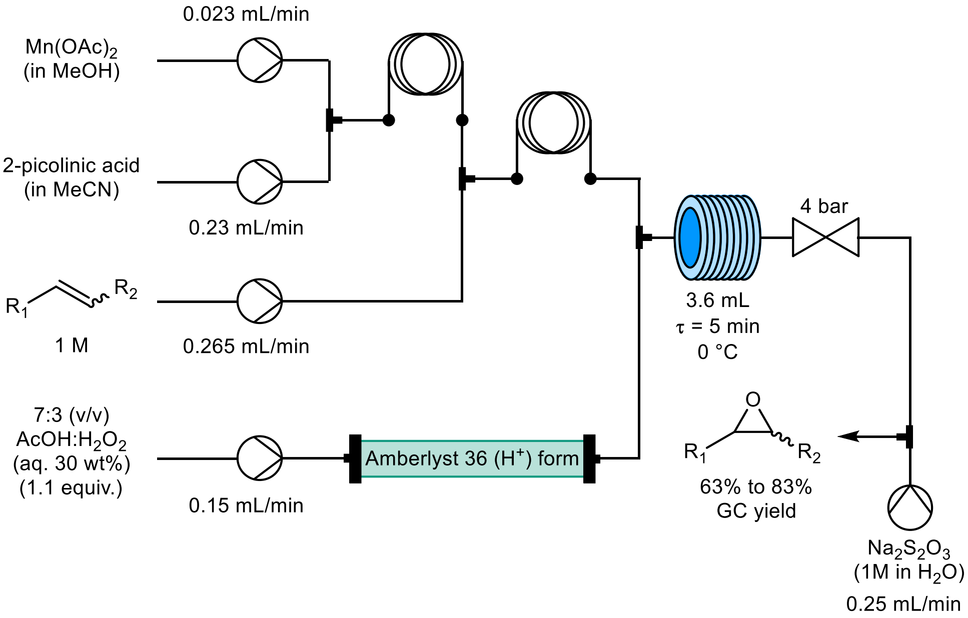
Several flow studies were conducted to evaluate the type of sulfonic acid resin and hydrogen peroxide concentration required for oxidant generation. Peracetic acid solutions were obtained in high yield and throughput using various Amberlyst resins. For safety and scalability, the optimal hydrogen peroxide concentration was determined to be 30 wt %, producing a 15 wt % peracetic acid solution in 19 min. Early flow experiments revealed gradual formation of an insoluble precipitate, likely Mn(II) polymeric species. This issue was resolved by performing the metal−ligand complexation step directly in flow. In batch, single-portion addition of the oxidant gave lower yields, prompting trials of split-ratio additions in flow, though these too underperformed. Optimization of the ligand-to-metal ratio showed that a 20:1 ratio restored yields in batch, leading to its adoption for flow studies. Subsequent optimization in flow using $Mn(OTf)_2$ (to reduce clogging and simplify operation) identified the best conditions as a 5-min residence time at 0 °C with a 20:1 ligand-to-metal ratio. The final integrated flow system combined *in situ* oxidant generation using a packed-bed reactor directly telescoped into the manganese-catalyzed epoxidation (Scheme 13). Three substrates—cyclooctene, 1-octene, and styrene—were successfully converted, affording yields of 83, 78, and 63%, respectively. Impressively, an 8-h scale up continuous run with 1-octene, produced 16.32 g of epoxide (78% yield, 2.04 g h^{-1}) without blockages.

Continuous flow reactors are well-positioned to enable chemoenzymatic cascades for producing value-added chemicals *via* telescoping.[91,92] The Paradisi group (Bern University), Novartis, and inSEIT coordinated to develop a telescoped process involving three continuous flow reactions to synthesize pyridine-containing chiral amines (Scheme 14).[93] Enantioselectivity was established using a transaminase, followed by *N*-Boc protection, and finally Suzuki-Miyaura coupling to form biaryl chiral amines. Crucially, employing water-immiscible solvents allowed solvent switching from enzymatic to chemical steps.

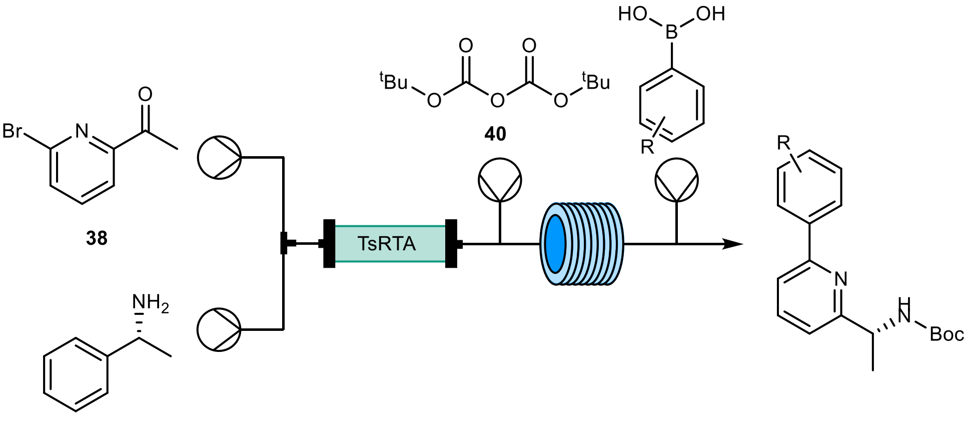
Starting with biotransformation optimization, transaminase TsRTA (*Thermomyces stellatus*) was selected for its broad activity and high enantioselectivity in batch. For sustainability, the enzyme was immobilized on EP403/S resin (Resindon ReliZyme), achieving excellent immobilization yield and 43% activity retention relative to the soluble enzyme. Continuous flow experiments showed promising 80% molar conversion in 20 minutes residence time.

Three water immiscible solvents—toluene, isopropyl acetate (iPAc), and methyl tert-butyl ether (MTBE)—were screened, all giving conversions of 44 to 58% after 24 h in batch. MTBE was chosen for continuous flow with 100 mM substrate. Although conversion in flow did not exceed 60% under varying conditions, this was acceptable since starting materials and amine donors could be recycled or carried into telescoped steps. To suppress undesirable Buchwald-Hartwig coupling of amines, both the desired amine and amine byproduct were *N*-Boc protected in flow. Optimized conditions using toluene enabled complete conversion in 30 min. The Suzuki-Miyaura coupling employed $[Pd(OAc)_2]_3$ as catalyst with heating to 100 °C in batch, successfully translated to continuous flow using a three-

Scheme 13. Continuous Flow Catalytic Epoxidation of Alkenes



Scheme 14. Forward Direction of Retrosynthesis for Fully Telescoped Continuous Flow Synthesis of Biaryl Pyridine-Containing Chiral Amines



solvent mixture with reduced catalyst and ligand loadings, achieving full conversion within 30 min at 100 °C.

