

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

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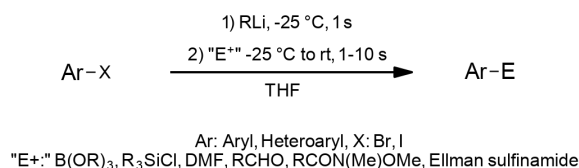
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Abstract: Two low-cost reactors for aryllithium generation and trapping with an electrophile in flow chemistry have been developed for use with small quantities of limiting reagent ($\leq 600 \mu\text{mol}$) using reductions in flow rates as the approach 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 ($< 5 \text{ mL min}^{-1}$) flow rates. From these studies, a glass chip mixer, and $250 \mu\text{m}$ tee-pieces were identified as suitable 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 aryl halide substrates.

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 synthesis in flash flow 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.



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

By adapting a general-purpose reactor design disclosed by Hafner for use in our laboratories[6, 7] 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 synthesis was 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 in turn lead to good conversion. Therefore, material demand is relatively high 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. This means that reducing the minimum quantities required for lithiation-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 allows an assessment of the utility of flow chemistry for a given lithiation-trapping sequence, on top of the intrinsic benefits of flow chemistry.

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[8, 9], or active mixing.[10] In contrast, approaches to scaling-up reactions in flow have been well covered.[11] 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 should be operable on smaller scales than those previously published but is available to those without access to specialised equipment or bespoke manufacturing.

Approach to the problem

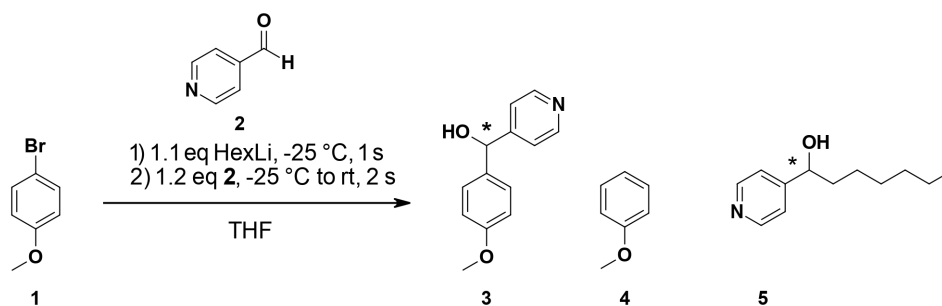
In any flow reactor, the volume of the reactor V , is dictated by the residence time R_t , required for optimal conversion and the volumetric flow rate Q , such that:

$$\frac{V}{Q} = R_t \quad (1)$$

Therefore 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 hold-up volume inherent to the reactor, which is particularly relevant at low injection volumes. 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.[12–14] 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.[13, 15–17]

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.[6, 18, 19] In this setup, the extent of aryl bromide conversion reflects the quality of mixing at a given flow rate and residence time. By keeping residence time constant while varying flow rate and mixer type and using 4-bromoanisole **1** as our test substrate (because of its slow metalation rate[20]), 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.



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

Results and discussion

Test setup and initial characterisation

Five candidate mixer designs were studied based both on evidence in the literature of their performance at low flow rates,[3, 13, 16] 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 cooling loop residence time of 20 s for each input solution for this arm of the work.[6, 21–25] 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	Supplier	Model number
Arrow		750	++	VICI	CM1XKF
Tee		250	++	VICI	CTCKF
Tee		500	+	Bola	F707-14
Herringbone chip		100-500	+++	LTF GmbH	T-29
Chicane chip		1000	+++	LTF GmbH	HTM-ST

Table 1: Mixer elements evaluated in this work.

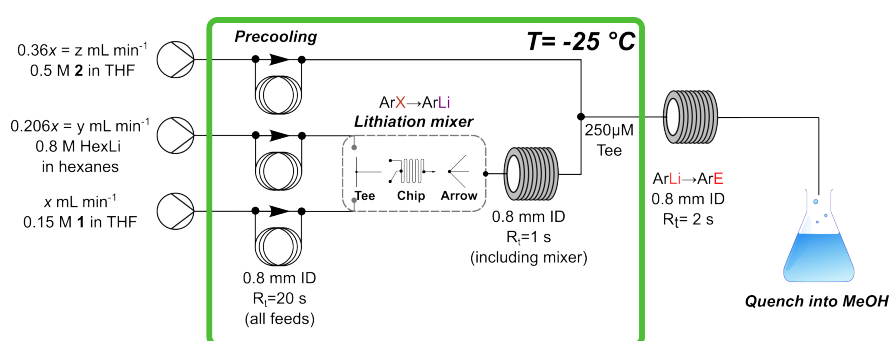


Figure 1: The test setup used for mixer evaluation. Flow rates ranged from $x=8.5 \text{ mL min}^{-1}$ to $2.125 \text{ mL min}^{-1}$.

