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Flow Microreactor Technology for Taming Highly Reactive Chloroiodomethyllithium Carbenoid: Direct and Chemoselective Synthesis of α-Chloroaldehydes

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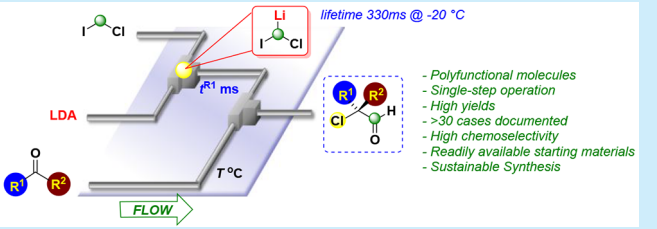
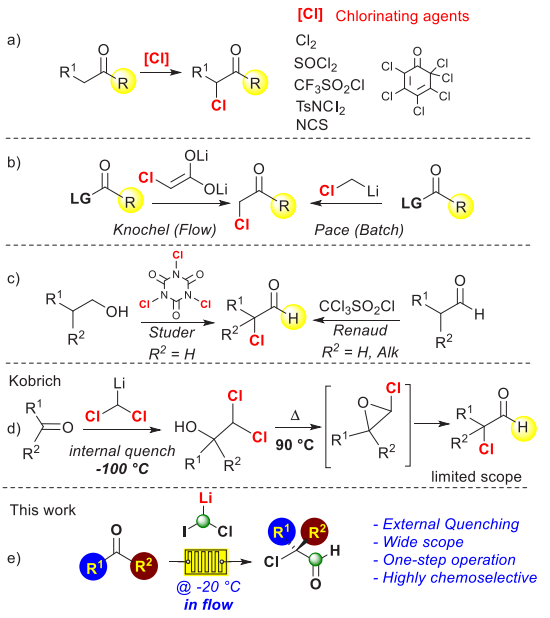
ABSTRACT: A straightforward flow synthesis of α-chloro aldehydes has been developed. The strategy involves, for the first time, the thermal unstable chloroiodomethyllithium carbenoid and carbonyl compounds. A batch versus flow comparative study showcases the superb capability of flow technology in prolonging the lifetime of the lithiated carbenoid, even at −20 °C. Remarkably, the high chemoselectivity realized in flow allowed for preparing polyfunctionalized α-chloro aldehydes not easily accessible with traditional batch procedures.



In organic synthesis and drug development, α-chlorinated carbonyls are useful building blocks.[1] The most general strategies for their preparation are based on α-chlorination of carbonyls with suitable chlorinating agents.[2] Numerous different chlorinating reagents could be used (Scheme 1a). Nevertheless, such halogenation reactions involve inorganic compounds (i.e., molecular chlorine) or polychlorinated organic molecules, which pose problems of waste streams, toxicity, and corrosivity, particularly on a large scale.[3,4] In addition, such halogenations could result with low regioselectivity and chemoselectivity, or multiple halogenations.[5] A different approach is based on the use of organometallic reagents able to transfer the halogenated carbon to a suitable carbonyl precursor. In fact, the acylation of lithium carbenoids has been reported by Pace, Luisi, and co-workers as an effective alternative to direct halogenation, tackling problems such as polyhalogenation and site selectivity (Scheme 1b).[6] Note that, because of the high thermal instability of the involved lithium carbenoids, this strategy requires the use of a large excess of carbenoid, very low temperatures (i.e., less than or equal to −78 °C) and the internal quenching procedure. However, the use of microreactor technology allowed for developing more sustainable flow protocols, for the preparation of α-chlorinated carbonyls. In fact, Knochel reported an attractive flow approach to α-chlorinated ketones based on the use of lithium chloroacetate in a Claisen reaction (Scheme 1b).[7]

Other approaches for the flow synthesis of α-haloketones have been recently reported by Ley[8] and Kappe.[9] In contrast to α-chloro ketones, the preparation of α-chloro aldehydes is less straightforward. Interestingly, Studer[10] reported the direct conversion of primary and secondary alcohols into the corresponding α-chloro aldehydes using trichloroisocyanuric

