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Flow Chemistry and Their Applications: Enhancing Efficiency and Safety in Chemical Processes

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ABSTRACT

This article examines how flow chemistry is employed in the realm of pharmaceutical research and development, focusing on continuous flow processes found in patent literature between 2016 and 2017. Flow chemistry offers advantages like improved yield and reproducibility, making it suitable for drug synthesis. Notable applications include the synthesis of Vaborbactam, Diphenhydramine hydrochloride, Olanzapine, amitriptyline hydrochloride, Brivaracetam, Grossamide and Boscalid, showcasing increased productivity and diastereoselectivity. Challenges in implementing flow chemistry, technological advancements, and its potential in pharmaceutical manufacturing are discussed. Additionally, chosen instances of uninterrupted manufacturing of Creating Active Pharmaceutical Ingredients (APIs) through ongoing flow procedures and agrochemicals are presented, highlighting the efficiency and sustainability of flow chemistry in complex molecule synthesis. These examples demonstrate its potential for efficient and eco-friendly drug and agrochemical development.

KEYWORDS: *Flow chemistry, Drug development, Continuous flow processes, Sustainability*

I. INTRODUCTION

In the past century, tremendous advancements have been made in chemical synthesis, granting scientists the remarkable capability to create chemical entities that were once unimaginable. Despite these achievements, the efficiency and sustainability of synthetic transformations continue to pose challenges in many processes. These constraints arise due to considerable waste generation, a substantial carbon footprint, and the requisite for adept personnel to manage arduous and time-intensive responsibilities. The chemical reactions themselves, along with their optimization, purification, and analysis, can be arduous and monotonous endeavors. [1]

The increasing acknowledgment and adoption of emerging technologies, including Combinatorial Chemistry, Organic Synthesis Enhanced by Microwaves (OSEM), High-Throughput Screening (HTS), and Computational Chemistry stand as prominent methodologies in the domain, have revolutionized the production and evaluation of fine chemicals. These advancements have paved the way for more efficient chemical research practices, supplanting traditional working methods. Consequently, researchers now have access to a broader array of products during the initial phases of pharmaceutical development, fostering innovation and accelerating progress in the field. [2]

Flow chemistry presents an innovative technology offering swifter, more straightforward, and consistently replicable routes for generating top-notch end products, thus emerging as a promising avenue for synthesis. Though continuous chemical processes have been well-established in the highly efficient petrochemical sector for a long time, encompassing everything from crude oil processing to refining and large-scale product manufacturing through continuous flow reactors and separators, implementing similar strategies in smaller-scale synthetic areas faces unique challenges. These difficulties are faced by industries dealing with active medicinal components, agrochemicals, and chemical intermediates, and similar realms often possess infrastructures and know-how tailored for batch production, which subsequently gives rise to challenges when integrating continuous flow methodologies. However, recognizing the potential benefits, efforts are being made to address these challenges and adapt the technology to suit the specific needs of these industries. [3]

Over the last ten years, multiple research papers have emphasized adaptability and obstacles linked with flow chemical processes and their incorporation with complementary methodologies.

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[3a, 4] Particularly, recent assessments have investigated the utilization of flow chemistry in various domains, such as the synthesis of natural products [5] ,pharmaceuticals [5b, 6] , and multi-step reactions. [6h, 7] Furthermore, extensive discussions have taken place regarding the benefits of flow chemistry in promoting green chemistry advancements [8] and the construction of reactor configurations [7c, 9] Nonetheless, a noticeable void prevails in the academic discourse when it comes to an all-encompassing exploration exclusively centered on the flow chemistry-driven synthesis of heterocycles, with a specific spotlight on the intricate realm of ring formation reactions. Heterocycles, holding a pivotal position in the domain of Organic Chemistry, remain a subject of paramount significance. However, the most recent scholarly work devoted to this realm traces back to the year 2011. [10] Although contemporary reviews do touch upon diverse facets of this emerging methodology, their focus predominantly gravitates towards other vital aspects, such as the merits and drawbacks inherent in its evolution. [11]

This, in turn, ushers in a pressing urgency for a dedicated review that not only delves into the synthesis of heterocycles through the prism of flow chemistry but also accentuates the most current breakthroughs, challenges, and latent opportunities within this dynamic arena. In the past, organic synthesis primarily relied on batch processes, involving round-bottomed flasks, test tubes, or sealed containers were commonly used. Nevertheless, in recent times, there has been a rising fascination among synthetic organic chemists regarding the application of ongoing flow methods. [12] Initially, these continuous flow processes found their primary use in the petrochemical and bulk chemicals domains, where specialized continuous plants provided substantial economic benefits. More recently, there's been a surge in utilizing continuous flow systems for producing refined chemicals, including natural products [13] and Active Pharmaceutical Ingredients (APIs), particularly within academic research contexts. Although the pharmaceutical sector primarily relies on versatile batch or semi-batch reactors, there's a noticeable growing interest in adopting continuous flow manufacturing techniques for APIs. [14]

ADVANTAGES

- Enables the performance of complex chemistry that is not suitable for batch scaling, including electrochemistry, microwave heating, and photochemistry.
- Enables exploration of extreme conditions, encompassing elevated and reduced temperatures as well as high pressures.
- Scalability is simplified due to consistent maintenance of mixing and heat transfer as scale increases.
- Improves safety by producing minimal quantities of unstable intermediates at any point, with the elevated surface area to volume ratio enabling precise management of exothermic reactions.
- Yields operational advantages such as elevated process efficacy, a minimized equipment footprint, compatibility with automated workflows, and seamless integration with process analytical technology. These facets collectively contribute to cost alleviation and an elevated level of reproducibility.

CHALLENGES

- Chemists are typically trained in batch chemistry, and most laboratories are set up for conducting experiments in batch mode.
- The current worldwide infrastructure and knowledge foundation predominantly favor batch chemistry, resulting in limited resources for continuous processing.
- Uncertainty regarding the implementation of Good Manufacturing Practices (GMP) in continuous processing, along with concerns about regulatory authorities' acceptance of flow chemistry.
- Handling of slurries and heterogeneous reactions in a continuous flow system.
- Fusing flow chemistry with ongoing work-up and isolation procedures, amplifying ecological advantages while curbing the overall environmental impact.

