

## Supporting Information

### **Scale-up of continuous biphasic liquid/liquid reactions under super-heating conditions: methodology and reactor design**

*Francesca Mandrelli, Alessia Buco, Lorenzo Piccioni, Florian Renner, Bertrand Guelat, Benjamin Martin, Berthold Schenkel and Francesco Venturoni\**

<sup>†</sup> Novartis Pharma AG, WSJ-042, 4002 Basel, Switzerland.

[francesco.venturoni@novartis.com](mailto:francesco.venturoni@novartis.com)

<b>1. General experimental method</b>	<b>S2</b>
<b>2. General procedure for Residence Time Distribution experiments</b>	<b>S2</b>
<b>3. Thermal stability experiment</b>	<b>S3</b>
<b>4. Kinetic determination</b>	<b>S4</b>
<b>5. Preparation of N-benzyl piperidine in microwave reactor</b>	<b>S5</b>
<b>6. Preparation of N-benzyl piperidine in continuous mode</b>	<b>S6</b>

**1. General experimental method:** All chemical were purchased as reagent grade and used without further purification, unless otherwise noted. Compound 5 and 6 were purchased internally from production facilities. HPLC analyses were performed in Agilent 1200, equipped with Zorbax column. NMR analysis was performed on a Bruker 400 MHz spectrometer in the specified deuterated solvent. The  $^1\text{H}$  NMR data is reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and integration. Reactions in microwave were performed in Biotage Initiator<sup>+</sup>.

## **2. General procedure for Residence Time Distribution experiments**

Residence Time Distribution experiments were performed with a biphasic model solvent system that resulted to be water and ethyl acetate, using a solution of toluene in ethyl acetate (4% v/v) as tracer. The experiments were performed at room temperature and atmospheric pressure. The setup comprises two SyrDos2 pumps, a six-way valve at the inlet of the reactor for the injection of the tracer and an UV-cell close to the outlet of the reactor connected to a spectrometer to measure the transmittance of the UV signal.

To perform these experiments, the reactor was first filled with ethyl acetate, when it was completely filled the two solvents were pumped in the correct ratio. The total flow rate was calculated based on the residence time that we wanted to investigate. Once the system reached the steady state, thus when the ratio between the solvents at the outlet was the same of the one at the inlet, 2 ml of the solution of the tracer were injected through the six-way valve and the measurement of the UV-absorption was started. The measurement was carried out for three residence times to be sure that all the amount of the tracer was released. The graphics resulting from the measurement of the UV signal correlated the absorbance with the time and they allowed us to characterize the behavior of the reactor varying the experimental parameters.

After having emptied the column and having measured the amount of the two solvents, the accumulation of the heavy phase was calculated as follows:

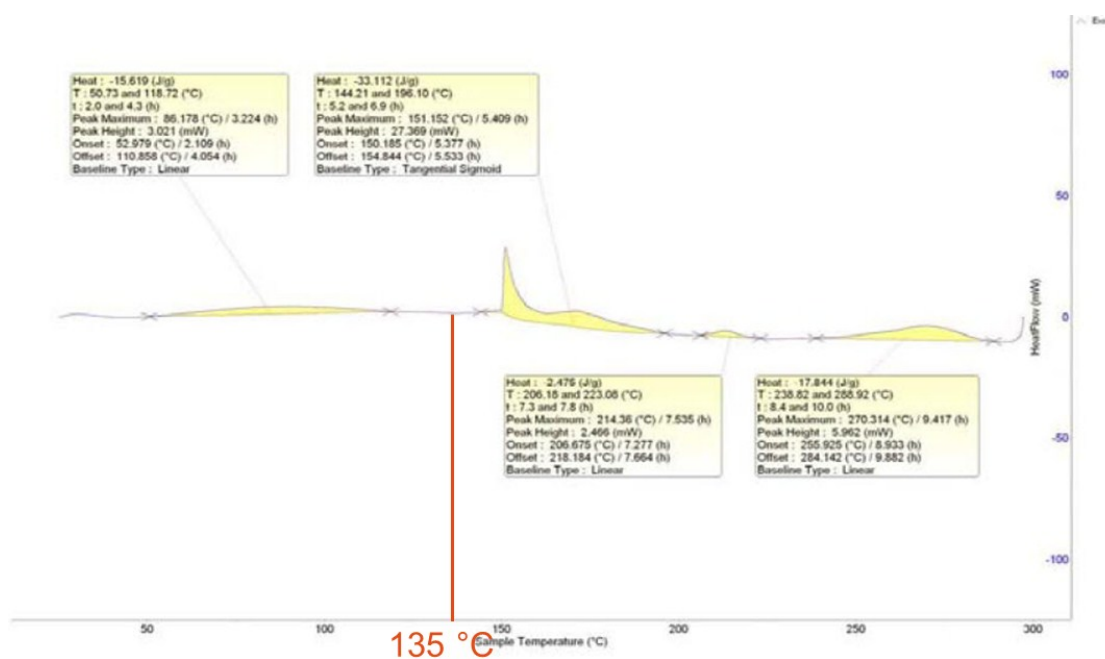
$$\text{Accumulation} = \frac{\text{Exp volume of water} - \text{Theoretical volume of water}}{\text{Total volume inside the reactor}} * 100$$

### 3. Thermal stability experiment

A Setaram experiment was performed to evaluate the heat released from the reaction and from eventual side reactions (gold plate steel tube with glass liner). Three solutions were prepared:

- Solution 1: 898 mg of benzylamine (1 eq) were diluted to 8 ml with Me-THF
- Solution 2: 3854,06 mg of 1,5-dibromopentane (2 eq) were diluted to 8 ml with Me-THF
- Solution 3: 739,14 mg of NaOH (2,2 eq) were diluted to 10 ml with water

6 ml of solution 1, 6 ml of solution 2 and 8 ml of solution 3 were combined and analyzed in a temperature range that goes from 25 °C to 300 °C.



**Figure 1.** Setaram experiment outcome

The resulting graphic shows four weak exothermic reactions happening within the investigated temperature range. The first one can be associated to the desired reaction, while the following to

decomposition reactions. Since the onset of the first decomposition reaction is around 150 °C, we defined the maximum process temperature at 135 °C.

