

Supporting Information

For

Scale-up and optimization of a continuous flow carboxylation of *N*-Boc 4,4-difluoropiperidine using *s*-BuLi in THF

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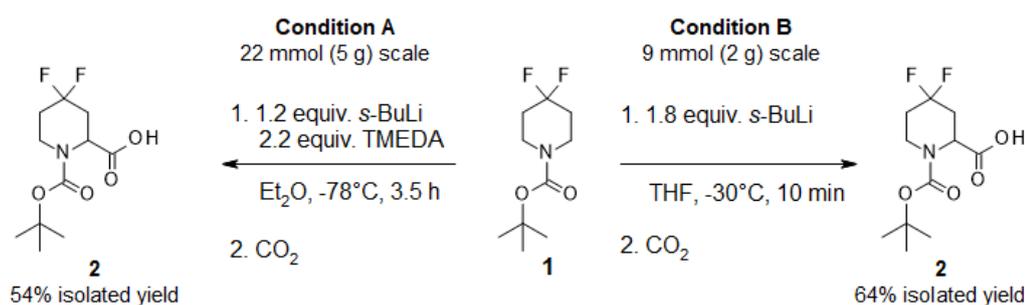
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1. General experimental details

Commercially available starting materials were used as received without further purification. Dry tetrahydrofuran and *s*-BuLi were purchased from Aldrich. *N*-Boc 4,4-difluoropiperidine was purchased from activate-scientific. All capillary tubing and microfluidic fittings were purchased from IDEX Health & Science. Flow reactions were performed using PTFE tubing. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ¹H-NMR spectroscopy. ¹H and ¹⁹F Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ADVANCE 400 MHz spectrometer at ambient temperature (298K) or elevated temperature (373K) using the residual solvent peak in CDCl₃ (δ H = 7.27 ppm, δ C = 77.16 ppm) and using TMS as internal standard. The multiplicity of ¹H NMR signals are indicated as s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, or combinations of thereof. Coupling constants *J* are quoted in Hz and are reported to the nearest 0.1 Hz. Where appropriate, averages of the signals that display multiplicity were used to calculate the value of the coupling constant. High resolution mass spectra (HRMS) were recorded on SYNAPT G2-SI Waters Q-TOF instrument equipped with an ESI source and a Waters Acquity H-class UPLC with diode array detector.

2. Synthetic procedures and characterization of compounds

2.1. Batch Protocols Lithiation / Carboxylation of *N*-Boc 4,4-difluoropiperidine



Scheme S1 : Carboxylation of *N*-Boc 4,4-difluoropiperidine in batch

Procedure condition A :

To a solution of *tert*-butyl 4,4-difluoropiperidine-1-carboxylate **1** (5 g, 22.6 mmol) in dry diethyl ether (225 mL) at -78 °C was added TMEDA (6.13 mL, 40.7 mmol). Following this, *s*-BuLi (29 mL, 41 mmol, 1.3 mol/L in cyclohexane) was added dropwise over 10 minutes. The reaction was stirred for 10 minutes at -78°C, during which time an orange color resulted. Then, the reaction was warmed to -40°C (immediate replacement of the dry ice/acetone bath with dry ice/MeCN bath) and stirred at this

temperature for 30 minutes. The reaction mixture was re-cooled to -78°C and CO_2 bubbled through the reaction mixture for 30 minutes (2 Dreschel bottles, one with CO_2 pellets in at room temperature, and an inverted one in between containing CaCl_2 , see Figure S1). Following CO_2 addition, the reaction was warmed to room temperature. The reaction was stirred at room temperature for 3h before being quenched with saturated aqueous NH_4Cl (30 mL) and water (5 mL) and the layers were separated. The aqueous layer was washed with diethyl ether (2x20mL) and the combined organic layers set to one side. The aqueous layer was acidified using 0.5 N HCl to approximately pH 3/4 and the mixture re-extracted with ethyl acetate (3x30mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by isolera (50 g SNAP column, equilibration hex:EA (100:0), 3 CV, DCM load, then hex:EA (100:0 to 0:100), 5CV then hex:EA (0:100), 8CV) to afford 3.22 g of acid **2** in 54% isolated yield.

