Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Self-Optimization of the Final Stage in the Synthesis of EGFR kinase inhibitor AZD9291 using an Automated Flow Reactor

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Contents

1 Chemicals

All chemicals were commercially available and used without further purification, unless otherwise stated: 2,4-dimethoxyaniline (Maybridge, 97%), triethylamine (Acros 99%), 3-chloropropionyl chloride (Acros 98%), hydrochloric acid (Fisher, 37%) biphenyl (Aldrich, 99.5% GC), acetonitrile (VWR, 99.9%). Anhydrous acetonitrile was obtained from departmental solvent purification system with a water content of 2.6 ppm. AZD9291 aniline **1** was supplied by AstraZeneca PLC.

2 Equipment

2.1 Automated Reactor

Reagents were pumped using Jasco PU980 dual piston HPLC pumps and streams were mixed using Swagelok SS-100-3 tee-pieces. A 3 mL reactor was fitted to a Cambridge Reactor Design Polar Bear Flow Synthesizer and the outlet was filtered with a Swagelok SS-2F-2 inline filter. Sampling was achieved using a VICI Valco EUDA-CI4W.06 sample loop with 0.06 µL injection volume. The reactor was maintained under fixed back pressure using an Upchurch Scientific 250 psi back pressure regulator. Polyflon PTFE tubing (1/16” OD, 1/32” ID) was used throughout the reactor. Glassware for anhydrous solutions was dried in an oven at 120 °C.

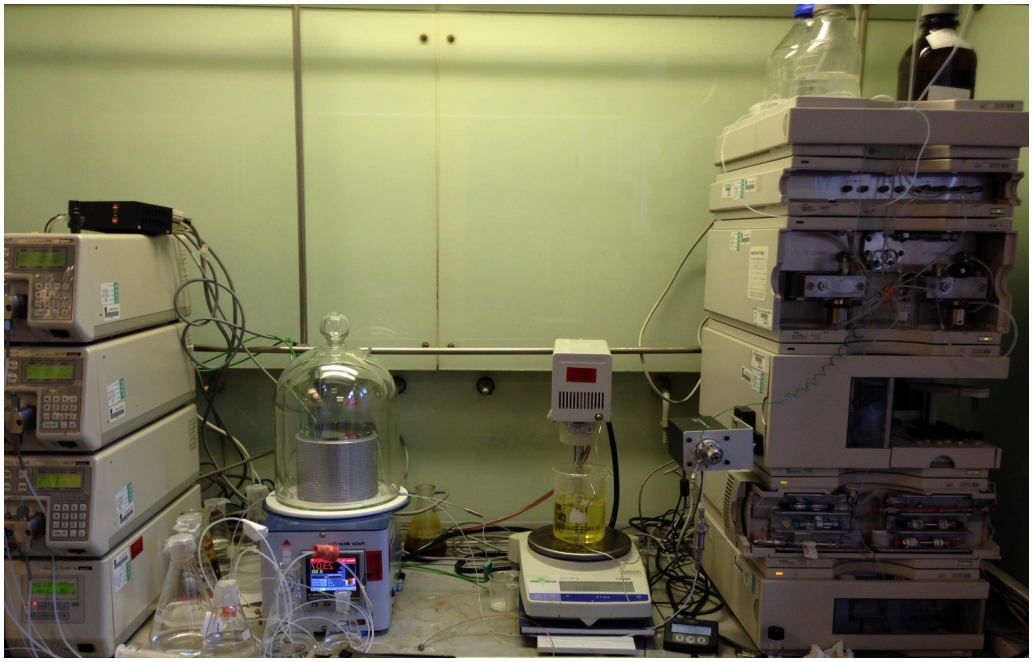


Figure S1 - Photo of automated flow reactor

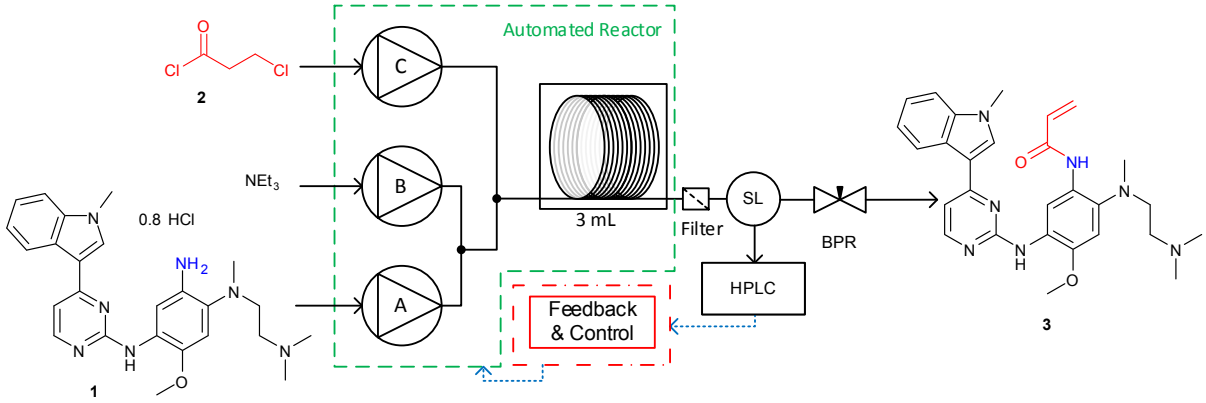


Figure S2 - Schematic for the automated reactor. The reagents are introduced to the reactor using dual piston pumps (A,B and C) with the pump streams mixing in consecutive mixing tees. The reactor outlet passes through an inline filter before being sampled for HPLC analysis. The whole reactor is maintained under a fixed back-pressure to prevent boiling at temperatures above the solvent boiling point

2.2 Optimization Procedure

An optimization program was written in MatLab that controlled the pump flow rates and reactor temperature; determined steady state; calculated a product yield; and controlled the inputs and outputs to and from the SNOBFIT algorithm. Whilst the reactor was reaching temperature, the pumps were set to 0.020 mL min^{-1}. When the reactor was at temperature, the pumps were set to the flow rates calculated by the algorithm and pumped for 1.5

residence times. When the reactor was at steady state, a HPLC sample was taken and the optimization moved on to the next experiment (Figure S3).

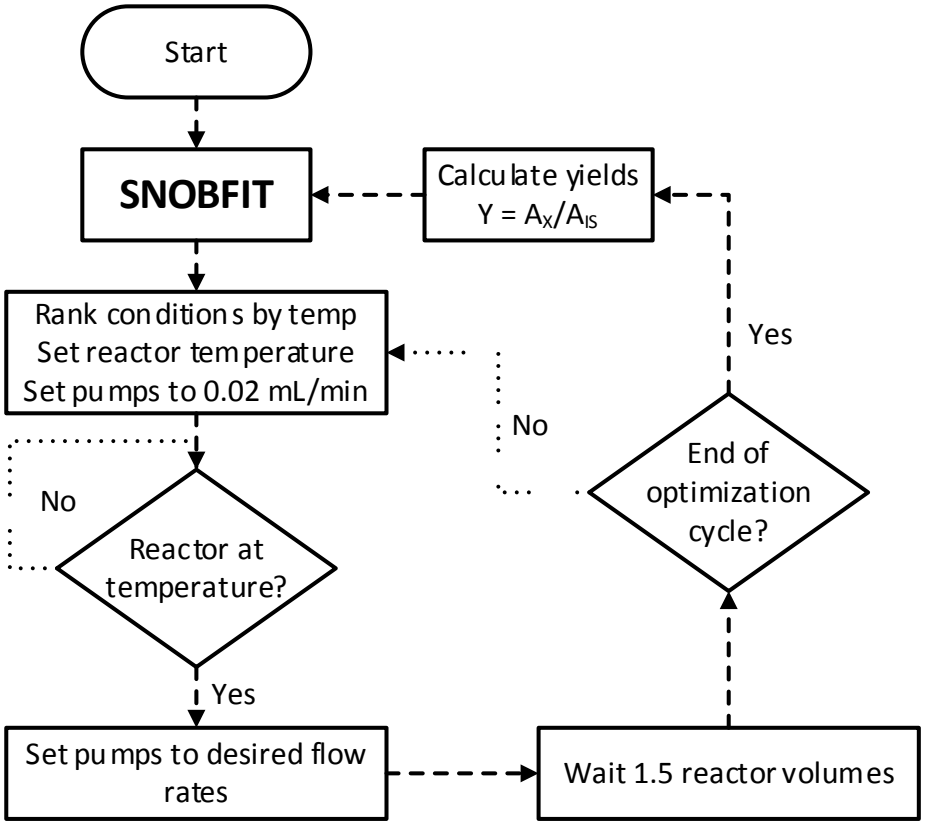


Figure S3 – Flow chart showing the important steps during the optimization program.

