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Review

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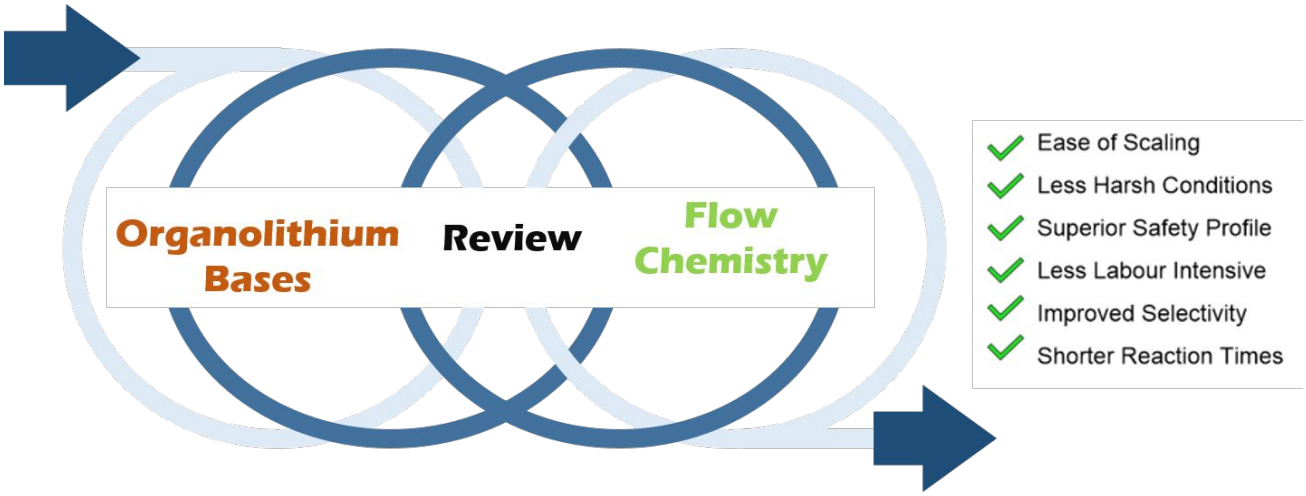
Organolithium Bases in Flow Chemistry: A Review

*Mark Power,[a,b] Emma Alcock[a,b] and Gerard P. McGlacken[a,b,c]**



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Abstract

Flow chemistry is a continually emerging and ever-growing area of synthetic organic chemistry. It provides an orthogonal approach to traditional batch chemistry, oftentimes allowing for more efficient routes to desired target molecules. It is generally accepted that flow chemistry offers a valuable change to the process landscape. From a process perspective, there are many advantages associated with flow chemistry over traditional batch chemistry, the most prominent of which is an increased safety profile with the use of highly reactive chemical species, such as organolithiums. These reagents are highly valuable species for the efficient synthesis of pharmaceutical intermediates. Disadvantageously, use of these reagents on commercial scale is severely hindered by the highly energetic nature of the reaction intermediates and their concomitant safety risk. Flow chemistry provides a viable platform for use of these reagents, offering a high degree of control over reaction parameters. In this review, we present a comprehensive account of the published literature implementing the use of organolithium reagents as strong bases for deprotonation reactions in a flow system.

Key Words: flow chemistry, organolithium, base, deprotonation

Introduction

Recent and rapid development of flow chemistry has, in many cases, led to an orthogonal approach to traditional batch chemistry. The translation of a synthetic protocol from batch to continuous flow, along with the development of new continuous flow chemistry, can have a plethora of benefits, including the development of new reactivity patterns, improved

reaction efficiency and enhanced scalability.[1,2,3] However, a cornerstone of flow chemistry is its enhanced safety profile. This facet of flow chemistry allows highly reactive reagents to be applied to large scale reactions, which would not be feasible using flask chemistry. A review by Stevens and co-workers,[4] illustrates how many hazardous reagents such as diazo, diazonium, azide and organometallic species are successfully and safely utilized in continuous processing.

Organometallic species such as organolithium and Grignard reagents are principal species in many organic transformations, but their scale-up is often hindered by their highly reactive nature. Flow chemistry has enabled a safer regime for the employment of organometallics and reviews by Nagaki,[5] Luisi[6] and Piccardi[7] have showcased many examples of organometallic chemistry transferred from a flask operation to a flow platform.

Organolithium reagents are among the most reactive and arguably important species, and their use is widespread across numerous synthetic transformations. The polar C-Li bond allows the reagent to act as a strong base or nucleophile in the formation of new C-C bonds. However, despite the undoubted usefulness of organolithium species in organic synthesis, their safety profile often hinders their scalability. The heat dissipation required when using these reagents is difficult to achieve, and so their use on an industrial scale has proven an onerous task. Additionally, large scale use of organolithium reagents results in the formation of precipitates, presenting the additional challenge of solubility. A continuous flow chemistry platform provides a viable alternative to traditional batch chemistry when considering these reactions. The high surface-to-volume ratio available in microreactors offers a means to circumvent a number of problems, due to much improved methods of heat dissipation and in turn, temperature control and energy transfer. Indeed, in certain applications, even higher reaction temperatures may be tolerated in flow.

Consequently, the use of organolithium reagents in continuous flow systems is a very topical area of research. Organolithiums can be used to facilitate lithium-halogen exchange reactions or used as strong bases in the construction of new molecular entities. The excellent reviews by Nagaki,[5] Luisi[6] and Piccardi[7] predominantly examine organolithium-mediated lithium-halogen exchange reactions.

This review aims to outline developments concerning the use of organolithium bases in a continuous process. To date, the concept of performing a deprotonation step *via* an organolithium species in flow chemistry has not been covered in a comprehensive review. Herein, we evaluate the existing literature involving organolithium species being employed as strong bases in continuous processes. One of our aims is to describe the rationale and infrastructure behind translating a process from batch to continuous flow, as well as detailing scalability.

This review will categorise the available literature by the organolithium base selected for the scheme, namely; *n*-butyllithium (*n*BuLi), lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS), *n*-hexyllithium (*n*HexLi), *sec*-butyllithium (*s*BuLi) and phenyllithium (PhLi). It is worth noting the use of *t*-butyllithium (*t*BuLi) in continuous flow

chemistry remains absent in the available literature. The structures of these organolithium bases are shown below with their respective pKa values(Figure 1).[8,9]

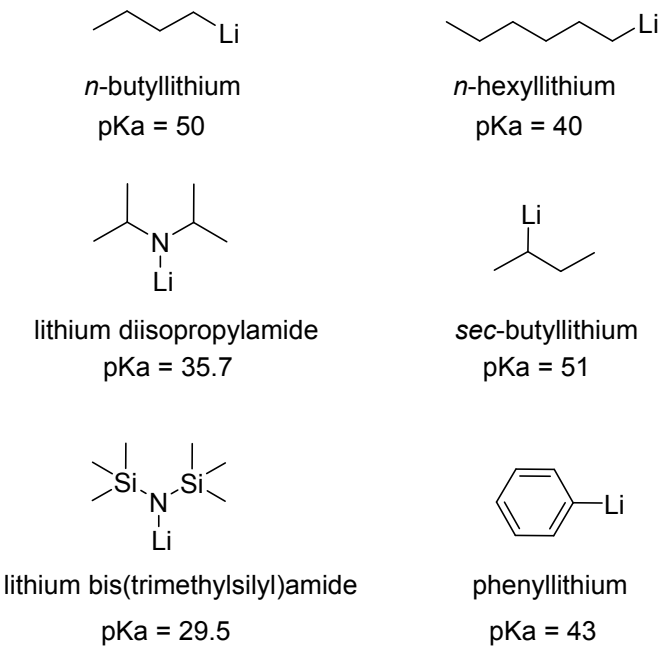

Figure 1 Chemical structures of organolithium bases

Figure 2 depicts the symbols used throughout to illustrate the variety of flow chemistry components discussed in this review.

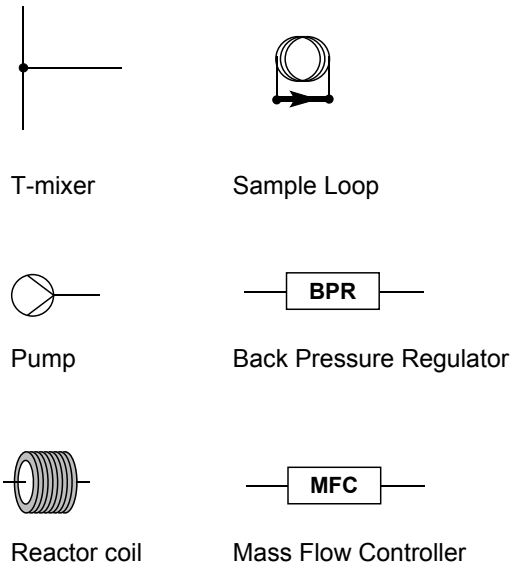

Figure 2 Overview of continuous flow symbols

n-Butyllithium (*n*BuLi)

n-Butyllithium is one of the most commonly employed organolithium reagents in organic synthesis.[10] A publication by Ley and co-workers outlines the use of *n*BuLi in the construction of disubstituted alkynes.[11] The authors designed a low temperature continuous

flow platform where *n*BuLi and a variety of monosubstituted aryl-alkynes were used to generate a series of disubstituted alkynes. The design of the system involves a series of five reactor coils, arranged to mimic the batch reaction. In batch, this reaction has inherent reactivity issues, resulting in the need for precise temperature control. The intermediate *ortho*-fluorinated arly lithium species has the tendency to undergo *ortho*-elimination if the temperature is not accurately controlled. This *ortho*-elimination pathway produces an unstable benzyne intermediate, which, coupled with the exothermic nature of this decomposition, presents a potential saftey risk upon scale-up. A flow chemistry system allows for precise reaction and temperature control, consequently removing the undesired *ortho*-elimination pathway and the concurrent safety risk.

This continuous process used three loading loops to supply the five-coil platform with their respective reagents. The alkyne moiety and the organolithium base were both pumped through pre-cooling units before coming together in the first reactor (RX 1) to generate the carbanion intermediate. This intermediate then progressed to meet a suitable electrophile, supplied to the system through a loading loop and a subsequent pre-cooling unit to react in reactor 2 (RX 2). All reactors and pre-cooling units were maintained at -40 ˚C. The authors tested five combinations of substituted aromatic alkynes and electrophile substrates on this platform to successfully afford products of type **1** in yields of 86-90% (Figure 3). Optimisation of temperature and *n*BuLi equivalents allowed the substrate scope to be expanded to *N*-methylimidazole and an Evans oxazolidinone auxiliary in yields of 75% and 53% respectively. Substituted fluoroaromatic substrates were also tolerated when reacted with different electrophiles at -50 ˚C *via* flourine directed *ortho*-lithiation. The authors report 13 such examples of *ortho*-substituted aryl products **2** in yields of 62-92% (Figure 4). It is worth noting that the presence of a nitrile group on the fluoroaromatic system meant only the use of LDA yielded the desired product. It is thought that the steric bulk of LDA was necessary to prevent addition to the nitrile group. These substituted fluoroaromatic substrates were additionally reacted with CO_2 at -50 ˚C to produce carboxylic acids **3** in yields of 64-74% (Figure 5). The nitrile containing fluoroaromatic once again required LDA to yield the desired product.

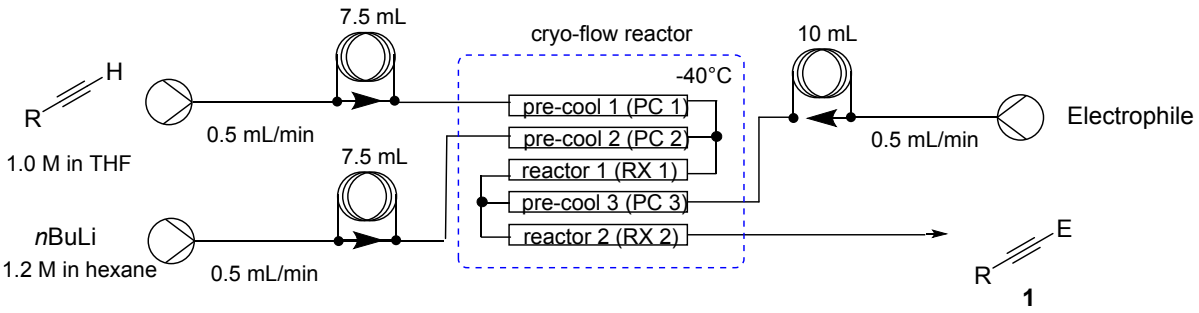

Figure 3 Initial Five-coil set-up for alkyne, *N*-methylimidazole and an Evans oxazolidinone auxiliary deprotonation and electrophile quench

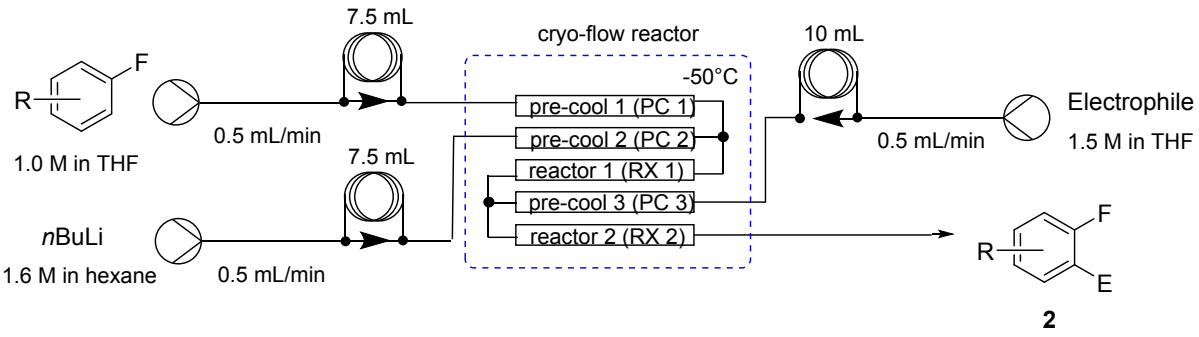

Figure 4 Five-coil set-up for the synthesis of aromatic building blocks using a fluorine directed *ortho*-lithiation approach

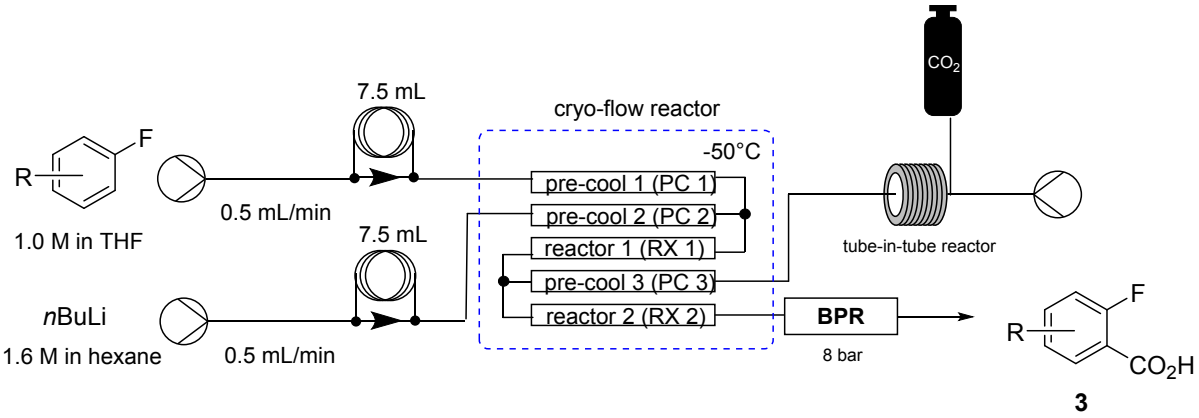

Figure 5 Five-coil set-up coupled with a tube-in-tube reactor to deliver CO_2 as the electrophile for the *ortho*-lithiated fluorine aromatics

In work by Yoshida[12], 'flash chemistry' is used to avoid the issues concerning competing β-elimination associated with the use of 2-halovinyllithium in batch mode, thereby allowing the creation of synthetically useful substituted alkenes by use of these unstable intermediates before they decompose. Initially, deprotonation of *trans*-1,2-dichloroethene by *n*BuLi yields 1,2-dichlorovinyllithium. In batch, this step requires cryogenic conditions, usually performed at -78 ˚C or below. At 0˚C in batch operation, with a slight excess of *n*BuLi and subsequent addition of benzaldehyde, no conversion to the desired product was attained. A flow scheme was designed to replicate these reaction conditions. The *trans*-1,2-dichloroethene and *n*BuLi were delivered to the system *via* syringe pumps and then brought together in a T-mixer to react for a short residence time. The resulting carbanion was then progressed to a second T-mixer where it was mixed with an electrophile stream to generate the desired product. It was noticed that an increase in residence time of the deprotonation step could favour the undesired β-elimination of the *trans*-1,2-dichlorovinyllithium. Additionally, in continuous flow, a much higher temperature of 0 ˚C gave optimal results. Lower temperatures resulted in a much reduced yield at a given residence time. Figure 6 illustrates a multi-step flow platform where subsequent deprotonation by *s*BuLi occurs after the electrophilic addition. A variety of electrophiles are used to quench this intermediate, resulting in the formation of disubstituted dichloroalkene products **4** in yields of 62-73% (Figure 6). It is worth nothing that in this scheme, a single deprotonation and substitution using only *n*BuLi and one electrophile was possible and the authors also synthesised these mono-substituted alkenes in yields of 85-93%.

The authors then turned their attention to synthesising disubstituted alkynes from *trans*-1,2-dichloroethene using a similar flow set-up. The key difference in this procedure was the residence time of the first deprotonation which was lengthened to 50.2 seconds to promote β-elimination, followed by a subsequent deprotonation by excess *n*BuLi. A quench with different electrophiles resulted in the formation of various disubstituted alkynes of type **5** in yields of 28-91% (Figure 7). The authors have established a correlation between residence time and the yield of either alkene or alkyne product, where the reaction conditions employed can be manipulated to generate either product in yields of up to 90%.

