Journal of Industrial and Engineering Chemistry xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Industrial and Engineering Chemistry

journal homepage: www.elsevier.com/locate/jiec

Review

Microfluidic asymmetrical synthesis and chiral analysis

Konstantin A. Kochetkov [a], Nataliya A. Bystrova [a], Pavel A. Pavlov [b], Maxim S. Oshchepkov [b], Aleksandr S. Oshchepkov [c,*]

[a] Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow 119991, Russia
[b] Mendeleev University of Chemical Technology of Russia, Miusskaya pl. 9, Moscow 125047, Russia
[c] Max Planck Institute for the Science of Light, Department of Physics, D-91058 Erlangen, Germany

ARTICLE INFO

Article history:
Received 24 April 2022
Revised 15 August 2022
Accepted 18 August 2022
Available online xxxx

Keywords:
Microfluidics
Asymmetrical synthesis
Chiral analysis
Microreactor
Chiral organocatalysis

ABSTRACT

In recent years, more attention has been paid to efficient, cost-effective and energy-saving technologies. In particular, there is a lot of recent information on the advantages of microfluidic technologies, combining economy, safety and environmental friendliness with reproducibility, high yields and high stereoselectivity of chemical reactions. Therefore, an important task is to generalize the available material on microfluidic technologies in order to identify new horizons of application in the field of a chiral synthesis. The difficulties of implementation microfluidic a chiral synthesis, its capabilities and prospects for further development are discussed in detail in this review. Various types of microfluidic reactors, synthetic schemes for carrying out chemical reactions are considered, and their comparison with traditional methods of synthesis is also given. Finally, a description is given of enantioselective analysis using microfluidic technologies and the possibilities for further improvement of microfluidics are discussed.

Contents

* Corresponding author.
E-mail addresses: const@ineos.ac.ru (K.A. Kochetkov), oshchepkov.m.s@muctr.ru (M.S. Oshchepkov), aleksandr.oshchepkov@mpl.mpg.de (A.S. Oshchepkov).

https://doi.org/10.1016/j.jiec.2022.08.025
1226-086X/

Please cite this article as: K.A. Kochetkov, N.A. Bystrova, P.A. Pavlov et al., Microfluidic asymmetrical synthesis and chiral analysis, Journal of Industrial and Engineering Chemistry, https://doi.org/10.1016/j.jiec.2022.08.025

Introduction

Major scientific and technological milestones of the last decades are associated with the miniaturization of all kinds of devices paralleled with improvement of their capabilities. Particular attention of organic chemists to this field stems from a range of advantages which microfluidics offer over other technologies: the use of small volumes of reagents, which is especially important for the compounds with high toxicity and explosiveness [1], a considerable reduction in the reagent consumption [2], the efficient heat and mass transfer, the control of conditions and reaction kinetics [3,4], a possibility to isolate the compounds sensitive to moisture and air, and a reduction in the amount of hazardous wastes. The practical advantages of using flow reactors for synthesis and their evaluation are considered in detail [2].

Microfluidics is recognized as the basic technology which provides reproducibility, easy automation and process safety, as evidenced by the large number of articles that have recently been published in this field [5–10]. Microfluidics (also known as microhydrodynamics) studies the behavior of small volumes and flows of fluids which are constrained to the submillimeter scale in any dimension. Microfluidic technologies exhibit precision control of the process fluids (on the micro-, nano-, pico- and femtoliter scale), which appears to be in extreme demand in chemistry, medicine, pharmacology, biology and many other areas of science and technology [8].

Commercial microfluidic devices are used in pharmaceutical [11,12] and analytical chemistry, chemical synthesis [13–16]. Industrial microfluidic systems applications are found in the synthesis of biologically active compounds [17–19] and in medical diagnostics [20]. Microfluidic systems for hydrogenation, oxidation, heating, and mixing of chemical compounds, combined with UV, IR, and NMR spectroscopy are available now [21]. The processes that are normally performed in the laboratory can often be miniaturized to a single chip, thus increasing both efficiency and mobility and reducing the required volume of samples and reagents. At the same time, microfluidics is one of the elements of ‘‘green chemistry”, which drives up the attention to its applied technologies [22–26].

A variety technologically diverse designs of microfluidic systems are available today for use in asymmetric synthesis [27–30]. Therefore, the use of such devices to obtain enantiomerically enriched substances is becoming more common, and the first reviews on the application of microfluidic technologies in certain areas of asymmetric synthesis have already appeared [31,32]. Thus, an important task is to generalize the available material on microfluidic technologies in order to identify new horizons of application in the field of a chiral synthesis. It also remains unclear what new possibilities for the implementation of this technique there are, that are different from achiral synthesis applications, and whether such possibilities exist at all.

Microfluidics in enantioselective synthesis

Advantages of microfluidic technologies in asymmetrical synthesis applications

Owing to the great demand for enantiomerically pure compounds in organic chemistry and the chemistry of biologically active substances, the development of effective methods for their production presents great interest both for pure and applied science. During the recent decades, asymmetric catalysis became one of the most common and attractive strategies for making chiral compounds due to its high efficiency and low resource demand. In this case, non-chiral starting compounds are transformed with high efficiency into enantiomerically pure products using small amounts of chiral catalyst under homogeneous or heterogeneous conditions. Nevertheless, despite tremendous advances in this field, only a few asymmetric catalysis processes have gained industrial application at the present time. Two main technical challenges can be identified: the need for quick optimization of the catalytic systems use and the high costs of process monitoring, upscaling and automation.

These problems of asymmetric catalysis itself [33] can be solved by introducing microfluidic technologies, which have a huge potential for integration with analytical methods and can be easily scaled up [19,31,32,34]. Another important task - the development of an optimal chiral catalyst for industrial implementation is also facilitated when microscopic quantities of substances are tested. At the same time, this approach can be beneficial not only for high-throughput screening and small-scale synthesis of certain substances, but also for continuous production of significant amounts of compounds with better efficiency and lower energy costs.

Finally, continuous multi-step synthesis of complex pharmaceutical ingredients has already demonstrated the full benefits of microchannel flow chemistry, which could transform and replace traditional multi-step organic synthesis [34]. There are examples already of multi-hundred-gram to kilogram scale production of active pharmaceutical ingredients and their intermediates [19]. It has been also shown that high chemo- and/or stereoselectivity can be achieved by strategic residence time control – the most important parameter in the development of continuous synthetic methods. Such precise reaction control cannot be accomplished in conventional batch reaction facilities [35]. With this in mind, the choice in favor of microfluidic technology or reactions in a flask depends significantly on the object of study.

The purpose of this review is to analyze the rapidly developing field of microfluidic systems use in asymmetric catalysis and chiral analysis. The examples of microfluidic technology applications in asymmetric synthesis over the last decade will be reviewed, which includes hydrogenation reactions, oxidation reactions, some nucleophilic reactions, along with some applications of industrial microfluidic reactors. This review will focus special attention on the differences between microfluidics and the traditional flask processes. In conclusion, the authors will share their opinion on the prospects of using this approach in asymmetric synthesis.

Microreactor synthesis reactions

Despite the rapid development of asymmetric catalysis under continuous flow conditions, among the first results there were few reactions with good enantioselectivity. This is attributed to the elevated temperatures that in-flow reactions were usually performed at in order to reduce the substance reactor residence time, whereas most traditional in the flask asymmetric catalytic methods are performed at low temperatures to increase enantioselectivity [36]. However, numerous successful examples of microfluidic reactor use are known today and the number of works in this field increases significantly every year, so here we will predominantly consider the most important works of recent years.

Hydrogenation

Catalytic hydrogenation is one of the most common reactions in both the laboratory and industrial scale, as many compounds can be reduced under relatively mild conditions, often with high chemo-, regio-, and stereoselectivity. One of the key trends in this area is the use of perfect displacement flow reactors and their use in microfluidic systems [37].

A reaction process for the asymmetric hydrogenation of acetophenone was developed using a T-shaped Micro/Milli reactor

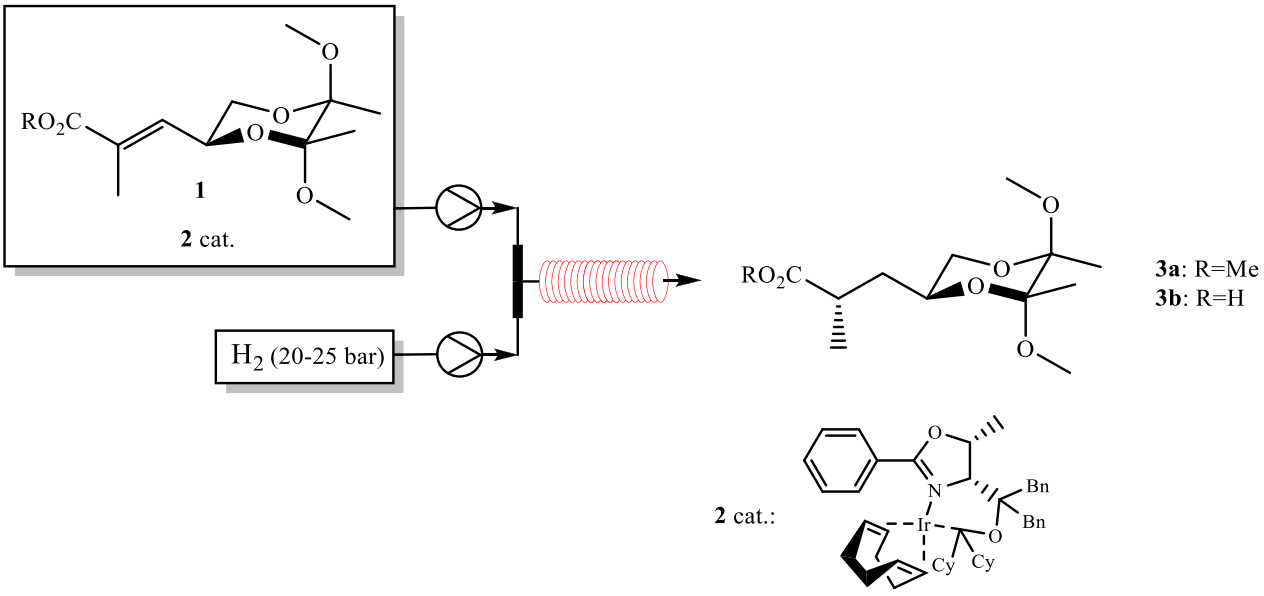
and a homogeneous (*S*)-RUCY®(RuCl[(*S*)-daipena][(*S*)-xylbinap]) catalyst [38]. The results made the following points clear: (1) the high importance of the catalyst feed that is separate from the starting material flow into the reactor to avoid a conversion rate decrease during continuous process operation; (2) the Micro/Milli reactor allows increased liquid phase hydrogen transfer rate as compared to conventional batch reactors with mechanized mixing. The reaction time for such reactor is only a few seconds, which amounts to one hundredth of the reaction time in a batch process reactor; (3) the per reactor production increase is controlled by adjusting the channel size and flow rate, and the resulting output with four single reactors is comparable to an industrial scale production [38].

Work on the asymmetric hydrogenation of a number of trisubstituted olefins in a gas–liquid flow reactor (Scheme 1) shows the flexibility in optimizing synthesis conditions by changing such parameters as pressure, solvent, temperature, and rhodium and iridium catalyst loads [39].

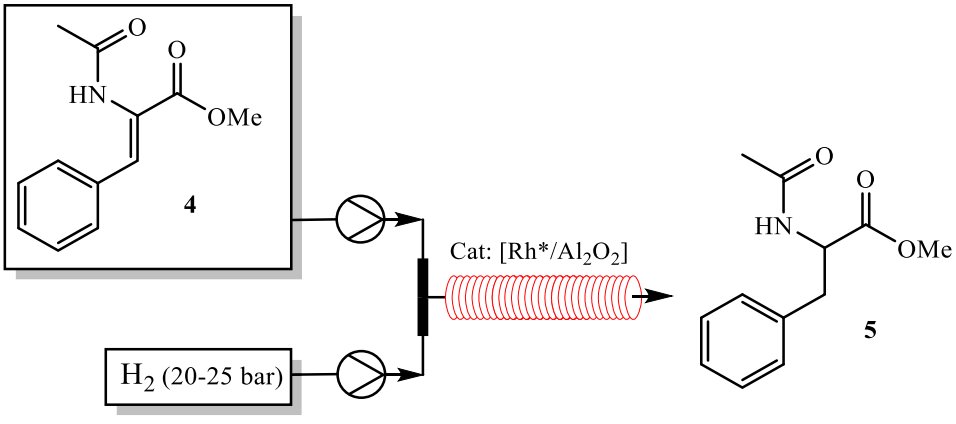
The catalysts were found to exhibit the highest activity and selectivity for the methyl ether **1** hydrogenation, resulting in a product with up to 75% *de* at 95% conversion. At the same time, a smaller amount of catalyst (1 mol%) was used to obtain the product.

Balogh et al. [40] have studied the enantioselective hydrogenation of a (Z)-α-acetamide cynnamic acid **4** where a chiral rhodium complex **6** with a phosphine-phosphamide ligand was used as a catalyst (Scheme 2), which provided high stereoselectivity in this reaction. The rhodium complex (Fig. 1) had been immobilized on a low-pore Al_2O_3 substrate, Phosphoro tungsten acid had been used as an anchoring agent.

The optimized heterogeneous conditions for the in the flask reaction were reproduced at the microreactor scale in a H-Cube® microfluidic system. It is designed to hydrogenate a continuous stream of substrate that flows through the system with an HPLC integrated pump. Pure hydrogen as obtained by water electrolysis was saturated by the reactant solution, preheated, if necessary and then transferred to a disposable CatCart® catalytic cartridge. This equipment includes a short (30 mm length, 4 mm diameter) stainless steel tube, filled with $[Rh(R)]BF_4/PTA/Al_2O_3$ heterogeneous catalyst. The device was working in hydrogen excess mode at1 bar pressure (hydrogen flow rate was set at 30 ml/min, solution flow rate at 0.1 ml/min), resulting in a gas–liquid mixture. These conditions allowed to obtain the target product **2** during short (~1 s at 0.1 ml/min flow rate) reactor residence time, allowing high yield and ≈ 99% stereoselectivity.



Scheme 1. Microflow olefins hydrogenation.



Scheme 2. Acetamidocinnamic acid hydrogenation.

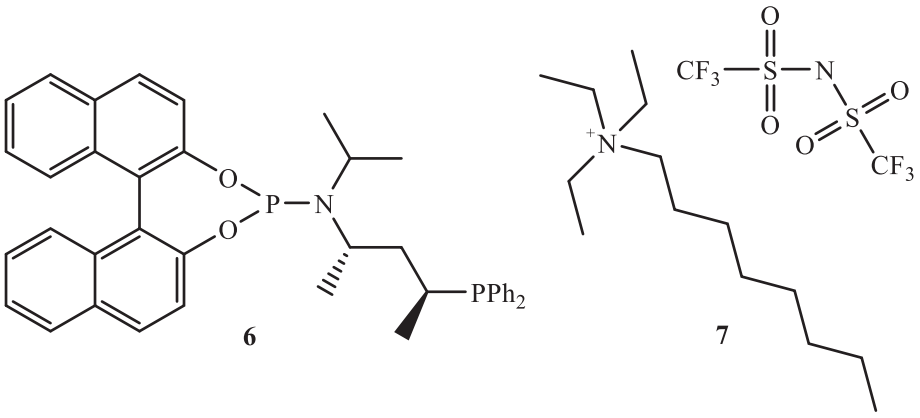


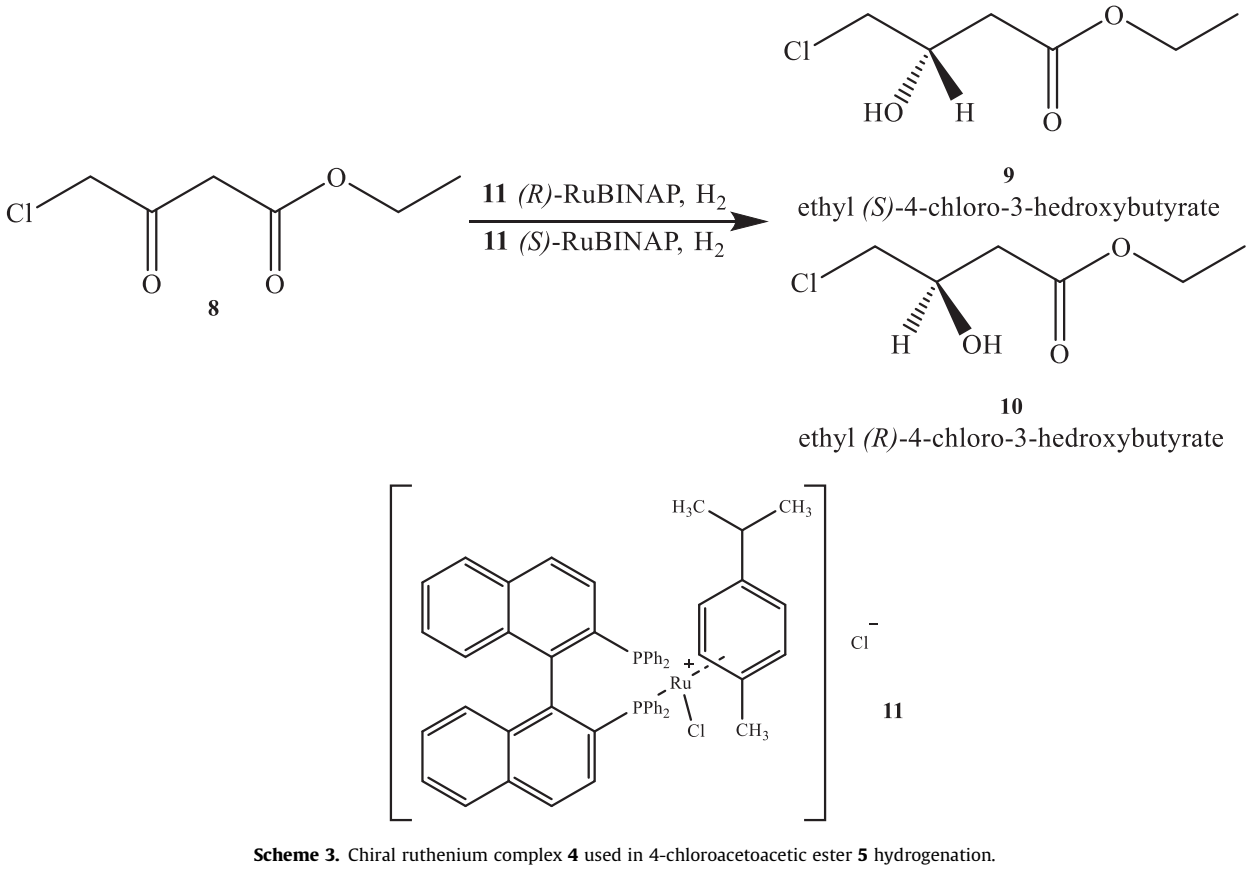
Fig. 1. Rhodium complex with phosphine–phosphoramide ligand **6**.

The development of chiral synthesis technology for continuous flow reactors has made it possible to downscale the reactor size and make transition to micro- and nanoscale reaction quantities. Technologically, there are three types of arrangements for the fixed or fluidized media in the microreactor microchannels: compacted layer, monolithic layer, or the use of homogeneous conditions (with no stationary surfaces).

Another paper [41] describes hydrogenation processes in a conical single-channel microreactor that used a broad range of chiral catalysts. High yields and enantioselectivity has been shown in all cases. However, as chemical synthesis microfluidics assumes that microchip (such as Chemtrix microfluidic reactor) sizes do not exceed 10–15 cm, this instance is better described as application of microfluidic technology to the H-Cube® installation and a single-channel reactor.

Subsequent studies [42,43] dealt with various stereoselective hydrogenation reactions using chiral catalysts; this time the Chemtrix (Labtrix) microreactor was used. β-Ketoesters (acetoacetic ester and 4-chloroacetoacetic ester **8**) were chosen as substrates for the synthesis of (*R*)- and (*S*)-4-chloro-3-hydroxybutirates **9, 10** [38], the biologically important molecules in the synthesis of L-carnitine (Scheme 3).

The ruthenium complexes with chiral ligands, such as (*R*)- or (*S*)-BINAP, were used as catalysts, along with *para*-cumene ruthenium complex **4** – (*R*)-[Ru(BINAP)Cl(*p*-methylcumene)]Cl **11**. All reactions were carried out under continuous conditions at 408 K in three different solvent phases: aqueous methanol, aqueous ethanol and octo triethylammonium bis(trifluoromethylsulfonium) imide [$N_{8,222}$] [Tf_2N] – methanol – water phase. The corre-



Scheme 3. Chiral ruthenium complex **4** used in 4-chloroacetoacetic ester **5** hydrogenation.

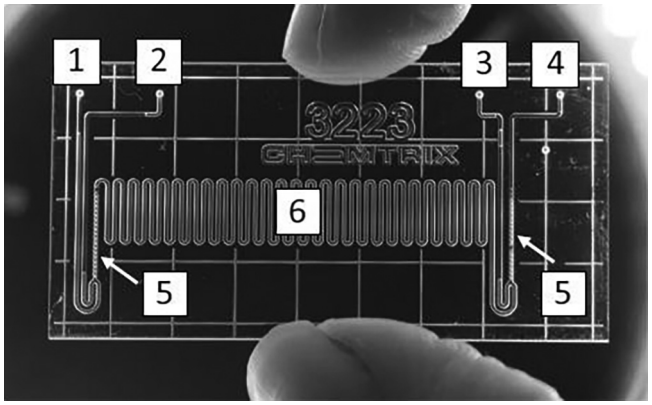


Fig. 2. Chemtrix type 3223 microfluidic reactor.

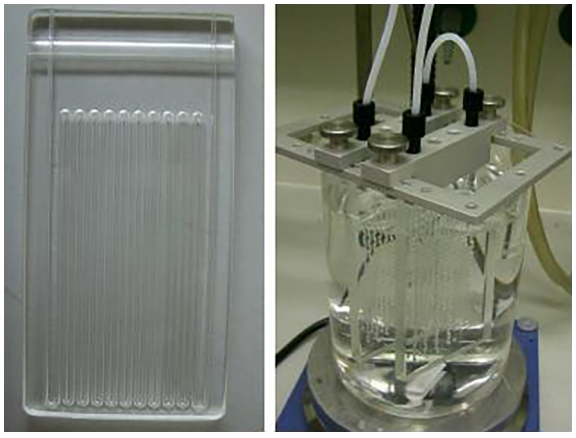


Fig. 3. Chemtrix microreactor cell. Reproduced with permission [47,48]. Copyright 2012, Beilstein-Institut.

sponding enantioselectivity factors, were 92.5%, 91.8%, 99.3% *ee* [42]. Although ethyl (*R*)-4-chloro-3-hydroxybutirate have been obtained earlier through stereoselective biotechnology methods, this alternative asymmetric hydrogenation strategy is less time-consuming.

