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Flow Chemistry in Drug Discovery: Challenges and Opportunities

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Contents

Abstract The spectacular development of new chemical reactions and processes under continuous flow has attracted particularly the attention of the pharmaceutical industry. The chance to carry out complex chemistry, the sustainability of the process, and the possibility of adapting new technologies to this technique have paved the way to the integration of flow chemistry into drug discovery. Thus, this book chapter covers essential aspects of flow chemistry and how a variety of technologies and catalytic methods can be used to enable new chemical space in drug discovery programs.

Keywords Drug discovery, Enabling technology, Flow chemistry, Integrated platforms, Novel chemical space

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1 Introduction

1.1 Introduction to Flow Chemistry

During the last 20 years, flow chemistry has been positioned as a very effective technology in the chemistry community and has gained the attention of researchers from both academia and pharma companies, which have both contributed vast number of publications covered by peer-reviewed articles in journals and in patents. Among these contributions, new synthetic chemistry approaches and important improvements of known batch procedures have been reported [1–3]. However, this technology has not been yet implemented in every synthetic laboratory as it is a disruptive technology and therefore very different from the traditional batch approach all chemists have been trained to perform.

The interest in flow chemistry resides on the capability to conduct chemical transformations in a continuous way by constant pumping of one or more solutions containing the reagents. A mixing point merges the solutions, triggering the reaction, which will continue through the channel where the stream is subjected to the required conditions (i.e., thermal, microwave, light, current, etc.). Following that, the resulting solution is collected in a flask ready for quenching or to be mixed with another solution in order to achieve multistep sequential reactions. In contrast to the batch mode [4, 5], the transformation takes place spatially along a tube, so their dimensions as well as the flow rate determine the residence time.

A great number of variables can be modified in continuous flow to control the reaction outcome, like temperature, reaction time, concentration, or energy source. The accurate control of these parameters usually provides more selective transformations, as side reactions can be avoided. As a result, better yields and purities are obtained. Continuous flow chemistry can also be used to control reactions in terms of extreme reactivity or safety; for instance, when handling hazardous reagents, unstable intermediates, or non-safe or toxic gases. Thus, risks associated with the scale-up of these transformations are reduced or completely avoided because the potentially dangerous species are generated in a small reactor size and reacted in situ (make and use concept). Furthermore, the elimination of headspace in comparison with the batch mode favors the control of low-boiling point solvents and reagents under pressurized flow reactors.

Another important feature is the control of highly exothermic self-accelerated reactions (“runaway” reactions). The better heat and mix transfer processes due to the high surface area-to-volume ratio allow for these transformations to be carried out under precise conditions, which are unattainable by traditional batch chemistry. Likewise, high-pressure reactions can be performed, thereby speeding up reaction times. Cryogenic conditions are commonly avoided as the unstable species, for instance organometallic intermediates, are present in the reaction line only for a few seconds. Thus, continuous flow serves as a “filter of safety” when a problematic reaction must be carried out, bringing back to the bench disregarded reactions commonly known as “forgotten chemistries.”

These facts overcome important limitations found in traditional batch approaches showcasing important benefits of the technology [6], and expanding the chemistry space available to the chemists (Fig. 1) [7], for instance, extremely fast reactions [8] that can take place in less than 1 s ("flash chemistry"). However, there are some common limitations that must be considered. One of the main concerns is the clogging of the flow system, which can happen at any point in the flow unit. This can be due to the accumulation of particles on certain parts of the channels, crystallization processes, chemical reaction fouling, or corrosion. In the last two cases, the problem can be solved using a compatible material. For the first two cases, a change in the solvent media, droplet reaction techniques, or an in-situ cleaning by using sonication are common approximations to overcome the formation of solids. If these approaches are not enough, a novel engineering design should be considered in order to create an appropriate flow unit. Pumping systems are crucial as they are the ones to keep the system continuously moving. Piston pumps offer the advantage that they can handle higher pressures; however, pulsation problems may lead to uneven mixing of reagent solutions. Syringe and peristaltic pumps can overcome this issue but only work at lower pressure. All in all, most of the common issues found in continuous flow are well-known and can be overcome by customizing the reactor according to reaction needs.

1.2 Flow Chemistry Setup

One of the most important benefits of continuous flow chemistry includes the possibility of adapting the reactor unit to the requirements of the reaction. As several pieces of equipment can be interchanged or replaced at different points, flow chemistry is a toolkit, which provides great versatility in terms of setup. Most parts of the flow system are connected by *tubing* whose composition depends on the pressure and nature of the reagents. For low and medium pressures (<30 bar), inert perfluorinated polymers such as PTFE, PEEK, PFA, and FEP are suitable. Instead, stainless steel or Hastelloy are common alternatives when high temperature and pressure are needed. A variety of pieces (nuts, ferrules) are also used to attach and fix the tubing properly (Fig. 2).

