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Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients

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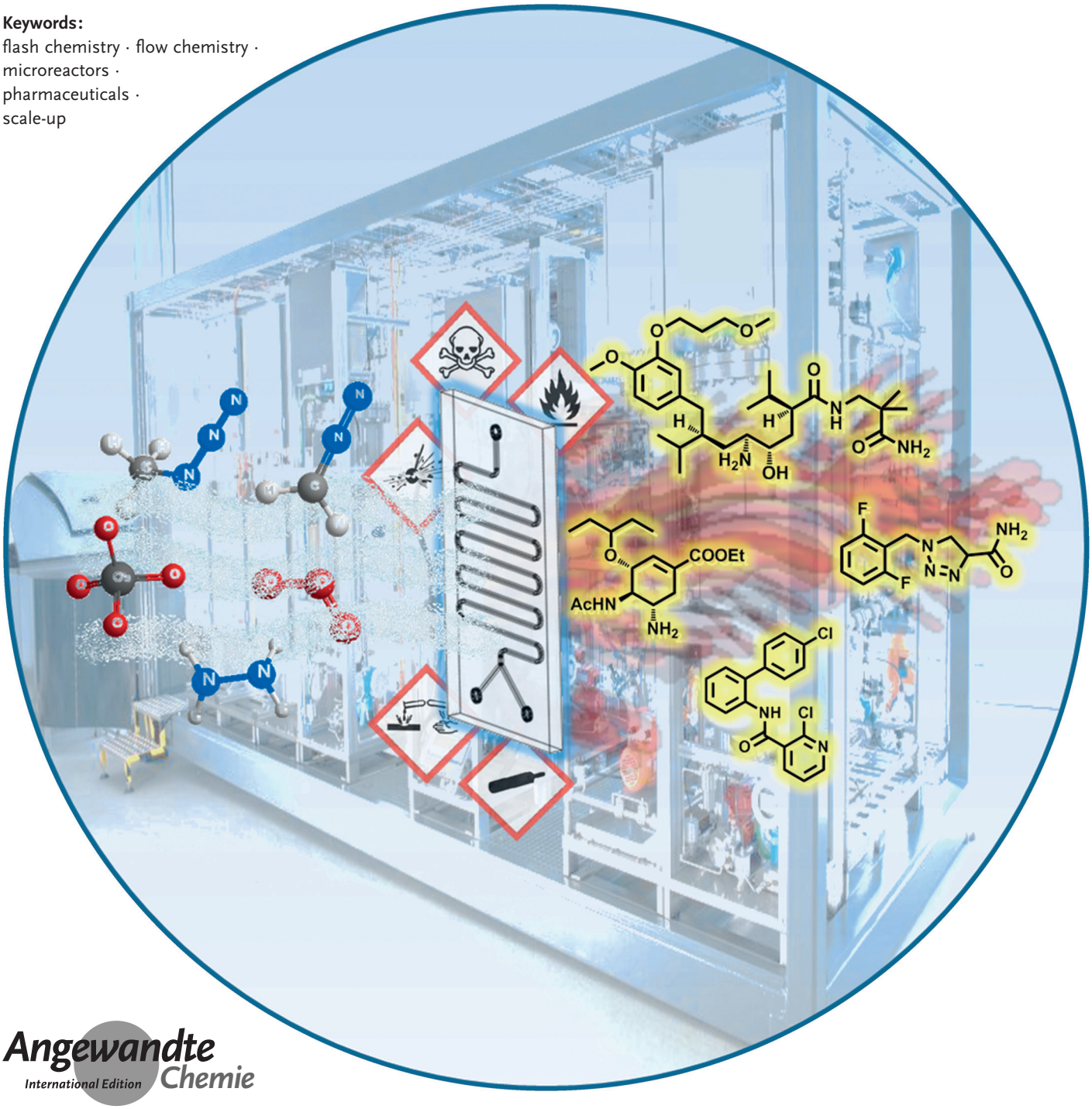

In the past few years, continuous-flow reactors with channel dimensions in the micro- or millimeter region have found widespread application in organic synthesis. The characteristic properties of these reactors are their exceptionally fast heat and mass transfer. In microstructured devices of this type, virtually instantaneous mixing can be achieved for all but the fastest reactions. Similarly, the accumulation of heat, formation of hot spots, and dangers of thermal runaways can be prevented. As a result of the small reactor volumes, the overall safety of the process is significantly improved, even when harsh reaction conditions are used. Thus, microreactor technology offers a unique way to perform ultrafast, exothermic reactions, and allows the execution of reactions which proceed via highly unstable or even explosive intermediates. This Review discusses recent literature examples of continuous-flow organic synthesis where hazardous reactions or extreme process windows have been employed, with a focus on applications of relevance to the preparation of pharmaceuticals.

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1. Introduction

Continuous-flow processes form the basis of the petrochemical and bulk chemicals industry, where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for high-performing, cost-effective, safe, and atom-efficient chemical operations. In contrast to the chemical industry which produces commodity products, however, the fine-chemical industry primarily relies on its existing infrastructure of multipurpose batch or semi-batch reactors. Fine chemicals, such as drug substances and active pharmaceutical ingredients (APIs), are generally considerably more complex than commodity chemicals and usually require numerous, highly diverse reaction steps for their synthesis (typically 6 to 10 synthetic steps) as well as multiple rounds of quenching, separation, and purification. These requirements, together with the comparatively low production volumes and often short life time of many of these materials, make versatile and reconfigurable multipurpose batch reactors the technology of choice for their preparation. However, the advantages of continuous-flow processing are also increasingly appreciated by the pharmaceutical industry and, thus, a growing number of scientists—from research chemists in academia to process chemists and chemical engineers in pharmaceutical companies—are now starting to employ continuous-flow technologies on a more routine basis.[1–7] An intriguing recent example of industrial importance is the development of a continuous end-to-end manufacturing plant for the preparation of Aliskiren by the Novartis-MIT Center for Continuous Manufacturing.[8] All intermediate synthetic steps, separations, crystallizations, drying, and formulation to the final pharmaceutical product were performed in one integrated, fully continuous process.[8]

Drug development typically starts with milligrams or a few grams of material for primary testing, but the production then quickly scales to tens of grams for early in vivo toxicity studies to hundreds of grams for further toxicology studies. If the compound progresses, kilograms of material are required for clinical trials, and several hundreds of tons per year are produced of a successful pharmaceutical product. Such scale-up over many orders of magnitude is clearly not trivial, and the better and more scalable the initial synthetic route, the faster these quantities can be delivered. Scaling is generally considerably easier for a continuous process than for a batch process, and flow routes developed and optimized in the laboratory often can be scaled to production quantities with minimal reoptimization and/or without major changes in the synthetic path.[6] Numbering-up of flow devices or scaling-up of the reactor volume increases the throughput, while the performance of the reactor can be largely conserved by keeping certain characteristics of the system constant ("smart dimensioning").[6] Alternatively, simply running a reactor for extended periods of time to generate the desired quantities of pharmaceutical intermediates or final products is often an acceptable strategy. In addition to easier, better defined scale-up routes, continuous-flow production offers distinct advantages in virtually all phases of drug development—from drug discovery up to the manufacturing process.[1,2,9] Small-diameter flow reactors (e.g. microreactors) offer unique transport capabilities for matter and energy because of their high surface area to volume ratios and inherently small reactor volumes.[3] Thus, heat can be applied and removed efficiently, allowing exquisite control of the reaction temperature.[3] The stability of small-diameter capillary reactors to high pressure enables access to safe operation at high temperatures.[10,11] The increased reaction rate at high temperatures, in turn, increases productivity and reduces the footprint of the equipment, thus leading to a more

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cost-effective overall process (i.e. process intensification).[10,12] In addition, automation and in-line monitoring improves the quality and uniformity of the products.[13]

Importantly, the exceptional heat-exchange efficiency of microreactors suppresses the formation of hot spots, temperature gradients, or accumulation of heat, and a concomitant decrease in reaction selectivity, even for fast and highly exothermic reactions.[3,4] Furthermore, the excellent heat- and mass-transfer characteristics of microreactors, together with the fact that the reaction is resolved along the length of the reaction channel, enables precise control of the residence time of intermediates or products, sometimes down to the microsecond level, by a thermal or chemical quench of the solution (Figure 1).[14] Syntheses that were previously "forbidden" for safety reasons, or even reactions simply not possible in batch, are thus manageable with relatively low risk.[14] Unstable or otherwise hazardous synthetic intermediates can be generated in situ inside a closed, pressurized system and converted directly into a more advanced, non-hazardous intermediate or product by combining multiple reagent streams.[3,4] Similarly, the reaction temperature can be changed rapidly along the reactor channel. This allows uninterrupted, continuous multistep reactions to be performed and eliminates the need to handle or store excessive amounts of potentially toxic, reactive, or explosive intermediates.[15] Since the actual reaction volumes in a microreactor/flow device are very small, safety concerns associated with hazardous reagents are further minimized. Moreover, the fraction of gas volume in a pressurized liquid-filled system is significantly reduced. This is crucial to avoid evaporation of low-boiling reagents or formation of explosive gas mixtures. The miniaturization, furthermore, has an immediate effect on radical chain reactions and the propagation of explosions is suppressed.[16] The application of flow/microreactors can thus drastically expand the safe operation range of current processes into what would conventionally be defined as a runaway or explosive regime.[10,17]

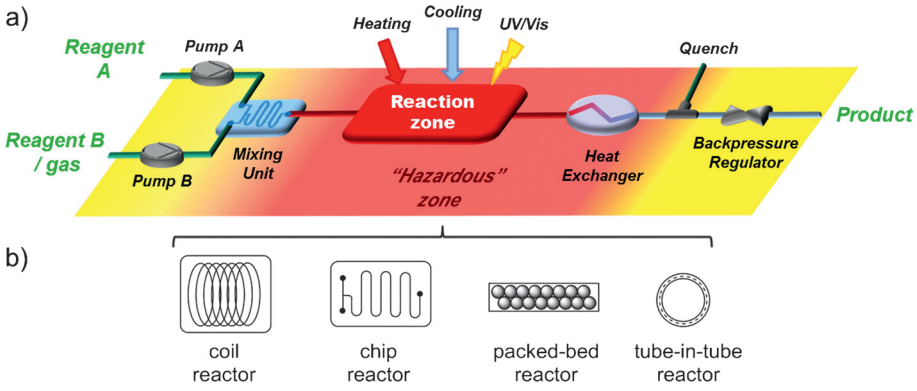

Figure 1. a) General concept of flow chemistry using microreactors. Reagents can be combined at precisely specified points along the reactor (residence time), heated, cooled, and quenched. The pressure resistance and high heat exchange efficiency allows high-temperature operation in superheated solvents. b) Graphical representation of continuous-flow reactors used in this Review.

Ultimately, the main objective in the design of every chemical process is to eliminate safety concerns by avoiding hazardous reaction conditions and by minimizing the use or generation of hazardous substances while, at the same time, preserving or maximizing the efficiency.[18] In many cases, however, the use of reaction conditions or reagents conventionally considered to be too hazardous can help considerably to reduce the reaction time and/or the number of reaction steps. In fact, the most time- and atom-efficient routes frequently demand the use of highly reactive, often low-molecular-weight, compounds or of otherwise problematic reaction conditions (e.g. very low or very high temperatures and pressures). For many decades, this chemistry was effectively excluded from the synthetic arsenal of organic chemists (in particular, on a larger scale), and costly and long alternative routes were chosen instead. With the advent of new technologies, the performance and safety envelope of chemistry expands and conventional definitions of "hazardous" or "harsh" reaction conditions are challenged.[17] In this Review we highlight recent literature examples of reactions that use extremely hazardous materials and/or process conditions in a continuous-flow mode, in particular when they relate to the manufacturing of

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David Cantillo obtained his PhD from the University of Extremadura, Spain in 2011. His PhD focused on the experimental and theoretical study of 1,3-dipolar cycloadditions of mesoionic compounds. During this time, he had short stays at the University of Graz, Austria, with Prof. C. Oliver Kappe and the Thompsons Rivers University, Canada, with Dr. Mora-Diez. In 2011 he joined the group of Prof. Kappe at the University of Graz as a postdoctoral associate, where he researches on continuous-flow processes and process intensification.

active pharmaceutical ingredients (APIs) or other important synthetic intermediates and transformations.

2. Hazardous Chemistry and Processes

In this Review we consider recently published flow processes which would be difficult or nearly impossible to perform safely and reliably in traditional batch equipment (Figure 2). These are generally reactions which require very careful control of process conditions to achieve robust chemical yields and selectivity. This clearly includes very fast, exothermic reactions, which might be limited by heat and/or mass transfer, and reactions involving highly unstable or explosive reactants or intermediates. Furthermore, it encompasses reactions performed at significantly elevated temperatures and/or pressures. Even though high-temperature operation in autoclave-type reactors has become a standard technique in chemical laboratories for milliliter-scale screening and optimization reactions, the transfer of these conditions to production scale in batch reactors might be lengthy and difficult.

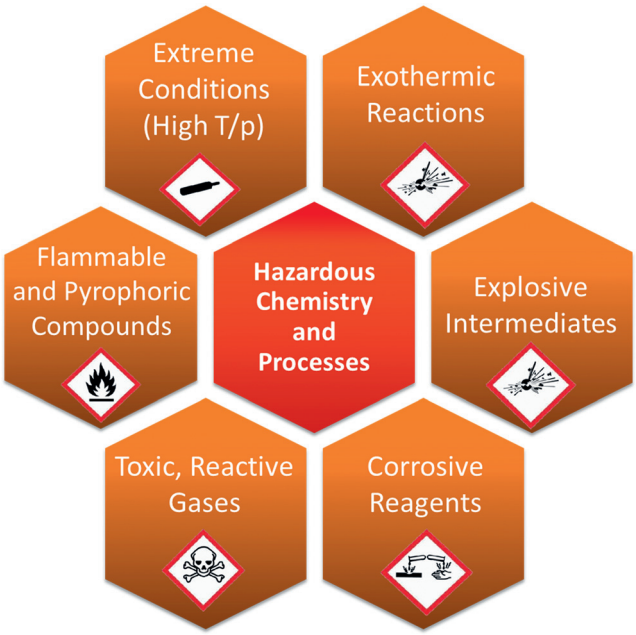


Figure 2. Hazardous chemistry and processes.

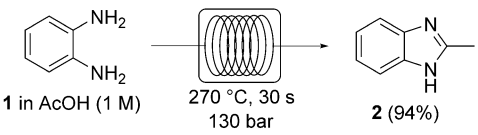
C. Oliver Kappe studied at the University of Graz with Prof. Gert Kollenz. After postdoctoral research with Prof. Curt Wentrup at the University of Queensland and with Professor Albert Padwa at Emory University, he moved back to the University of Graz in 1996 to start his independent academic career. In 1999 he became Associate Professor and in 2011 was appointed Full Professor for "Technology of Organic Synthesis". His research interests involve continuous-flow chemistry, API manufacturing, and process intensification technologies. Since 2011 he has been Editor-in-Chief of the Journal of Flow Chemistry.

The specific reasons why a particular reaction or process is hazardous and how microreactors can contribute to the overall safety of the process has been outlined in general terms in Section 1 and is further discussed in the individual sections below.

3. Extreme Process Windows

3.1. High-Temperature/High-Pressure Operation

It was not until the end of the 20th Century that autoclaves have become a regularly used apparatus in organic chemistry laboratories. In fact, it was not before the introduction of dedicated microwave reactors that high-temperature/high-pressure (high-T/p) operation (300 °C, 30 bar) has turned into a standard tool in synthetic organic chemistry.[19] Perhaps the main advantage of these microwave reactors, from an organic chemist perspective, is the ease with which reactions at temperatures above the boiling point of the solvent can be performed on a laboratory scale (< 30 mL). However, temperatures above 200 °C are generally outside the operation limits of most standard batch reactors in pharmaceutical manufacturing facilities and large-volume pressure reactors are very massive as well as costly. Flow reactors, on the other hand, can easily mimic the high-T/p capabilities of a batch microwave apparatus on scales up to the production scale.[20] The high-pressure resistance, together with the exceptional mass- and heat-transfer capacity of these devices often allows reactions to be performed with throughputs that are conventionally not possible. In recent years, Hessel and co-workers introduced the notion of "novel process windows", a concept to exploit the characteristics of microstructured reactors to intensify and increase the performance of chemical processes.[10] At the core of this approach is the realization that many chemical reactions can be intrinsically fast if the right conditions are applied and transport limitations are eliminated. An instructive example that highlights these principles is the generation of 2-methylbenzimidazole (**2**) by condensation of *o*-phenylenediamine (**1**) with acetic acid (Scheme 1).[21] A detailed kinetic analysis has shown that this condensation requires about 9 weeks to reach completion at room temperature. The reaction time can be reduced to 5 h near the reflux temperature of acetic acid (ca. 100 °C). The time required to achieve full conversion can be further reduced to 3 min at 200 °C in a sealed vessel



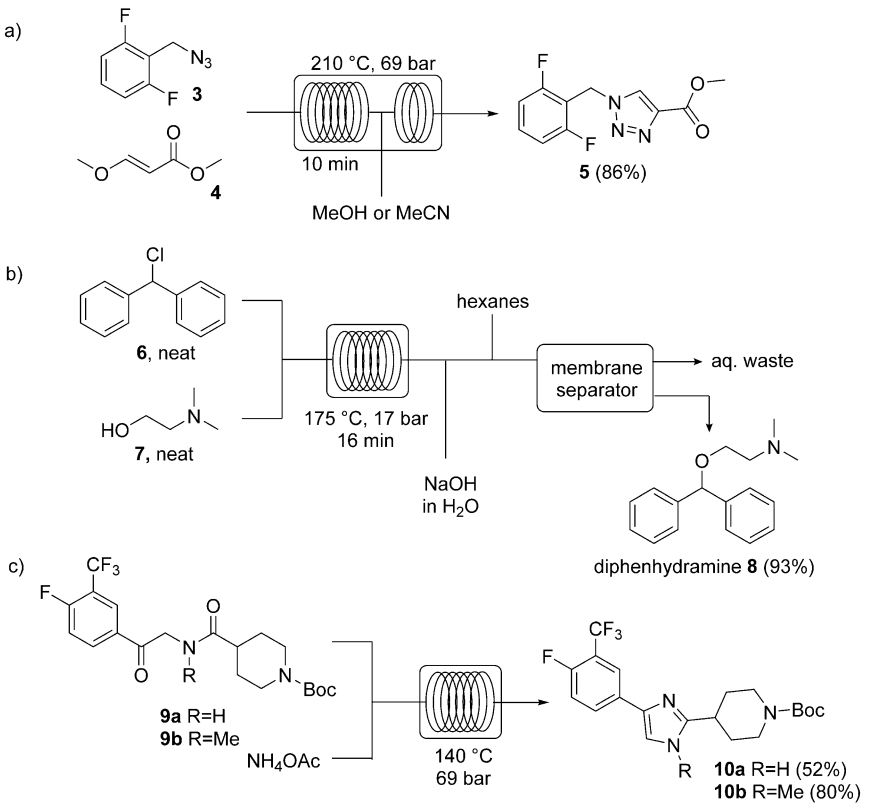
Scheme 1. Condensation of *o*-phenylenediamine with acetic acid under high-T/p continuous-flow conditions.[21]

microwave system, still leading to a clean benzimidazole product **2**.[21] Pushing the reaction to the limits of the high-temperature microwave reactor (270 °C, 29 bar) results in the condensation being so fast that it is difficult to appropriately evaluate the required reaction time, as a full conversion is already attained during the heat-up phase.[21] The reaction was subsequently successfully translated to a continuous process in a compact, bench-top flow reactor to provide benzimidazole **2** with a throughput of 51 g h^{-1} (94 %) in a 4 mL residence loop (Scheme 1).[21] Scale-up of the benzimidazole synthesis to an industrial scale was subsequently realized in a continuous-flow microwave reactor.[22] The reaction mixture was carried in a transparent microwave tube reactor (60 mL) which was heated in the microwave cavity of a 6 kW microwave reactor to 267 °C. The condensation was completed within a residence time of 34 s to give the product in 90 % yield (5 L h^{-1}).[22] Organ and co-workers accomplished the same transformation in a microwave-heated silicon carbide (SiC) tube reactor.[23] SiC is a strongly microwave absorbing, chemically exceedingly inert ceramic material which can be heated to extreme temperatures because of its high melting point (2700 °C) and low thermal expansion coefficient. At a reaction temperature of 313 °C and a back-pressure of 50 bar, the reaction was completed after a residence time of less than 6 s.[23]

In many laboratories, batch microwave reactors specifically designed for chemistry applications have essentially become the primary means for reaction optimization and laboratory (mL) scale synthesis.[19] The high-T/p procedures developed and optimized in these instruments form an ideal basis for translation to continuous-flow processing/manufacturing (microwave-to-flow paradigm).[20]

In fact, there is a rather wide range of valuable and robust synthetic transformations that readily accept harsh reaction conditions. Ultrahigh-temperature continuous-flow procedures have been realized for many such transformations, including Newman–Kwart rearrangements, Claisen and related pericyclic rearrangements, heterocycle synthesis, radical polymerization, and a variety of cycloadditon reactions.[21,24] In general, a delicate balance of reaction acceleration and decomposition of reagents or product have to be considered. A case in point is the formation of the triazole precursor **5** in the synthesis of Rufinamide (Scheme 2 a).[25] Hessel and co-workers accomplished this reaction by a 1,3-dipolar Huisgen cycloaddition of 2,6-difluorobenzyl azide (**3**) with (*E*)-methyl 3-methoxyacrylate (**4**) as the dipolarophile.[25] Perfect regioselectivity towards the desired 1,4-cycloadduct is afforded due to the presence of the methoxy leaving group in the dipolarophile **4**. The reaction could be conducted with neat reagents when the capillary microreactor was maintained at a temperature above the melting point of the product. The processed stream was then diluted with MeCN or MeOH prior to passing it through a back-pressure regulator and the crystalline product was obtained in the collection tank upon cooling.[25] Azides are notoriously heat-sensitive and decompose rapidly at elevated temperatures with concomitant evolution of nitrogen gas. Nevertheless, with the residence time controlled to 10 min, the catalyst-free reaction could be performed at a reaction temperature of 210 °C, thereby giving the triazol product **5** in excellent yields (86 %).[25] The intensified process increased the productivity three orders of magnitude compared to a previously published batch procedure.[25] An alternative, copper-catalyzed process was recently described by the Jamison research group,[26] and is discussed in detail in Section 4.5.4.

Snead and Jamison recently described the continuous-flow synthesis/purification of diphenhydramine hydrochloride (Scheme 2 b).[27] The compound is the active pharmaceutical ingredient in over-the-counter antihistamines such as Benadryl, Zzzquil, Tylenol PM, and Unisom. The global demand is more than 100 t per year. For the flow process, neat molten chlorodiphenylmethane (**6**) and neat *N*,*N*-dimethylaminoethanol (**7**) were pumped in a 1:1 stoichiometric ratio into a thick-walled perfluoroalkoxy alkane (PFA) tube reactor at 175 °C, with the desired API formed as the molten hydrochloride salt.[27] Hot aqueous NaOH was

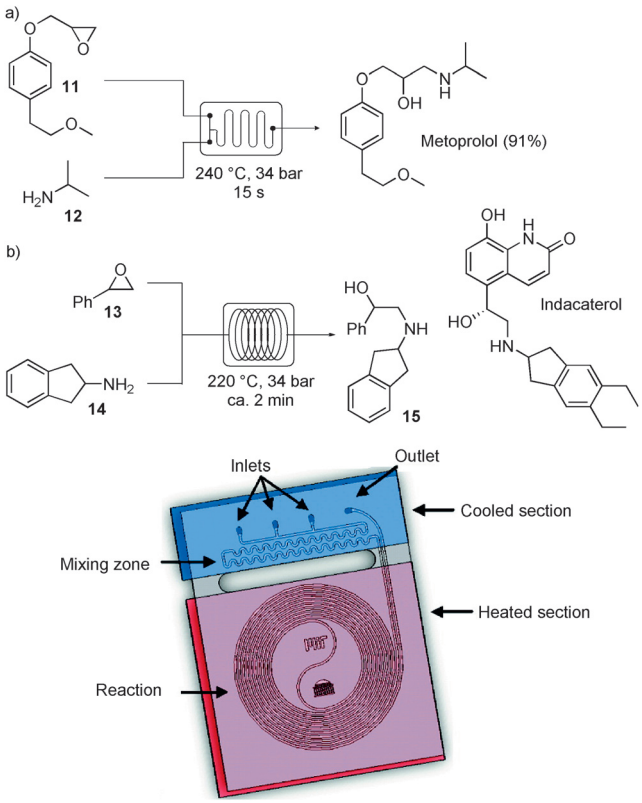


Scheme 2. Synthesis of APIs or advanced intermediates under high-T/p continuous-flow conditions.

combined with the reaction stream to neutralize the ammonium salt and, after releasing the pressurized system, hexane was added to extract the neutralized amine **8**.[27] The two phases were then separated in-line in a liquid–liquid membrane separator and the product was finally precipitated from the organic phase in 90% overall yield with hydrochloric acid. The flow system with an internal volume of 750 μL produced 2.4 g of the API per hour.[27]

A high-temperature continuous-flow synthesis of 4-substituted imidazoles **10a** and **10b** was described by chemists from Eli Lilly (Scheme 2c).[28] Cyclization of a model ketoamide with ammonium acetate on a small scale proceeded satisfactorily in a sealed tube. However, upon scale-up in traditional glassware, the reaction rate decreased markedly and multiple charges of ammonium acetate were required due to loss of ammonia from the reaction mixture at elevated temperatures.[28] Furthermore, large amounts of oligomers were formed during the cyclization of ketoamide **9a** when the reaction was performed at low temperatures (< 70 °C). Accordingly, the purity of the product dropped at larger scales in batch reactors, since the heat-up times lengthened. In contrast to the batch experiments, the reaction could be reproduced very well at 140 °C in stainless-steel plug-flow reactors (PFR) with internal volumes ranging from 4.5 mL up to 7.1 L. A quantity of 55 kg of ketoamide **9a** was processed in the 7.1 L reactor over 141 h under good manufacturing practice (GMP) conditions (theoretical residence time: 90 min). For the final flow reaction, the *N*-methyl derivative **9b** and ammonium acetate in methanol as solvent were combined in a T-shaped mixer and heated in a 221 mL PFR at 140 °C (residence time: 11 min) to give the corresponding imidazole **10b** in 80% yield of the isolated product.[28] A thermal cleavage of the Boc protecting group of the imidazole was subsequently carried out in a 221 mL PFR in MeOH/THF under supercritical conditions at 270 °C and 70 bar. With a measured residence time of 9.4 min, the crude deprotected imidazole **10b** was obtained in virtually quantitative yields.[28]

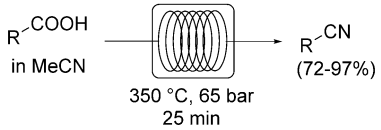
Chemists from MIT pointed out the importance of a reduced headspace by comparing the high-temperature aminolysis of epoxides in batch microwave and continuous-flow microreactor systems.[29,30] The reaction with low-boiling amines performed consistently better in the pressurized microreactor, because of the elimination of available headspace in the microreactor and the concomitant decrease in the amount of amine in the vapor phase. Since the amine was more volatile than the solvent, its vaporization decreased its concentration in solution, thus reducing the reaction efficiency. The flow aminolysis was then applied for the preparation of Metoprolol, a selective 1-adrenoreceptor blocking agent (Scheme 3a).[29] Complete conversion was obtained at 240 °C with a residence time of only 15 s by using a 34 bar back-pressure regulator. Under these conditions, a single 120 μL microreactor is capable of delivering 7.0 g h^{-1} of Metoprolol.[29] The same process was also successful for the preparation of a precursor in the synthesis of Indacaterol.[29] This reaction was further studied using the aminolysis of styrene oxide **13** with 2-aminoindane **14** as a model for the synthesis of Indacaterol (Scheme 3b).[30] The activation energy for the formation of the desired product **15** is higher



Scheme 3. High-T/p aminolysis reactions. Image adapted from Ref. [29] with permission. Copyright 2010, American Chemical Society.

than for the formation of the regioisomer and for secondary aminolysis, which suggests that performing this reaction at the highest possible temperature should improve the selectivity as well as accelerate the reaction. The reaction was studied extensively in a 120 μL microreactor, with a total amount of less than 5 g of styrene oxide and 2-aminoindane **14** consumed for optimization. Using the optimized conditions, the process was then scaled-up 100-fold in a stainless-steel tube reactor (12.5 mL). 163 mL of the reaction mixture was processed at a reaction temperature of 220 °C within 30 min, thereby generating 9 g of the desired product with 100% conversion and 78% yield as determined by HPLC.[30]

A rather drastic example of a high-T/p reaction is the uncatalyzed conversion of carboxylic acids into nitriles with acetonitrile as solvent/reagent (Scheme 4).[31] The acid–nitrile

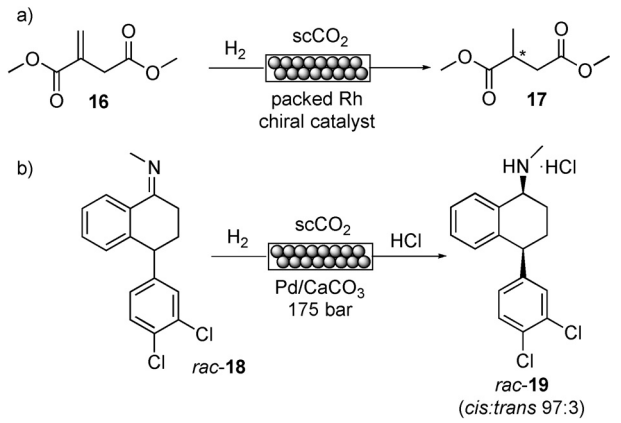


Scheme 4. Continuous-flow high-T/p acid–nitrile exchange reaction.

exchange reaction requires temperatures in excess of 300 °C to achieve the desired transformation at preparatively useful rates and is, therefore, of little practical use. However, the reaction performed well in a stainless-steel capillary reactor, with residence times of 25 min in supercritical MeCN

(scMeCN) at 350 °C and 65 bar.[31] Despite the extreme reaction conditions, the reaction was remarkably clean and tolerated several functional groups (Scheme 4).

