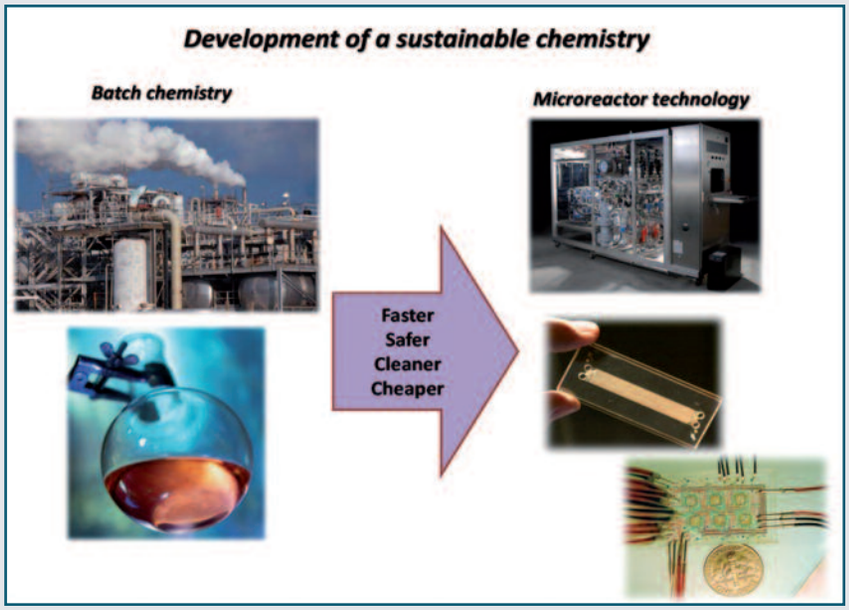

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MICROREACTOR TECHNOLOGY AS TOOL FOR THE DEVELOPMENT OF A SUSTAINABLE SYNTHETIC CHEMISTRY

The microreactor technology has the potential to change the way to perform synthetic chemistry. Efforts in this field need to be promoted at the best. This will reduce waste, increase the safety, save energy, improve the product quality, reduce the time for drug discovery and improve the reliability and quality of commercially available microreactors. Research, education and training can play a key role for the widespread use of this new technology.

Despite the rapid development of synthetic methodologies, wherever they have been achieved in catalysis, asymmetric synthesis, combinatorial chemistry and other fields, organic syntheses are still carried out in a very traditional way. In fact, reactions are typically performed in standardized glassware, which in essence have been known since Justus Liebig's time and even in the age of the alchemists. A main drawback for a new synthetic methodology, developed on the bench, is related to a bulk production that often needs a revision of the synthetic strategy subduing chemistry to the limit of the production processes. In addition, a rising ecologic consciousness is asking for a more sustainable and environmentally benign development suggesting the use of new and more "green" technology even in chemistry. It is emerging that miniaturization could be useful to face such challenge, as demonstrated by increasing interest in microreactor technology, microfluidic devices and chip-based microreactors to perform chemical reactions [1]. The term "microreactor" is widely used to describe a microstructured device in which chemical transformations take place in a very narrow space, and can find most applications in process and development chemistry. Microreactors basically consist of a network of channels, of sub-millimeter dimensions, embedded on a surface of different materials such as silicon, quartz, glass, metal, ceramic and polymer, and fabricated by precision engineering (Fig. 1) [2].

With reference to synthetic applications, glass or metal microreactors are most commonly employed even if new materials, compatible with sol-

vents and reagents, begin to be reported. To perform chemical syntheses within such reactors, reagents are brought together in a predetermined sequence in a designated region of the channel network where they are mixed and reacted. Although microreactors contain microstructures, they are not meant to perform small scale chemistry. It is important to note that microsystems are normally set up as flow-type reactors with a constant flow of solution through a microstructured reaction chamber or channel. Allowing for a "continuous flow" process, instead of batch processing, they can be employed for the synthesis from milligrams to kilograms amounts of material. The main features of microsystems stem from the small size of the microstructures that allow to perform three basic functions:

1) initiate and facilitate a reaction by efficient mixing of the reagents;
2) provide the time necessary to complete the reaction;
3) efficiently provide or remove heat.

As will be showed, it has been demonstrated that microreactors could be loaded with catalysts to carry out heterogeneous reactions, and in the near future, preloaded microreactors, ready to conduct a specific transformation, would become available. They can be constructed as components to perform single-unit operations such as mixing, heat exchange and separation, or as integrated reaction systems. Thus, microreactors hold the potential to be used at all stages of a chemical process. Microreactors offer a much improved control of the reaction parameters, such as temperature and relative concentrations and thus allow for higher yields, smaller amounts of by-products and higher selectivity.

The exquisite control of the reaction parameters realized in the microspace is ascribed to the following features:

1) improved surface-to-volume ratio. On a typical microreactor that could fit in the palm of the hand, this ratio is about 200 $cm^2 \cdot cm^{-3}$, compared with 1 $cm^2 \cdot cm^{-3}$ for a 100 mL glass flask and 0.06 $cm^2 \cdot cm^{-3}$ for a 1 m^3 batch reactor. As a result of this much improved surface-to-volume ratio, microreactors have a heat exchange capability that is many orders of magnitude higher than conventional vessels, regardless of the construction material;
2) fast mixing. Mixing by diffusion in conventional vessels would take too long; for this reason, mass transfer is achieved by turbulence and vigorous agitation. Undesired concentration gradients (hot spot), particularly during the dosing process, are unavoidable. Laminar flow, instead, dominates in microchannels, compared to vessels. With a channel width of less than 0.1 mm, it is difficult to produce turbulence. Under these conditions, mixing by diffusion become very fast and perfect mixing can be achieved in fraction of second. Also, due to the constant flow of the reactants, their relative ratios are constant securing reproducibility.

Other advantages related to the use of microreactors are:

1) safety. The capacity of one microreactor usually lies in the range from microliters up to a few milliliters. This, combined with the flame-arresting effect of the small channels, means that microreactors are inherently safe tools for laboratories, pilot plants and production sites. Potentially hazardous reactions can be handled much more easily because of the vastly reduced amounts of dangerous reactants and solvents.
2) "scale-out" and "numbering-up" allow for the production of large amount of material. Indeed, by just one reactor and flow rates between 1 and 100 mL per minute, from 100 mg up to 10 g of product can be synthesized per minute. In one hour, this would represent between 6 g and 600 g; in one day, this would amount between 144 g and 14 kg! With 10-fold or 100-fold parallelized arrays (numbering up), one can imagine that syntheses in the multi-kilogram or ton range are easily achievable [3].

