

Organomagnesium Based Flash Chemistry: Continuous Flow Generation and Utilization of Halomethylmagnesium Intermediates

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Cite This: *Org. Lett.* 2020, 22, 7537–7541



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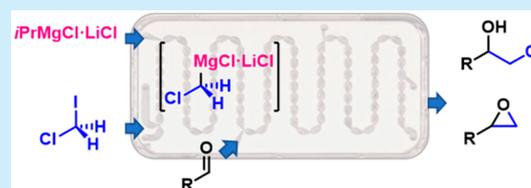
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ABSTRACT: The generation of highly unstable chloromethylmagnesium chloride in a continuous flow reactor and its reaction with aldehydes and ketones is reported. With this strategy, chlorohydrins and epoxides were synthesized within a total residence time of only 2.6 s. The outcome of the reaction can be tuned by simply using either a basic or an acidic quench. Very good to excellent isolated yields, up to 97%, have been obtained for most cases (30 examples).

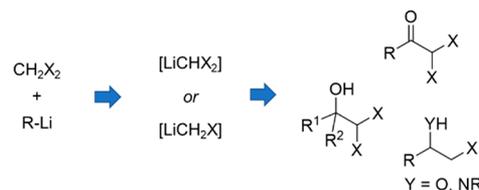


Organometallic reagents are among the most important and commonly utilized tools in organic synthesis.^{1,2} Organolithium and organomagnesium compounds were developed at the onset of the past century and are arguably the two most commonly employed organometallic species.^{3,4} The lack of several undesired side reactions have rendered organolithium reagents the method of choice in many cases.⁵ However, Grignard reagents are typically less expensive and more stable than their lithium counterparts.⁶ Their difference in cost is becoming more notable in recent years and is expected to increase further due to the high demand of lithium for batteries and fuel cells.⁷ Moreover, this growing demand, and the resulting increase of its mining and exploitation, has a significant negative environmental impact.⁸

The high reactivity of Grignard and especially organolithium reagents frequently requires low temperatures (e.g., $-78\text{ }^{\circ}\text{C}$) to achieve satisfactory selectivities.^{1,2,4,5} Slow addition of the reagent to the reaction is typically required, hampering the scalability of the chemical process. The use of continuous flow reactors has introduced robust scale-up strategies for these reactions, facilitating the use of noncryogenic conditions and thus application on industrial scale.⁹ Using micromixers, even highly unstable intermediates can be generated and utilized within milliseconds for organic reactions, enabling transformations that are not possible in batch.¹⁰ The term “flash chemistry” was coined by Jun-ichi Yoshida to describe this type of ultrafast reactions.¹¹ In this context, the generation of several unstable halomethyl lithium species has been reported during the past years. These intermediates can be handled with relative ease in flow reactors and used as convenient C1 building blocks (Figure 1A).¹²

The alternative magnesium carbenoid analogues, generated from halomethanes by halogen–magnesium exchange with a Grignard reagent, present several advantages. In addition to the potential economic factors favoring the use of magnesium instead of lithium, commercial Grignard reagents are more stable. Surprisingly, halomethyl magnesium intermediates have

A Halomethyl lithium carbenoid chemistry enabled by microreactors



B Continuous generation and utilization of a magnesium carbenoid (*this work*)

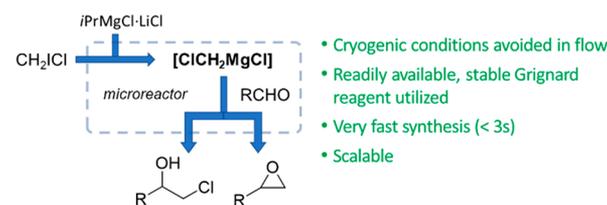


Figure 1. (A) Lithium carbenoid intermediates generated using continuous flow reactors and (B) alternative organomagnesium-based chemistry.