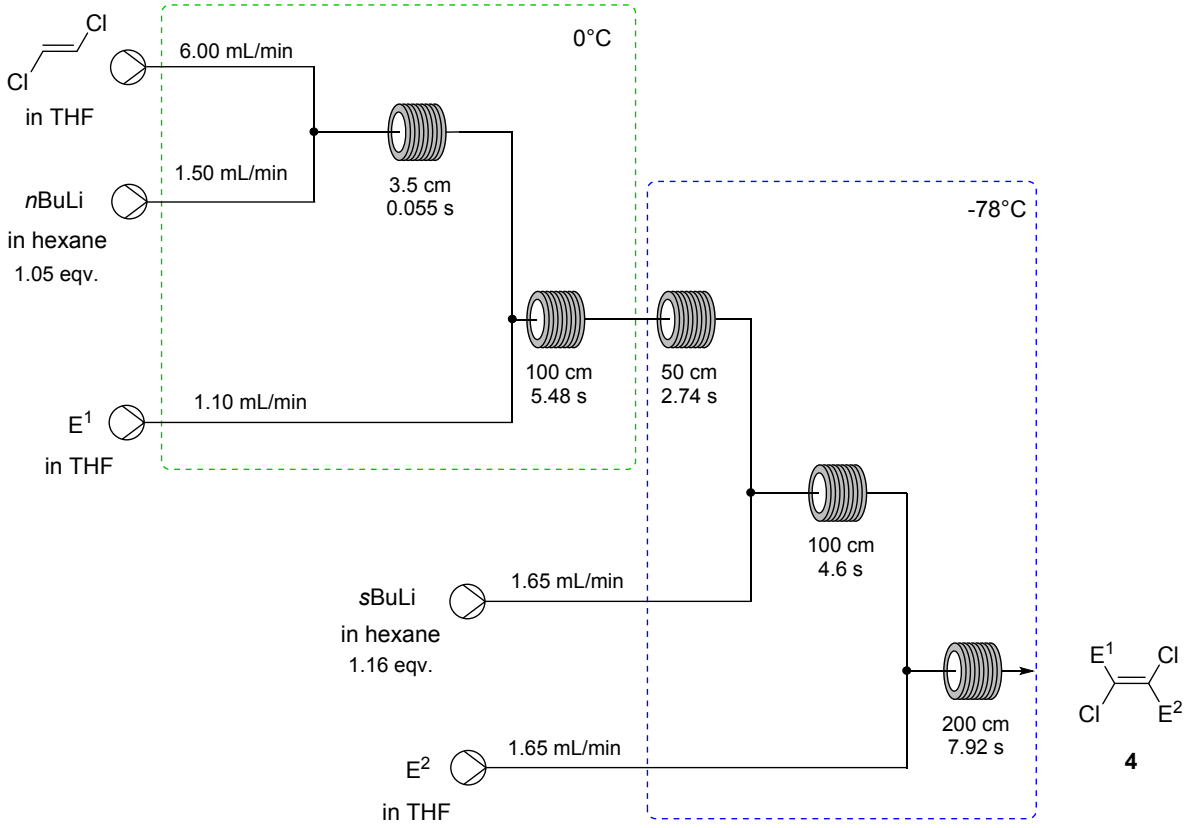

Figure 6 Flow platform for the synthesis of disubstituted dichloroalkenes

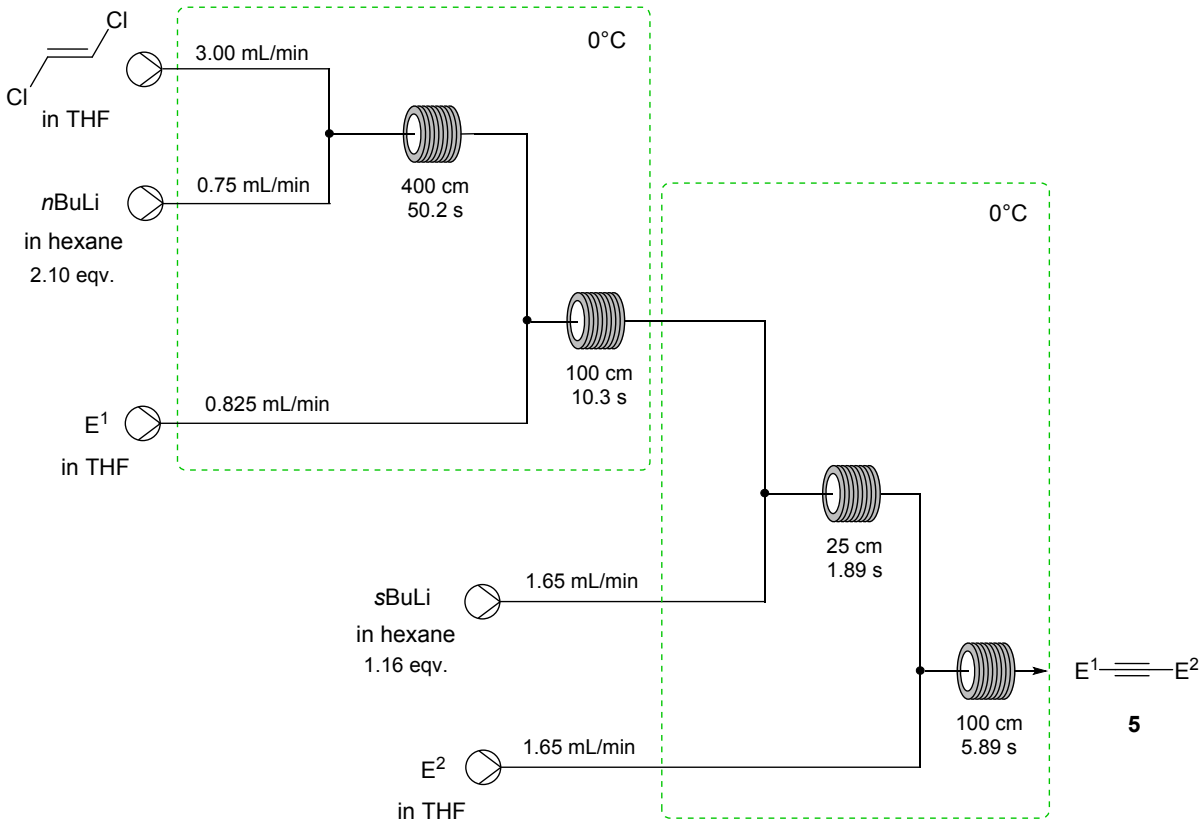

Figure 7 Flow platform for the synthesis of asymmetric disubstituted alkynes

In a publication by Watts and co-workers, the synthesis of Efavirenz, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI), is transferred from the common batch process to a continuous flow system.[13] The traditional batch synthesis commonly utilises *s*BuLi[14] or the significantly more hazardous *t*BuLi[15] to facilitate the deprotonation step. Using continuous flow chemistry, *n*BuLi can be used in place of these reagents offering a much more convenient synthetic route. A continuous process was designed whereby the substrate and organolithium base were reacted to form a lithiated intermediate, which advanced to meet the trifluoroacetylating agent, forming the product **6** in up to 70% yield after an anhydrous silica quench. As an added benefit, the batch process requires TMEDA as an additive while continuous flow circumvents this requirement, consequently simplifying the purification process. Optimisation of the reaction conditions resulted in the reaction being conducted at -40 ˚C, with a total residence time of 8.6 minutes using 2.5 equivalents of *n*BuLi and 2 equivalents of trifluoroacylating agent. The flow process is outlined with MX plates (used for their mixing structure) and VS plates (simply used to create the desired residence time) (Figure 8).

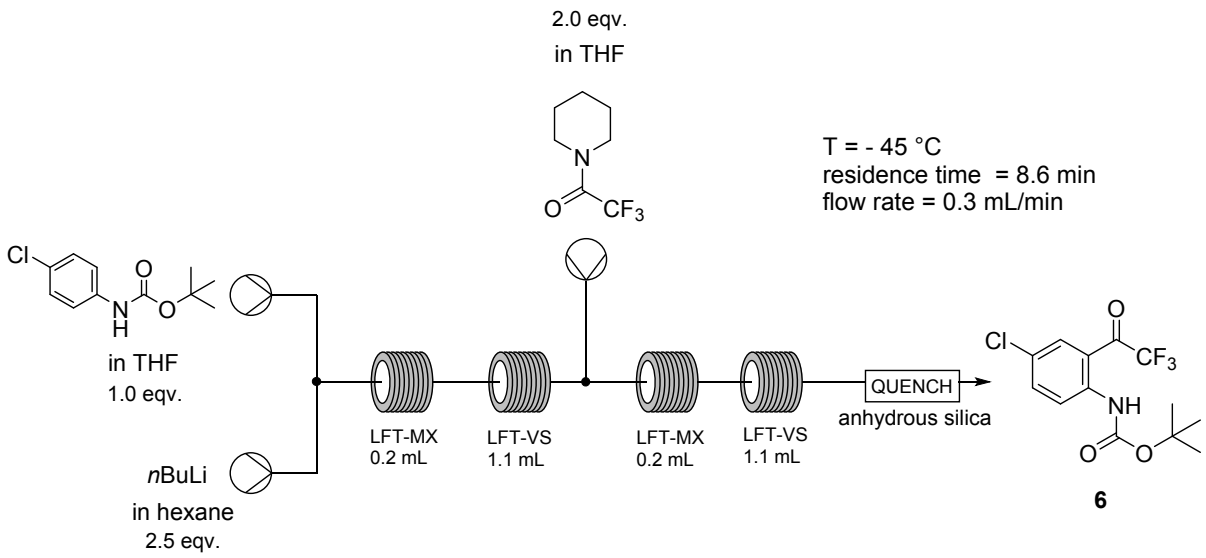

Figure 8 Flow system for the synthesis of a key intermediate in the production of Efavirenz

Similarly, work by Tagami and co-workers employs *n*BuLi in the synthesis of the API Eribulin Mesylate in a continuous flow system.[16] Eribulin Mesylate is a fully synthetic derivative of the structurally complex marine natural product halichondrin B, approved by the FDA in 2010 for the treatment of breast cancer.[17] In batch, the use of *n*BuLi requires cryogenic conditions to complete this step. However, using a continuous flow set-up devised by the authors, a more attainable temperature of -10 ˚C afforded better conversion to product. The continuous process concerned a solution of **7** being fed to the system by syringe pumps at 20 mL/min to meet a stream of *n*BuLi supplied by a syringe pump to facilitate deprotonation alpha to the sulfone. The lithiated species then advances to meet the aldehyde **8**, generating the desired product **9** in 95% yield (Figure 9). Advantageously, continuous operation of this process for 87 minutes led to the same conversion and product quality. Reactions performed at 10 ˚C initially increased yield to 96.5% but longer runs led to degradation of the desired product over time.

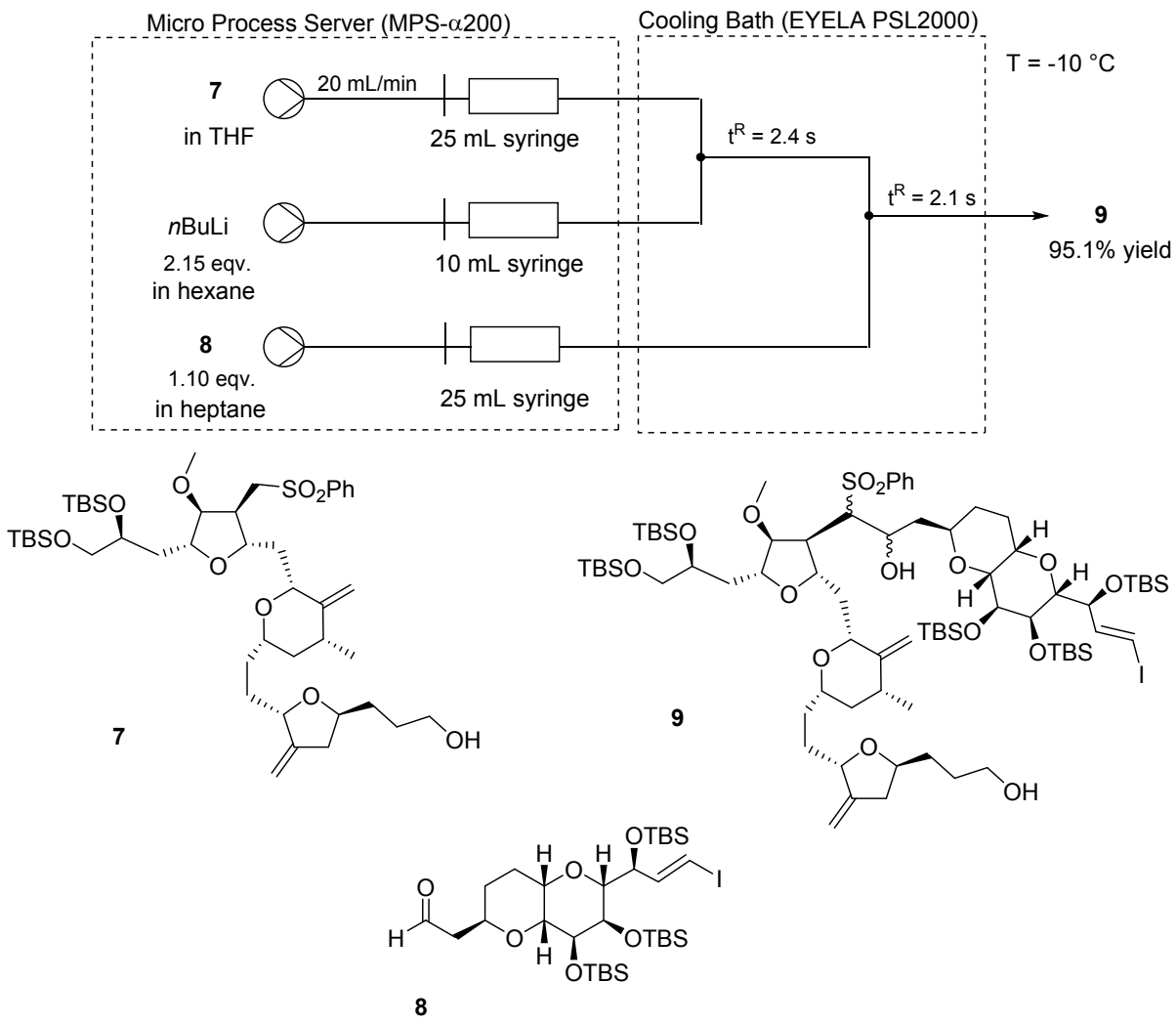

Figure 9 A continuous process to facilitate *n*BuLi mediated coupling in a key step during the synthesis of Eribulin Mesylate

In 2017, a paper by Hafner *et al*. describes a robust procedure for the generation and subsequent use of thermally unstable $CHCl_2Li$.[18] The use of $CHCl_2Li$ is widely reported in literature but the thermal instability of the species limits its application to industrial use. Additionally, when an organolithium base such as *n*BuLi is used to generate $CHCl_2Li$, cryogenic conditions of -78 ˚C to -100 ˚C are required to prevent the formation of a carbene species and consecutive degradation pathways. These temperature requirements add to the limitations of $CHCl_2Li$ use on an industry scale but, applicaion this reaction to a continuous flow scheme would obviate these limitations. These species serve as synthetically useful building blocks to many organic compounds. The authors devised a flow scheme where DCM and *n*BuLi are first supplied to the system by syringe pumps and reacted for a short residence time of 0.5 seconds to generate $CHCl_2Li$. This lithiated species is then exposed to an electophile for 0.5 seconds residence time. Initial optimisation found that a total of 1 second residence time, 1.3 equivalents of DCM, 1.2 equivalents of *n*BuLi and a combined flow rate of ~20 mL/min run at a temperature of -30 ˚C allowed the desired product to be successfully afforded in 96% yield when 3-methoxybenzaldehyde was used. Subsequently, a variety of carbonyl containing compounds were examined, including electron rich, electron poor and heterocylic electrophiles which afforded the corresponding carbinols with a

throughput of 4.25 mmol/min (~1 g/min) on a multigram scale. The authors also found that carbonyl compounds bearing pendant electrophilic functionalities such as bromine, fluorine and nitro groups were well tolerated. These electrophiles proved problematic in batch, displaying a tendency to undergo undesired side reactions or decompose in the presence of the organolithium. The flow protocol was used to generate nine dichlorocarbinols **10** in 82-99% yield (Figure 10). Additionally, $CHCl_2Li$-mediated chain homologation of phenyl boronic esters gave α-chloroboronic esters in yields of 70-89%.

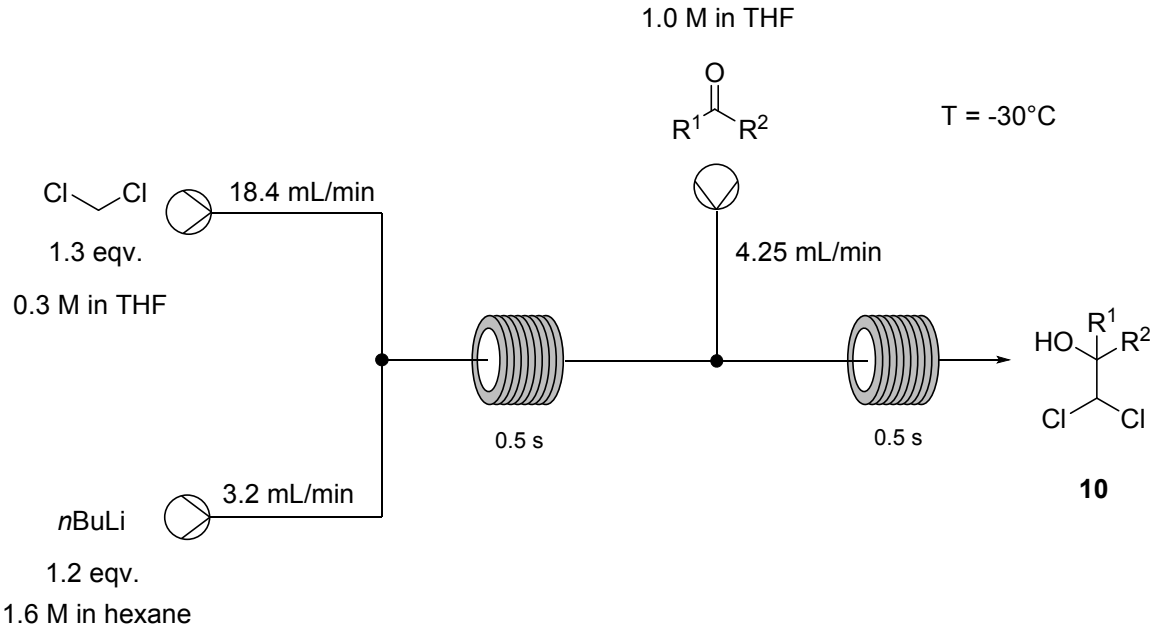

Figure 10 Continuous flow synthesis of dichlorocarbinols

Similarly, Schuster and co-workers report the optimisation of a continuous flow reaction set-up for the synthesis of a key intermediate **11** of the API Vaborbactam.[19] A review by Hughes also outlines a 2016 patent by Rempex for this synthesis.[20] Vaborbactam is a cyclic boronic acid β-lactamase inhibitor, commonly used to treat complicated bacterial urinary tract infections. The synthesis of a key intermediate in the process was translated to a flow platform due to batch operation requiring extremely low temperatures, in addition to reaction sensitivity to stoichiometry and mixing effects. An initial batch route involved a complex six-step synthesis, furnishing Vaborbactam in a yield of 30%.[21] The synthesis involves a Matteson homologation, which requires the anion $CHCl_2Li$. DCM is sufficiently deprotonated by *n*BuLi using THF as a co-solvent to prevent *n*BuLi precipitation at low temperature. The anion generated is fed into a subsequent reactor to meet the pinanediol boronate, where the Matteson homologation step occurs. Twelve GMP batches of this product were run affording an average 89% yield to produce 880 kg of product. In batch, this step required temperatures of -95 to -100 ˚C which yielded 75% of the desired compound in a diastereomeric ratio (d.r.) of 85:15. The employment of continuous flow technology allowed the temperature to be raised to more manageable -60 ˚C. Additonally, the reaction performance in flow resulted in a greatly increased d.r. of 95:5, and yield of 91%. Finally, the reproducibility of the synthesis in flow was far greater than the

correpsonding reaction in batch. The flow reaction was performed on a scale to produce 835 mg/min of intermediate **11** in the Vaborbactam synthesis (Figure 11).

