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

Electronic Supporting Information

A Self-Optimised Approach to Synthesising DEHiBA for Advanced Nuclear Reprocessing, Exploiting the Power of Machine-Learning

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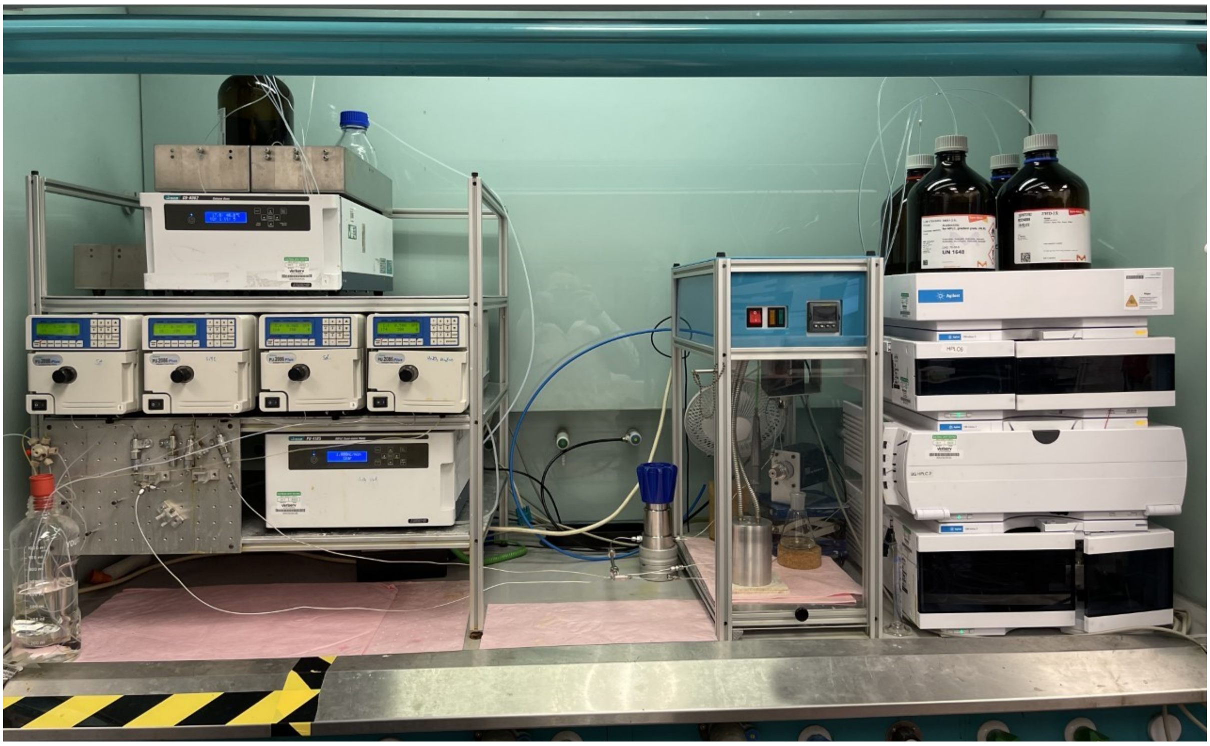
1.1 Self-Optimising Flow Reactor Platform Setup



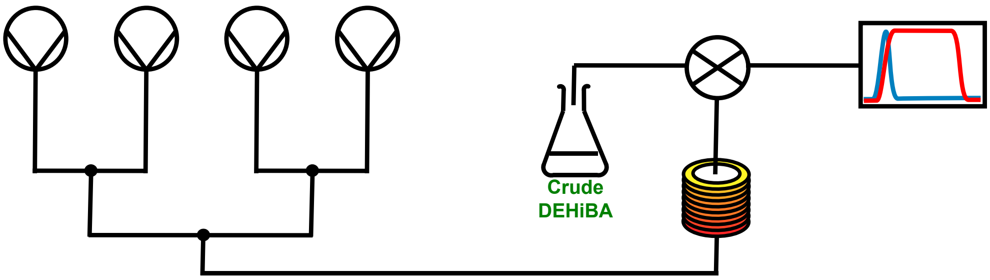


Figure S1 - The self-optimising flow reactor platform and its visual schematic

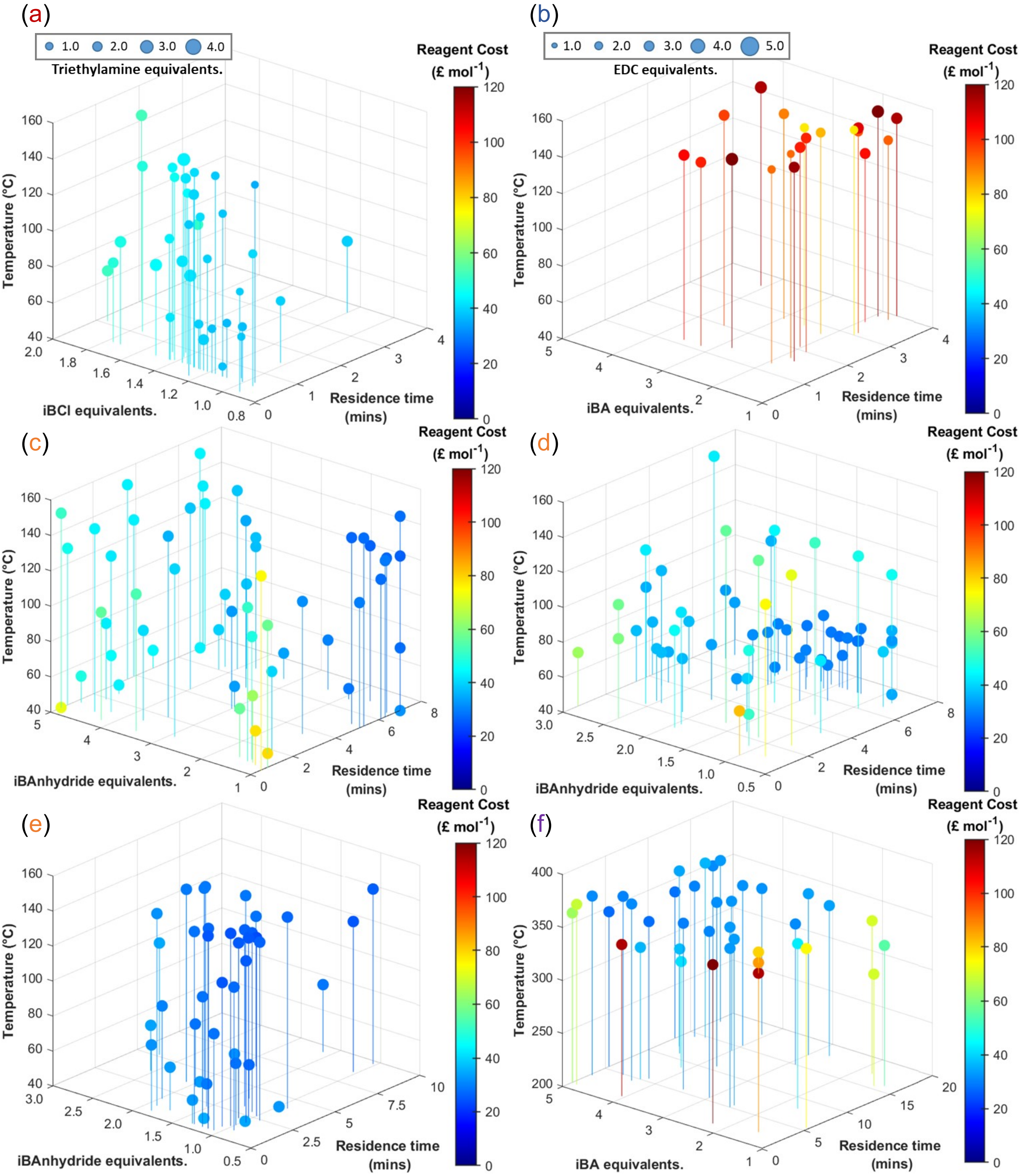
Reagents were made up to their desired concentrations in the stock solutions, loaded into glass bottles and primed on the dual piston reciprocating JASCO PU-2800 HPLC pumps. These solutions were then pumped where streams would be mixed using Swagelok SS-100-3 tee-pieces according to Figure 2. Tubular reactors were made from PFA, PTFE and 316 stainless steel tubing (1/16” OD), these were fitted to cylindrical aluminium blocks and heated via a Eurotherm 3200 temperature controller, this enabled the reaction mixtures to be heated rapidly. After the reactor, the tubing enabled rapid cooling back to roughly ambient temperature prior to an aliquot of the reaction solution being sampled using a VICI Valco EUDA-CI4W sample loop (4-port) with 0.5 and 0.06 μL injection volume. The sample was then fed directly into an Agilent 1260 Infinity II series HPLC instrument fitted with an Agilent Poroshell 120 EC-C18 reverse phase column (5 cm length, 4.6 mm ID and 2.7 μm particle size) for quantitative analysis. The flow system was maintained under a constant back pressure using an Upchurch Scientific back pressure regulator (100/250 psi) for all setups however route (e) also employed the Tescom™ 26-1762-22 control pressure regulator to achieve a pressure of 210 bar. The automated system was controlled using a custom written MATLAB program to enable real-time control and monitoring of all the optimisation variables. The machine-learning algorithms in MATLAB were initiated with Latin hypercube sampling where the number of experiments for this was $2n+1$, n being the number of variables. This formula guarantees that each dimension is divided into $n + 1$ subintervals, and that there will be one sample in each subinterval. This helps achieve a more even coverage of the parameter space, thus reducing the risk of missing important regions. The analytical data from this and following experiments enabled the generation of new conditions for the optimisation to proceed. To determine process metrics, biphenyl was included as an internal standard in reservoir 1 solutions, here the internal standard and compound signal areas allow for accurate calculations to be completed using calibration data previously obtained. During the process, Microsoft Teams screen sharing capability is also utilised to allow for the user to monitor the equipment remotely.

1.2 Reagent Costs

The lowest cost for each reagent was acquired as of March 2022 for the cost calculations used by this research.

Table S1: The reagent costs for the raw materials used in this research as of March 2022

Raw Material	Molecular weight (g mol^{-1})	Cost per mole (£ mol^{-1})
Di(2-ethylhexyl)amine (**DiEHA**)	241.46	18.18
Isobutyryl chloride (**iBCl**)	106.55	14.75
Isobutyric acid (**iBA**)	88.11	0.59
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (**EDC.HCl**)	191.77	23.96
4-dimethylaminopyridine (**DMAP**)	122.17	17.25
Isobutyric anhydride (**iBAnhydride**)	158.19	5.31
Triethylamine	101.19	1.68



1.3 Alternative Process Metric Plots to Figure 3

Figure S2: Six 4/5D plots demonstrating the reagent cost for routes (a-f), the synthetic route for each is defined above the plots for ease of comparison. A consistent colour bar is illustrated throughout, ranging between 0-80%, whilst the x, y, z and size ranges are subject to the parameter space for each optimisation, finally a reduced dataset has been presented for clarity.

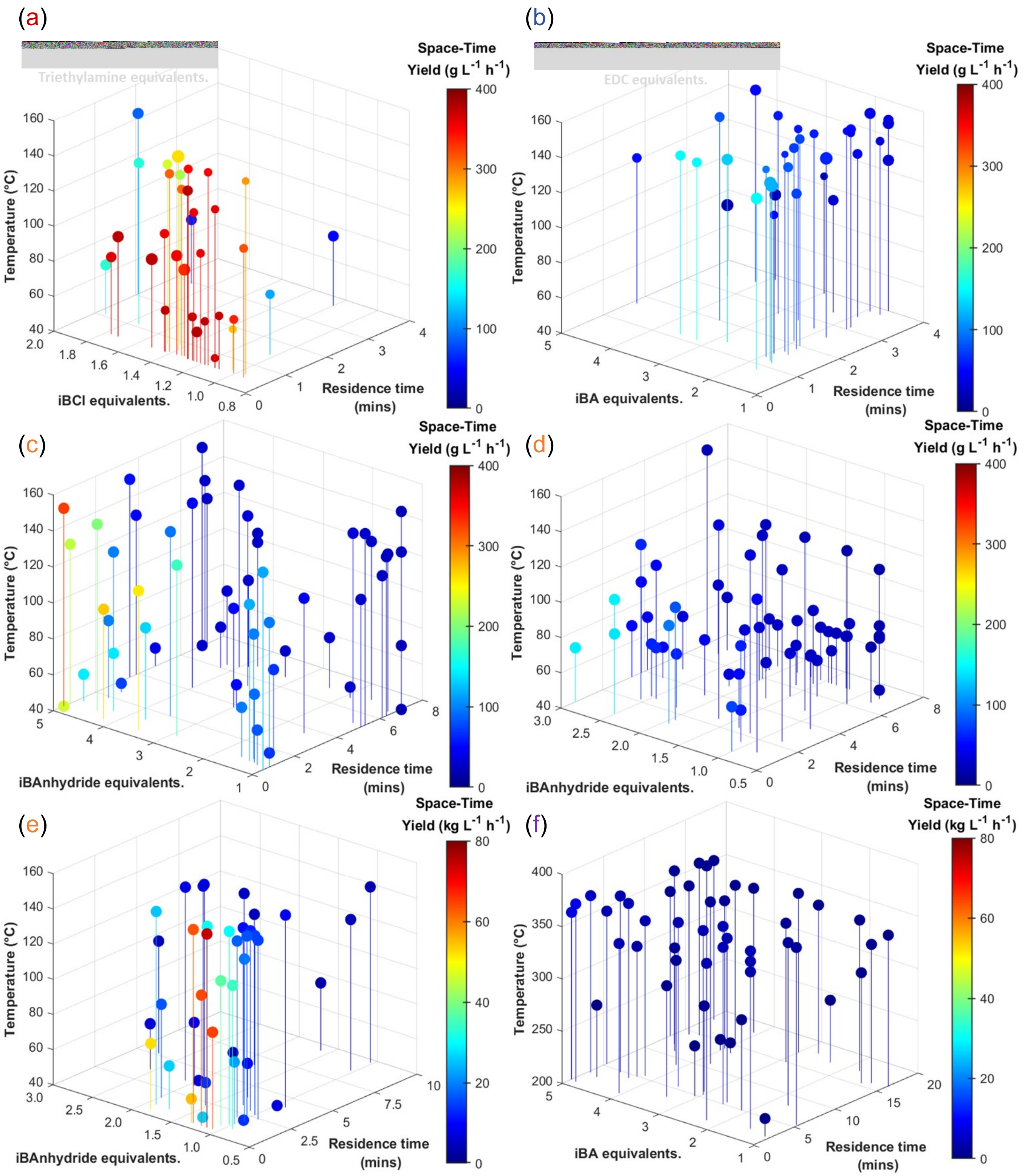


Figure S3: Six 4/5D plots demonstrating the space-time yield for routes (a-f), the synthetic route for each is defined above the plots for ease of comparison. A consistent colour bar is illustrated throughout, ranging between 0-80%, whilst the x, y, z and size ranges are subject to the parameter space for each optimisation, finally a reduced dataset has been presented for clarity.

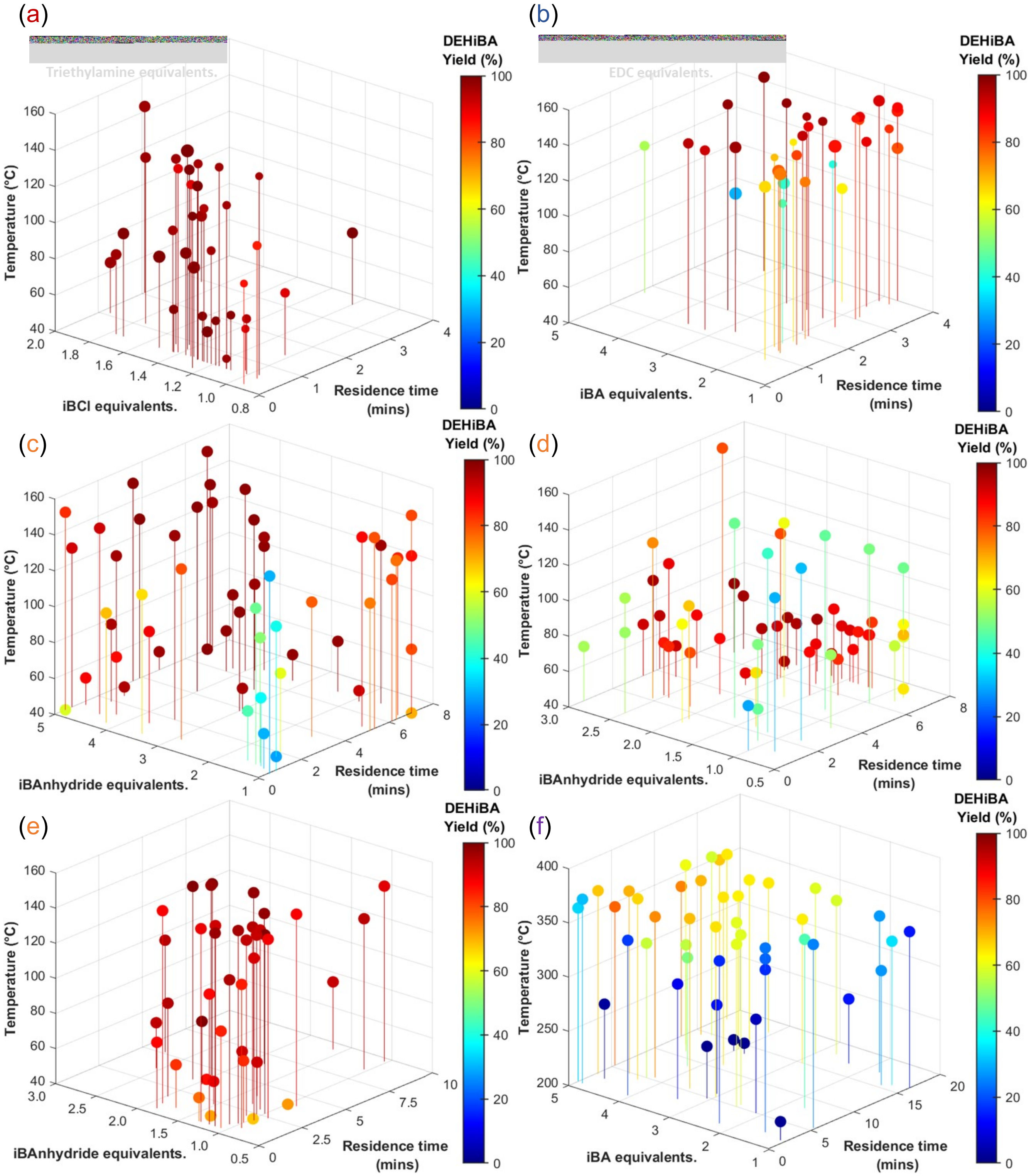


Figure S4: Six 4/5D plots demonstrating the product yield for routes (a-f), the synthetic route for each is defined above the plots for ease of comparison. A consistent colour bar is illustrated throughout, ranging between 0-80%, whilst the x, y, z and size ranges are subject to the parameter space for each optimisation, finally a reduced dataset has been presented for clarity.

1.4 The Optimum Conditions for Each Route Combined

A combination of tables 1-6 in the paper but with the colour scale normalised for better comparison of process metrics

Table S2: The optimum conditions from routes (a-f) with a normalised colour scale across each route

Route	Residence Time (min)	Equivalents. of iBA Derivative	Equivalents. of Reagent	Temperature (°C)	Yield of DEHiBA (%)	Reaction Mass Efficiency (%)	Space-Time Yield (g L^{-1} h^{-1})	Cost of DEHiBA (£ mol^{-1})
(a)	0.6	0.95	0.95	150	99.9	68.6	285	35
	0.5	1.19	1.15	35	99.9	64.8	374	37.4
	0.5	1.09	1.44	35.5	99.2	61.4	374	36.9
	0.5	1.09	1.19	70.5	98.4	64.1	371	36.9
	0.2	1.12	1.08	71	98.8	65.6	933	36.9
	0.2	1.24	1.18	124	99.9	63.2	944	38.5
(b)	1.4	1.66	2.53	169	75.6	29.9	98.2	79.7
	3.3	1.90	1.7	153	84.8	34.7	47.6	77.3
	0.7	4.90	2.64	150	91.2	20	240	151
	1.0	3.08	3.16	144	93.8	26.2	168	101
	3.1	2.20	2.5	149	95	33.3	57.1	77.1
	3.0	2.50	2.1	151	96.2	32.9	60	83.3
(c)	0.5	5.00	-	150	83.2	26.3	326	51.2
	7.0	1.00	-	127.5	86.1	70.4	24.1	26
	0.8	2.00	-	128.5	91.4	28.9	224	46.6
	0.9	3.00	-	143.5	91.8	31.5	200	43.7
	7.0	4.00	-	127.5	96	65.5	26.9	25.9
	6.5	1.80	-	127	97.5	60.6	29.4	27.1
(d)	0.7	2.50	-	105	54.2	26.5	145	58
	2.4	1.35	-	70.5	64.9	44.4	51.6	39
	7.0	2.35	-	69.7	86.8	62.4	23.2	28.4
	3.7	3.35	-	71.5	86.8	46.5	43.8	34.1
	7.0	4.35	-	69	90.5	59.9	24.2	28.6
	3.9	3.00	-	91.5	95.8	41.7	46.5	35.6
(e)	0.5	1.07	-	149	95.5	72.6	74700	24.9
	0.5	1.15	-	150	97.2	71.9	74110	24.9
	2.7	2.15	-	141.9	99.3	77.5	14720	23.6
	0.7	3.15	-	147.9	92.1	71.9	51590	25.4
	1.3	1.02	-	150	96	74.3	30090	24.5
(f)	1.7	5.00	-	366	52.3	23.8	7320	40.5
	4.8	4.60	-	369	69.8	33.5	3731	30
	6.3	5.60	-	353	71	34.7	2921	29.4
	5.5	6.60	-	348	73.7	37.4	3619	28.1
	13.2	7.60	-	338	74.3	33.8	1378	28.5
	10.6	8.60	-	339	75.6	34.4	1734	28
	5.4	5.00	-	346	77.7	35.4	3495	27.2

2 Experimental

2.1 HPLC and GC-FID Methods

HPLC analysis was performed on an Agilent 1260 Infinity II series HPLC instrument fitted with an Agilent Poroshell 120 EC-C18 reverse phase column (5 cm length, 4.6 mm ID and 2.7 µm particle size) with a binary pump and a variable wavelength detector.

