COMMUNICATION

Flow Technology for Telescoped Generation, Lithiation and Electrophilic (C_3) Functionalization of Highly Strained 1-Azabicyclo[1.1.0]butanes

Pantaleo Musci, Timo von Keutz, Ferdinand Belaj, Leonardo Degennaro, David Cantillo, C. Oliver Kappe* and Renzo Luisi*

In memory of Prof. Hans Reich for his outstanding contribution to the chemistry of organolithiums

P. Musci, Prof. Dr. L. Degennaro, Prof. Dr. R. Luisi
Flow Chemistry and Microreactor Technology FLAME-Lab
Department of Pharmacy – Drug Sciences
University of Bari "A. Moro"
Via E. Orabona 4, Bari, 70125 (Italy)
E-mail: renzo.luisi@uniba.it

T. von Keutz, Prof. F. Belaj, Dr. D. Cantillo, Prof. Dr. C. O. Kappe
Institute of Chemistry, University of Graz
Heinrichstrasse 28, 8010, Graz (Austria)
E-mail: oliver.kappe@uni-graz.at
Homepage: http://goflow.at

T. von Keutz, Dr. D. Cantillo, Prof. Dr. C. O. Kappe
Center for Continuous Flow Synthesis and Processing (CC FLOW)
Research Center Pharmaceutical Engineering GmbH (RCPE)
Inffeldgasse 13, 8010 Graz (Austria)

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Abstract: Strained compounds are privileged moieties in modern synthesis. In this context, 1-azabicyclo[1.1.0]butanes are appealing structural motifs that can be employed as click reagents or precursors to azetidines. We herein report the first telescoped continuous flow protocol for the generation, lithiation, and electrophilic trapping of 1-azabicyclo[1.1.0]butanes. The flow method allows for exquisite control of the reaction parameters, and the process operates at higher temperatures and safer conditions with respect to batch mode. The efficiency of this intramolecular cyclization/C3-lithiation/electrophilic quenching flow sequence is documented with more than 20 examples.

Strained compounds are considered privileged scaffolds amenable to a number of useful chemical transformations.[1] In recent work, Baran and coworkers highlighted the potential offered by strained bonds in organic synthesis.[2] In particular, the use of "spring-loaded" hetero- and carbocycles as "click reagents" for rapid and direct installation of small ring bioisosters onto heteroatoms was emphasized, including applications of this strategy in medicinal chemistry. Among such strained compounds, azabicyclo[1.1.0]butanes (**ABB**s) are emerging as useful reagents for the preparation of azetidines.[3] In fact, 1,3-functionalized azetidines can be obtained by strain-release of azabicyclo[1.1.0]butanes (Figure 1a).[4] In this context, Aggarwal reported an interesting approach for the preparation of azetidine boronic esters **1** (Figure 1b).[5] More specifically, the strategy involved the reaction of an alkyl (or aryl) boronate with lithiated 1-azabicyclo[1.1.0]butane (**ABB-Li**). **ABB-Li** was generated by C3-deprotonation of **ABB**, which in turn was prepared *in situ* from 2,3-dibromopropylamine. A remarkable aspect of this synthetic route is that it is the first-ever reported use of a C3-lithiated azabicyclo[1.1.0]butane.[6]

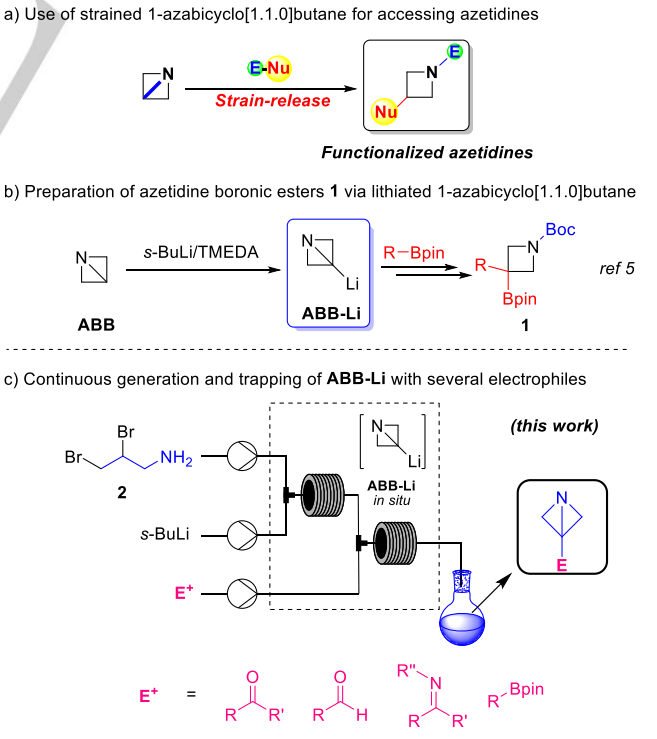
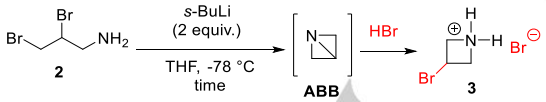


