Development of a Continuous Flow Process for a Matteson Reaction: From Lab Scale to Full-Scale Production of a Pharmaceutical Intermediate

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ABSTRACT: Within this paper, we present the design, development, and scale-up of a process for a continuous Matteson reaction to produce a key intermediate toward the β-lactamase inhibitor vaborbactam. This includes the successful implementation of the continuous concept at a multiton production scale for the API at Patheon, part of Thermo Fisher Scientific. The first-generation continuous flow production with its discontinuous downstream processing was further developed to a fully continuous production through installation of a continuous loop reactor. This enabled increased productivity and energy efficiency, eliminated volume and time bottlenecks, and reduced waste.

KEYWORDS: *flow chemistry, Matteson reaction, α-chloro-boronate, loop reactor, CSTR, organolithium chemistry*

1. INTRODUCTION

Continuous processing (CP) in API manufacturing offers the potential for increased efficiency, safety, quality, and flexibility relative to traditional batch processing. As a result, regulators and industry have developed a keen interest in promoting the adoption of CP in the manufacture of small-molecule APIs. There is also potential for CP to play a role in addressing the problem of drug shortages, since such processes generally require smaller equipment and facilities, resulting in lower capital costs to establish a manufacturing capability.[1,2]

Vaborbactam is a cyclic boronic acid β-lactamase inhibitor, which was discovered at Rempex Pharmaceuticals, a subsidiary of The Medicines Company, now part of Melinta Therapeutics.[3] In combination with Meropenem, it has recently been approved for the treatment of complicated urinary tract infections and pyelonephritis[4] under the commercial name "Vabomere".

The chemical process to manufacture vaborbactam (Scheme 1) presents several opportunities for implementation of CP in order to improve efficiency and scalability.

One key step in the synthesis of vaborbactam is the diastereoselective chain elongation of boronic ester **3** to α-chloroboronic ester **4**, which is performed under Matteson conditions[5] at low temperature (−95 to −100 °C).

This transformation involves (*i*) generation of (dichloromethyl)lithium, (*ii*) formation of boronate complex **3′**, and (*iii*) rearrangement of the latter to **4** (Scheme 2). The presence of zinc chloride is essential for achieving high diastereoselectivity, through both chelation control during the rearrangement[6] and suppression of epimerization of **4**.[7]

(Dichloromethyl)lithium is a labile species, which is prone to carbene formation through α-elimination of LiCl.[8] Consequently, formation of this reagent requires a very low temperature, at which (dichloromethyl)lithium behaves like a typical alkyllithium.[9]

The scale-up of a batch process for cryogenic lithiation chemistry is challenging. Typically, the reaction is controlled by using relatively high dilution and/or slow dosing protocols, which are dictated by the ability of the reactor to remove the reaction heat and the available cooling capacity. As a result, the productivity of the batch process is limited. Moreover, poor mixing may result in byproduct formation, due to local hot spots and/or incorrect local stoichiometries.

The conversion of this step from a batch to a flow process was necessitated by the low temperature requirements of this transformation. Achievement of such low temperatures becomes increasingly difficult in a plant setting with increasing scale, and it was apparent from the outset that a flow process for the Matteson reaction would be required for commercial manufacturing.
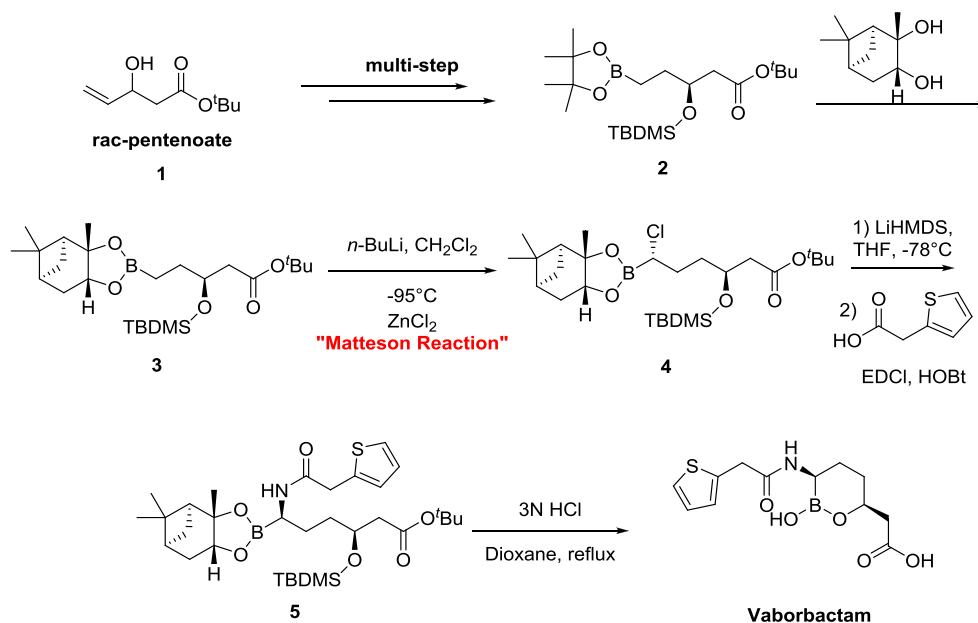
Therefore, we evaluated continuous flow technology for the synthesis of compound **4** to overcome the aforementioned issues.[10] Here, we report the successful development, scale-up, and implementation of a continuous flow process for the production of intermediate **4**.

