Continuous Flow Generation of Highly Reactive Organometallic Intermediates: A Recent Update

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Abstract

Reactive organometallic intermediates present a distinct opportunity for the creation of novel carbon-carbon and carbon-heteroatom bonds. Whereas their utility in synthesis is well-established, the thermal sensitivity of these species often imposes the requirement for specific reaction conditions, including strict control of reaction temperatures, concentrations, and use of additives. Moreover, their strong reactivity can pose challenges in achieving the desired selectivity. Since pioneering works in the 2000s, the advent of flow microreactor technology has revolutionized this field, expanding the possibilities of reactive organometallic intermediates within synthetic chemistry. In this review, we provide an overview of the recent advancements in this dynamic area, focusing on breakthroughs that have emerged within the past four years.

Introduction

Initially met with scepticism, flow chemistry has, after a physiological induction period, undeniably reshaped the landscape of organic chemistry, offering fresh opportunities for the synthetic community [1]. Across various domains of organic synthesis, including photo- and electrochemistry [2,3], heterogeneous catalysis [4], high-temperature/pressure processes [5], and more, the benefits of flow chemistry have been harnessed to enhance mass and heat transfer, improve safety [6-8], increase reaction efficiency, reduce waste, enhance scalability [9,10], and improve reproducibility [11,12]. However, the impact of continuous flow chemistry extends beyond the implementation of conventional batch procedures. Indeed, it has also boosted the

discovery of novel reaction pathways and retrosynthetic disconnections that are arduous or even impossible to explore using conventional batch processing.

Reactive organometallic intermediates, as unique tools for shaping carbon-carbon and carbon-heteroatom bonds in organic molecules, are a prime example. Despite their extensive use in synthesis, the high reactivity of these species is inextricably linked to their thermal instability, often necessitating specialized reaction conditions and cryogenic temperatures for their successful generation and use in synthesis [13]. Within the chemistry field involving these reactive organometallic intermediates, continuous flow microreactor technology has brought about a revolution. Since pioneering work of Yoshida in 2000s, the fusion of flow microreactor technology with the chemistry of reactive organometallic intermediates has marked a significant milestone in organic synthesis. Yoshida introduced the concept of space integration, relying on precise control of residence time, i.e., the time between mixing of reaction components to generate the intermediate and addition of the reaction partner [14, 15]. By reduction of the flow apparatus volume, residence times could be reduced to milliseconds, enabling the generation and rapid quenching of short-lived intermediates (with lifetimes far below <1 second) before their decomposition. This innovative approach, characterized by the fast generation and immediate utilization of highly reactive intermediates within an extremely brief and defined timeframe, was coined as *"flash chemistry"* (Figure 1). This approach represents a novelty compared to classical batch procedures as traditionally, when handling labile compounds, *in situ* (or internal) quenching sequences were employed. However, in some cases, side-products stemming from competing reactions between the reaction partner and reagents used to generate the intermediate could arise. Additionally, cryogenic temperatures were often necessary to limit the intermediate decomposition. With the advent of flow microreactor technology, short-lived organometallic intermediates can be generated in the absence of the reaction partner and/or at more sustainable reaction temperatures [16–21].

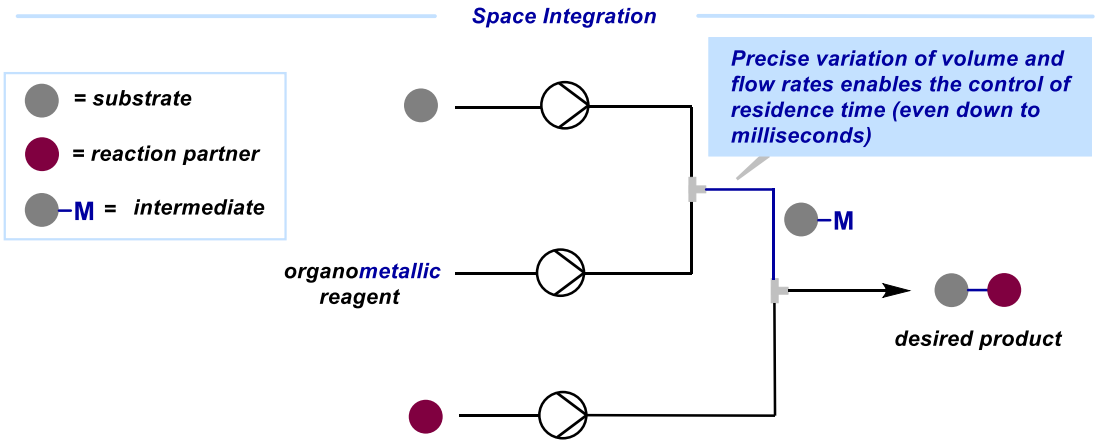


Figure 1. Schematic representation of the generation of unstable organometallic intermediates in flow microreactors

Handling extremely fast reactions, where the reaction rate exceeds the rate of diffusion (Damköhler number Da > 1, where Da is defined as the reaction rate divided by the mass transport rate), makes reaction mixing a crucial factor for success. Microreactors thus enable rapid mixing, mitigating the occurrence of side-reactions. Moreover, the utilization of flow-microreactor technology expands the possibilities for achieving protecting-group-free synthesis with organometallic compounds [22]. Furthermore, the merging of flow microreactor technology with organometallic chemistry can also have an impact on the sustainability of synthetic processes. This is achievable by enhancing product selectivity, thereby reducing waste, eliminating the need for energy-intensive cryogenic cooling, promoting protection-group-free synthesis to enhance atom and step economy, and facilitating on-demand synthesis, which ultimately reduces energy consumption during transportation [23]. To demonstrate and highlight the above-mentioned advantages, this review collates, compares, and critically discusses recent advancements in the field of continuous flow generation of highly reactive organometallic intermediates that have emerged over the past four years in detail. We have aimed to acknowledge significant contributions in this field, recognizing that it is not feasible to discuss all work within the scope of this review.

Our review is structured as follows:

1. Generation of organolithium reagents

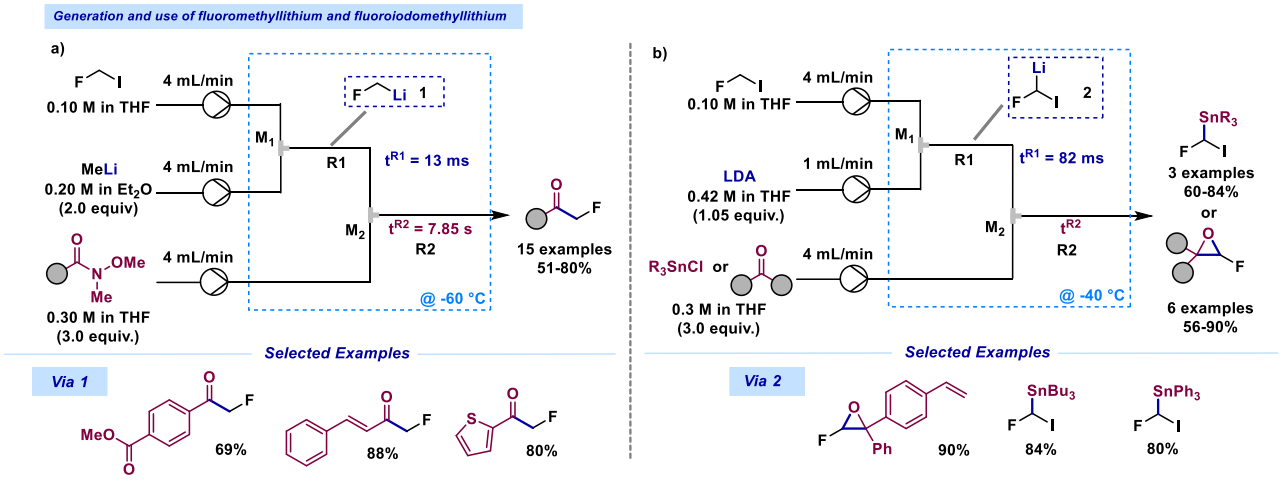
Organolithium compounds, initially documented over a century ago, continue to pique the curiosity of synthetic chemists, stimulating their creativity in the precise construction of carbon-carbon and carbon-heteroatom bonds [24]. The lithiation of organic compounds can be achieved by different mechanisms, such as halogen/lithium exchange, oxidative addition of lithium metal, directed lithiation with a lithium base, or addition of organolithiums to unsaturated systems (carbolithiation). Despite their well-known synthetic

utility, organolithium compounds require special precautions during handling due to their moisture-sensitivity. Furthermore, the high reactivity of organolithiums can generate selectivity issues and an accurate control of reaction conditions is required.

1.1 Generation of lithium carbenoids

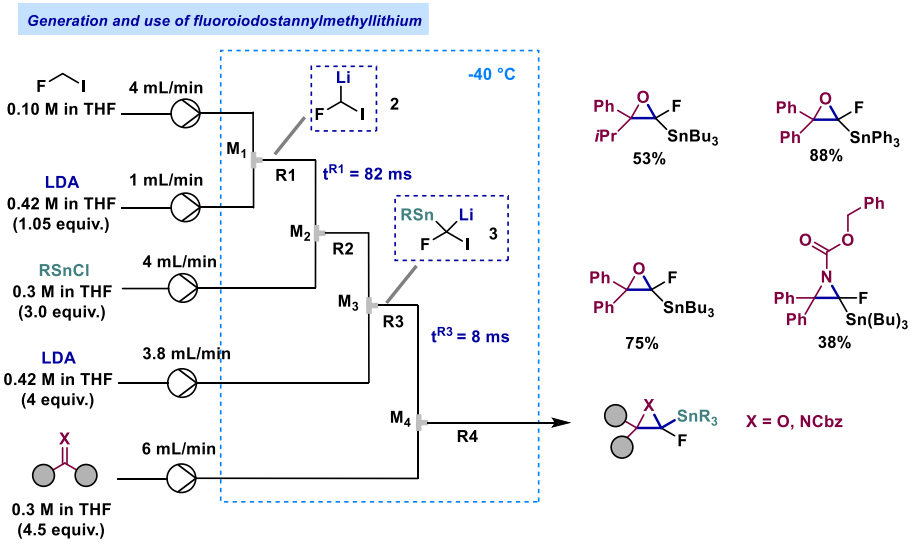
Lithium carbenoids are species simultaneously bearing an electropositive lithium atom and a nucleofugal halogen atom on the same carbon center. These organometallic intermediates have emerged as useful reagents since seminal works from Köbrich [25]. In spite of their valuable synthetic applications, these highly reactive intermediates are prone to undergo α-elimination, leading to the formation of putative carbene species. Pace and De Kimpe have described this temperature-dependent decomposition as the Achilles' heel of these lithium intermediates [26]. Consequently, to achieve a successful homologation reaction, cryogenic conditions (e.g., -78 °C) and *in situ* quenching (or Barbier-type protocol) are essential prerequisites. In recent years, owing to the substantial synthetic potential of lithium halomethyl carbenoids, multiple research groups have embarked on exploring flow chemistry to expand the scope of applications for these fleeting intermediates [27]. The research group led by Luisi has shown a keen interest in developing fluorohomologation strategies based on fluorinated lithium carbenoid in the past few years [28–31]. These approaches to fluoroalkylation predominantly relied on Barbier-type or *in situ* quenching conditions to mitigate the thermal instability associated with fluorinated lithium carbenoids. However, in some cases, the generation of these intermediates in the presence of the electrophilic partner (*in situ* quenching) hindered the process's efficacy. This was attributed to potential partial reactions between the electrophilic partner and the metalating reagent, leading to less efficient generation of the desired metalated intermediate. To address this challenge, Luisi and Nagaki devised a novel approach to harness the potential of flow technology in taming fluorinated methyllithium carbenoids under external quenching conditions [32]. In this work, Luisi and Nagaki employed a specialized flow microreactor system comprising two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) (Scheme 1). The procedure involved mixing fluoroiodomethane with the lithiating reagent (MeLi or LDA) in M1, generating the carbenoid in R1. Subsequently, the carbenoid was quenched with the electrophile solution in M2 and R2, yielding the desired product. By adjusting factors such as temperature and the length of R1, the researchers estimated the lifetimes of fluoromethyllithium **1** and fluoroiodomethyllithium **2**. For instance, **1**, derived from CH_2FI and MeLi, was produced at a temperature of -60 °C with a brief residence time (t^{R1}) of 12.9 ms (Scheme 1a). To assess the capabilities of flow microreactor technology, Weinreb amides were selected as model electrophilic partners, resulting in significantly higher yields of α-fluoroketones compared to traditional batch methods. Interestingly, the more stable nature of flouroiodomethyllithium **2**, compared to fluoromethyllithium **1**, was observed. Indeed, **2** was generated at -40 °C using a t^{R1} of 82 ms, and it was effectively trapped with chlorostannanes, and ketones as electrophiles (Scheme 1b). This methodology enabled the utilization of higher temperatures relative to the established

batch protocol, also allowing the use of challenging electrophiles unsuited for the internal quenching procedure.



Scheme 1. External quenching of short-lived fluorosubstituted methyllithiums

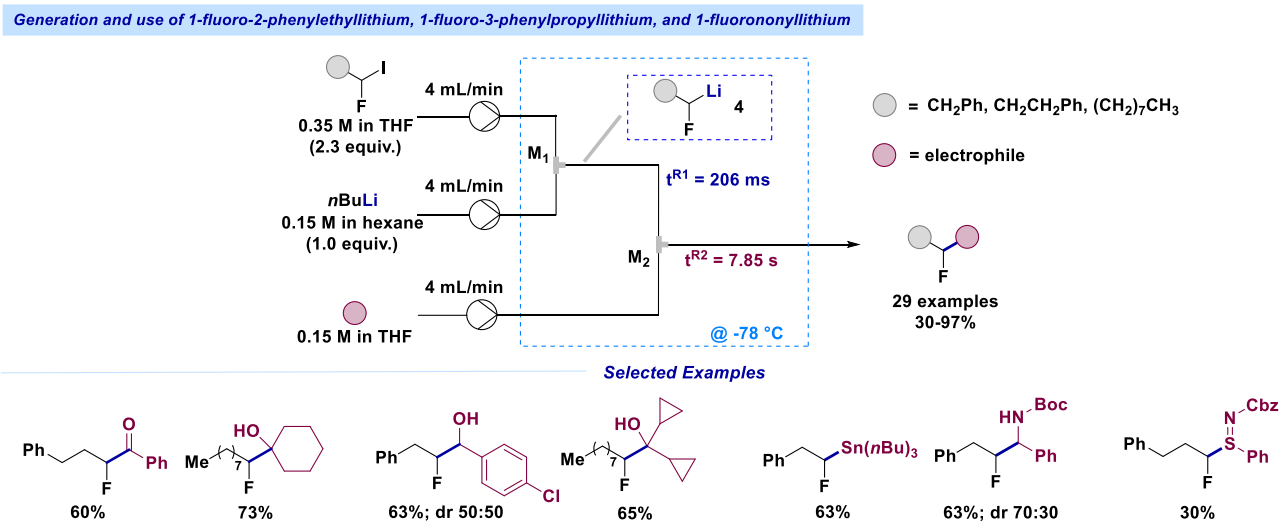
Furthermore, within the same study, Luisi and Nagaki detailed a "one-flow" strategy for synthesizing novel fluorinated three-membered heterocycles via a double lithiation/trapping sequence (Scheme 2). Employing a more complex flow setup, the fluoroiodostannanes produced in R2 underwent further deprotonation. The resulting fluoroiodostannylmethyllithium **3** was subsequently quenched with ketones in M4, leading to the formation of intriguing tetrasubstituted fluoro stannylated epoxides. Notably, the utilization of an imine as the electrophile led to the production of tetrasubstituted fluoro stannylated aziridines.



Scheme 2. Integrated flow microreactor system for the generation and use of unprecedented fluoroiodostannylmethyllithium

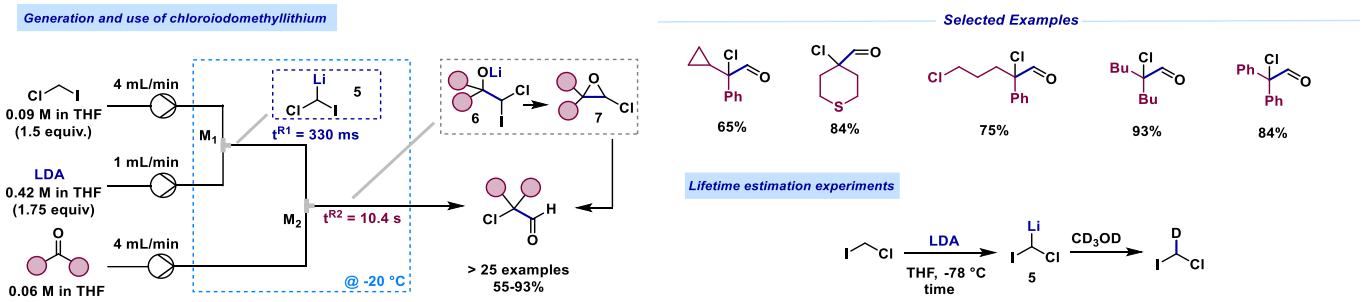
As a continuation of the study on fluorinated lithium carbenoids, Luisi and co-workers also described the lithiation of geminal fluoroiodoalkanes by lithium-halogen exchange reaction [33]. The authors initiated their

investigations by assessing the I-Li exchange in batch conditions. Whereas the internal quenching approach worked effectively with non-enolizable ketones such as benzophenones (90% isolated yield of the desired product), poor outcomes were observed with aldehydes, Weinreb amides, and enolizable ketones as electrophilic quenching partners. Attempts at external quenching in batch resulted in decomposition products, confirming the lability of the intermediate. Faced with these challenges, the authors shifted their focus to transferring the protocol into a flow setup, shown in Scheme 3. Operating at -78°C and with a residence time of 200 ms allowed the lithium-iodine exchange to complete before mixing of the carbenoid **4** with the Weinreb amide to afford the product in 71% yield. Conversely, shorter residence times and higher temperatures led to incomplete lithiation, resulting in co-existence between internal and external quenching regimes, leading to an unsatisfactory outcome. With the optimized parameters established, the authors undertook the monofluoroalkyl functionalization of a wide range of electrophiles, such as sulfinimidate esters, chlorostannanes, and chlorosilanes, enabling access to compounds that were previously challenging to synthesize (Scheme 3).



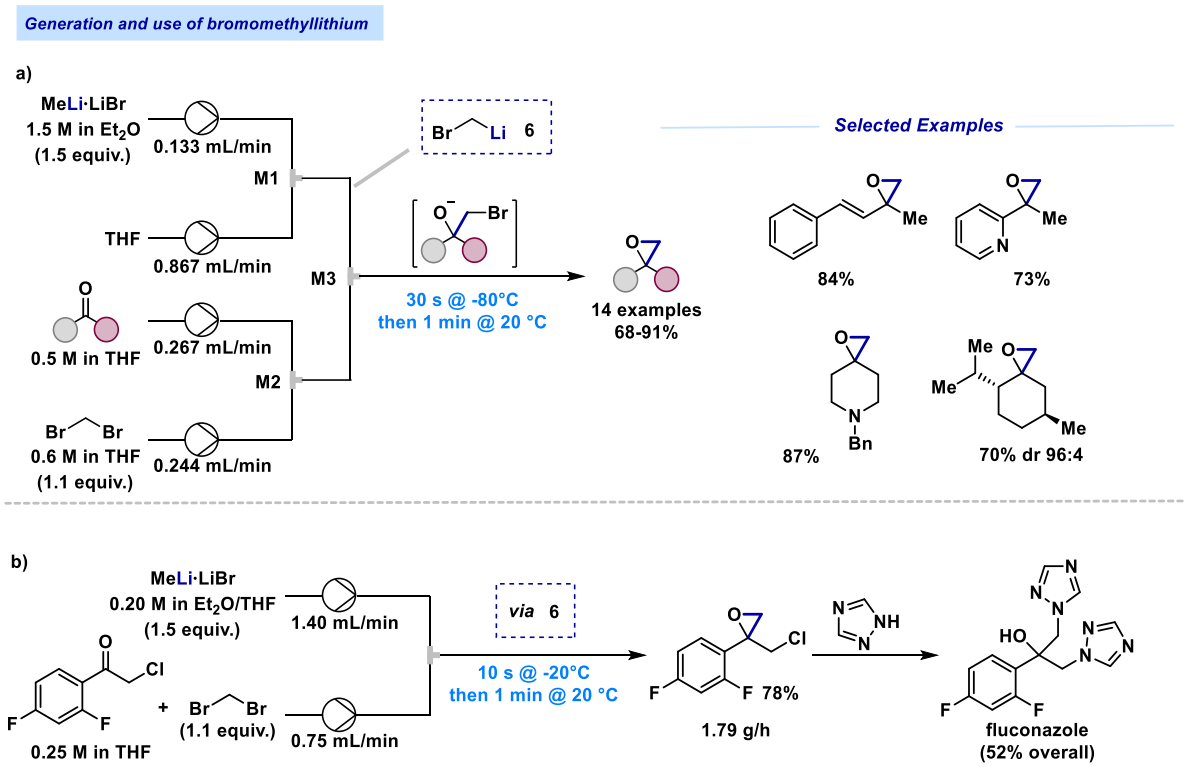
Scheme 3. Use of fluorohaloalkanes in nucleophilic fluoroalkylation chemistry

The same group recently reported the straightforward synthesis of α-chloroaldehydes, starting from chloroiodomethyllithium **5**, derived from deprotonation of chloroiodomethane, and ketones (Scheme 4) [34]. The proposed reaction mechanism encompasses the nucleophilic addition of a lithium carbenoid to ketones producing lithium alkoxide **6** which undergoes intramolecular substitution to afford epoxide **7**. Subsequent spontaneous Meinwald-type epoxide-aldehyde isomerization furnishes α-chloro aldehydes bearing quaternary centers. The optimized conditions shown in Scheme 4, which included detailed lifetime estimation experiments through deuterium-quenches, were employed to investigate the scope of the reaction. The method was successfully applied to di(hetero)arylketones, outperforming the batch internal quenching procedure. Notably, when alkylarylketones were employed as electrophiles, an acidic treatment was required to facilitate the chloride-1,2-shift (Scheme 4).



