

A Review of Inline Infrared and Nuclear Magnetic Resonance Applications in Flow Chemistry

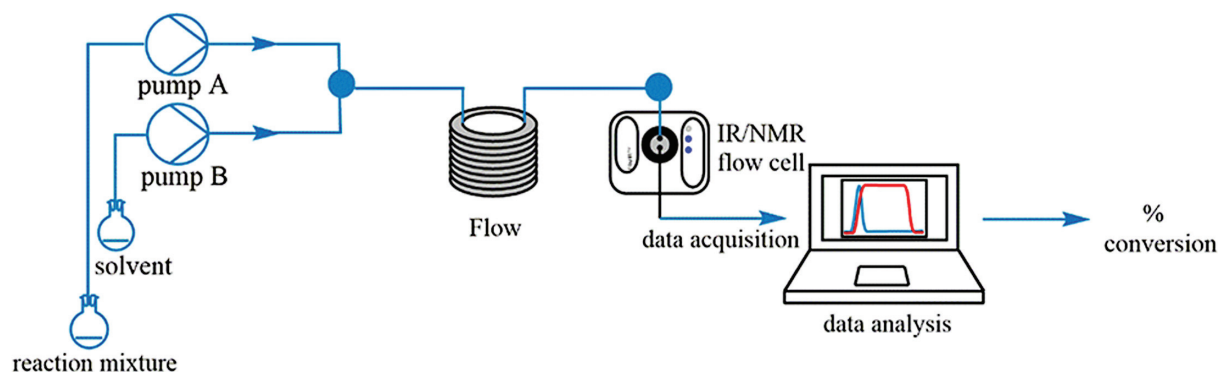
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Abstract

As a safe and efficient synthesis technique, flow chemistry has recently gained attention in the pharmaceutical, materials, and environmental protection industries. However, researchers always face challenges in handling samples and selecting sufficiently flexible analytical techniques. Generally, real-time process analysis is crucial for monitoring reactions. The combination of flow chemistry with real-time process analysis can be beneficial for studying reaction kinetics and thermodynamics, monitoring, and control of the chemical synthesis processes, reaction optimization of macro and microreactors, and qualitative and quantitative analyses of compounds. Thus far, studies investigating the combination of flow chemistry with inline monitoring have included ultraviolet–infrared spectroscopy, Raman spectroscopy, gas chromatography, mass spectrometry, liquid chromatography, nuclear magnetic resonance (NMR) spectroscopy, and other automated conventional or unconventional methods. This review sheds light on applying inline infrared and inline NMR spectroscopies in flow chemistry.

Keywords

- ▶ flow chemistry
- ▶ inline IR
- ▶ inline NMR
- ▶ real-time process analysis
- ▶ automation

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Introduction

In recent years, the field of organic synthesis has developed rapidly. Flow chemistry is a revolutionary achievement in the field of organic chemistry, which has advanced batch chemical synthesis and devices. The most significant features of flow chemistry are the efficiency improvement and increased safety of synthesis processes. Furthermore, common devices like microreactors are superior to batch reactors in terms of mixing time, temperature control, material consumption, and number of intermediate purification steps required for continuous experiments in both academia and industry.¹ However, early applications required manual sampling and transportation of samples to a central analytical laboratory. This process is unsafe and costly, often resulting in an inaccurate and untimely representation of process conditions and delays in analyzing results, which hinder the real-time tracking of process dynamics. Furthermore, the data-utilization insufficiency during this process leads to long development times. Process analysis techniques (PATs) are essential for collecting the results of experiments in any auto-operating platform. PAT devices include mass-flow controllers, as well as temperature, pressure, pH, and conductivity sensors, and they can provide valuable information about the state of the reactor system. Collecting real-time data using immersion probes will improve our understanding of chemical reactions and crystallization. This also eliminates the need to analyze physical interference with the reaction by sampling/quenching and to use time-consuming offline methods, such as high-performance liquid chromatography (HPLC). This is particularly beneficial for water- and/or oxygen-sensitive reactions, the formation of transient intermediates, or reactions for which safe and accurate sampling is difficult, which are often heterogeneous, pressurized, or performed at elevated temperatures.²

A PAT device can be integrated as an inline, online, or at-line sensor. In terms of process types, the PAT can be based on mass spectrometry or spectroscopy techniques, such as nuclear magnetic resonance (NMR), infrared (IR), Raman, and ultraviolet-visible (UV-vis) spectroscopies.³ The sampling frequency of PAT needs to be sufficiently high to capture all the variations during the dynamic experiment. Combined with real-time analysis during compound synthesis, real-time information on intermediates and by-products can be obtained, providing significant material, time, and cost savings. Therefore, combining reactors with inline monitors is particularly important.^{4,5} For example, the combination of microreactors with inline monitors promotes the safe and efficient synthesis of compounds. The integration of flow chemistry into a fully automatic microreactor platform will enable the convenient and efficient observation of the reaction progress. The establishment of kinetic models through the multi-dimensional optimization of reaction parameters can replace the existing labor- and cost-intensive inspection procedures, reduce waste generation, improve the efficiency of the production process, ensure overall sustainability, and guide the reac-

tion to achieve the ideal conditions. Additionally, manual intervention no longer becomes a requirement. There are many kinds of process-analysis techniques⁵⁻¹²; however, this review only discusses the application of inline IR and inline NMR in flow chemistry.

Introduction of Inline IR and NMR Technology

Real-time process-analysis systems include sampling systems, analyzers, sensor technologies, and data-analysis computers with specialized algorithms. These systems are typically located in the laboratory and are expected to operate unattended. The analysis information is usually converted into relevant processing information after its quality is ascertained in the onboard computer system before being transmitted to the process control system. As reliability increases, this information is employed more for closed-loop control rather than the historical open-loop approach, where researchers can view the analysis results to determine if the process control needs to be changed or the data need to be archived for future reference.¹³

Researchers can use inline IR spectroscopy to monitor the distinguishable characteristic peaks formed during the reaction process and obtain the structures of different compounds. Thus, this technique can help us rapidly detect the target compound and can be exploited for qualitative and quantitative compound analyses (analysis time ≤ 1 minute).¹⁴ Furthermore, it can be used for kinetic model prediction because of its high efficiency in collecting kinetic data. Regarding highly exothermic processes, accurate enthalpy and kinetic data are necessary to find safe and optimal operating conditions. This is usually achieved by batch experiments, often requiring large quantities of reactants. To address this problem, a microreactor combined with inline IR was applied to achieve continuous flow in a thermodynamic measurement platform.¹⁵ Inline IR can also be combined with other analysis methods, such as mass spectrometry, to form an inline analysis platform where IR is used to monitor the main components of the reaction. The highly sensitive mass spectrometry technique provides insights into the formation of by-products, enabling the study of complex optimization problems and the full discovery of the potential of inline analysis.¹⁶

NMR spectroscopy has many advantageous features: it is nondestructive and can provide accurate quantitative and structural information. Thus, it is a valuable tool for collecting accurate experimental data for complex processes. Such data are essential for a comprehensive understanding of the process and for the development of reliable process models. NMR can often distinguish structurally similar but distinct compounds in multicomponent mixtures. Furthermore, quantitative results, that is, the composition of the mixtures being studied, can be obtained with little or no calibration.¹⁷ Quantitative NMR spectroscopy has been widely employed to monitor reactions in a variety of devices.¹⁸⁻²² NMR spectroscopy can also be combined with other methods, such as HPLC, to identify complex mixture components.²³

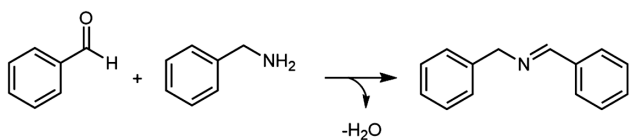


Fig. 1 Imine synthesis.