Automated yield analysis was calculated during optimizations by calculating the ratio between the desired product and internal standard peak, from HPLC. The SNOBFIT algorithm is a minimizing algorithm and was thus set to maximize the negative of this ratio. This number was translated to a product yield (after completion of the full optimization) by internally normalizing it against the ratio of all other aniline species peak areas and assuming that all aniline species had the same response factor. This was necessary as the small amounts of impurities would be impossible to isolate in quantities suitable for separate calibration runs. Summation of the normalized peak areas for all aniline compounds showed consistent mass balance (100 +/- 6% in both the AZD9291 studies and 100 +/- 7% with the model aniline **4**).

2.3 Analytical

NMR analysis was carried out using a Bruker 500 MHz fourier transform machine. Chemical shifts are quoted as parts per million (ppm) with reference to an internal solvent peak of $SiMe_4$ (TMS). Peaks are quoted as s (singlet), br s (broad singlet) d (doublet), t (triplet), variations thereof (e.g. dd doublet of doublets, dt doublet of triplets etc.) or multiplet (m).

Accurate mass MS was carried out using a Bruker MaXis Impact. IR was collected using a Bruker Alpha FT-IR. Copies of the NMR analysis is available at the end of the document.

At-line HPLC analysis was carried out using an Agilent 1100 HPLC. Method 1: Sigma Ascentis Express C18 (50 x 6.6 mm, 2.7 µm) column; A 0.1 % (v:v) aqueous trifluoroacetic acid, B 0.1 % (v:v) trifluoroacetic acid in acetonitrile; 5% to 95% B over 8.5 mins, to 5% B after 9.5 mins, post time 30 s; 1.2 mL min^{-1}, 254 nm, 20 °C. Method 2: Waters X-Bridge C18 (150 x 30 mm, 3.5 µm) column; A water, B acetonitrile, C 10% (v:v) aqueous trifluoroacetic acid; 5% to 38% B over 10 mins, to 95% B after 15 mins to 5% B after 15.1 mins, 3% C hold over 15.1 mins, post time 3 mins (5% B, 3% C); 1.0 mL min^{-1}, 210 nm, 40 °C. Offline LC-MS was obtained using an Agilent 1200 UHPLC and Bruker HCTultra Ion Trap Spectrometer.

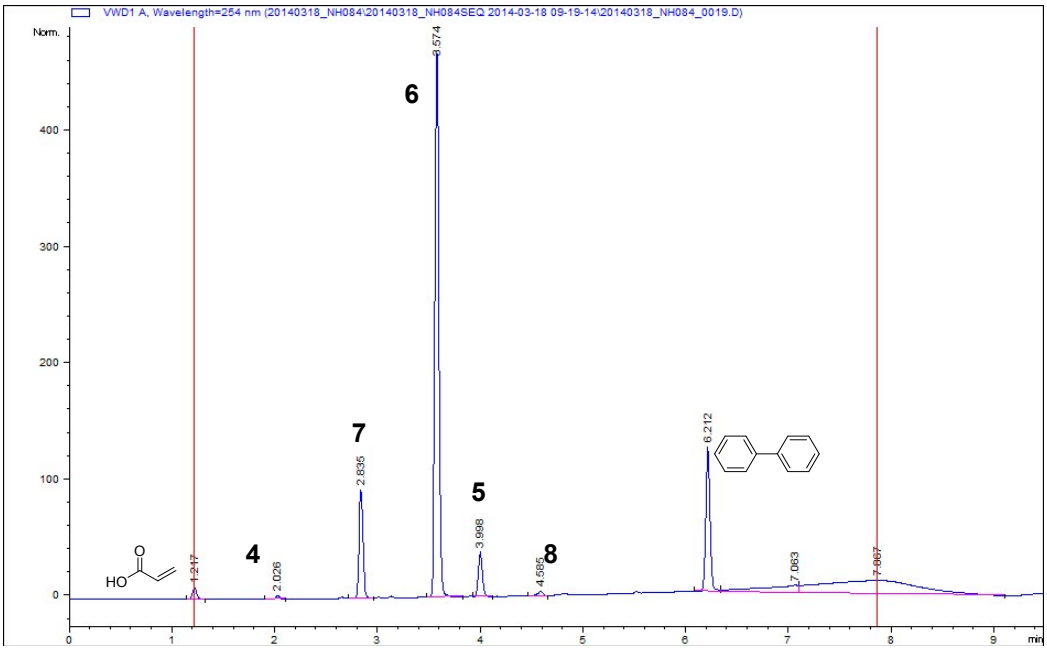


Figure S4 – Example HPLC for the model reaction (Method 1)

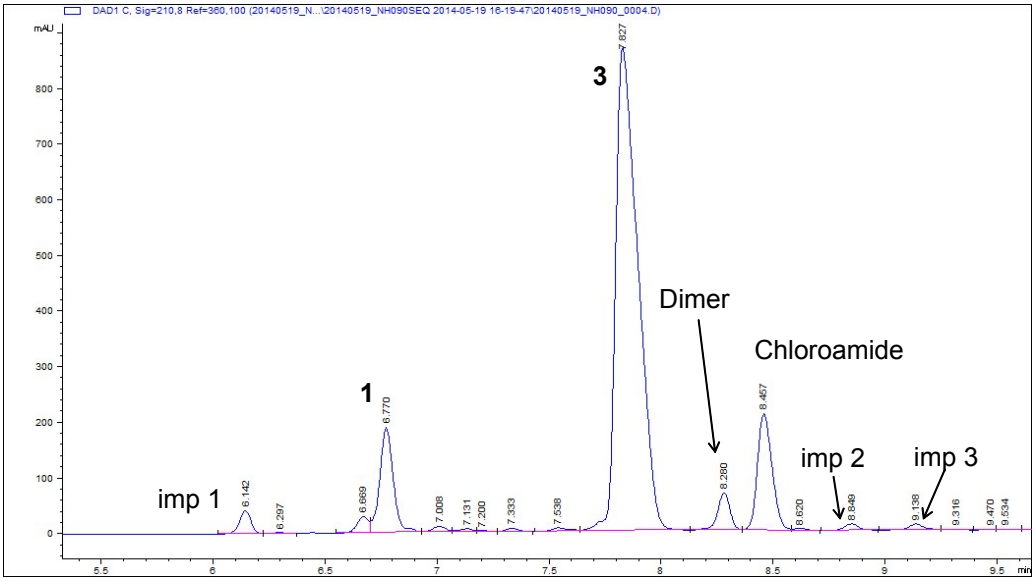


Figure S5 – Example HPLC for the AZD9291 reaction (Method 2) from 5.5 to 9.5 mins. The major impurities are labelled as imp 1-3.

3 Experimental

The automated reactor was set up according the schematic shown in Figure S2. Each reagent was pumped using Jasco PU-980 dual piston pumps and were mixed in Swagelok 316 stainless steel tee-pieces (SS-100-3). A 3 mL reactor coil was fitted to the mantle of a Polar Bear Plus Flow Synthesiser (Cambride Reactor Design). The reaction feed exited the reactor through a Swagelok 316 stainless steel inline filter (SS-2F-15) to a VICI Valco sample loop (EUDA) fitted with a 0.06 µL sampling valve (CI4W.06). The reactor was maintained under a back pressure of 250 psi by an Upchurch Scientific fixed pressure BPR. PTFE tubing (1/16" OD, 1/32" ID, Polyflon) was used throughout. HPLC analysis was carried out using an Agilent 1100. Pump solution reservoirs were prepared by dissolving the reagents in a mixture of acetonitrile and water (7:2, v:v) except the acid chloride **2**, which was prepared in anhydrous acetonitrile. Aniline **4** solution was filtered to remove particulates before use.

3.1 Pump Reservoir Solutions

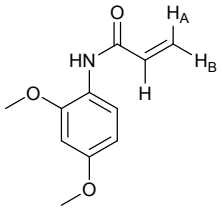
Pumps A and B: The desired reagents were dissolved in acetonitrile and water (7:2, v:v, MeCN:H_2O) under stirring at ambient conditions. Aniline **4** solution was filtered before use. Pump C: 3-chloropropionyl chloride was added to a dry quick-fit conical flask, fitted with a septum and purged with nitrogen. Anhydrous acetonitrile was added under stirring and nitrogen flow. The solutions were prepared according to the concentrations in Table S1.

