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Review

Continuous Flow Chemistry with Solids: A Review

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ABSTRACT: The effective handling of solids in a continuous flow process is one of the biggest perceived challenges remaining for modern flow chemistry. This Review aims to consider some of the continuous processes for chemistries involving solids which have been successfully implemented. Learnings from the design of these systems, and identification of the common blockers, will guide a generalized, strategic approach to drive the efficiency of future batch-to-flow development for challenging, heterogeneous systems. Assorted techniques for managing solids in continuous-flow synthesis will be presented herein through a series of case studies, and broken down into several key categories; solubility considerations, setup components and modularity, applications of ultrasonication, reactor type and continuous Grignard reactions.

KEYWORDS: *Continuous flow processing, heterogeneous, slurry, solids, fouling, clogging, blockage, continuous stirred tank reactors*

1. INTRODUCTION

The substitution of batch processing for continuous flow is a compelling opportunity to drive sustainable manufacture, and has been recognized as a "key green engineering research area" by the American Chemistry Society (ACS) Green Chemistry Institute (GCI) Pharma Roundtable.[1−3] Additionally, there are many practical drivers for adopting a flow process for the process chemist; safety considerations for hazardous, cryogenic and highly energetic chemistries, access to elevated temperatures and pressures, potential for increased throughput, and enablement of emerging synthetic platforms including photo- and electrochemistry.[4−15] While the pharmaceutical industry still heavily relies on batch equipment for large-scale drug manufacture, the adoption of continuous flow technologies is being addressed, and applied increasingly in a hybrid capacity coupled with batch to access the final active pharmaceutical ingredient (API).[16,17] In a recent review on integrated platforms for flow, the Nagy group highlight the scope for the development of continuous systems which cover all aspects of a process, from synthesis and crystallization, to formulation, linked to deliver the final product in a completely continuous fashion.[16] A "compact, reconfigurable system", described as being approximately the size of a fridge, has been reported as a proof-of-concept highlighting the opportunities posed by continuous processing for the future of drug manufacture.[18] In 2019, six on-market small-molecule drugs were reported to comprise examples of continuous technology in the manufacturing route. Three of these compounds are produced by Vertex, including lumacaftor, ivacaftor and tezacaftor, and the remaining three drugs are darunavir, abemaciclib and glasdegib, made by Johnson & Johnson, Eli Lilly & Company and Pfizer, respectively.[16,19] GSK are another pharmaceutical company active in the continuous manufacturing space, with facilities equipped for continuous production in Singapore.[20−23] A recent study in Organic Process Research and Development (OPR&D) found that the number of articles in the journal with a focus on continuous manufacture has grown from 2010 to 2019, and is spread between 20 and 30% industrial, 40−50% academic and 30−40% both.[24]

Despite this increased focus, the management of solids in a continuous process remains a significant challenge for modern flow chemistry. A study performed by Lonza in the early 2000s evaluating their current chemical processes was highlighted in a review by Hartman on managing solids in microreactors.[25,26] The study established that of eighty-six reactions studied, 70% are run as semibatch processes. The reactions were further assessed on the basis of homogeneity prior to transfer into large-scale or pilot manufacture, with greater than 60% involving solids. A subsequent investigation was conducted to identify potential opportunities for operating any of the eighty-six reactions as a continuous process, coupled with a cost-benefit analysis.[27] While it was recognized that taking advantage of continuous methodologies would be advantageous for 50% of the reactions assessed, 63% of these were considered poorly suited for microreactor technologies due to the presence of solids. Insoluble, solid material in a chemical reaction poses an additional challenge for continuous flow due to the buildup of solid particulates dispersed in the reaction's liquid phase, resulting in eventual blockage, also referred to as clogging or plugging. There are three ways in which solids may become dispersed within the liquid phase of a heterogeneous system in flow; hydrodynamic bridging, settling and fouling (Figure 1).[26,28]

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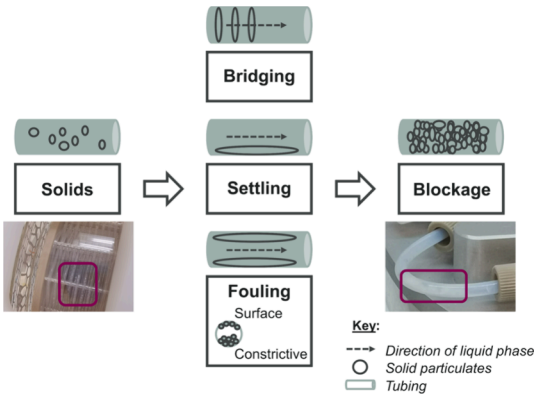

Figure 1. Three modes of solid dispersion in a tubular flow reactor which can lead to eventual blockage; bridging, settling and fouling.[26,28]

2. BLOCKAGES IN A CONTINUOUS FLOW PROCESS

The phenomenon of blocking in microfluidic systems can severely hamper the performance, and furthermore the application of these devices.[29] The Noël group have reviewed several reported methods for blockage detection in flow reactors, in particular for the precipitation of solids in the channels of microreactors.[30] Problems with blocking however are not limited to microreactor technologies, and Deadman et al. highlight that "Particulates represent one of the most troublesome materials to handle by flow chemists, due to their tendency to cause blockages in tubular flow reactors."[26,31] Bana et al. emphasize the importance of having stable uninterrupted operation for a continuous flow process, in particular for plant-scale manufacturers, noting that clogging can be a serious hindrance.[32]

Bridging occurs when solid particulates amass between the channel walls in clusters which are separated by the liquid phase, and results in rapid blockage.[33] Since the diameter of tubing used in a flow reactor and connecting lines will impact the likelihood of bridging, consideration of the relationship between particle size and diameter of tubing should help to mitigate bridging for transformations involving solids. The settling, or sedimentation behavior of solids, occurring near the base of the solution within a channel is impacted by the interaction of the solids with the channel walls and liquid phase. In the case of laminar flow, the size and velocity of the solid particles, in addition to the viscosity of the reaction solvent, will affect the settling velocity as partially described by Stokes' Law for drag force (F_d), which assumes spherical particles of uniform density.[34] Particles with a low settling velocity, which are less dense, or of similar density, to the reaction's liquid phase, will be tolerated in tubular flow better than particles with a high settling velocity. The risk of deposition of solids by settling is lowered for cases where the solids pass through the tubing at a faster velocity than the liquid phase. Effective mixing should facilitate the formation of a solid suspension, helping to reduce the likelihood of blockages occurring due to settling.

In the case of fouling or constriction, solids tend to buildup on all surfaces across the tube, worsening over time.[33] In a recent review on nonfouling flow reactors for nanomaterial synthesis, Besnard et al. refer to the commonly used definition for fouling by reactor engineers as "the accumulation of unwanted material on solid surfaces".[35] The authors classify fouling as local or traverse, referring to the degree of fouling on the reactor surface; local affecting only a small portion of the reactor, and traverse affecting a substantial cross-section of the tubing. Constrictive fouling is the extension of solid buildup from the reactor wall, affecting the total volume of the reactor to a larger extent through minimization of the tubing diameter available for flow.[35] Fouling within the reactor can result in longer process cycle-times due to repeated interruptions for cleaning. Identifying the source of fouling, with possible causes including precipitation of the product, impurity formation, insoluble starting materials, is crucial to identifying a mitigation strategy. Constrictive fouling may also affect the reactor properties, including for example available reactor volume, and hence residence time and heat transfer, in addition to the accuracy of flow rates. In these instances, operating in batch mode may be more appropriate. Effective mixing may help to minimize the extend of fouling. The process of fouling in microstructured devices for a variety of applications including biological, crystallization and chemical reactions, has been reviewed by Schoenitz et al.[36] Fouling in microchannels severely hampers the efficiency and performance of continuous flow microreactors, hindering uptake for solid-forming chemistries.[36]

Hartman et al. describe the impact of blocking in a microreactor for palladium-catalyzed aminations.[33] The authors detail their approach to understanding the root causes of the buildup of solids and resultant blockages. Their efforts enabled the identification of both bridging and constriction in the continuous setup, guiding a targeted way of tackling the different origins of system blockage. The authors selected this model system due to the well-known and established generation of stoichiometric quantities of inorganic salt. This salt byproduct precipitates from the reaction mixture due to poor solubility in the solvents routinely used in these transformations, including nonpolar solvents like toluene and THF. In their case, they found that ultrasound, or acoustic irradiation, prevented bridging, while fluid velocity considerations combined with growth rate predictions helped to tackle constriction.

While in the context of handling solids in continuous processing continuous crystallization is especially relevant, this topic has been extensively covered in a number of other reviews, including a recent publication which details its application in the manufacture of drug substance within the pharmaceutical industry, and is hence outside the scope of this particular Review.[16,37−40] Readers are directed to a 2021 OPR&D article by Johnson and Burcham at Eli Lilly and Company et al. for a guide, coined by the authors as "how-to information", to prevent fouling and clogging when developing and operating a continuous evaporation, crystallization or semicontinuous filtration process.[41]

The presence of an additional solid phase should not always be considered an insurmountable barrier for performing flow chemistry. Indeed, whether the solids are expected or unexpected has a part to play in the development of a continuous process, and for reactions in which solid formation is anticipated, the development of a flow process is somewhat guided. There are numerous examples reported throughout the literature of reactions performed in a continuous manner which involve solids, incorporating strategies either to remove or manage the presence of solids. Fundamentally, the nature and extent of solid formation in a particular reaction, from the presence of small solid particulates to a slurry, will impact the likelihood of establishing a successful flow protocol. Consid-

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

ering batch-to-flow development, some batch methods may have been developed with an intended product precipitation to facilitate the rejection of unwanted impurities, or shift the equilibrium toward product to drive the reaction forward, and enable a simplified workup and purification strategy by direct filtration of the product. In these cases, translation into continuous flow may require further optimization or process redesign to allow for a single homogeneous phase, possibly affecting the workup procedure.[42] Additionally, there are strategies which can be attempted to manage unexpected solid formation and reactor fouling during process development, including cleaning cycles, and the incorporation of duty and standby reactors. The latter dual operation mode involves alternating between two reactors to maintain continuous operation, thereby facilitating cleaning of one reactor while the other is used. Longer continuous runs can be used to test for the occurrence of clogging, which may appear upon scale-up of a flow process due to the unexpected/prolonged buildup of solids, and is something to monitor for at the process understanding stage of development. The following sections will further expand on these approaches and examples thereof.

3. GENERAL APPROACHES FOR HANDLING SOLIDS IN CONTINUOUS FLOW SYNTHESIS

a. Solubility of the Reaction Components. Baumann et al. refer to *flowability* as "the assessment of solubility of all starting materials, intermediates, and products under the processing conditions and consideration of the stability of feedstocks over the reaction timeframe."[43] Solubility of the components should be a primary consideration when reactions are progressed from batch into flow, with continuous platforms better suited to homogeneous systems. Hartman describes two overarching strategies for managing heterogeneous, liquid−solid systems in flow. These are active and passive measures.[26] Establishing the time point of solid formation in batch mode is critical; (a) solids may form over the course of a reaction due to precipitation of the final product, a byproduct or intermediate, (b) solids may be present due to poor solubility of one or more starting materials in the reaction solvent, and (c) solids may form when some or all of the reagents are mixed. Understanding at what point during the reaction the solids are formed, in addition to establishing the identity of the solids, can help to dictate the best pathway forward. This may be through altering the system to establish homogeneity − "active", or taking appropriate measures to manage the solids effectively in flow − "passive". It is worth noting that different challenges will be met during the development of a (potentially) heterogeneous flow process depending on whether established chemistry, where all solids present are known, for example the formation of Grignard reagents, or new, less established chemistries are being applied.

Changing the reaction solvent, re-evaluating the reaction concentration or increasing the reaction temperature are all relevant approaches to manage solubility in cases where manipulation of the system is an option.[43] It is worth noting that a reduction in the reaction concentration will likely come at the cost of an increased residence time for the reaction, and the increased solvent usage as a result of running the reaction under more dilute conditions will impact the sustainability of the overall process. The introduction of gases in flow can occasionally cause solid formation due to either localized temperature drop or rapid formation of insoluble intermediate/product. Changing how the gas is introduced to have a better control or having the gas−liquid mixing segment temperature controlled can help avoid the formation of solids.[44] For a solid-forming reaction in flow, consideration of the solvent system and selection of an appropriate solvent, or cosolvent, which facilitates the dissolution of all reaction components is a good starting point. The same applies for reagents which are poorly soluble in the reaction solvent since completely homogeneous feed solutions are desirable. It may not always be feasible to use an alternate solvent, for example due to reduced reactivity, or due to the reaction of materials with certain solvents, resulting in the formation of impurities. There are strategies which can be harnessed to facilitate pumping slurries (see later section on 3b (iii) Consideration of Pumps), however, this can be especially challenging at lab scale and employing low flow rates. Ultimately, removing the presence of any solids from a reaction will reduce the likelihood of clogging occurring during a flow process.

These are considered invasive approaches, and in certain circumstances it may not be possible to alter the reaction conditions in order to achieve a homogeneous system. This may be due to restrictions on a process or a potential impact on downstream chemistry. Changes are more likely to be implemented if they do not result in significant yield losses or longer residence times.[26] The Noël lab highlight two strategies for using a heterogeneous catalyst in continuous flow whereby the catalyst can either be managed as a solid suspension or immobilized within the reactor itself.[45] A packed-bed system, whereby the catalyst is immobilized on a column and the reaction stream is passed through, may be considered at the start of development of a continuous heterogeneous catalytic process to replace the use of loose catalyst in a batch reactor. The application of solid-supported reagents in a continuous process is not limited only to catalysts, and while packed-bed reactors are not covered extensively within this Review, select examples are highlighted.[46] For a review of hydrogenations in continuous flow and trickle bed reactors, the reader is directed to a recent industry perspective on the use of fixed bed reactors for continuous hydrogenation reactions applying trickle flow.[47] Packed-bed systems have also found extensive application in continuous biocatalytic transformations.[48−52] They are not however limited to flow hydrogenations and biocatalysis, with for example a recent application including the use of solid acid catalysts in the *N*-Boc deprotection of aromatic and aliphatic amine substrates.[53] Additional example applications include the use of a monolithic triphenylphosphine reagent in flow and solid $NaBH_4$.[54,55]

If a process cannot be simplified through modification of the reaction conditions, or this is not desirable, alternative methods which might help to manage the solids in flow and are noninvasive can be explored. Strategies include, but are not limited to, ultrasonication of the reactor and/or mixer(s) to break up any solid particulates present, use of wider-bore components, including tubing with an increased inner diameter (ID) to facilitate passage of solid suspensions through the setup without clogging, consideration of the most appropriate reactor for handling slurries, including continuous stirred tank reactors (CSTRs) as alternatives to tubular coil reactors, use of bespoke back pressure systems as a substitute for classical back pressure regulators (BPRs), and temperature control.[26,31] Readers are directed to a later section in this Review for examples of alternative types of continuous flow reactors suitable for running chemistry involving solids (refer to (d) Types of Flow Reactors Suitable for Reactions Involving

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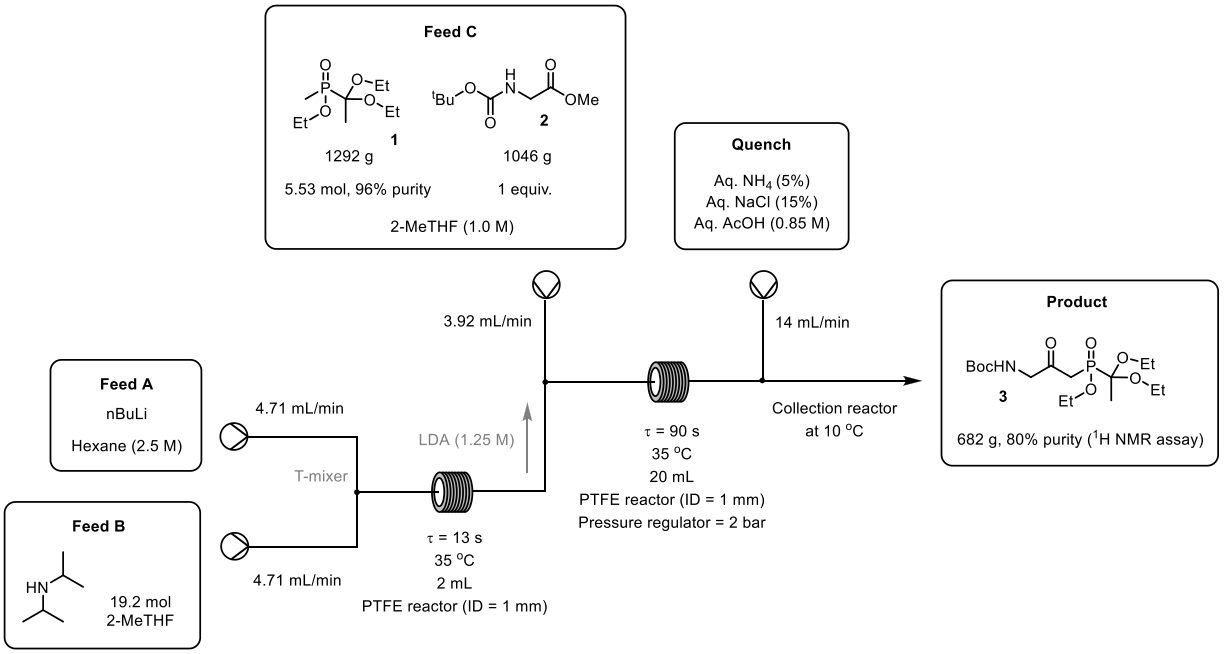

Figure 2. Continuous in situ generation of LDA and telescoped acylation reaction.[57]

Solids). For a detailed overview of flow reactors and associated components, in addition to relevant parameters and terminology for flow chemical synthesis, readers are directed to a recent Minireview by Hone and Kappe.[56]

It is the author's opinion that both manipulation of the system through re-evaluation of the reaction conditions like solvent, concentration and temperature to establish homogeneity, or the implementation of a custom setup design for managing solids, may require significant optimization effort. This is potentially a greater limitation in process development whereby the chemist(s) may be working to tight timelines with increased restrictions on resources. Strategies focusing on the handling and management of solids in a continuous flow reaction are discussed in detail herein, and presented through a select number of examples from the literature.

3a (i). Reaction Concentration. Researchers at AstraZeneca encountered issues due to clogging during the continuous preparation of compound AZD6906.[57] Clogging was observed in the check valves, resulting in poor and inconsistent performance of the high performance liquid chromatography (HPLC) pumps used for reagent delivery. Lithiumdiisopropylamine (LDA) was prepared in situ (Figure 2) and employed for the deprotonation of methyl phosphinate **1**, generating the phosphinate anion which reacted with an *N*-Boc-glycine methyl ester **2** at 25 °C to afford the desired product **3** following a quench (Figure 2). The authors discerned that the clogging incidents, occurred during longer continuous runs and were detectable by an increase in the system pressure. The temperature of the tubular reactor was raised to 35 °C to minimize clogging, which was thought to be viscosity-related. In an attempt to further reduce the impact of clogging, they rinsed the reactor with 2-MeTHF when the pressure reached close to the system limit, which was set to 20 bar in this case. A minimum concentration of 1 M LDA was required for the reaction, but clogging in the check valves proved problematic at concentrations near 1.4 M of base. Therefore, 1.25 M LDA in 2-MeTHF was determined to be the most suitable reagent concentration to achieve both rapid reaction times and also minimize the risk of clogging events.

Alonso and co-workers from GlaxoSmithKline (GSK) report on the use of lithium diisopropylamide in flow and describe clogging issues also related to reagent concentration, noting the irreversible precipitation of LDA when concentrations greater than 0.95 M in THF are used.[58] Dunn et al. at GSK also refer to challenges with solid formation for continuous organometallic chemistry, and associated clogging and over pressurization events. The authors report issues relating to solid formation during longer runtimes of their lab-scale continuous lithiation/iodination process using PhLi.[59] Machida et al. comment on the difficulties associated with reactor fouling in continuous processes which involve inorganic lithium salts, and report a cleaning approach in the absence of water for reactors used in continuous lithiations chemistry.[60]

Zhang et al. describe using reagent concentration as a strategy to mitigate reactor clogging in their flow synthesis of diaryl ketones.[61] Optimisation studies were conducted on a coupling reaction between the Grignard reagent phenylmagnesium bromide and substrate benzoyl chloride in THF to synthesize benzophenone. The reagent feeds were pumped to a T-piece mixer (ID = 1/32 in.), the resultant stream passed through a tubular reactor (ID = 1/16 in. and total volume = 120 mL) and a 1 M HCl quench was employed at the reactor outlet. Blockages were observed in the reactor coil at higher reagent concentrations; 1.2 and 0.8 mol/L phenylmagnesium bromide and benzoyl chloride, respectively. A yield of 72% for the biaryl product was obtained in the absence of any clogging event when the concentration of both feeds was halved; 0.6 and 0.4 mol/L for the respective reagents. A significant reduction in yield was obtained when the concentration of both feeds was halved again. Alternative solvents were explored, including 2-MeTHF, ether, dioxane and 1,2-dimethoxyethane, using the optimized reagent concentrations of 0.6 and 0.4 mol/L. System clogging was observed in all cases except for the reaction in 2-MeTHF which afforded the desired product in 85% yield.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

3a (ii). Pre-Mixing of Feed Solutions. The Ley group report a synthetic strategy to access butane-2,3-diacetal (BDA) protected compounds applying a continuous approach.[62] BDA protected D-mannitol product **4** was prepared from starting material D-mannitol **5** by reaction with 2,3-butanedione **6** in the presence of trimethyl orthoformate and camphorsulfonic acid (CSA) in methanol. Under batch conditions, D-mannitol **5** was observed to be initially insoluble, but proceeded to dissolve over the course of the reaction. The authors established that a completely homogeneous feed solution could be prepared by premixing D-mannitol **5** with trimethyl orthoformate and CSA in MeOH, and this premixed solution of reagents met the 2,3-butanedione **6** feed solution (Figure 3).[62,63]

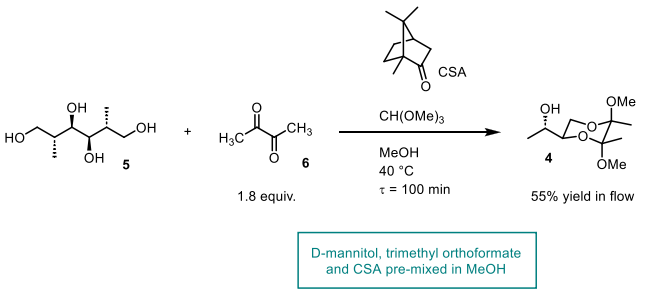

Figure 3. Reaction conditions for the continuous BDA-protection of D-mannitol **5**.[62]

3a (iii). Choosing the Reaction Solvent. Adapting the reaction solvent for a flow process to ensure a completely homogeneous solution and prevent clogging is a common strategy, and a general solubility screen may be performed to optimize the solvent system for a process.[64] Li et al. describe the positive benefits of operating their continuous aminolysis reactions under homogeneous conditions, reporting improved process control, and yields which were comparable or greater than in batch.[65] The authors established a solvent system which ensured homogeneity of all reaction components and noted that having a homogeneous reaction mixture for adapting a process into continuous flow using a plug flow reactor (PFR) at high temperature and pressure is ideal. However, it might not always be possible to choose the solvent solely to improve solubility of the reaction components. A particular reaction solvent may be required for other reasons, for example relating to reactivity, yield, selectivity, in addition to considerations for downstream workup and purification protocols like solvent swaps. Several topics relating to solvent system selection for a continuous process are presented herein, including the use of ionic liquids, considerations for organolithium reagents, application of liquid−liquid segmented flow, lessons from using THF and auxiliary solvents.