The same HPLC method was used for all routes and calibrations. Water (A, 18.2 MΩ) and acetonitrile (B) HPLC mobile phases were used, starting with a 50:50 method of A:B, the amount of A was reduced to 5% over 3 minutes and held here for a further 3 minutes before returning to 50:50 over 0.5 minutes at a flow rate of 1.50 mL min^{-1} and a column temperature of 30 °C. 210 nm was used to detect the product DEHiBA, whilst 254 nm was used to detect biphenyl.

GC analysis was carried out on an Agilent 7890B instrument fitted with an Agilent Technologies 7693 Autosampler and a HP-5 column (30 m x 0.32 mm, 0.25 µm film thickness), H_2 carrier gas, FID detector.

The same GC method was used throughout, starting at 40 °C and holding at this for 1 minute, then the temperature was ramped up to 55 °C over 1 minute and held here for a further 1 minute. The temperature was then gradually increased to 150 °C over 3.8 minutes. Finally the temperature was raised to 300 °C over 3 minutes before cooling to 40 °C.

2.2 Calibrations for Quantitative Analysis

All raw materials were purchased from suppliers and calibrated where possible via GC-FID and HPLC. N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA) was synthesised as well as purchased from a commercial supplier (Technocomm) for analytical calibrations to enable the quantitative analysis of all reactions for calculating key process metrics. Two calibration curves are shown in Figure S2 for HPLC and GC-FID:

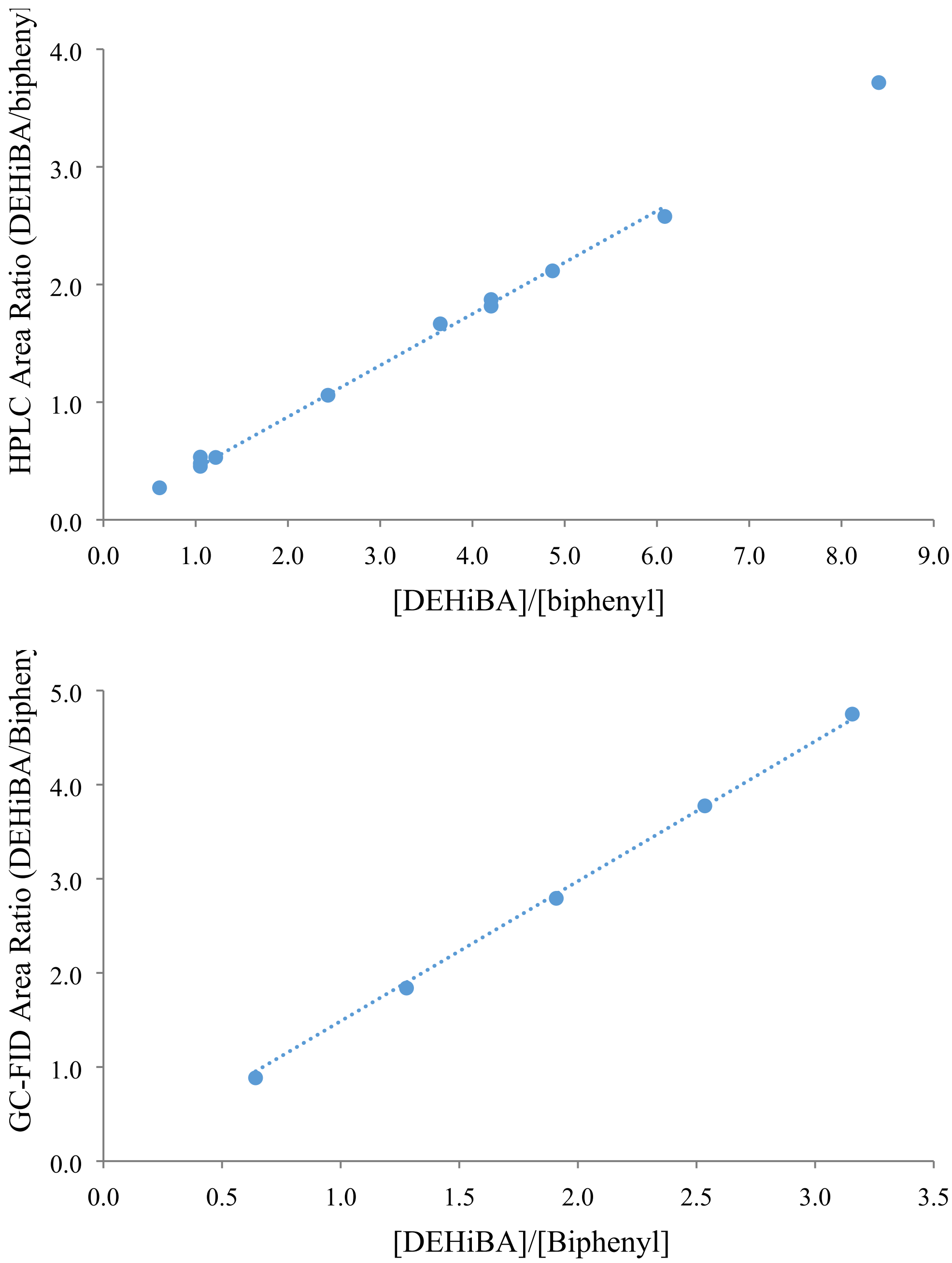
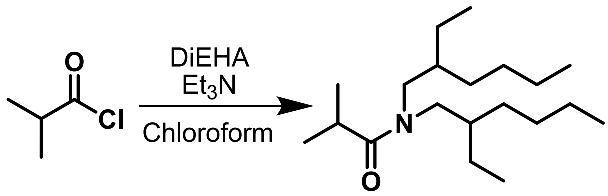


Figure S5: HPLC (top) and GC-FID (bottom) calibration curves for DEHiBA from the commercial supplier, our purified DEHiBA is also in agreement with these plots

2.3 Route (a) Acyl Chloride Route: Synthesis from Isobutyryl Chloride



Scheme S1: Amide bond formation using isobutyryl chloride and di(2-ethylhexyl)amine (DiEHA) to yield N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA)

2.3.1. Batch Chemistry:

Batch studies were conducted prior to any flow chemistry to ensure homogeneity and product formation. A range of common organic solvents were screened one of which being toluene, all reagents showed good solubility separately, however when combined in the reactor the solution instantly precipitated and stirring came to a halt at a concentration of 0.1 mol dm^{-3} due to the amount of precipitate. As solids are problematic in flow chloroform was adopted as the reaction solvent to solubilise the $Et_3N.HCl$ precipitate.

Di-2-ethylhexylamine (0.28 g, 1.16 mmol) and triethylamine (0.1450 g, 1.43 mmol) were combined with chloroform in a 10 mL volumetric flask. Likewise, Isobutyryl chloride (0.1483 g, 1.39 mmol) was combined with chloroform in a 10 mL volumetric flask. The di-2-ethylhexylamine solution was charged to an ice bath cooled 50 mL round bottom flask with stirring, slow addition of iBCl over 2 minutes gave a slightly yellow, homogenous solution that was left to stir for 4 hours at room temperature before HPLC analysis confirmed a 98% yield.

2.3.2. Continuous Flow Chemistry:

Reservoir solutions were prepared to the desired concentrations by dissolving the reagents in solvent with stirring at ambient conditions.

Setup (i):

Reservoir 1: Di(2-ethylhexyl)amine (6.0401 g, 0.025 mol, 0.05 mol dm^{-3}), triethylamine (10.5 mL, 0.075 mol, 0.15 mol dm^{-3}) and biphenyl (5.4127 g, 0.035 mol, 0.07 mol dm^{-3}) in chloroform (500 mL).

Reservoir 2: Isobutyryl chloride (5.3205 g, 0.05 mol, 0.05 mol dm^{-3}) in chloroform (1000 mL).

Reservoir 3: Chloroform.

Setup (ii):

Reservoir 1: Di(2-ethylhexyl)amine (6.0365 g, 0.025 mol, 0.05 mol dm^{-3}), and biphenyl (5.3974 g, 0.035 mol, 0.07 mol dm^{-3}) in chloroform (500 mL).

Reservoir 2: Isobutyryl chloride (2.6638 g, 0.025 mol, 0.05 mol dm^{-3}) and triethylamine (4.2 mL, 0.03 mol, 0.06 mol dm^{-3}) in chloroform (500 mL).

Reservoir 3: Chloroform.

Setup (iii):

Reservoir 1: Di(2-ethylhexyl)amine (12.0730 g, 0.05 mol, 0.1 mol dm^{-3}), and biphenyl (5.3965 g, 0.035 mol, 0.07 mol dm^{-3}) in chloroform (500 mL).

Reservoir 2: Isobutyryl chloride (5.3275 g, 0.05 mol, 0.1 mol dm^{-3}) in chloroform (500 mL).

Reservoir 3: Triethylamine (7.0 mL, 0.05 mol, 0.1 mol dm^{-3}) in Chloroform (500 mL).

Reservoir 4: Chloroform.

An example chromatogram is shown in Figure S3.

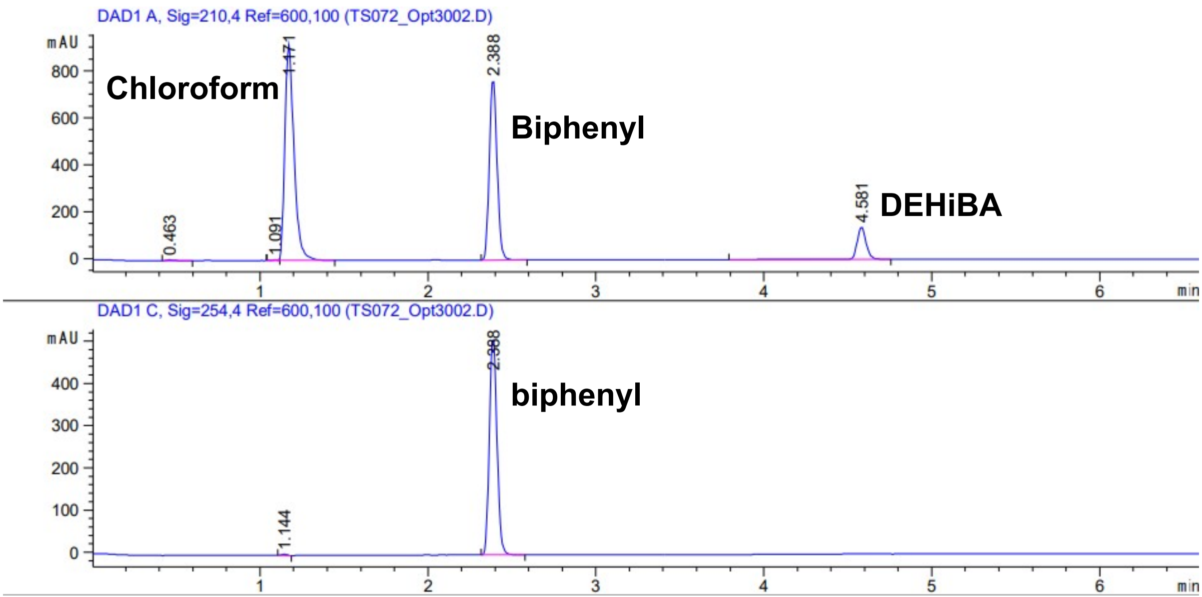


Figure S6: A typical HPLC chromatogram for route (a)

The flow platforms were set up according to Figure 2 all using a reactor volume of 2.7 mL with PFA tubing and a back pressure of 100 psi. The self-optimisation was conducted with respect to three continuous parameters for setups (i) and (ii): residence time, iBCl equivalents, and temperature. Whilst setup (iii) optimised four continuous parameters: residence time, iBCl equivalents, triethylamine equivalents, and temperature. The upper and lower parameter bounds are described in Tables S1. The initial objective for each optimisation was to maximise yield, then simultaneously maximize reaction mass efficiency and space-time yield.

Tables S3: Upper and lower parameter bounds for setups (i), (ii), and (iii). Equivalents are determined with respect to DiEHA

Setup (i)	**Residence time (mins)**	**iBCl equivalents.**	**Temperature (°C)**	**Triethylamine equivalents.**	**[DiEHA] in reactor (mol dm^{-3})**
Lower bound	0.5	0.95	35	3	0.01
Upper bound	10	3	150	3	0.01

Setup (ii)	**Residence time (mins)**	**iBCl equivalents.**	**Temperature (°C)**	**Triethylamine equivalents.**	**[DiEHA] in reactor (mol dm^{-3})**
Lower bound	0.5	0.95	35	1.14	0.01
Upper bound	10	3	150	3.6	0.01

Setup (iii)	**Residence time (mins)**	**iBCl equivalents.**	**Temperature (°C)**	**Triethylamine equivalents.**	**[DiEHA] in reactor (mol dm^{-3})**
Lower bound	0.5	0.95	35	0.95	0.01
Upper bound	5	2	150	4	0.01

2.3.3. Route (a) Data and Further Analysis

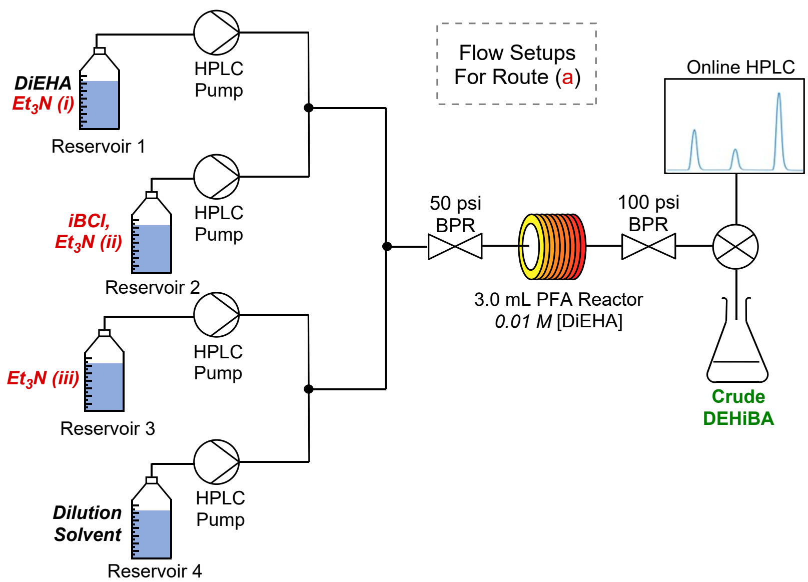


Figure S7: The various flow setups (i-iii) for route (a)

Three flow setups were investigated for route (a), each an attempt to improve on the last setup, with setup (iii) being discussed in the paper. The reservoir configuration and concentrations define the feasible parameter space for each self-optimisation, therefore this screening provides an insight into feasible reservoir configurations whilst allowing access to different parameter spaces to further the optimisation in the search for improved process metrics. The setups investigated here differed the location and amount of triethylamine in the reservoirs:

- Setup (i) combined a large excess of triethylamine with DiEHA in reservoir 1, to match the maximum possible equivalents of iBCl (3 with respect to DiEHA).
- Setup (ii) combined equal amounts of triethylamine and iBCl into reservoir 2.
- Setup (iii) separated each reagent into individual reservoirs for the optimisation of both the equivalents of iBCl and triethylamine.

Figure S7 illustrates these setups as well as the setups for routes (b-f). Despite the convenience and simplicity offered by setup (i), the optimisation was limited by its inability to vary the equivalents of triethylamine, this large and constant excess of triethylamine limited the RME to a theoretical maximum of 39.5%. Nevertheless setup (i) performed exceedingly well with minimal trade-off between the key process metrics. All the reactions conducted were high yielding at > 90%, and an optimum RME of 38.8% was achieved at just 40 °C, with 0.95 equivalents of iBCl, the large excess of triethylamine, and a 10 minute residence time which substantially diminished the STY. Impressively, several conditions were close to this optimum RME, but to their advantage, far outperformed in terms of productivity with the optimum requiring only a 0.5 minute residence time at 150 °C, achieving an RME of 38.4% and an exceptional improvement in STY to 367 g L^{-1} h^{-1}. This condition provided little trade-off between key process metrics, proving itself as the overall optimum condition in this case.

A clear trend between temperature and residence time was observed, with higher temperatures favouring lower residence times for the best conversion due to thermal degradation of starting materials. Therefore, in addition to improving the STY, shorter residence times aided to improve the RME. Overall route (a), setup (i) showed great promise, with the maximum RME and STY just 0.7% and 6 g L^{-1} h^{-1} from their theoretical maximum, in addition to the insignificant trade-off as demonstrated by the insignificant Pareto front (figure S4, ESI).

However, in an attempt to improve on this, setup (ii) was designed so that only a slight excess of triethylamine was maintained with respect to iBCl. This was initially promising, however starting material degradation over a period of just 6 hours resulted in a loss of reproducibility, with large yield losses in some cases, verifying the impracticality of combining triethylamine and iBCl. This degradation is caused by ketene formation which is highly reactive and in this case has degraded somewhat in the reservoir.

A plot comparing the RME and STY metrics for setups (i) and (iii) was produced and can be found in Figure S4.

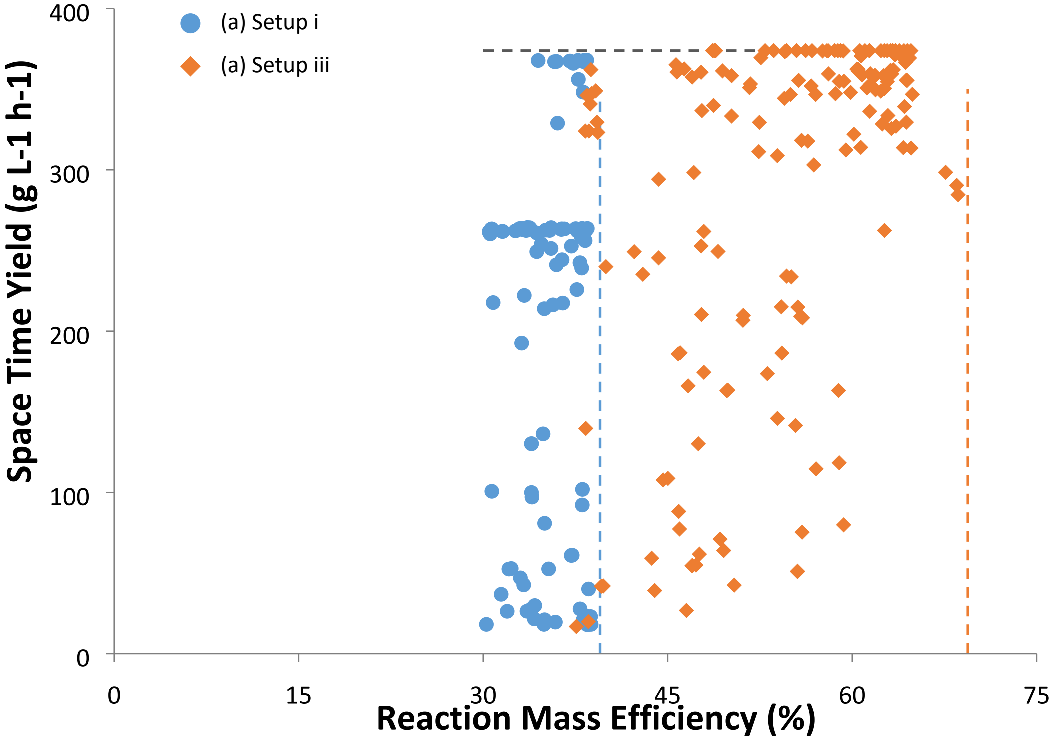


Figure S8: Reaction data for route a, setups (i) and (iii), where the dashed lines show the theoretical maxima for their accessible parameter space during each optimisation

A plot demonstrating the performance of route (a) even at 12 second residence times is shown in Figure S5 where little trade-off is observable even at these flow rates.

