Towards an approach to small-scale aryllithium flash flow chemistry using low-cost, low volume reactors.

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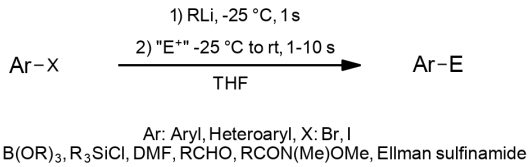
Abstract: Two low-cost reactors for aryllithium generation and trapping with an electrophile in flow have been developed for use with small quantities of limiting reagent (600 μmol) using reductions in flow rates as the approach to miniaturisation. To this end, a number of inexpensive, commercially available mixing elements were characterised via model lithium-halogen exchange reactions to determine their performance at low (< 5 mL min^{-1}) flow rates. From these studies, a glass chip mixer, and 250 μm tee-pieces were identified for use at low flow rates and therefore incorporated into the aforementioned reactors. These reactors were demonstrated to be suitable for the successful lithiation and trapping of a selection of ArX substrates.

Impact of flow: Organolithium chemistry greatly benefits from translation to flow. Increased heat transfer means that reactions may be run at higher temperatures than in batch, with drastically reduced reaction times. Moreover, the precise control of stoichiometry via flow rates, coupled with the improved mixing in flow leads to improved functional group tolerance and selectivity.

Introduction

Flash flow chemistry is a subset of flow chemistry pioneered by Yoshida and Nagaki.[1, 2] The technique is suited to fast chemical processes in which reactive intermediates are generated. A flash flow synthesis utilises residence times on the order of seconds, meaning that slower side reactions can often be out-competed by a faster dominant and desired process, provided sufficient in-reactor mixing has been achieved. The flash flow approach has been most successfully applied to the generation of aryllithiums from aryl halides, followed by trapping with an electrophile (**Scheme 1**) and has facilitated the clean lithiation and trapping of aryl halides that are: liable to aryne formation,[3] which bear esters,[2] nitriles,[4] and even ketones;[5] feats which are difficult if not impossible to achieve using 'in flask' (batch) chemistry. In addition to aryllithium chemistry, flash flow chemistry may be successfully applied to chemistry involving carbenoids[6] and saturated metalated heterocycles[7]. A number of excellent reviews covering many of these aspects of flash flow chemistry in greater detail have been published [8, 9].



Scheme 1: The lithiation-trapping sequence discussed in this work.

By adapting a general-purpose reactor design disclosed by Sedelmeier for use in our laboratories[10, 11] and using the conditions in **Scheme 1**, we have had considerable success running lithiation-electrophile trapping sequences in flow across a variety of synthetic and medicinal chemistry projects, enabling access to building blocks whose syntheses are impractical under batch conditions. To date, we have used tee mixers with an internal diameter of 500 μm but these mixers require fast flow rates for effective mixing which is crucial for good conversion. Therefore, material demand is relatively high (at least 5 mmol of each starting material) when 500 μm tee pieces are used (see following section). This can be an obstacle to using flash flow lithiation and trapping chemistry on a small scale because many precursors in a medicinal chemistry program are high value materials that require multi-step syntheses and are only available in small quantities. So, reducing the minimum quantities of material required for lithation-trapping in flow is an attractive proposition. Doing so will enable access to the intermediates required to complete a synthesis from limited amounts of starting material and also allows for more efficient initial investigations of flow conditions for a given substrate.

Yet, there is a paucity of literature on how to reduce the amount of starting material needed to execute lithiation-quench sequences in flow without specialised equipment enabling segmented flow[12, 13], or active mixing.[14] In contrast, approaches to scaling-up reactions in flow have been well covered.[15] In response, we set out to develop a flow reactor and accompanying conditions which allow for the successful lithiation and electrophile trapping of a wide scope of aryl substrates. Ideally, such a reactor setup should be operable

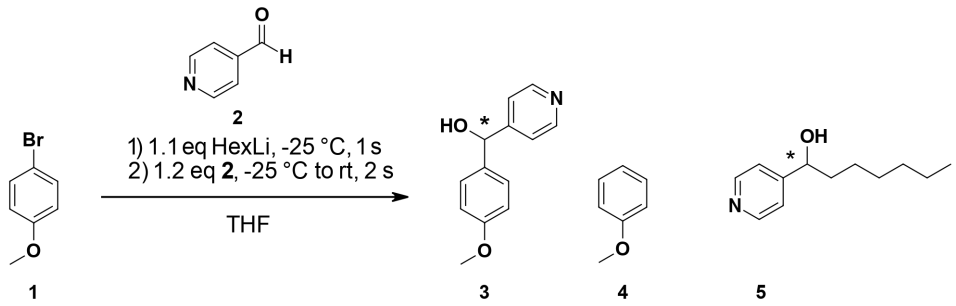
on smaller scales than those previously published but is reproducible by those without access to specialised equipment or bespoke manufacturing.

