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Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis

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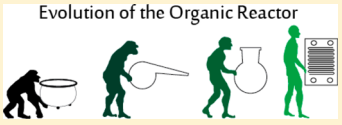
ABSTRACT: The synthesis of complex molecules requires control over both chemical reactivity and reaction conditions. While reactivity drives the majority of chemical discovery, advances in reaction condition control have accelerated method development/discovery. Recent tools include automated synthesizers and flow reactors. In this Synopsis, we describe how flow reactors have enabled chemical advances in our groups in the areas of single-stage reactions, materials synthesis, and multistep reactions. In each section, we detail the lessons learned and propose future directions.



SMALL DIMENSION CONTINUOUS REACTORS: A PRIMER

Continuous reactors have been used by chemical engineers for over a century. Only recently have scaled-down versions become available to the synthetic organic chemist.[1] These flow reactors offer advantages including: (1) controlled heat transfer, (2) controlled mixing (both fast and slow), (3) increased photon-flux in photochemical reactions, (4) increased electrode surface-to-reactor volume ratio (electrochemistry), (5) increased solution-solid phase interactions, (6) controlled use of highly reactive/toxic materials, and (7) increased capacity to run serial reactions. The small dimensions of a flow reactor are responsible for the first six advantages, while the inherent continuous feature enables the creation of continuous multistep processes with the promise of easy scale-up by increasing the number of reactors or the reactor dimensions.[2] The use of flow reactors also has challenges such as managing solids in flow, integration of reactor components (pumps, reactors, back-pressure regulators), and integration of new features (in-line monitoring and purification). Some of these challenges will be discussed.

Early flow reactors were built by engineers and were often complex modular units or silicon chips.[3] Today's flow reactors range from laboratory-built systems consisting of simple tubes and connectors to fully integrated commercial systems. Figure 1 depicts some of the devices used by our groups. Figure 1A illustrates single-stage reactors. Many of a flow reactor's most attractive attributes can be achieved with inexpensive tubing and fittings. Silicon chip reactors are preferred when using expensive compounds (<1 mg to 100 mg scale). Figure 1A displays our high-efficiency LED lamp reactor, but we also use mercury arc-lamp configurations.[4] Figure 1B features two of our turn-key flow reactor systems. The first is a Vaportec R2+/R4 meso-flow system linked to a flow IR. In this system, reaction progress can be monitored in real time. The second system is a Thales H-cube which produces hydrogen gas in real time. Commercial flow reactor systems are an excellent investment once a group has developed a working knowledge using simple devices.

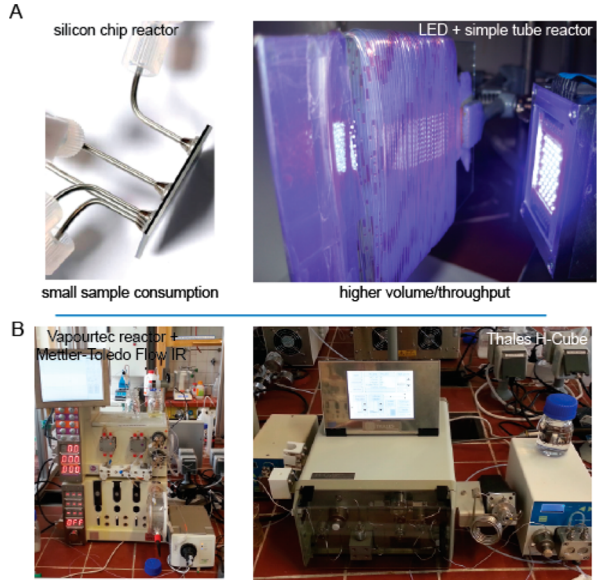


Figure 1. Flow reactors used in our groups: (A) reactor modules from simple tubing to silicon chips; (B) turn-key systems.

As with any new technique/technology, one must avoid both positive and negative hyperbole. Flow reactors are not a panacea,[5] but they do represent an excellent complement to traditional batch reactors.[6] The Jensen group has described where flow reactors should provide superior results relative to batch reactors.[7] Jensen's review relates the chemical engineering underpinnings to flow reactors in a manner that bridges the gap between engineers and chemists.

