Electronic Supporting Information

Flow synthesis of an α-amino boronic ester as key precursor of Bortezomib drug

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General Methods :

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen atmosphere, CH_2Cl_2 was continuously refluxed and freshly distilled from calcium hydride under nitrogen atmosphere. diisopropylethylamine and hexamethyldisilazane were distillated from KOH. All experiments using anhydrous solvent were performed under inert atmosphere of nitrogen, using dried apparatus employing standard techniques for handling air-sensitive materials. All reagents were obtained from commercial suppliers unless otherwise stated.

^{1}H NMR spectra were recorded on a Bruker DXP 300 spectrometer at 300 MHz and a Bruker DXP 400 spectrometer at 400 MHz; ^{13}C NMR spectra at 75 MHz. Data were reported as fellows : Chemical shifts (δ) are quoted in ppm relative to the residual solvent signal for $CDCl_3$ (δH=7.26 ppm; δC=77.16 ppm). The following abbreviations were used: δ (chemical shift), J (coupling constant), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), q (quartet), m (multiplet).

General Flow Methods :

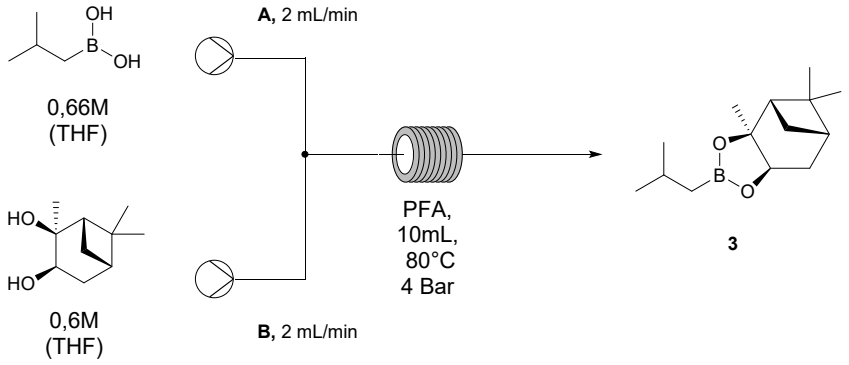
All our custom-made set up for the flow reaction were purchased on Cil-Cluzeau info labo (France, 33220 Sainte-Foy-La-Grande, shop.cluzeau.fr).

The flow system which was used in experiments and depicted in schemes was the following :

For the protection of boronic acid, either Vapourtec© R-series Flow Chemistry System using (PFA, 1/16'' OD x 1 mm ID) tubing and a 10 mL reactor (PFA, 1/16'' OD x 1 mm ID) with a back pressure regulator was used or the syringe pump PHD Ultra Harvard apparatus for the telescoped reaction with syringe SGE© and custom-made set up (PFA, 1/8'' OD x 1.59 mm ID).

The syringe pump PHD Ultra Harvard apparatus was also used for the diastereoselective Matteson reaction and the substitution with LiHMDS with syringe SGE and custom-made set up (PFA, 1/8'' OD x 1.59 mm ID). Each system was equipped with a 4-port PEEK switching valves, which one is plugged, in order to throw away the solution before entering the steady state and begin the collection. All the custom-made set up were dried and filled with dry THF before being used.

Synthesis of the pinanediol boronic ester 3 in flow :



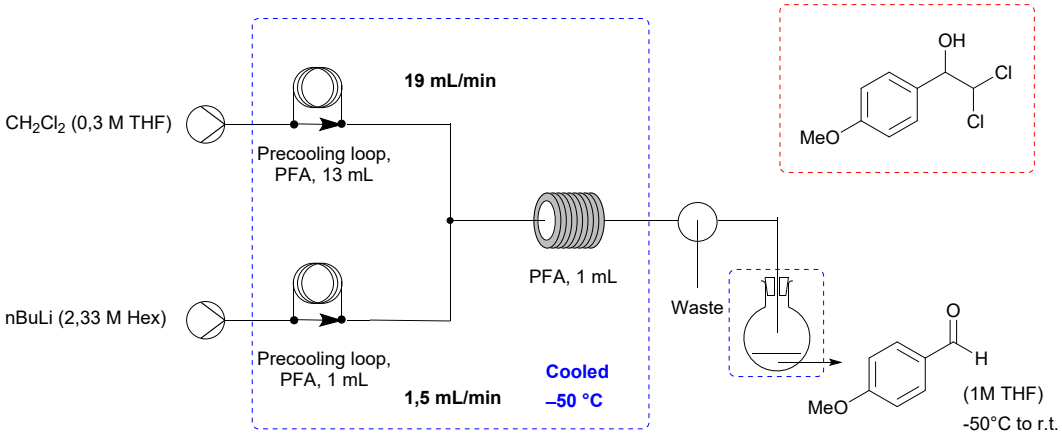
A solution of isobutylboronic acid (0.66 M THF) and (+)-pinanediol (0,6M THF) were pumped using Vapourtec© R4 device using peristaltic pump with a flow rate of 2 mL/min for each of them (total flow rate Q_T= 4 mL/min). They were mixed using a PFA "T-piece" with 0.5 mm ID before entering the 10 mL PFA reactor (ID = 1 mm, L = 12.7 m, t^R= 2 min 30s). After the system reached steady state (2 min), the solution was collected for 6 min and directly quenched with a saturated solution of NH_4Cl under vigorous stirring. The phases were separated, the aqueous layer was extracted 3 x EtOAc, the combined organic layers were washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated over vacuum. The crude was distilled with a Kugelrohr apparatus (bp = 130-140 °C, 1 mbar) to give the pinanediol boronic ester **3** as a clear oil (88 %, 6.3 mmol, 1.49 g). The analytical data are in accordance with the literature.[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, *J* = 8.8, 2.0 Hz, 1H), 2.34 (ddt, *J* = 14.3, 8.8, 2.4 Hz, 1H), 2.22 (dtd, *J* = 10.8, 6.1, 2.2 Hz, 1H), 2.05 (dd, *J* = 6.1, 5.0 Hz, 1H), 1.96 – 1.79 (m, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.14 (d, *J* = 10.8 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.84 (s, 3H), 0.81 – 0.75 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 51.3, 39.6, 38.2, 35.7, 28.8, 27.1, 26.6, 25.4, 25.3, 24.9, 24.1.

$[\alpha]_D^{25}$= +28.1 ($CHCl_3$, C = 1.0)