Scheme 4. Flow microreactor technology for taming highly reactive chloroiodomethyllithium carbenoid

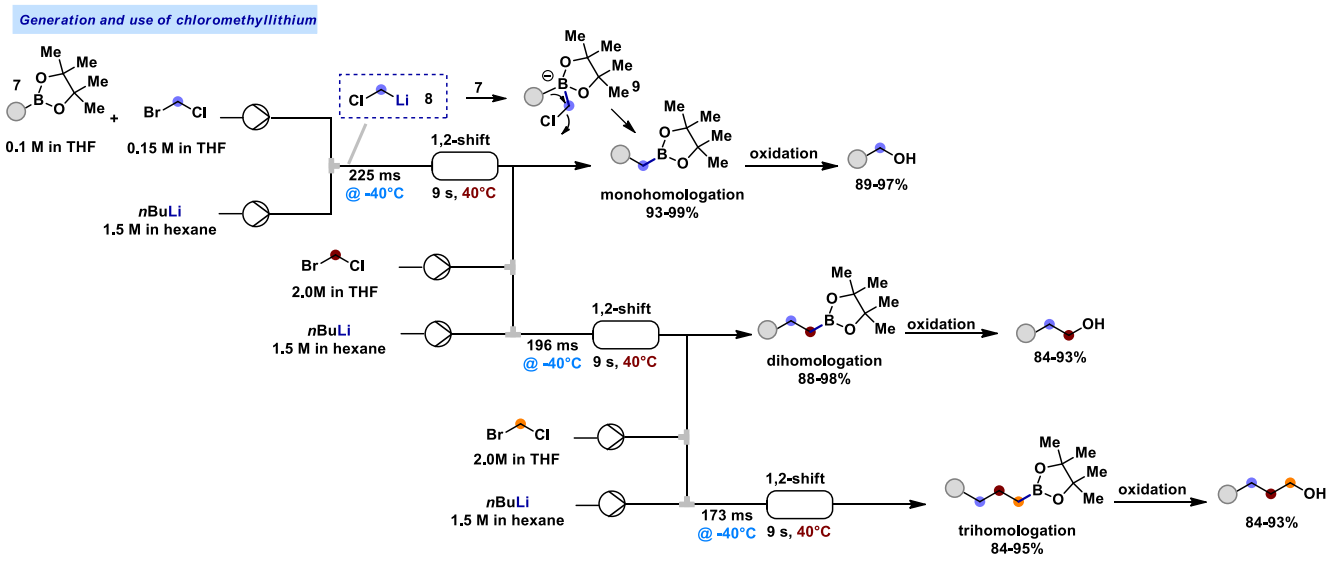
In a related protocol, Kappe and colleagues describe the efficient utilization of continuous flow microreactors in the synthesis of terminal epoxides, employing bromomethyllithium **6**, derived from dibromomethane, and various ketones using an internal quenching approach [35]. Unlike in Luisi's protocol, further rearrangement is not observed. MeLi•LiBr was found to be the optimal reagent for lithium-bromine exchange in preliminary batch investigations, using acetophenone as a model electrophile. The procedure was then transferred into a flow system consisting of PTFE tubing and T-mixers. A 1.5 M solution of MeLi•LiBr in diethyl ether was initially further diluted with THF to prevent clogging. The resulting solution was combined in M3 with a mixture of ketone and dibromomethane. The reactor unit was maintained at - 80°C for 30 s and subsequently warmed at 20°C for 1 min affording the desired epoxides in up to 91% yield. Generally, better results were obtained with electron-rich ketones in comparison to electron-poor ones. The procedure was also applied successfully to aliphatic and heteroaromatic electrophiles, and remarkable chemoselectivity was observed when employing *α,β*-unsaturated compounds, esters and protected amines as electrophiles. The applicability of this protocol was demonstrated with the synthesis of a fluconazole key intermediate (Scheme 5b). The key epoxide was produced on a 34 mmol scale for 3 uninterrupted hours, and directly used in a reaction with 1,2,4-triazole, affording anti-fungal agent fluconazole (5.4 g, 52% yield in two synthetic steps).



Scheme 5. Addition of *in situ* generated bromomethyllithium to ketones towards terminal epoxides

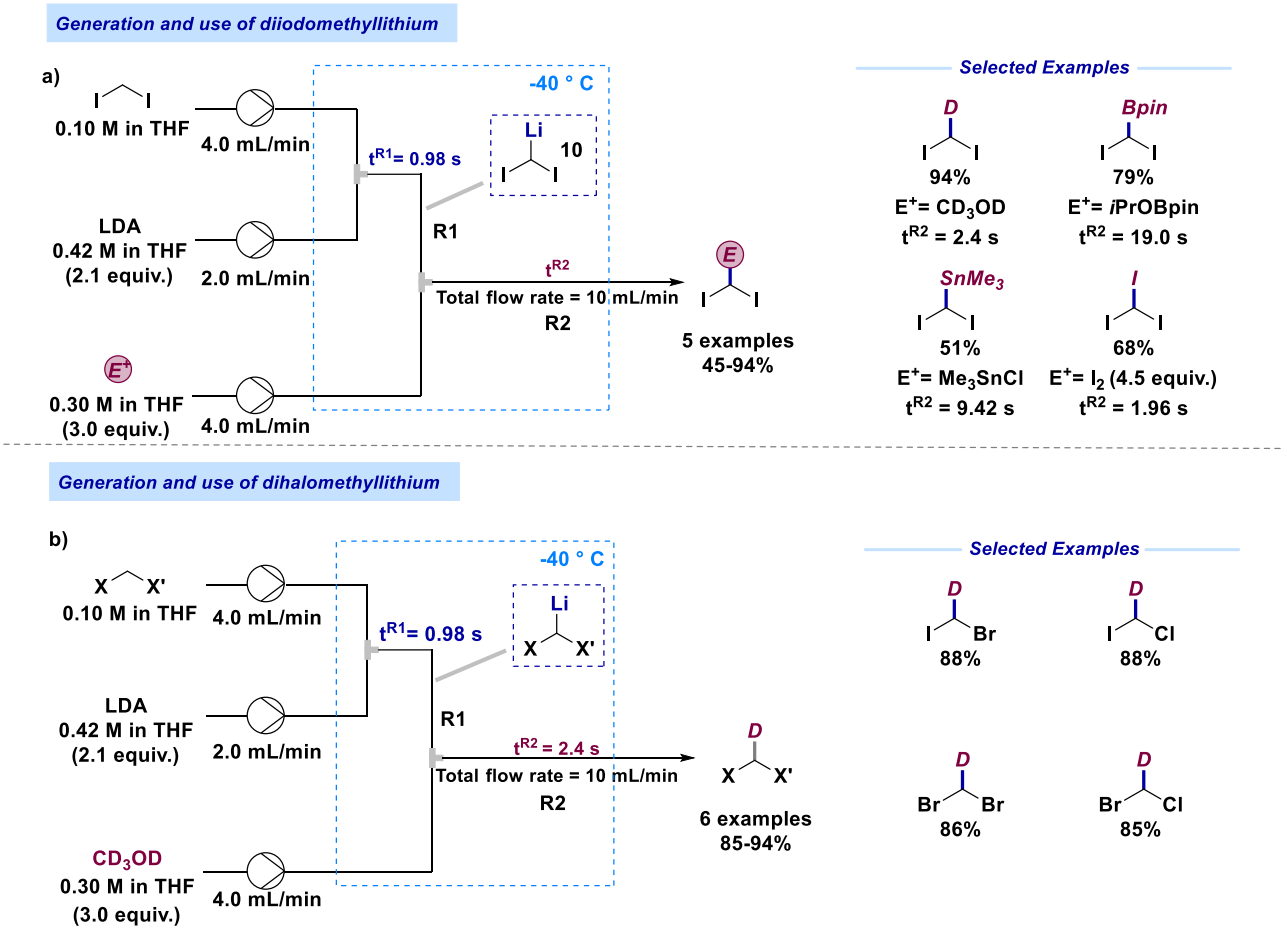
Kirschning recently reported a continuous flow version of the Matteson reaction to achieve iterative homologation reactions of terpenes (Scheme 6) [36]. This approach hinges on the generation of a highly unstable chloromethyllithium **8**, formed by treating chlorobromomethane with *n*BuLi, which subsequently reacted with a boronate **7**. The resultant adduct undergoes the Matteson rearrangement, culminating in the synthesis of the desired homologated boronate ester. Optimization of the reaction was divided in two sequential steps: (1) the generation and trapping of the carbenoid to give the boronate complex **9** and (2) the 1,2-aniotropic rearrangement of the ate complex in batch. Specifically, a solution of boronate and chlorobromomethane was mixed with a *n*BuLi solution in a T-shaped junction and passed through a tubular reactor. The reaction mixture was collected in a flask and subjected to heating, enabling the 1,2-aniotropic shift. The use of residence time between 200 to 300 ms and temperatures between −40 and 30 °C gave access to the homologation product with 83% yield. The authors subsequently replaced the T-mixer with a helical static mixer consisting of eight helical mixing elements that rotate in alternating left and right directions to significantly enhance speed and efficiency of mixing. This modification resulted in 99% yield of the homologated product. In the optimization of the second step, the use of 40 °C as reaction temperature and residence time of 9 s were found to be suitable conditions to achieve the aniotropic rearrangement in flow. By incorporating additional microfluidic units to the setup, the authors designed multiple homologations of terpene-based boronic esters. Indeed, the homologated product can be flowed directly into a second flow

device where a consecutive homologation step occurred. Furthermore, alcohols were produced from the corresponding boronate esters using a separate oxidation module.



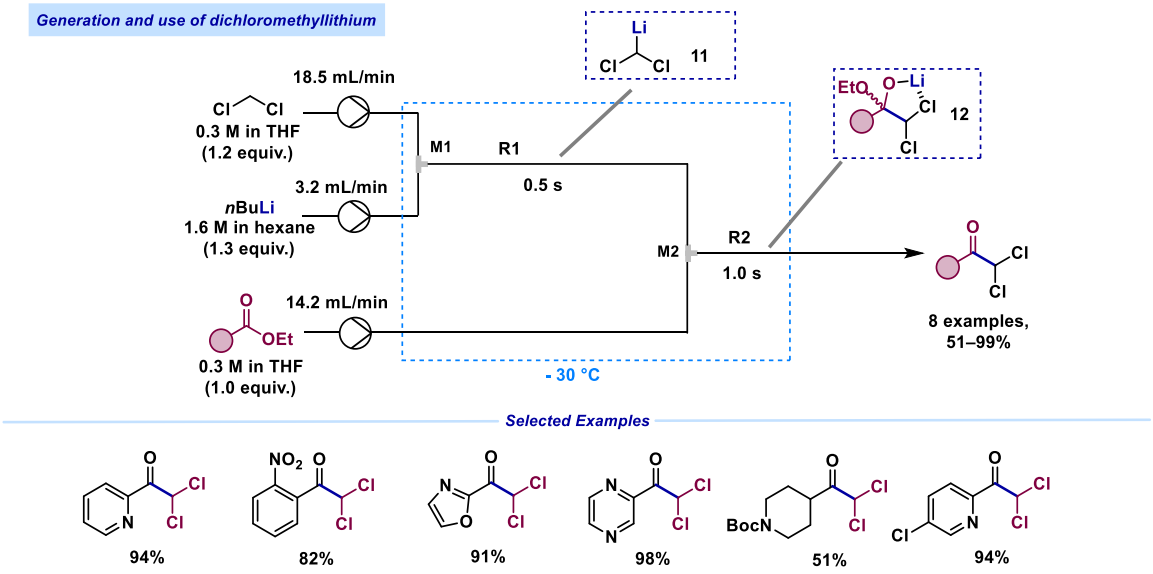
Scheme 6. Matteson reaction under continuous flow conditions

Recently, Nagaki reported the monodeuteration of various dihalomethanes through a deprotonation-deuteration sequence (Scheme 7) [37]. This methodology offers enhanced selectivity and yields through the external quenching of these transient intermediates compared to batch. In batch, both internal quenching and external quenching strategies did not provide the desired monodeuterated product in satisfactory yields. To overcome these challenges, the process was transferred into a continuous-flow apparatus, comprising two micromixers and two microreactors. Performing the reaction at -40° C and using a residence time in R1 (t^{R1}) of 0.98 s, the desired monodeuterated product was afforded in 94% yield. Running the process for 18 min afforded a gram scale amount of monodeuterated product (1.51g, 71% yield). The authors also showcased the functionalization of the diiodomethyllithium **10** using various electrophiles, such as *i*PrOBpin, trimethylstannylchloride, trimethylsilyltriflate, and molecular iodine (Scheme 7a). Monodeuteration and functionalisation of other symmetrical and unsymmetrical dihalomethanes was also evaluated, applying the external quenching conditions previously defined for diiodomethane (Scheme 7b).



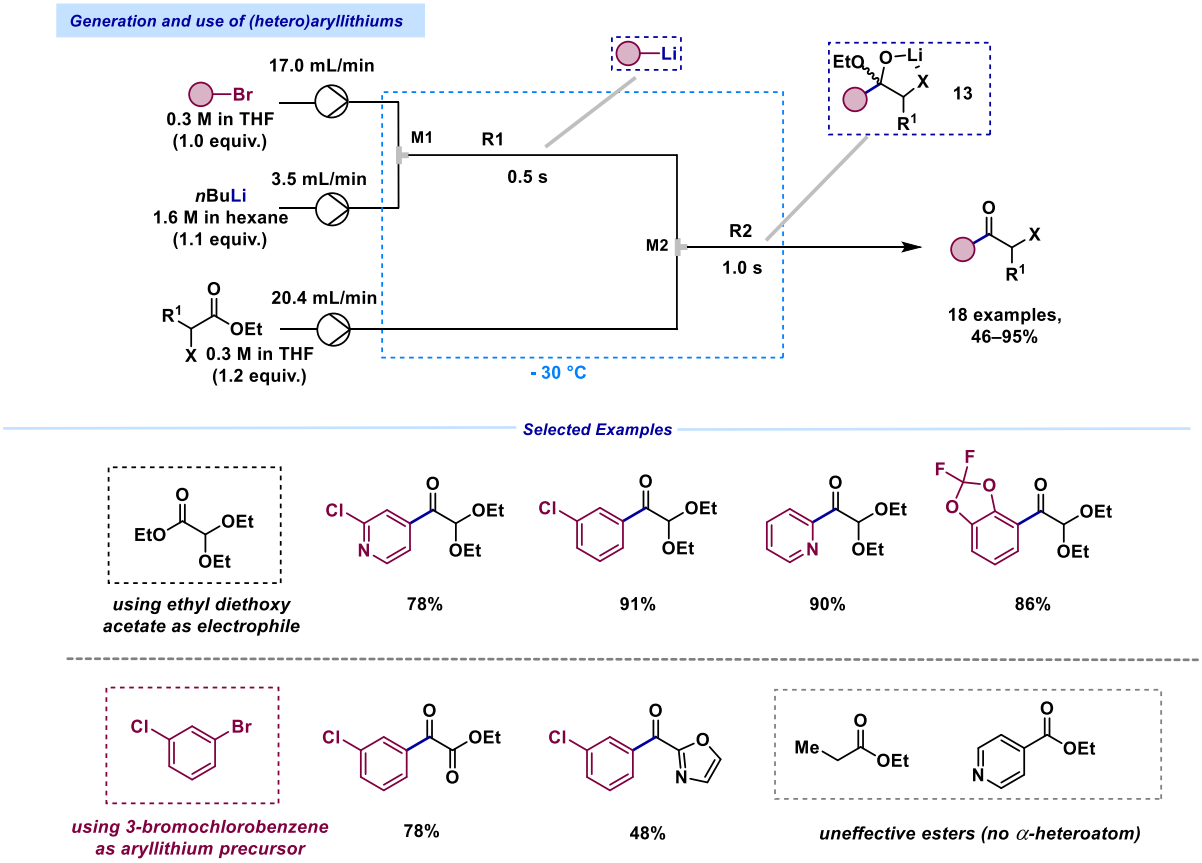
Scheme 7 a) Generation and functionalization of diiodomethyllithium under external quenching conditions; b) monodeuteration of different dihalomethanes

Sedelmeier and co-workers recently demonstrated the compatibility of flow microreactor technology with the needs of multigram-scale processes (Scheme 8) [38]. In particular, they developed a flow protocol for the generation of short-lived dichloromethyllithium **11** and its subsequent electrophilic quenching with aldehydes, yielding α,α'-bis-chloro carbinols [39]. Further developing this line of research, the group explored the addition of this reactive intermediate to esters aiming to synthesize glyoxal derivatives. Such intermediates serve as crucial building blocks for the preparation of medicinally relevant heteroaromatic compounds, including pyrazines, quinazolines, 1,2,4-triazines, oxazoles, thiazoles, imidazoles, and more [40]. Dichloromethyllithium **11** was generated by mixing dichloromethane with a solution of *n*BuLi in hexane, and then instantaneously quenched in-line with esters in M2 and R2, with a total residence time of only few seconds. The resulting mixture was directly quenched in a semi-batch manner by addition into a solution of aqueous acetic acid at room temperature, yielding the desired α,α'-bis-chloro ketones. The reaction proceeds *via* a putative stabilized tetrahedral intermediate **12,** preventing the formation of the undesired tertiary alcohol.



Scheme 8. Synthesis and utilization of dichloromethyllithium under continuous flow

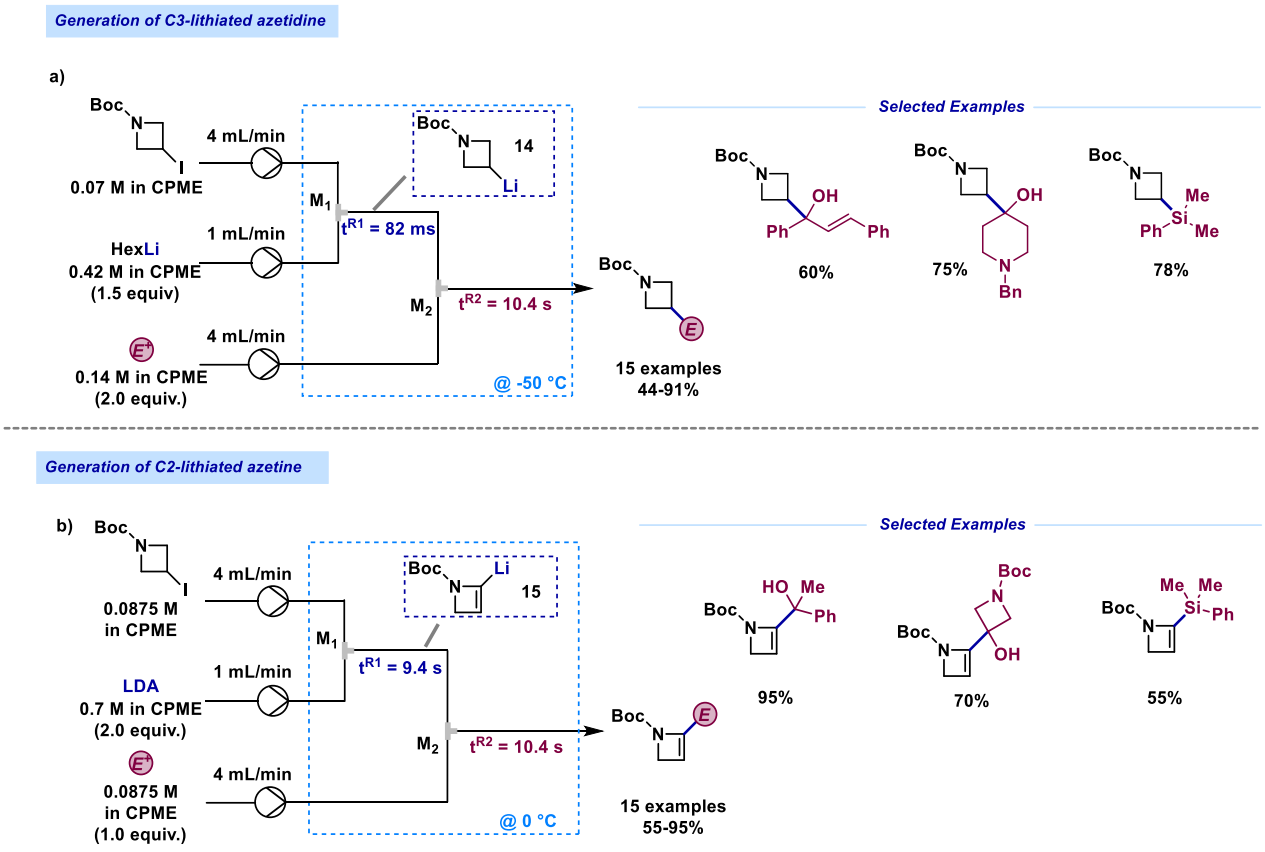
In the same study, the authors also detailed the high-yield synthesis of various keto-acetals by addition of (hetero)aryllithiums to ethyl diethoxy acetate and other ester derivatives (Scheme 9). In line with their previous report, the selectivity towards the mono-addition product was attributed to the stabilization provided by a lithium chelate of the tetrahedral adduct **13**. This suggestion was confirmed as exclusively tertiary alcohols were obtained from esters lacking an α-heteroatom due to their inability to stabilize the suggested tetrahedral intermediate.



