Flow Chemistry, Continuous Processing, and Continuous Manufacturing: A Pharmaceutical Perspective

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Flow chemistry has become a vibrant area for research over the past decade. This perspective is intended to capture insights on how these advances have and will continue to impact the development and commercialization of active pharmaceutical ingredients. A series of chemistry examples from a number of pharmaceutical companies will highlight the influence of flow chemistry on this industry.

Keywords: Flow chemistry, continuous processing, continuous manufacturing, PFR, CSTR, pharmaceutical, API, steady state, state of control, control strategy, drug substance, drug product (DP)

1. Introduction

The expansion of publications, presentations, and lectures on flow chemistry over the past decade has been remarkable. Once a field dominated by chemical engineers, flow techniques are now important tools for a much broader group of scientists throughout drug discovery, development, and manufacturing. Chemists and engineers in academia have also taken leading roles in drawing attention to the potential of flow to achieve results that would be poor, if not impossible, in traditional batch equipment [1]. Flow chemistry has great appeal among synthetic chemists since it expands the arsenal of chemical transformations available to create new molecules. Many of these advances have been described in articles published by this journal including those highlighted in other perspective articles [2]. This perspective will discuss the rise of flow chemistry and its role in the pharma industry through a series of published examples.

1.1. History of Continuous Processing in Other Industries. Within the fine chemical and commodity chemical industries, continuous processing is a commonly used technique. The development of continuous processes in these industries is driven primarily by economics associated with extremely high volume. Perhaps the first modern continuous process is the Haber–Bosch process [3] for the production of ammonia from hydrogen and nitrogen catalyzed by an immobilized iron catalyst (Scheme 1). Steam reforming of methane supplied the production of hydrogen gas [4] which, in turn, led to the availability of synthesis gas (CO/H_2) or "syngas." Syngas is a core feedstock to another important industrial continuous process, hydroformylation, or "oxo processes." [5] Oxo processes supply millions of metric tons of materials every year to the polymer industry. Examples like these are certainly inspirational and show the progressive impact of continuous methods, but the challenges in the pharmaceutical industry are quite different.

1.2. Challenges in the Pharmaceutical Industry. The pharmaceutical industry faces very different challenges than the fine and commodity chemical industries. Given the pioneering work by engineers and chemists a century ago, it would be tempting to assume that the technology was mature and need only be applied to pharma. This, however, is not the case as modern pharmaceutical manufacturing is rife with challenges that these other industries did not have to consider. Consider the follow differences (there are many more).

1.2.1. Structural Complexity. Three of the top selling small molecule drugs, atorvastatin, clopidogrel, and aripoprazole, are shown below. It is not difficult to see that complexity is high both in functional groups, heteroatoms, heterocycles, and, in most cases, stereochemistry. The impact of this complexity is felt in other areas such as control strategy for impurities, solubility, length of synthesis, and cost of goods [6]. Molecular complexity has continued to rise, and the drugs highlighted here might now represent relatively low/medium structural complexity by comparison. As an example, consider the structural complexity of the 36 amino acid peptide enfuvirtide [7].

1.2.2. Quality and Regulatory. The pharmaceutical industry is a heavily regulated industry. Regulatory requirements demand a detailed control strategy that ensures that material produced in the process will consistently meet critical quality attributes. This includes understanding of incoming impurities from feed stocks, reagents, and starting materials as well as understanding of impurity formation and purge points throughout the process. The detection and control of impurities at the 0.15% level are typical, and control at parts per million (ppm) levels is not uncommon [8]. Control of residual solvents, inorganics, and metals as well as polymorph/form control of the final active pharmaceutical ingredient (API) must also be established. Commercial manufacturing plant sites are also subject to detailed scrutiny by regulators, and significant efforts are made to establish and maintain robust systems. Failed inspections are a major source of drug shortage problems [9].

1.2.3. Quantity. A third difference relates to the API demand once launched. The commodity chemical industry deals in extremely high volumes and often requires continuous processing methods to meet demand and reduce cost. Pharmaceutical product quantities are rarely that high. Trends within pharma also indicate a movement towards lower dose drugs, which is reflected in lower peak volumes. Lower dosing can relate to higher potency API which poses cross contamination, cleaning, and operational health and safety challenges in manufacturing. For example, >60% of the phases 2 and 3 investigational drugs in the Eli Lilly pipeline have peak volume estimate below 2 metric ton (MT) per year [10]. These trends are not exclusive to Lilly as lower doses have also been observed throughout the overall industry (Figure 1) over the past 30 years. Peak volume may further drop in the future if a shift towards personalized medicine takes hold.

Lower peak volume assets pose a challenge for traditional batch infrastructure that is based on large tank sizes, typically 2000 gallon or larger. These low volume assets more appropriately fit into a pilot plant infrastructure, which is often not as

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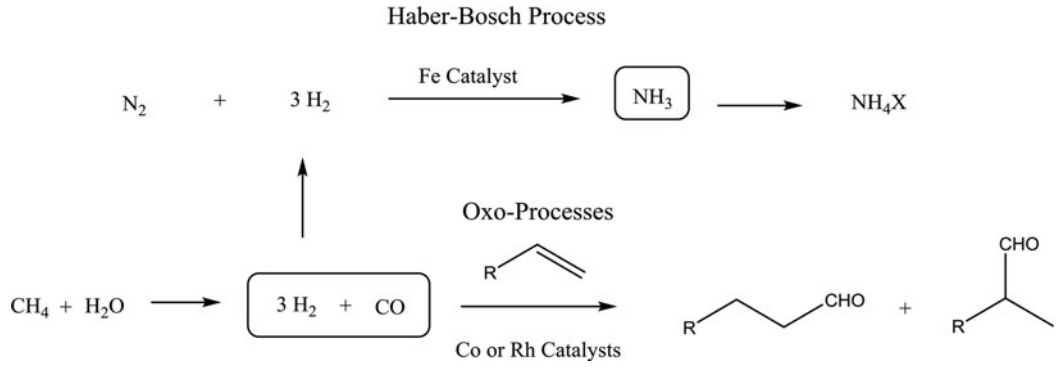


Scheme 1. Examples of continuous processes in the fine chemical industry

Typical daily dosages of top 10 best-selling small molecule drugs, 1985 and 2011

1985	mg/day		2011	mg/day
Tagamet	800	1	Lipitor	20
Zantac	150	2	Plavix	75
Adalat	60	3	Seretide	0.5/0.1 (fluticasone/salmeterol)
Feldene	20	4	Crestor	10
Inderal	160	5	Nexium	40
Tenormin	100	6	Seroquel	300
Naprosyn	750	7	Abilify	10
Voltaren	100	8	Singulair	10
Aldomet	1000	9	Zyprexa	10
Claforan	2000	10	Cymbalta	60

Source: IMS Health/Wood Mackenzie/prescribing information leaflets, US where available

Figure 1. Trends in small molecule pharmaceutical dosage

readily available or in short supply in manufacturing. Continuous manufacturing (CM) offers a unique cost-effective solution to this problem since these products can be produced from fume hood infrastructure rather than manufacturing plants.

