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Review

Flow approaches towards sustainability

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Luigi Vaccaro[a]*, Daniela Lanari,[b] Assunta Marrocchi[a], Giacomo Strappaveccia[a]

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Green chemistry and flow chemistry are ideal partners for accessing novel chemical spaces and define highly efficient synthetic tools. In this review article contributions have been selected according to the advantages offered in terms of features that are not immediately related to classic green metrics such as minimization of reaction time, optimization for time screening, waste minimization, safety improvement, process intensification and easy scale up, energy and cost efficiency. Such features make processes in flow highly interesting in terms of developing a green and sustainable chemistry.

1. Introduction

The term green/sustainable chemistry has been often used in several areas to introduce the efforts of academic and industrial scientists towards the development of new efficient chemical processes accounting also for their environmental impact.

Green chemistry may be considered as a modern scientific platform where the common effort of Academia, Industry and Government is converging to develop a sustainable civilization and in this context it is certainly clear that fundamental chemistry has an important role to play.

Probably, one of the most important steps in the evolution of green chemistry is closely related to the US Environmental Protection Agency (US EPA). In 1980's a significant change begun in the execution of environmental regulations and pollution prevention become the priority instead of end-of-pipeline control. In 1990, the Pollution Prevention Act was approved by the American Congress, and the US officially pointed the attention on the ''millions of tons of pollution'' and the related cost of ''tens of billions of dollars per year''.[1, 2] A complete design *ex novo* of the existing and necessary chemical processes was promoted and aimed at the pollution prevention. Modern chemistry must be designed to be intrinsically benign.

This scenario makes immediately evident the strategic role of synthetic chemists who should be able to develop new safer chemical tools. It is clear how the common interest of governments, industries and research institutions to cooperate is directed to solve environmental issues but also to reach common economic interests keeping the production highly efficient and environmentally sustainable.

Some evidences of this cultural shift in the chemical communities were detectable in a few previous actions. In fact, in 1985 was initially proposed the Responsible Care® initiative and the corresponding program was officially launched in 1988 by the American Chemistry Council (ACC), formerly the Chemical Manufacturers' Association (CMA).[3] Some of the fundamental principles of the Responsible Care® program are culturally related to the Anastas's 12 principles of green chemistry that represent one the most important reference to define this area both for teachers and researchers.[4] In 1987, Brundtland reported at the World Commission on Environmental and Development the seminal definition for "sustainable development" in "Our common future" highlighting the need for a better evaluation of World's resources.[5] The debate about the significance of sustainability involves different actors and some sociological or economical point of views should be included in the discussion to better focus the goal of sustainable chemistry and the role of science.[6]

Starting from the Pollution Prevention Act, a great attention must be paid to waste production and while the overall efficiency of a chemical process cannot be correctly evaluated by just using the yield and selectivity parameters other metrics are needed to better measure all the features of a synthetic procedure.[7] Among these, one of the simplest and very effective is the Environmental factor (E-factor) introduced by Sheldon.[8] This simple value is the ratio between the kilograms of waste produced per kilograms of desired product and gives the immediate idea of how an elegant and complex chemistry may results in a highly environmentally costly process. E-factor, atom economy[9] and the "12 Principles"[4] have emerged as key driving factors for the definition of sustainable chemical processes.

These green tools cannot be used as the sole guidelines to evaluate the efficiency of a process. In fact, innovations in all the areas of science and especially technical advancements are very important to define novel routes to access modern efficient chemistry. These aspects can be hardly measured.

In terms of efficiency, continuous flow processes performed in mini or microreactors,[10] are generally more effective than standard batch protocols and offer much higher throughput per unit volume and per unit time.[11] On the other side, as Kirschning et al. noticed,[12] for the development of synthetic approaches to fine chemical and pharmaceuticals the chemistry was based on batch processes as no flow equipment on the laboratory scale was available until very recently. As it happened for green chemistry where the initial synthetic strategy often requires to be completely redesigned to solve sustainability issues,[13] also in the case of flow, *ex novo* approaches are often required to combine the advantage of a novel batch-based synthetic tool with those of flow technology. Currently, several types of flow equipment are available to investigate flow chemistry also at a laboratory scale. Although at the beginning these equipments were essentially used to optimize classic laboratory organic transformations, more often they are becoming an important laboratory tool to discover novel and more efficient chemical processes.[14]

Flow chemistry represents an important opportunity for contributing towards the identification of efficient and modern strategy to develop the needed synthetic tools and greening chemical production. Anyway in our opinion, a significant step must be undertaken in order to define effective processes based on flow chemistry which are also able to drastically reduce waste and to operate in safer media taking green chemistry principles in flow.

In several cases, the synthetic procedures developed in flow do not fulfill several or the most important green chemistry metrics, but this may be rather obvious considering that most of them are based on mass calculation while for instance technological or safety advantages cannot be easily measured. Metrics proposed for green chemistry have been and are crucially important to develop a novel way of planning research and train a

novel generation of scientists, but they are just the answer to major chemical issues (e.g. waste production). It is also obvious that a novel technology, as flow, offers access to innovative solutions and, accordingly to better evaluate or measure the possible advantages offered, novel adequate metrics may be required.

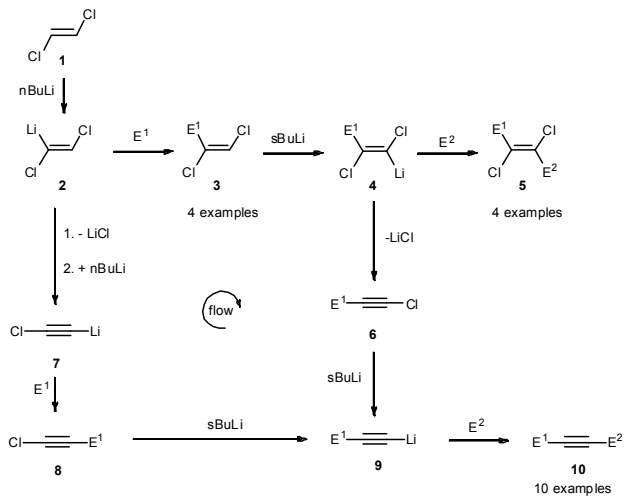
Green chemistry and flow chemistry are likely to be ideal partners for accessing novel chemical spaces and define highly efficient synthetic tools.

In this review, several scientific contributions dealing with flow chemistry have been reported and classified according to the advantages offered that are not always directly measurable by known green metrics. Contributions have been arranged into: minimization of reaction time; optimization for time screening; waste minimization; safety improvement; process intensification and easy scale up; energy and cost efficiency.

2. Minimization of reaction time

Several technologies have been adopted by chemists to speed up reactions minimizing the time for optimization process and therefore improving the overall efficiency of a synthetic strategy. Microwave, sonication and ultrasounds are widely employed in synthesis at this aim. An alternative approach is offered by flow. Adoption of unconventional reaction conditions aimed at speeding up the reactive event leads also to novel reactivity and different chemical outcome compared to batch processes.[14] In this context, technological innovation may lead in more selective and efficient processes paving the route to a greener access to desired molecules.

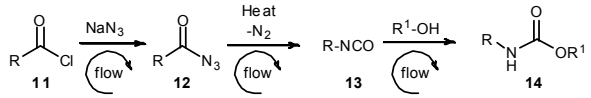
An example is given by Yoshida et al.[15] who applied flash chemistry benefits to the synthesis of alkenes and alkynes starting from *trans*-1,2-dichloroethene (**1**) (Scheme 1). In this case, flash chemistry allowed to generate highly reactive and unstable reactants, such us alkenyllithium compounds,[16] letting them to react at very precisely controlled temperature and residence time.[17] Indeed the first step, the deprotonation of dichloroethene generating 1,2-dichlorovinyllithium (**2**), it is usually performed at -78 °C in batch conditions. By using microreactors instead, it took place at 0 °C in only 0.055 seconds, after which the lithium reagent reacted with an electrophile to give the corresponding alkene **3** bearing two chlorine atoms. In this manner, alkenes **3** were obtained in 85-93% yields. Moreover, a second deprotonation of **2** can be conducted, at -78 °C and 4.6 seconds of residence time, to produce another lithium reagent **4**, which can reacts with a second electrophile to give the corresponding disubstituted 1,2-dichloroethene **5** in 62-73% yields (Scheme 1). Furthermore, 1,2-dichlorovinyllithium **4** in a prolonged residence time (50 seconds) at 0°C gave chloroacetylene **6**, which is then used to synthesize disubstituted alkynes **10** in 48-89% yields.



Features: Short residence time, avoiding isolation of highly reactive intermediates

Scheme 1 Synthesis of different alkenes and alkynes from trans-1,2-dichloroethene (**1**).[15]

An example of multistep reaction performed in microreactor has been reported by Jensen et al.[18] In particular, in this contribution the Authors performed a three-step synthesis in the same microreactor setup, introducing also a liquid-liquid microseparator to perform *in-line* work up. This approach was very effective in avoiding time-consuming separation and isolation of the intermediates **12** and **13**.[19] In this work the synthesis of carbamates starting from acid chlorides was reported (Scheme 2).

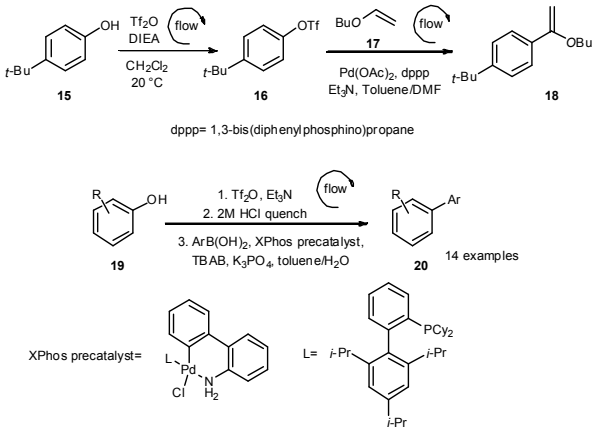


Features: Multistep telescoping reaction with in-line liquid-liquid extraction

Scheme 2 Multistep synthesis of carbamates.[18]

The first step was the phase-transfer reaction between aqueous azide and an acid chloride **11** to produce the corresponding acyl azide **12** and it was performed in a particular device, in which both the reaction and the separation of the two phases were performed. This approach was based on the use of a special *in-line* porous fluoropolymer membrane which allowed to separate the aqueous waste from the organic phase *in-line* without isolating any intermediate. The second step, the formation of isocyanates **13** from azide **12**, was performed in a microreactor packed with H-mordenite solid acid catalyst, HS-690. Finally the third step generated the carbamates **14** after reacting **13** with an alcohol. In this manner, ethyl phenyl carbamate, benzyl phenyl carbamate and methyl phenyl carbamate were produced in parallel, reaching 96-99% yields after 6-7 days of continuous work of the device.

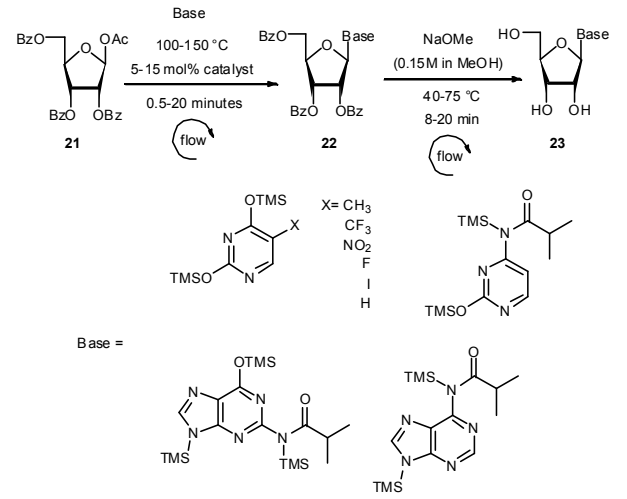
Other related and interesting contributions by Buchwald, Jansen et al. have been focused to coupling reactions using *in-situ* generated and reacted aryl triflates, avoiding time-consuming isolation. In this context the Authors developed a microreactor to perform Heck[20] and Suzuki[21] coupling reactions using triflates generated from the corresponding phenols as coupling reagents (Scheme 3).



Scheme 3 Heck and Suzuki coupling reactions performed in multistep microreactor device.[20, 21]

In the Heck reaction the formation of triflate was performed starting from the 4-*tert*-butylphenol (**15**) in dichloromethane with trifluoromethanesulfonic anhydride (Tf_2O) and diisopropylethylamine (DIEA). Then the reaction mixture was washed with a hydrochloric acid solution and extracted in a microseparator. Subsequently, the organic phase was distilled using a microfluidic device,[22] in which dichloromethane was distilled off and replaced by toluene and DMF. After solvent switching, 4-tert-butylphenyl triflate (**16**) reacted with *n*-butyl vinyl ether (**17**) giving the coupled product **18** in 80% yield. In similar fashion the Suzuki coupling was performed, but the formation of triflate was performed in toluene, and the coupling reaction in a water/toluene mixture, so there was no need for distillation and solvent exchange. In this manner 14 examples of Suzuki products **20** were synthesized in excellent yields (83-99%) with an average resident time reaction of 400 seconds for both steps.