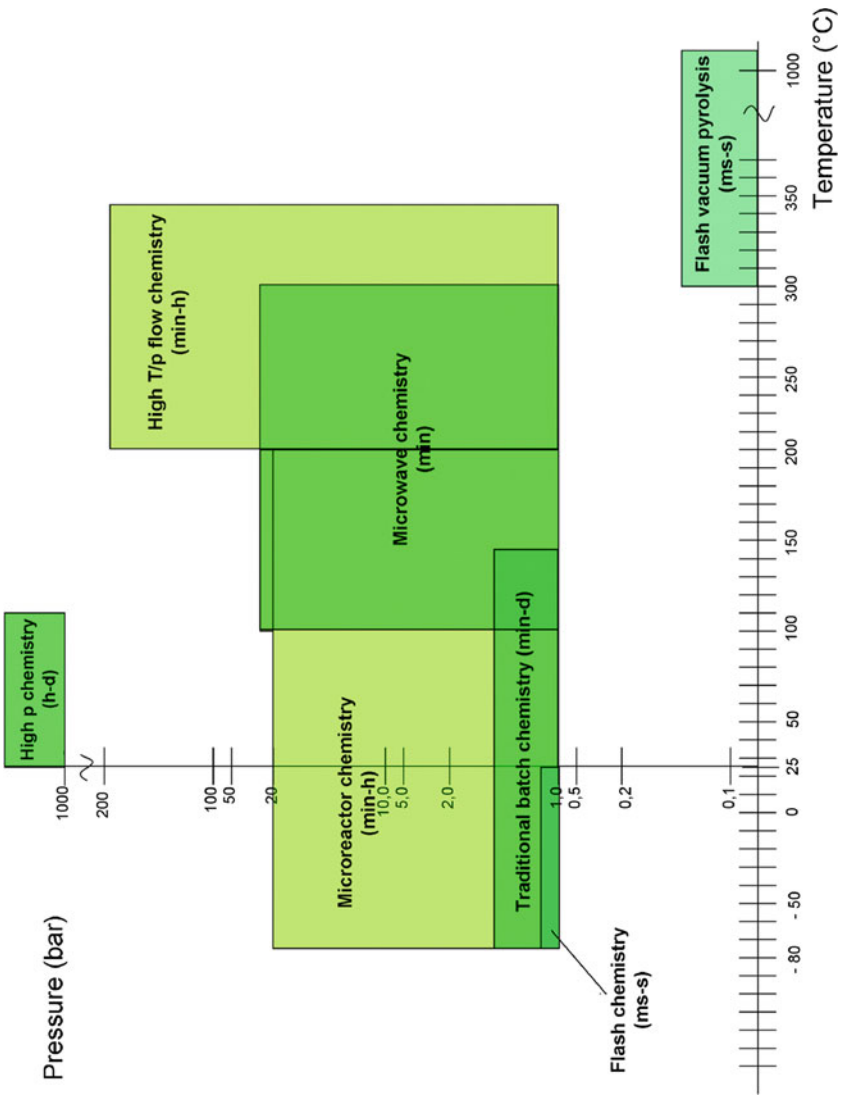

Fig. 1 Expansion of reaction parameters provided by flow chemistry. Reproduced with permission from Ref. [7]

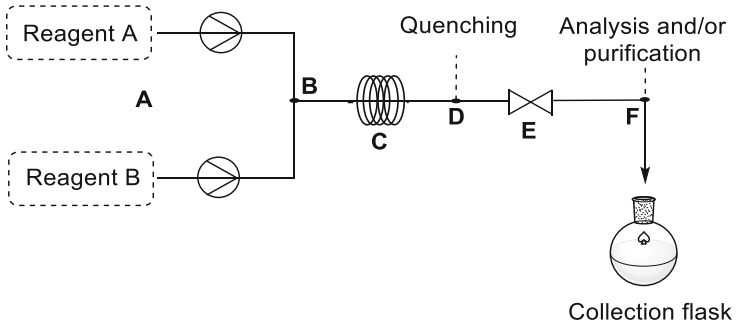

Fig. 2 General scheme of a flow system

(a) Very likely, *reagents delivery* is the first item to consider and a key element to run reactions in flow. Most commonly, reagents are introduced as solutions from a liquid delivery system in a sustained way to achieve the right mixing in the subsequent unit. To achieve that, three types of pumps can be envisioned depending on the flow rate, the nature of the solution, and the system pressure. Syringe pumps are the simplest and adequate for low flow rates, although they are limited to small-scale reactions and low pressurized systems. HPLC pumps work at high pressure, although pulsation issues and uneven delivery of solutions in terms of time can be observed specially at low flow rates preventing appropriate mixing. Recently, peristaltic pumps have appeared on the scene as a new solution using a central rotor that is constantly pushing the liquid through a flexible tube [9]. Deliveries at low flow rate are improved, but they can only work at limited system pressures. In the case of using gases, a gas bottle can be installed to the flow system by using a mass flow controller (MFC), which can control the amount of gas introduced into the reaction [10].

(b) The reaction starts at the *mixing point* where all reagents merge. Usually T or Y-shape connections are used to mix two or more streams before being introduced into the reaction unit. If a more efficient mixing is required, other special alternatives with optimal mixtures can be considered [11–13]. For instance, multilaminar mixers that separate both channels to micro streams to enhance the surface area and thereby facilitate diffusion [14].

In case of gas–liquid mixing, phases can be separated into two convergent lines separated by a gas permeable membrane: the "tube-in-tube" strategy developed by Ley and coworkers (Fig. 3). The gaseous reagent from the outer tube goes through the permeable membrane into the inlet tube to achieve the desired transformation [15].