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This synopsis is not meant to provide the reader with a review of the flow chemistry literature. Those who wish a detailed account of flow chemistry are encouraged to read seminal contributions and recent reviews.[8] Instead, we describe how two early adopters began using flow chemistry tools, the approaches we now use to conduct flow chemistry, and finally, how we view flow chemistry as an important element in the realization of automated systems for the on-demand production of small molecules.

APPLYING FLOW CHEMISTRY TO SINGLE STAGE REACTIONS

Our flow chemistry research began by using a stainless steel reactor where we performed continuous alkylation, acylation, cycloaddition, olefination, and transition-metal-mediated cross-couplings reactions (Figure 2A).[9] The reactions were transferred from known batch procedures to the microreactor, resulting in better or comparable yields. These experiments prompted exploration of reactions that present challenges in batch, such as trimethylaluminum-mediated amide bond formation or fluorinations using diethylaminosulfur trifluoride DAST (some advantages observed in flow are presented in Figure 2). Continuous amide bond formation mediated by trimethylaluminum enabled high-efficiency single-stage reactions, and the reaction was used as a key step in multistep reactions leading to the synthesis of bioactive compounds (Figure 2B). The DAST reactions enabled the safe use of this potentially explosive reagent (Figure 2C). We also demonstrated that radical-based dehalogenations, deoxygenations, and hydrosilylations in flow often exhibited superior selectivity and control relative to batch comparisons (Figure 2D).[9]

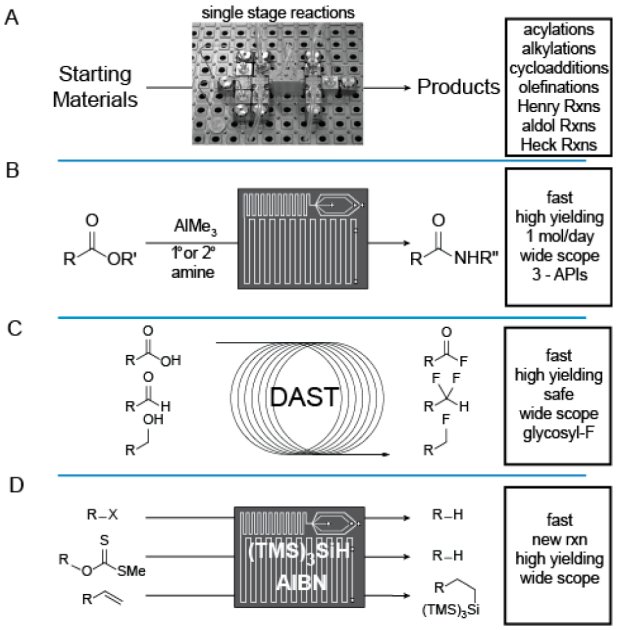

Figure 2. Early single-stage reactions performed in flow: (A) demonstration that a wide range of reactions could be run in flow; (B) safe amide formation using trimethylaluminum; (C) safe, continuous use of DAST; (D) reductions and hydrosilylations using tris(trimethylsilyl)silane.

We also began to use flow reactors to address problems associated with synthesizing oligosaccharides. Although many advances in carbohydrate chemistry have been achieved, the identification of high-yielding, stereoselective glycosylations remains a time- and resource-intensive activity. It was predicted that glycosylation reactions could be optimized using chip-based flow reactors and that these conditions would accelerate our automated oligosaccharide efforts.[9] We further speculated that larger-scale flow reactor-based glycosylations could enhance our solid-supported carbohydrate synthesis efforts. We have demonstrated that glycosylations in flow can be optimized using minimal amounts of precious starting monomers. In Figure 3A, we demonstrate that the product/byproduct ratio is strongly temperature dependent and later that these reactions could be scaled out to yield gram quantities of disaccharide products. Using the same flow reactor tools, oligosaccharides were synthesized continuously (Figure 3B).[9]

