Forbidden Chemistries — Paths to a Sustainable Future Engaging Continuous Processing

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Optimizing current chemical processes alone does not yield the improvements required in the fine chemical and pharmaceutical industries. At least partially, a switch from batch to continuous manufacturing is needed. Cost-, time-, and atom-efficient routes frequently demand the application of high temperatures, pressures, and concentrations, and/or the use of highly reactive reagents. These chemistries often cannot be employed in conventional reactors. Costly and long alternative synthetic routes are chosen instead. The application of continuous-flow microreactors allows to access "harsh" or "hazardous" reaction conditions and, furthermore, enables entirely new transformations.

Keywords: Microreactors, process intensification, extreme conditions, continuous processing, active pharmaceutical ingredients

Introduction

We face extraordinary challenges. Rapid population growth, dwindling resources, chemical pollution, and climate change are among the major challenges of our time. However, we also have opportunities we never previously had. This is particularly true for the chemical manufacturing industry. New technologies and processes are continuously being developed. Chemical processes have become more efficient, more refined, and also more complex. Reactions are run at increasingly intense process conditions involving high temperatures, pressures, and concentrations (high-T/p/C), and exotic catalysts or high-energy reagents are increasingly employed to drive desired transformations. Processes at high-T/p yield higher reaction rates and, thus, higher throughputs. Higher throughputs, in turn, allow a reduction of the reactor size and, consequently, reactor cost [1]. Higher concentrations, likewise, increase reaction rates and, additionally, reduce solvent waste. Furthermore, the use of high-energy reagents can considerably reduce the number of synthesis steps and improve product purity, thus simplifying work-up and increasing overall atom- as well as cost-efficiency. The major constraint for the application of more exotic reaction conditions is often related to process safety. For instance, faster, intensified reactions lead to higher heat production. To remove excess energy and to avoid severe temperature and concentration gradients, significant enhancement of heat- and mass-transfer is necessary. Conventional reactor design might become unsuitable for high-performance processes. To push current limits of pharmaceutical processes, fundamental research in both general chemistry and reactor technology is needed.

The Limits of Batch Chemistry

While commodity chemicals are usually produced in thoroughly optimized continuous production plants, pharmaceuticals and fine chemicals are typically synthesized in general-purpose reactors. In particular, stirred tank reactors are easy to handle and can be employed for a wide range of different operations. Hence, stirred tank reactors have been the "workhorse" of the pharmaceutical industry for centuries. However, despite their long history and prevalence in synthesis laboratories, batch-type reactors have some strong, well-recognized limitations. Most importantly, chemical reactions which proceed at extreme process conditions (e.g., high-T/p conditions) or have the potential to release large amounts of energy are difficult or impossible to implement in batch-type reactors. Thus, highly reactive but potentially valuable, atom- and cost-efficient reagents often cannot be employed in pharmaceutical manufacturing because of safety and process control concerns. Moreover, non-routine processes, such as high-T/p-, electrochemical, and photochemical processes, are difficult to implement and are traditionally hardly considered when a new route to a molecule is designed, even though, in this way, transformations may be accomplished which would be difficult to achieve by standard means. In general, it must be expected that generic stirred tank reactors are less performant compared to dedicated reactors and they do not necessarily allow an exhaustive exploitation of the inherent physiochemical characteristics of the particular chemical transformation at hand. Quite the contrary, the chemistry often needs to be adapted to meet the limitations of the reactor. In fact, since its inception, organic chemistry has been developed and synthesis routes have been designed with the specific attributes and constraints of batch vessels in mind (implicitly or explicitly) [2]. The chosen reaction temperatures are typically those conveniently accessible in standard laboratory equipment. Furthermore, since reactions are most easily performed at or close to atmospheric pressure, the chosen solvent not only modulates chemical reactivity of the solutes in manifold ways but also dictates the available temperature range. Pressurized reactors are needed to extend the accessible process windows above the atmospheric boiling point of the solvent. Similarly, the range of applicable reaction times is limited by various constraints. For instance, reaction mixtures need to be diluted and cooled or reagents have to be dosed slowly to tame ultra-fast reactions. These measures are in place to avoid concentration and temperature gradients with resulting loss of product selectivity and reproducibility. A transformation which would involve rapid generation of a highly reactive transient intermediate and immediate subsequent quench to generate a desired product is simply not feasible in conventional labware (Table 1).

