A Comment on Continuous Flow Technologies within the Agrochemical Industry

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Abstract

The Agrochemical sector operates on large scale within a highly complex environment. Cost effective products on an increasing scale, in a sustainable fashion, impose massive constraints on the industry. Here, we report a perspective around flow chemistry, with literature highlights on how the application of this technology can impact chemical processes (especially at the early stages of R&D) for Agrochemicals, with clear benefits in comparison to a traditional batch vessel - be it safety, quality or throughput. The value of flow chemistry for the business is clear and the number of examples reported in the literature will undoubtably continue to increase in the agrochemical industry.

Keywords: Agrochemicals, Flow chemistry, Continuous Processing, Enabling Technologies

Disrupting conservativism

By its very words the adoption of any new, disruptive, synthesis technologies for the preparation of our functional molecules will always be met by a high degree of conservatism (especially on moving up scale). This is only to be expected given the necessary up-front investment in plant and the expensive equipment required to carry out the necessary multitude of complex tasks. Moreover, the skill and knowledge base needed to design and make these compounds by traditional batch mode methods takes time, experience and considerable effort. Although the industry has become very good at what it does, inevitably, there is a lack of flexibility owing to the constraints required to deliver products rapidly to the marketplace. While the Pharma industry is a very high-risk business, the profit margins can be substantial,[1] by comparison, the Agrochemical sector operates on a bigger scale with much lower revenue margins – this is a highly complex environment whereby diverse and increasing world populations, climate change, unexpected disease and fungal outbreaks can be major additional barriers to success. The need therefore to provide cost effective products on an increasing scale, in a sustainable fashion, imposes massive constraints on the industry. To remain competitive and profitable there is a challenging dichotomy between maintaining the *status quo* and investing in new enabling, but disruptive, technologies that engage innovative ideas to satisfy future product lines while maintaining safety, sustainability and greater precision in the targeting of crop protection methods. This changing and more agile mindset is evolving into an Industry 4.0 concept whereby automation and data management, through machine learning and artificial intelligence methods, will become ever more impactful.[2] The logistics of the supply chain leading to decentralised manufacturing, greater flexibility and management of our chemical inventories are notably influencing how we work today.

However, as noted earlier by comparison with pharmaceutical companies the agrochemical industry often faces a different challenge, due primarily to the larger manufacturing volumes.[3] This results in a critical need to drive cost of goods to a minimum and to establish lean and robust manufacturing processes that can deliver 1000's tonnes per annum. The challenge is most pronounced for mid-sized products, in the range of 500 to 4000 tonnes per annum. Such products typically require larger manufacturing assets than in pharma but are often smaller than those utilised in other traditional bulk chemistry manufacturing units. Furthermore, batch assets tend to be better suited for multi-purpose needs in terms of kinetics and phase flexibility, and suppliers are generally more geared up for batch mode technology transfer.

So Why Move to Continuous Flow Technologies?

While well-known to and almost exclusively used by the petrochemical industry, continuous flow technologies have only in relatively recent years become an important platform in fine chemical research programs and during early-stage product development in other industries[4].

The increased research intensity in the area of flow chemistry over the last decade has reinvigorated the challenge to identify and strive for the right technology early in the chemical development process. Clearly, the perceived difficulties to entry in the field, most notably the need for chemists to acquire new skills and equipment together with the lack of understanding of what problems would be best solved by adopting these new methods, have all inhibited progress. This said, the early adopters of flow chemistry methods have been rewarded in numerous ways especially through enlightened management programs whereby chemists and chemical engineers work together to find solutions to specific challenges and through well accepted concepts associated with the technique leading to considerable process improvements, in particular the handling of exotherms[5], greater control of high/low temperatures and pressures[6], handling of organometallics[7] and other potentially hazardous or toxic intermediates[8]. Also, improvements through levels of process intensification, reaction telescoping and delivering on the Green agenda are clearly recognised benefits of the flow chemistry methods.[1,9] [The improved levels of reaction control, safety, especially in the use of reactive gases, and downstream continuous processing methods all play roles in advancing this technology. Given the rapidly developing data-rich world in which we live combined with these new principles we believe the time is right to embrace this machine-assisted approach to the synthesis of the next generation of agrochemical products. Reaction audit trails, improved real-time feedback of information, optimisation protocols, scale-up, and novel reaction discovery platforms all add further beneficial components into the mix by advancing our synthesis knowledge. Nevertheless, there is still a long way to go but the area is both expanding and evolving rapidly. Now is a good time to engage and fully exploit the learnings of the last two decades of research and development.

