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Chemical Flow: New Advances in the Production of Medicines

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1. INTRODUCTION

Continuous flow approaches have recently attracted a lot of attention from synthetic organic chemists as a viable alternative to the conventional batch method of conducting organic synthesis in sealed containers, such as test tubes or flasks with round bottoms.1 Up until recently, the petrochemical and bulk chemicals industries typically used specialised continuous facilities. Nevertheless, these methods have lately become more popular, especially in academic institutions, for the manufacture of fine chemicals, such as natural products2 and Active Pharma-ceutical Ingredients (APIs). There are many more applications of flow technology outside organic chemical production. A landmark investigation conducted by experts from the Novartis-MIT Centre for Continuous production in Cambridge uncovered the extraordinary end-to-end continuous manufacture of an API, aliskiren hemifumarate.4 The process details the steps to consistently execute the required reactions and further operations (such as quench, work up, isolation, and purification) crystallisations, drying, formulation, and chemical transformations and separations

transformations and separations into a fully automated continuous process is now possible. An astounding 100 g/hour of aliskiren is produced by the Novartis-MIT pilot plant, which has two synthetic steps: generating the API salt and crystallisation.. This tendency is caused by the basic characteristics of flow reactorswhich increases the reaction time and, in most cases, productivity when compared to a batch system.6 Measuring temperature is insufficient

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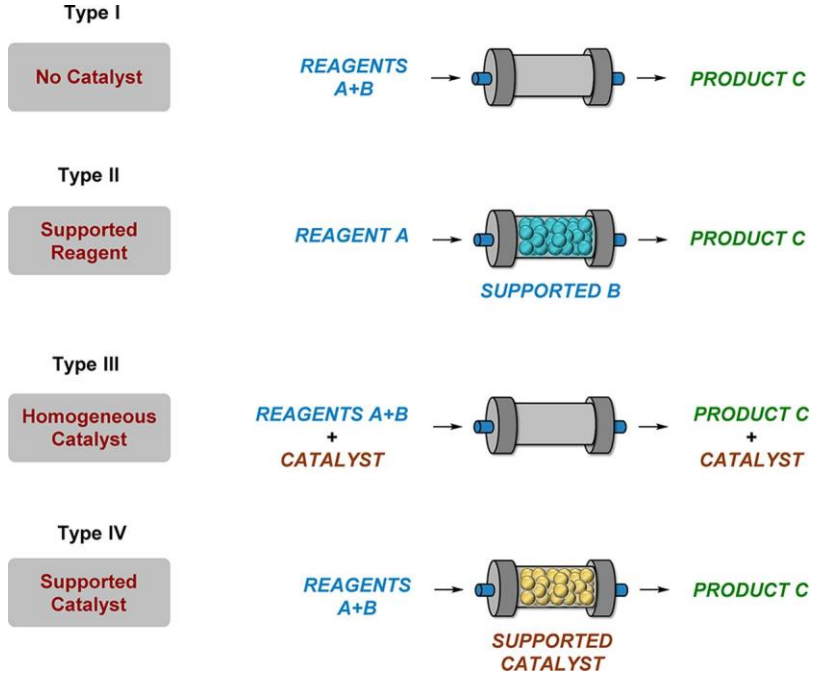


Figure 1. Types of continuous *fl*ow systems.

Being so small makes it easy to insert and remove a heating source, which in turn enables precise temperature control throughout the microreactor and safeguards against potentially harmful exothermic reactions that go unchecked. Not only does this facilitate transmission, but it also permits pinpoint tracking of the heat exchange. A more consistent and repeatable process may be achieved with a continuous flow system as opposed to a batch process since response factors such as temperature, pressure, and flow rate are easy to set up and monitor.7 Flow methods provide rapid screening of reaction conditions due to the limited volume required; after optimisation, the reaction may be scaled up. Problems like runaway reactions, inefficient miXing, and the formation of byproducts are among the many that could arise when a chemical process is scaled up. The earliest and most basic method for producing large quantities of chemicals in a microreactor is to extend the time the process is conducted, a technique called scaling-out. Compared to batch reactions, this should be easier in principle. The use of many reactors at once, a technique known as "numbering up," or the use of larger continuous reactors for the process are two alternative possibilities.8 Because it employs very minute quantities of chemicals, the microreactor may also remove certain safety issues. For instance, the operator's safety is ensured by reducing their contact with potentially harmful or poisonous substances. The brief residence length makes microreactors ideal for reactions involving reactive and transitory chemicals.

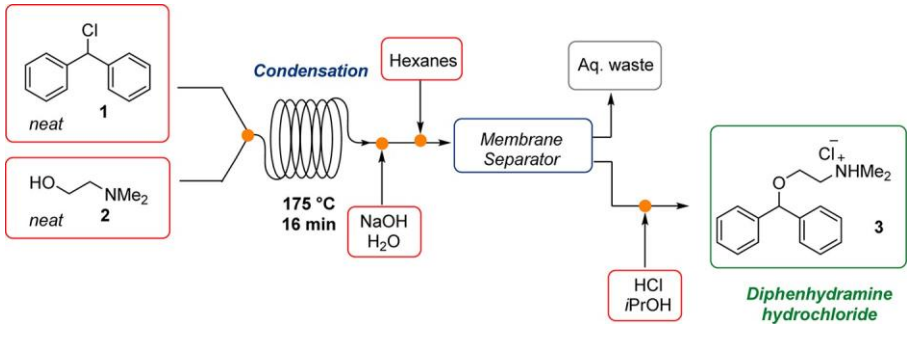
Microwave irradiation, photochemistry, inductive heating, electrochemistry, new solvent systems, microreactor technology, additive manufacturing, and catalysts or reagents that are aided are all instances of flow chemistry. This combination has

the potential to create an automated process with improved throughput.
In light of these advantages, it is not surprising that continuous processing is emerging as a technique that might significantly impact the synthesis of APIs (or API intermediates). The use of continuous flow conditions for the secure manufacture of organic intermediates and APIs was extensively examined in a recent research conducted by Professor Kappe and colleagues.10 According to what the authors have pointed out, there is now no risk in doing several synthetic operations that were previously disallowed under flow conditions. Using solvents that are above their boiling point, conducting reactions at high pressure, or using intermediates that might be explosive are all part of these processes. The topic of flow chemistry is at the forefront of innovation because it opens the door to better methods of producing crucial molecules.

Kobayashi and colleagues classify the continuous flow systems reported in the literature thus far into four broad groups, as shown in Figure 1.Eleventh, a type I reaction involves putting all of the chemicals into the reactor and then collecting the byproduct. The second kind of reactor is characterised by the substrate being passed through a solid that has been connected to one of the reactants. Should the procedure continue to

procedures that are not feasible to store or handle in completion, the ultimate reaction conventional batch processing. In addition, the amount of solvents and reagents needed is much less, making it easy and cost-effective to screen reaction conditions. This opens the door to automated library synthesis and faster processing times. This would make it easier to find a prospective medicine and produce it in bigger quantities for use in biological testing.
It is also easy to combine continuous flow synthetic methods with other auxiliary technologies to increase efficiency even further.9 Standard enabling technology combined with your desired feature. For types I and II processes, catalysts aren't required. To separate the product from the catalyst and any byproducts, a separation step is required at the conclusion of a type III reaction using a homogeneous catalyst, as the catalyst flows through the reactor with the reactants. Reagents in type IV reactions flow through a reactor that houses the catalyst. While in practice the product and catalyst do not need separation, catalyst immobilisation does necessitate a firm support. On top of that, the catalyst could be readily

Scheme 1. Continuous Flow Synthesis of Diphenhydramine Hydrochloride



recycled. Since catalytic techniques are currently crucial for the development of sustainable and efficient processes, the latter kind is often thought of as the most convenient way to carry out a reaction under continuous-flow circumstances.12 All four reactor typologies are used or combined in the cases discussed in this study. Finally, this study will go over type III and type IV flow

systems, concentrating on how stereoselective chiral organocatalysts are used. One potential issue with using microreactors to synthesise APIs is the possibility of the reactor being clogged, namely the channels becoming blocked owing to solid precipitation. For synthetic organic chemists, dealing with the precipitation of inorganic salts or insoluble materials during reactions is a regular occurrence. For example, when the reaction product separates from the reaction mixture and can be easily purified, this may be a suitable scenario

views, as well as potential and anticipated advancements in the field. Here is a list of typical reactor materials and the acronyms used for them, as we will be describing many kinds of continuous flow reactors: The acronyms FEP, PEEK, PFA, and PTFE stand for fluorinated ethylene propylene, polyether ether ketone, perfluoroalkyl alkanes, and polytetrafluoroethylene, respectively.