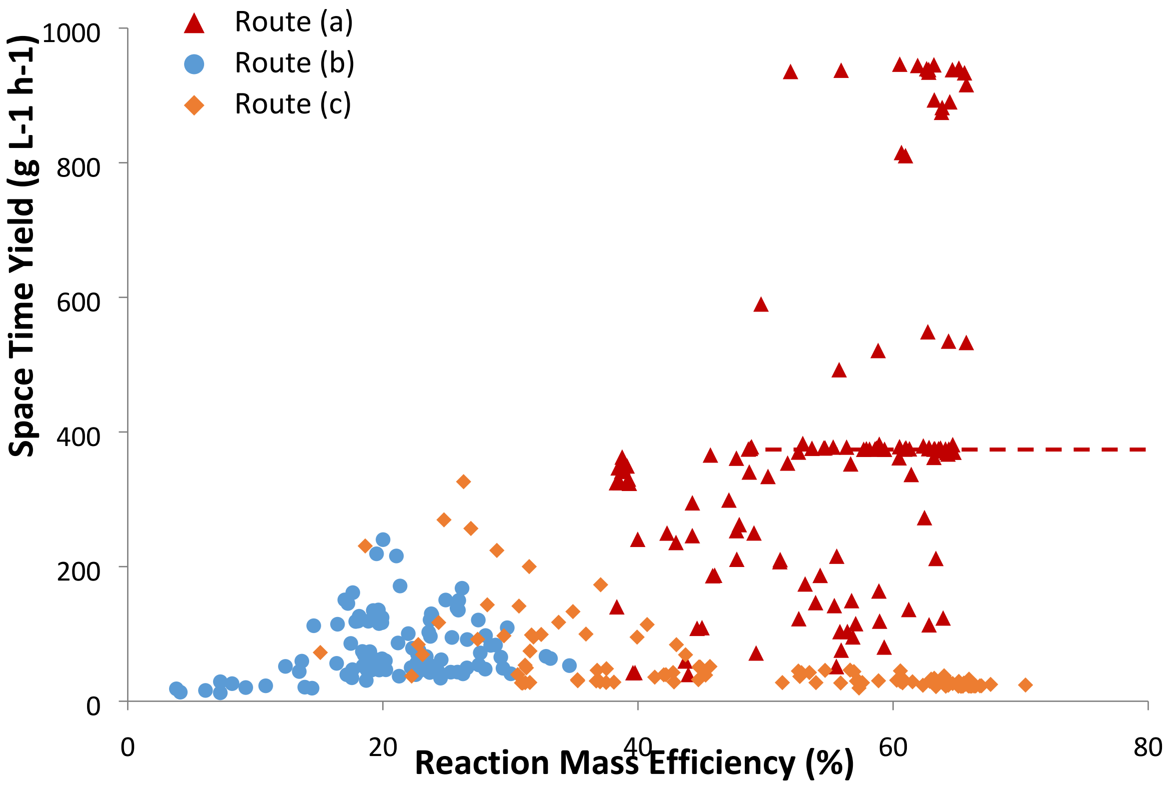


Figure S9: STY, RME Pareto fronts for routes (a-c) with the additional data from route (a) exploring residence times below 0.5 minutes the limit that was set in Figure 4 and shown by the dashed line as the upper STY limit

To further add to the data provided in the paper we have hereby included the entirety of the reaction conditions explored for route (a) and the outcome of each experiment.

Table S4: Reaction conditions and outcomes from the optimisation of setups (i) and (iii)

Setup	Residence time (min)	iBCl equivalents.	Triethylamine equivalents.	Temperature (°C)	DEHiBA Yield wrt DiEHA (%)	DEHiBA Yield (%)	Reaction mass efficiency (%)	Space-Time Yield (g L-1 h-1)	Cost of DEHiBA (£/mol)
(i)	6.7	2.18	3.00	41.9	99.4	99.4	33.9	27.8	50.6
(i)	3.5	2.56	3.00	65.9	98.8	98.8	32.3	52.8	56.6
(i)	9.4	1.64	3.00	78.5	98.5	98.5	35.9	19.6	43.0
(i)	1.4	2.01	3.00	93.1	97.5	97.5	33.9	130.2	49.0
(i)	5.0	2.76	3.00	103.8	98.5	98.5	31.5	36.8	59.8
(i)	8.6	1.09	3.00	125.9	98.2	98.2	38.4	21.4	34.9
(i)	3.0	1.30	3.00	140.8	97.9	97.9	37.2	61.1	38.1
(i)	3.5	2.56	3.00	65.9	98.2	98.2	32.1	52.5	56.9
(i)	1.4	2.01	3.00	93.1	97.4	97.4	33.9	130.2	49.1
(i)	3.0	1.30	3.00	140.8	97.7	97.7	37.2	60.9	38.2
(i)	6.2	2.07	3.00	45.0	98.9	98.9	34.2	29.8	49.2
(i)	7.0	2.62	3.00	45.0	98.5	98.5	32.0	26.3	57.7
(i)	7.0	2.20	3.00	45.0	98.6	98.6	33.6	26.3	51.3
(i)	7.9	0.95	3.00	40.0	97.2	100.0	38.7	23.0	33.1
(i)	0.7	0.95	3.00	40.1	91.4	96.3	36.4	244.3	35.2
(i)	10.0	0.95	3.00	40.1	97.3	100.0	38.8	18.2	33.1
(i)	6.4	0.95	3.00	40.0	95.1	100.0	37.9	27.8	33.8
(i)	8.4	0.95	3.00	49.8	95.8	100.0	38.2	21.3	33.6
(i)	10.0	0.95	3.00	150.0	96.8	100.0	38.5	18.1	33.3
(i)	10.0	1.75	3.00	150.0	97.3	97.3	34.9	18.2	45.2
(i)	10.0	0.95	3.00	150.0	96.5	100.0	38.4	18.0	33.3
(i)	7.8	0.95	3.00	150.0	96.5	100.0	38.4	23.1	33.3
(i)	0.7	1.72	3.00	149.9	98.2	98.2	35.4	262.4	44.4
(i)	0.7	2.68	3.00	149.9	98.0	98.0	31.6	261.8	58.8
(i)	0.7	0.95	3.00	149.3	90.3	94.9	36.0	241.1	35.7
(i)	0.7	1.97	3.00	149.6	98.2	98.2	34.4	249.3	48.0
(i)	0.7	3.00	3.00	40.0	97.9	97.9	30.5	261.6	63.7
(i)	0.7	2.40	3.00	40.0	98.1	98.1	32.6	262.2	54.6
(i)	0.7	2.70	3.00	40.0	98.0	98.0	31.5	261.9	59.1
(i)	0.7	3.00	3.00	40.0	98.1	98.1	30.5	262.0	63.6
(i)	0.7	2.98	3.00	149.9	98.0	98.0	30.6	260.3	63.4
(i)	0.7	3.00	3.00	150.0	98.1	98.1	30.6	262.1	63.6
(i)	0.7	1.95	3.00	40.2	98.0	98.0	34.4	260.9	47.9
(i)	0.7	2.99	3.00	150.0	98.0	98.0	30.5	261.7	63.6
(i)	0.7	3.00	3.00	96.8	98.1	98.1	30.6	261.4	63.6
(i)	10.0	3.00	3.00	150.0	97.2	97.2	30.3	18.2	64.2
(i)	0.7	2.19	3.00	40.3	98.3	98.3	33.5	262.4	51.3
(i)	0.7	1.80	3.00	40.0	98.3	98.3	35.1	262.6	45.5
(i)	0.7	3.00	3.00	103.2	98.2	98.2	30.6	262.5	63.5
(i)	0.7	3.00	3.00	48.4	98.1	98.1	30.6	262.2	63.6

(i)	0.7	3.00	3.00	62.3	98.3	98.3	30.6	262.7	63.4
(i)	0.7	3.00	3.00	71.7	98.1	98.1	30.6	262.3	63.6
(i)	0.7	3.00	3.00	131.9	98.3	98.3	30.6	262.7	63.4
(i)	0.7	3.00	3.00	65.9	98.4	98.4	30.6	262.9	63.4
(i)	0.7	3.00	3.00	136.1	98.4	98.4	30.6	262.9	63.4
(i)	0.7	3.00	3.00	103.1	98.5	98.5	30.7	263.2	63.3
(i)	0.7	3.00	3.00	124.0	98.4	98.4	30.6	262.9	63.4
(i)	0.7	3.00	3.00	135.5	98.5	98.5	30.7	263.1	63.4
(i)	0.7	3.00	3.00	148.4	98.6	98.6	30.7	263.4	63.3
(i)	0.7	3.00	3.00	40.7	98.3	98.3	30.6	262.7	63.4
(i)	0.7	3.00	3.00	149.6	98.4	98.4	30.6	262.9	63.4
(i)	0.7	3.00	3.00	112.9	98.4	98.4	30.6	262.9	63.4
(i)	0.7	2.99	3.00	74.2	98.4	98.4	30.7	263.0	63.3
(i)	0.7	3.00	3.00	102.9	98.3	98.3	30.6	262.8	63.4
(i)	0.7	3.00	3.00	87.5	98.5	98.5	30.7	263.2	63.3
(i)	0.7	3.00	3.00	75.1	98.5	98.5	30.7	263.2	63.3
(i)	0.7	2.99	3.00	69.7	98.5	98.5	30.7	262.8	63.2
(i)	0.7	3.00	3.00	86.6	98.5	98.5	30.7	263.2	63.3
(i)	0.7	3.00	3.00	130.5	98.5	98.5	30.7	263.2	63.3
(i)	0.7	3.00	3.00	110.1	98.5	98.5	30.7	263.2	63.3
(i)	0.7	2.33	3.00	126.6	98.7	98.7	33.1	263.6	53.2
(i)	0.7	2.29	3.00	101.4	98.5	98.5	33.2	263.2	52.7
(i)	0.7	2.27	3.00	127.2	98.6	98.6	33.3	263.4	52.3
(i)	0.7	2.23	3.00	75.9	98.7	98.7	33.4	263.6	51.8
(i)	0.7	2.36	3.00	93.8	98.6	98.6	33.0	263.6	53.7
(i)	0.7	2.33	3.00	118.0	98.7	98.7	33.1	263.7	53.2
(i)	0.7	2.31	3.00	54.3	98.7	98.7	33.2	263.8	53.0
(i)	0.7	2.29	3.00	107.0	98.7	98.7	33.2	263.7	52.7
(i)	0.7	2.28	3.00	149.4	98.6	98.6	33.2	263.3	52.6
(i)	0.7	2.27	3.00	99.2	98.5	98.5	33.2	263.2	52.5
(i)	0.7	2.26	3.00	114.0	98.6	98.6	33.3	263.5	52.2
(i)	0.7	2.25	3.00	148.2	98.6	98.6	33.3	263.4	52.1
(i)	0.7	2.25	3.00	142.4	98.4	98.4	33.3	262.9	52.1
(i)	0.7	2.24	3.00	74.0	98.5	98.5	33.4	263.1	52.0
(i)	0.7	2.28	3.00	126.2	98.6	98.6	33.3	263.4	52.5
(i)	0.7	2.26	3.00	147.6	98.4	98.4	33.3	262.8	52.3
(i)	0.7	2.26	3.00	117.7	98.6	98.6	33.4	263.5	52.1
(i)	0.7	2.23	3.00	119.3	98.5	98.5	33.4	263.1	51.9
(i)	0.7	2.25	3.00	150.0	98.7	98.7	33.4	263.6	52.0
(i)	0.7	2.24	3.00	150.0	98.4	98.4	33.3	262.8	52.0
(i)	0.7	2.23	3.00	149.9	98.5	98.5	33.4	263.3	51.8
(i)	0.7	2.23	3.00	150.0	98.6	98.6	33.5	263.5	51.7
(i)	0.7	2.20	3.00	149.4	98.5	98.5	33.6	263.3	51.3
(i)	0.7	2.23	3.00	150.0	98.7	98.7	33.5	263.6	51.7
(i)	0.7	2.22	3.00	150.0	98.9	98.9	33.6	264.2	51.5
(i)	0.7	2.22	3.00	150.0	98.5	98.5	33.5	263.3	51.7
(i)	0.7	2.22	3.00	149.9	98.7	98.7	33.5	263.8	51.6
(i)	0.7	2.21	3.00	150.0	98.8	98.8	33.6	264.0	51.3
(i)	1.8	3.00	3.00	150.0	98.6	98.6	30.7	100.7	63.3
(i)	0.7	2.21	3.00	150.0	98.6	98.6	33.5	263.6	51.4
(i)	0.7	2.20	3.00	150.0	98.5	98.5	33.5	263.2	51.4
(i)	0.7	2.20	3.00	150.0	98.8	98.8	33.6	264.0	51.2

(i)	0.7	2.17	3.00	149.5	98.9	98.9	33.8	264.1	50.8
(i)	0.7	2.19	3.00	150.0	98.6	98.6	33.6	263.6	51.2
(i)	0.7	1.34	3.00	48.4	98.3	98.3	37.2	252.7	38.6
(i)	0.7	1.93	3.00	108.9	98.9	98.9	34.7	254.0	47.2
(i)	9.0	1.18	3.00	148.4	98.7	98.7	38.1	20.6	36.0
(i)	4.6	1.09	3.00	148.9	98.6	98.6	38.6	40.1	34.7
(i)	0.8	0.95	3.00	87.8	89.6	94.3	35.7	216.3	35.9
(i)	2.0	0.95	3.00	88.3	87.9	92.5	35.0	80.9	36.6
(i)	0.7	1.29	3.00	146.2	98.6	98.6	37.5	263.5	37.8
(i)	0.7	1.73	3.00	146.5	98.6	98.6	35.5	251.3	44.3
(i)	3.2	0.95	3.00	113.9	88.7	93.4	35.3	52.6	36.3
(i)	0.7	1.48	3.00	133.3	98.6	98.6	36.6	263.4	40.6
(i)	0.7	1.74	3.00	136.2	98.9	98.9	35.5	264.2	44.4
(i)	0.7	1.11	3.00	149.3	98.7	98.7	38.5	263.6	35.0
(i)	0.7	2.13	3.00	51.1	98.6	98.6	33.8	263.5	50.3
(i)	0.7	1.19	3.00	136.4	98.7	98.7	38.0	263.7	36.3
(i)	1.2	0.93	3.00	141.8	87.3	94.2	34.9	136.3	36.5
(i)	1.6	0.90	3.00	142.4	84.6	94.0	33.9	99.9	37.2
(i)	1.6	0.90	3.00	150.0	84.7	94.2	34.0	97.1	37.1
(i)	0.7	1.53	3.00	88.3	98.5	98.5	36.4	263.1	41.4
(i)	0.7	1.53	3.00	95.6	98.6	98.6	36.4	263.4	41.3
(i)	0.8	1.51	3.00	95.8	98.6	98.6	36.5	217.4	41.1
(i)	7.8	0.94	3.00	99.2	87.7	93.3	35.0	21.1	36.5
(i)	3.6	0.90	3.00	50.1	83.1	91.9	33.3	42.7	37.9
(i)	3.3	0.90	3.00	53.7	82.3	91.5	33.0	47.0	38.2
(i)	0.7	1.17	3.00	112.7	98.1	98.1	37.9	262.1	36.2
(i)	7.4	0.90	3.00	150.0	85.2	94.7	34.2	21.6	36.9
(i)	0.8	2.94	3.00	41.1	98.3	98.3	30.8	217.7	62.6
(i)	1.0	2.26	3.00	45.2	98.1	98.1	33.1	192.6	52.6
(i)	0.8	1.17	3.00	108.1	98.3	98.3	38.0	239.1	36.0
(i)	0.8	1.17	3.00	112.9	98.0	98.0	37.9	242.4	36.2
(i)	0.7	1.17	3.00	51.2	98.2	98.2	38.0	262.3	36.1
(i)	0.7	1.16	3.00	93.9	98.3	98.3	38.0	261.2	36.0
(i)	0.8	1.24	3.00	128.6	98.2	98.2	37.6	225.8	37.1
(i)	0.9	1.83	3.00	140.1	98.4	98.4	35.0	213.9	46.0
(i)	0.7	1.05	3.00	75.2	96.7	96.7	38.0	258.3	34.8
(i)	0.7	1.11	3.00	76.6	98.1	98.1	38.2	262.1	35.3
(i)	0.7	1.22	3.00	87.9	98.1	98.1	37.7	262.1	36.9
(i)	0.7	0.90	3.00	88.1	83.1	92.4	33.3	222.1	37.8
(i)	0.7	1.09	3.00	53.6	98.0	98.0	38.3	261.9	35.0
(i)	0.7	1.12	3.00	63.4	98.0	98.0	38.2	261.9	35.4
(i)	0.7	1.09	3.00	63.8	98.0	98.0	38.3	261.7	35.0
(i)	0.7	1.09	3.00	65.5	97.9	97.9	38.3	261.6	34.9
(i)	0.7	1.15	3.00	54.5	98.1	98.1	38.0	262.2	35.8
(i)	0.7	1.19	3.00	61.1	98.2	98.2	37.9	262.4	36.3
(i)	0.7	1.09	3.00	80.2	98.0	98.0	38.3	256.1	35.0
(i)	0.7	1.09	3.00	84.6	97.9	97.9	38.3	261.5	35.0
(i)	0.7	1.12	3.00	67.8	98.0	98.0	38.2	261.9	35.3
(i)	0.7	1.18	3.00	77.4	98.1	98.1	37.9	262.1	36.3
(i)	0.7	1.18	3.00	89.2	98.3	98.3	38.0	262.5	36.2
(i)	0.7	1.13	3.00	109.9	98.0	98.0	38.1	261.8	35.6
(i)	0.5	1.23	3.00	65.6	98.3	98.3	37.7	367.9	37.0

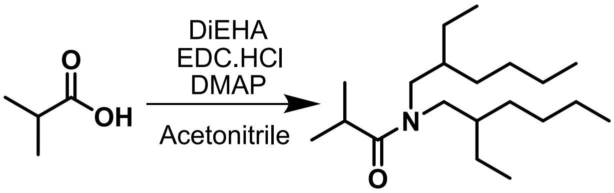
(i)	0.5	1.14	3.00	67.9	98.3	98.3	38.2	367.9	35.5
(i)	1.8	1.15	3.00	92.4	98.2	98.2	38.1	101.9	35.8
(i)	2.0	1.16	3.00	93.2	98.2	98.2	38.1	92.2	35.9
(i)	0.5	1.95	3.00	32.5	98.3	98.3	34.5	367.8	47.7
(i)	0.5	1.21	3.00	47.5	98.0	98.0	37.7	356.1	36.7
(i)	0.5	1.13	3.00	57.4	98.1	98.1	38.1	348.2	35.5
(i)	0.6	1.55	3.00	62.2	98.0	98.0	36.0	329.0	42.0
(i)	0.5	1.62	3.00	44.0	98.1	98.1	35.8	367.1	42.9
(i)	0.5	1.59	3.00	44.0	98.2	98.2	36.0	367.2	42.4
(i)	0.5	1.14	3.00	101.9	98.1	98.1	38.1	367.2	35.6
(i)	0.5	1.10	3.00	104.2	98.4	98.4	38.4	368.0	34.9
(i)	0.5	1.36	3.00	119.1	98.2	98.2	37.0	367.5	39.0
(i)	0.5	1.27	3.00	127.6	97.8	97.8	37.3	366.0	37.8
(iii)	2.1	0.98	0.98	46.6	70.8	72.3	49.6	64.0	46.1
(iii)	6.4	1.49	1.49	67.6	68.2	68.2	38.5	19.9	58.9
(iii)	3.3	1.94	1.94	81.5	97.8	97.8	47.3	54.9	47.8
(iii)	6.7	1.24	1.24	93.6	60.2	60.2	37.6	16.9	60.6
(iii)	4.0	1.58	1.58	106.8	92.0	92.0	50.4	42.5	45.0
(iii)	1.1	1.75	1.75	131.8	96.9	96.9	49.9	163.4	45.4
(iii)	5.4	1.32	1.32	133.8	77.0	77.0	46.5	26.8	48.9
(iii)	1.1	1.75	1.75	131.8	96.8	96.8	49.8	163.1	45.5
(iii)	3.3	1.94	1.94	81.5	97.1	97.1	47.0	54.6	48.2
(iii)	3.3	1.94	1.94	81.5	97.2	97.2	47.0	54.6	48.1
(iii)	1.0	1.88	1.88	65.2	97.3	97.3	47.9	174.5	47.2
(iii)	1.1	1.95	1.95	67.9	97.0	97.0	46.7	166.1	48.5
(iii)	1.4	1.90	1.90	68.9	96.9	96.9	47.5	130.2	47.6
(iii)	2.9	1.89	1.89	76.3	96.9	96.9	47.6	61.7	47.6
(iii)	0.9	1.45	1.45	123.8	97.1	97.1	55.8	209.2	40.7
(iii)	0.9	1.43	1.43	124.9	96.7	96.7	56.0	208.2	40.6
(iii)	2.3	2.00	2.00	140.0	96.9	96.9	46.0	77.3	49.2
(iii)	2.0	2.00	2.00	143.0	96.7	96.7	45.9	88.2	49.3
(iii)	0.5	1.18	1.18	131.4	97.3	97.3	62.3	348.8	36.5
(iii)	0.8	1.49	1.49	142.4	96.5	96.5	54.7	234.1	41.5
(iii)	0.8	1.52	1.52	144.9	97.0	97.0	54.2	215.1	41.8
(iii)	0.8	1.47	1.47	150.0	96.8	96.8	55.1	233.6	41.2
(iii)	0.5	0.99	0.99	100.8	92.6	93.1	64.4	329.6	35.5
(iii)	0.5	0.96	0.96	133.2	90.7	94.9	64.3	339.2	35.6
(iii)	0.5	1.27	1.27	145.7	96.2	96.2	59.3	354.9	38.4
(iii)	0.5	1.29	1.29	148.1	95.9	95.9	58.6	347.2	38.8
(iii)	0.5	1.22	1.22	71.7	97.0	97.0	61.2	350.8	37.2
(iii)	0.5	1.26	1.26	83.0	96.7	96.7	59.9	348.0	38.0
(iii)	0.5	1.15	1.15	87.5	96.6	96.6	62.6	350.5	36.4
(iii)	0.5	1.44	1.44	107.1	96.4	96.4	55.6	355.5	40.8
(iii)	0.5	0.95	0.95	144.7	89.5	94.2	63.6	327.0	36.0
(iii)	0.5	0.95	0.95	150.0	89.0	93.7	63.2	325.6	36.2
(iii)	0.5	0.99	0.99	150.0	89.8	90.3	62.5	328.4	36.6
(iii)	0.5	1.00	1.00	150.0	90.9	90.9	62.9	333.7	36.3
(iii)	0.7	1.06	1.06	65.8	92.9	92.9	62.6	262.4	36.4
(iii)	0.5	1.17	1.17	150.0	96.1	96.1	61.9	349.6	36.8
(iii)	0.5	0.99	0.99	35.0	86.1	87.4	60.1	322.1	38.0
(iii)	0.5	2.00	2.00	62.0	96.5	96.5	45.8	360.6	49.4
(iii)	0.5	1.13	1.13	118.0	96.8	96.8	63.3	362.0	36.0

