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Hybrid Enabling Technologies for Organic Synthesis

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Abstract: In this personal perspective, hybrid-enabling technologies refer to the integration of multiple methodologies, platforms, and technologies in organic synthesis to achieve more efficient, selective and sustainable chemical reactions. These technologies often combine with traditional or classical synthetic methods towards innovative synthetic approaches to address the challenges of conventional organic synthesis. This perspective emphasizes the utilization of enabling methods, with flow chemistry at the forefront, to achieve more sustainable production of biomolecules, agrochemicals as well as pharmaceuticals.

Keywords: Automation · Biocatalysis · Enabling technologies · Flow electrochemistry · Flow photochemistry · Hybrid technologies · Photoelectrochemistry

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1. Introduction

Organic synthesis, the art and science of designing molecular architecture, has been at the heart of chemical research in academia as well as in the pharmaceutical and agrochemical industries.[1] Traditionally, organic chemistry has relied on conventional techniques that seem no different than those utilized by Wöhler at the dawn of organic synthesis. The use of manual techniques, laborious trial and error methods and relying heavily on round-bottom flasks without any technological support often resulted in numerous challenges such as long reaction times, low yields, reproducibility issues, and harsh reaction conditions, which compromised the efficiency, accuracy, and safety. In recent years, the growing interest in sustainable chemistry has accelerated the development and use of modern methods and technologies, the so-called enabling technologies.[2] These transformational technologies overcame the limitations of existing approaches, paving the way for further innovation. Modern methods of synthesis, such as the utilization of continuous flow chemistry, diverse energy input methods, robotics, artificial intelligence and machine learning are becoming prevalent and being embraced at different stages of organic synthesis to be the holy grail of Chemistry 4.0.[3] The fundamental goal of these enabling technologies is to address some of the constraints of traditional organic synthesis, such as low efficiency, poor selectivity, waste generation, and laborious procedures, which is also consistent with the concepts of Green Chemistry.[4] Together with flow chemistry (Fig. 1), photoredox catalysis,[5] electrochemistry,[6] biocatalysis,[7] mechanochemistry,[8] as well as microwave heating[9] have already given access to divergent chemical transformations which were otherwise challenging or impossible by conventional means.

This personal perspective examines the importance of these technologies in organic synthesis, with a particular emphasis on fundamentals and major breakthroughs in conjunction with flow chemistry.

2. What are Enabling Technologies?

The term ‘*enabling technologies or enabling techniques*’ in the context of organic synthesis refers to both traditional and modern methods designed to accelerate synthetic transformations

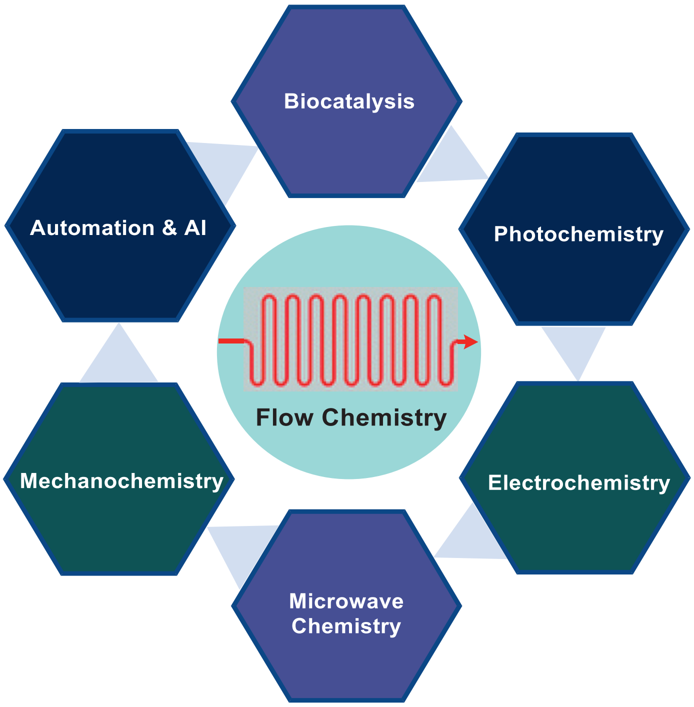

Fig. 1. Hybrid enabling technologies with flow chemistry at the forefront.

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and simplify the workup as well as the isolation of final products. These technologies include advanced synthetic procedures, instruments, energy inputs, reactors, and process analytical tools that can improve the efficiency, selectivity, scalability, and environmental sustainability of a synthetic process. Key examples of enabling technologies are flow chemistry, photoredox catalysis, electrochemistry, microwave-assisted organic synthesis (MAOS), mechanochemistry, biocatalysis, automated synthesis platforms, high-throughput synthesis, among others. Ultrasound, electromagnetic induction heating, hydrodynamic cavitation, infrared heating are some of the lesser-known enabling technologies in organic synthesis.[10] Moreover, with the growing influence of computers in daily life, artificial intelligence (AI), computational chemistry, automation, and machine learning are becoming increasingly prominent as *Enabling Technologies 2.0.*

3. Hybrid Technologies and Key Components

3.1 *Flow Chemistry*

Flow chemistry generally refers to reactions conducted in a continuous flow stream, as opposed to batch chemistry where chemicals and solvents are added to a flask. Continuous-flow chemistry offers better control of reaction parameters including temperature and pressure even at extremes without any substantial risk. Flow reactors are characterized by a high surface area to volume ratio, making heating and cooling more efficient. Additionally, because reactants are introduced in small amounts, reactions can be easily scaled up without archetypal safety concerns, hence offering an accelerated scale up from proof of concept to an industrial setup.[11]

