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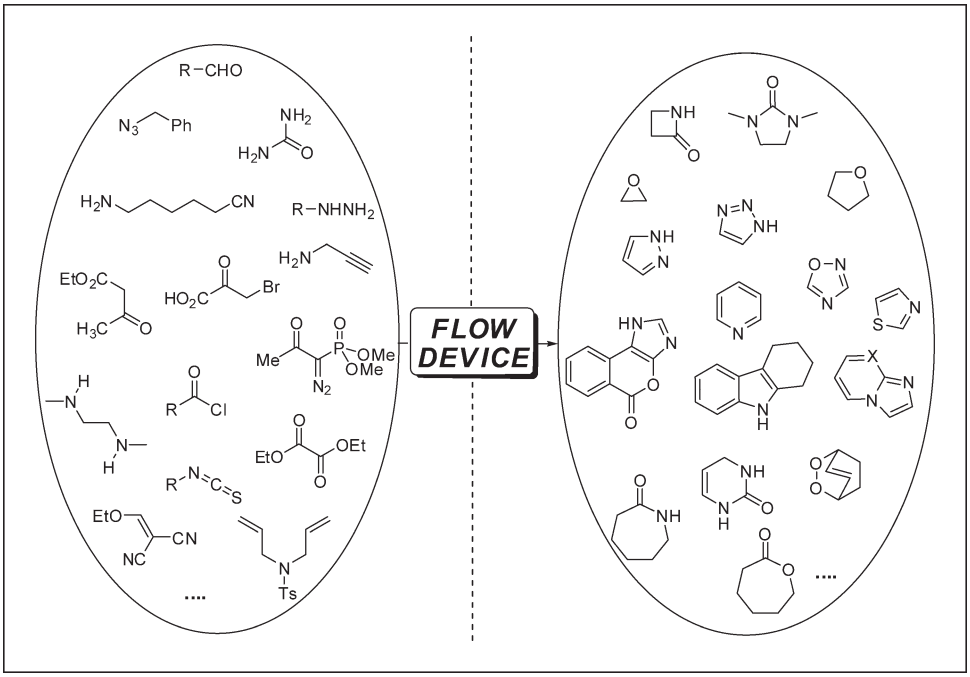

This review surveys the synthesis of heterocycles under continuous-flow conditions, including the use of chip-based microreactors, coil-based flow reactors, and capillary or tubular devices.

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Contents

		Page
1.	Introduction	11
2.	Three-membered ring heterocycles with one heteroatom	12
3.	Four-membered ring heterocycles with one heteroatom	13
4.	Five-membered ring heterocycles with one heteroatom	14
5.	Five-membered ring heterocycles with two heteroatoms	16
6.	Five-membered ring heterocycles with three heteroatoms	20
7.	Six-membered ring heterocycles with one heteroatom	22
8.	Six-membered ring heterocycles with two heteroatoms	26
9.	Seven-membered ring heterocycles with one heteroatom	27
10.	Eight-membered ring heterocycles with one/two heteroatoms	27
11.	Miscellaneous heterocycles	27
12.	Conclusions	28
	References and notes	29

1. INTRODUCTION

The use of continuous-flow reactors in organic synthesis offers many attractive features that have been widely reviewed [1–3]. Numerous advantages associated with the use of these devices have rendered this technology a potentially important tool for organic chemists. Faster, easier, and reproducible chemistry can sometimes be performed in flow reactors when compared with the traditional round-bottomed flask. So-called microreaction technology is generally defined as the continuous-

flow processing of reactions within structured channels of 10–500 μm diameter. Because of the high surface-to-volume ratio in microchannels of this type, heat transfer is very efficient and reaction temperatures in microreactors can be changed efficiently by application or removal of heat. In addition, enhanced mass transfer characteristics, safer synthesis of dangerous compounds, isolation of air- and moisture-sensitive chemistry, and reduction of hazardous waste are all realized using microreactors. The ability to efficiently optimize reaction conditions by control of residence time and rapid experimentation also add value to the technology by shortening production development lifecycles [1–3].

Traditionally, most synthetic transformations performed in microreactors have involved ambient or even low-temperature conditions to safely conduct highly exothermic processes [1–3]. In recent years, however, there has been an increased interest in executing synthetically valuable transformations also at elevated temperature conditions using sealed/pressurized continuous-flow microreaction devices [4]. In contrast to the classical use of microreaction technology involving exothermic processes at room temperature where the generated heat is efficiently removed from the system, here energy needs to be introduced to the microreactor applying appropriate heating principles. Dealing with comparatively slow reactions that are not controlled by the mixing process, the issue of channel dimensions/mixing becomes less critical. Therefore, the use of so-called ''mesofluidic'' (also termed ''mesoscale'' or ''milliscale'') continuous-flow reactors in a temperature range from 60 to 170°C, where channel/capillary/tube dimensions are often $\geq$500 μm and no dedicated (micro)mixing device is implemented, has dramatically increased over the past few years [5]. In this context, it has to be emphasized that high-temperature/high-pressure processing offers many distinct advantages as demonstrated by the recent success of microwave-assisted organic synthesis [6]. The use of sealed/pressurized microfluidic or mesofluidic continuous-flow reactors therefore appears perfectly suited to mimic both the rapid heating and the high temperatures attainable in a microwave chemistry experiment [7].

A particularly attractive feature of microfluidic and mesofluidic reaction technology is the ease with which reaction conditions can be scaled—without the need for reoptimization—through the operation of multiple systems in parallel (numbering-up, scaling-out), thereby achieving production scale capabilities [3].

In this review, we highlight recent examples from the literature (2003–2009) where heterocyclic molecules have been synthesized using a continuous-flow format (Fig. 1). As the emphasis of this survey is on synthetic variability, technical issues regarding the flow processing such as reactor material, flow rate, backpressure, *etc*. are generally not discussed in great detail. This information is contained in the original references.

2. THREE-MEMBERED RING HETEROCYCLES WITH ONE HETEROATOM

In 2002, Schüth and coworkers studied the silver-catalyzed oxidation of ethylene to ethylene oxide in a custom-made microreactor system [8]. As an example, 15% ethylene in a pure oxygen mixture could be processed although such reaction mixtures are highly explosive and thus cannot be used in a typical industrial process. Compared to the standard industrial process, similar selectivity and productivity for the microreactor oxygenation process were obtained. A similar catalyst based on silver—Ag/Cs/α-Al_2O_3—was prepared and applied for the oxidation of 1,3-butadiene in the gas phase by Otto *et al*. using the catalyst in a ~17% oxygen/argon stream in a temperature range of 150–320°C [9,10]. Similarly, the oxidation of ethylene to ethylene oxide was chosen as a model reaction in a study by Markowz *et al*. [11].

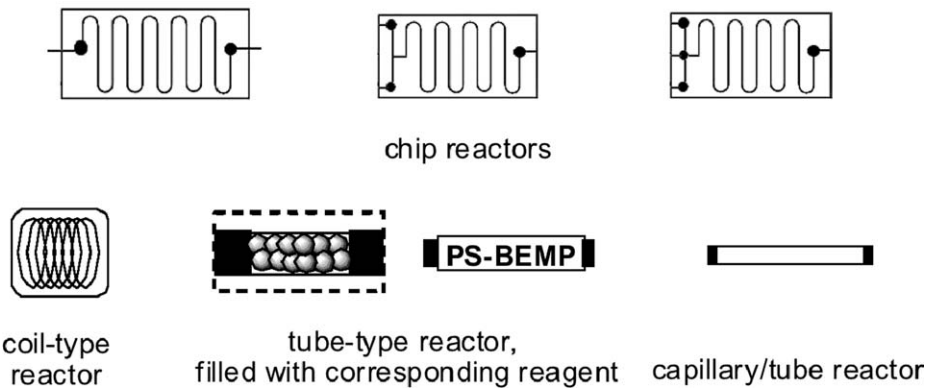
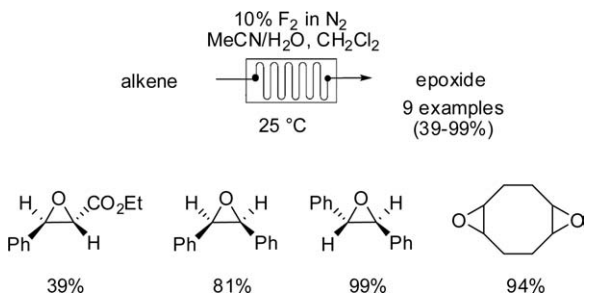


Figure 1. Graphical representation of continuous-flow reactors used in this review.

Scheme 1

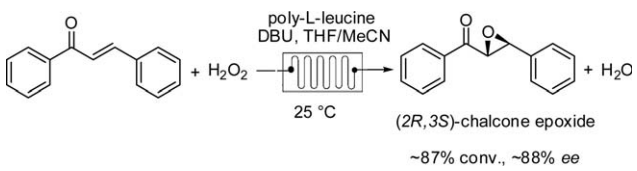


In this case, titanium silicalite was chosen as a heterogeneous catalyst and H_2O_2 as oxygen source. The obtained results on a microreactor scale could be successfully upscaled to a model pilot plant.

The epoxidation of various alkenes using the highly effective oxidizing agent HOF·MeCN has been recently demonstrated as an environmentally benign process using microreactor technology [12]. The oxidizing agent is *in situ* generated from a 10% F_2/N_2 gas mixture and wet MeCN and immediately subjected to a reaction with an acyclic or a cyclic alkene at room temperature (Scheme 1).

In a chemoenzymatic process, the immobilized form of *Candida antarctica* lipase B (Novozym® 435) was used for performing alkene oxidations [13]. The biocatalytic epoxidation process involves the lipase-catalyzed formation of a peroxy acid from a carboxylic acid and an oxygen donor such as H_2O_2 or urea–hydrogen peroxide complex through epoxide formation and regeneration of the carboxylic acid. The selected enzyme was found to perform optimally at 70°C, resulting in nearly quantitative yields in ~5 min residence time in the microreactor unit. Ethyl acetate was used as both solvent and reagent to provide acetic acid by *in situ* hydrolysis for the generation of the corresponding peracid.