(iii)	0.5	1.98	1.98	135.1	97.0	97.0	46.3	362.6	48.8
(iii)	0.6	1.26	1.26	53.1	96.3	96.3	59.5	312.3	38.3
(iii)	0.6	1.23	1.23	55.4	96.7	96.7	60.7	313.9	37.5
(iii)	0.6	1.09	1.09	84.9	96.2	96.2	64.2	313.7	35.5
(iii)	0.5	1.05	1.05	87.8	95.1	95.1	64.4	355.5	35.4
(iii)	0.5	1.50	1.50	94.1	96.7	96.7	54.5	344.3	41.7
(iii)	0.5	1.64	1.64	98.5	96.4	96.4	51.7	351.0	43.9
(iii)	0.5	1.05	1.05	106.2	95.1	95.1	64.5	355.4	35.4
(iii)	0.5	1.25	1.25	124.7	94.9	94.9	58.9	354.8	38.6
(iii)	0.5	1.25	1.25	51.3	97.0	97.0	60.4	362.5	37.7
(iii)	0.5	1.20	1.20	59.3	96.0	96.0	60.8	358.8	37.5
(iii)	0.5	1.14	1.14	130.5	94.4	94.4	61.5	353.0	37.1
(iii)	0.5	1.12	1.12	130.5	96.2	96.2	63.2	359.5	36.1
(iii)	0.5	1.18	1.18	74.7	96.2	96.2	61.5	359.6	37.1
(iii)	0.5	1.77	1.77	84.0	96.6	96.6	49.5	361.3	45.8
(iii)	0.5	1.70	1.70	85.0	95.9	95.9	50.2	358.4	45.1
(iii)	0.5	1.89	1.89	99.5	95.6	95.6	47.0	357.5	48.1
(iii)	0.5	1.23	1.23	102.1	96.6	96.6	60.5	361.0	37.6
(iii)	0.5	1.21	1.21	102.7	96.1	96.1	60.8	359.3	37.5
(iii)	0.5	1.16	1.16	108.0	95.9	95.9	61.9	358.6	36.8
(iii)	0.5	1.14	1.14	108.2	95.9	95.9	62.6	358.4	36.4
(iii)	0.5	1.47	1.47	54.8	96.6	96.6	55.0	346.7	41.3
(iii)	0.5	1.37	1.37	62.5	96.3	96.3	57.0	346.8	39.9
(iii)	0.5	1.17	1.17	74.2	96.0	96.0	61.7	357.3	36.9
(iii)	0.5	1.32	1.32	120.7	96.2	96.2	58.1	359.5	39.2
(iii)	0.5	1.06	1.06	91.3	96.3	96.3	64.9	346.8	35.2
(iii)	0.6	0.97	0.97	150.0	96.0	99.3	67.6	298.5	33.8
(iii)	0.6	0.95	0.95	150.0	96.6	100.0	68.6	284.6	33.3
(iii)	0.6	0.96	0.96	150.0	96.9	100.0	68.5	290.4	33.4
(iii)	0.6	1.06	1.06	102.2	96.1	96.1	64.8	313.5	35.2
(iii)	0.5	1.34	1.34	134.9	90.0	90.0	53.9	308.8	42.2
(iii)	0.5	1.66	1.66	140.9	90.1	90.1	47.8	336.7	47.4
(iii)	0.5	1.41	1.41	141.5	90.1	90.1	52.4	311.3	43.4
(iii)	3.2	1.73	2.86	65.0	100.0	100.0	43.7	59.2	43.6
(iii)	0.5	1.01	1.28	70.6	94.4	94.4	61.4	336.3	35.0
(iii)	0.5	1.39	2.16	87.7	100.0	100.0	52.9	373.9	37.4
(iii)	1.3	1.23	2.01	109.1	99.7	99.7	53.9	145.9	36.4
(iii)	0.8	1.54	2.95	90.6	100.0	100.0	44.3	245.4	40.9
(iii)	0.6	1.90	3.55	115.3	99.6	99.6	38.6	324.1	46.4
(iii)	0.6	1.78	3.51	150.0	99.3	99.3	39.3	323.2	44.8
(iii)	0.6	1.92	3.59	150.0	99.5	99.5	38.3	324.0	46.7
(iii)	0.8	1.77	2.98	35.4	100.0	100.0	43.0	235.2	43.9
(iii)	0.8	1.92	3.23	48.3	99.1	99.1	40.0	240.0	46.9
(iii)	0.5	1.97	3.47	49.0	99.0	99.0	38.4	346.1	47.7
(iii)	0.5	1.94	3.49	66.1	99.7	99.7	38.8	362.1	46.9
(iii)	1.3	1.08	1.73	35.0	94.4	94.4	55.4	141.5	36.1
(iii)	0.8	1.34	2.42	36.9	99.1	99.1	49.1	249.4	38.2
(iii)	0.7	1.46	2.47	37.4	99.1	99.1	47.7	252.8	40.0
(iii)	0.8	1.75	2.98	40.8	99.0	99.0	42.3	249.3	44.5
(iii)	0.5	1.25	2.15	36.2	99.8	99.8	52.6	369.6	36.6
(iii)	0.6	1.33	2.28	89.3	98.9	98.9	50.2	333.3	38.2
(iii)	0.5	1.08	1.85	109.7	98.8	98.8	56.7	352.0	34.5

(iii)	1.1	1.27	2.09	116.8	100.0	100.0	53.1	173.6	36.8
(iii)	0.9	1.20	2.37	95.1	100.0	100.0	51.1	209.8	35.8
(iii)	1.3	1.94	3.53	113.6	99.1	99.1	38.3	139.7	47.2
(iii)	0.9	1.32	2.62	131.1	99.1	99.1	47.7	210.3	37.9
(iii)	0.7	1.41	2.54	149.8	99.8	99.8	47.9	261.8	39.0
(iii)	0.5	1.52	2.30	60.8	100.0	100.0	48.9	373.9	40.7
(iii)	0.5	1.51	2.29	62.1	99.1	99.1	48.7	373.9	40.9
(iii)	0.5	1.66	2.51	74.4	98.6	98.6	45.7	365.2	43.3
(iii)	0.5	1.51	2.29	90.3	99.4	99.4	48.8	373.9	40.8
(iii)	0.6	1.96	3.35	121.1	99.5	99.5	39.3	329.5	47.3
(iii)	0.5	1.97	3.39	149.2	99.8	99.8	39.1	349.0	47.3
(iii)	0.5	1.98	3.41	150.0	99.3	99.3	38.8	347.2	47.7
(iii)	0.6	1.98	3.43	150.0	99.3	99.3	38.7	340.8	47.7
(iii)	1.0	1.21	2.05	42.0	100.0	100.0	54.3	186.4	35.7
(iii)	0.5	1.54	2.39	56.7	99.3	99.3	47.7	360.5	41.2
(iii)	0.6	1.38	2.42	69.1	99.0	99.0	48.7	339.9	38.8
(iii)	0.5	1.37	2.08	96.4	99.2	99.2	51.7	353.2	38.7
(iii)	0.9	1.34	2.34	100.5	100.0	100.0	51.1	206.7	37.2
(iii)	0.6	1.77	2.25	128.1	99.5	99.5	47.1	298.3	44.5
(iii)	0.6	1.95	2.50	132.1	99.7	99.7	44.3	294.2	47.1
(iii)	1.7	1.88	2.48	37.0	100.0	100.0	45.0	108.7	45.8
(iii)	1.7	1.88	2.48	45.3	99.3	99.3	44.6	107.7	46.2
(iii)	4.8	1.61	2.89	49.0	99.5	99.5	43.9	39.2	42.2
(iii)	3.3	1.25	1.26	65.5	89.5	89.5	55.6	50.9	40.9
(iii)	3.7	1.20	1.89	79.7	100.0	100.0	55.6	51.2	35.9
(iii)	4.5	1.79	3.44	87.9	99.2	99.2	39.6	41.8	45.0
(iii)	2.7	1.41	2.39	105.5	100.0	100.0	49.3	71.1	38.9
(iii)	2.3	1.01	1.51	114.9	95.6	95.6	59.3	79.9	34.6
(iii)	0.9	1.44	1.65	136.8	100.0	100.0	55.6	214.9	39.3
(iii)	1.0	1.74	2.46	142.1	99.5	99.5	45.9	185.9	44.1
(iii)	1.0	1.74	2.46	142.1	99.8	99.8	46.0	186.6	44.0
(iii)	2.3	1.01	1.51	114.9	90.2	90.2	55.9	75.3	36.7
(iii)	4.5	1.79	3.44	87.9	99.6	99.6	39.8	42.0	44.8
(iii)	1.1	1.03	1.41	71.4	93.4	93.4	58.9	163.2	35.7
(iii)	1.5	1.03	1.41	74.4	90.5	90.5	57.1	114.6	36.9
(iii)	1.5	1.03	1.41	74.4	93.4	93.4	58.9	118.4	35.7
(iii)	0.5	0.94	1.75	49.8	93.3	87.3	52.5	329.5	36.6
(iii)	0.5	0.94	1.27	106.2	90.5	85.1	56.4	317.8	37.6
(iii)	0.5	0.94	1.27	113.5	89.8	84.4	55.9	318.3	38.0
(iii)	0.5	0.94	1.17	148.6	89.3	84.0	56.9	303.0	38.1
(iii)	0.5	1.19	1.25	103.6	99.7	99.7	62.8	373.9	35.8
(iii)	0.5	1.38	1.86	118.3	99.4	99.4	53.6	373.9	38.8
(iii)	0.5	1.29	1.72	136.0	99.8	99.8	56.2	373.9	37.3
(iii)	0.5	1.48	1.66	136.1	99.5	99.5	54.7	373.9	40.2
(iii)	0.5	1.19	1.37	56.0	99.9	99.9	61.4	373.9	35.8
(iii)	0.5	1.06	1.10	60.5	93.9	93.9	62.9	354.7	36.0
(iii)	0.5	1.09	1.19	70.4	98.4	98.4	64.1	371.0	34.9
(iii)	0.5	1.44	1.49	105.7	99.4	99.4	56.7	373.9	39.6
(iii)	0.5	1.19	1.15	35.0	100.0	100.0	64.8	373.9	35.5
(iii)	0.5	1.12	1.09	37.2	97.8	97.8	64.7	369.3	35.5
(iii)	0.5	1.12	1.08	45.6	97.1	97.1	64.3	366.7	35.7
(iii)	0.5	1.16	1.12	63.9	99.1	99.1	64.5	373.9	35.7

(iii)	0.5	1.13	1.17	43.0	99.1	99.1	64.2	373.9	35.2
(iii)	0.5	1.29	1.88	50.4	99.6	99.6	54.5	373.3	37.4
(iii)	0.5	1.26	1.31	64.9	99.0	99.0	60.7	370.6	37.1
(iii)	0.5	1.34	1.47	68.4	99.1	99.1	57.9	373.9	38.3
(iii)	0.5	1.15	1.09	69.9	97.7	97.7	64.2	369.1	36.0
(iii)	0.5	1.22	1.16	78.3	99.1	99.1	63.1	373.9	36.5
(iii)	0.5	1.73	2.07	96.9	99.3	99.3	48.8	373.9	43.9
(iii)	0.5	1.34	1.27	110.5	99.4	99.4	60.5	362.4	38.1
(iii)	0.5	1.29	1.33	48.5	100.0	100.0	60.6	373.9	37.3
(iii)	0.5	1.45	1.38	62.6	99.0	99.0	57.6	373.7	39.9
(iii)	0.5	1.43	1.36	63.7	99.0	99.0	58.0	373.8	39.7
(iii)	0.5	1.21	1.16	104.2	99.2	99.2	63.3	373.9	36.4
(iii)	0.5	1.21	1.29	35.0	100.0	100.0	62.3	373.9	35.9
(iii)	0.5	1.09	1.44	35.5	99.2	99.2	61.4	373.9	34.5
(iii)	0.5	1.18	1.18	64.7	99.2	99.2	63.5	373.9	35.9
(iii)	0.5	1.18	1.19	108.8	99.1	99.1	63.3	373.9	36.0
(iii)	0.5	1.20	1.14	35.8	99.5	99.5	63.8	373.9	36.1
(iii)	0.5	1.19	1.13	56.3	98.3	98.3	63.5	371.3	36.3
(iii)	0.5	1.23	1.86	57.2	99.8	99.8	55.5	373.9	36.4
(iii)	0.5	1.32	1.25	94.1	99.5	99.5	61.0	373.9	37.7
(iii)	0.5	1.43	1.37	35.0	100.0	100.0	59.1	373.9	38.9
(iii)	0.5	1.40	1.34	37.0	99.4	99.4	58.8	373.9	39.1
(iii)	0.5	1.40	1.35	37.1	99.1	99.1	58.6	373.9	39.1
(iii)	0.5	1.14	1.08	103.0	95.8	95.8	63.1	361.7	36.5
(iii)	0.5	1.28	1.40	53.1	99.0	99.0	59.3	373.7	37.5
(iii)	0.5	1.24	1.18	117.6	99.2	99.2	62.6	373.9	36.8
(iii)	0.3	0.95	1.82	38.4	88.5	83.9	49.6	589.5	38.3
(iii)	0.3	1.05	1.43	88.1	94.1	94.1	58.8	520.5	35.8
(iii)	0.3	0.94	1.42	88.8	92.4	86.9	55.8	491.9	36.9
(iii)	0.3	1.11	1.13	89.9	97.9	97.9	64.3	534.4	35.3
(iii)	0.2	1.21	1.21	101.8	99.3	99.3	62.8	937.8	36.2
(iii)	0.2	1.21	1.23	106.8	99.5	99.5	62.6	939.1	36.2
(iii)	0.3	1.21	1.22	110.5	99.4	99.4	62.7	548.3	36.2
(iii)	0.2	1.20	1.20	119.1	98.9	98.9	62.8	934.0	36.2
(iii)	0.2	1.35	1.29	125.6	100.2	100.2	60.5	945.8	38.1
(iii)	0.2	1.74	1.66	125.7	99.2	99.2	52.0	935.0	44.2
(iii)	0.2	1.53	1.47	127.1	99.2	99.2	55.9	936.8	41.1
(iii)	0.2	1.09	1.07	150.0	94.6	94.6	63.2	892.7	36.2
(iii)	0.2	1.12	1.08	70.9	98.8	98.8	65.6	933.0	35.1
(iii)	0.2	1.15	1.14	89.9	99.3	99.3	64.6	937.6	35.3
(iii)	0.2	1.24	1.18	123.9	100.1	100.1	63.2	944.9	36.5
(iii)	0.2	1.14	1.11	128.4	99.6	99.6	65.2	939.9	35.2
(iii)	0.2	1.04	1.03	49.6	94.3	94.3	64.4	889.9	35.5
(iii)	0.2	1.03	1.00	54.4	92.6	92.6	63.8	874.3	36.1
(iii)	0.2	0.94	0.96	95.6	91.2	85.8	61.0	809.9	37.4
(iii)	0.2	0.97	0.97	96.1	88.8	86.3	60.7	814.6	37.7
(iii)	0.3	1.02	0.97	38.5	94.7	94.7	65.7	532.4	35.1
(iii)	0.8	1.05	1.00	58.2	92.5	92.5	63.4	211.6	36.4
(iii)	0.6	1.04	0.99	63.1	90.7	90.7	62.5	272.1	37.0
(iii)	0.2	1.05	1.01	94.8	93.4	93.4	63.8	881.4	36.1
(iii)	0.2	1.13	1.07	35.0	99.1	99.1	65.7	915.4	35.1
(iii)	0.2	1.29	1.23	70.4	100.0	100.0	61.9	943.9	37.2

2.4 Route (b) Coupling Reagent Approach: EDC.HCl Mediated Synthesis



Scheme S2: Amide bond formation using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and catalytic amounts of 4-dimethylaminopyridine (DMAP) to couple isobutyric acid (iBA) and Di(2-ethylhexyl)amine (DiEHA), yielding N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA)

2.4.1. Batch Chemistry:

Batch studies were initially conducted to ensure homogeneity and product formation via this route. Whilst later batch experiments were employed for kinetic understanding. Water and a range of common organic solvents including methanol, ethanol, tetrahydrofuran, *N,N*-dimethylformamide, dichloromethane, toluene, hexane, ethyl acetate, acetone, acetonitrile, and diethyl ether were screened to ensure the solubility of reagents. Acetonitrile, water, methanol, ethanol, *N,N*-dimethylformamide and chloroform were the only reagents to solubilise EDC.HCl, thus the only suitable solvents to transition this route into flow hence these were trialled in batch first.

Di-2-ethylhexylamine (0.2976 g, 1.22 mmol) and isobutyric acid (0.1157 g, 1.30 mmol) were combined in a round bottom flask, note the exotherm of this combination. EDC.HCl (0.2769 g, 1.43 mmol) and DMAP (0.0079 g, 0.07 mmol) were then combined with solvent (see above) in a 10 mL volumetric flask. Once the di-2-ethylhexylamine and iBA solution had cooled to room temperature the EDC.HCl solution was charged, the reaction was stirred at 30 °C for repeatability over 24 hours to yield a colourless and homogenous solution. HPLC analysis confirmed yields of 96.3%, 99.9%, 55.5%, 9.0%, 2.1%, and 0% for acetonitrile, dichloromethane, *N,N*-dimethylformamide, ethanol, methanol and water respectively.

Although dichloromethane was best yielding the environmental impact of this solvent and the low boiling point causing cavitation in the HPLC pumps as well as a restrictive temperature range meant that acetonitrile was best suited for this reaction in flow.

Studies without DMAP saw a reduction in yield for reactions in acetonitrile to 45.8%. Replacement with DIPEA resulted in yields between 31.4-23.3% with varying equivalents from 0.5 to 1.5.

Kinetic studies were investigated using a recirculating batch reactor where the solution was pumped through a vici sample loop connected to a HPLC for online analysis. As described in section 2.4.3. A similar methodology was used to the one above however temperature was varied and concentration, but equivalents were maintained.

2.4.2. Continuous Flow Chemistry:

Reservoir solutions were prepared to the desired concentrations by dissolving the described reagents in solvent with stirring at ambient conditions, except for EDC.HCl, that was heated to 30 °C until dissolution and maintained at this temperature throughout the optimisation.

Reservoir 1: Di(2-ethylhexyl)amine (8.0554 g, 0.0334mol, 0.1334 mol dm^{-3}), isobutyric acid (2.0568 g, 0.0233 mol, 0.0934 mol dm^{-3}), 4-diaminopyridine (0.2049 g, 0.0017 mol, 0.0067 mol dm^{-3}), and biphenyl (0.7722 g, 0.0050 mol, 0.0200 mol dm^{-3}) in acetonitrile (250 mL).

Reservoir 2: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.0320 g, 0.0367 mol, 0.1467 mol dm^{-3}) in acetonitrile (250 mL).

Reservoir 3: Isobutyric acid (2.8705 g, 0.0326 mol, 0.1303 mol dm^{-3}) in acetonitrile (250 mL).

Reservoir 4: Acetonitrile.

An example HPLC chromatogram is illustrated in Figure S6:

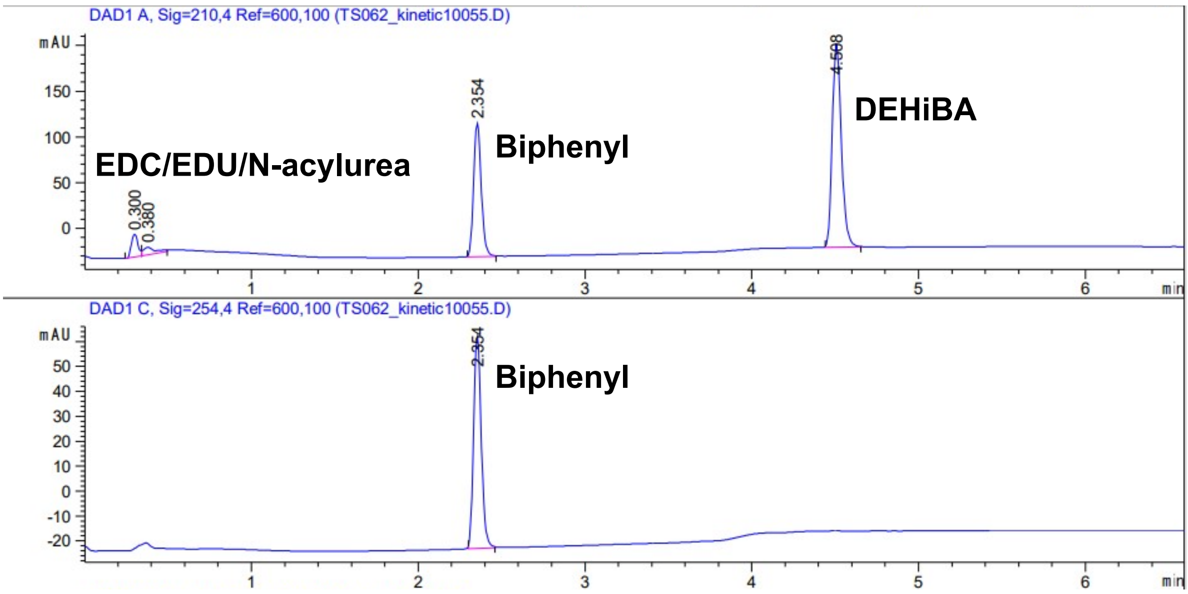


Figure S10: An example HPLC chromatogram from route (b)

The flow platform was set up according to Figure 2 using a reactor volume of 2.7 mL with PFA tubing and a back pressure of 100 psi. The self-optimisation was conducted with respect to four continuous parameters: residence time, iBA equivalents, EDC.HCl equivalents and temperature. The upper and lower parameter bounds for each are described in Table S3. The initial objective for each optimisation was to maximise yield, then simultaneously maximize reaction mass efficiency and space-time yield.