Approach to the problem

At a set residence time, flow rates can be lowered to minimise reactor volume and thus the starting material lost at the end of a synthesis to the internal volume of a reactor (defined here as the sum total of the volumes of any component through which any reagent or product mixture flow) and is particularly relevant at low injection volumes (defined here as the volume of the aryl halide stock solution that is pumped into the reactor prior to the system being stopped). However, reductions in flow rate need to be considered in context; successful flash flow chemistry relies on rapid, complete mixing. The extent of mixing depends on (but is not limited to) the flow rates of the incoming reaction streams and the efficiency of a given mixing element placed at or after the junction between reagent streams.[16, 17, 18] So as to mitigate the lowered mixing quality associated with a lower flow rate then, a judicious choice of mixing elements is crucial in work towards a flash flow reactor which is effective at low flow rates.

A number of approaches have been employed to assess the performance of various mixers in the literature including the Bourne and Villermeux-Dushman protocols, which use mixing dependent reactions at different flow rates to evaluate mixing time.[19, 20, 17, 21, 22]

While such protocols are useful in benchmarking mixing performance in a *general* way, we opted for a more specific approach using the lithiation of an electron-rich aryl bromide followed by reaction with an electrophile (**Scheme 2**); an approach favoured by those working on lithium-halogen exchange in flow.[23, 10, 24]



Scheme 2: The test reaction used to characterise the mixers studied.

In this method, the extent of aryl bromide consumption reflects the quality of mixing at the lithiation stage at a given flow rate. Therefore, the lithiation in flow of 4-bromoanisole **1** (selected as our test substrate because of its slow metalation rate[25]) and its trapping by aldehyde **2** to form alcohol **3** (the desired product), or conversion into anisole **4** was studied at constant (where possible) residence time while varying flow rate and mixer type. In this way, the presence of alcohol **3** and anisole **4** in the generated output streams would serve as markers of successful lithiation, whereas increased amounts of anisole **4** relative to alcohol **3** would suggest: instability of the lithiate under the experimental conditions, poor reagent solution quality or ineffective reagent mixing at the secondary trapping stage, leading to incomplete consumption of the lithiate prior to a protic quench. By-product **5** was expected and observed in all runs, due to the molar

excesses of HexLi and aldehyde **2** used. Through this arm of the work, we hoped to obtain data to inform the design of a general-purpose, cost-effective, low-volume, lithiation-trapping reactor capable of successfully processing both reactive and unreactive aryl halides.

Results and discussion

Test setup and initial characterisation

Six candidate mixer designs were studied based both on evidence in the literature of their performance at low flow rates,[17, 20, 3] and potential for scaling down. These are listed in **Table 1** and were incorporated into the test system described in **Figure 1**. Noting that residence times on the order of tens of seconds are typically used to pre-cool reaction streams in aryllithium chemistry, we used a precooling loop residence time of 20 s for each input solution for this arm of the work.[26, 27, 10, 28, 29, 30] Where practically possible, residence times for the lithiation and trapping stages were kept constant at 1 s and 2 s respectively.

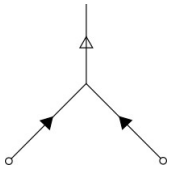
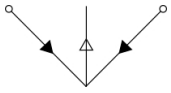
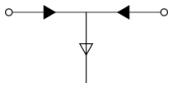
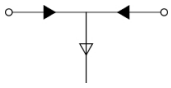
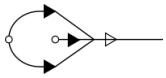
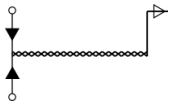
Mixer Type	Fluid path	Channel width /μm	Cost[a] / EUR	Supplier	Model number
Y		500	34	Idex	P-512
Arrow		750	143	VICI	CM1XKF
Tee		250	98	VICI	CTCKF
Tee		500	29	Bola	F707-14
Herringbone chip		100-500	299	LTF GmbH	T-29
Chicane chip		1000	600	LTF GmbH	HTM-ST

Table 1: Mixer elements evaluated in this work. a) Prices correct at time of writing.

