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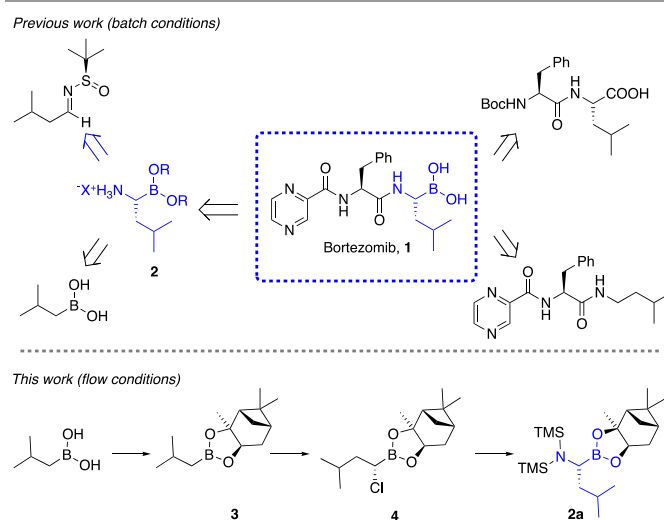
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The flow synthesis of the optically active α -amino boronate precursor of the Bortezomib drug is described, including a key a diastereoselective Matteson rearrangement. This reaction sequence provides an efficient, prompt and valuable strategy for the preparation of Bortezomib (<30 min total residence time over 3 steps for the flow synthesis of the protected *L*- boroleucine).

The demand for flexible and sustainable production of active pharmaceutical ingredients (API), drastically increased since the arise of the COVID-19 pandemic. Hence, the design of straightforward synthetic routes, a longstanding challenge for organic chemists, to provide fast and secured access to key intermediates or APIs became mandatory to secure national production and pharmaceutical independence. In that context, continuous flow synthesis could play a major role to support these goals,^{1–3} since it can provide some decisive benefits such as a firm grip on sensitive reactions^{4–6} and an easier scale-up.^{7,8} In this frame, Bortezomib **1** (VelcadeTM, CytomibTM), is a blockbuster drug (1,39 \$ billion in retail sales in 2020)⁹ prescribed for the treatment of myeloma and cell lymphoma.^{10–16} The structure of Bortezomib is derived from pyrazinoic acid, *L*-phenylalanine, and *L*-boroleucine moieties, which are connected through amide bonds. To the best of our knowledge, six diastereoselective total synthesis have been reported in the literature (all under batch conditions) and four of them relies on the diastereoselective preparation of the key enantiopure α -aminoboronic acid **2** (scheme 1).^{17–22} This fragment plays a major role in the biological activity of Bortezomib.¹³ In this

context, we now report a synthesis of the key enantiopure synthon **2a** under continuous flow conditions (Scheme 1).



Scheme 1. Synthetic path to Bortezomib and key precursors.

This flow synthesis was therefore planned in three steps as follow: 1) esterification of *i*-BuB(OH)₂ with (+)-pinanediol, 2) formation of the enantiopure α -chloro-boronic ester **4** from a diastereoselective Matteson rearrangement and 3) the final nucleophilic substitution to install the amino group.

Thus, a solution of isobutyl boronic acid in THF (1.1 equiv.) was easily reacted with a THF solution of (+)-pinanediol (1 equiv.) in a flow reactor at 80 °C to afford the boronic ester **3** within only $t^R = 2.5$ min (88 % yield, Scheme 2a). The next critical step involves the formation and reaction of the highly reactive carbenoid intermediate (LiCHCl₂) to add onto the boronate for subsequent Matteson rearrangement. The carbenoid generated by deprotonation of dichloromethane is only stable under cryogenic conditions, which severely hampers the use of this transformation on an industrial scale.^{23,24} However, flow technology has been shown to be an invaluable asset to control such unstable organolithium species in virtue of excellent