Table 1. The characteristics of continuous-flow microreactors offer new opportunities

Characteristics	Opportunities
Fast heating/cooling	Process intensification
Fast mixing	Application of "harsh" process conditions
Safety through miniaturization	Application of "hazardous" reagents
Steady state operation	Process integration
	Automation
	Straightforward scale-up

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Microreactors — The Way Forward?

In the last decade, technology associated with continuous-flow microreactor processing advanced to a point where it became virtually ubiquitously applicable in organic synthesis on all scales. Various dedicated appliances, including pumps, mixers, reactors of various design, continuous-flow separation units, and in-line analysis tools, have become available at affordable cost (Figure 1) [3]. The development of microreactors and auxiliary technology now allows the application of manufacturing principles to complex, comparatively low-volume materials which were previously reserved only to large-scale bulk chemicals. Continuous-flow microreactors offer distinct characteristics which make them very fitting for "extreme" chemistry ("harsh reaction conditions" [4] or the so-called "Novel Process Windows" [5]). Several comprehensive review articles have documented the utilization of microreactors for reagents and process conditions which would be too hazardous to apply in conventional reactors [4–7]. The achievements in this field are far too countless to mention in this Perspective Article. What is clear from these examples is that continuous-flow microreactors will make a fundamental contribution to how pharmaceuticals and fine chemicals are manufactured in the near future.

High-Temperature, Pressure, and Concentration (high-T/p/C)

The defining characteristic of microreactors is their small size. Nevertheless, since microreactors are typically operated continuously, with no downtime for charging and discharging, large amounts of products can be produced in comparatively small volumes. The small dimensions of microreactors offer enhanced heat and mass transfer. Microstructures fabricated into the channels additionally improve mass transport. Mass- and energy-transport limitations are reduced or eliminated, and the reaction can thus be performed close to intrinsic reaction rates.

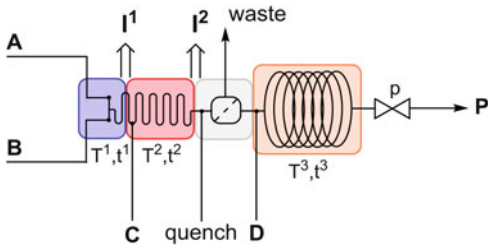
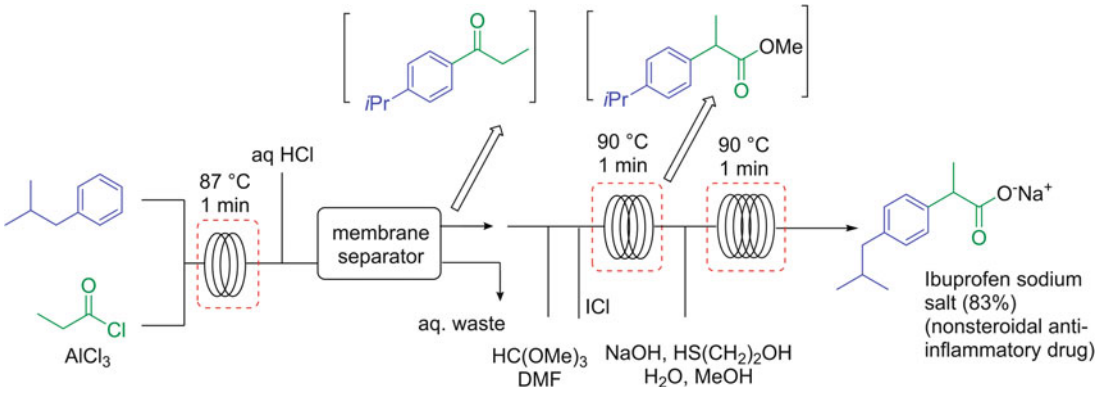


