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The Rocky Road to a Digital Lab

Peter Sagmeister[ab], Jason D. Williams[ab], and C. Oliver Kappe*[ab]

Abstract: The pharmaceutical industry has begun incorporating continuous manufacturing technology in synthetic routes toward active pharmaceutical ingredients (APIs). The development of smart manufacturing routes can be accelerated by utilizing digitalization, process analytical technology (PAT), and data-rich experimentation from an early stage. Here, we present the key aspects of implementing automated flow chemistry reactor platforms with real-time process analytics. Based on our experiences in this field, we aim to highlight the potential of these platforms to conduct self-optimization, automated reaction model building, dynamic experiments and to implement advanced process control strategies.

Keywords: Automated platform · Digitalization · Flow chemistry · PAT

Dr. Peter Sagmeister obtained his PhD in Chemistry at the University of Graz (Austria) in 2022 and had a research stay at the University of Calgary (Canada) during his studies. For his PhD, he worked in the group of Prof. C. Oliver Kappe and focused on digitalizing flow chemistry using real-time process analytics and control technology for data-rich experimentation. Peter is currently a senior scientist at Research Center Pharmaceutical Engineering GmbH (RCPE) in Graz, where he is developing methods contributing to the digitalization of the pharmaceutical industry.

Dr. Jason D. Williams studied for a Masters in Chemistry at the University of Sheffield, with a year industrial experience in medicinal chemistry at AstraZeneca (Alderley Park). He then began a PhD as part of the GlaxoSmithKline/University of Strathclyde collaborative PhD programme, under the supervision of Prof. William Kerr. After completing his PhD, Jason took up a position at RCPE GmbH, in the labs of Prof. C. Oliver Kappe, where he currently is a Principal Scientist. His research interests lie in the field of flow process development, specifically incorporating photochemical methods, as well as digitalization, automation and PAT utilization.

Prof. C. Oliver Kappe studied at the University of Graz with Prof. Gert Kollenz. After postdoctoral research with Prof. Curt Wentrup at the University of Queensland and with Prof. Albert Padwa at Emory University, he moved back to the University of Graz in 1996 to start his independent academic career, where he was appointed Professor for 'Technology of Organic Synthesis' in 2011. His research interests involve continuous flow and sustainable chemistry, API manufacturing, and process intensification technologies. Since 2017, he leads the Center for Continuous Flow Synthesis and Processing (CCFLOW) at RCPE GmbH.

1. Digital Lab – Where to Begin?

The rapid evolution of technology has an impact on our everyday lives. The high-value chemical manufacturing sector is not excluded from this evolution. However, the transition to smart manufacturing and a data-rich environment, known as Industry 4.0, is only happening at a relatively slow pace. The underutilization of technology and data within the pharmaceutical development and manufacturing environment leads to long process development times and often suboptimal production processes for manufacturing active pharmaceutical ingredients (APIs).[1,2]

Examples of data-rich experimentation for reaction optimization in continuous flow have been published almost exclusively by academic groups. The methods developed include self-optimization,[3–9] automated reaction model building,[10–15] dynamic experiments[16–19] and pre-programmed experiment sequences[20,21] applied to a variety of different chemistries. However, most data-rich experimentation is limited to single-step transformations. These developed reaction optimization methodologies are not only applicable in continuous flow but can also be adapted for batch optimization studies.[22,23]

Although a data-rich environment in medicinal chemistry is at a more advanced stage,[24,25] published reports of data-rich experimentation in industrial continuous process development are still scarce. Examples of such reports include: researchers from Pfizer used an automated platform for optimization of a challenging Suzuki coupling in an early drug discovery process.[26] In addition, Merck scientists have developed data-rich flow chemistry approaches to accelerate their early and late stage process development campaigns.[27–29]

The implementation of data-rich workflows requires a diverse group of people with different background knowledge, such as organic chemistry, chemical engineering, data science, computer science, and automation. Therefore, the communication between engineers and scientists has to be supported. Arguably, one of the biggest challenges is making the business case for this transition, as the results and benefits take years of implementation to come to fruition. Additionally, if there is not a true commitment from the leadership of the company to 'go digital', then resources and time can be wasted.

We decided to 'go digital' at CCFLOW some time ago and herein aim to provide an overview of the key elements for implementing an automated flow chemistry platform with real-time process analytics, based on our experiences in this area. In the first

*Correspondence: Prof. Dr. C. Oliver Kappe[ab], E-mail: oliver.kappe@uni-graz.at
[a]Center for Continuous Synthesis and Processing (CCFLOW), Research Center Pharmaceutical Engineering (RCPE), Inffeldgasse 13, 8010 Graz, Austria, [b]Institute of Chemistry, University of Graz, Heinrichstraße 28/1, 8010 Graz, Austria;

section, we describe the anatomy of an automated platform, based on its hardware, software and analytical components. Thereafter, we will highlight selected experimental applications of these autonomous platforms, with literature context.

2. The Anatomy of an Automated Platform

Automated flow chemistry platforms have been established in recent years, in industrial and academic laboratories.[30–35] In an ideal case, these platforms would design and plan their own synthetic route, self-optimize the reactions, build reaction models, identify all intermediates, discover new reactions and work 24/7, autonomously. All of the developed platforms are comprised of a hardware component (*e.g.* reactors, pumps and analytical instruments) and a software component (*e.g.* hardware control, experiment selection and data processing algorithms). In our case, the development of the automated flow chemistry platform started in 2018 and has been constantly improved over the following years.[36,37] We strongly focused on real-time process analytics, data analysis and interaction of the control system with a range of different algorithms (Fig. 1).

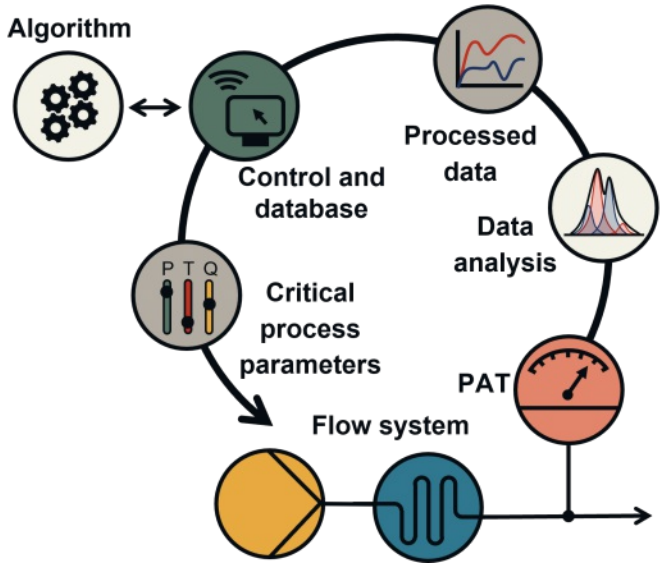

Fig. 1. An overview of the essential parts in an automated flow chemistry platform.