Flow Chemistry's Application to Pharmaceutical Research and Development

For researchers engaged in the field of pharmaceutical and fine chemicals, patent documents play a central role in disseminating scientific knowledge. This encompasses intricate pathways for the synthesis and design of complex molecules of pharmaceutical significance. This excerpt represents a segment of a series of evaluations designed to present innovative and practical chemistry drawn from recent patents and patent applications, some of which may not have been discussed in journal publications.[15] This analysis delves into the routes leading to approved drugs that involve at least one continuous flow step, as revealed in the patent records from 2016 to 2017. It's important to emphasize that the manufacturing processes for these

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drugs have not been revealed by the patent applicants. Consequently, manufacturing or intended for use in the future. We refrain from making assumptions about whether the flow chemical processes investigated in this study are now used for commercial purposes.

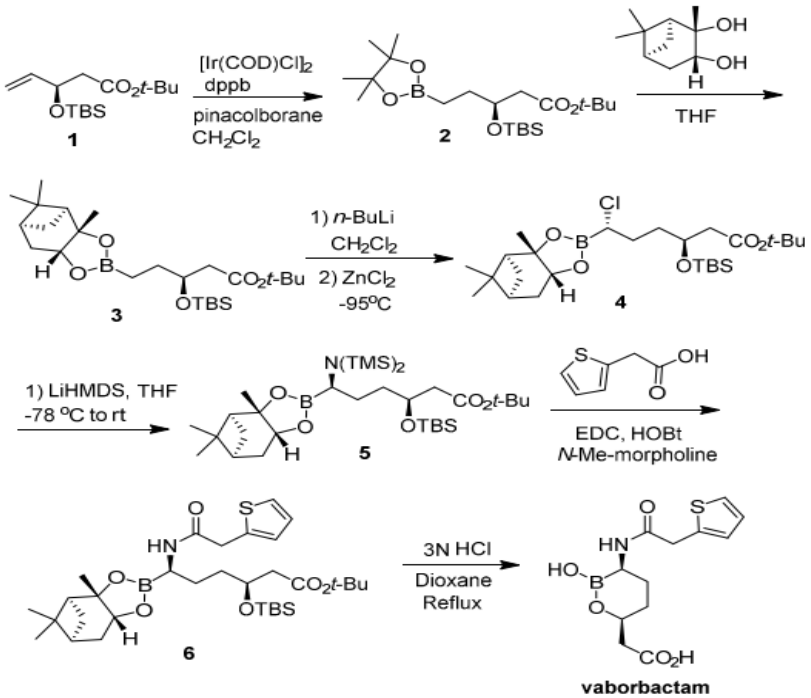
Although the petrochemical and bulk chemical industries have used flow chemistry and continuous processing extensively for a substantial amount of time, these techniques have also found their way into various stages of drug formulation. Recently, a surge of interest has been observed in the implementation of continuous processing technology in the pharmaceutical realm. On the adjacent side, Table 1 outlines the complexities associated with integrating flow chemistry, encompassing challenges tied to equipment, skill development, and adherence to regulations. Nevertheless, propelled by technological progress and a growing cohort of flow chemistry-savvy researchers, the advantages of this methodology are gaining traction. Continuous processing is being encouraged in the synthesis of active pharmaceutical ingredients (APIs) as a result of this trend. [16]

1. VABORBACTAM

Flow chemistry presents numerous benefits, such as enhanced diastereoselectivity, purity, reproducibility, yield, and heightened productivity. An illustrative instance showcasing the effectiveness of flow chemistry can be observed in the creation of Vabomere. This complex combination involves meropenem, an antibiotic from the carbapenem class, along with vaborbactam, a cyclic boronic acid beta-lactamase inhibitor. The FDA provided its approval for Vabomere on August 29, 2017, representing a significant advancement in combating intricate urinary tract infections caused by bacteria.

The path undertaken in Medicinal Chemistry to create vaborbactam involved a series of six steps, resulting in a combined yield of 30% (illustrated in Scheme 1) [17].

The synthetic process was initiated by generating TBS-protected β-hydroxy ester 1 through the utilization of lipase-catalyzed resolution, targeting the separation of the corresponding racemate. Then, using pinacoldiborane as a catalyst, iridium-catalyzed hydroboration created boronic ester (2), which underwent additional modifications to create pinanediol boronate ester. The subsequent step involved Matteson homologation of compound (3), conducted at temperatures ranging from -95 to -100 oC, introduced a -CHCl group stereoselectively, resulting in an 85/15 mixture of



Scheme 1. *Pathway for Creating Vaborbactam*

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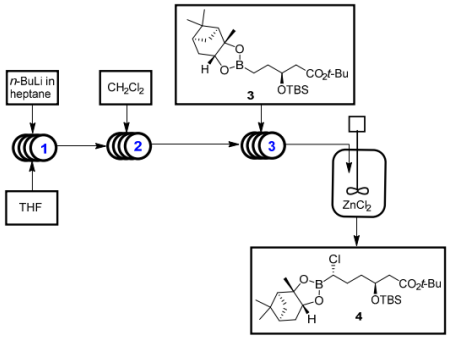
Distinct diastereomers emerged from the process. The introduction of stereo-specific nucleophilic displacement, utilizing LiHMDS, transformed the chloride, giving rise to silyl amine (5). This compound was subsequently amalgamated involving 2-thiopheneacetic acid, directed by EDC/HOBt, leading to the creation of compound (6). By applying HCl, the silyl protection was removed, retaining the diastereomeric ratio at 85/15 and yielding the cyclic boronate. Ultimately, the pure form of vaborbactam was acquired through crystallization within a dual-phase water/EtOAc system.

The employment of a continuous flow mode for the Matteson homologation stage underwent evaluation while vaborbactam was being developed. The intricacies of this continuous flow procedure are expounded upon in a patent application dated 2016, attributed to Rempex. [18][19]

The flow arrangement for executing Matteson homologation process is shown in Scheme 2 [18]. In the initial reactor (#1), a blend of n-BuLi in heptane was mingled with THF and chilled to -60 °C. The incorporation of THF as a co-solvent was imperative to avert the precipitation of n-BuLi at subzero temperatures. The output from reactor #1 was then guided into reactor #2, where a solution containing 39% dichloromethane in THF was introduced, facilitating the generation of LiCHCl2. Subsequently, the effluent from reactor #2 was blended in reactor #3 with a solution encompassing 29% of compound (3), utilizing a 1:10 ratio of heptane to THF. The resultant blend was promptly quenched into a solution maintained at -20 °C, consisting of 0.7 M ZnCl2 in THF. Although the quenching process involving ZnCl2 could also be conducted in a continuous flow manner, the outcomes in terms of yield were comparatively inferior and more variable than those achieved through batch processing.



