Supporting information

From alcohol to 1,2,3-triazole via multi-step continuous-flow synthesis of rufinamide precursor

Svetlana Borukhova,[a] Timothy Noël,[a,b] Bert Metten,[c] Eric de Vos[c] and Volker Hessel*[a]

Corresponding author's contact information: v.hessel@tue.nl

[a.] Department of Chemical Engineering and Chemistry, Technische Universiteit Eindhoven, Den Dolech 2, 5600 MB Eindhoven, Netherlands.
[b.] Department of Organic Chemistry, Ghent University, Krijgslaan 281 (S4), 9000 Ghent, Belgium.
[c.] S.A. Ajinomoto OmniChem N.V., Cooppallaan 91, 9230 Wetteren, Belgium.

1. General Reagent Information

Hydrogen chloride gas was purchased in 10 L bottle from Linde Gas Benelux. 2,6-difluorobenzyl alcohol was provided by S.A. Ajinomoto OmniChem N.V. The rest of the chemicals were purchased from Sigma-Aldrich and used as received without any additional purifications.

HPLC pumps were purchased from Knauer, while ETFE micro capillary reactors along with connections were purchased from IDEX Health & Science Technologies. Reagents were pumped via pumps into the ETFE T- or Y-mixers. Hastelloy tubing and stainless steel connections were ordered from Valco instruments.

2. General Analytical Information

NMR (Bruker- Avance 400 (400 MHz)) and GC-MS (Shimadzu GC-2010 Plus coupled to a Mass Spectrometer, Shimadzu GCMS-QP 2010 Ultra) were used for characterization of isolated products. ^{1}H- NMR and ^{13}C- NMR spectra were used to characterize and determine the purity of isolated products. ^{1}H chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) (0.00 ppm), while ^{13}C chemical shifts are reported relative to $CDCl_3$ (77.2 ppm). Multiplicity of the peaks is abbreviated as s - singlet, d - doublet, t - triplet, q- quartet, m- multiplet and br-broad. GC-FID was used to quantify product distribution. GC-MS was used to identify the decomposition products.

3. GC method

GC method for follow-up of 2,6-difluorobenzyl alcohol and chloride conversion

Parameter	Specification
Column	CP-Sil 5 CB
Length	30 m
Inner Diameter	250 µm
Film thickness	1.0 µm
Internal Pressure	1.8 psi (He)
Injection volume	0.2 µl
Split ratio	1/5
Injection temperature	220 ˚C
Detector temperature	280 ˚C
Air	300 ml/min
Steam	30 ml/min
Make up	25 ml/min
Initial temperature	80 ˚C (2 min)
Ramp 1	15 ˚C/min (till 200 C, hold 10 min)
Ramp 2	20 ˚C/min (till 240 C, hold 0 min)