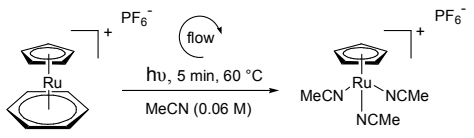
Jamison et al.[23] developed a multistep synthesis of nucleosides **22** and **23** starting from inexpensive *O*-benzyl protected ribofuranose (**21**) and a variety of nucleobases to give the corresponding β-anomer nucleoside **22**. The glycosylation reaction took place in a very short time (0.5-20 minutes) catalyzed by 2,6-di-tert-butyl-4-methylpyridinium triflate salt (5-15 mol%) in superheated acetonitrile (100-150 °C). Through this approach different nucleosides **22** were prepared with excellent yields (80-99%). The protocol could be scaled up to gram-scale by simply using a larger volume reactor, obtaining in 3.5 hours, 26 grams of a representative uracil nucleoside, with a production of 7.4 g h^{-1}. Similarly, fully deprotected nucleosides **23** were obtained by adding to the flow stream methanolic sodium metoxide (NaOMe) solution which was responsible for the benzoyl deprotection (Scheme 4). Using this protocol, different nucleosides **23** were synthesized in high yields (93-98%) circumventing the need to isolate and purify the intermediate products.



Scheme 4 Synthesis of nucleosides in multistep synthesis.[23]

Very short reaction time can be obtained in microreactor devices by exploiting fast mixing time. An example has been reported by Yang et al. dealing with the synthesis of aldo-naphthimidazole.[24] The protocol included the use of iodine as an oxidant in acetic acid solution, and unprotected aldoses (D-glucose, D-maltose and D-maltotriose) and 2,3-naphtalenediamine as starting materials. The first step was the condensation of naphtalenediamine with an aldose, forming the corresponding Schiff base that underwent to iodine oxidation leading the corresponding aldo-naphthimidazoles. By performing this transformation in a microreactor, the reduction of the reaction time by a 103-106 factor was possible. Indeed, in batch conditions the process took place in 21600 seconds, whereas in microreactor it took place in 10 seconds, obtaining even an increased yield from 71% to 86% respect to batch conditions.

Another interesting example of minimization of reaction time switching from batch condition to flow condition was reported by Jamison et al. who performed a photochemical preparation of the ruthenium complex **24** (Scheme 5).[25] More in details, in batch this type of reaction took place in 12-48 hours, but in flow only 5 minutes were necessary, and in addition the best concentration could be increased up to three times, from 0.02 M to 0.06 M, without decreasing the 99% yield. Furthermore the throughput of the reaction was also increased of 10 times with respect to the batch condition reaching a production of 1.56 g h^{-1}.



Features: Increased efficiency (reaction time, higher concentration, productivity) respect to batch conditions

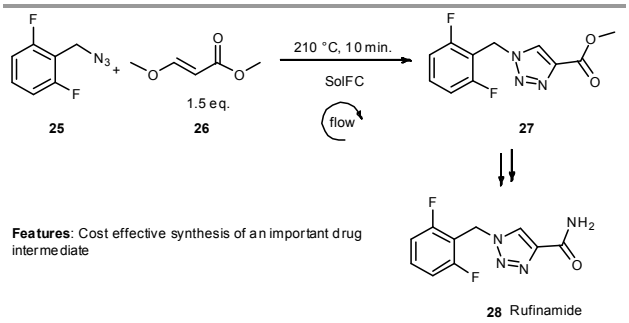
Scheme 5 Photosynthesis of ruthenium complex.[25]

"Novel Process Window",[10d, 14, 26] is a novel approach that consists in performing reactions at temperature much above the boiling point of the solvent. This approach was aimed at the reduction of the reaction time, but also may lead to a minimized environmental impact, when considering the energy contribution in life-cycle analysis.[27] As an example in the transformation of 1,3-dichloropropyl pivaloate into 3-chloro-2-hydroxypropyl ester, a 5760 fold decrease of the reaction time was achieved.[28] In this case the reaction was performed in *n*-butanol (b.p. = 117 °C) at 180-200 °C using water as a reagent and 4-buthyl imidazole as a base, and the best yield (60%) was reached in 5-10 minutes of residence time. A yield of 58% was anyway reached after only 30 seconds, whilst in the batch condition 48 hours of reaction were necessary to reach sufficiently high yield.

A catalyst-free direct condensation between acid chloride and alcohol was developed by Stevens et al. in a microreactor device.[29] In this case the use of flow conditions allowed in 5-7 minutes of residence time to reach the sufficient level of reactivity without the need of a catalyst and making the product purification step unnecessary which was particularly interesting in terms of cost. As an example, benzoyl chloride and methanol were converted in methyl benzoate within 300 seconds and 90% yield of the pure product was isolated after simple evaporation of the excess of methanol. Similar results were obtained for both aromatic and aliphatic acid chlorides using methanol, ethanol and isopropanol as alcohols. The HCl produced in the reaction could be collected by purging the reaction mixture with dry nitrogen and trapping the HCl vapour in water.

Another catalyst-free process with short reaction time was reported by Jensen et al. consisting in a direct oxidative amidation of aromatic aldehydes using as oxidant cheap aqueous hydrogen peroxide (30 wt%).[30] The reaction was performed in acetonitrile or in tert-butanol and electron-rich, -neutral, and –poor aromatic aldehydes were transformed into their corresponding amides using morpholine, pyrrolidine, piperidine, *N*-methyl-1-phenylmethanamine and D or L-proline tert butyl ester as amines. The reaction took place in 20-40 minutes obtaining 79-92% isolated yields.

Hessel et al.[31] developed a greener Huisgen cycloaddition to synthesize an important intermediate for an antiepileptic drug called Rufinamide (**28**). Cheap and non-toxic (*E*)-methyl 3-methoxyacrylate (**26**) was used as dipolarophile with 2,6-difluorobenzylazide (**25**) (Scheme 6). The initial batch procedure reported by Stevens et al.[32] required long reaction time (28 hours) and high temperature (135 °C) and was performed in solvent free conditions (SolFC), whereas solvent-free large scale batch processing of organic azide at high temperature is not recommendable due to the limited stability of azide compounds. Hessel et al.[31] optimized the conditions to apply continuous flow technology in order to shorten reaction time, indeed by optimizing the reaction temperature and balancing between the reactivity and the decomposition rate of the azide, they reached an optimal residence time of 10 minutes at 210 °C.

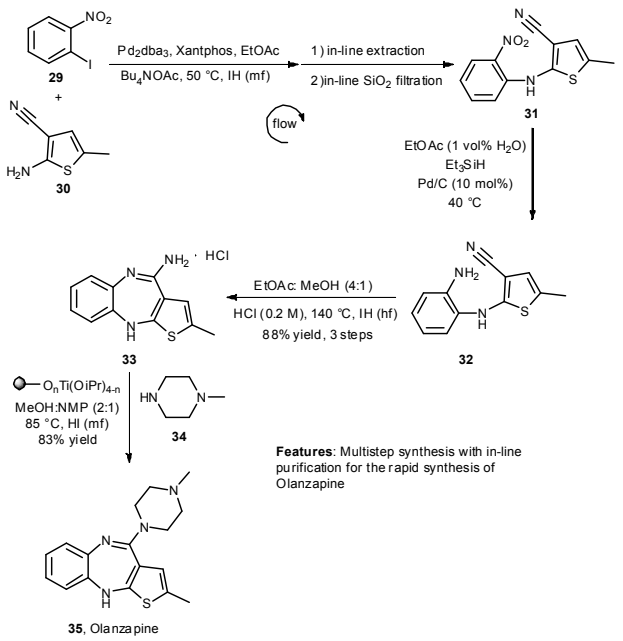


Features: Cost effective synthesis of an important drug intermediate

Scheme 6 Huisgen cycloaddition to synthesize a key intermediate to Rufinamide.[31]

Moreover, by performing the reaction at a temperature above the melting point of the product (136-137 °C) they prevented the reactor from clogging even if SolFC were used. They also optimized the purification process integrating it in the flow. The product was easily collected by diluting the reaction flow with methanol (15:1, v/v, methanol/product stream) and recrystallized upon cooling in the collection tank. In this way the product was obtained in 83% yield after simple filtration.

Kirschning et al.[33] adopted the high-frequency inductive heating (IH)[34] to accomplish the multistep synthesis of Olanzapine (**35**), an atypical antipsychotic. They performed all the synthesis in flow utilizing inductive heating as heat source essentially for the last two steps (Scheme 7). In particular, high-frequency gave the best results in the acid promoted cyclization, whereas medium frequency gave always impure product. The last step, catalyzed by a supported silica titanium Lewis acid, allowed to finally access Olanzapine (**35**), in 87% yield thanks to inductive heating, while conventional heating allowed only 80% yield. Moreover they performed all the purification *in-line* and conducted the first three steps continuously for 30 hours without chromatographic purification and solvent switching (all reactions were performed in ethyl acetate) obtaining the thieno[1,5]-benzodiazepine (**33**) in 88% yield. Even with the solvent switching for the last reaction, which is performed in methanol, the overall reaction time was still lower than the patented batch synthesis.



35, Olanzapine

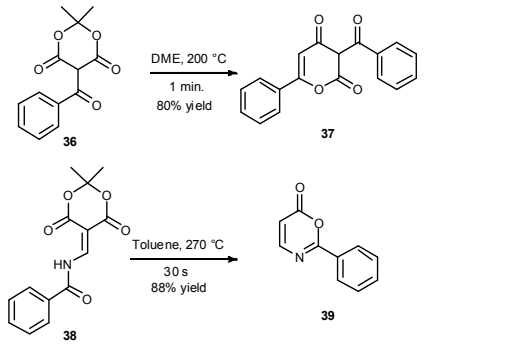
Scheme 7 Multistep continuous flow synthesis of Olanzapine **35**.[33]

The "Flash Flow Pyrolysis" (FFP) is a technique to perform high-temperature pyrolysis, that takes places in seconds or few minutes, in flow. In particular the possibility of accurate control of reaction time, reachable with the flow, allows a precise control of the reaction. Kappe et al.[35] applied this technique to the pyrolysis of some substrates among which benzoyl-Meldrum's acid (**36**), acylaminomethylene-Meldrum's acid (**38**) (Scheme 8), obtaining the desired pyrolysis product in a time ranging from 15 seconds to few minutes, highlighting the enormous advantage of microreactors to increase the temperature (in this example up to 340 °C) to obtain a quite instantaneous reaction, often without by-products.

3. Optimization for time screening

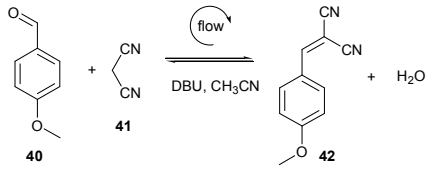
In the search for the optimal reaction conditions and especially at the scale up stage, any technology able to minimize the quantity of the starting material used and the time needed for its processing, are more than welcome. Flow chemistry and in particular microreactor technology, perfectly contribute in this direction by minimizing use of costly material thanks to the small volume reaction capacity,[36] and by reducing the time screening for the best reaction conditions exploiting automation, which enables the testing of hundreds of reactions per day.[37]

Jensen et al. developed an automated microreactor system which, with the use of a minimal amount of material, could allow the definition of the best reaction conditions within very short time screening.[38] The system was based on an *in-line* HPLC monitoring system which allowed a continuous check of the reactions, and different algorithms were used to self-optimize the reaction conditions automatically. Indeed the algorithms used through the analysis of the reaction yield were able to tune the operational parameters (residence time, temperature) changing them from time to time in order to achieve the best results.



Scheme 8 Flash Flow Pyrolisis example in flow.[35]

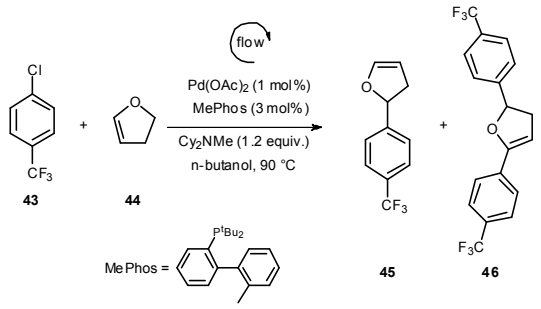
To demonstrate the robustness of this approach the Authors applied these technique to two different reactions namely the Knovenagel condensation reaction involving *p*-anisaldehyde (**40**) and malonitrile (**41**) catalyzed by 1,8-diazabicycl-[5.4.0]undec-7-ene (DBU) (Scheme 9), and the oxidation of benzyl alcohol to benzaldehyde, catalyzed by chromium trioxide. The Authors were able to optimize the Knovenagel reaction performing only 13 experiments, within 4.5 hours, reaching 77% yield.