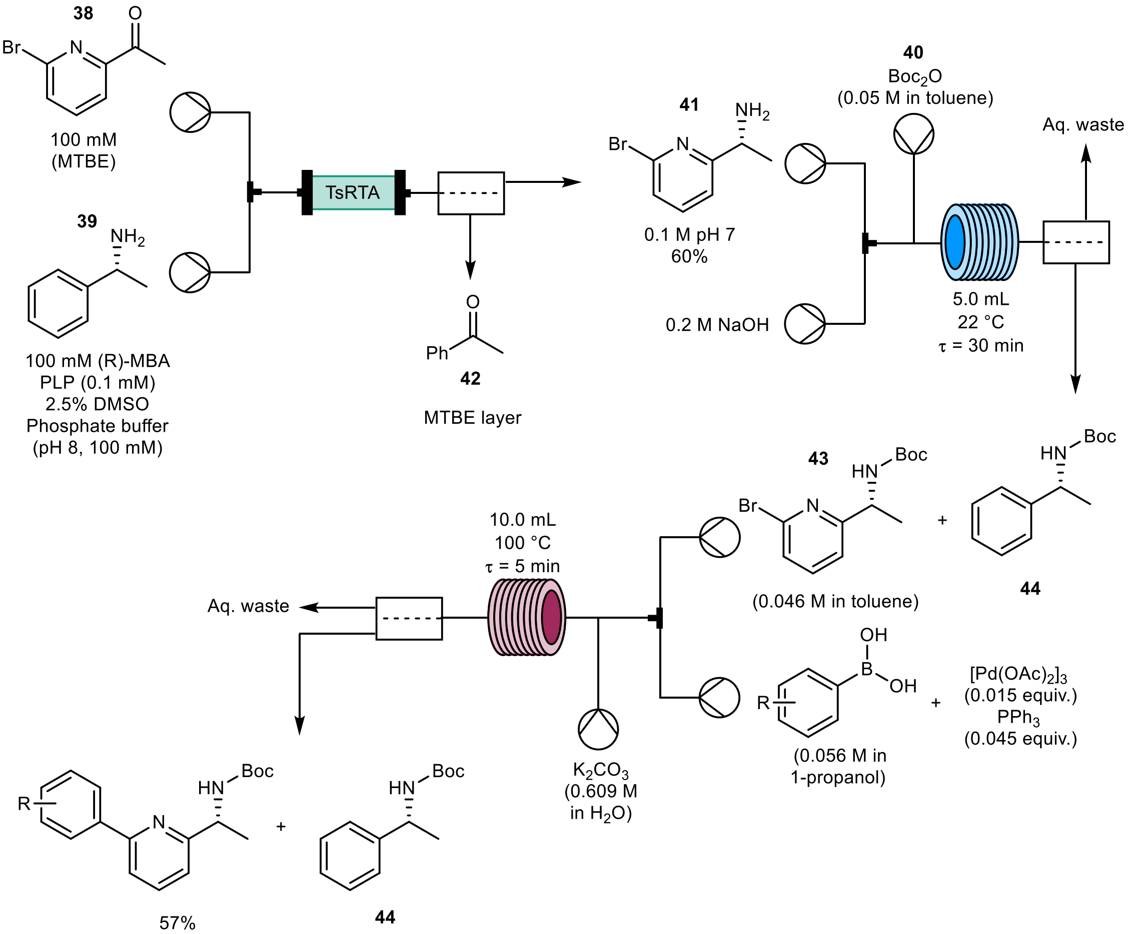
The fully telescoped system required no adjustments when connecting the three steps and operated continuously for over 50 h, delivering the final product in 57% yield with enantioselectivity >99% (Scheme 15). Space-time yields improved nearly 3-fold compared to batch (68 vs 25 mg L^{-1} h^{-1}).

■ PROCESS ANALYTICAL TECHNOLOGY (PAT)

The more analytical information that scientists have access to, the better systems can be designed, optimized, and scaled. The umbrella term, Process Analytical Technology (PAT) describes technological setups which allow chemists to analyze reactions or steps of a process and extract real time information, which can be used to adjust conditions "on-the-fly" or help identify transient intermediates which would be destroyed upon sample preparation (specifically in off-line analysis).[10] Continuous flow and PAT complement each other well, due to the ability for in-line, online, or at line analysis of the flow path. The number of publications where PAT is a key part is growing year on year and almost all the standard analytical tools used by chemists have been developed and demonstrated in continuous flow (GC, LC, LC-MS, MS, FT-IR, Raman, UV−vis, and NMR).[94] This section will look at case studies where successful collaborations between academic and industrial groups applied PAT to optimize and streamline reactions (Scheme 16A−C).

Advancements in the field of chemical digitization and fast-analysis PAT tools, such as in-line NMR or in-line FT-IR used with continuous flow reactors, have opened the gateway for fully automated (closed-loop) experimentation. For these setups to be realized, appropriate connections must be made between all components (hardware or software); such examples include central supervisory control and data acquisition (SCADA) as well as open platform communication unified access (OPC UA).[95] It is possible to envision—and in some cases, there are already good examples of—self-driving, fully automated laboratories that can be controlled remotely but operate effectively on their own accord.[96]

Scheme 15. Fully Continuous Chemoenzymatic Flow Synthesis of Biaryl Pyridine-Containing Chiral Amines

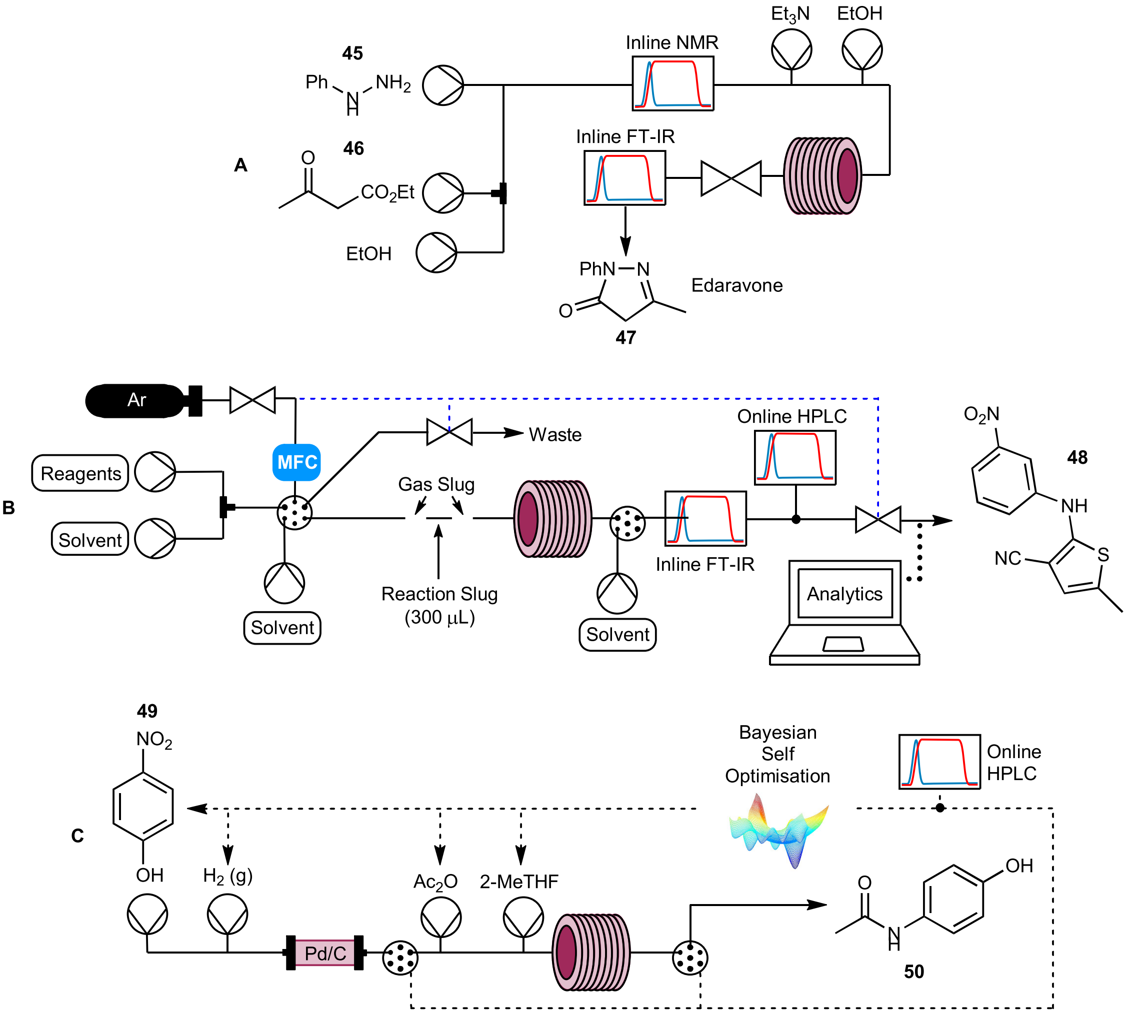


The Kappe Group, in collaboration with Boehringer Ingelheim USA, developed a closed-loop fully automated continuous flow reactor capable of optimizing a single reaction step for an intermediate toward linezolid, as well as two telescoped reaction steps for the synthesis of edaravone (Scheme 16A).[95] Multiple self-optimization algorithms were used to optimize space-time yield as well as % conversion (Latin hypercube, full-factorial Design-of-Experiment (DoE), and Bayesian-type models with comparisons between methods shown. It was also discovered that starting the optimization algorithms early and avoiding time/resources spent on preiterations was the most efficient. Furthermore, *E*-factor was also optimized by the model showing the power when these tools are combined for multiobjective optimization. Both in-line NMR and in-line FT-IR were employed as PAT tools due to their fast measurement times (~10 to 15 s) and an innovative gradient steady state check was applied which, in some cases, reduced the time to reach steady state by 1.5 reactor volumes less (typically requiring three reactor volumes). For the multistep reaction, after 85 iterations, a space-time yield of 5.42 kg L^{-1} h^{-1} was achieved, while also reducing the total equivalents of triethylamine and phenylhydrazine.