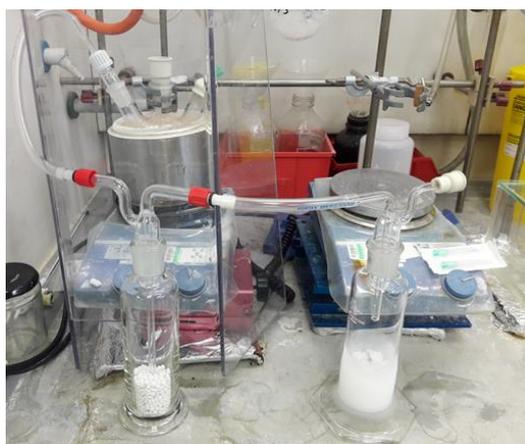
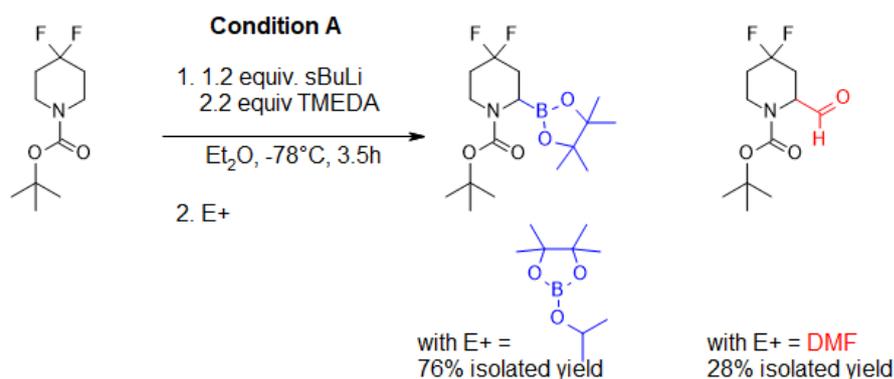


Figure S1 : Carboxylation Setup of *N*-Boc 4,4-difluoropiperidine in batch

Procedure condition B

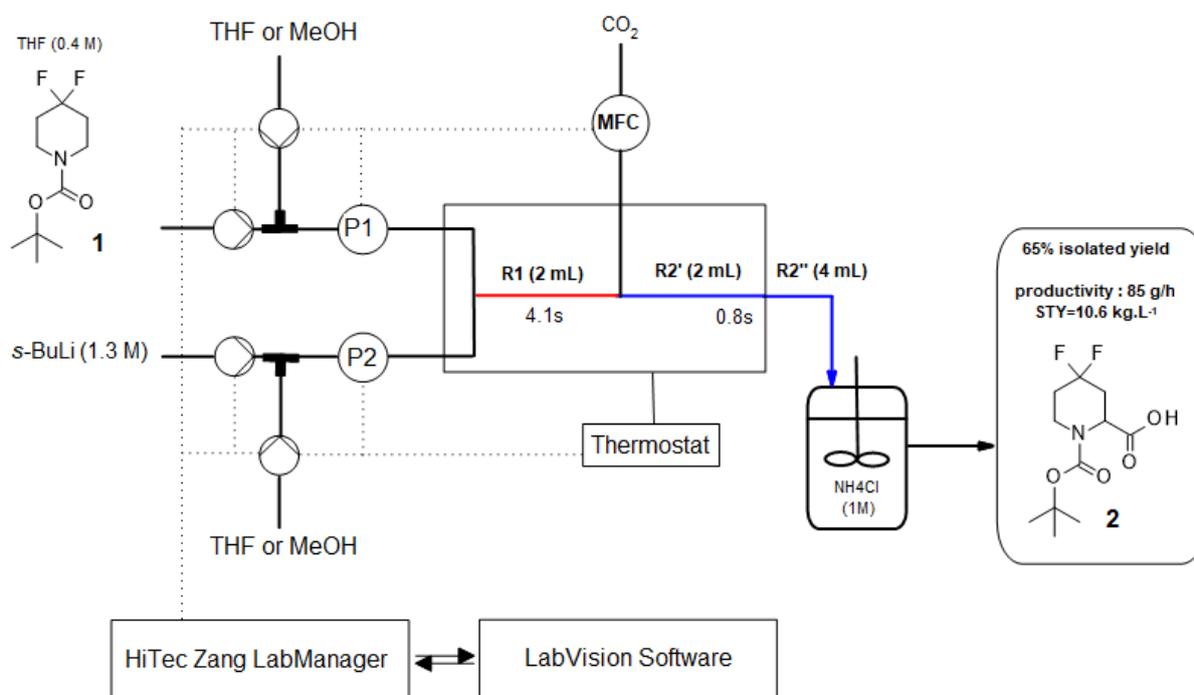
To a solution of tert-butyl 4,4-difluoropiperidine-1-carboxylate **1** (2 g, 9 mmol) in dry THF (90 mL) at -30°C was added *s*-BuLi (12.5 mL, 16.3 mmol, 1.3 mol/L in cyclohexane) dropwise over 10 minutes. The reaction was stirred for 10 minutes at -30°C , during which time an orange color resulted. CO_2 was bubbled through the reaction mixture for 30 minutes. The reaction was warmed to room temperature and quenched with saturated aqueous NH_4Cl (30 mL) and water (5 mL). The layers were separated. The aqueous layer was washed with ethyl acetate (20 mL) and the combined organic layers set to one side. The aqueous layer was acidified using 0.5 N HCl to approximately pH 3/4 and the mixture re-extracted with ethyl acetate (3x20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by isolera (50 g SNAP column, equilibration hex:EA (100:0), 3 CV, DCM load, then hex:EA (100:0 to 0:100), 5CV then hex:EA (0:100), 8CV) to afford 1.53 g of acid **2** in 64% isolated yield.