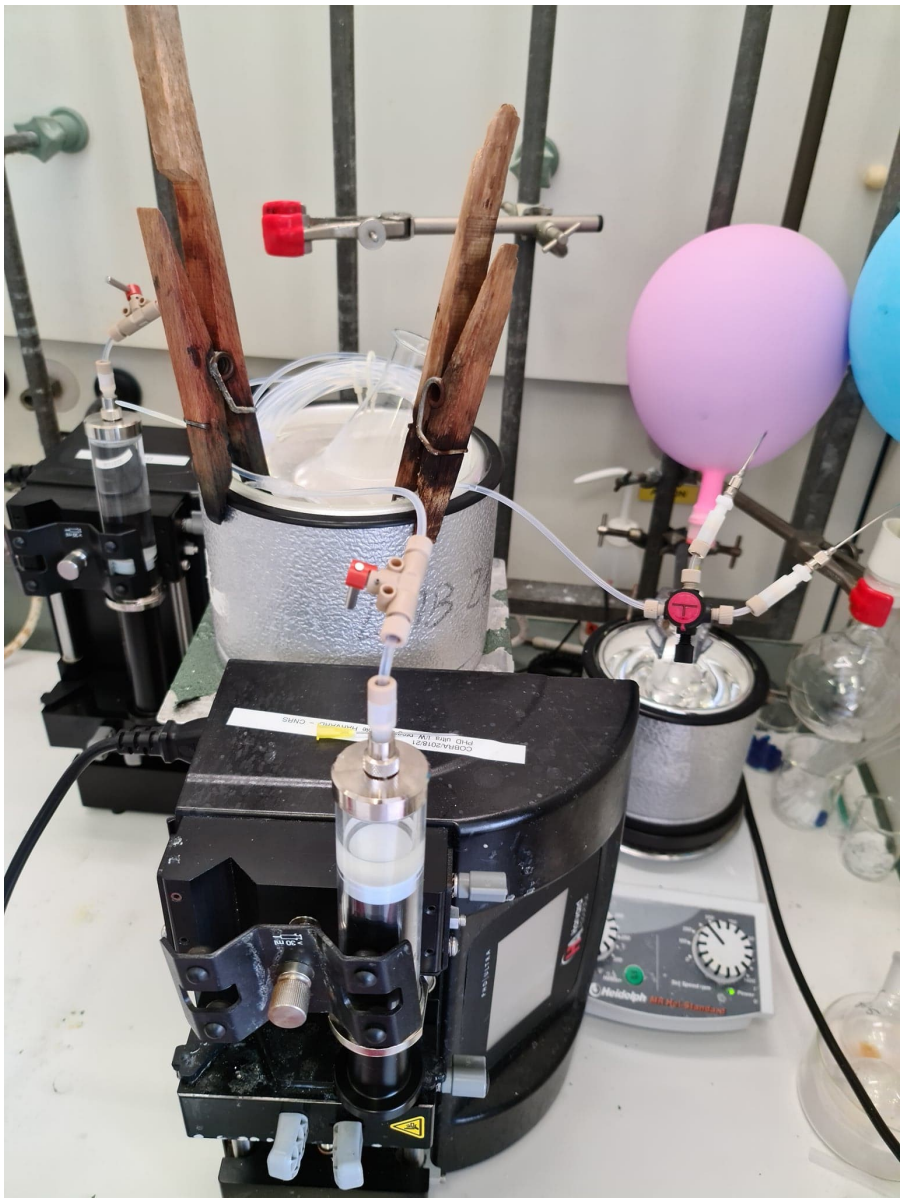
Test deprotonation of CH_2Cl_2 with *n*-BuLi in flow, reaction with *p*-anisaldehyde in a semi batch system.

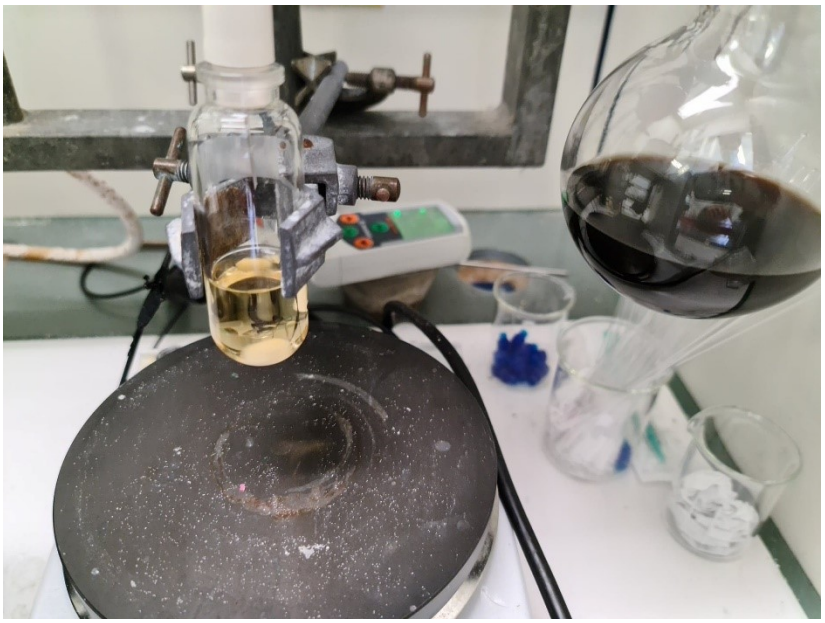


A first syringe pump PHD Ultra Harvard apparatus was charged with a 100 mL solution of dry CH_2Cl_2 (0.3M THF, 2.6 equiv.) in a 100 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 19 mL/min. A second syringe pump PHD Ultra Harvard apparatus was charged with a 10 mL commercial solution of n-BuLi (2.33 M Hex, 1.5 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was introduced with a flow rate of 1.5 mL/min. They were mixed using a PFA "T-piece" with 1 mm ID at -50°C before entering the 1 mL reactor (PFA, ID = 1.59 mm, L = 50 cm, Q_1= 20.5 mL/min, t^R= 2.9 s). After the system reached steady state (1 min 30s), the solution was collected for 28 s in a 10 mL schlenck flask containing solution of p-anisaldehyde (1M THF, 1 mL, 1 equiv.) under vigorous stirring at -50°C. Once the collection was done, the cooled bath was removed and the mixture was stirred at room temperature overnight (15 h). A saturated solution of NH_4Cl was introduced and the phases were separated. The aqueous layer was extracted 3x EtOAc, the combined organic layers were washed3x with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated over vacuum to give the α,α-dichlorobenzylic alcohol as an oil (100% conversion). The analytical data are in accordance with the literature.[2]

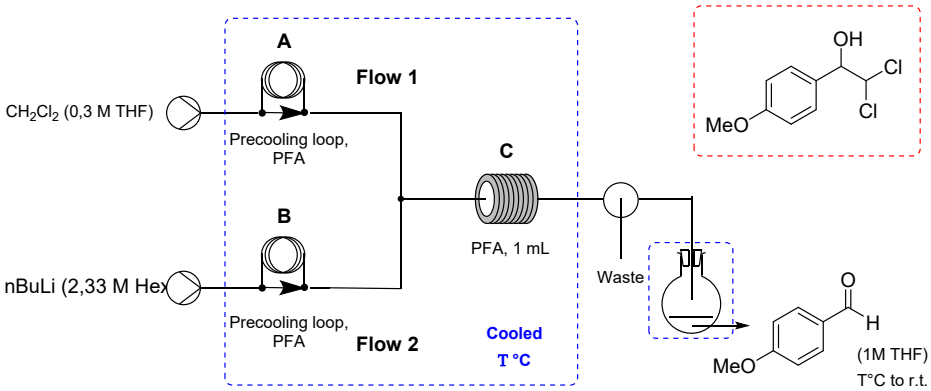
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 2H), 6.99 – 6.83 (m, 2H), 5.78 (d, *J* = 5.6 Hz, 1H), 4.93 (dd, *J* = 5.6, 3.6 Hz, 1H), 3.82 (s, 3H), 2.88 – 2.80 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 129.4, 128.4, 113.9, 78.6, 55.3.





Optimization of the reaction :

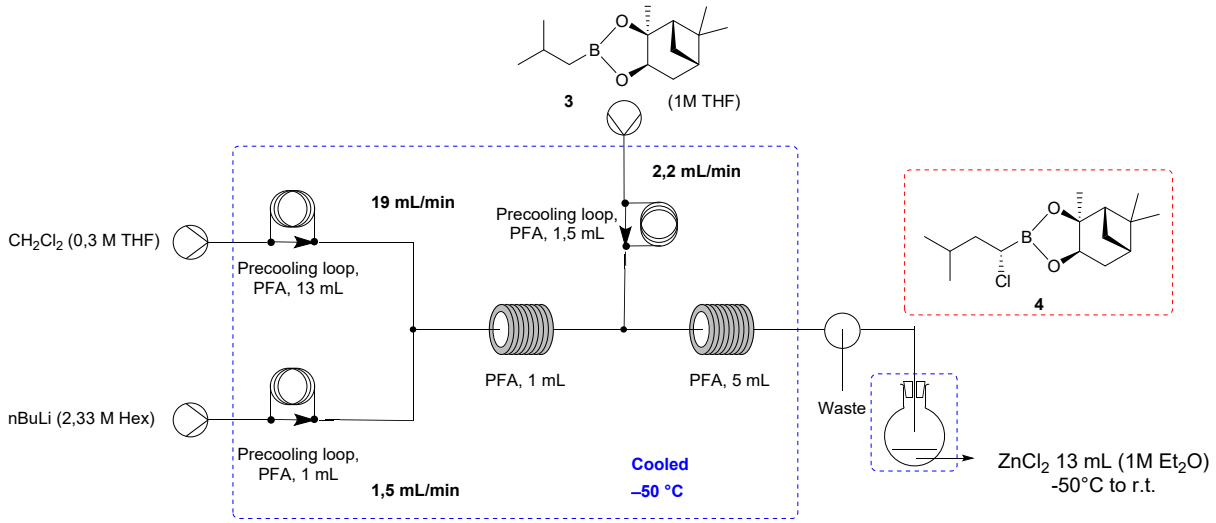


Loop A	Flow 1	Flow 2	Reactor C	t^R	Temperature	Conversion
1 mL	5 mL/min	1 mL/min	5 mL	50 s	-40°C	Full degradation*
1 mL	5 mL/min	1.5 mL/min	2 mL	18 s	-40°C	Full degradation*
1 mL	15 mL/min	1.5 mL/min	2 mL	7.3s	-40°C	1 %
8 mL	15 mL/min	1.5 mL/min	2 mL	7.3s	-50°C	13 %
8 mL	15 mL/min	1.5 mL/min	1 mL	3.6s	-50°C	64 %
13 mL	19 mL/min	1.5 mL/min	1 mL	2.9s	-50°C	Full conversion into the target product