Whether custom-built or commercially available, some basic zones can be identified in a standard flow reactor (Fig. 2).[12] Frequently when performing multistep synthesis or in a downstream processing, in-line separation devices and product purification accessories are also included. In addition, in-line or online process analytical technology (PAT) tools such as mass spectrometry, bench-top NMR, IR, UV-Vis and Raman spectroscopy, have been successfully incorporated to enable real-time reaction monitoring as well as reaction automation.[13] Furthermore, when connecting several modules in a single flow sequence, the achievement of multistep flow sequences and automated production platforms becomes feasible, which is particularly significant in the synthesis of active pharmaceutical ingredients (APIs).[14] Fig. 2 provides a general overview of key enabling technology components for the different zones of a modern flow chemistry setup, starting from the sample preparation (manual *vs.* automated), reactor design (coiled tube reactor, chip reactor and packed bed reactor), multiple energy input methods (traditional heating/cooling, photochemical, electrochemical, microwave and ultrasound) and catalysts (biocatalysis, organocatalysis, transition metal-catalysis), work up and extraction (membrane separation), PATs (in-line *vs.* online), product collection and purification as well as automation (AI and machine learning).

3.2 *Flow Chemistry With Enhancing Technologies*

Over the past two decades, chemistry has increasingly shifted towards greener and more sustainable approaches, focusing on systems that minimize waste and maximize efficiency. Continuous flow technology has emerged as an ideal platform in this regard, seamlessly integrating with a wide range of process intensification technologies and energy sources. This integration has created new opportunities, as innovative approaches continue to overcome the inherent limitations, enabling more challenging reactions with enhanced and synergistic benefits. While many energy sources, catalysis, and enhancing technologies have been incorporated into flow chemistry – the amalgamation of flow chemistry with automation technologies, biocatalysis, microwave chemistry, mechanochemistry, photoredox catalysis, and electrochemistry will briefly be discussed in this personal perspective.

3.2.1 *Biocatalysis*

Enzymes, nature's own catalysts, have seen a significant resurgence over the past two decades both in academia as well as the pharmaceutical industry.[15] This renewed interest is driven not only by their exceptional catalytic efficiency but also by advancements in recombinant technologies, which have enabled access to new synthetic transformations previously inaccessible through traditional synthetic methods.[16] Organic chemists are well aware of the exquisite regio- as well as stereoselectivity offered *via* enzymatic pathways, which typically remains a daunting task under

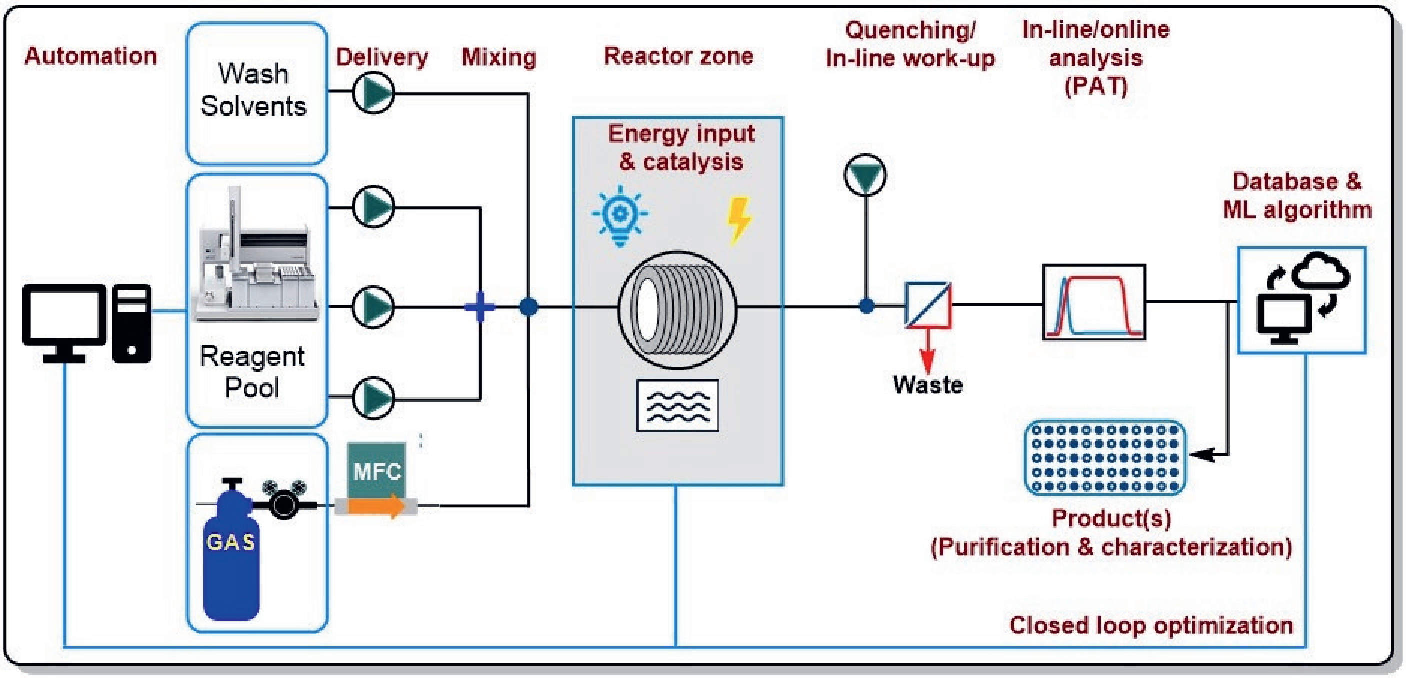

Fig. 2. General scheme for an automated flow setup along with typical components used in the assembly of continuous flow systems.

