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Match-Making Reactors to Chemistry: A Continuous Manufacturing-Enabled Sequence to a Key Benzoxazole Pharmaceutical Intermediate

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Supporting Information

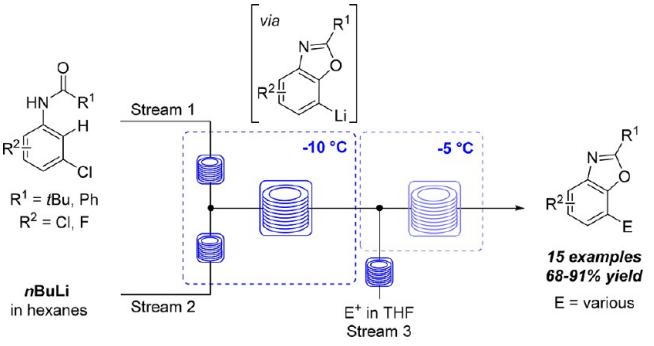
ABSTRACT: The focus of this study was to develop a chemical reaction sequence toward a key benzoxazole building block, required for clinical manufacturing of a lead candidate in the respiratory disease area. The chemistry consisted of initial low-temperature reactions with an organometallic reagent to generate the benzoxazole core, and was followed by noncryogenic transformations toward a sulfonamide substituent. With particular interest in continuous-flow manufacturing we attempted to integrate the entire sequence on lab scale. Subsequent in-depth process research, supported by PAT and calorimetry studies, revealed the critical parameters of each step, leading to a more rational attribution of mode of operation: flow, batch, or semibatch. Two bench-scale cascades of continuously stirred tank reactors (CSTRs) were constructed to meet the challenge of high exothermicity and solids formation and were key to smoothly upscaling the chemistry to deliver 17 kg of benzoxazole in superior yield, quality, and robustness.

INTRODUCTION

Continuous manufacturing will increasingly be applied where there is both an interest in extending the palette of permissible reaction conditions and enabling reaction outcomes which are highly challenging with the incumbent batch technology.[1] An opportunity in the emerging field of continuous manufacturing is the ability to match-make the ideal reactor to the chemistry in hand. In an established batch pilot plant the opposite is more often the case, with the accompanying compromises in efficiency when quality-critical attributes and reactor capabilities do not align. Considering the smaller reactor volume and lower capital cost of continuous plants, a tailored approach can be implemented, whereby the parameters identified as critical by detailed process development can be addressed by a subsequent bespoke reactor design and construction phase. In addition, the detailed knowledge gained in the laboratory development phase can be used to appropriately allocate flow or batch techniques to the sequence of operations, from chemistry, to workup, to purification.[2] In this way a line is drawn between flow, semibatch, and batch methods based on real process requirements and not on a desire to implement sequences in flow for their own sake.

Organometallic chemistry is a tremendous opportunity for continuous manufacturing[3] and has been applied to demonstrated effect in the industrial arena.[4] We have previously outlined a general methodology enabled by continuous flow processing toward substituted benzoxazoles starting from 3-halo-*N*-acyl anilines.[5] The transformation proceeded via base-mediated deprotonation, *ortho*-lithiation, and intramolecular cyclization to provide unstable lithiated benzoxazoles which were subsequently trapped by a range of electrophiles, Scheme 1. Efficient heat removal, mixing, and avoiding holding-times were identified as critical parameters and were the underpinning for operating in tubular reactors with precooling loops at subambient temperatures in continuous flow.

Scheme 1. Previously Communicated Continuous-Flow-Enabled Synthesis of Substituted Benzoxazoles from 3-Halo-*N*-acyl Anilines



Within our pipeline of projects in chemical development we identified a strong overlap with this methodology which could be used to increase the yield of a key benzoxazole building block. An active CXCR2 program in the chronic obstructive pulmonary disorder (COPD) disease area had undergone a synthesis evaluation phase, identifying optimal routes to the target squaramide receptor antagonist, Scheme 2.[6] All selected routes required the benzoxazole **1** as starting material, and cost evaluation highlighted this compound as the key contributor to the final cost-of-goods of the drug substance. In addition the supply chain for **1** was not robust, with an external contract manufacturing organization failing to meet the delivery request.

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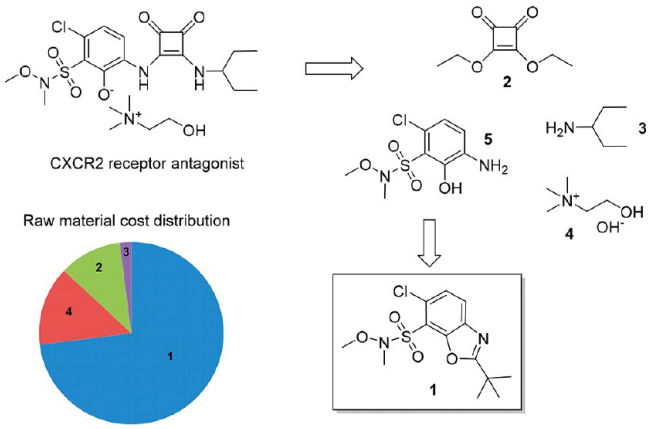
Scheme 2. Retrosynthesis of the CXCR2 Receptor Antagonist Identified Benzoxazole 1 as the Major Cost Contributor



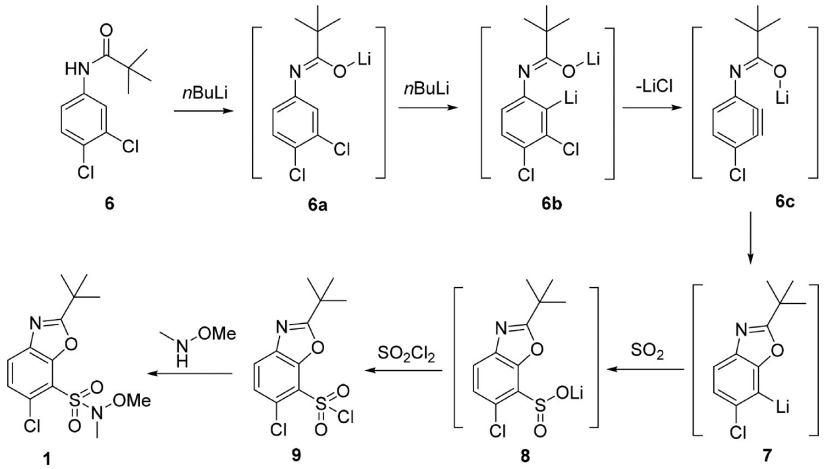
We therefore initiated the process research and development toward compound **1** and herein outline the transition from batch to flow, where appropriate, to achieve a more robust process with increased yield.

RESULTS AND DISCUSSION

Benzoxazole **1** is prepared from *N*-pivaloyl-protected 3,4-dichloro aniline **6** according to the chemical sequence summarized in Scheme 3.[7] Under controlled conditions, the addition of 2 equiv of *n*-butyl lithium to aniline **6** leads to both deprotonation of the pivaloyl-amide (**6a**) and regioselective *ortho*-lithiation of the aromatic ring (**6b**). The *ortho*-lithiated intermediate is highly unstable and eliminates lithium chloride to create a transient aryne (**6c**) which is immediately quenched intramolecularly by the nucleophilic tautomer of the lithiated pivaloyl-amide to provide compound **7**.[8] Compound **7** is highly nucleophilic, and timely trapping with sulfur dioxide delivers the lithium sulfinate **8** which has sufficient stability to be isolated and characterized. The standard synthetic sequence to compound **1** continues however with a dual oxidation/chlorination with sulfuryl chloride to provide the sulfonyl chloride **9**. Compound **9** was shipped as a stable intermediate during early manufacturing campaigns, but since identification as a compound with genotoxicity potential is further transformed in the same reactor to the sulfonamide-substituted benzoxazole **1** by nucleophilic substitution with Weinreb's amine, *N,O*-dimethylhydroxylamine. In batch mode the internal temperature of the reactor for this one-pot sequence would be initially set to −30 °C, and a strong scale dependency was observed with accumulated side products needing purging by crystallization of **1**. On a 30 g scale, an overall yield of 34% could be achieved in traditional batch mode.

First-Generation Continuous Process, Lab Scale. An initial lab-scale flow synthesis was devised in order to not only safely gain process familiarization with limited volumes but also determine if business benefits such as economy, yield, and safety could result from a straightforward continuous operation. As with our previous studies on model benzoxazoles, we selected tubular reactors and Teflon T-pieces in order to proceed with minimal complication and encounter the challenges as they presented themselves. A streamlined transition into continuous flow also enabled us to screen conditions "on-the-fly" which provided data much more rapidly than sequential batch reactions under cryogenic conditions ever could. As the chemistry proceeds stepwise through the sequence outlined in Scheme 3 the nature of the steps changes from fast highly exothermic reactions to compound **8** toward slower, less energetic functional group transformations to compound **1**. As such we chose to break the sequence down into three parts for our lab-scale studies: (i) cryogenic *n*-butyl lithium chemistry; (ii) suflur dioxide quench followed by oxidation/chlorination to the sulfonyl chloride **9**; and (iii) sulfonamide formation. We used our small-scale in-house automated flow reactor units for these studies, which we term the exploratory development units (ED-units).[9] This allowed us to both program and track flow rates provided by dual-barrel continuous syringe pumps, as well as set safety limits for acceptable temperature and pressure fluctuations. Reactors were loops of perfluoroalkoxy (PFA) tubing, and mixers were PTFE T-pieces. These units have been used for screening and early phase clinical supplies for numerous years, and the degree of mixing in T-pieces has been well characterized.[10] Although scale-up phenomenon will always apply, the ED-units permit a straightforward transition to our larger scale units, termed process development units (PD-units), which have an identical control system, but include pumps capable of higher throughput.

