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Supporting Information

Advanced Real-Time Process Analytics for Multistep Synthesis in Continuous Flow**

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Supporting Information

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1. Experimental Details

1.1. General experimental details

Solvents and chemicals were obtained from commercial suppliers and were used without any further purification unless otherwise noted. 2ClBA was purchased from TCI in >98% purity. H_2SO_4 (95%) and HNO_3 (68%) were obtained from VWR, and isopropyl acetate was purchased from ACROS Organics in >99% purity. Reference materials for 5-ASA, 3-ASA, 5A-2ClBA, 5N-2ClBA, 3-NSA, 5-NSA were obtained from TCI in >98% purity, 3A-2ClBA was obtained from Fluorochem (97%) and 3N-2ClBA was obtained from Apollo Scientific (99%).

HPLC analysis was performed using a Shimadzu LC20 system with a reversed phase C18 column (150 mm × 4.6 mm; 5 µm particle size) at 37 °C with a total flow rate of 1.5 mL/min. The following gradient program was applied: starting from 3% solvent B, the amount of solvent B was increased to 5% over 3 min, followed by an increase to 30% B over 4 min, an increase to 100% B over 3 min with a hold time of 2 min, and a final 3 min equilibration at 3% B. The mobile phases A (water/acetonitrile 9+1 v/v + 0.1% TFA) and B (acetonitrile + 0.1% TFA) were prepared from HPLC grade reagents.

Microwave experiments were performed in an Anton Paar Monowave 400 single-mode microwave instrument, producing controlled irradiation at 2.45 GHz. Reaction times refer to hold times at the indicated temperatures. The temperature was measured with an IR sensor on the outside of the reaction vessel.

1.1.1. Reactor Platform

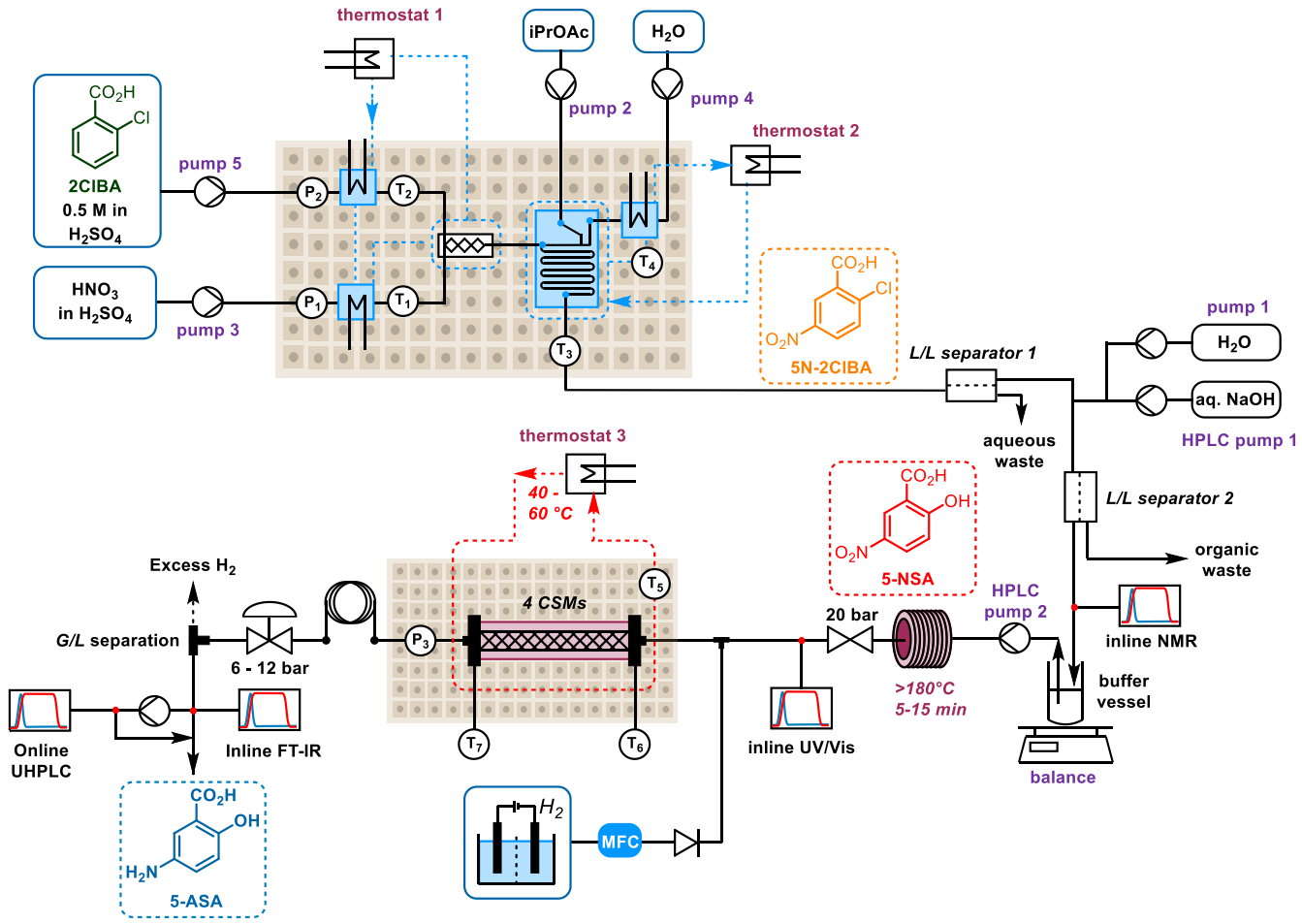


Figure S1. Detailed flow setup for the telescoped process.

The nitration was performed in a Modular MicroReaction System (Ehrfeld Mikrotechnik, MMRS). To work up the reaction mixture in preparation for the basic hydrolysis step, an acid/base switch was implemented, using two membrane-based separators (Zaiput, SEP-10). The reaction stream was analyzed inline by a benchtop NMR spectrometer (Magritek, Spinsolve Ultra 43 MHz, **Figure S1**) and collected in a buffer vessel, which was placed on a balance (Kern, KB 2400-2N). The hydrolysis step was performed in a stainless steel coil, which was placed on a coil heater (Uniqsis, HotCoil UQ1025-1). After passing through a back pressure regulator (Swagelok, KCB1H0A2B5P60000, max pressure 25.8 bar) the reaction mixture was analyzed inline with a UV/vis spectrometer (Avantes, AvaSpec-ULS2048 spectrometer with an AvaLight-DHc light source). A hydrogen generator (ThalesNano Energy, H-Genie) provided a flow of H_2 gas for the hydrogenation. This reaction was carried out in a shell-and-tube type reactor (Ehrfeld Mikrotechnik, Miprowa Reactor) equipped with electroplated Pd Catalytic Static Mixers (CSIRO/Precision Plating). The final reaction mixture left the pressurized system through a back pressure regulator (Equilibar, Zero Flow) linked to a pressurized argon supply, with an automated electronic regulator (Bronkhorst, EL-PRESS). The biphasic reaction mixture was separated in a home-built gas/liquid separator and the liquid phase was analyzed inline by an ATR FTIR spectrometer (Mettler Toledo, ReactIR 15) and online by a UHPLC system (Shimadzu, Nexera X2).

