

# Scale-Up and Optimization of a Continuous Flow Carboxylation of *N*-Boc-4,4-difluoropiperidine Using *s*-BuLi in THF

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**ABSTRACT:** We report a large-scale carboxylation of *N*-Boc-4,4-difluoropiperidine (**1**) enabled by a continuous flow process. The flow process involved *N*-Boc-directed  $\alpha$ -deprotonation using *s*-BuLi in THF and subsequent trapping with CO<sub>2</sub> gas. Flow chemistry enabled the safe and scalable preparation of 400 g of carboxylic acid **2** over the course of a day to support our medicinal chemistry research program.

**KEYWORDS:** continuous chemistry, carboxylation, organolithium, microreactor, flash chemistry, gas–liquid

## 1. INTRODUCTION

Carboxylic acids are useful and attractive building blocks in organic synthesis. Recently, the emergence of photochemical decarboxylative processes<sup>1</sup> has widened the scope of transformations offered by this key functionality. Among the known methods of preparation, carboxylation of organolithiums with abundant and inexpensive CO<sub>2</sub> remains one of the most attractive preparatory techniques available.<sup>2</sup> However, CO<sub>2</sub> gas handling and the safety concerns associated with the use of organolithiums in batch mode remain important hurdles to performing this chemistry on a large scale. In this context, the emergence of organolithium chemistry in continuous flow<sup>3</sup> and the concept of flash chemistry (pioneered by Yoshida<sup>4</sup>) offer an opportunity to develop an efficient, scalable, and safe solution to access carboxylic acids under flow conditions.<sup>5</sup>

## 2. BACKGROUND

*N*-Boc-4,4-difluoropiperidine-2-carboxylic acid (**2**) has recently emerged as a key intermediate requiring a large-scale synthesis. Acid **2** was initially prepared in batch starting from the considerably less expensive precursor *N*-Boc-4,4-difluoropiperidine (**1**) using the complex-induced proximity effect (CIPE) protocol for lithiation of *N*-Boc heterocycles reported by Beak.<sup>6</sup> This result was quite remarkable since side reactions could have arisen, such as the elimination of HF from the CF<sub>2</sub> group or intramolecular displacement of fluorine leading to cyclopropane formation (as observed following lithiation with 4-chloropiperidine).<sup>7,8</sup> The lithiated piperidine was subsequently trapped with CO<sub>2</sub> to afford **2** in 54% isolated yield when 5 g was used (condition A, Scheme 1).<sup>9,10</sup> O'Brien and co-workers reported an  $\alpha$ -carboxylation of *N*-Boc-pyrrolidines with *s*-BuLi, replacing the TMEDA/Et<sub>2</sub>O combination used in Beak's protocol by THF.<sup>11</sup>

In this case the metalation of *N*-Boc-pyrrolidines is faster than the well-known reaction between THF and *s*-BuLi. This simpler protocol was also applied to **1**, this time providing **2** in 64% isolated yield (condition B, Scheme 1). Decomposition of the

lithiated piperidine could be responsible for the moderate yield of this transformation, as recently disclosed by O'Brien on the pyrrolidine system.<sup>11</sup>

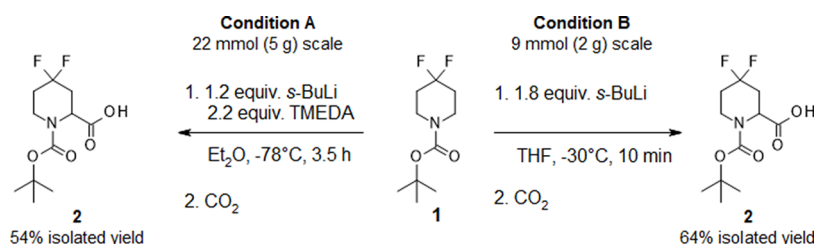
On the basis of this satisfactory result, scale-up in batch was considered and supported by several examples from process groups,<sup>12</sup> but limitations surrounding the handling of CO<sub>2</sub> gas and organolithium reagents combined with the relatively high dilution of the process prompted us to investigate a flow setup.