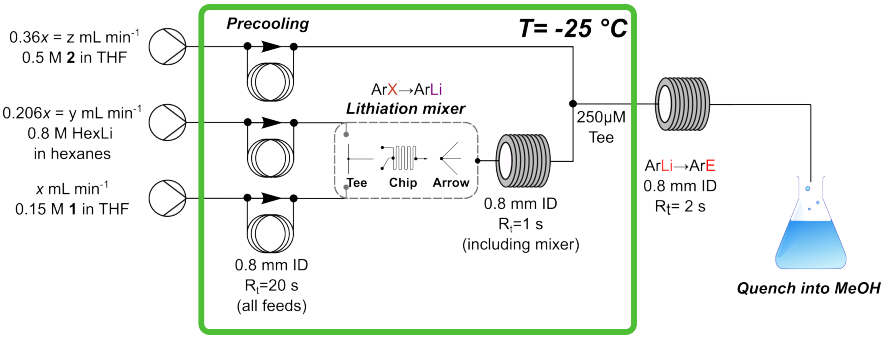


Figure 1: The test setup used for mixer evaluation. Flow rates ranged from x=4.25 mL min^{-1} to 1.063 mL min^{-1}.

For each mixer, the relative ratios of products derived from the lithiation of bromoanisole **1** (i.e. alcohol **3** formation and dehalogenation to **4**) were assessed as a way to determine conversion of bromoanisole **1** by LC-MS and ^{1}H NMR spectroscopy. Experiments were run iteratively, using decreasing flow rate ratios until the consumption of bromoanisole **1** was no longer complete, giving a 'limiting flow rate' for each mixer design. Product distribution as a function of flow rate and mixer design are reported in **Table 2** and visually summarised in **Figure 2**.

			HPLC Area % (PDA)			NMR Ratio[d]
Entry	Flow rate **1** : HexLi : **2** /mL min^{-1}	Mixer Design	**3**	**4**[c]	**1**	Ratio **3:1**
A	4.25 : 0.875 : 1.53	500 μm Y	65	23	13	80:20
B		500 μm Tee	73	11	16	66:33
C		250 μm Tee	88	12	<1	97:3
D		Arrow	66	15	19	80:20
E		Chicane	88	12	<1	97:3
F		Herringbone[a]	-	-	-	-
G	2.125 : 0.438 : 0.765	250 μm Tee	69	16	15	95:5
H		Chicane	86	14	<1	>99:1
I		Herringbone[a]	-	-	-	-
J	1.063 : 0.219 : 0.383	Chicane[b]	96	1	3	96:3
K		Herringbone[a]	-	-	-	-

a) Blockage or pump stall occurred at all flow rates. b) Lithiation residence time was 2 s, due to the set length of the mixing channel. c) Assignment based on $\lambda_{max} = 270$ nm observed in UV spectrum matching that of the literature and comparison with an authentic sample. d) Determined through integral ratios of aryl -OCH_3 signals. Anisole **4** was not detected in any of the reaction mixture samples processed for ^{1}H NMR analysis. We believe that the discrepancy between the HPLC and NMR data is in part due differences in sample preparation: direct sampling of reaction mixtures into a diluent was used for HPLC analysis, in contrast to NMR analysis where samples were concentrated under reduced pressure leading to leading to the potential loss of anisole **4** by evaporation.

Table 2: Product distribution as a function of mixer type and flow rate.