The H-Genie, pressure controller, coil heater, balance, pumps and thermostats were connected via RS232 to an interface hub (HiTec Zang, LabManager). Temperature sensors were connected to the LabManager via M8 and pressure sensors were connected via DIN (5-pin). All individual control and data points were sent via OPC UA to the SCADA system (Evon, XAMControl). The acquired spectra from the NMR were processed with an indirect hard model (IHM) in real-time by software monitoring the respective directory (S-PACT, ProcessLink) and the obtained concentrations were provided via OPC UA to XAMControl. The UV/vis spectrometer was

directly connected to XAMControl via DLL. The obtained UV/vis spectra were processed with a neural network (written in Python). The measured IR spectra were processed with a PLS model in ProcessLink and the results were send via OPC UA to XAMControl. Recorded UHPLC chromatograms were processed in real-time using the chromatography software (Shimadzu, LabSolutions v 5.93) and a report file in csv format was generated, then read by XAMControl. In the flow setup, standard perfluoroalkoxy alkane (PFA) tubing (0.8 mm or 1.6 mm i.d.), fittings, T-pieces manufactured from PTFE or PEEK were used as connectors. The flow equipment and accessories (T-pieces, check-valves, cartridge BPRs etc.) were obtained from Kinesis Ltd..

Figure S2. Photograph of the nitration and extraction setup.

Figure S3. Photograph of the acid/base extraction (left) and the hydrolysis setup (right).

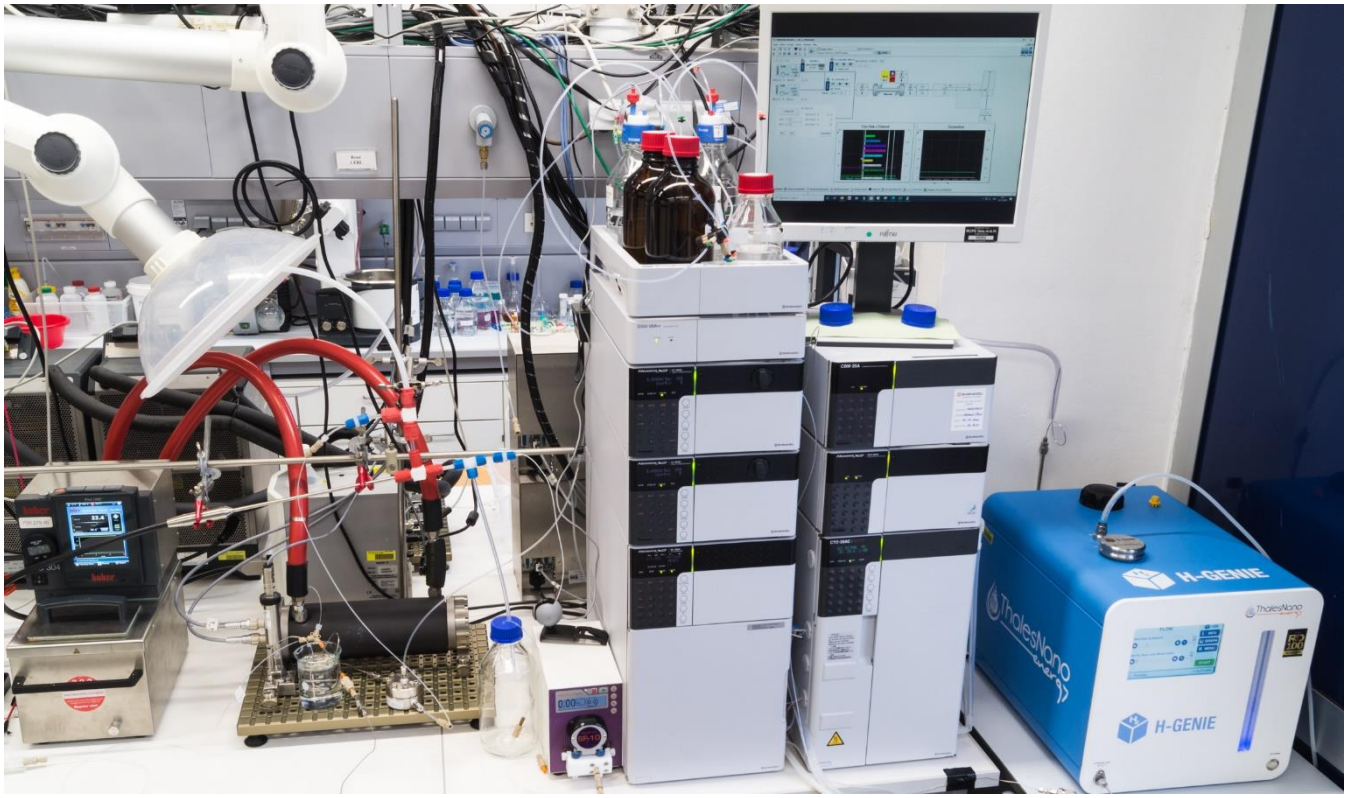


Figure S4. Photograph of the hydrogenation setup.