Scheme 3. One-Pot Synthesis of Benzoxazole 1 from *N*-Pivaloyl 3,4-Dichloro Aniline 6



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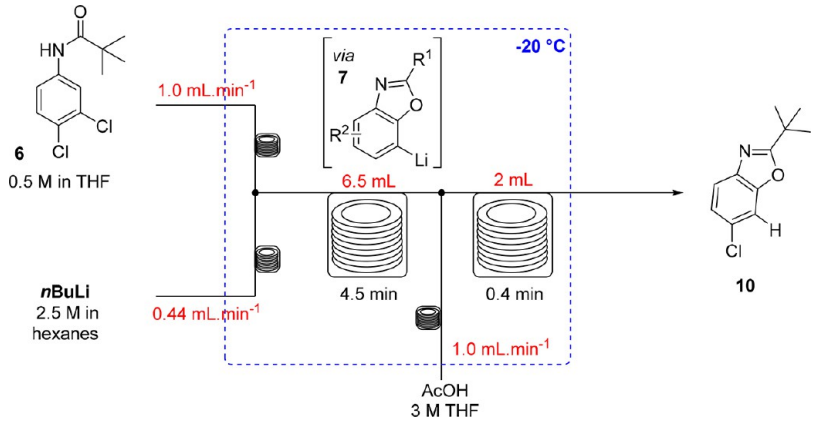
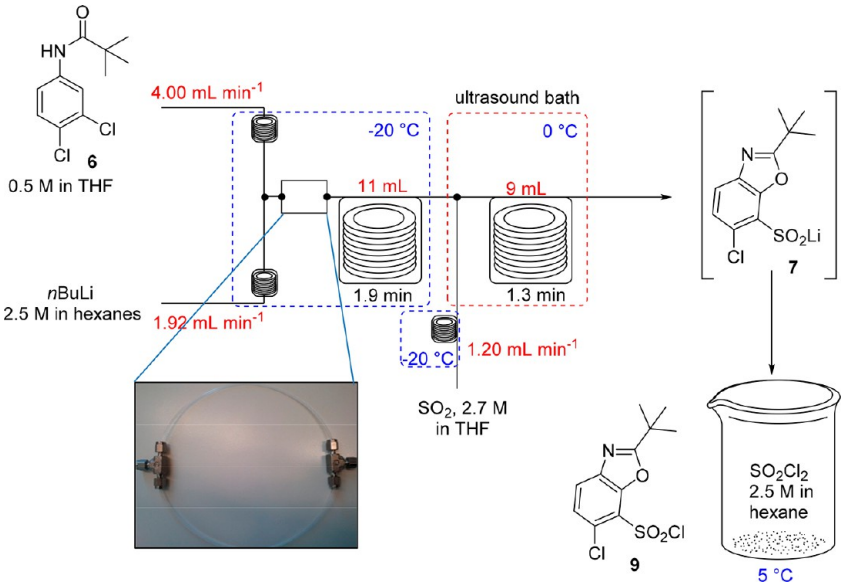
Scheme 4. Lab-Scale Continuous-Flow Setup for Studying the First Step with *n*-Butyl Lithium[a]



[a]Protic quench was provided by acetic acid.

Scheme 5. Lab-Scale Continuous-Flow Setup for Studying the Second Step with Sulfur Dioxide and Sulfuryl Chloride



In order to study the first step with *n*-butyl lithium independently of the subsequent two steps, we selected acetic acid as an electrophile and targetted the stable proton-quench compound **10**, Scheme 4. Precooling loops ensured that the set point of −20 °C could be attained in the streams prior to mixing in T-pieces. Following a screening to determine the optimum stoichiometry (2.4 equiv of *n*BuLi) and residence times (4.5 and 0.4 min respectively), the product **10** was obtained in 95% isolated yield and 99% selectivity.

With a reliable small-scale procedure for accessing lithiated intermediate **7** in hand, we switched the in-line electrophilic quench to a sulfur dioxide solution in THF, setting the temperature by experiment for this step to 0 °C. Semibatch quench of this combined stream was made into a solution of sulfuryl chloride in hexane at 5 °C to deliver sulfonyl chloride derivative **9** (general approach shown in Scheme 5). However, the partial insolubility of the sulfinate salt **8** formed after mixing with sulfur dioxide led to clogging of the PFA tubing, and so we resorted to ultrasound to disrupt the solid accumulation and keep the reaction medium flowing.[11] This proved sufficient for a demo-run, successfully converting 30 g of starting material to compound **9**. The first reactions with *n*-butyl lithium were considered *a priori* to be instantaneous, and so we were drawn to explore more efficient mixing in case this could streamline our process within the same ED-unit. A number of commercial micromixers were screened, but those with fine channels led to plugging. Staying within our remit of developing a lab-scale demonstration of the capabilities of flow processing, we found a pragmatic solution with a split-and-recombine reactor consisting simply of a T-piece to divide the stream immediately after *n*-butyl lithium addition and a T-piece to reunite the streams prior to an 11 mL residence volume coil (final conditions shown in Scheme 5). This effort brought the required residence time for the *n*-butyl lithium step down from 4.5 to 1.9 min allowing us to process a further 20 g of compound **6** over 4 h. This experiment confirmed that we had been, and most likely still were, highly mixing limited, but since scale-up of this laboratory setup was not our aim, we pushed forward to identify upcoming hurdles.

The final chemical step in the sequence to benzoxazole **1** was the conversion of the sulfonyl chloride **9** to the sulfonamide **1** by substitution with Weinreb's amine. The crude sulfonyl chloride **9** coming from the flow synthesis contained significant amounts of both residual sulfur dioxide and sulfuryl chloride. In

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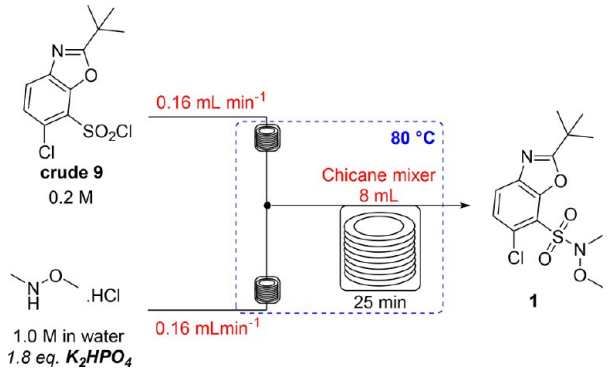
addition, and for reasons of convenience and safety,[12] the Weinreb amine was purchased as a hydrochloric acid salt and therefore required deprotonation prior to reaction with **6**. In order to limit the exothermy and avoid salt precipitation, we therefore opted for partial batch distillation of the reaction mixture to deplete the gaseous acidic components. The soluble reaction mixture could then be taken forward and combined with a basic aqueous solution of the Weinreb amine. Suitable bases were screened which were considered capable of deprotonating the amine (pK_a 4.8) but hydrolyzing the sulfonyl chloride **9** to the sulfonic acid at only trace levels, finally settling upon dipotassium hydrogen phosphate.[13] Screening of reaction residence time and temperature was conducted in the flow unit, with use of a glass chicane mixer chip from Little Things Factory[14] providing superior mixing of the organic and aqueous streams compared to an empty tube, Scheme 6. Operating at 80 °C the reaction required 25 min to reach full conversion, although this reaction time varied upward with increasing amounts of residual sulfur dioxide and sulfuryl chloride in the crude starting material stream.

Scheme 6. Lab-Scale Continuous-Flow Setup for Studying the Third and Final Step with Weinreb Amine To Provide Benzoxazole 1 with Sulfonamide Substitution



Since the projected maximal commercial volume of the drug candidate was significantly less than 100 ton/annum, we decided that the workup and crystallization of compound **1** could be sufficiently addressed by batch operations. The product stream containing crude compound **1** was combined with toluene and aqueous citric acid. Upon mixing and separation of the phases the organic phase was extracted once more with sodium bicarbonate prior to a complete distillative solvent-switch to toluene down to a desired concentration. *n*-Heptane was added to the heated solution at 50 °C, and a cooling ramp brought about the crystallization. After washing the filter cake with toluene/heptane and subsequently drying, benzoxazole **1** was delivered as off-white crystals.