Scheme 2. *Flow Chemistry for Vaborbactam Matteson Homologation Diagram*

The separation procedure was conducted using a batch strategy. After washing the quench solution sequentially with 1 M aqueous HCl, bicarbonate, and water. The concentrated organic layer was then immediately used for the following phase. A total of twelve sets adhering to the principles of Good Manufacturing Practice (GMP) were executed, resulting in an average yield of 89%. These sets collectively produced 880 kg of compound (4). [18]

Along with significant efficiency gains over batch mode, the continuous process also showed superior diastereoselectivity (95:5 versus 85:15), yield (91% versus 75%), and repeatability (91% versus 75%). While an explicit explanation for the increased selectivity in the flow mode was not provided, it can be reasonably inferred that enhanced mixing and temperature control played a role in achieving this result.

II. BRIVARACETAM

Incorporating flow chemistry techniques into the creation of brivaracetam provides advantages such as heightened throughput, a more compact operational setup, and diminished waste generation. Brivaracetam, known commercially as Briviact, gained authorization in Europe and the United States during the initial months of 2016. It serves as adjunct therapy for individuals with epilepsy, specifically targeting the management of partial-onset seizures.

A method for generating brivaracetam, elaborated upon in patent filings by UCB, is introduced through Scheme 3. [20] The synthetic process initiates with the condensation of valeraldehyde (7) and glyoxylic acid (8), with morpholine as the catalyst in a two-phase combination of water and heptanes. This results in the creation of furanone (10) with a yield of 96% after undergoing workup involving diisopropyl ether and concentration into liquid form. The subsequent phase entails a sequence of three steps carried out within a one-pot setup for reductive amination involving (S)-2-aminobutanamide (11).

The initial reaction generates an imine from 10 and 11 in 2-propanol (2-PrOH) at 5 oC. Subsequent to this, sodium borohydride (NaBH4) and ammonia are introduced to effectuate the reduction of the resulting imine. Following this, acetic acid (HOAc) is incorporated, and the solution is gently heated to 50°C for a duration of 16 hours, resulting in the formation of lactam (12). A mixture of 2-PrOAc and heptanes is then used to extract this lactam through crystallization, yielding an overall

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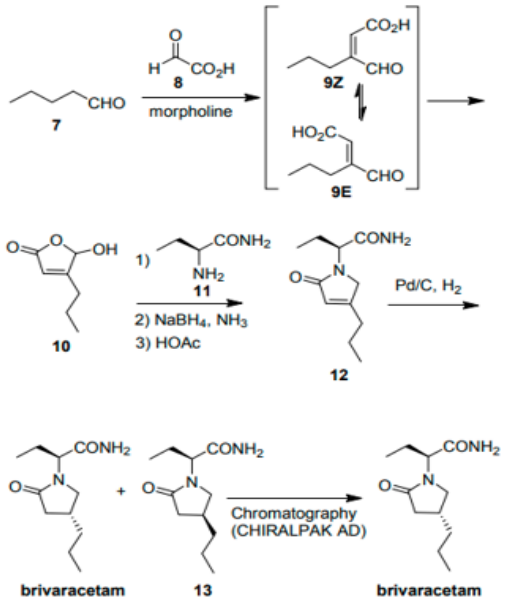
product of 88%. At the very end of the chemical phase, a palladium-on-carbon (Pd/C) catalyst is employed for the hydrogenation of the double bond, producing an almost equimolar combination of brivaracetam and its conjugated variant. its



Scheme 3. *Route of Brivaracetam*

diastereomer (13). The diastereomers are subsequently separated through multi-column continuous (MCC) chromatography and further crystallization from 2-PrOAc.

UCB, the attainment of an 80:20 combination of diastereomers in the hydrogenation phase using Pd/C is revealed in a patent submission. Citric acid, Pt/C with citric acid, or formic acid are all present during this procedure. [21] Evolving from this discovery, UCB has currently integrated an approach that merges continuous flow processing for all three stages with intermittent batchwise workups. [22a]

In the first phase of the continuous flow procedure, valeraldehyde (7) (in a quantity of 1.2 equivalents) and glyoxylic acid (8) (in a quantity of 1.0 equivalent) were seamlessly injected into a plug flow reactor operating at a temperature of 180°C, while sustaining a residence time of 5 minutes. Remarkably, this phase unfolded without the requirement for any catalyst or solvent. The recovery of unprocessed furanone (10) necessitated a batch quenching operation, involving the use of water, n-heptane, and 2-PrOAc. This yielded an 88% furanone (10) yield, along with 5-9% of 9E.

Advancing to the ensuing stage, the introduction of (S)-2-aminobutanamide (11) (equivalent to 1.0) in EtOH and furanone (10) (equivalent to 1.2) took place individually within plug flow reactor #1. The reactor functioned at a temperature of 40°C and maintained a residence time of 5 minutes, as illustrated in Scheme 4. After that, a continuous stirred tank reactor (CSTR) received the output from this reactor, where a continuous supply of NaBH4 (equivalent to 0.4) and ammonia was upheld, with a residence time of 10 minutes and a temperature of 40°C. Subsequently, the product from the CSTR was combined with HOAc (equivalent to 2.55) within a third plug flow reactor, maintaining a temperature of 105°C and a residence time of 9 minutes. This procedure yielded a 96% lactam (12) yield prior to the subsequent steps. Although specific purification process details were not provided, it is suggested that this was undertaken through batch processing with extractive workup [22a].

In the third step of the process, the hydrogenation was conducted using citric acid, resulting in improved diastereoselectivity. The hydrogenation process took place through a series of four reactors, all ingeniously designed as continuous stirred tank reactors (CSTR). To avoid any catalyst transfer, these reactors had a Rushton self-gas-inducing agitator and a filtering outlet. According to the requirements of the process, the temperature and catalyst dosage were accurately adjusted for each reactor. A mixture of 10% citric acid and 5% Pd/C suspended in water was heated to 60°C in the first reactor, subsequently subjected to a pressure of 20 bar of H2. In a seamless stream, a 20% aqueous solution of lactam (12) accompanied by 10% citric acid was mixed into reactor #1. Following a span of 40 minutes, the reactor achieved a stable equilibrium with 50% conversion and an 80/20 diastereomeric ratio in the resulting mixture. This combined solution was subsequently directed into reactor #2, where a similar catalyst-citric acid combination functioned under H2 pressure, aligning with the incoming stream of initial constituents.