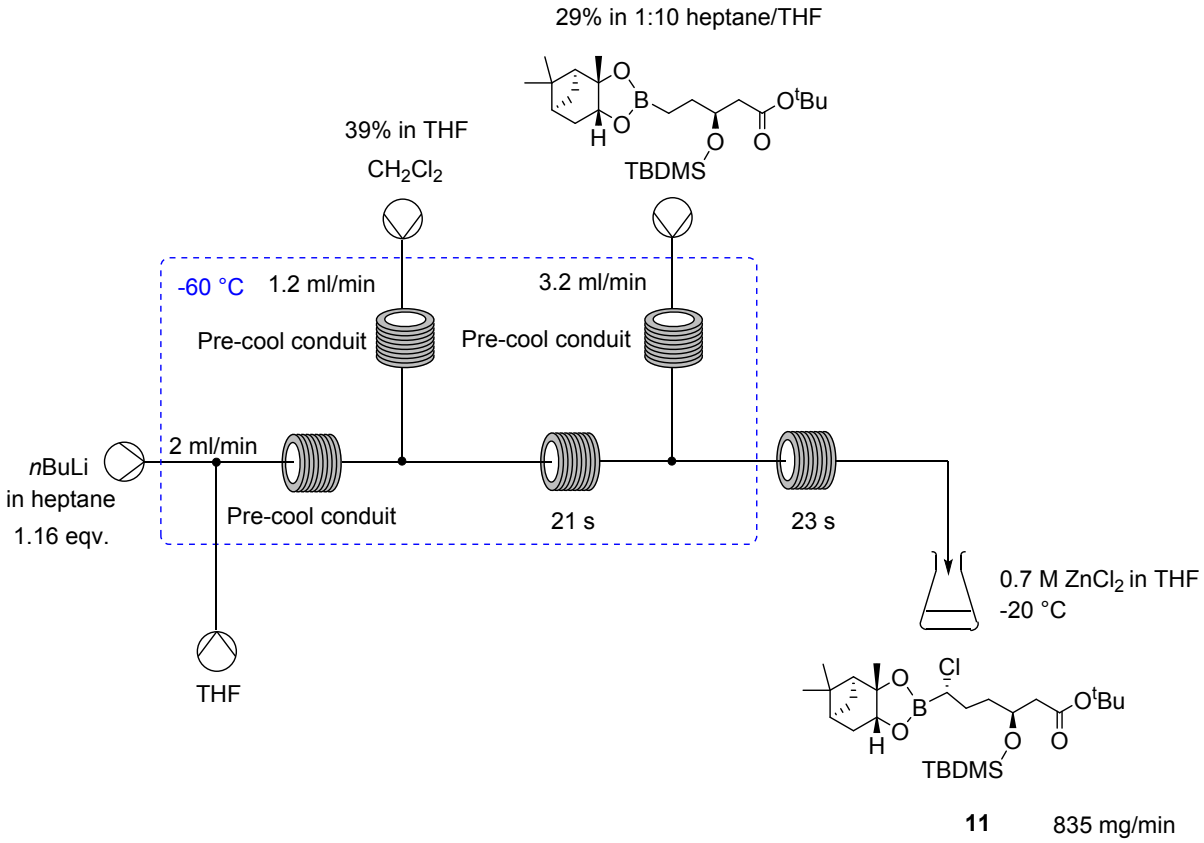

Figure 11 A continuous process for a fundamental Matteson homologation step in the synthesis of Vaborbactam

In the same review, Hughes describes the continuous flow synthesis of Lifitegrast, an API used to overcome dry eye.[20] In patents granted to SARcode, Lifitegrast is prepared *via* 3 fragments which are coupled through amide coupling steps.[22] Preparation of one fragment involves a low temperature carboxylation step. SARcode have recently filed a patent outlining the difficulties in batch scale-up, which resulted in lower yields and a tar-like material. To circumvent these issues, a continuous flow platform was designed for this particular step.[23] The starting material and TMEDA were introduced together at -78 ˚C where they then met a stream of 2.5 M *n*BuLi. The 2.5 M solution was preferentially chosen over the 1.5 M solution of *n*BuLi as it was found to have more consistent lot-to-lot quality. However, the commercially available 2.5 M *n*BuLi contained residues which had to be filtered out before use to avoid precipitates causing damage to the pumps. Filters were installed prior to the pumps to allow a steady flow of the feedstock base. Lowering the residence time to 3.6 minutes as well as increasing the starting material concentration to 10%, resulted in a higher conversion upon scale-up. Reaction with CO_2 in a subsequent reactor required a residence time of 1.6 minutes for complete conversion. The patent also noted that reaction of excess *n*BuLi with CO_2 generated valeric acid which proved to be problematic, as it froze in the lines. However, with optimal conditions, reproducible yields of 88-91% of product were achieved in several runs at 4-5 kg scale with a consistent product

purity of 97-98%. SARcode prepared a total of 22 kg of carboxylated product **12** (Figure 12). The flow process enabled higher yield, reproducibility and purity to be achieved on scale.

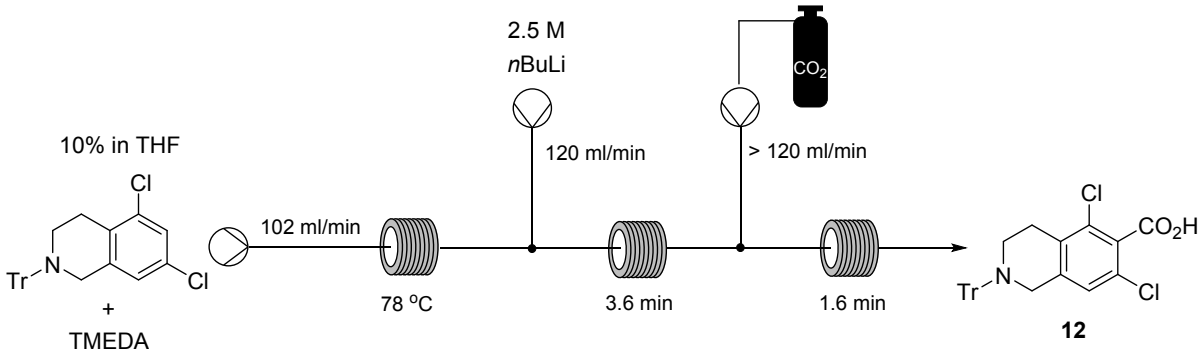

Figure 12 Continuous flow carboxylation to yield a central fragment in the synthesis of Lifitegrast

A publication by Stevens and co-workers addresses the thermal instability and safety concerns associated with the use of methoxy allene, or more specifically, the lithiated species.[24] Use of this lithiated species often provides the most efficient route to targets such as APIs, but these routes are often excluded due to lack of scale-up potential. Stevens envisioned that the precise control over reaction parameters and the exquisite heat transfer properties of a flow system would allow a successful translation of the unsafe batch synthesis to a continuous flow platform. Through many rounds of process optimisation, a three-step telescoped process was devised. Methyl propargyl ether was pumped by high-performance reciprocating pumps (syringe pumps) to meet a stream of KO^{t}Bu in dry THF, fed to the system through a sample loop, to generate the methoxy allene species with excellent conversion. Subsequently, the methoxy allene species generated is lithiated by a stream of *n*BuLi pumped to the reactor by two parallel syringe pumps. Syringe pumps, alongside sample loops, are often the chosen injection method of organolithium reagents for safety and chemical resistance reasons. As seen with many organolithium deprotonations in flow systems, efficient mixing is the cornerstone to successful conversions. The authors found that a regular T-connector and helical static mixing elements, inserted in a tubular reactor, afforded the optimal results, leading to conversions of up to 97%. The lithiated methoxy allene progressed to meet a stream of benzophenone which furnished the desired product **13** in a yield of 94% with a throughput of 28.5 g/h (Figure 13).

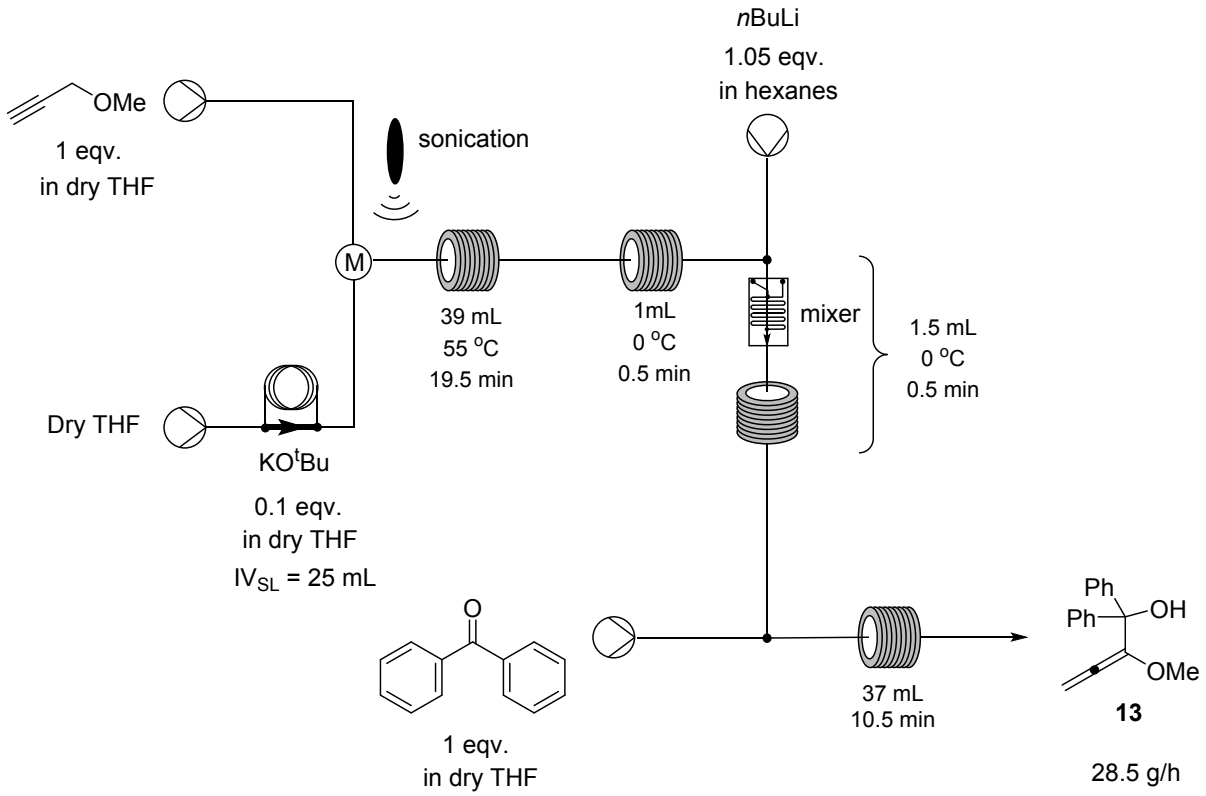

Figure 13 Continuous processing of the generation of lithiated methoxy allene and nucleophilic addition to benzophenone

Lithium Diisopropylamide (LDA)

LDA is a strong, non-nucleophilic base generated from diisopropylamine and *n*BuLi. Common to most organometallics, the use of LDA often requires cryogenic and carefully controlled reaction conditions.[10] Flow chemistry helps to alleviate issues associated with the use of LDA.

In a publication by Barker and co-workers, both the batch and corresponding flow lithiation reactions of 1,3,4-oxadiazoles are reported.[25] These 1,3,4-oxadiazoles are common motifs in bioactive compounds, such as, Raltegravir and Zibotentan. Prior to this paper it was reported that α-lithiation of 1,3,4-oxadiazoles resulted in ring fragmentation.[26] However, the authors in this case reported the α-lithiation of 1,3,4-oxadiazoles in batch mode with yields of up to 91%. Since the batch reaction required a temperature of -30 ˚C, the authors sought to develop a flow set-up to achieve less harsh reaction conditions. The reaction was performed initially on a small-scale flow system where the 1,3,4-oxadiazole and LDA solutions were transferred using peristaltic pumps to meet in a reactor coil, producing the lithiated species, which was subsequently quenched in a second reactor coil by a variety of electrophiles, also supplied *via* peristaltic pumps. In continuous flow, optimal conditions of 2.8 seconds residence time achieved complete consumption of starting material and a yield of 86%. Most importantly, the continuous process was successfully performed at a much higher temperature of 0 ˚C. This temperature proved unsuccessful in batch due to decomposition of the lithiated species. Various electrophiles were well tolerated, yielding

highly functionalised oxadiazoles **14** in yields up to 86% (Figure 14). These results were then applied to the synthesis of a key synthetic precursor of a cathepsin K inhibitor. An in-flow lithiation-substitution of the substrate 2-methyl-5-phenyl-1,3,4-oxadiazole with pivaldehyde was achieved in 95% yield.

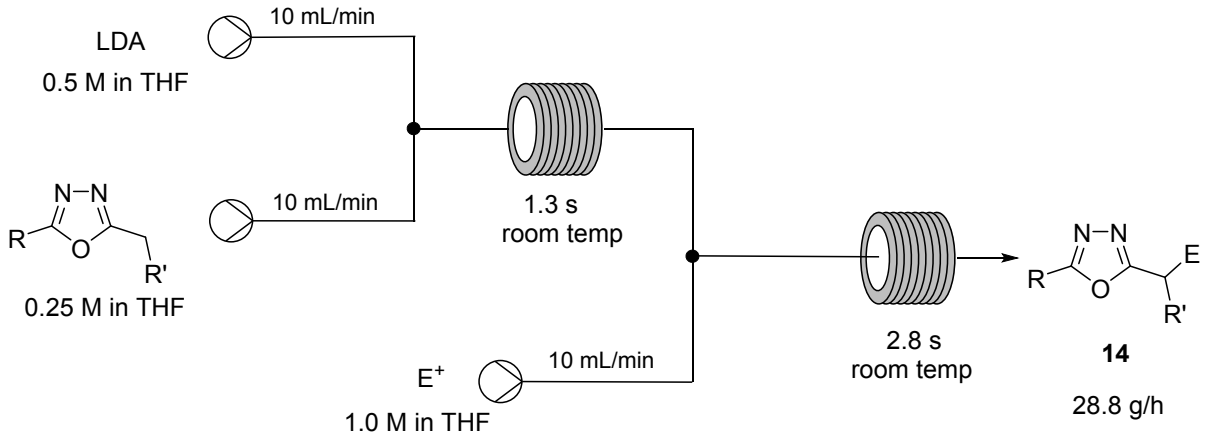

Figure 14 A continuous flow system for oxadiazole deprotonation and substitution

C-H lithiation facilitated by LDA is used to enable the iodination of 4-fluoro-2-(trifluoromethyl)-benzonitrile in a publication by Dunn *et al*.[27] The desired product is a key intermediate in the preparation of a selective androgen receptor modulator API. Both LDA and PhLi (discussed later) were identified as effective bases for the C-H lithiation step. The authors of this paper have previously carried out this reaction on gram scale, where a batch procedure yielded a 44% conversion to the 3-iodo product **15**. Increasing the reaction to a kilo scale was detrimental to the reaction outcome, giving the product in only 11% yield.[28] The moderate to low yields achieved were a result of the formation of multiple by-products. The authors hypothesised that the lithiated species was unstable under the reaction conditions and decomposed during the longer addition times. Localised hot spots, common to larger scale reactions, specifically resulting from the exotherm associated with the iodation step were also thought to negatively impact the yield. A possible solution to this issue involved the use of additional synthetic steps as well as a significant increase in material cost. Therefore, a continuous flow chemistry platform was designed to alleviate the energy transfer issues thought to be hindering the batch reaction. A small-scale reaction set was first performed to investigate the metalation step. Here, it became clear that careful control of short reaction times, maintenance of low temperatures during exothermic processes and precise reaction stoichiometry are key to ensuring optimal yield. The metalation and iodination steps are rapid and possess associated exotherms, so flow chemistry was targeted as an alternative approach. *In situ* NMR and IR were used to study the conversion of the 5-[Li] species to the thermodynamically preferred 3-[Li] species. These mechanistic insights drove the optimisation of the second-generation flow process which utilises standard syringe or HPLC pumps to supply the process with substrate, LDA and I_2 streams, where LDA resulted in a 30:1 preference for the desired 3-[Li] species. This optimised process produced 67% isolated yield with a throughput of 425 g/L/h (Figure 15). Remarkably, this flow process decreased the time required to synthesise 10 kg of product **15** from over a month to less than a week.

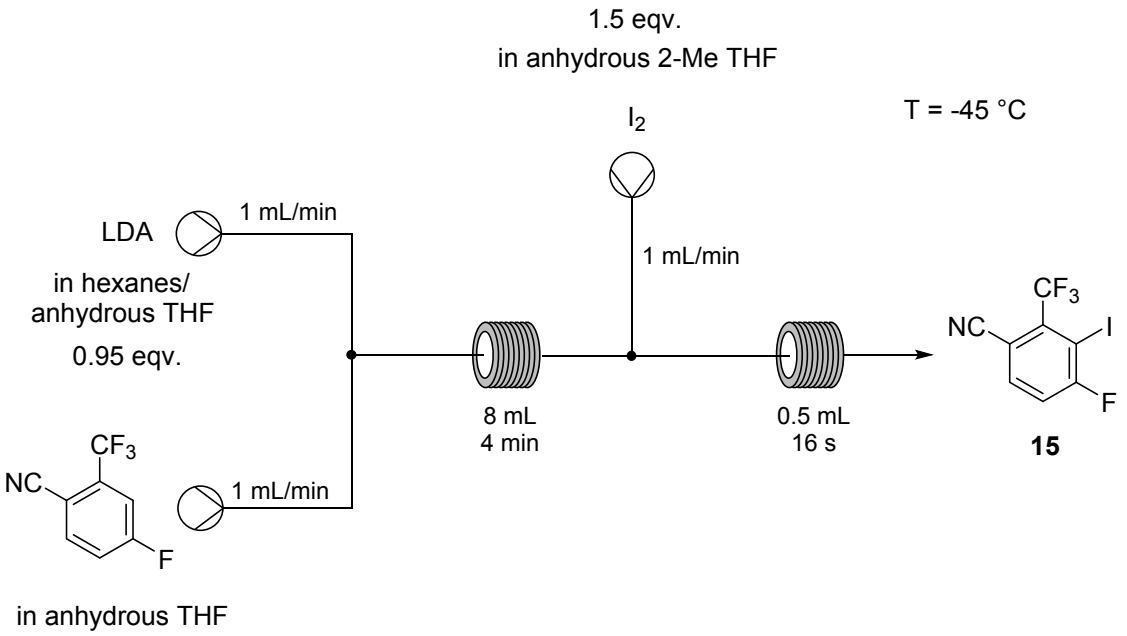

Figure 15 Flow synthesis of tetrasubstituted iodoarene

A publication by Alezra and co-workers outlines a three-step synthesis of quaternary α-amino acids based on the concept of Memory of Chirality (MOC).[29] The synthesis involves an intermolecular alkylation of an enolate where the initial chirality of the starting α-amino acid is 'memorized' only at low temperatures by a chiral conformation of a tertiary aromatic amide. The strict temperature requirements meant that the reaction was extremely difficult to scale. This prompted the authors to develop a flow chemistry platform applicable to the synthesis. A flow chemistry scheme was devised by Alezra and co-workers in a subsequent paper.[30] Initially, the authors investigated an optimisation of the two steps in this alkylation reaction in a flow-based system. Using ethyl iodoacetate as their alkylating agent, analysis of the reaction parameters revealed the optimum conditions were a temperature of -55 ˚C and a residence time of 35 seconds. The authors next turned their attention to the optimisation of the alkylation step where a variety of electrophiles were screened alongside parameters of temperature and *N,N'*-Dimethylpropyleneurea (DMPU) addition. A continuous flow process was engineered where three syringe pumps and two T-mixers were used to initially deprotonate the chiral substrate and subsequently trap the anion formed with various electrophiles. Overall, the enantiomeric excess obtained using the flow system was slightly lower than that of batch. However, the flow system allowed for 1) a residence time of less than 3 minutes, 2) a superior temperature to be employed and 3) the reaction to be considered scalable. Four separate electrophiles were trialled with yields of amino acids **16** between 42-99% (Figure 16) and enantiomeric excess (ee) values of 57-89%. A gram-scale synthesis was also conducted with ethyl iodoacetate and 1.2 g of product was obtained in 82% yield and 89% ee at -70 ˚C. However, despite the improved utility of the flow reaction, the reaction was found to be more sensitive to the nature of electrophile in the flow process compared to batch.

