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RESEARCH

Tandem continuous-flow α-C-H functionalization of pyrrolidine with aryl bromide-derived organolithium reagents

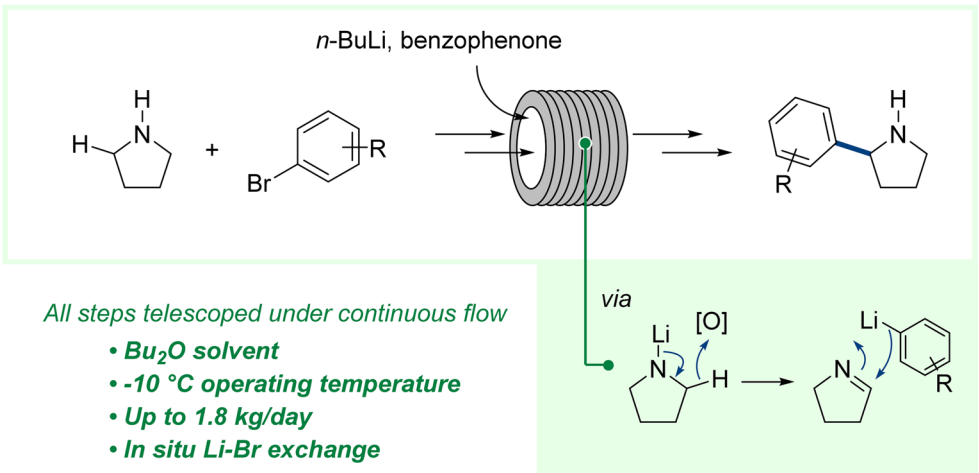
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Abstract

The α-functionalization of unprotected cyclic amines *via* organolithium reagents presents significant challenges for scale-up due to the extreme reactivity of the intermediates and the requirement for cryogenic control. A continuous-flow platform has been developed that enables the *in-situ* generation and telescoped use of organolithium reagents for the oxidative C–H functionalization of cyclic amines with organolithium reagents. The lithiation, oxidation, and nucleophilic addition sequence proceeds efficiently at −10 °C, offering precise thermal management and reproducible steady-state operation. The system furnishes α-aryl-substituted pyrrolidines in up to 54% yield with a productivity of ~40 g h^{-1}. Scope studies revealed solubility-limited precipitation for certain aryl lithium reagents, identifying solvent polarity as a critical design parameter for future expansion. This work establishes a safe, modular framework for executing highly energetic organolithium transformations under continuous-flow conditions, providing valuable guidance for translation to manufacturing scale.

Graphical Abstract



Keywords C-H functionalization · Continuous flow · Organolithium · Amines

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Abbreviations

API	Active pharmaceutical ingredient
Boc	Tert–butyloxycarbonyl
CPME	Cyclopentyl methyl ether
FDA	U.S. Food and Drug Administration
GC/FID	Gas chromatography with flame ionization detection
MTBE	Methyl tert–butyl ether
RSM	Regulatory starting material
t_R	Residence time
STY	Space–time yield
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine

Impact of flow

The amine α-C-H functionalization of amines using organolithium reagents is a powerful bond-forming reaction. However, the method necessarily requires multiple stoichiometric equivalents of pyrophoric organolithium reagents and oxidants, presenting significant safety challenges for scale-up. Here, we exploit the enhanced heat transfer and rapid mixing under continuous flow to allow this sequential reaction to be conducted safely at much higher temperatures (−10 °C vs. −78 °C), and much more rapidly (overall residence time ~ 1 min, vs. ~ 3 h batch reaction time) than the batch reaction permits.