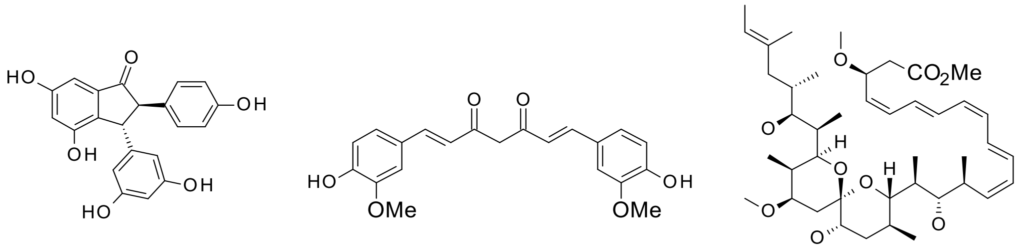
In addition to the above, flow chemistry offers several advantages and opportunities that also translate to both development scale and manufacturing scales. For example, there is a unique flexibility with respect to process control (in contrast to batch) such that processes can be aborted without significant material accumulation.[10] The system modularity can also simplify technical transfer, from pilot campaigns to manufacturing, whether between existing equipment or in different geographies. There are other potential advantages with respect to energy efficiency and process intensification,[11] and a clear benefit with respect to process safety versus typical large lab-scale experiments. As a result, chemistries that would be otherwise be considered inconceivable (or at least highly challenging) due to high energy or hazardous reagents/intermediates can be more readily enabled in flow on scale.[8]

The barriers to the implementation of flow chemistry revolve largely around investment costs and the specialization of equipment. These concerns are especially apparent when considering transfer of a well-established batch process into flow equipment. This emphasises the need to address the opportunity of flow early in the development stage plan. There is also the key factor of operational experience and knowledge in comparison to batch, and particularly the receptivity of an organization to a disruptive change. On a more technical level, flow processing in academia and in discovery laboratories is largely focused on the initial up-stream reaction. However on moving to larger scales there is an increased emphasis on efficient and sustainable down-stream processing methods (work-up, isolation etc.), Furthermore in light of the increased molecular complexity and associated solid-state characteristics of many of the new products considerable flexibility during the workup is of paramount importance.

In order to overcome a number of these challenges, therefore, flow chemistry assets in pilot operations and manufacturing will need to demonstrate a degree of versatility similar to their batch counterparts to create the additional short and long term business value. In the past, the step between the laboratory or pilot plant and manufacturing often triggered the design of a tailor-made continuous reactor with a limited use in other processes. Additionally, many of the approaches suitable for the pharmaceutical industry, such as parallelisation (numbering-up) or longer runtimes (scaling-out) are usually prohibitive for agrochemical manufacturing due to investment costs and lack of capacity. To facilitate the uptake of flow chemistry in agrochemical manufacturing, it is crucial to embrace modularity as key concept. This promotes a standardisation of units, similar to batch processing whilst lowering project costs and lead time.[12] This is key to lowering the barrier of resistance in terms of investments by having modules not built for one specific chemistry but enabling multi-purpose application based on the needs of respective chemical processes. Efforts in this direction have been undertaken by commercial reactor suppliers, but they often integrate mixing and residence time units in the same module thereby limiting versatility on scaleup. The application of integrated hybrid reactors, which make use of a combination of flow and batch units, also provides more operational flexibility compared to fully continuous processes and helps to reduce upfront investment in equipment. Such factors can support the continued uptake of flow chemistry and ensure that the right technology is selected for the right reasons at the right time.[13]

Flow chemistry gaining momentum in the Agrochemical Industry

Since natural products themselves often constitute excellent starting points for further structural development but can be problematic due to limited compound supply, synthesis has an important role to play since this leads to concomitant production of useful analogues for further biological evaluation. Indeed, there have been numerous total syntheses of natural products reported using integrated batch and flow methodology and some of those constitute potential development candidates as agrochemical leads (Fig 1.) [14-19]



(+)-Pauciflorol F
Anti-fungal agent [16]

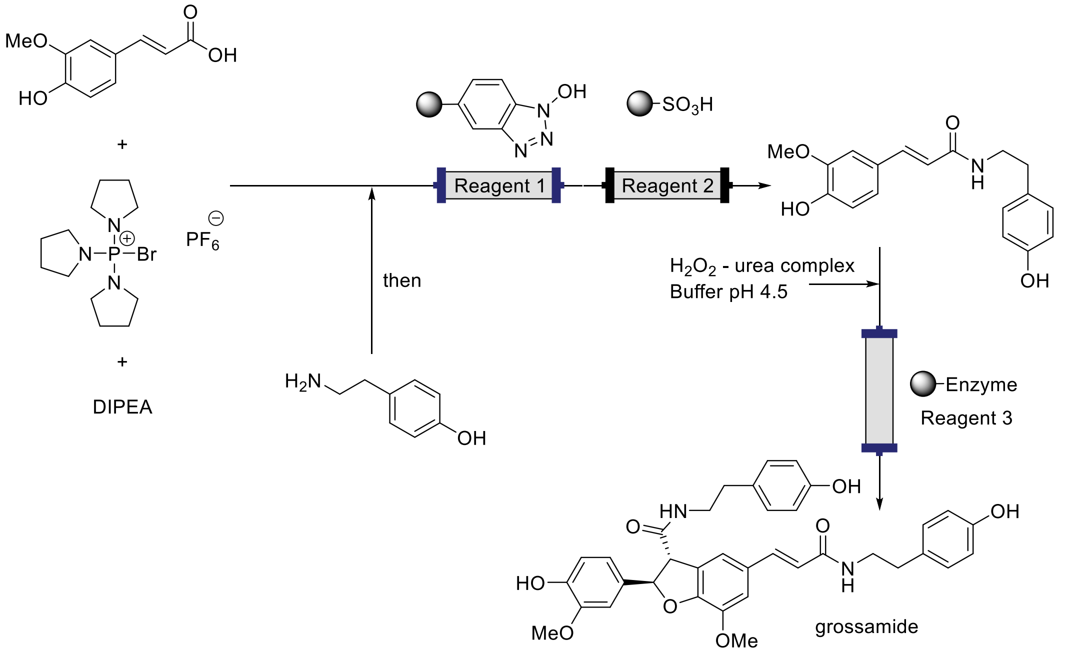
Curcumine
Anti-fungal agent [17]

Spirangien A methyl ester
Anti-fungal agent [19]

Figure 1. Selection of natural products with agrochemical activity, synthesised in flow.

