Supporting Information

Mass Spectrometric Directed System for the Continuous-Flow Synthesis and Purification of Diphenhydramine

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Materials and Methods

General procedure for the synthesis of DPH from bromo/chlorodiphenylmethane

Chemtrix reactor chip 3227 (SOR mixer, 19.5 μL) was loaded into a PPS chip holder equipped with Kalrez O-rings. This assembly was then placed on a Peltier element. A solution of chlorodiphenylmethane (2.0M) was prepared in dry ACN and loaded into a 1 mL syringe and connected to the first inlet of the reactor via FEP tubing (0.8 x 0.1mm) and an ETFE check valve. The outlet of the reactor was fed into a back pressure regulator and a pressure sensor via the same FEP tubing and a PEEK T-junction. Neat 2-dimethylaminoethanol and dry ACN were loaded into 1 mL syringes and attached to the second and third inlets of the chip as described above. Syringe pumps were used to deliver the chlorodiphenylmethane and 2-dimethylaminoethanol at a 1:1 molar ratio. Temperatures and flow rates were adjusted to screen temperatures ranging from 60-200 °C and residence times ranging from 15-600 seconds. The system was allowed to equilibrate for three residence times in between each new condition. An aliquot (1 μL) was taken from each reaction for MS analysis and the remaining sample was dried under vacuum and used for ^{1}H NMR analysis in $CDCl_3$. Samples are diluted 100-fold prior to analysis by nESI-MS.

General procedure for the synthesis of DPH from benzhydrol

Solutions (0.5M) were made for benzhydrol, methanesulfonyl chloride/*p*-toluenesulfonyl chloride, and dimethylaminoethanol. The chip(s) for the reaction were loaded into a PPS chip holder equipped with Kalrez o-rings, and the assembly was placed on a Peltier element. For the case of the two-chip synthesis, a home-built heating unit was also utilized. The solutions were loaded into 1 mL syringes and connected to the reactor(s) via FEP tubing (0.8 x 0.1mm) and an ETFE check valve. The outlet of the reactor was fed into a back pressure regulator and a pressure sensor via the same FEP tubing and a PEEk T-junction. Syringe pumps were used to deliver the reagents at the designated flow rates. An aliquot (1 μL) was taken from each reaction for MS analysis.

Quantitative MS analysis

An MS based calibration was made from mixtures of 0M, $1x10^{-7}$M, $1x10^{-6}$M, $2.5x10^{-6}$M, and $8x10^{-6}$M DPH with $3.88x10^{-6}$M DPH-D_3. Each point was measured with nESI in triplicate and the calibration is based on the DPH to DPH-D_3 ratio. Crude reaction samples were quantified by first diluting an appropriate amount (x10,000 typically) and then adding the same amount of internal standard. Each crude sample was diluted in duplicate and analyzed by nESI.

Continuous crystallization of DPH

N_2-segmented crystallization was achieved in which a mass-flow controller (Sierra, SmartTrak 100) was used to create N_2-segmented droplets followed by a quench-cooling with a dry-ice bath at -20 °C. The crystallization operating curve is shown in Fig S12. Note that while the crystallization takes place during quenching at the 30-sec residence time point, the crystal yield is determined at room temperature at the end of the crystallizer and is reflected on the operating curve. PFA tubing (1/16" OD 0.2" ID, IDEX Health & Science, Part No: 1500) and two T-mixers (IDEX Health & Science, Part No: P-632) was used in the crystallization set-up. EtOAc was added in line to the outlet of the reactor at 50:50 v/v or 6.49 μL/min in the T-junction corresponding to a total liquid flow rate of 12.98 μL/min along the crystallizer. This liquid was allowed to mix in a 1-ft length of tubing which was jacketed with an in-house fabricated tubing-heater sleeve. The temperature of this tubing section was maintained at 40 °C. This flow path was followed by

another T-mixer which mixes with N_2 gas whose flow rate is controlled by the mass-flow controller with the crystal solution and the N_2 segmented to control crystal size. The N_2 flow rate was 13 ± 3 μL/min. The length of the crystallizer was 121.92 cm, corresponding to a measured 2-min $\pm$ 10 sec residence time per segmented droplets. The composition of the droplet was detected using a combination of a phototransistor (Digikey) as well as a wireless USB microscope (Firefly, GT600). The image of the droplets and crystals were processed offline using ImageJ software after the crystallization process was completed. The outlet of the crystallizer was fed to a membrane filter (Whatman) suspended on a vacuum-pumped Erlenmeyer flask. The DPH crystals collected on the filter were rinsed with hexane prior to analysis.

Droplet reactor synthesis of DPH

Offline-droplet experiments were performed using a homebuilt electrospray ionization source. For diphenhydramine, reagents were mixed in-line using a T-mixer and off-line electrospray. Reactions were performed in a two-step manner. First, 500 mM benzhydrol was mixed with 500 mM methanesulfonyl chloride, then in the second step 20 equiv. of 2-(dimethylamino)ethanol were sprayed together. Typical conditions include a total flow rate of 10 μl/min, 120 psi N_2 and +5kV applied voltage. After the electrospray deposition was complete, the reaction product was rinsed from the collection surface and then analyzed by nanoESI. Samples were diluted at least 100-fold before analysis in order to quench the reaction and ensure no further reaction could occur during the analysis step. For two-step reactions, the washed material was drawn back into a syringe and mixed with the second-step reagent and then electrosprayed, collected, and washed as before.

General information on DPH crystallization optimization

Prior to crystallization, the solubility and stability of DPH (Sigma Aldrich, CAS: 147-24-0) in ACN (solvent) and EtOAc (anti-solvent) was measured using a reverse-phase ultra-high performance liquid chromatography (RP-UPLC) method (Waters Corp, PATROL UPLC Process Analysis System) to ensure no product decay and to determine the theoretical yield of the crystallization process. The method was developed using ACQUITY BEH C18 (130 Å pore size, 1.7 μm particle size, 2.1 mm ID X 100 mm) as the stationary phase, with ammonium formate buffer:methanol (80:20, v/v) at pH =10.0 as the mobile phase.

