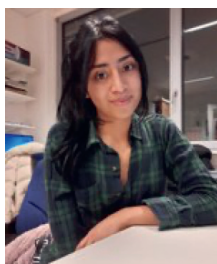


# Going with the $\mu$ Flow: Reinterpreting Energy Input in Organic Synthesis

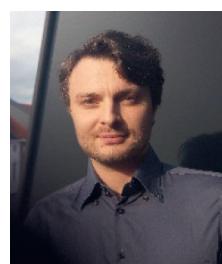
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**Abstract:** The popularity of microflow chemistry has skyrocketed in the last 20 years and more and more chemists are switching from macro-batch reactors to miniaturized flow devices. As a result, microfluidics is paving its way into the future by consolidating its position in organic chemistry not only as a trend but as a new, effective, and sustainable way of conducting chemistry, that clearly will continue to grow and evolve. This perspective highlights the most relevant examples of innovative enhancing technologies applied to microflow reactors aimed to improve and intensify chemical processes. The extensive applicability of microflow chemistry is further illustrated by briefly discussing examples of complex integrated microsystems and scale-up technologies, demonstrating ultimately that microflow chemistry has the potential to become the ideal technology for the future.

**Keywords:** Enabling technologies · Electrochemistry · Hydrodynamic cavitation · Microfluidics · Microfluidics plasma · Microsynthesis · Microwave · Photochemistry · Process intensification technology · Ultrasound



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synthesis of bioactive heterocycles.

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on the development of new synthetic methodologies in combination with enabling techniques.



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## 1. Introduction

Since its inception twenty years ago, the use of microfluidics applied to organic synthesis has caught the attention of the chemical and engineering communities. The immediate interest in microfluidics lies in its numerous benefits including the use of small quantities of reagents and solvents, minimal waste production, precise control of reaction conditions, integration of functionality for process intensification, safer and often faster protocols, reliable scale-up, and the possibility of performing multiphase reactions. In this perspective, we discuss how different enhancing technologies and energy sources have been successfully integrated with microfluidic devices through selected examples of past and recent developments. We begin with some introductory and fundamental aspects on the topic, followed by a short discussion on how the integration of microfluidics with different intensification technologies is a powerful combination that results in synergistic,

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improved, and even new reactivities. The perspective continues with a general overview of complex integrated microsystems and scaling-up technologies. Finally, we address challenges and future opportunities for this growing field.

### 1.1 Microfluidics and Microreactors

Microfluidics is defined as the science and engineering of systems in which fluid behavior differs from conventional flow theory primarily due to the small length scale of the system (laminar flow,  $Re \leq 250$ ).<sup>[1]</sup> In this sense, a microreactor is a micro-miniaturized device that consists of a network of micron-sized channels, tubes or chambers with a size between 10 to 500  $\mu\text{m}$  in inner diameter and low flow rates not exceeding  $\sim 1\text{ mL min}^{-1}$  (Fig. 1A).<sup>[2,3]</sup>

For use in synthetic chemistry, the channel network is connected to reservoirs containing the reagents, which are pumped through the microreactor in a specific sequence, mixed and allowed to react for a specific time (residence time). Typically, the entire device has a total size of a few centimeters (Fig. 1B).<sup>[4]</sup>

Whether a microfluidic device is custom-built or commercially available, microsystems typically comprise a number of components, including pumps for delivering reactants, flow meters/controllers, reactors with feedback-controlled heating/cooling units, separators for chemical workup between reaction stages, valves, backpressure regulators, sampling valves, and chemical analysis equipment.<sup>[5]</sup> Additionally, four primary types of microreactors can be identified, namely: i) coiled tubing reactors; ii) chip-based reactors; iii) packed-bed reactors and iv) tube-in-tube reactors (Fig. 1C).<sup>[6]</sup>

Microreactors are considered a chameleon technology in terms of design, fabrication, and integration, which extends their applicability to a wide number of fields ranging from materials science to medicine (Scopus 2022, Fig. 2A). Microfluidic devices can be made from a variety of materials, including silicon, quartz,

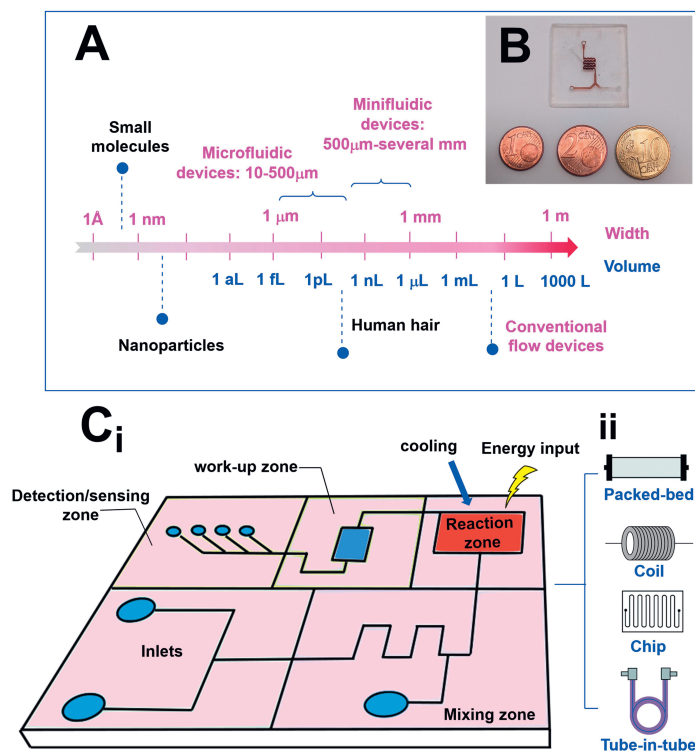


Fig. 1 (A) Scale size of microfluidics devices. (B) Size of a microfluidic flow cell compared to coins of different sizes (courtesy of LOMAC/KU Leuven). (C) (i) General representation of flow chemistry using microfluidic reactors. Reagents can be combined, heated, cooled, and quenched (ii) Graphical presentation of continuous-flow microreactors.

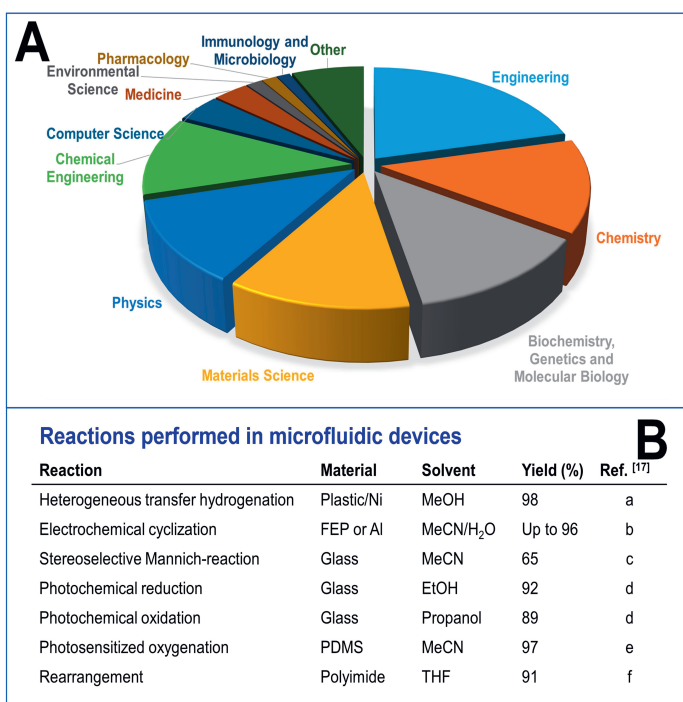


Fig. 2. (A) Distribution by area of articles published in the last 20 years in the field of microfluidics. (B) Relevant examples of reactions performed in microreactors.

glass, metals, and polymers.<sup>[7]</sup> There are also numerous microfabrication methods, including photolithography,<sup>[8]</sup> hot embossing,<sup>[9]</sup> dry/wet etching,<sup>[10]</sup> and so forth.