The Newman lab reports a creative strategy for managing solid-forming substitution reactions in continuous flow involving the generation of ionic liquids.[66] The authors acknowledge that substitution reactions, including acylations and alkylations, necessitate stoichiometric quantities of a base (B) to mop up any acid byproducts formed over the course of the reaction. However, insolubility of B-HX salts formed in the reaction can hamper the application of substitution reactions in flow. Alternative bases which still perform this critical scavenging function, but form an ionic liquid upon reaction with an acid instead of a solid precipitate, are shown to facilitate substitution reactions in flow without blockages occurring. This is proposed as an alternative solution to changing the reaction solvent or restricting the reaction concentrations to those which provide completely homogeneous conditions. The authors describe this approach as akin to a BASIL BASF process, whereby the base, *N*-methylimidazole was used in a condensation reaction between alcohols and chlorophosphines.[66,67] The conjugate acid which forms (imidazolium chloride, pK_a = 7.1) is a protic ionic liquid with a melting point of 70 °C and causes the formation of a separate liquid phase over the course of the reaction, minimizing the potential for issues in the process related to solids.[66,68]

Wietelmann et al. describe the potential for commercially available nBuLi solutions at concentrations of 1.6 and 2.5 M in hydrocarbon solvents to cause reactor blockages in continuous lithiations. The authors report that solvents like hexane have the potential to act in an antisolvent capacity for polar, lithiated compounds generated in such transformations. The resultant solids can cause clogging in particular in the channels of microreactors. They comment that THF can be used as a "donor solvent" to prevent the precipitation of salt byproducts including Li alkoxides.[69] Hexane is also commonly used in organometallic reactions as an "antifreeze" agent, reducing the freezing point of the reaction solution.[70]

Multiphasic chemical processes are ubiquitous, including catalytic reactions, crystallizations, hydrogenations (gas−liquid), biphasic aqueous−organic solvent systems, and solid−liquid reactions. The latter includes both solid-forming reactions, and reactions in which the some of the reaction components are insoluble. The Suzuki−Miyaura cross-coupling reaction for example is often conducted in aqueous organic solvent, employing insoluble inorganic bases, whereby mass-transfer is an important consideration in particular relating to the reaction kinetics. Aqueous−organic biphasic reactions have been implemented in continuous processes.[71,72] Liquid−liquid segmented flow is a viable approach for managing slurry-forming reactions in which a dual solvent system is used to achieve slug behavior.[26,73] To exhibit the desired slug flow pattern within a tubular reactor, the solvents employed must be immiscible. This strategy may be implemented to avert solid particulates from coming into contact with the reactor walls. A liquid−liquid segmented flow approach was trialled by Horie et al. for the continuous photodimerization reaction of maleic anhydride.[73] When the process was performed in aqueous−organic solvent, both the starting material anhydride and dimerization anhydride product proved susceptible to hydrolysis, generating the respective carboxylic acids. This example highlights the prospect of an incompatibility arising between particular reaction components and the desired solvent system. Additionally, introduction of a second solvent has the potential to hamper the efficiency of a chemical reaction.[33]

Merck reported a single clogging event which occurred during a solvent run in flow as part of a plant-scale synthesis toward verubecestat (MK-8931).[74] The authors describe the approach taken to understand the underlying root cause of this clogging event which had not been observed previously during the development process. When the solvent run was performed using THF at −20 °C with the flow rate set to 800 kg/h, a 16-fold reduction in the flow rate was noticed after 30 min. When the temperature was increased to 0 °C, the flow rate remained unchanged at 800 kg/h. After confirming that there were no

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

solid particulates present in the THF, and that it was unlikely water was entering the system, the authors deconstructed the flow setup in order to expose the parts most susceptible to blockage, including any filters and the static mixer. When no evidence of clogging could be identified, a number of pressure gauges were incorporated into the setup in order to monitor for a reduction in system pressure throughout another solvent run. A reduction in pressure was again observed, and the gauge positions directed the researches back to the filters and static mixer. These components were removed from the setup, albeit this time while cold, and solid material was observed on both the filter and static mixer. The solid was described as being off-white and fibrous, with the filter being clogged and the mixer coated in the solid material. It was postulated that the precipitation of solids in this case was likely occurring as a result of microscale hydrodynamic cavitation. This is thought to take place when solvent evaporates at a localized point in the system where there is a reduction in pressure. At this point in the investigation, a solvent run was performed using another lot of THF and no clogging was observed. Poly(THF) was identified as the contaminant responsible for the blockage, and while present in low quantities, it was determined that each lot of THF should be tested for poly(THF) prior to use in the process.

3a (iv). Use of Auxiliary Solvents. An approach used to prevent the accumulation of solid particulates downstream of the reactor is the introduction of an appropriate solvent which can act as an "auxiliary solvent" and ensure the complete dissolution of all reaction components prior to passing through fittings such as the back pressure regulator (BPR) (Figure 4).[75]

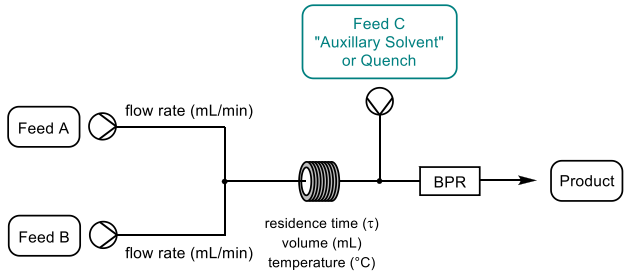

Figure 4. Generic flow setup showing the addition of an auxiliary solvent after the reactor outlet.[75]

The auxiliary solvent is introduced at the outlet of the reactor to meet the stream of reaction solution immediately upon exiting the reactor. This is a particularly useful strategy for processes which involve the in situ generation of insoluble organic or inorganic salt (by-)products in the reaction solvent which may be solubilized through the introduction of a suitable cosolvent at the end of reaction. Introduction of an auxiliary solvent helps to prevent blockages at the reactor exit, and is most suited to systems whereby the reaction components remain soluble at elevated temperatures and only precipitate upon cooling, following exit from a heated reactor. This is a quick and simple modification which can be made to a continuous setup, requiring only understanding of the product solubilities in alternative solvents, incorporation of a mixer at the reactor outlet, and access to an additional pump for introduction of the auxiliary solvent. However, in cases where the product or byproducts precipitate at high temperatures, blockages may still occur within the reactor coil itself.

This particular approach was used by Kelly et al. for adapting batch reactions performed using microwave heating, in which the final product was insoluble, into flow without further reoptimization of the reaction solvent, time or temperature.[75] One such example of this is the flow synthesis of 3-acetylcoumarin **7**. The reaction of salicylaldehyde **8** and ethylacetoacetate **9** in the presence of catalytic piperidine was performed in either ethyl acetate or ethanol, and the reactions run at 130 °C for 8 min in a microwave reactor. The batch yields varied between 72 and 78% depending on the scale of the reaction. When the reaction mixture was allowed to cool, precipitation of the coumarin product **7** was observed. With this knowledge, the authors opted to employ an auxiliary solvent when translating the reaction into continuous flow to ensure dissolution of the product prior to the reaction stream passing through the BPR. Acetone was selected due to the excellent solubility of the coumarin product in this organic solvent. Acetone was pumped to a T-piece mixer set after the reactor coil to mix with the reaction stream, and a homogeneous product stream passed through the BPR set at 100 psi. 3-Acetylcoumarin **7** was synthesized in flow in 74% yield taking advantage of this approach (Figure 5). A control reaction was performed in acetone as the reaction solvent affording only 10% yield of the product **7**.

The use of an acidic quench to mitigate reactor clogging was demonstrated by Snead and Jamison for a Friedel–Crafts acylation reaction (Figure 6).[76] The reaction of isobutylbenzene **10** and propionyl chloride **11** was optimized in continuous flow using Lewis acid $AlCl_3$ for activation of the acid chloride. The use of Brønsted acids as alternative activators to replace $AlCl_3$ was considered due to their solubility under the reaction conditions. These included acetic acid, sulfuric acid and hydrochloric acid. However, yields for the reaction did not appear promising, and instead the authors opted to design a flow setup capable of handling $AlCl_3$. The $AlCl_3$ was premixed with neat propionyl chloride, affording a

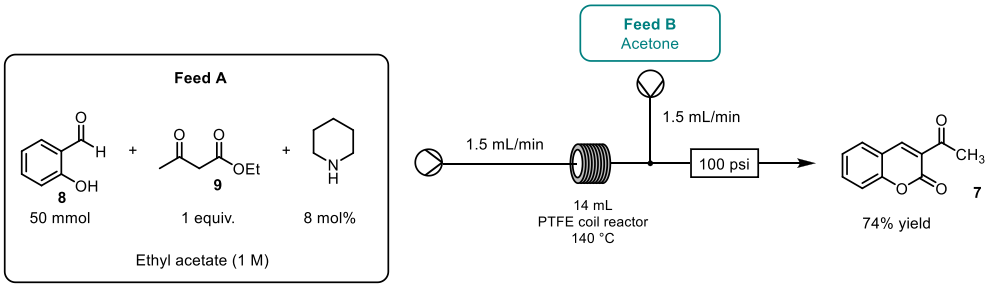

Figure 5. Continuous synthesis of 3-acetylcoumarin using acetone as an auxiliary solvent.[75]

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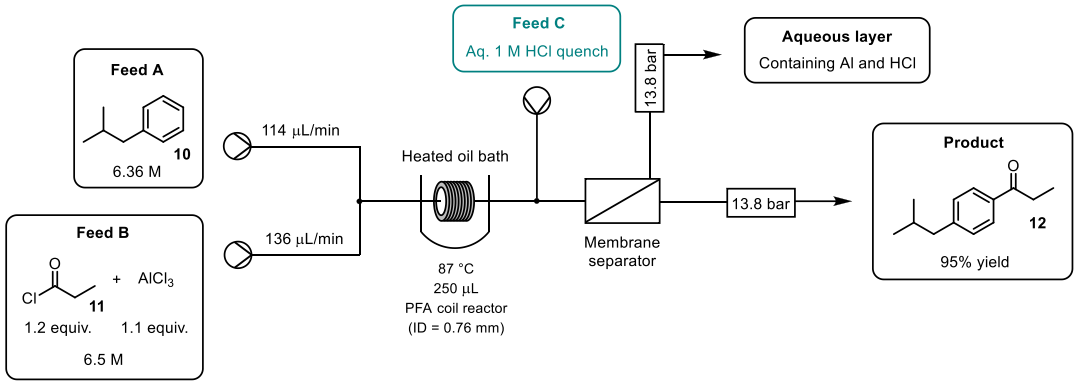

Figure 6. Continuous Friedel–Crafts acylation using aqueous acid as a quench.[76]

homogeneous reagent feed. A solution of 1 M HCl was introduced as a quench at the end of the reaction to solubilize the aluminum byproducts and mitigate reactor clogging. A liquid–liquid membrane separator, comprising a Zeflour membrane (1.0 μM pore size) between two stainless steel plates, was incorporated into the flow setup and Zaiput pressure regulators set to 200 psi connected to both aqueous and organic outlet lines.[77] The aqueous stream was removed by continuous separation to render the aryl ketone product **12** neat.

3a (v). Application of Temperature Control. Running reactions at elevated temperatures is another option to aid solubilization of any solids present. If the solids are as a result of poorly soluble starting materials, the reagent feeds can be heated, and if the solids form at the point of mixing of reagents, the mixer can also be heated. This can be achieved simply by submerging the mixer in a hot water bath. A flow reactor can be equipped with a heated reactor mixer assembly whereby the mixers are encased in a heated chamber along with the reactor coil itself (Figure 7).[78] In this case, the reagents are mixed at

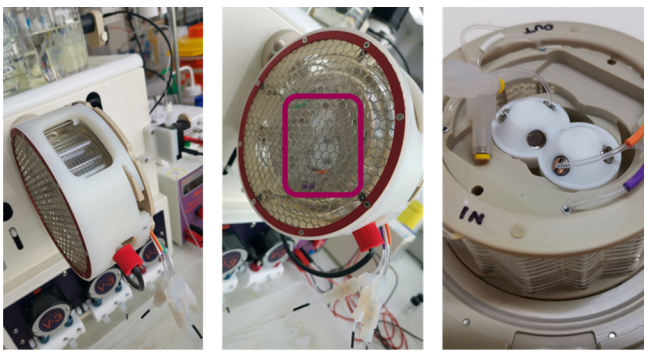

Figure 7. Heated coil flow reactor and mixer assembly.[78]

the temperature set for the coil reactor. Alternatively, if solids form as the reaction progresses, and the chemistry permits, the reactor temperature should be increased along its length, or a temperature gradient applied where multiple reactors are used in series, to aid dissolution of the particulates, and prevent blockages occurring. It should be noted that a reduction in the reaction time will typically be observed with increasing temperature, and therefore, it may be possible (or necessary) to implement a reduction in the residence time.

A continuous Curtius rearrangement toward the synthesis of compound AZD7648 was reported by scientists at AstraZeneca.[79] Precipitation of the cyclized product from the reaction solution was observed upon exiting the reactor which ultimately caused clogging in the system. The issue of clogging was circumvented by maintaining the temperature of the outlet stream above 70 °C, preventing solid formation and ensuring collection of a completely homogeneous solution at the end of reaction on multi kilo scale.

A continuous Mannich-type addition toward verubecestat (MK-8931) was reported by Merck Research Laboratories,[80,81] where temperature was shown to be an important parameter for preventing blockages in the system for the organometallic transformation. Reaction conversions by HPLC of 87, 87, 85 and 80% were obtained for the reaction when the temperature of the heat exchange reactor coils and micromixers were set to −10, 1, 22, and 38 °C respectively. The researchers observed that both the starting material, and resultant lithium anion, formed by deprotonation of the substrate using nHexLi, precipitated from the reaction solution at temperatures below −30 °C, introducing variation in the flow performance due to clogging. This example highlights the importance of robustness testing to identify the operating limits for a flow process with regards temperate to maintain solubility of the reaction components.

A Grignard alkylation reaction of a ketone substrate by allylmagnesium chloride (allylMgCl) was performed in a heterogeneous filter reactor.[82] Issues were encountered due to blockages, as a result of precipitation and buildup of solid magnesium alkoxide intermediate, which occurred within the filter unit contained in the reactor vessel. The researchers describe the solid as a 'sticky and highly viscous mass when it precipitates'. Increasing the temperature from 15 to 30 °C resolved the problem of clogging in the filter cartridge. For more details relating to the chemistry and filter reactor design refer to the later section on (e) Grignard Reactions in Continuous Flow.

Researchers at Eli Lilly and Company implemented heated transfer lines as a mitigation strategy for fouling in their flow equipment during a continuous process toward the manufacture of Merestinib (Figure 8)[43,83] This strategy was used in the amidation reaction of mixed anhydride **13** with an aryl amine **14** in THF at 60 °C to afford the product **15**. The reagents were mixed in a continuous stirred tank reactor (CSTR) prior to passing through a plug flow reactor (PFR) which was set in a water bath at 60 °C and the reaction proceeded with a residence time of ∼60 min. The reaction mixture became supersaturated when the temperature dropped below 35 °C upon exiting the reactor coil. It was not possible

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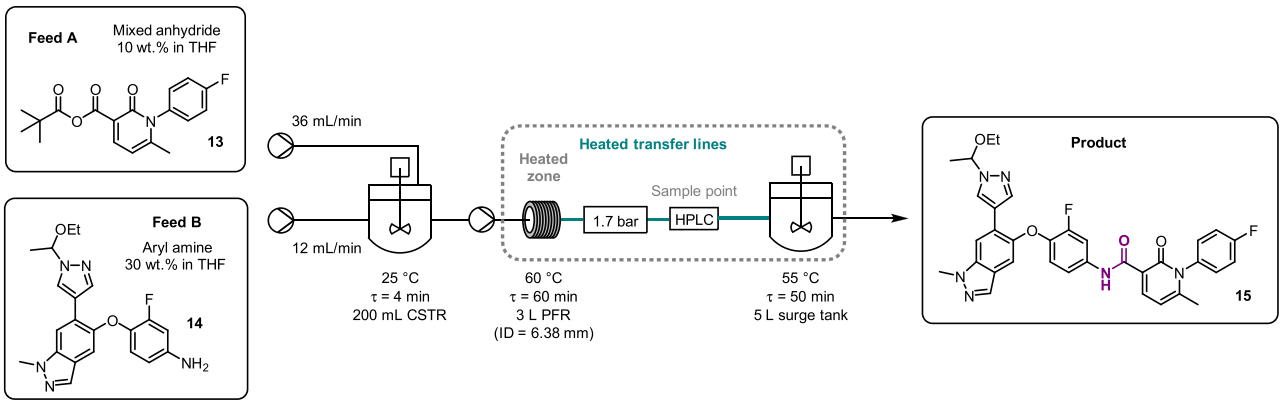

Figure 8. Continuous amidation showing heated transfer lines used to prevent equipment fouling.[43,83]

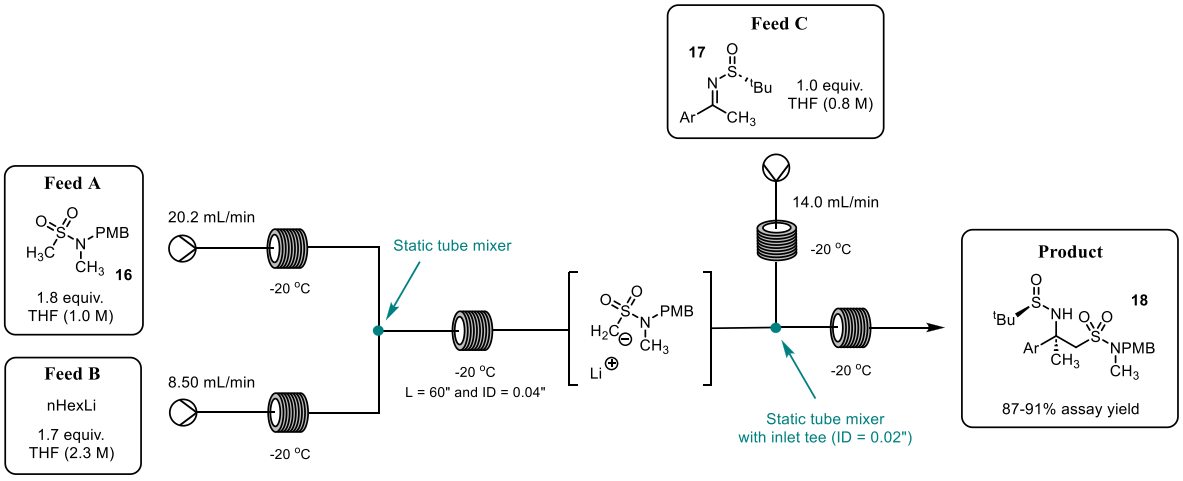

Figure 9. Continuous flow process for the deprotonation of a methylsulfonamide substrate by nHexLi to generate the lithium anion.[80]

in this case to reduce the solution concentration in order to ensure that the reaction components were completely soluble in THF at room temperature. The concentration was set at a certain level so as to maintain a fast kinetic profile for the reaction, albeit with an increased likelihood of equipment fouling due to handling a supersaturated solution. This was prevented simply by using heated jacketed lines to transfer the product stream from the reactor coil into a surge tank, with a sample point incorporated between these points to enable the acquisition of online samples for HPLC.

b. Modularity in the Continuous Flow Setup. The inherent flexibility gained by having modularity in a continuous flow setup is especially advantageous for reactions involving solids which have a greater tendency to be hampered by clogging incidents, applicable for example to organolithiation reactions. If fouling occurs, the accessibility gained from a modular setup, and the ability to replace specific components which are more susceptible to clogging, is beneficial.[43] Modular flow systems can aid mitigation of fouling issues in a continuous process. In particular, the use of a secondary arrangement of flow equipment, otherwise known as a "Duty Standby" setup, can help alleviate downtime or disruptions to the process due to fouling. This might involve the use of two separate reactors arranged in parallel so that one can be taken out for service or cleaning while the other is in operation. Baumann et al. highlight the importance of having a modular continuous flow setup.[43] A modular system offers increased flexibility due to facile replacement of individual parts, including mixers and tubular reactor coils. This is a particularly relevant strategy for process development within the pharmaceutical industry considering the operating scale.