Introduction

Nitrogen-containing heterocycles are key structural motifs in natural products and small molecule APIs. According to a report based on the US FDA approved drugs, 59% of small-molecule drugs contain a nitrogen heterocycle and as such, expedient syntheses toward functionalized *N*-heterocycles have become an important endeavor [1]. Activation of sp^3 C-H bonds in heterocycles is an attractive strategy for accessing complex substituted nitrogen heterocycles via the conversion of simple and readily accessible starting materials [2–4]. A variety of studies on the α-C-H bond functionalization of cyclic amines has been reported in recent years [5–19]. One commonly employed strategy for the effective C-H functionalization of pyrrolidine derivatives is through the use of a protecting group such as *N*-Boc (*t*-butyloxycarbonyl) to prevent reactivity at the amine site, while acidifying and directing reactivity towards the adjacent C-H bonds (Fig. 1a) [20] Seminal work by Beak et al. demonstrated the organolithium and (−)-sparteine-mediated α-deprotonation and functionalization of protected pyrrolidines [21]. The transformation is purported to proceed *via* initial deprotonation of the α-position to generate an α-lithiopyrrolidine complexed with the diamine additive, which is then reacted with an electrophile to afford an enantioenriched functionalized pyrrolidine. This strategy was utilized in the enantioselective preparation of α-arylpyrrolidines through the generation of the α-lithiopyrrolidine/diamine complex using the strong base s-BuLi and chiral ligand (−)-sparteine [8]. In-situ generation of 2-pyrrolidinozinc upon exposure of the activated complex to $ZnCl_2$ precedes a Pd-catalysed Negishi arylation to furnish enantioselective α-arylpyrrolidines in yields up to 87%. This approach was subsequently extended to the α-alkylation of pyrrolidines by Fu and co-workers, where following the generation of a racemic α-zincated *N*-Boc-pyrrolidine species, a Negishi cross-coupling was conducted employing unactivated secondary alkyl halides providing the desired enantiomer "in up to 96% *ee* [22].

An elegant protocol for the innate α-C-H functionalization of cyclic amines was reported by Seidel et al. in 2017 (Fig. 1b) [23]. This method gained access to high-value functionalized amines from commercially available, cheap nitrogen feedstocks. Inspired by the earlier work of Wittig and Hesse which found that lithiated amines acted as hydride donors to carbonyl compounds, [24] Seidel et al.. hypothesized that the transient imine by-product could be intercepted by a suitable nucleophile to generate α-functionalized amines. Practically, the nucleophile was typically a second (or more of the same) organolithium species used to generate the initial lithium amide. Crucially, and in contrast to some of the earlier work described, the amine is unprotected throughout. The method was successfully applied to the functionalization of late-stage intermediates varenicline and risperidone, both FDA approved drugs. The Seidel group have since incorporated the use of Grignard reagents, [25] and accessed C-H and N-H annulation reactions [26–28], condensation-based C-H functionalization, [29] and regioselective α-cyanation [30] and phosphonylation [31] among other transformations [32–34]. However, this technology also presents challenges which restricts its implementation on the manufacturing scale, including the use of sensitive organometallic reagents, cryogenic operating temperatures, and the need for slow addition of certain reagents to avoid thermal runaway and maximize selectivity.

Here, we attempt to overcome some of these challenges by optimizing an amine C-H functionalization protocol under continuous flow conditions (Fig. 1c). The advantages of conducting organolithium protocols under continuous flow have recently been reviewed [35–37]. The use of the enhanced mixing within microreactors has also allowed the exploitation of short-lived intermediates for synthesis, in so-called “flash chemistry” [38]. Improved heat and mass transfer can yield significant benefits, allowing greater