*the solution is turning from pale to very dark when it degrades

Synthesis of the α-chloro-pinanediol boronic ester 4 in flow :

<u>Combiend Batch/flow method :</u>



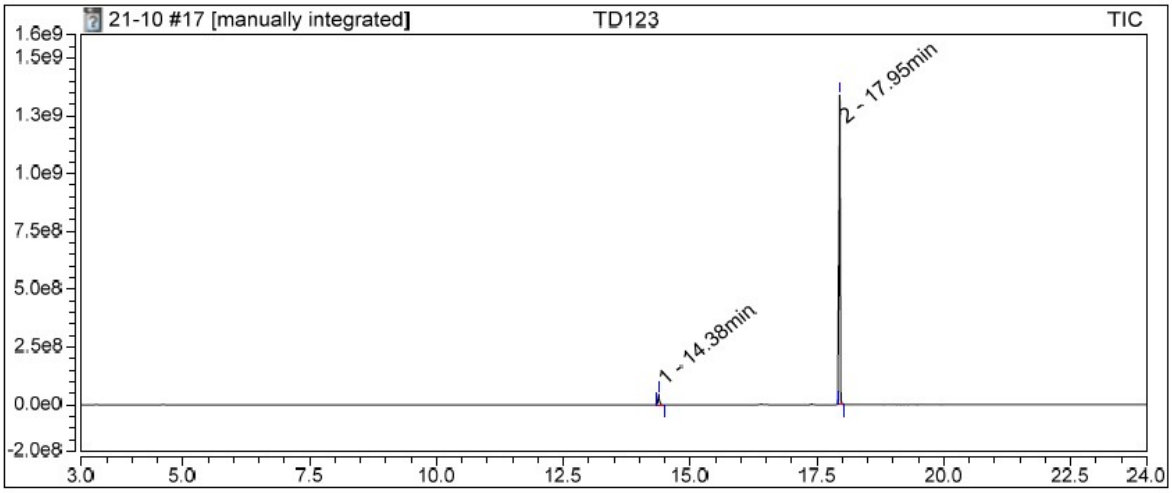
Time before quenching	Conversion
Overnight (16 h)	Full conversion (>95%)
Overnight (16 h, without $ZnCl_2$)	Complex mixture
1 h	Full conversion (>95%)
5 min	Full conversion (>95%)

A first syringe pump PHD Ultra Harvard apparatus was charged with a 100 mL solution of dry CH_2Cl_2 (0.3M THF, 2.6 equiv.) in a 100 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 19 mL/min. A second syringe pump pHD Ultra Harvard apparatus was charged with a 10 mL commercial solution of *n*-BuLi (2.33 M Hex, 1.5 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 1.5 mL/min. They were mixed using a PFA "T-piece" with 1 mm ID at -50°C before entering the 1 mL reactor (PFA, ID = 1.59 mm, L = 50 cm, Q_1= 20.5 mL/min, t^R= 2.9s). A third syringe pump PHD Ultra Harvard apparatus was charged with a 10 mL solution of pinanediol boronic ester **3** (1M THF, 1 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was introduced with a flow rate of 2.2 mL/min. It was mixed with the previous reaction mixture using a PFA "T-piece" (ID = 1 mm) at -50°C before entering the 5 mL reactor (PFA, ID = 1.59 mm, L = 250 cm, Q_2= 22.7 mL/min, t^R= 13 s). After the system reached steady state (1 min 30s), the solution was collected for 2 min 30s in a 100 mL round-bottom flask containing a commercially available solution of $ZnCl_2$ (1M Et_2O, 12 mL, 2.2 equiv.) under vigorous stirring at -50°C. Once the collection was done, the cooled bath was removed and the reaction monitored by ^{1}H NMR (micro-extraction). We saw that the reaction was done after only 5min. A saturated solution of NH_4Cl was introduced and the phases were separated. The aqueous layer was extracted 3x EtOAc, the combined organic layers were washed 5x with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated over vacuum to give the α-chloro pinanediol boronic ester **4** as an oil (94%, > 95% conv, > 97% purity, 5.2 mmol, 1.48 g). It was used without further purification. The analytical data are in accordance with the literature.[3]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.53 (dd, *J* = 10.0, 5.8 Hz, 1H), 2.42 – 2.19 (m, 2H), 2.09 (dd, *J* = 6.1, 4.9 Hz, 1H), 1.97 – 1.72 (m, 4H), 1.62 (ddd, *J* = 14.1, 8.3, 5.7 Hz, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.18 (d, *J* = 11.1 Hz, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.84 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 86.7, 78.5, 51.2, 42.8, 39.4, 38.3, 35.3, 28.5, 27.1, 26.3, 25.6, 24.0, 23.00, 21.2.

$[\alpha]_D^{25}$= + 42.0 ($CHCl_3$, C = 1.0)



