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Flow Chemistry – A Key Enabling Technology for (Multistep) Organic Synthesis

Jens Wegner,[a] Sascha Ceylan,[a] and Andreas Kirschning[a,*]

[a] Institut für Organische Chemie and Biomolekulares Wirkstoffzentrum (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany
Fax: (+49)-(0)511-762-3011; phone: (+49)-(0)511-762-4612; e-mail: andreas.kirschning@oci.uni-hannover.de

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Abstract: Laboratory scaled flow-through processes have seen an explosive development over the past decade and have become an enabling technology for improving synthetic efficiency through automation and process optimization. Practically, flow devices are a crucial link between bench chemists and process engineers. The present review focuses on two unique aspects of modern flow chemistry where substantial advantages over the corresponding batch processes have become evident. Flow chemistry being one out of several enabling technologies can ideally be combined with other enabling technologies such as energy input. This may be achieved in form of heat to create supercritical conditions. Here, indirect methods such as microwave irradiation and inductive heating have seen widespread applications. Also radiation can efficiently be used to carry out photochemical reactions in a highly practical and scalable manner. A second unique aspect of flow chemistry compared to batch chemistry is associated with the option to carry out multistep synthesis by designing a flow set-up composed of several flow reactors. Besides their role as chemical reactors these can act as elements for purification or solvent switch.

Keywords: enabling technologies; inductive heating; micro reactors; microwaves; multicomponent reactions; photochemistry

1 Introduction

1.1 Enabling Technologies

What is the overall outcome of almost two decades of combinatorial chemistry? Did organic synthesis benefit from that period of time which was governed by the enthusiasm of revolutionizing the preparation of organic molecules and creating huge compound libraries by extensive automation? What are our future prospects after the plan of combinatorial chemistry had failed to alter organic synthesis from being an art to become a sophisticated technology?

Some aspects of these questions need to be answered by those protagonists in the pharmaceutical industry who acted as front seat drivers on the road towards large numbers of test compounds. However, combinatorial chemistry did not provide larger numbers of new chemical entities for clinical use today, nor does combinatorial chemistry play a key role in the search for novel lead structures nowadays. But from the perspective of synthetic chemistry it has had a profound impact.[1] In fact, the important outcome of combinatorial chemistry is, that it gave the organic community a feeling for the importance of automation and improved technologies. Consequently, so-called *enabling technologies* have emerged in the past decade and have influenced the way organic synthesis is conducted to a very great extent.[2] In 2006 we covered enabling technologies in a conceptual review and defined them to be either traditional or new techniques whose purpose is to speed up synthetic transformations and importantly ease work-up as well as the isolation of products. Typical enabling technologies can be (i) *solid phase assistance* such as hetereogenized homogeneous reagents or catalysts,[3] (ii) *non-classical or new solvent systems* like supercritical fluids, perfluorinated solvents or ionic liquids,[4] (iii) *new heating devices* such as microwave (μw) irradiation or inductive heating,[5] and (iv) *new reactor de-*

Jens Wegner (*left*) was born in 1982 in Nordhorn, Germany. He studied chemistry at the Leibniz University Hannover. In 2008 he received his diploma degree and since then he is performing his doctoral studies at Hannover under the supervision of Prof. A. Kirschning with the aid of a scholarship by the Fonds der Chemischen Industrie. In 2010 he spent several months in the group of Prof. S. V. Ley at Cambridge University (U.K.). His research is focused on the development of an inductively heated mini flow system for organic synthesis. A key aspect of his research is the implementation of a multi-step reaction and an immobilized catalyst into mini flow systems.

Sascha Ceylan (*right*) was born in Augsburg, Germany, in 1981 and studied chemistry at Leibniz University Hannover and at Imperial College London under the guidance of Prof. A. G. M. Barrett (U.K.). He received his diploma degree in 2007 and thereafter began his doctoral studies in Hannover under the supervision of Prof. A. Kirschning. He received his PhD early 2011 and his scientific interest focuses on developing inductively heated micro flow systems. Currently, he is performing post-doctoral studies at Stanford University (B. M. Trost, USA) supported by the Alexander-von-Humboldt Foundation.

Andreas Kirschning (*middle*) studied chemistry at the University of Hamburg and Southampton University (U.K.). In Hamburg, he joined the group of Prof. E. Schaumann and received his PhD in 1989 working in the field of organosilicon chemistry. After a postdoctoral stay at the University of Washington (Seattle, USA) with Prof. H. G. Floss, supported by a Feodor–Lynen scholarship of the Alexander-von Humboldt foundation, he started his independent research at the Clausthal University of Technology in 1991, where he finished his habilitation in 1996. In 2000 he moved to the Leibniz University Hannover and became a director of the institute of organic chemistry. He is one of the editors of *RÖMPP online*, *Natural Products Reports* and *The Beilstein Journal of Organic Chemistry*. His research interests cover structure elucidation as well as the total synthesis and mutasynthesis of natural products, biomedical biopolymers, and synthetic technology (solid-phase assisted synthesis, microreactors, inductive heating).

signs such as continuous-flow or droplet reactors (Figure 1).[6]

Especially, flow systems provide an additional benefit because they close the gap between bench chemistry and chemical engineering by mimicking large-scale production on the laboratory scale.

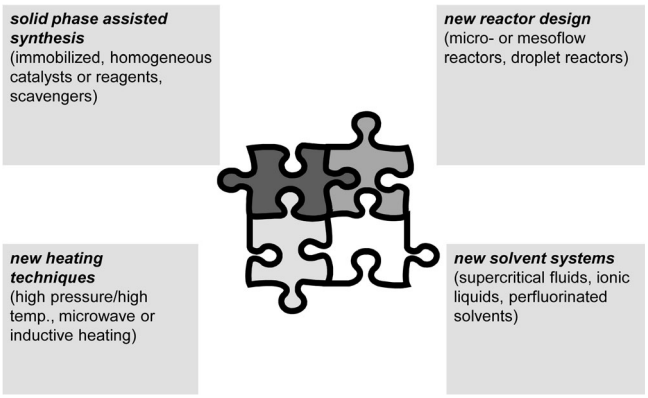


Figure 1. Selected examples of enabling technologies in organic synthesis.

Truly new synthetic technology platforms will require the combination of two or more of these enabling technologies for a given synthetic task. This also means that synthetic chemists will have to collaborate closer with material scientists, chemical engineers and developers for creating new equipment. It has to be emphasized that enabling technologies will not necessarily provide new reactions or make known reactions more selective. In fact, the quest for new, more selective reactions is primarily associated with the world of methodology development. In contrast, enabling technologies will enhance the efficiency of a process mainly by altering the set-up of the process.

In this report we shall mainly focus on flow processes with a practical, chemistry-driven view on the topic. Having collaborated with chemical engineers for more than a decade, we are aware of the fact that the way we introduce the topic here will not satisfy the world of engineers. Indeed, we shall not cover important aspects of how to mix reactants, residence time, heat and mass transfer or theoretical modeling and the mathematical description of reactor performance. In view of the fact that continuous processes

have had a long and successful tradition in the industrial environment, an overview on flow chemistry will not necessarily inspire chemical engineers. It is the chemist in the laboratory who just has started to gain access to flow chemistry and enjoys continuous, including multistep, processes. By now, commercial flow equipment is available so that this enabling technology will gain a much broader use in the near future. Currently, it seems as if two academic (reactor) schools have emerged over the last ten years since flow chemistry was introduced in a broader sense to synthetic chemists. These are micro- *vs.* mini- or mesoreactors.[7–9] Historically, miniaturization focused on micro flow reactors but recently the development has been directed towards the minireactors. These mainly differ in the channel diameter from the former reactor type. After the advantages and drawbacks of both reactor types have briefly been addressed, this report will focus on one technical aspect of flow processes followed by a chemically-driven one, both of which offer unique new opportunities for synthetic chemistry. Firstly, energy exchange can be controlled in a very different way in flow devices compared to classical batch reactors. In this report, we shall particularly focus on energy input including radiation. Secondly, multistep sequences can be performed in a completely different fashion in a flow system compared to conventional multistep synthesis. As we regard both topics to be of unique importance now and in the future, this review will address these topics specifically.[10]

1.2 Batch *versus* Flow Processes

Chemical synthesis in the laboratory has been carried out in standardized glassware and we have principally not changed our equipment since Justus Liebig's time. In contrast, continuous-flow processes are commonly found in the industrial environment of chemical and biotechnological production.[11] There are principal differences between batch and flow processes with respect to production time and yield. In batch production reaction time is determined by how long a vessel is held at a given temperature while in the flow regime the volume of the reactor and the bulk flow rate are crucial parameters. Stoichiometry in flow reactors is defined by the concentration of reagents and the ratio of their flow rate. In batch processes this is defined by the concentration of chemical reagents and their volumetric ratio. Production reaction time under batch conditions is calculated by how long a vessel is held at a given temperature. In contrast, in continuous processes the reactor volume and the bulk flow rate determine the production rate.

With miniaturized bench-sized flow systems being commercially available now continuous-flow processes can be operated in the common laboratory. Now important points such as facile automation, reproducibility, safety and process reliability due to constant reaction parameters (efficient mixing, temperature, time, amount of reagents, and solvent etc.) can be addressed and assured.[12] It has been shown that when pressure-resistant, microstructured flow reactors are employed the reaction temperature can be far above the solvent's boiling point up to supercritical conditions. A given reaction can be accelerated and the production rate of a flow device can be increased by submitting higher flow rates.

Multistep reaction sequences can be conducted in a completely different fashion in flow compared to batch processes. By employing several micro-structured flow reactors in a linear arrangement a continuous multistep process can be designed. Reagents can be introduced into the stream of reactants anywhere in the flow system at precisely the time that is required for the reaction. Additionally, chemistry in flow can be combined with packed-bed materials that are chemically functionalized with catalysts, reagents or for exploiting purification concepts with solid-phase scavengers, chromatographic separation or liquid/liquid extraction. Other important fields of application in flow chemistry are the combination with photochemical reactions as well as continuous synthesis using hazardous gases such as ozone, CO, or NO as reactants.

Finally, scale-up of a given reaction can be achieved rapidly with little or no process development work, by either changing the reactor volume or by running several flow reactors in parallel, provided that flows are recalculated to achieve the same residence times.

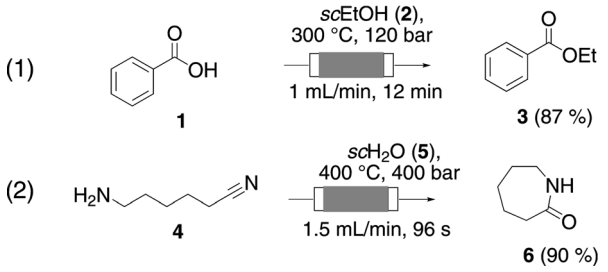
2 Flow Processes and Energy Input

Temperature control is a key issue to be considered when designing a chemical process with a given chemical reactor. Efficient heat transfer has to be guaranteed throughout the process and in microstructured flow devices rapid heat transfer is commonly well achieved. Therefore, microstructured flow systems have mainly served historically as tools to carry out very exothermic reactions using highly reactive reagents such as fluorine or to carry out synthesis with highly reactive intermediates such as organometallic reagents. This is still an important field of application as the elegant work by Yoshida's group continuously demonstrates.[13]

Only recently, research has also focused on external energy input and flow chemistry, e.g., for reactions that require heat or light. In this context, thermal energy can beneficially be combined with pressure-resistant flow reactors. This results in a reactor set-up for performing reactions under high temperature/high

pressure conditions allowing the continuous synthesis at high flow rates. Even supercritical conditions can easily be reached with such a set-up. Likewise, miniaturized flow set-ups are ideally suited for continuously carrying out photochemical reactions and scale-up can easily be achieved by the numbering up concept using many phototransparent reactor tubes in parallel.

In the following chapters the issue of external energy input as well as multistep flow processes will be covered in detail as they represent two techniques that are unique compared to batch mode synthesis or show several advantages over batch chemistry.



Scheme 1. Flow synthesis under supercritical conditions.

2.1 High Pressure/High Temperature Synthesis

2.1.1 Conventional Heating and Flow

Commonly, miniaturized flow devices are ideal tools for performing highly exothermic reactions that are carried out at ambient or low temperature. Beneficially, safety issues are matched due to the excellent mixing and heat transfer properties of miniaturized flow reactors.[6] Lately, flow chemistry has directed developments towards reactions that require longer reaction times under classical batch conditions and thus need to be heated in order to be rapidly carried out under continuous-flow conditions. For clarifying the situation one needs to keep in mind that a cold stream of reactants enters the reactor and residence times in a flow protocol ideally need to be in the order of a few minutes to allow high flow rates. Thus, rapid heating through the walls of a preheated reactor has to be guaranteed.[14]

If "flash" heating can be achieved and pressure-resistant microstructured flow reactors are chosen, the reaction temperature can be set well above the boiling point of the solvent. Even supercritical conditions can be achieved which results in a dramatic shortening of reaction times.[15]

A straightforward strategy to achieve rapid heating is based on incasing flow reactors in conventional external ovens. In order to circumvent the problem of slow heat transfer by convection Kappe and co-workers combined it with high pressure to achieve sufficiently high rates (Scheme 1).[16] By exploiting the special properties of alcohols such as ethanol at high temperature in the supercritical state [reaction (1)], the group performed the esterification of benzoic acid (**1**) under flow conditions.[16] Only at a high temperatures above 200 °C and at supercritical conditions could esterification to ethyl ester **3** be achieved. Poliakoff and co-workers studied supercritical water **5** in industrially relevant conversions under flow conditions.[17] For example, they showed that the one-pot hydrolysis followed by cyclization of 6-aminocapronitrile (**4**) to furnish ε-caprolactam (**6**) can be achieved under high pressure, high temperature conditions [reaction (2) in Scheme 1].

2.1.2 Microwaves and Flow

Recently, two enabling technologies, microwave irradiation (μw) and synthesis with flow reactors have been successfully combined. Heating with microwave irradiation is a direct method to heat the reactor from inside as long as all other reactor materials chosen are microwave transparent. Still, the technical set-ups as well as safety issues associated with microwaves have to be taken into account. If these issues are met, this combination of enabling technologies is a very practical approach, particularly as microwave chemistry is otherwise difficult to scale in a batch environment. In fact, under flow conditions only the reactor has to be heated and not the reservoirs containing the starting materials and products, respectively. Furthermore, microwave irradiation shows advantages when kinetic problems in solid phase/solution phase systems need to be overcome. Microwave irradiation allows one to create heat inside continuous-flow devices at locations where the interactions between the two phases occur.

2.1.2.1 Early Examples

The first reports on the development of continuous microwave reactors (CMR) were disclosed by Strauss and co-workers[18] in 1989 which was followed shortly after by a publication of Wang and co-workers in 1990.[19] First examples included Michael addition, Hofmann degradation, Williamson ether synthesis, esterification, the Baylis–Hillmann, and the Mannich reaction. These early studies relied on a custom-made microwave device equipped with metering, monitoring, and control devices for temperature, pressure, automatic shut-down, and energy distribution in order to suit all the necessary safety requirements. On the other hand Wang et al. used a domestic microwave oven with ten power settings, a Teflon tube and reac-

tor connected to a pump and collection vessel. Berlan and co-workers used a modified Maxidigest 350 (Prolabo) microwave reactor with a 66-mL quartz cylinder for carrying out homogeneous and heterogeneous reactions.[20] They described the acid-catalyzed esterification of acetic acid and the Claisen rearrangement of allyl phenyl ether at flow rates between 30 to 335 mL min^{-1}. Both reactions were conducted in a closed-loop mode. Esterifications are industrially highly important and Pipus and co-workers[21] provided an early example for a continuous process combined with microwave irradiation. The authors included in their studies a mathematical model which allowed them to predict conversions in the tubular flow microwave reactor. Kabza and co-workers used a domestic microwave oven and polyethylene reaction tube inside the reactor.[22] The polyethylene tube was filled with sulfonated polystyrene resin that served as an acidic catalyst in the Fischer-type esterification of isopentyl alcohol and acetic acid in a closed-loop mode. Esveld and co-workers developed a continuous microwave dry-media reactor for industrial pilot-scale applications.[23] It is based on a multi-mode tunnel microwave reactor equipped with a Teflon-coated glass fiber web conveyor and an open Pyrex support for the solid reaction media (Figure 2).

This reactor system was used for the solvent-free esterification reaction between stearic acid and stearyl alcohol using Montmorillonite™ clay as acidic catalyst yielding 100 kg of the waxy ester in 95% purity within a day.

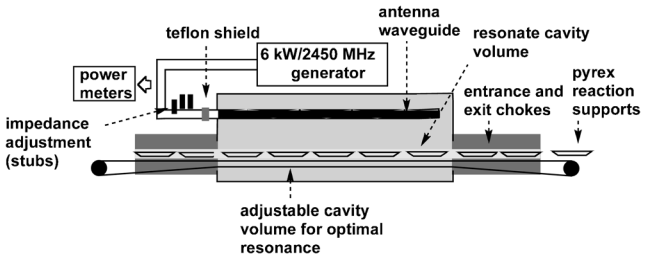


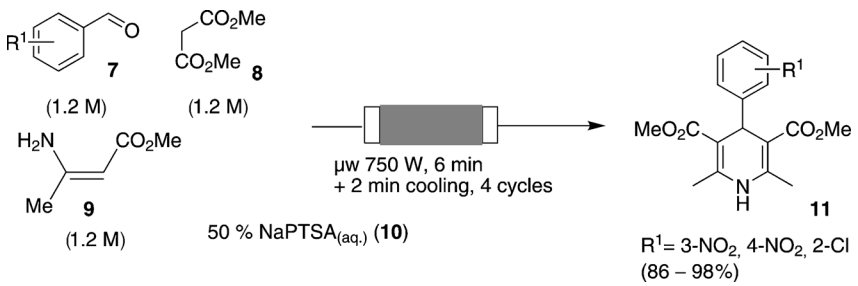
Figure 2. Schematic drawing of a multimode tunnel microwave reactor with conveyor and open Pyrex support developed by Esveld and co-workers.

In 2001, another continuous microwave reactor which was operated in a closed-loop mode was developed by Khadilkar and co-workers and was employed to scale-up the synthesis of Hantzsch esters (Scheme 2).[24] The reaction set-up utilized comprises of a modified kitchen microwave oven with an omega-shaped glass reactor inside with a rather large volume of 65 mL. Uncommonly, the group employed an aromatic hydrotrope solution system consisting of 50% sodium *p*-toluenesulfonate aqueous solution as solvent [NaPTSA$_{(aq.)}$] (**10**). According to the authors this solvent presents a safer medium for microwave synthesis. The heating protocol chosen for the closed-loop dihydropyridine ester **11** synthesis was based on a 6-min heating interval followed by a 2-min cooling interval for each of the four runs. The report describes the rapid and high-yielding synthesis of three dihydropyridine esters **11** in a 0.15 molar scale.

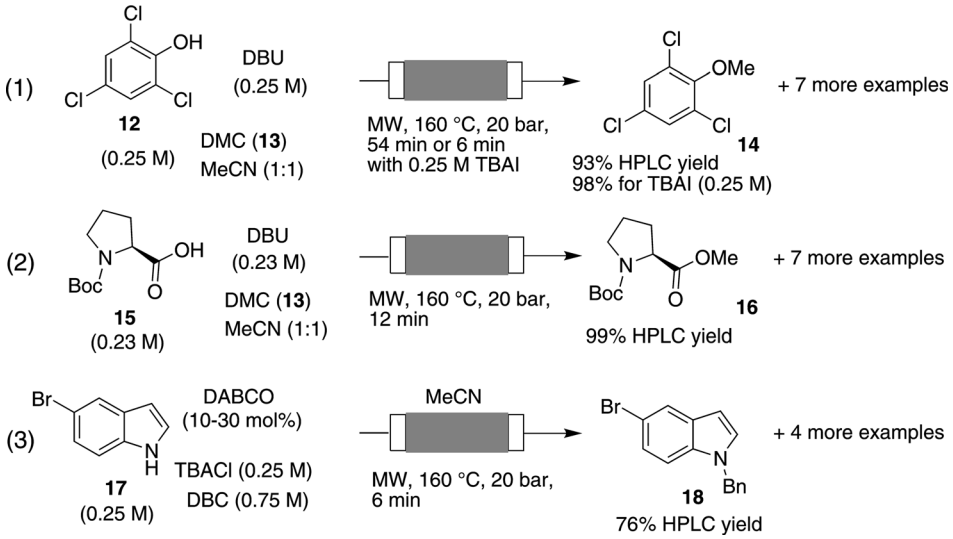
The same year Laporterie and co-workers[25] described a tailor-made continuous-flow microwave apparatus, which was constructed of a magnetron (2.45 GHz, 800 W), a waveguide of rectangular cross section, which was fitted with a circulator, a water load and a directional coupler. The quartz glass reactor was dipped through a Teflon guide into the waveguide. This set-up was used for ambient pressure reactions as the quartz reactor was equipped with a gas exit and an inert gas bubbler. That way large-scale acylations and sulfonylations of arenes under continuous-flow conditions were carried out.

2.1.2.2 Microwave-Assisted Continuous-Flow Synthesis using Flow Coils

A more efficient and less toxic way to methylate phenols and NH-containing hetarenes was disclosed by Shieh and co-workers (Scheme 3; entry 1).[26a] Instead of methyl iodide or dimethyl sulfate they employed dimethyl carbonate (**13**) (DMC) as methylating agent. The continuous synthesis inside a microwave reactor allowed the safe handling of DMC under high temperature and high pressure conditions. The authors used the Milestone ETHOS-CFR with inline pressure and temperature control as synthesis platform. Up to



Scheme 2. Hantzsch ester synthesis in a hydrotrope solution under microwave irradiation in a closed-loop mode.



Scheme 3. Microwave-assisted continuous-flow methylation and benzylation.

a 1900-fold reaction rate increase was achieved compared to conventionally heated batch processes at 90 °C. The authors extended their research onto the "large-scale" (up to 100 g) acid- and toxic reagent-free esterification of carboxylic acids to the corresponding methyl esters (Scheme 3; entry 2)[26b] and *N*-benzylation using dibenzyl carbonate (DBC) (Scheme 3; entry 3).[26c]

Jachuck and co-workers designed a continuous isothermal microwave flow reactor consisting of a 900 Watt Westpointe microwave and a tailor-made microreactor. The microreactor is composed of two parts, a) the reaction side and b) the heat transfer side. The former unit consists of microwave-transparent polytetrafluoroethylene (PTFE) while the latter part is made of alumina. The applicability of the system and the impact of microwave irradiation was demonstrated for the continuous isothermal oxidation of benzyl alcohol to benzaldehyde using iron(III) nitrate as oxidant.[27]

Based on the Emrys Synthesiser from Biotage AP, a single-mode microwave system, Wilson and co-workers developed a flow cell suitable for microwave-assisted continuous-flow synthesis.[28] Their flow cell was composed of 22 borosilicate glass coils encased in a borosilicate glass hull resulting in a total reaction volume of 4 mL (Figure 3). This flow cell is easily inserted from the bottom into the microwave cavity, hence the built-in IR sensor and the instrument software can be used. The group proved the feasibility of their continuous microwave reactor (CMR) with a set of reactions (S_NAr, esterification and Suzuki coupling) especially focusing on scale-up problems. The system's performance was superior in scale-up mode compared to batch processes using oil bath heating as was demonstrated for the nucleophilic aromatic substitution of 4-fluoro-3-nitroaniline (**19**) with phenethylamine (**20**) (Scheme 4). Indeed, a three-times higher yield after approximately 1/5 of the heating time was encountered when employing microwave-assisted closed-loop flow synthesis.