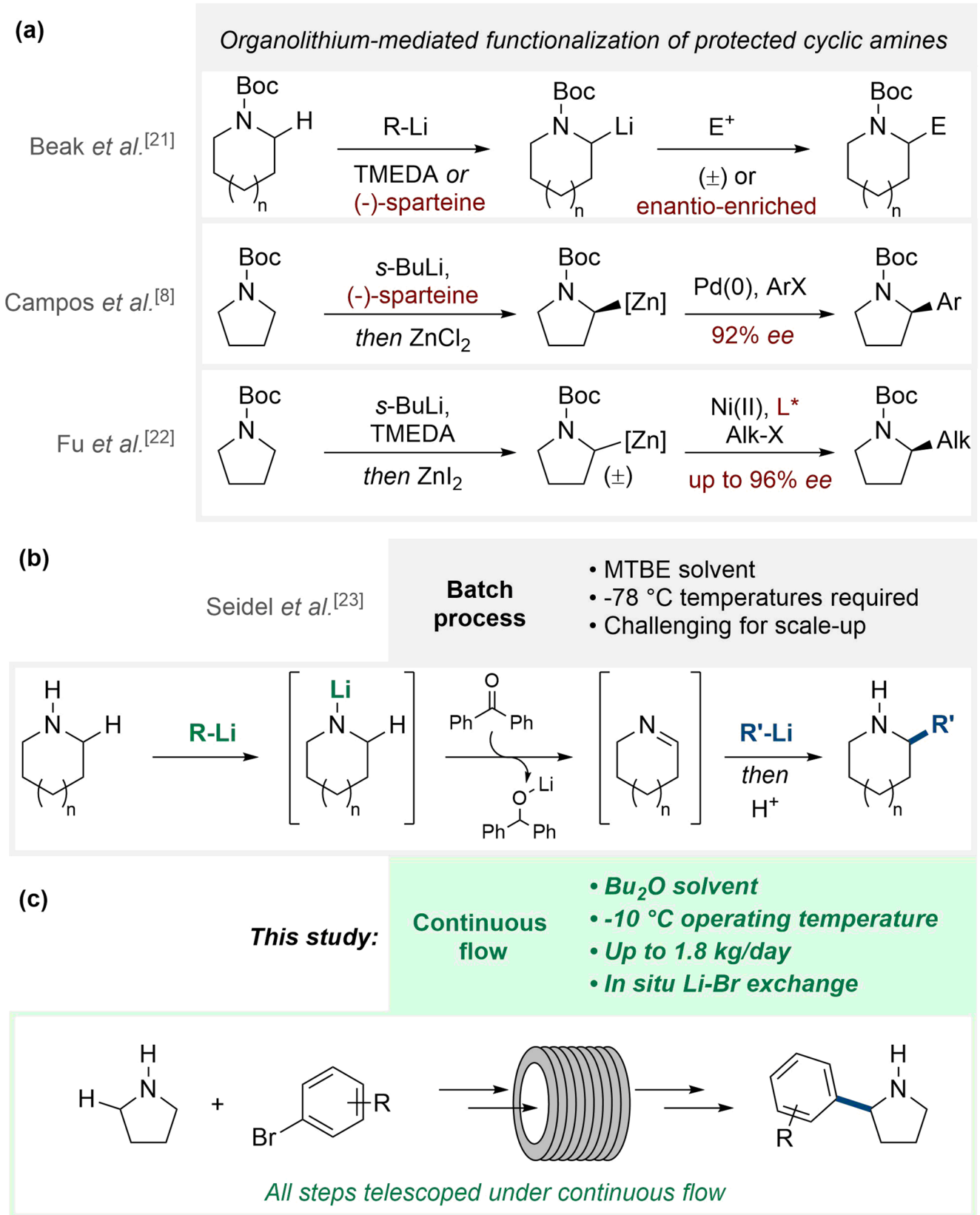


Fig. 1 (**a**). Selected examples of α-C-H functionalization of protected cyclic amines using organolithium reagents. (**b**). The C-H functionalization of unprotected cyclic secondary amines reported by Seidel et al. [23] (**c**) Overview of the continuous flow C-H functionalization of pyrrolidine described herein

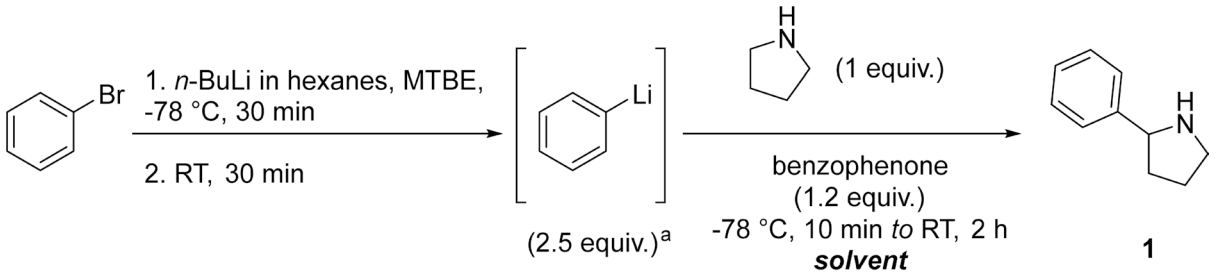
control of [39, 40], and in some cases elimination of the need for [41–43], cryogenic conditions. While C-H functionalization under continuous flow has been explored previously, the vast majority of amine functionalizations require the nitrogen atom to be protected, likely due to deleterious interactions with the transition metal catalysts used [44]. We therefore sought to develop a safe, scalable and efficient protocol for the continuous synthesis of α-substituted amines via the organolithium-mediated C-H functionalization of unprotected amines, applicable to both API and RSM manufacturing.