1.3. Flow Chemistry, Continuous Processing, and Continuous Manufacturing: Is There a Difference? In the chemical literature, the terms flow chemistry, continuous processing, and CM are often used interchangeably. These terms are certainly related as they involve the use of similar tools such as reactions in plug flow reactors (PFRs) or continuous stirred tank reactors (CSTRs). These descriptors differ, however, in the level of knowledge, robustness, and degree of application. In a similar way, a chemical reaction describes the fundamental bond making and breaking while a chemical process implies a practical end where the reaction functions in a robust state capable of reliable operation for extended periods of time. Cornforth described this uniquely by stating:

"The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole."

Cornforth's image can be applied to batch processing; however, the true ideal would be to add reactants while simultaneously collecting pure product from the system. This variation on Cornforth's ideal represents the basic operation of a continuous reaction in a CSTR, shown in a more sophisticated rendering in Figure 2 along with the second fundamental reactor type, a PFR.

A continuous process may simply represent a single unit operation such as a reaction surrounded by other batch unit operations (hybrid flow processes) or a more complex

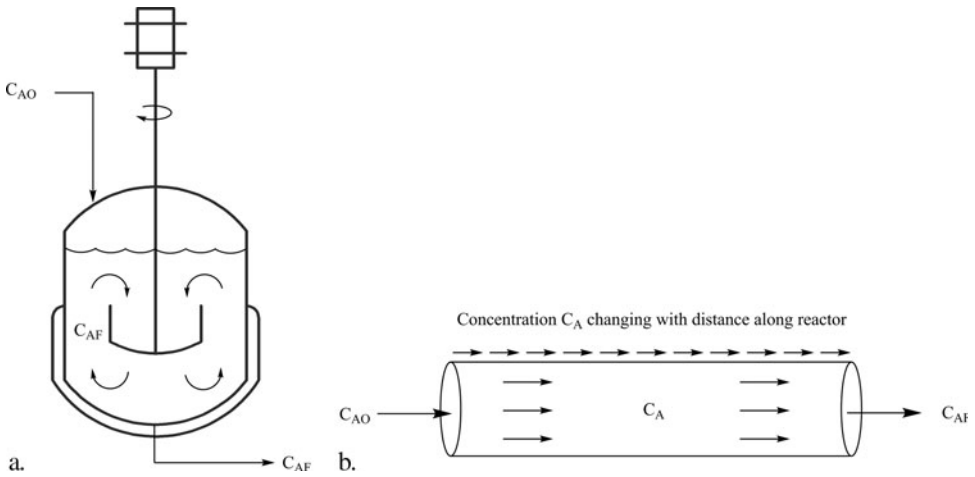


Figure 2. Two fundamental flow reactor types: CSTRs (1a) and PFRs (1b)