(c) Once reagents are properly mixed the reaction continues in the *reactor unit*. Depending on the nature of the transformation, different reactors can be used. It usually consists of a coil, a chip, or a packed-bed reactor (Fig. 4). *Coils* are usually an easy access alternative as they are made up of a tube, which has been

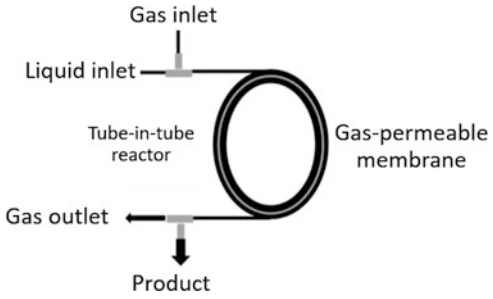

Fig. 3 General scheme of a tube-in-tube reactor

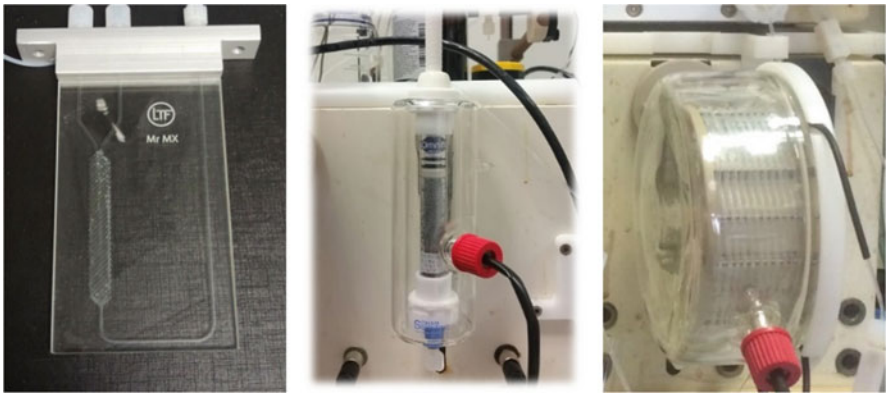

Fig. 4 Flow reactors from left to right: chip, packed-bed reactor, coil

wrapped around a circular support, and the material will depend on reagents and reaction conditions that will be used. *Chips* have been widely used in microfluidic thermal reactions due to the high surface area-to-volume ratio. Depending on the type of chemistry that is going to be developed, different materials can be used in these systems (e.g., glass, silicon, stainless steel). For instance, in photochemical reactions, the material needs to be permeable to light (glass). Recently, 3D printing technology has enabled the production of chips on-demand in order to adapt these devices into the flow unit [16, 17]. *Packed-bed reactors* are the best alternative when solid reagents or catalysts need to be used. It consists of a thicker tube that will contain the solid, and the other reagents as solution will flow through it. In the case of catalysts, they are usually immobilized [18].

Attending to electrochemical devices [19, 20], both cathode and anode electrodes are in close contact with the flow channel. While divided cell microreactors use a membrane to separate the cathode and anode channels, a sandwich disposition of the electrodes with the flow channel is commonly found in undivided cell microreactors (Fig. 5).

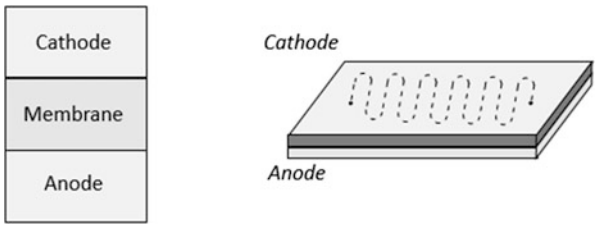

Fig. 5 Schemes of flow electrochemical reactors

One of the main drawbacks of flow chemistry is in-line precipitation of solids and the subsequent blockage of the system. Different solutions have been envisaged for this issue, i.e. the use of spiral tubing in combination with ultrasound irradiation [21] or the use of agitated cell reactors (ACR), which promote an efficient mixture through a lateral shaking of the reactor, thereby avoiding the precipitation of solids and preventing the separation of phases [22].

(d) Flow reactions are shut down at the *quenching point*. This can be done by a chemical agent, adding a quencher with an extra line containing or collecting over a quenching solution, depending on different parameters, such as solid formation or exothermicity. Another possibility is removing the effector; for instance: cooling the line in case of a thermal reaction, getting the solution out of the irradiation zone in the case of photochemistry or out of the electrical area in case of electrochemistry.

(e) *Back-pressure regulators* (BPR) are valves that maintain a constant pressure through the flow system. They are mainly used when gaseous reagents or intermediates participate in the transformation to keep the gas in solution and reduce possible residence time deviations. This gas can come also from the solvent when reactions are heated above their boiling point. Two kinds of devices can be found: either fixed when the regulator operates at predefined pressure or variable, which is able to adjust the system pressure to reaction needs.

Common aspects of flow chemistry equipment have been discussed above to provide a general idea of the different parts of the flow unit and show the versatility of the technology and how to adapt them to reaction requirements. In addition, the modularity of the technology affords new opportunities for attaching analytical equipment to follow the chemical transformation. It is possible to install different analytical techniques (LCMS, GC, NMR, etc.) to have a direct read out of the transformation [23–25]. A splitter device can sample the flow periodically and transfer them to the analytical equipment or spectroscopic methods can be attached in-line to collect the information as the reaction flows through. These techniques are non-destructive and allow real-time analysis of the reaction. Furthermore, purification techniques can also be added at the end of the flow unit, such as liquid–liquid separation, where the aqueous and organic layers are separated through a hydrophobic membrane [26]. Other alternatives are the use of scavengers to trap impurities at

some points of the flow unit [27] or gas separators if the previously mentioned tube-in-tube reactor is connected to a vacuum line.

All the different modules described in this section can be interconnected and automated to accelerate the optimization of reaction parameters, exploration of the chemical space, and overcome chemist's routine operations. In other words, accelerating the synthesis of organic molecules in a multistep way [28].