Table S5: The upper and lower bounds for the variables optimised in route (b)

	Residence time (mins)	iBA equivalents.	EDC.HCl equivalents.	Temperature (°C)	[DiEHA] in reactor (mol dm^{-3})

Lower bound	0.5	1.7	1.5	40	0.01
Upper bound	4	5.2	5	170	0.01

2.4.3. Route (b) Data and Further Analysis

Kinetic studies were conducted in batch making use of online sampling for reaction monitoring. Clear concentration and temperature trends are identifiable in Figure S7, all studies were conducted at 30 °C with 1.15 equivalents of EDC and 1.1 equivalents of iBA respective to DiEHA.

The increase in by-product formation has not been directly quantified due to complications with the co-elution of N-acylurea with other signals in both HPLC and GC for a range of methods.

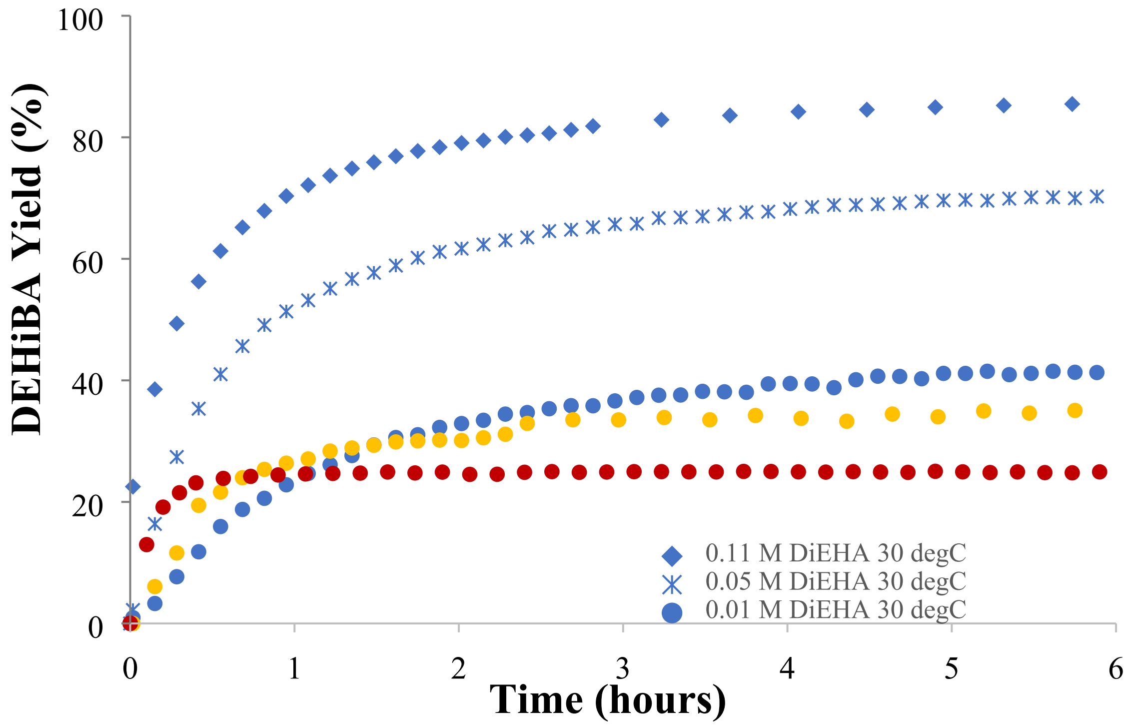
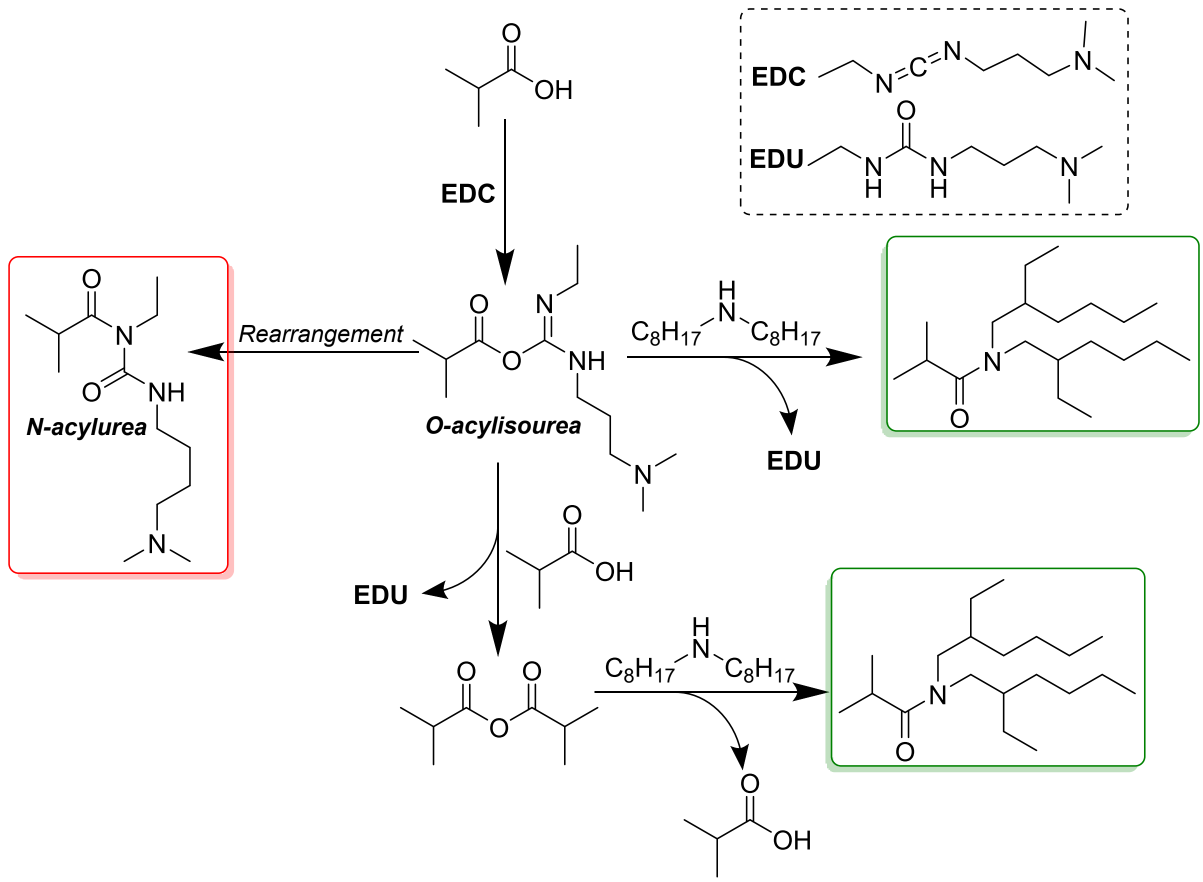


Figure S11: Kinetic studies for route (b) in batch at 30 °C with online sampling to a HPLC with 1.15 equivalents of EDC and 1.1 equivalents of iBA respective to DiEHA

The proposed reaction pathways that route (b) can take, discounting the inclusion of DMAP from the reaction can be found in Scheme S3.



Scheme S3: The proposed reaction pathways feasible for route (b), discounting DMAP

GC-FID trace demonstrating the coelution of DiEHA and the *N*-acylurea by-product from 7.8-8 minute retention time, whilst DEHiBA and biphenyl are sharp signals.

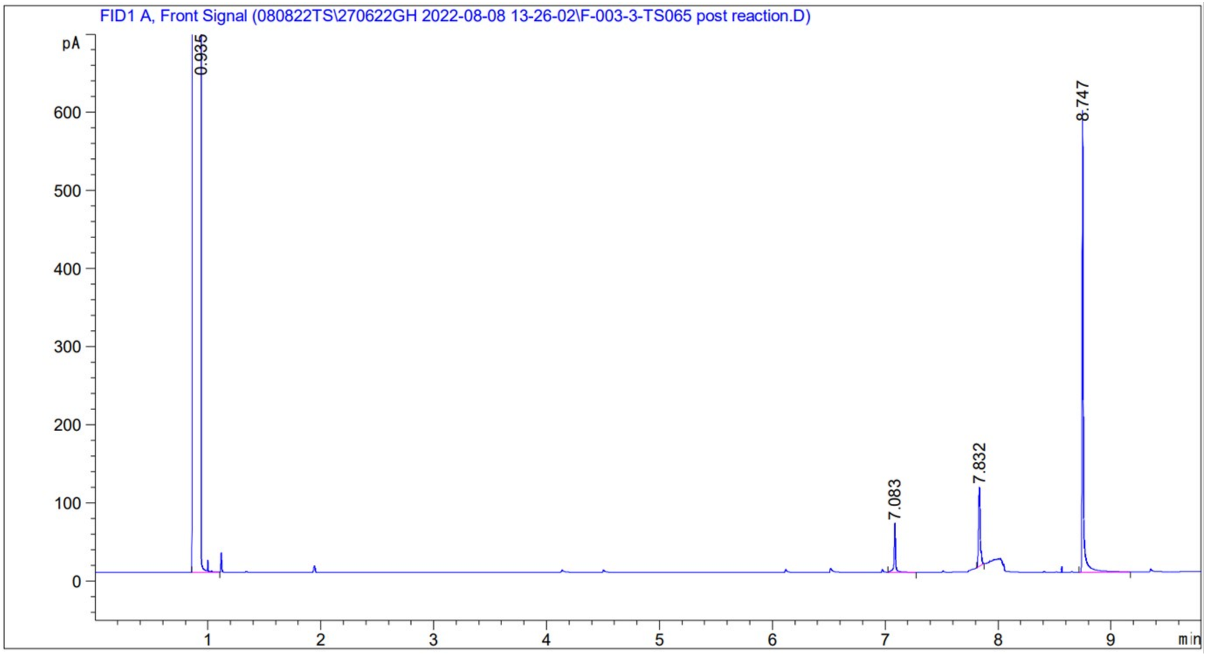
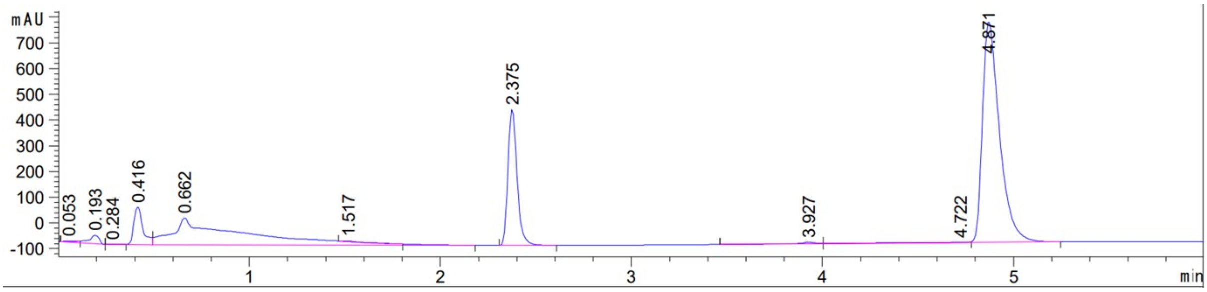


Figure S12: An example GC-FID trace of route (b) where biphenyl is observable at 7 minutes, DiEHA and N-acylurea coelute at 7.8-8 minutes and DEHiBA elutes at 8.7 minutes.

HPLC traces illustrating the overlap between EDC, EDU and the *N*-acylurea between 0.4 and 1.5 minutes. Biphenyl and DEHiBA are observable around 2.3 and 4.5-4.8 minutes respectively. Despite changes to the HPLC method these peaks were not resolved.



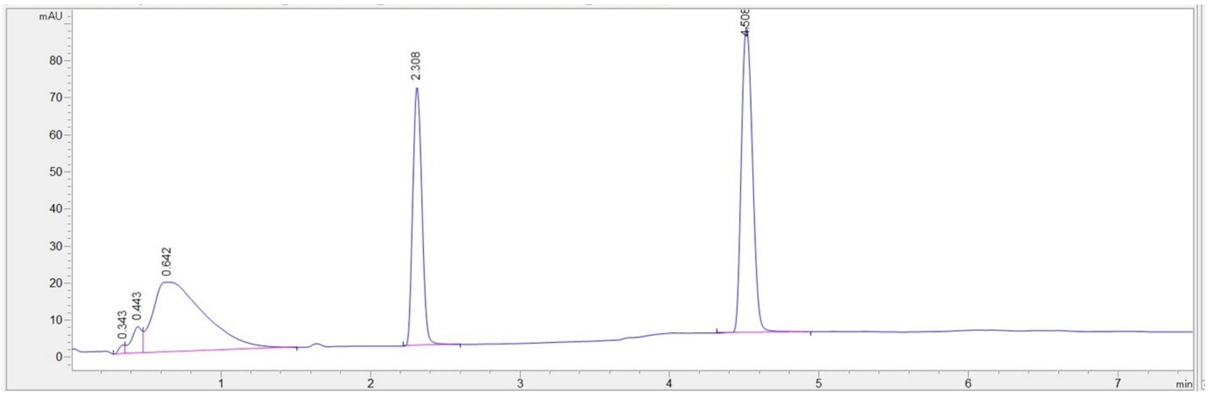


Figure S13: Typical HPLC traces for route (b) where EDC, EDU and the N-acylurea overlap between 0.4 and 1.5 minutes.

Table S4 provides the raw data for the experimental conditions exploited in the optimisation of route (b) and the performance metrics associated.

Table S6: complete dataset from the optimisation of route (b)

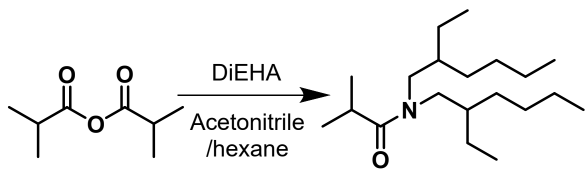
Residence time (min)	iBA equivalents.	EDC equivalents.	Temperature (°C)	DEHiBA Yield (%)	Reaction Mass Efficiency (%)	Space-Time Yield (g L^{-1} h^{-1})	Cost of DEHiBA (£/mol)
1.9	3.72	2.31	100.1	13.4	4.1	12.1	568.9
3.4	3.24	3.89	135.3	97.4	23.8	47.6	117.2
1.7	1.85	1.63	152.4	64.1	27.7	64.6	92.3
2.6	3.57	4.13	169.8	98.7	22.8	62.9	121.7
1.8	1.74	2.83	100.3	24.8	8.2	23.5	355.1
3.0	2.96	1.66	126.4	49.6	18.8	27.8	122.2
1.7	5.02	2.99	152.1	95.7	23.7	92.2	97.9
1.3	2.58	1.66	170.0	75.6	29.9	98.2	79.7
3.5	5.11	5.00	113.0	98.0	18.5	47.1	144.7
1.5	1.93	2.30	119.0	45.1	16.4	50.6	166.9

2.1	4.50	4.10	139.0	97.1	21.3	77.9	123.4
4.0	5.21	4.50	161.0	99.2	19.8	41.8	130.7
3.9	2.96	1.90	107.0	40.4	14.5	17.4	164.0
3.5	1.93	3.00	133.0	89.2	28.1	42.9	103.2
3.3	2.65	1.50	146.0	60.4	24.6	30.8	93.5
2.0	1.83	2.90	158.0	89.2	28.9	75.1	100.4
2.3	4.29	3.30	107.0	54.2	13.5	39.7	185.4
4.0	5.32	1.50	136.0	44.7	14.0	18.8	130.0
4.0	4.91	5.00	136.0	98.7	18.9	41.5	143.6
4.0	1.73	4.00	147.0	84.4	22.6	35.5	137.2
3.0	1.73	4.00	158.0	85.3	22.8	47.9	135.8
3.8	1.73	2.40	139.0	82.8	30.1	36.7	93.6
1.0	1.73	4.00	147.0	72.0	19.3	121.2	160.9
2.1	1.73	5.00	147.0	82.7	19.0	66.3	169.2
1.6	4.91	4.60	155.0	98.6	19.8	103.8	133.9
4.0	1.73	4.00	126.0	79.6	21.3	33.5	145.6
2.4	4.50	2.20	133.0	60.2	17.7	42.2	123.5
3.0	5.32	4.50	139.0	98.6	19.6	55.3	131.8
2.7	5.32	5.00	148.0	99.5	18.6	62.1	142.6
3.2	4.80	2.40	104.0	39.2	10.9	20.6	202.2
2.8	1.73	4.00	140.0	84.7	22.7	50.9	136.8
3.1	5.32	4.30	147.0	99.8	20.3	54.2	125.4
3.0	1.73	1.90	153.0	84.8	34.7	47.6	77.3
1.6	4.91	4.60	126.0	99.8	20.0	105.0	132.4
4.0	5.32	2.90	151.0	96.0	23.7	40.4	95.4
3.6	5.32	3.30	152.0	98.2	22.9	45.9	103.0
2.8	4.60	3.50	155.0	99.3	23.5	59.7	106.3
2.5	5.32	5.00	143.0	98.8	18.5	66.5	143.7
4.0	5.32	2.90	144.0	92.7	22.9	39.0	98.8
3.6	5.32	3.30	146.0	96.1	22.4	44.9	105.3
1.6	1.73	3.10	147.0	81.0	25.5	85.2	116.4
1.4	4.50	2.20	161.0	75.1	22.1	90.3	99.0
4.0	5.32	4.70	149.0	99.1	19.2	41.7	135.9
4.0	5.32	4.30	151.0	99.9	20.3	42.1	125.2
4.0	5.32	3.40	154.0	99.0	22.7	41.7	104.6
1.5	2.96	4.00	164.0	96.9	23.8	108.7	120.3
3.5	5.32	4.90	146.0	99.7	18.9	48.0	139.9
3.7	1.73	3.40	148.0	85.4	25.4	38.8	118.9

2.8	2.55	2.20	149.0	95.0	33.3	57.1	77.1
2.0	3.47	3.10	156.0	97.9	26.7	82.4	97.3
1.7	4.91	2.90	123.0	54.1	13.7	53.6	168.9
4.0	3.67	3.80	145.0	98.1	23.6	41.3	114.3
4.0	1.73	3.30	149.0	87.0	26.3	36.6	113.9
3.7	1.73	3.30	151.0	85.6	25.9	38.9	115.8
1.7	4.80	2.40	104.0	26.3	7.3	26.1	301.2
3.1	1.73	2.40	151.0	81.1	29.5	44.0	95.6
2.7	2.14	2.50	151.0	96.2	32.9	60.0	83.3
3.1	1.73	3.20	153.0	89.4	27.6	48.5	108.2
3.4	2.34	3.50	104.0	63.4	17.6	31.4	164.5
2.1	2.03	3.10	150.0	93.1	28.5	74.7	101.4
3.8	1.93	3.90	153.0	90.9	24.3	40.2	125.0
2.8	2.96	2.80	153.0	98.0	29.4	58.9	89.6
1.4	5.01	1.50	154.0	38.7	12.5	46.5	149.5
3.5	4.58	4.57	80.4	29.9	6.1	16.0	439.5
1.5	4.86	2.62	86.2	14.4	3.8	18.4	587.8
3.8	3.91	4.26	88.5	41.8	9.3	20.3	295.1
2.7	2.61	1.54	98.6	18.0	7.3	12.5	319.8
3.0	2.44	3.53	107.2	62.8	17.2	39.4	167.3
3.6	4.54	4.73	112.2	96.5	19.3	50.2	139.9
2.2	3.16	3.94	122.9	91.8	22.3	78.8	125.7
1.9	1.78	3.25	128.7	75.3	22.8	75.5	130.1
0.8	3.29	2.02	142.0	48.9	16.4	114.4	142.2
0.9	4.38	2.92	145.2	81.8	21.3	171.2	112.1
1.3	1.93	1.79	146.9	68.5	28.0	97.6	92.1
0.6	1.98	1.63	149.3	46.3	19.6	135.6	128.0
0.5	1.85	1.52	149.4	38.8	17.3	145.3	145.4
0.7	2.49	1.59	150.0	44.9	18.1	126.2	130.5
1.1	2.63	2.40	131.5	52.7	17.5	85.9	148.2
1.2	3.21	3.01	141.2	92.2	25.9	149.7	100.9
1.2	3.56	3.21	141.8	94.1	24.9	150.4	104.1
1.0	3.16	3.08	143.7	93.8	26.2	167.8	100.8
0.8	1.84	4.22	137.3	69.1	17.6	161.3	175.7
0.8	1.70	4.21	137.5	65.8	17.0	150.6	183.9
3.6	4.40	3.27	149.2	97.9	24.2	50.7	102.0
3.6	4.09	3.80	149.4	98.6	23.0	51.4	114.1
1.5	4.67	4.60	143.5	98.6	19.9	124.3	133.9

1.4	2.82	4.03	144.1	97.2	23.8	127.9	120.8
1.4	2.79	4.03	144.1	96.7	23.8	129.9	121.3
1.1	5.21	3.43	147.4	63.9	14.6	112.2	163.5
3.3	2.16	3.07	124.4	87.5	26.6	49.6	107.2
1.2	1.70	4.71	140.7	74.6	17.9	118.5	178.2
1.2	1.70	4.69	141.0	75.2	18.1	119.1	176.2
1.2	1.78	4.63	141.4	78.2	18.9	118.9	167.6
3.6	3.77	2.56	136.7	81.4	23.7	42.7	101.6
0.6	2.20	3.78	142.6	73.0	19.5	219.0	152.0
0.7	1.84	2.74	146.1	67.5	22.5	175.0	127.3
0.7	2.64	4.90	150.0	91.2	20.0	240.1	151.4
1.4	2.51	2.99	141.0	92.0	27.5	120.6	100.4
0.7	2.27	3.56	144.2	76.5	21.1	215.8	138.4
1.2	2.25	3.37	145.6	90.5	25.8	138.3	111.9
1.5	3.61	2.43	146.6	78.6	23.7	96.3	101.1
2.5	1.75	4.88	142.1	85.6	19.9	63.1	160.2
1.2	2.25	2.95	142.2	84.2	25.9	135.4	108.2

2.5 Routes (c) and (d) Solvated Synthesis From iBAnhydride



Scheme S4: Amide bond formations using isobutyric anhydride (iBAnhydride) and Di(2-ethylhexyl)amine (DiEHA) to yield N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA) but with two different solvent systems, acetonitrile and hexane

2.5.1. Batch Chemistry:

No major solubility issues were encountered for iBAnhydride over a range of common organic solvents therefore batch reactions were trialled using tetrahydrofuran, toluene, hexane, ethyl acetate, acetone, acetonitrile, and diethyl ether via the following procedure:

DiEHA (0.0845 g, 0.35 mmol) was combined with solvent in a 5 mL volumetric flask, similarly iBAnhydride (0.0554 g, 0.35 mmol) was charged with the same solvent to a 5 mL volumetric flask. These solutions were combined in a 25 mL round bottom flask whereby a large temperature rise (not measured) saw most solutions reach boiling points and condensate formed on glassware. Yields were not recorded for these reactions and the chemistry was transitioned into continuous flow without further batch investigations.