Having identified optimal conditions for a lab-scale synthesis of benzoxazole **1** in three continuous-parts, we proceeded to combine these operations into one continuous processing line. The resulting assembly is pictured in Figure 1 and contained three thermostated baths (one sonicated) and five pumps (four syringe-pumps and one Knaur pump). Since the sulfonamide formation is at the tail-end of the chemical sequence, and has in any case the slowest kinetics of the tranformations, a 200 mL wide-bore (1/4″) PFA tube was used to enable complete conversion, with insertion of static mixer elements to ensure sufficient mixing efficiency, plug flow and heat-transfer. The

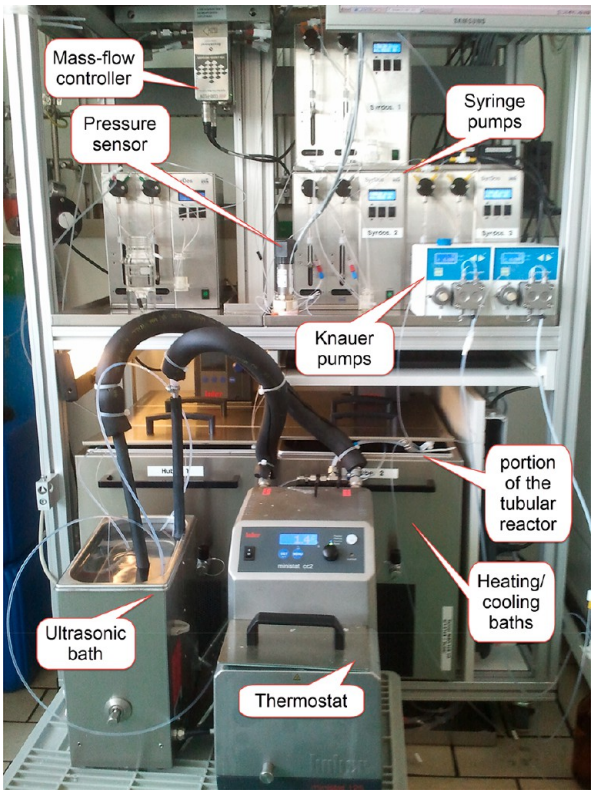


Figure 1. Lab-scale continuous-flow unit for preparing benzoxazole **1** in three chemical steps from *N*-pivaloyl 3,4-dichloro aniline **6**.

schematic of this three-step lab-scale unit is outlined in Scheme 7.

Unfortunately clogging of the lines in various positions plagued this ambitious attempt. Both switching of the narrow bore 1/16″ PFA tubing for larger 1/8″ tubing and dilution of the starting material steam (0.45 M) were of little effect, and the samples that could be taken showed mediocre conversion (60%). The lab-scale effort was put aside with the conclusion that sonication had proved unable to manage the solid generation in the PFA tubing. The batch partial distillation of the crude sulfonyl chloride solution of **9** to reduce gaseous acidic components had been left out of this fully continuous setup, and this shortcut had evidentally led to an excessive precipitation of the ammonium salts of the Weinreb amine. Although falling-film distillation could have been implemented in-line prior to the combination with Weinreb amine, this was outside the scope of this lab-scale study. Preferable was to take stock of the advantages discovered so far and then segregate batch and flow processes based on a more in-depth analysis of the sequence.

Notable was that the first two reactions to compound **8** had delivered a 94% *in situ* yield, compared to 57% in batch when operating in disconnected fashion in continuous flow. The third step, the amidation, step showed great potential with 95% yield in flow to crude compound **1**. Since we already envisaged that recrystallization of compound **1** was to be kept as a batch process, we knew from experience that an 80% yield for this purification step could be expected, giving an overall estimated yield of 70% for the flow-enabled process. Compared to the 34% overall yield of the purely batch process, the flow approach had clear potential, but only if the issues of solid-generation could be appropriately addressed. Having provided a sufficient

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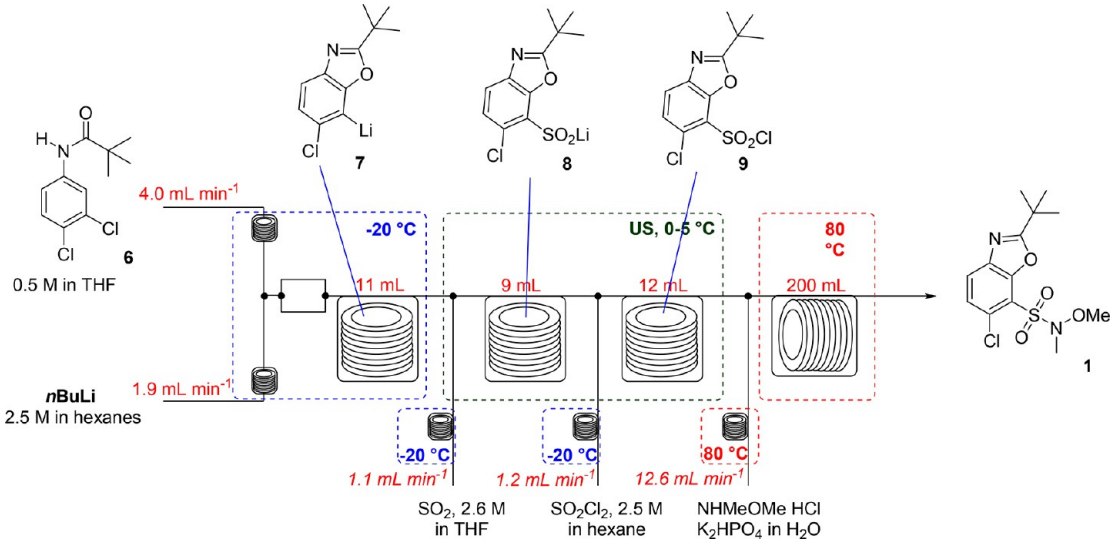
Scheme 7. Lab-Scale Continuous-Flow Schematic for Preparing Benzoxazole 1 in Three Chemical Steps from *N*-Pivaloyl 3,4-Dichloro Aniline 6



lab-scale proof-of-concept, and with the opportunity of supporting a 15 kg clinical phase I delivery in view, the team initiated an in-depth study of the chemistry.

In-Depth Process Development for a Second-Generation Mini-Pilot Process. In order to attribute the appropriate reactor to each chemical step we began by evaluating the heat-release profile of the sequence with reaction calorimetry in batch. The entire chemical sequence was run in an RC1 calorimeter in order to accurately measure the heat flow during each rapid dosing step, Figure 2.

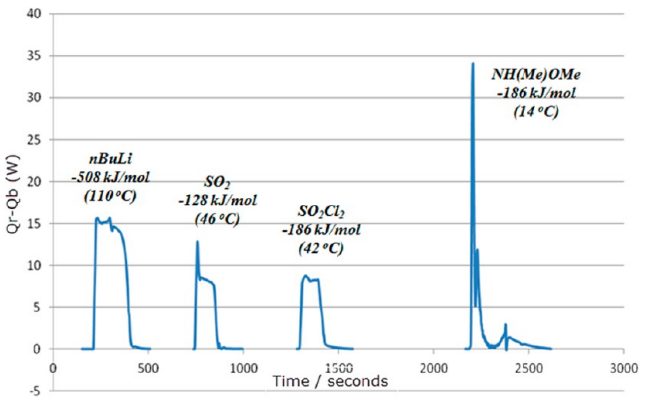


Figure 2. Heat-release profiles during an RC1 calorimetry study. Heat of reaction was determined from the area under the curves and is reported in kJ/mol of *N*-pivaloyl 3,4-dichloro aniline **6**. Calculated adiabatic temperature rise is reported in brackets.

As expected, with the serial dilution that occurs on stepwise addition of each reagent, the adiabatic temperature rise of each consecutive step decreases. Of particular note however is the very high adiabatic temperature rise of 110 °C following the *n*-butyl lithium addition. During this experiment the concentration profile of each intermediate was followed by online FT-IR analysis of characteristic signals, Figure 3. A complete overview of the trending concentrations could be obtained, which was particularly pleasing since few, if any, of these intermediates were expected to be stable enough to be obtained as isolated analytical references.

In order to render the data acquired by FT-IR quantitative, off-line ^{1}H NMR was also used to track key intermediates and byproducts. Once the mol % at a particular time point could be determined by NMR with an internal standard, the peak height by FT-IR could be correlated to this concentration at the same time point. In this way the continuous data stream coming from the noninvasive FT-IR could be used to build a kinetic model of the reaction progress at a variety of temperatures and concentrations. Particularly insightful was the plot shown in Figure 4 which depicts the dose-controlled transition from compound **6** to compound **7**. We determined that, at the slow dosing rate of *n*-butyl lithium in this experiment, both reactions were addition-controlled, but the rate of conversion of **6** into **6a** had to be much faster than that for **6a** to **7** in order to account for the sharp transitions observed in the concentration profiles of **6a** and **7**. As such the first equivalent of *n*-butyl lithium was almost entirely being employed in deprotonation of **6** to **6a**, with very little being made available for ring closure of **6a** to **7** (*via ortho*-lithiation and aryne formation).