Building upon this work the Kappe Research Group and Boehringer Ingelheim USA developed an automated continuous flow reactor system which could quickly optimize a reaction using PAT, while minimizing the amount of material required (Scheme 16B).[97] As mentioned before, flow reactors often require three-reactor volumes to reach a steady state optimum, but this could hinder their use for this task, especially if the material required is costly or difficult to synthesize. Furthermore, reducing the amount of material also improves the sustainability profile of this automated approach, making it more applicable to industrial applications. To do this the team utilized a slug flow continuous flow reactor where each optimization reaction was separated by a slug of inert gas. Using this approach, material consumption per experiment was reduced to just 10% of that required when compared to continuous flow. The PAT tools that were used were inline FT-IR and inline UHPLC and for the model reaction, a Buchwald-Hartwig amination to synthesize an intermediate for the synthesis of olanzapine. Three optimization methods were used (Bayesian optimization, DoE, and kinetic modeling). Chemometric modeling used data from the inline FT-IR and UHPLC to quantify the amounts of reaction components which could then be used for the optimization. The process was scalable, with the larger scale continuous flow reactor giving reproducible data.

In 2024, collaborators at the University of Leeds, AstraZeneca U.K., and Pfizer Ireland similarly demonstrated a two-step, multiobjective self-optimization for the synthesis of paracetamol (Scheme 16C).[98] For this work, the PAT tool was online HPLC, where samples from both steps were directed into the HPLC via a sample loop. A tube-in-tube phase separator was employed to remove any hydrogen before sampling for the HPLC and for telescoping. Initially, the first step (hydrogenation of 4-nitrophenol in a packed-bed three-phase reaction) and the second step (amidation of 4-aminophenol with acetic

Scheme 16. (A–C) Process Analytical Technologies Used in Flow



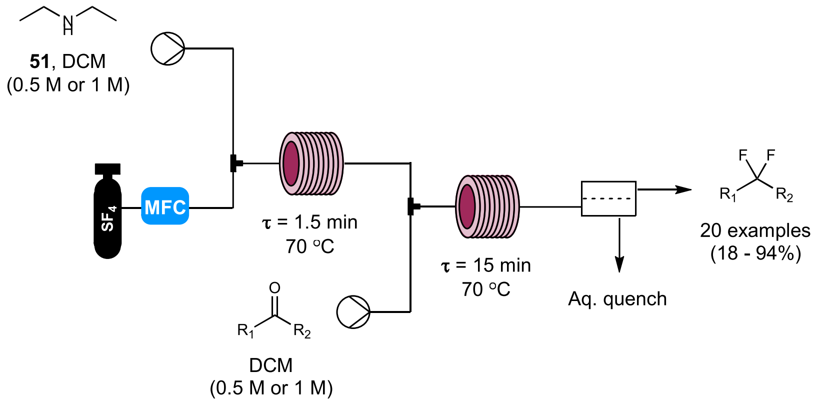
anhydride) were optimized separately to validate the method. A Bayesian optimization algorithm with an adaptive expected improvement acquisition function (BOAEI) was used, as this model can both explore the parameter space and find the optimal conditions based on the desired output in a nonbiased manner. Comparisons between the optimization of each single step individually and the telescoped process were made, with the latter requiring eight fewer experiments to reach the optimum condition of 85% yield. The process mass intensity (PMI) of the two telescoped reactions was roughly a quarter of that of the one-factor-at-a-time approach.

■ FORBIDDEN CHEMISTRIES

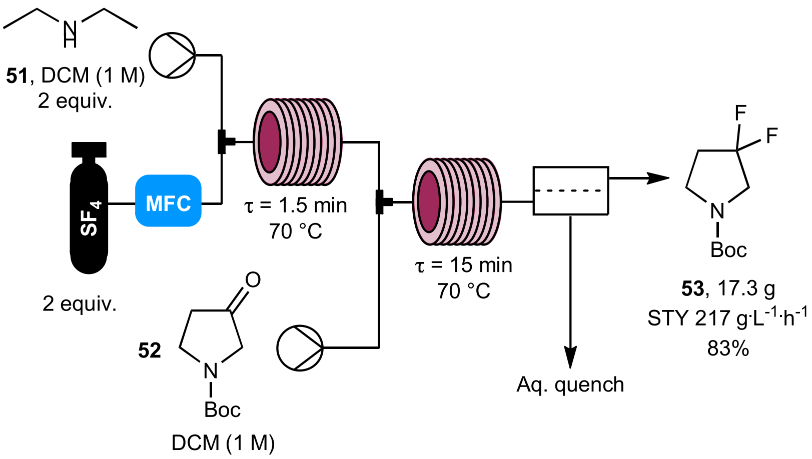
Chemistries that are too dangerous to perform in batch on preparative or large scale are referred to as “forbidden chemistries”.[46] These reactions typically involve unstable starting materials, toxic gases, or the formation of unisolable reactive intermediates which constitute significant process safety risks. Continuous flow reactors have enabled chemists to revisit this chemical space and explore hazardous yet synthetically valuable transformations at scale. The microchannels within flow reactors ensure that only small quantities of reactive species are present at any given time.[99] Moreover, the high reproducibility, potential for in-line reaction monitoring, and compatibility with automation and machine learning make flow systems ideal for such applications. When combined with telescoping to avoid isolation of dangerous intermediates, these advantages make continuous flow a powerful platform for examining traditionally inaccessible reactions. For instance, telescoping strategies have facilitated the generation and immediate consumption of hazardous intermediates thus minimizing exposure of operators to such compounds as demonstrated by the Charette group for the intensified flow synthesis of dithiothreitol.[100] The following section will discuss case studies where such forbidden transformations were rendered feasible to address industrial challenges, highlighting effective knowledge transfer between academic and industrial researchers.

The incorporation of fluorine atoms, and more specifically geminal difluoride moieties, in organic molecules has swiftly increased in recent years due to the enhanced metabolic stability and physicochemical properties these groups confer, which are attractive features for pharmaceutical development.[101] One effective strategy has been the deoxyfluorination of abundant ketone precursors using nucleophilic reagents such as DAST and Deoxo-Fluor.[102] DAST is commonly employed due to its commercial availability; however, its low boiling point and tendency to disproportionate into SF_4 and $(Et_2N)SF_2$ at elevated temperatures make it a serious explosive hazard, complicating scale-up for industrial processes. Although the deoxyfluorination of alcohols, acids, and aldehydes is well documented, ketone substrates pose greater reactivity chal-

Scheme 17. Deoxyfluorination of Ketones to Form Geminal Difluorides in Continuous Flow Scope



Scheme 18. Deoxyfluorination of *N*-Boc-3-pyrrolidinone 52 Scale Out Experiment



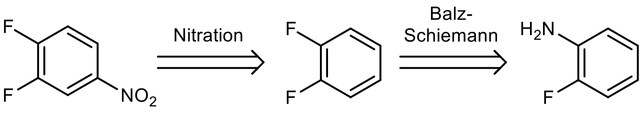
lenges and tend to generate significant quantities of the undesired vinyl fluoride byproduct. The Kappe group in collaboration with Lonza AG set out to develop this reaction in flow (Scheme 17).[103]

Initial batch experiments with cyclohexanone as a model substrate allowed the synthesis of the geminal difluoride using DAST in dichloromethane, though the vinyl fluoride impurity remained problematic—even upon switching to a continuous flow setup. Experimentation revealed that the order of addition was critical for optimizing conversion and selectivity. Building on this insight, the team transitioned to a gas−liquid continuous flow system, in which SF_4 and diethyl amine **51** react to generate DAST *in situ*, which then encounters the ketone precursor downstream to yield the desired product. This approach afforded complete selectivity and a 71% yield for 1,1-difluorocyclohexane. Notably, SF_4 reacts with moisture to form HF, posing significant operational safety risks; these were effectively mitigated by using in-line NaOH quenches. The optimized process was successfully extended to twenty different substrates, delivering good yields. In a scale-up demonstration, *N*-Boc-3-pyrrolidinone **52**—a key intermediate for certain APIs—was converted to its gem-difluoride analogue **53** with a spacetime yield of 217 $g{\cdot}L^{-1}{\cdot}h^{-1}$ and high selectivity (vinyl fluoride impurity reduced to 6%), in contrast to previous protocols that required low temperatures and reagent excesses to achieve comparable yields (Scheme 18). The success of this academic−industrial partnership encourages wider adoption of continuous flow technology as a reliable platform for taming potentially explosive and toxic gas-phase chemistries in the preparation of difluorinated pharmaceutical intermediates.

