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Forbidden chemistries go flow in API synthesis

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Abstract The application of continuous flow microstructured reactors for the production of complex molecules has gained significant momentum in recent years. Conventionally, a chemical process is designed to accommodate the limits of the available reactionware. Thus, reactions are often done under non-ideal conditions due to restraints imposed by the equipment. The small internal volumes of microreactors and their high surface area-to-volume ratios enable reactions to be run under conditions not easily accessible in traditional batch reactors. Furthermore, reactions previously impractical ("forgotten chemistry") or virtually impossible ("forbidden chemistry") to perform can be operated in these devices with little risk at various scales. In this review selected examples from the recent literature highlighting the above mentioned advantages of continuous processing are discussed.

INTRODUCTION

Flow chemistry is a very well-established technique for the large scale production of commodity chemicals. Continuous production eliminates the extra labor and cost of starting up and shutting down of a chemical process, thereby minimizing the formation of off-quality material during non steady-state operation and maximizing throughput. The repeated cycling of temperature and pressure from starting and stopping of a conventional batch production unit does not only decrease product quality and process reliability, but it is energy and time consuming and increases the complexity of the process. In contrast, a continuous reactor can be kept running 24/7. Furthermore, continuous processes can be closely controlled and are relatively easily automated and, thus, often require only few workers for their operation. High productivity and high cost efficiency are key factors for the competitiveness of the chemical industry. It is therefore not surprising, that continuous processing has become the standard production technique for the manufacturing of commodity chemicals in the early 20th century.

Chemists in academia and in the pharmaceutical and fine chemical industry have begun to exploit flow devices for their syntheses only comparatively recently (1). Pharmaceuticals are generally significantly more complex than commodity chemicals, and often require numerous, widely diverse reaction and purification steps for their preparation. Furthermore, the production volumes of these chemicals are low compared to those of commodity chemicals and the life time of many of these products are short. Thus, multipurpose batch reactors traditionally have been the default technology for the preparation of speciality and fine chemicals in universities and in industrial research and production centers around the world. In the last few decades, however, academic and industrial researchers have begun to experiment with continuous syntheses (1-3). In fact, many chemical manufacturers have now started to move some of their production to commercial scale continuous manufacturing processes (1). Latest advances in continuous flow technology and continuous downstream processing indicate that even the synthesis of highly complex molecules from simple starting materials, or the entire preparation of final, formulated pharmaceutical drugs could be ultimately done in fully continuous production units (4). Chemical reactions as well as purification and formulation steps, which are conventionally performed sequentially in tank reactors, are for this purpose integrated into a continuous production line. Many downstream processes, such as distillation, extraction or phase separations, are actually reasonably easily adapted for continuous processing and frequently run more effectively when conducted continuously. The chemical reactions themselves are often performed in continuous flow milli- or microreactors (2,3). Microreactors are devices with inner dimensions of the order of one or below one millimeter in size. While tank reactors with volumes of tens of cubic meters are common in chemical companies, the internal volumes of microreactors typically range from below 1 µL to a couple of liters for large reactors. The compact size of microreactors facilitates the control of process parameters, such as reaction temperature, pressure and reaction time (residence time). Furthermore, since the total volume of material processed at any time is drastically reduced, the safety of the process is generally significantly increased compared to the batch counterpart. These aspects make microreactors particularly