2.2. Lithiation of *N*-Boc 4,4-difluoropiperidine and trapping with various electrophiles



Scheme S2 : Trapping of lithiated *N*-Boc 4,4-difluoropiperidine with various electrophiles

2.3. Scale-up Lithiation / Carboxylation of *N*-Boc 4,4-difluoropiperidine with Erhfeld Platform in Flow



Scheme S3: Flow set-up lithiation / Carboxylation of *N*-Boc 4,4-difluoropiperidine

2.4. Procedure

Using the setup described in Scheme S3, a solution of piperidine **1** (176.8 g, 772 mmol, 0.4 M in THF) was pumped at a rate of 21 mL/min and mixed in a microreactor (before precooling) with a solution of *s*-BuLi (1.3 M in cyclohexane) pumped at a rate of 8.4 mL/min (1.3 equiv.) (both solutions were engaged simultaneously to the flow setup). The mixture was then passed through a first zone (2 mL, highlighted in red on the scheme) of the microreactor (total flow rate of 29.4 mL/min for a residence time of 4.1 s). The resulting solution of organolithium was then intercepted in the microreactor with a stream of CO₂ dispensed at a rate of 450 mL/min (2.4 equiv.). The resulting mixture reacted into the

second zone (2 mL, highlighted in blue on the scheme) of the reactor. Finally, the output stream was collected in a batch reactor (via 4 mL PTFE tubing) containing aqueous 1 M ammonium chloride (2 L).

The biphasic reaction mixture (*Aq-1* and *Org-1*) was separated. The aqueous layer was stored (*Aq-1*). The residual organic layer (*Org-1*) was diluted with 250 mL heptane and re-extracted with a further 400 mL of water. After vigorous stirring, the resulting aqueous layer was combined with *Aq-1*. 1.04 L of Citric acid was gradually added to this aqueous mixture until a pH of 3 was achieved (*Aq-2*). 1 L of isopropyl acetate and 100 mL of heptane were added to the aqueous solution (*Aq-2*). The mixture was stirred for 15 minutes and the layers separated. The organic layer (*Org-3*) was stored. The resulting aqueous layer (*Aq-3*) was re-extracted with 220 mL of isopropyl acetate and 40 mL of heptane to afford organic layer (*Org-4*). The organic phases *Org-3* and *Org-4* were combined and washed with brine (100 mL) and dried with Na₂SO₄. The organic phase was then evaporated to afford 165 g of the crude product. 75 mL of isopropyl acetate was added to the crude product. The resulting suspension was stirred at 40°C for 1 h before adding portion wise 225 mL of heptane over an additional hour. The suspension was then cooled down to 15°C and stirred 15 minutes. The suspension was filtered and washed successively with 30 mL (heptane/ isopropyl acetate 80/20), and twice with 15 mL of heptane. A sandy white solid was isolated and dried under vacuum at 40°C to afford the pure acid **2** (134 g, 65% yield¹, ¹H NMR purity>95%).