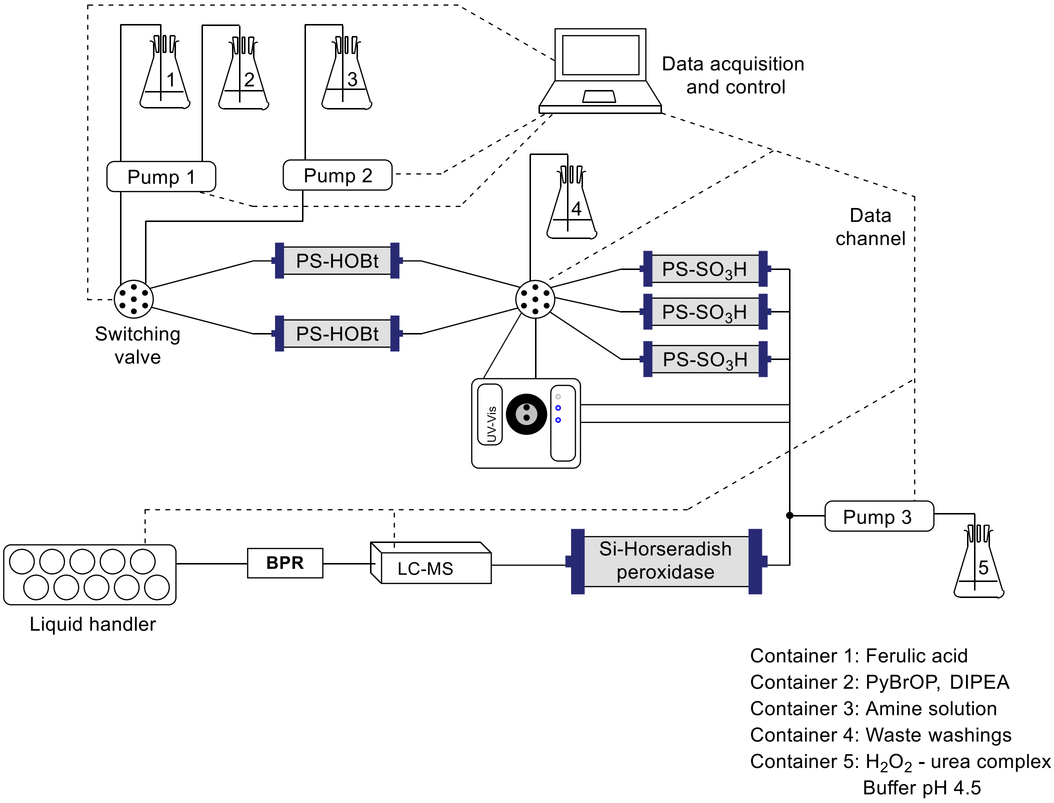
Most have been discovered through primary screening protocols and are typically classified as antifungal, antimicrobial and antiparasitic agents. Space here does not permit a full discussion of all the synthetic work that has been carried out consequently we will comment on just two illustrative examples.

In 2006, an early example of multistep continuous preparation of Grossamide,[20] a neolignin amide that is produced in many plants in response to pathogenic attack and has been shown to have a number of biological functions including potentially useful antimicrobial properties, was reported. The synthesis notably exemplifies the multiple use of immobilized reagents and scavengers which is a technology well suited to flow. Attractively, this synthesis makes use of small chemical building blocks namely ferulic acid and tyramine which, under classical amide coupling on a polymer supported hydroxybenzotriazole column (PS-HOBt), afford the corresponding product. This was then flowed through an immobilised horseradish peroxide to achieve excellent dimerization to give the natural product Grossamide in excellent yield (Scheme 1).



Scheme 1. Flow synthesis of Grossamide.