Figure S1. ^{1}HNMR for Table 1 Entries 1-4

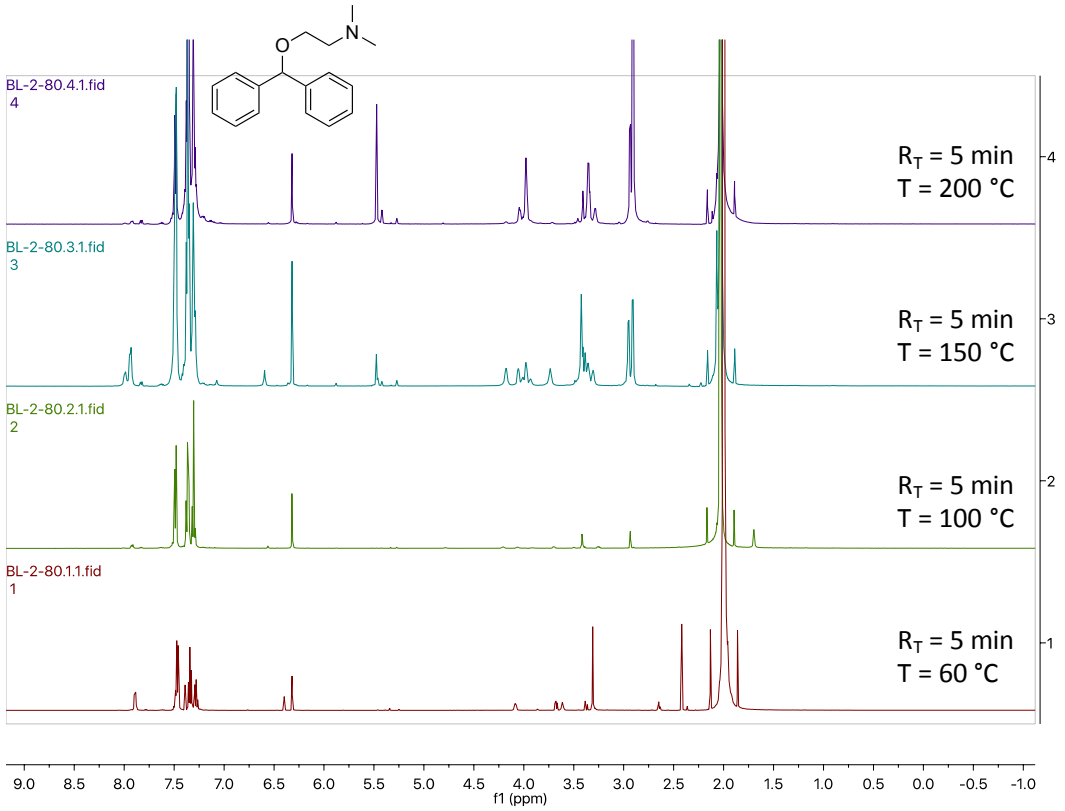

Figure S2. [1]HNMR for Table 1 Entries 5-8

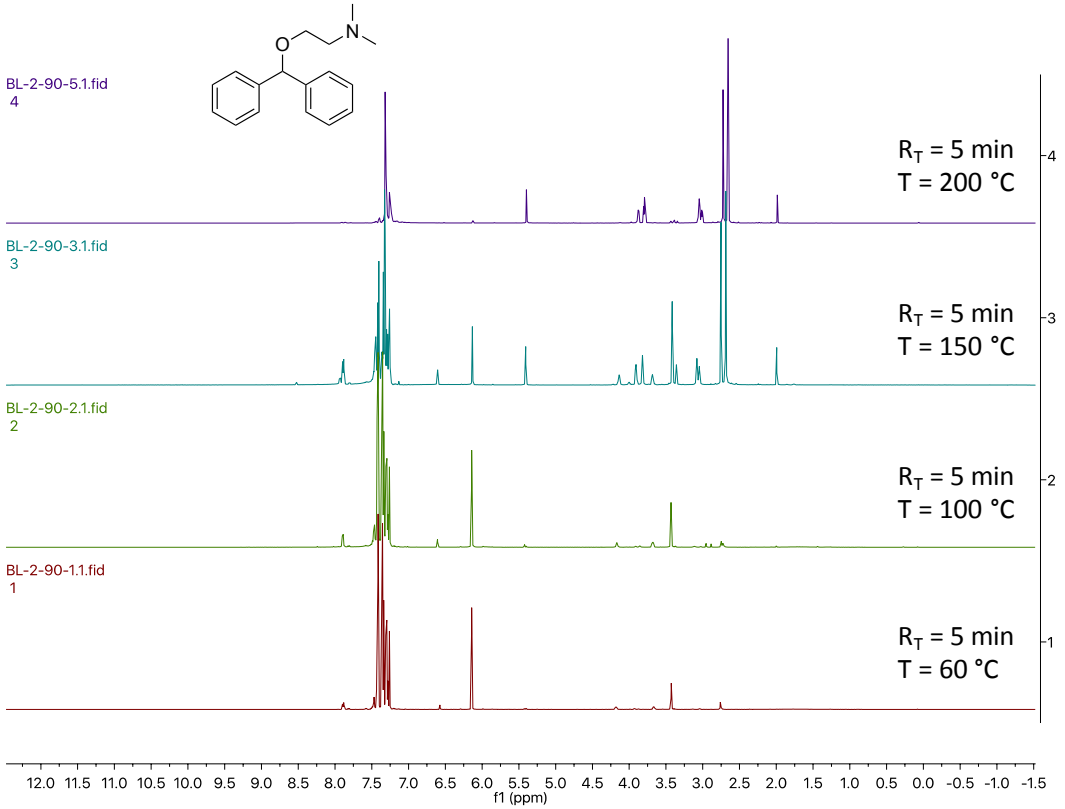

Figure S3. [1]HNMR for Table 1 Entries 9-12

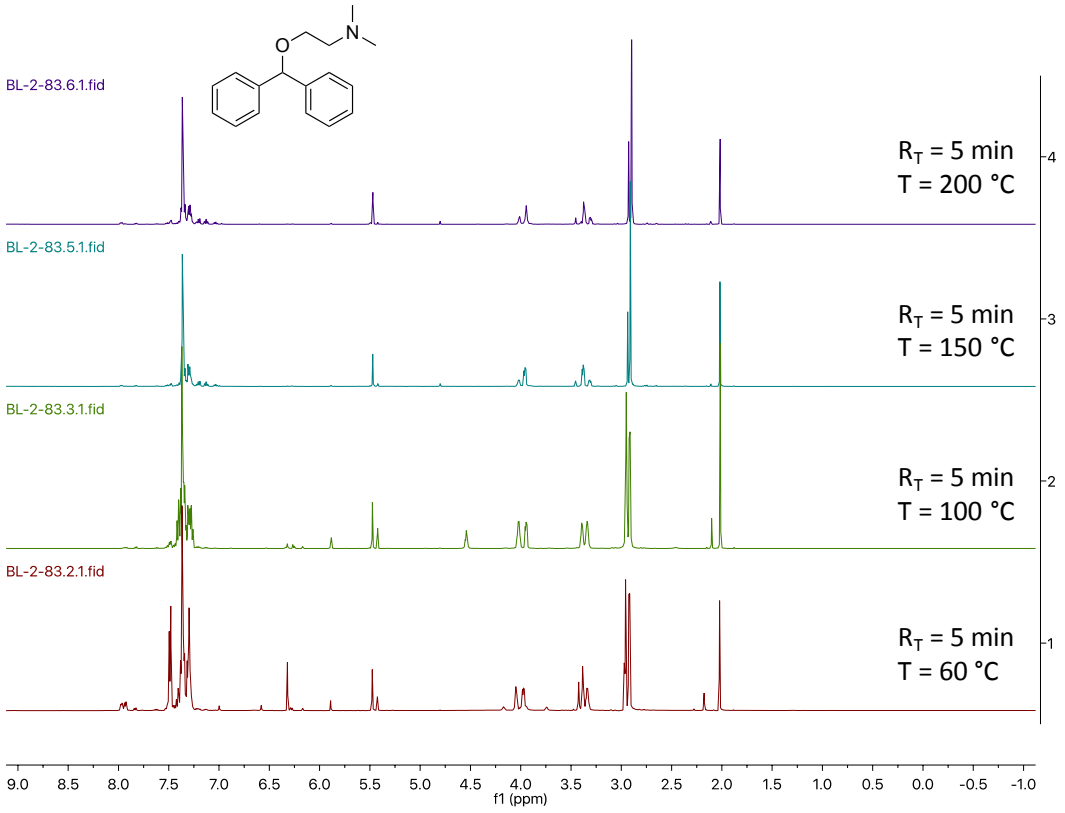

Figure S4. MS quantitation calibration curve for Figure 2

