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The History of Flow Chemistry at Eli Lilly and Company

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Abstract: Flow chemistry was initially used for speed to early-phase material delivery in the development laboratories, scaling-up chemical transformations that we would not or could not scale up batch for safety reasons. Some early examples included a Newman Kwart rearrangement, Claisen rearrangement, hydroformylation, and thermal imidazole cyclization. Next, flow chemistry was used to enable safe scale-up of hazardous chemistries to manufacturing plants. Examples included high-pressure hydrogenation, aerobic oxidation, and Grignard formation reactions. More recently, flow chemistry was used in Small Volume Continuous (SVC) processes, where highly potent oncolytic molecules were produced by fully continuous processes at about 10 kg/day including reaction, extraction, distillation, and crystallization, using disposable equipment contained in fume hoods.

Keywords: Flow chemistry · Industrial production · Small Volume Continuous (SVC) process

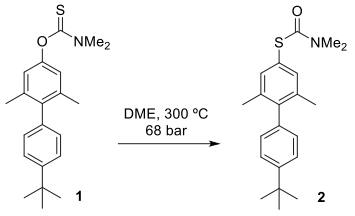
Introduction

In the 1970s and 1980s, Lilly used continuous reactions for large volume, high throughput processes with challenging chemistries. One of the drivers was productivity, needed because some of the products were more than 100 metric tons per year. Another driver was yield and selectivity. An ozonolysis reaction in a continuous stirred tank reactor (CSTR), and a cryogenic lithiation, coupling, and quench in plug flow reactors (PFRs) in series both had higher yield and better selectivity compared to batch. Subsequently, in the 1990s and early 2000s, there was very little flow chemistry development at Lilly. The flow chemistry group was disbanded, as the subject matter experts focused on enabling more efficient batch processes with their automation and process control expertise. Then, in 2006, a flow chemistry team was reestablished in the Chemical Process Research and Development department at Lilly. The team had several quick wins applying continuous processing to the early phase portfolio, scaling up chemical transformations that they would not or could not scale up batch for safety reasons, enabling speed to material production out of the development labs. Indeed, many others across the industry were using flow chemistry to enable better safety for reactions that have extreme exotherms, hazardous reagents, high pressures, and extreme temperatures.[1] In the early-2010s, the focus shifted to later stage processes with the goal of installing continuous chemistries in GMP manufacturing plants. Again, continuous processing was used for reactions that we would not or could not scale up batch, primarily for safety reasons. In the mid-2010s the focus of the continuous process development group shifted to small volume continuous (SVC) processes. At that time, a large portion of the portfolio was moving toward highly potent active pharmaceutical ingredients (APIs) with less than 1 metric ton per year expected demand, which had the potential to be delivered using fully continuous processing trains contained in fume hoods, optionally with disposable equipment.

Speed to Early-phase Material Delivery in the Development Laboratories

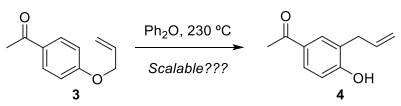
The continuous group first began with a few people dedicating part of their time, looking for opportunistic applications of flow chemistry in the portfolio. The group used continuous reaction to speed early phase material delivery by enabling safe scale-up of discovery chemistries, in collaboration with scientists from the discovery scale-up group.

In 2007, 200 g of *S*-thiocarbamate **2** (Scheme 1) was needed for toxicology studies.[2] At smaller scales, the discovery chemistry group had been making the *S*-thiocarbamate by Newman-Kwart Rearrangement (NKR) neat at 250 °C.[3] The Lilly internal process safety group deemed the process unacceptable for scale-up. Noting that a NKR utilizing a continuous flow reactor had been previously reported by Pfizer,[4] the process safety group recommended flow chemistry. The lab group delivered 200 g of the *S*-thiocarbamate using a PFR to run the NKR reaction in supercritical DME at 300 °C and 68 bar. DME was chosen because of solubility and because it simplified workup and isolation. Yield and purity were higher than for the batch process.



Scheme 1. Synthesis of *S*-thiocarbamate **2**.

In 2008, 80 g of an early-phase intermediate **4** (Scheme 2) was needed for toxicology studies.[5] It had previously been made at small scale in the discovery chemistry labs using a Claisen rearrangement[6] at 220 °C in diphenyl ether solvent in a batch reactor.



Scheme 2. Synthesis of intermediate **4**.

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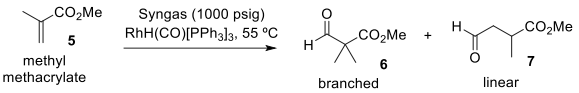
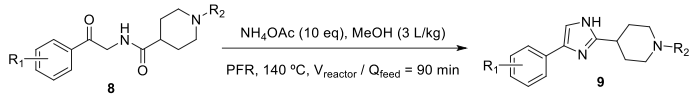
The chemical hazards lab identified this as potential for runaway reaction, therefore scale-up of the existing 220 °C batch reaction was forbidden. However, the reaction was safely scaled-up by running the Claisen rearrangement at 230 °C in a PFR using NMP solvent. The safety profile of the flow chemistry was deemed superior to batch because the PFR had higher heat transfer surface area per unit volume (A/V), and the fact that the PFR was held at a constant temperature, as opposed to the batch reactor heating ramp. In 2008, 170 kg of a branched aldehyde API starting material was needed for an early phase campaign. Continuous reaction, filtration, and multi-stage fractional distillation ran in laboratory fume hoods at 13 kg/day production rate to generate 178 kg of highly purified branched aldehyde **6**, which was used in a GMP pilot plant campaign. A 32 L pulsating coiled tube PFR was used for a hydroformylation reaction in which solids precipitated from the reaction mixture.[7] The reaction, shown in Scheme 3, used 1:1 CO:H_2 gas reagent at 68 bar pressure, 55 °C temperature, and RhH(CO)[PPh_3]$_3$ catalyst, with substrate to catalyst ratio (S/C) = 1000.