Moreover, microsynthesis ( $\mu\text{Syn}$ ) offers exquisite control on all those parameters with critical impact on the reaction outcome. The combination of flow chemistry and the small dimensions allows fast and precise adjustments of temperature, pressure, stoichiometric ratio, and catalysts. Nonetheless, new possibilities come with microreactors where flow parameters play a major role. Flow rate and residence time, are easily controlled with programmable syringe pumps, the flow path can be varied by modification in the geometry of microreactors. Finally, reagent transport can be timely controlled tweaking the injection frequency and the inlets location.<sup>[11]</sup>

It is evident that microreactors are a flexible technology that allows plenty of freedom in almost every aspect of fabrication. However, for synthetic applications, chemical compatibility with the substrate/solvents as well as ease and reproducibility of manufacturing are key factors to take into account. Beyond that, the possibilities are practically endless.

### 1.2 Why Go Micro? A Quick Overview of the Benefits of Microfluidic Systems versus Batch Methods

Microsynthesis emerged as the response to the question: Is a flask the ideal container for something as small as molecules? And although the answer seems clear, the truth is that standardized glassware in a modern laboratory does not look so different from that used by Wöhler at the dawn of organic chemistry. The incorporation of microfluidic devices into the chemist's toolbox brings new opportunities to tackle classical problems and explore new reactivities. In this context, the first examples of organic synthesis performed in microfluidic devices date back to the late 1990s and early 2000s.<sup>[12]</sup> Ever since, the field of microfluidics applied to flow chemistry has experienced an explosive growth toward both molecules and materials synthesis.<sup>[6,13]</sup>

The inherent benefits of performing chemistry in microfluidic devices are purely associated to the small size of the system, as heat and mass transfer are scale-dependent processes. In this re-

gard, the mass transport coefficients observed in a microreactor can range from 5 to 15 s<sup>-1</sup> as compared with 0.001–0.02 s<sup>-1</sup> in standard batch reactors. This means that complete mixing can be achieved within a few seconds or milliseconds.<sup>[6,14]</sup> Additionally, at a microscale the flow is usually laminar, as a result fluids are influenced by viscosity rather than inertia. Furthermore, large surface-area-to-volume ratios ensure thermal homogeneity across the reactor (10 000 and 50 000 m<sup>2</sup> m<sup>-3</sup> compared to 100 m<sup>2</sup> m<sup>-3</sup> from traditional reactors).<sup>[15]</sup>

These particular properties result in a series of benefits, including but not limited to: i) short reaction times (s/ms scale); ii) minimal reagent handling (nL scale); iii) selectivity (kinetic *versus* thermodynamic control of the reaction pathway); iv) green chemistry labels (minimal energy consumption and reduced waste production); v) improved safety (precise pressure and temperature control; safe handling of dangerous products/intermediates); and vi) secured reproducibility and reliability (related to high levels of automatization of the system).<sup>[11,16]</sup>

Finally, one of the biggest advantages of microfluidic technology compared to batch chemistry is the vast amount of valuable data that can be obtained from the system, in the sense that the combination of short reaction times and low volumes allows the rapid screening and optimization of large sets of reactions.<sup>[16a]</sup> The high throughput performances are reflected in the development of a wide range of reactions in microreactors spanning from C–C and C–heteroatom bond-forming reactions, to rearrangement, cycloaddition, reductions, oxidations, enzymatic and polymerization reactions, and others (Fig. 2B).<sup>[16c,17]</sup>

Moreover, microfluidics can be particularly useful in flash chemistry,<sup>[17f]</sup> the synthesis and development of active pharmaceutical ingredients (APIs),<sup>[18]</sup> the study of reaction mechanisms, and the extraction of kinetics.<sup>[16b]</sup>

## 2. The Empowerment of Microflow: Process Intensification Technologies Applied to Microfluidic Devices

In the last two decades, chemistry has evolved along greener, and more sustainable pathways, with an emphasis on systems that minimize waste and maximize efficiency. In this context, microflow devices appear to be the ideal green synthetic platform. However, despite the many advantages that microfluidics brings to organic synthesis, their size is associated with a few limitations such as low throughput production, clogging, precipitation, and complex manual intervention.

On the other hand, it is also undeniable that the ease of integration of microfluidic devices offers a simple but ideal interface to merge microflow systems with a broad spectrum of intensification process technologies and energy sources. Inventive approaches allowed to overcome the intrinsic limitations of microreactors while offering an enabling platform for challenging reactions, often bringing enhanced and synergic beneficial effects. This has undoubtedly expanded the applicability of microfluidics, allowing us to study chemical transformations at a microscale, and it will perhaps lead to a new way of practicing and understanding chemistry.

In the next section we will go through the most relevant examples of the implementation of innovative enabling technologies applied to microflow chemistry, we also discuss current challenges and future opportunities for the growing field, and ultimately hope to inspire our fellow chemists to explore and exploit the promising world of microfluidics.

### 2.1 Photochemistry

Over the past ten years, photochemistry has gained increasing attention not just as a novel tool to explore new reactivities but also as a sustainable and environment friendly technology. However, light penetration constitutes the biggest limitation when per-

formed under batch conditions, as reactor dimensions are strictly limited by the Lambert-Beer law and reaction media absorption. In this sense, photochemistry and microflow technologies are a fine fit for each other, as the micron-size of the channels solves the light penetration problem and enables unprecedented process intensification while providing uniform irradiation, reduction in both reaction times and byproducts formation, as well as facilitating the scale-up process.<sup>[19a]</sup> Initial studies were reported using glass capillaries reactors which have been now mostly replaced by PTFE tubing. Although the inner diameter of these coil reactors falls into the range of few hundreds μm, usually the reactions are set at a mmol scale and with rather long reaction times. Therefore, we refer the reader to previous reviews on the topic<sup>[19]</sup> and we will focus solely on the few reports of photocatalyzed microscale reactions.

Photomicroreactors have been widely exploited in a variety of reactions, including cycloadditions, reductions, oxidations, isomerizations, rearrangements.<sup>[20]</sup> Recently, Cazorla-Amorós *et al.* reported the complete oxidation of propene with TiO<sub>2</sub> as a photocatalyst using a packed-bed photo-microchip reactor illuminated with a low power LED light, achieving full conversion. The system was found to be highly efficient when compared to a conventional reactor and a microcapillary reactor (Fig. 3A).<sup>[21]</sup>

Additionally, remarkable work in the field has been done by Noël and coworkers, who developed luminescent solar concentrator photomicroreactors (LSC-PMs) which allow solar energy to be harvested efficiently and waveguide the energy to the microchannels (Fig. 3B).<sup>[22a,b]</sup> Furthermore, the same group reported an efficient and fast scaling-up strategy of LSC-PMs with up to 32 parallel channels, which has the potential to produce pharmaceuticals and other fine chemicals using solar energy (Fig. 3C).<sup>[22c,d]</sup> A fascinating application of microscale photocatalyzed reactions was recently reported by Kennedy and Stephenson. They realized a droplet microfluidic platform by optimizing a segmented flow setup with in-line ESI mass spectrometer.<sup>[23]</sup> Single nanoliter-sized droplets of the reagent mixture were fed from a compound library. The photocatalyst was added to the single droplets by mean of a T-junction and the reaction droplet reached the mass spectrometer