been far less studied than their lithium counterparts, and examples reported for their generation via halogen–magnesium exchange are limited.¹³ Although the starting reagents are relatively stable, the generated C1 organometallic intermediates rapidly decompose unless cryogenic temperatures are applied. The scarce examples described in the literature require temperatures as low as $-95\text{ }^{\circ}\text{C}$,¹⁴ very slow addition of the Grignard reagent, and long reaction times (>1 h) for reactions on relatively small scale (<2 mmol).¹⁵ We hypothesized that,

Received: August 14, 2020

Published: September 11, 2020



similar to flash chemistry reactions involving lithium reagents, the challenging generation and utilization of halomethylmagnesium intermediates could be harnessed using continuous flow technology. Indeed, improvements in the selectivity of other transformations involving several organomagnesium reagents have been described in the literature.¹⁶ Notably, to the best of our knowledge, the continuous generation of highly reactive C1 magnesium carbenoids has not been reported to date. Herein we describe a continuous procedure for the generation of chloromethylmagnesium chloride at noncryogenic temperatures. The reactive intermediate has been reacted in situ with aldehydes and ketones. Depending on the use of an acidic or a basic quench, chlorohydrins and epoxides were obtained.

Halogen–magnesium exchange in halomethanes is known to proceed at low temperatures with isopropylmagnesium chloride and with its lithium chloride complex.¹⁵ Lithium chloride can considerably accelerate the halogen–magnesium exchange,¹⁷ and thus the “turbo Grignard” *i*PrMgCl·LiCl was expected to be particularly suitable for the generation of unstable carbenoids at higher temperatures. Our preliminary batch experiments employing either CH₂I₂ or CH₂Cl₂¹⁸ and benzaldehyde as a model electrophile demonstrated that halogen–magnesium exchange takes place in under 2 min at –80 °C. In these experiments (Figure 2), *i*PrMgCl·LiCl in

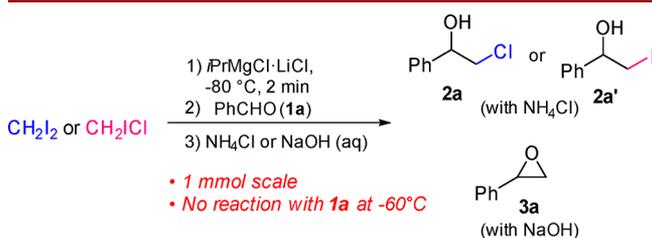


Figure 2. Preliminary batch experiments for the generation of chloromethylmagnesium chlorides and their reaction with benzaldehyde **1a**. Yields of ca. 95% (GC-FID) were achieved on 1 mmol scale at –80 °C for the three examples.

THF was slowly added to a vigorously stirred solution containing either of the two halomethanes in THF. After 2 min, a solution of benzaldehyde (**1a**) in THF was added. The reaction outcome could be readily tuned by simply selecting an acidic or a basic quench for the reaction mixture. When the reaction mixture was quenched with an aqueous 2 M solution of NH₄Cl, the expected chlorohydrin **2a** or iodohydrin **2a'** (with CH₂Cl₂ and CH₂I₂, respectively) were obtained (Figure 2). When an aqueous 1 M NaOH solution was used as quench instead, the corresponding epoxide **3a** was observed. Under these conditions, yields of ca. 95% (GC-FID) were obtained. However, batch experiments could be only performed on very small scale, and when the temperature was raised to –60 °C no conversion of benzaldehyde was observed. This indicates the low stability of the halomethylmagnesium intermediate even at –60 °C. Other major side products observed in these batch experiments were the reduction of the carbonyl group and nucleophilic addition of the Grignard reagent (see Figure S1 for details).

Continuous flow experiments were initially carried out using a setup made of PTFE tubing (0.5 mm i.d.) and PEEK T-mixers (0.5 mm thru hole). Reagent stoichiometries and the concentration of the Grignard reagent were optimized, using the reaction of benzaldehyde (**1a**) with CH₂Cl₂¹⁸ as a model

system (see Figures S2 and S3 in the Supporting Information for details). Excellent conversion and selectivity were obtained with 1.2 equiv of *i*PrMgCl·LiCl and 1.5 equiv of CH₂Cl₂, and importantly, the temperature could be increased from –80 °C to –60 °C without any decrease in reaction efficiency. Under these conditions, a 97% GC-FID yield was achieved after a 1 min residence time for the carbenoid generation, plus 2 min for its reaction with benzaldehyde.