Scheme 9 Self optimization of Knovenagel reaction.[38]

A similar methodology has been used by Jansen, Buchwald et al. to optimize the Heck reaction of 4-chlorobenzotrifluoride (**43**) and 2,3-dihydrofuran (**44**), using palladium (II) acetate as catalyst. Optimization of this process proved to be challenging due to the high tendency of the coupling product to promptly react with a second equivalent of aryl chloride (Scheme 10).[39]

The reaction reached full conversion in less than 10 minutes, and the automated system optimized the yield of the desired product by varying the residence time and the equivalents of alkene. Using this method the Authors optimized the reaction with only 19 experiments reaching a maximum of 83.1% yield. Moreover they scaled up the best reaction condition (5.5 minutes residence time and 5 equivalents of 2,3-dihydrofuran (**44**)) in a 7 mL glass reactor, reaching an output of 114 kg y^{-1} of the desired product.



Features: Self optimizing microreactor, short time screening, mesoscale flow reactor

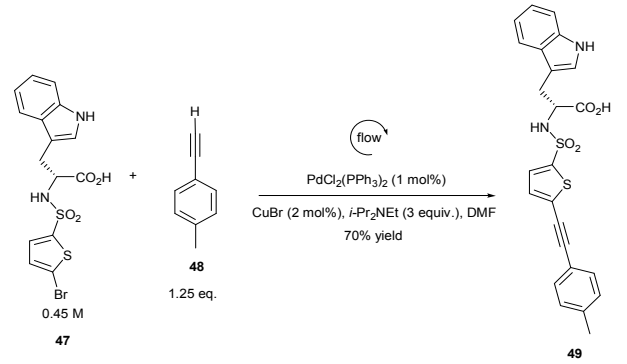
Scheme 10 Screening Heck reaction.[39]

Another self-optimizing system was reported by Poliakoff et al.[40] using supercritical CO_2 ($scCO_2$) as reaction medium. The self-optimization process was particularly important when $scCO_2$ was used as medium because the highly compressible nature of the solvent, related to its tunable density, introduced another variable to optimize in the reaction conditions compared to conventional media. Indeed, in this contribution, the Authors optimized three reaction conditions at once: temperature, pressure, and $scCO_2$ flow. They monitored the yield of the reaction by an *in-line* GLC and with a specific algorithm, the super modified simplex algorithm (SMSIM).[41] Optimization was directed towards the access of two different products starting from the same reagents i.e. 1-pentanol and dimethyl carbonate. The first product, methyl pentyl carbonate, could be obtained with a maximum 40% yield, while for the second, 1-methoxypentane, optimization led to a 70% yield.

The same Authors similarly studied the methylation of 1-pentanol using dimethyl carbonate (DMC) as methylating agent, and this time optimized four parameters at once (temperature, pressure, $scCO_2$ flow rate and the equivalents of methylating agent). In this way they obtained a successful 98% yield.[42]

Recently, the single-trajectory automated optimization was improved in a multitrajectory optimization by Jensen et al. in the study of a Paal-Knorr reaction between 2,5-hexanedione and ethanolamine in dimethyl sulfoxide analyzed using a micro IR flow cell for continuous *on-line* monitoring.[43]

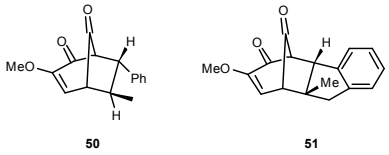
Another type of computer aided optimization screening using a microreactor system was developed by Fukuyama et al. (Scheme 11).[44] This method was not self-optimized but was able to easily perform up to 120 reactions by programming temperatures and flow rates (therefore residence time) and the equivalents of reactants. In this contribution, the Authors optimized and scaled up the synthesis of a matrix metalloproteinase inhibitor **49** based on a Sonogashira coupling. More in details, by repeating the use of the computer controlled system for four times they optimized one parameter at a time (temperature, residence time, alkyne and amine equivalents). In this manner they reached an optimum yield of 70% of the desired product in the 100 gram scale production.



Features: Fast screenig up to hundred of reaction conditions, fast scale up to 100g scale

Scheme 11 Optimized condition for the Sonogashira coupling.[44]

Beeler et al.[45] studied the transformations of densely functionalized bicyclo[3.2.1]octanoid scaffolds (e.g. **50**, **51**, Scheme 12) by exploiting "multidimensional reaction screening".[46] Following this approach new reactions can be discovered through screening of either multicomponent systems or reaction partners and catalysts with the final goal of accessing new chemical scaffolds and novel compounds of interest. Indeed bicyclo[3.2.1]octanoid scaffolds may react with two different electrophilic sites and one amphiphilic site, so they are perfect scaffolds to use in multicomponent reactions.

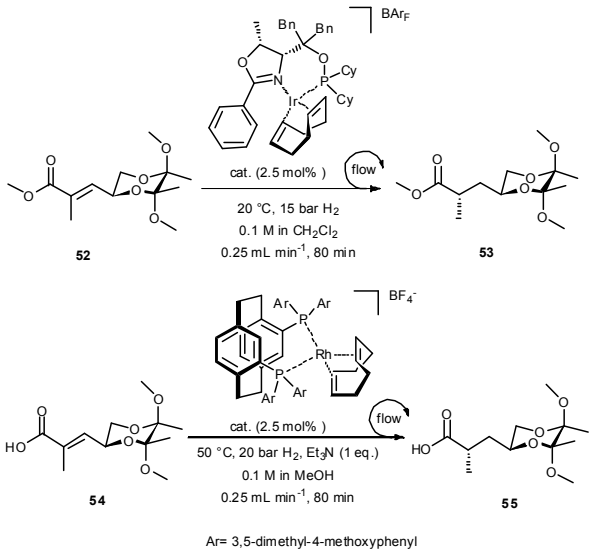


Features: Thousand of reactions screened on analytical scale

Scheme 12 The bicyclo[3.2.1]octanoid scaffolds used for "multidimensional reaction screening".[45]

The Authors used an automated microfluidic system able to execute from one to thousand analytical scale reactions, thanks to a 96-well reagent block and a particular sampling pulse system which allowed introducing in the microreactor the different reagents individually. In this manner contamination between each reaction "drop" was avoided. With this method, two different bicyclo[3.2.1]octanoid scaffolds (Scheme 12) were screened with 23 heteronucleophiles, 16 carbon/dipole nucleophiles and 16 electrophiles (reaction partners), using two non-nucleophilic bases i.e. 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Each reaction was performed with 1 μmol of substrate in a total volume of 24 μL, and more than 1000 reactions were screened and analyzed on an analytical scale.[45]

Another advantage of the reactor technology is the screening of hydrogenation reactions. Indeed, the flow reactor technique is more advantageous respect to the more tedious set up of batch screening, which requires multiple stainless steel reactors for parallel reactions. An example was reported by Ley et al.[47] in the asymmetric hydrogenation in a tube-in-tube reactor of trisubstituted olefins using a number of chiral iridium- and rhodium-based catalysts (Scheme 13).



Features: Continuous asymmetric hydrogenation, prolonged activity of catalyst

Scheme 13 Asymmetric hydrogenation in tube-in-tube reactor.[47]

Preliminarily, the Authors focused the attention on the identification of the best catalyst in terms of yield and diasteroselectivity. They found that best results were achieved by using an iridium-based catalyst which allowed to obtain a 90% conversion and a 76% diasteroselectivity. Further optimization of temperature, pressure, flow rate, reaction time, catalyst quantity and concentration of reagents gave a full conversion, but not an improvement in diasteroselectivity. These satisfactory results were obtained for the methylester trisubstituted olefin **52**. For the corresponding acid **54** the best reaction condition gave a conversion of 95% and a diasteroselectivity of only 59%. To improve the latter result the set up was modified adding a second reactor to replenish the reacted hydrogen. This solution was adopted because the dissolved hydrogen, which appeared a major factor for the reaction, deplenished as the reaction proceeds therefore reducing the efficiency of the process. In this way 99% of conversion and 67% of diasteroselectivity was accomplished for the preparation of **55**. Moreover to decrease the amount of catalyst used and to prolong its activity the Authors set up a recirculating flow reactor. With this set up the conversion with 1 mol% of catalyst increased from 49% to 75% maintaining identical diasteroselectivity outcome.

Although the microreactor technology allows performing hundred or even thousands of reactions in very short time, there is the necessity to optimize the reaction needed to reach the best reaction conditions. This aim can be achieved using the D-optimal designs, an algorithm used for analyzing for multi-factor experiments,[48] that avoids redundant data and reduces the number of reactions needed to perform to determine the best conditions. By this mean Rutjes et al.[49] were able to control and optimize up to 5 parameters (reaction time, temperature, concentration, and the stoichiometry of reactants, etc.) in the same time with only 180 experiments, thus reducing the screening time and the reactants used. This method was applied to the Swern-Moffatt oxidation of benzyl alcohol to benzaldehyde. Usually, this type of oxidation is performed at around -78 °C to avoid side reaction, but utilizing the microreactor technology, which permits a very short residence time (in this case the optimum was reached at 32 milliseconds), the reaction reached the best yield at 70 °C, almost 150 °C higher than the batch conditions.

In similar fashion, the removal of *p*-methoxyphenyl protecting group from 1-phenylethanamine was optimized taking in account three factors (temperature, stoichiometry and reaction time) performing 51 reactions in a total time of 5.6 hours consuming only 0.2 milligrams of substrate for each reaction.[50] Moreover the process was transferred to a preparative scale, leading to a production rate of the free amine of 213 mg h^{-1}.

Selway et al. integrated the flow microreactor technology with the structure-activity relationship (SAR) technique, with the aim of exploiting the rapid and automated synthesis of various compounds, at the same time, and identify the most promising candidate for a kinase inhibitor.[51] The approach relied on the use of microreactor which allowed a fast synthetic protocol, an automated biological assay to measure the activity of the compounds, and the algorithm-based evaluation of structure-activity relationship which automatically chose the next most promising compound to be synthesized. The Authors designed a structure-activity map with only 22 compounds closely similar to that obtained with 270 compounds. With this technique they discovered four new highly active compounds. Furthermore, considering that one design-synthesis-screening loop required 90 minutes, the overall time for the evaluation of all the 22 compounds was ca. 24 hours of automated work of the system, highlighting how this system could reduce the time required for preclinical drug discovery.[51]

4. Waste minimization

Most commonly research contributions, devoted to the adoption of flow conditions for the definition of novel synthetic tools, reported the use of diluted conditions suitable for performing the desired chemistry in flow.

Solvent actually represents a critical issue in developing a green synthetic tool both at a laboratory small-scale or in large production. The green chemistry principle number

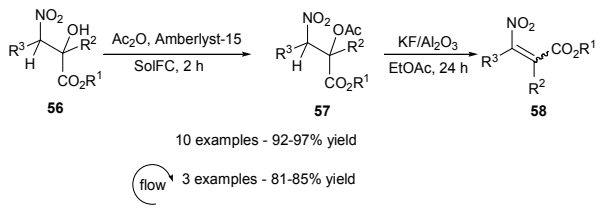
five points out that in view of realizing an environmentally-efficient process, the use of solvent should be made unnecessary or minimized. Generally, the largest contribution to waste is due to the solvents used for running the reaction, for the isolation and purification of the products.[52] Several of the solvents normally used, especially in fine chemical syntheses, are volatile and their dispersion in the environment is almost unavoidable (one example above all is given by dichloromethane, the 70% of which is inevitably dispersed). Attention is directed towards safer alternatives, supercritical fluids (mainly CO_2), ionic liquids, bio-based solvents and water are the most representatively investigated options. Anyway a careful evaluation of the actual beneficial effects of such media on the greenness of the process should be always accounted before considering them "green". A drastic option is the use of no solvent at all (solvent-free conditions, SolFC). In this latter case, chemistry should be developed in order to use reactants that are inherently stable to benefit from highly concentrated conditions or even requiring a catalytic activation to reach the needed reactivity.

Flow, in certain cases, may be the most efficient tool to reach the highest chemical and environmental efficiency. In fact, to minimize waste, reactants should be used in equimolar amounts and with the minimal quantity of additional solvents and heterogeneous catalysts may be very useful provided that they are easily recoverable and reusable. Adoption of classical mechanical mixing may lead to some practical difficulties with a generally inevitable physical degradation of the heterogeneous catalytic system hampering its recovery and reducing its efficient life.

An example of the use of flow has been reported in the synthesis of a large variety of β-nitroacrylates featuring the use of heterogeneous catalysts to minimize waste production, has been recently disclosed (Scheme 14).[53]

The synthetic approach reported is based on the SolFC acetylation of hydroxyl group of nitroalkanol precursors **56** and then subsequent acetic acid elimination induced by KF/Al_2O_3 as base. Adoption of flow conditions, allowed performing the process on sensitive substrates which lead to a complex mixture of products in batch conditions.

One of our specific interest concerns the application of flow conditions as a very efficient technical tool that in combination with the use of safer media such as water or SolFC or highly concentrated conditions, and with specifically designed heterogenous catalysts offer a very powerful tool for minimizing waste production and intensify the synthetic process. Some examples are given below.