To clarify for the schemes, the following is a list of colours used to denote different components: red for starting materials, green for products, yellow for isolated intermediate products, dashed yellow for nonisolated intermediates, and light blue for catalysts.

2. MULTISTEP SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS IN FLOW

Some examples of APIs that have been created continuously flow have been shown in

process. The problem this causes, however, becomes quite clear when applied to a flow system. For this reason, more sophisticated approaches to handling solids in continuous flow processes have emerged in recent years, even if more technical developments are necessary. We will concentrate on current breakthroughs in the continuous flow multistep synthesis of organic compounds that have found applications as APIs, as there have been many studies addressing the synthesis and manufacture of APIs and related advanced intermediates. Included in this category will be both reported and

undisclosed contributions from 2013–2015 in the literature. We will provide a comprehensive overview of the many approaches, tools, and synthetic procedures that have been used so far in an attempt to close the gap between pharmaceutical research and manufacturing.

In Section 2, we will examine the most prominent examples that surfaced in the literature in 2013 and 2014. In Section 3, we will go deeply into the most current works that have not been previously studied.

In Section 4, we take a high-level look into stereoselective organocatalysis in a flow environment, a very young and unexplored field of research. We hope that by demonstrating the method's versatility and laying the groundwork for further research in this area, we can improve our methods for the stereoselective synthesis of chiral medicines.

At the end of Section 5, we provide some general ideas on the topic and some reflections on the

Previous years' literature (2013 and 2014) will be reviewed.13 Highlighted will be the critical synthetic route leading to the target molecule and the significant advancements in each instance.

A number of well-known medications, such as Benadryl, Zzzquil, Tylenol PM, and Unisom, need more than 100 metric tonnes of diphenhydramine hydrochloride per year to meet the worldwide demand.

A continuous flow technique for synthesising 3,

developed by Jamison and colleagues in 2013, reduced

production time, waste, and purification phases in comparison to existing batch synthetic procedures (Scheme 1).In the optimised procedure, chlorodiphenylmethane 1 and dimethylethanolamine 2 were mixed using a 720 µL PFA tube reactor (i.d. = 0.5 mm), a residence duration of 16 minutes, and a temperature of 175 °C. Conducting the reaction above water's boiling point and without a solvent allowed for a high pace of reaction. Product 3, when obtained as molten salt—that is, at a temperature higher than the salt's melting point—could be easily transported in the flow system, in contrast to conditions.

The reactor's output was then combined with heated
Using 3 M NaOH will neutralise ammonium salts. A hexanes-based inline membrane separator was used to extract the neutralised tertiary amine upon quenching. Following treatment of the organic layer with HCl (5 M solution in iPrOH), diphenhydramine hydrochloride 3 was precipitated with an overall yield of 90% and an output of 2.4 g/h.

Atypical antipsychotics are characterised by less side effects than standard antipsychotics, including extrapyramidal symptoms, body rigidity, and involuntary tremors. One of the most peculiar ones is olanzapine 10,15, commercially known as