Figure 1. (a) Synthesis and use of strained 1-azabicyclo[1.1.0]butanes, (b) generation and use of lithiated derivatives (ref 5) and (c) proposed flow approach.

An important drawback of the reaction described above for its implementation on synthetically relevant scales is that it requires cryogenic conditions (-78 °C) and > 3 h reaction time. We hypothesized that a continuous flow protocol in which **ABB-Li** is generated and directly consumed in situ with a suitable electrophile in a telescoped process (Figure 1c) would result in a more convenient and scalable procedure. Continuous flow technology permits the design of modular, fit-for-purpose reactors that can be engineered for each reaction step and then assembled into a single machine for carrying out sequential telescoped processes.[7] Moreover, the utilization of microreactor technology typically enables the use of higher temperatures for this type of organometallic reactions,[8] often avoiding the use of cryogenic conditions.[9] We report herein the successful development of a convenient continuous flow protocol for the generation, lithiation, and electrophilic trapping of 1-azabicyclo[1.1.0]butanes, including unprecedented reactions of the lithiated cyclic intermediate with ketones, aldehydes and imines. The three reaction steps were combined in a flexible, modular machine that permitted an easy exchange of the electrophile without the need for re-optimization of the setup.

Our investigation was initiated with a series of batch experiments aimed to assess some critical parameters associated with this process. First, the substitution of the widely employed PhLi with *s*-BuLi for the conversion of dibromoamine **2** into **ABB** was evaluated. This would permit employing a single base for the two-step generation of **ABB-Li**. Second, the thermal stability of **ABB-Li** needed to be evaluated. Thus, dibromoamine **2** was reacted with 2 equiv of *s*-BuLi in THF at -78 °C, and the time required for complete conversion from **2** to **ABB** determined (Table 1). Due to the inherent lability of the **ABB** intermediate, it was reacted with HBr and quantitatively converted into bromo-derivative **3**, a compound that could be readily quantified by ^{1}H NMR monitoring (Table 1).

Table 1. Influence of the reaction time on the generation of **ABB** from **2** (batch)

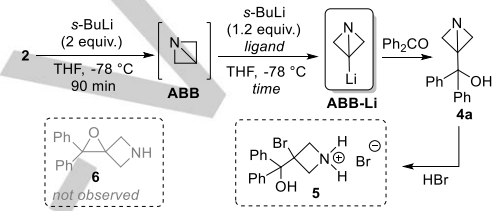


Entry	Time[a]	**3** Yield %[b]
1	15 min	66
2	30 min	72
3	60 min	73
4	**90 min**	**90**
5	105 min	79
6	120 min	77

[a]Time before the addition of HBr. [b]Yields calculated by ^{1}H NMR using 1,3,5-trimethybenzene as internal standard.

Gratifyingly, the reaction proceeded with reasonable yields using *s*-BuLi (Table 1, entries 1-3), and **ABB** could be obtained in 90% yield after 90 min (entry 4). Longer reaction times resulted in lower yields (entries 5 and 6). Assuming 90 min as the optimal reaction time for the generation of **ABB** from **2**, the C3-lithiation was examined next (Table 2). The lithiation of **ABB** was examined with respect to reaction time and effect of a ligand (Table 2). Benzophenone was used as a model electrophile.. The sequential lithiation/trapping reaction from **ABB** furnished 91% yield of strained alcohol **4a** after 75 min in the presence of TMEDA at -78 °C (Table 2, entry 3). In contrast, poor yield (29%) was observed in the absence of TMEDA (entry 4), stressing the importance of the ligand in accelerating the C3-deprotonation.[10] Slightly lower yields were obtained when shorter reaction times were employed (entries 1 and 2). To support the proposed structure of **4a**, quantitative conversion into the strain-released derivative **5** was carried out by reacting **4a** with an excess of HBr. Notably, the intramolecular strain release leading to spiro compound **6** was not observed.