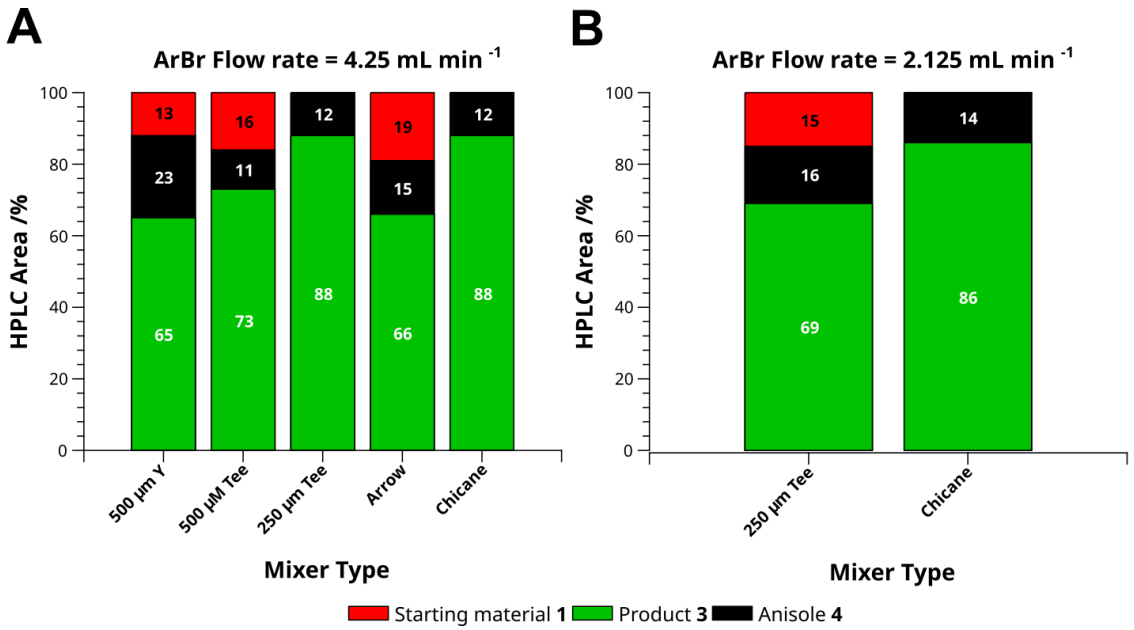


Figure 2: HPLC area percentages of starting material **1**, product alcohol **3** and protodehalogenated product **4** in reaction mixtures generated as part of the mixer characterisation experiment at the key flow rates of A) 4.25 mL min^{-1} and B) 2.125 mL min^{-1}.

As is seen in entries B and C of **Table 2** and in agreement with the literature,[24] a 500 µm bore Tee mixer shows lower consumption of bromoanisole **1** at a given flow rate compared to a smaller (250 µm) bore tee piece. Among the other mixer designs studied, the arrow and Y type mixers also exhibited low consumption of bromoanisole **1** at a relatively high flow rate (entries A and D), while the T-29 herringbone mixer had pump stall and back-pressure issues across the flow rate range under study, rendering the mixer impractical for our purposes (entries F, I and K). Interestingly, the HTM-ST chicane mixer performed consistently well across all flow rates (entries E, H and J) but a deterioration in mixing quality was suggested by the presence of some starting material at an ArBr flow rate of 1.063 mL min^{-1} ; this is despite the longer lithiation residence time (entry J).

While the drop in consumption was small at an ArBr flow rate of 1.063 mL min^{-1} and the product distribution compared favourably with the faster flow rates studied, we elected not to continue with this flow rate for a a few reasons: The first being that use of an ArBr flow rate of 1.063 mL min^{-1} would force a lithiation residence time of 2 s due to the fixed internal volume of the HTM-ST. Although this is clearly appropriate for bromoanisole **1**, it must be noted that this is a relatively unreactive substrate and so requires a longer residence time for complete lithiation. For the realisation of a general purpose reactor through which a variety of aryl halides may be metalated, with the resulting lithiates possessing varying degrees of stability, a residence time of 1 s represented to us the best compromise between enabling the metalation of a the widest range of substrates possible without keeping them in residence (and so at risk of decomposition) for an unnecessarily long time. This was a decision based on our historical experience of using a 1 s residence time across a number of substrates bearing many different functional groups. Our second concern was that any additional

decreases in internal volume at an ArBr flow rate of 1.063 mL min^{-1} that could be realised via shortening the precooling (see next section) loops would result in an reactor that could not be practically mounted into our syringe pump and cooling bath setup. To address this issue, tubing with a narrower internal diameter could be utilised but this introduced the risk of pump stall due to excessive back pressure along with an increased risk of blockage.

On the basis of these considerations and alongside the data, we selected an HTM-ST chicane-type mixer operating at an ArBr : RLi : electrophile flow rate of 2.125 : 0.438 : 0.765 mL min^{-1} as the central component of our reactor design. In parallel, we examined a reactor consisting of 250 μm Tee pieces and operating at an ArBr : RLi : electrophile flow rate of 4.25 : 0.875 : 1.53 mL min^{-1} as a lower cost alternative.

