

## External Trapping of Halomethylithium Enabled by Flow Microreactors

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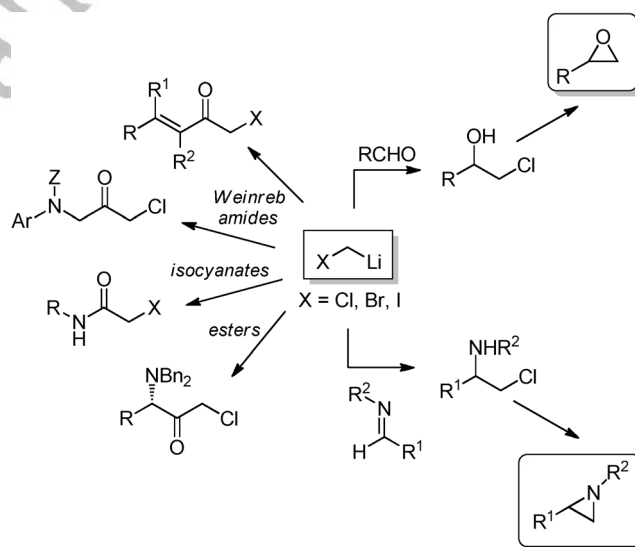
**Abstract:** This work demonstrates that the accurate control of the reaction parameters realized within microreactor systems allowed for a taming of the reactivity of thermally unstable intermediates such as haloalkyllithiums. The first example of effective external trapping of a reactive carbenoid such as the chloromethylithium is described. By using microreactor systems, a continuous flow synthesis of chloro alcohols and chloro amines could be achieved with high yields. By controlling the residence time the highly reactive chloromethylithium could be generated and reacted with electrophiles at temperatures much higher than in batch-mode and without internal quenching. The developed continuous-flow process matches the requirements for sustainability.

**Keywords:** carbenoids; flow chemistry; microreactor technology; organolithiums; sustainable chemistry

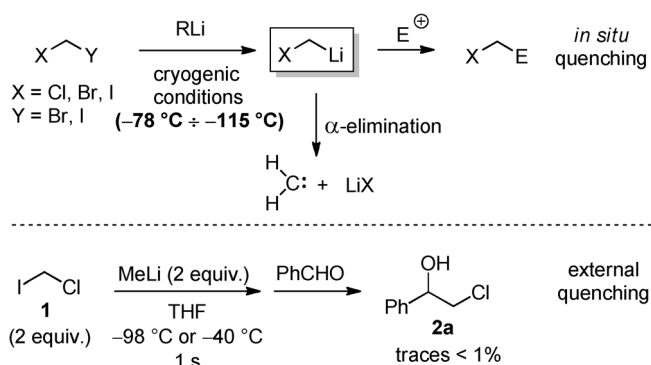
are precursors of useful building blocks such as epoxides and aziridines.<sup>[10]</sup>

Nevertheless, in order to exploit the nucleophilic reactivity, the generation of halomethylithiums requires a lithium–halogen exchange reaction under cryogenic conditions (usually below  $-78^{\circ}\text{C}$ ) in the presence of the electrophile (Scheme 2).<sup>[11]</sup> Such experimental factors are mandatory to reach high conversion and acceptable yields. The temperature for the lithium/halogen permutation reaction is a very important parameter in the use of such carbenoidic species. In fact, relatively high temperatures promote a metal-assisted  $\alpha$ -elimination with formation of carbene-like species and thus, they preclude the reactivity as nucleophiles.<sup>[12,13]</sup> Moreover, to the best of our knowledge, effective protocols for the external trapping, even at low temperature, of halomethylithiums have not been reported. For the sake of argument, we