## 3. PROCESS DEVELOPMENT

We performed the first laboratory flow experiments using a Vapourtec HPLC pump to dispense the solution of **1**, a Syrdos syringe pump to dispense *s*-BuLi, a 2 mL Uniqsis glass microreactor (R1), and a 2 mL coil PTFE reactor (R2') connected to the reactor collection vessel with a 0.5 mL piece of PTFE tubing (R2''). The temperatures (*T*) of both reactors (R1 and R2') were adjusted with a polar bear cooling system.<sup>13</sup> In the standard setup, a 0.4 M solution of **1** is mixed with a solution of *s*-BuLi (1.3 M in cyclohexane) in R1. Then the resulting mixture is intercepted by a stream of CO<sub>2</sub> dispensed by a Vapourtec SF10 peristaltic pump using a T-mixer directly connected to the output of R1. The heterogeneous mixture (gas/liquid) was then directed into R2' to achieve the trapping of the lithiated piperidine derivative with CO<sub>2</sub> (Scheme 2). The output stream was collected in a batch reactor containing aqueous 1 M ammonium chloride. With 1.3 equiv of *s*-BuLi and 1.34 equiv of CO<sub>2</sub> at *T* = −10 °C, 87% conversion was observed after residence times of 17.1 and 2.2 s in R1 and R2,<sup>14</sup> respectively (entry 1, Table 1). The lower control of the exotherm when the

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Scheme 1. Initial Batch Lithiation/Carboxylation Sequence Using *s*-BuLi

## Scheme 2. Flow Setup Used in the First Laboratory Experiments

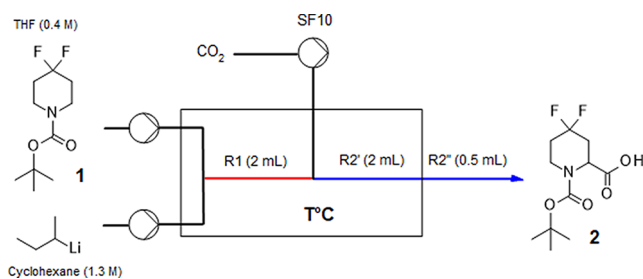


Table 1. Experimental Results for the Continuous Flow Carboxylation Reaction

entry	equiv of <i>s</i> -BuLi/ CO <sub>2</sub>	<i>T</i> [°C] <sup>d</sup>	flow rates of <i>s</i> -BuLi/1/CO <sub>2</sub> [mL/min]	residence times in R1/R2' <sup>c</sup> [s]	conv [%] <sup>a,b,f</sup>
1	1.3/1.34	-10	2/5/60	17.1/2.2	87
2	1.3/1.34	0	2/5/60	17.1/2.2	84
3	1.3/2	0	2/5/90	17.1/1.5	87
4	1.3/1.34	-10	2/5/60	17.1/2.7	91
5	1.6/1.34	-10	2.5/5/60	16.0/2.2	65
6	1.3/1.28	-10	2.8/7/80	12.2/1.7	94
7	1.3/1.28	-10	2.8/7/80	12.2/1.7	94 (58%/69 g <sup>e</sup> )

<sup>a</sup>Sampling was performed directly at the output of the process in an aqueous citric acid (1 M)/*i*-PrOAc mixture (1:1 v/v). <sup>b</sup>Conversion was determined at steady state by <sup>19</sup>F NMR spectroscopy. <sup>c</sup>The residence time  $t_{R2}$  was calculated with  $V_{R2} = V_{R2'} + V_{R2''}$ . <sup>d</sup>Temperature set on the cooling system. <sup>e</sup>Isolated yield/mass of starting material converted are given in parentheses. <sup>f</sup>The output stream was quenched in a vessel containing aqueous NH<sub>4</sub>Cl (1 M) cooled to 0 °C.

temperature was set to 0 °C seems to induce a decrease in conversion (entry 2, Table 1), likely stemming from side reactions of *s*-BuLi<sup>15</sup> and from a lower solubility of CO<sub>2</sub>. Augmentation of the number of equivalents of CO<sub>2</sub> injected displayed no significant impact on the conversion (entry 3, Table 1).<sup>16</sup> However, prolonging the residence time of the carboxylation step to 2.7 s (with R2'' = 1 mL) enhanced the conversion to 91% (entry 4, Table 1). Interestingly, when the amount of *s*-BuLi was increased to 1.6 equiv, the conversion dropped to 65% (entry 5, Table 1). We hypothesized that the excess *s*-BuLi reacts with CO<sub>2</sub> faster than the lithiated piperidine. Thereafter, we improved the productivity without negatively impacting the conversion (94%) by increasing all of the flow rates, leading to residence times of 12.2 and 1.7 s in R1 and R2, respectively (entry 6, Table 1). Finally, we ran a scale-up experiment over 111 min without interruption to transform 69 g of 1 into carboxylic acid 2 in 58% isolated yield (entry 7, Table 1).