Table S1 - Concentrations of the stock solutions for both optimizations

	Pump A		Pump B		Pump C	
	Reagent	Concentration / mol L^{-1}	Reagent	Concentration / mol L^{-1}	Reagent	Concentration / mol L^{-1}
Model	Aniline **4** Biphenyl	0.241 0.0156	Et_3N	3.73	Acid chloride **2**	1.00
AZD9291	Aniline **1** HCl Biphenyl	0.136 0.109 0.0255	Et_3N	1.20	Acid chloride **2**	0.500

3.2 Model Optimization Results

3.2.1 *N*-(2,4-dimethoxyphenyl)prop-2-enamide, 6



A standard for HPLC analysis was synthesized using the following procedure: 2,4-dimethoxy aniline (498 mg, 3.25 mmol) and triethylamine (1.15 mL, 8.26 mmol) were dissolved in acetonitrile. The black mixture was cooled to 0 °C (aq ice bath) and 3-chloropronionyl chloride (0.47 mL, 4.92 mmol) was added drop-wise with rigorous stirring. The reaction was stirred at 0 °C for 3 hours and then quenched with HCl (2M, 10 mL). Acetonitrile was removed under vacuum and the resultant residue was washed with dichloromethane (3 x 10 mL) The organic fractions were combined and washed with HCl (2M, 3 x 10 mL) and then dried (Na_2SO_4) and concentrated under vacuum to leave the crude product as a black flaky solid. Crystalizing from EtOAc–hexane gave the acrylamide (512 mg, 76%, 94 % purity) as dark brown plates, mp 119-121 °C; δ_H (500 MHz, $CDCl_3$, $SiMe_4$) 8.36 (1H, d, *J* 9.0, aryl 6-H), 7.68 (1H, br s, N-H), 6.48-6.50 (2H, m, aryl 3-H and 5-H), 6.40 (1H, dd, *J* 17.0 and 1.0, allyl 3-H_A), 6.27 (1H, dd, *J* 16.5 and 10.0, allyl 2-H) 5.72 (1H, dd, *J* 10.0 and 1.0, allyl 3-H_B), 3.87 (3H, s, methoxy 2-CH_3), 3.80 (3H, s, methoxy 4-CH_3); δ_C (125 MHz, $CDCl_3$, $SiMe_4$) 163.0 (aryl 4-C), 156.5 (CO), 149.2 (aryl 2-C), 133.0 (allyl 2-C), 131.6 (allyl 3-C), 121.2 (aryl 1-C), 120.8 (aryl 6-C), 103.8 (aryl 5-C), 98.6 (aryl 3-C) 55.7 (methoxy 2-C), 55.5 (methoxy 4-C); v_{max}/cm^{-1} (solid); 1453, 1467, 1506, 1536, 1612, 1652, 2942, 2973, 3010, 3233; m/z (ESI+) found $[M+H]^+$ 208.0968, $C_{11}H_{14}NO_3$ requires $[M+H]^+$ 208.0968.

3.2.2 Model Acrylamide Optimization

The optimization was carried out according to the limits described in Table S2 using the reactor described in Figure S2. The data from the optimization is displayed in Table S3.

Table S2 - Optimization limits used in the model compound self-optimization

Limits	**4** flow / mL min^{-1}	NEt_3 eq	**2** eq	Temperature / °C
Upper	0.100	4.5	0.9	0
Lower	0.400	20	2.1	130

*Table S3 – List of conditions and response of **6** for the model compound optimization. Optimum conditions are highlighted in green.*

Entry	**4** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **6** %
1	0.495	1.0	7.1	0.1	1.86	26.2
2	0.369	1.8	15.5	63.4	2.34	35.2
3	0.333	1.9	8.0	96.7	2.43	38.8
4	0.214	1.3	5.3	130.0	2.63	41.9
5	0.480	1.9	13.2	16.0	2.34	35.7
6	0.120	1.2	11.3	31.8	3.26	65.1
7	0.340	1.2	11.3	80.9	2.65	45.3
8	0.360	0.9	6.7	113.4	2.67	47.7
9	0.180	1.5	7.8	47.7	2.94	49.6
10	0.490	1.2	7.3	71.6	2.08	30.0
11	0.490	1.6	12.6	105.4	2.53	39.9
12	0.470	1.1	9.8	121.6	2.90	56.0
13	0.500	0.9	8.6	13.1	1.94	30.4
14	0.100	1.2	4.8	54.2	2.82	46.3
15	0.220	1.7	9.2	64.2	2.93	49.2
16	0.500	1.5	14.8	130.0	3.22	68.7
17	0.100	1.5	15.2	23.4	3.58	77.3
18	0.100	1.5	14.8	80.9	3.53	85.1
19	0.200	1.7	13.9	80.9	3.48	67.9
20	0.360	1.8	17.7	130.0	3.46	77.7
21	0.340	1.5	14.8	130.0	3.55	80.2
22	0.100	2.0	14.6	0.0	3.71	77.0
23	0.100	1.9	18.5	7.5	3.69	79.1
24	0.320	1.2	6.6	76.6	2.20	31.4
25	0.100	2.0	18.0	84.4	3.61	71.3
26	0.100	1.7	13.8	0.0	3.73	75.6

Entry	**4** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **6** %
27	0.100	1.9	15.3	76.3	3.79	77.5
28	0.100	2.1	15.5	79.9	3.74	75.4
29	0.150	1.2	9.8	105.5	3.44	64.8
30	0.220	1.2	11.9	130.0	3.77	91.1
31	0.200	1.0	8.7	15.9	3.00	51.5
32	0.100	2.1	19.5	74.8	3.53	81.1
33	0.100	1.4	9.9	82.7	3.56	69.1
34	0.100	1.8	12.9	89.2	3.64	71.7
35	0.100	1.7	16.3	117.8	3.82	91.9

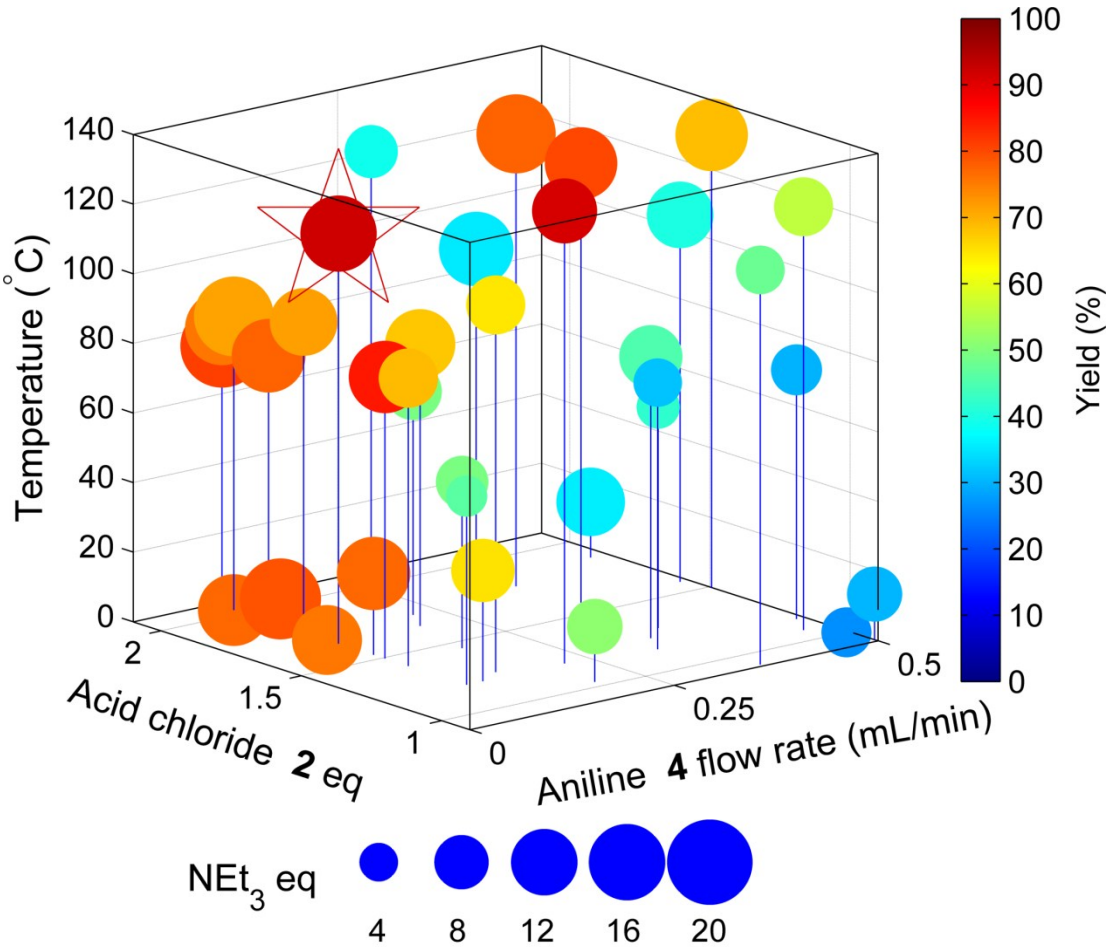


*Figure S6 - Multi-dimensional plot of the optimization of acrylamide **6**. The 3-axis plot show the aniline **4** flow rate (x-axis), acid chloride **2** eq (y-axis) and temperature (z-axis). The size of the point represents the eq of NEt_3, and the color represents the product yield. The optimum conditions: 12.2 min, 117.8 °C, 16 eq NEt_3, 1.7 eq **2** are highlighted by the star*

3.2.3 Impurity Results

The composition of the major impurities (maximum HPLC area ≥ 1%) is shown in Table for the conditions shown in Table S3. A visual representation showing the area of experimental space where the yield is highest is shown in Figure S7.

