

Generation and Use of Cyclopropenyllithium under Continuous Flow Conditions

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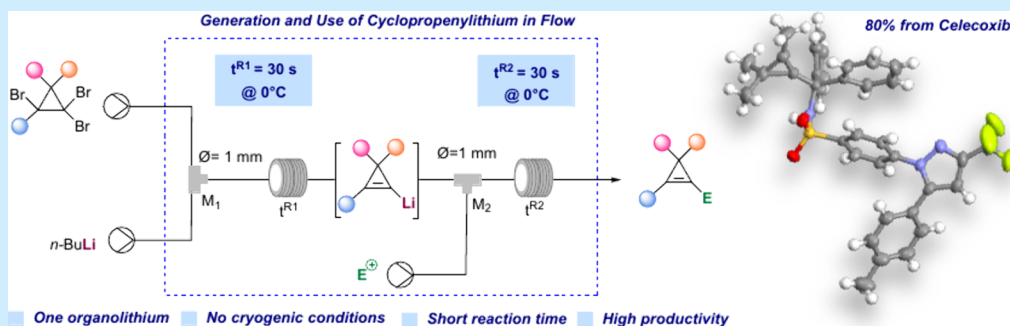
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ABSTRACT: The cyclopropane scaffold has emerged as a valuable platform in modern synthesis. Here, we present a streamlined flow-based approach for the generation of cyclopropenyllithium and its functionalization with various electrophiles in a single, continuous flow process. This method eliminates the need for laborious temperature changes and cryogenic conditions, and significantly reduces the process time from starting material to products. Compared to traditional batch processes, our flow approach enables the use of a single organolithium reagent and operates efficiently at 0 °C, avoiding the cool-warm-cool temperature cycles typical of batch methods. This not only simplifies the workflow but also enhances practicality, scalability, and extends the accessible chemical space.

Cyclopropanes are a fascinating class of strained, three-membered carbocyclic compounds characterized by the presence of a highly reactive carbon–carbon double bond. Their unique structural features, including significant ring strain (approximately 55 kcal/mol) and enhanced π -orbital bending, contribute to their remarkable reactivity, making them valuable intermediates in organic synthesis.¹ The chemistry of cyclopropanes is primarily guided by their intrinsic ring strain and the electronic properties of the substituents attached to the ring.² These compounds readily undergo a variety of transformations, including cycloadditions, rearrangements, and nucleophilic additions, often proceeding under mild conditions due to the release of strain energy.³ Notably, cyclopropanes are key intermediates in transition-metal-catalyzed reactions, including metal-carbene chemistry and cyclization processes that lead to the formation of more complex molecular architectures.⁴ Cyclopropanes have found extensive applications in modern synthetic methodologies, including the development of pharmaceuticals, natural product synthesis, and materials chemistry.⁵ Their ability to undergo controlled functionalization allows for the construction of highly diverse molecular scaffolds. Additionally, in recent years, bioorthogonal chemistry has leveraged the reactivity of cyclopropanes in strain-promoted reactions, further expanding

their utility in chemical biology.⁶ The main strategies for accessing cyclopropanes rely on efficient and selective synthetic approaches developed in recent decades. Among the established methods, transition metal-catalyzed cyclopropanation of alkynes with diazo compounds is widely employed, offering high selectivity and functional group tolerance.⁷ Additionally, dehydrohalogenation of gem-dihalocyclopropanes serves as a practical strategy, especially for the synthesis of substituted cyclopropanes.⁸ In this context, lithiated cyclopropanes Cp-Li represent valuable intermediates for the synthesis of suitably functionalized cyclopropanes that can undergo further transformations. The introduction of a lithium atom at the cyclopropane ring generates a highly strained and nucleophilic species, which can undergo electrophilic trapping, rearrangements, and cross-coupling reactions. The generation of lithiated cyclopropanes is typically achieved

