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Flow chemistry as green technology for the genesis and use of organometallic reagents in the synthesis of key building blocks and APIs – An update

Philipp Natho, Renzo Luisi *

FLAME-Lab, Flow Chemistry and Microreactor Technology Laboratory, Department of Pharmacy-Drug Sciences, University of Bari "A. Moro", Via E. Orabona 4, 70125, Bari, Italy

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ABSTRACT

The advent of flow chemistry and flow microreactor technology in organic synthesis has added a series of options to the toolbox of synthetic chemists by enabling access to chemical reactions, which had hitherto been little explored or impossible in classical batch methods. In this review article, we provide an update on recent reports (published since 2020) showcasing examples of flow technology enabling the genesis and use of highly reactive organometallic intermediates for the synthesis of key building blocks and active pharmaceutical ingredients. In addition to showcasing the known advantages of flow technology (e.g., safety, scalability and productivity) we also highlight its positive impact on the greenness of organic reactions.

1. Introduction

The *Twelve Principles of Green Chemistry,* although coined as early as 1998 by Paul T. Anastas and John C. Warner, are now as timely and relevant as ever, and the described framework serves as a widely accepted tool for the assessment of the sustainability (*greenness*) of a reaction, reaction sequence, or even industrial process for the synthesis of active pharmaceutical ingredients (APIs) [1–3]. Three of those twelve principles are concerned with *Design for Energy Efficiency* (i.e., energy requirements such as heating and cooling should be minimized), *Reducing Derivatives* (i.e., use of blocking groups, protection/deprotection etc. should be avoided if possible), and *Less Hazardous Chemical Syntheses* (i.e., synthetic methods should be designed with little or no hazards to environment and human health).

To achieve these objectives, scientists have for the past decades turned to the use of technology, and in particular the introduction of flow chemistry has had a significant impact on enabling not only hitherto *impossible* transformations in classical batch set-ups, but also on the sustainability of such reactions [4]. Specifically, flow reactors operate under steady-state conditions, thermal runaways are unlikely and the closed systems with reduced dimensions minimise exposure to (hazardous) chemicals (*Less Hazardous Chemical Syntheses*). In addition, exquisite control of the reaction parameters (i.e., temperature, pressure and time), extremely fast mixing and intensified heat transfer enable the generation and use of intermediates under milder conditions (*Design for Energy* Efficiency), and with greater control of chemical selectivity (*Reducing Derivatives*) than in classical batch chemistry. In some cases, seemingly *impossible* transformations – such as the generation and utilisation of highly unstable and reactive organometallic species – under batch conditions are enabled using flow technology. The potential and impact of continuous flow for synthetic chemistry has been recognized by various academic and industrial research groups, with their work being highlighted and critically evaluated in several excellent reviews [5–9].

The aim of this review is to collate and critically evaluate newly developed applications of flow technology for the genesis and use of organometallic intermediates for the synthesis of valuable key intermediates and APIs starting from 2020 – thus providing an update since our previous review on this topic given the fast-paced, continuous and impactful developments [5]. We will highlight the use of flow synthesis for the a) chemoselective generation of genuinely unstable organometallic intermediates from precursors containing electrophilic moieties, b) flash chemical approaches for the rapid interception of highly reactive intermediates before decomposition, and c) the flow-chemical application for the improved (i.e., shortened or higher yielding) synthesis of APIs or late-stage building blocks. Relevant and impactful reports that advance the development and application of flow technology will be introduced. Categorised by the *active* organometallic utilised for synthetic manipulation, this review has been structured into four sections, as

* Corresponding author.
E-mail address: renzo.luisi@uniba.it (R. Luisi).

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follows:

- Organolithium reagents
- Organosodium and organopotassium reagents
- Organomagnesium reagents
- Organocopper and organozinc reagents

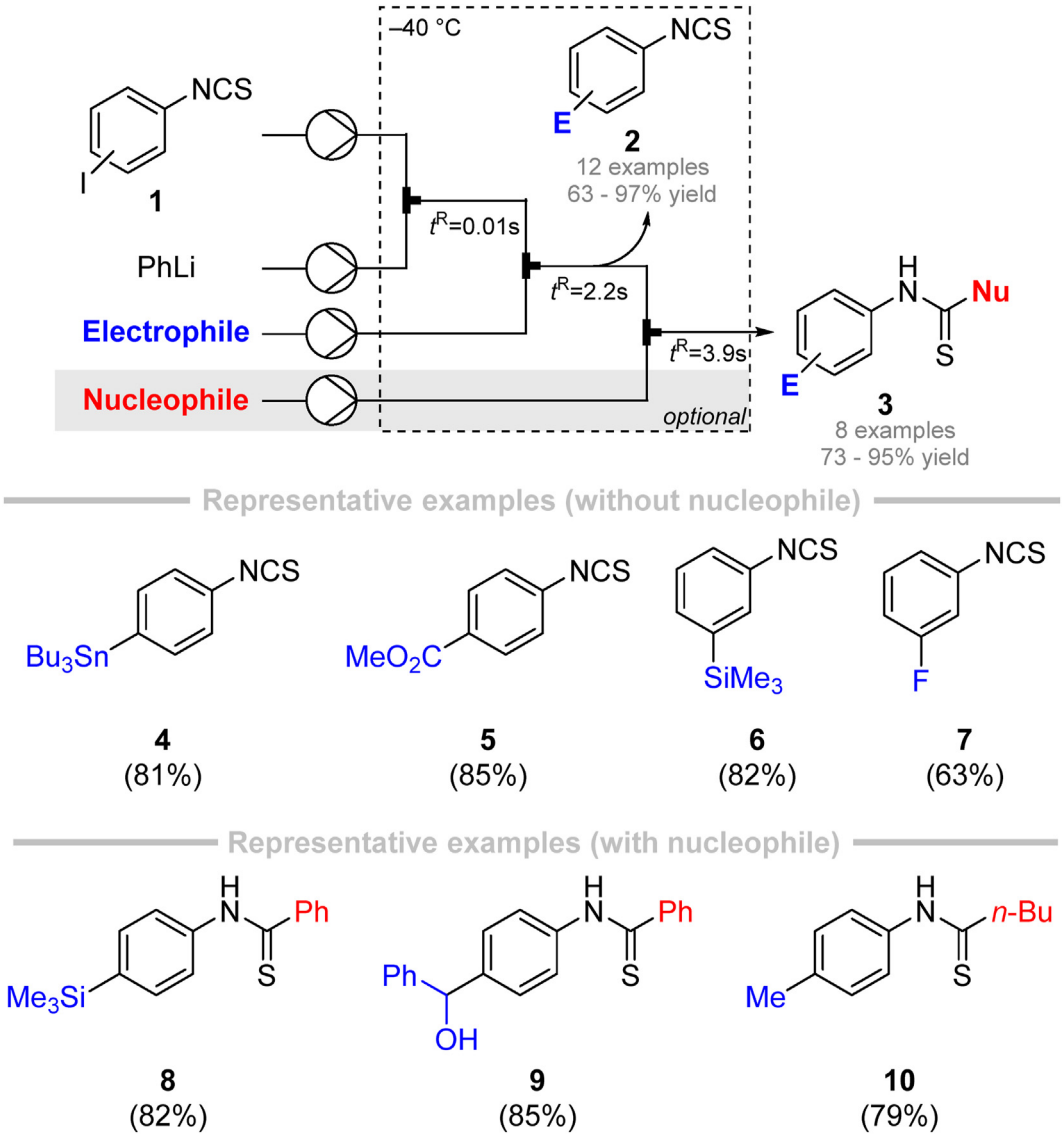
When discussing these methodologies, particular emphasis is placed on evaluating the synthetic utility of the protocols, the product scope with a view on key intermediates and APIs, and the extent to which some of the limitations and drawbacks of batch chemistry are addressed, therefore providing the reader with valuable insights into the current state of the "art" of flow technology.

2. Organolithium reagents

The utilisation of organolithium reagents for organic synthesis has been widely investigated. Their transfer to large-scale industrial settings has however not seldomly been limited by safety concerns, the requirement for cryogenic temperatures, and functional group incompatibilities. Given that flow technology offers a series of aforementioned advantages compared to classic batch chemistry, hitherto *impossible* lithiation reactions in batch have been shown to be feasible in flow.

Within this realm, the generation of organolithium species in flow has been dominated by lithium-halogen exchange. In most cases, an aryl-bromide or -iodide is treated with *n*- or *sec*-butyllithium to execute a lithium-halogen exchange within sub-second residence times, and the resulting organolithium species is subsequently treated with a suitable electrophile under flow conditions to yield the functionalised aromatic compound. Thus, a series flow procedures for the conversion of aryl halide to tetrasubstituted organosilanes [10], ferrocenyl azides [11], functionalised aryl azides [12], and ketones [13] have been developed since 2019.

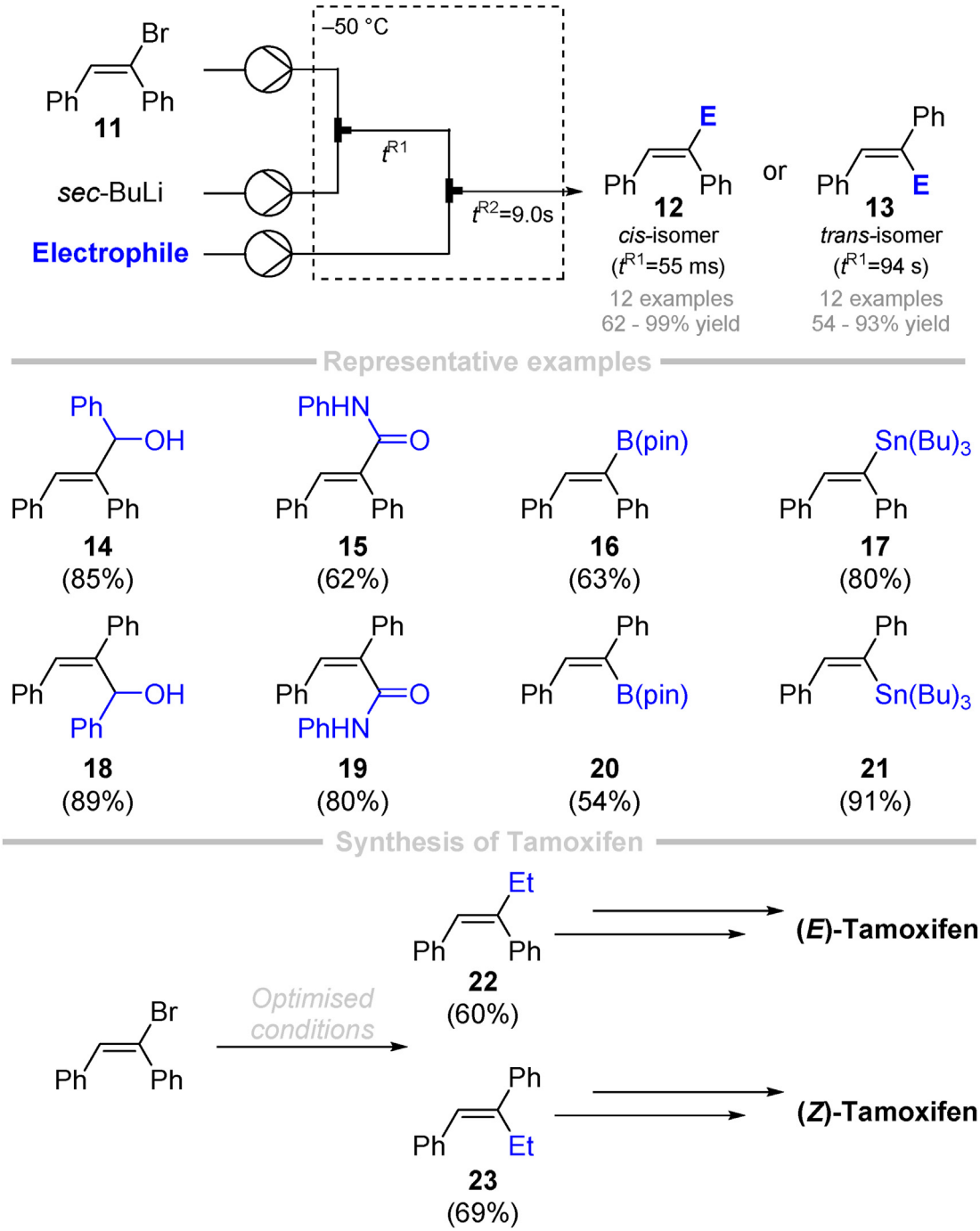
With the foresight to recognise the potential of performing *impossible* lithiations under flow chemistry, Kim and co-workers developed an integrated flow synthesis for the mono- and bis-functionalisation of isothiocyanate-substituted aryl halides (Scheme 1) [14]. Under batch conditions, lithiation of isothiocyanate-containing aryl halides by lithium-halogen exchange has been reserved to *ortho*-isothiocyanate--substituted substrates – at very low temperatures and short lithiation times – as the lithiated intermediate is stabilised by the *ortho*-directing effect. On the contrary, lithium-halogen exchange of *meta*- and *para*--isothiocyanate-substituted aryl halides **1** had not been reported under batch conditions. Using flow technology, direct lithiation of the *meta*- or *para*-position was successfully effected with phenyllithium and precise