Introduction to Inline IR and NMR Applications

Kinetic and Thermodynamic Studies

Designing chemical processes requires reliable data on the reaction kinetics. Using the imine syntheses of benzaldehyde and benzylamine as examples (►Fig. 1), Fath et al obtained and modeled the kinetic data using inline Fourier transform infrared (FTIR) spectroscopy, unsteady state conditions, and self-modeling curve resolution.²⁴ This automated microreactor system combined with continuous inline measurements allowed flow experiments to be performed with continuous changes in the flow rate (►Fig. 2). The availability of analytical results in real-time significantly reduced the reagent consumption and the time required to collect sufficient kinetic data. Scaling up from laboratory to pilot or production levels is important for industrial applications. Scaling requires a good understanding of mass and heat transfer, as well as the kinetic model itself. Fath et al used inline FTIR spectroscopy to achieve model-based upscale predictions of reactions in a high-heat-release model from the laboratory to the pilot plant.²⁴ Based on the study of the laboratory-scale dynamics, they successfully scaled the experimental model using FTIR measurements. They increased the channel diameter of the microreactor (inner diameter = 0.5 mm) to fit the nanoscale pilot reactor (diameter = 2 mm), considering the mixing efficiency, residence time distribution, and heat transfer.^{25,26}

Bazzoni et al demonstrated the inline monitoring of a flow photochemical reaction using one-dimensional (1D) and ultrafast two-dimensional (2D) NMR methods in a high magnetic field.²⁷ The reaction mixture exiting the flow reactor flowed through the NMR spectrometer and was directly analyzed. For simple substrates, suitable information could be obtained through 1D ¹H spectra; however, for molecules of higher complexity, the use of 2D experiments

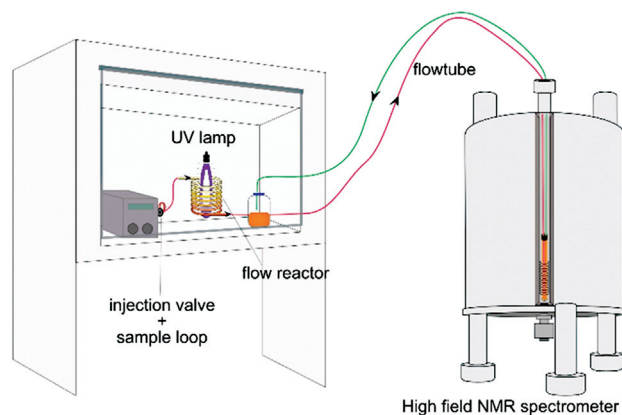


Fig. 3 Bazzoni et al's experimental setup.²⁷

was key in addressing signal overlaps and assignment issues. The experimental setup used in this study is represented schematically in ►Fig. 3. The custom-made flow reactor is connected to a commercial flow tube (InsightMR, Bruker) inserted into a 500 MHz spectrometer and an HPLC pump is used to control the sample flow. The flow tube comprises a 5 mm NMR tube tip and two 7 m long 0.5 mm ID peek capillaries that run to and from the tube tip through a thermostatic line. The entire flow tube has a volume of ca. 4 mL. The reaction mixture is introduced through the 5 mL injection loop, and it flows through the reactor to the NMR detection system. The flow stops during the NMR experiments. Note that for photochemical reactions, the reactivity is restrained to the section of the capillary exposed to light, and this allows the accurate estimation of the residence time even with a long capillary connecting the flow reactor to the analytical system (►Fig. 3). Reaction monitoring provides information on the reaction progress and kinetics and is crucial for mechanistic understanding and optimization.

For rapid reactions, microreactor NMR probes can be used to determine reaction kinetics at different temperatures.²¹ Scheithauer et al used a novel microreactor NMR probe that combines the advantages of online flow ¹H NMR spectroscopy and microreaction techniques.²⁸ The kinetic model of the reaction was developed, and the rate constants were fitted to

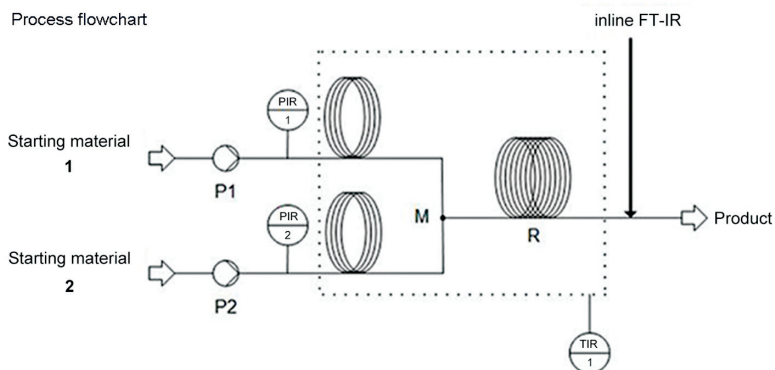
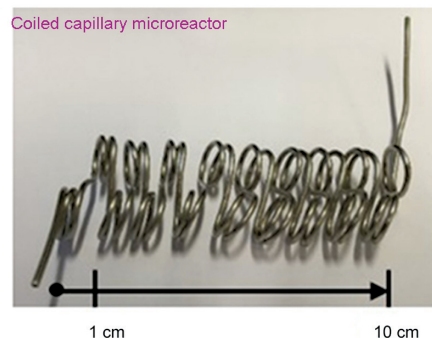