Since the same process used to produce small quantity is also used to synthesize larger amounts, no tedious scale-up studies are required. This results in huge space- and time-saving, improved productivity and ultimately sustainability.

The research interest in the field of microreactors technology and continuous flow processes has grown tremendously in the last decade that it is difficult, if at all possible, to report such results exhaustively here. However, since books and reviews on the field have been recently reported [4], a selection has been made and in this critical review relevant applications and proof of concepts appeared recently in the field of synthetic organic chemistry will be described. This contribution would try also to give an overview on the potential of miniaturization in the development of a sustainable chemistry.

Recent advances in microfluidic technologies

The growing interest towards integrated microfluidic chemical systems and progress in precision engineering, led to the development of more sophisticated microreactors useful for reaction discovery and reaction monitoring. Recently Jensen and Porco reported an automated silicon-based microfluidic reaction platform for rapid, low-volume, multidimensional reaction screening. The microfluidic system is capable of selecting chemical reagents and solvents, as well as varying reaction times and temperature. This device has been useful in preparing new chemical entities and discovering new chemical transformations (Fig. 2) [5].

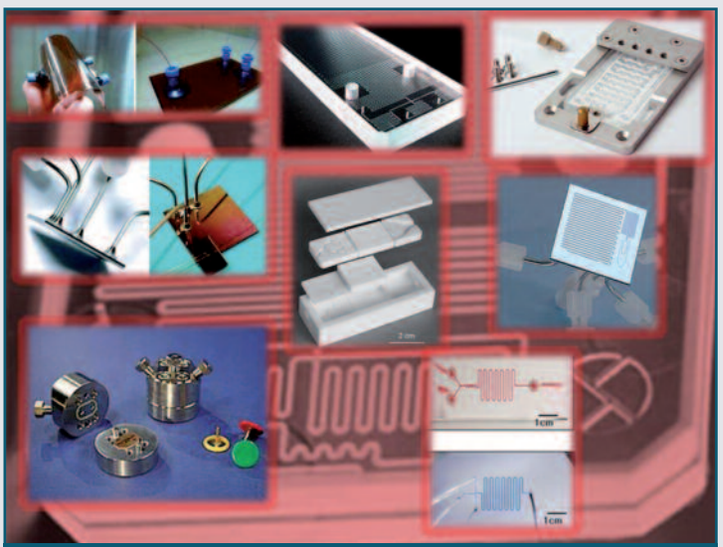

Fig. 1 - Examples of microreactors made of different materials

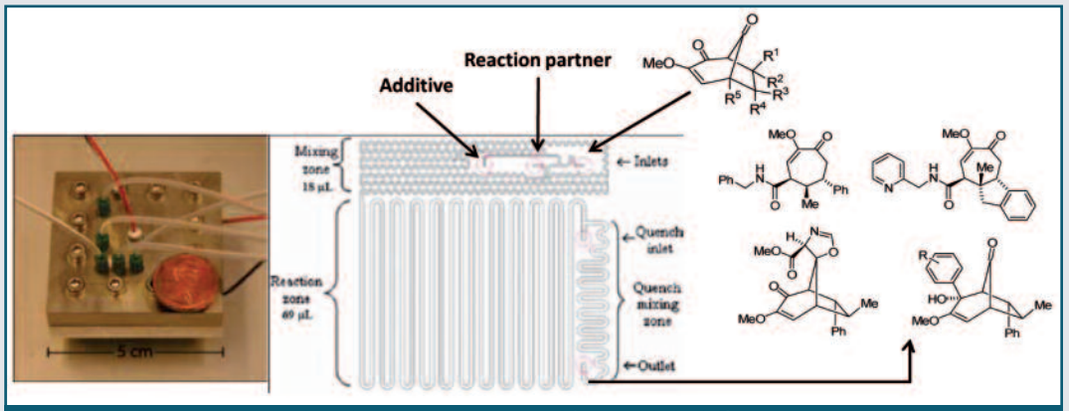

Fig. 2 - Integrated microfluidic systems for reaction development (copyright of ref. 5)

The search for integrated microchemical systems able to perform multiple reaction steps and streamline a synthetic process, led to the development of a device capable to perform a microfluidic distillation to exchange reaction solvents [6]. The device has been used to run a continuous flow palladium catalyzed Heck reaction between an aryl triflate and a vinyl ether (Fig. 3). The authors demonstrated that aryl triflates, which lack commercial availability, could be generate feeding the first microreactor with CH_2Cl_2 solutions of trifluoromethanesulfonic anhydride (Tf_2O), phenol and diisopropilethylamine (DIEA). The output, containing the triflate, subjected to a work-up procedure with an aqueous segmented flow of 2.0 M HCl followed by a liquid-liquid extraction (LLE), furnished a solution of purified triflates in CH_2Cl_2. This solution was combined with pure toluene (or DMF), keeping a dichloromethane-to-toluene volumetric ratio of 1:4, and then delivered to the microfluidic distillation device (Fig. 3). Gas-liquid segmented flow was established by combining nitrogen gas with the liquid stream, which enabled controlled flashing. Keeping the temperature of the distillation device at 70 °C, above the boiling point of CH_2Cl_2 (i.e., 40 °C) yet below the boiling point of toluene (i.e., 110 °C) or DMF (i.e., 153 °C), gave a vapor phase enriched with CH_2Cl_2 while the liquid phase was comprised mostly of toluene (or DMF) and aryl triflate. The solution of aryl triflates, in the suitable solvent, was then introduced in the last microreactor and subjected to the palladium catalyzed Heck reaction, furnishing the coupling product uninterruptedly.

Another example of integrated microreactor system for a self-optimization of the Heck reaction, has been reported by Jensen and Buchwald [7]. A significant feature of this automated system is the ability to perform optimization where *no a priori* information of the reaction parameters is required. The microreactor system employs a "black-box" optimization technique, directed by the Nielder-Mead Simplex Method, with the scope to maximize the yields of a Heck reaction by adjusting the equivalents of the alkene and the residence time (Fig. 4). Time and materials required for an optimization trial were minimized by performing reactions in an integrated silicon microreactor and incorporating an HPLC for inline monitoring of the reaction performance.

Optimal reaction conditions were determined after 19 automated experiments and required a relatively small amount of starting material. The reaction was also successfully scaled up 50-fold using the optimal conditions determined by the microreactor system.

It is important to note that the ability to perform a high throughput of sequential experiments, indicates that automated optimization in integrated microfluidics are suitable for reaction development, when kinetic information are limited, and could be applied to rapidly establish libraries of reaction data by optimizing a specific reaction or by optimizing the same class of reactions with different substrates and solvents.