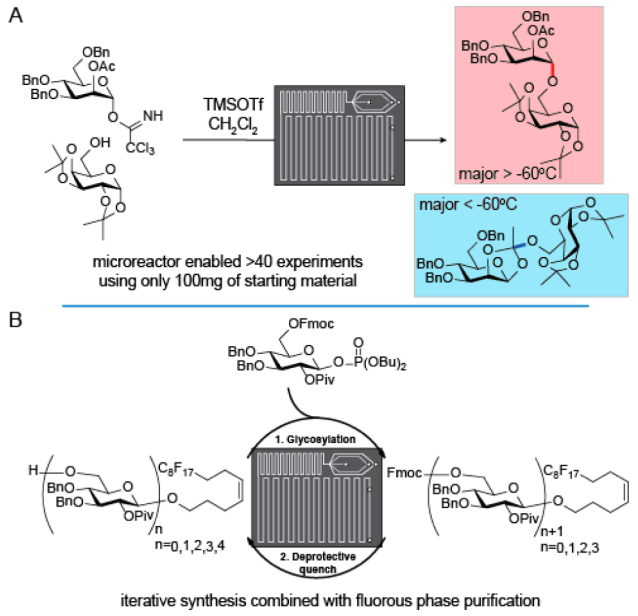

Figure 3. Glycosylations in flow: (A) optimization using a chip strategy; (B) synthesizing oligomers using an iterative approach.

As flow chemistry use grew, major limitations, such as handling solids, emerged.[10] Early flow reactors often featured dimensions <100 μm to maximize heat transfer/mixing or to enable ultrahigh pressures. Inadvertent introduction of particles (dust) or formation of a solid during a reaction resulted in clogging and often destruction of the devices.[11] Borrowing droplet reactor themes from the lab on a chip community,[12] we and others created droplet-based flow chemistry systems designed to handle the production of solids.[13] Elaborating on the solids in flow concept, we demonstrated that solid reagents or catalysts could be placed into cartridges and reagents pumped through the cartridges. We have successfully used proline to perform asymmetric aminoxylations (Figure 4A).[14] Previous examples of chiral pyrrolidine catalysts in flow required expensive soluble proline derivatives[9] or supported catalysts.[15] The advantage of proline is that it is very inexpensive. More recently, solid copper oxide was used to prepare transition-metal complexes (Figure 4B).[14] The use of metal salts such as copper oxide to prepare copper(I) complexes is both inexpensive and enables the rapid production of air and water sensitive species without using a glovebox. Synthesis and use of transition metal complexes in-flow is a growing area.[16]

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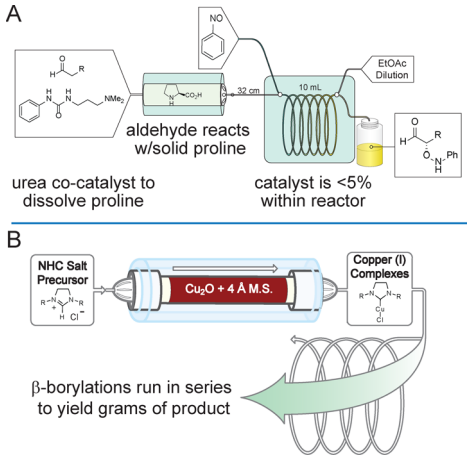

Figure 4. Synthesis and use of solids in flow: (A) solid to solution use of solid proline in flow; (B) flow approach to the synthesis of transition-metal complexes.

Photochemistry and flow reactors are a natural fit because the small fluid cross-sections that can be exposed to radiation provide higher photon-fluxes compared to batch reactors.[17] We have demonstrated that flow photochemistry yields superior results compared to batch including a recent example of single-electron-transfer (SET) reactions using $Ru(bpy)_3^{2+}$ complexes (Figure 5).[18] With regard to single oxygen reactions, we have

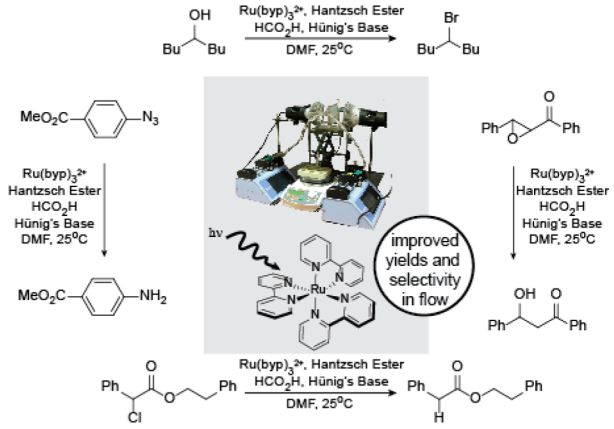

Figure 5. Gas/liquid photoreactions are ideal for flow: $Ru(bpy)_3^{2+}$-based SET reductions/brominations.

demonstrated that high velocity segmented flow systems yielded efficient ene, endoperoxidation and heteroatom oxidation reactions.[19] At high flow rates, the oxygen bubbles and fluid droplet sheer thinly along the walls of the reactor, increasing the surface area exposed to light as well as the gas–liquid surface area. The higher photon-flux in flow significantly decreased the reaction times for the SET reactions as well.

