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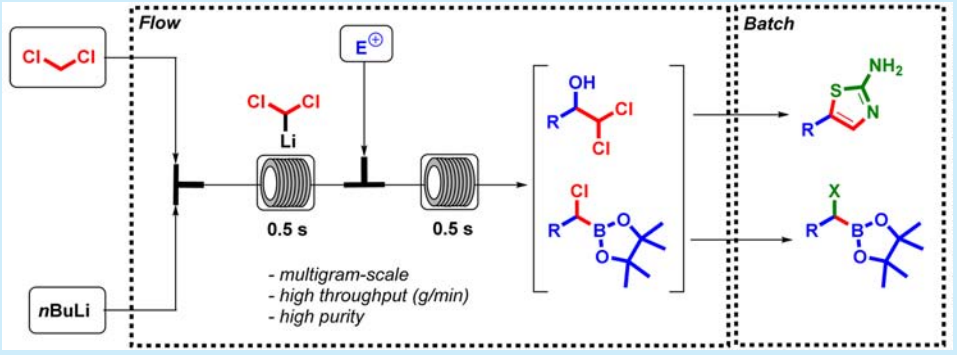
Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode

Andreas Hafner,* Valentina Mancino, Mark Meisenbach, Berthold Schenkel, and Joerg Sedelmeier*

Novartis Pharma AG, Novartis Campus, 4002 Basel, Switzerland

Supporting Information



ABSTRACT: A simple and robust procedure for the synthesis and use of thermally unstable dichloromethyllithium in continuous flow mode is described. By utilizing residence times in the range of milliseconds for the generation and electrophilic quench of dichloromethyllithium, the straightforward synthesis of dichlorocarbinols and benzylic pinacol esters was realized at reaction temperatures of −30 °C, whereas typical temperatures in traditional batch mode are below −78 °C. The excellent purity profile obtained from the flow process allows us to directly telescope the exiting flow stream into semibatch quenches for further modifications. All transformations gave the desired products in remarkable purity and yield on gram scale with no need for chromatography.

Various examples in the literature demonstrate the synthetic usefulness of dichloromethyllithium (DCMLi) as an organometallic intermediate in organic chemistry.[1] Addition of DCMLi to carbonyl compounds provides *β*,*β*-dichloromethyl carbinols, which represent useful building blocks for further functionalization toward entities such as epoxides, *O*,*O*-acetals, aldehydes, styrenes, *α*,*α*-dichloromethyl ketones, terminal alkynes, and many heterocyclic compounds.[1,2] In addition, among many other transformations, DCMLi allows the direct chain homologation of arylboronic esters,[3] giving access to valuable benzylic (*α*-chloro) boronic esters, a substrate class of enormous synthetic value.[4]

Although the broad applicability of DCMLi is well reported in the literature, its usage, especially on a larger scale, is limited due to the labile nature of the metallic species. The generation of dichloromethyllithium from dichloromethane and *n*BuLi or lithium amine bases (e.g., LiHMDS, LDA) in traditional batch mode requires very low cryogenic temperatures (IT = −78 to −100 °C) to suppress the formation of a carbene species and consecutive degradation pathways.[1−3,5] Consequently, the utilization of DCMLi in batch mode is restricted to either small-scale applications or requires specialized (expensive) low-temperature equipment.

Due to well-known issues and risks on scale-up of organolithium chemistries,[6] we envisioned benefitting from the advantages of continuous flow technologies[7] in order to gain enhanced control over the unstable DCMLi, to avoid its decomposition, and to pursue its in-line quench to limit its existence to a minimum.[8] A flow metalation platform facilitating the safe and reliable handling of DCMLi at noncryogenic temperatures would not only further promote its application in organic synthesis but also simplify the scale-up process of dichloromethyllithium reactions.

Previously, we reported on a continuous flow platform dedicated to organolithium chemistry which combines short residence times (<1 s) with high throughputs (∼1 g/min), allowing for the synthesis of numerous aryl boronic acids on a multigram scale.[9] Inspired by the identified advantages of this platform and with an appropriate scale-up concept toward higher throughputs (1800 mmol/h) in place,[10] we envisioned application of this concept to the synthesis and control of unstable DCMLi.

