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Flow chemistry remains an opportunity for chemists and chemical engineers

Ryan L Hartman

Flow chemistry has progressed considerably in recent years from basic laboratory techniques in organic synthetic chemistry to complex, multistep processes in practice. In this perspective review, missing links that represent opportunities for chemists and chemical engineers are examined. New avenues in reaction chemistry are expanding the molecular toolbox, which includes green and cascade catalysis. Next generation engineering concepts such as machine intelligence and sustainable manufacturing have become a reality, opening the door to interdisciplinary work unlike before. Emerging trends that have the potential to start new fields of research and technological advancements are also highlighted. Flow chemistry is rewriting the traditional chemistry laboratory and our scientific discovery infrastructure. Enormous opportunities remain for groundbreaking science and engineering from this exciting field that demands a well-trained workforce for its industrial practice. The groundwork is being laid now for industries of the future such as continuous-flow biologics, biopharmaceuticals, and implementation of the nanomaterials revolution.

Address
New York University, Department of Chemical and Biomolecular Engineering, 6 MetroTech Center, Brooklyn NY, 11201, United States

Corresponding author: Hartman, Ryan L (ryan.hartman@nyu.edu)

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Introduction

Flow chemistry has had a profound impact on science and engineering, creating new fields of research and opportunities for commercial technology [1,2,3••]. Performing reaction chemistry in flow continues to help catalyze development and growth in societies where the chemical manufacturing industry is important to the economy [4]. Flow chemistry has also helped established a new era of interdisciplinary innovation that is responsible for groundbreaking discoveries and technological advancements [5–8].

Chemists and chemical engineers in the energy industry have performed chemical reactions in continuous-flow for decades because of the economy of scale, chemical process safety, and the push for efficiency. Modular manufacturing and process intensification design concepts, growing more and more important in petrochemicals and commodities, are now emerging in fine chemical and pharmaceutical manufacturing. Laboratory reactors in the commodity chemicals industries are also similar in scale to continuous-flow pharmaceutical manufacturing equipment [1,2,3••]. Small footprint requirements, such as those in marine environments, indoor manufacturing facilities, or in mobile deployment operations all share in common design constraints that in turn reduce building energy consumptions. An opportunity exists for knowledge transfer of flow chemistry across the different segments of the chemicals industry.

Significant opportunity exists for flow chemistry in fine chemicals and pharmaceuticals research and manufacturing, which have long been carried out using batch-wise operations. Continuous-flow manufacturing is game-changing technology that could revolutionize affordability, reducing cost by as much as 40% and the lead-time for prescription drugs by 90%. This next-generation manufacturing could not only reduce the cost of healthcare, but it could also improve access to life-saving therapeutics in regions of the world where healthcare access is limited. Flow chemistry is critically important to the future of healthcare [1,2,3••].

Green chemistry is more important than ever before [6,9], and flow chemistry is enabling the faster discovery of greener catalysts and synthetic methodologies. Performing reaction chemistry in flow can also drastically reduce the environmental impacts in the laboratory and production scales. Certain classes of compounds, once deemed far too hazardous for use in synthesis and manufacturing, are also now within reach thanks to flow chemistry [10]. Taming unstable compounds or the exceptional control of runaway conditions using flow reactors has opened the door to greener routes to useful products [11,12]. Flow chemistry is making chemicals research and manufacturing both greener and safer.

The field of flow chemistry is evolving fast, drawing experts together from across disciplines. Opportunities

remain for chemists and chemical engineers to make important contributions in this field. In this perspective review, some of the missing links that represent opportunities are highlighted, which could lead to new fields of research and development. Emerging trends that build on the discoveries already made in flow chemistry are also discussed.