Results and discussion

One of the potential pitfalls of transferring the batch protocols as reported by Seidel into a continuous flow regime is the solubility of the reagents, and any products and by-products formed during the reaction. The solvent used for the batch process (MTBE) was not suitable for flow due to the formation of precipitates, so we sought an alternative ethereal solvent that would maintain solubility, and with acceptable safety and sustainability metrics [45]. A batch solvent screen for the C-H phenylation of pyrrolidine with PhLi formed by Li/Br exchange from bromobenzene was therefore conducted, prior to addition into the amine for the C-H functionalization (Table 1). 2-Phenylpyrrolidine (1) was obtained in comparable yields to the literature report (60%) on reaction in of cyclopentylmethyl ether (CPME), diisopropyl ether (iPr_2O) and dibutyl ether (Bu_2O) (entries 1,3,5). Due to the high volatility of iPr_2O and its tendency to undergo peroxide formation, it was ruled out as a suitable solvent for scale-up. Bu_2O is significantly cheaper than CPME and so was selected as the solvent for transfer to continuous flow. Crucially, throughout the course of the reaction no precipitates were observed. To further assess the viability of Bu_2O as a suitable solvent, the sequential addition technique was also investigated, using Bu_2O as the reaction solvent in both the lithium-halogen exchange and C-H functionalization steps (Entry 6), and gave only a modest drop in yield relative to the MTBE reaction, with the reaction mixture again remaining homogeneous throughout.

Initial studies under continuous flow were conducted on the same model system, with commercial PhLi acting both as the base to deprotonate the pyrrolidine and the nucleophile. A single reactor protocol was used, with one pump introducing a feed solution of the cyclic amine substrate and hydride accepter in Bu_2O into the reactor, and another delivering the organolithium reagent, also in Bu_2O (Scheme 1). The product feed was passed through a back-pressure regulator (5 bar) to stabilize flow and prevent bubble formation, and quenched into a reservoir of methanol. The model reaction was initially investigated with a short 30 s residence

Table 1 Batch solvent screen conducted for the C-H functionalization reaction of pyrrolidine. Yields reported were determined by GC/FID using 1,3,5-trimethoxybenzene as the standard

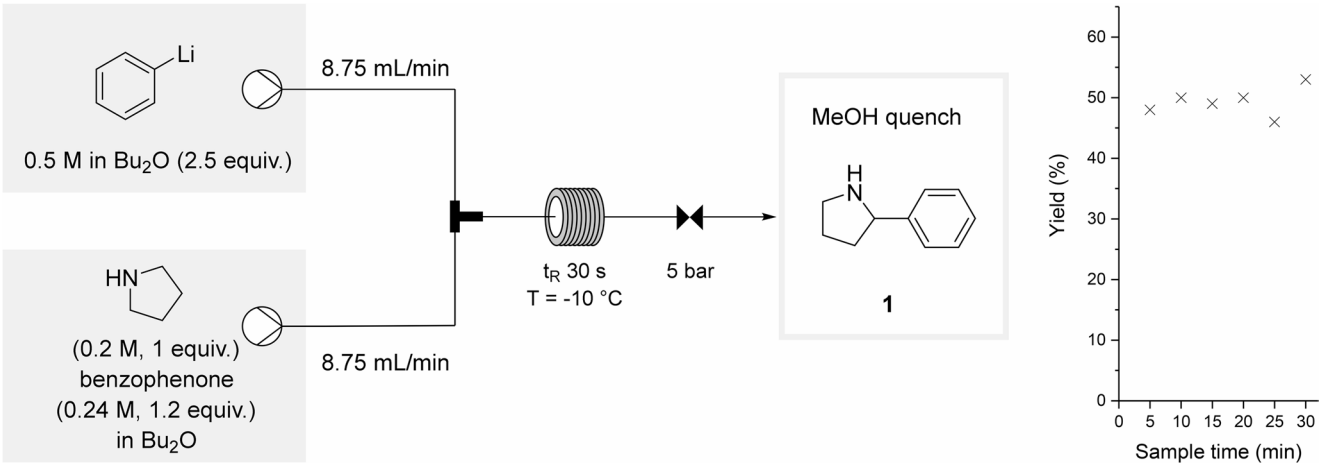


Entry	Solvent	Yield (%)[b]
1	CPME	53
2	Me-THF	29
3	iPr_2O	61
4	Heptane:THF (9:1)	39
5	Bu_2O	64
6[c]	Bu_2O	55