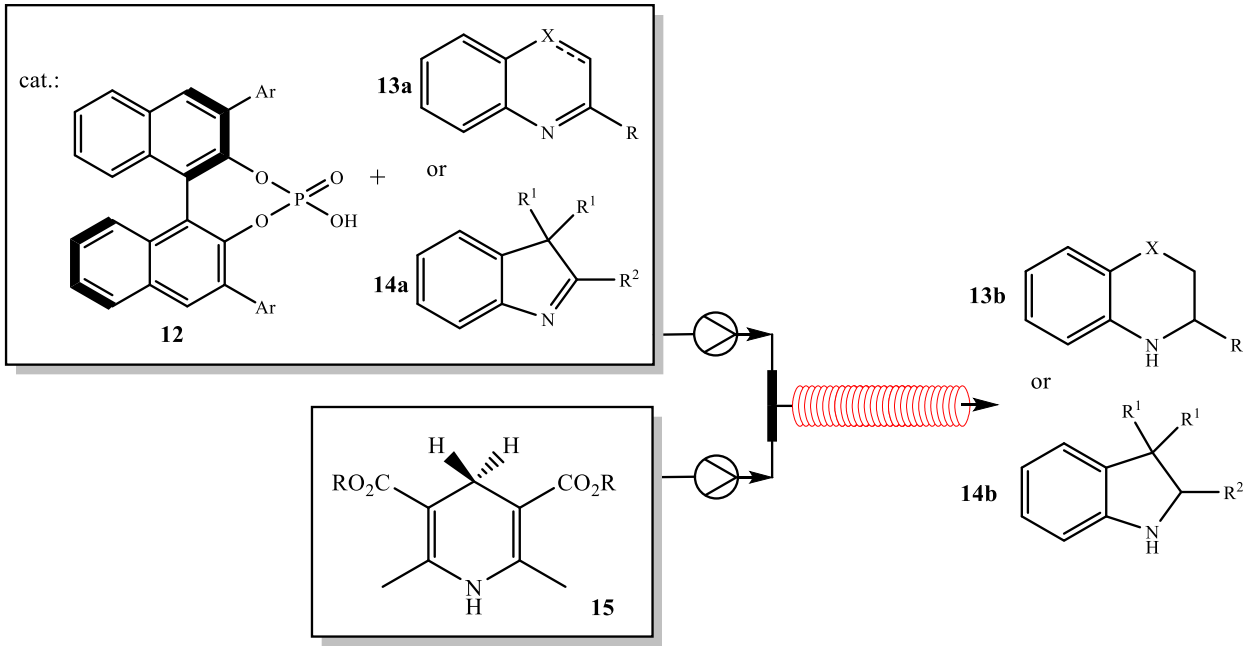
Usually, the reaction setups this field are based on the silica gel immobilized metalcomplex chiral catalysts or on the inert carriers with ionic liquids [44–46]. The powdered catalysts are then used in fluidized bed reactors where they retain their catalytic activity for prolonged time period [37].

The Chemtrix type 3223 microfluidic reactor consist of liquid medium inlet channel *1*, a gas medium inlet channel *2*, additional heating *3*, a static mixer *5* and a reaction space *6*; the final product exits from channel *4*. The channel width is 300 μm, height is 120 μm (Fig. 2).

Thus, the mixture of the substrate and the catalyst solution in the ionic liquid was injected into the microchip through channel *1*, and hydrogen gas was injected through channel *2*. Next, the mixing process with droplet formation took place in the mixer *5*. After going through the reaction space 6, the target reduced product was obtained at the outlet of channel *4*, with 92.5% *ee*. The report described reaction condition optimization for better selectivity, conversion rate and target product yield. The best solvent mixture of solvents was the methanol/water/ionic liquid.

Similar technology for stereoselective hydrogenation in a Chemtrix microfluidic reactor (Fig. 3) [47,48] was used for the reduction of various benzoxazines with aromatic substituents **13a, 14a** (Scheme 4). Chilal Brønsted acids **12** were used as catalysts, while dihydropyridine **15** served as the source of hydrogen.

The action results in the stereoselective hydrogentrans fertobenzoxazines providing optically active dehydrobenzoxazines **13b**, **14b**. The best yields and enantioselectivities were obtained when 0.5% (molar) substrate was used over one hour reaction time at 0.1 ml/min flow rate. The result comparison shows that common reactor yield is significantly lower than that in Chemtrix microfluidic reactor. In order to prove the general applicability of the developed method, this transformation was performed under microreactor conditions for a wide range of substrates. In all cases, high reaction yields and stereoselectivity factors were obtained for the final products.



Scheme 4. Hydrogenation process in Chemtrix microfluidic reactor.

Hydrogenation processes in continuous flow microreactors such as the H-Cube® discussed above are well covered in the literature. For example, there are known cases of microreactors being used for organic compounds nitro group reduction to amino groups with the preservation of the optically active center [49]. The known examples use palladium catalysts placed on inert substrates or on the steady layer of the CatCart® cartridge. Such systems have already seen industrial use in the medicinal substance synthesis. This way, EliLilly pharmaceutical company reported the reaction scale-up for the production of «LY500307», an anti-schizophrenia drug currently under development [18,50].

At a certain stage in the synthesis of this pharmaceutical substance, the double bond reduction process takes place to produce the optically active intermediate **18**, which is further transformed into the target drug molecule (Scheme 5).

This asymmetric hydrogenation was initially developed on a laboratory scale using microreactors. When the reaction load was scaled up to industrial production, a pilot plant that was similar to such reactor has been designed, where microfluidics technology was used to achieve maximum yield, high enantioselectivity and conversion rate of the reagents (Fig. 4).

Despite the large load of this pilot plant, the principle of microfluidic technology is maintained in continuous flow reactors (CFRs). The modern trend toward smaller reactor sizes and smaller reagent quantities allows the reactions to be carried out with high stereoselectivity using microchips.

Most asymmetric hydrogenation reactions under flow conditions are carried out using heterogeneous and homogeneous chiral complex metal catalysts, which leads to good yields and high stereoselectivity of the products. In all cases, in comparison with reactions in a flask, the reaction time is significantly reduced, the process becomes safer, environmentally friendly, and the optimization of synthesis conditions is facilitated.

Oxidation

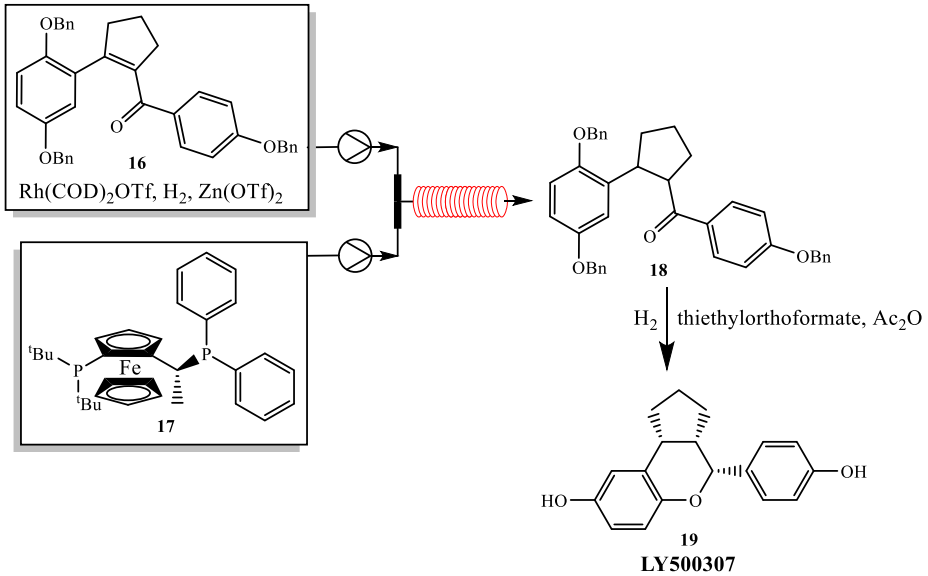
Oxidation processes can be effectively performed in microreactors under the same technological conditions as hydrogenation reactions. Literature provides a lot of examples where microfluidic technology is being employed to carry out oxidation reactions with oxygen gas used as an oxidizer in various processes. Also, a photooxidation method is known with the oxidizer being the *in situ* generated free radical particles or singlet oxygen. Thus, there are

Fig. 4. Pilot plant for the intermediate production in the synthesis of «LY500307». 73 Liter continuous flow reactor [51]. Copyright 2012, American Chemical Society.

known cases of using microreactors for alkene epoxidation [18,52] and ozonolysis [18] reactions, as well as of terpene [53] photooxidation.

There search reported in [54] was focused on the synthesis of a cyclic organic peroxide from a terpene in a microreactor with oxygen intake. The reaction setup included a LED to produce singlet oxygen to be used as an oxidizer. The reactor used in this research deserves special attention, as the reaction itself does not result in the formation of the optically active center [55]. The schematic design of the reactors used in this oxidation process is shown in Fig. 5.

The continuous stereoselective synthesis of Artemisinin peroxide, an anti-malaria pharmaceutical compound, has been successfully performed in a microfluidic system [16,41,42] which used several consecutive microreactors (Scheme 6). The authors suggest



Scheme 5. Intermediate 18 hydrogenation.

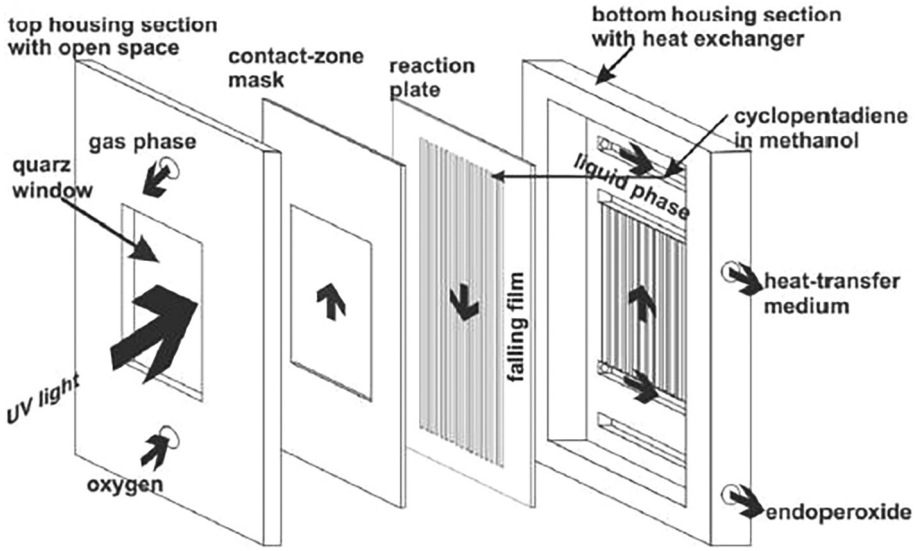
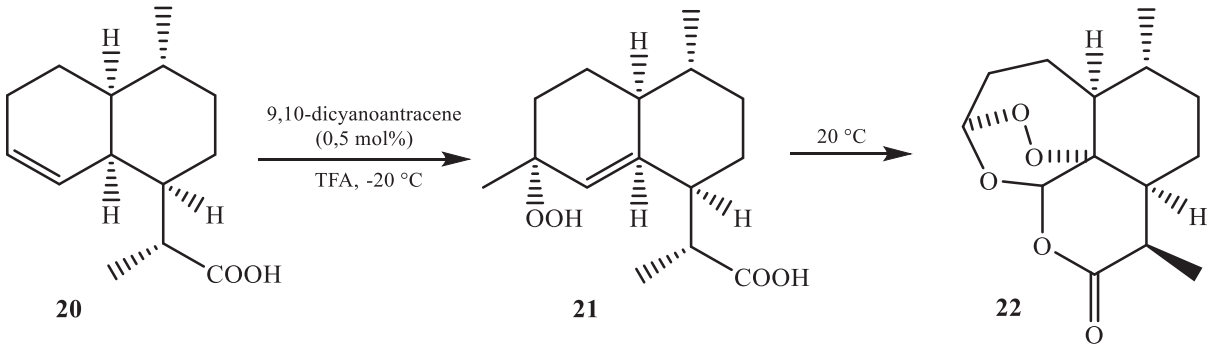


Fig. 5. Photooxidation microchip construction [55].

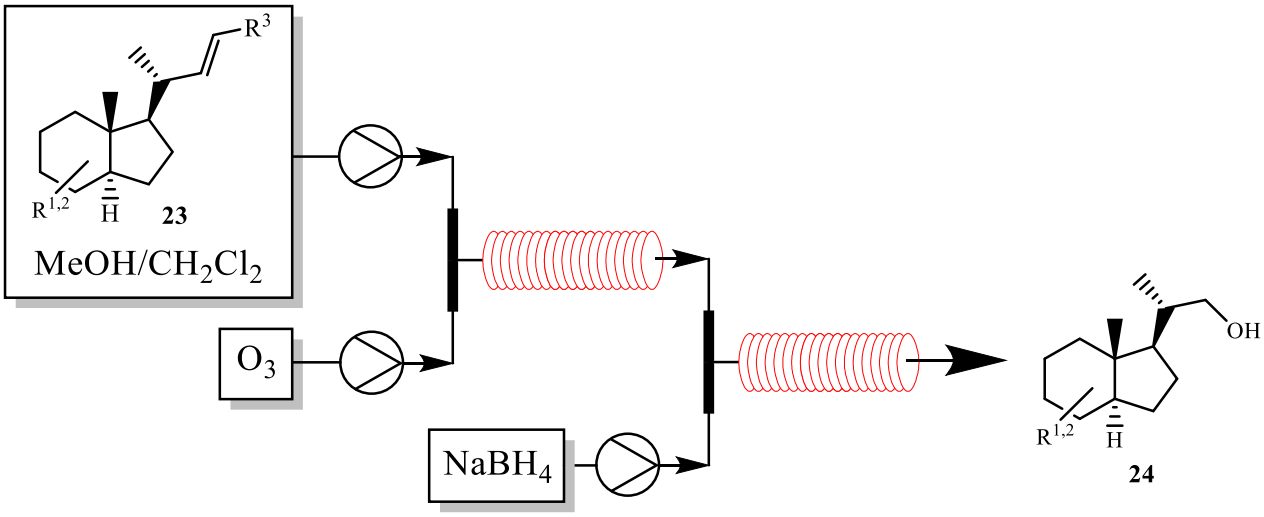


Scheme 6. Artemisinin **22** production pathway.

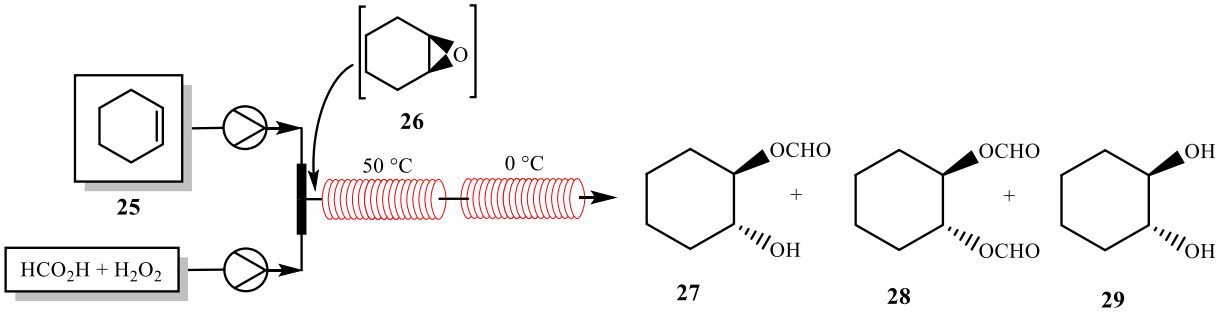
using the photooxidation reactor to combine several stages into one [56,57].

The reaction yield of 46% is comparable to the industrial production yield of 55%, which was obtained by Sanofi corporation. The photoxydation stage has more advantages in a continuous flow system as compared to the half-closed classical process, which improves Artemisinin **22** synthesis [58].

The ozonolysis reaction examples of optically active alkenes (Scheme 7) are of interest as well. The authors of the 2009 report [59] carry out alkene ozonolysis in a microreactor.



Scheme 7. Alkene **23** ozonolysis scheme [58].



Scheme 8. Diol **29** synthesis with cyclohexene **25** as starting compound.

The design of the microreactor used in this process bears close similarity with that of the microreactor shown in Fig. 5.

The design and construction of various microreactors which can be used in oxidation processes, in particular for the stereoselective diol production method, has been described in detail [18]. The research reported in [60] gives an example of cyclohexene **25** to diol conversion with the first stage carried out in a microreactor. The following hydrolysis takes place in a separate reactor resulting in the target cyclohexane-1,2-diol **29** (Scheme 8).

In general, there are not too many publications regarding microfluidic technology being used for oxidation processes, much less for stereoselective oxidation. The reason for such lack of data is probably the complexity of these processes and the formation of numerous byproducts that require additional extraction and identification stages, although the greater fire safety of the microfluidic approach should be noted.

C—C bond formation reactions under microreactor conditions

In the following sections, the main types of reactions of organic compounds carried out using microfluidic technologies will be considered. To facilitate the perception of the material, the Table 1 shows examples of comparing the two approaches on a number of basic processes occurring under the most similar conditions (under microfluidic conditions and in a flask). It follows from the data that a noticeable advantage of the microfluidic method is a sharp reduction in the reaction time, sometimes leading to an increase in yield, and in some cases, in the presence of racemization during the process, to an increase in enantioselectivity. Detailed reaction conditions are set out below in the relevant sections, since the advantages of the microfluidic approach differ depending on the type of reaction.

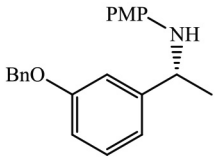
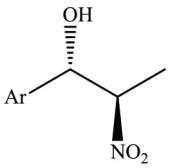
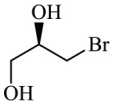
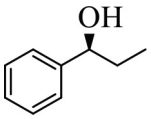
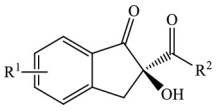
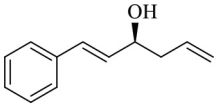
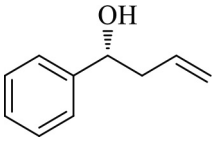
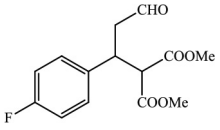
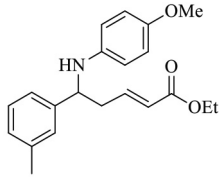
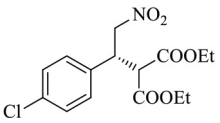
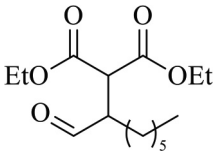
Shibasaki et al. in 2014 published pioneer work on a chiral coordination complex catalyzed asymmetric C—C bond formation reaction under flow conditions [74]. The *anti*-selective asymmetric nitroaldol reaction between *m*-methoxybenzaldehyde **30** and nitroethane **31** was studied as a route to produce the chiral precursor for AZD5423 **34** (Scheme 9A), an experimental phase II drug developed for the treatment of chronic obstructive pulmonary disease (COPD). The authors have developed a new heterobimetallic Nd/Na complex containing a chiral amide-based ligand with an appropriate spatial arrangement that provides high *anti*-diastereoselectivity, as opposed to the *syn*-preferred chelation patterns of most earlier catalytic systems [75]. The catalyst was deposited on a multilayer carbon nanotube matrix by self-assembly of the corresponding metal salts and the chiral ligand providing a robust heterogeneous material suitable for continuous flow conditions. 12.4 Grams (93% yield) of the chiral β-nitroalcohol **33** were obtained over 28 hour period, with *anti*/*syn* ratio of 93:7 and 88% *ee*. Compound **33** was then converted into AZD5423 **34** by nitro group reduction followed by copper-mediated *O*-arylation and trifluoroacetylation with 58% yield. Remarkably, the processing and isolation of the key chiral intermediate is greatly simplified by using the heterogeneous catalytic flow process, in contrast with the corresponding batch reaction.

Later, Shibasaki group expanded the use of an *anti*-selective asymmetric nitroaldol reaction catalyzed by a heterobimetallic Nd/Na complex into the continuous flow synthesis of the chiral intermediate AZD7594 **38** (Scheme 9B), another possible drug for asthma and COPD treatment (presently in Phase II clinical trials) [76,77]. The reaction between 1,4-benzodioxane-6-carbaldehyde **35** and nitroethane **31** was studied in a similar flow-through apparatus. It resulted in 8.9 gram (81% yield) of chiral adduct being synthesized in 20:1 *anti*/*syn* ratio and 95% *ee*. The nitro group in **36** was later reduced in usual batch process, the reaction mixture was then treated with HCl/MeOH mixture to yield the hydrochloride of aminoalcohol **37** – a key intermediate in the synthesis of AZD7594 **38**.

In 2017, Benaglia et al. used 3D printed flow reactors to carry out selective asymmetric nitroaldol reactions in the presence of a chiral Cu(II) complex, by using continuous method for the synthesis of adrenergic amines: metoxamine, metaraminol, and norephedrine (Scheme 10) [30]. These substances stereoisomers have different medical uses, such as anti-inflammatory agents or appetite suppressants, or hypotension treatments. The chiral complex was formed *in situ* from $Cu(OAc)_2$ and a chiral ligand obtained from camphor. Optimal reaction conditions were shown to be 30-minute residence time in ethanol (an environmentally friendly solvent) at −20 °C. The corresponding chiral β-nitro alcohols were synthesized under these conditions in good (72–90%) yields and high *ee* (86–90%), yet with diastereoselectivity (preference for *anti*-isomers) of only ~4:1. The target chiral amino alcohols were obtained by nitro group reduction (also, *O*-debenzylation in case of metaraminol), followed by continuous flow hydrogenation in the H-Cube Mini reactor, fitted with the cartridge containing 10% (mass) Pd/C catalyst. It is worth noting that the possibility of continuous inline removal and reuse of the homogeneous chiral catalyst was shown by simple filtration through a short silica column.

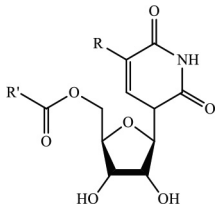
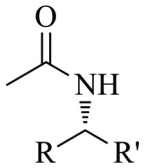
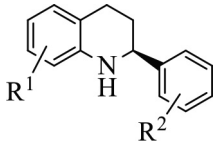
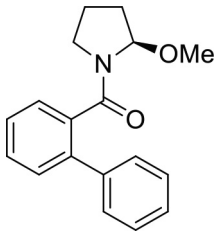
Continuous flow reactors have become a convenient platform for the safe, cost-effective and scalable use of gases in organic synthesis. Landis et al. perfomed the enantioselective hydroformylation of 2-vinyl-6-methoxynaphthalene **43** catalyzed by the chiral Rh-*bis*-diazaphospholane complex **46** in a tubular flow reactor, leading to the key chiral intermediate product **44** of the nonsteroidal anti-inflammatory drug (*S*)-naproxen **45** (Scheme 11) [55]. A flow reactor with series tube connection was used in this study, the reactor design provided residence time of 0.5–12 h. The toluene solutions of the chiral catalyst and substrate together with the synthesis gas (CO/H_2 1:1) were delivered separately into the reactor, and reaction conditions were precisely optimized, which, while maintaining regioselectivity, resulted in high conversion and enantiomeric excess. The total uptime of the reactor was 130 h, providing multi-gram quantities of the chiral aldehyde 7

Table 1
Comparison of the product yields of a number of typical asymmetric reactions carried out under microfluidic conditions and in a flask.

Reaction Type	M- microfl. L- batch	Formula	Product, (Schema)	Reaction time	T°C	Yield, %	*de*, % syn/anti	*ee*, %	Lit []
Si-hydrogenation	M L		122 (31)	2 h 18 h	0 0	82 80		83 98	[61]
Nitroaldol	M L		41 (11)	5 h 30 min	45 −20	91 96	70/30 75/25	92 90	[30]
Epoxide hydrolysis	M L		60 (16)	20 h 72 h	20 20	87 94		93 95	[62]
Aldehyde alkylation with Et_2Zn	M L		62 (17)	6 min 4 h	0 0	99 98		98 99	[63]
Hydroxylation	M L		77 (20)	2 h 24 h	0 −15	93 95		84 89	[64]
Hydroboration	M L		65 (18)	5 min 1 h	70 20	98 80		91 89	[65]
Allylboration	M L		109 (27)	6 min 16 h	0 0	96 89		92 96	[66]
Aldol condensation	M L		116 (29)	20 min 20 min	60 60	81 93		98 97	[67]
Aldol condensation	M L		92 (F6)	26 min 24 h	20 20	92 74	96/4 95/5	97 98	[47]
Michael Reaction	M L		68 (19)	5 min 1 h	60 RT	98 80		81 89	[68]
Photoredox Alkylation	M L		142 (36)	45 min 18 h	−15 −15	86 85		87 88	[69]
Enzyme Acylation Hydroxy group	M L		138 (35)	30 min 24 h	30 30	96 97	99 99		[70]

(*continued on next page*)

Table 1 (*continued*)

Reaction Type	M- microfl. L- batch	Formula	Product, (Schema)	Reaction time	T°C	Yield, %	*de*, % syn/anti	*ee*, %	Lit []
									
Enzyme Acylation Amino group	M L		129 (32)	1 h 24 h	30 30	96 97	99 99		[71]
Cascade Hydroxylation + Photocyclization	M L		145 (36)	1 h 1 h	55 55	64 7		96 95	[72]
Electrochemical oxidation	M L			n.m n.m	20 −15	71 10		64 48	[73]

PMP = *p*-methoxyphenyl.
n.m. not mentioned.

with 92% *ee*. Despite the non-reusable homogenous catalyst being chosen for this reaction, the catalyst load was relatively low; and the extra advantage of continuous flow versus batch setup was the safe use of the syngas.