New avenues in reaction chemistry

Discovery versus process chemistry

A decade ago, flow chemistry found versatile application in the traditional organometallic chemistry laboratory by providing high fidelity, transient information for process chemistry. This was then and still is today important for systems where the reaction times scales approach those of the transport phenomena, where the systems are multiphase, or when safety concerns exist. Deciding whether to go with the flow for 'discovery' was less obvious back then, demanding the pragmatic exercise of weighing one's time with the potential advantages or disadvantages. Now the field has developed where automated flow reactor technology can accelerate discovery too [13••].

The world will always need both homogeneous [14] and heterogeneous catalysts [15], but the immobilization of catalysts for organometallics synthesis remains an opportunity [16,17]. The use of laboratory flow reactors for the discovery of heterogeneous catalyst has longstanding merit. But what kind of reactor should one use? Whether it be in batch or flow, a discovery-driven experiment should provide sufficiently high resolution information to test one's hypotheses or to answer a shortlist of research/development questions. The experiment should also be safe, ideally green, cost-effective, and require a minimal amount of time to conduct. Satisfying those criteria could not only accelerate discovery, but providing scalable information could also reduce the lead time for manufacturing new compounds.

Flow chemistry continues to play an important role by 'process intensification' of the modern chemistry laboratory. Imagine discovering a new catalyst and acquiring information for scale-up in the same experiment. As an example, laboratory-scale packed-bed (or fixed-bed) reactors remain a workhorse in commodities [18] because they can provide scalable information on the catalytic activity and process design. Novel laboratory flow reactors in fine chemicals and pharmaceuticals could be evolving their discovery in a similar way [13••].

Green chemistry

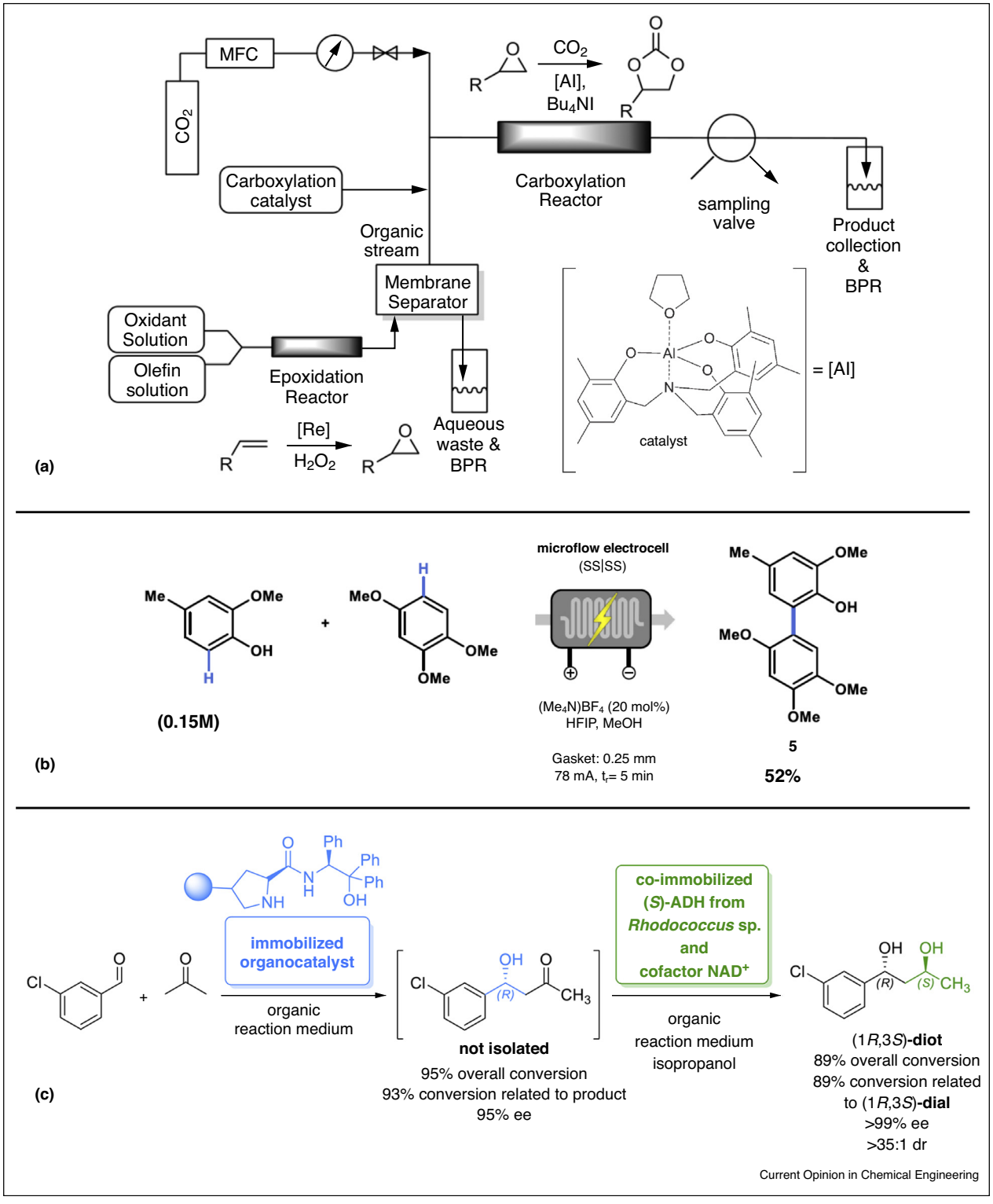
Considerable opportunity exists for the discovery and development of green chemistry in flow. The race to design more efficient catalyst, synthetic methodologies using renewable feedstocks, to reduce chemical waste, and to discover reaction pathways that require milder conditions is more important than ever before. Solvent-free synthesis, for example, has emerged as an opportunity for green chemistry [19], but the approach is a tradeoff of risk and reward in its engineering. In the absence of solvent, reaction rates can be accelerated and the need for separations eliminated, which is a gigantic step all in one. However, reaction products and by-products can precipitate in solvent-free systems, and in turn clog or foul equipment.

