

Mini-Review

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In-flow enantioselective homogeneous organic synthesis

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Abstract: The use of enabling technologies, such as flow reactors, three-dimensional-printed devices, and electrochemistry, in the stereoselective synthesis of enantio-enriched compounds is presented, with a special focus on the most significant contributions to the field reported in the last few years.

Keywords: stereoselective reactions, asymmetric catalysis, flow reactors, 3D-printed devices, chiral compounds

1 Introduction

Per Collins English dictionary, “Technology refers to methods, systems, and devices which are the result of scientific knowledge being used for practical purposes.” Hence, the application of science to develop new devices, systems, or methods is called technology. But the borders are not that clearly defined; indeed, science and technology are strictly related: technology may be considered the practical application of science, but, however, it can be used to do science.

Technology stimulates scientific progress by sustaining science with increasingly sophisticated devices and experimental equipment, but, at the same time, science continuously demands for revolutionary technologies. The importance of innovative technologies has been recognized also by the European Commission, which has identified key enabling technologies (KETs) as a priority within its Europe 2020 strategy. “KETs provide the basis for innovation in a range of products across all industrial sectors. They underpin the shift to a greener economy, are instrumental in modernizing Europe’s industrial base, and drive the development of

entirely new industries” [1]. These considerations also apply to organic synthesis, where the advent of the so-called “enabling technologies” has brought unprecedented opportunities and offered the possibility to develop new, more efficient, or faster reactions [2–5].

Significant progress in organic synthesis has been realized through the integration of two or more of these enabling techniques, [6] for example, by the combination of supported catalysts, alternative solvents, flow chemistry (new reactors design), and alternative heating techniques (including microwave-assisted synthesis).

Considering the numerous reviews published in the last few years in the field of continuous-flow reactions, we have decided to focus the present contribution only on the in-flow technology-assisted enantioselective synthesis and to limit the discussion especially on the most recent publications reporting the stereoselective synthesis of enantiomerically enriched compounds. The presentation is focused only on homogenous reactions and more specifically on (a) in-flow asymmetric catalysis, (b) continuous-flow stereoselective organophotoredox transformations, and (c) in-flow electrochemical stereoselective organic reactions. The use of heterogenized catalysts and catalytic reactors, immobilized enzymes, and continuous-flow biocatalysis is not included in the present contribution.

2 Continuous-flow stereoselective reactions

Flow chemistry is now universally recognized as a main enabling technology as it can ensure facile automation, reproducibility, safety, and process reliability [7–13]. Moving from batch to in continuo processes can potentially solve the major issues that prevent the industrialization of some synthetic methodologies and may allow to develop new processes of less environmental impact and potential cost saving [12].

Recently, industries have shown an increasing interest in the switch from batch to in continuo processes, which can potentially solve some problems, especially safety

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issues, related to the use of toxic reagents or the application of hazardous technologies or dangerous synthetic methods. As a result of a better control on the reaction parameters, performing reactions in continuo can improve safety, selectivity, and productivity and can represent a green and sustainable approach for the process development.

Different equipment are commercially available to run in continuo transformations. Most popular equipment are coils, micro/mesochip, and catalytic reactors, but also continuous stirred tank reactors are, nowadays, available even for laboratory scale, while they are already widespread in industries for large-scale applications. Additionally, pharma industries are considering the superior performances of continuous-flow technology over traditional batch production (precise control of reaction parameters, higher productivity) [14–16]. Therefore, not surprisingly, a large community of chemists and engineers, either in universities or in industries, is routinely working with continuous-flow technologies.

In this review, continuous-flow stereoselective reactions promoted by chiral catalysts, both organocatalysts [17,18] and metal-based catalysts [19,20], for the synthesis of chiral molecules, are presented and discussed.

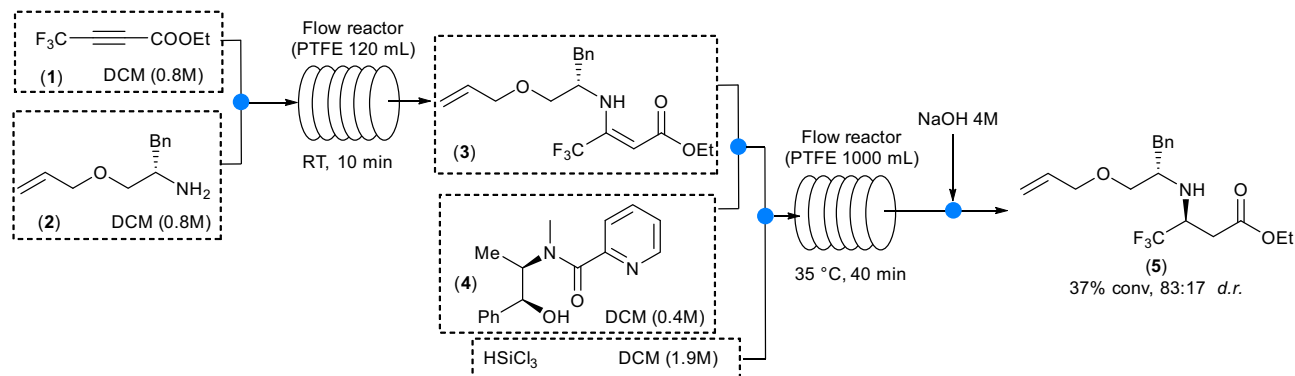
2.1 Homogenous asymmetric catalysis in flow

Despite the exponential growth of asymmetric organocatalysis in the last decades, and the advantages of merging it with flow chemistry, the area of continuous-flow asymmetric organocatalytic reactions remains relatively little explored and, until 2016, examples were mainly limited to the use of proline and its derivatives and of chiral phosphoric acids. Since asymmetric organocatalysis in flow was the objective of a recent review [18], we will here discuss only a few selected recent examples.