Fig. 2 Fath et al's microreactor setup for kinetic experiment.²⁴



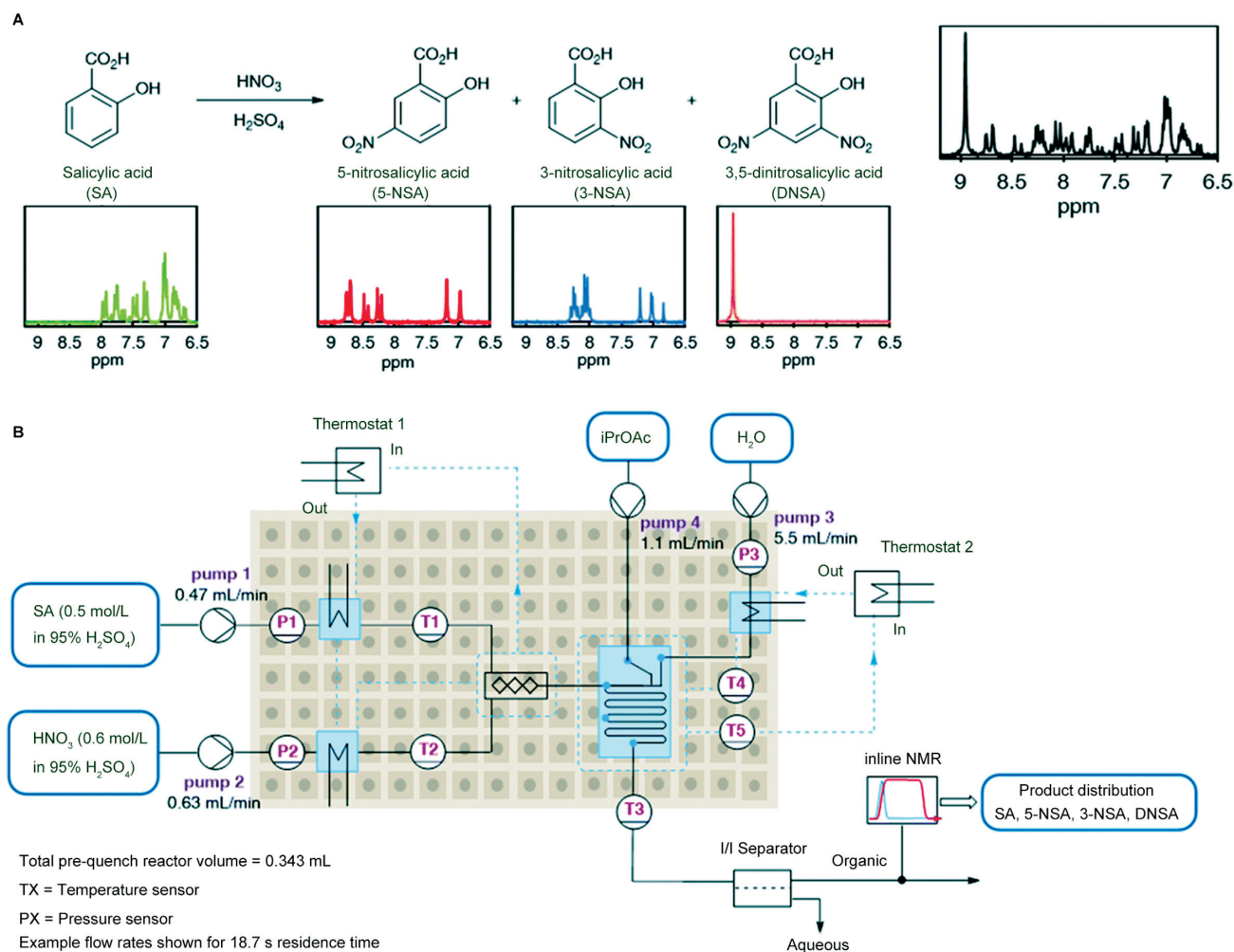


Fig. 4 Sagmeister et al.'s inline benchtop NMR in a complex nitration reaction in flow.³¹ (A) Reaction scheme and the representative low-field NMR spectrum. (B) Continuous flow chemistry. NMR, nuclear magnetic resonance.

the new experimental data. The kinetic model developed in this study described, for the first time, the kinetic effects of acetaldehyde and water over a wide range of temperature and pH values.^{28–30}

Sagmeister et al demonstrated the use of inline benchtop NMR to optimize a complex nitration reaction in flow, using a multivariate analysis statistical approach for data processing.³¹ They accurately quantified four overlapping species, which enabled the generation of a robust design for an experiment model with the accurate evaluation of dynamic experiments (► Fig. 4). Even if the data-acquisition period is very short (2.0 seconds), the advantages of benchtop NMR in flow-chemistry automation optimization, mechanism experiment, and process control were realized.

Rubens et al developed an automated polymer-synthesis platform based on an inline low-field NMR spectrometer.³² By monitoring the monomer conversion rates over the residence time range of the continuous reactor, the platform could construct accurate and efficient polymer kinetic curves. The machine-assisted self-optimization procedure allowed the reaction to be stopped at any given preselected conversion rate, resulting in unprecedented polymer-syn-

thesis reproducibility. Additionally, they proposed an automated synthesis platform based on continuous flow that can rapidly screen polymerization reactions. The platform used inline monitoring to obtain real-time analysis data. The software was developed to guide data acquisition and, most importantly, to enable the autonomous performance of reactions and analysis. Further algorithms could automatically detect errors in the experiment and purge the wrong data. The data were aggregated and made directly available in a machine-readable manner, enabling the creation of “big data” for dynamic information that was not subject to individual user biases and system errors (► Fig. 5).³³

Monitoring and Controlling the Chemical Synthesis Process

Inline IR can also be applied for the precise addition of reagents in continuous flow. Lange et al developed a method to precisely control the addition of reagents in a multistep operation.³⁴ Using inline IR monitoring and new LabVIEW software, additional pumps could be controlled to distribute more reagents in real-time, depending on the concentration

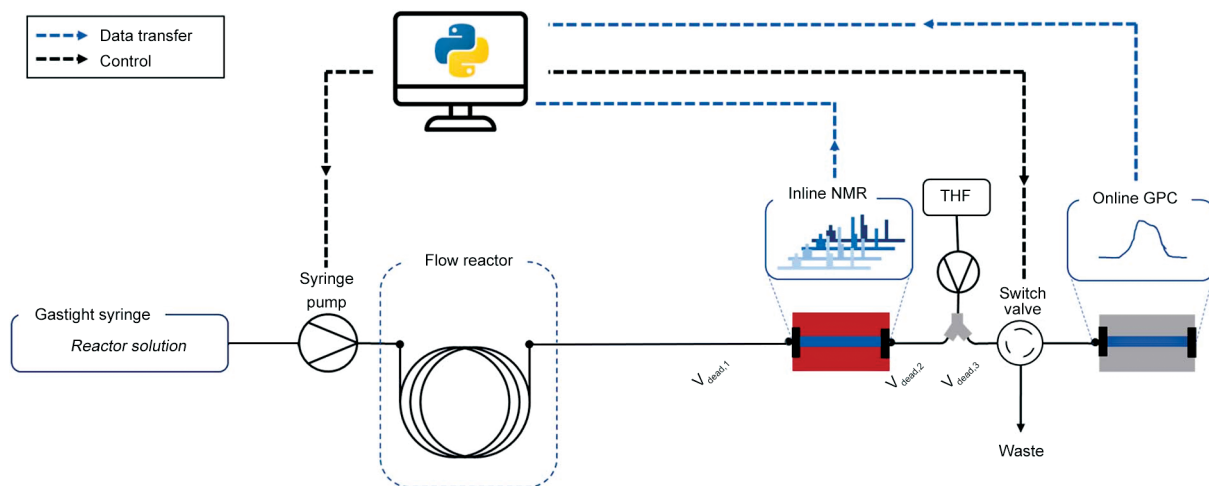


Fig. 5 Automated polymer screening platform.³³

of the reaction intermediates. This enabled accurate mixing at perfect times (which significantly improved the product quality) and the piecewise chemical-flow processing of extended reaction sequences.^{34,35}