HPLC method for follow up of 1,2,3-triazole formation

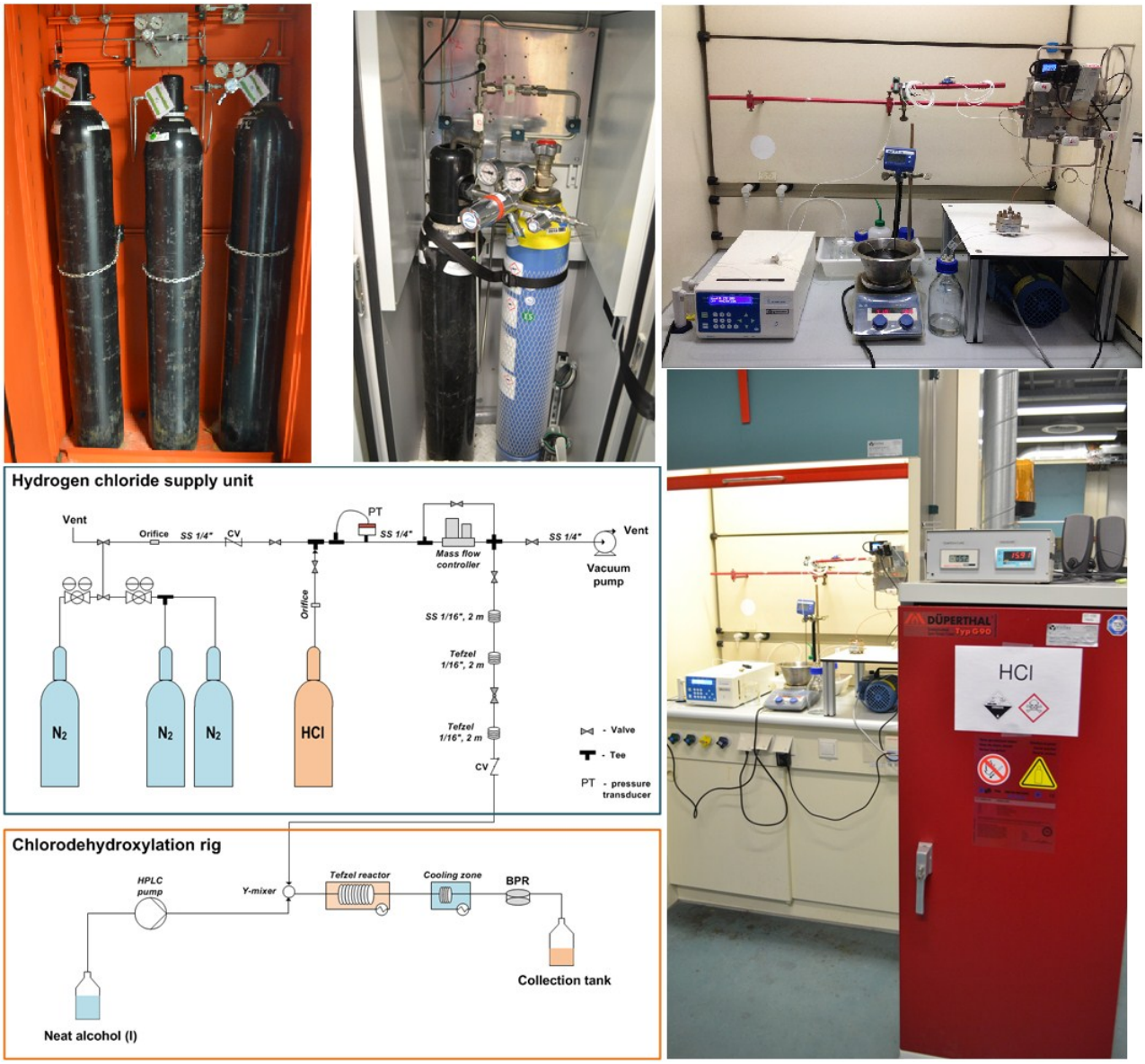
Parameter	Specification
Column	C18
Length	150 mm
Inner Diameter	4.6 mm
Pore size	5 µm
Column temperature	35 ˚C
Injection volume	1 µl
Eluent	775 ml of DW, 1 ml of Formic acid (98%), 150 ml MeOH, 75 ml THF
Detection	UV, 230 nm
Flow rate	1 ml/min
Running time	35 min

4. General Information Regarding experimental setups and experimental procedure

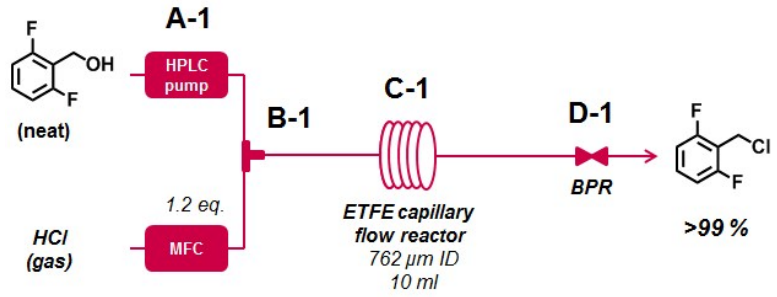
4.1 Continuous chlorodehydroxylation

4.1.1 Reaction setup for continuous chlorodehydroxylation

Scheme S1. Schematic representation of setup assembled for chlorodehydroxylation including hydrogen chloride gas delivery unit (with a permission from [1] Copyright © 2016, American Chemical Society). More detailed information on assembly and operation is available in ref. 1.