1,2-Difluorobenzene **55** is an important intermediate in the synthesis of various pharmaceuticals and agrochemicals. It can be readily converted to 3,4-difluoronitrobenzene, a key precursor in the production of the antibiotics linezolid and sutezolid, as well as the tyrosine kinase inhibitor abivertinib. An efficient route to 1,2-difluorobenzene **55** involves the Balz−Schiemann reaction of 2-fluoroaniline **56**, an inexpensive starting material (<\$16 kg^{-1}) followed by nitration to form **54**. Conventional large-scale synthesis proceeds *via* diazotization of 2-fluoroaniline followed by thermal decomposition of the isolated diazonium salt (Scheme 19). Although isolation and drying of this intermediate improve decomposition efficiency, they present significant safety hazards.[104]

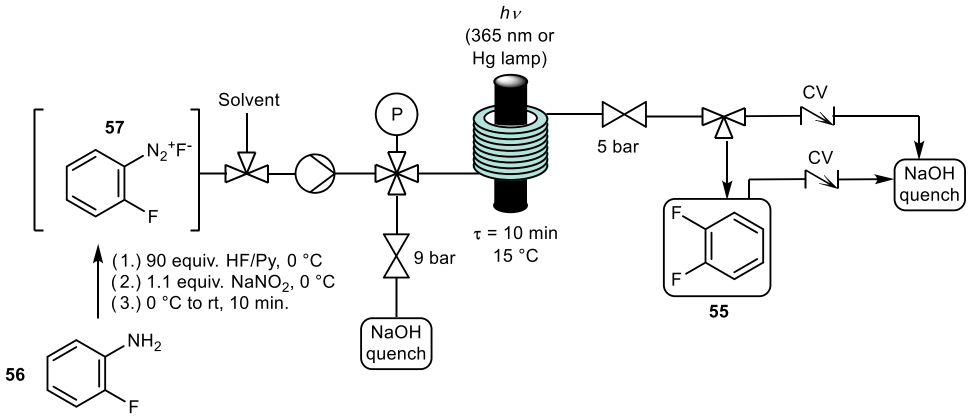
To address these risks, water-free, one-pot methods employing HF/pyridine have been developed to generate and decompose the diazonium species directly.[105] Building on this, collaborators from the Kappe Research Group and SEQENS SAS (France) explored continuous-flow photochemical decom-

Scheme 19. Retrosynthetic Plan for 1,2-Difluoronitrobenzene

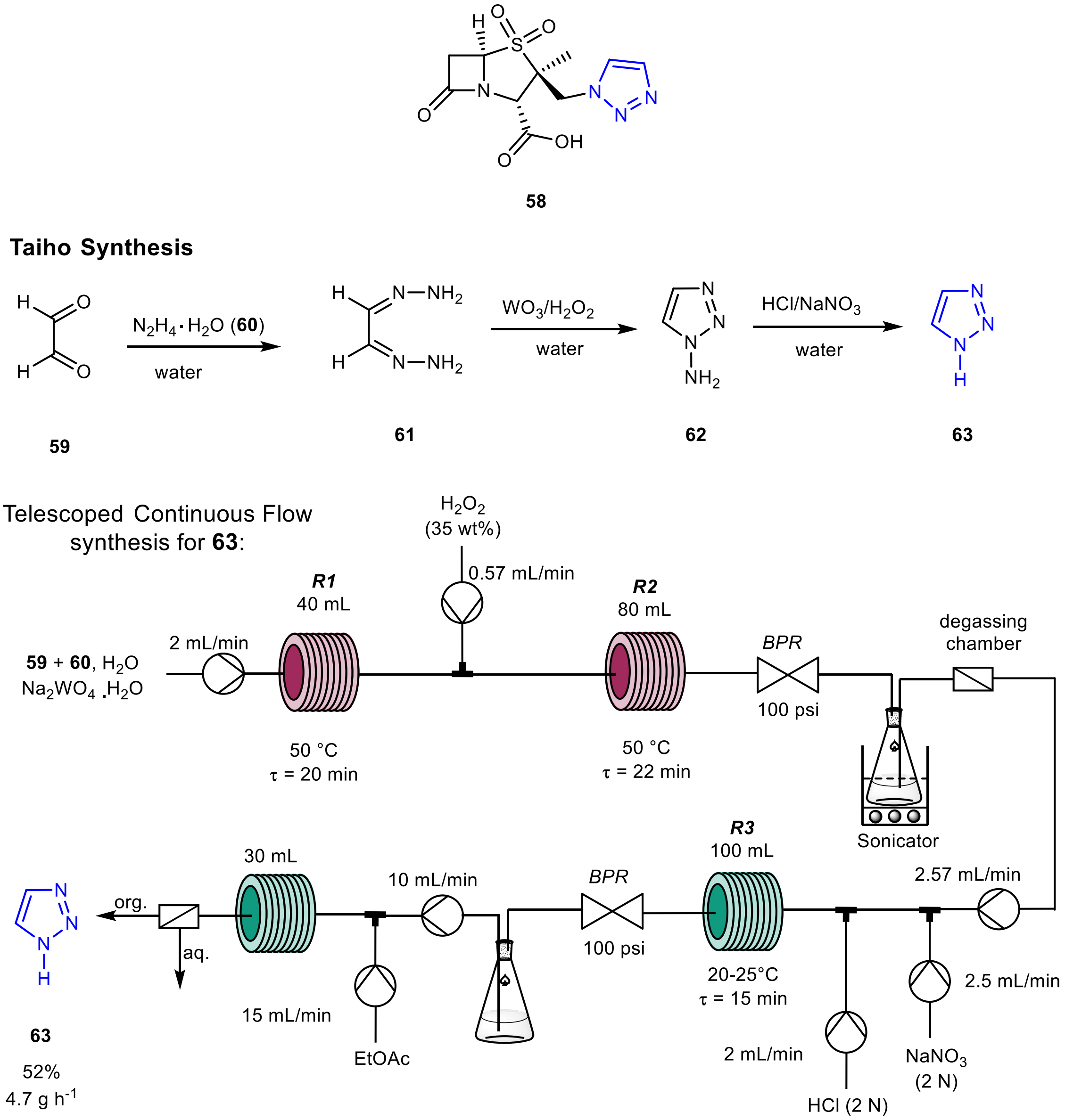


54 **55** **56**

Scheme 20. Continuous Photochemical Fluorodediazoniation Reaction

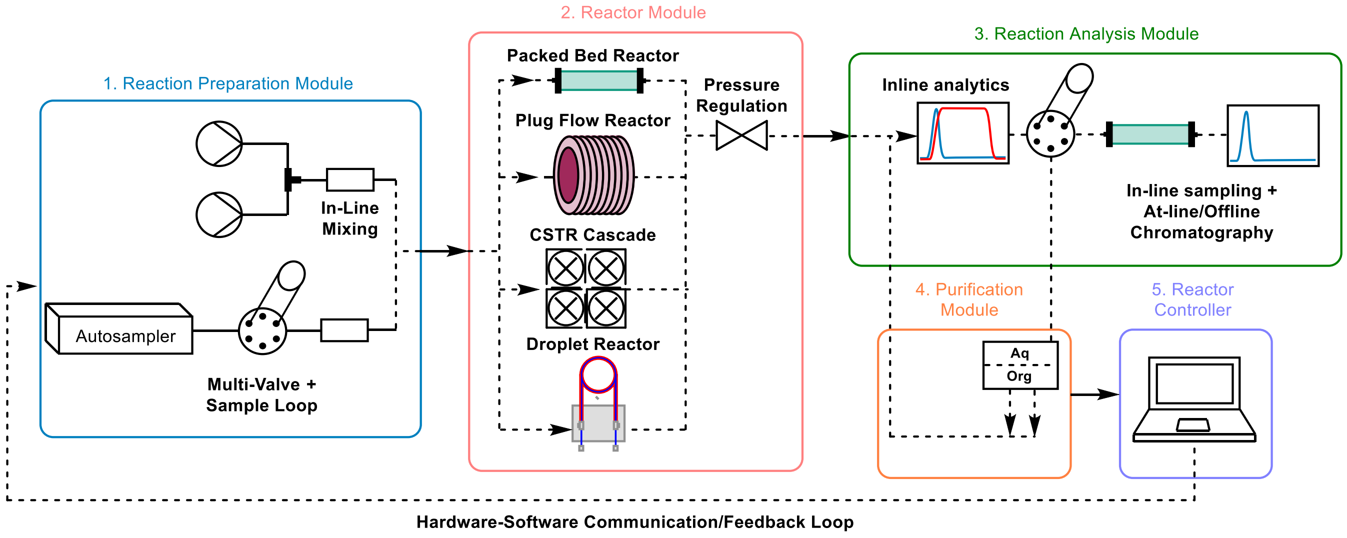


Scheme 21. Telescoped Continuous Flow Synthesis of 1,2,3-Triazole 63



position of the diazonium salt *in situ*. Photochemical methods enable access to high-energy reaction pathways under mild conditions, while continuous-flow reactors mitigate the light penetration limitations imposed by the Beer−Lambert law and expand the viable materials of construction to those with more light permeability such as PFA and PEF.[106] Although thermal