As a starting point for our investigation, we used our previously optimized flow setup consisting of simple PTFE T-pieces (i.d. = 0.5 mm) as mixing elements and PFA tubing as tubular reactors (i.d. = 0.8 mm). Total flow rates of ∼20 mL/min per mixing element are essential to ensure highly efficient mixing and short mixing times (∼500 ms), which are key

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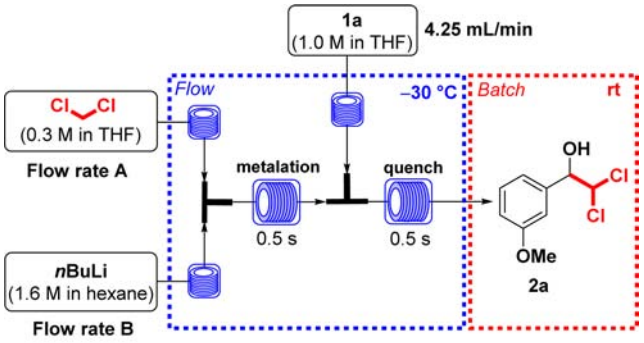
factors to obtain clean reaction profiles (for more details, see the Supporting Information).

To explore the chemistry of DCMLi, we first chose the transformation of 3-methoxybenzaldehyde (**1a**) to the corresponding carbinol (**2a**) as a test reaction (Scheme 1). An initial

Scheme 1. Optimization of Reaction Conditions for the Dichloromethylation of 3-Methoxybenzylaldehyde 1a



DCM (A) mL/min (equiv)	*n*BuLi (B) mL/min (equiv)	conversion to **2a**[a] [a%]
17.0 (1.2)	2.92 (1.1)	89
18.4 (1.3)	2.92 (1.1)	91
18.4 (1.3)	3.20 (1.2)	96
19.8 (1.4)	3.45 (1.3)	96

[a]Conversion was determined by HPLC at λ = 210 nm.

set of experiments was performed to determine the optimal reaction stoichiometry. Full conversion of 3-methoxybenzaldehyde (**1a**) was achieved using 1.3 equiv of dichloromethane and 1.2 equiv of *n*BuLi, and the desired dichloromethylated product **2a** was obtained in 96 area % HPLC yield after 1 s total reaction time (Scheme 1). It should be noted that no decomposition or fouling was observed during the flow operations; however, in batch mode, immediate decomposition and darkening of the reaction solution was observed at −30 °C.[3a]

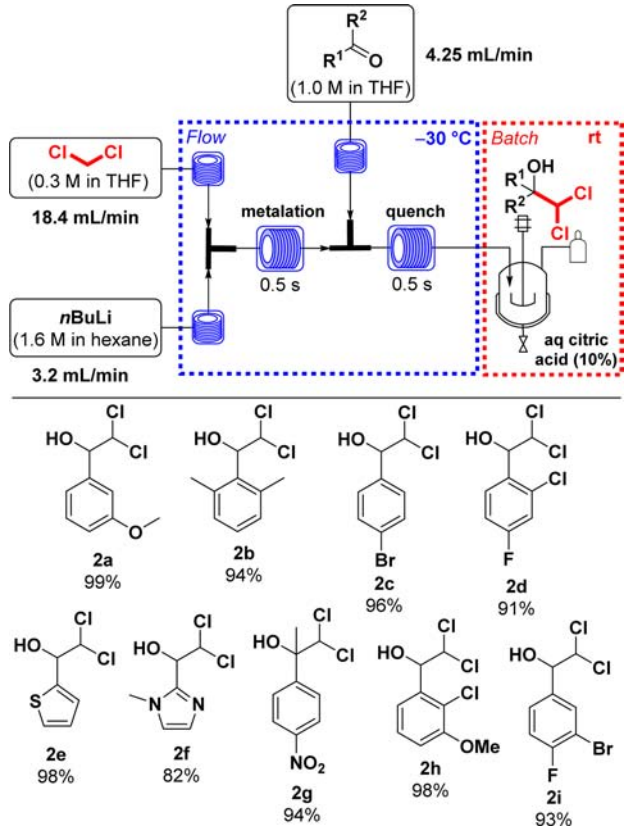
With the optimized reaction conditions for the dichloromethylation of aldehydes in hand, we investigated the scope of this procedure by reacting various aldehydes with DCMLi following the flow procedure depicted in Scheme 2.

Starting from a 0.3 M solution of dichloromethane in THF, DCMLi was rapidly prepared in a first reactor (0.5 s) by mixing with a commercially available solution of *n*BuLi (1.6 M in hexane) at JT = −30 °C. The freshly prepared DCMLi was mixed in a second reactor (0.5 s) with a solution of aldehyde (1.0 M in THF), followed by a semibatch quench onto aqueous citric acid (10%, 0.5 equiv) at room temperature.