No.	Peak Name	Retention Time min	Area counts*min	Relative Area %
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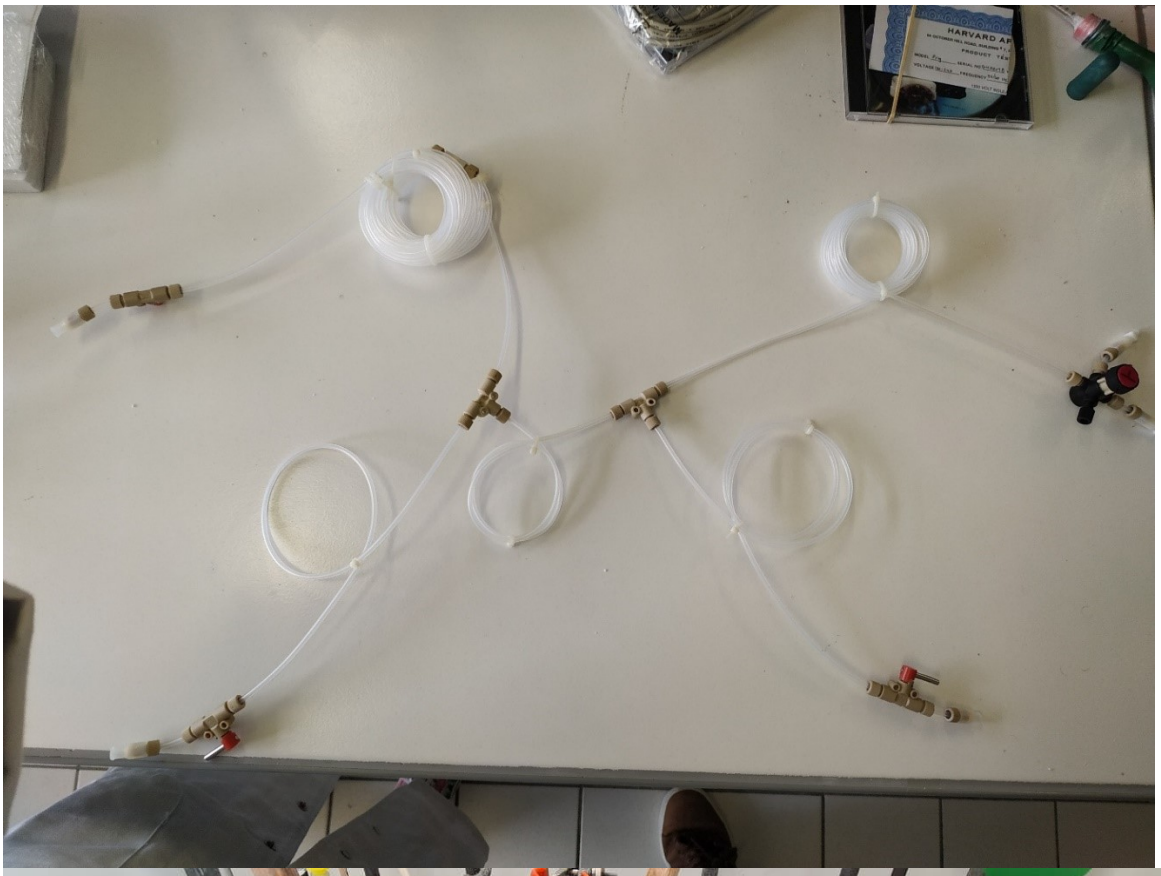
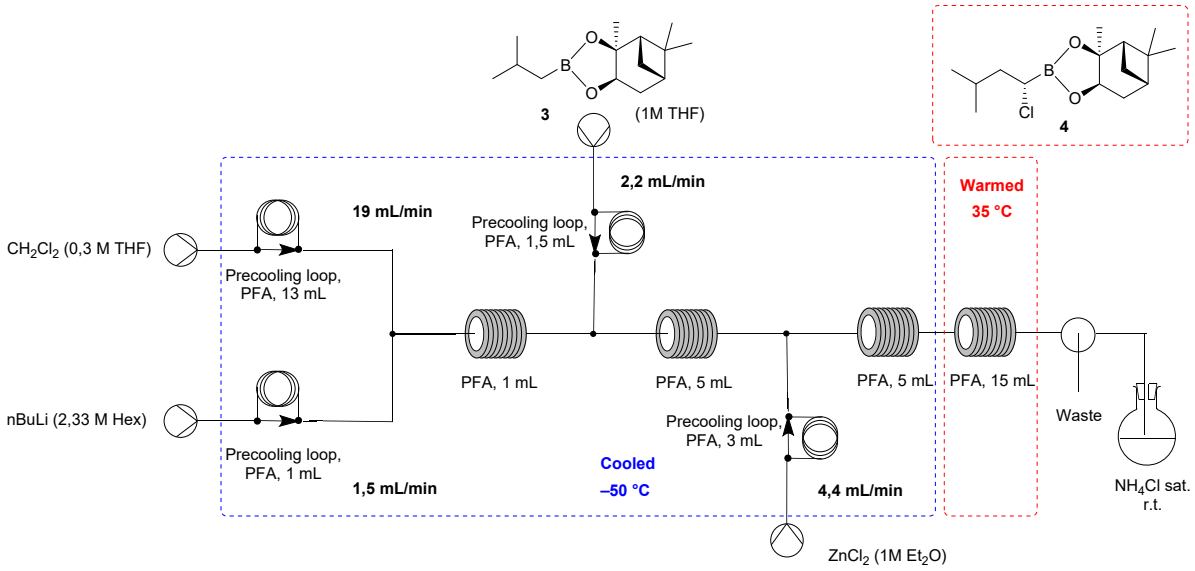
2		17.945	35286036.920	97.20
Total:			**36302349.346**	**100.00**

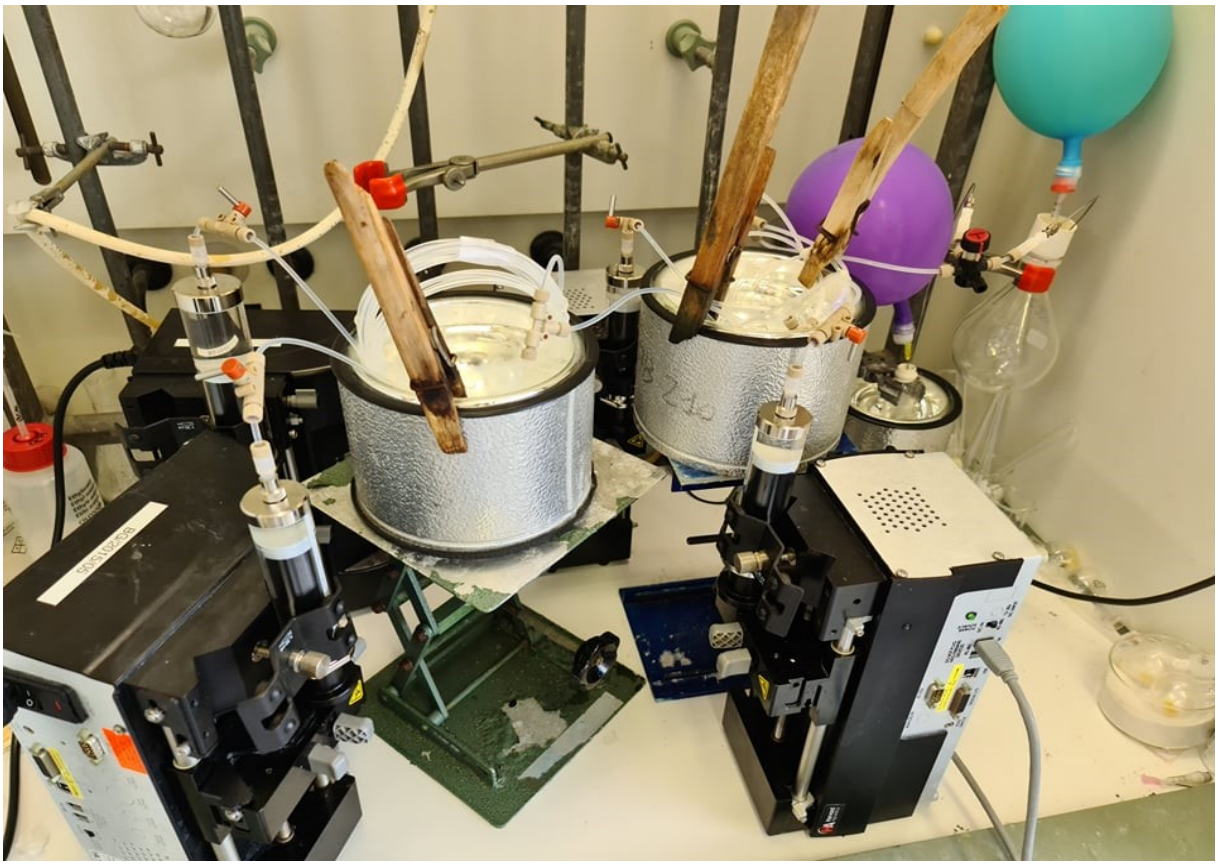


General All-Flow Method :