Scheme 22. Schematic Representation of a Generalized Automated Flow Platform and Its Composite Modules



flow decomposition of 2-fluoroaryl diazonium salts has been demonstrated, it requires temperatures up to 200 °C and solvent switch to high-boiling solvents, necessitating isolation of the salt prior to reaction. Furthermore, the minimized amount of dangerous HF/pyridine handled in the flow reactor and in-line quenching helps bolster process safety and protect the operator.

Initial experiments for diazonium salt generation were carried out in batch. The reaction proceeded efficiently at 0 °C within 5 min, and the resulting diazonium salt was stable for up to 20 h at room temperature. Thermal decomposition of the diazonium salt was also explored in batch; however, after several optimization attempts, this approach was abandoned due to low yields, formation of tar-like products, and the potential incompatibility of flow pumps with high-temperature, corrosive mixtures.

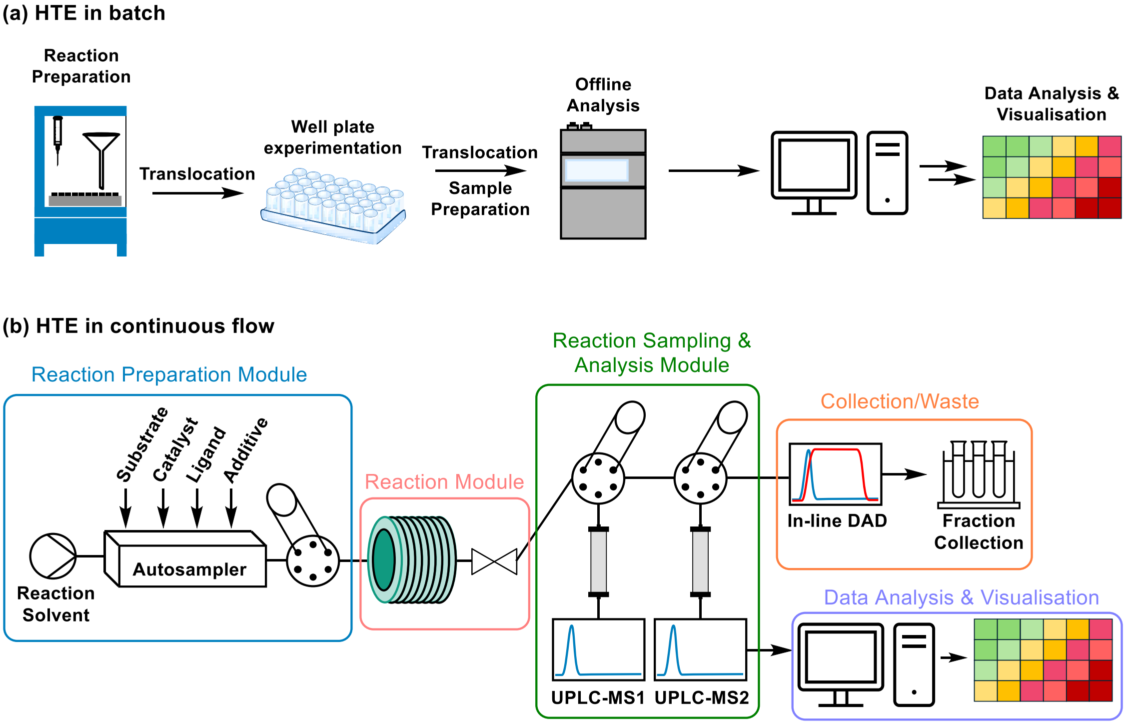
Development of the photochemical decomposition was initiated through UV–Vis studies, which revealed a weak absorption tail at 365 nm (at concentrations from 0.05 to 5 mM). Batch irradiation at this wavelength for 26 h resulted in 52% conversion by ^{19}F NMR, with no evidence of tar formation.

For continuous-flow adaptation, solvent screening identified trifluorotoluene as the optimal medium. Using a medium-pressure mercury lamp, the reaction was optimized with 90 equiv of HF/pyridine, a 12.5-min residence time, and a substrate concentration of 0.4 M, providing an HPLC yield greater than 95%. To enhance safety and sustainability, the mercury lamp was replaced with LED light sources (supplied by Vapourtec). A low-power 365 nm LED (16 W output) afforded a moderate NMR yield of 77%, whereas a high-power LED combined with wider-diameter tubing achieved yields comparable to those obtained under mercury lamp conditions. Recycling of the HF/pyridine extracts—with periodic replenishment—enabled up to 20 cycles with only a minimal decrease in reactivity.

To assess the long-term performance of the light sources, large-scale steady-state experiments were conducted under optimized conditions. The high-power LED system operated continuously for nearly 1 h before a decline in conversion occurred, attributed to partial reactor fouling. In contrast, the mercury lamp setup sustained steady operation for approximately 30 min before similar fouling was observed. Under steady-state conditions (45 min), the high-power LED yielded 16.7 mmol of product, corresponding to a productivity of 1.9 g h^{-1}. While reactor fouling remains a limitation, further optimization is expected to permit continuous operation beyond 1 h (Scheme 20).

Highly exothermic reactions are challenging on an industrial scale due to risk of reaction runaway occurring if the cooling system fails.[107] This problem was identified for the synthesis of 1,2,3-triazole which is an important building block in the manufacturing of active pharmaceutical ingredients (API)[108] such as tazobactam **58**, found in the *β*-lactamase inhibitor Tazocin.[109] In 2017, a global shortage of this drug occurred due to supply chain issues, prompting the development of a second-generation synthesis of tazobactam. The new route, developed by Taiho Pharmaceutical Co., demonstrated a fully telescoped process carried out in water, in which glyoxal **59** reacted with hydrazine hydrate **60**.[110] Even though the second-generation synthesis was deemed suitable, safety concerns were associated with step 2 of the synthesis (H_2O_2 oxidation). The addition of hydrogen peroxide was found to be highly exothermic (−525 kJ), leading to an adiabatic temperature rise of +211 °C. To mitigate these challenges, Pfizer collaborated with the Wu group from the National University of Singapore to develop a continuous flow process for the synthesis of 1,2,3-triazole (Scheme 21).[111] Step 1 involved the generation of glyoxal bishydrazone **61**, with gentle heating being crucial for this reaction to occur efficiently. Wider tubing (from 1/16th to 1/8th outer diameter) was necessary as particles formed when the two streams met, resulting in partial clogging. To reduce this risk, both streams were premixed resulting in a simplified process requiring only one pump. Step 2 targeted an oxidative cyclization reaction using hydrogen peroxide and water-soluble sodium tungstate hydrate ($Na_2WO_4{\cdot}2H_2O$) as catalyst. When steps 1 and 2 were telescoped, 1-amino-1,2,3-triazole **62** was obtained in a 65% yield. The final deamination step was performed under acidic conditions using hydrochloric acid and sodium nitrite. The order of addition was crucial for this step as under batch conditions the acid was added first resulting in precipitate formation. By reversing the order of addition—sodium nitrite then hydrochloric acid—the reaction proceeded smoothly. A fully telescoped flow process was trialed next whereby a degassing step was necessary due to the evolution of nitrogen after step 2. Using a sonicated flask as a hold vessel enabled this process before the reaction mixture was directed

Scheme 23. (a) HTE Workflow in Batch Where Each Unit Operation can be Performed Manually, Autonomously, or a Combination of Both. (b) HTE Workflow in Flow Where Each Unit Operation is Performed Autonomously



into a Zaiput liquid−liquid separator for the continuous separation of product from the aqueous stream. When collecting the organic phase over a 3-h period product **63** was generated in a yield of 52% and a productivity of 4.71 g h^{-1}.