Scheme 9. Generation of (hetero)aryllithiums and instantaneous in-line quenching with esters as electrophiles

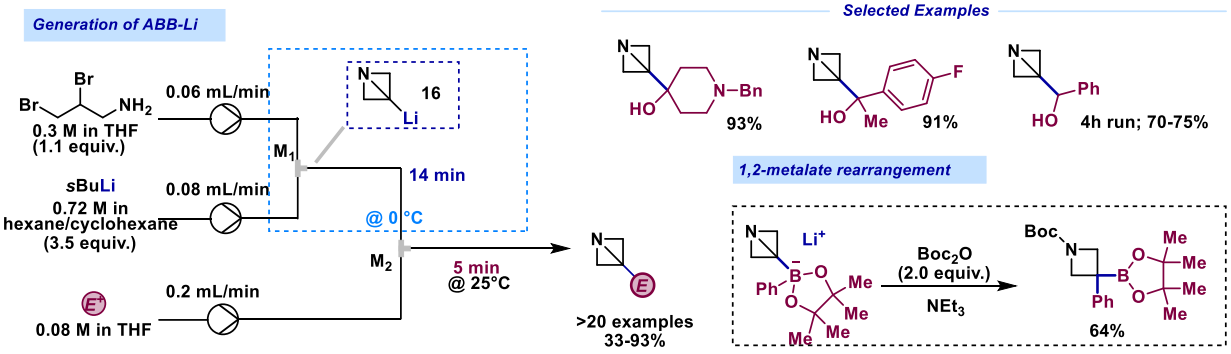
1.2 Lithiation of non-aromatic (hetero)cycles

In addition to halogenated aromatics, also non-aromatic (hetero)cycles can be lithiated using flow technology. In 2021, Luisi reported a divergent regioselective lithiation of 3-iodo-1-Boc-azetidine, dependent on the choice of lithiating reagent (Scheme 10) [41]. Specifically, azetidine **14** was exclusively formed *via* lithium-iodine exchange upon treatment of the starting material with a solution of hexyllithium. Optimal outcomes were obtained by conducting the reaction at -50 °C, utilizing 1.5 equiv. of the organolithium and adopting a residence time of 82 ms for the metalation step (Scheme 10, a). In contrast, subjection of the same starting material to LDA, promoted the exclusive formation C2-lithiated azetine **15** through an elimination/lithiation sequence. Leveraging a similar flow apparatus, a range of diversely 2-functionalized azetines were prepared in good to excellent yields (Scheme 10, b). In both cases, the developed flow protocol delivers superior results compared to batch protocols.



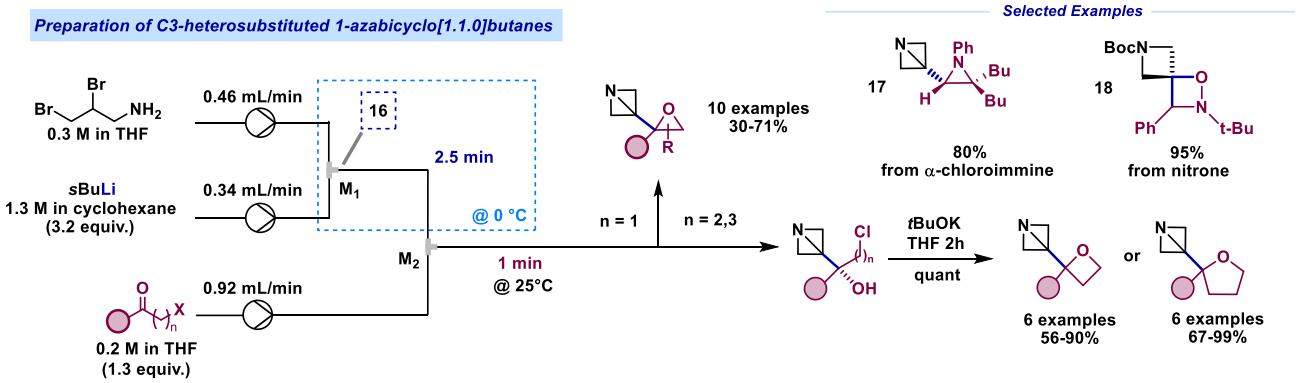
Scheme 10. Continuous flow generation of a) C3-lithiated azetidine and b) C2-lithiated azetine

Over the past few years, there has been a renewed interest towards the synthesis, functionalization, and strain-release reactions of 1-azabicyclo[1.1.0]butanes [42, 43]. Luisi and Kappe recently reported the first telescope sequence of preparation, lithiation and electrophilic trapping of 1-azabicyclo[1.1.0]butane (ABB) in a continuous flow apparatus with two reactors operating at different temperatures (Scheme 11) [44]. Notably, using a residence time of 14 min at 0°C for the generation and metalation of ABB, and a residence time of 5 min for the electrophilic trapping, the desired product was obtained in 92% yield. When the transformation was performed in batch at 0 °C, a modest 50% yield was observed. This demonstrates that the utilization of flow technology enables precise control of reaction variables, allowing operations at elevated temperatures while maintaining enhanced safety conditions and superior performance compared to batch mode. A broad scope utilising a range of electrophiles was reported, demonstrating a remarkable functional group tolerance. Upon using phenyl pinacolboronate as electrophile, the resulting funtionalized-ABB underwent strain release in presence of Boc_2O in a basic medium. The 1,2-boron to carbon migration of the phenyl group, afforded the corresponding functionalized azetidine in 64% yield.



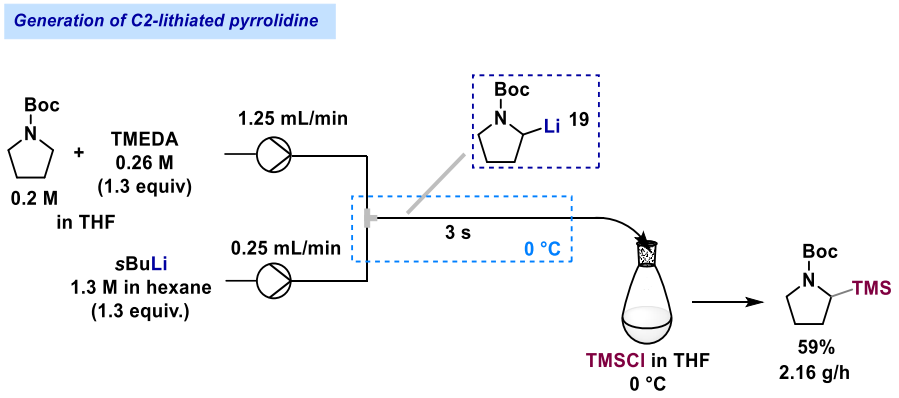
Scheme 11. Continuous flow generation, lithiation and electrophilic functionalization of 1-azabicyclo[1.1.0]butanes

More recently, Luisi and co-workers expanded the scope of this methodology reporting the trapping of lithiated ABB **16** with α-, β- and γ-chloroketones in a flow reactor (Scheme 12) [45]. After spontaneous or base-induced intramolecular cyclization, a range of ABBs bearing 3-, 4- and 5-membered oxygenated rings as C3-substituents were obtained (Scheme 14). Interestingly, the same approach was extended to the use of α-chloroimines and nitrones as electrophilic partners, obtaining aziridine-ABB motif **17** and spirocycle **18**.



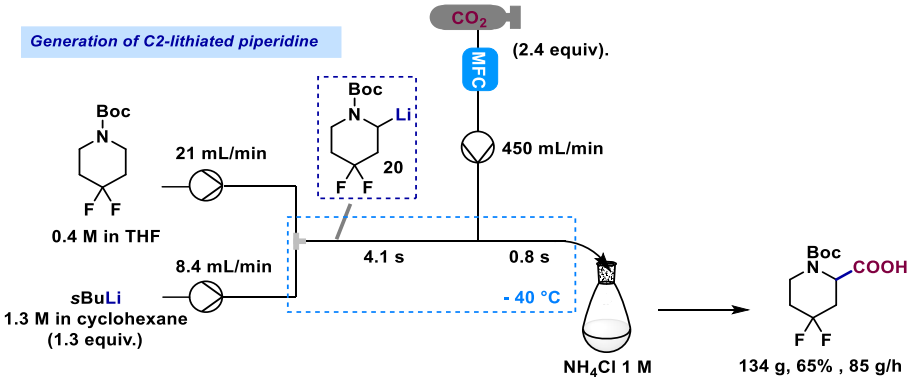
Scheme 12. Continuous flow preparation of C3-heterosubstituted 1-azabicyclo[1.1.0]butanes

Advancing to heterocycles of larger ring sizes, O'Brien reported the functionalization of *N*-Boc-pyrrolidine by a lithiation-trapping sequence under continuous flow conditions (Scheme 13) [46]. The implementation of flow microreactor technology enabled this transformation in higher yields and in milder conditions compared to previous batch reports, which necessitated low temperatures (-78 °C), extended reaction times (3.5 hours), and larger quantities of TMEDA as an additive [47]. In a continuous flow setup, however, lithiation of the substrate was successfully accomplished at 0 °C in 3 s and the reactive intermediate **19** was quenched in a solution of TMSCl in THF at 0 °C, affording the desired product in 59% yield.



Scheme 13. Continuous flow lithiation-trapping of *N*-Boc pyrrolidine

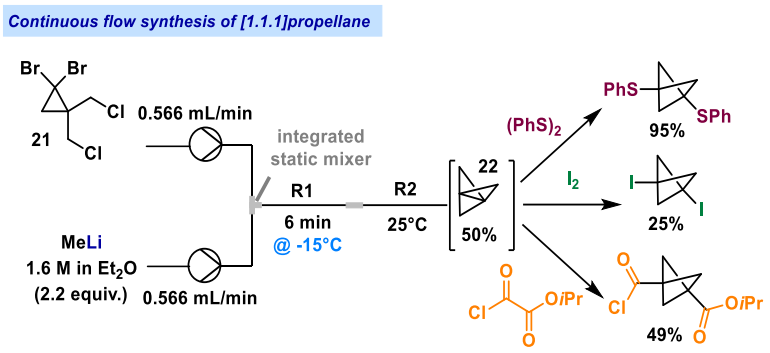
In a similar vein, Tissot independently described a continuous flow method for the carboxylation of *N*-Boc-4,4-difluoropiperidine (Scheme 14) [48]. Lithiation of *N*-Boc-4,4-difluoropiperidine was achieved by treatment with *s*BuLi at -40 °C and the lithiated piperidine **20** was subsequently intercepted by a stream of CO_2 delivered through a Vapourtec SF10 peristaltic pump. The reaction mixture was then collected in a 1 M ammonium chloride solution achieving 94% conversion and 58% yield of the product. The process was shown to be readily scalable, employing Syrdos pumps alongside a Brooks mass flow controller for reagents delivery. Notably, the system was remotely monitored through integrated temperature and pressure sensors, programmed to halt operations in the event of leaks or pressure build-ups. To effectively manage the exothermic nature of the process, a temperature of -40 °C was set. These adjustments led to maximal conversion of 98%, yielding 65% of the desired product with a noteworthy productivity of 85 g/h.



Scheme 14. Continuous flow synthesis of *N*-Boc-4,4-difluoropiperidine-2-carboxylic acid

Highly strained all-carbon cyclic systems have also been subject to investigation. For example, Baumann introduced a continuous flow approach for the synthesis of [1.1.1]propellane and its straightforward derivatization into bicyclo[1.1.1]pentane derivatives in a flow set-up (Scheme 15) [49]. The tetrahalide precursor **21** is lithiated using methyllithium in a static mixer and two reactors operating at distinct temperatures, promoting intramolecular cyclisation. Under optimized conditions, [1.1.1]propellane can be produced in 50% yield, and simple washes were found to be suitable purification prior to derivatization

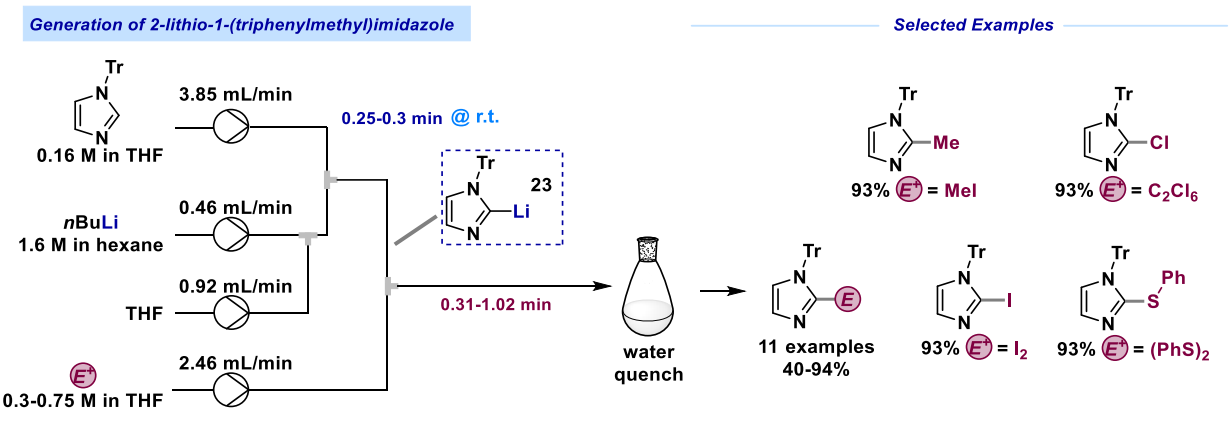
reaction, avoiding purification by distillation, which is required post conventional batch processes. The synthesised [1.1.1]propellane was then derivatised to several important BCP motifs.



Scheme 15. A continuous flow synthesis of [1.1.1]propellane and its derivatization

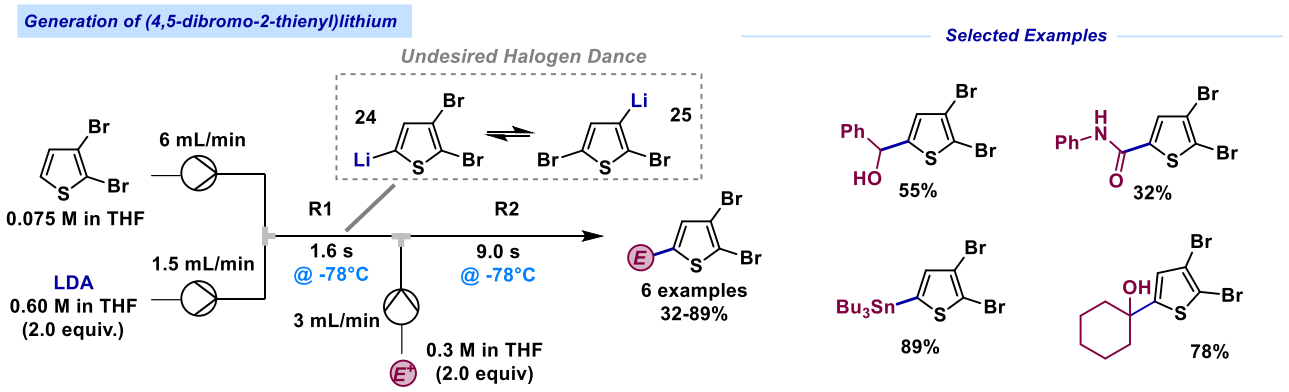
1.3 Lithiation of (hetero)aromatics

The lithiation of (hetero)aromatics, crucial building blocks for complex molecules with applications across various pharmaceuticals to materials science, using flow technology has also been described. For example, Miller and co-workers developed a platform for the functionalization of *N*-protected imidazoles, which find widespread applications in pharmaceuticals, agrochemicals, ionic liquids and as stabilizing agents for carbenes, under continuous flow conditions (Scheme 16) [50]. The strategy relied on the rapid formation of 2-lithio-1-(triphenylmethyl)imidazole **23** by deprotonation of 1-tritylimidazole using *n*BuLi, followed by electrophilic quenching in batch. Careful optimisation of the process revealed that a residence time of 1.5 minutes with a 200 cm coil of 1 mm inner diameter yielded the best outcomes. To further enhance efficiency, an additional THF inlet was integrated to enable direct *n*BuLi dilution in flow. Following their optimized reaction conditions, and incorporating an additional reaction coil, the authors performed the inline electrophilic quenching in a fully telescoped process. To test the robustness of the methodology, a prolonged run of 4 h was performed, using benzaldehyde as the electrophile, affording the desired product with a stable 70-75% yield.



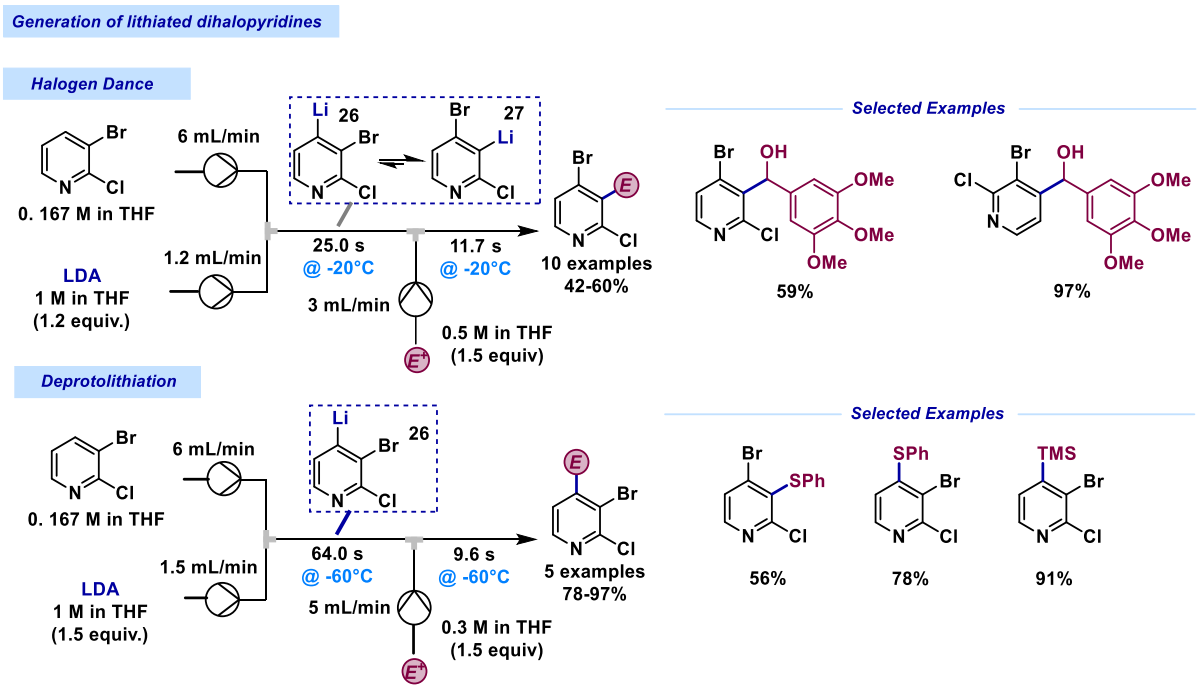
Scheme 16. Continuous flow functionalisation of imidazole

In 2020, Okano disclosed a continuous flow approach for the selective trapping of (4,5-dibromo-2-thienyl)lithium **24**, generated by deprotonation of 2,3-dibromothiophene (Scheme 17) [51]. This intermediate is known to undergo fast halogen dance isomerization producing the more stable thienyllithium **25**. By precise control of the residence time, selective generation and trapping of intermediate **24** was achieved by treatment of 2,3-dibromothiophene with LDA under flow conditions. Using a residence time of 1.6 seconds, before addition of an electrophile, electrophilic quenching superseded the rate of isomerisation, avoiding a mixture of product isomers. A range of electrophiles, including carbonyl compounds, isocyanates, and chlorostannanes were shown to be suitable electrophiles.



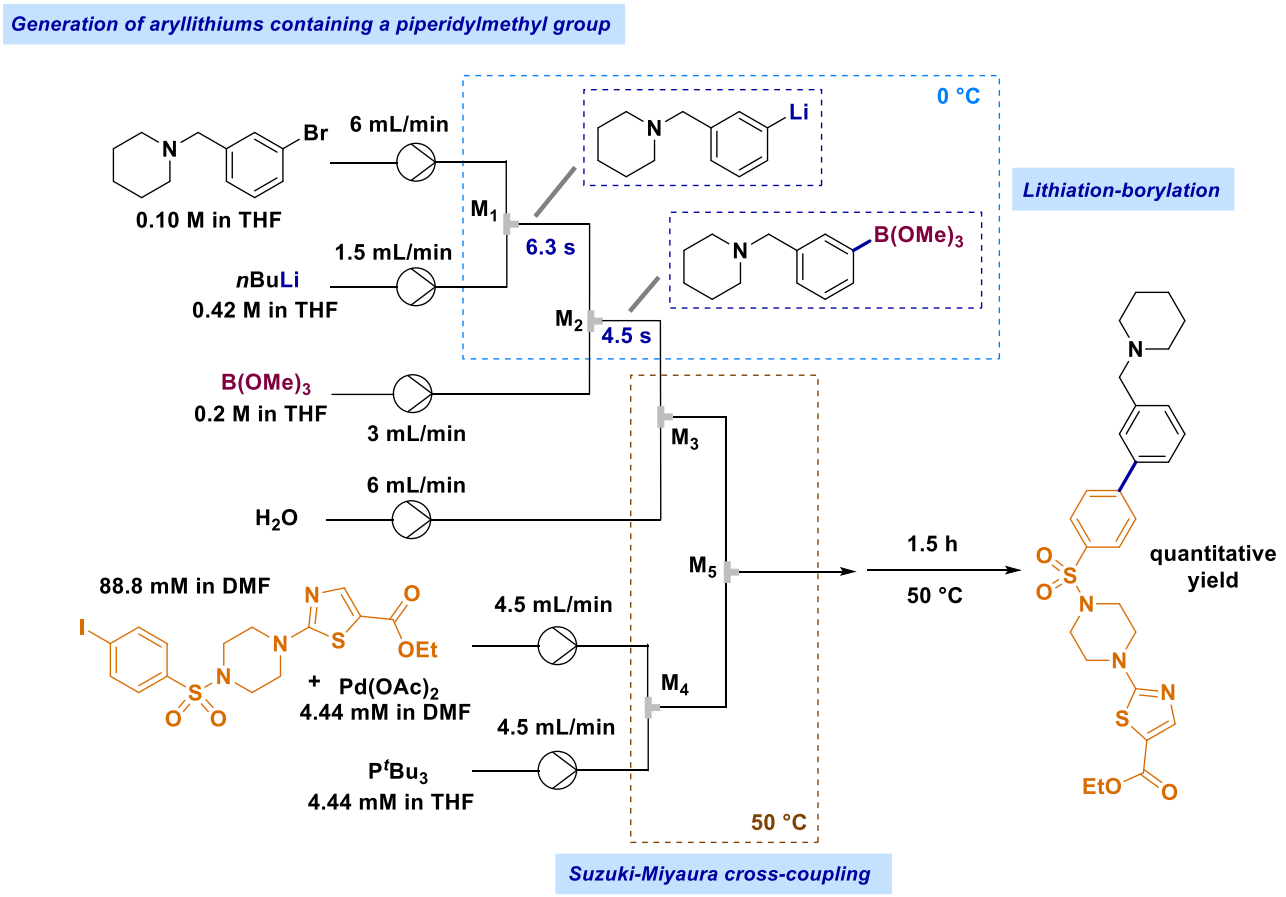
Scheme 17. Generation and trapping of (4,5-dibromo-2-thienyl)lithium

In contrast, Legros recently reported the first instance of divergent lithiation of dihalopyridines in a flow apparatus, achieving precise control of the desired halogen dance (Scheme 18) [52]. To this end, the authors leveraged halogen dance isomerisation (**26**, **27**) accessing different functionalized dihalopyridines *via* trapping with suitable electrophiles. Initially, 2-chloro-3-bromopyridine was continuously reacted for 69.8 s with freshly prepared 1 M LDA solution in THF at various temperatures and quenched with deuterated methanol. At lower temperatures (-60 °C), the major product was identified as 2-chloro-3-bromo-4-D-pyridine, whereas at -20° C the halogen dance effect prevailed, yielding 2-chloro-4-bromo-3-D-pyridine as the principal product. This clear distinction underscores that kinetics governs deprotolithiation phenomenon, whereas the rearrangement is subject to thermodynamic control. With the optimized condition in hand, the electrophile scope was successfully explored, accessing functionalized dihalopyridines. It is important to point out that application of this methodology to 3-fluoro-4-iodopyridine proved challenging.