Table S4 – Composition of products for each experiment shown in Table S3.

Entry	Conditions				Yield / %			
	4 / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	**4**	**5**	**7**	**8**
1	0.495	1.0	7.1	0.1	0.0	68.4	4.4	0.5
2	0.369	1.8	15.5	63.4	0.0	58.2	5.5	0.4
3	0.333	1.9	8.0	96.7	0.3	54.0	5.7	0.4
4	0.214	1.3	5.3	130.0	0.0	51.0	6.3	0.6
5	0.480	1.9	13.2	16.0	0.0	57.6	5.5	0.6
6	0.120	1.2	11.3	31.8	0.5	21.1	12.6	0.8
7	0.340	1.2	11.3	80.9	0.3	47.6	6.1	0.5
8	0.360	0.9	6.7	113.4	0.5	47.1	3.8	0.6
9	0.180	1.5	7.8	47.7	0.0	39.3	9.3	0.6
10	0.490	1.2	7.3	71.6	0.0	63.7	5.0	0.3
11	0.490	1.6	12.6	105.4	0.0	54.4	4.7	0.4
12	0.470	1.1	9.8	121.6	0.7	40.4	1.6	0.5
13	0.500	0.9	8.6	13.1	0.5	63.0	5.3	0.4
14	0.100	1.2	4.8	54.2	0.0	42.7	9.6	0.5
15	0.220	1.7	9.2	64.2	0.0	40.8	8.7	0.5
16	0.500	1.5	14.8	130.0	0.4	28.2	1.4	0.7
17	0.100	1.5	15.2	23.4	0.5	6.4	15.0	0.9
18	0.100	1.5	14.8	80.9	0.5	3.5	9.9	0.9
19	0.200	1.7	13.9	80.9	0.0	21.4	10.0	0.7
20	0.360	1.8	17.7	130.0	0.3	19.1	1.5	0.8
21	0.340	1.5	14.8	130.0	0.5	17.1	0.9	0.8
22	0.100	2.0	14.6	0.0	0.0	7.8	13.9	0.6
23	0.100	1.9	18.5	7.5	0.0	5.7	14.4	0.8
24	0.320	1.2	6.6	76.6	0.0	62.0	5.5	0.3
25	0.100	2.0	18.0	84.4	0.0	15.8	12.2	0.7
26	0.100	1.7	13.8	0.0	0.0	8.6	14.6	0.9
27	0.100	1.9	15.3	76.3	0.0	7.1	14.1	0.8
28	0.100	2.1	15.5	79.9	0.0	10.2	13.1	0.8

Entry	Conditions				Yield / %			
	4 / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	**4**	**5**	**7**	**8**
29	0.150	1.2	9.8	105.5	0.0	23.5	10.3	0.7
30	0.220	1.2	11.9	130.0	1.0	5.4	0.8	1.0
31	0.200	1.0	8.7	15.9	0.0	36.9	9.9	0.6
32	0.100	2.1	19.5	74.8	0.0	4.9	12.6	0.8
33	0.100	1.4	9.9	82.7	0.0	16.7	13.0	0.7
34	0.100	1.8	12.9	89.2	0.0	13.9	13.2	0.7
35	0.100	1.7	16.3	117.8	0.0	2.7	3.9	0.9

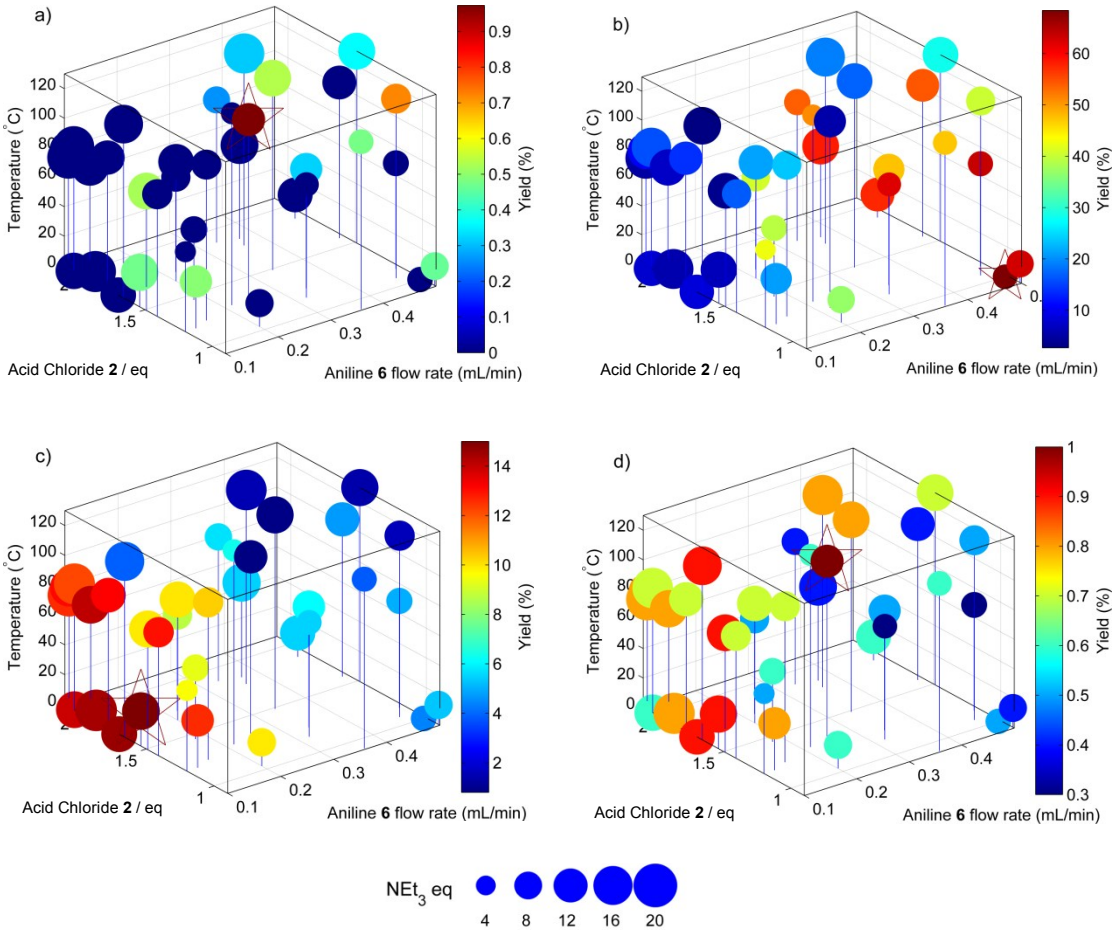


*Figure S7 – Impurity maps showing the compositions of the major impurities: aniline **4** (a), chloroamide **5** (b), enolate **7** (c) and dimer **8** (d).*