Scheme 2

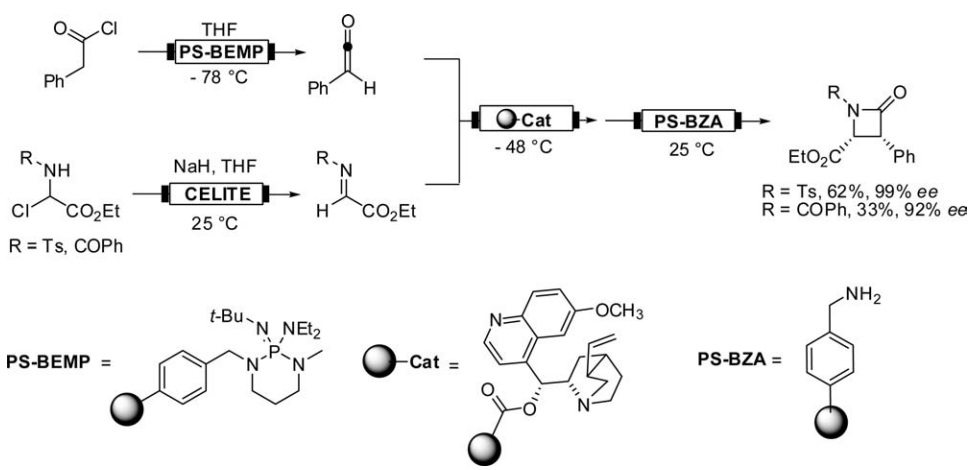


Kee and Gavriilidis disclosed poly-L-leucine-catalyzed asymmetric chalcone epoxidations in a microstructured PEEK flow reactor [14]. The reaction proceeds in two steps—a deprotonation step, where the oxidizing reactive species is formed and an epoxidation step to obtain the oxidized product. In-depth studies on the influence of various reaction parameters such as temperature, residence time, concentration of reactants, and catalyst were performed (Scheme 2).

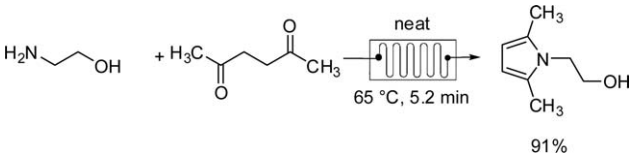
3. FOUR-MEMBERED RING HETEROCYCLES WITH ONE HETEROATOM

In 2001, Lectka and coworkers demonstrated a very simple and efficient concept for the use of polymer-supported reagents in a continuous-flow asymmetric preparation of β-lactams [15]. The asymmetric quinine-based catalyst was prepared by immobilizing the corresponding quinine on high-loading Wang resin (100–200 mesh, 1.6–3 mmol/g) using various linkers. Because of the lack of commercially available flow instrumentation at that time, a simple ''flow-by-gravity'' setup was constructed connecting chromatography columns in sequence filled with the polymer-supported reagents. Starting with acid chlorides (to generate corresponding ketenes) and α-chloroamines (to generate imines) or directly with imines, small series of β-lactams were generated sequentially. In addition, a prepacked column with benzyl amine resin was used at the end of the flow

Scheme 3



Scheme 4



sequence to assure the required high purity of the final products in relatively good yields (Scheme 3).

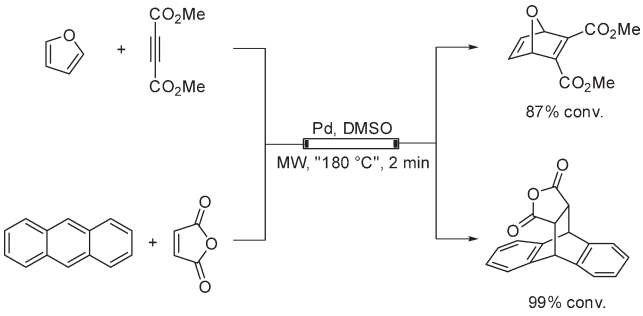
4. FIVE-MEMBERED RING HETEROCYCLES WITH ONE HETEROATOM

Demonstrating the advantages of flow chemistry in microreactors was the goal of a recent study by Schwalbe *et al*. [16]. By using commercially available flow instrumentation, various reaction behaviors have been studied, whereby different combinatorial approaches were applied in some of the cases. One model reaction was the exothermic Paal–Knorr condensation of ethanolamine and acetonylacetone. Because of the very efficient temperature control in the microreactor used, the reaction proceeded with 91% yield in a throughput rate of 260 g/h directly from the neat starting materials, thus preventing the waste of organic solvent (Scheme 4).

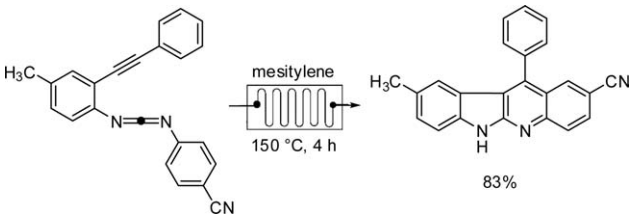
A custom-built microcapillary reactor was used by Shore and Organ [17] for performing a Diels–Alder cycloaddition reaction under microwave flow conditions. A thin Pd film on the inner surface of inexpensive glass capillaries was used, displaying excellent heating behavior under microwave irradiation conditions. Several dienes and dienophile reaction partners were used to demonstrate the usefulness of this synthetic approach, whereby different substituted furans could be prepared (Scheme 5).

The thermal C^2–C^6 cyclization of enyne-carbodiimides in the preparation of indolo[2,3-*b*]quinolines was demonstrated by Schmittel *et al*. as part of a study on the influence of internal (substituent) and external (polarity of solvents) effects on this type of cyclization

Scheme 5



Scheme 6



[18]. One of the prepared enyne-carbodiimides was further subjected to thermolysis at 150°C under flow conditions to provide the expected indolo[2,3-*b*]quinoline in 83% yield within 4 h (Scheme 6).

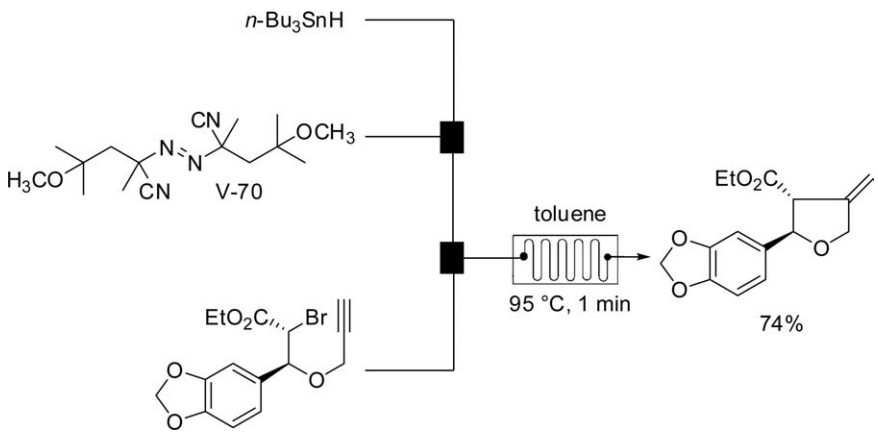
Radical reactions of organic halides with either tin hydride or tris(trimethylsilyl)silane and radical initiators such as V-40, V-65, V-70, or AIBN were carried out in a chip microreactor by Ryu and coworkers [19]. On a gram scale, a tetrahydrofuran derivative—a key intermediate for the synthesis of the naturally occurring furfuran lignans paulowin and samin—was prepared in a 185-min run, providing 7.6 g (74%) of the desired product (Scheme 7).

Recently, Kappe and coworkers reported the application of a high-temperature, high-pressure mesofluidic flow reactor for various high-temperature chemistry reactions [7a]. For example, in a scale-up run, a Fischer indole synthesis was performed resulting in the preparation of 25 g (96%) of 2,3,4,9-tetrahydro-1*H*-carbazole starting from phenylhydrazine and cylohexanone within 1 h at 200°C using an acetic acid/2-propanol (3:1) mixture as a solvent, thus preventing precipitation of the formed product (Scheme 8). Applying microwave heating to a glass flow cell—a standard 10-mL Pyrex vial filled with sand [20] or with glass beads [21]—the latter synthesis has been previously achieved using somewhat lower temperatures.

In general, high-temperature/pressure continuous-flow systems have proven to be suitable for the synthesis of a broad range of cyclic and acyclic products as well as for the preparation of thiophene and pyrrole heterocycles by Darvas *et al*. [22]. All of the performed syntheses were achieved at temperatures above 150°C and at up to 200 bar of pressure, in some of the reactions using supercritical conditions for the used solvents.

As a part of research on various attractive pharmacologically active molecules at Pfizer, the [3+2] dipolar cycloaddition of a stabilized azomethine ylide with 12 different electron-deficient alkenes to form *N*-benzylpyrrolidines was examined under flow conditions [23]. The reactive ylide was generated *in situ* from (benzyl(methoxymethyl)trimethylsilylmethyl)amine in the presence of a catalytic amount of CF_3COOH. The outcome of the reaction in terms of yields was shown to be strongly

Scheme 7



dependent on the reactivity of the dipolarophiles. The more reactive alkenes such as ethyl acrylate, *N*-methylmaleimide, or (*E*)-2-nitrostyrene provided the desired products in 77–83% yield, whereas the use of the less reactive (*E*)-crotononitrile or ethyl methacrylate resulted in somewhat lower yields of 59–63%. Reaction optimization was performed in a temperature range of 20–100°C and pressures of 7–9 bar with reaction times in the range of 10–60 min. When using ethyl acrylate, the authors were able to scale-up the process to obtain 30 g (87%) of ethyl-*N*-benzylpyrrolidine-3-carboxylate in 1 h (Scheme 9).

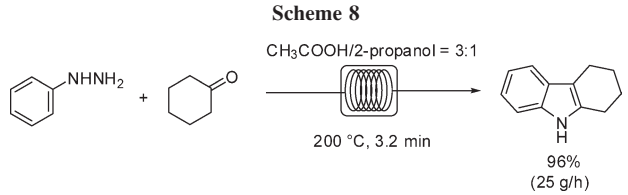
The same synthetic approach was applied by Ley and coworkers to prepare 3-nitropyrrolidines under flow conditions [24]. The initial optimized procedure, based on the use of the strong CF_3COOH to generate a reactive dipole, was modified so that a reloadable fluoride monolith could be used providing the fluoride ions to catalyze the 3-nitropyrrolidine formation. The new concept helped reducing the reaction temperatures from 60–120°C to 50–80°C and also to shorten the reaction times and increase the yields when compared with the method using CF_3COOH. Furthermore, selective nitro-reduction over RaNi catalyst afforded the corresponding 3-amino-*N*-benzylpyrrolidines, whereas using Pd/C resulted in reduction–debenzylation toward the corresponding 3-amino-NH-pyrrolidines.

An oxidative cyclization of alkenols could be effectively and safely performed in a flow manner using oxone ($2KHSO_5.KHSO_4.K_2SO_4$) as an oxidizing agent without the need for any catalytic species [25]. Using aqueous conditions, a selection of cyclic ethers were prepared in a very short reaction time (5–10 min), under mild conditions (80°C) and in satisfactory conversions (70–99%). The potentially explosive oxone was then safely quenched with 30% aq. $Na_2S_2O_3$ to prevent any hazardous events (Scheme 10).