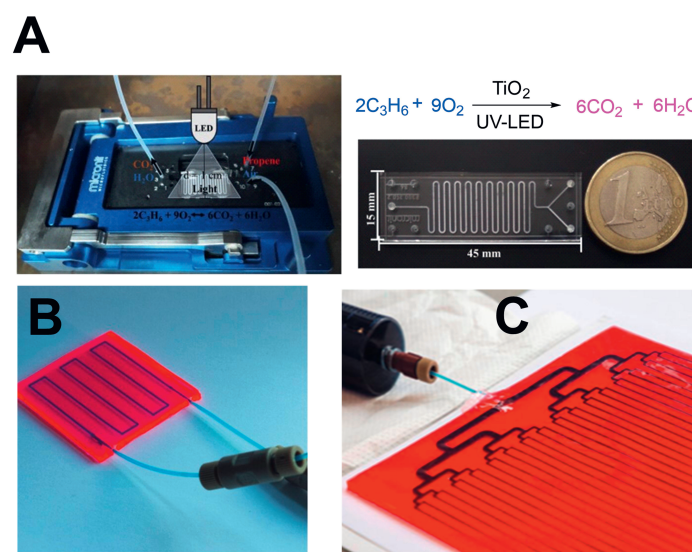


Fig. 3. (A) Experimental set up used for the photocatalytic oxidation of VOCs and picture comparing the size of the microfluidic chip reactor with a 1€ coin. Reprinted with permission from ref. [21]. Copyright 2017 Elsevier Ltd. All. (B) Luminescent solar concentrator-based photomicroreactor (LSC-PM). Reprinted with permission from ref. [22d]. Copyright 2017 Springer Nature Switzerland AG. (C) Numbering-up of luminescent solar concentrator-based photomicroreactor. Reprinted with permission from ref. [22d]. Copyright 2017 Springer Nature. Switzerland AG.



after visible light irradiation. The optimized conditions allowed the analysis of the reaction droplets at a speed of 0.3 samples/s.

## 2.2 Electrochemistry

The revival of electrochemistry in the organic synthetic community has been successfully extended to the world of microflow, and that is not a coincidence, as it has been shown that the use of microreactors in electrochemistry not only brings a number of advantages but also solves old and persistent technical problems. Typically, in electrochemical reactions, SET processes are initiated at the surface of an electrode when substrates or electron mediators are transported from the bulk of the solution to the surface of the electrodes. The shorter diffusion distances to the electrodes and the large electrode surface-to-volume ratios ensure a substantial increase in the mass transfer, as a result, higher yields and reduced reaction times are observed. Additional advantages related to the use of microelectro reactors include the elimination/reduction of the need for supporting electrolytes as the ohmic drop is minimized,<sup>[24]</sup> and the rapid heat exchange that prevents heat build-up in the setup.<sup>[25]</sup>

Pioneering work in the field has been done by Jensen and coworkers by introducing a microfluidic redox-neutral electrochemistry ( $\mu$ RN-eChem) platform with broad applicability to SET chemistry (radical-radical cross-coupling, Minisci-type, and nickel-catalyzed  $C(sp^2)$ -O cross-coupling reactions). The simultane-

ous generation of reactive intermediates at the electrodes allowed for selective reactions enhanced by the rapid molecular diffusion through the microfluidic channels, overcoming the degradation of key intermediates (Fig. 4A).<sup>[26]</sup> Moreover, important advancements were also made by Noël (Fig. 4B) and Wang (Fig. 4C), who reported the synthesis of sulfonamides and thiuram disulfides, respectively, observing in both cases significant improvements in the microreactor approach over conventional batch methods, as the desired products were produced in higher yields and shorter reaction times.<sup>[25a,27]</sup>

The unique characteristics of micro electrochemistry are also relevant for scale-up and automatization purposes. Jensen and coworkers demonstrated the scalability potential of their  $\mu$ RN-eChem, by designing a three-layer stacked microfluidic flow cell with a 12-fold productivity increase.<sup>[26]</sup> Also in this context, Baran, Minter, and Neurock, recently described a scalable electroreduction of arenes. The reaction conditions developed in batch at a 0.1 mmol scale were easily scaled-up in flow up to 100 g using a numbering-up strategy by stacking several electrodes in parallel (Fig. 5).<sup>[28]</sup>

## 2.3 Microwave

Microwave (MW) heating is currently a well-established technology that is included in the basic portfolio of heating devices in an organic chemistry laboratory. MW irradiation ranges from

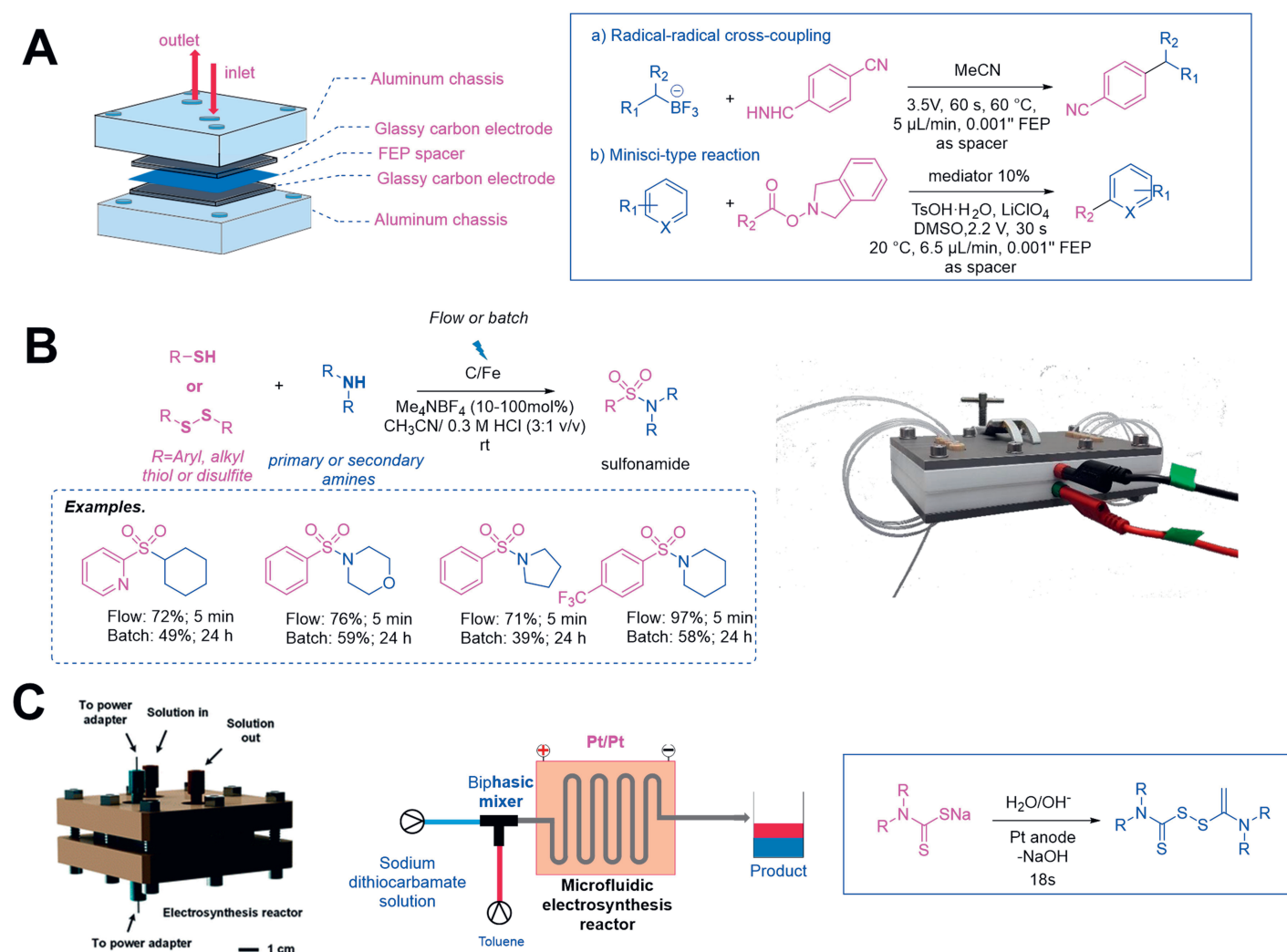


Fig. 4 (A) Schematics of  $\mu$ RN-eChem flow cell and application. (B) Reduction of reaction times in the electrochemical synthesis of sulfonamides and electrochemical flow cell. Reprinted with permission from ref. [27a]. Copyright 2019 American Chemical Society. (C) Electrolysis of sodium dithiocarbamate to generate thiuram disulfide and schematics of the microfluidic reactor. Reprinted with permission from ref. [27b]. Copyright 2021 Royal Society of Chemistry.



