CHAPTER 11

Flow Chemistry: Sequential Flow Processes for the Synthesis of Heterocycles

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11.1. Introduction

The challenges in modern organic chemistry go from the discovery of new entities based on increasing knowledge of reaction mechanisms to the embracing of sustainability issues in lab and industry scales. The inherent characteristics of flow chemistry setups, including increase of surface-to-volume ratio, intensification of heat and mass transfer phenomena (particularly important in exothermal reactions), critical control over concentration, use of high diluted solutions (important for stoichiometrically controlled reactions, as well as intramolecular reactions), the opportunity to use different activation modes (such as photon- and electron-activation, allowing to explore new reaction mechanisms), safety and reproducibility, open the way to new compounds in a sustainable manner. Furthermore, scale up production is easily enabled under flow conditions, as flow devices are compact and can be reconfigured according to the output needed. The possibility of combining flow methodologies with artificial intelligence and robotics is another advantage.(1-4)

With the current environmental concerns, displayed by society and regulatory authorities, both academia and industrial organic chemists, turned their attention to the sustainability and eco-friendliness of continuous manufacturing, the flow chemistry. The opportunity

to establish continuous flow processes, which allow new reactions which cannot be performed under conventional conditions, high reproducibility and control of the several stages in a time-efficient manner, combined with improved safety and less margin for human error, is highly beneficial.(5-7)

From the synthetic chemistry point of view, the modular nature of most flow chemistry systems is one of the main advantages. The opportunity to couple different reactors, in-line purification methods and addition of reactants at different stages makes continuous manufacturing a very versatile process. Another desirable feature is the different catalytic processes which can be promoted under continuous flow. These technologies can be applied using homogeneous and heterogeneous catalytic systems including photocatalytic, biocatalytic and enantioselective catalytic systems. The variety of chemical transformation currently being explored under continuous flow systems, will provide an endless source of possibilities and increase the value of these methodologies in years to come.(8-11)

The sustainability of flow chemistry processes was recognized by the CHEM21 project,(12) by awarding a green flag for continuous-flow reactions, in opposition to an amber flag for those performed under batch conditions.(13) The green nature of flow processes is of major relevance, as it provides gains in multiple stages of chemical development, from small scale lab productions to kilogram scale and full scale manufacturing, leading to considerable improvements in both chemical optimization and process intensification and therefore corresponding to the synergy between synthetic chemistry and chemical engineering.(14)

In recent years, the development and application of continuous flow systems in the synthesis of molecules bearing heterocycles, crucial scaffolds in organic chemistry and particularly relevant in the search of bioactive compounds,(15) was object of a giant leap. It is probably the most revolutionary tool in the field of organic synthesis, by completely replacing the classic glassware and instrumentation to fully automated laboratories, enabling chemists to focus their attention in work planning and design.(16-20)

In this chapter, we aim to highlight the most recent developments in heterocyclic synthesis using sequential or consecutive continuous flow systems, providing important examples of high-value molecules currently being prepared using these methodologies, in both academic and industrial context. Often called as reaction telescoping, as more than one chemical transformation occurs without isolation of formed intermediates, multi-step/sequential/consecutive flow systems allow in-line purification and introduction of required reagents at any given point of the flow setup.(1, 21) Nevertheless, one-step syntheses of emblematic heterocycles are also included.

## 11.2.1. *Three-membered ring heterocycles*

Three-membered heterocycles, namely oxirane and aziridines (or their unsaturated counterparts) azirines, are very relevant building blocks for synthetic chemists.(22) Due to their inherent ring strain, three-membered heterocycles display high chemical reactivity and therefore are susceptible to a variety of electrophiles and nucleophiles, which has been known and exploited for the construction of various compounds, including several APIs.

Epichlorohydrin and glycidol, two important oxiranes used as synthetic precursors to relevant APIs bearing β-amino alcohol moieties (e. g., propranolol, alprenolol and naftopidil),(23) were synthesized under flow conditions from bio-based glycerol through sequential hydrochlorination/dichlorination process. Using pimelic acid as the catalyst, glycerol was converted into 1,3-dichloro-2-propanol that was *in situ* transformed into a mixture of glycidol and epichlorohydrin (2:3) (Scheme 11.1), separable by an in-line membrane separation system.
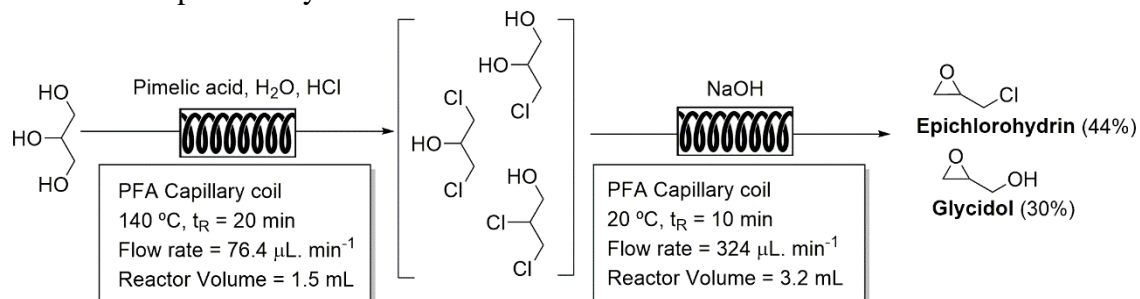

Scheme 11.1. Synthesis of glycidol and epichlorohydrin, important APIs synthetic intermediates, using a multi-step flow system.

The Neber reaction of activated oximes is a well stablished synthetic pathway to 2*H*-azirines.(24) Using continuous-flow techniques, 2*H*-azirines can also be prepared from oxime precursors *via* Neber reaction. Mesylation of the oxime by reaction with MsCl in the presence of Et₃N at 40 ℃ in a tubular flow coil, followed by base promote cyclization at room temperature in a glass column filled with silica supported pyridine (PySiO₂) and silica gel (SiO₂) gave the target three-membered heterocycles. The diaryl-2*H*-azirines prepared (isolated yield after in-line purification up to 87%) were converted into aziridines bearing nitrile and trifluoromethyl substituents through a continuous flow procedure. The nitrile derivatives were prepared, in good yield and good *cis*-diastereoselectivity (dr >19:1), by mixing a solution of the 2*H*-azirine in acetonitrile with sodium cyanide in a tubular reactor coil at room temperature during 5 min. Following the preparation of 2*H*-azirines, the sequential reaction with trimethyl(trifluoromethyl)silane in a fluoride monolith maintained at 50 ℃ followed by a tubular flow coil (10 mL volume, 50 ℃, 5 min residence time) allowed the synthesis of trifluoromethyl substituted aziridines as pure *cis* diastereoisomers (Scheme 11.2).(25)
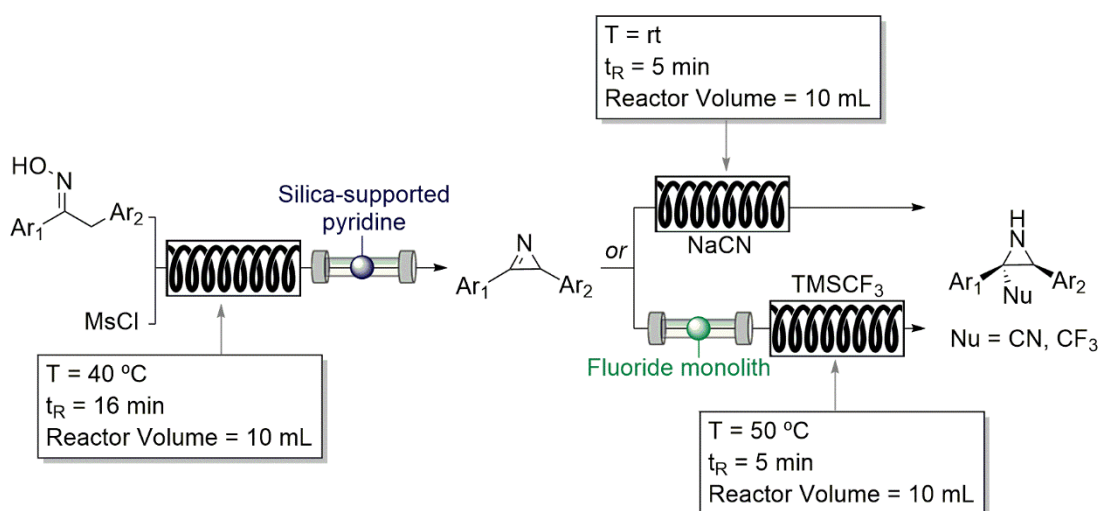
Scheme 11.2. Sequential Neber rearrangement and nucleophilic addition to prepare 2*H*-azirines and aziridines.

Fused-aziridines were also prepared under flow conditions and further derivatized through nucleophilic opening of immobilized aziridines, illustrating the utility of flow chemistry as a tool for functionalization through consecutive reactions. Zakrzewski *et al.* used 3,3,5,5-tetramethylmorpholin-2-one as starting material and promoted a palladium-catalyzed $C(sp^3)$-H activation to afford 2,2,6-trimethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-one. In-line purification techniques, including a QuadraSil AP® (Pd scavenger) and a catch-release Isolute SCX-3 gel® (amine scavenger), were carried out to achieve the product in high yield and high purity. The aziridine, while on the SCX-3 column, is immobilized by sulfonic acid protonation, which makes it susceptible to ring-opening via nucleophilic attack when a nucleophile (water, methanol, or hydrazoic acid generated *in situ* from trimethylsylil azide, $TMSN_3$) is pumped through the resulting column. This synthetic procedure afforded the derivatized products in good yields. The use of a solid-state support significantly facilitated the reaction procedure giving the final products in good yields, minimized the number of purification steps, and shortened the reaction time. (Scheme 11.3).(26)
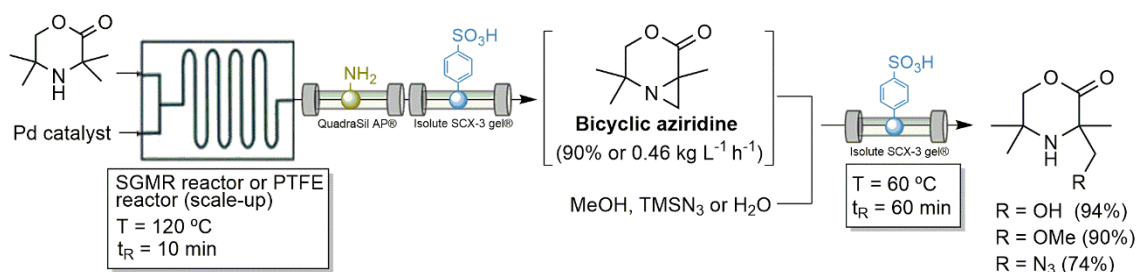

Scheme 11.3. Sequential C-H activation for the synthesis of fused aziridines and nucleophilic ring-opening.