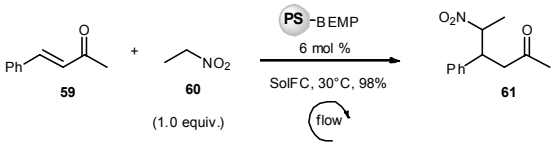
Features: Applicability in flow of unstable susbstrates

Scheme 14 Preparation of β-nitroacrylates **58**.[53]

The use of several polymer-supported organic bases for the activation of different types of C-,[54] N-,[54c, f,] O-,[54b, f, 55] S-[54f, 56] P-,[57] nucleophiles has been investigated. In particular, in the activation of nitrocompounds for the Michael addition to α,β-unsaturated compounds,[54e] it has been disclosed the first use by this research group of flow technique to prepare β-nitro carbonyls in very high chemical efficiency and low environmental impact measured by E-factor of the flow procedure. Most recently it has been optimized this process reporting a novel protocol in flow, and the most relevant green metrics for all the known protocols used to access γ-nitroketones, have been compared (Scheme 15).[58]

These calculations furnished a further proof that flow approach in combination with the use of SolFC, a reusable heterogenous catalyst, equimolar amounts of reagents, and minimal use of organic solvent to recover the final products was able to dramatically reduce the reaction waste. In fact, the E-factor associated to this protocol was lower than the other literature reports, even when it has been calculated without considering the recycling of the catalyst and the solvent recovery.[58]

In flow, solid catalyst can be easily and successfully recovered and reused. Ethyl acetate as a green option included in green solvents lists,[52] was chosen as solvent for product recovery, and also thanks to its adequate boiling point its full recovery could be almost fully achieved.



Metrics for reprepesetative flow synthesis of **61** (including catalyst and solvent recovery)

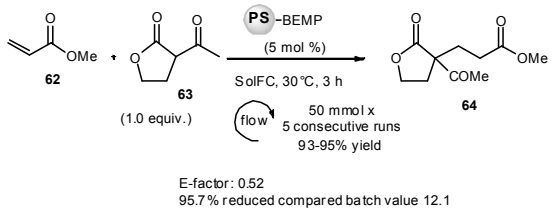
Atom Economy: 100%	E-Kernel: 0.02%	E-factor: 0.066
Reaction Mass Efficiency: 98%	E-Excess: 0%	PMI: 1.066
	E-Aux: 0.042	

Features: Very low waste production using flow, high throughput volume thanks to SolFC

Scheme 15 Preparation of β-nitrocarbonyls as **61**.[54e, 58]

This approach has also been applied to other Michael additions.[54b, c] For example, in the case of the reaction of methyl acrylate (**62**) with dicarbonyl **63** has been promoted by tert -butylimino-2- diethylamino-1,3 -dimethylperhydro- 1,3,2- diazaphosphorine supported on

polystyrene (PS-BEMP) under SolFC (Scheme 16), the protocol was repeated for five consecutive runs and the efficiency of the catalyst was unchanged. The E-factor of the process in flow is 0.52 with a reduction of 95.7% compared to the 12.1 value obtained in the batch process.[54c]



Features: Improved stability and recoverability of the solid catalyst, minimal waste production

Scheme 16 Michael addition in flow under SolFC.[54c]

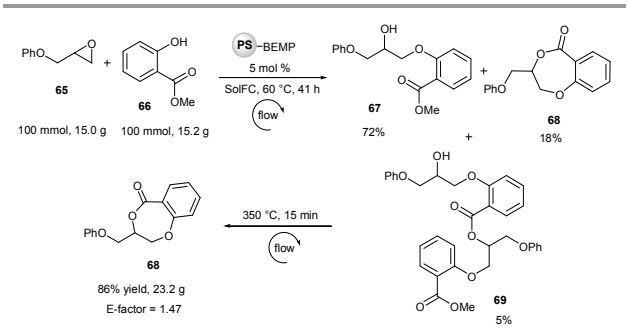
A similar result has been obtained in the search for a highly efficient protocol for the hydrophosphonylation of aromatic and aliphatic aldehydes catalyzed by PS-BEMP under SolFC. Several α-hydroxyphosphonates were prepared in quantitative yields and low E-Factor values, thanks to a simple workup procedure that allowed the use of a little amount of organic solvent. By using flow, a larger scale procedure was set enabling to further reduce the E-Factor of the process by 92.7–96.3%.[57]

It should be noticed that in all cases , the reported comparison between batch and flow procedures is only representative. In fact, while flow also allows performing larger scale processes, it also offers the opportunity to optimize solvent amounts while keeping the physical integrity of the solid catalyst that can be easily reused. In batch, this is not directly possible, because the solid catalyst is crunched by the mechanical stirring thus often creating practical issues in its recovery and in the isolation of the products.

Another application of Green SOC Perugia approach has been reported in the PS-BEMP catalyzed phenolysis of epoxides under SolFC (Scheme 17).[55] In this case using the newly defined flow procedure a 99.5% E-factor reduction was achieved compared to literature (0.74 *vs* 240). In this work it has also been reported an innovative two-step synthesis of the representative oxathiepinone **68** featuring a very low E-factor of 1.4. By applying flow approach the mixture of products **67**-**69** coming from the phenolysis of **65**, including the "bis-product" **69**, could be completely converted into the derivative **68** very satisfactorily.

Similarly, by using as solid base a Rasta-immobilized 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), it was performed the ring-opening of epoxides by thiols under SolFC achieving a 97% E-factor reduction from 15.3 (average of literature results under SolFC) to 0.46 (average on Green SOC flow).[54b]

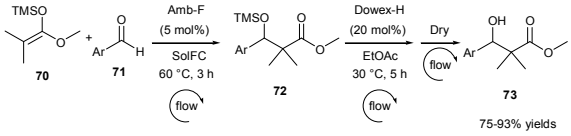
This use of flow, SolFC or highly concentrated conditions, and heterogenous catalysts, has been also applied to another class of transformations based on the fluoride ion activation of Silicon-Carbon, Silicon-Nitrogen, and Silicon-Oxygen bonds.[60]



Features: Very low waste production using flow

Scheme 17 Preparation of oxathipinone **68** in flow.[55]

A waste-minimized synthesis of β-hydroxy esters **73** could be achieved[61] after a batch optimization of the conditions for activating methyl trimethylsilyl dimethylketene acetal (KSA) (**70**) towards the reaction with aldehydes **71**. Macroreticular polystyryl trimenthylammoniun fluoride (Amberlyst-F, Amb-F) was the best fluoride source and SolFC were necessary to reach the sufficient reactivity. Amb-F (5 mol% dried) was able to promote the Mukaiyama aldol process allowing to access the corresponding silylated products **72**. De-silylation step, was promoted by 20 mol% of Dowex 50Wx8 H that allowed the routinely employed over-stoichiometric amounts of aqueous HCl to be replaced. Aldehydes featuring electron-withdrawing gropus gave best results by adding 50 mol% of water. Final products **73** could be isolated pure form in 73-92% yields after a drying step (Scheme 18). This three-step protocol based on two different solid catalysts allowed to significantly reduce the waste production. Anyway, the optimal efficiency of the process could be achieved by using flow. A three-step protocol was defined for the E-factor minimized preparation of β-hydroxy esters. EtOAc was used in minimal amount as medium to pass the reaction mixture from one reactor to the other after the completion of each process. The protocol featured a 98.7% E-factor reduction from 127 (average of literature results) to 1.7 (average obtained in flow).[61] Vaccaro et al. have recently dedicated special attention to fluoride activation of Si-N bonds especially in the β-azidation of α,β-unsaturated ketones[62] and carboxylic acids.[63] These processes can be efficiently performed following very few procedures.[62, 63, 64]

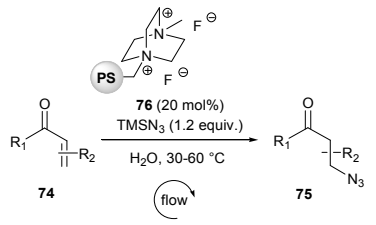


Features: Hight throughput volume thanks to SolFC, stabiility and reusability of the catalysts thanks to flow

Scheme 18 E-factor-minimized preparation of β-hydroxy esters **73**.[61]

Although in a preliminary protocol satisfactory E-factor values were achieved (ca. 22) in the β-azidation of α,β-unsaturated ketones **74** catalyzed by Amb-F under SolFC,[62c] an important limit of known polymer-supports was identified: the reaction mixture showed an evident tendency to stick with the polymer

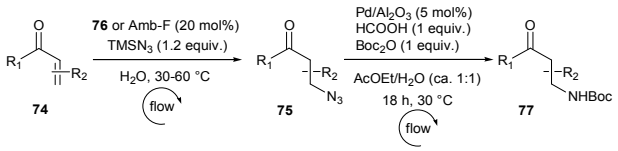
resin suggesting that known polymers designed to be swelled and used in organic solvents (typically dichloromethane) may not be completely adequate for being used in greener reaction media and in related flow conditions.



Features: Higher efficiency, stability and reusability of the catalysts in flow

Scheme 19 PS-DABCOF$_2$-catalyzed β-azidation of enones **74**.[62]

Vaccaro et al. , starting from their long experience on the use of water as reaction medium,[65] have exploited this possibly greener medium to increase the reactivity of the system. In addition, the idea was to improve dispersion of the reaction mixture and avoid organic fouling caused by the sticking of the reaction mixture within the polymeric matrix. With this aim a novel ammonium fluoride source supported on polystyrene was designed and prepared using 1,4-diazabicyclo[2.2.2]octane (DABCO) moiety (Scheme 19). Starting from different types of polystyrene chlorides (PS)-Cl, the corresponding bis-fluoride PS-DABCOF$_2$ **76** catalysts were prepared (Scheme 19). The flow procedure was also used for the definition of a multistep protocol for the preparation of the corresponding *N*-Boc-β-amino ketones **77** by coupling the β-azidation step with a Pd/Al_2O_3-catalyzed azido group reduction and concomitant amino group protection due to instability if the unprotected β-amino ketones (Scheme 20).[62b, c]



Features: Multistep protocol, major stability of reactants in flow

Scheme 20 Multistep synthesis of *N*-Boc-β-amino ketones **77**. [62b,c]

PS-DABCOF$_2$ (10 mol%) has been also efficiently used in the promotion of the azidolysis of epoxides by $TMSN_3$. Flow procedure, including also the desilylation step in the presence of 20 mol% of Dowex-H, allowed the related 1,2-azido alcohols to be prepared in excellent yields (95-97%) and low E-Factor values (1.6-2.1) corresponding to a further ca. 90% reduction of the waste production compared to already green batch protocol. The azidolysis and the azido group reduction was also coupled by defining a flow procedure that allowed the preparation of 1,2-amino alcohols with 2.9-4.2 E-factor values.[64]

An efficient and sustainable procedure for the chemoselective cyanosilylation of carbonyls has been developed by using triphenylphosphine on polystyrene (PS-TPP, 2-5 mol%) as heterogenous catalyst and TMSCN (1.1-1.5 equivalents) as a cyanide source.[66] Among the large variety of substrates 72-99% yields were obtained with E-factor values ranging between 5 and 10. In this contribution, a comparison between the use of flow in recycling or continuous direct modes was reported. E-factors obtained were very low 0.16 or 0.47 and comparable results were obtained in the two versions of flow showing that differences may be evident depending on the reaction scale used. It should be noticed that protocols using cyclic mode flow are a sort of batch-like procedures scaled-up where flow is used as an alternative tool to mix the reactants while preserving the integrity of the heterogeneous catalyst and the stability of labile reactants or intermediates. In most of the cases, optimization of the chemical process in batch may be roughly used to set-up flow procedure.

Continuous direct flow protocols instead, may offer some additional advantages in terms of controlling reactivity of the process, although their definition requires different or additional optimization of the starting batch chemistry.

In a recent contribution dealing with Suzuki coupling, flow has been used to minimize the waste associated to this fundamental chemical process widely employed in different fields such drug discovery or organic semiconductor synthesis.[67] In these type of transformations major contributions to waste are represented by toxic dipolar aprotic reaction media used[52a] and the normal need for silica gel chromatography to isolate desired products. Obviously, palladium used as catalyst should be desirable in heterogeneous form, easily recoverable reusable and featuring the minimal leaching.

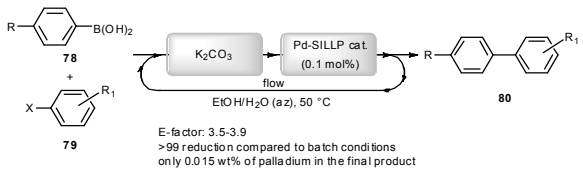
Based on the "release and catch" phenomenon concerning palladium catalytic systems,[68] it has been envisaged that a unique chemical outcome could be obtained by exploiting cyclic flow mode.

In fact, during the Pd-catalyzed process after oxidative addition, the "heterogeneous palladium" is released and then after reductive elimination it re-precipitates.[69] This phenomenon is closely related to Pd-leaching and it depends on the reaction medium, on the base, on the type of support, and of course on temperature used.

Using a palladium source based on supported ionic liquid phase (SILP) the reaction conditions have been optimized in order to use ethanol azeotrope as reaction medium and accordingly K_2CO_3 as base due to its insolubility in this medium. It should be noted that the adoption of azeotropes is very interesting in order to use media with combined polarity properties, but that can also be easily recovered and reused without requiring costly recovery or disposal issues.