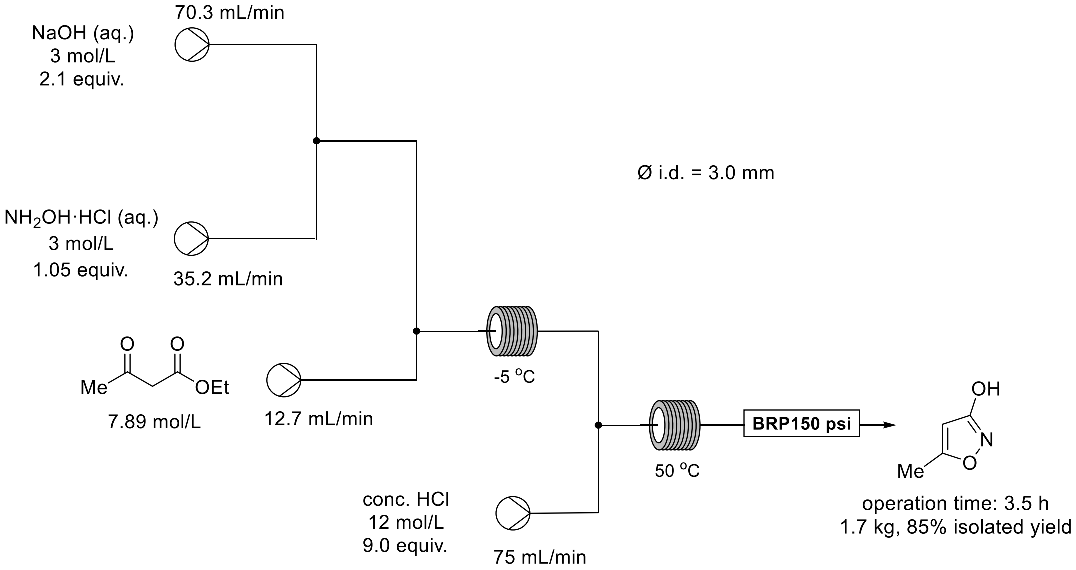
The process is clearly more complex than indicated in a simple chemical scheme since in-line scavenging is required to afford clean product flow streams and there is a need for further added oxidant (H_2O_2-Urea) to drive the enzyme coupling and cyclization. Moreover the associated engineering of the system was advanced at its time (in 2006!) since multiple pumps, control valves, packed reagent and scavenger columns together with appropriate controlling analytics (UV and LC-MS), liquid changing devices, reagent reservoirs were also needed to automate this simple two-step process (Scheme 2). This level of sophistication of equipment also allows for rapid reconfiguration to generate a library of different amides for biological evaluation.



Scheme 2. Comprehensive scheme for the flow synthesis of Grossamide.

The other natural products shown in fig 1 all demonstrate further aspects and potential opportunities for flow chemistry for agrochemical applications but have not been highlighted in this short review. We consider however that the integrated batch and flow synthesis of Spirangien A[19] methyl ester arguably stands as a testimony to the power of the technology to accelerate complex molecule synthesis. The details of this synthesis are not discussed here and the reader is advised to consult the work for specific information. However, there are many salient observations worthy of some comment. Firstly, that flow chemistry steps featured in over 60% of the reactions leading up to the total synthesis. In the majority of these there are recognisably gains in terms of safety, scale-up, reaction selectivity and efficiency over conventional batch alternatives. Once the homogenation reaction sequences were developed in flow they proved to be robust. Clearly the reactions and the systems described in this work provides the basis for other polyketide syntheses and novel analogue preparation.

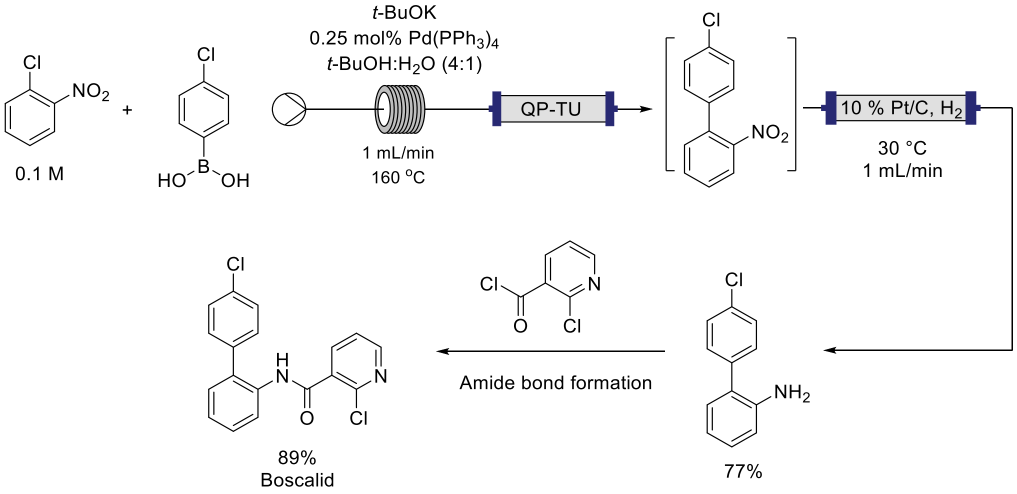
Possibly of more relevance to the industry however is the use of these methods for the continuous flow preparation of compounds of potential commercial importance. The first of these is the continuous flow synthesis of Hymexazol® a broad-spectrum fungicide.[21] After optimisation of the individual steps, a scaled-up reactor configuration produced 1.7 Kg in excellent 99% purity of the final product in only 3.5 hours. All solvents used in the product extraction process and work up were readily recyclable. Four metering plunger pumps were used to drive the flow streams through Hastelloy steel coils and three T shaped mixers (Scheme 3). The optimised flow process was reported to reduce reaction times and significantly reduce side reactions.



Scheme 3. Flow synthesis of hymexazol.

Introduced by BASF in 2003 as a potent fungicide owning to its succinate dehydrogenase inhibitory activity Boscalid® has since been the centre of attention for efficient synthesis campaigns including those using flow methodology.

Early work by Kappe reported on two key steps on the way to producing Boscalid® in flow.[22] The first of these involved a high temperature Suzuki/Miyaura coupling of chloro-2-nitrobenzene with 4-chlorophenylboronic acid through a flow coil operating at 160^0C and subsequent passage, after scavenging with Quadrapure thiourea (QPTU), through an H-cube hydrogenation reactor to reduce the nitro substituent selectively in 77% overall yield. The final amide coupling to give Boscalid® was known previously (Scheme 4).