Scheme 1. Kim's integrated flow synthesis for the mono- and bis-functionalisation of isothiocyanate-substituted aryl halides.

control of the residence time of 0.01 s, thus preventing additional step-count from protection/deprotection sequences. From the lithiated intermediate a range of functional groups, for example stannyl-, silyl-, ester- and alkyl-groups, were introduced in up to 97% yield (**4**–**7**). Excitingly, further product modification was achieved within the same flow setup by introduction of a nucleophile through a third T-mixer. Bis-functionalised substrates **8**–**10** were isolated in up to 95% yield after a total residence time of approximately 6 s. More recently, it was shown that also cyano-, nitro- and vinyl-groups were tolerated under lithium-halogen exchange conditions to provide stannylated, alkylated or protonated products when trapped with suitable electrophiles [15,16].

In addition to enabling *impossible* lithiations in the presence of reactive functional groups, careful control of the residence time can also influence the regiochemical outcome of α-anionic stilbene functionalisation (Scheme 2). Kim and co-workers demonstrated that *cis*-α-bromo stilbene **11** could be lithiated with *sec*-butyllithium by lithium-halogen exchange under flow conditions at −50 °C, and subsequently trapped with suitable electrophiles to yield trisubstituted stilbenes [17]. The regiochemical outcome, resulting from rapid *cis-trans* isomerisation of the α-anionic stilbene intermediate, was influenced by careful control of the residence time. Energetically less favourable functionalised *cis*-stilbene **12** was obtained after a very short residence time of 55 ms, whereas full isomerisation to the energetically more stable *trans*-stilbene **13** was observed after a residence time of 94 s. Such careful control of product regioselectivity – especially with a view on the synthesis of APIs – reduces excessive waste generation from purification of wanted isomers

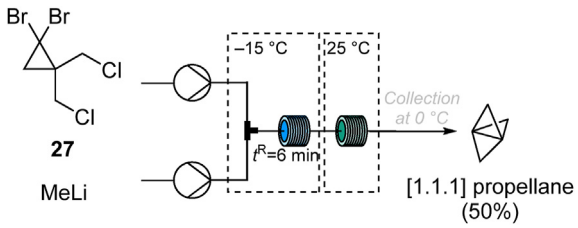


Scheme 2. Kim's regioselective synthesis of α-functionalised stilbenes via control of *cis*-trans isomerisation in flow.

from unwanted isomeric by-products, thus contributing to the overall sustainability benefit of the methodology. An investigation of the electrophile scope revealed that alkylated, amidated, chlorinated, silylated and borylated stilbene derivatives **14**–**21** could be obtained regioselectively with this methodology in up to quantitative yield. Notably, applicability to the pharmaceutical industry was demonstrated as gram-scale quantities of ethylated analogues **22** and **23**, which are late-stage precursors of (*E*)-Tamoxifen (full estrogen agonist) and (*Z*)-Tamoxifen (estrogen-dependent breast cancer management agent) respectively, were produced within 12 min of continuous flow operation.

The impact of these significant advances of utilizing flow technology for otherwise challenging lithium-halogen exchange/functionalisation reactions has been impressively demonstrated by various applications to pharmaceutically relevant late-stage intermediates and APIs in recent years. To this extent, Kappe's flash chemistry approach for synthesis of a late-stage intermediate of the SARS-CoV-2 drug remdesivir stands out as particularly timely and useful (Scheme 3) [18]. At a controlled temperature of −30 °C across the entire flow set-up, the free amine-group of pyrrolotriazinamine **24** was protected with bidentate protecting group 1, 2-bis(chlorodimethylsilyl)ethane using a residence time of 1.4 s, before LDA was introduced to neutralise the acidic by-products. Lithium-halogen exchange was then effected using *n*-butyllithium with a residence time of 0.8 s, before lactone **25** was introduced to yield the desired late stage intermediate **26**. Most notable, the process exhibited an exceptional stability over a longer processing period with assay yields varying by <2% over 2 h, providing 16.9 g of the glycosylated product **26** (60% yield), corresponding to a high space-time yield of 10.4 kg L^{-1} h^{-1}. Although the isolated yield is 14 percentage points lower than in the comparable batch approach, the drastic reduction of reaction time, the increase in reaction temperature from −70 °C to −30 °C, more facile scale-up opportunities and improved safety considerations demonstrate the advantages of this flow chemical approach. In addition, this telescoped synthesis reduces the number of work-up and purification steps, and in turn waste creation, thus adding further sustainability aspects to this methodology. Similar approaches were applied to the synthesis of late-stage intermediates of type 2 diabetes mellitus drugs canagliflozin and dapagliflozin [19,20], and a histone deacetylase inhibitor [21].

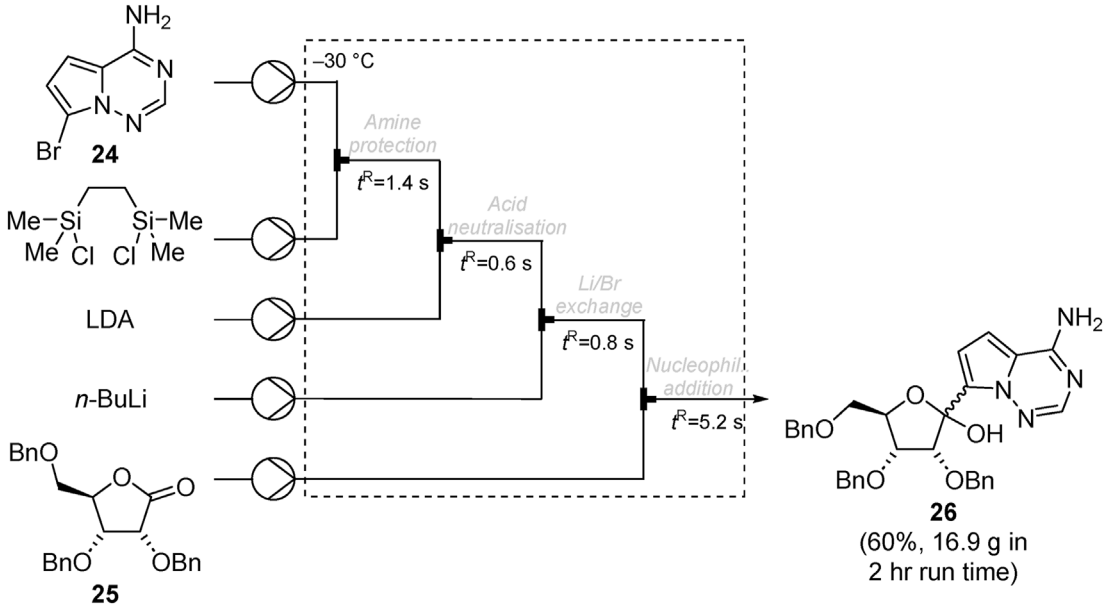
Lithium-halogen exchange under flow chemical conditions is, however, not limited to aryl halides, as also alkyl halides have been shown to be suitable precursors. As such, Donnelly and Baumann have recently reported that under flow conditions tetrahalide **27** can be converted to



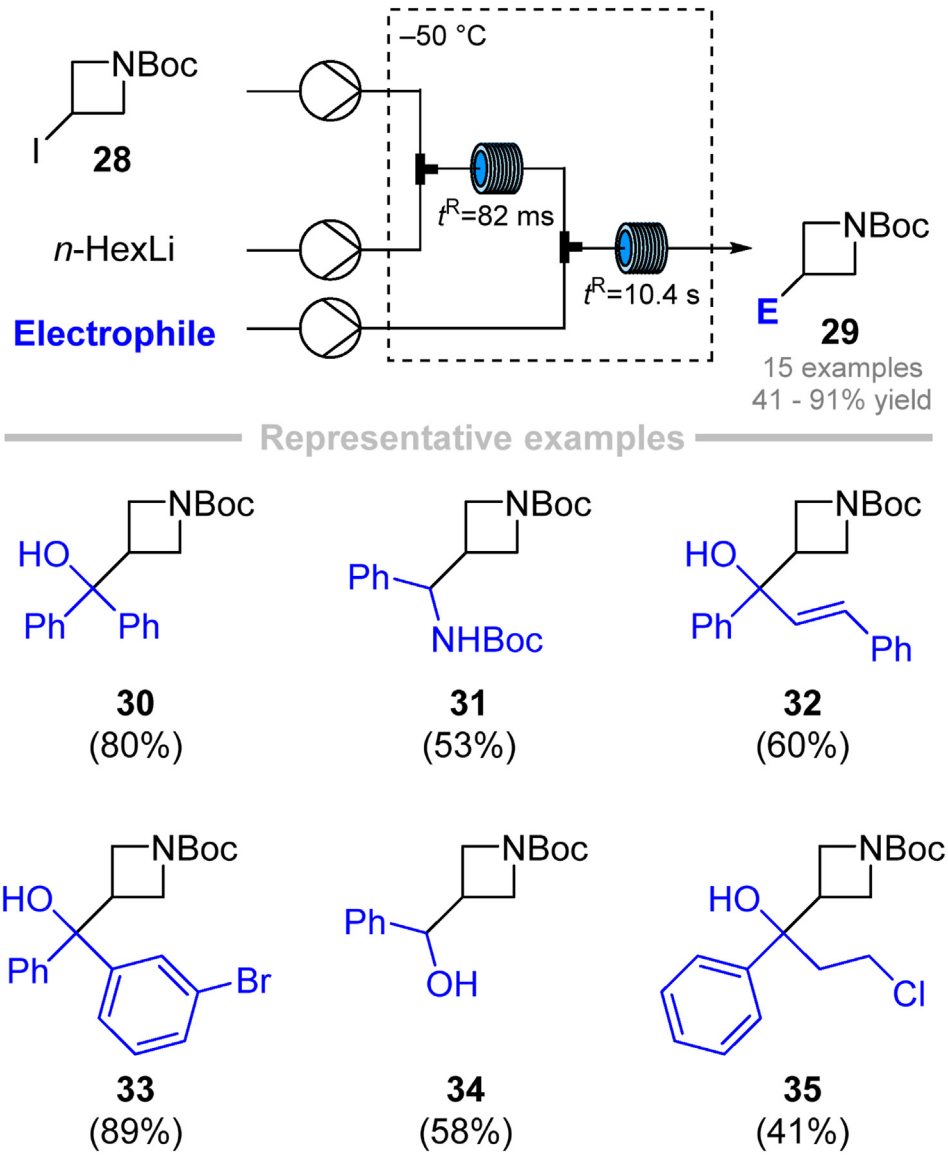
Scheme 4. Donnelly and Baumann's flow chemistry approach to [1.1.1]propellane.