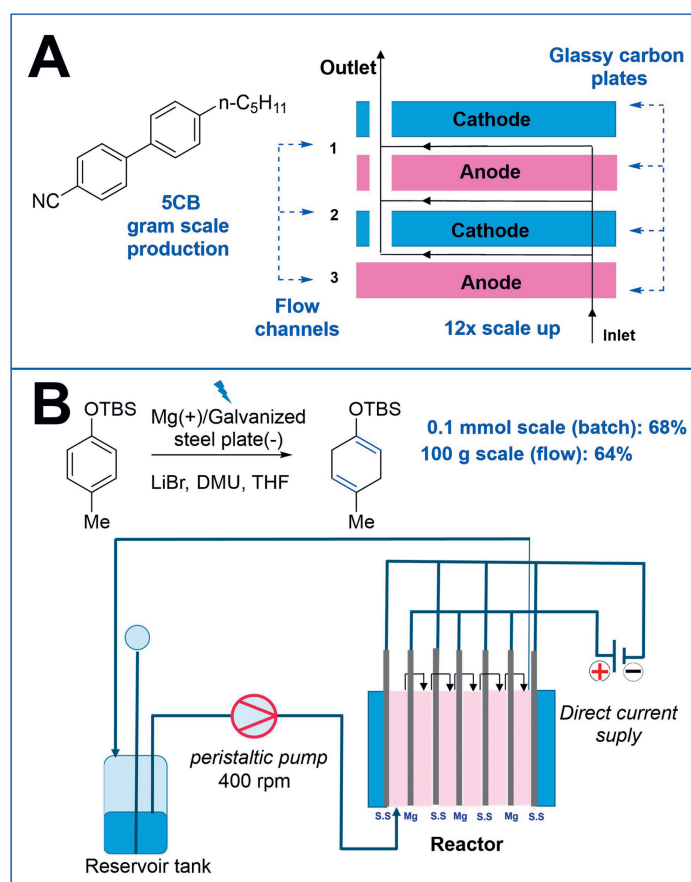


Fig. 5. (A) Schematics of a three-layer stacked large-scale  $\mu$ RN-eChem flow cell. (B) 100 g scale up in flow for the electrochemical Birch reduction.

300 MHz to 300 GHz, with common ovens operating at 2.45 GHz and industrial reactors at 915 MHz. 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 green technology.<sup>[29]</sup> 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. Therefore the small diameter of the microreactors perfectly meets the requirements for the application of MW irradiation, which is especially crucial when scaling up MW-assisted reactions.<sup>[30]</sup> This was demonstrated by Horikoshi and coworkers, who developed a pilot-plant scale for continuous-flow microwave-assisted chemical reactions combined with microreactors (Fig. 6).<sup>[31]</sup>

Advantageously, continuous-flow MW-assisted organic synthesis (CF-MAOS) attenuates the problems of microwave heating while maximizing its intrinsic benefits, providing a tool for the safe and fast optimization of reaction conditions especially when performed in meso- and microreactors.<sup>[30]</sup>

Remarkable work in the realm of microflow MW-assisted organic synthesis has been performed by Organ and coworkers who reported a custom-built microcapillary reactor, obtaining excellent conversions in a variety of reactions, showing dramatic rate enhancements compared to room-temperature conditions (Fig. 7A).<sup>[32]</sup>

In addition, MW irradiation has also been exploited by means of inductive heating (IH) of conductive materials and superparamagnetic nanoparticles (fixed bed materials inside of flow microcapillary reactors), as an alternative indirect heating technology to promote chemical transformations (see section 2.5).<sup>[33]</sup>

More recently, Hur *et al.* developed a microwaveable PDMS microfluidic reactor, which was applied to the synthesis of amides. The concept offers an affordable and easily accessible platform that could be adapted to the existing technology (CEM Discover, Fig. 7B).<sup>[34]</sup> It is interesting to note that most of the work published in microflow MW-assisted organic synthesis has actually been

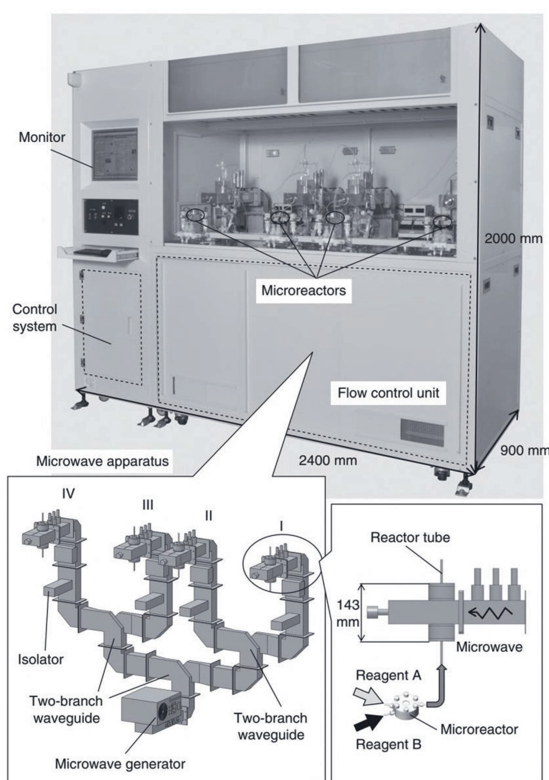


Fig. 6. Overview of the pilot plant for continuous flow microwave-assisted chemical reactions combined with micro-reactors and block diagram of the pilot plant. Reprinted with permission from ref. [31]. Copyright 2015 Wiley-VCH Verlag GmbH.

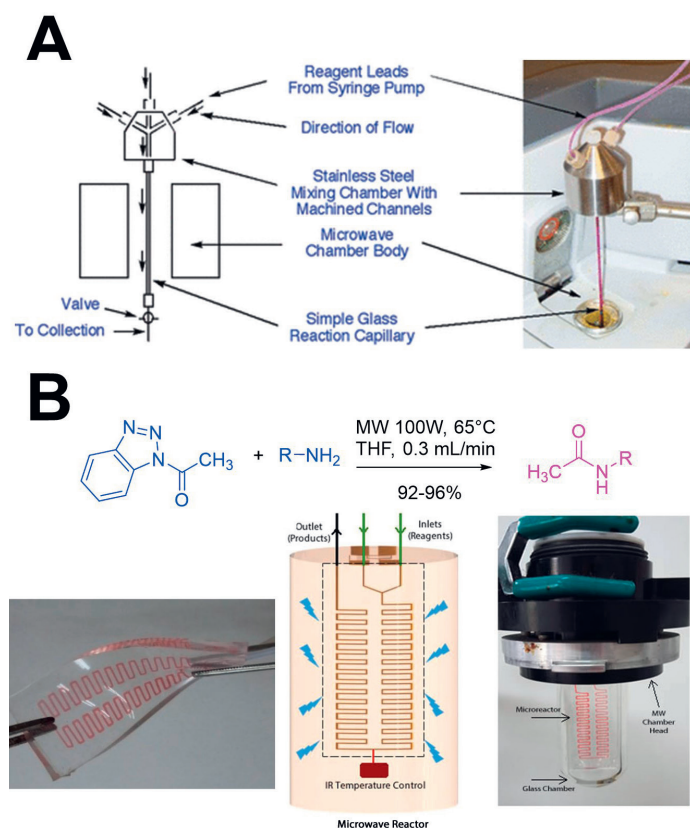


Fig. 7. (A) Continuous flow MW microcapillary. Reprinted with permission from ref. [32]. Copyright 2005 American Chemical Society. (B) Picture of the 3D-microreactor inserted in the CEM Discover cavity and the synthesis of acetamides. Reprinted with permission from ref. [34]. Copyright 2018 John Wiley & Sons, Inc

performed in microcapillaries, which suggests that there is still plenty of opportunities and challenges to be addressed in the field.