3b (i). Choice of Mixer. The efficiency of macromixing in milliflow reactors and micromixing in microflow reactors was evaluated by Gobert and Thomassen using residence time distribution (RTD) and Villermaux–Dushman methods, respectively.[84] The Villermaux–Dushman protocol is widely used for assessing mixing performance. It is a comparative study whereby two competitive reactions are run in parallel, and the quantity of product formed, which is detectable by an analytical technique such as Ultraviolet–visible (UV–vis) spectroscopy, dictates the mixing efficiency of the reactors.[84,85] Tubular coil reactors of varying internal diameter (ID), chip reactors and static, T- and Y-piece mixers were evaluated in the study. Flow rate and tubing ID proved critical parameters for achieving efficient mixing in tubular reactors, with lower flow rates giving longer micromixing times. Gobert et al. comment that solids handling is a factor that will impact the decision to use a chip versus a small tubular coil reactor.[84] The geometry of mixing differs for T-piece and arrowhead mixers (Figure 10), while static mixers can be incorporated into the reactor in-line itself to aid micromixing. Static mixers are specially engineered with fixed, motionless internal design features.[86] This class of mixer can be a potential solution for slurry-forming reactions which require high mixing efficiency. They

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work well for a biphasic reaction stream delivered at high flow rates through a reactor, but are impractical for slower reactions.[87,88] It can prove especially important for solid-containing transformations to critically evaluate the performance of the different mixers available so as to strike a balance between minimizing clogging and optimizing mixing efficiency, and the performance of static mixers in 'precipitating environments for pharmaceutical production' has been evaluated by Kreimer et al.[89] The mixing time for a range of commercially available micromixers, in addition to 1/8 in. and 1/16 in. T-unions, was investigated by Reckamp et al.[90] As might be expected, microchannels offered better mixing than T-piece mixers, but the authors highlight that desired flow rate will dictate the most appropriate mixer for a process, with particular mixers providing efficient mixing at lower flow rates, and others more suitable across a wider range of flow rates.[90] Mixing characteristics and performance, in addition to flow mechanisms, in micro T and arrow mixers have recently been described by the Salvetti group.[91]

Merck Research Laboratories evaluated the efficiency of mixing for a deprotonation step in flow of methyl sulfonamide substrate **16** by *n*-hexyllithium (nHexLi) base toward the synthesis of verubecestat, MK-8931 (Figure 9).[80,92] The resultant lithium anion of **16** reacts with chiral substrate **17** to afford the final product **18**. The reaction appeared to be heavily affected by the mixing of substrate **16** and base feed streams. Several static mixers were tested in the continuous deprotonation step; a T-piece mixer (ID = 1/20 in.) and three T-piece mixers set up in series, described as "combine-split-recombine tees", an Upchurch Scientific static T-piece mixer and a Koflo Stratos tubular mixer.[80] Readers are directed to the Supporting Information of this publication for technical details of the specific mixers used. Additionally, several commercially available micromixers, including static mixing tees, are described by Schwolow and co-workers.[93] Another setup, tested to better resemble plant-scale mixing, was a tee attached to a Koflo Stratos tubular static mixer which was set downstream. On kilogram scale, fouling was observed in the static T-piece mixer due to the susceptibility of the 10 μm frits to become blocked by solid particulates. Despite the potential for excellent mixing, the utility of the static T-piece mixer was hampered by its susceptibility to blockages. While the static tube mixer provided less effective mixing, frequent blockages in the mixer were avoided and the reduction in mixing efficiency could be circumvented by doubling the flow rate through the mixer to afford comparable conversions by HPLC. The reaction conversion was further improved by using a 1/50 in. instead of a 1/20 in. inlet tee in conjunction with the static tube mixer. However, this mixer setup employed in the deprotonation step was still susceptible to clogging events after operating the flow process for 35−45 min. The authors emphasize the importance of performing larger-scale flow experiments in the laboratory with longer run times to evaluate the robustness of the process, to identify any potential risk factors for continuous manufacture. The researchers considered the possible factors contributing to the repeated blockages in the current setup, noting that fouling persisted in the system even with dry reagent solutions, and the rate of fouling increased when the temperature was raised from 0 to 20 °C. It was suspected that decomposition of the lithium anion species was responsible for the repeated clogging events. The process was run smoothly for over 1 h at steady state when the micromixers and heat exchange reactor coils were further cooled to −20 °C, reducing the potential for decomposition at the point of mixing (Figure 9).

Individual continuous stirred tank reactor (CSTR) stages may be used to deliver mechanical agitation and are single units which can be linked in series. These differ to static mixers which are considered motionless, as they provide active mixing with each stage comprising a cross stirrer to give a total stage volume of 2 mL (Figure 10).[87,94] The cascade CSTR is suitable for handling bi- and triphasic systems; gas−liquid, liquid−liquid, liquid−solid and gas−liquid−solid.[87]

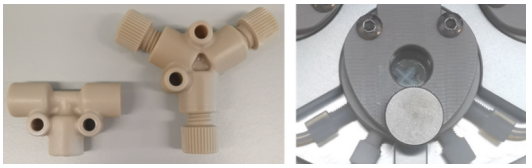

Figure 10. Types of mixers including T-piece and arrowhead mixers, in addition to a CSTR stages with cross stirrer (left to right).[95]

Dolman et al. report a Magnetically Driven Agitation in a Tube (MDAT) mixer for use in laboratory-scale continuous flow processes.[96] The objective was to design a mixer which would be resistant to blockages, while still providing good mixing, and without the necessity for using higher flow rates to aid the mixing efficiency. Increasing the flow rate of the reagent streams to facilitate improved mixing is not always feasible since it directly impacts the residence time, and a reduced residence time could be detrimental to the reaction conversion. While microreactor channels provide highly effective mixing, they are susceptible to clogging by solids, and filtration of all feed solutions is recommended to avoid blockages occurring in chip reactors due to the presence of small, inconspicuous solid particulate material. It is highlighted that while a reduction in overall reaction concentration may prevent clogging at the point of mixing, it would impact the rate of reaction and increase the quantity of solvent waste generated during large-scale operation.[96] Additionally, scaling the MDAT mixer would likely be challenging, and therefore its use limited to small-scale applications rather than for commercial or pilot plant. The MDAT mixer consists of a HPLC column containing two magnetic stir-bars, attached to a T-piece mixer, and set over a magnetic stirrer-plate. The authors used the fourth Bourne competition reaction to evaluate the mixing time, and the experimental procedure for this method of mixing characterization described within the article.[96,97] They observed faster mixing with the MDAT mixer, which was also found to be less effected by flow rate, compared to T- and multilaminar mixers, and emphasize that the mixer is resistant to clogging.[97] The MDAT mixer was applied in the optimization of several continuous organometallic reactions under cryogenic conditions, and without blockages occurring in the flow setup, including the in-line formation of LDA by reaction of 2 equiv nBuLi with diisopropylamine (1.25 M in THF).

Static mixers are less effective at managing solid-forming reactions which necessitate lower flow rates since this class of mixer typically cannot provide fast mixing at low flow rates.[88] A dynamic mixer was designed and built in-house, inspired by the MDAT mixer previously reported by researchers at Merck.[43,88,96] Several stir bars were encased in polytetrafluoroethylene (PTFE) tubing (OD = 1/4 in.). Some PTFE balls were included in the tubing to act as spacers, set between each

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

stir bar. The segment of tubing used in the dynamic mixer contained a setup of S1−B1−S2−B2−S3-B3-S4 (where S = stirrer bar and B = PTFE ball) which was 6 cm in length, and a T-piece was incorporated at the start of the PTFE tubing to facilitate addition of the two desired reagents (Figure 11). The

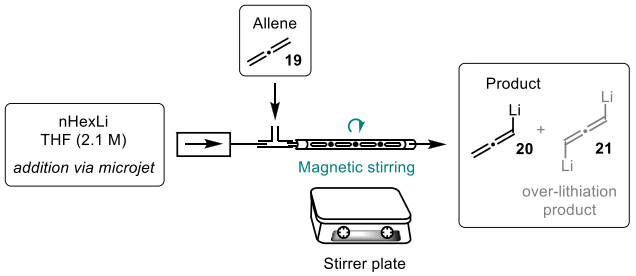

Figure 11. Continuous lithiation of allene using a custom built dynamic mixer.[88]

improved mixing provided by the "high-speed spinning-motioned stir bars", in contrast to a T-piece mixer, enabled the authors to perform a continuous lithiation reaction of allene **19** by nHexLi (0.65−0.80 equiv) at 0 °C in THF to give the product **20** (Figure 11). The lithiating reagent was added by a microjet into the mixer directly. The continuous flow reaction was operated under steady-state conditions for several hours without any blockages occurring due to precipitation of the overlithiation product **21**, formed as a result of double addition by lithium into allene **19**. The authors comment that the PTFE housing used to contain the stir bars offered poor thermal conductivity and noted that the bath temperature would be better set to −20 °C to ensure that the mixer temperature is not raised above 0 °C during the reaction.

A segmented flow tubular reactor (SFTR) has been applied to the continuous synthesis of calcium carbonate by means of precipitation (Figure 12).[98] The development of an SFTR and

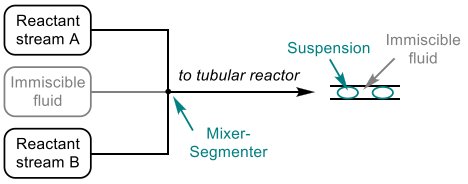

Figure 12. Segmented flow tubular reactor (SFTR) showing mixer-segmenter and resultant reaction stream consisting of pockets of segmented suspension and immiscible fluid.[98]

the "scale-out" concept for the production of powders by continuous precipitation is discussed by Jongen et al.[99] The authors describe a SFTR suitable for lab-scale operation which comprises a micromixer and segmenter. A micromixer is used to provide efficient mixing of the two reactants, and the segmenter introduces an immiscible fluid. This causes the reaction mixture to become separated into portions, described by the authors as microbatch volumes, which are divided by the immiscible fluid. The segments pass through a tubular reactor and are retained in a decantation unit at the end of the system to collect the precipitated powder. They discuss the use of different micromixers, for example a caterpillar mixer, and newer micromixers including impinging jet mixers and separation layer mixers, which help to mitigate fouling at the mixing point in the system.[99]

McQuade et al. outline a microfluidic reactor design which enables the synthesis of solid particulate material without clogging occurring in the reactor.[100] The technology uses monodisperse droplet flow to sequester the solids formed from the tubing walls. The device comprises a syringe pump for the carrier phase and two syringe pumps for the dispersed phases. A blunt-edge needle is used to manage the injection of reagents. The droplets of disperse phase generated are described by the authors as individual reactors which can contain the solids, preventing them from interacting with the reactor channels.

3b (ii). Use of Wider-Bore Components. The enhanced mixing provided by active stirring within a CSTR stage promotes the suspension of solid particulates in solution, enabling improved handling of slurry-forming reactions.[95] However, when multiple stages are setup in series, settling of the solid particles may occur in the connecting tubes and lead to clogging. Short-lengths of wider-bore tubing should be used to reduce the likelihood of settling occurring. For reactions run at elevated temperatures in order to maintain solubility of all the reaction components, the tubing between each unit can be lagged to provide insulation, and prevent precipitation of solids as the solution begins to cool between the stages. The Ley group reports using wider-bore tubing in their setup to avoid blockages when flowing slurries.[31,101] Battilocchio report the importance of having a wider ID for the perfluoroalkoxy alkane (PFA) reactor coil used in their flow setup to avoid blockages.[101] Select examples of varying diameter tubing is shown for comparison (Figure 13). A back pressure regulator

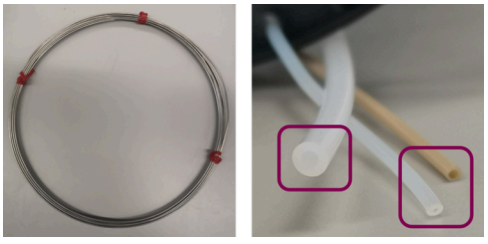

Figure 13. Select examples of varying diameter tubing including stainless steel tubing, PTFE (ID = 1.5 mm), PTFE (ID = 0.5 mm) and polytetheretherketone (PEEK) (ID = 1 mm) from left to right.

prototype designed in the Ley group, in the form of a nitrogen gas-filled pressure chamber, with an inlet line of ID = 1/16 in., was found to incur blockages during testing with a slurry-forming reaction. The Swagelok connector used at the entry point of the pressure chamber was restricting the slurry flow, resulting in blockages in the tubing. To prevent this from occurring, the inlet line was swapped for one with an increased ID of 3/16 in.[31] A bespoke continuous stirred tank reactor (CSTR) cascade, comprising 5 individual stages, was developed for application in photochemical flow reactions which are heterogeneous.[102] Two reactor designs were built; CSTR 1 and CSTR 2, and the connecting tubing between each stage for CSTR 1 and 2 had an ID of 2.5 mm and 0.7 mm, respectively. The researchers observed that CSTR 2 was more susceptible to blockages due to the narrow-diameter tubing used between stages, also noting that problems with back-mixing between the individual stages were lessened. When fluid mixes in the opposite direction to the flow of the fluid, described as back-mixing, unwanted mixing of reacted and unreacted materials in solution takes place, and this has the

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

potential to impact reaction yield and selectivity. CSTR 1 contrastingly suffered from back-mixing but was overall more effective at managing solutions containing solids without reactor clogging. These examples highlight the importance of considering the internal diameters of all components in a flow setup when attempting solid-forming chemistries. This includes not only the reactor tubing, but connecting lines, connectors, mixers, and components which typically have narrow-bore parts, for example traditional back pressure regulators.

3b (iii). Consideration of Pumps. It was previously alluded to that the occurrence of fouling is not limited to the reactor but may also take place in components which are made up of narrow-bore parts including mixers, BPRs and connectors. Fouling of the equipment has the potential to affect the pressure drop of the system, and so transient fouling, which causes fluctuations in the pressure, can disrupt the delivery of fluid by the pumps, making it challenging to maintain a steady flow.[12] Ensuring the consistent flow and delivery of the reagent feed streams is more manageable in cases where the fouling process occurs gradually, and hence, the changes in pressure drop are slow. This results in inconsistent reagent delivery, impacting the residence time, and causing ambiguity with regards stoichiometry, for example, in cases where multiple feeds are introduced by independent pumps at defined flow rates. If the flow is suspected to be inaccurate due to solid formation, a flow meter can be incorporated, in conjunction with several pressure transmitters across the setup, to monitor for fouling. Hartman et al. studied palladium-catalyzed C−N bond-forming reactions and investigated the impact of bridging and constriction due to solid formation in microreactors.[33] At higher flow rates they observed that the pressure change was reduced indicative of a lower rate of fouling. This correlation was supported by a constriction model for the rate of solid deposition in the reactor. The authors propose that blockages, which result from constriction, could be prevented by increasing the flow rate.

Claes et al. set out to design a continuous flow process for an aminolysis reaction using heterogeneous feed solutions and reagent concentrations of 0.5 M or greater.[64] Their objective was to perform a series of screening reactions in a microwave reactor in order to initially establish suitable batch conditions, and the optimum reaction solvent (refer to 3a (iii) Choosing the Reaction Solvent). A pulsatile flow reactor was used to deliver a continuous process in which both the feed and product solutions were heterogeneous. The reactor was reported to be capable of managing solid loadings of up to 22 mass% (m%) when the concentration of 0.85 M of the substrate, a 4-chloropyrimidine derivative **22**, was employed. A maximum yield of 97% for the desired product **23** was obtained with 6 equiv of ammonia, temperature 210 °C and a residence time of 5 min (Figure 14). A peristaltic pump was employed to manage the pyrimidine-containing starting material solution **22** as a slurry, in the polar, aprotic solvent

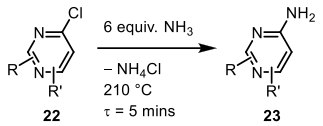

Figure 14. Reaction conditions for the continuous aminolysis of substrate **22**.[64]

N-butylpyrrolidinone (NBP). This adjustment coupled with the use of pulsatile flow prevented settling of the solid particulates in the tube connected to the feed pump for reagent delivery. An additional preventative measure implemented by the authors to prevent sedimentation occurring in the pump head of the pulsator was to feed the slurry from the top, allowing gravity to assist in keeping the material flowing.

Snead and Jamison describe the use of different pumps in their flow setup toward the synthesis of ibuprofen.[76] The researchers employ a 1 M HCl quench at the end of a Friedel−Crafts acylation reaction to remove residual concentrated $AlCl_3$. Readers are directed to the section on (iv) Use of Auxiliary Solvents for further discussions on the use of this acidic quench by the researchers. An in-line membrane separator is used to remove the aqueous stream, containing Al, HCl and H_2O, from the organic product stream, which is telescoped into the next flow stage. The authors comment that syringe pumps were unsuitable for use in the quench reaction since they gave a stagnated flow of 1 M HCl, and that an inconsistent delivery of the quench solution could result in slugs of $AlCl_3$ remaining in the reaction stream, which have the potential to cause clogging. A syringe pump was used for delivery of the reagent feed solution containing propionyl chloride mixed with $AlCl_3$, while a HPLC pump was used for the quench addition. HPLC pumps or double piston pumps tend to deliver more consistent flow and minimize pulsation when compared to syringe pumps.[103]

Researchers at Massachusetts Institute of Technology (MIT) reported the design of a novel solid-feeding slurry pump to support continuous heterogeneous photoredox reactions in their custom photo-CSTR system which was highlighted in the previous section of this Review (refer to 3b (ii) Use of Wider-bore Components).[102] This slurry pump was designed to pump feed solutions containing insoluble materials into the CSTR setup (Figure 15). The stainless-steel

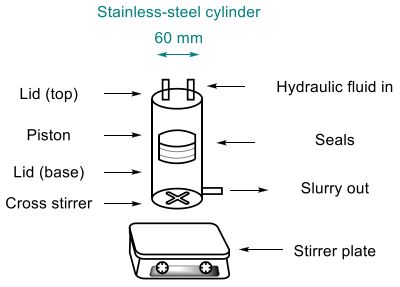

Figure 15. Schematic of a custom built slurry pump by researchers in the Jensen lab.[102]

cylindrical pump contains a cross stirrer bar to maintain a slurry suspension. The pump consists of a piston which is set inside the cylinder, separating the feed solution from an inert hydraulic liquid, in this case acetonitrile, and the hydraulic pressure applied controls the flow of the solid-containing feed solution at the outlet. The slurry flow exiting the pump is improved by incorporating a vibration motor at the outlet point. To test the pump, samples of an 8.3 wt % biphasic liquid−solid solution of Na_2CO_3 in DMF were collected every 10 min over a period of 100 min. The theoretical mass (%) was plotted versus time (mins), and showed the theoretical mass to be between 98.4 and 103.0% across the time points. The utility of this pump was demonstrated by the delivery of a slurry for a

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

metalloredox cross-electrophile coupling reaction in flow, using a photo flow CSTR cascade developed in-house. The pump was used to feed the insoluble inorganic base Na_2CO_3 in *N*,*N*-dimethylacetamide (DMA).