Green chemistry continues to be at the forefront of discovery in flow. Performing synthesis in flow can expand possible reaction conditions, enable photocatalysis, heterogeneous catalysis, and the use unconventional solvents or reagents [9]. Advances in synthesis with molecular oxygen [20], carbon dioxide [21,22•] (Figure 1a), and hydrogenations [23] undergird practical and safe use of gaseous feedstocks [24]. Unconventional solvents used at elevated temperatures and pressures, for example, supercritical CO_2 [21], have tremendous potential for implementation in practice. Indeed, many opportunities remain for the discovery of greener chemistry using flow. Surgical catalysis with multifunctional catalytic materials is needed to prepare fine chemicals from petroleum or renewable feedstocks that vary widely in their compositions. Polymers are also on everyone's minds, given their broad utility and in some cases poor recyclability. Flow chemistry will surely play an important role in the design of next-generation biodegradable polymers, thereby reducing carbon footprints.

Mitigating hazardous compounds

Flow chemistry inherently provides a safe means by which reactions involving unstable, toxic, or otherwise hazardous reagents/intermediates, including multistep syntheses, can be designed. Excellent works have highlighted the use of diazonium derivatives, peroxides, nitrations, sulfonations, direct halogenations, azides, ozonolysis, hydrogenations, cyanides, carbonylations using carbon monoxide, ammonia, and phosgene reaction chemistry, to name a few [10,27]. In all cases, performing the reactions in flow allows for precise control of the hazards associated with each chemistry, which may include highly exothermic reactions that are prone to runaway [11,12]. Implementation of such compounds in total synthesis has emerged plausible, in some cases greener routes to useful products [10]. Tremendous opportunities remain, as a vast number of existing batch-wise operations or the manufacture of new target molecules that harness hazardous compounds may be designed in continuous-flow. Doing so could also lead to new research in synthetic chemistry, chemical process safety, and traditional chemical reaction engineering. For instance, the complex mechanisms associated with organometallic synthesis, which may also include multiphase mixtures, create the opportunity for the development of non-elementary runaway reaction criteria coupled to multivariate optimizations. Narrow ignition and extinction and at elevated temperatures, for example, in the