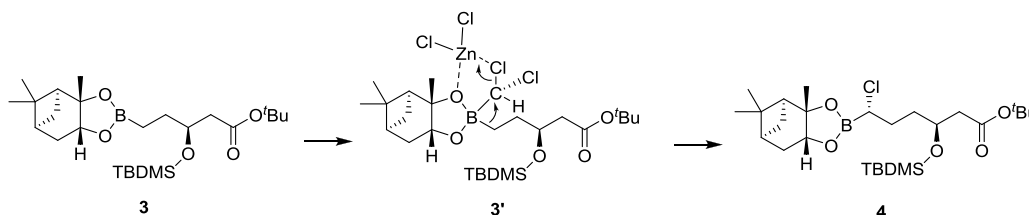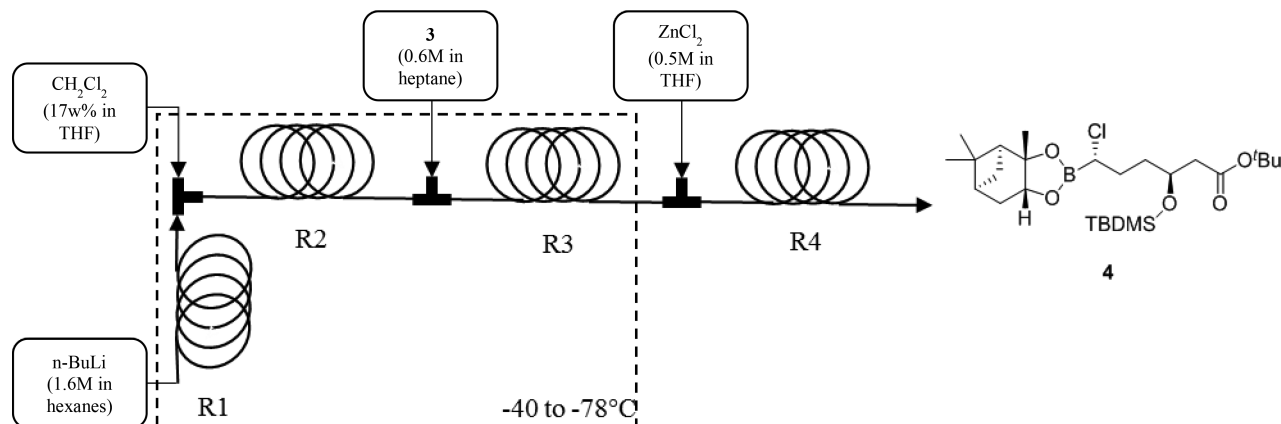**Scheme 1. Synthesis of Vaborbactam Drug Substance**

Scheme 2. Mechanism of the Matteson Homologation Reaction

Scheme 3. Flow Setup Used in First Laboratory Experiments

The latter includes the integration of the flow process in an existing pilot plant and full cGMP production environment.[11] The first-generation continuous flow production with a discontinuous downstream processing was further developed to a fully continuous production through installation of a continuous loop reactor to increase productivity and overcome volume and time bottlenecks, reduce waste, and increase energy efficiency.

2. PROCESS DEVELOPMENT

2.1. Initial Feasibility Study. The first laboratory experiments were performed in a flow setup consisting of

stainless steel T-pieces as mixing elements and stainless steel tubing as coiled tubular reactors (Scheme 3). The system was controlled using four HPLC pumps, and temperature control was achieved by placing the first three reactors (R1–R3) in a cooling bath. Reactor 4 (R4) was operated at ambient temperature.

Reactor R1 (heat exchanger) was installed to sufficiently cool the n-BuLi solution prior to the deprotonation of dichloromethane in reactor R2. The thus formed (dichloromethyl)lithium was reacted with substrate **3** in reactor R3 forming borate complex **3′**, which rearranges to **4** upon contact with zinc chloride in reactor R4. The effluent was

Table 1. Experimental Results for Continuous Flow Matteson Reaction

experiment no.	temperature [°C]		residence time [s]				HPLC [area%]	
	R 1−3	R4	R1	R2	R3	R4	compd 3	compd 4
batch mode	−	−	−	−	−	−	25	75
1	−40	20	20	20	10	10	90	10
2	−40	20	20	20	20	10	90	10
3	−78	20	20	10	10	10	55	45
4	−78	20	20	20	10	10	20	80
5	−78	20	20	20	20	10	10	90

collected, quenched with aqueous HCl, and analyzed by HPLC.

Two process parameters were initially varied, i.e. reaction temperature and residence time. The temperatures used were obtained by changing the medium in the cooling bath, whereas residence time was increased or decreased by adjusting the length of the reactors. The results obtained are summarized in Table 1.

Anticipating that short residence times would allow the Matteson reaction to be executed at higher temperature, the first experiments were performed at −40 °C. Unfortunately, this resulted in poor conversion of substrate 3 (entries 1 and 2). At lower temperature (−78 °C), an ~1:1 mixture of unconverted substrate 3 and the desired product 4 was obtained (entry 3). Consecutive increase of the residence time in reactors R3 and R4 improved this to a 10:90 mixture (entry 5). From this, the target compound 4 was isolated in 86% yield. The diastereomeric ratio of the product was 89:11. This highly encouraging result, demonstrating proof of concept for the synthesis of 4 in a continuous flow setup, prompted us to further optimize this approach.