It was our intention to develop a flexible flow reactor system, which could be augmented with additional unit operations (*e.g.* quench, phase separation). This would allow any flow-suitable chemical transformation to be operated in the automated platform. Sensors and actuators should communicate with a distributed control system (DCS), which has a calibration or driver for each instrument (Fig. 2). Simple sensors often merely provide a current (4–20 mA) or voltage value. For more complex actuators (*e.g.* pumps, thermostats), the physical connection with the DCS is generally achieved using a local area network (LAN) cable, or serial connection (RS-232 or RS-485). The communication with such instruments is achieved by a specific protocol, such as transmission control protocol (TCP), Modbus, profibus or NAMUR. An automated system can be further expanded by the addition of multiple DCS units, under the orchestration of a supervisory control and data acquisition (SCADA) software, generally *via* Open Platform Communication Unified Architecture (OPC UA) protocol.

Process analytical technology (PAT) is essential for determining experimental results within any autonomously operating platform.[38,39] PAT can be integrated as an inline, online, or atline sensor.[40] PAT devices can be as simple as mass flow meters, temperature, pressure, pH or conductivity sensors, which provide valuable information about the state of the reactor system. More advanced process analytics, which provide structural information on process species, can be based on spectroscopy (*e.g.* NMR, FTIR, Raman, UV/vis) or mass spectrometry.

These aforementioned instruments can provide the control system with fast results (generally <15 sec per data point), to make data-driven (automated) decisions and control the process in real time. While atline or online chromatography provides information about impurity profiles and trace impurities, it requires longer measuring times, due to the separation of species.

The collected raw spectral or chromatographic data from PAT must be processed in real time, to supply concentration values for the analytes of interest. This can be either achieved by using commercial software or by compiling custom processing algorithms in open-source software environments. Our experiences with data processing have mainly focused on four different techniques: integration, indirect hard modeling (IHM), partial least squares (PLS) regression and artificial neural networks (ANNs).

Integration is the most common technique, as it is the easiest to implement.[40] Isolated peaks can be integrated, and the obtained

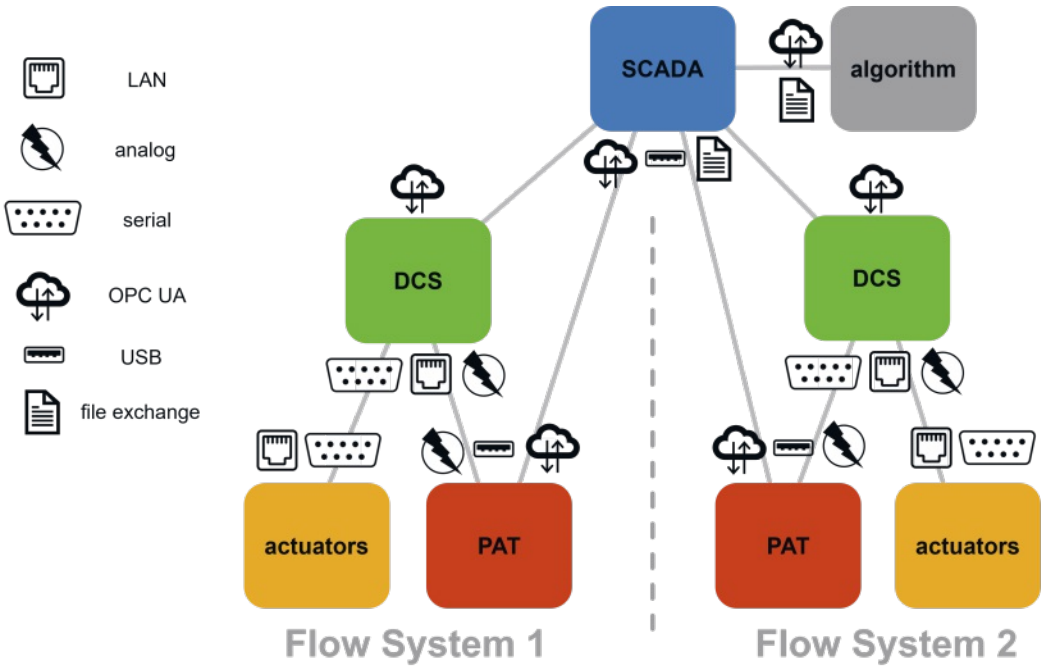

Fig. 2. Connectivity between hardware and software components in an automated flow chemistry platform made up of multiple distributed control system (DCS) units, controlled by a central supervisory control and data acquisition (SCADA) system.

response area can be correlated to an analyte concentration using an external calibration. We have used integration as processing method for UHPLC[20,21,36,37] or isolated peaks in FTIR[36] or NMR spectra.[41,42] However, process streams typically contain multiple different chemical species. Therefore, the spectral data obtained from these process streams often contain multiple overlapping signals. When dealing with such data, more advanced techniques such as PLS regression, IHM, or ANNs can be used to deconvolute the spectrum.

PLS regression is a statistical approach, which finds a relationship between a dependent variable and multiple independent variables. The dependent variable is the prediction outcome (*e.g.* the concentration of a specific compound), whereas the independent variables represent all influencing spectral areas. The training data set for PLS ideally covers all factors affecting the spectrum, such as concentration, temperature, or pH. Preparing a good quality training and validation dataset that includes all of these effects is time consuming. However, this approach is probably the most commonly utilized advanced technique to analyze complex mixtures in real time.[43–46] In our laboratory this is the method of choice for FTIR analysis.[6,21,37]

IHM is a spectral hard modeling technique that describes a pure component spectrum using numerous Gaussian or Lorentzian peaks.[47,48] These pure component models can then be combined into a mixture model. This technique originated for the interpretation of FTIR and Raman spectra[49–51] and has more recently been used with NMR spectroscopy.[52–55] One benefit of IHM is that the model's constraints can be adjusted to capture peak broadening or peak shifts. The amount of training and validation data can be minimized and, in the case of NMR, one-point calibrations are possible. Therefore, IHM has been our method of choice to process NMR spectra.[6,15,37]

Finally, ANNs are also utilized as a data processing tool in the PAT community.[56–63] Reliable models are only obtained by training with large data sets. These training sets can comprise simulated and real spectra from the process. Before training ANNs, the training data can be manipulated to emulate baseline shifts or peak shifts to get a more extensive training data set. ANNs have been used in our platform to process NMR and UV/vis data.[37] We also utilized ANNs in an approach called data fusion.[64–66] Therein, multiple data streams from different PAT devices can be combined to predict the output parameters of interest.[67]

The obtained concentration values then need to be further processed with filters to avoid outliers (*e.g.* an air bubble going through the flow cell) and to smooth noisy signals. This processed data is fed into a database and the control system. The control system is the heart of the autonomous system and is based on commercial software or has been developed for certain autonomous platforms in open-source programming languages. The currently used SCADA system within our labs is based in C# programming language and uses the commercial software *XAMControl* (evon GmbH).