We anticipated that further increase of the reaction temperature would lead to very short reaction times, most probably in the range of 1–2 s. Such rapid reactions can be difficult to handle due to mass transfer limitations using simple T-mixers, particularly in combination with low flow rates (<2 mL/min).¹⁹ To further evaluate this issue, a Villermaux–Dushman protocol²⁰ was employed to determine the mixing time of the T-mixer (see Supporting Information). Mixing times of >1 s were obtained for the T-mixer during the experiment when a flow rate of less than 2 mL/min was utilized (Figure S5). As expected, higher flow rates decreased the mixing time, but a flow rate of >6 mL/min was required to achieve a mixing time below 0.5 s. On the other hand, a plate-based micromixer (FlowPlate Lab microreactor, LL-mixer, Hastelloy, 0.24 mL volume)²¹ showed a much better mixing performance at low flow rates (e.g., 0.5 s vs 1.3 s for the FlowPlate vs T-mixer at 1.4 mL/min flow rate), in agreement with previous studies,²² and therefore this system was selected for further optimizations at higher temperatures.

The plate-based reactor system comprised three input feeds and an output line (Figure 3A) (for a detailed view of the experimental setup, see Figure S6 in the Supporting Information). Thus, two solutions containing the halomethane

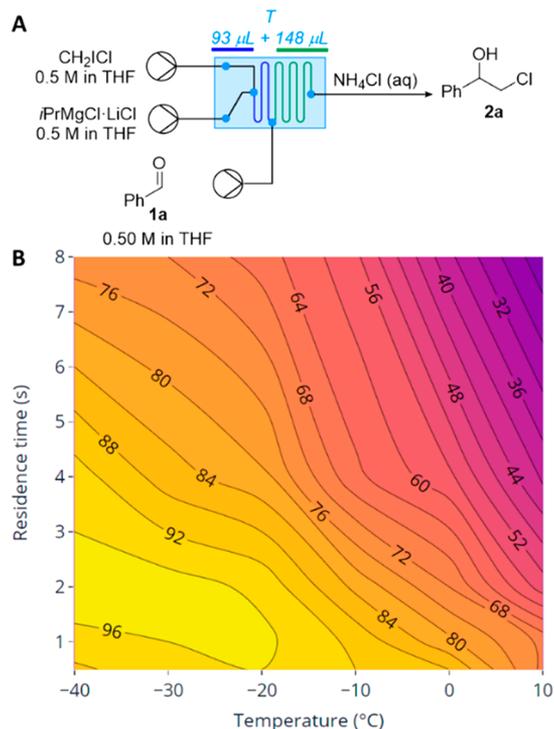


Figure 3. (A) Schematic view of the continuous flow setup utilized for the generation and utilization of chloromethylmagnesium chloride and (B) contour plot representing the effect of the temperature and the residence time for the carbenoid generation on the final yield. Data points are collected in Table S1.