Fluids near or above their critical point generally have unique physical and chemical properties.[32] For example, the density, viscosity, and diffusivity of supercritical solvents as well as the solubility of chemicals can be easily tuned by varying the pressure and temperature. Since the operation window of continuous-flow reactors is often in a temperature range up to 350 °C and a pressure range up to 250 bar, a supercritical state for many organic solvents can be attained.[11] Carbon dioxide reaches its supercritical state ($scCO_2$) under relatively mild conditions ($T_c = 31.1$ °C, 73.9 bar) and $scCO_2$ is, therefore, among the most frequently used supercritical fluids. The application of $scCO_2$ in continuous flow is now reasonably established for reactions such as hydrogenations, hydroformylations, and condensations.[32–34] Leitner and co-workers recently demonstrated the enantioselective continuous-flow hydrogenation of dimethylitaconate **16** over a Schrock–Osborn-type rhodium complex with supercritical carbon dioxide as the mobile phase (Scheme 5a).[33] The hydrogenation catalyst was supported in an ionic



Scheme 5. Continuous-flow hydrogenations in fixed-bed reactors using $scCO_2$ as the mobile phase.

liquid phase in a fixed-bed reactor (5 mL volume). Turnover numbers of $>100\,000$ and a space-time yield (STY) of 750 $g\,L^{-1}\,h^{-1}$ were achieved at a reaction temperature of 40 °C (120 bar).[33]

Similarly, the hydrogenation of racemic sertraline imine **18** in a fixed-bed flow reactor using $scCO_2$ as solvent was studied by the Poliakoff group in collaboration with researchers at AstraZeneca (Scheme 5b).[34] (4*S*)-Sertraline imine **18** is an intermediate in the synthesis of *cis*-(1*S*,4*S*)-sertraline hydrochloride **19**. Sertraline hydrochloride is the active ingredient in Zoloft, a drug used as a treatment of depression and other anxiety-related disorders. The best results were obtained with a $Pd/CaCO_3$ catalyst at a reaction temperature of 40 °C (175 bar). Under optimized conditions for the hydrogenation, dechlorination and dehydrogenation side reactions were suppressed nearly completely, with a chemoselectivity of >99 % achieved. Racemic sertraline was formed with excellent diastereoselectivity in a *cis*/*trans* ratio of 97:3.[34]

Equipment made out of pressure- and corrosion-resistant tubing that can be operated at temperatures well above 300 °C and pressures up to 280 bar has also become available, thereby allowing the generation of water in its near- and supercritical state.[35]

3.2. Operation at Very High Pressure

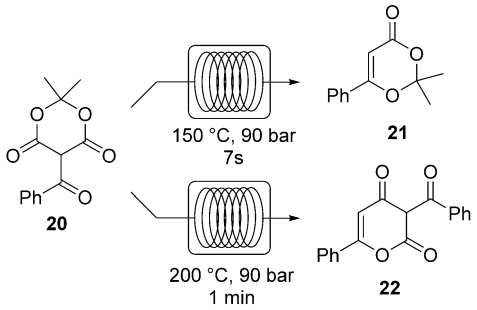
In the examples outlined above, pressure is important for maintaining a solvent in the liquid state or increasing the concentration of a gas in a liquid phase (see also the following sections). The rate constant or the equilibrium constant of a reaction usually depends only weakly on pressure in the pressures range normally encountered in synthesis laboratories. Above about 1 kbar, however, pressure becomes an important reaction parameter also for pure liquid-phase reactions, and both the rate and equilibrium can be influenced.[36] Generally, the pressure dependence of the equilibrium constant is related to a change in the molar volumes (ΔV) when reactants are converted into products. Similarly, the pressure dependence of the rate constant is associated with the activation volume ($\Delta V^{\neq}$). Reactions that are accompanied by a negative activation volume can be accelerated by increasing pressure, and the equilibria are shifted toward the side of the products for transformations with negative reaction molar volumes.[36] The use of continuous-flow operation in the very high pressure regime is still in its infancy, however.[37]

3.3. High-Temperature/Low-Pressure Operation

In flash vacuum thermolysis or pyrolysis (FVP), a substrate is distilled or sublimated under vacuum through a hot tube at very high temperatures (typically 200 to 1100 °C) and the products are collected afterwards in a cold trap.[38] The low pressure avoids adverse intermolecular secondary reactions and the continuous flow ensures that individual molecules spend only a very short time in the hot reaction zone (in the order of milliseconds).[38] By using this method even highly reactive substances can be quenched without decomposition, thus allowing the isolation and/or spectroscopic characterization of reactive intermediates and short-lived molecules. Moreover, FVP is also used as a valuable synthetic tool for the preparation of many interesting stable compound classes that are often difficult to prepare by other means.[38]

A serious limitation of the classic FVP procedure, however, is the requirement that the substrate must be volatile at low pressures, since poorly volatile precursors simply decompose on heating in the inlet tube. Furthermore, FVP is difficult to scale up. In some cases, it is possible to obtain the same products as in a conventional FVP experiment by performing the reaction in a solution phase in an inert solvent under continuous-flow conditions ("flash-flow pyrolysis").[39] The combination of the high-T/p capability with the powerful heating and cooling capacity is thereby

crucial in performing these experiments. Indeed, it was shown that the thermal decomposition of benzoyl Meldrum's acid **20** can be tuned by using a liquid-phase high-T/p continuous-flow method to provide either the 1,3-dioxin-4-one intermediate **21** or the oxoketene dimer **22** by precisely controlling the residence time and temperature (Scheme 6).[39] At a reaction temperature of 150 °C (90 bar back pressure), the decomposition of benzoyl Meldrum's acid required only 7 s for completion, thereby providing the acylketene-acetone **21** adduct in a selectivity close to 90 %.[39] At 200 °C, with a residence time of 1 min, on the other hand, the dimer **22** was formed with almost complete selectivity (ca. 98 %).[39]



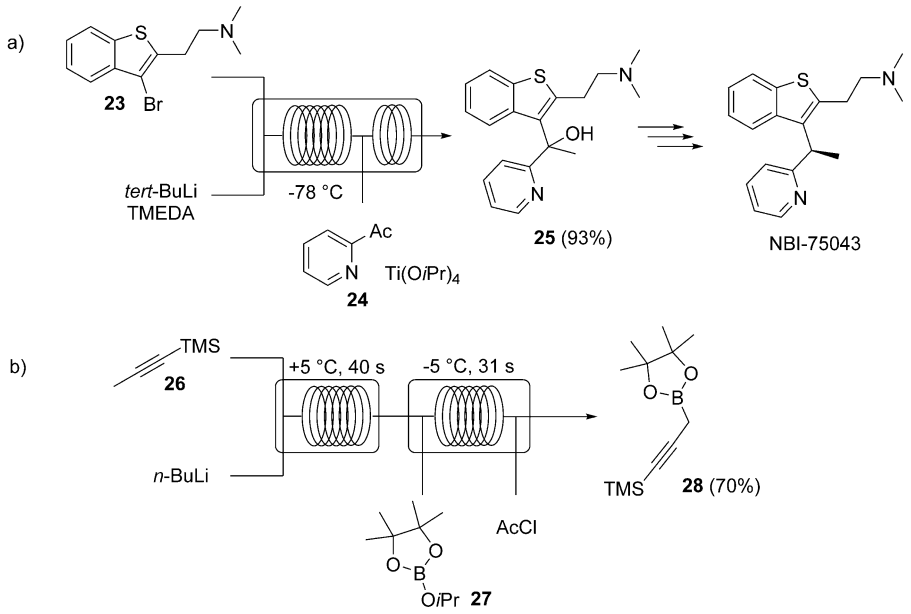
Scheme 6. Liquid-phase high-T/p continuous-flow pyrolysis of Meldrum's acid.

In general, drastic rate accelerations are expected with increasing temperature, according to the Arrhenius Equation $[k(T) = A \cdot \exp(-E_a/RT)]$. This allows a smaller footprint of the reaction vessel at a given throughput and, thus, improves the safety and economy of the process. Additionally, the application of extreme or exotic reaction conditions enables entirely new or "off-road" chemistry.[40] Many further examples of reactions executed under unusual process conditions will be discussed in the following Sections.

4. Hazardous Chemistry

4.1. Very Fast and/or Exothermic Reactions

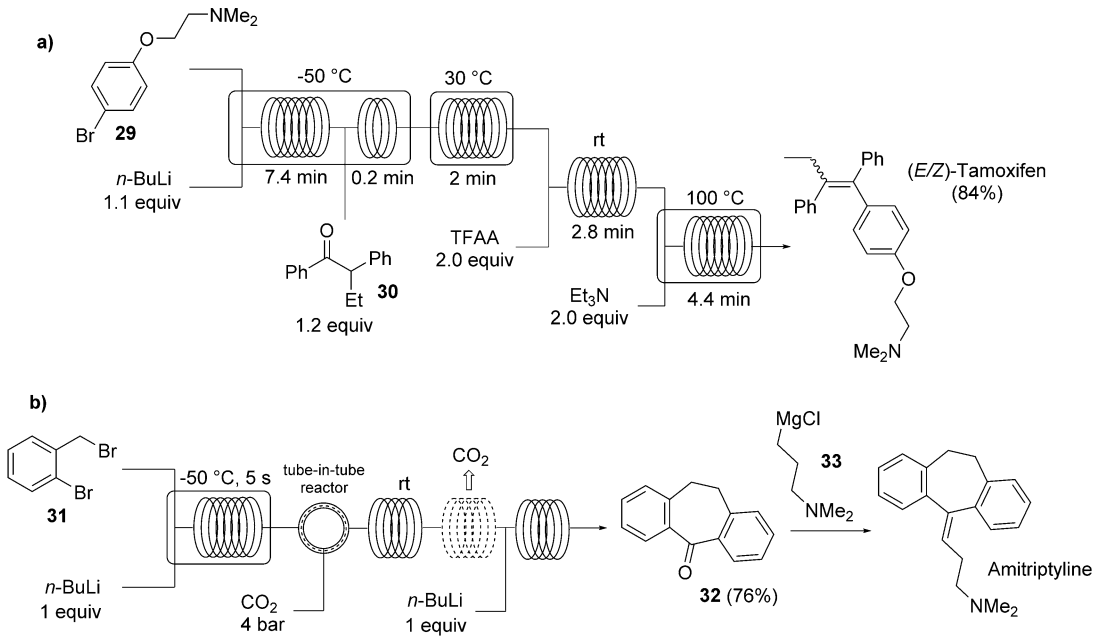
Mass and heat transfer can become limiting for fast or highly exothermic reactions.[41] In these cases, reagents generally have to be dosed slowly to the reaction mixture or the mixture has to be diluted or cooled to reduce reaction rates and to guarantee adequate mixing and heat exchange. The rate of heat transfer is directly proportional to the surface area ($\sim d^2$), while the heat generated in an exothermic reaction is proportional to the volume of the reactor ($\sim d^3$). Thus, dissipation of heat becomes increasingly difficult upon scale-up and increasingly long addition times become necessary to maintain the temperature at an acceptable level. An instructive example was presented by chemists at Neurocrine Biosciences and Irix Pharmaceuticals (Scheme 7 a).[42] During the synthesis of NBI-75043, a histamine receptor antagonist examined for the treatment of insomnia, a lithium–halogen exchange reaction on compound **23** and a subsequent addition to 2-acetylpyridine (**24**) was necessary.[42] The reactions worked nicely on a small scale in batch, but the exothermic nature of these two steps meant that the addition time would have to be prohibitively long on a larger scale. Thus, the reaction was performed in continuous flow in stainless-steel tube reactors. A solution of *tert*-BuLi and trimethylethylenediamine (TMEDA) was combined with a solution of compound **23** in a static mixer at −78 °C. The mixture passed through a first coil reactor submerged in a bath at −78 °C and was then combined with a stream of 2-acetylpyridine (**24**) and



Scheme 7. Continuous-flow lithium-exchange reactions and follow-up chemistry.

$Ti(OiPr)_4$ in a second T-mixer. The lithium derivative of **23** reacted with acetylpyridine in a second tube reactor before the processed mixture was collected in a stirred container with methanol. Optimized conditions gave the desired product **25** in 93 % conversion (Scheme 7 a).[42]

Similarly, researchers from Boehringer Ingelheim Pharmaceuticals established a synthesis of the borolane **28**, a versatile reagent for site-selective propargylations of carbonyl and imine compounds (Scheme 7 b).[43] The reaction worked quite satisfactory on a small scale in batch, but the yields strongly decreased with longer dosing times of the intermediate lithiated derivative of **26** to the borate **27**.[43] A batch process for the preparation of propargyl borolane **28**



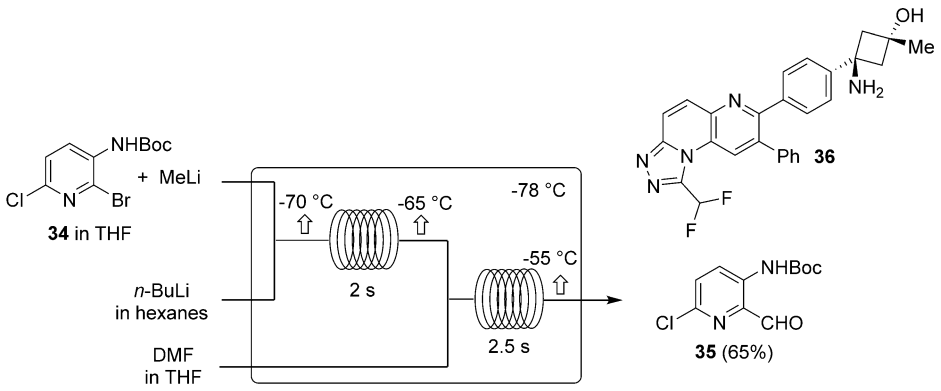
Scheme 8. Examples of multistep API synthesis involving *n*-butyllithium.

was thus unlikely to afford reproducible and satisfactory yields on a larger scale. A continuous-flow process, on the other hand, reproduced well from a small scale to production, and 318 kg of the propargyl borolane were produced in total in > 91 % purity.[43]

More recently, Ley and co-workers devised a continuous-flow multistep synthesis of (*E*/*Z*)-Tamoxifen, a compound used for the treatment of estrogen-receptor-positive breast cancer (Scheme 8 a).[44] The process employed a series of telescoped synthetic transformations using five pumps and five coil reactors, as well as four different temperature regimes. The sequence started with a continuous-flow lithium–halogen exchange reaction by combining precooled solutions of bromoarene **29** with *n*-butyllithium. The mixture passed through a first residence coil at −50 °C and the output stream was then quenched in-line with ketone **30** (prepared by a Grignard reaction in a separate flow process).[44] The mixture passed through a short residence loop and was then heated to 30 °C in a subsequent loop to complete the addition of the lithium arene to the ketone. The lithium alkoxide was then acetylated with a fourth stream of trifluroacetic anhydride at ambient temperatures, followed by a triethylamine-mediated elimination to form the final product in a fifth coil reactor at 100 °C. To prevent the solvent mixture from boiling, the whole system was pressurized to 7 bar using a back-pressure regulator. The synthesis was run continuously for 80 min to provide 12.4 g of pure (*E*/*Z*)-Tamoxifen with an *E*/*Z* ratio of 25:75 in 84 % yield based on the aryl bromide **29**. This corresponds to drug material for over 900 days of treatment for one patient.[44]

Along the same lines, the multistep synthesis of Amitriptyline by Kupracza and Kirschning involved three consecutive lithium–halogen exchange reactions (Scheme 8 b).[45] 1-Bromo-2-(bromomethyl)benzene (**31**) and 1 equiv of *n*-butyllithium were fed into the reactor to afford the [(2-bromophenethyl)phenyl]lithium intermediate by a Wurtz-type coupling reaction followed by a second lithium exchange reaction. The lithium intermediate was then quenched with carbon dioxide before additional *n*-butyllithium was added to furnish the tricyclic ketone **32** in an overall yield of 76 % of the isolated product.[45] The authors used a gas-addition tool to load the carbon dioxide into the system. This device consists of two chambers, one carrying the liquid phase and the other carrying the gaseous phase, separated by a gas-permeable Teflon membrane. The technique was pioneered by the Ley research group and is discussed in more detail in the following sections. A second gas-permeable membrane was used to remove excess carbon dioxide from the mixture before the second charge of *n*-butyllithium was fed into it (Scheme 8 b). The synthesis of Amitriptyline was completed by a continuous-flow addition of Grignard reagent **33** to ketone **32** and subsequent high-temperature dehydration (30 s, 200 °C).[45]

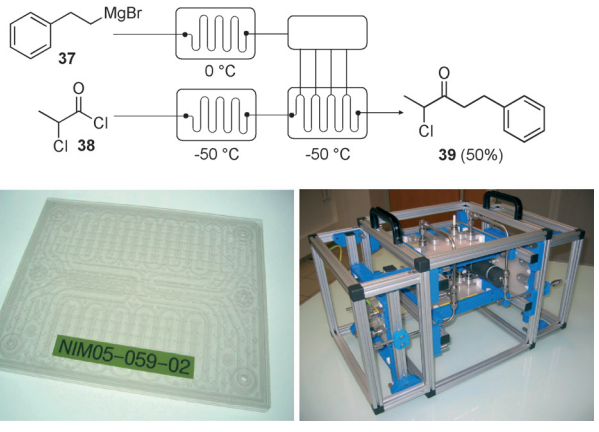
Flow conditions have, in fact, been applied for a rather large number of reactions with organolithium and related organometallic compounds.[46] Chemists from Merck employed a flow process for the formylation of **34** during their multistep, kilogram-scale synthesis of the allosteric Akt kinase inhibitor **36** (Scheme 9).[47] The entire synthesis involved 17 convergent reaction steps, with 10 steps for the longest linear sequence, and did not require chromatography. For the continuous-flow formylation, a solution of the lithium amide of **34** in THF was preformed from the amine and MeLi. The solution was fed into a stainless-steel tube reactor with an internal diameter of 6.35 mm, which was immersed in a dry-ice/acetone bath. The stream of the amide was mixed with *n*-BuLi, to form the dianion in a first residence tube, and the dianion was then combined with the DMF/THF feed solution. The product stream was finally fed into an aqueous quench solution for neutralization and workup.[47] Even with an



Scheme 9. Flow preparation of pyridyl aldehyde **35**.

impressive combined flow rate of 175 mL min^{-1}, efficient cooling of the system was still maintained, and the purity profile of aldehyde product **35** exceeded that of the batch procedure.[47] A preparative-scale run conducted for one hour consumed the lithium amide derived from 1 kg of bromide **34**.[47]

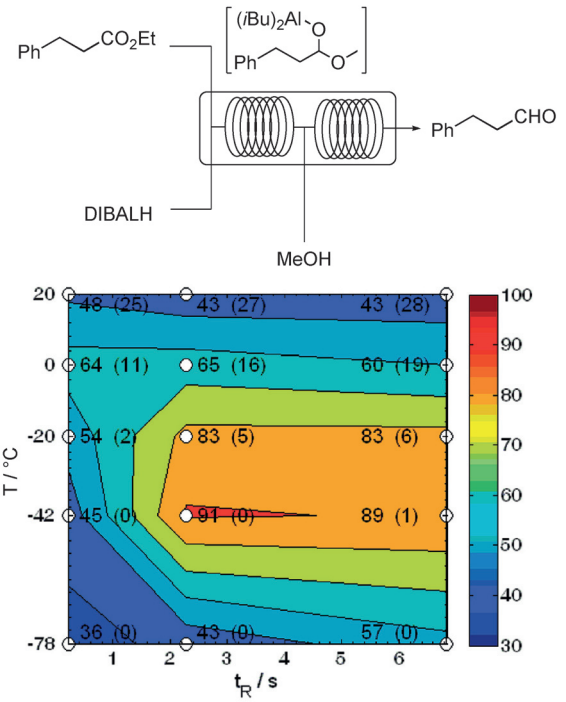
A team from Lonza performed a two-step continuous-flow lithium exchange and coupling reaction to produce nearly 700 kg of a not further disclosed product.[48] Cost savings of approximately 9% compared to batch production were calculated.[48] Furthermore, in a collaboration between Lonza and Corning, a continuous microreactor for a very challenging, exceptionally exothermic and rapid Grignard addition of stoichiometric amounts of phenylethylmagnesium bromide (**37**) to 2-chloropropionyl chloride (**38**) was developed (Scheme 10).[49] The formation of hot spots or insufficient mixing, and a consequent stoichiometric imbalance, leads to a range of side products. A multi-injection microreactor was developed to keep the reaction under control and to maximize selectivity, thereby emulating the common batch technique of dropwise addition of a reagent. The microreactor provided four injection points as well as mixing and residence zones at each injection point. The Grignard feed was split into four feeds for injection at the four inlet points, while the acyl chloride was injected directly into the multi-injection reactor (Scheme 10). The yield for this specific reaction was 50%. With the reagents at a concentration of about 10 wt% in the feed solutions, the reactor is capable of producing 100 kg of the final product **39** per week (Scheme 10).[49]



Scheme 10. Top: Reaction of a Grignard reagent with an acyl chloride. Bottom left: Glass microstructure. Bottom right: The multi-injection reactor is capable of producing 100 kg of final product per week for this specific reaction. The annual production capacity of five reactors is 25 metric tons. Images reproduced from Ref. [49a] with permission. Copyright 2008, Wiley-VCH.

Particularly noteworthy in this context are the pioneering contributions from the Yoshida group.[14,50] A variety of lithium–halogen exchange reactions for the synthesis of highly unstable aryllithium intermediates have been demonstrated in numerous publications.[50] The aryllithium intermediates were formed with residence times as short as 1.5 ms at −70 °C and were subsequently immediately quenched by the addition of an electrophile.[50] Extensive decomposition of the intermediate aryllithium reagents could be avoided by precisely controlling the residence time of these short-lived species in the microreactor by feeding in a quench solution containing the electrophile. This approach was further demonstrated for room-temperature Moffatt–Swern oxidations on a micromolar scale.[51] Swern oxidations are typically performed below −50 °C in batch to prevent the exothermic decomposition of the "activated" DMSO intermediate by a Pummerer rearrangement. In Yoshida's work, the sulfonium ion was generated in a micromixer from trifluoroacetic anhydride and DMSO at temperatures as high as 20 °C, and the mixture was then subsequently combined with the alcohol and triethylamine in two further micromixers to yield the carbonyl compound.[51] Similar strategies were applied by others to conduct Swern oxidations at unusually high reaction temperatures.[52,53] Kemperman and co-workers, for example, used an analogous process for the laboratory-scale synthesis of 4-androstene-13,17-dione from testosterone at −20 °C with a throughput up to 117 g L^{-1} h^{-1} under optimized conditions.[53]

A related microreactor strategy has further been successful for the partial reduction of carboxylic esters to aldehydes with diisobutylaluminum hydride (DIBAL-H; Scheme 11).[54,55] This reaction is typically accompanied by significant over-reduction to the alcohol and it is thus generally preferred to fully reduce esters to the alcohol and then selectively reoxidize the alcohol to the aldehyde. Again, the reaction mixture can be quenched precisely in microreactors when the amount of desired intermediate or product is at its maximum (Scheme 11). Webb and Jamison accomplished essentially full conversion and complete selectivity into the aldehyde with residence times below 50 ms at a nominal temperature of −78 °C.[54] Remarkably, the extrapolated throughput was 10.4 mol of starting material per day using a reactor with an internal volume of only 23 μL.[54] As pointed out by Ducry and Roberge, such



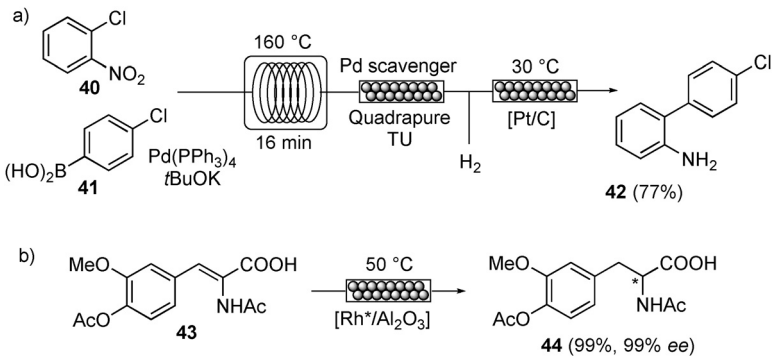
Scheme 11. Highly reactive intermediates can be generated in continuous-flow microreactors and directly quenched to form stable intermediates/products. Top: Selective DIBAL-H reduction of esters to aldehydes. Bottom: Contour plots showing the effect of reaction temperature (T) and residence time (t_R) on the amount of aldehyde. Reproduced from Ref. [54a] with permission. Copyright 2012, American Chemical Society.

reactions are virtually impossible in batch reactors on an industrial scale, since the limited half-life of the organoaluminium intermediate would not accept the extended dosage times required to maintain isothermal operation.[55]

4.2. Hydrogenation

Catalytic hydrogenation is one of the most powerful reactions available to the synthetic organic chemist and many functional groups can be reduced under relatively mild conditions, often with high chemo-, regio-, and stereoselectivity.[56] Numerous heterogeneous and homogeneous catalysts with high hydrogenation activity are now available, and the scope of hydrogenation chemistry has become very large.[56] Moreover, molecular hydrogen is readily available, inexpensive, and not toxic. However, hydrogen is highly flammable and it forms an exceptionally wide range of combustible or detonatable air mixtures and has an extraordinarily low ignition energy. The burning velocity is one order of magnitude higher than for other flammable fuel/air mixtures, thus indicating its high explosive potential and the difficulty of confining hydrogen flames.

For hydrogenation reactions, the transport of hydrogen to the catalyst is frequently the rate-limiting step and efficient agitation to support a rapid transport of H_2 from the gas phase to the catalyst is crucial. Transport limitations make gas–liquid reactions significantly more complex than single-phase reactions and inherently difficult to scale. Furthermore, since the solubility of hydrogen in organic solvents is generally low, high-pressure operation is essential for the hydrogenation to proceed at an acceptable rate. Additionally, hydrogenation is exothermic, and some means of efficient heat removal must be provided. Many of these process challenges can naturally be addressed by using continuous-flow technology. For this reason, continuous-flow hydrogenations have found quite extensive application in the chemical industry and, since the introduction of commercial bench-top high-pressure hydrogenators, it has been rapidly adopted also in organic synthesis laboratories.[57] Flow hydrogenations are commonly carried out in packed-bed reactors over heterogeneous catalysts.[58] As a consequence of the very large interfacial areas and short diffusion paths in these reactors, a particularly effective contact between the gas, liquid, and solid phase is provided. Furthermore, since the substrate flows continuously through the catalyst bed, extraordinarily high catalyst-to-substrate ratios can be realized. Catalyst separation from the product is trivial, as hydrogenation reactions are generally genuinely heterogeneous processes and the metals do not appreciably leak from the bed. The products obtained upon hydrogenation are thus usually free of any contaminating reagents. A large number of publications describing reactions in commercially available flow hydrogenation devices on a laboratory scale demonstrate their usefulness and impact on the synthetic community.[58–60] An interesting example is the two-step continuous-flow synthesis of 2-amino-4′-chlorobiphenyl (**42**), a key intermediate for the industrial preparation of the fungicide Boscalid (Scheme 12 a).[59] The reaction comprises an initial palladium-catalyzed high-temperature Suzuki–Miyaura cross-coupling of 1-chloro-2-nitrobenzene (**40**) with 4-chlorophenylboronic acid (**41**) and a subsequent hydrogenation to the aniline **42**. The reported batch procedure for the Suzuki coupling required reaction times of 8 to 18 h at 65–100 °C to achieve completion.[59] Preliminary optimization of this reaction in a batch microwave reactor and further tuning in a high-pressure microtubular flow reactor reduced the reaction time to 16 min at a reaction temperature of 160 °C,



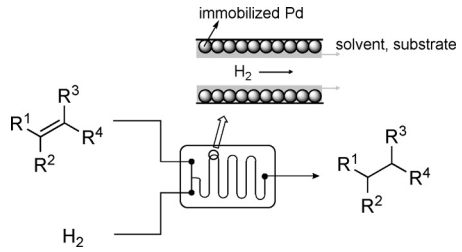
Scheme 12. Hydrogenation in fixed-bed reactors.

thereby affording the desired 4′-chloro-2-nitrobiphenyl in approximately 90% yield.[59] For the subsequent hydrogenation, the palladium from the Suzuki reaction had to be removed to prevent a palladium-catalyzed reductive dehalogenation. This was achieved by passing the reaction stream from the coupling step directly through a macroporous Quadrapure thiourea (TU) resin cartridge to scavenge the Pd metal from the solution. The nitro compound was subsequently hydrogenated over Pt/C at 30 °C in a commercial flow hydrogenation device to afford 2-amino-4′-chlorobiphenyl (**42**) in 77% overall yield (Scheme 12a).[59]

The asymmetric hydrogenation of several (*Z*)-α-acetamidocinnamic acid derivatives, such as the L-DOPA precursor **43**, over a rhodium catalyst with a chiral hybrid phosphine-phosphoramidite ligand was demonstrated by Bakos and co-workers (Scheme 12b).[60] The rhodium complex was immobilized on a mesoporous Al_2O_3 support using phosphotungstic acid as an anchoring agent and the immobilized catalyst was then used as a packed-bed reactor in a commercially available flow hydrogenator. The reaction was run continuously for 6 h to furnish the product with a conversion over 99% and with > 99% enantioselectivity.[60]

An alternative to bed reactors is to immobilize the catalyst directly on the channel walls of a continuous-flow microreactor. There are a number of strategies to prepare channel-supported catalysts, including polymer coatings, immobilization of nanoparticles, and direct deposition of metals onto the channel surfaces.[61,62] In a seminal contribution by Kobayashi and co-workers, palladium was immobilized on a glass microchannel reactor with a rectangular cross-section (200 μm × 100 μm).[61] The hydrogen and substrate flow rates were adjusted so that the liquid was carried at the surface of the channels while the gas flowed through the center of the channels (annular flow). By using this system the hydrogenation reactions proceeded at atmospheric pressure and room temperature with a residence time as short as 2 min. The pure products were obtained by simple evaporation of the solvent (Scheme 13).[61]

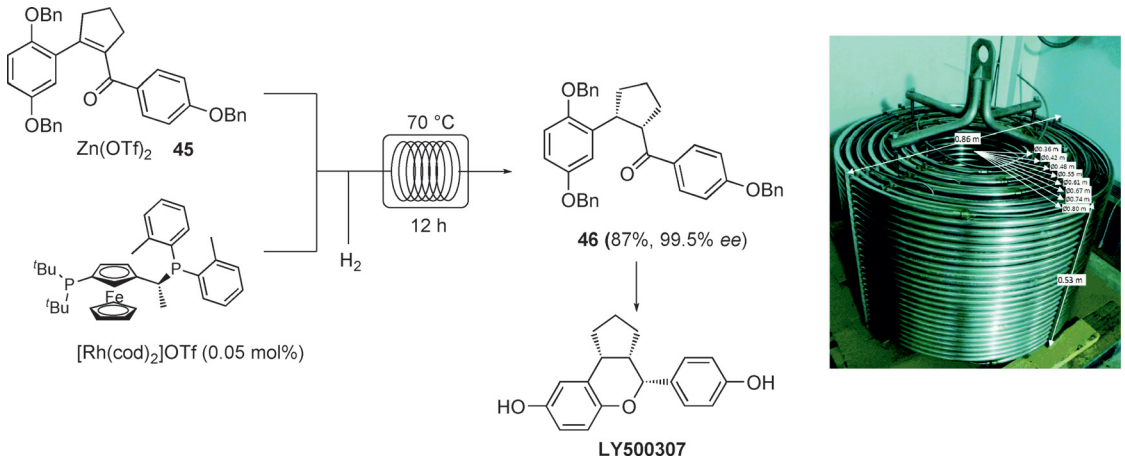
Enantioselectivity is often higher and more predictable with homogeneous catalysts. Furthermore, catalytic activity



Scheme 13. Hydrogenation with the catalyst immobilized on the surface of the channel.