[1.1.1] propellane – an important isostere in drug discovery for *para*-substituted phenyl rings, alkynyl groups and *tert*-butyl groups with increased three-dimensionality (Scheme 4) [22]. As such, tetrahalide **27** was treated with methyllithium at −15 °C within 6 min residence time, before the temperature was raised to room temperature for complete conversion. Although the isolated yield of 50% was significantly lower than the yield obtained in the batch approach (up to 80%), the flow chemical method is characterized by its scalability and sustainability aspects, in particular the reduced energy requirements, and waste creation by easier purification of the product. Derivatisation of the product into valuable unsymmetrical bicyclo[1.1.1]pentane ester/acid chloride building blocks under continuous photochemical flow conditions showcased the utility of the developed process.

The synthesis and derivatisation of highly strained cyclic systems using flow technology was also extended to heterocyclic ring systems. Luisi and co-workers describe a methodology for the C3-functionalisation of azetidines (Scheme 5) – a common motif in biologically active compounds, including Baricitinib (JAK inhibitor) and Azelnidipine (calcium channel blocker) [23]. To this end, *N*-Boc-3-iodoazetidine **28** was treated with *n*-hexyl lithium with a short residence time of 82 ms at −50 °C, to prevent the formation of by-products resulting from self-quenching of the secondary alkyllithium, before suitable electrophiles were added *via* a second T-mixer for external quenching. In addition to imines and trimethyl borate, various carbonyl-containing electrophiles, including ketones, α,β-unsaturated ketones and aldehydes were shown to be suitable to provide functionalised azetidines **30**–**35**. Notably, the reaction proceeded with high chemoselectivity, as competitive lithium-halogen exchange (substrate **33**) or β-elimination (substrate **35**) were not observed. Related lithium-halogen exchange protocols for the iterative



Scheme 3. Kappe's flash chemistry approach to organometallic C-glycosylation for the synthesis of Remdesivir.

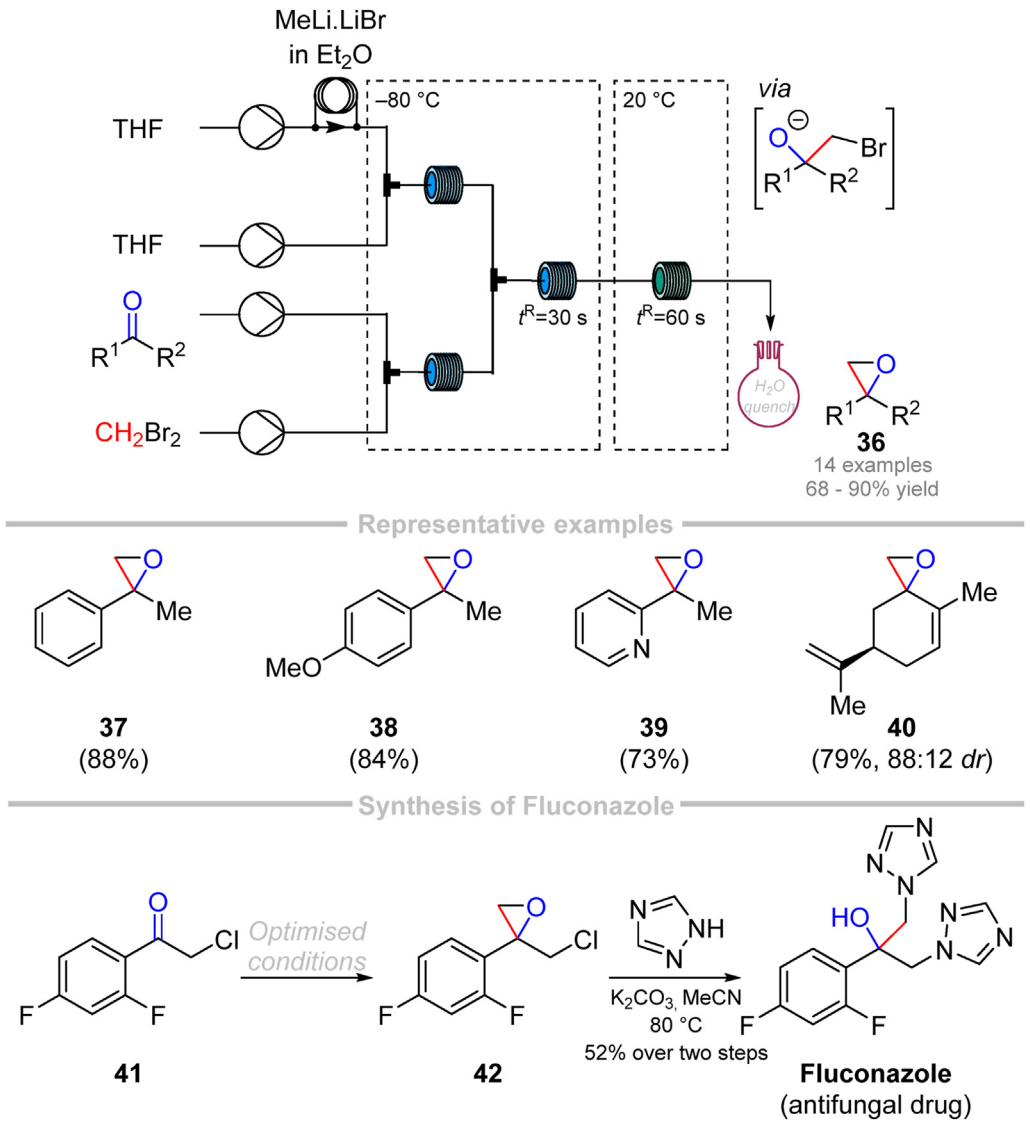


Scheme 5. Luisi's flow chemistry approach to C3-functionalisation of azetidines by lithium-halogen exchange.

homologation of terpenes [24], monofluoroalkylation of electrophiles [25], and the introduction of chiral secondary alkyl groups [26] have recently been reported.

Given the versatility of the carbonyl group in synthetic chemistry, its construction and derivatisation by lithium-halogen exchange protocols under flow chemistry has attracted considerable interest. For example, the well-studied conversion of ketones to terminal epoxides with (bromomethyl)lithium has been translated to flow technology by Kappe (Scheme 6) [27]. To this end, highly reactive and short-lived (bromomethyl)lithium was generated from cheap and abundant dibromoketone and methyllithium lithium bromide complex solution in THF at −80 °C. The nucleophilic intermediate was successfully tamed to allow addition to the ketone within a residence time of 30 s under an internal quenching regime. Further 1 min at room temperature promoted intramolecular ring closure by substitution of the bromide by the transient alkoxide. A series of aliphatic ketones and substituted aryl ketones were converted to the corresponding terminal epoxides **36** in 68–90% yield, with electron-rich substrates generally performing better than electron-poor ones. In contrast to the widely applied Corey-Chaykovsky epoxidation, the current method is also suitable for the epoxidation of α-chloroketones and is hence a complementary approach. This tolerance enabled the shortening of the commercial synthesis of the antifungal drug Fluconazole by one synthetic step from α-chloroketone **41**. A related protocol for the synthesis of chlorohydrins and epoxides from aldehydes and Turbo-Grignard reagents was reported by the same group [28].

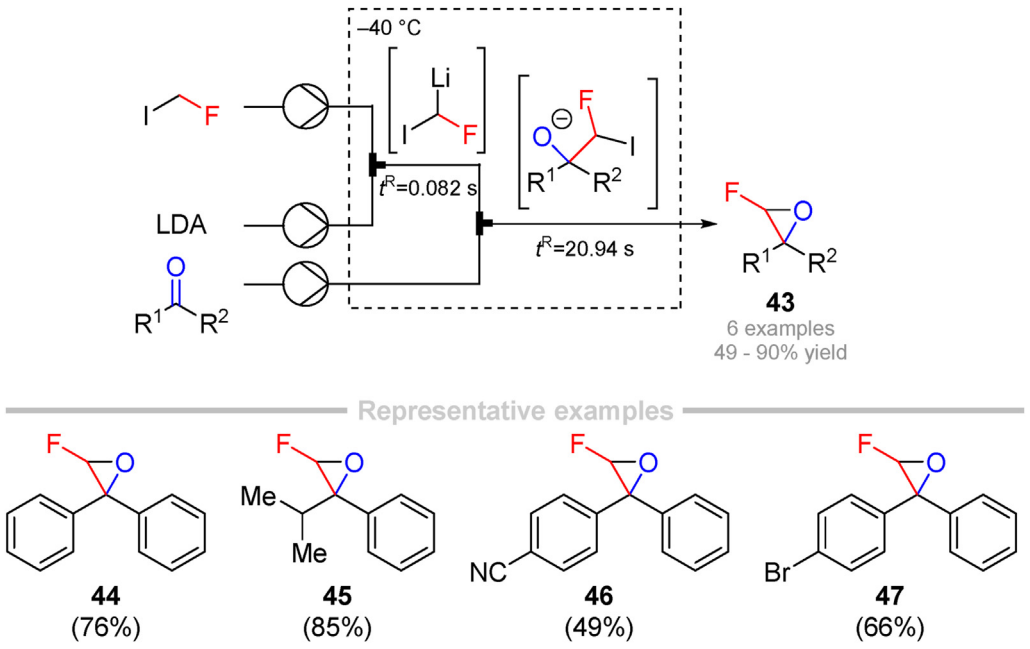
In contrast to generation of organolithium species by lithium-halogen exchange, lithiation by C(*sp3*)-H deprotonation using flow technology is comparatively underexplored. With a view to close this gap, several research groups turned to employing dihalomethanes as C(*sp3*)-H lithiation precursors. For example, Luisi and Nagaki generated fluoroiodomethyllithium by treatment of fluoroiodomethane with lithium diisopropylamide in flow at −40 °C (Scheme 7) [29]. Appreciating the high chemical reactivity and instability of this intermediate, careful control of the residence time for lithiation at 82 ms was required, before external quenching with various electrophiles. Thus, similar to the protocol reported by Kappe (cf. Scheme 6), fluoroiodomethyllithium was reacted with a series of ketones to yield fluorinated epoxides **43** in up to 90% yield (selected examples **44**–**47**); hence significantly outperforming those obtained with batch chemistry. In a related protocol (Scheme 8), Luisi and co-workers demonstrated that the use of chloroiodomethane, instead of fluoroiodomethane, chemoselectively furnished α-chloroaldehydes **48**, as a result of a fast Meinwald-type rearrangement of the intermediate α-chloroepoxide [30].



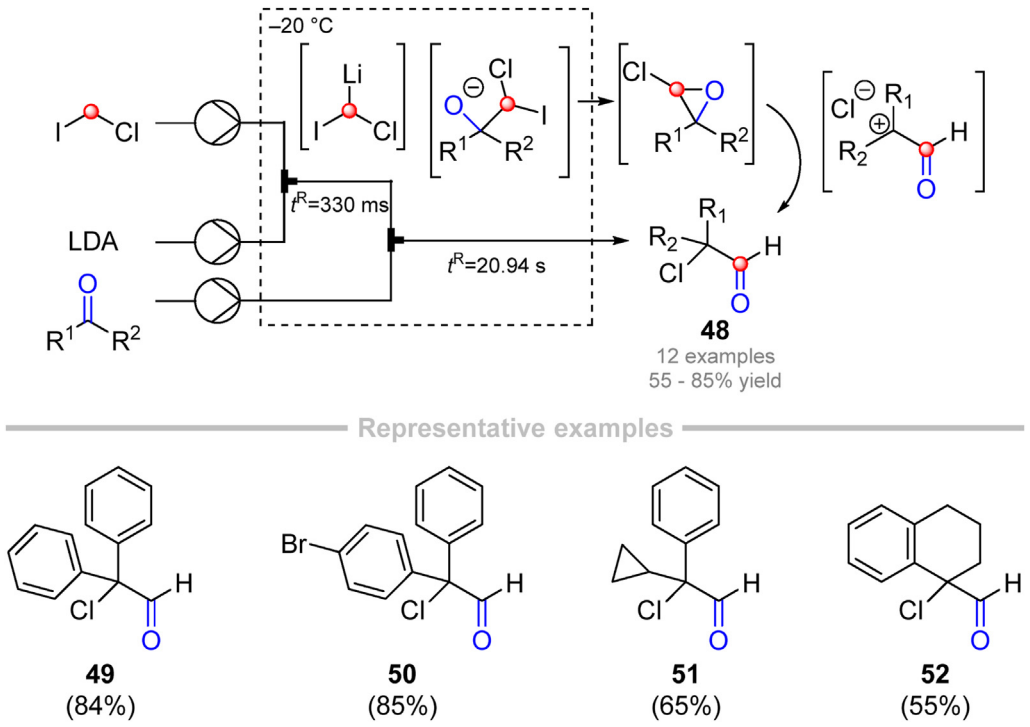
Scheme 6. Kappe's continuous flow synthesis of terminal epoxides from ketones using *in situ* generated bromomethyl lithium.