In order to explore deviation scenarios we devised an NMR experiment where dosing of *n*-butyl lithium was significantly faster and a local hot spot was certain to exist. At a faster dosing rate we reasoned that we might shift away from a purely dose-controlled addition and begin to accumulate *n*-butyl lithium which could then be employed for not only selective deprotonation of **6** to **6a** but also a parallel ring closure from **6a** to **7**. This would put lithiated benzoxazole **7** in the presence of starting material **6**, a situation that we expected to compromise the selectivity of the reaction due to proton transfer between the acidic **6** and basic **7**.[15] The half a mount of *n*-butyl lithium (1.05 instead of 2.10 equiv) was added quickly to the starting material at −35 °C and a sample quenched with deuterated methanol at various time points. Figure 5 shows the ^{1}H NMR spectra at 0.5 and 2.5 h where lithiated starting material **6a**, lithiated benzoxazole **7**, and other compounds can be identified as deuterium-quenched species (compound **6** could not be tracked by NMR due to background deuterium exchange of the acid NH proton). At 0.5 h (Figure 5a) compound **6a** was the predominant product as expected, but already present was 10% of compound **7** which had evidently formed in parallel due to non-dose-controlled conditions

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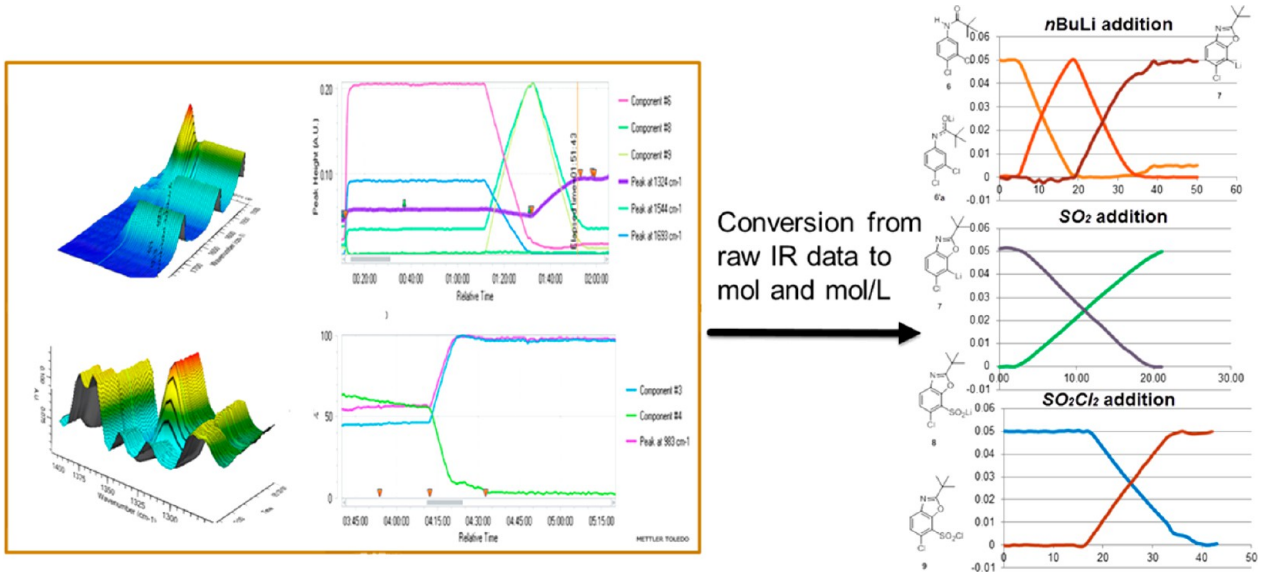

Figure 3. Concentration profiles were obtained based upon online FT-IR tracking of characteristic signals.

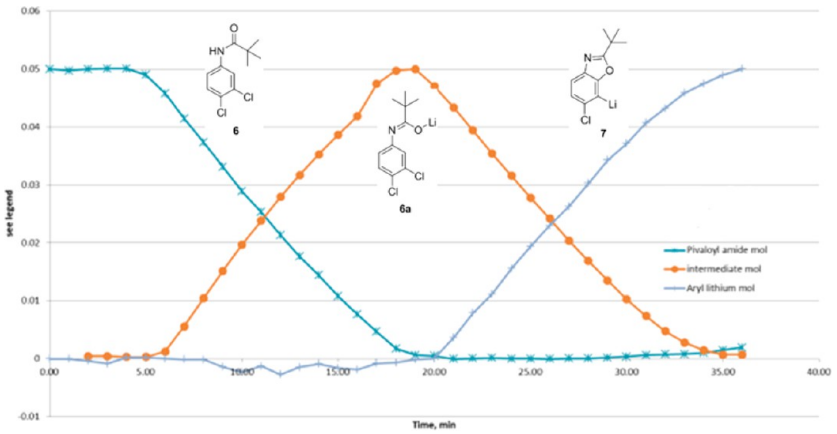

Figure 4. Concentration profiles derived from FT-IR data show the transformation of compound **6** into compound 7 via deprotonated compound **6a**.

brought about by accumulation of *n*-butyl lithium. Since a 9:1 ratio of **6a** to 7 was integrated, by subtraction this required that residual starting material **6** was still present in an approximately 5% amount to account for the 1.05 equiv of *n*-butyl lithium initially added (otherwise a ratio of 10.0:0.5 of **6a** to 7 would have been observed if all **6** had been consumed). By 2.5 h, Figure 5b, the newly identified proton-quench byproduct **10** had appeared in a 1:1 ratio with cyclized compound 7, as would be expected by the complete proton transfer from residual starting material **6** (initially 5%) to compound 7 (reduced now from 10 to 5%), with Figure 5c showing reference spectra of the proton-quenched byproduct **10** prepared separately. Based on this NMR study we concluded that if the chemistry was conducted under conditions where there was coexistence of compounds **6** and 7 we would always generate byproduct **10** by proton transfer if sufficient time was given.[16] In this way we determined that a slow dosing rate would be a critical parameter if we wanted to avoid a local-zone effect, i.e. an accumulation of *n*-butyl lithium in the dosage area in batch. This was certainly a compatible criterion for the batch equipment which would otherwise reliably generate a hot spot in the dosage area based on the calorimetry data outlined above.

Regarding the stability of compound 7, similar NMR experiments with a slower dosing of 2.1 equiv of *n*-butyl lithium (i.e., seeking to eliminate the possible presence of residual starting material **6** in the presence of lithiated 7, even during the dosing period) demonstrated that at −15 °C the lithiated intermediate 7 could be held for up to 1.5 h without significant degradation. However, if the temperature was raised to 0 °C then up to 70 mol % of a new byproduct identified as dimeric **11** was formed within 1.5 h, Table 1. The data strongly suggested that dimeric **11** was being formed from desired intermediate 7 at this temperature.[17] In complement, FT-IR tracking at three temperatures (10, 0, and −10 °C) confirmed the temperature sensitivity, and the kinetic data were used to set a maximal internal temperature of −10 °C for the ideal process.[18]

In conclusion to these mechanistic studies, we took the NMR and FT-IR data together and realized that in order to retain the high purity of lithiated intermedate 7 the ideal process would require a long *n*-butyl lithium dosing time and good mixing to avoid a local-zone effect and the resulting issues of proton transfer from residual **6**, as well as hot spots. However, the holding time of 7 should be as short as possible to avoid decomposition in general and dimerization to **11** in particular.

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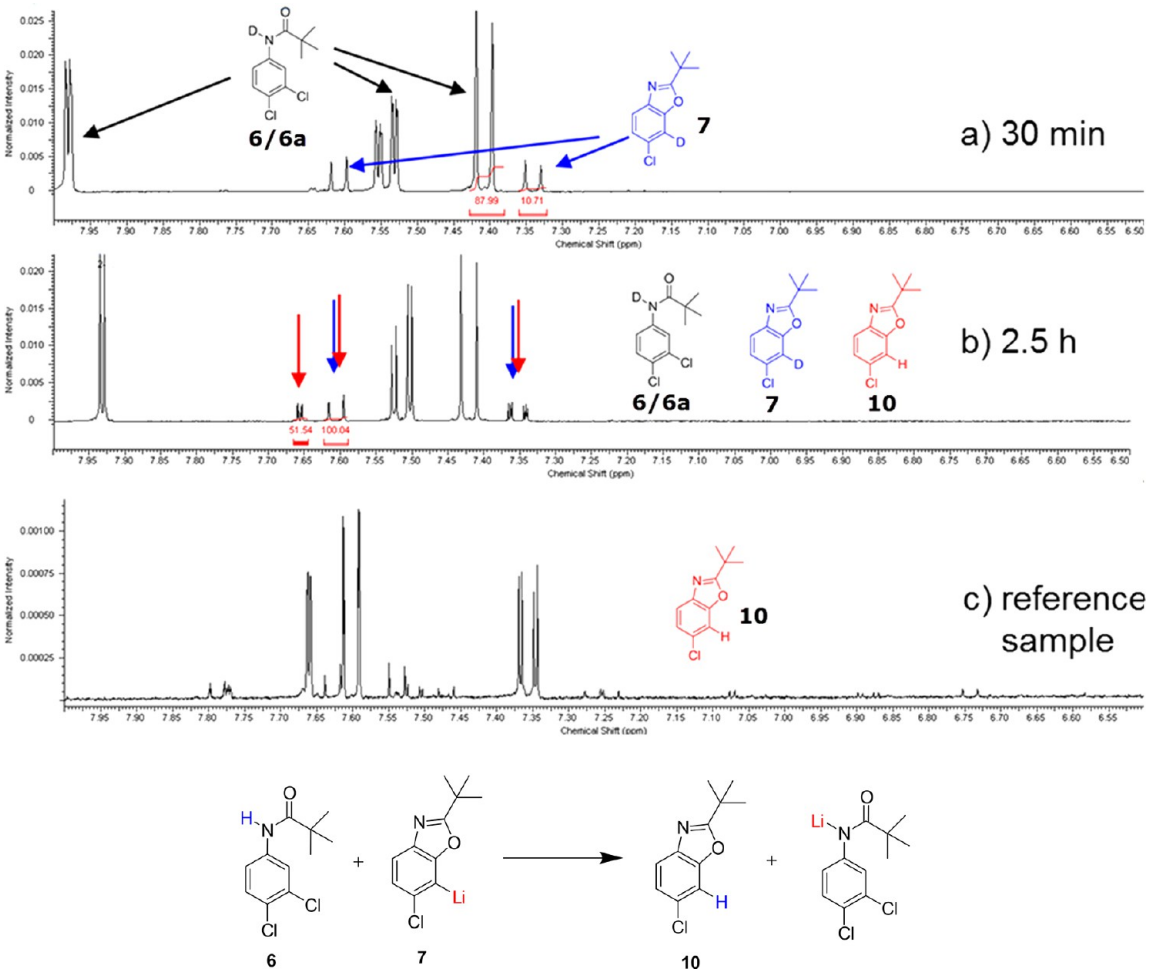

Figure 5. Successive NMR experiments at half-dosing of *n*-butyl lithium demonstrated the proton exchange between compounds **6** and **7** to generate proton-quench byproduct **10**.

