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Continuous Flow Synthesis of Terminal Epoxides from Ketones Using in Situ Generated Bromomethyl Lithium

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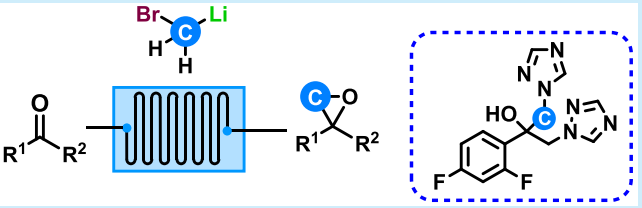
Supporting Information

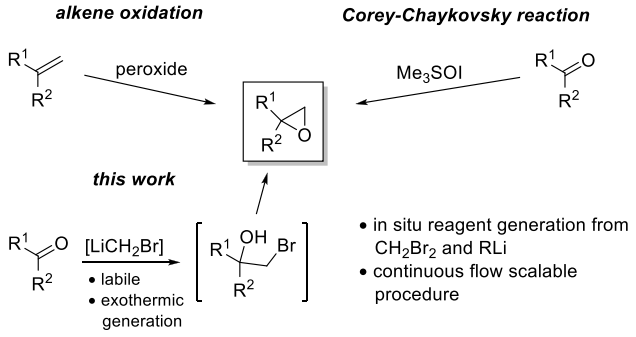
ABSTRACT: A scalable procedure for the direct preparation of epoxides from ketones has been developed. The method is based on the carefully controlled generation of (bromomethyl)lithium ($LiCH_2Br$) from inexpensive CH_2Br_2 and MeLi in a continuous flow reactor. The reaction has shown excellent selectivity for a variety of substrates, including α-chloroketones, which typically fail under classic Corey−Chaykovsky conditions. This advantage has been used to develop a novel route toward the drug fluconazole.



Epoxides are a very important class of compounds in organic chemistry. They are present in a number of naturally occurring materials such as epoxomicin as well as in synthetic drugs with antibiotic and anticancer properties like carfilzomib or troleandomycin. Yet epoxides are most often prepared and used as intermediates for the synthesis of other scaffolds.[1] Their facile ring-opening via S_N2 reactions utilizing suitable nucleophiles is a convenient method for the preparation of β-substituted alcohols for a wide range of applications.[2]

The synthesis of epoxides is frequently carried out by oxidation of alkenes using peroxides.[3] 2,2-Disubstituted terminal epoxides can also be prepared from ketones by the Corey−Chaykovsky reaction using trimethylsulfoxonium or trimethylsulfonium iodide (Scheme 1).[4] An alternative to the Corey−Chaykosvky reaction is the utilization of (halomethyl) lithium species as a C-1 source, which were extensively studied in the 1960s.[5] (Bromomethyl)lithium ($LiCH_2Br$) is particularly attractive, since it can be generated from inexpensive CH_2Br_2 and an alkyl lithium reagent.[6] It readily reacts with carbonyl groups forming the corresponding bromomethyl alkoxide, which can cyclize to the desired epoxide.[7] However, $LiCH_2Br$ is highly unstable even at temperatures as low as −120 °C, and therefore, it can only be generated in situ. Even at low temperatures, addition of the lithium base to the reaction mixture has to be performed very slowly,[7a] which severely limits the scalability and potential application of this synthetic approach.

Scheme 1. Preparation of 2,2-Disubstituted Terminal Epoxides



Continuous flow microreactors are valuable tools to carry out difficult transformations in which very efficient mixing and heat transfer are required. We envisioned that the in situ generation of $LiCH_2Br$ and its utilization for the synthesis of epoxides from ketones could be carried out in a controllable and scalable manner using this technology. In fact, other (halomethyl)lithium reagents have already been successfully generated and utilized in continuous flow mode, namely the more stable (dibromomethyl)lithium,[8] (chloromethyl)-lithium,[9] and (dichloromethyl)lithium.[10] Generation of (dichloromethyl)lithium[11] and (fluoroiodomethyl)lithium[12] has been recently reported in batch mode. Notably, $LiCHCl_2$ showed relatively high stability in solution at low temperatures.[11,13]

Herein we describe a continuous flow procedure for the preparation of epoxides from ketones using (bromomethyl) lithium as reagent, which is in situ generated from CH_2Br_2. In addition to a very good tolerance with a variety of functional groups, this method features very selective epoxidation of α-chloroketones, which cannot be achieved by the classic Corey-Chaykovsky reaction employing trimethylsulfonium or trimethylsulfoxonium iodide. Moreover, the procedure has success-

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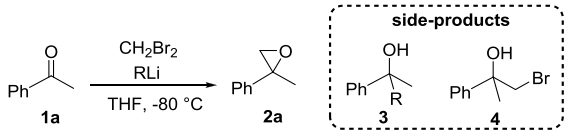
fully been applied to the preparation of the active pharmaceutical ingredient (API) fluconazole, featuring a key epoxidation step.