Scheme 1. Strategies To Access α-Halo Carbonyls



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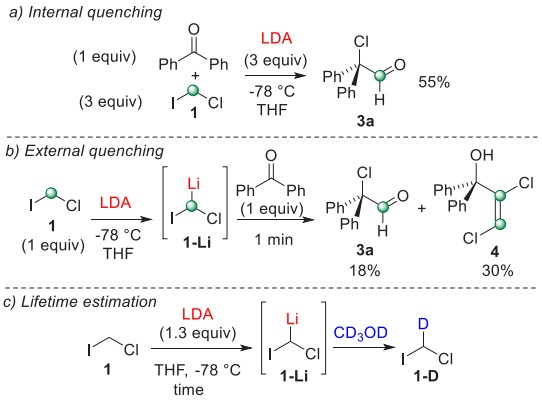
acid, while Renaud[11] used trichloromethanesulfonyl chloride as an α-chlorinating agent for aldehydes (Scheme 1c). Notwithstanding the usefulness of these strategies, they are based on toxic or reactive reagents, and starting materials not always readily available. Moreover, with the exception of few cases shown by Renaud, these approaches cannot be applied to a direct synthesis of α-chloro aldehydes bearing quaternary centers. A different approach, based on carbonyl homologation followed by a Meinwald-type epoxide−aldehyde isomerization, was reported in the 1970s by Kobrich (Scheme 1d).[12] Nevertheless, the process required the internal quenching of the unstable dichloromethyllithium at very low temperature (−100 °C) and, as a second step, a thermally induced isomerization. Inspired by Kobrich's seminal work, and counting on our experience in the use of flow chemistry as sustainable technology for taming reactive intermediates,[13] we report herein a direct one-step synthesis of functionalized α-chloro aldehydes bearing quaternary centers (Scheme 1e).

Even if the genesis of dichloromethylithium in continuous flow conditions was recently reported,[13d] our investigation considered a dihalocarbenoid generated from readily available chloroiodomethane **1**, for two reasons: (1) the installation of a better leaving group (i.e., iodine) would favor the formation of the α-chloroepoxide, precursor of the α-chloro aldehyde; and (2) chloroiodomethane (with a boiling point (bp) of 108 °C) could be an environmentally safer alternative to the low-boiling dichloromethane (bp = 39.6). Moreover, since we were unable to find previous reports on the use of chloroiodomethyllithium **1-Li** in the direct preparation of α-chloro aldehydes, we speculated that it would have been interesting to explore this tactic. As reported in Scheme 2, first we tested **1-Li** in the reaction with benzophenone, in batch at −78 °C, and under internal quenching conditions. With our delight, we observed the direct formation of the α-chloro aldehyde **3a** in 55% yield. Next, the same reaction was run under external quenching conditions, with trapping of **1-Li** just after 1 min (Scheme 2b).

Scheme 2. Testing Reactivity and Lifetime of Dihalocarbenoid 1-Li in Batch

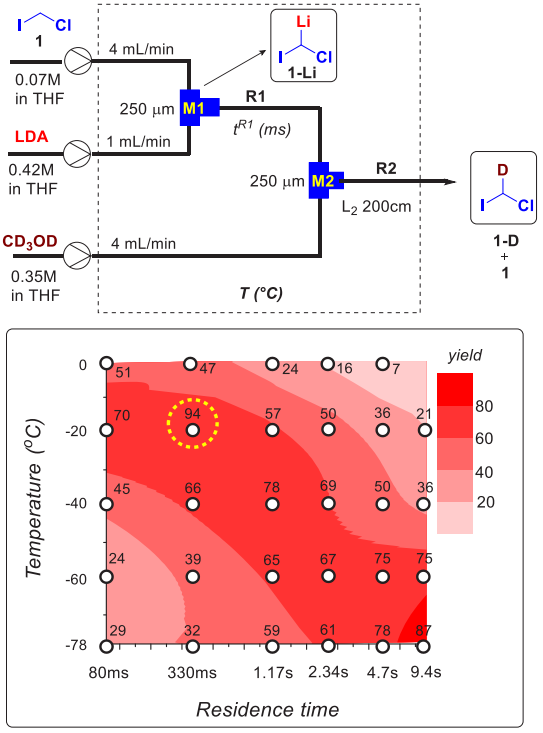


time	recovery (1 + 1-D)	1-D (%D)	1-D (yield %)
1 min	32%	70%	22%
5 min	20%	70%	14%
15 min	17%	68%	12%

lifetime of 1-Li: >60% is lost @ -78 °C after 1min !