Kim and coworkers developed a microchemical system for continuous flow catalytic reactions with catalyst-immobilized magnetic particles [8]. The system consists of a microseparator and a capillary microtube reactor (Fig. 5). The separator cleanly parts the product stream from the fresh feed stream and completely recovers spent catalyst particles. The continuous, self-regulated microchemical system allows to investigate catalytic reactions in a way that has never been possible in microsystems. A significant reduction in the amount of catalyst used for a reaction can be realized. This microfluidic device has been used in the dioxygenation reactions using only 10% of the catalyst needed for batch reaction, and could be used repeatedly for many different reactions with subsequent solvent cleaning.

A ground-breaking application of microreactor technology consists in the development of microstructured devices (or chips) with functionalized microchannel walls, allowing for chemical transformations in flow. The principle is similar to that operating in pass-flow technology [9] but such devices should not suffer of pressure drops along the channel and should

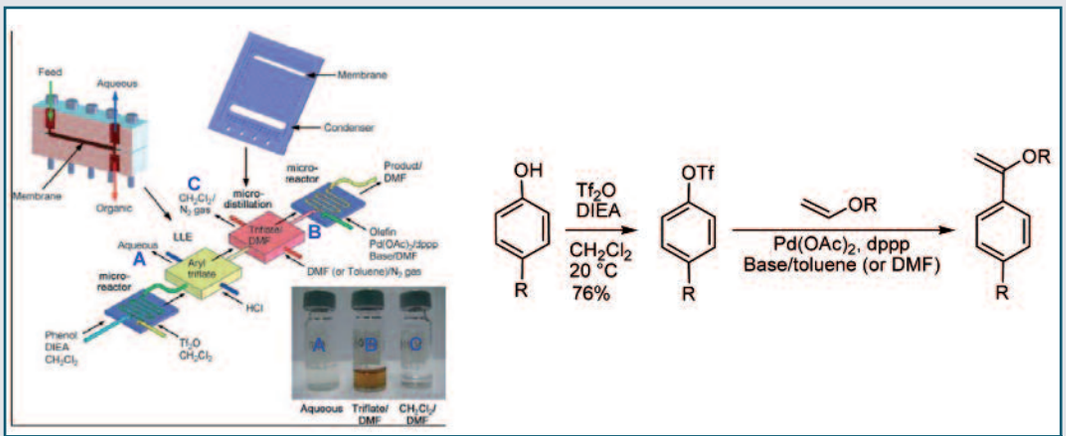

Fig. 3 - Microchemical system for a continuous flow Heck-type reaction with triflates (copyright of ref. 6)

not need packed bed material. The development of this kind of microfluidic devices could result advantageous from a chemical and economic point of view because small chips for specific tasks and for high throughput chemical development would become available at least at laboratory level. Examples of this kind of microreactors have been reported recently by Verboom and coworkers. This research group developed silicon glass microreactors having immobilized catalysts on the microchannel walls. The catalyst can be anchored on the surface exploiting polymer brushes obtained by atom-transfer radical polymerization. In a first report [10], it has been showed how the surface of the inner wall of a silicon glass microreactor could be coated with polyglycidylmethacrylate (PGMA) polymer brushes whose thickness was regulated by varying the polymerization time. To the PGMA polymer brushes was attached the organic catalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and the microreactor tested in a Knoevenagel condensation between benzaldehyde and malonitrile (Fig. 6a). The catalytic activity was depending on the thickness of the polymeric layer and the device could be used for 25 times with no decrease of the catalytic activity. Another polymer-brush-based material, recently reported [11], has been applied to the formation and *in situ* immobilization of silver and palladium nanoparticles which formed a catalytic coating for the inner wall of a glass microreactor (Fig. 6b). This microreactor with Pd-nanoparticles on the microchannels was very efficient in heterogeneous catalyzed reactions such as the Heck reactions. In this case it was demonstrated that the nanostructure releases Pd active species into solution in a controlled way depending on the thickness of the polymer-nanoparticle layer. Nevertheless this result shows that, in principle, heterogeneous metal-catalyzed chemical reaction could be performed in microreactors.

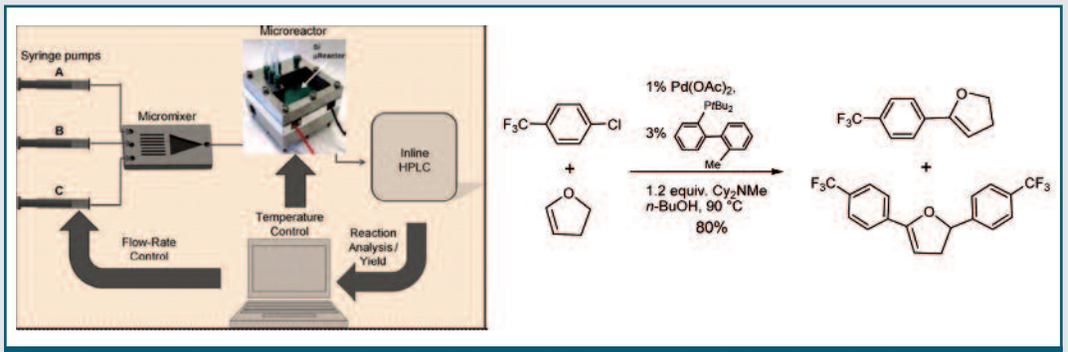

Fig. 4 - Automated microreactor system for self-optimization of the Heck reaction. Syringe A contains the aryl chloride, amine base, and palladium source; syringe B contains the alkene; syringe C contains n-butanol (copyright of ref. 7)

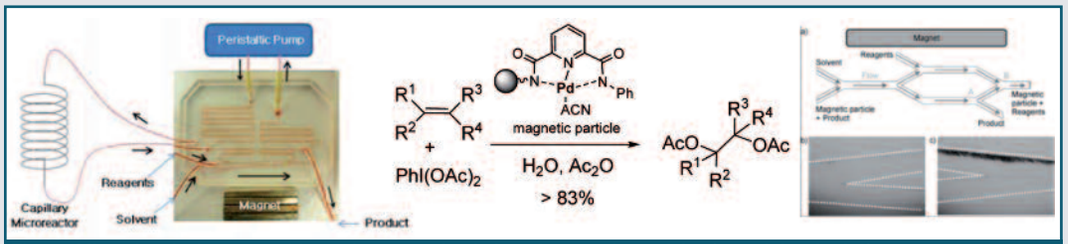

Fig. 5 - Microchemical system with continuous recirculation of magnetic particles (copyright of ref. 8)

Another example of molecular transformations by catalyst-immobilized microflow devices has been reported by Uozumi and coworkers [12], who developed the installation of a polymeric metal catalysts on the microchannel wall of a microreactor by means of the "ship-in-a-bottle" molecular convolution method [13]. The microchemical device, containing a membrane of polymeric palladium catalysts inside a microchannel reactor at the laminar flow interface of the channel, has been applied to palladium-catalyzed Suzuki-Miyaura reactions of aryl, heteroaryl, and alkenyl halides with arylboronic acids. Under such microflow conditions, the instantaneous production of biaryl compounds is achieved quantitatively within 5 sec of residence time in a defined channel region.