11.2.2. Four-*membered ring heterocycles*

Flow setups combined with microwave, photochemical synthesis or conventional heating have been used for the synthesis of β-lactams. The β-lactam ring, part of the structure of penicillins,(27, 28) were synthesized using the Wolff-Staudinger cascade reaction. The formal [2+2] cycloaddition of *in situ* generated ketenes with imines was performed under continuous flow at high temperature (185 ºC), using microwave irradiation, with the final heterocycles being prepared in moderate to very good yields (30-85%) and stereoselectivities.(29)

The flow preparation of a β-lactam synthetic intermediate of the stimulant drug methylphenidate hydrochloride (Ritalin®) has been recently reported by Gérardy *et al.* exploring two flow methodologies. The quantitative conversion of the tosylhydrazone to the β-lactam intermediate of this drug was obtained using a conventional flow thermolysis within 5 min residence time at 180 ºC, yet, using a photolysis flow setup almost quantitative conversions where obtained within one hour of reaction and operating at temperature bellow 40 ºC (Scheme 11.4).(30)
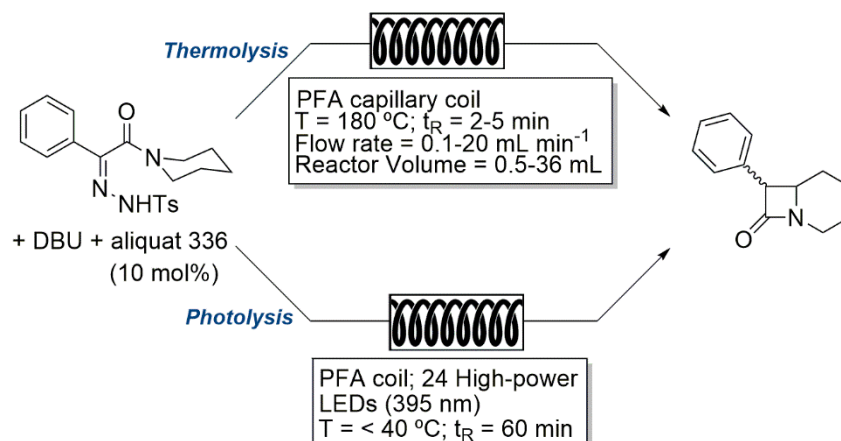
Scheme 11.4. Synthesis of a β-lactam synthetic intermediate of Ritalin®, using flow thermolysis or photolysis.

11.2.3. *Five-membered ring heterocycles*

Five-membered ring heterocycles play a major role in organic chemistry as they possess a plethora of applications. Among them, pyrrole is an iconic structure, is widespread in nature and in many pharmaceutical active agents. Hantzsch(31) and Paal-Knorr(32, 33) pyrrole synthesis are classical methodologies used for the synthesis of this heterocycle. These one-pot reactions were successfully performed under flow conditions, however, by its nature there is no need for sequential setups.

The Hantzsch pyrrole synthesis, involving the reaction of β-ketoesters with ammonia (or primary amines) and α-haloketones, was successfully performed under continuous flow conditions to synthesize pyrrole-3-carboxylic acids from commercially available *tert*-butyl acetoacetates, amines and 2-bromoketones followed by deprotection of the carbocyclic acid with *in situ* generated HBr. Pyrroles were obtained in good yields using DIPEA as catalyst and DMF as solvent and introducing the reactant solutions in a preheated microreactor at 200 °C and 5.0 bar, with a flow rate of 62.5 μL.min^{-1}, with a total reaction time of 8 min. Scale-up of the synthesis of 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid under the stablished flow conditions allowed to obtain 850 mg (63% yield) of the compound in 2.5 h flow time (Scheme 11.5).(34)
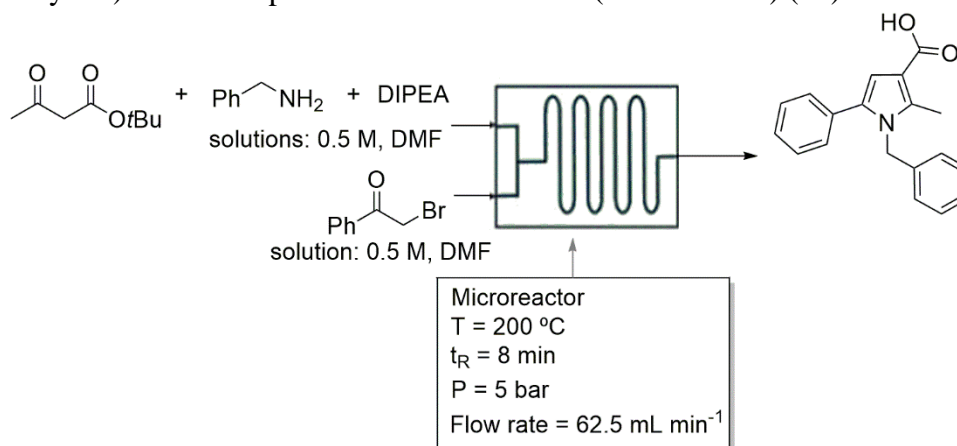
Scheme 11.5. Synthesis of 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid *via* Hantzsch synthesis under flow conditions.

Nieuwland *et al.* described a facile approach to optimize and perform pyrrole synthesis *via* Paal-Knorr cyclocondensation using flow chemistry. This reaction has industrial relevance, even though it requires thermal control, since it is highly exothermic, which make it a good candidate to be performed under flow conditions.(35) Using 2,5-hexanedione, and ethanolamine or ethylamine in amine:diketone ratio of 5/1 or 10/1, respectively, the pyrrole was obtained quantitatively after 100 s at 20 ºC. In order to quench the excess of primary amine used in the reaction, acetone was added through a third stream, leading to the formation of the corresponding imine as a secondary product. This step was included to allow a better determination of the optimal reactional conditions via off-line GC-MS analysis. Scaled up in continuous flow using microstructured flow reactor, allowed the production of a pyrrole derivative at a rate of 55.8 g per hour, (Scheme 11.6).(35) The same type of reaction was later explored by Cranwell *et al.*, but this time using a gas phase reactant (ammonia). The variety of scaffolds achieved with this methodology was very diverse, with the yield appearing to be dependent on the steric hindrance.(36)
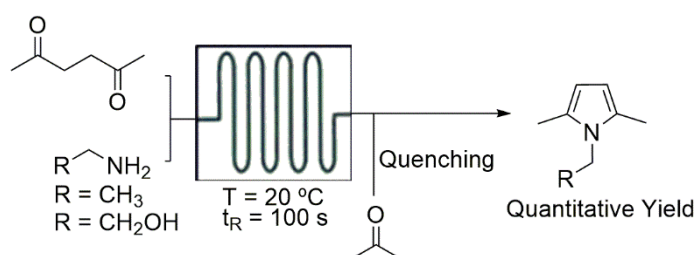

Scheme 11.6. Paal-Knorr synthesis of pyrrole.

The Fischer indole synthesis is a widely applied strategy to obtain indole derivatives using flow processes. Kappe and coworkers, achieve the synthesis of tetrahydrocarbazole in 90% yield, at 200 ºC (t_R of 3 min) in a 16 mL stainless steel coil affording 25 g of tetrahydrocarbazole within 1 h.(37) Using a monomodal microwave synthesizer heated at 150 ºC, coupled with a HPLC system, allowing a t_R of 4 min, Bagley *et al.* achieved the synthesis of tetrahydrocarbazole in 90% yield.(38, 39) Increasing the reaction temperature to 240 ºC and using a new single-mode microwave applicator, developed to perform reactions under flow conditions as it generates a uniform electromagnetic field within its resonant cavity, tetrahydrocarbazole was produce at a rate of 115 g h^{-1}.(39) The same heterocycle was obtained effectively using a ETFE tubing packed with Amberlite IR 120 H (100 mg) and sealed with cotton wool at 90 ºC within a residence time of 5 minutes.(40) The same reaction conditions were applied for the synthesis of pyrido[2,3-*a*]carbazole derivatives (40-90% yield) from phenylhydrazines and 5-oxodecahydroquinoline *via* the Fischer indole synthesis (Scheme 11.7a).(40)

The sustainability associated with the flow process was increased using ionic liquids as recyclable solvent for the synthesis of 3-methylindole. The Fischer indole synthesis was performed in high yields, with the initial generation of phenylhydrazone from phenylhydrazine and propanal, followed by cyclization catalyzed by $ZnCl_2$ in 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM][BF4]) at 200 ºC for 4 min. The ionic liquid used as solvent was successfully recycled four times in the flow reaction without any significant loss of activity (Scheme 11.7b).(41)

7-Ethyltryptophol, a very important synthetic intermediate for the synthesis of the API etodolac, was prepared using flow Fischer reaction and available starting materials, ethylphenylhydrazine hydrochloride and dihydrofuran, catalyzed by HCl in

methanol/H$_2$O (2:1) at 150 ºC within a short residence time (3 min). This can be considered an efficient transformation (40-50% yield) since it is a more challenging reaction system, which is able to form several side-products (Scheme 11.7c).(42)
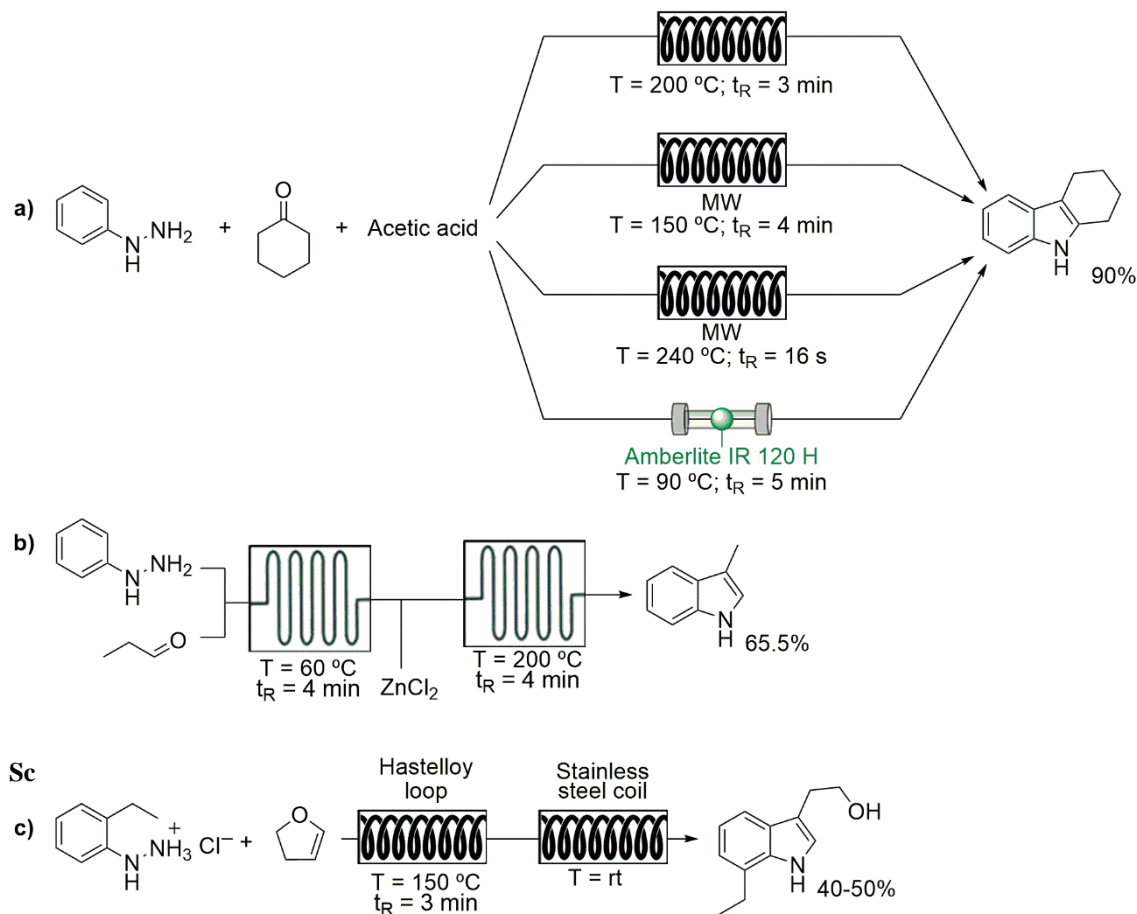