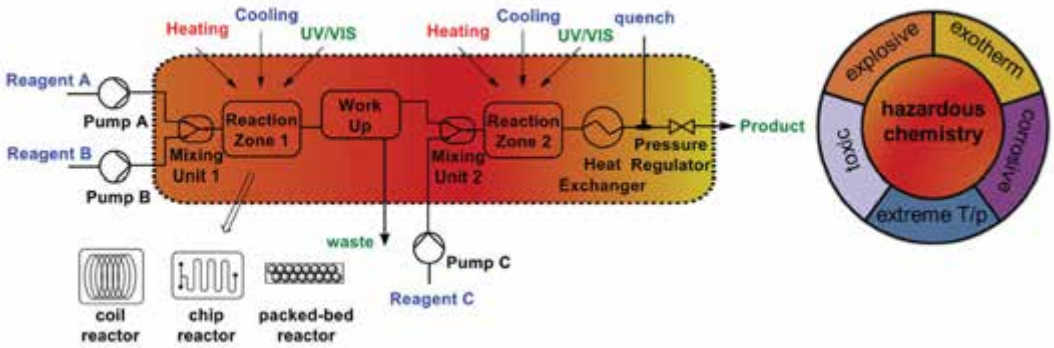


Figure 1. General concept of flow chemistry in microreactors. Reagents can be combined at precisely specified points and the conditions can be rapidly changed along the reaction path. Unit operations can be integrated to give a fully continuous production line. The pressure resistance and high heat/mass transport capability allow high temperature operation in superheated solvents.

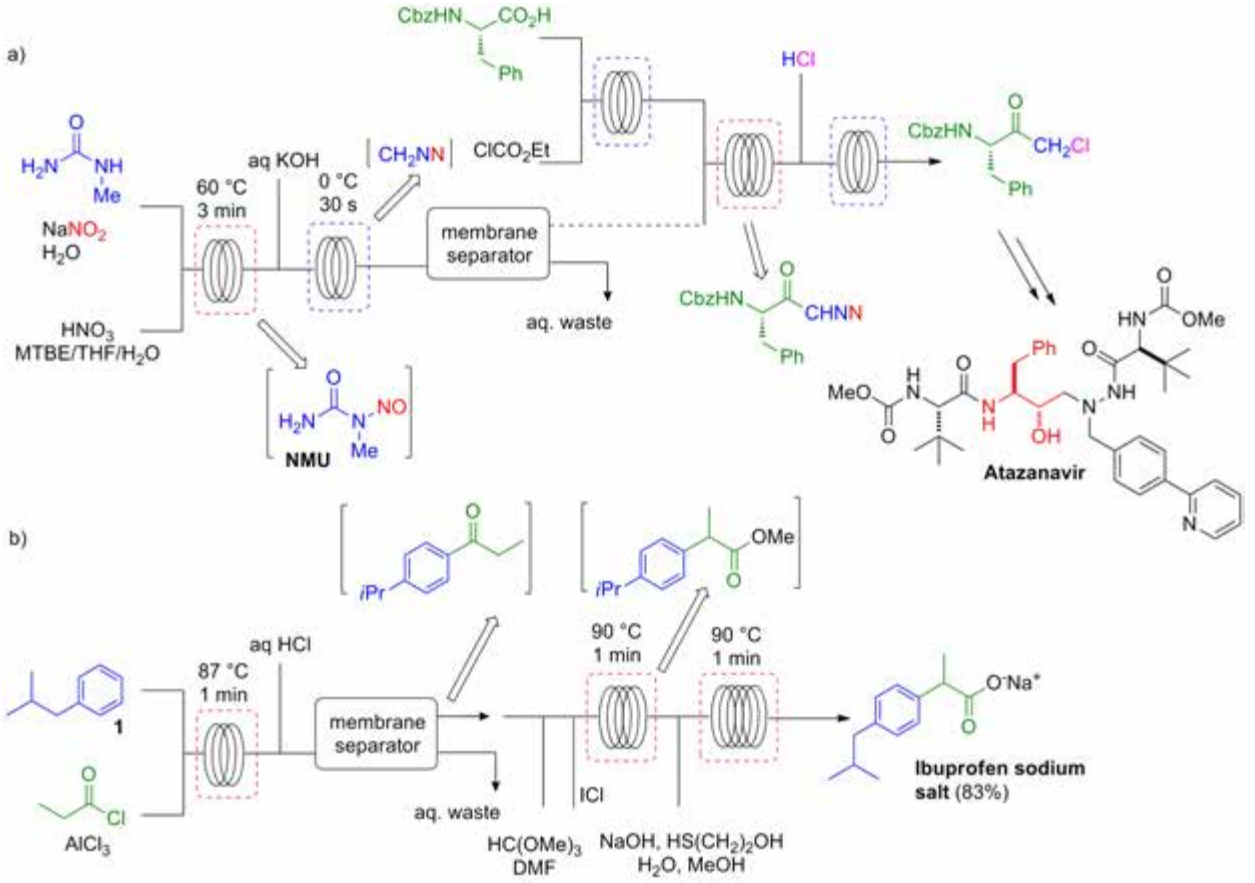
suited for "hazardous" chemistries such as reactions involving toxic, unstable or explosive intermediates (5). These intermediates can be generated from benign precursors inside the closed, pressurized environment of the microreactor and subsequently directly converted to a more advanced, nonhazardous product by feeding in multiple reagent streams and manipulating reaction conditions along the reaction path (Figure 1).