2.2. Further Optimization. Improvement of the diastereoselectivity of the reaction was the main objective of the optimization program. Application of a larger excess of zinc chloride—which in the batch protocol provided product 4 with a diastereomeric ratio of >95:5—resulted in clogging of reactor R4. The latter also occurred when the rearrangement reaction was performed at lower temperature (by placing reactor R4 in the cooling bath).

Consequently, it was decided to modify the flow reactor setup (Scheme 4). In contrast to the original approach, the zinc-catalyzed rearrangement reaction was no longer performed in a flow reactor. Instead, the process stream leaving the flow reactor was quenched in a batch reactor containing a

precooled zinc chloride solution. Undesired precipitation of solid material was further prevented by diluting both the substrate and n-BuLi solutions with THF.

Initial experiments at −80 °C resulted in near full conversion of substrate 3 (>98%) and provided 4 in excellent diastereomeric excess (d.r. 97.7:2.3). It should be noted that the reaction was fairly slow at this low temperature and required a relatively large excess of n-BuLi to reach (near) full conversion in this setup. This excess of reagent led to side product formation if the reaction mixture had warmed up prior to the quench.

2.3. Pilot Run. The laboratory scale flow reactor setup was transferred to the piloting site to allow familiarization of the staff with the new reaction concept and development of the required analytical methods. Next, based on the parameters of the optimized process, a plant layout capable of producing the required amount of approximately 40 kg of 4 was designed, built and operated. Analogous to the optimized laboratory protocol, the mixing of dichloromethane and n-BuLi, and reaction of (dichloromethyl)lithium with a solution of 3, was performed in a flow reactor; the subsequent rearrangement reaction in the presence of zinc chloride was performed by introducing the flow into the vortex of the reaction mixture in batch reactor stirred by a reclined impeller. The size of this reactor and the volume of zinc chloride solution inside defined the size of a single batch.

The laboratory setup yielded several g/min of a 29 w/w% solution of 4. For further scale up, we decided to retain the tube reactor concept to meet our volume demand.
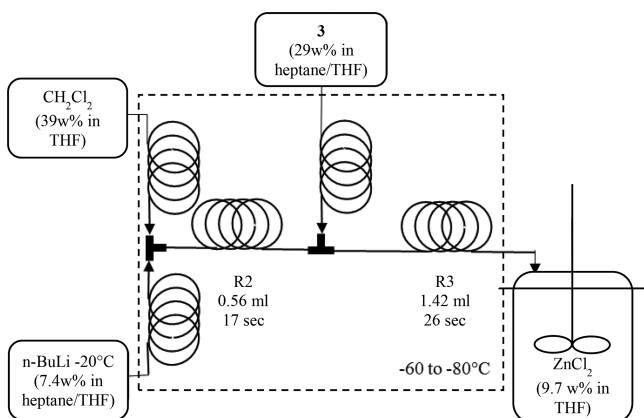
General Setup of the Pilot Flow Reactor. All mixers and tubes of the pilot reactor were built inside a vertically mounted piece of stainless steel tube that acted as a cooling jacket for the whole setup (Scheme 5). At the bottom, an entry for the coolant was mounted, whereas a lateral coolant exit and a flange — through which all substrate and product flows went — was mounted at the top. To realize the increased capacity, we decided to increase the diameter and the tube length. In this way, residence times remained unchanged and clogging of the reactor by small solid particles was avoided.

Precooling of Flows. All substrate flows (solutions of 3, n-BuLi, and dichloromethane), were cooled by a predefined length of tubing before they were mixed.

Mixing of Flows. Turbulent mixing of the flows at the low temperature is required to obtain the high diastereoselectivity. The viscosity of the liquids at these low temperatures is rather high (compare, e.g., the viscosity of pure THF at −80 °C is approximately 2.4 mPas); hence, we decided to use additional mixing elements. These were placed inside the cooling tube in a way to be able to remove them easily from the reactor in the unlikely event of a blockage.

Residence Times. The residence times were kept as defined in the previous laboratory experiments. As the overall scale-up

Scheme 4. Improved Flow Setup for the Matteson Reaction

Scheme 5. General Setup of the Pilot Flow Reactor
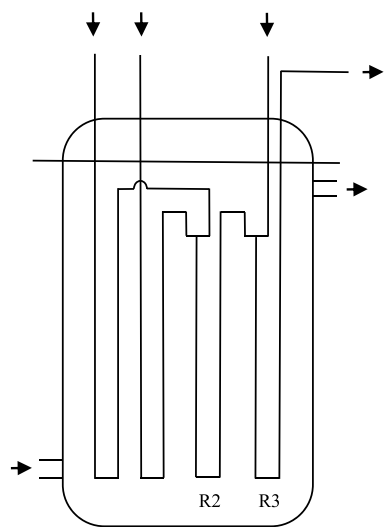
was achieved by increasing both the diameter and the length of the tubes, we took measures to increase radial mixing of the respective reaction mixtures.

To increase flexibility the reactor was built in a standard metal workshop. Adjustment to different low-temperature reactions is easily possible by exchanging the mixers and tuning the lengths of the tubing in the different sections. The reactor does not contain any "long lead-time" items that could lengthen the setup time of the equipment.

Results. With the scaled-up flow reactor in place, the process was further optimized. Therefore, in a first series of shorter test runs (entries 1−3) a fine-tuning of the equivalents of *n*-BuLi, residence times, and reaction temperature was performed.