The biggest problem with esterification is the reversibility of the reaction in most cases. Schnoor et al used inline IR for calibration during continuous esterification.³⁶ The full potential of inline attenuated total reflectance–FTIR spectroscopy of continuous reactor units was revealed by introducing a new calibration method that bridges the gap among continuous synthesis, measurement, calibration, and analysis on a bench scale (→**Fig. 6**). Further, fully automatic reaction mixture calibration under process conditions was achieved. The use of different components highlights the robustness of the calibration method in determining the kinetic parameters. Transform-based calibration significantly improves the precision of the analysis. The difference is that the new method requires only two formulated calibra-

tion mixtures. In this way, this method can also be applied to large-scale processes, and it allows the use of a single measurement setup from the laboratory to the industrial scale.³⁶

Marchand et al utilized a fast and mobile-compatible diffusion NMR experiment that enabled the collection of accurate diffusion data for samples with flow rates of up to 3 mL/min.¹⁹ This assay was employed to monitor the continuous-flow synthesis of Schiff bases with a temporal resolution of approximately 2 minutes. Wu et al conducted operational NMR studies of anthraquinone/ferrocyanide-based redox flow batteries (RFBs) on a low-cost and compact 43 MHz desktop system,³⁷ revealing the reactive intermediates and crossovers in reduction–oxidation cells. The operating-table NMR approach is expected to be widely used for flow electrochemical studies in different applications, including RFBs, carbon dioxide capture and utilization, ammonia synthesis, desalination, and organic electrochemical syntheses.

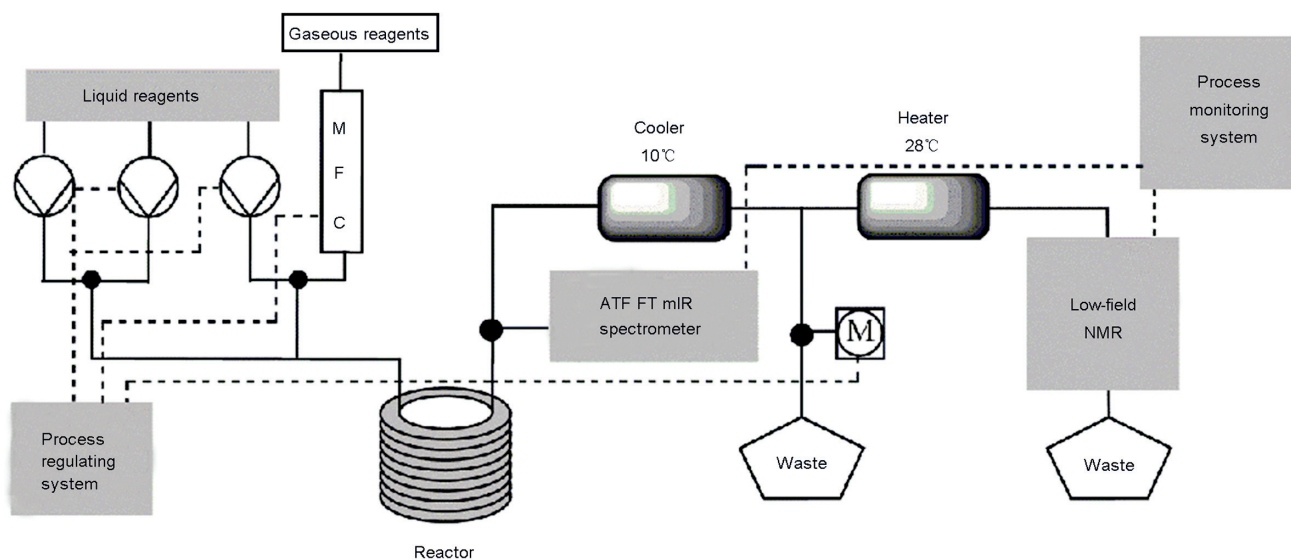


Fig. 6 Schnoor et al's inline IR for calibration in continuous esterification reaction.³⁶ IR, infrared.

Reaction Optimization of Macro- and Microreactors

Since combining inline monitoring with a platform for automated reaction optimization can improve efficiency, Fath et al developed an enhanced autonomous microfluidic reactor platform for organolithium and epoxide reactions that continuously combined inline FTIR spectroscopy with inline mass spectrometry (►Fig. 7).¹⁶ The self-optimization platform achieved model-free autonomous optimization without manual intervention and was employed to determine the optimal reaction conditions for organic synthesis involving complex reaction mechanisms. Inline FTIR measurements were used to monitor the main components of the reaction, whereas the highly sensitive mass spectrometry provided insights into the formation of by-products. Unlike the case in previous studies, no chromatographic separation was performed before the mass spectrometry; thus, greatly accelerating the analytical process. This research presented a new method for solving complex multi-dimensional optimization problems and maximizing product yield and purity.¹⁶

Simon et al improved the efficiency of the multiphase catalytic hydrogenation reaction using inline IR spectrometry.³⁸ One of the main potential disadvantages of heterogeneous catalytic hydrogenation is substrate failure, which leads to catalyst deactivation. Functional/heterocyclic tolerant multiphase hydrogenation reactions could be evaluated efficiently and rapidly using automated continuous flow and real-time analysis platforms. Simon et al used inline FTIR and inline ultra-HPLC (UHPLC) as orthogonal analytical methods to rapidly acquire and quantify major chemicals (substrates, products, and all additives) using a mobile platform (►Fig. 8). Therefore, changes in the reaction results and the stability of additives to the reaction conditions were evaluated. In particular, real-time quantification of chemicals by FTIR using advanced data-analysis models (partial least squares regression [PLS]) helped them to generate quantitative data early in development and understand the sensitivity to reaction conditions with different functional groups and

heterocycles. The method was applied to the reduction of nitrobenzene compounds with a heterogeneous catalyst (Pd/Al₂O₃) and hydrogen (►Fig. 9). The experimental workload was significantly reduced.³⁸

Van den Broek et al used a microreactor with inline IR analysis for the Vilsmeier–Haack formylation (►Fig. 10) to produce thermally labile intermediates in continuous flow (►Fig. 11).³⁹ The main drawback encountered in using UV to measure the formation of unstable intermediates was that real-time analysis could not be conducted without using additional solvents, such as acetonitrile. This drawback was overcome by connecting the Mettler Toledo FlowIR IR flow cell to the microreactor outlet. The data obtained from this inline IR analysis provided insights not available from other sources, where the reaction time, temperature, and molar ratio were easily optimized as process parameters. Thus, the reaction scale was expanded, and the continuous production of 2-formyl pyrrole was successful, with a yield of 5.98 g/h. Similarly, inline IR can be used to monitor the preparation of standard reagents, which is easier than titration or gas chromatography/NMR techniques. In particular, inline IR combined with flow chemistry can optimize the reaction conditions and expand the reaction scale for the formation of format reagents.^{40,41}

Henry et al performed the thermal decomposition of alkoxy alkyne under flow conditions and subsequently captured amide and ester with amine and alcohol.⁴² Using inline IR monitoring of temperature and flow-rate changes, the process of alkoxy alkyne conversion into amide was monitored. The conversion rates of EtO, iPrO, and tBuO alkoxy alkyne were greater than 95% in the reaction time of 10 minutes.