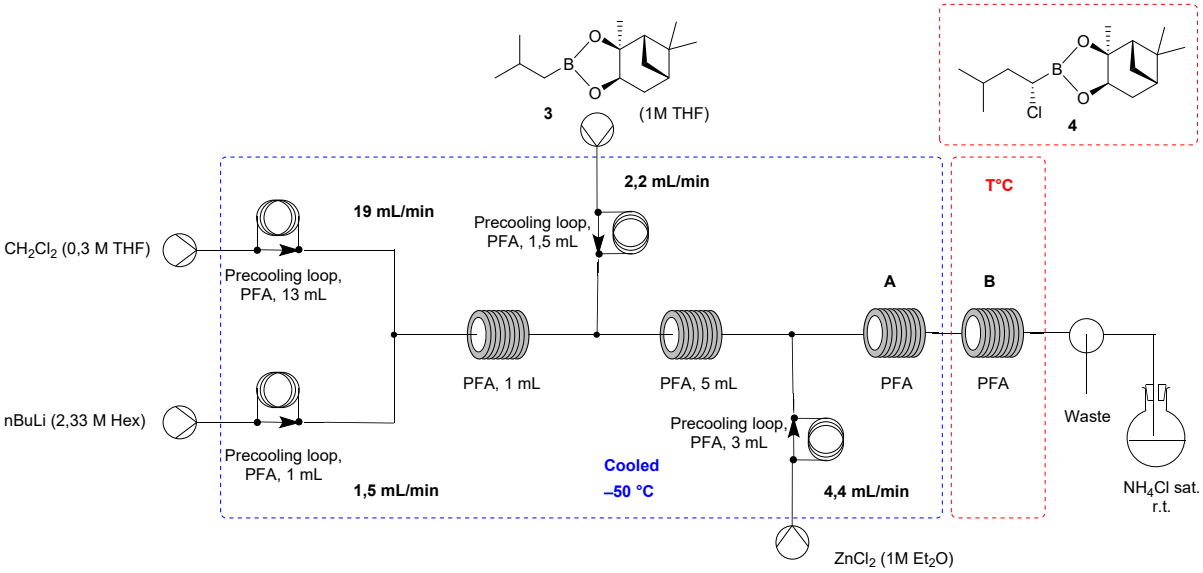


A first syringe pump pHD Ultra Harvard apparatus was charged with a 100 mL solution of dry CH_2Cl_2 (0.3M THF, 2.6 equiv.) in a 100 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 19 mL/min. A second syringe pump pHD Ultra Harvard apparatus was charged with a 10 mL commercial solution of n-BuLi (2.33 M Hex, 1.5 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 1.5 mL/min. They were mixed using a PFA "T-piece" with 1 mm ID at -50°C before entering the 1 mL reactor (PFA, ID = 1.59 mm, L = 50 cm, Q_1= 20.5 mL/min, t^R= 2.9s). A third syringe pump pHD Ultra Harvard apparatus was charged with a 10 mL solution of pinanediol boronic ester **3** (1M THF, 1 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 2.2 mL/min. It was mixed with the previous reaction mixture using a PFA "T-piece" (ID = 1 mm) at -50°C before entering the 5 mL reactor (ID = 1.59 mm, L = 250 cm, PFA, Q_2= 22.7 mL/min, t^R= 13 s). A fourth syringe pump pHD Ultra Harvard apparatus was charged with a commercially available 25 mL solution of $ZnCl_2$ (1M Et_2O, 2 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 4.4 mL/min. It was mixed with the previous reaction mixture using a PFA "T-piece" with 1 mm ID at -50°C before entering the 5 mL reactor (PFA, ID = 1.59 mm, L = 250 cm, Q_3= 27.1 mL/min, t^R= 11.07s) and then warmed up at 35 °C in a 15mL reactor (ID = 1.59 mm, L = 750 cm PFA, Q_3= 27.1 mL/min, t^R= 33.2s). After the system reached steady state (2 min 30s), the solution was collected for 1 min 10s in a 100 mL round-bottom flask containing a saturated solution of NH_4Cl at room temperature under vigorous stirring. Once the collection was done, the phases were separated, the aqueous layer was extracted 3x EtOAc, the combined organic layers were washed 5x with a saturated solution of NaCl,

dried over $MgSO_4$, filtered and concentrated over vacuum to give the α-chloro pinanediol boronic ester **4** as an oil (88%, 90% conv, 2.59 mmol, 736 mg).

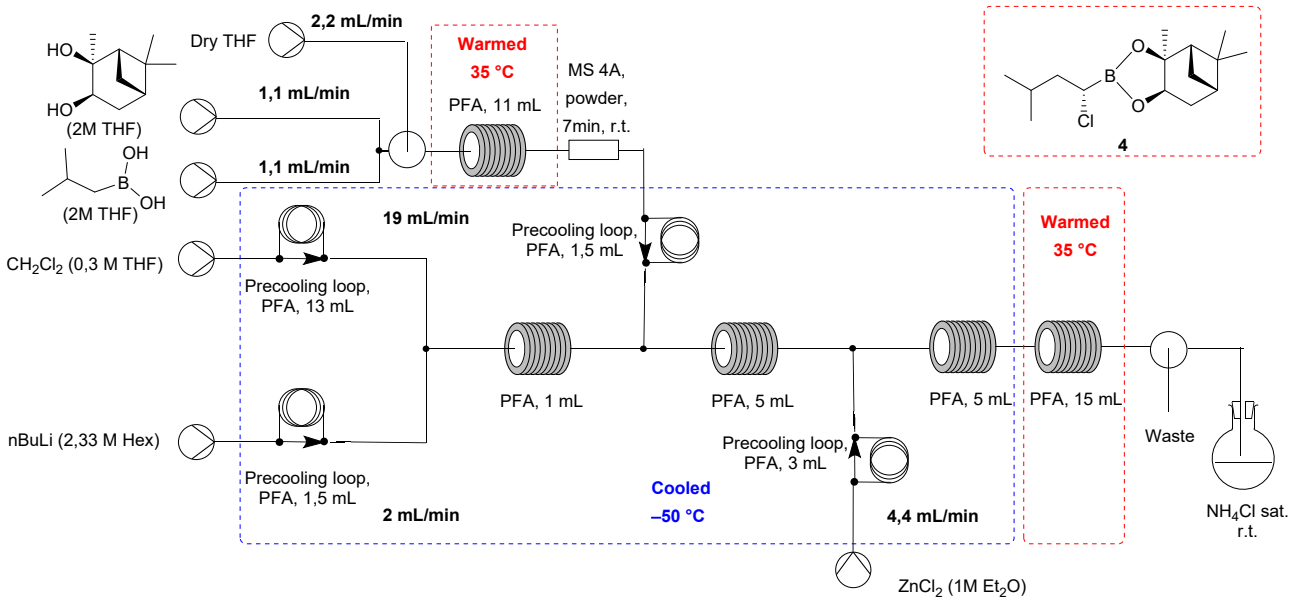


Optimization of the reaction :



Reactor A	Reactor B (T°C)	t^R	Conversion
5mL	0 mL	11s	23 %
5mL	10 mL (r.t.)	33s	85 %
5mL	15 mL (30 °C)	44 s	90 %

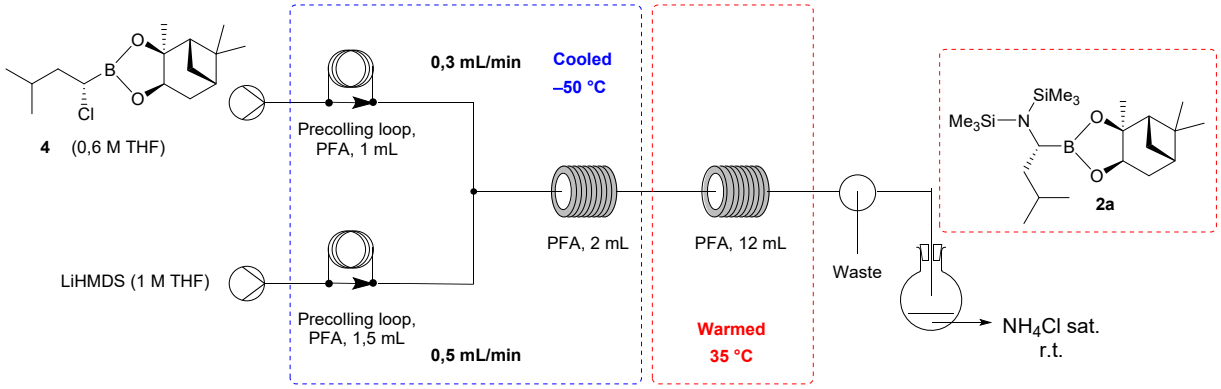
Telescoped boronic ester synthesis and Matteson reaction in flow for the synthesis of 4.