Upon reaching the fourth reactor, the targeted conversion rate reached an impressive 99%.

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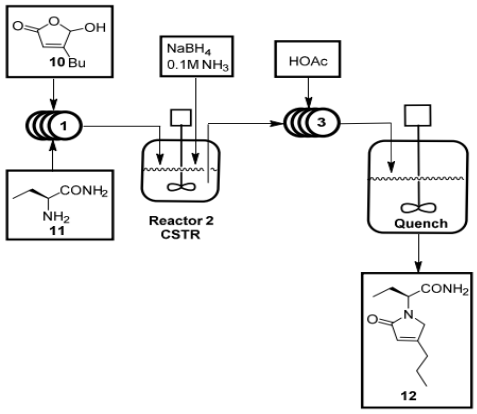

Scheme 4. *Ongoing Flow Setup for the Reductive Amination Step in the Synthesis of Brivaracetam*

maintaining the established 80/20 ratio between diastereomers. Importantly, the intricate procedures for working up and isolating the crude product were omitted from disclosure. [22a]

To segregate the diastereomers with their established 80/20 proportion, a stationary phase recognized as CHIRALPAK AD was effectively employed, partnered with a mixture of n-heptane and ethanol (EtOH) in a balanced 45/55 ratio, and operating at a stable temperature of 25°C. The ensuing refined brivaracetam underwent a subsequent recrystallization process within 2-PrOAc. It's noteworthy to acknowledge the collaborative effort between UCB and Novasep during the 1990s, which pioneered the pioneering utilization of continuous flow chromatography, particularly employing simulated moving bed chromatography, in the production of Keppra. This pivotal collaboration stands as an early exemplar of continuous processing within the sphere of active pharmaceutical ingredient (API) manufacture. [22b]

SEQUENTIAL PRODUCTION OF ACTIVE PHARMACEUTICAL INGREDIENTS THROUGH FLOW-BASED APPROACHES

Within this segment, we shall examine specific instances extracted from the literature of 2013 and 2014, showcasing the ongoing flow production of Active Pharmaceutical Ingredients (APIs) [23]. Our emphasis will be on the notable advancements accomplished in each case, alongside the primary synthetic pathway employed to attain the ultimate target molecule.

III. DIPHENHYDRAMINE HYDROCHLORIDE

Diphenhydramine hydrochloride acts as the API in various widely utilized medications like Benadryl, Zzzquil, Tylenol PM, and Unisom.

The global demand for this substance surpasses 100 tons annually. In 2013, Jamison and co-researchers established a continuous flow method for manufacturing diphenhydramine hydrochloride. Their aim was to reduce waste, simplify purification steps, and cut down production time in comparison to existing batch synthetic pathways (Scheme 5). [24] After achieving the optimized conditions, a direct mixture of chlorodiphenylmethane (1) and dimethylethanolamine (2) was fed into a 720 µL PFA tube reactor with an inner diameter of 0.5 mm, operating at a temperature of 175°C and a residence time of 16 minutes. By conducting the reaction above the boiling point of compound (2) and without using solvents, a rapid reaction rate was achieved. The resultant product (3), acquired as a molten salt (above the salt's melting point), could be conveniently transported within the flow system—an approach not feasible on the same scale using traditional batch conditions.

Following reactor output, it was merged with preheated 3 M NaOH solution to counteract any ammonium salts. After the quenching phase, the neutralized tertiary amine was effectively isolated into hexanes using a membrane separator incorporated in the flow. The separated organic layer was subsequently treated with a 5 M HCl solution in iPrOH, leading to the precipitation of diphenhydramine hydrochloride (3). The complete yield of this ongoing flow procedure reached 90%, producing at a rate of 2.4 g/h.

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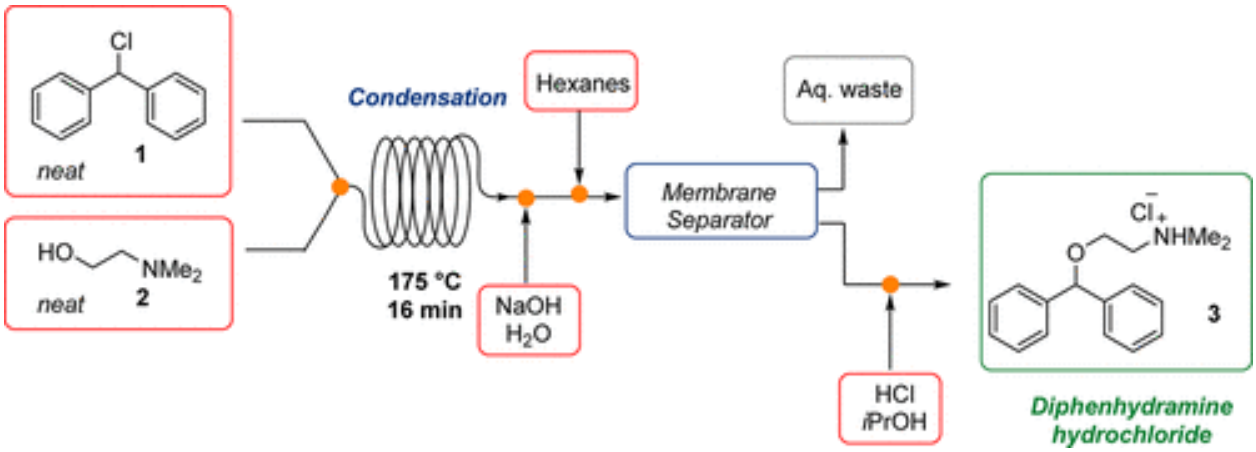

Scheme 5. *Continuous Flow Production of Diphenhydramine Hydrochloride*

In the realm of antipsychotic drugs, atypical medications offer an advantage over classical antipsychotics by causing fewer side effects.
like involuntary tremors, body stiffness, and extrapyramidal reactions. An example of a significant atypical antipsychotic is olanzapine (10), available as Zyprexa, and used for managing schizophrenia and bipolar disorders. [25]