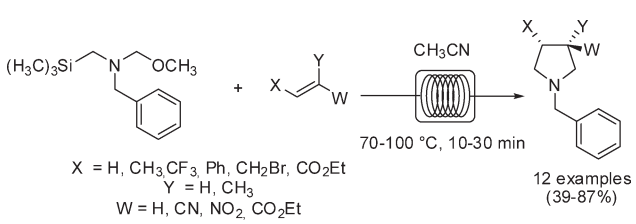
The synthesis of tetra-substituted furans was described by Bremner and Organ in 2007 [26]. By using a modified microwave reactor, the authors were able to prepare several substituted furans by applying a multicomponent reaction approach. Seven different aromatic aldehydes were readily transformed in the presence of cyclohexylisocyanide and dimethyl acetylenedicarboxylate (DMAD) into the corresponding heterocyclic products (Scheme 11).

Inductive heating of magnetic particles in an electromagnetic field is an important feature of magnetic materials. Coating of these magnetic particles with a silica shell preserves on the one side their superparamagnetic behavior, whereas on the other side provides the possibility to functionalize the latter particles thus providing additional catalytic properties. This concept was used by Kirschning and coworkers to perform various synthetic transformations (Suzuki and Heck C-C couplings and Buchwald-Hartwig amination), based on silica-coated and Pd-functionalized Fe_3O_4/Fe_2O_3 particles. Furthermore, the synthesis of a substituted dihydrofuran

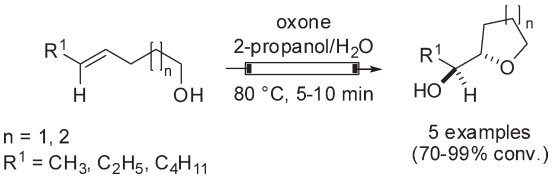
Scheme 8



Scheme 9



Scheme 10



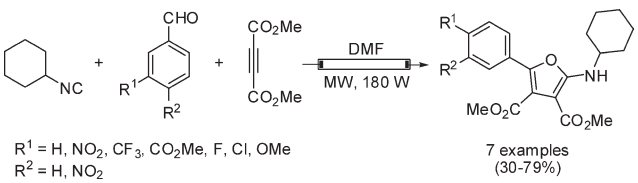
(Scheme 12), based on a ring-closing metathesis with Grubbs second-generation catalyst, immobilized on the surface of the magnetic particles was performed [27].

An interesting combination of simultaneous synthesis and reaction analysis was demonstrated by Trapp *et al.* [28]. By using microcapillaries of 2-cm length with a nano-Pd/siloxane surface coating and hydrogen gas as carrier, extraordinary fast hydrogenations were observed for a 22-member compound library. To extend the scope of this approach for the investigation of reaction kinetics, ring-closing metathesis was also performed in a similar manner by using Grubbs second-generation catalyst. Finally, by combining the two different types of capillaries and an analytical column, *N*-trifluoroacetylpyrrolidine was synthesized from *N,N*-diallyltrifluoroacetamide within 6 min with 49% overall yield (Scheme 13).

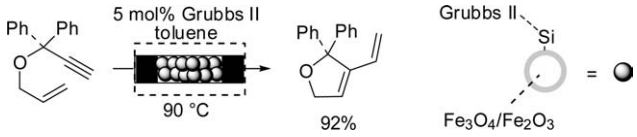
Supporting a Hoveyda-type ligand on the surface of siliceous mesocellular foam *via* [3+2] ''click'' cycloaddition and following treatment with Grubbs second-generation catalyst provided an efficiently immobilized ruthenium-based metathesis catalyst [29]. The latter was used in a circulating flow reactor to prepare different products, including pyrroles (Scheme 14).

The ''flow-by-gravity'' concept was recently exploited by Nishizawa and coworkers to synthesize an indole derivative from an yne-aniline [30]. Using a small glass column prepacked with silica-supported HgOTf and silica gel in a 2:3 ratio, the desired product could be obtained by elution of the starting material with CH_2Cl_2 through the column. As the authors aimed to better describe the usefulness of the silica-supported silaphenylmercuric triflate as solid-supported reagent, the reaction was repeatedly performed for another 20 runs with quantitative yields, demonstrating the low leaching degree of mercury (Scheme 15).

Scheme 11



Scheme 12



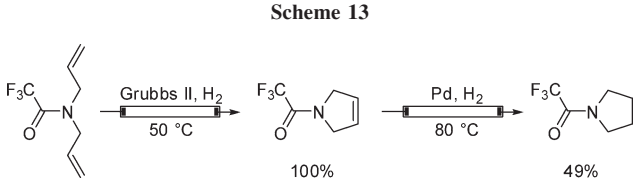
5. FIVE-MEMBERED RING HETEROCYCLES WITH TWO HETEROATOMS

A substituted thiazole system has been prepared in 85% yield by condensation of thioacetamide with ethyl 3-bromo-2-oxopropanoate in a flow manner using the heating/catalysis concept of Kirschning and coworkers using superparamagnetic silica-coated nanoparticles in an electromagnetic field [27]. Garcia-Egido *et al.* reported on the Hantzsch synthesis of six different 2-aminothiazoles using a T-shaped glass microflow system under electroosmotic-driven flow [31]. The reaction proceeded at 70°C temperature for 30 min. Fanetizole, a pharmaceutical agent for the treatment of rheumatoid arthritis, was prepared (Scheme 16).

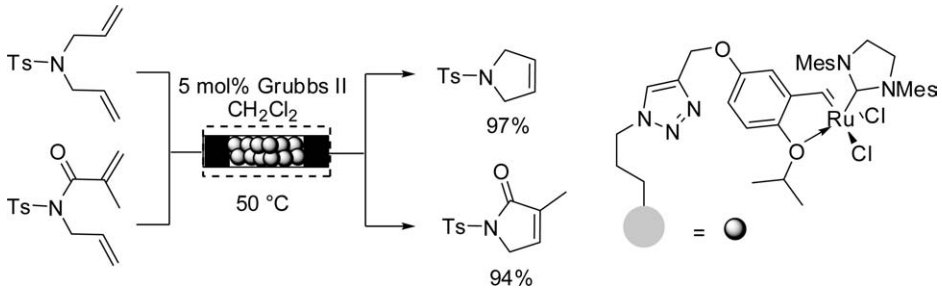
Reacting various isothiocyanates and ethyl isocyanoacetate provided a bifurcated route to the preparation of thiazoles and imidazoles in a modular flow reactor [32]. Yields in the range of 50% of the desired thiazole were obtained. Assuming that the product is being trapped onto the PS-BEMP, an α-bromoketone was subsequently flowed through the PS-BEMP column, thus eluting the residual material as the regioisomeric imidazole, resulting in combined yields of 79–99%. However, when reacting carbon disulfide with alkyl isothiocyanates, only the corresponding thiazoles in good yields and purities were obtained (Scheme 17).

Ley and coworkers also investigated the formation of 4,5-disubstituted oxazoles in flow by mixing isocyanides and acid chlorides on a glass chip at 60°C, forming a reactive adduct which was further processed through a column of PS-BEMP, thus forming the final product [33]. The unreacted acid chloride was scavenged by a column filled with Quadrapure-BZA (macroporous benzyl amine resin). In this manner, a library of 36 compounds was generated, with yields in the range of 83–98% (Scheme 18). This reaction was later applied by the same group for the evaluation of a newly designed polymer reactor for large-scale flow synthesis [34].

Scheme 13



Scheme 14



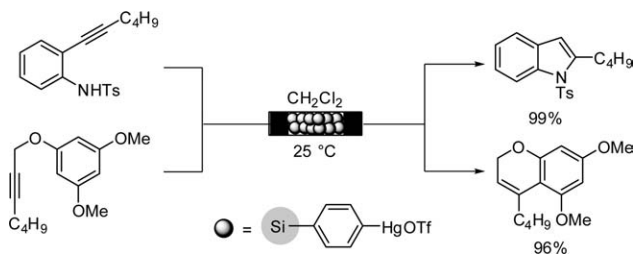
An automated microfluidic platform for reaction screening was applied for reaction discovery based on bicycle[3.2.1]octanoid scaffolds [35]. Elucidation of the continuous-flow reaction of the latter scaffolds with isonitriles revealed the formation of spirooxazolines *via* [3+2] cycloaddition at the bridgehead ketone in 1:1 diastereomeric ratio (Scheme 19). The formed products were further hydrolyzed to provide ring-opened formamides.

The condensation of 1,3-diketones with phenylhydrazine was conducted in a mesofluidic flow system to give pyrazolones and indazolones in good yields [22]. The synthesis of Rimonabant, an antiobesity drug acting as a central cannabinoid receptor antagonist, has been attempted in a three-step process. As a key step in the synthesis, a tetra-substituted pyrazole core was obtained *via* cyclocondensation reaction of 1,3-diketoester and 2,4-dichlorophenylhydrazine·HCl at 125°C for 16 min in 80% yield (Scheme 20) [36].

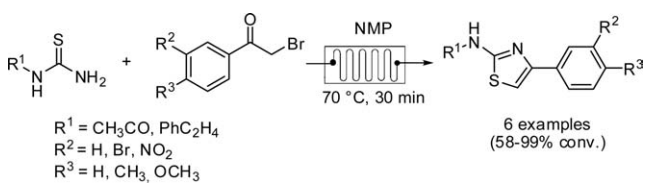
Garcia-Edigo *et al*. investigated the capabilities of an automated microreactor-based system to prepare libraries of pyrazoles by means of a Knorr reaction [37]. A 21-product library was obtained combining flow processing and on-line analysis (LC-UV-MS system) of the reaction products using a combinatorial chemistry approach (Scheme 21). Pyrazoles with various substitution pattern were the synthetic result of the effort of Haswell and coworkers to show the synthetic use of a borosilicate glass microreactor driven by electroosmotic flow, whereby two streams (of 1,3-diketone and hydrazine hydrate) were joined together thus leading to the formation of the corresponding products [38].