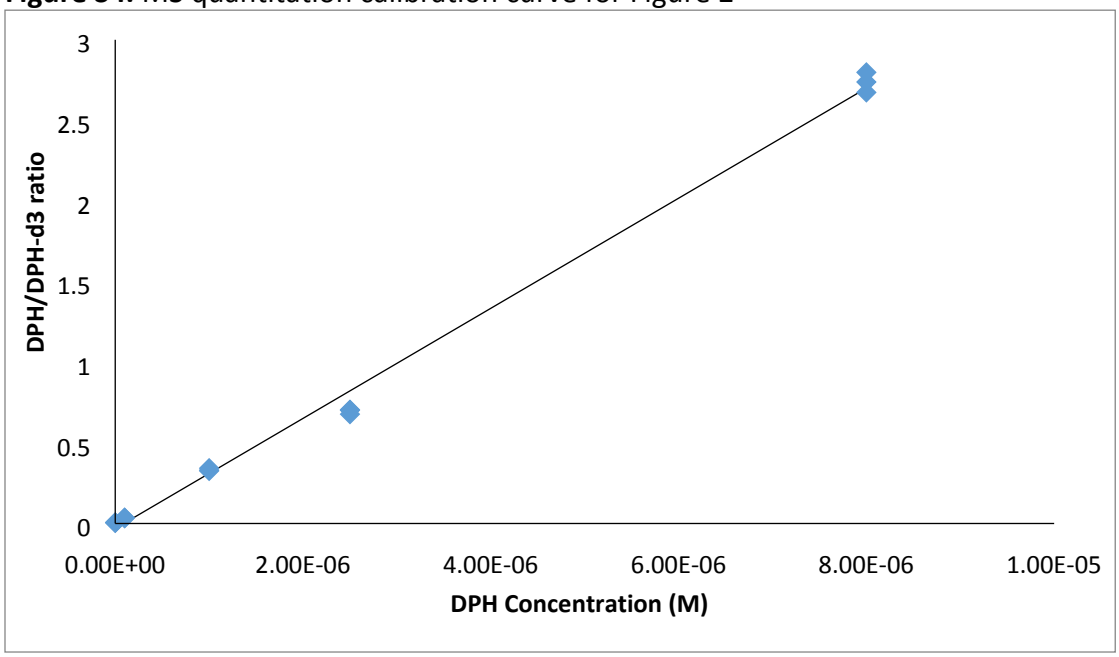

Figure S5. MS/MS of m/z 270 byproduct

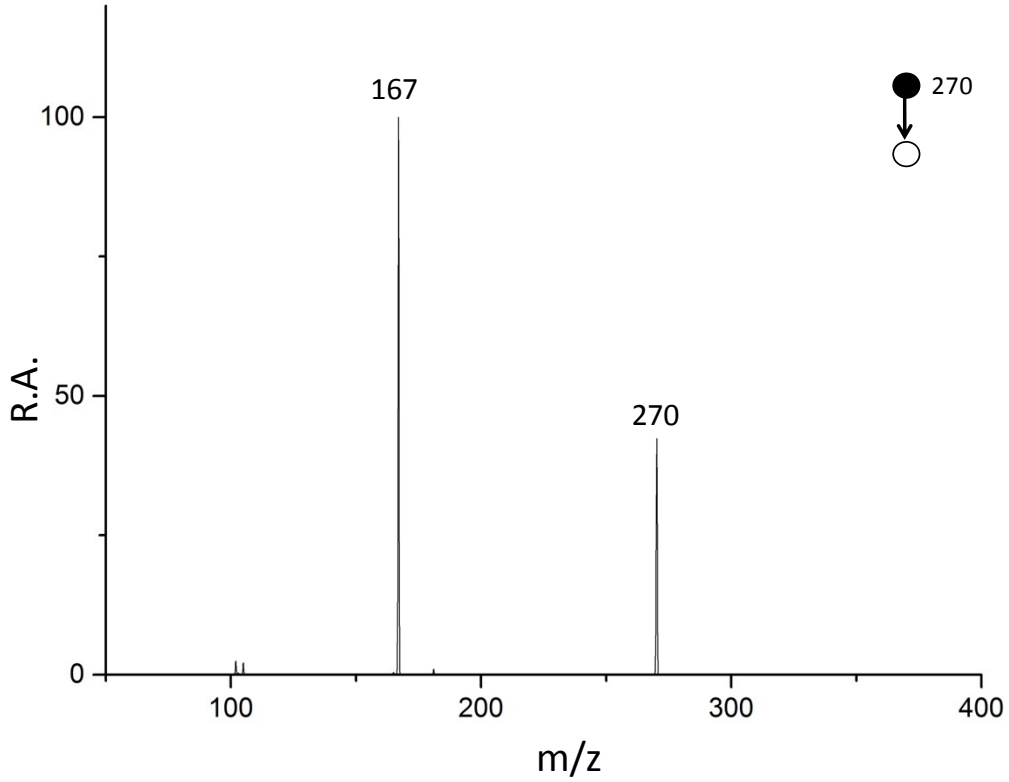

Figure S6. Dependence of DPH solubility on temperature

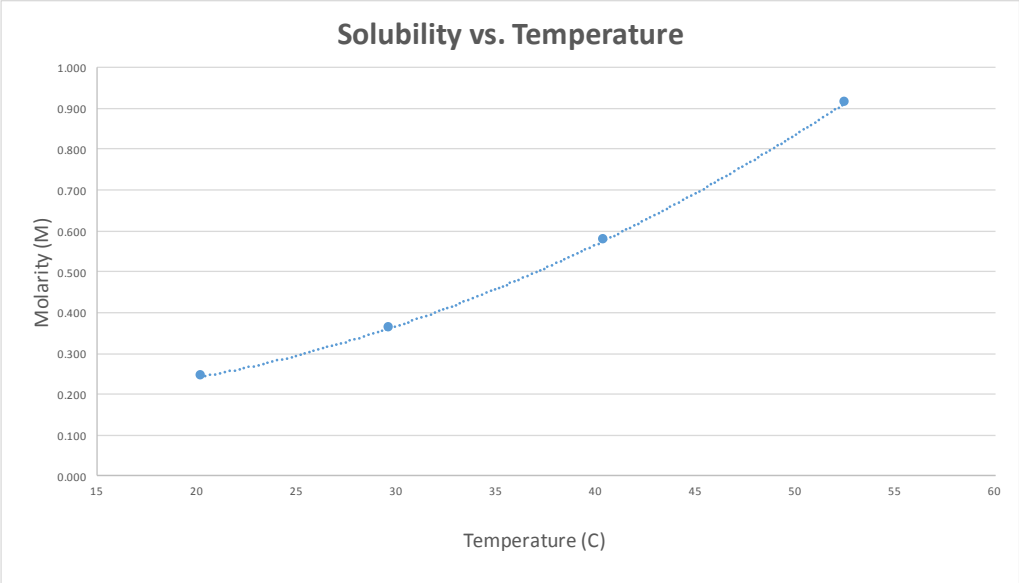

Figure S7. Optimization of DPH crystallization with EtOAc as an antisolvent