## 2.4 Ultrasound and Sonochemistry

Sonochemistry refers to the use of ultrasound waves (US) to alter properties or promote reactivity. Most sonochemical reactions are conducted at ultrasonic frequencies between 20 and 100 kHz with intensities high enough to cause cavitation in the liquid medium.<sup>[35]</sup> This phenomenon describes the generation of microbubbles or cavities, and their subsequent growth to a maximum size followed by violent collapse leading to significant local energy dissipation (local hot spots).<sup>[36]</sup>

Ultrasound can assist reactions either chemically (through local hot spots and radical processes) or physically (by improving mass and heat transport rates), resulting in reaction acceleration and high conversions rates. Ultrasound-induced chemistry has the potential to be applied to almost any type of reaction;<sup>[36]</sup> however, on a macroscale, many ultrasound-assisted transformations lack reproducibility in part because cavitation energies depend on external parameters (frequency, intensity, dissolved gas, *etc.*), and solvent properties. Contrary to macroreactors, microfluidics devices are ideal for accurate temperature, frequency, and pressure amplitude control along with effective mixing and short residence times. In this sense, the combination of sonication and microflow reactors leads to synergistic effects and brings numerous benefits in terms of higher selectivity and lower waste generation, while preventing pipe clogging.<sup>[37]</sup>

Although US can be easily adapted to microreactors by simply submerging capillaries/tubing in ultrasonic baths, this strategy is energetically inefficient with problems associated with both temperature and power control.<sup>[37,38]</sup> In this sense, homemade micro-sono-reactors have been developed by assembling PTFE with

piezoelectric actuators. The microreactor was used in Pd-catalyzed couplings of anilines and aryl halides, obtaining the products in excellent yields (>95%) within 60–90 s (Fig. 8A).<sup>[39]</sup>

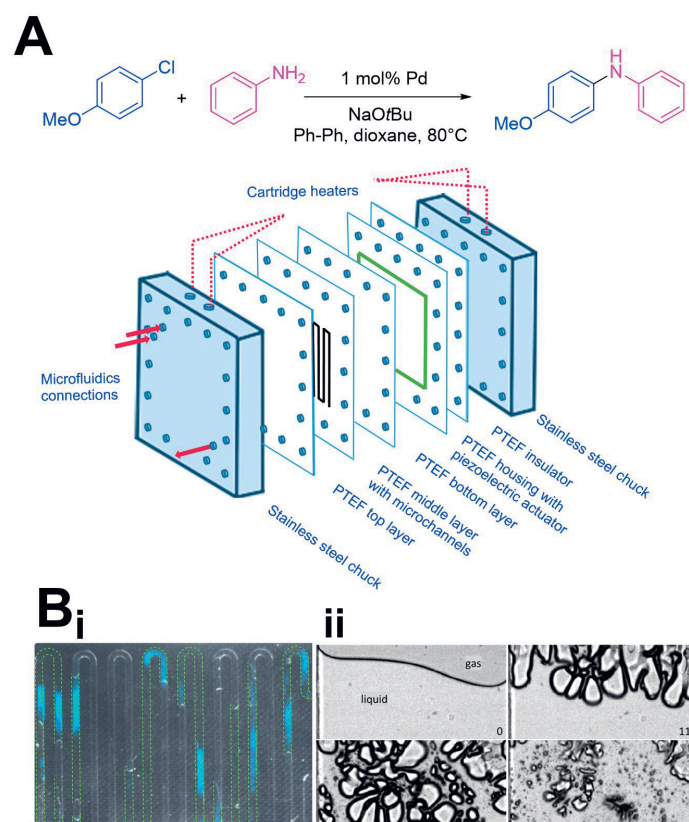


Fig. 8. (A) Micro-sono-reactor applied to a Pd-catalyzed coupling reaction. (B) Luminol chemiluminescence from cavitation bubbles. (ii) bubble distribution near a gas–liquid interface. Reprinted with permission from ref. [40]. Copyright 2011 MDPI (Basel, Switzerland).

Although sonication is most commonly used to promote liquid flow and avoid deposition, ultrasound-induced chemistry has also been exploited further. Current research aims to explore sonochemical processes themselves with the aid of microfluidics, such as cavitation collapse as well as associated phenomena like sonoluminescence and radical production. In a relevant work reported by Ohl and coworkers the suitable conditions for sonoluminescence and sonochemistry were studied by using bubbles confined within a narrow channel of a microfluidic device, with the bubbles assuming a planar pancake-like shape. The formation of hydroxyl radicals and the emission of light (sonoluminescence) were observed as a result of the bubbles collapsing. In addition, it was suggested that the observation of chemical reactions was closely related to the gas–liquid interfaces, where spatial control over them could be used to control sonochemical reactions.<sup>[40]</sup>

Finally, large-volume applications of ultrasound-assisted chemistry are also feasible by simply numbering-up in parallel multiple microreactors.

## 2.5 Electromagnetic Induction Heating

The process of heating an electrically conductive object by applying a medium frequency field (15–25 kHz), resulting in a selective and practically immediate increase in temperature, is known as electromagnetic induction heating (IH). This phenomenon is based on magnetic inductive hyperthermia, which describes how magnetic hysteresis loss generates heat when magnetic nanoparticles are exposed to a constantly changing magnetic field (Néel



relaxation). In addition, a very strong, rapidly alternating magnetic field is able to conduct eddy currents in any conductive material placed in close proximity to the field, which can also heat the metal by induction.<sup>[41]</sup>

Contrary to microwave irradiation, electromagnetic induction does not have an effect on solvents or reactants, but instead selectively heats conductive or superparamagnetic materials. The latter simplifies both setup and temperature control significantly as fewer parameters have to be considered. Typically, high-performance polymers and glass are used as reactor materials due to their transparency to inductive fields.<sup>[42]</sup>

Electromagnetic induction heating is a clean, affordable and energy-saving technology that has been widely used in the industry for processes such as surface hardening, melting, brazing, sealing. Nevertheless, it was first applied to organic synthesis in 2008 by Kirschning *et al.*, who introduced the technique as an alternative indirect heating technology that was implemented and developed from the beginning using microfluidic devices. The authors investigated a number of organic reactions using superparamagnetic nanoparticles, including oxidations, Buchwald–Hartwig amination, Wittig reactions, palladium-catalyzed couplings, metathesis, and Claisen rearrangements (Fig. 9). In most of cases the inductive heating combined with flow proved superior to batch processes in terms of reaction times and/or isolated yields.<sup>[43]</sup>

Currently, superparamagnetic particles are used as an initial source of heating as they can be superheated (up to 500 °C). In general, magnetic nanoparticles can change their heating profiles depending on the percentage of output power, the type of material, and even the shape and size of the particles. Furthermore, the heating material can be chemically inert and be used only to heat up the reaction system, or can have also a catalytic role.<sup>[30]</sup> The latter case was nicely illustrated by Organ and coworkers, who used inductive heating to specifically activate a thin coating layer of Au, Cu or Pd inside of a microreactor to promote a three component reaction.<sup>[44]</sup> Finally, Kirschning made use of the conductive qualities of copper wire and used it as both heating material and catalyst to promote copper-catalyzed transformations (Fig. 10).<sup>[45]</sup>

## 2.6 Miscellaneous and Hybrid Technologies

**Hydrodynamic cavitation (HC):** HC is the process in which high energy is released in a flowing liquid upon bubble implosion due to decrease and subsequent increase in local pressure.<sup>[46]</sup> The massive quantity of energy produces localized hot spots with transitory temperatures above 10,000 K and pressures exceeding 1000 atm, powerful enough to cause chemical reactions or physical transformations. HC has been widely used in the food-processing industry, biodiesel production and water disinfection.<sup>[47]</sup>

Hydrodynamic cavitation is generated by passing a liquid through a nozzle throat constriction (throttling valve, orifice plate, venturi). As the liquid passes through the constriction, its kinetic energy/velocity sharply increases at the expense of its rapidly decreasing pressure. As a consequence, a large number of vapor cavities are formed, which then collapse and release energy as the pressure returns.