Last year, our group reported the stereoselective synthesis of trifluoromethylamine mimics of retro-thiorphan, an inhibitor of metalloproteinase neutral endopeptidase [21].

The crucial step is the stereoselective, catalytic trichlorosilane-mediated reduction of fluorinated enamine **3** in the presence of catalytic amounts of chiral picolinamide **4**. By studying the synthetic sequence in flow, it was possible to synthesize an advanced intermediate of retro-thiorphan in a two-step process that affords the compound **5** without the need of purification procedures of the intermediates; chiral amine **5** was isolated in up to 87:13 diastereoisomeric ratio. The reaction steps performed under continuous-flow conditions are reported in Scheme 1. The commercially available fluorinated alkyne **1** was reacted with the *O*-allyl-protected phenyl alaninol ether **2** to afford enamine **3** with a complete conversion after 10 min residence time. Compound **3** was then reacted with trichlorosilane in the presence of the chiral Lewis base **4**. The reduction step required long residence times to obtain reasonably good conversion; to increase the yield, the reactor was heated up to 35°C, obtaining compound **5** in up to 37% isolated yield, but with lower diastereoselectivity, whereas at room temperature, the product was isolated in 20% yield and 95:5 d.r. (diastereoisomeric ratio). Although yields and d.r. were not totally satisfying, this study represents an example of how the synthesis of enantiomerically pure, pharmaceutically relevant products could be achieved through a multistep continuous-flow process.

Recently, an in-flow asymmetric aldol reaction of 3-chloro-benzaldehyde **7** with acetone was reported to be catalyzed by prolinamide derivative **6** (Singh's catalyst) used in a combination of buffer (pH 7)/2-propanol [22]. The project aims to realize a two-step one-flow process in an aqueous medium combining organo- and biocatalysis and the first example of a continuous-flow



Scheme 1: Continuous-flow synthesis of a precursor of retrothiorphan.

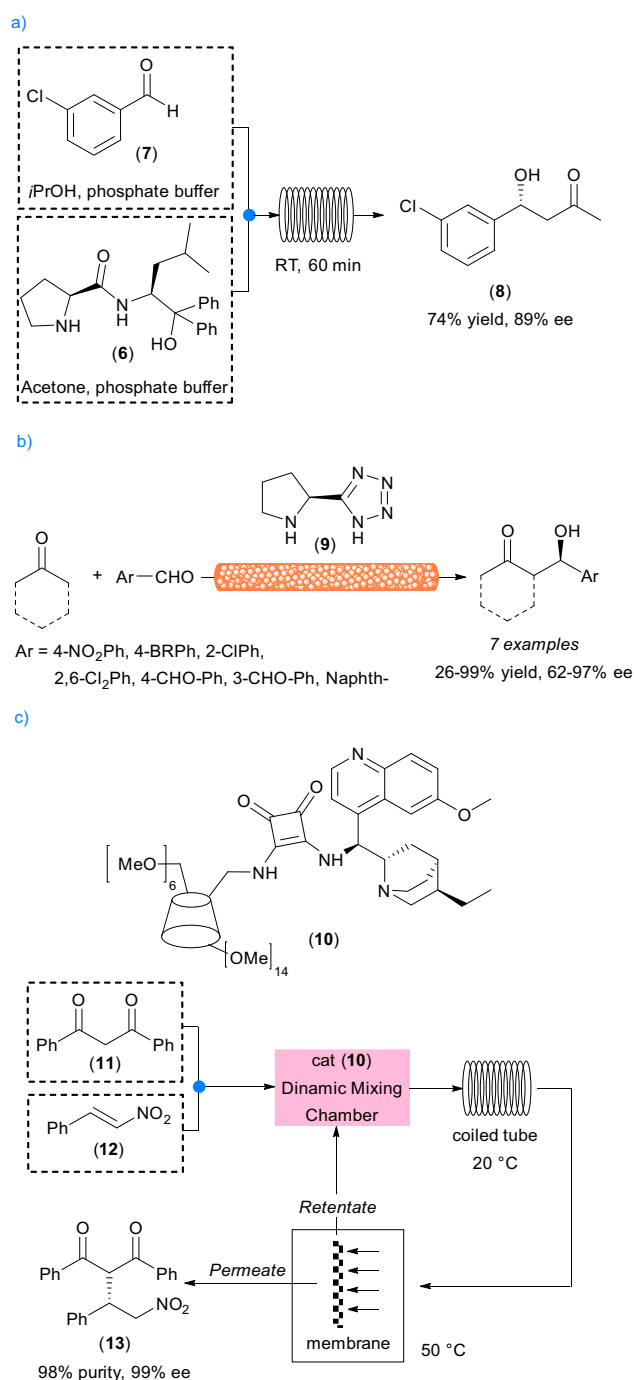
organocatalytic reaction with a hydrophobic substrate in water.