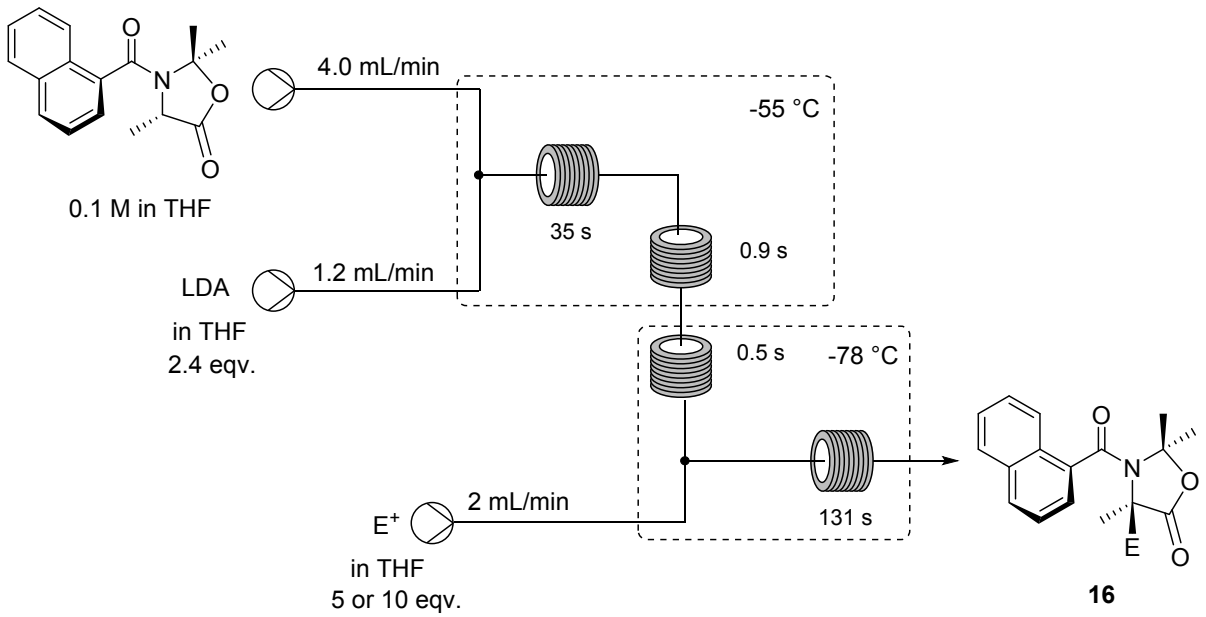

Figure 16 Flow deprotonation and alkylation reactions *via* 'Memory of Chirality'

As a base, LDA was investigated by the Ley Group in a search for reactivity patterns not possible in batch mode.[31] The authors decided to focus on homologation reactions using dibromomethane esters. Here, the dibromomethane must be cleanly metalated as a key first step. Consuming LDA at -90 ˚C can take several minutes in this reaction and so short mixing times are undesirable. However, the lithiated dibromomethane species generated from the first step is an unstable species, with a short half-life, with decomposition taking place even at temperatures as low as -90 ˚C. Consequently, generating this species is unsuited to large-scale batch reactions. Flow chemistry was applied to the methodology, and displayed efficient mixing with well controlled residence times, thus alleviating the decomposition issues seen in batch. A continuous process was devised where CH_2Br_2 and LDA were supplied by peristaltic pumps, to be pre-cooled in 0.5 mL coils at -90 ˚C and where LDA was delivered *via* a sample loop. The anion was formed in an initial 8 mL reactor coil over a four minute residence time and was subsequently reacted with a variety of heterocycles. Reaction with pyridines, thiophenes or isoxazoles were all tolerated, and the yields obtained from these reactions were higher than the corresponding batch process. Additionally, heterocycles which were reported to fail under batch conditions were successfully reacted with dibromomethane in a flow system. The authors also focused their attention on developing new reactivity patterns not possible in batch mode involving the use of esters with an α-proton. In batch mode, the use of esters with α-protons resulted only in starting material. When lithiated dibromomethane was added to an ester it could be protonated to form dibromoketones **17** or a second equivalent of base can deprotonate at the α-position to form the α-dibromo-enolate intermediate. However, if an α-proton is present in the ester, the second equivalent of base will preferentially remove this over the dibromo-proton and thus, protonation of the kinetic intermediate reforms the starting material. The authors deduced that efficient mixing and suppression of back mixing would allow the intermediate to exist long enough to be quenched by acid and not react with a second equivalent of base. Furthermore, the precise temperature control accompanied by

the flow set-up would allow unstable intermediates, which could not survive in batch, to be harnessed. In batch attempts, several runs obtained an optimal yield of 10% of 1,1-dibromo-3-phenylpentan-2-one product. In a continuous flow system, there was an increase to 49% yield with 42% recovery of starting material (Figure 17). Increasing the lithiated dibromomethane species to 4.4 equivalents resulted in a dramatically increased yield of 95% of **17**. As a result, more complex substrates could be utilised and successfully subjected to these conditions. It was found that substrates which were considered poor in batch were successful in flow, albeit in modest yields. The authors finally demonstrated a scaled example of their chemistry where 1.74 g of the dibromoketone from α-methylcinnamyl ethyl ester was obtained in 25 minutes in 87% yield.

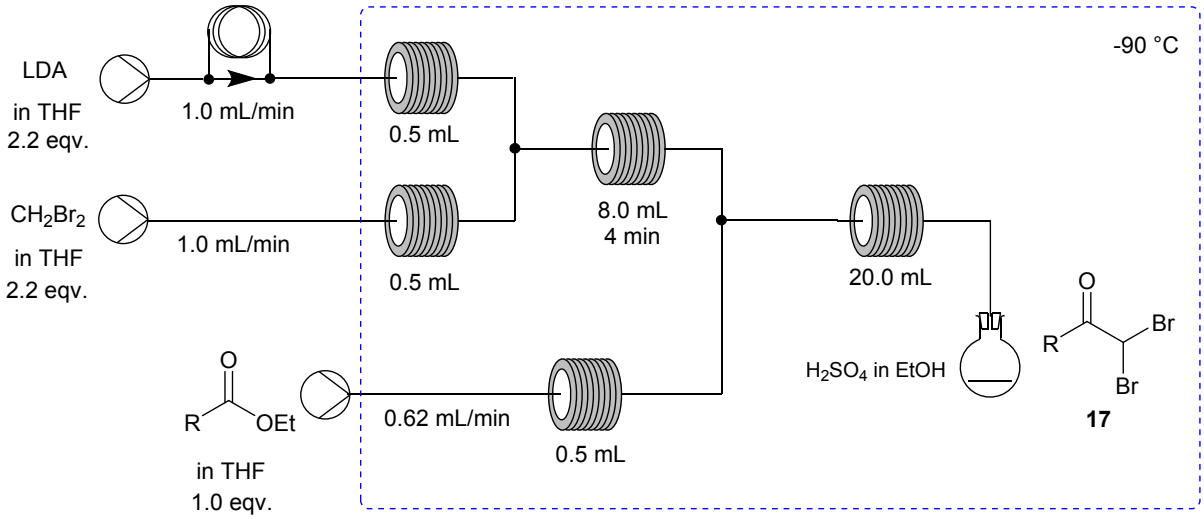

Figure 17 The synthesis of dibromoketones using LDA for dibromomethane deprotonation in a flow system

In work by Kappe and co-workers a method for the direct lithiation of terminal alkynes and heterocycles with subsequent carboxylation is described.[32] The paper outlines the use of two organolithium bases; LiHMDS and LDA. Kappe uses LDA for the conversion of heterocyclic substrates to their corresponding carboxylic acids. A flow system was designed where a variety of heterocycles were supplied to the system to meet a stream of LDA. The organolithium base deprotonated the heterocycle after 3 seconds residence time to yield an anion which progressed to meet CO_2. The CO_2 was introduced to the system through a mass flow controller at a rate of 30 mL/min, and facilitated carboxylation after 0.5 seconds residence time. The carboxylate synthesised was then quenched by a mixture of water and acetic acid (10:1). Attempts to quench the reaction with only water result in immediate clogging of the system and so acetic acid was required. Kappe reports that six heterocyclic substrates were tolerated to form products **18** with yields of 43-79% (Figure 18). An increase in LDA equivalents proved to be an ineffective method of increasing yield but increasing the CO_2 equivalents to 1.9 did result in a small increase in yield.

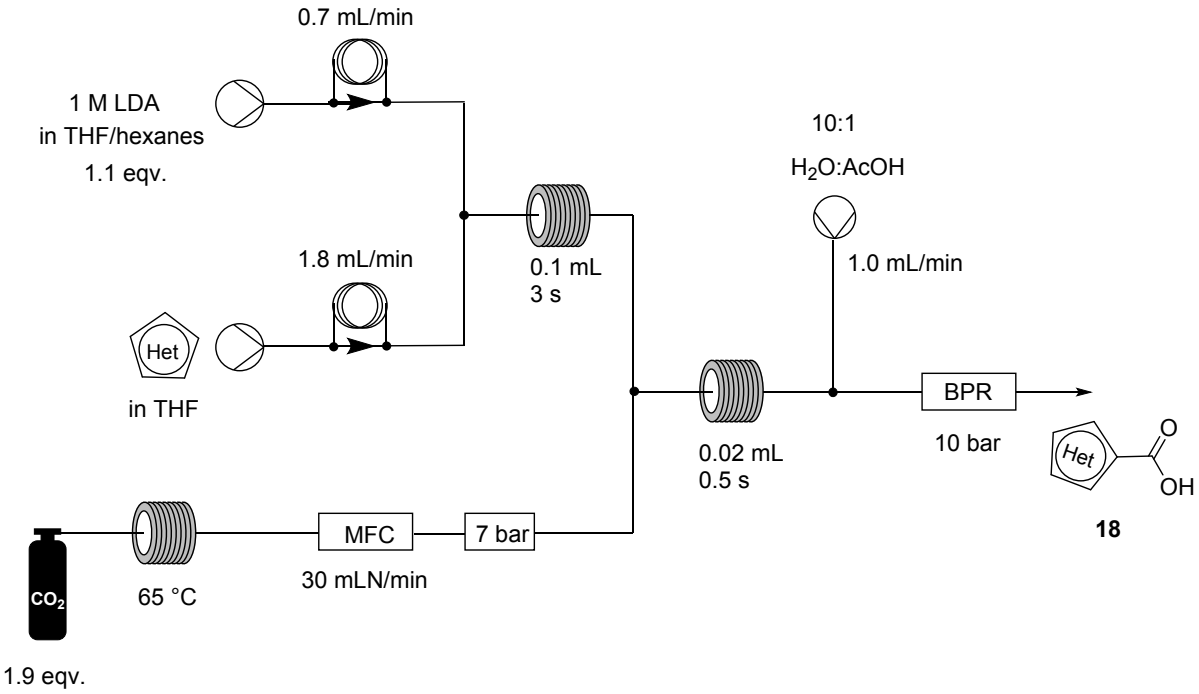

Figure 18 LDA mediated carboxylation of heterocycles in flow

LDA is once again utilised by Kappe and co-workers in a report wherein the authors showcase the ability to monitor a multistep continuous flow process, by multiple inline analytical techniques known as process analytical technology (PAT).[33] The authors chose to study a multistep organolithium transformation that involved treating an ester substrate with LDA to yield the corresponding enolate, which was subsequently reacted with an electrophilic aldehyde. The flow microreactor system used for the reaction was coupled to inline IR, inline NMR and online UPLC to allow real time reaction monitoring. Product quantification was made possible through the use of inline ^{1}H NMR. ReactIR was used to quantify the irreversible deprotonation by LDA. The carbonyl stretch of the starting material can be observed at 1730 cm^{-1} which rapidly disappears due to the deprotonation by LDA even at the shortest attempted residence time of 3.9 seconds. Additionally, a concentration versus response curve of ester showed its limit of quantification to be ~10% of the initial concentration used, implying that over 90% of material was successfully deprotonated. As with most flow processes, the authors initially optimised the system through investigation of temperature, LDA loading and electrophile loading variability. As Kappe illustrates, the process was found to operate most favourably at 20 ˚C which is of great benefit in terms of energy savings as cooling is not required. The authors then demonstrated the scale-up possibilities of this platform where the process operated over 70 minutes to produce **19** with a productivity rate of 4.2 g/h (Figure 19).

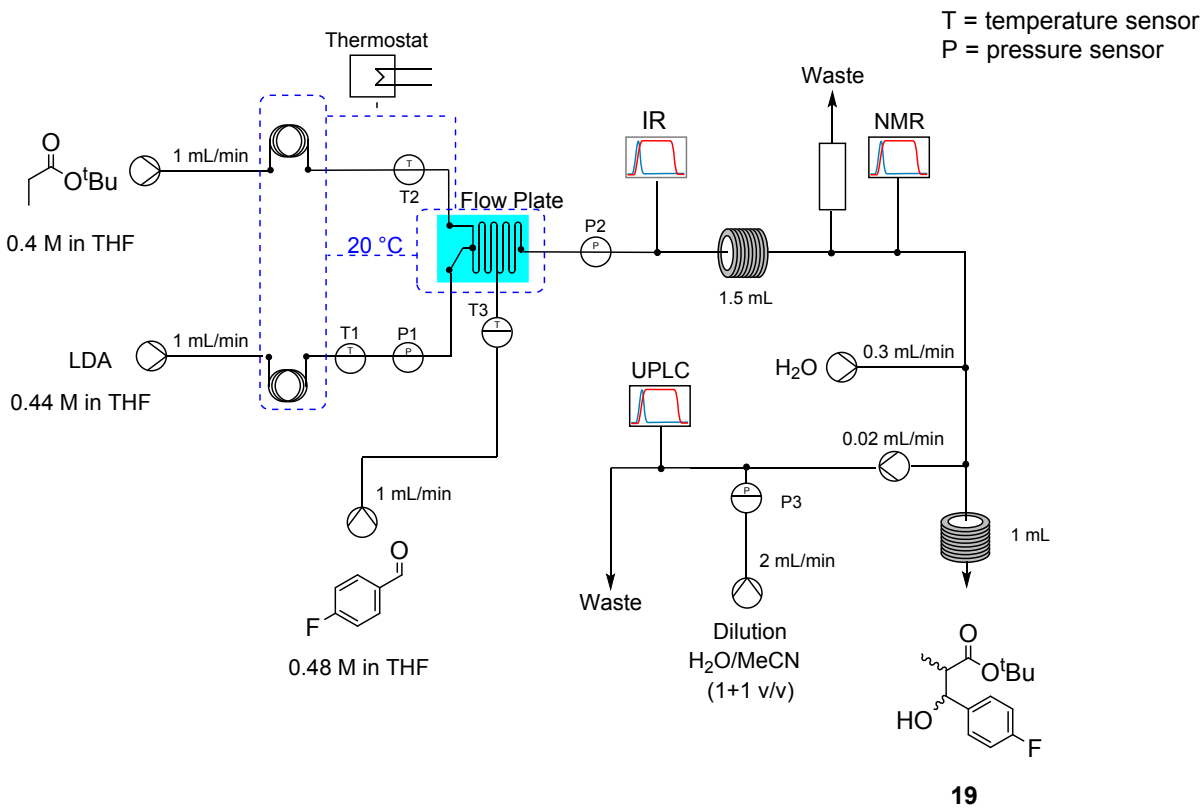

Figure 19 The use of PAT instruments in a flow system to optimise ester deprotonation and addition to an electrophile

LDA prepared *in situ*

LDA is a readily available organometallic reagent, marketed in various solutions and concentrations, allowing for end-user convenience. However, the use of commercial LDA is not without its limitations. Problems with reliable supply and fluctuations in quality and accurate concentration certainly limits the use of commercial LDA. For this reason, LDA is commonly generated *in situ* by reaction of *n*BuLi with diisopropylamine (DIPA). *In situ* generation of LDA results in increased accuracy and reactivity.[34] Regarding production of LDA in a continuous flow system, an additional reactor coil can be added to the set-up to pregenerate LDA.

In 2017, Knochel and co-workers utilised the *in situ* generation of LDA for the formation of α-hydroxy amides.[35] Herein, an ambient temperature flow method for nucleophilic amidation and thioamidation to yield carbamoyllithium intermediates is described. Subsequent reaction of these intermediates with carbonyl containing compounds successfully furnished α-hydroxy amides **20** in good to excellent yields of 58-95% (Figure 20). Ketal, acetal and aryl halide functionalities were well tolerated in this reaction. The process was also successfully extended to include the synthesis of α-keto amides in moderate to good yields of 61-82%, by employing Weinreb amides and structurally related *N*-morpholino amides. Additonally, the lithiation of thioformamides in the presence of *N*-morpholine benzamides provided a reliable route to valuable α-keto thioamides in 41-98% yield using this protocol. Furthermore, the authors found that under these optimised flow conditions, no side-products derived from lithiation of the electrophile were found.

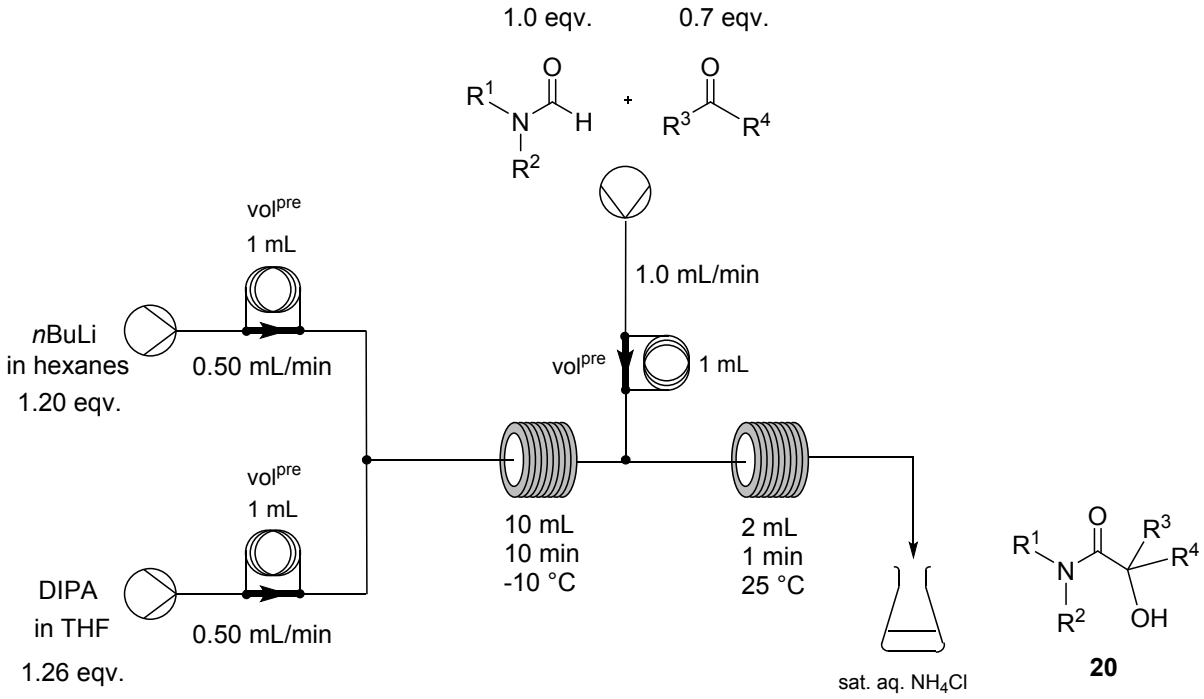

Figure 20 The generation of α-hydroxy amides in a flow system

In similar work published by Ossola and co-workers, a continuous flow system was engineered to promote the epimerization of 3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid. This chemistry, facilitated by the *in situ* generation of LDA, provides a flow chemistry platform for the synthesis of unnatural amino acids, allowing for known literature procedures to be significantly shortened.[36] The authors outline numerous methods attempted to successfully epimerize the substrate **21**. LDA was identified as the most suitable organolithium to enable this epimerization. Advantageously, the authors also identified short reaction times as a key factor in the success of the epimerization. Short reaction times of <60 seconds would be difficult to conduct in batch mode and a consequential decrease in yield would be expected. A continuous process was envisaged to facilitate the short reaction times necessary for these epimerizations, allowing for process scale-up. *n*BuLi and diisopropylamine were readily mixed at -20 ˚C to generate LDA which progressed to meet (*R*)-*cis*-**21** at -15 ˚C, yielding (*S*)-*trans*-**21** respectively (Figure 21). The authors successfully produced 17 g of (*S*)-*trans*-**21** using this method in 55% yield and with a throughput of 55 g/h, demonstrating the scalability of the process.