$\alpha$ -Haloalkyllithiums are often referred to as carbenoids because of their dichotomic reactivity (as nucleophiles and electrophiles) that has been exploited to carry out various fundamental synthetic transformations.<sup>[1]</sup> Since the seminal works by Kobrich during the 1960s, the importance of this class of organometallic reagents in synthetic chemistry has been widely demonstrated.<sup>[2]</sup> In fact, reactive species such as haloalkyllithiums, have been thoroughly employed for homologation-type reactions of various carbonyl derivatives such as aldehydes,<sup>[3]</sup> ketones,<sup>[4]</sup> imines,<sup>[5]</sup> acyl halides,<sup>[6]</sup> esters,<sup>[7]</sup> Weinreb amides<sup>[8]</sup> and isocyanates<sup>[9]</sup> (Scheme 1). In addition, the direct introduction of a halomethyl unit into carbonyl compounds and imines gives access to  $\beta$ -halo alcohols and amines that



**Scheme 1.** Synthetic use of halomethylithiums in homologation reactions.



**Scheme 2.** Genesis and reactivity of halomethylolithiums.

reinvestigated the external trapping reaction of chloromethylolithium (CML) generated by reaction of chloriodomethane **1** with MeLi at  $-98^{\circ}\text{C}$  and  $-40^{\circ}\text{C}$  (Scheme 2). Attempts at trapping with neat benzaldehyde after only 1 second failed in both cases. Only traces of chlorohydrin **2a** were detected by GC-MS analysis.

For this reason, we have taken into consideration the possibility to use the advantages of microreactor technology, in order to control the thermal (and chemical) instability of CML, to avoid decomposition and pursuing its external quenching in a more sustainable way. Seminal works by Yoshida and co-workers, demonstrated that flow microreactors enable reactions involving highly unstable organolithiums even in the presence of sensitive functional groups (i.e., carbonyl, ester, nitro groups).<sup>[14]</sup>

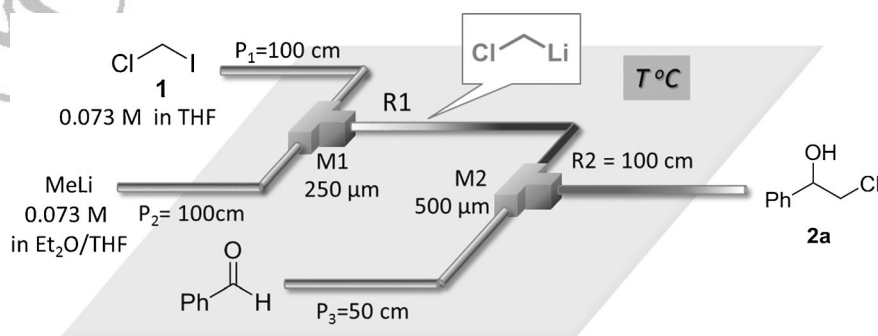
The same author introduced the concept of flash chemistry that is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce the desired compounds with high selectivity.<sup>[15]</sup>

The main advantages of microreactors and continuous flow systems lie in the improved heat and mass transfer, short residence times, precise reaction control, with possibility to automate the process, higher safety in using reactive and hazardous materials and more sustainability.<sup>[16]</sup> In continuation of a research

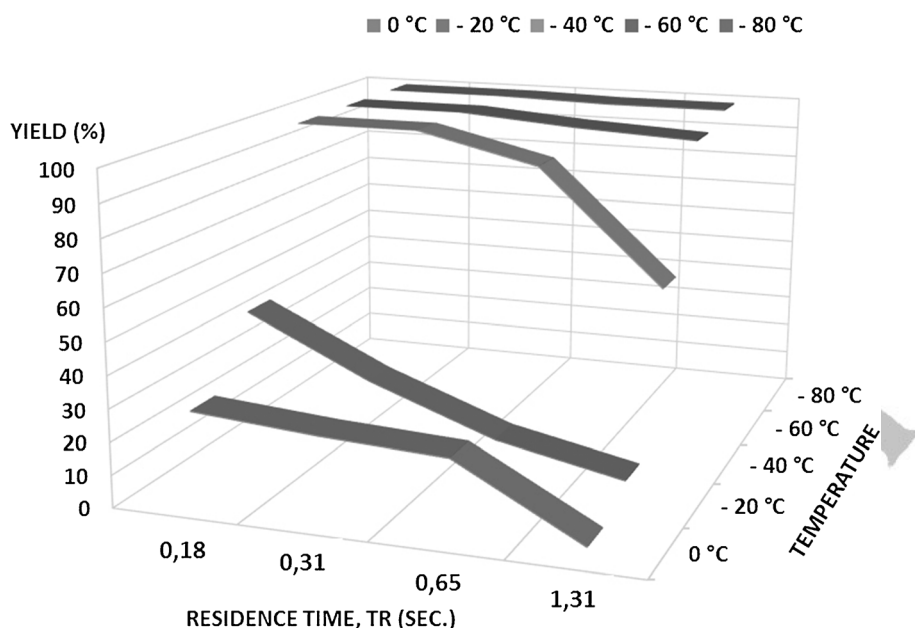
activity aimed at developing more sustainable chemical processes mediated by organolithiums and organocatalysts by using flow microreactor technology,<sup>[17]</sup> we report herein a preliminary study on the external trapping of CML generated under the flow regime. For this study, we used a flow microreactor system consisting in two T-shaped stainless steel micromixers (M1 and M2), three pre-cooling units (P1, P2 and P3) and two microtube reactors (R1 and R2) (Figure 1).