A long optimization work allowed us to find the correct conditions to afford the product in yield and enantiomeric excess (ee) comparable to the batch reaction. A solution of 3-chloro-benzaldehyde 2-propanol and phosphate buffer, mixed with the mixture of Singh's catalyst, 2-propanol, acetone, and phosphate buffer, was pumped into a coil Teflon tube reactor. After equilibration of the reaction, the eluted sample was collected and quenched by dropwise addition into a solution of dichloromethane (DCM)/2.0 M HCl; after usual work up with DCM, product **8** was isolated in 74% conversion and 89% ee (Scheme 2a). One of the main issues associated with the use of homogeneous organocatalysts in flow is the high loading that these catalysts usually required to show good performances in terms of yields and stereoselectivity (20% for the initial reports, down to 1–5% that is currently used). Moreover, at the end of the reaction, a separation step is required to recover the product and, possibly, to recover and recycle the chiral catalyst.

Nakashima and Yamamoto reported a completely different approach for the use of nonsupported organocatalyst in flow [23]. Proline-tetrazole **9** packed into an empty column was used as a reactor; low polarity organic solvents, where the catalyst is not soluble in, were selected to run the reaction in continuo, without consumption and loss of catalytic activity (Scheme 2b). Therefore, the catalyst acts as a heterogeneous system as it is in a different phase than the reagents and the reaction solvents, but its immobilization on a solid support is not required.

The column was employed in the aldol reaction between ketones and different aromatic aldehydes in low-polar organic solvent (AcOEt), reused many times and used for reactions on 10 mmol scale, also in two different transformations, like nitro aldol and the Mannich reactions; it was observed that the system affords better ee with the addition of 3% water. Products were obtained often in higher than 70% yields. To assess the catalyst performances, the authors introduced a new reaction metric, the process catalyst mass efficiency (PCME), which is defined as the actual mass of catalyst used or catalyst consumption in the process relative to the moles of the desired product. Although the nonsupported proline tetrazole showed low PCME with respect to other solid-supported organocatalysts, this approach proved to be simple and efficient in the aldol reactions.

The last example discussed in this section allows us to introduce the concept of membrane separation. The membrane-assisted recovery of homogeneous catalysts [24] is sustainable with low-energy consumption, and



Scheme 2: Examples of organocatalyzed transformations in flow.

- (a) Stereoselective aldol reaction in aqueous medium,
 (b) stereoselective aldol reaction with insoluble catalyst,
 (c) stereoselective Michael addition with membrane separation.

its use in flow chemistry is feasible, scalable, and easily implemented in continuous-flow processes (Scheme 2c).

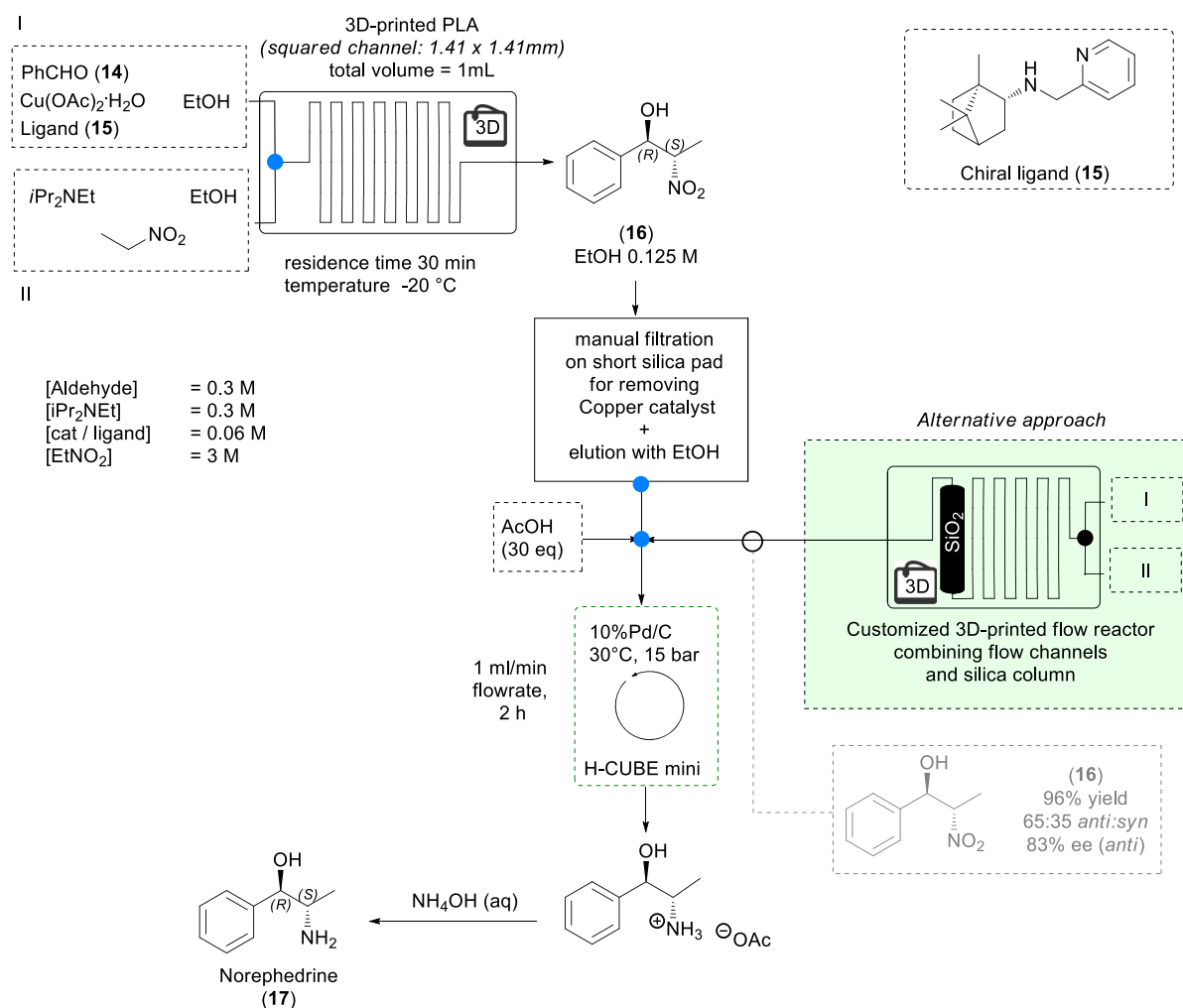
The molecular weight gap between the catalyst and the other components as well as the absolute catalyst retention by the membrane are the two main factors responsible for the efficiency of the strategy that usually