[a] Obtained as a solution in MTBE: hexanes ~ 2:1 v: v

[b] yields determined by GC/FID using 1,3,5-trimethoxybenzene as an internal standard

[c] Bu2O was also used as the solvent for the initial lithium-halogen exchange step, in place of MTBE



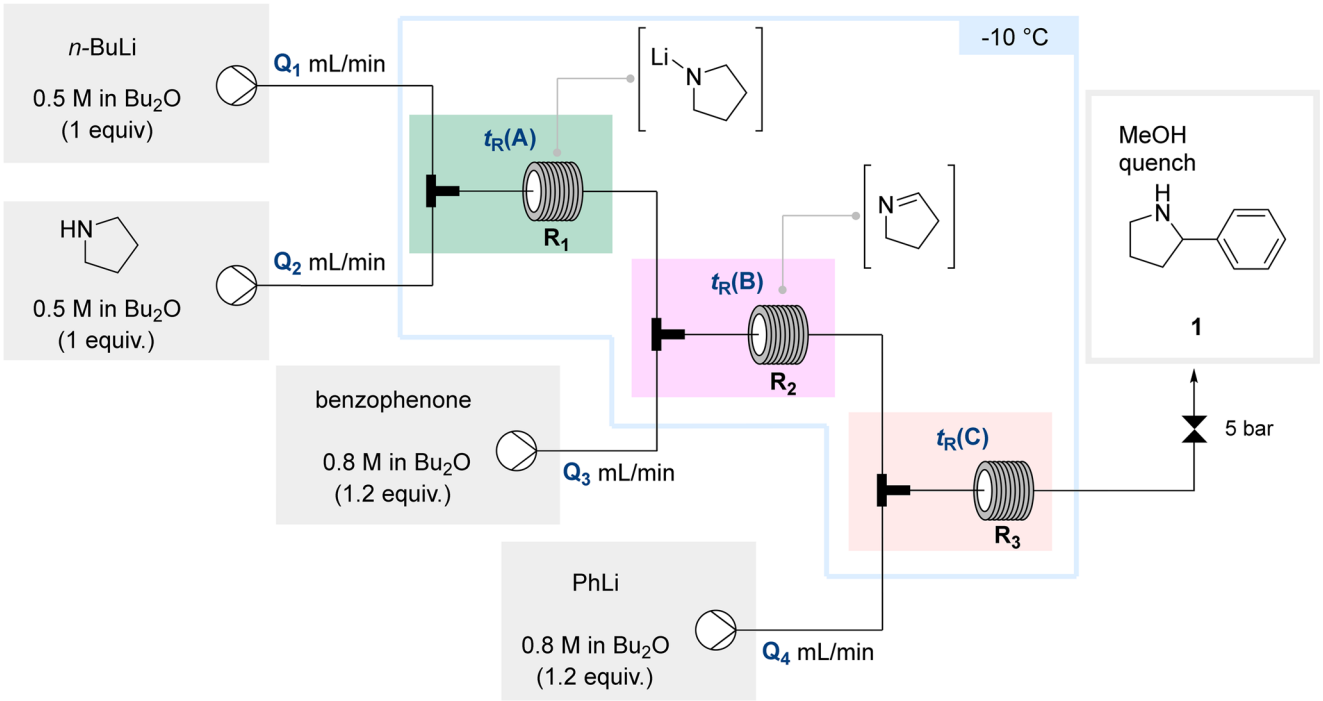
Scheme 1 Demonstration of steady state in the continuous flow synthesis of 1-phenylpyrrolidine through the reaction of pyrrolidine and PhLi in the presence of hydride acceptor benzophenone. Samples were taken at 5 min intervals for a duration of 30 s and yields determined by GC/FID using 1,3,5-trimethoxybenzene as an internal standard

time, using high flow rates to ensure sufficient mixing on the short reaction timescale and at a more scalable reaction temperature of − 10 °C. Pleasingly, the desired functionalized amine 1 was successfully afforded in 50% yield. Analysis of the reaction output demonstrated that steady-state was achieved within 5 min and reproducible results were obtained over six samples (30 min).