All data streams, from process analytics to actuator controllers, are bundled within this SCADA system. Different code blocks can be executed to, for example, assign new flow rates (based on a desired residence time and reagent stoichiometries), switch valves at certain time points, or calculate objectives (*e.g.* space-time yield, E factor) from measured process outcomes. The communication between the control system and algorithms for data-rich experimentation in third party software can be accomplished by either simple file exchange or OPC UA communication.

3. Controlled API Production

The pharmaceutical industry is encouraged by regulatory agencies, such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), to integrate process analytics and control technology (PACT) to continuous manufacturing from an early stage in development.[68] PAT and data-rich experimentation can maximize the knowledge gained from each experiment during early process development. Critical process parameters (CPPs) can be more rapidly identified and a control strategy to reach critical quality attributes (CQAs) can be implemented. This supports the decision made during scale up and helps to implement a digital twin for pilot and production scale (Fig. 3A).

During lab optimization, the amount of PAT should be increased to a maximum, to accelerate process development and facilitate scale-up (Fig. 3B). Reaction kinetics and impurity profiles can be identified and are valuable information for the control strategy. During the scale-up, the amount of PAT within the process can be reduced to only essential process analytics. Simple sensors, such as temperature, pressure, flow rates, and conductivity, in combination with robust hybrid reaction models, can predict process deviations. Additionally, complex sensors such as NMR, FTIR or Raman are high in initial investment and maintenance costs.

We envisage the collection of reaction data during lab-scale optimization as two different approaches. The first approach is to find an optimum for the reaction and build a reaction model

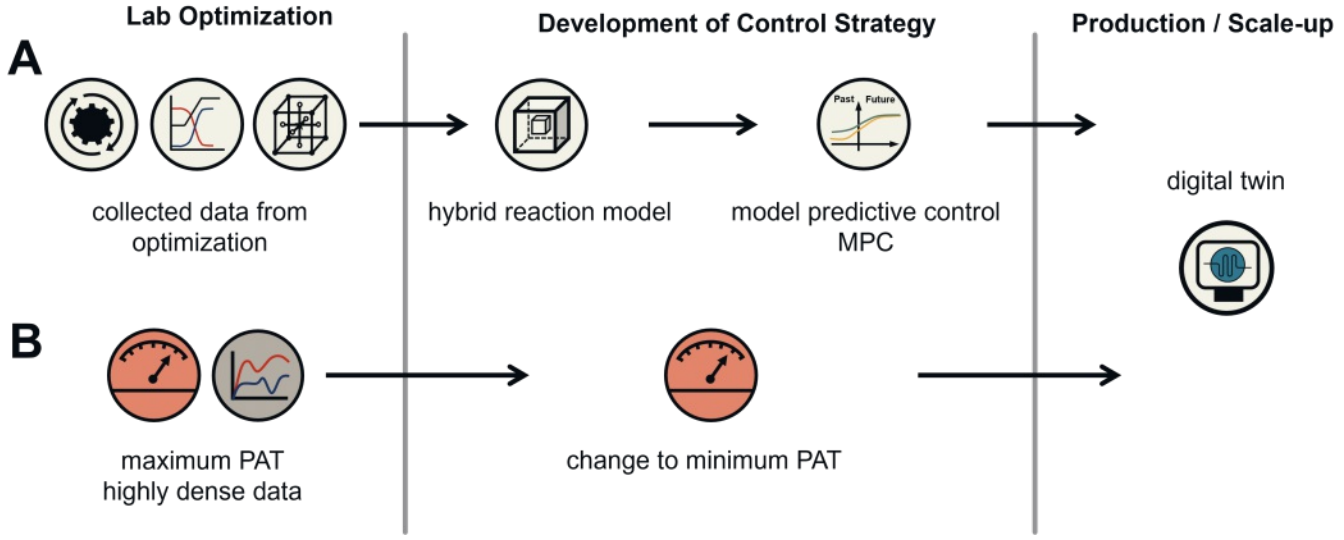

Fig. 3. Implementation of PAT and data-rich experimentation throughout different stages in process development, toward a fully functional digital twin, usable in a production environment.

around this point. An optimum in a broad process space with multiple manipulable variables can be found with self-optimization. This should not only be limited to continuous variables (*e.g.* flow rates), but also include discrete or categorical variables, such as the design of the reactor, different reagents, solvents or catalysts. After the categorical variables are identified (reactor length, reagents, *etc.*) and process variables are narrowed to a smaller range, automated response surface modeling can be a successful way to provide a robust reaction model.

The second approach is to collect kinetic data for the investigated reaction. This can be accomplished by steady-state experiments or dynamic experiments and can be used to build either mechanistically-accurate models, or simplified models based on the observed species. The collected optimization data can then be used to build hybrid reaction models for applications including model predictive control (MPC).

There has been only a handful examples of process control demonstrating automated flow chemistry published in the literature.[44,69–72] The possible reason for this might be that, up to now, the main focus was to automate the platforms, translate batch protocols to flow and explore new reactions with flow technology. In academic laboratories, chemistry platforms are mainly run during the space of a working day and therefore there is no need for such a complex process control system. The integration of a digital twin in a production facility is time consuming, however, can provide several advantages.[73] The instrumentation used can be monitored, and predictive maintenance can be used to spot faults in equipment earlier. Model predictive control can be used to automatically adjust CPPs to maintain CQAs in real time. In case out-of-spec material is produced, real-time release strategies (*e.g.* diversion to waste) or surge tanks can be used.

4. Self-optimization

Self-optimization platforms reduce the labor-intensive task of finding the optimum of a reaction. Our envisioning of a self-optimization platform follows the following general stages (Fig. 4A). 1) The optimization algorithm plans new experimental values and sends them to the control and database. 2) The control software calculates the new process parameters from the variables, sets them, then waits until the system is in steady-state. 3) After analyzing the results with process analytics and processing the data, the control software calculates the derived objectives from the results of the PAT. 4) The final values for the objectives are sent to the optimization algorithm, which suggests a new experiment. Flexibility in choice of the optimization algorithm was important, therefore the algorithm is not directly embedded in the control system.

Self-optimization algorithms can be classified as local or global and single- or multi-objective algorithms.[3,74] A local single objective algorithm is, for example, the Nelder-Mead simplex (NMSIM) algorithm, which has been used with numerous automated flow chemistry platforms.[75,76] The algorithm represents the experimental points as a simplex of n–1 points (where n is the number of optimization variables). In the next iteration of the algorithm, the poorest performing point is substituted by a new experimental point. This creates a new simplex and gradually converges on a local optimum.