Scheme 3. Synthesis of aldehyde **6**.

It was safer to scale-up the process in flow because the gas supply was physically restricted, the reactor operated nearly completely liquid filled, the PFR had high A/V, and the reactor was smaller than batch for the same daily throughput. Downstream from the reaction, branched aldehyde was separated from linear aldehyde by-product, and from the catalyst/ligand, by continuous multi-stage fractional distillation. The desired branched aldehyde averaged about 97% purity before distillation and 99.5% after. Product quality from the continuous process was superior when compared to the batch option, which consisted of a TEMPO-catalyzed oxidation in methylene chloride solvent. The batch process generated 128 kg waste per 1 kg product. In contrast, the continuous process, including purification by fractional distillation, ran solvent-free and only generated about 1 kg waste per kg product.

In 2008, an imidazole cyclization reaction was required in the GMP sequence for an early phase campaign.[8] The reaction is shown in Scheme 4.



Scheme 4. Synthesis of imidazole **9**.

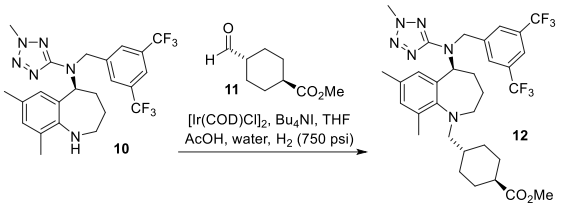
Imidazoles are common pharmacophores in pharmaceutical compounds,[9] and many synthetic approaches are known.[10] However, in this example the batch reaction by established protocols did not scale adequately due to polymeric degradation of both starting material and product in the transitional temperature regime where the kinetics of polymerization were favored over cyclization. This phenomenon decreased yield upon scale-up, and the polymeric material hindered workup and isolation. Compared to a batch reaction, the flow chemistry overcame these problems by rapid, precise, scalable heating and cooling times in the high A/V PFR, and consistent time at the productive reaction temperature at all scales. 29 kg of GMP intermediate **9** was successfully produced using a superheated PFR running the imidazole cyclization in methanol at 140 °C and 60 bar. Methanol was chosen as the reaction solvent because it simplified workup and isolation. As part of the development work documented in the thermal cyclization paper, Lilly characterized a wide range of PFRs for axial dispersion, pressure drop, heat and mass transfer, and their impact on conversion versus distance (see table 10 in ref. [8]).

Lilly's discovery chemistry scale-up group has continued to use flow chemistry to enable speed to early material delivery. Two additional published examples are a [3+2] cycloaddition of nitrones at 240 °C[11] and a SNAr reaction at 200 °C,[12] both run in high temperature, high pressure PFRs.

Enabling Safe Scale-up of Hazardous Chemistries to Manufacturing Plants

Although H_2 is the most economical and environmentally friendly reducing agent, high pressure H_2 reactions pose severe safety risks and require expensive, high-pressure autoclaves and explosion bunkers in batch processing. Similarly, O_2 is the most economical and environmentally friendly oxidizing agent. However, the safety hazards of an explosive mixture of organic solvent with oxygen have stymied the use of aerobic oxidations in pharmaceutical manufacturing facilities, where multi-use stirred-tank reactors are not designed to mitigate the safety hazards of aerobic oxidations. Lilly developed coiled tube and vertical bubble flow pipes-in-series PFRs for continuous high-pressure gas/liquid reactions that require low catalyst loading, long reaction times, sufficient heat and mass transfer rates for reaction times on the order of 5–12 h, with low axial dispersion. These have enabled high pressure hydrogenations and aerobic oxidation reactions to run safely in pharmaceutical manufacturing plants.

In 2013, a vertical bubble flow pipes-in-series reactor design enabled Evacetrapib penultimate **12** production at 2000 kg scale in GMP manufacturing (Scheme 5).[13]

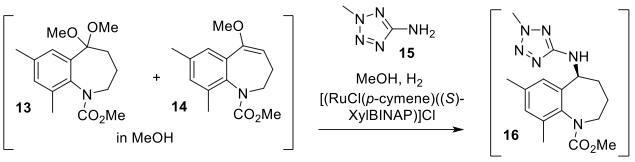


Scheme 5. Ir-catalyzed reductive amination to produce **12**.