1.1.2. Connectivity

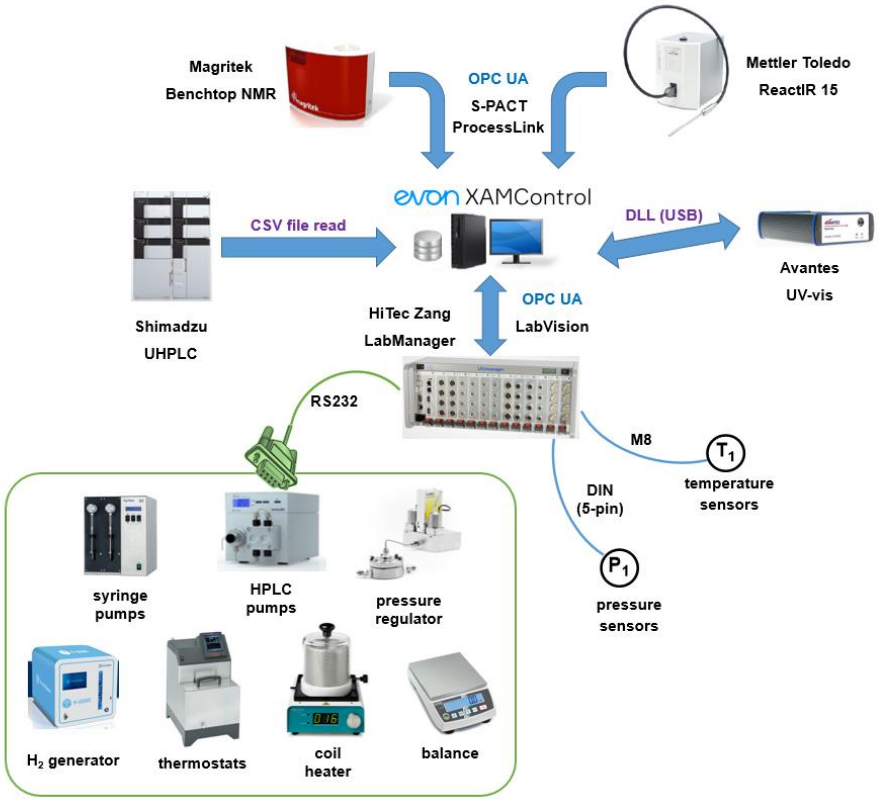


Figure S5. Diagram showing the connectivity of equipment used in this study, leading to a system fully integrated in XAMControl.

Table S1. List of equipment that was used in this study, its interfacing and communication with XAMControl.

Instrument Type	Make/model	Quantity	Interface	Communication with XAMControl
T sensor	Ehrfeld, 0501-2-1004-X	7	M8	Connection to LabManager, LabVision OPC UA server
P sensor	Ehrfeld, 0518-1-60x4-F	3	DIN 5-pin	Connection to LabManager, LabVision OPC UA server
Pump (syringe)	HiTec Zang, SyrDos2 90 bar	2	RS232	Connection to LabManager, LabVision OPC UA server
Pump (syringe)	HiTec Zang, SyrDos2 25 bar	3	RS232	Connection to LabManager, LabVision OPC UA server
Pump (HPLC)	Knauer, Azura P 4.1S	2	RS232	Connection to LabManager, LabVision OPC UA server
Pressure regulator	Bronkhorst, EL-PRESS	1	RS232	Connection to LabManager, LabVision OPC UA server
H_2 generator	Thales Nano Energy, H-Genie	1	RS232	Connection to LabManager, LabVision OPC UA server
Thermostat	Huber, Ministat 240	2	RS232	Connection to LabManager, LabVision OPC UA server
Thermostat	Huber, CC-304	1	RS232	Connection to LabManager, LabVision OPC UA server
Coil heater	Uniqsis, Hotcoil UQ1025-1	1	RS232	Connection to LabManager, LabVision OPC UA server
Balance	Kern, KB 2400-2N	1	RS232	Connection to LabManager, LabVision OPC UA server
NMR	Magritek, Spinsolve Ultra 43 MHz	1	USB	PEAXACT ProcessLink OPC UA
FTIR	Mettler-Toledo, ReactIR 15	1	USB	PEAXACT ProcessLink OPC UA
UV/vis	Avantes, AvaSpec-ULS2048	1	USB	DLL connection
UHPLC	Shimadzu, Nexera X2	1	Ethernet	Shimadzu LabSolutions, csv report

1.1.3. Control Software

XAMControl is a SCADA software platform for industrial automation. Different communication and field bus protocols are supported for the integration of actuators and sensors. The control of integrated actuators is executed via a cyclic code, which is comparable to PLC technology. The XAMControl platform supports .net DLLs (dynamic link libraries), which are stored in the database and loaded each time the application is started. This allows the integration of external libraries. The process flow sheet, including all sensors and actuators in XAMControl is shown below (**Figure S6**). Coding within XAMControl is done in the C# (C sharp) programming language. XAMControl also adds the possibility to track and plan predictive maintenance on equipment, by recording the time for which they have been in use. This is an important feature for industrial scale processing, to prevent failure during long term operation.

Integrating lab equipment into a single operating system is a significant challenge, especially on lab scale, due to the different communication protocols and connectivity used by different manufacturers. The use of OPC UA servers, communicating with a client (Softing GmbH, dataFEED, **Figure S7**) acts to greatly simplify these connections.