requires a size enlargement of the catalyst, realized by conjugation to dendrimers or by embedding in soluble polymers. Kisszekely and Alammar prepared β -cyclodextrins functionalized with cinchona-thiourea and squaramide derivatives as enlarged organocatalysts for the addition of diketones to β -nitrostyrene [25].

After preliminary tests in batch, the homogeneous catalysts were used under optimized conditions in the model reaction in the continuous-flow reactor. The scheme of the continuous catalysis–separation platform is shown in Scheme 2c. Among the different membranes tested, the best performing system showed a 100% rejection of catalyst **10** and less than 5% rejection of the other species. This result was possible due to the large gap in the size of the catalyst and the reactants. During the integrated synthesis–separation process, the outcome of the flow reactor, containing the crude reaction mixture, was directed to a cross-flow membrane cell.

The permeate stream with high concentrations of product **13** ($41 \text{ g}\cdot\text{L}^{-1}$) has a purity of 92%. The retentate stream *in situ* recycled 100% of catalyst **10** and 50% of the 2-MeTHF solvent. A fresh solution of diketone **11** and *trans*- β -nitrostyrene **12** was pumped into a dynamic mixing chamber where it met the recycled stream. From the evaluation of the effect of recirculation on the productivity, purity, and concentrations, it turned out that the best results could be obtained with 50% recirculation, with the membrane thermoregulated at 50°C , to prevent the precipitation of the product. Product **13** was isolated by crystallization with 98% final purity and 99% e.e. The robustness and reusability of the catalyst were demonstrated over 18 days of operation, operating at up to 100°C in the flow reactor.

The three-dimensional (3D) printing technology represents a very promising tool that has found increasing applications in organic synthesis. The 3D printing is an



Scheme 3: In-flow stereoselective organic synthesis in 3D-printed reactors.

additive manufacturing technique consisting in the production of 3D solid objects through the successive layering deposition of material [26]. It has been not only used for the realization of many fluidic devices [27] and catalyst-embedded devices to promote different chemical transformations [28,29] but also for pharmaceutical manufacturing [30]. At the moment, despite the numerous synthetic methodologies reported, only few of them are related to the synthesis of chiral molecules.

In 2017, our group reported the first stereoselective catalytic synthesis of norephedrine, metaraminol, and methoxamine accomplished under fluidic conditions using homemade fuse deposition modeling 3D-printed mesoreactors [31]. The common synthetic strategy for these products of pharmaceutical interest involves a catalytic, stereoselective nitroaldol reaction between benzaldehyde **14** and nitroethane performed under flow conditions in the presence of chiral copper complex catalyst obtained combining $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ with chiral ligand **15** derived from camphor. This transformation was performed using a poly lactic acid (PLA) 3D-printed mesoreactor. The crude nitro aldol **16** obtained from this process was then subjected to a short silica-pad filtration (to remove the copper catalyst that is not compatible with the hydrogenation process) before proceeding to an in-flow hydrogenation of the nitro group. The detailed process for the synthesis of norephedrine is summarized in Scheme 3. Many mesoreactors, differing in channel shapes and dimensions, as well as different copper complexes and reaction conditions were investigated. The best results were obtained when the synthesis of nitro alcohol **16** was performed using a PLA 3D-printed mesoreactor in the presence of complex $[\text{Cu}]\text{-15}$ at -20°C with a 30 min as residence time. The Pd/C catalyzed hydrogenation of the crude product performed in the presence of acetic acid afforded the desired norephedrine **17** in 90% overall yield, 65:35 *anti:syn* ratio and with an enantiomeric excess of 80% for the *anti*-isomer.