MOTIVATIONS FOR AUTOMATION IN FLOW CHEMISTRY AND TECHNOLOGY-DRIVEN MANUFACTURING

Widespread adoption of autonomous experimentation in multidisciplinary chemistry has reduced labor requirements, increased throughput, and accessed greater experimental precision.[112−115] Flow chemistry is an ideal platform for automation as traditional hardware can be readily integrated into autonomous workflows. Autonomous flow reactors are agnostic to the chemistry under study, meaning the capital expenditure required to implement automation is offset by the expansive scope of applications The topics discussed herein are essential aspects of pharmaceutical discovery, development, and manufacturing. We will examine how state-of-the-art experimentation, employing autonomous flow chemistry as the core design principle, is evolving our approach to these topics. We will also identify opportunities for further development of these technologies and predict how they will shape the future of chemical discovery and manufacturing.

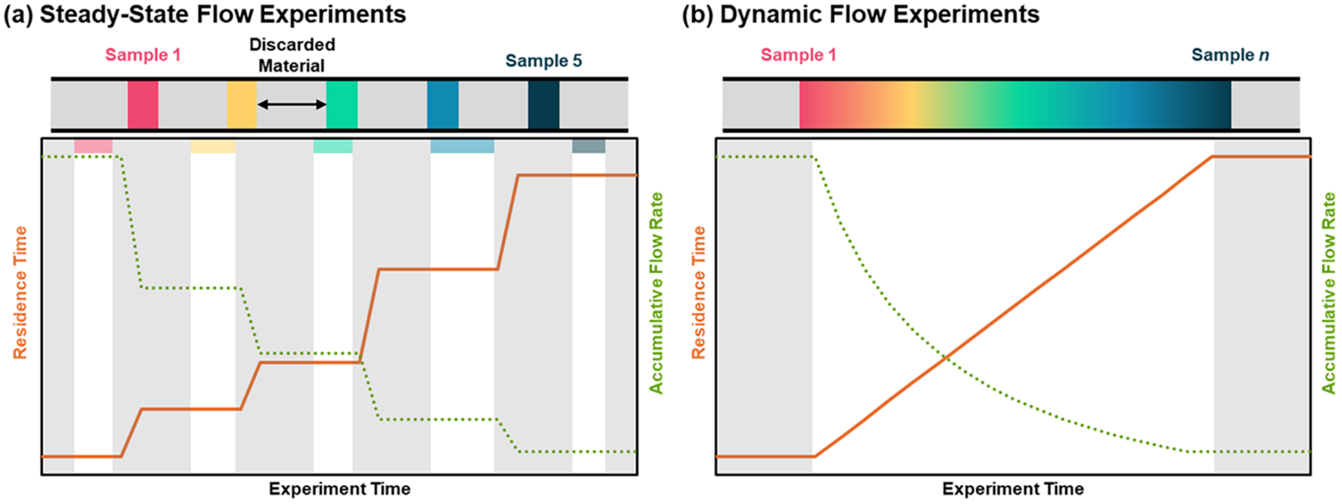
END-TO-END AUTONOMOUS CONTINUOUS MANUFACTURING

Continuous flow is mainly employed in conjunction with batch processing to leverage the strengths of each technique where necessary.[116−119] Comparatively, end-to-end integrated continuous manufacturing (ICM) platforms have been developed for small-molecule API production. This sees critical unit operations in chemical manufacturing including reaction, purification, crystallization, dosing, and packaging condensed into a single, uninterrupted flow path. Integrated PAT enables feedback control of the platform for autonomous parameter adjustment in response to deviations (Scheme 22).[120−124] This ensures consistent product quality while avoiding the environmental and financial pressures of reprocessing or disposing off out-of-specification material. Additionally, ICM platforms can operate on small volume scales thereby reducing their operational footprint[125−127] and allowing for portable manufacturing.[122,128,129]

Trout and co-workers utilized ICM for the production of Aliskiren Hemifumurate in tablet form.[130] Flexible throughput adjustment from 20 to 100 g h^{-1} offered excellent supply chain resiliency while switching from batch to flow cut unit operations from 21 to 14 steps for more efficient and fiscal manufacturing. Autonomous process control ensured adequate residence time in each vessel while analyzing critical material attributes ensured consistent product quality. At a nominal processing time of 47 h, a throughput of 45 g h^{-1} could be realized to access 2.7×10^6 tablets per annum. Processing was demonstrated over 10 days of operation and the tablets produced were uniform in appearance, size, and dosage, with rapid dissolution rates and passing final release testing specifications. Since then, ICM has been extended to cGMP operations, notably by Eli Lilly in preparation of Prexasertib monolactate monohydrate for clinical trials.[131] Continuus Pharmaceuticals have demonstrated the explicit design of an ICM platform across both miniaturized[132] and pilot reactor scales.[133] Translating a generic process from batch to ICM was predicted to achieve an ∼90% reduction in fixed capital investment while reducing the cost of goods sold regarding API generation and tablet formation by 33.6 and 29.4%, respectively.

ICM platforms integrate the fundamental principles of Green Chemistry,[134,135] Quality by Design,[136,137] and Quality by

Scheme 24. Visualization of the Reactor Channel (Top) and Corresponding Flow Rate/Residence Time Plot (Bottom) For: (a) Steady-State Experiments in Flow; (b) Dynamic Experiments in Flow[a]



[a] Gray regions represent non-analyzed fluid elements discarded to waste (a) en route to steady-state; (b) at steady-state. Colored regions represent analyzed fluid elements with unique experimental parameters.

Control[138] into a single autonomous flow path to permit safe, sustainable, and robust chemical manufacturing.[19,139] However, the uptake of ICM remains limited due to the complexity of multistep syntheses and the variability of unit operations required. Greater flexibility and modularity in ICM platform design will permit a broader manufacturing scope while process development tailored toward ICM will ensure transferability to such platforms.

FLOW-BASED HIGH THROUGHPUT EXPERIMENTATION FOR REACTION SCREENING

High throughput experimentation (HTE) is ubiquitous in molecular discovery[140−142] with a remarkable reputation in the pharmaceutical industry.[143,144] The multiwell plate format of batch HTE allows cost-effective and time-efficient experimentation while automation has advanced experimental efficiency (Scheme 23a).[113]