For the Matteson reaction, the previous **General all flow** method was used with a flow rate of 2 mL/min for the n-BuLi inlet as modification and a precooling loop of 1.5 mL. For the formation of the boronic ester, A first syringe pump PHD Ultra Harvard apparatus was charged with a 20 mL solution of pinanediol (2M THF, 1 equiv.) in a 50 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 1.1 mL/min. A second syringe pump PHD Ultra Harvard apparatus was charged with a 20 mL solution of the boronic acid (2M THF, 1 equiv.) in a 50 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 1.1 mL/min. They were mixed using a PFA "T-piece" with 1 mm ID before entering the 11 mL reactor at 35°C (PFA, ID = 1.59 mm, L = 5.5 m, Q= 2.2 mL/min, t^R= 5 min). Before reaching the precooling loop for the Matteson reaction, the reaction mixture passed through 3 consecutive cartridges containing MS 4Å (features for the total 3-cartridge system: 13 mm ID, 210 mm length, 15.6 g MS 4Å, powder, t^R= 7 min). Thanks to a 4-port PEEK switching valves, which one is plugged, located before the reactor, the mixture could be pushed through the system using a third syringe pump PHD Ultra Harvard apparatus which was charged with a 50 mL solution of dry THF in a 50 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 2.2 mL/min. As soon as the mixture left the cartridge, all the syringe pump of the Matteson were turn on (see above for corresponding set-up). After the system reached steady state (2 min 30s), the solution was collected for 1 min 30 in a 100 mL round-bottom flask containing a saturated solution of NH_4Cl at room temperature under vigorous stirring. Once the collection was done, the phases were separated, the aqueous layer was extracted 3x EtOAc, the combined organic layers were

washed 5x with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated over vacuum to give the α-chloro pinanediol boronic ester **4** as an oil (85%, 88% conv, 2.83 mmol, 766 mg).

Synthesis of the α- hexamethyldisilazane-pinanediol boronic ester 2a in flow :



A first syringe pump PHD Ultra Harvard apparatus was charged with a 15 mL solution of α-chloro-pinanediol boronic ester **4** (0.6M THF, 1 equiv.) in a 25 mL SGE Syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 0,3 mL/min. A second syringe pump PHD Ultra Harvard apparatus was charged with a 25 mL solution of LiHMDS (1M THF, 1.5 equiv.) in a 25 mL SGE syringe, and connected to the system through a 2-way valve on/off. It was pushed with a flow rate of 0.5 mL/min. They were mixed using a PFA "T-piece" (ID =1 mm) at -50°C before entering the 2 mL reactor (PFA, ID = 1.59 mm, L = 600 cm, Q_1= 20.5 mL/min, t^R= 2.9s) and then warmed before entering the 12 mL reactor (PFA, ID = 1.59 mm, L = 250 cm, Q_1= 20.5 mL/min, t^R= 2.9 s). After the system reached steady state (2 min), the solution was collected for 20 min in a 100 mL round-bottom flask containing a saturated solution of NH_4Cl at room temperature under vigorous stirring. Once the collection was done, the phases were separated, the aqueous layer was extracted 3x EtOAc, the combined organic layers were washed 5x with a saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated over vacuum to obtain as a crude, a pale yellow-orange oil which was distilled with a Kugelrohr apparatus at 170/180°C (2 mbar) (a first fraction of impurities comes at 130-140 °C, and orange oil impurities remains in the boiling flask at the end), to give as a clear oil the α- hexamethyldisilazane-pinanediol boronic ester **2a** (75%, 2.76 mmol, 1.13 g). The analytical data are in accordance with the literature.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 8.7, 1.9 Hz, 1H), 2.64 (dd, *J* = 8.4, 7.0 Hz, 1H), 2.31 (ddt, *J* = 14.3, 8.8, 2.4 Hz, 1H), 2.25 – 2.14 (m, 1H), 2.02 (dd, *J* = 6.1, 5.0 Hz, 1H), 1.95 – 1.71 (m, 3H), 1.61 (ddd, *J* = 13.4, 8.5, 6.3 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 4H), 1.11 (d, *J* = 10.8 Hz, 1H), 0.89 (d, *J* = 4.5 Hz, 3H), 0.87 (d, *J* = 4.4 Hz, 3H), 0.83 (s, 3H), 0.10 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 84.4, 82.7, 77.3, 50.7, 50.6, 44.3, 38.6, 37.3, 35.1, 34.6, 27.7, 27.5, 26.2, 25.5, 24.5, 23.2, 22.6, 21.9, 21.8, 1.8, 1.1.

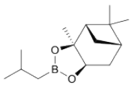
$[\alpha]_D^{25}$= +3.9° ($CHCl_3$, C = 1.0)

1 C. A. Kettner and A. B. Shenvi, *J. Biol. Chem.*, 1984, **259**, 15106–15114.

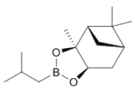
2 D. Naskar and S. Roy, *Tetrahedron*, 2000, **56**, 1369–1377.

3 S. P. A. Hinkes and C. D. P. Klein, *Org. Lett.*, 2019, **21**, 3048–3052.

4 A. S. Ivanov, A. A. Zhalnina and S. V. Shishkov, *Tetrahedron*, 2009, **65**, 7105–7108.



f1 (ppm)