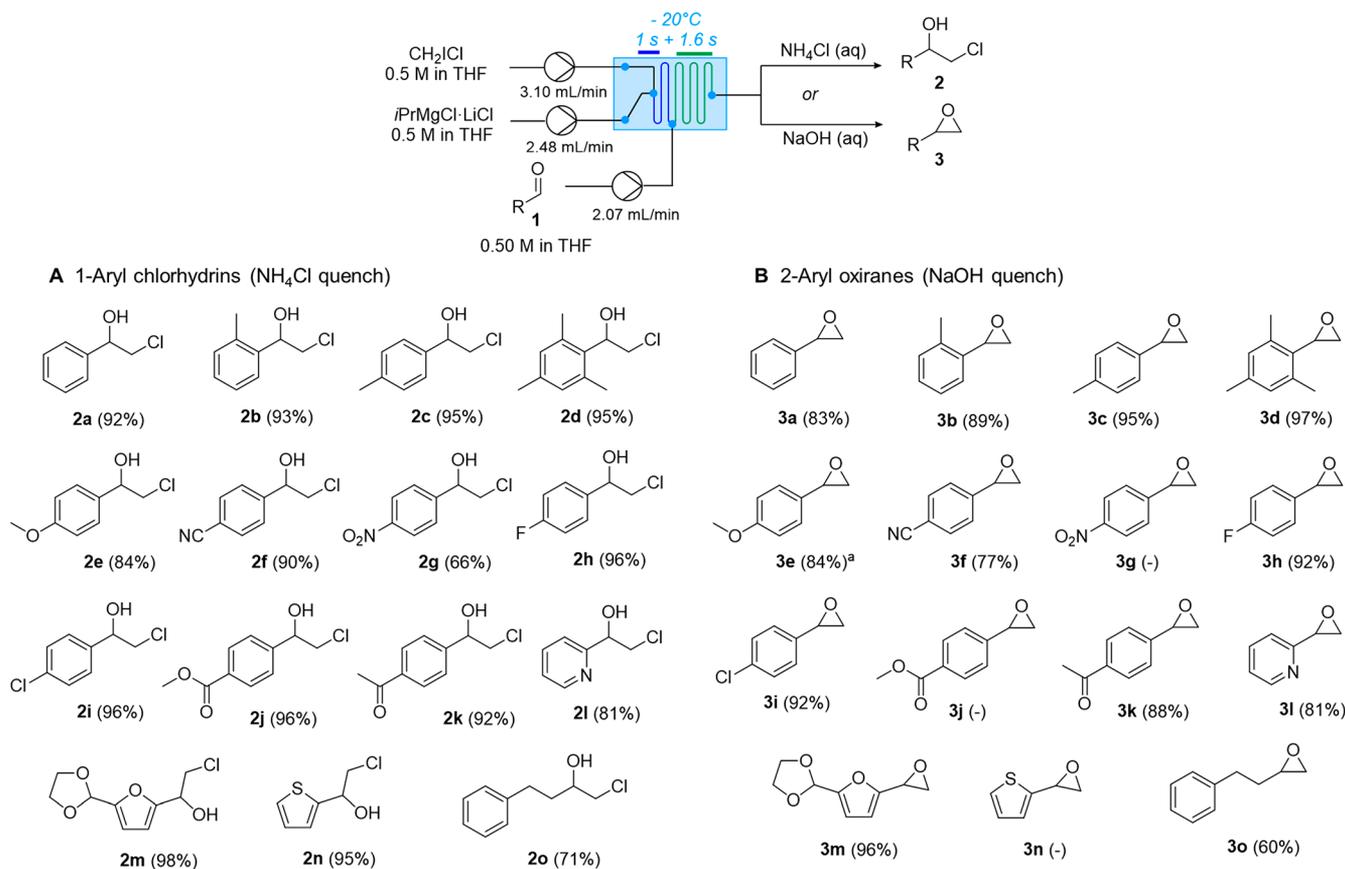


Figure 4. Reaction scope for (A) 1-aryl chlorohydrins **2** and (B) 2-aryl oxiranes **3** via in situ generated chloromethylmagnesium chloride. ^aCompound **3e** rearranged to the corresponding 3-arylpropanal during column chromatography.

and the Grignard reagent were initially mixed and reacted within a 93 μ L reactor volume. Then, a third feed containing the aldehyde **1a** was introduced and mixed with the solution containing the chloromethylmagnesium intermediate. The residence volume for the second step in the plate reactor was 148 μ L. The crude reaction mixture was quenched at the reactor output, initially with a 2 M solution of NH₄Cl. The optimal reaction conditions were thoroughly evaluated by varying the reactor temperature and the solution feed flow rates. As anticipated, excellent results were obtained with very short residence times at relatively high temperatures (Figure 3B). Importantly, at temperatures between -40 °C and -20 °C excellent yields (>96%) could only be achieved with residence times for the first step of 1–3 s, rendering this transformation virtually impossible to perform in batch at these temperatures. Indeed, longer residence times (4–8 s) resulted in a significant decrease of the reaction yield, most probably due to decomposition of the carbenoid intermediate. Ultimately, a 1 s reaction time for the chloromethylmagnesium intermediate generation and 1.6 s for the reaction with the electrophile at -20 °C were selected as optimal conditions.