Optimization experiments were carried out feeding the microflow system with a 0.073 M THF solution of chloriodomethane **1**, a commercially available solution of methylolithium in diethyl ether/THF 0.073 M, and a 0.1 M THF solution of benzaldehyde in THF (Figure 1). The reactants were introduced into the microreactor system by using syringe pumps. The residence times in R1 ( $t^{\text{R}}$ ) were determined by choosing properly the length of the microtube reactor R1 (see the Supporting Information) and the flow rates. In the search for the optimal reaction conditions, equimolar amounts of **1** and MeLi were used and the stoichiometric ratio between CML and the electrophile (PhCHO) was kept at 2 equiv. to 1 equiv., respectively. With the aim to tame the thermal instability of CML, the most important parameters varied in the optimization study were the temperature and the residence time. The results obtained are summarized in the plot in Figure 2.

We were pleased to find that CML could be effectively trapped with benzaldehyde working at low temperatures (below  $-60^{\circ}\text{C}$ ) in a wide range of residence times (i.e., 0.18–1.31 s). In fact, adduct **2a** was formed in high yields ( $>93\%$ ) under these reaction conditions. In addition, from these data we could speculate that the lithium/halogen exchange reaction is a very fast process and that CML could survive long enough to allow its external trapping. In fact, high yields were observed with either 0.18 s or 1.31 s as residence time. Conducting the reaction using longer residence times resulted in a drop of the yields. The thermal instability was faced by conducting the process at higher temperature. Working at  $-40^{\circ}\text{C}$ , it was possible to get higher yields of **2a** only by using shorter residence



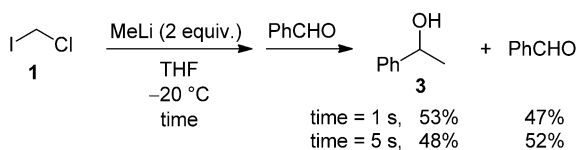
**Figure 1.** Flow microreactor system employed for the external trapping of chloromethylolithium.



**Figure 2.** External quenching of CML: effect of temperature and residence time on the yields. All the experiments were conducted using 2 equiv. of **1**, 2 equiv. of MeLi and 1 equiv. of PhCHO.

times (0.18–0.31 s). Longer residence times were deleterious for the yields. The reactions were conducted even at  $-20^{\circ}\text{C}$  and  $0^{\circ}\text{C}$ . In both conditions, the trapping product **2a** was observed, with moderate yields using very short residence time (0.18 s). Nevertheless, using 0.18 s as the residence time allows for the external trapping of CML at  $0^{\circ}\text{C}$  leading to **2a** with 28% yield. These observations are quite surprising and prove the potential of microreactor systems. In fact, external trapping of CML at  $0^{\circ}\text{C}$  in batch conditions was practically impossible.<sup>[18]</sup> However, we attempted the external trapping of CML at  $-20^{\circ}\text{C}$  after 1 sec and 5 sec (Scheme 3) but only adduct **3**, deriving from the nucleophilic attack of MeLi to benzaldehyde, was recovered together with unreacted aldehyde.