Combining microwave heating and flow processing allowed the preparation of various 5-amino-4-cyanopyrazoles in a flow cell made of 11.5 m of fluoropolymer tubing wrapped around a specially designed Teflon part so that it could be fitted into the cavity of a single-mode microwave reactor [39]. Methanol solutions of hydrazine and ethoxymethylene malononitrile were premixed in a T-piece and then flowed through the flow cell while being heated to 100–120°C. The reaction mixture

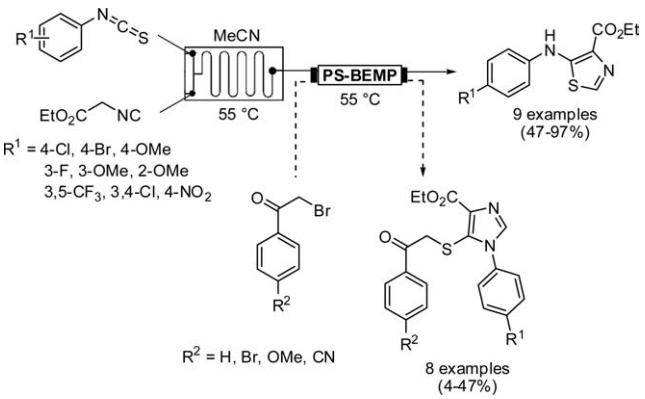
Scheme 15



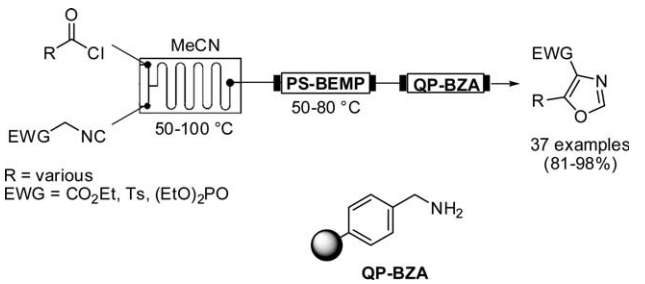
Scheme 16



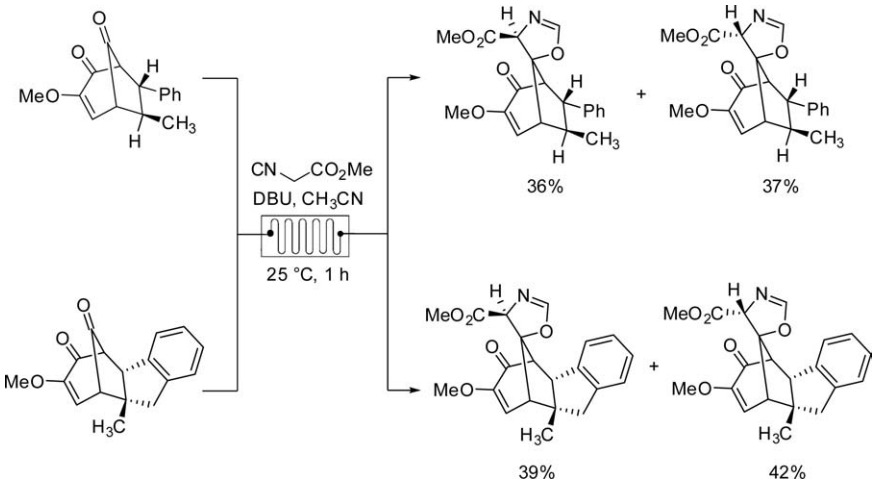
Scheme 17



Scheme 18



Scheme 19



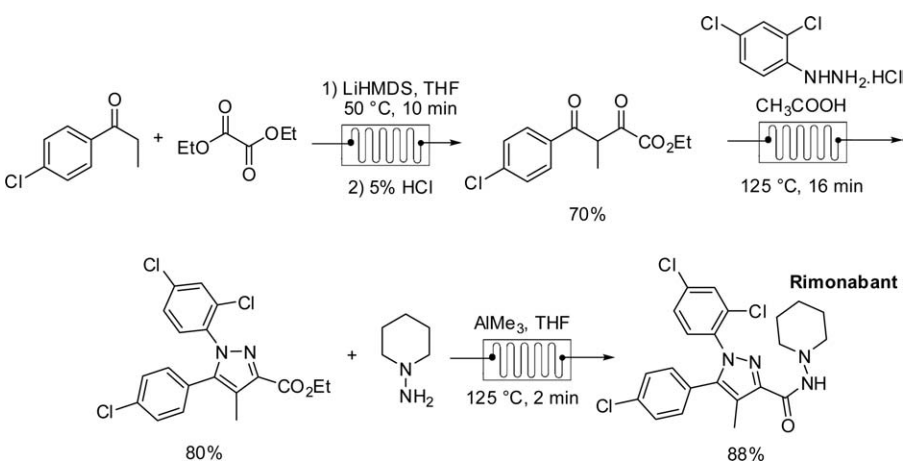
was then processed through a column filled with benzylamine resin, thus removing the starting electrophile and any remaining uncyclized intermediates, and further through a charcoal-filled column for removing any colored impurities. This sequence provided the desired products in good to high yields purity, enabling them to be used in further transformations without any additional purification (Scheme 22).

The 3,5-dimethylpyrazole synthesis from acetylacetone and anhydrous hydrazine was one of the reactions chosen by Kim and coworkers for the evaluation of newly designed inorganic polymer-derived microreactors [40].

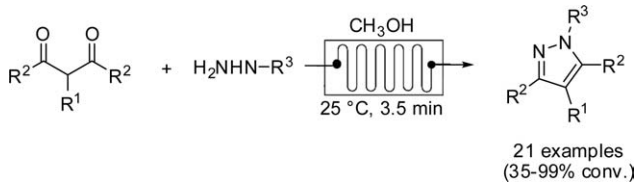
By investigating the behavior of a potentially hazardous pyrazole nitration process, Pelleter and Renaud attempted the use of a flow process [41]. To test the in-house available flow instrumentation, the synthesis of 3-methyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-ol and 3-methyl-1-phenyl-1*H*-pyrazol-5-ol was chosen. Reacting ethyl acetoacetate with the corresponding aromatic hydrazines at 100–115°C resulted in the formation of the expected products.

Yne-ones are useful starting materials in a large number of heterocyclic syntheses. Ley and coworkers described a palladium-catalyzed acylation protocol with terminal alkynes to prepare yne-ones and their further transformation into various heterocycles [42]. After mixing a solution of $Pd(OAc)_2$ (1 mol %) and Hünig's base in CH_2Cl_2 with a solution of an acid chloride and a terminal acetylene in CH_2Cl_2 *via* a T-piece, the formed reaction mixture was heated in a convection flow coil at 100°C for 30 min. Exiting the heated coil, the processed mixture is flown through a scavenger column filled with Amberlite polyol resin (IRA-743) to remove any excess of the acid chloride. Purification over a $CaCO_3$ cartridge, sulfonic acid resin, and Quadrapure-thiourea columns was performed before combining with a stream of a selected hydrazine while at the same time taking

Scheme 20



Scheme 21



analytical samples. In a second coil, the reaction mixture is now kept for another 20–30 min at temperatures from 25 to 100°C to obtain the pure substituted pyrazoles in 57–86% yield (Scheme 23).

In a comparison study between batch microwave and conventionally heated continuous-flow processes, three different reactions were tested—pyrazole and imidazole formation and the Diels–Alder reaction of 2,3-dimethylbutadiene with acrylonitrile [7b]. For the pyrazole synthesis, the optimized batch microwave conditions—180°C, 1 s reaction time—could be directly translated to a flow process, whereby 225.8 g of 3,5-dimethyl-1-phenylpyrazole was formed in 1 h. In a similar manner, ~51 g of 2-methylbenzimidazole were synthesized by reacting *o*-phenylenediamine with acetic acid under neat conditions at 270°C.

The continuous synthesis of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones starting from 3-amino-4-(arylamino)-1*H*-isochromen-1-ones was recently disclosed by Stevens and coworkers [43]. The ring closure was achieved by reacting the corresponding isochromenones and orthoesters in the presence of catalytic amounts of *p*-TsOH at room temperature. Using the optimized conditions, nine different 1*H*-isochromeno[3,4-*d*]imidazol-5-ones were prepared in moderate to good yields and maximum output of 2.2 g/h under continuous-flow conditions (Scheme 24).

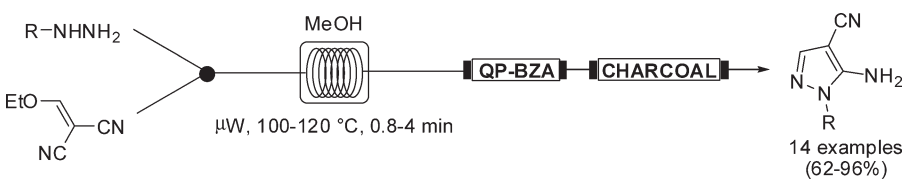
The synthesis of 1,3-dimethyl-2-imidazolidinone (DMI) was evaluated as a route to continuous chemical fixation of the ''greenhouse gas'' CO_2 [44]. A stream of CO_2 was mixed with *N*,*N*′-dimethylethylenediamine and processed under supercritical flow conditions (200–300°C, 60–160 bar pressure) over various mesoporous silica catalysts to result in the formation of DMI. Among the different assessed catalysts, MCM-41 and HMS-type mesoporous silica were found to be very efficient and superior to γ-Al_2O_3 and SiO_2-Al_2O_3, suggested earlier by BASF (Scheme 25).

Multicomponent 2*H*-2-imidazoline formations, based on the reaction of acetone with benzylamine to form the corresponding imine and following Lewis acid-catalyzed cyclocondensation with *p*-nitrobenzylisocyanide, were used in the activity screening of ferrocene-based Lewis acid-catalyst complexes. Assuring high throughput in the reaction optimization, a continuous-flow reaction MS detection system was used. Among the screened catalysts, AgOTf proved to be superior in activity compared with the other Lewis acids and was further implemented into the described studies, initially being ligated with different ferrocene ligands to form catalyst complexes, which were then used in the imidazole formation [45].