Rueping et al studied the asymmetric organocatalytic hydrogenation of benzoxazine, quinoline, and hydrogen in italic compounds in a continuous-flow microreactor.⁴³ The combination of the ReactIR flow cell and microreactor as the inline monitoring equipment optimized the reaction parameters rapidly and easily. The reduction effect, yield of the separated product, and enantiomer selectivity were all improved.

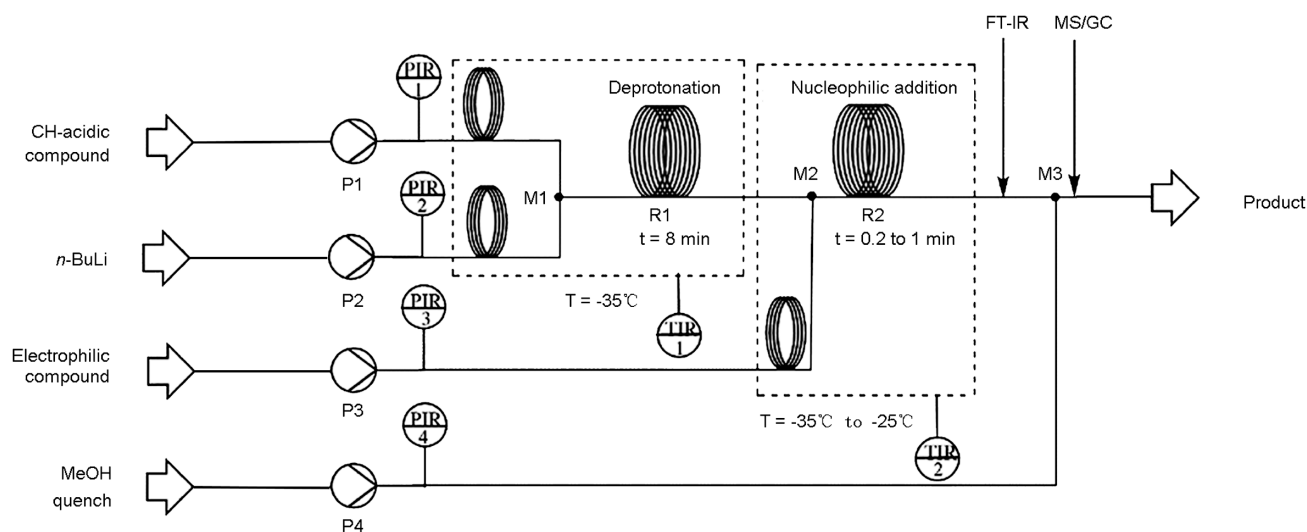


Fig. 7 Fath et al's microreactor setup for organometallic synthesis with *n*-butyllithium.¹⁶

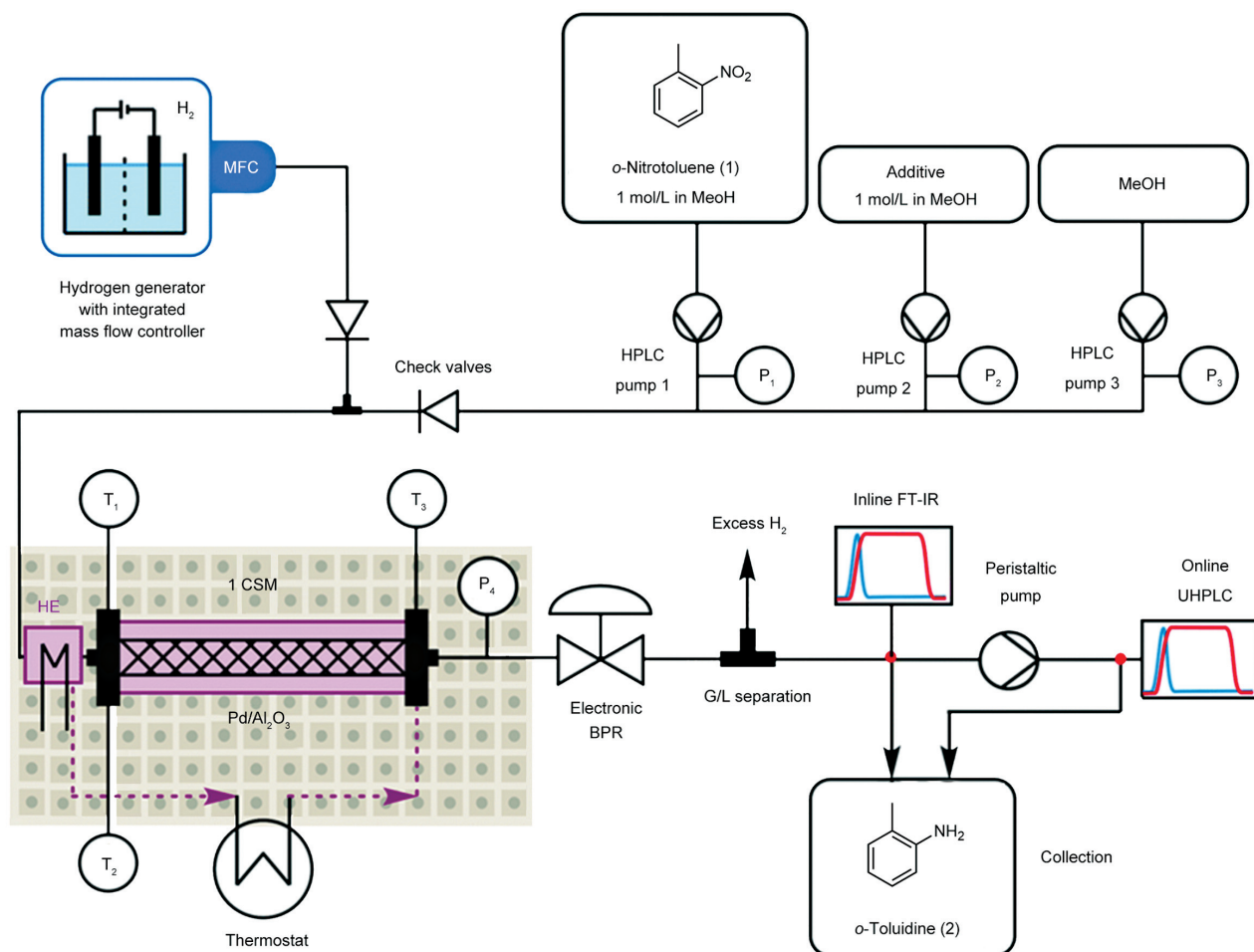


Fig. 8 Simon et al's flow reactor and analytics setup in the hydrogenation reaction.³⁸