Optimizations were performed by taking IPC samples of the reaction stream just before entering the zinc chloride quench.

In a second series (entries 4−7) several pilot batches were run at the optimized reaction conditions, with a total of 15 h of collection time each. All products were collected as an approximately 50% solution in THF.

From Table 2 it becomes obvious that the flow reactor can be operated continuously over a long period of time, proving

Table 2. Pilot Plant Runs

	boronic ester (3)	α-chloroboronic ester (4)		
pilot run no.	input [kg]	output [kg]	purity HPLC [area %]	isolated yield [%]
1	13.90	15.20	95.6	99.1
2	13.90	15.36	97.4	100.1
3	13.90	15.30	96.7	99.7
4	24.80	25.60	94.8	93.5
5	24.80	25.30	94.6	92.4
6	24.80	24.35	94.7	88.9
7	24.80	24.90	95.1	91.0

the robustness of the setup and providing α-chloroboronic ester **4** with high yield (>90%) and high selectivity (diastereomer ratio >95:5). Hence the decision was taken to further scale up this process to commercial scale.

2.4. Commercial Manufacturing. Prior to commercial manufacturing a refined laboratory flow reactor setup was built in our R&D laboratories to investigate ranges for process

validation. The advanced laboratory setup consisted of vessels for the feed solutions (each equipped with adjustable flow meters), the custom designed flow reactor, cooling devices, and the quench vessel corresponding to the equipment used for the previous pilot campaign. Additionally, various temperature and pressure sensors were installed and connected to a laboratory process control system to allow for detailed characterization of the reaction and to implement automatization to speed up the screening program.

With this setup, detailed investigations were performed to optimize reaction conditions and parameters such as temperature and pressure, with a strong focus on residence times in the different flow reactor sections. The implemented lab process control system ensured quick screening of reaction conditions. In addition, a safety concept for *n*-BuLi handling and defined reaction start-up and shutdown was established.

The continuous flow process in the refined lab setup was conducted using the parameters shown in Table 3 as a starting point for the large-scale process validation.

Table 3. Parameter Set Used for Experiments in the Refined Laboratory Setup

	concentration [%]	molar ratio [mol equiv]	temp [°C]
boronic ester (**3**) in THF	29.0	1	−75
n-BuLi solution	25.0	1.4	
CH_2Cl_2 in THF	39	4.2	
$ZnCl_2$ in THF	11.8	2.4	−25

With the detailed knowledge of the most favorable reaction conditions, a production-scale flow reactor was assembled and operated at one of the pharmaceutical production facilities. With this equipment, several hundred kilograms of intermediate **4** were produced in the registration campaign in very high purity and yield. In order to increase the productivity, a second, identical flow reactor line was installed, which was fed from the same feed vessel as the first flow reactor line. With this assembly, a process validation campaign yielded several metric tons of intermediate **4** in the same high quality. The product, process, and equipment successfully passed an audit performed by the FDA in 2017.

As can be seen from Table 4 the isolated product had a very high purity, and the results from the advanced laboratory setup

Table 4. Results of the Commercial cGMP Production Campaign

	result ref. exp. lab.	result reg. campaign	result val. campaign
purity of **4** (HPLC, %area)	>98	>98	>98
starting material (**3**)	0.7	<1.0	<1.0
side product	0.6	<1.0	<1.0
single unspecified impurity	<0.1	<0.1	<0.1
diastereomer of **4** (HPLC, %area)	2.6	1.7	1.4
yield [%] (**4**)	93	91	96

were reproduced very well on production scale. By having better control over the zinc chloride quench during production, the diasteromeric ratio was even further improved on scale. In addition, the product could be isolated in very

Scheme 6. Two Envisaged Concepts: Continuous Loop Reactor (Left) and Continuous Stirred-Tank Cascade (Right) for Rearrangement with Zinc Chloride in the Matteson Reaction

continuous loop quench   continuous stirred-tank cascade quench
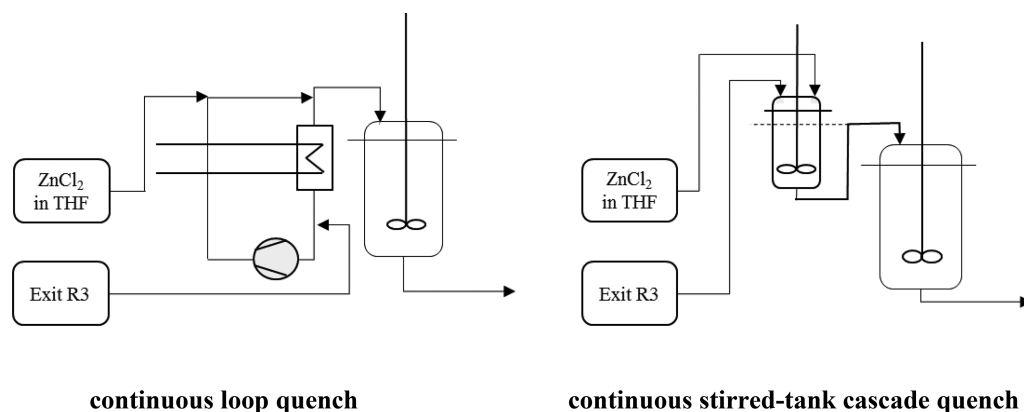
good yield, demonstrating high control over the reaction and clean conversion in the custom designed flow reactor.