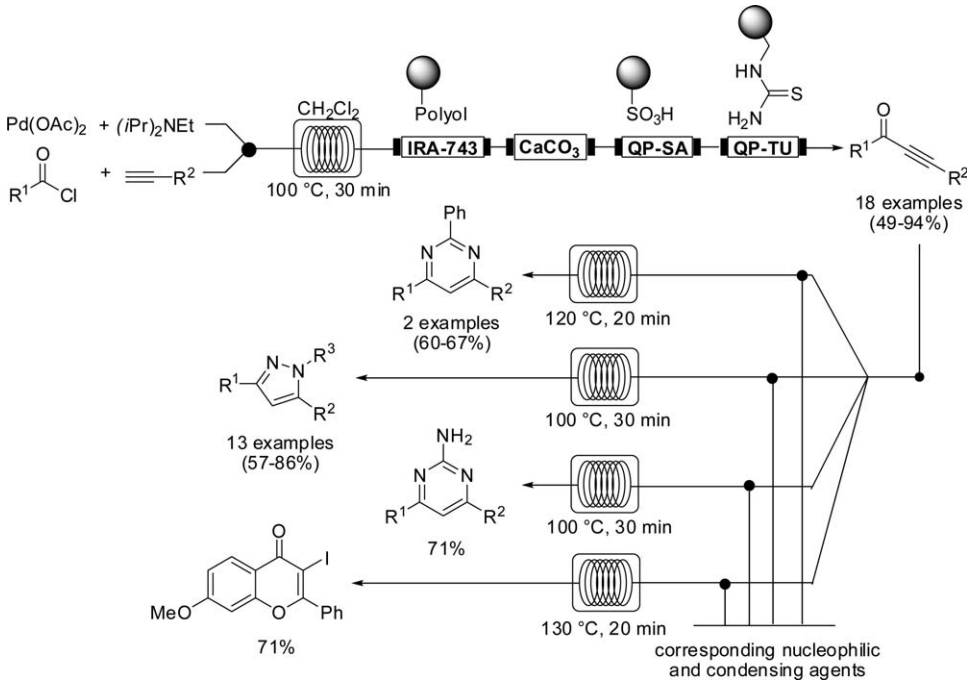
Highly functionalized imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine carboxylic acids and carboxamides were synthesized in a fully automated continuous-flow manner by Cosford and coworkers [46]. Using readily available starting materials such as 2-aminopyridines and bromopyruvic acids and catalytic amounts of *p*-toluenesulfonic acid in a single microreactor unit, nine different cyclic products were obtained in 52–72% yield. As a second synthetic step, the formation of carboxamides under flow conditions was optimized. A standard coupling cocktail for an amide bond synthesis, EDC/HOBt/DIPEA, at 75°C for 10-min reaction time resulted in complete conversions. Combining the two separate synthetic steps proved to be challenging, because the presence of *p*-toluenesulfonic acid in the reaction mixture after the cyclization step hindered the amide bond formation in the second step. The solution was found in the use of excess base and amine in the second step. Applying the optimized conditions—residence time of 20 min and 100°C temperature in the first microreactor—and then combining the stream, containing the formed imidazo[1,2-*a*]pyridine-2-carboxylic acid exiting the first microreactor, with a solution of EDC/HOBt and amine/DIPEA in the second microreactor at 75°C for 10 min, resulted in a single continuous-flow process to produce various imidazo[1,2-*a*]heteroaryl-2-carboxamides in moderate to good yields (Scheme 26).

As a part of a study devoted to the flow preparation of butane-2,3-diacetal (BDA)-protected tartrate derivatives, substituted 1,3-dioxolane has been obtained

Scheme 22



Scheme 23



in 83% yield by mixing a stream of dimethyl-L-tartrate in methanol with a stream of butanedione and trimethylorthoformate in acetonitrile in a 1:1 ratio and further pumping the mixed reagents over a Quadrapure sulfonic acid resin, prepacked in a column (Scheme 27). To ease the *in situ* reaction monitoring, a flow IR equipment was connected to the outgoing reaction stream [47].

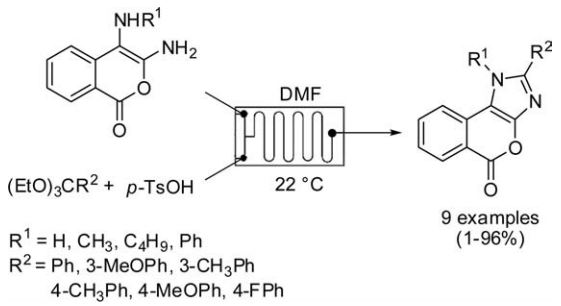
6. FIVE-MEMBERED RING HETEROCYCLES WITH THREE HETEROATOMS

The Huisgen [3 + 2] cycloaddition of acetylenes with azides to form 1,2,3-triazoles, followed by recent modifications by Meldal and Sharpless involving Cu(I) catalysis (nowadays referred as CuAAC or ''click'' chemistry), is a still expanding area in organic synthesis, material science, and cell biology. The reasons for the popularity of the CuAAC lie in the properties of the 1,2,3-triazole scaffold, the robustness of the cycloaddition process, and in the high regioselectivity and generality of the reaction.

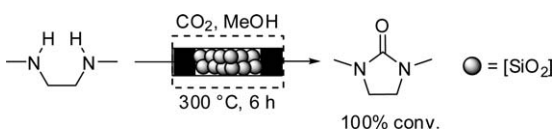
One published example of microwave synthesis under continuous-flow conditions deals with the [3+2] cycloaddition of DMAD with benzyl azide in toluene as reaction medium [48]. The continuous-flow step was developed to substantiate the scalability of the studied process. After initial batch optimization of solvent, temperature, and reaction time, the best conditions were transferred to the continuous-flow procedure, which used a commercially available Kevlar-enforced Teflon coil positioned in the cavity of a single-mode microwave flow reactor providing the desired cycloadduct in 70% yield.

Tseng and coworkers described the fabrication and evaluation of a microfluidic screening platform, capable of performing 32 ''CuAAC/click'' reactions in parallel. Analyzing the reactions by LC-MS, the authors obtained comparable results to those obtained from a 96-well system, identifying nine of the prepared compounds as ''hits'' [49].

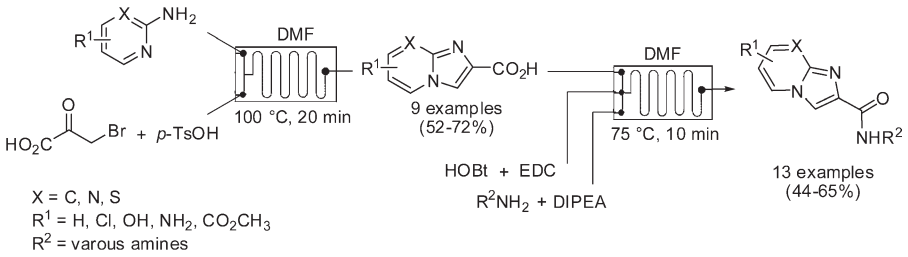
Scheme 24



Scheme 25



Scheme 26



In 2007, Ley and coworkers reported the use of a polymer-supported copper catalyst (copper-modified base Amberlyst A-21 resin) [50] for the preparation of various 1,2,3-triazoles in a flow manner. However, being attached to the resin by a weak coordination bond, the copper species were leached to some extent while processing the reaction mixture. To solve this issue, the processed reaction mixture was passed over a Quadrapure thiourea metal-scavenging resin (QP-TU) and to remove any unreacted azide—over a phosphine resin (PS-PPh2). Collecting the reaction stream and removing of the solvent under vacuum provided 14 different 1,2,3-triazoles in very good yields and excellent purities (Scheme 28).

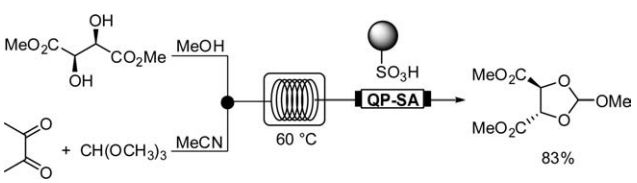
A ''CuAAC/click chemistry'' approach was found as a solution for the removal of a functionalized phosphine oxide from a reaction mixture [51]. Two possible solutions were suggested by the authors—either using an immobilized azide and catalytic amounts of CuI together with *N,N′*-diisopropylethylamine to permanently bind the phosphine oxide to the solid phase as a 1,2,3-triazole or using a carboxylic acid-functionalized azide and capture of the formed acidic 1,2,3-triazole with polymer-supported Na_2CO_3 (Scheme 29).

Ley and coworkers extended their studies on the Huisgen [3+2] dipolar cycloaddition implementing an *in situ* generation of the alkyne from an aldehyde and the Bestmann-Ohira reagent as the initial step in a sequential-flow process, followed by capturing of the latter in a ''CuAAC/click chemistry'' reaction with an azide in the presence of a Cu(I) source as a catalyst [52]. Applying a diverse set of polymer-supported reagents—Quadrapure benzylamine resin, Amberlyst-15 sulfonic acid, Amberlyst-15 dimethyl amine (A-21), immobilized Cu(I) catalyst on a basic support (A-21·CuI), and Quadrapure-thiourea (QP-TU)—a collection of substituted 1,2,3-triazoles with high purity was prepared (Scheme 30).

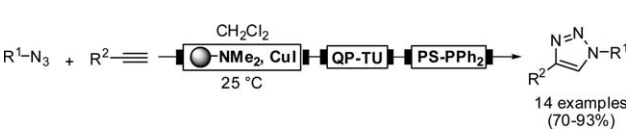
Recently, Bogdan and Sach introduced a new concept for performing the [3+2] dipolar cycloaddition of azides and alkynes under flow conditions [53]. Speculating that even Cu(0) sources such as copper wire or copper turnings have shown earlier catalytic properties in the 1,2,3-triazole formation, the authors presented a newly designed flow rector made out of copper, thus removing the need to use of any additional copper catalyst. Furthermore, the reactive azides used in these studies were *in situ* generated using the corresponding alkyl halides and simple sodium azide. The concept proved successful and was used in a small compound library synthesis, whereby 31 substituted 1,2,3-triazoles were prepared at 150°C and 5 min by flowing a DMF solution of an alkyl halide, an alkyne, and NaN_3 through the copper tubing reactor.

Lately, mechanistic insights into the [3+2] dipolar cycloaddition of azides and alkynes were disclosed by Kappe and coworkers [54]. By a continuous-flow approach using copper-in-charcoal (Cu/C) as an immobilized source of Cu catalyst, the reaction of benzyl azide and phenylacetylene in acetone as a solvent was studied. Different Cu sources and pretreatment methods were used before it became evident that the catalytically active species in the ''CuAAC/click chemistry'' involving Cu(0) metal species is most likely connected to a surface layer of Cu_2O. Leaching experiments were able to prove that a homogeneous mechanism is in operation when using Cu/C as a catalyst. Under flow conditions, this eventually leads to leaching of Cu into the solution phase. On a small scale, efficient in-line scavenging could be performed using activated charcoal or Quadrapure-thiourea resin, whereas for large-scale experiments, an extractive work-up with ethylenediaminetetraacetic acid was shown to be the method of choice.