The Ir-catalyzed reductive amination shown in Scheme 5 required high H_2 pressures to keep the catalyst loading low enough for an economically viable process. Remarkably, the hydrogenation at 50 bar H_2 pressure was categorized as a low-risk operation by the manufacturing plant. The main reason for the favorable safety categorical rating was that the PFR operated outside the building, an aspect that is not realistic in traditional batch processing. The continuous reactor, hydrogen supply cylinders, and hydrogen separation and venting could be located outside for a PFR because they were always sealed, in contrast to a batch autoclave which must be opened periodically. The new reductive amination synthetic route was lower cost and lower environmental footprint compared to the previous well-developed route which utilized a batch sodium triacetoxyborohydride (STAB) process.[14] In addition, the previous synthetic route presented challenges of handling, dispensing and storage of large quantities of STAB. The batch STAB process also evolved H_2 during reaction and workup, which was a safety hazard. Capital cost for the 360 L flow reactor and supporting infrastructure was €2.5 million, which was at least

an order of magnitude less than it would have cost to install a new hydrogenation bunker with batch autoclave capable of the same overall throughput.

In 2014, the vertical bubble flow pipes-in-series reactor design was also adopted by Takasago, a world leader in high-pressure batch asymmetric hydrogenation. They used it for the manufacture of Lilly's Evacetrapib step 1 direct asymmetric reductive amination (DARA)[15] with [RuCl(*p*-cymene)((*S*)-XylBINAP)]Cl homogeneous catalyst, shown in Scheme 6.

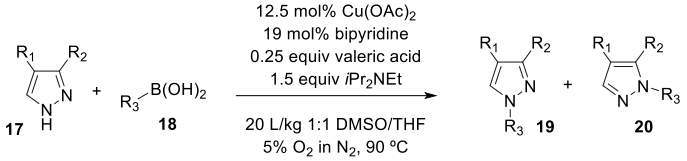


Scheme 6. Manufacture of Lilly's Evacetrapib step 1 direct asymmetric reductive amination (DARA)[15] with [RuCl(*p*-cymene)((*S*)-XylBINAP)]Cl homogeneous catalyst.

3200 kg of intermediate **16** was produced in a validation campaign. The bubble flow reactor operated at 50 bar H_2 pressure and 125 °C. Takasago favored the continuous reaction option because of high throughput in a small reactor compared to batch. As part of the DARA process development, alternative PFR designs were evaluated at research and pilot scale, including coiled tubes, horizontal pipes in series, and vertical pipes in series.[16] Vertical pipes in series were selected as the best option because of better scalability compared to coiled tubes and higher vapor/liquid mass transfer rates compared to horizontal pipes. Surging was minimized by using Froude number design guidelines taken from the commodity chemicals industry.[17]

The same type of vertical pipes in series bubble flow PFR is also effective for aerobic oxidations. Furthermore, synthetically versatile catalytic aerobic oxidation methods have been developed using homogeneous Pd catalysts.[18] Molecular oxygen oxidations are already used for commodity chemicals,[19] but multi-product pharmaceutical manufacturing plants do not have the specialized capabilities to safely run these reactions. A key to running aerobic oxidations safely in a multi-use facility is to dilute oxygen with nitrogen below the flammability window so that it is not possible to form explosive mixtures with organic solvents. On the other hand, the key to reaction performance is to maintain a high enough dissolved oxygen concentration to sustain the catalyst cycle, which is not feasible using dilute oxygen in a batch reactor. Lilly scientists worked in an academic collaboration to develop continuous processes that could run O_2 oxidations in dilute air.[20]

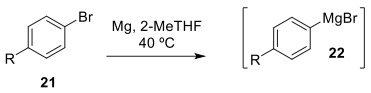
In 2017, an aerobic Chan–Lam coupling was scaled up to GMP production in a vertical bubble flow pipes-in-series PFR to manufacture the penultimate (**19**) of an API[21] (Scheme 7).



Scheme 7. Production of intermediate **19**.

Homogeneous reaction conditions were designed for the challenging C–N coupling. 5% O_2 in N_2 served as the reagent gas, ensuring that reactor compositions would not enter the flammability window.[22] In the vertical pipes-in-series reactor, 50 bar reactor pressure maintained sufficient O_2 partial pressure, multiple stages in series in the PFR turned over headspace gases quickly, and continuous flow achieved high enough vapor–liquid mass transfer rates to minimize decomposition of the homogeneous catalyst.[23] The pharmaceutical industry is striving for greener processes,[24] and this is one more step in that direction. The chemistry in Scheme 7 represents a class of reactions that is notoriously difficult to scale, but it is enabled by flow chemistry. The work exemplifies a robust strategy for safe, scale agnostic implementation of aerobic oxidations in pharmaceutical manufacturing.