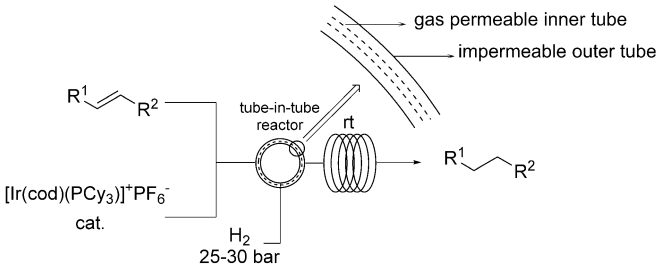
as well as the purity profile and enantioselectivity of the reaction can change over time for fixed catalysts. A detailed understanding of degradation kinetics is then required so that the catalyst can be replaced in time. Continuous-flow hydrogenations with stable, homogeneous catalysts might thus be preferred. Such reactions can be realized in high-pressure, tubular-flow reactors in a segmented gas–liquid flow regime. This approach was used by chemists from Eli Lilly for the synthesis of **46**, the penultimate intermediate for the production of LY500307, a potent, selective estrogen receptor β agonist (Scheme 14).[63] The synthesis involved the continuous high-pressure asymmetric hydrogenation of ketone **45** with rhodium-Josiphos as catalyst and $Zn(OTf)_2$ as promoter. For the pilot-scale reaction, a 73 L coiled-tube reactor was employed (Scheme 14). The asymmetric hydrogenation was coupled with a continuous downstream work-up, comprising liquid–liquid extraction in a three-stage mixer-settler, semi-batch solvent exchange, continuous crystallization, and filtration. Product **46** was obtained consistently with more than 99% *ee*.[63]

A somewhat intermediate approach is the use of continuous gas–liquid–solid slurry reactors.[64] In this mode, no decline of catalyst activity over time is expected, but the catalyst can still be easily removed from the reaction mixture by a subsequent filtration. Importantly, the advantages associated with microreactors, such as enhanced mass and heat transfer, are preserved.[64]



Scheme 14. Hydrogenation using homogeneous catalysts. Image reproduced from Ref. [63] with permission. Copyright 2012, American Chemical Society.

For gas–liquid reactions, the gas flow is usually controlled by a calibrated mass-flow controller, and the gaseous and liquid feeds are combined in an appropriate mixer upstream to the cartridge or residence reactor. A convenient laboratory tool to saturate gases into liquids was developed by the Ley research group.[65] The device is based on a tube-in-tube configuration with the inner tube made of Teflon AF-2400.[65] Teflon AF-2400 is a copolymer of tetrafluoroethylene and perfluorodimethyldioxolane and has a highly porous, amorphous structure, while the chemical resistance and mechanical strength is comparable to that of standard PTFE. Accordingly, the AF-2400 tube serves as a robust, hydrophobic, permeable membrane which selectively allows a wide variety of gases, but not liquids, to cross. This membrane is enclosed within a thick-walled impermeable outer tube (e.g. PTFE or stainless steel). Typically, the gas (e.g. CO, CO_2, H_2, ethene, ethyne, or SO_2) is carried between the outer tube and the inner tube. The gas crosses the semipermeable membrane and dissolves into the liquid carried within the AF-2400 tubing.[65–67] This configuration is mainly used to saturate the liquid reagent feed with the gaseous reagent prior to heating the gas-saturated stream in a subsequent bed reactor or coil reactor (Scheme 15).[66,67] An alternative design where the inner tube carries the gaseous reagent allows heating the liquid reaction feed in the outer chamber.[68] The commercially available gas-loading device has found a variety of diverse applications in recent years, as highlighted in the following Sections.[65,69]



Scheme 15. Hydrogenation with a tube-in-tube reactor as the gas-addition module.[66] cod = cyclooctadienyl.

4.3. Oxidations with O_x species

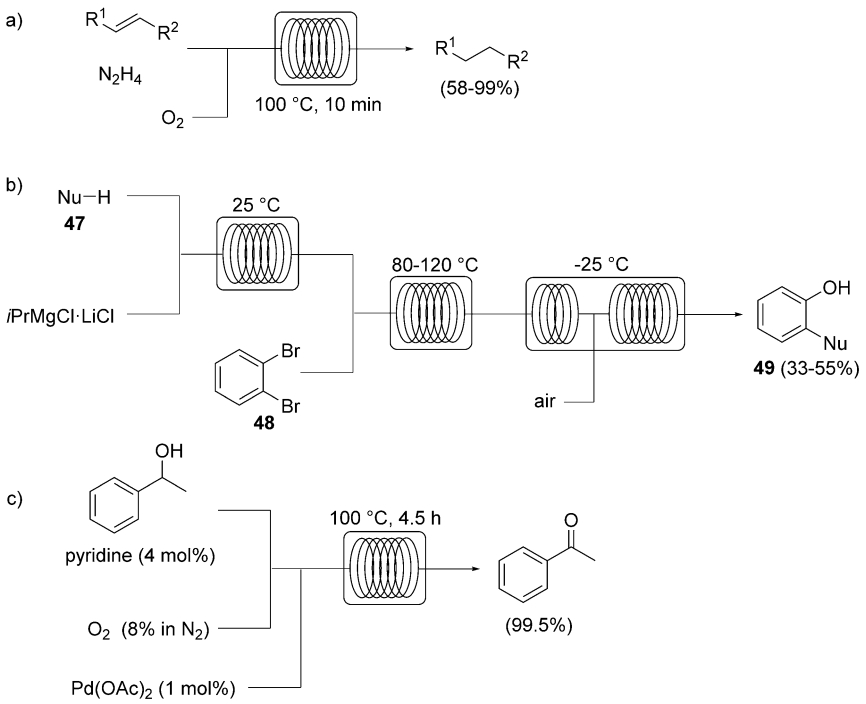
4.3.1. Air, Oxygen

As a consequence of their low cost and negligible environmental impact, molecular oxygen or air would be virtually ideal oxidants. Highly efficient methods for the preparation of bulk chemicals by liquid-phase oxidations with O_2 have been developed, and several commodity chemicals, such as cyclohexanol/cyclohexanone (KA oil), cumene hydroperoxide, *tert*-butyl hydroperoxide/*tert*-butyl alcohol, and terephthalic acid, are produced on an enormous scale by aerobic oxidation of petroleum-based starting materials. Importantly, a variety of versatile, selective, and mild methods for the aerobic oxidation of complex organic molecules, such as the oxidation of alcohols to aldehydes or ketones, or oxidative C–O, C–N, and C–C coupling reactions have been developed in the last decade.[70] Reactions with gaseous oxygen are associated with unique safety risks and process challenges. The reactions are generally highly exothermic and the heat of the reaction can be difficult to dissipate. The consequential non-isothermal conditions reduce reaction selectivity and product quality and pose serious safety hazards. Dangers of thermal runaways are significant, and, depending upon the composition, temperature, and pressure, the reaction mixture can ignite spontaneously. Flow microreactor technology provides a means to control the exotherm and hence minimize over-oxidation of sensitive products. Furthermore, since the reactor headspace is considerably reduced, the formation of explosive gas-phase mixtures and chances of auto-ignition are minimized. The techniques used for continuous-flow oxidations with oxygen gas are in principle the same as those discussed for hydrogenations. The liquid reagent feed is mixed with the gaseous feed and the combined stream then passes through a catalyst bed or a residence reactor.

High-pressure fixed-bed reactors were used quite extensively to study the aerobic or O_2 oxidation of alcohols to aldehydes and ketones. Good single-pass conversions and high aldehyde selectivity were obtained with a variety of supported catalysts, including Ru/Al_2O_3,[71] Fe_2O_3/SiO_2,[72] and palladium on various supports,[73] both in $scCO_2$ and in conventional solvents. Catalyst deactivation and metal leaching has usually not been observed over the reported run times.[71–73] Hence, in simple cases the products can be obtained in high yields simply by evaporation of the solvent, or the processed solution can be directly used in a downstream process without the presence of contaminating catalyst or reagents in the reaction stream. Researchers at Imperial College London in collaboration with Pfizer demonstrated this approach for a telescoped oxidation-Wittig reaction.[71]

A catalyst-free generation of diimide by oxidation of hydrazine monohydrate ($N_2H_4{\cdot}H_2O$) with molecular oxygen was recently performed in a PFA tube reactor (Scheme 16a).[74] The diimide was generated in the presence of an alkene and immediately utilized as a hydrogenation transfer agent for the reduction of the alkene to the corresponding alkane. This gas–liquid approach provided full conversion and perfect selectivity for a variety of alkenes after residence times of only 10 to 30 min (100 °C) by employing 4–5 equiv of the hydrazine precursor. Several functional groups sensitive to reduction in transition-metal-catalyzed hydrogenations, such as silyl ether, halogenes, and Cbz protecting groups, easily resisted the applied conditions and the alkanes were obtained in almost quantitative yields.[74]

An analogous set-up was used by the Jamison group for the monooxygenation of Grignard reagents with gaseous O_2 or air (Scheme 16b).[75] Yields of around 50 to 90% were obtained for a range of phenols, with either electron-withdrawing or -donating groups, at temperatures of −25 to +25 °C after a residence time of 3.4 min (17 bar). The synthesis was then further extended by an upstream in situ generation of the aryl magnesium species starting from 1,2-

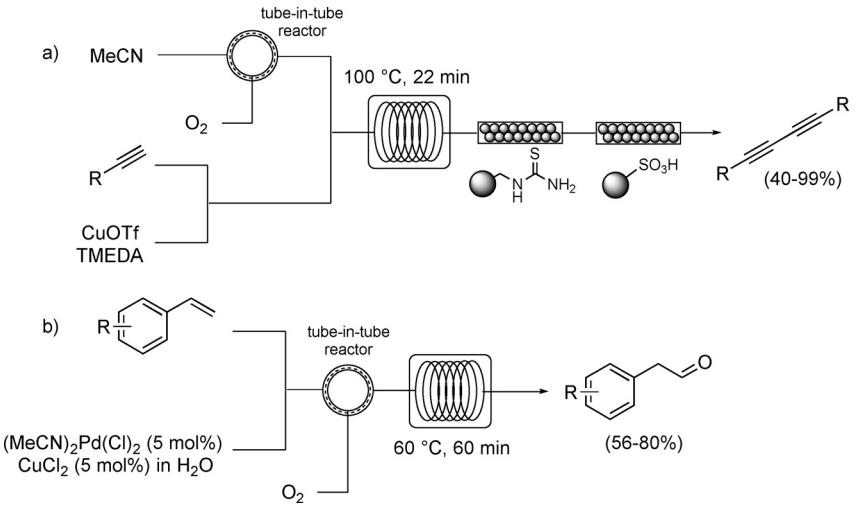


Scheme 16. Continuous-flow aerobic/O_2 oxidation.

dibromobenzene (**48**), *i*PrMgCl·LiCl, and a nucleophile **47**. Benzynes were formed as intermediates at 80 to 120 °C from the dibromobenzene and the isopropylmagnesium chloride, and a subsequent addition of the nucleophile gave the arylmagnesium species. Aerobic monooxygenation finally afforded phenols **49** in approximately 50 % overall yield from the three-step continuous-flow process (Scheme 16 b).[75]

A broad range of effective aerobic oxidations that use homogeneous palladium catalysts have been developed over the past years.[70] These reactions have remarkable synthetic scope and utility.[70] The stability of the palladium catalyst, however, is highly sensitive to the dissolved oxygen concentration and even temporary periods of poor gas–liquid mixing can lead to catalyst decomposition by irreversible agglomeration of the homogeneous Pd^0 species into metallic palladium. This feature makes Pd-catalyzed aerobic oxidation reactions rather unforgiving with respect to operational variation and represents a distinct challenge in scaling up a batch process. However, Stahl and co-workers together with chemists from Eli Lilly successfully performed the Pd-catalyzed oxidation of 1-phenylethanol with diluted O_2 (8 % in N_2) in a 7 L stainless-steel tube reactor on a kilogram scale to give acetophenone in near quantitative yield (Scheme 16 c).[76]

A continuous-flow copper-catalyzed Glaser–Hay acetylene homocoupling reaction was described by Ley and co-workers (Scheme 17 a).[77] The O_2 was loaded into the reaction mixture using the tube-in-tube gas-loading tool, and the gas-saturated solution then passed through a tubular reactor at 100 °C. The copper and the amine base were then removed from the flow stream by passing it through a cartridge of polymer-supported thiourea and polymer-supported sulfonic acid, respectively. The 1,3-butadiynes were isolated in up to quantitative yields, generally without the need for chromatography.[77] A similar strategy was successful for the anti-Markovnikov Wacker oxidation of styrenes to afford arylacetaldehydes (Scheme 17 b).[78] With 5 mol % [Pd-$(MeCN)_2Cl_2$] and $CuCl_2$ in *t*BuOH/toluene/H_2O as solvent, full conversion and good selectivity to the aldehydes were achieved at 60 °C within one hour residence time (56–80 % yield).[78]



Scheme 17. Oxidation with a tube-in-tube reactor as the gas-addition module.

4.3.2. *Singlet Oxygen*

Singlet oxygen, $^1O_2$, can be generated either through chemical processes or, more commonly, by photoexcitation of molecular oxygen in the presence of a photosensitizer.[79] Even though singlet oxygen is used rather widely in contemporary organic synthesis, its application in the pharmaceutical industry on a large scale has proven difficult. There are several scale-up limitations associated with photochemical reactions in general, and with singlet oxygen chemistry in particular when using traditional batch reactors.[7] According to the Beer–Lambert law, the photochemical reaction effi-

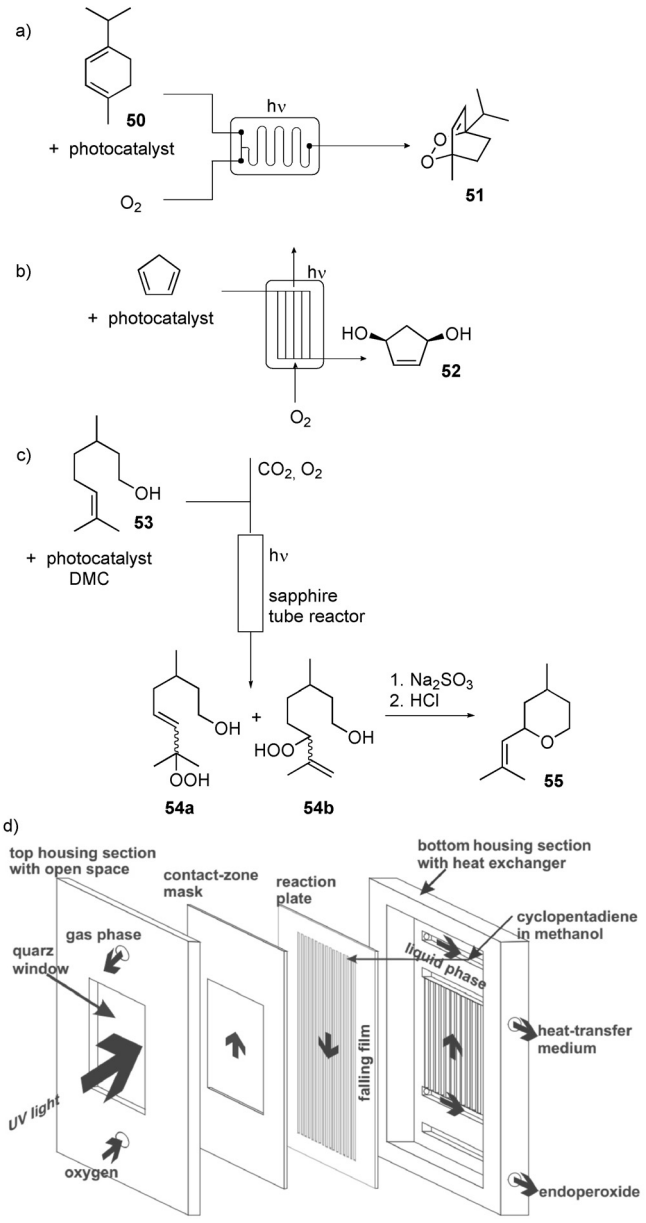
ciency decreases exponentially when the path length or concentration of the substrate/catalyst is increased. Satisfactory results are consequently difficult to maintain at the scales and concentrations compatible with industrial-scale processes.[7] Furthermore, $^1O_2$ is highly reactive and explosion hazards have to be considered.

Several authors have described the application of continuous-flow microreactors for the generation and utilization of singlet oxygen. De Mello and co-workers fabricated a glass microreactor with 50 μm deep channels for the generation of $^1O_2$ (Scheme 18a).[80] A solution of rose bengal and terpinene **50** in methanol and a stream of oxygen were introduced into the reactor and irradiated with an overhead tungsten lamp. Since the effective optical path length in the microchannels is only several μm, an unusually high concentration of sensitizer (5×10^{-3} M) could be used, thus leading to >80% conversion of α-terpinene **50** into ascaridole (**51**) after a residence (irradiation) time of less than 5 s. As a consequence of the small internal volume of the microreactor, however, the productivity was rather small (0.18 μmol min^{-1}).[80]

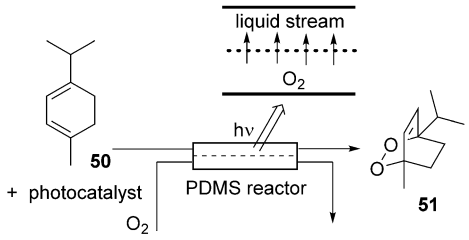
A falling-film microreactor manufactured by the Institut für Mikrotechnik, Mainz, was used by Jähnisch and Dingerdissen to accomplish the [4+2] cycloaddition of $^1O_2$ to cyclopentadiene (Scheme 18b).[81] The reaction plate had 32 parallel microchannels of 300 μm depth. Cyclopentadiene and rose bengal in MeOH were transported to the upper part of the reactor plate and then flowed downwards in the reactor through gravity. The oxygen was fed countercurrently to the liquid. This set-up gave a liquid film of 20 μm and a gas–liquid interface of 20000 m^2 m^{-3}. 4-Cyclopenten-1,3-diol (**52**) was isolated in 20% yield after reduction of the intermediate *endo*-peroxide.[81]

The choice of permissible solvents for singlet oxygen reactions is very limited. Traditionally, these reactions are performed in nonflammable solvents, such as CH_2Cl_2, $CHCl_3$, or CCl_4, but from an environmental standpoint, these solvents are no longer acceptable. Chemists from the University of Nottingham reported the synthesis of ascaridole (**51**) in $scCO_2$.[82] In a typical experiment, liquid CO_2, O_2, and the organic reactant containing the photosensitizer (5,10,15,20-tetrakis(pentafluorophenyl)porphyrin) were pumped into a sapphire tube housed in a stainless-steel holder. Quantitative conversion was achieved in a single pass through the reactor. The photoreactor operated with unchanged efficiency without any noticeable fouling of the sapphire tube for over 8 h to yield 96 mL of **51**. This approach could be extended to the oxidation of citronellol (**53**) by using dimethyl carbonate (DMC) as a cosolvent (Scheme 18c). The reaction gives a mixture of the hydroperoxides **54a** and **54b**, both of which can be converted into rose oxide **55** upon reduction and acidification. Thus, the effluent reaction mixture was collected directly in an aqueous solution of Na_2SO_3 to reduce the hydroperoxides to the corresponding alcohols. Subsequent acidification of the aqueous phase with HCl gave **55** as a mixture of *cis* and *trans* isomers in a selectivity of 98%.[82]

Kim and co-workers pioneered the fabrication of multichannel microreactors made of gas-permeable poly(dimethylsiloxane) (PDMS) and their use for gas–liquid reactions (Scheme 19).[83] In a typical dual-channel set-up, one of the channels carries the liquid feed, while the other channel often



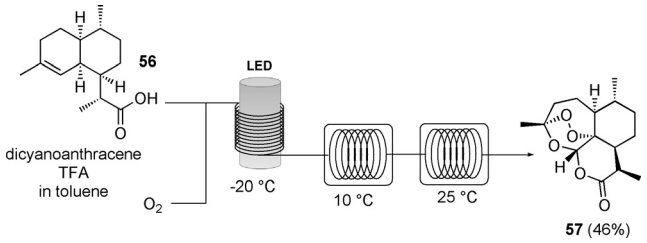
Scheme 18. a–c) The use of $^1O_2$ in different continuous-flow reactors. d) Image of a falling film reactor (bottom). Image reproduced from Ref. [81] with permission. Copyright 2005, Wiley-VCH.



Scheme 19. Schematic illustration of the dual-channel microreactor. The liquid-carrying channel was protected with a polyvinylsilazane (PVSZ) coating.[83]

carries a gas. The gas diffuses through the PDMS membrane separating the two channels, thus providing a continuous supply of gaseous reagents. PDMS is reasonably stable in polar organic solvents such as DMF, DMSO, or acetonitrile, but many common nonpolar solvents diffuse into the PDMS polymer and cause the material to swell. The stability of the reactor can be increased by coating the outside surfaces of the liquid-carrying channel with a suitable polymer.[83] Since the PDMS microreactors are transparent to visible light, they have been successfully used for ene and cycloaddition reactions with singlet O_2 (Scheme 19).[83]

The group of Seeberger used a simple tube reactor to accomplish the ene reaction of citronellol (**53**) and $^1O_2$.[84] Fluorinated ethylene propylene (FEP) tubing of 14 mL internal volume was wrapped around a Schenk photochemical reactor containing a 450 W medium-pressure mercury lamp. By using this setup, a conversion of citronellol of above 95% was obtained after a residence time of 48 s with tetraphenylporphyrin (TPP) as photosensitizer, and a roughly 1:1 mixture of the corresponding alcohols was isolated after reduction of the intermediate hydroperoxides in 88% yield (2.5 mmol min^{-1}).[84] This method proved to be suitable for a variety of further ene reactions as well as cycloadditions with $^1O_2$.[84] A similar photoreactor was recently deployed for the photochemical key step in the multistep preparation of artemisinin **57** (Scheme 20).[85,86] Artemisinin is currently the



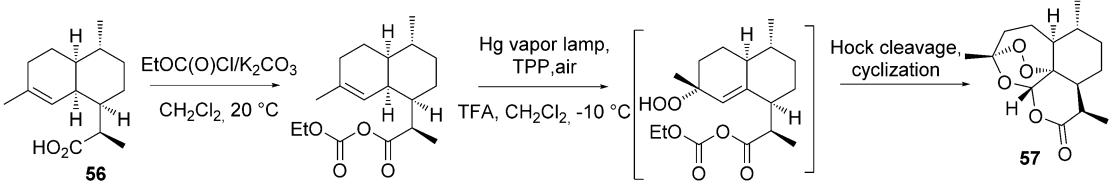
Scheme 20. Schematic overview of the flow reactor for the continuous synthesis of artemisinin.

most effective antimalarial drug, but its availability from natural sources is limited. The semisynthesis starts from dihydroartemisinic acid (**56**), which in turn can be prepared by hydrogenation of the readily accessible artemisinic acid.[74] Central in the synthesis of artemisinin is an ene reaction of dihydroartemisinic acid with singlet oxygen. The reaction is followed by cleavage of the oxygen–oxygen bond (Hock cleavage), and finally addition of triplet oxygen. This triggers a spontaneous cascade of condensation reactions that culminates in the formation of the endoperoxide group of artemisinin (Scheme 20). The whole reaction sequence was ultimately performed as a single fully continuous chemical process that did not require purification or work-up of any intermediates. Dihydroartemisinic acid (**56**), the photosensitizer (dicyanoanthracene), and trifluoroacetic acid in toluene were mixed with a stream of oxygen gas and passed through the photoreactor at −20 °C.[85] After the photoreactor, the mixture was heated in a further tube reactor to accomplish the acid-catalyzed Hock cleavage as well as the subsequent oxidation with triplet oxygen and the concomitant condensation to the final product. Pure artemisinin was obtained in 46% yield after a total residence time of about 12 min in the flow set-up.[85] In a follow-up study, the authors described the multistep continuous synthesis of several artemisinin-derived APIs.[87]

Notably, a photochemical singlet oxygenation in the preparation of artemisinin (**57**) from artemisinic acid has recently been developed by Sanofi, and constitutes one of the few examples of a large-scale batch process involving $^1O_2$ (Scheme 21).[88] For the Sanofi process, the overall yield of isolated pure, crystalline artemisinin (**57**) was 55% starting from the artemisinic acid. The full-scale plant at the Sanofi facility in Garessio, Italy, has produced commercial quantities of artemisinin since 2013. The production of 60 tons of artemisinin is expected for 2014, with an average batch size of 370 kg isolated artemisinin. However, as pointed out by the authors,[88] a photooxidation step in a full-flow system instead of a semibatch process could be advantageous, thus leading to future process improvements.

4.3.3. *Ozone*

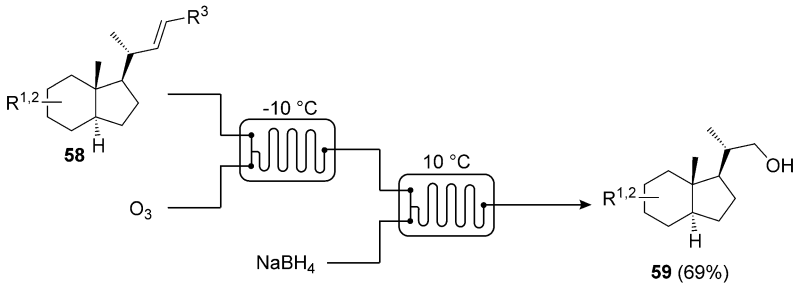
Ozonolysis reactions are generally accompanied with the formation of explosive mixtures of oxygen/ozone with solvent vapor in the gas phase and, additionally, explosive ozonides and/or hydroperoxides in the liquid phase. Furthermore, the extraordinary reactivity of ozone towards many functional groups combined with the low solubility of ozone in many solvents entail that the reaction is typically limited by mass transfer, even at very low temperatures. The first ozonolysis of organic compounds in a microreactor was published by Jensen and co-workers in 2006.[89] The microreactor consisted of 16 individual microchannels (600 μm wide, 300 μm deep, and 23 mm long). The reaction solutions were delivered to the microreactor using a syringe pump, while the O_3 flow was controlled by a mass-flow controller (6–7% O_3 in O_2). The processed reaction mixture was immediately quenched by a quench solution and diluted with nitrogen gas. The reactor



Scheme 21. Sanofi process for the generation of artemisinin from dihydroartemisinic acid. TPP = tetraphenylporphyrin.

design was evaluated using simple model reactions, such as the oxidation of triethyl phosphite, octylamine, and 1-decene. Virtually complete conversion and high selectivity (up to 100%) were obtained with essentially stoichiometric amounts of ozone at contact times as short as 1 s at room temperature.[89]

Jähnisch and co-workers developed a fully continuous two-step reaction sequence for the preparation of vitamin D analogues that consisted of ozonolysis of a double bond and a subsequent reduction (Scheme 22).[90] Both steps were



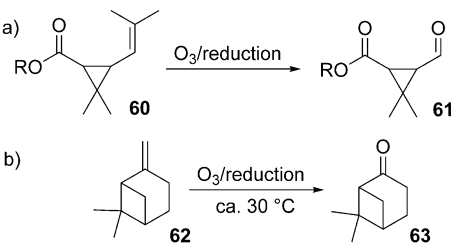
Scheme 22. Flow schemes for ozonolysis in microreactors.

integrated in a continuous-flow microplant with a five-channel microreactor as its core element (14 μL internal volume each). For the two-step reaction sequence, the substrate solution in $MeOH/CH_2Cl_2$ and O_3/O_2 were dosed into the five-channel microreactor at around −10 °C. A microflow-through cell for online FTIR analysis and process control, integrated close to the reactor outlet, allowed observation of the formation of the aldehyde and a peroxide species. The processed reaction mixture was then passed through a gas separator. The liquid phase was combined with a mixture of $NaBH_4$ in DMF and the stream passed further through a second five-channel mixer and a 5 m residence time module. A throughput of 1.2 mmol min^{-1} substrate was achieved under optimized conditions. The reaction mixture was collected over 5.5 min to give 2.9 g of the desired product after column chromatography (69% yield). This equates to a productivity of 0.76 kg day^{-1} of the isolated alcohol **59**.[90]

In addition to microreactors, capillary- and tube-based flow reactors have been used for continuous-flow ozonolysis. A dedicated general-purpose continuous-flow ozonolysis system for laboratory-scale applications was introduced in 2011.[91] The flow ozonolysis reactor was designed for ozonolysis at atmospheric pressure from −25 °C to room temperature. The instrument used an O_2 gas cylinder to supply a built-in O_3 generator. The generated O_3 was quantified in an internal analyzer and passed through a Teflon frit to mix it into the precooled substrate feed. The ozonolysis then occurs in a 4 mL Teflon tube wrapped around a refrigeration unit. After the reaction mixture had passed through the reaction loop, it was quenched with a quench solution supplied by two further syringe pumps.[91]

Despite the risks and challenges associated with ozone reactions, several industrial-scale processes using O_3 for the synthesis of pharmaceutical intermediates have been developed in the last few years.[92] Most of these reactions involve cleavage of an alkene double bond. These reactions have been traditionally performed with heavy metal oxides such as permanganate or chromic acid. Since even traces of metals in pharmaceutical or cosmetic products are unacceptable, meticulous and expensive purification is required. Thus, there is a huge incentive to replace conventional oxidation methods by ozonolysis as expertise and equipment to run these reactions on scale becomes available. An impressive example is the ozonolysis of chrysanthemum monocarboxylic acid ester (**60**) by Lonza (Scheme 23a).[93] The process was optimized to produce 0.5 t of **61** per day in a continuous mode in a 450 L loop reactor.[93]

Similarly, chemists from the Dishman Group described the synthesis of nopinone (**63**) starting from β-pinene (**62**; Scheme 23b).[94] Nopinone is a key intermediate in the production of the prostaglandin receptor antagonist S-5751. About 50–100 g of the product was produced per hour in a microreactor in about 80% yield and with a purity in excess of 98%.[94]

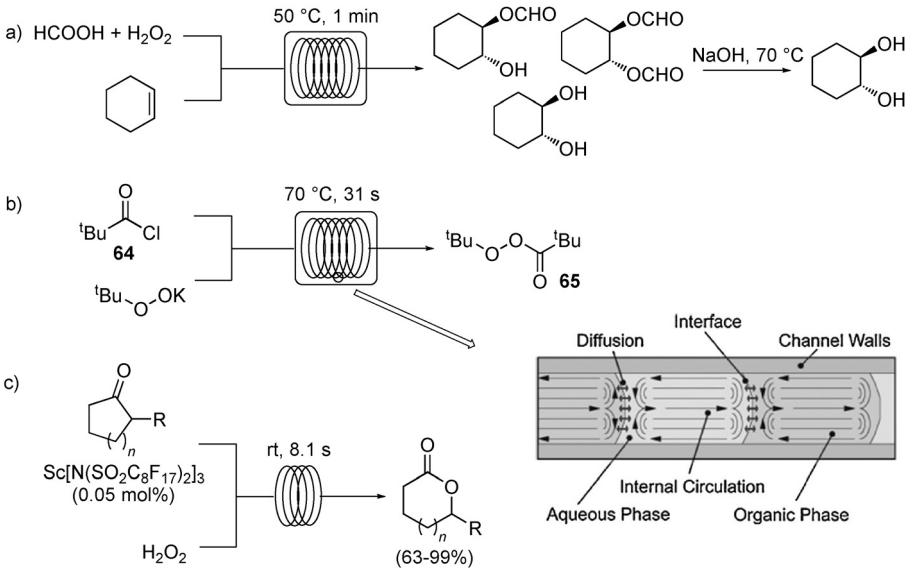


Scheme 23. Industrial ozonolysis in microreactors.