Thanks to the developments in microfluidics, lab-on-a-chip gives the opportunity to strictly control and monitor the cavitation phenomenon at a microscale. In contrast to macroscale, where cavitation bubbles are typically hard to manipulate, microfluidics devices provide ideal platforms to design and conduct smart experiments in which the collapse energy of cavitation bubbles can be precisely harnessed. Within this context, cavitation-on-a-chip has found mostly applications in biomedicine and nanomaterial synthesis.<sup>[48]</sup>

**Microfluidics plasma:** In plasma-based chemistry, gas discharge plasmas, generated from different power sources, provide

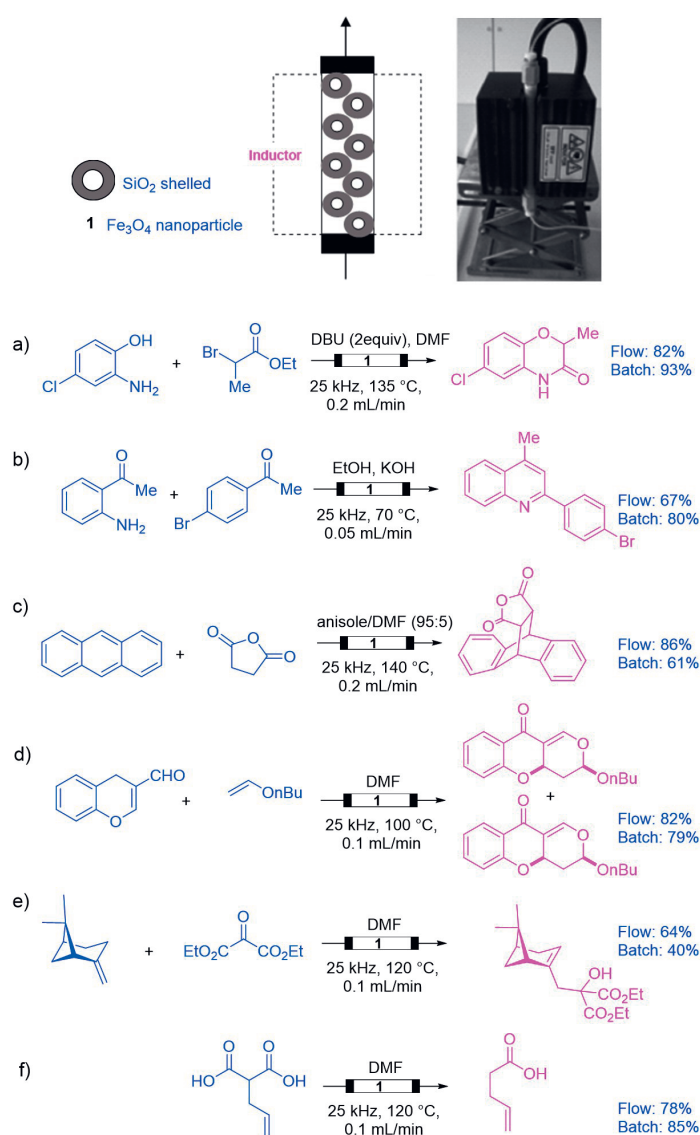


Fig. 9. Flow reactor filled with magnetic nanoparticles and flow inductive heating-assisted synthesis of heterocycles. Reprinted with permission from ref. [43]. Copyright 2012 John Wiley & Sons.

a high-energy state that initiates ionization or electron impact-induced chemical reactions.<sup>[30]</sup> The main applications of the technology involve water treatment, volatile organic compounds (VOCs) decomposition, CO<sub>2</sub> conversion, nitrogen fixation, food preservation, surface modification, plasma medicine.<sup>[49]</sup> The benefits of plasma-based chemistry include the enhancement in the reactivity of species and the acceleration of chemical reactions. However, non-thermal plasmas tend to be unsteady and nonuniform, and their operation under sub-optimal conditions leads to excessive reaction rates and quenching of reactive species. In this sense, the integration of microfluidics and non-equilibrium plasmas, so-called microfluidic plasmas, not only allow the precise and effective mass and heat transport *via* the microfluidic system but also provide an extremely reactive medium full of high energy plasma-generated species. Applications of microfluidic plasmas include nanomaterials fabrication, surface modification, environmental application, micro total analysis systems, and organic synthesis.<sup>[50]</sup>

Microfluidic plasma-assisted methods bring opportunities to synthesize chemicals in a catalyst-free manner. Tatoulian *et al.* explored the feasibility of microfluidic plasmas as a synthetic tool, by fabricating a microfluidic chip linked to an AC high-voltage source to generate plasma within microchannels. They investigated the plasma activation of aliphatic C–H bonds by performing



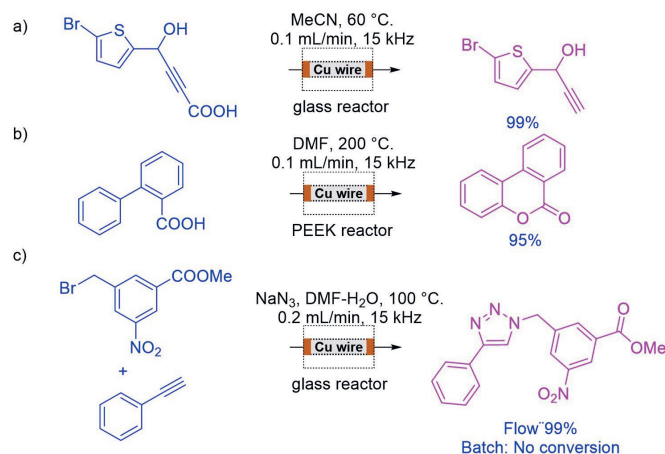


Fig. 10. Reactor filled with copper wire and continuous copper-catalyzed Huisgen 'click' cycloadditions, decarboxylations and cyclizations under inductive heating conditions.

a controlled partial oxidation of cyclohexane with  $O_2$  plasma (Fig 11A).<sup>[51]</sup>

**Infrared heating:** Infrared heating is the process by which infrared radiation (wavelength 0.78 to 1000 m) is absorbed by a material, resulting in molecular vibrations and the release of radiant energy in the form of heat. Infrared heating is an energy-efficient technique with numerous advantages, including a fast heating rate/response and uniform heating. It is also recognized as an energy-saving technology that consists of typically versatile, simple, and compact equipment.<sup>[52]</sup>

IR heating is still in its infancy, with most applications found in food processing operations, however, this technology has great potential to be applied to synthetic chemistry as demonstrated by Zappimbalso *et al.* who recently investigated the solvent-free synthesis of squaraines and croconaines by condensation reactions. They used and compared different energy sources (mechanochemistry, conventional heating, and IR irradiation) finding that

IR heating led to considerably shorter reaction times and reduced energy consumption compared to the other techniques.<sup>[53]</sup>

To the best of our knowledge, there are no applications of IR heating paired with microflow. Nonetheless, the low penetration depth of IR irradiation and the small diameter of channels in microreactors seems like another perfect match, which brings numerous opportunities to enhance this technology in the future.