3b (iv). Types of Back Pressure Regulators. A back pressure regulator (BPR) is a device commonly employed at the end of a continuous flow setup and post reactor outlet. Operating at increased pressure enables reactions to be superheated, meaning that they can be performed above the boiling point of the solvent and the reaction solution is maintained in its liquid phase. Traditional back pressure regulators tend not to tolerate particular matter very well due to their small-bore components, and while the ideal solution for a reaction in flow is to select a reaction solvent which ensures solution homogeneity throughout the reaction, this is not always be feasible.[31] A BPR which facilitates manual pressure control offers greater flexibility, whereby the user can vary the pressure (bar) over the course of a reaction by turning an adjustable knob on the BPR device (Figure 16). This screw-knob is used to restrict the flow of liquid through an inert section of tubing housed within the BPR device to manually adjust the pressure during a solvent run or reaction, and the pressure readout will be visible on the reactor screen. If a blockage occurs within the BPR or prior to the device, for example in a reactor coil or mixer, causing the reaction stream to be halted, and an increase in the pressure readout, the knob may be adjusted to facilitate the resumption of flow of the liquid through the BPR. In the case of systems which require elevated temperatures to ensure complete homogeneity and solubility of all the reaction components, a heated back pressure regulator may be incorporated, and the desired temperature of the reaction solution maintained up to sample collection, helping to prevent precipitation of solids after the reaction stream exits a heated reactor assembly.[104] The absence of small orifices in some commercially available BPRs provides an increased robustness to clogging, and while not suitable for slurry-forming reactions, they are more capable of tolerating small amounts of particulate matter in reaction solutions.[105]

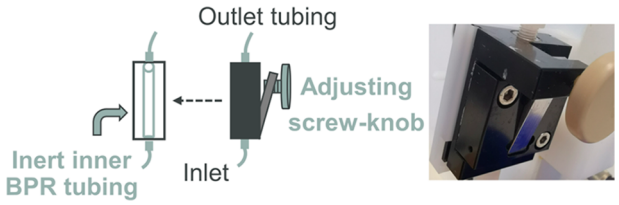

Figure 16. Manually adjustable back pressure regulator (BPR).[106]

Due to the susceptibility of back pressure regulators to blockages by solid particulate material, an alternative approach was implemented by the Ley group specifically for reactions which form slurries, and a prototype device built from commercially available parts (see also 3b (ii) Use of Wider-bore Components).[31] The device was designed to be used in conjunction with the an agitated cell reactor (ACR) of 100 mL fixed volume, specifically at flow rates greater than 5 mL/min.[107] Further details on this type of reactor can be referred to in a later section (refer to (d) Types of Flow Reactors Suitable for Reactions Involving Solids). The utility of this pressure chamber was demonstrated for reactions which form slurries due to poor solubility of the product in the reaction solvent.[31] A series of α-enol-γ-keto esters **24** were synthesized from aryl ketone substrates **25** in the presence of diethyl oxalate **26** to test the operation of the pressure chamber coupled to the ACR (Figure 17).[31] The aryl keto ester product **26** was expected to precipitate from the reaction solution, forming a thick slurry. This system presented an ideal model to evaluate the effectiveness of the pressure regulation device for avoiding blockages in a continuous solid-forming synthesis. The ACR cells contain ceramic, cylindrical agitators which enable solid particulates to remain suspended in the reaction solution as the mixture moves through the reactor. The reaction mixture was intercepted by an aq. HCl quench which promoted precipitation of the desired α-enol-γ-keto ester product **24**. The slurry was collected into the pressurized vessel following the quench addition and the outlet valve can be kept partially open to ensure the continuous release of reaction mixture into another vessel for collection and subsequent isolation. The resultant slurries were analyzed by ^{1}H NMR spectroscopy and the reaction conversions varied between 60

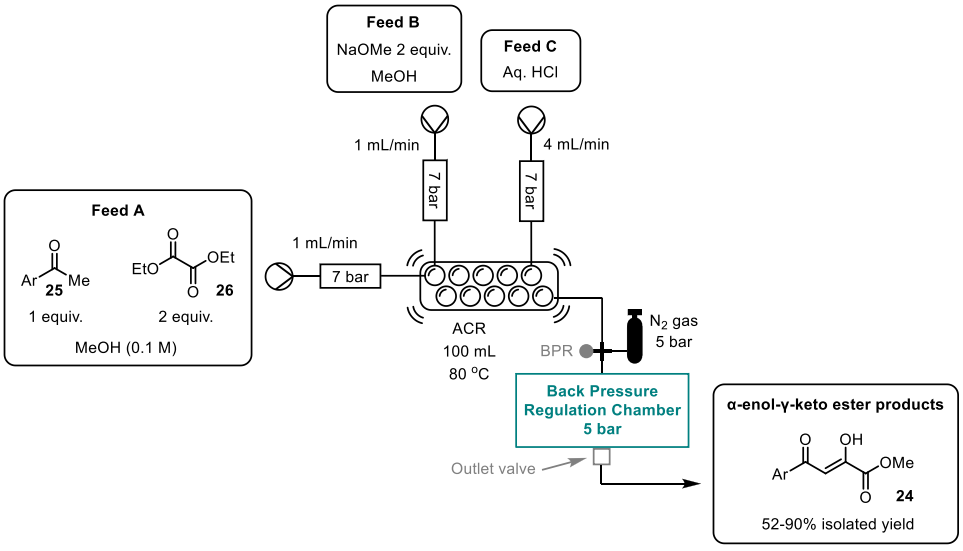

Figure 17. Use of an agitated cell reactor coupled with a bespoke BPR device for the continuous synthesis of α-enol-γ-keto esters as slurries.[31]

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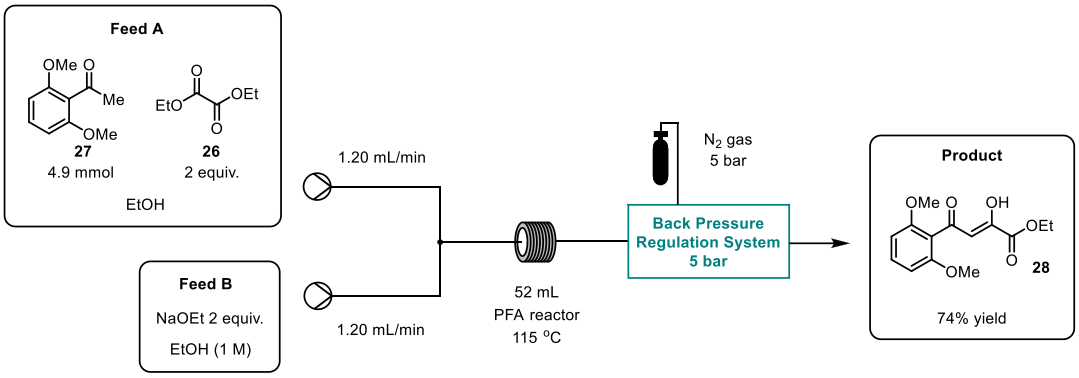

Figure 18. Continuous Claisen rearrangement in a Uniqsis FlowSyn coupled with a bespoke BPR device.[101]

and 95%. The yields for the isolated aryl ketone products **24** were slightly lower (52−90%).

Battilocchio et al. further demonstrated the utility of this device developed in-house by performing a Claisen condensation as a proof-of-concept, reacting substrate **27** and diethyl oxalate **26** in the presence of a base (Figure 18). This particular reaction was initially optimized using a microwave reactor but proved challenging when attempted in flow due to precipitation of the product, resulting in blockages.[101] Additional discussions relating to this work can be found in sections on 3a (v) Application of Temperature Control and 3b (ii) Use of Wider-bore Components. The problem was exacerbated when higher concentrations of basic sodium ethoxide solution were used, and unfortunately lowering the overall reaction concentration resulted in incomplete conversion to the product **28**. While in this case it was determined that flow offered little benefit over the batch process, the reaction proved a good example to test the back pressure regulator designed for solid-forming reactions.[31,101] A Uniqsis FlowSyn was used and the pressure chamber, set to 5 bar, was connected at the end of the system, directly after the heated reactor coil.[108] Given the nature of the reaction, and high potential for blockages due to solid formation, a 52 mL reactor coil made using wide diameter (OD = 1/8 in.) PFA tubing was employed. The Claisen reaction was run successfully in a continuous manner without blockages.[101]

c. Applications of Ultrasonication. The strategy of ultrasonication or pulsed agitation has been applied as a preventative measure for the buildup of solid particulates in a flow reaction, including for photochemical transformations.[33,73,109,110] Examples of the application of ultrasonication, in addition to pulsed agitation, are presented for an oxidation reaction, the α-functionalization of esters, a hydroformylation reaction, a photodimerization, a palladium-catalyzed C−N cross-coupling, the precipitation of barium sulfate, and last a photocatalytic oxidation reaction.

Sedelmeier et al. demonstrate the benefit of subjecting their flow setup to pulsed ultrasonication in a series of continuous oxidations to prevent blockages in the reactor due to solid deposition and fouling (Figure 19).[110] Their objective was to perform a series of transformations in flow employing potassium permanganate ($KMnO_4$) as an oxidant, including the conversion of aldehydes, alcohols and nitroalkanes to the corresponding carboxylic acid, and oxidation of nitroalkanes to the respective carbonyl product in a Nef reaction.[111] The product obtained in the Nef reaction is dictated by the quantity of oxidant employed, with one equivalent giving the

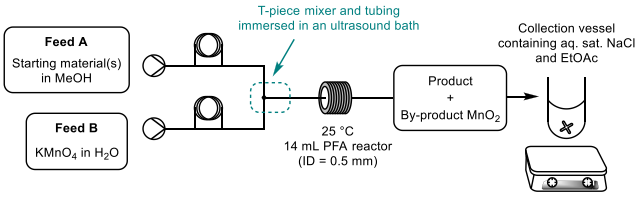

Figure 19. Flow diagram showing T-piece and tubing subject to ultrasonication for solid-forming oxidation reactions with $KMNO_4$.[110]

aldehyde/ketone, and an excess affording the carboxylic acid. The stoichiometric byproduct, manganese dioxide was insoluble in the reaction solution, precipitating at the point of mixing of the reagent feeds, and causing fouling downstream in the reactor coil. Since the byproduct was formed in the T-piece mixer, a simple solution could be implemented to enable the process to proceed unaffected by the presence of solids. The reagent feeds were mixed at a T-piece which was submerged in an ultrasonication bath. Constant versus pulsed sonication was tested, with only 5 s pulses, separated by 1 min intervals, necessary to mitigate blockages. The approach did not solubilize the solids but the particulates were better dispersed in the solution and could pass through the coil without resulting in reactor fouling from solid aggregation within the tubing. In this case, modification of the flow setup through incorporation of an ultrasound bath at the point of reagent mixing was substantial to manage the solid-forming reaction, and alteration of the chemical system to ensure complete dissolution of all reaction components was not required.

The generation of lithium diisopropylamide (LDA) was performed in-line in a flow synthesis to form α-functionalized esters **29** via the lithium enolate.[92,112] The process consisted of three continuous, telescoped steps followed by an aqueous quench; formation of the organolithium reagent from *tert*-butyl propionate substrate **30**, deprotonation to give the enolate intermediate, and last addition of an electrophile in the form of methyl formate **31** to deliver the final product. Blockages were encountered at the point of reaction of the lithium enolate with the substrate electrophile. An ultrasonic bath was employed at this stage in the system to manage the solid formation and prevent blockages from occurring. The tubular reactor coil, in addition to the T-piece mixers, set before and after the reactor, were submerged in the ultrasound bath (Figure 20). The Noël lab have demonstrated the application of ultrasonication to avoid blockages in their microflow setup for the continuous

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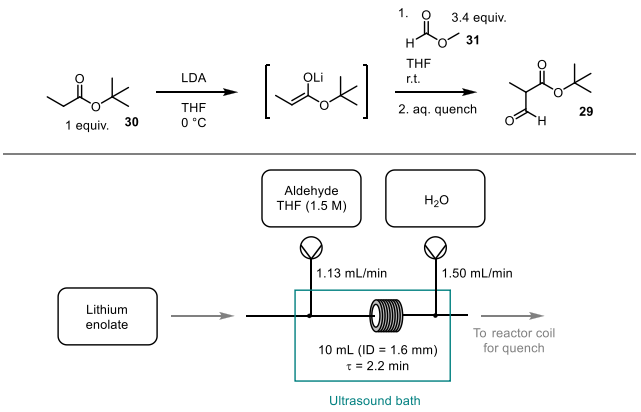

Figure 20. Reactor and T-piece mixers submerged in an ultrasonic bath to prevent clogging during an electrophilic addition reaction.[112]

flow synthesis of diaryliodonium triflates, opting to submerge both the mixer and reactor in an ultrasound bath.[113]

The application of a pulsating flow coiled tubular plug flow reactor (PFR) has been demonstrated by Eli Lilly and Company in a continuous solid-forming, triphasic gas−liquid−solid reaction. The desired branched aldehyde product **32** was formed by a hydroformylation reaction of methyl methacrylate **33** in the presence of a rhodium catalyst, with some of the linear aldehyde byproduct **34** resultant (Figure 21).[114,115]

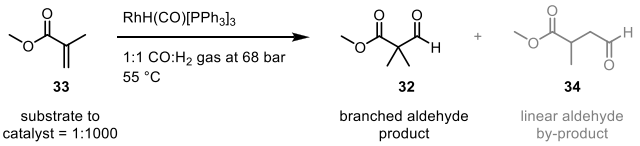

Figure 21. Multiphasic, solid-forming hydroformylation reaction in a pulsating tubular coil PFR.[114,115]

Horie et al. report the benefit of using ultrasound vibrations to ensure the efficient passing of any precipitated solid material through a microreactor (Figure 22).[73] They conducted the

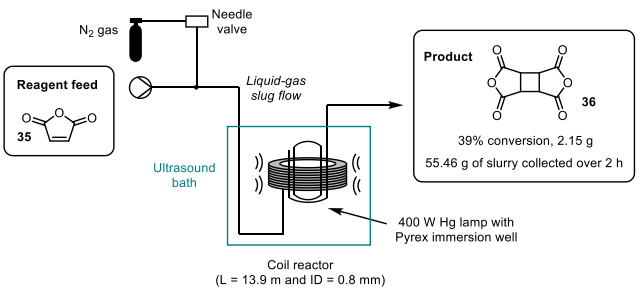

Figure 22. Continuous photodimerization of maleic anhydride with the reactor submerged in an ultrasound bath.[73]

photodimerization of maleic anhydride (MA) **35** in a microreactor as a continuous slug flow process, and with ultrasonication the reaction could be operated in continuous mode for over 16 h without blockages occurring. Slug or segmented flow is a two-phase flow pattern and for liquid−gas processes describes the behavior of flow through the reactor tubing, where "slugs" of liquid are separated from gaseous bubbles.[44,116] In order to establish this behavior, N_2 gas was introduced into the reaction stream as a "spacer".[73] This differs to a plug flow regime, which describes the flow pattern for a single phase liquid stream within a continuous tubular reactor. This reaction was previously discussed in the context of multiphasic reactions due to the application of a liquid−liquid segmented flow approach (refer to 3a (iii) Choosing the Reaction Solvent). The product of the photodimerization of MA **35**, cyclobutene tetracarboxylic dianhydride (CBTA) **36**, is largely insoluble in the organic reaction solvents used in this reaction. The authors speculated that the improved irradiation gained by running their photochemical transformation in flow, coupled with the enhanced mixing offered by microreactor technologies would help to manage the solid formation more effectively.[5] In batch, the suspension of precipitated product **36** in solution, resultant from agitation by rapid stirring has the potential to interfere with the light irradiation. The setup involved coiling a length of fluorinated ethylene propylene (FEP) tubing of varying internal diameter (ID = 0.5−1.6 mm) around a quartz beaker, which was submerged in an ultrasound bath. The beaker acted as containment for the 400 W Hg lamp fitted with a Pyrex immersion well. The authors opted for FEP tubing due to its malleability in contrast to glass for coiling around a beaker, its suitable transparency considering the wavelengths of UV irradiation required, and the material was suspected to be resistant to any buildup of solids on the inner walls of the tubing due to its low coefficient of friction. The beaker in its entirety thus acted as the photochemical reactor. A T-piece mixer was incorporated into the setup prior to the reactor inlet for introduction of inert N_2 gas, delivering the desired slug flow behavior. The control reaction of a simple plug flow, single liquid stream approach was tested and blockages were observed within the first hour of a continuous run. Reaction conversions were observed to improve with decreasing tubing ID, but lower flow rates were required to achieve the longer residence times. Clogging occurred when tubing of ID = 0.5 mm was used at a flow rate of 0.10 mL/min. Tubing with ID = 0.8 mm was determined to be most optimal for preventing blockages while still affording appreciable reaction conversions. The reaction stream was collected immediately upon exiting the reactor for workup and isolation, preventing any potential clogging issues toward the end of the continuous setup.

Hartman et al. report the use of ultrasound as a means to prevent bridging of solid particulates, and subsequent plugging in their microreactor setup for the synthesis of biaryls in a palladium-catalyzed amination reaction.[33] Readers are directed to sections on 2. Blockages in a Continuous Flow, 3a (iii) Choosing the Reaction Solvent and 3b (iii) Consideration of Pumps for additional discussions related to this work by the Hartman group. The cross-coupling studied involved the reaction of 4-chloroanisole **37** with 1 equiv aniline **38** in the presence of XPhos precatalyst and sodium tert-butoxide base (NaOtBu) in 1,4-dioxane at 80 °C to afford the biaryl product **39** (Figure 23).

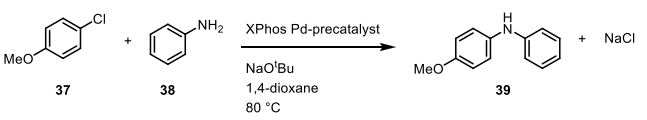

Figure 23. Pd-catalyzed amination reaction conditions.[33]

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Bridging occurred in the microreactor due to the precipitation of stoichiometric amounts of inorganic NaCl salt byproduct from the reaction mixture, in addition to constriction due to accumulation of the byproduct on the inner walls of the reactor. The particle size of the salt was minimized by subjecting the reaction mixture to ultrasound, and the impact of bridging, and subsequent plugging, was reduced. This was achieved by submerging a PFA capillary microreactor in an ultrasonic bath. The impact of insoluble salt byproducts for a continuous flow process was further studied by the Hartman group in context of commercial tubing. A palladium-catalyzed amination using the ligand XPhos was again utilized as the model reaction, and blockages by NaCl were probed for PFA and stainless steel tubing, in addition to a silicon microreactor.[117]

Kuhn et al. also use palladium-catalyzed C−N bond-forming methodology to show the capability of their microreactor setup of managing slurry-forming reactions, without any occurrence of blockage.[118] Their continuous flow setup differs to the approach used in the previous examples described, in which a reactor is immersed in an ultrasonic bath.[33,73,110] In their case, a custom-built setup is described which aims to more effectively deliver ultrasound irradiation to the solid-containing reaction solutions, and their Teflon microreactor has been designed with a piezoelectric actuator built into the reactor.[119] The authors considered a more efficient method for ultrasonic irradiation of the reaction solution, proposing that the water contained within an ultrasound bath could be limiting the delivery of acoustic irradiation to the reactor, and that the general setup may lack adequate control of the frequency of irradiation. The authors considered the chemistry involved for their model amination reaction, and opted to use solely PTFE as the material of construction for the microreactor, postulating that a reactor built from silicon oxide would be more susceptible to etching under conditions of high temperature and pH. The piezoelectric actuator was embedded in the reactor, and the complete setup constructed in a sandwich-like manner with multiple layers stacked together (Figure 24). The different PTFE layers include the inlet and outlet channels, access points for the inclusion of cartridge heaters, the microreactor, piezoelectric actuator and an insulating layer. A test palladium-catalyzed coupling reaction between 4-chloroanisole and aniline was performed in at 80 °C in dioxane with a residence time of 90 s, giving full conversion to the desired product and a 95% isolated yield. In addition to the bespoke microreactor, there were some other measures taken by the authors to minimize the potential of clogging and blockages in the whole system; (a) the reagent feeds were premixed in a T-piece at 15 °C prior to passing through the microreactor, and (b) an auxiliary H_2O/EtOAc quench was incorporated into the setup post reactor to ensure dissolution of any salt particulates.