(Bromomethyl)lithium can be generated either by deprotonation of bromomethane or lithium−halogen exchange of a bromomethyl halide species. Since gaseous bromomethane is not readily available, the lithium−halogen exchange pathway using CH_2Br_2 as starting material was selected as the most practicable and economical method. Our investigation began with a series of preliminary batch experiments intended to screen for the optimal organolithium reagent for lithium−halogen exchange (Table 1). Acetophenone (**1a**) was used as

Table 1. Screening of Organolithium Reagents for the Preparation of Epoxide 2a from Acetophenone (1a) via in Situ Generated $LiCH_2Br$[a]



entry	organolithium reagent	conversion[b] (%)	selectivity[b,c] (%)
1	LDA	98	<1
2	LHMDS	–	–
3	BuLi	93	75
4	MeLi	96	89
5	MeLi·LiBr	>99	91

[a]Conditions: 0.43 mmol of acetophenone, 1.7 mL of dry THF, 1.20 equiv of CH_2Br_2, 1.05 equiv of organolithium reagent, 10 s at −80 °C, then 10 min at rt. [b]Determined by GC−FID peak area integration. [c]Selectivity to desired product **2a** with respect to all side products, including **3** and **4**.

model substrate. The reaction mixtures were analyzed by GC−MS and GC−FID, as several potential side reactions, including the formation of structures **3** and **4**, were expected to occur (see Scheme S8 for more details). Compound **3**, formed by nucleophilic addition of the alkyllithium reagent to the carbonyl group, was the main side product observed. Side product **4** resulted from premature quench of the reaction mixture before the cyclization took place. Thus, formation of **4** could be easily avoided. As expected, sterically hindered organolithium reagents like lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS) did not provide the desired epoxide **2a** (Table 1, entries 1 and 2). Using these reagents, deprotonation of the halomethane rather than lithium−halogen exchange was generally observed, with only negligible amounts of the desired epoxide **2** being formed. Methyllithium performed better than *n*-butyllithium (entry 3 vs 4). Although similar conversions were obtained with both reagents, the selectivity was higher for the less nucleophilic MeLi. Notably, best results were obtained using methyllithium as its lithium bromide complex. This improvement can be ascribed to stabilization of the bromomethyl lithium intermediate with the LiBr salt, which increases its half-life time in solution.[14]

The procedure was then transferred to a continuous-flow process. The initial setup consisted of PFA tubing (0.8 mm i.d.) and T-connectors (0.5 mm through-hole) as mixing elements (Figure 1). The reactants were introduced into the system as four liquid feeds using syringe pumps. In addition to solutions of the substrate (0.5 M), CH_2Br_2 (0.6 M) and