Figure 1



Three recent examples of flow chemistry in areas with exciting opportunities for novel synthesis protocols. **(a)** Use of CO_2 gaseous feedstock in a carboxylation of olefins to cyclic organic carboxylates performed in a packed-bed microreactor [Republished with permission of The Royal Society of Chemistry, from Ref. [22•]; permission conveyed through Copyright Clearance Center, Inc.] **(b)** An electrochemical arene-phenol C–C cross-coupling using a modular, scalable microflow reactor [Laudadio, G., de Smet, W., Struik, L. et al. *J. Flow Chem.* (2018) 8: 157. https://doi.org/10.1007/s41981-018-0024-3.] [25••]. **(c)** Continuous-flow cascade synthesis of 1,3-diols based on the immobilization of organocatalysts and biocatalysts [Reprinted with permission from Ref. [26•]. Copyright 2014 American Chemical Society.].

oxidative coupling of methane, further introduce interesting yet challenging new opportunities to mitigate hazardous conditions [28,29].

Electrification in synthesis

The design of electrochemical synthesis in flow, although limited in practice, has significant potential. Harnessing free electrons to activate organic substrates introduces a mild, versatile, and green alternative in synthesis. A few examples in flow include the electrochemical reduction of furfural to furfuryl alcohol [30], anodic oxidation of thioethers [25••], and a new arene-phenol cross-coupling method (see Figure 1b) [25••], with enormous potential for the synthesis of more environmentally friendly polymer precursors [31,32]. Recent reviews have done an excellent job of highlighting the existing challenges in electrochemistry [33] and electrochemical reactor designs [34,35] while the opportunity remains for electrocatalysis in organic synthesis. The transport of electrons via electron carriers, high-surface-area electrodes, and advanced materials that sustain their catalytic activity, in addition to conventional heat and mass transport resistances, introduces unique challenges that makes electrochemistry in flow very attractive to the engineer. Electrification further introduces the opportunity to use plasma, the fourth state of matter, in organic synthesis [36], which presents its own set of interesting challenges such as dissipation, a high interfacial contact area in multiphase flows, plasma-liquid mass transport, to name a few. Microfluidics for these reasons have found early application in this field, but science has only discovered the 'tip of the iceberg'.

Cascade catalysis

An aspirational goal of catalysis continues to be the design of multifunctional heterogeneous catalysts for cascade reactions or 'one-pot' syntheses. Synthetic methodologies may also be designed to mimic nature [37,38], and the design of heterogeneous catalysts for 'one-pot' enzymatic catalysis is a hurdle to preparative synthetic biology [39]. Tremendous efforts by biologists and chemists have been directed towards understanding cascade networks, with recent progress made in the field of flow chemistry (e.g. Figure 1c) [26•,40,41,42]. However, how to address the challenge of reaction complexity with catalyst and reactor design remain vastly unexplored. Cascade reactions on the same catalyst's surface is one approach, while the design of cascade reactors is another. Deeper understanding of how to exploit chemoselectivity, regioselectivity, and stereoselectivity of heterogeneous bio/chemocatalysts is needed. The large number of reaction parameters combined with complex mechanisms create the opportunity for computer-aided catalyst design by machine intelligence.