**Ultrasound-assisted hybrid technologies:** Acoustic energy, through the use of ultrasound, plays a fundamental role in microfluidics as it has been demonstrated to be a successful way to reduce the size of agglomerate particles (solids produced during a given reaction that accumulate along the walls of a flow reactor), preventing the clogging of the microreactor channels. This, together with the ease with which ultrasound can be applied to microreactors, has fostered the development of several strategies involving its combination with various energy sources. In this context, hybrid techniques like sonoelectrochemistry, MW-sonication, and photo-sonication can be found in the literature.<sup>[54]</sup> This last combination was exploited by Yoshida and coworkers who devised a hybrid microreactor for the efficient photodimerization of maleic anhydride. Normally, this reaction gives precipitated products, which clog a conventional microreactor, limiting its application. Yoshida and coworkers solved the problem by devising a microreactor that uses liquid/gas slug flow and ultrasonication. Under such conditions, the microreactor could be operated for more than 16 h continuously without clogging. The approach improved product quality, conversion, and reduced waste production (Fig. 11B).<sup>[55]</sup>

**Electrophotochemistry:** Photoelectrocatalysis is another emerging area where microfluidic technology has great potential. Unoptimized home-made setups have been employed thus far as this novel activation mode is still in its infancy. Nonetheless, it can be assumed that photoelectrocatalysis will soon infiltrate the field of microfluidics, as Noël predicted. In this regard, additional research on crucial chemical engineering aspects is required to improve reactor designs. Since scale effects are important in both electrochemistry and photochemistry, microreactors can provide synergetic benefits for the reproducibility and scalability of photoelectrocatalysis.<sup>[56]</sup>

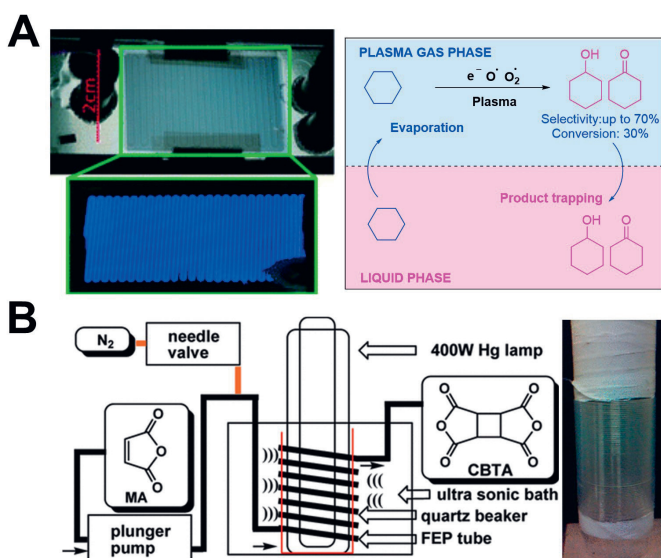


Fig. 11. (A) Illustration of the microfluidic plasma setup for the oxidation of cyclohexane. Reprinted with permission from ref. [51]. Copyright 2018 The Royal Society of Chemistry. (B) Flow cell for maleic anhydride dimerization under photochemical and ultrasonic irradiation. Reprinted with permission from ref. [55]. Copyright 2010 American Chemical Society.

### 3. Microreactor Scale-Up Approaches: Making the Most of Microflow

The transition from a lab scale to production scale is not a simple task. Typically, a variety of additional factors, such as process safety and cost efficiency, must be also considered. In addition, the hydrodynamics and transport properties need to be maintained at each scale, complicating the scale-up process even further. Within this context, microreactor technology is a powerful technique with the potential to overcome some long-lasting scaling-up problems. Compared to batch reactors, microreactors have better batch-to-batch reproducibility and controllability.

There are several strategies for scaling-up with microflow devices, namely i) longer operation times combined with increasing the throughput by using higher flow rates; ii) numbering-up, and iii) size up (Fig. 12A).

The use of longer operation times is the most straightforward scaling-up technique. It basically, consists of pumping continuously reagents to the microdevice until the desired amount of product is produced. Typically, the scale-up device is the same used for optimization. This strategy can yield up to a few hundred grams of product, making it ideally suited for the first stages of a drug discovery process.<sup>[57]</sup> Santos and collaborators described a robust microfluidic platform for synthesizing diverse types of homogeneous nanoparticles with mass production rates of up to 242.8 g per day (Fig. 12B).<sup>[58]</sup>

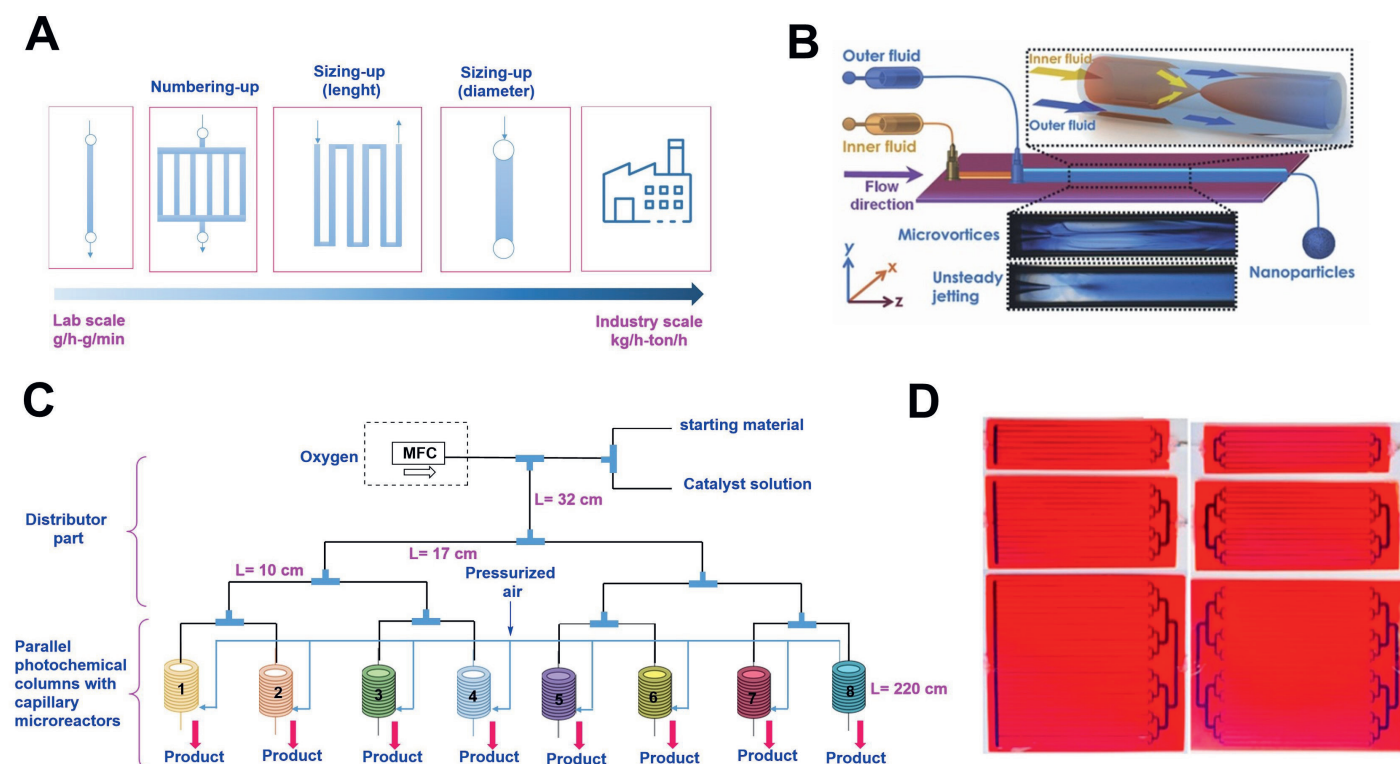


Fig. 12. (A) Microreactor scale-up strategies. (B) High throughput microcapillary reactor for synthesis of nanoparticles. Reprinted with permission from ref. [58]. Copyright 2015 Wiley-VCH. (C) Schematic overview of a 8-capillary microreactor system. (D) Internal numbering-up of a solar reactor with 8, 16 and 32 parallel microchannels. Reprinted with permission from ref. [22d]. Copyright 2018 American Chemical Society.