The stable noisy optimization by branch and fit (SNOBFIT) algorithm has been successfully employed to find a global single objective optimum in flow chemistry systems.[77–80] The algorithm is gradient-free, meaning it does not need information of the chosen objective function. The optimum is approximated with stochastic linear and quadratic surrogate models. Surrogate models can relate process inputs to complex optimization problems. The stochastic nature of the surrogate models improves the stability against noise.

Global multi-objective algorithms are especially of interest for process chemistry, since the best process conditions often have

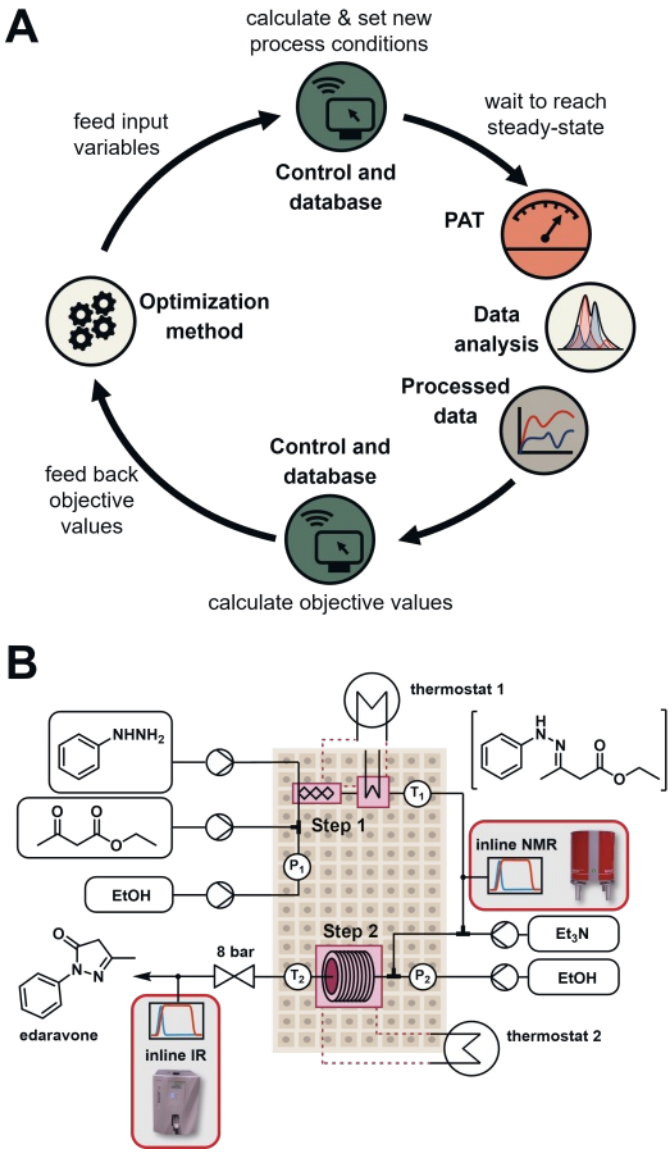

Fig. 4. A) The different stages during a self-optimization experiment. B) Simplified process scheme for the two-step synthesis of edaravone.

contradictory objectives (*e.g.* space-time yield versus product purity). Multi-objective algorithms often use a Bayesian optimization method.[4,81,82] In such methods, the sample data is described using Gaussian process surrogate models. Specific acquisition functions choose the next point to be investigated, balancing between regions which currently have fewer data points (exploration) and regions of known good performance (exploitation).

Typically, chromatography (HPLC or GC) is used as PAT in self-optimization platforms. The advantage of chromatography is that it provides a detailed reaction profile of products and impurities. However, the relatively slow speed of analysis has limited either the reaction complexity (the number of optimizable variables and their accessible ranges) or increased the run time of such platforms for multi-step reactions.[7,9,83]

Our approach was to use fast inline process analytics, namely FTIR and NMR, for the telescoped synthesis of the API edaravone. (Fig. 4B).[6] In combination with advanced data processing (chemometric analysis), the major reaction intermediate could be accurately quantified. A Bayesian optimization algorithm was used to optimize this two-step reaction. In total, seven different variables could be tuned to find the optima for three objectives.

In order to further improve self-optimization platforms, the recorded data should be assessed more critically and a mechanism to identify false positive results should be integrated. Repetition

of experiments throughout the optimization could identify a drift over time (*e.g.* catalyst degradation) and provide more confidence in the obtained data set.

5. Reaction Model Building

Self-optimization algorithms provide the operator with an optimum of the reaction. However, these algorithms generally work as a 'black-box' and do not provide detailed reaction knowledge for further modeling and scale-up studies. Design of experiments (DoE) is a popular approach in the pharmaceutical industry to obtain a reaction surface model.[84,85] Selected experiments within the design space are chosen to identify interaction effects of variables for process optimization.[86] These experiments can be based on different designs, for example full factorial or a face centered design. A multiple linear regression model, including linear, interaction, and quadratic terms, is used to describe the design space. DoE has been extensively used in flow chemistry to optimize reactions, however, the acquisition of data and the analysis part are separated.[14,87–89] This typically requires specialist knowledge in performing the experiments and interpreting the results. Our intention was to connect the execution of experiments and automate the model-building and analysis.[15]

Optipus, an open-source software written in python, can autonomously carry out the complex process of fitting and evaluating reaction models in an iterative fashion, as reactions are performed (Fig. 5A).[15] The boundaries and experimental design for Optipus have to be defined by the user, then the algorithm executes the first set of experiments. The model confidence is constantly evaluated by the measures of R^2 and Q^2, coefficient of determination and predictive relevance, respectively. Additionally, the repeatability of the experimental data is assessed in each experimental step. Another important feature is that the software automatically detects outliers within the experimental data set. If an observed response shows an error of >4 standard deviations from the model-predicted response, the experiment is marked as an outlier.

Optipus has been demonstrated for two different reactions: S_NAr and a photochemical benzylic bromination, each following a different approach (Fig. 5B). The first approach uses two cycles of experimental design: the first to build a broad reaction model, then a more defined one around the initially identified optimum. The second approach uses a self-optimization algorithm to define the optimum reaction space, then performs an experimental design study within this region. Both approaches resulted in excellent quantitative reaction models, relating the input variables (4 and 6 for the first and second reactions, respectively) to the output objective of space-time yield.

The limitation of the software so far is that it can only build the reaction model for one objective. To correctly identify squared terms, a face centered design has to be used. Having *n* variables, a face centered design includes 2^n experiments for the factorial design and an additional $2n$ experiments for the face centered points.