2.5. Toward a Fully Continuous Process. Although the continuous processing setup followed by batch zinc chloride including rearrangement provides product with the desired quality, it resulted in the quench operation becoming the volume bottleneck of the process. Therefore, we designed a fully continuous system to increase throughput.

This section focuses on the development, scale-up, and implementation in production of a continuous workup process.

Up to this state of process development the boronate adduct was formed from intermediate **3** in a custom designed multistep tube reactor as described above, and the initial adduct was rearranged to intermediate **4** with zinc chloride in THF at <−20 °C in a batch reactor (Scheme 2).

The complete amount of zinc chloride and THF are precharged and precooled. After complete addition of one batch of material produced in the tube reactor to the zinc chloride quench solution and warming up, the mixture was washed and neutralized in a batch process by subsequent aqueous washes. An azeotropic "put and take" distillation with tetrahydrofuran was used to remove water and adjust the target concentration.

In transforming this "continuous plus discontinuous" sequence into a fully continuous process, three individual operations were addressed: (a) the quench with zinc chloride in THF at <−20 °C; (b) the batch sequence of aqueous washes; (c) the distillation procedure. While the latter two targets were achievable using established technologies with conventional equipment for countercurrent extraction and continuous distillation, the first target needed to be proven.

We investigated two technical settings, as outlined in Scheme 6, to realize a continuous quench of the reaction stream from the continuous flow tube reactor. The first concept consists of a loop reactor, where a small volume is circulated with a pump at a high flow rate and temperature is controlled by a heat exchanger. The second concept consists of a small volume continuous stirred-tank reactor (CSTR), where temperature control is realized via the cooling jacket. Furthermore, both concepts contain a second, larger CSTR. In both settings equilibrium and molar ratios are controlled by the flow rates of the tube reactor stream (<−60 °C) and the stream of the zinc chloride in THF stock solution (∼25 °C). The stable product solution is then directed to a buffer tank for further continuous downstream processing.

Below a certain working scale both concepts show similar benefits. The productivity of the overall process is increased as the time-consuming precooling of the zinc chloride solution is eliminated. The cooling efficiency and therefore the energy efficiency are increased due to the better volume-to-surface ratio. In addition, better temperature control due to the small volume promised a positive effect on product quality. Therefore, both processes were set up and tested in the R&D laboratory.

In the loop quench concept the feed of the boronate adduct reaction mixture from the original tube reactor R3 enters the loop and is rapidly mixed with a flow of preconditioned zinc chloride solution in THF propelled by a centrifugal pump. The temperature of the product mixture is controlled by a heat exchanger and a temperature sensor. The product solution exits the loop by an overflow device, and consumed zinc chloride is constantly replenished to the loop to keep the molar ratio at equilibrium. A valve allows collecting in process control (IPC) samples before the product solution enters the collection vessel.

In the stirred tank cascade concept, the feed of the boronate adduct reaction mixture from the original tube reactor R3 enters the CSTR and gets rapidly mixed. The temperature of the product mixture is controlled by a cooling jacket via a temperature sensor. The product solution exits the CSTR by an overflow device to keep a constant fill level, and consumed zinc chloride is constantly fed to the CSTR to keep the molar ratio at equilibrium. A valve allows collecting in process control samples before the product solution enters the collection vessel.

For the first proof of concept the established parameters regarding molar ratio of zinc chloride and temperature of the quench solution from the already established batch quench were used. Both settings — the CSTR as well as the loop quench — initially showed promising results regarding product quality and yield. The opportunity to draw in process control samples and determine product quality and conversion directly after the quench enabled us to screen various settings with respect to possible operational windows. Samples were taken after each variation of a process parameter when steady state in the continuous quench system had been reached. The time to reach equilibrium was determined in a > 2 h run, where samples were taken every 15 min for each laboratory setting. Variation of the concentration of the zinc chloride stock solution (10% to 20%) or variation of the flow rate of this

solution, both effecting various molar equivalents of zinc chloride, resulted in different amounts of undesired diastereomer formed. The same trend as in the batch quench was observed for both concepts, where a higher amount of zinc chloride (>2.0 mol equiv) led to improved product quality. As we had hoped, the two concepts behaved differently to the batch quench when we tested variations of the quench temperature. The observed product quality at elevated temperatures for the CSTR system (≥−10 °C demonstrated) and the loop system (>0 °C demonstrated) were as good as the best results in the batch quench at <−20 °C. To the best of our knowledge, these elevated temperatures tolerated in the rearrangement in the Matteson reaction have not been reported to date, and both continuous quench systems in consequence allow for novel operating windows with regards to process temperature. This observation can be explained by the extremely fast and rigorous mixing at the entry point of the boronate adduct reaction stream.

Both concepts, the quench loop and the CSTR, showed higher temperature tolerance and both could be operated at an elevated temperature of ≥ −10 °C and still yielded product with high diastereomeric purity (see Table 5).

Table 5. Results of Quenching Experiments

entry	ZnCl$_2$ quench mode	temp [°C]	molar ratio ZnCl$_2$ [mol equiv]	diastereomer of **4** [HPLC, %area]
1	batch mode lab	−25	2.4	2.6
2	CSTR	≥−10	2.1	0.9
3	loop	≥−10	2.1	1.3

As both concepts worked well and delivered results comparable with respect to product quality, yield, and operational windows, the decision was taken to move forward with the loop reactor. This was based on process safety, costs, and scalability aspects. A general comparison of the two concepts is outlined in Table 6.