traditional methods. In recent times, we have seen a lot of applications of enzymatic pathways for the synthesis of active pharmaceutical ingredients (APIs) and key starting materials (KSMs).[17] Aside from the usual benefits of enhanced heat and mass transfer of continuous-flow processes, flow biocatalysis may also allow the introduction of somewhat harsh reaction conditions, which may widen the scope of biocatalysis in synthetic organic chemistry.[7] Another, prevalent issue in batch biocatalysis is product build-up, leading to enzyme inhibition and in turn decreased productivity. Flow chemistry can easily address all of these problems, including automation, high throughput reaction screening and scaling up.[18] Reactor design is also important while transferring an enzymatic process from batch to flow mode. Currently, packed-bed reactors (PBRs) are the most promising and broadly used reactors for flow biocatalysts. In these column-shaped reactors, the heterogeneous biocatalyst takes up around half of the reactor volume. Because of the high surface to volume ratio, reactants passing through the PBR can convert to the targeted products at high reaction rates. The latest advancement in (micro)reactor design for flow biocatalysis is the use of 3D-printed reactors,[19] which allows for customized reactor designs in consideration of the reaction challenges. Further, enzyme immobilization has numerous advantages, including stabilizing the biocatalyst and minimizing conformational changes that cause leaching and inactivation.[20] The most important factors that should be considered when assessing the suitability of a heterogenous biocatalyst for use in a flow reactor have been nicely outlined (Fig. 3).[21]

Recently, there has been a surge in the merging of biocatalysis with photochemistry[22] and electrochemistry.[23] Both enhancing technologies offer unique benefits in terms of mild, biocompatible reaction conditions with a broader scope while preserving high regio- and stereoselectivity. Light can be used to (i) excite the substrate before the reaction proceeds, or (ii) to activate the biocatalyst.[22a] In order to adapt photobiocatalytic reactions to a flow configuration, different types of reactors have been developed, *e.g.* to avoid the high temperature-induced decline in enzyme stability while ensuring proper light penetration into the photobioreactor.[24] Overall, continuous flow photobiocatalysis and electrobiocatalysis have introduced new reactivities and alternate pathways to increase the sustainability of biotransformations, including cofactor regeneration. The synergistic capacity of flow chemistry to control asymmetric processes has been investigated in conjunction with microwave biocatalysis[25] and enzymatic electrochemistry.[26]

The primary challenge currently is to obtain industrially relevant processes, given both techniques have reactor/instrumentation restrictions. Furthermore, artificial intelligence and machine learning-based technologies are making inroads into the field of continuous flow biocatalysis with the ultimate goal of automation. The utilization of these sophisticated computational tools has the potential to revolutionize the development of more efficient biocatalysts, as well as high-throughput process optimization and screening.[27]

3.2.2 *Microwave*

Microwave (MW) heating is already a well-established technology that is included in the basic portfolio of heating devices in an organic chemistry laboratory.[9] Nowadays, the use of MW is extensively widespread in almost every facet of chemistry, as it provides efficient volumetric heating and short reaction times while being a sustainable and environmentally friendly technology. Nonetheless, MW irradiation has a limited penetration depth that is defined by the dielectric properties of the material, which heavily restricts the scale of the reactions. In that sense, the combination of MW heating and flow technology offers a good solution since the narrow diameter of the flow reactors enables better and consistent penetration of MW irradiation, which addresses the issue of scaling MW-assisted processes.[28] Barham *et al.* have systematically summarized the use of flow reactors for MW applications.[29] Currently, high-power magnetrons with waveguides or resonant cavities that operate at 2.45 GHz (ISM frequency band) are the mainstay of microwave heating devices that are frequently coupled with continuous flow devices.[29,30] Nevertheless, for many organic solvents, 2.45 GHz does not correspond to the frequency with the maximum dielectric loss, leading to suboptimal dielectric heating.[30]

In this context, our research group has reported the development of a microfluidic microwave chip reactor based on a complementary split ring resonator (CSRR) that can operate at a wider, adjustable frequency range (about 2 GHz or 6–12 GHz) and can reach temperatures up to 120 °C within seconds using an input power of 4.4 W (Fig. 4). The µw-µf-CR (microwave-microfluidic chip reactor) demonstrated applicability in several organic transformations, including an exothermic reaction, fluorination, and a two-step amidation with a throughput of up to 0.48 $\mathrm{mmolh^{-1}}$ employing microliter volume reactors.[31] Exploration of variable frequency effects as well as use of automation could be a significant advancement towards fast, tailored, and efficient microwave heating methodologies in the field of microfluidics.

3.2.3 *Photoredox Catalysis*

It was only during the last decade that photoredox catalysis emerged as a powerful tool in synthetic organic chemistry, providing the possibility to functionalize molecules by means of rad-