Scheme 11.7. Fischer indole synthesis under flow conditions.

As an example of the application of flow processes in the synthesis of compounds with indole core, we highlight one example reported by Baumann *et al*. on the total flow synthesis of an auxin mimic-based herbicide (Scheme 11.8).(43) A total of four steps were established in order to achieve the final product (80% overall yield), bearing an indole core and an oxadiazole core. The synthesis of the heterocycle was achieved through reduction of the nitrobenzene derivative and intramolecular cyclization using a Thales Nano H-cube® system, operating in full hydrogen mode (internal pressure 15 bar) with flow rate of 1.3 mL/min, and acetic acid as catalyst (10 mol%), which allowed quantitative conversion into the desired indole. This translates to a throughput of 3.7 g of product/h in 93% of isolated yield. The condensation of the indole-3-carboxylate with hydrazine and the reaction of the formed acyl hydrazine with triphosgene in a heated (55 °C) flow coil led to the synthesis of 3*H*-[1,3,4]oxadiazol-2-one unit, which after purification by passage through a scavenging cartridge of QP-DMA (*N,N*-dimethylbenzylamine polystyrene) yield the desired product in 91% of isolated yield.
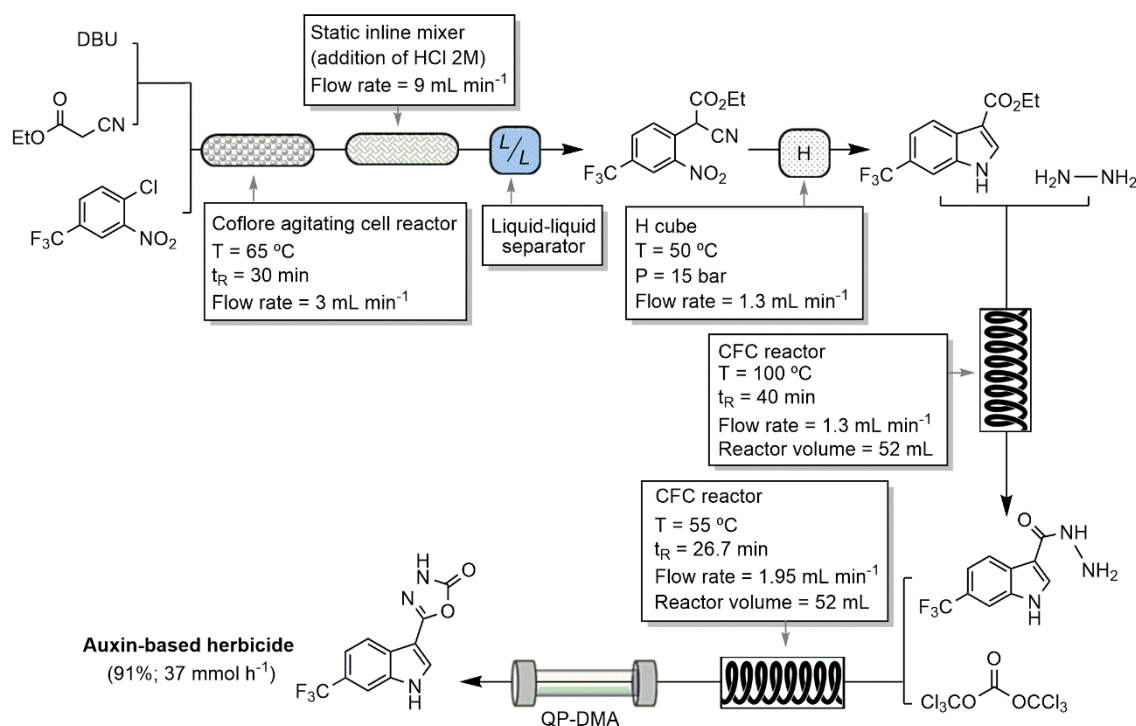
Scheme 11.8. Synthesis of an auxin-based herbicide bearing the indole and the oxadiazole cores using flow chemistry.

The γ-lactam ring (pyrrolidin-2-one) is present in several synthetic and natural biologically active compounds.(44) Tsubogo *et al.* reported the asymmetric catalytic synthesis of (R)- and (S)-rolipram and derivatives under heterogeneous conditions using commercially available starting materials. Briefly, they promoted a multistep flow synthetic procedure, applying heterogeneous catalysts, without the need to isolate intermediates or by-products throughout the process. Aldehyde and nitromethane were converted into the nitroalkene with > 90% yield, in the presence of a base (silica-supported amine and crushed anhydrous calcium chloride). The asymmetric 1,4-addition of malonate to the obtained nitroalkene was performed using a chiral polymer-supported (PS) calcium catalyst (PS-(S)-pybox-calcium chloride, where pybox is pyridinebisoxazoline) affording the γ-nitro ester intermediate in 84% yield with 94% enantiomeric excess. The reduction of the γ-nitro ester using a polysilane supported palladium/carbon (Pd/DMPSi-C, where DMPSi is dimethylpolysilane) catalyst, followed by cyclization afforded selectively the pyrrolidone in 74% yield with 94% enantiomeric excess, Scheme 11.9. The hydrolysis and decarboxylation of the ester group to obtain rolipram (50% yield, 96% e. e.) were also achieved under flow conditions using o-xylene and water as solvent through silica-supported carboxylic acid and Celite. (45)
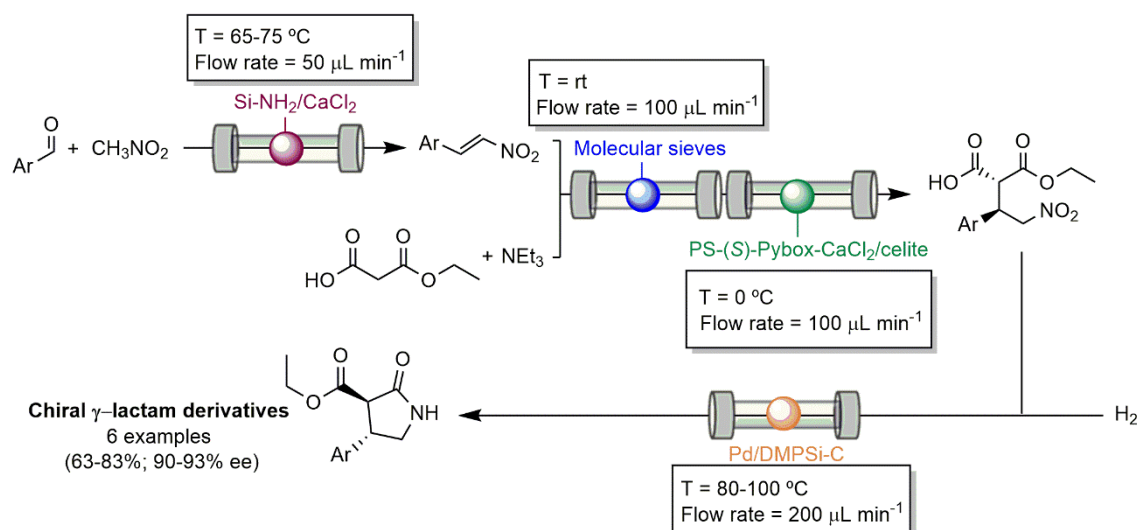
Scheme 11.9. Flow sequential synthesis of chiral γ-amino acid derivatives with γ-lactam moiety.

Imidazopyridines are bicyclic heterocycles also with great interest for medicinal chemists.(46-49) As an application of flow processes in drug discovery, focus will be given to the work developed by Guetzoyan *et al.*,(50) on the synthesis of GABA$_A$ agonists - GABA$_A$ receptor is the therapeutic target for benzodiazepines, general anesthetics and barbiturates.(51, 52) Two commercially available drugs were obtained – zolpidem, a sedative/hypnotic drug and alpidem, an anxiolytic drug – as well as twenty other imidazo[1,2-*a*]pyridines. In addition to the total synthesis by flow processes, in-line evaluation of the binding affinity of the compounds to HSA (human serum albumin) by frontal affinity chromatography was also performed, as an example of interface development between synthesis and bioassays, setting a starting point for an automated drug discovery platform. The heterocycle synthetic step is shown in Scheme 11.10. The unsaturated ketone, obtained by the acid catalyzed condensation between ethyl glyoxylate and acetophenone in reactors packed with polymer supported sulfonic acid resin (QP-SA) at 120 ºC, was further transformed into the ketimine derivative by reaction with an aminopyridine derivative in the MgSO$_4$ packed column at 50 ºC. The subsequent 5-exo cyclization step was carried out in the CFC reactor heated at 120 ºC. The QP-SA (Quadrapure-sulphonic acid resin) column allowing the retention of unreacted aminopyridine (scavenger) and the Biotage® SP1 column performed in-line chromatographic purification.(50)
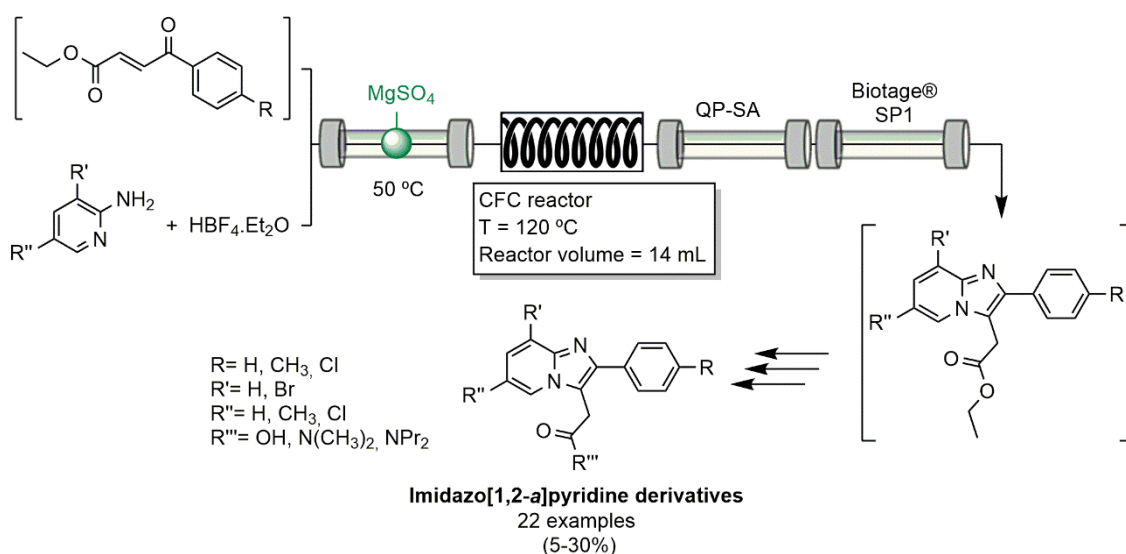
Scheme 11.10. Flow multi-step synthesis of GABA$_A$ agonists with imidazopyridine scaffold.