Our conclusion was that this paradoxical situation excluded the possibility of using batch equipment on manufacturing scale, since a long dosing time would equate to a long holding time of **7** during dosing, and the mixing efficiency of large batch reactors was expected to decrease on increasing volume. In flow equipment the dosing time is quasi-equivalent to the mixing time and can be rapid with judicious choice of flow rates and mixer type. Heat removal can also be excellent due to the higher surface-area-to-volume ratio compared to batch. Finally, the holding time of **7** could also be short in continuous flow since the next reagent would intercept the reaction mixture after a short time defined by the flow rates and volume of the selected equipment. The combination of calorimetry, FT-IR, and NMR studies therefore consistently pointed us toward carefully designed continuous flow equipment to handle the first step of the sequence toward compound **1**.

NMR-based stability experiments on the lithium sulfinate **8** resulting from sulfur dioxide quench showed that it was entirely stable at the low temperature required for the *ortho*-lithiation. The first signs of decomposition according to SETARAM calorimetry began at 97 °C. Equally sulfonyl chloride **9** was found to be stable in the reaction medium, with NMR holding experiments at room temperature over 3 days showing no sign of degradation. Background hydrolysis of **9** by the aqueous solution of the Weinreb amine was to be expected, however, and screening of the base required to deprotonate the Weinreb amine salt (*vide supra*) had already led us to select dipotassium hydrogen phosphate. Further inorganic carbonate and phosphate bases were included in the extended screening, but dipotassium hydrogen phosphate led to the least decomposition of compound **9** over an extended period at 30 °C according to quantitative HPLC, Table 2.

Sulfonyl chloride **9** was found to hydrolyze to the sulfonic acid only at elevated pH. Conversely, low pH led to ring-opening hydrolysis of the oxazole moiety in compound **1** to provide a phenolic compound. As such we avoided extreme acidity or basicity by only dosing 40% of the full 10 equiv of aqueous dipotassium hydrogen phosphate solution to the sulfonyl chloride, the remaining 60% coming premixed with the Weinreb amine in aqueous solution.

Having determined the kinetics for each of the byproduct pathways, summarized in Figure 6, these pathways were incorporated into the Dynochem-based kinetic model to enable an overall simulation of the reaction within the flow reactor equipment (see the Supporting Information).

In order to effectively select the appropriate flow reactor we needed to tackle the issue of solid-generation which had been a critical issue on lab scale. Lithium chloride is a prime suspect as a precipitant in all chemistries between organolithium reagents and chloro-aromatics. Commercial solutions of lithium chloride are available at 0.5 M in tetrahydrofuran, and the maximum possible concentration in our chemistry was calculated at 0.3 M

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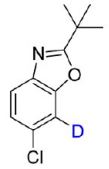
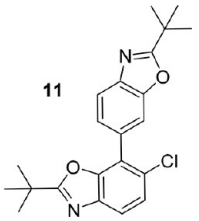
Table 1. Operating at 0 °C: Tracking of Byproducts Generated during the *n*-Butyl Lithium Step by ^{1}H NMR after Quench with Deuterated Methanol



deuterium quenched 7



Time of monitoring	Mol% by ^{1}H NMR		
	Deuterium-quenched 7	Dimeric byproduct 11	Unspecified byproducts
Directly after *n*BuLi addition	100	0	0
Temperature equilibrated back to 0°C (t = 0)	81	13.3	6
t = 10 mins.	65	25	10
t = 1.5 hrs.	14	70	16

Table 2. Hydrolysis of Sulfonyl Chloride 9 after Mixing with Aqueous Base at 30 °C[a]

Base	pH at start	pH after 1 hr	Decomposition of 9
0.9 M $NaHCO_3$	9	7-8	63%
1.1 M K_2CO_3	12	8	76%
0.9 M Na_3PO_4	12	6-7	44%
0.9 M K_2HPO_4	10	5-6	14%

[a]Decomposition was measured by HPLC with internal standard (toluene).

(1.0 equiv). However, since our solution contained dissolved substrates, and we operated at subambient temperatures, we initiated a seeding experiment to determine if we were operating under conditions of supersaturation. Small, but successive amounts of lithium chloride (0.03 eq. then 0.04 equiv) were spiked into the mixture of starting material **6** and *n*-butyl lithium at −30 °C, but gratifyingly no crystallization event was observed over a 2 h aging period.[19]

Lithium sulfinate intermediate **8** is a known solid, and so as a next step we prepared it in a separate experiment and recirculated a concentrated suspension by peristaltic pump between two glass vessels with a gravity overflow between

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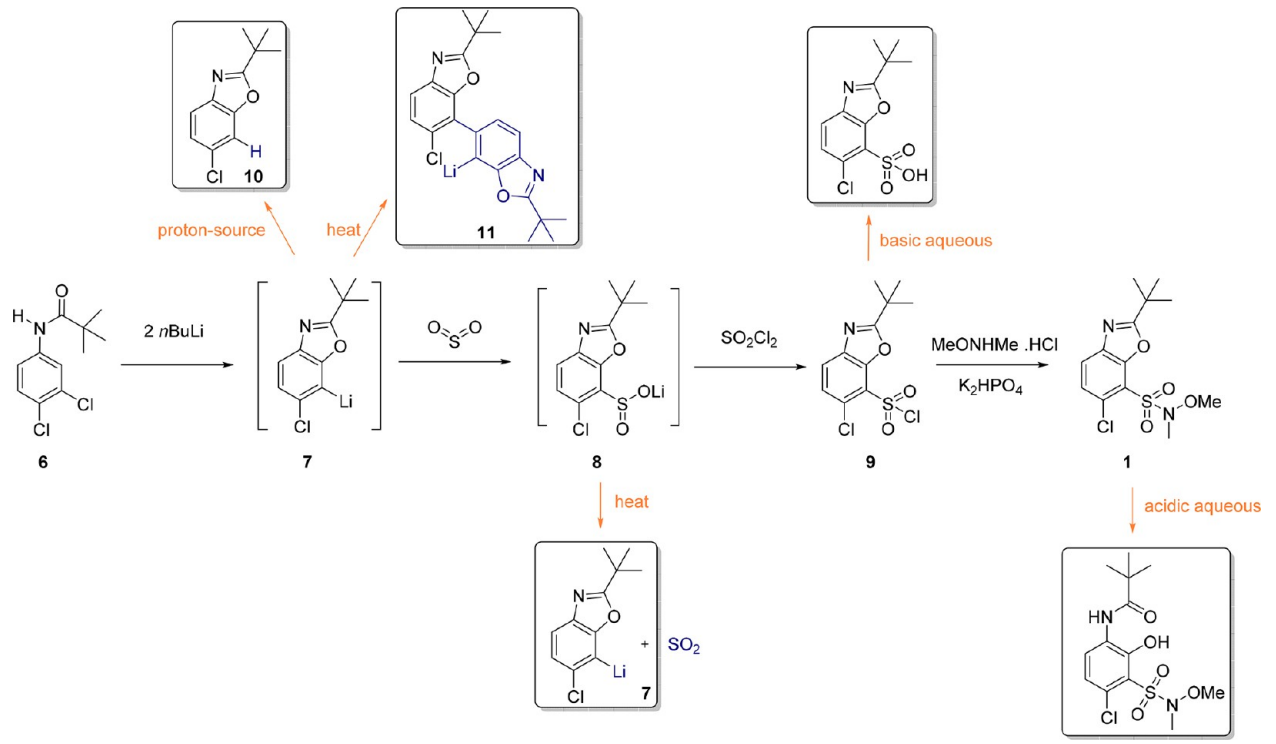

Figure 6. Summary of the elucidated byproduct pathways based on chemical stability studies which relied on NMR, FT-IR, and HPLC data.

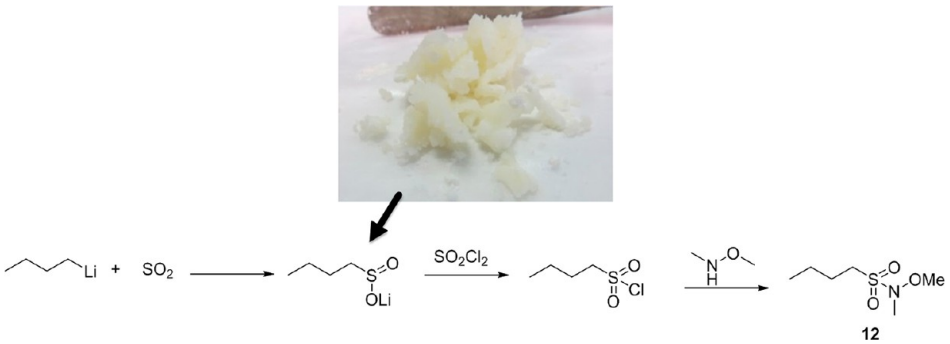

Figure 7. Identification of compound **12** in crude compound **1**, which derives from the lithium salt of *n*-butyl sulfinate, found to be a waxy solid (pictured).

them.[20] Over 24 h no accumulation of solids at the bottom of the vessels or at the overflow junction was observed.