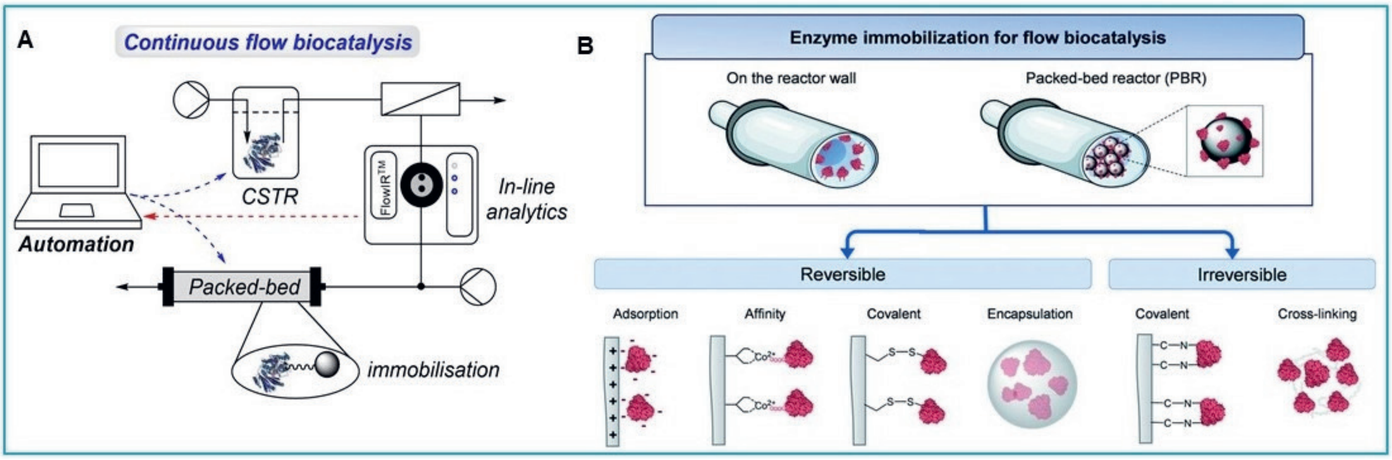

Fig. 3. A) A continuous flow setup for a biocatalytic reaction; B) Enzyme immobilization strategies. Reprinted with permission from ref. [21] Copyright 2021 The Royal Society of Chemistry.

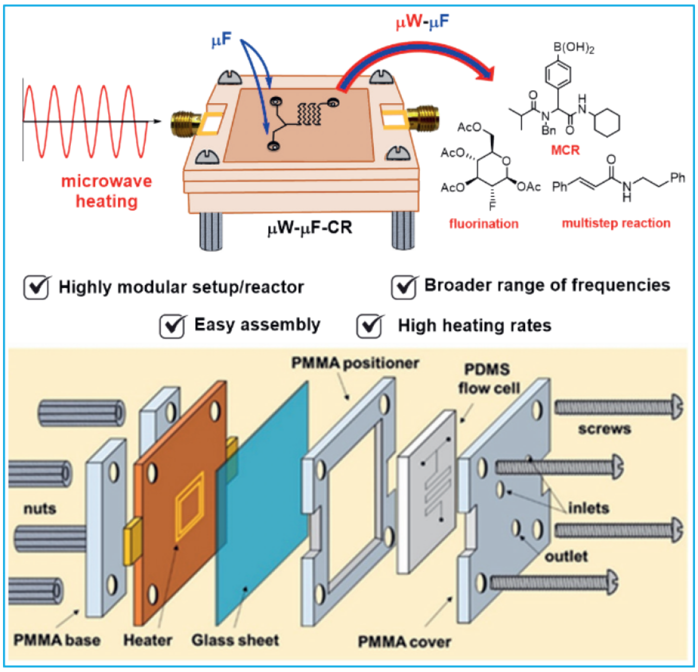

Fig. 4. A microwave-microfluidic chip reactor for microwave assisted organic synthesis (MAOS) in continuous flow. Reprinted with permission from ref. [31] Copyright 2024 The Royal Society of Chemistry.

ical processes using mild conditions and the simple irradiation of reaction mixtures with visible light.[32] The reactive intermediates can be generated through different mechanisms that have led to the development of the field in different directions.[33] Nonetheless, performing photochemistry under batch conditions often encounters limitations related to light penetration (light attenuation, Fig. 5A). Flow photochemistry,[5] on the other hand, offers several advantages, including efficient and uniform irradiation of the reaction mixture, which leads to faster and cleaner reactions, while also addressing the scalability concerns. Depending on the specific requirements of the transformation, photoflow reactors are available in various designs *viz.* coiled reactors, microfluidic chips, tube-in-tube systems, columns, and falling film reactors. A critical feature of any photoreactor is the transparency of its construction materials, ensuring effective light transmission for optimal reaction efficiency.

A simple photoflow reactor consists of a coil, surrounded by, or placed adjacent to a dedicated light source to ensure uniform irradiation. Its construction has been well described in the literature (Fig. 5B).[34] The choice of light wavelength depends on the absorption characteristics of the photocatalysts or substrates involved in the transformation, while popular artificial light sources include mercury-based light sources for UV applications, compact fluorescent light bulbs (CFL), light emitting diodes (LEDs), and solar energy. The modularity of the reactor has allowed for flexible adaptation of the tubing to various reactor configurations for better irradiation, including loop, towel, and spiral architectures.[35]

In addition to in-house-built reactors, there is now a wide range of commercially available photoflow reactors (Fig. 5C). While these are more expensive than custom-built options, they offer numerous benefits, including excellent process reproducibility, reliability, rapid optimization, and high-quality outcomes. Our research group has been active in the field of flow compatibility of alkyl radical precursors towards a variety of reactions.[36]

3.2.4 *Electrochemistry*

Synthetic electrochemistry focuses on the redox transformations of organic compounds enabled by the application of an electric potential.[37] This allows the exchange of electrons with the substrate toward net oxidative and reductive processes. Similarly to photoredox catalysis, this technique allows for milder reaction conditions and overcomes the use of stoichiometric redox reagents with associated higher safety and lower environmental impact. An important difference lies in the kinetics involved as the exchange of electrons between substrates and electrodes is a heterogeneous process limited by mass transfer rates.[6a] The latter aspect poses serious challenges in batch conditions and demands considerations regarding mixing and distance between electrodes as both parameters influence the mass transfer. Flow electrochemistry allows for better control of the reaction conditions leading to higher conversion and selectivity.[6] Moreover, electrochemical flow cells are usually designed in order to minimize the distance between the electrode surfaces which often overcomes the need for supporting electrolytes. Therefore, continuous flow setups should not be considered merely as a mean for scaling up an electrochemical reaction but instead as a true enabling technique to promote a wider application of electroorganic synthesis in every laboratory. Electrochemical flow reactors are typically composed of a casing supporting the electrode plates, equipped with inlet and outlet attachments and screwed together with a spacer in between for different reactor designs and volume. Finally, similar to photoflow reactors, commercially available electrochemical flow reactors are also available on the market (Figs. 6A-6D).