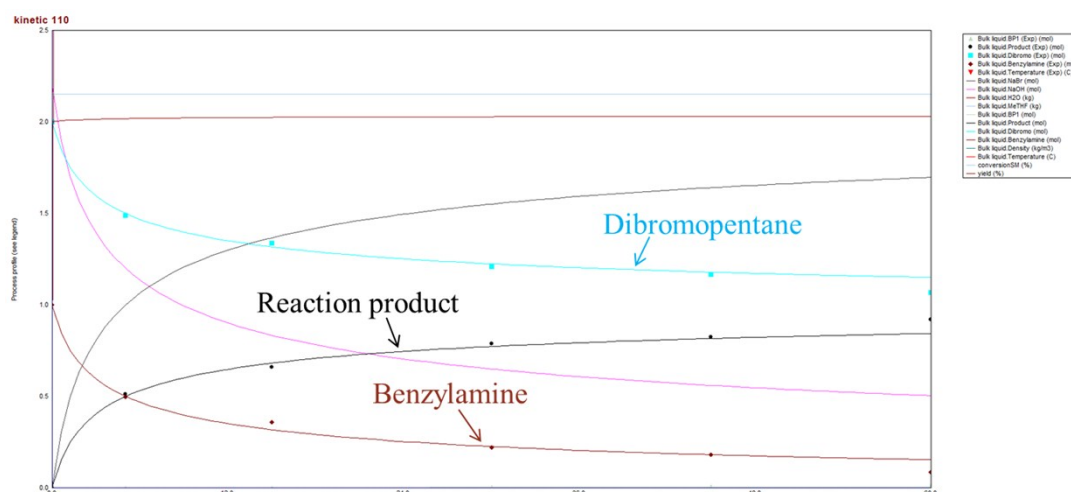
#### 4. Kinetic determination

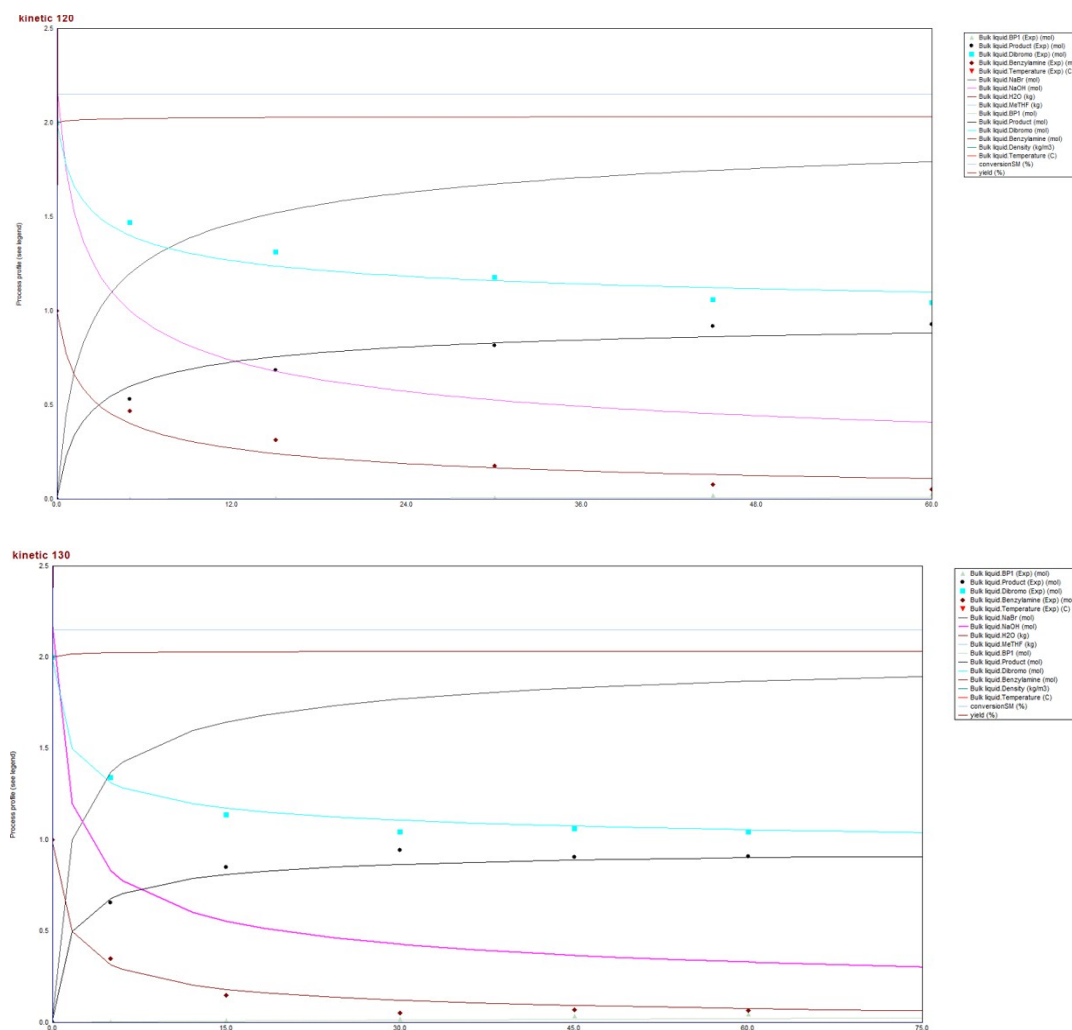
The kinetic of the reaction was studied performing microwave experiments following the described procedure. Three temperatures (110 °C, 120 °C, 130 °C) were investigated for different reaction times (5 min, 15 min, 30 min, 45 min, 60 min). The obtained data were then analyzed with DynoChem. In order to obtain a reliable model to perform virtual experiments, the kinetic parameters were fitted to experimental data:

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
Process		General model template: To edit, use the DynoChem Excel toolbar and menu.																							
1	Phase	Bulk liquid	liquid (set volume)																						
2		Temperature		C	Plot																				
3		Volume		L																					
4		Density		kg/m3	Plot																				
5		Qr		W																					
6		Benzylamine		mol	Plot																				
7		Dibromo		mol	Plot																				
8		Product		mol	Plot																				
9		BP1		mol	Plot																				
10		MeTHF		Kg	Plot																				
11		H2O		Kg	Plot																				
12		NaOH		mol	Plot																				
13		NaBr		mol	Plot																				
14																									
15																									
16																									
17	Reactions in Bulk liquid																								
18	Reaction	k>	2.95E-01	L3/mol3.s	at	140 C	Ea>	71.028 kJ/mol	dHr	kJ/mol	*	Benzylamine	+	Dibromo	+	2 NaOH	>	Product	+	2 NaBr	+	2 H2O			
19	DEC2	k>	8.01E-04	L2/mol2.s	at	140 C	Ea>	142.262 kJ/mol	dHr	kJ/mol	*	Product	+	Dibromo	+	NaOH	>	BP1	+	NaBr	+	H2O			
20																									

Elementary reactions

The results of the fitting for the three investigated temperature are reported in the following graphics:





**Figure 2.** Fitting of experimental data at 110, 120 and 130 °C

## 5. Preparation of N-benzyl piperidine in microwave reactor

In a typical experiment benzylamine (1 equivalent, 0.53 M) and 1,5-dibromopentane (2 equivalent) were dissolved in Me-THF, while the base (3 equivalents, 2.2 M) was dissolved in water. The two phases were combined in a vial of appropriate size equipped with a magnetic stirrer. The vial was then placed inside the microwave reactor and after having set the parameters the reaction was started. Each single experiment was analyzed by HPLC assay diluting 100  $\mu$ l of organic phase to 10 ml with acetonitrile and injecting 2  $\mu$ l of the resulting solution.

## 6. Preparation of N-benzyl piperidine in continuous mode

Three feedstock solutions were prepared:

- 23.57 g of benzylamine in 185 ml of Me-THF
- 101.17 g of 1,5-dibromopentane in 185 ml of Me-THF
- 26.40 mg of NaOH in 296 ml of water