Reactor and process optimisation

With our mixing elements nominated, the reactor systems illustrated in **Figure 3** were assembled for further evaluation. For convenience, we opted for a variant of the HTM-ST chicane mixer, the HTM-ST-3-1, which has longer static mixing paths with an additional input that could be used for an electrophile input in place of the 250 μm Tee piece utilised for the reactor described in **Figure 1**. As a means to further reduce internal reactor volume, pre-cooling loops were shortened to 10 s each, a decision that was rationalised through previous work on similar substrates[10] and the data in **Table 3**, which show a conservation in reaction profile across cooling times. As an aside, a pre-cooling time of 10 s delivered satisfactory performance at a bath temperature of -55 °C in the test reactions used (see supplementary information). These data, coupled with those in **Table 2** led us to assemble the reactors depicted in **Figure 3**. When compared with other reactor systems reported in the literature (**Table 4**), we note that both the chip and Tee- based reactors in **Figure 3** have relatively low throughput and internal volumes, rendering them more suitable for small-scale synthesis.

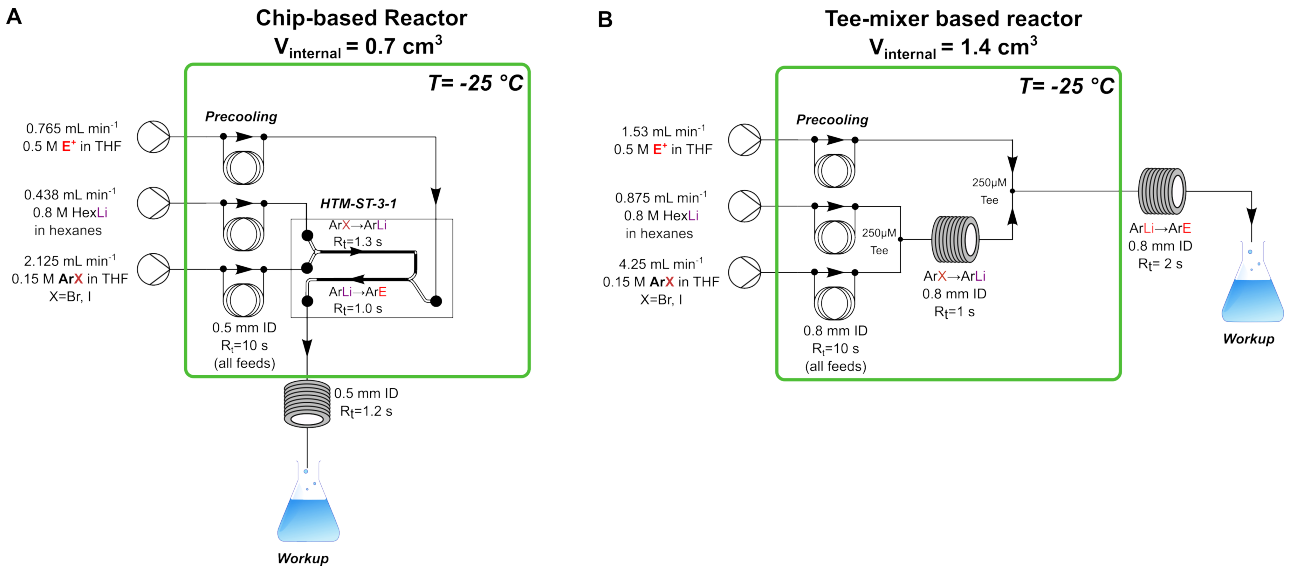
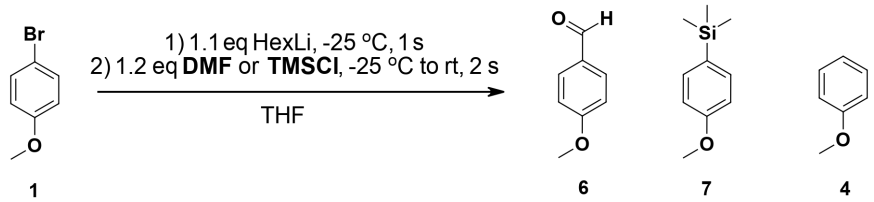


Figure 3: **A:** A miniaturised, chip-based reactor for the lithiation and trapping of aryl halides. **B:** A lower cost Tee-piece based reactor with a larger internal volume compared to the chip-based reactor.