Schotten et al optimized the continuous-flow synthesis of difluoromethyl trimethyl silane (TMSCF₂H) with the Ruppert-Prakash reagent (TMSCF₃) using inline real-time NMR and temperature measurements (→ **Fig. 12**).⁴⁴ These measurements

were used to maximize the spatiotemporal yield to ensure the safety of the heat-release process. Thus, the spatiotemporal yield was three times that of the reported batch procedure, with 25 g of pure TMSCF₂H isolated after 105 minutes.

Traditional substrate scope



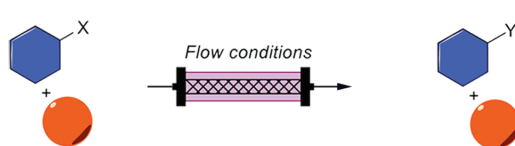
- + Electronic and steric effects
- + Quantitative with regards to yield
- Limited substrate accessibility
- No information regarding secondary functionality

Robustness (intermolecular) screening



- + Information on secondary functionality
- + Simple to implement
- + Semi-quantitative with regards to substrate, product and additives
- No information on electronic and steric effects
- Offline analysis

The approach outlined in Simon et al' work



- + Measured at partial and full conversion
- + Catalyst performance over time
- + Precise parameter control in flow
- + Automated and real-time analysis
- No information on electronic and steric effects
- More advanced calibration and modeling techniques

Fig. 9 Simon et al's continuous flow and real-time analytics platform for catalytic reaction screening.³⁸

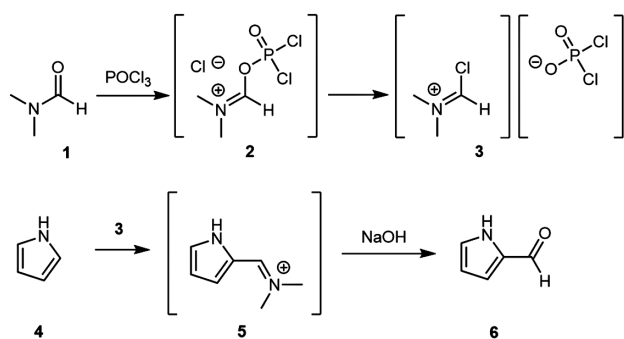


Fig. 10 Vilsmeier-Haack formylation of pyrrole.

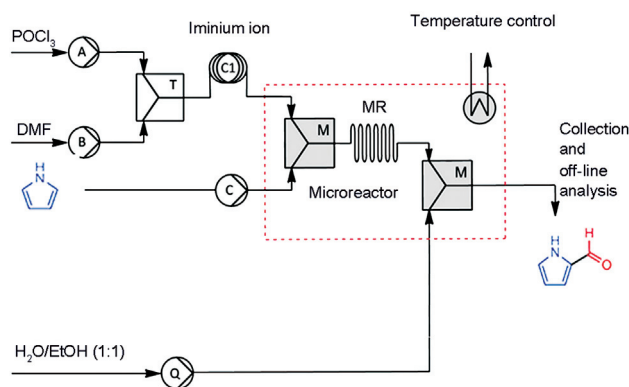


Fig. 11 Schematic drawing of the microreactor setup.

Qualitative and Quantitative Analysis of Compounds

In addition, to its qualitative function in continuous-flow synthesis, inline IR can be used for quantitative analyses in continuous-flow synthesis.⁴⁵ Rao et al used IR spectroscopy to understand the processes of ketonization and sulfonation to form tetrasubstituted acyclic olefins.⁴⁶ Ketene formation and sulfonation were monitored with ReactIR in a two-step one-pot reaction. A univariate quantitative model was established based on the peak height of the ketone-carbonyl IR spectrum of raw materials. The model was used to determine the starting material consumption rate and the endpoint for various reaction conditions. For the second step of the reaction, the vinyl sulfonate formation step, the entire IR

spectrum was analyzed, and offline HPLC data were collected to measure the ratio of the *E* to *Z* tetrasubstituted methyl ethyl sulfonate products. A multivariate PLS model was developed using principal component analysis and PLS regression to quantitatively predict the relative contents of the *E* and *Z* stereoisomers in the new reaction.

The use of NMR spectroscopy to obtain both quantitative and qualitative information was particularly beneficial for the study of complex reaction systems containing multiple components. Maiwald et al used ¹³C NMR quantitative spectroscopy to study the chemical equilibrium of a formaldehyde-water-methanol ternary liquid mixture.⁴⁷ Their study considerably expanded the range of data on the composition of these complex mixtures, such as the distribution of formaldehyde among different species. Experiments conducted independently in two laboratories showed that NMR spectroscopy could provide systematically reliable quantitative data, with an absolute error generally less than 0.5%.

Conclusion

The combination of continuous-flow and real-time process analyses considerably improves chemical synthesis; however, this approach is fraught with challenges, such as the summit overlap generated in IR or Raman spectra of different compounds with similar structures. Overlapping peaks hinder the quantitative analysis of the spectra, and extensive and cumbersome calibration procedures are often required for all components over a wide concentration range. The ability of inline desktop NMR is occasionally limited by its low spectral resolution, which also leads to the abovementioned problems. The disadvantages of NMR spectroscopy are its low sensitivity (i.e., low detection limit) and low signal-acquisition rate. In most cases, the increase in the signal-acquisition rate comes at the expense of sensitivity. To minimize the influence of the detector on the concentration distribution, the benchtop NMR instruments currently in the market are limited to operating within a narrow temperature window close to the operating temperature of the magnet, and the instruments are used at 28°C. Therefore, active temperature control of compact NMR probes is very promising in the field of reaction monitoring; however, it is yet to be studied and developed.