1.3 Types of Transformations

A wide variety of transformations involving homo- or heterogeneous reactions can be carried out in continuous flow. In heterogeneous *gas–liquid reactions*, a large excess of the gas counterpart is necessary to favor the miscibility in the organic solvent. Microreactors are a convenient alternative as they eliminate the common headspaces found in batch chemistry, thereby increasing the interfacial area between the gas and liquid phases. Thus, for high pressures, manipulation of non-safe gases or scaling-up a reaction, flow chemistry provides a very convenient approach. Another type of heterogeneous transformations for which flow chemistry provides a better interaction of phases are *solid–liquid reactions* [29]. The solid material is immobilized in a packed-bed reactor and the liquid phase is pumped through it. In this manner, the large excess of solids remains in the flow system thereby allowing for subsequent reactions and facilitating work-up processes. If a gaseous reagent is participating in the process a *gas–liquid–solid reaction* is assumed, hydrogenation being the most common example [30].

Regarding homogeneous transformations in flow chemistry, the reactivity in *liquid–liquid reactions* is also enhanced due to the small reactor size. The challenge remains in maintaining a constant distribution of the fluid without affecting the residence times [31]. In this regard, flow rates should be carefully controlled to increase mass transfer efficiency.

Beyond conventional considerations of flow chemistry, the combination with photo-, mechano-, and electrochemistry is revolutionizing traditional chemistry approaches [32, 33].

2 The Drug Discovery Process in Pharma

Pharmaceutical companies invest large amounts of money and time to launch a new drug on the market, this take on average more than 12 years with an estimated cost of more than 1,000 million euros [34]. This process entails the preparation of a vast number of molecules, which therefore makes the drug discovery process both long and tedious. Moreover, drug discovery is a highly competitive field as different companies are working to achieve the best drug candidate for a limited number of protein targets or diseases [35, 36].

Fig. 6 Stages in the drug discovery process

The drug discovery process is divided into several stages from initial target identification to the selection of the clinical candidate (Fig. 6).

- Target validation-Hit identification

  The first step of drug discovery is the identification and validation of a protein target, which is linked to a potential treatment of a certain disease. Then a first set of binders, also known as initial *hits*, needs to be identified as a starting point in order to develop the chemistry part of the program. Several strategies can be found to meet this end: high throughput screening (HTS) [37], chemical genomics [38], virtual screening [39], and fragment-based screening [40] (by using X-ray diffraction analysis or NMR techniques). The combination of these strategies with the most appropriate assays is necessary to select the best scaffolds to go through the next stage [41].
- Hit to Lead (HtL)

  Once those hits are identified, which are usually molecules with micromolar activities at the target protein, further modifications of the structure are envisioned and carried out to establish structure–activity relationships (SAR) [42]. In parallel, their physicochemical properties are profiled to build the corresponding structure–property relationships (SPR). Typically, iterative design-synthesize-test cycles are used to evolve the chemistry program. First designing the molecules to be prepared, then they are synthetized and screened biologically. Data are collected and used in the next generation of molecules to be made. This iterative approach allows for both the improvement of binding affinity and pharmacokinetic (PK) properties of the molecules prepared. Optimally, compounds with nanomolar activity as well as suitable selectivity and pharmacokinetic profile (*leads*) are selected for subsequent test in in vivo models.
- Lead Optimization (LO)

  At this stage, the optimization is focused on improving selectivity and ADMET properties (Absorption, Distribution, Metabolism, Excretion, Toxicity) in vivo of the compounds to establish their Pharmacokinetic/Pharmacodynamic relationships (PK/PD). This ratio will define the potential therapeutic window of suitable candidates that can be subjected to human testing.
- Late Lead Optimization (LLO)

  The compounds with a suitable therapeutic window are prepared at multigram amounts to complete all preclinical studies needed in order to support their proposal as a new drug for human use to the regulatory agencies.

  Based on the different stages of the drug discovery program, the synthesis of molecules varies from the single milligram scale in HtL to 50-gram scale for the selected candidate. The generation of a wide variety of molecular entities at different scales is a key feature in drug discovery, for this reason, the

development of new technologies that can accelerate this process is therefore highly desirable.

3 Flow Chemistry as a Tool to Improve Drug Discovery

As we have seen so far, drug discovery is a high-cost process that is also associated with various risks that may end the course before delivering a drug candidate. Pharma companies are looking to diverse alternatives to reduce cycle times and attrition rates by accelerating the fast generation of the required data to stop unsustainable programs and focus efforts to progress the most promising ones.

Flow chemistry can be one of these alternatives. For instance, streamlining the preparation of a *Hit* in gram amounts to be tested in vivo without requiring a time-consuming re-designing of its synthesis. This simple advantage may reduce production time from weeks or months to just a few days. For the aforementioned reasons, flow reactor technology is continuously growing as a discovery technology and is being implemented in pharmaceutical companies [43–48] notwithstanding the fact it was initially primarily used in academia for the synthesis of Active Pharmaceutical Ingredient (API) manufacturing [49].

Flow has also been associated with the preparation of challenging molecules. For instance, it has proved its value as a tool to introduce C(sp^3) fragments and escape from flatland [50]. This abovementioned point is important in order to explore different dispositions of donor, acceptor, lipophilic or hydrophilic groups so as to find the most preferred interaction with the target protein, thereby improving their binding properties [51, 52].

3.1 Green Components of Flow Chemistry

Despite the well-established methodologies to prepare drug candidates [53–55], there is a recent tendency to develop chemical transformations from a more sustainable point of view that have indeed made the introduction of continuous flow very interesting from a green perspective [56–58]. Interestingly, the chances of combining continuous flow with catalytic methodologies or novel synthetic approaches (e.g., photochemistry, electrochemistry, ultrasounds, microwave irradiation, biomass reagents) open the doors to explore chemical space difficult-to-achieve by traditional methods.