			HPLC Area % (PDA)		
Entry	Product	Precooling loop R_t /s	**1**	**4**	**Prod.**
A	**6**	10	5	8	84
B		20	1	9	85
C	**7**	10	3	20	76
D		20	1	17	78

Table 3: Effect of precooling loop residence time on reaction profile for two model reactions. Reactions were run using the chip-based reactor described in **Figure 2** of the supplementary information. Data at a bath temperature of -55 °C are available in the supplementary information.

Source	ArX→ArLi mixing element	ArX flow rate / mL min^{-1}	Reactor volume / cm^3	ArX Throughput / mmol min^{-1}
Nagaki[a], 2008[24]	T	6.00	2	0.6
Jia, 2013[31]	T then inline	2.7	1.3[b]	0.4
Browne, 2014[27]	Y	**1.0**	94	0.4
Sedelmeier, 2016[10]	T	17	9	5.1
Nagaki[a], 2023[32]	T	4	2	0.6
This work	T	4.25	1.4	0.6
	HTM-ST-3-1	2.125	**0.7**	**0.3**

Table 4: A comparison of the flow rates, internal volume and aryl halide throughput of a selection of reactor systems in the literature. Minimum values are highlighted in bold. a) Volumes quoted are representative due to the variety of residence times used in these works. b) Precooling line volumes not reported.

We then determined the lowest volume of aryl halide stock solution necessary for a reliable lithiation-trapping synthesis in both reactors shown in **Figure 3** by determining the yields (via HPLC) of two model reactions as a function of the aryl halide injection volume. In designing the experiment, we opted for aryl halide-electrophile combinations that formed a homogeneous solution upon workup. This allowed analytical samples to be afforded by simple dilution and minimised the yield losses associated with a more involved workup.

Starting first with the reaction of pivaldehyde with bromoanisole **1** and quenching into MeOH, we could see that the chip-based reactor was able to generate a reasonable (45%) yield of fluoroarene **9** from a 2 mL injection volume (corresponding to a 56 mg input of **1**). To assess the relevance of metalation rate on yield, we also reacted bromoarene **8**, a substrate which metalates rapidly relative to **1**[25], with TMSCl. Data are reported in **Figure 4**.

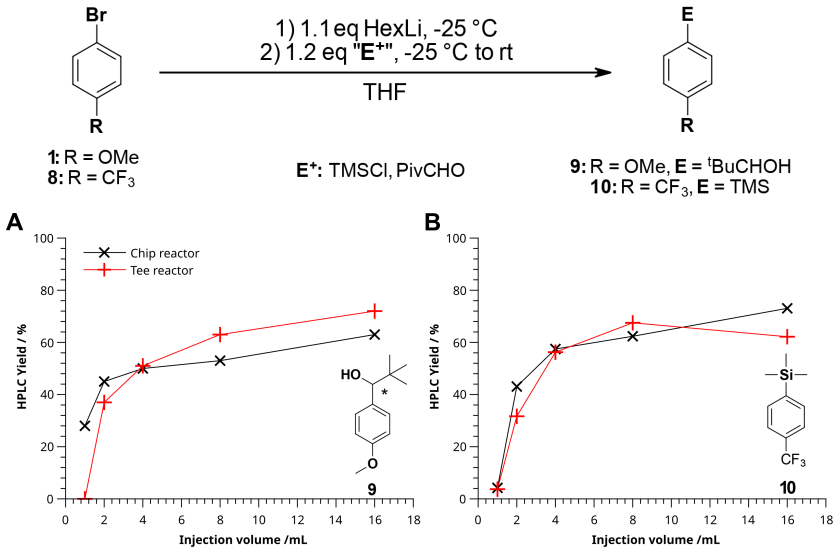


Figure 4: Top: Aryl halide-electrophile pairs combinations used to generate injection volume- yield curves. **Bottom:** Injection volume- yield curves for each product synthesised. The in-flow synthesis of fluoroarene **10** in the chip reactor was run in duplicate; the mean yield is shown.

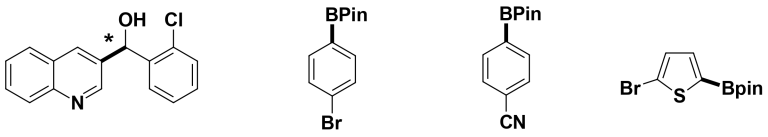
We note that yields for both reactor designs start to plateau at injection volumes greater than 4 mL across both substrates; that is to say, past an injection volume of 4 mL, the primary influence on yield for each aryl halide-electrophile pair seems to be their intrinsic reactivity under these conditions rather than reactor volume. On this basis, we suggest the following aryl halide material inputs for these reactor systems (**Table 5**).

