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Technical Note: On the Selection of Precooling Loops for Low-Temperature Continuous Flow Chemistry

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ABSTRACT: Precooling lines are often used in cryogenic flow chemistry, but factors affecting their performance are not well characterized. We present a systematic study on the effects of flow rate, residence time, and internal diameter on the cooling performance of a selection of tubing commonly used in flow chemistry systems using tetrahydrofuran (THF) and 2-methyl tetrahydrofuran (2-MeTHF) as the solvents. On the basis of our findings, guidelines for minimum residence times for effective precooling are suggested. A general model for precooling was derived and evaluated. The model demonstrates reasonable agreement with experimental values and may be useful for identifying sufficient precooling times for other solvents. The scope and limitations of precooling as a temperature management strategy are explored in a series of lithiation reactions on aryl bromides in a flow. We surmise that, while precooling in flow is important, it is not the only factor relevant in stabilizing extremely reactive species in isolation.

KEYWORDS: *Flow chemistry, Precooling, Heat exchange, Cooling bath, Organometallics*

1. INTRODUCTION

Proper temperature control is key to the success of any chemical process, and operating chemical processes in continuous flow can enable superior heat and mass transfer relative to operation in batch mode.[1] This is especially relevant when reactive intermediates such as organolithiums, carbenes, and carbenoids are involved, and it is for this reason that reactions involving the generation and manipulation of these species benefit greatly from running in flow mode. Indeed, it has been demonstrated over a number of decades that running in flow allows for controlled reactions of species that are impossible to scale, if not accessed outright, in batch.[2]

While much work on thermal management in flow has understandably focused on exotherm and process temperature control *after* reagent mixing (e.g., through judicious tubing diameter selection, numbering-up, and control of flux) as a means of controlling intermediate stability,[3,4] one strategy to control reaction temperature that has received relatively little attention in the organometallic flow chemistry literature is that of the reagent precooling stages that are incorporated into many published flow reactors.

Precooling stages are usually realized as tubes through which reagent feed solutions flow and are used to set the initial "prereaction" temperature of individual reagents prior to a mixing/reaction event,[5] and the efficacy of precooling may affect process temperature. We found that, on a random sampling of organometallic flow literature cited in two contemporary reviews,[6,7] precooling loops if described ranged in volume and by extension residence time from around 6 s to 250 s, were constructed from PFA, PTFE, or stainless steel, and were between 0.8 and 1.6 mm in internal diameter (Figure 1).

This variability in conditions signaled a possibility that reagent input flows in different publications may have had significantly different temperatures inline relative to the reported bath/cooling fluid temperature. It also implied that no standard practice exists for reagent precooling as part of a process-temperature-control strategy. We therefore thought it desirable[8] to understand differences between the inline and external (or bath) temperatures in the literature space without recourse to mathematical models unfamiliar to the bench chemist as well as offer some preliminary guidelines for implementing precooling stages. Given the vast majority of publications we sampled (20 out of 23; see the Supporting Information) use tetrahydrofuran (THF) as the primary solvent (i.e., the solvent whose volume fraction is greatest at the lithiation section of a reactor), we focused our work on the same solvent, such that the data generated and trends observed could be applied to the widest possible scope of organometallic reactions reported in flow, thereby enabling critical assessment of the suitability of precooling lines reported in earlier work. It should also be noted that, at time of writing, a number of very recently reported manufacturing campaigns involving an organometallic flow step use THF as the primary solvent,[9,10] though 2-methyl tetrahydrofuran (2-MeTHF) now receives interest[11] as a more sustainable alternative. Of course, any guideline is no substitute for proper process and plant

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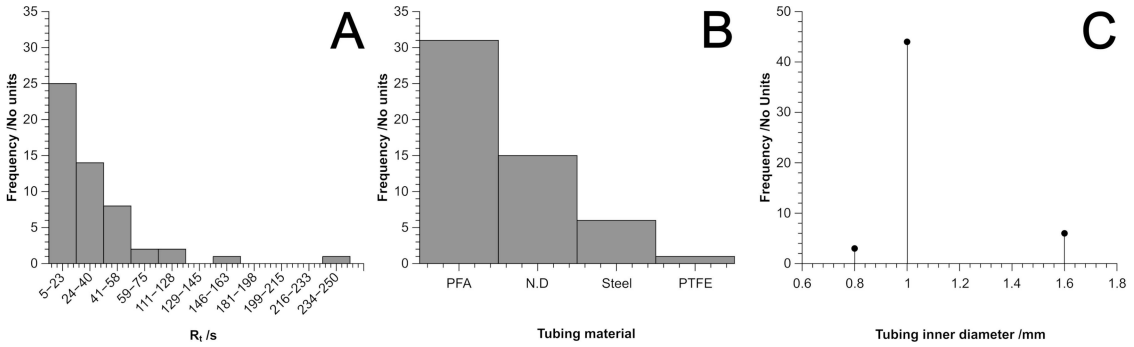


Figure 1. Frequency distributions in literature: A) precooling line residence times, B) materials of construction, and C) internal diameters used for precooling lines across a selection of published flow reactors. Publications from which the data were sourced are listed in Section 3 of the Supporting Information. N.D: Not described.

understanding and must be viewed in the context of the process being developed.