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77.06 CDCl3
76.64 CDCl3
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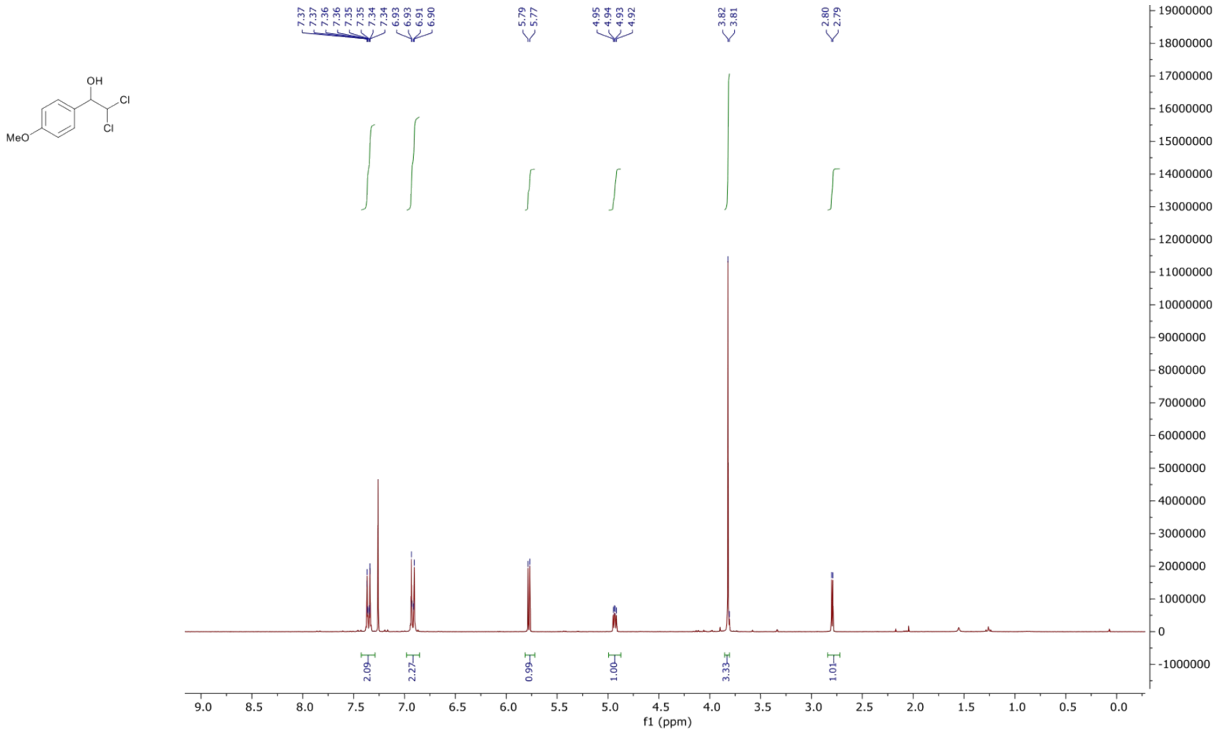
f1 (ppm)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5.79
5.77
4.95
4.94
4.93
4.92
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2.80
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2.09
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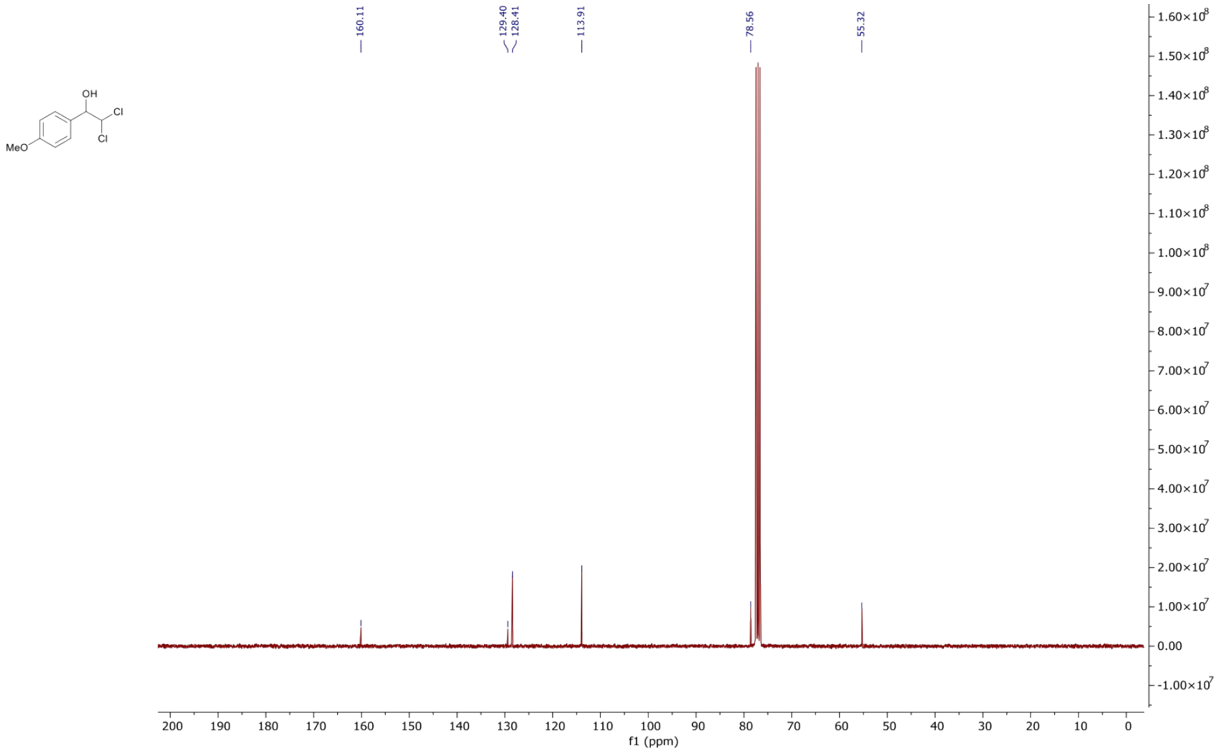
1.01
f1 (ppm)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MeO