In addition to dihalomethanes, *N*-Boc protected pyrrolidines [31] and piperidines [32], as well as alkylated aromatics are also well-suited substrates for C(*sp3*)-H deprotonation. Within the latter category, Barker and co-workers built on their previous work on the lithiation-substitution of 1,3,4-oxadiazoles under flow conditions [33], and have recently reported a flash chemistry approach for the metalation-substitution of 5-alkyltetrazoles – a common motif in drugs, e.g., the antithrombotic agent Cilostazol or leukotriene D4 receptor antagonist Tomelukast (Scheme 9) [34]. A thorough study on flow conditions, including thermal imaging of the reactor to direct solvent choice, and a study on residence time distributions led to optimal conditions displayed in Scheme 9. A variety of electrophiles, including ketones, aldehydes, Weinreb amides and alkylating agents were tolerated to produce the desired alkylated products **55**–**57** in up to 95% isolated yield – up to 30% points higher than in the comparable batch set-up, thus reducing waste creation from undesired side products. With regards to the sustainability impact it is also worth noting that the use of flow methodology reduced the energy impact significantly in this case, as lithiations of this type would normally require the use of cryogenic temperatures. Methylated derivative **57** represents the cumyl-protected analogue of a patented anaesthetic. With regards to the 5-alkyltetrazole scope, acetal groups, distal trifluoromethyl-, phenyl-, and amino-groups were tolerated to produce allylated products **58**–**60**. Another application of flow technology to the C(*sp3*)-H lithiation-functionalisation sequence for the synthesis of a late-stage pharmaceutical intermediate has been developed by GSK scientists [35].

In addition to enabling challenging deprotonation of C(*sp3*)-centers, organolithiums have been found to be equally suited for the direct functionalisation of C(*sp2*)-centers. This can, for example, be achieved by direct deprotonation and this area has hitherto been well-explored. Recent extensions in this field have been the 2-lithiation/functionalisation of 1-(triphenylmethyl)imidazole by Miller [36], as well as the divergent lithiation/functionalisation of 2,3-dihalopyridines by Legros and co-workers [37]. More recently emerging, however, is the possibility to promote dimerization and oligomerisation of alkenes promoted by organolithium reagents under flow conditions. For example, Yorimitsu reported that styrenes can undergo controlled reductive dimerization in flow (Scheme 10) [38]. To this end, highly short-lived radical anions of styrene are rapidly generated by treatment with lithium 4,4′-di-*tert*-butylbiphenylide which dimerize to form an intermediate 1,4-dilithium species **61**. Due to the fast mixing regime in the flow setup unwanted polymerisation was suppressed. Trapping of this intermediate with dichlorodiarylsilanes, and subsequent oxidation in batch with DDQ, afforded a range of 2,5-diarylsiloles **64**–**67**. It is worth pointing out that, although a variety of substituted styrenes successfully underwent this dimerization, reoptimisation of the residence time, lithium base equivalents, T-mixer diameter and reactor temperature was required in most cases; therefore somewhat hampering



Scheme 7. Luisi and Nagaki's continuous flow synthesis of fluoro-substituted epoxides from ketones using *in situ* generated fluoroiodomethyllithium.

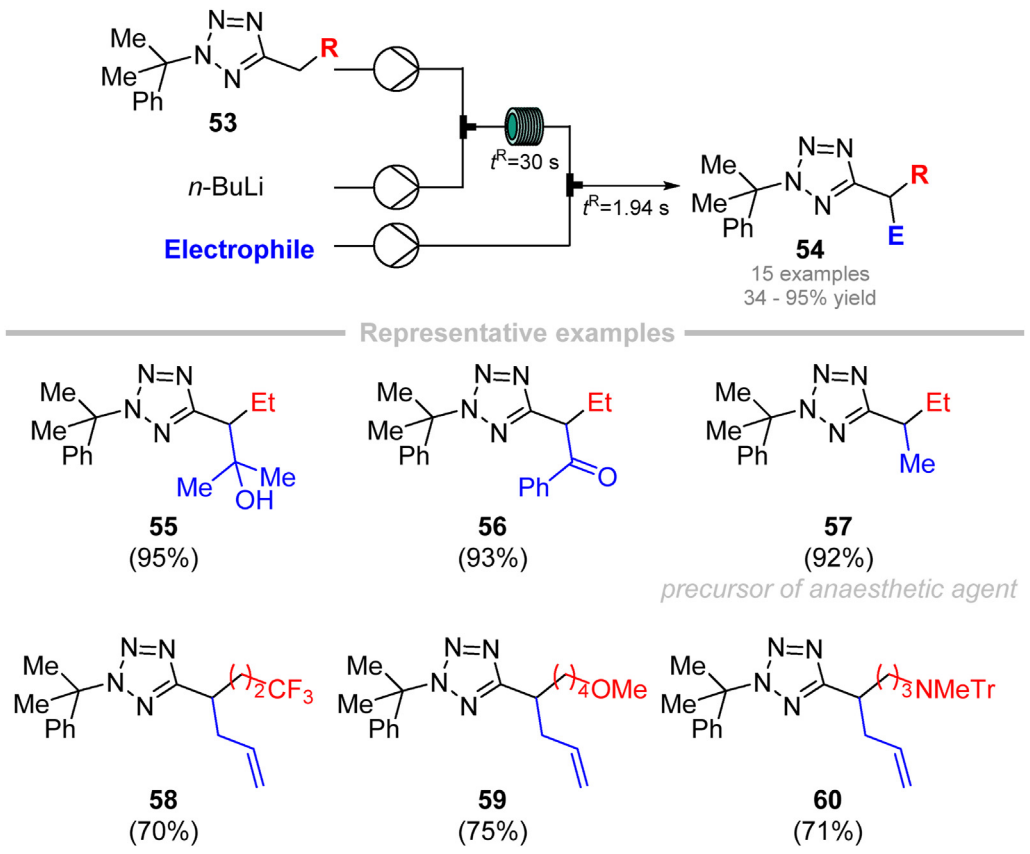


Scheme 8. Luisi's continuous flow synthesis of α-chloroaldehydes.

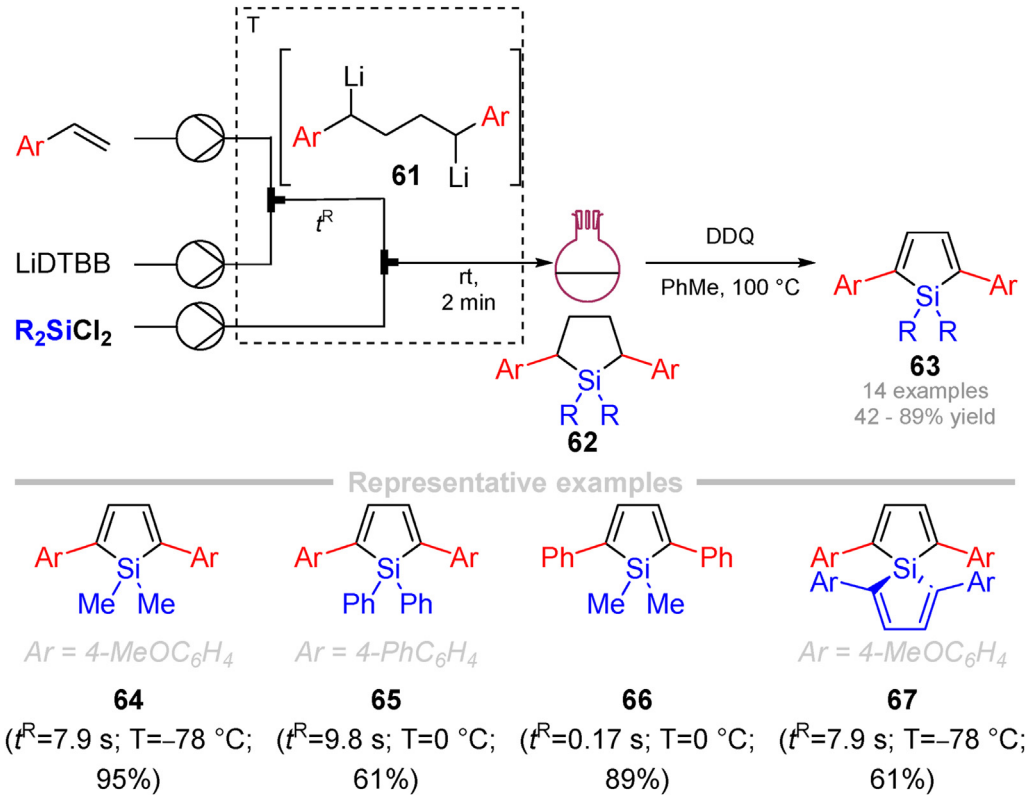
the broad applicability of this method.

Polymerisation under flow conditions, on the other hand, was reported by Vuluga and co-workers (Scheme 11) [39]. With a view to address the increasing demand for functionalised feedstock-derived oligomers to replace oil-based moieties for the development of more sustainable materials, low molar mass polymyrcene (PMYR) was synthesised under flow conditions from myrcene – a naturally occurring terpene derivative. Anionic polymerisation of myrcene was initiated with *n*-butyllithium and, unlikely from a comparable batch process, the number of monomer units in the oligomer could be precisely tailored by careful control of the reactor residence time (t^R = 19 s, M_n = 450 *vs* t^R = 600 s, M_n = 2100), before being capped by CO_2 to introduce a carboxylic acid end-group as a functional handle. Such careful control of product selectivity not only simplifies product isolation and increases potential economic impact, but also contributes to sustainability aspects in the form of waste prevention through minimisation of undesired side products. In a conceptually related report, Nagaki and co-workers describe the *sec*-butyllithium-promoted polymerisation of styrene [16].

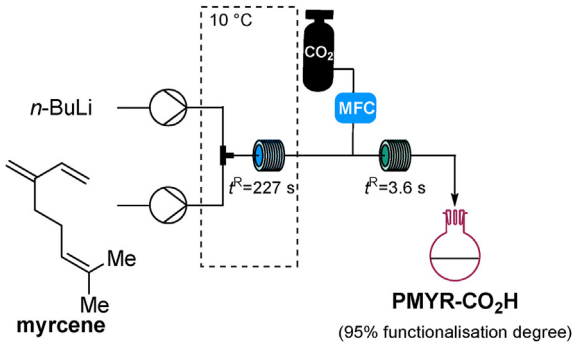
Last, lithiation and subsequent functionalisation of protonated heteroatom functionalities (e.g., alcohols, amines, thiols) under flow conditions



Scheme 9. Barker's continuous flow synthesis approach for the metalation-substitution of 5-alkyltetrazoles.