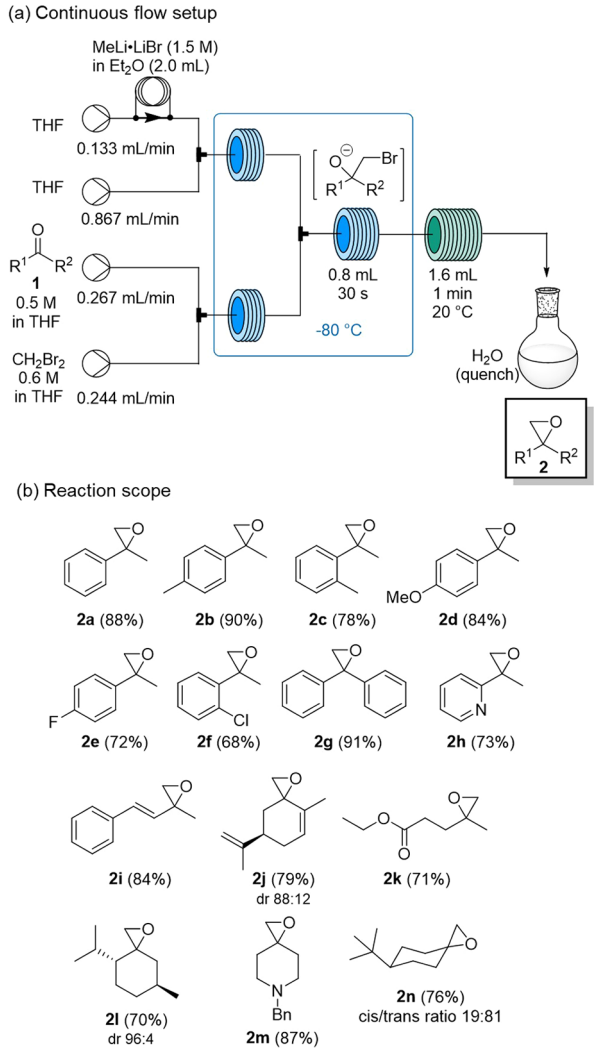


Figure 1. (a) Schematic view of the continuous flow setup for the synthesis of epoxides from ketones by in situ generated $LiCH_2Br$ and (b) reaction scope (isolated yield) (0.67 mmol scale).

commercially available MeLi·LiBr (1.5 M) in Et_2O, a supplementary THF feed was utilized to dilute the organolithium reagent and screen its concentration during reaction optimization. The MeLi·LiBr complex was insoluble in THF below 0 °C at the original 1.5 M concentration. Thus, the additional THF feed was utilized to control the MeLi concentration and avoid clogging of the system. The diluted MeLi·LiBr solution was mixed with a stream containing the already mixed reactants **1** and CH_2Br_2 (Figure 1). Under optimal conditions, the process setup could be reduced to two feeds with a premixed solution of ketone and CH_2Br_2 (vide infra). "Pre-cooling" loops were implemented before the mixer to ensure that the reactant streams were mixed at the desired temperature. The reaction mixture was maintained at −80 °C for 30 s in a residence time unit and subsequently warmed to 20 °C in a second residence time tubing. During the residence time unit at room temperature the cyclization of the bromomethyl alkoxide intermediate takes place. The reaction mixture was collected in a flask containing water as quench under stirring. The amount of reagents and concentration were reoptimized under continuous flow conditions (see the Supporting Information). The optimal conditions for the model substrate comprised 1.10 equiv of CH_2Br_2 and 1.50

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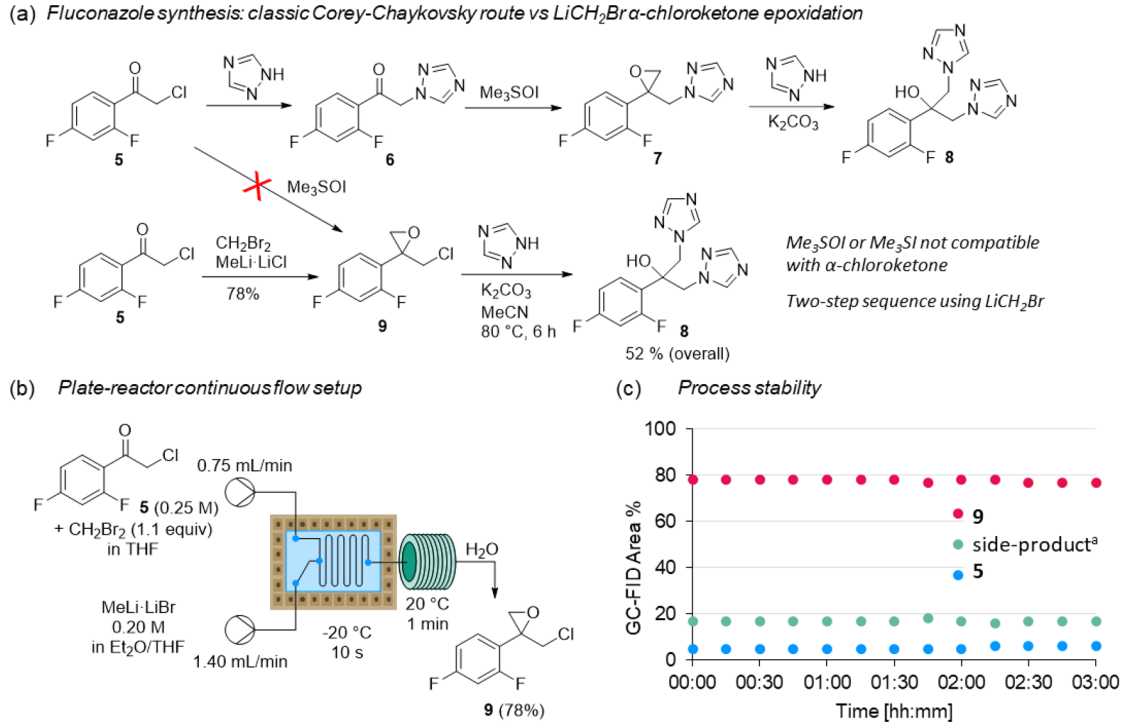