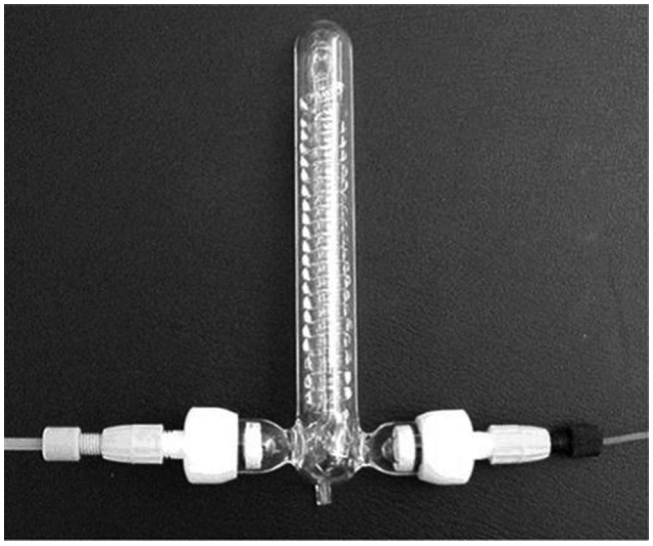
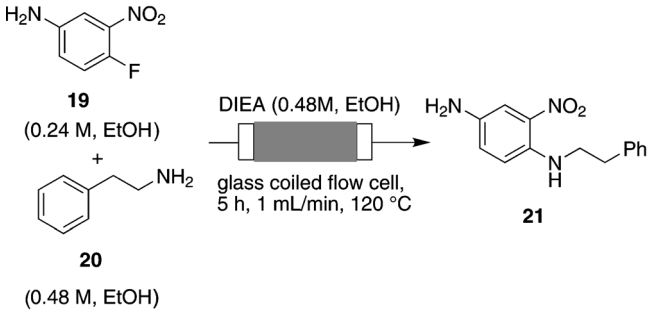


Figure 3. Microwave borosilicate glass coil used by Wilson et al. as well as Ley et al. (from ref.[28]).

In the course of their investigations on microwave-assisted non-metal-catalyzed intramolecular alkyne cyclotrimerization, Ley and co-workers developed a microwave-assisted continuous-flow protocol.[29] Triyne **22** dissolved in dry DMF was pumped through a glass coil (Figure 4) fitted in an Emrys microwave synthesiser from Biotage AG which was connected to a back pressure regulator. In this way 1 g of tetrahydrofuran **23** (Scheme 5) was produced, a process which should easily be expandable to a multiple gram-scaled flow protocol.



Entry	Heating	Temp. [°C]	Flow [mL/min]	Time	Conv. [%]
1	no	r.t.	0	5 h	0
2	oil batch	100	0	18 h	20
3	CMR	120	1	5 h	54

Scheme 4. Comparison study of nucleophilic aromatic substitution.

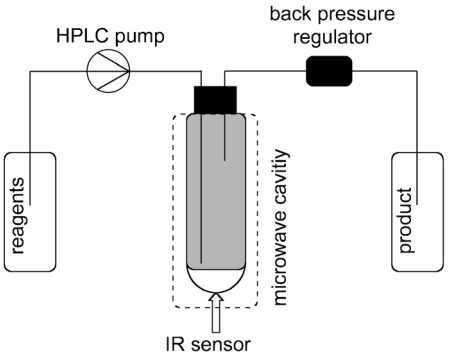
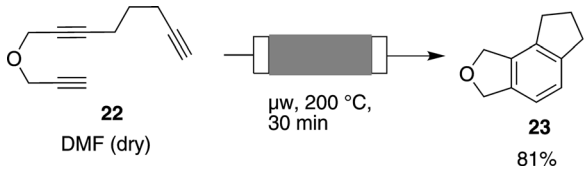
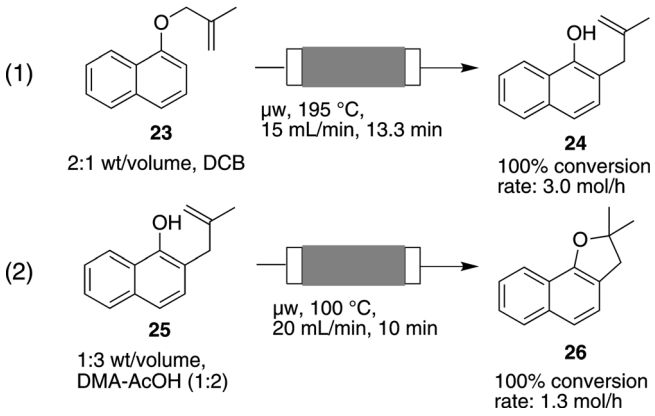


Figure 4. Schematic drawing of a microwave synthesizer with a glass-tube reactor.



Scheme 5. Cyclotrimerization of triyne **22** by Ley and coworkers.

Moseley and co-workers examined the scale-up of six different reactions important for the development of pharmaceutical lead candidates.[30] Hence, the Newman–Kwart rearrangement, the *ortho*-Claisen rearrangement (Scheme 6, entry 1), an acid-catalyzed benzofuran synthesis (Scheme 6, entry 2), an alkylation reaction, a Heck–Mizoroki reaction, and an S_NAr reaction were investigated under continuous microwave conditions using the Milestone FlowSYNTH, a Milestone MircoSYNTH platform modified with a 200-mL PTFE tube reactor protected and stabilized by glass-fiber reinforced PEEK sheath and a steel frame. Production rates of 0.5–3.0 mol/h could easily



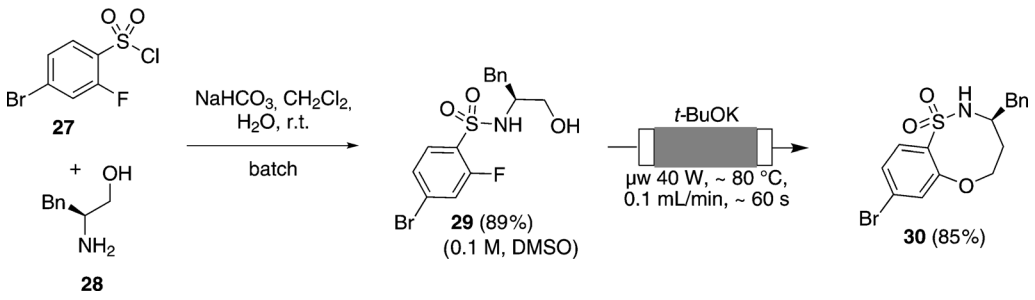
Scheme 6. Microwave-assisted Claisen rearrangements in the flow mode.

be achieved without major changes of conditions employed in the batch experiments. However, clogging of the pump due to the turbid reaction mixture had to be overcome. Indeed, this is a common problem in continuous synthesis even though the set-up that was utilized should have been able to cope with slurries.

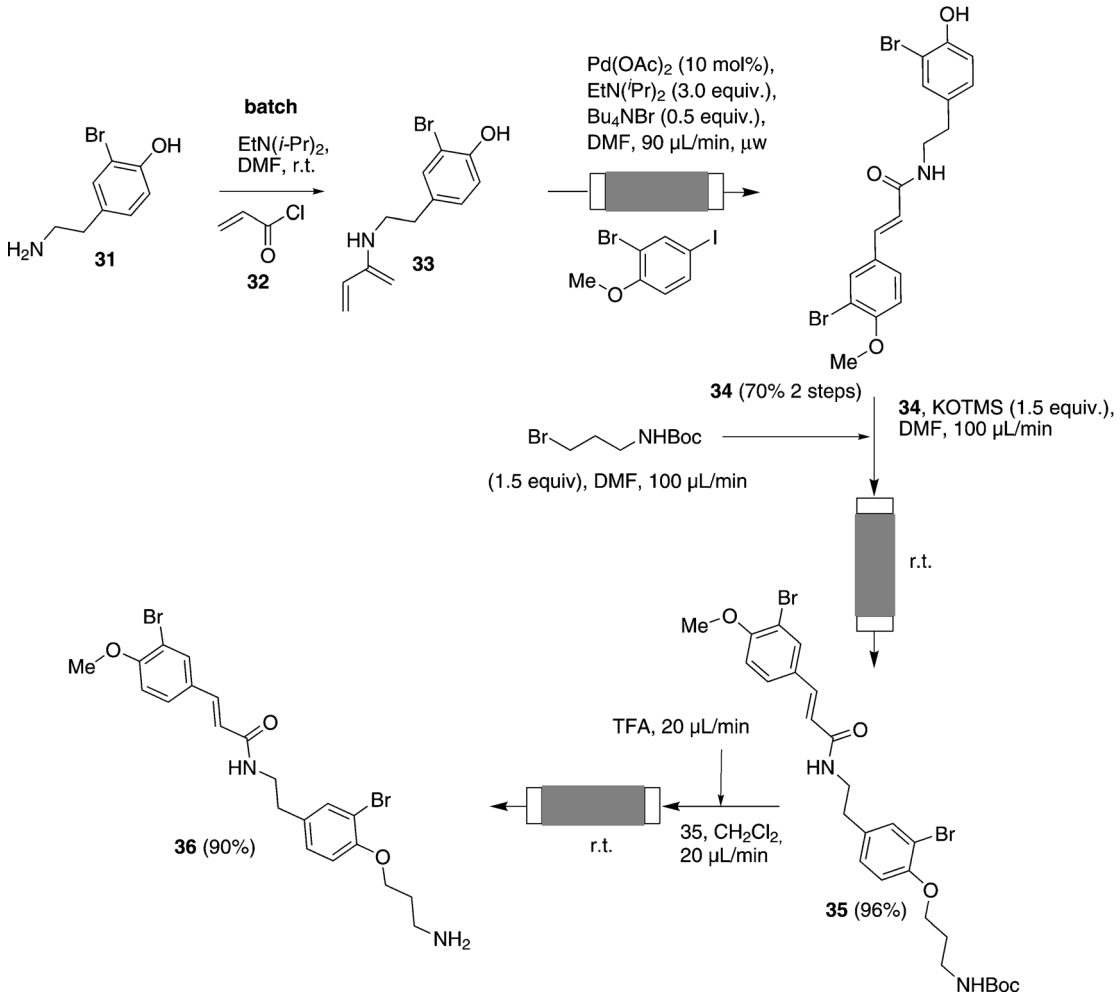
Recently, Organ and co-workers published two reports focusing on the large-scale flow synthesis by pursuing a scale-out strategy.[31] First, they investigated the synthesis of 19 benzofused sultam cores in 5 to 10 g scale, which were used as scaffolds for diversity-oriented synthesis (DOS) (Scheme 7). The synthesis was based on a two-step procedure starting with a nucleophilic substitution of sulfonyl chlorides **27** with chiral 1,2-amino alcohols **28**. Having optimized the sequence in the batch mode, the protocol was transferred to the microwave-assisted flow synthesis using a capillary microwave reactor (see also Chapter 2.1.2.4).

Thus, aryl fluorides **29** were continuously cyclized with a residence time of only 60 s and each sultam building block **30** was obtained after 2.5 h production time which was due the low concentration (0.1 M). Clearly, the corresponding batch process required prolonged process time.

In a second publication, Organ's group reported the gram-scale synthesis of tyramine-based natural products under flow conditions. The protocol was based on a four-step procedure consisting of an acylation conducted in batch mode, a microwave-assisted, continuous-flow Heck reaction, as well as an alkylation followed by a Boc-deprotection conducted in flow but at room temperature (Scheme 8). Generally it is possible to carry out the first three steps under continuous-flow conditions without the need for work-up and purification as all three steps are performed in DMF. After mixing the reagents and substrates for the acylation, they loaded the reaction mixture into a syringe and combined it as a stream with



Scheme 7. Large-scale synthesis of sultam building blocks

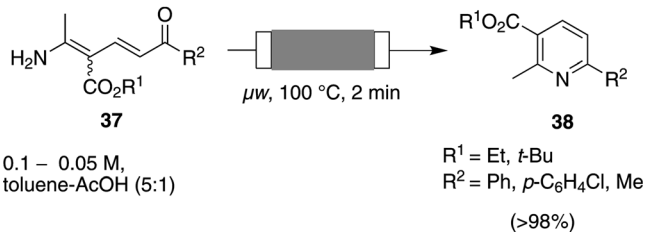


Scheme 8. Four-step protocol for the synthesis of tyramine-based natural product analogues.

the substrate and reagents needed for the Heck reaction.

2.1.2.3 Microwave-Assisted Continuous-Flow Synthesis in Glass Vial-Type Reactors

Bagley and co-workers disclosed the use of a glass-tube reactor (Figure 4) over a Teflon heating coil in the microwave-assisted continuous-flow Bohlmann–Rahtz cyclodehydration reaction.[32] A 0.1 M solution of **37** in toluene-AcOH (5:1) was pumped either through a standard pressure-rated glass tube (10 mL) equipped with a tailor-made steel head and sand filling between two drilled frits or through a Teflon heating coil both fitted into a monomodal microwave synthesizer (from CEM Microwave Technology Ltd.).



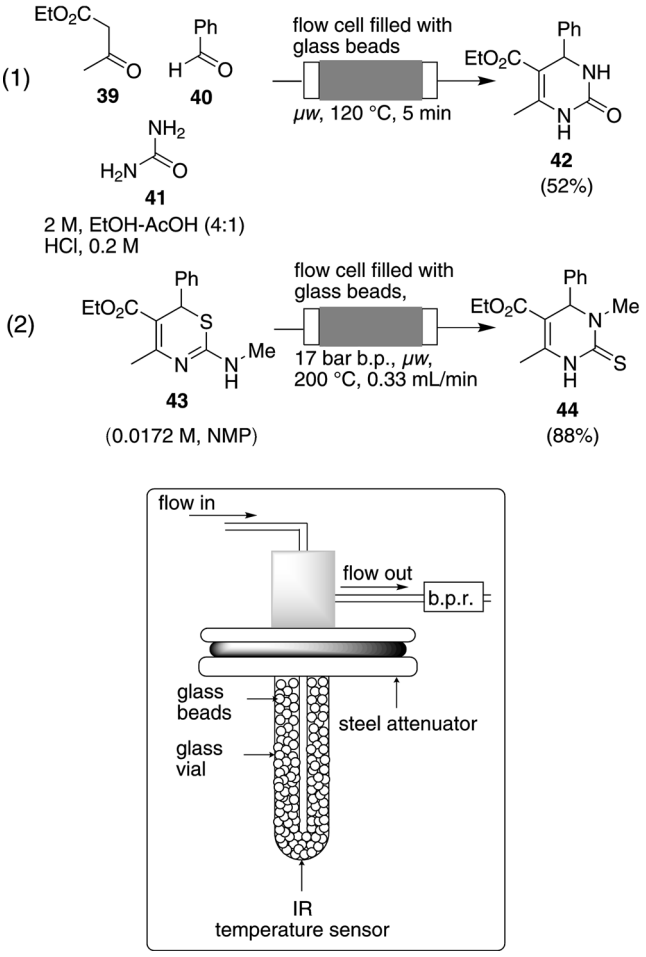
Scheme 9. Bohlmann–Rahtz cyclodehydration reaction by Bagley et al.

Two minutes residence time were sufficient to achieve complete conversion (>98%) and formation of pyridine derivative **38** (Scheme 9). A Teflon heating coil gave the same results although a residence time of five minutes had to be chosen and almost twice as much magnetron energy had to be employed. This process could be scaled-up from the microscale to production scale utilizing the same reaction parameters first collected in microwave-assisted batch reactions.[33] The transfer towards a continuous process was first carried out with a single-mode stop-flow microwave reactor (CEM Voyager®) and a 10-mL glass flow reactor. Next, mesoscale continuous processing in a multimode Milestone BatchSynth™ microwave synthesizer operated with a FlowSynth™ platform was achieved. With that apparatus, the highest substrate processing rate of all investigated platforms was achieved, namely 0.5 mmol min^{-1}. Based on this thorough optimization the continuous hydrolysis of chloromethylthiazole and the Fischer indole synthesis by microwave acceleration were achieved.

Kappe and co-workers[34] made use of a CEM Voyager CF single-mode microwave system to conduct continuous-flow Biginelli reactions (Scheme 11, entry 1). As flow cell a 10-mL microwave glass vial filled with 2-mm-sized glass beads was chosen in order to increase the residence time by microchannel formation (Scheme 10, bottom). Additionally, the microwave-assisted rearrangement of differently substituted thiazines **43** (Scheme 10, entry 2) under batch and under continuous-flow conditions were conducted.

A similar set-up was chosen by Rueping and coworkers[35] for the acid-catalyzed hydroarylations and hydroalkylations of styrene to yield two small collections of hydroarylated styrenes and hydroalkylated styrenes with very good *para*-selectivity for electron-rich arenes (Scheme 11).

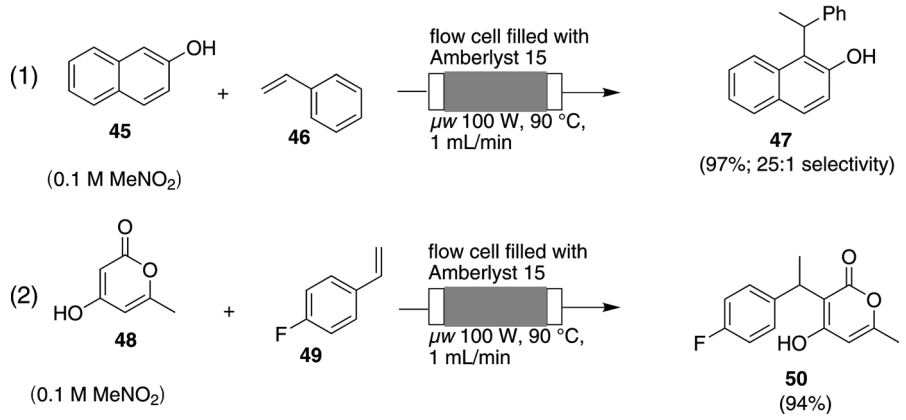
Instead of using sand or glass beads as fixed bed materials the polymeric catalyst Amberlyst 15 was employed and the reaction was conducted at 90 °C with a rather high flow rate of 1 mL min^{-1}.



Scheme 10. Microwave-assisted continuous Biginelli reaction and rearrangement (*top*), schematic drawing of microwave cavity and flow cell employed (*bottom*).

2.1.2.4 Microwave Superheated Metal Particles in Flow Reactors

Organ and co-workers developed a microcapillary reactor for microwave-assisted continuous-flow synthesis[36–39] as well as sequential, parallel synthesis.[40] The flow reactor consisted of a stainless steel holder and a mixing chamber and the set-up was based on two alternative designs (Figure 5). The first one has three inlet ports that merge into one outlet, while the second one consists of four pairs of two inlet ports that merge into four different outlets. The latter design is used for sequential parallel synthesis. Furthermore, each of the outlets is connected to an inexpensive glass capillary tube that has a potential inner diameter range from 0.2–1.15 mm. These custom-built capillary reactors are placed in a Smith Creator Synthesiser microwave device (Biotage AG). The same group used their monocapillary reactor for microwave-assisted continuous-flow Suzuki–Miyaura couplings (Scheme 12, entry 1), ring-closing metathesis



Scheme 11. Microwave-assisted, acid-catalyzed continuous-flow hydroarylation and hydroalkylation of styrenes.

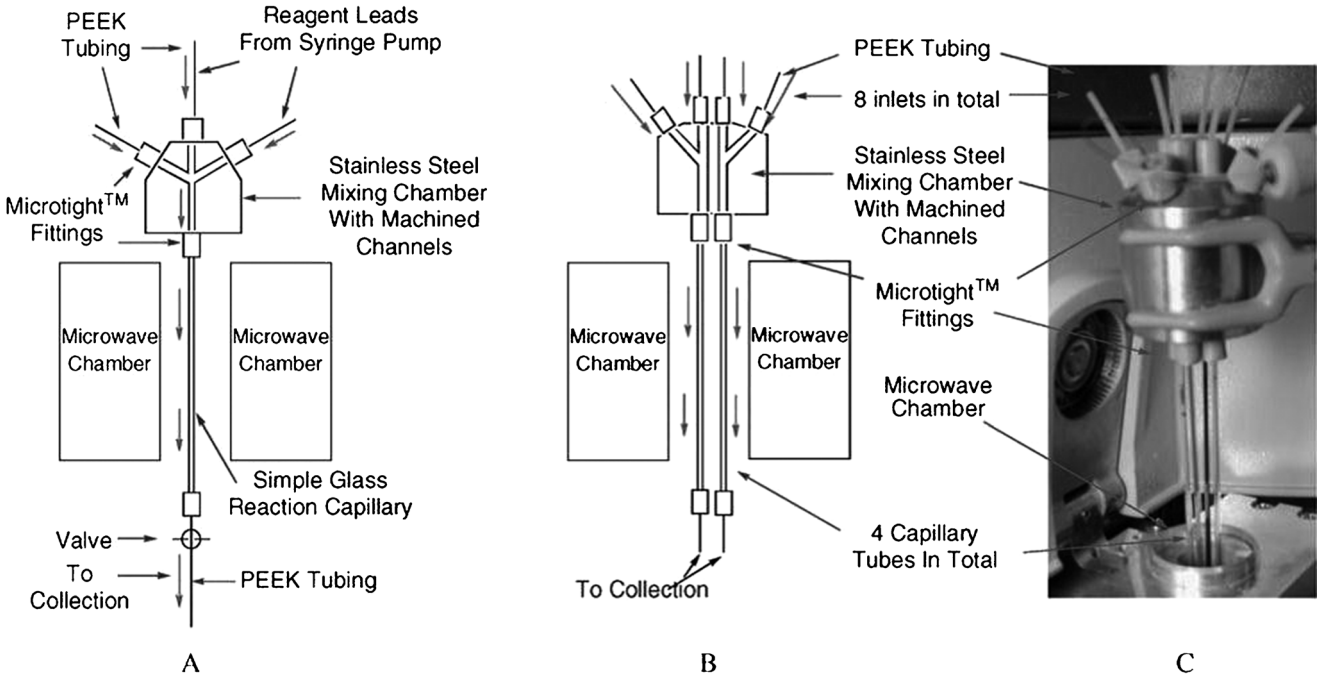


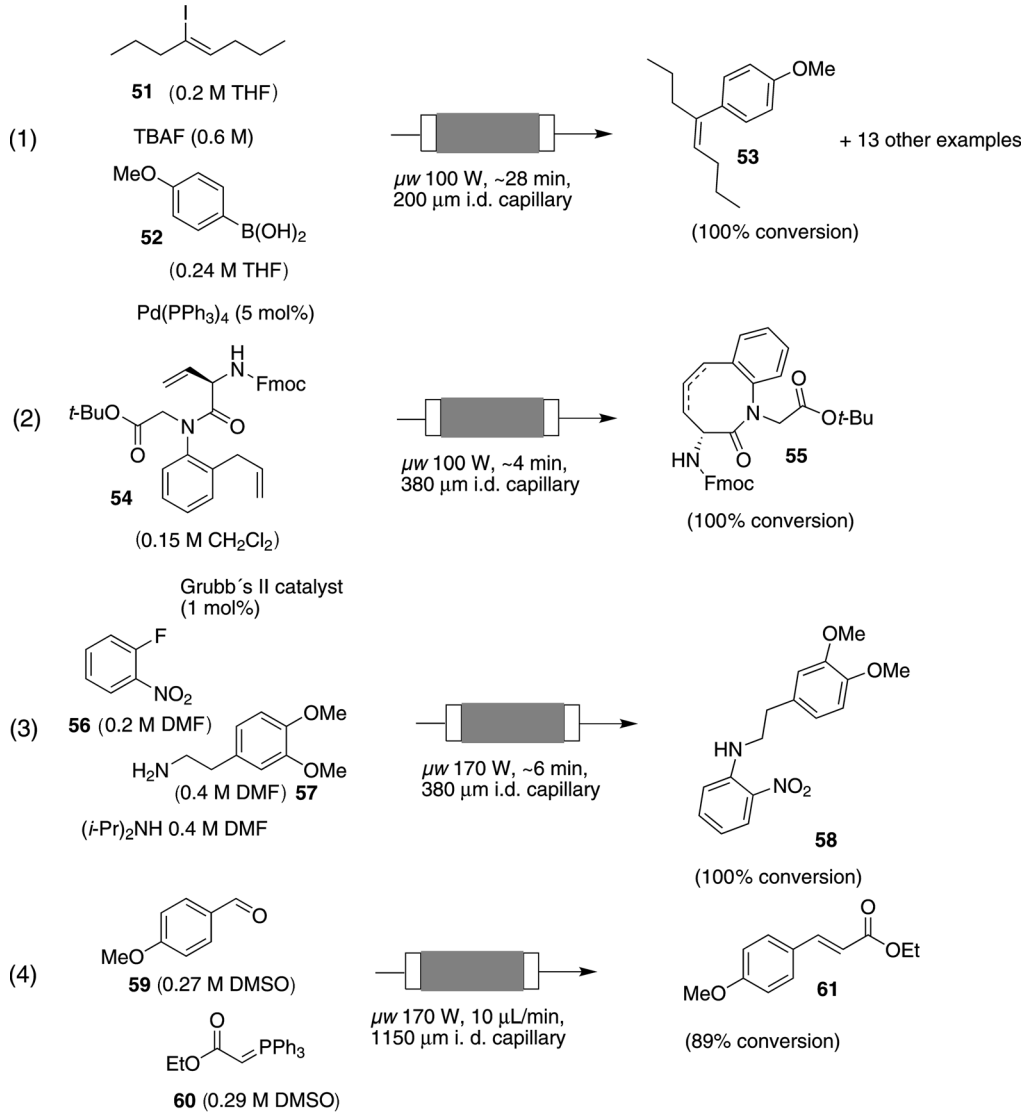
Figure 5. Schematic drawing of Organ's capillary reactors inside a microwave cavity (from ref.[40]).