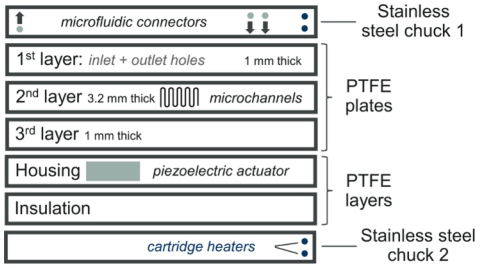

Figure 24. Schematic for the construction of a bespoke Teflon microreactor with stacked layers.[118]

A flow reactor suitable for large-scale, solid-forming reactions which are facilitated by ultrasound irradiation has been reported by Delacour et al.[120] The reactor was developed in-house, comprising a PFA coil reactor housed within an aluminum box (ID = 2 mm and total volume ≈12 mL), which could be linked to up to six ultrasonic transducers. Using their custom ultrasound millireactor (USMR), 14 g/h of barium sulfate could be synthesized when the ultrasound irradiation was set to 0.48 W/mL. The precipitation of barium sulfate was tested in an ultrasound microreactor (USμR) for comparison purposes, albeit at a substantially higher load power of 38 W/mL. A 2 orders of magnitude reduction in productivity was observed for the USμR, and 0.12 g/h barium sulfate could be obtained. Improved mixing efficiency was also observed by Delacour et al. in the custom built ultrasound millireactor (USMR) compared with the ultrasound microreactor (USμR), and the authors postulated that this was due to the increase in flow rate used, 0.2 mL/min and 2 mL/min for the USμR and USMR respectively.[120] Mixing as a parameter relevant to scale-up in sonochemical reactors has been evaluated for multiphasic systems including solid−liquid systems.[121]

As previously alluded to, when ultrasonic waves are transmitted through aqueous media within a reactor-containing box, in an "indirect" fashion, the efficiency of irradiation is potentially reduced relative to what might be achieved via a "direct" reactor-transducer setup. Implementation of a "direct" strategy comes with different challenges, for example relating to temperature control and large-scale operation. According to Dong et al., no ultrasound microreactors with a transducer directly coupled to the reactor have been reported for setups of greater than 2 mL of reactor volume.[122] The authors report a custom build millireactor enabling *meso*-scale continuous multiphasic photocatalytic reactions (Figure 25).[122] They selected a three-phase photocatalytic transformation starting from 4-(trifluororomethyl)benzyl alcohol **40** to give the aryl aldehyde product **41**, and involving TiO_2 particles (solid phase) to test the ability of their reactor to handle a solid suspension. The aryl carboxylic acid **42** was reported to be observed as a side-product in the reaction. This is an aerobic process necessitating the use of O_2 (gas) and performed in acetonitrile (liquid) at room temperature with 365 nm LEDs. A 4.1 m length of borosilicate glass capillary (ID = 2.2 mm and total volume = 12.88 mL) was coiled around an irradiating cylinder. This was then connected to a sonotrode, which provides the mechanical vibrational energy, and a cooling shell. Modifications to a Langevin transducer facilitated a larger area of radial ultrasound irradiating waves enabling larger-scale reactions. The ultrasonic millireactor was encased in an illuminating box. The study explored (a) the impact of ultrasound on the reaction conversion at different concentrations of TiO_2 (1, 2, and 5 mg/mL) and residence times (14, 28, and 55 min), and (b) the effect of ultrasound on the reaction conversion and selectivity at varying substrate concentrations (1, 2, and 5 mM) with a residence time of 55 min and TiO_2 concentration of 5 mg/mL. Ultrasonication was applied in pulses, with the ON/OFF time = 12.5/12.5 s and at a power of 60 W to prevent any increase in temperature when the ultrasound was applied continuously, and a satisfactory suspension of the TiO_2 was maintained with pulsed sonication. The application of ultrasound prevented aggregation of TiO_2

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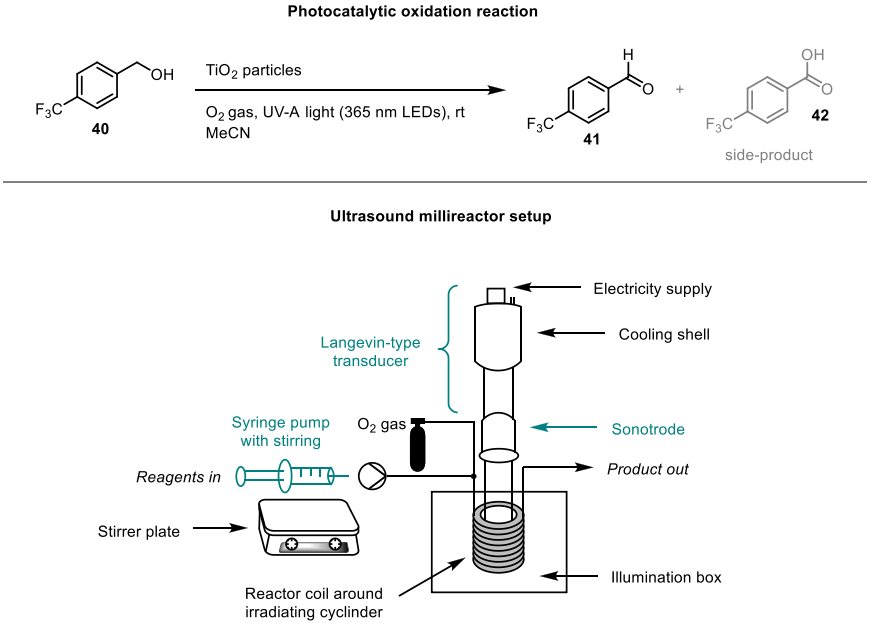

Figure 25. Continuous photochemical oxidation reaction catalyzed by TiO_2 particles run in a bespoke ultrasound millireactor.[122]

nanoparticles in the reactor, and the slurry could be continuously passed through the coil to achieve higher conversions in contrast to control reactions in the absence of ultrasound irradiation. The penetrating light was thought to have access to a greater surface area of overall catalyst when the particles existed as a suspension in the reaction solution compared with catalyst particles settling within the reactor.[122]

The contribution of different setup parameters involved in running a sonochemical system for heterogeneous chemistries and reactor design considerations are discussed by Gogate et al., in an effort to homogenize and simplify the outlook of sonochemical reactors in large-scale applications.[121] The authors discuss several criteria including frequency of irradiation, power rating, physicochemical properties of the liquid phase, and last the geometrical design, which considers the arrangement and diameters of the transducer and reactor within the overall setup. A comparison of ultrasound horn and bath reactors is presented as two commonly utilized setups.[121] To improve the consistency of ultrasonic irradiation delivered, transducers in ultrasound baths will often employ a horn to widen the surface for irradiation.[122] Some recent examples of novel reactor designs employing less conventional approaches to reactor geometry are also described in this article.

Ultrasound has also been applied in continuous crystallizations, and sonocrystallization refers to the application of ultrasonic irradiation to control the nucleation and growth process. These phases of crystallization can benefit from ultrasonication and some ultrasound parameters have been explored specifically for continuous sonocrystallization in a millifluidic device by the Mazzei group.[123] The authors probed the continuous crystallization of adipic acid as an isothermal process using a piezoelectric element in a millichannel chip reactor. This unique reactor for sonocrystallization was built in-house, and the rate of crystallization and particle size was found to be impacted by the ultrasonic frequencies applied.[123]

d. Types of Flow Reactors Suitable for Reactions Involving Solids. The dominant reactor types used for continuous processing are plug flow reactors (PFRs) and continuous stirred tank reactors (CSTRs).[124] Types of alternative reactors to microchip and PFR coil reactors are outlined here which can be better suited to solid-forming chemistry. These include CSTRs and agitated cell reactor (ACR) technologies, in addition to spinning disc and oscillatory flow reactors.[69,95,107,125−127] Other reactor types capable of handling solids include Taylor Vortex and capillary force trap reactors.[128,129] A comprehensive article reviewing the use of CSTRs for continuous chemical synthesis has recently been published; covering mixing efficiency, handling of solids in flow and scale-up considerations.[130] Thus, for a detailed overview of flow chemistry in CSTRs, including single stage operation and cascade setups, readers are directed to this 2023 review in Reaction Chemistry and Engineering (Figure 26).

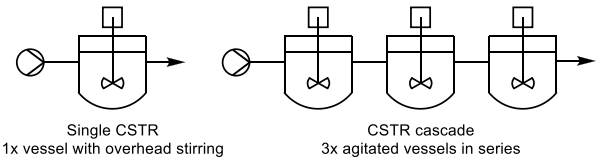

Figure 26. Single CSTR versus cascade CSTR build.[130]

A summary of the application of CSTR technology in the context of handling slurries is reviewed herein. Cherkasov et al. highlight that CSTRs 'facilitate chemical manufacture in continuous flow and have been used for decades' and "excel at solid handling".[130] CSTRs are vessels equipped for active stirring or agitation in which reagent streams are continuously pumped into a tank and the product stream is continuously removed. Their capacity to handle solids is well established, and traditionally this class of reactor is applied to larger-scale reactions. While reactions run in a single CSTR stage give a broad residence time distribution (RTD), the RTD becomes narrower following the incorporation of each additional vessel into the cascade. Cherkasov et al. report that the extent of the spread of a reaction's RTD has an impact on the selectivity, quality and throughput, with a narrower RTD being

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

favorable.[130] In particular, a setup comprising several CSTRs in series has found extensive application in continuous crystallizations since they are better able to handle reactions involving solids.[130] A cascade CSTR system is less susceptible to blockages than a coil reactor since it comprises a number of tanks which facilitate active mixing, connected by short lengths of wider-bore tubing or pipe. The connections are designed to be short in length to minimize the potential of clogging as a result of solids settling in the connecting tubing. For reactions run at elevated temperatures, the lines between two CSTR vessels need to be lagged to maintain temperature during the transfer of a reaction mixture or slurry.

Designed for running continuous flow processes in a laboratory setting up to kilogram scale, the commercially available agitated cell reactor (ACR), is particular suited to biphasic liquid−solid reactions i.e. slurries.[107,130] This ACR reactor setup, comprising a cascade of 10 CSTR cells connected by interstage channels, incorporates dynamic, active agitation provided laterally, and enables solid suspensions to be processed in flow. This agitated cell reactor has been demonstrated by the Ley group using a salt-forming reaction, which was previously discussed in relation to ultrasonication (c. Applications of Ultrasonication).[109] The authors considered the setup suitable for running solid-forming reactions up to 5 kg scale, and demonstrated the utility of this reactor with the production of 208 g of *N*-iodomorpholinium hydroiodide salt **46** in 9 h (Figure 27). A solution of morpholine **47** in

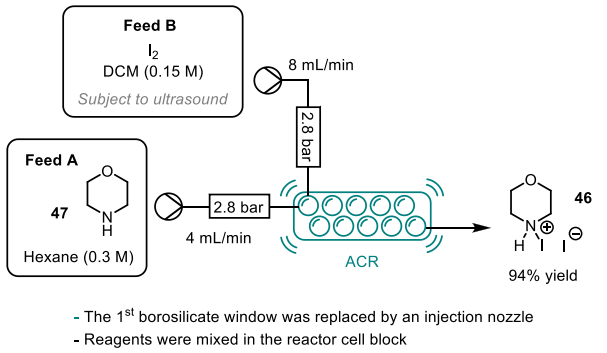

Figure 27. Reaction conditions for the delivery of *N*-iodomorpholinium hydroiodide salt in continuous flow using an agitated cell reactor.[109]

hexane was mixed with a solution of iodine in DCM in the reactor unit as slight blocking was observed when the reagent streams were mixed at a T-piece set prior to the ACR.

This agitated cell reactor has since been applied in the management of solid-forming reactions or slurries for numerous heterogeneous chemistries. Select examples include (a) the generation of an amine salt as part of a multistep natural product synthetic strategy,[63] (b) a continuous phosphorylation reaction, with the ACR technology proving critical for mitigating clogging issues in the flow process due to precipitation of triethylamine hydrochloride,[131] (c) the synthesis of an intermediate toward the final indole product, with the ACR system at 8 Hz agitation capable of managing a 10% solid by volume suspension for over 14 h,[132] (d) a continuous reductive deoxygenation reaction,[133] and (e) a lithiation reaction at −20 °C, which while unsuccessful due to lack of conversion to the desired product, proceeded without blockages occurring due to the precipitation of one of the reaction components when the ACR was used.[134]

A cascade CSTR system was designed and optimized by the Kapur and Blacker groups at the University of Leeds, UK for application in the laboratory to tackle multiphasic chemical synthesis in flow.[87,95] This cascade CSTR consists of five individual stages, each equipped with a cross stirrer bar, and connected in series using PTFE tubing (OD = 1/8 in. and ID = 1/16 in.). The complete unit sits on an anodized aluminum thermal base plate which can be heated on a standard stirrer-hot plate and has a pressure rating of 6.89 bar (100 psi). The application of individual CSTR stages as active mixers has been discussed previously (refer to 3b (i) Choice of Mixer). The researchers report that having 5 × 2 mL reactor stages linked in series, in contrast to having 1 × 10 mL individual CSTR, gives greater uniformity of reaction conditions, and the system behavior is closer to that of a well-mixed plug-flow reactor. This cascade CSTR setup was demonstrated through a series of multiphasic reactions, including a liquid−liquid biphasic reaction in toluene/H_2O, and a solid−liquid−gas triphasic hydrogenation reaction catalyzed by palladium. A continuous diastereomeric crystallization was performed to demonstrate the utility of this lab-scale CSTR setup for handling slurries in flow (Figure 28).[87] The isolated yield of crystalline solid **48** obtained from a single reactor volume (RV) of 10 mL was 1.8% for the continuous resolution of carboxylic acid substrate **49** and tetrahydroisoquinoline **50**, and the yield of product increased to 24% after approximately 4 h of operation or 13 RV. The productivity of this crystallization in batch and flow was reported to be 8.2 g L^{-1} h^{-1} versus 31 g L^{-1} h^{-1} respectively. This system has found utility in small-scale batch and continuous flow reactions for heterogeneous chemistries and homogeneous hydrogenations which are air-sensitive, and the technology is reported to facilitate scale-up and rapid translation of experiments from batch to flow, since it can be operated effectively in both modes.[135]

Another example of a commercially available CSTR setup available for running chemistries in flow involving solids comprises reactors equipped with a stirrer bar which facilitate reaction volumes between 5 to 40 mL and can be operated over a temperature range of −10 °C to +150 °C.[125] The design of a small-scale CSTR cascade setup, comprising six individual reactor vessels complete with cross-stirrers, was reported by Mo and Jensen, and its utility demonstrated for several solid-forming chemical reactions.[136] A sulfonylation reaction was run for 8 h in a continuous manner using a cascade of 3 CSTRs without any incidence of clogging observed, with a reported solid loading of 4.1 wt %. The absence of any significant clogging event was supported by a plot of relative pressure (ΔP/bar) versus time (min).

As with the coil reactors, adaptations can be made to a standard CSTR setup to fulfill specific reaction requirements, and a custom build continuous flow reactor cascade suitable for heterogeneous chemistry on large-scale, comprising five units to give a total reactor volume of 500 mL, has been implemented by Falß et al.[130,137] The researchers report using a "novel reactor concept" to run a Buchwald−Hartwig amination reaction in continuous flow to access an intermediate in the synthesis of a pharmaceutical compound, employing a bulky *N*-heterocyclic carbene (NHC) palladium precatalyst [Pd(IPr*)(cin)Cl]. A reactor setup was built in the lab for gram-scale preparation of the desired coupled product, and incorporated the process of sonication to prevent

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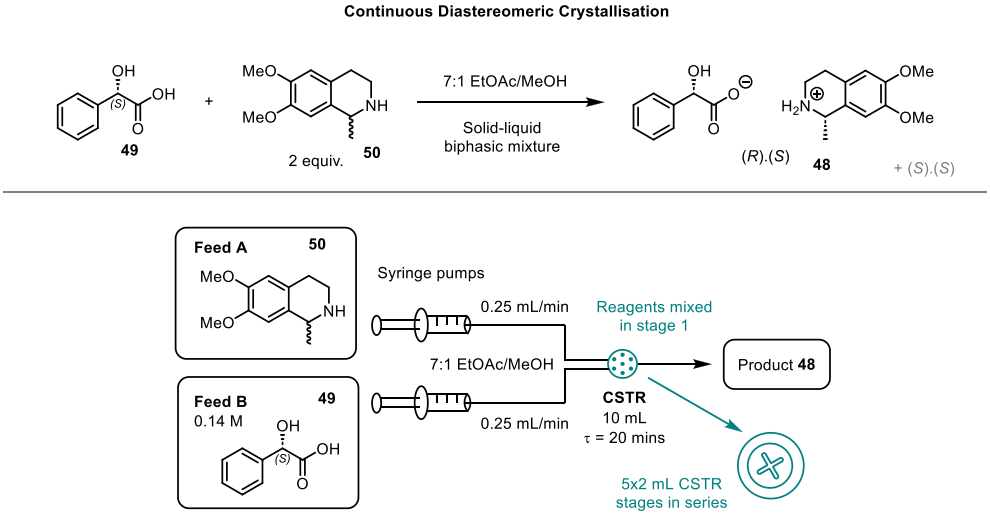

Figure 28. Continuous crystallization of salsolidine and (*S*)-mandelic acid.[87]

blockages occurring in the system. Ultrasonication was required for the larger-scale lab synthesis since ten times the concentration of reactant and base was used than for the reactions conducted on microscale to mimic process-relevant conditions. A PTFE reactor coil (ID = 1.5 mm and total volume = 10.9 mL) was submerged in an ultrasound bath heated to 70 °C to prevent crystallization of the KBr side product, and resultant clogging of the tubular reactor. The CSTR technology developed to perform reactions on mesoscale offered the benefit of having no unagitated connecting lines, helping to prevent clogging as the reaction mixture flowed between the individual reactor units. The reaction mixture exiting the final reactor stage was met with a stream of water at a T-piece mixer. This ensured dissolution of the KBr byproduct prior to passing through the back pressure regulator, thereby avoiding clogging at this point, and in the lines between the reactor and mixer-settler.

CSTRs have found application in continuous photocatalytic transformations which are heterogeneous, and a recent example involves the use of a multimode photo-CSTR setup.[138] Jensen et al. at Massachusetts Institute of Technology (MIT) in the United States, supported by the Novartis MIT Centre for Continuous Manufacturing, developed a CSTR cascade specifically for running visible-light photoredox reactions involving solids in flow. The researchers report a novel solid-feeding technique coupled with a CSTR cascade setup, made up of five individual stages equipped with cross stirrer bars, to manage these heterogeneous reactions (Figure 29).[102] This setup was previously alluded to within this Review in context of modularity (refer to 3b (ii) Use of Wider-bore Components and 3b (iii) Consideration of Pumps).

The utility of this bespoke CSTR cascade was demonstrated for silyl radical-mediated metallophotoredox cross-electrophile coupling reactions in flow. The inorganic base Na_2CO_3 was used as it is insoluble in both reaction solvents, DME and DMA. This provided a suitable model biphasic solid−liquid reaction mixture to test the CSTR cascade for its ability to manage slurries. Specifically, the cross-coupling reaction of a pyran **43** and aryl methyl ester **44** in the presence of a photocatalyst, Ni catalyst, tris(trimethylsilyl)silane and Na_2CO_3 was tested. The reaction was performed in dry DME at 35 °C, and the system purged with argon to exclude

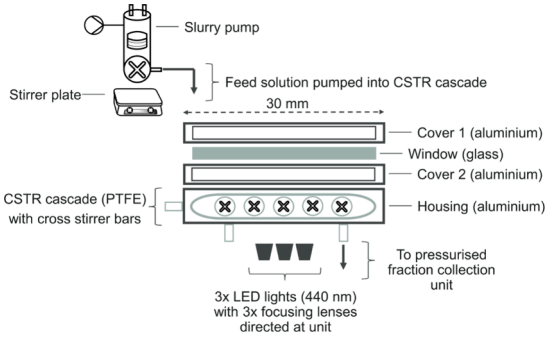

Figure 29. Schematic of a photoflow cascade CSTR and slurry pump setup developed in the Jensen lab for running heterogeneous photochemical reactions.[102]

O_2. After 13 h of running the photoredox reaction in flow, using their custom slurry pump and CSTR cascade setup with blue LEDs (440 nm), a 77% yield (100% conversion) was obtained for the gram-scale synthesis of cross-coupled product methyl 4-(tetrahydro-2*H*-pyran-4-yl)benzoate **45**, amounting to a productivity for the reaction of 77 mg of product generated per hour (Figure 30).[102] The researchers highlighted that the reaction was run over a long period of time in the absence of clogging.

Spinning disc reactor technologies provide active, dynamic mixing, and have been applied in two classes of organolithium reaction; deprotonation and Br/Li exchange, with both transformations facilitated by the organolithium reagents nBuLi and nHexLi.[69] Wietelmann et al. report on a reactor

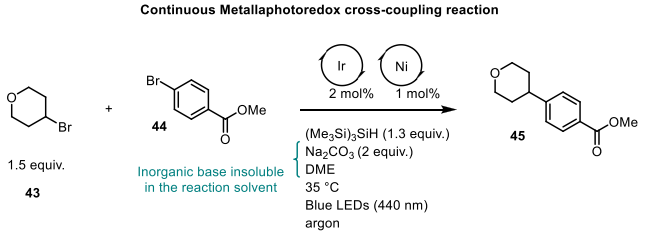

Figure 30. Reaction conditions for a continuous heterogeneous photochemical reaction.[102]

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

capable of managing heterogeneous, salt-forming reactions and dispersions containing a high percentage of solids.[139] This technology combines both plug flow and CSTR mixing regimes within the reactor to eliminate the potential for backmixing, and the high shear forces generated in the CSTR zone prevent solid deposition in the channels.[69] A schematic showing the application of this disc reactor technology for the continuous dynamic Br/Li exchange reaction of aryl substrate **51** to give the desired product **52** is shown (Figure 31).

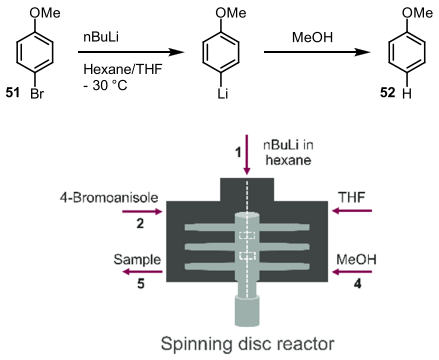

Figure 31. A simple schematic of a spinning disc reactor for the Br/Li exchange reaction of 4-bromoanisole in flow.[69]

Chaudhuri et al. describe the scale-up in flow of a heterogeneous photocatalytic transformation using a photochemical rotor-stator spinning disc reactor (pRS-SDR) setup.[140] The degradation of aqueous methylene blue under aerobic, photochemical conditions by TiO_2 was performed in this reactor due to its capability of managing slurries. The authors describe the pRS-SDR as being particularly suited to performing challenging photochemical reactions involving solids in continuous flow. A schematic of a pRS-SDR highlighting the cylindrical stator housing and rotor is shown (Figure 32).[127] A recent publication in OPR&D describes the

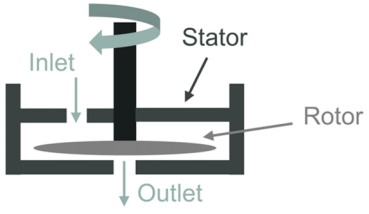

Figure 32. Schematic of a rotor-stator spinning disc reactor.[127]

application of a spinning electrode electrochemical reactor for scale-up electroorganic synthesis which can be operated in batch mode but also continuously via a cascade setup using three reactors set in series.[141] The authors highlight that slurries can be processed using this reactor technology in the absence of clogging or fouling of the reactor and electrodes, respectively.