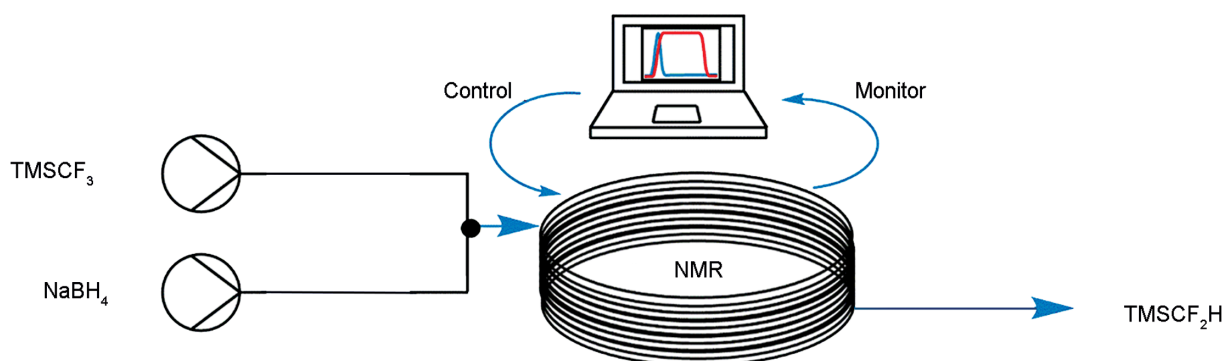


Fig. 12 TMSCF₂H synthesis. TMSCF₂H, difluoromethyl trimethyl silane.

In addition, to continuous-flow reaction monitoring, inline IR and inline NMR spectroscopy can be adopted to monitor photoelectric reactions in complex biological fluids⁴⁸ and material changes⁴⁹ or to safely detect⁵⁰ amino acid activity for obtaining proof of polymerization behavior,⁵¹ among many areas.

Typically, fast process analyses, such as spectroscopy techniques (NMR, FTIR, and Raman) are used for dynamic experiments. HPLC, which runs for 10 to 30 minutes, is usually too slow to capture the dynamics of the system. However, it can be used to confirm and validate experimental points quickly. In addition, HPLC instruments have been used as offline PAT devices in combination with a fraction collector or as an inline process-analysis device with special interfaces that allow samples to clump together before analysis. UHPLC (run time ≤ 5 minute) may offer a good balance between fast data acquisition and sensitivity to trace impurities. These instruments can provide fast results to control systems (often < 5 seconds per data point) to make data-driven (automated) decisions and control processes in real-time. Although online or inline chromatography provides information on impurity profiles and trace impurities, long measurement times between mixing and first data acquisition are required due to the separation of species. Therefore, more appropriate data-processing methods are required. The introduction of algorithm-assisted synthesis and machine learning is currently driving fundamental evolution in the way laboratory procedures are conducted. Although human intuition can only partially predict optimal conditions, these computer-based methods can significantly improve the accuracy and precision of chemical syntheses. Automation and digitalization provide opportunities to respond more rapidly to future challenges. However, chemists cannot accomplish this transformation alone; therefore, we must be open to collaborating with other disciplines to make the leap and go digital.

Conflict of Interest

None declared.

References

- Brandão P, Pineiro M, Pinhoe Melo TMVD. Flow chemistry: towards a more sustainable heterocyclic synthesis. *Eur J Org Chem* 2019;2019(43):7188–7217
- Workman J Jr, Lavine B, Chrisman R, Koch M. Process analytical chemistry. *Anal Chem* 2011;83(12):4557–4578
- Morin MA, Zhang WP, Mallik D, Organ MG. Sampling and analysis in flow: the keys to smart, more controllable, and sustainable fine-chemical manufacturing. *Angew Chem Int Ed Engl* 2021;60(38):20606–20626
- Lee WG, Zell MT, Ouchi T, Milton MJ. NMR spectroscopy goes mobile: using NMR as process analytical technology at the fume hood. *Magn Reson Chem* 2020;58(12):1193–1202
- Fabry DC, Sugiono E, Rueping M. Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems. *React Chem Eng* 2016;1(02):129–133
- Littwin G. Heat transport characteristics of additively manufactured periodic open cellular structures as novel catalyst supports. *Chemieingenieurtechnik (Weinh)* 2020;92(09):1345
- Fath V, Kockmann N, Otto J, Röder T. Self-optimising processes and real-time-optimisation of organic syntheses in a microreactor system using Nelder–Mead and design of experiments. *React Chem Eng* 2020;5(07):1281–1299
- Fitzpatrick DE, Battilocchio C, Ley SV. A novel internet-based reaction monitoring, control, and autonomous self-optimization platform for chemical synthesis. *Org Process Res Dev* 2015;20(02):386–394
- Ingham RJ, Battilocchio C, Hawkins JM, Ley SV. Integration of enabling methods for the automated flow preparation of piperazine-2-carboxamide. *Beilstein J Org Chem* 2014;10:641–652
- Skilton RA, Parrott AJ, George MW, Poliakov M, Bourne RA. Real-time feedback control using online attenuated total reflection Fourier transform infrared (ATR FT-IR) spectroscopy for continuous flow optimization and process knowledge. *Appl Spectrosc* 2013;67(10):1127–1131
- Moore JS, Jensen KF. Automated multitrajectory method for reaction optimization in a microfluidic system using online IR analysis. *Org Process Res Dev* 2012;16(08):1409–1415
- Moore JS, Jensen KF. “Batch” kinetics in flow: online IR analysis and continuous control. *Angew Chem Int Ed Engl* 2014;53(02):470–473
- Sagmeister P, Williams JD, Kappe O. The rocky road to a digital lab. *Chimia (Aarau)* 2023;77(05):300–306
- Andrews GP, Jones DS, Senta-Loys Z, et al. The development of an inline Raman spectroscopic analysis method as a quality control tool for hot melt extruded ramipril fixed-dose combination products. *Int J Pharm* 2019;566:476–487
- Ładosz A, Kuhnle C, Jensen KF. Characterization of reaction enthalpy and kinetics in a microscale flow platform. *React Chem Eng* 2020;5(11):2115–2122
- Fath V, Lau P, Greve C, Weller P, Kockmann N, Röder T. Simultaneous self-optimisation of yield and purity through a successive combination of inline FT-IR spectroscopy and online mass spectrometry in flow reactions. *J Flow Chem* 2021;11(03):285–302
- Brächer A, Kreußler LM, Qamar S, Seidel-Morgenstern A, von Harbou E. Application of quantitative inline NMR spectroscopy for investigation of a fixed-bed chromatographic reactor process. *Chem Eng J* 2018;336:518–530
- Poljanšek I, Šebenik U, Krajnc M. Characterization of phenol-urea-formaldehyde resin by inline FTIR spectroscopy. *J Appl Polym Sci* 2006;99(05):2016–2028
- Marchand A, Mishra R, Bernard A, Dumez JN. Online reaction monitoring with fast and flow-compatible diffusion NMR spectroscopy. *Chemistry* 2022;28(52):e202201175
- Brächer A, Hoch S, Albert K, et al. Thermostatted micro-reactor NMR probe head for monitoring fast reactions. *J Magn Reson* 2014;242:155–161
- Brächer A, Behrens R, von Harbou E, Hasse H. Application of a new micro-reactor ^1H NMR probe head for quantitative analysis of fast esterification reactions. *Chem Eng J* 2016;306:413–421
- Schmid E, Rondeau S, Rudszyk T, Nirschl H, Guthausen G. Inline NMR via a dedicated V-shaped sensor. *Sensors (Basel)* 2023;23(05):2388
- Cardoza LA, Almeida VK, Carr A, Larive CK, Graham DW. Separations coupled with NMR detection. *Trends Analyt Chem* 2003;22(10):766–775
- Fath V, Lau P, Greve C, Kockmann N, Röder T. Efficient kinetic data acquisition and model prediction: continuous flow microreactors, inline fourier transform infrared spectroscopy, and self-modeling curve resolution. *Org Process Res Dev* 2020;24(10):1955–1968
- Fath V, Szmajis S, Lau P, Kockmann N, Röder T. Model-based scale-up predictions: from micro- to millireactors using inline fourier transform infrared spectroscopy. *Org Process Res Dev* 2019;23(09):2020–2030
- Heinze M, Starke S, Händler M, et al. Combination of nuclear magnetic resonance spectroscopy and nonlinear methods to