IV. OLANZAPINE

In 2013, a team of researchers led by Kirschning introduced a sophisticated Continuous Flow Multistep Synthesis Method for Producing Olanzapine (10). They harnessed inductive heating (IH) as an advanced technology, which played a pivotal role in significantly reducing reaction durations and enhancing the overall process efficiency. [26] Inductive heating, a nonconventional heating technique, leverages the induction of an electromagnetic field (at medium or high frequency, depending on nanoparticle sizes) to rapidly heat magnetic nanoparticles, leading to swift temperature elevation. [27] The synthetic pathway, depicted in Scheme 6, commenced with the coupling of aryl iodide (4) and aminothiazole (5), utilizing Pd2dba3 as the catalyst and Xantphos as the ligand. This Buchwald-Hartwig coupling was executed within a PEEK reactor filled with 0.8 mm steel beads, applying inductive heating at 50 °C with a frequency of 15 kHz. AcOEt was chosen as the solvent due to its compatibility with subsequent reaction steps. After quenching with distilled H2O and in-line extraction utilizing a glass column, the crude mixture underwent passage through a silica cartridge to eliminate the Pd catalyst. Following this, the obtained nitroaromatic compound (6) underwent reduction using Et3SiH within a fixed-bed reactor equipped with a Pd/C catalyst at a temperature of 40 °C. This process yielded aniline (7) with an almost complete yield. Remarkably, the catalyst maintained its effectiveness for over 250 hours. Subsequently, the reactor output was combined with HCl (0.6 M methanol solution) and subjected to high-frequency heating (800 kHz) at 140 °C to facilitate acid-catalyzed cyclization, leading to the formation of product (8) with an impressive overall yield of 88%. Notably, this three-step sequence required no alteration of solvents, and the total reactor volume was approximately 8 mL.

The last phase encompassed the replacement of compound (8) with piperazine (9). The transformation occurred within a 3 mL PEEK reactor, employing MAGSILICA as an inductive substance and silica-supported Ti(OiPr)4 as a Lewis acid. Olanzapine (10) was attained with an 83% yield through inductive heating of the reactor at 85 °C using a medium frequency of 25 kHz.

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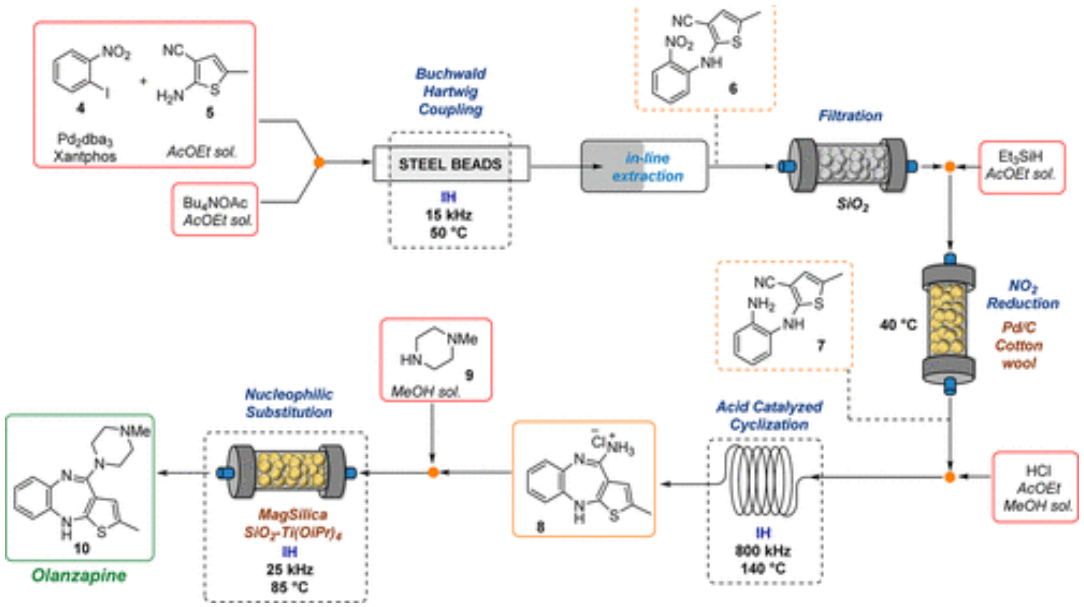

Scheme 6. *Continuous Flow Production of Olanzapine*

V. AMITRIPTYLINE HYDROCHLORIDE

Amitriptyline, categorized as a tricyclic antidepressant (TCA), is recognized for its ability to obstruct sodium, calcium, and potassium channels. Its applications encompass the treatment of a wide array of conditions, including migraines, tension headaches, anxiety episodes, and specific symptoms associated with schizophrenia. The conventional synthetic approaches for its production begin with the initiation of lithiated benzyl bromide (11) to synthesize dibenzosuberone (13) via Wurtz dimerization. Subsequently, A one-pot Parham cyclization utilizing CO2 as an electrophile is utilized. The generated ketone (13) subsequently reacts with Grignard reagent (14), and then water is eliminated, resulting in the formation of the ultimate active pharmaceutical ingredient (API) (16).

In 2013, Kirschning and Kupracz introduced an innovative continuous flow approach for the creation of Amitriptyline (16), adhering to the established synthetic pathway (Scheme 7). [28]

In comparison to the conventional batch procedure, the continuous multistep synthesis of compound (16) provides a number of advantages, especially when working with reagents in the gaseous phase (like CO2) and highly reactive intermediates (like aryl- and alkyllithium compounds). First, benzyl bromide (11) and nBuLi underwent lithiation in a steel reactor coil with an inner diameter of 1.0 mm and a volume of 0.5 mL at a temperature of -50 °C. The required aryl bromide (12) was produced in just 5 seconds with an outstanding yield of 79% after being quenched with MeOH.