Oscillatory baffled reactors are tubular reactors which exhibit plug flow behavior, possessing baffles spaced out internally along the tubing to achieve active mixing of the reaction mixture, and commonly used for crystallizations these reactors can manage solid suspensions.[142] Readers are directed to an OPR&D review by McGlone and co-workers on "Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization" for further information.[126] Oscillatory flow reactors have also been applied in continuous photocatalytic reactions, for example the Ir/Ni dual photoredox catalytic cross-electrophile coupling reaction in continuous flow to form a new $C(sp_2)-C(sp_3)$ bond using a heterogeneous inorganic base.[143] Another example includes the semiheterogeneous dual Ni/carbon nitride photocatalytic carbon−nitrogen bond-forming reaction in flow.[144]

The ability of a baffleless oscillatory flow reactor to manage solids has been explored by Doyle et al., and this work probes the use of an oscillatory flow reactor without baffles for heterogeneous solid−liquid reactions.[142] The researchers employed a Hastelloy tubular reactor to be used in oscillatory flow, with an inner diameter of 4.6 mm, expected to be suitable for handling slurries under turbulent, oscillatory flow. Pulsation was applied to the system by a pulsator pump, with both the amplitude and frequency of pulsations in the reactor coil adjustable. The system was monitored with sensors for any sudden pressure increase caused by constriction in the tubing as a result of blockages occurring due to the buildup of solids. The synthesis of *N*,*N*′-(1*E*,2*E*)-ethane-1,2-diylidenedicyclohexanamine (EDDC) **53** by precipitation in ethanol was used to test the ability of the baffleless oscillatory flow reactor to handle a solid-forming reaction (Figure 34).[142] The EDDC product is poorly soluble in ethanol, and was prepared from starting materials cyclohexylamine **54** (2 mol) and glyoxal **55** (1 mol), forming only water as a byproduct. This slurry-forming reaction was performed for suspensions of 5.8 and 7.9 wt % over 5 and 2 h respectively in the absence of blockages. A phase transfer catalysis reaction was also trialled in the baffleless oscillatory reactor setup (Figure 33).[142] Dichlorocarbene (DCC) **56**, formed by reaction with the organic solvent chloroform in the presence of aq. NaOH, was immediately reacted with cyclohexene **57** to give 7,7-dichlorobicyclo[4.1.0]heptane **58**. This biphasic aqueous−organic reaction employed Et_2MeN as a phase transfer catalyst. The reaction was run in a coil reactor at 80 °C with a residence time of 4.5 min, and a pulsation amplitude and frequency of 70.4 mm and 3.68 Hz, respectively. Feed A containing 35 wt % aq. NaOH (12.51 M) was pumped at a flow rate of 7 mL/min to meet feed B, containing the substrate **57** (0.50 M) and catalyst (1.170 M) in chloroform, at 14 mL/min. Clogging was observed when the reaction was run for over 20 min, and the researchers postulated that the reactor's performance was impacted by the generation of byproduct $CO_{(gas)}$ in the reaction, resulting in pulsation dampening and clogging. Specifically, the authors report an approximate 10-fold reduction in the rate of energy dissipation in the reactor coil, and the oscillation dampening could be attributed to the compressibility of the gas formed within a closed system.

e. Grignard Reactions in Continuous Flow. The preparation of Grignard reagents, involving the activation of magnesium metal, is increasingly being performed in flow as routine, and being a hazardous and exothermic reaction it is a ideally placed for being adopted into a continuous platform.[145,146] However, the caveat of running this reaction in flow is the potential for blockages due to the presence of solids. Therefore, a standard, unified approach toward the preparation of these reagents to mitigate clogging events in the flow process is desirable. Some strategies employed to manage solids in continuous Grignard reactions are discussed herein, including an interrupted flow approach, the application of a magnesium trap, a filter reactor setup and packed magnesium column.

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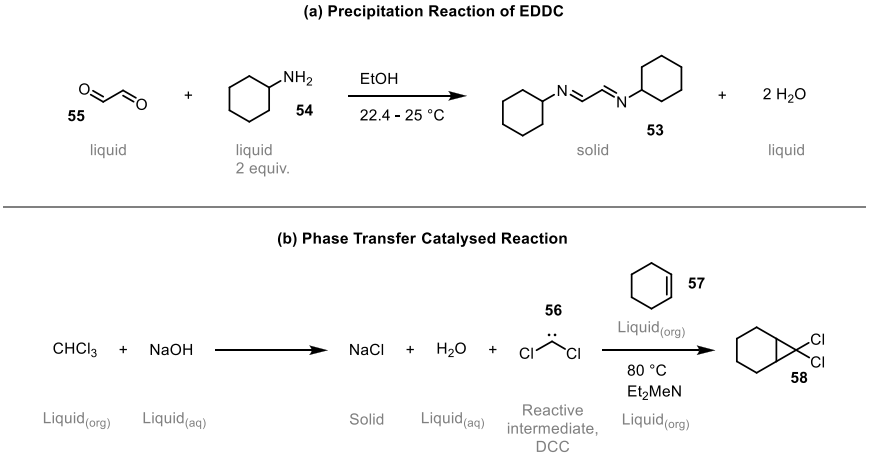

Figure 33. (a) Precipitation reaction and (b) phase transfer catalysis in continuous flow using a baffleless oscillatory reactor.[142]

The continuous formation of a Grignard reagent from 4-chlorotetrahydropyran (4-Cl-THP) **59**, and subsequent reaction with a morpholine amide substrate **60** in an addition reaction to afford the desired ketone product **61** following an acetic acid/water quench, was performed in a cascade CSTR setup using three tanks connected in series (Figure 34).[147] The

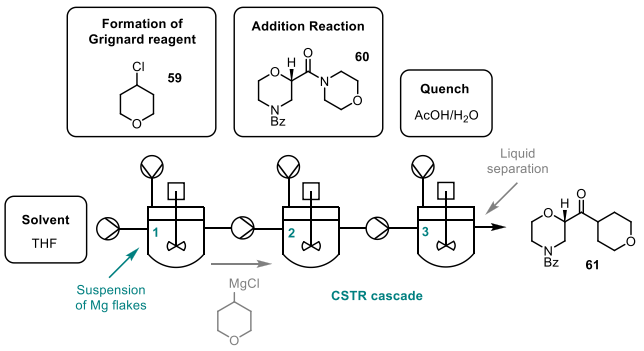

Figure 34. CSTR cascade setup for Grignard reagent formation (CSTR-1), addition reaction with morpholine amide (CSTR-2) and quench (CSTR-3).[147]

first 250 mL of CSTR was designated for Grignard reagent production, and the substrate was introduced into the vessel containing a solution of suspended Mg flakes. THF was used as the solvent and fed into the same CSTR while the Mg solid was maintained in this vessel. The researchers carefully considered the design behind pumping freshly formed Grignard reagent from CSTR-1 into CSTR-2 so as to prevent Mg solid entering the transfer lines, thereby mitigating the potential for any blockages. They hoped to prevent clogging in the outlet tubing from CSTR-1 through accumulation of Mg solid on a screen at the point of exit. The authors report using an automated pressure swing cylinder to maintain the desired flow rate to pump Grignard reagent out of the first tank and into the second to meet with the morpholine amide. Approximately once every minute, a portion of the reaction mixture was pumped out of CSTR-1 and following each transfer, a reverse-purge of nitrogen gas was administered. It was observed during the process that the solubility of the Grignard reagent was poor and it appeared to precipitate out of the reaction mixture, and at this point an alternative Barbier reaction was explored.

The formation of a Grignard reagent in continuous flow was performed in a CSTR by reaction of an aryl bromide with sequestered magnesium solids, at 40 °C in 2-MeTHF, and full conversion to the desired product achieved with a residence time of 60 min in one CSTR vessel. Both the purity of the Ar-MgBr reagent obtained and the safety profile was improved for the flow protocol in comparison to batch.[114] The Mg solid was introduced into the reactor every 4 h to equal the consumption rate, and the optimum schedule of timings for Mg recharge into the vessel was determined through simulations.[146] A settling pipe was incorporated within the CTSR to contain the solid Mg particles in the tank and an additional settling trap placed after the CSTR vessel (Figure 35).[124] The design and

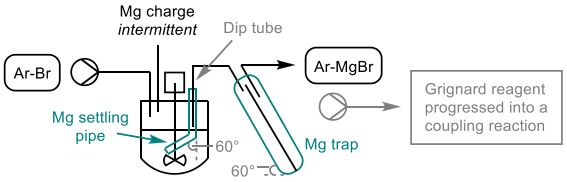

Figure 35. CSTR setup for the formation of Grignard reagent including settling pipe and trap to sequester solid magnesium.[124]

location of the settling pipe in the tank considered the rapid agitation rate required to ensure a suspension of the solid Mg and was demonstrated to successfully sequester the Mg within the CSTR, separating the solid and liquid phases.[146] The trap set post reactor outlet was used to retain any Mg solid particles which left the vessel in the product solution stream so as to avoid progressing any Mg into subsequent vessels or stages. A large-scale manufacture of the Grignard reagent for use in an API synthesis was run in a 100 L CSTR at 45% capacity. A 0.85 M solution of the Grignard reagent was prepared on 4000 L scale by this method and progressed into a Kumada coupling reaction.[114] This example highlights the advantageous application of a solids settling strategy for separation of a biphasic solid−liquid reaction mixture, in addition to the use of rapid agitation in a CSTR for managing a suspension of solid particles for the continuous flow preparation of a Grignard reagent.

Another approach for preparing Grignard reagents in continuous flow involves using a column packed with magnesium, and this strategy has been explored by Huck et

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al. (Figure 36).[148] Magnesium insertion into (hetero)aryl and alkyl bromide and iodide substrates afforded the corresponding

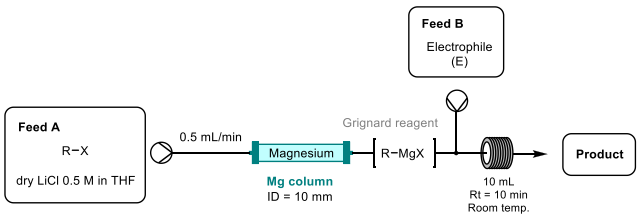

Figure 36. General method for the continuous flow preparation of a Grignard reagent using a magnesium packed column and telescoped reaction of the organomagnesium reagent with an electrophile.[148]

organomagnesium reagent by this packed Mg column approach. A procedure was developed for activation of the magnesium and reaction conditions optimized for the preparation of phenylmagnesium bromide from bromobenzene. Following activation of the magnesium metal, the authors observed clogging due to the precipitation of solid in both the column and outlet tubing, which was found to be soluble in both toluene and in 0.5 M LiCl in THF. A general method which prevented any blockages was then developed, with 1:1 THF/toluene used as the solvent system for the magnesium activation stage, and following this step a solution of the aryl bromide substrate and LiCl was passed through the column dissolved in THF. The resultant Grignard reagent could be telescoped into a second stage and the reaction stream combined with an electrophile to deliver the desired compound. Flow conditions differed for the synthesis of alcohol, amide, *tert*-butyl ester and ketone products, and either a chip or coil reactor was employed depending on the electrophile used.

Pedersen et al. describe a minireactor setup (Figure 37) for heterogeneous Grignard chemistry, which was alluded to

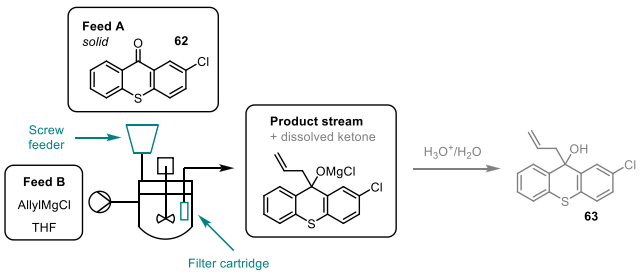

Figure 37. Filter reactor showing filter unit contained within the vessel for a Grignard alkylation reaction.[82]

previously in the context of mitigating clogging incidents by increasing the temperature (refer to 3a (v) Application of Temperature Control).[82] Specifically, a Grignard alkylation reaction was performed toward an intermediate in the synthesis of the pharmaceutical compound zuclopenthixol hydrochloride (Clopixol).[82] Ketone starting material **62** was reacted with allylmagnesium chloride (allylMgCl) in THF to generate the desired magnesium alkoxide in a CSTR-like vessel with a filter positioned at the exit point (Figure 38). The desired intermediate alcohol **63** is formed upon hydrolysis of the magnesium alkoxide. AllylMgCl was pumped as a solution in THF into the filter reactor and ketone substrate introduced as a solid using a screw feeder. The filter reactor facilitated solid retention and the filter unit could be removed and replaced to prevent clogging by solid particulates building up in the filter. To provide a large filter area the unit was designed to be cylindrical and was introduced from the top of the vessel for ease of replacement.

f. A Case Study in Process Development. An example of the problematic nature of solid formation for a continuous flow process in development is highlighted in the optimization of a cyclopropanation reaction as part of the synthetic route toward the ATR inhibitor AZD6738.[149] Different strategies were trialled during the development of the cyclopropyl sulfoximine moiety from the first scale-up reaction to plant scale, including batch, flow and CSTR processes (Figure 38). Challenges with solid formation were encountered at various points during the development of flow stages including blockages at the point of mixing of reagents and in the reactor.

The Bolm conditions used for the scale-up process (a) were combined with a deprotection step as part of the workup for the first generation kilo scale process (b), to afford the cyclopropyl sulfoximine product **64** from substrate **65** (Figure 38).[150] On small scale in the lab, this reaction gave ∼70% yield in batch, which was reduced to 40% when the process was run on a one kilogram scale. Degradation of product **64** was suspected to be the cause of the yield loss as a result of the hold time following the acidic deprotection step. A reaction involving tetrabutylammonium bromide (TBAB) as a phase transfer catalyst was developed in flow so that the transformation could proceed at high temperature and over a short time period, to minimize the likelihood of product decomposition. With reaction conditions established, several Design of Experiment (DOE) studies were performed, in a Uniqsis FlowSyn reactor equipped with an IMM static mixer. However, the formation of solid inorganic byproduct, KBr resulted in blockages occurring in the mixer. The setup used in the manufacturing process was designed to avoid any potential blockages due to solid formation at the point of mixing (Figure 39). The aqueous feed of potassium hydroxide was added by a pump and the second organic feed, which comprised all the other reagents in anisole, was sprayed into the reactor unit through a nozzle, with only minor formation of solids reported.

A change to the primary deprotection step for the second generation process (c) in batch incurred problems for the flow reaction downstream (Figure 38). A 4 M solution of KOH in anisole was used to remove the trifluoroacetamide (TFAc) protecting group at 20 °C to afford compound **66**. The resultant solution of **66** could be taken forward into the subsequent flow stage, but issues were encountered due to the formation of KBr, which under the reaction conditions caused reactor blockages. The solvent system, which was changed from H_2O-anisole to anisole only, was thought to result in the reduced solubility of the inorganic byproduct. While two batches of the cyclopropane were synthesized using this approach, the repeated blockages did not provide a very robust process.

The final plant scale process involved an acidic deprotection as the first step, followed by an extraction of **66** into 2-MeTHF (Figure 38). The process delivered six batches on 76 kg scale (71% average yield) of the sulfoximine **66** for use as a solution in 2-MeTHF in the subsequent cyclopropanation reaction. A CSTR setup with four reactor units in series was used for the cyclopropanation, the workup performed in batch, and following a solvent swap into isopropanol, the HCl salt was obtained (Figure 40). This CSTR cascade comprising four

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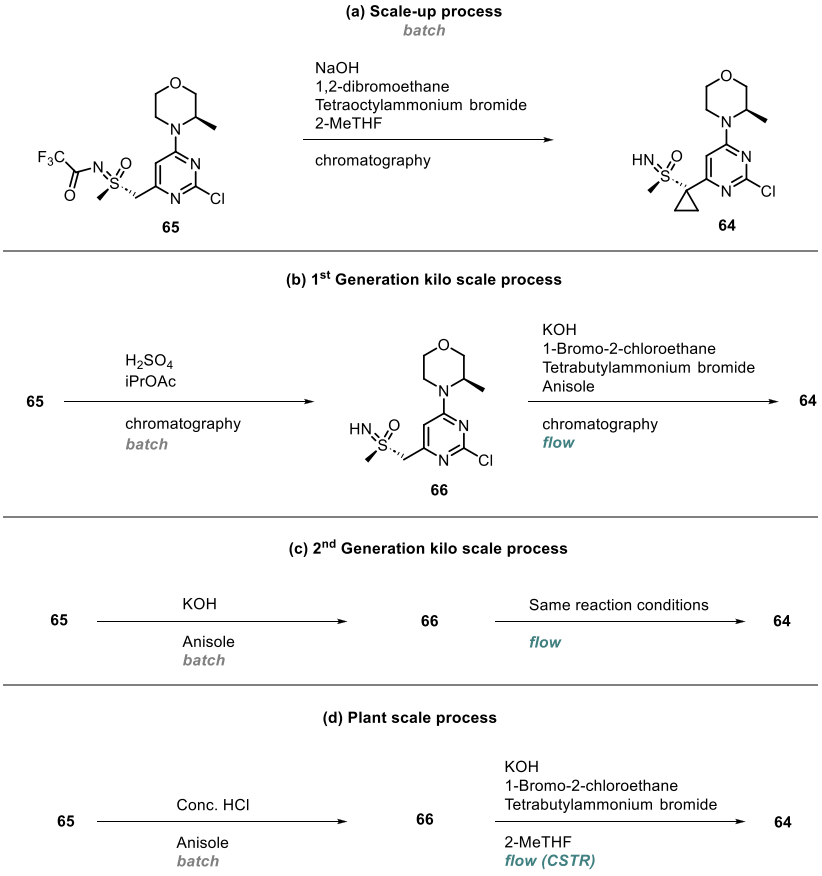

Figure 38. (a) Scale-up, (b) 1st, (c) 2nd and (d) plant scale process reaction conditions for the formation of cyclopropyl sulfoximine **64**.[149]

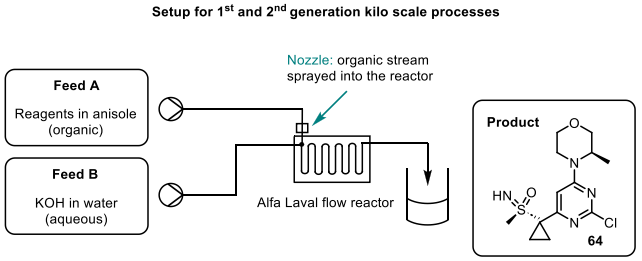

Figure 39. Flow setup for the synthesis of the cyclopropyl sulfoximine product.[149]

vessels runs under gravity to ensure material transfer in an overflow process.[149]

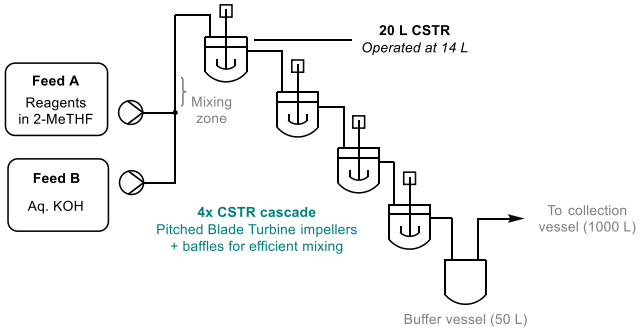

Figure 40. CSTR cascade used in the plant scale manufacture.[149]

While dealing with solids in continuous flow can be challenging in all scales, within large scale process chemistry such as pharmaceuticals, these challenges can mean a complete rethink of the strategy to deliver that compound. In cases where the advantages in flow are so great when compared to the batch process, for example doubling the yield or safely using explosive or very toxic materials, continuous flow may still be considered, and efforts toward solving the solid formation will still be sought out. Some of the techniques described herein, such as the use of ultrasonicating, may be difficult to adapt on large scale continuous flow at the moment, however, it does not mean that process chemistry groups will not manage to adapt it in the future if it is required.

4. SUMMARY AND CONCLUSIONS

While the presence of solids in a chemical reaction should not necessarily deter the chemist from applying continuous methodology, it is important to recognize that in certain cases batch may be the more suitable approach for solid-forming chemistries. Furthermore, certain factors dictate the viable strategies which may be harnessed to manage a particular flow process involving solids, and there are several questions which should be addressed at the start of development.

- *Can the reaction conditions be altered to afford a homogeneous system?* It is critical to establish the scope for manipulation of the reaction conditions at the beginning of development, as this will determine the ability to apply invasive and/or noninvasive approaches. If the reaction conditions are fixed, then consideration of

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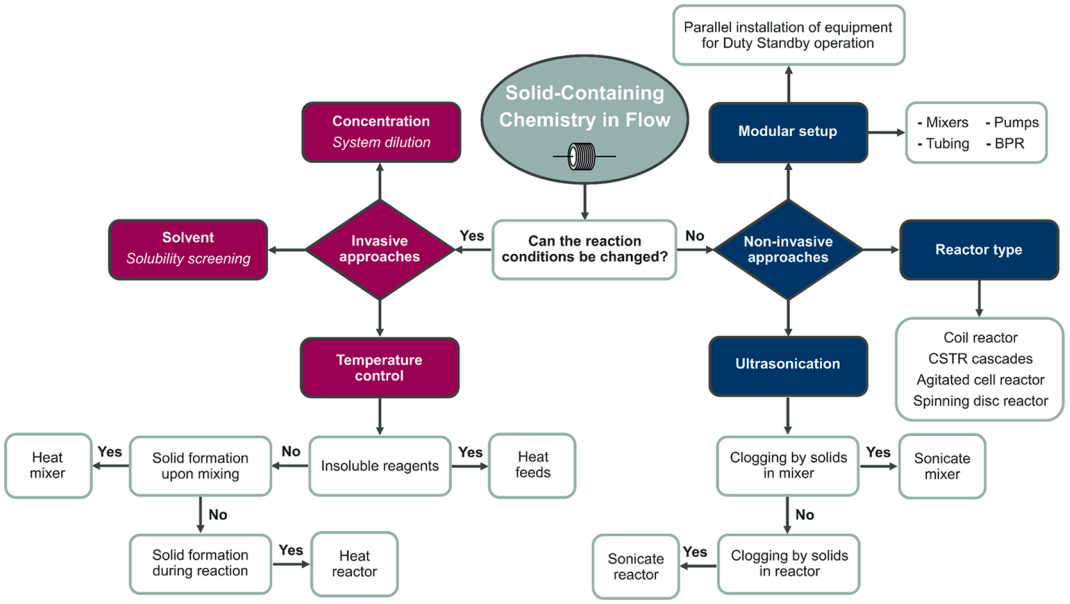

Figure 41. Flowchart to aid the development of a continuous flow process involving solids.

the various strategies to manage the presence of solids will be the only practical route.