One of the most remarkable examples of flow chemistry applied to drug development is the synthesis of prexasertib. Prexasertib is a checkpoint kinase inhibitor drug with dual activity, towards Chk1 and Chk2, which work as key regulators in cellular DNA damage response pathways. Preclinical trials showed the promising antitumor activity of prexasertib, which was selected to pursuit its development in clinical trials.(53-59)

To ensure the production of a safe and high-quality drug for human use, Cole *et al.* developed a seven-step synthetic route for large-scale production of prexasertib (24 kg). The last four steps were performed under continuous flow conditions – condensation of a nitrile with a hydrazine to form a pyrazole derivative – heterocycle formation step (Scheme 11.11), followed by a S$_N$Ar reaction between the pyrazole derivative and a pyrazine, amine deprotection and salt formation. Using this continuous flow process prexasertib was prepared in Kg scale, identifying several advantages comparing with more conventional methodologies, such as better yield and impurity rejection, efficient solvent stripping with enhanced performance in terms of product stability, elimination of isolation steps, increased quality assurance, possibility of use of online process analytical technology and process automation.(60)
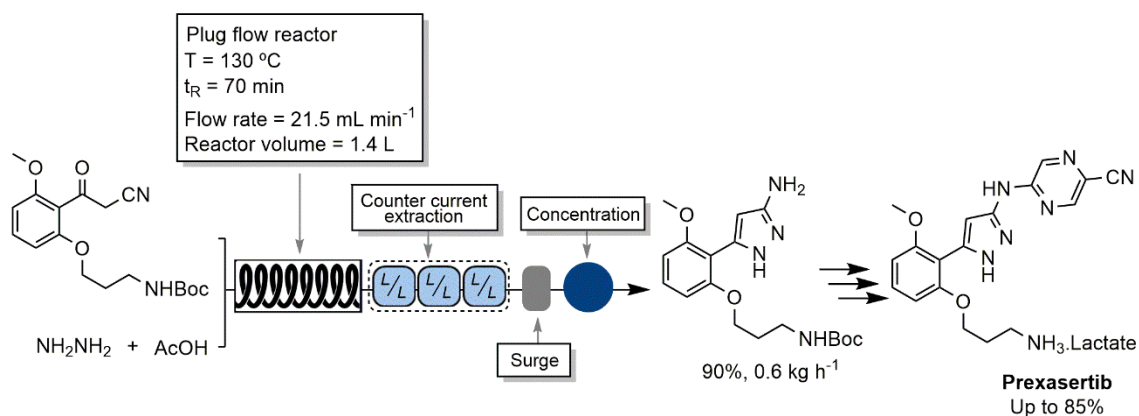
Scheme 11.11. Heterocycle synthesis step on prexasertib preparation under flow conditions.

In what concerns five-membered ring heterocycles bearing three nitrogen atoms, triazoles are an interesting class of heterocyclic compounds, efficiently obtained using "click" reactions and with a broad spectrum of bioactivities.(61-65) Beyond de synthesis of the triazole, "click" chemistry have been applied in a multitude of synthetic strategies(66) and also as strategy for macrocyclization. In the synthesis of cyclic peptoids, for example, the peptoid backbone cyclization was, considered as the most challenging aspect in the synthesis of this class of compounds.(67) The multicomponent Ugi reaction can be applied in the synthesis of peptoid-like molecules, by exploring the click copper-catalyzed intramolecular cycloaddition reaction between an azide moiety and an alkyne moiety. Indeed, Kappe *et al.* reported the synthesis of cyclic peptoid molecules following this synthetic approach under flow conditions (Scheme 12.11). Formamide in acetonitrile was mixed with the Burgess reagent (also in MeCN) and pass through a PFA coil at 50 ºC to afford the isocyanide, which was mixed with a solution of the azide prepared by reaction of 2-bromoacetic acid dissolved in acetonitrile with tetrabutylammonium azide in PFA coil at 100 ºC. Paraformaldehyde and *tert*-butylamine were constantly pumped with a flow rate and mixed with the outcome of the isocyanide generation and the azide formation in a cross shaped mixing device. The reaction was performed in a PFA coil tube at 80 ºC to yield the Ugi product in 80% yield without further purification and avoiding the handling of potentially toxic and/or explosive intermediates. The Cu catalyzed azide-alkyne cycloaddition was performed heating the resulting solution in a copper coil at 140 °C. (68)
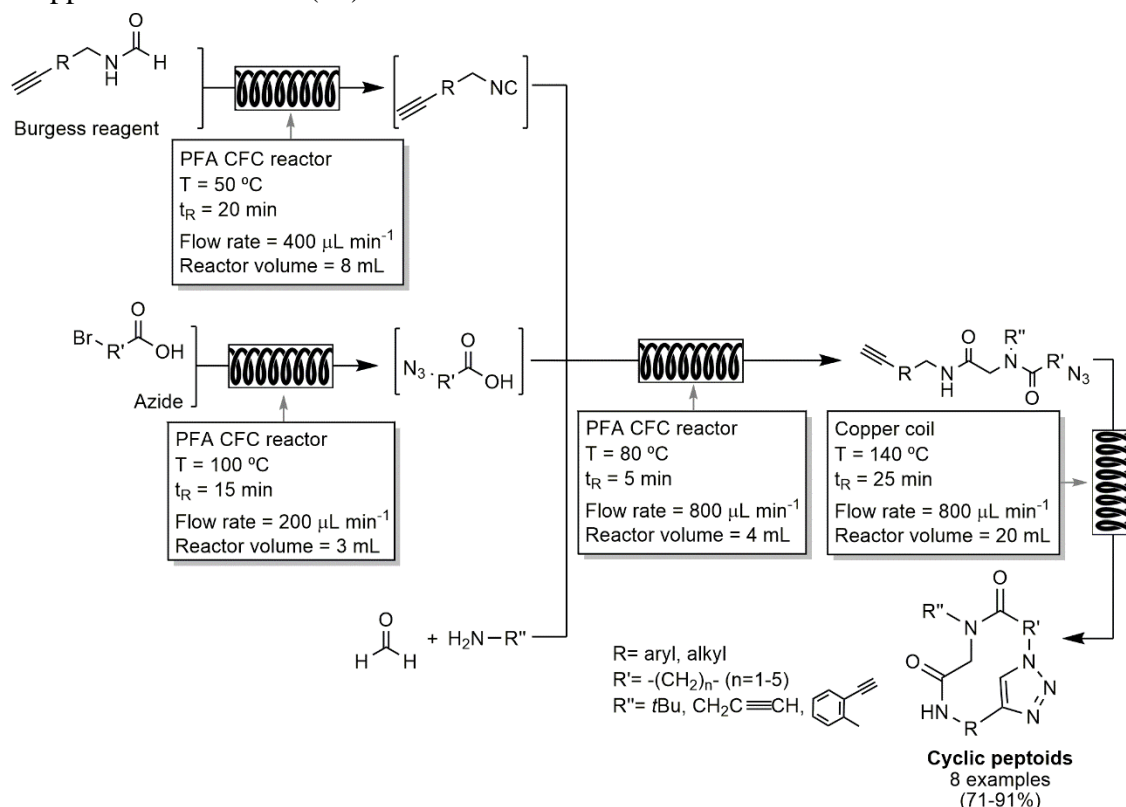
Scheme 11.12. Flow chemistry for the synthesis of cyclic peptoids *via* Ugi reaction followed by copper-catalyzed click intramolecular cycloaddition.

The continuous flow synthesis of rufinamide, an antiepileptic drug with a broad spectrum of efficacy and high tolerability,(69) has caught the attention of several groups working in the field of flow chemistry.(70, 71)

Borukhova *et al*. described the synthesis of a rufinamide precursor under flow conditions, using 2,6-difluorobenzyl alcohol as the starting material. The alcohol is converted *in situ* into 2,6-difluorobenzyl chloride by reacting with hydrogen chloride gas. Water is generated as the sole by-product, jointly with the immediate consumption of the synthesized 2,6-difluorobenzyl azide in the 1,3-dipolar cycloaddition to yield triazole, which minimize the risk associated with detonation of organic azides, improve the sustainability of the overall process. The use of (*E*)-methyl-3-methoxyacrylate as dipolarophile in the cycloaddition step is a safer and cheaper alternative to the corresponding alkyne dipolarophile (for example propiolamide, would lead to the formation of the rufinamide precursor).(72) Scheme 11.13 summarizes the synthesis of this important antiepileptic drug.
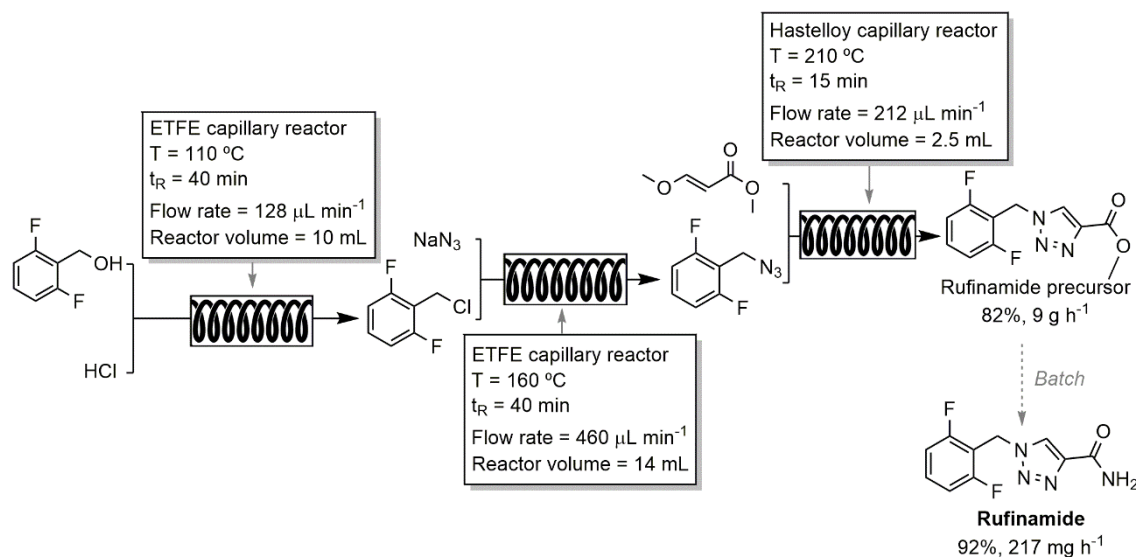
Scheme 11.13. Flow synthesis of antiepileptic drug rufinamide.