The article [78] talks about enantioselective addition of trisilyl cyanide to benzaldehyde **47** under chiral catalysis **49** in a microreactor. The T-shaped microreactor was used to optimize the reaction conditions for the enantioselective lanthanide–PIBOX complexes catalyzed silylation of benzaldehyde (Scheme 12). Compared to the conventional batch procedure, higher conversion was observed along with shorter reaction times. The Lu(III)-based microreactor process provided essentially the same enantioselectivity as the batch process (73% *ee* vs 76%), while the Yb(III) catalysts were less effective in microreactors (enantiomeric excess of 53% as opposed to 72% in batch reactions). Ce(III) use resulted in low selectivity in both types of processes (1% and 11% *ee* respectively). The study of the additives influence showed that the enantioselectivity in the Yb catalyzed reaction carried out in the microreactor could be increased to 66%, while only a slight improvement, up to 78% *ee*, was observed for the reaction with Lu.

This T-shaped microreactor turned out to be rather popular in organic synthesis; for example, the Suzuki reaction [79] was carried out in it, and the same microreactor was used in heterogeneous catalysis as reported in [80].

The β-arylation of ketones with lithylation at the first stage and subsequent borylation with the 1,4-coupling reaction was successfully performed under cascade conditions. This reaction cascade makes it possible to obtain aryl bromides **50** quickly, safely and efficiently at room temperature followed by their conversion to arylborates and subsequent asymmetric 1,4-addition using a rhodium catalyst resulting in the target product **52** being formed with up to 99.5% *ee* (Scheme 13) [81].

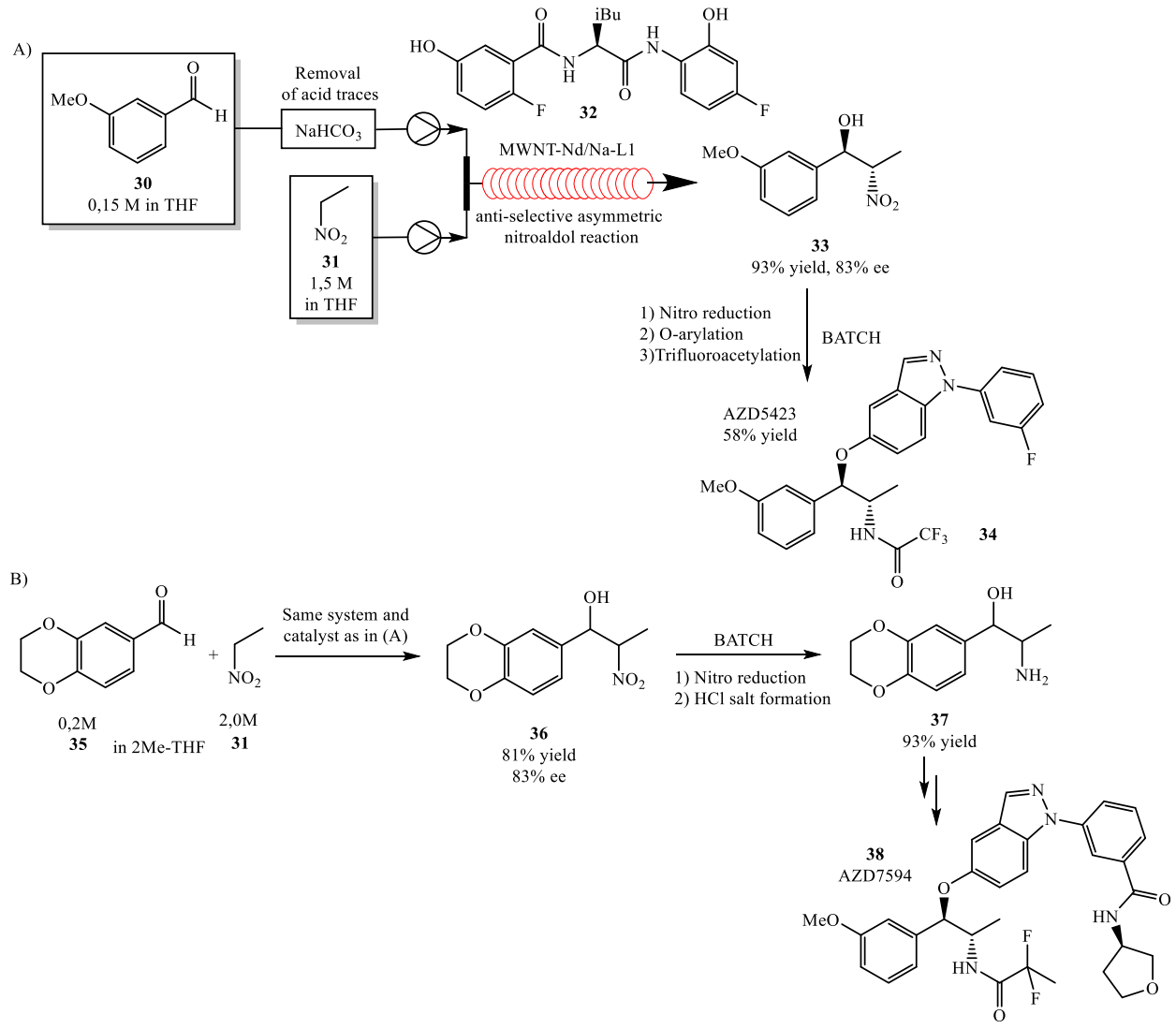
The use of microreactors with a catalyst implanted on a polymeric carrier is well known. Thus, the glyoxylate-ene reaction with a polymer-bound bis-(oxazoline)-complex on a polymeric carrier **56** and a copper catalyst was successfully carried out in a microreactor (Scheme 14).

The isolated products were 85–95% enantiomerically pure. Catalyst recycling did not affect enantioselectivity [82].

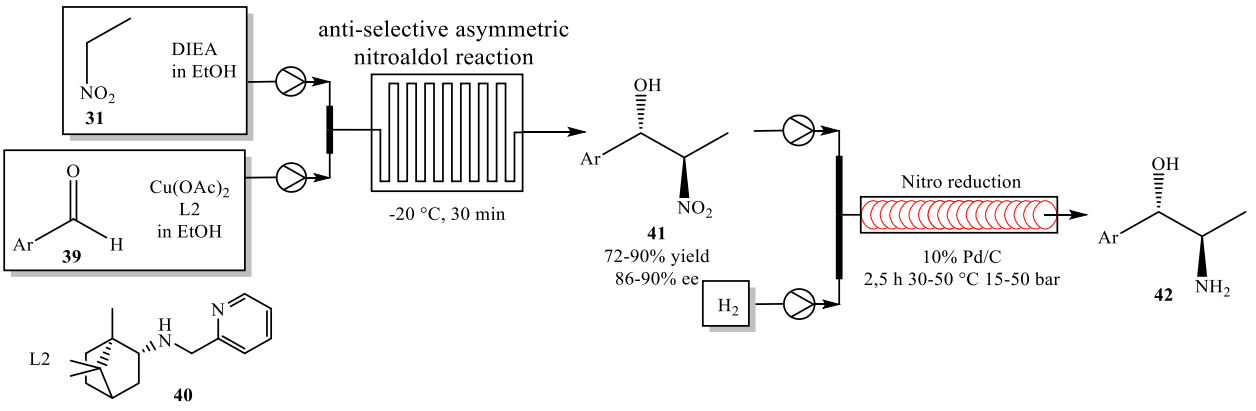
Kirschning and his group developed a method for enantiomeric separation of terminal epoxides using immobilized chiral cobalt complexes **59** in a microfluidic chip [62] (Scheme 15). Epibromohydrine **58** enantioselective ring opening was successfully carried out in a continuous flow mode to give **60** with 53–93% enantiomeric purity and 76–87% yield.

Enantiomerically pure alcohols were synthesized from aldehydes and diethylzinc using 3-*exo*-piperazinozoboronenol with a polymeric carrier **61** [63]. Catalysis load of 10 molar percent in this experiment turned out to be enough for the synthesis. The corresponding secondary alcohols were obtained in high yields and selectivity over 6 h at 0 °C (Scheme 16).

The system was stable for 20 h, over this period the high stereoselectivity level remained unchanged while a slight drop in conversion was observed (conversion ~85% after 30 h). It is



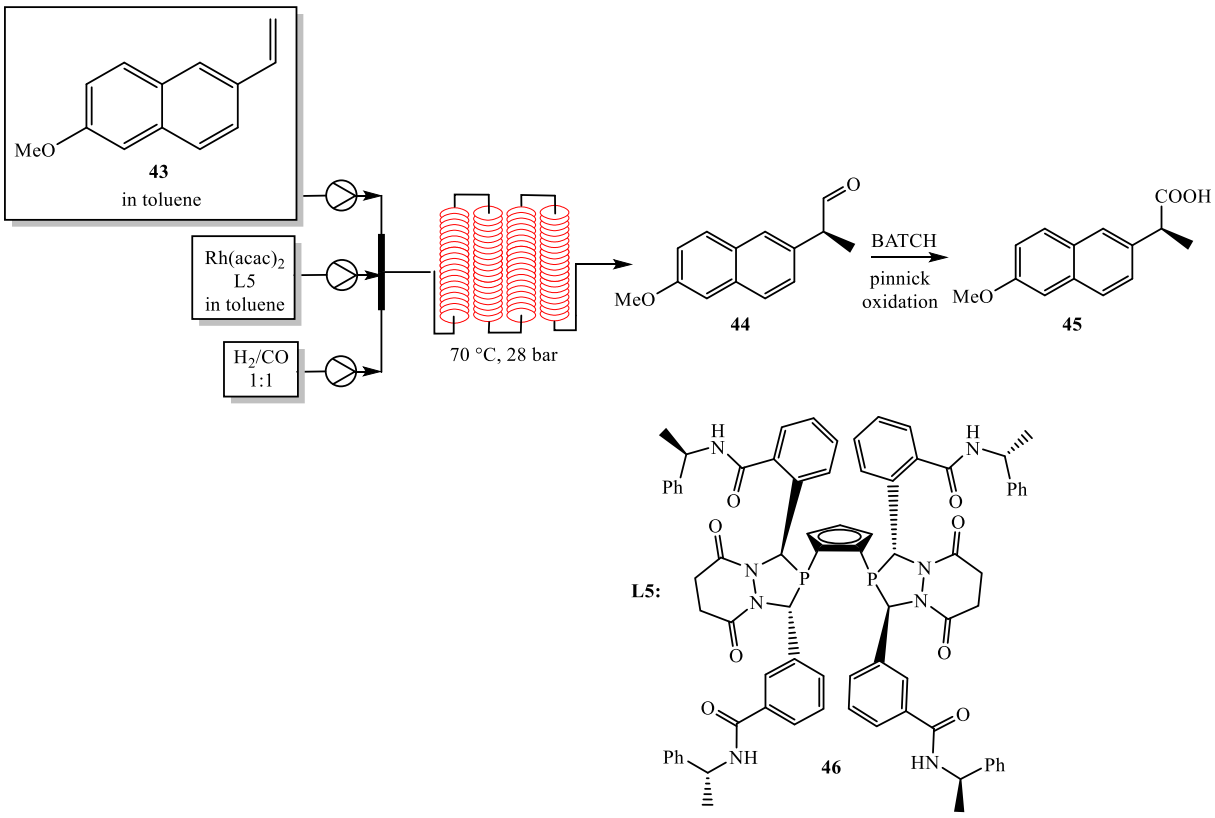
Scheme 9. Synthesis of key chiral intermediates of stage II experimental drugs under combined flow and batch reaction conditions.



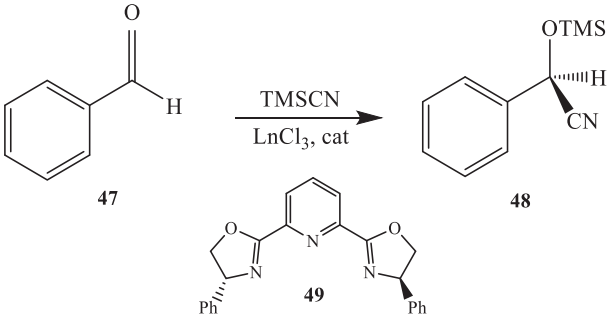
Scheme 10. Asymmetric flow-through synthesis of norephedrine, metharaminol, and methoxamine [30].

noteworthy that this single experiment produced 13 g of the target alcohol with 98% *ee*.

A complex batch and continuous process has been recently developed by Pastre [65] for the gram scale synthesis of goniothalamine. The asymmetric approach that used (−)-Ipc$_2$B(allyl), resulted in the formation of (*S*)-goniothalamine intermediate compound 65 in 98% yield and 91,5% enantiomeric excess along with 1.8 gram per hour production rate (Scheme 17). In the final step, the ring closure metathesis reaction was investigated in both batch and flow modes. For the flow mode, the residence time after fur-



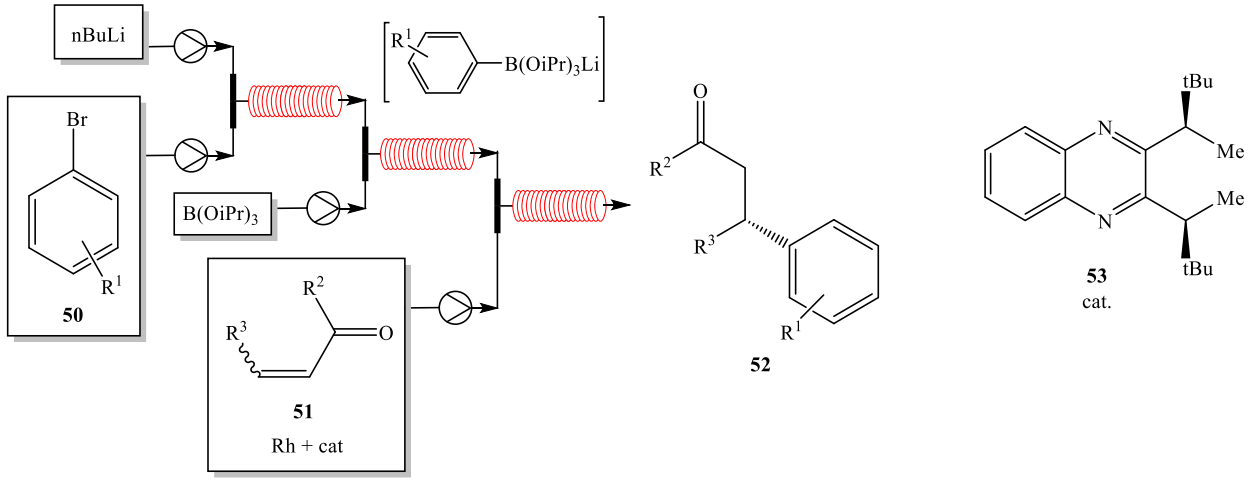
Scheme 11. Continuous enantioselective synthesis of the chiral naproxen precursor [55].



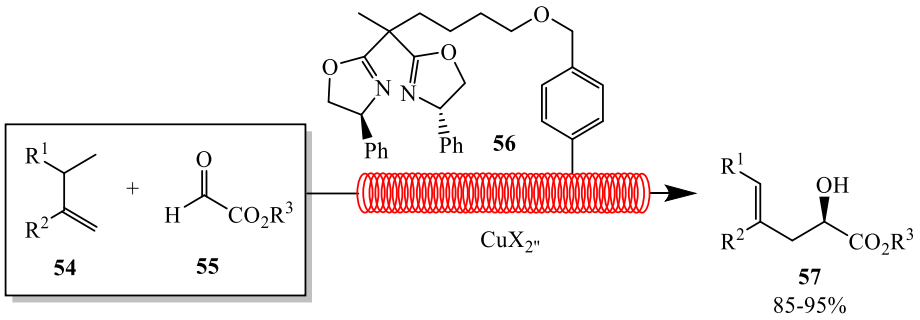
Scheme 12. Addition of trimethylsilylcyanid to benzaldehyde [78].

ther optimization could be reduced to 16 min with good selectivity and yield of the target product. In this context, a coaxial tube-in-tube reactor was investigated for the *in situ* ethylene removal to favor of ring closure rather than cross-metathesis. These results provide further proof of the flow chemistry effectiveness for organometallic reactions. A total of 7.75 g of goniothalamine was obtained using the developed complex flow and batch methods.

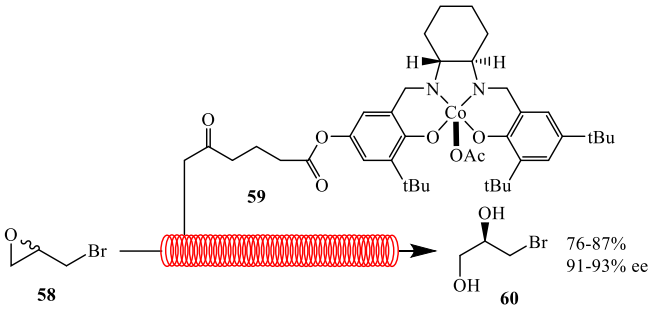
A joined Anglo-French team published their report [83] on the first continuous *Z*-selective olefin metathesis process that goes on in a flow mode under Grubbs type catalyst action, which was later used in the synthesis of pheromones and macrocyclic odorants.



Scheme 13. Ketone β-arylation [81].



Scheme 14. Glyoxylate-ene reaction using a microreactor with a grafted catalyst [68].

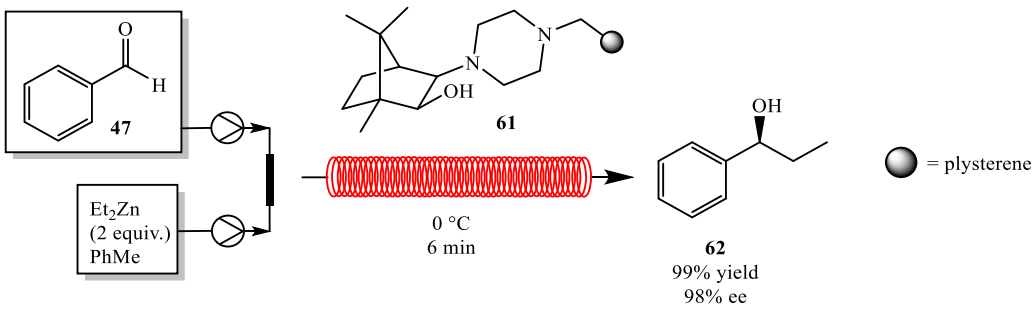


Scheme 15. Epibromohydrine separation [62].

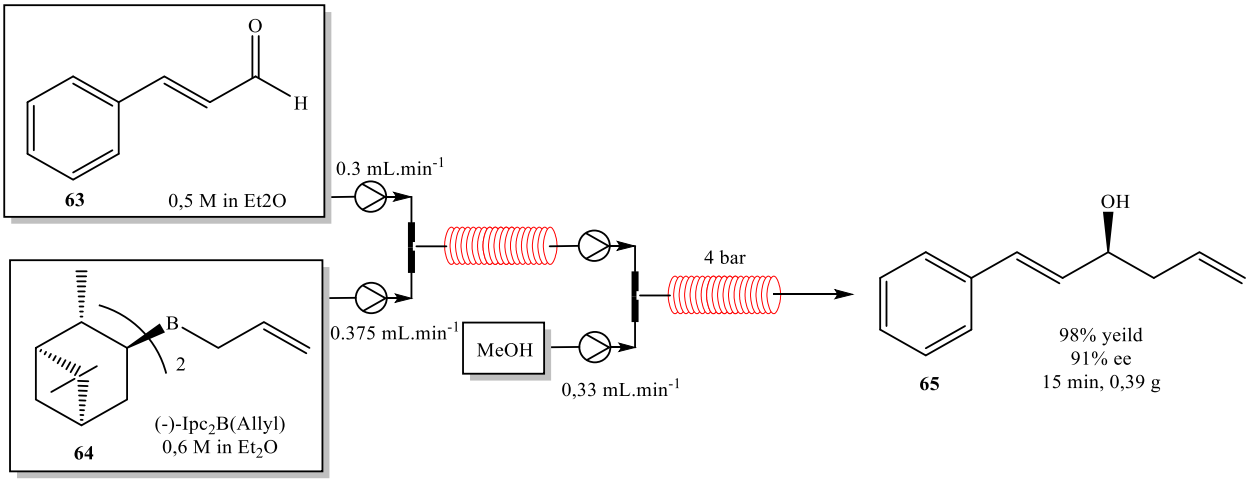
In addition to the previously noted, this section also demonstrated other advantages of the processes discussed, as the ease of cascade reactions, better heat/mass transfer, the possibility of effective, safe and scalable use of gases in metalorganic synthesis. Despite a number of advances, the use of continuous flow reactions (compared to the successful development of asymmetric reactions catalyzed by transition metals in batch mode) is still only a potential technology for industrial application. Problems including reactor design, catalyst stability and deactivation, maintaining the necessary pressure, capillary clogging, etc., remain unresolved by large part [25].

Chiral organocatalysis

The use of metal-free organocatalysts for stereoselective synthesis has great potential, since it is expedient both from an economic and environmental point of view [24,32]. Numerous phosphoric and amino acids, alkaloids, and their various derivatives are applied as organocatalysts for different asymmetric carbon-heteroatom and C—C bond formation reactions. Chiral



Scheme 16. Synthesis of enantiomerically pure secondary alcohol [63].



Scheme 17. Goniothalamine intermediate compound **65** synthesis [65].