3.2.4 Impurity Identification with LCMS

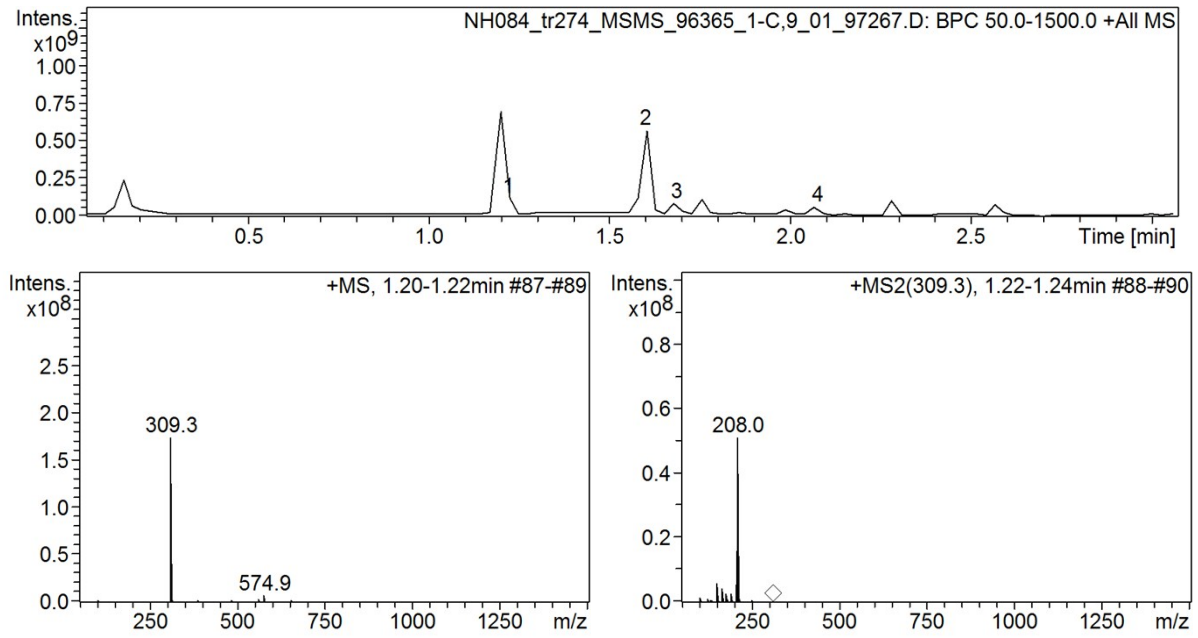


*Figure S8 – LC XIC chromatogram (above) and MS-MS spectra of compound t_R 1.22 min (below). Analysis determined that the peak was enolate **7** (other compounds: 1 is acrylamide **6**, 3 is chloroamide **5**)*

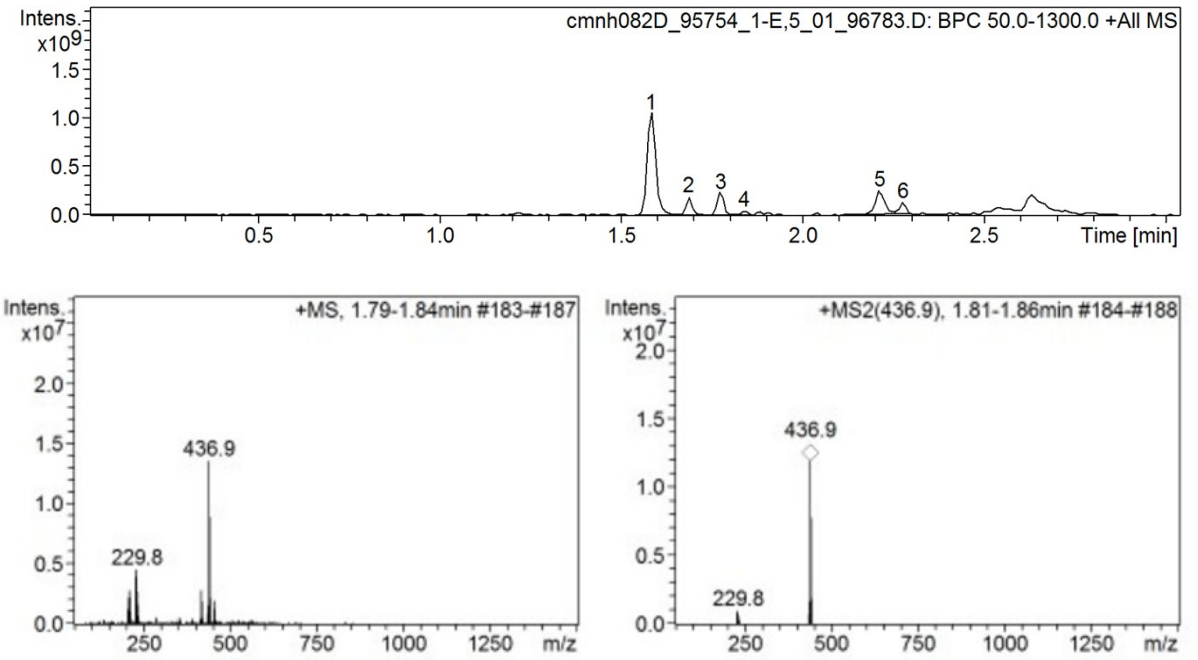


*Figure S9 – LC XIC chromatogram (above) and MS-MS spectrum of compound t_R 1.80 min (below). Structural analysis determined that the peak corresponded to dimer **8** (1 is acrylamide **6**, 3 is chloroamide **5**).*

3.2.5 Enolate Optimization

Another optimization was run, to maximize the amount of **7**, and find experimental regions where the impurity formation is high. The yields of by-product **7** from the original optimization (Table S3 and Figure S6) were inputted to SNOBFIT as preliminary data and the algorithm continued from the last data set. The results from the additional optimization are shown below in Table S5.

It should be expected that the optimum region of **7** (Figure S10) is similar to that of the acrylamide **6**, as the acrylamide is a precursor for the formation of the enolate. However, **7** is formed in higher yields at much lower temperatures, suggesting two possibilities for it formation. Firstly, as the reaction from **6** to **7** (Scheme 2) is likely to be reversible, it is possible that increased temperatures favor the acrylamide **6** in the equilibrium. Secondly, it could be that increased temperatures favor the onward reaction of **7** with another molecule of **6**, resulting in the formation of the dimer **8b** – although LC-MS analysis strongly suggests this route is not favored.

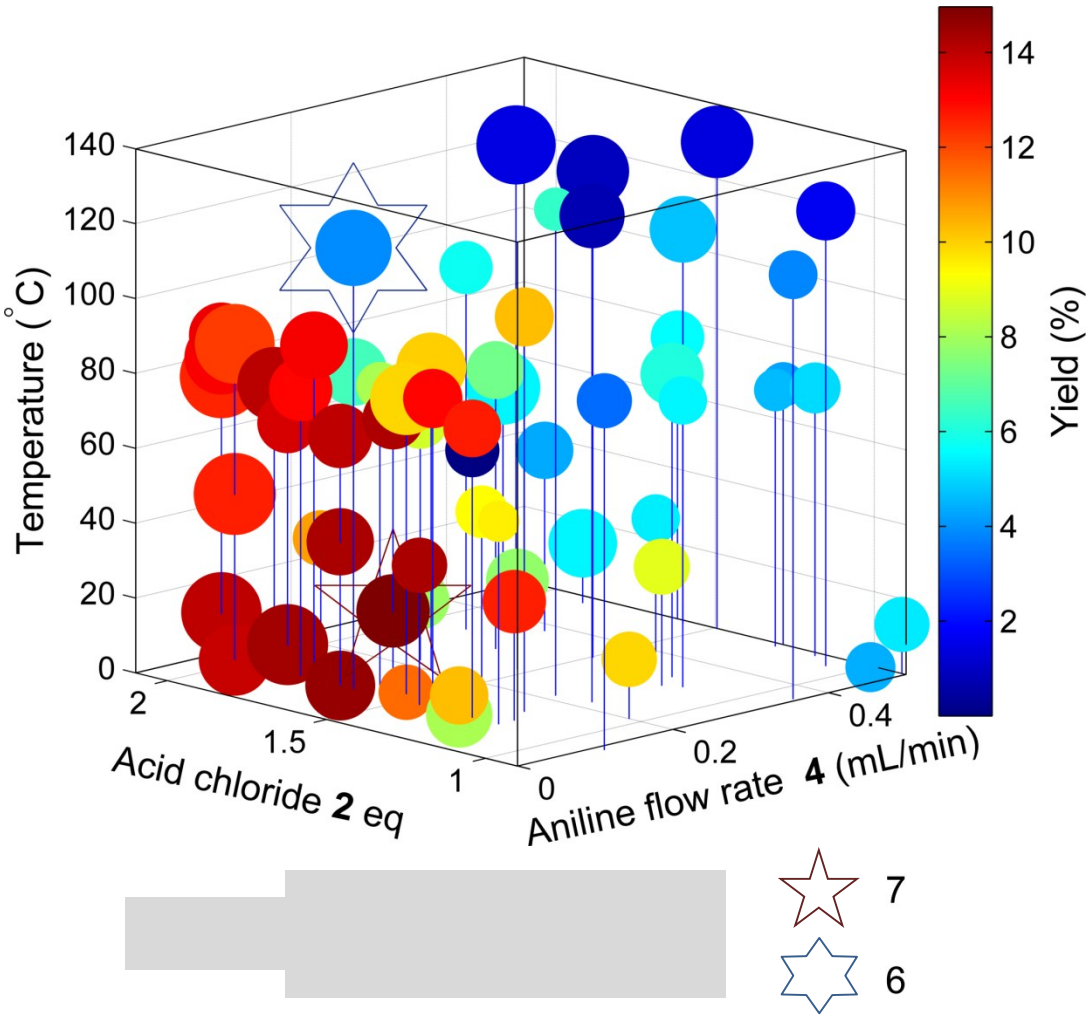


*Figure S10 - Multi-dimensional plot, showing the results of the optimization of enolate **7**. The 3-axis plot show the aniline **4** flow rate (x-axis), acid chloride **2** eq (y-axis) and temperature (z-axis). The size of the point represents NEt_3 eq, and the colour represents the product yield. The optimum conditions: 0.1 mL min^{-1} **4**, 117.8 °C, 1.5 eq **2**, 15.2 eq NEt_3 and 12.7 min are highlighted by the 5-pointed star. The optimum conditions of **6** are highlighted by the 6-pointed star.*