Using this continuous flow protocol, a series of 1-aryl chlorohydrins **2** (Figure 4A) and 2-aryl oxiranes **3** (Figure 4B) were synthesized. All reactions were carried out using the optimal conditions described above without any further modifications. Thus, all compounds were prepared within a total residence time of 2.6 s. The generation of chlorohydrins **2** or oxiranes **3** could be tuned by simply utilizing an acidic or a basic quench, respectively. Alkylaryl-substituted aldehydes gave excellent yields toward chlorohydrins (**2a–d**) and very good to

excellent yields of oxiranes (**3a–d**). The presence of strongly withdrawing groups, such as nitro, nitrile, or fluorine, generally decreased the yield. Yet, good yields were achieved for several specific cases (**2g–i**, **3h–i**), except compound **3g** which decomposed during isolation. Milder electron-withdrawing groups displayed a less prominent effect, and good to excellent yields were also obtained (**2f**, **2j–k**, **3f**, **3k**). The presence of an ester group was tolerated with the acid quench, and compound **2j** was obtained in high yield. By employing a basic quench with 1 M NaOH, however, the ester group was hydrolyzed (**3j**). Notably, good selectivity was also obtained in the presence of a ketone (**2k**, **3k**), most probably due to the higher reactivity of the aldehyde (ketones can also be derivatized using this strategy, *vide infra*).

Nitrogen-, sulfur-, and oxygen-containing heterocyclic aldehydes were also successfully converted to the corresponding chlorohydrins (**2l–n**) and oxiranes (**3l–m**). The method failed for the generation of compound **3n**. In this case, a mixture of unidentified products was obtained. In general, yields for chlorohydrins were slightly higher than for epoxides. Notably, due to the high conversion and selectivity obtained in most cases, isolation of the products was very straightforward by extraction. It should be emphasized that a productivity of 1 mmol/min was achieved using a reactor with only a 240 μ L volume and 2.6 s residence time. In a long-run experiment, preparation of **2c** was performed for 2 h to evaluate the stability of the continuous flow setup. The conversion to the target chlorohydrin remained constant during the entire operation (see Figure S8). Workup of the crude reaction mixture yielded 20.3 g (96%) of **2c**.

An additional set of reactions was carried out with other carbonyl compounds of interest (Figure 5). Methyl o-

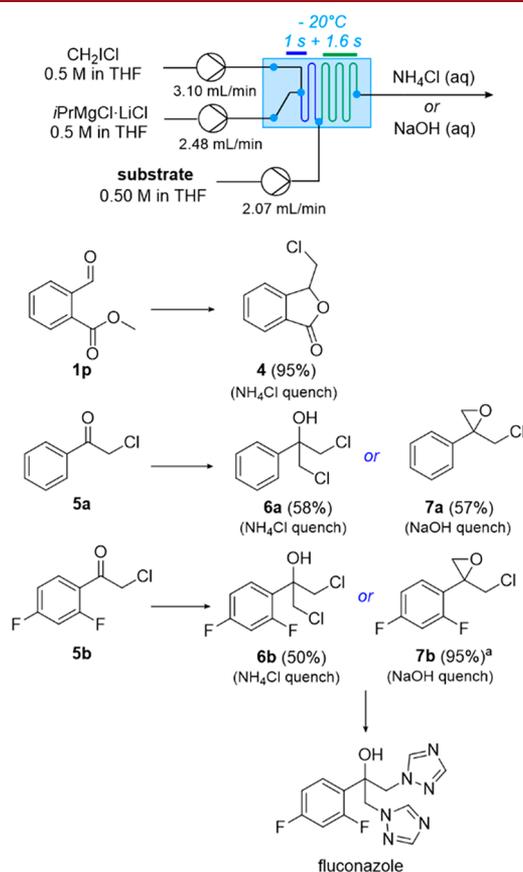


Figure 5. Further transformations of interest using in situ generated chloromethylmagnesium chloride. ^a Synthesis of **7b** was carried out with a substrate concentration of 0.2 M instead of 0.5 M.