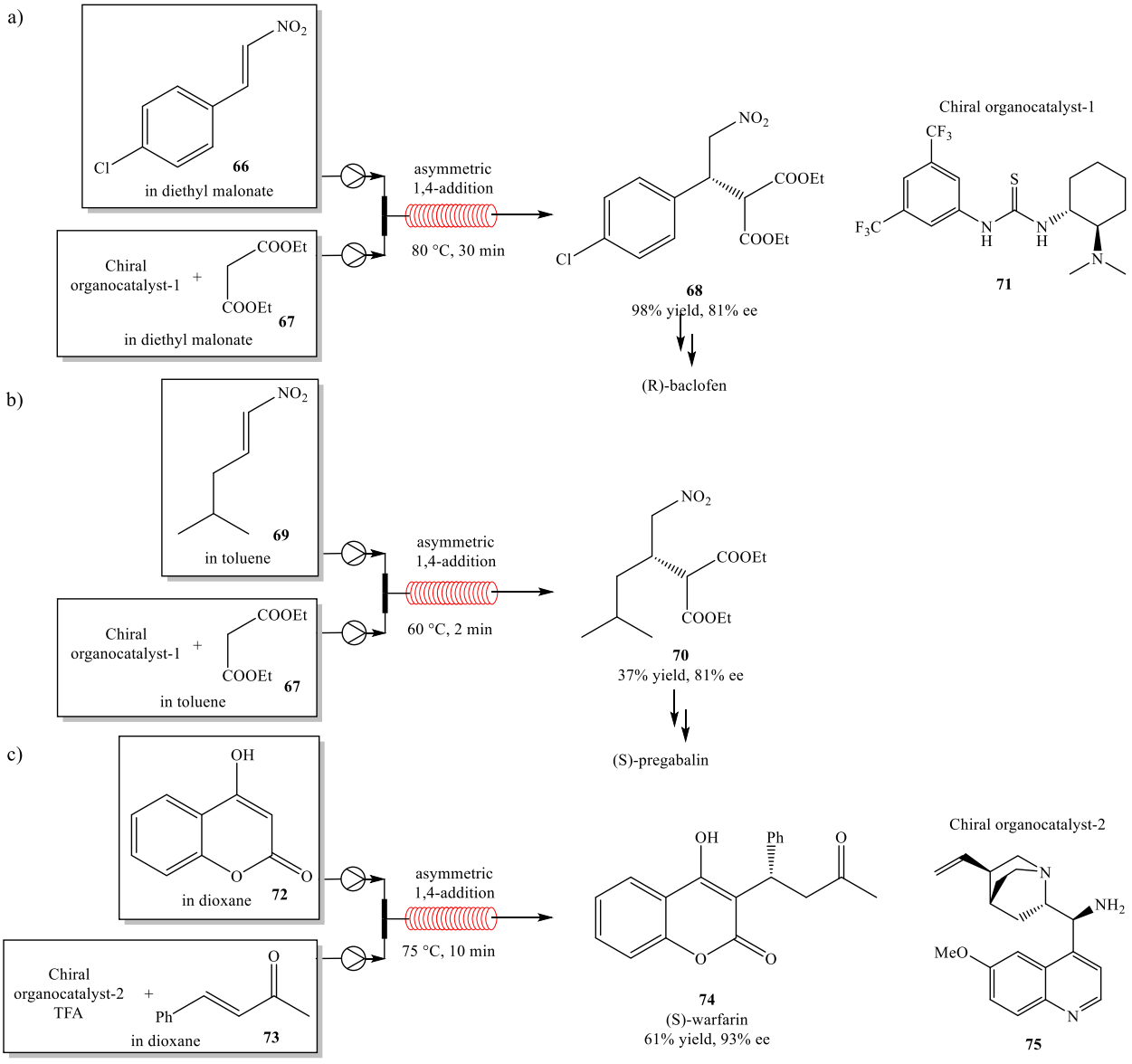
organocatalysts, due to their molecular diversity, wide range of applications, low toxicity, they are stable at different reaction conditions, have proven to be considerably useful for the batch synthesis of optically active drug molecules and other enantiomerically enriched bioactive products [84].

New opportunities arise when organocatalysis methodology gets applied to continuous flow conditions in microreactors [31,32]. Early reports on enantioselective organocatalytic synthesis of chiral products under continuous flow conditions were presented by Benaglia [68], whose group used soluble organocatalysts in a 10 μl glass microreactor. Initially, the enantioselective synthesis of baclofen precursor was performed by reacting *para*-chloro-β-nitrostyrene **66** with an excess of diethylmalonate **67** in the presence of a bifunctional thiourea organocatalyst **71** (Scheme 18A). Under optimal conditions (30-min residence time and 80 °C), the process was scaled up to a large-sized tubular reaction vessel, and the target baclofen precursor **68** was obtained in 98% yield and 81% *ee*.

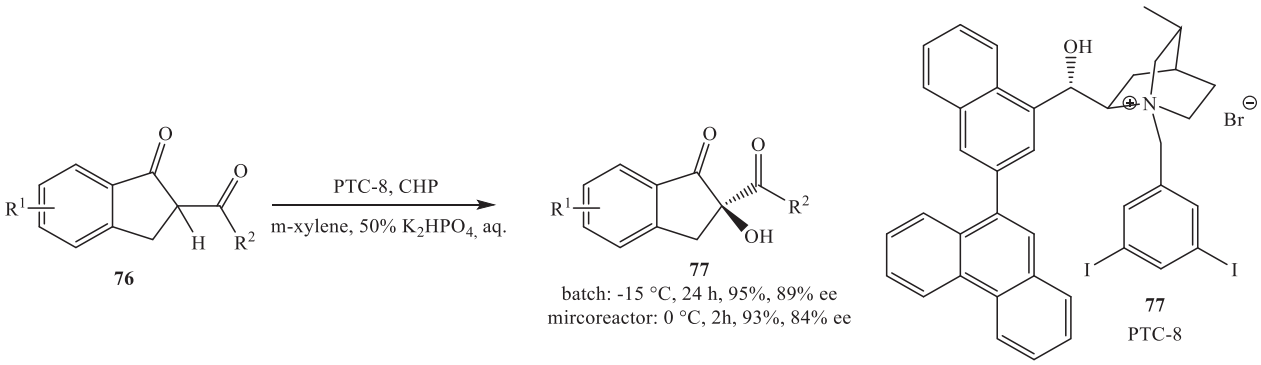
The enantioselective synthesis of pregabalin **70** precursor was performed by the interaction of diethylmalonate **67** with the corresponding aliphatic nitroalkene **69** in the presence of the same chiral thiourea catalyst **71** (Scheme 18B). Although under the best conditions (2-min residence time at 60 °C) the reaction provided a conversion rate of only 37%, the chiral precursor **70** was obtained with nice yield of 1 g per hour and enantiomeric excess of 81%. The enantioselective Michael addition of 4-hydroxycoumarin **72** to benzylidenacetone **73** in the presence of a chiral primary amine catalyst **75** based on a cinchona alkaloid and trifluoroacetic acid as a co-catalyst was studied for the warfarin asymmetric synthesis **74** [68] (Scheme 18C). Using a 10 μl microreactor at 75 °C, the product was obtained in good yields (93% *ee*) with conversion (61%) in 10 min.

The researchers from China [64] used similar catalyst to carry out the asymmetric α-hydroxylation of β-dicarbonyl compounds in a flow microreactor to see high yields (up to 93%) and good enantiomeric selectivity (up to 84% *ee*) The reaction times in this case were around two hours, which is an order of magnitude shorter than that for the traditional setup (Scheme 19).

A two-step flow-through asymmetric synthesis of chiral γ-nitro butyric acids – the key intermediates of GABA analogs baclofen,



Scheme 18. Enantioselective synthesis of γ-aminobutyric acid derivatives of API precursors **68, 70** as well as (*S*)-warfarin **74** in homogeneous organocatalytic flow-through processes.

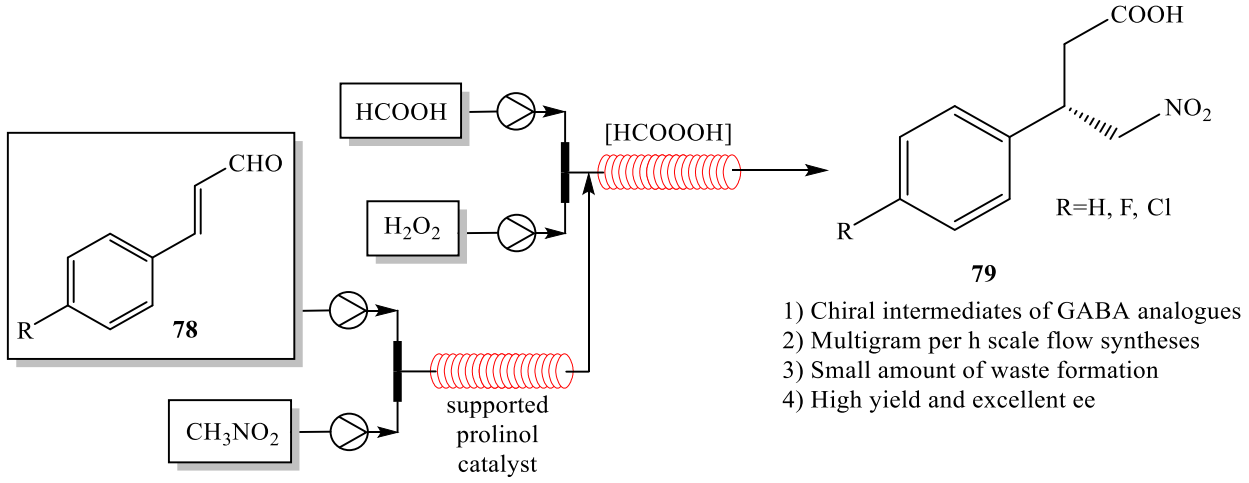


Scheme 19. Asymmetric α-hydroxylation of β-dicarbonyl compounds [64].

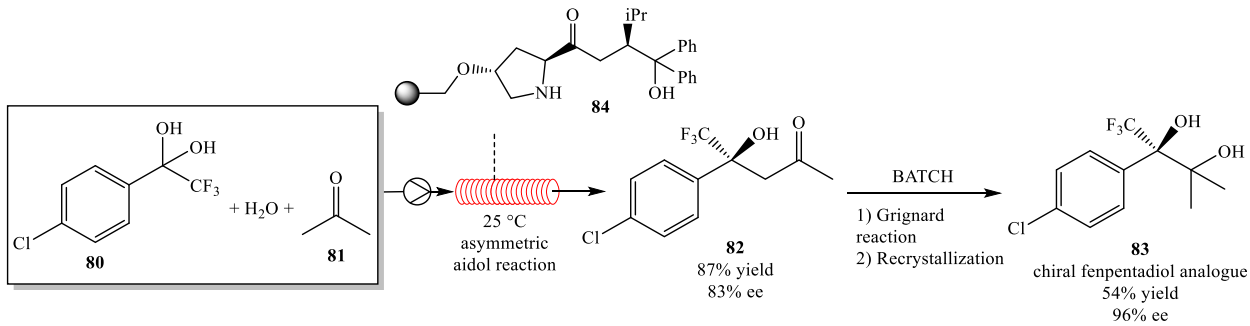
phenibut, and fluorophenibut – was implemented on a multigram scale (Scheme 20) [85]. The process involves enantioselective Michael addition facilitated by the heterogeneous polystyrene-based organocatalyst followed by peroxy acid mediated *in situ* aldehyde oxidation. High throughput under optimal conditions compared to previous approaches to serial production resulted in a simple approach to valuable optically active substances.

The Kobayashi group in 2021, suggested an effective flow conditions using a polystyrene-based prolinamide as a chiral organocatalyst to enantioselective aldol reactions of trifluoroacetophenones with ketones [26]. Initially, the reaction was studied under batch conditions, where the inherent reversibility of the aldol reaction led to racemization over long reaction times. In contrast, the flow-through conditions placed a continuous stream of substrate in contact with a local excess of the catalyst, albeit for a short residence time, thus minimizing racemization and thereby guaranteeing a high enantiomeric excess. Also, prolonged catalyst life was observed (over 195 h). This process has been successfully implemented to the synthesis of the chiral analog of phenpentadiol **83** (Scheme 21), the compound with reported antidepressant activity. For this purpose, the trifluoromethylated chiral diole **80** was prepared by enantioselective aldol reaction under optimized flow conditions using acetone **81** as an environmentally friendly solvent and then converted to the corresponding tertiary alcohol by the Grignard reaction with methylmagnesium bromide under batch conditions.

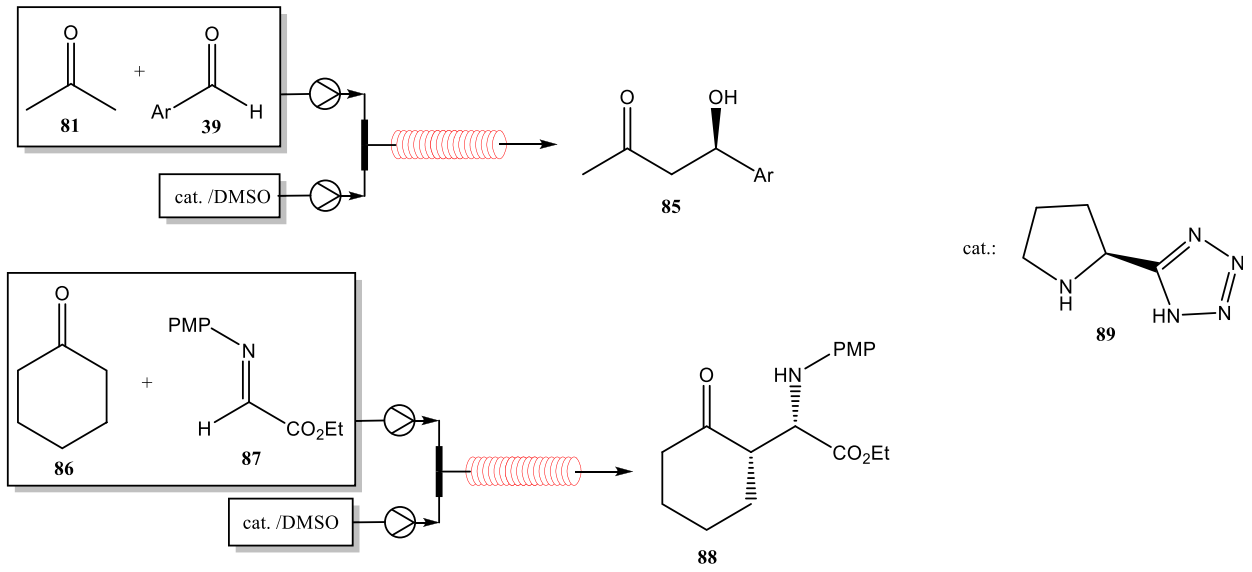
Optimal conditions for stereoselective aldol condensation were determined using a microreactor (Scheme 22) [86]. The reactor



Scheme 20. Asymmetric synthesis of chiral γ-nitro butyric acids [85].



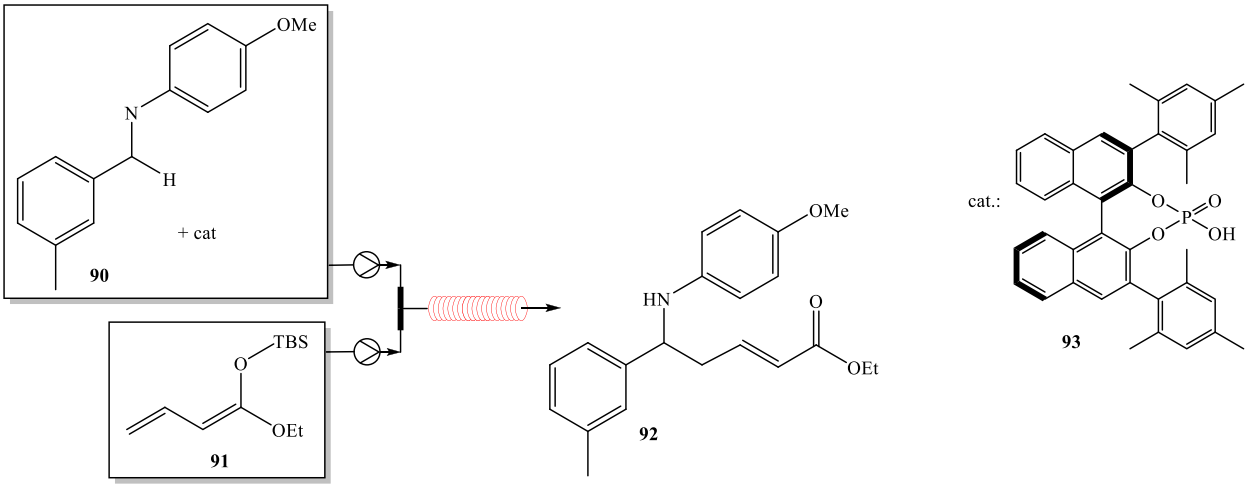
Scheme 21. Continuous enantioselective synthesis of a phenpentadiol chiral analog.



Scheme 22. Asymmetric aldol condensation and Mannich reactions [86].

design included a 1 ml glass vessel, a rectangular mixing zone, and a residence channel. The authors used 5-(pyrrolidin-2-yl)tetrazole **89** as a chiral catalyst at 5–10% molar concentration to form the product. The optimal reaction time at 60 °C was only 10 min. Also, organocatalytic aldol reactions were carried out in a microreactor with lower catalyst loads under continuous flow conditions. Condensation of various aromatic aldehydes **39** with acetone **81** catalyzed by the chiral 5-(pyrrolidin-2-yl)tetrazole **89** greatly accelerates the process at a reduced catalyst content in the reaction mixture (5 mol %, 20 min) and temperature (60 °C) [86]. Mannich reaction performed under the same conditions results in a high product yield with over 95% *ee* and a diastereomeric ratio of 10:1.

To demonstrate the versatility of this methodology, several syntheses were performed that used the derivatives of the original



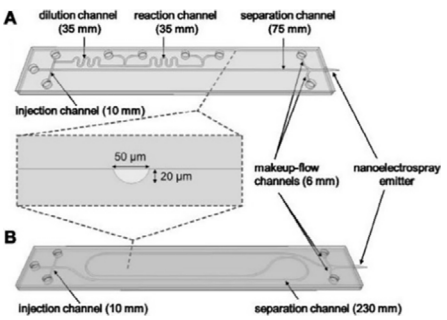


Fig. 6. Flow-through reactor for enantioselective Mannich reaction [47].

substrate. In all cases, good enantioselectivity was observed, but the yield was low when bulky substituents were used. Continuous-flow microreactors are appropriate for accelerating a variety of reactions and facilitating their upscaling. They are becoming a valuable alternative to traditional batch reactors for synthetic chemistry [52,86].

The German authors report an enantioselective Mannich reaction on a microchip catalyzed by Brønsted acid (Fig. 6) [47,48]. The study used a microreactor made according to the authors' own specifications by iX-factory company [47,48] (Fig. 7). The authors connected the microchip to a mass-spectrometer to identify the compounds formed. They used enantioselective microchip separation technology and a combination of enantioselective organocatalysis, enantiomer separation, and mass spectrometric detection in a single microarray. The results showed a very good correlation with laboratory experiments in the flask. The microchip design used by this group makes it possible to detect and identify reaction intermediates by mass spectrometry and can become a useful tool for studying reaction mechanisms.

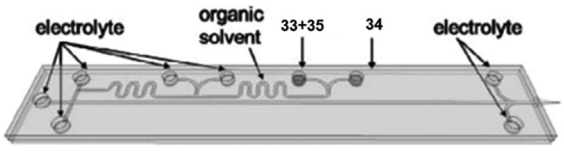
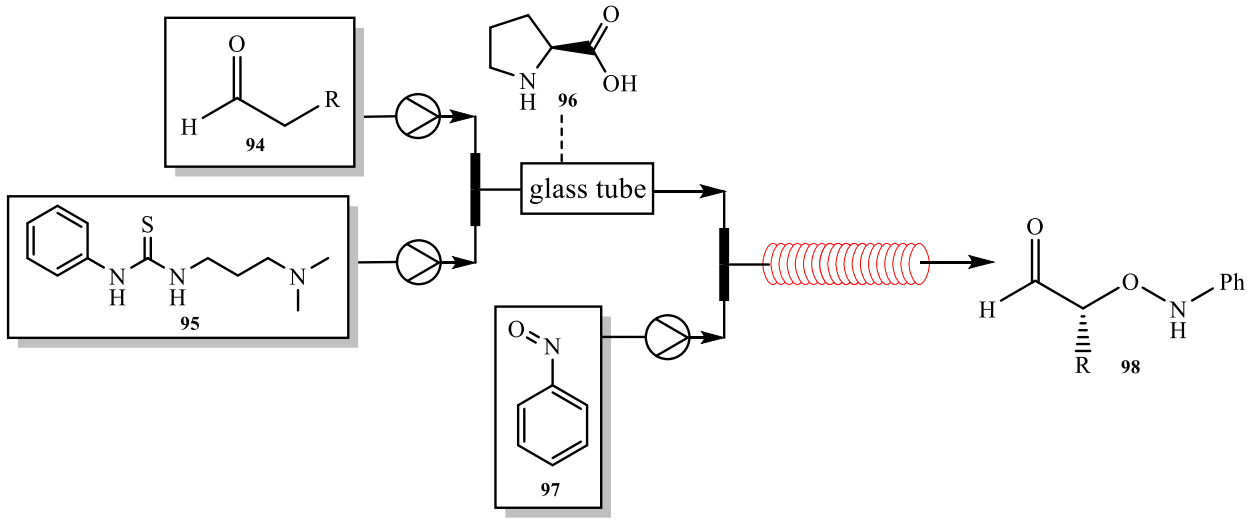


Fig. 7. Reagent injection scheme for the microchip [47,48].

A single-channel straightforward microfluidic reactor was used for the stereoselective α-oxyamination reaction [87]. The authors used L-proline **96** as an auxiliary chiral component. The reaction was carried out with a large number of substrates and a limitation was found, for example, hexanal did not enter into the oxyamination reaction. The system is designed in such a way that in the first step, a solution of aldehyde **94** and urea **95** is injected through a compacted L-proline layer to form a catalytic intermediate (presumably oxazolidinone). This catalyst solution is then combined with the nitrosobenzene **97** flow, resulting in α-oxyamination **98** (Scheme 23).

The microreactor used in these experiments [88] was the Vapourtec R series reactor system, which includes HPLC pumps for solvent and reagent injection, low-temperature tubular reactor containing a glass column, filled with 1 g of L-proline and a low-temperature 10 ml Teflon coil plus a tubular reactor that allows each reagent stream to be cooled before mixing (Fig. 8). This basic



Scheme 23. Aldehyde α-oxyamination [78].

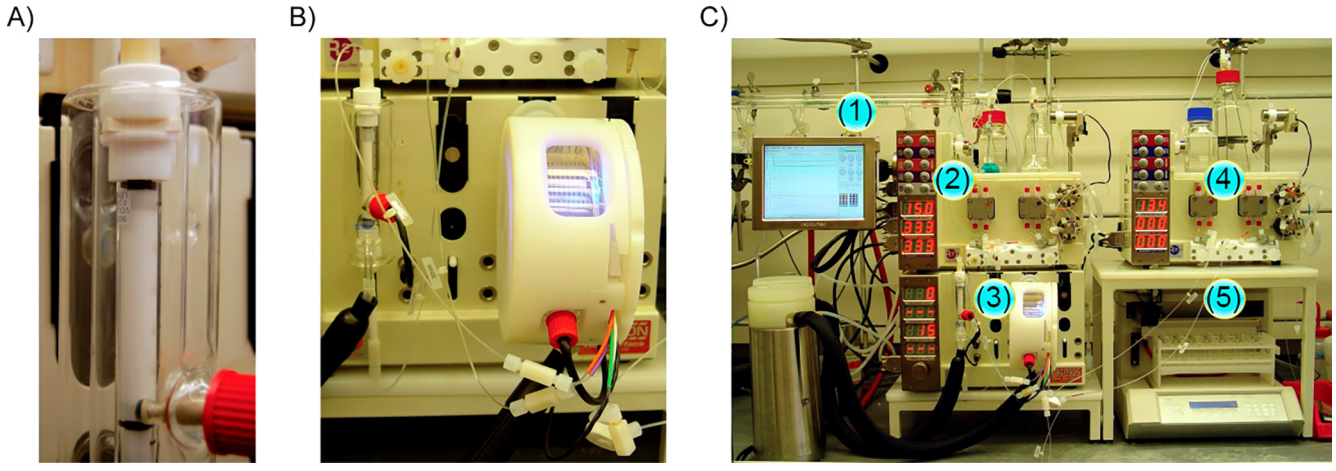


Fig. 8. General reactor setup. (A) A glass Omnifit column is packed with 1 g of proline. (B) The column is then placed in-line with a 10 mL PFA coiltube reactor (3). (C) The components are connected to HPLC pumps (2, 4) for solvent and reagent inputs. The reactor is controlled by a computer (1) in order to program the timing of the reagent and solvent inputs and fraction collection (5). Reproduced with permission. [87] Copyright 2011, Beilstein-Institut. Vapourtec R series reactor system [88].

setup can be adapted for use with a broad selection of other catalysts by replacing proline, for example, with a combination of transition metal salts with chiral ligands [52,87].