Scheme 2. Continuous Flow Synthesis of Olanzapine

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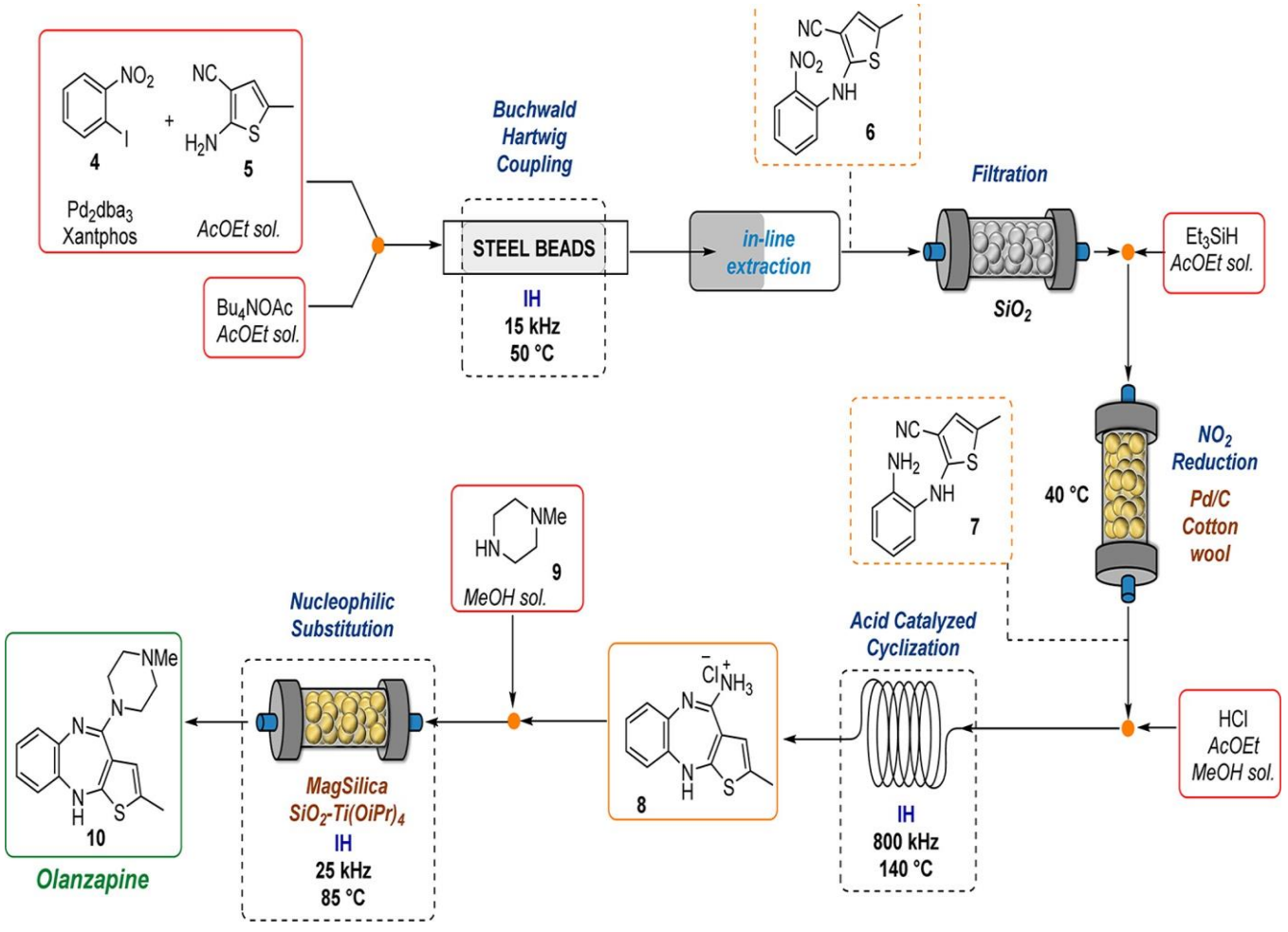
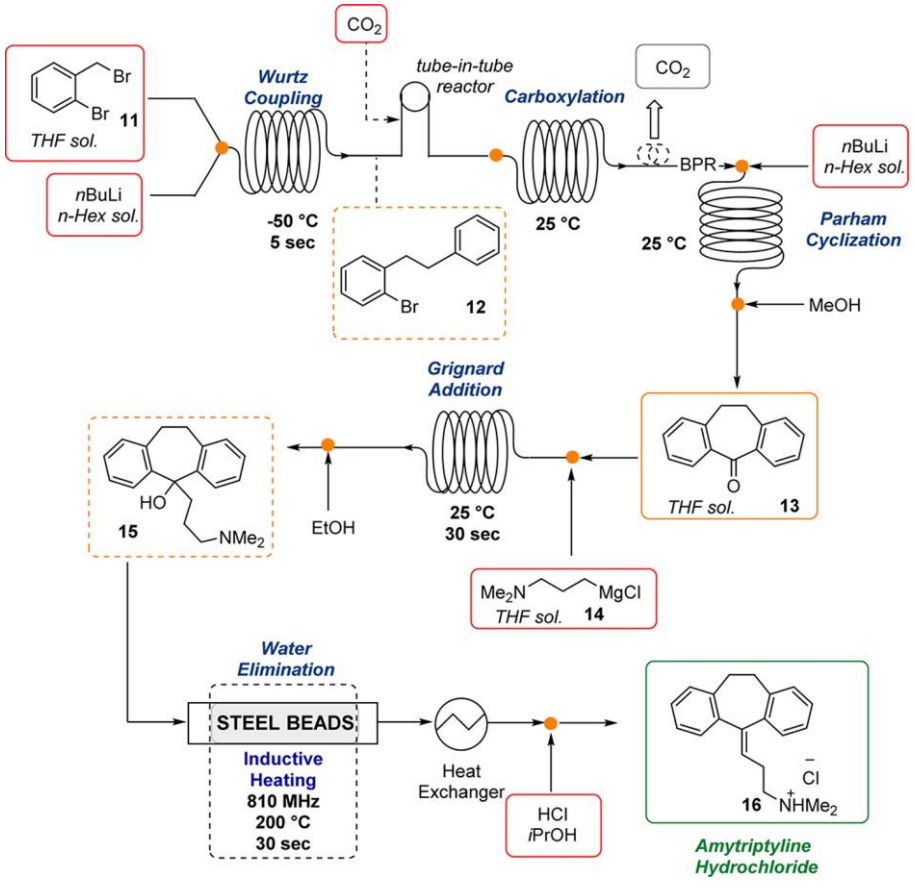
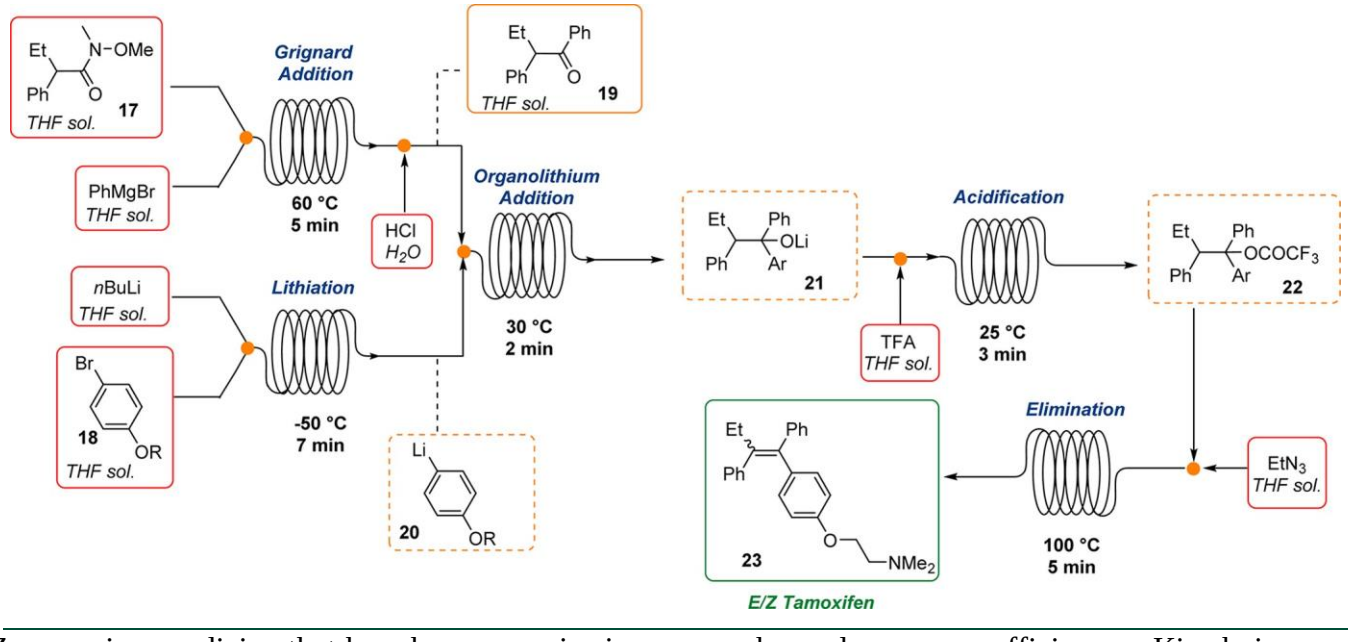


Scheme 3. Continuous Flow Synthesis of Amytriptyline Hydrochloride



Scheme 4. Continuous Flow Synthesis of Tamoxifen



Zyprexa is a medicine that has shown promise in treating schizophrenia and bipolar disorder. Using inductive heating (IH), a technique that drastically reduced reaction durations and enhanced process efficiency, Kirschning and colleagues developed the multistep continuous flow synthesis of olanzapine 10 in 2013.16 Inductive heating is based on the use of magnetic

nanoparticles and an electromagnetic field to uickly increase their temperature. The frequency