¹H NMR (400 MHz, CDCl₃) δ 8.95 (br s, 1H), 5.15–4.93 (m, 1H), 4.27 – 4.02 (m, 1H), 3.31 (m, 1H), 2.82 – 2.67 (m, 1H), 2.24 – 1.77 (m, 3H), 1.48 (s, 9H). (*rotamers are present*)

¹⁹F NMR (376 MHz, CDCl₃) δ -92.62 – -93.02 (m, J = 242.3 Hz, 1F), -103.83 (d, J = 242.1 Hz, 1F). (*rotamers are present*)

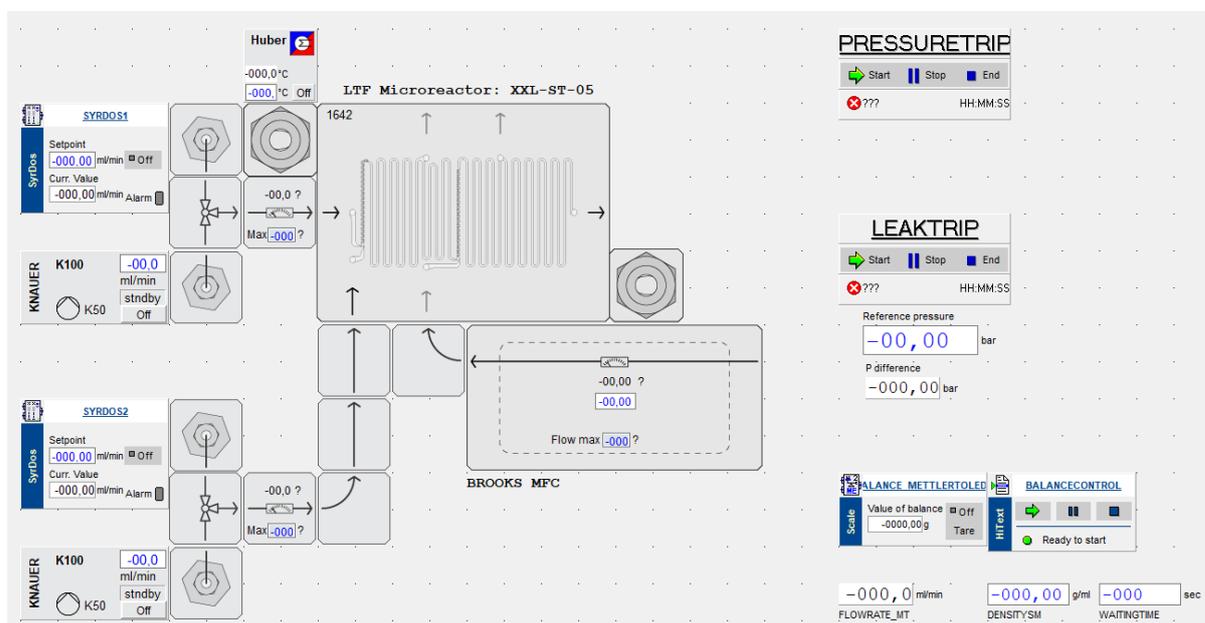
¹³C NMR (126 MHz, DMSO-*d*₆, 75°C) δ 171.73, 154.87, 122.66 (dd, J = 243.3, 238.8 Hz), 80.27, 52.69, 38.57, 34.53 (t, J = 24.4 Hz), 32.89 (t, J = 22.8 Hz), 28.37.

HRMS (ESI) [M-H]⁻=264.1047 calcd. for C₁₁H₁₆NO₄F₂=264.1047; found 264.1052

¹ Yield calculation was based on the total amount of reagents engaged in the process, 772 mmol of **1**.