2. RESULTS AND DISCUSSION

2.1. Determination of Experimental Conditions: Importance of Heat Transfer Fluid and Units of Measure

2.1.1. Preliminary Remarks. We describe the efficacy of precooling in terms of ΔT, defined as the absolute value of the difference between the bath temperature, T_{bath}, and the inline temperature, T_{inline}, at the end of the precooling line under investigation, or, $\Delta T = |T_{bath} - T_{inline}|$. Since ΔT was observed to be independent of bath temperature across the temperature range of interest (−80 to 0 °C, Supporting Information Section 1.3.1), we were able to gather accurate data on temperature trends in spite of any thermal drift in the cooling bath. We used class 1 K-type thermocouples adapted for use in flow chemistry systems[12] for all measurements in the orientation depicted in Figure 2.[13]

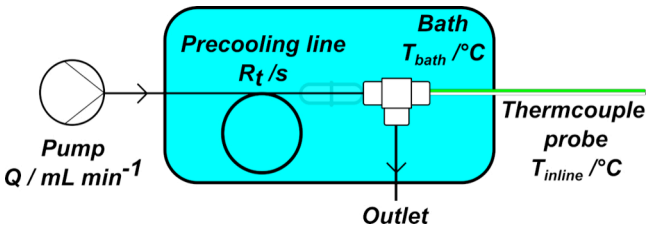


Figure 2. Schematic of the measurement system with thermocouple orientation and discussed parameters shown. Residence times correspond to volumes of tubing submerged in the bath exclusively.

K-type thermocouples are commercially available in smaller sizes and at lower cost compared to the Pt100 probes typically used in process chemistry but are less accurate. Depending on their exact construction, K-type thermocouples also have a faster response rate compared to Pt100 probes. Since errors are not reported for class 1 K-type thermocouples at temperatures below −40 °C, we assume an error of ±2.5 °C based on measurements against a reference Pt100 probe. Further details are available in Section 1.3.2 of the Supporting Information. Due to equipment constraints, we utilized a stirred dry ice: acetone bath in all work. This was on the basis of three observations: the first being that temperature differences between different sampling locations in a dry ice:iPrOH solvent bath were markedly reduced on agitation. Second, in early precooling line length tests of the type depicted in Figure 2, ΔT was minimized at lower residence times when the bath was agitated compared to when it was not. Finally, ΔT reached its minimum at lower residence times when either acetone or MeOH were used as bath solvent in place of iPrOH *and* the bath was agitated.

We understood this solvent dependence in terms of the viscosity. The relatively high viscosity of iPrOH likely impedes forced convective heat transfer[14] compared with solvents like acetone or MeOH. These solvents may be expected to have higher rates of forced convective heat transfer due to their lower viscosity relative to that of iPrOH at similar temperatures, leading to their superior cooling performance. This is despite their lower heat capacities compared with iPrOH. A more detailed discussion of these observations is in Sections 1.3.3 and 1.3.4 of the Supporting Information.

In light of our results, we strongly recommend the agitation of dry ice baths when they are used for flow chemistry, in conjunction with the use of a low-viscosity solvent like acetone or MeOH, for optimal cooling performance. However, the limitations of dry ice solvent baths on scale (e.g., the need to regularly recharge them, the exposure risks, and the difficulty in agitating such a bath when a flow reactor is immersed within it) are considerable. Limitations such as these led us to suggest that a reactor cooling approach built around a suitably powered recirculating chiller is employed for any subsequent development or production work.

2.1.2. Determining Key Flow Parameters. When considering precooling, it is intuitive that an increased residence time, R_t, for a feed solution in a precooling loop will tend to reduce the difference between the bath and internal temperatures irrespective of flow rate, Q, at a given tubing volume, V. However, intuition is no substitute for experimental validation. So, we assessed what the major driver of cooling inside a precooling loop may be when flow rates and residence times representative of low-temperature organometallic chemistry (based on our survey in Figure 1) were used. This was undertaken via an experimental design that interrogated ΔT as a function of flow rate at constant residence time and ΔT as a function of residence time at constant flow rate by using differing lengths of PTFE tubing with internal diameter of 0.9 mm (Figure 3).