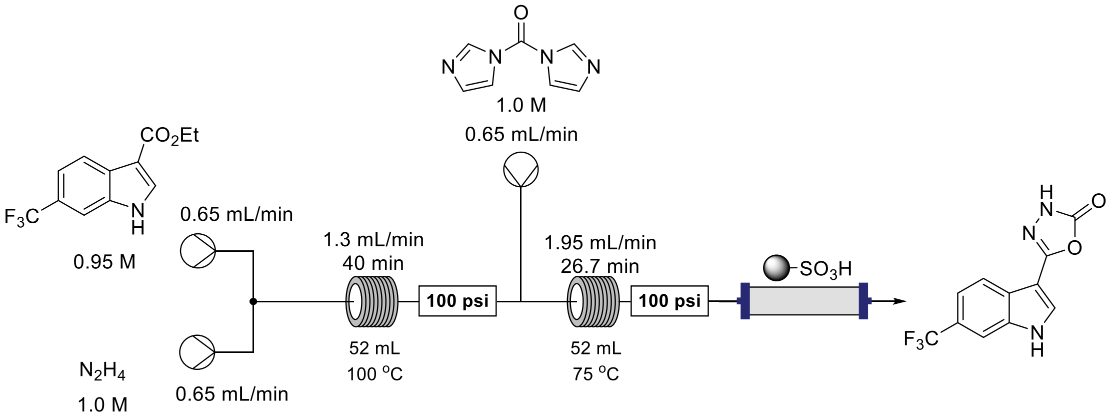


Scheme 4. Flow synthesis of Boscalid.

Recently, using a similar reaction sequence adapted to run on a multi-jet oscillating disk (MJOD) continuous flow reactor platform, a group at the University of Bergen, Norway reported the production of Boscalid® at a rate of around 8.4 gh^{-1} in 42% overall yield for the three steps. In the route a lower temperature (80 ˚C) Suzuki/Miyaura coupling was used and was followed by a cobalt boride reduction step to efficiently convert the nitro group to the required amine substituent. The final coupling was achieved through *in situ* formation of an iminosulfanone using $SOCl_2$ followed by condensation with 2-chloropyridine-3- carboxylic acid.

Useful further details of the MJOD flow reactor are described in the report but are not disclosed here. The semi continuous nature of the intermediate work-up during this route needs development prior to moving up-scale. Nevertheless, the ability to handle solid cobalt boride using mechanical oscillation in the MJOD is a very attractive feature of the process.

In 2017 Baxendale reported a concise and scaleable flow synthesis of auxin mimics based upon indole carboxylate derivatives as herbicidal agents. Of special note was the fully telescoped process for the conversion of ethyl 6-(trifluoromethyl) -1H-3 indolecarboxlyate to a 1,3,6-oxadiazolinone derivative in excellent yield and purity by using a final clean-up cartridge packed with Quadrapure sulfonic acid resin (QPSA) (Scheme 5)[23]