Next-generation engineering

Novel unit operations and *in situ* characterization

The transformation of batch-wise processes to continuous-flow has led to the innovation of some interesting unit operations. Many synthetic methodologies introduce unique challenges that require innovative thinking. For instance, solvent switching, use of crystalline materials, non-ideal thermodynamics, homogeneous catalyst, air/moisture sensitive compounds, and multiphase mixtures are all common in the synthesis laboratory. Breakthroughs by many notable laboratories have overcome these challenges by rethinking unit operations from both traditional and non-traditional perspectives, which further undergirds the importance of chemists and engineers working together in this field. Packed-beds [23], modular cartridges [8], photochemical reactors [43,44], plasma reactors [36], catalytic membrane reactors [45], and electrochemical reactors [25••], to name a few, have emerged through the discovery of flow chemistry. Likewise, separations such as counter-current multistage extraction [46], coiled-tube crystallizations [47], and continuous distillations [3••] have enabled multistep syntheses in flow. Some industrial groups have even designed pragmatic flow chemistry operations using continuous-stirred tank reactors and commercial tubing [3••]. Not losing sight of traditional reaction engineering theory [48] will continue to be important as new catalysts and methodologies motivate novel unit operations.

Novel unit operations that are coupled to electromagnetic radiation enable *in situ* and *in operando* spectroscopy directly at the point of reaction or separation, and thus high fidelity, transient information is available [49]. Innovative designs with nuclear magnetic resonance, infrared, UV–vis, Raman, and so on, have made major breakthroughs in the design of catalytic materials for important classes of chemical reactions. Depending on the goals, *in situ* methods can aid manufacturing too. Opportunities remain for novel analytical methods that can interface with aggressive reaction conditions, analyze multiphase flows faster, or decode catalysis on the atomic scale. Deep learning algorithms designed to interface such analytical methods for rapid decision making, whether in manufacturing or discovery, also promise to advance the field of flow chemistry.

Solids handling

Clogging in continuous-flow synthesis is an unending challenge with no perfect solution for all scenarios. How to handle solids is often methodology specific, and thus engineers should ideally work with synthetic chemists early in discovery in anticipation of any clogging issues. Clogging can sideline either discovery or manufacturing efforts, and for these reasons literature documents various strategies to address the problem [50]. Alas, where reactive precipitation is important, many techniques rely on insufficient understanding of the nucleation kinetics. Further complicated by multiphase flows and the complex thermodynamics often encountered in organic synthesis one should not be surprised that opportunities remain for a deeper understanding of solids handling. When insufficient understanding of

the first principles is available, then a risk management approach may be adopted [1].

Scaling out a flow reactor is among the most pragmatic approaches to handle solids, but there is still much room for innovation. Device or equipment surfaces, where solids can either deposit or nucleate, are typically exposed to reacting fluids for extended periods. How does one control where and when the solids form? Co-crystallization or nucleation in an optical field [51] could find broad utility in solids handling. *In situ* monitoring combined with machine intelligence, such as computer vision, is another opportunity for smart manufacturing when clogging persists.