In this latter case, **3a** formed in a low 18% yield jointly to a 30% yield of the side product **4**, likely deriving from an eliminative dimerization of the highly chemically unstable **1-Li**.[6c] With the aim to get some insights on the lifetime of **1-Li** at −78 °C, a simple chemical method based on a lithiation/deuteration sequence, and quantitative GC and MS analysis was set up (Scheme 2c).[14] The results of this study show that quenching of **1-Li** after 1 min produced **1-D** in 22% yield, with an entire recovery (**1** + **1-D**) of 32%. Thus, ∼70% of **1** is lost upon lithiation, likely as a consequence of the chemical instability of **1-Li**. Prolonging the time up to 15 min, before electrophilic quenching, resulted in a 17% recovery (**1** + **1-D**) with >80% loss of **1**. By using this simple approach, regardless of the kinetic of the lithiation process, we could estimate the lifetime of the lithium carbenoid **1-Li** (i.e., <1 min) assessing its unsuitability for an external quenching protocol. With the aim to validate the flow microreactor technology, and the flash chemistry approach,[15] we conducted the same study on the reactivity and lifetime of carbenoid **1-Li** under continuous flow conditions. A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) was used for this purpose (see Scheme 3).

Scheme 3. Testing Reactivity and Lifetime of Dihalocarbenoid 2 in Flow



Reacting **1** with LDA in **M1** generates intermediate **1-Li** that could be transferred in **M2**, where it is quenched (trapped) with CD_3OD. Several experiments were performed, varying the temperature (T) and the residence time in R1 (t^{R1}) and the solution of each experiment directly analyzed by GC and MS techniques, in order to assess mass recovery and deuterium content. Analysis of the collected data allowed us to generate the contour map reported in Scheme 3.

Under flow conditions (Scheme 3), the highest yields of **1-D** (94%) could be obtained at short residence times (t^{R1} = 330 ms) and at relatively high temperature (−20 °C). Note that the yields reported in this contour map consider both the recovery of **1** and **1-D** and the deuterium content (see the Supporting Information). Remarkably, a rather wide operative