- *Can any additional process knowledge be gained from batch experiments?* If there is scope to alter the reaction conditions to ensure a homogeneous system, then supporting experiments can be performed to guide the selection of a suitable invasive strategy. These may be (a) establishing the chemical identity of the solid(s) present, and (b) gathering solubility data in a selection of solvents and across a broad temperature range.
- *Can a modular setup be applied for the continuous flow process?* Introducing modularity into a continuous flow system is especially relevant for solid-forming chemistries, as it provides increased flexibility, presenting the option for exchanging individual components.
- *Is there the potential for unexpected solid formation?* In-line process analytical technologies (PAT) can help to provide increased process control during the operation of a flow process involving solids?[151,152] If no solids are observed during the development process of a flow stage, performing an extended run is essential to rule out the potential for clogging incidences over longer time periods. Incorporation of pressure sensors for example would enable detection of clogging events due to the unexpected buildup of solids in a continuous flow process.

A flowchart is presented below which should aid the development of a challenging flow process involving solids, detailing some important considerations, and separating invasive approaches from noninvasive ones (Figure 41). These general strategies are relevant to the development of a continuous flow process, whereby the presence of solids is expected, and are applicable both for the adaption of established batch conditions into flow or the implementation of flow methodology directly.

Within this Review, we have shown that while there is currently no silver bullet that fixes all the issues when it comes to solids in continuous flow, a systematic collection of management strategies exist for adapting continuous flow to suspensions, which are demonstrated through the different examples from literature.

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Author Contributions

The manuscript was written by H.L.D.H and C.J.M. All authors have given approval to the final version of the manuscript.

Notes

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ABBREVIATIONS

ACR, agitated cell reactor; ACS, American chemical society; Al, aluminum; AllylMgCl, allylmagnesium chloride; $AlCl_3$, Aluminum chloride; API, active pharmaceutical ingredient; ATR, ataxia telangiectasia and Rad3-related; BDA, butane-2,3-diacetal; BPR, back pressure regulator; nBuLi, *n*-butyl lithium; CBTA, cyclobutene tetracarboxylic dianhydride; CSA, camphorsulfonic acid; CSTR, continuous stirred tank reactor; DCC, dichlorocarbene; DMA, *N,N*-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N,N*- dimethylformamide; DMP, 2,2-dimethoxypropane; DOE, design of experi-

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

ment; DTU, Technical University of Denmark; EDDC, *N*,*N*′-(1*E*,2*E*)-ethane-1,2-diylidenedicyclohexanamine; EtOAc, ethyl acetate; FEP, fluorinated ethylene propylene; GCI, green chemistry institute; GSK, GlaxoSmithKline; HCl, hydrochloric acid; nHexLi, *n*-hexyl lithium; HPLC, high performance liquid chromatography; H_2O, water; ID, inner diameter; IPA, isopropyl alcohol; $KMnO_4$, potassium permanganate; LDA, lithium diisopropylamine; LED, light-emitting diode; MA, maleic anhydride; MDAT, magnetically driven agitation in a tube; MeOH, methanol; 2-MeTHF, 2-methyltetrahydrofuran; MIT, Massachusetts Institute of Technology; MSMPR, mixed-suspension mixed-product removal; MTBE, methyl *tert*-butyl ether; $NaBH_4$, sodium borohydride, Na_2CO_3, sodium carbonate; NaOH, sodium hydroxide; NBP, N-butylpyrrolidinone, NHC, *N*-heterocyclic carbene; OFR, Oscillatory Flow Reactor; OD, outer diameter; OPR&D, Organic Process Research and Development; PAT, process analytical technologies; PEEK, polyetheretherketone; PFA, perfluoroalkoxy alkane; PFR, plug flow reactor; PhLi, phenyllithium; pRS-SDR, photochemical rotor-stator spinning disc reactor; PTFE, polytetrafluoroethylene; RTD, residence time distribution; RV, reactor volume; SFTR, continuous segmented flow tubular reactor; SMDD, Small Molecule Design and Development; TBAB, tetrabutylammonium bromide; THF, tetrahydrofuran; TFAc, trifluoroacetamide; THF, tetrahydrofuran; THP, tetrahydropyran; TiO_2, titanium dioxide; USMR, ultrasound millireactor; USμR, ultrasound microreactor, UV−vis, ultraviolet−visible

REFERENCES

(1) Jiménez-González, 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*, 900−911.

(2) Poechlauer, P.; Manley, J.; Broxterman, R.; Gregertsen, B.; Ridemark, M. Continuous Processing in the Manufacture of Active Pharmaceutical Ingredients and Finished Dosage Forms: An Industry Perspective. *Org. Process Res. Dev.* **2012**, *16*, 1586−1590.

(3) 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.

(4) Capaldo, L.; Wen, Z.; Noel, T. A field guide to flow chemistry for synthetic organic chemists. *Chem. Sci.* **2023**, *14*, 4230−4247.

(5) Rehm, T. H. Flow Photochemistry as a Tool in Organic Synthesis. *Chemistry* **2020**, *26*, 16952−16974.

(6) Hartman, R. L. Flow chemistry remains an opportunity for chemists and chemical engineers. *Curr. Opin. Chem. Eng.* **2020**, *29*, 42−50.

(7) Guidi, M.; Seeberger, P. H.; Gilmore, K. How to approach flow chemistry. *Chem. Soc. Rev.* **2020**, *49*, 8910−8932.

(8) Noel, T.; Cao, Y.; Laudadio, G. The Fundamentals Behind the Use of Flow Reactors in Electrochemistry. *Acc. Chem. Res.* **2019**, *52*, 2858−2869.

(9) Bogdan, A. R.; Dombrowski, A. W. Emerging Trends in Flow Chemistry and Applications to the Pharmaceutical Industry. *J. Med. Chem.* **2019**, *62*, 6422−6468.

(10) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117*, 11796−11893.

(11) Akwi, F. M.; Watts, P. Continuous flow chemistry: where are we now? Recent applications, challenges and limitations. *Chem. Commun.* **2018**, *54*, 13894−13928.

(12) Cardoso, D. S. P.; Šljukić, B.; Santos, D. M. F.; Sequeira, C. A. C. Organic Electrosynthesis: From Laboratorial Practice to Industrial Applications. *Org. Process Res. Dev.* **2017**, *21*, 1213−1226.

(13) Cambie, D.; Bottecchia, C.; Straathof, N. J.; Hessel, V.; Noel, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276−341.

(14) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20*, 2−25.

(15) Maljuric, S.; Jud, W.; Kappe, C. O.; Cantillo, D. Translating batch electrochemistry to single-pass continuous flow conditions: an organic chemist's guide. *J. Flow Chem.* **2020**, *10*, 181−190.

(16) Domokos, A.; Nagy, B.; Szilágyi, B.; Marosi, G.; Nagy, Z. K. Integrated Continuous Pharmaceutical Technologies—A Review. *Org. Process Res. Dev.* **2021**, *25*, 721−739.

(17) Srai, J. S.; Badman, C.; Krumme, M.; Futran, M.; Johnston, C. Future Supply Chains Enabled by Continuous Processing—Opportunities Challenges May 20−21 2014 Continuous Manufacturing Symposium. *J. Pharm. Sci.* **2015**, *104*, 840−849.

(18) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system. *Science* **2016**, *352*, 61−67.

(19) Badman, C.; Cooney, C. L.; Florence, A.; Konstantinov, K.; Krumme, M.; Mascia, S.; Nasr, M.; Trout, B. L. Why We Need Continuous Pharmaceutical Manufacturing and How to Make It Happen. *J. Pharm. Sci.* **2019**, *108*, 3521−3523.

(20) Thayer, A. M. End-To-End Chemistry. https://cen.acs.org/articles/92/i21/EndEnd-Chemistry.html (accessed 2024-01-04).

(21) Palmer, E. GSK opens $95M continuous production operation in Singapore. https://www.fiercepharma.com/manufacturing/gsk-opens-130m-continuous-production-facilities-singapore (accessed 2024-01-04).

(22) Rogers, L.; Jensen, K. F. Continuous manufacturing - the Green Chemistry promise? *Green Chem.* **2019**, *21*, 3481−3498.

(23) O'Brien, A. G.; Liu, Y. C.; Hughes, M. J.; Lim, J. J.; Hodnett, N. S.; Falco, N. Investigation of a Weak Temperature-Rate Relationship in the Carbamoylation of a Barbituric Acid Pharmaceutical Intermediate. *J. Org. Chem.* **2019**, *84*, 4948−4952.

(24) Cole, K. P. What Elements Contribute to a High-Quality Continuous Processing Submission for OPR&D? *Org. Process Res. Dev.* **2020**, *24*, 1781−1784.

(25) Roberge, D. M. An Integrated Approach Combining Reaction Engineering and Design of Experiments for Optimising Reactions. *Org. Process Res. Dev.* **2004**, *8*, 1049−1053.

(26) Hartman, R. L. Managing Solids in Microreactors for the Upstream Continuous Processing of Fine Chemicals. *Org. Process Res. Dev.* **2012**, *16*, 870−887.

(27) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries? *Chem. Eng. Technol.* **2005**, *28*, 318−323.

(28) Solids and Slurries Handling in Flow Reactors https://www.amt.uk/solids-in-flow (accessed 2023-10-03).

(29) Dressaire, E.; Sauret, A. Clogging of microfluidic systems. *Soft Matter* **2017**, *13*, 37−48.

(30) Dong, Z.; Wen, Z.; Zhao, F.; Kuhn, S.; Noël, T. Scale-up of micro- and milli-reactors: An overview of strategies, design principles and applications. *Chem. Eng. Sci.: X* **2021**, *10*, 100097.

(31) Deadman, B. J.; Browne, D. L.; Baxendale, I. R.; Ley, S. V. Back Pressure Regulation of Slurry-Forming Reactions in Continuous Flow. *Chem. Eng. Technol.* **2015**, *38*, 259−264.

(32) Bana, P.; Orkenyi, R.; Lovei, K.; Lako, A.; Turos, G. I.; Eles, J.; Faigl, F.; Greiner, I. The route from problem to solution in multistep continuous flow synthesis of pharmaceutical compounds. *Bioorg. Med. Chem.* **2017**, *25*, 6180−6189.

https://doi.org/10.1021/acs.oprd.3c00407
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(33) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. Overcoming the Challenges of Solid Bridging and Constriction during Pd Catalyzed C-N Bond Formation in Microreactors. *Org. Process Res. Dev.* **2010**, *14*, 1347−1357.
(34) Tilton, J. N. Fluid and Particle Dynamics. In *Perry's Chemical Engineers' Handbook*, 7th ed.; Perry, R. H., Green, D. W., Maloney, J. O., Ed. McGraw-Hill Education: 1997; pp 6-1−6-54.
(35) Besenhard, M. O.; Pal, S.; Gkogkos, G.; Gavriilidis, A. Non-fouling flow reactors for nanomaterial synthesis. *React. Chem. Eng.* **2023**, *8*, 955−977.
(36) Schoenitz, M.; Grundemann, L.; Augustin, W.; Scholl, S. Fouling in microstructured devices: a review. *Chem. Commun. (Camb)* **2015**, *51*, 8213−28.
(37) Eren, A.; Civati, F.; Ma, W.; Gamekkanda, J. C.; Myerson, A. S. Continuous crystallization and its potential use in drug substance Manufacture: A review. *J. Cryst. Growth* **2023**, *601*, 126958.
(38) Zhang, D.; Xu, S.; Du, S.; Wang, J.; Gong, J. Progress of Pharmaceutical Continuous Crystallization. *Engineering* **2017**, *3*, 354−364.
(39) Orehek, J.; Teslic, D.; Likozar, B. Continuous Crystallization Processes in Pharmaceutical Manufacturing: A Review. *Org. Process Res. Dev.* **2017**, *25*, 16−42.
(40) Jiang, M.; Braatz, R. D. Designs of continuous-flow pharmaceutical crystallizers: developments and practice. *Cryst. Eng. Comm/* **2019**, *21*, 3534−3551.
(41) Johnson, M. D.; Burcham, C. L.; May, S. A.; Calvin, J. R.; McClary Groh, J.; Myers, S. S.; Webster, L. P.; Roberts, J. C.; Reddy, V. R.; Luciani, C. V.; Corrigan, A. P.; Spencer, R. D.; Moylan, R.; Boyse, R.; Murphy, J. D.; Stout, J. R. API Continuous Cooling and Antisolvent Crystallization for Kinetic Impurity Rejection in cGMP Manufacturing. *Org. Process Res. Dev.* **2021**, *25*, 1284−1351.
(42) Filipponi, P.; Gioiello, A.; Baxendale, I. R. Controlled Flow Precipitation as a Valuable Tool for Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 371−375.
(43) Baumann, M.; Moody, T. S.; Smyth, M.; Wharry, S. Overcoming the Hurdles and Challenges Associated with Developing Continuous Industrial Processes. *Eur. J. Org. Chem.* **2020**, *2020*, 7398−7406.
(44) Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 327−360.
(45) Wen, Z.; Wan, T.; Vijeta, A.; Casadevall, C.; Buglioni, L.; Reisner, E.; Noel, T. Photocatalytic C-H Azolation of Arenes Using Heterogeneous Carbon Nitride in Batch and Flow. *Chem. Sus. Chem.* **2021**, *14*, 5265−5270.
(46) Baxendale, I. R.; Brocken, L.; Mallia, C. J. Flow chemistry approaches directed at improving chemical synthesis. *Green Process Synth.* **2013**, *2*, 211−230.
(47) Masson, E.; Maciejewski, E. M.; Wheelhouse, K. M. P.; Edwards, L. J. Fixed Bed Continuous Hydrogenations in Trickle Flow Mode: A Pharmaceutical Industry Perspective. *Org. Process Res. Dev.* **2022**, *26*, 2190−2223.
(48) Planchestainer, M.; Contente, M. L.; Cassidy, J.; Molinari, F.; Tamborini, L.; Paradisi, F. Continuous flow biocatalysis: production and in-line purification of amines by immobilised transaminase from Halomonas elongata. *Green Chem.* **2017**, *19*, 372−375.
(49) Tamborini, L.; Previtali, C.; Annunziata, F.; Bavaro, T.; Terreni, M.; Calleri, E.; Rinaldi, F.; Pinto, A.; Speranza, G.; Ubiali, D.; Conti, P. An Enzymatic Flow-Based Preparative Route to Vidarabine. *Molecules* **2020**, *25*, 1223.
(50) Benítez-Mateos, A. I.; Contente, M. L.; Roura Padrosa, D.; Paradisi, F. Flow biocatalysis 101: design, development and applications. *React. Chem. Eng.* **2021**, *6*, 599−611.
(51) Britton, J.; Majumdar, S.; Weiss, G. A. Continuous flow biocatalysis. *Chem. Soc. Rev.* **2018**, *47*, 5891−5918.
(52) Cosgrove, S. C.; Mattey, A. P. Reaching New Biocatalytic Reactivity Using Continuous Flow Reactors. *Chemistry* **2022**, *28*, No. e202103607.
(53) Wu, J.; Zheng, C.; Li, B.; Hawkins, J. M.; Scott, S. L. Efficient, continuous N-Boc deprotection of amines using solid acid catalysts. *React. Chem. Eng.* **2021**, *6*, 279−288.
(54) Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. Flow synthesis of organic azides and the multistep synthesis of imines and amines using a new monolithic triphenylphosphine reagent. *Org. Biomol. Chem.* **2011**, *9*, 1927−37.
(55) Gilmore, K.; Vukelić, S.; McQuade, D. T.; Koksch, B.; Seeberger, P. H. Continuous Reductions and Reductive Aminations Using Solid NaBH4. *Org. Process Res. Dev.* **2014**, *18*, 1771−1776.
(56) Hone, C. A.; Kappe, C. O. Towards the Standardization of Flow Chemistry Protocols for Organic Reactions. *Chemistry-Methods* **2021**, *1*, 454−467.
(57) Gustafsson, T.; Sörensen, H.; Pontén, F. Development of a Continuous Flow Scale-Up Approach of Reflux Inhibitor AZD6906. *Org. Process Res. Dev.* **2012**, *16*, 925−929.
(58) Alonso, M.; Garcia, M. C.; McKay, C.; Thorp, L. R.; Webb, M.; Edwards, L. J. Use of Lithium Diisopropylamide in Flow: Operability and Safety Challenges Encountered on a Multigram Scale. *Org. Process Res. Dev.* **2021**, *25*, 988−1000.
(59) Dunn, A. L.; Leitch, D. C.; Journet, M.; Martin, M.; Tabet, E. A.; Curtis, N. R.; Williams, G.; Goss, C.; Shaw, T.; O'Hare, B.; Wade, C.; Toczko, M. A.; Liu, P. Selective Continuous Flow Iodination Guided by Direct Spectroscopic Observation of Equilibrating Aryl Lithium Regioisomers. *Organometallics* **2019**, *38*, 129−137.
(60) Machida, K.; Kawachi, H.; Iwasaki, R.; Sakaguchi, T.; Murakami, A.; Nishiyama, A., Efficient Cleaning Method for Flow Reactors in Flow Lithiation Reactions Under Water-free Conditions. *Org. Process Res. Dev.* **2023**. DOI: 10.1021/acs.oprd.3c00321
(61) Zhang, C. T.; Zhu, R.; Wang, Z.; Ma, B.; Zajac, A.; Smiglak, M.; Xia, C. N.; Castle, S. L.; Wang, W. L. Continuous flow synthesis of diaryl ketones by coupling of aryl Grignard reagents with acyl chlorides under mild conditions in the ecofriendly solvent 2-methyltetrahydrofuran. *RSC Adv.* **2019**, *9*, 2199−2204.
(62) Carter, C. F.; Baxendale, I. R.; Pavey, J. B.; Ley, S. V. The continuous flow synthesis of butane-2,3-diacetal protected building blocks using microreactors. *Org. Biomol Chem.* **2010**, *8*, 1588−95.
(63) Wan, L.; Kong, G.; Liu, M.; Jiang, M.; Cheng, D.; Chen, F. Flow chemistry in the multi-step synthesis of natural products. *Green Synth. Catal.* **2022**, *3*, 243−258.
(64) Claes, J.; Vancleef, A.; Segers, M.; Brabants, B.; Leblebici, M. E.; Kuhn, S.; Moens, L.; Thomassen, L. C. J. Synthesis of amines: From a microwave batch reactor to a continuous milliflow reactor with heterogeneous feed and product. *Chem. Eng. Process.:Process Intensif.* **2023**, *183*, 109252.
(65) Li, B.; Bader, S.; Guinness, S. M.; Ruggeri, S. G.; Hayward, C. M.; Hoagland, S.; Lucas, J.; Li, R.; Limburg, D.; McWilliams, J. C.; Raggon, J.; Van Alsten, J. Continuous flow aminolysis under high temperature and pressure. *J. Flow Chem.* **2020**, *10*, 145−156.
(66) K. Kashani, S.; Sullivan, R. J.; Andersen, M.; Newman, S. G. Overcoming solid handling issues in continuous flow substitution reactions through ionic liquid formation. *Green Chem.* **2018**, *20*, 1748−1753.
(67) Seddon, K. R. A taste of the future. *Nat. Mater.* **2003**, *2*, 363−365.
(68) Greaves, T. L.; Drummond, C. J. Protic Ionic Liquids Properties and Applications. *Chem. Rev.* **2008**, *108*, 206−237.
(69) Wietelmann, U.; Klösener, J.; Rittmeyer, P.; Schnippering, S.; Bats, H.; Stam, W. Continuous Processing of Concentrated Organolithiums in Flow Using Static and Dynamic Spinning Disc Reactor Technologies. *Org. Process Res. Dev.* **2022**, *26*, 1422−1431.
(70) Rathman, T. L.; Schwindeman, J. A. Preparation, Properties, and Safe Handling of Commercial Organolithiums: Alkyllithiums, Lithium sec-Organoamides, and Lithium Alkoxides. *Org. Process Res. Dev.* **2014**, *18*, 1192−1210.
(71) Shaughnessy, K. H. Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions. *Chem. Rev.* **2009**, *109*, 643−710.