Ultrasound irradiation has been widely explored in organic synthesis not only to favor heterogeneous processes, but also to induce new chemical reactivities [59]. This energy source facilitates the development of faster procedures under mild reaction conditions. Thus, its integration into continuous flow is very convenient to avoid clogging in microreactors, thereby broadening their applicability in drug discovery. However, scaling of these reactors is still a work in progress, as

problems associated with uniform irradiation and low energy transfer efficiencies need to be overcome [60].

The ability of microwave heating (MW) to shorten reaction times allows the preparation of biologically active compounds in a much faster way, reducing cycle times in drug discovery. These applications have been widely described in literature [61, 62] and are particularly useful in many cross-coupling reactions involving transition metals as they usually have long reaction times. Despite the advantages shown in batch mode, there are some drawbacks concerning the scalability of such reactions mainly due to the limited penetration of the microwave irradiation. To overcome this, continuous flow setups have been investigated to exploit this technique in the drug discovery process, furnishing interesting transformations in organic synthesis [63, 64].

In addition to the previously mentioned methodologies, flow chemistry has also been considered for the synthesis of high-valued chemicals from renewable biomass [65]. This promising approach represents a sustainable alternative to limited fossil sources, as it is considered a virtually infinitive reservoir that can be used for the production of organic derivatives such as polyols, furanoids, or carboxylic acids. In this regard, microreactors provide better heat and mass transfer processes, which are mostly required for these multiphasic systems [66].

3.2 Diversity Oriented Synthesis (DOS) in Flow

The development of technologies, which can support the rapid generation of chemical entities, is a common goal to reduce cycle times and accelerate the finding of the potential clinical candidate. Thus, sequential synthesis is perfectly compatible with flow reactors and enables the preparation of chemical libraries for rapid screening vs biological targets. This is highly interesting for the pharmaceutical industry as it can be linked with automated compound synthesis. Thus, various reagents can be loaded into the flow system and the products are collected separately after multiple possible combinative processes. By using segmented flow, different micro-reactions are flowing continuously between an inert solvent, which separates the reaction droplets [67]. A subsequent analysis and purification of each reaction allows for the preparation of a diverse set of chemical entities.

Diversity Oriented Synthesis has appeared in recent years as an interesting tool to access novel chemical space [68]. It aims to generate a functionally diverse library based on a collection of compounds with known molecular structures of high complexities, which can interact with different biological targets [69]. In this manner, substantial chemical space can be covered by considering different small-molecular shapes and obtaining a diverse set of compounds with varying biological activities [70, 71]. For instance, unstable organometallic reagents can be prepared and reacted in situ with a variety of simple starting materials providing a set of diverse chemical analogues (Fig. 7). The generation of highly energetic intermediates can also be controlled in flow and it has been used to perform reactions in less

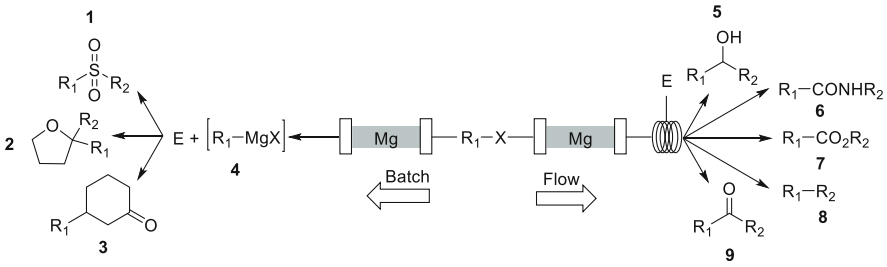

Fig. 7 Preparation of Grignard reagents in flow and reaction with electrophiles

than a second. This concept named as "flash chemistry" allows to carry out chemical transformations, which are unattainable by other methodologies [72].

3.3 Catalysis in Flow

The pharmaceutical industry is constantly requiring new chemical transformations to synthetize bioactive molecules in drug discovery programs. To achieve that end, new catalytic methodologies under flow conditions provide an opportunity to enable difficult chemistries or to improve well-established methodologies [73, 74].

3.3.1 Hetero- and Homogeneous Catalysis

Transition metal catalyzed transformations have clearly revolutionized synthetic chemistry. A convenient application of this synthetic field under continuous flow is the use of transition metal complexes as supported catalysts [29], by allowing the reuse of the catalyst in subsequent reactions. Among the variety of transition metals used for these purposes (gold, zirconium, iron), palladium-complexes have been most common due to their numerous synthetic applications, such as the Sukuki-Miyaura, Sonogashira, Heck or Negishi cross-couplings. These complexes have been immobilized on various solid supports, among which silica proved to be one of the most effective ones (Fig. 8) [75]. In addition, heterogeneous reactions can be carried out in flow with solid metal sources to prepare organometallic agents on-demand. For instance, Grignard reagents and organozinc species are synthetized as unstable intermediates by flowing the corresponding halo-derivative to a previously activated packed-metal [76].

The limitations associated with the applicability of supported catalysts, such as a possible leaching found in some palladium-catalyzed transformations [77], can be overcome under homogeneous catalysis [78], which present important advantages such as a better control of the catalyst loading. Although this approach is less friendly for the environment as recycling of the catalyst can be more challenging, some efforts have been done to overcome this issue. For instance, separation by

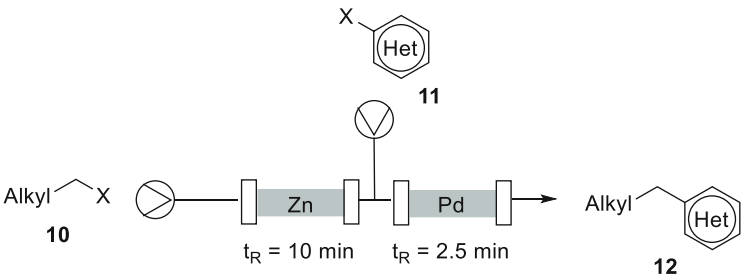

Fig. 8 Zinc insertion-Negishi coupling to introduce C(sp^3) motifs

liquid–liquid extraction, nanofiltration and recirculation were described as alternatives to reuse expensive and often toxic catalytic metals [79].