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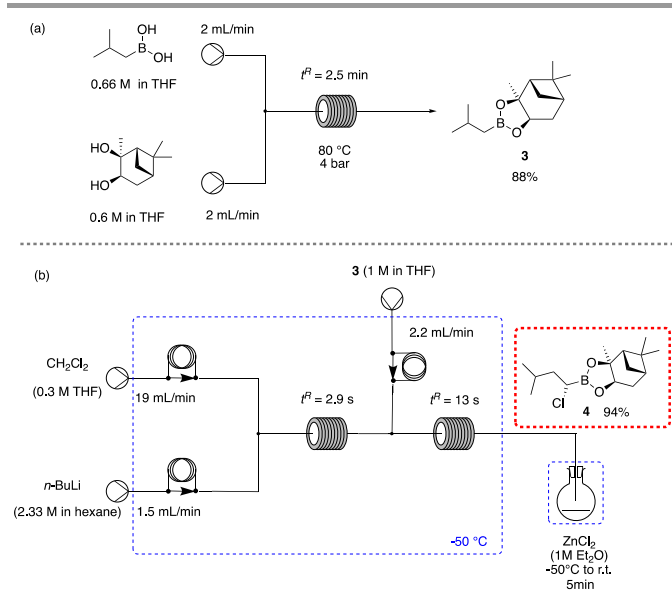
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mixing and fine tuning of the reaction time.^{5,25–27} In this line, Sedelmeier reported a breakthrough in halogenomethyl lithium chemistry/Matteson rearrangement by the deprotonation of the inexpensive CH_2Cl_2 ,²⁸ which was then applied by Schuster in the large scale synthesis of a Vaborbactam intermediate.²⁹ More recently, Kirschning extended the methodology to the metal-halogen exchange of ClCH_2Br with a specific static mixer,³⁰ whereas Luisi described the synthesis of chloroaldehydes from the unstable $\text{ClCH}(\text{Li})\text{I}$ and ketones.³¹ In our case, it was decided to perform the transformation of *i*-butyl boronate **3** into target compound **4** with common and accessible equipment (simple T-shaped mixer notably) and with widely available CH_2Cl_2 as reagent for easier reproducibility. Thus, after optimization (see ESI for details), we implemented the formation of the LiCHCl_2 and its subsequent trapping with the chiral boronate **3** as follow: a precooled commercial solution of *n*-BuLi (1.6 equiv, 2.33 M in hexane) was mixed with a precooled diluted solution of CH_2Cl_2 in THF (2.5 equiv, 0.3 M) to form the CHCl_2Li with a flow rate of 20.5 mL/min and a very short residence time ($t^R = 2.9$ s, Scheme 2b). A third flow inlet was then connected to the flow system: a solution of boronate **3** (1 equiv.) with a flow rate of 2.2 mL/min was then injected to perform the Matteson step that occurred in a second reactor ($t^R = 13$ s), the outlet being collected into a flask containing a commercial solution of ZnCl_2 (2 equiv., 1 M in Et_2O) at -50 °C and let rise to room temperature after collection (scheme 2b).



Scheme 2. Flow set-ups for (a) the formation of boronate **3** (T-mixer with ID = 1 mm, Reactor tubing with ID = 1 mm, L = 12.7 m); and (b) the Matteson reaction to provide **4** (T-mixer with ID = 1 mm, Reactor tubing with ID = 1.59 mm, L₁ = 50 cm, L₂ = 250 cm).

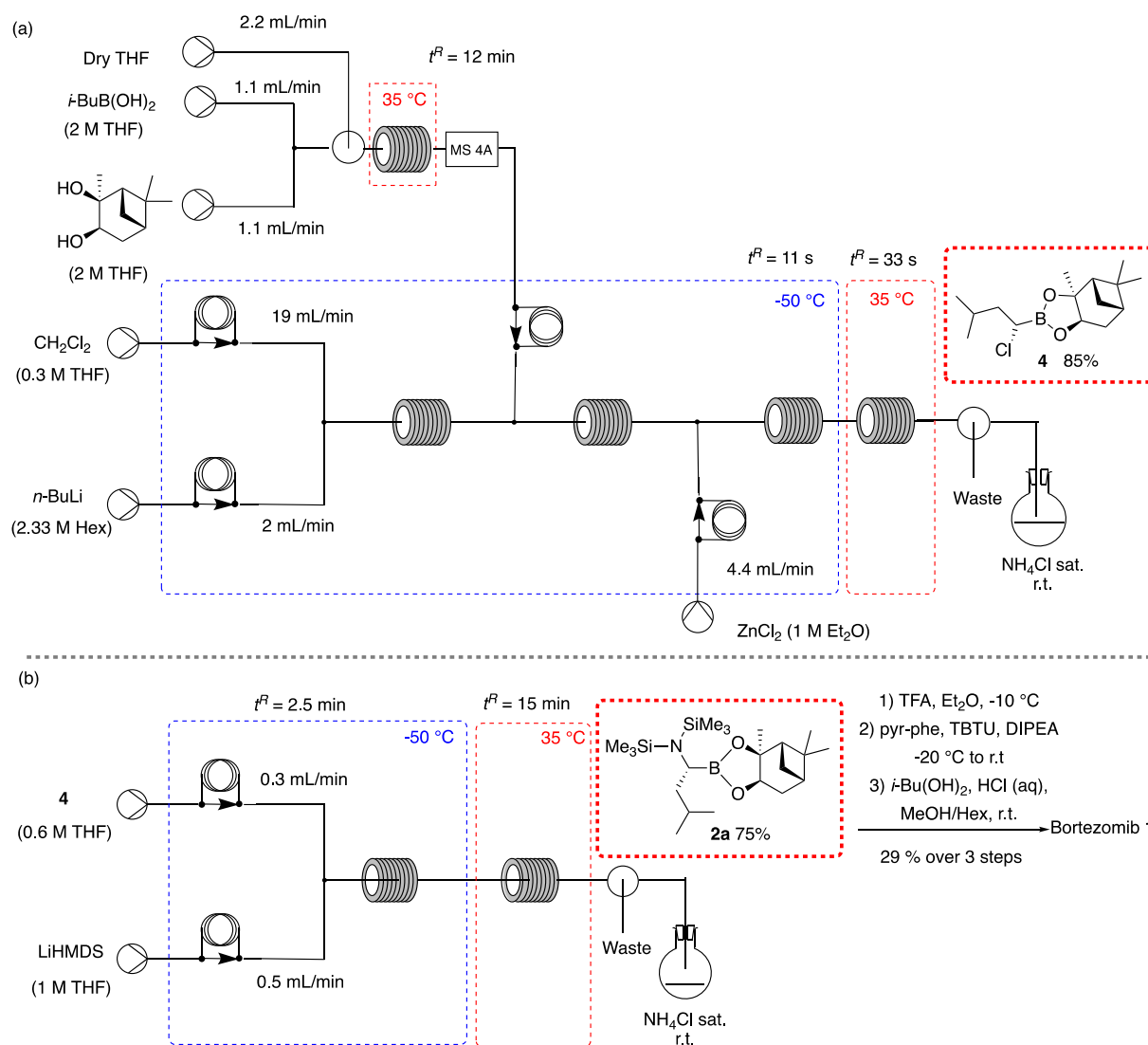
The reaction was monitored by ^1H NMR and we were very pleased to observe a full conversion into the desired diastereomer after 5 min in the flask. This sequence was highly effective and provided the chiral α -chloro-boronic ester **4**, with a space-time yield of 7.2 kg/h/L (94% yield, Scheme 2b) and with an excellent purity (> 97%) after a simple aqueous work-up. The