By charging the base and the palladium catalyst on different reactive chambers, the Suzuki coupling of different phenyl boronic acids **78** and aryl halides **79** (Scheme 21) performed very efficiently and the recovery of Pd catalyst was very simple

since the catalyst was safely charged into the glass column and it was not mixed with the inorganic consumed base. Although the catalyst was used for just representative 4 runs, a TON of ca. 3800 has been anyway obtained and further runs may clearly lead to higher values. Using this flow approach, a significant advantage in terms of waste production was evident as products **80** could be directly isolated in pure form without requiring any further purification. In fact, E-factor values obtained were very low and in the range 3.5–3.9 or in the range of 18.7–21.6 in the case that recovery of the reaction medium was not considered in the calculations. Waste production has been reduced by more than 99% compared to batch protocols that featured E-factor values of 3180–5100 resulting from the need of product chromatography purification and the use not easy to recover mix of solvents (1:1/EtOH:water). These results have been possible just thanks to the adoption of flow technology in a cyclic mode and cannot be otherwise obtained.



Features: Higher efficiency, stability and reusability of the catalyst in flow, product purification step not needed

Scheme 21 Waste-minimized Suzuki coupling in cyclic-mode flow.[67]

With the similar intention of exploiting "release and catch" phenomenon in Pd-catalyzed reaction, the Green SOC approach has been extended to Heck reaction. In this case, ethanol azeotrope was not an efficient medium and it was found found that acetonitrile azeotrope gave very satisfactory results comparable to classic DMF/water medium normally used. In this case the most efficient base was a tertiary amine immobilized on polystyrene but that was also able to trap part of the reprecipitated palladium. Therefore in this case Pd-SILLP catalyst and solid amine were mixed together in the same reactor and could be both recovered and reused after additional washing by free amine. Overall efficiency was very high and performing the process at 120-130 °C, Pd release and catch phenomenon was completely efficient in order to isolate the final coupling product with a very low of Pd content of only 4.5 ppm.[70]

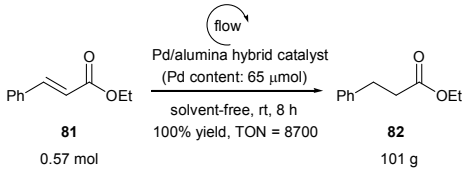
Within the development of self-optimising flow reactors described previously, Bourne, Poliakoff et al.[71] have contributed taking into consideration different criteria in order to develop a more sustainable flow process. In the optimization of methylation of alcohols using dimethyl carbonate in supercritical CO_2, it was compared yield (referred to the alcohol consumed), space–time yield (STY) (mass of product formed per volume of the reactor per unit time), E-factors (including or not CO_2 contribution), and weighted space time yield (STY × *Yield)*. Besides the specific results obtained, this contribution is rather interesting as an effort to furnish a useful tool in the not trivial process of making correct decisions towards sustainability.[71]

5. Safety improvement

The words flow and safety may cross each other in different contexts generally resulting in an improvement of the efficiency of a process, may be economical, chemical or often both. It has been pointed out in several occasions how beneficial can be the adoption of flow techniques in the manipulation of reactive reagents, in the chemical exploitation of unstable intermediates or in the controlling of highly toxic materials.[10]

Accordingly, flow approach can also become a strategic tool to optimize safety of a process conducted on larger scale. In flow, there are often several advantages for minimizing side reactions and therefore the formation of undesired, potentially toxic by-products which may be only separated by tedious and costly procedures. Generation of reactants extremely difficult to handle (hydrogen, diazomethane, hypofluoric acid, just to name few)[11, 72] posses an operational hazard with the need of high-pressure or autoclave conditions, and special safety precautions. To such issue flow can furnish the appropriate solution.

Hydrogenation in flow is a striking example in this context and this topic has been object of several contributions.[11] Recently, Kobayashi et al. reported a continuous-flow hydrogenation using polysilane supported palladium/alumina hybrid catalysts.[73] The new catalysts promoted the reductions of unsaturated C–C bonds and a representative nitro group, a removal of carbobenzyloxy (Cbz) group and a dehalogenation reaction on representative substrates. The processes were conducted using a variable amount of H_2 (different values of flow rate or 0.15 MPa fixed pressure) depending on the reaction, using safe reaction media or even solvent-free conditions. In the representative case of the hydrogenation of ethyl cinnamate (**81**) the catalyst retained high activity for at least 8 hours leading to the production of 101 grams of the corresponding saturated ester and reaching a 8700 TON value (Scheme 22). For the different examples presented TON values ranged from 1200 to 2700. Very importantly, Authors reported no leaching of palladium in the product. The flow system used was self-assembled.



Features: No Pd-leaching, continuous and safe use of the new heterogeneous catalysts

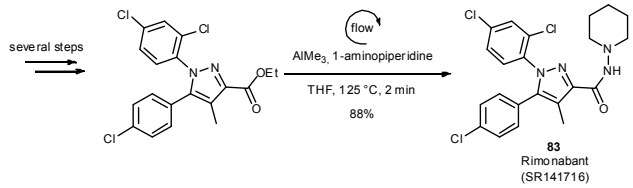
Scheme 22 Continuous-flow hydrogenation using Pd/alumina hybrid catalyst.[73]

Seeberger et al. have reported a safe and efficient high-throughput method for the amide bond formation mediated by trimethylaluminium using a flow microreactor system.[74]

The Authors contributed in this direction considering the wide utility of amide bond formation. Although aluminium–amides are unstable at elevated temperatures and easily gave rise to exothermic events even at room temperature. The activation of amine using aluminium-based promoters is frequently employed to avoid multistep sequences (typically starting from esters and consisting in hydrolysis, activation and amide bond formation).

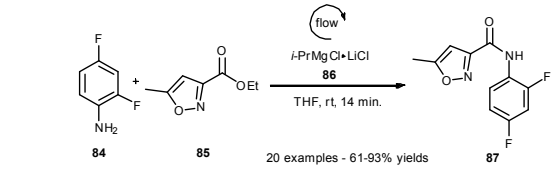
After comparing classical heating, microwave reactors and microreactors flow system, the Authors proved that efficiency heating of the microreactor was comparable to that of microwave allowing the amide-formation process to be completed after 2 minutes of retention time. In flow, the use of equimolar amounts of reagents was possible except in the case of secondary amines that required 1.5 equivalents of amine and trimethylaluminium. The protocol has been performed on a 8 mmol scale but in representative cases the system has been left to run for longer time converting also 200 mmol of starting ester. Reactor setup consisted of a simple three-way T-type mixer through which the three reactants were mixed before entering a microfluidic reactor.

Anyway, it should be also noted that dilution is acceptable and large volumes of solvent are not necessary. The method has been representatively inserted into a multistep sequence and exploited for the synthesis of structurally simple but pharmaceutically active substances Efaproxiral and Rimonabant **83** (scheme 23).[74]



Scheme 23 Trimethylaluminium mediated amide bond formation in continuous flow microreactor for the synthesis of Rimonabant **83**.[74]

A similar process has been reported by Alcázar et al. by using an isopropylmagnesium chloride (Bodroux reaction) in place of trimethylaluminium (Scheme 24).[75] Setting of the flow system in this case has been defined in order to preliminary mix amine **84** (0.65 M) and Grignard reagent **86** (1.3 M) (generally in a 1:1.5 ratio) in a microreactor system and then the resulting mixture was mixed in another microreactor with a more diluted solution of the ester **85** (generally 0.216 M) and the residence time has been regulated by adding a final 5 mL coil. Products could be also collected after an *on-line* work procedure by pumping the final reaction mixture through Amberlyst A-15 and replacing the classical HCl batch quenching. Generally the method was efficient and the Authors have directed their efforts towards an useful study on the compatibility of the functional groups and on the selectivity of the process by covering the chemical situations that most commonly were encountered in medicinal chemistry.

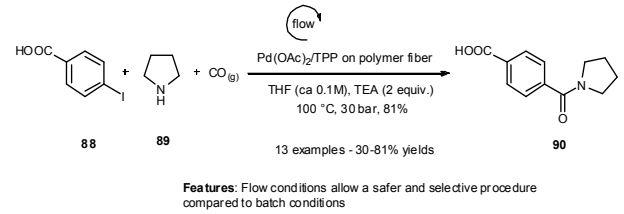


Scheme 24 Preparation of amides mediated by isopropylmagnesium chloride under continuous flow conditions.[75]

Csajági et al. reported the aminocarbonylation of carboxylic acids by direct introduction of external CO gas in a pressurized flow reactor system (Scheme 25).[76] This was a micro/meso fluidic continuous flow system that capable of reaching temperatures and pressures between room temperature and 200 °C and up to 150 bar, respectively. The system worked by flowing substrates through a low-volume stainless steel reaction line and let them react continuously on preloaded catalyst/reagent cartridges.

Several heterogeneous Pd-catalysts, organic bases, and reaction media, have been tested finding that polymer-supported tetrakis(triphenylphosphine)palladium, tiethylamine (TEA) and THF gave the best results. Influence of both pressure and temperature was also investigated concluding that the best combination to reach highest conversion and selectivity was 30 bar of CO pressure and 100 °C. This flow procedure allowed the safe use of high pressure CO but also led to better results in comparison to batch protocols (autoclave or flask using CO-filled balloon).

Reaction time calculated on residence time was ca. 2 minutes, in the representative case of the reaction of 4-iodobenzoic acid (**88**) with pyrrolidine (**89**), product was isolated in 96% conversion and 75% purity after solvent removal. *In-line* HPLC preparative chromatography furnished the 98% pure product **90** in 81% yield (Scheme 25). Leaching of palladium was not evaluated.



Scheme 25 Aminocarbonylation by introducing CO to a pressurized continuous flow reactor.[76]

This protocol furnishes a good example of the use of flow technique to simplify optimization of the reaction conditions allowing safer protocols. It also gives the opportunity to make some additional comments on the green/efficiency aspects. Large volumes of THF were used

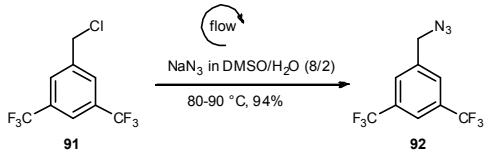
for this protocol and an evaluation of the method by known mass metrics (E-factor, RME, etc) would be poor and not able to measure, by giving a precise number, the advantage in terms of safety and time consumption.

Kopach et al. reported an interesting and detailed study on the synthesis of 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene (**92**) (Scheme 26).[77] In this process azide chemistry was involved and therefore several safety concerns must be addressed. Attention must be paid to avoid formation of insoluble explosive heavy-metal azide salts. Another issue was related to the formation of hydrazoic acid which is highly volatile and toxic compound that can be formed in the reactor headspace during conventional batch processing requiring significant engineering controls.

The Authors took as reference a work by Alvarez et al. where nucleophilic substitution reaction between 3,5-bis-(trifluoromethyl) benzyl chloride (**91**) and sodium azide was performed in DMSO using diethyl ether for the work up and achieving an E-factor of 112.[78]

In a preliminary optimization study in batch the Authors proved that higher efficiency could be achieved by using aqueous DMSO, and heptanes or isooctane could be used more efficiently for the isolation of the desired azide **92**. In batch it has been possible to achieve an E-factor of ca. 20, with an improvement of more than 80% compared to Alvarez's route.

In order to improve the overall safety profile, the process to produce azide **92** was optimized by setting a microcapillary tube reactor. Two different systems where investigated and the reactor having a length-to-diameter ratio 99360:1 (ca. 64 larger than the other one) gave the best results apparently confirming the sought effect for which narrower channel increases the linear velocity of the liquid for a given flow rate may increase mixing along the length of the tube.



Features: Comparison of batch, flow and phase-transfer protocols, where flow conditions allows a safe control of hydrazoic acid and by-product formation

Scheme 26 Improved synthesis of 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene (**92**) in batch and microflow.[77]

The microcapillary tube reactor process has proved to be able to minimize potential hazards associated with hydrazoic acid condensation in the reactor headspace also allowed for safe operation at higher processing temperatures than in analogous batch processing systems. The major drawback was related to the heptane/isooctane aqueous workup needed to isolate the target azide. E-factor achieved was 22, that was comparable to batch process but it must be considered that a measure of the safety of the system was not given.

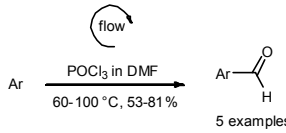
The Vilsmeier-Haak reaction is a well established synthetic method for the preparation of aromatic aldehyde *via* formylation of electron-rich arenes. $POCl_3$ is used to generate the actual formylating agent, also known as the Vilsmeyer-Haack reagent, from an amide (typically DMF). Such intermediate chloroiminium ion carries specific thermal hazards due to thermal instability possibly generating thermal runaway.

Nieuwland, Rutjes et al. have applied the flow chemistry approach to Vilsmeier-Haak formylation to be used for industrial scale.[79] Taking advantage of the efficiency in heat dissipation of the microreactor technology, the protocol featured enhanced safety and did not require a cooling system.