6. Dynamic Experiments

The iterative model building and self-optimization approaches require that the flow system reaches steady state for each experimental set point. If a new experimental point is investigated, set points are changed, and the automated platform usually waits roughly three residence times to ensure a steady state. This dramatically increases the material consumption for each experiment, and the data collected between experiments are typically neglected. However, the transient data between two different steady states can prove to be highly valuable for reaction optimization.[16]

In batch chemistry, the investigation of different reagent stoichiometries is a labor- and resource intensive task. Each investigated point is an individual experiment and needs to be prepared and analyzed. In comparison, in a continuous flow dynamic experiment the change of the reagent equivalents can be captured

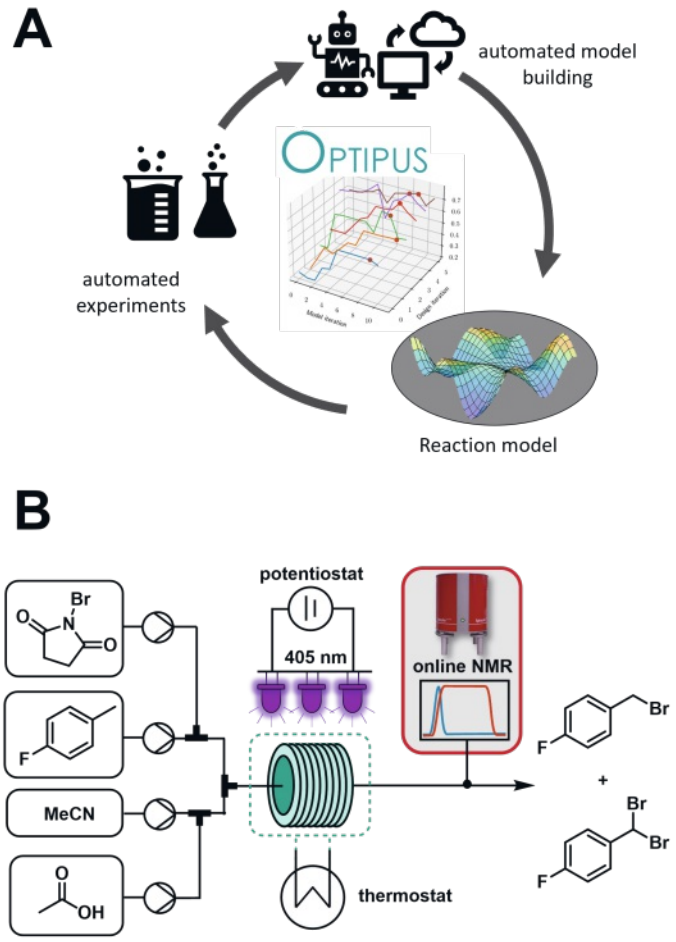

Fig. 5. A) The concept of Optipus, executing fully autonomously experiments and building a reaction model in real time. B) Simplified process scheme for the model reaction a photochemical benzylic bromination.

within one experiment, by gradually changing the input flow rates. During dynamic experiments, one or multiple variables are changed by a defined ramp. This dynamic change can be either linear between two steady states or a non-linear screen through a whole design space.

The sampling frequency of the PAT needs to be fast enough to capture all variations during the dynamic experiment. Typically, fast process analytics such as spectroscopic instruments (NMR, FTIR, Raman) are used for dynamic experimentation. HPLC (run times of 10–30 min) is typically too slow to capture the dynamics of the system. However, it can be used to confirm and validate the experimental points taken by a fast PAT.[18] Additionally, HPLC has been utilized as offline PAT in combination with a fraction collector or as atline process analytics with special interfaces that allow the samples to be parked before analysis.[90] UHPLC (run times <5 min) might be a good compromise for fast data acquisition and sensitivity for trace impurities.

The data acquired from the PAT need to be traced back to their corresponding input conditions by well-characterized reactor models, including the axial diffusion and residence time distribution. The utilization of transient reaction data allows quick scanning through a design space, or kinetic analysis in flow.[17,19,28,91] Additionally, the acquired data can be used for parameterizing or validating simulations in modeling software.

7. Outlook

The world is moving toward a sustainable future. The chemical and pharmaceutical industry must contribute to this goal. Optimization of reactions in flow is typically highly labor-inten-

sive and consumes a lot of material. The digitalization of laboratories allows for faster and more efficient process development, but still has several drawbacks and limitations that must be addressed.

A significant current restriction of these methods is the amount of material needed in the reaction optimization. This material consumption can be drastically reduced by implementing a droplet flow reactor system, as reported by the group of Jensen, amongst others.[10,12,13] In this type of reactor system, only a small reaction droplet, separated by an immiscible solvent or gas, is created. In the near future, we expect to see more of such systems used for data-rich experimentation.

Multi-step reaction cascades are still very difficult to optimize, because of the large number of optimization variables and the results of the previous steps influencing the later ones. Additionally, incompatibilities between steps, such as solid formation, are a big challenge for automated platforms. The data generated during process development must be stored and managed in an efficient manner. Only then can the process optimization data be utilized to accelerate the development of similar processes.

In order to unlock the full potential of digitalization in flow chemistry, educational institutions have to adapt their curricula to provide graduates with the skill set of tomorrow. Pharmaceutical companies have to utilize this knowledge, which is often spread across several different departments. Therefore, the operational strategy must provide resources, as well as support communication and collaboration between these departments. Small and medium-sized companies, with less focus on the implementation of new technologies, are often lacking resource and expertise in one or more of the required fields. This knowledge gap can be filled by either external contracting or strategic hiring decisions.

Traditionally, chemistry was driven by labor-intensive manual lab work. Automation and digitalization are an opportunity to more rapidly address the challenges in the upcoming future. However, chemists will not be able to do this transformation on their own. Therefore, we have to open up to collaboration with other disciplines, to take the leap and go digital.