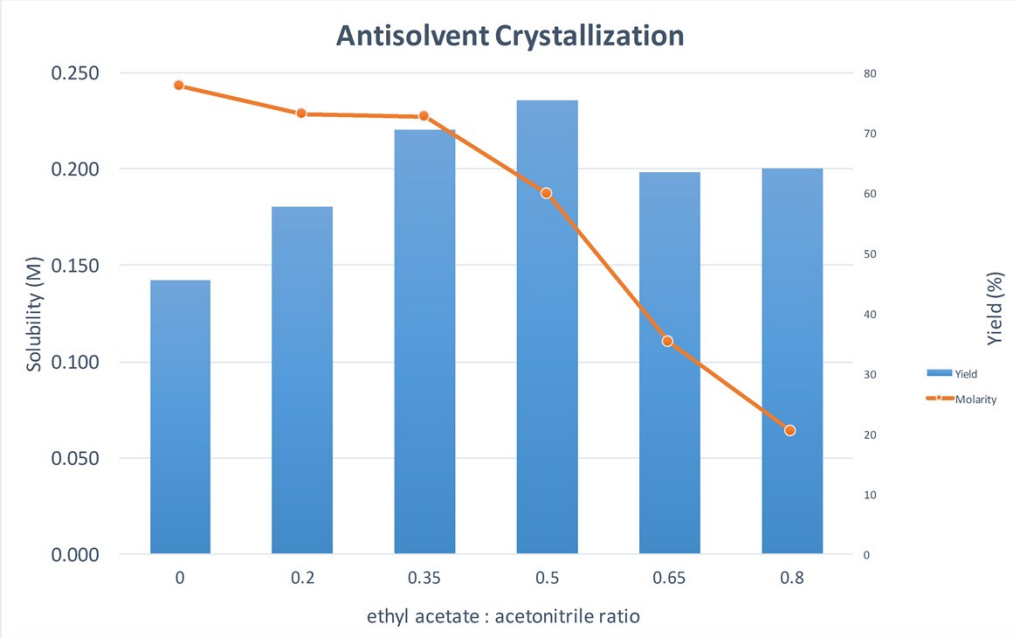

Figure S8. Picture of DPH crystallization

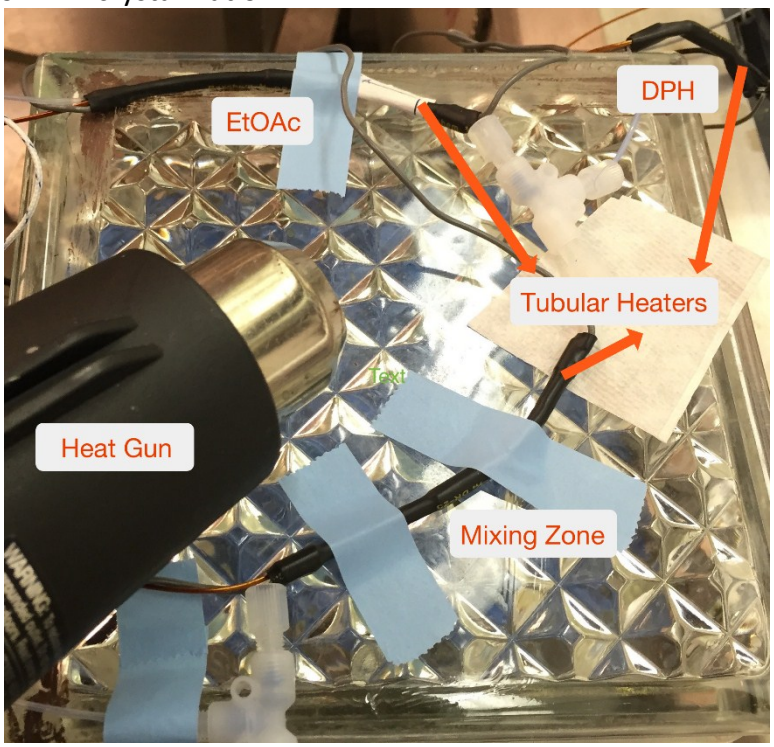

Figure S9. Droplet distribution for DPH crystallization across 3 residence times (RT). (Top) 1st RT, (Middle) 2nd R_T, and (bottom) 3rd R_T.