There are known cases of "Domino-reaction" in a system consisting of several similar microreactors (Scheme 24) [52,89]. Due to this setup, a high stereoselectivity of the process is achieved when using L-proline. The microfluidic system was developed for a stepwise Michael addition reaction. In the first microreactor, the first Michael addition occurs, resulting in an intermediate compound, which then reacts in the second microreactor with another Michael acceptor (e.g., an unsaturated carbonyl compound), and so on, resulting in the successive formation of up to four new stereocenters in the substrate molecule. The final aldol condensation leads to a highly functionalized six-membered ring with six asymmetric centers.

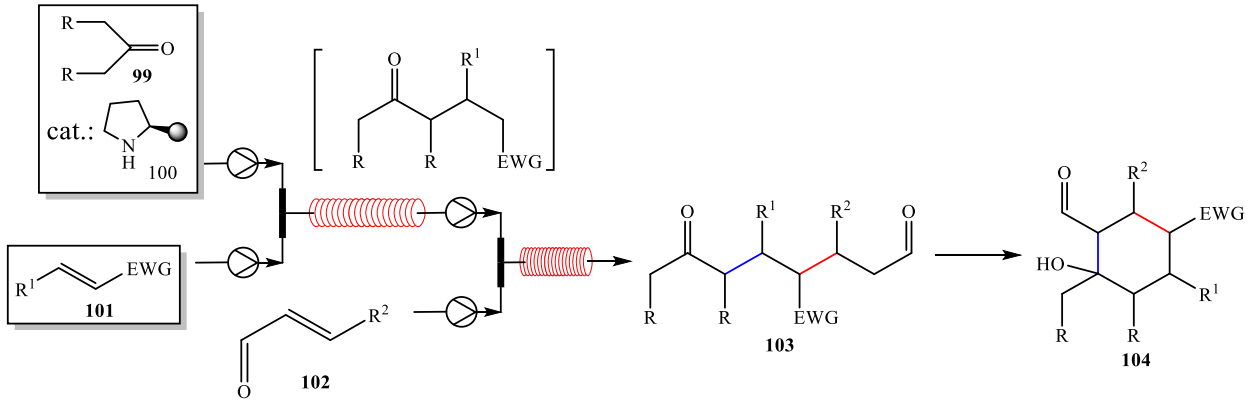
A fully integrated microfluidic system for asymmetric organocatalysis and simultaneous analysis of the resulting compounds by electrospray mass spectrometry developed by Belder and coworkers [47] for the Mannich reaction using Brønsted acid catalysts (Scheme 25). The product was obtained with an enantiomeric purity of about 70%.

For the asymmetric aldehyde allylboration in a continuous flow, a Brønsted catalyst was successfully used; the catalyst was obtained by co-polymerization of the corresponding BINOL derivative with styrene and divinylbenzene followed by phosphorylation (Scheme 26). The optimized flow system made it possible to synthesize 4.6 g of (*R*)-1-phenylbut-3-ene-1-ol **109** with 91% enantiomeric purity over 28 h of continuous experiment [66].

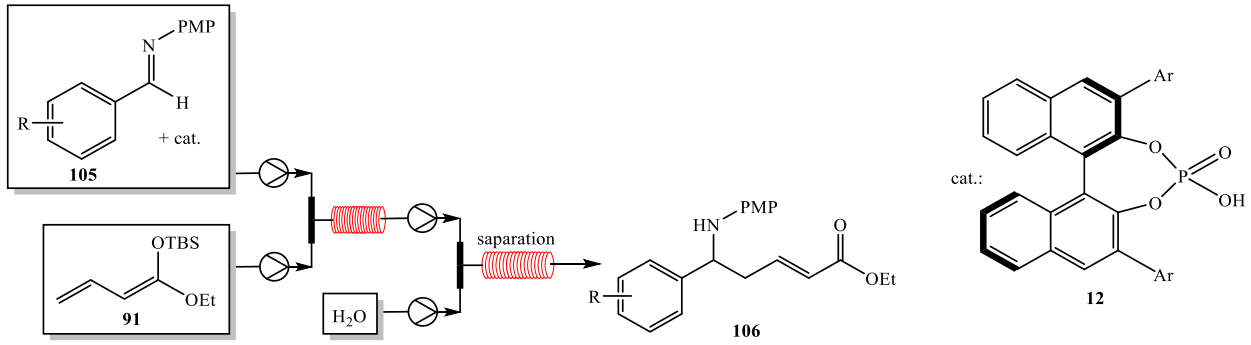
Asymmetric aldol condensation reactions were also conducted in a continuous flow using immobilized peptide catalysts based on proline derivatives, which were immobilized on Merrifield resin containing 8% 1,4-divinylbenzene as a crosslinking agent [90] (Scheme 27). Under optimized flow conditions the aldol reaction of *p*-nitrobenzaldehyde **110** and cyclohexanone **86** was carried out under the control of instrumental methods of analysis for over 45 h. The technique yielded 4.87 g of chiral aldol **112** in 30 h with high enantiomeric (97%) and diastereomeric (92%) purity.

A continuous flow process has been developed for the asymmetric synthesis of chiral aldehyde, the key chiral intermediate in the (−)-paroxetine synthesis **116** (Scheme 28). The key stage of the process was the enantioselective Michael reaction that was conducted solvent-free in the presence of *cis*-4-hydroxydiphenylprolinol on a polystyrene matrix as a heterogeneous organocatalyst [67]. The absence of solvent combined with the reliable catalyst allowed a significant increase in the production rate of the final product up to 1 g per hour. The process provided high chemo- and stereoselectivity, producing minimal waste, as demonstrated by a combined E-factor of 6.22.

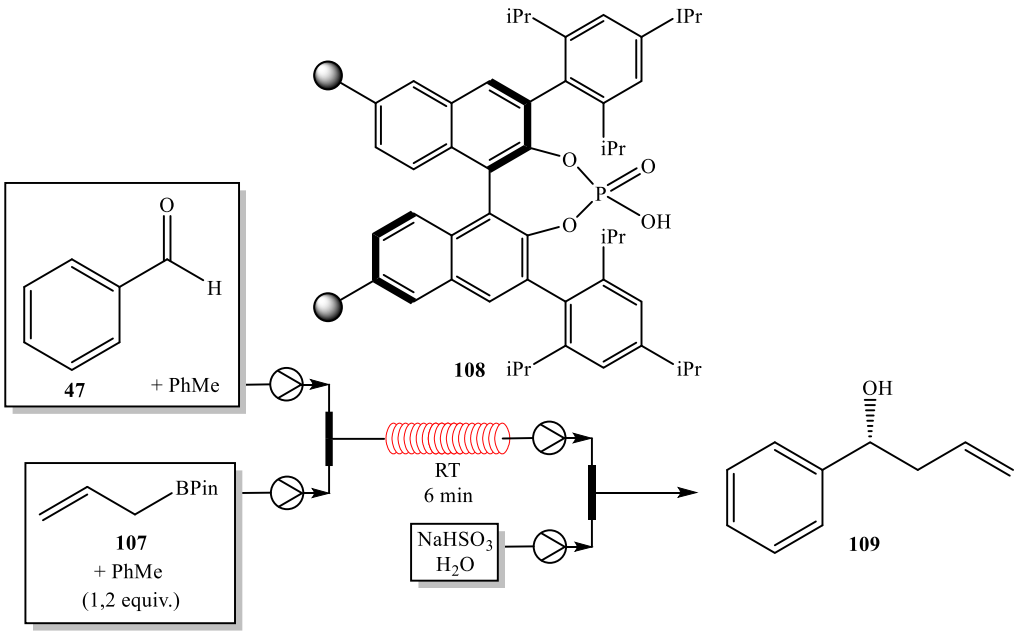
In some cases, unsatisfactory enantioselectivity results were obtained, possibly due to long process times at relatively high temperatures. Pandey and co-workers [91] studied the 1,6-conjugated addition of nitroalkanes to *p*-quinonmetides under microfluidic conditions. Under optimal reaction conditions (base – DBU, solvent – DMSO/PhME (98:2), flow rates A and B – 5 ml/min, residence time – 10 min, temperature 80 °C) using ethyl nitroacetate as nucleophile, the corresponding product was obtained in 55% yield. Efficiency comparison of the batch versus continuous processes for compounds **117** and **118** indicates better yields (80%) of **119** under microflow conditions (Scheme 29), which is much higher than in the flask (54%) over a longer time of 72 h. The enantioselective version of this reaction was carried out in a microreactor using 20% molar solution of quinine or quinidine. When the reaction was carried out at 80 °C, product 3d was obtained in 51% and 33% yields, respectively, but, in both cases, a racemic mixture was formed.



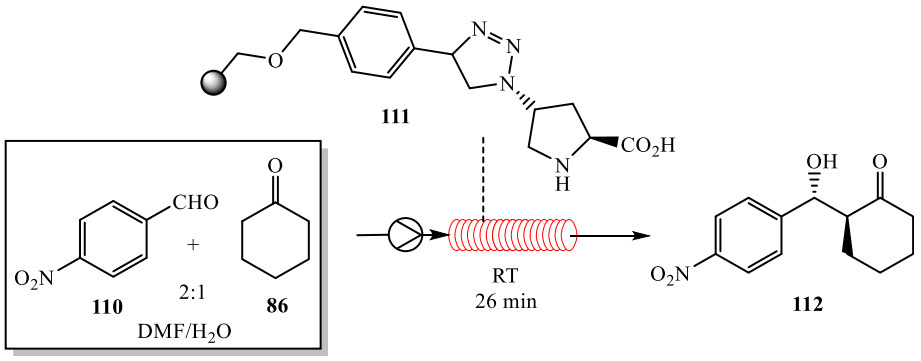
Scheme 24. Domino-reaction.



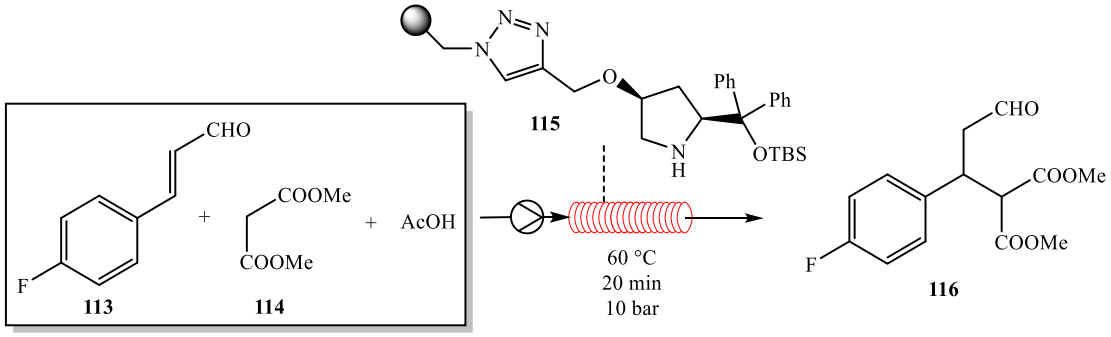
Scheme 25. Integrated Mannich reaction apparatus [47].



Scheme 26. (*R*)-1-Phenylbut-3-ene-1-ol synthesis [66].

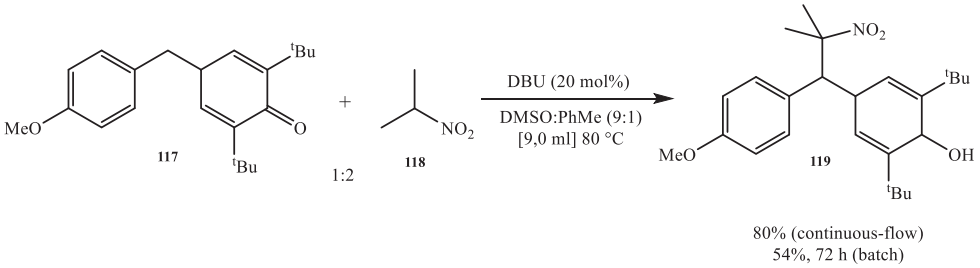


Scheme 27. Aldol condensation reaction using a grafted proline-based catalyst.

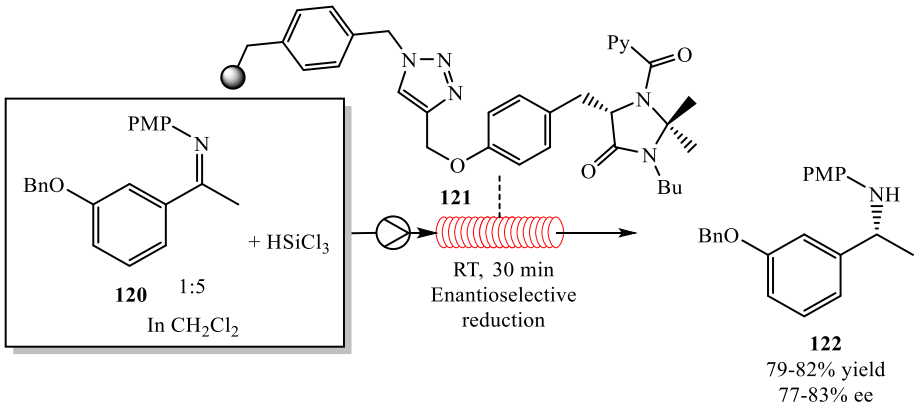


Scheme 28. Multigram-scale continuous flow organocatalytic synthesis of chiral aldehyde [67].

The Benaglia group used chiral *N*-picolylimidazolidinone **121** on a solid carrier as an effective heterogeneous organocatalyst for enantioselective reduction of imines with trichlorosilane [61]. Under batch conditions, the reused the immobilized catalyst demonstrated selectivity and activity close to its homogeneous analogue. The researches applied this heterogeneous catalyst in a condensed bed flow system to synthesize 1-(*m*-benzyloxyphenyl)-ethylamine **122**, a valuable chiral precursor of various substances such as rivastigmine, a cholinesterase inhibitor used to treat Alzheimer's disease (Scheme 30) [92]. During the 6-h synthesis followed by alkaline treatment, the chiral amine **122** was synthesized in 79–82% yield at 77–83% *ee*. The same authors used a corresponding strategy of reduction with trichlorosilane using various homogeneous chiral picolinamide catalysts for batch and continuous synthesis of intermediate products for the anti-parkinsonian agent rasagilin as well as tamsulosin used for pro-



Scheme 29. 1,6-Conjugated addition of nitroethyl acetate to *p*-quinonmetide.



Scheme 30. Synthesis of the chiral precursor of rivastigmine by enantioselective reduction in a continuous flow. (PMP = *p*-methoxyphenyl).

static hyperplasia treatment. In these cases, moderate enantioselectivity was achieved with the use of chiral organocatalysts, so easily removable chiral auxiliary substances were used as the elements of stereochemistry control to obtain the target enantiopure amino compounds.

Thus, enantioselective catalysis is often used to produce the desired stereoisomer. Compared to non-stereoselective reactions, most known enantioselective catalytic reactions use carefully designed catalysts that are more sensitive to reaction factors. Many problems can be solved by using continuous-flow reactors, which facilitate precise control of reaction conditions. On the other hand, high sensitivity can hinder the development of continuous multistep processes because incoming impurities can have a detrimental effect on the catalytic process. In addition, many of the described reactions use lower temperatures coupled with rather long reaction times to achieve high enantioselectivity. Without changing other parameters, long reaction times are usually independent of the flow conditions simply because too low a flow rate can result in inefficient mixing. In addition, since most chiral catalysts are expensive and contain transition metals, they should ideally be continuously processed for recycling. Consequently, although enantioselective batch reactions have been successful even in many industrial settings, developing enantioselective catalytic reactions in continuous flow is still a challenge, especially given the higher stability standards [93].

At the same time, the microfluidic technology allowed the screening of numerous parameters, such as temperature, solvent influence, reactant concentration, reaction time, catalyst loads, and catalyst/reagent combinations, for various reactions, leading to a rapid search for optimal reaction conditions that guarantee high chemical and stereochemical efficiency. Reactions carried out under continuous flow conditions show significant reaction time reduction and improved performance, compared to reactions in a flask. The enantioselectivity of the processes is generally not lower than the results obtained under conventional conditions.

Thus, while organocatalysis is a well-established methodology, especially for obtaining enantiomeric compounds, it can expand its possibilities even further when used in a continuous flow setup. Therefore, the use of flow chemistry for organocatalytic reactions helps to overcome the main problem associated with organocatalysis: the high catalyst loads. Moreover, many important products, in particular the precursors of physiologically active compounds, can easily be obtained in gram quantities using chiral organocatalysts in continuous flow reactors. Organocatalysts immobilized on a variety of carriers are also highly efficient and are already widely used, which opens up approaches to their industrial applications.

Chemo-enzymatic reactions

Microfluidics has proven particularly useful in green chemistry because it has reduced the amount of required organometallic catalyst and "harsh" solvents, and also brought down the number of synthetic steps [93]. On the other hand, the use of systems containing enzymes and living cells allows reactions to be carried out under mild conditions, creating new synthesis pathways, improving regio- and stereoselectivity, and removing protection setup and removal reactions that require the use of harsh reagents from the synthesis. Microfluidic bioreactors, designed to use very small amounts of substances, solve the problem of enzymatic reactions screening [94].

The researches that published a 2005 report [95] used a T-shaped simple microchip to carry out the reaction of preparing a diol **124** from an epoxide **123** (Fig. 9). The use of enzymes for catalyst leads to a high stereoselectivity of the process (up to 95% *ee*). Interestingly, the microchip was integrated with a chiral electrophoresis system, making it possible to immediately separate and identify the reaction products [95]. The compounds were separated at 8.5 pH using 50 mmol/L borate buffer containing 15 mmol/L heptakis-6-sulfato-β-cyclodextrin as a chiral component. Under these conditions, the product and adduct could be simultaneously separated into their respective enantiomers in less

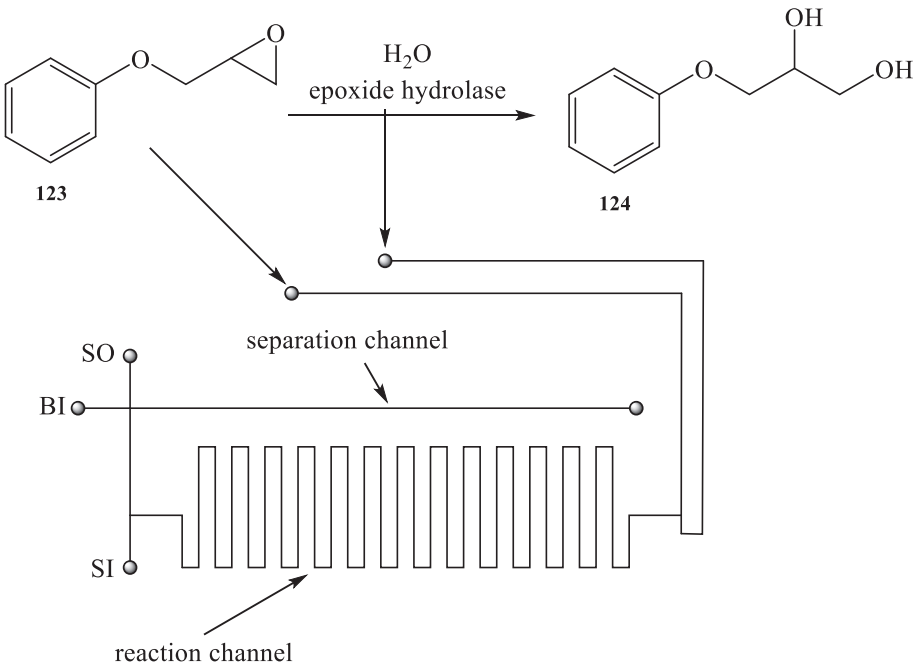


Fig. 9. Epoxide **123** opening reaction.

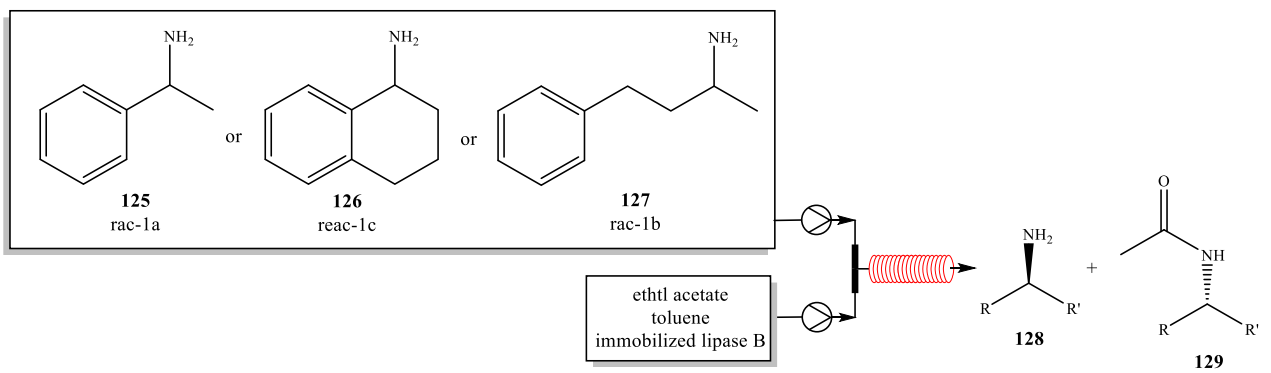
than 90 seconds. Fluorescence detection using a deep UV laser (Nd: YAG = 266 nm) was used to detect the analytes.

The article [71] discusses kinetic separation of the amine racemate mixture by stereoselective acylation with ethyl acetate, when catalyzed by various immobilized forms of lipase B from *Candida antarctica* (Scheme 31). The reactions were carried out in a flow-through microreactor; the temperature varied from 0 to 70 °C. This reaction with immobilized CaLB was also performed in a flask under the same conditions. The results demonstrated for the first time that different modes of enzyme immobilization were optimal in lipase-catalyzed kinetic resolution of racemic amines for different types of substrates or reaction conditions. Immobilization methods that limit enzyme mobility in combination with flexible substrates were useful for maintaining selectivity at elevated temperatures. On the other hand, immobilization methods limiting enzyme mobility in combination with rigid substrates resulted in poor reactivity and selectivity at low temperatures. As the sample analysis shows, it takes about 24 h to complete the separation of the stereoisomers in the flask, whereas the separation time in the microreactor is only 1 h.

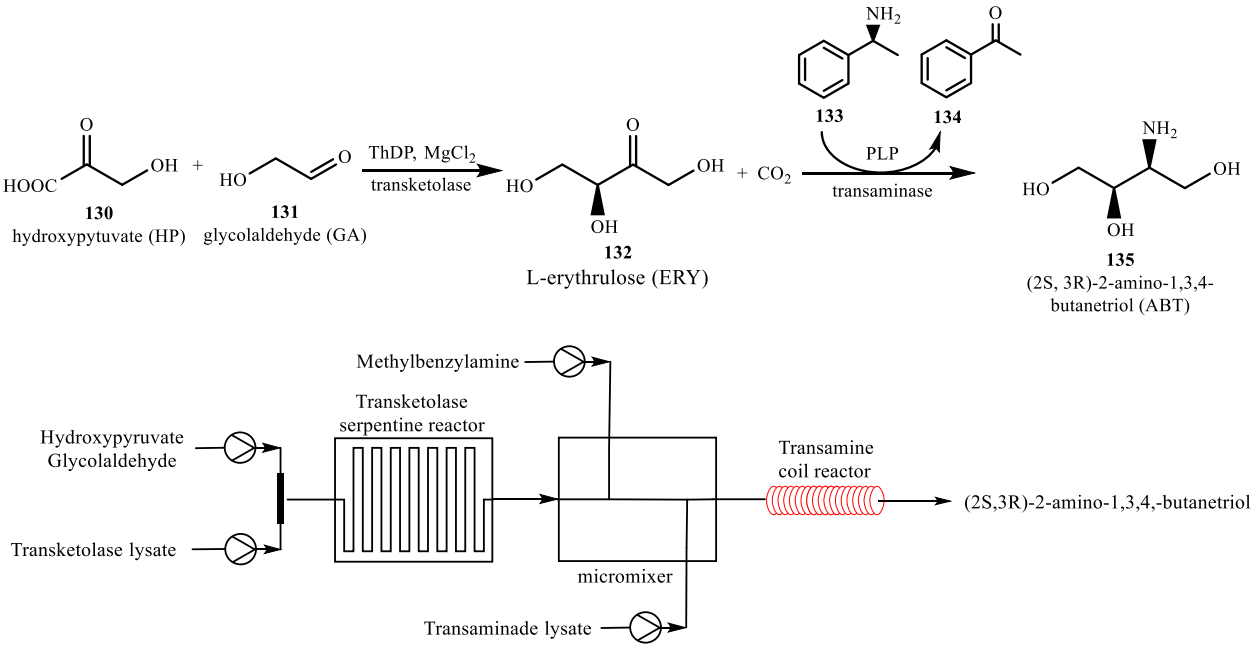
In 2018 Gruber et al. reported [96] a convenient microreactor synthetic pathway for (2*S*,3*R*)-2-aminobutane-1,3,4-triol (ABT) – a building block for the synthesis of protease inhibitors and detoxicating medicines. It is a two-step synthesis (see Scheme 32 for the reaction and the general reactor outline). During the reaction conditions optimization, the desired parameters for a successful cascade reaction were obtained.