A clue in determining the complete source of unwanted solids was the observation of the alkyl sulfonamide **12** in the ^{1}H NMR of the crude benzoxazole **1**, which was presumed to derive from the combination of residual *n*-butyl lithium and sulfur dioxide, Figure 7. The lithium salt of *n*-butyl sulfinate was synthesized and isolated and found to be a waxy solid, capable of sticking to glass surfaces. A useful observation was that it could be washed off with fresh tetrahydrofuran. In summary we would therefore have to design a continuous reactor capable of handling a solid lithium salt, and we would have to introduce intermittent cleaning with tetrahydrofuran for the 15 kg clinical supply campaign.

Reactor Selection and Design. The process development had revealed that selection of a suitable reactor would have to be made taking into account multiple requirements: heat management; avoiding local concentration zone effects; avoidance of holding times; and resistance to plugging. Three types of reactors were made on the basis of comparison: a large semibatch reactor; a tubular reactor (i.e., a pipe); and a cascade of continually stirred tank reactors (cascade of CSTRs, i.e. a series of stirred batch reactors with overflow junctions), Table 3.

Based on these summaries we made the following selection: for the first two chemical steps in the sequence to the sulfinate **8**, where exothermy, local-zone effects, holding time, and plugging were all found to be critical parameters, we selected an approach using a cascade of CSTRs.[21] Not only do cascades resist plugging if correctly proportioned,[22] but multipoint addition of reagent enables the heat of reaction to be spread across more than one vessel. Mixing efficiency at each addition point would require study, but the NMR experiments suggested that it needed to be on the order of seconds but not instantaneous. Equally, residence time distribution would also require characterization, but our expectation was that a cascade of CSTRs could be designed to operate on the order of minutes rather than hours and would therefore be sufficient to avoid the byproducts resulting from extended holding of aryl lithium **7**. We selected a batch reactor for the third and final chemical step

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Table 3. Comparison of Three Ideal Reactors for Synthesis of Benzoxazole 1

	Semi-Batch Reactor (≈ 1000 L)	Tubular Reactor (≈ 20 L)	Cascade of CSTRs (≈ 20 L)
Heat-management	Poor heat removal per unit of volume imposes long dosing times	Excellent heat transfer per unit of volume allows for a fast reaction. Initial hot spot of a few seconds at the addition point	Good heat transfer per unit of volume allows for a fast reaction. Hot-spot formation can be reduced by addition at multiple points
Local-zone effects	High, due to low mixing efficiency	No local zone if the mixing zone is well designed	Effect much less pronounced than in the semi-batch reactor due to the reduction in dimensions
Avoidance of holding times	Impossible since slow dosing is required to mitigate exothermicity	Residence times in the order of seconds or below are accessible if necessary	Residence times in the order of 10 s or higher are accessible
Resistance to plugging	Not plugging	Sensitive to plugging	Higher robustness to plugging than a tubular reactor
Conclusions	Suitable for later steps in the sequence that are less exothermic and generate more stable compounds	Despite a potential for excellent heat-transfer, a tubular reactor is unsuitable due to plugging risk	Suitable for early steps that are exothermic and concentration-zone sensitive. Material of construction important for heat-removal. Plugging avoidance requires study

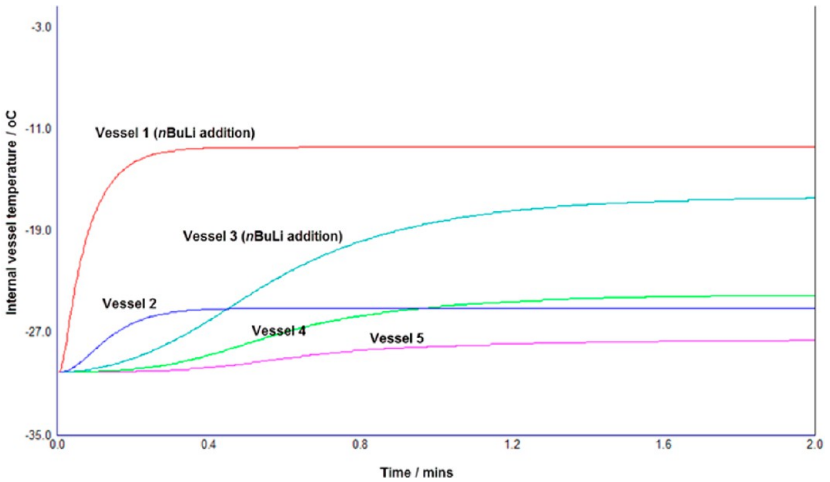

Figure 8. Heat profiles for the start-up phase of each vessel of the first CSTR planned to handle the *n*-butyl lithium step.

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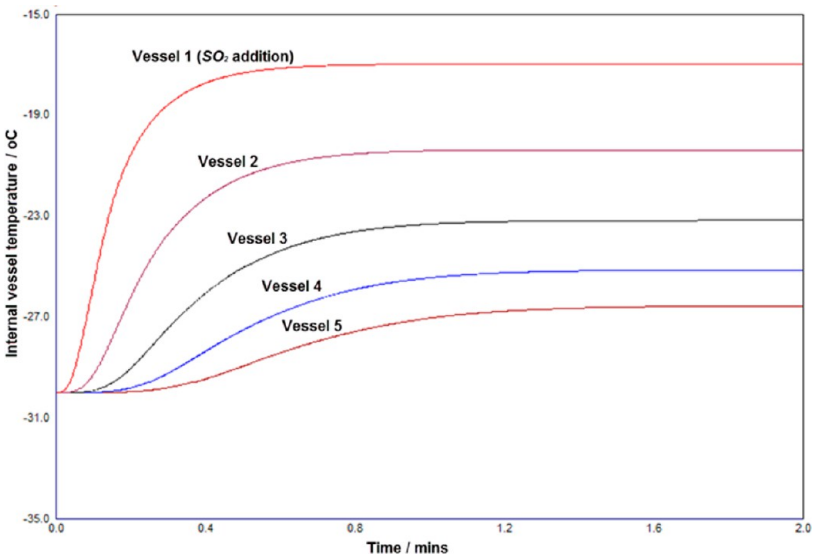

Figure 9. Heat profiles for the start-up phase of each vessel of the second CSTR planned to handle the sulfur dioxide addition step.

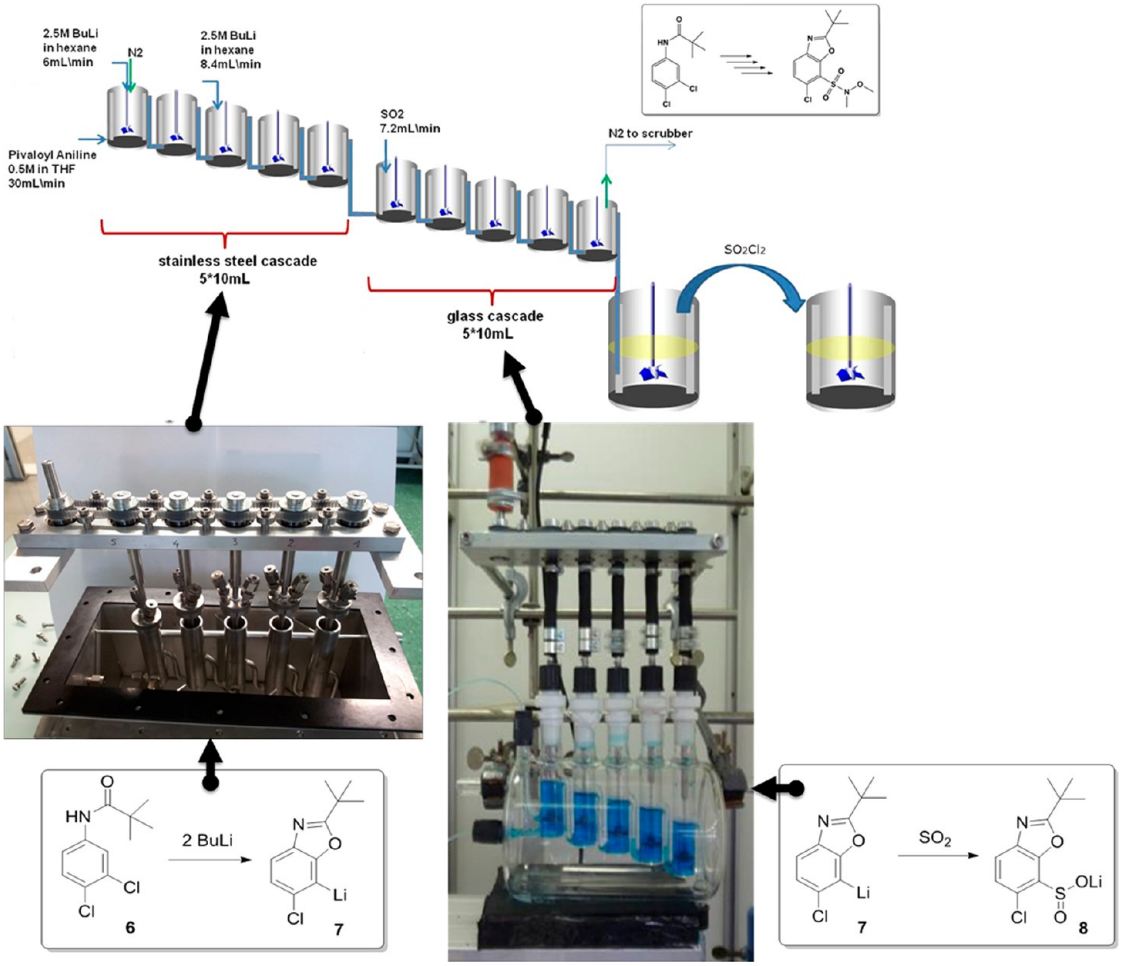

Figure 10. Overall setup of the sequence from compound **6** to benzoxazole **1** is shown as a schematic. Pictured are the prototype cascades of CSTRs constructed for the *n*-butyl lithium step (left, in stainless steel, opened) and the sulfur dioxide addition step (right, in glass, closed and filled with colored solution).

to benzoxazole **1** where all these factors were no longer critical. The junction between the two equipment types would be semibatch with a strategy required to manage the transition between nonstop flow and sequential batch operations.