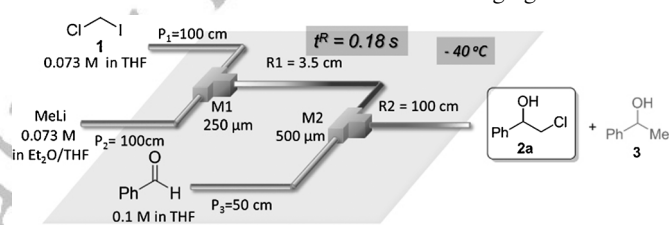
The amount of the lithiating agent was investigated next. The flow microreactor system depicted in Table 1, was fed with variable amounts of **1** and MeLi by using a residence time of 0.18 sec and working at  $-40^{\circ}\text{C}$ . The results reported in Table 1 show how yields and conversions are dependent on the ratio of **1** and MeLi. Maximum conversion and selectivity could be obtained using 2 equiv. of **1** and 2 equiv. of MeLi.



**Scheme 3.** External quenching of chloromethylolithium (CML) in batch conditions.

With the aim to minimize degradative  $\alpha$ -elimination of CML, according to pioneering studies by Villieras,<sup>[19]</sup> and recent findings by Pace and co-workers,<sup>[8–9]</sup> the use of the complex MeLi–LiBr was also considered (Table 2). The use of the microflow system in Figure 1, with 0.31 s and 0.65 s of residence time at

**Table 1.** Evaluation of the amount of lithiating agent.



<b>1</b> (equiv.)	MeLi (equiv.)	<b>2a</b> <sup>[a]</sup>	<b>3</b> <sup>[a]</sup>	PhCHO <sup>[a]</sup>
1.1 <sup>[b]</sup>	1.1 <sup>[b]</sup>	66%	17%	17%
1.5 <sup>[c]</sup>	1.5 <sup>[c]</sup>	75%	15%	10%
2 <sup>[d]</sup>	2 <sup>[d]</sup>	> 98%	–	–
2.5 <sup>[e]</sup>	2.5 <sup>[e]</sup>	> 98%	–	–
3 <sup>[f]</sup>	3 <sup>[f]</sup>	> 98%	–	–

<sup>[a]</sup> Yields calculated by <sup>1</sup>H NMR.

<sup>[b]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>; PhCHO 3 mL min<sup>-1</sup>.

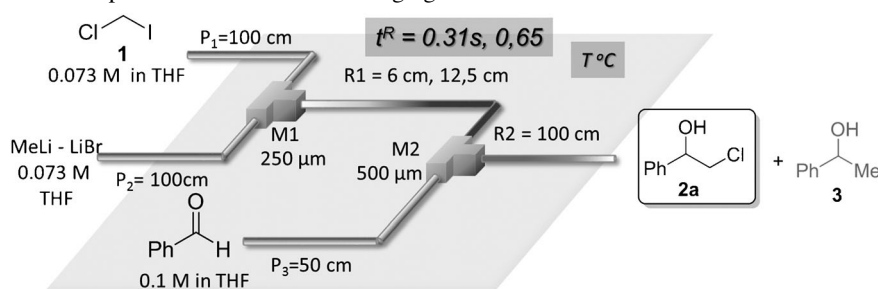
<sup>[c]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>; PhCHO 2.2 mL min<sup>-1</sup>.

<sup>[d]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>; PhCHO 1.65 mL min<sup>-1</sup>.

<sup>[e]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>; PhCHO 1.32 mL min<sup>-1</sup>.

<sup>[f]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>; PhCHO 1.1 mL min<sup>-1</sup>.

**Table 2.** Evaluation of the complex MeLi-LiBr as lithiating agent.



$t^R$ (s)	Temp. [°C]	<b>2a</b> <sup>[a]</sup>	<b>3</b> <sup>[a]</sup>	Note
0.31 <sup>[b]</sup>	0	–	–	clogging
0.31 <sup>[b]</sup>	–20	> 98%	0	–
0.31 <sup>[b]</sup>	–40	> 98%	–	–
0.65 <sup>[c]</sup>	0	–	–	clogging
0.65 <sup>[c]</sup>	–20	74%	– <sup>[d]</sup>	–
0.65 <sup>[c]</sup>	–40	84%	– <sup>[e]</sup>	–

<sup>[a]</sup> Yields calculated by <sup>1</sup>H NMR.