Five members cyclic carbonates can be produced from epoxides and one carbon synthon. Phosgene traditionally used for this purpose has been replaced by less hazardous carbon dioxide.(73) The reaction of carbon dioxide and epoxide is an efficient approach for the production of cyclic carbonates and is one of the few industrially relevant reactions utilizing carbon dioxide.(74)

Sathe *et al*. used olefins as substrates for oxidative carboxylation reaction under flow conditions (Scheme 11.14). Hydrogen peroxide was applied as the oxidative agent and methyltrioxorhenium (MTO) as the catalyst for the epoxidation reaction, associated with a *N*-donor ligand (3-methylpyrazole). For the epoxide carboxylation step, an amino trisphenolate complexed aluminum catalyst, with tetrabutylammonium iodide (TBAI) co-catalyst was selected. Using 2 mol% catalyst loading in the presence of 10 mol% TBAI in a stainless steel tubing packed with sand heated at 100 °C, complete conversion of styrene oxide to styrene carbonate was observed in 40 min. Between the two reactors, a membrane-based separator was placed, in order to remove the unreacted hydrogen peroxide, since it would be unfavorable for the carboxylation step. The epoxidation and carboxylation of substituted styrenes and aliphatic olefins was achieved in overall yield between 56 and 91%, however, the process was unsucessfull for the transformation of internal olefins.(75)
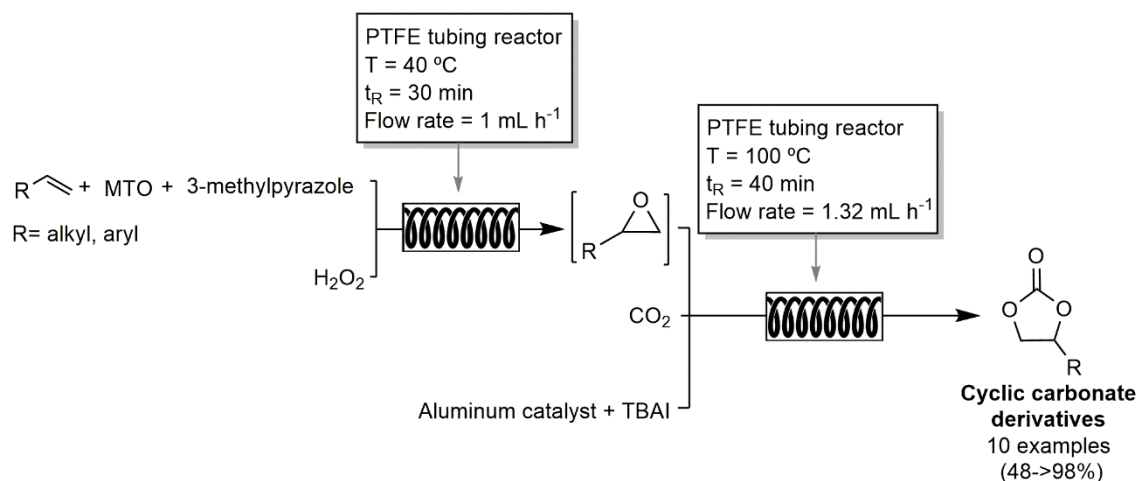
Scheme 11.14. Synthesis of cyclic carbonate derivatives from olefins *via* two-step oxidative carboxylation using a flow setup.

Oxazole and oxazoline-containing products are also versatile molecules, namely for natural product synthesis, and have caught attention due to their presence in several products with interesting biological activities.(76-78) Siphonazoles, a new class of natural products of bacterial origin, first reported in the beginning of this century, present an unusual feature – the presence of two oxazole moieties.(79, 80) A multistep flow procedure was developed to prepare the *O*-methyl siphonazole, and the steps leading to the synthesis of the functionalize oxazole are depicted in Scheme 11.15.(81)

The *in situ* coupling of dimethoxycinnamic acid, activated by CDI, with threonine *tert*-butyl ester hydrochloride was carried out at 110 ºC during 50 min, followed by the addition of diethylaminosulfur trifluoride (DAST) leading to the cyclodehydration of the amide intermediate, at 75 ºC during 25 min, affording the oxazoline in high yield. A set of heterogeneous scavengers (sulfonic acid (QP-SA) to remove Et_3N, imidazole and residual threonine *tert*-butyl ester; a tertiary amine (QP-DMA) to remove acid residues; $CaCO_3$ and SiO_2 fluorinated reactants and residues) were used in the inline purification of the oxazoline prior to the oxidation to the corresponding oxazole, using a mixture of $BrCCl_3$ and DBU at 110 ºC during 50 min. The flow sequence afforded the oxazole carboxylic acid in multigram quantities without the need to perform any traditional workup or purification steps.
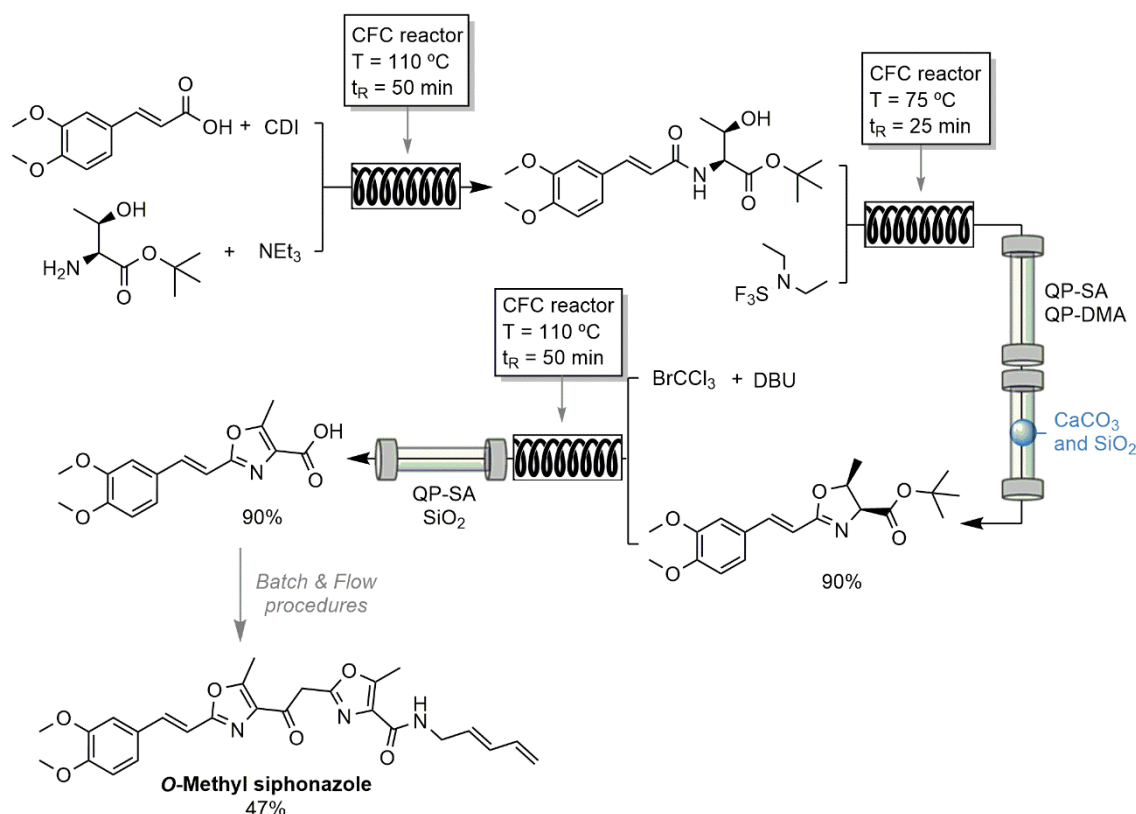
Scheme 11.15. Synthesis of an oxazole synthetic intermediate of *O*-methyl siphonazole under flow conditions.

1,2,4-Oxadiazoles, used in medicinal chemistry as bioisosteres of amide and ester functional groups, were prepared in a single continuous flow chemistry procedure. Using commercially available hydroxylamine, nitriles, carboxylic acids and aminopyridines as starting materials, 1,2,4-oxadiazoles and imidazo[1,2-a]pyridin-2-yl-1,2,4-oxadiazoles, were prepare *via* intramolecular cyclodehydration. The combination of EDC/HOBt/DIPEA (1:1:1) provided the best conditions for complete conversion of benzoic acids to the corresponding 1,2,4-oxadiazole derivative through the reaction with amidooximes previously formed by the reaction of hydroxylamine and alkyl and aryl nitriles. The general approach to obtain the oxadiazole derivatives is depicted in Scheme 11.16.(82)
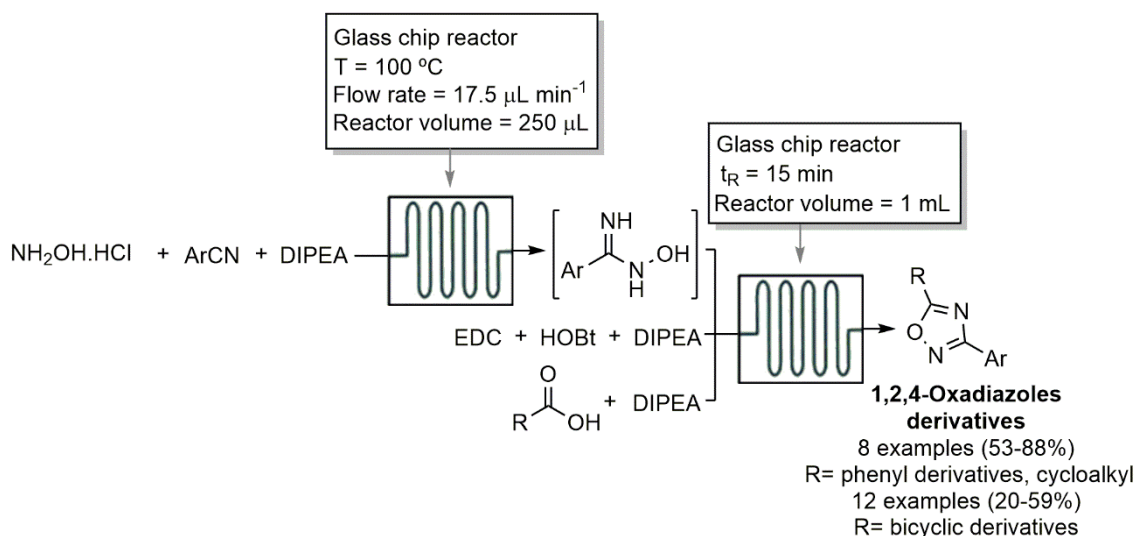
Scheme 11.16. Synthesis of 1,2,4-oxadiazole derivatives using multi-step flow chemistry.