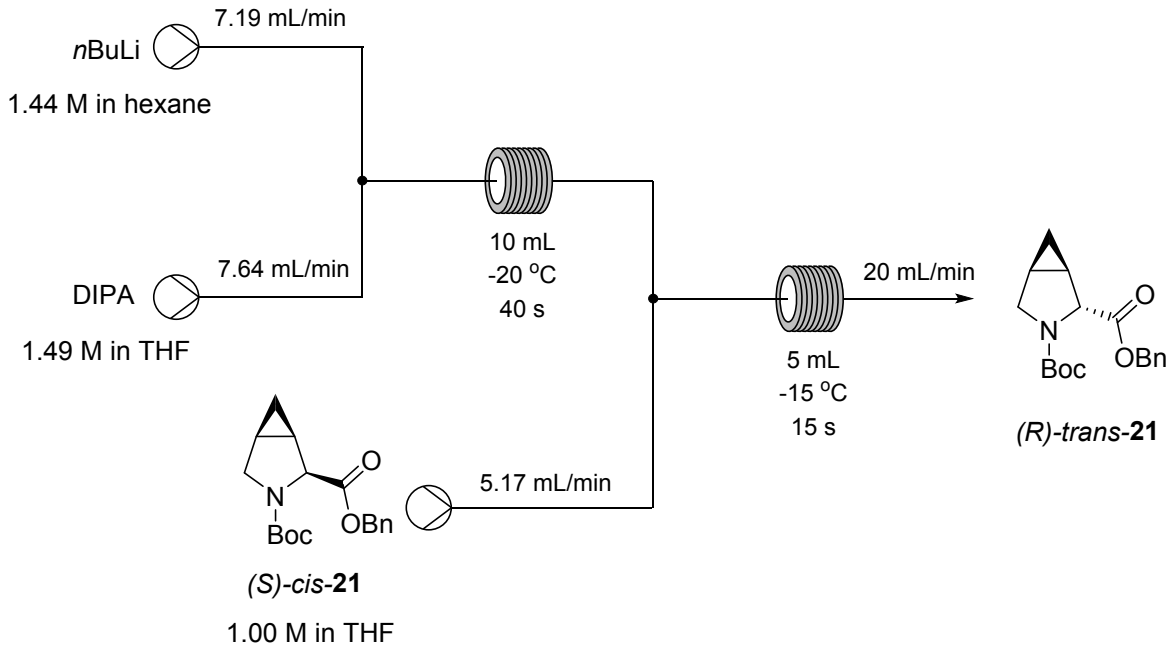

Figure 21 LDA mediated epimerisation in a flow system

A paper by Pontén and co-workers at AstraZeneca recently highlighted the use of continuous flow chemistry in the synthesis of gastroesophageal reflux inhibitor AZD6906.[37] Several problems were encountered throughout the batch synthesis of this API. Initial batch reactions required the use of cryogenic reaction conditions to overcome a potential exotherm and degradation of starting material. This would lead to numerous problems on scale-up. Secondly, the highly toxic reagent methyl dichlorophosphine presented serious safety concerns. Finally, for the batch reaction to proceed, a costly phosphonate reagent **22** was required in two-fold excess to prevent the acidic protons of the product formed quenching the anion created *in situ*. To overcome these issues, a continuous flow system was devised. It was anticipated that a flow system would prevent exposure of product to the anion formed, therefore removing the requirement for an additional equivalent of **22**. It would also reduce chemist exposure to the hazardous methyl dichlorophosphine. An optimisation period identified a reaction temperature of 35 ˚C, a residence time of 90 seconds and an LDA concentration of 1.25 M to yield the best results, whilst concurrently allowing issues of solubility and clogging to be avoided. The authors discontinued the use of commercial grade LDA due to inter-batch variability. With the equivalents of LDA employed proving critical to the reaction, the authors instead turned to generating the 3 equivalents of LDA required *in situ*. This allowed for more consistent reaction results to be achieved and made the previously required degassing process redundant. Using these conditions 1.3 kg of phosphinate **22** was processed yielding sufficient amounts of **23** to proceed to the final stage of API synthesis (Figure 22).

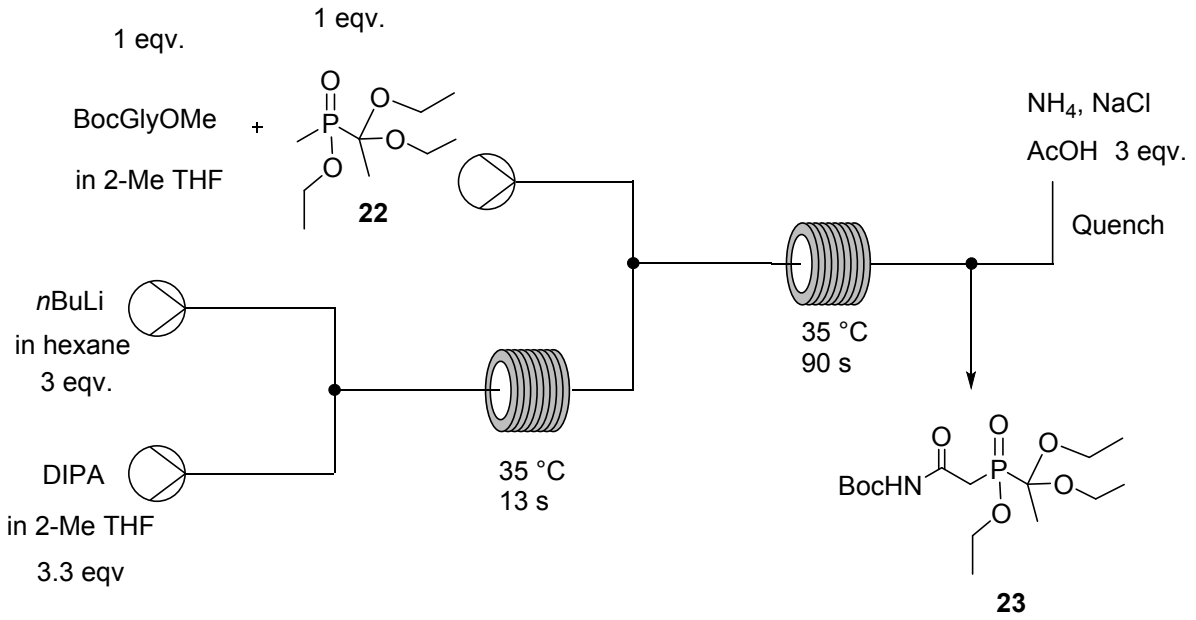

Figure 22 A flow platform to facilitate efficient synthesis of a key intermediate in the steps to AZD6906 synthesis

Wirth and co-workers report the optimisation of a continuous flow system for the safe and efficient use of ethyl diazoacetate to access tertiary diazoalcohols in good yields.[38] As is common with the use of diazo compounds, the use of ethyl diazoacetate is accompanied by an undesirable safety profile, and poor thermal stability.[39] This diazo reagent is commonly combined with LDA to generate a highly reactive ethyl lithiodiazoacetate. This lithiated reagent decomposes rapidly even at low temperatures, seriously hindering its use in a batch reaction where low yielding and varying reaction results are commonly encountered. Within this publication, the authors describe a flow chemistry platform using syringe and peristaltic pumps to allow more efficient and safe handling of this chemical species. The LDA is generated in line by combining streams of *n*BuLi and diisopropylamine which was subsequently reacted with ethyl diazoacetate to produce the lithiated species. Trapping of this lithiodiazoacetate reagent with various ketones furnished diazoalcohols **24** in yields of 12-71% (Figure 23). As well as efficiently handling the unstable lithiodiazoacetate species, the yield of products generated in flow is higher than the corresponding batch reactions, providing a much more reliable method.

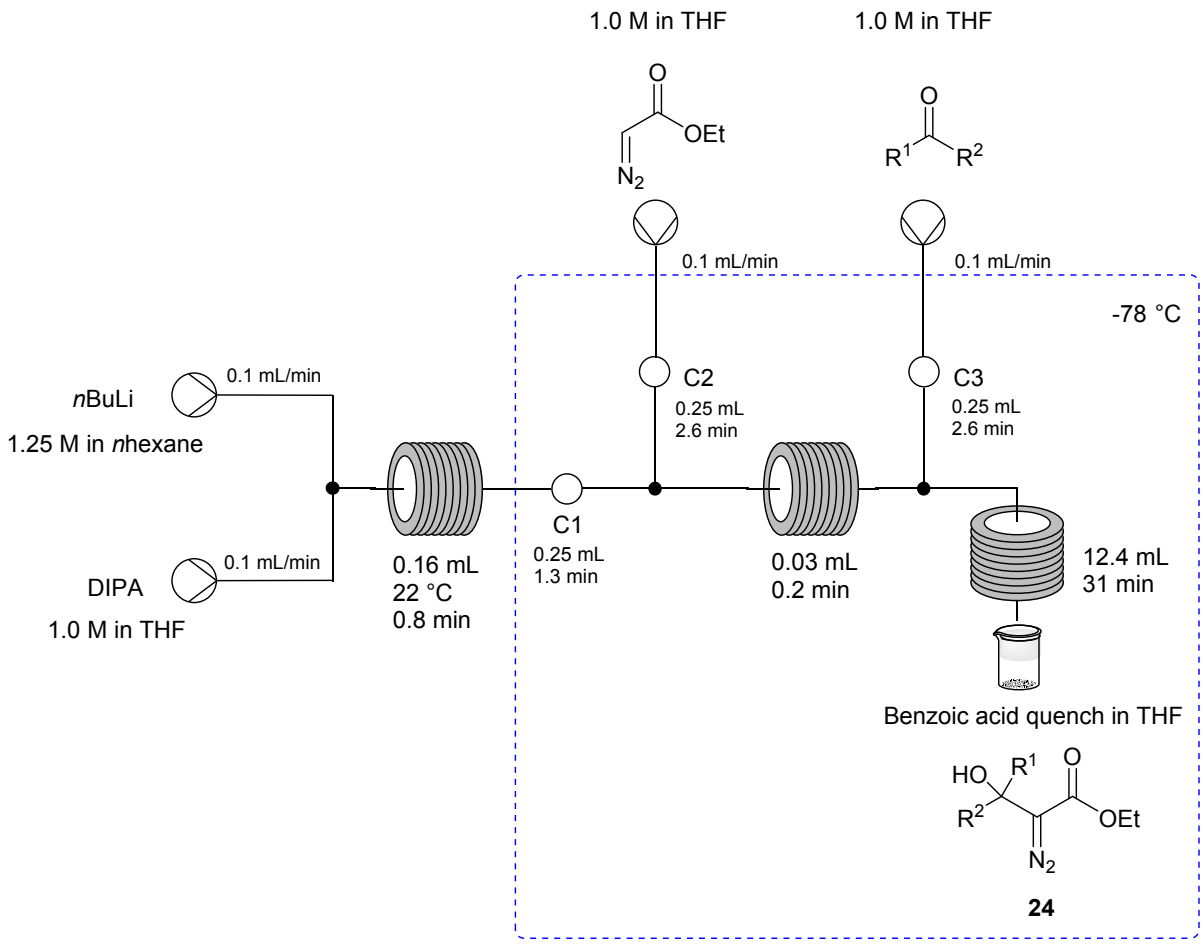

Figure 23 Continuous flow lithiation of ethyl diazoacetate

Work by Wong and co-workers also exploits an in-line generation of LDA for the construction of organic electronic materials. The metalating agent is used in a lithiation-borylation sequence for the generation of thiophene building blocks.[40] These building blocks can then be further functionalised to allow direct access to a range of high performance organic electronic materials. The authors initially employed *n*BuLi as the base for the process. However, the regioselectivity of the reaction soon became an issue. Generation of mixtures of 2- and 5-substituted products, particularly boronic esters, which proved difficult to separate, prompted the authors to switch to LDA. The steric properties of LDA prompted exclusive lithiation of the 5-position. The authors describe a telescoped procedure where LDA is generated in-line and reacted with the thiophene substrate. Subsequent reaction with the boronic ester gave product **25** with a high regioselectivity (17:1) and an excellent yield of 88% (Figure 24). The synthesis had a total residence time of 37 minutes and operated under more efficient temperatures than those observed in batch mode. The flow chemistry platform can be efficiently scaled up without the requirement for cryogenic conditions and without sacrificing the selectivity found in batch.

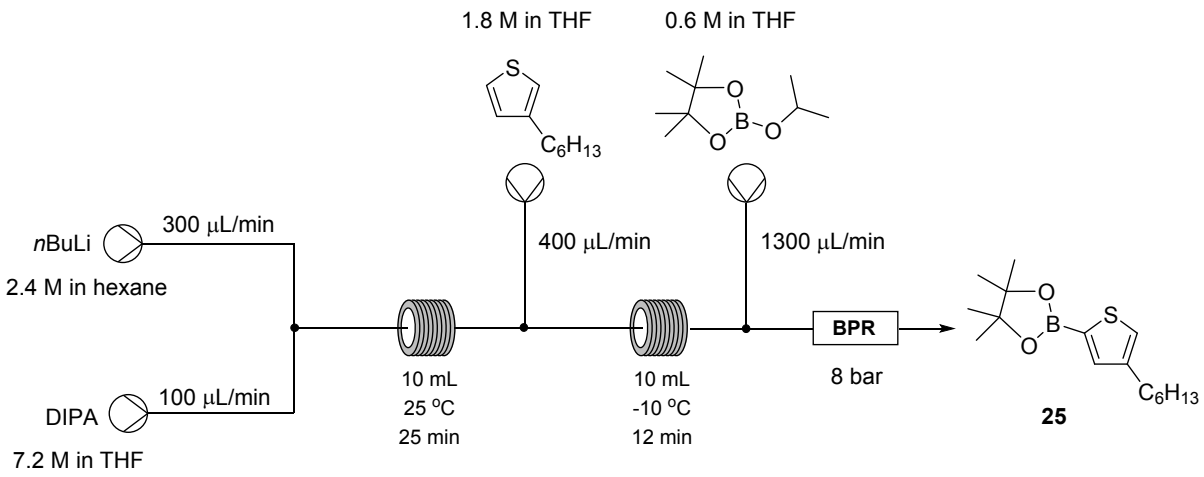

Figure 24 A continuous process for the regioselective lithiation-borylation of 3-hexylthiophene

A final example of in line LDA generation in a continuous flow system is described by Kappe and co-workers.[41] Herein, a multistep process to directly functionalise esters at the α-position, *via* their enolate, is described (Figure 25). Due to inherent reactivity issues associated with lithium enolates, it was postulated this reaction would be ideally suited to a continuous flow platform. The authors first optimised a reaction sequence using *t*-butyl propionate, where it was found that with two equivalents of LDA, a 30 second residence time and at a temperature of 0 ˚C furnished the desired product in yields up to 90%. The flow system also incorporated an ultrasound bath which immersed the section of the flow set-up involving the electrophile addition as a precautionary measure to circumvent issues arising from solid formation. The authors then turned their attention to optimising a reaction using methyl propionate, which lacks the bulky O^{t}Bu group and consequently has more complex selectivity issues. Homo-Claisen condensation products are a commonly observed by-product from this reaction. This reaction requires temperatures of -78 ˚C during the enolate formation step. However, the authors suggest that the reaction is most likely not limited by mass transfer, but instead the poor selectivity results from similar reaction rates for the ester deprotonation reaction and the homo-Claisen condensation reaction. Six examples of α-alkylated esters of type **26** are reported to be successfully generated in 29-80% yields. Additionally, scaling of the process is simply achieved by collecting the crude reaction mixture from the output for longer periods of time.

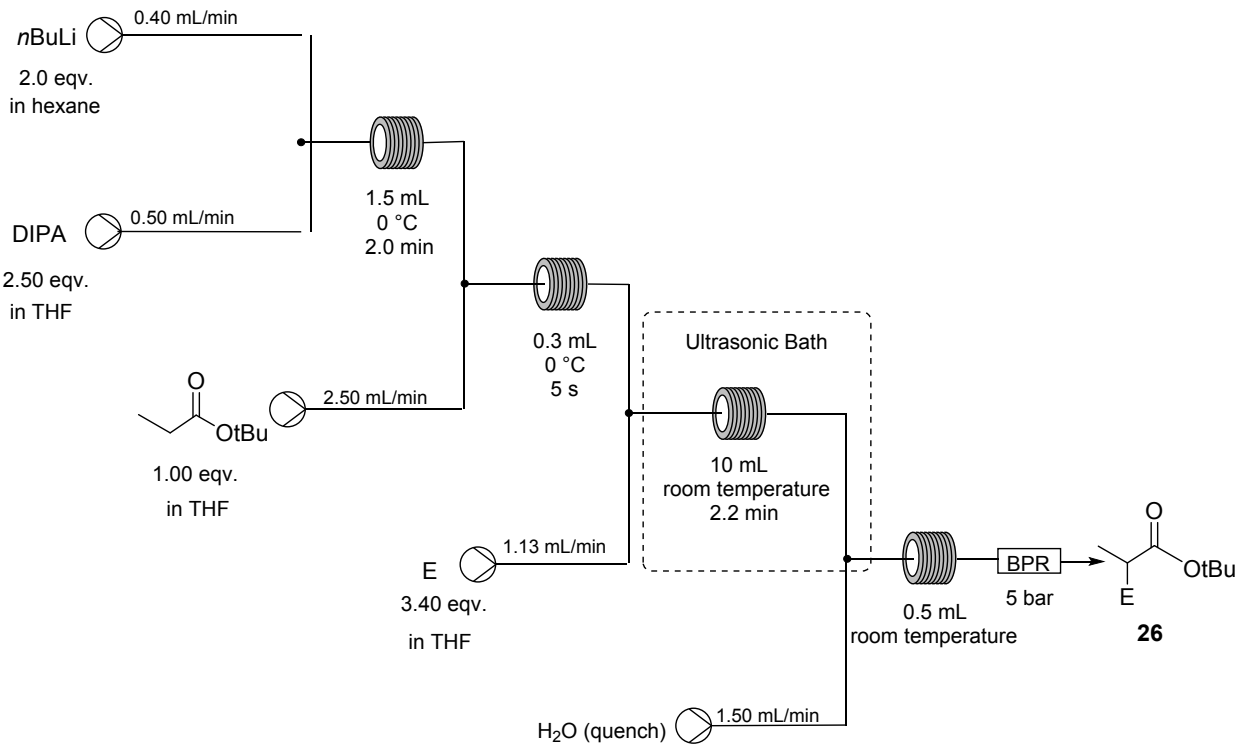

Figure 25 Continuous flow of ester deprotonation and α-functionalisation

LiHMDS

Lithium hexamethyldisilazide or LiHMDS is a lithiated organosilicon compound which is commonly used as a strong, non-nucleophilic base.[42] A publication by Ley and co-workers outlines the synthesis of a family of casein kinase I inhibitors using a continuous flow system.[43] Analogues of imidazo[1,2-*b*]pyridazine were prepared *via* a three-step sequence involving the formation of a ketone moiety, α-bromination and subsequent condensation with 3-aminopyridazine to yield a key fragment of the target molecule (Figure 26). The authors designed a scalable multistep assembly to efficiently and directly deliver pure product on a multigram scale. The first step of the three-step sequence involved the use of LiHMDS. Using high pressure pumps, the authors observed difficulties with the use of organolithiums, associated with rapid decompositon and difficulties with exotherm control. To sidestep these issues, a dual sample loop injection system was developed. One sample loop served to deliver the organolithium base to the system while the second loop stored a second loading of base for later injection. This dual sample loop was cooled through submersion in a Dewar flask of water/dry-ice before addition. LiHMDS was employed to deprotonate picoline substrates **27** which would react with an ester to afford products of type **28** (Figure 26).