*Table S5 – List of conditions and response for the optimization of enolate **7**. The original conditions and response from the first optimization are greyed out. The optimum conditions are highlighted in green*

Entry	**4** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **7** %
1	0.495	1.0	7.1	0.1	0.31	4.4
2	0.214	1.3	5.3	130.0	0.40	6.2
3	0.369	1.8	15.5	63.4	0.37	5.5
4	0.333	1.9	8.0	96.7	0.36	5.7
5	0.480	1.9	13.2	16.0	0.36	5.4
6	0.120	1.2	11.3	31.8	0.63	12.5
7	0.340	1.2	11.3	80.9	0.36	6.0
8	0.360	0.9	6.7	113.4	0.21	3.7
9	0.180	1.5	7.8	47.7	0.55	9.3
10	0.490	1.2	7.3	71.6	0.35	5.0
11	0.490	1.6	12.6	105.4	0.30	4.7
12	0.470	1.1	9.8	121.6	0.09	1.6
13	0.500	0.9	8.6	13.1	0.34	5.3
14	0.100	1.2	4.8	54.2	0.58	9.5
15	0.220	1.7	9.2	64.2	0.52	8.6
16	0.500	1.5	14.8	130.0	0.07	1.4
17	0.100	1.5	15.2	23.4	0.69	14.7
18	0.100	1.5	14.8	80.9	0.41	9.7
19	0.200	1.7	13.9	80.9	0.52	9.8
20	0.360	1.8	17.7	130.0	0.06	1.4
21	0.340	1.5	14.8	130.0	0.04	0.9
22	0.100	2.0	14.6	0.0	0.67	13.7
23	0.100	1.9	18.5	7.5	0.67	14.1
24	0.320	1.2	6.6	76.6	0.38	5.4
25	0.100	2.0	18.0	84.4	0.62	11.9

Entry	**4** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **7** %
26	0.100	1.7	13.8	0.0	0.72	14.4
27	0.100	1.9	15.3	76.3	0.69	13.7
28	0.100	2.1	15.5	79.9	0.65	12.8
29	0.150	1.2	9.8	105.5	0.54	10.1
30	0.220	1.2	11.9	130.0	0.03	0.7
31	0.200	1.0	8.7	15.9	0.58	9.9
32	0.100	2.1	19.5	74.8	0.55	12.2
33	0.100	1.4	9.9	82.7	0.67	12.8
34	0.100	1.8	12.9	89.2	0.67	12.9
35	0.100	1.7	16.3	117.8	0.16	3.8
36	0.100	1.3	12.4	0.0	**0.26**	8.1
37	0.260	1.5	11.1	23.8	0.50	7.7
38	0.100	1.7	12.8	38.4	0.73	14.1
39	0.100	1.5	10.5	74.7	0.73	14.1
40	0.100	0.9	8.6	93.3	0.12	3.4
41	0.100	1.5	8.6	2.5	0.62	11.4
42	0.100	1.3	9.6	5.1	0.56	10.2
43	0.160	1.9	8.9	32.1	0.57	10.7
44	0.100	1.9	10.4	66.7	0.68	13.5
45	0.370	1.4	6.6	38.3	0.37	5.3
46	0.100	2.0	18.9	44.3	0.64	12.3
47	0.100	1.7	11.7	66.7	0.68	13.7
48	0.100	2.1	11.9	85.9	0.65	13.0
49	0.100	2.1	18.2	11.8	0.67	13.6
50	0.100	1.5	8.7	37.3	0.72	14.1
51	0.380	1.7	9.2	48.3	0.29	4.3
52	0.100	1.3	8.3	71.5	0.00	0.0
53	0.100	1.6	6.3	82.7	0.49	8.1
54	0.310	1.2	8.9	31.8	0.53	8.9
55	0.490	1.3	5.2	68.5	0.33	4.6
56	0.300	1.7	9.5	74.5	0.44	7.2
57	0.500	1.6	8.1	75.2	0.38	5.5
58	0.100	1.8	11.2	76.5	0.68	12.7
59	0.220	1.7	9.6	16.1	0.48	7.8
60	0.270	2.1	12.9	67.7	0.39	6.4

Entry	**4** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **7** %
61	0.500	1.3	5.6	69.5	0.30	4.2
62	0.100	1.3	9.4	77.3	0.66	12.5

3.3 AZD9291 Optimization

The Optimization of **3** was carried out according to the limits displayed in Table S6. A list of conditions and responses from the optimization are displayed in

*Table S6 – Boundary limits for the optimization of **3***

Limit	**4** flow / mL min^{-1}	NEt_3 eq	**2** eq	Temperature / °C
Minimum	0.080	2.2	0.75	80
Maximum	0.150	15	3.0	150

*Table S7 – List of conditions and responses for the optimization of **3**. Optimum conditions are highlighted in green.*

Entry	**1** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **3** %
1	0.100	1.3	5.0	80.1	1.80	37.1
2	0.118	2.4	9.4	149.8	2.87	68.0
3	0.130	0.9	3.7	141.1	2.97	53.7
4	0.100	1.9	5.0	105.4	3.52	72.3
5	0.120	1.0	3.3	106.3	2.37	47.3
6	0.080	0.8	2.2	150.0	1.99	55.8
7	0.150	1.9	8.6	150.0	2.93	67.8
8	0.080	0.8	2.6	93.6	1.80	41.1
9	0.080	2.8	7.6	99.6	3.82	79.4
10	0.080	2.4	6.3	107.1	2.69	57.1
11	0.100	1.4	5.4	119.4	1.98	51.1
12	0.150	0.8	2.6	147.6	2.21	51.3
13	0.090	3.0	9.5	88.2	2.70	71.2
14	0.120	2.4	6.5	104.4	3.23	77.1
15	0.110	3.0	8.0	106.1	3.59	82.3
16	0.110	2.7	10.5	123.9	4.49	88.9
17	0.120	1.0	3.3	86.6	2.15	48.8
18	0.100	0.9	2.5	106.3	2.41	56.7
19	0.110	1.8	4.8	124.0	3.18	83.2

Entry	**1** / mL min^{-1}	**2** / eq	NEt_3 / eq	Temperature / °C	A_x/A_{IS}	Yield **3** %
20	0.090	3.0	9.9	124.2	3.86	85.6
21	0.080	1.8	4.7	103.0	3.34	75.1
22	0.100	1.4	6.7	110.9	2.81	69.3
23	0.130	3.0	13.8	123.3	4.29	83.2
24	0.090	2.4	6.4	123.3	3.47	81.6
25	0.120	3.0	14.9	141.1	3.77	75.7
26	0.100	3.0	10.6	111.0	3.14	74.0
27	0.090	3.0	13.6	124.1	3.35	74.7
28	0.140	3.0	11.4	138.3	3.77	81.0
29	0.110	1.3	4.3	145.6	3.36	72.0
30	0.120	1.1	5.3	121.7	2.49	61.6
31	0.150	3.0	10.9	123.4	3.69	80.7
32	0.130	3.0	11.1	124.1	3.84	86.5
33	0.130	3.0	14.9	132.6	3.39	86.1
34	0.080	3.0	9.5	103.0	3.93	80.1
35	0.150	3.0	13.1	122.5	3.34	68.5
36	0.090	1.0	2.6	124.9	2.82	62.8
37	0.090	2.4	6.4	125.2	3.37	79.9
38	0.110	2.1	6.7	141.2	3.25	81.3
39	0.130	1.4	5.4	119.4	2.58	65.7
40	0.110	3.0	12.4	122.4	3.56	71.5
41	0.150	2.2	11.0	123.3	2.83	67.3
42	0.150	2.7	13.4	123.8	2.47	68.0