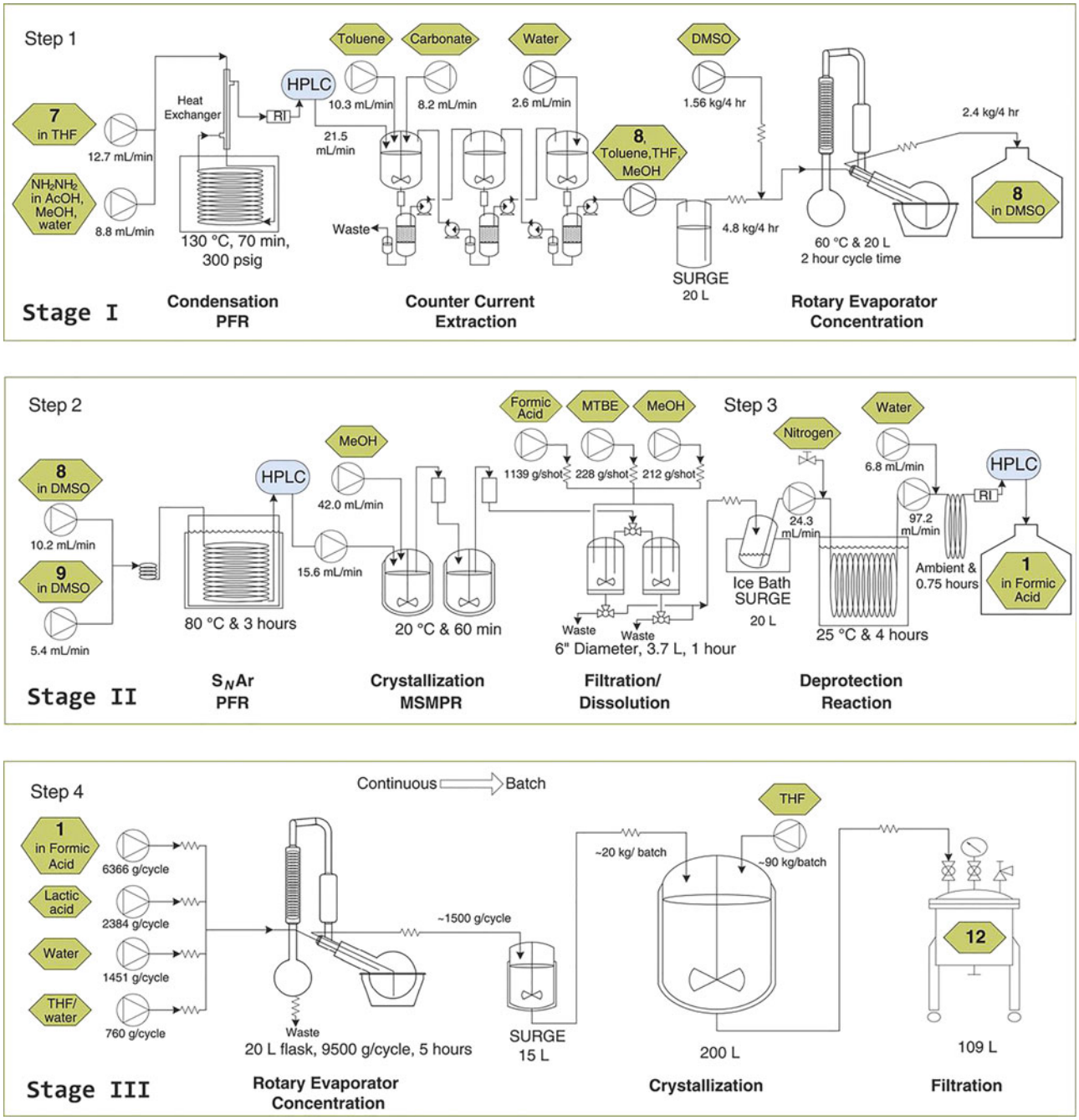


Figure 3. Continuous GMP operation for prexasertib monolactate monohydrate (reprinted with permission from Science 2017, 356, 1144–1150. Copyright 2017 American Association for the Advancement of Science)

assembly of unit operations or steps. Continuous manufacturing implies yet another degree of integration where the entire sequence of unit operations is linked in a continuous train to deliver the drug substance (DS) or drug product (DP) under Good Manufacturing Practices (GMP) conditions. There are examples of DP CM processes including wet granulation [11] and direct compression [12] processes that have run under GMP conditions. The first multi-step GMP DS CM process has been reported which involved 3-steps and 8 continuous unit operations in the synthesis of prexasertib (Figure 3) [13].

A well-developed batch process must produce material that meets all critical quality attributes for the API. The process must be robust over multiple batches within a representative equipment set. This demonstration of a control strategy culminates in a process which is validated at the site of commercialization [14]. The expectations are not different for a continuous process where the control strategy must also be consistently demonstrated. In a continuous process, however, material is accumulated over time and must demonstrate a "state of control" which the Food and Drug Administration (FDA) defines as "a set of controls that consistently provides assurance of continued process performance and product quality." [15] State of control relates to product quality and is not the same as steady state which describes process dynamics.

The linking of DS and DP CM processes is a logical and worthwhile goal since this integration can truly leverage the power of CM to produce drugs in on demand fashion. Important advances have been made in this area by researchers at MIT and Novartis for the synthesis and formulation of aliskiren hemifumarate [16]. Further work by MIT has resulted in a small refrigerator-sized reconfigurable system for the synthesis and formulation of multiple drugs including diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam, and fluoxetine hydrochloride (Figure 4) [17]. While these processes have not been run under GMP conditions to date, they do show the potential of this approach and how rapidly the area is advancing.

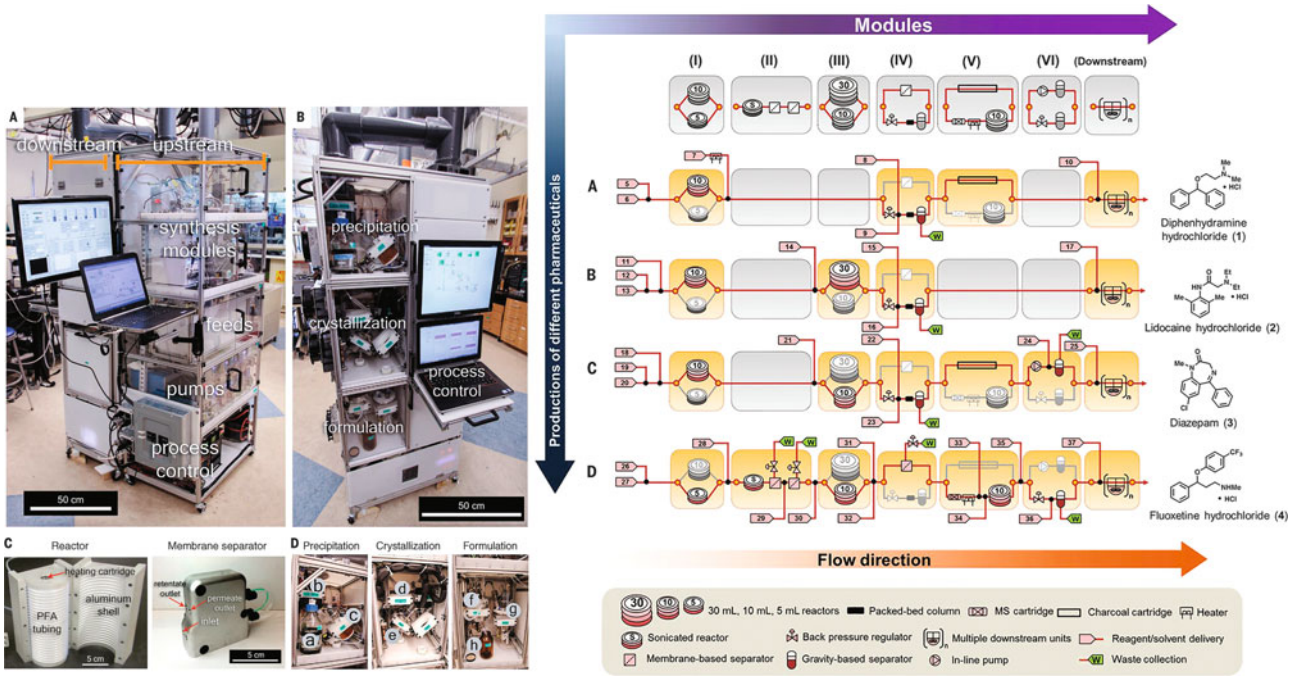
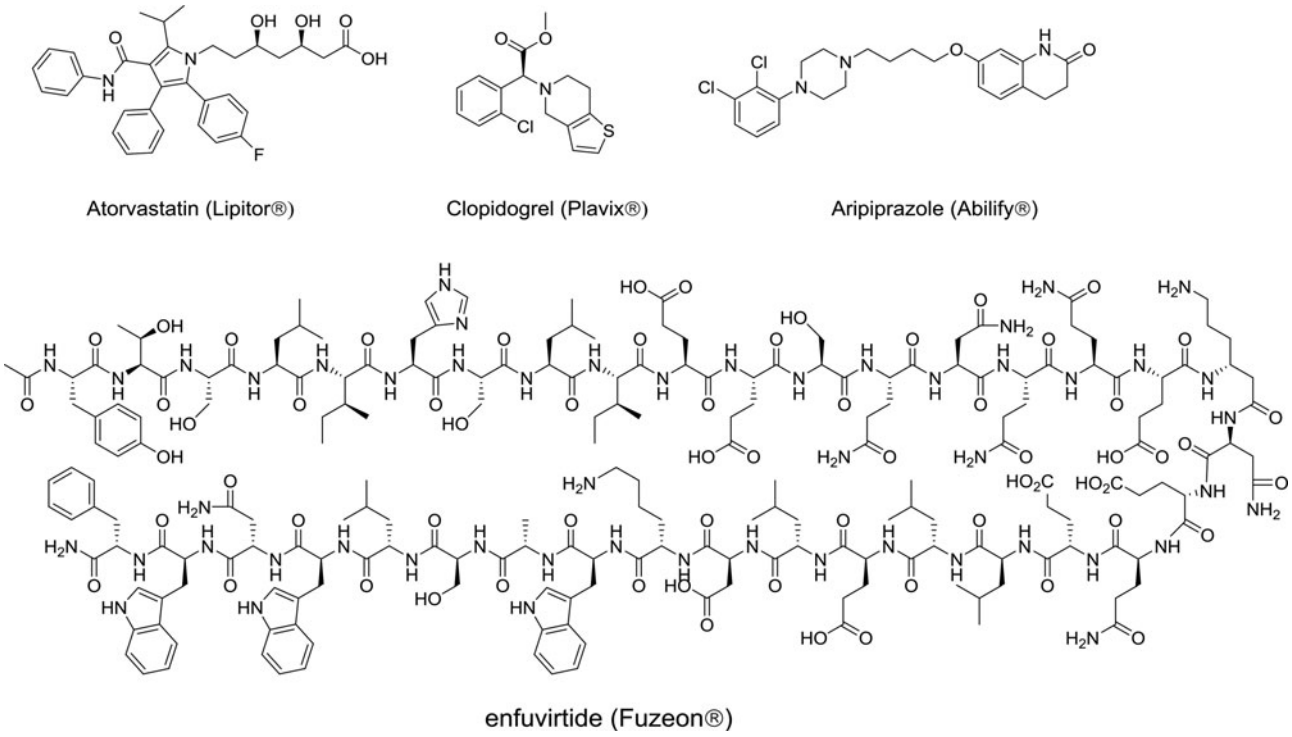