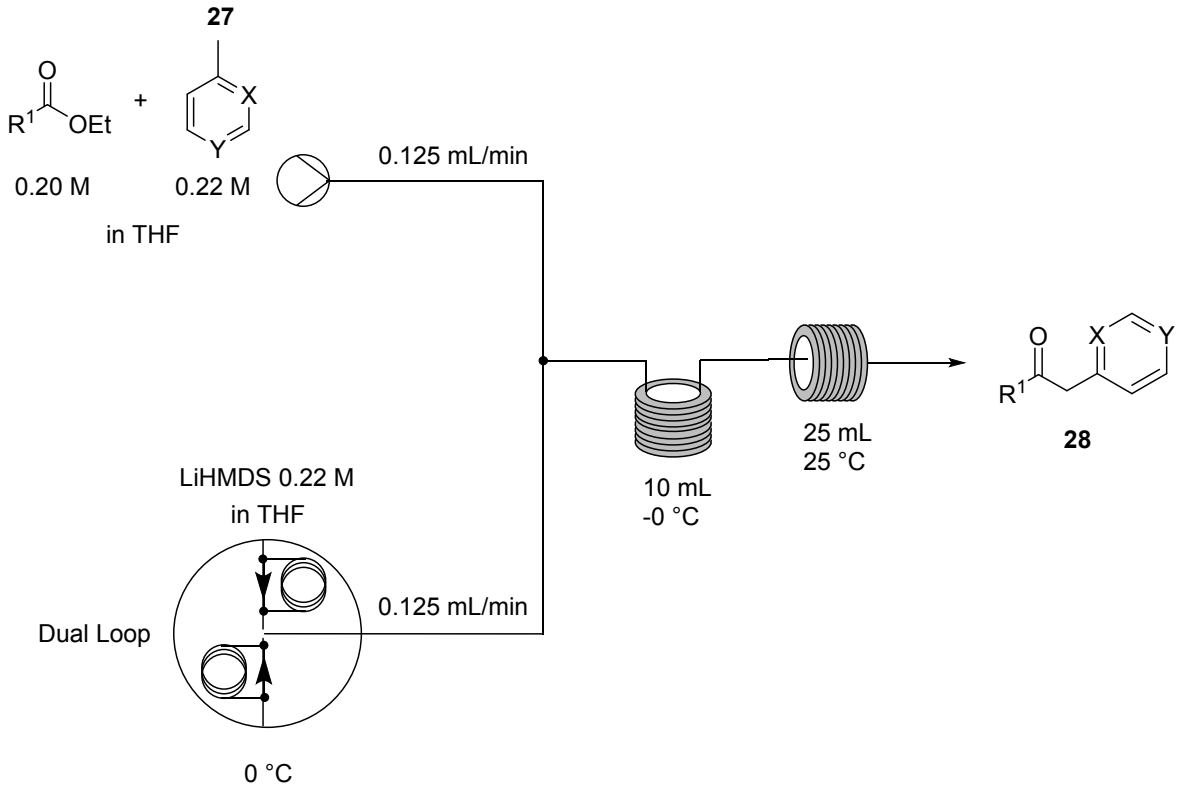

Figure 26 LiHMDS mediated deprotonation and addition to ester substrates

However, LiHMDS was unable to deprotonate a particular 2-picoline substrate and so the authors turned to *n*BuLi. Due to competitive nucleophilic addition of the organolithium to the ester function, the fluorophenyl ester and picoline substrate could not be premixed (Figure 27). Instead, the picoline substrate and *n*BuLi were mixed in a T-mixer and allowed to react in a 5 mL coiled reactor held at -78 °C. The azaenolate generated was then quenched by the ester in a 15 mL reactor coil at ambient temperature. This reaction sequence produced the corresponding ketone **29** in 65% yield on a 50 mmol scale.

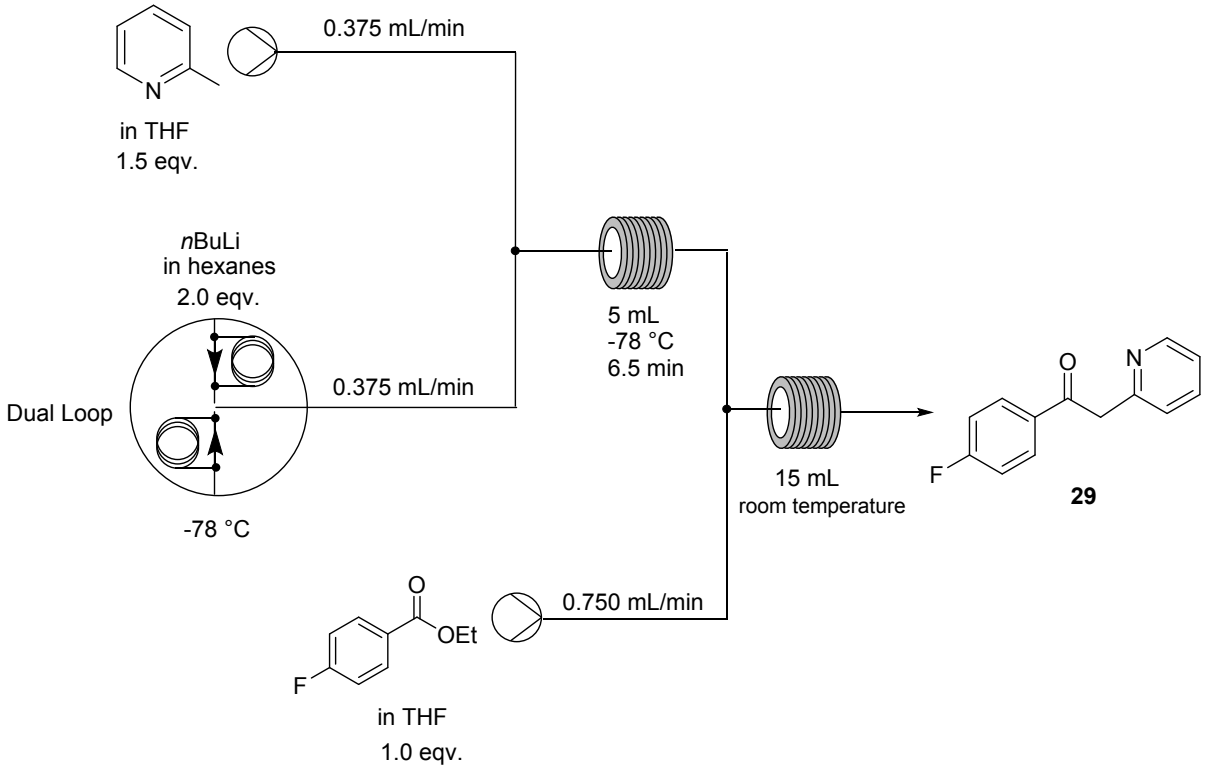

*Figure 27 n*BuLi deprotonation using a dual-loop system in the first step of the preparation of a family of casein kinase I inhibitors

A paper, previously discussed, outlining work by Kappe and co-workers using LDA in continuous flow for the carboxylation of heterocycles also describes the application of this system to the carboxylation of alkynes.[32] LiHMDS was the organolithium base used in this reaction to rapidly furnish a variety of carboxylic acids in less than 5 seconds. Only a slight excess of LiHMDS was required. The LiHMDS and the alkyne were pumped by HPLC pumps and loaded in individual sample loops to meet in a T-mixing unit before passing through a 0.1 mL coiled reactor for a residence time of 3 seconds to allow lithiation occur. The lithiated alkyne then progressed to a second T-mixer where CO_2 was introduced. The product of the carboxylation then advanced to a third and final T-mixer where it was quenched by H_2O, producing carboxylic acids **30** in good to excellent yields of 66-90% (Figure 28). Both electron rich and electron poor aromatic alkynes were well tolerated but the phenol and 3-ethynylpyridine substrates tested were unsuccessful due to precipitation of the organometallic intermediate in the reactor.

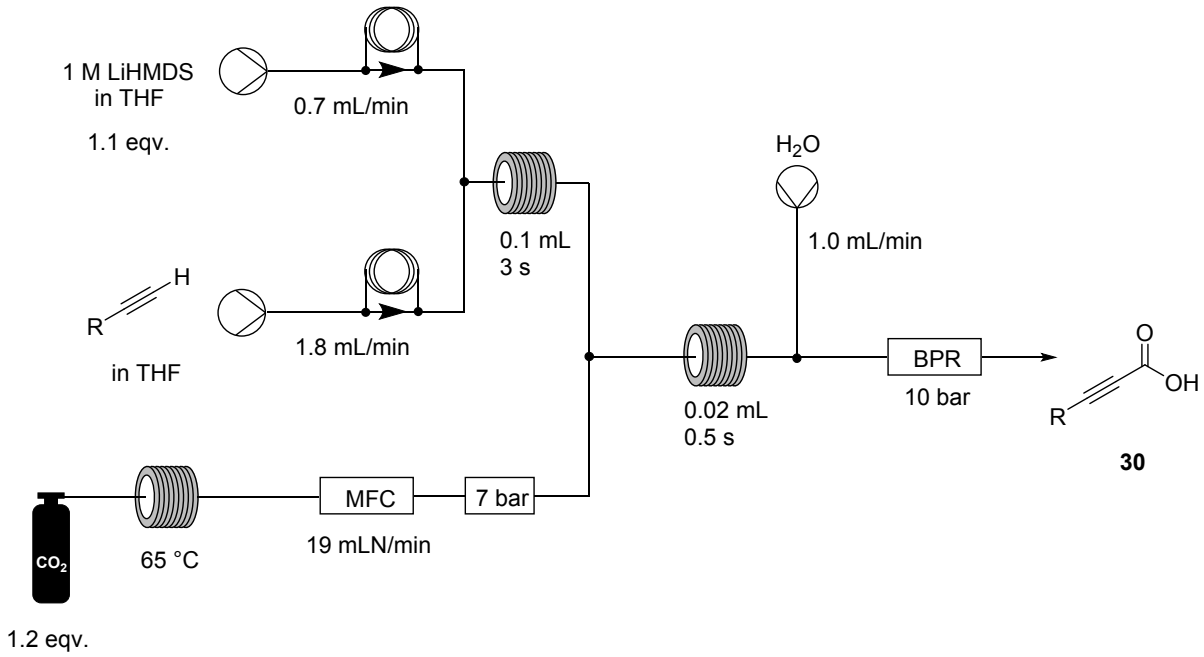

Figure 28 A flow process for the carboxylation of alkyne substrates using CO_2

A paper by Knochel and co-workers describes a continuous flow system which uses LiHMDS and chloroacetic acid to enable selective chloromethylenation of functionalised esters.[44] This Claisen homologation reaction is, for the first time, extended to bis-chloromethylenation using dichloroacetic acid which results in a direct route to the under explored α,α′-bis-chloroketones. The authors report a flow system capable of producing both mono and bis-α-chloroketones in good to excellent yield in several seconds. The ester and chloroacetic acid are premixed and pre-cooled before being supplied to the system *via* a peristaltic pump. It is combined with LiHMDS, which has been pre-cooled, in a T-mixer to generate the lithiated intermediate. This intermediate is then quenched by HCl to produce mono- or bis-α-chloroketones **31** (Figure 29). The reaction scheme is highly economical in terms of reagents and reaction time, has a breadth of application across a wide variety of substrates and demonstrates potential for successful scale-up.

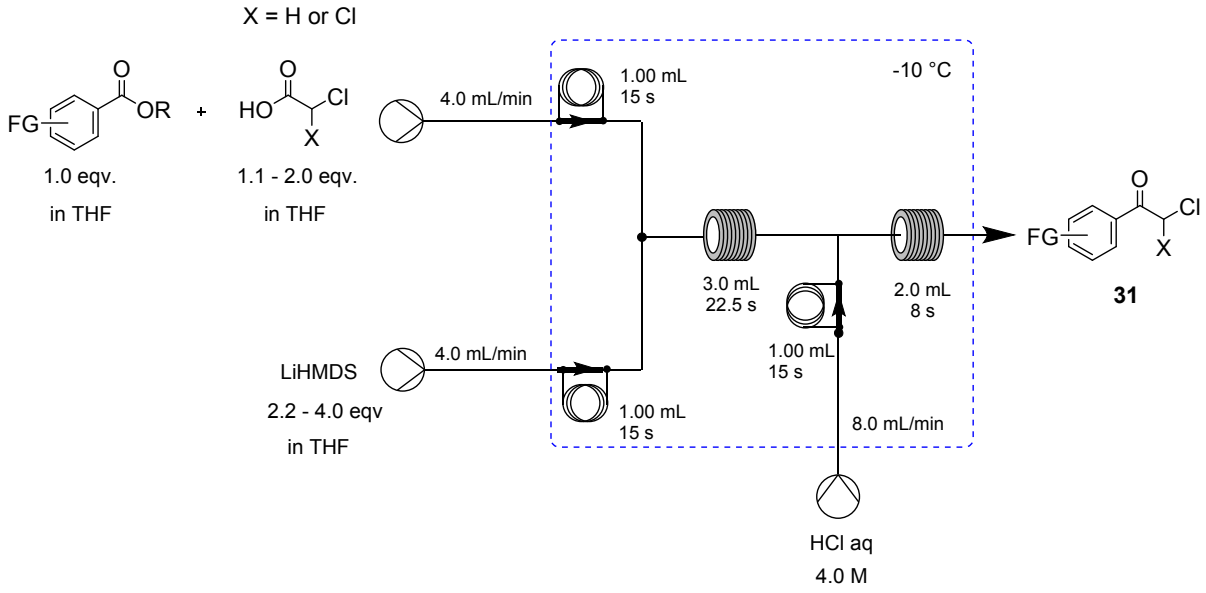

Figure 29 Continuous flow chlorohomologation of aromatic esters leading to bis-α or mono-chloroketones

A paper by Kappe and co-workers describes a scalable continuous flow system designed for the concise synthesis of α-difluoromethyl-amino acids.[45] The difluoromethyl group (CHF_2), delivered by the reagent fluoroform, is a moiety found in an increasing number of pharmaceutical and agrochemical products. Fluoroform is an attractive source for the introduction of this motif and is generated on large scale as a reaction by-product. Its global warming potential means the release of the gas into the atmosphere is restricted. The organolithium base LiHMDS is employed to deprotonate both an ester substrate and fluoroform (CHF_3), the latter forming an electrophilic singlet difluorocarbene. This difluorocarbene moiety can then react with the anionic ester substrate, enabling the synthesis of α-difluoromethyl amino acids **32.** These compounds are potent and selective irreversible inhibitors of their respective α-amino acid decarboxylases. This served as motivation for the authors to extend this flow methodology to the synthesis of Eflornithine. The authors first performed batch reactions which proved unsuccessful yielding only 2% conversion after a 6 hour reaction. Resulting from this, the authors turned their attention to developing a continuous flow system to provide a more efficient route to the target. The continuous system used two syringe pumps to feed the ester and LiHMDS into the system. The deprotonation occurs at -30 ˚C in a 2 mL reactor coil with a residence time of 4 minutes. Fluoroform is then introduced to the system with the aid of a mass flow controller. The solution was processed through two remaining reactors for a total residence time of 20 minutes. Optimum reaction conditions were found to use two equivalents of base. The process is applicable to several substrates yielding good results when mono-esters, malonates and amino acids **32** were examined (Figure 30). Although the process is readily scalable, application on an industrial scale would have to involve a plan for removal and ideally, recycling of excess fluoroform.

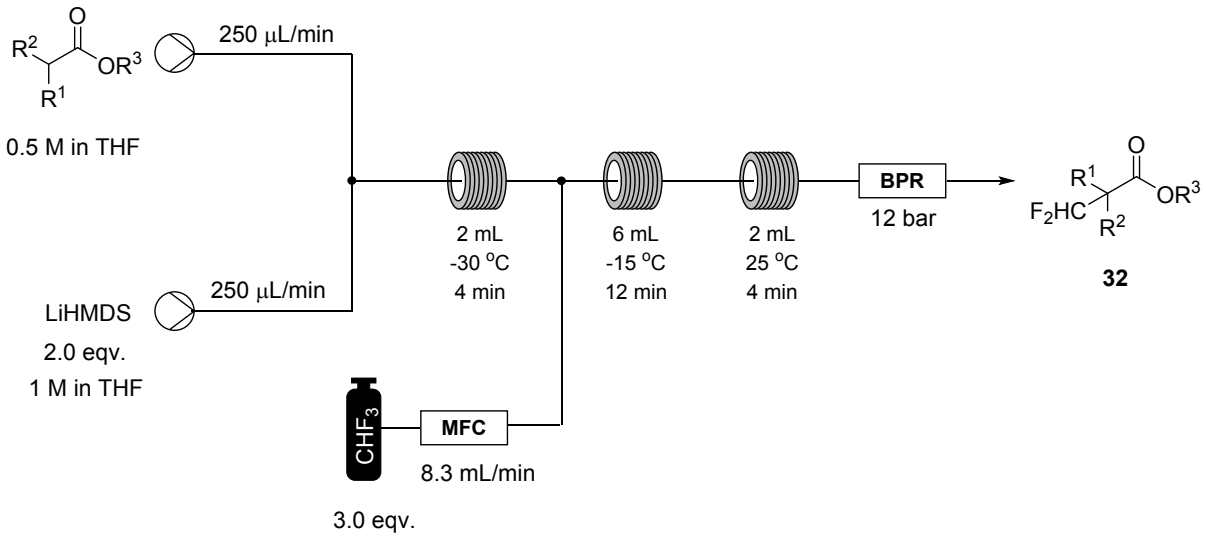

Figure 30 Continuous flow α-difluoromethylation using fluoroform

A 2017 patent application from Alphora also involves the use of LiHMDS in a continuous flow system towards a more efficient route to ingenol mebutate.[46] Ingenol mebutate **35** is a protein kinase C activator that is approved in the U.S. and Europe for the topical treatment of actinic keratosis, which can potentially develop into skin cancer. The Baran group found that only 1.1 mg of ingenol mebutate could be isolated from 1 kg of plant material.[47] However, ingenol (**33**) itself, can be found in much larger quantities of 275 mg/kg, from the seeds of the plant *E. lathryis*. Thus, a semi synthesis of ingenol mebutate from ingenol was attempted. Leo Laboratories developed a multistep batch synthesis, involving protection and deprotection of the hydroxyl group, to provide ingenol mebutate in 37% yield.[48] In an attempt to streamline the synthesis, Alphora devised a more direct route to ingenol mebutate using a flow chemistry platform. The flow system involved a premixed solution of the organolithium base and ingenol undergoing acylation, facilitated by the use angelic anhydride (**34**) at 0 ˚C, followed by a 1M HCl quench at 25 ˚C (Figure 31). This continuous process allowed for a single step, protecting group free synthesis of ingenol mebutate, in 40% yield, with much improved regioselectivity for the C3 position.

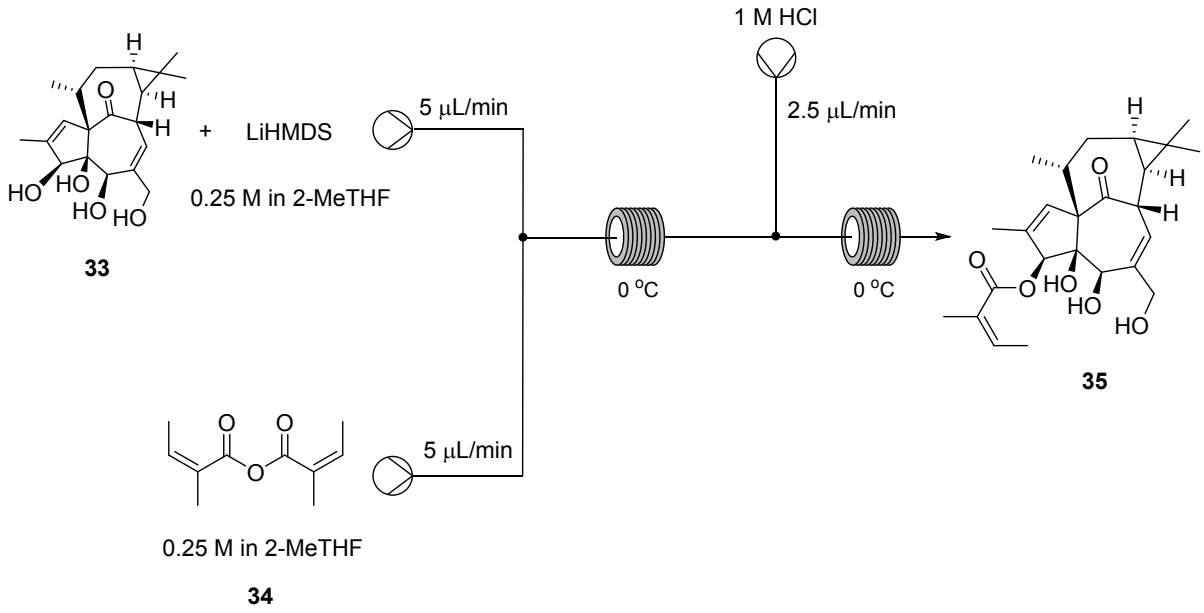

Figure 31 Continuous processing of ingenol mebutate

Finally, work by Vilé *et al.* identifies LiHMDS as the optimal organolithium base for a continuous flow platform which facilitates the enantiospecific cyclization of methyl *N*-(*tert*-butoxycarbonyl)-*N*-(3-chloropropyl)-*D*-alaninate to 2-methylproline derivative **36**, *via* a previously mentioned 'Memory of Chirality' approach.[49] Flow technology was applied to this reaction scheme to improve the scalability and safety profile and to remove the need for cryogenic conditions. Additionally, the authors anticipated an improved throughput from a flow-based system. A continuous flow platform was devised where the substrate was delivered by a HPLC pump to meet 1.2 equivalents of LiHMDS in a 1 mL reactor coil at -10 ˚C for a residence time of 30 seconds (Figure 32). The reactions were firstly performed on a 1 g scale where the use of LiHMDS enabled an isolated yield of **36** of 96% and an ee of 97%. The authors then scaled the initial 1 g process to run continuously for 6 hours with a productivity of 11 g/h to yield 66 g of pure product while preserving enantioselectivity. The exquisite control of reaction parameters usually required for 'Memory of Chirality' protocols, positions flow approaches as an ideal technology to properly apply these concepts in practice. The flow process designed, proved superior to the corresponding batch operation as it operates a temperature of -10 ˚C compared to the batch temperature of -60 ˚C, with a residence time of 30 seconds compared to the batch reaction time of 2 hours. Additionally, the continuous set-up allows for the process to be readily scaled to a multigram scale.