The field of synthetic electrochemistry is evolving rapidly, driven by advancements in new reactivity paradigms such as paired-electrolysis,[38] reductive transformations,[39] electrochemical C-H activation and cross coupling reactions,[40] as well as late-stage functionalization of pharmaceuticals and biomolecules under mild reaction conditions.[41] Overall, the transition from batch to flow electrochemistry is enhancing scalability, safety, and reproducibility, making synthetic electrochemistry more practical for industrial production while also providing opportunities for further innovations.

3.2.5 *Photoelectrochemistry*

Photoelectrochemistry combines the strengths of both photocatalysis as well as synthetic electrochemistry while mitigating their drawbacks. It eliminates the need for stoichiometric oxidants or reductants in photochemical processes and prevents unwanted dimerization, common in electrochemical reactions.[42] This topic is relatively young, and the majority of applications are still under batch conditions.[43] Nonetheless, we will look at some ground-breaking findings that were reported using flow photoelectrochemistry.

Ackerman and coworkers, in 2020, published an early example of photoelectrochemistry applied to C-H trifluoromethylation of arenes using a custom-built reactor system. In this study, although both photochemical and electrochemical processes were involved, they occurred separately.[44] The flow setup was equipped with a turbulence promoter for the improved mixing and connected to a transparent FEP tube irradiated by Kessil lamps. Major advancement in the field has been made by Noël and coworkers[45] on the heteroarylation of C(sp^3)-H bonds that merges the electrochemically induced radical-polar crossover concept with HAT photocatalysis. To ensure effective light penetration (Kessil 390 nm LEDs), an FTO (fluorine doped tin oxide) glass slab coated with a thin layer of Pt nanoparticles was integrated as a transparent electrode (Fig. 6D). An analogous report was published by De Ketelaere and Heugebaert for the *N*-arylation of different azoles under electrolyte-free conditions.[46] Overall, the amalgamation of innovative reactor designs and commercially available inexpensive electrode materials will drive flow photoelectrochemistry towards large-scale commercial applications. As the field is still under development, we can expect highly efficient, automated,

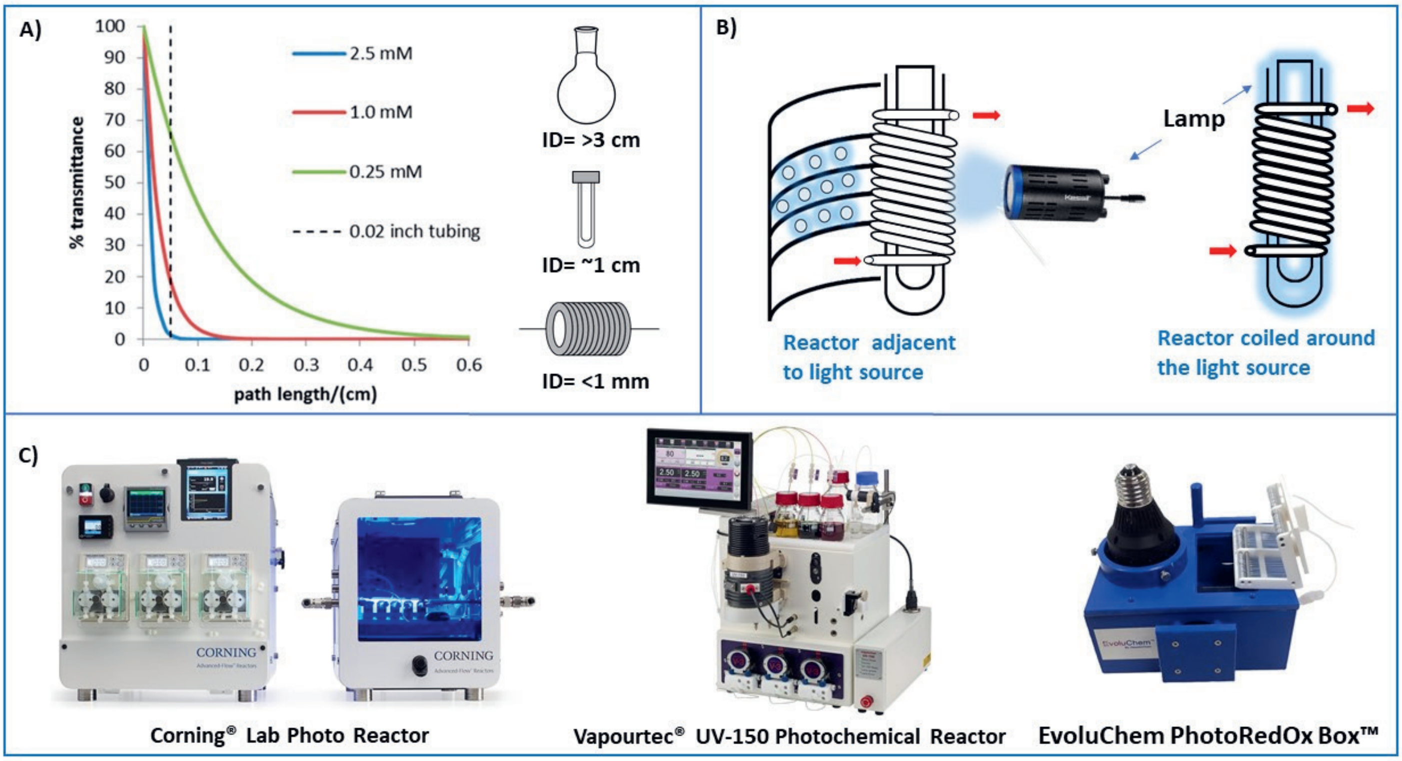

Fig. 5. A) Light attenuation due to reactor dimensions; B) A simplified version of a photoflow reactor; C) Commercially available photoflow reactors. Images are reproduced with permission from the respective companies.

and sustainable flow-based photoelectrochemical systems that may revolutionize synthetic chemistry.