of the field depends on the size of the nanoparticles.17

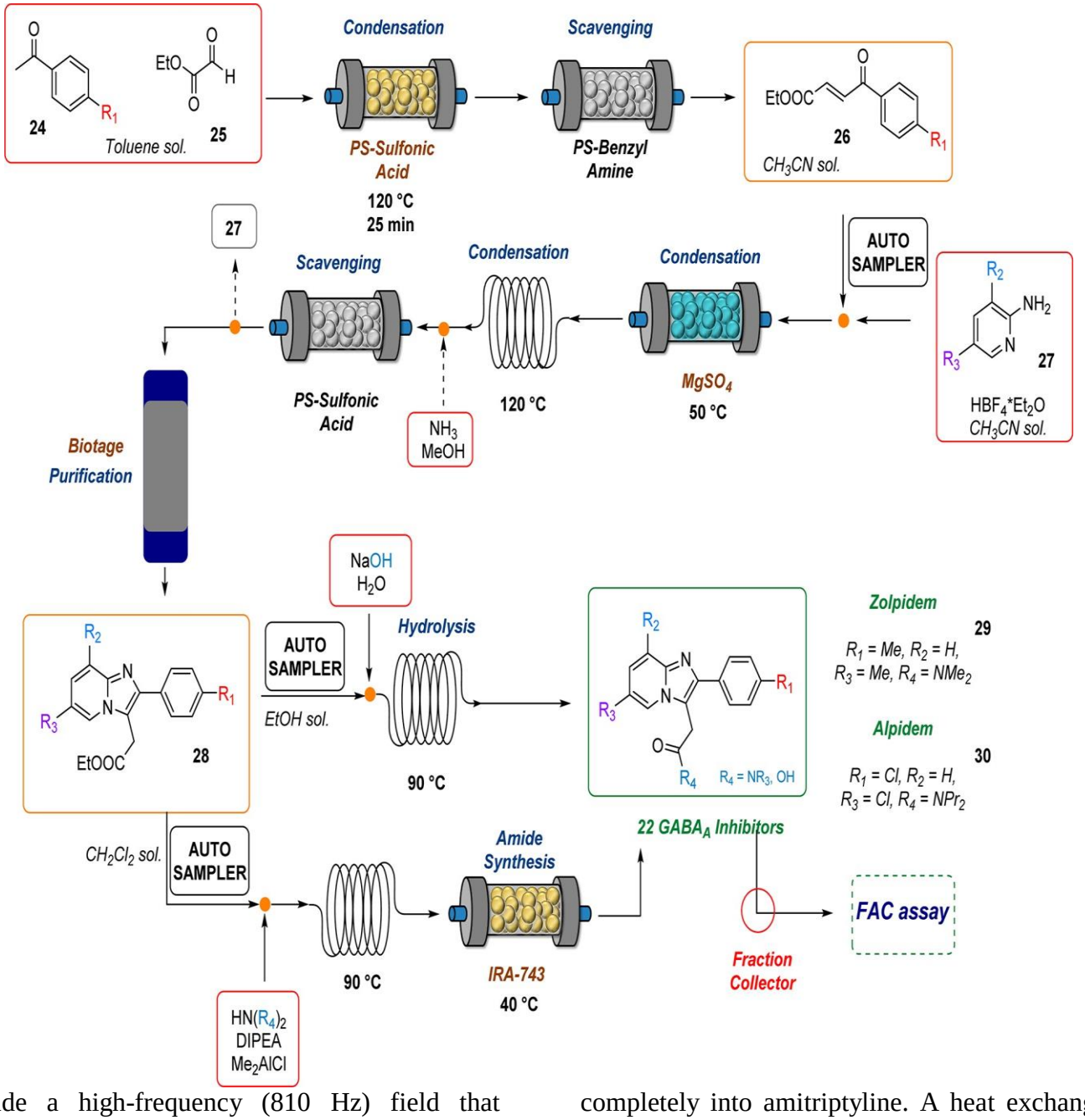
Aryl iodide 4 and aminothiazole 5 were combined in the first stage of the synthesis, as illustrated in Scheme 2, with Pd2dba3 acting as a catalyst and Xantphos as a ligand. In a PEEK reactor with 0.8 mm steel beads, the Buchwald-Hartwig coupling process was conducted under inductive heating to 50 °C (15 kHz). Because AcOEt worked with a few of the

sections of the subsequent reply. After quenching with distilled water and in-line extracting in a glass column, the crude mixture was passed through a silica cartridge to remove the Pd catalyst. Then, in a fixed bed reactor containing Pd/C, nitroaromatic compound 6 was reduced with Et3SiH at 40 °C. With the catalyst's continued activity for more than 250 hours after use, the yield of aniline 7 was virtually quantitative. Hydrochloric acid, in a 0.6 M methanol solution, was added to the reactor's output before being heated at 140 °C using high frequency heating (800 kHz). Product 8, which was synthesised using acid catalysed cyclization, had an overall yield of 88%. It is astounding that the three-step procedure did not need any solvent change, considering the whole reactor capacity is only around 8 mL.
Compound 8 was then replaced with piperazine 9 in a 3 mL PEEK reactor that used MAGSILICA as the inductive material and silica-supported Ti-(OiPr)4 as the Lewis acid. Inductively heating the reactor to 85 °C with a medium frequency of 25 kHz resulted in an 83% yield of olanzapine 10. Amitriptyline and other tricyclic antidepressants block salt, potassium, and chloride channels. Some medical ailments it may ease include tension headaches, migraines, anxiety attacks, and even some types of schizophrenia.

health issues. The standard procedure for producing dibenzosuberone 13 involves starting with lithiated benzyl bromide 11, then employing CO2 as an electrophile in a Wurtz dimerization and one-pot Parham cyclization reaction. The removal of water followed the reaction of ketone 13 with Grignard reagent 14, resulting in API target 16.
Kirschning and Kupracz (2013) developed a new method for the continuous flow synthesis of Amitriptyline 16 (Scheme 3), building on this well-established synthetic process.18 There are several advantages to conducting the multistep synthesis of 16 in continuo over the traditional batch approach, especially when dealing with gas phase reagents (CO2) and extremely reactive intermediates (aryl- and alkyllithium compounds). A 0.5 mL steel reactor coil with an inner diameter of 1.0 mm was used to conduct the first lithiation reaction involving nBuLi and benzyl bromide 11 at -50 °C. A mere 5 seconds of quenching with MeOH was sufficient to effectively extract the target aryl bromide 12 with a yield of 79%. Prior to delving into the telescoped synthesis of ketone 13, the ideal reaction conditions for first Wurtz coupling were identified. S. V. Ley's19 tube-in-tube reactor method allowed for the direct injection of CO2 to the raw stream of reactants. The carboXylation step, which took place at 25 °C, required 0.5 mL of PFA reactor coil (i.d. = 0.8 mm). A second stream of nBuLi was added to the reaction mixture after the gas was removed. An inner diameter of 0.8 mm and 0.5 mL of PFA reactor coil were used for the final phase of cyclization at 25 °C. With a total residence time of around 30 seconds and an extraction yield of 76%, dibenzosuberone 13 was obtained after adding MeOH. When put in context with the fact that the 13-unit batch synthesis required a 2-hour reaction time at -100 °C and yielded 56% on its own, the flow methodology's better performance becomes clear.
After the pure ketone 13, which had been

recovered from the multistep flow synthesis, was mixed with Grignard reagent 14 at 25 °C with a residence duration of about 30 s using a 0.5 mL PFA reactor coil (i.d. = 1.0 mm). Carbinol 15, which was obtained by protonating the crude reaction mixture with EtOH, was subjected to inductive heating in a 0.3 mL cartridge steel reactor (i.d. = 4.0) in order to remove water.

Scheme 5. Continuous Flow Synthesis of $GABA_A$ Inhibitors



inside a high-frequency (810 Hz) field that included 0.8 mm steel beads. In under 30 seconds at 200 °C, the original chemical was converted completely into amitriptyline. A heat exchanger was required to cool the raw mixture to room temperature. It took recrystallization from an

EtOH/Et2O combination and the addition of HCl (1 M solution in isopropanol) to eventually get the 17-methyl amitriptyline hydrochloride salt in 71% yield.

Compared to traditional batch methods, there are a lot of benefits to using organometallic reagents using flow chemistry. This includes the following: the quick and stoichiometric reaction of Weinreb amide 17 in a 10 mL PFA reactor coil at 60 °C; the safe handling of very reactive organometallic intermediates; and the ability to accurately regulate the temperature of potentially exothermic reactions. By allowing the mixture to dwell for 5 minutes and then quenching it with HCl aq, a 97% yield of ketone 19 was obtained. Aryl bromide 18 and nBuLi were lithiated at the same time using a 10 mL PFA reactor coil at -50 °C. In a 0.4 mL PFA reactor coil at -50 °C with a 10-second residence time, the aryl lithium compound 20 and a ketone 19 THF solution were added after a 7-minute reaction. A brief period of heating followed. Put the 5 mL of PFA reactor coil in a 30-degree oven for 2 minutes. Once the 10 mL PFA reactor coil had

been added to the crude lithium alkoXide 21, it was heated to 25 °C for three minutes. Afterwards, triethylamine was used to remove trifluoroacetate 22 from two 10 mL PFA reactor coils that had been heated to 100 °C for a total of five minutes. The

measuring substrates and reagents together.20 Given this situation,

Using telescoped synthesis, tamoxifen 23 was created as an E/Z combination.

Due to the air sensitivity and high reactivity of substances like organolithium and Grignard compounds, the lab of Steven Ley explored a new flow platform using fluoropolymer peristaltic pumps. It was shown in 2013 that this technology may be utilised to synthesise the antagonist prodrug tamoXifen 23, which is used to treat breast cancer in all its phases.21 This approach integrated four distinct chemical processes into a single stream with little human intervention, as shown in Schema 4, therefore reducing dangers associated with handling organometallic chemicals.