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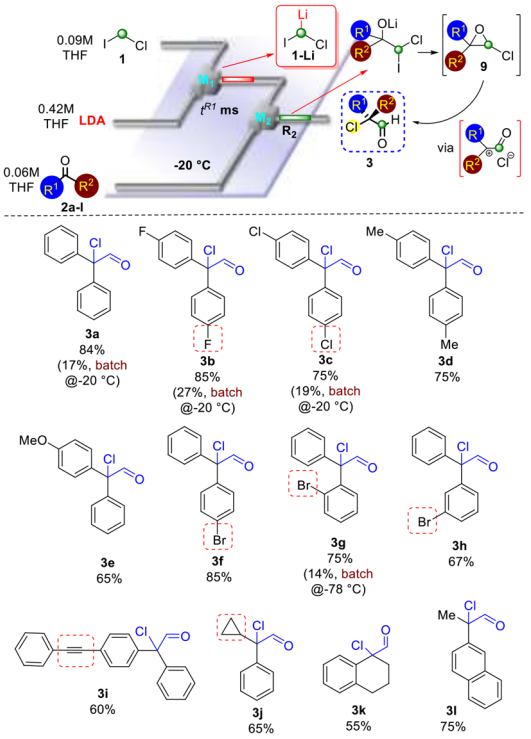
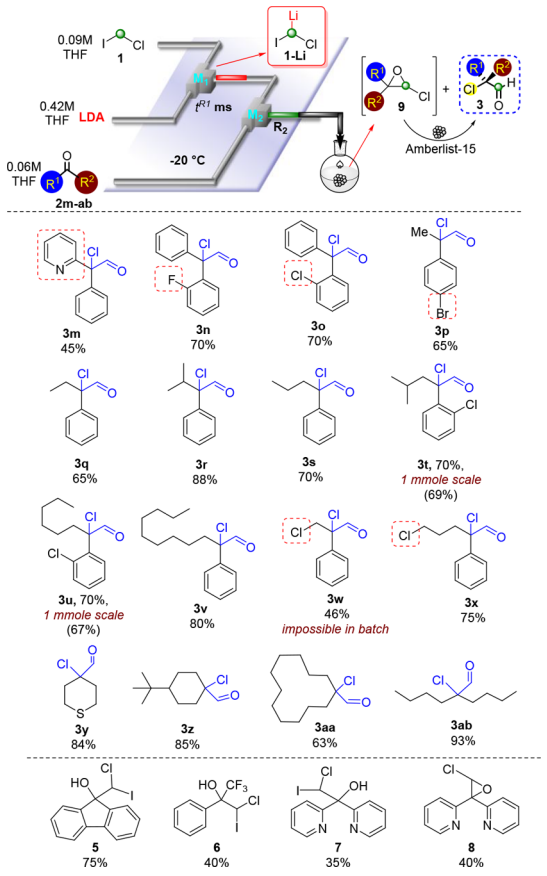
window is observed under flow conditions (the red diagonal in the contour map). In fact, lowering the reaction temperature resulted in prolonging of the lifetime of **1-Li**. For example, **1-D** could be obtained in 87% yield running the flow system at −78 °C with a residence time of 9.4 s. These results clearly highlight the capability of flow microreactor technology to control the lifetime of very reactive intermediates, such as a dihalocarbenoid, under conditions (i.e., −20 °C, external trapping) that seems to be unsuitable in batch.[16] With the optimized conditions in hand, the scope of this flow methodology was examined (see Scheme 4).

Scheme 4. Optimized Flow Synthesis for Direct Access to α-Chloro Aldehydes



Under optimized conditions (−20 °C, t^{R1} = 330 ms), and using benzophenone as a carbonyl acceptor, the α-chloro aldehyde **3a** was directly recovered in 84% yield. It is likely that the formation of **3a** is a consequence of a fast Meinwald-type rearrangement of α-chloroepoxide **9** via carbonyl α-cation (vide infra). When the same reaction was conducted under batch conditions at −20 °C, and using the internal quenching protocol (Scheme 2), **3a** was recovered only in a low 17% yield. The use of symmetrical and nonsymmetrical substituted ketones gave access to the corresponding α-chloro aldehydes **3b**−**3l** with good yields and high level of chemoselectivity. In fact, the presence of sensitive functionalities such as halogens (F, Cl, Br) on the phenyl ring, potentially incompatible with the lithiation conditions, was completely tolerated, returning very clean reaction mixtures. Additional functional groups, such as a heterocyclic ring as in **3m** (Scheme 5), or the triple bond as in **3i** (Scheme 4) could be easily installed in the α-chloro aldehyde backbone. The method was not only limited to di(hetero)arylketones but could be applied to some alkylarylketones. In fact, α-chloro- and α-aryl-substituted aldehydes **3j**−**3l** were easily prepared in good to excellent

Scheme 5. Flow Synthesis, Followed by Acidic Treatment to α-Chloroaldehydes



yields by using this direct flow approach. The cyclopropyl ring (in **3j**), as well as the cyclic structure (in **3k**), were compatible with this flow protocol. Note that all these molecules would require a multistep approach for their preparation and cannot be obtained in satisfactory yields using this strategy under traditional batch conditions.

To further prove the superb performance of this flow approach, with respect to batch operation, we perform some representative reactions on diarylketones (**2b** and **2c**) under internal quenching conditions at −20 °C (Scheme 4). The reaction proceeded with low conversion furnishing α-chloroaldehydes **3b** and **3c** in 27% and 19% yields, respectively. Under the same batch conditions, the more challenging ketones **2g**—bearing an *o*-bromophenyl moiety—gave complex reaction mixtures and product **3g** was observed in 14% yield. A slightly different behavior was observed when diarylketones **2m**−**2o**, arylalkylketones **2p**−**2x**, and dialkyl ketones **2y**−**2ab** were employed under optimal flow conditions (Scheme 5). In fact, in this case, a mixture of the desired α-chloroaldehyde **3** and its precursor chloroepoxide **9** was obtained.