Scheme S2. Schematic representation of setup assembled for continuous chlorodehydroxylation



Component	Description	Scheme
A-1	Knauer HPLC pumps of Smartline 1050 series	
B-1	Y-mixer (P-512 from IDEX-HS)	
C-1	ETFE tubing of 1/16” external diameter and 0.03” internal diameter (1530L from IDEX-HS)	
D-1	Equilibar back pressure regulator	

4.1.2 Experimental procedure for continuous chlorodehydroxylation of 2,6-dilfuorobenzyl alcohol

The HPLC pump was first purged with isopropanol and then with the 2,6-difluorobenzyl alcohol. The reactor tubing was connected directly to the pump and the reactor was filled with alcohol. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 0.128 ml/min (1.1 mmol/min). The pressure was set to 12 bar at the Equilibar back pressure regulator (BPR), the heating plate was turned on and reaction temperature was set. After three times a residence time of 40 min, the product was collected into a vial containing water and ethyl acetate. The product was extracted and organic phase was analysed further with GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, *J*= 4 Hz, 1H), 6.92 (t, *J*= 8 Hz, 2H), 4.67 (s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 162.45 (d, *J*= 7 Hz), 159.94 (d, *J*= 7 Hz), 132.63 (t, *J*= 10 Hz), 114.08 (t, *J*= 9 Hz), 111.61 (q, *J*= 5 Hz), 32.40 (t, *J*=5 Hz).