Taking advantage of the powerful possibility offered by 3D printing technology to realize *ad hoc* devices, we described also the fabrication of a new fluidic device, in which the presence of flow channels (where the chemical transformation takes place) is combined with a short column of silica (necessary for the removal of the copper catalyst). In this case, the nitroaldol intermediate **16** was obtained in 96% yield, 65:35 *anti:syn* ratio, and 83% ee for the *anti*-isomer, which afforded norephedrine **17** after the earlier described in-flow hydrogenation process (Scheme 3, green box).

In the same year, Hilton group published the use of a 3D-printed polypropylene continuous-flow column reactor as component of a continuous-flow system for the synthesis of achiral bicyclic and tetracyclic heterocycles [32].

Among all the examples reported, it was shown that this fluidic device can be successfully used for the synthesis of compound **18**, a precursor of the erythrina alkaloid family. In dichloroethane as a solvent of choice, the reaction proceeded in the presence of more than stoichiometric amounts of $\text{BF}_3 \cdot \text{OEt}_2$ at $0.1 \text{ mL} \cdot \text{min}^{-1}$ of flow rate, leading to the formation of **18** in 45% yield as a single diastereoisomer (Scheme 4a).

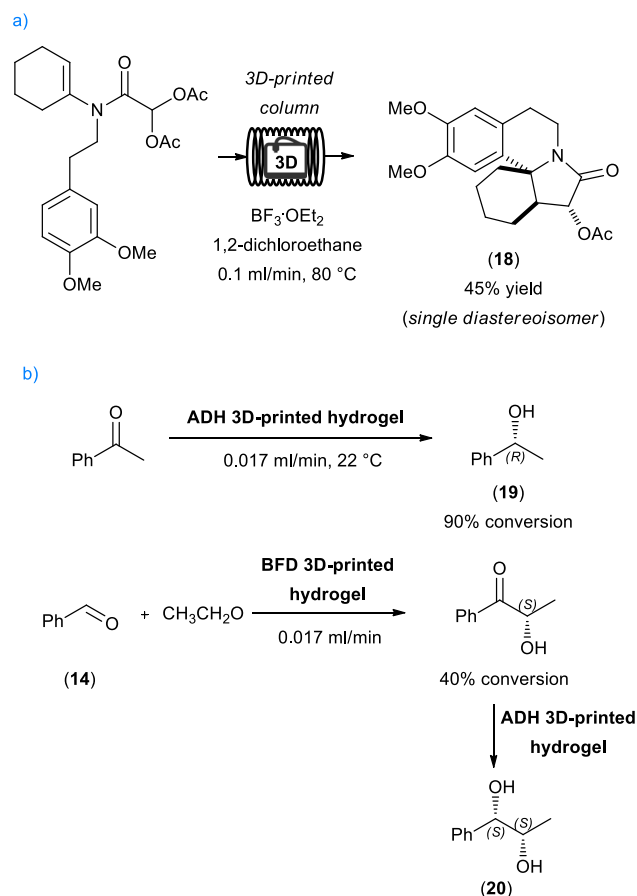
In 2019, Franzreb and coworkers developed 3D-printed hydrogel lattices for enzyme entrapment, which were inserted into 3D-printed reactor housings operating under continuous-flow condition to perform different enzymatic reactions [33].

An alcohol dehydrogenase from *Lactobacillus brevis* and a benzoylformate decarboxylase from *Pseudomonas putida* were entrapped in a crosslinked poly(ethylene glycol) diacrylate-based hydrogel and used to promote the synthesis of (*R*)-phenylethanol **19** and (1*S*,2*S*)-1-phenylpropane-1,2-diol **20**, respectively (Scheme 4b). Stable product formation was observed over a period of 72 h for all enzymatic systems, even if the reaction rates of entrapped enzymes in the continuous-flow system were lower than those of the reactions performed under batch conditions.

2.2 Continuous-flow organophotoredox transformations

Dual catalysis of photoredox and organocatalysis has emerged in the last 10 years as a powerful synthetic tool. MacMillan and coworkers first demonstrated that unprecedented synthetic approaches could be opened to produce chiral molecules that are otherwise difficult to prepare with traditional strategies [34]. After the initial discoveries of MacMillan, a number of dual organophotoredox catalytic reactions were reported. Two reviews, by Yoon *et al.* and Bach *et al.*, were published in the last 4 years, summarizing the findings [35,36].

To our knowledge, until today, only three successful continuous-flow examples of dual catalysis exist [37–39]. Those continuous-flow experiments showed a drastic increase in productivity, up to 100-fold. The high-molar extinction coefficients of organic dyes and metal complexes prevent most of the internal reactor volume to receive efficient irradiation: under batch conditions, most of the light is absorbed in the first few millimeters of the solution. In continuous flow, the increased surface-to-volume ratio of the microreactors is exploited to achieve much higher levels of irradiation.



Scheme 4: Examples of 3D printing applications to flow reactions. (a) Synthesis of erythrin core under flow condition using a 3D-printed column, (b) 3D-printed enzyme flow-through reactor.