To prepare larger quantities of the desired compound and improve safety, our process was transferred to a new platform. The large-scale implementation included the use of Syrdos syringe pumps to deliver *s*-BuLi and 1, and a Brooks mass flow controller (MFC) was used for CO<sub>2</sub> (Scheme 3). The lithiation/carboxylation sequence was performed in a single glass microreactor (XXL-ST-05, Little Thing Factory)<sup>17</sup> with integrated heat exchangers connected to a thermostat. The microreactor was made of two sections (R1 = 2 mL and R2' = 2 mL) to control the lithiation and carboxylation reactions sequentially.<sup>18</sup> Pressure sensors (P1 and P2) were installed on a Modular Micro-Reaction System (MMRS) manufactured by Ehrfeld Mikrotechnik.<sup>19</sup> The pumps, MFC, thermostat, and pressure sensors were connected to a HiTec Zang LabManager and controlled by LabVision software (Scheme 3). During the process, LabVision Software was programmed to stop all of the

## Scheme 3. Large-Scale Flow Setup and XXL-ST-05 Microreactor

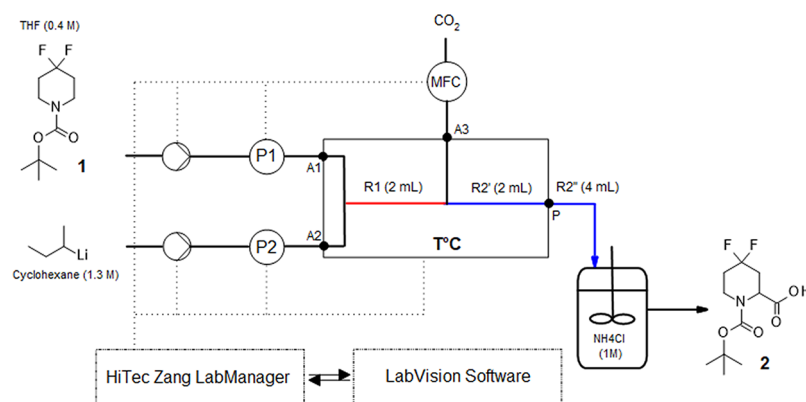


Table 2. Experimental Results for Optimization and Scale-Up of the Carboxylation Process

entry	equiv of <i>s</i> -BuLi/CO <sub>2</sub>	T [°C] <sup>d</sup>	flow rates of <i>s</i> -BuLi/1/CO <sub>2</sub> (mL/min)	residence times in R1/R2 <sup>c</sup> [s]	conv. [%] <sup>a,b,f</sup>
1	1.3/1.28	−10	2.8/7/80	12.2/4	81
2	1.3/1.6	−10	2.8/7/100	12.2/3.3	84
3	1.3/2.4	−10	2.8/7/150	12.2/2.3	87
4	1.3/2.4	−20	2.8/7/150	12.2/2.3	94
5	1.4/2.4	−20	2.8/7/150	12.2/2.3	92
6	1.3/2.4	−20	8.4/21/450	4.1/0.8	83 (41%/44 g <sup>e</sup> )
7	1.3/2.4	−40	8.4/21/450	4.1/0.8	98 (65%/177 g <sup>e</sup> )

<sup>a</sup>Sampling was performed directly at the output of the process in an aqueous citric acid (1 M)/*i*-PrOAc mixture (1:1 v/v). <sup>b</sup>Conversion was determined at steady state by <sup>19</sup>F NMR spectroscopy. <sup>c</sup>The residence time  $t_{R2}$  was calculated with  $V_{R2} = V_{R2'} + V_{R2''}$ . <sup>d</sup>Temperature set on the cooling system. <sup>e</sup>Isolated yield/mass of starting material converted are shown in parentheses. <sup>f</sup>The output stream was quenched in a vessel containing aqueous NH<sub>4</sub>Cl (1 M) cooled to 0 °C.

pumps and the MFC automatically when the pressure built up to 10 bar or a leakage occurred (see the Supporting Information).