For more than 100 years, Grignard reactions have been one of the most powerful and efficient organic chemistry methodologies for C–C bond formation.[25] However, Grignard reactions are also among the most challenging reactions from both operational and safety perspectives due to initiation difficulties and runaway potential. In 2013, a continuous Grignard formation reaction was run in a CSTR with sequestered Mg solids. The flow chemistry had improved safety and purity compared to batch. The reaction is shown in Scheme 8.[26]

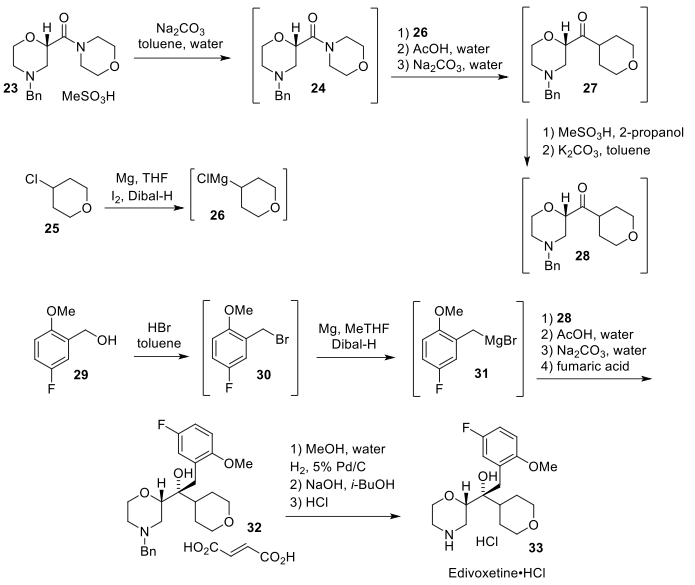


Scheme 8. Grignard reaction to produce **22**.

Dissolved aryl bromide was continuously pumped into the reactor containing a large molar excess of activated Mg metal, while Grignard reagent solution was continuously pumped out. Solid Mg flakes were sequestered in the reactor. Fresh Mg particles were added every four hours to match consumption rate. The freshly added metal rapidly activated as soon as it stirred with existing Grignard solution without the need for any additional activating agent. The reaction achieved 99.9% conversion with a 60 minute mean residence time (τ) in a single CSTR operating at 41 °C. The two main methods/devices that were used to prevent solid Mg from exiting the system were the settling pipe inside the CSTR and the Mg settling trap immediately downstream from the CSTR. A 100 L Grignard formation reactor, operating at the 45 L fill level, was used to manufacture 4000 L of 0.85 M solution of **22**, which served as an API starting material. Forward processing of the Grignard reagent into a Kumada coupling reaction was done in 8000 L batch vessels. There were significant safety advantages of running the reaction in a 100 L CSTR instead of an 8000 L batch reactor. The Grignard formation reaction was highly exothermic, initiation was difficult, and the reaction had runaway potential; therefore, minimizing the size of the reactor minimized risk. The continuous Grignard reaction maintained high instantaneous magnesium equivalents (4–8 eq) while requiring only 1.04 equivalents of magnesium overall for the campaign, thus minimizing the amount of Mg to quench at the end, and therefore minimizing the corresponding liberated H_2.

The commercial route for edivoxetine·HCl presented two additional opportunities for converting batch Grignard formation reactions to continuous: the metallations of compounds **25** and **30** as shown in Scheme 9.

Much of Lilly's early development work on continuous Grignard formation reactions in 2008–2011 was done on these two edivoxetine steps. Lilly manufacturing decided against scaling-up a benzyl bromide Grignard formation to their 8000-L facility using traditional batch processing because of safety hazards. However, the continuous Grignard formation reaction was deemed safe to operate in the same facility, because the Grignard



Scheme 9. Metallations of compounds **25** and **30** in the production of Edivoxetine·HCl.

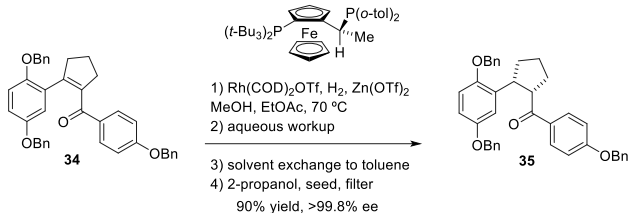
CSTR was much smaller. A portable 100 L CSTR was connected between 8000 L batch feed and product tanks. The edivoxetine clinical program ended just before the 8000 L validation campaign started, but the adoption of the Grignard CSTR paid dividends on future projects at the same manufacturing site. The formation of Grignard reagent **26** has also been developed at research and pilot scale to mitigate both the safety hazards and the racemization potential.[27] In a Barbier process, Grignard reagent formation and coupling reactions occur simultaneously in a single reactor.[28] In addition to a Barbier Grignard CSTR, ketone product **28** solution was continuously quenched in a second CSTR and continuously neutralized in a third CSTR in series. The telescoping of three CSTRs in series minimized racemization, achieving *in situ* >99% crude ee, which was significantly higher than the previous well-developed batch process. Furthermore, by achieving >99% crude purity, the continuously produced ketone had the potential to be telescoped into the next synthetic step without the need for ee upgrade by crystallization. The continuous process was deemed safer than batch because of smaller reactor size, less diisobutylaluminum hydride initiation reagent, and less Mg quench.[29] As mentioned above, the edivoxetine program was discontinued before this process was run in the manufacturing plant; nevertheless, the Grignard CSTR approach was adopted by Lilly manufacturing and used for GMP production of another asset, presented below.

Small Volume Continuous (SVC)

Described earlier in this article, a continuous thermal imidazole cyclization produced 29 kg GMP intermediate **9** at about 8 kg/day, and a continuous hydroformylation produced 178 kg API starting material **6** at about 13 kg/day, using only laboratory fume hoods. By running the reactions, workup, distillation, crystallization, and filtration all fully continuous, pilot scale material was generated without using any large vessels or pilot plant. These successful proof of concepts in 2008 provided Lilly with incentive to develop more SVC processes in fume hoods.