With a cascade of CSTRs the choice of number of connected vessels is a balance between simplicity (less vessels) and narrower residence-time distribution (more vessels). If residence-time distribution is too broad, the selectivity of the

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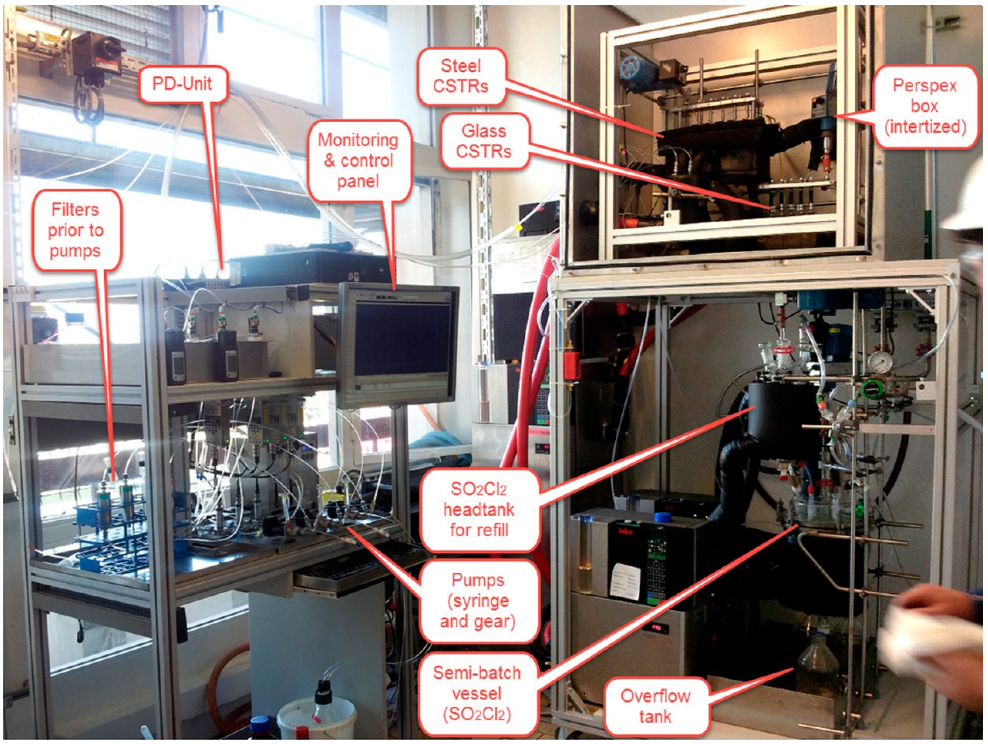

Figure 11. Mini-plant setup for continuous processing of starting material **6** to sulfonyl chloride **9**. The PD-unit is on the left-hand side and on the upper right the two cascades of CSTRs with semibatch quench vessel on the lower right mounted on the mobile skid.

reaction can suffer by virtue of back-mixing. Using the kinetic model, so far used to predict byproduct levels, we could also simulate a variety of vessel numbers for the *n*-butyl lithium step. In addition the material of construction was varied *in silico*, and the heat profile in each of the five vessels of the cascade was predicted. Our aim was to have the cooling medium set to −30 °C[23] and ensure that the internal temperature in the vessels never exceeded −10 °C, a value chosen to avoid formation of the dimeric compound **11** discovered in our search for temperature-sensitive byproducts (*vide supra*). Based on running a variety of setups we selected a five vessel cascade constructed of stainless steel and opted for a two-point dosing of *n*-butyl lithium into vessel 1 and vessel 3 (1.1 equiv then 1.3 equiv) in order to limit the maximal hot spot temperature. Mixing time was calculated to be complete within approximately 4 s, and the required residence time in the entire cascade of CSTRs was calculated to be 1.4 min (see the Supporting Information). The outcome of the simulation for the start-up in this first step in the theoretical five-vessel CSTR is shown in Figure 8, with vessels 1 and 3 evidently stabilizing as warmest due to the dosing of *n*-butyl lithium.

For the second chemical step we preferred a single dosing of sulfur dioxide and would not be able to use stainless steel due to the high acidity of the reaction medium due to the nature of sulfur dioxide. However, borosilicate glass was considered ideal as reactor material since we needed to be able to visualize the reactor contents to determine what degree of accumulation of solids was taking place. Again a five-vessel CSTR was selected, and heat profiles based on simulation are shown in Figure 9. The maximal steady-state vessel temperatures were considered suitable for this reaction step based on the knowledge gained from the studies into byproduct pathways deriving from compounds **7** and **8**. The required residence time was calculated to be 1.1 min.

A specific design for each CSTR vessel was further refined based on feedback from the simulation software, allowing vessel dimensions, impeller size, and stirring rate to be selected to match our requirements. An on-site workshop then built the prototypes pictured in Figure 10. Of particular mention is the overhead stirring system that operated by cam-belt.

Since the lithium sulfinate **8** and sulfonyl chloride **9** were found to be sufficiently stable,[24] the decision was taken that the outlet of the second cascade would mark the boundary between batch and flow. While sulfonyl chloride was found to be chemically stable in hexane over multiple days at room temperature, a phase separation was observed after only a few hours. This meant that the solution would have to be freshly prepared at regular intervals, and so the receiver vessel postioned downstream of the cascades was sized so that it would need refilling approximately once per hour.[25]

Finally sulfonyl chloride **9** would be converted to target benzoxazole **1** by reactive extraction with the hydrochloride salt of Weinreb's amine and dipotassium hydrogen phosphate as outlined above. For the clinical supply campaign these operations would take place in the existing batch pilot-plant equipment with a 12 h periodicity, meaning that sulfonyl chloride **9** would be accumulated every hour into a batch reactor for half a day prior to conversion to crude compound **1** in one lot. Equally, crystallization of compound **1** from isoproylacetate and heptane would be made on accumulated batches of crude compound **1** in order to limit the number of manufacturing operations requiring pilot-plant personnel.

Pilotation of the Second-Generation Process: Combining Flow and Batch. The process-development unit (PD-unit) was tasked with pumping and process control, while adjacent mobile skids were installed for housing the two cascades of CSTRs and the semibatch quench vessel, Figure 11. Overflow tanks were installed, connected to the highest point

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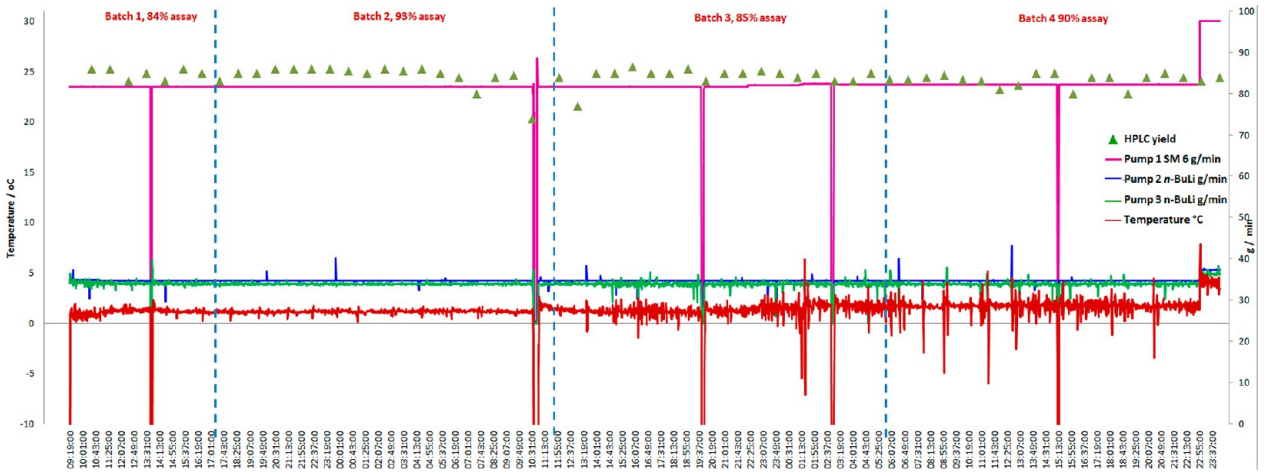

Figure 12. 72 h Continuous manufacturing campaign, profiling HPLC assay yield of compound **9** (green triangles), pump flow rates (purple, blue, and green traces; see legend for details), and temperature in the semibatch reactor (red trace). The chart is divided into the four batches, with assay yield of compound **9** given according to HPLC.