3. General Flow Configuration

3.1. HiTec Zang Control Unit and LabVision Software



Scheme S4: Schematic of all components in LabVision

3.2. Flow carboxylation setup

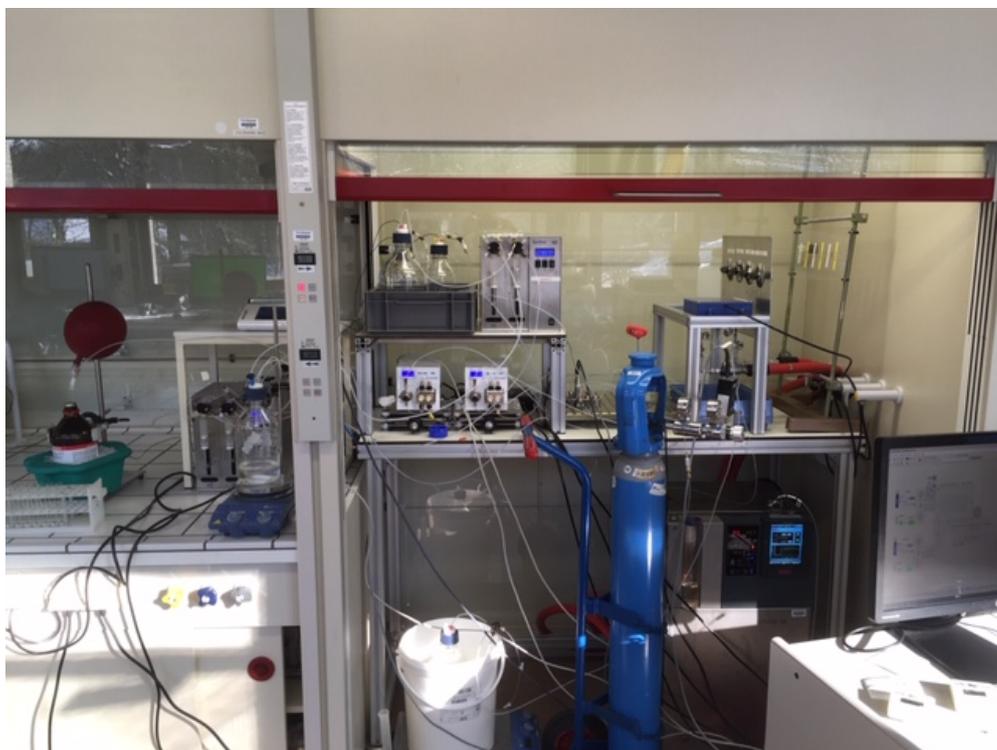


Figure S2: Flow carboxylation setup

3.3. Little Things Factory microreactor (XXL-ST-05) with integrated heat exchanger.

Wetted material	Internal volume	Mixing structure	Max pressure	Cross section	Reaction zone lithiation	Reaction zone carboxylation
Borosilicate glass	8 mL	ST-Mixer	14 bars	2.2 x 2.2 mm	2 mL	2 mL

Table S1: XXL-ST-005 microreactor specifications

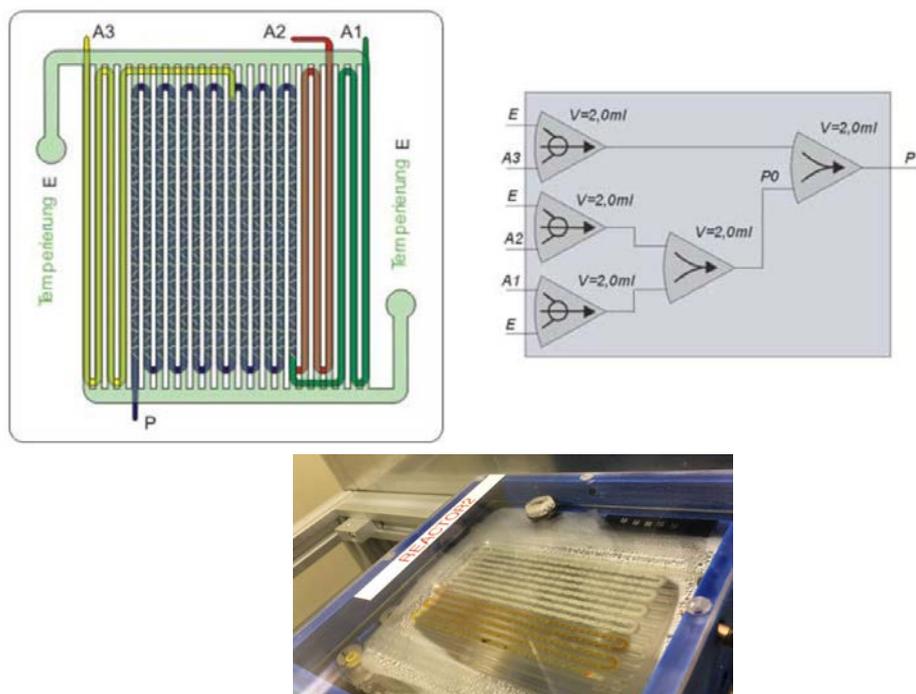


Figure S3: Schematic of the XXL-ST-005 microreactor

The XXL-ST-005 microreactor were connected to a thermostat (Huber). The temperature of the cooling/heating was set on the LabVision software and communicated *via* an RS232 interface with the thermostat.