Table 2. Optimization of the sequential generation and lithiation of **ABB** (batch).



Entry	Time[a]	Ligand[b]	Yield **4a** [%] [c]
1	45 min	TMEDA	53
2	60 min	TMEDA	86
3	**75 min**	**TMEDA**	**91**
4	60 min	none	29

[a] Time interval for the generation of ABB-Li. The electrophile was subsequently added and the reaction stirred at rt for 5 min. [b]1.2 equiv of ligand used. [c]Yields calculated by ^{1}H NMR using mesitylene as internal standard.

An additional set of experiments was performed to assess the feasibility of a one pot procedure, consisting of a sequential intramolecular cyclization/C3-lithiation/electrophilic quenching. Thus, the generation of **ABB-Li** from **2** was carried out using 3.2 equiv of *s*-BuLi/TMEDA. The reaction was performed at three different temperatures (-78 °C, -50 °C and -20 °C). Yields of **4a** were determined after different lithiation times (Table S1). Notably, higher temperatures had a positive effect by increasing the reaction rate, albeit negatively affected yields, most likely by promoting the decomposition of **ABB-Li**. Thus, when the reaction was carried out at -78 °C, **4a** could be obtained with 95% yield after 3 h, while at -50 °C **4a** was formed in 90% yield after 2 h. At -20 °C, **4a** was formed with only 70% yield after 1.5 h. Even longer reaction times (>1.5 h) caused a significant drop of the yield at this temperature.

On the basis of the optimization study conducted under batch conditions, the next step was to transfer the one pot process into a flow reactor. A flow system (Figure 2), consisting of two T-shaped micromixers (M1, M2), and two coil reactors (R1, R2), kept at two different temperatures, was employed for optimization purposes (see Supplementary Material for details). To our delight, the reaction performed very well under continuous flow conditions. Importantly, higher temperatures were compatible with the process. Thus, **4a** was obtained in 85% yield at -20 °C and

remarkably, a 92% yield was achieved at 0 °C. These results are in contrast with their batch counterparts: when the same transformation was carried out at 0 °C in a batch vessel, a modest 50% yield of **4a** was obtained. It is worth pointing out that under flow conditions the ligand TMEDA was not required.

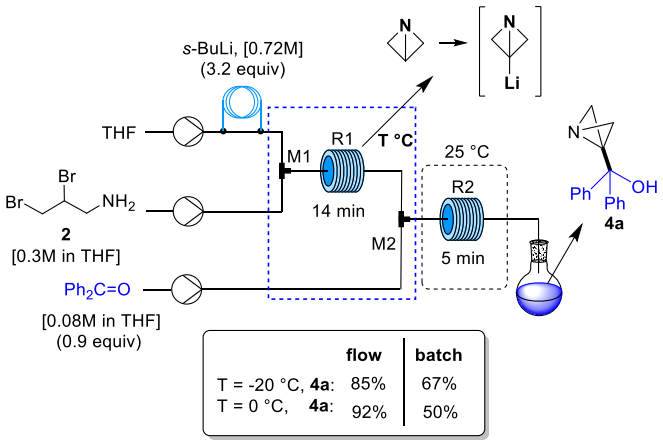
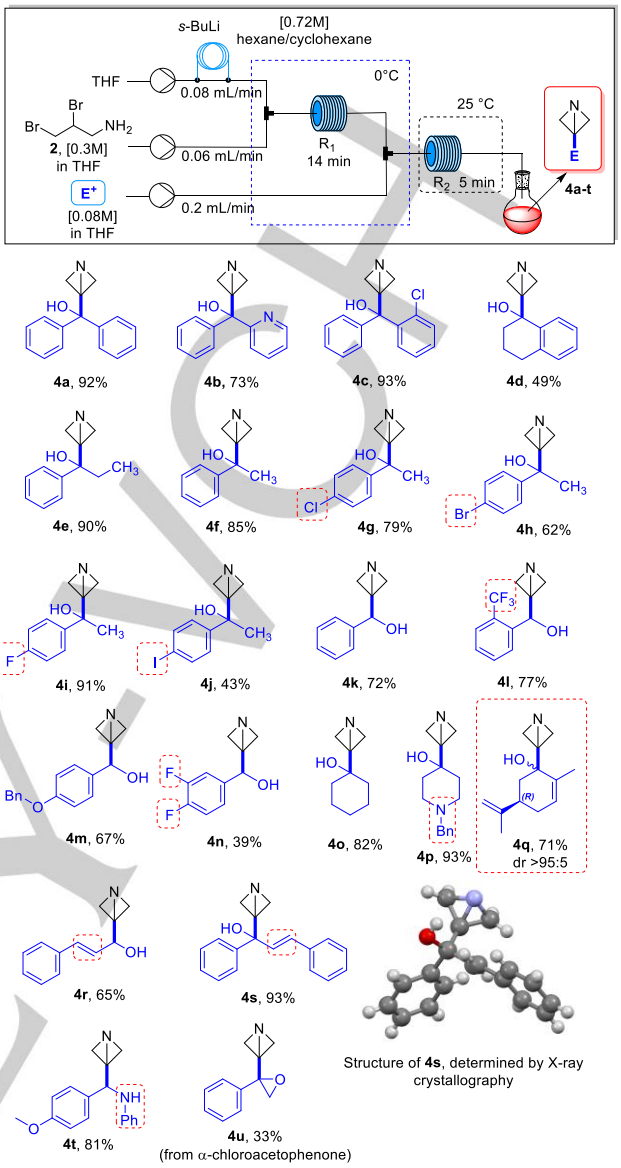