From a visual inspection of the graphs in Figure 3, it is clear that changes in residence time at constant flow rate effect larger changes in ΔT and that, when flow rate is varied but residence time is held constant, ΔT does not change significantly. Spearman rank correlation coefficients[15] also suggest stronger correlations of residence time with ΔT than

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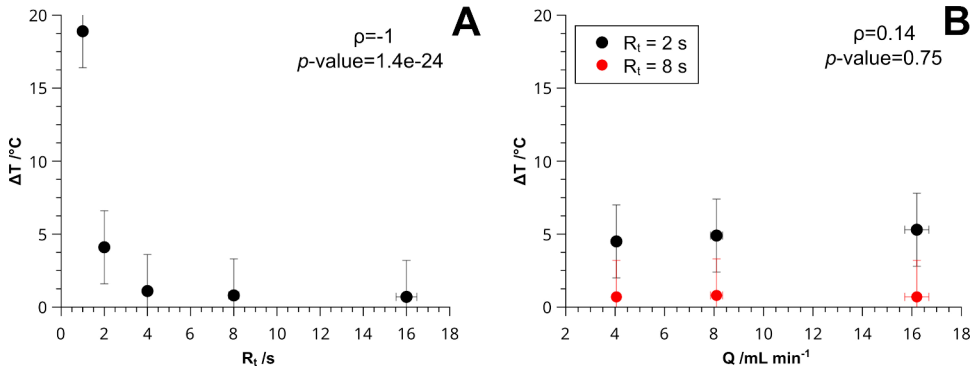


Figure 3. A) Effect of residence time, R_t, at 8 mL min^{-1} on the difference between bath and inline temperature, ΔT. B) Effect of flow rate, Q, at constant residence times. PTFE tubing with a measured internal diameter of 0.9 mm (OD = 1.6 mm) was used. Correlation coefficients are Spearman's rank coefficients. Error bars in the y axis are set at ± 2.5 °C and have been estimated via error propagation (Section 1.3.2 of the Supporting Information). Measurements were taken in a stirred (500 rpm) dry ice/acetone bath at a temperature between −55 and −60 °C as the cooling bath and THF as the flowing solvent. All THF was dosed into the system at room temperature (ca. 22 °C).

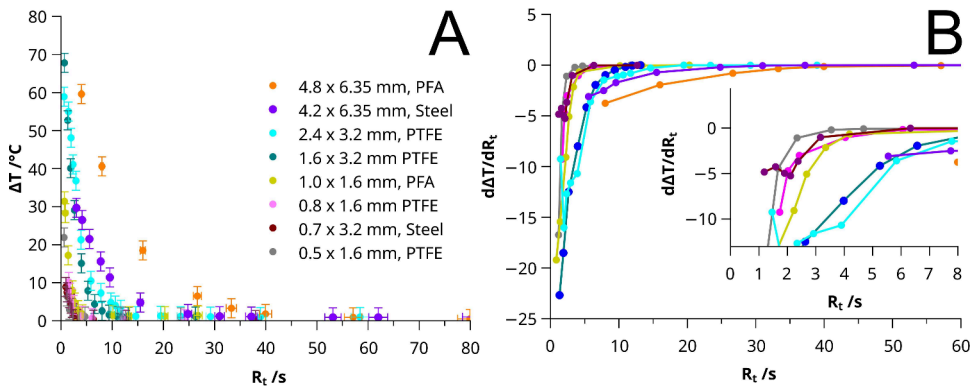


Figure 4. A) Difference between bath and inline temperature, ΔT, as a function of residence time, R_t, for a selection of tubing sizes common in the cryogenic flow chemistry literature. Tubing dimensions are expressed as ID × OD. B) The derivative plots for the data points in A). Error bars in the x axis represent ±3.2% of the plotted residence time and have been estimated via error propagation; see Supporting Information Section 1.3.5. Error bars in the y axis are set at ±2.5 °C and have also been estimated via error propagation. Measurements were taken in a stirred dry ice/acetone bath at a temperature between −55 and −60 °C as the cooling bath and THF as the flowing solvent. All THF was dosed into the system at room temperature (ca. 22 °C).

with flow rate (ρ = −1 vs ρ = +0.14, respectively). Furthermore, when a Gaussian process regression model is trained on the data in Figure 3 and R^2 values are used to assess the importance of R_t and Q in isolation on the predictive power of the resulting models using a "leave one feature out" analysis,[16] residence time is the biggest predictor ($R^2_{R_t}$ = 0.99 vs R^2_Q = 0.05). With this data in hand, we worked under the assumption that subsequent experiments should be designed around residence time as opposed to flow rate.