Organocatalysis and enantioselective catalysis have also been performed in flow using either homogeneous or heterogeneous catalyst to generate scaffolds in an enantioselective manner [80–82].

3.3.2 Biocatalysis

Biocatalytic methods under continuous flow have been developed to improve the interaction between the enzyme and the organic substrate [83]. Immobilizing the enzyme on solid supports and flowing the substrates through this bed allows an increase in the surface area thereby improving the efficiency and selectivity along with an increase of the overall turnover number (TON) of the protein. This is particularly useful because some enzymes are only available in small quantities and they can be recycled avoiding purification steps.

3.3.3 Photocatalysis

During the last years, photoredox catalysis has been positioned as an outstanding alternative for the synthesis of organic molecules [84, 85]. Despite the wide range of useful transformations reported in batch chemistry until now, some common limitations associated with the use of light are yet unsolved. For instance, scalability processes are limited due to the attenuation of light as a function of distance (Bouguer-Lambert-Beer law), which reduces the penetration of photons over the entire reaction mixture. On the other hand, over-irradiation can cause the formation of side products that complicates purification processes. These issues associated with the use of photochemistry in batch mode can be overcome with continuous flow photochemical microreactors that ensure a homogeneous and effective irradiation. In this manner, more selective transformations and an acceleration of the reaction times are achieved [86–90]. In this way, high value building blocks have been synthetized

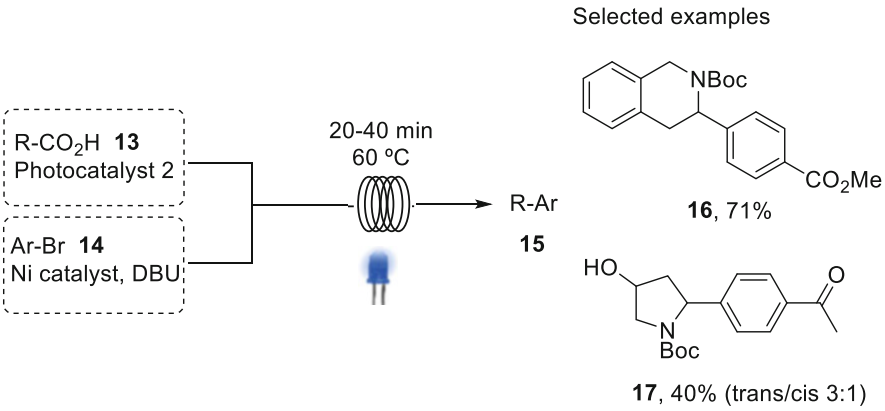

Fig. 9 Example of dual photoredox and nickel catalysis in flow

in drug discovery programs broadening chemical space, which cannot be obtained otherwise (Fig. 9) [91–93].

3.4 Electrochemistry in Flow

Electrochemistry has also been merged with organic synthesis as a disruptive technology for the development of sustainable methodologies [94–98]. The chance to carry out an organic reaction by using an electric current as a cheap reagent generates a greener alternative to strong oxidizing or reducing agents, by increasing safety and a smaller footprint. These transformations start with a mass transfer reaction of the substrate from the solution to the electrode surface. Then, the substrate is adsorbed onto the electrode and an electron transfer process occurs thereafter generating the product. Finally, the product is desorbed from the electrode and diffuses back to the liquid phase.

Electrochemical reactions are typically regarded as heterogeneous transformations in which both mass and charge transfer regimes must be considered. As a consequence, vigorous stirring is required in batch mode because only molecules in close contact with the electrodes are ready to react. The recent development of electrochemical machinery in continuous flow has overcome this problem as it offers a substantially enlarged surface area-to-volume ratio, thereby increasing the reproducibility and selectivity of the process [99]. In this regard, a great number of flow cells have been reported to date illustrating their versatility in organic synthesis [19, 20]. The green benefits of flow electrochemistry make it a valuable tool for the generation of new drug candidates in drug discovery programs [100, 101]. In particular, electrochemical transformations are extremely useful in late state functionalization as they avoid de novo synthesis of the derivatives, which may take weeks or months. The biological study of the new set of analogues obtained can