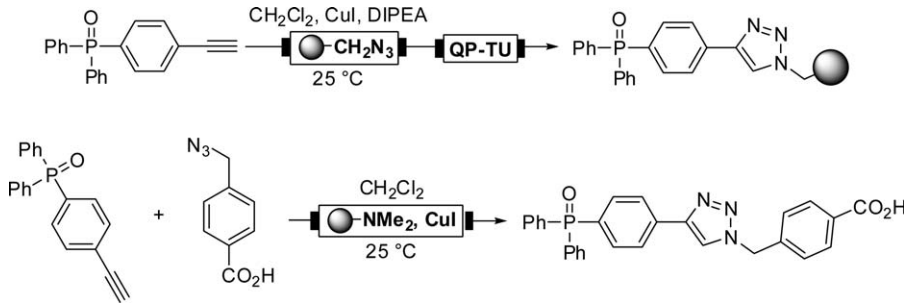
Scheme 27



Scheme 28



Scheme 29



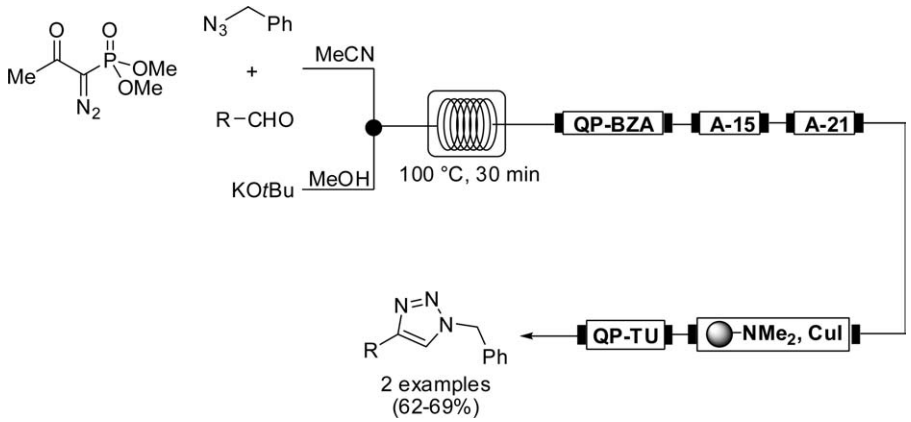
In 2009, the synthesis of 5-amino-1-ethyl-1*H*-1,2,3-triazole-4-carboxamide from β-azidoethylphenyl azide was described under continuous-flow conditions [55]. Previous literature reports on the synthesis of this triazole suffered from low yields and considerable safety hazards because of the use of ethyl azide. For this reason, Storz and coworkers developed a new synthetic process more amenable for industrial application. Replacing the ethyl azide with a far more stable azide reagent such as β-azidoethylphenyl azide delivered the solution to the problem. The latter compound was prepared and extensively tested to ensure the safe use under the conditions further to be used in the synthesis of the desired triazole. As an additional guarantee, a continuous-flow synthetic process was envisaged. Using cyanoacetamide to generate *in situ* a reactive ketenimine under basic conditions, the [3+2] cycloaddition was optimized with the help of ''design of experiment'' studies to find the optimal range for the reaction by varying the stoichiometry, base and solvent type, and reaction temperature. With the optimal conditions in hand, the reaction took only 2 min at 65°C in *N*-methylpyrrolidine as a solvent of choice and 1.5 equiv of NaOH as a base. Furthermore, the obtained 1,2,3-triazole was subjected to batch desulfurization to deliver the desired 5-amino-1-ethyl-1*H*-1,2,3-triazole-4-carboxamide in 90% yield.

A rapid sequential-flow synthesis of 1,2,4-oxadiazoles was developed by Cosford and coworkers [56]. A stream of an aromatic nitrile in DMF and a stream of hydroxylamine hydrochloride and Hünig's base in DMF were combined in a 1000 μL chip at 150°C followed by cooling in a capillary submerged in an ice bath. In a T-piece, the corresponding acid chloride or succinic anhydride was slowly added to the flow, and the reaction mixture was then passed through a 1.5-m capillary before being heated in a second chip at 200°C. The so-processed reaction mixture was then collected and purified to deliver the expected products. Shortening the reaction times to minutes from hours allowed the quick preparation of nine different 1,2,4-oxadiazoles in good yields (Scheme 31). Replacing the acid chloride with succinic anhydride delivered three further 1,2,4-oxadiazoles.

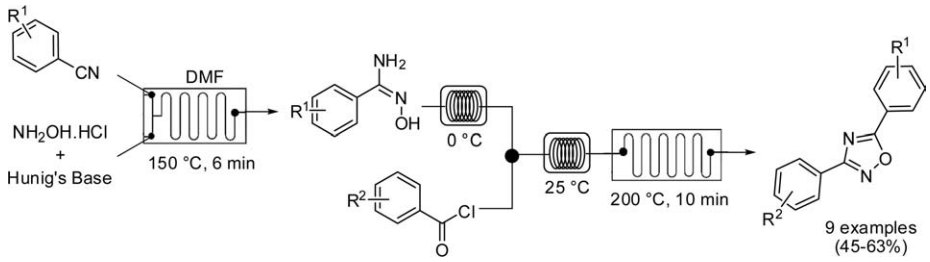
7. SIX-MEMBERED RING HETEROCYCLES WITH ONE HETEROATOM

A Bohlmann–Rahtz-type pyridine synthesis was used as a model reaction to evaluate the use of a sand-filled glass microwave flow reactor cell [20]. The synthesis of ethyl 2-methyl-6-phenylnicotinate was conducted *via*

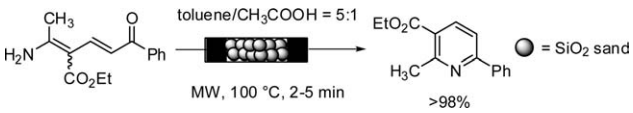
Scheme 30



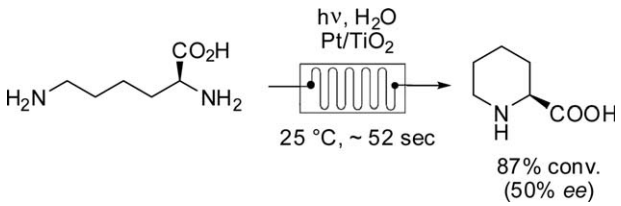
Scheme 31



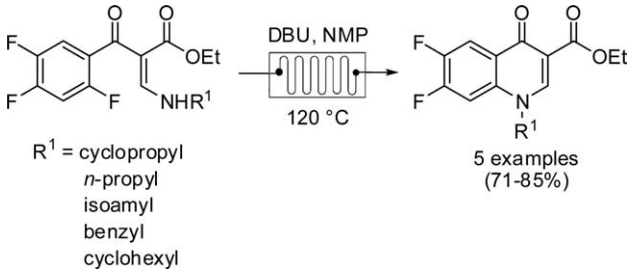
Scheme 32



Scheme 33



Scheme 34



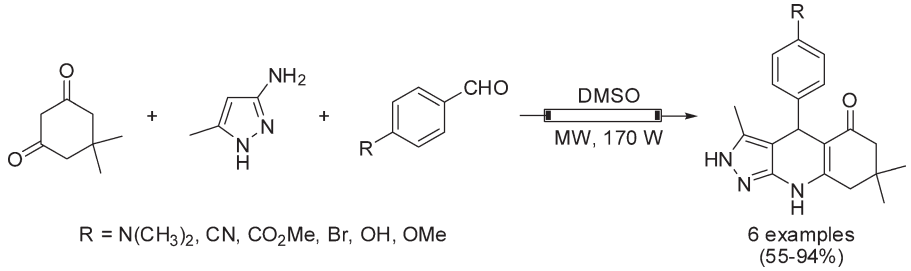
cyclodehydration of ethyl 2-(1-aminoethylidene)-5-oxo-5-phenylpent-3-enoate in a toluene-acetic acid mixture at 100°C for 2–5 min, providing the desired pyridine product in >98% yield (Scheme 32).

A TiO_2-modified microchannel glass chip was used by Kitamori and coworkers to perform a photocatalytic redox-combined synthesis of L-pipecolinic acid from L-lysine [57]. As a reduction site, Pt had to be loaded onto the TiO_2 film by photodeposition. The so-prepared microchip was then further used to prepare the L-pipecolinic acid by irradiating a stream of L-lysine with a high-pressure mercury lamp, resulting in 87% conversion (Scheme 33).

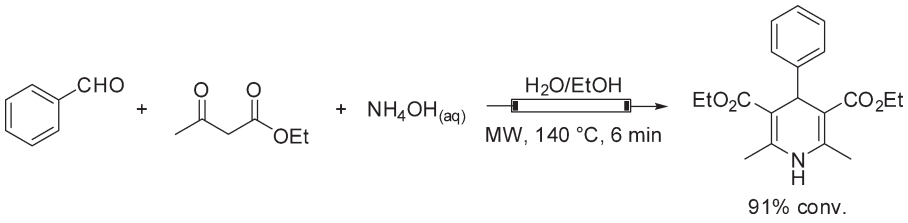
Schwalbe *et al*. developed a multistep microreactor library approach toward fluoroquinolone antibiotics such as Ciprofloxacin (Scheme 34) [58]. Five sequential microreactor transformations were required to generate the desired products. Starting with commercially available building blocks and after including two diversity generating steps in the synthetic sequence, a number of Ciprofloxacin analogs were synthesized in good yields and purities (Scheme 34). When applied to Ciprofloxacin, the synthesis generated 57% overall yield of product in five steps and with a purity exceeding 90%.

The use of multicomponent reaction sequences has become increasingly popular in the preparation of potentially active target compounds. Such a condensation reaction, using an aromatic aldehyde, dimedone, and a pyrazole to give quinolinone derivatives, has also been

Scheme 35



Scheme 36



conducted in a flow mode under microwave heating. A glass capillary reactor (1180 μm in length) provided good yields of six different reaction products (Scheme 35) [26].

Looking for an alternative to batch microwave synthetic protocols, which are inherently difficult to scale, Leadbeater and coworkers reported the use of a continuous-flow microwave instrument, allowing the processing of nearly 800 mL reaction mixture in 25 min operating at 140°C with a 36 mL/min flow rate for the preparation of a 1,4-dihydropyridine *via* a Hantzsch condensation reaction [59] (Scheme 36).

Nowadays, nanoparticles draw a lot of attention in various areas of chemical research. One of these areas is their application as efficient catalysts for organic syntheses. Recently, Gross and coworkers reported on the reaction of propargylamines with aromatic and aliphatic methyl ketones to form α-substituted pyridine derivatives [60]. The propargylamine component usually tends toward side reactions, thus dividing the addition-cyclization-aromatization reaction process into separate flow steps was necessary to prevent the formation of side products. Two different heterogeneous catalysts delivered good results and were subsequently used in the flow process—montmorillonite K10 with 3 Å molecular sieves for the imine/enamine intermediate formation and Au nanoparticles impregnated on alumina for the cyclization/aromatization step. Full conversion of the intermediates was achieved at 125°C by mixing in a slight excess of oxygen from a compressed air source in a short-time flow reaction process (Scheme 37).

The potent $5HT_{1B}$ receptor antagonist 6-methoxy-8-(4-methyl-1,4-diazepan-1-yl)-*N*-(4-morpholinophenyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide developed recently by AstraZeneca was synthesized in a multistep flow process developed by Ley and coworkers [61]. Starting from 3-fluoro-4-nitroanisole and 1-methylhomopiperazine, the authors were able to prepare the final product using a well-optimized combination of flow microreactors, while incorporating polymer-supported reagents and scavengers facilitating product isolation and purifications in the designed flow process (Scheme 38).