Machine intelligence, automation, and cyber security

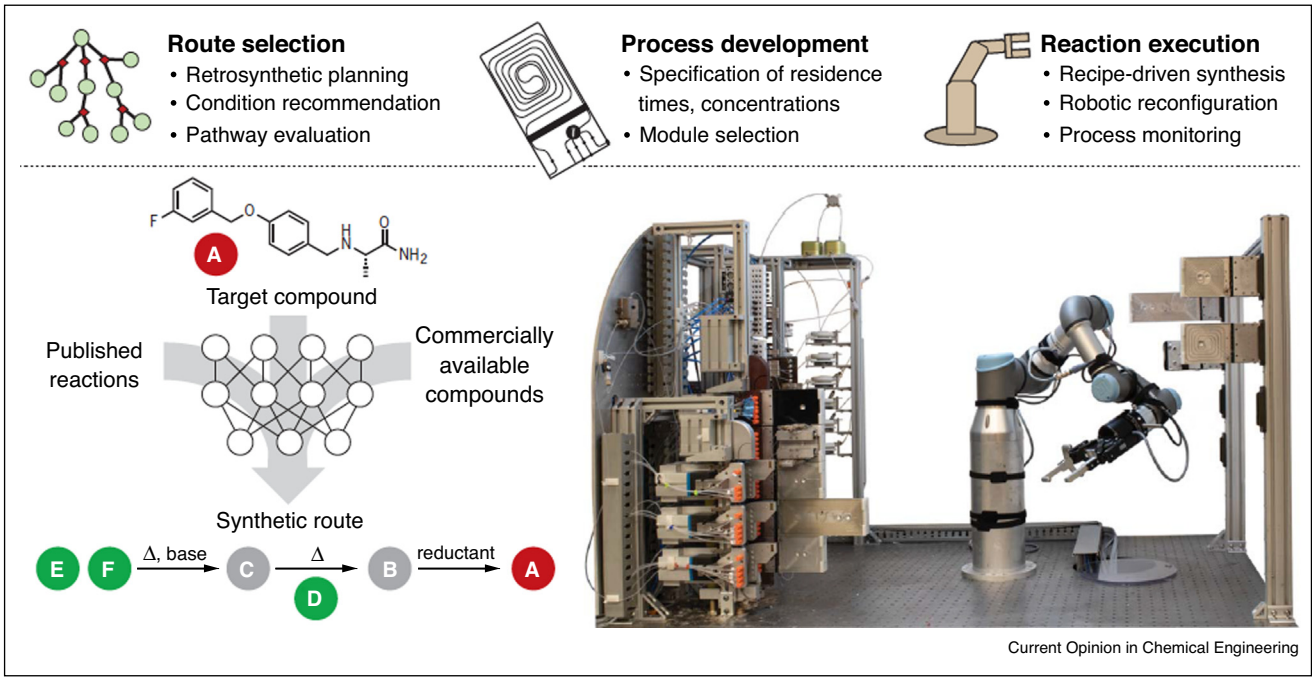
The virtual chemist of the future is now [13••,52,53]. Streamlined knowledge transfer between virtual reality, the synthesis laboratory, and chemical manufacturing is evolving fast, and deep learning algorithms that can decipher synthesis methodologies and recommend conditions or catalysts [54] for a given set of goals are facilitating a revolution in flow chemistry. Convergence of interdisciplines has also played an important role in the automation of flow chemistry [55], which has led to the integration of robotics in the laboratory environment for discovery (see Figure 2) [13••]. The age of the 'robochemist' that can perform experiments could prove to be ubiquitous in helping chemists discover new compounds and synthetic methodologies. Recent reviews capture a glimpse of the future of automated flow chemistry [55–57].

Although the use of artificial neural networks for chemical process diagnostics is not an entirely new concept it could facilitate a deeper and more efficient understanding of the continuous-flow manufacture of fine chemicals and pharmaceuticals. Enormous amounts of data are generated to meet regulatory requirements, which create the potential for real-time data analytics, advanced multivariate optimizations, and big data analysis. On-the-fly changes guided by machine intelligence could make manufacturing safer and more efficient. As an example, autonomous organic reaction search engines can aid in understanding reactivity early in discovery [52,53]. Cyber security experts are strategically positioned to play an important role, especially in remote or autonomous operations or when virtual communications between unit operations are vital. One can expect more and more interdisciplinary convergence, with opportunities for knowledge transfer between fine chemicals and pharmaceuticals and the bulk and commodity chemicals industry.