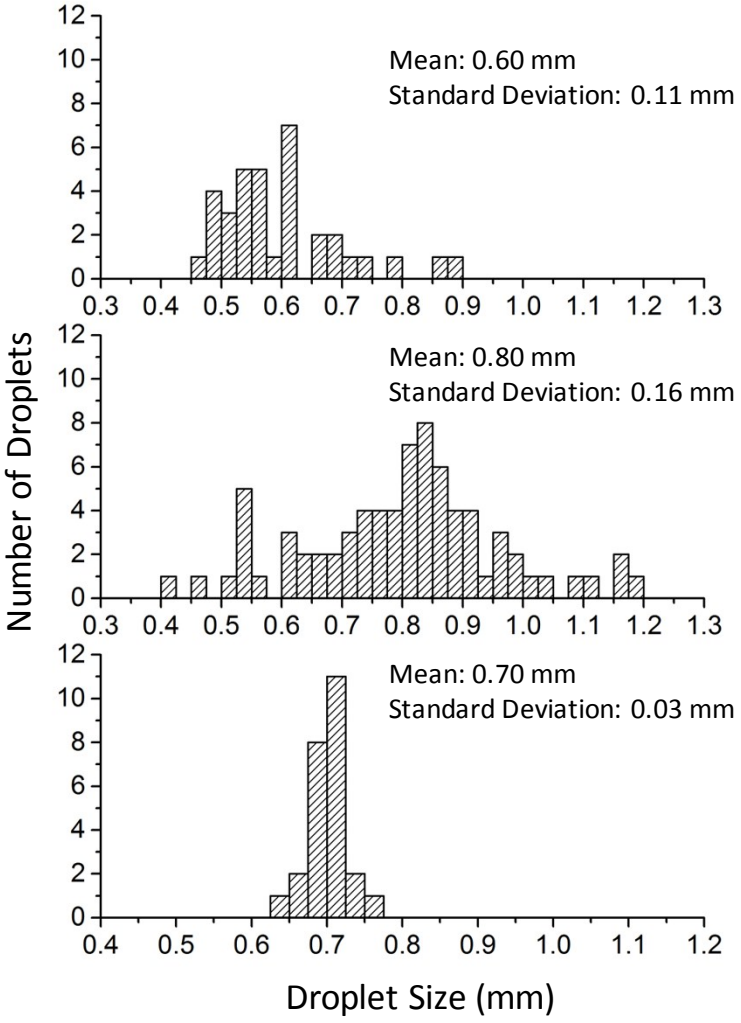

Figure S10. nESI-MS of DPH crystal

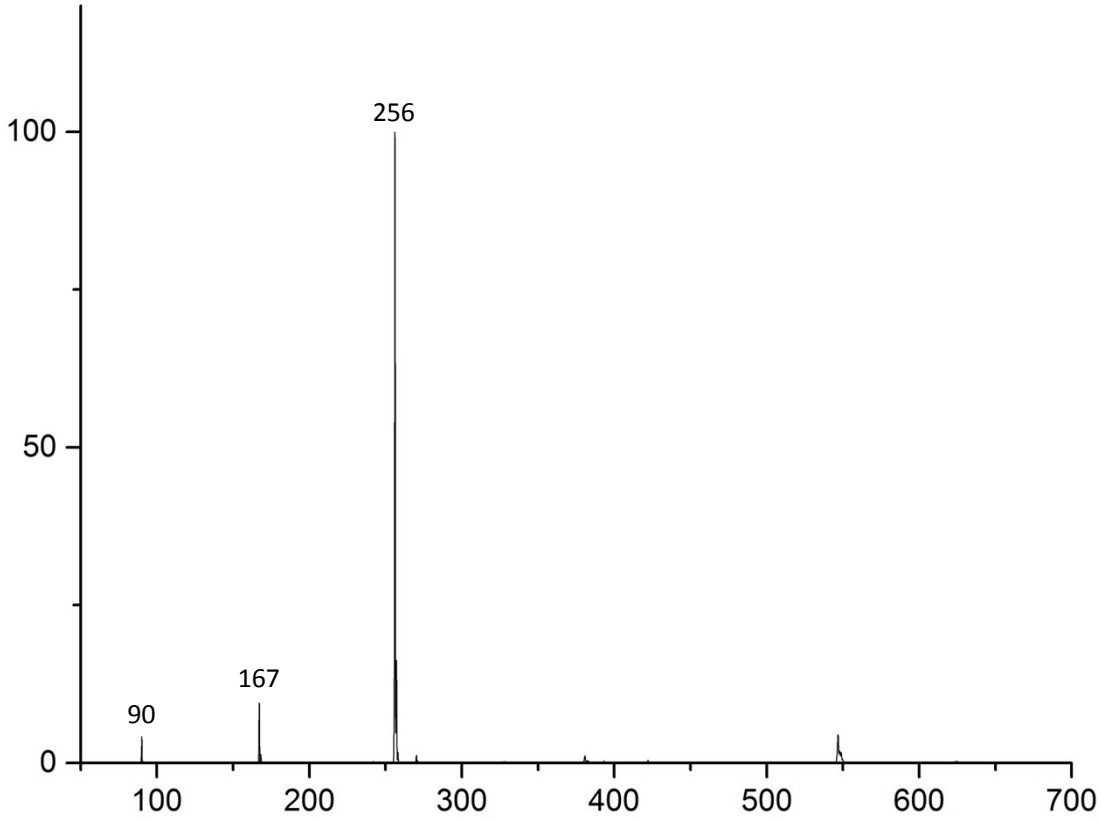

Figure S11 ^{1}HNMR of DPH crystal

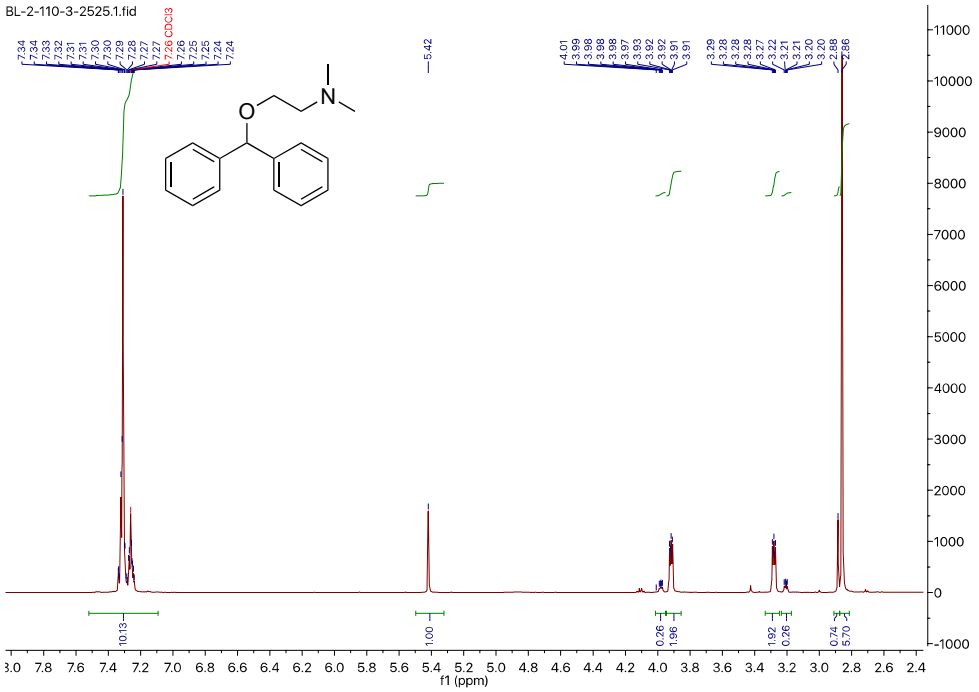