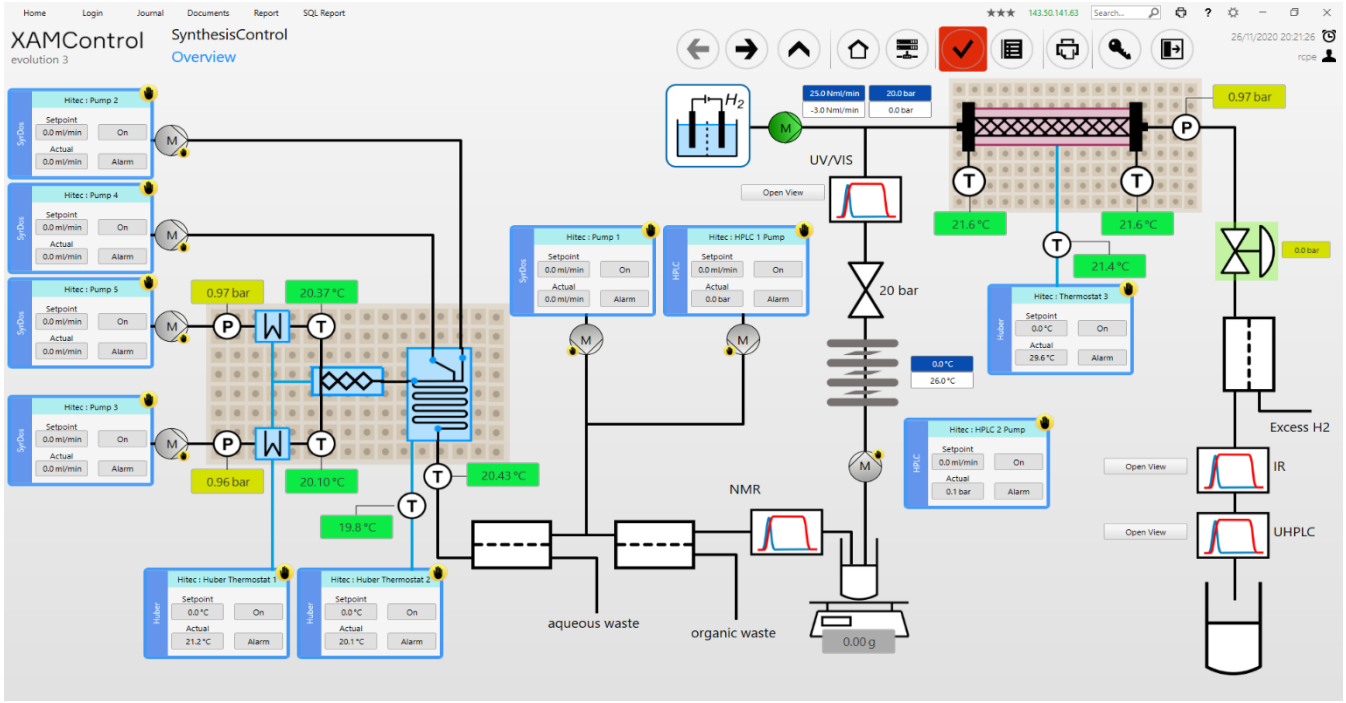


Figure S6. An overview of the telescoped process setup in XAMControl. All instruments can be monitored and adjusted directly from this view.

Figure S7. Screenshot showing a partial list of integrated components, connected to XAMControl via the dataFEED OPC UA client (Softing GmbH).

2. PAT Instrument Details

2.1. Inline NMR

2.1.1. General Details

Inline NMR reaction monitoring was accomplished by recording ^{1}H spectra using a low field benchtop 43.795 MHz NMR spectrometer (Magritek, Spinsolve Ultra 43 MHz). Shims were performed with the flow cell filled with either reaction mixture or an aqueous 0.5 M NaOH solution and referenced to the water peak at 5.00 ppm. Typically, a "QUICKSHIM: ALL" was performed in the Spinsolve software (Magritek) and shim values were below 0.4 Hz linewidth at 50%, below 7.5 Hz linewidth at 0.55% and a signal to noise ratio above 20,000.

The spectra were typically recorded in the reaction monitoring mode with a pulse angle of 90 °, acquisition time of 6.4 s, repetition time of 10.0 s and a single scan. The recorded spectra were automatically read and processed with an indirect hard model (for development of the model in PEAXACT, see Section 2.1.3) by ProcessLink (S-PACT). The obtained concentration prediction was provided by ProcessLink via OPC UA to the SCADA system (XAMControl, Evon). The total time for each measurement (including recording, saving, processing and transferring data) was roughly 10-12 s.

2.1.2. Process Integration

After the second phase separation, the entirety of the process stream (at this point, dissolved in aqueous NaOH) was analyzed by a benchtop NMR spectrometer. Prior to entering the NMR, a T-piece with a back pressure regulator (2.8 bar) was installed. In the case of a blockage (causing an increase in pressure) within the NMR flow-through cell, it would open to avoid any damage to the NMR instrument. The reaction mixture then entered a 6-port valve at port 4 (**Figure S8**). When in position P 1, the process stream left the valve through port 3 and went through the benchtop NMR glass flow-through cell (internal volume = 800 µL, length = 550 mm) and entered again at port 6. Finally, the process stream left for the next reaction step through port 5. The 6-port valve in position P 2 allowed the NMR to be shimmed on an aqueous 0.5 M NaOH solution, without disrupting the process stream.

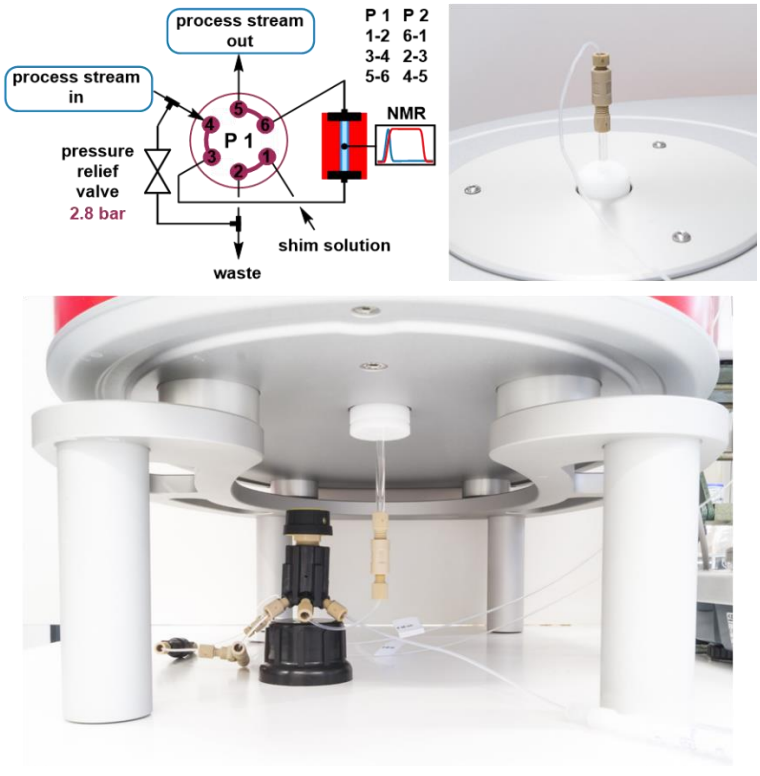


Figure S8. Annotated photo of the benchtop NMR instrument used for inline analysis.

2.1.3. Data Analysis Through Indirect Hard Modeling

Measurements of Training and Validation Solutions

Training and validation solutions were prepared by weighing the correct amounts of 2ClBA, 3N-2ClBA and 5N-2ClBA into a 10 mL volumetric flask. 200 µL of iPrOAc was added and the flask was filled with 0.5 M NaOH to the 10 mL mark (**Table S2**). The solutions were typically sonicated and stored in the fridge prior to use. The general measuring procedure was as followed (see Section 2.1.1.). The Knauer Azura HPLC pump, tubing and flow cell were purged with aqueous 0.5 M NaOH prior to flushing the system with 6 mL of the training or validation solution to avoid cross contamination. The solution was then circulated through the NMR with a flow rate of 1.0 mL/min (**Figure S9**). For each training or validation level, roughly 100 spectra were acquired.