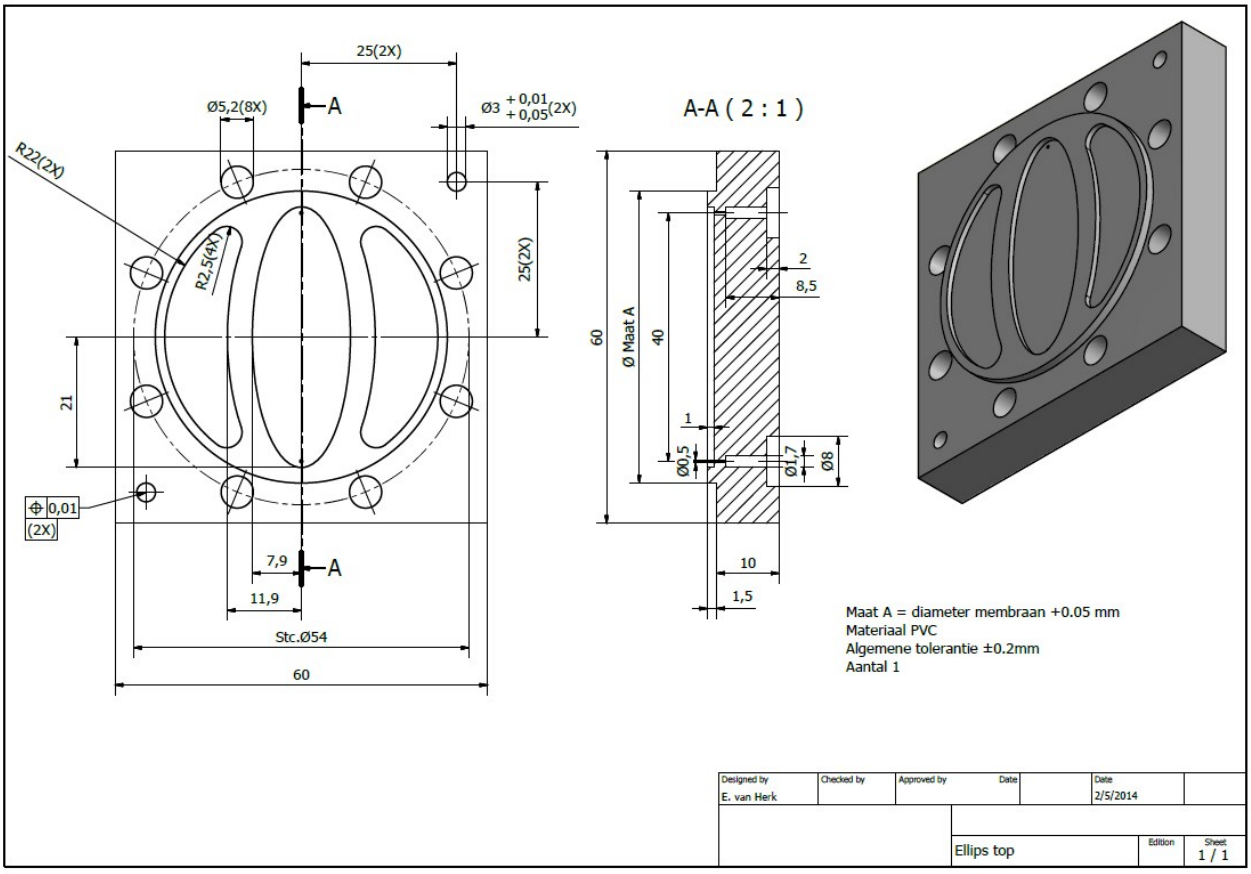
4.2 Continuous 2-step synthesis

4.2.1 Reaction setup for 2-step continuous synthesis of 2,6-dilfuorobenzyl azide

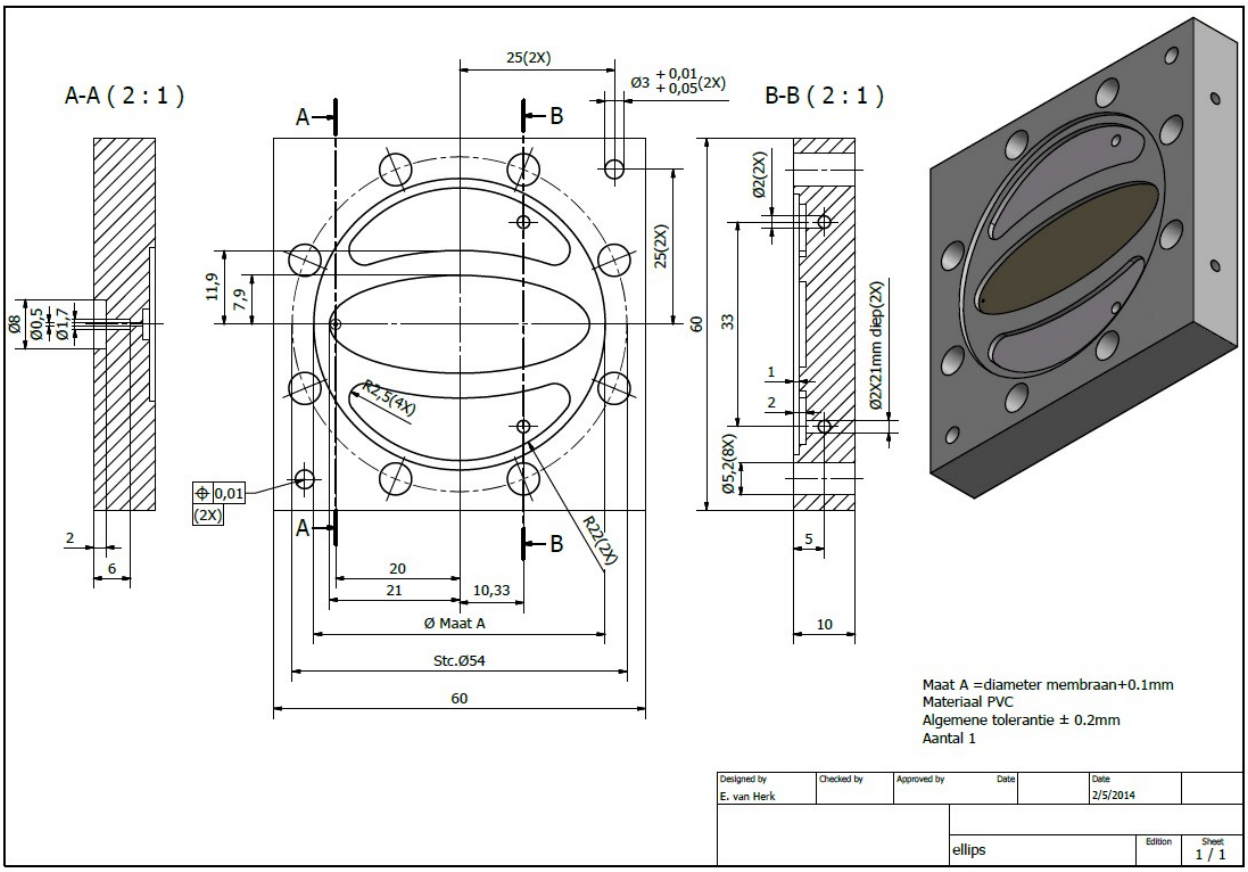
Reaction setup for 2-step synthesis consisted of the chlorination setup, shown in scheme S1, connected to a liquid- liquid separator, shown in scheme S3. Two inserts were modelled and fabricated from ETFE. Inserts were used to compress hydrophobic Zefluor membrane (P5PQ047), available from Pall Corporation. Two stainless steel holders were used to create a shell for the separator.