In addition, several other things were happening in the 2010s that were encouraging Lilly and other pharmaceutical companies to pursue fully continuous processes. Many new investigational medicines had lower projected volumes, higher potency, and smaller patient populations relative to historical small-molecule APIs.[30] Over the past decade, the FDA consistently advocated for continuous processing in pharmaceutical manufacturing,[31] which was certainly influential on Lilly's investments in continuous. An end-to-end SVC process for aliskiren hemifumarate was published out of the Novartis/MIT partnership in 2013.[32] The Mascia publication and supporting spin-off papers were landmark documents that helped Lilly and other companies gain internal support for further investment in continuous processing. Indeed, pharmaceutical companies like GSK, Novartis, and Pfizer were all investing in continuous.[33] Academic groups continued to develop multi-step continuous processes as well. For example, the Ley group developed multi-step continuous processes using a combination of solution-based chemistry and reagents on solid supports.[34] Others were investing in miniaturization of API continuous production plants the size of refrigerators, for example the Defense Advanced Research Projects Agency (DARPA).[35]

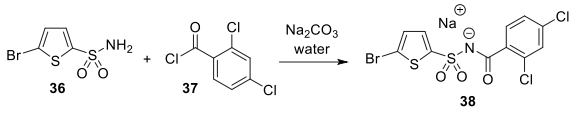
Next for Lilly, in 2010, 144 kg of advanced intermediate **35** (Scheme 10) was produced in a laboratory hydrogenation bunker and laboratory fume hoods, including continuous reaction, extraction, distillation, crystallization, and semi-continuous filtration. The continuous asymmetric hydrogenation was run in a 73 L coiled tube reactor operating at 68 bar H_2 pressure.[36]



Scheme 10. Asymmetric hydrogenation reaction to produce **35**.

Enantioselective reduction of tetrasubstituted alkenes is particularly challenging.[37] Furthermore, Lilly manufacturing had no existing batch autoclave capable of high enough pressures to enable low enough catalyst and ligand loading for an economically viable process. Asymmetric hydrogenation had been done in continuous reactors in the past,[38] so continuous was investigated as an alternative to investing in batch high-pressure autoclave capacity. The Lilly group designed an inexpensive, coiled tube PFR for this homogeneously catalyzed high-pressure asymmetric hydrogenation. The continuous reaction was followed by continuous extraction, solvent exchange distillation, crystallization, and semi-continuous filtration. The continuous crystallization was accomplished in mixed-suspension, mixed-product removal (MSMPR) stirred tanks. The crystallization greatly benefitted from continuous processing because it relied on kinetic rejection of a chiral impurity. Kinetic impurity rejection was superior in flow compared to batch because the MSMPRs operated in the kinetic regime with constant steady state supersaturation.

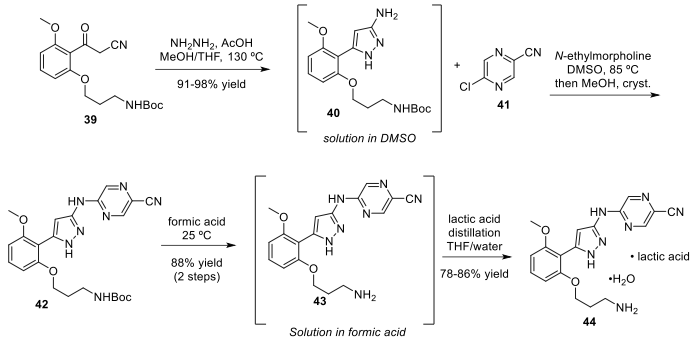
Lilly manufacturing leadership took special interest in the continuous lab hood production, recognizing it as an opportunity to expand cytotoxic API capacity in the commercial facility. Therefore, they requested development of fully continuous wet-end processes for the final two steps of Tasisulam, a cytotoxic oncolytic API.[39] Shown in Scheme 11, Schotten–Baumann reaction conditions were used for a new telescoped synthetic route that directly formed the final sodium salt (**38**) from sulfonamide **36** and acid chloride **37**, avoiding intermediate crystallization of the free acyl sulfonamide.[40]



Scheme 11. Schotten-Baumann reaction for the synthesis of **38.**

In 2010, this SVC Schotten–Baumann reaction, extraction, distillation, and crystallization process generated 20 kg API at 5 kg/day throughput contained in laboratory fume hoods. The process used inexpensive, portable, disposable laboratory glassware, eliminating potential for cross-contamination to other cytotoxic APIs. Throughput of 5 kg/day was sufficient for commercial scale production of this highly potent API. Potential for operator exposure was reduced by keeping the entire continuous process in fume hoods. Counter-current multi-stage extraction minimized product loss to the aqueous waste and sufficiently rejected a key benzoic acid impurity. The flow process also had fewer isolations and greener reagents and solvents compared to the batch process alternative.[41] The Tasisulam program ended before the process ran in GMP manufacturing, but the SVC capability investment paid off on other assets, described below.