However, stirring the crude mixture of **3** and **9** under mild acidic conditions in the presence of Amberlist-15 cleanly provided the chloroaldehyde **3**. In this way, aldehydes **3m**−**3z** and **3aa**−**3ab** were obtained in good yields and chemoselectivity. Remarkably, the excellent group tolerance, realized under flow conditions, allowed using enolizable ketones, or ketones bearing electrophilic moiety such as 2-chloro-1-phenylethan-1-one (**2w**) and 5-chloro-1-phenylbutan-1-one (**2x**) that furnished **3w** and **3x** in 46% and 75% yield,

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respectively. Interestingly, **3w** was impossible to obtain under batch conditions, even at −78 °C and using the internal quenching protocol. Other interesting examples are chloroaldeyde **3y**, bearing a heterocyclic core, and macrocyclic aldehyde **3aa**, and aliphatic aldehyde **3ab** difficult to prepare using a direct approach from simple feedstocks. However, some limitations were observed with the use of fluorenone and trifluoromethylphenylketone, converted to the corresponding dihalohydrins **5** and **6**, respectively (Scheme 5, bottom).[17] It is likely that intramolecular cyclization does not occur under these reaction conditions. In addition, the use of di(2-pyridyl)ketone resulted in a mixture of dihalohydrin **7** and chloroepoxide **8**. Attempts to induce the rearrangement of **8** resulted in the recovery of unreacted starting material or decomposition under harsh conditions. The reluctance of **8** to undergoing this Meinwald-type rearrangement could be explained according to McDonald's study,[18,19] with the involvement of a carbonyl α-cation that would be destabilized by electron-withdrawing substituents such as the 2-pyridyl ring (see Scheme 5). Such electronic effects could justify the results obtained using ketones **2n** and **2o** (see Scheme 5), where an incomplete rearrangement occurred.

In conclusion, in this work, we demonstrated that highly unstable lithium dihalocarbenoid can be tamed by taking advantage of the flash chemistry approach and using microreactor technology. Under continuous flow conditions, the direct synthesis of α-chloroaldehydes bearing a quaternary center was feasible; the reaction showed a high level of chemoselectivity and could be realized at −20 °C under external quenching conditions. In contrast, the same approach cannot be employed using batch operations. Remarkably, we introduced an effective method for estimating the lifetime of fleeting species either under batch or under flow conditions. Further results exploiting this approach are available in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01085.

Characterization data for the prepared molecules, list of electrophiles, and conditions for optimizing and run flow reactions (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Author Contributions

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to the memory of Prof. Jun-ichi Yoshida (Kyoto University).

■ REFERENCES

(1) (a) Britton, R.; Kang, B. α-Haloaldehydes: Versatile Building Blocks for Natural Product Synthesis. *Nat. Prod. Rep.* **2013**, *30*, 227−236. (b) Kimpe, N. D.; Verhe, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1988. (c) West, M. S.; Mills, L. R.; McDonald, T. R.; Lee, J. B.; Ensan, D.; Rousseaux, S. A. L. Synthesis of Trans-2-Substituted Cyclopropylamines from α-Chloroaldehydes. *Org. Lett.* **2019**, *21*, 8409−8413. (d) Chen, T. Q.; MacMillan, D. W. C. A Metallaphotoredox Strategy for the Cross-Electrophile Coupling of α-Chloro Carbonyls with Aryl Halides. *Angew. Chem., Int. Ed.* **2019**, *58*, 14584−14588.

(2) Oestreich, M. Strategies for Catalytic Asymmetric Electrophilic α Halogenation of Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324−2327.

(3) Cantillo, D.; Kappe, O. C. Halogenation of organic compounds using continuous flow and microreactor technology. *React. Chem. Eng.* **2017**, *2*, 7−19.