Fernandez-Suarez *et al*. investigated a domino Knoevenagel/Diels–Alder reaction sequence on a glass microchip reactor [62]. The reaction of *rac*-citronellal or 2-(3-methylbut-2-enyloxy)benzaldehyde with 1,3-dimethylbarbituric acid or Meldrum's acid in the presence of ethylenediamine acetate provided a series of tricyclic adducts in 59–75% yield (Scheme 39) and 6-min reaction time. Additionally, the synthesis of three different cycloadducts in a parallel way on a single microchip was also demonstrated.

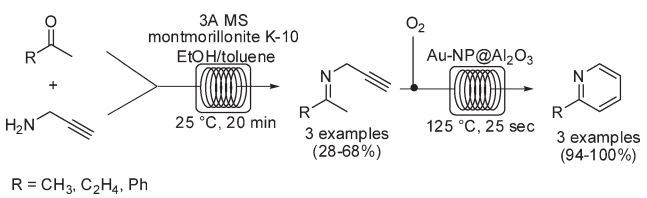
By using a commercially available microreactor, Acke and Stevens described the continuous-flow preparation of a series of 3,4-diamino-1*H*-isochromen-1-ones *via* modified Strecker reaction, requiring the use of toxic HCN [63]. The reagents—2-formylbenzoic acid in acetic acid and aromatic amines with potassium cyanide as stock solutions—were introduced into the reactor ensuring the *in situ* formation of HCN and an imine inside the microreactor. Within a total reaction time of 40 min, the corresponding isochromenones were obtained in 49–75% yield (Scheme 40).

Applying the simple ''flow-by-gravity'' concept, Nishizawa and coworkers were able to prepare 4-butyl-5,7-dimethoxy-2*H*-chromene in 96% yield [30]. Silica-supported HgOTf was used to catalyze the intramolecular alkyne cyclization toward the desired product (see Scheme 15).

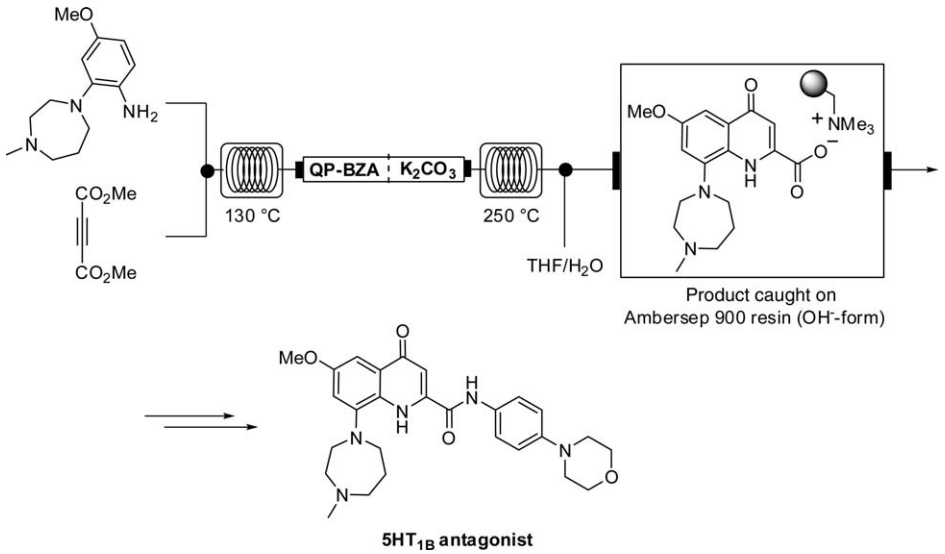
Oxone ($2KHSO_5.KHSO_4.K_2SO_4$) was used by Uozumi and coworkers as an oxidizing agent for the oxidative cyclization of alkenols [25]. Using aqueous conditions, *threo*-tetrahydropyranyl alcohol was prepared in 90% conversion from the starting acyclic alcohol.

Ley and coworkers described a palladium-catalyzed acylation protocol using terminal alkynes to prepare yne-ones and their further transformation into various heterocycles [42]. The formed yne-ones, after in-line purification, are directed to a second coil, where, after the addition of ICl solution in dichloromethane *via* a T-

Scheme 37



Scheme 38

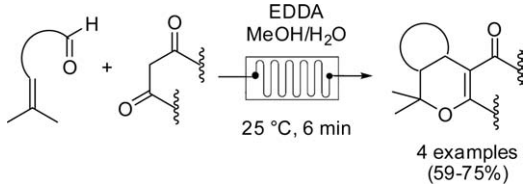


piece, the reaction mixture was circulated for another 20 min at room temperature. This process delivered the corresponding flavone derivative after reaction work-up in 71% yield (see Scheme 23).

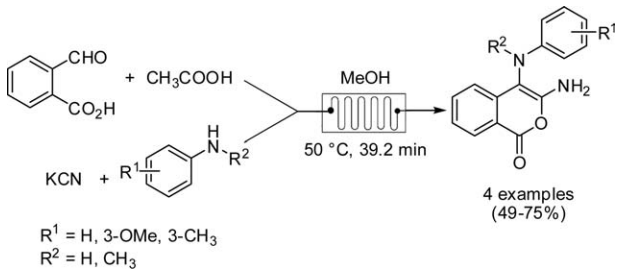
The Baeyer–Villiger oxidation is an important organic process leading to the formation of lactones or esters from the corresponding cyclic ketones or aldehydes. One environmentally friendly way of performing the oxidation reaction is the use of hydrogen peroxide as an oxidant in the presence of a catalyst as the waste is water. On the other hand, the use of H_2O_2 has a few disadvantages—less reactivity, regioisomeric product formation, and product hydrolysis. Mikami *et al*. have exploited the use of very low amounts <0.1 mol % of $Sc[N(SO_2C_8F_{17})_2]_3$ as a catalyst to promote the Baeyer–Villiger oxidation of various cyclic ketones in a nanoflow device [64,65]. Solutions of the corresponding ketone in benzotrifluoride were mixed with a stream of 30% H_2O_2 at room temperature to result in the formation of the corresponding lactone. High yields and selectivities were achieved only in few seconds when compared with a batch experiment, which took 5-h reaction time (Scheme 41a).

Another possibility to perform a Baeyer–Villiger oxidation in a flow manner was reported recently by Gonzalez-Núñez and coworkers [66]. Supercritical CO_2 was flown at 250 bar and 40°C through a reservoir containing the substrate and then through a column packed with [2-percarboxyethyl]-functionalized silica (ratio ketone/peracid was 1:3) to provide quantitative yields of the expected products (Scheme 41b). Hydration of the functionalized silica was found to be of importance for the reaction outcome. The used solid reagent could be

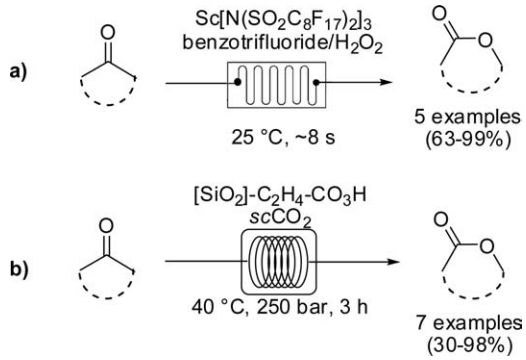
Scheme 39



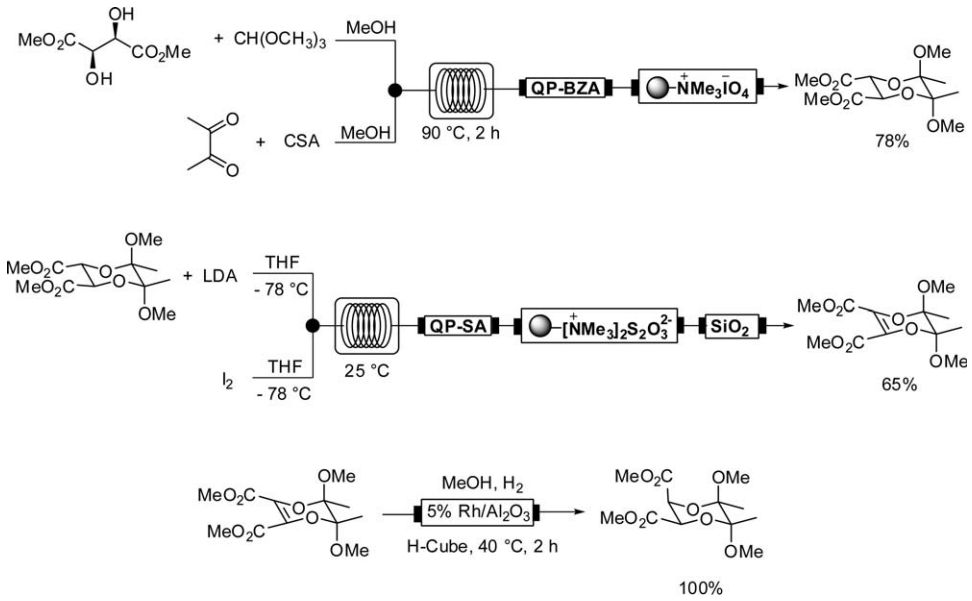
Scheme 40



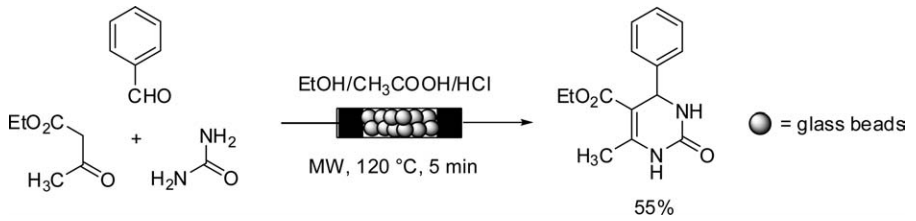
Scheme 41



Scheme 42



Scheme 43



simply recycled with 70% H_2O_2 in the presence of an acid.

8. SIX-MEMBERED RING HETEROCYCLES WITH TWO HETEROATOMS

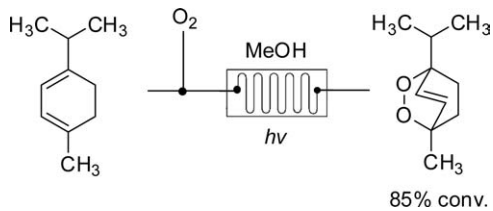
A series of substituted pyrimidines was prepared by mixing a flow stream containing an yne-one with a stream of guanidine hydrochloride solution (ethanol/water 1:1) and following heating at 130°C for 20 min (see Scheme 23) [42].