Scheme S3. Liquid-liquid membrane based separator (with a permission from [1]. Copyright © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

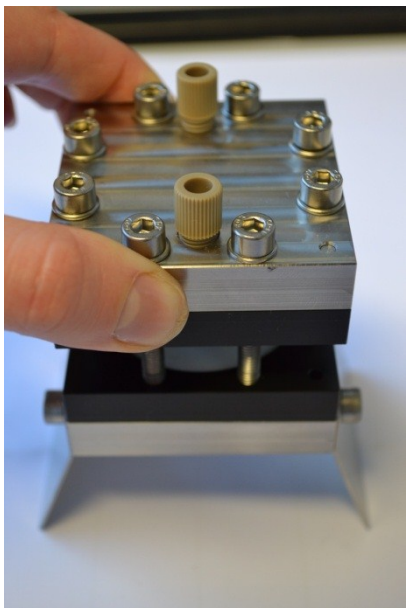
a. Design of the top insert with two drillings for inlet of slug-flow and outlet of aqueous phase.



b. Design of the bottom insert with single drilling for outlet of organic phase.



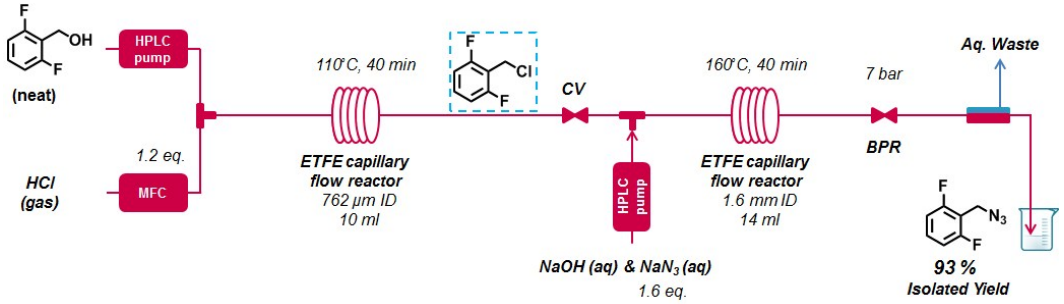
c. Photograph of a liquid-liquid separator with white membrane in between two inserts.



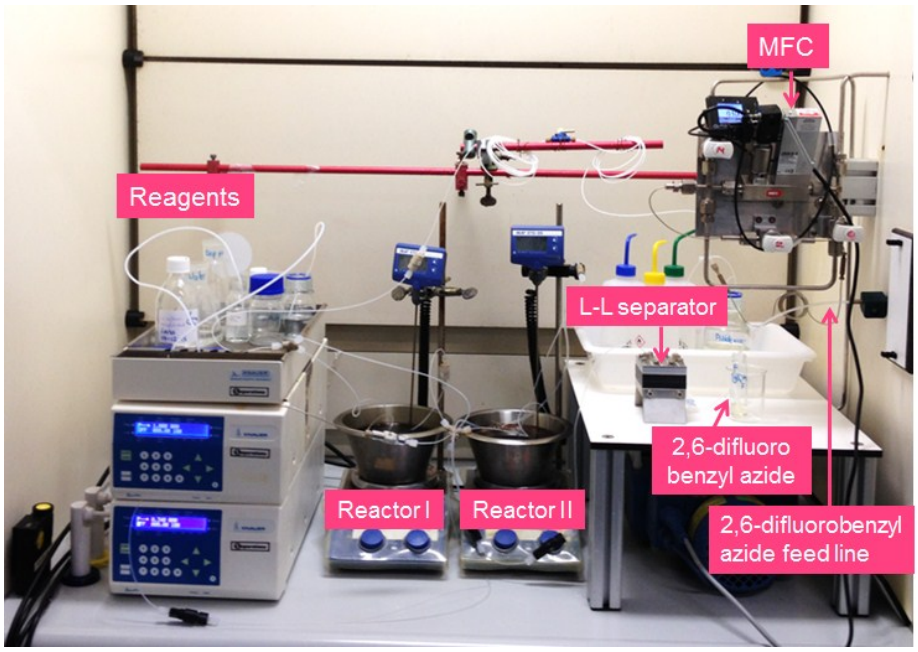
4.1.1 Experimental procedure for 2-step continuous synthesis