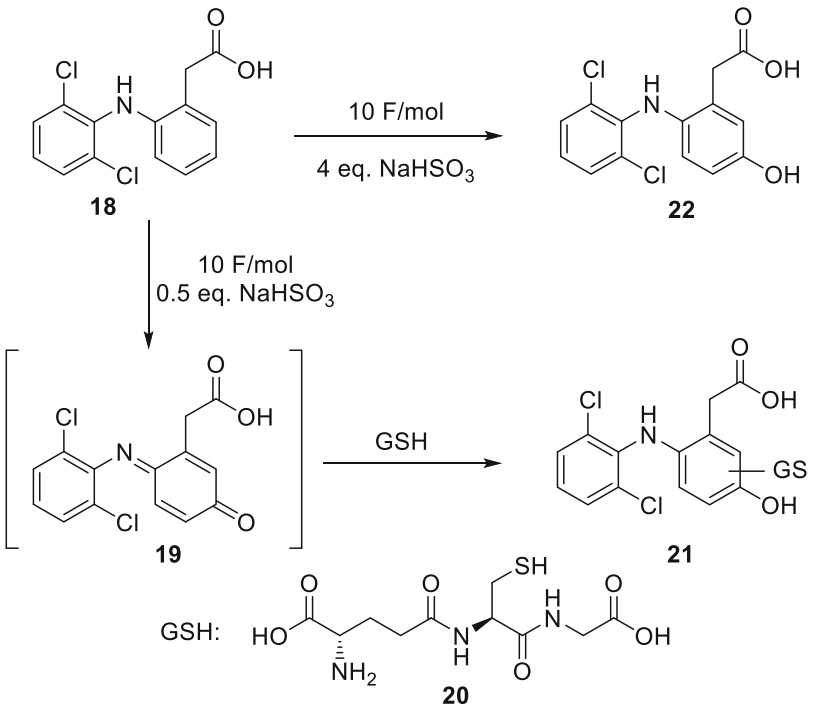

Fig. 10 Electrochemical preparation of metabolites in flow

provide valuable information in terms of metabolic stability or pharmacokinetics. For instance, oxidative processes can reveal the most susceptible positions to be oxidized in vivo, simulating CYP450 oxidation (Fig. 10). This late state electrochemical derivatization can drive decision making in drug discovery programs, accelerating the discovery of better drug candidates.

3.5 Library Synthesis and Automation Using Flow

Discovering a new drug is a slow and expensive process in which most attritions are due to different parameters related to the chemical structure of the molecule (e.g., toxicity, pharmacokinetics, cost of materials) [102]. One bottleneck is the synthesis of a great number of chemical entities, which can facilitate a better understanding of structure–activity relationships required for drug discovery program. In this regard, the corresponding cycle design-to-test usually takes various weeks, which is also an inconvenience for obtaining data rapidly. Furthermore, field competition makes the search of innovative technologies necessary to accelerate the drug discovery process.

Parallelization approaches using automated systems speed up the synthesis of drug candidates and can increase chemical diversity in a fast and effective manner, accelerating decision making in drug discovery programs while helping the scientist

to maximize time, for instance in the exploration of new synthetic methodologies [28, 103–105]. They are generally based on an autosampler to load the reagents into the system and a fraction collector for reaction compilation. Thus, novel chemical series can be synthetized in a fast and efficient manner, by providing suitable information during early stages and expanding drug discovery capabilities. Typically, series of compounds in flow are made in a sequential way using plug flow approaches [106]. The optimization of synthetic routes can also be carried out in automated systems in combination with Design of Experiments (DoE) exploration [107]. A considerable reduction of cost, time, and human error is achieved because an array of reaction variables is optimized by using advanced algorithms.

Traditional methods for reaction optimization imply the generation of vast data, which require important amounts of starting materials. High throughput experimentation (HTE) techniques offer the opportunity to carry out the reaction optimization on smaller scale in order to identify the best reaction hotspots [108, 109]. The automated version of HTE has been envisioned in the pharmaceutical sector as an opportunity to catapult both reaction discovery and development due to the rapid generation of information [110]. However, the analysis of the automated reactions is relatively slow and it limits the benefits of the technology. The coupling with analytical techniques such as mass spectroscopy (MS) overcomes this issue [111, 112]. Through the continuous flow approach the screening datapoints can be scaled up and many issues can be resolved through the use of microfluidic cell-chips [113]. For instance, installation of proper equipment allows for carrying out 1,500 chemical combinations in a day with real-time analysis data, which speeds up drug discovery programs (Fig. 11) [114].

3.6 Artificial Intelligence (AI) and Flow Chemistry

Artificial Intelligence (AI) has also been implemented in continuous flow automated systems [115, 116]. These platforms are capable of selecting the best synthetic routes from scientific databases by utilizing a chemical programming language, which controls molecular assembly [117]. Thereafter, the system is able to test different reaction parameters and execute the synthesis of chemical libraries robotically. Ideally, the continuous flow approach should be compatible with different reaction conditions allowing for the translation of small-scale synthetic reactions to larger amounts if required. The integration of AI in continuous flow platforms provides a considerable advance in the preparation of drug candidates without human intervention (Fig. 12) [118].

The aforementioned area of automation and the variety of technologies that can be adapted to continuous flow made possible the development of fully integrated systems comprising design, synthesize, and test cycles [119]. Algorithmic predictions, purification steps, and biological screening can be combined in automated platforms to reduce the optimization time required for a drug candidate [120]. Typically, the experimentation is compartmentalized and several days are required from