formylbenzoate (**1p**), for example, generated benzofuranone **4** in excellent yield via an intramolecular cyclization of the magnesium alkoxide intermediate. α -Chloro ketones **5a** and **5b** generated 1,3-dichloro derivatives **6** and epoxides **7**, upon quench with NH_4Cl and NaOH . Epoxide **7b** (and alternatively the chlorhydrin **6b**) is a key intermediate in the preparation of the WHO essential medicine fluconazole (Figure 5).^{12g,23} This strategy provides a useful alternative procedure for the epoxidation of α -chloro ketones, as the generally employed Corey–Chaykovsky reagents typically fail for this type of substrate.

In summary, we have developed a continuous flow procedure for the generation and utilization of chloromethylmagnesium chloride, a highly unstable intermediate that cannot be employed in batch unless cryogenic conditions are applied. Implementation of a micromixer and flow technology enabled exceedingly fast generation of the organomagnesium species within a 1 s residence time at -20°C . Continuous addition of a solution containing an aldehyde or a ketone resulted in a highly selective protocol for the preparation of 1-aryl chlorohydrins **2** or 2-aryl epoxides **3**, depending on the acid or basic character of the reaction quench employed. With a total reaction time of only 2.6 s, excellent yields have been obtained in most cases for a wide variety of substrates. A productivity of 1 mmol/min was achieved using a reactor with an internal volume of only 240 μL . These values result in an

impressive space–time yield of 250 mol/L/h. Importantly, the use of a plate-based microreactor with excellent control over heat and mass transfer facilitates direct scalability following a “smart dimensioning” concept.^{21,24}

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02725>.

Experimental details, description of side reactions, preliminary flow optimizations, Villermaux–Dushman protocol, details on the flow setup, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to the memory of Professor Jun-ichi Yoshida. The CC FLOW Project (Austrian Research Promotion Agency FFG No. 862766) is funded through the Austrian COMET Program by the Austrian Federal Ministry of Transport, Innovation and Technology (BMVIT), the Austrian Federal Ministry of Science, Research and Economy (BWF), and by the State of Styria (Styrian Funding Agency SFG).

■ REFERENCES

- (1) *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004.
- (2) *Handbook of Functionalized Organometallics: Application in Synthesis*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005.
- (3) Grignard, V. Sur quelques nouvelles combinaisons organo-métalliques du magnésium et leurs application à des synthèses d'alcools et d'hydrocarbures. *Compt. Rend.* **1900**, *130*, 1322–1325.
- (4) Wietelmann, U.; Klett, J. 200 Years of Lithium and 100 Years of Organolithium Chemistry. *Z. Anorg. Allg. Chem.* **2018**, *644*, 194–204.
- (5) *The Chemistry of Organolithium Compounds (2 parts)*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons, Ltd: Chichester, West Sussex, 2004.

(6) *Advances in Organometallic Chemistry*, Vol 32.; Stone, F., West, R., Eds.; Academic Press, Inc.: San Diego, CA, 1991.

(7) (a) Grosjean, C.; Miranda, P. H.; Perrin, M.; Poggi, P. Assessment of World Lithium Resources and Consequences of Their Geographic Distribution on the Expected Development of the Electric Vehicle Industry. *Renewable Sustainable Energy Rev.* **2012**, *16*, 1735–1744. (b) Martin, G.; Rentsch, L.; Höck, M.; Bertau, M. Lithium Market Research – Global Supply, Future Demand and Price Development. *Energy Storage Mater.* **2017**, *6*, 171–179.