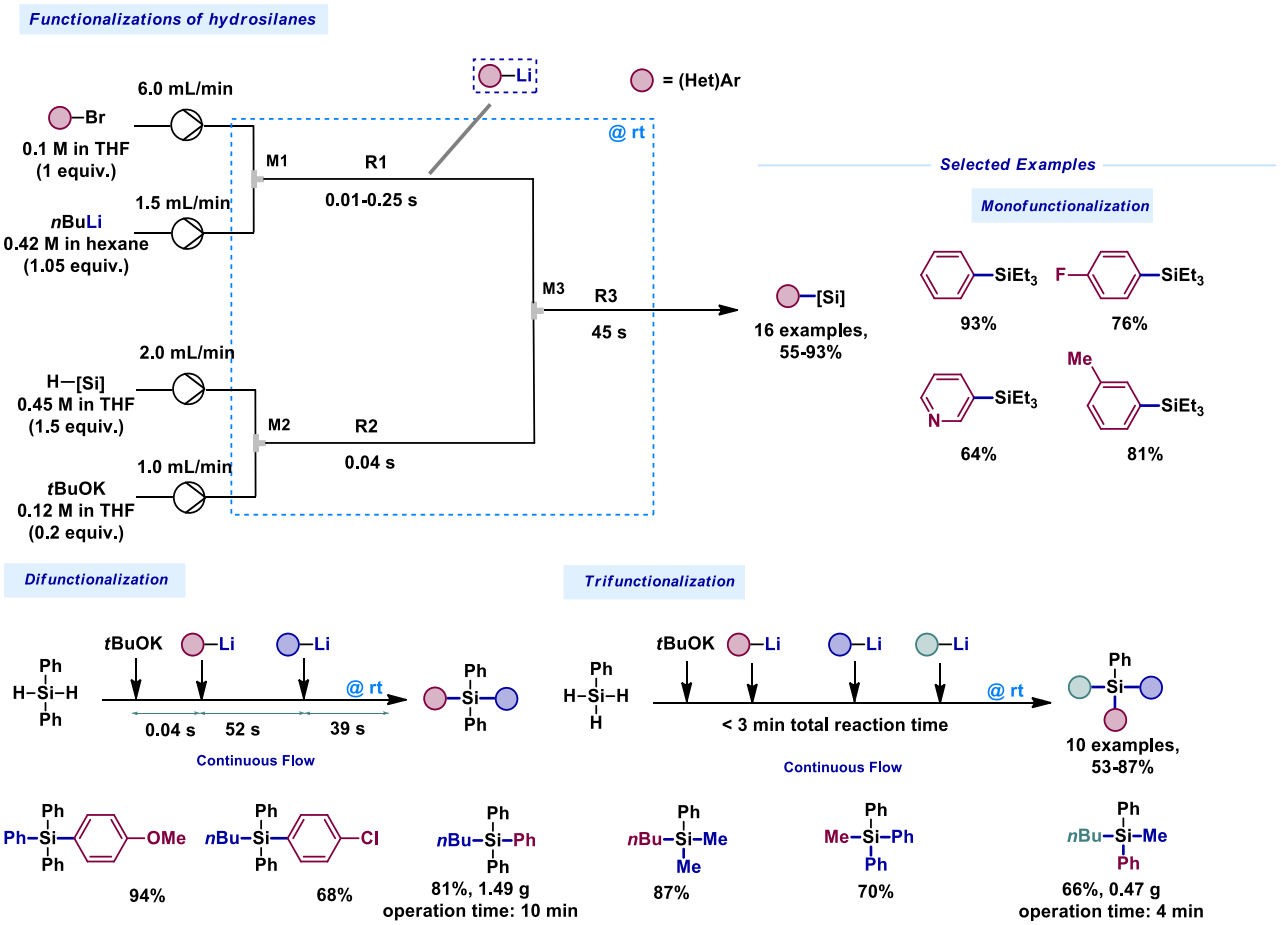
Scheme 18. Divergent lithiation of 2,3-dihalopyridines under continuous flow conditions

In 2019, Nagaki and coworkers reported the generation of aryllithiums containing a piperidylmethyl group through a Li-Br exchange reaction, followed by their selective functionalization using boronic esters [53]. Furthermore, they integrated this lithiation-borylation sequence with Suzuki–Miyaura cross-coupling to obtain nitrogen-containing biaryl compounds. The current approach was shown to produce a late-stage intermediate of a histone deacetylase (HDAC) inhibitor (Scheme 19).



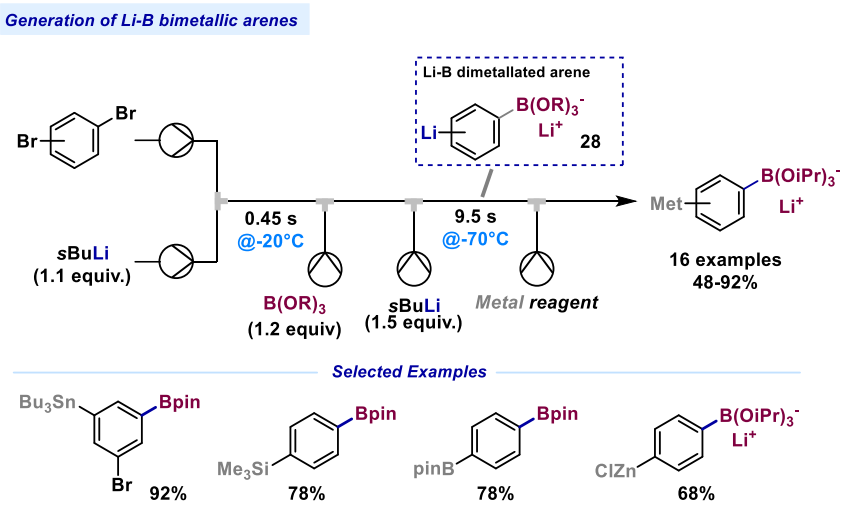
Scheme 19. Continuous flow generation of aryllithiums bearing a piperidylmethyl group

In previous reports, several examples of mono-functionalisation of organosilanes were described, yet the poly-functionalisation of organosilanes is an area of only few reports. To close this gap, Dong-Pyo Kim and Heejin Kim reported a method for poly-functionalisation of non-functionalised hydrosilanes *via* sequential reactions in flow technology involving diverse organolithiums and facilitated by catalytic *t*BuOK (Scheme 20) [54]. Specifically, generation of functionalised aryllithiums at room temperature by lithium-halogen exchange of heteroaryl bromides and subsequent in-line treatment with a solution of hydrosilane and *t*BuOK produced the desired functionalized organosilanes. Remarkably, this atom-economic approach enables not only the single functionalization of Si–H bonds in hydrosilanes but also the di- and tri-functionalization, achieved through sequential organolithium additions within an integrated flow system. The robustness and practicality of the protocol were validated by gram-scale synthesis of functionalised hydrosilanes.



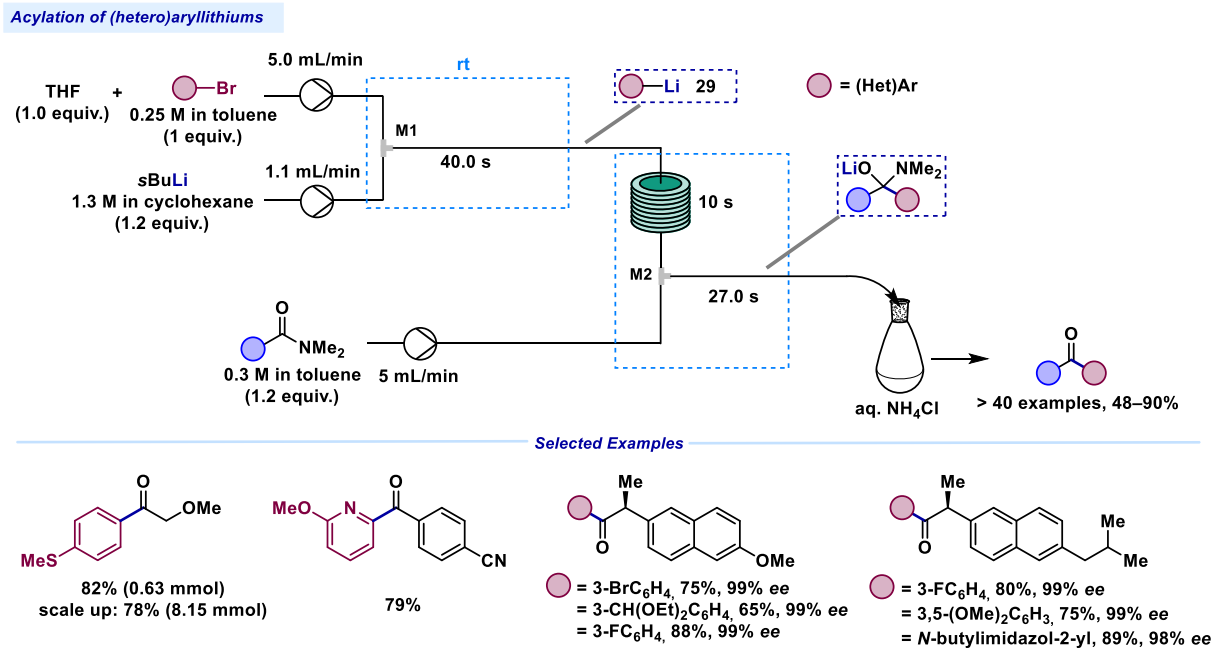
Scheme 20. Poly-functionalization of hydrosilanes in continuous flow.

A further contribution in the vein of in-line polyfunctionalization of substrates was reported by Nagaki and co-workers. They reported the continuous flow generation of dimetallated aromatic compounds, which were harnessed for consecutive selective cross-coupling reactions (Scheme 21) [55]. An initial mono-metallation of dibromoarenes by lithium-halogen exchange was promoted at -20 °C using a very short-residence time, allowing subsequent trapping with $B(OiPr)_3$ to afford lithium boronate complexes. A second lithiation step afforded Li-B-dimetallated intermediate **28**. These species were successfully engaged in various reactions with diverse electrophiles, generating stannylated, silylated and zincated arylboronic esters. The utility of the afforded substrates was demonstrated by the synthesis of a range of chemoselective cross-coupling products. In a similar vein, the same group reported a continuous flow protocol for the synthesis of functionalised aryl azides by step-wise lithiation/functionalisation sequences from polybromoarenes. [56]



Scheme 21. Synthesis of dimetallated arenes under continuous flow conditions

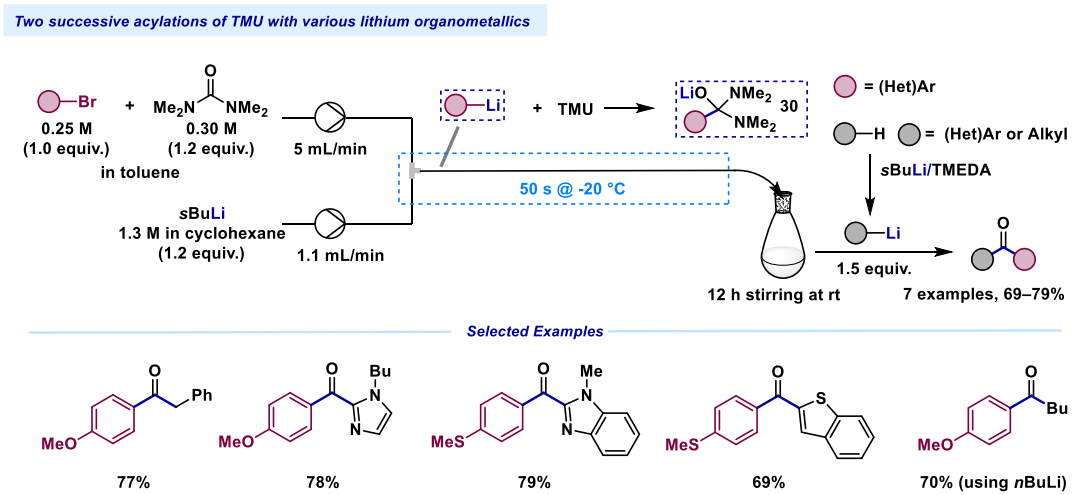
In 2021, Knochel and coworkers reported a continuous flow acylation method for (hetero)aryllithiums using diverse functionalized *N,N*-dimethylamides as acylating agents (Scheme 22) [57]. The lithiation of a range of aryl and heteroaryl bromides was efficiently achieved at room temperature within 40 s, *via* lithium-bromine exchange reaction using *s*BuLi. The ensuing intermediate **29** was subsequently in-line quenched at -20 °C with various *N,N*-dimethylamides, using a residence time of 27 s. The developed methodology finds application in the synthesis of chiral naproxene and ibuprofen ketone derivatives, by reacting different aryllithiums with naproxene and ibuprofen derived *N,N*-dimethylamides.



Scheme 22. A continuous flow acylation of (hetero)aryllithiums with *N,N*-dimethylamides

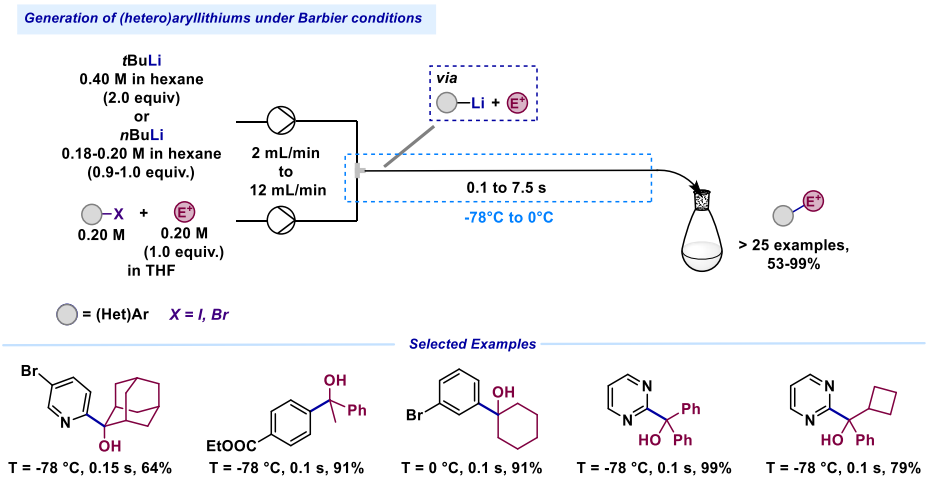
Additionally, a semi-batch protocol was devised for the creation of unsymmetrical ketones *via* a one-pot, stepwise bis-addition of two different lithium organometallics to 1,1,3,3-tetramethylurea (TMU) (Scheme 23).

Aryllithiums were generated under Barbier-type conditions in the presence of TMU, yielding tetrahedral intermediate **30.** Treatment of this intermediate with a second aryl- or alkyllithium in batch and subsequent work-up afforded bis-arylated or aryl-alkylketones in up to 79% yield.



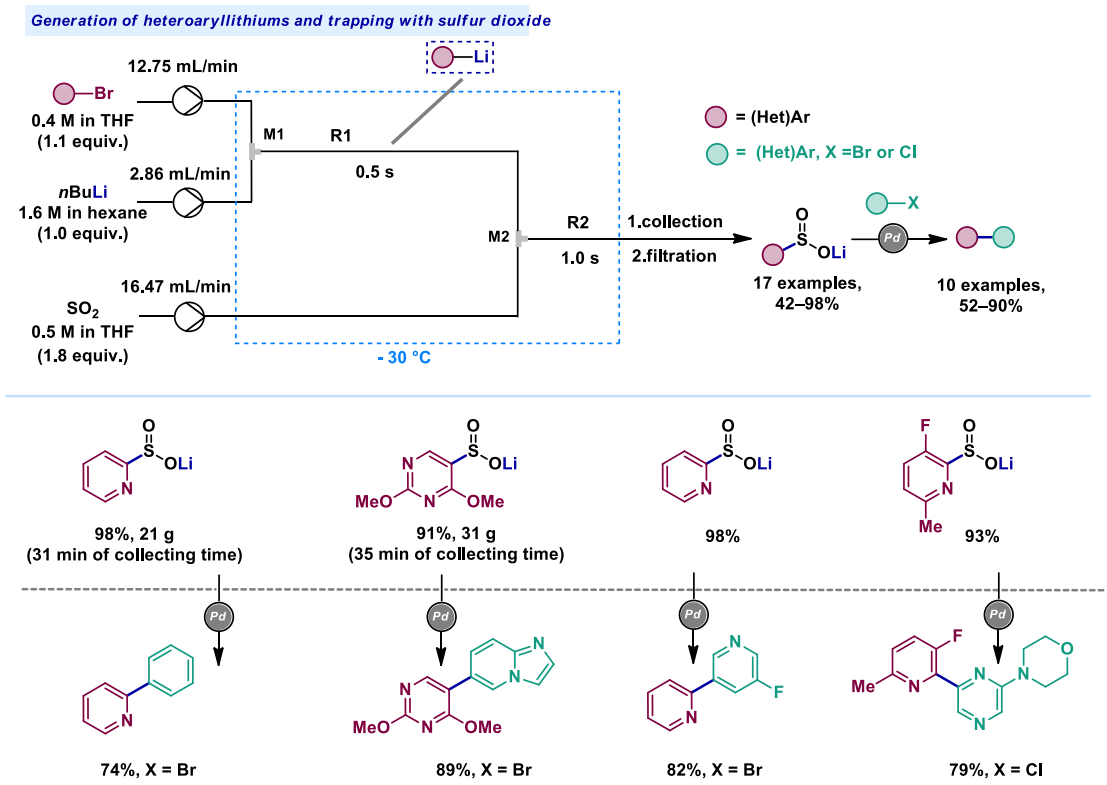
Scheme 23. Preparation of unsymmetrical ketones through semi-batch approach

In the same year, Knochel also demonstrated that much more sensitive aryllithium intermediates can be generated under continuous flow methodology (Scheme 24) [58]. Thus, a premixed solution of functionalized (hetero)aryl halide and the appropriate electrophile was treated with a lithiating agent in a micromixer before being directed through a reactor, yielding the desired final products. To ensure precise temperature control during the transformation, the entire system was immersed in a cooling bath. Remarkably, the adept control of reaction time allowed for the successful generation of halo-substituted (hetero)aryllithiums as well as aryllithiums bearing ester functionalities.



Scheme 24. Generation and trapping of sensitive (hetero)aryllithiums through lithium-halogen exchange reaction

The advantages of employing flash chemistry to handle and utilise such highly unstable organometallic intermediates have naturally attracted the attention of pharmaceutical companies. In 2020, Sedelmeier and colleagues from Novartis Pharma AG reported the continuous flow preparation of heteroaryl sulfinates by the reaction of unstable heteroaryllithium intermediates with sulfur dioxide (Scheme 25) [59]. A range of produced lithium sulfinate salts were subsequently employed in C(sp^2)–C(sp^2) cross-couplings under batch conditions to produce diverse bis-heteroaryl compounds of pharmaceutical relevance, achieving yields that ranged from moderate to excellent.