The translation to a production size loop reactor was chosen for its simplicity and low cost. It is highly pressure resistant and consequently can be operated in a safe mode. However, the strongest benefit is the scalability, as the ratio of the circulated volume at high flow to the input feed guarantees equal quality when the input is increased, e.g. by numbering up the tube reactor lines in front of the quench loop.

The loop reactor for a continuous rearrangement reaction was installed in the production facility and attached to the already existing tube reactor for the continuous Matteson reaction. It was constructed from regular tubing and a pump to circulate the volume. The temperature in the loop was

controlled by a standard secondary closed brine chilling circuit. Zinc chloride solution in THF was fed directly to the loop at room temperature. The loop reactor was constructed to be portable and can be operated to support full commercial quantities.

A demonstration campaign was successfully completed, operating the Matteson tube reactor including the loop reactor quench and subsequent continuous mode downstream operations. Several hundreds of kilograms of intermediate **4** were produced with high chemical purity (>98%area by HPLC) and yield (97%), even having a lower content of the undesired diastereomer (0.8% compared to 1.4%area; Table 7). The table compares production results of the original zinc

Table 7. Comparison of Zinc Chloride Quench in Batch Mode vs Loop Reactor

	result val. campaign ZnCl$_2$ batch mode	result ref. exp. lab. loop reactor	result demo campaign loop reactor
purity (HPLC, %area)	>98	>96	>98
intermediate 3	<1.0	0.6	<1.0
side product	<1.0	1.3	<1.0
single unspecified impurity	<0.1	<0.1	<0.1
diastereomer of **4** (HPLC, %area)	1.4	1.3	0.8
yield [%] (**4**)	96	97	97

chloride quench in batch mode and continuous mode loop reactor results of the laboratory reference experiment and the subsequent demonstration pilot campaign. Values represent typical quality and yield.

As a result, the custom designed loop reactor allowed us to increase the required temperature from <−20 to 0 °C and reduce the formation of the undesired diastereomer from 1.4% to 0.8% while maintaining the same chemical purity and yield. The use of counter current extractions for neutralization and salt removal improved extraction efficiency and reduced aqueous waste. A continuous azeotropic distillation with THF for efficient water removal yielded the target product intermediate **4** as an anhydrous, approximately 50% solution in THF.

3. CONCLUSION

An initially unscalable laboratory batch process for the Matteson reaction has been successfully converted into a continuously operated manufacturing process. This served as a proof of concept and motivated further development to reach, within the timelines of a pharmaceutical development project

Table 6. Comparison of Continuous Concepts for Scale-up

	Cascade Quench	Loop Quench
Quality	Comparable to batch process	Comparable to batch process
Process safety	Not pressure resistant if small stirred-tank reactor is constructed of glass	Highly pressure resistant, safe mode of operation
Costs	High costs for small pressure resistant stirred tank in hastelloy	Low costs as it simply consists of a tube, a pump and a heat exchanger
Scalability	Risk of hot spots and formation of side product in case of increased capacity/throughput	Easily scalable as the volume circulated at high flow is significantly higher than the reaction mixture entering and exiting the loop
Operational window	Elevated temperatures can be tolerated (up to −10 °C demonstrated)	Elevated temperatures can be tolerated (up to 0 °C demonstrated)

designated for "fast track" development, the maturity and reliability to pass a dedicated FDA preapproval inspection.

By replacing the initial batch mode zinc chloride quench into a fully continuous production, the process was further intensified, increasing its productivity and selectivity, and significantly improving its scalability. A customized loop reactor system for the rearrangement with the Lewis acid in the Matteson reaction was developed and scaled up to production scale. Several hundreds of kilograms of intermediate **4** were produced under conditions of full cGMP in a demonstration campaign, thus representing the successful application of the process in a large scale pharmaceutical production. This new process allows for industrial scale production with improved economics and a reduced ecological footprint.

4. EXPERIMENTAL SECTION

Comparative Lab Experiment (Batch Mode).[3] (3S,6S)-tert-Butyl 3-(tert-butyldimethylsilyloxy)-6-chloro-6-[(2S,6R)-2,9,9-trimethyl-3,5-dioxa-4-boratricyclo[6.1.1.02,6]-decan-4-yl)hexanoate (**4**).

The batch mode experiment was conducted according to the procedure described in the literature, using 2.5 M n-BuLi in hexane. While the literature reported an isolated yield of 88%, the conversion in our hands was 75 area% **4** vs 25 area% **3** (HPLC) - see: Table 1, experiment no. "batch mode").

Initial Feasibility Study.[11] *Experimental Setup.* The continuous flow setup as outlined in Scheme 3 was used.

The setup was made of stainless steel and was built using 1/16″ spiraled tubing (internal diameter: 1 mm). The system was controlled using four Gilson 307 HPLC pumps, and temperature control was achieved using a cooling bath with different media to maintain the desired reaction temperature.

A 1.6 M stock solution of n-BuLi in hexane, 17% stock solution of dichloromethane in THF, 0.6 M of the compound **3** stock solution in THF, and 0.5 M of zinc chloride stock solution in THF were prepared and used in the continuous flow process. The starting materials were kept under a nitrogen atmosphere and dry solvents (<0.01% water by Karl Fischer) were used to prepare the stock solutions.