Two HPLC pumps were first purged with isopropanol. 2.6 gr (65 mmol) of NaOH and 26 gr (400 mmol) of NaN_3 were dissolved in water to yield 100 ml of solution. The first pump was purged with 2,6-difluorobenzyl alcohol, while the second with demi water. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). All the reactors were connected and immersed into heating baths. A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 128 µl/min (1.1 mmol/min). Another pump was set to 128 µl/min to pump pure water, and mixed streams flowed into a second reactor of 24 ml (1.6" ID). For this experiment two inline cartridge BPRs of 7 bar pressure were used. One BPR was attached first, after a significant pressure was attained within the reactor, the second BPR was attached. The first heating bath was set to 110 ℃, while second to 70 ℃. After one residence time (40 min), the pure water solution was replaced by the NaOH and NaN_3 solution and the flowrate was gradually increased to 460 µl/min. The second heating bath was set to 160 ℃. After the period equivalent to two residence times, the BPR outlet was connected to the inline liquid-liquid separator. An ultra-low volume adjustable BPR was attached to the aqueous outlet and a pressure of 2 psi was set. Meanwhile, 2,6-difluorobenzyl azide was collected at the organic side via a tubing of 20 cm with 250 µm ID. The first millilitre of the product was discarded, which was followed by a collection.

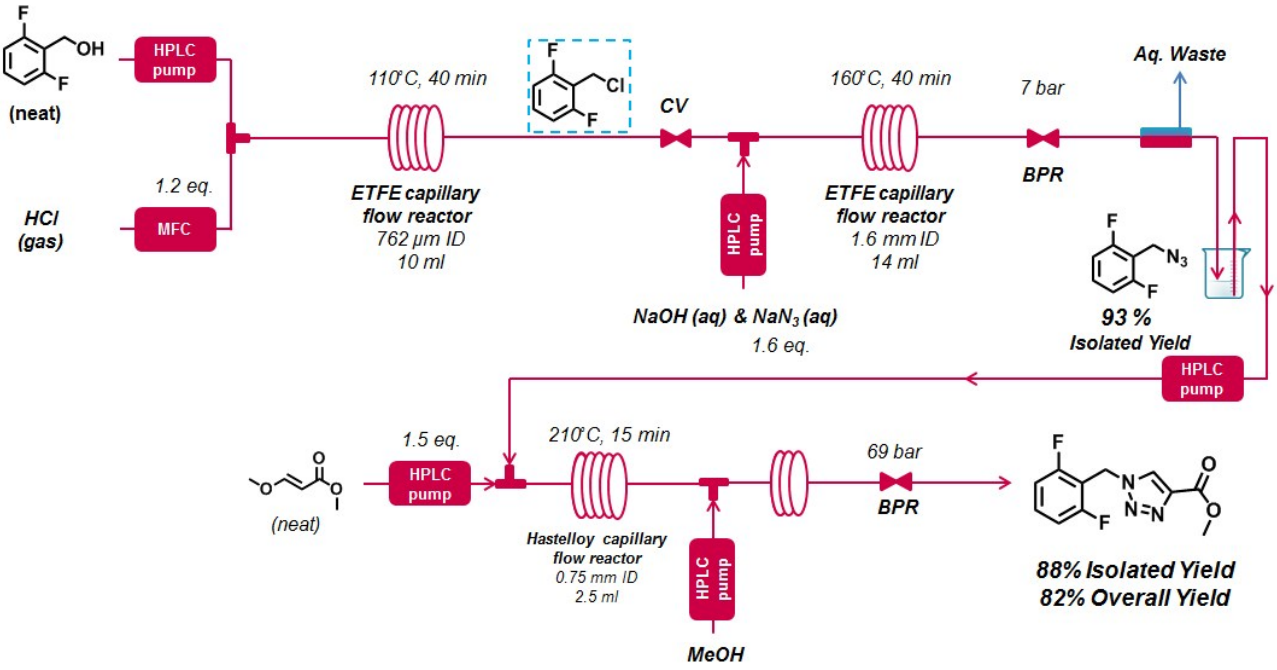
Scheme S4. Schematic representation of setup assembled for 2-step continuous synthesis