SELECTED LITERATURE EXAMPLES

Tight integration of production, purification and consumption of an intermediate becomes particularly valuable when the compound is too unstable to be transported or stored. The continuous on-demand-on-site generation of diazomethane (CH_2N_2) was recently demonstrated by DSM Fine-Chemicals (6). Diazomethane is a strongly poisonous, carcinogenic and explosive gas. Due to the tremendous safety risks associated with the generation and use of diazomethane it is hardly used as reagent in industrial production. However, diazomethane is an exceptionally versatile and potent C1-building block in organic synthesis. Reactions with diazomethane often proceed clean and rapidly at room temperature, often producing nitrogen as the sole byproduct. DSM's generation of CH_2N_2 involved the continuous production of *N*-methyl-*N*-nitrosourea (NMU) from an aqueous feed of *N*-methylurea and sodium nitrite, and a second feed containing an acid in an organic solvent (Scheme 1a). NMU is clearly one of the most atom-economic CH_2N_2 precursors. However, since *N*-nitroso-*N*-methylurea itself is carcinogen, mutagen, teratogen and unstable at temperatures above ca. 20°C, it has been mostly replaced by other (*N*-methyl) nitrosamides. In the continuous flow reactor, NMU is without isolation directly converted to CH_2N_2 by feeding in a potassium hydroxide solution. CH_2N_2 is subsequently extracted into an organic phase and separated from the aqueous waste stream by a hydrophobic membrane. The generated ethereal solution of CH_2N_2 is then available for a variety of chemical transformations, including the synthesis of a-chloroketones, key building blocks for the synthesis of several HIV-protease inhibitors such as atazanavir (Scheme 1a). Similar strategies for the continuous generation of organic solutions of diazomethane have been explored by several other research groups, and these methods have been successfully applied to perform a variety of chemical transformations with CH_2N_2 as reagent (7,8).

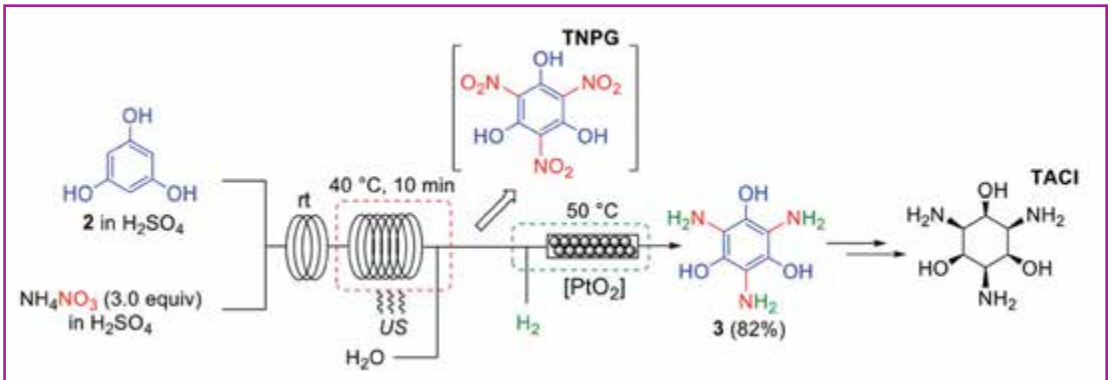
Using reactive but inexpensive and readily available reagents researchers from the Massachusetts Institute of Technology accomplished a multistep continuous-flow synthesis of ibuprofen (Scheme 1b) (9). The complete reaction sequence, including three bond-forming steps, a liquid–liquid extraction and a membrane-based phase separation, was accomplished within a residence time of three minutes. The synthesis started with mixing neat isobutylbenzene with a solution of $AlCl_3$ in propionyl chloride. Only a slight excess of propionyl chloride and $AlCl_3$ was necessary to afford the intermediate aryl ketone in excellent selectivity within 1 min residence time at 90°C. The Friedel-Crafts acylation was followed by an exothermic in-line quench of $AlCl_3$ with aqueous HCl and subsequent liquid-liquid phase separation in a membrane phase separator. The organic phase was then combined with trimethyl orthoformate in DMF (*N*,*N*-dimethylformamide) and neat iodine monochloride (ICl), and the reaction sequence continued with a 1,2-aryl migration. Remaining ICl was subsequently quenched with 2-mercaptoethanol and the ester was finally hydrolyzed under aqueous/organic biphasic conditions to form the ibuprofen sodium salt. The use of highly aggressive reagents in a minimum amount of solvent ($AlCl_3$ in propionyl chloride and neat ICl), in combination with high temperature operation allowed the completion of the whole reaction sequence with unprecedented speed in an overall yield of 83%. A scale-up of the process allowed the synthesis of ibuprofen at a rate of 8.09 g h^{-1} using a reactor with an overall footprint of half the size of a standard laboratory fume hood (Scheme 1b).