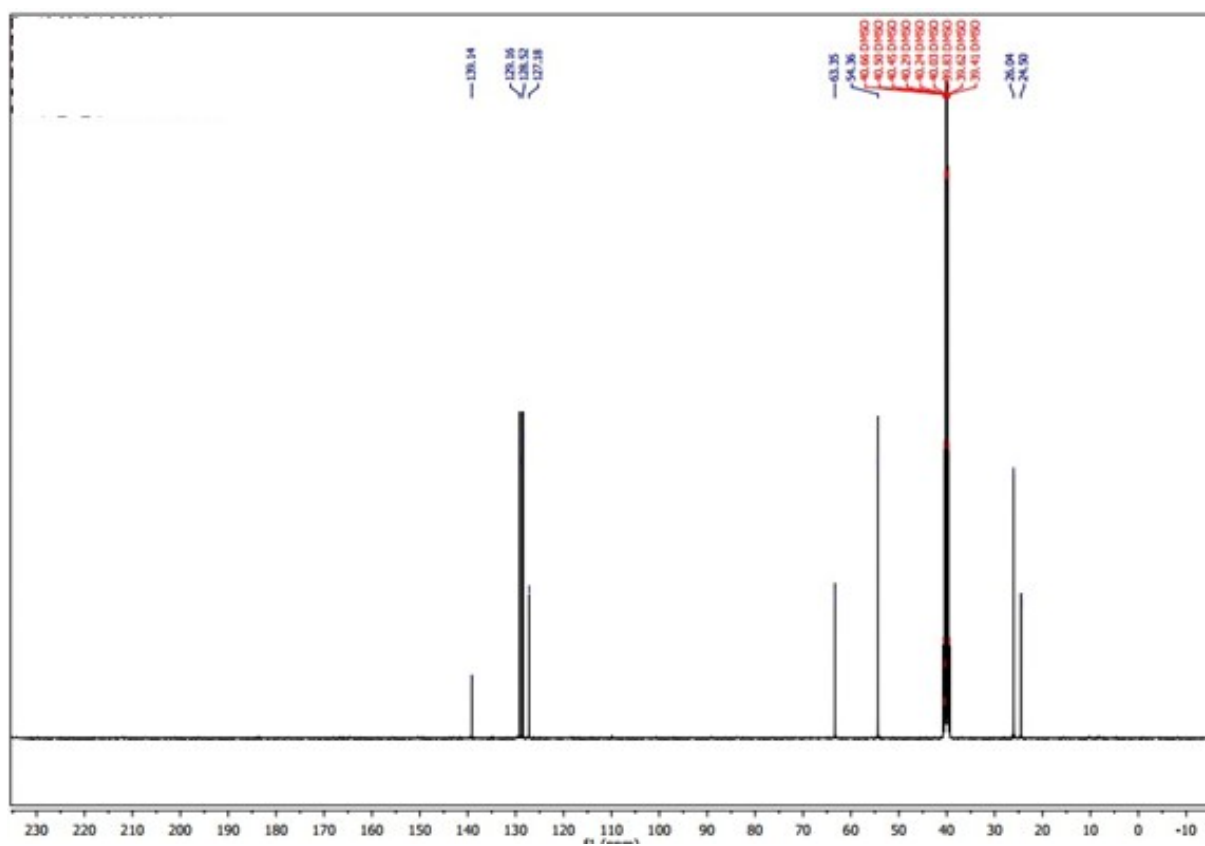
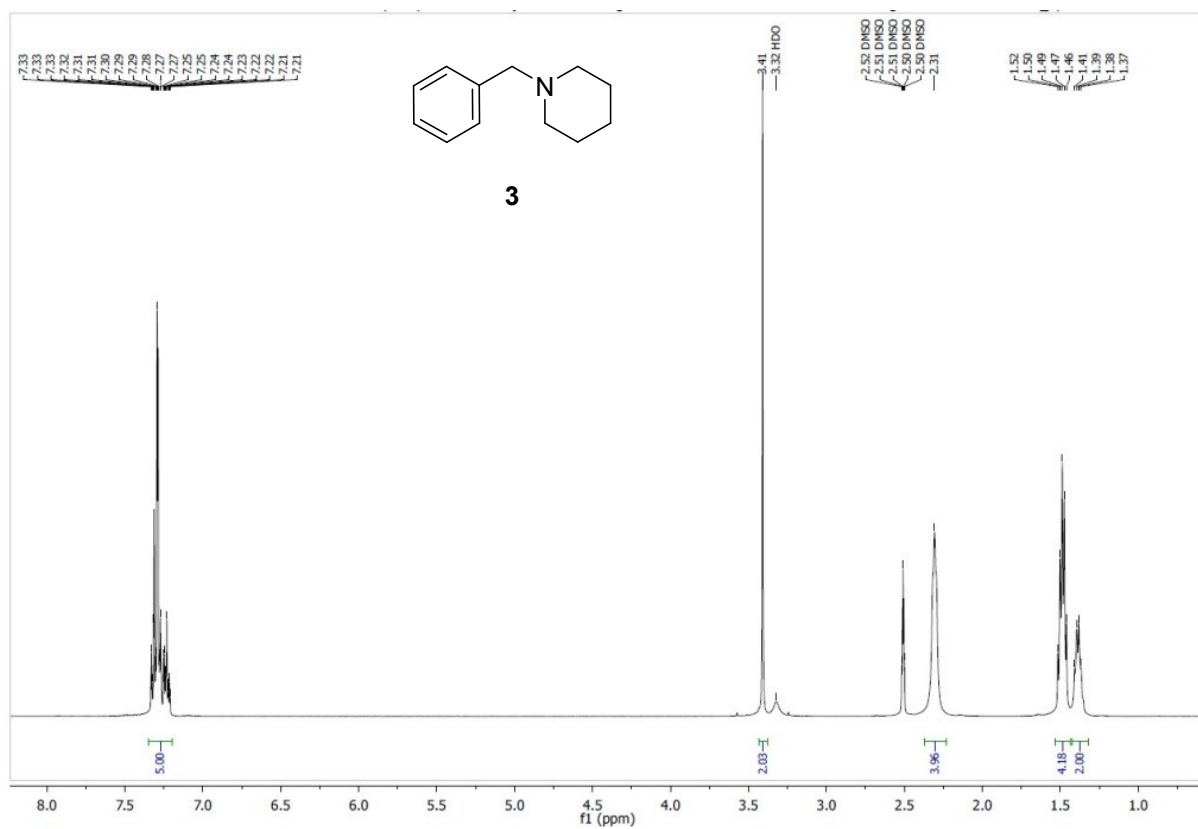
The reactor was first filled with pure solvents (water and Me-THF, 1:1.25 v/v) at room temperature and ambient pressure. Then the system pressure was set up to 7 bar. After the system reached a stable pressure and having checked that there were no leakages the heating was started. Once the system reached the desired temperature, the experiment was started. The pumps were switched to pump the solution, for the first few minutes all the reagents were pumped with the same flow rate (3 ml/min) to let them reach the inlet of the reactor in the same moment, then the flow rates were corrected:

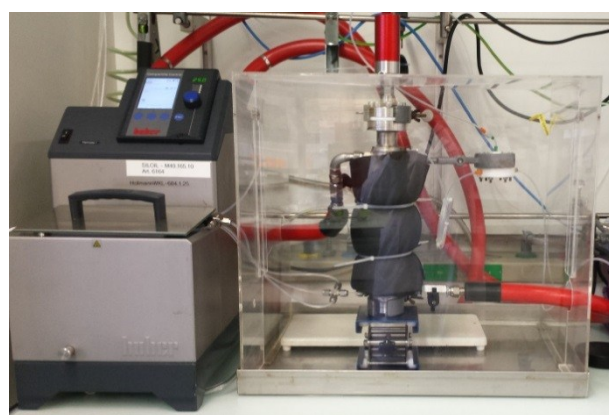
- Benzylamine in Me-THF: 1.45 ml/min
- Dibromopentane in Me-THF: 1.70 ml/min
- NaOH in water: 2.05 ml/min

Samples were collected at the outlet of the system at room temperature. Five samples were collected at steady state, each one for 15 minutes.

The samples collected at steady state were combined and added of a 1M HCl solution 554.7 ml. the organic phase was separated and the aqueous extracted with 250 ml of Me-THF. The aqueous phase was added of 600 ml of NaOH 1M and extracted with fresh Me-THF. The organic layer was collected, dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure to afford 17 g of purified product as yellowish oil.

$^1\text{H}$  NMR (400 MHz,  $\text{d}_6$ -DMSO) ppm 1.37-1.41 (m, 2 H), 1.46-1.52 (m, 4 H), 2.31 (m, 4 H), 3.41 (s, 2 H), 7.21-7.33 (m, 5 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{d}_6$ -DMSO) ppm 25.5, 26.0, 54.4, 65.4, 127.2, 128.5, 129.1, 139.0.





**Figure 3.** Setup for the continuous reaction