In 2014, an SVC fume hood production process was designed, developed, and run in GMP manufacturing to synthesize 24 kg prexasertib monolactate monohydrate (**44**, Scheme 12), in this case a cytostatic oncolytic molecule.[42]



Scheme 12. Synthesis of prexasertib monolactate monohydrate **44**.

As shown in Scheme 12, the first three steps were run continuously, as was the formic acid distillation at the start of the final step. The manufacturing site only had four fume hoods at the time, therefore the process was divided up into three individual sections, holding dissolved intermediates in drums between each continuous run. The final API crystallization, filtration, and drying were done batchwise. In the continuous flow train, the condensation reaction to form pyrazole **40** used fewer equivalents of hydrazine compared to the batch alternative. The commercial scale PFR was only 1.5 L and contained only 20 g of hydrazine at any time. Continuous counter-current extraction reduced residual hydrazine from 6000 ppm to <2 ppm and reduced residual acetic acid and the deprotected pyrazole impurity, without losing significant amounts of product to the aqueous layer. This extraction eliminated the need for isolating the product, which had tested Ames positive and was potentially genotoxic, while achieving assay yields of 97–99%. The DMSO solution of **40** was then coupled with pyrazine **41** in an S_NAr reaction, conducted in a PFR at 85 °C. A continuous crystallization, immediately downstream the S_NAr reaction, was important to the impurity control strategy, as it rejected pyrazine-related and regioisomeric impurities. The purity of the crystallized solids from the MSMPRs after the second step was >99.8 area% by UPLC. Fully automated dual filters, alternating back and forth once every hour, filtered, washed, and dissolved the intermediate into the solvent for the next continuous reaction in the sequence, which eliminated manual handing of the cytostatic intermediate. A gas-liquid PFR was used for the removal of the Boc group to afford a solution of the API. Nitrogen gas was used to continuously sweep the CO_2 and isobutylene from the PFR, which improved the impurity profile. In the final flow unit operation, formic acid was reduced to <1 equivalent by stripping, eliminating a cytostatic formate salt isolation. Overall, the continuous process reduced waste by 62%, eliminated three isolations, and reduced handling of potent compounds compared to batch.

After the successful proof of concept for prexasertib, the decision was made to build a new €35 million facility to do the same type of continuous SVC processing in fume hoods for other low volume, highly potent APIs. The new SVC facility included enough fume hoods and supporting feed vessels to run at least three synthetic route steps simultaneously, including reactions and separation steps, at about 10 kg per day throughput. The SVC facility was completed in 2017 and immediately used for GMP production of 204 kg of LY3023414 (**50**) for clinical trials (Scheme 13, Fig. 2).[43]

The SVC facility was awarded the International Society of Pharmaceutical Engineering (ISPE) Facility of the Year Award for Innovation, largely because of the flow chemistry and purification advantages in the LY3023414 process. The chemistry for the multistep flow process is shown in Scheme 13 and ran continuously and simultaneously. The Grignard reagent was unstable; however, in flow it was immediately telescoped into the transmetalation. The more stable zincate intermediate **47** was immediately telescoped into the Negishi coupling reaction, where it reacted with a quinoline **48**. Fig. 2 shows that the continuous process train was composed of 3 PFRs, 3 CSTRs, 3 continuous extractors, 2 continuous evaporators, 3 surge points, 3 MSMPRs in series for anti-solvent and cooling crystallization, and dual agitated filters. Continuous crystallization in MSMPRs had been used in the past for non-GMP production of multi kg quantities of API,[44] and for GMP production of multi kg quantities of API penultimates.[45] A key quinoline dimer impurity formed at about 1% relative to the API in the Negishi coupling reaction. The dimer impurity had very poor solubility in any of the solvent systems investigated during the batch crystallization development. However, the dimer was rejected very well kinetically in the continuous crystallization. Continuous API crystallization proved superior to batch for kinetic impurity rejection, and it eliminated a re-crystallization, because two crystallizations had been required for reliable rejection of the quinoline dimer impurity in the previous batch manufacturing campaign. Three on-line HPLCs maintained quality assurance and quality control for the silylation, Grignard formation, and Negishi coupling reactions. Disposable PFRs eliminated cross contamination potential from the reactors. Fume hoods provided process containment for this highly potent oncolytic API. Numerical modeling was necessary for quantifying overall RTD for the entire flow train and determining lot genealogy.

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Bret Huff established and drove flow chemistry at Eli Lilly. The accomplishments represented in this manuscript would not have happened without him. Ulf Tilstam was the lead chemist for the Newman Kwart thermal rearrangement. This manuscript is in memory of him. The following are co-authors of the major works cited. Jeffry Niemeier was an engineer in the chemical hazards laboratory who flagged hazardous chemistries in the portfolio and advised many of the batch to flow conversions for safety reasons. Jennifer McClary Groh was a continuous process engineer on the hydroformylation, Grignard formation, and the SVC processes. She was key to the development and success of SVC. Carla Luciani's numerical modeling made it possible to understand complex RTDs, develop strategies for diverting, and determine lot genealogies. Luke Webster was the main process engineer for the Scheme 13 and Fig. 2 process that ran in the new SVC facility. Wei-Ming Sun was the automation engineer who made all of this work possible. Amy Jines, Brian Haeberle, Chris Polster, Christopher Burcham, Derek Berglund, Jeremy Merritt, Steven Myers, Nick Zaborenko, Philip Hoffman, and Shankar Vaidyaraman were engineers that developed these flow processes. Antonio Navarro, Carlos Mateos, David Mitchell, Eric Moher, Jake Remacle, Michael Kobierski, Neil Kallman, Radhe Vaid and Shon Pulley were chemists who designed, developed and led the chemistry efforts.