Table 4. Mass-Flow and Quality Attributes for the 72 h Continuous-Enabled Campaign to Benzoxazole 1

batch no.	kg of **6** (100%), pumped as 13 mol % THF solution	*in situ* yield of **9** (%)	purity of **9** (A%)	*in situ* yield of crude **1** (%)	kg of **1** by HPLC assay (mol %)	kg of isolated **1**	Overall yield to **1**	Purity of **1** (A%)
1	3.32	84.0	92.8	67.7	3.04	5.64	62.8	99.6
2	3.32	93.0	91.8	80.6	3.62			
3	3.32	85.0	91.7	79.0	3.55	6.02	67.0	99.8
4	3.32	90.0	89.0	85.3	3.83			

of each CSTR in the event of clogging, and a perspex box was placed over the two CSTRs in order to safely inertize this area to limit ice formation on the outer reactor walls.

Common to our ED- and PD-units, process monitoring and control would be mediated by HITEC ZANG software, with safety ranges on pressure, temperature, and flow rate preprogrammed to trigger an automated pump stop. Residence times in the first and second CSTRs were set to 1.4 and 1.1 min respectively, and so with a volume of 50 mL each (5 × 10 mL vessels) the flow rate for the 0.5 M starting material solution **6** was set to 25 mL/min. The flow rates for the other feeds were assigned accordingly, and a familiarization campaign was initiated. Four 12 h runs were completed, with interruptions of the pumps required due to two principle issues, both occurring on the *n*-butyl lithium line: irregular flow due to degassing of the dissolved nitrogen and butane, and inaccurate flow rate of *n*-butyl lithium due to suboptimal performance of the magnetic gear pump. Satisfied to have identified these technical issues prior to the manufacturing campaign, we nonetheless proceeded to crystallize the processed crude benzoxazole **1** in three batches and were able to deliver a total 4.9 kg of **1** in excellent purity above 99.5 A%. The overall yield was 65%, notably higher than the benchmark of 34% for the optimized batch process, and there was clearly space for technical improvement. An in-line degasser was installed prior to the pumps, which were themselves replaced with better suited microannular gear pumps. Now with the pilot-plant operators experienced in this novel sequence of flow and batch operations, and the change in equipment, the full manufacturing campaign was initiated. The campaign ran continuously for 72 h, with the cycle time for batch conversion of sulfonyl chloride **9** to crude **1** set to once every 18 h. The pressure, temperature, and HPLC profiles for the flow part to compound **9** can be seen in Figure 12.

With the more optimal setup the campaign proceeded smoothly. As can be seen from the pressure profile for pump 1 (starting material, purple line), five cleaning periods were manually triggered based on a visual control of the buildup of solids on the inner surface of the glass CSTR (switch to solvent visible as sudden pressure drops, as well as temperature drops (red line) due to a drop in exothermy). When at steady state the quality of compound **9** was evenly high, averaging at 88% assay yield, and although the four reactive extractions in batch delivered yields of crude **1** with some degree of variability (68−85%), the outcome was well within the predefined quality and quantity limits, Table 4. The four batches of crude **1** were combined into two crystallization batches delivering 5.6 and 6.0 kg of benzoxazole **1** in high purity (99.6 and 99.8 A% respectively). The material prepared according to this process met all testing requirements and was released ready for use in clinical manufacturing.[26]

In summary the campaigns delivered a total of 17 kg of isolated compound **1**, with the second campaign (72 h) achieving an overall 65% yield. According to raw material calculations, the near doubling in yield to benzoxazole **1** had a predictably major effect on the total product cost of the manufacturing of the CXCR2 receptor antagonist drug candidate, with conservative calculations delivering a 35% reduction in costs. More than this, a robust supply of the building block had been ensured for future manufacturing supplies.[27]

CONCLUSIONS

In conclusion a demonstration of the potential of continuous manufacturing had been established on the lab scale for the entire sequence from anilide **6** to benzoxazole **1**. This effort highlighted the need for a better ability to handle solid formation, and so a PAT- and calorimetry-supported process

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development was conducted which revealed the quality critical attributes for each step in the sequence. The rational allocation of batch, semibatch, and flow reactors then followed, making use of kinetic modeling and simulation tools not only to predict optimal operating conditions for the chemistry but also for the design of the flow reactors for the low-temperature steps. The driver for flow was a combination of the need for maintaining low temperature despite high exothermy, with a strictly minimal dosing and holding time to avoid byproduct formation. Cascades of CSTRs were selected with different materials of construction and, despite the need to process solid lithium salts, served their purpose well in the ensuing campaign in the bespoke mini-plant which delivered 17 kg of benzoxazole **1** with superior yield and high quality.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00254.

General description of techniques; experimental procedures, calorimetry data and kinetic model (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Differential scanning calorimetry (gold capsule, sample under argon) of the Weinreb amine as a hydrochloride salt identified a large energy release (−1695 J/g) from 150 °C, which is brought forward to 110 °C in the presence of rust. The amine is considered more hazardous as the free base, since the boiling point is only 43 °C and it decomposes rapidly.

(13) Triethylamine, Hunigs base, 2,6-lutidine, sodium hydroxide, sodium bicarbonate, tetrabutylammonium hydroxide, and magnesium oxide were screened. The impact of using tetrabutylammonium bromide as a phase-transfer catalyst was also explored.

(14) http://www.ltf-gmbh.com/produkte/microreactors.html, accessed 5th January 2016.

(15) Compound **6a** also contains an acidic proton, *ortho* to the pivalamide group on the aromatic ring. However the source of the proton was not identified within this study, and so for simplicity we only mention compound **6** as a source of protons from here onwards in the discussion.

(16) A proton-transfer mechanism was also observed during the organolithium step in: Thaisrivongs, D. A.; Naber, J. R.; McMullen, J. P. *Org. Process Res. Dev.* **2016**, *20*, 1997−2004.

(17) The mechanism of formation of dimeric byproduct **11** was not investigated, but the authors considered as possibilities either an aryne-mediated mechanism or the common Wurtz coupling which proceeds by nucleophilic aromatic substitution.

(18) Viscosity is expected to increase with decreasing temperature, which will have a negative effect on mixing efficiency. Fortunately THF is considered a low viscosity solvent (dynamic viscosity at 0 °C approximately 0.58 mPa.s, at −20 °C approximately 0.78 mPa.s), and so this effect was considered negligable.

(19) When the mixture was left to stir overnight at −30 °C, a brown suspension was observed the next morning, and on emptying the

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reactor, the residual solids were still visible on the glass walls. However this was thought to be due to decomposition rather than precipitation. Fresh tetrahydrofuran easily dissolving the solid.

(20) The following organometallic bases were screened in an attempt to completely avoid formation of a suspension; however, the original *n*-butyl lithium was retained (with *n*-hexyl lithium showing no difference in reactivity): iPrMgCl (no reaction); LiHMDS (no reaction); LDA (poor selectivity). In addition a screening of cosolvents was made, but to little effect.

(21) Rotor-stator spinning disk reactors were not available in our inventory, but have been evaluated elsewhere and would in principle be considered a suitable alternative: (a) Meeuwse, M.; van der Schaaf, J.; Schouten, J. C. *AIChE J.* **2012**, *58*, 247−255. (b) Oxley, P.; Brechtelsbauer, C.; Ricard, F.; Lewis, N.; Ramshaw, C. *Ind. Eng. Chem. Res.* **2000**, *39*, 2175−2182.

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(23) The temperature set point for the heat transfer fluid was determined to be −30 °C based on the optimal overall heat transfer coefficient (U-value), which was a balance of the specific heat capacity, conductivity, and viscocity of the selected thermofluid (SilOil M40 and Dowtherm) at various temperatures.

(24) Freshly prepared compound **9** solution was held over 3 days at room temperature under inert gas, and no decrease in quality by ^{1}H NMR was observed.

(25) The receiver vessel was fixed in the rack, and so diversion of the reaction mixture to a second receiver was not possible due to the required extra space. As such, during the short transition time between lots there would be no sulfuryl chloride at hand to react with compound **8** which would continue to feed into the unique vessel. Considering the stability of the lithium sulfinate **8** and the short cross-over time this was considered acceptable. During normal operation compound **8** would encouter varying equivalents of sulfuryl chloride in the receiver vessel, as it was filled with reaction mixture from the cascades. In a control experiment we combined freshly prepared compound **8** with various equivalents of sulfuryl chloride solution at 0 °C (8, 16, 24 equiv, neat; set point in batch was 1.6 equiv) and gratifyingly observed no adverse effect on quality of compound **9** by sequential offline ^{1}H NMR experiments over a 24 h period.

(26) The ensuing campaign using benzoxazole **1** was to be conducted under GMP conditions; however, due to the steps being early in the synthesis scheme, the synthesis of **1** described in this article was under non-GMP conditions.

(27) For future supplies on a larger scale we explored approaches which would be free of solid formation within the flow equipment. The two options were to use a substoichiometric amount of *n*-butyl lithium to avoid formation of the waxy solid lithium *n*-butyl sulfinate or to run the sulfur dioxide quench in semibatch. Both approaches proved successful, albeit with a slight compromise in yield for the first option, but further development was in any case halted due to clinical termination of the drug candidate.

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