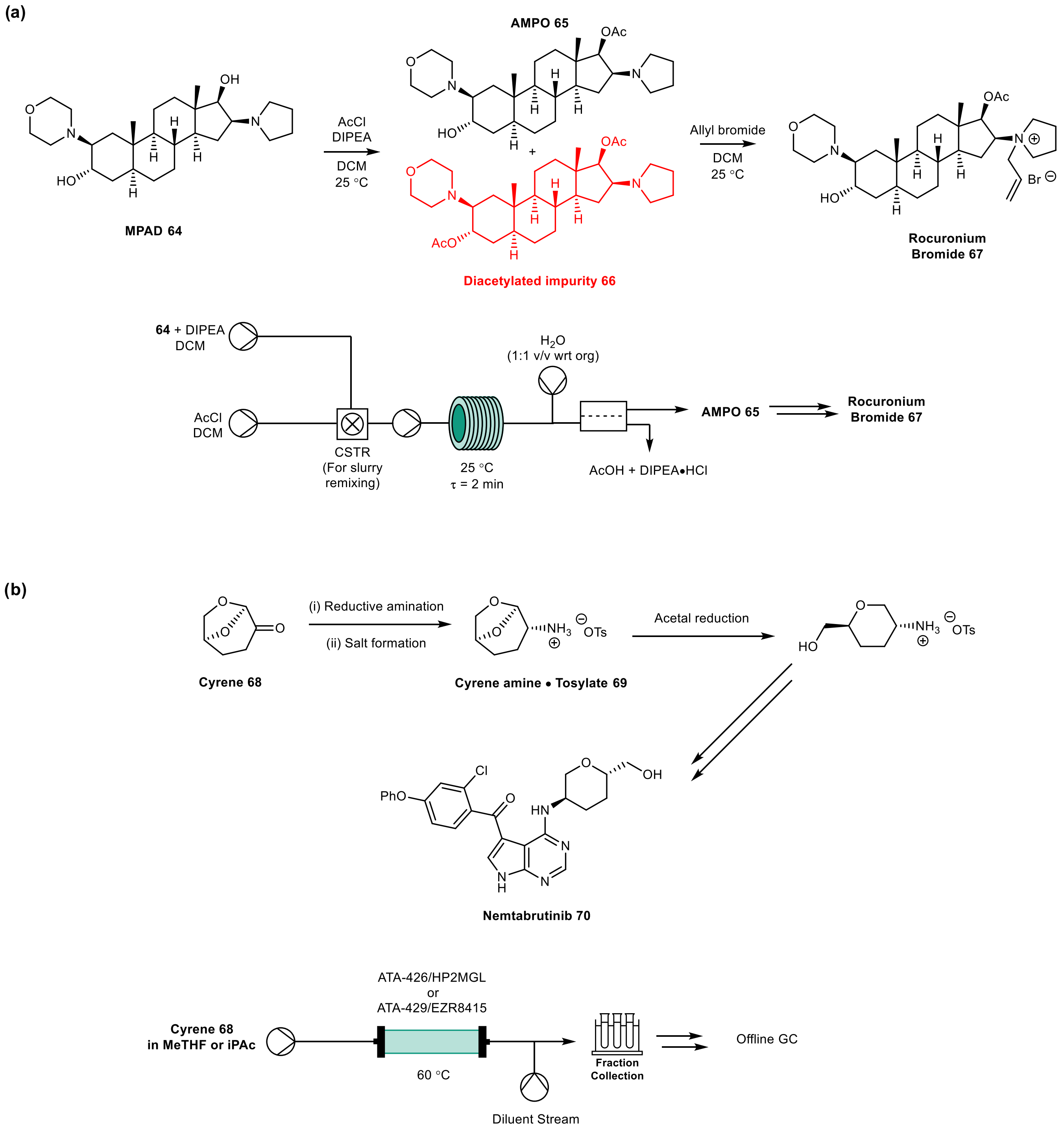
Pfizer demonstrated that traditional HTE workflows can be readily adapted in flow using an autonomous flow reactor for high throughput screening on nanomolar scales.[145] Vast arrays of reaction mixtures could be prepared using 1 μL aliquots taken from up to 192 reagent stock solutions and up to 12 reaction solvents could be studied. A throughput of 1500 reactions per 24 h was achieved and analytical bottlenecks were avoided by running two at-line UPLC-MS instruments in parallel. In-line DAD analysis and fraction collection also facilitated the preparation of milligram quantities of material if needed. Studying a Suzuki-Miyaura cross-coupling, 5760 experiments were executed and analyzed within 92 h; consuming just 65 μg of substrate per reaction. The platform examined a challenging bromo-oxindole electrophile present in 13 of Pfizer's parallel medicinal chemistry (PMC) libraries. PMC optimization in flow across 576 experiments achieved a success rate of ∼5% while all earlier batch campaigns had failed entirely (Scheme 23b). Importantly, the HTE-optimal conditions were readily scalable in batch with minimal process alterations required to accomplish an 81% product yield. The same platform accelerated the development of a photoredox Minisci reaction installing bicyclo[1.1.1]pentanes as benzoate bioisosters. After 475 reactions in <12 h, mild and broadly applicable reaction conditions were identified. The conditions could be translated to synthetically relevant scales and when deployed in a PMC format to 11 heterocycles and 3 redox active esters achieved a 55% success rate.[146] Since these seminal works, advancements in flow-based HTE have enabled picomole-scale reaction screening,[147] reaction discovery and optimization using gaseous reagents,[148] and kinetic experimentation.[149]

Condensing HTE workflows into a modular flow platform accelerates the discovery, optimization, and screening of diverse chemical transformation portfolios with minimal material consumption. This makes flow-based HTE well-suited for deployment in drug discovery, route scouting, and early phase process development. Given the volume of high-quality data generated in short time frames, flow-based HTE may become central to training evolutionary machine learning algorithms to tackle each of the aforementioned fields.[150−152] In doing so, initial screening space will be minimized to judicious reaction selection with a high probability of success thereby further accelerating discovery and development.

DYNAMIC EXPERIMENTATION IN INDUSTRIAL PROCESS DEVELOPMENT

Traditional flow chemistry studies reaction parameters at steady-state operation resulting in time-consuming and materially demanding experimentation (Scheme 24a).[153] A more efficient means of experimentation is to analyze a reaction within the transient region between two steady-states arising from instantaneous parameter variation (Scheme 24b).[154,155] Termed dynamic experimentation, flow rate ramping was initially exploited for expedited temporal reaction profiling.[156,157] Since then, dynamic experimentation has been broadly extended across design space, including: temperature,[158,159] reagent stoichiometry,[160] concentration,[161] solvent composition,[162] irradiation time in photochemistry,[163,164] and substrate identity.[165] Impressively, multivariate dynamic experimentation in flow has been performed with up to five variables altered at once[166] and across multiphasic chemistry.[167] With the requirement for instantaneous and accurate parameter

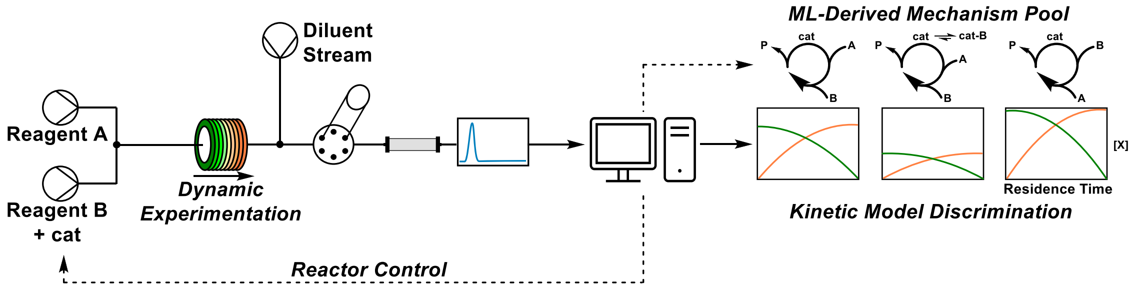
Scheme 25. (a) Synthesis of Rocuronium Bromide and the Corresponding ICM Platform for Step 1 of the Route; (b) Synthesis of Nemtabrutinib and the Automated Flow Reactor Used for Dynamic Experimentation during Process Development of the Transamination Step



variation, autonomous flow reactor platforms are omnipresent in dynamic experimentation.

Reaction response surfaces are a vital aspect of process design, risk mitigation, and the identification of areas for further development. Researchers at Merck demonstrated that three-dimensional surface response models could be derived using multidimensional flow rate ramps for a base-mediated Knoevenagel reaction.[168] Using an automated flow reactor with tandem in-line and offline analysis, enabled by at-line sampling, the effect of residence time and base equivalents was studied. Two experiments employing simultaneous linear flow rate ramps in parallel and orthogonal directions was sufficient to explore all four quadrants of the design space. Comparatively, a single experiment varying base equivalents in a nonlinear, sinusoidal trajectory while varying residence time linearly facilitated more data-rich experimentation without increasing reagent consumption or experimental duration. Guidelines on how to best implement multidimensional, nonlinear dynamic

Scheme 26. Automated Flow Reactor for Autonomous Kinetic Experimentation Using Dynamic Experiments and Machine Learning



experiments for enhanced experimental efficiency have since been published.[169]

After suffering from shortages during the COVID-19 pandemic,[170,171] the preparation of Rocuronium Bromide using an integrated continuous manufacturing platform offering supply chain robustness was reported by Continuus Pharmaceuticals (Scheme 25a).[172] Their refined synthetic route required the acylation of MPAD, however, overcharges of acetyl chloride promoted impurity formation and increased product losses during downstream purification. Transient exploration of acetyl chloride equivalents within the bounds of 0−2 equiv identified 1.3 equiv to be optimal while the effects of overcharging/under-charging the reagent could be quantified to guide stricter process control limits.

Dynamic experimentation has also accelerated the transfer of biocatalytic processes from batch to continuous flow (Scheme 25b). The transamination of the renewable feedstock cyrene to cyrene amine en route to the cancer treatment Nemtabrutinib was reported by Merck.[173,174] For operational simplicity, the process was transferred to flow using a packed-bed reactor (PBR) and an immobilized ATA-426/HP2MGL biocatalyst.[175] Kinetic profiling in flow via dynamic flow rate experiments revealed that sluggish reaction kinetics and catalyst deactivation made the reaction inefficient in flow. Process development identified the evolved ATA-429/EZR8415 biocatalyst to be more active while exchanging the isopropyl acetate reaction solvent for 2-MeTHF provided enhanced purification. Scaled to >50 kg input in flow, the developed conditions cut processing time almost 2-fold due to a 4-fold reduction in residence time and reduced the catalyst charge by 65%. The final product was isolated as a tosylate salt in 78% yield and >200:1 d.r compared to the 73% yield and 23:1 d.r achieved without flow-guided development.