(RCM) (Scheme 12, entry 2), nucleophilic aromatic substitutions (S_NAr) (Scheme 12, entry 3), and a heterogeneous Wittig reaction (Scheme 12, entry 4).[36]

This monocapillary microwave flow reactor also served to achieve the first multicomponent reaction in flow mode, assisted by microwave irradiation.[37] It yielded small libraries of tetrahydropyrazolo[3,4-*b*]quinolin-5(6*H*)-ones (**65**) (Scheme 13, entry 1) and tetrasubstituted furans **69** (Scheme 13, entry 2).

The more advanced multiple capillary reactor was employed in a sequential synthesis furnishing two small compound libraries by S_NAr (2×2 parallel libraries) and by Suzuki–Miyaura cross-coupling reaction (4×2 parallel libraries). During the course of these investigations[36] coating of the capillary wall with a thin film of palladium was observed and consequently a better conversion and higher temperature under identical microwave power input. This palladium deposit on the inner capillary surface[38] showed catalytic activity in Suzuki–Miyaura and Heck reactions in the absence of additionally added catalyst (Scheme 14, entries 1 and 2).

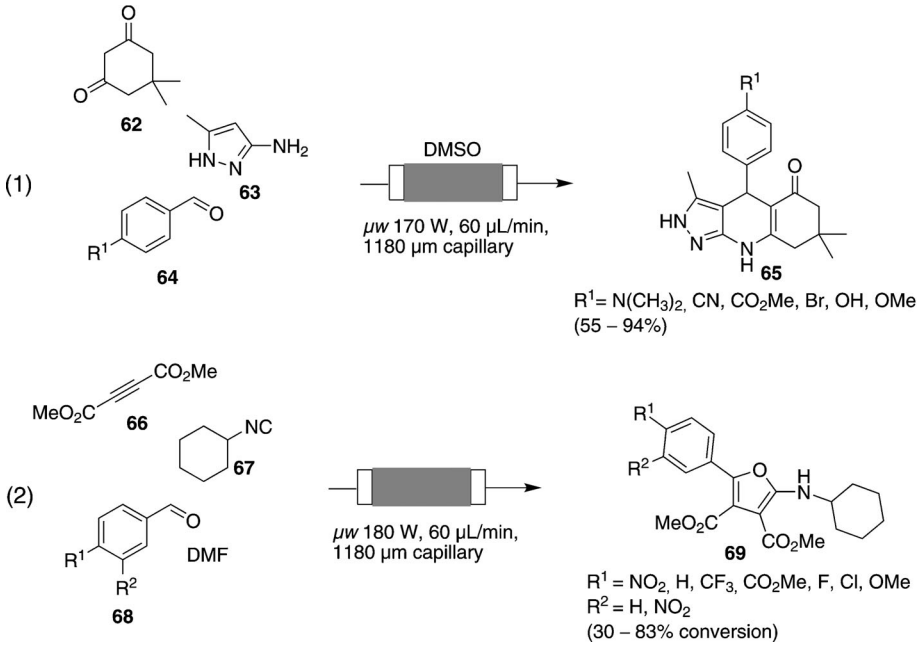
High and very fast conversions were achieved at temperatures of about 200 °C, at a low power input (30 W). Leaching of Pd turned out to be low (<2–19 ppm). These Pd-coated capillaries also showed catalytic activity in Diels–Alder cycloadditions (Scheme 14, entry 3)[39] as well as in sequential intermolecular amination/intramolecular Heck transformations (Scheme 14, entry 4)[41] although for the latter



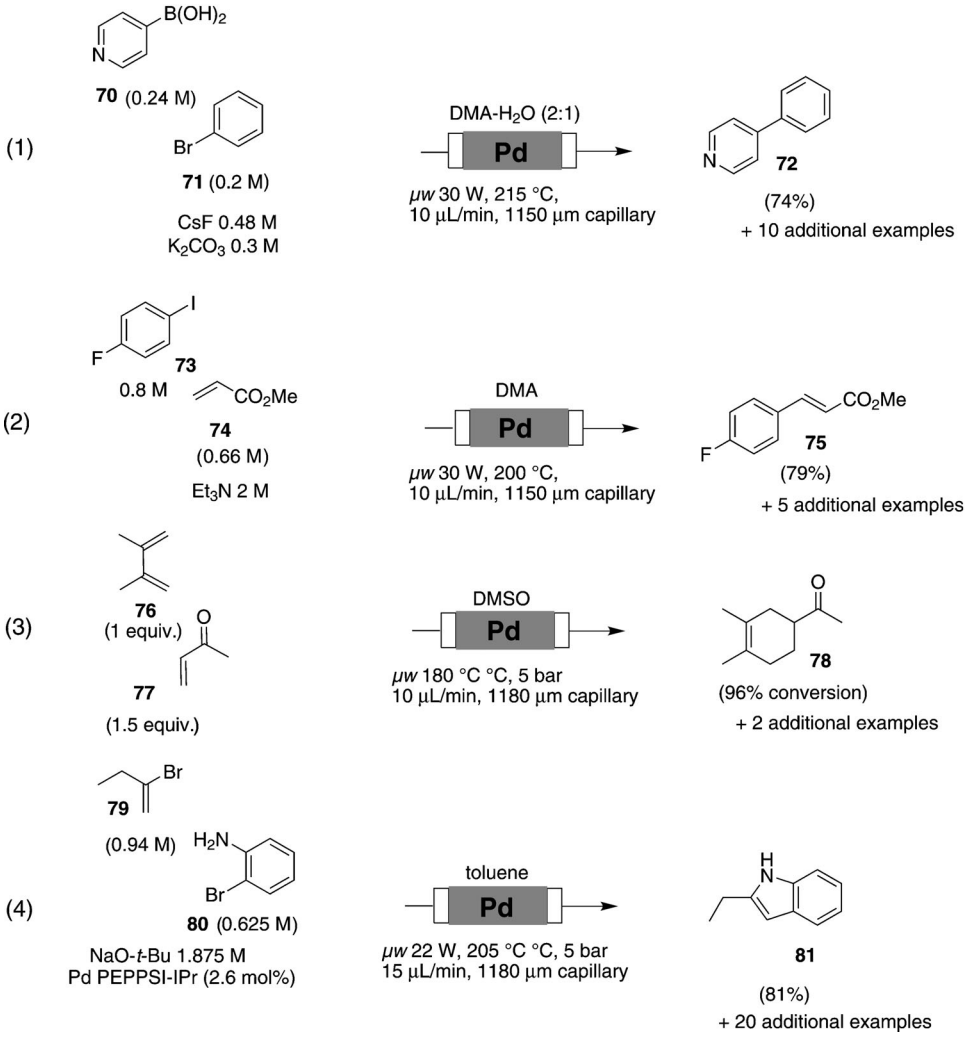
Scheme 12. Flow synthesis with a glass capillary reactor by Organ and co-workers.

example a combination of palladium film and homogeneous palladium catalyst was necessary. The co-dependency on both Pd sources very likely relies on the catalytic effect for the Heck reaction and the excellent heating properties under microwave irradiation of the Pd film while the homogeneous Pd source serves to catalyze the amination step. In all applications the microwave-activated palladium film was far superior to conventionally heated Pd-coated capillaries.

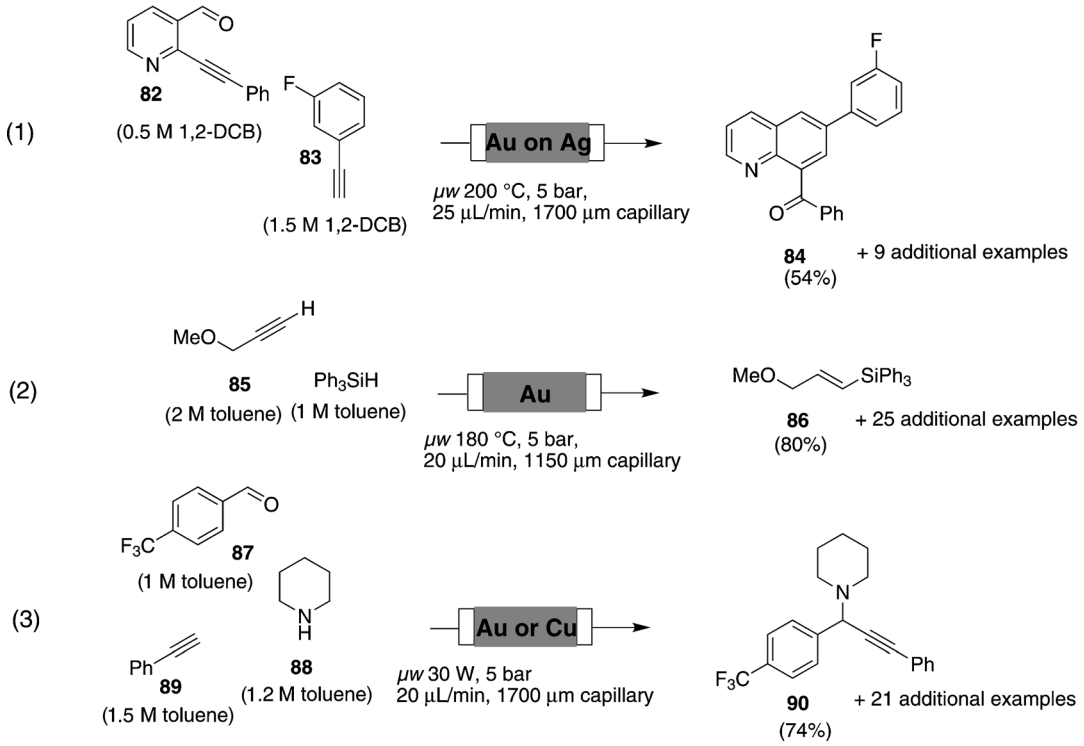
The portfolio of metal-coated capillaries in microwave-assisted continuous-flow organic synthesis can be extended to other metals such as gold[42–44] and copper.[44] The gold film was successfully employed in benzannulation reactions of aryl aldehydes **82** with alkynes **83** (Scheme 15, entry 1).[42] In this case, due to adhesion and performance problems, the gold film was precipitated on a transparently-thin silver layer inside the capillary. Again the metal film served two purposes, being both a heatable source as well as a catalytically active species. For the gold-catalyzed hydrosilylation of terminal alkynes **85** (Scheme 15, entry 2) a two-step deposition procedure of gold was chosen which gave a metal film with the required good adhesion, robustness and catalytic activity.[43] For the microwave-assisted continuous preparation of propargylic amines **90** gold or copper coated capillaries were used (Scheme 16, entry 3).[44] In this application the copper film performed superior to the gold film. A very important aspect of Organ's studies is the first and so far most accurate temperature measurement for the superheated metal films using an FLIR Systems Thermovision™ A320 high definition IR camera. Therefore, a window was machined into the end of the irradiation waveguide which allowed them to install the camera in such a way that it can be fo-



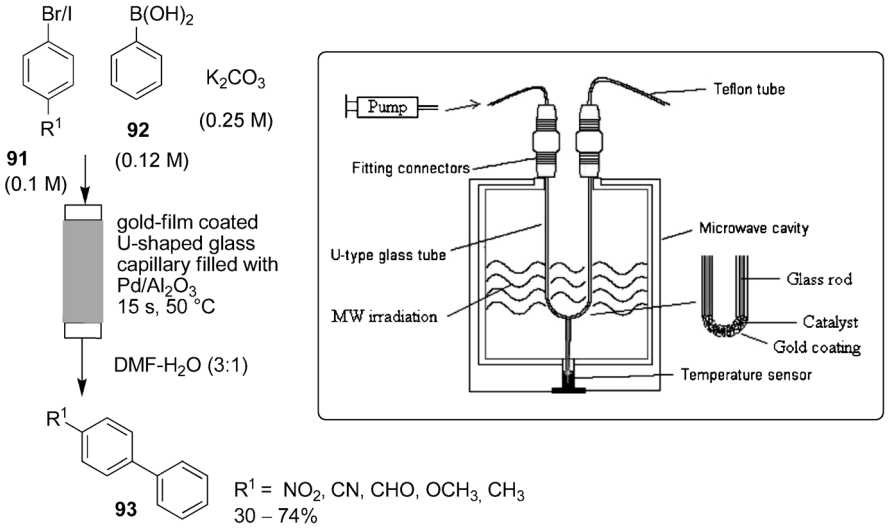
Scheme 13. Microwave-assisted multicomponent reactions in flow mode.



Scheme 14. Microwave-assisted flow synthesis using a Pd-coated glass capillary reactor.



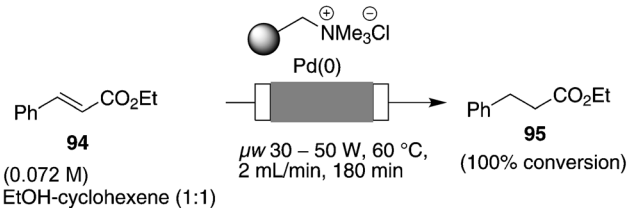
Scheme 15. Flow synthesis with gold-, gold/silver- and copper-coated glass capillary reactors.



Scheme 16. Schematic drawing of Fletchers'and Haswell's gold-coated capillary microwave flow reactor and Suzuki–Miyaura cross coupling reaction (from ref.[45]).

cused down to only a few pixels resulting in a far more accurate measurement than built-in IR sensors which, due to the small diameter of the capillary, also scan the surrounding air and thus provide only average temperature data. Indeed, the data obtained from a built-in IR sensor and the camera were significant, 185 °C versus about 950 °C. These results provide a very good rationale for the tremendous reaction rate enhancement of metal film-catalyzed microwave-assisted continuous-flow reactions.

Instead of coating the inner wall of the flow capillary with a metal film, Fletcher, Haswell and co-workers much earlier used a combination of palladium being supported on silica or on alumina in a U-shaped glass capillary. The outside of the capillary at the bottom section was coated with a gold film which allowed efficient absorption of microwave irradia-



Scheme 17. Microwave-assisted Pd nanoparticle-catalyzed hydrogenation.

tion.[45] The adsorbed palladium material was located inside the U-shaped capillary next to the gold surface. The capillary was mounted within the cavity of a Discover microwave system (CEM Ltd.) (Scheme 16). The authors demonstrated that the combination of the gold film with palladium on Al_2O_3 gave best results in Suzuki–Miyaura cross-coupling reactions with contact times as short as 15 s to 60 s (Scheme 16).

Kirschning, Kunz, and Kappe developed a custom-made PASSflow™ flow reactor that contained a porous composite glass/polymer material shaped as Raschig rings and doped with palladium nanoparticles. This catalytic fixed bed was used to study the conversion of ethyl cinnamate **94** to dihydrocinnamate **95** under transfer hydrogenation conditions (Scheme 17).[46] These PASSflow™ reactors were encased by a conventional oven or inserted into a CEM Voyager continuous-flow single mode microwave system (microwave heating).

It was shown that, by using microwave irradiation, not only a six times higher catalytic activity was achieved but also an improved reusability for at least ten repetitive reaction cycles using ethanol as solvent became possible.[47] The work sheds light on the possibility of creating palladium nanoparticle hot-spots under microwave irradiation.

Ley and co-workers reported on the microwave-assisted Suzuki cross-coupling reaction and prepared a library of differently functionalized biaryl compounds.[48b] Polyurea microencapsulated palladium catalyst (Pd EnCat™) served as catalyst.[48a] Importantly, the group investigated different microwave heating conditions in batch as well as under flow mode. Altogether eleven boronic acids and 31 aryl halides and triflates, respectively, were chosen to generate a potential library of 341 compounds. Tetra-*n*-butylammonium acetate served as base which allowed simple work-up by filtration and elution through a base-scavenging cartridge. Firstly, the impact of different microwave-heating protocols in batch were investigated and heating at 50 W with simultaneous cooling turned out to be beneficial compared to conventional heating at 120 °C. This protocol was then transferred to the flow mode. A continuous glass U-tube was packed with Pd EnCat™ and this reactor was inserted into an Emrys synthesizer from Biotage AB (Figure 6). The outlet of the reactor was connected to a flow cartridge filled with Amberlyst 15 (SO_3H form) and a back-pressure regulator (40 bar). The heating profile had to be adjusted to pulsed 50 W microwave irradiation (50 W for 30 s, 18 s cooling), because the polymer matrix collapsed and melted after prolonged continuous use of the reactor. With the new continuous-flow protocol in hand the authors noticed the dramatic improvement of yields and purity compared to the corresponding batch reactions. Even the synthesis of previously unsuccessful reactions now gave good yield and good purity of the crude products (Scheme 18). Notably, the same reactor set-up served to repeat the Suzuki–Miyaura reaction without the necessity to regenerate or replace the catalyst.

Pericás and co-workers developed immobilized chiral oxazoline-based P,N ligands for the enantioselective allylic amination (Scheme 19).[49] By applying microwave irradiation with a power input of 1 W, which was below the threshold that heating of the so-

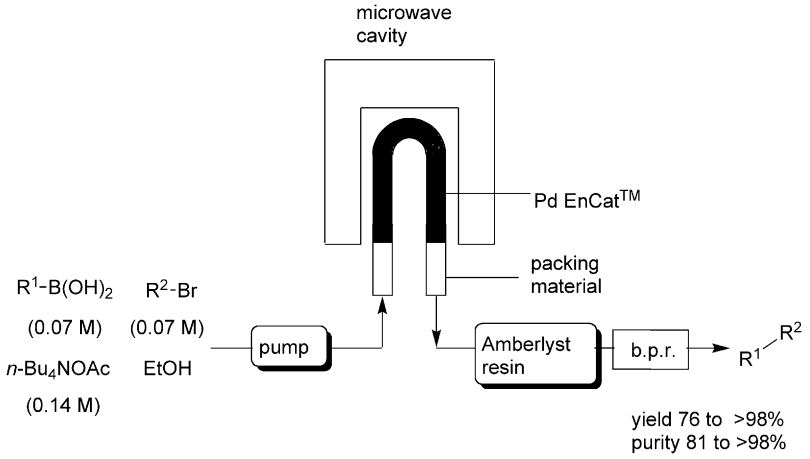
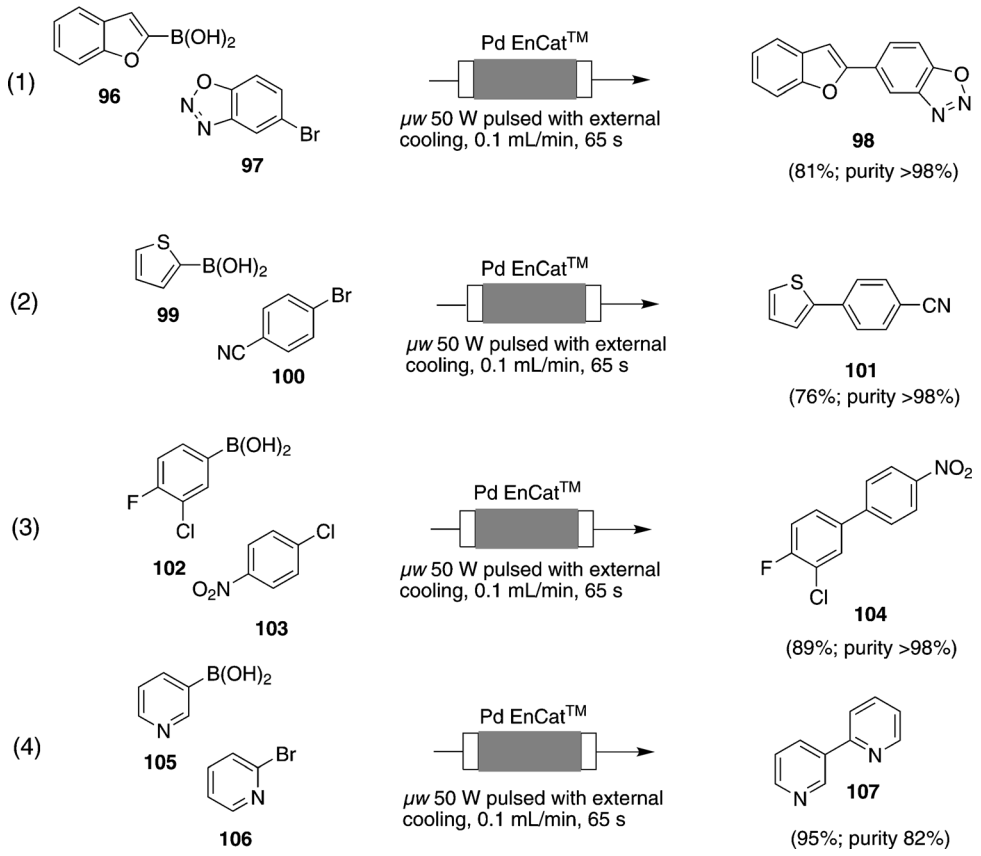
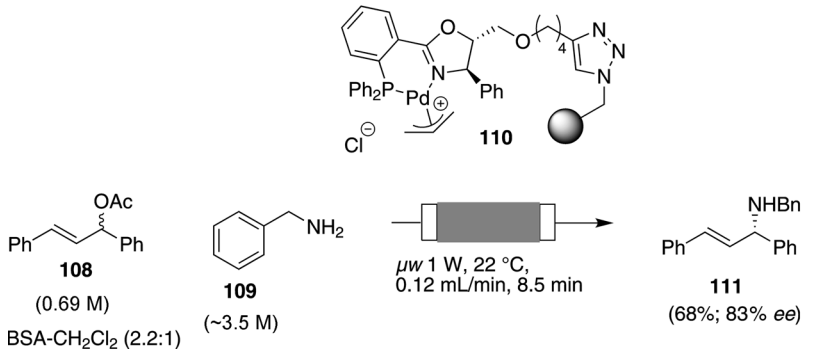


Figure 6. Schematic drawing of the flow set-up used by Ley and co-workers.