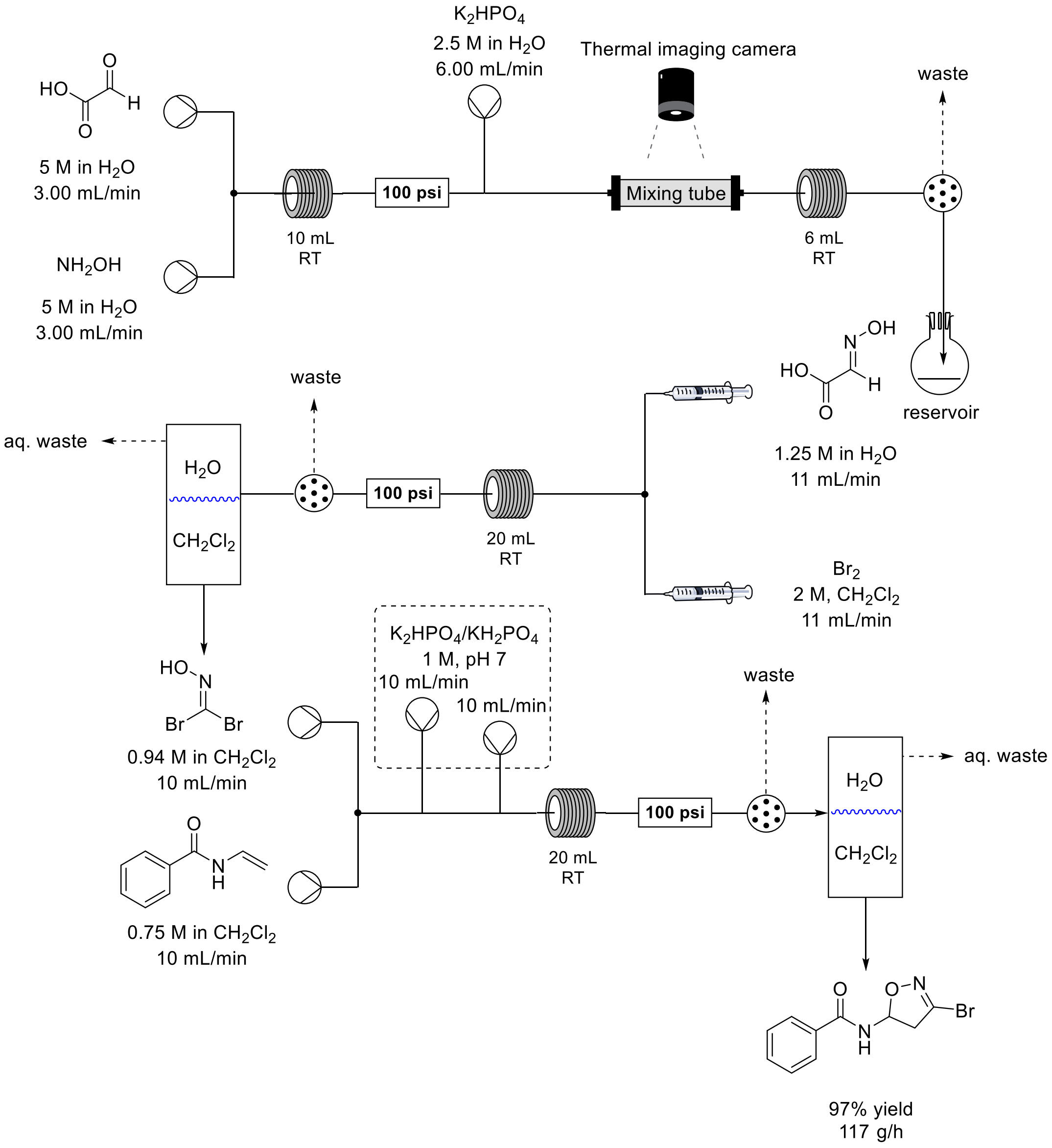


Scheme 5. Flow synthesis of Auxin mimics.

The final two examples are from our own laboratories and nicely exemplify other useful consequences that arise from the application of continuous flow methods.

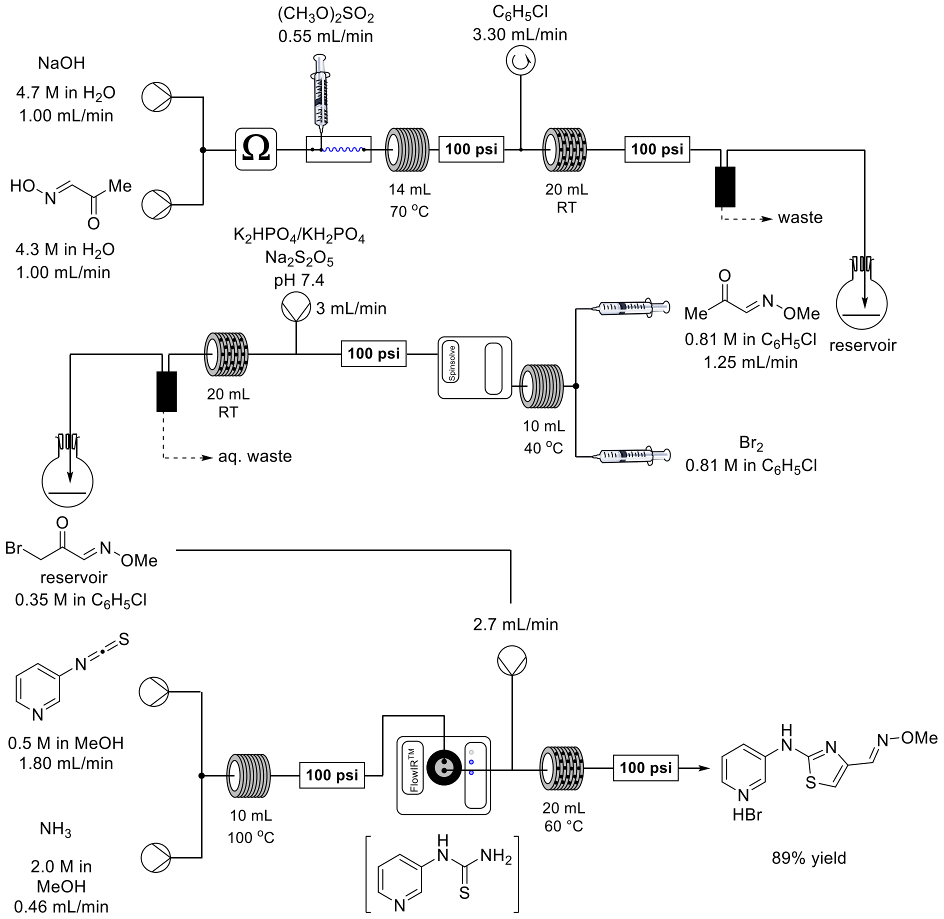
A program was designed to afford quantities of dibromoformaldoxime (DBFO).[24] This was needed as a reactive intermediate on route to 3-bromoisoxazolines via [3+2] cycloaddition of the resulting bromonitrile oxide with olefins. The issues in this work were significant such that large scale batch preparation was deemed unacceptable for safety reasons as indicated by differential scanning calorimetry (DSC) on certain intermediates and problematic exothermic reactions. The proposed use and safe handling of volatile and toxic reagents such as bromine were also major concerns.