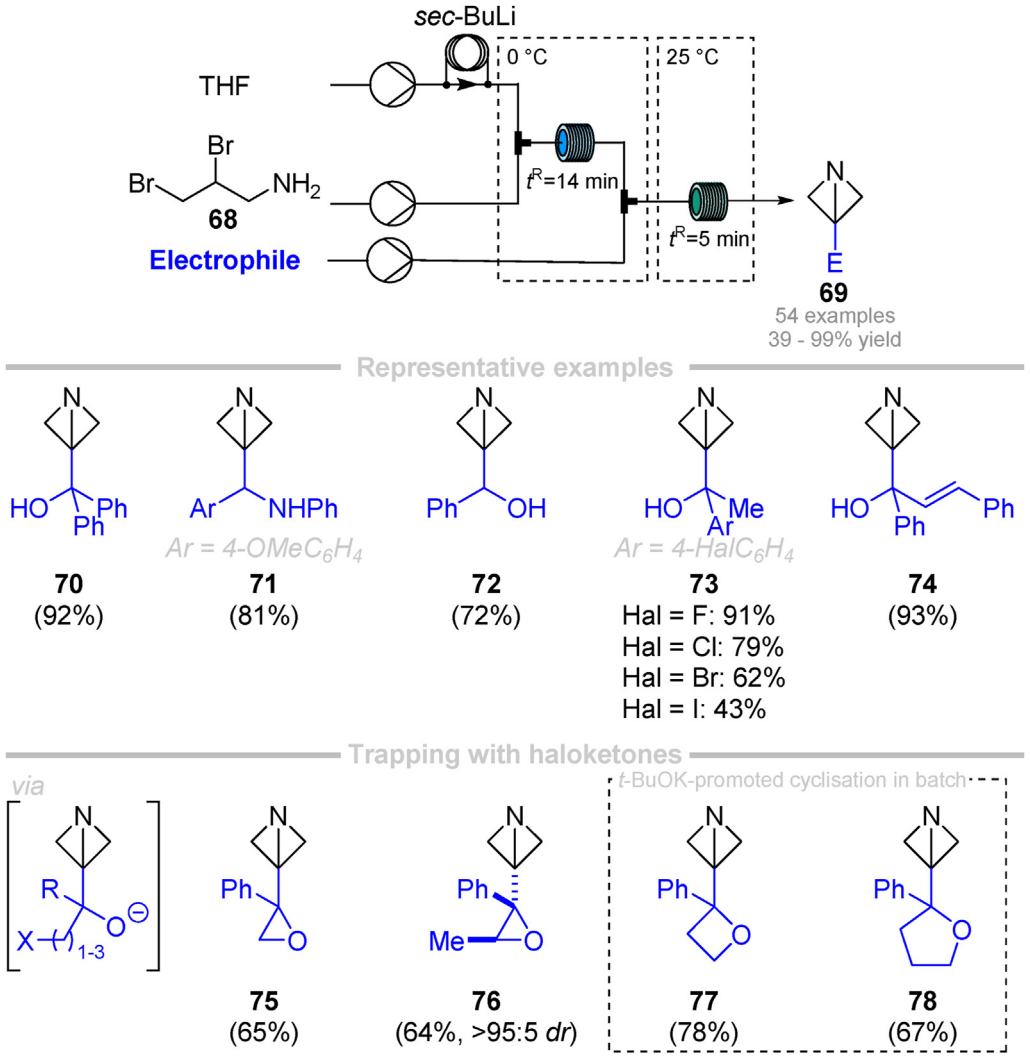
Scheme 10. Yorimitsu's controlled reductive dimerization of styrenes.



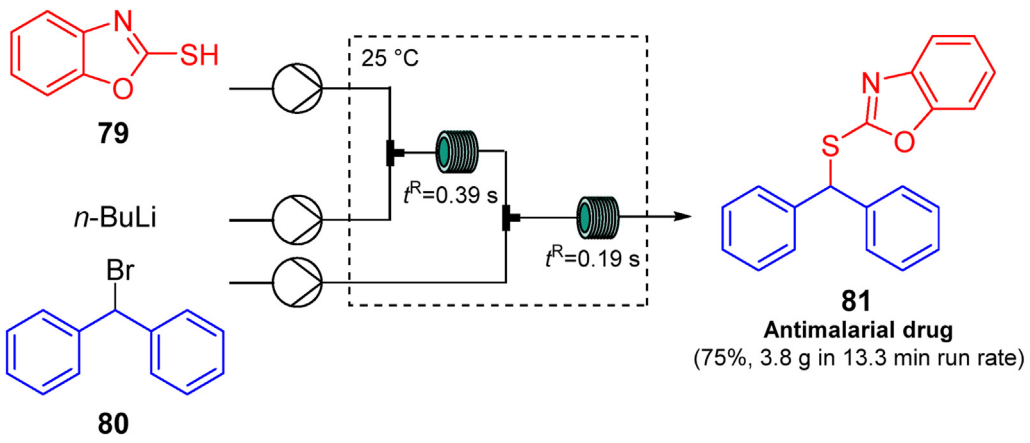
Scheme 11. Vuluga's anionic synthesis and end-functionalisation of polymyrcene in a flow microreactor setup.

present a seemingly straightforward yet useful route for the creation of molecular complexity. This is, for example, showcased by Luisi and Kappe's recent work on the construction of functionalised 1-azabicyclo[1.1.0]butanes (ABB) – highly strained C(*sp3*)-rich compounds important for drug discovery – using flow chemistry (Scheme 12) [40]. The dibromo amine **68** was treated with *sec*-butyllithium at 0 °C with a residence time of 14 min to promote formation of the ABB-Li intermediate, which was then trapped with various electrophiles by an external quenching regime in a second reactor tubing at room temperature for 5 min. Compared to the reported batch synthesis higher yields, as well as avoidance of cryogenic temperatures, and no requirement for the use of TMEDA hare obvious advantages with a view on the sustainability impact of this methodology. A range of suitable electrophiles, including diarylketones, alkyl aryl ketones, imines and aldehydes afforded the functionalised ABBs **69** in modest to excellent yields. High chemoselectivity was observed with α,β-unsaturated ketones (**74**) and halogenated aryl ketones (**73**); although a trend is visible that yield is decreased when aryls are substituted with halogens with higher tendency for lithium halogen exchange. In a recent extension of this work, Luisi and co-workers trapped the ABB-Li intermediate with aromatic α-, β- or γ-haloketones, which either *in situ* or after treatment with *tert*-potassium butoxide underwent intramolecular ring closure to yield the corresponding oxiranes, oxetanes or tetrahydrofuranes (**75**–**78**) [41]. An application of a thiol-lithiation and nucleophilic substitution for the synthesis of an anti-malarial drug **81** using flow technology was reported by Kim (Scheme 13) [42].

The protocols introduced within this section have enabled access to a wide variety of key building blocks, active pharmaceutical ingredients or substrates which have hitherto only been accessible with difficulty. Nonetheless, they are united by their requirement for oxygen- and moisture-free and, in many cases, also cryogenic conditions. To circumvent such stringent requirements, which often are challenging to reproduce at scale, pioneering work by Torrente-Murciano demonstrated that the use of deep eutectic solvents (DES), and segmented flow between DES-containing carrier phase and the dispersed substrate organic phase facilitates stable



Scheme 12. Flow mediated electrophilic functionalisation of highly strained 1-azabicyclo-[1.1.0]butanes.

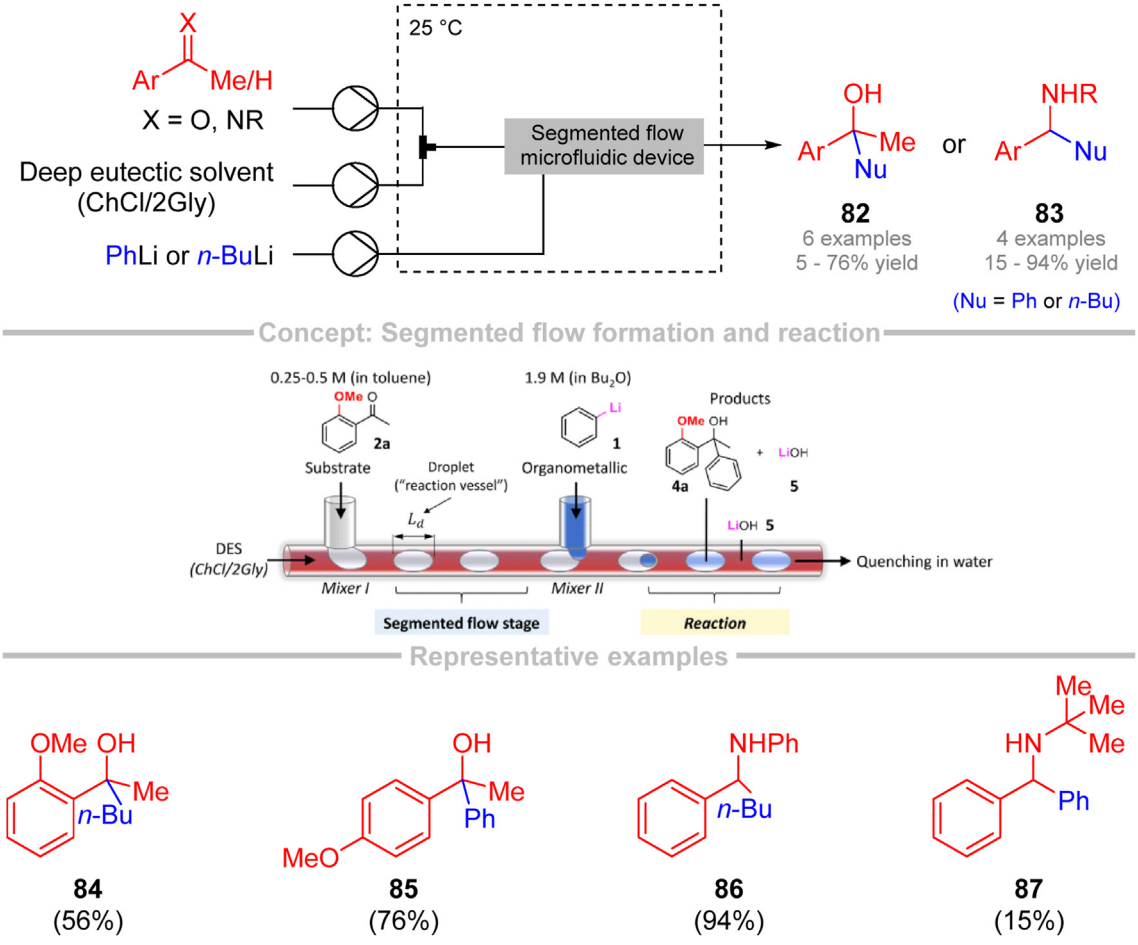


Scheme 13. Kim's ultrafast synthesis of antimalarial drug **81** in a capillary microreactor.

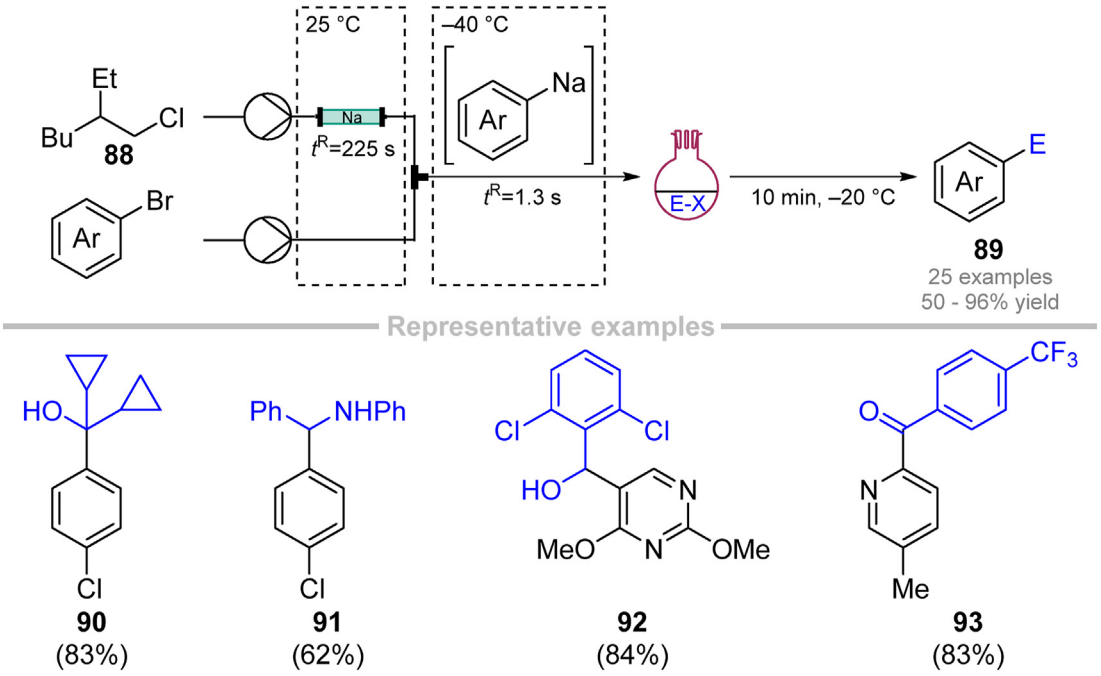
and moisture-tolerant reactions between organolithium compounds with ketones and imines at room temperature to provide alcohols **82** and amines **83** in up to 94% yield (Scheme 14) [43]. Such user-friendly and tolerant procedure constitutes a paradigm shift for the wider application of continuous flow setups in organic synthesis, although exploration of a wider range of substrates is required for practical applications.