The n-BuLi solution was cooled to the reaction temperature in the continuous flow reactor R1 prior to reacting with dichloromethane. The cooled n-BuLi reacted with dichloromethane in reactor R2. The obtained lithium species subsequently reacted with the substrate pinanediol boronate **3** in reactor R3 to form a second intermediate which was then rearranged upon contact with zinc chloride in reactor R4. The product leaving the reaction mixture produced in R4 was collected under a nitrogen atmosphere, quenched with a 1 N HCl solution, and analyzed for the contents of compounds **3** and **4**.

Two parameters were adjusted in the initial continuous flow feasibility study: the reaction temperature and residence time. The temperature was adjusted by changing the composition of the dry ice and acetone mixture in the cooling bath, and the residence time in each continuous flow reactor was increased or decreased by adjusting the length of the continuous flow reactors R1, R2, R3, and R4. The results obtained are summarized in Table 1.

Further Optimization.[11] *Experimental Setup.* The continuous flow setup as outlined in Scheme 4 was used.

The setup was made of stainless steel and was built using 1/16″ spiraled tubing (internal diameter: 1 mm). The additions

of dichloromethane and the pinanediol boronate **3** solution were controlled using Gilson 307 HPLC pumps with internal damper, the addition of n-BuLi solution was controlled using Harvard Apparatus Syringe Pump 11 Plus, and the temperature control was achieved using a cooling bath Haake KT900W Cryostat to achieve the desired reaction temperature (Table 8).

Table 8. Reaction Conditions for the Continuous Flow Process

cooling bath temperature	−60 °C
Flow rate of n-BuLi solution	2.0 mL/min (1.0 equiv)
Flow rate of dichloromethane solution	1.2 mL/min (3.0 equiv)
Flow of pinanediol boronate **3** solution	3.2 mL/min (0.86 equiv)

The continuous flow reactor R2 was 142 cm, and the continuous flow reactor R3 was 315 cm.

A stock solution of n-BuLi (7.4 wt %) was prepared by diluting a 2.8 M n-BuLi solution in heptane with THF. For example, a flask was added with 40 mL (35.5 g) of THF under a nitrogen atmosphere and then cooled to <−60 °C, and then 14.4 g (20.3 mL) of a 2.8 M (25.6 wt %) n-BuLi solution in heptane was added into the flask while keeping the temperature below −60 °C. A stock solution of dichloromethane (39.0%) in THF was prepared by mixing 90.0 mL (119.3 g) of dichloromethane in 210 mL (186.3 g) of THF. A stock solution of substrate **3** was prepared by first preparing a pinanediol boronate **3** (77.9 g) solution in heptane (38.0 wt % of compound **3**) and then adding 24.1 g of THF. A stock solution of zinc chloride (9.7 wt %, 0.7 M) in THF was prepared by dissolving 22.2 g of zinc chloride in 233 mL (206.7 g) of THF.

When starting the setup, the dichloromethane flow was started first, followed by starting the flow of the pinanediol boronate **3** solution, and then followed by starting of the n-BuLi solution. A prerun of 7 min to 10 min was performed, and the reaction mixture from the prerun that passed the continuous flow reactor R3 was collected and discarded. Afterward, the reaction mixture from the continuous flow reactor R3 was added to 90 mL of zinc chloride solution (at about −20 °C) for 15 min. The amount of zinc chloride corresponded to more than 2.1 equiv of substrate **3**. Regular HPLC samples were taken to check conversion and side product formation.

The reaction mixture in the zinc chloride vessel was washed twice with 1 M HCl (46 mL for each wash), followed by two washes with water (46 mL for each wash). The obtained solution was concentrated by distillation under vacuum at a temperature of below 50 °C to an about 17 mL target volume. For complete removal of water by azeotropic distillation, 20 mL of THF were added to the residue and the solution was concentrated under vacuum to an about 30 mL target volume. The cycles were repeated until the target water content of less than 0.1% by Karl Fischer titration was reached.

Reproducible results were obtained with over 99% conversion (typically <1% of substrate **3** remaining) and >70% yield. Depending on the amount of n-BuLi used, about 1−3% of side product was observed. The diastereomeric excess of compound **4** produced in this setup was higher than 95:5.

Pilot Run.[11] The continuous flow process described in the section "Further Optimization" was implemented successfully to produce 180 kg of product **4**, thus demonstrating the

scalability of the process. A continuous flow setup as outlined in Scheme 5 was used.

Preparation of the reaction solutions included a solution of pinanediol boronate **3** (29 wt %) in heptane/THF, a solution of dichloromethane (39 wt %) in THF, a 0.7 M zinc chloride solution in THF, and an *n*-BuLi stock solution in heptane/THF, prepared by cooling 44 kg of THF to −60 °C and subsequently mixing with 17.5 kg of *n*-BuLi solution in heptane in 40 min at about −60 °C.