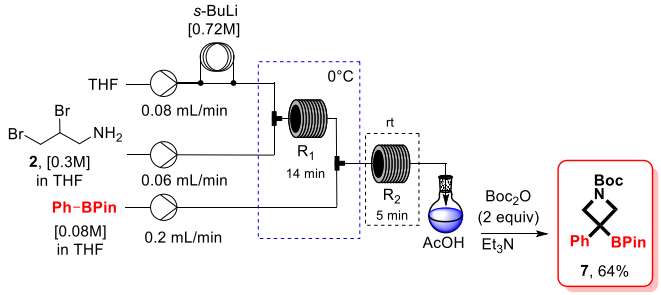
Figure 2. Continuous flow synthesis of C3-functionalized 1-azabicyclo[1.1.0]butane.

Next, the scope and functional group tolerance of the continuous flow process was investigated (Scheme 1). This substrate screen was carried out on a small scale, using NMR monitoring of the crude reaction mixtures to assess the reaction outcome. Characterization of the reaction products was performed using isolated samples from the batch reactions. Product isolation from the reaction mixtures obtained under flow conditions was performed on a larger scale under intensified conditions (*vide infra*). Notably, several unprecedented C3-functionalized 1-aza[1.1.0]bicyclobutanes **4a-u** were obtained in good to excellent yields. Di(hetero)aryl ketones provided the corresponding carbinols **4a-c**. The use of alkyl aryl ketones successfully afforded adducts **4e-j** with good chemoselectivity. The presence of halogens (**4g-j**) was also well tolerated. In the case of non-aromatic ketones, no enolization was observed, and compounds **4o-q** were obtained in good NMR yields. Remarkably, derivatization of (*R*)-carvone proceeded smoothly with high chemo- and stereoselectivity (**4q**).[11] Good results were also obtained when aldehydes were used as substrates (**4k-n**). α,β-Unsaturated aldehydes and ketones were also suitable starting materials under our reaction conditions, furnishing exclusively the 1,2-addition products **4r** and **4s**. Notably, the expected C3-functionalized 1-azabicyclo[1.1.0]butane structure of **4s** could be confirmed by X-ray analysis (Scheme 1).[12] An imine was also evaluated as electrophile, furnishing strained amine **4t**. With α-chloroacetophenone as the substrate, electrophilic addition of **ABB-Li** to the carbonyl group was followed by intramolecular cyclization, providing epoxide **4u** in moderate yield.