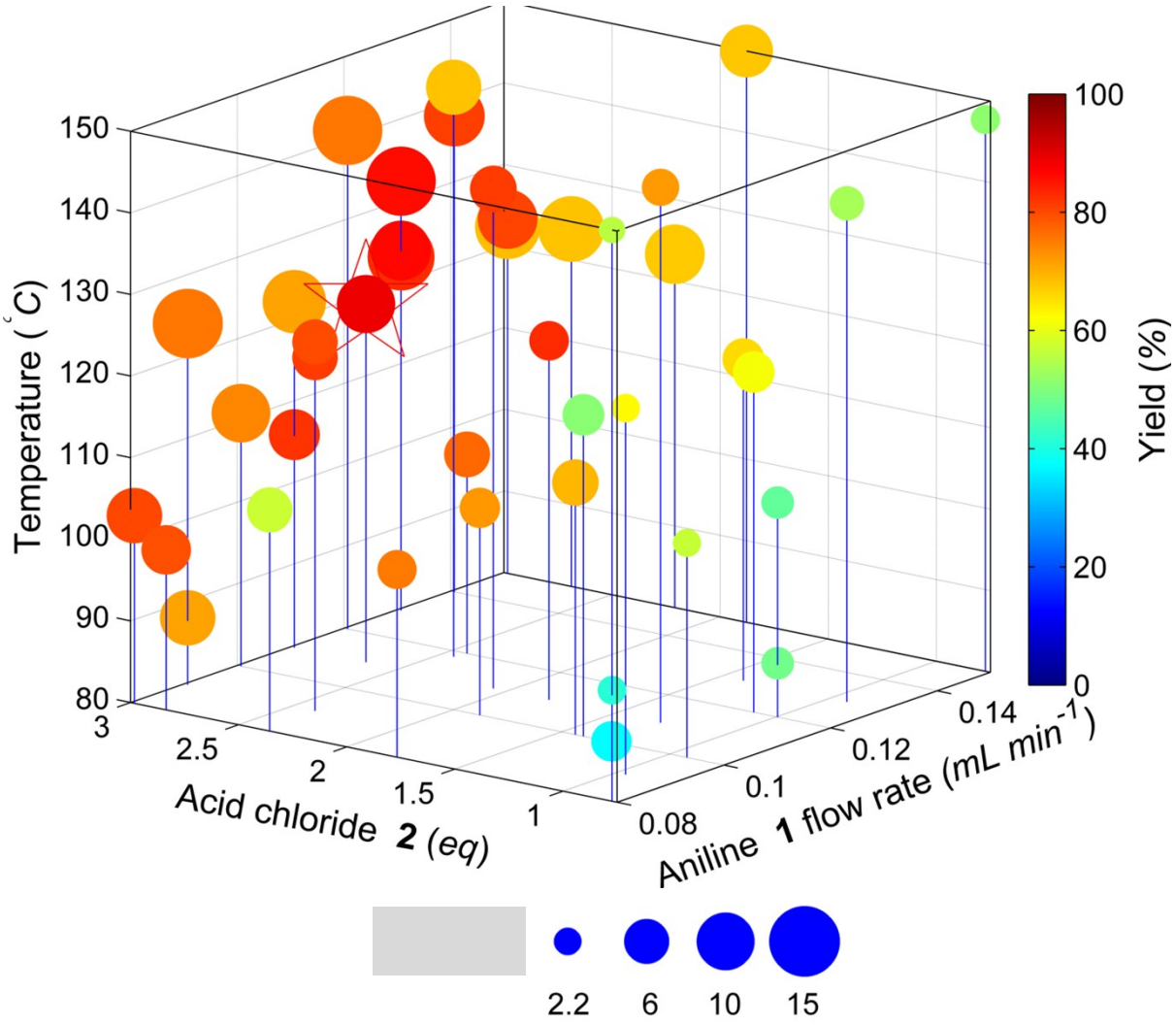


*Figure S11 - Multidimensional plot of the optimization of acrylamide **3**. The 3 axis flow rate shows the aniline **1** flow rate (x-axis), acid chloride **2** eq (y-axis) and temperature (z-axis). The size of the point corresponds to the triethylamine eq, the color is the yield. Optimum conditions: 9.36 min, 123.9 °C, 10.5 eq NEt_3, 2.7 eq **2** are highlighted by the star.*

3.3.1 AZD9291 Impurity Results

Entry	Conditions				Yield / %					
	1 / mL min^{-1}	**3** / eq	NEt_3 / eq	Temp / °C	Imp 1	**1**	Dimer	Chloro-amide	Imp 2	Imp 3
1	0.100	1.3	5.0	80.1	0.3	57.3	1.6	1.2	0.0	0.4
2	0.118	2.4	9.4	149.8	0.3	21.4	4.7	3.1	0.0	0.4
3	0.130	0.9	3.7	141.1	1.9	39.9	0.3	0.0	0.0	0.6
4	0.100	1.9	5.0	105.4	0.3	14.1	4.2	1.8	0.0	0.8
5	0.120	1.0	3.3	106.3	0.6	44.6	2.1	0.6	0.3	0.6
6	0.080	0.8	2.2	150.0	3.0	34.3	0.9	0.0	0.0	0.8

Entry	Conditions				Yield / %					
	1 / mL min^{-1}	**3** / eq	NEt_3 / eq	Temp / °C	Imp 1	**1**	Dimer	Chloro-amide	Imp 2	Imp 3
7	0.150	1.9	8.6	150.0	0.7	25.9	0.4	0.0	0.3	0.6
8	0.080	0.8	2.6	93.6	0.7	48.5	2.3	0.6	0.3	0.8
9	0.080	2.8	7.6	99.6	0.0	5.1	6.7	4.0	0.6	0.7
10	0.080	2.4	6.3	107.1	0.4	29.8	2.1	2.1	1.3	0.6
11	0.100	1.4	5.4	119.4	0.8	41.4	0.7	0.4	0.6	1.3
12	0.150	0.8	2.6	147.6	1.4	40.8	0.4	0.4	0.2	0.8
13	0.090	3.0	9.5	88.2	0.3	12.3	4.2	4.5	0.7	0.7
14	0.120	2.4	6.5	104.4	0.4	5.7	4.4	3.6	0.6	0.6
15	0.110	3.0	8.0	106.1	0.3	1.3	4.6	4.6	0.5	0.7
16	0.110	2.7	10.5	123.9	0.0	2.6	1.8	1.1	1.2	0.8
17	0.120	1.0	3.3	86.6	0.2	39.2	2.4	1.4	0.6	0.8
18	0.100	0.9	2.5	106.3	0.8	33.3	2.5	0.7	0.3	1.0
19	0.110	1.8	4.8	124.0	0.4	7.8	1.1	0.7	0.4	0.7
20	0.090	3.0	9.9	124.2	0.5	4.6	0.9	1.3	0.7	0.8
21	0.080	1.8	4.7	103.0	0.3	9.3	4.7	2.0	0.8	0.8
22	0.100	1.4	6.7	110.9	0.4	18.3	2.7	1.4	0.7	0.9
23	0.130	3.0	13.8	123.3	0.0	6.9	2.2	1.7	1.1	0.9
24	0.090	2.4	6.4	123.3	0.4	8.9	0.9	0.8	0.6	0.8
25	0.120	3.0	14.9	141.1	0.0	15.4	1.0	0.8	0.8	0.8
26	0.100	3.0	10.6	111.0	0.0	11.2	3.0	3.1	1.0	0.7
27	0.090	3.0	13.6	124.1	0.0	14.9	0.7	2.1	1.1	0.8
28	0.140	3.0	11.4	138.3	0.0	10.4	0.5	1.0	0.8	1.2
29	0.110	1.3	4.3	145.6	1.2	19.3	0.4	0.3	0.0	1.0
30	0.120	1.1	5.3	121.7	0.7	29.5	0.7	0.5	0.6	1.0
31	0.150	3.0	10.9	123.4	0.0	7.2	1.7	2.3	1.3	0.8
32	0.130	3.0	11.1	124.1	0.0	3.5	1.5	1.8	1.0	0.9
33	0.130	3.0	14.9	132.6	0.0	4.1	0.7	1.4	1.2	0.7
34	0.080	3.0	9.5	103.0	0.0	3.9	4.8	3.3	0.8	1.1
35	0.150	3.0	13.1	122.5	0.0	18.6	1.5	2.1	1.0	0.9
36	0.090	1.0	2.6	124.9	1.4	27.0	0.6	0.2	0.8	1.1
37	0.090	2.4	6.4	125.2	0.5	9.4	0.8	0.8	0.9	0.9
38	0.110	2.1	6.7	141.2	0.5	10.7	0.7	0.0	0.4	1.4
39	0.130	1.4	5.4	119.4	0.4	22.9	1.1	1.0	0.7	0.9