<sup>[b]</sup> Flow rate: **1** = 4.5 mL min<sup>–1</sup>; MeLi = 4.5 mL min<sup>–1</sup>; PhCHO 3 mL min<sup>–1</sup>.

<sup>[c]</sup> Flow rate: **1** = 4.5 mL min<sup>–1</sup>; MeLi = 4.5 mL min<sup>–1</sup>; PhCHO 2.2 mL min<sup>–1</sup>.

<sup>[d]</sup> 26% of unreacted PhCHO.

<sup>[e]</sup> 16% of unreacted PhCHO.

–40 °C and –20 °C allowed to obtain **2a** with good yields. However, even if CML could survive slightly longer times at higher temperature, the microflow system was found to be more subject to clogging problems. Such problems hampered the use of the microflow systems at 0 °C. For these reasons we decided to use the microflow system in Figure 1 in the presence of MeLi.

After assessing the optimal conditions to perform the generation and trapping of CML in a microflow system, the scope of the methodology was probed (Table 3). The reactions were conducted at –40 °C using 0.18 s as residence time. We were pleased to find that the CML could be effectively trapped with several electrophilic entities in very good to excellent yields. The reaction occurred smoothly with carbonyl compounds (aldehydes and ketones) leading to chloroalcohols **2b–l** (Table 3, entries 1–11) The reaction proceeded with excellent results even with notoriously difficult carbonyl derivatives such as enolizable ketones (entries 9, 11) or nitro-substituted aromatic aldehyde (entry 5).<sup>[20]</sup> The microflow system proved to be successful for trapping of CML even with hindered or heterosubstituted aldehydes (entries 4 and 6). The microflow system allows also the reaction of CML with imines leading to chloro amines **2m–p** in good yields and without traces of aziridines deriving from an intramolecular cyclization (Table 3, entries 12–15).<sup>[5a,b]</sup> The process has been effectively applied also to a Weinreb amide and an isocyanate obtaining ad-

ducts **2q** and **2r**, respectively (Table 3, entries 16 and 17).

The developed process was further tested in the presence of a chiral ligand such as (–)-sparteine.<sup>[21]</sup> Yoshida reported recently on the possibility to control the stereochemistry of lithiated intermediates in the presence of this chiral ligand and in a microflow system.<sup>[22]</sup> The microflow system reported in Table 4 was fed with a solution containing an equimolar amount of **1** and (–)-sparteine and a solution of MeLi. The reaction was conducted at several temperatures and with a fixed residence time of 0.31 s. According to the results obtained in the absence of the chiral ligand (*vide infra*), good yields of adduct **2a** were observed at temperatures below –40 °C. Nevertheless, the effect of the chiral ligand was negligible, the sample of **2a** always being racemic.

The performance of the process was also evaluated by running the microflow system in Figure 1, under the optimized conditions, for 4 h without any problem. Chlorohydrins **2a** and **2e** were prepared with a productivity of 1–1.5 g h<sup>–1</sup>. This aspect is important considering the interest in the use of lithium halocarbenoids for continuous flow synthesis.<sup>[23]</sup>

In conclusion, this work tries to harness the role and potentials of microflow systems in modern synthetic chemistry. We have demonstrated that the accurate control of the reaction parameters, in a microreactor system, allowed for a taming of the reactivity of thermally unstable intermediates such as haloalkyllithiums. Controlling the residence time, the highly re-