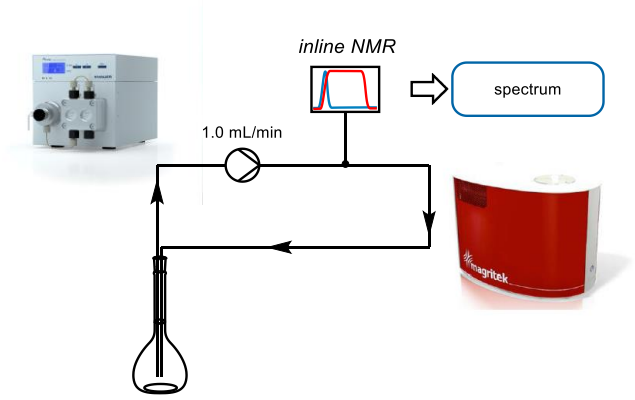


Figure S9. Setup for the NMR measurements, showing the NMR, Knauer HPLC pump and vessel filled with the respective training or validation solution.

Table S2. Overview of the prepared solutions for the training set (pure_2ClBA, pure_3N-2ClBA, pure_5N-2ClBA, Level_1 to Level_4) and validation set (Val_1 and Val_2).

Entry	2ClBA	3N-2ClBA	5N-2ClBA	[2ClBA]	[3N-2ClBA]	[5N-2ClBA]
	(g)	(g)	(g)	(M)	(M)	(M)
pure_2ClBA	0.2603	0	0	0.166	0	0
pure_3N-2ClBA	0	0.2998	0	0	0.149	0
pure_5N-2ClBA	0	0	0.3076	0	0	0.153
Level_1	0	0	0	0	0	0
Level_2	0.2381	0.0305	0.2446	0.15207	0.01513	0.12135
Level_3	0.3478	0.0493	0.1247	0.22214	0.02446	0.06187
Level_4	0.0138	0.0760	0.5149	0.00881	0.03771	0.25546
Val_1	0.0530	0.1102	0.4390	0.03385	0.05467	0.2178
Val_2	0.4716	0.0000	0.0000	0.30121	0	0

Building the Indirect Hard Model

Indirect hard modeling was carried out in PEAXACT 5.3 software (S-PACT), using the following workflow:

1. The acquired training set spectra (roughly 100 spectra per level) were read into PEAXACT and a single mean spectrum was calculated, resulting in one representative spectrum for each level.
2. Pretreatment model: All spectra were processed with the same pretreatment conditions: baseline correction (Straight Line Subtraction), phasing (Auto, Negative Peak Penalization), and spectral alignment of the highest peak (water) to 5.00 ppm. The global range was set from 6 to 9 ppm to avoid processing parts of the spectrum containing no relevant information.

3. Generation of pure component models: Peaks were added empirically and stepwise (8-12 peaks per pure component) to the model until the residuals were roughly below two orders of magnitude (~1%) with respect to the largest peak. The Fitting mode was set to maximal interaction, allowing the greatest flexibility within the model.
4. Generation of mixture model: A weighted sum of each pure component model represents the mixture model, including flexible but constrained peak parameters. The peak position was allowed to shift up to 0.25 ppm, in order to compensate for the different shifts in the recorded spectra, due to different NaOH concentrations.
5. Calibration model and validation: The training set was comprised of the pure component spectra and four different component mixtures (Level_1 to Level_4). The calibration model provided a performance indicator of model error, the root-mean-square error of calibration ($RMSE_C$). Additionally, to perform cross-validation (CV), the training set was divided into subgroups (k fold = 2) by concentration level. The CV algorithm generates reduced data sets to get a performance indicator of model error, the root-mean-square error of cross validation ($RMSE_{CV}$). To validate the model, the root-mean-square error of validation ($RMSE_V$) was calculated from the validation set. To explore the robustness of the model, the spectra for Val_1 were analyzed as single spectra (i.e. not averaged) and a prediction was performed on all of the recorded spectra. The predicted vs. true plots for the finalized models, including validation sets, are shown in **Figure S10**, with the relevant statistics appended.