Scheme 18. Selected examples of Suzuki–Miyaura cross-coupling reactions.



Scheme 19. Microwave-assisted continuous synthesis of enantioenriched allylamines using immobilized Pd catalyst **110**.

lution could be observed, an increase in reaction rate was detected though.

The authors provide two explanations for this unexpected observation. Either the selective heating of the immobilized Pd(II) complex or the enhanced mobility of the polymer matrix due to heat conduction from the complex may be responsible for the rate acceleration. The experiments were carried out in a CEM discover microwave fitted with a $^{1}/_{4}$ inch internal diameter Teflon tube containing the immobilized Pd catalyst. The system was operated at ambient pressure and at a flow rate of 0.12 mL min^{-1} which equals a residence time of about 8.5 min. During a total operation time of 3 h the conversion dropped from initially 85% to constantly 54% but the enantiomeric excess increased from 81% to 86% *ee*. This reactor set-up led to the production of gram quantities of enantioenriched allylamines.

2.1.3 Inductive Heating and Flow

Heating by magnetic induction is a technology which has been known in the chemical industry for years and was mainly applied for heating metal production reactors. Furthermore, it is used in melting, sintering, and tempering processes or finishing treatment of alloys.[50] Lately, heating by magnetic induction has found its way into gluing processes and contraction of working pieces.[51] On the other hand, a very new approach to use the benefits of inductive heating is its application in medicinal chemistry. Therefore, magnetic and conductive nanoparticles are infiltrated into tumor cells and a strong magnetic field is applied to destroy the tumor by the developed heat. This effect is called hyperthermia.[52] which also enabled the development of biochemical analysis protocols.[53] Until recently, no application of magnetic induction as a heating technology in organic laboratory synthesis including the combination with flow devices was reported.

In 2008 Kirschning et al. introduced inductive heating as an alternative indirect heating technology by utilizing ferromagnetic fixed-bed materials inside flow reactors.[54] When superparamagnetic nanoparticles based on Fe_2O_3/Fe_3O_4 coated with silica gel or alternatively conductive materials like steel beads or copper are exposed to an externally applied electromagnetic field with medium (10–100 kHz) or high frequency (>100 kHz) these materials are inductively heated up. With respect to iron oxide the nanoparticle superparagmagnetism is based on magnetic inductive hyperthermia which is associated with loss of magnetic hysteresis thus creating heat (Néel relaxation).[55] Alternatively, a very strong rapidly alternating magnetic field induces eddy currents on any conductive material such as steel beads or copper wire when placed in the vicinity of that field. That happens to a lesser extent with magnetic materials which mainly produce heat through the so-called hysteresis effect.

Importantly, only conductive or superparamagnetic materials are selectively heated by the inductor which simplifies the technical set-up of a flow system to a great extent. Typically, glass or high-performance polymers such as polyether ether ketone (PEEK) have been used as reactor material so far. Unlike microwave irradiation, electromagnetic induction does not have an effect on solvents or reactants, so that fewer parameters have to be considered and thus temperature control is simplified. When higher temperatures than the solvent's boiling point need to be generated, PEEK (polyether ether ketone) or ceramic reactors equipped with an in-line back-pressure regulator are well suited (Figure 7).

For comparing inductive heating with the heating efficiency of microwave irradiation and conventional oil bath heating, Kirschning et al. chose the high temperature sigmatropic Claisen rearrangement of allyl aryl ether **113** to phenol **114** as a suitable example (Scheme 20). This reaction was chosen because it only proceeds with moderate yield, a prerequisite for such a study. It was found that under batch conditions both heating methods based on electromagnetic radiation gave similar results with respect to reaction time and transformation and were superior to oil bath heating.

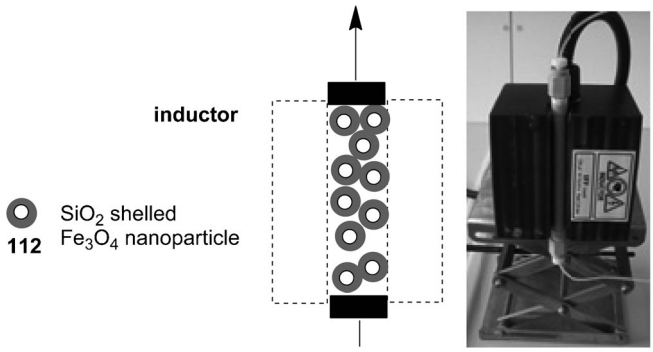
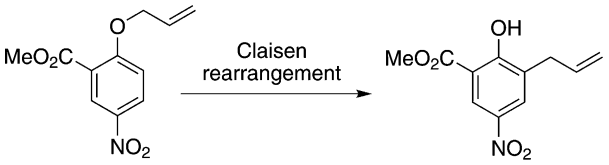


Figure 7. Flow reactor filled with magnetic nanoparticles (*left*) and PEEK reactor encased with an inductor (*right*).

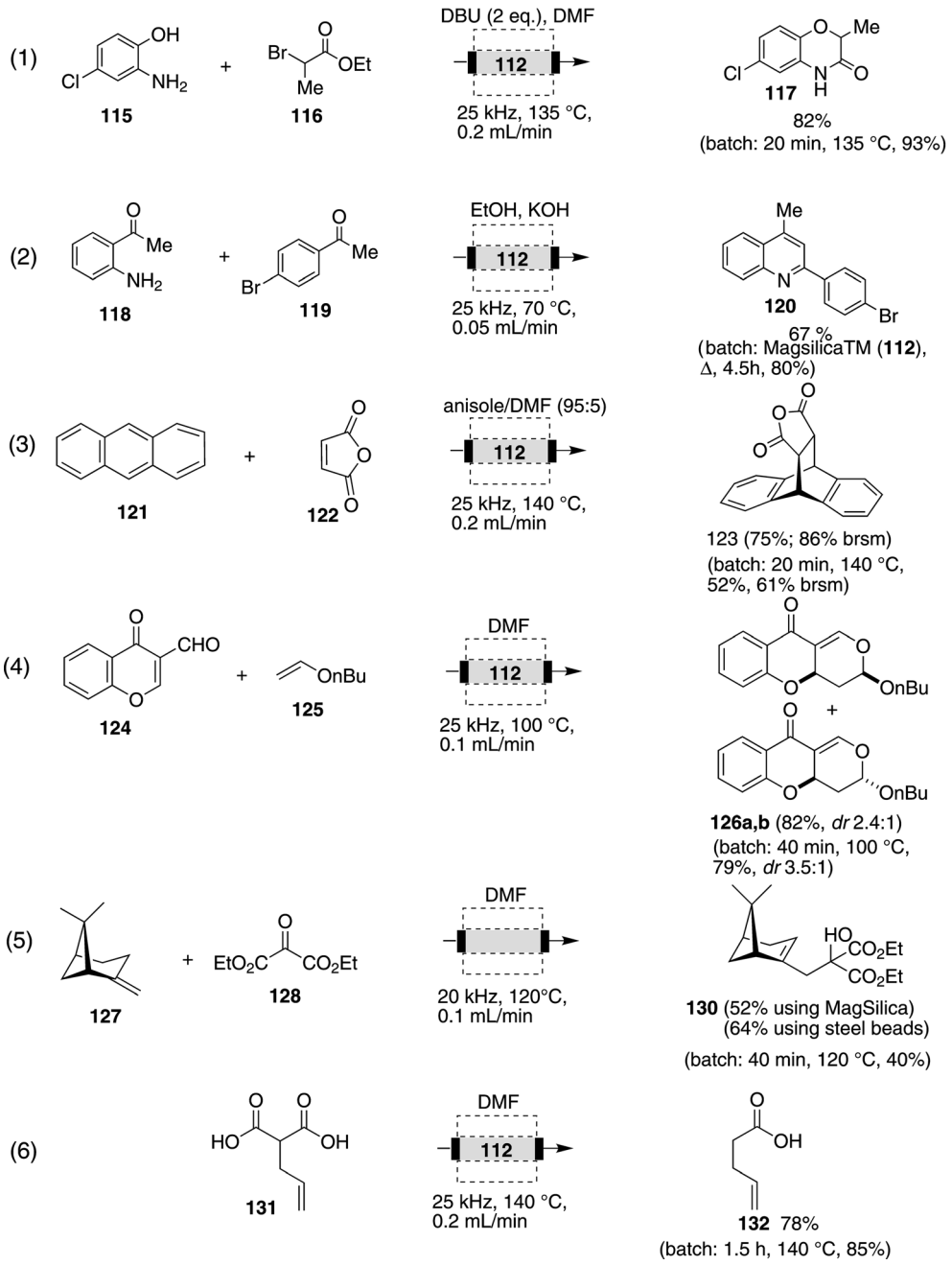


113 **114**

	Conditions	Yield [%]
oil bath	200 °C, toluene, 120 min,	17
μ*w* heating	SiC, 200 °C, toluene, 120 min	38
inductive heating	25 kHz, 200°C, MagSilica™, toluene, 120 min	39

Scheme 20. Comparison between conventional heating (external oil bath), microwave irradiation and inductive heating under batch conditions.

In the course of detailed investigations[54,56] some diverse reactions such as condensations (Scheme 21, entry 1 and 2) and pericyclic reactions (Scheme 21, entry 3–6) were conducted. As heatable materials silica-coated MagSilica™ superparamagnetic nanoparticles based on Fe_2O_3/Fe_3O_4 were employed as well as steel beads or copper wire. Steel beads are well suited in cases when side reactions or a low yield were encountered for MagSilica™-heated transformations. These may result from hydrolytic processes on the

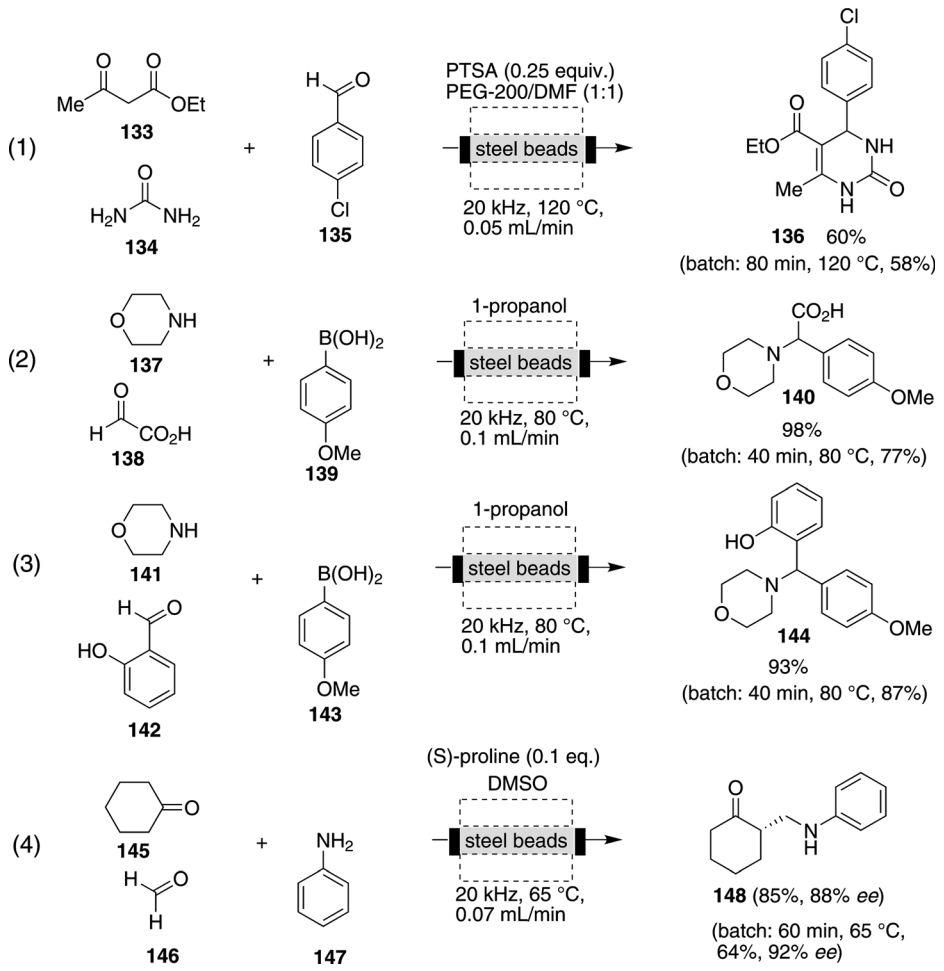


Scheme 21. Continuous-flow synthesis of heterocycles by condensations and pericyclic reactions.

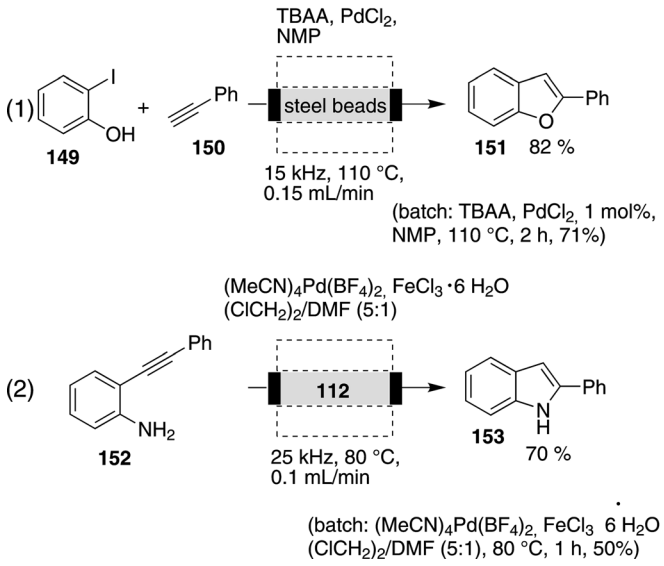
surface of the silica core. In the majority of cases the inductive heating combined with flow turned out to be superior to batch processes with respect to reaction times and/or isolated yields.

Furthermore, inductive heating under flow conditions is ideally suited to carry out multicomponent reactions (MCR).[56] The Biginelli reaction (Scheme 22, entry 1) yielding tetrahydropyrimidines **136**, the boron Mannich reaction or Petasis reaction (Scheme 22, entries 2 and 3) and the asymmetric organocatalyzed Mannich reaction affording β-amino ketone **148** (Scheme 22, entry 4) are high-yielding examples.

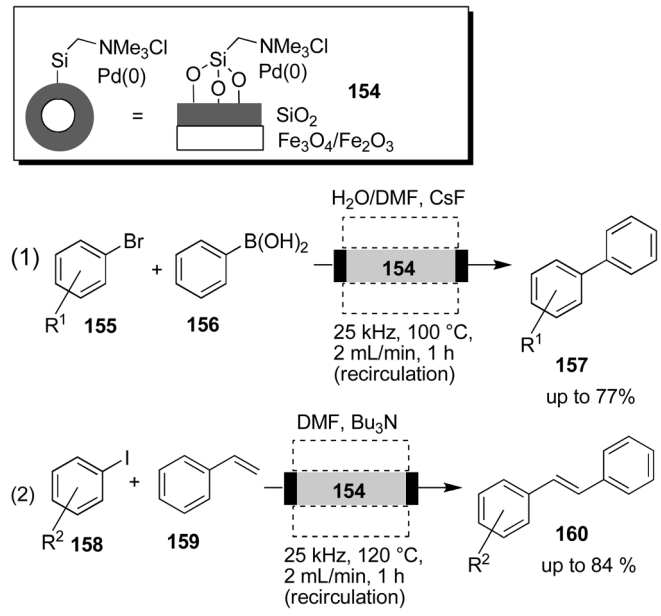
Also transition metal-catalyzed reactions were performed under flow conditions using an inductively heated fixed bed (Scheme 23). The catalysts were employed homogeneously as well as heterogeneously (Scheme 24). Thus, MagSilica™ nanoparticles served as source of heat to conduct the palladium-catalyzed two-step tandem reaction composed of a Sonoga-



Scheme 22. Inductively heated continuous-flow multicomponent reactions.



Scheme 23. Palladium-catalyzed inductively heated cyclizations under flow conditions.



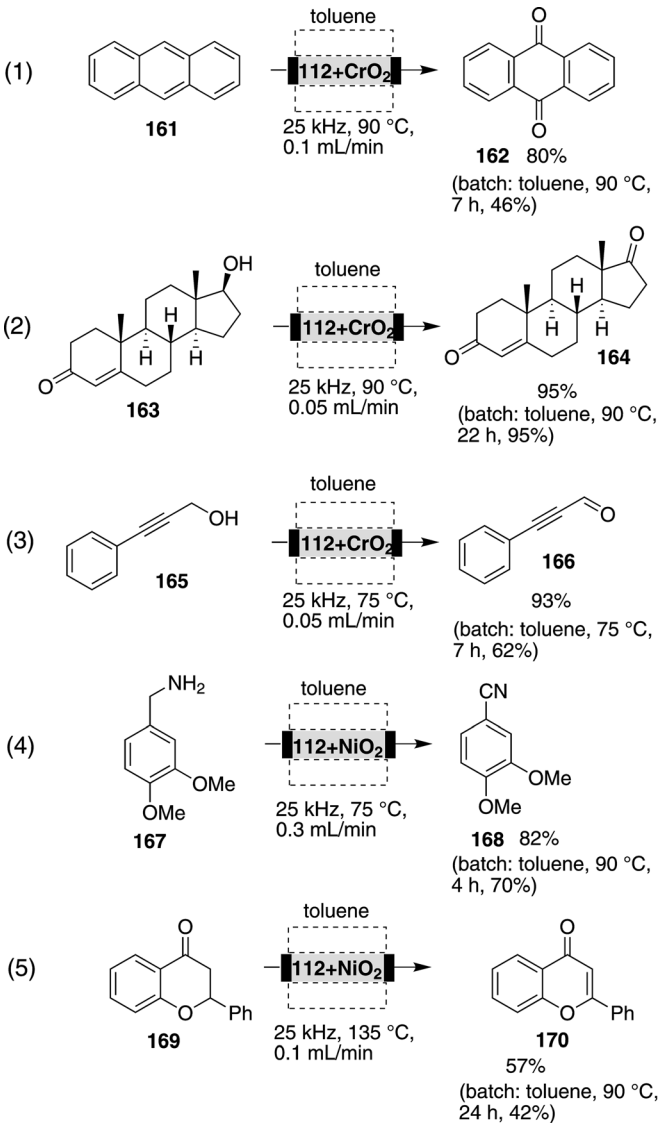
Scheme 24. Inductively heated immobilized Pd-catalyzed C–C coupling reactions under flow conditions.

shira–Hagihara reaction followed by a 5-*endo-dig* cyclization to yield benzofuran **151** (Scheme 23, entry 1) and a 5-*endo-dig* cyclization to afford the indole derivative **153** (Scheme 23, entry 2).

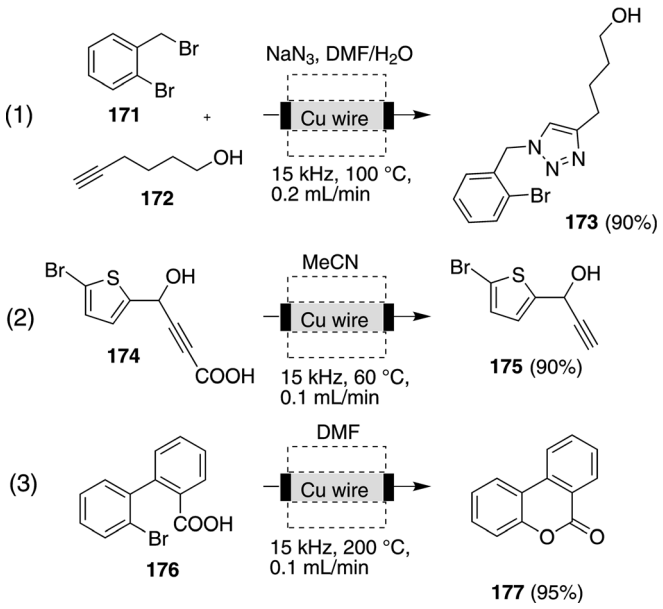
In addition, palladium nanoparticles were immobilized on the silica shell of MagSilica™ and served as catalysts in Suzuki and Heck cross-coupling reactions (Scheme 24). Although recyclability is an advantage of immobilized catalysts the catalytic system lost its activity after three runs despite the fact that leaching was low (entry 1: 34 ppm Pd; entry 2: 100 ppm Pd).

Besides transition metal-mediated C–C coupling reactions, oxidations are highly important, particularly in the industrial context. It was shown that solid phase oxidations[57] can be performed by mixing different solid oxidants like MagTrieve™ (CrO_2) or nickel peroxide (NiO_2) with MagSilica™. These mixed fixed beds remain solid as the oxidation proceeds under inductive heating conditions which minimizes the issue of metal contamination. Thus, very diverse oxidations were achieved which included anthracene **161** (Scheme 25, entry 1), primary and secondary alcohols (Scheme 25, entries 2 and 3), benzylamines to nitriles (Scheme 25, entry 4) and dehydrogenations (Scheme 25, entry 5).

Since copper wire shows conductive properties it can, in principle, be employed as an inductively heatable material. The Kirschning group has combined this property with the possibility of using copper as a catalyst (Scheme 26). The heating profile of copper turnings/wire inside a PEEK or glass reactor is depicted in



Scheme 25. Continuous CrO_2- and NiO_2-promoted flow oxidations under inductive heating conditions.



Scheme 26. Continuous copper-catalyzed Huisgen "click" cycloadditions and decarboxylations and cyclizations under inductive heating conditions.

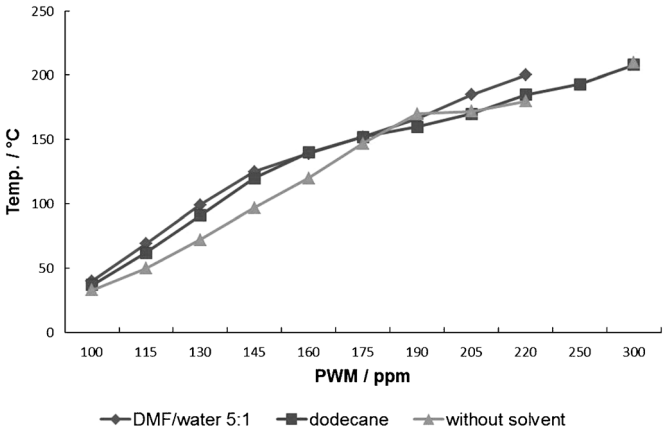


Figure 8. Heating profile of copper wire, measured without solvent, with degassed dodecane and with degassed DMF/water (5:1), 15 kHz.

Figure 8 revealing that 200 °C solvent temperatures can be reached at low power input.[58]

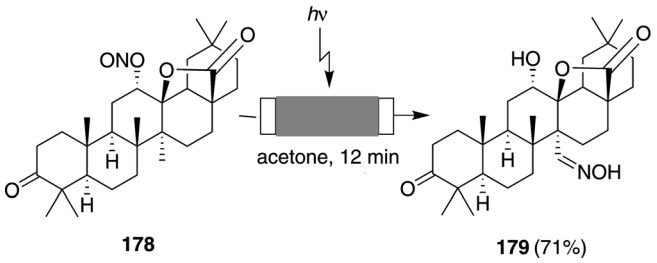
In that sense, the Huisgen "click" cycloaddition that yields triazoles becomes possible combined with prior *in situ* formation of the alkyl azide (Scheme 26, entry 1). Additionally, the copper-mediated decarboxylation of propargylic carboxylic acids was performed under flow conditions (Scheme 26, entry 2) as well as the copper-mediated cyclization of aryl carboxylic acids (Scheme 26, entry 3).