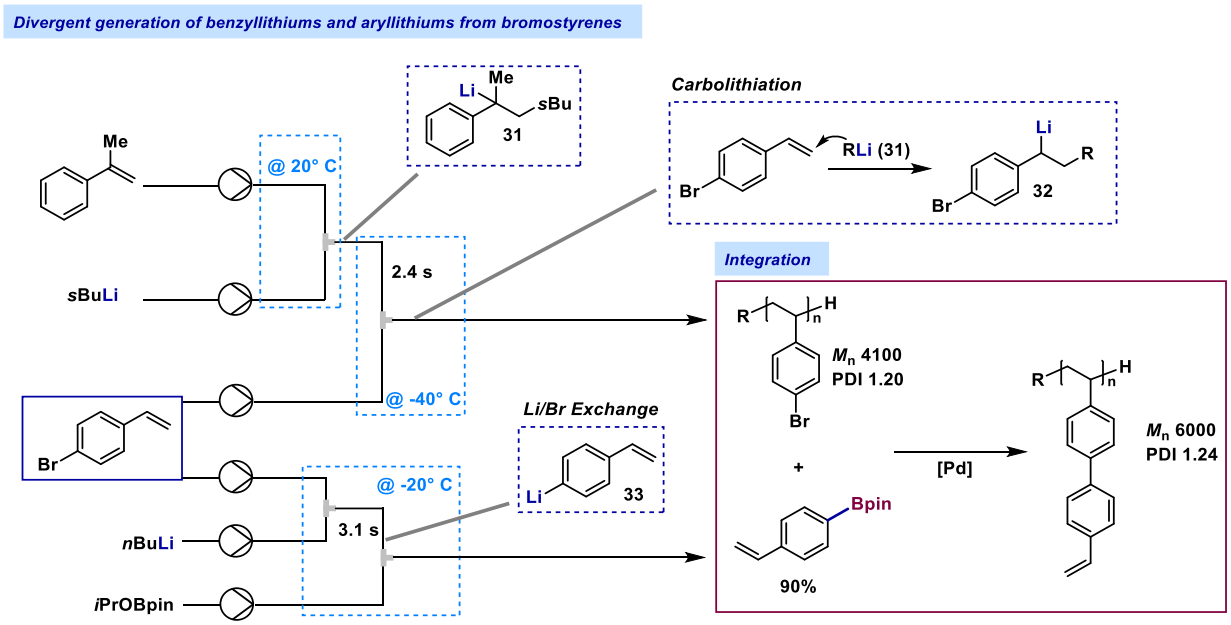


Scheme 25. Synthesis of heteroaromatic sulfinates in continuous flow

1.4 Lithiation of the benzylic position of (hetero)aromatics

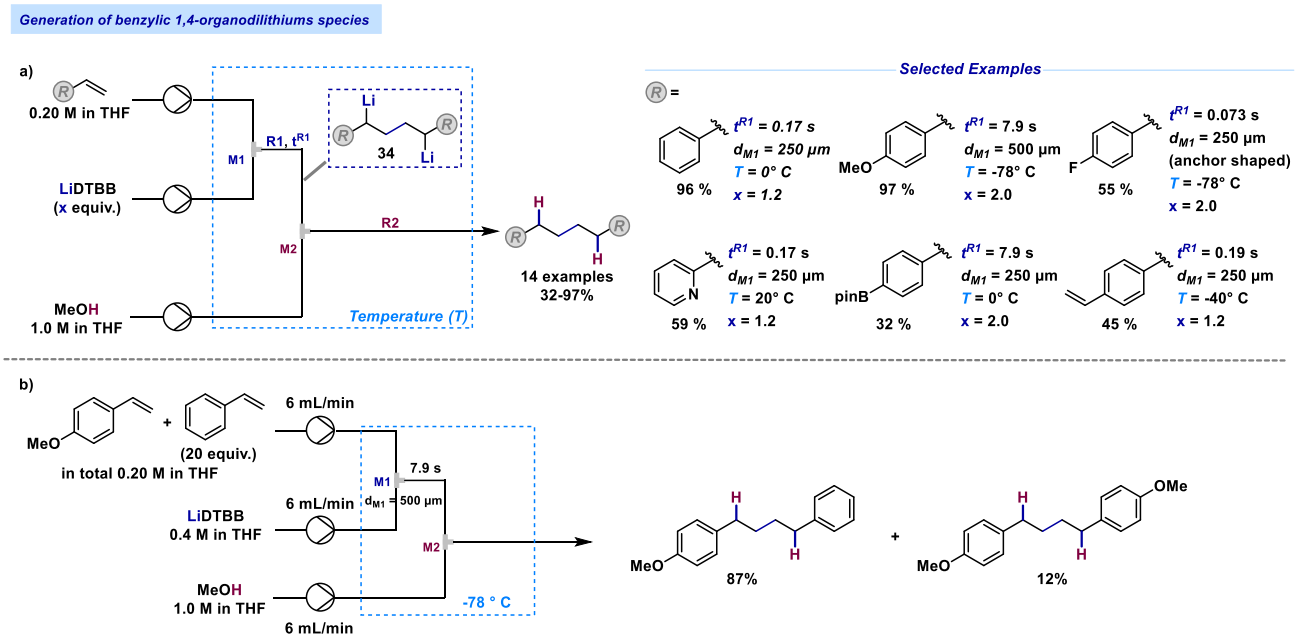
The lithiation-substitution approach at benzylic positions stands as a widely embraced strategy for introducing new benzyl functional groups, offering versatility across a diverse spectrum of starting materials [60]. In this context, Nagaki reported the generation of benzyllithium **32** or aryllithium **33** intermediates from bromo-substituted styrenes by carbolithiation or lithium-halogen exchange, respectively. The chemoselectivity is switchable simply by varying the lithium-base (Scheme 26) [61]. Using flow microreactor technology, organolithium intermediate **31** was generated from α-methylstyrene and *s*BuLi at room temperature. The resulting solution of **31** was then mixed with 20 equivalents of 4-bromostyrene to generate benzyl-lithiated intermediate **32** by carbolithiation. This intermediate was engaged in an anionic polymerization processes. Under optimized conditions, the competitive lithium-halogen exchange reaction was suppressed. When *n*BuLi was used as the lithiating agent at 0 °C, the authors achieved the formation of

aryllithium intermediate **33**, which were trapped with a range of electrophiles, including iodides, isocyanates, aldehydes, chlorostannanes, chlorinating agents, and borates. The authors demonstrated the integration of these two chemoselective transformations with the Pd catalysed coupling between poly-4-bromostyrene and the 4-vinylphenyl boronic ester.



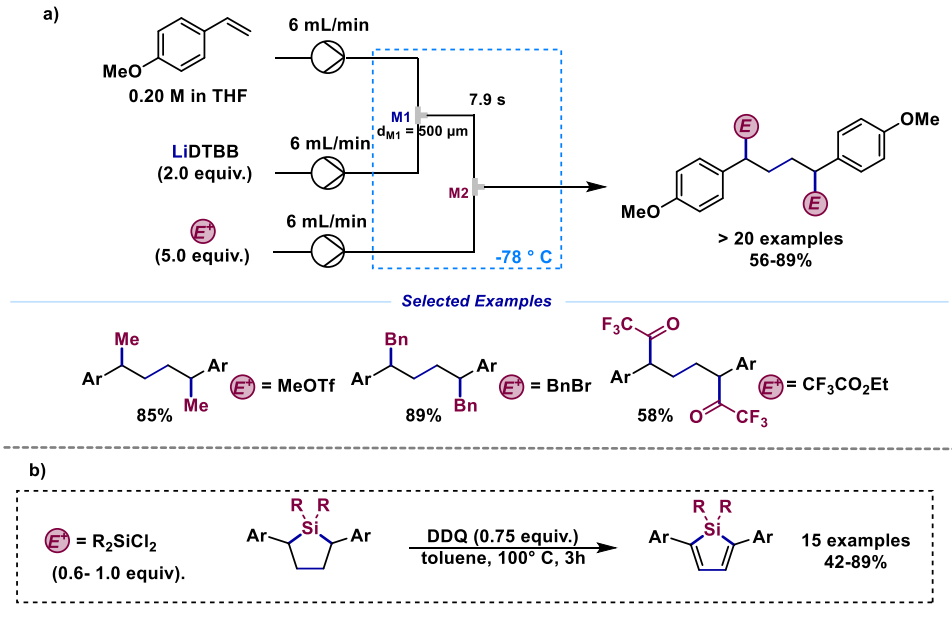
Scheme 26. Switchable chemoselectivity of lithiated intermediates generation in continuous flow

In a similar vein, Yorimitsu independently showcased the efficiency of flow chemistry in generating benzylic 1,4-organodilithiums by reduction of styrenes with lithium arenide, followed by dimerization (Scheme 27) [62]. Unwanted polymerization, which is often favoured in batch systems, is successfully suppressed under flow conditions in favour of the bis-lithiated dimer **34**. The authors speculate that the extremely high mixing-efficiency ensures almost instantaneous homogeneity, playing a pivotal role in taming 1,4-dianions. A range of different homo-coupled dimers was successfully delivered in up to 97% yield. Cross-dimerization of two different styrenes was also successfully achieved in 87% yield, when *p*-methoxystyrene was premixed with 20 equivalents of styrene. Only 12% yield of the homo-coupled *p*-methoxystyrene dimer was observed.



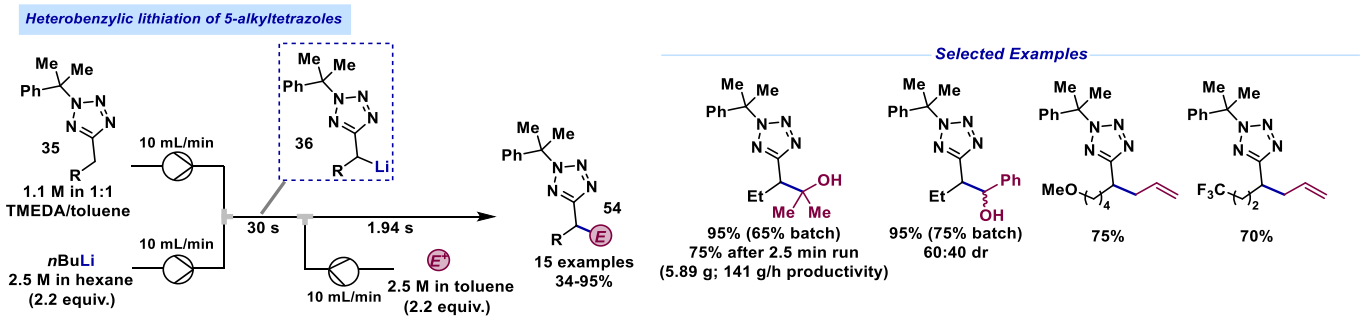
Scheme 27. Flow microreactors to avoid polymerization of benzylic 1,4-organodilithiums species. a) Reductive dimerization of various styrenes; b) cross-dimerization of two different styrenes

The bis-lithiated dimers could not only be protonated, but also trapped with a range of electrophiles, further enhancing the added product complexity achieved within one synthetic operation. Notably, methylation, allylation, benzylation, trimethylsilylation, and trifluoroacetylation were all successfully accomplished (Scheme 28, a). The authors then shifted their focus to the synthesis of silacyclopentanes, reacting 1,4-dilithiated homo- and hetero-dimers with various dichlorosilanes (Scheme 28, b). The resulting silacyclopentanes could be further oxidized to diarylsiloles by treatment with DDQ in toluene.



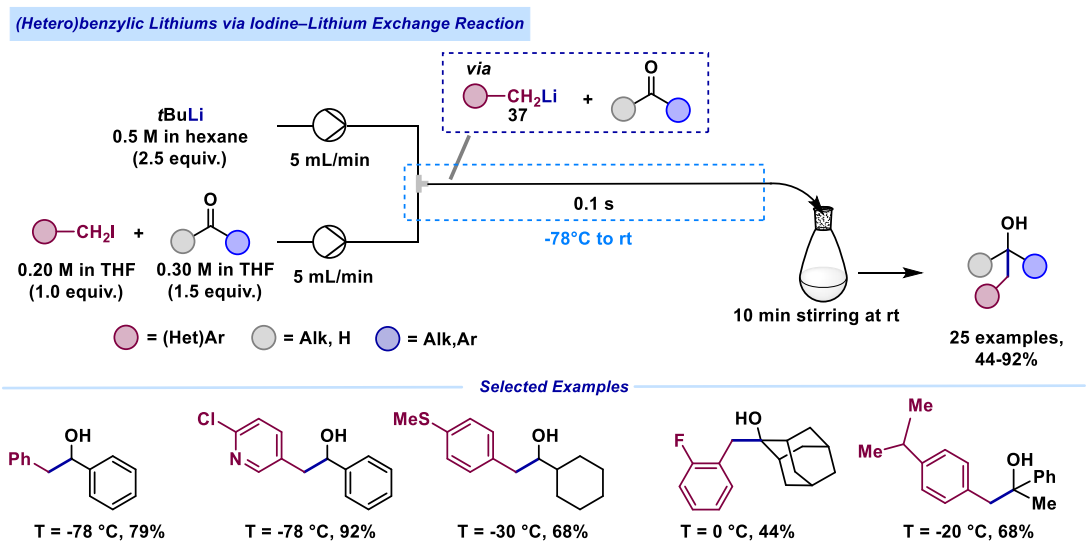
Scheme 28. a) Reaction of benzylic 1,4-organodilithiums species with various electrophiles; b) preparation of 3,4-unsubstituted 2,5-diarylsiloles

The advantages of flow microreactor technology can be expanded to encompass the benzylic lithiation in heteroaromatic substrates. In this context, Barker and co-workers have recently reported an efficient and high-yield method for the lithiation and functionalization of 5-alkyltetrazoles (Scheme 29) [63]. Although successful also in batch mode, energy-intensive cooling to up to –78 °C was required for successful conversion. In a continuous flow setup, comprising two peristaltic pumps, a T-junction, and a 28 cm reactor, the desired reaction was run at room temperature. Notably, thermal imaging was employed to investigate the lithiation-step, revealing a peak temperature of 70°C and an average temperature of 55° C within the reactor, leading to boiling of the solvent. The striking exothermic nature of the process necessitated the use of toluene/TMEDA 4:1 mixture for tetrazole **35** dissolution instead of pure THF. Quenching of the lithiated intermediate **36** was performed in-line by a third inlet stream. The substrate scope involved a broad spectrum of electrophiles and *N*-cumyl-5-alkyltetrazoles, affording good to excellent yields that consistently outperformed the traditional batch procedure. Additionally, a 2.5 min run was performed, using *N*-cumyl-5-propyltetrazole and acetone as electrophile, resulting in 75% isolated yield (5.89 g, productivity of 141 g/h) and showcasing the robustness of the process.



Scheme 29. Benzylic functionalisation of 5-alkyltetrazoles using flow microreactor technology

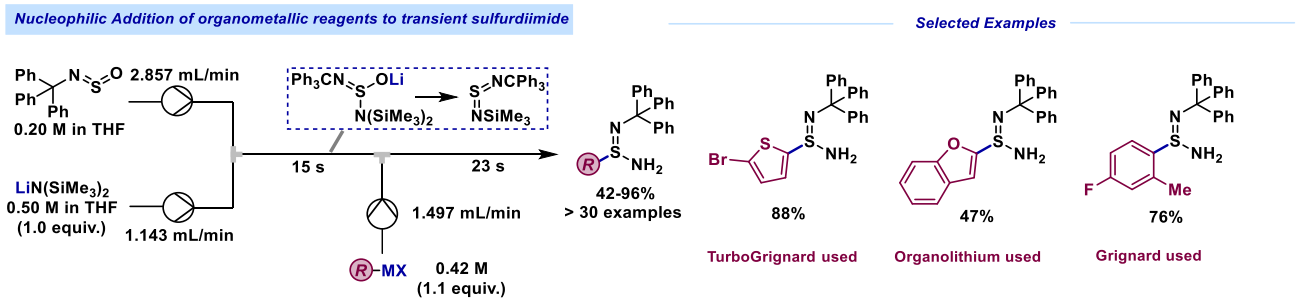
In 2020, Knochel and coworkers achieved the generation of (hetero)benzylic lithium intermediates by an iodine–lithium exchange reaction involving benzylic iodides (Scheme 30) [64]. The authors described an internal quenching approach (i.e., Barbier conditions) where the transient organolithium intermediate **37** was formed in the presence of the electrophilic partner. Specifically, a solution of benzylic iodide and carbonyl-containing electrophile, was treated with *t*BuLi. This process led to the formation of the desired benzylic secondary and tertiary alcohols in generally synthetically useful yields. Interestingly, scale-up was achieved without additional optimization. In this line of research, the same research group recently reported a strategy for the generation and trapping of chiral secondary alkyllithiums under Barbier-type conditions providing products with high yields and remarkable enantiomeric excess (90-98%) [65].



Scheme 30. Continuous flow generation of (hetero)benzylic lithiums *via* iodine–lithium exchange reaction under Barbier conditions

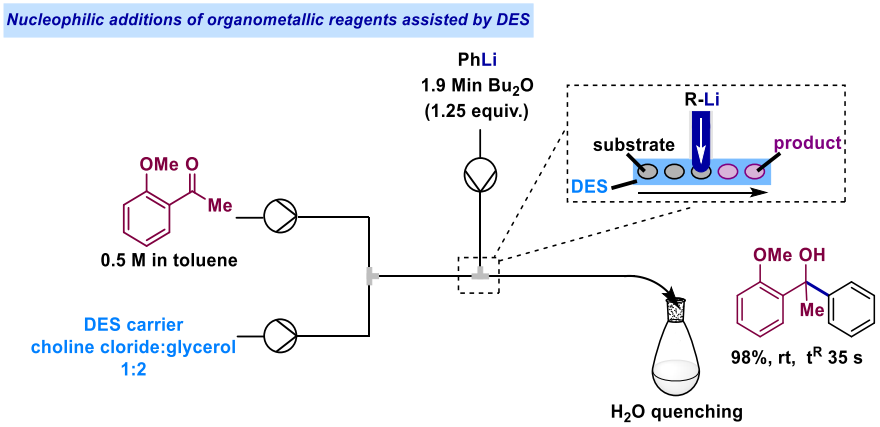
1.5 Nucleophilic addition of preformed organolithiums to electrophiles

Whereas previous sections have focused on the *in situ* lithiation of a precursor, which would proceed to act as a nucleophile, the nucleophilic addition of commercially available organolithium reagents to electrophiles under flow technology has also been described. For example, Poisson and Luisi recently proposed the synthesis of NH_2-sulfinamidines utilizing flow technology (Scheme 31) [66]. The initial step involved the nucleophilic addition of $LiN(SiMe_3)_2$ to of *N*-trityl sulfinylamine. The complete formation of the sulfurdiimide was observed within 15 s of residence time at room temperature. The resulting diimide was trapped by addition of another organometallic nucleophile, generating functionalized sulfinamidines in good to excellent yields. The reaction also worked with excellent selectivity upon internal quenching conditions employing iodo- or bromoarenes and *n*-butyllithium in flow. Therefore, the halogen-lithium exchange reactions occurred selectively in the presence of the electrophilic sulfurdiimide, that finally reacted with the *in situ* prepared organolithiums releasing the corresponding S-aryl sulfinamidines.



Scheme 31. Continuous flow nucleophilic addition of organometallic reagent to transient sulfurdiimide

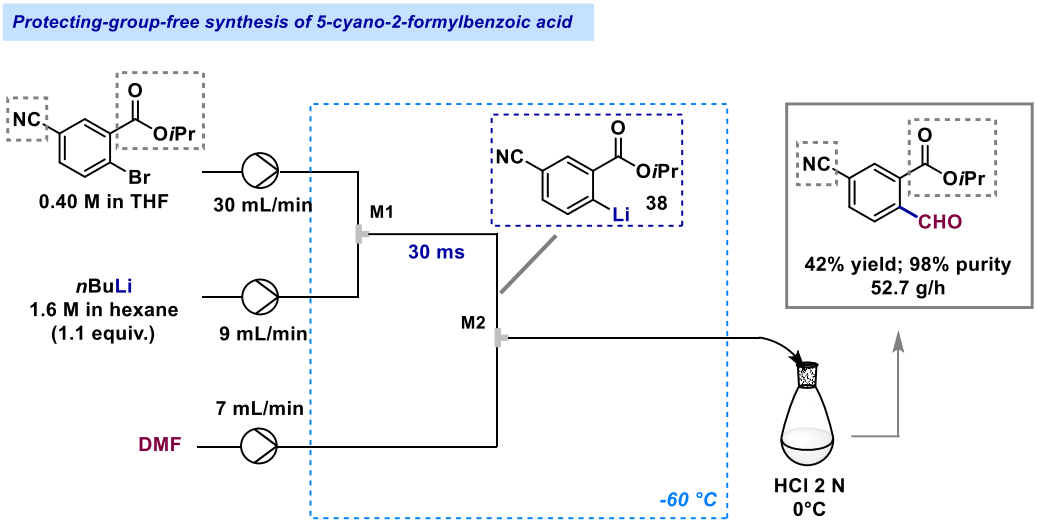
In 2022, Torrente-Murciano and Hevia introduced an innovative approach that marks the first instance of combining deep eutectic solvents (DES) and organometallic chemistry under continuous flow conditions (Scheme 32) [67]. In this work, the nucleophilic addition of organometallic reagents to carbonyl-like compounds was studied. The mixing of the DES carrier phase, for example choline chloride:glycerol 1:2, with a solution of 2-methoxyacetophenone in toluene, resulted in a segmented flow regime. Precise modulation of the flow rates between the DES phase and the substrate phase facilitated the optimal alignment of the dispensed organolithium and the incoming droplet of the electrophile solution, leading to a 98% yield of the desired product with a residence time of 35 s. Remarkably, these reactions were conducted at room temperature under atmospheric conditions, utilizing a non-toxic and biodegradable reaction medium. In addition, the described set-up is tolerant to different DES, various organolithiums, Grignard reagents, and carbonyl-like compounds.



Scheme 32. Continuous flow addition of organometallic to carbonyl-like compounds assisted by deep eutectic solvents (DES)

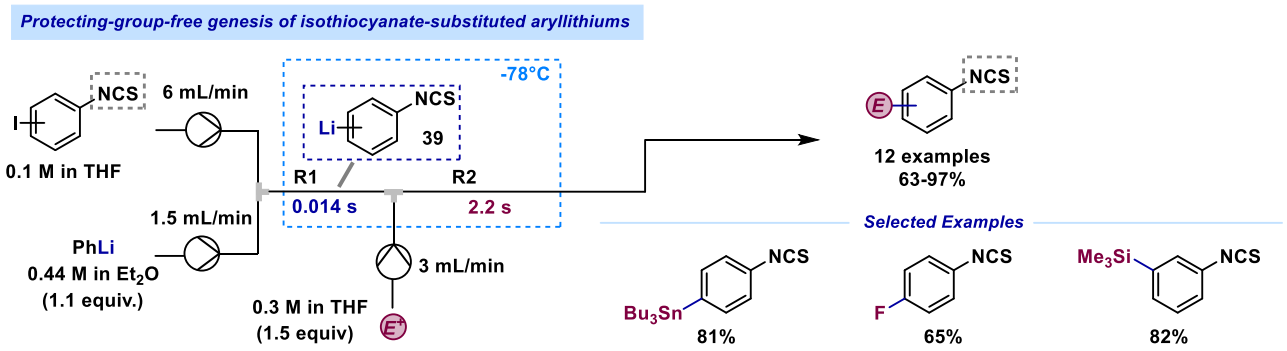
1.6 Generation of organolithiums in the presence of other reactive functional groups

Organolithium species rapidly react with electrophilic groups such as carbonyl, nitro, or cyano groups. For this reason, chemoselectivity issues sometimes arise when these electrophilic groups are not supposed to engage in the desired transformation. This frequently results in laborous protection-deprotection sequences. In the last decade, Yoshida demonstrated the potential of flow microreactor technology for protecting-group-free flow synthesis [22,68,69]. In 2019, Fukuda and Kawamoto harnessed this concept to devise a procedure for the synthesis of 5-cyano-2-formylbenzoic acid, relying on the Br-Li exchange on isopropyl 2-bromo-5-cyanobenzoate, followed by formylation [70]. The continuous flow system allowed for the generation of the active aryllithium intermediate **38** and its subsequent quenching/formylation at -50 °C. Authors state that the Br-Li exchange takes place within 0.1 s at this temperature, leaving the carboisopropoxy and cyano groups untouched. A 270 min run was successfully conduced, achieving the preparation of 237 g of product, without the requirement of chromatography (Scheme 33).