2.2. Effect of Residence Time on ΔT

2.2.1. Studies on THF. Working from the information in Figure 1, we studied the cooling characteristics of THF flowing through a set of tubing constructed from PTFE, PFA, or 316 stainless steel, ranging from an internal diameter of 0.5 mm to 4.8 mm and an outer diameter from 1.6 to 6.35 mm. Given our assumption that flow rate does not affect cooling behavior relative to residence time, we sampled across residence times in the tubing set by varying the flow rate. The data are presented in Figure 4.

We opted not to fit the data in Figure 4 since preliminary exponential fits demonstrated unsatisfactory reduced χ^2 values despite the R^2 values being close to 1 for each candidate equation. This implied that simple exponential decay may be an incomplete model, possibly due to the error margins in the experimental data. From the data in Figure 4, we see that shorter residence times could be used to minimize ΔT with narrower ID tubing when compared to wider ID tubing. This was particularly clear when comparing ID = 4.8 mm to ID = 2.4 mm or narrower tubing. Transitioning to steel may be advantageous in terms of minimizing ΔT at shorter residence times when wider diameter tubing is utilized. A visual assessment of the numerical derivatives of the cooling curves in Figure 4 enabled more detailed observations:

- For tubing of ID ≤ 1 mm, a residence time of at least 6 s is necessary to minimize ΔT.
- For tubing between 1.6 and 2.4 mm, an R_t of at least 15 s is more appropriate.
- For the largest tubing considered in this work (ID = 4.2 and 4.8 mm), a cooling residence time of at least 40 s is necessary for the change in ΔT to minimize.[17]

These observations are summarized in Table 1 with OD:ID ratios shown for context.

2.2.2. Alternative Solvents. Although *most* work sampled in our literature used THF as the primary solvent, this is no guarantee that THF will remain the lithiation solvent of first choice for low-temperature organometallic flow chemistry far

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Table 1. Recommended Precooling Residence Times for THF Streams in a Selection of Flow Chemistry Relevant Tubing with Outer: Inner Diameter Ratios Shown[a]

Tubing ID/mm	Tubing OD/mm	OD:ID ratio/No units	Minimum R_t/s
0.5[a]	1.6	3.2	6
0.7[b]	3.2	4.6	6
0.8[a]	1.6	2	6
1.0[c]	1.6	1.6	6
1.6[a]	3.2	2	15
2.4[a]	3.2	1.3	15
4.2[b]	6.35	1.5	40
4.8[c]	6.35	1.3	40

[a]Tubing materials were: a) PTFE, b) 316 stainless steel, and c) PFA.

into the future. As more emphasis is placed on sustainability criteria as part of route and condition selection, it is possible that 2-MeTHF will become more widely adopted as the process solvent of choice. Although the per-liter cost of 2-MeTHF is currently higher than that of THF [prices per liter: 76 GBP (THF) vs 139 GBP (2-MeTHF), averaged across three leading chemical suppliers for the anhydrous grade of either solvent], 2-MeTHF can be accessed from renewable sources, form cleaner phase separations on aqueous workup, and also form azeotropes that may facilitate intermediate drying. Some lithiated species may also exhibit higher stability in 2-MeTHF than in THF.[18] With these factors in mind, we assessed the precooling requirements for 2-MeTHF in PTFE tubing of ID = 0.8 and 1.6 mm (Figure 5). The same exercise was attempted for toluene but was unsuccessful due to persistent overpressuring of our pumps. Given the comparable viscosities of toluene,[19] 2-MeTHF,[20] and THF,[21] the reasons for these overpressures are unknown.

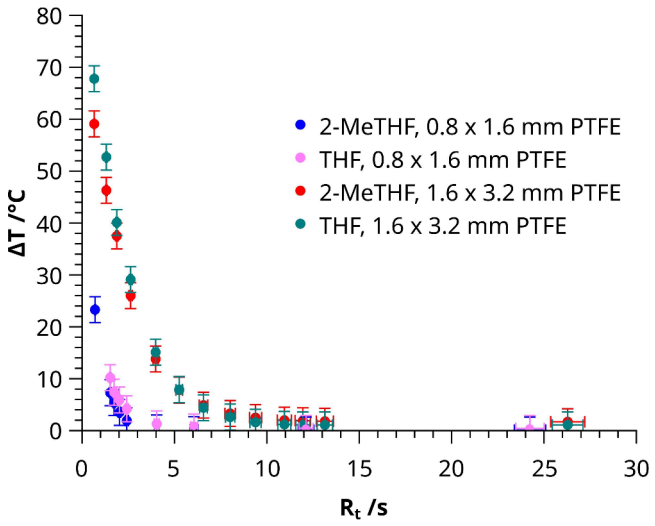


Figure 5. Difference between bath and inline temperature, ΔT, as a function of residence time, R_t, for 2-MeTHF. Reference data for THF from Figure 4 are included for comparison. Error bars in the x axis represent ±3.2% of the plotted residence time and have been estimated via error propagation; see Supporting Information Section 1.3.5. Error bars in the y axis are set at ±2.5 °C and are also estimated via error propagation. Measurements were taken in a stirred dry ice/acetone bath at a temperature between −50 and −60 °C as the cooling bath. All solvent was dosed into the system at room temperature (ca. 22 °C).