Figure 4. Reconfigurable system for continuous production and formulation of APIs (reprinted with permission from Science 2016, 352, 61–67. Copyright 2016 American Association for the Advancement of Science)

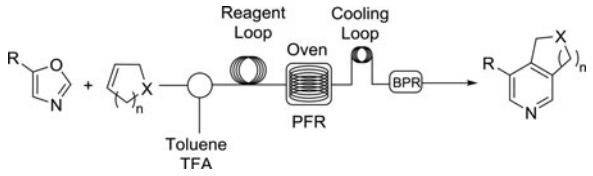
Projecting value for flow depends greatly on the phase of development. For example, a chemist in discovery research would put a premium on novel flow chemistry applications that could increase structural diversity [18] or reduce cycle time [19] vs. standard batch approaches. The intent in this area is not to develop continuous processes to make kilogram quantities of material but rather to use flow to make milligrams of materials to drive structure-activity relationships (SAR) quickly. For example, Martin and Britton have reported the development of a flow-enabled (230 °C, 750 psi) inverse electron demand Kondrat'eva reaction [20] for the synthesis of annulated pyridines. This methodology was then applied to the synthesis of a series of 7-substituted cyclopenta- and cyclohexa[*c*]pyridines [21] which were part of a SAR focused on activity as aldosterone inhibitors (Scheme 2).

Hoffmann-La Roche nicely applied flow concepts to the entire sequence of a BACE 1 SAR (Scheme 3) [22]. This included integrated flow-based synthesis, purification, bioassay, quantification of purity, and concentration. This impressively reduced cycle time (advanced building blocks ➔ to SAR data) from days to 1 h.

Scientists at AbbVie have also leveraged flow techniques in the development of a fully automated compound generation system to speed SAR [23]. Using this system, a library of 48 compounds (10 mg samples) can be completed in 3 days, $^{1}/_{4}$th the