In the representative example of pyrrole, flow reactor has been set in order to mix $POCl_3$ and DMF to form the needed chloroiminium ion intermediate that was then delivered into the microreactor where was mixed with pyrrole. Final reaction mixture was quenched with H_2O/ethanol and iminium ion if still present was hydrolyzed in a solution of NaOH (0.27 M) (Scheme 27).

The optimization of the protocol has been accomplished by solving several issues. If $POCl_3$ did not completely convert into the corresponding iminium ion, when mixed to pyrrole, it reacted vigorously with pyrrole to form polymers, thereby clogging the reactor. This issue has been solved by exploiting an *in-line* IR analysis and concluding that 90 seconds were needed for the complete consumption of $POCl_3$ and complete formation of Vilsmeyer-Haack reagent. Optimal conditions for the reaction of pyrrole and chloroiminium ion were individuated at 60 °C, reaction time of 180 seconds, and a molar ratio of 1.5. Some attempts to reduce the use of DMF were also investigated but greener media tested gave lower conversion. With this idea in mind, final extraction of the product could have been developed in a safer medium while the Authors reported the use diethyl ether.

The approach proved to be effective in solving small-scale as well larger scale (6.0 g h^{-1}) issues and the protocol has been satisfactorily extended to other aromatics.

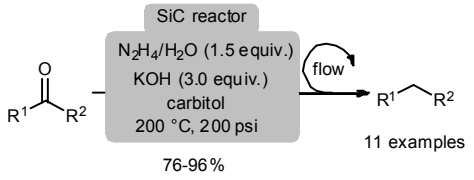


Features: Flow conditions allows a safe control of Vilsmeyer-Haack reagent formation avoiding thermal runaway and side polymerization of aromatic substrates

Scheme 27 Controlled Vilsmeier−Haack formylation of electron-rich arenes.[79]

Jensen et al. recently reported an effective contribution to the Wolff–Kishner reduction.[80] The Authors highlighted the main safety issue related to this process concerning the

handling of anhydrous hydrazine, isolation of the hydrazone intermediate and possible formation of azine by-products. In addition, materials generally used for the construction of flow reactors may give rise to serious issues. In fact, metals (stainless steel reactors) promotes hydrazine decomposition, glass is attacked by bases at elevated temperatures. To overcome these general limitations, the Authors have prepared a microreactor made of silicon carbide (SiC) (Scheme 28).[80]



Scheme 28 Wolff-Kishner reductions in flow using SiC microreactor.[80]

The SiC microreactor allowed to perform Wolff–Kishner reductions safely and in short times allowing the isolation of several products with high yields. The silicon carbide reactor proved to be highly stable under the needed harsh reaction conditions.

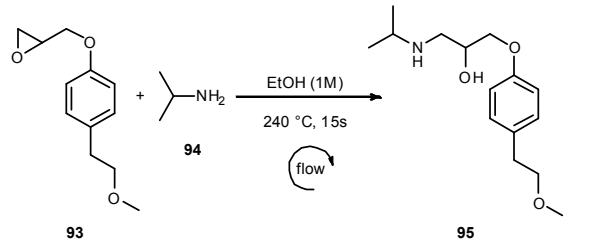
Another recent contribution on the use of flow to control the reactivity of hydrazine has been reported by Kappe et al.[81] Oxidation of hydrazine is used as the most direct route to generate diimide (N_2H_2) a valuable transfer hydrogenation agent.[82] Kappe et. al defined a continuous process based on the use of microreactors to adopt high temperature/pressure in a safe and controllable manner in order to generate *in-situ* and catalyst-free diimide from hydrazine monohydrate ($N_2H_4{\cdot}H_2O$) and molecular oxygen. Diimmide generated was used to selectively reduce alkenes to the corresponding alkanes. Short reaction times could be obtained thanks to the high surface-to-volume area and to high-temperature/ high-pressure conditions reachable in the newly defined gas–liquid continuous-flow system. Most importantly, the same data cannot be reproduced by using classic batch conditions.[81]

Wang, and Noël et al. recently disclosed a valuable procedure for the one-pot Stadler–Ziegler reaction, a practical synthetic tool to form C-S bonds.[83] They found that $[Ru(bpy)_3Cl_2]{\cdot}6H_2O$ was an effective photoredox catalyst that if irradiated with visible light, promoted the mild preparation of arylsulfides directly from arylamines and aryl/alkylthiols. This method solved intrinsic safety issues related to the presence of intermediates potentially explosive. In fact, the usual need of isolating a diazonium salt intermediate was avoided and the amount of diazosulfide was highly minimized. A microreactor flow protocol has been reported further minimizing the safety concerns especially at larger scale. The Stadler–Ziegler reaction was significantly accelerated in flow allowing faster production (13.2 mmol h^{-1}) if compared to batch (0.17 mmol h^{-1}) for a representative case.[83]

6. Process intensification and easy scale-up

The continuous flow technology and the process intensification research are nowadays very often related together.[84] Flow and microreactor technologies have often proved to be efficient tools to improve the productive use of chemical transformations.[85] In fact, intensification of a process can be achieved thanks to faster reaction times and higher productivity evaluated as the grams produced per hour per reactor volume, or also considering the possibility of combining many microreactors in parallel at the same time (numbering up).[84b] More recently, in the development of scaled up processes by flow technology, investigations are also directed on the evaluation of cost, environmental issues[86] and Life Cycle Assessment[87] to better evaluate the actual sustainability of the scaling up process.

Jamison et al.[88] described the aminolysis of epoxide in superheated ethanol comparing the results obtained in batch microwave and those obtained in microreactors. Especially when volatile amines were used, the use of microreactor allowed the increase of yield and selectivity in respect to batch under microwave irradiation. This behavior relied on the reduction of available headspace, between batch microwave and microreactor; indeed due to vaporization of the amine, its concentration decreased in solution and so the reactivity of the reaction. In particular, the reaction between 1-phenylcyclohexene oxide and 1-propylamine (b.p. 48 °C) in batch microwave condition gave only 19% of the corresponding β-amino alcohol, whereas in microreactor at 240 °C, temperature not achievable in microwave due to the high pressure (~ 500 psi), 68% of the desired product was obtained. This approach was applied to the continuous synthesis of a hypertension drug, Metoprolol **95** (Scheme 29) which was obtained in 91% yield, using 15 seconds of residence time at 240 °C. Scaling up these conditions allowed obtaining from a single microreactor (120 μL volume) 61 kg y^{-1} of this drug, and 17 microreactor operating in parallel could synthesize 1 t y^{-1} of **95**.



Scheme 29 Synthesis of Metoprol (**95**) in flow.[88]

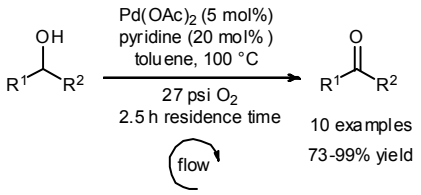
A recent example on the advantage of using flow when scaling up a synthesis compared to batch approach was

reported by Yu et al.[89] Nitration of p-difluorobenzene was examined considering that this type of reaction can suffer from the several side reactions leading to sulfonated, dinitro and phenol byproducts. Exploiting a fast and precise heat and reaction time control in flow, these products could be minimized. In fact, by confronting continuous and batch approaches, the former reached a 98% yield and a purity of 99% of the crude product isolated only after extraction, proving that no by-products were formed. On the other side, batch conditions reached a yield of 80% with 99% pure product only after distillation. Moreover the Authors scaled up this process achieving an output of 6.25 kg h^{-1}. They also reported the recycling of acidic waste by adding directly 1 equivalent of HNO_3 to the waste in every run, and adjusting the concentration of sulfuric acid to more than 80 wt%. The same acidic mixture can be utilized directly for the subsequent runs.

A challenging approach to flow technology is to apply it to biocatalysis, due to long residence time and multiphase media which are common employed in biotransformations. An example has been reported by Gasparini et al.[90] using an Agitated Tube Reactor (ATR), which consists in a dynamically mixed reactor relying on loose agitator elements and mechanical shaking of the reactor body for mixing. This type of mixing allows to perform processes with long reaction time and slurry conditions. The Authors reported the enantiomeric resolution of DL-alanine mixture by the selective oxidation of D-alanine to the corresponding α-ketoacid by D -amino acid oxidase and obtaining an enantioenriched mixture of L-alanine. Multiphase reaction conditions, include the presence of gas (oxygen), liquid (alanine solution) and solid (enzyme immobilized within whole cells). The process was performed both in batch and flow condition, and scaled up to 4 L in batch and 10 L in flow, the results evidenced how much convenient was to scale up this type of bioprocess in a flow mode. Indeed, in batch condition 36% conversion was achieved while 94% conversion was reached in flow. Moreover, using the 10 L flow the oxygen consumed was reduced to from 0.75 to 0.25 ((L h^{-1})/L), highlighting that in batch oxygen was used in large excess and wasted. An important feature of this approach was the avoidance of blockage, despite the presence of organic debris, thanks to the ATR flow technology.

An example of scaling up a reaction involving a gas as reactant was reported by Ley et al.[91] They described the synthesis of carboxylic acid using CO_2 in a Tube-in-Tube reactor membrane. The Authors used a gas permeable membrane tubing of a inert copolymer of tetrafluoroethylene and 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole which possessing a high gas permeability can be exploited as an effective delivering method of a gas to a liquid flow stream. The reactor consisted in an outer tube, where the reaction mixture was flowed, and an inner tube, comprising the gas permeable membrane, which allowed the gas to be delivered in the reaction mixture. Using this system the Author synthesized 10 different carboxylic acids (75-100% yields) starting from the corresponding Grignard reagents, and using CO_2 as reactant. Moreover, the scalability of this system was investigated performing the process on a 20 mmol scale, just adopting a larger reactor and obtaining the same results as the smaller set-up, highlighting the straightforward scalability of the flow process.

Another example of using gas with flow technology in a easy scalable manner was reported by Stahl et al.[92] where an aerobic oxidation of alcohol catalyzed by palladium acetate was described. The scalability of this process was particularly difficult because if, even temporarily, the mixing of gas-liquid mixture was poor, the catalyst could undergo to irreversible decomposition *via* agglomeration of the homogeneous palladium species. The optimal gas-liquid mixture mixing was obtained by accurate control of the oxygen/catalyst ratio and reagents flow rates in order to always warrant the presence of the oxygen in the mixture. This result was particularly important because the temperature of the reaction could be increased to 60 °C compared to the 25 °C achievable in batch condition where an increase brought to a rapid decomposition of the catalyst due to the not optimal gas-liquid mixture mixing. The reaction time from batch to flow decreased from 18 hours to 45 minutes for the oxidation of 1-phenylethanol to acetophenone. The scope of the reaction was investigated (Scheme 30) and good yields in a multigram-scale were achieved. Scalability of the process was also proved by performing the aerobic oxidation of 1-phenylethanol to acetophenone in a 1 kg scale obtaining 99.5% yield of the desired product and proving the reliability of continuous-flow tube reactors as a platform for development of a large-scale aerobic oxidation.



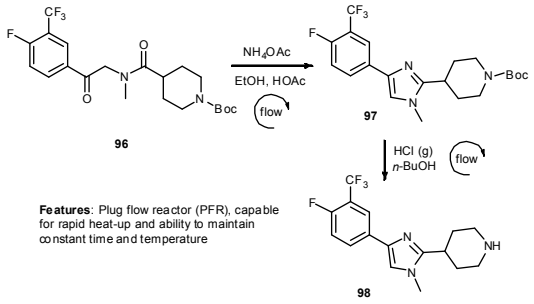
Features: In flow faster reactions, higher stability and effciency of the catalyst

Scheme 30 Substrate scope of alcohol oxidation.[92]

Another type of transformations which represents a challenge for scaling up is that requiring the photochemical activation. Seeberger et al.[93] described the photoexcitation of oxygen to singlet oxygen and its use as oxidant. The flow apparatus consisted in a fluorinated ethylene propylene tubing wrapped around a Schenk photochemical reactor containing a 450 W medium pressure mercury lamp. Substrate and oxygen were pumped in the tubing with a flow rate of 5 mL min^{-1} for the substrate solution and 10 mL min^{-1} for the oxygen. In this manner photo-oxidation of substrates such as alkenes,

a hydroxyl sulfide and furan were performed with good yields (63-95%). The productivity of the system reached the 2.5 mmol min^{-1} which represented an unprecedented productivity at a minimal environmental impact for this kind of reaction.

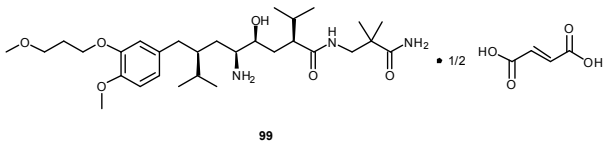
A two consequent steps process, consisting in a high temperature cyclization and thermal deprotection of *N*-Boc protecting group, were both performed by May et al.[94] in continuous-flow to produce the key 1*H*-substituted imidazole intermediate **98** (Scheme 31). Both steps were conducted on a 1 kg scale in a plug flow reactor (PFR), which was capable of rapid heat-up to reach a productive temperature regime and ability to maintain constant time and temperature when scaled-up. This contribution pointed out the possibility to achieve low volume commercial scale throughput in a laboratory hood infrastructure.