The production of the tetrasubstituted target alkene 23, which is accomplished using a flow synthesis, began with the Grignard addition of PhMgBr to

produced with an 84% yield (25:75) from aryl bromide 18. One patient might be treated for almost 900 days, or the equivalent of taking a dose every 5 seconds, using the 12.4 g of pure API that was produced from an 80-minute continuous flow method.

Improper integration of the chemical and biological sciences might result in wasted time and money spent on medication development. In 2013, Ley's group investigated the feasibility of developing a method to integrate chemical synthesis with biological assays22 in the search for novel pharmaceuticals. They synthesised chemicals using a flow chemistry platform and used frontal affinity chromatography (FAC) for inline screening.23 Among a small group of 22

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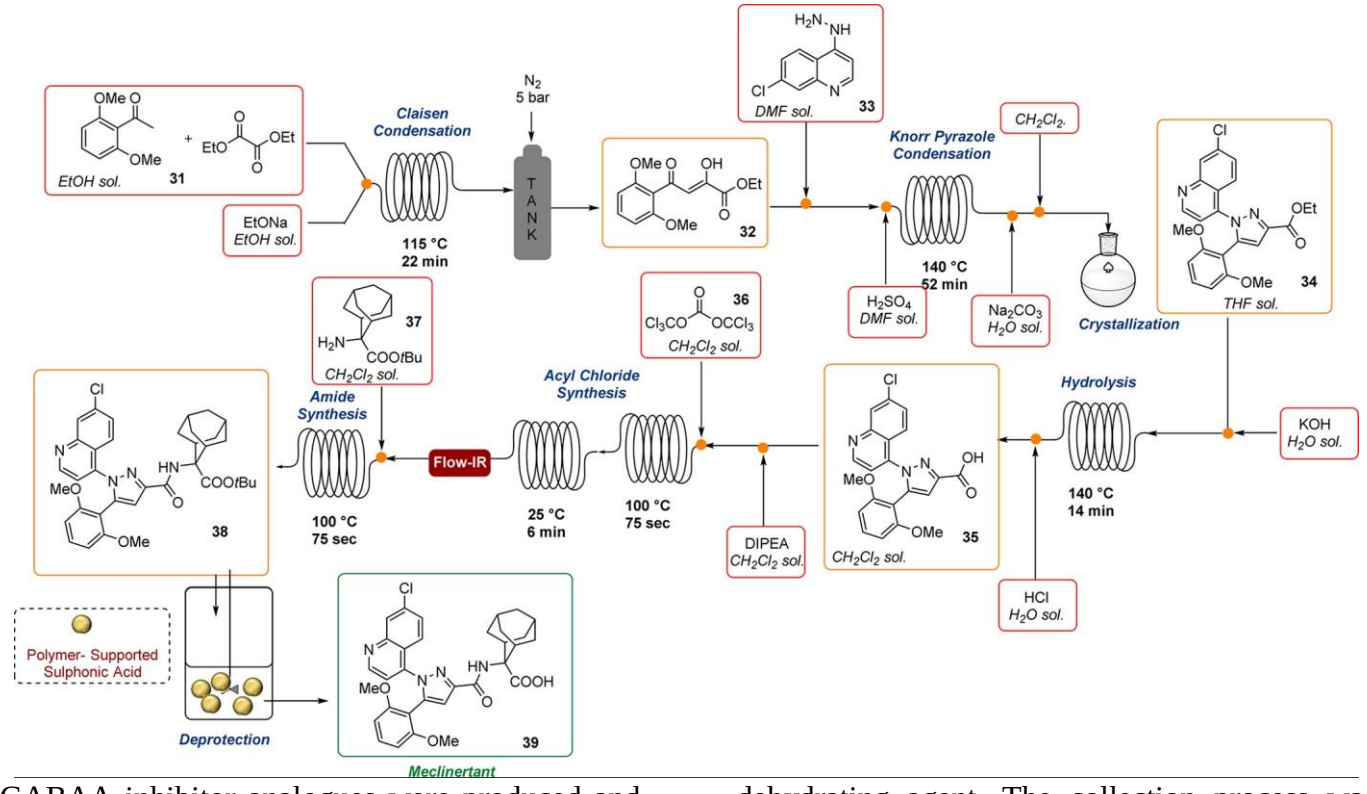
Scheme 6. Continuous Flow Synthesis of Meclinertant



GABAA inhibitor analogues were produced and evaluated in a continuous manner (Scheme 5). Two of them are agonists of GABAA receptors that are utilised as active medicinal ingredients: alpidem for anxiety and sleeplessness and zolpidem for certain brain problems. The imidazopyridines to which these compounds belong are active against cancer, viruses, and microbes.

The synthesis of imidazopyridines in continuous flow started with the acid-catalyzed condensation of ethyl glyoXalate 25 with ketone 24. A reactor containing 2 grammes of polymer-supported sulfonic acid was used for the reaction, which was carried out at 120 °C with a residence duration of 25 minutes. A cartridge containing 3 g of polymer-supported benzyl amine was used to scavenge the excess of 25 after the crude mixture was run through it. With an excellent yield ranging from 76% to 85%, three products were recovered without the requirement for workup or additional purifications. At 50 °C, three α,β-unsaturated ketones 26 and three aminopyridines 27 were pumped into a reactor containing MgSO4 as a dehydrating agent. The collection process was carried out using an auto sampler. The matching imines were quickly produced under superheating conditions and then 5-exo cyclized into a 14 mL reactor coil at 120 °C. It was possible to recover the excess aminopyridine 27 by injecting NH3 into MeOH to release the bound material after the crude reaction mixture had gone through a column filled with polymer-supported sulfonic acid. Eight imidazopyridines were obtained after in-line chromatographic purification using the Biotage system. In the final stage of the synthetic process, molecular diversity was introduced into the imidazopyridine scaffold through the use of an auto sampler to regulate two separate reactions. The first reaction involved the saponification of 28 ester moieties with NaOH aq. in a 14 mL reactor coil at 90 °C. The second reaction involved converting 28 esters into corresponding amides.

Through the use of Me2AlCl and two distinct secondary amines (HN(R4)2). To eliminate Al compounds, the reaction mixture was heated at 90

°C in a 14 mL reactor coil and then passed through a cartridge

containing IRA-743 polyol resin. It just took four days to get a library of twenty-two imidazopyridine derivatives using this flow method. The synthetic platform ended with the introduction of a fraction collector. After the appropriate dilution, 10 µL aliquots were automatically obtained for each reaction output and submitted to FAC analysis.
The employment of machine-assisted flow methodologies24 allows for better efficiency and high throughput, however batch methods are still the most common approach for executing chemical reactions. Ley and colleagues published a study in 2013 (Scheme 6) that directly compared the flow multistep synthesis of the selective neurotensine probe SR48692 (Meclinertant) with traditional batch preparation.25 The authors of this case study set out to determine if flow technology might solve several synthetic problems—such as solid precipitation and the buildup of byproducts—and speed up a multistep synthesis (i.e., improve yields or decrease reaction times). Product 32 is produced in 60% yield after 3 hours of stirring in an initial Claisen condensation between ketone 31 and ethyl glyoXalate in the presence of NaOEt as a base and EtOH as a solvent in a batch operated at room temperature. A speedier approach was to superheat the reaction in flux, which involves heating the solvent over its boiling point. For example, a 52 mL PFA reactor coil was heated to 115 °C with a residence period of 22 minutes, yielding 32 of the respective products in 74% yield. An impromptu pressurised stainless-steel tank was constructed to address solid accumulation issues; this tank was meant to conduct the reaction constantly, without the risk of precipitation or obstruction, using 5 bar of nitrogen.
In a DMF reaction, the following was carried out with 32 and a commercially available hydrazine 33:

5. OUTLOOK AND PERSPECTIVES

It is hardly surprising that pharmaceutical companies have also begun to focus on flow chemistry for the preparation of active pharmaceutical ingredients (APIs) given the obvious benefits of continuous flow technologies in the industrial process. The potential to integrate flow-based chemical synthesis with new analytical tools for in-process monitoring and enabling technologies to expedite isolation and purification steps is driving this trend, which will only grow stronger in the years to come.
Microreactors provide many benefits, including as tiny dimensions, improved mass and heat transfer coefficients by 1-2 orders of magnitude, high volumetric productivity, and laminar flow conditions, as well as high surface to volume ratios. When considering potential uses in industrial synthesis, it is important to consider the following factors: low power consumption; greater safety owing to minimal quantity of materials utilised in the process; and cheap operating, maintenance, and manufacturing costs. Scalability in parallel is also an appealing characteristic.