Scheme 2. Examples of structural complexity



Scheme 3. Flow-enabled synthesis of annulated pyridines

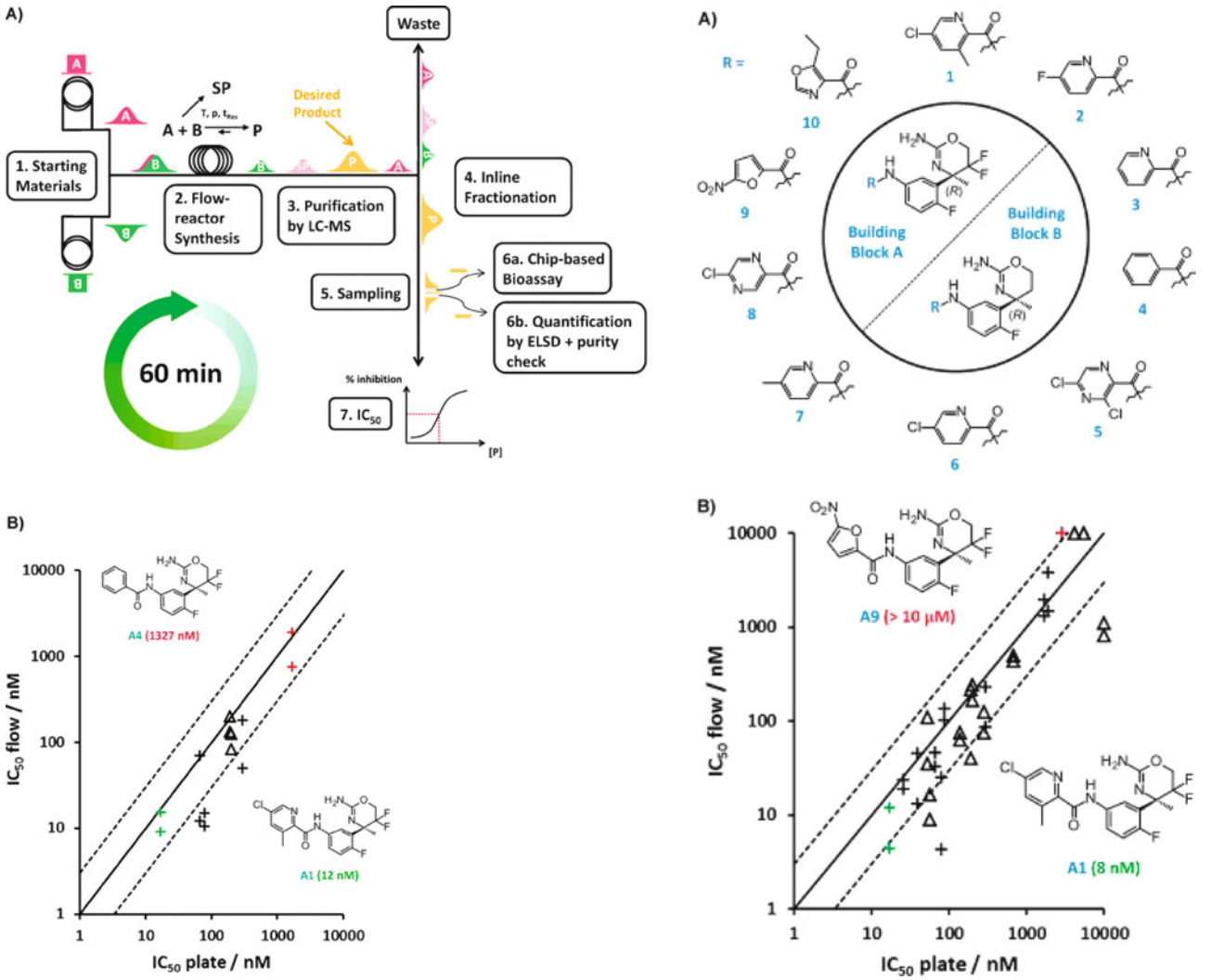
cycle time of a typical non-integrated process [24]. This has been applied by Tu and coworkers (also at AbbVie) for the synthesis of a series of triazoles via ultrasound-induced click chemistry in a copper reactor [25].

Other examples of integrated systems enabling rapid compound generation in discovery include recent work in the lead optimization space from Novartis and MIT [26]. Sanofi has also reported an approach to library generation for BCR-Abl kinase inhibitors [27]. Single flow-based reactions can also have a powerful impact on the ability to expand molecular diversity in an SAR. Vertex reported a continuous photoredox Csp^3–Csp^2 coupling reaction and applied this to rapidly generate a series of alkyl-substituted quinazolines [28]. Merck has reported the development of immobilized ketoreductase enzyme for the asymmetric reduction of a broad range of pro-chiral ketones to form chiral secondary alcohols in packed bed systems [29]. AbbVie reported the flow-enabled (390 °C, 100 bar) synthesis of fused pyrimidinone and quinolone derivatives [30]. This approach led to the synthesis (mg) and scale up (g) of a series of compounds for testing. Likewise, Amgen has also explored a two-step flow approach for gram-scale synthesis of [1,2,4] Triazolo[4,3-a]pyridines [31].

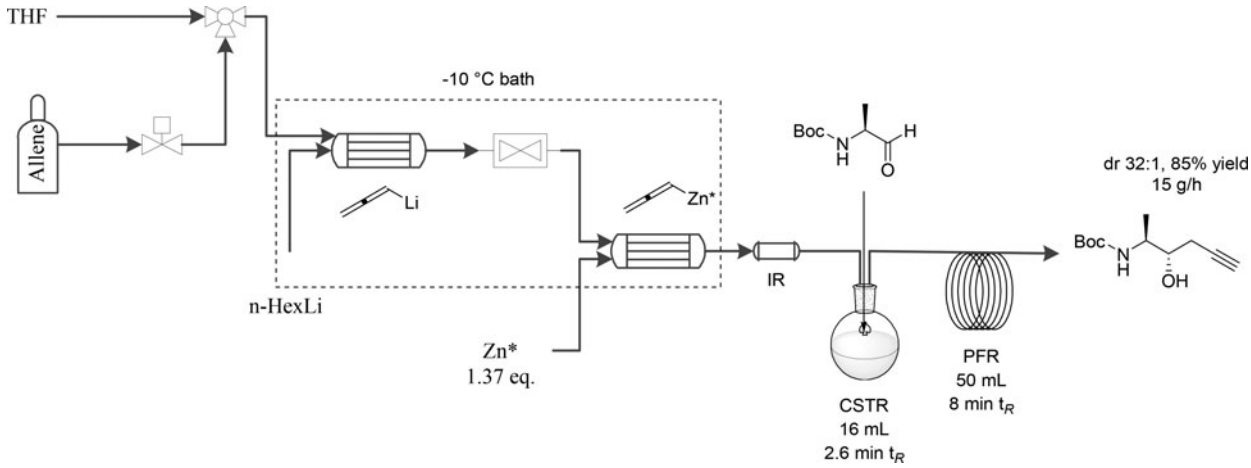
In many cases, a process developed using flow tools will also provide a way to scale up material that would otherwise require multiple steps due to scale-related challenges. Speed to material delivery is important especially in the early phases of development when this activity is often on the critical path. Pfizer and Snapdragon reported the synthesis of a chiral β-amino alcohol through a novel propargylation reaction that utilizes flow to intercept an unstable allenyllithium intermediate (Scheme 4) [32]. This process was used to provide intermediate scale supply (15 g/h). This novel approach leveraged the mixing and heat removal capabilities of flow to conduct a reaction that would have otherwise not been possible in batch.