11.2.4. *Six-membered ring heterocycles*

Six-membered heterocyclic ring systems constitute a very relevant class of compounds in the field of organic and medicinal chemistry, being present in multiple commercialized drugs. Among some of the most recent examples, we highlight the flow synthesis of an enantiomeric pure dihydropyridinone derivative – (3R,4R)-3,4,6-triphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one – using an immobilized chiral benzotetramisole (PS-supported BTM) analogue as the organocatalyst. Briefly, the catalyst-free reaction of phenylacetic acid and pivaloyl chloride yield the phenylacetic anhydride, which through domino Michael addition/cyclization reaction with a chalcone-type tosylimine led to the desired product in high yield (70%) and excellent enantiomeric excess (> 99%) (Scheme 11.17). An in-line control (FTIR analysis) and a work-up procedure (liquid-liquid separator) were also included in the flow setup.(83)
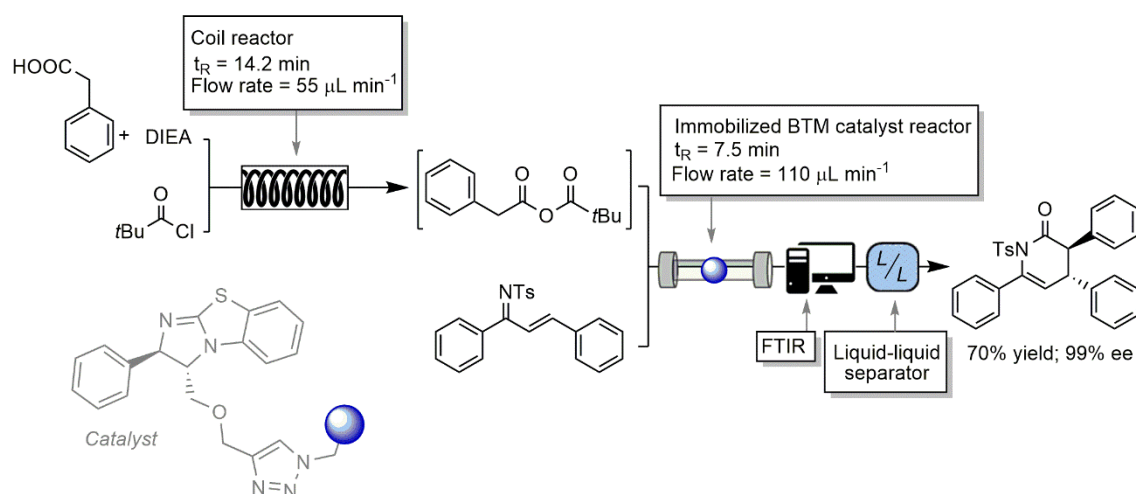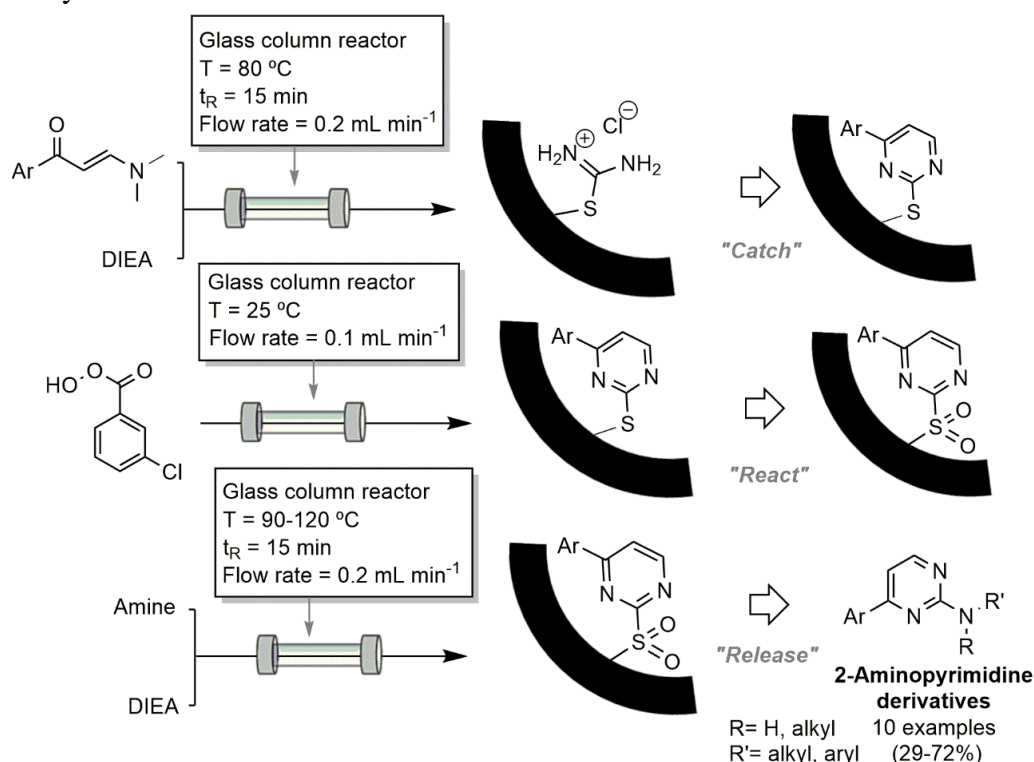

Scheme 11.17. Flow synthesis of a dihydropyridinone derivative with in-line analysis and work-up.

Another relevant heterocyclic core is the quinoxaline, a bicyclic moiety consisting of a benzene ring fused with a pyrazine ring, displaying a wide plethora of bioactivities, as extensively reviewed in the literature.(84-86)   The multi-step flow synthesis of quinoxaline derivatives in a safe manner has been reported by Martin *et al.*. The setup allowed the reactions to occur without requiring the isolation of diazoketone intermediates, potentially explosive compounds, as well as to minimize operators exposure to phenylenediamine intermediates,(87) an important feature as these compounds are classified as carcinogenic.(88, 89) Further, in-line purification was also carried out under the described methodology, by using a QP-TU pad (polymer supported thiourea - metal scavenger), a PS-TsCl (polymer supported tosylchloride) or PS-TsNCO (polymer supported isocyanate - scavenger of unreacted diamine and reduced quinoxaline derivatives), and a PS-Ts-NHNH$_2$ (polymer supported tosylhydrazine - scavenger for the residual diazoketone), with the final quinoxaline derivatives being obtained in variable yields (21-96%) (Scheme 11.18).(87)
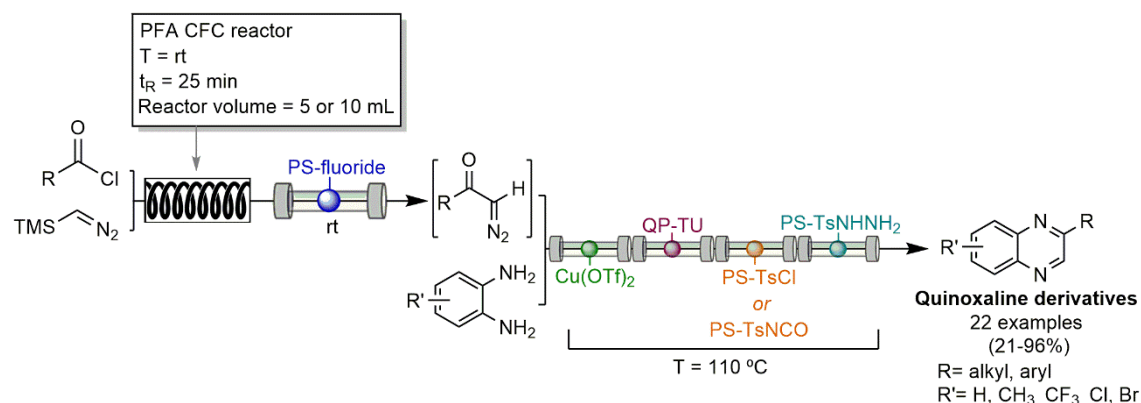
Scheme 11.18. Multistep flow synthesis of quinoxaline derivatives.

Ingham *et al*. described a very interesting flow setup, using a monolith-supported synthetic procedure to prepare 2-aminopyrimidine derivatives, by a "catch-react-release" methodology. This approach consists of immobilizing one of the reagents on a solid support, which is then exposed to different conditions. Briefly, immobilized thiouronium chloride reacts with different enaminones in the presence of *N,N*-diisopropylethylamine (DIEA) – cyclization step ("catch"). Next, the formed heterocycle reacts with *meta*-chloroperoxybenzoic acid (*m*-CPBA), in a monolith oxidative activation. As the last step, the oxidized heterocycle reacts with amine derivatives in the presence of DIEA, leading to an amine displacement of 2-aminopyrimidine derivatives ("release" step) (Scheme 11.19).(90) Using the described procedure *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine, a known precursor in the synthesis of tyrosine kinase inhibitor Imatinib,(91) was obtained in 48% yield, overcoming problems associated with the low solubility of some intermediates.


Scheme 11.19. "Catch-react-release" flow procedure for the synthesis of 2-aminopyrimidine derivatives.