Total synthesis and sustainable manufacturing

Flow chemistry has evolved to a state where implementation is now possible, thanks to innovations over the last

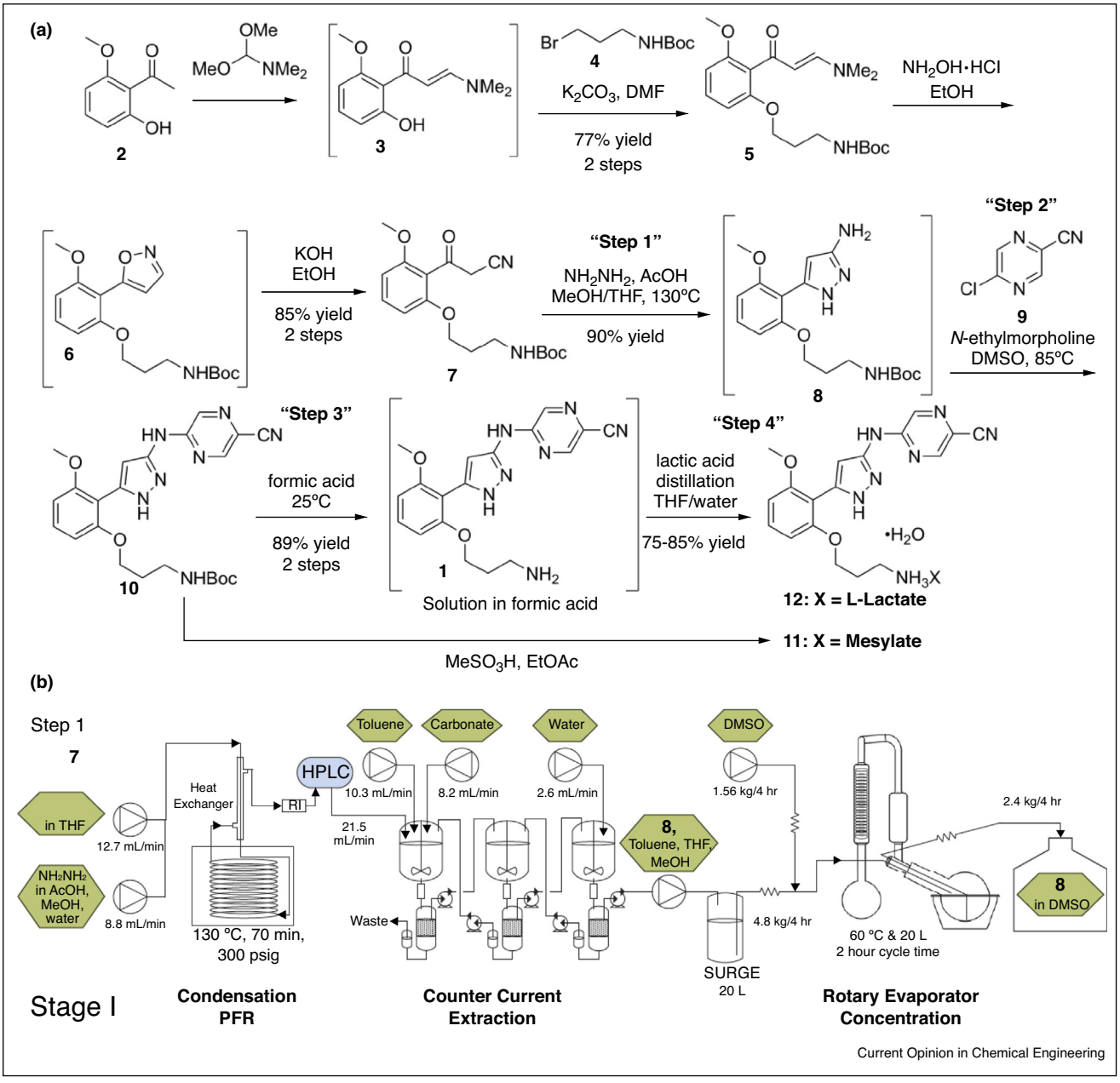
Figure 2



Machine intelligence combined with automation technology continues to revolutionize organic synthesis in flow. Artificial intelligence (AI) can now help design multistep organic syntheses facilitated with state-of-the-art robotics and reconfigurable reaction platforms. The use of AI with chemical reaction engineering fundamentals can discover new methodologies/novel catalysts, while providing, at the same time, scalable information for manufacturing. [From Ref. [13••]. Reprinted with permission from AAAS.].