Scheme 33. Protecting-group-free synthesis of 5-cyano-2-formylbenzoic acid in continuous flow

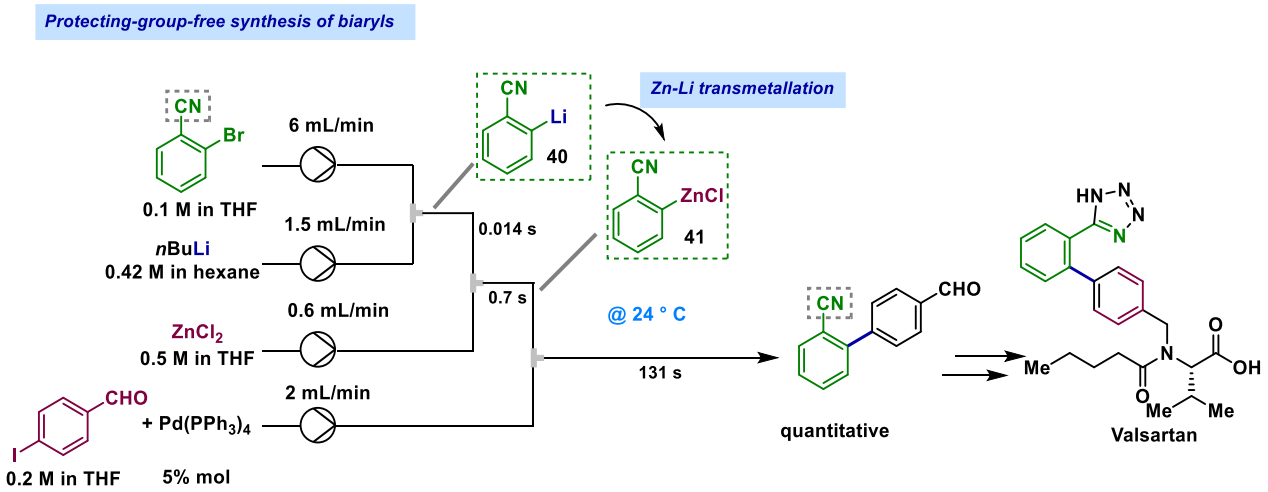
Within the context of lithiation in the presence of electrophilic groups, Kim and collaborators reported the continuous flow generation of aryllithiums bearing an isocyanate group at the *meta*- or *para*-position (Scheme 34) [71]. The importance of the isocyanate functional group in organic synthesis and medicinal chemistry stems from its potential to be transformed into diverse derivatives such as thioamides, thioureas, or carbamothiolates. However, its inherent electrophilicity and reactivity imposes challenges in generating organometallic reagents bearing this functionality in conventional batch reactors. This challenge was overcome using flow technology. Iodoarenes bearing the isocyanate moiety were selected as the perfect substrates for halogen-lithium exchange using phenyllithium. Lithium-iodine in R1 afforded intermediate **39**, which was subsequently trapped in M2 and R2 with tributylstannyl chloride. Optimal conditions were identified at -40°C, with a residence time of 14 milliseconds, achieving efficient generation of the desired products. A range of electrophiles were suitable to trap the intermediate **39**, achieving methylations, acylations, fluorinations, silylations and stannylations.



Scheme 34. Continuous flow generation and functionalization of isothiocyanate-substituted aryllithiums

Nagaki's group showed that using flow-technology, aryl nitriles are also tolerant to a sequence of lithiation, zincation and Negishi coupling to afford biaryls (Scheme 35) [72]. The aryllithium species **40**, afforded by

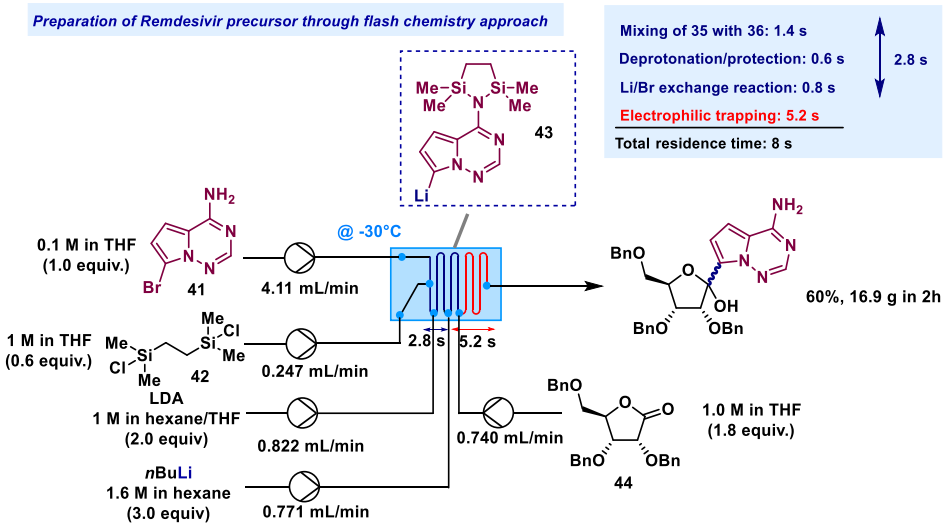
lithium-bromine exchange with *n*-butyllithium, was immediately transmetallated with $ZnCl_2$ to yield arylzinc species **41** carrying an electrophilic moiety. The zinc intermediate **41** was then reacted with an aryl halide containing an electrophilic functionality and a Pd catalyst to promote the desired Negishi coupling. The applicability of this protocol was demonstrated by the high-yielding preparation of a key-intermediate *en-route* to angiotensin II receptor blocker Valsartan.



Scheme 35. Protecting-group-free flow synthesis of biaryl derivative *en-route* to Valsartan

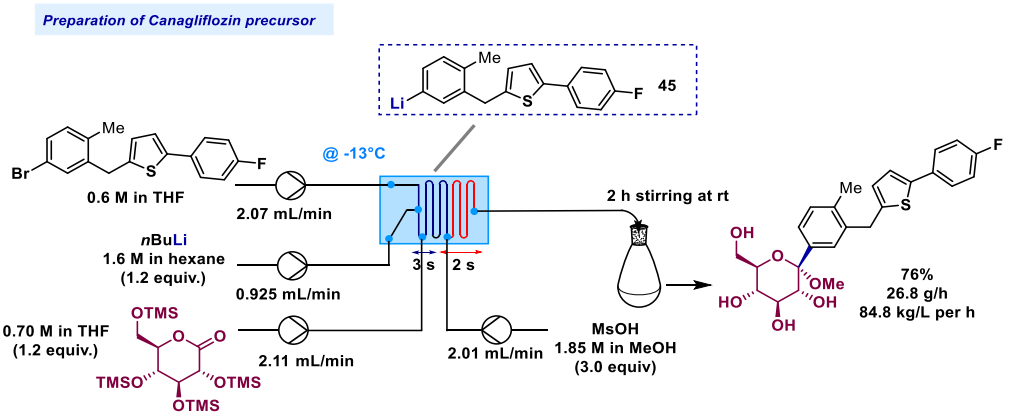
1.7 Organolithium compounds in the synthesis of biologically relevant compounds

Not only can such key building blocks of pharmaceutical relevance be produced using flow technology, but more importantly also the syntheses of (precursors to) commercial active pharmaceutical ingredients have been reported. For example, Kappe and co-authors have responded to the increased interest in antivirals following the COVID-19 pandemic by developing a synthesis method for a precursor of Remdesivir (Scheme 36) [73]. This flash chemistry approach offers milder reaction conditions and reduced production costs compared to the previously reported procedures [74, 75]. The proposed telescope strategy consists of (a) the silyl-protection of the amino group in 7-bromopyrrolotriazinamine **41**, (b) lithium-halogen exchange reaction, (c) and the nucleophilic attack of the lithium intermediate **43** on *O*-benzyl-D-ribonolactone **44**. Hence, five solution-feeds and four reactors were employed to carry out the transformation using an Ehrfeld FlowPlate. Specifically, a solution of 7-bromopyrrolotriazinamine **41** was mixed with a solution of 1,2-(bisdimethylchloro)silylethane **42**. A solution of LDA was then introduced to perform the selective deprotonation of the amino group. Subsequent lithium-halogen exchange reaction with a very short residence time of 0.8 s produced intermediate **43**, which was trapped using a solution of *O*-benzyl-D-ribonolactone. The stability of the process was confirmed by preparation of 16.9 g of glycosylated product.



Scheme 36. Organometallic C‑Glycosylation en route to Remdesivir

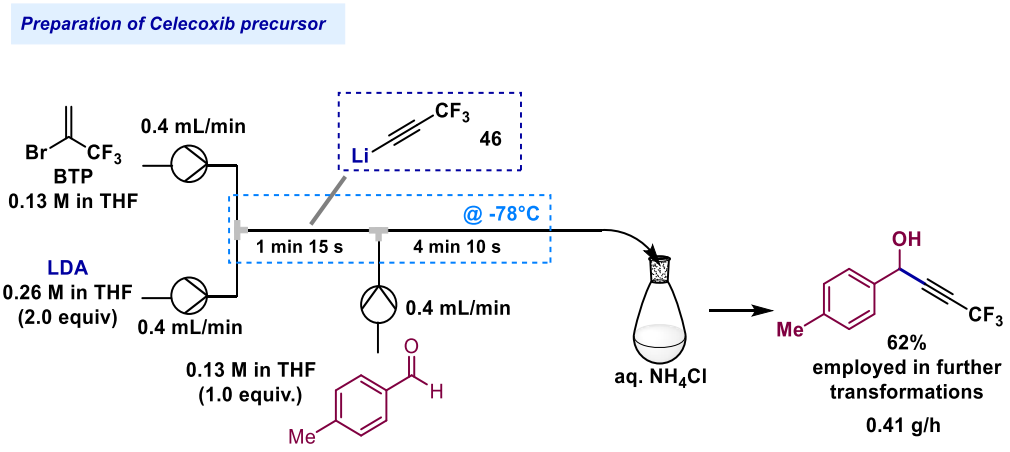
In 2021, Kappe reported another such *C*-glycosilation procedure, followed by methoxylation, for the synthesis of a key intermediate towards antidiabetic drug Canagliflozin (Scheme 37) [76]. The procedure involved continuous reaction of the aryl bromide precursor with *n*BuLi to initiate lithium-halogen exchange. The lithiated arene **45** was then subjected to a glycosylation-methoxylation sequence, consisting of trapping with trimethylsilyl-protected D-(+)-glucono-1,5-lactone and methoxylation with methanesulfonic acid. Progress of the reaction was monitored in real time by tracking the absorption signal resulting from the carbonyl-stretch using inline FTIR. Under optimized conditions, obtained by careful design of experiment (DoE)-study, the robustness of the system was tested in a long-duration experiment for 40 min, achieving over 99% conversion, and a remarkable 85% selectivity towards the desired product.



Scheme 37. Flow-batch hybrid synthesis of canagliflozin precursor

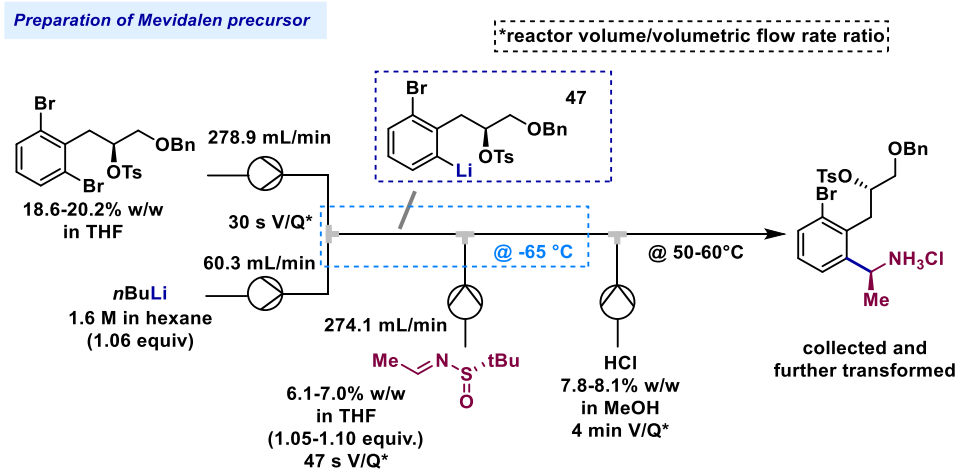
Jubault reported a novel flow-synthesis for a key intermediate of the widely prescribed anti-inflammatory drug Celecoxib (Scheme 38) [77]. As such, key lithiated trifluoropropylene intermediate **46** was obtained by a sequence of deprotonation-elimination-deprotonation. This transient species was subsequently captured using a solution of *p*-tolualdehyde. Remarkably, using a total residence time of less than 6 minutes, the

desired propargylic alcohol was obtained with a 62% yield, exhibiting a sufficient purity to be directly used in the subsequent synthetic stages towards the active pharmaceutical ingredient.



Scheme 38. Generation and trapping of trifluoropropynyl lithium in continuous flow

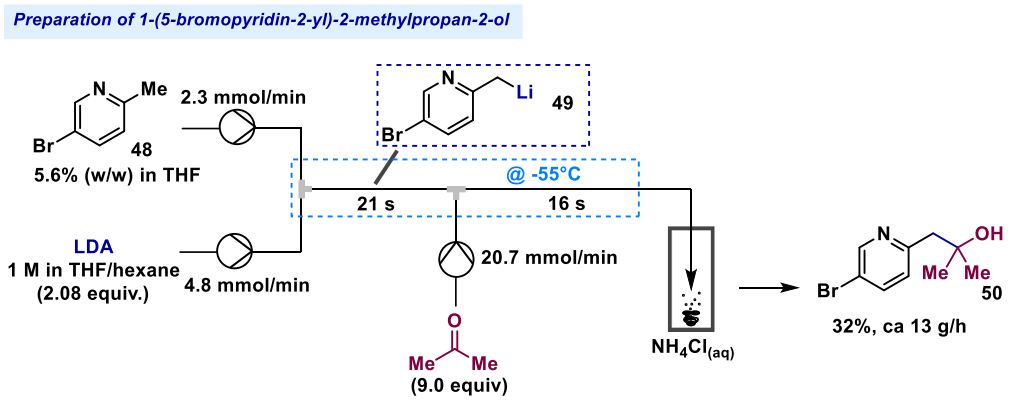
In 2020, Cole described the use of flow chemistry to execute a pivotal step within the scalable synthesis of Mevidalen (LY3154207), a positive allosteric modulator of the human dopamine D1 receptor (Scheme 39) [78]. Their synthetic approach relied on a lithium-halogen exchange on a functionalized dibromoarene and subsequently capturing the transient intermediate **47** with enantiomerically pure *N-tert*-butylsulfinyl imine. The resulting lithium salt was in-line quenched using a prechilled solution of HCl in methanol. This quenching not only facilitated the termination of the reaction but also enabled the cleavage of the chiral auxiliary to afford the key intermediate *en route* to Mevidalen.



Scheme 39. Organometallic step of the scalable synthesis of Mevidalen

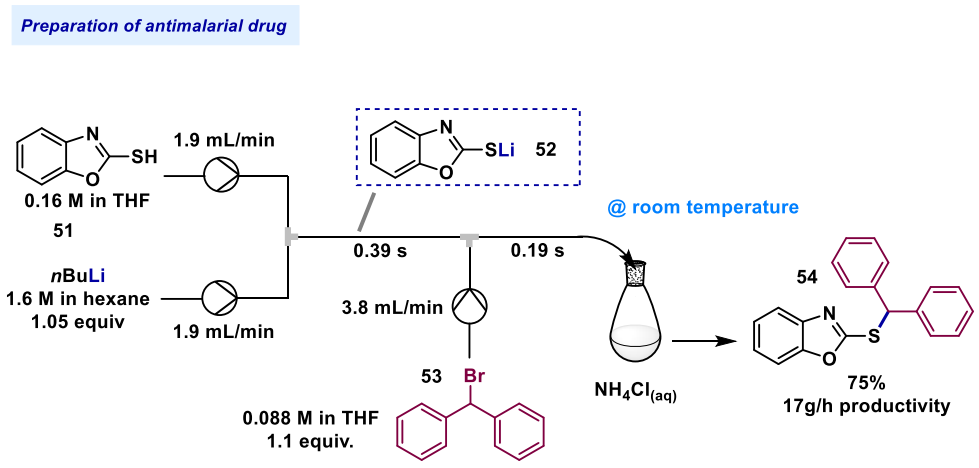
Edwards and colleagues reported the continuous flow metalation of methylpyridine precursor **48** to synthesize 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **50**, an active pharmaceutical ingredient in preclinical development (Scheme 40) [79]. This route relies on the benzylic deprotonation of **48** followed by the electrophilic quenching of the transient lithium intermediate **49** with acetone. The electrophilic trapping

step was performed at -55 °C with a residence time of 16 s. The quenching of the resulting lithium alkoxide was carried out in a semi-batch manner, with the resulting solution dripping into a stirred aqueous NH_4Cl solution. Operating the system for 16 hours, the process yielded ca. 210 g of alcohol **50**, with an isolated yield of 32%. The final scaled-up process was conducted on a 500 g scale.



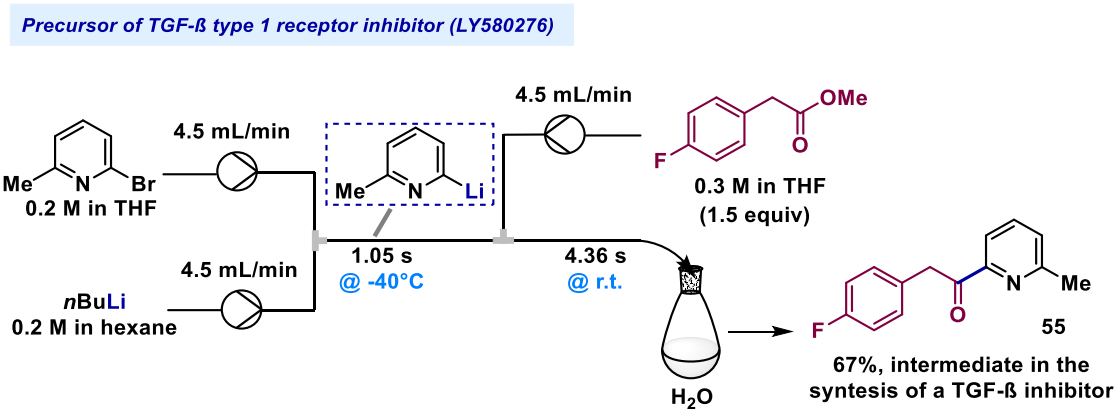
Scheme 40. Continuous flow organometallic synthesis of 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol

Also the synthesis of 2-(benzhydrylthio)benzo[d]oxazole **54**, an antimalarial drug was reported using flow technology (Scheme 41) [80]. An external quenching regime, where the lithium thiolate is generated first, followed by the addition of the electrophile **53** is an absolute necessity for the success of this sequence. As such, thiol **51** was deprotonated with *n*BuLi, before the resulting lithium-thiolate **52** was reacted with benzhydryl bromide **53** in the second capillary. This strategy drastically reduced the reaction time, compared to the batch procedure, as a total residence time of only 0.58 s afforded the final product in 75% yield. This process was also scaled up to obtain a remarkable productivity of 17 g/h. In a different avenue of research, oxazoles have also been utilized as a non-toxic carbon-bound masked CN source for the generation of CN-substituted aryls under flow conditions.[81]



Scheme 41. Ultrafast synthesis of 2-(benzhydrylthio) benzo[*d*]oxazole **54** in continuous flow

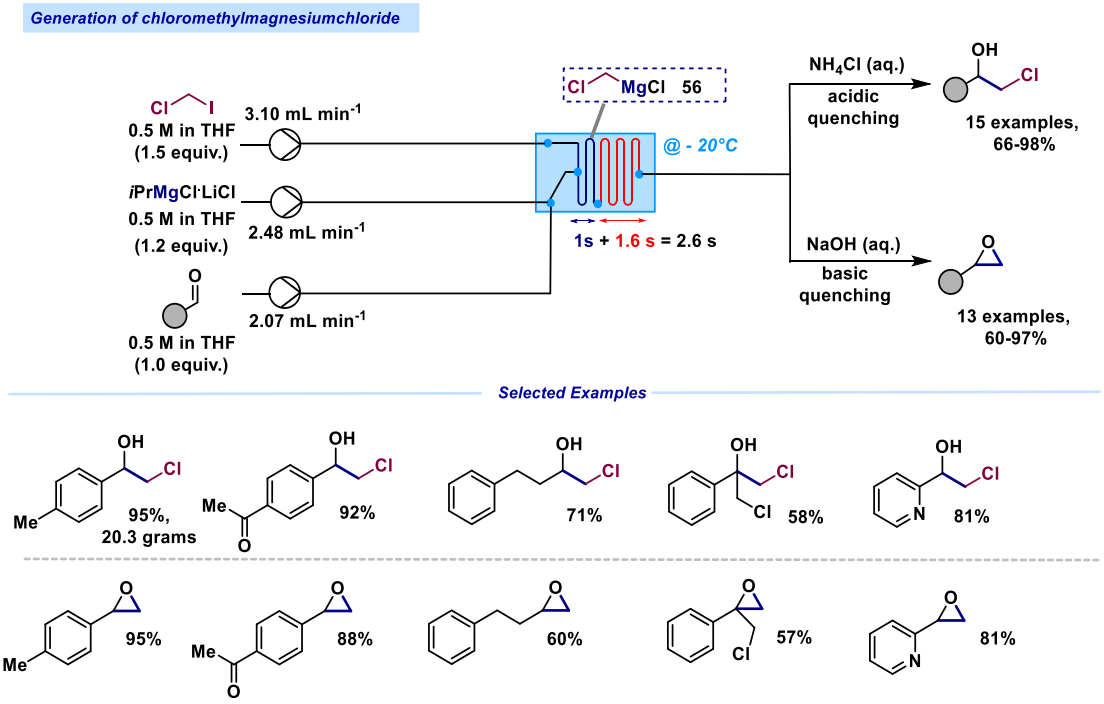
In a recent report, Ye showcased the potential of flow chemistry in the manipulation of 2-lithiated pyridines for the synthesis of a late-stage intermediate for the synthesis of a TGF-β inhibitor Scheme (34) [82]. In contrast to Edwards' report (Scheme 42), lithium-halogen exchange is desired, instead of benzylic deprotonation. In addition, the ketone moiety in the product exhibits greater reactivity towards organometallic species than the ester functionality in the substrate, so that meticulous control over reaction conditions is of importance. Lithium-halogen exchange was performed at -40 °C using a residence time of 1.05 seconds, whereas the subsequent electrophilic trapping was achieved at 25°C within 4.36 seconds, to afford the desired ketone **55** in 67% yield.