One of the most distinguishing characteristics of microreactors is their extraordinarily high surface area-to-volume ratio. The specific surface area of microreactors is typically two orders of magnitude higher than that of traditional tank reactors (2,3). The high surface area-to-volume ratio entails significantly enhanced heat-exchange capabilities. Accumulation of heat and formation of hot-spots can be suppressed and the devices can be quickly heated or cooled. Additionally, due to the small inner dimensions, mass transport is considerably improved in microstructured reactors. Thus, strongly exothermic and very fast reactions can be safely implemented in microreactors and syntheses that have been previously considered difficult or even impossible to perform are now beginning to be manageable with little risk (5,10).



Scheme 1. In continuous flow reactors multiple reaction and purification steps can be integrated in a continuous production line, rendering transport or storage of intermediates unnecessary.

Among the notoriously difficult to control synthetic transformations are nitration reactions. Nitrations are typically highly exothermic and, moreover, secondary reactions at higher temperatures often lead to explosive products. Indeed, among the most frequent and most destructive industrial chemical accidents have been those involving nitration reactions. It is therefore not surprising that microreactor technology has found quite considerable usage for nitration reactions on a laboratory scale and, additionally, a number of commercial scale continuous nitration plants are currently in operation (11). A recent example of a nitration in a flow system is the generation of trinitrophloroglucinol (TNPG) from phloroglucinol **2** (12). TNPG is an intermediate in the synthesis of chelating agents, such as 1,3,5-triamino-1,3,5-trideoxy-cis-inositol (TACI), which have widespread applications in medicine and industrial processes (Scheme 2). The synthesis of trinitrophloroglucinol involves three successive nitrations. The first nitration of the electron rich starting material **2** is extraordinary fast and exothermic. To dissipate the heat generated in the initial nitration and to prevent a thermal runaway, the first nitration was performed in a residence capillary of 1 mm inner diameter at room temperature. Residence time for the slower subsequent nitrations was provided in a second residence tube of 1.6 mm inner diameter. Since the final product of the three successive nitrations is unstable and explosive, the nitration was