Within this constrained tubing set, we note no significant difference between the residence times necessary to stabilize ΔT for 2-MeTHF streams and the THF streams discussed in Section 2.2 within our experimental system. Thus, it is possible that the recommendations in Table 1 may also apply to 2-MeTHF although additional verification is recommended.

2.2.3. Toward an Elementary Model for Precooling. Even though THF is widely used in organometallic flow chemistry and may be superseded by 2-MeTHF, these are not the only solvents used. To generalize our findings without an impractically large experimental burden, we derived a simple mathematical model based on Newton's law of cooling adapted to forced convection[22] by substituting in key solvent parameters and a residence time term. A full derivation is shown in Section 2.1 of the Supporting Information. With an appropriate model, reported thermophysical constants for a given solvent can be used to estimate its precooling requirements in flow. The model takes the form of eq 1:

$$\Delta T = \left| (T_{bath} - T_{input}) \exp\left(\frac{-Nu\,\mu_{\bar{T}}}{Pr\,\rho_{\bar{T}}} \left(\frac{\pi D}{2Q} + \frac{4R_t}{D^2} \right) \right) \right| \quad (1)$$

The exponential term can be understood as containing a solvent parameter, **S**:

$$\frac{-Nu\,\mu_{\bar{T}}}{Pr\,\rho_{\bar{T}}}$$

and two geometrical parameters that we designate **A** and **B**:

$$\underbrace{\frac{\pi D}{2Q}}_{\mathbf{A}} + \underbrace{\frac{4R_t}{D^2}}_{\mathbf{B}}$$

T_{input}, Nu, and $\mu_{\bar{T}}$ are the input temperature, the Nusselt number, and the dynamic viscosity for the flowing solvent, respectively. The Prandtl number, Pr, is defined as

$$Pr = \frac{C_{p\bar{T}}\mu_{\bar{T}}}{k_{\bar{T}}}$$

$C_{p\bar{T}}$ and $k_{\bar{T}}$ represent the flowing solvent specific heat capacity and thermal conductivity values, respectively. Finally, $\rho_{\bar{T}}$, D, Q, and R_t represent density, tube inner diameter, volumetric flow rate, and residence time. The subscript $\bar{T}$ indicates that values measured or reported at the bulk mean fluid temperature, $0.5(T_{bath} + T_{input})$, are to be used.

Our key assumptions were that tubing wall thickness and construction are negligible; i.e., the temperature of the tubing wall is equal to that of the bath, and the flow is laminar across the experimental range ($Re < 2300$, $Re = (\rho QD)/\mu A$, $A = 0.25(\pi D^2)$; calculated values for our work were typically $150 < Re < 1200$; the flow is hydrodynamically developed ($l_t > 0.05ReD$) where D = diameter and l_t = precooling line length; and the value for the Nusselt number, Nu, is 3.66 when $l_t > 0.05RePrD$ and can be estimated using eq 2 when it is shorter (i.e., the flow is thermally developing):

$$Nu \approx 3.66 + \frac{0.065(D/l_t)RePr}{1 + 0.04[(D/l_t)\mathrm{RePr}]^{2/3}} \quad (2)$$

2.2.3.1. Usage and Validation. In validating the model using THF as the solvent, we found that the **A** term is small relative to the **B** term, such that eq 1 can be approximated to eq 3:

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$$\Delta T \approx \left| (T_{\text{bath}} - T_{\text{input}}) \exp\left(\frac{-Nu\,\mu_{\bar{T}}}{Pr\,\rho_{\bar{T}}} \left(\frac{4R_t}{D^2} \right) \right) \right| \quad (3)$$

The differences in magnitude between the **A** and **B** terms imply that the effect of flow rate can be discounted. This accords with our results in Section 2.1 which demonstrate the greater influence of residence time compared to flow rate for cooling a solvent input. When eq 3 is used to simulate cooling behavior and reported values for $\mu_{\bar{T}}$, $C_{p\bar{T}}$, $k_{\bar{T}}$, and $\rho_{\bar{T}}$ at 250 K (−23 °C, the approximate bulk mean fluid temperature for most of our experiments)[21,23] are used, the model gives reasonable agreement with the experimentally determined residence times necessary for a minimization in ΔT (Table 2) but *not* the absolute values of ΔT, particularly in the exponential region.