In essence, organic flow synthesis combined with the required technical set-up induced the development of new modes of heating such as induction that had been unknown in the laboratory environment up to that point.

2.2 Photochemistry in Microstructured Reactors

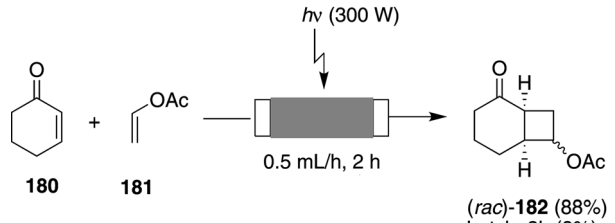
Photochemistry offers many advantages over heated reactions as energy input can be controlled precisely. Furthermore, photochemistry complements thermal reactions, e.g., for pericyclic reactions. However, it is rare for photochemical processes to be realized on an industrial scale, partly because specialized reaction vessels with a light source are required in which the light source, like medium- and high-pressure mercury lamps, xenon lamps or halogen lamps, ideally is placed in the center of the reaction mixture. The design of such vessels poses a difficulty on an industrial scale and tends to generate a large amount of heat and therefore requires additional cooling systems.

Photochemical reactions are typically carried out under batch reaction conditions and only recently have they been combined with continuous-flow processes.[59] These studies suggest that photochemical flow processes are far more effective on a large-scale than the corresponding batch approach. The concept of numbering up by using several microreactors in parallel is regarded to be ideally suited to achieve the industrial production of large amounts of photochemical products. This set-up ensures uniform irradiation to the entire reaction solution particularly because the depth of a microreactor is commonly small (100–1000 μm), maximum penetration of light and thus irradiation even of relatively concentrated solutions can straightforwardly be achieved. Importantly, the production rate of a photochemical process can easily be adjusted in a microphotoreactor. To change the irradiation time of the photochemical processes one can increase the flow rate of the system. As microstructured reactors possess high heat transfer coefficients cooling that may be required during a photochemical process is achieved efficiently and without greater efforts. Further miniaturization is possible with the use of light-emitting diodes (LEDs) instead of conventional light sources.[60]



178 **179** (71%)

Scheme 27. Photochemical Barton reaction under flow conditions.



180 **181** (*rac*)-**182** (88%) batch: 2h (8%)

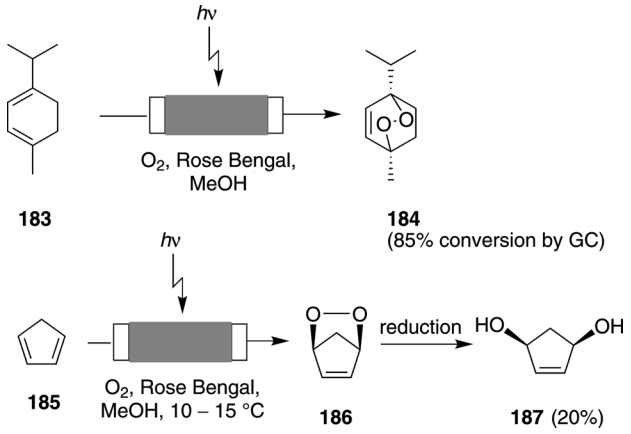
Scheme 28. Photochemical [2+2]cycloaddition under flow conditions.

A complex example of a continuous photoprocess is the Barton reaction of steroidal derivative **178** to yield the bridged γ-lactone **179** (Scheme 27).[61] Three microstructured reactors (total path length 2.2 m) were tested (quartz, soda lime glass and Pyrex) and Pyrex turned out to be superior using a 15 W black light. The authors also demonstrated that numbering up of microreactors is a valid concept for large-scale photochemistry. Thus by using several reactors (1000 μm wide, 500 μm deep and 1 m total length) applying eight 20-W black lights, gram amounts of the Barton product **179** were prepared within 20 h.

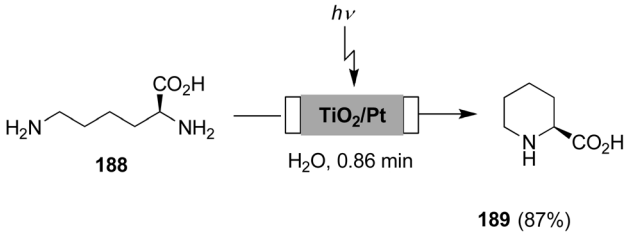
Fukuyama et al.[62] described the photochemical [2+2]cycloaddition of cyclohex-2-enone (**180**) with vinyl acetate (**181**) in a commercially available microreactor based on FOTURAN® glass[63] (Scheme 28). The reactor was equipped with a high-pressure mercury lamp (300 W). At a flow rate of 0.5 mL h^{-1} (residence time 2 h) the product **182** was obtained in 88% yield compared to 8% under comparable batch conditions.

Microstructured flow-reactor devices are particularly appealing when reactive intermediates need to be generated *in situ* and directly used in chemical transformations. Dye-sensitized photooxygenation of α-terpinene (**183**) to ascaridole **184** is an illustrative example of generating and utilizing singlet oxygen under continuous flow conditions (Scheme 29).[64] Likewise, photooxygenation of cyclopentadiene (**185**) followed by reduction yielded 2-cyclopenten-1,4-diol (**187**).[65]

Recently, photochemistry in microstructured reactors was extended to catalytic processes, by immobi-



Scheme 29. Dye-sensitized photooxygenations in microstructured reactors.

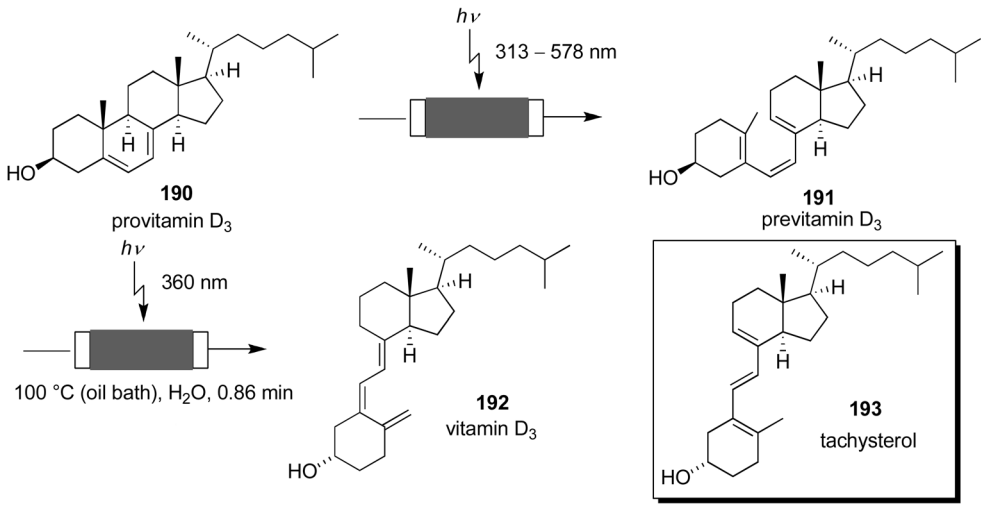


Scheme 30. Photocatalytic synthesis of L-pipecolinic acid **189**.

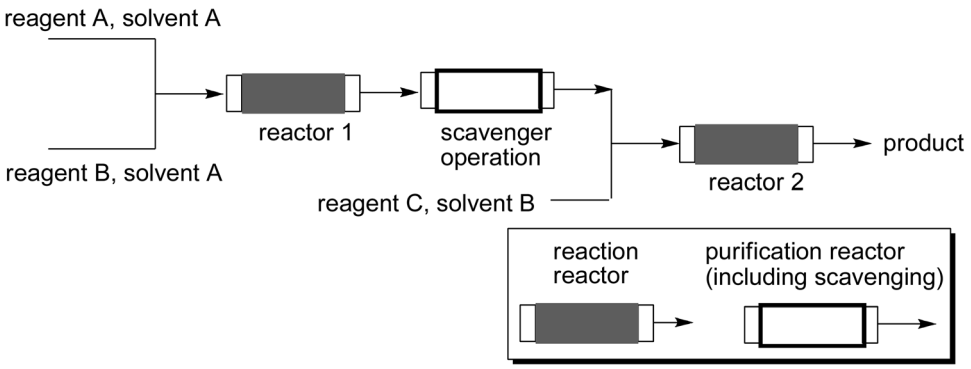
lizing catalytically active species, e.g., on the inner walls of the microreactor. In principle, these microstructured devices have great potential in waste-water treatment. Synthetically, several examples of photocatalytic reactions using TiO_2 as catalyst have been reported.[66] An interesting example was disclosed by Takei et al.[67] Photocatalytic degradative cyclization of L-lysine (**188**) yielded L-pipecolinic acid (**189**) (Scheme 30) using a microstructured reactor (770 μm channel width) which was coated with TiO_2 (300 nm thickness) and doped with Pt (0.2 wt%) for installing reductive properties. The reaction rate was about 70 times greater compared to the corresponding batch process. Noteworthy, the enantiomeric excess (*ee*) did not change.

A particular powerful example of how photomicroreactors can be used in organic synthesis was recently published by the Takahashi group.[68] Vitamin D_3 (**192**) is an industrial product that is photochemically prepared from provitamin D_3 (**190**) *via* previtamin D_3 (**191**) (Scheme 31). The first photoelectrocyclic ring opening does also yield tachysterol **193** which is in photochemical equilibrium with previtamin D_3 **191**. The second step is a thermal 1,7 hydride shift and results in vitamin D_3 **192** from previtamin D_3 **191**. In order to achieve a high degree of transformation a second photomicroreactor was attached that was heated in an oil bath. This set-up allows one to photochemically shift the equilibrium from tachysterol **193** back to previtamin D_3 **191** which is thermally transformed into vitamin D_3 **192**. Thus, the authors were able to collect **192** in 32% isolated yield (60% crude) under optimized flow conditions which compares well with the current industrial process that commonly furnishes less than 20% yield of vitamin D_3 **192**.

It must be noted, that the introduction of miniaturized flow reactors to the conventional chemical laboratory will very likely initiate a renaissance of photochemistry. Thus, here we can clearly see that new technologies can feed back to synthetic chemistry and initiate new research efforts and options for new applications.



Scheme 31. Photocatalytic synthesis of vitamin D_3 **192**.



Scheme 32. Principal multistep continuous-flow set-up and roles of flow devices as reactors and purification devices (for clarity reasons, two types of graphical presentations are used in the following schemes, one showing a synthesis the other one representing a purification reactor).

3 Multistep Flow Synthesis

One can take full advantage of the specific features of continuous-flow reactors by combining several chemical transformations sequentially within one process. A multistep synthetic sequence in the flow mode relies on several reactors in line with the great benefit that intermediates are not isolated but are directly transferred into the next flow reactor (Scheme 32). In reality, compromises are inevitable so that synthetic sequences are split into two or more shorter sequences and in between each partial sequence the product of the flow synthesis is isolated before being subjected to the next flow sequence. One reason why dissecting a multistep flow synthesis is necessary can be a switch of solvents. In this chapter we will cover both complete multistep flow syntheses as well as segmented multistep syntheses using flow reactors.

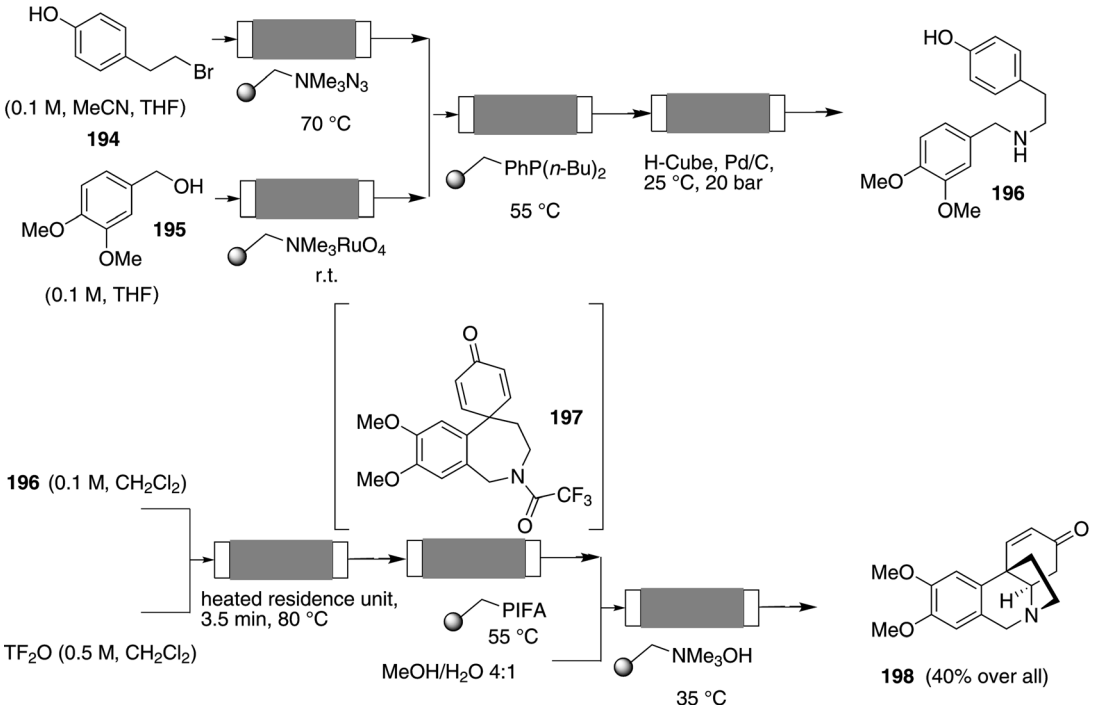
Multistep flow synthesis appears to be a straightforward process (Scheme 32), but the laboratory situation unfolds the challenges of multistep synthesis. Commonly, for each additional reaction step a stream of reactants or building blocks has to be pumped into the system. Ideally, one needs to optimize flow rates for each stream as well as the residence times in each flow reactor. Also different reaction temperatures and back pressures have to be optimized and adjusted for each reaction "compartment". Furthermore, it is not enough to optimize the principal reaction conditions like concentrations, homogeneity, temperature or the choice of reagents when conducting each individual reaction. But when the product stream leaving the first reactor reaches the second reactor the following reaction has to proceed smoothly under similar conditions with respect to flow rate and solvent as was found for the first transformation. Thus, the conditions for the first reaction cannot be optimized by itself but commonly the conditions of the second reaction have to be taken into account from the very beginning. It goes without saying that every additional reaction step of such a continuous multistep process leads to an even more complex system.

Some of these problems such as removal of by-products can be minimized by using solid phase-bound scavenging reagents.[69] Alternatively, a solvent switch can be achieved by employing the catch and release technique.[69b] Here, the product from the previous step is first trapped on a functionalized fixed bed inside the reactor before being released by pumping in the new solvent along with an appropriate releasing agent.

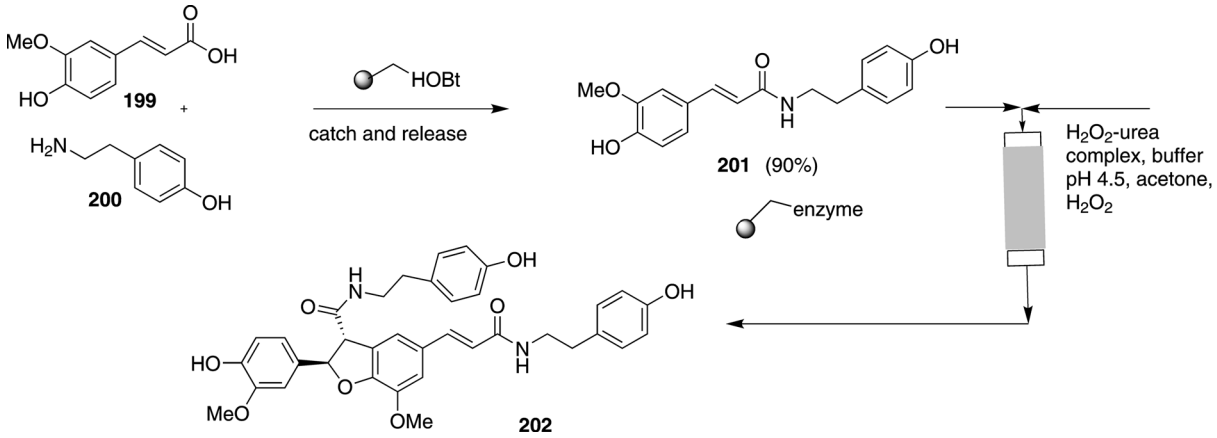
An early and very illustrative example of a multistep flow synthesis of a complex natural product was disclosed by Ley et al. who produced (±)-oxomaritidine (**198**) in six steps in 40% yield (Scheme 33).[70] As a starting point bromide **194** was converted to the corresponding azide with an azido-functionalized reactor. Staudinger phosphinimine formation was achieved in the reactor followed by an aza-Wittig reaction with the aldehyde that was obtained separately by oxidation of the corresponding alcohol **195** to yield an imine which was reduced by a commercial H-Cube hydrogenator to afford amine **196**. In fact, this is an example of a catch and release technique in which the trapped phosphinimine is released by the aldehyde.

As the following transformations were incompatible with THF as solvent, a manual solvent switch to dichloromethane had to be carried out and **196** was N-protected using triflic anhydride as reagent. Then, the aromatic ring was oxidized by solid phase-bound hypervalent iodine reagent PIFA to effect phenolic coupling. Deprotection of the amine initiated the spontaneous 1,4-addition which afforded the final compound. Noteworthy, **198** could be produced in 20 mg yield in more than 90% purity as judged by NMR spectroscopy.

A second early example for the application of a multistep synthesis of the natural product grossamide under flow conditions was also published by the Ley group.[71] Immobilized HOBt initiated the sequence



Scheme 33. Multistep flow synthesis of (±)-oxomaritidine.

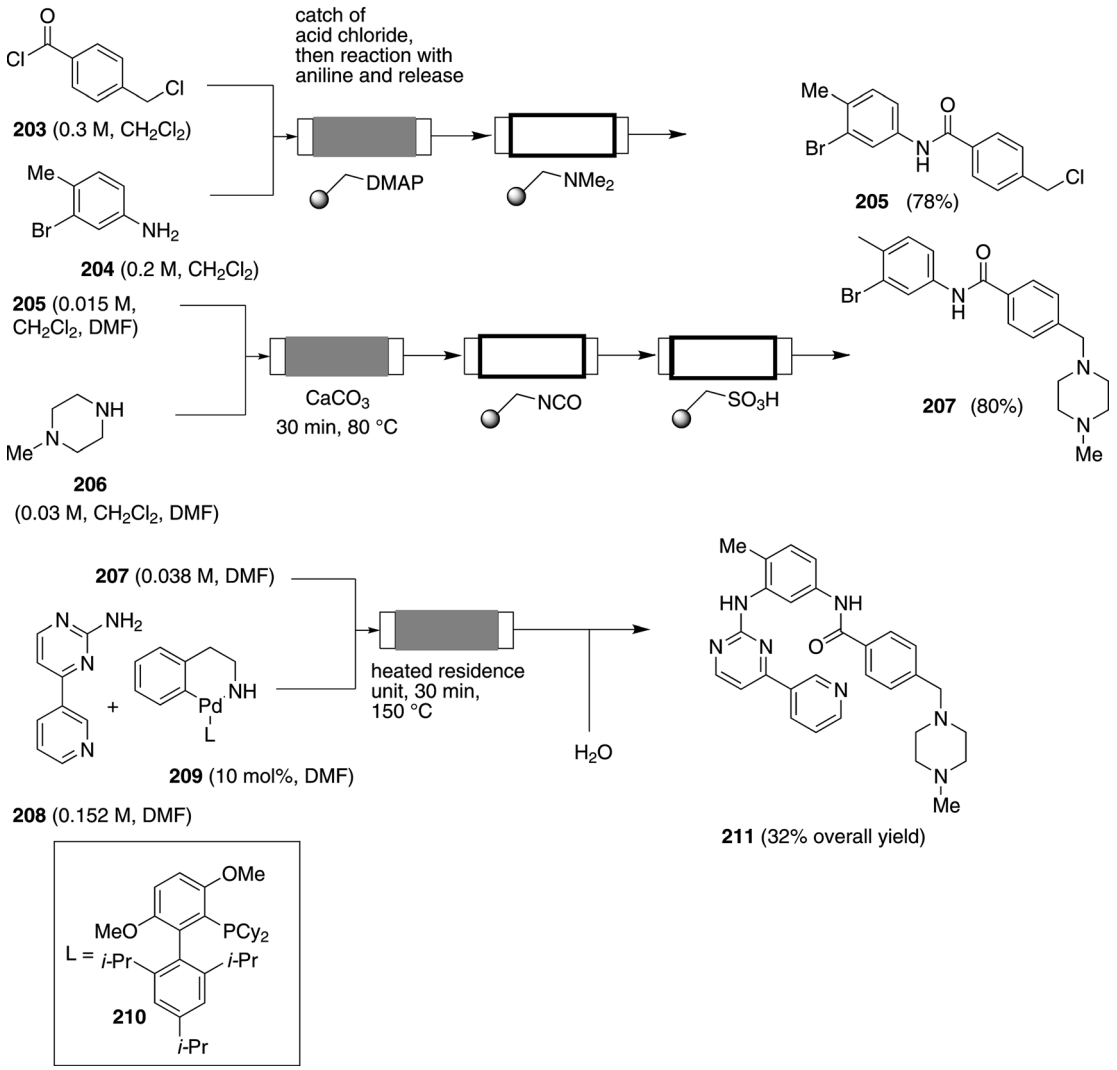


Scheme 34. Multistep flow synthesis of alkaloid grossamide (**202**).

by coupling carboxylic acid **199** with amine **200** to yield amide **201**. Afterwards the crude product was directly subjected to a second flow reactor that contained immobilized horse radish peroxidase (type II) to yield the final product **202** in unspecified yield (Scheme 34).

A third illustrative example from the same laboratory is the synthesis of imatinib (**211**) (Scheme 35) which is reported to be one of the APIs (active pharmaceutical ingredients) from Gleevec.[72] Again a catch and release protocol initiated the sequence. Immobilization of acid chloride **203** onto poly-DMAP inside the reactor followed by pumping a stream of amine **204** through the fixed bed released amide **205**. This intermediate product could not directly be used as the next step required different concentrations. Therefore, the authors employed a UV autosampler that automatically submitted fractions of different concentrations to the next step.