3.4 Pumps and mass flow controller (MFC)

The system was equipped with two Syrdos pumps (SYRDOS1 and SYRDOS2) to deliver the reagents and two Knauer Azura HPLC pumps to clean the system between each run. Each pump was controlled *via* a RS232 interface by a control module (HiTec Zang LabManager) and his associated software (HiTec Zang LabVision). The mass flow controller (MFC Brooks with CO₂ specification) was also controlled *via* the same control module.

3.5 Pressure

Pressure probes were connected to the HiTec Zang LabManager and the data were recorded in the LabVision software. Data points were collected every 1 second. Pressure probes (P1 and P2) were

placed in front the microreactor. This configuration enabled us to identify pressure increase due to some precipitation inside of the microreactor. For example, in Run 1 and 2, the pressure increases slightly (<1bar) along approximately 90 min of processing. During the run 3, the pressure increases up to 7 bars due to accumulation of Li salt in the reactor. In between each 90 min run, the bottle of s-BuLi was replaced and the reactor washed with THF and MeOH (see washing procedure below).



Figure S4 : Pressure profile recorder with LabVision

3.6 Washing procedure

Before starting the washing procedure, Syrdos pumps and the Massflow controller must be stopped. Thereafter, the two three-way valves were switched towards the washing solution lines (Scheme S3). Firstly, dry THF was pumped at a rate of 20 mL/min (10 mL/min on each Knauer Azura HPLC pumps) during 5 minutes towards the microreactor. Then, dry THF was replaced by dry MeOH (using three-way valves, not depicted on Scheme S3 for the sake of clarity). Dry MeOH was pumped at a rate of 10 mL/min during 10 minutes. Finally, dry THF was pumped at a rate of 10 mL/min during 10 minutes. At the end of the cleaning procedure HPLC pumps were stopped and the three-way valves were switched back towards the reagent lines. The Massflow controller, followed by the Syrdos pumps were restarted to continue the production process. The overall cleaning procedure (25 minutes) was performed after the consumption of each bottles of s-BuLi to prevent clogging.

3.7 Safety procedure

-High pressure automatic shutdown: if the pressure increased above 10 bars the LabVision Software automatically turned off all pumps for safety reason (see Figure S4 for HiText script).

-Low pressure automatic shutdown (Leak trip): if the monitored pressures (P1 or P2) experienced a decrease of pressure superior to 0.9 bar compare to the pressure at steady state (REFPRESSURE), the LabVision software automatically turned off all pumps for safety reason (see Figure S5 for HiText script).

```

begin if (!P1>10) or (!P2>10) then

    !SYRDOS1.ON=0
    !SYRDOS2.SETP=0
    !PUMPSM.ON=0
    !PUMP_WASH1.ON=0
    !PUMPWASHSM.ON=0

    !SYRDOS1.SETP=0
    !SYRDOS2.SETP=0
    !PUMPSM.F_W=0
    !PUMP_WASH1.F_W=0
    !PUMPWASHSM.F_W=0
    !BROOKSMFC_SETPOINTVALUE=0

    MessageBox("Overpressure reached. Pump has been switched off", "Overpressure Warning!", MB_Show)
    while IsMessageBoxOpen=True repeat
    Beep
    wait 1 sec
    end while

end if
Goto begin