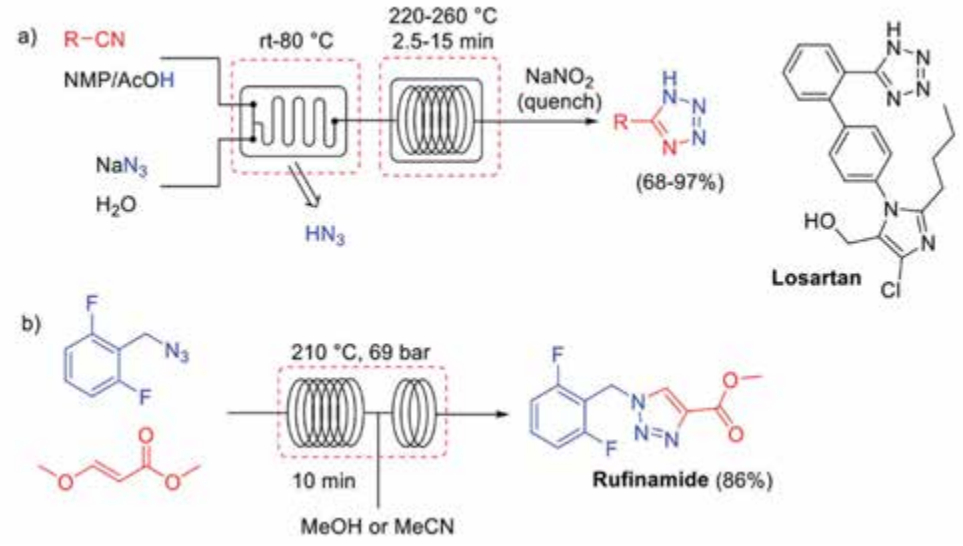
Scheme 2. Multistep nitration of an electron rich starting material in continuous flow.

coupled with a subsequent continuous flow hydrogenation in a fixed bed reactor to afford the desired product, triaminophloroglucinol **3**, in a continuous process without the need to isolate intermediates.

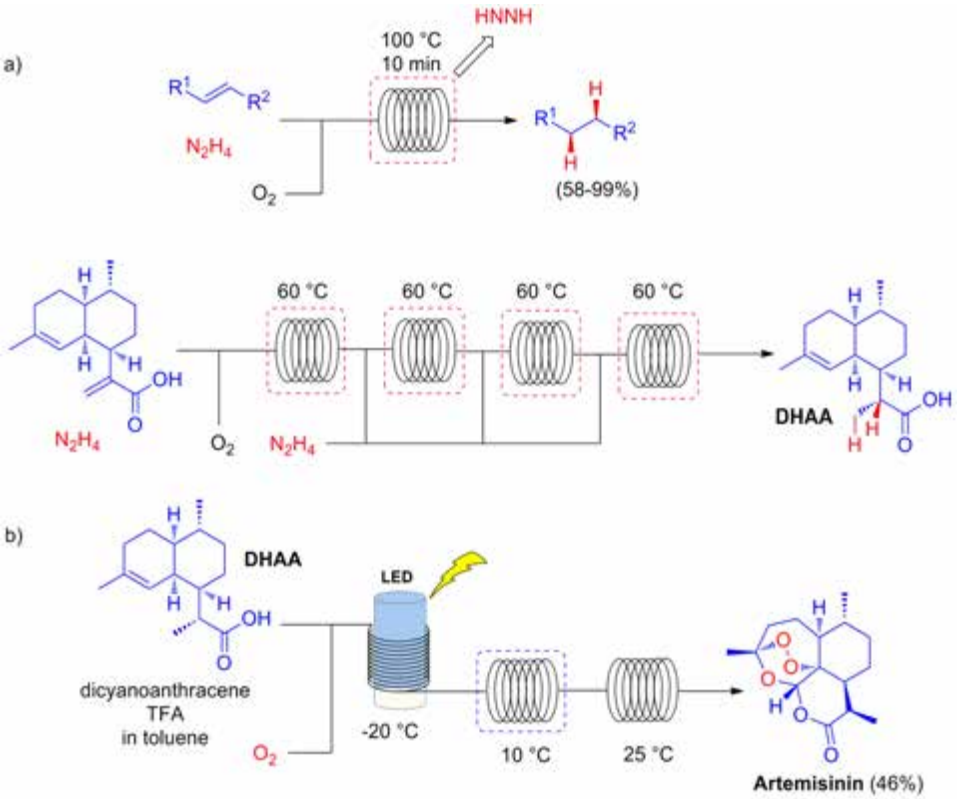
Microreactors not only provide a means to control fast or exothermic reactions, but the distinct operation characteristics of microreactors have enticed researchers to deliberately exploit extreme process conditions ("Novel Process Windows") (13). Chemical reactions frequently can be performed within remarkably short reaction times if the right conditions are applied and transport limitations are eliminated. A wide range of valuable and robust synthetic transformations readily accept very harsh reaction conditions and can be dramatically accelerated at high temperatures without sacrificing reaction yield or purity. Since the introduction of dedicated microwave reactors, high-temperature/high-pressure operation has become very common in research laboratories. Microreactors easily match the high temperature/high pressure capability of modern microwave reactors (14). In contrast to microwave syntheses, however, continuous flow microreactor protocols can be straightforwardly scaled to commercially relevant production scales.