Scheme 42. Continuous flow preparation of LY580276

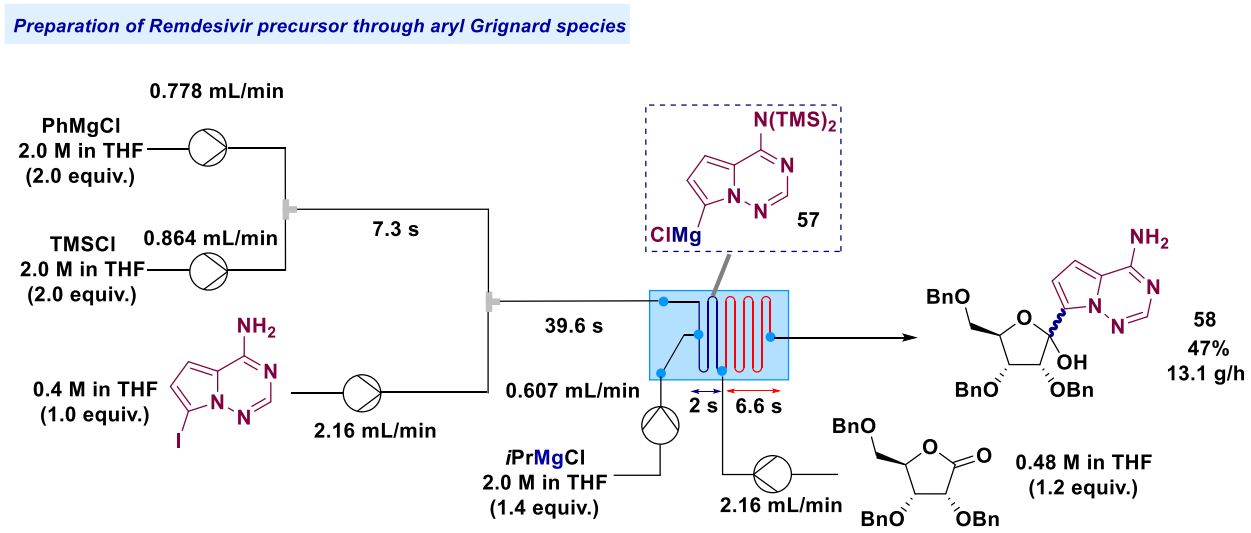
2. Generation of organomagnesium reagents

The continuous generation and utilization of organolithium intermediates has been discussed so far. Pioneering work by researchers such as Knochel, Alcazár and others has laid the foundation for applying the principles of flash chemistry to various other organometallic intermediates, including Grignard reagents.[83,84] For example, Kappe and colleagues broadened the flash chemistry principles to the relatively less-investigated iodine-magnesium exchange reaction using iPrMgCl·LiCl, commonly referred as "turbo Grignard", enabling the generation of chloromethylmagnesiumchloride **56** within 1 s from chloroiodomethane (Scheme 43) [85]. This highly unstable intermediate was promptly quenched in-line with aldehydes or ketones, within a residence time of 1.6 s, yielding chlorohydrins (under acidic quenching conditions) or epoxides (under basic quenching conditions). The robustness of the flow set-up was confirmed by a long-run experiment, where the system operated uninterrupted for a duration of 2 h, producing 20.3 g of 2-chloro-1-(p-tolyl)ethan-1-ol, with a productivity of 1 mmol/min. Notably, under batch conditions, the expected chlorohydrin was not observed when the reaction was conducted at -60 °C, underscoring the fleeting nature of the reaction intermediate.



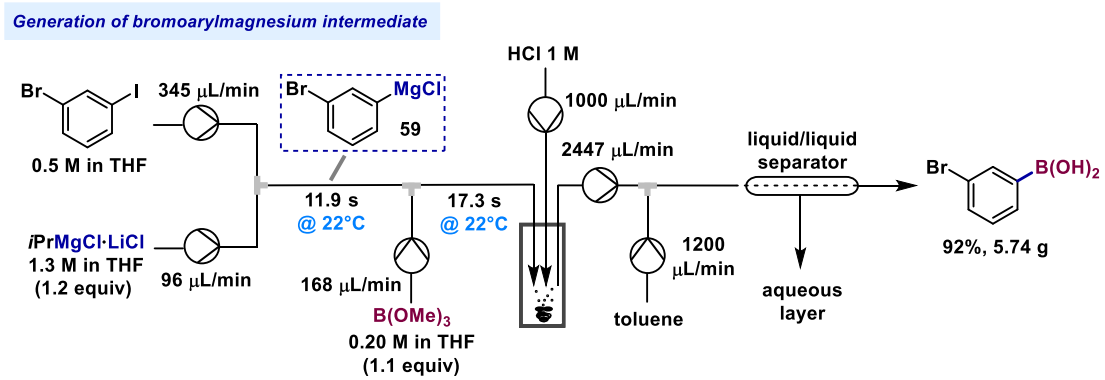
Scheme 43. Generation and utilization of chloromethylmagnesiumchloride under continuous flow

Kappe's group made substantial efforts to improve the synthesis of Remdesivir, the first drug approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of COVID-19 [86]. In particular, the *C*-glycosylation proved challenging, and a proposed solution was the use of a Grignard reagents, as opposed to a lithiated nucleophile (Scheme 44). As previously discussed, the free amine of iodinated pyrrolotriazinamine was silyl-protected, and the resulting intermediate was then combined in-line with *i*PrMgCl to the form Grignard reagent **57**. Pyrrolotriazinamine **57** underwent the desired glycosylation to afford the desired addition product **58** in 47% yield. Although this procedure did not significantly improve product yields compared to the reported batch protocol, the authors emphasized how the continuous flow approach notably improved processability. Unlike the batch protocol, which required three different temperatures and suffered from high exothermicity, the flow approach operated at room temperature with a total residence time of only 56 seconds for the three-step sequence.



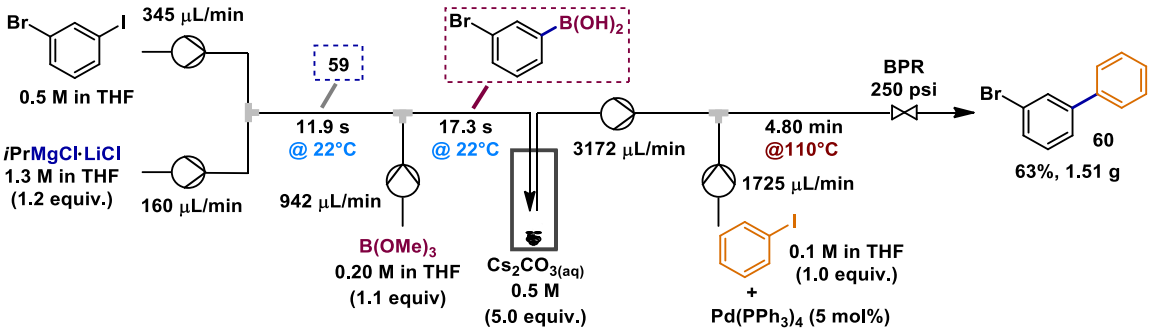
Scheme 44. C-Glycosylation *en route* to Remdesivir using organomagnesium intermediate

In 2023, Lebel and Fourquez introduced a method for the continuous synthesis of bromoarylboronic acids, involving the generation of highly reactive bromoarylmagnesium intermediates, which were conveniently managed using flow microreactor technology (Scheme 45) [87]. For example, 3-bromoiodobenzene underwent selective magnesium-iodine exchange by mixing with a commercially available solution of iPrMgCl·LiCl. The resulting Grignard intermediate **59** was quenched with $B(OMe)_3$ in the second microreactor (borylation completed in less than 20 s at 22 °C), followed by an in-line 1 M aqueous HCl workup within a continuously stirred tank reactor (CSTR). Subsequent in-line liquid/liquid separation afforded the desired arylboronic acid in 92% yield, when conducted on a larger scale of 28.6 mmol, operating the system for 3 h.



Scheme 45. Magnesitation and borylation of bromoiodoarene in continuous flow

As an extension to their work, the authors performed a sequence of the above-mentioned borylation, followed by a continuous flow Suzuki cross-coupling in a telescoped process. During the quench in in the continuously stirred tank reaction, Cs_2CO_3 was introduced as the base, before a solution of Pd- catalyst and iodobenzene were introduced in another inlet. Operating at 110 °C with a residence time of 4.8 mins afforded the desired biaryl **60** in 63% yield (Scheme 46).



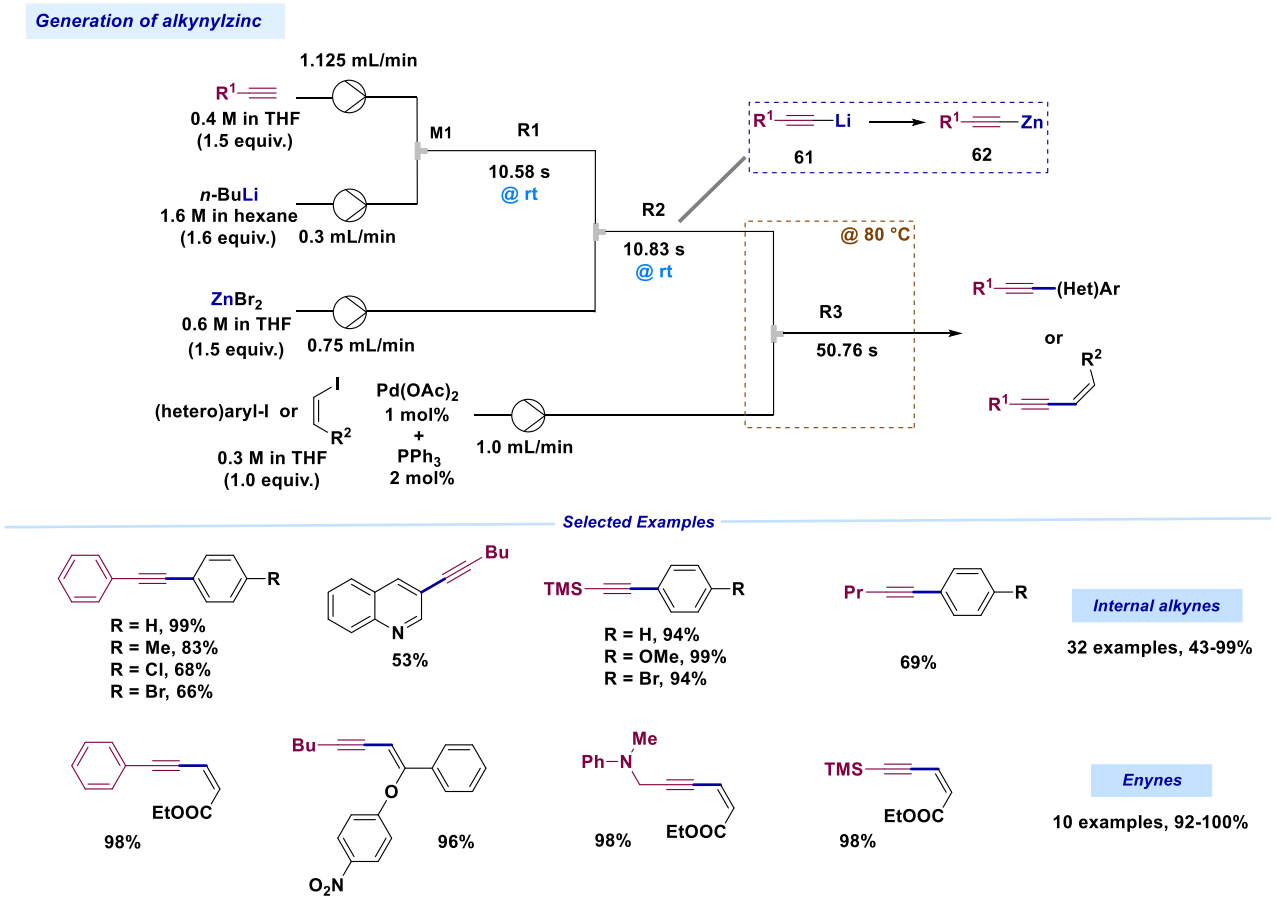
Scheme 46. Suzuki-coupling of 3-bromophenylboronic acid and iodobenzene in continuous flow

3. Generation of organozinc reagents

Also organozinc compounds serve as versatile reagents for establishing various types of bonds in organic compounds, including C(sp^2)-C(sp^2), C(sp^3)-C(sp^3), C(sp)-C(sp^2), and C(sp^2)-C(sp^3) bonds. However, despite their synthetic versatility, the use of organozinc reagents has been constrained due to their sensitivity, coupled with the presence of only few operationally simple preparation protocols. These challenges can be addressed by continuous flow chemistry.

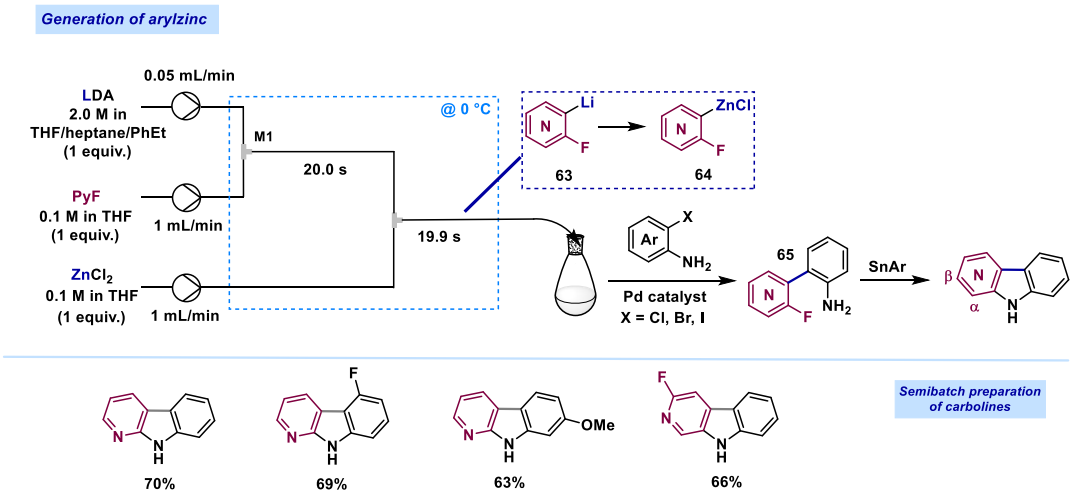
Notably, Knochel has played a pioneering role in advancing the on-demand preparation of organozinc reagents under continuous flow conditions, rejuvenating this field. For example, Knochel's approach involves the generation of zinc species by a lithiation (or magnesitation)/transmetalation sequence with zinc salts [88] The efficacy of this method hinges on the rapid lithiation (or magnesitation) of substrates, which outpaces the transmetalation with zinc salts. This methodology has found wide application in functionalizing various compounds, including unsymmetrical azobenzenes [89] (hetero)arenes bearing sensitive functional groups [90] and 1,2-dicyanobenzene [91]. Its value has also been recognized adopted by other authors such as Buchwald [92, 93] and Loren [94].

In 2019, Lin and colleagues harnessed this concept for the synthesis of unsymmetrical alkynes and enynes (Scheme 47) [95]. Initially, an organolithium deprotonated terminal alkynes in M1 and R1, with a residence time (t^{R1}) of 10.58 s, generating lithium acetylide **61**. This intermediate was then transmetalated with a $ZnBr_2$-solution within a residence time of 10.83 in R2 (t^{R2}). The resulting alkynylzinc reagent **62** was engaged in a C(sp)–C(sp^2) Negishi cross-coupling reaction with various aryl or vinyl iodides, ultimately yielding internal alkynes and enynes in generally good to excellent yields.



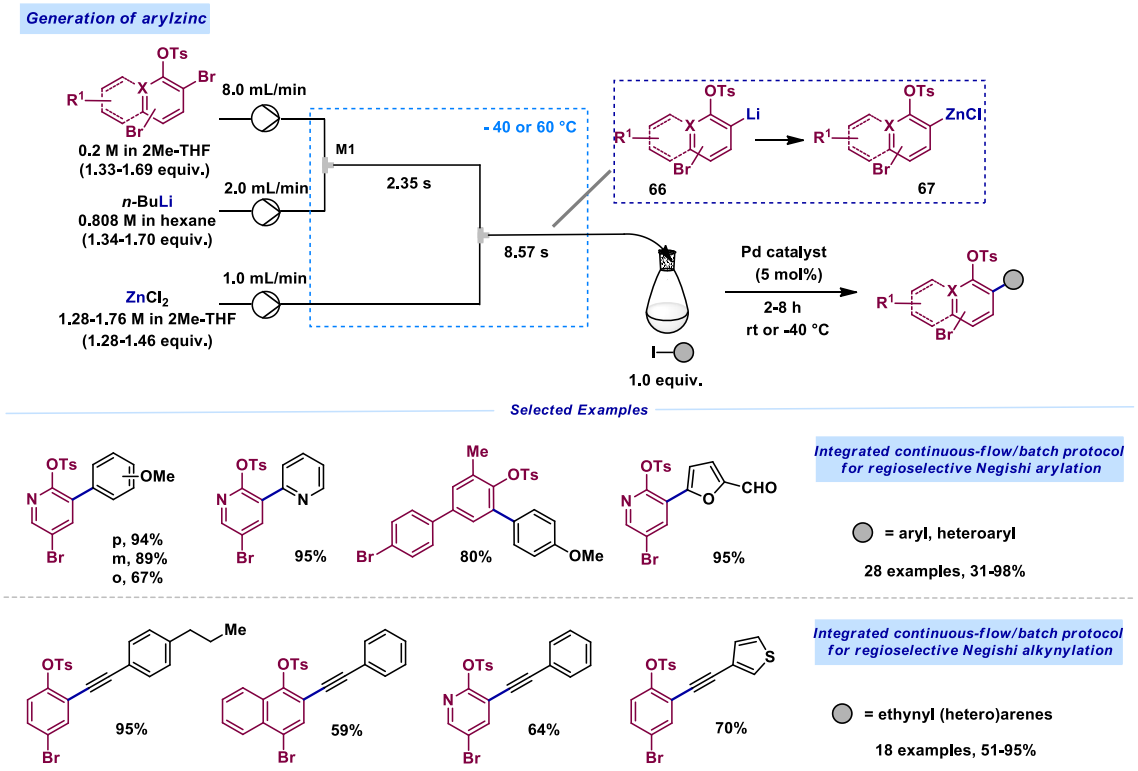
Scheme 47. Generation of alkynylzinc and its subsequent Negishi reaction in continuous flow

Building on Knochel's work, Roesner reported an efficient approach for the preparation of various α - and β-functionalized carbolines (Scheme 48) [96]. This process involved a sequence of *ortho*-lithiation, zincation, Negishi cross-coupling, and intramolecular nucleophilic aromatic substitution. *Ortho*-lithiation of fluoropyridines within 20 s at 0 °C, followed by zincation of organolithium species within 20 s **63** provided arylzinc **64**. Negishi cross-coupling of **64** in batch with 2-haloanilines furnished the 2-aminobiaryl derivative **65**, which underwent an intramolecular nucleophilic aromatic substitution to affording the desired carbolines. Whereas this sequence was shown to be fully operable under batch conditions, flow conditions expedited the generation of thermally labile lithiated intermediates and enhanced their safety during handling.