3. Organosodium and organopotassium reagents

Although organolithium reagents have been most widely explored under flow chemistry conditions, other alkali metal-functionalised organic intermediates have been shown to have several advantages, including enhanced reactivity, moderate toxicity and higher cost effectiveness. For example, Knochel and co-workers pioneered the use of continuous flow techniques for the selective preparation and functionalisation of sodium- and potassium organometallics of (hetero-)aromatic systems. To this end, they have recently reported a safe, on-demand methodology for the preparation of sodiated organometallic intermediates by the use of (2-ethylhexyl)sodium (Scheme 15) [44]. This hexane-soluble reagent was prepared by pumping 3-(chloromethyl)heptane **88** through a glass column packed with solid sodium particles with a residence time of 225 s at room temperature. Addition of a suitable (hetero)aromatic substrate *via* a



Scheme 14. Hevia and Torrente-Murciano's deep eutectic solvent-assisted organometallic reactions in flow.



Scheme 15. Knochel's Br/Na-exchange in continuous flow.

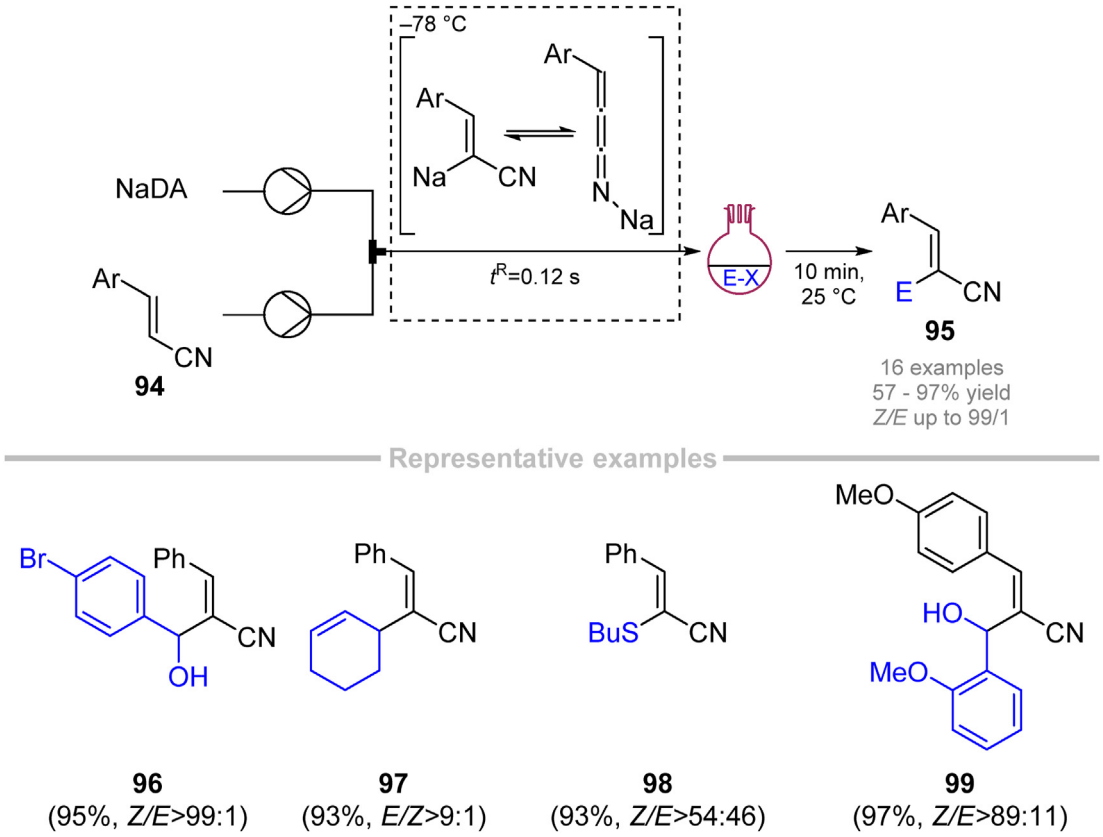
T-mixer at −40 °C enabled in-line Br/Na-exchanges of substituted aryl bromides, 2-bromopyridine, or 2-bromothiazole within a residence time of 1.3 s. The sodiated aromatics were quenched in batch with common electrophiles, including aldehydes, ketones, imines, Weinreb amides, to afford the functionalised aromatics **90**–**93** in good to excellent yields. This protocol was also amenable to the direct sodiation of benzothiophene, imidazole and 1,3-dimethoxybenzene, and after further optimisation to the lateral sodiation of alkyl-(hetero)arenes [45].

An alternative method for the preparation and functionalisation of sodiated organometallics using continuous flow techniques was reported by the same group [46]. Knochel and co-workers report sodium diisopropylamide (NaDA) as an efficient base for the regioselective sodiation and functionalisation of substituted acrylonitriles (Scheme 16). Thus, NaDA in dimethylethylamine was combined with a substituted acrylonitrile **94** in a T-mixer and allowed to react at −78 °C with a residence time of only 0.12 s. The sodiated intermediates were subsequently trapped with a series of electrophiles, such as aromatic aldehydes, ketones, and even 3-bromocyclohexene (with 10 mol% of CuCN.2LiCl as a catalyst), at room temperature in batch to afford the trisubstituted alkenes **95** in good to excellent yields and generally good *E*/*Z*-ratios – with aromatic aldehydes the *Z*-isomer was preferentially obtained; whereas the *E*-isomer was the major product for sterically hindered ketones. This work was extended to acrylates and alkenyl sulfides, and advantageously no reoptimisation of the conditions, including residence times, was required.

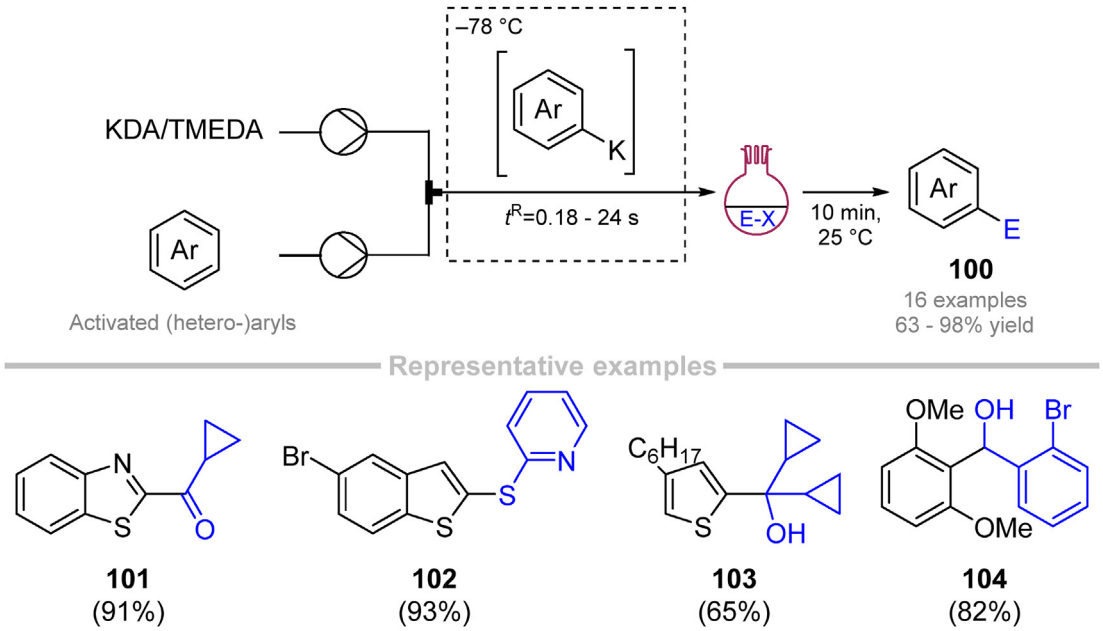
The use of diisopropylamide bases in continuous flow is however not limited to lithium diisopropylamide and sodium diisopropylamide but was also extended to potassium diisoproylamide (KDA). Thus, Knochel report the lithium-salt-free generation of potassium diisopropylamide (Scheme 17) [47]; classically prepared *in situ* by Schlosser's method from a lithium base and potassium *tert*-butoxide. In contrast, in Knochel's report KDA was generated by mixing potassium pieces suspended in hexane with diisopropylamine and TMEDA, before adding isoprene. The resulting solution was combined with appropriate (hetero-)aromatics *via* a T-mixer in a flow-setup cooled to −78 °C to perform metalation with residence times of 0.2–24 s. Subsequent batch-quenching at −40 °C with various electrophiles, including ketones, aldehydes, Weinreb amides, elemental iodine afforded the corresponding functionalised aromatics **101**–**104** in modest to excellent yields (42–98%). Although a screen of the (hetero)arene scope showed good tolerance for thiophene-containing systems, pyrazines and methoxylated benzenes, reoptimisation of the metalation residence time was required, and indole – a prominent heterocycle in various APIs and natural products – was not explored as a heteroaromatic substrate. In an extension it was shown that this method was also suitable for the formation of benzylic potassium organometallics of methyl-substituted arenes.

An application of benzylic potassium organometallic formation and functionalisation for the synthesis of APIs has been disclosed by Kim [48]. Specifically, Kim and co-workers reported a consecutive three-step flow synthesis of ibuprofen from low-cost *p*-xylene using sequential and chemoselective C–H metalation (Scheme 18). Unlike in Knochel's work, benzylic metalation of *p*-xylene was effected using *in situ* generated Schlosser's base from *tert*-butyllithium and potassium *tert*-butoxide, and the resulting organopotassium intermediate – formed with a residence time of 3.14 s – was quenched with methyl trifluoromethansulfonate to afford *p*-ethyl toluene **105** in 94% yield. Further chemoselective C–H metalation using Schlosser's base at −40 °C, with significantly increased residence time up to 63 s, and trapping with 2-iodopropane provided the penultimate intermediate, 1-ethyl-4-isobutylbenzene **106**, in 93% yield. Synthesis of ibuprofen was then completed by a third chemoselective metalation of the sterically more available benzylic proton using *in situ* generated Schlosser's base. The organopotassium intermediate was subsequently quenched with gaseous carbon dioxide, introduced through a mass flow controller, to afford ibuprofen in 57% yield on a gram-scale (2.3 g in 10 min) – significantly lower than Schlosser's original batch procedure [49]. Although the reduced isolated yield, as well as the requirement for cryogenic temperatures would hitherto limit the application of this methodology in the pharmaceutical context, it exemplifies the current trend of utilizing flow technology for the synthesis of APIs.