As summarized in Scheme 2, various β,β-dichloromethyl carbinols were smoothly synthesized and isolated on gram scale in excellent purity and high yield following a simple extractive workup and evaporation of the organic solvents. Thus, the exiting flow streams were of such high quality that no time-consuming purification such as a chromatography or crystallization was required.

Electron-rich (**2a**,**b**), electron-poor (**2d**,**g**), as well as heterocyclic carbinols (**2e**,**f**) were readily prepared with a throughput of 4.25 mmol/min (~1 g/min) on multigram scale.

Scheme 2. Synthesis of Dichlorocarbinols in Continuous Flow Mode[a,b]



[a]Reactions were performed on 21.25 mmol scale (5 min run). [b]Isolated yield is given.

Remarkably, carbonyls bearing pendant electrophilic functionalities such as bromine, fluorine, and nitro, which are prone to undergo undesired side reactions or to decompose in the presence of organolithium species under conventional batch conditions, reacted smoothly with DMCLi to give the desired products.

To further demonstrate the synthetic value of DCMLi in continuous flow mode and to emphasize the outstanding purity profile of these transformations (>95 area % at λ = 210 nm in all cases), we imagined directly telescoping our continuous flow stream into an additional semibatch transformation. As a test reaction, we were aiming for the direct conversion of the dichloromethylated alcohol **2a** into the corresponding aminothiazole **3a**. Even though the direct telescoping toward aminothiazole **3a** was feasible and conversion by HPLC was high, the precipitation of **3a** from the THF/MeOH solvent mixture was found to be impractical. In contrast, compound **3a** precipitated nicely from pure MeOH. Consequently, the carbinols **2** were used as evaporation residues after a simple extractive workup in traditional batch mode.

Thus, as outlined in Scheme 3, different aminothiazoles[11] were directly accessible in good yields by treatment of the dichloromethylated alcohols **2** with KOH and thiourea without further optimization.

With the gained knowledge of formation and consumption of DCMLi in continuous flow mode, we made an effort to expand the product diversity by changing the third input stream from carbonyl compounds to other electrophiles.

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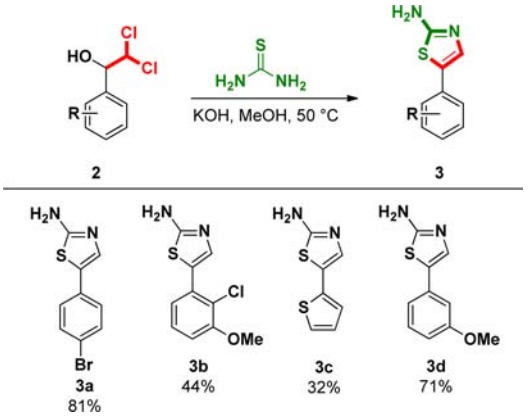
Scheme 3. Synthesis of Aminothiazoles from Dichlorocarbinols[a,b]



[a]Reactions were performed on gram scale (for more details, see the Supporting Information). [b]Isolated yield is given.

The reaction of haloorganolithium compounds with boronic esters discovered by Matteson et al.[3,12] is one of the most interesting homologation reactions in organic chemistry, especially due to the impressive work of the Aggarwal group over recent years demonstrating its synthetic power to build up multiple carbon−carbon bonds in a (stereo)controlled fashion.[13] The key step for modifying boronic esters involves the nucleophilic attack of α-halocarbanions at the boron atom forming a borate complex, followed by a [1,2]-rearrangement.

DCMLi is capable of chain elongation of boronic esters to give α-chloroboronic esters as useful entities in organic synthesis.

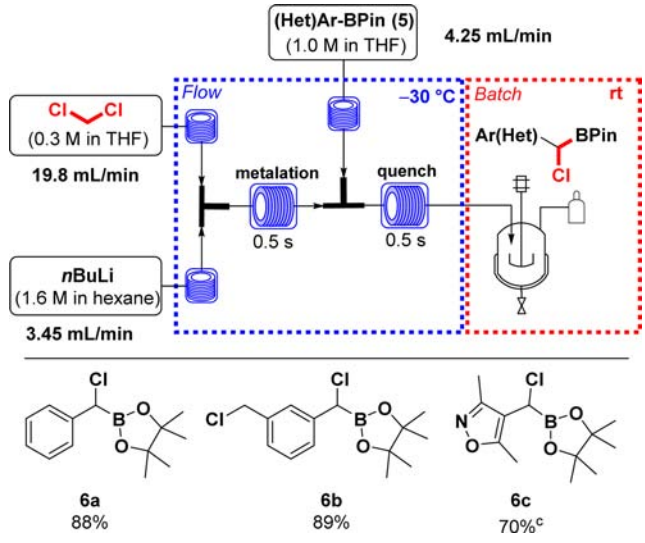
To assess this chemistry in continuous flow mode, we relied on our previously reported procedure and solely optimized the equivalents of reagent by a slight adaption of flow rates. After a quick optimization using phenylboronic pinacol ester (**5a**), we were pleased to obtain the desired benzylic chloroboronic pinacol ester **6a** in good yields by using a slight excess of dichloromethane (1.4 equiv) and *n*BuLi (1.3 equiv) under otherwise identical flow conditions.