Neumann and Zeitler reported the in-flow reaction between bromo-malonate **21** and octanal **22** catalyzed by MacMillan imidazolidinone (triflate salt) **23** in the presence of photocatalyst Eosin Y and 2,6-lutidine to afford α -alkylated aldehyde **24** [37]. Two different reactor setups were designed: one using glass microreactor technology together with light emitting diodes at 530 nm and the other using polyfluoroethylene high performance liquid chromatography (HPLC) tubing wrapped in coils around the 23 W compact fluorescent lamp household bulb, which was immersed in a cooling bath, as depicted in Scheme 5a. With this setup, an optimal irradiation was achieved with large reactor volumes and lengths (10.5 mL and 21 m of length). The reaction under flow condition still exhibits high enantioselectivity and high yields, leading to product **24** in up to 86% yield and up to 87% ee. Moreover, a 107-fold increase in productivity with respect to the batch conditions was achieved, due to the more efficient irradiation.

An organocatalytic photocyclization–transfer hydrogenation cascade reaction was published by Rueping and

Sugiono, using 2-amino-chalcones as the reagent, phosphoric acid **25** as the chiral catalyst, and Hantzsch ester **26** as the reducing agent [38].

For the continuous-flow setup, a glass microreactor immersed in a thermostated water bath was used. Directly next to it, a high-pressure mercury lamp irradiated the reactor from the side. This methodology allowed to prepare differently substituted isoquinolines in very high yield and ee, starting from readily available 2-aminochalcones (Scheme 5b). In particular, the flow setup showed a significant increase in productivity due to the more efficient irradiation. Moreover, the continuous removal of the product from the irradiation source avoided over-irradiation that can lead to undesired background reactions.

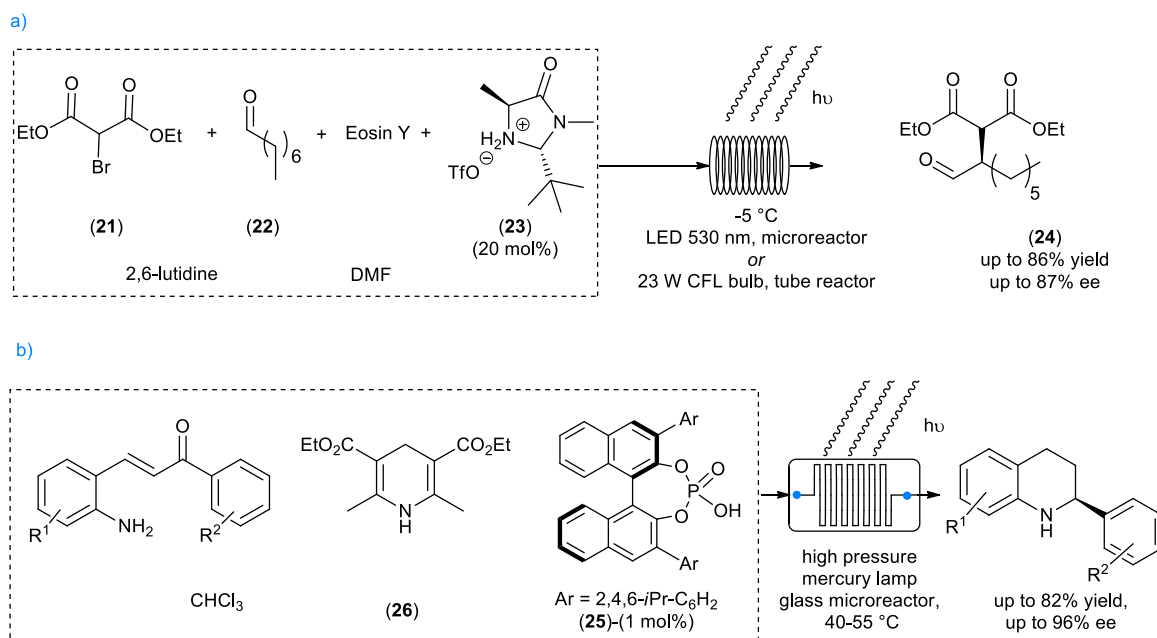
These two examples highlight some of the major advantages of conducting photoredox catalytic reactions in flow: the more efficient irradiation in the reaction vessel, the ease of scalability and the continuous removal of the product from the light source to avoid side-reactions (photodegradation and/or undesired reactions).

More recently, Meng et al. reported the use of photomicroreactors to perform the enantioselective photooxygenation of β -dicarbonyl compounds; in-batch and in-flow reactions were compared [39].

Differently modified cinchonine-derived phase-transfer catalysts were synthesized and used in the enantioselective photo-organocatalytic aerobic oxidation of β -dicarbonyl compounds with up to 97% yields and high enantioselectivities (up to 90% ee). Furthermore, when the reaction was carried out in a flow photomicroreactor, up to 97% yields and up to 86% ee were reached in less than 1 min.

In 2021, our group reported the stereoselective visible light catalytic cyclization of bis(enones), an easy entry to enantiomerically enriched cyclopentanes [40]. One of the more innovative strategies to build cyclic system is offered by the photoredox activation of aryl enones. We have studied the possibility to control the absolute stereochemistry of the final product, in a metal-free procedure, to generate enantioenriched cyclopentane rings.

The introduction of a chiral auxiliary, such as Evans' oxazolidinones, into the bisenone chain offers a straightforward and convenient option to stereocontrol the light-driven cyclization. After the cyclization and the removal of the oxazolidinones that could recover, the functionalized 1,2-*trans* cyclopentane could be isolated in good yield and up to 83:17 enantiomeric ratio. When the reaction was performed in continuo, in a homemade coil photoreactor, high yields were observed. The cyclization was also successfully realized in a 3D-printed mesoreactor, without any change in the diastereoselectivity of the process (Scheme 6).