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

a) Blockage occurred at all flow rates. b) Lithiation residence time was 2s, due to length of mixer. c) Assignment based on $\lambda_{max} = 270\text{nm}$ observed in UV spectrum matching that of the literature and comparison with an authentic sample. d) Determined through integral ratios of aryl -OCH₃ signals. Anisole **4** was not detected in any of the reaction mixture samples processed for ¹H NMR analysis.

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

For each mixer, the relative ratios of lithiation-derived products (i.e. alcohol formation and dehalogenation) were assessed to determine conversion of **1** by LC-MS and ¹H NMR spectroscopy. Experiments were run iteratively, using decreasing flow rate ratios until the consumption of **1** reached a minimum value, giving a ‘limiting flow rate’ for each mixer design. Species **5** was present in all output streams due to the stoichiometry used. Conversion as a function of flow rate and mixer design are reported in **Table 2**.

As is seen in entries A and B of **Table 2** and in agreement with the literature,[19] a 500 μ m bore Tee mixer shows lower conversion at a given flow rate compared to a smaller (250 μ m) bore tee piece. Among the other mixer designs studied, the arrow mixer also exhibited relatively low conversion at a relatively high flow rate (entry C), while the T-29 herringbone mixer had (blockage) issues across the flow rate range under study, rendering the design impractical in this setup (entries G and I). Interestingly, the HTM-ST chicane mixer performed consistently well across all flow rates (entries D, F and H) but a deterioration in mixing quality was suggested by the presence of some starting material at an ArBr flow rate of 1.03 mL min⁻¹; this is despite the longer lithiation residence time (entry H). On the basis of these 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 μ m 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 2** 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**. Pre-cooling loops were shortened to 10 s each as a means to further reduce internal reactor volume. This was rationalised by previous work on similar substrates[6] and the data in **Table 3**, which show a conservation in reaction profile across cooling times.

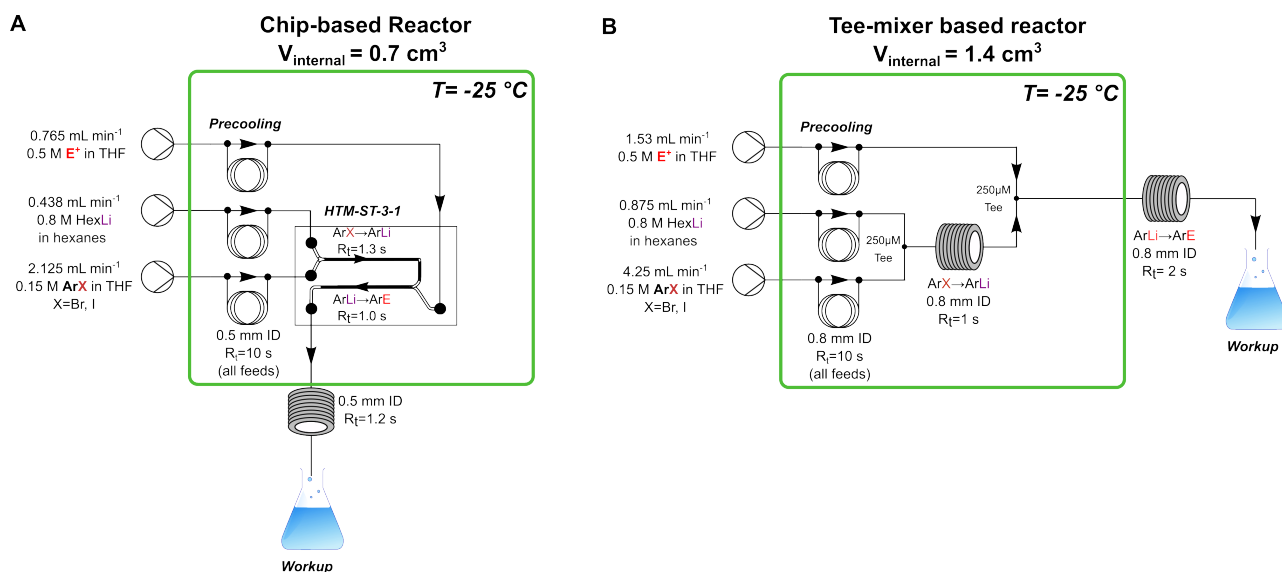
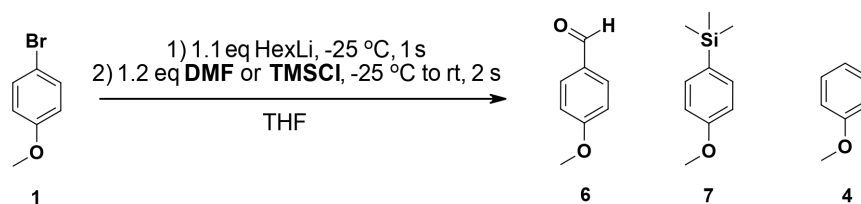