Figure 1. In continuous-flow microreactors, reagents can be combined at precisely specified points along the reactor (residence time). The high heat exchange efficiency allows rapid change of reaction conditions. The pressure resistance enables operation in superheated solvents. A, B, C, D = reagents; I = intermediates; P = product; T, t, p = temperature, residence time, pressure

These features yield unique prospects for process intensification [4, 5]. Furthermore, the small volume of microreactors entails that less material or energy is released from the reactor in the case of an accident [8]. In fact, the material content in microreactors is often too small to cause serious damage to human health or the environment. As a result, reagent and process conditions can be safely employed which otherwise would need to be avoided. For instance, the use of continuous-flow microreactors allowed several research groups to synthesize active pharmaceutical ingredients (APIs) at high temperatures under solvent-free conditions. In a pharmaceutical process, solvent use accounts for about 60% of the overall energy consumption and about 50% of the post-treatment greenhouse gas emissions [9]. Careful solvent selection, or omitting solvents altogether, can have an enormous positive environmental impact. A notable example is the multistep continuous-flow synthesis of ibuprofen by Jamison and Snead from the Massachusetts Institute of Technology (MIT) (Scheme 1) [10]. 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 only 3 min. 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%. This reaction would be very difficult to perform in the presented form in batch, in particular on an industrial scale. A scale-up of the flow process allowed the synthesis of ibuprofen at a rate of 8.09 g/h using a reactor with an overall footprint of half the size of a standard laboratory fume hood (Scheme 1) [10].

Gaseous Reagents

Continuous-flow microreactors present a virtually ideal platform for reactions with gaseous reagents [11–16]. Gases can be dosed into the flow system with precise stoichiometry using mass flow controllers, and intense mixing with the liquid phase can be achieved. Furthermore, high-pressure operation increases the concentration of gases in the liquid phase. Combustion and explosion hazards are reduced in channels of small diameter, and consequently, reactions can be performed under unusually harsh process conditions in a safe and controllable manner [11–16]. An early breakthrough of continuous-flow microreactor technology was accomplished with the introduction of continuous-flow high-pressure hydrogenation reactors [12]. Catalytic hydrogenation reactions with H_2 are among the most powerful reactions available to synthetic organic chemists. However, H_2 is a highly flammable gas and has an extraordinarily low ignition energy. Furthermore, since the solubility of hydrogen in organic solvents is exceedingly low, high-pressure operation is essential for the



Scheme 1. Synthesis of an active pharmaceutical ingredient (APIs) under high-T/p/C continuous