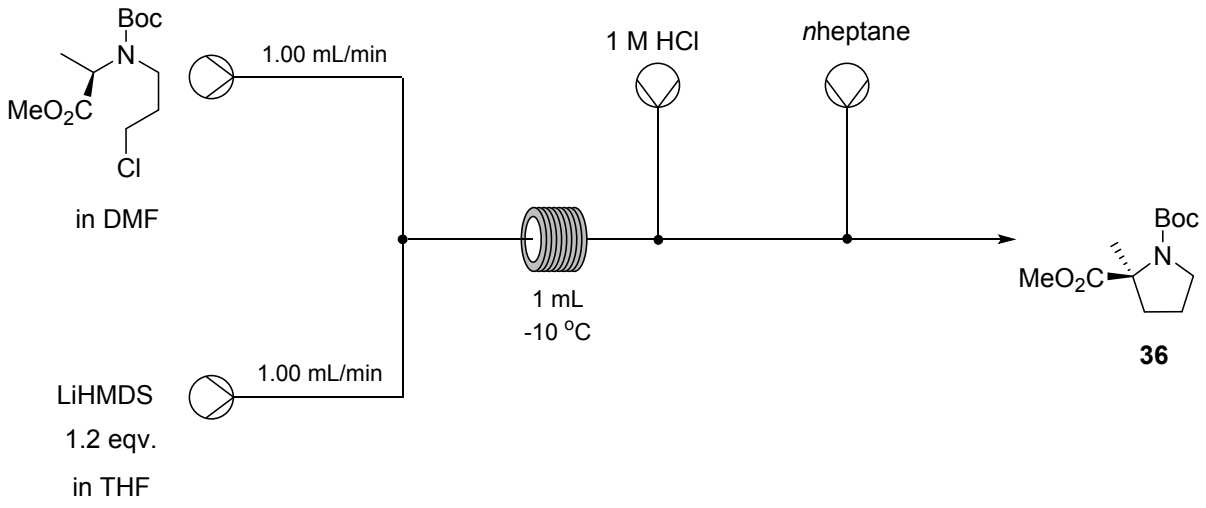

Figure 32 Continuous flow processing of asymmetric intramolecular cyclisations *via* 'Memory of Chirality'

Other Organolithium Bases

Phenyllithium

Phenyllithium or lithobenzene is an alternative organolithium reagent to the commonly used reagents discussed above.[10] Although not as prevalent in the literature as *n*BuLi or LDA, it is often employed to carry out similar reactions. In a paper by Dunn *et al.* previously discussed, PhLi is also used as an organolithium base to enable the iodation of 4-fluoro-2-(trifluoromethyl)-benzonitrile. This process proceeds *via* C-H lithiation and subsequent treatment with iodine under continuous flow conditions.[27] PhLi was chosen by the authors since it was seen to promote formation of the 3-iodo isomer to a greater extent than LDA, which resulted in varying amounts of the unwanted 5-iodo isomer. The initial continuous process designed by the authors involved PhLi and 4-fluoro-2-(trifluoromethyl)-benzonitrile meeting in a 10 mL reactor coil at -70 ˚C for 20 minutes to facilitate the lithiation step. The lithiated intermediate progressed to meet a stream of I_2 delivered by a syringe pump in a second reactor coil for a residence time of 10 minutes, yielding the desired 3-iodo product **37** on gram scale with a throughput of 57 g/L/h and yields of 63% (Figure 33). The authors then attempted to run the process on pilot scale size, however progress was hindered by the tendency of PhLi to add to the nitrile, lowering yields to 50%. Additionally, this caused solid formation during longer runs. Despite these clogging events, 6.85 kg of product was generated over *ca*. 7 days of continuous processing, involving multiple start/stop declogging events.

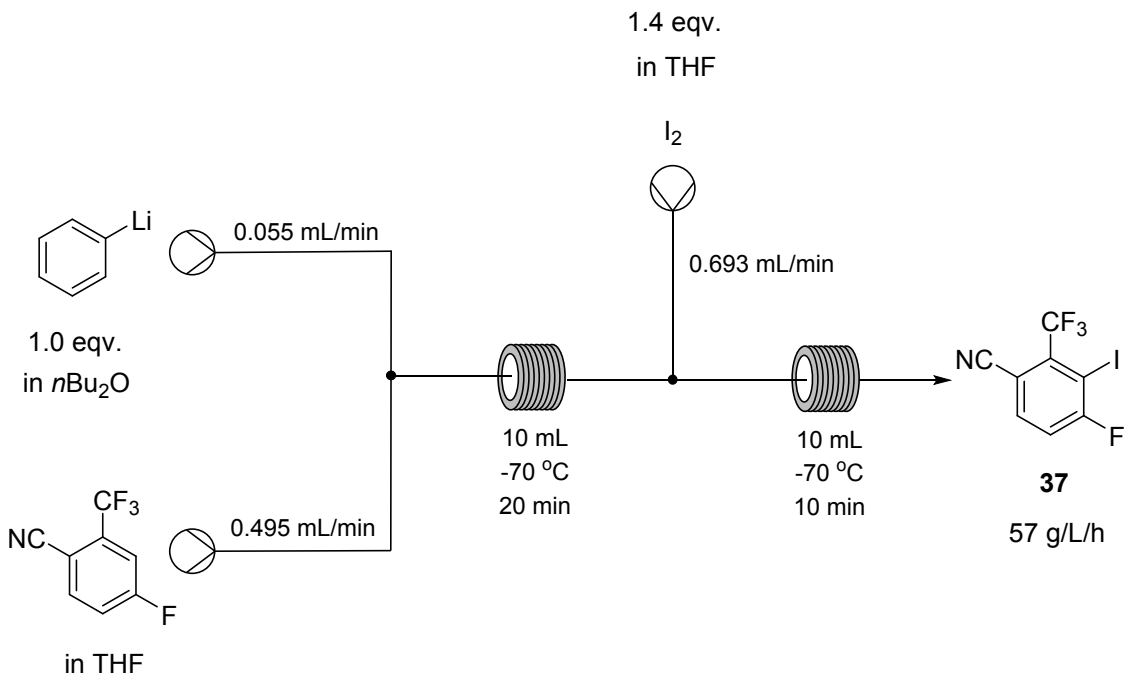

Figure 33 Continuous flow synthesis of a key intermediate for API development *via* PhLi deprotonation

sec-Butyllithium

sec-Butyllithium or *s*BuLi is another choice of organolithium base which is often used in synthesis as a powerful organolithium reagent.[10] *s*BuLi is a stronger base than *n*BuLi, but is less nucleophilic. Work by Luisi and co-wokers investigated an alternative route to C4-functionalised 1,2,3,4-tetrahydroisoquinolines (THIQs), due to their significant relevance within medicine.[50] A flow chemistry platform consisting of three syringe pumps, two independently sized T-mixers and two tube reactors was designed to carry out these functionalisations. The enantiopure substrate and *s*BuLi are supplied independently to the system, furnishing the lithiated intermediate. Various electrophiles are then introduced to the system to yield the desired products **38**/**39**. It became apparent to the authors that the reaction was temperature dependent. Contingent upon the reaction temperature, two possible mechanistic pathways were possible. When the temperature was held at -48 ˚C for the duration of the reaction, production of a range of laterally substituted aziridines **38** was possible, in yields of 48-90% (Figure 34). Subsequent to deprotonation, increasing the temperature to 0 ˚C allowed for the synthesis of C4-functionalised tetrahydroisoquinolines **39** in yields of 54-95% (Figure 35). The devised continuous flow process allowed for comprehensive isomer control. Furthermore, it allowed direct synthesis of THIQs, of which only two known examples exist in batch.

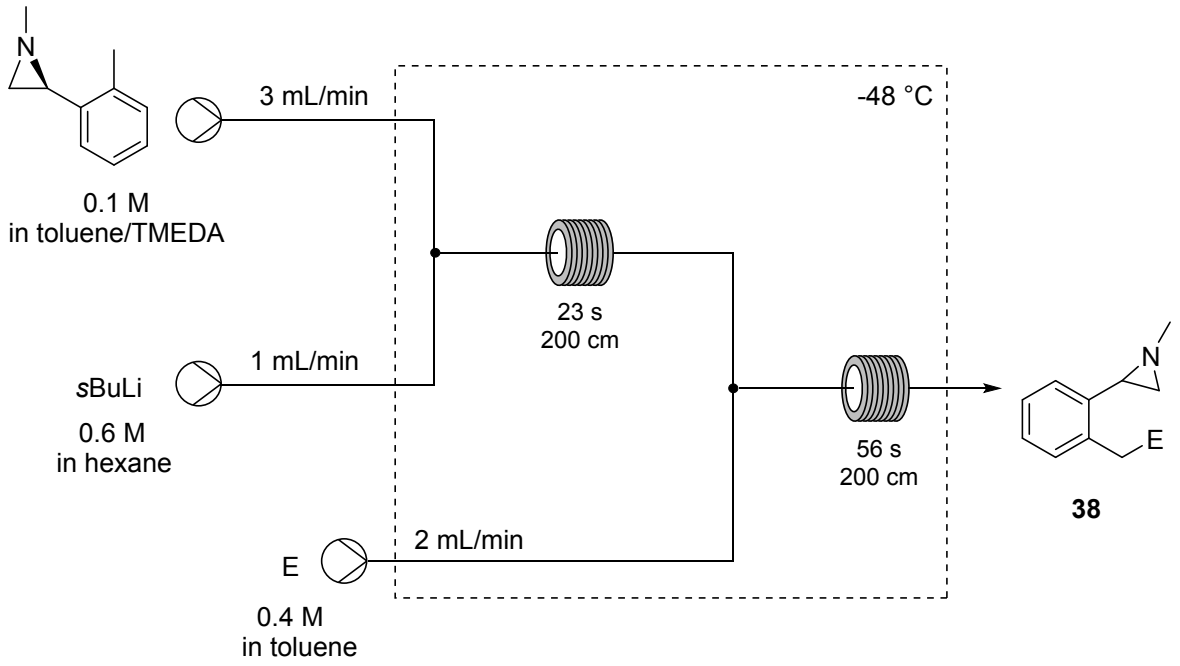

Figure 34 Continuous flow system which generated laterally substituted aziridines

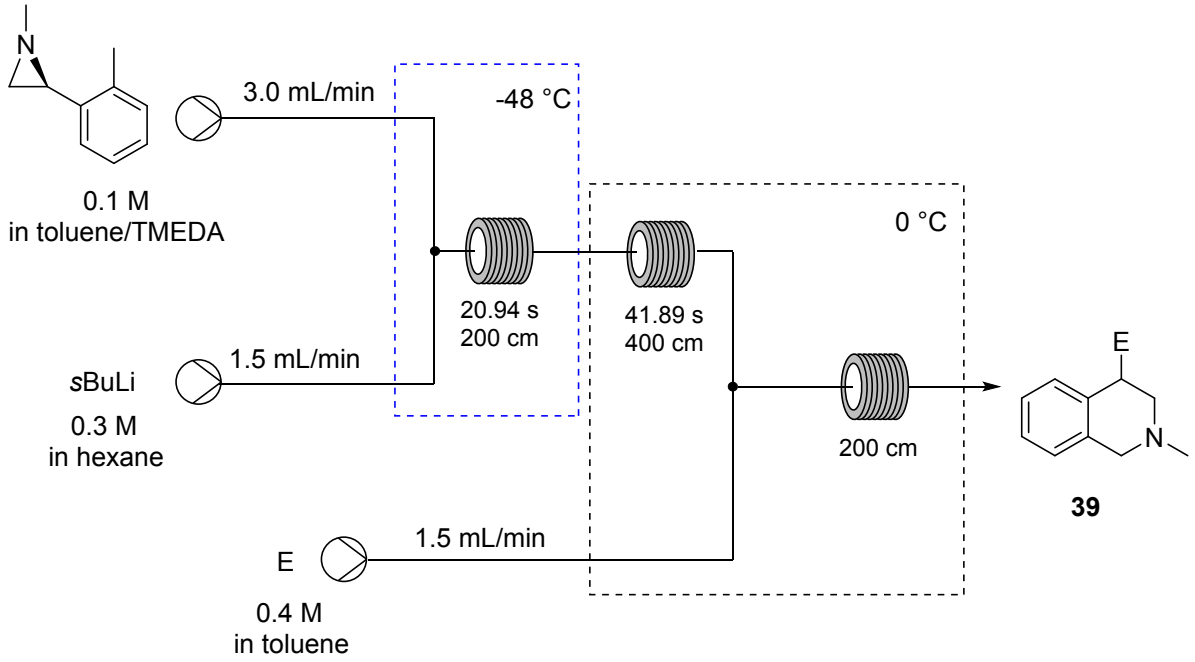

Figure 35 Continuous flow system which enabled lateral-lithiation-thermal isomerisation of aziridines

n-Hexyllithium

n-Hexyllithium or *n*HexLi is an organolithium base which can usually be used in place of *n*BuLi.[51] It is often used on plant scale as a cost effective and industrially safe organolithium reagent. Additionally, in terms of flow chemistry liquid by-products are often easier to deal with than their gaseous counterparts. Work by Thaisrivongs *et al.* reports the design of a continuous flow chemistry platform for the synthesis of Verubecestat, a drug which reached

Phase III trials for Alzheimer's disease before being discontinued.[52] The batch synthesis of this drug candidate is problematic from the outset. The protocol proceeds *via* a Mannich-type addition of a methyl sulfonamide to a chiral Ellman-type sulfinyl ketimine. Excess sulfonamide and cryogenic reaction conditions were required for the batch procedure, even after several optimisation attempts. The authors hypothesised that the mixing rate of the reactive species generated in the initial step was the key parameter for optimal conversion to the desired target. It was found that both the nucleophile and lithium anion irreversibly deprotonate the electrophile, competing with the Mannich-type reaction. It was thought a flow system would offer improved mixing and could alter this key parameter, preventing the irreversible deprotonation, by limiting the exposure of the ketimine from its lithiated intermediate. In the development of the continuous platform the authors investigated the effects of four different variables: 1) mixers, 2) flow rates, 3) residence times and 4) stoichoimetry. Knowing that lithiation of the substrate was a relatively fast reaction, the authors rationalised that once the two input streams were completely homogenised then *n*HexLi would fully deprotonate the ketimine. Two different integration tees were identified as competent mixers, with the Koflo Stratos static tube mixer ultimately chosen. Encouraged by successful mixing results, the authors proceded to devise a scheme where a third and fourth pump were added to facilitate the Mannich-type reaction and an in-line quench. After optimisation, the designed system afforded a yield of 87% and a diastereoselectivity of 92:8 of **40** (Figure 36). Finally, the authors studied the effect of stoichiometry on the reaction where preliminary batch experiments were used as a foundation for the continuous flow process. Several flow runs showed that when equimolar amounts of all reagents were used only 64% conversion was observed. However, when 1.5 equivalent of nucelophile, 1.7 equivalent of *n*HexLi and 1.8 equivalent of methyl sulfonamide were employed optimal conversion was achieved. Additionally, the flow system removed the requirement for cryogenic reaction conditions and reaction temperatures between -10 ˚C and 1 ˚C offered optimal results. Disappointingly, the authors were met with a challenege when attempting to scale the reaction to kilogram scale. Clogging was observed, and the problem appeared to increase with a rise in temperature. A decomposition event was thought to occur at the point of *n*HexLi mixing with methyl sulfonamide at the increased temperature. To avoid this issue, the heat exchanges and micromixers were cooled to -20 ˚C which, when coupled with optimised flow rates and stoichiometry, enabled the reaction to be successfully run for over 1 hour with a constant conversion of 90-91%.

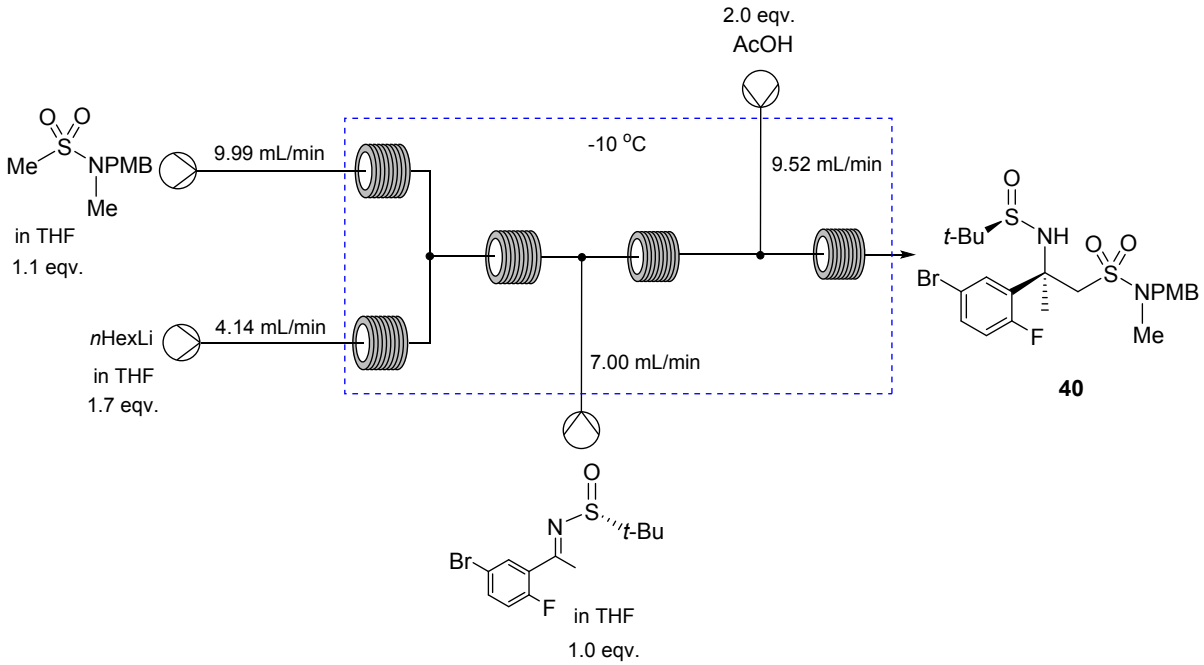

Figure 36 Continuous processing of the Mannich-type addition required in the manufacturing of Verubecestat

Work by Luisi and co-workers illustrates the use of *n*HexLi in a continuous flow system to generate a dilithium enolate intermediate pivotal in the synthesis of cyclopentyl mandelic acid (CPMA).[53] The authors describe a telescoped process in which *n*HexLi and phenylcyclopentylacetic acid are mixed in a coiled reactor at 20 ˚C for a residence time of 5 minutes yielding the dilithium enolate intermediate. The flow platform designed uses syringe pumps to feed the reagents to the system and a sample loop is used to deliver *n*HexLi to the system. The intermediate then progresses to meet molecular oxygen in a second coiled reactor at 20 ˚C to yield the desired product **41**, CPMA (Figure 37). The optimisation initially used a continuous flow set-up for each step of the synthesis independently. With the optimised parameters in hand, a telescoped process was examined, yielding a conversion of 57%, with a 44% isolated yield. Minor modifications to the system resulted in an increase in both conversion and isolated yield, 90% and 65% respectively. This process is superior to the traditional methods employed to access CPMA as the use of *n*HexLi and less than 10% O_2 in N_2 allows the platform to be considered industrially safe and scalable.