Despite the availability of technology to produce micro-reactors from silicon, glass, steel, and other metals, their widespread application is surprising. The need for an active, stable catalyst and very rapid reactions is a problem because of the short residence durations involved. Recent research by a large pharmaceutical manufacturer found that while continuous processing would improve approximately half of their synthesis reactions, 63% of those reactions could not be done in a microreactor at the time because of solids. Finally, the most important thing is to create microreactors that can handle solids and are adaptable enough to be employed in continuous plants with several purposes. Some recent multistep synthesis flows are also included in this study, demonstrating the tremendous development achieved in this field. It is possible to imagine many more significant technical improvements in the future. When thinking about the economics of flow processes, it's important to keep in mind that it often takes more time and sometimes not trivial expenditures to construct such processes compared to batch processes.
Furthermore, existing installations may be reluctant to

be replaced because of the perceived high risk associated with micro reactors, which is exacerbated by their tiny size, susceptibility to fouling and clogging, leakage between channels, and the lack of information on their dependability and life on stream. Additional drawbacks of catalytic reactors include the possibility of catalyst deactivation, the need to repack or reactivate the reactor often, and the reactor's dependability over an extended period of time while operating. One major advantage of in-flow processes, nevertheless, is the ability to realise very flexible modules that can carry out on-demand synthesis. The result will be a regional distribution and manufacturing network that can adapt more quickly to changes in demand thanks to "ad hoc" tailoring of industrial processes that alter production size and timing. For instance, (micro)reactors technology has made it possible to synthesise unique molecules with less risk of medicine shortages, and in-situ preparation of explosive and dangerous chemicals is now a real possibility.

Lastly, our capacity to carry out catalytic, enantioselective reactions in flow is an important and likely to be the focus of future research. All of the reaction sequence examples reported in the last few years pertain to the synthesis of achiral compounds or the racemic form of a chiral product; there is a lack of development in the stereoselective synthesis of chiral products. The utilisation of chiral catalytic reactors to produce pharmaceutically relevant enantiomerically pure compounds was only made possible in 2015 thanks to the Kobayashi report on Rolipram11. But

A successful use of catalytic reactors in an applied process requires optimisation and study of various subjects, including activation, efficiency, longevity, degradation, and probable reactivation of supported chiral catalysts.

Future difficulties may include integrating the whole manufacturing process into a single, all-in-continuo process, in addition to the synthesis of complicated compounds. There are a number of potential benefits: moving directly from research to manufacturing will reduce overall process timelines and speed up time to market. In addition, by integrating and colocating production processes in one facility, one may get savings on COGS (cost of products sold), have more flexibility, have a smaller footprint, and reduce inventory. According to reference 4, the astounding outcome for the manufacturing of alkiskiren's final tables has

opened new avenues in this area; however it should be noted that the whole in *fl*ow manifacturing of aliskiren tablets was accomplished by studying only the two *fi*nal steps of the synthesis, a condensation reaction starting from an advancedprecursor of the *fi*nal product where the absolute con*fi*guration of all four stereocenters has been already established. The future challenge is to accomplish e*ffi*cient synthesis of enantiomerically pure products under continuous *fl*ow conditions and integrate the in *fl*ow synthesis in a single "allin *fl*ow" process featuring also in line analysis, puri*fi*cation, and crystallization steps, and leading to the production of the *fi*nal, ready for the market drug. The road is long and full of obstacles, but, considering the impressive progress made in the continuous *fl*ow technologies in the past few years, the *fi*nal goal might be accomplished in shorter times than expected.

REFERENCES

(aBerlin: De Gruyter, 2014. Flow Chemistry by Darvas, F., Hessel, V., and Dorman, G. (b) As published in Lab Chip 2014, 14, 3206, by Jensen, K. F., Reizman, B. J., and Newman, S. G. Copyright 2013 by Wiley-VCH, Weinheim. Topics covered in W. Reschetilowski's Microreactors in Preparative Chemistry. (d) The Second Edition of Microreactors for Organic Synthesis and Catalysis, T. Wirth, Weinheim, 2013: Wiley-VCH. Environmental Chemistry 2012, 14, 38 (e) "Wagener, Ceylan, and Kirschning" (2011) in "Chemistry Communicatons," volume 47, number 4583, written by Wiles and Watts (f). (g) A work with the DOI 50, 7502 was published in the 2011 edition of Angew. Chem., International Edition by Hartman, R. L., McMullen, J. P., and Jensen, K. F. (h) Wiles and Watts report that there were 47,652 articles published in the Chemistry journal in 2011. (i) Chemical Engineering Technology, vol. 32, no. 16,55, 2009, written by V. Hessel. This article is a comprehensive review of flow synthesis of natural products. It was written by Pastre, J. C., Browne, D. L., and Ley, S. V. and was published in the Chemical Society Review in 2013. For example, a more contemporary example may be found in Newton et al. (2014) in Angew. Chem., Int. Ed. 53, 4915. Other relevant works include Carter et al., Pearson et al., de C Alves et al., Lange et al., Thansandote and Ley.

A paper titled "Continuous Manufacturing in the Pharmaceutical Industry" was published in the "Journal of Medical Chemistry 2012, 55, 4062" by Malet-Sanz and Susanne, which is referenced as (3). (b) In the

publication "Org. Process Res. Dev. 2013, 17, 1472," Poechlauer, Colberg, Fisher, Jansen, Johnson, Koenig, Lawler, Laporte, Manley, Martin, and O'Kearney-McMullan were all listed as authors. This sentence is copyrighted from an article published in the journal Organised Process Research and Development in 2011. It was written by a group of authors including Jimenez-Gonzalez, C., 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., and Manley, J. (d) An extensive range of pharmaceutical-related subjects are covered in this 2015 Journal of Pharmaceutical Science paper by Baxendale et al.

(a) A work with the DOI 52, 12359 was published in the 2013 edition of Angew. Chem. by Mascia, Heider, Zhang, Lakerveld, Benyahia, Barton, Braatz, Cooney, Evans, Myerson, and Trout. (a) The name and affiliation of several authors are listed in the publication "Org. Process Res. Dev. 2014, 18, 402," including Heider, Born, Basak, Benyahia, Lakerveld, Zhang, Hogan, Buchbinder, Wolfe, Mascia, Evans, Jamison, and Jensen.
(a) In the "Annals of Chemical Engineering," International Edition 2014, 53, 5750, Rodrigues, T., Schneider, P., and Schneider, G. wrote the paper. b) In the Journal of the National Chemistry, Elvira, K. S., Solvas, X. C., Wootton, R. C. R., and deMello, A. published an article in 2013 (3, 905).
6. (a) Organic Process Research and Development cited in Plouffe and Macchi (2014), 18, 1286. Published in 2013 by Springer, "Green Chemistry" by S. G. Newman and K. F. Jensen, page 15, 1456. In 2011, Wegner, Ceylan, and Kirschning published an article in Chem. Commun., 47, 4583.
Wu, H.; Khan, M. A.; Hussain, A. S. 2007, Chemical Engineering Communications 194, 760.
Article cited as "Organised Process Research and Development" by Anderson (2012), page(s) 1528–1569.
Hessel, V., Kralisch, D., Kockmann, N., Noel, T., and Wang, Q. published a paper in ChemSusChem 2013, 6, 746. The authors of the article "Adv. Synth. Catal. 2012, 354, 17" were Kirschning, Wegner, and Ceylan.
Article 54, 6688 was referenced by Gutmann, Cantillo, and Kappe in 2015 in the International Edition of the Journal of Chemical Engineering.
Published in Nature 2015, volume 520, page 329.
Anastas, P. T.'s The Green Chemistry Textbook, written by Tsubogo, Oyamada, and Kobayashi, was published in 2004 in New York by Oxford University Press.