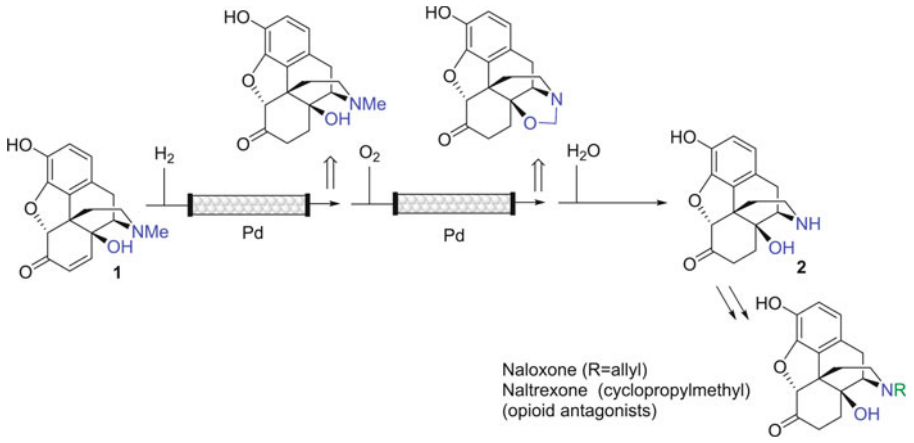
hydrogenation to proceed at an acceptable rate. High-pressure hydrogenation autoclaves are therefore typically required. Since the future of pharmaceutical products is often uncertain, investment in high-pressure hydrogenation installations is risky and often not advisable. Continuous-flow microreactors, on the other hand, allow running high-pressure hydrogenations with little investment. Hence, continuous-flow hydrogenation has found quite extensive application in the chemical industry [13] and, with the introduction of commercial bench-top high-pressure hydrogenators, has rapidly spread to synthesis laboratories [12]. An equally strong development is expected for other gaseous reagents. Indeed, a primary goal of green chemistry must be the development of processes with small molecular weight reagents, such as H_2, O_2, NH_3, CO, and CO_2, as direct sources for hydrogen, oxygen, nitrogen, and carbon. In particular, catalytic liquid phase oxidations with O_2 will play a vital role in sustainable manufacturing. Currently, heavy metal oxides are most often employed in oxidation reactions. Purification is difficult since heavy metals must be removed to trace levels in the final product. Oxidation reactions are, thus, avoided if possible in API synthesis. Replacing older generation processes based on classical stoichiometric oxidants with processes based on O_2 needs to be a major focus of chemical research. Many researchers have shown in the last decades that a wide range of oxidations can be driven by O_2 as primary oxidant. However, the use of O_2 in combination with flammable organic solvents is widely regarded as an almost insurmountable safety challenge. Safety and other challenges associated with reactions with O_2 (e.g., gas–liquid mass transport, exothermicity, etc.) can be elegantly addressed by continuous-flow microreactors [14]. A recent example is the generation of noroxymorphone (**2**), the ultimate precursor for a range of opioid antagonists such as naloxone and naltrexone (Scheme 2) [15, 16]. The reaction sequence starts from 14-hydroxymorphinone (**1**) and produces the desired product in a three-step synthesis employing only hydrogen, oxygen, and water as stoichiometric reagents. A related transformation was demonstrated on a kilogram scale [16].

High-Energy Reagents

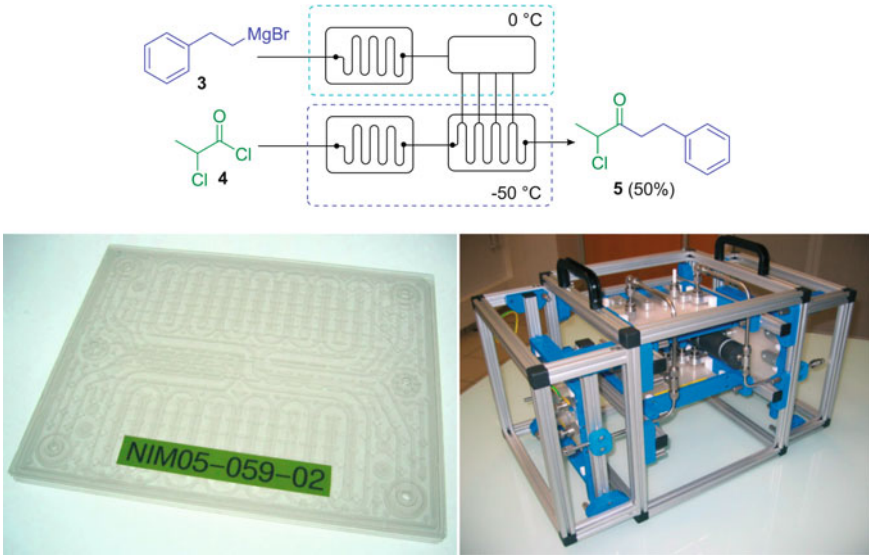
Continuous-flow processes have been developed for a vast plethora of notoriously hazardous transformations, including nitration reactions [17], reactions with ozone [18], hydrogen peroxide, azides, phosgene, cyanides, isocyanides, diazo- [19], and diazonium compounds. Several review articles offer extensive accounts on this subject [5–7]. In particular, fast transformations with organometallic reagents benefit tremendously from the advantages offered by continuous-flow microreactors. An interesting example, which nicely demonstrates the wide-ranging possibilities opened by continuous-flow processing in microreactors, is the Grignard addition of phenethylmagnesium bromide **3** to the acyl chloride **4** [20]. This reaction was developed by a cooperation of chemists and engineers from Lonza AG, Corning and the University of Ottawa. The addition of phenethylmagnesium bromide **3** to the acyl chloride **4** is highly exothermic and fast. Insufficient mixing results in stoichiometric imbalance at the dosing point and causes a range of side reactions. This is further aggravated by the formation of hot spots. In the laboratory, the reaction would be performed in small vessels of few milliliter volume cooled to −78 °C in a dry ice bath. However, dissipation of heat becomes increasingly difficult upon scale-up and severe hot-spots can form at the dosing point. Even lower temperatures, dilution, or long addition times are necessary to maintain a homogenous temperature. The team from Lonza and Corning developed a multi-injection microreactor to keep the reaction under control and to maximize product selectivity. The microreactor provided four injection points as well as mixing and residence zones. The reactor was directly attached to a heat exchange layer. The Grignard feed was split into four feeds at the four inlet points, while the acyl chloride was injected directly into the multi-injection reactor (Scheme 3). Computational fluid dynamics (CFD) modeling was performed to optimize the design of the mixing zones. The microreactor developed for this particular Grignard addition was capable of producing 100 kg of the final product per week. An installment with five reactors has an annual capacity of 25 tons of final product [20]. Similarly, a continuous-flow lithium exchange reaction to produce nearly 700 kg of a not further disclosed product was reported by a team from Lonza [21].