(4) Wagner, C.; El Omari, M.; König, G. M. Biohalogenation: Nature's Way to Synthesize Halogenated Metabolites. *J. Nat. Prod.* **2009**, *72*, 540−553.

(5) (a) Hudlicky, M.; Hudlicky, T. *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, Ltd.: Hoboken, NJ, 1983. (b) Wuts, P. G. M.; Greene, T. W. *Green Protective Groups in Organic Synthesis*, 4th Edition; Wiley: Hoboken, NJ, 2006.

(6) (a) Köbrich, G. The Chemistry of Carbenoids and Other Thermolabile Organolithium Compounds. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473−485. Köbrich, G. Aus der Chemie der Carbenoide und anderer thermolabiler Organolithium-Verbindungen. *Angew. Chem.* **1972**, *84*, 557−570. (b) Kowalski, C. J.; Haque, M. S. Bromomethyl Ketones and Enolates: Alternative Products from Ester Homologation Reactions. *J. Org. Chem.* **1985**, *50*, 5140−5142. (c) Blakemore, P. R.; Hoffmann, R. W. Formation of Olefins by Eliminative Dimerization and Eliminative Cross-Coupling of Carbenoids: A Stereochemical Exercise. *Angew. Chem., Int. Ed.* **2018**, *57*, 390−407. (d) Pace, V.; Castoldi, L.; Monticelli, S.; Rui, M.; Collina, S. New Perspectives in Lithium Carbenoid Mediated

Homologations. *Synlett* **2017**, *28*, 879−888. (e) Parisi, G.; Colella, M.; Monticelli, S.; Romanazzi, G.; Holzer, W.; Langer, T.; Degennaro, L.; Pace, V.; Luisi, R. Exploiting a "Beast" in Carbenoid Chemistry: Development of a Straightforward Direct Nucleophilic Fluoromethylation Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 13648−13651. (f) Gessner, V. H. Stability and Reactivity Control of Carbenoids: Recent Advances and Perspectives. *Chem. Commun.* **2016**, *52*, 12011−12023. (g) Capriati, V.; Florio, S. Anatomy of Long-Lasting Love Affairs with Lithium Carbenoids: Past and Present Status and Future Prospects. *Chem. - Eur. J.* **2010**, *16*, 4152−4162. (h) Colella, M.; Tota, A.; Großjohann, A.; Carlucci, C.; Aramini, A.; 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. (i) 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.

(7) Ganiek, M. A.; Ivanova, M. V.; Martin, B.; Knochel, P. Mild Homologation of Esters through Continuous Flow Chloroacetate Claisen Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 17249−17253.

(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) Pinho, V. D.; Gutmann, B.; Miranda, L. S. M.; de Souza, R. O. M. A.; Kappe, C. O. Continuous Flow Synthesis of α-Halo Ketones: Essential Building Blocks of Antiretroviral Agents. *J. Org. Chem.* **2014**, *79*, 1555−1562.

(10) Jing, Y.; Daniliuc, C. G.; Studer, A. Direct Conversion of Alcohols to α-Chloro Aldehydes and α-Chloro Ketones. *Org. Lett.* **2014**, *16*, 4932−4935.

(11) Jimeno, C.; Cao, L.; Renaud, P. Trichloromethanesulfonyl Chloride: A Chlorinating Reagent for Aldehydes. *J. Org. Chem.* **2016**, *81*, 1251−1255.

(12) Grosser, J.; Werner, W. Zur Umlagerung von Li-Alkoxiden aus Dichlormethyllithium und Carbonylverbindungen in α-Chloroxirane und α-Chloraldehyde. *Chem. Ber.* **1973**, *106*, 2610−2619.