Table 2. Evaluation of the Model Described by Equation 3[a]

Tubing ID/mm	Minimum R_t[b]/s	ΔT Stabilization time[c] (calculated)/s	R^2 (normalized[d] ΔT)/No units
0.5	6	3	0.88
0.8	6	6	0.73
1.0	6	6	0.87
1.6	15	13	0.93
4.8	40	90	0.99

[a]Underlying data are reported in Figures S4 and S5 of the Supporting Information. R^2 values were evaluated between calculated and experiments ΔT values at the same residence times. [b]Minimum R_t values are from Table 1. [c]Stabilization time refers to the time taken for the gradient of the calculated R_t vs ΔT curves to visually plateau. [d]Normalization refers to min−max normalization where the maximum ΔT value in a condition is set to 1.

Given the discrepancies in experimental and calculated ΔT values we observe in our modeling, we suggest the model is best suited to predict the residence times necessary for ΔT to stabilize, rather than predicting exact ΔT values for a given condition. We also note that the model exhibits considerable deviations from experimental data at a narrow tubing ID, e.g., at 0.5 mm, which is probably due to the assumption of negligible wall thickness becoming unsound when tubing OD:ID ratios are large. These deviations are not captured in R^2, and so, caution is urged in its use as an evaluation metric.

2.3. Application to Cryogenic Flow Chemistry: Scope and Limitations

To probe the practical significance of our results, we examined how precooling might affect the qLC yield of the lithiation-formylation of the benzyne precursor **1** (Figure 6), a substrate used in flow chemistry campaigns in our laboratories and for which an understanding of the thermal stability would be useful. The parameters we studied were: different input concentrations, precooling residence times, and external temperature conditions using the reactor system depicted in Figure 7.[24] Reaction outcomes are listed in Table 3. The operating temperature space was identified *via* small-scale runs in a chip-type reactor.[25]

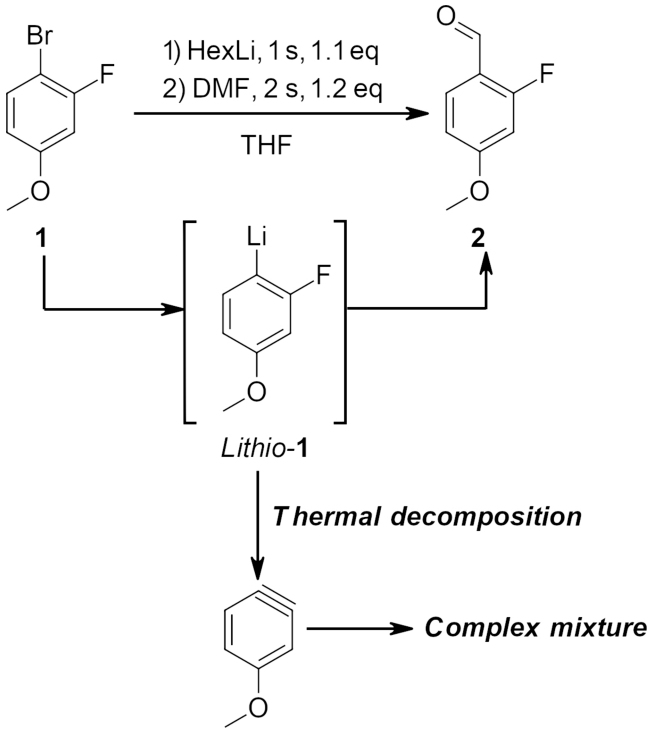


Figure 6. Lithiation-formylation of aryl bromide **1** used to benchmark precooling in this work.

Table 3. Effect of Precooling and Bath Temperature, T_{bath}, on the qLC Yield for the Lithiation-Formylation of 1 Dosed into a Flow Reactor at 17 mL min^{-1}

Entry	[**1**]/mol dm^{-3}	R_t (Precooling)/s	T_{bath}/°C	T_{inline}/°C	ΔT/°C	T_{react}/°C	qLC yield/%
1	0.3[a]	20	13	12	1	37	0
2	0.3	0[b]	−2	13[c]	15	34	11
3	0.3	2	−1	10	11	28	48
4	0.3	20	−3	−3	0	18	78
5[d]	0.3	20	−3	−4[e]	1	17	79
6[d]	0.3	20	−2	−2	0	19	78
7	0.5[f]	20	−3	−3	0	44	0
8	0.5	20	−20	−20	0	13	85
9	0.5	20	−11	−10	1	23	80
10	0.5	20	−8	−8	0	27	67