4.3.4. H_2O_2, HOX

The redox potential of hydrogen peroxide for the half-reaction H_2O_2/H_2O is approximately 1.8 V and, thus, one would expect H_2O_2 to be a quite powerful oxidant.[95] However, hydrogen peroxide by itself is in fact a relatively poor oxidizing agent. Therefore, the main industrial application of hydrogen peroxide is as a rather mild, nonselective radical oxidant in operations such as the bleaching of paper, cellulose, and textiles.[95] The hydrogen peroxide has to be activated for reactions more relevant for organic synthesis, such as epoxidations or Baeyer–Villiger oxidations. This is typically achieved by converting H_2O_2 into peroxy acids in a preceding step. An on-site continuous-flow microreactor process for the production of peracetic acid from acetic acid, hydrogen peroxide, and sulfuric acid as catalyst was first demonstrated in 2009.[96] The production capacity of the microreactor with an internal volume of less than 10 mL was 10 kg peracetic acid per hour.[96]

Alternatively, strategies to generate the peroxy acids in situ from carboxylic acids and hydrogen peroxide have been developed and were employed for the two-phase liquid–liquid continuous-flow Prilezhaev epoxidation/hydrolysis of



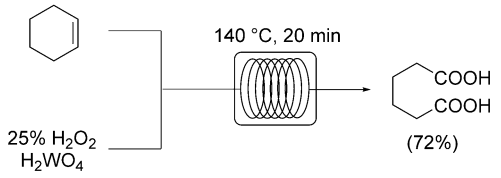
Scheme 24. Oxidations with XO_2H under liquid–liquid segmented-flow conditions. Image reproduced from Ref. [98] with permission. Copyright 2011, Elsevier.

cyclohexene to *trans*-1,2-cyclohexanediol (Scheme 24a).[97] Full conversion for the epoxidation step was obtained after a residence time of 1 min at 50 °C, and cyclohexanediol was isolated in 86% yield after hydrolysis.[97]

Biphasic reactions strongly benefit from the high mixing capabilities and high surface-area-to-volume ratios of small-diameter microreactors. The two-phase synthesis of *tert*-butyl peroxypivalate (**65**) from aqueous *tert*-butyl hydroperoxide (TBHP) and KOH as well as neat pivaloyl chloride (**64**) under flow conditions was studied by Illg et al. (Scheme 24b).[98] In the segmented flow regime, the conversion and yield increased from 16% to 47% with increasing flow rate at a constant residence time of 42 s (10 °C). This can be explained by an increase of internal circulations inside the immiscible slugs at larger flow rates and a correspondingly enhanced mass transfer between the liquid phases. By increasing the reaction temperature to 70 °C, it was possible to decrease the process time to 31 s and the product was obtained in a maximum yield of 67% (Scheme 24b).[98]

Similarly, a scandium-catalyzed biphasic Baeyer–Villiger oxidation in 30% aqueous hydrogen peroxide and trifluorotoluene as solvent could be completed after reaction times of only a few seconds at room temperature in a microreactor with a channel cross-section of about 30 μm (Scheme 24c).[99] Several simple ketones, including 2-methylcyclopentanone and -hexanone, were transformed into the corresponding lactones with high regioselectivity and without appreciable hydrolysis.[99]

In a series of seminal publications, Sato and Noyori have described a variety of oxidative transformations with hydrogen peroxide as the oxidant by using $Na_2WO_4{\cdot}2H_2O$ as a catalyst.[100] Most notably, a solvent-free direct oxidation of cyclohexene to adipic acid was reported by Sato, Aoki, and Noyori in 1998.[101] Adipic acid is the basic building block for a range of products and about 3 million tons of adipic acid are produced annually worldwide. The tungstate catalyst used in Noyori's procedure forms a water-soluble peroxo complex, which dissolves in aqueous H_2O_2. The solubility of cyclohexene in water, on the other hand, is exceedingly small and the oxidation of cyclohexene, therefore, necessitates an interphase mass transfer before the reactants come into contact. Accordingly, an ammonium hydrogen sulfate phase-transfer catalyst (PTC) is usually added to the reaction mixture to achieve sufficient contact between the hydrophobic substrate and the hydrophilic reagent and catalyst.[100,101] A PTC-free procedure was performed in continuously stirred tank reactors on a pilot scale with tungstic acid (H_2WO_4) as the catalyst and H_2SO_4 and H_3PO_4 as promoters.[102] However, the oxidation required a reaction time of 10 h at a reaction temperature of 90 °C and, thus, rather large reactors would be necessary to achieve industrially relevant productivities. A high-temperature continuous-flow procedure for the synthesis of adipic acid, on the other hand, gave complete oxidation of cyclohexene to adipic acid after 20 min residence time at a reaction temperature of 140 °C with only 1 mol% H_2WO_4.[103] The neat cyclohexene and a solution of tungstic acid in 25% aqueous H_2O_2 were pumped as two separate feeds into a T-mixer (Scheme 25).

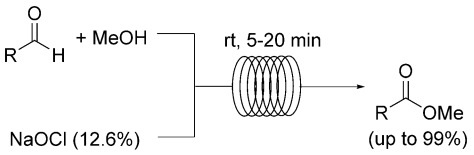


Scheme 25. Continuous-flow synthesis of adipic acid.[103]

The resulting two-phase liquid–liquid segments entered a 25 mL PFA residence tube. After a few minutes in the residence time reactor, the mixture became completely homogeneous as the cyclohexene is oxidized to more polar, more water-soluble products. The mixture passed through the residence tube and left the reactor through a back-pressure regulator, which was held at 80 °C. After the processed mixture left the back-pressure regulator, the adipic acid immediately precipitated and the pure acid was isolated by filtration and washing with cold 1 N HCl. The reaction was run for 1 h to provide 12 g (84 mmol; 72%) of pure, crystalline adipic acid after a simple filtration step.[103] An analogous continuous-flow synthesis of adipic acid by the oxidation of neat cyclohexene with aqueous hydrogen peroxide was described by Hessel and co-workers.[104] The process used $Na_2WO_4{\cdot}2H_2O$ as a catalyst and $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ as

a phase-transfer catalyst. Improved mixing was achieved by using a packed-bed reactor containing glass spheres.[104]

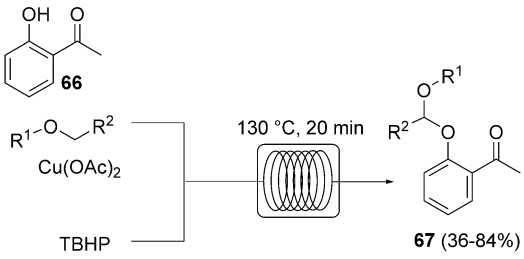
A liquid–liquid two-phase continuous-flow oxidation utilizing a 12.6% aqueous solution of sodium hypochlorite as a stoichiometric oxidant, ethyl acetate as organic solvent, and tetrabutylammonium bromide as catalyst was described by the Jamison group (Scheme 26).[105] The process was



Scheme 26. Two-phase continuous-flow oxidation with sodium hypochlorite.

capable of oxidizing secondary alcohols to ketones in good selectivities after residence times of 20 to 30 min at room temperature. Primary alcohols and aldehydes were generally directly oxidized to methyl esters in the presence of 10 equivalents of MeOH. Benzylic alcohols possessing strong and weak electron-donating groups, however, could be selectively oxidized to aldehydes in good yields after residence times of 5 to 15 min.[105]

Reddy and co-workers developed a homogeneous dehydrogenative cross-coupling reaction using *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 27).[106] The procedure is capable of coupling 2-carbonyl-substituted phenols **66**

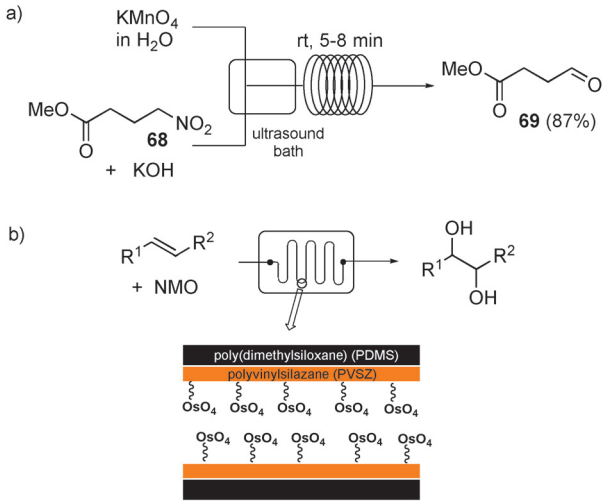


Scheme 27. $Cu(OAc)_2$-catalyzed dehydrogenative cross-coupling of 2-carbonyl-substituted phenols with ethers.

as well as β-ketoesters with simple ethers to generate acetal products **67**. The reaction was carried out with $Cu(OAc)_2$ as the catalyst in the respective ether as solvent and required approximately 3 h heating under reflux to achieve good yields. An obvious safety issue results from the combination of a peroxide with ethers at high temperatures. Therefore, a translation of the synthesis to a continuous-flow format was attempted.[106] A solution of the copper catalyst and the 2-hydroxyacetophenone substrate **66** in ether as solvent and commercially available TBHP in decane were passed through a glass static mixer and subsequently heated in a coil reactor at 130 °C. With a residence time of 20 min, conversion and yields similar to those under microwave batch conditions were obtained (Scheme 27).[106]

4.3.5. Metal Oxides

A potassium permanganate mediated Nef oxidation of nitroalkanes to their carbonyl derivatives in a tubular flow reactor was performed by the Ley group (Scheme 28a).[107] Even though stoichiometric quantities of manganese dioxide



Scheme 28. Oxidations with metal oxides.

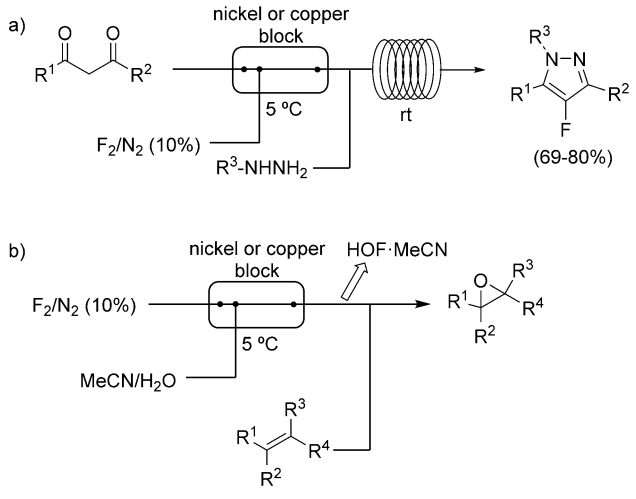
precipitated during the reaction, the blockage of the reactor was avoided by submerging the T-mixer and the beginning of the subsequent reactor tubing in an ultrasound bath. The heterogeneous reaction mixture was then pumped through the remaining coil reactor and exited the flow system as a fine suspension. By using 0.8 equivalents of $KMnO_4$, various nitroalkanes were converted into aldehydes after residence times of 5 to 8 min at room temperature. Two equivalents of the permanganate resulted in the aldehydes being directly oxidized to the carboxylic acids.[107]

Kim and co-workers immobilized OsO_4 in a PDMS microchannel reactor (Scheme 28b).[108] The microreactor was coated with polyvinylsilazane to increase its chemical resistance and to allow the covalent attachment of poly(4-vinylpyridine)-NCO to the channel wall through urethane bridges. The tertiary nitrogen atoms in the *para* position of the repeating pyridine unit could be used for the immobilization of the OsO_4. The thus-prepared microreactor was then used for dihydroxylation reactions with *N*-methylmorpholine *N*-oxide as the stoichiometric oxidizing agent. A residence time of 10 min in the microreactor with an internal volume of about 40 μL was enough to achieve full conversions at room temperature, thereby resulting in a productivity of around 1.0 mmol h^{-1} (Scheme 28b). The reactor was operated continuously for 10 h without degradation of the catalytic performance. Similarly, cleavage of carbon–carbon double bonds with $NaIO_4$ as a stoichiometric oxidant could be completed within reaction times of about 7 min at room temperature.[108]

4.4. Halogenation Reactions

Halogenation reactions are a ubiquitous class of transformations in synthetic organic chemistry. The introduction of chloro, bromo, and iodo atoms into organic molecules is often required to generate reactive intermediates during the preparation of fine chemicals. Furthermore, the introduction of fluorine in organic compounds is becoming increasingly important in the production of agrochemicals and pharmaceuticals, as the resulting compounds typically exhibit enhanced biological properties such as increased lipophilicity, bioavailability, and metabolic stability. The most inexpensive and atom-economical halogenation procedure involves elemental diatomic halogens (X_2) or the corresponding hydrogen halides (HX) as reagents. Unfortunately, these reagents are difficult to handle, corrosive, and highly toxic substances. The most impressive example is elemental fluorine (F_2), a highly poisonous, colorless gas. Its extreme reactivity makes it especially difficult to handle and to store. As it even reacts with silicon and quartz, specially designed metal alloys are required as containers to allow the storage of diluted mixtures of fluorine in N_2.

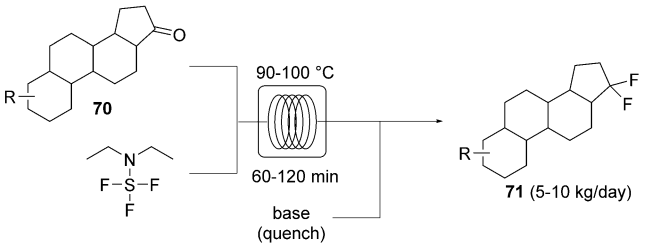
Microreactor technology has been shown to be a useful tool for halogenation reactions. Even fluorination reactions with elemental F_2 can be performed in a safe and controllable manner in microreactors, as demonstrated by the extensive contributions from the research groups of Sanford, Chambers, and others.[109–113] In the pioneering work of Chambers and Spink, a microreactor fabricated from a block of nickel (or copper) was described which was specifically designed to perform fluorination reactions with elemental fluorine.[112] The reactor showed excellent performance for the fluorination of β-dicarbonyl compounds.[112] Such fluorinations in macrobatch systems typically afford only very low conversions.[113] In a more recent study the same reactor was applied for the two-step synthesis of 4-fluoropyrazole derivatives (Scheme 29a).[114] After the fluorination reaction of the β-dicarbonyl compound, an organic hydrazine was introduced into the system through a T-mixer to generate the desired fluorinated pyrazoles in good yields.[114] The in situ generation



Scheme 29. Reactions with elemental fluorine.

of the highly effective oxidizing agent HOF·MeCN from fluorine gas and wet acetonitrile was performed in an analogous microreactor.[115] A spontaneous reaction of HOF·MeCN with alkenes at room temperature gave the corresponding epoxides in excellent yields (Scheme 29b).[115]

Alternative easier-to-handle fluorinating agents such as Selectfluor and diethylaminosulfur trifluoride (DAST) have also been utilized for fluorination reactions in flow.[116] DAST is a volatile, corrosive compound which reacts violently with water and decomposes to form explosive compounds upon heating. An interesting application of DAST was provided by Bayer Schering Pharma during the geminal difluorination of the 17-keto steroid **70** (Scheme 30).[117] The semibatch process

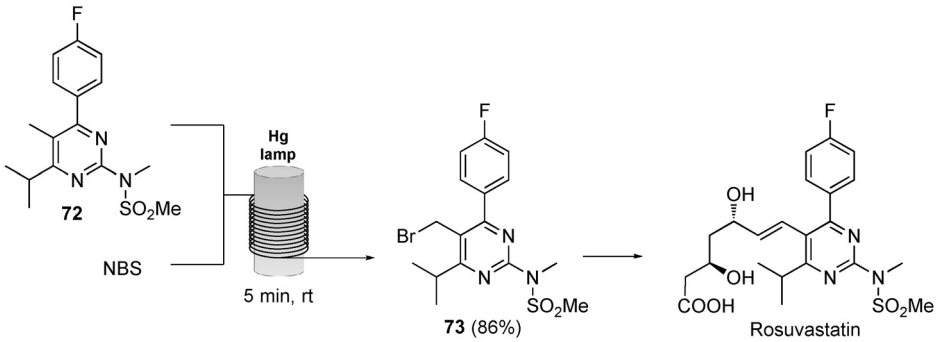


Scheme 30. Fluorinations with DAST.

resulted in a rather slow reaction at 90 °C with simultaneous decomposition of DAST. In contrast, by using a 500 mL tube reactor, a flow process could be performed safely with a productivity of 5–10 kg per day of the desired difluoro-derivative **71**.[117]

Likewise, Cl_2 gas and Br_2 have been employed for the direct chlorination and bromination of organic compounds using microreactors.[118,119] Typically, a solution of the substrate in a suitable solvent and elemental halogen are fed into the reactor as separate feeds using a suitable mixer. A similar experimental setup was used in a continuous-flow procedure for the photobromination of benzylic compounds using NBS as the bromine source.[120] The tubular reactor was made from light-transparent FEP tubing wrapped around a household compact fluorescent lamp. This setup was suitable for the selective benzylic monobromination of a broad range of substrates within residence times of 13 to 50 min at temperatures of 0 to 60 °C.[120] Časar and co-workers used a similar tubular photoreactor for their preparation of a 5-(bromomethyl)pyrimidine precursor of Rosuvastatin, a drug mainly used for the treatment of dyslipidemia (Scheme 31).[121] The photoreactor was built using a FEP tubing with an inner diameter of 0.8 mm and a 150 W medium-pressure Hg lamp. After a residence time of 5 min in the photoreactor, 98% conversion was obtained and 86% of the desired product **73** was isolated after recrystallization. In contrast, 13 h reaction time was required in the batch mode on a 200 mmol scale with the same 150 W mercury lamp. The productivity of the 18 mL photoreactor was 58.3 mmol product per hour.[121]

An example of mono-iodination of aromatic compounds in flow was presented by the group of Yoshida.[122] Electrophilic I^+ was generated electrochemically from the anodic oxidation of I_2 in MeCN. The resulting active $(MeCN)_2I^+$



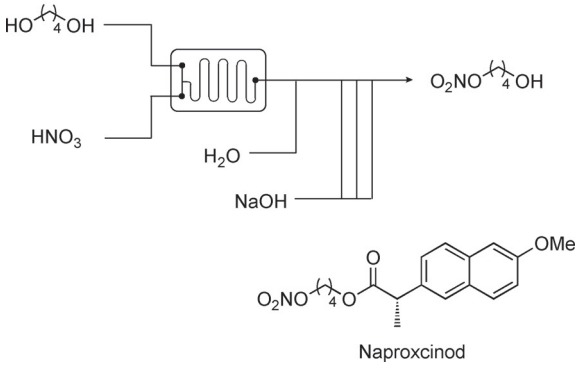
Scheme 31. Light-induced benzylic brominations in continuous flow.

species reacted with dimethoxybenzenes to give the corresponding iodinated benzenes.[122]

4.5. Hazardous Reactions with Nitrogen Compounds

4.5.1. Nitration Reactions

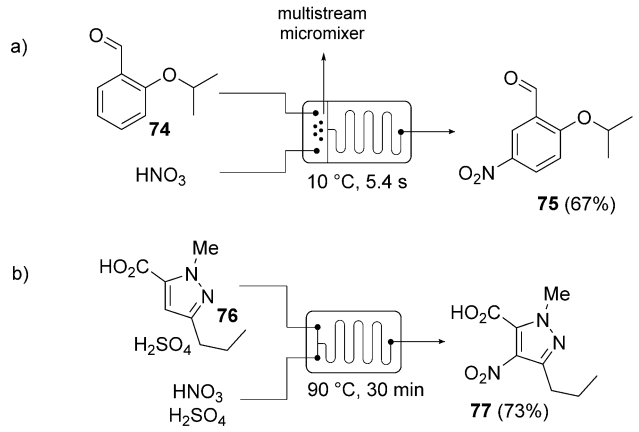
Among the most frequent and most destructive accidents in the chemical industry have been those involving nitration reactions.[123] Nitric acid, the most common nitration agent, is a highly corrosive substance as well as a powerful oxidant. Additionally, nitration mixtures and often also the nitration products are sensitive and liable to violent decomposition. Since nitration reactions are typically performed at reaction temperatures close to the runaway temperature, the strong exothermicity of these reactions is particularly problematic.[123] The better control of the reaction conditions in microreactors improves safety and suppresses side reactions.[124–126] It is not surprising, therefore, that continuous-flow nitrations have found quite considerable usage, and several continuous nitration plants on a commercial scale are currently in operation.[124,125] Notably, in a collaboration of IMM and Xi'an Huian Chemical Industrial Group, a microreactor system for the continuous production of around 10 kg h^{-1} of nitroglycerin was developed. Since the nitroglycerin is intended exclusively for medicinal use, stringent quality requirements have to be met and it is produced under GMP conditions.[124] A recent comprehensive review covers the current state of continuous-flow nitrations.[125] An impressive example of a continuous-flow nitration on a production scale is the formation of a nitrate-building block in the synthesis of Naproxcinod, an anti-inflammatory drug, by DSM (Scheme 32).[127] The reaction starts with the mixing of the nitric acid with the substrate/solvent emulsion in a Corning microreactor system. The microreactor device provides the heat transfer and mixing capability required for the nitration step. At the end of the residence unit, the reaction is diluted by adding water and the mixture is then partially neutralized by a stepwise addition of caustic soda to stabilize the mixture for further downstream processing (Scheme 32). Intensive mixing of the immiscible organic and the water phase for proper neutralization and efficient removal of the heat from the dilution and neutralization are also crucial at this stage.[127] The reactor had an internal volume below 150 mL and a capacity to process about 13 kg h^{-1} in this specific nitration process. The individual reactor modules were then "numbered-up" to a production unit with a total capacity of approximately 100 kg h^{-1} (Scheme 32).[127]



Scheme 32. Production bank with four identical reactors for continuous nitration and reaction scheme. Image reproduced from Ref. [127b] with permission. Copyright 2009, American Chemical Society.

A batch procedure for the nitration of 2-isopropoxybenzaldehyde (**74**) with red fuming HNO_3 was developed by Olszewski and co-workers (Scheme 33a).[128] An attempt to scale the reaction to one kilogram resulted in a drastic drop in reaction selectivity and yield (30%), because of reduced mixing efficiency and cooling performance on a larger scale.[128] An in-house-built continuous-flow silicon–glass microreactor with integrated micromixer, 75 μL reaction channel, cooling chamber, and five miniature temperature sensors gave the product after residence times of only 5.4 s in 67% product yield. In total, 26 g of the product was produced in 2 h.[128]

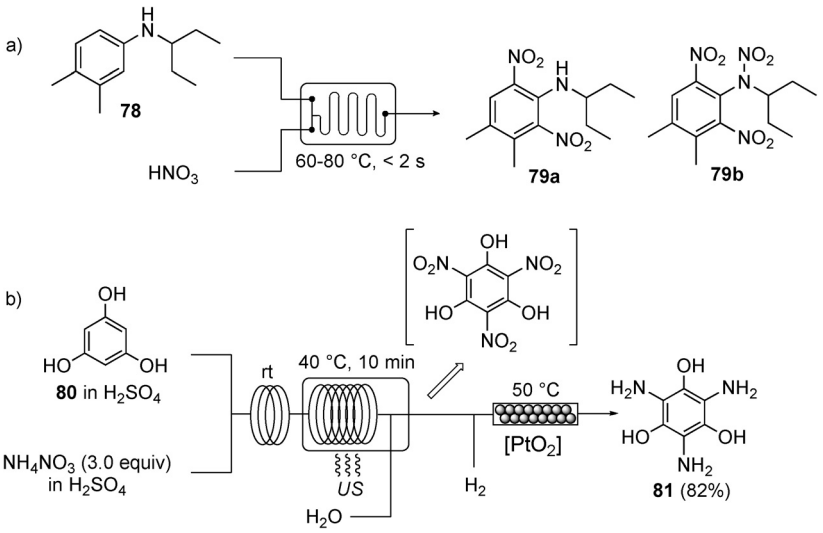
Along the same lines, a 70 mL CYTOS stainless-steel microreaction system was employed for the nitration of pyrazole-5-carboxylic acid **76** to generate **77**, a key intermediate in the synthesis of Sildenafil (Scheme 33b).[129] The



Scheme 33. Continuous-flow nitrations in microreactors.

process was operated at 90 °C with a residence time of 30 min, thereby resulting in a throughput of 5.5 g h^{-1}.[129]

Two nitration steps are necessary for the synthesis of dinitroherbicide **79** (Scheme 34 a). In the conventional two-step approach, aniline **78** is nitrated with diluted nitric acid, and after isolation, the mononitro intermediate is treated with



Scheme 34. Multistep nitrations under continuous flow.

additional concentrated nitric acid. Chen and co-workers demonstrated that the concentration of the nitration mixture can be safely increased using microreactor technology.[130] For the flow process in a 0.2 mL multichannel microreactor, both nitrations were conducted with 65 % nitric acid at temperatures of 60 °C to 80 °C and residence times of less than two seconds without isolation of the intermediate.[130] A continuous run for 1 h provided 0.54 kg of the products **79 a** and **79 b** in 97 % overall yield. This corresponds to a daily output of approximately 13 kg for a single microreactor with a total internal volume of approximately 200 μL.[130]

Three successive nitrations are even required for the synthesis of trinitrophloroglucinol (TNPG). A subsequent hydrogenation gives triaminophloroglucinol (**81**), an intermediate in the synthesis of certain powerful cation chelating agents. In this case, not only is the first nitration of the strongly electron-rich phloroglucinol (**80**) extraordinary fast and exothermic, but, furthermore, TNPG is a highly unstable and explosive compound. Thus, a telescoped flow process for nitration and subsequent hydrogenation was devised (Scheme 34 b).[131] A solution of the phloroglucinol in sulfuric acid and a solution of NH_4NO_3 in sulfuric acid were mixed in a T-shaped static mixer and the combined solution passed through a first residence capillary of 1 mm inner diameter at room temperature. The first residence capillary dissipates the heat generated in the initial nitration and prevents a thermal runaway. The residence time for the slower subsequent nitrations was provided by a second residence tube at 40 °C (1.6 mm inner diameter). The TNPG thus formed is not soluble in sulfuric acid and precipitates from the reaction mixture. Hence, the second residence tube was immersed into a thermostated ultrasound bath to prevent clogging. The processed stream was then combined with a stream of water to quench the reaction and to redissolve the precipitated TNPG. The homogeneous solution was finally directly hydrogenated with H_2 over PtO_2 in a fixed-bed high-pressure hydrogenator to give **81** in an overall yield of 82 %.[131]

4.5.2. Diazo Compounds

Diazomethane, CH_2N_2, is a volatile, poisonous, and carcinogenic substance (the boiling point of CH_2N_2 is −23 °C). The high reactivity and the extraordinary sensitivity to explosive decomposition makes the handling of CH_2N_2 challenging and has severely limited its widespread use in laboratories and industry. However, diazomethane is an exceptionally versatile and potent C1 building block in organic synthesis. Reactions with diazomethane are usually very fast and clean, often producing nitrogen as the sole by-product. CH_2N_2 is a particularly reactive methylation agent for a variety of nucleophiles and, additionally, it provides an elegant and short way to convert carboxylic acids and ketones into their respective higher homologues. Interest of the chemical industry in diazomethane chemistry has increased markedly in recent years, particularly because of its use in the synthesis of modern HIV protease inhibitors (Figure 3). Many of the new-generation viral protease inhibitors approved for HIV treatment contain a chiral amino alcohol structure in the central core (Figure 3). Even though a number of industrial syntheses of this structure have been developed, the synthesis from protected amino acids and diazomethane in a modified Arndt–Eistert reaction gives the most direct and cost-effective route. This approach is attractive since the reaction with diazomethane does not compromise the chiral integrity of the amino acid.

The generation and use of diazo and diazonium compounds in microreactors have been explored by several

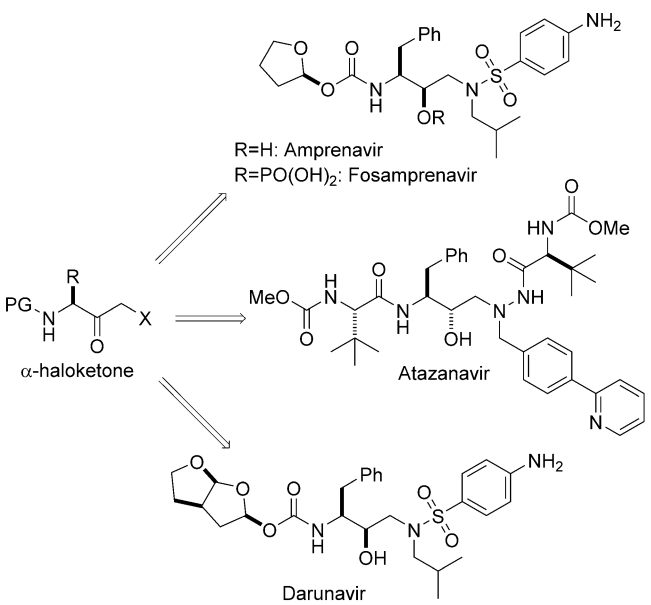
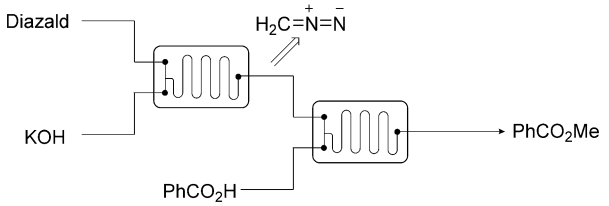


Figure 3. HIV protease inhibitors derived from α-haloketones.

groups and was recently reviewed.[132] A simple flow process for the production and in situ conversion of diazomethane comprises a feed containing a suitable *N*-nitrosoamine and a second feed of a potassium hydroxide solution. The two feeds are combined in a microreactor to produce the diazomethane. A third feed with the substrate is subsequently mixed into the reactor to convert the substrate into the diazomethane follow-up product. This approach was successfully used for the methylation of benzoic acids (Scheme 35).[133] However, an excess of the acid is required to neutralize the base used to generate the diazomethane.

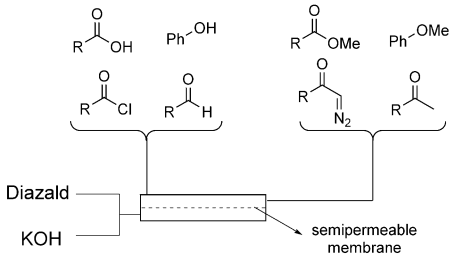


Scheme 35. In situ generation and consumption of diazomethane.