```

Figure S5 : HiText script for high-pressure shutdown

```

begin !PDIFF1= !REFPRESSURE-!P1

if (!REFPRESSURE-!P1 >0.9) or (!REFPRESSURE-!P2 >0.9) then

    !SYRDOS1.ON=0
    !SYRDOS2.ON=0
    !PUMPSM.ON=0
    !PUMP_WASH1.ON=0
    !PUMPWASHSM.ON=0

    !SYRDOS1.SETP=0
    !SYRDOS2.SETP=0
    !PUMPSM.F_W=0
    !PUMP_WASH1.F_W=0
    !PUMPWASHSM.F_W=0
    !BROOKSMFC_SETPOINTVALUE=0

    MessageBox("Lowpressure reached. Pump has been switched off", "Lowpressure Warning!", MB_Show)
    while IsMessageBoxOpen=True repeat
    Beep
    wait 1 sec
    end while

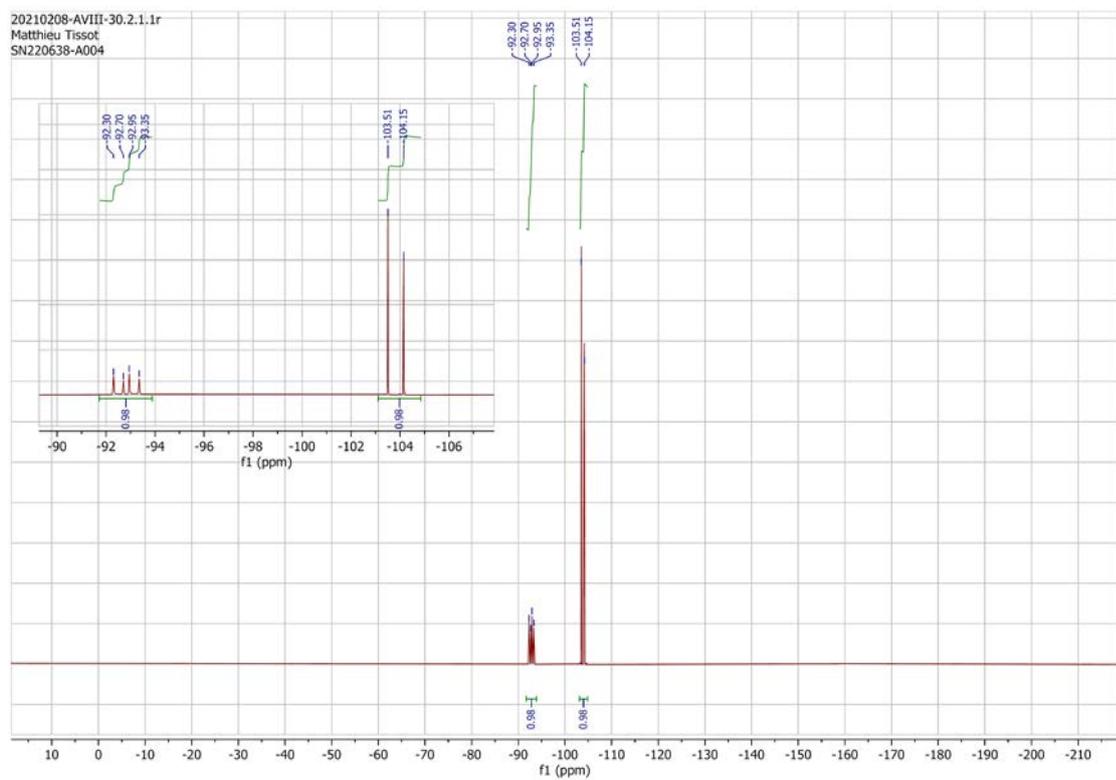
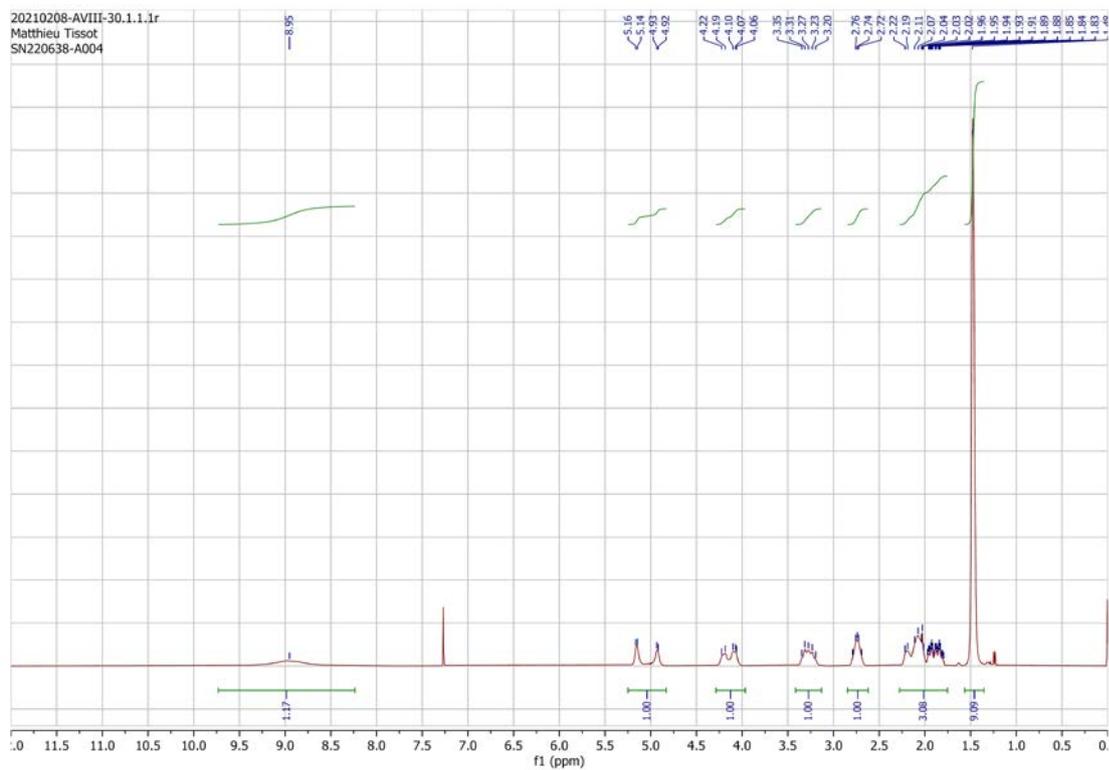
end if
Goto begin