Microfluidic devices have found also application in the kinetic and mechanistic studies as well as in reaction development and optimization. Ley and coworkers, in collaboration with Mettler-Toledo company, developed a microflow cell for "inline" monitoring of ongoing reactions based upon ATR technology [14]. This new micro analytical tool could be useful in the optimization and synchronized control of continuous chemical processes, because it is able to address important points such as: 1) stoichiometry of multistep synthesis; 2) real-time inline monitoring without sampling and analysis off-line; 3) real-time monitoring of reactive intermediates; 4) manipulation and control on hazardous compounds; 5) qualitative monitoring of product formation; 6) extrapolation of kinetic data.

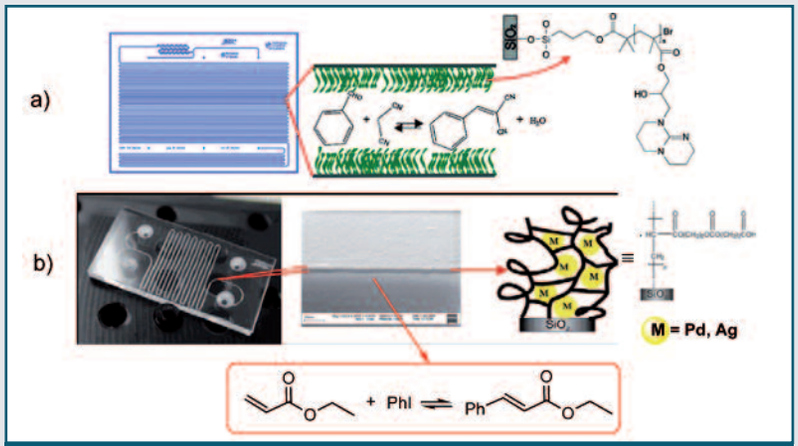

Fig. 6 - Polymer-brush based microreactors for heterogenous catalysis (copyright of ref. 10, 11)

Microreactor technology in cross-coupling reactions

Cross-coupling reactions, such as Suzuki, Negishi, Heck, Kumada, Stille, Sonogashira and Buchwald-Hartwig, have become milestones for carbon-carbon bond formation. The development of

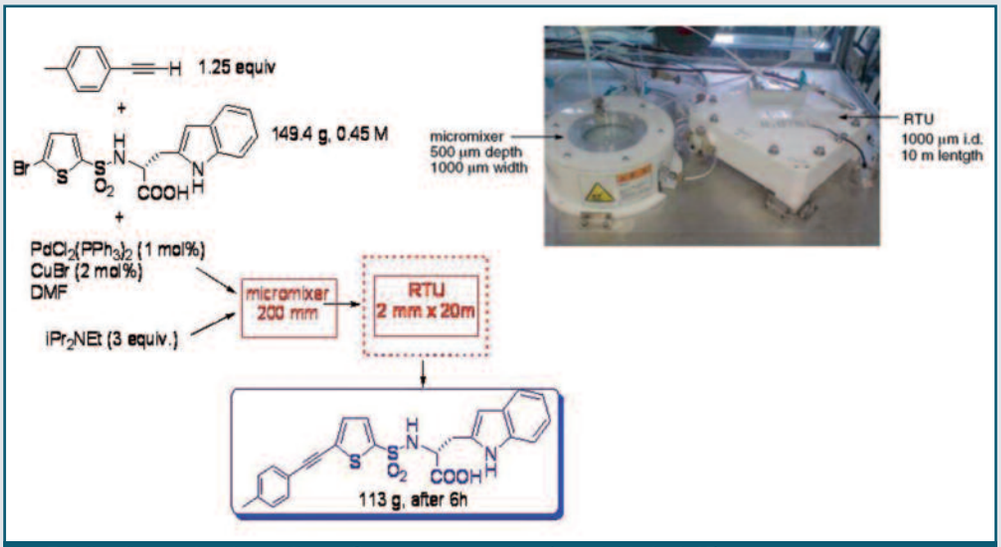

Fig. 7 - Microflow system for multigram Sonogashira coupling. (copyright of ref. 15)

new metal-complexes and ligands, securing high yields and low catalyst loading, allowed the use of microflow systems in cross-coupling reactions. Fukuyama and coworkers, reported an automate microreactor system consisting of a micromixer, a residence time unit (RTU, 1000 µm id and 10 m length), two pumps, and a fraction collector that has been used for an automatic and fast optimization of a Sonogashira reaction leading to a matrix metalloproteinase inhibitor (Fig. 7) [15]. The optimal conditions were applied to a 10 g scale synthesis using the same microreactor system. By using another microflow system composed of a T-shaped micromixer (200 µm id) and a stainless tube reactor (2000 µm id and 20 m length), a 100 g scale production was made possible. The real and practical advantage of this system is its ability to eliminate the time lag between optimization and production, as well as to shorten total processing time.

Barrow and Wirth investigated various Heck couplings carried out using segmented flow conditions to accelerate the reactions [16]. The main advantage of segmented flow in comparison with a continuous laminar flow, is the generation of internal circulation within segments leading to an improved mixing. It is important that the segmented phase, that should be immiscible with the reaction phase, must not interfere with, or dissolve any of the reaction components, and must have a boiling point compatible with the reaction conditions (Fig. 8).

The segmented flow method has been successfully applied to Heck coupling of alkenes using arene-diazonium salts instead of aryl halides. Diazonium salts were formed *in situ* from aniline derivatives under acidic conditions. A main drawback with the use of diazonium salts in conventional flask chemistry is the risk for rapid and uncontrolled explosions, making their use generally hazardous especially on large scale. Nevertheless, an advantage of microflow systems is the safe generation of reactive hazardous intermediates in a continuous flow due to the handling of only very small volumes within a confined environment.