Figure S12. Positive mode nESI-MS for the continuous flow synthesis of **5**

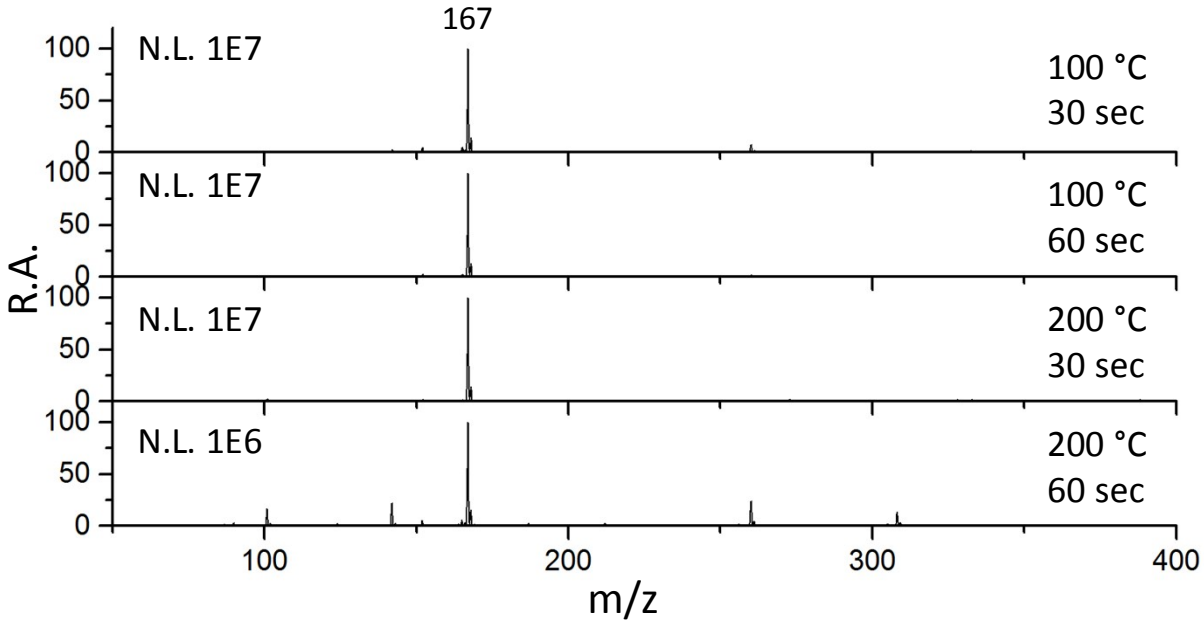

Figure S13. Negative mode nESI-MS for the continuous flow synthesis of **5**

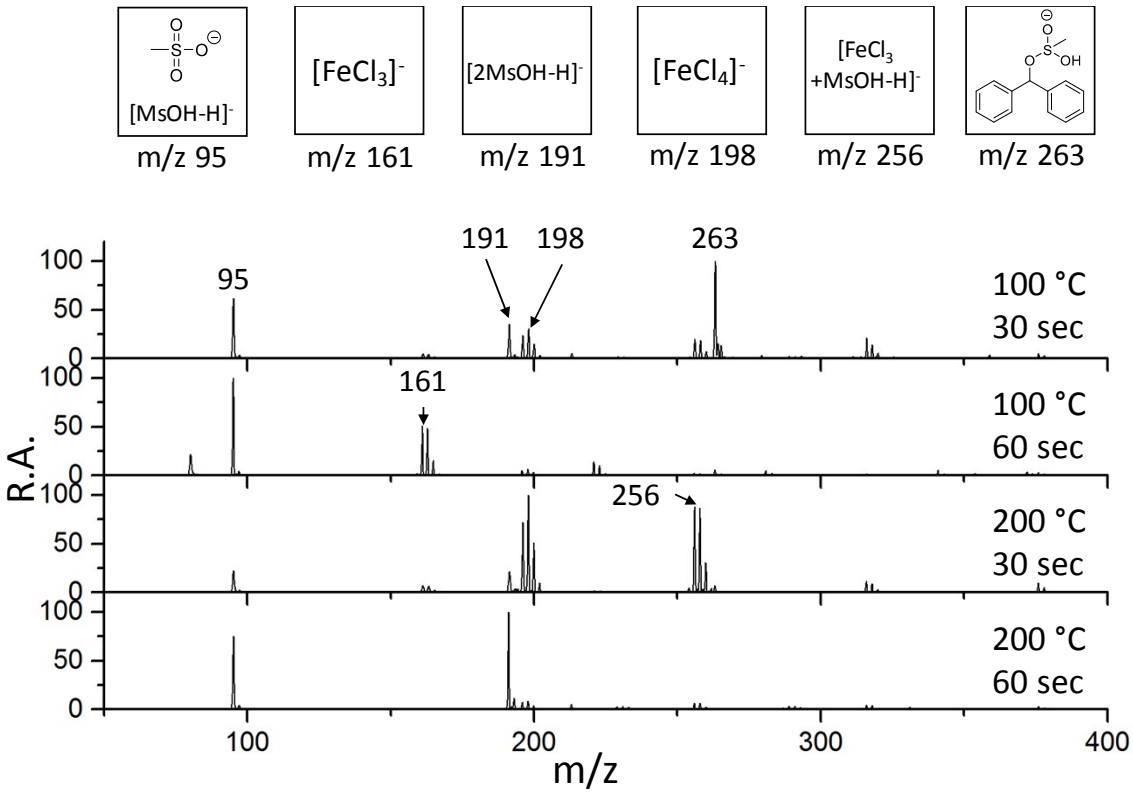