```

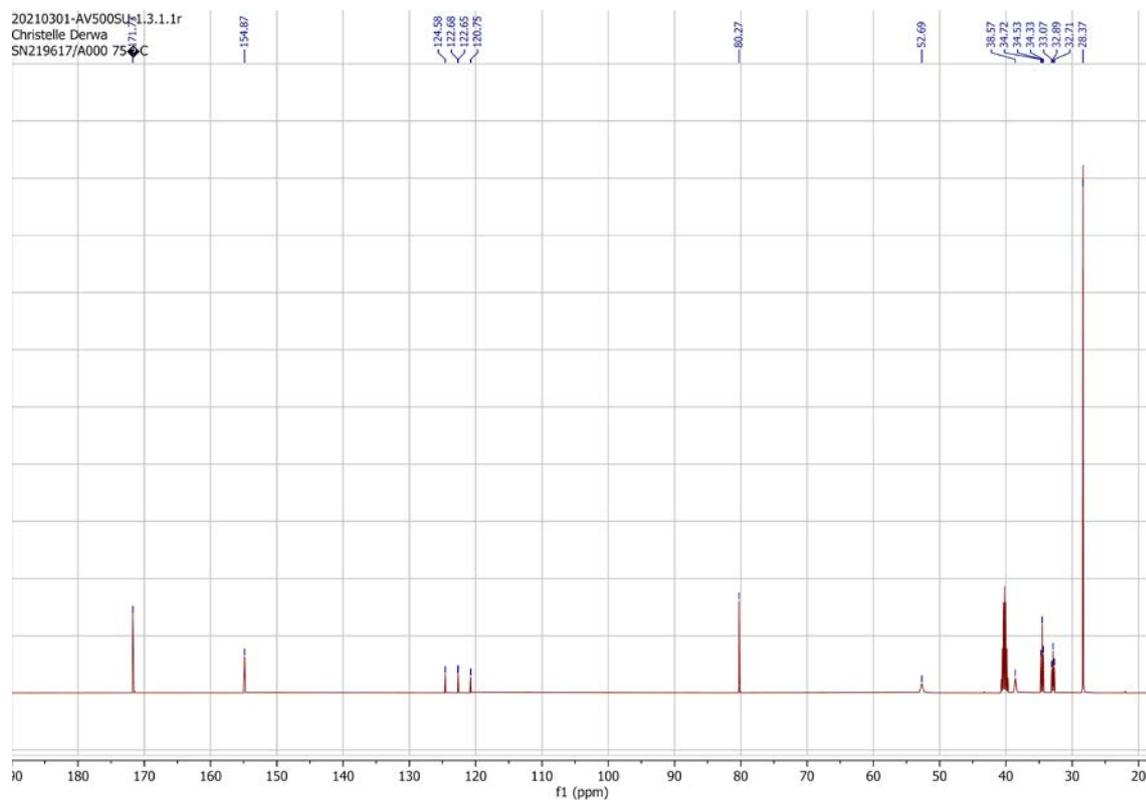
Figure S6 : HiText script for leak trip shutdown

4. NMR Spectra

4.1 ^1H and ^{19}F NMR of compound **2** after isolation (CDCl_3)



4.2 ^{13}C of compound **2** after isolation (DMSO- d_6 -75°C)



4.3 ^{19}F NMR of compound at steady state after Citric acid aqueous solution/*i*-PrOAc work up