The use of Schlosser's base has most recently also enabled the *ex situ* generation of bare trifluoromethylanion from fluoroform in continuous flow setups (Scheme 19) [50]. Introduction of the trifluoromethyl group into organic molecules is of upmost importance in medicinal chemistry as it has been shown to improve therapeutic efficacy, permeability and metabolic stability of drug molecules and the use of fluoroform as a precursor of the trifluoromethylanion is in line with the principles of green chemistry, given the conversion of a greenhouse gas into synthetically/medicinally useful substrates, and the atom economy of such transformation. Given the inherent challenge of gas/liquid interfaces for

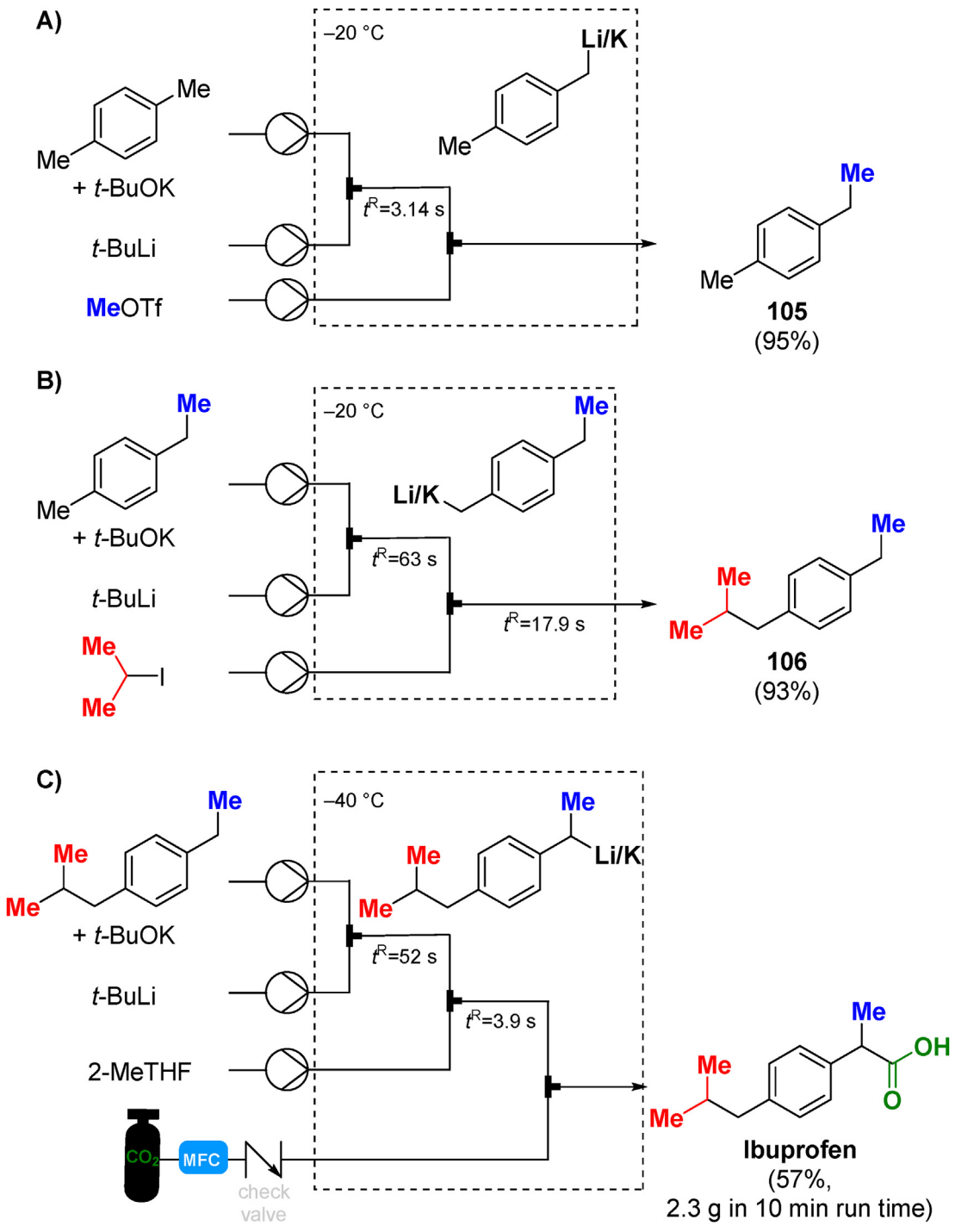


Scheme 16. Knochel's sodiation and functionalisation of substituted acrylonitriles in continuous flow.



Scheme 17. Knochel's preparation of functionalised aryl potassium organometallics in continuous flow.

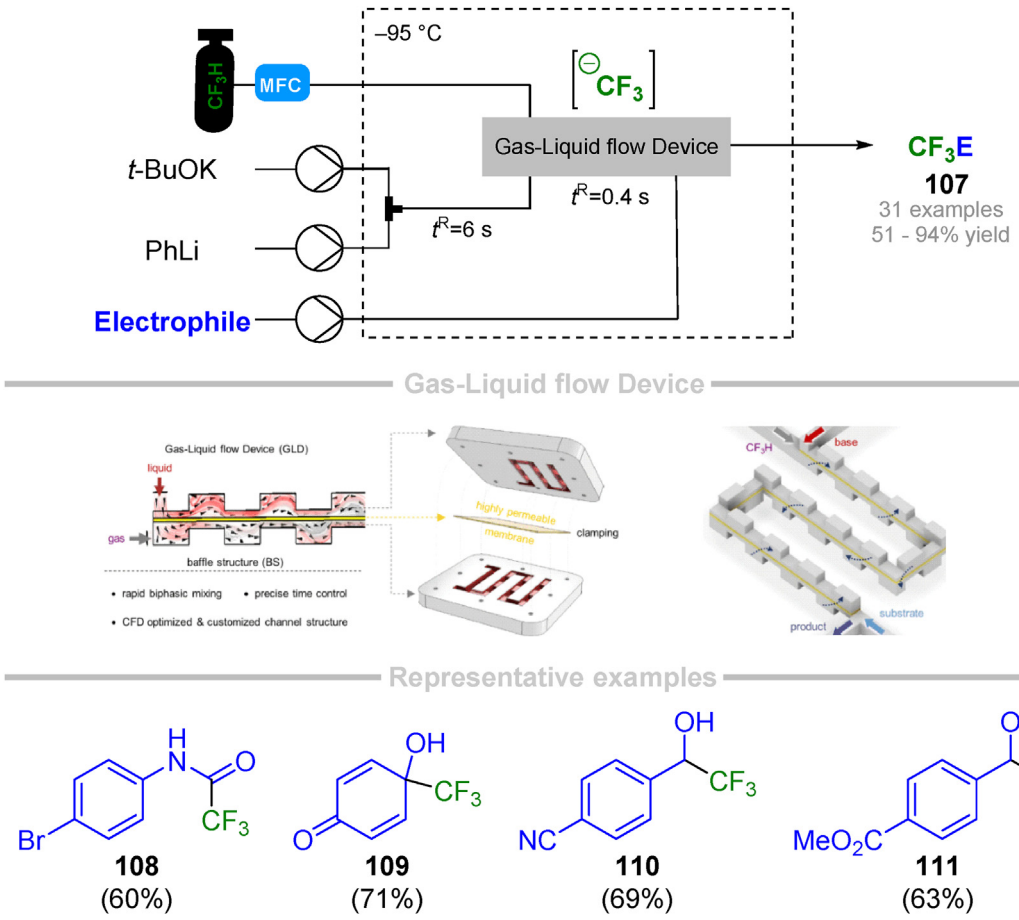
reactivity, and the short lifetime of the trifluoromethyl anion it has hitherto most frequently been generated and used *in situ*, thus narrowing down the reaction scope and posing chemoselectivity challenges. To solve these challenges, Kim and co-workers have devised a customised gas-liquid flow device (upper and lower channel with staggered baffle structure with a highly permeable nanoporous membrane inbetween) based on computational fluid dynamics calculations, which allowed efficient biphasic mixing between gaseous fluoroform and a solution containing Schlosser's base for the *ex situ* generation of the trifluoromethyl anion. Introduction of an electrophile (e.g., ketones, aldehydes, isocyanates etc.) at −95 °C trapped the generated anion to obtain the trifluoromethylated products in (e.g., **108**–**111**) 51–94% yield. Notably, this protocol was amenable to the chemoselective trifluoromethylation of substrates bearing two electrophilic functional groups (**109**–**111**) which typically fail to deliver desired products under classical *in situ* batch conditions .



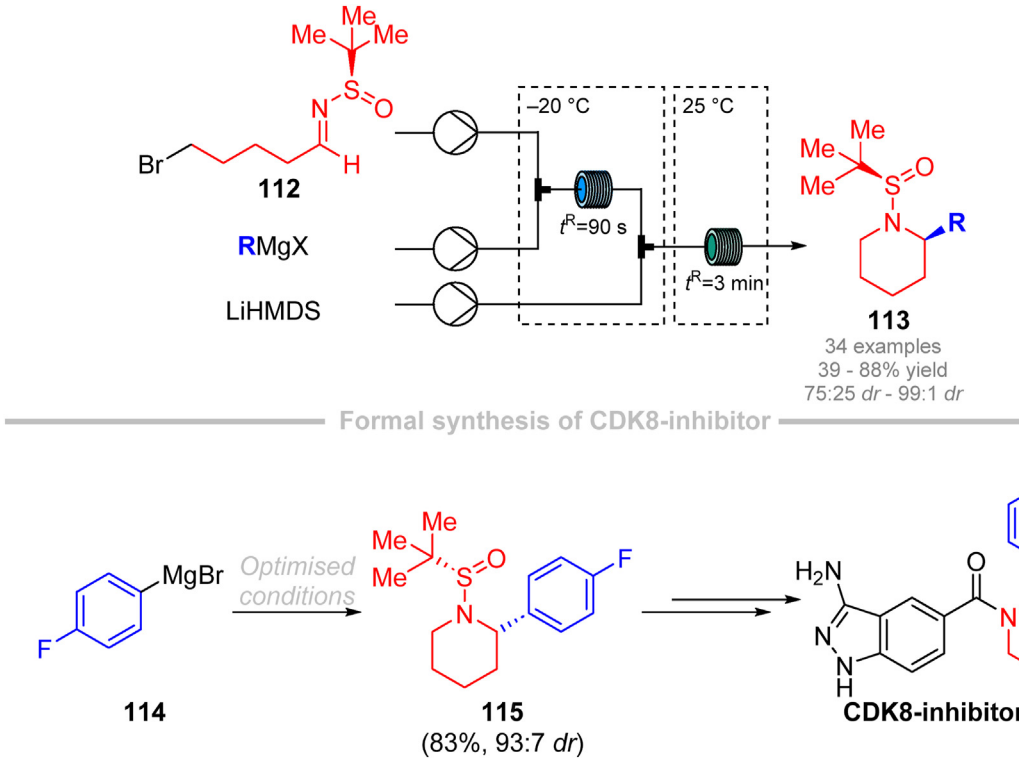
Scheme 18. Kim's three-step synthesis of Ibuprofen by a unified sequence of chemoselective C–H metalations in continuous flow.

4. Organomagnesium reagents

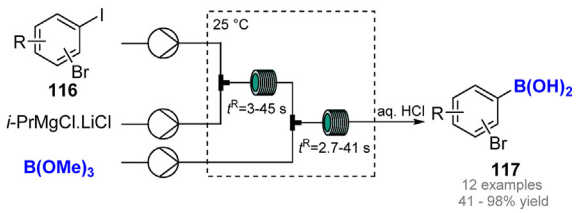
Magnesium completes the series of alkali- and alkaline earth metals that have found application in organometallic chemistry under flow conditions; with organomagnesium reagents having been some of the most widely employed species in organometallic chemistry – most often used in the form of Grignard reagents. Such reagents have recently been shown to enable the conversion of *N*-(*tert*-butylsulfinyl)-bromoimines to α-chiral piperidines (Scheme 20), which are important motifs in APIs such as Mefloquine (antimalarial medicine) [51]. As such, pre-cooled solutions of an *N*-(*tert*-butylsulfinyl)-bromoimine **112** and a suitable Grignard reagent were mixed at −20 °C for 90 s to induce the chiral formation of ε-halo sulfinamides, with the *tert*-butylsulfinyl group serving as a chiral auxiliary. To promote intramolecular cyclisation, LiHMDS was introduced through a second T-mixer and allowed to react at room temperature, affording a series of α-chiral piperidines **113** in generally good yields and diastereomeric ratios, with both substituted aryl-groups, as well as alkyl groups being readily tolerated. Applicability to the pharmaceutical industry was showcased, as piperidine **115** could be readily converted into a CDK8-inhibitor. Yet, the impact of further substituents on the *N*-(*tert*-butylsulfinyl)-bromoimine on the outcome of the reaction was not discussed, somewhat limiting the utility of the method for the synthesis of more highly substituted piperidines. This protocol has also been shown to be suitable for the synthesis of α-chiral pyrrolidines [52].