Controlling Reactive Intermediates by Accurate Control of Residence Time

A defining feature of flow processes is that the reaction is resolved in a spatial coordinate. What proceeds in temporal sequence in batch reactors occurs along the length of the channels in the flow reactor (Figure 1). This can be elegantly exploited for multistep reactions [22]. Telescoped sequences of potentially mutually incompatible reactions can be accomplished by mixing reagents at appropriate points. Thus, reagents, catalysts, and energy are introduced into the flow system at the right position and in the right form. Reagents are added at precisely specified points as the reaction stream passes through the channel of the flow reactor and the reaction conditions are adjusted along the reaction channel to accommodate the specific needs of each consecutive transformation (Figure 1). In contrast to multistep batch experiments, where the whole installment needs to be heated or cooled to adjust the reaction conditions for subsequent transformations, in flow

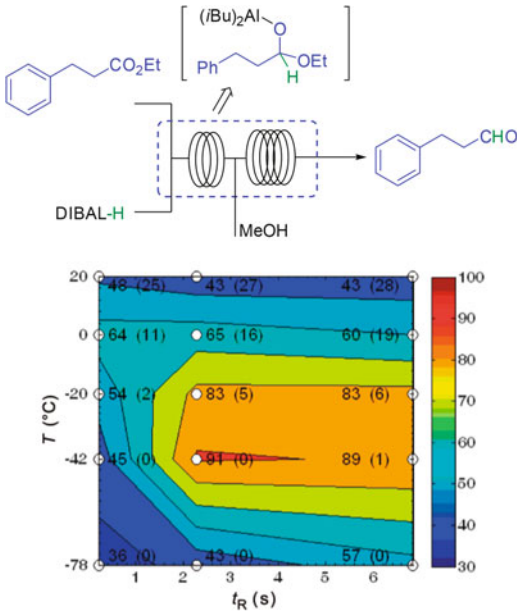


Scheme 2. Generation of noroxymorphone employing only hydrogen, oxygen, and water as stoichiometric reagents



Scheme 3. Top: Reaction of a Grignard reagent with an acyl chloride; bottom left: glass microstructure; bottom right: the multi-injection reactor is capable to produce 100 kg of final product per week for this specific reaction. Images reproduced with permission from Ref. [20]. Copyright 2008, Wiley-VCH