Filipponi *et al.* prepared a library of dihydropyridazine-3-carboxylic acid derivatives using sequential flow chemistry. Dynamically mixed tubular (DMT) reactors were employed in two of the synthetic steps. This type of reactor allows to overcome a serious drawback of conventional flow systems, as they allow reactions to proceed even when solids are formed. Briefly, different anilines react with $NaNO_2$ affording a diazonium salt intermediate, which further reacts with a pyranone derivative to give a hydrazone intermediate. In the last step, requiring the presence of a base (K_2CO_3) and with a temperature increment, the hydrazone cyclizes to the final product (Scheme 11.20). (92, 93) Using this continuous process the *p*-bromophenyl derivative was obtained with a productivity over 9.6 g/h, with high purity, avoided the safety problems usually associated with the diazonium salts. This family of compounds is relevant in drug discovery, as they are known for interacting with bromodomain containing proteins, a druggable target with increasing interest in pharmacology.(94, 95)
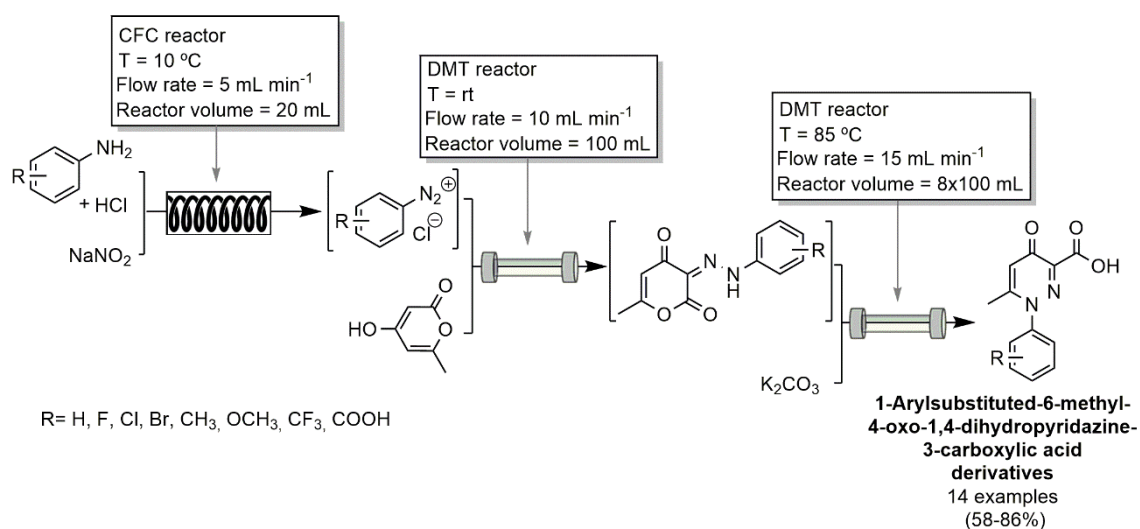
Scheme 11.20. Multi-step flow chemistry using DMT reactors.

Thioquinazolinone derivatives were prepared *via* a multistep flow process by Kim *et al.*, through the generation of two organolithium intermediates, putting into evidence the safety inherent to flow chemistry. The full process takes place at room temperature, without isolation of any of the intermediates and with high efficacy, since compounds are prepared quickly (up to 10 seconds) in very high yields (75-98%). Briefly, *o*-bromophenyl-isothiocyanate reacts with *n*BuLi, affording 2-isothiocyanatophenyl lithium intermediates, which further react with a phenyl isocyanate, achieving a lithium thiolate intermediate. The final step consists in the reaction of this last intermediate with functionalized benzyl bromide to attain the desired thioquinazolinone derivates (Scheme 11.21).(96)
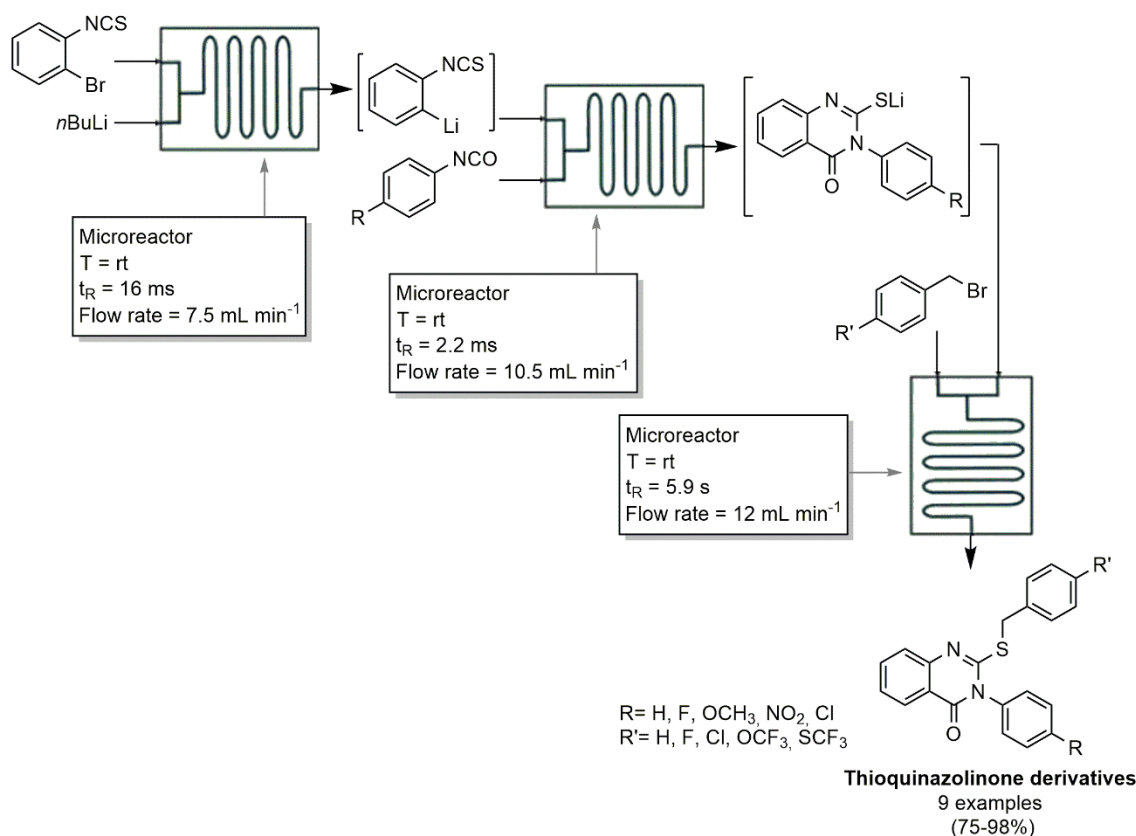
Scheme 11.21. Flow multi-step synthesis of thioquinazolinone derivatives, using organolithium intermediates.

The multi-step flow synthesis of six-membered ring heterocycles bearing oxygen atoms has been less explored. Nevertheless, the synthesis of pyranonaphthoquinone derivatives under sequential flow reactions was reported by Osorio-Planes *et al*., using a heterogeneous catalytic system consisting of a chiral squaramide immobilized in polystyrene. The continuous flow setup consists of two sequential steps (Michael reaction and a cyclization step), performed at room temperature. The heterogeneous chiral organocatalyst enabled high enantioselective Michael reaction and the final products were achieved in high yield and enantioselectivity (Scheme 11.22).(97)
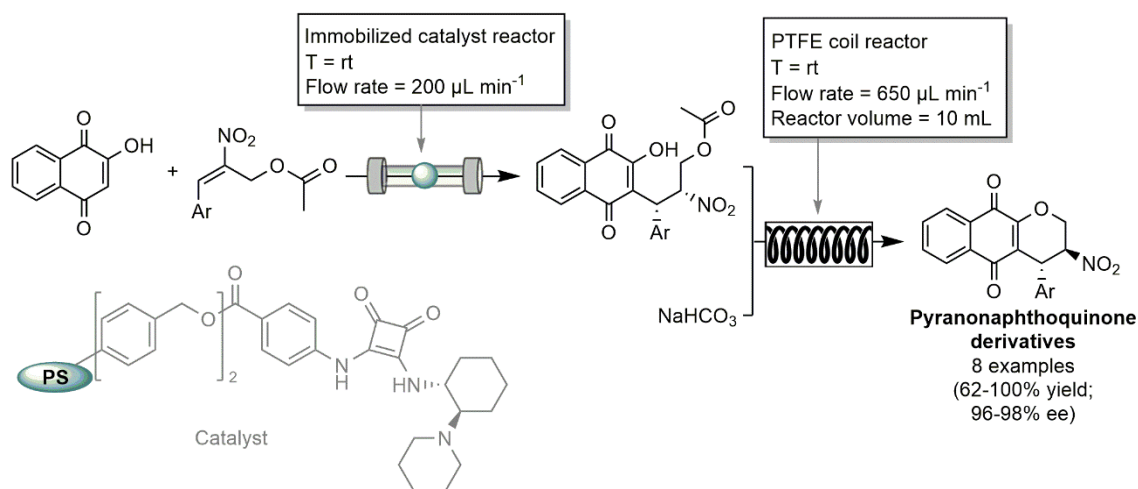
Scheme 11.22. Flow enantioselective multi-step synthesis of pyranonaphtoquinone derivatives.

Artemisin, a natural product with outstanding relevance in the field of medicinal chemistry as it presents a strong antimalarial activity, has been a synthetic challenge for organic chemists. Its complex framework, with multiple rings, includes two which are crucial for its biological activity - a six-membered lactone and cyclic endoperoxide synthons.(98) Artemisinic acid is the usual starting material for the synthesis of artemisin, since it is easier to extract from natural sources or through biotechnological processes. It was used by Lévesque *et al*. to prepare artemisin (200 g/day) in a continuous-flow photochemical setup (Scheme 11.23), using tetraphenylphorphirin as photosensitizer. In the first step, photooxidation of dihydroartemisinic acid generates the corresponding teritary allylic hydroperoxide intermediates, which is protonated in the presence of an acid, leading to the migration of the allylic group and formation of the corresponding hemiketal, which opens affording an enol intermediate, key for the final formation of artemisin.(99)
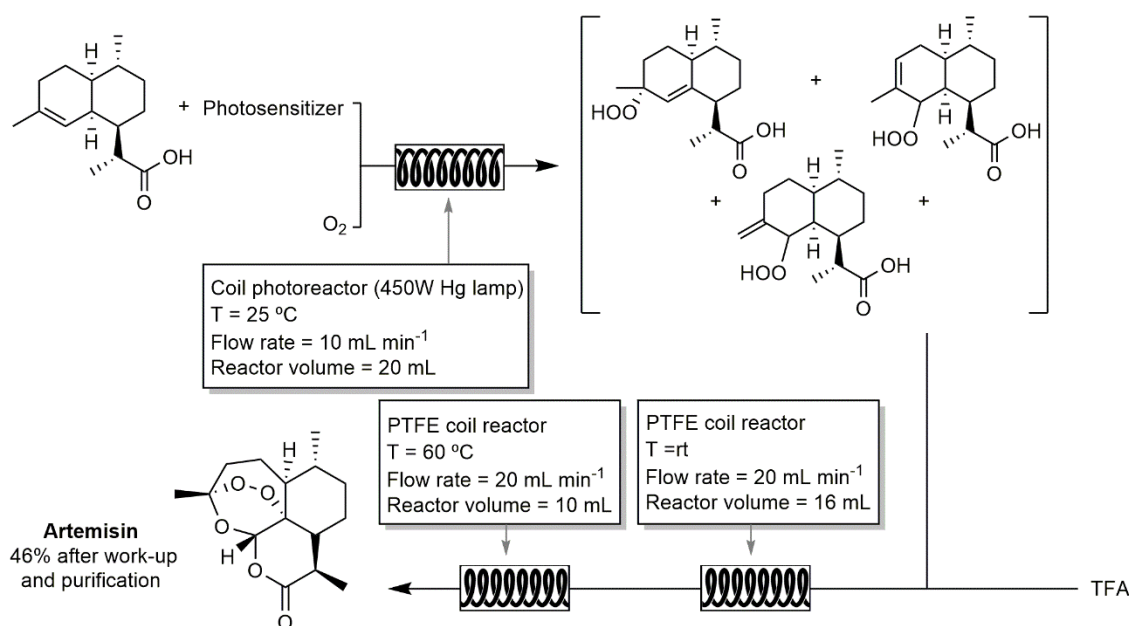
Scheme 11.23. Synthesis of artemisin from dihydroartemisinic acid under flow conditions.