An industrial continuous-flow process for the generation of organic solutions of diazomethane was disclosed by Aerojet in 1998.[134] A stream of an *N*-methyl-*N*-nitrosoamine in an organic solvent is combined with a stream of an aqueous inorganic base. The aqueous and organic phases are permitted to settle, and the phases are separated. The diazomethane is continuously recovered as an organic solution and can be fed directly to a batch or a further continuous-flow reactor for a subsequent reaction. The generation of the diazomethane can be further coupled with an upstream continuous-flow process for the preparation of the nitroso compound from harmless *N*-methyl compounds and aqueous sodium nitrite.[134–136] A related process based on a continuous membrane-separator was reported by DSM.[136] The organic phase containing the diazomethane passes through a hydrophobic membrane, whereas the aqueous phase of the reaction mixture, including waste salts, is retained by the membrane and is directed into a quench solution.[136]

The activated acids required for Arndt–Eistert or related reactions are extremely water- and base-sensitive. For these reactions it is, therefore, essential that the diazomethane is adequately purified. Proctor and Warr from Phoenix Chemicals described a continuous-flow process capable of producing up to 60 metric tons per year of anhydrous diazomethane.[137,138] CH_2N_2 was generated from a feed of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) in a high-boiling solvent (DMSO) and a second feed of potassium hydroxide in water. The CH_2N_2 gas was continuously stripped from the aqueous solution by a stream of nitrogen to a reaction vessel, where it was consumed in a downstream reaction.[137,138] The full-scale diazomethane plant has been in operation for several years without incident and has successfully produced ton quantities of products.[138]

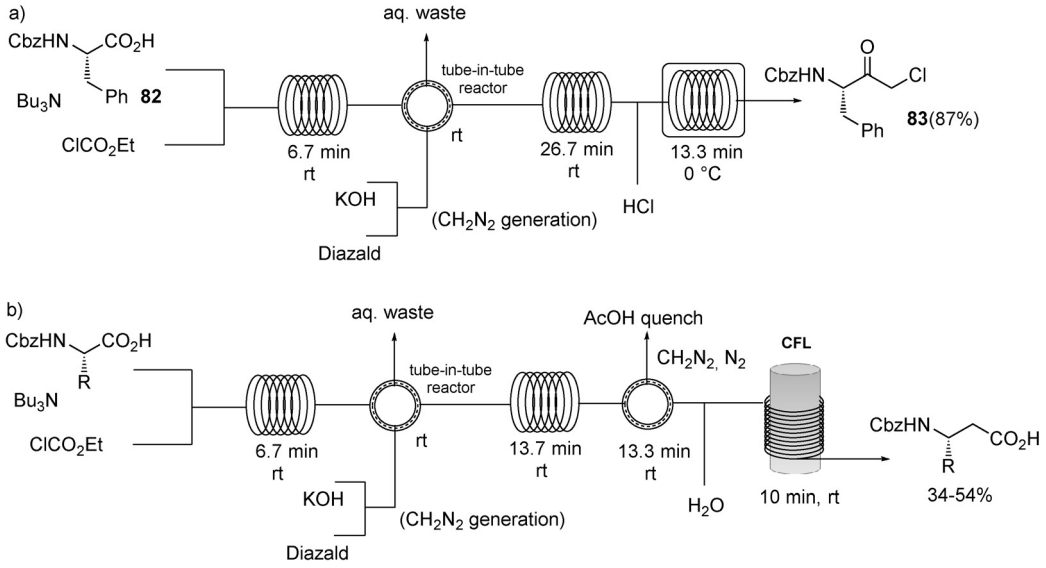
Kim and co-workers used the PDMS dual-channel microreactor (cf. Scheme 19) to integrate generation, separation, and consumption of diazomethane in a continuous-flow microsystem (60 μL residence volume).[139] The microreactor consisted of two parallel channels separated by a gas-permeable, 45 μm thick PDMS membrane. Diazomethane was produced from Diazald and KOH in the lower channel and gaseous CH_2N_2 diffused through the membrane to the upper channel where it reacted with the substrate carried within. Diffusion of diazomethane into the walls of the dual-channel reactor was avoided by coating the channels with a PVSZ polymer. Various reactions, including the synthesis of a diazoketone from the respective benzoyl chloride, were performed in the upper channel. The reactor provided the desired products in excellent yields with throughputs of around 1 mmol per day (Scheme 36).[139]



Scheme 36. Dual-channel microreactor with membrane for generation, separation, and reactions of diazomethane.

By incorporating the synthesis, separation, and consumption into a single device, the transport or diffusion paths and, hence, decomposition of the unstable CH_2N_2 reagent are reduced. Furthermore, the on-demand generation-purification-consumption of diazomethane eliminates human exposure and the need to store this hazardous compound. An analogous approach using a commercial tube-in-tube reactor allowed the laboratory-scale generation of anhydrous diazo-

methane in mmol per hour quantities.[140] The inner tube of the device was made of hydrophobic, gas-permeable Teflon AF-2400 with an internal volume of 2 mL and was enclosed within a thick-walled impermeable outer tube (PTFE; 3.2 mm outer diameter). Diazomethane was generated in the inner tube from a methanolic solution of Diazald and a solution of KOH, while the substrate solution was carried and reacted in the outer chamber. Two equivalents of Diazald in the inner tube sufficed to obtain quantitative conversion for esterifications, cyclopropanations, and [2+3] cycloadditions, with throughputs of around 1.8 mmol h^{-1}. The set-up was later extended to achieve the direct transformation of protected α-amino acids to their corresponding α-chloro ketones in a fully continuous, multistep reaction sequence (Scheme 37a).[141] A



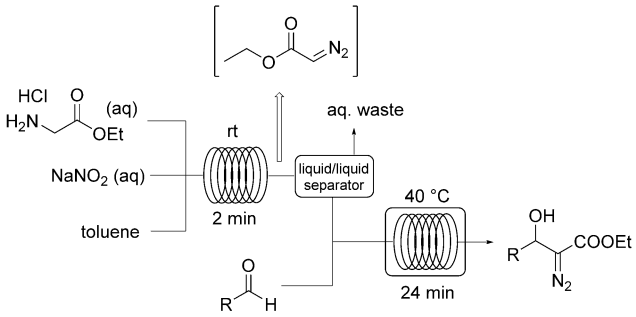
Scheme 37. Generation of anhydrous CH_2N_2 and its consumption by using a tube-in-tube reactor.

residence loop and a T-mixer were attached upstream to the outer tube of the tube-in-tube reactor and a further residence loop and a T-piece were connected downstream to the reactor (Scheme 37a). The activation agent and the amino acid **82** were pumped into the system with two syringe pumps. The mixed anhydride was formed in the first residence loop at room temperature and passed through the outer chamber of the tube-in-tube reactor. In the tube-in-tube reactor the anhydride was supplied with a continuous stream of anhydrous diazomethane from the inner tube. Formation of the diazoketone was completed in a second residence loop before the mixture was finally quenched with an excess of an ethereal solution of HCl at 0 °C. The HCl destroys any excess CH_2N_2 and reacts with the diazoketone to furnish the desired α-chloroketone **83** in a third residence loop. The pure α-chloroketone **83** was collected and isolated by chromatography in 87% yield after the continuous-flow three-step reaction sequence. The system was run continuously for about 4.5 h to produce 1.84 g of the enantiopure α-chloroketone **83**.[141]

A modified system allowed the four-step synthesis of β-amino acids from the respective protected α-amino acids (Scheme 37b).[142] A Wolff rearrangement of the diazoketones with accompanying interception of the intermediate ketenes with water provided β-amino acids from α-amino acids. The Wolff rearrangement was performed either photochemically in a photoreactor or, alternatively, catalyzed by Ag_2O packed into a cartridge reactor.[142] An additional tubing of gas-permeable Teflon AF-2400 was attached between the second residence coil and the photoreactor to remove any excess diazomethane and, furthermore, the nitrogen generated during diazoketone formation (Scheme 37b). The permeable tubing was immersed in an alcoholic solution of acetic acid to immediately quench any diazomethane diffused through it. The continuous-flow setup was used to prepare a variety of β-amino acids from the corresponding N-protected α-amino acids in around 50% overall yields after column chromatography (Scheme 37b).[142]

As a less-explosive replacement for diazomethane, (trimethylsilyl)diazomethane ($TMSCHN_2$) can be employed for certain applications, and its use in continuous-flow reactors was explored by several research groups.[143] $TMSCHN_2$ is a commercially available, transportable liquid but because of its high price and its limited purity, it has not yet found general and widespread acceptance as a safe substitute for diazomethane.

Similarly to diazomethane, ethyl diazoacetate (EDA) is an important synthon in organic chemistry. This compound can be prepared by reaction of glycine ethyl ester with sodium nitrite in water as solvent. Chemists from DSM have produced ethyl diazoacetate in a series of Corning microreactor modules, in which an acidified aqueous solution of glycine ethyl ester hydrochloride was mixed with an aqueous solution of sodium nitrite.[136] Immediately upon its formation, the ethyl diazoacetate was extracted into an organic solvent and the organic phase was continuously separated from the aqueous phase.[136] Kim and co-workers extracted ethyl diazoacetate from the aqueous reaction solution with toluene and used a microseparator with a PTFE membrane for separation of the organic phase.[144] The ethyl diazoacetate was used for continuous downstream reactions, such as addition to aldehydes to generate α-hydroxydiazo compounds (Scheme 38).[144]

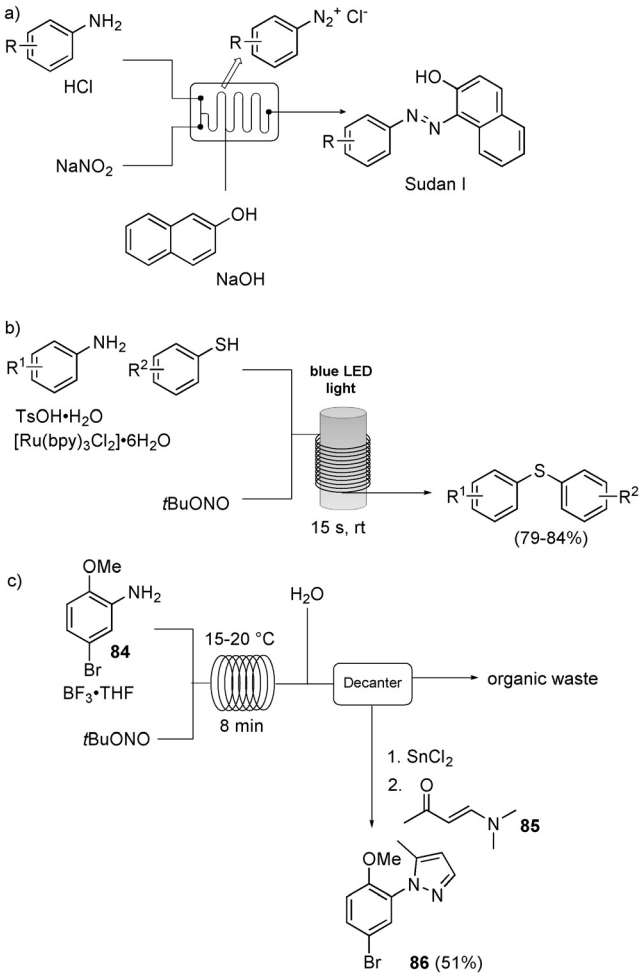


Scheme 38. Cascade generation, separation, and reaction of ethyl diazoacetate with various aldehydes.

4.5.3. ***Diazonium Compounds***

Challenges associated with diazonium salts predominantly arise from the thermal instability of diazonium intermediates and the evolution of large volumes of nitrogen gas during many of its transformations (e.g. Sandmeyer or related reactions). The use of diazonium salts in industry is thus generally subject to stringent safety procedures. The formation of diazonium salts and their subsequent in situ transformation in microreactors was first reported in 2002 by de Mello and co-workers.[145] A feed of aniline and HCl was combined with a feed of sodium nitrite in a nanochip with a total internal volume of 2.55 μL. The diazonium chloride was formed in a first integrated residence unit and immediately reacted with a solution of β-naphthol and sodium hydroxide in a second residence unit to generate the azo dye Sudan I (Scheme 39 a).[145,146] In a subsequent study, the group used isoamyl nitrite to synthesize aryl chlorides from anilines in a modified Sandmeyer reaction under non-aqueous conditions.[147] On-line Raman spectroscopy allowed the disappearance of the aniline to be monitored and dynamic optimization of the reaction conditions.[147] Similar basic reactor designs were used by other research groups for reactions involving aryldiazonium salts as intermediates, including Sandmeyer-type reactions,[148] Meerwein arylation,[149] and Heck reactions.[150] A particularly interesting example is the continuous-flow synthesis of arylsulfides by a photocatalytic Stadler–Ziegler reaction.[151] A solution of the aniline, a thiol, and $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ as photocatalyst was combined with a solution of *tert*-butylnitrite. The mixture subsequently passed through a PFA capillary microreactor irradiated with blue LED light (Scheme 39 b). A residence time of only 15 s was required in the 460 μL photoreactor to obtain full conversions, and up to 14 mmol h^{-1} product could be isolated in around 80 % yield.[151]

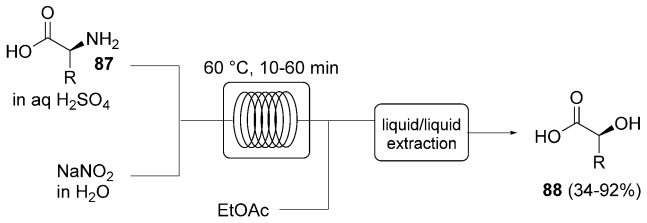
Chemists from Pfizer reported a four-step synthesis of an *N*-arylpyrazole.[152] *N*-aryl- or -alkylpyrazole moieties are present in multiple blockbuster drugs including Celecoxib, Rimonabant, Sildenafil, and the recently approved lung cancer drug Crizotinib. Pfizer's synthesis started with diazotization of aniline **84** by combining an aniline/$BF_3\cdot$THF mixture with *tert*-butylnitrite (Scheme 39 c). The formation of the diazonium fluoroborate was finished after 8 min residence time in a 400 mL PTFE plug-flow coil reactor. To



Scheme 39. In situ diazotization and reactions in continuous flow.

remove any impurities and any excess *tert*-butylnitrite from the diazotization step, the effluent reaction mixture was mixed with a water stream and the biphasic mixture entered a glass standpipe decanter for phase separation. The organic layer was continuously removed as a waste stream, while the aqueous phase was directed into a batch reaction vessel containing $SnCl_2$. Reduction with tin(II) chloride provided the corresponding hydrazine, which in turn reacted with ketoenamine **85** in a subsequent one-pot reaction to give the desired *N*-arylpyrazole **86**.[152] After approximately 3 min residence time in the PTFE reaction coil, the diazonium salt started to crystallize from the mixture. Nevertheless, the authors reported continuous operation for about 8 h without pressure buildup as a result of solid agglomeration, and kilogram quantities of the desired material were synthesized.[152]

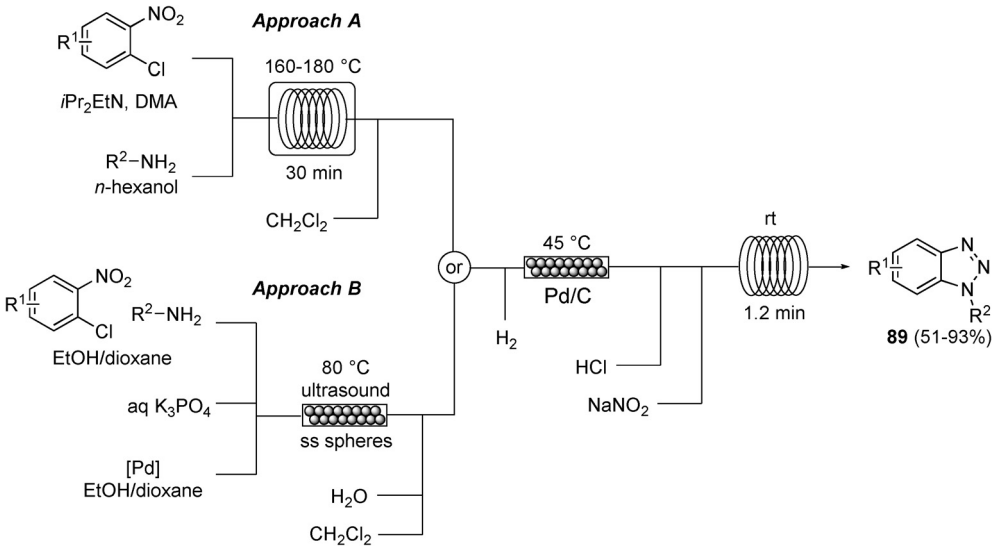
Ley and co-workers described an efficient stereoselective synthesis of α-hydroxy acids **88** from the corresponding naturally occurring α-amino acids (Scheme 40).[153] A solution of the amino acid **87** in aqueous sulfuric acid and a solution of aqueous sodium nitrite were introduced into the flow reactor. At a reaction temperature of 60 °C, the diazotization was completed after 10 to 60 min before the hydroxy acid was isolated by multiple automated continuous extractions. The



Scheme 40. Flow diazotization with multiple extractions.

pure (*R*)-hydroxy acids were obtained in yields of around 90% upon drying and concentration of the organic phase. The reaction with valine as the substrate was conducted on a 20 g scale over a 24 h period without any manual intervention.[153] The *R* enantiomer of hydroxyvaline derived from this process was used as the starting material for the total synthesis of (−)-enniatin B by Ley and co-workers.[154]

A multistep continuous-flow synthesis of 1-substituted benzotriazoles **89** starting from chloronitrobenzenes and amines was developed by Chen and Buchwald.[155] The sequence started with the formation of a C–N bond between chloronitrobenzenes and amines (Scheme 41). Depending on



Scheme 41. Multistep synthesis of 1-substituted benzotriazoles.

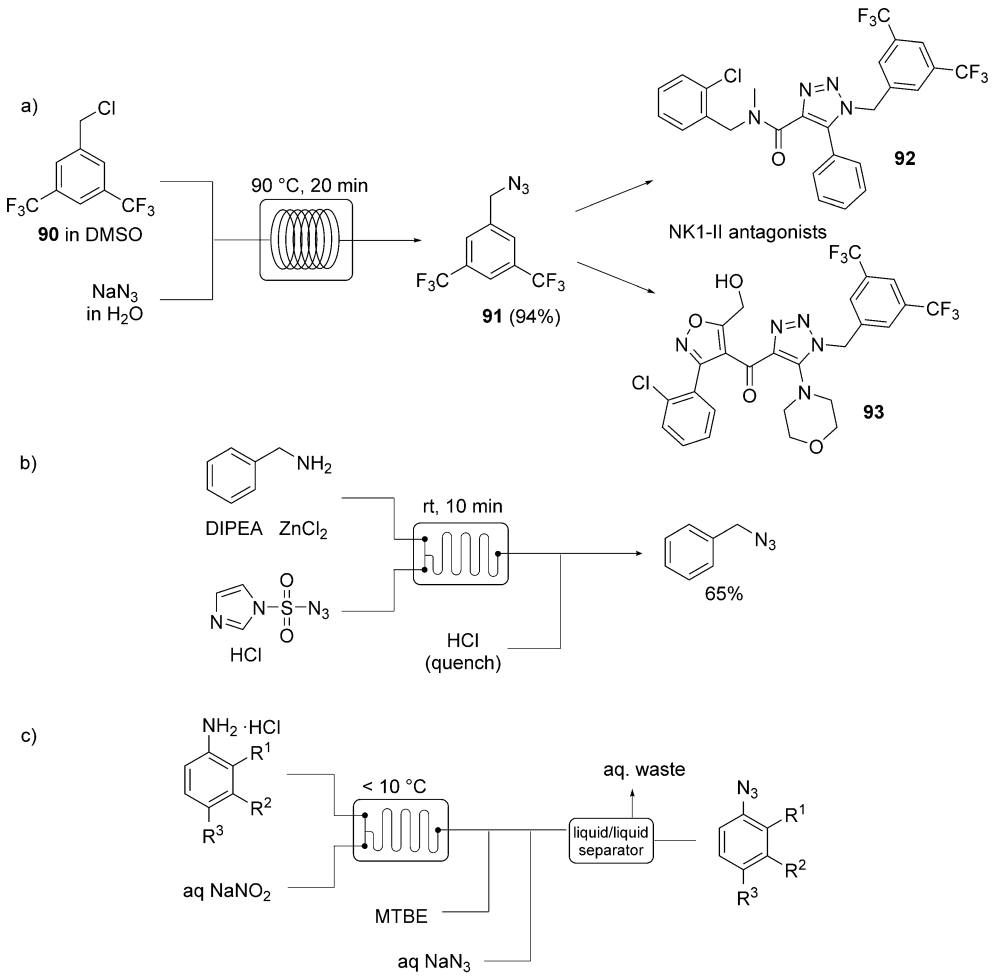
the electronic properties of the chloronitrobenzene, the C–N bond formation was achieved either by nucleophilic aromatic substitution in a high-temperature coil reactor or by a Pd-catalyzed C–N cross-coupling reaction of a biphasic solution of substrate, base, and palladium catalyst in a bed reactor packed with stainless-steel spheres at 80 °C. In both cases, the solution was directly mixed with H_2 gas and the resulting gas–liquid segmented flow passed through a Pd/C packed-bed reactor (Scheme 41). The reaction stream was subsequently combined with aqueous HCl and aqueous $NaNO_2$ to accomplish diazotization of the amine and cyclization to the substituted benzotriazole. Purification of the crude mixture by column chromatography afforded the desired products in 51–93% yield.[155]

4.5.4. ***Hydrazoic Acid, Azides***

Azides are one of the most reactive organic groups energetically, and their formation commonly requires severely toxic and explosive reagents. In particular, hydrazoic acid itself is a very volatile (b.p. 37 °C), explosive, and poisonous compound (comparable to HCN). Thus, HN_3 has relatively little relevance as a reagent in today's laboratories, and utmost care has to be exercized whenever HN_3 is expected to be formed during a reaction. Not surprisingly, numerous continuous-flow processes involving azides have been described in the past years. Unlike a traditional batch reactor, a flow reactor can be run essentially liquid-filled, thus removing any potentially explosive vapor-phase headspace. Combined with the low internal volumes of flow reactors, this allows reactions with azides/HN_3 to be performed relatively safely and at temperatures which would be unfeasible in conventional batch vessels.

Chemists at Eli Lilly required large amounts of azide **91** for the synthesis of the triazoles **92** and **93**, compounds with potent NK1 antagonist activity (Scheme 42a).[156] The initial batch reactions were conducted with benzyl chloride **90** and NaN_3 in a two-phase DMSO/H_2O mixture. The reaction was completed within three hours at 40 °C under optimized conditions in a highly agitated batch reactor. However, mass-transfer limitations became apparent when the reaction was performed on a 250 mL scale in a standard mechanically stirred glass reactor. The reaction conditions were then modified to allow a continuous-flow synthesis of the desired azide. The reaction could be conducted in a 20 mL stainless-steel tube reactor with an inner channel diameter of approximately 0.6 mm at a reaction temperature of 90 °C, thereby reducing the reaction time to 20 min. 25 g of benzyl chloride **90** were converted into the azide within an operation time of 3 h (94% yield).[156]

The formation of benzyl azide from benzylamine using imidazole-1-sulfonylazide hydrochloride as the diazotransfer reagent was reported by Rutjes and co-workers.[157] Initial optimization reactions were performed in a 92 μL glass microreactor with two integrated mixers and a residence time unit (Scheme 42b). A solution of benzylamine, diisopropylethylamine (DIPEA), and $ZnCl_2$ was combined with a second solution of imidazole-1-sulfonylazide hydrochloride. After the mixture had passed through the residence unit it was quenched in a second mixer with a solution of HCl in ethyl acetate. Sixty multivariate optimization experiments were conducted in the microreactor, consuming only 400 mg

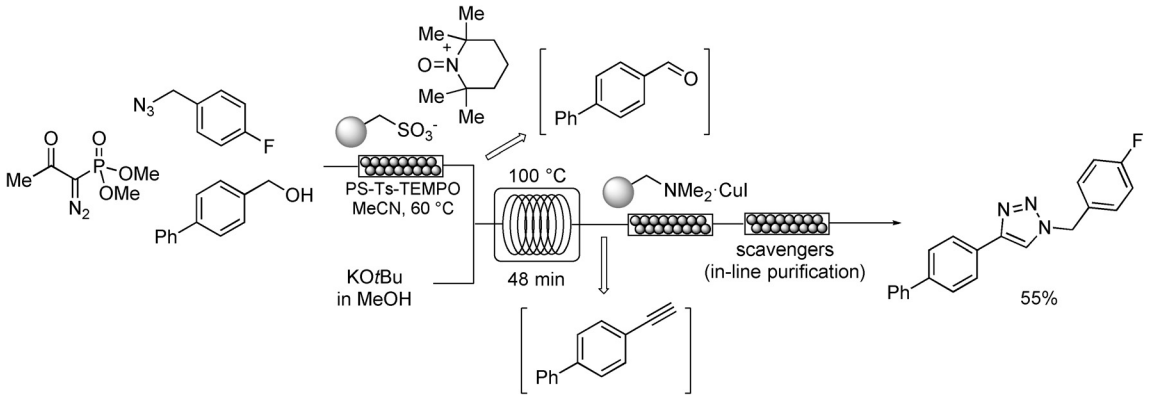


Scheme 42. Continuous-flow synthesis of azides.

of benzylamine. The optimized conditions were then used to process 1.4 g of benzylamine in a 20 mL stainless-steel reactor.[157]

Researchers at Aldrich applied a continuous process for the synthesis of aromatic azides starting from the corresponding anilines (Scheme 42c).[158] The diazonium salt was first generated in a glass microreactor from an aqueous feed of the aniline hydrochloride and sodium nitrite. An organic solvent and aqueous sodium azide were then fed in to convert the diazonium salt into the azide. The processed stream was finally collected and the organic phase was separated. The organic phase contained the azides in > 95 % purity in concentrations of around 0.5 M. Typically, the microreactor was run for 5–6 h to provide 100 to 200 g of the azide.[158]

Azides are the key intermediates for the synthesis of triazoles by the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC). Several approaches to perform CuAAC in microreactors have been reported, most of them using immobilized copper(I) sources.[159] An impressive example of a multistep synthesis of 1,2,3-triazole was presented by Ley and co-workers.[160] They were able to synthesize triazoles starting from aldehydes or alcohols and azides by a continuous reaction and purification sequence. Aldehydes were converted into the homologated alkynes with the Bestmann–Ohira reagent within 30 min residence time at 100 °C in a 10 mL PFA tube reactor. The preparation of the alkyne was then coupled with the in situ generation of the aldehydes from the respective alcohols and, additionally, direct subsequent conversion of the alkynes into triazoles by addition of benzyl azide (Scheme 43).[160] The processed stream was purified in-line in a series of scavenger cartridges (Scheme 43). The solvent



Scheme 43. Multistep flow synthesis of 1,2,3-triazoles.

was removed in vacuum and crystallization provided the desired 1,2,3-triazole in 55% overall yield.[160]

Despite the appealing advantages of fixed-bed catalytic reactors, such as simple catalyst separation, there is strong evidence that the CuAAC involves a homogeneous Cu^I species in the catalytic cycle and, consequently, copper gradually leaches from the catalyst bed.[161] The copper can be removed from the reaction stream in-line by using immobilized metal scavenger cartridges.[159–161] This is a powerful purification technique, but the scavenger cartridges have to be periodically replaced, thus interrupting the flow process. Therefore, CuAAC with homogeneous copper catalysts are often preferred. Hessel and co-workers extensively studied CuAAC under high-T/p conditions.[25,162] Excellent yields for the reaction of phenyl azide with phenylacetylene could be obtained with only 1 mol% $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst at 180°C after a residence time of 10 min in a PFA tube reactor (88% yield).[162] The reaction mixture was quenched in-line with ethyl acetate and an aqueous EDTA solution and the two phases were subsequently separated in a liquid–liquid membrane separator (Scheme 44a). The EDTA extraction reduced the copper content in the organic phase to 159 ppm with a single extraction stage.

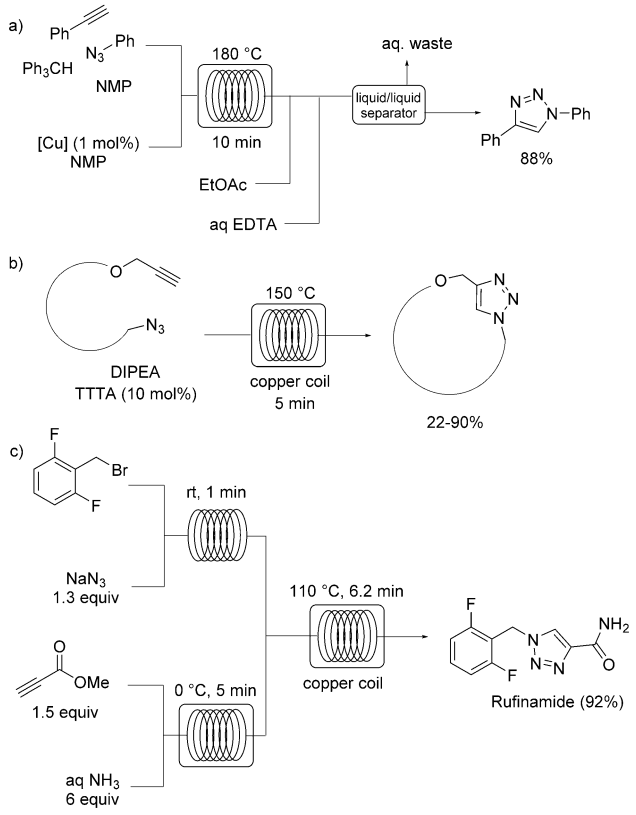
An interesting approach to form CuAAC was presented by Bogdan and Sach.[163] The CuAAC was performed in a continuous-flow mode using a copper coil as a reactor.[163,164] Notably, successful cycloadditions were performed at temperatures of around 150°C by using DMF/H_2O mixtures as the solvent without any additional Cu source. By using this approach, a variety of triazole-containing macrocycles comprised of 12- to 31-membered rings were synthesized in good to excellent yields after 5 to 10 min residence time (22–90%, Scheme 44b).[164] The high macrocyle-to-dimer ratio obtained in the copper coil was attributed to a "pseudodilution" effect arising from the large copper surface.[164]

By using a copper coil, Jamison and co-workers accomplished the continuous-flow total synthesis of Rufinamide, starting from a difluoro-substituted benzyl bromide, sodium azide, and methyl propiolate (Scheme 44c, cf. Scheme 2a).[26] Difluorobenzyl azide was prepared from the corresponding difluorobenzyl bromide and sodium azide, while the otherwise costly and unstable propiolamide was formed from methyl propiolate and aqueous ammonia. Both feeds were merged and the combined stream passed through a copper tubing at 110°C. The overall average residence time was 11 min, and Rufinamide was afforded in 92% overall yield.[26]

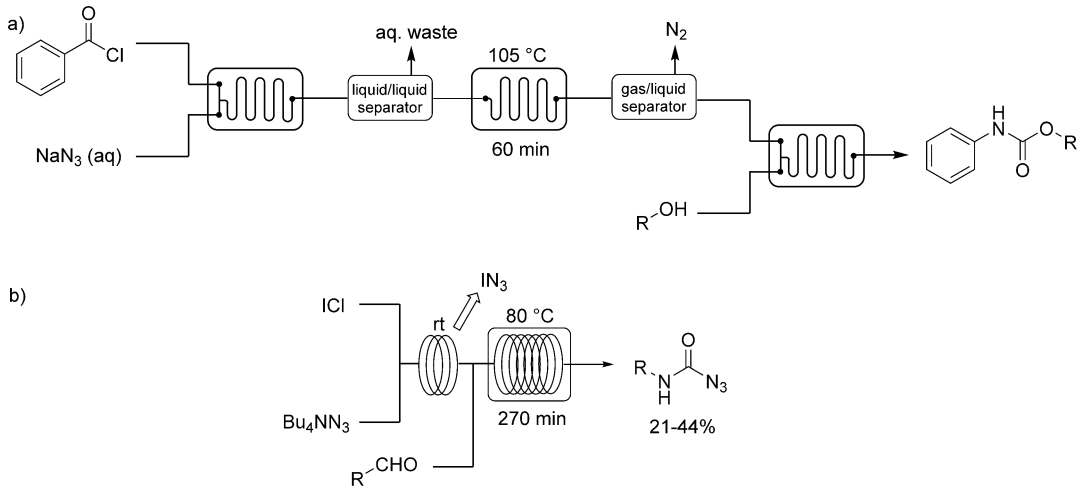
Jensen and co-workers integrated the synthesis of acyl azides, Curtius rearrangement, and subsequent quench in a multistep continuous-flow microreactor (Scheme 45a).[165] The first step, the reaction of aqueous sodium azide with benzoyl chloride in toluene under phase-transfer conditions to produce the organic azide, was immediately followed by a continuous separation of the aqueous and organic mixture in a membrane-based microseparator. The formation of the isocyanates from the acyl azides in the second reaction step was either performed by heating the azide to 105°C for 60 min in a standard microreactor or, alternatively, in a bed reactor with a solid acid as catalyst. The released nitrogen was removed in a second separator unit and the carbamate was finally formed by mixing the generated isocyanate with an alcohol in a third microreactor. With flow rates of 1 μL min^{-1} for the aqueous and organic reagents, the productivity of the microreactor was about 80–120 mg per day (Scheme 45a).[165] Even though the productivity is modest, the reactor could be operated uninterrupted for several days to produce preparatively relevant quantities.