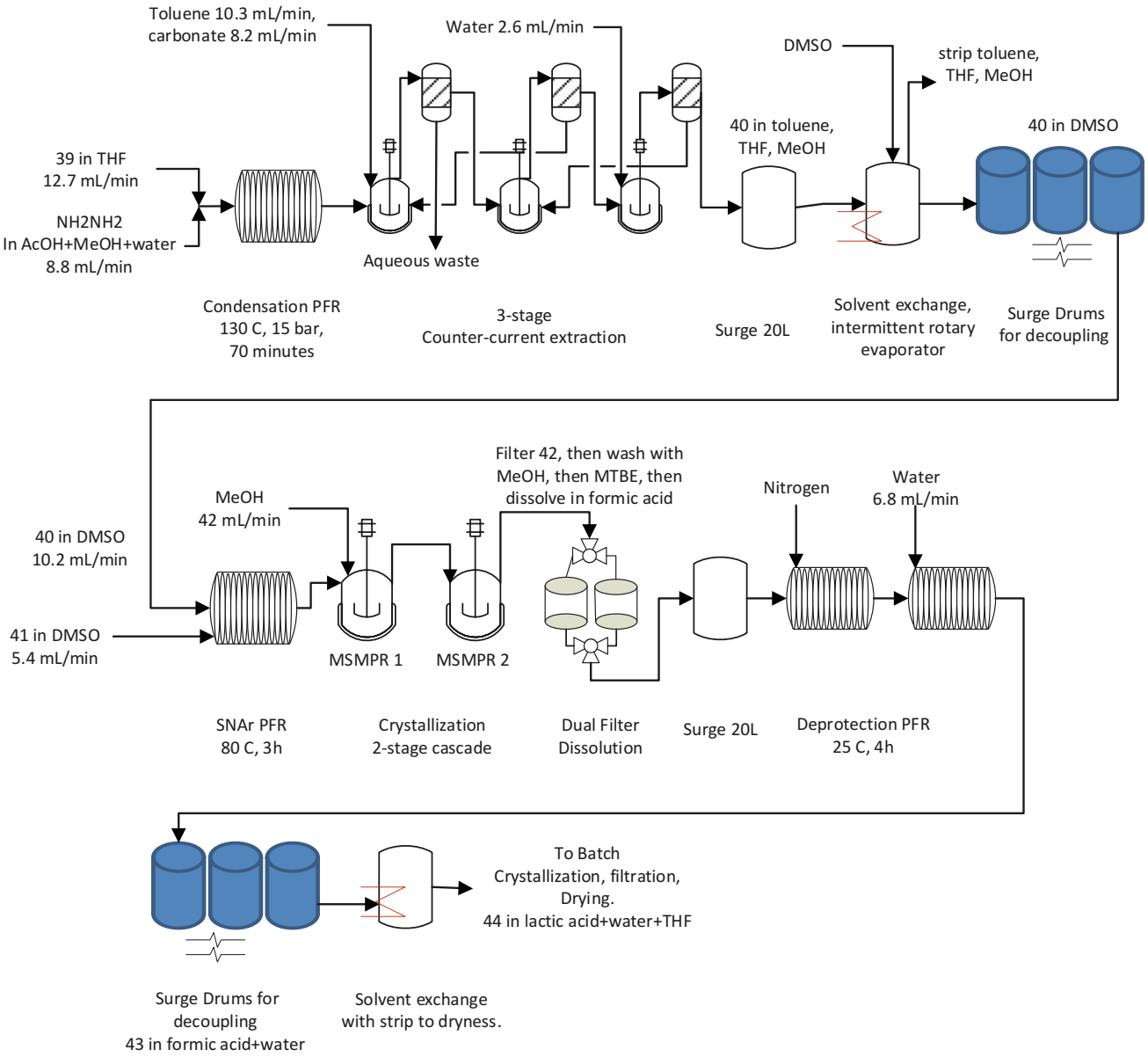
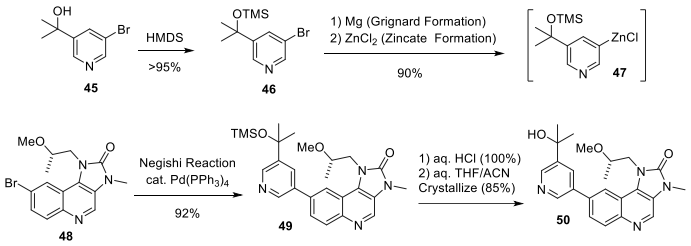


Fig. 1. Process flow diagram for prexasertib SVC flow train split into three sections by surge drums.



Scheme 13. Synthesis of LY3023414 (**50**).