A further small improvement in yield was obtained by increasing the residence time in the reactor to 2 min by increasing its length (see supporting information, section S4.1, Fig. S1). Variations in temperature were found to have minimal impact on yield, with reactions conducted at -27 °C, -10 °C and 27 °C providing the product in a comparable yield (see Fig. S2). For subsequent reactions we elected to run reactions at -10 °C to control any exotherm, but this is a significant improvement on the temperatures of -78 °C used for the batch protocol. Thus far, the protocol uses the same organolithium species as both the base and nucleophile. To enhance the scope of the continuous flow reaction, a sequential addition route was adopted to facilitate single unit optimization of each reaction step and with *n*-BuLi as the deprotonation/lithiation source, reserving the more expensive organolithiums only for nucleophilic addition. Four pumps were utilized to introduce separate feed solutions containing pyrrolidine, *n*-BuLi, benzophenone, and PhLi (Scheme 2). Single unit optimization studies were then conducted by monitoring the effect of parameter variation at each step on the overall product yield (Table 2). First, the effect of residence time at each step was considered. The residence time was altered through varying the reactor volume appropriately, maintaining a consistent flow rate. Based on the results described above, a temperature of − 10 °C and short residence times were applied to the system. Variations of residence time at each sequential step showed little effect on the overall reaction yield, with the only change causing a significant drop in yield being reduction of t_R(A) (the residence time for deprotonation of the pyrrolidine) to 1 s causing a low yield of 33%. Increases in this residence time beyond 15 s did not further improve the yield. Changes to the other two residence times t_R(B) and t_R(C) led to no significant changes in yield, and under optimal conditions (t_R(A) = 15 s, t_R(B) = 30 s, t_R(C) = 30 s) 2-phenylpyrrolidine was afforded in 50–55% yield with a total residence time of 1.25 min (entries 2,5,8).

With yields already comparable to those achieved under batch conditions in Bu_2O (55%), the effect of individual pump flow rates at a fixed cumulative residence time was also examined (Table 3). However, increasing the flow rates Q_3 and Q_4 (with adjusted reagent concentrations and reactor coil length to maintain overall stoichiometry and residence time, respectively) resulted in no significant improvements in product output, with yields of 54–55% observed.

An advantage of implementing a sequential addition route is the ability to generate bespoke organolithium reagents on demand and in parallel with key intermediates for downstream functionalization. Early screening experiments demonstrating lithium-halogen exchange with BuLi and aryl bromides were conducted (see Supplementary information, section S4.2). The most important result of these experiments was that the lithiation failed entirely when conducted in Bu_2O under continuous flow. This was surprising, given that the same reaction proceeded in good yield under batch conditions (see Table 1, Entry 6). However, it has previously been reported that solvation of *n*-BuLi in THF gives rise to dimeric and tetrameric aggregates in equilibrium with one another, with the former being the more reactive species [46]. The failure to react under continuous flow in Bu_2O is likely a result of a reduced reaction rate due



Scheme 2 Sequential addition route for the continuous flow C-H functionalization reaction. Reagent reservoirs are shown in grey, and parameters varied during optimization are shown in bold. All reactors were immersed in an isopropanol bath at a temperature of − 10 °C

Table 2 Optimization of residence times in multi-step continuous flow C-H functionalization

Series	Entry	$t_R(A)$ (s)	$t_R(B)$ (s)	$t_R(C)$ (s)	Yield (%)[a]
$t_R(A)$	1	1	30	30	33
	2	15	30	30	50
	3	30	30	30	49
$t_R(B)$	4	15	15	30	50
	5	15	30	30	55
	6	15	60	30	53
$t_R(C)$	7	15	30	15	51
	8	15	30	30	53
	9	15	30	60	53