- analyze the copolymerization of phosphonic acid derivatives. *J Appl Polym Sci* 2019;136:48256
- 27 Bazzoni M, Lhoste C, Bonnet J, et al. In-line multidimensional NMR monitoring of photochemical flow reactions. *Chemistry* 2023;29(20):e202203240
- 28 Scheithauer A, Brächer A, Grützner T, et al. Online ¹H NMR spectroscopic study of the reaction kinetics in mixtures of acetaldehyde and water using a new microreactor probe head. *Ind Eng Chem Res* 2014;53(45):17589–17596
- 29 Wakabayashi S, Takumi M, Kamio S, Wakioka M, Ohki Y, Nagaki A. Flow-chemistry-enabled synthesis of 5-diethylboryl-2,3'-bipyridine and its self-assembly dynamics. *Chemistry* 2023;29(09):e202202882
- 30 Bernstein MA, Stefinović M, Sleight CJ. Optimising reaction performance in the pharmaceutical industry by monitoring with NMR. *Magn Reson Chem* 2007;45(07):564–571
- 31 Sagmeister P, Poms J, Williams JD, Kappe CO. Multivariate analysis of inline benchtop NMR data enables rapid optimization of a complex nitration in flow. *React Chem Eng* 2020;5(04):677–684
- 32 Rubens M, Van Herck J, Junkers T. Automated polymer synthesis platform for integrated conversion targeting based on inline benchtop nmr. *ACS Macro Lett* 2019;8(11):1437–1441
- 33 Van Herck J, Abeysekera I, Buckinx AL, et al. Operator-independent high-throughput polymerization screening based on automated inline NMR and online SEC. *Digit Discov* 2022;1(04):519–526
- 34 Lange H, Carter CF, Hopkin MD, et al. A breakthrough method for the accurate addition of reagents in multi-step segmented flow processing. *Chem Sci (Camb)* 2011;2(04):765–769
- 35 Qian Z, Baxendale IR, Ley SV. A continuous flow process using a sequence of microreactors with in-line IR analysis for the preparation of N,N-diethyl-4-(3-fluorophenyl)piperidin-4-ylidenemethyl benzamide as a potent and highly selective δ -opioid receptor agonist. *Chemistry* 2010;16(41):12342–12348
- 36 Schnoor JK, Schulte LD, Liauw MA. Heat on – calibration of ir spectroscopy at process conditions for continuous esterification. *Chemieingenieurtechnik (Weinh)* 2020;92(10):1467–1473
- 37 Wu B, Aspers RLEG, Kentgens APM, Zhao EW. Operando benchtop NMR reveals reaction intermediates and crossover in redox flow batteries. *J Magn Reson* 2023;351:107448
- 38 Simon K, Sagmeister P, Munday R, Leslie K, Hone CA, Kappe CO. Automated flow and real-time analytics approach for screening functional group tolerance in heterogeneous catalytic reactions. *Catal Sci Technol* 2022;12(06):1799–1811
- 39 Van den Broek SAMW, Leliveld JR, Becker R, et al. Continuous flow production of thermally unstable intermediates in a micro-reactor with inline IR-analysis: controlled vilsmeier–haack formylation of electron-rich arenes. *Org Process Res Dev* 2012;16(05):934–938
- 40 Brodmann T, Koos P, Metzger A, Knochel P, Ley SV. Continuous preparation of arylmagnesium reagents in flow with inline IR monitoring. *Org Process Res Dev* 2011;16(05):1102–1113
- 41 Menges-Flanagan G, Deitmann E, Gössl L, Hofmann C, Löb P. Scalable continuous synthesis of grignard reagents from in situ-activated magnesium metal. *Org Process Res Dev* 2020;24(02):315–321
- 42 Henry C, Bolien D, Ibanescu B, et al. Generation and trapping of ketenes in flow. *Eur J Org Chem* 2015;2015(07):1491–1499
- 43 Rueping M, Bootwicha T, Sugiono E. Continuous-flow catalytic asymmetric hydrogenations: reaction optimization using FTIR inline analysis. *Beilstein J Org Chem* 2012;8:300–307
- 44 Schotten C, Howard JL, Jenkins RL, Codina A, Browne DL. A continuous flow-batch hybrid reactor for commodity chemical synthesis enabled by inline NMR and temperature monitoring. *Tetrahedron* 2018;74(38):5503–5509
- 45 Koch C, Posch AE, Goicoechea HC, Herwig C, Lendl B. Multi-analyte quantification in bioprocesses by Fourier-transform-infrared spectroscopy by partial least squares regression and multivariate curve resolution. *Anal Chim Acta* 2014;807:103–110
- 46 Rao KS, St-Jean F, Kumar A. Quantitation of a ketone enolization and a vinyl sulfonate stereoisomer formation using inline IR spectroscopy and modeling. *Org Process Res Dev* 2019;23(05):945–951
- 47 Maiwald M, Fischer HH, Ott M, et al. Quantitative NMR spectroscopy of complex liquid mixtures: methods and results for chemical equilibria in formaldehyde-water-methanol at temperatures up to 383 k. *Ind Eng Chem Res* 2003;42(02):259–266
- 48 Tang D, Gong M, Yu J, Guo L, Di J. System-level performance prediction for infrared systems based on energy redistribution in infrared images. *IEEE Trans Ind Electron* 2022;69(02):2000–2011
- 49 Svatunek D, Eilenberger G, Denk C, et al. Live monitoring of strain-promoted azide alkyne cycloadditions in complex reaction environments by inline ATR-IR spectroscopy. *Chemistry* 2020;26(44):9851–9854
- 50 Zhou G, Emerson K, Majusiak E, Anderson C, Sudah O. Safe scale-up of processes containing hazardous species in the headspace with inline IR. *Org Process Res Dev* 2012;16(02):204–213
- 51 Freudenberg J, Binder WH. Chirality control of screw-sense in aib-polymers: synthesis and helicity of amino acid-functionalized polymers. *ACS Macro Lett* 2020;9(05):686–692