The first step reactor is shown in Scheme 33(a). The serum with transketolase and the substrate are introduced into the upper part of the reactor constructed from two polymethylmethacrylate plates. Scheme 33(b) shows the device for mixing the products of the first reaction with a co-substrate in a Y-shaped connector for the next step catalyzed by transaminase which is injected into the center of the unit. Overall, microfluidic technologies made it possible to reduce the reaction time by more than an order of magnitude, and to obtain a higher purity intermediate compound.

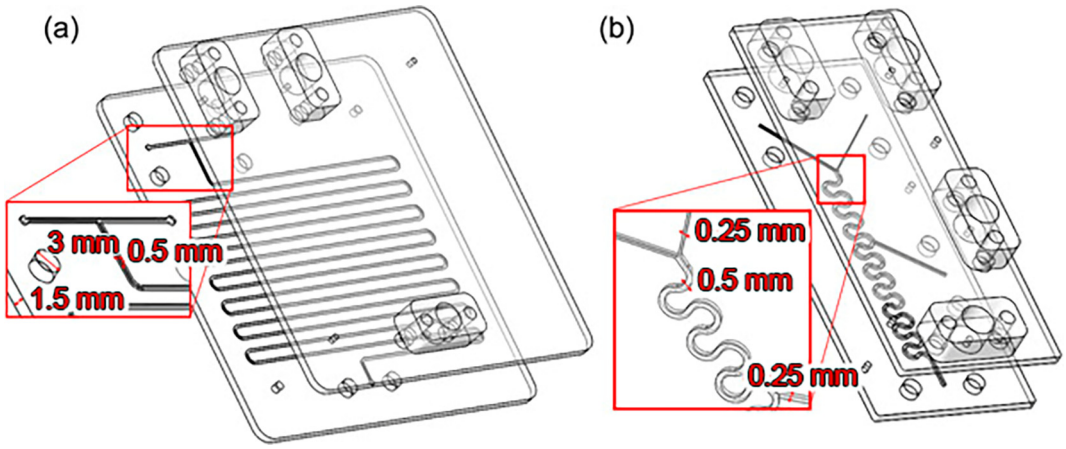
The article [97] discusses the acylation reaction of the primary hydroxyl group of uridine derivatives in a flow microreactor with the Lipozyme TLIM enzyme obtained from *Thermomyces lanuginosus*. The resulting nucleoside analogs, such as azidothymine, telbivudine, and doxyfluridine, are used in medicine as antiviral and antitumor drugs. Previous attempts to perform this type of synthesis involved other enzymes, such as CAL-B. This reaction requires longer time (24 h) to achieve the desired result [70]. The reaction



Scheme 31. Acylation reaction with ethyl acetate catalyse by various immobilized forms of lipase B [71].



Scheme 32. ABT synthesis and general reactor outline.



Scheme 33. First (a) and second (b) stage reactors. (Reactor tube diameters vary from 0.25 to 0.5 mm). Reproduced with permission [96], Copyright 2017, John Wiley and Sons GmbH.

was carried out with various substrates (Scheme 34). The yield of esters 3 was 80–99% under the following optimal conditions: solvent DMSO/*tert*-amyl alcohol ratio of 1:14; substrate uridine/vinylaurate ratio of 1:9; 30 °C reaction temperature; 30 min reaction time in a flow microreactor (Scheme 34).

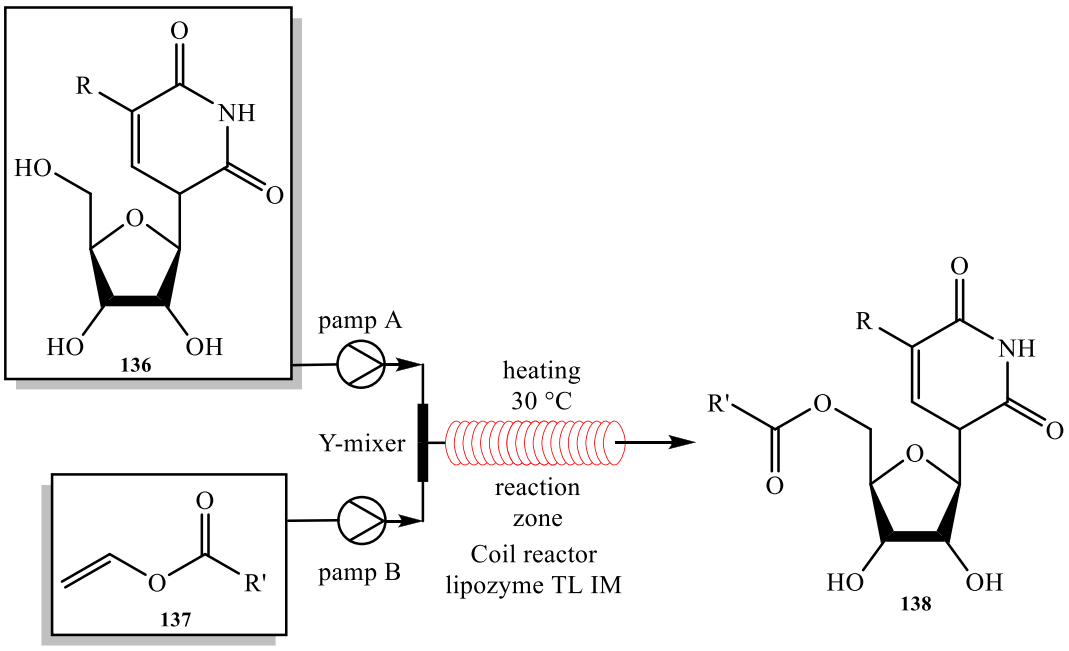
It is also important to note that, despite the wide structural and chemical diversity of natural enzymes, relatively few have been successfully applied to industrial processes. The research published in 2019 [29] used a directed evolution (DE) method to circumvent this limitation. DE – a method that imitated natural selection – was used in combination with droplet microfluidics that allows to analyze multiple enzyme variants on a super short timescale thus creating new enzymes with individual characteristics. The DE development in recent years highlights the most important advances toward high-throughput enzyme optimization requirements.

Recently, a microfluidic bioreactor has been proposed as an environmentally friendly alternative to conventional synthesis for L-DOPA and dopamine enzymatic production in a sequence of reactions with respective yields of 30% and 70% [98]. In addition, a 780-fold scale-up experiment was performed to reach milliliter volumes while maintaining the yields and biocatalyst as in its microscale counterpart. This scheme is notable for reducing reagent consumption by immobilizing the catalyst on a carrier medium, which can then be used in a compacted bed reactor, thereby extending the life of the enzyme.

It has to be emphasized that the time for enzymatic reactions carried out in microreactors decreased on average by an order of magnitude, from several days to several hours. The use of such technologies opens up the possibility of science "automation" [99]. The synergetic combination of artificial intelligence, low cost, high performance, and standardized analysis could potentially increase the efficiency of low-molecular-weight drug discovery [100].

Photochemical, electrochemical and other reactions

In the last 10 years, joint photoredox and organocatalysis has emerged as a powerful synthetic tool. McMillan and his colleagues

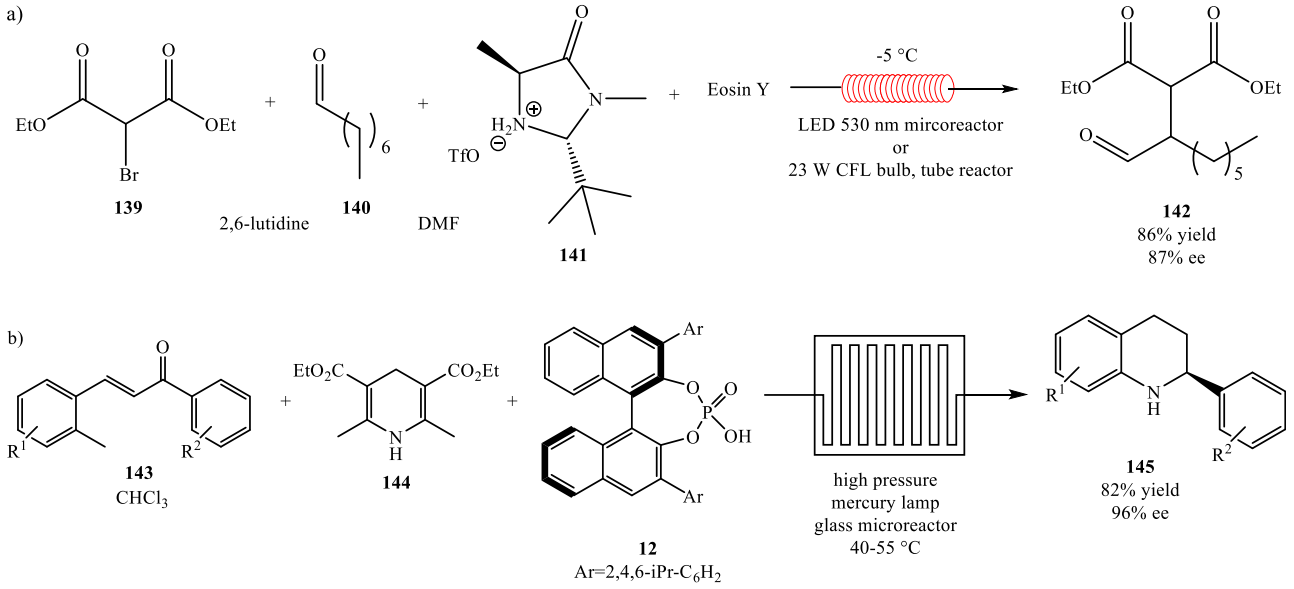


Scheme 34. Acylation reaction of the primary hydroxyl group in uridine derivatives [70].

have demonstrated for the first time that it is possible to design unprecedented synthetic approaches to chiral molecules, which are difficult to implement with traditional strategies [101].

Later on, Neumann and Zeitler reported the reaction between brommalonate **139** and octanal **140** catalyzed by McMillan imidazolidinone (triflate salt) **141** in the presence of the photocatalyst eosin Y and 2,6-lutidine to form α-alkylated aldehyde **142** [69]. Two different reactor installations were proposed: one using glass microreactor technology along with 530 nm LEDs, and another using a polyfluoroethylene HPLC tube wound on coils around a 23 W compact fluorescent lamp that was immersed in a cooling bath (Scheme 35A). With this setup, optimum irradiation was achieved for the large tube volume and length (10.5 ml volume and 21 m reactor length). The reaction under flow conditions still exhibits high enantioselectivity and yields, providing product **142** in yields up to 86% and enantiomeric purity up to 87%. A 107-fold increase in productivity was achieved compared to the reaction under batch conditions due to more efficient irradiation.

An organocatalytic cascade hydrogenation reaction with photocyclization and transfer published by Ruping and Sugiono used 2-aminochalcones as reagents, chiral phosphoric acid **12** as a chiral catalyst, and Hantzsch ester **144** as a reducing agent [72]. A glass microreactor immersed in a thermostatically controlled water bath was used for the continuous-flow setup. A high-pressure mercury lamp placed next to it irradiated the reactor from the side. This methodology produced a variety of substituted isoquinolines in very high yields and enantioselective excesses, starting with the readily available 2-aminochalcones (Scheme 35b). In particular,



Scheme 35. Examples of continuous flow organophotoredox conversions. (a) Dual catalysis of α-alkylated McMillan aldehydes optimized by Zeitler and Neumann for continuous flow conditions [69]. (b) Rupping and Sugiono reductive cascade cyclization [72].

the flow-through unit showed a significant increase in productivity due to more efficient irradiation. Also, continuous product removal from the irradiation source prevents excessive irradiation, which can lead to undesirable background reactions.

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

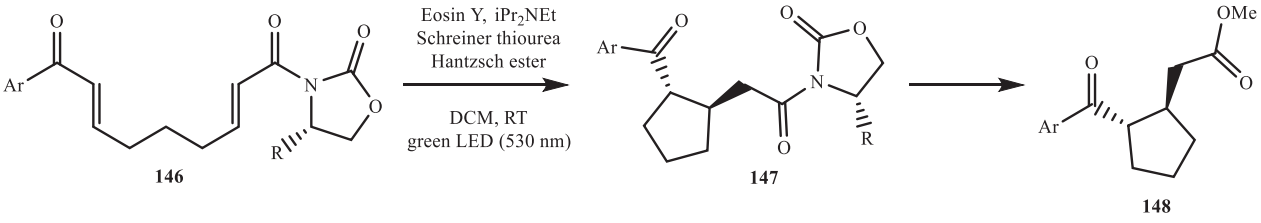
In 2021, a stereoselective catalytic cyclization of bis(enones) under visible light was reported, allowing an easy transition to enantiomerically enriched cyclopentanes [102]. One of the most innovative strategies for building a cyclic system uses photoredox activation of arylenones. The possibility of the absolute final product stereochemistry control in a metal-free technique for obtaining enantio-enriched cyclopentane rings was implemented.

The introduction of a chiral substance, such as Evans oxazolidinones, into the bis(enone) chain offers a simple and convenient version of stereoselective light-controlled cyclization. After the cyclization and removal of the oxazolidinones, the functionalized 1,2-*trans*-cyclopentane could be isolated in good yield and an enantiomeric excess of up to 65%. When the reaction was carried out in continuous mode, in a self-made coil photoreactor, high yields were observed. Cyclization was also successfully implemented in a 3D-printed mesoreactor without changing the stereoselectivity of the process (Scheme 36).

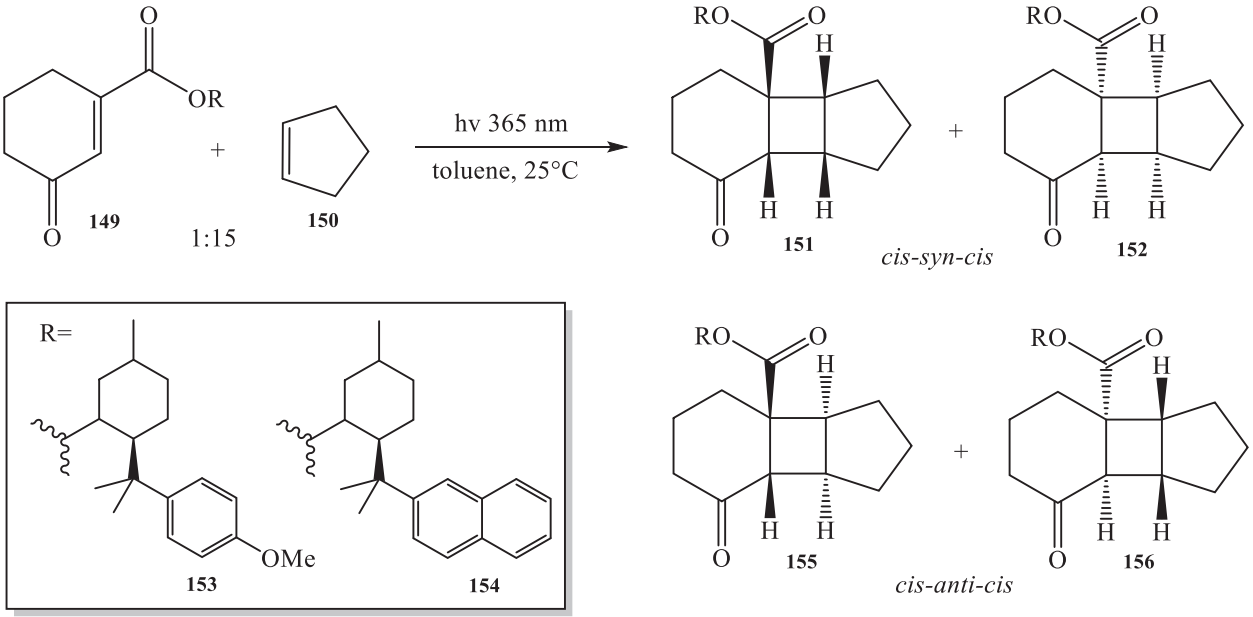
Terao research group [103] performed the diastereoselective [2+2] photocycloaddition of chiral cyclohexenone **149** with cyclopentene **150** using a microreactor equipped with UV-LED lamps (Scheme 37). A respectable conversion rate with good stereoselectivity was achieved even for very high reagent concentration, while conversion in the flask under the same conditions is low. This can be explained by the fact that the very narrow reaction channel in the microreactor ensures good light penetration according to the Lambert-Beer law. This method has been used both for laboratory scale [103,104], and industrial processes [105–107].

Wei et al. [108] published their study of photocatalytic decarboxylation of α,β-unsaturated carboxylic acids in visible light resulting in the chiral CBDC intermediate, which is a key step in the complete synthesis of (+)-epigalcatin (Scheme 38). Lisiecki and Czarnocki [109] improved the two-step total yield from 21% (quartz cell irradiated by a medium-pressure mercury lamp) to 65% (continuous flow photomicroreactor irradiated with UV light).

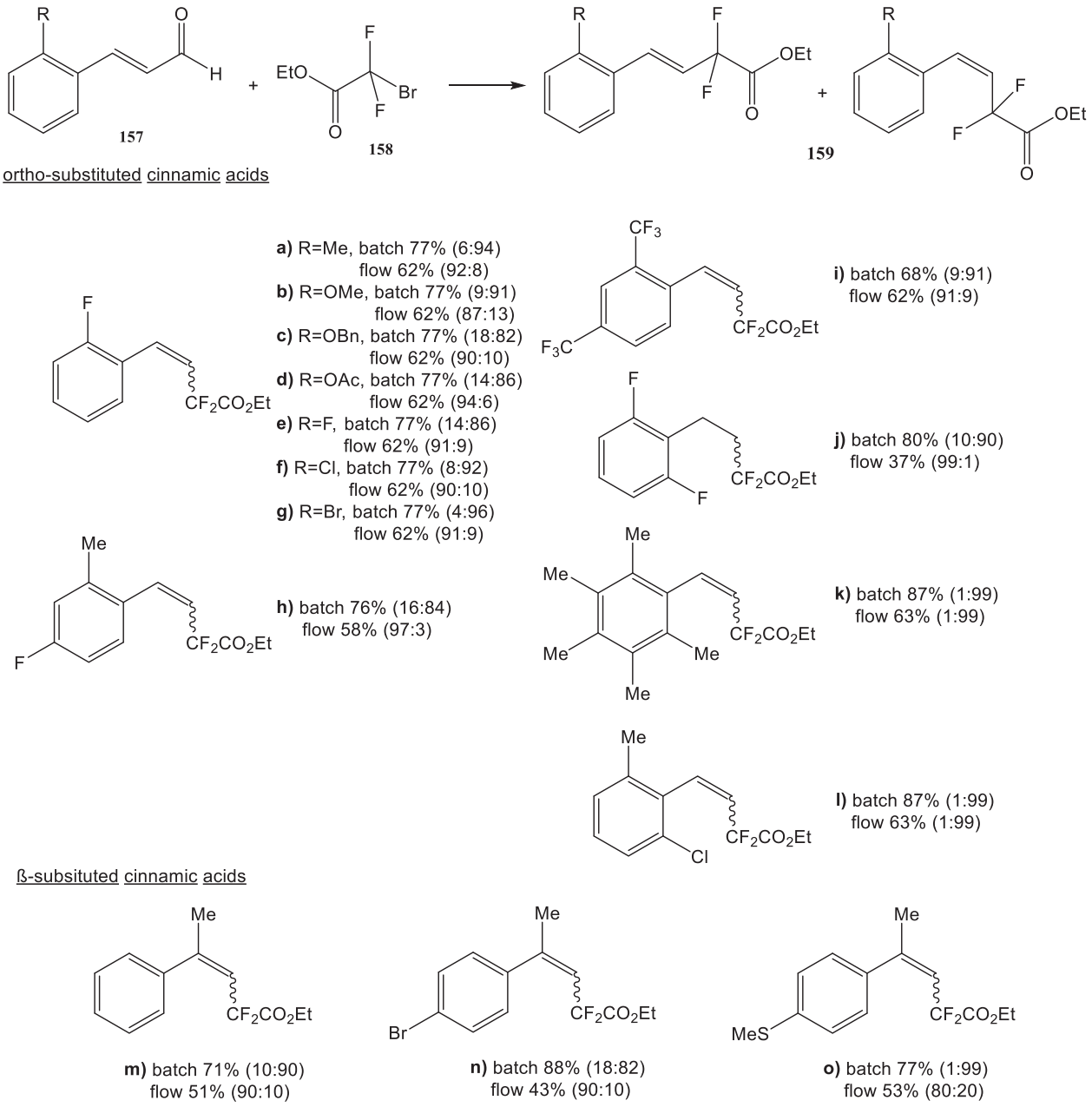
In recent years, significant progress has been made in the field of radical difluoroalkylation reactions, especially the ones that proceed through photoredox catalysis in visible light [108–110]. *fac*-Ir(ppy)$_3$ was used as a photocatalyst. Microreactors have been used to achieve high conversions in a short time [111], which allow accelerated photocatalytic reactions due to improved mass transfer characteristics and irradiation profile. Under optimal reaction conditions, with increased catalyst loading and concentration, reaction time is reduced to 15 min, resulting in excellent *E*-selectivity (62%, 92:8) [112]. Longer residence times result in higher yields but lower stereoselectivity. The *ortho*-substituted cinnamic acids reactions were then studied both in a flask and in a microreactor (Fig. 5). The authors have found that cinnamic acids containing



Scheme 36. In-flow photoredox-organocatalytic reactions.



Scheme 37. Diastereoselective [2+2] photocycloaddition of chiral cyclohexenone and cyclopentene.



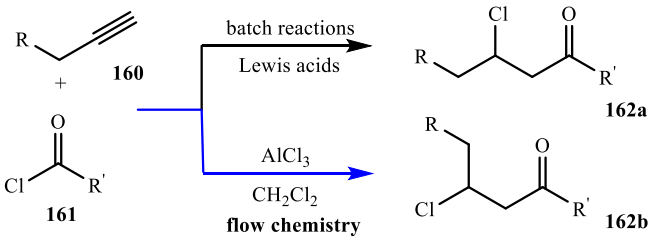
Scheme 38. Flask and microreactor setups for the decarboxylating difluoromethylation.

neutral, donor, and acceptor substituents can undergo difluoromethylation with high.

Z-selectivity in the flask, while the corresponding *E*-isomer can be easily obtained under microfluidic conditions. Greater preference for the *Z*-isomer was observed as the substituent steric volume was increased (F < Cl < Br). Interestingly, when both *ortho*-positions were occupied by large groups, high *Z*-selectivity was observed both for flask and microreactor setups.

A Swiss research team [112] performed a continuous intramolecular cyclization of halogenalkyl-substituted α-aminoethers via memory of chirality, using lithium bis-(trimethylsilyl)amide as a base and methyl *N*-(tert-butoxycarbonyl)-*N*-(3-chloropropyl)-D-alaninate as a model reagent. Reaction parameters such as temperature, residence time, reagent stoichiometry as well as base type and concentration were optimized for maximum yield and enantiomeric purity of the cyclized product. Under optimal conditions, this reaction productivity reaches 11 g per hour. A microreactor allows better temperature control when compared to the standard flask methods, resulting in milder operation temperatures and permitting product synthesis with high enantioselectivity and complete aminoether conversion within a few seconds of residence time in the reaction volume.