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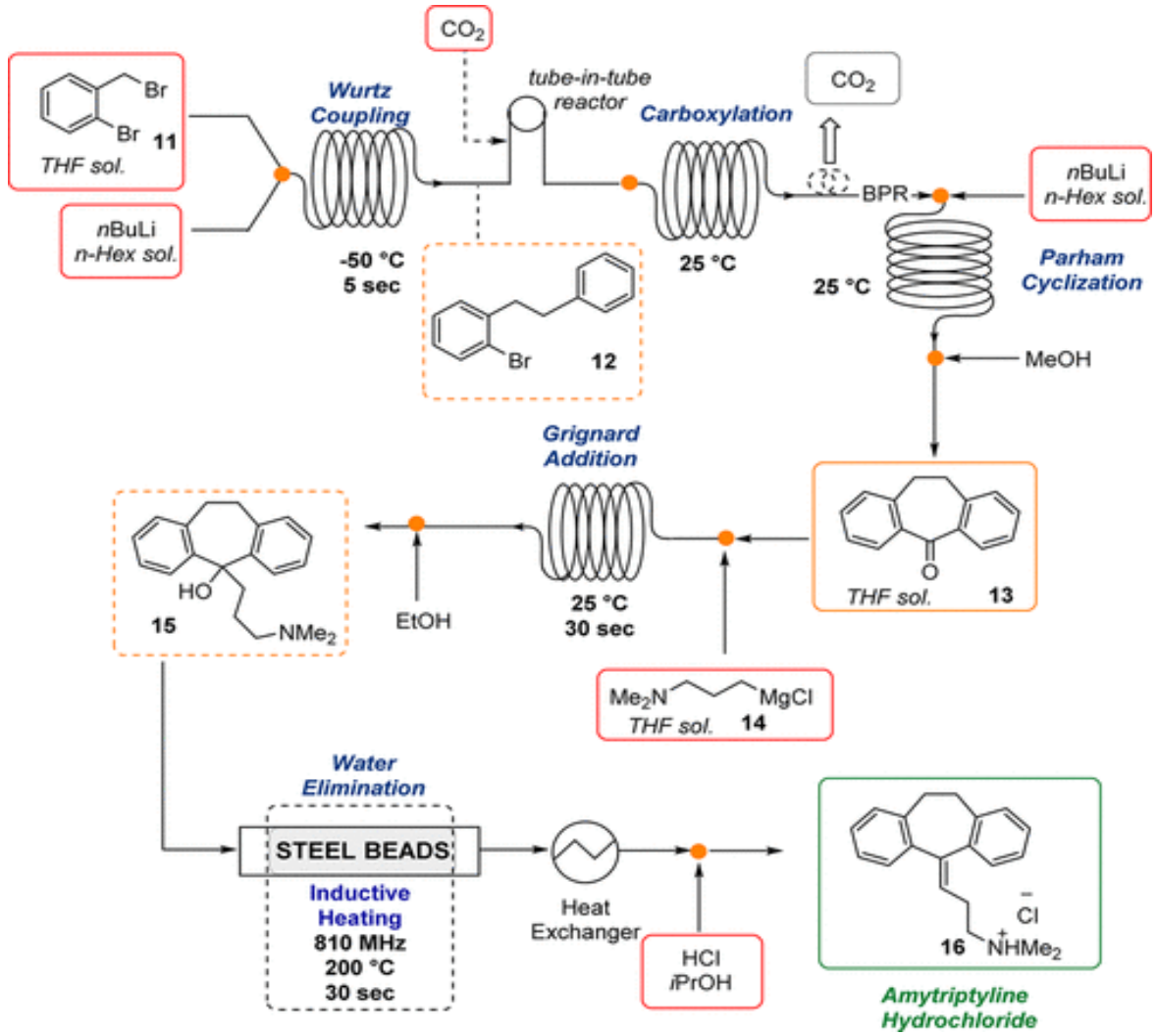

Scheme 7. *Continuous Flow production of Amytriptyline Hydrochloride*

After meticulously refining the initial Wurtz coupling conditions, the focus shifted to the continuous synthesis of ketone (13). Employing S. V. Ley's innovative tube-in-tube reactor technology, a direct infusion of CO2 was seamlessly integrated into the crude reactant stream. Carrying out the carboxylation process, a 0.5 mL PFA reactor coil, boasting an inner diameter of 0.8 mm, was employed. This operation was conducted at a stable temperature of 25°C. Post-gas elimination, the subsequent step involved a continuous infusion of nBuLi into the reaction blend. The ultimate cyclization step was executed utilizing a 0.5 mL PFA reactor coil, with an inner diameter of 0.8 mm, also maintained at 25°C. With the introduction of MeOH, the successful isolation of dibenzosuberone (13) ensued, yielding an impressive 76%. This remarkable outcome was achieved within an overarching residence time that spanned approximately 30 seconds.

In comparison to the corresponding batch synthesis of compound (13), which demanded a reaction duration of 2 hours at -100 °C and yielded a modest isolated yield of only 56%, the flow methodology displays heightened performance. After successfully completing the multistep flow synthesis to obtain pure ketone (13), it was dissolved in THF (tetrahydrofuran) and subjected to a reaction with Grignard reagent (14).

The reaction occurred within a 0.5 mL PFA (perfluoroalkoxy) reactor coil with an internal diameter of 1.0 mm, functioning at 25 °C and maintaining a residence time of around 30 seconds. Afterward, the unrefined reaction mixture underwent protonation using EtOH, leading to the development of carbinol (15). To remove water

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from the carbinol, inductive heating technology was applied. This involved placing a 0.3 mL cartridge steel reactor filled with steel beads, having an internal diameter of 0.8 mm, within a high-frequency field (810 Hz). After a 30-second residence time at 200 °C, the initial substance underwent complete transformation into amitriptyline. To bring the unrefined mixture to room temperature, a heat exchanger was installed. Ultimately, the isolation of amitriptyline hydrochloride salt (16) was achieved with a yield of 71% by adding a 1 M solution of HCl in isopropanol and then recrystallizing from an EtOH/Et2O mixture. A 0.5 mL PFA (perfluoroalkoxy) reactor coil with an internal diameter of 1.0 mm and a residence duration of roughly 30 seconds was used throughout the entire procedure. The unfinished reaction mixture was then protonated with EtOH. leading to the formation of carbinol (15). To extract water from the carbinol, inductive heating technology was employed, involving the placement of a 0.3 mL cartridge steel reactor filled with steel beads having an inner diameter of 0.8 mm, within a high-frequency field (810 Hz). Following a residence time of 30 seconds at 200 °C, the initial material underwent complete conversion into amitriptyline. To cool the crude mixture to room temperature, a heat exchanger was incorporated. Ultimately, by introducing a 1 M solution of HCl in isopropanol and subsequently recrystallizing from an EtOH/Et2O mixture, the isolation of Amitriptyline Hydrochloride salt (16) was accomplished, resulting in a yield of 71%.

Applications of Flow Chemistry in Agrochemical

Just like other prominent chemical sectors, the agrochemical market encounters numerous transformations and obstacles.

There are three primary challenges confronting the industry:

- The persistence of pest resistance and its repercussions on the sustained effectiveness of agrochemical products.
- A more rigorous regulatory landscape.
- Escalating costs of goods.