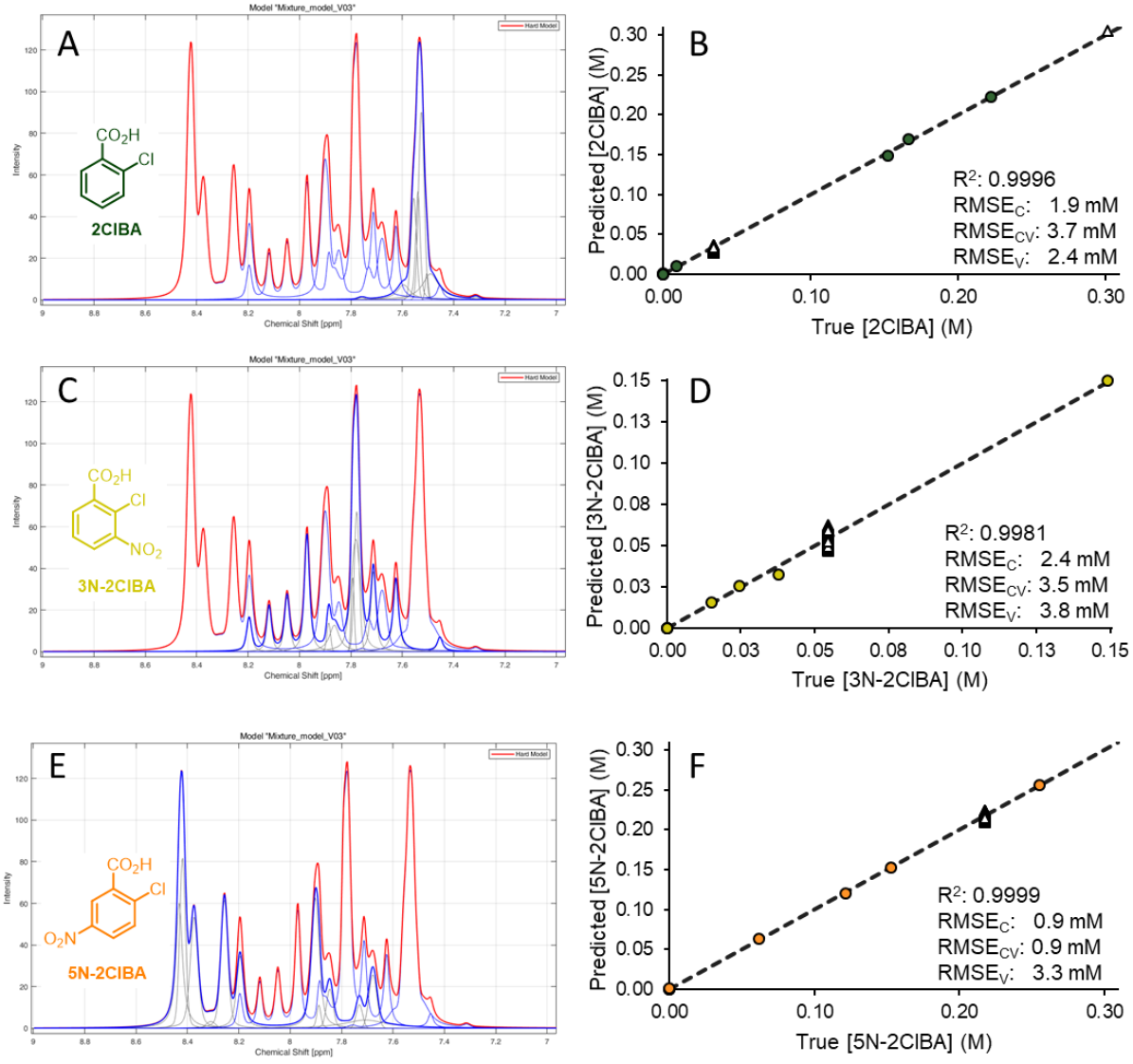


Figure S10. The overall mixture model is highlighted in spectra A, C and E (red). The pure component models (blue) are depicted for **2CIBA**, **3N-2CIBA** and **5N-2CIBA** in A, C and E, respectively. Predicted vs true plots for the IHM of each reaction component (B, D, F), with the target line (y = x) appended. Colored circles show the training set data, and white triangles show the validation set data. Key statistics are summarized next to each graph, demonstrating the fitting parameters and error ($RMSE_C$ error of calibration, $RMSE_{CV}$ error of cross validation, $RMSE_V$ error of validation).

2.1.4. Estimation of the NaOH concentration by NMR

The idea was to estimate the NaOH concentration by comparing the position of the water peak with the position of the iPrOAc singlet peak in the recorded NMR spectrum. The calibration data with different NaOH concentration was generated as followed. The input solution for pump 1 was prepared by dissolving 4.0329 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA, 6.451 g of NaOH and 2.9019 g of iPrOAc with H_2O in a 100 mL volumetric flask filled up to the mark with H_2O. The input solution for pump 2 was prepared dissolving 4.0337 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA, 1.6605 g of NaOH and 2.9310 g of iPrOAc with H_2O in a 100 mL volumetric flask filled up to the mark with H_2O. The flow rates of pump 1 and pump 2 were adjusted to change the NaOH concentration during the experiment (**Figure S11**). The mixture was then analyzed by inline NMR and the recorded spectra were processed with PEAXACT 5.3 software (S-PACT). All spectra were processed with the same pretreatment conditions: baseline correction (Linear Fit Subtraction), phasing (Auto, Negative Peak Penalization), and spectral alignment of the highest peak (water) to 5.00 ppm. The global range was set from 1 to 3 ppm to avoid processing parts of the spectrum containing no relevant information. An indirect hard model was used to analyses the peak position of iPrOAc. In total three peaks were added to the IHM to fit the spectrum of iPrOAc (**Figure S12**). The peak position was allowed to shift up to 0.3 ppm, in order to compensate the different NaOH concentrations. The position of the iPrOAc singlet was plotted against the concentration of the NaOH. After removal of outliers the correlation was analyzed with a linear regression (**Figure S13**).

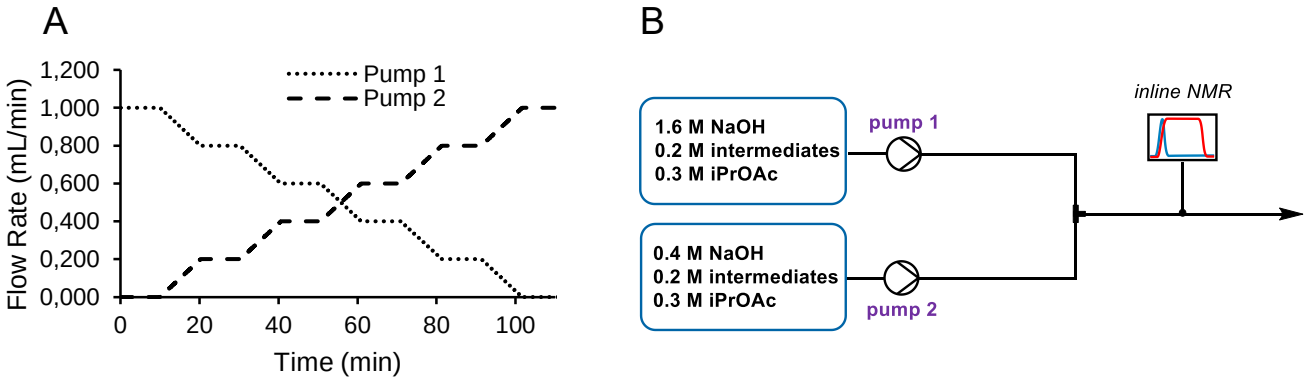


Figure S11. **A)** Flow rates of pump 1 and pump 2 during the recording of the calibration data. **B)** Flow setup for the recording of calibration data.