Adam McFarland, Jonas Buser and Matthew Embry in the NMR lab elucidated reaction mechanisms. Gordon R. Lambertus, Jeffrey Roberts and Brad Campbell developed online HPLC for most of the flow chemistry steps that ran in Lilly manufacturing. Ric Miller, Jeff Lewis, Mike Heller, Bill Diseroad, John Howell, and Joe Phillips were highly skilled senior specialists that constructed and ran flow chemistry processes in the labs. Most of the work represented in this paper was enabled by close collaborations with D&M continuous solutions partners Ed Deweese, Paul Milenbaugh, James Stout, John Schafer, Jonathan Adler, and Ed Plocharczyk. Senior engineer, Rick Spencer was key to the tech transfer of these continuous processes to the Kinsale, Ireland manufacturing site. He made these processes possible in GMP manufacturing. Aoife Corrigan, Declan Hurley, Jim Cashman, John Murphy, Marie Kissane, Nessa Mullane, Niall Kerrigan, Olivia Gowran, Paul Sheehan, Raymond Boyse, Regina Lynch, Bruce Parker, Richard Spencer, and Robert Moylan made flow chemistry a reality in Kinsale. Tohru Yokozawa and Takao Saito developed the reactions that were run in manufacturing at Takasago.

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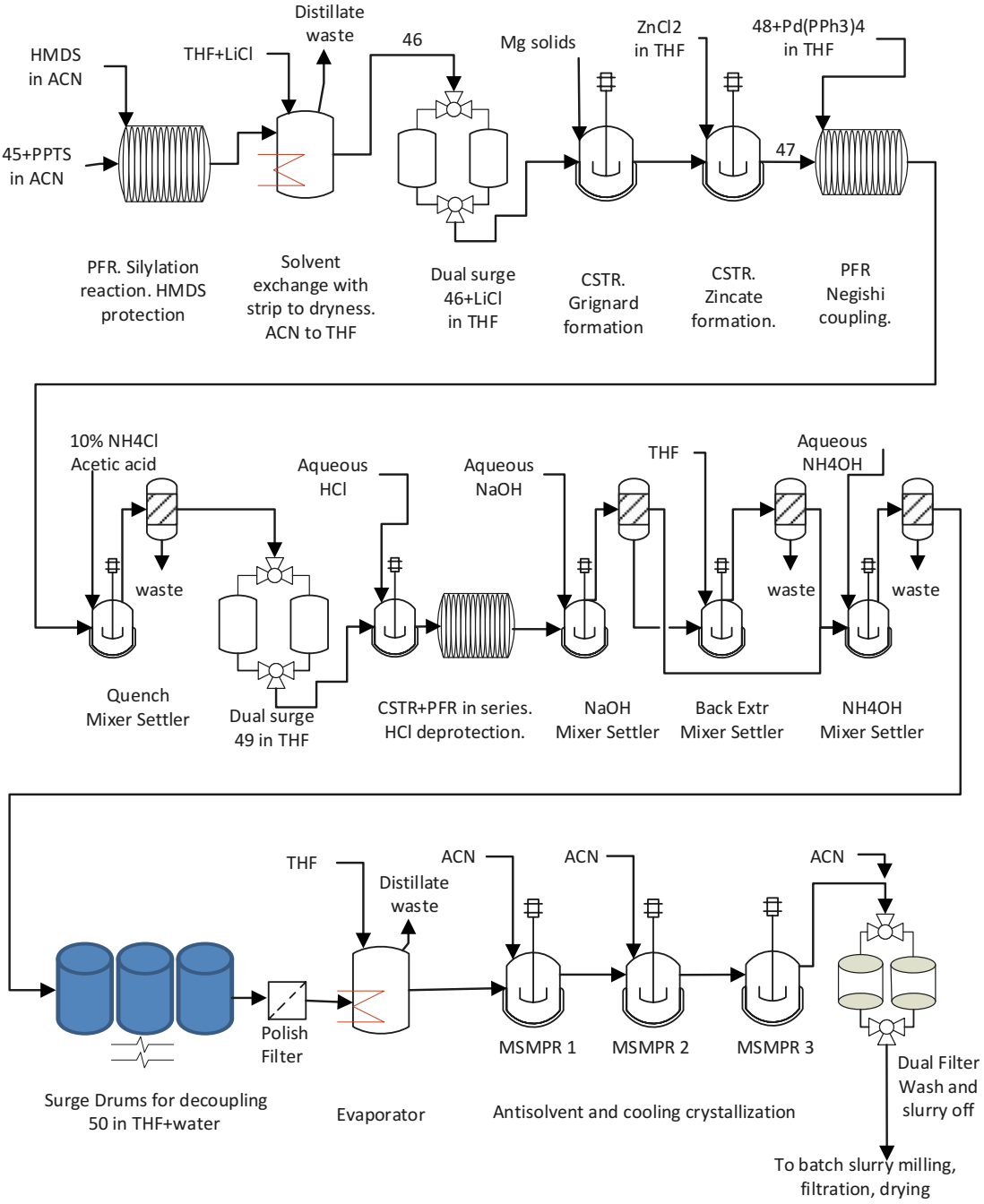

Fig. 2. Process flow diagram for LY3023414 SVC flow train in the new facility.

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