(13) Refer to: (a) Pinho, V. D.; Gutmann, B.; Kappe, C. O. RSC Adv. 2014, 4, 37419 for a few cases that aren't included in this study.
(b) In the Organ. Process Res. Dev. 2014 article, LaPorte et al. cite Spangler, Hamedi, Lobben, Chan, Muslehiddinoglu, and Wang as sources: 18, 1492. c) Sterk, D.; Jukic, M.; Casar, Z. Organic Process Research and Development 2013, 17, 145.
(d) As published in the Chemical Communications article by Hopkin, Baxendale, and Ley (2010, 46, 2450). (e) In the article "Org. Biomol. Chem. 2010, 8, 1798," the authors Venturoni, Nikbin, Ley, and Baxendale discuss the topic. (f) In the article "Org. Process Res. Dev. 2010, 14, 432," Bedore, Zaborenko, Jensen, and Jamison were cited.
(g) Comm. — Eur. J. 2010, 16, 12342, by Qian, Z., Baxendale, I. R., and Ley, S. V.
Chemical Science 2013, 4, 2822 (Snead & Jamison, 2014).
The thieno[1,5]benzodiazepines were patented in 1986 by Chakrabarti and Tupper of Lilly Industries Ltd. (15).
(16) In the 2013 issue of the Angew. Chem. International, Hartwig, Ceylan, Kupracz, Coutable, and Kirschning published their findings in article 52, 9813.
(17) In an article published in 2008 in the International Edition of the Journal of Applied Chemistry, Ceylan et al.
(a) Kupracz and Kirschning (2013) published in Adv. Synth. Catal. 355, 3375.
(19) In the International Edition of Angew. Chem. published in 2011, Polyzos, A., O'Brien, M., Petersen, T. P., Baxendale, I. R., and Ley, S. V. reached a result of 50, 1190.
(20) Published in 2007 in Journal of the American Chemical Society, this article was written by Usutani, Tomida, Nagaki, Okamoto, Nokami, and Yoshida.
(21)Researchers Murray, Browne, Pastre, Butters, Guthrie, and Ley published a paper in Organic Process Research and Development in 2013 with the DOI: 17.1192.

(22)In a recent publication, Werner et al. provided an example in their article published in 2014 in the International Edition of the Journal of Chemical Education (Angew. Chem., 53, 1704). Chemical Science 2013, 4, 764 (Guetzoyan, L., Nikbin, N., Baxendale, I. R., & Ley, S. V.). Twenty-fourth, in Ley, S. V., Fitzpatrick, D. E., Myers, R. M., Battilocchio, C., and Ingham, R. J., 2015, 54, 2.
The authors of the article "Battilocchio et al. (2013) 19:7917" are Battiloco, Deadman, Nikbin, Kitching, Baxendale, and Ley.
Lange et al. (2011) published a paper in the Journal of Chemical Science with the DOI 2, 765.
Huisgen, R., 1961, Proc. Chem. Soc. 357.
The authors of the article "Org. Process Res. Dev. 2014, 18, 1567" are Zhang, P., Russell, M. G., and Jamison, T. F.
Leśvesque and Seeberger published an article in Angew. Chem., International Edition, 2012, 51, 1706.
(30) As published in the 2014 issue of Chem. Commun., the authors Gilmore, Kopetzki, Lee, Horvath, McQuade, Seidel-Morgenstern, and Seeberger discuss the topic in length.

(31) Check out this article published in 2015 by Poh, J.-S.; Tran, D. N.; Battilocchio, C.; Hawkins, J. M.; and Ley, S. V. for some instances of continuous flow synthetic techniques.
(b) As published in the European Journal of Chemistry in 2015, Fabry, Ronge, and Rueping were the authors of the article with the DOI name 21, 5350. (c) In the article "Chem. Sci. 2015, 6, 1120," the authors Tran, Battilocchio, Lou, Hawkins, and Ley discuss the work of their colleagues. (d) In the European Journal of Organic Chemistry (2015), Vukelic et al. published a paper with the DOI: 2015, 3036. The authors of the article "Org. Biomol. Chem. 2015, 13, 7633" are Alves, L. C., Desidera, A. L., de Oliveira, K. T., Newton, S., Ley, S. V., and Brocksom, T. J. (f) Britton et al. (2015) published in the Chem. — Eur. J. 21, 10660. (g) In an article published in 2015 in Organic Letters, Gauthier, D. R., Jr., Sherry, B. D., Cao, Y., Journet, M., Humphrey, G., Itoh, T., Mangion, I., and Tschaen, D. M. discuss many topics. (h) “RSC Adv. 2015, 5, 1268” by Viviano, Milite, Rescigno, Castellano, and Sbardella. , in Souto, J. A., Stockman, R. A., and Ley, S. V., et al., Organic Biomol. Chemistry 2015, 13, 3871. [j] In RSC Advances 2015, 5, 58798, He, W., Fang, Z., Yang, Z., Ji, D., and Guo, K. "Journal of Organic Chemistry" from 2015, volume 80, issue 4590, authored by Salvador, Pieber, Neu, Torvisco, Andrade, and Kappe. (32), Flow by Martin, A., Siamaki, A., Belecki, K., and Gupton, B. J. Chemistry 2015, 5, 145. (33).(a) In a 1993 article published in the Journal of Medical Chemistry, Ries et al. (36, 4040) discuss several compounds that have been found in medicinal chemistry. (b) The authors of the article "Org. Process Res. Dev. 2007, 11, 81" are Reddy, K. S., Srinivasan, N., Reddy, C. R., Kolla, N., Anjaneyulu, Y., Venkatraman, S., Bhattacharya, A., and Mathad, V. T.
the work of Gottessein and Knauber, L. J., Organ. Chem. 2008, 73, 8631.
(d) Beilstein, Kumar, Ghosh, and Mehta Organometallic Chemistry 2010, 6, 25.
The authors of the article "Org. Process Res. Dev. 2015, 19, 551" are Pellegatti and Sedelmeier.
The authors of the article are: Alfonsi, K., Colberg, J., Dunn, P. J., Fevig, T., Jennings, S., Johnson, T. A., Kleine, H. P., Knight, C., Nagy, M. A., Perry, D. A., and Stefaniak, M. Green. Chemistry 2008, 10, 31.
In their 2015 article published in Organic Letters, Lau et al. (36) cite Galvań, A., Merchant, R. R., Battilocchio, C., Souto, J. A., Berry, M. B., and Ley, S. V.(37) Research in Organic Processes, published in 2014, 18, 1560 by Ouchi, Battilocchio, Hawkins, and Ley.38) Snead and Jamison's 2015 article in the International Edition of Angew. Chem., volume 54, page 983(39) Bogdan et al. published an article in 2009 with the DOI 48, 8547 in the International Edition of the Journal of Chemical Engineering.. forty(a) Pierce et al. (1998) (Journal of Organic Chemistry, 63, 8536)The authors of the publication "Synth. Commun. 1997, 27, 4373" are Radesca, Lo, Moore, and Pierce.This sentence is paraphrased