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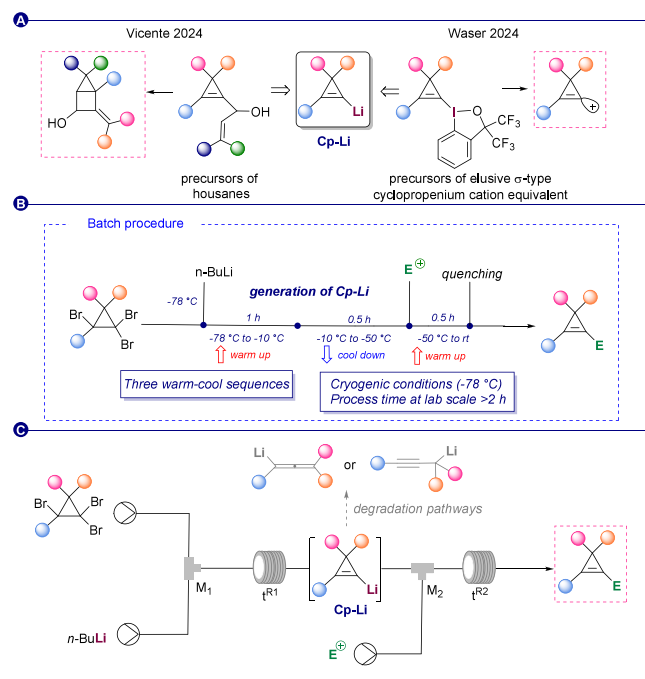
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via direct lithiation using organolithium reagents, such as butyllithium, or most typically by metal–halogen exchange starting from readily available halogenated cyclopropenes.⁹ Due to the significant ring strain and the presence of the π -system, these species exhibit unique reactivity patterns compared to other organolithium compounds. Notably, lithiated cyclopropenes are instrumental in the development of novel synthetic methodologies, particularly in the formation of functionalized cyclopropanes and their derivatives, which are valuable motifs in medicinal and materials chemistry. Recently, Waser reported for the first time a σ -type cyclopropenium cation equivalent leveraging on **Cp-Li** as key reactants (Scheme 1, A).¹⁰ In addition, Vicente developed an elegant

Scheme 1. Use of **Cp-Li and Generation of **Cp-Li** in Batch and Flow**



synthesis of housanes from hydroxyalkylated cyclopropenes obtained using once again **Cp-Li** as the key intermediate.¹¹ Other remarkable contributions on the use of lithiated cyclopropenes have been reported by Marek.¹² One of the widely employed method for the generation of **Cp-Li**, is by a lithium/halogen exchange reaction of trihalocyclopropanes which can be easily obtained from the reaction of haloolefins and a dihalocarbene.¹³

The reported experimental protocol for the generation of **Cp-Li** uses *n*-BuLi as lithiating agent, THF or Et₂O as the solvent and three laborious warm-cool sequences before final quenching with electrophilic partners (Scheme 1, B). However, scaling up this batch protocol for the synthesis and functionalization of cyclopropenes presents significant challenges and fails to meet the increasingly stringent sustainability and environmental impact requirements of the modern chemical industry. In this context, the adoption of modern technologies, such as flow chemistry, is crucial for developing synthetic processes that are more sustainable, efficient, and safe.¹⁴ Building on our expertise in flow chemistry,¹⁵ we present a straightforward and streamlined approach for the generation of **Cp-Li** and its subsequent functionalization with electrophiles in a continuous-flow fashion, starting from readily

available trihalocyclopropanes. This flow process employs a single organolithium reagent, *n*-BuLi, and operates at significantly higher temperatures than traditional batch methods, eliminating the need for warm-cool cycles and enhancing both practicality and scalability. Remarkably, the competitive degradation pathways¹⁶ of **Cp-Li** are completely suppressed under flow conditions (Scheme 1, C). Accordingly, our investigation began using the flow setup reported in Table 1, consisting of two T-mixers (M1 and M2), each followed by