3.2.6 *Mechanochemistry*

Mechanochemistry offers solvent-free or solvent-minimized reaction conditions, aligning with green chemistry principles.[47] However, the traditional ball milling has some limitations in terms of scalability and safety for large-scale reactions. Towards this end, twin-screw extrusion (TSE) provides a scalable, continuous alternative to well-studied batch mechanochemistry.[8] TSE allows fine-tuning of reactor design, including screw configuration, temperature control, and feeding rates, enabling efficient and sustainable organic synthesis for solids. A few review articles go into great depth about pioneering studies on TSE along a 'how-to' guide for designing extrusion reactions towards various organic transformations.[8] It is worth noting that such continuous processes have demonstrated better space-time yields compared to traditional mechanochemical methods. Reactive extrusion holds significant promise for industrial adoption, particularly in sustainable and continuous chemistry (Fig. 7). Future research should

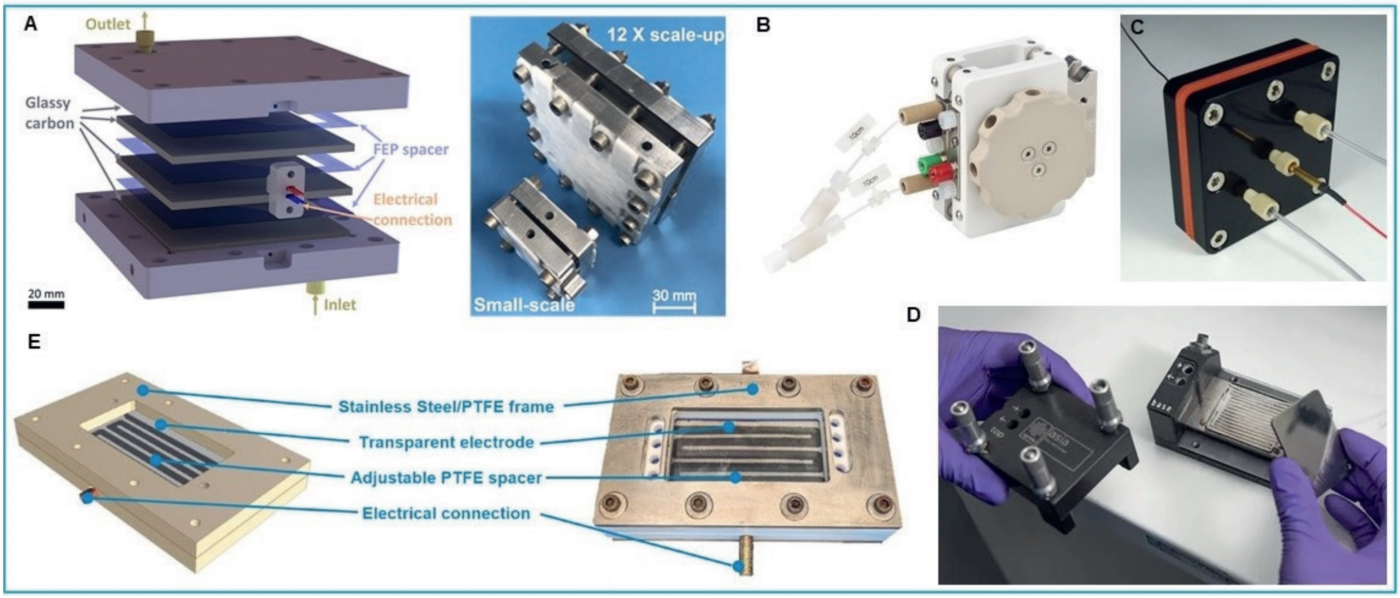

Fig. 6. A) Electrochemical reactor employed for SET redox neutral reactions. Reprinted with permission from ref. [6a] Copyright© 2020 AAAS; B) Electrochemical ion reactor Vapourtec®; C) Electrochemical reactor from Analytical Sales & Services; D) Electrochemical reactor from Syrris®. Images are reproduced with the permission from the respective companies; E) In-house microreactor for electrophotocatalysis and heteroarylation of C(sp^3)-H bonds. Reprinted with permission from ref. [45] Copyright© 2023 John Wiley & Sons, Inc.

focus on expanding the scope of reactions, improving purification processes, and integrating hybrid continuous reactors for multi-step syntheses. Very recently, Capaldo and coworkers reviewed efforts in photomechanochemistry involving the merger of light energy and mechanical forces under solvent-minimized reaction conditions.[48] The authors also discussed selected examples to showcase the available technologies such as manual grinding, vortex and shaker mixing, rod milling, and ball milling in a hybrid manner with visible light.