decade or so. In the laboratory, plug and play modular systems that use cartridge reactors/separators now allow the discovery of drugs on-demand [8]. Automated, continuous-flow pilot plants have further demonstrated total syntheses of small molecules from raw materials, and they can also reduce the cost, lead time, and chemical waste by a comparison to batch-wise manufacture [1,2]. The market opportunity for existing and new organic molecules in flow is exceptional, as traditional batch-wise operations account for the majority, at least in the domestic market, over the disruptive chemical manufacturing technology. Major industrial efforts are evolving the local culture, which has likely contributed to reasonable growth (e.g. Figure 3) [1,2,3••,43]. Existing, versatile,

Figure 3



The field has rapidly progressed from laboratory-scale modular units capable of total syntheses to full production drug manufacturing. **(a)** In this recent example, Eli Lilly & Company reported an eight reaction-step, synthesis protocol for continuous-flow manufacture of prexasertib monolactate monohydrate. Note here the compounds in brackets correspond to un-isolated intermediates, while the yields were calculated from the production scale. **(b)** The process flow diagram of **Stage I** highlights transformation of intermediate nitrile **7** to form pyrazole **8** in a plug flow reactor followed by purification *via* counter-current extraction and a solvent switch to DMSO [From Ref. [3••]. Reprinted with permission from AAAS.].

or depreciated batch-wise equipment are other possible explanations why emerging, international chemical manufacturing markets have experienced more significant growth in the implementation of flow chemistry technology. As legislation drives improvements in healthcare access and more affordable drugs, one can expect more and more cost-driven changes, in parallel with the green revolution, within the fine chemicals and pharmaceuticals sector such as continuous-flow manufacturing.

Emerging applications in mobile deployment, defense-related, and space travel present new and interesting, yet challenging opportunities for flow chemistry. A common challenge in these areas is synthesis with limited resources. Other design constraints, such as very limited space and weight requirements, also demand novel engineering. Process intensification is likely to be of continued interest, especially as novel reactor and separator designs and cascade catalysis are further innovated. Improvements in molecular management of flow processes are already underway that could significantly reduce the environmental impacts, but 'sustainable' engineering in this space is ultimately linked to product lifecycles. Work is needed to connect upstream continuous-flow manufacturing with downstream product lifecycle assessments [58,59], as the fate of the compounds we synthesize in flow is an important consideration that process modeling experts have much to offer.

Summary and outlook

Flow chemistry is evolving fast, drawing experts together from across disciplines, and creating new fields of research with broad applications. Existing challenges remain, though not insurmountable, that present opportunities for chemists and chemical engineers to work together. A knowledge gap naturally exists, possibly due to community-wide barriers [60] and the teaching dilemma of interdisciplinary work at the cost of the traditional curricula. Capital expenditures of flow equipment, both laboratory and production scales, are often higher than batch equipment that may have already depreciated. Local manufacturing culture and the availability of skilled workforce are additional barriers that have already shown signs of dissolving by ongoing industrial, government, and academic teamwork. On that note, further multi-institution partnerships are needed, as enormous potential remains for flow chemistry in both discovery and practice.

Lessons learned in flow chemistry have laid the groundwork to discover and manufacture the next generation of therapeutics and advanced materials. As an example, continuous-flow biologics or biopharmaceuticals are in their infancy, yet many of the challenges/opportunities discussed in this perspective could impact those areas of science. Similarly, the nanomaterials revolution has generated a vast opportunity for the discovery of new synthesis methodologies of materials with targeted properties. Flow chemistry has already begun to make possible the bottom-up design of heterogeneous catalysts, in addition to nanotechnology for aerospace and defense-related applications. One caveat; however, in these new directions is the need for skilled workforce.

Conflict of interest statement

Nothing declared.

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