The last 10 years of flow chemistry have shown that one can perform almost any reaction continuously. The future for single-stage reactions in flow must concentrate on using the unique properties of flow reactors (time, pressure, temperature, photon-flux, etc.) to create novel chemistry. Two promising directions that are yielding novel chemistry include working at fast flow rates to generate and immediately use reactive intermediates[20] or working outside of normal process windows.[21] As an example, we are performing singlet oxygen endoperoxidations on substrates that would undergo deleterious side reactions if performed slowly. While we feel that productivity gains and the transitioning of unsafe reactions to flow remain important, these efforts now represent more specialized contributions.

Integrating in-line analytical devices with single-stage reactions also represents an area where further development is desperately needed. Proof-of-concept optimization systems are established, but these systems will not be broadly applied until real-time monitoring of complex reaction mixtures or optical purity becomes both affordable and easily accessible.[22] In addition, continued basic research is required to accelerate optimization, such as strategies to enable continuous variation of noncontinuous variables. For example, classic solvent polarity[23] or Lewis acid scales[24] are essential to apply automated Design of Experiments or other statistical approaches.[25] Moving the field toward more automated reactions will accelerate our pace of discovery.

APPLYING FLOW CHEMISTRY TO MATERIALS SYNTHESIS AND USE OF MATERIALS IN FLOW

Flow chemistry offers the opportunity to prepare novel materials.[26] We have utilized fluid dynamics, heat transfer, and serial reaction attributes of flow reactors to realize the synthesis of novel capsules, faster polymerizations, and functionalized nanoparticles. Using known monodisperse droplet-forming devices,[27] we have produced novel polymeric and inorganic capsules. Our first example demonstrated that polyamide capsules could be produced using simple reactors and that by controlling flow rate, the size of the capsules could be readily varied. Later examples took advantage of the low turbulence found in flow reactors to create novel spinulose capsules that could not be produced in batch experiments (Figure 6A).[27] We have also leveraged the precise control of reaction parameters to produce monodisperse silica capsules from $SiCl_4$ (Figure 6B).[27]

Flow chemistry, as described previously, enables rapid heating (or cooling). Using this principle, we performed reversible addition–fragmentation chain transfer polymerizations in flow to realize the synthesis of poly(*N*-

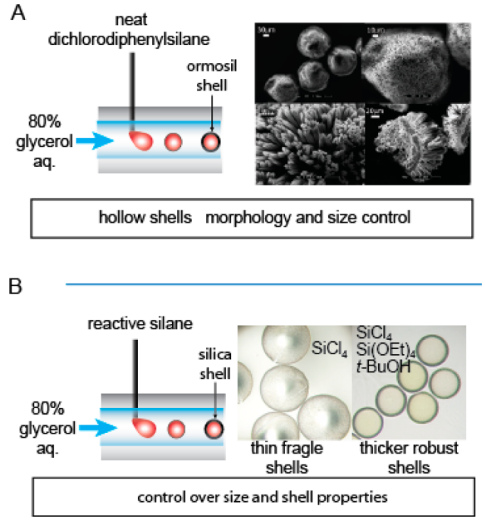

Figure 6. Microcapsule production using a monodisperse droplet-forming flow device: (A) ormosil capsules formed in flow form organized spiny texture; (B) monodisperse silica capsules formed from reactive silica monomers.