from a publication by Dai, Long, Luo, Kulesza, Reichwagen, and Guo (Lonza Ltd.) in 41.Method for cyclization-based efavirenz synthesisForeign application WO2012097510, 2012 PCTAngew. Chem., International Edition 2015, 54, 4945 (42), Correia, C. A., Gilmore, K., McQuade, D. T., and Seeberger, P. H.(43) Ghislieri, D.; Gilmore, K.; Seeberger, P. H. Angew. Chem., Int. Ed. 2015, 54, 678.(44) In Comprehensive Asymmetric Catalysis, Supplement 1, edited by Jacobsen, Pfaltz, and Yamamoto, published by Springer in 2004 in New York, it is mentioned by Okhuma and Noyori.(b) Trindade and Afonso (2009) published in the Chemical Review, volume 109, page 3401.Read (a) Tsubogo, T., Ishiwata, T., and Kobayashi, S. Angew. Chem., Int. Ed. 2013, 52, 6590 for a few reviews on continuous flow stereoselective catalytic methods (45).(b) ACS Catal. 2013, 3, 928 (Zhao, D.; Ding, K.).c) In their 2009 article "Beilstein Journal of Organic Chemistry," Mak, X. Y., Laurino, P., and Seeberger, P. H. published at 10.3762/bjoc.5.19, the authors acknowledge their work.The authors Andrade, Kroutil, and Jamison published an article in 2014 describing continuous flow enzymatic Organic Letters, 16, 6092, article d, discusses catalysis."Org. Lett. 2014, 16, 3496," published not long ago by Hashimoto, K., Kumagai, N., and Shibasaki, M., presents a few examples of chiral organometallic compounds in flow chemistry.(f) The following was co-authored by "Gree" Castano, Gallo, Cole-Hamilton, Dal Santo, Psaro, and Caselli: the 2014 issue of the journal "Nature Chemistry" (16.3202).Methods for Enantioselective Organocatalysis (46a)Published by Wiley VCH in 2007, Reactions and Experimental Procedures is edited by Dalko, P. I.(a) Organocatalysis of Inverse Forces [List, B. ed.], Materials in Current Chemistry, Vol. 291, Springer, New York, 2009, p.

A few recent research on continuous flow stereoselective organocatalysis may be found in (a) Atodiresei, I.; Vila, C.; Rueping, M. ACS Catal. 2015, 5, 1972 (47). The paper "Current Organocatalysis 2015, 2, 79" was authored by Puglisi, Benaglia, Porta, and Coccia. (c) In a 2015 article published in Chem. Commun., Finelli, F. G., Miranda, L. S. M., and de Souza, R. O. M. A. discussed in ChemCatChem 2014, 6, 3286 (48). The authors of the article "Green Chemistry 2015, 17, 2012−2026" are Cantillo and Kappe. The authors of the article are Gursel, noel, wang, and hessel.

a score of four("Adv. Synth. Catal. 2015, 357, 1093" was written by Munirathinam, Huskens, and Verboom). (b) Rodríguez-Escrich and Pericàs are referenced in the paper "Eur. J. Org. Chem. 2015, 6, 1173." Copyright © 2013 "Green Chemistry" by Puglisi, Benaglia, and Chiroli, 15, 1790. For further details, see reference 45a. (50)(a) Carroccia, Musio, Degennaro, Romanazzi, and Luisi (Papers 3, 29) published a paper in the Journal of Flow Chemistry in 2013. (b) The compound is discussed in the published work "Beilstein J. Org. Chem. 2011, 7, 1671" by Opalka, S. M., Longstreet, A. R., and McQuade, D. T. in Angew. Chem., International Edition 2009, 48, 2699 c) "Beilstein Journal of Organic Chemistry 2013, 9: 2457" (a) by Sugiono and Rueping; (b) by Odedra and Seeberger (51). (b) The source "Beilstein J. Org. Chem. 2012, 8, 300" cites work by Rueping, Bootwicha, and Sugiono (2012). includes works by S. Fritzsche, S. Ohla, P. Glaser, D. Giera, M. Sickert, C. Schneider, and J. Belder; published in Angew. Chem., International Edition 2011, 50, 9467. Rossi, Benaglia, Puglisi, De Filippo, and Maggini came up with the idea for the paper "J. Flow Chem. 2015, 5, 17" (52). (53) No. 7, 1395, Symmetry 2015 Organic Letters, issue 9, pages 413, was published by Xie et al. (2007) with co-authors Yue, Du, Zhu, Deng, and Chen and includes the following authors: Porta, R., Benaglia, M., Coccia, F., Rossi, S., and Puglisi, A.

(55)For a few recent reviews of photochemistry in flow, see (a) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noel, T. Chem. - Eur. J. 2014, 20, 10562. (b) Gilmore and Seeberger made an acknowledgment in Chem. Rec. 2014, 14, 410.

published in 2014 by Booker-Milburn et al. in the Chemical and Engineering Journal, volume 20, page 15226-2.
(d) The subject is discussed by Garlets, Nguyen, and Stephenson in the paper "Isr. J. Chem. 2014, 54, 351.
Organic Letters (2012), 14, 2658, the paper by Neumann and Zeitler (ref. 56).
(57)(a) In 2000, the authors Hafez, A. M., Taggi, A. E., Wack, H., Drury, W. J., III, and Lectka published an article in Organic Letters, 2, 3963.
(b) In 2001, the authors Hafez, A. M., Taggi, A. E., Dudding, T., and Lectka published an article in the Journal of the American Chemical Society, volume 123, pages 10853.
Organic Letters published a paper by Chiroli, Benaglia, Cozzi, Puglisi, Annunziata, and Celentano in 2013 with the DOI number 15, 3590.
Article published in 2014 in the Journal of Industrial Chemistry, volume 54, page 381. (59) In their 60-page study, Porta, Benaglia, Chiroli, Coccia, and Puglisi examined... Mandoli, A., Puglisi, A., Porta, R., Jumde, R. P., and Chiroli, V. wrote the article "Green Chemistry" (2014), 16, 2798.
The number 61(a) Viklund, Svec, Frechet, and Irgum brought up the topic in a 1996 Chemistry of Materials paper. In 2000, Peters, E. C., Svec, F., and Frechet, J. M. published an article in Adv. Mater. with the same title.The authors of the paper "ChemSusChem 2014, 7, 3534" are Cozzi, Porta, Gualandi, Puglisi, Mandoli, and Benaglia.The authors Cozzi, Benfatti, and Zoli were included in the 2009 edition of Angew. Chem. (International Edition), specifically on pages 1313–1314.(b) In the Chemical-Asian Journal, 2047, Benfatti, F., Benedetto, E., and Cozzi, P. G. published in 2010 on page 5.Sixty-four(a) According to Duan and Li (2014) in Catal. Sci. Technol., 4, 311.(b)Alkaloids in Synthesis and Catalysis from Cinchona by Song, C. E. Wiley-VCH, Weinheim, 2009; Melchiorre, P. Chemical Engineering: International Edition 2012, 51, 9748c)Our research has only found one publication that discusses the use of a supported amino-Cinchona derivative to improve the efficiency of aldol reactions in water, and this is limited to batch methods (65)a) Zhou, J., Wan, J., Ma, X., and Wang, W. published in the Journal of Organic Biomolecular Chemistry (2012), volume 10, page 4179.For further information, see b) Wang, Ma, Wan, Cao, and Tang (2012) 40, 5715.Organic Letters, Dalton Trans. 2007, 9, 599 (66(McCooey and Connon, 2011)."Adv. Synth. Catal. 2015, 357, 377" was written by Porta, Benaglia, Coccia, Cozzi, and Puglisi.(68)Undisclosed discovery by Porta, R., Benaglia, M., and Puglisi, A.The authors of the 2015 publication in Organic Biomolecular Chemistry were J. Izquierdo, C. Ayats, A. H. Henseler, and M. A. Pericas."Chem. - Eur. J. 2014, 20, 2367" was penned by Osorio-Planes, L., Rodríguez-Escrich, C., and Pericaș, M. A..