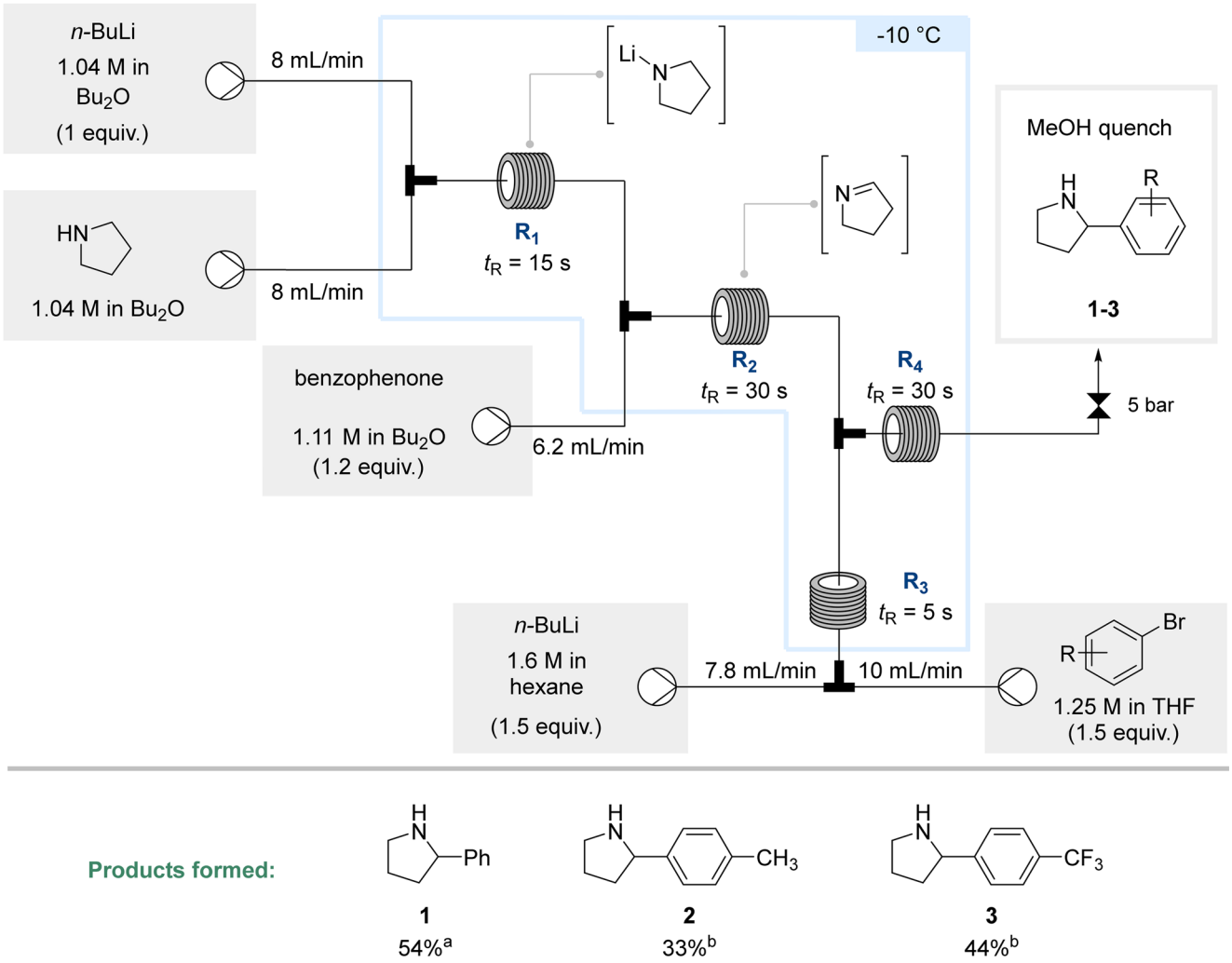
[a] Yields determined by GC/FID using 1,3,5-trimethoxybenzene as an internal standard, contained in the pyrrolidine feed solution

Table 3 The effect of varying flow rates Q_3 and Q_4 maintaining a consistent t_R,

Entry	[Pyrrolidine][a] (M)	Q1 (mL/min)	[BuLi][a] (M)	Q2 (mL/min)	[Benzophenone][a] (M)	Q3 (mL/min)	[PhLi][a] (M)	Q4 (mL/min)	Yield[b] (%)
1	0.5	8	0.5	8	0.8	6	1	6	55
2	0.5	8	0.5	8	0.533	9	0.6	10	54
3	0.5	9	0.5	9	0.6	9	0.675	10	54

[a] To account for flow rate changes, the concentrations of individual feeds was altered to maintain overall reaction stoichiometry

[b] Yields determined by GC/FID using 1,3,5-trimethoxybenzene as an internal standard