2.5.2. Flow Chemistry

Reservoir solutions were prepared to the desired concentrations by dissolving the reagents in solvent with stirring at ambient conditions.

Route (c)

Reservoir 1: Di(2-ethylhexyl)amine (4.2307 g, 0.0175 mol, 0.0701 mol dm^{-3}), and biphenyl (2.6969 g, 0.0175 mol, 0.0700 mol dm^{-3}) in acetonitrile (250 mL).

Reservoir 2: Isobutyric anhydride (2.7754 g, 0.0175 mol, 0.0702 mol dm^{-3}) in acetonitrile (250 mL).

Reservoir 3: Acetonitrile.

Route (d)

Reservoir 1: Di(2-ethylhexyl)amine (10.8706 g, 0.0450 mol, 0.0900 mol dm^{-3}), and biphenyl (5.4092 g, 0.0351 mol, 0.0702 mol dm^{-3}) in acetonitrile (500 mL).

Reservoir 2: Isobutyric anhydride (7.1190 g, 0.0450 mol, 0.0900 mol dm^{-3}) in acetonitrile (500 mL).

Reservoir 3: Acetonitrile.

An example HPLC chromatogram is illustrated in Figure S8:

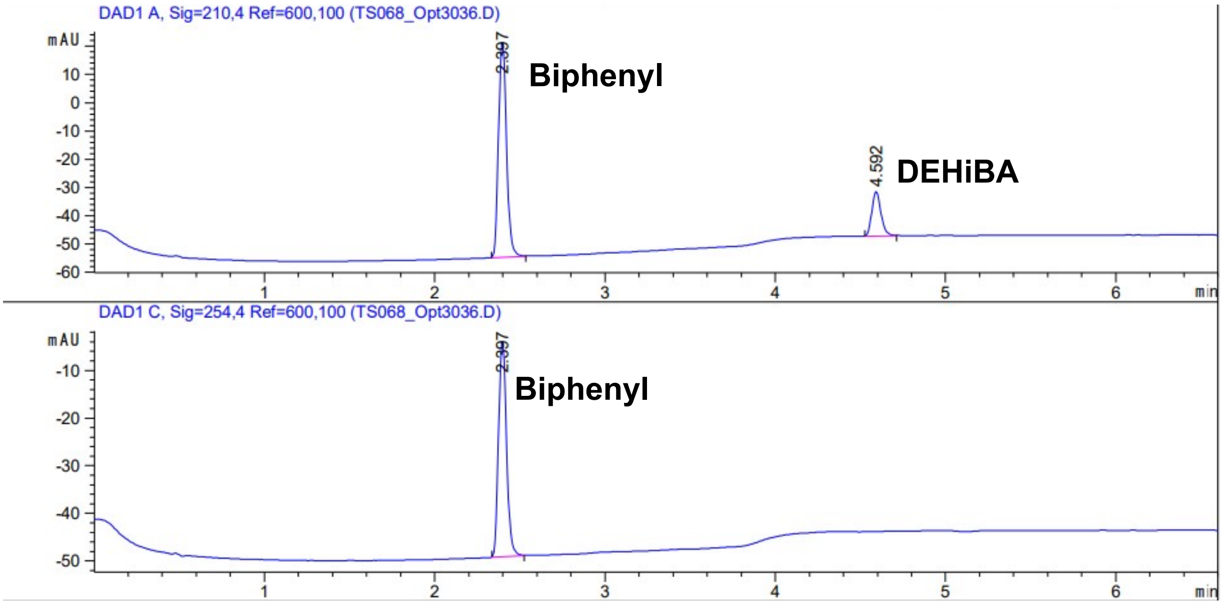


Figure S14: An example HPLC chromatogram from route (c/d)

The flow platform was set up according to Figure 2 using a reactor volume of 2.7 mL with PFA tubing and a back pressure of 100 psi. The self-optimisation was conducted with respect to three continuous parameters: residence time, iBAnhydride equivalents, and temperature. The upper and lower parameter bounds for each are described in Table S5. The initial objective for each optimisation was to maximise yield, then simultaneously maximize reaction mass efficiency and space-time yield.

Table S7: The upper and lower bounds for the variables optimised in route (c) and (d), top and bottom table respectively

Route (c)	Residence time (mins)	iBAnhydride equivalents.	Temperature (°C)	[DiEHA] in reactor (mol dm^{-3})
Lower bound	0.5	1	40	0.01
Upper bound	7.5	5	150	0.01

Route (d)	Residence time (mins)	iBAnhydride equivalents.	Temperature (°C)	[DiEHA] in reactor (mol dm^{-3})
Lower bound	0.5	1	40	0.01
Upper bound	7.5	3	150	0.01

2.5.3. Routes (c-d) Data and Further Analysis

A comparison between the performance metrics, RME and STY demonstrates the improved performance of the reaction in acetonitrile over that of the reaction in hexane although similar trade-off curves are apparent.

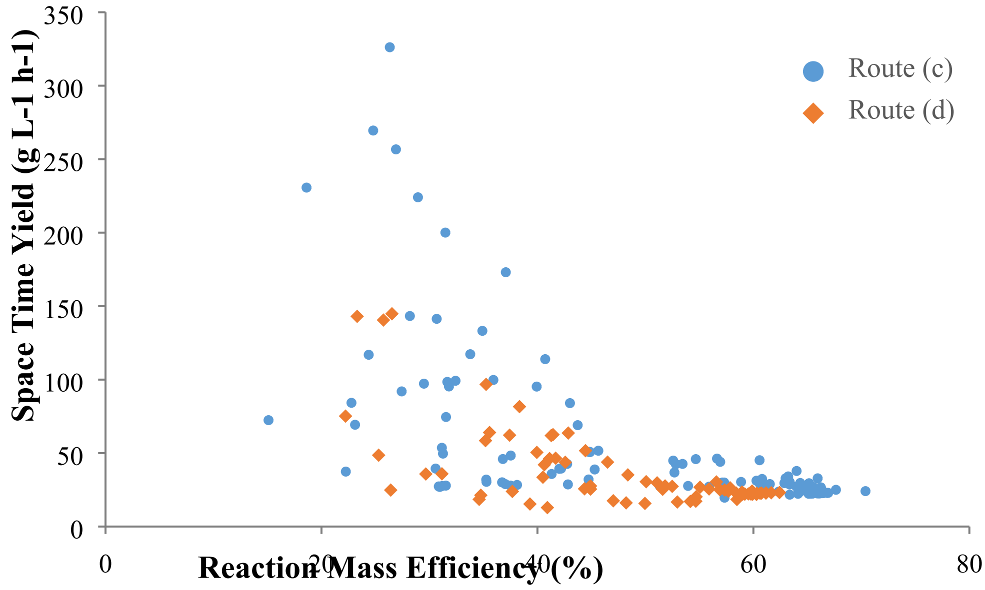


Figure S15: RME, STY comparison between routes (c) and (d)

Table S6 provides the raw data for the experimental conditions exploited in both optimisations and the performance metrics associated.

Table S8: complete dataset from the optimisation of routes (c) and (d)

Route	Residence time (min)	iBAnhydride equivalents.	Temperature (°C)	DEHiBA Yield (%)	Reaction Mass Efficiency (%)	Space-Time Yield (g L-1 h-1)	Cost of DEHiBA (£/mol)
(c)	0.5	1.00	40.0	18.5	15.1	72.4	121.3
(c)	0.5	5.00	40.0	58.8	18.6	230.7	72.5
(c)	7.0	1.00	40.0	70.1	57.3	19.6	31.9
(c)	7.0	5.00	40.0	98.4	31.2	27.6	43.3
(c)	3.8	3.00	95.0	98.3	44.9	50.7	33.1
(c)	3.8	3.00	95.0	100.0	45.6	51.6	32.5
(c)	3.8	3.00	95.0	98.2	44.8	50.7	33.1
(c)	0.5	1.00	150.0	29.8	24.4	116.9	75.1
(c)	0.5	5.00	150.0	83.2	26.3	326.2	51.2
(c)	7.0	1.00	150.0	80.6	65.9	22.6	27.8
(c)	7.0	5.00	150.0	97.5	30.9	27.3	43.7
(c)	6.7	3.20	54.5	98.0	42.8	28.7	34.2
(c)	0.9	1.60	67.5	44.6	29.5	97.2	57.0
(c)	1.0	1.40	109.5	50.9	35.9	99.8	48.0
(c)	7.0	4.90	122.5	96.3	31.0	27.0	43.7
(c)	6.3	4.20	81.0	97.8	35.3	30.4	39.4
(c)	6.9	2.20	103.5	97.3	54.0	27.7	29.2
(c)	0.9	2.90	135.0	79.4	37.1	173.1	40.3

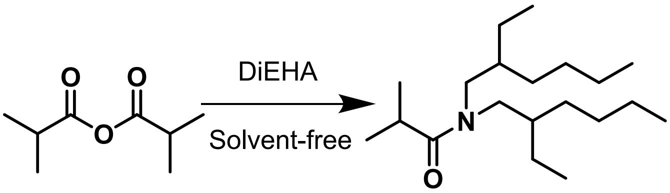
(c)	6.4	4.00	141.0	98.2	36.7	30.1	38.2
(c)	0.8	1.00	48.0	28.3	23.1	69.3	79.2
(c)	6.2	1.90	73.5	94.7	57.1	30.0	28.4
(c)	1.7	1.30	87.0	59.8	43.7	69.0	40.0
(c)	0.8	1.40	127.0	47.8	33.8	117.3	51.0
(c)	6.0	4.20	62.5	97.7	35.3	31.9	39.5
(c)	0.8	1.30	78.0	37.5	27.4	92.0	63.7
(c)	0.5	3.50	117.5	65.4	26.9	256.7	53.5
(c)	6.9	4.90	133.0	98.1	31.5	27.9	43.0
(c)	6.7	1.90	46.0	92.7	55.9	27.1	29.1
(c)	0.7	1.20	59.5	30.1	22.8	84.2	77.8
(c)	6.8	3.80	114.0	96.7	37.5	27.9	37.8
(c)	0.9	4.50	143.5	91.8	31.5	200.0	43.7
(c)	1.2	4.90	55.0	87.7	28.2	143.3	48.0
(c)	1.2	4.30	72.0	86.5	30.7	141.3	45.2
(c)	6.6	3.90	88.0	97.3	37.0	28.9	38.1
(c)	0.5	4.20	101.0	68.7	24.8	269.5	56.1
(c)	2.5	4.70	45.0	95.0	31.5	74.5	43.2
(c)	6.8	3.80	109.0	98.3	38.1	28.3	37.2
(c)	6.4	2.00	128.0	97.8	57.3	30.0	28.1
(c)	5.2	1.20	145.5	87.0	66.0	32.8	26.9
(c)	6.9	2.40	68.0	97.5	51.3	27.7	30.2
(c)	1.9	4.70	83.0	95.4	31.7	98.5	43.1
(c)	1.3	3.70	91.0	88.3	34.9	133.2	40.8
(c)	1.9	4.60	122.0	96.1	32.4	99.2	42.2
(c)	4.8	5.00	50.0	96.6	30.6	39.5	44.1
(c)	3.9	5.00	128.5	98.7	31.3	49.6	43.2
(c)	5.4	3.40	134.5	98.5	41.3	35.8	35.0
(c)	3.6	5.00	150.0	98.4	31.1	53.6	43.3
(c)	7.0	1.00	80.5	79.8	65.3	22.4	28.0
(c)	7.0	1.00	123.0	79.6	65.1	22.3	28.1
(c)	4.1	2.00	130.5	96.7	56.6	46.2	28.4
(c)	5.9	1.00	134.5	79.1	64.7	26.3	28.3
(c)	4.4	2.20	67.5	95.3	52.8	42.5	29.9
(c)	7.0	1.00	75.5	79.9	65.4	22.4	28.0
(c)	6.1	1.00	119.0	80.6	65.9	25.9	27.8
(c)	7.0	1.00	127.5	86.1	70.4	24.1	26.0
(c)	3.7	2.90	54.0	95.9	44.8	50.8	33.4
(c)	0.8	1.00	120.5	38.9	31.8	95.3	57.6
(c)	3.6	1.50	115.0	78.3	53.4	42.6	31.8
(c)	6.3	1.00	128.5	76.2	62.3	23.7	29.4
(c)	7.0	1.00	131.0	77.5	63.4	21.7	28.9
(c)	5.1	1.00	111.0	75.2	61.5	28.9	29.8
(c)	7.0	1.00	126.5	80.8	66.1	22.6	27.7
(c)	4.2	4.00	142.5	98.4	36.8	46.0	38.2
(c)	5.3	1.00	146.5	79.7	65.2	29.5	28.1
(c)	0.8	5.00	128.5	91.4	28.9	224.1	46.6
(c)	7.0	1.00	130.0	81.8	66.9	22.9	27.4
(c)	2.0	3.50	142.5	97.2	39.9	95.3	36.1
(c)	7.0	1.00	144.0	81.7	66.8	22.9	27.4
(c)	2.2	3.00	100.0	94.2	43.0	84.0	34.5
(c)	7.0	1.00	128.5	80.1	65.5	22.4	28.0

(c)	3.1	1.00	128.5	69.6	56.9	44.0	32.2
(c)	5.2	1.00	143.5	78.7	64.3	29.7	28.5
(c)	4.1	2.10	107.0	96.0	54.7	45.9	29.1
(c)	3.6	1.30	126.0	82.9	60.6	45.1	28.8
(c)	5.1	1.00	129.0	76.9	62.9	29.6	29.1
(c)	5.2	2.30	146.0	97.6	52.7	36.8	29.7
(c)	3.7	1.80	54.0	84.7	52.6	44.9	31.2
(c)	5.3	1.00	124.5	77.5	63.4	28.7	28.9
(c)	6.1	1.80	128.0	97.1	60.3	31.2	27.2
(c)	6.8	1.00	129.0	80.7	66.0	23.3	27.7
(c)	4.7	1.40	146.0	90.7	64.0	37.8	26.9
(c)	4.5	3.20	67.5	97.8	42.8	42.6	34.3
(c)	6.5	1.80	127.0	97.5	60.6	29.4	27.1
(c)	6.9	1.00	127.0	78.4	64.1	22.3	28.5
(c)	5.5	1.60	145.0	95.7	63.2	34.1	26.6
(c)	1.4	2.60	89.0	81.3	40.7	113.9	37.5
(c)	4.5	1.00	118.5	74.4	60.8	32.4	30.1
(c)	7.0	2.00	126.0	98.3	57.6	27.5	27.9
(c)	7.0	1.20	127.5	89.3	67.6	25.0	26.2
(c)	6.0	3.00	77.0	98.0	44.7	32.0	33.2
(c)	7.0	2.00	126.5	98.3	57.6	27.5	27.9
(c)	7.0	1.50	127.5	96.0	65.5	26.9	25.9
(c)	7.0	1.00	128.0	81.3	66.5	22.8	27.5
(c)	4.9	2.90	54.0	97.1	45.3	38.8	33.0
(c)	7.0	1.00	121.0	81.1	66.3	22.7	27.6
(c)	6.9	1.40	127.0	93.8	66.2	26.7	26.0
(c)	5.8	1.00	145.0	79.7	65.1	26.9	28.1
(c)	7.0	1.00	145.5	80.7	66.0	22.6	27.7
(c)	6.5	1.00	116.5	78.7	64.3	23.7	28.5
(c)	7.0	1.80	126.5	97.8	60.7	27.4	27.0
(c)	2.5	2.90	134.5	47.7	22.3	37.4	67.1
(c)	4.9	3.30	104.0	98.2	42.0	39.3	34.7
(c)	6.5	1.10	127.5	83.5	65.7	25.2	27.4
(c)	6.2	1.60	128.5	95.9	63.4	30.3	26.5
(c)	7.0	1.00	143.0	81.2	66.4	22.8	27.6
(c)	4.6	1.00	146.5	77.0	63.0	32.8	29.1
(c)	4.0	3.90	108.0	98.6	37.5	48.3	37.6
(c)	7.0	1.00	124.0	80.9	66.1	22.7	27.7
(c)	6.3	1.90	128.0	97.6	58.9	30.4	27.6
(c)	7.0	1.00	144.5	80.9	66.2	22.7	27.7
(c)	4.9	3.30	119.0	98.6	42.2	39.4	34.5
(c)	6.6	1.10	127.5	84.3	66.3	25.1	27.1
(c)	7.0	1.60	128.0	96.8	64.0	27.1	26.3
(d)	4.8	2.12	46.9	89.6	48.4	35.2	32.8
(d)	2.6	2.53	69.7	84.9	41.3	61.9	37.2
(d)	6.6	1.54	81.7	88.6	56.9	25.1	29.7
(d)	1.2	1.94	95.7	62.0	35.2	96.8	45.9
(d)	3.6	2.74	105.9	89.2	41.1	46.3	36.7
(d)	6.0	0.95	127.0	49.5	39.3	15.4	46.9
(d)	2.2	1.17	141.2	42.7	31.2	35.9	57.1
(d)	7.0	2.74	70.0	96.2	44.4	25.7	34.0
(d)	7.0	1.41	58.6	87.9	58.9	23.5	29.2

(d)	7.0	1.67	52.5	93.2	57.3	24.9	29.0
(d)	7.0	0.80	45.0	64.6	54.7	17.2	34.7
(d)	5.9	1.30	60.4	83.1	57.9	26.3	30.2
(d)	7.0	1.23	69.5	86.2	61.7	23.0	28.6
(d)	7.0	0.80	75.7	69.1	58.5	18.4	32.5
(d)	7.0	1.21	69.7	86.8	62.4	23.2	28.4
(d)	7.0	3.00	150.0	79.9	34.8	21.3	42.7
(d)	7.0	1.18	77.3	82.4	59.9	22.0	29.7
(d)	7.0	1.22	68.2	85.3	61.2	22.8	28.9
(d)	7.0	1.23	68.5	85.6	61.2	22.9	28.9
(d)	7.0	1.23	68.6	82.9	59.2	22.1	29.8
(d)	7.0	1.23	68.5	83.5	59.8	22.3	29.6
(d)	7.0	1.23	68.7	83.9	59.9	22.4	29.5
(d)	7.0	1.23	68.7	83.7	59.9	22.3	29.5
(d)	7.0	1.23	68.8	83.5	59.7	22.3	29.6
(d)	7.0	1.23	68.8	82.5	59.0	22.0	29.9
(d)	7.0	1.23	68.9	83.7	59.8	22.3	29.5
(d)	7.0	1.24	68.8	85.2	60.8	22.8	29.0
(d)	7.0	1.23	68.9	83.6	59.8	22.3	29.5
(d)	7.0	1.23	69.0	84.4	60.3	22.5	29.3
(d)	7.0	1.23	69.0	83.9	60.0	22.4	29.4
(d)	7.0	1.23	69.1	83.2	59.5	22.2	29.7
(d)	7.0	1.23	69.1	84.8	60.6	22.6	29.1
(d)	7.0	1.23	69.1	84.3	60.3	22.5	29.3
(d)	7.0	1.23	69.2	82.7	59.2	22.1	29.8
(d)	7.0	1.23	69.1	65.7	47.0	17.6	37.6
(d)	0.7	1.01	65.3	28.6	22.2	75.2	82.3
(d)	5.4	1.50	64.5	86.9	56.6	30.4	30.1
(d)	6.6	2.10	69.0	96.6	52.5	27.4	30.3
(d)	7.0	1.85	69.5	95.8	55.9	25.6	29.2
(d)	7.0	1.55	70.0	90.1	57.7	24.1	29.3
(d)	4.8	1.65	138.5	60.8	37.7	23.9	44.3
(d)	6.2	1.65	62.5	88.8	55.1	26.8	30.3
(d)	7.0	1.45	69.0	90.5	59.9	24.2	28.6
(d)	2.4	1.35	70.5	64.9	44.4	51.6	39.0
(d)	6.6	2.75	79.0	97.5	44.9	27.6	33.6
(d)	6.5	2.10	45.0	95.4	51.8	27.7	30.7
(d)	7.0	1.35	69.5	85.3	58.4	22.8	29.7
(d)	6.6	0.80	71.5	57.0	48.2	16.1	39.4
(d)	2.2	2.55	128.0	73.6	35.6	64.0	43.1
(d)	4.0	2.75	57.5	92.4	42.6	43.8	35.4
(d)	3.4	3.00	69.0	91.8	39.9	50.5	37.1
(d)	7.0	1.15	73.5	81.9	60.3	21.9	29.6
(d)	7.0	0.80	113.5	48.3	40.9	12.9	46.4
(d)	1.1	0.80	127.0	29.9	25.3	48.6	75.0
(d)	7.0	2.10	63.5	95.0	51.6	25.4	30.9
(d)	4.2	3.00	70.0	93.4	40.6	42.1	36.5
(d)	3.7	2.15	71.5	86.8	46.5	43.8	34.1
(d)	7.0	0.80	81.5	62.6	53.0	16.7	35.8
(d)	1.5	1.10	94.5	49.9	37.4	62.2	48.1
(d)	1.5	1.10	58.0	46.9	35.2	58.5	51.2
(d)	7.0	0.80	69.5	64.0	54.2	17.1	35.0

(d)	0.7	3.00	70.5	53.6	23.3	143.0	63.7
(d)	0.7	2.50	85.5	52.6	25.7	140.5	59.7
(d)	3.7	0.80	81.5	52.9	44.8	26.7	42.4
(d)	3.9	3.00	91.5	95.8	41.7	46.5	35.6
(d)	1.5	1.95	104.0	67.7	38.3	81.6	42.1
(d)	0.7	2.50	105.0	54.2	26.5	144.8	58.0
(d)	5.9	2.00	121.5	80.4	44.9	25.5	35.8
(d)	5.8	2.20	65.5	94.7	50.1	30.5	31.5
(d)	7.0	0.80	74.5	59.0	50.0	15.8	38.0
(d)	4.8	1.15	138.5	47.0	34.6	18.5	51.6
(d)	2.5	1.65	150.0	47.8	29.7	35.8	56.3
(d)	4.9	2.75	70.0	88.0	40.5	33.6	37.3
(d)	2.3	2.15	70.5	80.0	42.9	63.6	37.0
(d)	6.6	1.05	77.0	71.6	54.7	20.3	33.2
(d)	2.4	0.80	137.5	31.2	26.4	24.8	71.9
(d)	2.5	2.45	69.0	83.7	41.4	62.6	37.3
(d)	5.7	2.00	70.0	91.5	51.1	29.7	31.5

2.6 Route (e) Solvent-free Direct Amidation with iBAnhydride



Scheme S5: Amide bond formation reaction using isobutyric anhydride (iBAnhydride) and Di(2-ethylhexyl)amine (DiEHA) to yield N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA) in the absence of solvent

Reservoir one was prepared by dissolving the biphenyl in Di(2-ethylhexyl)amine with stirring at ambient conditions.