These conditions were then directly used to synthesize a few α-chloroboronic esters on gram scale in very good purity and good yields following simple filtration through a plug of silica gel (Scheme 4). Notably, for the formation of the α-chloroboronic esters both transformations, the borate complex formation and the [1,2]-shift occurred within the flow setup.

Given the high quality of the exiting flow stream, we directly quenched the α-chloroboronic esters onto various nucleophiles in semibatch mode. As exemplarily shown in Scheme 5, the crude reaction solution containing the α-chloroboronic ester can be directly reacted with alcoholates or Grignard reagents to afford secondary benzylic boronic pinacol esters or methoxylated analogues in good to very good yields following a simple extractive workup and evaporation of the solvents.

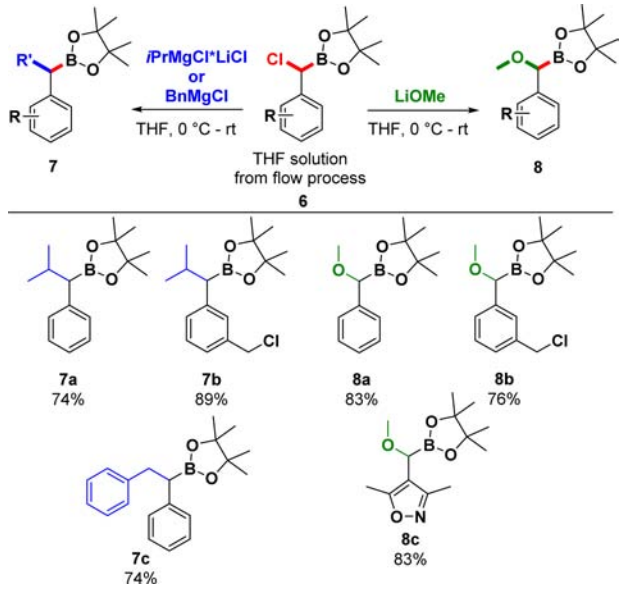
In conclusion, we developed a simple and robust continuous flow process for the generation and in-line consumption of DCMLi on multigram scale following a reaction sequence of *n*BuLi-mediated deprotonation of dichloromethane, electrophilic quench, and semibatch workup. This flow procedure mitigates the typical issues associated with organometallic chemistry on scale and makes the DCMLi reagent more reliable and easy to use under noncryogenic reaction conditions. The presented flow procedure allows for the preparation of valuable

Scheme 4. DCMLi-Mediated Chain Homologation of Boronic Pinacol Esters[a,b]



[a]Reactions were performed on 4.25 mmol scale (1 min run); [b]Isolated yield is given. [c]**6c** showed a strong tendency for decomposition toward the corresponding alcohol after isolation.

Scheme 5. Functionalization of α-Chloroboronic Esters[a,b]



[a]Reactions were performed on 4.25 mmol scale. 1 min of the appropriate flow process was directly quenched on the appropriate reagent in THF at 0 °C in a semibatch manner without any additional purification step. [b]Isolated yield is given.

building blocks within 1 s total reaction time and a remarkable throughput of ~255 mmol/h.

We demonstrated the usefulness of DMCLi in the dichloromethylation of carbonyl compounds and the homologation of phenyl boronic ester toward valuable α-chloro boronic esters. The straightforward concept together with the very high purity profile of the flow process allows for the direct coupling of the flow step with different semibatch quenches, which makes it highly useful for the synthesis of various broadly applicable building blocks. We believe that this concept greatly

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enhances the synthetic utility of DCMLi in organic synthesis and appeals attractive to the scientific community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03753.

Detailed experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: andreas.hafner@bayer.com.
*E-mail: joerg.sedelmeier@novartis.com.

ORCID

Andreas Hafner: 0000-0002-5600-6669
Joerg Sedelmeier: 0000-0002-9683-7918

Notes

The authors declare no competing financial interest.

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