Kim reported another example of improved segmented flow mediated synthesis based on a microreactor consisting of two microfluidic channels separated by a thin membrane favoring an intimate contact between gas and liquid phases [17]. Gas flowing in one microchannel can diffuse into the liquid flowing in the other microchannel through the thin membrane. An oxidative Heck reaction carried out in this dual-channel (DC) microreactor, using gaseous oxygen as oxidant, shows the significant improvement that can be made over the traditional batch reactor and the conventional segmental microreactor in terms of yield, selectivity, and reaction time (Fig. 8). The reported DC microreactor could be a powerful tool for gas-liquid microchemistry.

Microreactor technology in heterocyclic chemistry

Microreactors have been successfully employed also in heterocyclic synthesis. Interest in heterocyclic chemistry is due to wide applications of those compounds in coordination chemistry, material sciences, as intermediates in a variety of synthetic transformations and mainly in medicinal chemistry. Herein, we have briefly collected some recent reports describing the preparation of various heterocyclic scaffolds such as pyrrolidines, tetrazoles, oxadiazoles, pyridines, imidazoles, furofuran derivatives, indoles, and piperidines by using continuous flow microreactors jointly to

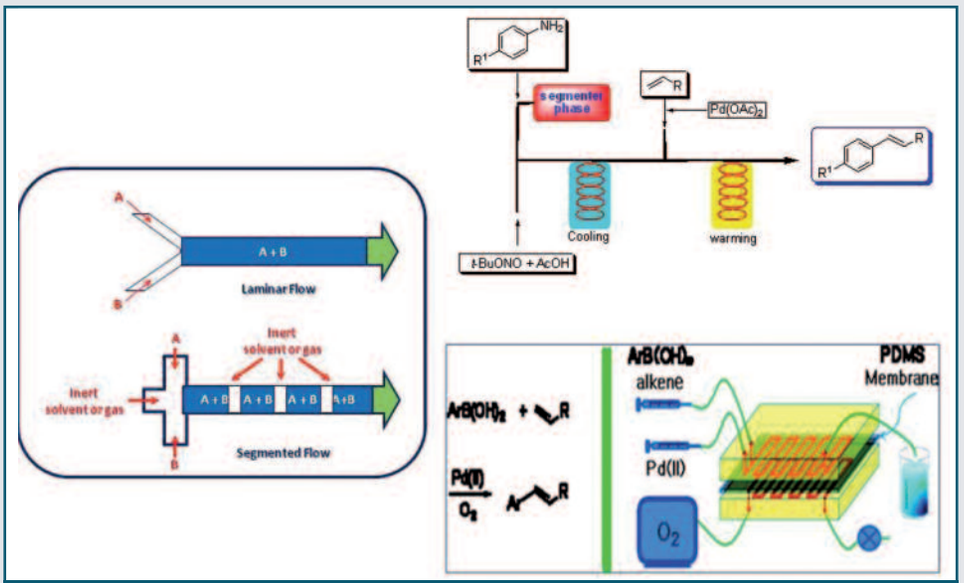

Fig. 8 - Segmented flow technique for Heck reactions (copyright of ref. 16, 17)

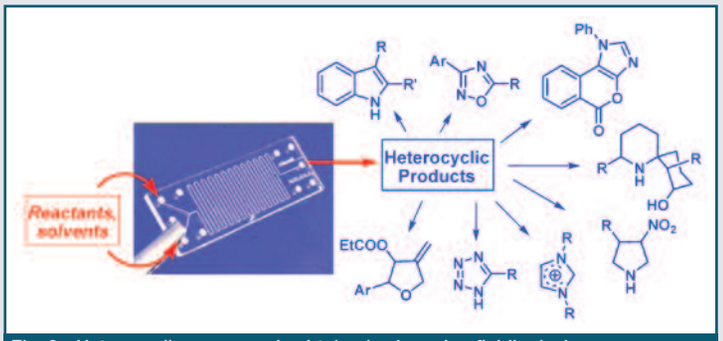

Fig. 9 - Heterocyclic compounds obtained using microfluidic devices

automation methods and immobilized reagents (Fig. 9).

Recently, Ley and coworkers [18] reported a convenient preparation of 3-nitropyrrolidines and related compounds as potentially useful building blocks for synthesis of pyrrolidine-based derivatives that have been shown to display a wide variety of biological activities. In order to introduce structural diversity in the pyrrolidine ring, a dipolar cycloaddition process, involving nonstabilized azomethine ylides and nitro alkenes, has been chosen. By using the R2+/R4 flow system commercially available from Vapourtec, equipped with a scavenger resin, a reasonable number of 3-nitropyrrolidines were quickly prepared.

A general and scalable method for the continuous flow synthesis of 5-substituted 1*H*-tetrazole derivatives has been described by Kappe and coworkers. The heterocyclic scaffold has been generated by addition of HN_3, obtained from NaN_3 and acetic acid, to a nitrile in a microreactor coupled to an intensified high-temperature/high-pressure flow addition step [19]. Under optimized conditions tetrazole derivatives were formed almost quantitatively and with residence times of a few minutes, providing excellent purities and yields of isolated products. Existing protocols for batch tetrazole synthesis report reaction times of several hours (or even days), and in many cases the reaction mixtures were heterogeneous because of the presence of reagents, additives, or catalysts of low solubility. Key-step of this protocol is the *in situ* generation of toxic and explosive HN_3 within the microreactor environment and the use of extreme temperatures for the reaction to occur. The catalyst-free method uses inexpensive NaN_3, environmentally friendly solvents, and does not require any other additive.

Cosford and coworkers reported a rapid synthesis of bis-substituted 1,2,4-oxadiazoles from arylnitriles utilizing three microreactors, two of which involve superheating of the solvent [20]. The 1,2,4-oxadiazole scaffold is commonly found in biologically active molecules being an amide or ester bioisoster. Typically, the "batch" synthesis of these heterocycles has been carried out by reacting arylnitriles with hydroxylamines to give the aldoximes then cyclized by reaction with acyl chlorides. Cyclization is generally a difficult and time-consuming step and often requires sealed tube conditions and long reaction times. In contrast, by this continuous flow microreactor system, a multiday multisteps preparative procedure has been shortened to several minutes demonstrating, as proof-of-concept, the rapid synthesis of focused libraries of 1,2,4-oxadiazole scaffold. The same authors reported the synthesis of the interesting imidazo[1,2-a]pyridine scaffold found in compounds with anticancer, antiviral, and antimicrobial activities and in modulators of the nervous central system [21]. In this work was described the first continuous flow synthesis of imidazo[1,2-a]pyridine-2-carboxylic acids from 2-aminopyridines and bromopyruvic acid using a single microreactor, while with two microreactors a library of amidic derivatives was obtained.