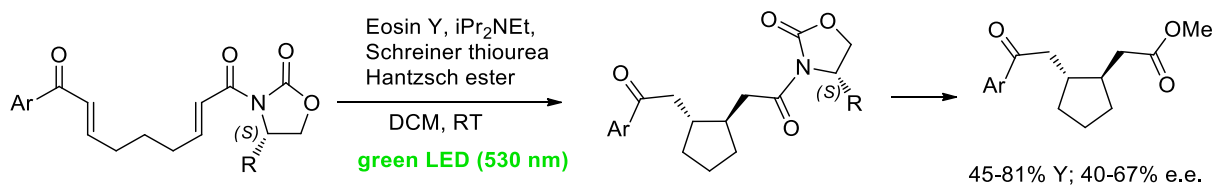
Scheme 5: Examples of continuous-flow organophotoredox transformations. (a) MacMillan's dual catalysis of α -alkylated aldehydes optimized by Zeitler and Neumann for continuous flow conditions, (b) Rueping and Sugiono's reductive cascade cyclization reaction flow setup.

2.3 Electrochemistry

The application of electrochemical methods to the synthesis of organic molecules has witnessed a renaissance in the past few years. Undoubtedly, the replacement of oxidizing/reducing chemical agents by electricity is a great step toward the development of sustainable chemical processes. Despite the long history of electroorganic synthesis, this renewed interest in organic synthesis is relatively recent. This is probably due to a lack of equipment to develop standardized electrochemical protocols [41]. It is not surprising, then, that the development of equipment to perform organic reactions in flow helped the synthetic chemists to explore new possibilities with electrochemistry [42,43]. Continuous-flow electrolysis is performed by pumping the solution of the reagents between the two electrodes, with a typically small interelectrode gap. Usually, the reaction can be carried out with low concentrations of supporting electrolyte or even without

supporting electrolyte at all, since the short distance between the two electrodes reduces the ohmic resistance. Moreover, the continuous removal of the reaction mixture minimizes the possibility of overoxidation, which is one of the main problems of electrolysis under batch conditions [44,45]. Finally, microreactors offer high surface-to-volume ratios and enable precise control over temperature, residence time, flow rate, and pressure. In addition, efficient mixing, enhanced mass and heat transfer, and handling of small volumes lead to simpler scaling-up protocols and minimize safety concerns. Nevertheless, achieving stereocontrol in the electrochemical process, where “electrons” are used as reagents, remains a major challenge [46].

The electrochemical transformation of an achiral material to a chiral (enantioenriched) molecule can be achieved, according to Rueping's classification, by using chiral electrodes, chiral media, and chiral auxiliaries. As chiral media, we intend a chiral electrolyte, a chiral mediator, or a chiral

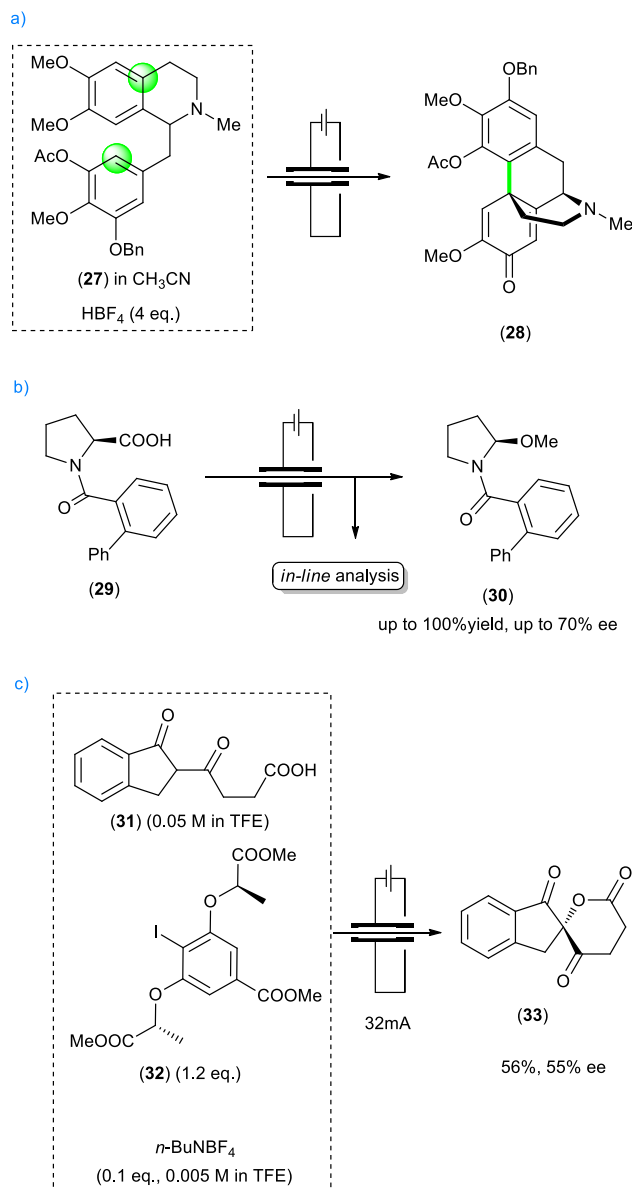


Scheme 6: Continuous-flow organophotoredox cyclization reactions.

catalyst (organic, enzyme, and metal-based). Since excellent recent reviews highlighted the modern aspects of electrochemistry, in this article, we will report few selected recent examples of electrochemical stereoselective transformations performed in flow to underline the potentialities of the technology.