These challenges align with the decline in the introduction of new molecules in the agrochemical field. Despite synthesizing a greater number of compounds (2.7 times more) and increasing R&D costs (from $152 million in 1995 to $256 million in 2005), the introduction of new molecules has decreased. To overcome these challenges, the application of various techniques such as structure-, fragment-, and target-based design of active compounds is necessary. Furthermore, the adoption of intensified and highly efficient synthesis techniques holds significant importance [24]. This application note presents valuable insights gathered from patents filed by major agrochemical companies, namely Syngenta and Dow Agrosciences. These patents highlight the utilization of flow chemistry for synthesizing active compounds as a means to overcome these challenges. Flow chemistry reactors prove to be valuable tools for chemists as they reduce energy and material consumption, ultimately lowering production costs. The short residence time within these reactors enables rapid synthesis of molecules and offers access to novel structures for the development of new compounds.

The provided reactions serve as examples:

1. GROSSAMIDE

Back in 2006, a noteworthy instance emerged, spotlighting a multistep methodology for the continuous production of grossamide [29] – an essential neolignin amide manifesting in numerous plants as a defense mechanism against pathogenic threats. This compound assumes diverse biological roles, notably showcasing potential as an antimicrobial agent. What sets this synthesis apart is its ingenious incorporation of immobilized reagents and scavengers, a technological approach seamlessly aligning with flow-based processes. What's particularly appealing is the incorporation of readily available chemical building

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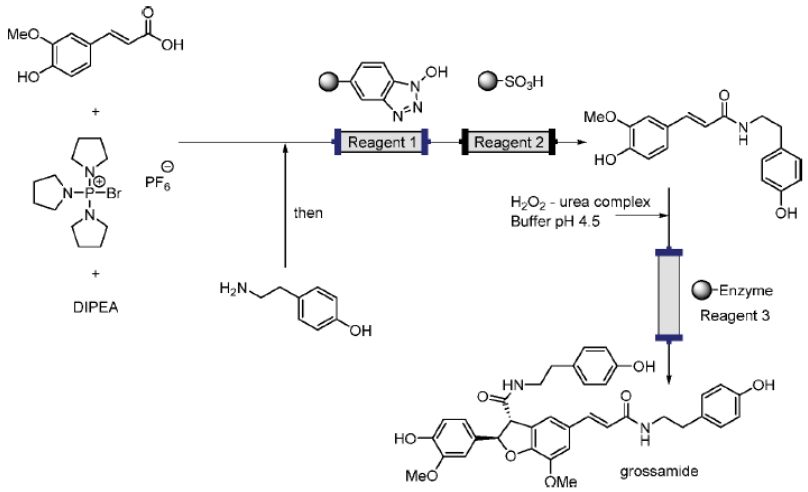

Scheme 8. *Flow Synthesis of Grossamide*

blocks, namely ferulic acid and tyramine. Through the application of traditional amide coupling conditions within a polymer-supported hydroxybenzotriazole (PS-HOBt) column, these compounds are transformed into the targeted product. The subsequent stage involves guiding the resultant substance through a dedicated module hosting immobilized horseradish peroxidase, thereby orchestrating a remarkably effective dimerization process. Consequently, this efficient process yielded grossamide in a excellent yield (Scheme 8).

The intricacies of the described procedure transcend the simplicity of a basic chemical outline. The attainment of uncontaminated product flow pathways demands the incorporation of in-line scavenging. Additionally, the stimulation of enzyme coupling, and cyclization mandates the introduction of supplementary oxidant (H2O2-urea). It's worth highlighting that the engineering of this system displayed an impressive degree of sophistication, particularly considering its era (circa 2006).

The automation of this ostensibly biphasic procedure necessitated a combination of numerous pumps, control valves, and filled reagent and scavenger columns. Furthermore, the integration of meticulous analytical instruments, including UV and LC-MS systems, fluid switching mechanisms, and reagent repositories, was undertaken to ensure precise control. This heightened degree of equipment refinement not only smoothed out the procedural workflow but also facilitated prompt reconfiguration, thus empowering the creation of a versatile array of distinct amides for subsequent biological appraisal (Scheme 9).

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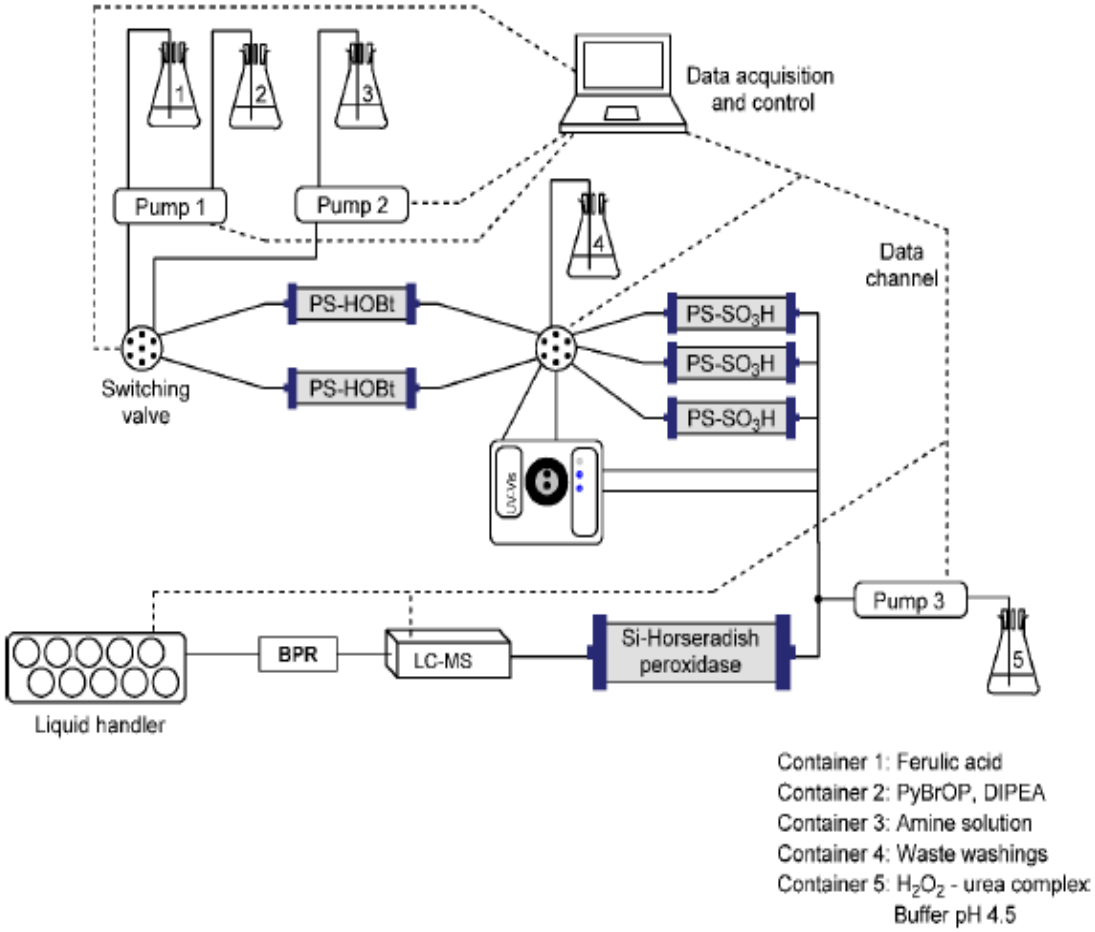