Merck has leveraged the enhanced mixing capabilities in flow to improve the performance of an organometallic reaction (Scheme 5) [33]. Rapid metalation and organolithium addition to a chiral ketamine in flow allowed for improved yield (↑18%), efficiency (<1 s τ) and allowed the process to operate under non-cryogenic conditions. Merck has also reported yield and efficiency benefits in running an intramolecular hydrosilation reaction in flow [34].

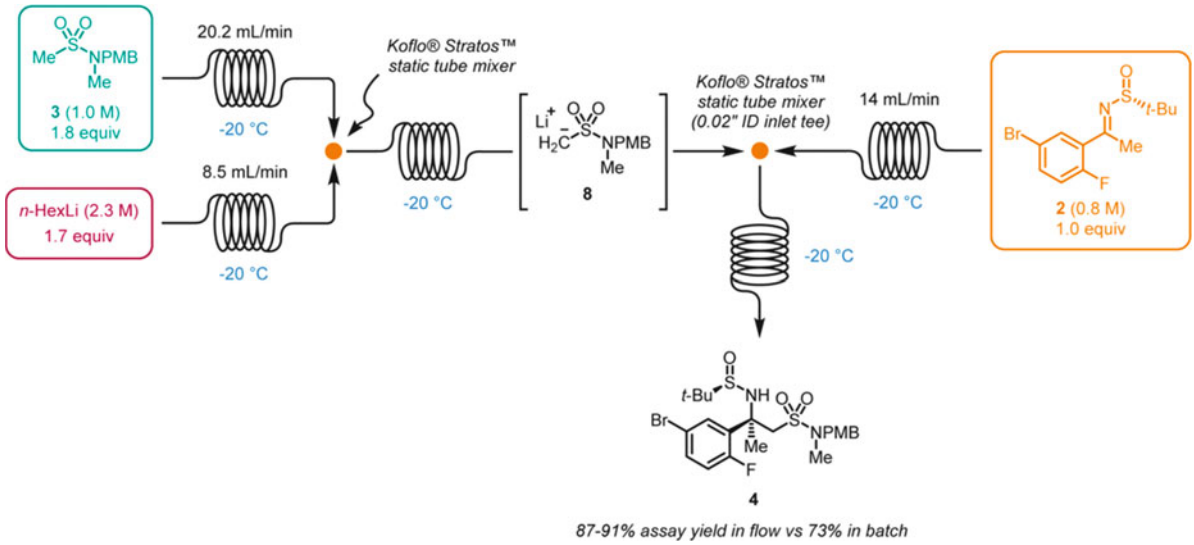
In a similar fashion, Astra Zeneca has reported benefits using flow in the synthesis of reflux inhibitor AZD6906 through a Claisen-type condensation between the anion of a phosphinate ester and N-Boc-glycine methyl ester [35]. Takeda [36] and GSK



Scheme 4. Seamless flow-based SAR (M. Werner et al. Angew. Chem., Int. Ed. 2014, 53, 1704–1708. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)



Scheme 5. Flow-enabled propargylation via metalation and trapping of allene



Scheme 6. Metalation and addition into chiral ketamine (reprinted with permission from Org. Process Res. Dev. 2016, 20, 1997–2004. Copyright 2016 American Chemical Society)

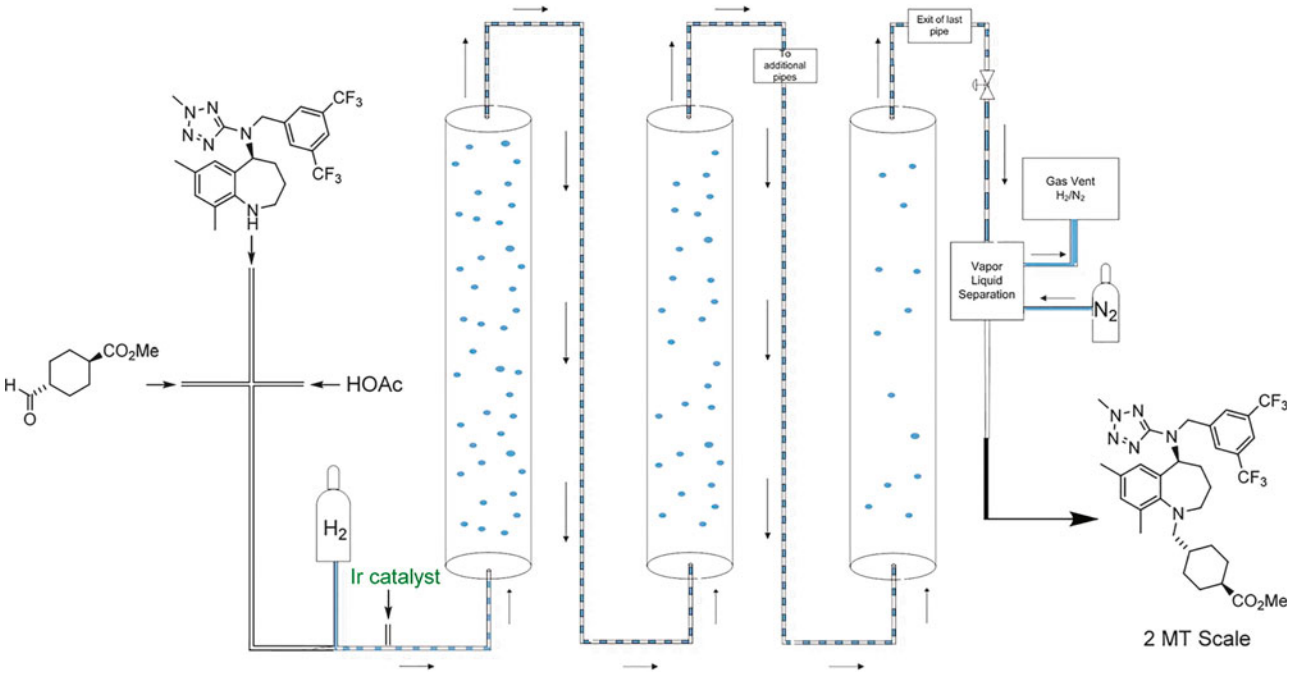


Figure 5. Continuous high pressure reductive amination in pipes-in-series reactor