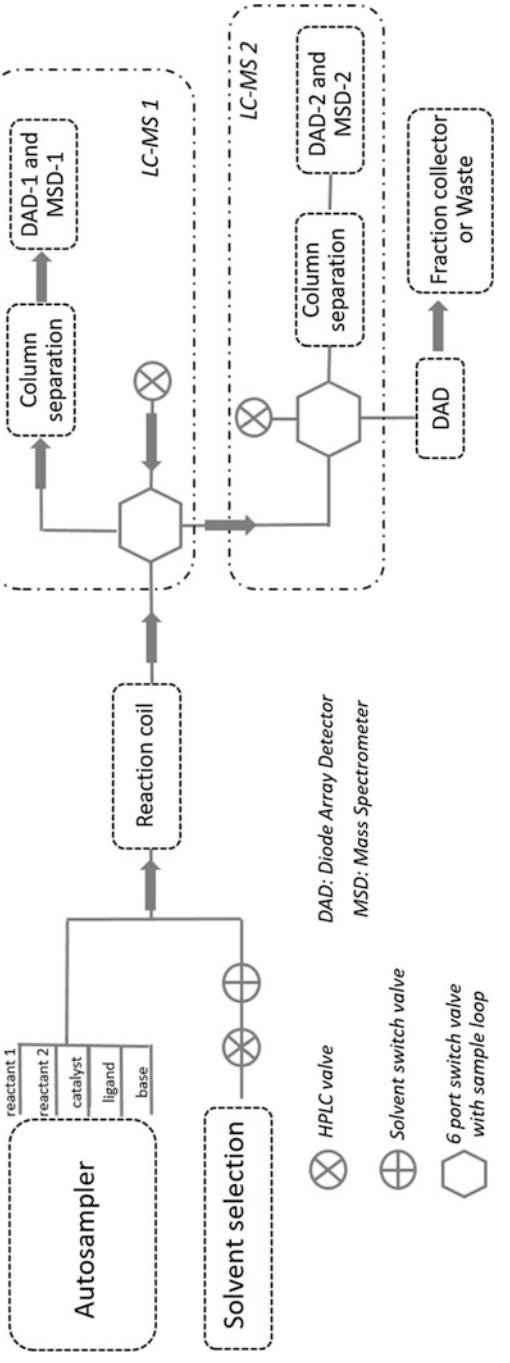

Fig. 11 Pfizer HTE platform

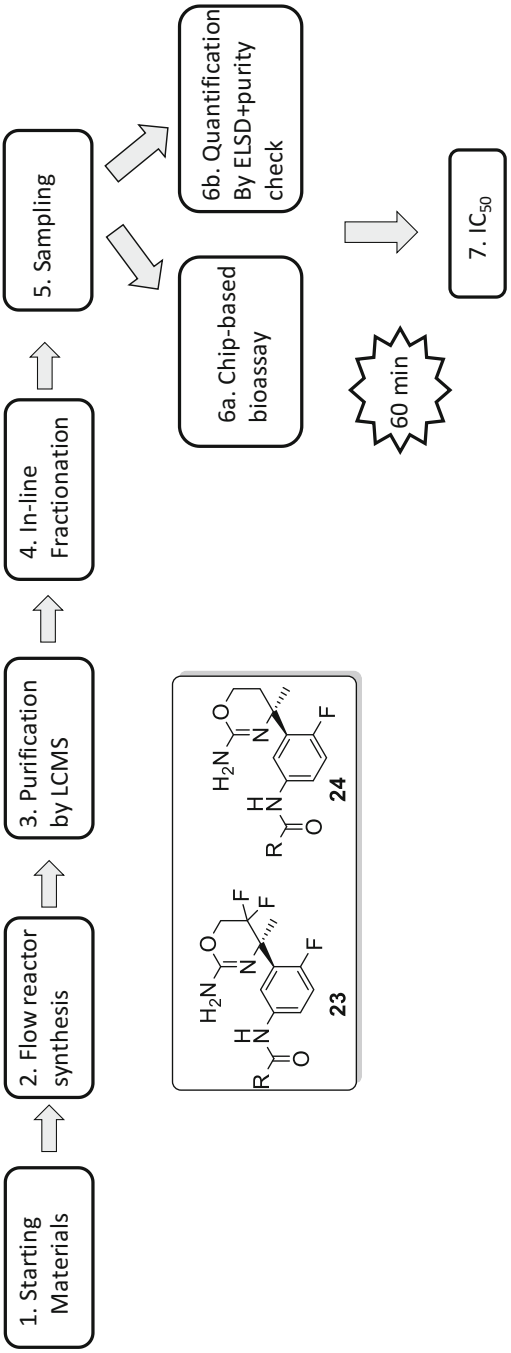

Fig. 12 Hoffman-La Roche platform for drug optimization

design to test. By using this methodology, a more rational approach is achieved, as the SAR data obtained from the drug candidates are used to design the next generation more efficiently [121]. These strategies will drastically reduce time, cost, and materials as well as accelerating library production and opening new avenues for understanding the drug discovery process.

4 Conclusions and Outlook

To sum up continuous flow chemistry offers unique opportunities for drug discovery. From expanding the medicinal chemist's toolbox to accelerating design-synthesize-test cycle through the integration of automation and AI.

Various aspects make flow chemistry extraordinarily attractive for the generation of bioactive target compounds such as drugs or natural products. First, flow chemistry enables forgotten and underused chemistries making them parallelizable for the rapid generation of organic molecule analogues expanding accessible chemical space. Then, an array of technologies can be installed to construct unique molecules, which could be problematic to synthetize otherwise. Altogether, the sustainable approach provided by flow chemistry has made this technology very convenient to obtain bioactive molecules during the drug discovery process and for reaction scale-up in industrial environments.

Nevertheless, there are still challenges where flow chemistry yet needs to demonstrate its value. Parallel batch and automated approaches are well established and can perform diverse chemistries regardless of the solubility of the mixture, a limitation in flow. Thus, chemists can run 1,536 reactions per plate in a well-plate format. Flow chemistry can achieve comparable numbers of reactions. Chemists should consider it as a complementary technology to other existing platforms. It is always an interesting approach for flow medicinal chemists to look for transformations that are not useful in batch to be translated in continuous flow and essentially make the best of it.

In the following chapters key authors will describe different applications in the drug discovery setting. This overview will provide the reader with a broad understanding of how flow chemistry can help medicinal chemists to improve the way in which clinical candidates can be discovered.

Compliance with Ethical Standards

Ethical Approval: This manuscript is a review of previously published accounts, as such, no animal or human studies were performed.

Informed Consent: No patients were studied in this chapter.

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