Nevertheless, an overall flow preparative system was devised. This was built up by examining the individual chemical steps plumbed together to give final telescoped protocol (Scheme 6). This platform was capable of delivering 3-bromoisoxazolines at a rate of 117 gh^{-1} in excellent yield. Careful pH adjustment was needed along with a reservoir trapping stage. Thermal camera imaging monitored for exotherms and new full tube in line mixing was necessary to give clean high yield product. This method showed versatility not only in accommodating such challenging chemistry, but also in its use to produce a library of 3-bromoisoxazoline analogues.



Scheme 6. Multistep flow synthesis and use of DBFO to generate 3-bromoisoxazolines.

In a further technically challenging synthesis program, where again flow chemistry methodology was an obvious alternative to classical batch processes, a convergent continuous multistep preparation of some thiazoles for use as herbicides was developed.[25,26] Again, while a batch mode preparation on a small scale was possible, the process hazards were unsurmountable on large scale. As before all the individual steps in the reaction scheme were carefully evaluated before being transferred to the flow platform (Scheme 7).



Scheme 7. Multistep flow synthesis of O-methyl oxime thiazoles.

The scheme shown describes the preparation of a single methyloxime substituted thiazole but can obviously be modified for library preparation depending upon the isothiocyanate input stream. Useful in-line NMR monitoring of the oxime bromination step also facilitated reaction understanding and optimisation. This synthesis powerfully illustrates the ability to generate hazardous materials in-line and consume these rapidly in the next synthesis stage to mitigate against product decomposition and thereby better manage the chemical inventories. Other take-home messages from this work relate to the robustness of the procedures, improved safety, flexibility of the platform towards reconfiguration and overall labour-saving events through use of advanced machine learning concepts.

A final statement

The successful exploitation of a flow opportunity requires an interdisciplinary team of chemists, chemical engineers and specialist support teams (PAT, data scientists, mechanical engineers, etc.), where the added-value of the ultimate process is unambiguous and benefits in comparison to a traditional batch vessel, be it safety, quality or throughput are clear. This requires visible chemical mechanisms and methodologies early in the development cycle to both identify and make compelling cases for going continuous, together with managerial support and an openness to levels of risk.

The value of flow chemistry for the industry is clear and the number of examples will undoubtably continue to increase industry. The continued change in mindset towards the associated risks and opportunities, and an enhanced understanding and appreciation of the opportunities of continuous processing all point towards an inevitable increased uptake of tubular reactors, continuous stirred-tank vessels and continuous down-stream processing technologies in future manufacturing.

Adoption of the methods at an earlier stage in the discovery process will undoubtedly also facilitate and improve the continuity across all molecular synthesis working environments and help promote innovation and creativity.

References

1. Poechlauer, P.; Colberg, J.; Fisher, E.; Jansen, M.; Johnson, M. D.; Koenig, S. G.; Lawler, M.; Laporte, T.; Manley, J.; Martin, B.; O'Kearney-McMullan, A., Pharmaceutical Roundtable Study Demonstrates the Value of Continuous Manufacturing in the Design of Greener Processes, Org. Process Res. Dev. 2013, 17, 1472-1478

2. (a) Uhlmann, E.; Hohwieler, E.; Geisert, C., Intelligent production systems in the era of industry 4.0-Changing mindsets and business models, Journal of Machine Engineering, Vol.17, No. 2, 2017; (b) Whysall, Z.; Owtram, M.; Brittain, S., "The new talent management challenges of Industry 4.0, Journal of Management Development 2019, 38, 118-129; (c) Ibarra, D.; Ganzarain, J.; Igartua; J. I., Business model innovation through Industry 4.0: A review, Procedia Manufacturing, 2018, 22, 4-10.

3. a) Gehen, S.; Corvaro, M.; Jones, J.; Ma, M.; Yang, Q., Challenges and Opportunities in the Global Regulation of Crop Protection Products, Org. Process Res. Dev. 2019, 23, 10, 2225–2233; b) According to FAO.org, 5.9 Mtons of crop protection agents were used in 2018. http://www.fao.org/

4. (a) Malet-Sanz, L.; Susanne, F., Continuous Flow Synthesis. A Pharma Perspective, J. Med. Chem. 2012, 55, 4062. (b) Jimenez-Gonzalez, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B.- S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, R. E.; Dell'Orco, P.; Noorman, H.; Yee, S.; Reintjens, R.; Wells, A.; Massonneau, V.; Manley, J., Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers, Org. Process Res. Dev. 2011, 15, 900. (c) Baxendale, I. R.; Braatz, R. D.; Hodnett, B. K.; Jensen, K. F.; Johnson, M. D.; Sharratt, P.; Sherlock, J.-P.; Florence, A.

J., Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance. May 20–21, 2014 Continuous Manufacturing Symposium, J. Pharm. Sci. 2015, 104, 781. (d) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-flow technology a tool for the safe manufacturing of active pharmaceutical ingredients, Angew. Chem., Int. Ed. 2015, 54, 6688. (e) Baumann, M.; Baxendale, I. R., The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry, Beilstein J. Org. Chem. 2015, 11, 1194−1219. (f) Porta, R.; Benaglia, M.; Puglisi, A., Flow chemistry: recent developments in the synthesis of pharmaceutical products, Org. Process Res. Dev. 2016, 20, 2−25.