On the other hand, numbering-up of microreactors is the most common method to scale-up. Two different approaches can be distinguished: i) internal and ii) external numbering-up. Internal numbering-up is achieved by placing several microchannels in parallel and using a single pumping and mixing unit. Nevertheless, this requires an equal pressure drop over the different parallel channels, which is sometimes difficult to achieve. Noël and coworkers successfully used this approach for the photocatalytic aerobic oxidation of thiols to disulfides, in which the system split up the gas–liquid flow into eight different photomicroreactors using simple T-mixers as the basic splitting components (Fig. 12C).<sup>[59]</sup> Recently, the same group pioneered the scaling-up of luminescent solar concentrator photomicroreactors with up to 32 parallel channels with standard deviations of less than 10% (Fig. 12D).<sup>[23]</sup>

In contrast, external numbering-up is the strategy of placing several microreactors in parallel so that each device has its individual pumping system and process control unit. While external numbering-up ensures that the same processing conditions are obtained in each individual device, the approach is costly since each unit has its own pumps, heating system, flow controllers, *etc.*<sup>[57]</sup>

Sizing up refers to the increment of the productivity of microreactors by a dimension enlarging strategy. In this sense, three different approaches can be recognized: (i) an increasing length approach which increases the channel length whilst keeping the channel diameter constant, (ii) a geometric similarity approach and (iii) a constant pressure drop approach which involve a simultaneous increase of both channel length and diameter. Typically, active mixers are used in these millireactors to achieve the same characteristic increase in heat and mass transfer as in microreactors. Such a strategy enables scaling from pilot scale to production scale with relatively few development experiments.<sup>[60,61]</sup>

#### 4. Complex Integrated Microsystems

We have consistently underlined the ease of integration of microreactors as one of its primary features throughout this perspective. However, we have only addressed this characteristic in the context of merging microsystems with diverse power inputs and scaling-up. This ‘ease of integration’ concept, however, extends further as it also implies the ability to couple several functional units to perform multi-step synthesis. In this context, a typical synthetic process usually includes multiple steps that must be completed sequentially using traditional batch techniques. Nonetheless, these processes can be easily completed in a fast and continuous manner with designed microreactors, thus simplifying the whole procedure with improved efficiency. The latter demands a proper flow of chemicals and the correct orchestration of the reactions at each step.<sup>[11]</sup> The synthesis of a wide range of APIs has proved the enormous value of microfluidics in multistep processes.<sup>[61]</sup>

Finally, the concept of integration is also relevant in the sense of adapting functional modules such as automatics, online/inline analytics, and feedback to microreactors. Microfluidic devices have also been successfully integrated with a number of online/inline analytics including HPLC, Raman spectroscopy, IR, NMR.<sup>[62]</sup> Online/inline detectors can reduce the time and reagent consumption, and provide instant feedback on optimization. Moreover, several automated algorithms have been developed and integrated into microreactors to interpret real-time data and adapt to subsequent conditions. As demonstrated by Jensen and coworkers, who reported automated optimization algorithm platforms for the optimization of a Paal–Knorr and a Suzuki–Miyaura cross-coupling reaction, they were able to obtain complete optimization conditions within 38 and 96 experiments respectively (Fig. 13A and 13B).<sup>[62b,63]</sup>

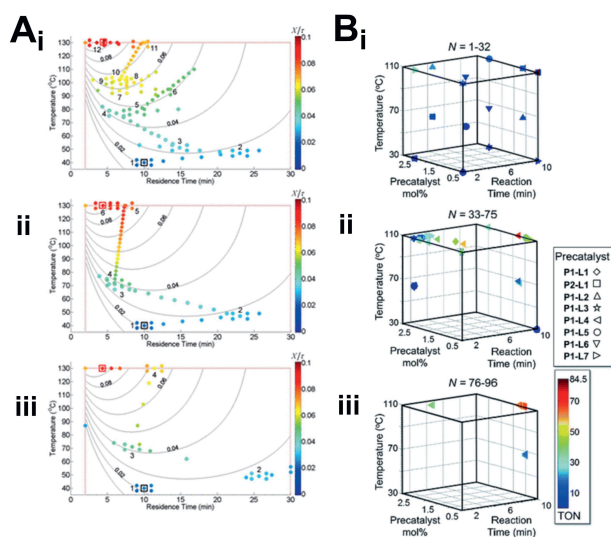


Fig. 13. (A) Maximization of the production rate of the Paal-Knorr reaction. The initial DoE of each trajectory is numbered. (i) Steepest descent method. (ii) Conjugate gradient method. (iii) Armijo conjugate gradient method. Reprinted from ref. [62b]. Copyright 2016 American Chemical Society. (B) Optimization routes followed by the automated system for a specific case, where (i), (ii), and (iii) refer to initialization, quadratic response surface refinement, and convergence, respectively. Reprinted from ref. [63]. Copyright 2016 Royal Society of Chemistry.

## 5. Conclusions and Future Opportunities

Microreactors, initially born as a lab curiosity, have since long attracted the attention of the chemical community due to their unique characteristics related to the low laminar flow regime and fast mass/heat transfer. The latter brings a number of advantages when applied to organic synthesis, including short reaction times, improved yields, high levels of safety and reproducibility, selectivity, and even unique reactivities that are not achievable in macro batch reactors.

Throughout this perspective we have briefly discussed some fundamental aspects related to microfluidics and microreactors, focusing mainly on the application of the most relevant synthetic technologies/energy sources used for process intensification, either alone or in combination. Demonstrating that the combination of microfluidics with intensification technologies is a powerful mixture that results in synergistic and improved results, frequently solving technical problems associated with the technologies themselves and opening the door to the exploration of new chemistries.

We have also discussed and provided examples of how microfluid systems can be efficiently scaled-up and proved that the benefits of microfluidics are not restricted to a lab scale but instead have real-world applications in the chemical and pharmaceutical industry.

We went on to show how automated algorithms have been successfully integrated into microfluidic devices for rapid reaction optimization. This sort of complex integrated system offers an ideal platform for drug discovery while saving valuable resources in terms of chemicals and time.

Microfluidic devices are a green adaptable technology that has been widely applied to a variety of fields from biomedicine to material science. In the context of organic synthesis, microfluidics has been applied to almost every known chemistry including homogenous catalysis, photochemistry, electrochemistry, enzymatic, multistep reactions. This proves that with some creativity, the benefits of microfluidics can be easily extended and adapted to suit the requirements of almost any situation.

Nonetheless, every coin has two sides.  $\mu$ Syn is still a young research field, which has barely reached two decades of explora-

tion and there is still plenty of work ahead before microreactors could become a piece of standard lab equipment. Some of the challenges and opportunities that have to be addressed in order to broaden the applications of  $\mu$ Syn include:

- i) Further exploration of different chemistries in microfluidics/microreactors by integration with more energy sources and enhancing technologies.
- ii) Continued innovations in chemical compatibility in terms of reactor material and process equipment.
- iii) Continued innovations in the field of inline/online monitoring by integrating more and different analytical equipment; the latter could accelerate the use of automated systems to discover, develop, and optimize chemistry processes.
- iv) Increased research into the automation of laboratory and process systems to facilitate feedback control, optimization, automated screening, and data collection, which could beneficially impact the drug discovery process.
- v) Research and development in the integration of functional unit systems in microfluidic devices, that facilitate otherwise tedious chemical operations, such as separation, filtration, purification, in-line evaporation.
- vi) Active collaborations in the areas of chemistry, physics, materials, chemical and reaction engineering, industrial process, and digital control engineering in order to improve reactor designs and scale-up processes.
- vii) Further research in scale-up of microreactors toward high productivity/stability to help to bridge the gap between academia and industry.

Finally, we hope that this perspective will inspire some of our fellow chemists to explore the ever-exciting field of microfluidics, which will clearly continue to grow in the decades to come.

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