The continuous flow process was conducted using the following steps: the continuous flow setup was cooled to −60 to −70 °C, and the *n*-BuLi/THF flow was started at 7 kg/h for about 20 min until the temperature of the flow reached −25 °C. Then the flow was adjusted to 2.55 kg/h. The substrate **3**/Heptane/THF flow was started at 3.97 kg/h. After about 15 min the dichloromethane/THF flow was started at 1.4 kg/h. After 30 min the reaction solution was no longer neutralized and discarded but quenched with zinc chloride at −20 °C and collected. After the reaction mixture was collected for 4 h, the substrate **3** in Heptane/THF flow was adjusted to 3.91 kg/h based on IPC results. After a total collection time of 15 h, a new portion of zinc chloride solution was used for collection and the product was collected for an additional 15 h. Once the IPC results confirmed completion of the reaction, the solutions from the quenching step were combined and washed twice with 114.5 kg of HCl (3.4%) per portion. Subsequently the organic phase was washed twice with 113 kg of water each. The product solution was concentrated by distillation under vacuum at a temperature of less than 50 °C. Azeotropic removal of water was performed by repeated distillation cycles with THF until a water limit of NMT 0.02% by KF was reached. In total, 43.5 kg of solution of product **4** were collected, which showed a content of 58.2 wt % product **4** in THF, resulting in 92% isolated yield (calculated "as is"; see Table 2, entry 5).

Refined Laboratory Runs for Investigating Ranges for Process Validation.[11] *Experimental Setup.* A continuous flow setup made of stainless steel spiraled tubing similar to the one outlined in Scheme 4 was used in the lab for determination of ranges for process validation. An additional preceding mixing point was added to directly prepare the *n*-BuLi in heptane/THF solution.

The tubings for precooling of the incoming *n*-BuLi in heptane solution and THF were about 0.5 m long, the tubing for the resulting *n*-BuLi in heptane/THF solution was 6 m long, the continuous flow reactor R2 was in the range of about 1.5 to 3 m long, the continuous flow reactor R3 was about 6 m long, and the tubings for precooling of the dichloromethane stock solution entering R2 and for the pinanediol boronate **3** stock solution entering R3 were about 0.5 m long.

The tubing length and diameters were adjusted based on the experiments' scale and reaction conditions. The continuous flow process in the refined lab setup was conducted according to parameters given in Table 3, using a flow of 2.0 mmol/min **3** in THF as a starting point for the large-scale process validation.

All feed streams were introduced via pressurized vessels, and the flow rates of the various reagents were adjusted through corresponding adjustable flow meters.

IPC (HPLC) was used to determine the reaction conversion, and the reaction solution was evaluated based on the presence of substrate **3** or the presence of a side product caused by a follow up reaction. If the amount of substrate **3**

exceeded the limit, then the *n*-BuLi flow was increased, else the *n*-BuLi flow was decreased.

The reaction intermediate produced in the continuous flow reactor was collected in a stirred quench vessel, which contained the zinc chloride solution at −25 °C.

The quenched reaction solution was further purified via extraction and distillation. The first two extractions were performed by using 1 M HCl at room temperature. The third extraction was performed using 5% NaHCO₃, the fourth extraction by water at room temperature. Finally the product **4** solution was concentrated by distillation under vacuum at a temperature less than 50 °C.

The continuous flow process for the production of **4** described above achieved good reproducibility and provided 93% isolated yield and high purity (HPLC area%: >98% **4**, 0.7% **3**, 0.6% side product, <0.1% single unspec. impurity) and diastereoselectivity (HPLC area%: 2.6% undesired diastereomer of **4**) in the refined laboratory experiment.

Toward a Fully Continuous Process − Loop Quench. A standard lab experiment, as described in "Refined Laboratory Runs for Investigating Ranges for Process Validation", was used for converting pinanediol boronate **3** to intermediate **3′**.

The reaction intermediate **3′** solution produced by the continuous flow reactor was further processed in a quench loop reactor as follows:

A 10−20% solution of zinc chloride was dosed into a circulating loop and cooled via a cooling heat exchanger to −30 °C to −50 °C. At the same time the reaction mixture from the flow reactor with approximately −70 °C was dosed into the loop. A high pumping velocity was applied to achieve quick mixing of the flow of the preconditioned zinc chloride solution in the loop reactor. The supernatant liquid was transferred into a receiving vessel/storage reactor for the following workup procedure (aqueous washes, azeotropic drying, and concentration), which was done as described in "Refined Laboratory Runs for Investigating Ranges for Process Validation".

Result. 97% isolated yield (as-is), purity HPLC area%: >96% **4**, 0.6% **3**, 1.3% side product, <0.1% single unspec. impurity, 1.3% undesired diastereomer of **4**.

Toward a Fully Continuous Process − Continuous Stirred Tank Cascade Quench. A standard lab experiment, as described in "Refined Laboratory Runs for Investigating Ranges for Process Validation", was used for converting pinanediol boronate **3** to intermediate **3′**.

The reaction intermediate **3′** solution produced by the continuous flow reactor was further processed in a continuous stirred reactor cascade setup as follows:

The reaction mixture from the flow reactor was collected in a small quench reactor, containing a 10−20% solution of zinc chloride in THF at −30 to −50 °C. The contents continuously leaving the small reactor via an outlet were further transferred to a bigger storage reactor, while reaction mixture **3′** and zinc chloride solution were continuously fed to the small reactor. The quench solution was stirred in the bigger reactor at −10 to 0 °C until completion of the flow reactor run. Subsequent workup (aqueous washes, azeotropic drying, and concentration) was then performed in the same reactor, as described in "Refined Laboratory Runs for Investigating Ranges for Process Validation".

Result. 88% yield (as-is), purity HPLC area%: >95% **4**; 0.9% **3**; 2.3% side product; <0.7% single unspec. impurity; 0.8% undesired diastereomer of **4**. Note: the lower isolated yield in this experiment was assessed to be only a result of variations in

the standard flow reactor run used for this stirred tank cascade quench experiment.

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Notes

The authors declare no competing financial interest.

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