5. Brocklehurst, C.E.; Lehmann, H.; La Vecchia, L. Nitration Chemistry in Continuous Flow using Fuming Nitric Acid in a Commercially Available Flow Reactor, Org. Process Res Dev. 2011, 15, 6, 1447–1453.

6. Zhang, P.; Russell, M. G.; Jamison, T. F., Continuous Flow Total Synthesis of Rufinamide, Org. Process Res. Dev. 2014, 18, 1567

7. Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J., Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode, Org. Lett. 2017, 19, 4, 786–789

8. Movsisyan, M.; Delbeke, E.I.P; Berton, J.K.E.T.; Battilocchio, C.; Ley, S.V.; Stevens, C.V., Taming hazardous chemistry by continuous flow technology, Chem. Soc. Rev. 2016, 45, 4892-4928

9. Ott, D.; Borukhova, S.; Hessel, V., Life cycle assessment of multi-step rufinamide synthesis – from isolated reactions in batch to continuous microreactor networks, Green Chemistry 2016, 18, 1096-1116.

10. Cole, K.P.; Groh, J.M.; Johnson, M.D.; Burcham, C.L.; Campbell, B.M.; Diseroad, W.D.; Heller, M.R.; Howell, J.R.; Kallman, N.J.; Koenig, T.M.; May, S.A.; Miller, R.D.; Mitchell, D.; Myers, D.P.; Myers, S.S.; Phillips, J.L.; Polster, C.S.; White, T.D.; Cashman, J.; Hurley, D.; Moylan, R.; Sheehan, P.; Spencer, R.D.; Desmond, K.; Desmond, P.; Gowran, O. Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions, Science, 2017, 356, 1144–1150.

11. Soni, S.; Sharma, L.; Meena, P.; Roy, S.; Nigam, K.D.P., Compact coiled flow inverter for process intensification, Chemical Engineering Science, 193, 2019, 312-324

12. Suppliers (e.g. Chemtrix, ISCO) are increasingly making equipment standardised.

13. Within the agrochemical sector, the largest active ingredient, *i.e.* glyphosate, is produced on scale above 750 ktons/annum. Although difficult to unambiguously affirm, it is highly likely continuous technology is used in various stages of its synthesis process, see review: Whiteker, G.T., Applications of the 12 Principles of Green Chemistry in the Crop Protection Industry, Org. Process Res. Dev., 2019, 23, 2109-2121.

14. Pastre, J.C.; Browne, D.L.; Ley, S.V. Flow chemistry syntheses of natural products, Chem. Soc. Rev., 2013, 42, 8849-8869.

15. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K., A flow process for the multi-step synthesis of the alkaloid natural product oxomaritidine: a new paradigm for molecular assembly, Chem. Comm., 2006, 2566-2568

16. Kim, H.; Nagaki, A.; Yoshida, J.-I., A flow-microreactor approach to protecting-group-free synthesis using organolithium compounds, Nat. Comm., 2011**,** *2*, 264-269.

17. Carmona-Vargas, C. C.; de C. Alves, L.; Brocksom, T. J.; de Oliveira, K. T., Combining batch and continuous flow setups in the end-to-end synthesis of naturally occurring curcuminoids, Reaction Chem. Eng., 2017, 2, 366-374.

18. Lücke, D.; Dalton, T.; Ley, S. V.; Wilson, Z. E., Synthesis of Natural and Unnatural Cyclooligomeric Depsipeptides Enabled by Flow Chemistry, Chem. Eur. J., 2016, 22, 4206-4217

19. Newton, S.; Carter, C. F.; Pearson, C. M.; de C. Alves, L.; Lange, H.; Thansandote, P.; Ley, S. V., Accelerating Spirocyclic Polyketide Synthesis using Flow Chemistry, Angew. Chem. Int. Ed., 2014, 53, 4915-4920.

20. Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. ; Preparation of the Neolignan Natural Product Grossamide by a Continuous-Flow Process, Synlett, 2006, 0427-0430.

21. Ma, X.-P.; Chen, J.-S.; Du, X.-H., A Continuous Flow Process for the Synthesis of Hymexazol, Org. Process Res.Dev., 2019, 23, 1152-1158.

22. Glasnov, T. N.; Kappe, C. O., Towards a Continuous-Flow Synthesis of Boscalid, Advanced Synthesis & Catalysis 2010, 352, 3089-3097.

23. Battilocchio, C.; Bosica, F.; Rowe, S. M.; Abreu, B. L.; Godineau, E.; Lehmann, M.; Ley, S. V., Continuous Preparation and Use of Dibromoformaldoxime as a Reactive Intermediate for the Synthesis of 3-Bromoisoxazolines, Org. Process Res. Dev. 2017, 21, 1588-1594.

24. Godineau, E.; Battilocchio, C.; Lal, M., Building up a Continuous Flow Platform as an Enabler to the Preparation of Intermediates on Kilogram Scale, CHIMIA 2019, 828-831.

25. Godineau, E.; Battilocchio, C.; Lehmann, M.; Ley, S. V.; Labes, R.; Birnoschi, L.; Subramanian, S.; Prasanna, C. S.; Gorde, A.; Kalbagh, M.; Khade, V.; Scherrer, A.; O’Sullivan, A. C., A Convergent Continuous Multistep Process for the Preparation of C4-Oxime-Substituted Thiazoles, Org. Process Res. Dev., 2018, 22, 955-962.