The conditions optimized on the Vapourtec setup (flow rates, temperature, and residence times R1 and R2<sup>14</sup>) were tested on the new setup. A decrease in conversion was observed (81% cf. 94% previously), suggesting that the temperature of the system was not well-maintained (entry 1, Table 2). Moreover, the amount of CO<sub>2</sub> applied to the reaction (1.6 or 2.4 equiv) did not appreciably affect the conversion (84% and 87%, respectively), further supporting this argument (entries 2 and 3, Table 2). As a result, we decreased the temperature further to −20 °C, which afforded 94% conversion (entry 4, Table 2). Increasing the amount of *s*-BuLi afforded a slight decrease in conversion (92%; entry 5, Table 2), as observed with the previous setup. To maximize the productivity of the process, the flow rates for all of the reagents were increased 3-fold to afford 83% conversion (entry 6, Table 2). To control the exotherm, the temperature was decreased to −40 °C, resulting in 98% conversion (entry 7, Table 2). The optimized conditions were run over 95 min<sup>20</sup> with no interruption, and 134 g of 2 was obtained in 65% overall yield with a productivity of 85 g/h (entry 7, Table 2). At times, lithium salt precipitation was observed at the mixing point between 2 and *s*-BuLi, which led to clogging and an increase in pressure in the system. Consequently, a washing procedure<sup>21</sup> (THF/MeOH/THF) was used during the production campaign (see the Supporting Information for a detailed flow setup and procedure) between each run, resulting in the preparation of up to 400 g of acid 2 over the course of a day.<sup>22</sup>

#### 4. CONCLUSION

An organolithium flow platform allowing the preparation of multigram quantities of key carboxylic acid 2 has been developed. This gas–liquid flow protocol highlights the use of *s*-BuLi and CO<sub>2</sub> to enable the carboxylation of *N*-Boc-4,4-difluoropiperidine with a product throughput of 85 g/h in an 8 mL reactor, corresponding to a space-time yield of 10.6 kg L<sup>−1</sup> h<sup>−1</sup>. The safety and robustness of the process was ensured by the integration of our equipment with a control system. Ongoing work within our research group will further expand this platform to new organometallic reactions.

#### 5. EXPERIMENTAL SECTION

**Typical Procedure for the Scaled-Up Flow Lithiation/Carboxylation Sequence.** With the setup described in Scheme 3, 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 (after 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 in the flow setup). The mixture was then passed through a first zone of the microreactor (volume of 2 mL and a total flow rate of 29.4 mL/min, giving a residence time of 4.1 s). The resulting solution of organolithium was then intercepted in the microreactor with a stream of CO<sub>2</sub> dispensed at a rate of 450 mL/min (2.4 equiv). The resulting mixture reacted in the second zone 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) (Scheme 1). The jacket of the batch reactor was set at 0 °C during the collection.

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 of heptane and re-extracted with a further 400 mL of water. After vigorous stirring, the resulting aqueous layer was combined with Aq-1, and 1.04 L of citric acid was gradually added to this aqueous mixture until a pH of 3 was achieved (Aq-2). Isopropyl acetate (1 L) and 100 mL of heptane were added to Aq-2, and the mixture was stirred for 15 min. The layers were separated, and 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 another organic layer (Org-4). The organic phases Org-3 and Org-4 were combined, washed with brine (100 mL), and dried with Na<sub>2</sub>SO<sub>4</sub>. The organic phase was then evaporated to afford 165 g of the crude product, to which 75 mL of isopropyl acetate was added. The resulting suspension was stirred at 40 °C for 1 h before 225 mL of heptane was then cooled to 15 °C, stirred for 15 min, filtered, and washed successively with 30 mL of 80:20 heptane/isopropyl acetate and twice with 15 mL of heptane. A sandy white solid was isolated and dried under vacuum at 40 °C to afford pure acid 2 (134 g, 65% yield, NMR purity >95%).

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.1c00092>.

Experimental procedures and NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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(18) All of the reagents were pre-cooled in the microreactor (red, green, and yellow sections in the microreactor scheme) before entering the reaction zones (blue section).

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(20) A run of 95 min corresponds to the consumption of a bottle of *s*-BuLi (800 mL).

(21) The complete washing procedure was performed in 25 min between each run.

(22) During the production campaign, three runs of 95 min were performed with one washing procedure between each run.