Figure S14. Positive mode nESI-MS for the two step droplet synthesis of DPH (**3**)

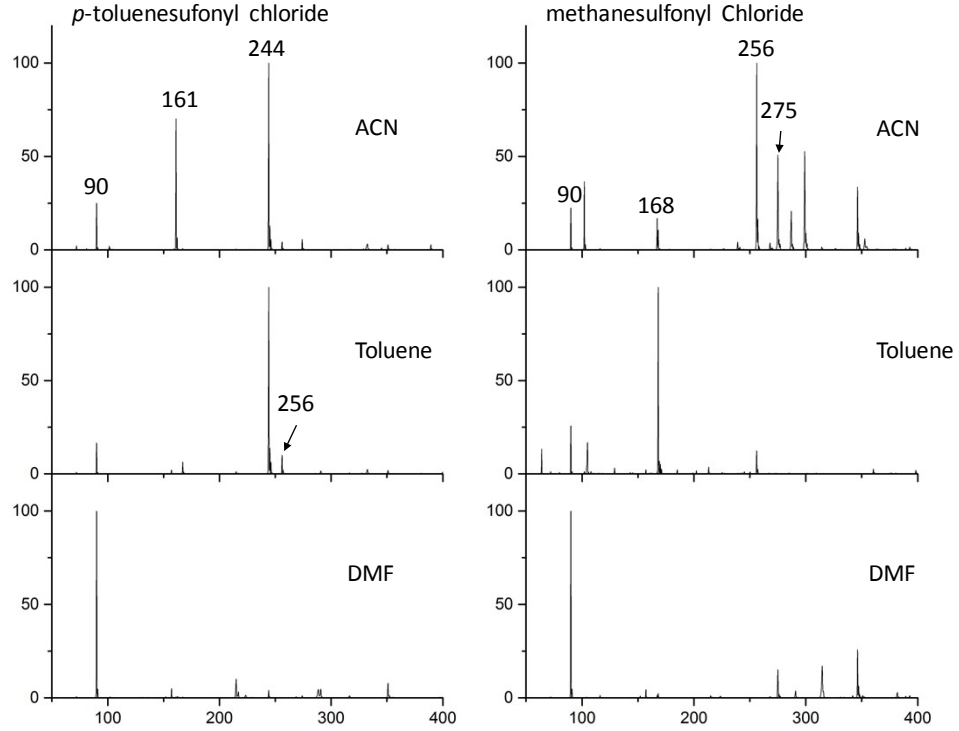

Figure S15. Two-step synthesis of DPH (**3**) from benzhydrol with the inclusion of TEA