**Table 3.** Scope of the generation and external trapping of CML in a microflow system.

Entry	Electrophile	Product	Yield <sup>[a]</sup>
1			<b>2b</b> 92%
2			<b>2c</b> 98%
3			<b>2d</b> 80%
4			<b>2e</b> >98%
5			<b>2f</b> 72%
6			<b>2g</b> >98%
7			<b>2h</b> 70%
8			<b>2i</b> 98%
9			<b>2j</b> 80%
10			<b>2k</b> 70%
11			<b>2l</b> 98%
12			<b>2m</b> 83%
13			<b>2n</b> 85%
14			<b>2o</b> 75% <sup>[b]</sup>
15			<b>2p</b> 78% <sup>[c]</sup>
16			<b>2q</b> 70%
17			<b>2r</b> 75%

**Table 4.** Attempts for microflow-enabled enantioselective addition of CML.

$t^R$	Temp. [°C] <sup>[a]</sup>	<b>2a</b> [%] <sup>[b]</sup>	PhCHO [%] <sup>[b]</sup>	<i>er</i> ( <b>2a</b> ) <sup>[c]</sup>
0.31 s	-20	25	75	50:50
0.31 s	-40	82	18	50:50
0.31 s	-60	98	2	50:50
0.31 s	-80	98	2	50:50

<sup>[a]</sup> Flow rate: **1** = 4.5 mL min<sup>-1</sup>, MeLi = 4.5 mL min<sup>-1</sup>, PhCHO 3 mL min<sup>-1</sup>.

<sup>[b]</sup> Yields calculated by <sup>1</sup>H NMR.

<sup>[c]</sup> Ascertained by chiral HPLC analysis.

active chloromethylolithium could be generated and reacted with electrophiles at temperatures much higher than in batch-mode and without internal quenching. Under the microflow conditions, the reaction of chloromethylolithium with a broad variety of electrophiles has been accomplished. The process has also elements of sustainability. To the best of our knowledge, this work represents the first example of the effective external trapping of a reactive carbenoid such as the chloromethylolithium.

## Experimental Section

### Procedure

The employed flow microreactor system consists of two stainless steel T-shaped micromixers, M1 ( $\phi = 250 \mu\text{m}$ ) and M2 ( $\phi = 500 \mu\text{m}$ ), two stainless steel microtube reactors, R1 (inner diameter  $\phi = 1000 \mu\text{m}$ , length  $L = 3.5 \text{ cm}$ ), and R2 (inner diameter  $\phi = 1000 \mu\text{m}$ , length  $L = 100 \text{ cm}$ ), and three stainless steel tubes as pre-cooling units, P1 (inner diameter  $\phi = 1000 \mu\text{m}$ , length  $L = 100 \text{ cm}$ ) and P3 (inner diameter  $\phi = 1000 \mu\text{m}$ , length  $L = 50 \text{ cm}$ ). The microreactor was dipped in a cooling bath at  $-40^\circ\text{C}$ . A solution of  $\text{ClCH}_2\text{I}$  **1** (0.073 M) in THF (flow rate: 4.50 mL min<sup>-1</sup>) and a solution of MeLi (0.073 M) in THF (flow rate: 4.5 mL min<sup>-1</sup>) were introduced into M1 by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile

<sup>[a]</sup> Yields of isolated products.

<sup>[b]</sup> A mixture of diastereomers was isolated, *dr*: 60:40.

<sup>[c]</sup> A mixture of diastereomers was isolated, *dr*: 50:50.

(0.1M) in THF (flow rate: 1.65 mL min<sup>-1</sup>) in M2. The resulting solution was passed through R2. After a steady state had been reached, the product solution was collected for 60 s or longer while being quenched with NH<sub>4</sub>Cl (saturated aqueous solution, 1 mL). The reaction mixture was poured into water (10 mL) and extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum. Flash chromatography on the crude afforded the chloromethyl-substituted products **2a–r**.