Entry	Conditions				Yield / %					
	1 / mL min^{-1}	**3** / eq	NEt_3 / eq	Temp / °C	Imp 1	**1**	Dimer	Chloro-amide	Imp 2	Imp 3
40	0.110	3.0	12.4	122.4	0.0	16.2	1.0	1.5	1.1	1.4
41	0.150	2.2	11.0	123.3	0.0	21.3	1.1	1.6	1.0	1.0
42	0.150	2.7	13.4	123.8	0.0	20.2	1.0	1.2	0.9	1.0

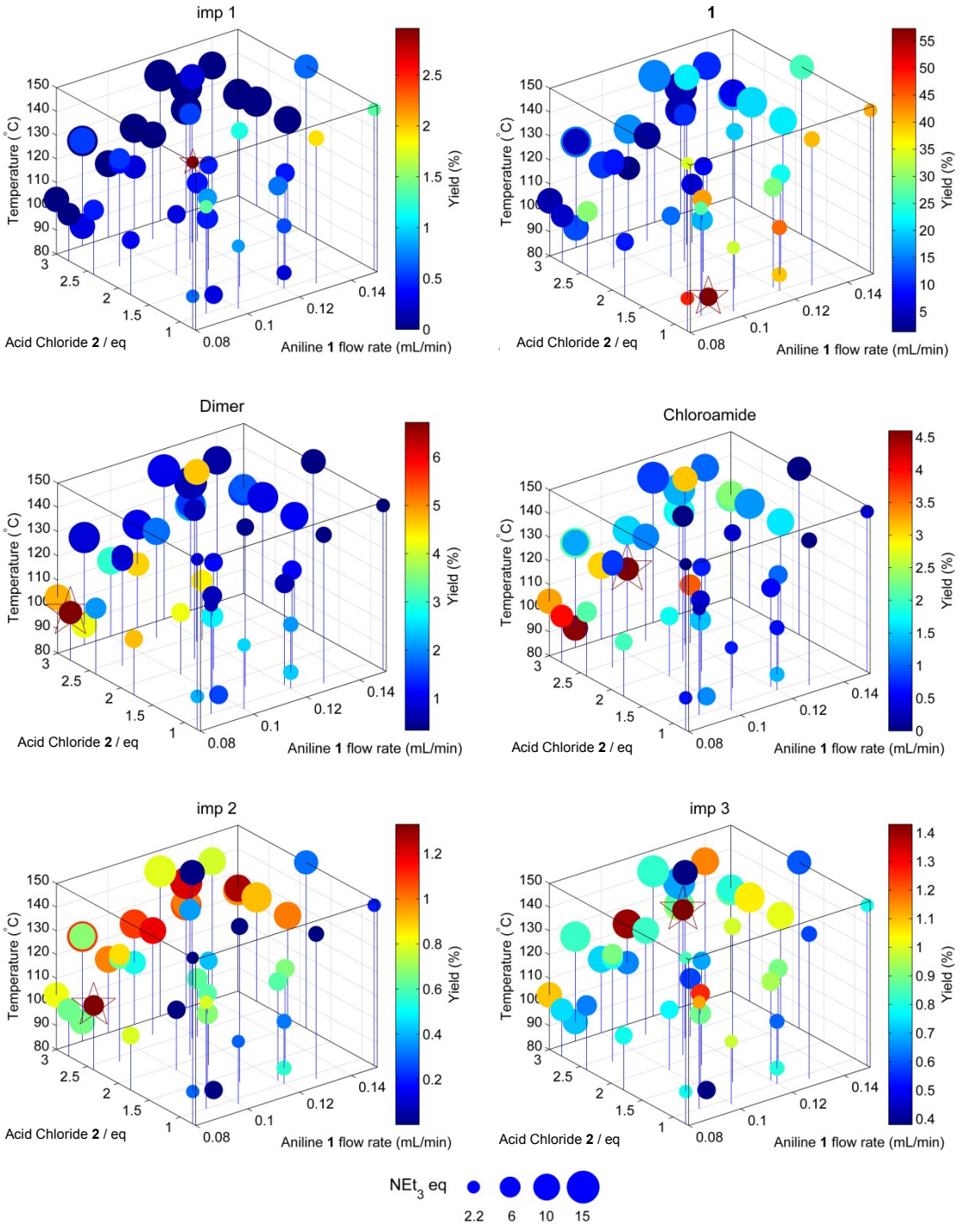
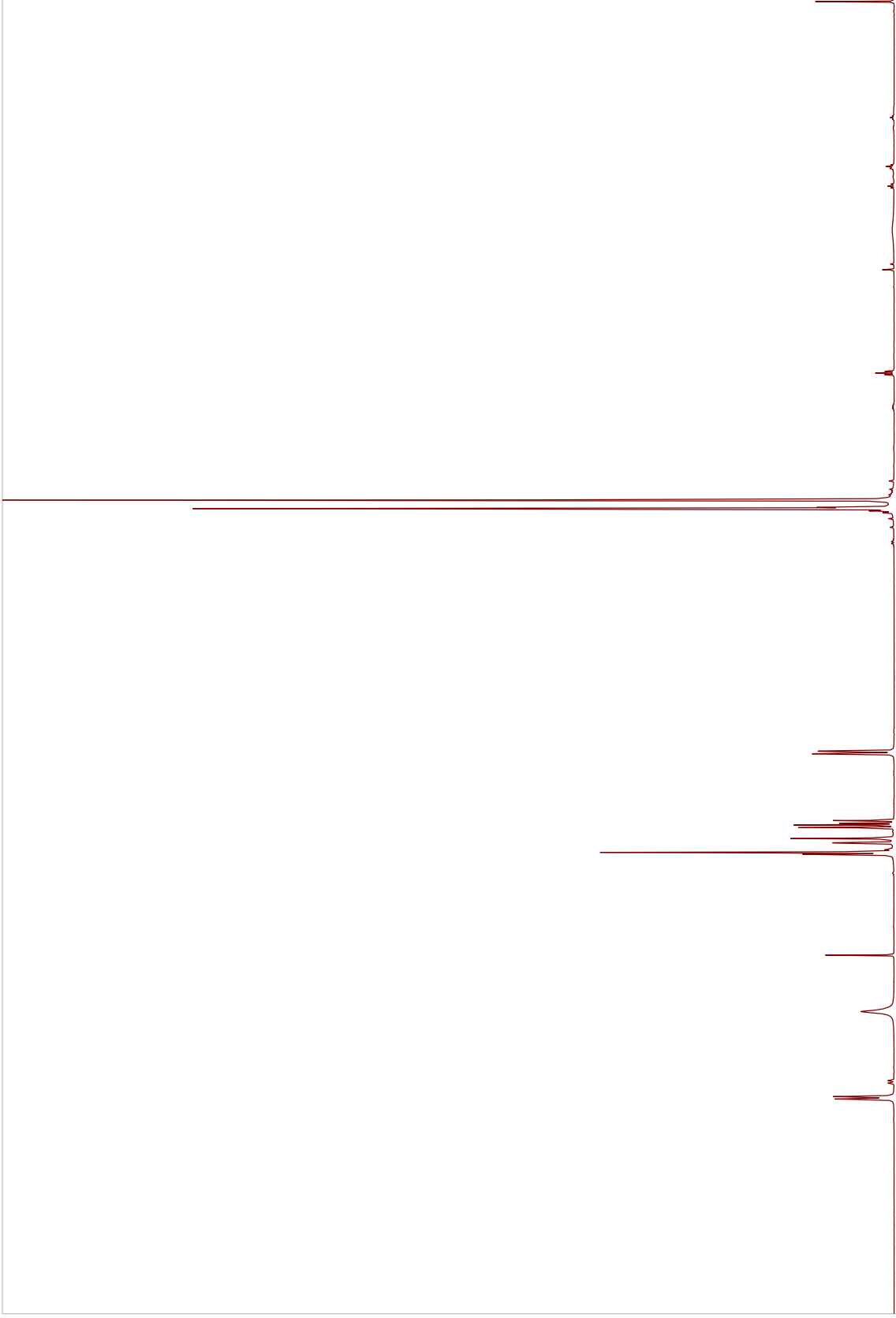
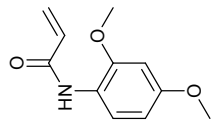


Figure S12 – Impurity maps showing the composition of different products as displayed in Figure S5

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