A new simple design of an electrochemical microreactor was described in a 2020 report [73] where it was used to oxidize an L-proline derivative using the memory of chirality effect at room temperature under continuous flow conditions. Compared to batch processes, organic electrosynthesis in microfluidic reactors has certain advantages because it provides shorter reaction times, easier optimization and scaling, safer operating conditions, and high selectivity (e.g., reduced over-oxidation). Flow-through electrochemical reactors also provide high surface to volume ratio and



Scheme 39. Alkyne acylation reaction products.

make it possible to eliminate the background electrolyte due to the very short electrode spacing. Comparison of Hofer Moest-type electrochemical oxidation at room temperature in batch and flow regimes suggests that continuous flow electrolysis provides a good yield (71%) and a higher enantiomeric excess (64%) than the batch process [73]. These results show that continuous flow has the capacity to act as a new asymmetric synthesis technology to replace some aspects of traditional periodic electrochemical processes.

Microfluidic systems have been successfully applied to the synthesis of oligosaccharides, offering a practical pathway for stereoselective glycosylation [113]. This was achieved through efficient mixing, rapid heating and cooling, rigorous temperature and residence time control as well as efficient mass transfer, all of which ensure perfect reaction kinetics. As a result, key synthetic intermediates for oligosaccharides were obtained on the multigram scale under microfluidic conditions, ultimately leading to the synthesis of asparagine-related oligosaccharides (*N*-glycans) and *Helicobacter pylori* lipopolysaccharides.

Continuous flow technology can be applied to develop *E*-selective synthesis of β-chlorovinyl ketones, by acylation of alkynes by Friedel-Craft reaction, which prevents simple *E* to *Z* isomerization under $AlCl_3$ catalyzed reaction conditions. Compared to batch reactions (Scheme 39), this method provides fast, pure, highly productive, and stereoselective route for the synthesis of *E*-β-chlorovinylketones **162** [114].

In summary, the microfluidic approach extends to an increasing number of enantioselective processes and, in some cases, allows for effective cascade reactions that are not possible under other conditions.

Enantioselective analysis *via* microfluidic technologies.

The separation and identification of enantiomers is of great importance in chiral synthesis, yet at the same time it poses a serious challenge as most of their chemical and physical properties are identical. There are many methods for laboratory scale stereoisomer separation and today-one of the most rapidly developing trends in microfluidics is the technology that combines the separation and identification of miniscule amounts of enantiomeric molecules on a single chip. Chirality analysis using miniaturized chips offers several advantages: shorter time (e.g., for complicated multidimensional separations), ameliorated compactness (can be critical for carrying out chiral analysis in space), and simplified multiplexing and system integration (applicable for rapid screening of enantioselective catalysts) [115]. Chiral chip technology is used in fields as diverse as high-throughput screening in pharmaceuticals [116] and deep space exploration missions [117].

Macroscale chiral separation is usually performed by chromatography with enantioselective stationary phases. Alternative method for the separation of enantiomers is to convert them into diastereomers by interaction with a suitable chiral compound. Since the diastereomers have non-identical chemical and physical properties, they can be separated and identified by conventional analytical methods. One convenient miniaturized technique for enantiomer separation is capillary electrophoresis (CE) with chiral components added to the electrolyte [12,17,118].

Lab-on-a-chip technology involves miniature capillary electrophoresis, also called "microchip electrophoresis" (MCE), integrated into the chip [70,119]. Advantages of the MCE include not only smaller analytical units and minimal sample consumption, but also improved analysis rate (seconds rather than minutes) [28]. A typical electrophoresis chip consists of two glass or polymeric plates connected by a network of microfluidic lines. The lines are narrow channels with typical cross-section dimensions of 10–60 μm. After high voltage is applied to a network filled with liquid, electrophoretic separation take place. The standard chip layout for electrophoresis contains a long microfluidic separation channel that is intersected a shorter sample inlet channel. For enantiomeric separation, a chiral selector is added to the electrolyte solution, cyclodextrin derivatives are often used for this purpose as they form a toroidal structure with an internal hydrophobic cavity [110]. Chiral separation selectivity is the result of the intermediate diastereomeric host–guest complexes formation and adsorption interactions with resulting entities that differ in their electrophoretic mobility. There are also other components that are employed for the electrophoretic enantiomers' separation: crown-ethers, inorganic and nanomaterials, organometallic comnpounds and proteins. One of the commonly used methods for identifying enantiomers without separation is their interaction with polarized light, often referred to as "chiral detection," also suitable for microchips. This effect can also be used for enantioselective analysis [38,85]. Microarray electrophoresis has been used for chiral separation of other compounds such as peptides [117,120], neurotransmitters [117,121] and pharmaceuticals [7,38].

The detection is performed by optical (usually fluorescent) sensor [122], by electrochemical or mass-spectrometric detectors [113]. When using a short separation channel a few millimeters in length and high voltage, it was possible to achieve the fastest separation rate of chiral compounds [123]. This method allowed basic separation of dansyl fluorophore-labeled amino acids in approximately 800 ms. A mixture of three racemic amino acids: norvaline, glutamic acid and phenylalanine was enantioselectively separated in a single pass over 3.5 s. The method has also been applied to the chiral separation of other pharmaceuticals. This is particularly attractive for small amounts of samples, as recently demonstrated by analysis of trace amounts of D-Asp and D-Glu in rat brain and human samples [124]. These results show the enormous opportunities of microfluidic chip technology to significantly reduce the enantiomeric analysis time required by traditional methods.

Analytical methods like 2D high performance liquid chromatography or 2D gel electrophoresis have multidimensional separation because a single dimension is often insufficient to separate enantiomers. The article [125] describes the use of three-dimensional poly(methylmethacrylate) microfluidic chip with polycarbonate nanomembranes which were electrically switchable for that were automatically opened by a pre-programmed detection signal. Conventional electrophoresis first separated the amino acids in the microchip achirally, and after that chiral micellar electrokinetic chromatography separated the individual enantiomers of each amino acid, all processes completed in 10 min. Electrochromatography is a combination of chromatography and electrophoresis, which applies a stationary phase with an immobilized component for chiral separation. For instance, cyclodextrin-modified polyacrylamide microfluidic chips used as the stationary phase for separation of amino acid enantiomers in two minutes [126].

Another approach combines enantioselective synthesis with an on-chip analysis, it can be used to obtain diastereomers followed by standard achiral MCE. This was demonstrated for the of amino

acid enantiomer separation where the fluorescent pyranose derivative served simultaneously as a diastereomerization reagent and a fluorescent label. In this manner, all necessary synthetic transformations were achieved on the microfluidic chip at once in less than two minutes [127].

Compared to the methods mentioned above, analytical devices based on microfluidic paper can solve several problems simultaneously using a single strip, which increases the detection speed and reduces the cost [128,129]. Such devices offer a number of advantages over traditional methods, including faster analysis times, lower reagent and sample consumption, lower cost, ease of operation, and better suitability for *in situ* detection. However, MCE applications have some limitations in terms of simultaneous detection of multiple analytes, and depending on the nature and quality of the carrier, they may exhibit different specificities and sensitivities leading to false negative or false positive results and therefore need further improvement [130]. Nonetheless, paper microfluidics has not only made simple diagnostic devices available worldwide, but has also become a key technology enabling biomedical research [131,132].

For example, the simultaneous detection of sucrose, fructose, and glucose was achieved by using cascade enzymatic reactions. Three enzymes were employed to detect sucrose, one enzyme to detect fructose, and two enzymes to detect glucose. Sucrose was analyzed using invertase, glucose oxidase, and peroxidase to perform the catalytic reaction [96].

There is a large number of Baclofen and phenylalanine chiral separation methods, including chromatographic, capillary electrophoretic, and electrochromatographic techniques. But the most effective was the method that uses the microfluidic paper [133,134].

The advancement of pharmaceutical analytical methods represents one of the most important aspects of chiral drug development. Recent progress in microfabrication and microfluidics involves new approaches to the drug analysis, including screening, active testing, and metabolism studies [135]. Microfluidic chip techniques such as lab-on-a-chip technology, three-dimensional (3D) cell culture, organ-on-a-chip and droplet techniques have been developed. Recently, quite a lot of research has been published on this subject, especially in the field of organs-on-chips [136–140]. The possibilities of using microfluidic technologies are truly multifaceted. Microfluidic chips in combination with various detection methods are well suited for high-throughput drug screening, detection and mechanistic testing.

Miniature analytical systems are perfect for spaceflight since the size and mass of the permitted substance is extremely limited. Exo Mars rover carries an analytical component (16.5 kg by mass) for life detection [117]. The portable analytical device (11 kg) is designed for enantioselective detection of amino acids and other biogenic amines on Mars [141,142]. The technology of this device is based on the microchip electrophoresis discussed above.

Thus, microfluidic chips for chirality screening, despite being mostly new technologies, that demonstrate nice prospects in enantioselective analysis. Microfluidics enable applications that require high efficiency, rapid analysis, portable instrumentation, and minimal sample loads. Although separation methods such as chiral chip HPLC or chiral chip electrochromatography have their advantages, but the best separation method at the moment is MCE. Probably in the future this microfluidic technique for enantioselective analysis may become the standard method. Integrated microfluidic chips combining different functions will encourage the development of enantioselective detection tools, stereoselective syntheses, biological assays with various fields of application. Integrated optical components such as light sources, microlenses, and waveguides will further reduce the instrument size, so portable enantioselective microanalysis systems capable of real-time chirality detection of actual samples will be available soon. For example, a group of German scientists has proposed a new method [143], that combines continuous-flow catalysis and real-time online HPLC/MS analysis on a single device with a single chip. In particular, this method allows using Lab-on-a-Chip technology to carry out enantioselective analyses at the nanoliter scale and, in addition to investigating the immobilized organocatalysts durability, to study their dynamic behavior of stereoselectivity and stationary state while minimizing resource consumption and waste generation. A reconfigurable system for automated optimization of various chemical reactions has also been proposed [144]. Using microfluidics for chiral analysis is a new approach with awesome results, such as separating enantiomers at record rates and developing integrated laboratory enantioselective chips [125].

Optimizations of reaction conditions and appropriate enantioselective catalysts are labor-intensive, time-consuming, and expensive. Consequently, the combination of fast, multitask enantioselective synthesis and microarray analysis leads to will lead to the creation of a new generation of high-performance, robotic systems well integrated in laboratories. [145].

Conclusions

Developments in microtechnology have given incredibly powerful new tools to the synthetic chemist. However, the successful synthesis of an enantiomerically pure chiral molecule requires not only high chemical efficiency and chemoselectivity of the process, but also high reaction stereoselectivity combined with the subsequent isolation of the product in its unmodified form and its chiral analysis.

In recent years, significant advances have been made in microreactor asymmetric catalysis. These devices have been successfully used for rapid screening and low catalyst loads, integrated online analysis, and multistep synthesis with unstable intermediates. Microfluidic technology enables rapid screening of various reaction parameters, such as temperature, solvent, reaction time, reagent and catalyst concentration and ratio, leading to a rapid search for optimal reaction conditions that guarantee high chemical and stereochemical efficiency. For this reason, the progress of enantioselective synthesis using multistep flows, and with in situ-generated unstable intermediates, as well as with various catalytic systems, deserves attention not only in terms of discovering new catalysis methods, but also as a potential technique for the practical synthesis of valuable chiral compounds in cascade asymmetric catalysis. There is a reason to expect that studies of catalysis in microfluidic stream will also contribute to the utilization of asymmetric synthesis catalysts that are ineffective in flask reactions.

The application of microreactors to optimizing asymmetric synthesis conditions is particularly valuable due to the possibility of using instrumental analysis methods, such as mass spectrometry, embedded directly in the microreactor. In the future, such technology may become able to replace the traditional synthesis in a flask. Undoubtedly, the microreactor is a powerful tool for both homogeneous and heterogeneous asymmetric reactions. The examples of homogeneous asymmetric catalysis in microreactors have shown that such reactions can lead to high yields and enantioselectivity with shorter reaction times and lower catalyst loads. Obviously, it is highly desirable to reuse homogeneous chiral catalysts. Despite the success of nanofiltration in this respect, the method of catalyst immobilization is better studied and has already demonstrated its usefulness. In some instances, heterogenized catalysts show higher enantioselectivity than the corresponding homogeneous catalysts. In most cases, however, catalysts have not been tested for long life, although this is essential for continu-

ous production. The greatest success in asymmetric synthesis has been the use of immobilized chiral reagents on a carrier in a chip. Good results have been shown for reactions with high enantioselectivity and lower catalyst loads. Significant advances have been achieved for enantioselective catalysis in a continuous flow. In this case, chiral catalysis represents a key approach for attaining high selectivity and hence for waste reduction. The use of continuous flow technology promotes the transfer of asymmetric reactions to practical applications. The processes that are carried out under continuous flow conditions show beneficial reductions in reaction time and improved productivity compared to flask reactions, and in some cases the stereoselectivity is also improved.

At the same time, since homogeneous catalysts dominate the current practice of asymmetric reactions, they will inevitably be reused in multistep flow processes, therefore innovative catalyst immobilization strategies, especially those developed for continuous flow conditions, are urgently needed. However, given the large number of known synthetically important reactions, further expansion of successful examples is needed to fully demonstrate the feasibility and potential of continuous flow methods for them.

Enzymatic catalysis has been successfully applied in asymmetric synthesis and it also represents a promising approach for continuous production. In line with the rapid advances in asymmetric synthesis, more and more successful examples of enzymatic catalysis in continuous flow are becoming known. On average, the time of enzymatic reactions that are carried out in microreactors has been reduced by several times compared to standard methods. Successful cases of multistep synthesis in a continuous flow involving enantioselective catalysis represent the real pathway for the synthesis of complex pharmaceutical ingredients [16]. Nevertheless, since the throughput of these methods is usually low, more research is needed to solve the above-mentioned problems using new automated engineering methods [144] and technologies such as artificial intelligence [125,126], before the multistage continuous enantioselective production can be widely implemented in the pharmaceutical and fine chemical industries. The use of microfluidics for chiral analysis is a new approach with impressive results, including the separation of enantiomers at record rates and the creation of integrated enantioselective chip laboratories.

Microfluidics is becoming an integral part of modern preparative chemistry since it allows better control over the conditions and the course of the reaction compared to conventional flask synthesis. Still, microfluidic syntheses have several disadvantages that do not yet allow the widespread use of microreactors. These disadvantages include those inherent for this technology, the small reactor size and the low flow rates, which are partially offset in practice by the parallel use of several reactors.

Despite the rapid development of these technologies over the last 20 years, microreactors are still relatively new and unfamiliar method of experimentation. A large number of unsuccessful attempts to implement these technologies in asymmetric synthesis also contribute to this fact. The implementation of new technologies in microfluidics with the use of microchips, microarrays for synthesis has little coverage in the literature. At the same time, the trend toward smaller reactor sizes and smaller amounts of reagents allows for highly selective microarray reactions. But as a new tool, this technology is sure to find its niche soon, both in scientific circles and in industrial production. Despite the challenges that scientists working in this field still face, microfluidics has enormous potential and this field is developing rapidly. Taking advantage of the properties of small-volume fluids, this area enables research at a new level. Rigorous control of system parameters to ensure synthesis accuracy and efficiency makes microfluidic circuits an ideal tool. Undoubtedly, one of the main directions of future investigations in this field will be expanding the application of asymmetric reactions along with new chiral catalysts into the synthesis of more complex substances.

Chemical processes in microfluidic reactors already cover complex cascade enantioselective reactions, but their full-fledged development can bring great prospects for many areas of fundamental chemistry and greatly facilitate the new drugs research. Especially worth mentioning is the cost effectiveness, safety, and environmental friendliness of these methods, which, combined with the reproducibility of such indicators as high yields and stereoselectivity, are bound to attract the attention of applied chemists. Another impulse for the development of chiral pharmaceutical synthesis methods based on flow chemistry is the need to reduce environmental impact of future manufacturing processes. Thus, it can be expected that even closer attention will be paid to the associated environmental effects, as well as to the application of new, more efficient methods for asymmetric processes that have not yet been used for chiral synthesis under flow conditions.

CRediT authorship contribution statement

Konstantin A. Kochetkov: Investigation, Supervision, Conceptualization. **Nataliya A. Bystrova:** Data curation, Formal analysis. **Pavel A. Pavlov:** Writing – original draft, Validation, Writing – review & editing. **Maxim S. Oshchepkov:** Data curation, Funding acquisition, Project administration. **Aleksandr S. Oshchepkov:** Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors (Konstantin A. Kochetkov, Pavel A. Pavlov, Maxim S. Oshchepkov) would like to thank the Russian Science Foundation, project № 22-73-10076. Nataliya A. Bystrova and Konstantin A. Kochetkov would like to thank the Ministry of Science and Higher Education of the Russian Federation for the financial support of the present study".

References

[1] C.-C. Lee, G. Sui, A. Elizarov, C.J. Shu, Y.-S. Shin, A.N. Dooley, J. Huang, A. Daridon, P. Wyatt, D. Stout, H.C. Kolb, O.N. Witte, N. Satyamurthy, J.R. Heath, M.E. Phelps, S.R. Quake, H.-R. Tseng, Science 310 (2005) 1793–1796, https://doi.org/10.1126/science.1118919.
[2] R.L. Hartman, J.P. McMullen, K.F. Jensen, Angew. Chem. Int. Ed. 50 (2011) 7502–7519, https://doi.org/10.1002/anie.201004637.
[3] T. Asai, A. Takata, Y. Ushiogi, Y. Iinuma, A. Nagaki, J. Yoshida, Chem. Lett. 40 (2011) 393–395, https://doi.org/10.1246/cl.2011.393.
[4] T. Illg, V. Hessel, P. Löb, J.C. Schouten, ChemSusChem 4 (2011) 392–398, https://doi.org/10.1002/cssc.201000368.
[5] D.E. Fitzpatrick, C. Battilocchio, S.V. Ley, ACS Cent. Sci. 2 (2016) 131–138, https://doi.org/10.1021/acscentsci.6b00015.
[6] A.F. de Almeida, R. Moreira, T. Rodrigues, Nat. Rev. Chem. 3 (2019) 589–604, https://doi.org/10.1038/s41570-019-0124-0.
[7] C. Liu, J. Xie, W. Wu, M. Wang, W. Chen, S.B. Idres, J. Rong, L.-W. Deng, S.A. Khan, J. Wu, Nat. Chem. 13 (2021) 451–457, https://doi.org/10.1038/s41557-021-00662-w.
[8] M.B. Plutschack, B. Pieber, K. Gilmore, P.H. Seeberger, Chem. Rev. 117 (2017) 11796–11893, https://doi.org/10.1021/acs.chemrev.7b00183.
[9] S.T. Knox, N.J. Warren, Chem. Eng. 5 (2020) 405–423, https://doi.org/10.1039/C9RE00474B.
[10] B. Gutmann, C.O. Kappe, J. Flow Chem. 7 (2017) 65–71, https://doi.org/10.1556/1846.2017.00009.
[11] D.L. Hughes, Org. Process Res. Dev. 24 (2020) 1850–1860, https://doi.org/10.1021/acs.oprd.0c00156.
[12] M. Baumann, T.S. Moody, M. Smyth, S. Wharry, Org. Process Res. Dev. 24 (2020) 1802–1813, https://doi.org/10.1021/acs.oprd.9b00524.