Figure 2. (a) Classic fluconazole synthesis including the Corey−Chaykovsky reaction as key step and novel route via a $LiCH_2Br$ epoxidation. (b) Continuous flow setup for the synthesis of intermediate **9**. (c) GC−FID monitoring of a 3 h flow run (11.3 mmol/h, 34 mmol scale) using the setup depicted in Figure 2b. [a]The side product observed corresponded to the nucleophilic addition of MeLi to the ketone.

equiv of MeLi·LiBr. Flow rates utilized are collected in Figure 1a.

With the optimal conditions in hand, a series of ketones was transformed to their corresponding epoxides using the continuous flow setup (Figure 1b). Good to excellent yields were obtained in all cases. Electron-rich ketones (e.g., **2a**, **2d**, **2g**) performed better than electron-poor substrates (e.g., **2e**, **2f**, **2h**) due to a larger amount side product **3** formed in the later cases. A slight decrease in product yield was observed for ortho-substituted aryl ketones (**2b** vs **2c**). Aliphatic ketones could also be successfully converted to the corresponding epoxides (**2k**, **2l**, **2m**, **2n**). Notably, the method was selective in the presence of electrophilic moieties such as α,β-unsaturated carbonyl compounds (**2i**, **2j**), esters (**2k**), and protected amines (**2m**). The high selectivity obtained for all reactions enabled a simple workup procedure consisting of a liquid−liquid extraction with diethyl ether of the aqueous solution obtained after quenching the reaction mixture with water. Evaporation of the organic phase furnished the desired epoxides without further purification in most cases.

At this point, we turned our attention to applying this novel continuous flow epoxidation procedure to the preparation of an active pharmaceutical ingredient (API). We were particularly interested in the synthesis of fluconazole, an important drug for the treatment of fungal infections listed in the WHO's list of essential medicines.[15]

One of the key steps in the classic synthesis of fluconazole is the generation of epoxide **7** from ketone **6** using the Corey−Chaykovsky reaction (Figure 2a).[16] Before the epoxidation takes place, the chlorine needs to be substituted by 1,2,4-triazole due to the incompatibility of the Corey−Chaykosky reagent with α-chloroketones. Notably, the current method, based on the generation of $LiCH_2Br$, was selective for α-chloroketones as well. This enabled a new pathway toward fluconazole in which α-chloroketone **5** was directly epoxidized to **9**. This new intermediate (**9**) could then be treated with 2 equiv of 1,2,4-triazole to furnish fluconazole, saving one synthetic step (Figure 2a).

It has been shown in the past that excellent mixing can often circumvent the need of cryogenic conditions for mass-transfer limited ultrafast organolithium reactions.[17−19] Furthermore, the results obtained using simple T-junctions are often difficult to scale for mixing dependent exothermic reactions.[20] For these reasons, and due to our interest in a robust procedure for the preparation of fluconazole on scale, the results described above were transferred to a scalable platform based on a plate microreactor (Lonza FlowPlate).[21] As anticipated, the plate-based reactor performed better because of its enhanced heat-transfer and mixing characteristics (see the Supporting Information for details).[21] Notably, the key epoxide intermediate **9** could be prepared in this reactor at a relatively high temperature of −20 °C (Figure 2b). In this case, only two feeds were utilized for the continuous flow system, as the ketone **5** and dibromomethane were premixed. The residence time in the plate reactor at −20 °C was shortened to 10 s. The cyclization step was performed within 1 min residence time at 20 °C in a capillary reactor.