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[1] A. Gioiello, A. Piccinno, A. M. Lozza, B. Cerra, *J. Med. Chem.* **2020**, *63*, 6624, https://doi.org/10.1021/acs.jmedchem.9b01956.
[2] J.-C. M. Monbaliu, J. Legros, *Lab Chip* **2022**, https://doi.org/10.1039/D2LC00796G.
[3] P. Müller, A. D. Clayton, J. Manson, S. Riley, O. S. May, N. Govan, S. Notman, S. V Ley, T. W. Chamberlain, R. A. Bourne, *React. Chem. Eng.* **2022**, *4*, 987 https://doi.org/10.1039/D1RE00549A.
[4] K. C. Felton, J. G. Rittig, A. A. Lapkin, *Chemistry–Methods* **2021**, *1*, 116, https://doi.org/10.1002/cmtd.202000051.
[5] A. M. Schweidtmann, A. D. Clayton, N. Holmes, E. Bradford, R. A. Bourne, A. A. Lapkin, *Chem. Eng. J.* **2018**, *352*, 277, https://doi.org/10.1016/j.cej.2018.07.031.
[6] P. Sagmeister, F. F. Ort, C. E. Jusner, D. Hebrault, T. Tampone, F. G. Buono, J. D. Williams, C. O. Kappe, *Adv. Sci.* **2022**, *9*, 2105547, https://doi.org/10.1002/advs.202105547.
[7] A. M. K. Nambiar, C. P. Breen, T. Hart, T. Kulesza, T. F. Jamison, K. F. Jensen, *ACS Cent. Sci.* **2022**, *8*, 825, https://doi.org/10.1021/acscentsci.2c00207.
[8] C. Mateos, M. J. Nieves-Remacha, J. A. Rincón, *React. Chem. Eng.* **2019**, *4*, 1536, https://doi.org/10.1039/C9RE00116F.
[9] A. D. Clayton, E. Pyzer-Knapp, M. Purdie, M. Jones, A. Barthelme, J. Pavey, N. Kapur, T. Chamberlain, J. Blacker, R. Bourne, *Angew. Chem. Int. Ed.* **2022**, https://doi.org/10.1002/anie.202214511.
[10] B. J. Reizman, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786, https://doi.org/10.1021/acs.accounts.6b00261.
[11] B. J. Reizman, K. F. Jensen, *Org. Process Res. Dev.* **2012**, *16*, 1770, https://doi.org/10.1021/op3001838.
[12] L. M. Baumgartner, C. W. Coley, B. J. Reizman, K. W. Gao, K. F. Jensen, *React. Chem. Eng.* **2018**, *3*, 301, https://doi.org/10.1039/C8RE00032H.
[13] B. J. Reizman, Y. M. Wang, S. L. Buchwald, K. F. Jensen, *React. Chem. Eng.* **2016**, *1*, 658, https://doi.org/10.1039/c6re00153j.
[14] A. Echtermeyer, Y. Amar, J. Zakrzewski, A. Lapkin, *Beilstein J. Org. Chem.* **2017**, *13*, 150, https://doi.org/10.3762/bjoc.13.18.
[15] S. Knoll, C. E. Jusner, P. Sagmeister, J. D. Williams, C. A. Hone, M. Horn, C. O. Kappe, *React. Chem. Eng.* **2022**, *7*, 2375, https://doi.org/10.1039/D2RE00208F.
[16] S. Mozharov, A. Nordon, D. Littlejohn, C. Wiles, P. Watts, P. Dallin, J. M. Girkin, *J. Am. Chem. Soc.* **2011**, *133*, 3601, https://doi.org/10.1021/ja1102234.
[17] L. Schrecker, J. Dickhaut, C. Holtze, P. Staehle, M. Vranceanu, K. Hellgardt, K. K. (Mimi) Hii, *React. Chem. Eng.* **2023**, *8*, 41 https://doi.org/10.1039/D2RE00271J.
[18] F. Florit, A. M. K. Nambiar, C. P. Breen, T. F. Jamison, K. F. Jensen, *React. Chem. Eng.* **2021**, *6*, 2306, https://doi.org/10.1039/D1RE00350J.
[19] C. A. Hone, N. Holmes, G. R. Akien, R. A. Bourne, F. L. Muller, *React. Chem. Eng.* **2017**, *2*, 103, https://doi.org/10.1039/c6re00109b.
[20] R. Lebl, S. Bachmann, P. Tosatti, J. Sedelmeier, K. Püntener, J. D. Williams, C. O. Kappe, *Org. Process Res. Dev.* **2021**, *25*, 1988, https://doi.org/10.1021/acs.oprd.1c00258.
[21] K. Simon, P. Sagmeister, R. Munday, K. Leslie, C. A. Hone, C. O. Kappe, *Catal. Sci. Technol.* **2022**, *12*, 1799 https://doi.org/10.1039/d2cy00059h.
[22] S. A. Biyani, Y. W. Moriuchi, D. H. Thompson, *Chemistry–Methods* **2021**, *1*, 323, https://doi.org/10.1002/cmtd.202100023.
[23] M. Christensen, L. P. E. Yunker, P. Shiri, T. Zepel, P. L. Prieto, S. Grunert, F. Bork, J. E. Hein, *Chem. Sci.* **2021**, *12*, 15473, https://doi.org/10.1039/d1sc04588a.
[24] A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* **2019**, *62*, 6422, https://doi.org/10.1021/acs.jmedchem.8b01760.
[25] G. Schneider, *Nat. Rev. Drug Discov.* **2018**, *17*, 97, https://doi.org/10.1038/nrd.2017.232.
[26] D. Perera, J. W. Tucker, S. Brahmbhatt, C. J. Helal, A. Chong, W. Farrell, P. Richardson, N. W. Sach, *Science* **2018**, *359*, 429, https://doi.org/10.1126/science.aap9112.
[27] B. M. Wyvratt, J. P. McMullen, S. T. Grosser, *React. Chem. Eng.* **2019**, *4*, 1637, https://doi.org/10.1039/c9re00078j.
[28] J. P. McMullen, B. M. Wyvratt, *React. Chem. Eng.* **2023**, *8*, 137 https://doi.org/10.1039/D2RE00256F.
[29] J. A. Jurica, J. P. McMullen, *Org. Process Res. Dev.* **2021**, *25*, 282, https://doi.org/10.1021/acs.oprd.0c00496.
[30] C. P. Breen, A. M. K. Nambiar, T. F. Jamison, K. F. Jensen, *Trends Chem.* **2021**, *3*, 373, https://doi.org/10.1016/j.trechm.2021.02.005.
[31] S. Chatterjee, M. Guidi, P. H. Seeberger, K. Gilmore, *Nature* **2020**, *579*, 379, https://doi.org/10.1038/s41586-020-2083-5.
[32] M. Rubens, J. Van Herck, T. Junkers, *ACS Macro Lett.* **2019**, *8*, 1437, https://doi.org/10.1021/acsmacrolett.9b00767.
[33] A. Bédard, A. Adamo, K. C. Aroh, M. G. Russell, A. A. Bedermann, J. Torosian, B. Yue, K. F. Jensen, T. F. Jamison, *Science* **2018**, *361*, 1, https://doi.org/10.1038/s41570-018-0031-9.
[34] C. W. Coley, D. A. Thomas, J. A. M. Lummiss, J. N. Jaworski, C. P. Breen, V. Schultz, T. Hart, J. S. Fishman, L. Rogers, H. Gao, R. W. Hicklin, P. P. Plehiers, J. Byington, J. S. Piotti, W. H. Green, A. J. Hart, T. F. Jamison, K. F. Jensen, *Science* **2019**, *365*, eaax1566, https://doi.org/10.1126/science.aax1566.
[35] Z. Crandall, K. Basemann, L. Qi, T. L. Windus, *React. Chem. Eng.* **2022**, *7*, 416, https://doi.org/10.1039/D1RE00265A.
[36] P. Sagmeister, J. D. Williams, C. A. Hone, C. O. Kappe, *React. Chem. Eng.* **2019**, *4*, 1571, https://doi.org/10.1039/C9RE00087A.
[37] P. Sagmeister, R. Lebl, I. Castillo, J. Rehrl, J. Kruisz, M. Sipek, M. Horn, S. Sacher, D. Cantillo, J. D. Williams, C. O. Kappe, *Angew. Chem. Int. Ed.* **2021**, *60*, 8139, https://doi.org/10.1002/anie.202016007.
[38] J. Workman, B. Lavine, R. Chrisman, M. Koch, *Anal. Chem.* **2011**, *83*, 4557, https://doi.org/10.1021/ac200974w.
[39] M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2022**, *26*, 1766, https://doi.org/10.1021/acs.oprd.2c00102.
[40] M. A. Morin, W. Zhang, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2021**, *60*, 20606, https://doi.org/10.1002/anie.202102009.
[41] P. Sagmeister, D. Kaldre, J. Sedelmeier, C. Moessner, K. Püntener, D. Kummli, J. D. Williams, C. O. Kappe, *Org. Process Res. Dev.* **2021**, *25*, 1206, https://doi.org/10.1021/acs.oprd.1c00096.
[42] P. Sagmeister, J. D. Williams, C. A. Hone, C. O. Kappe, *React. Chem. Eng.* **2019**, *4*, 1571 https://doi.org/10.1039/C9RE00087A.
[43] E. Mercer, J. Mack, F. Tahir, D. Lovett, in 'Multivariate Analysis in the Pharmaceutical Industry', Elsevier, **2018**, pp. 385, https://doi.org/10.1016/B978-0-12-811065-2.00019-9.
[44] F. Tahir, E. Mercer, I. Lowdon, D. Lovett, *Control Eng. Pract.* **2018**, *77*, 225, https://doi.org/10.1016/j.conengprac.2018.06.003.