[13] K.F. Jensen, Microfluidics for Chemical Synthesis: Flow Chemistry, ArXiv180205611 Phys. Q-Bio. (2018). http://arxiv.org/abs/1802.05611 (accessed November 15, 2021).
[14] T. Fukuyama, M.T. Rahman, M. Sato, I. Ryu, Synlett 2008 (2008) 151–163, https://doi.org/10.1055/s-2007-1000884.
[15] C.-C. Lee, T.M. Snyder, S.R. Quake, Nucleic Acids Res. 38 (2010) 2514–2521, https://doi.org/10.1093/nar/gkq092.
[16] J. Jiao, W. Nie, T. Yu, F. Yang, Q. Zhang, F. Aihemaiti, T. Yang, X. Liu, J. Wang, P. Li, Chem. Eur. J. 27 (2021) 4817–4838, https://doi.org/10.1002/chem.202004477.
[17] N. Kockmann, M. Gottsponer, B. Zimmermann, D.M. Roberge, Chem. Weinh. Bergstr. Ger. 14 (2008) 7470–7477, https://doi.org/10.1002/chem.200800707.
[18] B. Gutmann, D. Cantillo, C.O. Kappe, Angew. Chem. Int. Ed. 54 (2015) 6688–6728, https://doi.org/10.1002/anie.201409318.
[19] K. Lovato, P.S. Fier, K.M. Maloney, Nat. Rev. Chem. 5 (2021) 546–563, https://doi.org/10.1038/s41570-021-00288-z.
[20] B.J. Hindson, K.D. Ness, D.A. Masquelier, P. Belgrader, N.J. Heredia, A.J. Makarewicz, I.J. Bright, M.Y. Lucero, A.L. Hiddessen, T.C. Legler, T.K. Kitano, M. R. Hodel, J.F. Petersen, P.W. Wyatt, E.R. Steenblock, P.H. Shah, L.J. Bousse, C.B. Troup, J.C. Mellen, D.K. Wittmann, N.G. Erndt, T.H. Cauley, R.T. Koehler, A.P. So, S. Dube, K.A. Rose, L. Montesclaros, S. Wang, D.P. Stumbo, S.P. Hodges, S. Romine, F.P. Milanovich, H.E. White, J.F. Regan, G.A. Karlin-Neumann, C.M. Hindson, S. Saxonov, B.W. Colston, Anal. Chem. 83 (2011) 8604–8610, https://doi.org/10.1021/ac202028g.
[21] T. Noël, S. Kuhn, A.J. Musacchio, K.F. Jensen, S.L. Buchwald, Angew. Chem. Int. Ed. 50 (2011) 5943–5946, https://doi.org/10.1002/anie.201101480.
[22] S.J. Haswell, P. Watts, Green Chem. 5 (2003) 240–249, https://doi.org/10.1039/b210539j.
[23] M.C. Bryan, P.J. Dunn, D. Entwistle, F. Gallou, S.G. Koenig, J.D. Hayler, M.R. Hickey, S. Hughes, M.E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F.J. Weiberth, Green Chem. 20 (2018) 5082–5103, https://doi.org/10.1039/C8GC01276H.
[24] D. Krištofíková, V. Modrocká, M. Mečiarová, R. Šebesta, ChemSusChem 13 (2020) 2828–2858, https://doi.org/10.1002/cssc.202000137.
[25] J. Liao, S. Zhang, Z. Wang, X. Song, D. Zhang, R. Kumar, J. Jin, P. Ren, H. You, F.-E. Chen, Green Synth. Catal. 1 (2020) 121–133, https://doi.org/10.1016/j.gresc.2020.08.001.
[26] C. Yue, Y. Yamashita, S. Kobayashi, Green Chem. 23 (2021) 1989–1994, https://doi.org/10.1039/D0GC04202A.
[27] M.T. Guo, A. Rotem, J.A. Heyman, D.A. Weitz, Lab Chip 12 (2012) 2146–2155, https://doi.org/10.1039/C2LC21147E.
[28] A. Günther, K.F. Jensen, Lab Chip 6 (2006) 1487–1503, https://doi.org/10.1039/B609851G.
[29] F.W.Y. Chiu, S. Stavrakis, Electrophoresis 40 (2019) 2860–2872, https://doi.org/10.1002/elps.201900222.
[30] S. Rossi, R. Porta, D. Brenna, A. Puglisi, M. Benaglia, Angew. Chem. 129 (2017) 4354–4358, https://doi.org/10.1002/ange.201612192.
[31] A. Puglisi, S. Rossi, Phys. Sci. Rev. 6 (2021) 20180099, https://doi.org/10.1515/psr-2018-0099.
[32] N. Sugisawa, H. Nakamura, S. Fuse, Catalysts 10 (2020) 1321, https://doi.org/10.3390/catal10111321.
[33] K. Ding, Z. Wang, Homochiral Metal–Organic Coordination Polymers for Heterogeneous Enantioselective Catalysis: Self-Supporting Strategy, in: Handb. Asymmetric Heterog. Catal., John Wiley & Sons, Ltd, 2008: pp. 323–355. https://doi.org/10.1002/9783527623013.ch9.
[34] T. Yu, Z. Ding, W. Nie, J. Jiao, H. Zhang, Q. Zhang, et al., Chem. Eur. J. 26 (26) (2020), https://doi.org/10.1002/chem.202082661.
[35] I.M. Mándity, S.B. Ötvös, F. Fülöp, ChemistryOpen 4 (2015) 212–223, https://doi.org/10.1002/open.201500018.
[36] F.E. Valera, M. Quaranta, A. Moran, J. Blacker, A. Armstrong, J.T. Cabral, et al., Angew. Chem. Int. Ed. 49 (2010) 2478–2485, https://doi.org/10.1002/anie.200906095.
[37] T. Chinnusamy, S. Yudha, M. Hager, P. Kreitmeier, O. Reiser, ChemSusChem. 5 (2012) 247–255. https://doi.org/10.1002/cssc.201100444.
[38] T. Yamamoto, O. Tonomura, A. Nagaki, J. Chem. Eng. Jpn. 53 (2020) 73–77, https://doi.org/10.1252/jcej.19we083.
[39] S. Newton, S.V. Ley, E.C. Arcé, D.M. Grainger, Adv. Synth. Catal. 354 (2012) 1805–1812, https://doi.org/10.1002/adsc.201200073.
[40] S. Balogh, G. Farkas, J. Madarász, Á. Szöllősy, J. Kovács, F. Darvas, L. Ürge, J. Bakos, Green Chem. 14 (4) (2012) 1146, https://doi.org/10.1039/c2gc16447g.
[41] C. de Bellefon, T. Lamouille, N. Pestre, F. Bornette, H. Pennemann, F. Neumann, V. Hessel, Catal. Today 110 (2005) 179–187, https://doi.org/10.1016/j.cattod.2005.09.002.
[42] P. Kluson, P. Stavarek, V. Penkavova, H. Vychodilova, S. Hejda, D. Vlcek, et al., Chem. Eng. Process. Process Intensif. 111 (2017) 57–66, https://doi.org/10.1016/j.cep.2016.11.004.
[43] P. Kluson, P. Stavarek, V. Penkavova, H. Vychodilova, S. Hejda, M. Bendova, Chem. Eng. Process. Process Intensif. 115 (2017) 39–45, https://doi.org/10.1016/j.cep.2017.02.002.
[44] U. Hintermair, T. Höfener, T. Pullmann, G. Franciò, W. Leitner, ChemCatChem 2 (2010) 150–154, https://doi.org/10.1002/cctc.200900261.
[45] A. Riisager, R. Fehrmann, M. Haumann, P. Wasserscheid, Eur. J. Inorg. Chem. 2006 (2006) 695–706, https://doi.org/10.1002/ejic.200500872.
[46] C.P. Mehnert, Chem. Eur. J. 11 (2005) 50–56, https://doi.org/10.1002/chem.200400683.
[47] S. Fritzsche, S. Ohla, P. Glaser, D.S. Giera, M. Sickert, C. Schneider, et al., Angew. Chem. Int. Ed. 50 (2011) 9467–9470, https://doi.org/10.1002/anie.201102331.
[48] M. Rueping, T. Bootwicha, E. Sugiono, Beilstein J. Org. Chem. 8 (2012) 300–307, https://doi.org/10.3762/bjoc.8.32.
[49] R. Porta, Stereoselective catalytic reactions under continuous flow conditions, (2017). https://doi.org/10.13130/R-PORTA_PHD2017-03-28.
[50] P. Kluson, P. Stavarek, V. Penkavova, H. Vychodilova, S. Hejda, N. Jaklova, P. Curinova, J. Flow Chem. 9 (2019) 221–230, https://doi.org/10.1007/s41981-019-00043-y.
[51] M.D. Johnson, S.A. May, J.R. Calvin, J. Remacle, J.R. Stout, W.D. Diseroad, N. Zaborenko, B.D. Haeberle, W.-M. Sun, M.T. Miller, J. Brennan, Org. Process Res. Dev. 16 (2012) 1017–1038, https://doi.org/10.1021/op200362h.
[52] M. Benaglia, A. Puglisi, R. Porta, F. Coccia, Curr. Organocatal. 2 (2015) 1-1. https://doi.org/10.2174/2213337202666150513002701.
[53] K. Sakeda, K. Wakabayashi, Y. Matsushita, T. Ichimura, T. Suzuki, T. Wada, et al., J. Photochem. Photobiol. Chem. 192 (2007) 166–171, https://doi.org/10.1016/j.jphotochem.2007.05.019.
[54] R.C.R. Wootton, R. Fortt, A.J. de Mello, Org. Process Res. Dev. 6 (2002) 187–189, https://doi.org/10.1021/op0155155.
[55] M.L. Abrams, J.Y. Buser, J.R. Calvin, M.D. Johnson, B.R. Jones, G. Lambertus, C.R. Landis, J.R. Martinelli, S.A. May, A.D. McFarland, J.R. Stout, Org. Process Res. Dev. 20 (2016) 901–910, https://doi.org/10.1021/acs.oprd.5b00406.
[56] K. Gilmore, D. Kopetzki, J. Weon Lee, Z. Horváth, D. Tyler McQuade, A. Seidel-Morgenstern, et al., Chem. Commun. 50 (2014) 12652–12655, https://doi.org/10.1039/C4CC05098C.
[57] D. Kopetzki, F. Lévesque, P.H. Seeberger, Chem. Eur. J. 19 (2013) 5450–5456, https://doi.org/10.1002/chem.201204558.
[58] J. Turconi, F. Griolet, R. Guevel, G. Oddon, R. Villa, A. Geatti, M. Hvala, K. Rossen, R. Göller, A. Burgard, Org. Process Res. Dev. 18 (2014) 417–422, https://doi.org/10.1021/op4003196.
[59] S. Hübner, U. Bentrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Küpper, K. Jähnisch, Org. Process Res. Dev. 13 (2009) 952–960, https://doi.org/10.1021/op9000669.
[60] A. Hartung, M.A. Keane, A. Kraft, J. Org. Chem. 72 (2007) 10235–10238, https://doi.org/10.1021/jo701758p.
[61] R. Porta, M. Benaglia, R. Annunziata, A. Puglisi, G. Celentano, Adv. Synth. Catal. 359 (2017) 2375–2382, https://doi.org/10.1002/adsc.201700376.
[62] W. Solodenko, G. Jas, U. Kunz, A. Kirschning, Synthesis 2007 (2007) 583–589, https://doi.org/10.1055/s-2007-965877.
[63] L. Osorio-Planes, C. Rodríguez-Escrich, M.A. Pericàs, Org. Lett. 14 (2012) 1816–1819, https://doi.org/10.1021/ol300415f.
[64] X.-F. Tang, J.-N. Zhao, Y.-F. Wu, Z.-H. Zheng, C.-F. Ma, Z.-Y. Yu, L. Yun, G.-Z. Liu, Q.-W. Meng, Synth. Commun. 50 (2020) 2478–2487, https://doi.org/10.1080/00397911.2020.1781183.
[65] J.C. Pastre, P.R.D. Murray, D.L. Browne, G.A. Brancaglion, R.S. Galaverna, R.A. Pilli, S.V. Ley, ACS Omega 5 (2020) 18472–18483, https://doi.org/10.1021/acsomega.0c02390.
[66] L. Clot-Almenara, C. Rodríguez-Escrich, L. Osorio-Planes, M.A. Pericàs, ACS Catal. 6 (2016) 7647–7651, https://doi.org/10.1021/acscatal.6b02621.
[67] S.B. Ötvös, M.A. Pericàs, C. Oliver Kappe, Chem. Sci. 10 (2019) 11141–11146, https://doi.org/10.1039/C9SC04752B.
[68] S. Rossi, M. Benaglia, A. Puglisi, C. Filippo, M. Maggini, J. Flow Chem. 5 (2015) 17–21, https://doi.org/10.1556/JFC-D-14-00030.
[69] M. Neumann, K. Zeitler, Org. Lett. 14 (2012) 2658–2661, https://doi.org/10.1021/ol3005529.
[70] Q. Wu, A. Xia, X. Lin, J. Mol. Catal. B Enzym. 54 (2008) 76–82, https://doi.org/10.1016/j.molcatb.2007.12.023.
[71] Z. Boros, P. Falus, M. Márkus, D. Weiser, M. Oláh, G. Hornyánszky, J. Nagy, L. Poppe, J. Mol. Catal. B Enzym. 85–86 (2013) 119–125, https://doi.org/10.1016/j.molcatb.2012.09.004.
[72] E. Sugiono, M. Rueping, Beilstein J. Org. Chem. 9 (2013) 2457–2462, https://doi.org/10.3762/bjoc.9.284.
[73] T. Hardwick, R. Cicala, T. Wirth, N. Ahmed, Sci. Rep. 10 (1) (2020), https://doi.org/10.1038/s41598-020-73957-6.
[74] K. Hashimoto, N. Kumagai, M. Shibasaki, Org. Lett. 16 (2014) 3496–3499, https://doi.org/10.1021/ol501432h.
[75] C. Palomo, M. Oiarbide, A. Laso, Eur. J. Org. Chem. 2007 (2007) 2561–2574, https://doi.org/10.1002/ejoc.200700021.
[76] A. Nonoyama, N. Kumagai, M. Shibasaki, Tetrahedron 73 (2017) 1517–1521, https://doi.org/10.1016/j.tet.2017.01.066.
[77] H.L. Carter, A.W. Connor, R. Hart, J. McCabe, A.C. McIntyre, A.E. McMillan, N.R. Monks, A.K. Mullen, T.O. Ronson, A. Steven, S. Tomasi, S.D. Yates, Chem. Eng. 4 (2019) 1658–1673, https://doi.org/10.1039/C9RE00118B.
[78] C. Jönsson, S. Lundgren, S.J. Haswell, C. Moberg, Tetrahedron 60 (2004) 10515–10520, https://doi.org/10.1016/j.tet.2004.08.080.
[79] G.M. Greenway, S.J. Haswell, D.O. Morgan, V. Skelton, P. Styring, Sens. Actuators B Chem. 63 (2000) 153–158, https://doi.org/10.1016/S0925-4005(00)00352-X.
[80] T. McCreedy, N.G. Wilson, Analyst 126 (2001) 21–23, https://doi.org/10.1039/B007223K.
[81] W. Shu, S.L. Buchwald, Angew. Chem. 124 (2012) 5451–5454, https://doi.org/10.1002/ange.201202221.
[82] A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, Tetrahedron Asymmetry. 15 (2004) 3233–3244, https://doi.org/10.1016/j.tetasy.2004.08.015.

[83] J. Morvan, T. McBride, I. Curbet, S. Colombel-Rouen, T. Roisnel, C. Crévisy, D.L. Browne, M. Mauduit, Angew. Chem. 133 (2021) 19837–19842, https://doi.org/10.1002/ange.202106410.
[84] B. Han, X.-H. He, Y.-Q. Liu, G. He, C. Peng, J.-L. Li, Chem. Soc. Rev. 50 (2021) 1522–1586, https://doi.org/10.1039/D0CS00196A.
[85] S.B. Ötvös, P. Llanes, M.A. Pericàs, C.O. Kappe, Org. Lett. 22 (2020) 8122–8126, https://doi.org/10.1021/acs.orglett.0c03100.
[86] A. Odedra, P.H. Seeberger, Angew. Chem. Int. Ed. 48 (2009) 2699–2702, https://doi.org/10.1002/anie.200804407.
[87] S.M. Opalka, A.R. Longstreet, D.T. McQuade, Beilstein J. Org. Chem. 7 (2011) 1671–1679, https://doi.org/10.3762/bjoc.7.197.
[88] International Flow Chemistry Equipment|Vapourtec Ltd, Vapourtec. (n.d.). https://www.vapourtec.com/ (accessed November 15, 2021).
[89] L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi, R. Luisi, J. Flow Chem. 3 (2013) 29–33, https://doi.org/10.1556/jfc-d-13-00003.
[90] C. Ayats, A.H. Henseler, M.A. Pericàs, ChemSusChem 5 (2012) 320–325, https://doi.org/10.1002/cssc.201100570.
[91] R. Pandey, R.V. Anand, ACS Omega 3 (2018) 13967–13976, https://doi.org/10.1021/acsomega.8b01971.
[92] M.W. Jann, Pharmacotherapy 20 (2000) 1–12, https://doi.org/10.1592/phco.20.1.1.34664.
[93] R. Eichhorn, Phys. Rev. Lett. 105 (2010) 034502, https://doi.org/10.1103/PhysRevLett.105.034502.
[94] A.C. Oliveira Fernandes, Micro Scale Reactor System Development with Integrated Advanced Sensor Technology: A Modular Approach to the Development of Microfluidic Screening Platforms, Technical University of Denmark, Kgs. Lyngby, 2017.
[95] P. Schulze, M. Ludwig, F. Kohler, D. Belder, Anal. Chem. 77 (2005) 1325–1329, https://doi.org/10.1021/ac048596m.
[96] P. Gruber, F. Carvalho, M.P.C. Marques, B. O'Sullivan, F. Subrizi, D. Dobrijevic, J. Ward, H.C. Hailes, P. Fernandes, R. Wohlgemuth, F. Baganz, N. Szita, Biotechnol. Bioeng. 115 (2018) 586–596, https://doi.org/10.1002/bit.26470.
[97] L.-H. Du, J.-H. Shen, Z. Dong, N.-N. Zhou, B.-Z. Cheng, Z.-M. Ou, X.-P. Luo, RSC Adv. 8 (2018) 12614–12618, https://doi.org/10.1039/C8RA01030G.
[98] E.J.S. Brás, C. Domingues, V. Chu, P. Fernandes, J.P. Conde, J. Biotechnol. 323 (2020) 24–32, https://doi.org/10.1016/j.jbiotec.2020.07.016.
[99] G. Schneider, Nat. Rev. Drug Discov. 17 (2018) 97–113, https://doi.org/10.1038/nrd.2017.232.
[100] P.D. Santis, L.-E. Meyer, S. Kara, Chem. Eng. 5 (2020) 2155–2184, https://doi.org/10.1039/D0RE00335B.
[101] D.A. Nicewicz, D.W.C. MacMillan, Science. 322 (5898) (2008) 77–80, https://doi.org/10.1126/science.1161976.
[102] F. Medici, S. Resta, P. Presenti, L. Caruso, A. Puglisi, L. Raimondi, S. Rossi, M. Benaglia, Eur. J. Org. Chem. 2021 (2021) 4521–4524, https://doi.org/10.1002/ejoc.202100397.
[103] K. Terao, Y. Nishiyama, S. Aida, H. Tanimoto, T. Morimoto, K. Kakiuchi, J. Photochem. Photobiol. Chem. 242 (2012) 13–19, https://doi.org/10.1016/j.jphotochem.2012.05.021.
[104] H. Maeda, H. Mukae, K. Mizuno, Chem. Lett. 34 (2005) 66–67, https://doi.org/10.1246/cl.2005.66.
[105] A. Vasudevan, C. Villamil, J. Trumbull, J. Olson, D. Sutherland, J. Pan, S. Djuric, Tetrahedron Lett. 51 (2010) 4007–4009, https://doi.org/10.1016/j.tetlet.2010.05.119.
[106] T. Horie, M. Sumino, T. Tanaka, Y. Matsushita, T. Ichimura, J. Yoshida, Org. Process Res. Dev. 14 (2010) 405–410, https://doi.org/10.1021/op900306z.
[107] M. Nettekoven, B. Püllmann, R.E. Martin, D. Wechsler, Tetrahedron Lett. 53 (2012) 1363–1366, https://doi.org/10.1016/j.tetlet.2012.01.010.
[108] X.-J. Wei, W. Boon, V. Hessel, T. Noël, ACS Catal. 7 (2017) 7136–7140, https://doi.org/10.1021/acscatal.7b03019.
[109] K. Lisiecki, Z. Czarnocki, Org. Lett. 20 (2018) 605–607, https://doi.org/10.1021/acs.orglett.7b03974.
[110] T. Chatterjee, N. Iqbal, Y. You, E.J. Cho, Acc. Chem. Res. 49 (2016) 2284–2294, https://doi.org/10.1021/acs.accounts.6b00248.
[111] D. Cambié, C. Bottecchia, N.J.W. Straathof, V. Hessel, T. Noël, Chem. Rev. 116 (2016) 10276–10341, https://doi.org/10.1021/acs.chemrev.5b00707.
[112] T. Noël, Y. Su, V. Hessel, Beyond organometallic flow chemistry: the principles behind the use of continuous-flow reactors for synthesis, in: T. Noël (Ed.), Organomet. Flow Chem., Springer International Publishing, Cham, 2016: pp. 1–41. https://doi.org/10.1007/3418_2015_152.
[113] S.-C. Hung, M.M.L. Zulueta, Glycochemical Synthesis: Strategies and Applications, John Wiley & Sons, 2016.
[114] H. Koo, H.Y. Kim, K. Oh, Org. Chem. Front. 6 (2019) 1868–1872, https://doi.org/10.1039/C9QO00217K.
[115] Y. Gao, Y. Luo, J. Qin, B. Lin, Electrophoresis 29 (2008) 1918–1923, https://doi.org/10.1002/elps.200700384.
[116] P. Mikuš, K. Maráková, Electrophoresis 30 (2009) 2773–2802, https://doi.org/10.1002/elps.200900173.
[117] S. Nagl, P. Schulze, S. Ohla, R. Beyreiss, L. Gitlin, D. Belder, Anal. Chem. 83 (2011) 3232–3238, https://doi.org/10.1021/ac200150w.
[118] B.P. Mason, K.E. Price, J.L. Steinbacher, A.R. Bogdan, D.T. McQuade, Chem. Rev. 107 (2007) 2300–2318, https://doi.org/10.1021/cr050944c.
[119] W. Ehrfeld, V. Hessel, H. Löwe, Microreactors: New Technology for Modern Chemistry, Wiley-VCH Verlag, Weinheim, 2000.
[120] X.Y. Gong, D. Dobrunz, M. Kümin, M. Wiesner, J.D. Revell, H. Wennemers, P.C. Hauser, J. Sep. Sci. 31 (2008) 565–573, https://doi.org/10.1002/jssc.200700461.
[121] M.A. Schwarz, P.C. Hauser, Anal. Chem. 75 (2003) 4691–4695, https://doi.org/10.1021/ac030148b.
[122] S. Götz, U. Karst, Anal. Bioanal. Chem. 387 (2007) 183–192, https://doi.org/10.1007/s00216-006-0820-8.
[123] N. Piehl, M. Ludwig, D. Belder, Electrophoresis 25 (2004) 3848–3852, https://doi.org/10.1002/elps.200406028.
[124] Y. Huang, M. Shi, S. Zhao, J. Sep. Sci. 32 (2009) 3001–3006, https://doi.org/10.1002/jssc.200900026.
[125] B.Y. Kim, J. Yang, M. Gong, B.R. Flachsbart, M.A. Shannon, P.W. Bohn, J.V. Sweedler, Anal. Chem. 81 (2009) 2715–2722, https://doi.org/10.1021/ac802630p.
[126] H.-F. Li, H. Zeng, Z. Chen, J.-M. Lin, Electrophoresis 30 (2009) 1022–1029, https://doi.org/10.1002/elps.200800359.
[127] K.W. Ro, J.H. Hahn, Electrophoresis 26 (2005) 4767–4773, https://doi.org/10.1002/elps.200500370.
[128] J. Aksorn, S. Teepoo, Talanta 207 (2020) 120302, https://doi.org/10.1016/j.talanta.2019.120302.
[129] E.L. Rossini, M.I. Milani, E. Carrilho, L. Pezza, H.R. Pezza, Anal. Chim. Acta 997 (2018) 16–23, https://doi.org/10.1016/j.aca.2017.10.018.
[130] J. Hu, S. Wang, L. Wang, F. Li, B. Pingguan-Murphy, T.J. Lu, F. Xu, Biosens. Bioelectron. 54 (2014) 585–597, https://doi.org/10.1016/j.bios.2013.10.075.
[131] T. Akyazi, L. Basabe-Desmonts, F. Benito-Lopez, Anal. Chim. Acta 1001 (2018) 1–17, https://doi.org/10.1016/j.aca.2017.11.010.
[132] A.T. Singh, D. Lantigua, A. Meka, S. Taing, M. Pandher, G. Camci-Unal, Sensors 18 (2018) 2838, https://doi.org/10.3390/s18092838.
[133] S.A. Zaidi, Biosens. Bioelectron. 94 (2017) 714–718, https://doi.org/10.1016/j.bios.2017.03.069.
[134] A.M. Zeid, J.J.M. Nasr, F. Belal, M. Walash, N. Kaji, Y. Baba, Microchem. J. 160 (2021) 105770, https://doi.org/10.1016/j.microc.2020.105770.
[135] P. Cui, S. Wang, J. Pharm. Anal. 9 (2019) 238–247, https://doi.org/10.1016/j.jpha.2018.12.001.
[136] Y. Li, C. Liu, X. Bai, F. Tian, G. Hu, J. Sun, Angew. Chem. Int. Ed. 59 (2020) 3486–3490, https://doi.org/10.1002/anie.201913882.
[137] Y. Yu, Q. Wang, C. Wang, L. Shang, Eng. Regen. 2 (2021) 96–104, https://doi.org/10.1016/j.engreg.2021.08.003.
[138] Nanomotor-Derived Porous Biomedical Particles from Droplet Microfluidics - Liu - 2022 - Advanced Science - Wiley Online Library, (n.d.). https://onlinelibrary.wiley.com/doi/full/10.1002/advs.202104272 (accessed August 15, 2022).
[139] L. Sun, F. Bian, Y. Wang, Y. Wang, X. Zhang, Y. Zhao, Proc. Natl. Acad. Sci. 117 (2020) 4527–4532, https://doi.org/10.1073/pnas.1921281117.
[140] Y. Yu, J. Guo, B. Ma, D. Zhang, Y. Zhao, Sci. Bull. 65 (2020) 1752–1759, https://doi.org/10.1016/j.scib.2020.06.002.
[141] A.M. Skelley, J.R. Scherer, A.D. Aubrey, W.H. Grover, R.H.C. Ivester, P. Ehrenfreund, F.J. Grunthaner, J.L. Bada, R.A. Mathies, Proc. Natl. Acad. Sci. 102 (2005) 1041–1046, https://doi.org/10.1073/pnas.0406798102.
[142] J.L. Bada, M.A. Sephton, P. Ehrenfreund, R.A. Mathies, A.M. Skelley, F.J. Grunthaner, A.P. Zent, R.C. Quinn, J.-L. Josset, F. Robert, O. Botta, D.P. Glavin, Astron. Geophys. 46 (6) (2005) 6.26–6.27, https://doi.org/10.1111/j.1468-4004.2005.46626.x.
[143] H. Westphal, R. Warias, H. Becker, M. Spanka, D. Ragno, R. Gläser, C. Schneider, A. Massi, D. Belder, ChemCatChem 13 (2021) 5089–5096, https://doi.org/10.1002/cctc.202101148.
[144] A.-C. Bédard, A. Adamo, K.C. Aroh, M.G. Russell, A.A. Bedermann, J. Torosian, B. Yue, K.F. Jensen, T.F. Jamison, Science 361 (2018) 1220–1225, https://doi.org/10.1126/science.aat0650.
[145] Y. Gao, Z. Shen, H. Wang, Z. Dai, B. Lin, Electrophoresis 26 (2005) 4774–4779, https://doi.org/10.1002/elps.200500283.