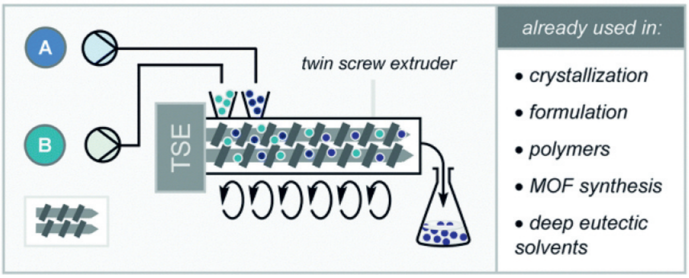

Fig. 7. Reactive extrusion for continuous flow synthesis of solids. Reprinted with permission from ref. [8a] Copyright© 2022 Royal Society of Chemistry.

3.2.7 *Process Analytical Technology (PAT)*

Real-time data gathering in organic synthesis has been simplified *via* the merger of continuous-flow technologies and various analytical tools.[49] Online as well as inline analytical methods can simply cut down on processing requirements, sometimes even eliminating the sample processing completely. The integration of various analytical tools, such as IR, NMR, and UHPLC, within a modular microreactor system allows for efficient control and optimization of multistep transformations. Rodriguez-Zubiri and Felpin have provided an analytical tool guide to help chemists decide which analytical instruments to integrate into continuous-flow reactors (Fig. 8).[13] The authors highlighted the importance of PAT tools in understanding chemical transformations, optimizing reaction parameters, and mitigating risks associated with hazardous reagents or unstable intermediates. Furthermore, the integration of PAT tools with machine learning and AI paves the way for automated and autonomous chemistry, contributing to the advancement of Chemistry 4.0.

3.2.8 *Automation and AI*

The identification and development of synthetic routes to novel molecules remain a largely manual process requiring a time investment from expert chemists which is often a bottleneck in small-molecule drug discovery. In recent times, the integration of automation with flow chemistry has enhanced the ability to conduct high-throughput experiments.[50,51] Automated flow systems have the ability to rapidly test a variety of reaction conditions, while collecting the data in real-time, leading to increased efficiency of reaction optimization and faster development of new synthetic routes. The field is currently evolving with a few recent contributions which fit within the scope of this perspective.

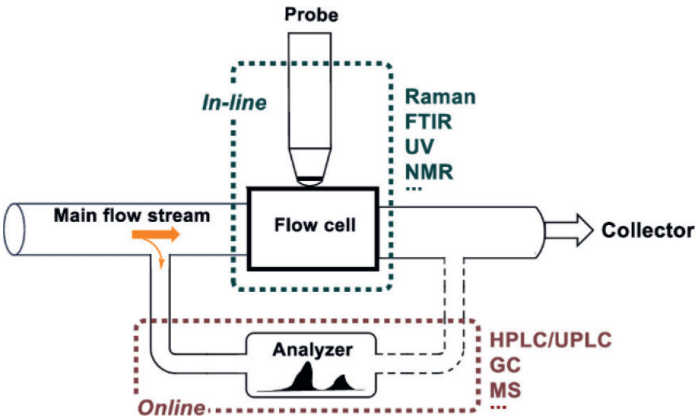

Fig. 8. In-line *vs.* online analyser setups for PATs. Reprinted with permission from ref. [13]. Copyright© 2022 American Chemical Society.

Jamison, Jensen and coworkers reported an open-source software suite for artificial intelligence-driven synthetic planning and a robotically controlled continuous flow experimental platform for scalable and easily reproducible synthesis (Fig. 9A).[52] This strategy for computer-augmented synthesis planning (CASP) is demonstrated for the synthesis of 15 drug and drug-like molecules. Over time, the results generated by these automated experimental platforms along with the increased availability of reaction data will enable chemists to robotically realize syntheses based on AI recommendations, in turn enabling experts to focus on new ideas.

Recently, Noël and coworkers described an automated robotic platform (RoboChem) to streamline the optimization of photochemical reactions (Fig. 9B).[53] The robotic platform consists of a liquid handler, syringe pumps, a continuous-flow photoreactor attached to an in-line nuclear magnetic resonance (NMR) system for rapid analysis. RoboChem used a closed-loop Bayesian optimization (BO) approach to systematically explore and optimize the reaction conditions customized for the specific requirement of the substrates. In addition to the optimization studies, RoboChem has been successfully scaled up to a diverse set of photocatalytic reactions covering various facets of photocatalysis, such as hydrogen atom transfer photocatalysis,[54] photoredox catalysis,[5] and metallaphotocatalysis.[33]

Electrochemical continuous-flow platforms face challenges in handling small material volumes, and potential electrode fouling may go unnoticed due to the enclosed nature of the flow cell. These issues become more noticeable during the transition from batch to single-pass electrochemical reactions. Integration of continuous-flow electrochemical reactions with automated control may lead to enhanced efficiency and scalability.[52] In order to address these issues, Eggenweiler, Kappe, Laudadio and coworkers have designed and implemented a new, slug-based automated electrochemical flow platform (Fig. 9C).[55] Demonstrating its utility for medicinal chemistry applications, the automated electrochemical platform successfully performed C-N cross-couplings of E3 ligase binders with diverse amines (44 examples without human intervention). In addition, Design of Experiments (DoE) optimization was also performed for a previously unsuccessful library target, resulting in a notable 6-fold increase in reaction yield.

Machine learning algorithms are increasingly being used to optimize flow chemistry processes.[56] By analysing large datasets from continuous experiments, machine learning models can identify optimal reaction parameters, predict reaction outcomes, and even suggest novel reaction pathways. This integration of AI with flow chemistry holds great potential for accelerating the discovery of new synthetic routes and improving the efficiency of existing processes. On a similar note, computational chemistry can play an important role in the design and optimization of flow reactors.[57] Simulations can predict how reagents will behave under different continuous flow conditions, helping to design more efficient reactors and reaction systems.[58] Therefore, by combining computational modelling with flow chemistry, researchers can optimize reaction conditions without the need for extensive trial-and-error experimentation.