(8) (a) Wanger, T. C. The Lithium Future-Resources, Recycling, and the Environment. *Conserv. Lett.* **2011**, *4*, 202–206. (b) Dewulf, J.; Van der Vorst, G.; Denturck, K.; Van Langenhove, H.; Ghyoot, W.; Tytgat, J.; Vandeputte, K. Recycling Rechargeable Lithium Ion Batteries: Critical Analysis of Natural Resources Savings. *Resour. Conserv. Recycl.* **2010**, *54*, 229–234.

(9) (a) 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. (b) 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. (c) Colella, M.; Nagaki, A.; Luisi, R. Frontispiece: Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. - Eur. J.* **2020**, *26*, 2020.

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

(11) Yoshida, J.-I. *Flash Chemistry. Fast Organic Synthesis in Microsystems*; John Wiley and Sons Ltd.: Chichester, West Sussex, 2008.

(12) (a) Colella, M.; Tota, A.; Takahashi, Y.; Higuma, R.; Ishikawa, S.; Degennaro, L.; Luisi, R.; Nagaki, A. Fluoro-Substituted Methylithium Chemistry: External Quenching Method Using Flow Microreactors. *Angew. Chem., Int. Ed.* **2020**, *59*, 10924–10928. (b) Degennaro, L.; Fanelli, F.; Giovine, A.; Luisi, R. External Trapping of Halomethylithium Enabled by Flow Microreactors. *Adv. Synth. Catal.* **2015**, *357*, 21–27. (c) 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. (d) 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. (e) 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. (f) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. Dichloromethylithium: Synthesis and Application in Continuous Flow Mode. *Org. Lett.* **2017**, *19*, 786–789. (g) 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 Fluoroiodomethylithium to Carbonyl-Like Compounds. *Org. Lett.* **2019**, *21*, 584–588. (h) Musci, P.; Colella, M.; Sivo, A.; Romanazzi, G.; Luisi, R.; Degennaro, L. Flow Microreactor Technology for Taming Highly Reactive Chloroiodomethylithium Carbenoid: Direct and Chemoselective Synthesis of α -Chloroaldehydes. *Org. Lett.* **2020**, *22* (9), 3623–3627.

(13) Satoh, T. Recent Advances in the Chemistry of Magnesium Carbenoids. *Chem. Soc. Rev.* **2007**, *36*, 1561–1572.

(14) Seyferth, D.; Lambert, R. L.; Hanson, E. M. Halomethyl-Metal Compounds. XL. Trimethylsilyl-Substituted Bromomethylithium and -Magnesium Reagents. Trimethyltindibromomethylmagnesium Chloride. *J. Organomet. Chem.* **1970**, *24*, 647–661.

(15) (a) Braun, H. A.; Meusinger, R.; Schmidt, B. 2-Iodoethanols from Aldehydes, Diiodomethane and Isopropylmagnesium Chloride.

Tetrahedron Lett. **2005**, *46*, 2551–2554. (b) Nishimura, R.; Murie, V.; Soldi, R.; Clososki, G. (Chloromethyl)magnesium Chloride-Lithium Chloride: A Chemoselective Reagent for the Synthesis of Functionalized Aromatic Chlorohydrins. *Synthesis* **2015**, *47*, 1455–1460. (c) Koyama, Y.; Lear, M. J.; Yoshimura, F.; Ohashi, I.; Mashimo, T.; Hiram, M. Efficient Construction of the Kedarcidin Chromophore Ansamacrolide. *Org. Lett.* **2005**, *7*, 267–270. (d) Nishimura, R. H. V.; Toledo, F. T.; Lopes, J. L. C.; Clososki, G. C. Efficient Synthesis of Chlorohydrins Using ClCH₂MgCl-LiCl. *Tetrahedron Lett.* **2013**, *54*, 287–290.