Figure 2: **A:** A miniaturised, chip-based reactor for the lithiation and trapping of aryl halides. **B:** A lower cost Tee-piece based reactor with a larger internal volume compared to the chip-based reactor.



Entry	Product	Precooling loop R_t /s	HPLC Area % (PDA)		
			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 2A**.

With this information in hand, we assessed the lowest injectable volume for each reactor required for a productive lithiation-trapping synthesis by determining the spectroscopic yields of two model reactions in the reactors as a function of 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 either by concentration under reduced pressure or simple dilution and minimised the yield losses associated with a more involved workup.

Starting first with the reaction of pivaldehyde with **1** and quenching into MeOH, we could see that the chip-based reactor was able to generate a reasonable (49%) yield of **9** from a 2 mL (corresponding to a 56 mg input of **1**) injection volume. To ensure this phenomenon was consistent across different substrates, we also reacted bromoarene **8** with TMSCl, the rationale being that **8** has a faster rate of metalation relative to **1**[20]. Data are reported in **Figure 3**. Due to the volatility of product **10**, it was necessary to determine yields directly from reaction mixtures via quantitative HPLC.

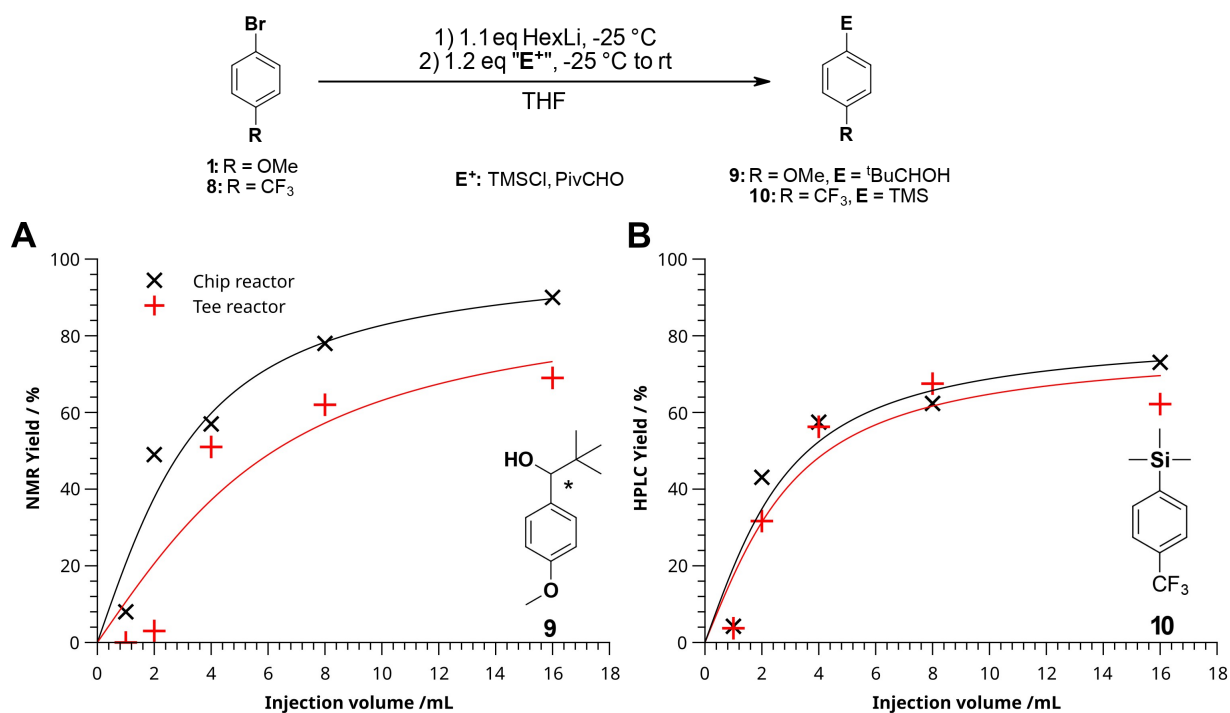


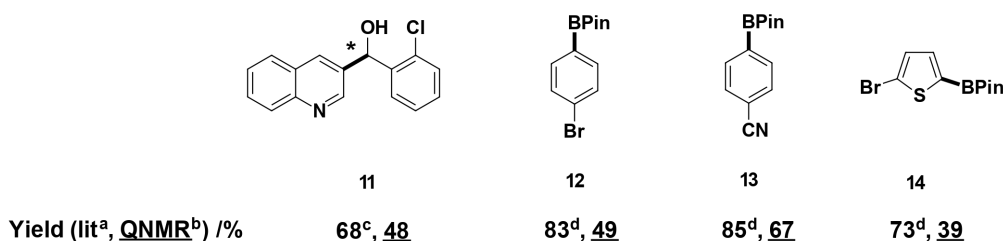
Figure 3: **Top:** Aryl halide-electrophile pairs combinations used to generate injection volume- yield curves. **Bottom:** Injection volume- yield curves for each product synthesised. The in-flow synthesis of **10** in the chip reactor was run in duplicate; the mean yield is shown. Lines of best fit take the form $y = a \arctan(bv)$, where y = yield, a and b are constants and v is the injection volume.

We note that both reactor designs start to plateau in yield at injection volumes greater than 4 mL across both substrates, with limited evidence that the chip reactor can furnish higher yields of product at lower injection volumes relative to the tee-mixer based reactor. 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. This is indicative of a steady state condition being reached. On this basis, we suggest the following aryl halide material inputs for these reactor systems (**Table 4**).

M_r / g mol ⁻¹	Mass required / mg
150	90
250	150
350	210
450	270