In contrast, Brandt and Wirth synthesized carbamoyl azides starting from aromatic aldehydes and IN_3 (Scheme 45b).[166] IN_3 was generated inside a microreactor from a stream of iodine monochloride (ICl) and a solution of tetrabutylammonium azide (Bu_4NN_3). IN_3 was formed in situ in the microreactor, and an aldehyde was then added to the reagent stream. The combined streams passed through a heated capillary with an internal volume of 196 μL. The intermediate acyl azide underwent a Curtius rearrangement to the corresponding isocyanate and finally gave stable carbamoyl azides by a reaction with excess Bu_4NN_3.[166]

Similarly to triazoles, tetrazoles can be synthesized by a Huisgen 1,3-diploar cycloaddition of azides to nitriles. Interest in tetrazole chemistry has increased rapidly over the past years, mainly because of the role of the tetrazole moiety as a metabolically stable surrogate for the carboxylic acid functionality in pharmaceutically active agents. Most notably, the biphenyl tetrazole motif is a key structural element in angiotensin II receptor antagonists, including Losartan, Valsartan, Candesartan, Irbesartan, and Olmesartan. A high-temperature continuous-flow process for the 1,3-diploar



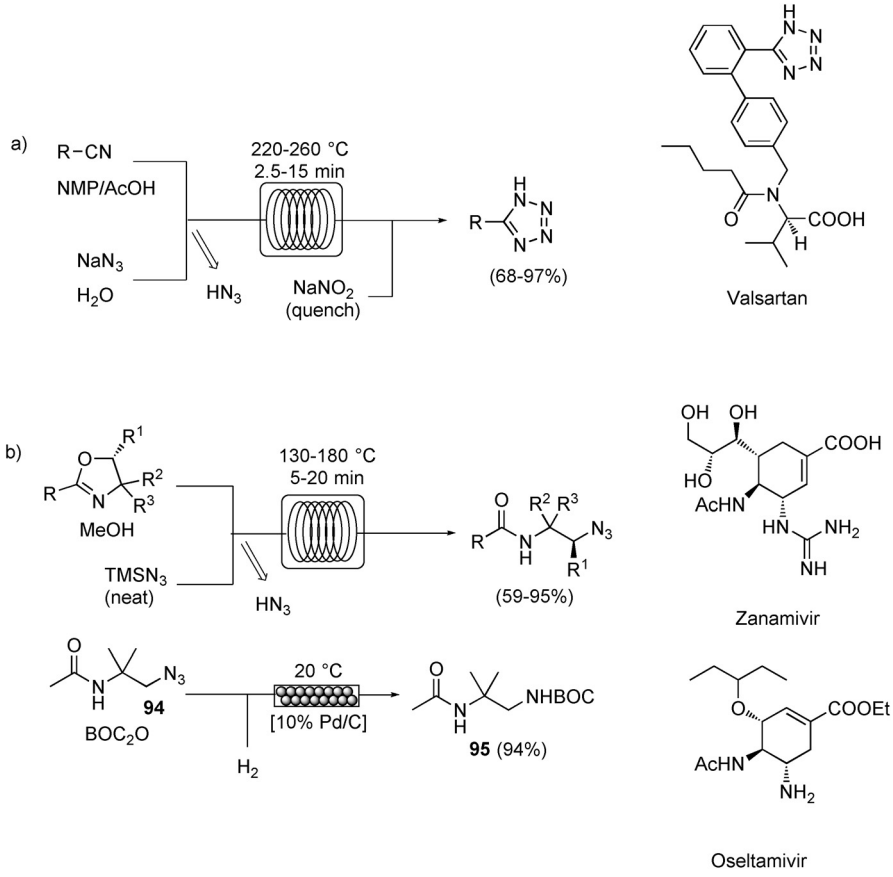
Scheme 44. Copper-catalyzed azide–alkyne cycloaddition reactions. TTTA = tris-((1-*tert*-butyl-1*H*-1,2,3-triazoyl)methyl)amine.



Scheme 45. Synthesis and rearrangement of acyl azides.

cycloaddition of hydrazoic acid to nitriles was reported in 2010.[167] The volatile and explosive hydrazoic acid was generated in situ by mixing aqueous sodium azide and acetic acid inside a suitable mixer, and the HN_3 was subsequently consumed by addition to nitriles in an ensuing heated coil reactor (Scheme 46 a).[167] The post-reaction stream was thermally quenched in a heat exchanger and unconsumed hydrazoic acid in the effluent product stream was immediately destroyed with aqueous $NaNO_2$. The cycloadditions were typically carried out at temperatures of 220 °C to give complete conversions at residence times of around 10 min. However, when benzonitrile was used as the model substrate, the 1,3-dipolar cycloaddition could be safely performed at a reaction temperature of 260 °C, thereby reducing the reaction time to only 2.5 min, without compromising product purity or yield. Productivities of 18.9 $g\,h^{-1}$ of 5-phenyltetrazole were attained (89 % yield) by using a 10 mL tube reactor.[167] A similar high-T/p process for tetrazole synthesis was described by the Jamison group.[168]

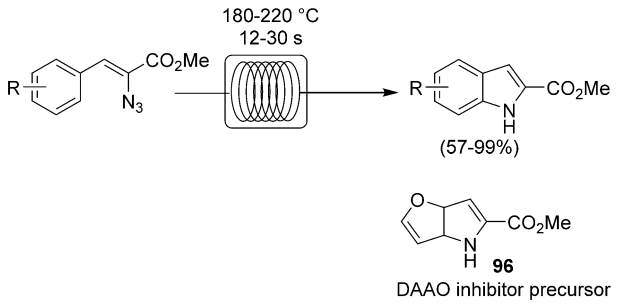
A somewhat related strategy was pursued for the synthesis of *N*-(2-azidoethyl)acylamides from oxazolines (Scheme 46 b).[169] The ring opening of oxazolines with an inorganic azide is a key step in the preparation of neuraminic acid analogues, such as the neuraminidase inhibitors Zanamivir and Oseltamivir. The HN_3 was produced from a feed of neat trimethylsilyl azide ($TMSN_3$) and a second feed of the substrates in MeOH. Solvolysis of $TMSN_3$ with MeOH provided hydrazoic acid, and a subsequent S_N2 ring opening of the oxazolines with HN_3 furnished the desired *N*-(2-azidoethyl)acylamides. The authors coupled the reaction with a direct hydrogenation of the azides to afford the selectively monoacylated diamines. To prevent migration of the *N*-acetyl group upon hydrogenation, azide **94** was mixed with di-*tert*-butyl dicarbonate (Boc_2O) to



Scheme 46. Continuous-flow reactions with in situ generated HN_3.

intercept the freshly formed amino group by formation of the Boc-protected *N*-(2-*a*minoethyl)acetylamide **95** (Scheme 46b).[169]

A high-temperature procedure for the continuous-flow thermolysis of azidoacrylates to yield indoles was reported by the Seeberger group (Scheme 47).[170] The reaction was

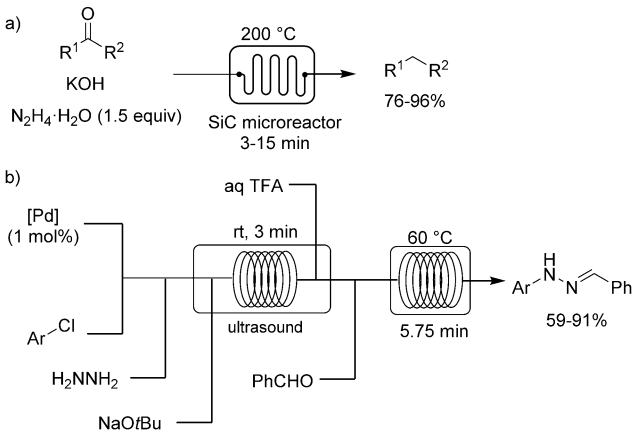


Scheme 47. Thermolysis of organic tetrazoles and azides.

completed after residence times as short as 12 s at 220 °C in a 2 mL stainless-steel reactor. In the case of the preparation of pyrrole **96**, a precursor for a D-amino acid oxidase (DAAO) inhibitor, the reaction was run for 21 min to produce 8.5 g of the desired material.[170] Similarly, photolysis of aryl azides in the presence of water to give 3*H*-azepinones was reported.[171]

4.5.5. ***Hydrazine***

The high toxicity of hydrazine (N_2H_4), together with its high heat of combustion and corrosiveness, makes it problematic for use on a large scale. However, hydrazine is a readily available, powerful bifunctional nucleophile and reducing agent. It condenses with various bifunctional electrophiles to generate valuable heterocycles such as indoles, pyrazoles, and triazoles, key building blocks for the preparation of a vast range of pharmaceuticals. Jensen and co-workers used a 470 μL silicon carbide (SiC) microreactor to perform a Wolff–Kishner reduction (Scheme 48a).[172] SiC is an



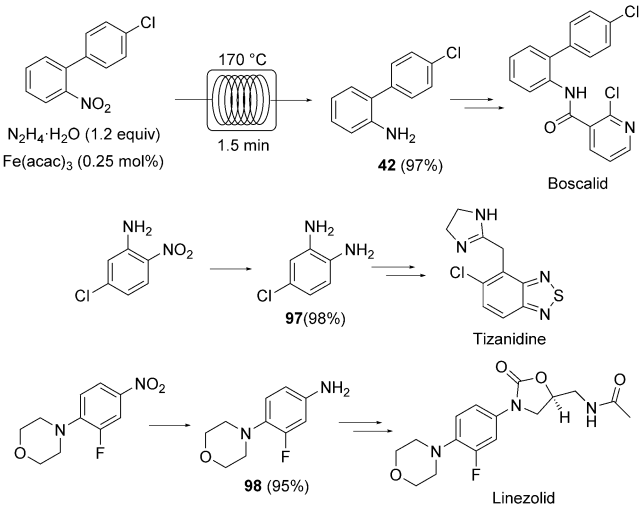
Scheme 48. Hydrazine as a reagent in continuous-flow reactions.

almost completely corrosion-resistant material which, furthermore, exhibits excellent heat stability and thermal conductivity. The reactions were conducted at 200 °C with only 1.5 equivalents of hydrazine hydrate and 3 equiv of KOH. A 3 to 15 min residence time was enough to convert the carbonyl functionalities of several ketones into methylene groups (76–96% yield). For the conversion of benzophenone, for example, this amounted to a daily productivity of 15.1 g and an excellent space–time yield of 61.9 $kg\,L^{-1}\,h^{-1}$. The required reaction time in the microreactor is about two orders of magnitude lower than standard reaction times in conventional batch reactors. This remarkable productivity is possible due to the combination of the high physical and chemical stability of the reactor material in addition to the absence of reactor headspace in the pressurized system.[172]

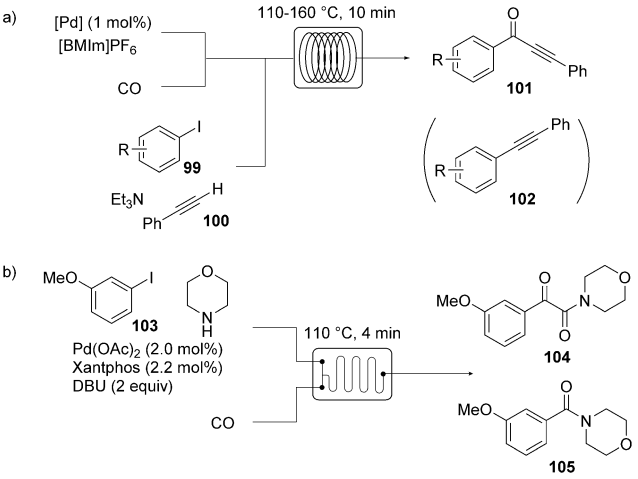
A direct palladium-catalyzed C–N cross-coupling with aryl chlorides and hydrazine was developed in the group of Buchwald (Scheme 48b).[173] Thus, solutions of precatalyst, aryl chloride, hydrazine, and base were mixed consecutively, and introduced into a first residence unit at room temperature. The residence unit was immersed in an ultrasound bath to prevent clogging as a result of NaCl precipitation during the coupling reaction. Upon exiting the residence unit, the mixture was combined with a stream of aqueous TFA to dissolve the NaCl and to catalyze a subsequent hydrazone formation. The reaction mixture was finally merged in-line with benzaldehydes and went through a second residence unit at 60 °C. Offline workup and purification gave the desired hydrazones in 59 to 91% yield. Similarly, by introducing β-diketones instead of aldehydes, a cyclocondensation directly afforded 1-arylpyrazoles in good yields (> 69%).[173]

The continuous-flow synthesis of 1*H*-pyrazoles from hydrazine monohydrate and 1,3-diketones was described by Haswell and co-workers.[174]

A selective iron-catalyzed reduction of nitroarenes to anilines with hydrazine hydrate as a stoichiometric reducing agent was developed using a microwave reactor as a convenient device to screen and optimize small-scale reactions.[175] The reaction gave essentially quantitative conversions and yields after 2 to 8 min reaction time at 150 °C using only 0.25 mol% $[Fe(acac)_3]$ as a precatalyst and a 20% excess of $N_2H_4{\cdot}H_2O$. Fe_3O_4 nanocrystals were generated in situ from $[Fe(acac)_3]$ by reduction with the hydrazine. The highly active nanocrystals then catalyzed the selective reduction of the nitro group. The reaction was then successfully translated to a continuous-flow format. With nitrobenzene as the model substrate, the reaction was completed after 1.5 min at 150 °C in a 20 mL stainless-steel reactor. Importantly, the in situ formed colloidal Fe nanocatalyst remains in solution during flow nitration, but a few minutes after the reaction solution left the back-pressure regulator, Fe_3O_4 nanocrystals started to aggregate and precipitate. Simple filtration of the processed mixture to remove the Fe_3O_4, followed by filtration through a plug of silica gel to remove excess hydrazine and water gave the aniline products in excellent yields and purities after evaporation of the solvent. The flow process was then applied for the preparation of the Boscalid intermediate 4-chloro-2′-aminobiphenyl (**42**) by selective reduction of the corresponding nitro compound (Scheme 49; see also Scheme 12a for



Scheme 49. Fe_3O_4-catalyzed reductions using hydrazine.



Scheme 50. Gas–liquid continuous-flow carbonylation. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Xanthpos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, $[BMIm]PF_6$ = 1-butyl-3-methylimidazolium hexafluorophosphate.

a selective hydrogenation with H_2). At a reaction temperature of 170 °C, 7.9 g of the pure aniline product could be produced within an operation time of 7–8 min (97 % yield).[175] By using the same approach, anilines **97** and **98**, intermediates in the synthesis of Tizanidine and Linezolid, were prepared from the corresponding nitroarenes (Scheme 49). In both cases, the desired amino compounds were obtained in excellent yields and selectivities. In a subsequent study, the Fe_3O_4 nanocrystals were immobilized onto basic alumina and packed in a cartridge. The catalyst cartridge could be utilized for the continuous-flow reduction of nitro compounds with hydrazine without apparent leaching over a run time of several hours.[176]

4.6. Reactions with Toxic and/or Reactive Low-Molecular-Weight Carbon Compounds

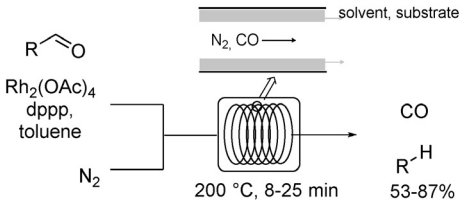
4.6.1. Carbon Monoxide

Carbon monoxide is a highly useful C1 building block for the synthesis of aldehydes, ketones, carboxylic acids, and carboxylic acid derivatives. Indeed, among the largest-volume processes in industrial homogeneous catalysis are platinum-group metal-catalyzed carbonylation reactions, such as the carbonylation of propene and methanol to produce *n*-butanal and acetic acid, respectively. However, because of its toxicity and volatility, laboratories in academia and the fine chemical industry frequently resort to more convenient, often solid carbon monoxide precursors.[177] As discussed at several points throughout this Review, continuous-flow and microreactor technologies provide a simple way to accurately dose gaseous reagents to a liquid feed and, furthermore, facilitates high-pressure operation as well as gas–liquid mass transfer. A microflow reactor for palladium-catalyzed carbonylative Sonogashira coupling and amidation reactions in an ionic liquid (IL) as solvent was demonstrated by the research group of Ryu (Scheme 50a).[178] The ionic liquid containing the Pd catalyst was first mixed with CO—fed in from a carbon monoxide gas bottle and a mass-flow controller—and afterwards with the substrates **99** and **100** in two consecutive micromixers. The multiphase stream (ionic liquid/substrate/CO) then passed into a heated capillary tube reactor. Reactions in the microreactor were considerably cleaner compared to batch reactions under otherwise identical conditions and provided the acetylenic ketones **101** as the sole products. A batch process, in contrast, gave significant amounts of the Sonogashira coupling product **102**. The substrate phase dissolved in the IL phase at the reaction temperature, whereas the solubility of CO in the viscous ionic liquid is very low.[178] Accordingly, the selectivity of the reaction is controlled by the diffusion efficiency of CO into the liquid segments. The large interfacial gas–liquid contact area attained in the microreactor prevented depletion of carbon monoxide in the liquid phase and, hence, reduced the formation of the side product **102**. The efficient gas–liquid exchange in microreactors cannot be easily reproduced by mechanically stirred batch reactors.[178]

Similarly, Buchwald, Jensen, and co-workers conducted a Pd-catalyzed aminocarbonylation of morpholine with aryl iodides **103** and bromides in a 78 μL microreactor (Scheme 50b).[179] In contrast to conventional batch reactions at near atmospheric pressure, aminocarbonylation in the microreactor at elevated CO pressures produced significant quantities of α-ketoamide **104**, in addition to the amide **105**.[179] An increase in the temperature favored amide formation, whereas elevated CO pressures enhanced α-ketoamide formation.[179]

De Mello and co-workers studied the Pd-catalyzed aminocarbonylation in annular- and segmented-flow regimes.[180] Although an annular-flow regime will generate a high interfacial surface area between the gaseous and the liquid phase, the low effective residence volume of the liquid phase in the microchannel typically results in short residence times for the liquid reagents. A segmented-flow regime, on the other hand, generally provides better control over the reaction time.

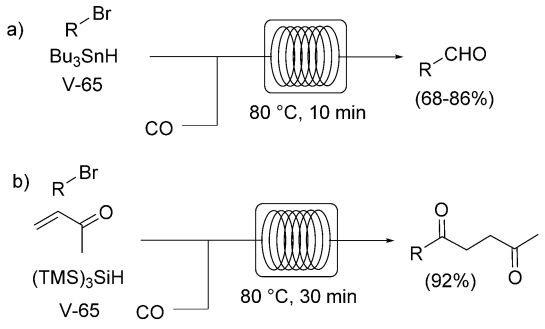
On the other hand, a rhodium-catalyzed Tsuji–Wilkinson decarbonylation was best performed in an annular-flow



Scheme 51. Continuous-flow decarbonylation of aldehydes using N_2 as a stripping gas.

regime (Scheme 51).[181] The rhodium-mediated decarbonylation generally proceeds efficiently even at temperatures near room temperature. However, a stable rhodium-carbonyl complex is formed in this process along with the decarbonylated product. Early attempts to make the system catalytic failed because the electronically depleted Rh–CO complex does not participate in the oxidative addition to the aldehyde C–H bond, and loss of the CO ligand to regenerate the active species does not proceed at significant reaction rates at temperatures below 220 °C. The carbon monoxide released during the high-T/p continuous-flow decarbonylation was removed from the mixture by a continuous stream of N_2 as a stripping gas, thus driving the equilibrium to the product and regenerating the active catalyst. In the annular flow regime, the CO was carried with the N_2 stream through the center of the tubing whereas the liquid feed travels as a thin annular film on the wall of the channel. This approach allowed the catalytic decarbonylation of a variety of aldehydes with $[Rh_2(OAc)_4]$ as the precatalyst and 1,3-bis(diphenylphosphino)propane (dppp) as the ligand within residence times of only 8 to 25 min at 200 °C in toluene as solvent (Scheme 51).[181]

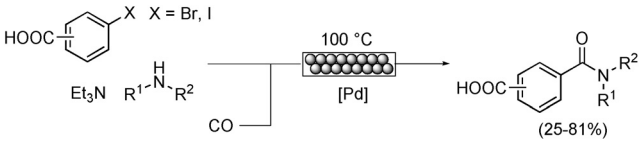
In addition to transition-metal-catalyzed carbonylation reactions, radical-based reactions of alkyl halides with CO gas and tin hydride were conducted in microflow reactors (Scheme 52).[182] Thermally induced radical carbonylations



Scheme 52. Radical carbonylations using a continuous microflow system.

usually require high partial pressures of CO and adequate gas–liquid mixing to ensure that the concentration of carbon monoxide around the radical centers is high enough to compete with a premature quenching by the tin hydride. For the flow reactions, a solution containing an aliphatic halide, Bu_3SnH or $(TMS)_3SiH$ as radical mediators, and the rapidly decomposing 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65) as radical initiator was mixed with a stream of CO and fed into the reactor at 80 °C. A range of radical carbonylation reactions, including three-component coupling reactions with methyl vinyl ketone and acrylonitrile as radical traps, were carried out with excellent yields in residence times of 10 to 30 min (Scheme 52).[182]

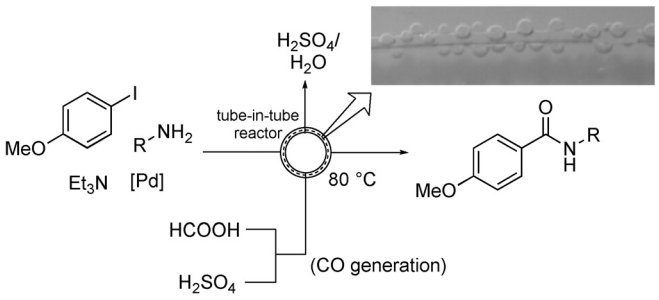
A packed-bed reactor was used by Long and co-workers for palladium-catalyzed aminocarbonylation reactions.[183] The palladium–phosphine complex was covalently bound to the silica support material, and the material was then packed into a 45 cm PTFE tubing. The reactor was applied for the synthesis of radiolabeled amides by ^{11}CO carbonylative cross-coupling. Since ^{11}CO only has a short half-life of 20.4 min, fast reactions are essential. Good radiochemical yields (> 64 %) and purities (> 93 %) of the crude products were obtained after residence times of about 10 min.[183] Using a catalyst cartridge packed with polymer-supported tetrakis(triphenylphosphine)palladium and a carbon monoxide pressure of 30 bar, Csajági et al achieved selective aminocarbonylation after residence times of only approximately 2 min at 100 °C.[184] The products were isolated in moderate to good yields after column chromatography (Scheme 53).[184]



Scheme 53. Aminocarbonylations in a packed-bed reactor.

Continuous-flow cross-coupling reactions in packed-bed reactors with immobilized catalyst/ligand systems have become widely popular in the past years. However, since the catalytic cycle for these kinds of transformations involves a homogeneous Pd^{II} species, the transition-metal catalyst will usually leach out of the catalyst bed.[185] This effect often becomes only evident when experiments are performed over an extended time period.[185] Thus, the use of a homogeneous (pre)catalyst in combination with an appropriate catalyst recycling technology might be preferred, particularly for larger scale experiments.[186]

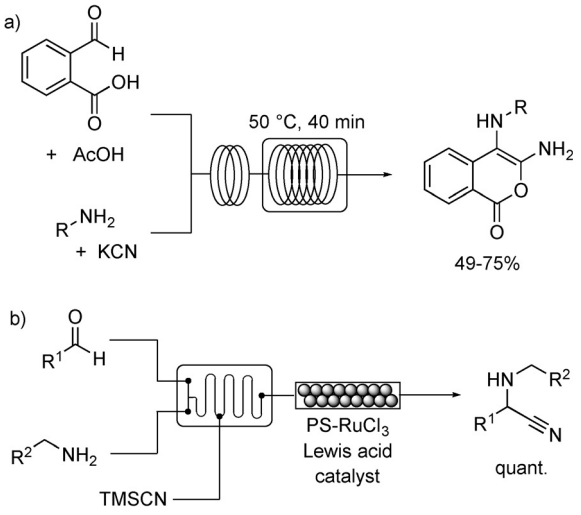
Ryu and co-workers described the generation and consumption of carbon monoxide in a tube-in-tube reactor.[187] The inner tube was made of gas-permeable Teflon AF2400, while the outer tube was made of stainless steel. Carbon monoxide was generated in the inner tube by dehydration of formic acid in sulfuric acid at elevated temperatures (Morgan reaction). The CO diffused through the membrane and was consumed in the outer chamber by an aminocarbonylation with 4-iodoanisole (Scheme 54). A residence time of about 160 min was required in the outer tube at a reaction temperature of 80 °C. As a consequence of the very limited residence volume of the outer chamber, the throughput of the system was rather low (ca. 1 mmol per day).[187]



Scheme 54. Carbonylation reaction with ex situ generated CO in a tube-in-tube reactor. Inset: detailed view of the semipermeable Teflon AF2400 tube releasing CO bubbles to the reaction mixture. Image adapted from Ref. [187] with permission. Copyright 2013, American Chemical Society.

4.6.2. ***Cyanides and Isocyanides***

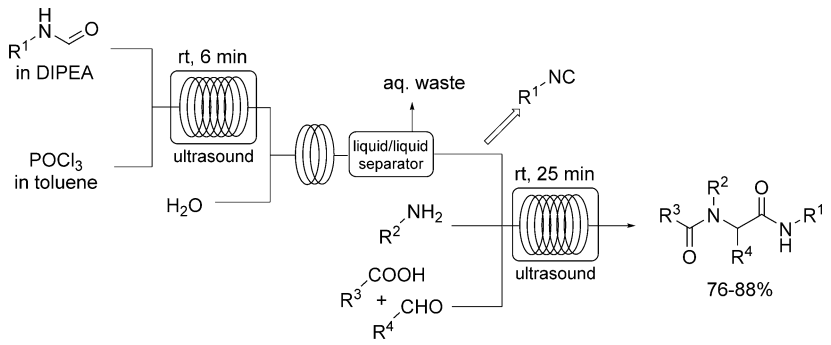
The in situ generation and use of HCN in a continuous-flow system can be accomplished by mixing an inorganic cyanide source, such as potassium cyanide, with an acidic feed. The generated HCN can then be consumed in a subsequent reaction. This approach was used by the Stevens research group for Strecker reactions[188] and Strecker-type multicomponent transformations.[189] For the synthesis of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, a feed of 2-formylbenzoic acid and acetic acid was combined with a methanolic solution of KCN in a microreactor (Scheme 55a).[189] A Strecker reaction with concomitant intramolecular nucleophilic ring closure in a subsequent 45 mL residence loop at 50 °C gave the desired isochromen-1-ones after a residence time of 40 min in 49–75% product yield (Scheme 55a).[189]



Scheme 55. In situ generation and use of HCN.

Wiles and Watts used trimethylsilyl cyanide (TMSCN) in a borosilicate glass microreactor for the synthesis of α-aminonitriles from amines and aldehydes in a Strecker reaction (Scheme 55b).[190] The aldehydes and amines were first mixed in the microreactor to form the aldimine in a microchannel. TMSCN was subsequently introduced into the reactor and the combined mixture went through a catalyst bed with a polymer-supported Lewis acid. No competing cyanohydrin formation was observed by using this two-step strategy, and the α-aminonitriles were isolated in quantitative yields after evaporation of the solvent.[190] This method was suitable for the synthesis of a small compound library containing 51 α-aminonitriles (Scheme 55b).[191]

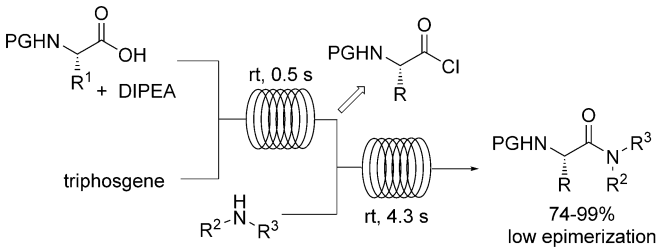
A similar technique as that developed for the generation and purification of ethyl diazoacetate was applied by Kim and co-workers for the preparation of isocyanides (cf. Scheme 38), a class of compounds with an extremely unpleasant odor.[192] A feed containing the amide and diisopropylethylamine (DIPEA), and a feed of $POCl_3$ in toluene were combined and pumped through a residence coil at room temperature (Scheme 56). The residence coil was immersed in an ultrasonic bath to prevent precipitation of the insoluble $iPr_2NEt{\cdot}HCl$ salt. Dehydration of the amide was completed after a residence time of 6 min. Water was then added to remove water-soluble $iPr_2NEt{\cdot}HCl$ and phosphate salts, and the two phases were finally separated. The purified toluene solution of isocyanide was directly used in downstream reactions, including Passerini three-component and Ugi four-component reactions (Scheme 56). Yields were around 80% after residence times of only 13 to 25 min.[192]



Scheme 56. In situ generation, extraction, separation, and reaction of isocyanides.