Reservoir 1: Di(2-ethylhexyl)amine (400 g, 1.66 mol), and biphenyl (8.7588 g, 0.0568 mol).

Reservoir 2: Isobutyric anhydride (477 g, 3.02 mol).

Reservoir 3: Acetonitrile.

An example HPLC chromatogram is illustrated in Figure S10.

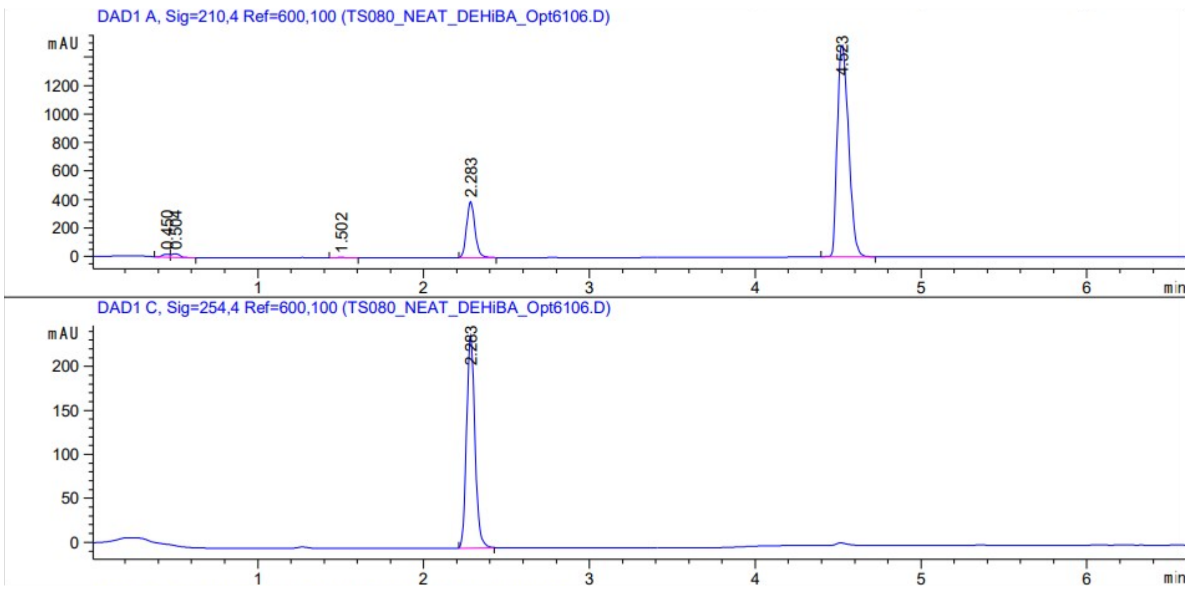


Figure S16: An example HPLC chromatogram from route (e)

The flow platform was set up according to Figure 2 using a reactor volume of 4.0 mL with stainless steel tubing and a back pressure of 100 psi.

The self-optimisation was conducted with respect to three continuous parameters: residence time, iBAnhydride equivalents, and temperature. The upper and lower parameter bounds for each are described in Table S7. The initial objective for each optimisation was to maximise yield, then simultaneously maximize reaction mass efficiency and space-time yield.

Table S9: The upper and lower bounds for the variables optimised in route (e)

	Residence time (mins)	iBAnhydride equivalents.	Temperature (°C)	[DiEHA] after reactor (mol dm^{-3})
Lower bound	0.5	0.9	40	0.4
Upper bound	10	3	150	0.4

2.6.1 Route (e) Data and Further Analysis

A comparison between the trade-off between the solvated and solvent free synthesis of DEHiBA from iBAnhydride, whereby the trends are contrasting.

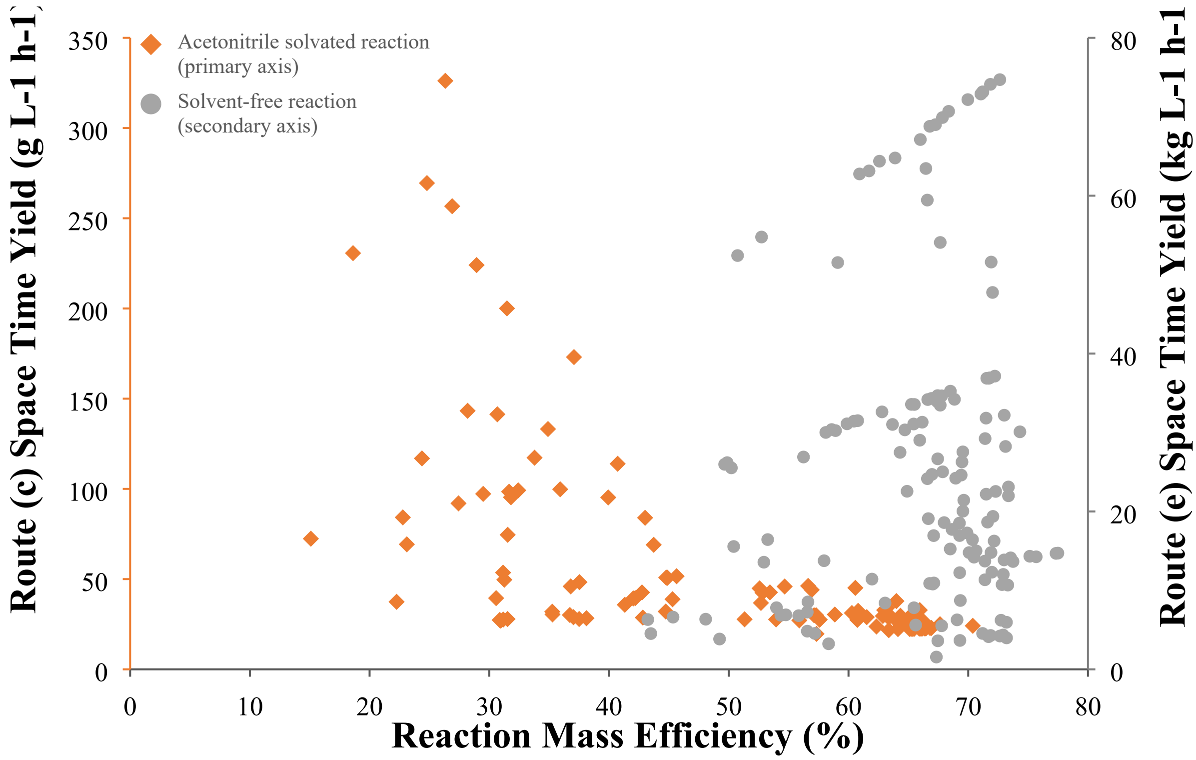


Figure S17: A comparison between the RME, STY trade-off curves for the solvated and solvent free reaction of iBAnhydride and DiEHA

Table S8 provides the raw data for the experimental conditions exploited in the optimisation of route (e) and the performance metrics associated.

Table S10: complete dataset from the optimisation of route (e)

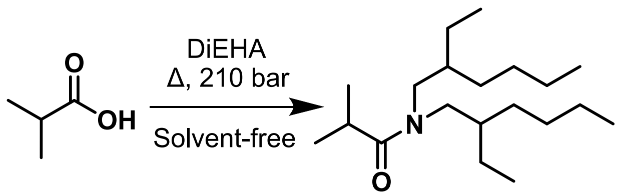
Residence time (min)	iBAnhydride equivalents.	Temperature (°C)	[DiEHA] in reactor (M)	DEHiBA Yield (%)	Reaction Mass Efficiency (%)	Space-Time Yield (kg L^{-1} h^{-1})	Cost of DEHiBA (£/mol)
2.8	1.00	139.0	2.1352	79.6	62.0	11.4	29.5
22.2	1.00	139.0	2.1352	86.5	67.3	1.6	27.2
4.0	2.00	40.0	1.5793	86.0	48.1	6.3	33.5
4.0	1.00	40.0	2.1390	72.5	56.6	7.2	32.4
2.0	1.00	40.0	2.1390	67.9	52.9	13.6	34.6

6.8	2.16	41.9	1.5153	92.1	49.2	3.8	32.2
6.0	1.00	50.0	2.1390	84.1	65.6	5.6	27.9
3.7	2.54	65.9	1.3817	93.7	45.3	6.6	33.8
3.7	2.54	65.9	1.3817	89.4	43.2	6.3	35.4
9.4	1.61	78.5	1.7605	92.8	58.3	3.2	28.8
1.7	1.98	93.1	1.5850	94.9	53.2	16.4	30.2
1.7	1.98	93.1	1.5850	89.9	50.4	15.6	31.9
5.1	2.75	103.8	1.3189	94.5	43.5	4.5	34.7
6.0	1.00	100.0	2.1390	93.3	72.7	6.2	25.2
8.6	1.05	125.9	2.1037	93.9	71.9	4.3	25.3
3.2	1.26	140.8	1.9608	94.3	66.8	10.9	26.3
8.6	1.05	125.9	2.1037	95.2	72.9	4.4	24.9
3.2	1.26	140.8	1.9608	94.8	67.1	10.9	26.2
3.0	1.00	150.0	2.1390	92.3	72.0	12.3	25.4
1.0	1.00	150.0	2.1390	85.8	66.9	34.3	27.4
8.8	0.90	149.7	2.2170	92.1	72.6	4.2	25.6
9.4	0.90	128.8	2.2176	92.9	73.2	4.0	25.5
8.0	0.90	138.2	2.2176	90.3	71.2	4.5	26.2
6.2	1.88	139.0	1.6288	97.9	56.6	4.8	28.8
6.6	1.85	125.7	1.6436	98.0	57.2	4.5	28.6
3.7	2.10	150.0	1.5403	99.3	54.0	7.8	29.5
4.3	2.00	150.0	1.5783	100.0	55.8	6.8	28.8
4.2	1.98	150.0	1.5857	96.8	54.3	6.8	29.6
4.2	1.98	150.0	1.5857	97.6	54.8	6.9	29.4
1.1	1.27	150.0	1.9513	91.9	64.7	30.3	27.1
3.2	1.17	150.0	2.0170	91.8	67.0	10.8	26.6
1.0	1.47	150.0	1.8346	88.3	58.1	30.0	29.4
2.7	1.13	150.0	2.0475	98.3	73.0	13.9	24.6
2.5	0.90	128.9	2.2139	89.2	70.5	14.2	26.4
3.2	0.94	135.5	2.1885	89.2	71.4	11.3	25.9
1.1	1.02	150.0	2.1206	85.6	66.2	31.3	27.6
1.2	1.05	150.0	2.0979	86.4	65.9	29.0	27.5
8.9	0.98	108.2	2.1530	91.3	71.7	4.1	25.6
2.1	1.10	140.1	2.0661	93.2	69.9	17.3	25.8
1.0	0.99	148.3	2.1490	86.3	67.7	33.5	27.1
1.4	0.99	148.3	2.1470	85.5	67.0	24.7	27.4
4.1	0.91	149.4	2.2125	87.6	69.3	8.7	26.8
1.0	1.91	149.7	1.6184	87.5	50.2	25.5	32.3
1.6	0.90	150.0	2.2139	90.4	71.5	22.2	26.0
1.1	0.92	150.0	2.1985	81.7	65.4	31.1	28.4
1.0	1.35	140.6	1.9033	91.7	62.8	32.6	27.6
2.0	1.16	140.8	2.0237	91.5	67.1	16.9	26.6
2.9	1.11	142.3	2.0604	92.6	69.3	12.2	26.0
1.0	0.98	148.2	2.1564	83.2	65.5	33.6	28.1
1.0	1.07	122.3	2.0888	88.8	67.4	34.7	26.8
1.0	1.08	140.5	2.0815	86.2	65.3	33.6	27.7
1.0	1.29	145.9	1.9362	87.0	60.8	31.5	28.8
2.7	1.01	150.0	2.1278	94.8	73.5	14.1	24.8
1.0	1.07	122.3	2.0888	94.4	71.7	36.9	25.2
1.0	1.08	140.5	2.0815	90.5	68.5	35.2	26.4
1.0	1.29	145.9	1.9362	83.9	58.6	30.4	29.8
2.7	1.01	150.0	2.1278	92.1	71.4	13.7	25.6

1.0	1.36	119.1	1.8988	87.6	59.9	31.1	29.0
1.0	1.01	143.3	2.1290	85.9	66.6	34.2	27.4
2.0	0.90	149.7	2.2139	86.8	68.7	17.7	27.1
6.3	0.94	150.0	2.1824	91.8	73.2	6.0	25.3
4.3	0.90	109.7	2.2139	82.8	65.5	7.8	28.4
1.0	1.36	118.9	1.8951	86.4	58.9	30.2	29.4
1.0	1.13	124.7	2.0457	96.4	71.5	36.9	25.1
2.2	0.97	148.6	2.1575	89.3	70.4	16.4	26.1
1.4	0.90	97.6	2.2139	87.9	69.5	26.3	26.8
1.0	1.73	64.6	1.6974	82.5	49.9	26.2	33.2
6.3	0.90	86.9	2.2139	85.7	67.8	5.5	27.5
2.7	1.00	141.9	2.1397	97.0	75.7	14.3	24.2
1.4	0.90	150.0	2.2139	85.8	67.9	25.0	27.4
1.0	1.39	105.8	1.8789	89.5	60.5	31.4	28.5
1.9	0.97	132.5	2.1636	91.2	72.1	19.4	25.5
1.2	0.98	136.9	2.1565	81.7	64.3	27.5	28.6
1.4	1.00	138.4	2.1393	89.0	69.4	24.6	26.4
1.0	0.93	121.8	2.1963	84.5	67.8	34.6	27.4
2.0	0.93	134.3	2.1920	89.3	71.6	18.6	25.9
9.7	1.04	139.9	2.1107	90.2	69.3	3.7	26.2
2.4	0.90	141.9	2.2139	88.6	70.1	14.8	26.6
1.0	0.90	102.6	2.2139	80.5	63.7	31.0	29.2
5.7	1.04	134.8	2.1104	89.9	69.1	6.3	26.3
1.9	0.92	136.1	2.1989	86.5	69.3	18.5	26.8
9.5	0.92	150.0	2.2038	84.6	67.5	3.6	27.5
2.2	1.53	53.0	1.8020	89.6	58.0	13.8	29.2
3.9	1.36	59.3	1.8989	92.0	63.1	8.4	27.5
3.5	1.95	75.8	1.6003	99.6	56.6	8.5	28.5
0.6	1.60	90.5	1.7649	93.4	59.1	51.5	28.4
1.8	1.30	111.2	1.9356	99.3	69.6	20.0	25.1
1.0	1.07	122.3	2.0833	95.1	72.2	37.1	25.0
2.7	1.09	129.2	2.0690	99.7	75.1	14.3	24.0
1.0	1.07	122.3	2.0833	94.5	71.8	36.9	25.2
2.7	1.00	141.9	2.1352	99.3	77.5	14.7	23.6
1.1	1.81	149.4	1.6623	94.9	56.2	26.9	29.2
2.7	1.00	141.9	2.1352	99.1	77.3	14.7	23.7
0.5	1.22	140.0	1.9868	94.9	68.4	70.7	25.9
0.5	1.00	140.0	2.1352	91.0	71.1	72.9	25.7
0.5	1.15	150.0	2.0336	97.2	71.9	74.1	24.9
1.9	1.01	81.5	2.1286	87.4	68.0	18.6	26.9
0.5	1.11	122.5	2.0583	89.1	66.8	68.8	26.9
1.5	1.00	75.2	2.1352	83.1	64.9	22.6	28.2
0.5	1.07	149.0	2.0867	95.5	72.6	74.7	24.9
1.2	1.00	120.2	2.1352	91.6	71.5	31.8	25.6
1.3	1.02	150.0	2.1199	96.0	74.3	30.1	24.5
1.7	1.05	136.7	2.1027	95.6	73.4	22.0	24.8
1.6	1.06	146.1	2.0946	96.0	73.4	23.1	24.7
0.5	1.12	149.2	2.0526	90.8	67.8	69.9	26.5
3.5	1.04	133.3	2.1066	95.3	73.3	10.7	24.8
1.3	1.04	139.3	2.1060	92.9	71.4	29.2	25.4
0.8	1.00	142.4	2.1352	92.3	72.0	47.7	25.4
1.7	1.16	150.0	2.0240	94.6	69.6	21.4	25.6

0.5	1.32	150.0	1.9203	88.9	61.7	63.1	28.2
2.8	1.00	150.0	2.1352	94.5	73.7	13.7	24.8
0.7	1.00	147.9	2.1352	92.1	71.9	51.6	25.4
0.5	1.05	134.9	2.0986	86.8	66.5	63.4	27.3
2.3	1.02	143.3	2.1269	92.8	72.2	16.3	25.3
2.1	1.02	143.2	2.1267	89.1	69.3	16.9	26.4
0.5	1.11	84.6	2.0558	81.4	60.9	62.8	29.5
1.8	1.12	125.4	2.0505	89.3	66.7	19.1	26.9
3.5	1.00	146.8	2.1352	93.3	72.8	10.7	25.1
0.5	1.07	95.1	2.0836	84.1	63.9	64.8	28.3
0.5	1.05	149.9	2.1032	92.7	71.2	73.2	25.5
1.6	1.02	143.3	2.1238	93.1	72.3	22.5	25.2
0.5	1.16	150.0	2.0239	89.7	66.0	67.1	27.0
2.4	1.06	149.5	2.0907	92.6	70.7	15.0	25.6
0.5	1.03	149.9	2.1151	92.2	71.2	73.1	25.6
1.0	1.00	144.9	2.1351	88.2	68.8	34.2	26.6
3.1	1.02	128.3	2.1268	93.8	72.9	12.0	25.0
0.5	1.22	114.2	1.9861	86.9	62.6	64.4	28.3
1.2	1.01	150.0	2.1315	93.7	73.0	32.2	25.0
0.5	1.34	53.5	1.9066	76.6	52.7	54.8	32.9
1.0	1.30	41.5	1.9306	71.1	49.7	26.0	35.2
1.3	1.00	149.1	2.1352	93.6	73.1	28.2	25.0
1.3	1.08	117.4	2.0818	91.6	69.5	27.5	26.0
1.4	1.08	119.2	2.0818	87.7	66.6	24.2	27.1
0.5	1.01	135.5	2.1330	86.3	67.3	69.0	27.2
1.0	1.08	110.9	2.0811	88.9	67.4	33.9	26.8
2.5	1.00	114.7	2.1352	92.1	71.9	14.8	25.4
0.6	1.07	150.0	2.0888	88.8	67.7	54.1	26.8
1.3	1.03	149.1	2.1164	87.2	67.4	26.7	27.0
0.6	1.06	150.0	2.0957	87.1	66.6	59.4	27.2
2.3	1.28	142.6	1.9475	97.2	68.5	15.2	25.6
0.5	1.86	77.5	1.6375	87.0	50.7	52.4	32.1
0.5	1.15	142.7	2.0303	94.8	70.0	72.2	25.5
1.5	1.05	136.1	2.1019	89.9	69.0	24.2	26.3

2.7 Route (f) Direct Thermal Amidation From iBA



Scheme S6: A direct thermal amidation reaction to yield N,N-di-(2-ethylhexyl)isobutyramide (DEHiBA) by forcing isobutyric acid (iBA) and Di(2-ethylhexyl)amine (DiEHA) together via elevated temperatures and 210 bar of pressure

Reservoir one was prepared by dissolving biphenyl in Di(2-ethylhexyl)amine with stirring at ambient conditions.