Next, benzyl chloride **205** was subjected to a nucleophilic substitution with piperazine **206** and purified by means of a catch and release protocol with immobilized sulfonic acid. The final step of the synthesis was the Hartwig–Buchwald coupling of **207** and **208**. At this stage significant optimizations had to be conducted due to solubility problems and precipitation issues. Additionally, rapid completion of the reaction could only be achieved at an unusually high tempera-

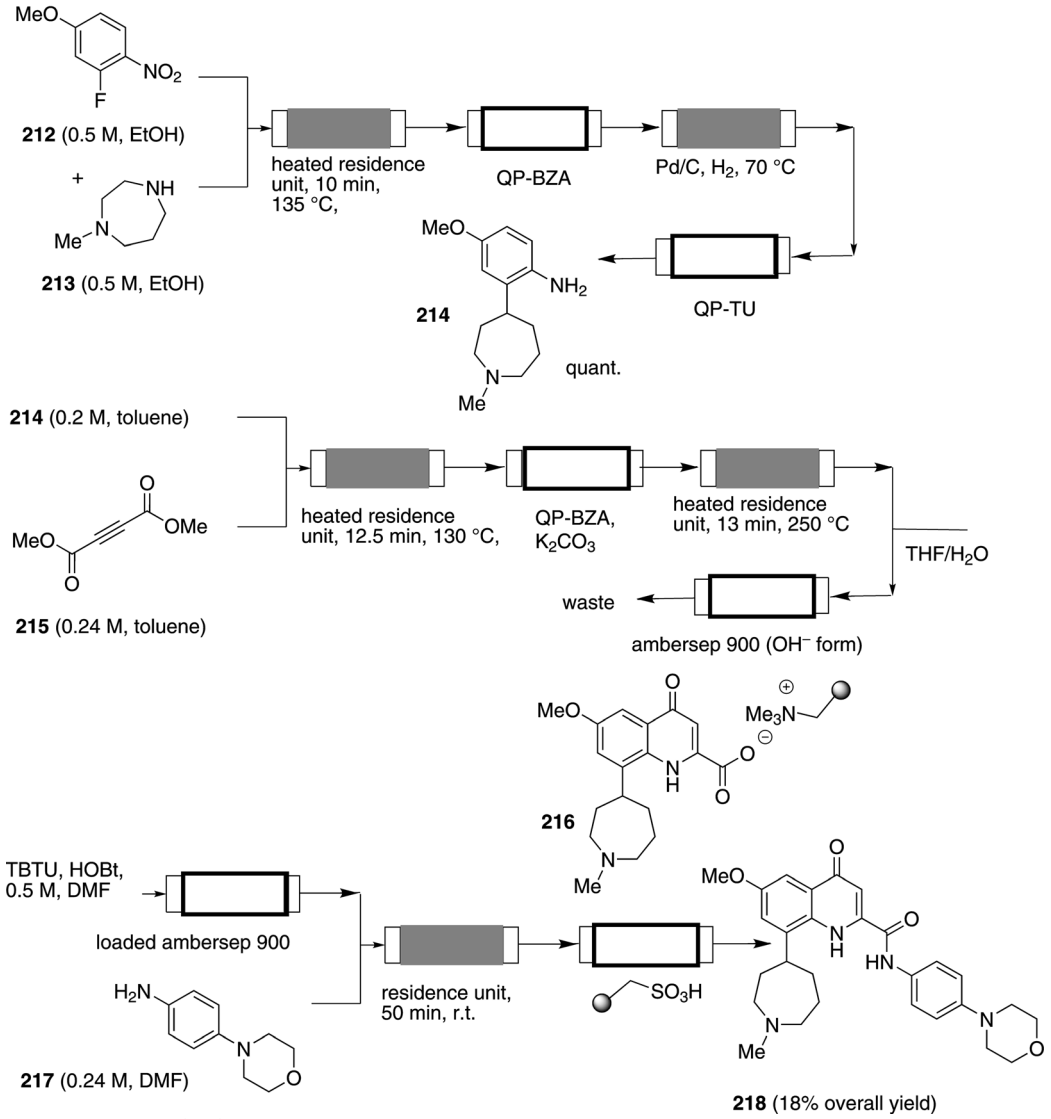


Scheme 35. Multistep flow synthesis of **211**.

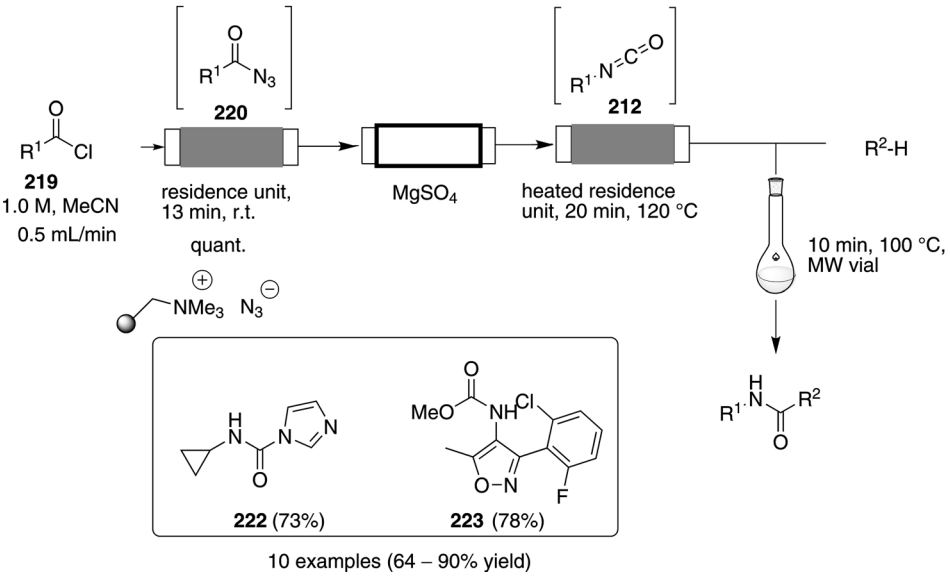
ture. Integrated column chromatography had to be conducted to remove by-products affording the desired compound **211** in 32% yield for the whole sequence.

The synthesis of quinolone derivative (*rac*)-**218**, which acts as a $5HT_{1B}$ antagonist, was also achieved in a multistep flow sequence (Scheme 36).[73] The synthesis commenced from commercially available nitroarene **212** and diamine **213** which were transformed by a nucleophilic aromatic substitution and a reduction step into **214** making use of a scavenging protocol. At this stage the solvent had to be changed from ethanol to toluene which required a simple isolation step. Next, **214** was reacted with alkyne **215** and cyclized to the intermediate product **216** that was trapped on a basic resin. The synthesis was completed by an amide coupling to provide the final compound **218** in 18% yield over six steps without the need for any additional purification.

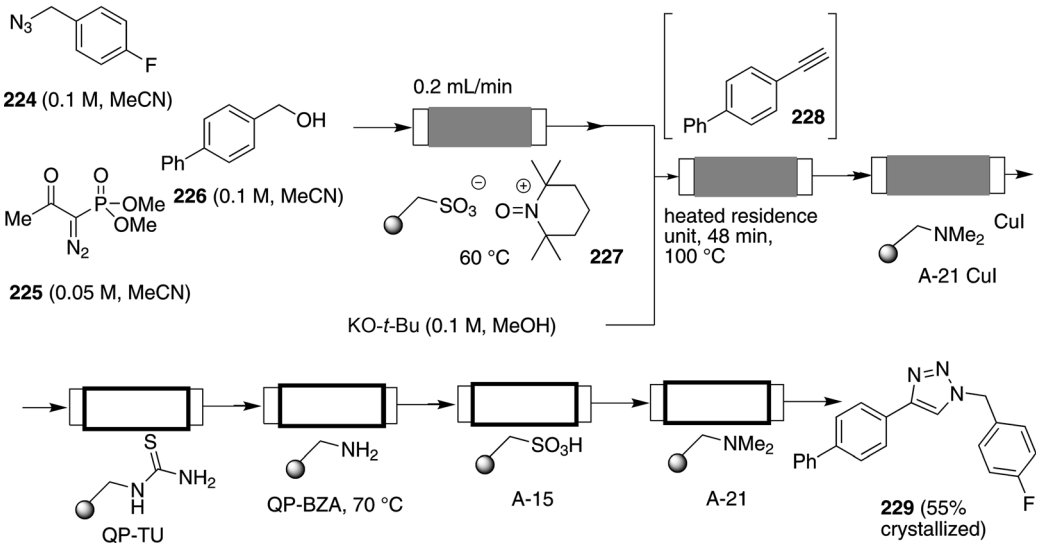
Multistep flow synthesis is ideally suited for generating medicinally relevant libraries of selected compound scaffolds. Thus, different urea or carbamate derivatives can be accessed starting from a variety of acyl chlorides **219** in acetonitrile which were pumped through a monolithic column, functionalized with sodium azide (Scheme 37).[74] The resulting acyl azides **220** were formed quantitatively and were subsequently dried using a second cartridge filled with magnesium sulfate. This was crucial as any remaining water would prevent the following step to proceed. The acyl azides underwent Curtius rearrangement by being heated in a convection coil for 20 min. At this stage the product was collected in a microwave vial which already contained suitable nucleophiles. The whole mixture was then heated for 10 min in a microwave chamber to ensure full conversion. The products were isolated as virtually pure materials by simple evaporation of the solvent. Interestingly, the monolith could be refunctionalized several times without any



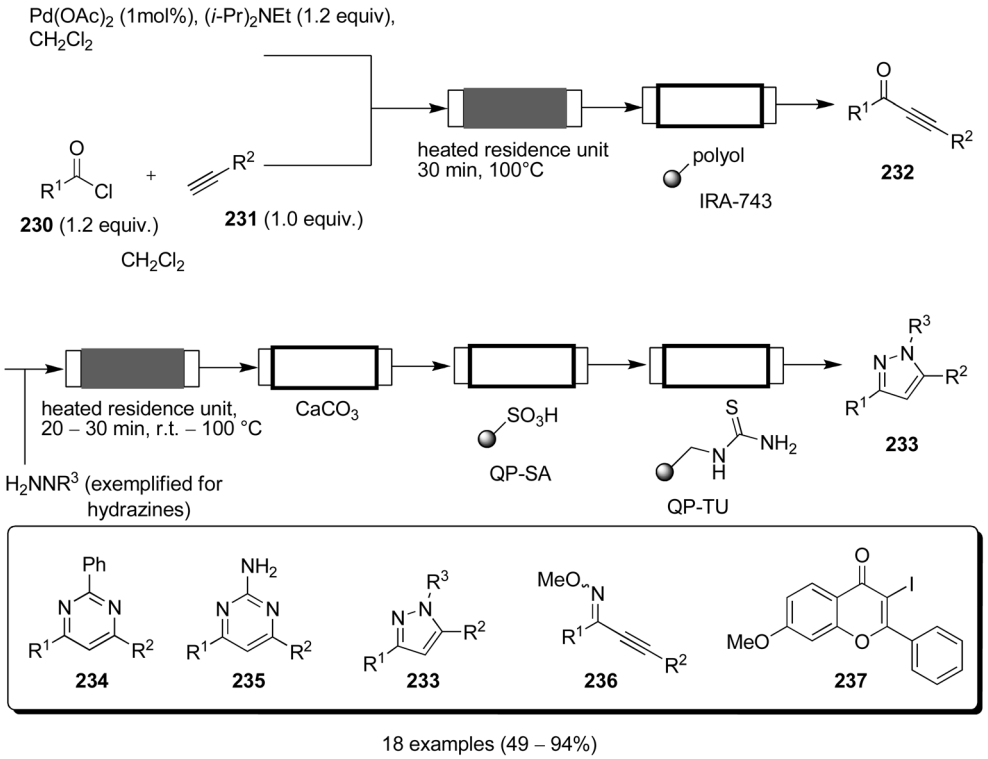
Scheme 36. Flow synthesis of (*rac*)-quinolone derivative **218**.



Scheme 37. The flow synthesis of acyl azides followed by Curtius rearrangement.



Scheme 38. Multistep synthesis of triazole **229** starting from benzyl alcohols **226**, azides **224** and the Bestmann–Ohira reagent **225**.



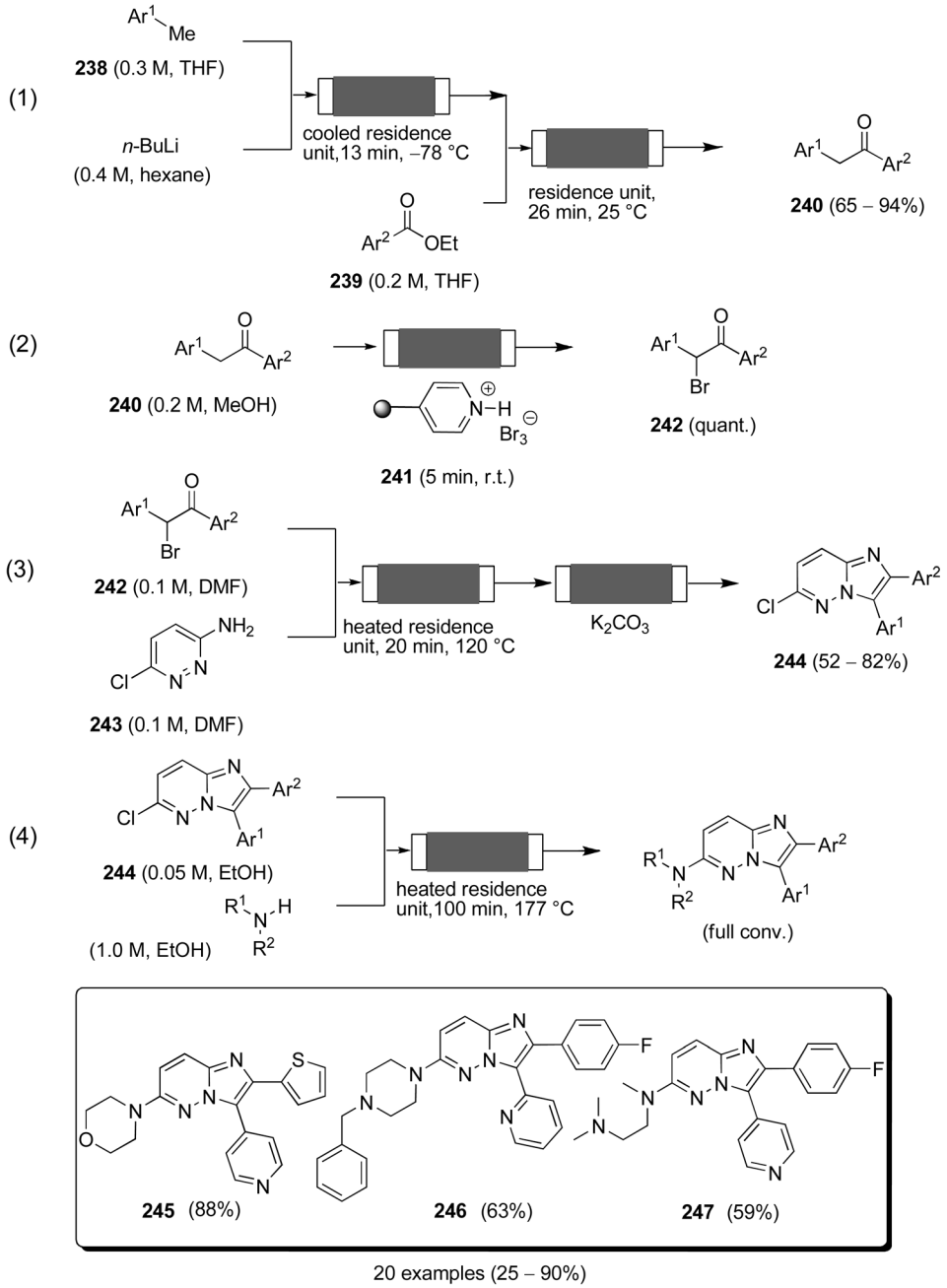
Scheme 39. Synthesis of pyrazoles **233** as well as pyrimidines **234** and **235**, methoxyimino derivatives **236** and chromones **237**.

decrease of activity. Alternatively, the last step can also be conducted in a flow mode.[75] In terms of scalability the preparation of 0.9 mmol of ureas such as **222** or carbamates like **223** was achieved within 1.5 h while acyl azides **220** were obtained on a 30-mmol scale within 1 h.

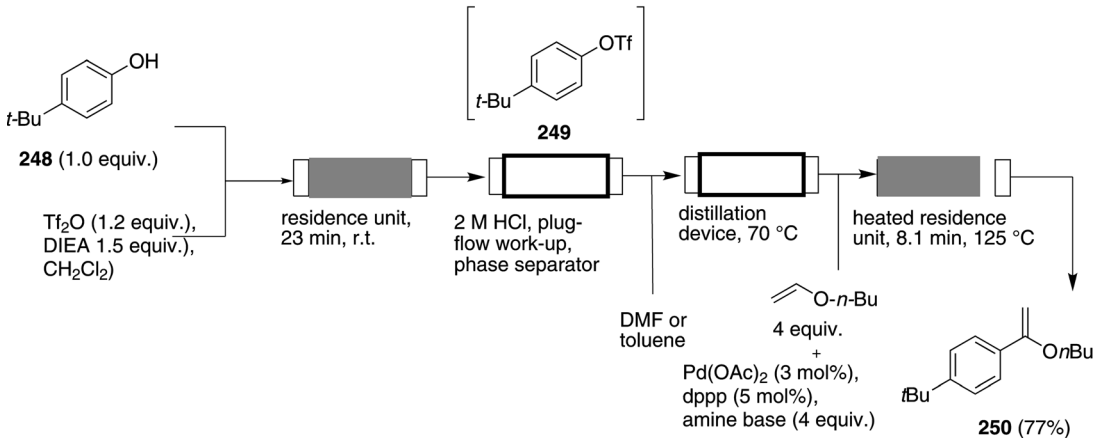
Also triazoles have been accessed by a multistep flow protocol (Scheme 38).[76] The required alkynes were obtained from readily available aldehydes that were reacted with the Bestmann–Ohira reagent (**225**). Thus, aryl azide **224** and benzyl alcohol **226** in acetonitrile were flushed as a mixture through an Omnifit column filled with immobilized TEMPO **227** resulting in the oxidation to the required aldehyde. Triazole formation was achieved in a third cartridge that contained a copper source. Purification of **229** was ach-

ieved with different in-line scavenger columns to afford the final product in 55% yield and 95% purity. In essence, the work describes the synthesis of one triazole **229** as well as a small variety of alkynes using preformed aldehydes.

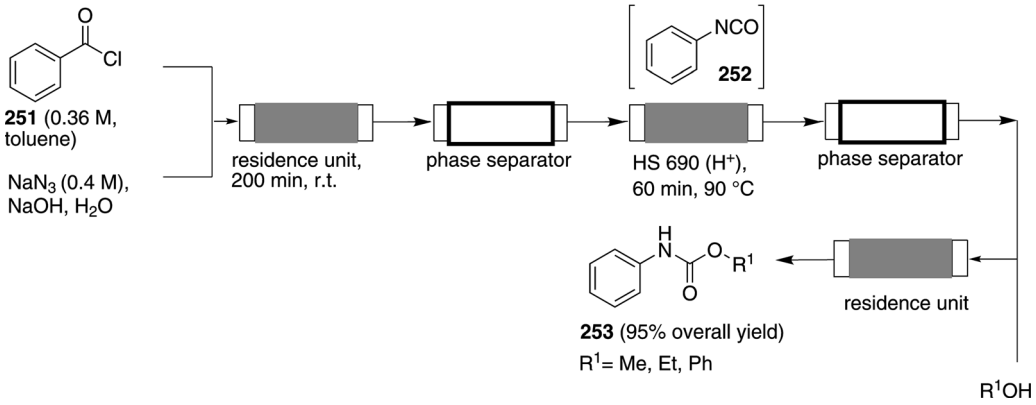
Very recently a convenient and efficient synthesis of ynones **232** and their further application in the synthesis of heterocycles was reported (Scheme 39).[77] Ynones were obtained by the palladium-catalyzed coupling of acyl chlorides with terminal alkynes in 63–95% isolated yield. In the following, hydrazines, hydroximes, benzamidines or iodine choride were added to the stream that afforded the corresponding heterocyles (pyrimidines, pyrazoles, methoxyimino derivaties and chromones). By-products were removed by a complex scavenging protocol. With IRA-743 any excess of acyl chloride was trapped, calcium carbonate deprotonated the ammonium salts and removed the evolving HCl, the QP-SA led to protonation and salt formation of the remaining bases and finally, QP-TU removed any metal impurities. Final purification consisted either of simple removal of the solvent or of an aqueous work-up.



Scheme 40. Preparation of a small library of imidazo[1,2-*b*]pyridazines by multistep flow synthesis.



Scheme 41. Heck reaction with continuous solvent switch.

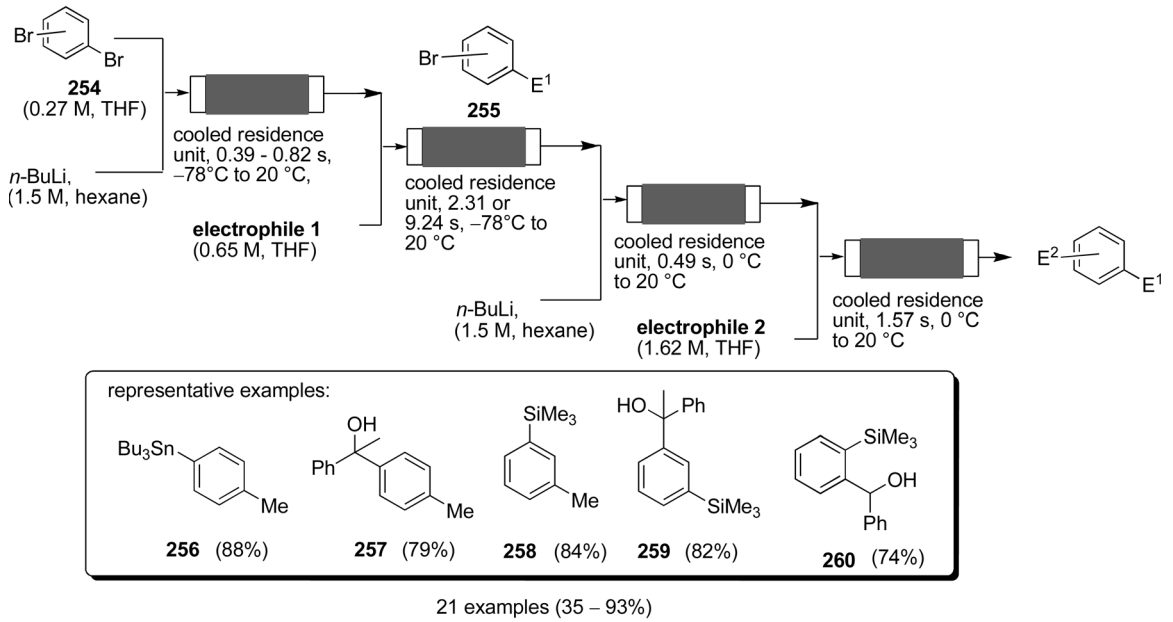


Scheme 42. Curtius rearrangement with in-line work-up.

Multistep flow syntheses also served to produce a library of differently substituted imidazo[1,2-*b*]pyridazines which are potential casein kinase I inhibitors (Scheme 40).[78] The synthesis started with the formation of benzyl anions from toluene precursors **238** and subsequent reaction with esters **239**. Here, a custom-made two-loop injection system served to transfer the organometallic species over an extended time. After warming to room temperature in a second reactor the ketones **240** were directly isolated by precipitation. These ketones were subjected to a second flow system for α-bromination using immobilized hydrobromide perbromide **241** since, in previous experiments, the use of elemental bromine did not provide the desired α-bromo ketones **242** in good purity. Advantageously, by employing the functionalized polymer dibromination could be avoided after careful adjustment of the flow rate. Next, a classical condensation using aminopyridazines **243** led to the desired imidazo[1,2-*b*]pyridazine **244** framework in 82% yield (10-mmol scale). The final step consisted of a nucleophilic aromatic substitution at elevated temperatures to fully convert the chlorides into the aminoimidazo[1,2-*b*]pyridazines **245**–**247**. Final isolation and purification was either achieved by direct removal of the solvent or by a catch and release protocol with solid-phase bound sulfonic acid.