Table 1. Optimization Study

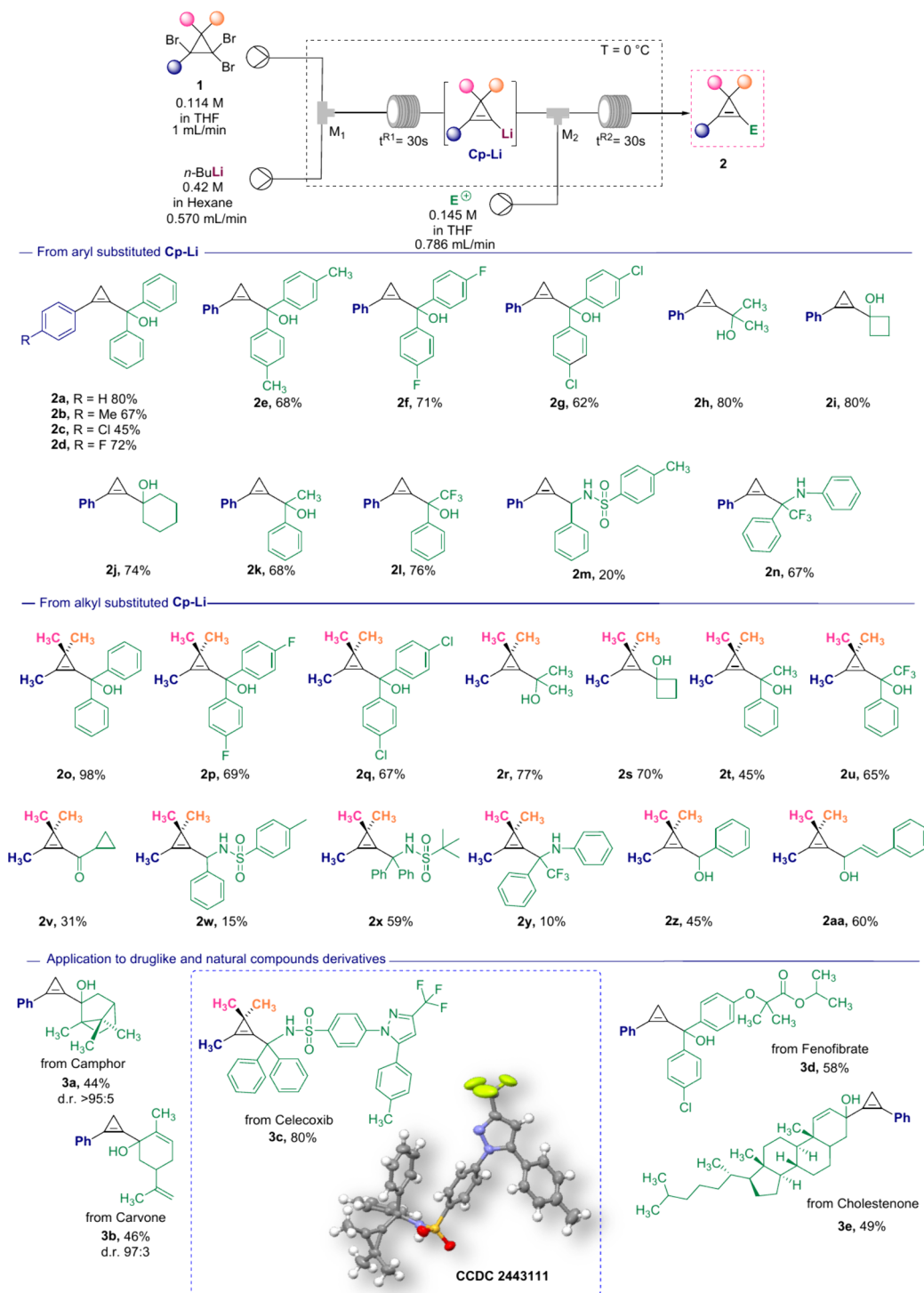
Entry	T (°C)	t ^{R1} (s)	t ^{R2} (s)	Ph ₂ C=O (equiv)	yield 2a (%) ^a
1	0	15	30	1.5	50
2	0	15	30	0.7	52
3	0	15	30	1	57
4	-20	15	30	1	65
5	25	15	30	1	0 ^b
6	0	15	40	1	54
7	0	10	30	1	37
8	0	7.5	30	1	33
9	0	30	30	1	80
10	0	60	30	1	52
11 ^c	0	batch reaction		1	43 ^c

^aNMR yields calculated using 1,3,5-trimethoxybenzene as the internal standard. ^bClogging observed. ^cReaction conducted using the traditional batch procedure with quenching at 0 °C.

a coil (R1 and R2) with volumes of 0.78 and 1.18 mL, respectively. Starting with trihalocyclopropane **1a**, and using *n*-BuLi, the putative **Cp-Li** was generated in M1 and R1 and then transferred to M2, where it reacted with benzophenone, selected as a model electrophile, to yield cyclopropene **2a**.