The implementation of dynamic experimentation to process development has been enabled by autonomous flow chemistry. The ability to traverse design space in a more rapid and efficient way has facilitated the identification of optimal reaction conditions while providing insights into suboptimal process operation. These aspects will make flow-based dynamic experimentation vital in streamlining the transfer of chemical processes to manufacturing scales.

CLOSED-LOOP SELF-OPTIMIZATION AT STEADY-STATE

Autonomous experimentation in flow can be used to train evolutionary machine learning algorithms and guide the design of subsequent experiments. This creates a self-sustaining, closed-loop feedback system for the data-driven self-optimization of chemical processes. A broad range of transformations have been optimized using such platforms, including: flash chemistry,[176−178] photochemistry,[179,180] electrochemistry,[181,182] molecular and heterogeneous catalysis,[183,184] and biocatalysis.[185] Machine learning can even accelerate the development of bespoke flow reactor designs for enhanced continuous processing capabilities.[186,187] Optimization can be performed using single-objective or multiobjective criteria using continuous, discrete, or multivariable design space.[179,183,188] Bayesian algorithms which factor the cost of experimentation[189] and constrict design space with each iteration[190] have been developed for even greater efficiency.

Self-optimization has aided the development of continuous manufacturing routes toward small-molecule APIs such as Osimertinib,[191] Edaravone,[95] and Sonidegib,[192] Apixaban,[193] and in the crystallization of Paxlovid.[194] Flow-based optimization of multiphase reactions is a particular challenge as reactor geometry and fluid dynamics directly influence reaction performance. Hybrid flow paths telescoping different reactor types can resolve this issue.[172,192,195] The self-optimization of a continuous, telescopic route to paracetamol combined a PBR stage for a three-phase nitroreduction and a PFR stage for a single-phase amidation.[98] Optimization using a BOAEI algorithm and multipoint sampling[196] was used to achieve an 85% overall yield within 12 iterations. Simultaneous optimization of each step provided a 4-fold reduction in process mass intensity (PMI) when compared to discrete optimization of each step. Simultaneous optimization of the reaction sequence leverages the trade-offs between steps arising from the complex physical and chemical interdependencies.[197] Mutli-phase reactions can also impact downstream workup and purification making the isolation of critical materials challenging or inefficient. Simultaneous optimization of both the reaction and purification steps can identify suitable input conditions to maximize reaction productivity and purification efficiency while reducing development time and minimizing processing costs.[198,199] The Pareto frontier describes the distribution of equally ideal operating conditions as a tradeoff between conflicting optimization objectives. This is a natural consequence of multiobjective optimization where no single solution exists.[200] In the context of process development, the Pareto frontier can be used to guide process development depending on the overarching campaign objectives.

Self-optimization in continuous flow is materially intensive and therefore not suited for deployment in early phase process development. Droplet flow reactors use segmented flow to access microlitre scale reactions while mitigating nonsteady-state operation by removing axial dispersion effects.[201] Autonomous droplet flow reactors have been exploited for materially efficient self-optimization in continuous flow,[202−207] stopped-flow,[26,208] and oscillatory flow modes.[209−211] However this field remains relatively underexplored in the context of industrial process development.

MERGING DYNAMIC EXPERIMENTATION WITH DATA-DRIVEN OPTIMIZATION

A more experimentally efficient approach to exploring design space in self-optimization is to employ dynamic experimentation (Scheme 26).

Researchers at Merck paired an evolutionary gradient-based search algorithm with DoE for the multiobjective self-optimization of an S_NAr reaction.[212] Dynamic flow rate experiments exploring residence time and reagent equivalents in a circular trajectory around the center point enabled iterative center point generation. Beyond self-optimization, transient experiments navigated a broad design space to examine reaction sensitivity to process deviations facilitating reaction modeling. Jensen and co-workers in collaboration with Pfizer created a bespoke dynamic optimization (DynO) platform pairing dynamic flow with Bayesian optimization.[213] In silico parametric analysis using their optimization model outperformed the popular Dragonfly package[214] in continuous design space for multiobjective optimization. Single-objective optimization of a homogeneous ester hydrolysis reaction exploring residence time and base equivalents achieved a 93% product yield in a single iteration.

Process optimization via serendipitous parameter variation can afford phenomenological insights into the underlying chemistry. Conversely, a priori mechanistic knowledge can facilitate judicious process optimization.[215,216] Bourne and co-workers in collaboration with AstraZeneca showed that residence time ramping experiments at a set temperature in tandem with machine learning accelerated mechanistic model discrimination and kinetic parameter estimation.[217] The computational approach considers all mass-balance allowed pathways based on the known chemical inputs, intermediates, and outputs. Model identification is weighted toward mechanistic simplicity and convergence of the experimental and simulated integral rate data. Multiple pharmaceutically relevant reactions were studied, with reactions reaching completion within 10 s being accessible, and a low residual error between the experimental and simulated data being observed. The combination of automated experimentation and machine learning afforded a 24 and 106% reduction in material consumption compared to steady-state experimentation and full-factorial DoE optimization, respectively. The platform was also applicable to complex scenarios involving noninteger reaction orders and catalytic reactions.[218]

CONCLUSIONS AND OUTLOOKS

The value of collaborations between academia and the fine chemical industries has resulted in numerous impactful case studies that showcase the synergy that can be gained and exploited when joining forces to solve key challenges in relation to developing and implementing new synthesis technologies such as continuous flow chemistry. While these efforts have been documented for almost two decades recent years have shown that such intersectoral collaborations are becoming more common practice while a clear trend is visible showing that new synthesis modes such photochemistry, electrochemistry, biocatalysis and process automation are areas of high interest. Importantly, this not only shows how academic developments can be expanded by the help of industrial laboratories, but it also allows industrial thinking and related metrics to be applied to realize processes that are scalable, sustainable and safe. Moreover, in the context of autonomous flow chemistry platforms this strategy permits more efficient and ambitious process development while maximizing sustainability and robustness in continuous manufacturing. With computer-aided planning, data-driven experimentation, and autonomous platforms; the journey between reaction discovery, process development, and continuous manufacture will be greatly accelerated.[219−221]

This will require future generations of chemists to possess a wide skillset and it is encouraging to see the publication of guides for newcomers,[222−224] simplified platforms,[225] and undergraduate training being developed.[226] Industrial-academic collaborations act as a vehicle for translating the needs of the chemical industry into the training of new chemists. Such partnerships will be vital for the development of holistic curricula combining chemistry, engineering, coding, and data science. While most of the case studies available in the literature are based on traditional partnerships between one academic and one industrial collaborator, new opportunities may lie in broader models such as consortia and bespoke research centers that specialize in key aspects for modern chemical technologies. This should not be limited geographically but rather attract collaborations and funding across borders. The success of such research centers in fostering sustainable collaborations between academia and industry is already visible through their leading role in the field which does not only provide for training and upskilling but also enables new ideas to be explored and translated into tools and processes that impact industrial developments in general. As shown in this perspective, continuous flow synthesis is a widely adopted technology with a proven record of innovative chemical processes that overcome existing limitations (safety, efficiency, sustainability etc.). The strategic link between researchers from academia and industry has become a critical guide for success as it offers additional synergy and momentum to expand current capabilities while enabling researchers to make inroads toward novel technologies that will determine the success of technology-aided chemistry in the future.

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‖The authors P.J., R.B., and D.C. contributed equally. CRediT: **Philip Jamieson** conceptualization, data curation, formal analysis, writing - original draft; **Ruairi Bannon** conceptualization, data curation, formal analysis, writing - original draft; **Davin Cronly** conceptualization, data curation, formal analysis, writing - original draft; **Megan Smyth** formal analysis, project administration, supervision, writing - original draft; **Scott Wharry** formal analysis, project administration, supervision, writing - original draft; **Thomas S. Moody** project administration, supervision; **Gavin Lennon** data curation, formal analysis, project administration, writing - original draft, review & editing; **Marcus Baumann** conceptualization, funding acquisition, project administration, supervision, writing - review & editing.

Notes

The authors declare no competing financial interest.

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DEDICATION

We dedicate this publication to Prof. Steven V. Ley—a pioneer in the field of continuous flow chemistry—on the occasion of his 80th birthday.

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