4.6.3. ***Phosgene***

Phosgene is highly toxic to humans even at small quantities, and therefore the handling of phosgene requires very special safety measures. Industrially, phosgene is produced by passing a gaseous mixture of CO and chlorine continuously in an approximately stoichiometric ratio over granulated activated carbon. The phosgene is generally immediately used on site, for example, for the production of isocyanates. Thus, the chemical does not have to be stored and any transport paths can be kept short. Phosgene is seldom used in research laboratories. A microflow generation of acid



Scheme 57. Peptide synthesis by rapid and strong activation of carboxylic acids with triphosgene.

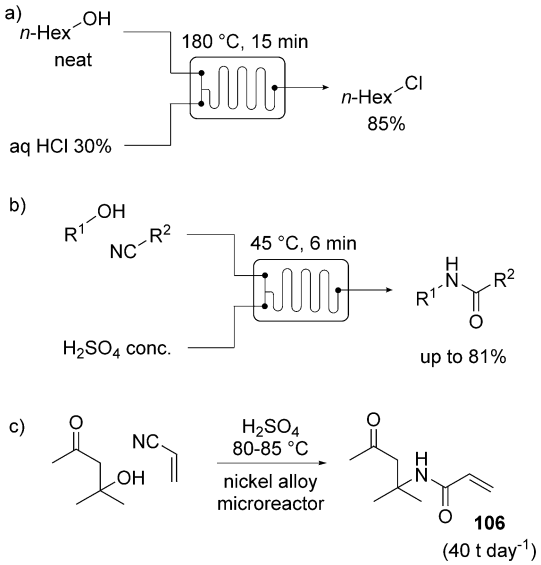
chlorides from protected amino acids, triphosgene, and DIPEA was demonstrated by the research group of Takahashi (Scheme 57).[193] Phosgene was presumably generated from this mixture as an intermediate, and the phosgene immediately reacted with the carboxylic acid to form the acid chloride. Complete conversion into the acid chloride required only 0.5 s at room temperature, and the active species was then immediately quenched with amines, including *N*-methylamino acids, to give amides or dipeptides in yields > 74% after residence times of 4.3 s at ambient temperature. By carefully controlling the residence time of the highly active acid chloride, racemization could be limited to less than 3% in all cases (Scheme 57).[193] In principle, the activation of acids with phosgene or triphosgene would only generate CO_2 and HCl as waste, and its use has, therefore, significant advantages over traditional coupling procedures.

4.7. Miscellaneous Reactions

As illustrated by several examples throughout this Review, the use of high-performance reactor materials and reactor designs allows high-T/p processing of even highly corrosive reaction media. The high throughput and relatively simple structures of microreactors facilitates the use of unconventional, possibly expensive or difficult to process reactor materials, which would otherwise be unfeasible to employ for traditional large-scale batch reactors.

A recently published example is the direct uncatalyzed chlorodehydroxylation of *n*-alkylalcohols with highly corrosive hydrochloric acid (Scheme 58a).[194] The reaction was performed with the neat alcohols and 30% aqueous hydrochloric acid in a borosilicate microreactor with 1 mL internal volume. While 1-butanol and concentrated aqueous HCl form a homogeneous phase at room temperature, the longer-chain alcohols become increasingly immiscible with aqueous HCl. Nevertheless, for *n*-hexanol, the corresponding chloride was obtained with essentially quantitative conversion within 15 min reaction time at 180 °C in a segmented-flow regime, and the product was isolated in 85% yield by phase separation of the processed stream.[194] Similarly, chlorodehydroxylation with hydrogen chloride gas in gas–liquid reactions have been reported.[195]

A continuous-flow Ritter reaction with concentrated sulfuric acid was presented by Wirth and co-workers.[196] A reaction solution containing a secondary or tertiary alcohol



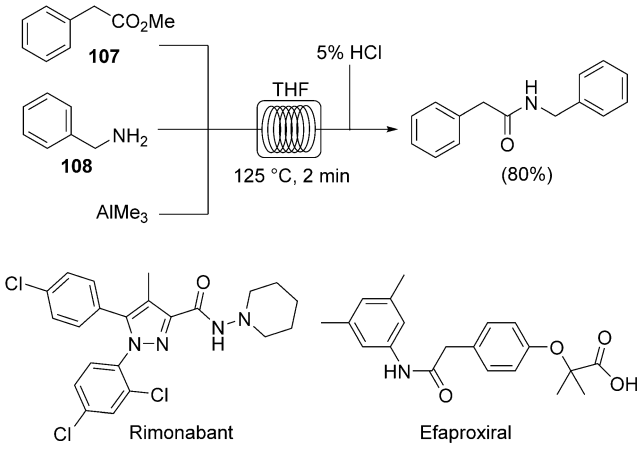
Scheme 58. Continuous-flow reactions involving concentrated acids.

and 1 to 1.5 equiv of the nitrile in acetic acid as solvent was combined with 85% H_2SO_4. The corresponding amides were obtained in good yields after a residence time of 6 min at a reaction temperature of 45 °C (Scheme 58b). Formamides were obtained from tertiary alcohols by this procedure by using sodium cyanide as the HCN source.[196]

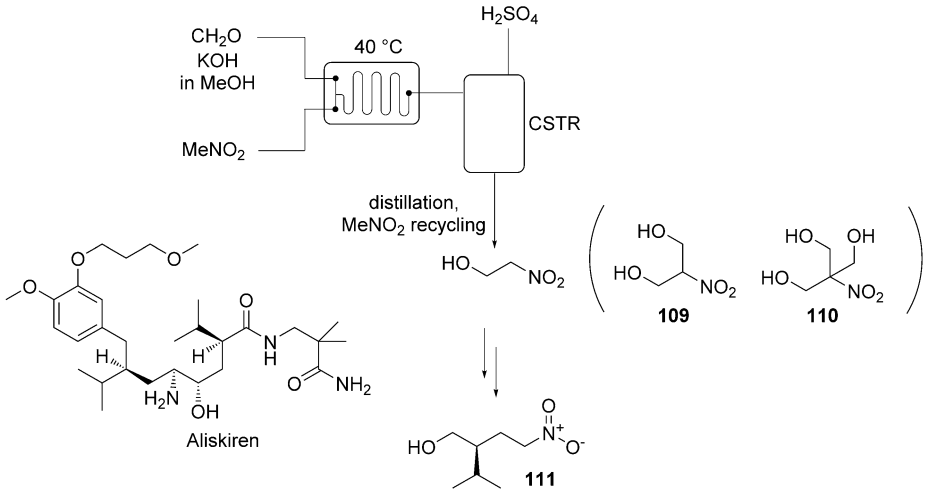
DSM executed an exothermic Ritter reaction in a metal-based flow reactor designed by the Institut für Mikroverfahrenstechnik, Karlsruhe.[197] The reaction was used for the selective preparation of the acrylamide monomer **106** (Scheme 58c). As a consequence of the high heat-transfer capacity of the continuous reactor, decomposition and tar formation was reduced and the yields increased from 55 to 78%. The reactor was capable of producing 1–2 tons of reaction mixture per hour.[197]

Seeberger and co-workers described the direct formation of an amide bond from esters and amines by using highly pyrophoric and difficult to handle trimethylaluminum as a mediator.[198] Initial optimization in a microwave reactor reduced the reaction time from 4–16 h to only 2 min at 130 °C in THF as the solvent. The process was then translated to a continuous-flow format using a 16 mL tube reactor.[198] The three reactants were introduced in equimolar amounts into a simple X-mixer, and the mixture was finally quenched in-line by an HCl solution. Reactions were typically performed on an 8 mmol scale to provide the amides in yields of > 70% for most substrates. The reaction with substrates **107** and **108** was scaled to 0.2 mol without the need to modify the reaction conditions (Scheme 59). The procedure was applied for the synthesis of Rimonabant and Efaproxiral, two pharmaceutically active substances.[198]

In a collaboration between Lonza and Novartis a mini-plant for the synthesis of 2-nitroethanol from formaldehyde and nitromethane was assembled (Scheme 60).[199] Nitroethanol was needed as an intermediate in the synthesis of *(S)*-2-isopropyl-4-nitrobutan-1-ol (**111**). Kilogram quantities of this compound were required during the development of a syn-



Scheme 59. Trimethylaluminum-mediated synthesis of amides.



Scheme 60. Synthesis of 2-nitroethanol in a continuous miniplant, including reaction and work-up operations.

thesis of Aliskiren. Since lower nitroalkanes are potentially explosive, a continuous-flow process for the production of nitroethanol was developed. Paraformaldehyde was first depolymerized with KOH, and the resulting homogeneous solution was then combined with nitromethane in a microreactor. An excess of nitromethane is crucial to get good selectivity to 2-nitroethanol and to reduce the further reaction of nitroethanol with formaldehyde to form di- and triols **109** and **110**, respectively. Thus, recirculation of nitromethane is required to make the process economically attractive. The Henry reaction was performed in a microreactor within a residence time of a few minutes at 40 °C. Since nitromethane forms explosive salts with potassium hydroxide, the reaction mixture was subsequently acidified with concentrated sulfuric acid in a continuously stirred tank reactor (CSTR) before the excess $MeNO_2$ was removed by distillation. $MeNO_2$ was finally condensed and recycled back into the process. A CSTR was the most appropriate reactor for the neutralization step since it was capable of dealing with the solid K_2SO_4. In total, more than 5 kg of 2-nitroethanol were produced by the miniplant in yields of around 90 %.[199]

5. Summary and Outlook

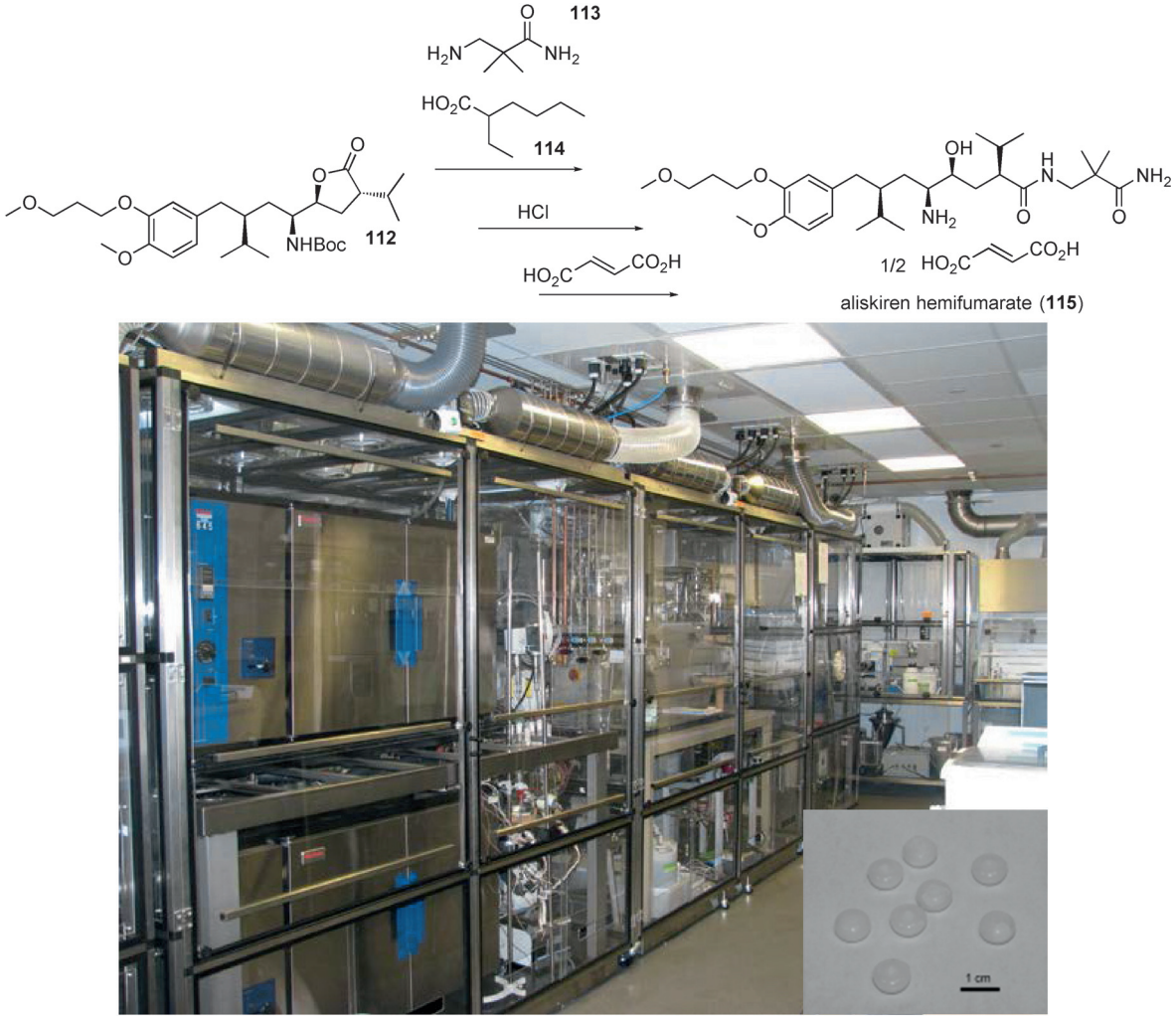
Continuous operation is arguably the most appropriate method to produce large volumes of a product uniformly, consistently, and reliably. The devices discussed herein—somewhat loosely referred to as microreactors throughout this Review—encompass reactors with channel diameters ranging from $< 100\ \mu m$ (i.e. microreactors) to a few millimeters (meso-/millireactors) and operate at flow rates from a few $\mu L\ min^{-1}$ to many $mL\ min^{-1}$. As a result of the excellent mass and heat-transfer performance of small-diameter reactors and the comparatively low reactor volumes, these devices are uniquely suited for very fast and exothermic reactions, or for high-T/p operation. Furthermore, the spatial resolution of the chemical process along the reaction channel of the flow reactor enables a very rapid change of the reaction conditions and a precise control of the reaction time. Multiple reaction steps and work-up procedures can be integrated into a single device, and reactions involving highly unstable, reactive, or explosive intermediates are thus facilitated.

In general, synthetic chemists have a plethora of reagents and chemical transformations at their disposal, but the most atom-economic and shortest synthesis route frequently demands problematic reaction conditions or reagents (cf. Figure 2). It seems reasonable to apply engineering and appropriate technology as the primary means to reduce the hazards associated with a chemical process, rather than avoiding hazardous chemistry by employing potentially costly and long alternative synthetic routes. It should be emphasized that not only can certain existing synthetic routes towards APIs be improved by using microreactors—the full potential of this technology unfolds when the chemistry right from the start is designed and developed specifically for flow. In fact, entirely new chemical routes and reaction conditions, which are hardly feasible with traditional batch equipment, can be contemplated. Moreover, process development and scale-up could be accelerated by employing continuous-flow reactors from early stages of the drug-discovery process.

Even though current pharmaceutical and fine-chemical production is by far dominated by batch processing, several examples of commercial-scale reactions performed in continuous-flow reactors have been published in the past few years. Continuous processing in micro- or mesoreactors constitutes a significant means for process intensification and process automation, but it still provides the flexibility

required by the fine-chemical industry. The use of "exotic" reagents and extreme ("off-road") process conditions in combination with modern reactor technology offers the promise of smaller plant footprints, lower equipment and production cost, less waste and emissions, and increased safety. Thus, it seems clear that in the near future, many large-scale batch processes, where thousands of kilograms of potentially corrosive, toxic, or explosive chemicals have to be mixed and stirred for an extended period of time, are replaced by continuous processes.

A recent, very active area of research is the integration of individual process steps in the synthesis of a critical intermediate or final product into a single, fully continuous production line.[15] In this context, Seeberger and co-workers very recently demonstrated robust, self-contained chemistry modules for common synthetic transformations (oxidation, olefination, Michael addition, hydrogenation, and saponication).[200] Each module accomplished a particular reaction along with suitable downstream purification. By combining these modules in the respective order, three different classes of molecules were produced (β-amino acids, γ-amino acids, and γ-lactams). Five active pharmaceutical ingredients present in generic or patented medications were produced in good overall yields by using this approach (49–75%).[200] The incorporation of all unit operations, including mixing of reagents, multiple chemical transformations, in-line/real-time analysis, separations, and work-ups into one continuous process is certainly a challenging endeavor and necessitates holistic optimization of multiple operations. A first prototype process for the uninterrupted, end-to-end continuous production of finished drug tablets was presented by the Novartis-MIT Center for Continuous Manufacturing.[8] The process started by combining the neat, melted chemical intermediate **112** with amine **113** and the acid catalyst **114** (Scheme 61). The reaction was followed by in-line extraction, phase separation in a membrane-based liquid–liquid separator, and subsequent continuous crystallization/filtration. The reaction proceeded by an acid-catalyzed removal of the Boc protecting group with concentrated HCl, quenching with NaOH, and a second continuous work-up. A subsequent reactive crystallization with fumaric acid yielded aliskiren hemifumarate **115** as a purified, final salt. Continuous drying and formulation afforded the final tablets with a uniform visual appearance and comparable size and dosage as



Scheme 61. End-to-end, integrated continuous manufacturing plant for the synthesis of Aliskiren. The inset shows the formulated tablets. Image adapted from Ref. [8a] with permission. Copyright 2013, Wiley-VCH.

commercial tablets. The total throughput of the continuous plant corresponded to 2.7×10^6 tablets per year. The number of unit operations could be reduced to 14, from 21 for the batch process, and the residence time in the plant was nearly an order of magnitude shorter than the sum of the processing times needed for the batch process (47 h compared to ca. 300 h). The entire plant had a footprint of only 2.4×7.3 m^2, and was entirely enclosed in a container-like structure (Scheme 61).[8]

Such continuous production plants do not only eliminate the storage or transportation of chemical intermediates across different unit operations or facilities, but self-contained, small-footprint end-to-end manufacturing plants could streamline and shorten supply chains by delivering pharmaceuticals or other critical products on-demand and on-site when and where they are needed most. Undoubtedly, there is still a long way to go before we will routinely see refrigerator-sized (or even smaller) highly process intensified and integrated units that can produce complex pharmaceuticals anywhere in the world within short notice, but the future may be closer then we believe.[201,202]

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Angew. Chem. **2015**, *127*, 6788–6832

[1] For a discussion on continuous manufacturing in pharma, see a) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062; b) P. Poechlauer, J. Colberg, E. Fisher, M. Jansen, M. D. Johnson, S. G. Koenig, M. Lawler, T. Laporte, J. Manley, B. Martin, A. O'Kearney-McMullan, *Org. Process Res. Dev.* **2013**, *17*, 1472; c) A. M. Thayer, *Chem. Eng. News* **2014**, *92(21)*, 13; d) P. Poechlauer, J. Manley, R. Broxterman, B. Gregertsen, M. Ridemark, *Org. Process Res. Dev.* **2012**, *16*, 1586; e) C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B.-S. Yang, D. A. Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau, J. Manley, *Org. Process Res. Dev.* **2011**, *15*, 900.

[2] For a further discussion on continuous-flow manufacturing in pharma, see I. R. Baxendale, R. D. Braatz, B. K. Hodnett, K. F. Jensen, M. D. Johnson, P. Scharrat, J.-P. Sherlock, A. J. Florence, *J. Pharm. Sci.* **2015**, *104*, 781.

[3] For extensive treatises on microreactor and continuous-flow technology, see a) *Flow Chemistry* (Eds.: F. Darvas, V. Hessel, G. Dorman), De Gruyter, Berlin, **2014**; b) *Microreactors in Preparative Chemistry* (Ed.: W. Reschetilowski), Wiley-VCH, Weinheim, **2013**; c) *Microreactors in Organic Synthesis and Catalysis*, *2nd ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**; d) *Handbook of Micro Reactors* (Eds.: V. Hessel, J. C. Schouten, A. Renken, Y. Wang, J.-i. Yoshida), Wiley-VCH, Weinheim, **2009**; e) *Chemical Reactions and Processes under Flow Conditions* (Ed.: S. V. Luis, E. Garcia-Verdugo), RSC Green Chemistry, **2010**.

[4] For recent general reviews on flow chemistry, see a) K. F. Jensen, B. J. Reizmana, S. G. Newman, *Lab Chip* **2014**, *14*, 3206; b) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; *Angew. Chem.* **2011**, *123*, 7642; c) N. G. Anderson, *Org. Process Res. Dev.* **2012**, *16*, 852; d) I. R. Baxendale, L. Brocken, C. J. Mallia, *Green Process. Synth.* **2013**, *2*, 211; e) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519; f) M. Baumann, I. R. Baxendale, S. V. Ley, *Mol. Diversity* **2011**, *15*, 613; g) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 144; *Angew. Chem.* **2015**, *127*, 146.

[5] For reviews highlighting green chemistry features, see a) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38; b) C. Wiles, P. Watts, *Green Chem.* **2014**, *16*, 55; c) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456; d) J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331.

[6] For reviews discussing continuous manufacturing examples, see a) P. Plouffe, A. Macchi, D. M. Roberge in *Flow Chemistry*, *Fundamentals*, *Vol. 1*. (Eds.: F. Darvas, V. Hessel, G. Dorman), De Gruyter, Berlin, **2014**, p. 139; b) I. Dencic, V. Hessel in *Microreactors in Organic Synthesis and Catalysis*, *2nd ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**, p. 373.

[7] For other topics, see for example: a) flow photochemistry: Y. Su, N. J. W. Straathof, V. Hessel, T. Noel, *Chem. Eur. J.* **2014**, *20*, 10562; b) flow electrochemistry: K. Watts, A. Baker, T. Wirth, *J. Flow Chem.* **2014**, *4*, 2; c) radiopharmaceutical synthesis: A. M. Elizarov, *Lab Chip* **2009**, *9*, 1326; d) materials chemistry: R. M. Myers, D. E. Fitzpatrick, R. M. Turner, S. V. Ley, *Chem. Eur. J.* **2014**, *20*, 12348; e) asymmetric synthesis: D. B. Zhao, K. L. Ding, *ACS Catal.* **2013**, *3*, 928; f) biocatalysis: J. M. Bolivar, B. Nidetzky, *Green Process. Synth.* **2013**, *2*, 541; g) natural products synthesis: J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849.

[8] a) S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, B. L. Trout, *Angew. Chem. Int. Ed.* **2013**, *52*, 12359; *Angew. Chem.* **2013**, *125*, 12585; b) P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2014**, *18*, 402.

[9] T. Rodrigues, P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 5750; *Angew. Chem.* **2014**, *126*, 5858.

[10] a) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746; b) V. Hessel, D. Kralisch, N. Kockmann, *Novel Process Windows*, Wiley-VCH, Weinheim, **2014**.

[11] T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274.

[12] a) D. Reay, C. Ramshaw, A. Harvey, *Process Intensification—Engineering for Efficiency*, *Sustainability and Flexibility*, Elsevier, Oxford, **2008**; b) A. Górak, A. I. Stankiewicz, *Annu. Rev. Chem. Biomol. Eng.* **2011**, *2*, 431.

[13] a) B. J. Reizman, K. F. Jensen, *Org. Process Res. Dev.* **2012**, *16*, 1770; b) J. S. Moore, K. F. Jensen, *Angew. Chem. Int. Ed.* **2014**, *53*, 470; *Angew. Chem.* **2014**, *126*, 480; c) R. A. Skilton, A. J. Parrott, M. W. George, M. Poliakoff, R. A. Bourne, *Appl. Spectrosc.* **2013**, *67*, 1127; d) M. F. Roberto, T. I. Dearing, S. Martin, B. J. Marquardt, *J. Pharm. Innovation* **2012**, *7*, 69; e) S. E. Hamilton, F. Mattrey, X. Bu, D. Murray, B. McCullough, C. J. Welch, *Org. Process Res. Dev.* **2014**, *18*, 103; f) D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner, S. V. Ley, *Rapid Commun. Mass Spectrom.* **2012**, *26*, 1999.

[14] J.-i. Yoshida, *Flash Chemistry*: *Fast Organic Synthesis in Microsystems*, Wiley, Chichester, **2008**.

[15] For reviews on multistep continuous processes, see a) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; b) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; c) B. Ahmed-Omer, D. A. Barrow, T. Wirth, *ARKIVOC* **2011**, *4*, 26.

[16] K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem. Int. Ed.* **2004**, *43*, 406; *Angew. Chem.* **2004**, *116*, 410.
[17] N. Kockmann, D. M. Roberge, *Chem. Eng. Technol.* **2009**, *32*, 1682.
[18] D. A. Crowl, J. F. Louvar, *Chemical Process Safety*: *Fundamentals with Applications*, *3rd ed.*, Prentice-Hall, Upper Saddle River, **2012**.
[19] a) C. O. Kappe, A. Stadler, D. Dallinger, *Microwaves in Organic and Medicinal Chemistry*, *2nd ed.*, Wiley-VCH, Weinheim, **2012**; b) *Microwaves in Organic Synthesis* (Eds.: A. de La Hoz, A. Loupy), Wiley-VCH, Weinheim, **2012**.
[20] For a recent review describing the translation of microwave batch to continuous-flow procedures ("microwave-to-flow paradigm"), see T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2011**, *17*, 11956.
[21] M. Damm, T. N. Glasnov, C. O. Kappe, *Org. Process Res. Dev.* **2010**, *14*, 215.
[22] R. Morschhäuser, M. Krull, C. Kayser, C. Boberski, R. Bierbaum, P. A. Püschner, T. N. Glasnov, C. O. Kappe, *Green Process Synth.* **2012**, *1*, 281.
[23] a) J. M. Sauks, D. Mallik, Y. Lawryshyn, T. Bender, M. Organ, *Org. Process Res. Dev.* **2014**, *18*, 1310; b) for related examples, see K. Engen, J. Sävmarker, U. Rosenström, J. Wannberg, T. Lundbäck, A. Jenmalm-Jensen, M. Larhed, *Org. Process Res. Dev.* **2014**, *18*, 1582.
[24] a) T. Razzaq, T. N. Glasnov, C. O. Kappe, *Chem. Eng. Technol.* **2009**, *32*, 1702; b) T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1321; c) H. Kobayashi, B. Driessen, D. J. G. P. van Osch, A. Talla, S. Ookawara, T. Noël, V. Hessel, *Tetrahedron* **2013**, *69*, 2885; d) U. Tilstam, T. Defrance, T. Giard, *Org. Process Res. Dev.* **2009**, *13*, 321; e) T. Iwasaki, J.-i. Yoshida, *Macromolecules* **2005**, *38*, 1159.
[25] S. Borukhova, T. Noel, B. Metten, E. de Vos, V. Hessel, *ChemSusChem* **2013**, *6*, 2220.
[26] P. Zhang, M. G. Russell, T. F. Jamison, *Org. Process Res. Dev.* **2014**, *18*, 1567.
[27] D. R. Snead, T. F. Jamison, *Chem. Sci.* **2013**, *4*, 2822.
[28] S. A. May, M. D. Johnson, T. M. Braden, J. R. Calvin, B. D. Haeberle, A. R. Jines, R. D. Miller, E. F. Plocharczyk, G. A. Rener, R. N. Richey, C. R. Schmid, R. K. Vaid, H. Yu, *Org. Process Res. Dev.* **2012**, *16*, 982.
[29] M. W. Bedore, N. Zaborenko, K. F. Jensen, T. F. Jamison, *Org. Process Res. Dev.* **2010**, *14*, 432.
[30] N. Zaborenko, M. W. Bedore, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2011**, *15*, 131.
[31] D. Cantillo, C. O. Kappe, *J. Org. Chem.* **2013**, *78*, 10567.
[32] X. Han, M. Poliakoff, *Chem. Soc. Rev.* **2012**, *41*, 1428.
[33] U. Hintermair, G. Franciò, W. Leitner, *Chem. Eur. J.* **2013**, *19*, 4538.
[34] P. Clark, M. Poliakoff, A. Wells, *Adv. Synth. Catal.* **2007**, *349*, 2655.
[35] For recent examples, see a) E. Garcia-Verdugo, Z. Liu, E. Ramirez, J. Garcia-Serna, J. Fraga-Dubreuil, J. R. Hyde, P. A. Hamley, M. Poliakoff, *Green Chem.* **2006**, *8*, 359; b) C. Yan, J. Fraga-Dubeuil, E. Garcia-Verdugo, P. A. Hamley, M. Poliakoff, I. Pearson, A. S. Coote, *Green Chem.* **2008**, *10*, 98; c) J. Fraga-Dubreuil, M. Poliakoff, *Pure Appl. Chem.* **2006**, *78*, 1971; d) J. Fraga-Dubreuil, E. Garcia-Verdugo, P. A. Hamley, E. M. Vaquero, L. M. Dudd, I. Pearson, D. Housley, W. Partenheimer, W. B. Thomas, K. Whiston, M. Poliakoff, *Green Chem.* **2007**, *9*, 1238.
[36] *High Pressure Chemistry*: *Synthetic*, *Mechanistic*, *and Supercritical Applications* (Eds.: R. van Eldik, F.-G. Klärner), Wiley-VCH, Weinheim, **2008**.
[37] For reviews, see a) W. Verboom, *Chem. Eng. Technol.* **2009**, *32*, 1695; b) F. Benito-López, R. J. M. Egberink, D. N. Reinhoudt, W. Verboom, *Tetrahedron* **2008**, *64*, 10023.
[38] a) C. Wentrup, *Aust. J. Chem.* **2014**, *67*, 1150; b) H. McNab, *Aldrichimica Acta* **2004**, *37*, 19.
[39] D. Cantillo, H. Sheibani, C. O. Kappe, *J. Org. Chem.* **2012**, *77*, 2463.
[40] G. M. Keserű, T. Soós, C. O. Kappe, *Chem. Sov. Rev.* **2014**, *43*, 5387.
[41] N. Kockmann, *Transport Phenomena in Micro Process Engineering*, Springer, Berlin, **2008**.
[42] T. D. Gross, S. Chou, D. Bonneville, R. S. Gross, P. Wang, O. Campopiano, M. A. Ouellette, S. E. Zook, J. P. Reddy, W. J. Moree, F. Jovic, S. Chopade, *Org. Process Res. Dev.* **2008**, *12*, 929.
[43] D. R. Fandrick, F. Roschangar, C. Kim, B. J. Hahm, M. H. Cha, H. Y. Kim, G. Yoo, T. Kim, J. T. Reeves, J. J. Song, Z. Tan, B. Qu, N. Haddad, S. Shen, N. Grinberg, H. Lee, N. Yee, C. H. Senanayake, *Org. Process Res. Dev.* **2012**, *16*, 1131.
[44] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1192.
[45] L. Kupracza, A. Kirschning, *Adv. Synth. Catal.* **2013**, *355*, 3375.
[46] For selected further examples relating to API synthesis, see a) X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Dev.* **2004**, *8*, 455; b) E. Riva, S. Gagliardi, M. Martinelli, D. Passarella, D. Vigo, A. Rencurosi, *Tetrahedron* **2010**, *66*, 3242; c) A. E. Cervera-Padrell, J. P. Nielsen, M. J. Pedersen, K. M. Christensen, A. R. Mortensen, T. Skovby, K. Dam-Johansen, S. Kiil, K. V. Gernaey, *Org. Process Res. Dev.* **2012**, *16*, 901; d) E. Riva, A. Rencurosi, S. Gagliardi, D. Passarella, M. Martinelli, *Chem. Eur. J.* **2011**, *17*, 6221; e) B. Pieber, T. Glasnov, C. O. Kappe, *RSC Adv.* **2014**, *4*, 13430.
[47] P. Grongsaard, P. G. Bulger, D. J. Wallace, L. Tan, Q. Chen, S. J. Dolman, J. Nyrop, R. S. Hoerrner, M. Weisel, J. Arredondo, T. Itoh, C. Xie, X. Wen, D. Zhao, D. J. Muzzio, E. M. Bassan, C. S. Shultz, *Org. Process Res. Dev.* **2012**, *16*, 1069.
[48] N. Kockmann, M. Gottsponer, B. Zimmermann, D. M. Roberge, *Chem. Eur. J.* **2008**, *14*, 7470.
[49] a) P. Barthe, C. Guermeur, O. Lobet, M. Moreno, P. Woehl, D. M. Roberge, N. Bieler, B. Zimmerman, *Chem. Eng. Technol.* **2008**, *31*, 1146; b) D. M. Roberge, N. Bieler, M. Mathier, M. Eyholzer, B. Zimmermann, P. Barthe, C. Guermeur, O. Lobet, M. Moreno, P. Woehl, *Chem. Eng. Technol.* **2008**, *31*, 1155.
[50] a) J.-i. Yoshida, A. Nagaki, T. Yamadayoshida, *Chem. Eur. J.* **2008**, *14*, 7450; b) J.-i. Yoshida, *Drug Discovery Today* **2013**, *10*, 53; c) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; d) J.-i Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9895.
[51] T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2005**, *44*, 2413; *Angew. Chem.* **2005**, *117*, 2465.
[52] a) J. R. McConnell, J. E. Hitt, E. D. Daugs, T. A. Rey, *Org. Process Res. Dev.* **2008**, *12*, 940; b) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Asian J.* **2010**, *5*, 799.
[53] J. J. M. van der Linden, P. W. Hilberink, C. M. P. Kronenburg, G. J. Kemperman, *Org. Process Res. Dev.* **2008**, *12*, 911.
[54] a) D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 568; b) D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 2465.
[55] L. Ducry, D. M. Roberge, *Org. Process Res. Dev.* **2008**, *12*, 163.
[56] a) P. N. Rylander, *Hydrogenation Methods*, Academic Press, New York, **1990**; b) P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**; c) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience: New York, **2001**.
[57] For a review on continuous-flow hydrogenations, see M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem* **2011**, *4*, 300.
[58] For selected recent applications of continuous-flow packed-bed hydrogenation reactors, see a) M. Baumann, I. R. Baxendale, C. H. Hornung, S. V. Ley, M. V. Rojo, K. A. Roper, *Molecules*

2014, *19*, 9736; b) R. J. Ingham, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Beilstein J. Org. Chem.* **2014**, *10*, 641; c) M. J. Fink, M. Schön, F. Rudroff, M. Schnürch, M. D. Mihovilovic, *ChemCatChem* **2013**, *5*, 724; d) S. Lou, P. Dai, S. E. Schaus, *J. Org. Chem.* **2007**, *72*, 9998; e) M. Irfan, E. Petricci, T. Glasnov, M. Taddei, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1327.