Scheme 31 Two continuous flow step synthesis of 1*H*-substituted imidazole intermediate **98**.[94]

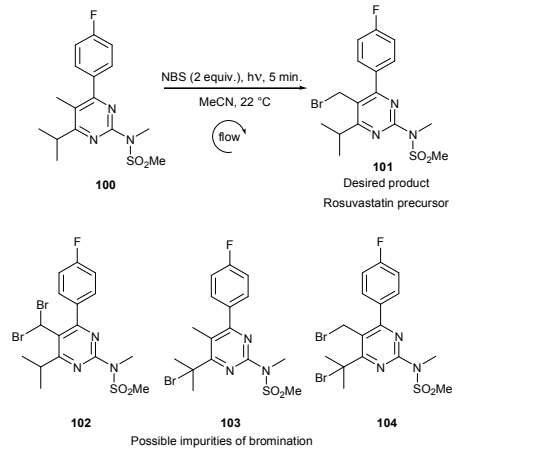
A continuous flow process was developed by Wang et al.,[95] for the industrial operation plant for of the catalytic oxidation of cyclohexene to adipic acid using H_2O_2 as oxidant. This approach relied on a catalytic recyclable catalyst system based on H_2WO_4, H_2SO_4 and H_3PO_4 which displayed a very high catalytic activity and stability towards H_2O_2 and that can be reused up to 20 times. Moreover the process was set in an organic-solvent free environment and allowed the preparation of adipic acid in 95% yield and 99% purity of the crude reaction mixture. This process was scaled up to a 316 L stainless steel pipe.

Trout et al.[96] reported the first example of an end-to-end integrated continuous manufacturing plant for aliskiren hemifumarate **99** (Scheme 32). Flow conditions were used for the synthesis, purification, formulation and also the formed final tablet production in one tightly controlled process. The total throughput of the plant was 45 g h^{-1}, which could be adjusted between 20 g h^{-1} and 100 g h^{-1} by changing control setpoints in the plant. The overall process residence time was about 47 hours, which was an order of magnitude lower than the residence time of batch process, which is 300 hours. The tablet production process operated efficiently for up to eight hours and the tablets produced respects all the specifications concern residual solvent, amount of impurity and concentration of active principle.[96]



Scheme 32 Aliskiren hemifumarate **99** synthesized from end-to-end continuous manufacturing.[96]

Ley et al.[97] reported a sustainable, mild and easy scalable method to hydrate nitriles for accessing the corresponding primary amide. This method relied on the use of MnO_2 as catalyst, which is difficult to handle in batch due to its tedious work-up. Adoption of flow technique in combination with a MnO_2 packed column, circumvented this problem. The Authors performed the hydration of several nitriles in mild conditions (40-100 °C) using a residence time ranging from 3 to 30 minutes, and always obtaining quantitative yields without any purification step. The catalyst packed in the column could be reused up to 100 times without reduction of its catalytic activity. Moreover, they scaled up to 400 mmol the hydration of pyrimidine-2-carbonitrile, with a throughput of 45 mmol h^{-1}.



Scheme 33 Photochemical bromination of **100** in continuous flow mode.[98]

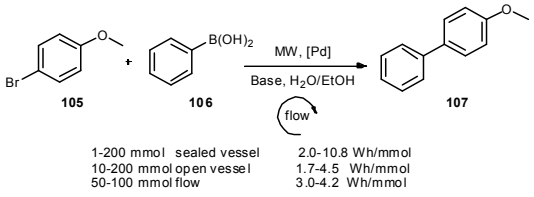
Časar et al.[98] used *N*-bromosuccinimide (NBS) to develop the flow photochemical bromination of **101**, a precursor of Rosuvastatin, a drug for the high cholesterol management. The challenge of scaling up this process resided in the impurities produced during the reaction (Scheme 33). In particular, this process was impossible to scale up in batch conditions because **101** can only be prepared in 82% of purity and 88% yield after recrystallization. Flow technology helped the scale-up the preparation of the desired product **101**, also reaching a purity of 93% with 86% yield. Moreover the productivity of the system was of 58.3 mmol h^{-1}, respect to a productivity in batch of only 13.6 mmol h^{-1}.

7. Energy and cost efficiency

Energy savings and cost efficiency are intertwined requisites that every sustainable process should meet. Performing reactions in flow conditions constitute indeed an ideal approach to address such issues because under these conditions it is generally possible to define an easy scale-up, to avoid isolation of reactive intermediates, to improve heat/mass transfer and possibly to combine an *in-line* purification.

Microwave (MW) heating has emerged as a valuable technique for improving energy efficiency and therefore often compared to flow conditions.[99]

Leadbeater et al. have investigated the role of microwave heating, conventionally heated batch and conventionally heated continuous-flow approaches on enhancing energy efficiency defined as the energy consumption on the basis of millimoles of product formed (Wh $mmol^{-1}$).[100] As test reactions for this study Hantzsch synthesis of 1,4-dihydropyridines, Suzuki coupling of 4-bromoanisole (**105**) with phenylboronic acid (**106**) and the preparation of *N*-phenylpiperidine from aniline and 1,5-dibromopentane were considered. The representative example of Suzuki coupling is discussed herein (Scheme 34).



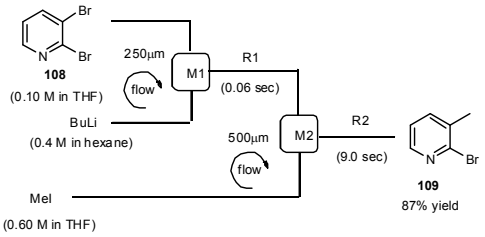
Features: Experimental conditions study to maximize energy efficiency

Scheme 34 Energy efficiency study of the MW-promoted Suzuki-coupling.[100]

Initially, the Authors exploited the Suzuki coupling employing different processing methods, namely in an open and sealed vessel, in a monomode and in a multimode MW unit. Regardless the mode used, the energy efficiency increased moving from 10 mmol to 100 and 200 mmol scale. Finally, the reaction was performed using conventional heating in continuous-flow mode. At this aim, adjustments to the experimental procedure had to be done as the presence of an over-stoichiometric amount of Na_2CO_3 could cause the clogging of the reactor. Sodium hydroxide (NaOH) that was completely soluble in ethanol/water was chosen as alternative. The biphenyl product **107** though was still not soluble and therefore it was diluted with ethyl acetate as soon as it came out from the heated area. The reaction was run on 50 and 100 mmol scale with total energy consumption of 4.2 and 3.0 Wh $mmol^{-1}$, respectively. The entire process required the following steps: the heating up of the room temperature to 140°C, solvent passing through the coil reactor (2.8 mL min^{-1}), reaction mixture passing through the reaction and again solvent flowing through the reactor for washing up.

In conclusion, for the Suzuki coupling protocol the energy efficiency increased accordingly with the scale increase, furthermore the energy efficiency values for the 100 mmol scale process performed with microwave heating and continuous flow reactor were comparable.

Flow microreactors have been increasingly employed to perform chemical processes in a more efficient manner. If they are compared to conventional batch macroreators a better heat/mass transfer is feasible and furthermore microreactors have optimal features for running fast and highly exothermic reactions.[101] Yoshida et al. illustrated the advantages of using flow microreactor for the synthesis of substituted pyridines applying a protocol for the formation of a pyridyllithium ion followed by its quenching with a variety of electrophiles.[102] The protocol was optimized by using 2,3 dibromopyridine (**108**) and butylithium (BuLi) for the Br/Li exchange and Methyl Iodide (MeI) as electrophile (Scheme 35).

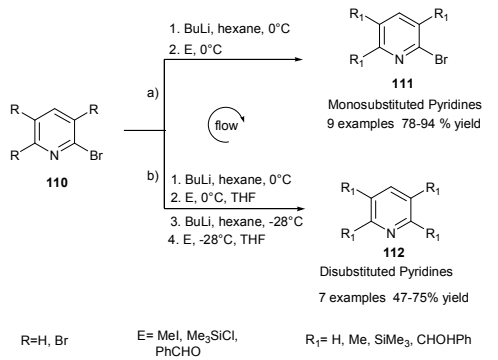


Features: No need to apply crygenic conditions

Scheme 35 Flow-microreactor conditions in the optimized synthesis of monosubstituted pyridines **109**.[102]

When a conventional macroreactor was employed the reaction had to be run using cryogenic condition in order to avoid the decomposition of pyridyllithium species and the formation of by-products. Switching to microreactor instead, the Authors were able to obtain excellent yields even at temperatures as high as 0°C. Reagents were conveyed, after passing through a micromixer M1, to a microtube reactor R1 (residence time = 0.06 seconds) then the intermediate was mixed with MeI in M2 to finally give the desired product in R2 after a residence time of 9.0 seconds. The generality of the protocol was tested with different bromopyridines **110** and electrophiles as illustrated in Scheme 36 (pathway *a*) consistently obtaining good to excellent results (78-94% yields).[102]

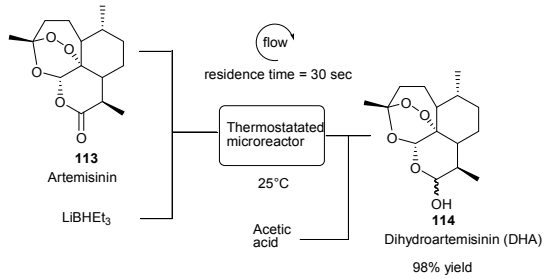
A microreactor was also used to synthesize a set of disubstituted pyrdines **112** using a sequential introduction of two different electrophiles without isolating the monobromopyridine intermediate (Scheme 36, pathway *b*). The generation of the second pyridyllithium intermediate followed by introduction of the electrophile were conducted at -28 °C because of the less stability of such compound. In conclusion, the method resulted to be more efficient than others described and using conventional batch macroreactors as it allowed the reaction to be performed without employing cryogenic conditions.[102]



Features: Reactions performed at higher temperatures compared to those employed in macroreactors

Scheme 36 Scope of the flow-microreactor protocol for the synthesis of mono- **111** and disubstituted pyridines **112**.[102]

Lapkin et al.[103] published an optimized flow protocol for the stoichiometric reduction of Artemisinin (**113**) to Dihydroartemisinin (**114**, DHA) that is an important intermediate in the Artemisinin combination therapies for the treatment of *Plasmodium falciparum* malaria (Scheme 37).[104]



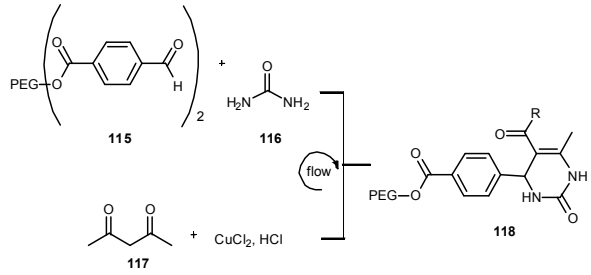
Features: Stoichiometric reduction, high selectivity and productivity, throughput increased of over 40 times compared to that of conventional batch process

Scheme 37 Schematic representation of the flow process for the reduction of Artemisinin **113** to Dihydroartemisinin **114**.[103]

Preliminarily, a screening in batch condition to find the best reducing agent was performed. Stoichiometric amount of triethylboronhydride ($LiBHEt_3$) resulted to be the best reagent either in terms of reaction times and yields. When 3 equivalents of $LiBHEt_3$ were used Artemisinin (**113**) was converted to Dihydrorartemisinin (**114**) in 94% yield after 10 minutes at 2 °C with high chemoselectivity as no by-products were detected. The reduction was further tested in flow condition using THF as solvent. A residence time as low as 30 seconds allowed the complete conversion of Artemisinin to product in 98% yield. Furthermore the reaction was performed at 25 °C, thus reducing the overall energy intensity consumption compared to the traditional batch mode where cooling was necessary. In order to develop a more sustainable protocol, the Authors replaced THF with a biomass-derived solvent namely 2-Me-THF, conversion was found to be slightly lower but still very high (> 96%). In conclusion thanks to full conversion and short residence time a high overall productivity of **114** (1.60 kg h^{-1} L^{-1}) was obtained.[103]

Polymer supported synthesis offers the unique advantages of easy work up and recovery of the catalyst by filtration or, if it is soluble in the reaction mixture (e.g. PEG-bound reagents), by ultrafiltration tecniques.[105] Furthermore when it is combined with flow technologies improvements in terms of efficiency, energy consumption and safety are obtained.[100, 36]

Schermann et al. successfully employed PEG-supported aqueous flow reaction coupled with ultrafiltration as separation technique for the synthesis of a variety of heterocycles. The Biginelli reaction used for the preparation of 3,4-dihydropyrimidin-2(*1H*)-ones **118** (DHPMs) was optimized (Scheme 38).[106] Best results were obtained when PEG-bound aldehyde **115** (previously synthesized by the Authors) 0.095M in water was mixed with pentane-2,4-dione (**117**) (4 equivalents) and then pumped to a T-piece with a premixed aqueous solution of urea (**116**) (4 equivalents), $CuCl_2$ (10%) and HCl (12.5 %). The reaction mixture was heated at 60°C through a convection flow coil (CFC) for a residence time of 167 minutes. Upon exiting from CFC the reaction mixture was recovered in a stirred 50 mL ultrafiltration cell (SUFC) to afford after concentration products in 72% and 79% yield respectively. Finally, basic hydrolysis afforded products released from PEG support.