Scheme 3 Telescoped continuous synthesis of 2-arylpyrrolidines *via* the organolithium-mediated C-H functionalization of pyrrolidine, incorporating an in-situ aryllithium generation. [a] Yield determined by ^{1}H NMR and GC/FID using 1,3,5-trimethoxybenzene as the internal standard, contained in the pyrrolidine feed solution. [b] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard, contained in the pyrrolidine feed solution

to different speciation of the organolithium species, while under batch conditions the longer reaction times permitted the reaction to proceed. However, adjusting the residence time for the Li/Br exchange to from 0.5 to 30 s did not yield any improvement. An alternative lithiation protocol under flow conditions was deployed, reacting the aryl bromide in THF with a commercial solution of *n*-BuLi in hexanes. The lithium-halogen exchange was then incorporated into the model flow protocol *via* a 5-pump configuration as depicted in Scheme 3. The process proceeds as follows: lithiation of the pyrrolidine substrate in reactor 1 (R_1), followed by the introduction of benzophenone acting as the hydride acceptor resulting in the formation of pyrroline intermediate in reactor 2 (R_2), the aryllithium species synthesized in parallel in reactor 3 (R_3) then undergoes nucleophilic addition to the pyrroline intermediate furnishing the desired functionalized amine in reactor 4 (R_4).

Pleasingly, the model product 2-phenylpyrrolidine was furnished in 54% yield, identical to that obtained when employing commercial phenyl lithium. The optimized sequential addition route would offer ~ 40 g h^{-1} productivity, equating to a space-time yield (STY) of 1.08 kg L^{-1} h^{-1}. The STY of the batch phenylation of pyrrolidine is ~ 9 g L^{-1} h^{-1}, [23, 47] highlighting the substantial process intensification achieved through reduced reaction times, telescoping of steps, and continuous operation. On expansion of the aryllithium scope to 4-bromotoluene and 4-bromobenzotrifluoride, lower yields of 33% and 44% of the respective functionalized pyrrolidines were obtained, concomitant with precipitation of a brown solid leading to reactor clogging. It is suspected that the hexane present in the reaction mixture

leads to precipitation of highly polar aryllithium reagents or intermediates, whose solubility properties may differ from those in the 2-phenyl pyrrolidine reaction. Though we have not re-optimized the process for these substrates, it is likely that the use of more concentrated commercial *n*-BuLi in hexanes solution may ameliorate this issue, since the combined solvent mixture would have a reduced overall hexane content and higher polarity.

Conclusions

A proof-of-concept demonstration of the C-H functionalization of unprotected cyclic amines has been developed under continuous flow operation. Single unit optimization of a telescoped, multi-step process featuring a 5-pump assembly incorporating in-situ lithium-halogen exchange led to an optimized protocol that delivers the product in comparable yields to the batch reaction, and with an output of 40 g h^{-1}. Unlike the batch reaction, the requirement for extreme cryogenic temperatures is circumvented, and there is no risk of accumulation of reactive organolithium species. The reaction was conducted in Bu_2O, which afforded the necessary dissolution of reagents and intermediates, but which has a much higher flashpoint than Et_2O used in the batch report. Though further optimization may be required for specific alternative substrates, we believe this study demonstrates that α-C-H functionalization of cyclic amines using organolithium reagents can be achieved safely and at scale by leveraging a continuous flow approach.

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Authors' contributions The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. Individual contributions were as follows: LJN: investigation, visualization, writing – original draft, writing – review & editing; AAR: writing – review & editing; SD: writing – review & editing; MS: project administration, supervision, writing – review & editing; TSM: funding acquisition, resources, supervision, writing – review & editing; SW: supervision, writing – review & editing; KF: project administration, supervision; PD: writing – review & editing; DWR: funding acquisition, writing– review & editing; JMT: funding acquisition, supervision, writing – review & editing; MJM: conceptualization, funding acquisition, project administration, supervision, writing – review & editing; PCK: conceptualization, funding acquisition, project administration, supervision, writing – original draft, writing – review & editing.

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Data availability The supplementary information accompanying this manuscript contains additional experimental results, full procedures and characterization data for compounds synthesized.

Declarations

Competing interests The authors declare no competing interests.

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47. Calculated on a reaction-volume basis. The concentrations of organolithium reagents were not provided, so this value assumes PhLi and nBuLi concentrations of 2 M.

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