4. Conclusions

Flow chemistry has emerged as a cornerstone technology in the landscape of modern organic synthesis, providing significant

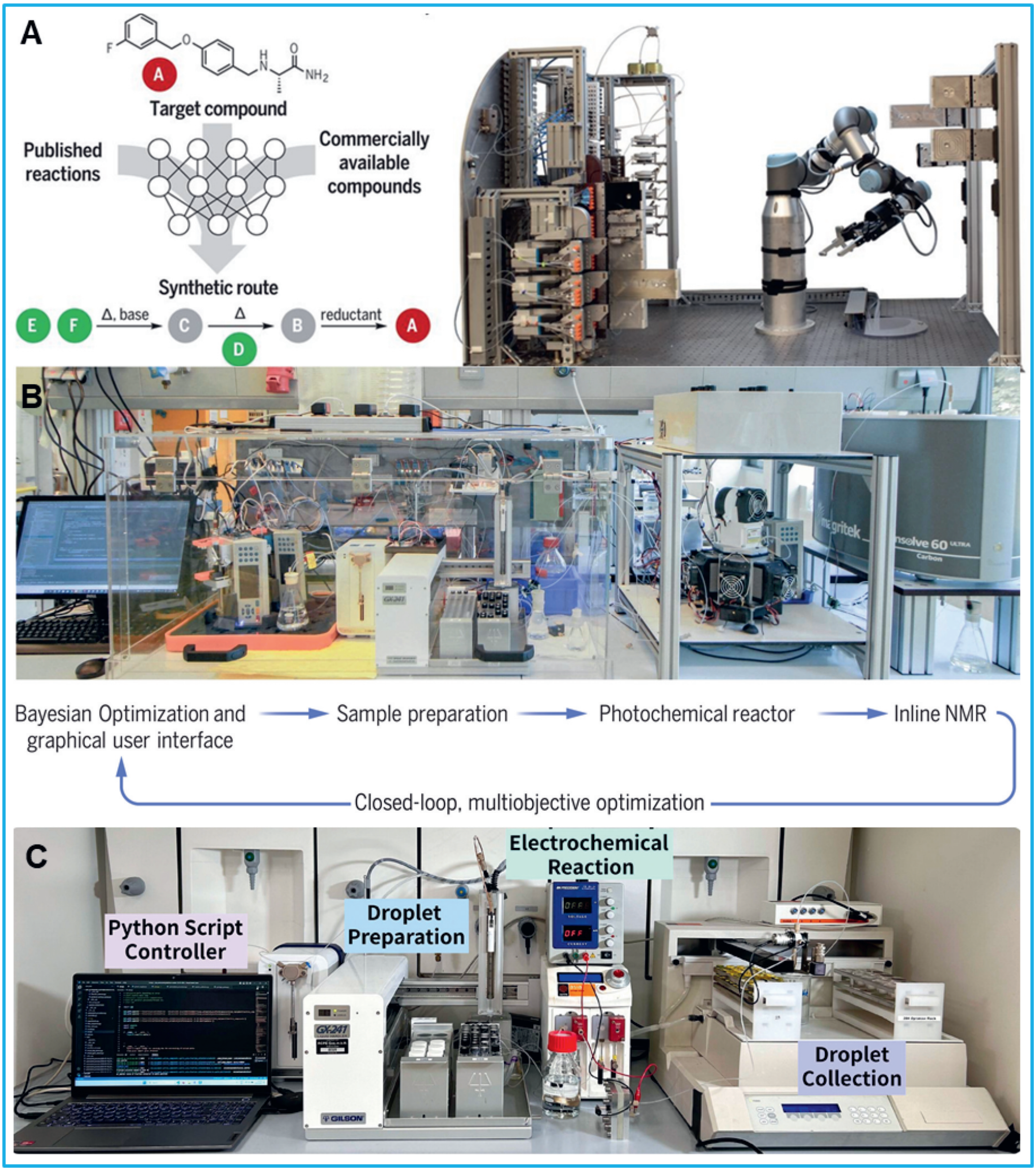

Fig. 9. A) Robotically controlled continuous flow experimental platform. Reprinted with permission from ref. [52] Copyright© 2020 AAAS; B) RoboChem – a photochemical automated continuous-flow platform. Reprinted with permission from ref. [53] Copyright© 2024 AAAS; C) Electrochemical automated continuous flow platform. Reprinted with permission from ref. [55] Copyright© 2024 John Wiley & Sons, Inc.

advantages over classical batch chemistry. Its ability to enhance reaction efficiency, improve control of reaction conditions, and scale processes for industrial production has made it vital in fields such as pharmaceuticals, fine chemicals, and green chemistry. The integration of flow chemistry with other advanced technologies, such as photoredox catalysis, synthetic electrochemistry, microwave chemistry, mechanochemistry, biocatalysis, PATs, automation and machine learning, promises to further enhance its capabilities, making it a key tool for driving innovation in organic synthesis. As the desire for more sustainable, efficient, and scalable chemical processes grows, flow chemistry is poised to play a central role in shaping the future of organic synthesis as well as contributing to Chemistry 4.0. Its ability to reduce waste, improve safety, and enable the rapid construction of complex (bio) molecules makes it a gamechanger in the chemical industry. The examples discussed in this personal perspective show the variability and synthetic utility of flow setups that can be utilized in a manual or automated manner. It is expected that these hybrid enabling technologies, together with flow chemistry, will play a central role in future industrial applications. Achieving these goals will likely require the development of standardized protocols and flow setups. Given the wide range of flow system configurations available, establishing standardized methodologies will be essential for broader industrial adoption and efficiency.

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