[a][HexLi] = 2.3 M, Q_{HexLi} = 2.45 mL min^{-1}, [DMF] = 1.0 M, Q_{DMF} = 6.12 mL min^{-1}. [b]Precooling lines were suspended outside of the cooling bath. [c]Sub-ambient T_{inline} value is from immersion of the relevant thermocouple in the cooling bath. [d]Replicate run of entry 4. [e]Reading is within the estimated ± 2.5 °C error of the thermocouples used within the temperature range. [f][HexLi] = 2.3 M, Q_{HexLi} = 4.05 mL min^{-1}, [DMF] = 1.6 M, Q_{DMF} = 6.35 mL min^{-1}.

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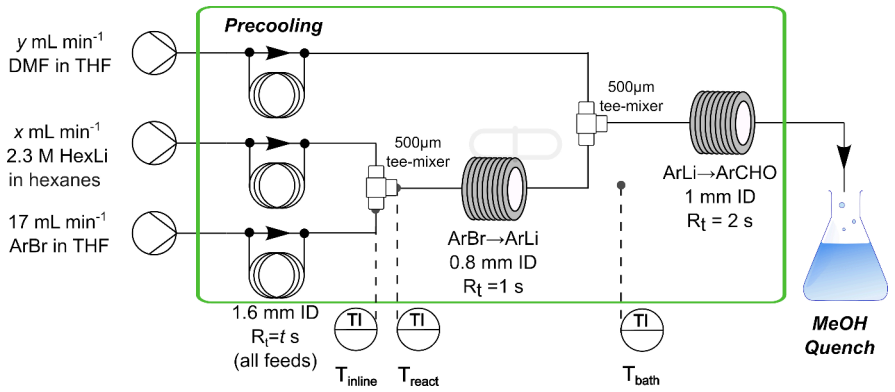


Figure 7. Flow reactor used to assess the importance of precooling. Three K-type thermocouples reported: T_{inline}, the inline temperature at the end of the ArBr precooling loop; T_{react}, the inline temperature immediately after the combination of incoming ArBr and HexLi; and T_{bath}, the temperature of the cooling bath.

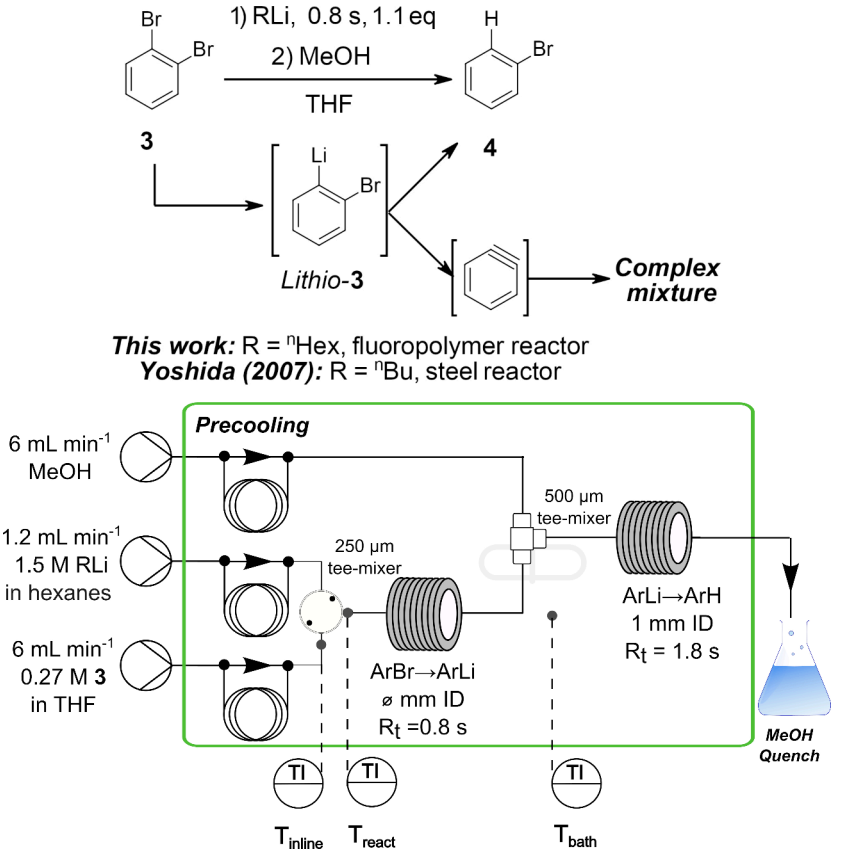


Figure 8. Top: the lithiation-protonation of bromoarene **3**. Bottom: The reactor system used to benchmark the work of Yoshida[27] with our own. 1.6 × 3.2 mm PTFE tubing was used in the construction of our reactor.