The optimization study revealed the independency of reaction performances from benzophenone/tribromocyclopropane **1a** ratio (Table 1, entries 1–3) and highlighted the temperature as a game changer parameter: lowering it to -20 °C furnished **2a** in 65% yield, whereas conducting the **Cp-Li** generation at room temperature (25 °C) caused clogging of the flow system (Table 1, entries 3–5). The residence time in R2 (t^{R2}) left the reaction outcome unaffected (Table 1, entry 6). Conversely, the residence time in R1 (t^{R1}) was a crucial parameter for the complete lithium/bromine exchange reaction to generate **Cp-Li**. Reducing t^{R1} from 15 to 7.5 s led to a significant drop in the yield of **2a** (Table 1, entries 3, 7–8). On the contrary, increasing t^{R1} to 30 s improved the yield to 80% (Table 1, entry 9). However, further extending the residence

Scheme 2. Scope of the Continuous Flow Generation and Electrophilic Trapping of Cp-Li



time to 60 s resulted in a lower yield of 52% (Table 1, entry 10). Additionally, performing the reaction via the traditional batch procedure, where Cp-Li was generated and subsequently quenched at 0 °C with the electrophile, resulted in a lower 43% yield of 2a (Table 1, entry 11). In addition, no reaction with bromobutane resulting from the Br/Li exchange reaction was observed in the absence of a pi-electrophile. Based on these results, the conditions in entry 9 were identified as optimal and used for the subsequent scope exploration (Scheme 2). First, aryl-substituted tribromocyclopropanes 1b–d were evaluated in the reaction with benzophenone, affording the correspond-

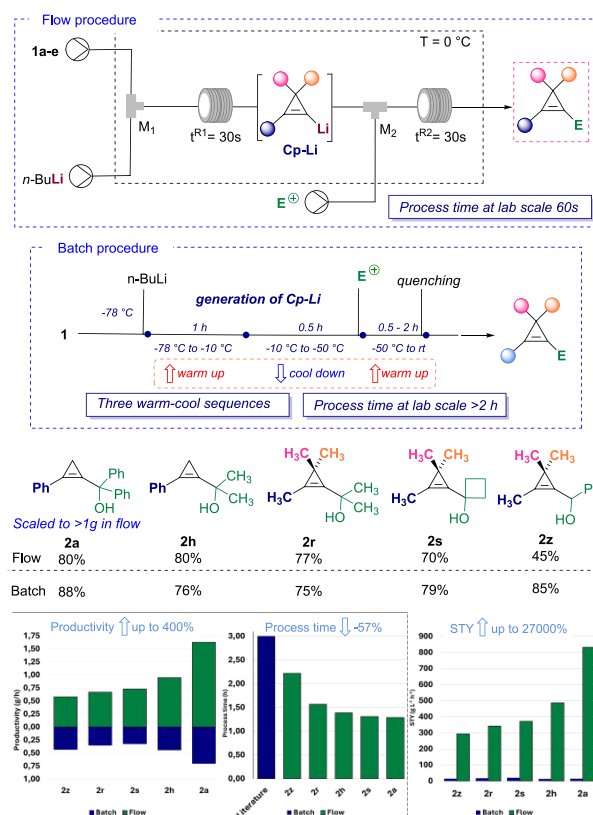
ing cyclopropene products 2b–d in moderate to good yields (45–72%). These results demonstrate the feasibility of extending the protocol to other aromatic systems. Subsequently, the use of 1a with various aromatic ketones delivered the corresponding cyclopropenes 2e–g in good yields. Likewise, reactions with enolizable and aliphatic ketones successfully produced adducts 2h–k in good to excellent yields, reaching up to 80%. The protocol was also compatible with trifluoromethyl ketones, as exemplified by the formation of cyclopropene 2l in 76% yield. Moreover, imines were found to be competent electrophiles, leading to amino-cyclopropenes

2m and **2n** in yields that varied depending on the nature of the substituent. Notably, cyclopropene **2n**, bearing a CF₃ group on the imine carbon, was obtained in 67%.