Researchers at Lonza in collaboration with the University of Graz developed a high-temperature continuous flow protocol for the synthesis of tetrazoles utilizing hydrazoic acid (Scheme 3a) (15). The tetrazole moiety serves as a metabolically stable surrogate for the carboxylic acid functionality in several 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. Hydrazoic acid (HN_3) is a very volatile, exceedingly explosive and toxic compound. HN_3 is thus not used as reagent in today's laboratories and its use or generation during a synthesis is commonly circumvented by using NaN_3 in combination with Lewis acids or by resorting to reagents such as Bu_3SnN_3 or Me_3SiN_3 as HN_3 surrogates. Often is the synthetic route changed altogether to prevent the potential *in-situ* formation of explosive azides. Several characteristic aspects of continuous flow microreactors were of crucial importance for the successful implementation of the tetrazol synthesis. The synthesis started with the generation of hydrazoic acid in a static glass mixer by combining an aqueous feed of sodium azide and a feed of the respective nitrile in an acidic solution. The generation of HN_3 was immediately followed by its consumption by 1,3-dipolar cyloaddition to the nitrile in an ensuing high-temperature coil reactor (Scheme 3a). The post-reaction stream was finally thermally quenched in a plate heat-exchanger and unconsumed hydrazoic acid in the effluent product stream was destroyed with aqueous sodium nitrite. With benzonitrile as the model substrate, the reaction could be performed at a reaction temperature of 260°C within a residence time of only 2.5 min. Thus, in a tube reactor of only ~10 mL internal volume, ~19 g h^{-1} of 5-phenyltetrazole were produced in 89% yield (15).

A plethora of further processes employing azides in continuous flow microreactors have been published in the last years. Azides are notoriously heat sensitive and



Scheme 3. Highly intensified processes involving azides as reagents have been performed in continuous flow micro- or milli-reactors.



Scheme 4. Continuous flow reactions with gaseous reagents.

decompose rapidly at elevated temperatures with concomitant evolution of nitrogen gas. Nevertheless, with carefully controlled reaction temperatures and residence times, highly intensified processes with productivities orders of magnitudes higher compared to batch procedures have been developed. The example shown in Scheme 3b highlights an example where an alkyl azide is processed at 210°C providing a rapid access to the anticonvulsant drug Rufinamide (16,17).

Increasingly popular in recent years has become the usage of microreactors to conduct gas-liquid reactions. In fact, continuous flow reactors are virtually ideal systems for reactions with gaseous reagents. The small diameters of the reaction channels offer superior mixing for multi-phase reactions, while high pressure operation increases the amount of the gas dissolved in the liquid phase. Furthermore, using flow-based systems, gaseous reagents can be easily and accurately dosed and mixed into the liquid phase. Importantly, combustion and explosion hazards are reduced in microreactors and, consequently, reactions can be performed under unusually harsh process conditions in a safe and controllable manner. The advantages of a flow system for gas-liquid reactions was impressively demonstrated for the catalyst-free generation of diimide by oxidation of hydrazine monohydrate ($N_2H_4 \bullet H_2O$) with molecular oxygen (18,19). Diimide is an effective and selective reagent for the syn-hydrogenation of unpolarized carbon-carbon double and triple bonds. In principle, the oxidation of hydrazine with molecular oxygen would be the most atom-economic way to generate diimide. However, the un-catalyzed oxidation of hydrazine to diimide is relatively slow in traditional batch reactions and a fairly large excess of hydrazine is usually required due to extensive over oxidation to nitrogen gas and a rapid competing disproportionation of diimide. In contrast, diimide was formed efficiently in a pressurized continuous flow tube reactor and the reagent could be directly used for the hydrogenation of alkenes (Scheme 4a). Perfect selectivity was obtained for a variety of alkenes after residence times of 10 to 30 min at 100°C employing 4-5 equiv of hydrazine (18). This approach was recently employed for the selective syn-hydrogenation of artemisinic acid to dihydroartemisinic acid (19).