Aryl halide M_r / g mol^{-1}	Mass of aryl halide required / mg
150	90
250	150
350	210
450	270

Table 5: Masses of substrate required for a reaction using 4 mL of aryl halide at 0.15 M — the volume of aryl halide input solution at which both reactors give comparable yields.

Finally, to determine the preparative utility and to benchmark the chip reactor in **Figure 3** against other designs in the literature, we processed a selection of aryl halides previously synthesised in flow (**Scheme 3**). In doing so, we report two separate yields from independent experiments: The first is the yield as a function of the number of moles of aryl halide used to prepare injection solutions and accurately reflects the total material need using the reported reactors, which we refer to as the 'injection' yield. This approach contrasts with the second, more typical approach we used, in which the yield is reported as a function of the number of moles of aryl halide passed through a reactor at steady state, where output is collected for an interval of time only after the reactor is at steady state, allowing for quantitative yields.

On the basis of successful test reactions and our observation that many transformations involving an aryllithium intermediate utilise commodity electrophiles, we pre-primed the reactor with the HexLi and electrophile feeds for 20 s prior to initiating the aryl halide injection, so that variations in the arrival time of these feeds at the mixing chip would not adversely affect aryl halide consumption (see supporting information). Under these conditions, collection of the output stream was commenced once the aryl halide solution pump was started.



	11	12	13	14
Yield /% lit[a]	68[c]	83[d]	85[d]	73[d]
QNMR[b]	48	49	67	39
QNMR- Steady State	N.D	53	79	49

Scheme 3: QNMR yields for the in-flow synthesis of a selection of aryl compounds. a) Yields reported on the basis of the reactor system operating at steady state. b) QNMR yields were recorded on the crude mixtures after workup. c) Isolated yield.[31] d) GC yield from the crude reaction mixture against an internal standard[33]. When accounting for the internal volume of the chip-based reactor, a reaction using a 4 mL injection volume of aryl halide at 0.15M will have an estimated maximum yield of 87.5 % (based on the assumption that for every 4 mL aryl halide injected, 0.5 mL will be lost in the volume of aryl halide precooling loop, final output line and the HTM-ST-3-1 mixing element) unless a method to flush the reactor is employed. N.D. — Not determined.

Although both the steady state and total yields do not compare well against those previously reported in the literature, it must be noted that no attempt was made to optimise reaction conditions for these substrates. Interestingly, there are only minor differences between the steady state yields and the 'injection' yields, suggesting that sacrificing reagent stock solutions to bring the reactor to a steady state is of limited advantage and serves primarily to show the yield independent of the reactor volume.

Finally, we found that there is no need to treat reaction mixtures generated from collection of the entire output of the chip-based reactor after the aryl halide pump was initiated any differently to reaction mixtures that were generated at steady state; the crude ^{1}H NMR profiles of boronates **12** to **14** were similar in each case.

Conclusion & outlook

As part of the development of an approach to conducting small-scale flash flow chemistry, we report two low-volume, low-cost flow reactors suitable for the lithiation of a range of aryl halides, followed by trapping with an electrophile at low flow rates ($<$ 5 mL min^{-1}). These reactors can be constructed without recourse to costly or bespoke equipment and their utilisation allows small amounts of substrate (100-300 mg of aryl halide) to be successfully processed, making flash flow lithiation and trapping more accessible to those who routinely work on small scale, e.g. medicinal and total synthesis chemists. We believe our work may also enable further minimisation, e.g. via a segmented flow approach, which can benefit from low flow rates[13].

Supporting information

See supporting information for: full experimental materials, methods, photos, a bill of parts for the equipment used and key spectral data.

CRediT author statement

Conceptualization: R.S.M.; Funding acquisition: A.J.R.; Investigation: J.A.K.C. and R.S.M.; Methodology: J.A.K.C. and R.S.M.; Project administration: R.S.M.; Resources: A.J.R.; Supervision: A.J.R. and R.S.M.; Writing – original draft: J.A.K.C. and R.S.M.; Writing - review & editing: J.A.K.C., A.J.R. and R.S.M.;

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Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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