(13) (a) Bogdan, A. R.; Dombrowski, A. W. Emerging Trends in Flow Chemistry and Applications to the Pharmaceutical Industry. *J. Med. Chem.* **2019**, *62*, 6422−6468. (b) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology-A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6728. (c) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892−4928. (d) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode. *Org. Lett.* **2017**, *19*, 786−789. (e) Colella, M.; Tota, A.; Takahashi, Y.; Higuma, R.; Ishikawa, S.; Degennaro, L.; Luisi, R.; Nagaki, A. Fluoro-substituted Methyllithium Chemistry Based on a Novel External Quenching Method Using Flow Microreactors *Angew. Chem., Int. Ed.* **2020**, DOI: 10.1002/anie.202003831. (f) Colella, M.; Nagaki, A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. - Eur. J.* **2020**, *26*, 19−32.

(14) After quenching with CD_3OD, the reaction mixture was subjected to quantitative analysis without requiring any workup. See the Supporting Information for details.

(15) (a) Yoshida, J.-I. *Flash Chemistry: Fast Organic Synthesis in Microsystems*; Wiley−Blackwell, 2008. (b) Nagaki, A. Recent topics of functionalized organolithiums using flow microreactor chemistry. *Tetrahedron Lett.* **2019**, *60*, 150923. (c) Degennaro, L.; Carlucci, C.; De Angelis, S.; Luisi, R. Flow technology for organometallic-mediated synthesis. *J. Flow Chem.* **2016**, *6*, 136−166.

(16) (a) Nagaki, A.; Tokuoka, S.; Yamada, S.; Tomida, Y.; Oshiro, K.; Amii, H.; Yoshida, J. Perfluoroalkylation in Flow Microreactors: Generation of Perfluoroalkyllithiums in the Presence and Absence of Electrophiles. *Org. Biomol. Chem.* **2011**, *9*, 7559. (b) Degennaro, L.; Fanelli, F.; Giovine, A.; Luisi, R. External Trapping of Halomethyllithium Enabled by Flow Microreactors. *Adv. Synth. Catal.* **2015**, *357*, 21−27. (c) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode. *Org. Lett.* **2017**, *19*, 786−789. (d) Degennaro, L.; Maggiulli, D.; Carlucci, C.; Fanelli, F.; Romanazzi, G.; Luisi, R. A direct and sustainable synthesis of tertiary butyl esters enabled by flow microreactors. *Chem. Commun.* **2016**, *52*, 9554−9557. (e) Giovine, A.; Musio, B.; Degennaro, L.; Falcicchio, A.; Nagaki, A.; Yoshida, J.-i.; Luisi, R. Synthesis of 1,2,3,4-tetrahydroisoquinolines by microreactor-mediated thermal isomerization of laterally lithiated arylaziridines. *Chem. - Eur. J.* **2013**, *19*, 1872−1876. (f) von Keutz, T.; Cantillo, D.; Kappe, C. O. Continuous Flow Synthesis of Terminal Epoxides from Ketones Using in Situ Generated Bromomethyl Lithium. *Org. Lett.* **2019**, *21*, 10094−10098.

(17) The dihalohydrin could be converted to the corresponding chloroepoxide under basic conditions, and subsequently into the migration product under acidic catalysis. However, this two-step sequence was beyond the scope of this work, because we were looking for a more direct approach. This sequence is under investigation in our laboratory and will be reported in due course.

(18) (a) McDonald, R. N.; Cousins, R. C. Molecular Rearrangements. 13. Kinetics and Mechanism of Rearrangements of Some Ring-Substituted α-Chlorostyrene Oxides and Trans-β-Chlorostyrene Oxides. *J. Org. Chem.* **1980**, *45*, 2976−2984. For a related study, see: (b) Vyas, D. J.; Larionov, E.; Besnard, C.; Guénée, L.; Mazet, C. Isomerization of Terminal Epoxides by a [Pd−H] Catalyst: A Combined Experimental and Theoretical Mechanistic Study. *J. Am. Chem. Soc.* **2013**, *135*, 6177−6183.

(19) For similar reactivity, see: Pace, V.; Castoldi, L.; Mazzeo, E.; Rui, M.; Langer, T.; Holzer, W. Efficient Access to All-Carbon Quaternary and Tertiary α-Functionalized Homoallyl-Type Aldehydes from Ketones. *Angew. Chem., Int. Ed.* **2017**, *56*, 12677−12682.

https://dx.doi.org/10.1021/acs.orglett.0c01085
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