Applying a modified Radziszewski reaction, Stark and coworkers demonstrated that homosubstituted 1,3-dialkylimidazolium ionic liquids can be prepared continuously in high yield (70-90%) and purity (>95%) using readily available starting materials and a microreactor system [22]. This technology reduces the energy and solvent required for the preparation of 1,3-dialkylimidazolium-based ionic liquids in comparison to conventional methods. The corresponding imidazolium salts showed high thermal stabilities, relatively low viscosities, thus fulfilling the requirements for solvent application.

A continuous flow reaction system was applied to a gram scale synthesis of key intermediates for the preparation of furofuran lignans [23]. In this paper, Ryu and coworkers reported that typical radical chain reactions, in presence of tributyltin hydride and tris(trimethylsilyl)silane, can be successfully carried out using microreactors in a continuous flow system. The advantage is the possibility to perform such a reaction, which usually uses quickly decomposing radical initiators, within a very short time, in comparison with a conventional batch system. By a synergic use of conventional batch chemistry and microreactor techniques, a multigram synthesis of the poison-arrow frog alkaloids analog perhydrohistrionicotoxin has been accomplished [24]. From a synthetic point of view, the overall sequence starts from an enantiopure δ-lactone and an alkyne to furnish a tricyclic isoxazolidine intermediate, and subsequently, the enantiopure perhydrohistrionicotoxin spiropiperidine structure (Fig. 10).

The main chemical transformations of the batch synthesis of this toxin has been transferred into flow mode, thus establishing procedures that potentially allow for the production of a multi-gram quantities of chemical intermediates by continuous processing. The improved seven-step sequence of the total synthesis, by using a microreactor platform, involved only two chromatographic separations, and most products could be isolated in sufficiently pure condition by simple filtration through a minimal amount of silica or alumina. Moreover, the authors demonstrated that flow processing, when involving the use of strong organometallic bases such as *n*-butyllithium, LDA and KHMDS can be performed with equal efficiency as batch processing, but at temperatures of 0 °C or higher, rather than 78 °C.

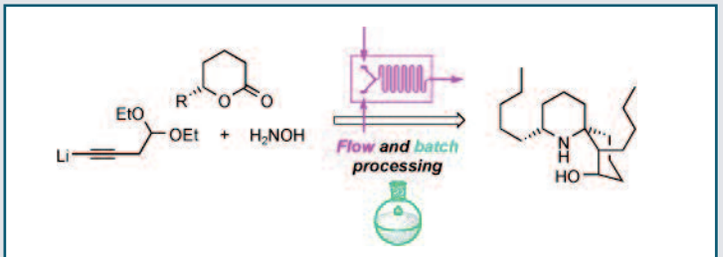

Fig. 10 - Integrated multigram flow synthesis of histrionicotoxin

Microreactor technology in reactions mediated by shorth-lived intermediates

Microflow devices have been found to be very effective in controlling extremely fast reaction, involving highly unstable intermediates, allowing the introduction of the concept of flash chemistry. Flash chemistry is defined as "*a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity and reaction times ranging from milliseconds to seconds*". This concept has been successfully applied to several organic reactions involving highly reactive organolithium intermediates. Functionalized organolithiums are widely used in modern synthetic chemistry, [25] they exhibit high reactivity toward electrophiles, giving fast and exothermic reactions, and usually require very low temperature and controlled reaction conditions for their generation in order to avoid byproducts and decomposition.

Some examples have been selected in order to show the advantages of microfluidics in organolithium chemistry.

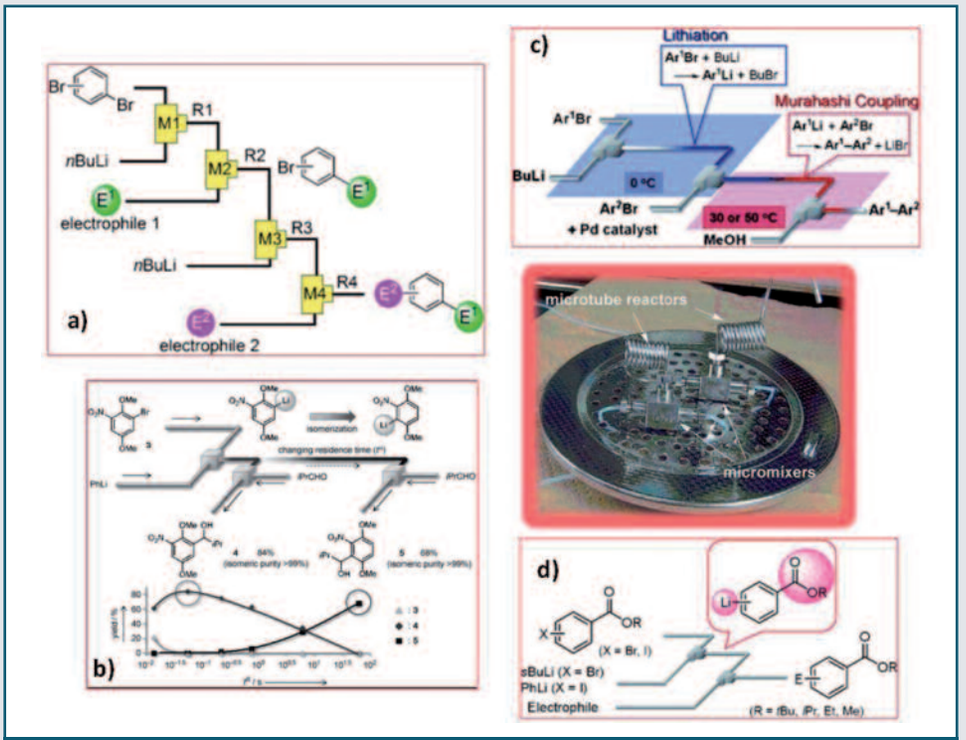

Fig. 11 - Flash chemistry using organolithiums: a) sequential Br-Li exchange and electrophile trapping; b) switch between thermodynamic and kinetic nitroaryllithiums; c) sequential Br-Li exchange and Murahashi coupling; d) generation of functionalized aryllitiums (copyrights of ref. 26-29)

It has been demonstrated that microflow systems, consisting of stainless steel micromixers and teflon or stainless steel microtubes, are useful for a sequential introduction of two electrophiles into *p*-, *m*-, and *o*-dibromobenzenes by Br-Li exchange reactions occurring at much higher temperatures than those required in conventional macro-batch systems [26]. These results represent a straightforward and powerful route to disubstituted benzene derivatives and show, at the same time, the potential of microflow systems for the integration of chemical reactions that involve highly reactive intermediates (Fig. 11a).