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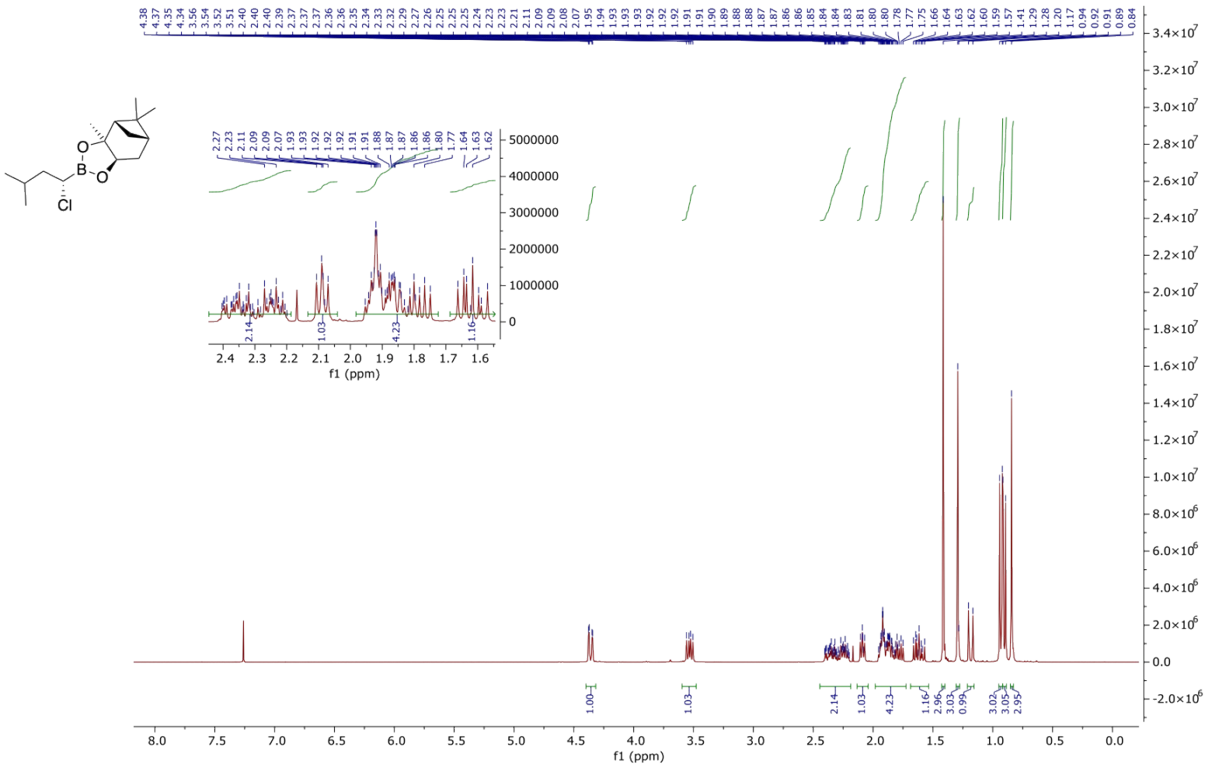
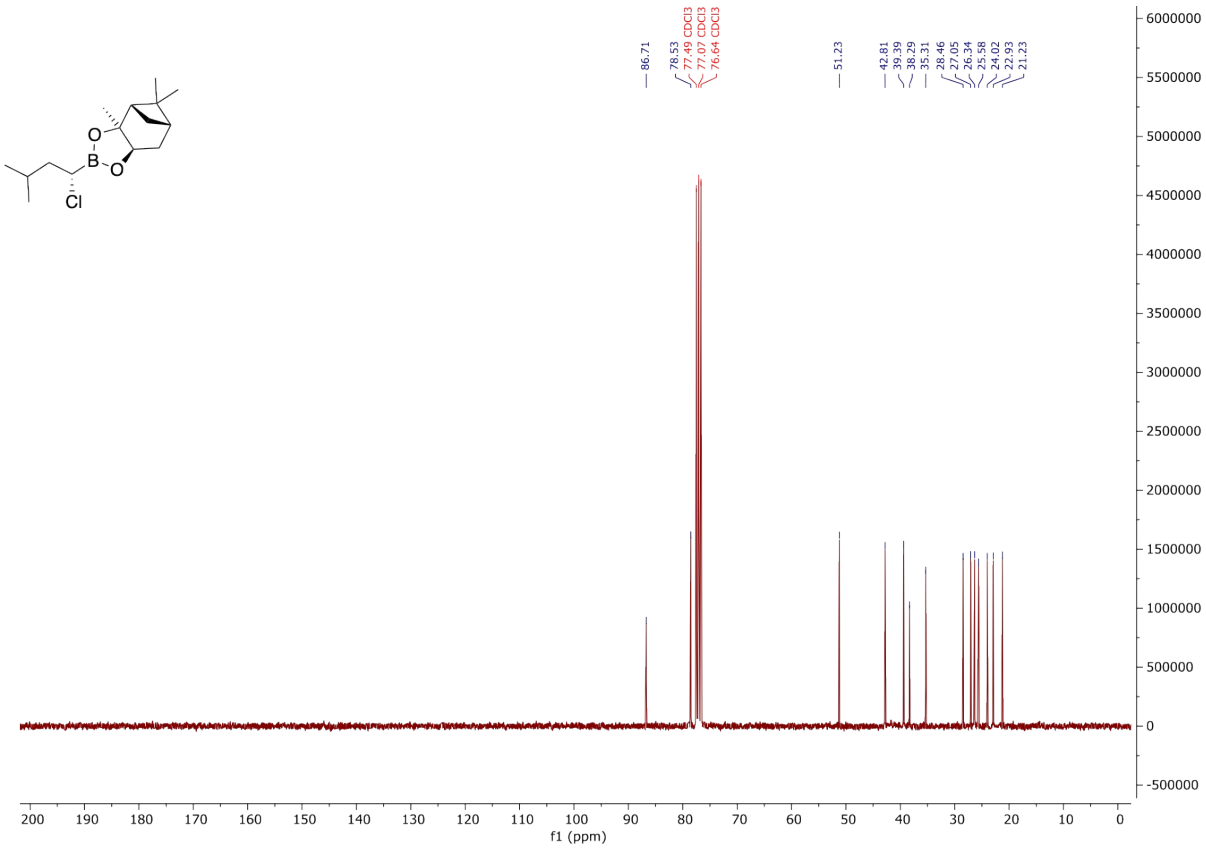
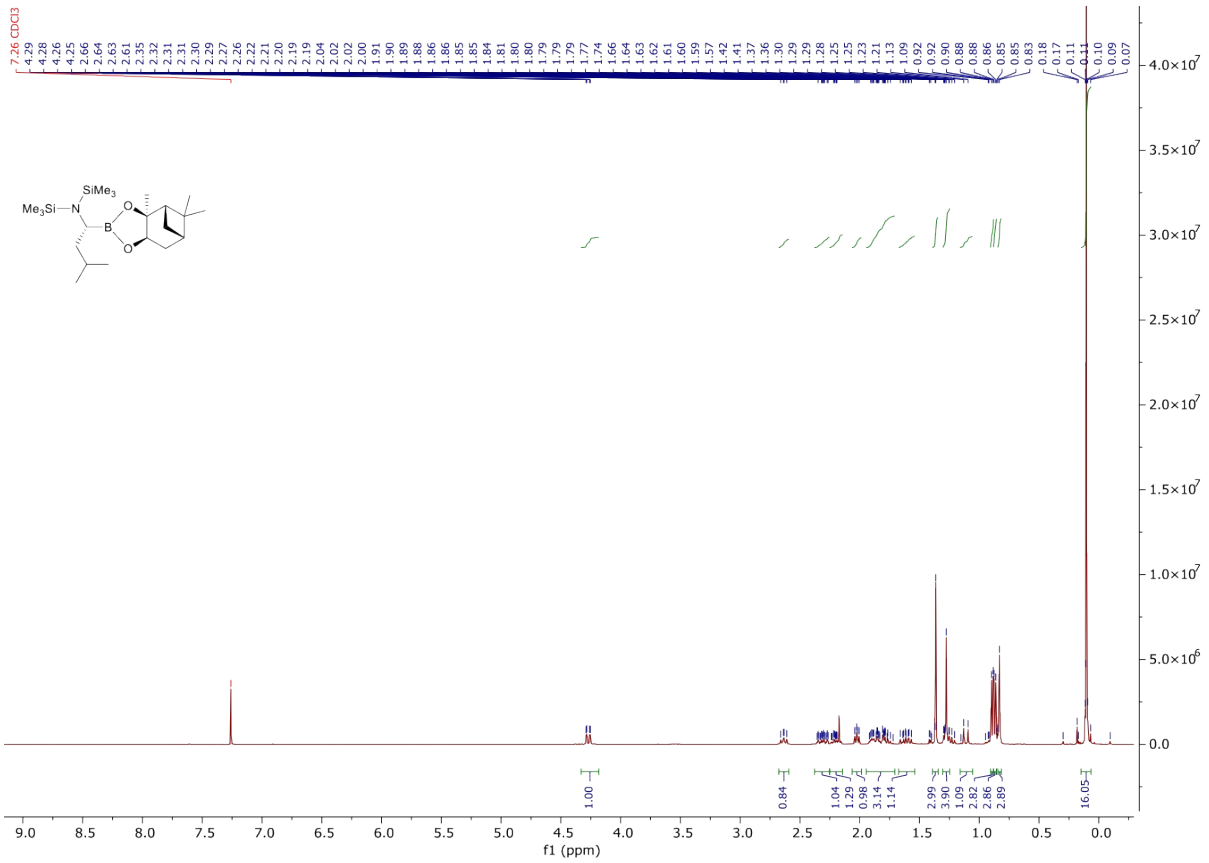
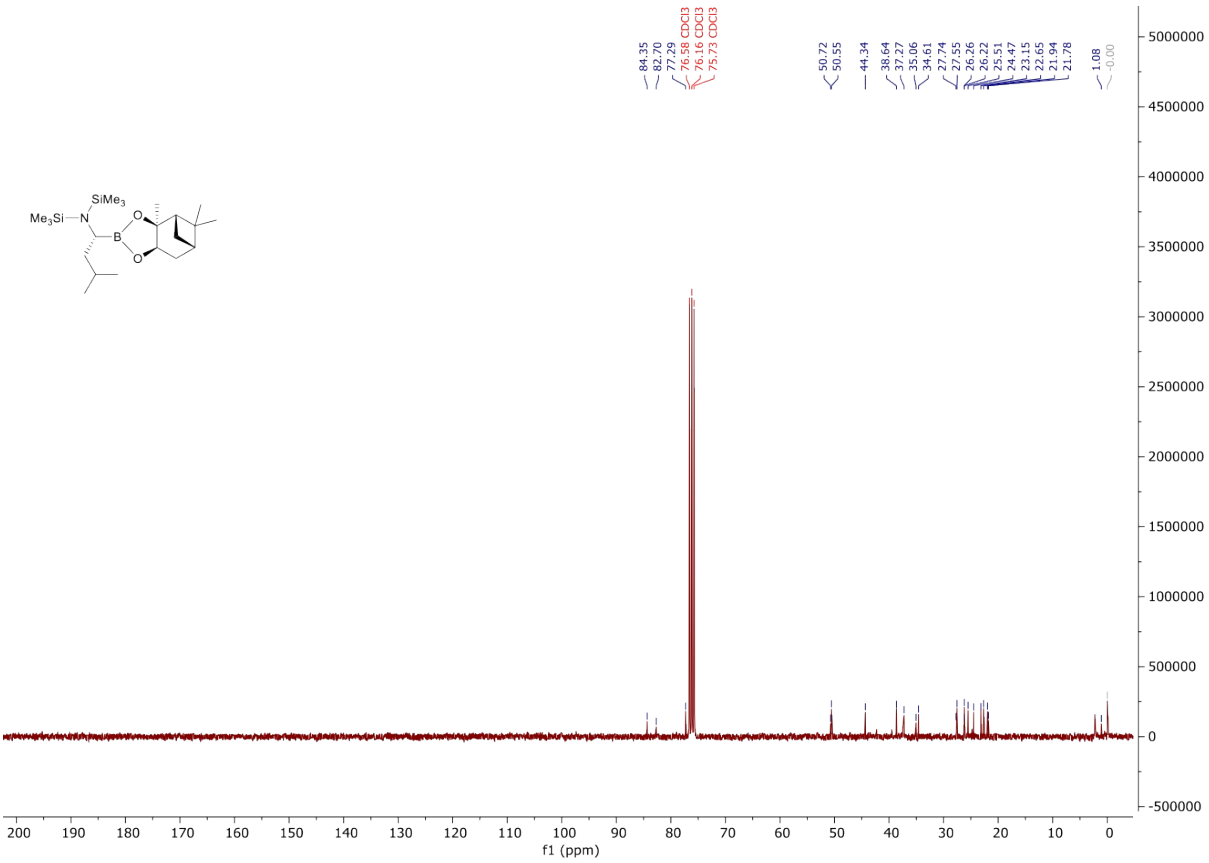
55.32
f1 (ppm)


f1 (ppm)


86.71
78.53
77.49 CDCl3
77.07 CDCl3
76.64 CDCl3
51.23
42.81
39.39
38.29
35.31
28.46
27.05
26.34
25.58
24.02
22.93
21.23
f1 (ppm)


7.26 CDCl3
SiMe3
Me3Si
N
B
O
f1 (ppm)


84.35
82.70
77.29
76.58 CDCl3
76.16 CDCl3
75.73 CDCl3
50.72
50.55
44.34
38.64
37.27
35.06
34.61
27.74
27.55
26.26
26.22
25.51
24.47
23.15
22.65
21.94
21.78
SiMe3
Me3Si
N
B
O
f1 (ppm)