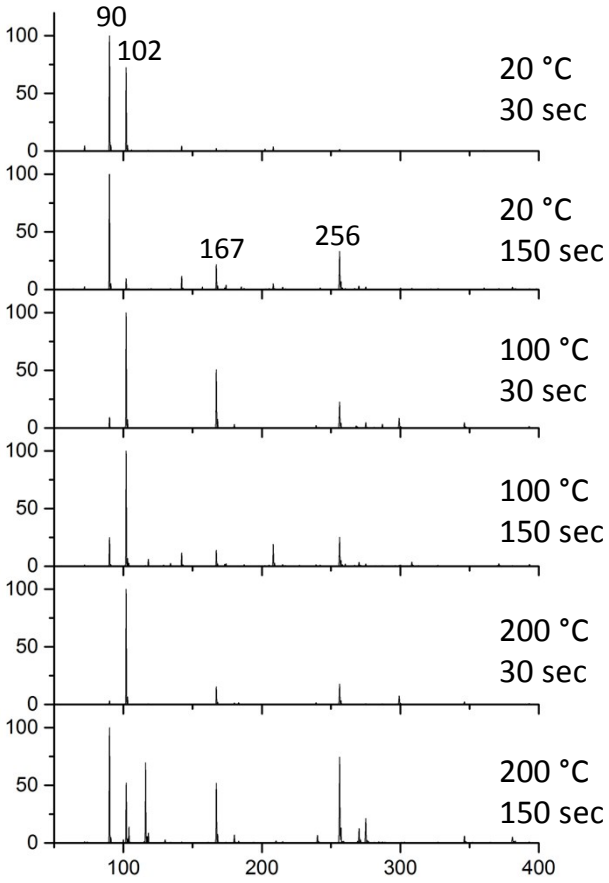

Figure S16. Design drawings for the multi-step reactor system

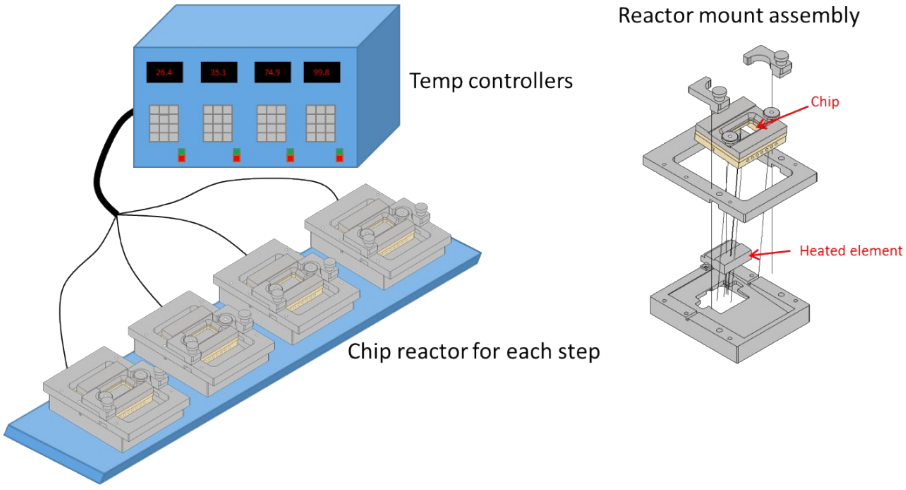

Table S1. Full dataset of DPH synthesis from benzhydrol.

Entry	Temp. (°C) (1/2)	R_T (min)	Stoich. (X:Y)	Solvent	Conv.[a] (%)	3%[b]	Entry	Temp. (°C) (1/2)	R_T (min)	Stoich. (X:Y)	Solvent	Conv.[a]	3%[b]
1	150/200	0.50/0.067	1:1	ACN	32.1	-	**13**	150/200	0.50/0.067	1:1	DMF	35.6	-
2	150/200	1.0/0.13	1:1	ACN	20.2	4.85	**14**	150/200	1.0/0.13	1:1	DMF	37.8	-
3	150/200	2.5/0.33	1:1	ACN	54.9	5.63	**15**	150/200	2.5/0.33	1:1	DMF	44.9	-
4	150/200	5.0/0.66	1:1	ACN	55.2	34.5	**16**	150/200	5.0/0.66	1:1	DMF	32.7	-
5	150/175	2.5/0.33	1:1	DMF	47.5	-	**17**	150/200	0.50/0.067	1:1	Toluene	12.3	-
6	150/175	5.0/0.67	1:1	DMF	41.5	5.93	**18**	150/200	1.0/0.13	1:1	Toluene	12.0	-
7	150/175	2.5/0.25	1:2	DMF	43.0	6.79	**19**	150/200	2.5/0.33	1:1	Toluene	0.75	-
8	150/175	5.0/0.5	1:2	DMF	49.6	8.73	**20**	150/200	5.0/0.66	1:1	Toluene	1.59	-
9	150/175	0.50/0.067	1:1	DMF	4.69	-	**21**	150/200	1.0/0.13	1:1	Toluene	12.0	-
10	150/175	1.0/0.13	1:1	DMF	20.8	-	**22**	150/200	1.0/0.10	2:1	Toluene	17.1	0.15
11	150/175	2.5/0.33	1:1	DMF	47.5	-	**23**	150/200	1.0/0.08	3:1	Toluene	6.85	0.14
12	150/175	5.0/0.66	1:1	DMF	41.5	-	**24**	150/200	1.0/0.67	4:1	Toluene	23.1	0.29

[a]Qualitative calculation of conversion from MS calculated by taking into account starting materials, intermediates, byproducts, and product. [b]Quantitative calculation of yield from MS