The halogen-lithium exchange reactions have been also integrated with a Pd-catalyzed Murahashi coupling in a flow reactor (Fig. 11c) [27]. The use of a soluble Pd catalyst was needed in order to avoid clogging in the microflow system. However, it is worth noting that this kind of coupling reactions are very difficult if not impossible to realize in macrobatch reactors.

By using the microreactors technology, some useful transformations involving nitrosubstituted aryl lithiums, which are very difficult to generate in a conventional manner, have been developed. Yoshida and coworkers reported a microflow system for the generation and transformation of *o*-, *m*-, and *p*-nitrophenyllithium reagents (Fig. 11b) [28]. The authors demonstrated that by changing the residence time it was possible to induce the isomerization of the nitroaryllithium realizing a controlled switch between kinetic and thermodynamic organolithiums.

Microflow systems have been found to be very useful for the generation of *m*-, *p*- and *o*-alkoxycarbonyl-substituted aryllithium compounds by virtue of precise residence time and temperature control [29]. By choosing appropriate conditions, it has been possible to prepare not only *tert*-butoxycarbonyl-substituted aryllithiums, at much higher temperatures than those required for conventional macrobatch reactors, but also the more unstable isopropoxycarbonyl-, ethoxycarbonyl- and methoxycarbonyl-substituted aryllithiums, which are practically impossible to obtain in conventional macrobatch reactors (Fig. 11d). This method allows for a straightforward introduction of substituents into the benzene ring of alkyl benzoates without protecting the alkoxycarbonyl group. These results illustrated new possibilities of organic synthesis via unstable functionalized organolithiums.

The flow microreactor system is a powerful tool for introducing substituent on aziridines and oxiranes by using the aziridinyl [30] and oxiranyl [31] anion methodology. Such reactive intermediates are very sensitive to the reaction conditions undergoing side reactions, decomposition or lost of the configurational integrity soon after their generation. Yoshida and coworkers, reported that flow microreactors could be very efficient in the lithiation/electrophile trapping sequence of aziridines [32] and oxiranes [33] (Fig. 12). α-Aryloxiranyllithiums have been generated without decomposition or isomerization by virtue of the short residence times and efficient temperature control offered by microreactors, and insights into the chemical and configurational stabilities of oxiranyllithiums have been also obtained. Such reactive species have been generated at higher temperature with respect to macrobatch systems (i.e. for styrene oxide -78 °C in microreactor vs -98 °C in macrobatch), and repeating the sequence of deprotonation and electrophilic trapping within an integrated flow

microreactor system, a stereoselective synthesis of tetrasubstituted epoxides has been achieved. Analogously, by reaction of *N-tert*-butylsulfonyl (Bus) aziridines with *n*-BuLi, *N*-Bus-aziridinyllithiums were effectively generated in a microflow system and trapped with several elctrophiles. Once again, such reactive intermediates were generated at higher temperature with respect to macrobatch conditions showing the potential of microfluidic devices.

Microreactors in radiopharmaceutics

It has become increasingly recognized that microreactors may be very useful in radiopharmaceutics to produce radiotracers or radioligands for molecular imaging in living subjects. Positron Emission Tomography (PET), for example, makes use of radiotracers and represents a powerful tool for diagnosis in oncology, neurology, cardiology and rare diseases. The principle of this technique relies on incorporation of positron-emitting radionuclides such as ^{18}F, ^{11}C, ^{13}N and ^{15}O into the tracer molecules.

Microfluidic devices offer several advantages in the synthesis of radiotracers. First of all, microflow systems can create an environment where all the reactions involving short-lived radioisotopes are fast and high-yielding, and second the devices can be controlled remotely with safety for the operators. Currently radiopharmaceuticals are prepared using large scale Automated Synthesis Modules (ASMs), which present several limitations: excessive dilution of the labeling agents, significant dose decay and high costs [34]. The recent research focused on two novel approaches to microfluidic radiosynthesis: the flow-based approach, where the reactions take place in running solutions; the batch-mode approach, where fixed amounts of reagents are used in each step. A typical example of an apparatus based on the first approach is the microchannel reactor reported by Brady (Fig. 13a) [35] for the synthesis of the widely used 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), or, for the same purpose, the disc reactor reported by Gillies (Fig. 13b) [36].

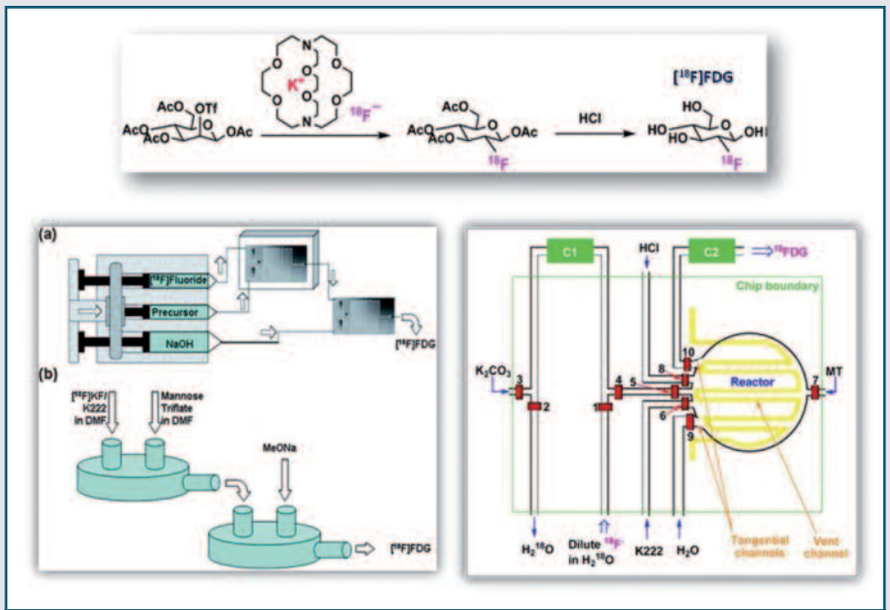

Fig. 13 - Example of microfluidic device for the synthesis of radiotracers

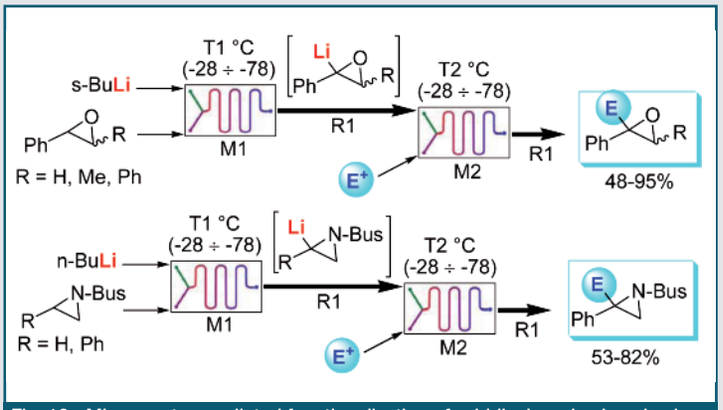

Fig. 12 - Microreactor-mediated functionalization of aziridinyl- and oxiranyl anions

The advantages of this approach are the followings: speed of reactions, thanks to the rapid mixing of the reagents; low auto-radiolysis, since a very little radioactivity is present at the reaction interface at any point into the microchannel, improved yields, the presence of feedback loops allowing for a tuning of the input parameters such as flow rate or temperature.