target compound **4** was thus directly used for the next step without further tedious purification.

We then focused on the possibility to perform a fully telescoped flow process from isobutyl boronic acid to the stereospecific 1,2-metallate rearrangement through the introduction of the commercially available ZnCl_2 solution via an additional inlet. Thus, solutions of (+)-pinanediol (1 equiv.) and isobutyl boronic acid (1 equiv.) were injected through two separate inlets and reacted in a tubing reactor at 35 °C to form **3** ($t^R = 5$ min, Scheme 3a). The next step involving pyrophoric and sensitive organolithium compounds, the water formed during the formation of boronate **3**, was removed inline by using a packed-bed reactor filled with 4 Å molecular sieves ($t^R = 7$ min, Scheme 3a). This flow system was then connected to the set-up for the Matteson rearrangement including a supplementary inlet with a solution of ZnCl_2 . The reaction between LiCHCl_2 and **3** occurred was performed at -50 °C ($t^R = 11$ s) before being heated at 35 °C in a further reactor ($t^R = 33$ s) and finally quenched by connecting the outlet to a saturated aqueous solution of NH_4Cl (Scheme 3a). This telescoped sequence allows to afford the target **4** in very good yield (85% over two steps). Therefore, this last optimisation led to the implementation of a fully concatenated flow synthesis of a key intermediate α -chloro-boronic ester from available starting chemicals, starting from commercially available materials in a single operation, without isolation of intermediates nor tedious purification, apart from a final aqueous work-up.

Last, we moved to the development of the final step to access the target amino boronate **2a**, i.e. the installation of the amino residue with the use of LiHMDS (Scheme 3b). A solution of the chloroboronic ester **4** (1 equiv) was successfully reacted with a solution of LiHMDS (2.8 equiv) in a flow reactor cooled at -50 °C ($t^R = 2.5$ min) before being warmed to 35 °C in a second reactor ($t^R = 15$ min) to ensure full conversion. The reaction was carried out on a 3.69 mmol scale (20.5 min of collection) to afford the key precursor **2a** in 75% yield after purification (Scheme 3b). The completion of the synthesis of Bortezomib **1** was finally achieved from this key intermediate under classical batch reaction conditions, as already depicted in the literature (Scheme 3b).²⁰

In summary, we have achieved the flow synthesis of the strategic α -amino boronic ester **2a**, key precursor of the drug Bortezomib **1**. This protocol involved telescoped reactions and classical equipment for flow chemistry. The total residence time for the flow steps is around 30 min, which represents a significant productivity gain with regards to the batch operations. Moreover, a single final purification is needed to ensure a high purity level. The protocol delineated within this study offers thus a fast and practical access to this key intermediate, and therefore drastically shortens the access to Bortezomib. Moreover, this protocol would also be further applied to other APIs, containing α -aminoboronic acid derivative.^{32–34}



Scheme 3. (a) Flow synthesis of α -chloro-boronic ester **4** from (+)-pinanediol (see ESI for details regarding the set-up); (b) Flow synthesis of the α -amino boronic ester **2a** (T-mixer with ID = 1 mm, Reactor tubing with ID = 1.59 mm, $L_1 = 600$ cm, $L_2 = 250$ cm) and batch conversion into Bortezomib **1**.

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There are no conflicts to declare.

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