Dihydroartemisinic acid (DHAA) is the starting material for the semi-synthesis of artemisinin, currently the most

effective antimalarial drug. The key step in the current semi-synthesis of artemisinin is an ene reaction of DHAA with singlet-oxygen. The reaction is followed by cleavage of the oxygen-oxygen bond and subsequent addition of triplet oxygen. This triggers a cascade of condensation reactions that culminates in the formation of the final product (Scheme 4b). The whole reaction sequence was performed by chemists from Max-Planck Institute for Colloids and Interfaces, Germany, as a fully continuous chemical process (20,21). DHAA, a photosensitizer and an acid catalyst were mixed with a stream of oxygen gas and passed through a continuous photoreactor. After the photochemical step, the mixture was heated in a tube reactor to accomplish the cleavage of the oxygen-oxygen bond as well as the subsequent oxidation with triplet oxygen and the concomitant condensation to artemisinin (21). Pure artemisinin was obtained in 46% isolated yield after a total residence time of ~12 min in the flow reactor (21). Even though the value of singlet oxygen as a cheap and green reagent in contemporary organic synthesis is rather well appreciated, its utilization in the chemical industry on a larger scale is well below expectations. This is largely attributable to the fact that photochemical reactions are inherently difficult to scale-up in traditional batch reactors. Furthermore, the high reactivity and short lifetime of singlet oxygen gives rise to serious safety concerns and technical challenges. The application of continuous flow microreactors for photo reactions on a commercial scale is destined to increase in the near future (22).

CONCLUSION AND OUTLOOK

With increasing environmental and economic pressure on the chemical industry, the need to use energy and materials more effectively increases. Established chemical processes have to be intensified and new reagents and chemistries need to be developed. As technology advances, new synthesis paradigms become accessible. By moving from traditional batch operation to continuous reactions in microreactors, the safe operating range of chemical processes often can be dramatically broadened. Reactions can be performed under hitherto unfeasible reaction conditions in microstructured devices (such as high concentrations, high temperature and/or pressure). Furthermore, reactions involving unstable, explosive or otherwise hazardous intermediates can be operated relatively easily and safely on scales up to the production scale. The shortest and most elegant synthesis of a molecule often demands the use of hazardous reagents or challenging process conditions. Continuous flow microreactors provide a means to develop these chemistries to their full potential.

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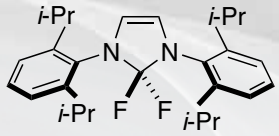

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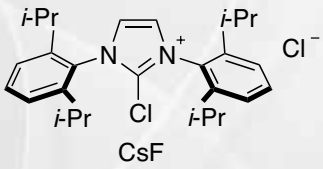

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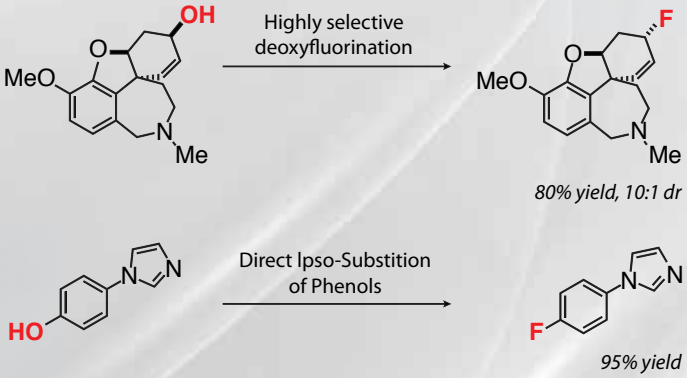

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