https://doi.org/10.1021/acs.oprd.3c00407
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(72) Naber, J. R.; Buchwald, S. L. Packed-bed reactors for continuous-flow C-N cross-coupling. *Angew. Chem., Int. Ed. Engl.* **2010**, *49*, 9469−74.
(73) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. Photodimerization of Maleic Anhydride in a Microreactor Without Clogging. *Org. Process Res. Dev.* **2010**, *14*, 405−410.
(74) Rivera, N. R.; Kassim, B.; Grigorov, P.; Wang, H.; Armenante, M.; Bu, X.; Lekhal, A.; Variankaval, N. Investigation of a Flow Step Clogging Incident: A Precautionary Note on the Use of THF in Commercial-Scale Continuous Process. *Org. Process Res. Dev.* **2019**, *23*, 2556−2561.
(75) Kelly, C. B.; Lee, C.; Leadbeater, N. E. An approach for continuous-flow processing of reactions that involve the in situ formation of organic products. *Tetrahedron Lett.* **2011**, *52*, 263−265.
(76) Snead, D. R.; Jamison, T. F. A three-minute synthesis and purification of ibuprofen: pushing the limits of continuous-flow processing. *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 983−7.
(77) Snead, D. R.; Jamison, T. F. End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts. *Chem. Sci.* **2013**, *4* (7), 2822.
(78) Heated mixing tube reactor - Features. https://www.vapourtec.com/products/flow-reactors/temperature-controlled-mixing-tube-features/ (accessed 2023-10-05).
(79) Mallia, C. J.; McCreanor, N. G.; Legg, D. H.; Stewart, C. R.; Coppock, S.; Ashworth, I. W.; Le Bars, J.; Clarke, A.; Clemens, G.; Fisk, H.; Benson, H.; Oke, S.; Churchill, T.; Hoyle, M.; Timms, L.; Vare, K.; Sims, M.; Knight, S. Development and Manufacture of a Curtius Rearrangement Using Continuous Flow towards the Large-Scale Manufacture of AZD7648. *Org. Process Res. Dev.* **2022**, *26*, 3312−3322.
(80) Thaisrivongs, D. A.; Naber, J. R.; McMullen, J. P. Using Flow To Outpace Fast Proton Transfer in an Organometallic Reaction for the Manufacture of Verubecestat (MK-8931). *Org. Process Res. Dev.* **2016**, *20*, 1997−2004.
(81) Glasnov, T. N.; Kappe, C. O. The Microwave-to-Flow Paradigm: Translating High-Temperature Batch Microwave Chemistry to Scalable Continuous-Flow Processes. *Chem.—Eur. J.* **2011**, *17*, 11956−11968.
(82) Pedersen, M. J.; Holm, T. L.; Rahbek, J. P.; Skovby, T.; Mealy, M. J.; Dam-Johansen, K.; Kiil, S. Full-Scale Continuous Mini-Reactor Setup for Heterogeneous Grignard Alkylation of a Pharmaceutical Intermediate. *Org. Process Res. Dev.* **2013**, *17*, 1142−1148.
(83) Cole, K. P.; Reizman, B. J.; Hess, M.; Groh, J. M.; Laurila, M. E.; Cope, R. F.; Campbell, B. M.; Forst, M. B.; Burt, J. L.; Maloney, T. D.; Johnson, M. D.; Mitchell, D.; Polster, C. S.; Mitra, A. W.; Boukerche, M.; Conder, E. W.; Braden, T. M.; Miller, R. D.; Heller, M. R.; Phillips, J. L.; Howell, J. R. Small-Volume Continuous Manufacturing of Merestinib. Part 1. Process Development and Demonstration. *Org. Process Res. Dev.* **2019**, *23*, 858−869.
(84) Gobert, S. R. L.; Kuhn, S.; Braeken, L.; Thomassen, L. C. J. Characterization of Milli- and Microflow Reactors: Mixing Efficiency and Residence Time Distribution. *Org. Process Res. Dev.* **2017**, *21*, 531−542.
(85) Fournier, M.-C.; Falk, L.; Villermaux, J. A new parallel competing reaction system for assessing micromixing efficiency - Experimental approach. *Chem. Eng. Sci.* **1996**, *51*, 5053−5064.
(86) Static Inline Mixers. https://www.koflo.com/static-mixers.html (accessed 2023-12−18).
(87) Chapman, M. R.; Kwan, M. H. T.; King, G.; Jolley, K. E.; Hussain, M.; Hussain, S.; Salama, I. E.; González Niño, C.; Thompson, L. A.; Bayana, M. E.; Clayton, A. D.; Nguyen, B. N.; Turner, N. J.; Kapur, N.; Blacker, A. J. Simple and Versatile Laboratory Scale CSTR for Multiphasic Continuous-Flow Chemistry and Long Residence Times. *Org. Process Res. Dev.* **2017**, *21*, 1294−1301.
(88) Li, H.; Sheeran, J. W.; Clausen, A. M.; Fang, Y. Q.; Bio, M. M.; Bader, S. Flow Asymmetric Propargylation: Development of Continuous Processes for the Preparation of a Chiral beta-Amino Alcohol. *Angew. Chem., Int. Ed. Engl.* **2017**, *56*, 9425−9429.
(89) Kreimer, M.; Zettl, M.; Aigner, I.; Mannschott, T.; van der Wel, P.; Khinast, J. G.; Krumme, M. Performance Characterization of Static Mixers in Precipitating Environments. *Org. Process Res. Dev.* **2019**, *23*, 1308−1320.
(90) Reckamp, J. M.; Bindels, A.; Duffield, S.; Liu, Y. C.; Bradford, E.; Ricci, E.; Susanne, F.; Rutter, A. Mixing Performance Evaluation for Commercially Available Micromixers Using Villermaux-Dushman Reaction Scheme with the Interaction by Exchange with the Mean Model. *Org. Process Res. Dev.* **2017**, *21*, 816−820.
(91) Camarri, S.; Mariotti, A.; Galletti, C.; Brunazzi, E.; Mauri, R.; Salvetti, M. V. An Overview of Flow Features and Mixing in Micro T and Arrow Mixers. *Ind. Eng. Chem. Res.* **2020**, *59*, 3669−3686.
(92) Power, M.; Alcock, E.; McGlacken, G. P. Organolithium Bases in Flow Chemistry: A Review. *Org. Process Res. Dev.* **2020**, *24*, 1814−1838.
(93) Schwolow, S.; Hollmann, J.; Schenkel, B.; Röder, T. Application-Oriented Analysis of Mixing Performance in Microreactors. *Org. Process Res. Dev.* **2012**, *16*, 1513−1522.
(94) Thakur, R. K.; Vial, C.; Nigam, K. D. P.; Nauman, E. B.; Djelveh, G. Static Mixers in the Process Industries—A Review. *Chem. Eng. Res. Des.* **2003**, *81*, 787−826.
(95) fReactor Home Page. https://www.freactor.com/index.html (accessed 2023-10−03).
(96) Dolman, S. J.; Nyrop, J. L.; Kuethe, J. T. Magnetically driven agitation in a tube mixer affords clog-resistant fast mixing independent of linear velocity. *J. Org. Chem.* **2011**, *76*, 993−6.
(97) Baldyga, J.; Bourne, J. R.; Walker, B. Non-isothermal micromixing in turbulent liquids: Theory and experiment. *Can. J. Chem. Eng.* **1998**, *76*, 641−649.
(98) Vacassy, R.; Lemaître; Hofmann, H.; Gerlings, J. H. Calcium carbonate precipitation using new segmented flow tubular reactor. *AIChE J.* **2000**, *46*, 1241−1252.
(99) Jongen, N.; Donnet, M.; Bowen, P.; Lemaître, J.; Hofmann, H.; Schenk, R.; Hofmann, C.; Aoun-Habbache, M.; Guillemet-Fritsch, S.; Sarrias, J.; Rousset, A.; Viviani, M.; Buscaglia, M. T.; Buscaglia, V.; Nanni, P.; Testino, A.; Herguijuela, J. R. Development of a Continuous Segmented Flow Tubular Reactor and the "Scale-out" Concept - In Search of Perfect Powders. *Chem. Eng. Technol.* **2003**, *26*, 303−305.
(100) Poe, S. L.; Cummings, M. A.; Haaf, M. P.; McQuade, D. T. Solving the clogging problem: precipitate-forming reactions in flow. *Angew. Chem. Int. Ed. Eng.*. **2006**, *45*, 1544−8.
(101) Battilocchio, C.; Deadman, B. J.; Nikbin, N.; Kitching, M. O.; Baxendale, I. R.; Ley, S. V. A machine-assisted flow synthesis of SR48692: a probe for the investigation of neurotensin receptor-1. *Chemistry* **2013**, *19*, 7917−30.
(102) Pomberger, A.; Mo, Y.; Nandiwale, K. Y.; Schultz, V. L.; Duvadie, R.; Robinson, R. I.; Altinoglu, E. I.; Jensen, K. F. A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2699−2706.
(103) Broeckhove, K.; Shoykhet, K.; Dong, M. W. Modern HPLC Pumps: Perspectives, Principles, and Practices. *LCGC North America* **2019**, *37*, 374−384.
(104) Heated back pressure regulator - Features. https://www.vapourtec.com/products/flow-reactors/heated-back-pressure-regulator-features/#:~:text=The%20heated%20back%20pressure%20regulator,as%20the%20reaction%20temperature%20reduceshttps://www.vapourtec.com/products/flow-reactors/heated-back-pressure-regulator-features/#:~:text=The%20heated%20back%20pressure%20regulator,as%20the%20reaction%20temperature%20reduces. (accessed 2023-11-27).
(105) Zaiput Flow Technologies Back Pressure Regulators https://www.zaiput.com/product/back-pressure-regulators/ (accessed 2023-10-03).

https://doi.org/10.1021/acs.oprd.3c00407
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(106) The E-Series Flow Chemistry System. https://www.vapourtec.com/products/e-series-flow-chemistry-system-overview/ (accessed 2024-05-01).
(107) Coflore ACR Laboratory Scale Flow Reactor. https://www.amt.uk/coflore-acr (accessed 2023-10-03).
(108) The FlowSyn System. https://www.uniqsis.com/paFlowSystem.aspx (accessed 2023-10-05).
(109) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. Continuous Flow Processing of Slurries: Evaluation of an Agitated Cell Reactor. *Org. Process Res. Dev.* **2011**, *15*, 693−697.
(110) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. $KMnO_4$-Mediated Oxidation as a Continuous Flow Process. *Org. Lett.* **2010**, *12*, 3618−3621.
(111) Nef, J. U. Ueber das zweiwerthige Kohlenstoffatom. *Justus Liebigs Ann. Chem.* **1894**, *280*, 291.
(112) von Keutz, T.; Strauss, F. J.; Cantillo, D.; Kappe, C. O. Continuous flow multistep synthesis of α-functionalized esters via lithium enolate intermediates. *Tetrahedron* **2018**, *74*, 3113−3117.
(113) Laudadio, G.; Gemoets, H. P. L.; Hessel, V.; Noël, T. Flow Synthesis of Diaryliodonium Triflates. *J. Org. Chem.* **2017**, *82*, 11735−11741.
(114) Johnson, M. D.; Braden, T.; Calvin, J. R.; Campbell Brewer, A.; Cole, K. P.; Frank, S.; Kerr, M.; Kjell, D.; Kopach, M. E.; Martinelli, J. R.; May, S. A.; Rincon, J.; White, T. D.; Yates, M. H. The History of Flow Chemistry at Eli Lilly and Company. *Chimia* **2023**, *77* (5), 319.
(115) Johnson, M. D.; May, S. A.; Kopach, M. E.; Groh, J.; White, T. D.; Cole, K. P.; Braden, T. M.; Merritt, J. M. Continuous Reactors for Pharmaceutical Manufacturing. Nagy, Z., El Hagrasy, A., Litster, J., Eds.; In *Continuous Pharmaceutical Processing*; AAPS Advances in the Pharmaceutical Sciences Series; Springer: Cham, 2020; Vol. *42*, pp 23−50.
(116) Holland, F. A.; Bragg, R. Gas-liquid two-phase flow. *Fluid Flow for Chemical Engineers*, 2nd ed.; Butterworth Heinemann: 1995; pp 219−267.
(117) Chen, Y.; Sabio, J. C.; Hartman, R. L. When solids stop flow chemistry in commercial tubing. *J. Flow Chem.* **2015**, *5*, 166−171.
(118) Kuhn, S.; Noel, T.; Gu, L.; Heider, P. L.; Jensen, K. F. A Teflon microreactor with integrated piezoelectric actuator to handle solid forming reactions. *Lab Chip* **2011**, *11*, 2488−92.
(119) Zhang, P. Sensors and actuators. In *Advanced Industrial Control Technology*, Zhang, P., Ed. William Andrew Publishing: 2010.
(120) Delacour, C.; Stephens, D. S.; Lutz, C.; Mettin, R.; Kuhn, S. Design and Characterization of a Scaled-up Ultrasonic Flow Reactor. *Org. Process Res. Dev.* **2020**, *24*, 2085−2093.
(121) Gogate, P. R.; Sutkar, V. S.; Pandit, A. B. Sonochemical reactors: Important design and scale up considerations with a special emphasis on heterogeneous systems. *J. Chem. Eng.* **2011**, *166*, 1066−1082.
(122) Dong, Z.; Zondag, S. D. A.; Schmid, M.; Wen, Z.; Noël, T. A meso-scale ultrasonic milli-reactor enables gas-liquid-solid photocatalytic reactions in flow. *J. Chem. Eng.* **2022**, *428*, 130968.
(123) Jamshidi, R.; Rossi, D.; Saffari, N.; Gavriilidis, A.; Mazzei, L. Investigation of the Effect of Ultrasound Parameters on Continuous Sonocrystallization in a Millifluidic Device. *Crys. Growth Des.* **2016**, *16*, 4607−4619.
(124) Johnson, M. D.; May, S. A.; Kopach, M. E.; Groh, J. M.; Braden, T.; Shankarraman, V.; Merritt, J. M. Design and Selection of Continuous Reactors for Pharmaceutical Manufacturing. *Chemical Engineering in the Pharmaceutical Industry* **2019**, 367−385.
(125) CSTR Flow reactor features https://www.vapourtec.com/products/flow-reactors/cstr-flow-reactor-features/ (accessed 2023-10-03).
(126) McGlone, T.; Briggs, N. E. B.; Clark, C. A.; Brown, C. J.; Sefcik, J.; Florence, A. J. Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization. *Org. Process Res. Dev.* **2015**, *19*, 1186−1202.
(127) Manzano Martinez, A. N.; van Eeten, K. M. P.; Schouten, J. C.; van der Schaaf, J. Micromixing in a Rotor-Stator Spinning Disc Reactor. *Ind. Eng. Chem. Res.* **2017**, *56*, 13454−13460.
(128) Sczechowski, J. G.; Koval, C. A.; Noble, R. D. A Taylor vortex reactor for heterogeneous photocatalysis. *Chem. Eng. Sci.* **1995**, *50*, 3163−3173.
(129) Ng, S. S. Y.; Walker, D. M.; Hawkins, J. M.; Khan, S. A. 3D-printed capillary force trap reactors (CFTRs) for multiphase catalytic flow chemistry. *React. Chem. Eng.* **2022**, *7*, 1297−1306.
(130) Cherkasov, N.; Adams, S. J.; Bainbridge, E. G. A.; Thornton, J. A. M. Continuous stirred tank reactors in fine chemical synthesis for efficient mixing, solids-handling, and rapid scale-up. *React. Chem. Eng.* **2023**, *8*, 266−277.
(131) Yao, H.; Wan, L.; Zhao, X.; Guo, Y.; Zhou, J.; Bo, X.; Mao, Y.; Xin, Z. Effective Phosphorylation of 2,2′-Methylene-bis(4,6-di-tert-butyl) Phenol in Continuous Flow Reactors. *Org. Process Res. Dev.* **2021**, *25*, 2060−2070.
(132) Baumann, M.; Baxendale, I. R.; Deplante, F. A concise flow synthesis of indole-3-carboxylic ester and its derivatisation to an auxin mimic. *Beilstein J. Org. Chem.* **2017**, *13*, 2549−2560.
(133) Karadeolian, A.; Patel, D.; Bodhuri, P.; Weeratunga, G.; Gorin, B. Continuous Flow Process for Reductive Deoxygenation of ω-Chloroketone in the Synthesis of Vilazodone. *Org. Process Res. Dev.* **2018**, *22*, 1022−1028.
(134) Usutani, H.; Nihei, T.; Papageorgiou, C. D.; Cork, D. G. Development and Scale-up of a Flow Chemistry Lithiation-Borylation Route to a Key Boronic Acid Starting Material. *Org. Process Res. Dev.* **2017**, *21*, 669−673.
(135) Guan, F.; Kapur, N.; Sim, L.; Taylor, C. J.; Wen, J.; Zhang, X.; Blacker, A. J. A universal reactor platform for batch and flow: application to homogeneous and heterogeneous hydrogenation. *React. Chem. Eng.* **2020**, *5*, 1903−1908.
(136) Mo, Y.; Jensen, K. F. A miniature CSTR cascade for continuous flow of reactions containing solids. *React. Chem. Eng.* **2016**, *1*, 501−507.
(137) Falß, S.; Tomaiuolo, G.; Perazzo, A.; Hodgson, P.; Yaseneva, P.; Zakrzewski, J.; Guido, S.; Lapkin, A.; Woodward, R.; Meadows, R. E. A Continuous Process for Buchwald-Hartwig Amination at Micro-, Lab-, and Mesoscale Using a Novel Reactor Concept. *Org. Process Res. Dev.* **2016**, *20*, 558−567.
(138) Ali, R. S. A. E.; Meng, J.; Jiang, X., Multimode Photo-CSTR (Continuous Stirred Tank Reactor) Setup for Heterogeneous Photocatalytic Processes. *Org. Process Res. Dev.* **2023**. DOI: 10.1021/acs.oprd.3c00328
(139) SpinPro R10 - Flow reactor, for chemical process development and production. https://www.flowid.nl/spinpro-r10-flow-reactor-for-chemical-process-development-and-production/ (accessed 2023-10−09).
(140) Chaudhuri, A.; Zondag, S. D. A.; Schuurmans, J. H. A.; van der Schaaf, J.; Noel, T. Scale-Up of a Heterogeneous Photocatalytic Degradation Using a Photochemical Rotor-Stator Spinning Disk Reactor. *Org. Process Res. Dev.* **2022**, *26*, 1279−1288.
(141) Petrović, N.; Malviya, B. K.; Kappe, C. O.; Cantillo, D. Scaling-up Electroorganic Synthesis Using a Spinning Electrode Electrochemical Reactor in Batch and Flow Mode. *Org. Process Res. Dev.* **2023**, *27*, 2072−2081.
(142) Doyle, B. J.; Gutmann, B.; Bittel, M.; Hubler, T.; Macchi, A.; Roberge, D. M. Handling of Solids and Flow Characterization in a Baffleless Oscillatory Flow Coil Reactor. *Ind. Eng. Chem. Res.* **2020**, *59*, 4007−4019.
(143) Debrouwer, W.; Kimpe, W.; Dangreau, R.; Huvaere, K.; Gemoets, H. P. L.; Mottaghi, M.; Kuhn, S.; Van Aken, K. Ir/Ni Photoredox Dual Catalysis with Heterogeneous Base Enabled by an Oscillatory Plug Flow Photoreactor. *Org. Process Res. Dev.* **2020**, *24*, 2319−2325.
(144) Rosso, C.; Gisbertz, S.; Williams, J. D.; Gemoets, H. P. L.; Debrouwer, W.; Pieber, B.; Kappe, C. O. An oscillatory plug flow photoreactor facilitates semi-heterogeneous dual nickel/carbon

https://doi.org/10.1021/acs.oprd.3c00407
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

nitride photocatalytic C-N couplings. *React. Chem. Eng.* **2020**, *5*, 597−604.
(145) Silverman, G. S. R.; P, E., Safe Handling Practices of Industrial Scale Grignard Reagents In *Handbook of Grignard Reagents*; CRC Press: Boca Raton, 1996; Vol. *64*, pp 79−87.
(146) Wong, S.-W.; Changi, S. M.; Shields, R.; Bell, W.; McGarvey, B.; Johnson, M. D.; Sun, W.-M.; Braden, T. M.; Kopach, M. E.; Spencer, R. D.; Flanagan, G.; Murray, M. Operation Strategy Development for Grignard Reaction in a Continuous Stirred Tank Reactor. *Org. Process Res. Dev.* **2016**, *20*, 540−550.
(147) Kopach, M. E.; Roberts, D. J.; Johnson, M. D.; McClary Groh, J.; Adler, J. J.; Schafer, J. P.; Kobierski, M. E.; Trankle, W. G. The continuous flow Barbier reaction: an improved environmental alternative to the Grignard reaction? *Green Chem.* **2012**, *14* (5), 1524.
(148) Huck, L.; de la Hoz, A.; Diaz-Ortiz, A.; Alcazar, J. Grignard Reagents on a Tab: Direct Magnesium Insertion under Flow Conditions. *Org. Lett.* **2017**, *19* (14), 3747−3750.
(149) Goundry, W. R. F.; Dai, K.; Gonzalez, M.; Legg, D.; O'Kearney-McMullan, A.; Morrison, J.; Stark, A.; Siedlecki, P.; Tomlin, P.; Yang, J. Development and Scale-up of a Route to ATR Inhibitor AZD6738. *Org. Process Res. Dev.* **2019**, *23*, 1333−1342.
(150) Okamura, H.; Bolm, C. Rhodium-Catalyzed Imination of Sulfoxides and Sulfides: Efficient Preparation of N-Unsubstituted Sulfoximines and Sulfilimines. *Org. Lett.* **2004**, *6*, 1305−1307.
(151) Food and Drug Administration. *Guidance for Industry PAT: A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*; FDA Off. Doc., 2004; Vol. *September 16*.
(152) Simon, L. L.; Pataki, H.; Marosi, G.; Meemken, F.; Hungerbühler, K.; Baiker, A.; Tummala, S.; Glennon, B.; Kuentz, M.; Steele, G.; Kramer, H. J. M.; Rydzak, J. W.; Chen, Z.; Morris, J.; Kjell, F.; Singh, R.; Gani, R.; Gernaey, K. V.; Louhi-Kultanen, M.; O'Reilly, J.; Sandler, N.; Antikainen, O.; Yliruusi, J.; Frohberg, P.; Ulrich, J.; Braatz, R. D.; Leyssens, T.; von Stosch, M.; Oliveira, R.; Tan, R. B. H.; Wu, H.; Khan, M.; O'Grady, D.; Pandey, A.; Westra, R.; Delle-Case, E.; Pape, D.; Angelosante, D.; Maret, Y.; Steiger, O.; Lenner, M.; Abbou-Oucherif, K.; Nagy, Z. K.; Litster, J. D.; Kamaraju, V. K.; Chiu, M.-S. Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review. *Org. Process Res. Dev.* **2015**, *19*, 3−62.

https://doi.org/10.1021/acs.oprd.3c00407
Org. Process Res. Dev. XXXX, XXX, XXX−XXX