The use of alkyl-substituted cyclopropenes was also demonstrated to be feasible under continuous flow conditions. Specifically, 1,1,2-tribromo-2,3,3-trimethylcyclopropane **1e** was successfully lithiated under optimized flow conditions to generate the corresponding cyclopropenyllithium intermediate (**Cp-Li**), which was subsequently reacted with aromatic ketones to afford cyclopropenes **2o–2q** in yields of up to 98% (Scheme 2). Similarly, the use of enolizable ketones provided derivatives **2r–2t** in good yields, confirming the versatility of the method. A cyclopropyl-substituted Weinreb amide also served as a competent electrophile, affording the corresponding cyclopropenyl ketone **2v** in a moderate 31% yield, likely due to the inherent instability of the product. In contrast, imines reacted only marginally with **Cp-Li** derived from **1e**, yielding products **2w–y** in good to modest yields. Notably, these low-yielding compounds were difficult to obtain under traditional batch conditions, where yields remained below 10%. Interestingly, both benzaldehyde and cinnamaldehyde reacted efficiently, providing derivatives **2z** and **2aa** in 45% and 60% yield, respectively. To further highlight the versatility of the flow methodology, we explored its application to functionalized electrophiles derived from natural products or bioactive compounds (Scheme 2). Notably, reactions with Camphor and Carvone afforded the corresponding functionalized cyclopropenes **3a** and **3b** in 44% and 46% yield, respectively, and no conjugate addition products have been observed (the observed modest yields are likely due to enol/aldol side reactions). Remarkably, the use of an imine derived from the COX-2 inhibitor Celecoxib delivered the desired adduct **3c** in 80% yield. Similarly, the lipid-lowering drug Fenofibrate underwent selective addition at the carbonyl group, furnishing product **3d** in 58% yield. Finally, Cholestenone reacted to provide adduct **3e** in 49% yield.

As a final assessment, to demonstrate the superior performance of the flow process over the traditional batch procedure, we conducted a benchmarking study using selected literature-reported compounds (Scheme 3). Specifically, we compared productivity, space-time yields, and overall process time for the synthesis of cyclopropenes **2a**, **2h**, **2r**, **2s**, and **2z**, all performed at the same scale in both batch and flow conditions. Remarkably, the flow methodology consistently outperformed batch processing, delivering significantly higher productivity (up to 400% enhancement), improved space-time yields (up to 270 fold), and a notable reduction in process time (–57% reduced time). As a representative example, compound **1a** was processed on a 1.2 g scale using just 21 min of continuous flow processing, affording the product in 80% yield. This corresponds to a productivity of 1.63 g/h, effectively doubling the reported productivity of the corresponding batch protocol. While certain substrates (e.g., **2z**) showed reduced yields in flow compared to batch, the flow process's consistent reproducibility and superior performance overall establish its advantage over batch operations. In conclusion, we have developed the first flow-based method for the generation of **Cp-Li**, followed by its efficient electrophilic functionalization. The flow process enables the safe and straightforward handling of *n*-BuLi as the sole organolithium reagent, even at elevated temperatures (0 °C), representing a clear advancement over traditional batch protocols. This approach delivers higher yields, enhanced productivity, and significantly reduced

Scheme 3. Benchmarking Reported Batch Processing vs Flow Protocol



reaction and processing times. Moreover, the method proved applicable to a range of bioactive and functionalized electrophiles, displaying a high degree of chemoselectivity. Overall, this strategy provides a streamlined and versatile platform for the synthesis of cyclopropenyl derivatives, addressing the growing demand for novel structural motifs in drug discovery and contributing to the development of more sustainable synthetic methodologies.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.5c01516>.

Copy of ¹H, ¹⁹F, and ¹³C NMR of the prepared molecules and X-ray data (PDF)

Accession Codes

Deposition Number 2443111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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