In a scale-out experiment, the continuous process was carried out uninterrupted for 3 h, which corresponds to a 34 mmol scale. GC−FID monitoring of the reaction mixture collected from the reactor output (Figure 2c) demonstrated constant conversion and selectivity thorough the complete run. The only side product observed during the process was the alcohol resulting from the nucleophilic addition of MeLi to the ketone (analogous to compound **3**; see Table 1). After a simple extraction with diethyl ether, epoxide **9** was directly subjected to treatment with 2.00 equiv of 1,2,4-triazole to

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obtain 5.4 g of the desired fluconazole **9** in 52% yield over two steps.

In summary, we have developed a safe and scalable procedure for the epoxidation of ketones, based on the generation of (bromomethyl)lithium in a continuous flow reactor. The reactive intermediate was generated in situ from inexpensive CH_2Br_2 and readily available MeLi. This chemistry, difficult to carry out in batch in a controllable manner, has been performed in multigram scale under continuous flow conditions. Compared to the classic Corey-Chaykosky reaction, the present methodology has shown to be superior for the epoxidation of α-chloroketones, which typically fail using Me_3SOI or Me_3SI as reagents. This advantage has been exploited to establish a novel route for the preparation of the drug fluconazole, featuring the epoxidation of a α-chloroketone as the key step. A robust preparative method has been achieved by transferring the continuous procedure to a readily scalable plate-based platform.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04072.

Experimental procedures, supplementary figures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Jacobsen, E. N. Asymmetric Catalysis of Epoxide Ring-Opening Reactions. *Acc. Chem. Res.* **2000**, *33*, 421−431. (b) Padwa, A.; Murphree, S. S. Epoxides and Aziridines - A Mini Review. *Arkivoc* **2006**, *37*, 6−33.

(2) Schneider, C. Synthesis of 1,2-Difunctionalized Fine Chemicals through Catalytic, Enantioselective Ring-Opening Reactions of Epoxides. *Synthesis* **2006**, *2006* (23), 3919−3944.

(3) (a) Sello, G.; Fumagalli, T.; Orsini, F. Recent Developments in Epoxide Preparation. *Curr. Org. Synth.* **2006**, *3*, 457−476. (b) Grigoropoulou, G.; Clark, J. H.; Elings, J. A. Recent Developments on the Epoxidation of Alkenes Using Hydrogen Peroxide as an Oxidant. *Green Chem.* **2003**, *5*, 1−7.

(4) Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ($(CH_3)_2SOCH_2$) and Dimethylsulfonium Methylide ($(CH_3)_2SCH_2$). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(5) (a) Köbrich, G. The Chemistry of Carbenoids and Other Thermolabile Organolithium Compounds. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473−485. (b) Köbrich, G.; Akhtar, A.; Ansari, F.; Breckoff, W. E.; Büttner, H.; Drischel, W.; Fischer, R. H.; Flory, K.; Fröhlich, H.; Goyert, W.; et al. Chemistry of Stable α-Halogenoorganolithium Compounds and the Mechanism of Carbenoid Reactions. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41−52.

(6) Matteson, D. S. Bromomethyllithium. In *Encyclopedia of Reagents for Organic Synthesis*; DOI: 10.1002/047084289X.rb306.

(7) (a) Michnick, T. J.; Matteson, D. S. (Bromometyhyl)lithium: Efficient in Situ Reactions. *Synlett* **1991**, *1991*, 631−632. (b) Cainelli, G.; Tangari, N.; Ronchi, A. U. Chemistry of α-Halometalcompounds. *Tetrahedron* **1972**, *28*, 3009−3013. (c) Cainelli, G.; Ronchi, A. U.; Bertini, F.; Grasselli, P.; Zubiani, G. Chemistry of α-Halometal Compounds. *Tetrahedron* **1971**, *27*, 6109−6114.

(8) Hartwig, J.; Metternich, J. B.; Nikbin, N.; Kirschning, A.; Ley, S. V. Continuous Flow Chemistry: A Discovery Tool for New Chemical Reactivity Patterns. *Org. Biomol. Chem.* **2014**, *12*, 3611−3615.

(9) Degennaro, L.; Fanelli, F.; Giovine, A.; Luisi, R. External Trapping of Halomethyllithium Enabled by Flow Microreactors. *Adv. Synth. Catal.* **2015**, *357*, 21−27.