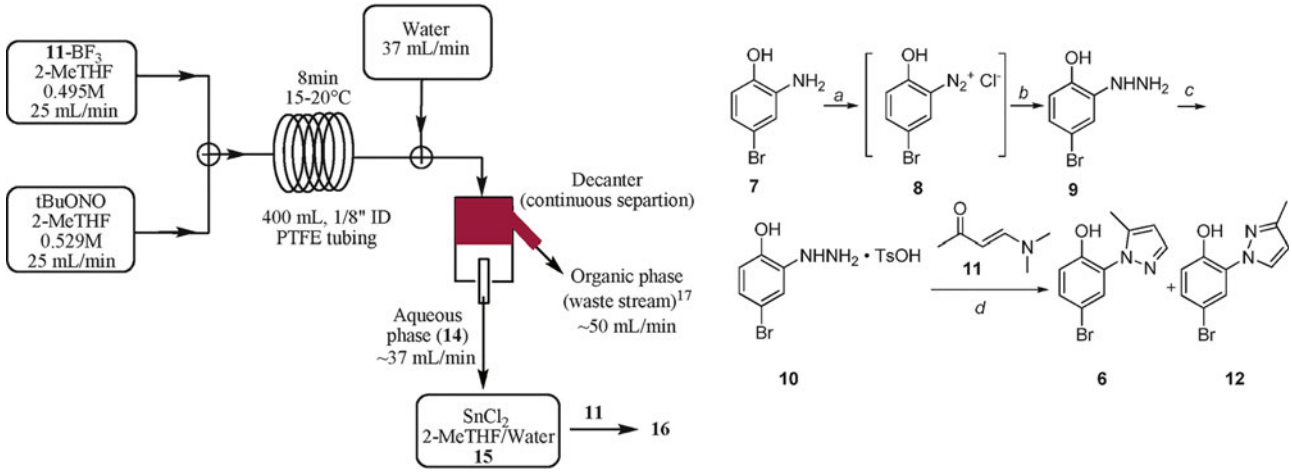
[37] have also leveraged flow for the formation of boronic acids or esters via metalation and trapping.

As material requirements rise, safety considerations are increasingly important. Many flow applications are born out of concerns raised in the chemical hazards laboratory. High energy reactions such as the Grignard reaction [38] or Henry reaction [39] are often flagged for safety concerns and become excellent candidates for flow. It is important to note that, while running a process in flow may provide many safety benefits, it does not follow that flow processes are inherently safe. Pfizer reported the 3-step synthesis of substituted pyrazoles which involved two high energy intermediates, a diazonium salt and a substituted hydrazine (Scheme 6) [40]. A flow-based system was used to provide high heat removal capability and minimize the amount of material in the system at a given time. The 3-step process was successfully scaled up to provide 488 g of pyrazole product.

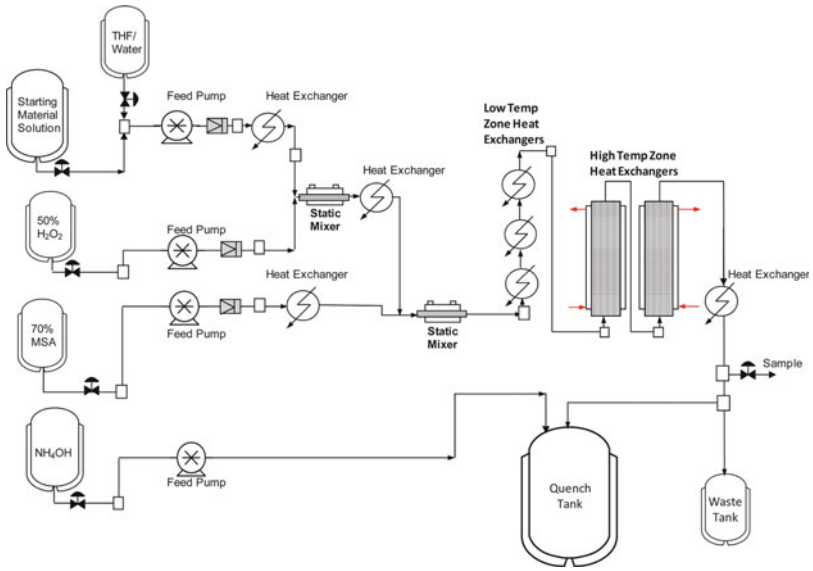
Hydrogenation and hydrogenolysis reactions are very useful within pharma. The use of hydrogen, often times with a flammable organic solvent, increases safety risk within a manufacturing facility. Typical batch infrastructure is also limited to less than 7 bar (100 psi) unless specialized high-pressure autoclaves are purchased. In 2016, Lilly published details of a continuous high pressure (>50 bar) iridium-catalyzed reductive amination reaction under GMP conditions (Figure 5) [41].

In this example, a continuous pipes-in-series reactor [42] operates at very high liquid fill level (~99%) resulting in very low hydrogen levels in the reactor at any time. In manufacturing the reactor, hydrogen and vapor liquid separation was also outside the plant infrastructure. These two features provide significant safety advantages and allowed the process to run as a low risk safety operation, something unheard of for a hydrogenation reaction. Over 2 MT of the penultimate intermediate in the synthesis of evacetrapib were produced in 95% isolated yield after batch workup and crystallization. Importantly, the cost to install the infrastructure was 1/10th the cost of installing high-pressure batch equipment. Other vapor liquid reactions have been demonstrated in this type of reactor including aerobic oxidation [43] and hydroformylation [44].