experiments, the mixture is simply carried through residence units at constant temperatures. Combined with the extraordinarily efficient mass- and energy-transport capabilities of microreactors, this attribute enables exceptionally rapid adjustment of reaction conditions. Thus, in addition to conventional multistep reactions, even reaction sequences involving very reactive intermediates become feasible with relative ease. This was extensively used in the past for the generation and subsequent consumption of short-lived intermediates [6, 7]. Often, the reactions were accomplished at reaction temperatures significantly higher than those typically employed for batch procedures ("flash chemistry) [23, 24]. For instance, Swern oxidations, typically performed below −50 °C, have been performed at temperatures as high as 20 °C. Excessive decomposition of the activated dimethyl sulfoxide (DMSO) in a Pummerer rearrangement was avoided by carefully controlling residence time and rapidly transferring the intermediate to the next stage of the reactor [25]. Similar strategies were used for the selective reduction of carboxylic esters to aldehydes with diisobutylaluminum hydride (DIBAL-H; Scheme 4) [26]. This reaction is usually accomplished by full reduction of the ester to the alcohol and subsequent selective reoxidiation to the aldehyde. In the continuous-flow microreactor, the reaction mixture can be quenched precisely when the amount of desired product is at its maximum (Scheme 4). This was exploited by researchers from MIT for the selective one-step reduction of esters to the corresponding aldehydes. Residence times below 50 ms were needed at a nominal temperature of −78 °C [26]. As pointed out by researchers from Lonza, such reactions are virtually impossible in batch reactors on an industrial scale [27]. The short half-life of the organo-aluminium intermediate would not allow for the extended dosage times required to maintain isothermal operation on larger scales in batch. Numerous other related examples have been published in the scientific literature [6–7, 23, 24].



Scheme 4. Highly reactive intermediates can be generated in continuous-flow microreactors and directly quenched to form stable 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 with permission from Ref. [26]. Copyright 2012, American Chemical Society

Reagents Too Reactive to Ship or Store

The basic strategy outlined in the previous section has been further developed into a quite general approach for the in-line generation of reactive intermediates. The reactive intermediate is thereby most commonly generated by combining two respective precursors (e.g., aldehyde and DIBAL-H). In addition to chemical generation by combining reagents, preparation of the reactive species by thermal, photochemical, or electrochemical excitation of an appropriate precursor can be envisaged. Although these latter strategies are currently significantly less explored, they have the potential to open new, exciting prospects for organic synthesis [23]. To avoid interference with downstream transformations, subsequent or concomitant in-line purification can be employed to remove undesired components from the reactive species. Several separation methods based on a variety of physicochemical principles have been explored. For instance, in-line purification by continuous in-line extraction and subsequent phase separation through a hydrophobic membrane has become a quite established practice in recent years. Additionally, removal of by/side-products in fixed-bed cartridges

filled with immobilized scavengers has been extensively demonstrated. An elegant and highly promising approach relies on the use of selectively permeable membranes for the selective separation of the desired intermediate (e.g., size-selective membranes for the separation of low molecular weight reagents). The integration of generation, purification, and consumption eliminates human exposure and the need to ship or store the potentially hazardous reagent ("on-site, on-demand" generation). Moreover, incorporation of synthesis, separation, and consumption of an unstable reagent into a single, compact device reduces transport paths to milli- or micrometers and transport times to seconds or even milliseconds and, hence, minimizes decomposition. In the last years, such strategies have been successfully implemented by researchers for the generation of very reactive reagents [28]. Some of these reagents, such as diazomethane (CH_2N_2), ethyl diazoacetate, carbon monoxide (CO), hydrogen cyanide (HCN), and isocyanides, are normally used only reluctantly or are entirely banned from synthesis laboratories.

It can be expected that many further, ever more unstable reagents will be made accessible by such approaches. It also can be expected that computer modeling and simulation will play a fundamental role in the design and optimization of next-generation, multistep microreactors. To take full advantage of the multistep reactor, the individual reactor zones need to be adapted and optimized for their specific purpose (e.g., separation, mixing, heat exchange, etc). Unconventional reactor designs of almost arbitrary complexity can be realized by modern manufacturing processes like 3D printing [29]. A thorough understanding of the physiochemical characteristics of the reaction including transport processes, mechanism, kinetics, and thermodynamics is thereby required to devise and optimize the design of each reaction zone. A multidisciplinary approach involving computational physicists and chemists, experimentalists, engineers, and materials scientists is essential for the full development of this field.