In particular, the disc-shaped microreactor reported by Gillies, inducing a turbulent mixing of the incoming precursors and the [^{18}F]fluoride ion solutions, leads an increased yield of each synthetic step spending less than a second inside the reactor. Each step requires a reactor, but it is very easy to link many reactors for a multi-step synthesis. The only limitation of this apparatus lies in the construction materials, often polycarbonate and SU-8 polymers, which limit the choice of the solvent to be used. An alternative microfluidic approach is based on a batch-mode of operations in all steps and requires efficiency of material transfer. This technology is named Chemical Reaction Circuit (CRC), since all the processes take place on the same chip or on the same compartment of the chip, avoiding the transfer of the intermediates and reducing the exposure of the [^{18}F] containing species to surface area of the reactor or of the channel walls. The most recent CRCs are composed of a flow layer containing the coin-shaped reactor and a control layer, which contains the valves and the radiator vent (Fig. 13). The device receives diluite [^{18}F]fluoride ion from the cyclotron, which is trapped on an ion exchange column, followed by release into the loop containing the K_2CO_3 solution. Solvent exchange, fluorination and hydrolysis occur in a second loop, which is very close to the first one. The presence of on-chip valves allows to control directions of the reagents and the isolation of incompatible reactants. Also in this case the biggest limitation is the construction material, polydimethyldiloxane (PDMS), which is very reactive towards [^{18}F]fluoride ion, leading to a loss of radioactivity.

Another important challenge in radiopharmaceuticals and microfluidic technology is the possibility to incorporate [^{18}F]fluoride anion into organic molecules, and in particular into the aromatic ring of arenes, for which clas-

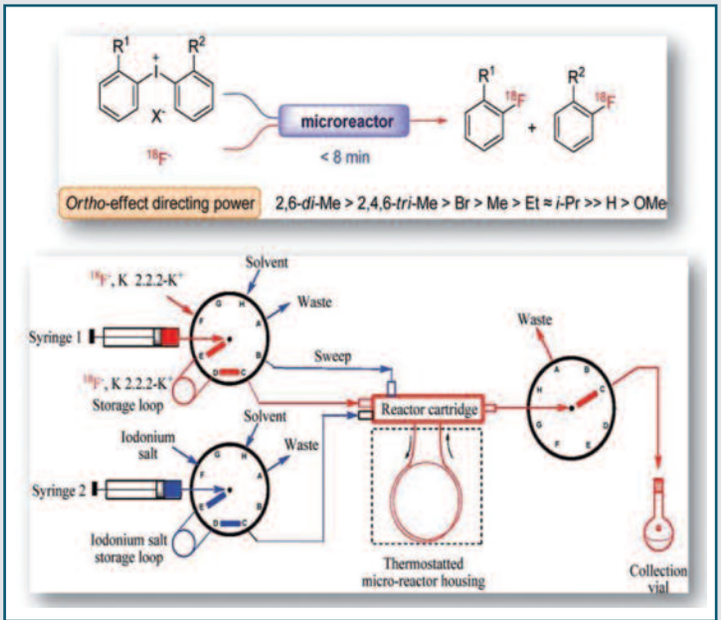

Fig. 14 - Aryliodonium salts for microreactor mediated aromatic fluorination with [^{18}F] fluoride anion

sical aromatic nucleophilic substitution is a disfavored process. Recently, Chun and coworkers explored the reactions of diaryliodonium salts with [^{18}F]fluoride ion by using a commercially available microreactor (Fig. 14) [37].

They compared the reaction outcomes in either a no-carrier-added state (NCA), that is at high specific radioactivity, or a carried-added state (CA), that is at low specific radioactivity. In the first case the [^{18}F]fluoride ion was dried in presence of K222-K_2CO_3, while in the second case in presence of K222-KF. By a syringes system the reagent solutions were loaded into their storage loops and then introduced into the reactor at constant flow rate. After quenching, the radioactivity was quite high (about 80%) and similar for the two methodologies. Furthermore, the reactions of CA and NCA [^{18}F]fluoride anion with *ortho*-substituted diaryliodonium salts gave access to [^{18}F]fluoroarenes in very high radiochemical yields, even for salts containing electron-donating alkyl or methoxy groups.

Conclusion

All the examples, selected from the recent literature, reported in this critical review show potentials of microflow systems and how this technology could completely change the way to perform chemical synthesis in research laboratory as well as in chemical sites. The major challenge facing chemical synthesis with continuous flow microreactors is acceptance. Need to be confident that continuous flow synthesis offers clear benefits compared with traditional batch reactions, including enhanced safety, efficiency, cost-effectiveness, waste and reagent-use minimization [38]. However, three important aspects should be also highlighted: 1) this emerging field is highly interdisciplinary involving synthetic chemists, chemical engineers, process chemists; 2) microreactor technology can be seen as useful tool for a sustainable development, 3) the integration of automation into continuous flow systems presents an efficient new approach to reaction development.

Although microreactors will never fully replace batch processing, the clear benefits and the increasing number of reactions that can be developed and investigated with this technology certainly make it appealing.

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RIASSUNTO

Tecnologia dei microreattori come strumento per lo sviluppo di una chimica sintetica sostenibile

La tecnologia dei microreattori offre la possibilità di cambiare il modo di condurre le sintesi chimiche. Pertanto, andrebbero incoraggiate le ricerche in questo settore. Ciò porterà ad una sensibile riduzione degli scarti, ad un aumento della sicurezza di processo, ad un risparmio energetico nella produzione, ad un aumento di qualità dei prodotti, una riduzione dei tempi nella scoperta di nuovi farmaci e ad un miglioramento della qualità e affidabilità dei microreattori. La ricerca e la formazione possono avere un ruolo chiave nel favorire un ampio utilizzo di questa nuova tecnologia.