[59] T. N. Glasnov, C. O. Kappe, *Adv. Synth. Catal.* **2010**, *352*, 3089.

[60] S. Balogh, G. Farkas, J. Madarász, A. Szöllősy, J. Kovács, F. Darvas, L. Ürge, J. Bakos, *Green Chem.* **2012**, *14*, 1146.

[61] J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305.

[62] For further examples of hydrogenation reactions with the catalyst immobilized on the channel wall, see a) T. Haywood, P. W. Miller, *ChemCatChem* **2014**, *6*, 1199; b) R. Lin, X. Ma, T. R. Fielitz, S. O. Obare, R. Y. Ofoli, *Catal. Commun.* **2012**, *18*, 168; c) J. J. W. Bakker, M. M. P. Zieverink, R. W. E. G. Reintjens, F. Kapteijn, J. A. Moulijn, M. T. Kreutzer, *ChemCatChem* **2011**, *3*, 1155; d) O. Trapp, S. K. Weber, S. Bauch, T. Baecker, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008**, *14*, 4657; e) A. Iles, M. Habgood, A. J. de Mello, R. C. R. Wootton, *Catal. Lett.* **2007**, *114*, 71.

[63] M. D. Johnson, S. A. May, J. R. Calvin, J. Remacle, J. R. Stout, W. D. Diseroad, N. Zaborenko, B. D. Haeberle, W.-M. Sun, M. T. Miller, J. Brennan, *Org. Process Res. Dev.* **2012**, *16*, 1017.

[64] a) D. I. Enache, G. J. Hutchings, S. H. Taylor, R. Natividad, S. Raymahasay, J. M. Winterbottom, E. H. Stitt, *Ind. Eng. Chem. Res.* **2005**, *44*, 6295; b) D. I. Enache, G. J. Hutchings, S. H. Taylor, E. H. Stitt, *Catal. Today* **2005**, *105*, 569; c) D. I. Enache, G. J. Hutchings, S. H. Taylor, S. Raymahasay, J. M. Winterbottom, M. D. Mantle, A. J. Sederman, L. F. Gladden, C. Chatwin, K. T. Symonds, E. H. Stitt, *Catal. Today* **2007**, *128*, 26; d) B. Buisson, S. Donegan, D. Wray, A. Parracho, J. Gamble, P. Caze, J. Jorda, C. Guermeur, *Chim. Oggi-Chem. Today* **2009**, *27*, 12; e) A.-K. Liedtke, F. Bornette, R. Philippe, C. de Bellefon, *Chem. Eng. J.* **2013**, *227*, 174.

[65] a) M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2010**, *12*, 1596; b) for a recent review, see M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349.

[66] M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale, S. V. Ley, *Chem. Sci.* **2011**, *2*, 1250.

[67] S. Newton, S. V. Ley, E. C. Arc, D. M. Grainger, *Adv. Synth. Catal.* **2012**, *354*, 1805.

[68] M. A. Mercadante, C. B. Kelly, C. X. Lee, N. E. Leadbeater, *Org. Process Res. Dev.* **2012**, *16*, 1064.

[69] For a theoretical modeling of the gas-transport properties of the Teflon-AF2400 device, see L. Yang, K. F. Jensen, *Org. Process Res. Dev.* **2013**, *17*, 927.

[70] a) R. A. Sheldon, I. W. C. E. Arends, G.-J. ten Brink, A. Dijksman, *Acc. Chem. Res.* **2002**, *35*, 774; b) S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; *Angew. Chem.* **2004**, *116*, 3480; c) S. S. Stahl, *Science* **2005**, *309*, 1824.

[71] N. Zotova, K. Hellgardt, G. H. Kelsall, A. S. Jessimanc, K. K. (M.) Hii, *Green Chem.* **2010**, *12*, 2157.

[72] D. Obermayer, A. M. Balu, A. A. Romero, W. Goessler, R. Luque, C. O. Kappe, *Green Chem.* **2013**, *15*, 1530.

[73] a) Z. Hou, N. Theyssen, A. Brinkmann, K. V. Klementiev, W. Grünert, M. Bühl, W. Schmidt, B. Spliethoff, B. Tesche, C. Weidenthaler, W. Leitner, *J. Catal.* **2008**, *258*, 315; b) M. Caravati, J.-D. Grunwaldt, A. Baiker, *Appl. Catal. A* **2006**, *298*, 50; c) G. Jenzer, T. Mallat, A. Baiker, *Catal. Lett.* **2001**, *73*, 5.

[74] a) B. Pieber, S. T. Martinez, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2013**, *52*, 10241; *Angew. Chem.* **2013**, *125*, 10431; b) B. Pieber, T. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2015**, *21*, 4368.

[75] Z. He, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3353; *Angew. Chem.* **2014**, *126*, 3421.

[76] X. Ye, M. D. Johnson, T. Diao, M. H. Yates, S. S. Stahl, *Green Chem.* **2010**, *12*, 1180.

[77] T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale, S. V. Ley, *ChemSusChem* **2012**, *5*, 274.

[78] S. L. Bourne, S. V. Ley, *Adv. Synth. Catal.* **2013**, *355*, 1905.

[79] P. R. Ogilby, *Chem. Soc. Rev.* **2010**, *39*, 3181.

[80] R. C. R. Wootton, R. Fortt, A. J. de Mello, *Org. Process Res. Dev.* **2002**, *6*, 187.

[81] K. Jähnisch, U. Dingerdissen, *Chem. Eng. Technol.* **2005**, *28*, 426.

[82] R. A. Bourne, X. Han, M. Poliakoff, M. W. George, *Angew. Chem. Int. Ed.* **2009**, *48*, 5322; *Angew. Chem.* **2009**, *121*, 5426.

[83] a) C. P. Park, R. A. Maurya, J. H. Lee, D.-P. Kim, *Lab Chip* **2011**, *11*, 1941; b) R. A. Maurya, C. P. Park, D.-P. Kim, *Beilstein J. Org. Chem.* **2011**, *7*, 1158.

[84] F. Lévesque, P. H. Seeberger, *Org. Lett.* **2011**, *13*, 5008.

[85] D. Kopetzki, F. Levesque, P. H. Seeberger, *Chem. Eur. J.* **2013**, *19*, 5450.

[86] F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706; *Angew. Chem.* **2012**, *124*, 1738.

[87] K. Gilmore, D. Kopetzki, J. W. Lee, Z. Horváth, D. T. McQuade, A. Seidel-Morgenstern, P. H. Seeberger, *Chem. Commun.* **2014**, *50*, 12652.

[88] J. L. Turconi, F. Griolet, R. Guevel, G. Oddon, R. Villa, A. Geatti, M. Hvala, K. Rossen, R. Göller, A. Burgard, *Org. Process Res. Dev.* **2014**, *18*, 417.

[89] Y. Wada, M. A. Schmidt, K. F. Jensen, *Ind. Eng. Chem. Res.* **2006**, *45*, 8036.

[90] S. Hübner, U. Bentrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Küpper, K. Jähnisch, *Org. Process Res. Dev.* **2009**, *13*, 952.

[91] M. Irfan, T. N. Glasnov, C. O. Kappe, *Org. Lett.* **2011**, *13*, 984.

[92] S. G. Van Ornum, R. M. Champeau, R. Pariza, *Chem. Rev.* **2006**, *106*, 2990.

[93] M. Nobis, D. M. Roberge, *Chim. Oggi-Chem. Today* **2011**, *29*, 57.

[94] M. Exner, H. Pluim, P. Dyer-Smith, *Chim. Oggi-Chem. Today* **2011**, *29*, 59.

[95] C. W. Jones, *Applications of Hydrogen Peroxide and Derivatives*, Royal Society of Chemistry, Cambridge, **1999**.

[96] a) F. Ebrahimi, E. Kolehmainen, I. Turunen, *Org. Process Res. Dev.* **2009**, *13*, 965; b) F. Ebrahimia, E. Kolehmainen, P. Oinas, V. Hietapelto, I. Turunen, *Chem. Eng. J.* **2011**, *167*, 713.

[97] a) A. Hartung, M. A. Keane, A. Kraft, *J. Org. Chem.* **2007**, *72*, 10235; see also: b) B. A. M. W. van den Broek, R. Becker, F. Kössl, M. M. E. Delville, P. J. Nieuwland, K. Koch, F. P. J. T. Rutjes, *ChemSusChem* **2012**, *5*, 289.

[98] T. Illg, V. Hessel, P. Löb, J. C. Schouten, *Chem. Eng. J.* **2011**, *167*, 504.

[99] a) K. Mikami, Md. N. Islam, M. Yamanaka, Y. Itoh, M. Shinoda, K. Kudo, *Tetrahedron Lett.* **2004**, *45*, 3681; b) K. Mikami, M. Yamanaka, Md. N. Islam, T. Tonoi, Y. Itoh, M. Shinoda, K. Kudo, *J. Fluorine Chem.* **2006**, *127*, 592.

[100] a) R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977; b) Y. Kon, Y. Ono, T. Matsumoto, K. Sato, *Synlett* **2009**, 1095.

[101] K. Sato, M. Aoki, R. Noyori, *Science* **1998**, *281*, 1646.

[102] Y. Wen, X. Wang, H. Wei, B. Li, P. Jin, L. Li, *Green Chem.* **2012**, *14*, 2868.

[103] M. Damm, B. Gutmann, C. O. Kappe, *ChemSusChem* **2013**, *6*, 978.

[104] M. Shang, T. Noel, Q. Wang, V. Hessel, *Chem. Eng. Technol.* **2013**, *36*, 1001.

[105] A. B. Leduc, T. F. Jamison, *Org. Process Res. Dev.* **2012**, *16*, 1082.

[106] G. S. Kumar, B. Pieber, K. R. Reddy, C. O. Kappe, *Chem. Eur. J.* **2012**, *18*, 6124.

[107] J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618.
[108] K. C. Basavaraju, S. Sharma, R. A. Maurya, D.-P. Kim, *Angew. Chem. Int. Ed.* **2013**, *52*, 6735; *Angew. Chem.* **2013**, *125*, 6867.
[109] For a review on continuous-flow fluorinations, see H. Amii, A. Nagaki, J.-i. Yoshida, *Beilstein J. Org. Chem.* **2013**, *9*, 2793.
[110] a) N. de Mas, A. Günther, M. A. Schmidt, K. F. Jensen, *Ind. Eng. Chem. Res.* **2003**, *42*, 698; b) K. Jähnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Löwe, C. Wille, A. Guber, *J. Fluorine Chem.* **2000**, *105*, 117.
[111] C. B. McPake, G. Sandford, *Org. Process Res. Dev.* **2012**, *16*, 844.
[112] R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883.
[113] R. D. Chambers, M. P. Greenhall, J. Hutchinson, *Tetrahedron* **1996**, *52*, 1.
[114] J. R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, B. Patel, *Beilstein J. Org. Chem.* **2011**, *7*, 1048.
[115] C. B. McPake, C. B. Murray, G. Sandford, *Tetrahedron Lett.* **2009**, *50*, 1674.
[116] a) T. Gustafsson, R. Gilmour, P. H. Seeberger, *Chem. Commun.* **2008**, 3022; b) M. Baumann, I. R. Baxendale, S. V. Ley, *Synlett* **2008**, *12*, 2111; c) M. Baumann, I. R. Baxendale, L. J. Martin, S. V. Ley, *Tetrahedron* **2009**, *65*, 6611; d) D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 8486.
[117] U. Budde, *Statuskolloquium Mikroverfahrenstechnik*, Deutsche Bundesstiftung Umwelt, Osnabrück, **2007**.
[118] a) H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns, K. Jähnisch, *Chimia* **2002**, *56*, 647; b) H. Matsubara, Y. Hino, M. Tokizane, I. Ryu, *Chem. Eng. J.* **2011**, *167*, 567.
[119] a) P. Löb, V. Hessel, H. Klefenz, H. Löwe, K. Mazanek, *Lett. Org. Chem.* **2005**, *2*, 767; b) R. Becker, S. A. M. W. van den Broek, P. J. Nieuwland, K. Koch, F. P. J. T. Rutjes, *J. Flow Chem.* **2012**, *2*, 87; c) T. Fukuyama, M. T. Rahman, N. Kamata, M. Tokizane, Y. Fukuda, I. Ryu, *J. Flow Chem.* **2013**, *3*, 4.
[120] D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 223.
[121] D. Šterk, M. Jukič, Z. Časar, *Org. Process Res. Dev.* **2013**, *17*, 145.
[122] K. Midorikawa, S. Suga, J.-i. Yoshida, *Chem. Commun.* **2006**, 3794.
[123] J. Barton, R. Rogers, *Chemical Reaction Hazards*, IChemE, Trowbridge, **1997**.
[124] A. M. Thayer, *Chem. Eng. News* **2005**, *83(22)*, 43.
[125] A. A. Kulkarni, *Beilstein J. Org. Chem.* **2014**, *10*, 405.
[126] a) L. Ducry, D. M. Roberge, *Angew. Chem. Int. Ed.* **2005**, *44*, 7972; *Angew. Chem.* **2005**, *117*, 8186; b) J. Pelleter, F. Renaud, *Org. Process Res. Dev.* **2009**, *13*, 698; c) C. E. Brocklehurst, H. Lehmann, L. L. Vecchia, *Org. Process Res. Dev.* **2011**, *15*, 1447.
[127] a) S. Braune, P. Pöchlauer, R. Reintjens, S. Steinhofer, M. Winter, O. Lobet, R. Guidat, P. Woehl, C. Guermeur, *Chim. Oggi-Chem. Today* **2009**, *27*, 26; b) A. M. Thayer, *Chem. Eng. News* **2009**, *87(11)*, 17.
[128] P. Knapkiewicz, K. Skowerski, D. E. Jaskólska, M. Barbasiewicz, T. K. Olszewski, *Org. Process Res. Dev.* **2012**, *16*, 1430.
[129] G. Panke, T. Schwalbe, W. Stirner, S. Taghavi-Moghadam, G. Wille, *Synthesis* **2003**, 2827.
[130] Y. Chen, Y. Zhao, M. Han, C. Ye, M. Danga, G. Chen, *Green Chem.* **2013**, *15*, 91.
[131] D. Cantillo, M. Damm, D. Dallinger, M. Bauser, M. Berger, C. O. Kappe, *Org. Process Res. Dev.* **2014**, *18*, 1360.
[132] a) B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298; b) S. T. R. Mueller, T. Wirth, *ChemSusChem* **2015**, *8*, 245.
[133] a) M. Struempel, B. Ondruschka, R. Daute, A. Stark, *Green Chem.* **2008**, *10*, 41; b) E. Rossi, P. Woehl, M. Maggini, *Org. Process Res. Dev.* **2012**, *16*, 1146.
[134] T. G. Archibald, F. Oaks, J. C. Barnard, S. Springs, H. F. Reese, "Continuous process for diazomethane from an *N*-methyl-*N*-nitrosoamine and from methylurea through *N*-methyl-*N*-nitrosourea". (Aerojet-General Corporation). US Patent 5,854,405, **1998** (CAN130:83188).
[135] M. Struempel, B. Ondruschka, A. Stark, *Org. Process Res. Dev.* **2009**, *13*, 1014.
[136] P. Poechlauer, *Chim. Oggi-Chem. Today* **2012**, *30*, 51.
[137] L. D. Proctor, A. J. Warr, *Org. Process Res. Dev.* **2002**, *6*, 884.
[138] L. Proctor, *Industrialisation of Diazomethane—The Application of Flow Technology Towards Hazardous Chemistry*, **2006**. http://www.chemspecevents.com/europe/images/uploads/chemsource/4_-_1_Proctor.pdf Chemsource 2006, Elements of Success—P, Si, F & N. ChemSpec Events Homepage (accessed on September 4th of 2014).
[139] R. A. Maurya, C. P. Park, J. H. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2011**, *50*, 5952; *Angew. Chem.* **2011**, *123*, 6074.
[140] F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590.
[141] V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 1555.
[142] V. D. Pinho, B. Gutmann, C. O. Kappe, *RSC Adv.* **2014**, *4*, 37419.
[143] a) L. J. Martin, A. L. Marzinzik, S. V. Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320; b) P. Pollet, E. D. Cope, M. K. Kassner, R. Charney, S. H. Terett, K. W. Richman, W. Dubay, J. Stringer, C. A. Eckert, C. L. Liotta, *Ind. Eng. Chem. Res.* **2009**, *48*, 7032.
[144] R. A. Maurya, K.-I. Min, D.-P. Kim, *Green Chem.* **2014**, *16*, 116.
[145] R. C. R. Wootton, R. Fortt, A. J. de Mello, *Lab Chip* **2002**, *2*, 5.
[146] For further applications of microreactors for the synthesis of azo dyes on various scales, see a) H. Salimi-Moosavi, T. Tang, D. J. Harrison, *J. Am. Chem. Soc.* **1997**, *119*, 8716; b) H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara, T. Kitamori, *Chem. Commun.* **2001**, 2662; c) C. Wille, H.-P. Gabski, Th. Haller, H. Kim, L. Unverdorben, R. Winter, *Chem. Eng. J.* **2004**, *101*, 179; d) H. Pennemann, S. Forster, J. Kinkel, V. Hessel, H. Löwe, L. Wu, *Org. Process Res. Dev.* **2005**, *9*, 188; e) P. M. Günther, F. Möller, T. Henkel, J. M. Köhler, G. A. Groß, *Chem. Eng. Technol.* **2005**, *28*, 52.
[147] R. Fortt, R. C. R. Wootton, A. J. de Mello, *Org. Process Res. Dev.* **2003**, *7*, 762.
[148] a) L. Malet-Sanz, J. Madrzak, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 5324; b) L. Malet-Sanz, J. Madrzak, R. S. Holvey, T. Underwood, *Tetrahedron Lett.* **2009**, *50*, 7263; c) Z. Yu, Y. Lv, C. Yu, *Org. Process Res. Dev.* **2012**, *16*, 1669.
[149] N. Chernyak, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12466.
[150] B. Ahmed-Omer, D. A. Barrow, T. Wirth, *Tetrahedron Lett.* **2009**, *50*, 3352.
[151] X. Wang, G. D. Cuny, T. Noël, *Angew. Chem. Int. Ed.* **2013**, *52*, 7860; *Angew. Chem.* **2013**, *125*, 8014.
[152] B. Li, D. Widlicka, S. Boucher, C. Hayward, J. Lucas, J. C. Murray, B. T. O'Neil, D. Pfisterer, D. Samp, J. VanAlsten, Y. Xiang, J. Young, *Org. Process Res. Dev.* **2012**, *16*, 2031.
[153] D. X. Hu, M. O'Brien, S. V. Ley, *Org. Lett.* **2012**, *14*, 4246.
[154] D. X. Hu, M. Bielitza, P. Koos, S. V. Ley, *Tetrahedron Lett.* **2012**, *53*, 4077.
[155] M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247; *Angew. Chem.* **2013**, *125*, 4341.
[156] M. E. Kopach, M. M. Murray, T. M. Braden, M. E. Kobierski, O. L. Williams, *Org. Process Res. Dev.* **2009**, *13*, 152.
[157] M. M. E. Delville, P. J. Nieuwland, P. Janssen, K. Koch, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Eng. J.* **2011**, *167*, 556.
[158] M. Weber, G. Yilmaz, G. Wille, *Chim. Oggi-Chem. Today* **2011**, *29*, 8.
[159] a) C. D. Smith, I. R. Baxendale, S. Lanners, J. J. Hayward, S. C. Smith, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 1559; b) I. R.

Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017; *Angew. Chem.* **2009**, *121*, 4077; c) S. Ceylan, T. Klande, C. Vogt, C. Friese, A. Kirschning, *Synlett* **2010**, 2009; d) C. O. Kappe, E. Van der Eycken, *Chem. Soc. Rev.* **2010**, *39*, 1280.

[160] I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017; *Angew. Chem.* **2009**, *121*, 4077.

[161] M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe, *Adv. Synth. Catal.* **2010**, *352*, 323.

[162] A. C. Varas, T. Noël, Q. Wang, V. Hessel, *ChemSusChem* **2012**, *5*, 1703.

[163] A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849.

[164] a) A. R. Bogdan, K. James, *Chem. Eur. J.* **2010**, *16*, 14506; b) A. R. Bogdan, K. James, *Org. Lett.* **2011**, *13*, 4060.

[165] H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5704; *Angew. Chem.* **2007**, *119*, 5806.

[166] J. C. Brandt, T. Wirth, *Beilstein J. Org. Chem.* **2009**, *5*, 30.

[167] a) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2010**, *49*, 7101; *Angew. Chem.* **2010**, *122*, 7255; b) B. Gutmann, D. Obermayer, J.-P. Roduit, D. M. Roberge, C. O. Kappe, *J. Flow Chem.* **2012**, *1*, 8.

[168] P. B. Palde, T. F. Jamison, *Angew. Chem. Int. Ed.* **2011**, *50*, 3525; *Angew. Chem.* **2011**, *123*, 3587.

[169] B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, *Chem. Eur. J.* **2011**, *17*, 13146.

[170] A. G. O'Brien, F. Lévesque, P. H. Seeberger, *Chem. Commun.* **2011**, *47*, 2688.

[171] F. R. Bou-Hamdan, F. Lévesque, A. G. O'Brien, P. H. Seeberger, *Beilstein J. Org. Chem.* **2011**, *7*, 1124.

[172] S. G. Newman, L. Gu, C. Lesniak, G. Victor, F. Meschke, L. Abahmane, K. F. Jensen, *Green Chem.* **2014**, *16*, 176.

[173] A. DeAngelis, D.-H. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 3434; *Angew. Chem.* **2013**, *125*, 3518.

[174] C. Wiles, P. Watts, S. J. Haswell, *Org. Process Res. Dev.* **2004**, *8*, 28.

[175] a) D. Cantillo, M. Baghbanzadeh, C. O. Kappe, *Angew. Chem. Int. Ed.* **2012**, *51*, 10190; *Angew. Chem.* **2012**, *124*, 10337; b) D. Cantillo, M. M. Moghaddam, C. O. Kappe, *J. Org. Chem.* **2013**, *78*, 4530.

[176] M. M. Moghaddam, B. Pieber, T. Glasnov, C. O. Kappe, *ChemSusChem* **2014**, *7*, 3122.

[177] L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, *23*, 685.

[178] M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236.

[179] E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1734; *Angew. Chem.* **2007**, *119*, 1764.

[180] a) X. Gong, P. W. Miller, A. D. Gee, N. J. Long, A. J. de Mello, R. Vilar, *Chem. Eur. J.* **2012**, *18*, 2768; b) P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, J. Passchier, A. Gee, *Chem. Commun.* **2006**, 546.

[181] B. Gutmann, P. Elsner, T. Glasnov, D. M. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2014**, *53*, 11557; *Angew. Chem.* **2014**, *126*, 11741.

[182] T. Fukuyama, Md. T. Rahman, N. Kamata, I. Ryu, *Beilstein J. Org. Chem.* **2009**, *5*, DOI: 10.3762/bjoc.5.34.

[183] P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, H. Audrain, D. Bender, J. Passchier, A. J. Gee, *Angew. Chem. Int. Ed.* **2007**, *46*, 2875; *Angew. Chem.* **2007**, *119*, 2933.

[184] C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Ürge, F. Darvas, *Org. Lett.* **2008**, *10*, 1589.

[185] a) D. Cantillo, C. O. Kappe, *ChemCatChem* **2014**, *6*, 3286; b) R. Greco, W. Goessler, D. Cantillo, C. O. Kappe, *ACS Catal.* **2015**, *5*, 1303.

[186] T. Noel, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010.

[187] C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup, I. Ryu, *Org. Lett.* **2013**, *15*, 2794.

[188] T. S. A. Heugebaert, B. I. Roman, A. De Blieck, C. V. Stevens, *Tetrahedron Lett.* **2010**, *51*, 4189.

[189] D. R. J. Acke, C. V. Stevens, *Green Chem.* **2007**, *9*, 386.

[190] C. Wiles, P. Watts, *Org. Process Res. Dev.* **2008**, *12*, 1001.

[191] C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, 5597.

[192] S. Sharma, R. A. Maurya, K.-I. Min, G.-Y. Jeong, D.-P. Kim, *Angew. Chem. Int. Ed.* **2013**, *52*, 7564; *Angew. Chem.* **2013**, *125*, 7712.

[193] a) S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 851; *Angew. Chem.* **2014**, *126*, 870; b) S. Fuse, N. Tanabe, T. Takahashi, *Chem. Commun.* **2011**, *47*, 12661.

[194] B. Reichart, G. Tekautz, C. O. Kappe, *Org. Process Res. Dev.* **2013**, *17*, 152.

[195] a) P. Tundo, P. Venturello, E. Angeletti, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2157; b) P. Tundo, M. Selva, *Green Chem.* **2005**, *7*, 464; c) P. Tundo, *Pure. Appl. Chem.* **2012**, *84*, 441.

[196] a) J. C. Brandt, S. C. Elmore, R. I. Robinson, T. Wirth, *Synlett* **2010**, 3099; b) L. Audiger, K. Watts, S. C. Elmore, R. I. Robinson, T. Wirth, *ChemSusChem* **2012**, *5*, 257.

[197] I. Dencic, V. Hessel in *Microreactors in Organic Synthesis and Catalysis*, *2n ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**, p. 435; I. Dencic, V. Hessel in *Microreactors in Organic Synthesis and Catalysis*, *2n ed.* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2013**, p. 436.

[198] T. Gustafsson, F. Pontën, P. H. Seeberger, *Chem. Commun.* **2008**, 1100.

[199] D. M. Roberge, C. Noti, E. Irle, M. Eyholzer, B. Rittiner, G. Penn, G. Sedelmeier, B. Schenkel, *J. Flow Chem.* **2014**, *4*, 26.

[200] D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 678; *Angew. Chem.* **2015**, *127*, 688.

[201] The US Defense Advanced Projects Agency's (DARPA) Battlefield Medicine program has announced a research project termed Pharmacy on Demand (PoD) where end-to-end continuous manufacturing of US Food and Drug Administration (FDA) approved pharmaceuticals using miniaturized devices is proposed. For further details, see E. J. Choi, G. S. F. Ling, *PDA J. Pharm. Sci. Technol.* **2014**, *68*, 312.

[202] For recent examples of continuous API syntheses not discussed in this Review, see a) (*R*)-Rolipram: T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329; b) Ibuprofen: D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, 54, 983; *Angew. Chem.* **2015**, *127*, 997; c) Vildagliptin: L. Pellegatti, J. Sedelmeier, *Org. Process Res. Dev.* **2015**, *19*, 551; d) Doravirine: D. R. Gauthier , Jr., B. D. Sherry, Y. Cao, M. Journet, G. Humphrey, T. Itoh, I. Mangion, D. M. Tschaen, *Org. Lett.* **2015**, *17*, 1353; e) Taxadienone: S. G. Krasutsky, S. H. Jacobo, S. R. Tweedie, R. Krishnamoorthy, A. S. Filatov, *Org. Process Res. Dev.* **2015**, *19*, 284; f) Telmisartan: A. Martin, A. Siamaki, K. Belecki, B. Gupton, *J. Flow. Chem.* DOI: 10.1556/JFC-D-15-00002; ; g) Efavirenz: C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945; *Angew. Chem.* **2015**, *127*, 5028.

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