Table 4: Masses of substrate required for a 4 mL injection of aryl halide at 0.15 M, the volume at which both reactors demonstrate similar productivity.

Finally, to determine the preparative utility and to benchmark the chip reactor in **Figure 2** against other designs in the literature, we processed a selection of aryl halides previously synthesised in flow (**Scheme 3**). In doing so, we report the yield as a function of the total mass of aryl halide used to prepare injection solutions, so as to more accurately reflect material needs. On the basis of successful trial reactions (see supporting information) 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 ArX injection, so that variations in the arrival of these feeds at the mixing chip would not adversely affect ArX consumption.



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.[26] d) GC yield from the crude reaction mixture against an internal standard[27]. 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 a maximum yield of 82.5 % unless a method to flush the reactor is employed.

Although the 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. Furthermore, we report the yields in **Scheme 3** as a function of the *total* amount of substrate material committed to a reaction. This is in contrast with the more usual approach found in the literature in which yield is reported as a function of starting material input once steady state has been reached, and reaction output has been collected for a given amount of time. This means that yields reported at steady state in the literature are not impacted by material being retained in the internal volume of the reactor in the same way that yields based on the total volume of limiting reagent are. This is especially relevant when the ratio of the injection volume:reactor volume ratio is small.

Conclusion

As part 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 ($< 5 \text{ mL min}^{-1}$). These reactors can be constructed without recourse to costly or bespoke equipment and their utilisation allows small amounts of substrate (100-300 mg of ArX) to be successfully processed, making flash flow lithiation and trapping more accessible to those who routinely work on small scale, e.g. medicinal chemists. We believe our work may also enable further minimisation, e.g. via a segmented flow approach, which can benefit from low flow rates[9]. These are being evaluated in our laboratories.

CRedit author statement

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