[45] D. Patra, A. K. Mishra, *TrAC - Trends Anal. Chem.* **2002**, *21*, 787, https://doi.org/10.1016/S0165-9936(02)01201-3.
[46] P. Sagmeister, J. Poms, J. D. Williams, C. O. Kappe, *React. Chem. Eng.* **2020**, *5*, 677, https://doi.org/10.1039/D0RE00048E.
[47] F. Alsmeyer, W. Marquardt, *Appl. Spectrosc.* **2004**, *58*, 986, https://doi.org/10.1366/0003702041655421.
[48] F. Alsmeyer, H.-J. Koß, W. Marquardt, *Appl. Spectrosc.* **2004**, *58*, 975, https://doi.org/10.1366/0003702041655368.
[49] E. Kriesten, D. Mayer, F. Alsmeyer, C. B. Minnich, L. Greiner, W. Marquardt, *Chemom. Intell. Lab. Syst.* **2008**, *93*, 108, https://doi.org/10.1016/j.chemolab.2008.05.002.
[50] E. Kriesten, F. Alsmeyer, A. Bardow, W. Marquardt, *Chemom. Intell. Lab. Syst.* **2008**, *91*, 181, https://doi.org/10.1016/j.chemolab.2007.11.004.
[51] J. Meyer-Kirschner, M. Kather, A. Pich, D. Engel, W. Marquardt, J. Viell, A. Mitsos, *Appl. Spectrosc.* **2016**, *70*, 416, https://doi.org/10.1177/0003702815626663.
[52] N. Zientek, C. Laurain, K. Meyer, A. Paul, D. Engel, G. Guthausen, M. Kraume, M. Maiwald, *Magn. Reson. Chem.* **2016**, *54*, 513, https://doi.org/10.1002/mrc.4216.
[53] S. Kern, K. Meyer, S. Guhl, P. Gräßer, A. Paul, R. King, M. Maiwald, *Anal. Bioanal. Chem.* **2018**, *410*, 3349, https://doi.org/10.1007/s00216-018-1020-z.
[54] S. Kern, L. Wander, K. Meyer, S. Guhl, A. R. G. Mukkula, M. Holtkamp, M. Salge, C. Fleischer, N. Weber, R. King, S. Engell, A. Paul, M. P. Remelhe, M. Maiwald, *Anal. Bioanal. Chem.* **2019**, 3037, https://doi.org/10.1007/s00216-019-01752-y.
[55] M. Bornemann-Pfeiffer, J. Wolf, K. Meyer, S. Kern, D. Angelone, A. Leonov, L. Cronin, F. Emmerling, *Angew. Chem. Int. Ed.* **2021**, *60*, 23202, https://doi.org/10.1002/anie.202106323.
[56] T. Väänänen, H. Koskela, Y. Hiltunen, M. Ala-Korpela, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 1343, https://doi.org/10.1021/ci0101051.
[57] E. C. Ferreira, D. M. B. P. Milori, E. J. Ferreira, R. M. Da Silva, L. Martin-Neto, *Spectrochim. Acta - Part B At. Spectrosc.* **2008**, *63*, 1216, https://doi.org/10.1016/j.sab.2008.08.016.
[58] S. Kern, S. Liehr, L. Wander, M. Bornemann-Pfeiffer, S. Müller, M. Maiwald, S. Kowarik, *Anal. Bioanal. Chem.* **2020**, *412*, 4447, https://doi.org/10.1007/s00216-020-02687-5.
[59] F. Fricke, M. Brandalero, S. Liehr, S. Kern, K. Meyer, S. Kowarik, R. Hierzegger, S. Westerdick, M. Maiwald, P. M. Hubner, *IEEE Trans. Emerg. Top. Comput.* **2021**, 1, https://doi.org/10.1109/TETC.2021.3131371.
[60] J. R. Long, V. G. Gregoriou, P. J. Gemperline, *Anal. Chem.* **1990**, *62*, 1791, https://doi.org/10.1021/ac00216a013.
[61] F. Despagne, D. Luc Massart, *Analyst* **1998**, *123*, 157, https://doi.org/10.1039/a805562i.
[62] D. Caramelli, J. M. Granda, S. H. M. Mehr, D. Cambié, A. B. Henson, L. Cronin, *ACS Cent. Sci.* **2021**, *7*, 1821, https://doi.org/10.1021/acscentsci.1c00435.
[63] J. Liu, M. Osadchy, L. Ashton, M. Foster, C. J. Solomon, S. J. Gibson, *Analyst* **2017**, *142*, 4067, https://doi.org/10.1039/C7AN01371J.
[64] T. Casian, A. Farkas, K. Ilyés, B. Démuth, E. Borbás, L. Madarász, Z. Rapi, B. Farkas, A. Balogh, A. Domokos, G. Marosi, I. Tomută, Z. K. Nagy, *Int. J. Pharm.* **2019**, *567*, 1, https://doi.org/10.1016/j.ijpharm.2019.118473.
[65] R. R. de Oliveira, C. Avila, R. Bourne, F. Muller, A. de Juan, *Anal. Bioanal. Chem.* **2020**, *412*, 2151, https://doi.org/10.1007/s00216-020-02404-2.
[66] N. O' Mahony, T. Murphy, K. Panduru, D. Riordan, J. Walsh, *2016 27th Irish Signals Syst. Conf.* **2016**, 1, https://doi.org/10.1109/ISSC.2016.7528449.
[67] P. Sagmeister, R. Hierzegger, J. D. Williams, C. O. Kappe, S. Kowarik, *Digit. Discov.* **2022**, *1*, 405, https://doi.org/10.1039/D2DD00006G.
[68] S. L. Lee, T. F. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, L. X. Yu, J. Woodcock, *J. Pharm. Innov.* **2015**, *10*, 191, https://doi.org/10.1007/s12247-015-9215-8.