As seen in Table 3, inline feed solution temperatures at precooling residence times of 20 s are close to the bath temperature. Shorter precooling residence times introduce a significant difference between the bath and inline temperatures (Table 3, entries 1−3).

Critically, inline temperatures affect the lithiation zone temperature, T_{react}, which is directly correlated with the qLC yield of **2** ($\rho = -1$; see Supporting Information Section 2.5). For instance, when T_{react} exceeds 30 °C, a considerable drop in yield (entry 2) is noted, and when $T_{react} \geq 37$ °C, no product is observed at all (entries 1 and 7). However, the results must be viewed in context. High yields at increased concentrations of **1** can be obtained via lowering T_{bath} (entries 8 and 9). Doing so reduces T_{react} to a value less than the decomposition temperature of *lithio*-**1**, *despite the precooling being equally as effective in minimizing* ΔT *as in previous runs* (entries 7 and 8).

In addition to proper precooling, the diameter of the lithiation line and the material of construction are also important. An example is the lithiation-protonation of **3** via the notoriously reactive *lithio*-**3** (Figure 8) for which the reaction outcome is drastically affected by the variation of the diameter of the lithiation line (Table 4, entries 1−3). This is a documented phenomenon.[3,26]

When we benchmark our work against that of Yoshida et al.,[27] we note that yield trends translate but are somewhat displaced (lower yields at increased T_{bath}, Table 4, entries 1, 5,

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Table 4. Results for the Lithiation-Protonation of Bromoarene 3

Entry	R_t (Precooling) /s	MOC[a]	ϕ_{ArLi}/mm	T_{bath}/°C	T_{inline}/°C	ΔT/°C	T_{react}/°C	Yield[b]/%
1	50	FP	0.5	−70	−68	2	−64	57
2	50	FP	0.8	−71	−70	1	−62	51
3	50	FP	1.0	−70	−69	1	−54	3
4	50	FP	0.5	−64	−63	1	−31	0
5	50	FP	0.5	−60	−59	1	−25	0
6	50	FP	0.5	−82	−81	1	−77	86
7[c]	—[d]	ST	0.5	−85	—	—	—	44
8[c]	—	ST	0.5	−70	—	—	—	70
9[c]	—	ST	0.5	−60	—	—	—	7

[a]Material of construction used for the reactor. FP = Fluoropolymer; ST = Steel. [b]GC or LC yield. [c]From Yoshida et al.[27] [d]Not reported.

6 cf. 8−9), the most likely explanation being differences in materials of construction.

3. CONCLUSION AND IMPLICATIONS FOR PRACTICE

Precooling lines are often used in organometallic flow chemistry but are under-characterized. Using inline thermometry, we assessed the minimum residence time necessary to minimize the difference between bath and inline temperatures for streams of THF and 2-MeTHF across a selection of tubing sizes commonly used in the literature. Based on our data for THF, we suggest a minimum residence time of 6 s for ID ≤ 1.0 mm tubing, 15 s for tubing ≤ 2.4 mm, and 40 s for ID ≥ 4 mm to minimize temperature differences depending on material of construction. Preliminary data suggest that 2-MeTHF may behave similarly to THF under precooling. Truncating precooling residence times can affect the operating temperature of a reaction with yield implications.

For particularly reactive substrates, precooling is only part of an effective temperature management strategy and must be considered alongside the tubing diameters and materials. Given our focus on THF, it may not be appropriate to translate our minimum precooling line lengths to other solvents without additional validation given the differences in heat capacity, viscosity, and thermal conductivity that other solvents exhibit. As a first step toward applying our findings to other solvents, we derived and validated a simple mathematical model based on Newton's law of cooling. The model predicts minimum precooling times reasonably well but not absolute differences in temperature at a given residence time.

Regardless of the solvent used for a process, our results lead us to encourage the assessment and use of appropriately long precooling lines and inline temperature probes to determine reagent input temperature and reactive zone temperatures with a view for assessing and controlling intermediate thermal stability. Doing so may improve material and equipment choices for development, bespoke synthesis, and scale-up.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.6c00246.

Raw experimental data and Python scripts used for data analysis (ZIP)

Experimental procedures, additional characterization studies (effect of bath temperature, agitation, and solvent on cooling efficacy), error estimation descriptions, derivation and validation of precooling model, reaction chromatograms, equipment photos, and literature survey details (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We dedicate this paper to our colleague, friend, and mentor, Mr. Aaron Rigby, on the occasion of his retirement.

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