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## References

- [1] a) M. Braun, in: *The Chemistry of Organolithium Compounds*, (Eds. Z. Rappoport, I. Marek), John Wiley and Sons, Chichester, **2004**; b) H. Siegel, *Top. Curr. Chem.* **1982**, *106*, 55–78; c) H. Hermann, J. C. W. Lohrenz, A. Kühn, G. Boche, *Tetrahedron* **2000**, *56*, 4109–4115; d) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697–756; e) V. Pace, *Aust. J. Chem.* **2014**, *67*, 311.
- [2] G. Köbrich, A. Akhtar, F. Ansari, W. E. Breckoff, H. Büttner, W. Drischel, R. H. Fischer, K. Flory, H. Fröhlich, W. Goyert, H. Heinemann, I. Hornke, H. R. Merkle, H. Trapp, W. Zündorf, *Angew. Chem.* **1967**, *79*, 15; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 41.
- [3] a) K. M. Sadhu, D. S. Matteson, *Tetrahedron Lett.* **1986**, *27*, 795; b) T. J. Michnick, D. S. Matteson, *Synlett* **1991**, 631; c) D. C. Kapeller, F. Hammerschmidt, *J. Am. Chem. Soc.* **2008**, *130*, 2329.
- [4] a) J. M. Concellón, H. Cuervo, R. Fernández-Fano, *Tetrahedron* **2001**, *57*, 8983; b) V. Pace, L. Castoldi, W. Holzer, *Adv. Synth. Catal.* **2014**, *356*, 1761; c) J. Barluenga, L. Llavona, P. L. Bernad, J. M. Concellón, *Tetrahedron Lett.* **1993**, *34*, 3173; d) J. Barluenga, B. Baragaña, J. M. Concellón, *J. Org. Chem.* **1999**, *64*, 2843.
- [5] a) J. M. Concellón, H. Rodríguez-Solla, C. Simal, *Org. Lett.* **2008**, *10*, 4457; b) J. M. Concellón, H. Rodríguez-Solla, P. L. Bernad, C. Simal, *J. Org. Chem.* **2009**, *74*, 2452; c) J. A. Bull, T. Boultonwood, T. A. Taylor, *Chem. Commun.* **2012**, *48*, 12246; d) T. Boultonwood, D. P. Affron, A. D. Trowbridge, J. A. Bull, *J. Org. Chem.* **2013**, *78*, 6632.
- [6] J. Barluenga, J. L. Fernandez-Simon, J. M. Concellon, M. Yus, *J. Chem. Soc. Perkin Trans. 1* **1989**, 77.
- [7] a) J. Barluenga, B. Baragaña, A. Alonso, J. M. Concellón, *J. Chem. Soc. Chem. Commun.* **1994**, 969; b) J. Barluenga, B. Baragaña, J. M. Concellón, *J. Org. Chem.* **1995**, *60*, 6696; c) J. Barluenga, B. Baragaña, J. M. Concellón, A. Piñera-Nicolás, M. R. Díaz, S. García-Granda, *J. Org. Chem.* **1999**, *64*, 5048; d) C. J. Kowalski, R. E. Reddy, *J. Org. Chem.* **1992**, *57*, 7194.
- [8] a) V. Pace, W. Holzer, G. Verniest, A. R. Alcántara, N. De Kimpe, *Adv. Synth. Catal.* **2013**, *355*, 919; b) V. Pace, L. Castoldi, W. Holzer, *J. Org. Chem.* **2013**, *78*, 7764.
- [9] V. Pace, L. Castoldi, W. Holzer, *Chem. Commun.* **2013**, *49*, 8883.
- [10] a) J. B. Sweeney, in: *Aziridines and Epoxides In Organic Synthesis*, (Ed.: A. Yudin), Wiley-VCH, Weinheim, **2006**, pp 117–144; b) V. Capriati, S. Florio, R. Luisi, *Chem. Rev.* **2008**, *108*, 1918; c) L. Degennaro, P. Trincherà, R. Luisi, *Chem. Rev.* **2014**, DOI: 10.1021/cr400553c.
- [11] An isolated work reports the generation and *in-situ* trapping of CML at –15 °C under sonochemical conditions by using lithium metal, see: C. Einhorn, C. Allavena, J.-L. Luche, *J. Chem. Soc. Chem. Commun.* **1988**, 333.
- [12] A tactic to prolong the life-time of consists in the introduction of anion-stabilizing groups, for examples, see: a) S. Florio, V. Capriati, R. Luisi, *Curr. Org. Chem.* **2004**, *8*, 1529; b) X. Sun, P. R. Blakemore, *Chem. Eur. J.* **2013**, *19*, 16342, and references cited therein.
- [13] Examples of "stabilized" chloro carbenoids stable at room temperature have been recently reported, see: C. Kupper, S. Molitor, V. H. Gessner, *Organometallics* **2014**, *33*, 347, and references cited therein.
- [14] a) A. Nagaki, J. Yoshida, *Microreactor Technology in Lithium Chemistry*, in: *Lithium Compounds in Organic Synthesis from Fundamentals to Applications*, (Eds.: R. Luisi, V. Capriati) Wiley-VCH, Weinheim, **2014**, p 491; b) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264.
- [15] a) J.-i. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, **2008**; b) J. Yoshida, *Chem. Commun.* **2005**, 4509; c) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; d) J. Yoshida, *Chem. Rec.* **2010**, *10*, 332; e) J.-i. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.
- [16] For selected reviews and books see: a) W. Ehrfeld, V. Hessel, H. Lowe, in: *Microreactors*, Wiley-VCH, Weinheim, **2000**; b) V. Hessel, S. Hardt, H. Lowe, in: *Chemical Micro Process Engineering*, Wiley-VCH, Weinheim, **2004**; c) T. Wirth, in: *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, 2<sup>nd</sup> edn., **2013**; d) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem.* **2011**, *123*, 7642; *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; e) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; f) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38.
- [17] a) A. Giovine, B. Musio, L. Degennaro, A. Falcicchio, A. Nagaki, J. Yoshida, R. Luisi, *Chem. Eur. J.* **2013**, *19*, 1872; b) L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi, R. Luisi, *J. Flow Chem.* **2013**, *3*, 29; c) V. Pace, R. Luisi, *ChemCatChem* **2014**, *6*, 1516.
- [18] All the attempts for the trapping of CML at 0 °C failed. We were aware that at higher temperature the expected chlorohydrin could cyclize giving the corresponding epoxide. However, <sup>1</sup>H NMR analysis of the crude reaction mixture revealed the presence of benzaldehyde and traces of adduct **3**.