(16) For recent examples, see: (a) Odille, F. G. J.; Stenemyr, A.; Pontén, F. Development of a Grignard-Type Reaction for Manufacturing in a Continuous-Flow Reactor. *Org. Process Res. Dev.* **2014**, *18*, 1545–1549. (b) Brodmann, T.; Koos, P.; Metzger, A.; Knochel, P.; Ley, S. V. Continuous Preparation of Arylmagnesium Reagents in Flow with Inline IR Monitoring. *Org. Process Res. Dev.* **2012**, *16*, 1102–1113. (c) Deng, Q.; Shen, R.; Zhao, Z.; Yan, M.; Zhang, L. The Continuous Flow Synthesis of 2,4,5-Trifluorobenzoic Acid via Sequential Grignard Exchange and Carboxylation Reactions Using Microreactors. *Chem. Eng. J.* **2015**, *262*, 1168–1174. (d) Hamlin, T. A.; Lazarus, G. M. L.; Kelly, C. B.; Leadbeater, N. E. A Continuous-Flow Approach to 3,3,3-Trifluoromethylpropenes: Bringing Together Grignard Addition, Peterson Elimination, Inline Extraction, and Solvent Switching. *Org. Process Res. Dev.* **2014**, *18*, 1253–1258. (e) Newby, J. A.; Blaylock, D. W.; Witt, P. M.; Pastre, J. C.; Zacharova, M. K.; Ley, S. V.; Browne, D. L. Design and Application of a Low-Temperature Continuous Flow Chemistry Platform. *Org. Process Res. Dev.* **2014**, *18*, 1211–1220. (f) Battilocchio, C.; Baxendale, I. R.; Biava, M.; Kitching, M. O.; Ley, S. V. A Flow-Based Synthesis of 2-Aminoadamantane-2-Carboxylic Acid. *Org. Process Res. Dev.* **2012**, *16*, 798–810. (g) Petersen, T. P.; Becker, M. R.; Knochel, P. Continuous Flow Magnesium of Functionalized Heterocycles and Acrylates with TMPMgCl-LiCl. *Angew. Chem., Int. Ed.* **2014**, *53*, 7933–7937. (h) Tricotet, T.; O'Shea, D. F. Automated Generation and Reactions of 3-Hydroxymethylindoles in Continuous-Flow Microreactors. *Chem. - Eur. J.* **2010**, *16*, 6678–6686.

(17) Ziegler, D. S.; Wei, B.; Knochel, P. Improving the Halogen-Magnesium Exchange by Using New Turbo-Grignard Reagents. *Chem. - Eur. J.* **2019**, *25*, 2695–2703.

(18) Attempts to perform the reaction with noniodine halomethanes (e.g., CH₂Br₂) provided poor results. CH₂ICl was ultimately selected instead of CH₂I₂ due to its higher cost efficiency.

(19) Schwolow, S.; Hollmann, J.; Schenkel, B.; Röder, T. Application-Oriented Analysis of Mixing Performance in Microreactors. *Org. Process Res. Dev.* **2012**, *16*, 1513–1522.

(20) Commenge, J.-M.; Falk, L. Villermaux-Dushman Protocol for Experimental Characterization of Micromixers. *Chem. Eng. Process.* **2011**, *50*, 979–990.

(21) Roberge, D. M.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. Industrial Design, Scale-Up, and Use of Microreactors. *Chim. Oggi* **2009**, *27*, 8–11.

(22) Reckamp, J. M.; Bindels, A.; Duffield, S.; Liu, Y. C.; Bradford, E.; Ricci, E.; Susanne, F.; Rutter, A. Mixing Performance Evaluation for Commercially Available Micromixers Using Villermaux-Dushman Reaction Scheme with the Interaction by Exchange with the Mean Model. *Org. Process Res. Dev.* **2017**, *21*, 816–820.

(23) Szeto, J.; Vu, V. A.; Malerich, J. P.; Collins, N. Multi-Step Continuous Flow Synthesis of Fluconazole. *J. Flow Chem.* **2019**, *9*, 35–42.

(24) (a) 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. (b) 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.