Waldvogel and Opatz reported the total synthesis of (–)-oxycodone, a semisynthetic opioid derived from naturally occurring thebaine that presents a significantly higher oral bioavailability than morphine. It was prepared by a fully regio- and diastereoselective electrochemical 4*a*-2'-coupling of a 3',4',5'-trioxygenated laudanosine derivative [47]. The authors performed a first optimization study on the racemic compound **27** as starting material. Boron-doped diamond (BDD) anode in combination with a platinum cathode in acetonitrile containing a small amount of aqueous HBF₄ as acidic electrolyte to prevent amine oxidation proved to be the best combination. It was observed that BDD showed higher performances for dehydrogenative couplings than other materials. They then performed an extensive screening of reaction parameters, including temperature, current density, reactant concentration, and stoichiometry of acidic additive, both in batch electrolysis and in continuous-flow mode. The desired product **28** was obtained in up to 69% yield in batch and up to 57% yield in flow. The same reaction was then carried out on the enantiopure compound **27** to afford enantiopure derivative **28** that was further elaborated to the desired (–)-oxycodone. Noteworthy, this complex transformation was operationally simple and afforded fully regio- and diastereoselectivity in good yields (Scheme 7a).

Wirth described the electrolysis of *N*-(2-phenyl)benzoyl proline **29** through an acyliminium ion intermediate to afford an enantiomerically enriched α -alkoxyamino compound. The reaction proceeds via the electrochemical decarboxylation of substrate **29** and oxidation of the resulting radical to the iminium ion, which is trapped by methanol. The presence of the bulky substituent at the nitrogen atom is responsible for the face selectivity of the nucleophilic addition and leads to the formation of product **30** that maintains the same configuration of the starting material at the stereocenter [48]. The authors also developed a rapid and reliable analytical method to evaluate the outcome of the stereoselective electrochemical alkoxylation by coupling the flow system to a 2D-HPLC. This allowed to obtain the percentage yield and the percentage enantiomeric excess of each experiment within 15 min. The possibility of obtaining the desired information directly from the reaction mixture, without isolation or purification step, can dramatically speed up the optimization process and is an additional



Scheme 7: Stereoselective electrochemical transformations in flow. (a) Stereoselective aryl-aryl coupling, (b) electrolysis of proline **29**, (c) electrochemical lactonization mediated by promoter **32**.

benefit of performing the reaction in flow. The authors made an extensive optimization of reaction parameters, such as material of the anode, reaction temperature, flow rates, distance of the electrodes, and charge. Product **30** was obtained in high yields (up to 100%) and enantioselectivities up to 70% ee within a short period. The reaction was also scaled-up, and the products were isolated without loss in enantioselectivity (Scheme 7 b).

The same group reported the enantioselective electrochemical lactonization of diketo acid derivatives, using chiral iodoarenes as redox mediators [49]. Hypervalent

iodine(III) reagents are generated via anodic oxidation and can be used to realize several transformations without using a stoichiometric oxidant, such as *m*CPBA, 3-chloroperbenzoic acid. After extensive optimization in batch, the authors investigated the lactonization of diketo acid **31** to lactone **33** in the presence of the chiral iodoarene **32** and *n*-Bu₄NI as mediators, using platinum as anode and cathode materials, in 2,2,2-trifluoroethanol as a solvent as fluorinated solvents are known to stabilize iodine(III) reagents. They obtained lactone **33** in 56% yield and 55% ee in the first enantioselective reaction with iodine(III) reagents generated in an electrochemical flow microreactor, as shown in Scheme 7c.

3 Conclusion

The advent and the full development to a mature age of several, new or rediscovered, technologies have given a new impulse to the organic synthesis and offered incredibly powerful tools at the service of the creativity of the synthetic chemist. Alternative and more efficient heating systems, microwave, and ultrasound technologies, mechanochemistry, electroorganic synthesis, flow chemistry, and photoredox catalysis were all successfully used to speed up reactions or simplify the isolation and/or the analysis of the product, or to efficiently perform nonconventional transformations that would be impossible to realize without the decisive support of a new technique or an innovative technology. Safer processes could be developed taking advantage of continuous-flow technologies [50].

However, in the synthesis of an enantiomerically pure chiral molecule, not only the chemical efficiency and the chemoselectivity of the process should be reached but also the stereochemical outcome of the reaction must be efficiently controlled. One of the major challenges in the field is to develop telescoped stereoselective processes, thus avoiding isolation of intermediates and maximizing efficiency, practicality, and environmental impact [51–56]. Moreover, in this area, much space for improvement still exists; for example, the introduction of automation in organic chemistry is a hot topic, and in the last years, extraordinary achievements in automated synthesis have been reported [57–59].

It is easy to predict in a near future, the publication of novel applications and significant breakthroughs in new, challenging, but highly rewarding, fields [60,61].

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