At this point, we would like to highlight one recent example of flow chemistry applied to the synthesis of six-membered ring heterocycles bearing different types of heteroatoms. The synthesis of 6-amino-2,2,7-trifluoro-4*H*-benzo-[1,4]-oxazin-3-one, through a three-step nitration/hydrogenation/cyclization synthetic route is summarized in Scheme 11.24. One of the main advantages of this sequential approach is to avoid operator handling of labile and explosive synthetic intermediates.(100) Naturally occurring benzoxazinones have been considered useful lead compounds for new herbicide development, namely due to environmental, toxicological and economic impact of synthetic herbicides.(101, 102)
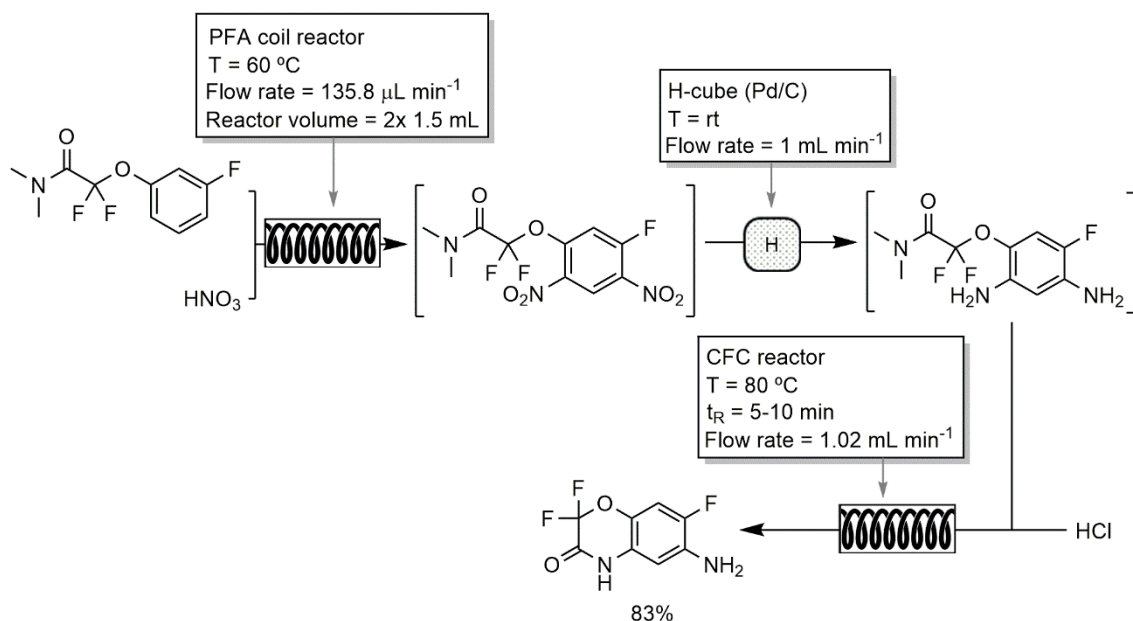
Scheme 11.24. Multi-step flow synthesis of a benzoxazinone herbicide.

11.2.5. *Seven-membered ring heterocycles*

Hartwig *et al.* reported the multi-step flow synthesis of an important benzodiazepine, olanzapine, used in clinical practice as an antipsychotic drug. Briefly, a Buchwald-Hartwig reaction was performed between 1-iodo-2-nitrobenzene and one aminothiazole. Further, nitro group reduction and acid-promoted cyclization occurs to afford the seven membered-ring heterocycle, which after thermal condensation with *N*-methylpiperazine affords the API (Scheme 11.25).(103)
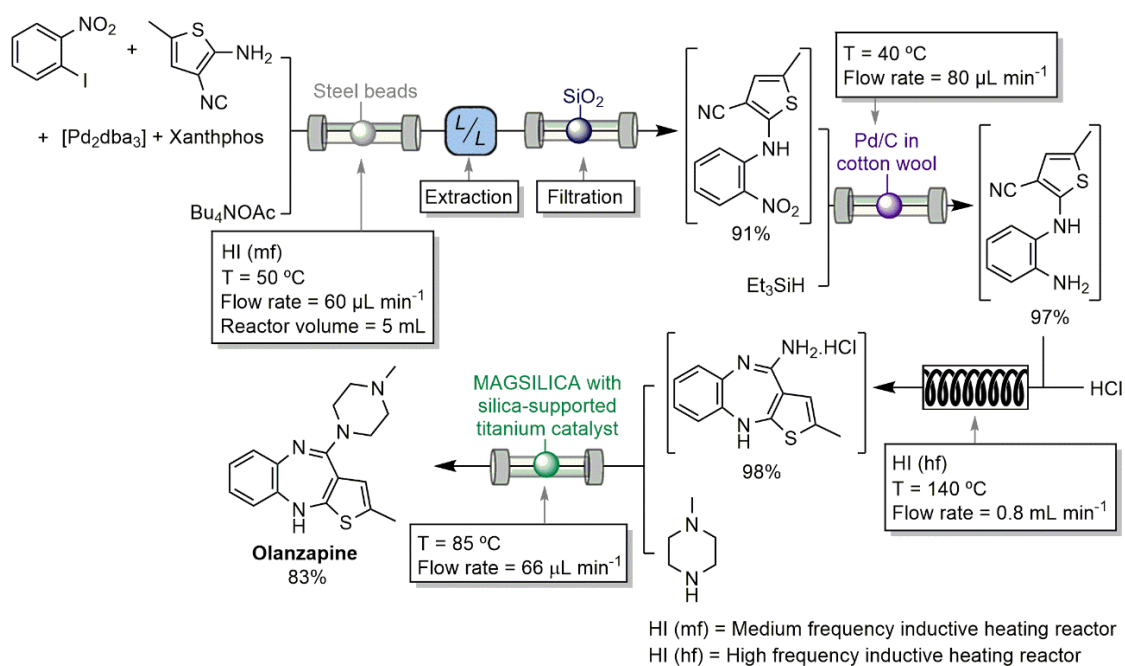
Scheme 11.25. Flow multi-step synthesis of olanzapine (Zyprexa®).

Recently, the use of a multi-step flow setup for the synthesis of another API – diazepam – was reported as a sustainable process. Although other examples were previously reported in literature concerning the flow synthesis of this drug,(104) Bédard *et al.* reduced the E-factor for this synthesis by 4-fold (from 36 to 4). This cutback was accomplished by a multifactorial approach, but the replacement of ethyl acetate by 2-methyltetrahydrofuran was a key player for this significant reduction. Diazepam was produced by an amidation reaction (between benzophenone and chloroacetyl chloride) followed by cyclization (Scheme 11.26).(105)
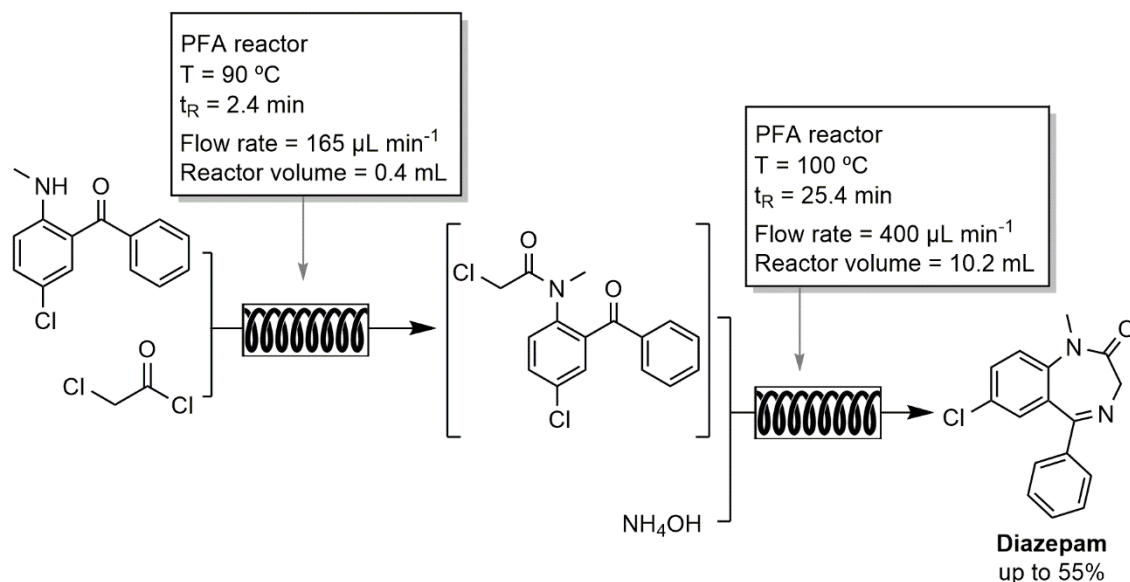
Scheme 11.26. Flow multi-step synthesis of diazepam (Valium®).

11.3. Conclusions and Perspective

In the past few decades, continuous-flow organic synthesis went from an unexplored technique, based on "do-it-yourself" systems to one of the most revolutionary tools for organic chemists, changing the face of many research labs from typical glassware and batch procedures to fully automatized processes. The scaffold diversity attained using continuous-flow apparatus, in the field of heterocyclic compounds synthesis, makes this technique a versatile and valuable approach for academia and industry, for the preparation of high-value products, such as fine chemicals, APIs and natural products.

The possibility to perform sequential reaction steps in a closed flow system enhances the possibilities to perform complex, and even unexplored, chemical transformations in an efficient, safe, profitable, and scalable manner. While process intensification is already when of the main advantages of applying continuous-flow systems, the future of flow chemistry, especially in drug discovery settings, will likely be oriented to increase new molecules output, integrating multicomponent and multistep synthesis, purification and in-process control, accelerating the overall drug discovery process and hit identification.

11.4. References

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