Transformation Not Possible in Batch Reactors

Continuous-flow microreactors not only allow the execution of reaction sequences which would be impractical or unsafe to perform in traditional tank reactors. Genuinely novel transformations which would not be possible in tank reactors can be accomplished. This was perhaps most impressively shown in a series of publications by J.-i. Yoshida of Kyoto University [23, 24]. Their approach relied on the abovementioned possibility to generate and directly consume a reactive intermediate. Using microreactors, reaction sequences can be accomplished where reaction times from generation to consumption are only in the order of milliseconds. This is possible since residence times in the individual reactor zones of a continuous-flow microreactor can be chosen to be almost arbitrarily small using appropriately designed mixers/heat exchangers. Thus, even the most short-lived intermediates can be generated and successfully employed for subsequent transformations. To demonstrate this principle, two simple hypothetical reactions are shown in Figure 2. In both cases, reagents A and B react to form

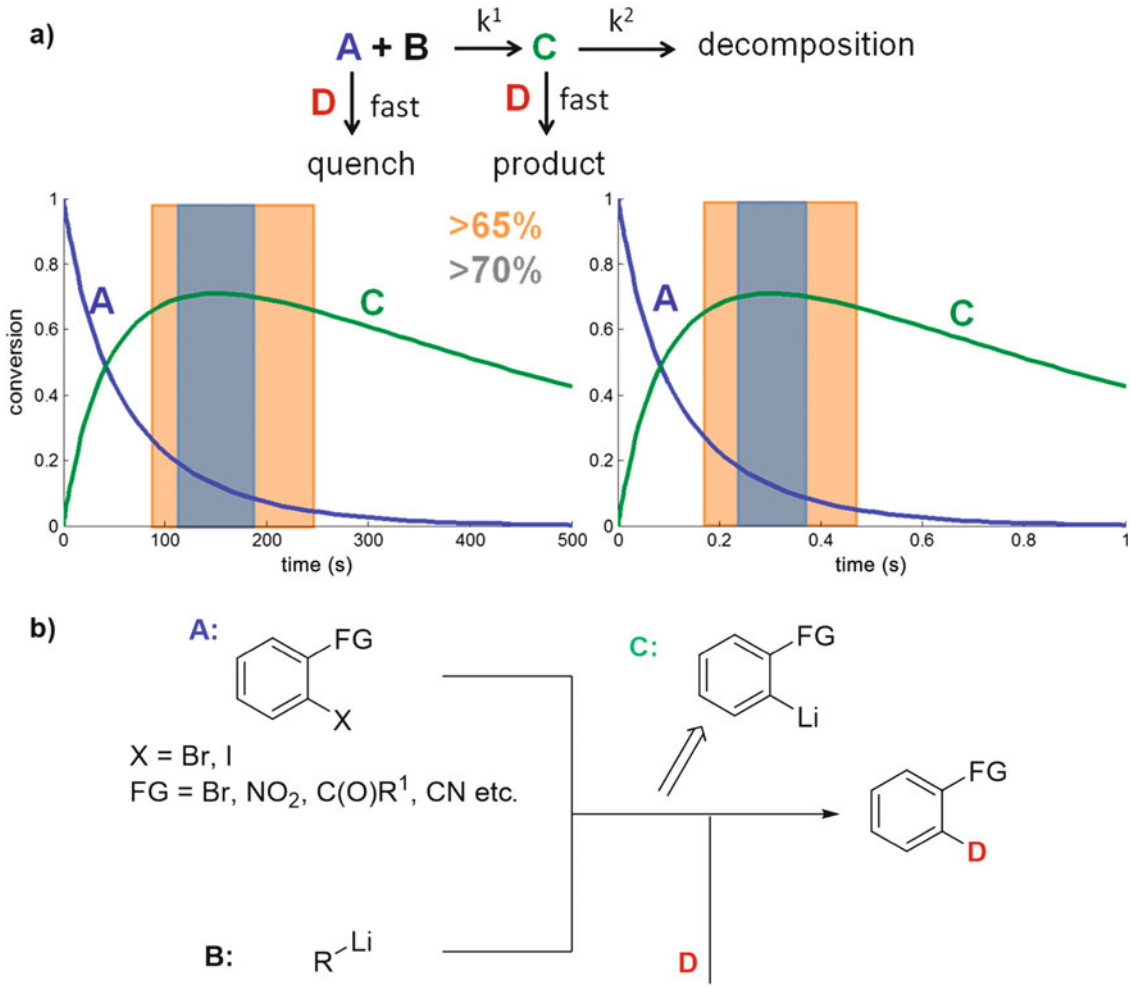


Figure 2. a) A transformation which requires rapid generation of a short-lived intermediate (C) and direct subsequent consumption (reagent D) may be difficult or impossible to implement in batch reactors; left: k^1 = 1 10^{-2} L/(mol s) and k^2 = 0.2 10^{-2}/s; right: k^1 = 5 L/(mol s) and k^2 = 1/s. b) Some practical examples [23, 24]

the desired intermediate C (rate constant k^1). The intermediate is unstable and decomposes with a rate constant k^2. Alternatively, the intermediate C reacts in an essentially instantaneous reaction with reagent D to give the desired product. However, reagent D would also quench the reagent A and, thus, cannot be in the reaction mixture during generation of intermediate C. For the first example, the rate constants were assumed to be $1\ 10^{-2}$ L/(mol s) and $0.2\ 10^{-2}$/s, respectively. With these rate constants, reagent D would need to be added to the reaction mixture in a time window ranging from about 80 s to about 4 min after reagents A and B were mixed to achieve >65% product. If >70% product is desired, the window narrows to an interval starting at 2 min and closing after 3 min. This reaction is doable in batch reactors (at least on a laboratory scale). However, if the reaction rates would be 500 times higher (k^1 = 5 L/(mol s) and k^2 = 1/s), reagent D would have to be added between ~0.17 and ~0.51 s after A and B have been mixed for yields >65% or between ~0.24 and ~0.37 s for yields >70%. Even neglecting complications regarding heat and mass transfer, it is clear that this