Scheme 9. *Comprehensive Scheme for the Flow Synthesis of Grossamide*

VI. BOSCALID

Back in 2003, BASF unveiled boscalid as a robust fungicide, harnessing its prowess in inhibiting succinate dehydrogenase activity. Since then, efficient synthesis approaches, including flow methodologies, have been the focus of attention.

Initial endeavors by Kappe delineated pivotal stages within the flow-based synthesis of boscalid. [30] The inaugural stride encompassed a high-temperature Suzuki−Miyaura coupling, wherein chloro-2-nitrobenzene engaged with 4-chlorophenylboronic acid within a flow coil maintained at 160 °C. Following scavenging utilizing Quadrapure thiourea (QPTU), the amalgam traversed through an H-cube hydrogenation reactor, inducing the selective reduction of the nitro substituent. This orchestrated sequence yielded a remarkable overall output of 77%, as showcased in Scheme 10.

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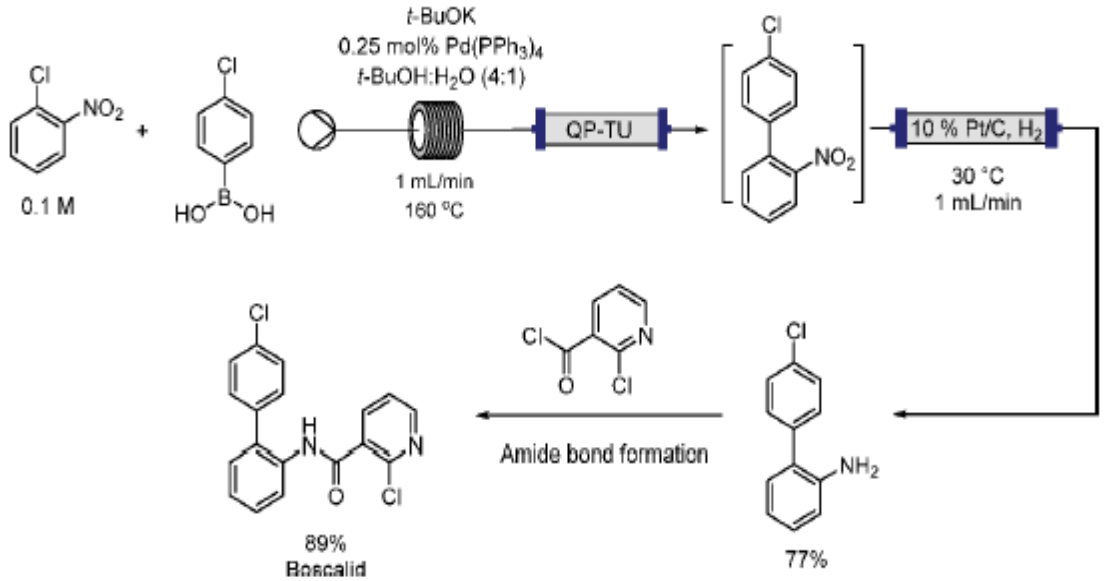

Scheme 10. *Flow Synthesis of Boscalid*

The decisive amide coupling pivotal in the creation of boscalid marked its status as a firmly established reaction. Notably, researchers from the University of Bergen in Norway embarked on a parallel path, adapting and aligning it to function seamlessly on a multijet oscillating disk (MJOD) continuous flow reactor platform. This innovative approach led to the remarkable achievement of producing boscalid at an impressive velocity of around 8.4 g/h, culminating in an overall efficiency rating of 42% over the three-stage sequence. [31] Within this trajectory, the Suzuki−Miyaura coupling was conducted at a moderated temperature (80 °C), succeeded by an adept cobalt boride reduction phase that ingeniously transformed the nitro group into the requisite amine counterpart. The final stride encompassed the in-situ generation of an iminosulfanone through SOCl2, subsequently merging with 2-chloropyridine-3-carboxylic acid. While the comprehensive insights into the MJOD flow reactor are confined to the report, it's crucial to note that the semi-continuous nature of the intermediate workup phase within this process underscores the demand for further refinements before any scaling endeavors. Nonetheless, the intriguing dimension added by the capacity to manipulate solid cobalt boride via mechanical oscillation in the MJOD methodology introduces a captivating dimension to the synthesis.

VII. CONCLUSION

The past century has witnessed significant progress in chemical synthesis, but challenges in efficiency and sustainability persist. Combinatorial Chemistry, Computational Chemistry, and emerging technologies have enhanced fine chemical production, enabling access to a wider range of products in drug development. Flow chemistry stands out as a promising approach, offering faster and reproducible pathways for high-quality drug synthesis. Notable applications in Notable applications include the synthesis of Vaborbactam, Diphenhydramine hydrochloride, Olanzapine, amitriptyline hydrochloride, Brivaracetam, Grossamide and Boscalid synthesis demonstrate increased productivity and improved diastereoselectivity. Despite obstacles in integrating flow chemistry into smaller-scale industries, ongoing efforts aim to adapt it for chemical intermediates and pharmaceuticals. The examples of continuous flow production of Active Pharmaceutical Ingredients (APIs) and agrochemicals highlight its potential in offering efficient and sustainable methods for complex molecule synthesis. Technological advancements and growing expertise in flow chemistry are driving its adoption in pharmaceutical manufacturing, holding the promise of a more efficient and eco-friendly future.

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