Commonly, the yields for the flow protocols were higher compared to the corresponding batch reactions. Although the transformations were not conducted in a strictly linear multistep sense, this is a telling example how technical adjustments and thorough optimization of conditions may lead to improved efficiency and variety in flow synthesis. Other related examples for multistep syntheses under flow conditions include the formation of peptides,[79] the use of in-line IR analysis for sugar synthesis[80] and the use of tagged phosphine reagents.[81] But these aspects are not covered in this review.

Jensen and co-workers[82] developed a two-step protocol for the Heck reaction by combining phenol activation with the Pd-catalyzed cross-coupling (Scheme 41). Phenol **248** was first transformed into the corresponding triflate ester **249** and subsequently coupled with *n*-butyl vinyl ether using micro and membrane flow reactors. The main topic of their stud-

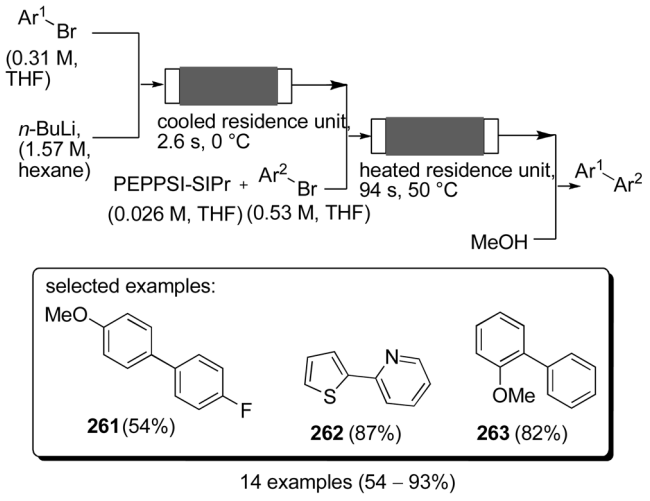


Scheme 43. Continuous double functionalization of dibromoarenes.

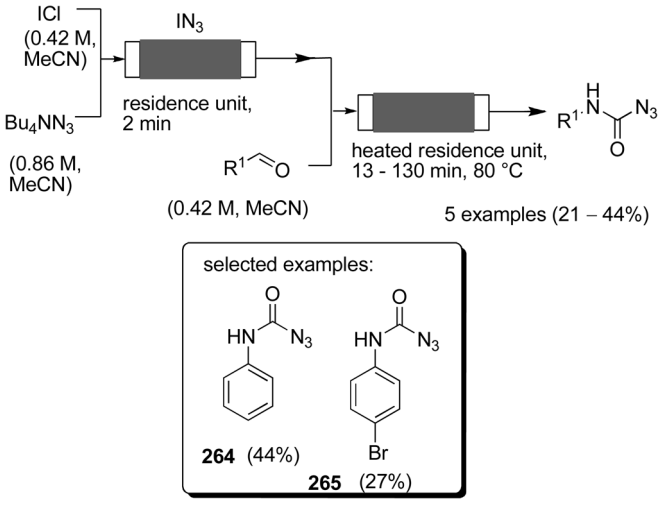
ies dealt with the integration of work-up devices. The membrane reactor was operated in a plug-flow mode so that an aqueous work-up could be integrated. A continuous micro distillation device was developed for this synthesis which allowed carrying out the solvent switch from dichloromethane to DMF or toluene required to perform the Heck reaction. This distillation device was heated to 70 °C thereby removing dichloromethane from the liquid phase through a PTFE membrane.

The same phase separators were used to enable in-line work-up for the preparation of three carbamates by the Curtius rearrangement (Scheme 42).[83] Firstly, an acyl chloride was transformed into the corresponding acyl azide which was followed by an integrated aqueous work-up. Upon heating of the solution the Curtius rearrangement took place and in a second separation step the evolving nitrogen gas was released. Finally, reaction with three different alcohols furnished the final products. The continuous operation allowed the authors to prepare 80–120 mg of product per day.

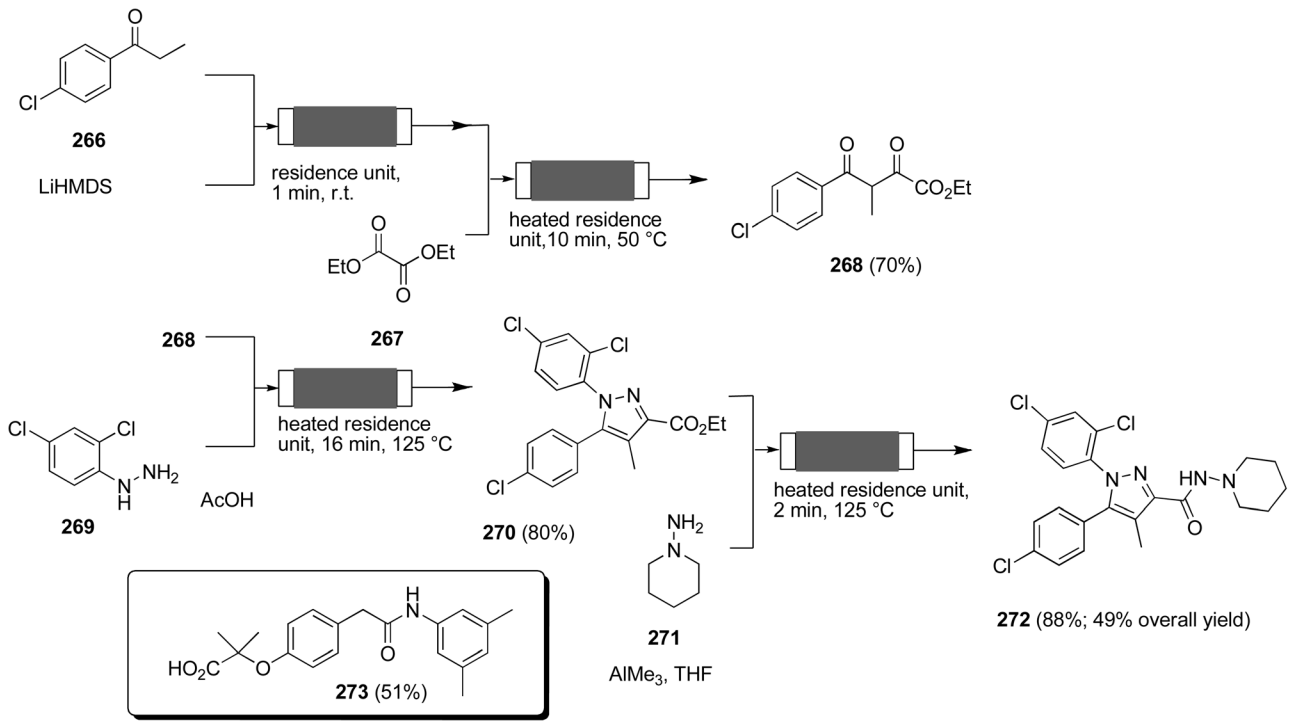
Yoshida and his group can be regarded as one of the pioneers in the field of organometallic reactions using microreactors.[84] For example, cooled tube reactors (ID: 1.0 mm) effect the orthogonal functionalization of different dibromobenzenes (Scheme 43). In the first step a bromine/lithium exchange took place



Scheme 44. Continuous preparation of biarenes **261–263** *via* aryllithium intermediates.



Scheme 45. Generation of iodine azide under flow conditions and Curtius rearrangement.

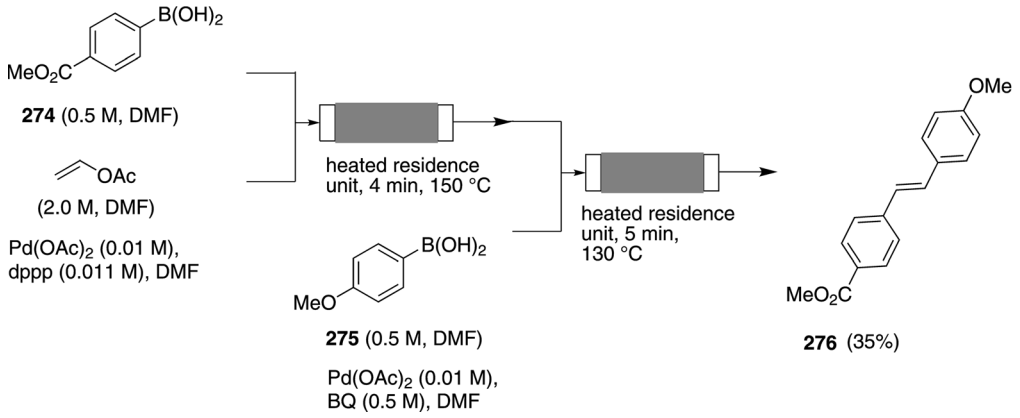


Scheme 46. Multistep flow synthesis of rimonabant **272** and efaproxiral **273**.

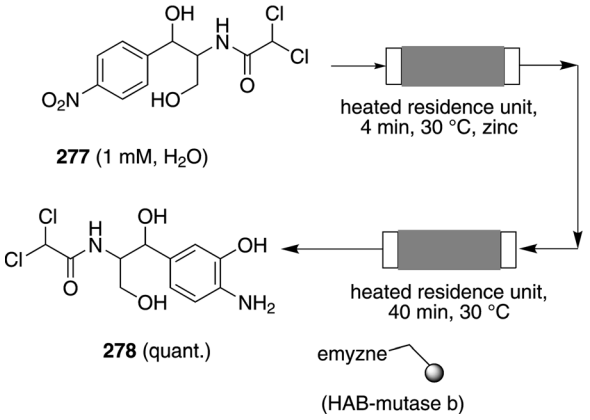
and this highly reactive intermediate was immediately reacted with an appropriate nucleophile. The second step repeated the first one in the sense that the remaining bromide was lithiated while trapping with a second nucleophile took place thereby introducing two functional groups during one continuous process. Importantly, all synthetic steps were conducted at room temperature unlike batch conditions that commonly require temperatures well below 0 °C. The authors noted that a high flow rate and small channel dimensions were crucial for optimum results. Unfortunately, all yields were only determined by LC-MS or GC.

More recently, the same group used this technique to prepare several bisarenes by coupling the lithiated arene with a second aryl bromide, palladium-catalyzed under homogeneous conditions (Scheme 44).[85] Again, high flow rates and short residence times are crucial and enabled a high throughput.[86]

Besides organometallic reactions, the Yoshida group also disclosed important studies on the issue of the effective mixing of reagents in microreactor systems. However, a further discussion of these achievements would exceed the scope of this review and the interested reader is guided to the literature.[87] Wirth and co-workers utilized flow systems to generate highly reactive intermediates such as highly explosive and toxic iodine azide in only minute amounts (Scheme 45).[88] IN_3 was generated in the first step by combining streams of iodine chloride and tetra-*n*-bu-



Scheme 47. Continuous-flow vinylation of boronic acids.

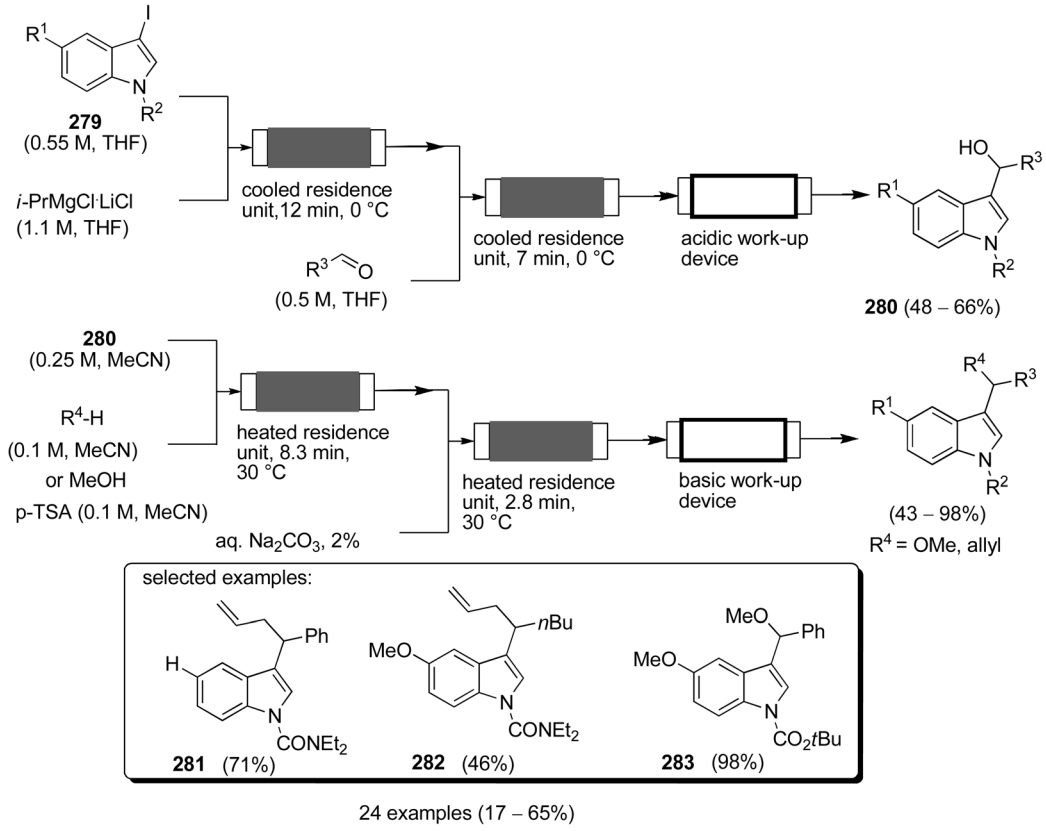


Scheme 48. Continuous preparation of phenolamine **278** from nitroarene **277** by combining metal-mediated reduction with enzyme-catalyzed rearrangement of hydroxylamines.

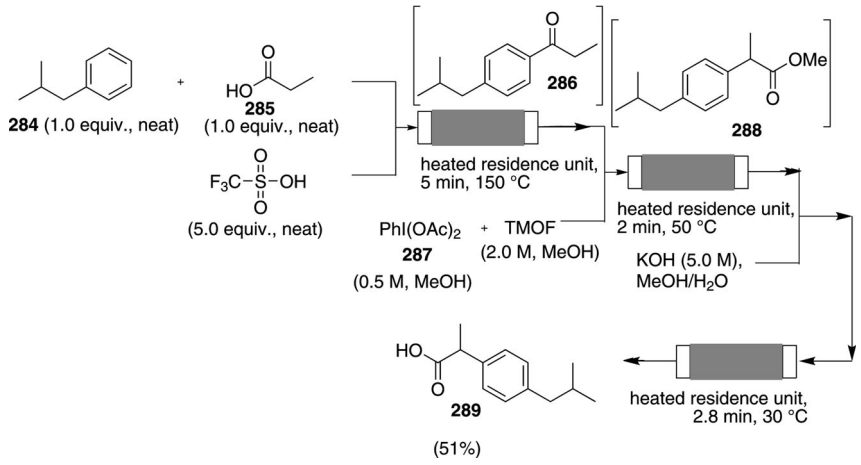
tylammonium azide. This intermediate was then directed towards a third stream containing the appropriate aldehyde which resulted in the formation of isocyanates. These underwent as described in Scheme 37 and Scheme 42 the Curtius rearrangement upon heating. It was demonstrated that common HPLC tubing can be employed as micro reactor channels (ID: 0.25 mm). Although yields were only moderate, it was claimed that the flow reactions generally proceeded more cleanly than the corresponding batch reactions.

Seeberger et al. used PTFE tube reactors (ID: 1.0 mm) to perform the multistep synthesis of rimonabant and efaproxiral (Scheme 46).[89] Initially, the group had optimized the trimethylaluminium-mediated formation of amides that allowed them to shorten the reaction time from 4–16 h for the batch mode down to 2 min for the flow mode. Deprotonation of ketone **266** and C–C coupling with diethyl oxalate **267** gave β-keto ester **268** that, however, had to be purified manually. The second step yielded the pyrazole core **270** from hydrazine which was followed by the trimethylaluminium-mediated amidation to yield rimonabant **272**. In a similar manner efaproxiral **273** was synthesized. The same group also performed multi-peptide couplings using flow reactors, but manual isolation of every intermediate was still necessary.[90]

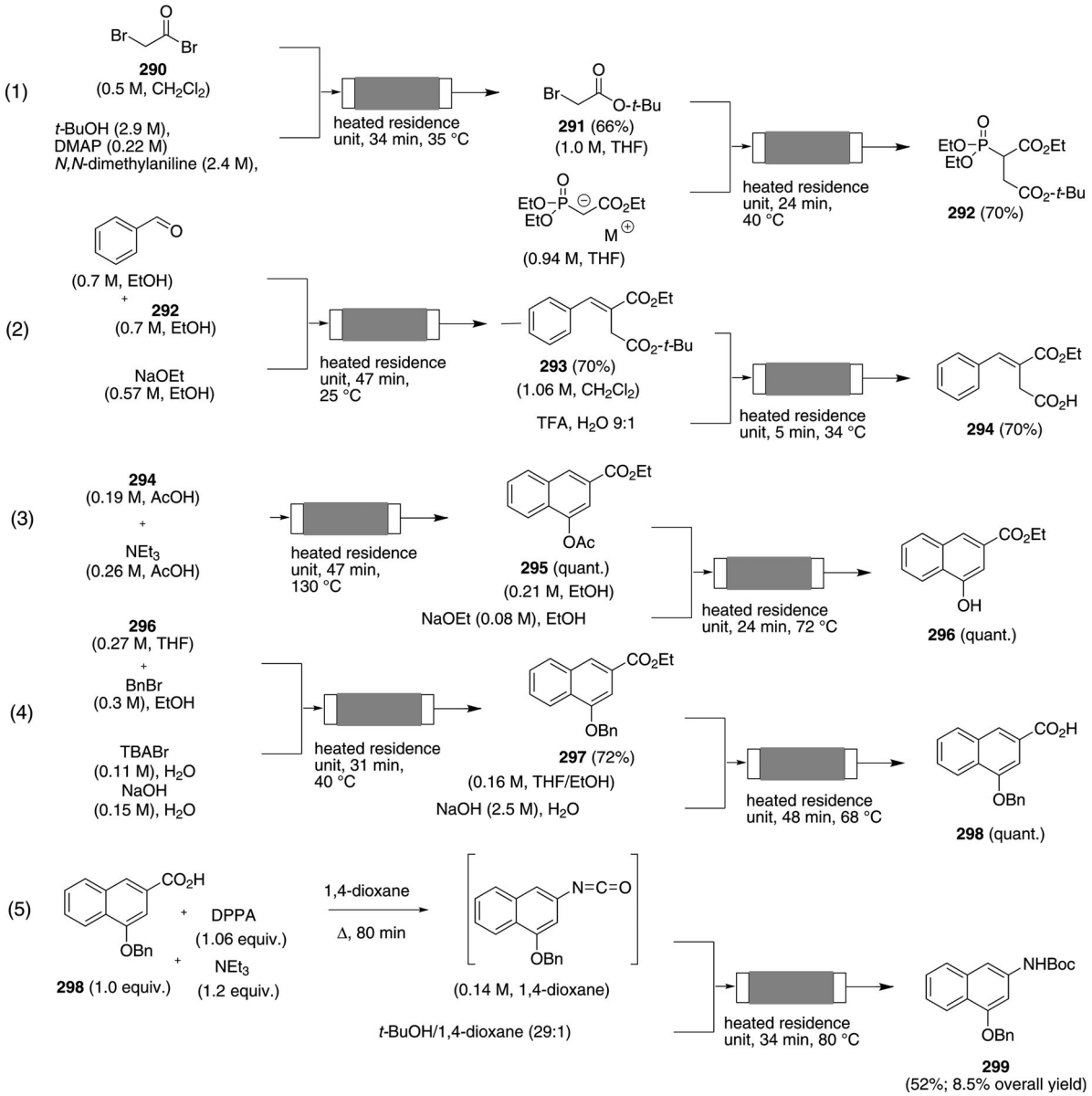
Larhed and co-workers developed the first vinylation for boronic acids **274** in flow reactors and incorporated this reaction in a two-step protocol to yield the disubstituted styrene **276** (Scheme 47).[91] Again, common HPLC tubing (ID: 1.0 mm) served as micro reactor channels that made a scale out of the first reaction to 10 mmol possible.



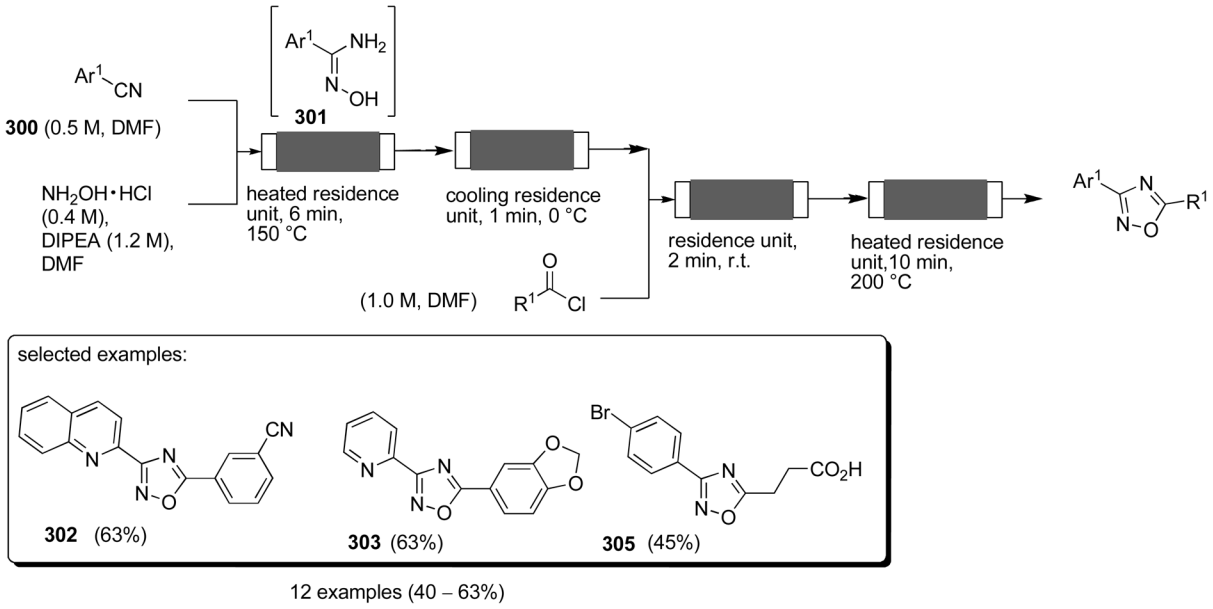
Scheme 49. Multistep functionalization of 3-iodoindole **279** under flow conditions.



Scheme 50. Multistep synthesis of ibuprofen **289** with miniaturized flow equipment.



Scheme 51. Multistep flow synthesis of aminonaphthalenes **299**.



Scheme 52. Synthesis of 1,2,4-oxadiazoles **302–304** using microchip flow devices.