- 1 [19] R. Tarhouni, B. Kirschleger, M. Rambaud, J. Villieras, *Tetrahedron Lett.* **1984**, 25, 835. 1  
2  
3 [20] It is worth mentioning that the preparation of chloro- 2  
4 hydrin **2f**, performed in batch-mode under internal 3  
5 quenching conditions, proceeded with very low yields. 4  
6 [21] a) I. Marek, *Advances in Carbolithiation*, in: *Lithium* 5  
7 *Compounds in Organic Synthesis from Fundamentals to* 6  
8 *Applications*, (Eds.: R. Luisi, V. Capriati), Wiley-VCH, 7  
9 Weinheim, **2014**, p 329; b) J.-F. Normant, in: *Organo-* 8  
10 *lithiums in Enantioselective Synthesis*, Vol. 5, (Ed.: 9  
11 D. M. Hodgson), Springer, Berlin, **2003**, p 287; c) S. 10  
12 Klein, I. Marek, J.-F. Poisson, J.-F. Normant, *J. Am.* 11  
13 *Chem. Soc.* **1995**, 117, 8853. 12  
14 [22] Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* 13  
15 **2011**, 133, 3744. 14  
16 [23] For recent examples, see: a) J. Hartwig, J. B. Metter- 15  
17 nich, N. Nikbin, A. Kirschning, S. V. Ley, *Org. Biomol.* 16  
18 *Chem.* **2014**, 12, 3611; b) T. Broom, M. Hughes, B. G. 17  
19 Szczepankiewicz, K. Ace, B. Hagger, G. Lacking, R. 18  
20 Chima, G. Marchbank, G. Alford, P. Evans, C. Cun- 19  
21 ningham, J. C. Roberts, R. B. Perni, M. Berry, A. 20  
22 Rutter, S. A. Watson, *Org. Process Res. Dev.* DOI: 21  
23 10.1021/op400090a. 22  
24  
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## 8 External Trapping of Halomethylolithium Enabled by Flow Microreactors

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Renzo Luisi\*