Features: Ultrafiltration technique to recover the supported product reduces the amount of organic solvent employed

Scheme 38 Aqueous Biginelli reaction in flow employing PEG-supported aldehydes.[106]

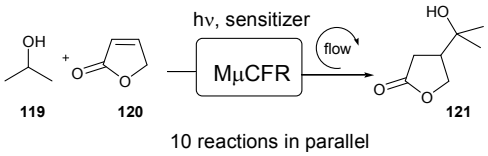
Biginelli reaction for the synthesis of DHPMs was also performed in DMF for comparison with aqueous conditions leading to poor yields accompanied by the formation of unidentified PEG-linked compounds. In conclusion, water resulted to be the reaction medium of choice for PEG-supported Biginelli reaction in flow avoiding the use of big volumes of potentially toxic and dangerous organic solvents. The amount of waste water generated by the aqueous flow process was comparable to that formed for the synthesis and work up in organic solvents.

The same Authors also exploited the feasibility of performing the Baylis-Hillmann reaction under flow condition. PEG_{2000}-supported aldehyde was employed instead of PEG_{4000} to avoid viscosity problems during pumping operation.

Microflow photochemistry is a promising field that has seen a growing number of applications. The specific features of microreactors i.e. narrow reaction channels and small dimensions allow deep penetration by light and superior temperature control.[10f, 107] Current application possibilities are limited by the fact that only individual reaction can be performed *in-series*.

Oelgemöller et al. set up a multimicapillary flow reactor (MμCFR) and evaluated its use by performing the well-known sensitized addition of alcohols to furanones.[108]

The delivery system was constituted pump connected to by 10-syringes. Two bundles of five fluorinated ethylene propylene copolymer capillaries were wrapped around two Pyrex glass columns and the UVA fluorescent tubes were placed in the center of such columns. Process optimization for increasing space, time and resources efficiencies was evaluated as well as the production of a library.



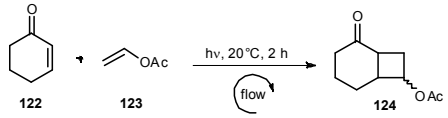
Features: Time-saving process, increased energy efficiency, no cooling water required

Scheme 39 Sensitized addition of isopropanol to 2(5*H*)furanone in a MμCFR.[108]

As test reaction the addition of isopropanol (**119**) to 2(5*H*)-furanone (**120**) was chosen (Scheme 39). The MμCFR was first applied to sensitizer screening employing a range of aromatic ketones with 4,4'-dimethoxy-benzophenone (DMBP) being the best option, without sensitizer no reaction occurred. A second screening to establish the best concentration of DMBP, revealed that when 10 mM of DMBP was employed a 90% conversion of furanone to product was obtained. Furthermore light penetration profiles at 365 nm revealed a complete transmission through the microcapillary reactor giving better performances compared to batch conditions, where due to a much larger path lengths, transmission efficiencies are lower. The influence on furanone **120** concentration was also investigated and was varied in the range from 33.3 mM to 200mM. As expected the conversion dropped as the concentration increased, with an acceptable threshold of 23% yield when concentration of furanone was 83.3 mM. Reaction scale-up allowed the production of 0.5 grams of product **121** in 94% yield. Finally, a small 3x3 library product was prepared. The new MμCFR offered the advantages of time savings and 30% less energy consumption and did not required cooling water, compared to batch reactor.[108]

Photochemical reaction are considered a powerful tool in synthetic chemistry in particular for the construction of four-membered carbon and heterocycles.[109] When such reactions are performed in a microreactor it is possible to perform the process by employing compact-light sources as LED, in fact the short path length of the microchannels allows for a more efficient light penetration enhancing therefore the energy efficiency of the process. Ryu et al. have evaluated the energy consumption in the continuous microflow [2+2] photocycloaddition reaction by using different light sources (Scheme 40).[110]

Photoinduced [2+2] cycloaddition of cyclohexenone (**122**) with vinyl acetate (**123**) was examined employing two different microreactors namely reactor type A made of Foturan glass equipped with two channels (1000 μm in width, 500 μm in depth, and 1.4 m in length), the other one, type B covered by a quartz plate with a single channel (1000 μm in width, 300 μm in depth, and 2.35 m in length) (Scheme 40). First, a comparison between flow mode and conventional batch mode was performed using a 300W light source high pressure mercury lamp. When reactors type A and B were employed cycloaddition product was obtained with comparable yields of 88% and 85% at 20 °C after a residence time of 2 hours. On the contrary when the same reaction was performed using a 10 mL pyrex flask the yield was only 22% after 4 hours irradiation. Then, when a short-power light source was tested (15W black light) the reaction performed in microreactor type A gave **124** in only a modest yield, while microreactor type B allowed cycloadduct product **124** to be obtained in 82% yield.



Microreactor type A or type B
Light sources: high energy Hg lamp, black light lamp

Features: Energy efficiency with black light lamp is 20 times greater than that of Hg lamp

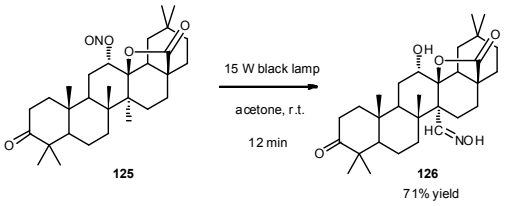
Scheme 40 [2+2] cycloaddition of cyclohexenone (**122**) with vinyl acetate (**123**) performed in microreactor type A or type B.[110]

The values of yield per watt per hour (yield W^{-1} h^{-1}) outlined that the energy efficiency of the black light is about 20 times greater than that of the mercury lamp. The optimized protocol for the [2+2] cycloaddition using microreactor type B and energy saving 15W black lamp was extended to other cyclohexenones with olefins giving consistently good results and yield comparative with those obtained using high energy consuming Hg lamp.

The same Authors have also extensively studied the Barton reaction for the flow synthesis of a key intermediate for the preparation of miceric acid A exploiting the influence of light sources and filters (Scheme 41).[111] Nitrite photolysis (Barton reaction) of steroidal compound **125** led to the steroidal intermediate **126** through a selective C-H bond cleavage at the β-position *via* 1,5-radical translocation from O to C .

Initially, this reaction was optimized using microreactor type C (1000 μm in width, 107 μm in depth, and 2.2 m in length, 0.2 mL hold-up volume) in combination with a soda lime glass top and high-energy Hg lamp, however

those conditions were not the best as the microreactor top caused a significant light decline at 365 nm (that is the wavelength for the reaction to occur), furthermore the heat generated by the Hg lamp was responsible for the decomposition of the substrate especially when the lamp source was set a 5 cm distance from the reactor and the temperature rose to 50 °C.



Features: Energy efficiency 10 times greater than that obtained with high energy Hg lamp, scale-up process

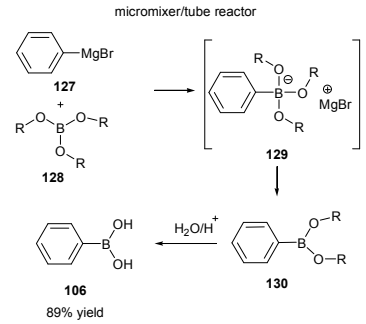
Scheme 41 In flow study of the Barton nitrite photolysis of a steroidal intermediate to yield the corresponding oxime.[111]

Therefore the Authors opted for a 15W black light source that has maximum peak wavelength at 352 nm combined with pyrex glass microreactor top that has the advantage of better transparency. The residence time was adjusted from 6 to 12 minutes taking into account the lower energy of the lamp (Scheme 41). These conditions allowed to reach a 71% yield of the desired oxime **126** with an energy efficiency ten times greater than that obtained with the Hg-lamp. Gram-scale synthesis of **126** was also accomplished using a different microreactor namely microreactor type D (1000 μm in width, 500 μm in depth, and 0.5 m in length, 8.0 mL hold-up volume). DMF was employed as reaction medium instead of acetone reaction to avoid solubility issues with the steroidal precursors. Light source was supplied by eight 20W black light lamps and after continuous operation for 20 hours it was possible to obtain 3.1 grams of desired product **126** (60% yield).[111]

Yoshida et al. reported on the use of a photochemical flow reactor to promote the [2+2+1] cycloaddition of an alkene, or alkyne and CO (namely Pauson-Khand reaction). The Authors highlighted the importance of the depth of microreactor channel. In fact, optimal results were obtained using 200 μm instead of 500 μm. Related to this aspect, the batch version of the reactor realized using the same Hg-lamp used for the flow, gave poorer results. The continuous flow was left to work up to 1 hours with high efficiency.[112]

At the Clariant site in Frankfurt, Hessel and co-workers have been involved in an industrial production-scale process namely *Phenyl Boronic Acid Process* (Scheme 42).[113]

The synthesis of aryl and alkyl boron compounds is of great importance as they are key reagents in the production of valuable fine chemicals and pharmaceutical via Suzuki coupling. Unfortunately, conventional batch protocols for the arylation or alkylation steps on a trivalent boron precursor by use of a metallo-organic compound such as a Grignard reagent suffers of many drawbacks that make this process uneconomic and associated with a large manufacturing cost. Such disadvantages are related to the formation of many by-products, the need of cryogenic temperatures and moisture-avoiding conditions, energy supply for refluxing during the Grignard reagent synthesis and distillation of the crude product and several cooling-heating cycles in the purification steps. The target solution was therefore to use a micromixer/tube reactor for employing the same reagents used in the batch condition to increase the yield and decrease the energy consumption. The best performance obtained in the microreactor was an HPLC yield of 89% that exceeded the best result in the industrially employed stirred tank process by nearly 25%.



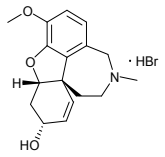
Features: Decreased amount of by-products, room temperature allowed, energy efficiency increased

Scheme 42 Formation of the desired product in the *Phenyl Boronic Acid Process*.[113]

Furthermore, the amount of by-products was decreased from 10-15% to 5-10% thus facilitating the purification steps. Noticeably, the energy efficiency of the process was also increased as the employment of the microreactor allowed the reaction to occur even at ambient temperature with no need to reach temperatures as low as -35°C, in addition only one cycle of heating-cooling was necessary. A pilot-scale configuration have been set-up that allowed to perform scale-up studies at throughputs as high as 10 L h^{-1} enabling the production of about 6 kilograms of phenyl boronic acid (**106**) per day.

Exergy analysis (an evaluation of the most work it is possible to get out of a system at a given state in a given environment) and exergetic life-cycle assessment (combination of exergy analysis with existing life-cycle techniques)[114] are used to quantify all the natural energy and material resources are used for a certain process generally by putting all resources into a single unit (Joules of exergy) which facilitates decision or evaluation making.[114, 115] Van der Vorst et al. recently reported an interesting paper dealing with the adoption of exergetic life cycle assessment to evaluate the importance of novel and greener technologies that would actually allow the decision about the best route to target compounds. The real pharmaceutical industry case about synthesis of Galantamine·HBr (**131**) has been selected and the three

different processes used over the time for preparing this target have been compared (Scheme 43).[115]



131, Galantamine

Features: 41% saving of resources consumption using flow technology

Scheme 43 Galantamine·HBr (**131**).[115]

One kilogram of Galantamine·HBr (MW = 368.27 g mol^{-1}), possessed a cumulative exergy extracted from the natural environment (CEENE) of 21 GJ which is equivalent to the exergy content of 490 kilograms gasoline (exergy of gasoline = 43 MJ kg^{-1}).

By changing the chemistry and by implementing new technology, the resources consumption of nine step pharmaceutical production process to **131** could be reduced by 41% saving the equivalent of 200 kilograms of gasoline per Kg of API **131**.

Conclusions

In conclusion, green chemistry takes obvious advantage of any technological advancement especially if new technologies allow novel chemical processes to be realized and high chemical and environmental efficiency to be achieved. At this concern flow technology is certainly one of the most interesting available tools that can be used to develop a greener and sustainable chemistry.

As in many other partnerships, it is not always trivial to tell if two partners can truly fruitfully contribute to each other goals but certainly green and flow get along together well and represent two research areas that have a long route ahead and several possible journeys to share.

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Notes and references

[a]*Laboratory of Green Synthetic Organic Chemistry, CEMIN - Dipartimento di Chimica, Università di Perugia Via Elce di Sotto, 8; Perugia, Italia. Fax: +39 075 5855560; Tel: +39 075 5855541; E-mail: luigi.vaccaro@unipg.it; www.chm.unipg.it/greensoc*

[b]*Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 06123 Perugia, Italy*

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