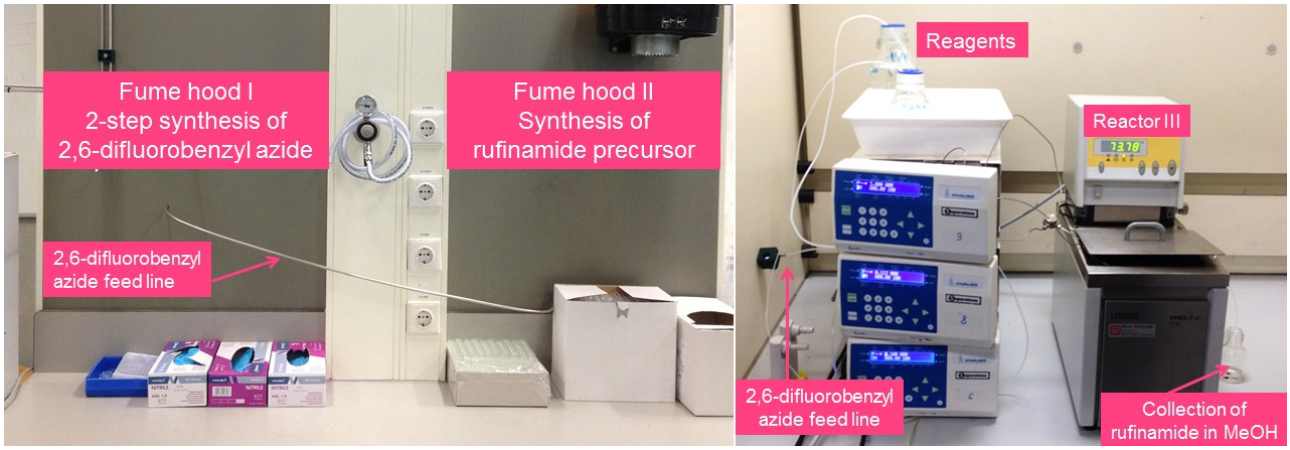
Scheme S5. Photograph of a setup for 2-step continuous synthesis



4.3 Synthesis of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate



Scheme S6. Schematic representation of setup assembled for 3-step continuous synthesis of rufinamide precursor.



Experimental procedure for 3-step continuous synthesis of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate:

All HPLC pumps were purged with isopropanol and later with either 2,6-difluorobenzyl azide, EMMA or methanol. The collected 2,6-difluorobenzyl azide was pumped at 100 µl/min (0.7 mmol/min) into a T-mixer to mix with EMMA, pumped at 112 µl/min (1.05 mmol/min), in order to proceed into 3.2 ml Hastelloy micro capillary reactor. MeOH was pumped at 3.2 ml/min (15 v/v) to dilute the product stream. A closed heating bath (Lauda Proline 8) was heated to 210 ℃ and 15 min residence time was allowed for the reaction to take place. After passing through a mixing zone of 1 ml volume Hastelloy micro capillary (0.04" ID) and BPR of 1000 psi, the product was collected. The collected solution was cooled to room temperature and later to 5 ℃ in the fridge overnight. The precipitated product was then filtered and dried under vacuum overnight. Yield 88%; mp 136-137 ℃; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 7.49 (m, *J*= 4 Hz, 1H), 7.15 (t, *J*= 8 Hz, 2H), 5.71 (s, 2H), 3.80 (s, 3H); ^{13}C (100 MHz, DMSO-d6) δ 162.43 (d, *J*= 8 Hz), 160.98, 159.95 (d, *J*= 7 Hz), 138.90, 132.30 (t, *J*= 10 Hz), 129.91, 112.38 (q, *J*= 5 Hz), 111.25 (t, *J*= 19 Hz), 51.25, 41.77 (t, *J*=4 Hz).