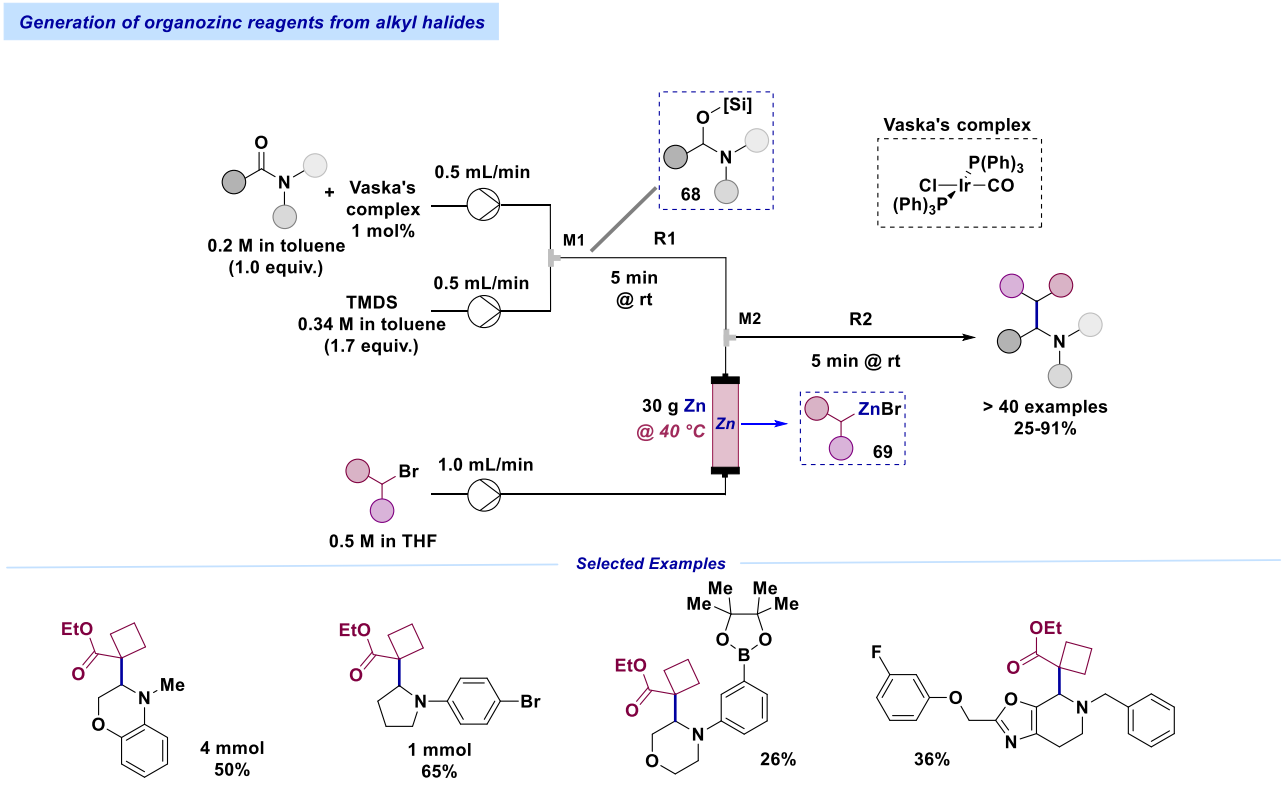
Scheme 48. Continuous flow generation of arylzinc by Zn/Li transmetalation

In the same line of research, Kim also reported an integrated continuous-flow/batch protocol for a lithiation/transmetalation/Negishi-coupling sequence of polyhalo-substituted (hetero)aryl tosylates (Scheme 49) [97]. Notably, the metalation was directed by the tosyl-group to regioselectively occur in the *ortho*-position. Thus, the process initiated with a lithium-halogen exchange reaction resulting in the formation of a lithiated intermediate **66**, which was transmetallated with $ZnCl_2$ in flow, generating the desired organozinc **67** within 10.92 s. In batch, the organozinc reagent was coupled with suitable (hetero)aryl iodides. The procedure was successfully extended to various polyhalo-functionalized (hetero)aryl tosylates and (hetero)aryl iodides, obtaining the desired *ortho*-arylated products in good to excellent yields. Building on this success, the same research group expanded their methodology to encompass the *ortho*-selective alkynylation of diverse polyhalo-functionalized (hetero)aryl tosylates, employing iodoethynyl (hetero)arenes as coupling partners [98]. Application of a metalation/zinc-transmetalation sequence has recently been reported by Kelly and co-workers toward the synthesis of KRAS G12C inhibitor Divarasib [99]. Moreover, a rapid Simmons-Smith cyclopropanation flow process involving the *in situ* production of the zinc carbenoid species has also been recently disclosed by Cabrera, Alemán et al [100].



Scheme 49. Continuous flow generation of arylzinc and utilization in Negishi arylation and alkynylation

An alternative approach to *in situ* continuous flow preparation of zinc species was introduced by Alcázar. This method entails the on-demand preparation of organozinc reagents by passing alkyl bromides through a column containing metallic zinc. The resulting organozinc solutions can be seamlessly employed in subsequent inline-transformations, including Reformatsky reactions [101] and visible-light-accelerated Negishi cross-couplings [102, 103] Using the present technique, researchers at Janssen designed an automated high-throughput platform for synthesizing C(sp^3)-enriched drug-like molecules [104]. In 2023, Alcázar, Dixon, and de la Hoz extended this automated protocol to facilitate the reductive coupling of tertiary amides with organozinc reagents (Scheme 50) [105]. Specifically, a solution of tertiary amide and Vaska's complex was mixed in M1 with the reducing agent tetramethyldisiloxane (TMDS). The resulting mixture was allowed to react in R1, affording the hemiaminal intermediate **68**. Nucleophilic attack of organozinc reagent **69**, generated by passing an alkyl-bromide through a column packed with zinc powder, formed the desired C(sp^3)–C(sp^3) bonds. The developed automated synthetic platform demonstrated remarkable efficiency, allowing for the synthesis of compounds at a rate of four reactions per hour, making it well-suited for library synthesis.



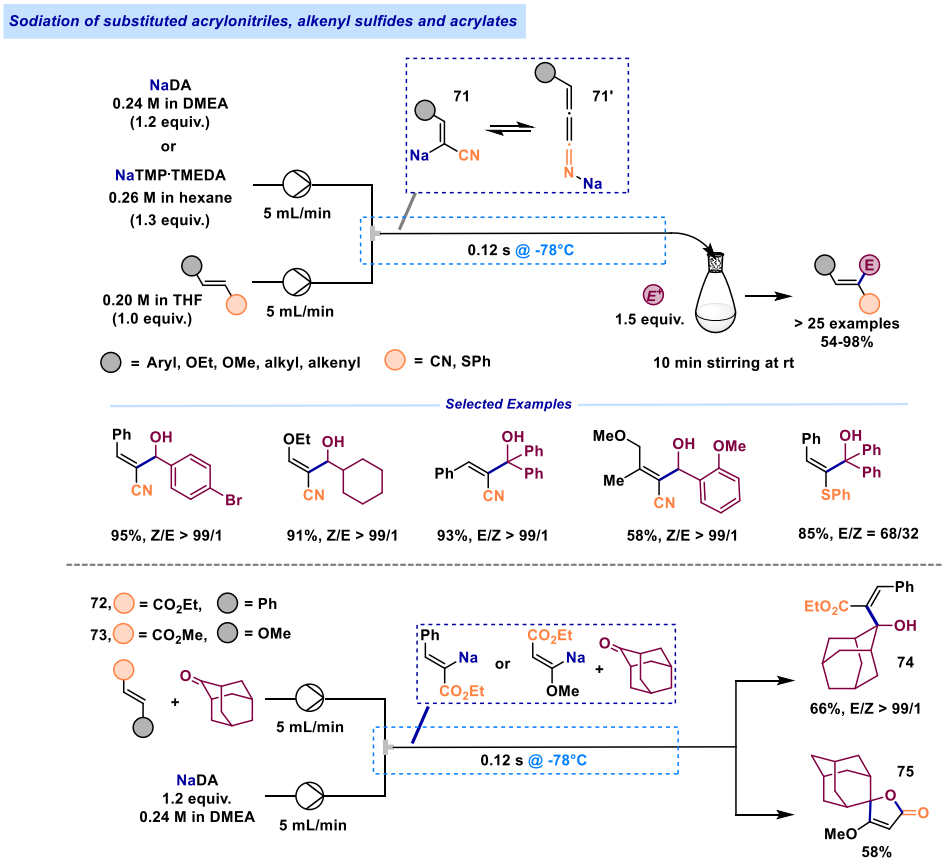
Scheme 50. Continuous flow generation of organozinc reagents from their corresponding alkyl halides

4. Generation of organosodium reagents

The abundant presence of sodium in the Earth's crust, coupled with the affordability and low toxicity of sodium salts, should drive widespread adoption of organosodium compounds in synthetic chemistry. However, despite pioneering works in the 1930s [106, 107] the realm of organosodium chemistry remained relatively uncharted for decades due to their inherent thermolability, limited stability and solubility, particularly in ethereal solvents. Schlosser and Mordini [108], Mioskowski [109], and Mulvey [110] recognized the high potential within organosodium chemistry, which has recently experienced a renaissance thanks to the contributions of Collum [111–113], Chiba [114], Takai and Asako [115], Lu [116], Hevia [117] and Capriati [118].

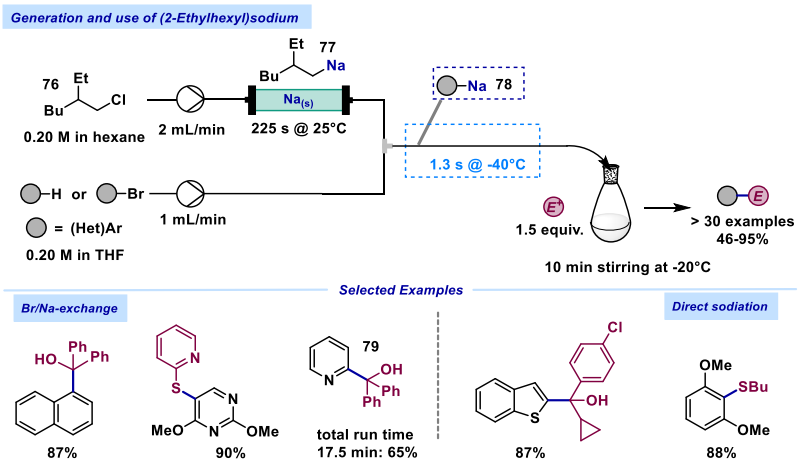
In 2018, Knochel reported the first sodiation of (hetero)arenes under continuous flow conditions adopting NaDA (sodium diisopropylamide) as the sodium base [119]. Knochel further advanced the field by achieving the continuous flow sodiation of different substituted acrylonitriles with sodium diisopropylamide (NaDA) in DMEA (dimethylethylamine), resulting in organosodium compounds **70** which were subsequently captured in batch with various electrophiles (Scheme 51) [120]. The stereochemical outcome of this process depended on the electrophile adopted, with aldehydes favoring *Z*-diastereoisomers and ketones mostly yielding *E*-diastereoisomers. The diastereoselectivity observed with ketones was attributed to an equilibration between the sodiated nitrile **71** and cumulene **71'**. This same reaction sequence was successfully applied to the

sodiation and functionalization of alkenyl sulfides. Under Barbier-conditions, and using sodium 2,2,6,6-tetramethylpiperidide (NaTMP) as the sodiating agent, the protocol was also extended to acrylates.



Scheme 51. Sodiation of substituted acrylonitriles, alkenyl sulfides and acrylates under continuous flow

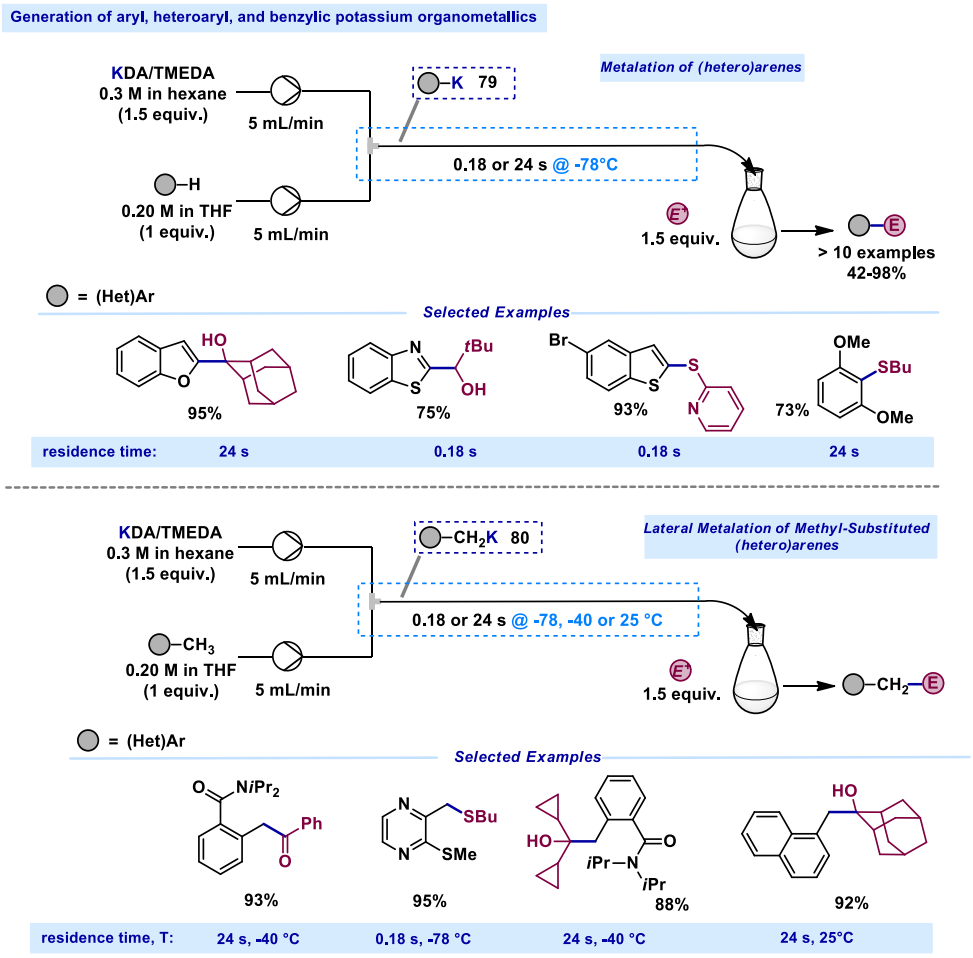
In 2021, the same group introduced an on-demand continuous flow protocol for the preparation of (2-ethylhexyl)sodium, a hexane-soluble organosodium reagent for sodium-bromine exchange reactions and directed metalation (Scheme 52) [121]. (2-Ethylhexyl)sodium **77** was generated by pumping alkyl chloride **76** through a packed-bed reactor filled with sodium particles at -40 °C with a residence time of 1.3 s. This reagent was then reacted in-line with (hetero)aryl bromides or (hetero)arenes, resulting in arylsodium intermediates **78** *via* sodium-bromine exchange or directed metalation, respectively. These organosodium intermediates were subsequently quenched in batch mode with a wide array of electrophiles, including ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides, and alkyl iodides. To obtain tertiary alcohol **79**, an in-line quenching of the organosodium intermediate with benzophenone was set-up. Remarkably, the flow system was run continuously for 17.5 min, underscoring the robustness and scalability of the procedure.



Scheme 52. Continuous flow generation of (2-ethylhexyl)sodium and its use for sodium-bromine exchange and directed metalation

5. Generation of organopotassium reagents

Similar to organosodium compounds, also potassium organometallic intermediates have received only limited attention. Nonetheless, few examples have been reported. Knochel made a noteworthy contribution by detailing the continuous flow metalation of functionalized (hetero)aryl potassium organometallics, employing potassium diisopropylamide (KDA) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in a hexane/THF mixture (Scheme 53) [122]. The generation of organopotassium intermediates **79** was performed in continuous flow conditions at -78 °C, with residence times of 0.18 or 24 s depending on the specific (hetero)arene. Just as demonstrated with organosodium intermediates, these potassium organometallics were subsequently trapped in batch with various electrophiles. Moreover, the protocol was expanded to include the lateral metalation of methyl-substituted (hetero)arenes, yielding benzylic potassium organometallics **80** that were also quenched with a variety of electrophiles. Notably, more commonly used lithium diisopropylamide was found ineffective for this transformation.

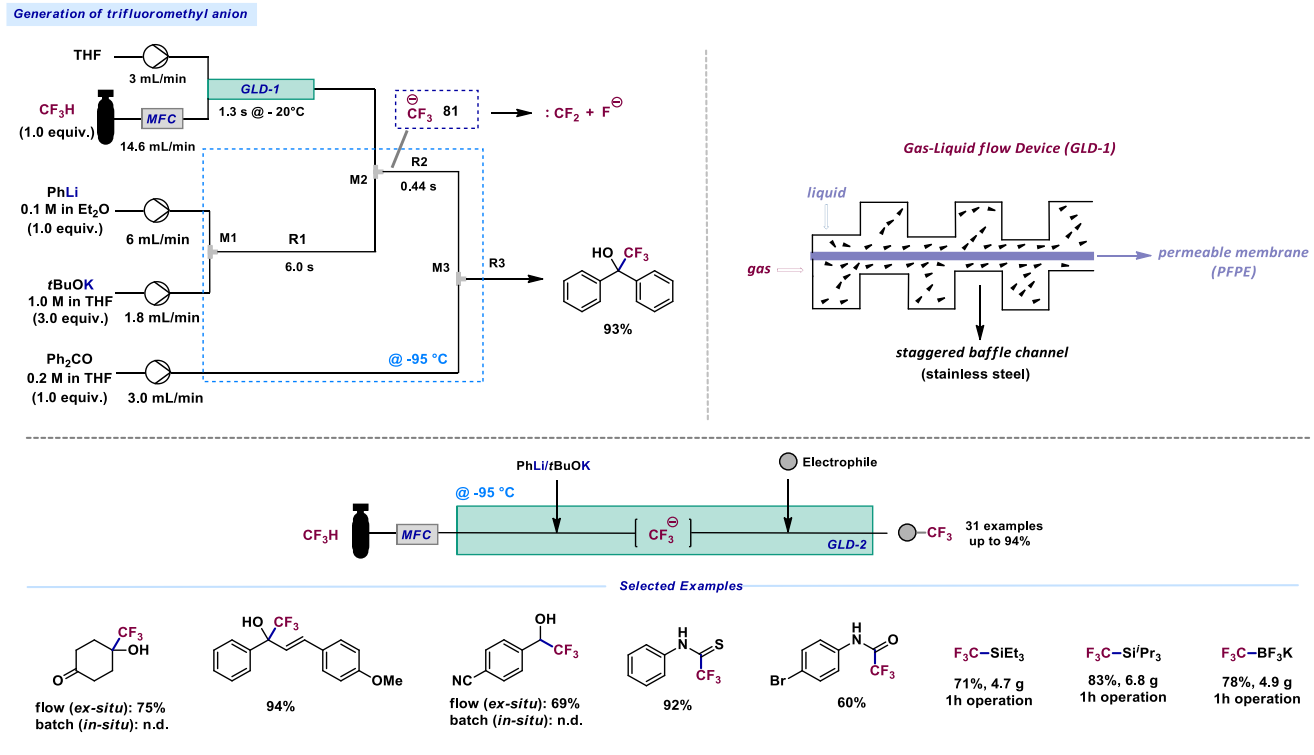


Scheme 53. Continuous flow preparation of functionalized aryl, heteroaryl, and benzylic potassium organometallics

Organopotassium chemistry under flow conditions may well be suitable to solve another long-standing issue in synthetic chemistry, that is the functionalisation of fluoroform. Whereas utilizing the trifluoromethyl anion *via* deprotonation of fluoroform appears to be the most direct approach for nucleophilic trifluoromethylation on paper, in practice, this method faces significant hurdles. Trifluoromethyl anion is notorious for its extreme instability, swiftly decomposing into difluorocarbene even at low temperatures. Although an internal quenching sequence might prove useful in specific cases, it can lead to selectivity issues, limiting the efficiency and applicability of the reaction. The opportunity of metalateing fluoroform under continuous flow conditions was previously explored by Ley [123], and Kappe [124, 125].

In 2022, Dong-Pyo Kim and Heejin Kim newly delved into this transformation devising a gas-liquid flow device (GLD) for the generation of a bare CF_3^- anion under external quenching conditions starting from fluoroform (Scheme 54) [126]. For this purpose, they created a dissolver consisting of a highly permeable nano-porous membrane made of perfluorinated polyether (PFPE) sandwiched between two stainless steel channels patterned with staggered baffle structures to induce rapid biphasic mixing. By employing computational fluid dynamics (CFD), they meticulously evaluated the number and height of the baffles, as well as the porosity

and thickness of the membrane, to optimize the interfacial contact between gas and liquid. Once the optimized conditions for rapid dissolution of fluoroform in THF were established, they investigated the generation of trifluoromethyl anion **81**. Whereas various potassium and lithium bases proved ineffective, Schlosser's base successfully metalated fluoroform. With a residence time in R2 (t^{R2}) of 0.4 s at -95 °C, the authors generated trifluoromethyl anion and then trapped it with benzophenone, resulting in the trifluoromethylated alcohol in 93% yield. Building on the insights gained, the authors also developed a second generation of their integrated flow device that facilitated the generation of the intermediate and its subsequent quenching with the electrophile, allowing them to explore the reaction scope using various electrophiles, including ketones, aldehydes, an ester, isocyanates, and isothiocyanates. This work underscores the potential of this technology in realizing reactions that prove challenging when traditional approaches are employed. Schlosser's base has recently also found application in the metalation and functionalisation of THF under flow conditions.



Scheme 54. Continuous flow generation and synthetic utilization of trifluoromethyl anion

Conclusion

This review has discussed the power of flow chemistry to generate and use highly unstable and transient organometallic intermediates for the rapid build-up of molecular complexity – demonstrated by a wide array of protocols showcasing the synthetic possibilities added to chemists' toolbox in the last four years. In numerous synthetic scenarios, the distinct advantages of flow technology, as compared to traditional batch chemistry, predominantly revolve around establishing safer and more controlled reaction conditions. This, in

turn, enables the development of more efficient and secure protocols. However, the scope of flow chemistry extends beyond the implementation of batch procedures and safety considerations. Firstly, the precise control of reaction time, as well as the enhanced mixing of reagents, allows for meticulous reaction design with high product selectivity. Within the scope of the review, this has been impressively demonstrated by e.g., lithiations in the presence of functional groups susceptible to nucleophilic attack. These reactions are proved to be extremely challenging, if not impossible, to conduct in batch. Secondly, it has – particularly in the last few years – contributed to the renaissance of almost forgotten chemistry, including organosodium and organopotassium chemistry. Remarkably, such protocols were not only academically interesting, but also facilitated the chemistry which had hitherto proved challenging with "classic" organolithium or Grignard reagents; e.g., the functionalization of fluoroform. Thirdly, we have seen a strong move towards application to active pharmaceutical reagents and key building blocks, enabled by the availability of more robust set-ups and the ever-expanding toolkit of reactions suitable to flow technology. We expect to see more such applications in the future. Despite these significant advances, some challenges remain. As with other technologies, also flow chemistry is faced by technological limits, so that e.g., heterogenous reactions are only difficult to process within flow due to the risk of clogging of tubing. In addition, despite the clear advantages in many reported reactions over its batch counterpart, adoption of the technology in academic labs has been only slow, due to the unavailability of suitable equipment, or of the relevant expertise which has found its way into undergraduate chemistry courses only very slowly. We hope that the ever-growing reports on challenges solved by flow technology support a more rapid adoption within the community. Last, with a view on further synthetic challenges to be addressed: for example, protocols involving chiral syntheses have only scarcely been reported, so that we anticipate further results with this regard in the years to come.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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