reaction is not feasible in batch reactors. However, various intriguing examples along these lines have been successfully demonstrated in the last few years using continuous-flow microreactors. Often, transformations were enabled which traditionally would need protecting group strategies or other potentially costly detours. These transformations are discussed in greater detail elsewhere in this special issue in Journal of Flow Chemistry.

Outlook: Advancing Sustainability through "Hazardous" Chemistry

In 1998, the concept of green chemistry and the 12 principles of green chemistry has been formulated by Anastas and Warner at the US Environmental Protection Agency (EPA) [30]. The overall objectives of green chemistry are both simple and persuasive: (1) reduce waste, particularly hazardous waste; (2) as many atoms as possible should be incorporated into the final product and, conversely, as few as possible should end up in byproducts and waste; (3) use catalysts rather than stoichiometric reagents; (4) reduce consumption of energy; (5) minimize risks of accidents; (6) avoid hazardous materials or process conditions; (7) maximize safety. Important progress has been made in many research areas associated with green chemistry. New, efficient, and more productive catalysts have been developed; solvents and reagents have been replaced by safer and environmentally more benign ones; materials and energy are increasingly recycled. However, putting the principles of green chemistry into practice often requires tradeoffs. For instance, the use of highly reactive reagents might compromise the safety of a chemical process and increases the inherent risk potential. On the other hand, short, atom economic, and high yielding synthesis routes frequently demand the use of highly reactive, often low molecular weight reagents. We believe that it is particularly in the realm of "harsh" process conditions [1, 4, 5] and "hazardous" chemistry [6, 7] where continuous-flow microreactor technology offers tremendous potential. Due to the small reactor volumes, heat/mass transfer improves and reactions become intrinsically safer. Thus, significantly harsher process conditions can be applied. Even though the vast majority of operations in the pharmaceutical industry are currently executed in stirred tank reactors, an increasingly strong pressure for cost- and atom-economic processes will drive growing adaption of continuous-flow microreactors [31]. Most importantly, the development and application of novel, innovative reactor technologies enable entirely new transformations, open new synthetic routes, and let us rethink the manufacturing process as a whole.

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