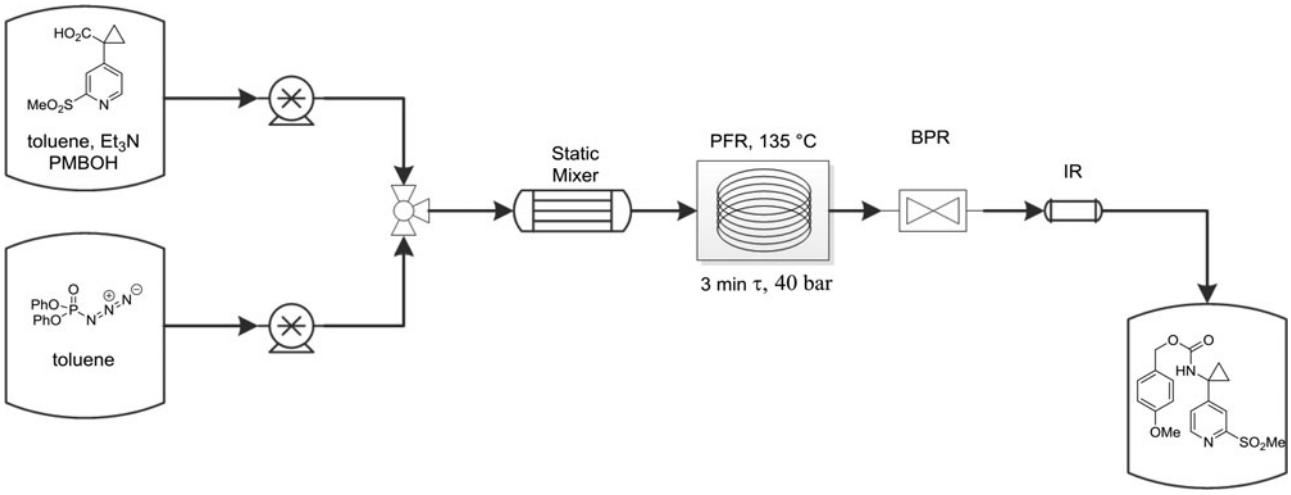
Still, other drivers may relate to advantages of scale (high and low), containment of highly potent or cytotoxic materials [45], and quality control/assurance [46] benefits of steady state operation. Publications of flow processes within pharma detailing pilot or commercial scale operations are not common, and those run under GMP conditions are even more scarce [47, 48]. Publications in this space are important as they shed light on the development challenges in flow. In 2014, BMS reported a continuous benzylic hydroperoxide rearrangement reaction utilizing hydrogen peroxide and strong acid (Scheme 7) [49]. This reaction



Scheme 7. 3-Step synthesis of a substituted pyrazole (reprinted with permission from Org. Process Res. Dev. 2012, 16, 2031–2035. Copyright 2012 American Chemical Society)



Scheme 8. Pilot-scale oxidative rearrangement (reprinted with permission from Org. Process Res. Dev. 2014, 18, 1492–1502. Copyright 2014 American Chemical Society)



Scheme 9. Curtius reaction development and scale up

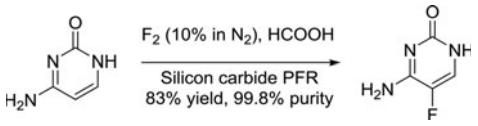
carried significant safety risk for thermal runaway due to the high heat of reaction and low thermal onset in a number of solvent compositions. Detailed reaction engineering and modeling descriptions are included and underscore the detail required in executing a continuous process on scale. The process was operated at laboratory, kilo, pilot, and commercial scale with total flow rates up to 800 mL/min.

Another important paper describing pilot scale continuous Curtius rearrangement was recently published by Boehringer Ingelheim [50] for the synthesis of a CCR1 antagonist. The Curtius rearrangement has long been a reaction conducted in flow due to the use of an azide-based reagent and the formation and potential accumulation of acyl azide and isocyanate intermediates. The authors report the development of both CSTR and PFR approaches at kilogram scale. A 48-kg pilot-scale demonstration was conducted using the PFR approach (Scheme 8). Furthermore, green chemistry metrics were gathered for all of the approaches demonstrated which served as an aid to select the most desirable pathway for further development (Scheme 9).

Sanofi has reported the 1-step flow-enabled synthesis of the antifungal flucytosine using fluorine gas [51]. Flucytosine is a World Health Organization (WHO) essential medicine and part of a recommended first line treatment of Cryptococcal meningitis, a fungal infection common to those with compromised immune systems. The previous approach involved a 4-step synthesis which made the drug prohibitively expensive for those in underdeveloped countries. The new approach developed by Sanofi is a 1-step continuous process that utilizes fluorine gas and cytosine as a low cost starting material. The process has been demonstrated at pilot scale delivering high purity and good yield (Scheme 10).

2. Conclusions and Future Prospects

Throughout this perspective, examples from pharmaceutical discovery, and development and manufacturing groups from around the world have been highlighted. The power of flow has been seen in all phases of pharmaceutical development from hit to lead discovery to manufacturing. The uptake of flow in the earlier phases of drug discovery will only lead to more applications in development and manufacturing. Development organizations are starting to see this now, and efforts to expand capabilities are evident. Further expansion within pharma requires scientists with the ability to learn and apply skills from multiple disciplines outside their own expertise. Externally, the scale up of drug candidate will require a buildup of capabilities within the Contract Manufacturing Organization (CMO) network. New flow-enabled reactions have also been developed, and a few were highlighted in this article. Novel reaction development in flow is challenging, and this is a space where industry and academia must partner. The application of CM to the DP space is already a reality with several continuous processes operating on commercial products. Looking forward, we should expect to see other examples of DS CM and longer term of the merging of DS and DP. The latter, while appealing in concept, has many business and technical challenges that must be dealt with. New areas of interest include electrochemistry where publications have shown unique bond forming chemistry [52, 53] including reactions in flow cells [54, 55]. Flow chemistry concepts have been developed for rapid automated flow-based approaches to peptide synthesis [56]. Finally, there were several examples of automated flow synthesis in this article. The increased use of automated systems and synthesis machines will become more sophisticated and useful. Efforts to automate reaction optimization in flow are underway [57–59], and these stand to become more refined and powerful with the help of machine learning neural networks [60]. These new tools, in the hands of chemists and engineers, have the potential to help improve decision making and accelerate research. As a final note, the purpose of this article was to highlight the efforts and represent the challenges of flow within the pharma industry. As such, the important role of academia in the development of flow chemistry was out of scope and therefore underrepresented. Other published review articles [61, 62] highlight this area and perhaps a future perspective paper could explore the specific topic of industry/academia research collaborations.



Scheme 10. Continuous synthesis of flucytosine

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