Ley and coworkers prepared BDA-protected tartrate in 78% yield by mixing a stream of dimethyl-L-tartrate and trimethylorthoformate in methanol with a stream of butanedione and DL-camphorsulfonic acid in methanol in 1:1 ratio and further processing the mixture over benzylamine (QP-BZA) and periodate resins. The obtained enantiopure BDA tartrate could be further converted into its *meso* derivative *via* oxidation with elemental iodine and following purification with a sequence of polymer-supported reagents—sulfonic acid resin (QP-SA), thiosulfate resin, and a short silica plug to remove any excess diisopropylamine, iodine, and inorganic salts. In the final step, flow hydrogenation with Rh/Al_2O_3 in a H-Cube flow hydrogenation instrument was performed to obtain a spatially desymmetrized BDA-protected tartrate in 100% yield (Scheme 42) [48].

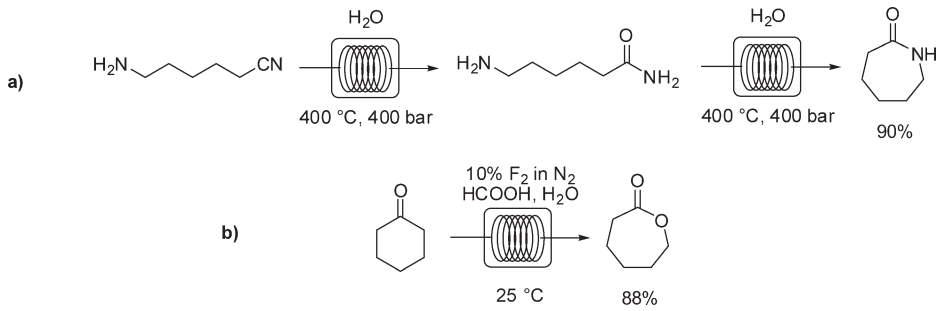
Trapp *et al*. used short microcapillaries with Grubbs second-generation catalyst/siloxane surface coating and helium gas as carrier to perform ring-closing metathesis as a part of a high-throughput catalyst screening [28]. One of the few cyclic products, prepared by combining reaction and on-line analysis, was 3,6-dihydro-1,2-dithiine.

Using a microwave-heated glass flow cell filled with glass beads, Kappe and coworkers reported on the well-known multicomponent Biginelli reaction, going from

Scheme 44



Scheme 45



milligram to 25 g/h scale [21]. The standard 10-mL reaction vessel was charged with 2-mm-sized glass beads, thus creating microchannels, which affect the residence time of the reaction mixture in the microwave heating zone (Scheme 43).

Ascaridole, a naturally occurring bicyclic monoterpene formerly used as an antihelmintic reagent, was prepared in a microfabricated glass chip from α-terpinene *via* singlet oxygen oxidation [67]. The starting material was mixed with a sensitizer in MeOH as a solvent before the introduction into the reactor chip. Pure oxygen was mixed with the reaction mixture, followed by ''on-chip'' irradiation with an unfiltered 20-W tungsten lamp at a very shallow distance to result in 85% effective conversion of α-terpinene into ascaridole (Scheme 44).

9. SEVEN-MEMBERED RING HETEROCYCLES WITH ONE HETEROATOM

The synthetic preparation of ε-caprolactam *via* the Beckmann rearrangement of cyclohexanone oxime is an industrially valuable process as the ring-opening polymerization of ε-caprolactam produces Nylon-6. In 2002, Ikushima *et al*. developed a continuous-microflow process, based on the latter process, using supercritical water [68]. In a Hastelloy C-276 alloy-based flow system, working at ~400°C and 400 bar pressure, the reaction was greatly enhanced, whereas negligible amounts of 6-aminocaproic acid as a by-product were observed. Addition of minor amounts of mineral acid (HCl or H_2SO_4) could further speed-up the reaction rates without affecting the yield. Poliakoff and coworkers disclosed a different synthetic strategy toward the synthesis of ε-caprolactam based on near- and supercritical flow conditions, using water as solvent, reactant, and catalyst. In a two-step hydrolysis-cyclization reaction of 6-aminocapronitrile as a starting material, 90% of ε-caprolactam could be obtained in less than 2 min (Scheme 45a) [69].

A two-phase gas–liquid microreactor was developed for the oxidation of alcohols and ketones to lactones using fluorine [70]. Baeyer–Villiger oxidation of cyclohexanone was achieved by mixing 10% F_2 gas in nitrogen with wet formic acid (5% H_2O) as reaction medium at room temperature to deliver 88% of ε-caprolactone (Scheme 45b).

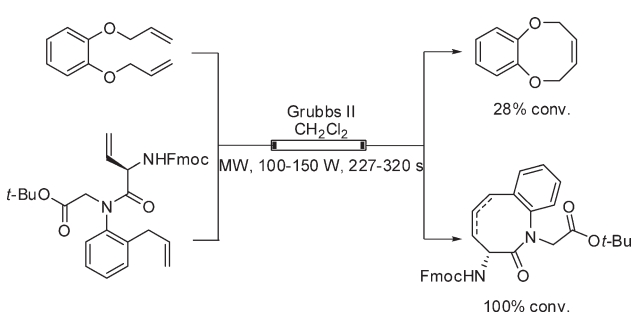
10. EIGHT-MEMBERED RING HETEROCYCLES WITH ONE/TWO HETEROATOMS

A microwave-heated microcapillary reactor was used by Comer and Organ for performing a ring-closing metathesis reaction [71]. Benzoazocinone and benzodioxocine were obtained in short reaction times with the aid of 1% Grubbs second-generation catalyst (Scheme 46).

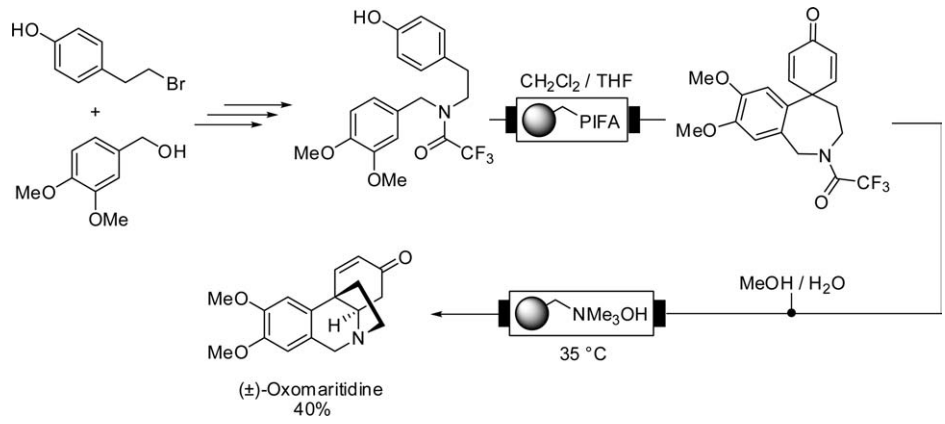
11. MISCELLANEOUS HETEROCYCLES

(±)-Oxomaritidine, a natural alkaloid, was prepared in a multistep synthesis in a completely flow fashion [72]. Initially, a reactive azide is *in situ* generated as well as the corresponding aldehyde and then both streams are combined over a column filled with a polymer-supported phosphine to furnish an imine intermediate. The formed imine solution was subjected to continuous-flow hydrogenation using an H-Cube flow hydrogenation instrument, delivering a secondary amine. Further reaction of the obtained amine with trifluoroacetic anhydride on a glass microchip at 80°C leads to the corresponding amide. In the last step, polymer-supported

Scheme 46



Scheme 47



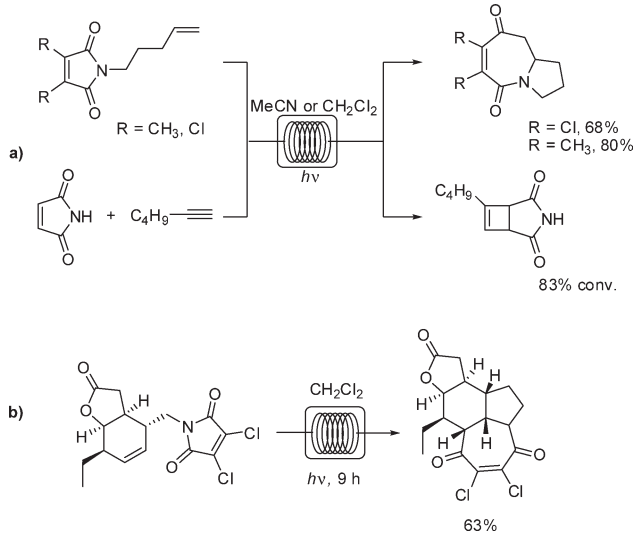
(ditrifluoroacetoxyiodo)benzene performed an oxidative phenolic coupling, generating a seven-member tricyclic intermediate. The latter, upon deprotection of the secondary amine over a hydroxide ion-exchange resin, underwent spontaneous cyclization to give the desired Amarilidaceae alkaloid (±)-oxomaritidine in 90% purity in 40% yield and 6-h synthesis time (Scheme 47).

One great advantage of a flow chemistry process is the fact that, once established, the small-scale synthetic conditions can be very easily translated to a large-scale production without the need of reoptimization of the reaction conditions. Using customized immersion well equipment, a UV reactor for performing continuous-flow organic photochemistry was developed by Booker-Milburn and coworkers [73]. In a [2+2] photocycloaddition process, maleimide and 1-hexyne were reacted to deliver 6-butyl-3-azabicyclo bicyclo[3.2.0]hept-6-ene-2,4-dione in MeCN as a solvent. Operating the reactor for 24 h resulted in the formation of 685 g of the desired cycloadduct. In the same manner, 7,8-dimethyl-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6, 9-dione was prepared. Through an UV-promoted intramolecular [5+2] photocycloaddition process of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione, 175 g of the bicyclic azepine was obtained (Scheme 48a).

Lately, the same group used the UV-flow chemistry approach described above for the synthesis of (±)-neostenine (Scheme 48b) [74].

An UV-flow reactor based on the same principle was also developed and used for the synthesis of cyclobutanetetracarboxylic dianhydride by photodimerization of maleic anhydride [75]. However, the formed product tends to precipitate. To overcome this problem, the authors used a combination of N_2 gas and an ultrasound bath to prevent sedimentation of the product and to ease its transportation throughout the flow system.

Scheme 48



12. CONCLUSIONS

Although the field of continuous-flow organic synthesis is rather young, the examples collected in this review demonstrate that a variety of heterocyclic structures have already been generated in flow mode using different formats ranging from classical microreactor technology all the way to multistep syntheses in mesofluidic flow reactors incorporating scavenger resins. It remains to be seen if continuous-flow reactors will be used more often in the future in both academic and industrial laboratories. As there are numerous continuous-flow devices commercially available today, it is clearly up to the synthetic chemist to decide if a molecule should be synthesized in continuous flow or batch mode.

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