(10) (a) Hafner, A.; Filipponi, P.; Piccioni, L.; Meisenbach, M.; Schenkel, B.; Venturoni, F.; Sedelmeier, J. A Simple Scale-up Strategy for Organolithium Chemistry in Flow Mode: From Feasibility to Kilogram Quantities. *Org. Process Res. Dev.* **2016**, *20*, 1833−1837. (b) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode. *Org. Lett.* **2017**, *19*, 786−789.

(11) Khutorianskyi, V. V.; Klepetářová, B.; Beier, P. Vicarious Nucleophilic Chloromethylation of Nitroaromatics. *Org. Lett.* **2019**, *21*, 5443−5446.

(12) (a) Monticelli, S.; Colella, M.; Pillari, V.; Tota, A.; Langer, T.; Holzer, W.; Degennaro, L.; Luisi, R.; Pace, V. Modular and Chemoselective Strategy for the Direct Access to α-Fluoroepoxides and Aziridines via the Addition of Fluoroiodomethyllithium to Carbonyl-Like Compounds. *Org. Lett.* **2019**, *21*, 584−588. (b) Colella, M.; Tota, A.; Großjohann, A.; Carlucci, C.; Sheikh, N. S.; Degennaro, L.; Luisi, R. Straightforward chemo- and stereoselective fluorocyclopropanation of allylic alcohols: exploiting the electrophilic nature of the not so elusive fluoroiodomethyllithium. *Chem. Commun.* **2019**, *55*, 8430−8433.

(13) For a recent review describing the stability of this type of compounds, see: Gessner, V. H. Stability and reactivity control of carbenoids: recent advances and perspectives. *Chem. Commun.* **2016**, *52*, 12011−12023.

(14) Pace, V.; Castoldi, L.; Holzer, W. Chemoselective Additions of Chloromethyllithium Carbenoid to Cyclic Enones: A Direct Access to Chloromethyl Allylic Alcohols. *Adv. Synth. Catal.* **2014**, *356*, 1761−1766.

(15) *WHO Model List of Essential Medicines*; https://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf (accessed November 2019).

(16) Szeto, J.; Vu, V.-A.; Malerich, J. P.; Collins, N. Multi-step continuous flow synthesis of fluconazole. *J. Flow Chem.* **2019**, *9*, 35−42.

(17) Yoshida, J. I.; Takahashi, Y.; Nagaki, A. Flash Chemistry: Flow Chemistry That Cannot Be Done in Batch. *Chem. Commun.* **2013**, *49*, 9896−9904.

(18) Colella, M.; Nagaki, A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. - Eur. J.* **2019**, x DOI: 10.1002/chem.201903353.

(19) For an example involving CH_2Br_2 on pilot scale, see: Broom, T.; Hughes, M.; Szczepankiewicz, B. G.; Ace, K.; Hagger, B.; Lacking, G.; Chima, R.; Marchbank, G.; Alford, G.; Evans, P.; et al. The Synthesis of Bromomethyltrifluoroborates through Continuous Flow Chemistry. *Org. Process Res. Dev.* **2014**, *18*, 1354−1359.

DOI: 10.1021/acs.orglett.9b04072
Org. Lett. XXXX, XXX, XXX−XXX

(20) Lévesque, F.; Rogus, N. J.; Spencer, G.; Grigorov, P.; McMullen, J. P.; Thaisrivongs, D. A.; Davies, I. W.; Naber, J. R. Advancing Flow Chemistry Portability: A Simplified Approach to Scaling Up Flow Chemistry. *Org. Process Res. Dev.* **2018**, *22*, 1015−1021.
(21) (a) Roberge, D. M.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. Industrial design, scale-up and use of microreactors. *Chim. Oggi* **2009**, *27*, 8−11. (b) Kockmann, N.; Roberge, D. M. Scale-up concept for modular microstructured reactors based on mixing, heat transfer, and reactor safety. *Chem. Eng. Process.* **2011**, *50*, 1017−1026. (c) Kockmann, N.; Gottsponer, M.; Roberge, D. M. Scale-up concept of single-channel microreactors from process development to industrial production. *Chem. Eng. J.* **2011**, *167*, 718−726.

DOI: 10.1021/acs.orglett.9b04072
Org. Lett. XXXX, XXX, XXX−XXX