Reservoir 1: Di(2-ethylhexyl)amine (400 g, 1.66 mol), and biphenyl (8.7588 g, 0.0568 mol).

Reservoir 2: Isobutyric acid (475 g, 5.39 mol).

Reservoir 3: Acetonitrile.

An example HPLC chromatogram is illustrated in Figure S12 using the HPLC method previously described.

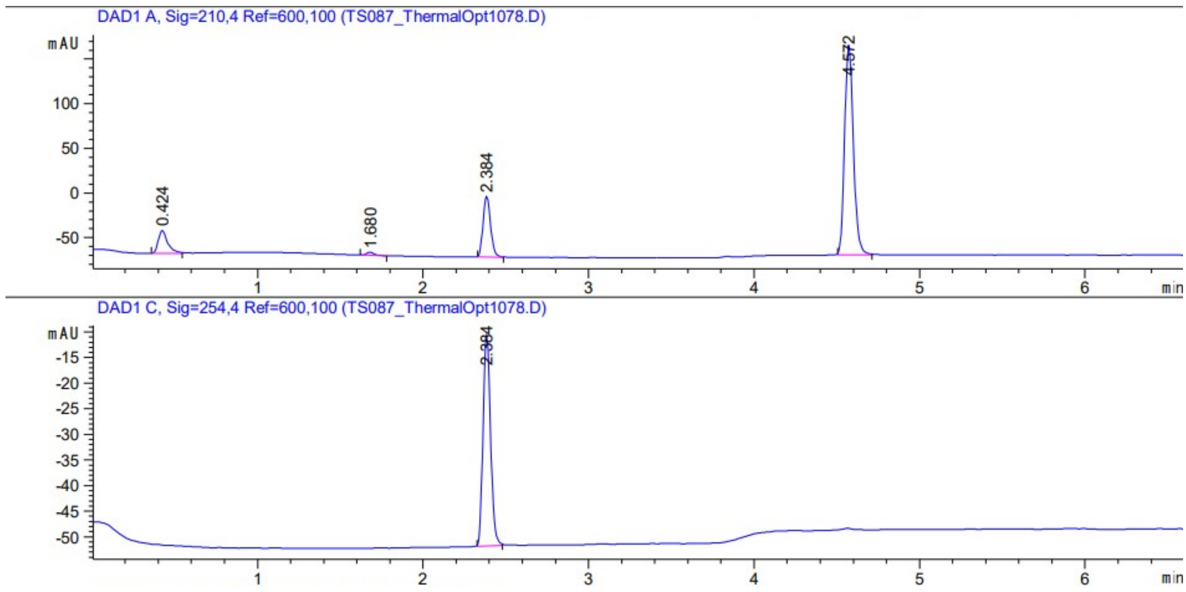


Figure S18: An example HPLC chromatogram from route (f)

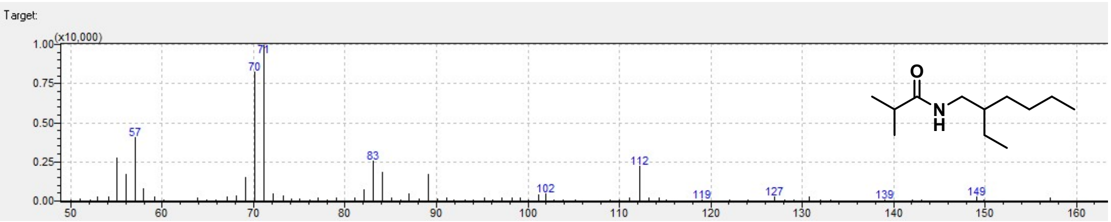
The flow platform was set up according to Figure 2 using a reactor volume of 4.0 mL with stainless steel tubing a back pressure regulator set to 210 bar before the sample loop and a back pressure of 100 psi following the sample loop. The self-optimisation was conducted with respect to three continuous parameters: residence time, iBA equivalents, and temperature. The upper and lower parameter bounds for each are described in Table S9. The initial objective for each optimisation was to maximise yield and reaction mass efficiency, then simultaneously maximize reaction mass efficiency and space-time yield.

Table S11: The upper and lower bounds for the variables optimised in route (f)

	Residence time (mins)	iBA equivalents.	Temperature (°C)	[DiEHA] after reactor (mol dm^{-3})
Lower bound	1	0.9	200	0.4
Upper bound	18	5	370	0.4

2.7.1 Route (f) Data and Further Analysis

GC-MS used to identify the unknown signal that was in fact the thermal degradation



product of DEHiBA:

Figure S19: GC-MS chromatogram for the degradation product of DEHiBA

A concise dataset (Table S10) demonstrating the trend between conditions and the area ratio for the signals at 0.5 and 1.7 minutes. The signal at 0.5 minutes increases with increasing iBA equivalents predominantly whilst the signal at 1.7 minutes intensifies with both an increase in temperature and residence time.

Table S12: Area ratios for the signals at 0.5 and 1.7 minute retention times

0.5 min signal	1.7 min signal	Residence time (min)	iBA equivalents.	Temperature (°C)
0.57	0.08	5.00	2.50	330.0
0.45	0.15	5.00	2.50	350.0
0.43	0.23	5.00	2.50	370.0
1.03	0.16	5.92	5.00	344.9
0.98	0.14	5.04	5.00	345.5
1.00	0.15	5.43	5.00	346.1
0.80	0.16	5.50	4.21	348.3
0.65	0.19	5.50	3.52	356.9
0.53	0.18	5.50	3.00	356.9
0.41	0.18	5.50	2.50	356.9
0.85	0.07	8.85	4.14	300.0
0.49	0.03	17.19	2.35	259.5
0.61	0.03	6.03	3.07	282.0
0.82	0.11	10.99	4.53	298.6
0.14	0.25	15.99	1.28	332.8
0.22	0.28	8.15	1.68	355.7
0.54	0.37	18.00	4.08	338.0
0.64	0.29	13.98	4.00	341.1

0.80	0.59	14.75	4.66	364.7
0.80	0.53	12.09	4.73	365.6
0.41	0.34	18.00	2.73	341.9
0.07	0.28	17.34	1.76	344.3
0.03	0.21	16.40	1.00	344.4
0.38	0.38	18.00	2.78	345.4
0.82	0.31	14.35	4.81	342.2
0.95	0.42	17.62	5.00	347.1
0.89	0.48	17.64	4.98	352.0
0.90	0.49	18.00	4.91	352.2
0.76	0.01	13.54	3.81	209.7
0.80	0.01	13.47	4.00	210.3
0.68	0.32	15.34	4.01	351.1
0.72	0.18	6.34	4.48	352.7
0.47	0.36	17.12	3.00	352.3
0.48	0.35	16.41	3.06	352.3
0.42	0.36	17.30	3.05	352.6
0.58	0.29	10.78	3.75	354.9
0.86	0.22	13.17	5.00	338.0
0.87	0.18	10.65	5.00	338.7
0.94	0.19	5.43	2.91	359.1
0.40	0.16	5.13	2.87	359.5
0.20	0.07	15.47	1.40	305.6
0.77	0.07	5.00	4.30	324.3
0.82	0.14	9.42	5.00	324.3
0.46	0.23	14.96	2.89	332.8

Table S13: complete dataset for the optimisation of route (f)

Residence time (min)	iBA equivalents.	Temperature (°C)	[DiEHA] in reactor (M)	DEHiBA Yield (%)	Reaction mass efficiency (%)	Space-Time Yield (g L^{-1} h^{-1})	Cost of DEHiBA (£ mol^{-1})
5.0	2.5	330.0	1.874	44.6	30.0	3122	44.1
5.0	2.5	350.0	1.874	59.7	40.2	4181	33.0
5.0	2.5	370.0	1.874	59.5	40.1	4169	33.1
5.9	5.0	344.9	1.306	77.8	35.4	3210	27.2
5.0	5.0	345.5	1.306	77.3	35.2	3745	27.4
5.4	5.0	346.1	1.306	77.7	35.4	3495	27.2
5.5	4.2	348.3	1.444	73.7	37.4	3619	28.1
5.5	3.5	356.9	1.592	68.6	38.7	3713	29.6
5.5	3.0	356.9	1.724	65.0	39.9	3809	30.7
5.5	2.5	356.9	1.874	59.1	39.8	3765	33.3
8.8	4.1	300.0	1.459	50.0	25.6	1541	41.3
17.2	2.3	259.5	1.925	14.1	9.8	295	139.2
6.0	3.1	282.0	1.705	13.7	8.3	724	146.2
11.0	4.5	298.6	1.385	55.9	27.1	1317	37.4
16.0	1.3	332.8	2.377	34.4	30.2	956	55.1
8.1	1.7	355.7	2.186	44.7	35.7	2241	42.9
18.0	4.1	338.0	1.469	64.4	33.2	982	32.1
14.0	4.0	341.1	1.486	63.4	33.1	1260	32.5
14.8	4.7	364.7	1.362	57.9	27.6	999	36.2

12.1	4.7	365.6	1.351	60.8	28.7	1271	34.5
18.0	2.7	341.9	1.802	58.5	37.7	1094	33.9
17.3	1.8	344.3	2.151	27.4	21.5	635	70.3
16.4	1.0	344.4	2.534	14.2	13.4	409	132.6
18.0	2.8	345.4	1.786	55.7	35.5	1032	35.7
14.3	4.8	342.2	1.337	69.4	32.4	1210	30.3
17.6	5.0	347.1	1.306	68.0	30.9	942	31.2
17.6	5.0	352.0	1.309	64.4	29.4	894	32.9
18.0	4.9	352.2	1.320	64.3	29.6	882	32.8
13.5	3.8	209.7	1.527	1.3	0.7	27	1573.4
13.5	4.0	210.3	1.485	1.3	0.7	27	1593.3
15.3	4.0	351.1	1.484	63.9	33.3	1154	32.2
6.3	4.5	352.7	1.394	71.0	34.7	2921	29.4
17.1	3.0	352.3	1.724	59.1	36.3	1113	33.8
16.4	3.1	352.3	1.707	59.4	36.1	1156	33.7
17.3	3.0	352.6	1.710	56.2	34.2	1038	35.6
10.8	3.8	354.9	1.539	64.6	35.1	1726	31.6
13.2	5.0	338.0	1.306	74.3	33.8	1378	28.5
10.6	5.0	338.7	1.306	75.6	34.4	1734	28.0
5.4	2.9	359.1	1.749	60.9	38.0	3663	32.7
5.1	2.9	359.5	1.762	59.0	37.1	3782	33.7
15.5	1.4	305.6	2.315	27.3	23.3	764	69.6
5.0	4.3	324.3	1.428	56.8	28.4	3031	36.6
9.4	5.0	324.3	1.306	75.2	34.3	1950	28.2
15.0	2.9	332.8	1.755	64.0	40.1	1403	31.1
2.5	1.5	350.0	2.268	16.7	13.9	2826	114.5
1.6	2.3	350.0	1.955	16.9	11.9	3879	115.5
2.3	3.5	360.0	1.587	46.9	26.3	6182	43.3
2.5	1.5	360.0	2.268	21.4	17.8	3626	89.2
2.5	1.5	370.0	2.268	23.9	19.9	4048	79.9
2.5	1.5	350.0	2.268	16.7	13.9	2829	114.4
1.6	2.3	350.0	1.955	16.3	11.5	3733	120.0
2.3	3.5	360.0	1.587	46.4	26.0	6113	43.8
2.5	1.5	360.0	2.268	22.0	18.3	3731	86.7
2.5	1.5	370.0	2.268	25.8	21.4	4367	74.1
1.1	5.0	359.8	1.306	33.2	15.1	7224	63.7
1.1	5.0	359.9	1.306	32.6	14.8	7257	65.0
1.1	5.0	360.0	1.308	32.6	14.9	7282	64.9
1.1	5.0	360.0	1.307	33.3	15.2	7194	63.6
4.2	3.4	359.9	1.620	61.1	35.1	4409	33.1
4.7	3.9	360.0	1.516	64.7	34.6	3938	31.7
3.1	3.4	360.0	1.626	56.1	32.4	5488	36.0
2.0	1.1	217.2	2.469	1.9	1.8	446	970.4
4.8	3.1	248.2	1.708	1.4	0.8	92	1453.5
2.8	4.8	268.8	1.345	2.7	1.3	239	784.2
5.0	2.1	286.7	2.011	5.6	4.1	422	348.3
3.3	3.4	306.2	1.625	10.6	6.1	978	191.2
1.4	4.1	343.1	1.475	18.1	9.4	3584	114.0
4.1	2.4	346.1	1.902	35.3	24.1	3037	55.7
5.5	3.1	363.2	1.703	53.1	32.2	3072	37.7
5.5	3.1	363.2	1.705	57.2	34.7	3326	35.0
5.5	3.0	368.5	1.711	58.9	35.9	3423	34.0

4.5	3.8	361.4	1.525	61.7	33.2	3951	33.2
4.5	4.0	361.5	1.496	64.2	33.8	4006	32.0
4.6	3.9	362.0	1.514	64.5	34.4	3960	31.8
4.7	3.9	362.3	1.501	65.9	34.8	3908	31.2
5.2	2.7	368.5	1.812	56.6	36.7	3717	35.0
5.1	5.0	369.9	1.312	65.7	30.0	3176	32.2
5.1	5.0	370.0	1.306	68.4	31.1	3292	31.0
4.1	4.4	356.8	1.407	45.4	22.4	2907	45.9
4.1	4.3	357.0	1.419	59.7	29.7	3873	34.8
4.0	4.1	359.1	1.471	60.4	31.2	4185	34.1
3.9	4.9	364.5	1.316	68.3	31.3	4283	31.0
3.8	3.8	361.9	1.518	59.8	32.0	4495	34.3
4.3	4.4	366.8	1.417	66.4	33.0	4059	31.3
4.8	4.6	368.6	1.368	68.5	32.8	3641	30.6
4.8	4.6	368.6	1.371	69.8	33.5	3731	30.0
4.9	2.7	356.2	1.802	51.4	33.1	3531	38.6
4.8	2.7	356.4	1.804	49.9	32.2	3483	39.7
4.9	2.9	362.6	1.741	54.5	33.9	3646	36.6
4.8	2.9	363.2	1.757	54.9	34.4	3736	36.3
5.5	2.4	360.0	1.914	49.4	34.1	3216	39.6
5.5	2.3	360.3	1.926	48.0	33.3	3141	40.8
5.5	2.4	362.7	1.922	49.2	34.0	3211	39.8
5.5	2.5	367.9	1.874	52.3	35.2	3330	37.6
5.5	3.1	347.1	1.699	50.8	30.7	2935	39.4
5.4	3.2	354.5	1.675	56.0	33.3	3236	35.9
2.4	4.9	363.6	1.321	58.3	26.9	6116	36.2
3.2	5.0	369.1	1.312	67.9	31.1	5153	31.1
3.3	5.0	369.2	1.312	69.9	32.0	5184	30.3
5.5	1.1	369.5	2.502	25.0	23.3	2128	75.2
4.1	3.5	354.0	1.601	46.0	26.1	3387	44.1
3.7	3.7	354.4	1.561	52.4	28.9	4095	38.9
4.2	3.3	357.4	1.647	54.4	31.8	4020	37.0
5.2	2.9	370.0	1.757	57.5	36.0	3644	34.6
2.9	4.3	361.2	1.432	58.3	29.3	5326	35.6
3.1	3.7	364.4	1.543	58.0	31.6	5324	35.2
4.7	3.6	370.0	1.567	63.8	35.4	4020	31.9
4.5	3.6	370.0	1.582	63.8	35.7	4241	31.8
4.3	2.7	363.2	1.822	52.0	33.9	4152	38.1
1.9	4.3	366.5	1.434	48.6	24.4	6917	42.7
1.6	4.1	369.7	1.470	45.5	23.5	7619	45.3
1.0	4.9	370.0	1.324	31.1	14.3	7684	68.0
3.4	2.6	367.2	1.833	46.5	30.5	4715	42.5
2.7	3.2	370.0	1.659	49.6	29.2	5773	40.6
3.4	2.5	370.0	1.882	45.2	30.6	4656	43.5
3.6	2.4	370.0	1.894	45.2	30.8	4434	43.5
2.2	3.9	358.9	1.498	43.1	22.7	5480	47.7
4.0	4.1	367.4	1.462	64.7	33.2	4411	31.9
4.0	4.0	369.0	1.486	64.6	33.8	4538	31.9
1.9	3.9	370.0	1.510	49.5	26.3	7396	41.4
2.5	3.7	366.4	1.559	51.9	28.6	6105	39.3
3.4	4.6	368.4	1.377	66.2	31.9	5067	31.6
1.5	3.8	370.0	1.524	39.4	21.1	7610	52.0

3.5	4.6	370.0	1.365	65.6	31.3	4764	32.0
1.7	5.0	366.2	1.306	52.3	23.8	7320	40.5

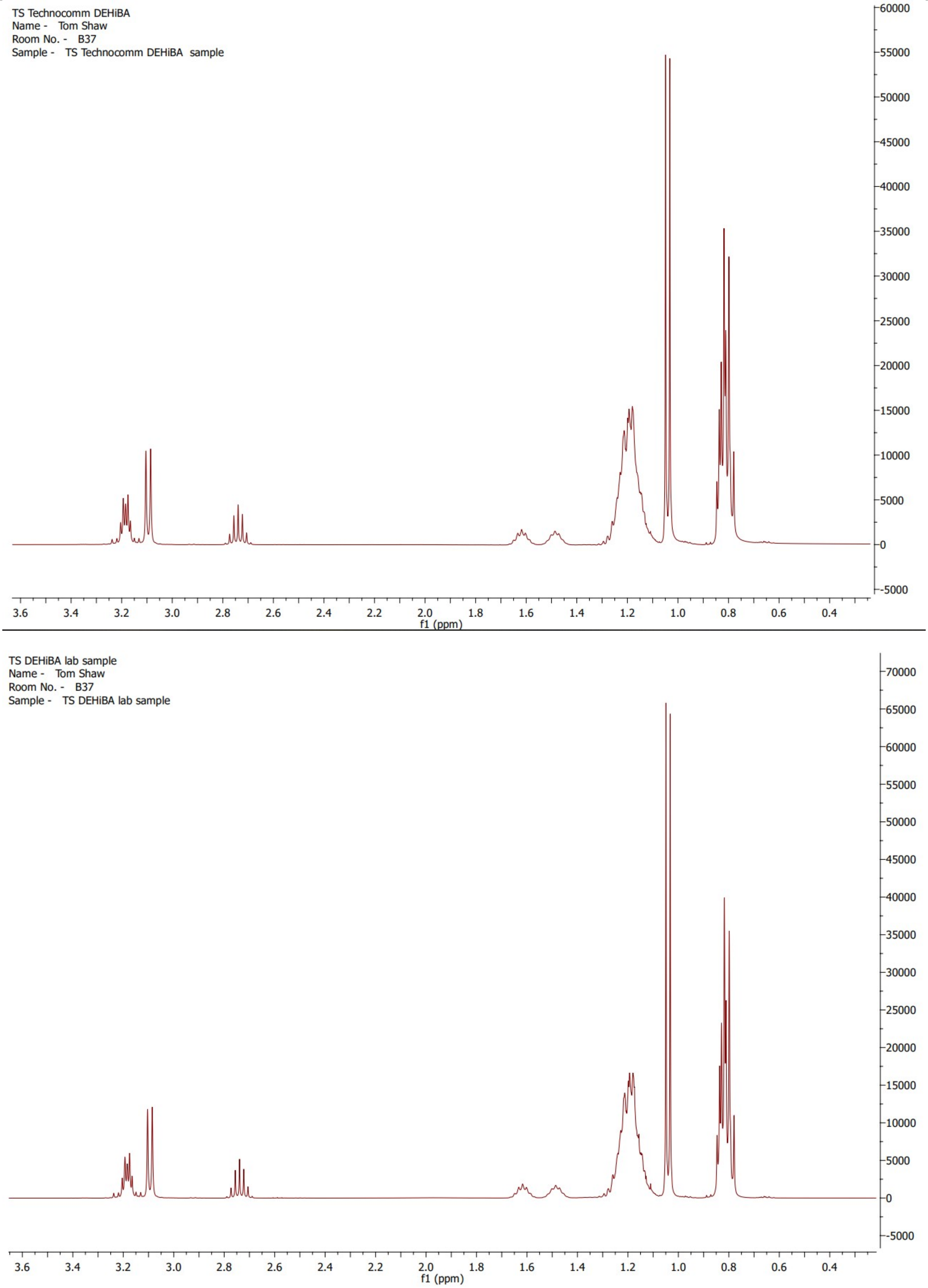


Figure S20: [1]H NMR spectra of DEHiBA from the commercial supplier (top) compared with DEHiBA manufactured and purified in this work