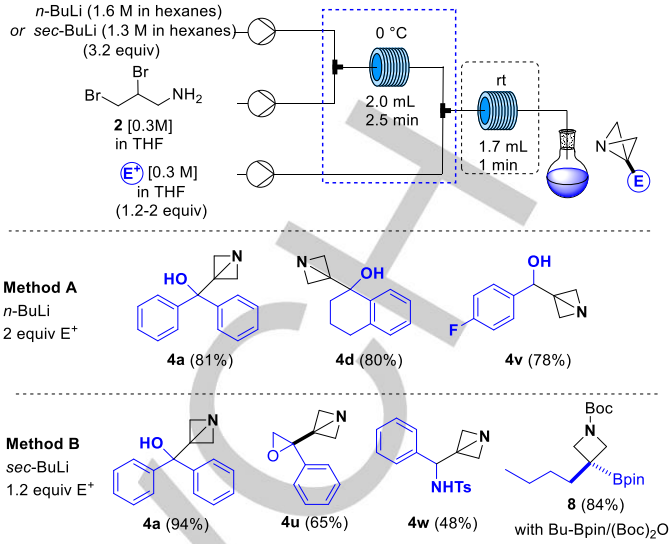
Scheme 1. Continuous flow synthesis of C3-functionalized strained 1-azabicyclo[1.1.0]butanes. NMR yields using 1,3,5-trimethoxybenzene as standard are shown.

To further evaluate the applicability of this telescoped process, we examined Aggarwal's 1,2-metalate rearrangement[5] under continuous flow conditions (Scheme 2).[13] By simply introducing a solution of phenylboronate (PhBPin) as the electrophile feed, the entire sequence consisting of intramolecular cycliczation, C3-lithiation, electrophilic trapping and strain release via 1,2 B to C migration, was accomplished in an one-flow fashion obtaining functionalized azetidine **7** in 64% yield.



Scheme 2. Continuous flow synthesis of azetidine boronic esters via a telescoped cyclization/lithiation/electrophilic trapping and strain release sequence.

After assessing the functional group tolerance of this flow synthesis of C3-functionalized 1-azabicyclo[1.1.0]butanes, we decided to further develop the continuous flow process to increase its efficiency and productivity (Scheme 3). To our delight, in addition to s-BuLi, the less expensive and milder n-BuLi could also be utilized as base (Methods A and B, Scheme 3). The concentration of both reagents could be increased to 1.6 M and 1.3 M for n-BuLi and s-BuLi, respectively. Thus, the commercial solutions of the reagents in hexanes were directly used without dilution. The increased concentration had a significant positive effect on the rate of formation of **ABB-Li**. Under these intensified conditions, the flow rates of the reagent feeds could be increased, resulting in a shortened residence time of only 2.5 min (Scheme 3). The total residence time, including the reaction with the electrophile (1 min) was 3.5 min. Gratifyingly, the improved conditions also increased the yields of products **4** in some cases. Compound **4d**, for example, with which an NMR yield of 49% has been observed with the previous conditions, was isolated in 80% yield after column chromatography. 1-Azabicyclo[1.1.0]butane **4a** was isolated in 94% and 81% yield using sec- and n-BuLi as the base, respectively (Scheme 3). The yield was also significantly higher for **4u** (65%). Under the intensified conditions, amine **4v** could also be prepared, as well as the azetidine boronic ester **8**. Importantly, the continuous flow procedure proved to be sufficiently robust: a long run experiment using benzaldehyde as electrophile revealed that that the continuous flow reactor can produce a constant yield of 70-75% of **4k** over a 4 h period (see Figure S2 in the Supporting Information), with a productivity of ca. 9 mmol/h for a 3.7 mL reactor.



Scheme 3. Continuous flow synthesis of C3-functionalized 1-azabicyclo[1.1.0]butane under intensified conditions. Isolated yields after column chromatography are shown.

In conclusion, in this work we have demonstrated that with the aid of flow technology it is possible to develop a straightforward protocol for the generation of strained 1-azabicyclo[1.1.0]butane, its C3-lithiation and further electrophilic functionalization in a single machine that executes the three-step telescoped sequence. The process has proven to be robust, and a new class of strained azacycles was made available for further use as click reagents for bioconjugation chemistry,[14] and as precursors of functionalized azetidines.

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Keywords: Flow chemistry • Flash Chemistry • Organolithiums • Strained azacycles • Azetidines

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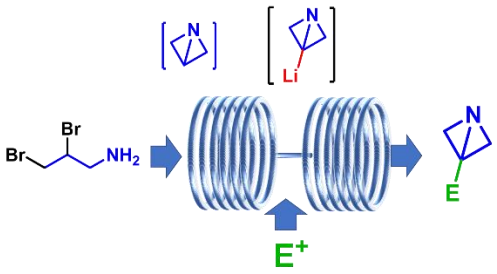

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