[69]I. Castillo, J. Rehrl, P. Sagmeister, R. Lebl, J. Kruisz, S. Celikovic, M. Sipek, D. Kirschneck, M. Horn, S. Sacher, D. Cantillo, J. D. Williams, J. G. Khinast, C. O. Kappe, *J. Process Control* **2023**, *122*, 59, https://doi.org/10.1016/j.jprocont.2022.12.009.
[70] S. Sacher, I. Castillo, J. Rehrl, P. Sagmeister, R. Lebl, J. Kruisz, S. Celikovic, M. Sipek, J. D. Williams, D. Kirschneck, C. O. Kappe, M. Horn, *Chem. Eng. Res. Des.* **2022**, *177*, 493, https://doi.org/10.1016/j.cherd.2021.10.034.
[71] A. Mesbah, J. A. Paulson, R. Lakerveld, R. D. Braatz, *Org. Process Res. Dev.* **2017**, *21*, 844, https://doi.org/10.1021/acs.oprd.7b00058.
[72] R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 144, https://doi.org/10.1002/anie.201409356.
[73] A. Bamberg, L. Urbas, S. Bröcker, M. Bortz, N. Kockmann, *Chem. Eng. Technol.* **2021**, *44*, 954, https://doi.org/10.1002/ceat.202000562.
[74] A. D. Clayton, J. A. Manson, C. J. Taylor, T. W. Chamberlain, B. A. Taylor, G. Clemens, R. A. Bourne, *React. Chem. Eng.* **2019**, *4*, 1545, https://doi.org/10.1039/C9RE00209J.
[75] V. Fath, N. Kockmann, J. Otto, T. Röder, *React. Chem. Eng.* **2020**, *5*, 1281, https://doi.org/10.1039/d0re00081g.
[76] D. Cortés-Borda, E. Wimmer, B. Gouilleux, E. Barré, N. Oger, L. Goulamaly, L. Peault, B. Charrier, C. Truchet, P. Giraudeau, M. Rodriguez-Zubiri, E. Le Grognec, F.-X. Felpin, *J. Org. Chem.* **2018**, *83*, 14286, https://doi.org/10.1021/acs.joc.8b01821.
[77] A. D. Clayton, L. A. Power, W. R. Reynolds, C. Ainsworth, D. R. J. Hose, M. F. Jones, T. W. Chamberlain, A. J. Blacker, R. A. Bourne, *J. Flow Chem.* **2020**, *10*, 199, https://doi.org/10.1007/s41981-020-00086-6.
[78] N. Holmes, G. R. Akien, A. J. Blacker, R. L. Woodward, R. E. Meadows, R. A. Bourne, *React. Chem. Eng.* **2016**, *1*, 366, https://doi.org/10.1039/c6re00059b.
[79] N. Holmes, G. R. Akien, R. J. D. Savage, C. Stanetty, I. R. Baxendale, A. J. Blacker, B. A. Taylor, R. L. Woodward, R. E. Meadows, R. A. Bourne, *React. Chem. Eng.* **2016**, *1*, 96, https://doi.org/10.1039/c5re00083a.
[80] R. A. Skilton, A. J. Parrott, M. W. George, M. Poliakoff, R. A. Bourne, *Appl. Spectrosc.* **2013**, *67*, 1127, https://doi.org/10.1366/13-06999.
[81] K. Y. Nandiwale, T. Hart, A. F. Zahrt, A. M. K. Nambiar, P. T. Mahesh, Y. Mo, M. J. Nieves-Remacha, M. D. Johnson, P. García-Losada, C. Mateos, J. A. Rincón, K. F. Jensen, *React. Chem. Eng.* **2022**, *7*, 1315, https://doi.org/10.1039/D2RE00054G.
[82] B. J. Shields, J. Stevens, J. Li, M. Parasram, F. Damani, J. I. M. Alvarado, J. M. Janey, R. P. Adams, A. G. Doyle, *Nature* **2021**, *590*, 89, https://doi.org/10.1038/s41586-021-03213-y.
[83] A. D. Clayton, A. M. Schweidtmann, G. Clemens, J. A. Manson, C. J. Taylor, C. G. Niño, T. W. Chamberlain, N. Kapur, A. J. Blacker, A. A. Lapkin, R. A. Bourne, *Chem. Eng. J.* **2020**, *384*, 123340, https://doi.org/10.1016/j.cej.2019.123340.
[84] A. Gioiello, V. Mancino, P. Filipponi, S. Mostarda, B. Cerra, *J. Flow Chem.* **2016**, *6*, 167, https://doi.org/10.1556/1846.2016.00012.
[85] S. A. Weissman, N. G. Anderson, *Org. Process Res. Dev.* **2015**, *19*, 1605, https://doi.org/10.1021/op500169m.
[86] R. Leardi, *Anal. Chim. Acta* **2009**, *652*, 161, https://doi.org/10.1016/j.aca.2009.06.015.
[87] C. A. Hone, A. Boyd, A. O'Kearney-Mcmullan, R. A. Bourne, F. L. Muller, *React. Chem. Eng.* **201**9, *4*, 1565, https://doi.org/10.1039/c9re00180h.
[88] C. Waldron, A. Pankajakshan, M. Quaglio, E. Cao, F. Galvanin, A. Gavriilidis, *Ind. Eng. Chem. Res.* **2019**, *58*, 22165, https://doi.org/10.1021/acs.iecr.9b04089.
[89] C. J. Taylor, A. Baker, M. R. Chapman, W. R. Reynolds, K. E. Jolley, G. Clemens, G. E. Smith, A. J. Blacker, T. W. Chamberlain, S. D. R. Christie, B. A. Taylor, R. A. Bourne, *J. Flow Chem.* **2021**, *11*, 75, https://doi.org/10.1007/s41981-020-00135-0.
[90] C. P. Haas, S. Biesenroth, S. Buckenmaier, T. van de Goor, U. Tallarek, *React. Chem. Eng.* **2020**, *5*, 912, https://doi.org/10.1039/D0RE00066C.
[91] J. S. Moore, K. F. Jensen, *Angew. Chem. Int. Ed.* **2014**, *53*, 470, https://doi.org/10.1002/anie.201306468.