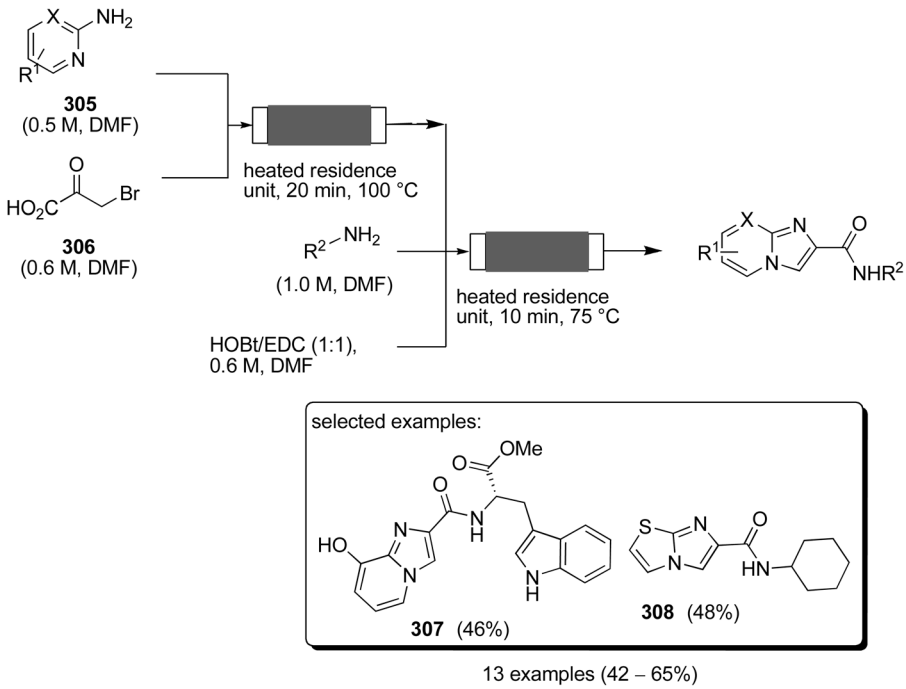
A rather early but nonetheless important two-step flow synthesis relied on packed bed reactors for the synthesis of aminophenols **278** by metal catalysis as well as biocatalysis (Scheme 48).[92] While the first reactor contained zinc necessary to reduce the nitro group in arene **277** to the corresponding hydroxylamine, the second reactor was charged with immobilized HAB mutase b that catalyzed the rearrangement of the intermediate hydroxylamine to the corresponding aminophenol **278**. Remarkably, the flow system was continuously operated for 24 h with a production rate of 0.24 mg h^{-1} per mg protein.

O'Shea et al. utilized glass chip reactors [inner diameter (ID): 0.2 mm] for the two-step synthesis of 3-subsituted indoles (Scheme 49).[93] The study particularly focused on the in-line aqueous purification of the reaction products. Initially, 3-iodoindole **279** was transformed into the corresponding magnesium species which was trapped with an aldehyde in the following step. The acidic work-up was conducted with a liquid-liquid extractor that removed any salts and organometallic impurities. Then, purification of the intermediate product **280** was achieved by transferring it through a short plug of silica. Further functionalization was carried out with acid and an appropriate nucleophile R^4–H. Again in-line purification was conducted followed by manual column purification.

The McQuade group used a simple flow reactor composed of HPLC tubing (ID: 1.0 mm) and tees to achieve the three-step synthesis of ibuprofen (**289**) without purifying intermediates (Scheme 50).[94] The combined streams of neat isobutylbenzene (**284**), propionic acid (**285**) and triflic acid furnished the Friedel–Crafts product **286** after only 5 min (residence time). Upon addition of trimethyl orthoformate (TMOF) and iodosobenzene diacetate (**287**) by a third stream the desired 1,2 aryl migration to **288** was successfully promoted. The final saponification was achieved by merging the acidic product stream with a basic stream. Ibuprofen (**289**) was purified by column chromatography (70%) or simple recrystallization (51%).

A systematic comparison study between batch and flow processes for the preparation of potential anticancer agent precursors based on aminonaphthalenes **299** was executed by Tietze et al (Scheme 51).[95] The synthesis commenced with bromoacetyl bromide **290** and proceeded *via* intermediates **291–298** utilizing the Wittig–Horner olefination, Friedel–Crafts acylation and the Curtius rearrangement. Although every intermediate of the synthesis was isolated and purified manually, this work is an illustrative example for the application of flow chemistry in a complete or fragmented multistep manner and it provides details on how to technically pursue the adjustment of single reactions in a multistep flow system. It also needs to be pointed out that the flow synthesis was accelerated by a factor of 3–10 with similar or even better yields compared to the batch mode sequence.

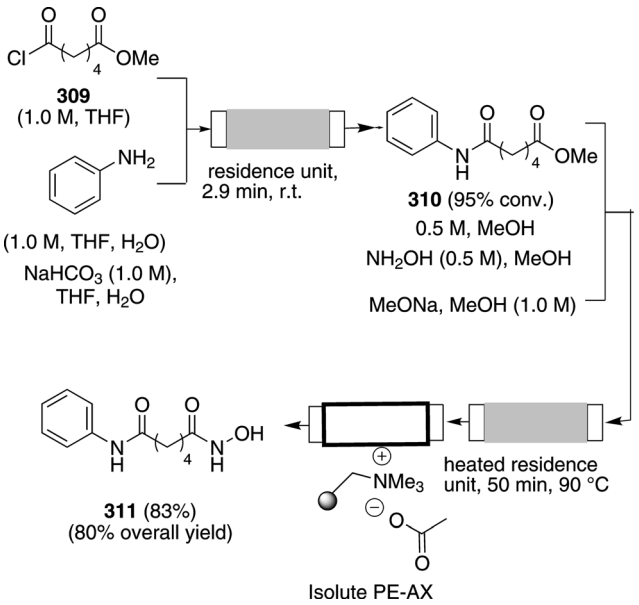
Cosford et al. used micro reactor chips (1000 μL) and HPLC tubes to develop a two-step synthesis of 1,2,4-oxadiazoles (Scheme 52).[96] The study mainly focused on the adjustment of ratios and temperatures and the optimized conditions led to the production of 40–80 mg of **302–304** within 35 min while in a conventional experimental set-up the reaction time was in the range of days. Still, the purification of the final products was based on HPLC.



Scheme 53. Two-step flow synthesis of imidazo[1,2-*a*] heterocycles.

More recently, the same microchip system served to generate a small library of imidazo[1,2-*a*] heterocycles **307**–**308** *via* a two-step protocol starting from 2-aminopyridienes **305** and α-bromoacetic acid (**306**) (Scheme 53).[97] Interestingly, the Mur ligase inhibitor was prepared in 46% yield compared to only 16.4% under batch conditions.

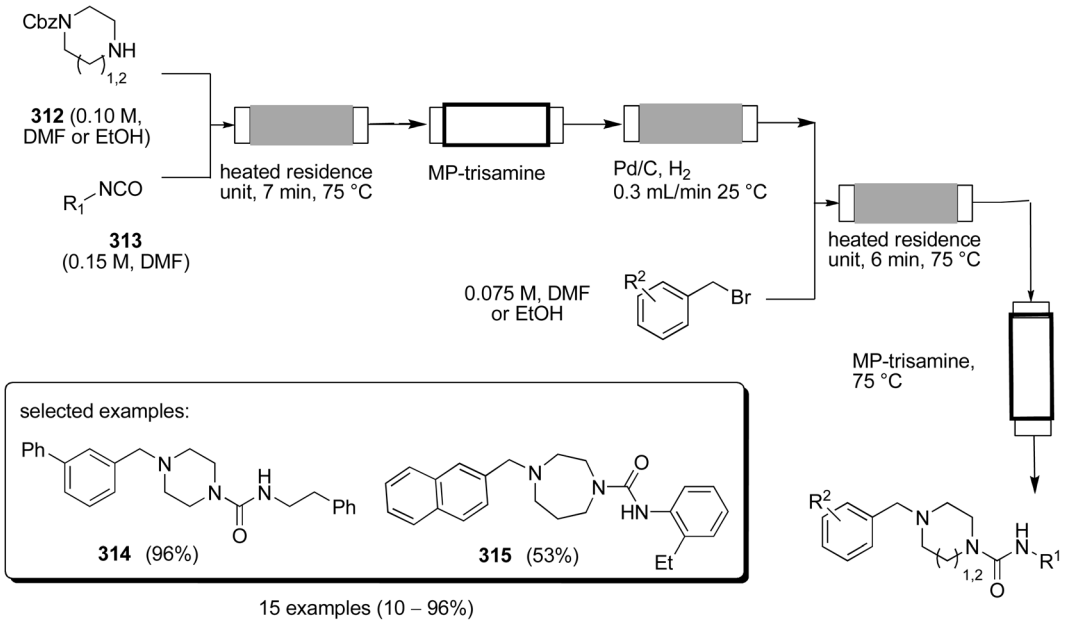
Employing a Vapourtec R2-R4 system with HPLC tubing channels (ID: 1.0 mm) Martinelli et al. developed a flow synthesis of hydroxamic acids **311** starting from the corresponding esters (Scheme 54).[98] It was shown that on average an increase in the isolated yield of about 20% could be achieved compared to the batch mode. Aniline and acid chloride **309** gave amide **310**, which was transformed in the second reactor to the target hydroxyamic acid **311**. By-products such as unreacted carboxylic acid were removed by a packed bed column that contained an immobilized quaternary amine.



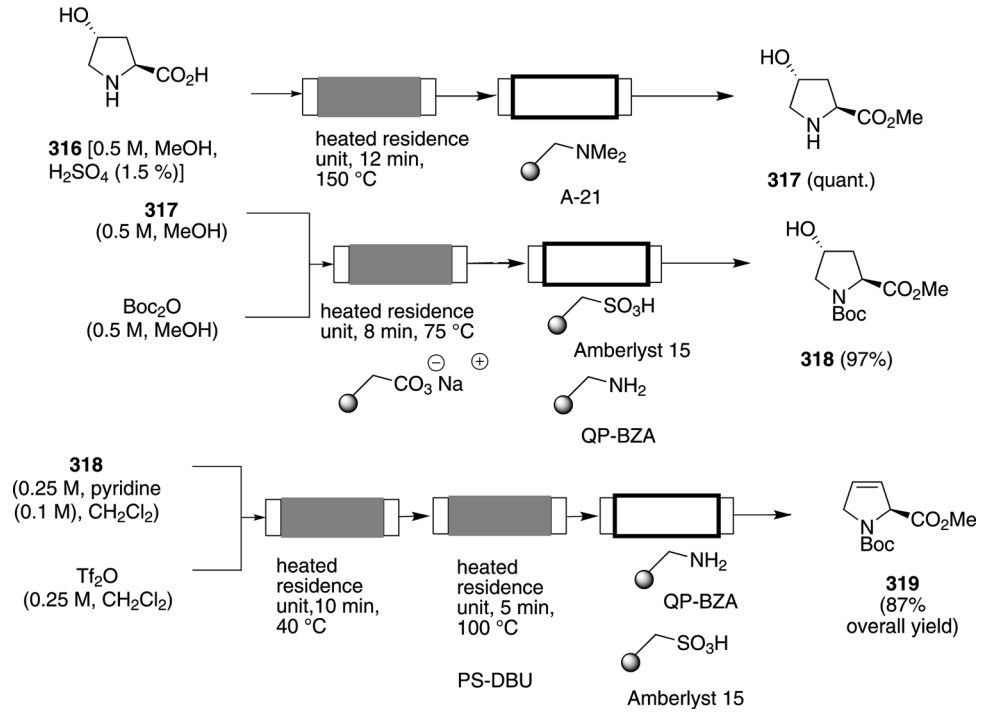
Scheme 54. Two step flow synthesis of hydroxamic acids **311**.

An interesting synthesis of ligand frameworks, for example, for CCR8 receptors was published by Ulven et al. (Scheme 55).[99] Omnifit columns and HPLC tubing (ID: 1.0 mm) served as reactors and were combined for the synthesis of 15 different piperazines after final HPLC purification. The synthesis commenced by combining monoprotected piperazine **312** with isocyanate **313** to yield the corresponding carbamates. Excess of isocyanate was removed by a cartridge that contained an immobilized trisamine reagent. Next, hydrogenation removed the Cbz group and a third stream of benzyl bromide was then combined with the intermediate amine. Finally, a second purification column removed excess of benzyl bromide to yield the target piperazines **314** and **315**.

A four-step synthesis of *N*-Boc-3,4-dehydro-L-proline methyl ester (**319**) was disclosed by Tamborini et al.[100] Starting from L-proline Fisher esterification and subsequent scavenging of unreacted starting material and sulfuric acid furnished pure **317** after evaporation of the solvent (Scheme 56). Then, Boc protection was performed in conjuncton with an in-line scavenging purification step which was followed by



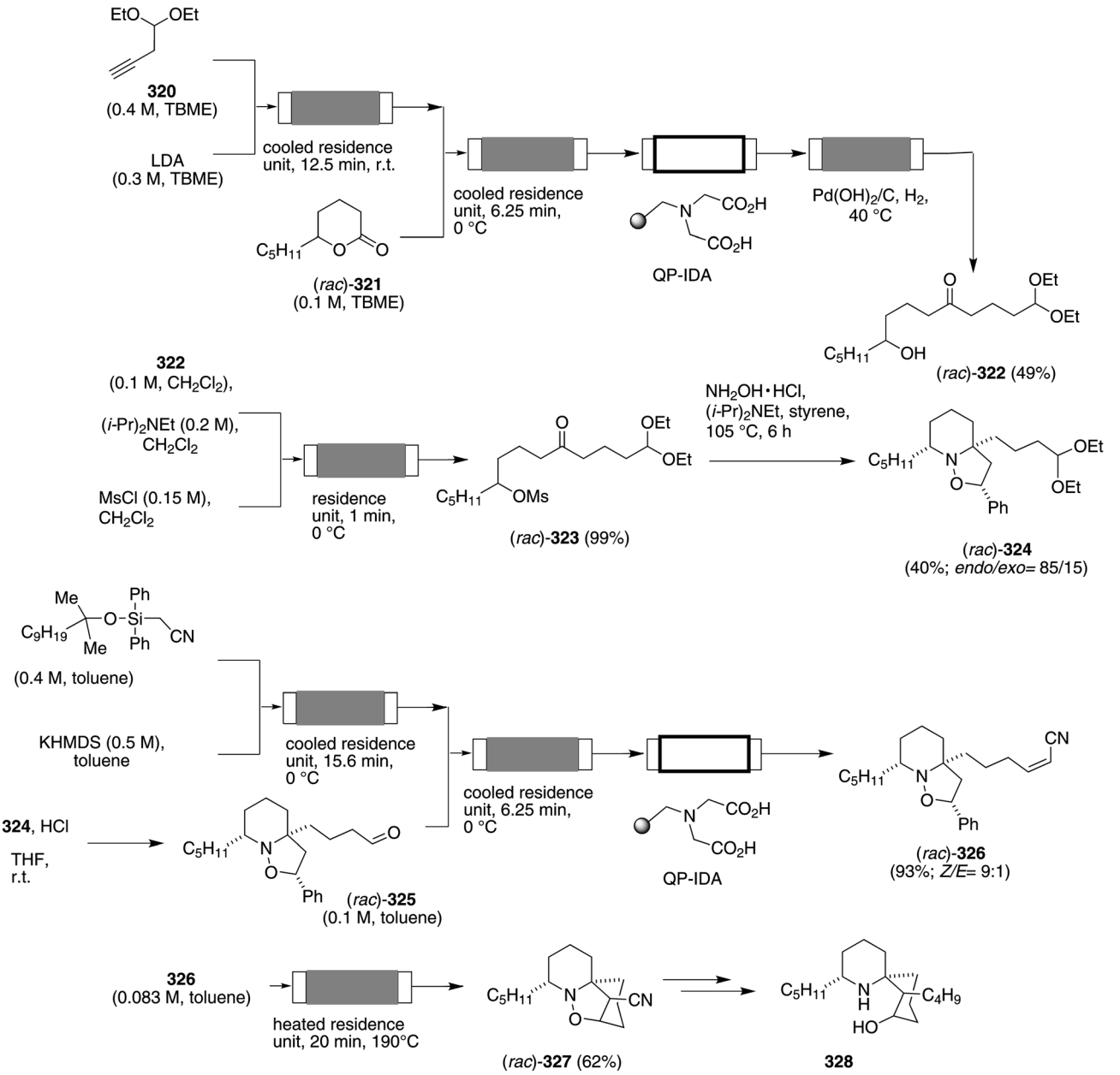
Scheme 55. Mutistep flow synthesis of piperazine derivatives.



Scheme 56. Flow synthesis of Boc-protected 3,4-dehydro-L-proline methyl ester (**319**).

activation of the hydroxy group and elimination to yield the target 3,4-dehydro-L-proline methyl ester **319**. Noteworthy, both transformations required harsher conditions in the batch mode and additionally, racemization was encountered. Again scavenger columns served to remove impurities before the product was collected after removal of the solvent. The authors also demonstrated that the whole process yielded 9 g of the 3,4-dehydro-L-proline derivative within 12 h.

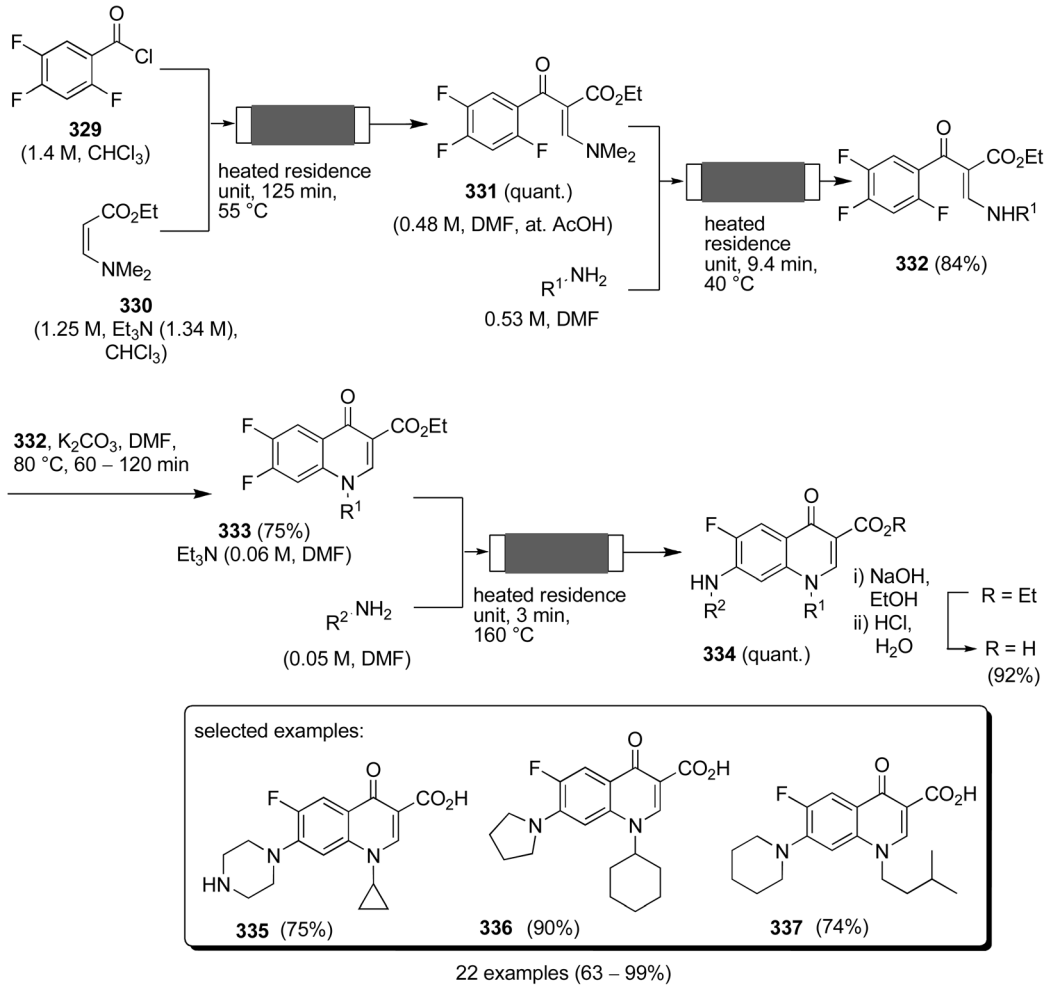
Holmes and his group took full advantage of flow reactors as well as of batch and microwave techniques to produce gram quantities of the natural product (−)-perhydrohistrionicotoxin (**328**) (Scheme 57).[101] A



Scheme 57. Formal total synthesis of *rac*-perhydrohistrionicotoxin (**328**) using flow chemistry.

combination of a Vapourtec R2-R4 device, HPLC tube reactors (ID: 1.5 mm), a continuous hydrogenator and a micro mixer chip was chosen to perform the synthesis. Deprotonation of alkyne **320** was followed by the merger of the lithiated species with a stream of lactone **321** and subsequent hydrogenation of the intermediate alkyne to afford ketone **322** in 49% yield after column chromatography. When performing the alkynylation and the hydrogenation in two separated flow steps the yield could be raised to 80% without the need of chromatographic purification. Next mesylation of the hydroxy group yielded **323** in quantitative yield. As the following microwave-assisted reaction was performed on a large scale in the batch mode this step was not modified for the flow device. The following Peterson olefination was again performed in the flow mode providing the product with good selectivities and yield. Finally, the cycloreversion-cycloaddition step was conducted in a metal coil reactor and furnished racemic **327**. The last three steps were performed under classical batch condition. This work nicely demonstrates that batch and flow steps have to be carefully chosen for each individual step in order to get best results.

Making use of the Cytos microreactor system Schwalbe and co-workers produced a variety of ciprofloxacin derivatives (Scheme 58).[102] Here, the system was operated in the plug-flow mode and every reac-



Scheme 58. Flow synthesis of ciprofloxacin derivatives.

tion was highly optimized with regard to flow rate, temperature and stoichiometries so that only simple aqueous work-up had to be conducted for the purification of each intermediate. Starting from trifluoroarylacyl chloride **329** a Baylis–Hilman-type reaction yielded enone **331**. Next, *ipso*-substitution employing different amines created a variety of possible products. The resulting amino enones **332** were cyclized by nucleophilic aromatic substitution, a step that was repeated in an intermolecular fashion to introduce a second amino substituent at the arene moiety to give **334**. Finally, saponification liberated the carboxylate and gave ciprofloxacin derivatives **335**–**337**. However, it has to be noted that each single step was performed separately. Nevertheless, the authors demonstrated that the sequence can be conducted in preparative relevant scale (e.g., $0.38\,g\,h^{-1}$ for the first step and $1.8\,g\,h^{-1}$ for the last one).

For additional examples of multistep flow syntheses the reader is kindly referred to additional references.[103]

4 Perspectives and Outlook

Despite the tremendous progress in the development of new chemical methodologies over the past decades there is a quest for new enabling technologies and their combination thus allowing us to speed up synthesis and to simplify purification or isolation of the desired products. Furthermore, the time from bench to production, particularly of fine chemicals or pharmaceuticals, is still too long mainly because syntheses developed in the laboratory often cannot be transferred into large-scale production without substantial optimization. Miniaturized flow-through processes are definitely a significant breakthrough towards improved efficiency through automation and process optimization.

In this report we stressed that flow chemistry – being one enabling technology – can ideally be combined with energy input for carrying out endothermic reactions. Energy input may be in the form of heat to create supercritical conditions or alternatively radia-

tion to carry out photochemical reactions in a highly practical and scalable manner.

A second unique aspect of flow chemistry compared to batch chemistry is associated with the option to carry out multistep synthesis by designing a flow set-up composed of several flow reactors. Besides their role as chemical reactors these can act as elements for purification or solvent switch as particularly was demonstrated by the groups of Ley, Yoshida and Jensen.

Many aspects of synthesis can be handled with flow devices: (i) synthesis of a few milligrams of a compound required in drug discovery, (ii) the synthesis of building blocks in multigram scale for parallel synthesis, (iii) the preparation of kilogram quantities for clinical research and even (iv) the production of fine chemicals. Importantly, flow devices are a crucial link between bench chemists and process engineers.

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