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isopropylacrylamide) polymers. The polymerizations in flow were faster compared to batch while exhibiting similar polydispersities and provided easy access to these materials, enabling us to functionalize the chain ends with sugars for use in glycopolymer arrays (Figure 7A).[28] Building on this materials

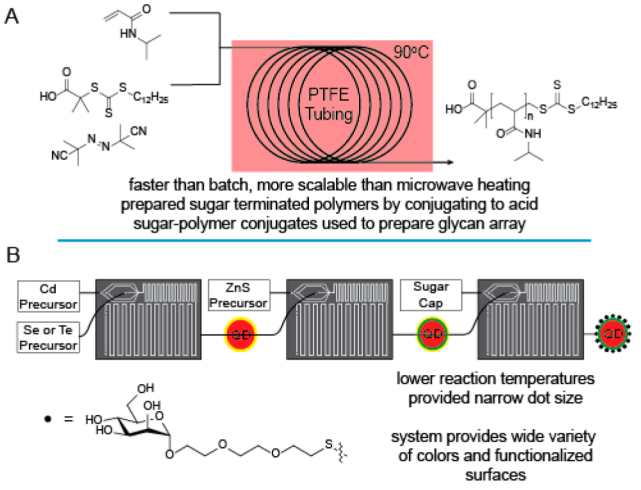

Figure 7. Producing polymers and nanoparticles in flow: (A) RAFT polymerizations are achieved with much faster rates; (B) multistage synthesis of carbohydrate-functionalized quantum dots.

in flow theme, we created a three-stage process to synthesize monodisperse CdSe or CdTe dots, cap them with ZnS and finally terminate with sugars. The process could be used to vary both the quantum dot size (and thus color) as well as the identity of carbohydrates presented on the surface (Figure 7B).[29]

Flow synthesis is a powerful tool for producing novel materials. We predict that the serial attributes of flow reactors will enable novel block copolymer syntheses where block length is controlled by residence time between reactors. Flow reactor synthesis will also enable the production of composite capsules and fibers. We imagine that novel self-assembled materials will be constructed using elongational fields formed in flow.[30] There are thus far only a few publications of materials synthesized in stages similar to our efforts with quantum dots. The ability to produce reactive surfaces and immediately functionalize them without purification opens many possibilities. We further predict that automated nanoparticle synthesizers will enable start-up companies to produce novel probes on demand and also allow academic researchers to synthesize libraries of potential probes.

APPLYING FLOW CHEMISTRY TO MULTISTEP REACTIONS

Using flow to perform multistep reactions was achieved early on.[2a,31] Many of these early efforts used supported reagents or scavengers. We entered this field by recognizing that the next challenge was to create continuous processes where valuable targets are produced using no supported species or intermediate purifications. Our first example was the three-step synthesis of ibuprofen from commercially available starting materials. The system required a batch crystallization at the end of the synthesis, but the intermediate steps required no workup or purifications (Figure 8A).[32]

The next major progression was a highly efficient continuous synthesis of an active pharmaceutical agent whose current cost

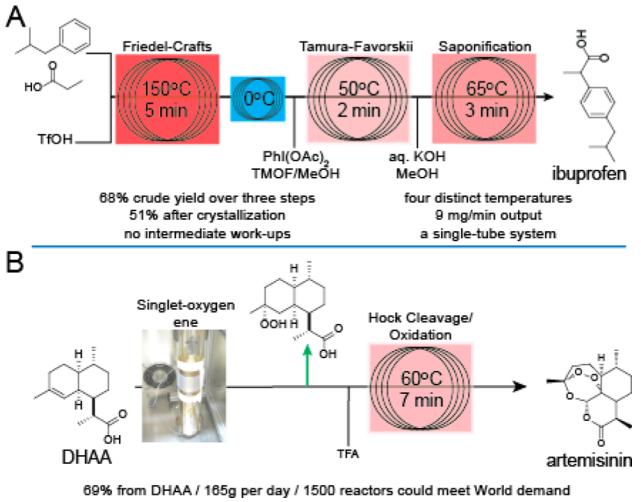

Figure 8. Multistep continuous syntheses without intermediate purification: (A) three-stage synthesis of ibuprofen; (B) two-stage synthesis of artemisinin.

limits access to those who need it most. This was recently accomplished with a continuous photochemical route to the antimalarial artemisinin. The route begins from dihydroartemisinic acid (DHAA; Figure 8B),[19] a starting material now available on large scale via fermentation.[33] DHAA first undergoes a singlet oxygen-based ene reaction to yield a peroxide. The peroxide is combined with trifluoroacetic acid and undergoes a Hock cleavage followed by further oxidation with $^3O_2$ to yield artemisinin. The original reactor used a mercury arc lamp and provided 39% yield of artemisinin from DHAA. Recently, we have demonstrated that the process could be optimized to 69% yield from DHAA. The increased yield leads to a throughput of 165 g of artemisinin per day.[19] We are now telescoping this process to continuously synthesize the artemisinin-based active pharmaceutical ingredients artemether, artemotil, and artesunate.