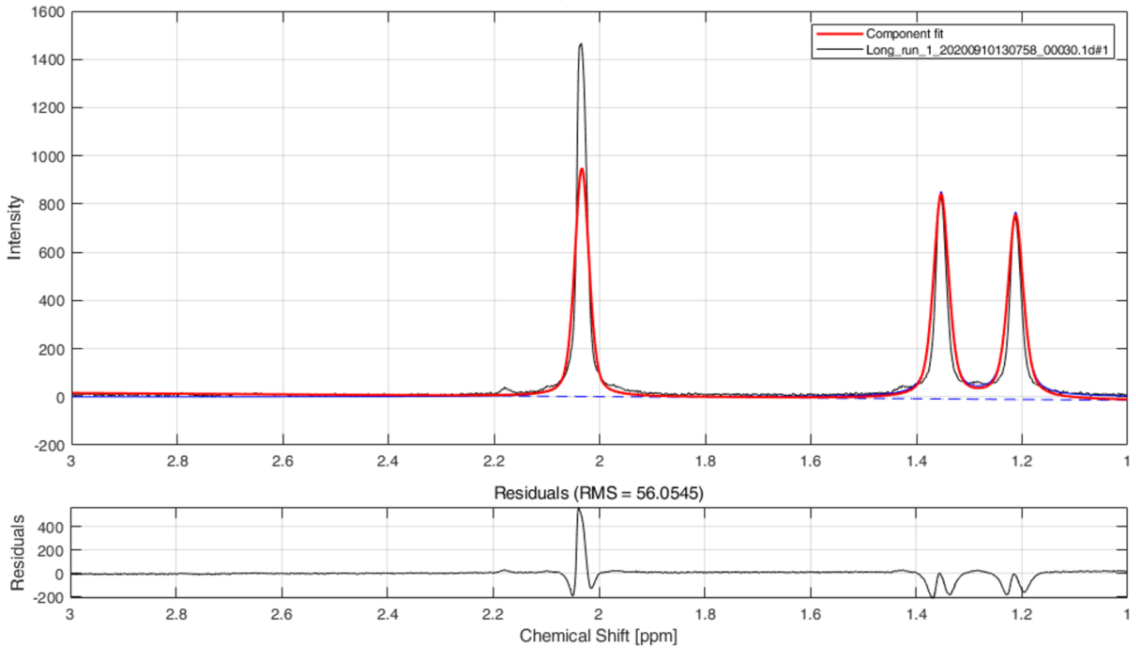


Figure S12. Indirect hard model (red) of a recorded iPrOAc spectrum (black).

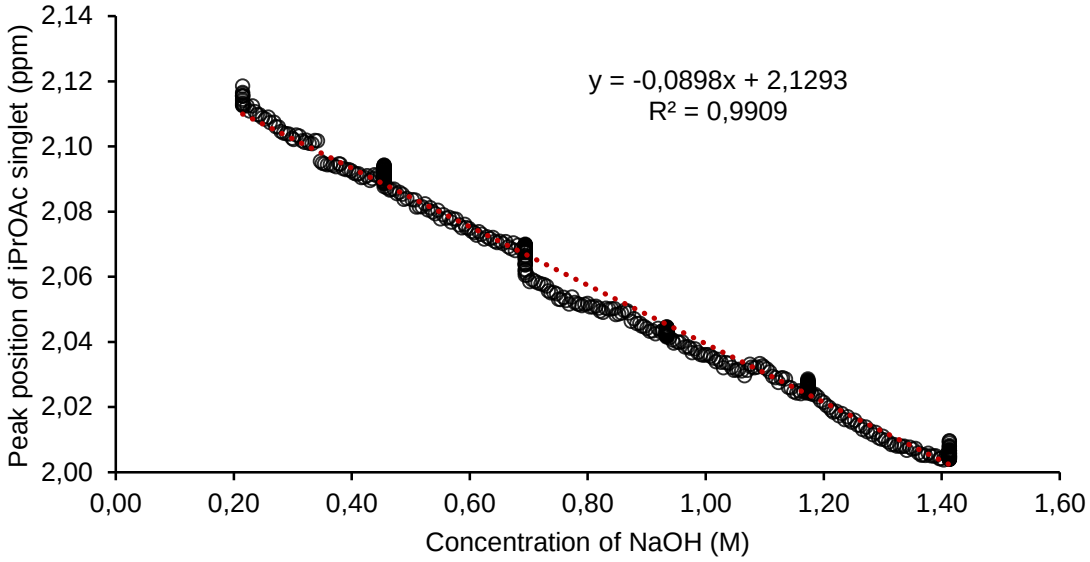


Figure S13. Calibration curve for estimating the NaOH concentration by the peak position of iPrOAc.

2.2. Inline UV/Vis

2.2.1. General Details

Inline UV/Vis spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-ULS2048 spectrometer, with an Avantes AvaLight-DHc lamp as light source. The spectrometer was connected via USB and was initially controlled using Avasoft 8.7 software. The integration time was set to 20 ms and an average of 100 measurements was used per data point, resulting in a sampling time of 2 s. Using both the deuterium and the halogen lamp, the range between λ 199 – 769 nm was recorded. Before each experiment in continuous mode, a single background reference (light source turned off) and a single solvent spectrum were saved and used for data processing. These features which are included in the Avasoft 8.7 software, were also implemented into XAMControl via DLL, using a USB connection.

2.2.2. Process Integration

For the implementation of inline UV/Vis absorption analysis, several limiting constraints had to be considered, including: the corrosive nature of the process stream, the low transmittance of the undiluted reaction mixture and the elevated pressure required for the downstream hydrogenation (12 bar). In addition, a low volume is required to prevent additional broadening of the residence time distribution and to ensure rapid equilibration of the analyzed reaction mixture. Therefore, a four-way connector made from PEEK was adapted to pass a transparent 1.6 mm o.d. PFA tubing (0.8 mm i.d.) through. Perpendicular to the transparent tubing, two optical 400 µm waveguides from Avantes (FC-UV400-1-SR-FIA) were attached (from the light source and to the detector respectively), to measure the absorbance through the PFA tubing, resulting in a maximum optical path of only 0.8 mm. Using this setup, any exposure to the corrosive, pressurized reaction stream could be eliminated and no additional hold-up volume was created. However, due to the poor resulting signal to noise ratio with this “shine through” approach, one bifurcated fiber-based reflection probe (FCR-7UVIR200-2-1.5x100) was mounted perpendicularly to the PFA tube (**Figure S14**). This flow cell was installed after the BPR of the hydrolysis step and before the gas-liquid mixing point of the hydrogenation.

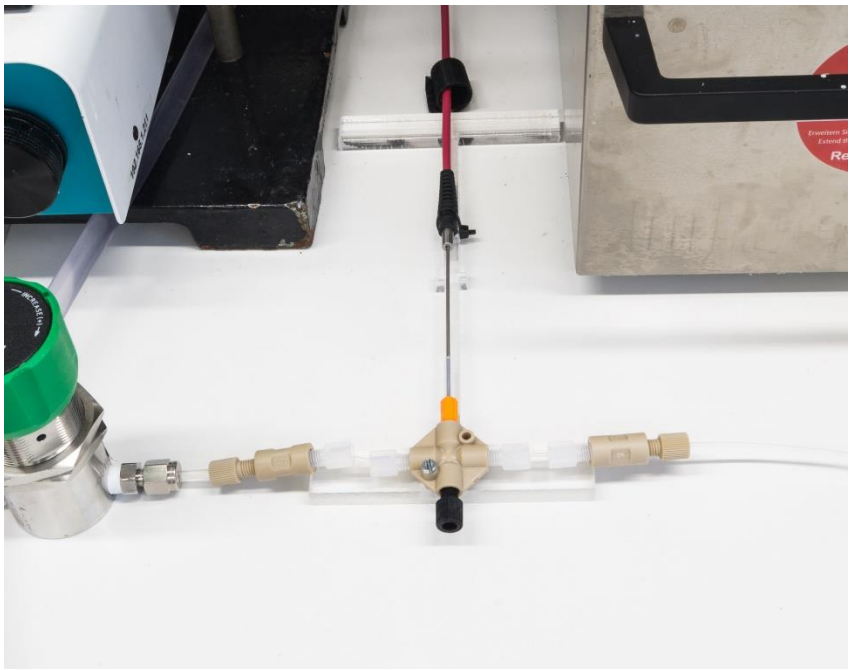


Figure S14. Photograph of the optical reflection flow cell for inline UV/Vis absorption measurements.