Scheme 19. Kim's ex-situ generation and utilisation of bare trifluoromethyl anion in flow.



Scheme 20. Ye's synthesis of α-chiral piperidines via a highly diastereoselective continuous flow protocol.



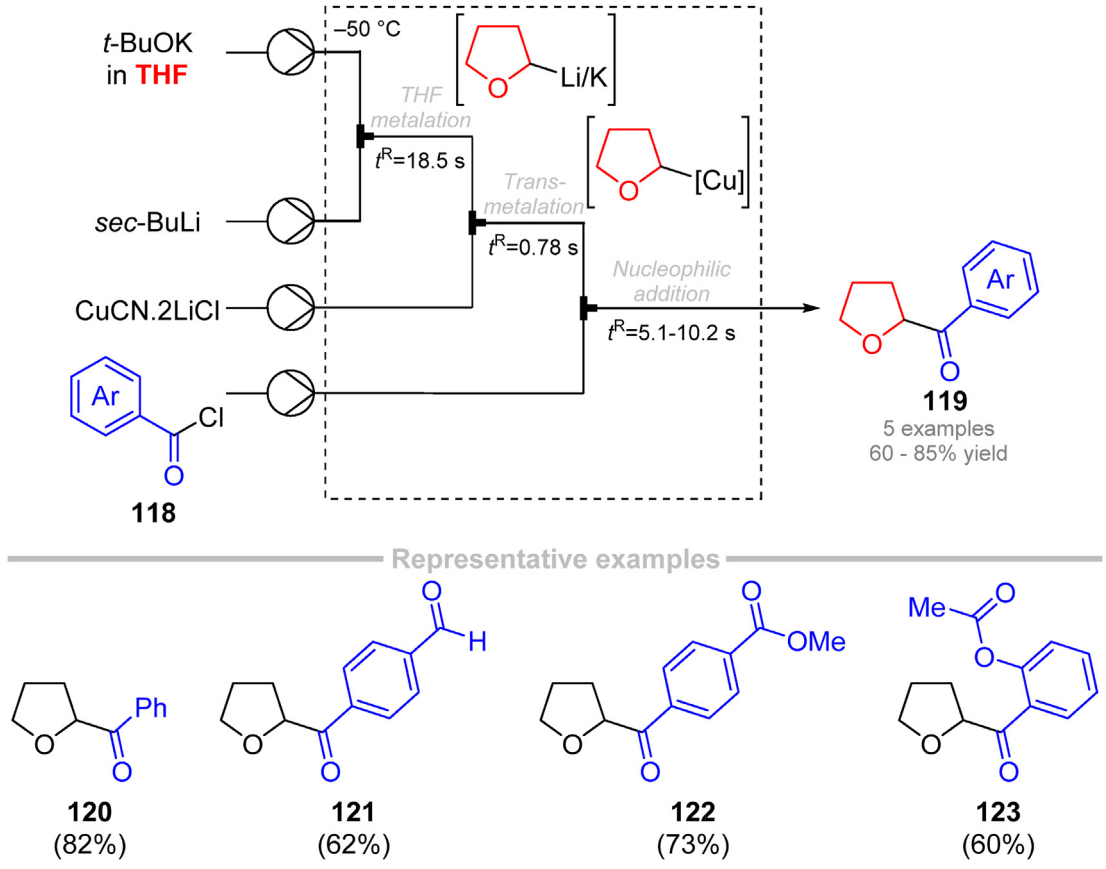
Scheme 21. Lebel's chemoselective borylation of bromoiodoarene in continuous flow.

In addition to acting as nucleophiles, Grignard reagents have often been used as metal/halogen exchange reagents. For example, Lebel and co-workers have shown that bromoarylboronic acids could be chemoselectively generated from bromoiodoarenes and Turbo Grignard reagents with high energy efficiency, as cryogenic conditions were not required under flow conditions (Scheme 21) [53]. The aryl-Grignard intermediate was trapped with trimethyl borate in flow conditions and subsequently hydrolysed to yield boronic acids **117**. Various substituents, including halogens, ethers, nitriles and even ketones were tolerated on the aryl-Grignard reagent, and competitive halogen exchange with bromides was not found to occur. Although such chemoselectivity is useful, starting material-dependent re-optimisation of both residence times was required for optimal results, and heteroaromatic systems were not studied, thus somewhat limiting the practicality of this method. Applications for the metal/halogen exchange using Grignard reagents in flow were recently reported by Eli Lilly and Snapdragon Chemistry Inc. scientists for the synthesis of a key building block of migraine drug Lasmiditan [54], and by Kappe for the synthesis of SARS-CoV-2 drug Remdesivir [55].

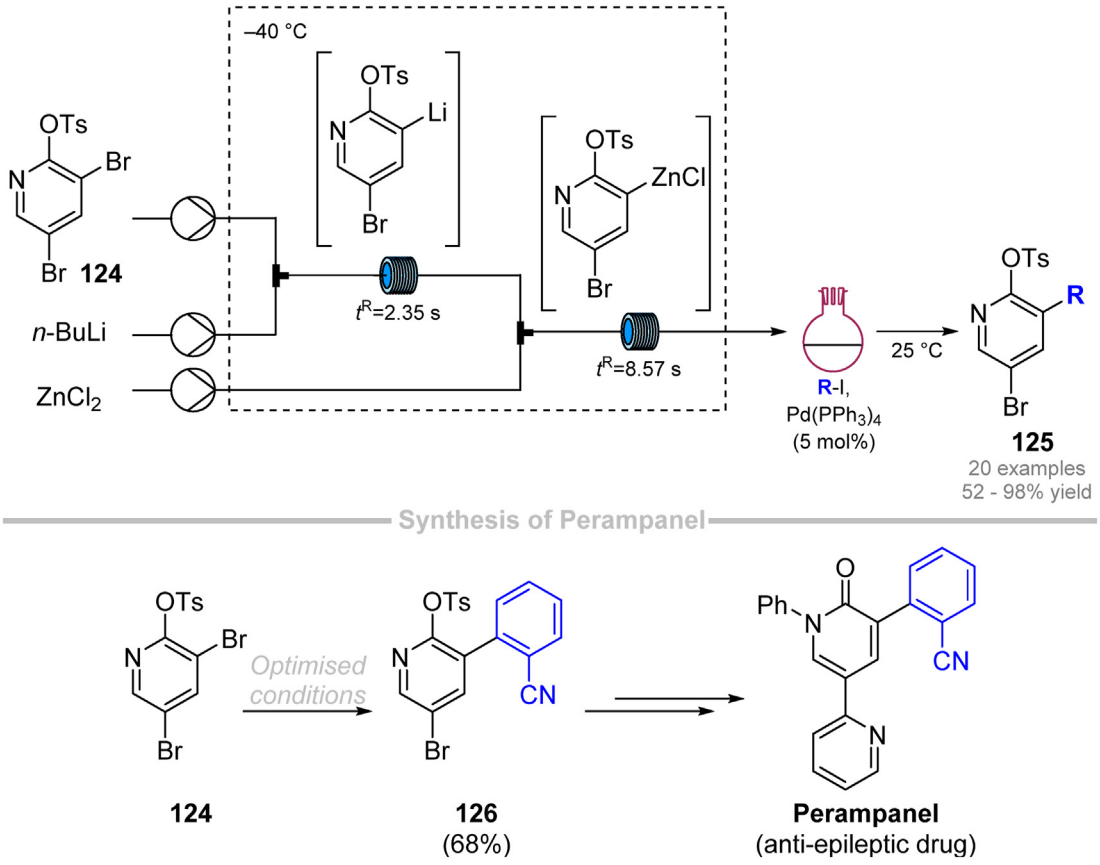
5. Organocopper and organozinc reagents

In addition to organometallics containing main groups metals, also those with transition metals have attracted increased attention. In particular, cupration and zincation protocols stand out as particularly useful to finetune reactivity and chemoselectivity. The latter has been showcased by Kim for the selective α-functionalisation of THF – a motif commonly found in natural products and APIs (Scheme 22) [56]. Yet, the direct C–H metalation/functionalisation of THF is hampered by the instability of α-anionic THF, which is prone to undergo decomposition by a retro [3 + 2]-cycloaddition pathway. Closing this gap, Kim and co-workers demonstrated that under flow conditions, THF could be α-metalated using *in situ* generated Schlosser's base from potassium *tert*-butoxide and *sec*-butyllithium, preventing unimolecular decomposition. Subsequent transmetalation in flow with CuCN.2LiCl allowed chemoselective reactions with acyl chlorides to afford ketones **120**–**123** in 60–85% yield; whereas only trace amounts of the desired products could be obtained from the α-lithio/potassium intermediates as a consequence of overaddition. Notably, the chemoselectivity was further demonstrated as aroyl chlorides bearing additional electrophilic side chains (i.e., aldehydes or esters, **121**–**123**) were obtained in good yields; showcasing the advantages of flow technology in this instance.

Initial lithiation, followed by transmetalation also allows access to organozinc intermediates, as recently showcased by the tosyloxy-directed lithiation/zincation of polyhalo-substituted (hetero)aryl tosylates in continuous flow, which adds another protocol to the hitherto well-explored area of regioselective zinc insertion into aryl polyhalides (Scheme 23) [57]. To this end, the tosylate-group acted as a directing group for the *ortho*-lithium/halogen exchange on bromo-pyridine **124** with *n*-butyllithium within a residence time of 2 s. Transmetalation was achieved by introduction of a solution of zinc chloride in 2-MeTHF within less than 9 s residence time, which was utilised for Negishi



Scheme 22. Kim's direct C–H metalation and functionalisation of tetrahydrofuran in flow.



Scheme 23. Kim's regioselective ortho-arylation of polyhalo-substituted aryl tosylates in a continuous flow/batch protocol.

couplings in batch affording functionalised pyridines **125**. The applicability of this protocol to the pharmaceutical industry was demonstrated with the synthesis of antiepileptic drug Perampanel. Thus, *ortho*-selective zincation of 3,5-dibromo-2-tosyloxypyridine **124** and subsequent Negishi coupling furnished biaryl **126** in 68% yield under the developed conditions. Synthesis of the desired API was achieved by further Stille coupling and one-pot tosyl-group deprotection/Chan-Lam coupling in a total of four synthetic steps; reducing the current synthetic sequence by two steps. A further protocol for the lithiation/zincation/Negishi coupling sequence under flow conditions was also reported by Roesner [58].

6. Conclusions

In the last few years, flow chemistry has continued to change the way organic chemists – both in academia and industry – plan synthetic routes. First, flow technology has enabled a series of *forbidden* transformations of either highly unstable intermediates, or such that high levels of chemoselectivity were required in the presence of reactive functional groups. Second, especially in the case of organosodium and organopotassium chemistry, flow technology has led to a revival of somewhat forgotten chemistry and demonstrated the possible advantages of such intermediates over more frequently used organolithium or organomagnesium reagents. Last, given the inherent advantages of flow technology over classical batch chemistry, we have witnessed a rapid increase in the number of applications of flow chemistry for the pharmaceutical industry especially over the last few years. In addition, various aspects of the Twelve Principles of Green Chemistry were successfully addressed by recently developed methodologies. In particular, the application of flow methodology enabled reaction designs with higher energy efficiency as several metalation protocols, which under batch conditions would require cryogenic reaction conditions, were feasibly run at (or just below) room temperature. In addition, flow methodology allowed careful control of product selectivity (e.g., *E*-vs. *Z*-isomers) and multi-step telescoped synthesis, thus reducing waste formation and derivatisation steps. Last, their inherent closed design supports less hazardous chemical synthesis by lowering the risk of thermal runaways and exposure to (hazardous) chemicals. We expect that in the coming years further advances towards more sustainable reaction design using flow methodology will be made.

Nonetheless, remaining challenges including the upper scaling limit or reactor clogging still require addressing in further research. With first results having recently been reported, for the future we expect to also see flow technology enabling enantioselective syntheses under milder and practical conditions.

Declaration of competing 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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