Organic chemistry has been driven by the creation of efficient synthetic methods. We believe that continuous multistep reactions can accelerate the development of efficient chemical processes. Landmark efforts by others have demonstrated that natural products can be rapidly constructed in flow[2] and that medicinal chemistry activities can be accelerated using flow.[34] We propose that multistep flow chemical processes will enable the low cost manufacturing of medicines. In particular, we propose that methods/processes that enable multistep syntheses without supported reagents or scavengers and with only minimal works ups and a single terminal purification step are critical for the manufacturing of key active pharmaceutical ingredients such as antiviral and antimalarial compounds. We posit that creating completely continuous synthesis is a significant academic challenge that requires new chemistry, an improved merging of chemistry and engineering principles, new analytic monitoring tools, and new continuous purification strategies.

Our multistep successes combined with those of others indicate a trend toward automated continuous synthesis. The field is rapidly moving toward automated optimization systems to improve single-step reactions, two-step automated systems that can perform routine chemistry,[35] and systems that can produce radioactive probes continuously.[36] We predict that in the next few decades automated continuous synthesizers

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handling a broad range of chemistry will be realized. Furthermore, these automated procedures will be readily conveyed between laboratories using coded information designed to communicate information directly from one synthesizer to another.

Challenges that prevent our immediate transition to this automated future do exist, of course. They range from the material compatibility of O-rings and pumps to delivering a larder of chemicals. In addition, we must continue evolving continuous workup and purification strategies. We have pushed this area forward by merging a single-step nucleophilic aromatic substitution and a simulated moving-bed chromatographic step.[37] While the process works very well, the effort required two separate sets of expertise and many months of effort to solve both chemistry and purification problems.

■ CONCLUSIONS

Over the last 185 years, our community has advanced bonding models to the point where we can understand and predict most reactivity. Our training methods have enabled the total synthesis of any natural product that nature can produce, and our field can rapidly mobilize to address diseases such as HIV. While new chemical methods that are more efficient and capable of building complexity in fewer steps are essential motivators, we believe that learning to perform our *existing* cadre of reactions more efficiently is also critical. The creation of automated oligonucleotide and peptide synthesizers has enabled a generation of nonchemists to take advantage of chemical synthesis. Our success in the creation of automated oligosaccharide synthesizers that utilize a more complex array of chemistry compared to oligonucleotide and peptide synthesizers demonstrates that automated synthesis is not limited. The automated synthesis of small molecules offers the potential to synthesize medicines at reduced cost, thus making them more affordable to those who need them. Automated synthesis also offers the potential to place small molecule synthesis in the hands of nonspecialists. We conjecture that flow chemistry is the technology that will enable automated continuous synthesis.

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Notes

The authors declare no competing financial interest.

Biography

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D. Tyler McQuade was born in Atlanta, GA, and raised in the Santa Cruz Mountains of California. He received a B.S. in Chemistry and a B.S. in Biology from the University of California—Irvine and a Ph.D. in Chemistry from University of Wisconsin—Madison under the guidance of Professor Samuel Gellman. His formal education was completed by a NIH Fellowship at MIT with Professor Timothy Swager. Currently, he is a Professor of Chemistry and Biochemistry (effective August 2013) at Florida State University and simultaneously a Group Leader at Max Planck Institute for Colloids and Interfaces. Peter H. Seeberger studied chemistry and biochemistry in Erlangen (Germany) and Boulder (CO). After completing his Ph.D. and performing research at the Sloan-Kettering Cancer Center Research in New York he built an independent research program at MIT where he was promoted to Firmenich Associate Professor of Chemistry with tenure after just four years. After six years as Professor at the Swiss Federal Institute of Technology (ETH) Zurich he assumed positions as Director at the Max-Planck Institute for Colloids and Surfaces in Potsdam and Professor at the Free University of Berlin. In addition he serves as Affiliate Professor at the Sanford–Burnham Institute for Medical Research (La Jolla, CA) and honorary Professor at the University of Potsdam.

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