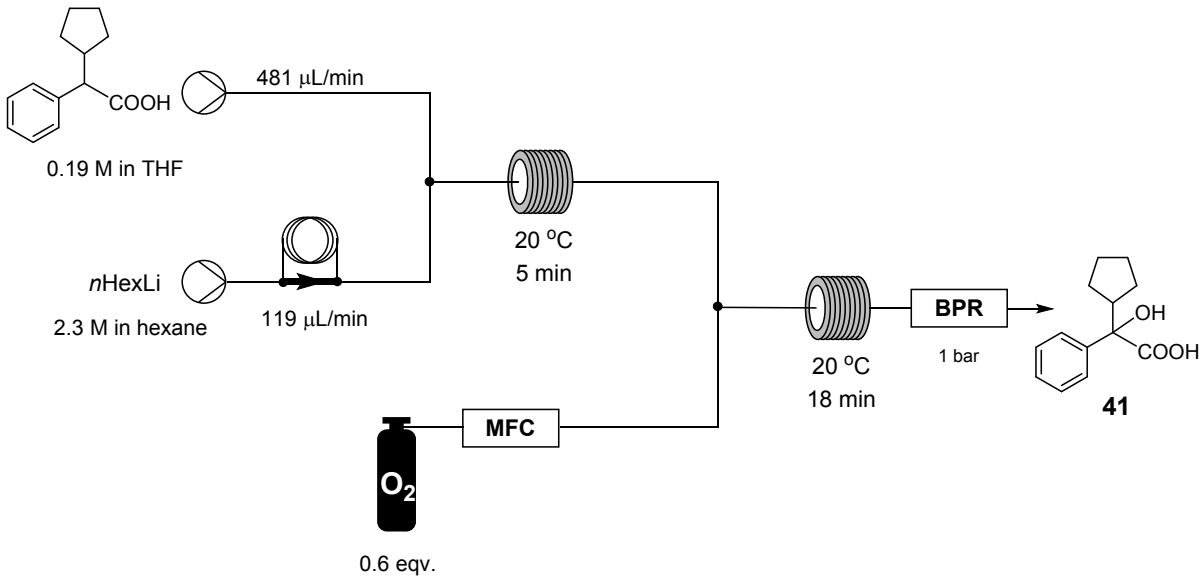

Figure 37 A continuous flow platform for *n*HexLi mediated α-lithiation and subsequent oxidation

Tertiary butyl esters are a commonly found moiety throughout APIs and natural products. Luisi and co-workers report a concise continuous flow system for the introduction of this functionality into various organic compounds.[54] Aryl and heteroaryl alkynes are reacted with *n*HexLi in a microfluidic system to perform direct *tert*-butoxycarbonylation. *n*HexLi is first reacted with the alkyne substrate, which is then progressed to meet a stream of $(Boc)_2O$ resulting in the generation of ester **42** in yields of 50-95% (Figure 38). This process proceeded at temperatures ranging from -40 to 20 ˚C. Syringe pumps fed reagents to the system where they were pre-cooled in P1, P2 and P3. The substrate and *n*HexLi were brought together in a T-mixer before reacting to generate the deprotonated species. The temperatures applied to the system were substrate dependent, with a wide variety of substrates being well tolerated.

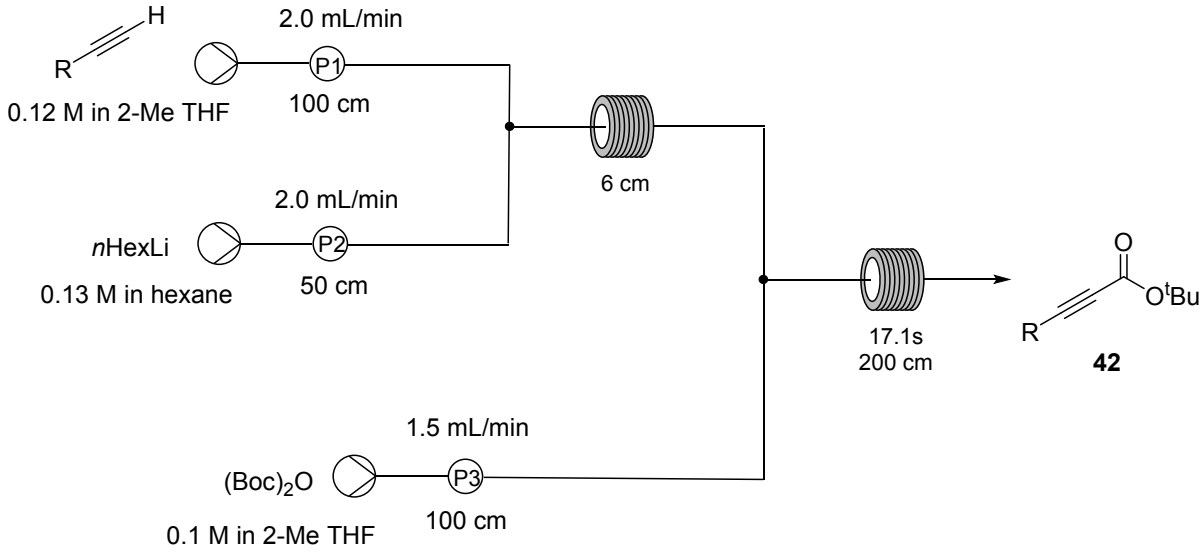

Figure 38 A continuous flow system to enable *tert*-butoxycarbonylation of aryl and heteroaryl substrates

Work by Bio and co-workers used *n*HexLi to facilitate the preparation of a chiral β-amino alcohol through asymmetric propargylation in flow.[55] The direct metalation of allene gas is a potentially attractive strategy for propargylation reactions. Allene is an inexpensive and readily available reagent but its use is accompanied by a serious safety concern. Furthermore, cryogenic conditions are required for the lithiation step. Continuous flow technology affords methodology where allene gas can be utilised efficiently for this reaction protocol. The requirement for cryogenic conditions can be eliminated on account of the improved heat transfer in flow technology. The use of an MFC allows gases to be accurately used in a continuous flow system. The authors found that allene gas could be rapidly dissolved as gas/liquid slugs in THF, by controlling the flow rate of the THF delivered by a HPLC pump and the MFC controlled allene gas. The deprotonation step was initially analysed by FlowIR, where the lithiated allene species appeared as a strong absorbance at 1864 cm^{-1}. The formation of the dilithiated allene species became apparent by the appearance of an absorption at 1900 cm^{-1}. This species proved problematic as it precipitated, resulting in clogging of the reactor, noticeable by a sharp increase in system pressure. Slow laminar flow and poor mixing causes a low allene versus *n*HexLi ratio which was postulated as the cause of this issue. This problem was rectified by simply increasing the amount of allene gas added to the system in combination with the use of high-speed spinning-motioned stir bars, which ensured sufficient mixing and prevented clogging. These modifications enabled the continuous synthesis of allenyl lithium at 0 ˚C for multiple hours. Further optimisation identified the most efficient chiral ligand, and necessary additive, to establish a continuous platform for asymmetric allenylzinc propargylation. The flow process began with the allene/THF dissolution meeting a stream of *n*HexLi to generate the allenyl lithium reagent. This was subsequently transmetalated with a chiral zinc complex (Zn*) to furnish a chiral allenylzinc complex, whose formation was monitored by FlowIR. This complex proceeded to meet a solution of enantiopure Boc-L-alaninal **43** in a 25 mL continuous stirred tank reactor (CSTR) at room temperature. The authors found that product d.r. was sensitive to the mode of mixing between the aldehyde and the allenylzinc chiral complex. The CSTR mixer was chosen as it produced optimal d.r. for of the reaction. This is outflowed to a 50 mL tubular reactor to create the desired overall residence time of 10.6 minutes at ambient temperature to provide for the asymmetric propargylation (Figure 39). This continuous set-up produced the desired β-amino alcohol **44** in 85% yield and a d.r. of 32:1 and a production rate of 15 g/h.

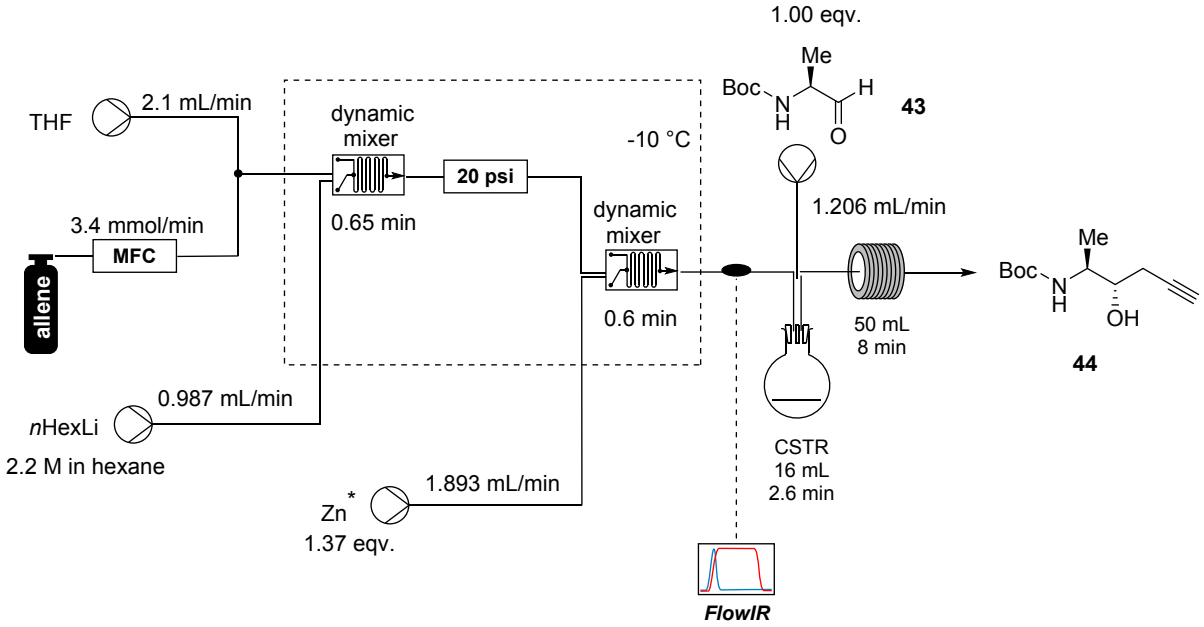

Figure 39 Continuous flow platform for lithiation of allene gas to facilitate the generation of homopropargyl β-amino alcohol

The final example of the use of *n*HexLi in continuous flow describes the scale-up of a robust lab-scale procedure to an industrial scale. A publication by Mleczko and co-workers reports the use of *n*HexLi and fluoroaromatic compounds to generate 2,3-difluorotoluene (DFT) **45** or 2,3-difluorobenzaldehyde (DFBA) **46** (Figure 40) respectively.[56] DFT is a useful intermediate for the synthesis of pharmaceuticals, electronics and in the agrochemical industry. However, the lithiated intermediate generated en route is a highly reactive species, known to participate in several runaway reactions. The paper uses preliminary microreactor technology (MRT) based laboratory experiments as a foundation for scaling DFT and DFBA synthetic processes. MRT was viewed as a preferable route to scale the process due to its superior heat transfer capabilities. Both synthetic routes have significant associated exotherms, leading to potential runaway reactions in a large-scale batch reactor. Thus, the laboratory studies with the fluoroaromatics were performed in a low temperature (LT) microreactor. The reactions were performed at a temperature of -45 ˚C with a throughput of 10 g/h. In these reaction runs, DFT **45** and DFBA **46** were successfully synthesised in yields of 95% and 90% respectively. The authors then repeated these experiments in an industrial standard LT unit. The LT unit used three parallel piston-membrane pumps to minimise pulsations in the continuous process. Temperatures were also measured directly in the product stream, downstream from the reaction modules. Due to the exotherm associated with the process step, the process required ~5 minutes of residence time to efficiently remove the heat produced, particularly in the challenging DFT route. In order to sustain stable operation during the DFT synthesis the throughput had to be reduced from 1.07 to 0.5 kg/h. Higher throughputs lead to runaway reactions in the second stage of the process. Using the optimised conditions in the LT unit gave a yield of 95% for both DFT and DFBA synthesis. Additionally, it was possible to scale both the DFBA and DFT processes by a factor 100 and 50, respectively, with no negative impact on performance. Overall, the continuous process was superior to the corresponding batch

process. Regioselectivity of 94% was achieved in the continuous process in contrast to 90% in the batch operation. Furthermore, through the MRT operation approximately 40 kg of product was synthesised in 24 hours using a total volume of 3 L. In batch mode, only 20 kg of product could be produced per 400 L batch in 24 hours. Finally, a more scalable temperature of -45 ˚C was required in the continuous flow process, unlike the -70 ˚C temperature necessary in batch mode.

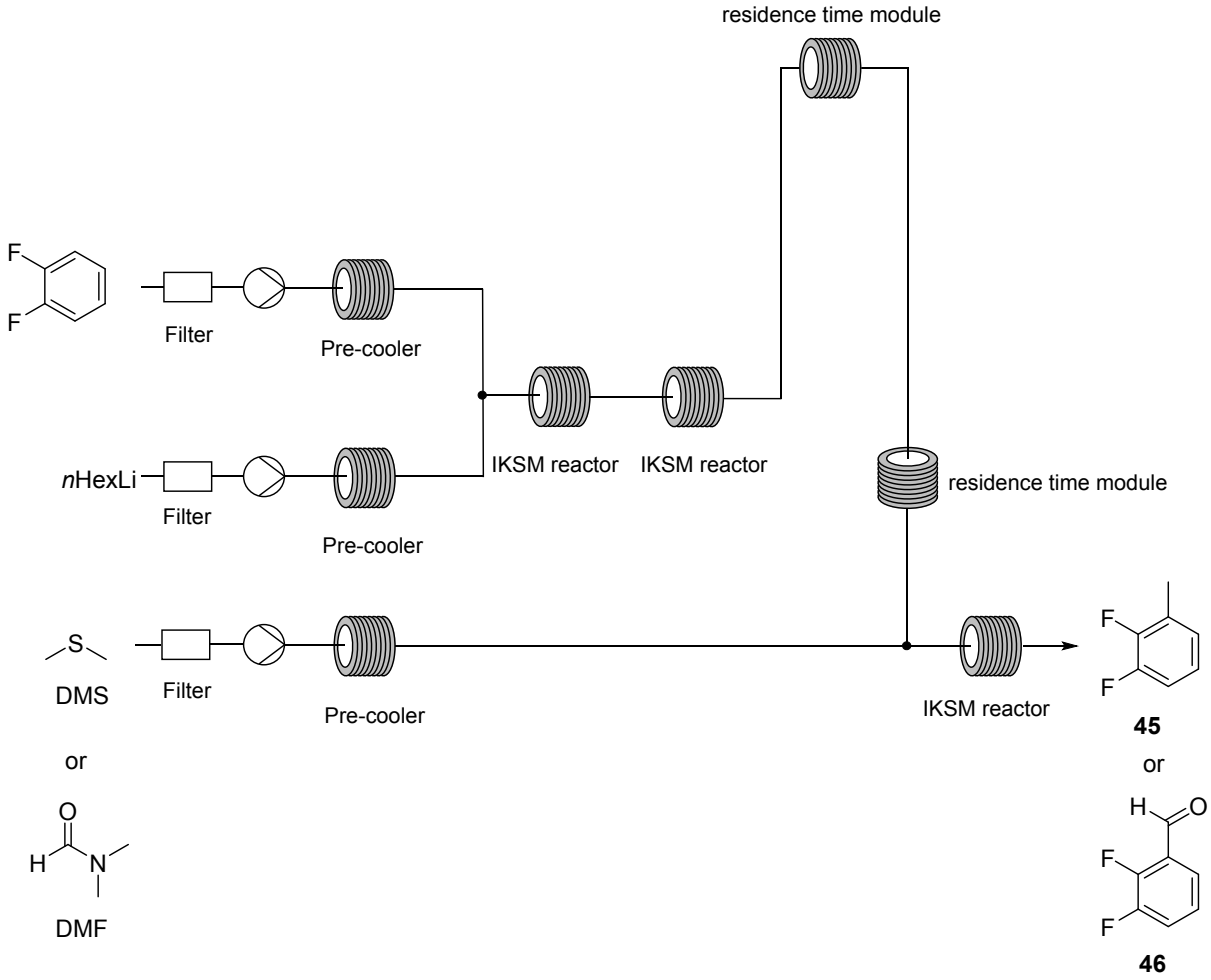

Figure 40 LT unit continuous processing of DFT and DFBA

Conclusion

Deprotonation chemistry using organolithium bases is a mainstay of organic synthesis. However, many organolithium reagents come with a non-ideal safety profile and typically, this type of chemistry is carried out at low temperature (often -78 °C). Thus, scale-up of these protocols in an industrial context is difficult. At the very least, direct synthetic routes, which prove highly efficient at small scale, are replaced by more convoluted ones on scale-up. Ultimately, predicted issues surrounding scale-up can lead to new chemistries and thus new molecular entities and associated biological activities, being unexplored.

Flow chemistry has the potential to avoid most of the pitfalls associated with organolithium chemistry in batch, through the use of highly efficient mass and heat transfer, precise control of residence times and mixing apparatus.

This review paper aims to underline the importance, and associated benefits, of continuous processing for the handling and employment of organolithium reagents in organic synthesis, paying specific attention to deprotonation chemistry. The papers cited herein demonstrate how cryogenic conditions are easier to control or can be eliminated in flow processes, leading to reduction in the number of synthetic steps, faster processing times, more selective reactions, higher conversions and improved safety profiles. Continuous flow chemistry has also allowed many unsuccessful or so-far-impossible batch mode reactions to be successfully performed.

Flow platforms offer variety within their systemic design where individual system modules can be interchanged for specific reaction control. Different pumps can be used for different reaction requirements. For example, on small scale, syringe pumps used alongside sample loops are often the chosen injection apparatus for organolithium reagents, due to their improved safety and chemical resistance profile. Furthermore, Process Analytical Technology (PAT) tools are becoming more commonly integrated in continuous processes to identify key parameters for reaction success, aiding the efficiency and scalability of a given process. Finally, flow enables efficient telescoping of reaction schemes. In simple, yet critically important examples, we see the generation of LDA *in situ*, which avoids issues around concentration and precipitation associated with the commercially available base.

All that said, it would be amiss to exclude the challenges still faced when using organolithium reagents in continuous flow. Thus, this review also highlights these problems, which include the persistent formation of precipitates, which leads to clogging of reaction systems. Importantly however, some strategies are emerging to alleviate this problem, such as the filtering of feed stock solutions, accurate temperature control and the development of clean-in-place techniques.

Additionally, certain elements of established small-scale organolithium batch chemistry, are still widely unexplored in flow. For example, powerful asymmetric processes involving lithium (aza)enolates,[57-60] have not been investigated in flow. Furthermore, flow chemistry offers the potential to re-engage with the use of *t*BuLi as a reagent. The safety profile of *t*BuLi often causes chemists and industrialist to avoid its use. However, *t*BuLi is a very useful reagent for many organic reactions,[10] and undoubtedly flow chemistry has the potential to add this reagent to our repertoire.

While flow chemistry is now considered a mainstream technology in Pharma,[61] the examples depicted in this review showcase how organolithium-base-mediated methodologies, often deemed difficult to scale-up due to their safety profile and heat transfer properties, can be cleanly handled and scaled in flow.

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