2.2.3. Data Analysis Through Neural Network

Measurements of Training and Validation Solutions

Training and validation data was acquired either from diluting pure components to mixture samples (**Table S3**), temperature ramps from 20 °C to 210 °C of the hydrolysis step, to provide 0-100% conversion of the input material (**Figure S75** and **Figure S76**) and pre-existing process data. The data was randomized and 25% of the data was used for validation.

Table S3. Overview of the prepared solutions for the training set.

Entry	[2ClBA] (M)	[3N-ClBA] (M)	[5N-2ClBA] (M)	[3-NSA] (M)	[5-NSA] (M)
Mixture_1	0.152	0.015	0.121	0.000	0.000
Mixture_2	0.034	0.055	0.218	0.000	0.000
Mixture_3	0.222	0.024	0.062	0.000	0.000
Mixture_4	0.009	0.038	0.255	0.000	0.000
Mixture_5	0.007	0.004	0.009	0.073	0.241
Mixture_6	0.004	0.021	0.097	0.036	0.145
Mixture_7	0.000	0.038	0.166	0.018	0.073

Preprocessing of the Data and Building the Neural Network

The results from the NMR were smoothed using a Savitzky-Golay filter (window of 25 and 3rd order polynomial treatment), normalized, and fed forward by the difference in residence time between the two instruments (20 min). The obtained UV/vis spectrum (2048 data points) was normalized and the range was reduced to 242 nm to 768 nm (1900 data points). Additionally, to reduce the inputs of the neural network every 20 values were averaged (corresponding to 5-6 nm) providing 95 data points as inputs. The layers in the entire neural network were connected with the ReLu function (**Figure S15**). In the first neural network the 95 inputs of the UV/vis were projected as 95 neurons and further reduced to 64 and 32 neurons. The NMR input of 3N-2ClBA and 5N-2ClBA was merged with the last 32 neurons of the first neural network and then interpreted. For interpretation, the second neural network started with 34 neurons and was further reduced to 18, then 8 and 4 neurons. The last 4 neurons should already represent the concentration of 3N-2ClBA, 5N-2ClBA, 3-NSA and 5-NSA. This output was then merged with the NMR input of 2ClBA providing the final model output. In total 19,352 parameters could be trained for the training parameters of the different levels (**Figure S16**). Typically, 5000 epochs, a batch size of 5000, and the Adam optimization algorithm was used for each iteration of training. The model with the best validation loss (based on mean square regression) was saved. Additionally, during training different regularizer penalties and layer weight constrains were tested. For the best model a loss of 7.4×10^{-5} and an accuracy of 0.974 could be achieved. The errors for 3N-2ClBA, 5N-2ClBA, 3-NSA and 5-NSA were <1.0 mM, 2.9 mM, <1.0 mM and 2.8 mM, respectively. It must be considered that the error of the UV measurement at a specific time point should include the error of the NMR model output as well. The predicted vs. true plots for the finalized models, including validation sets, are shown in **Figure S17**.

```
#%% define the model
model_path_name = 'MI_UV_NMR_process_4.hdf5'
# input from NMR 2ClBA
NMR1 = Input(shape=(1,))
# input from NMR 3N-2ClBA and 5N-2ClBA
NMR2 = Input(shape=(2,))
# input from UVvis measurements & 1st NN
UVvis = Input(shape=(95,))
hidden11 = Dense(95,activation='relu')(UVvis)
hidden12 = Dense(64, activation='relu', kernel_regularizer=l2(0.1), bias_regularizer=l2(0.1))(hidden11)
model1 = Dense(32, activation='relu')(hidden12)
# merge NMR results from 3N-2ClBA and 5N-2ClBA and outputs of 1st NN
merge1 = concatenate([NMR2, model1])
# interpretation model  = 2nd NN
hidden21 = Dense(34, kernel_constraint=maxnorm, activation='relu')(merge1)
hidden22 = Dense(18, activation='relu')(hidden21)
hidden23 = Dense(8, activation='relu')(hidden22)
model2 = Dense(4, activation='relu')(hidden23)
# merge NMR results from 2ClBA and outputs of 2nd NN
output = concatenate([NMR1, model2])
model = Model(inputs=[NMR1, NMR2, UVvis], outputs=output)

# summarize layers
print(model.summary())

# compile the keras model
model.compile(loss='mse', optimizer='adam', metrics=['accuracy'])
# checkpointer
learning = ReduceLROnPlateau(monitor='val_loss', factor=0.2, patience=20, min_lr=0.001)
checkpointer = ModelCheckpoint(filepath = model_path_name, monitor='val_loss', verbose=1, save_best_only=True)

#train the model with validation split
Epochs = 5000
hist = model.fit([NMR1_train, NMR2_train, UVvis_train], Y_random_train, epochs=Epochs, batch_size=5000,
                 verbose=1, validation_split = 0.25 , callbacks=[checkpointer, learning])
```

Figure S15. Python code for the neural network.

Layer (type)	Output Shape	Param #	Connected to
input_21 (InputLayer)	(None, 95)	0	
dense_43 (Dense)	(None, 95)	9120	input_21[0][0]
dense_44 (Dense)	(None, 64)	6144	dense_43[0][0]
input_20 (InputLayer)	(None, 2)	0	
dense_45 (Dense)	(None, 32)	2080	dense_44[0][0]
concatenate_13 (Concatenate)	(None, 34)	0	input_20[0][0] dense_45[0][0]
dense_46 (Dense)	(None, 34)	1190	concatenate_13[0][0]
dense_47 (Dense)	(None, 18)	630	dense_46[0][0]
dense_48 (Dense)	(None, 8)	152	dense_47[0][0]
input_19 (InputLayer)	(None, 1)	0	
dense_49 (Dense)	(None, 4)	36	dense_48[0][0]
concatenate_14 (Concatenate)	(None, 5)	0	input_19[0][0] dense_49[0][0]

Total params: 19,352
Trainable params: 19,352
Non-trainable params: 0

Figure S16. Summary of the model showing the trainable parameters for each layer.

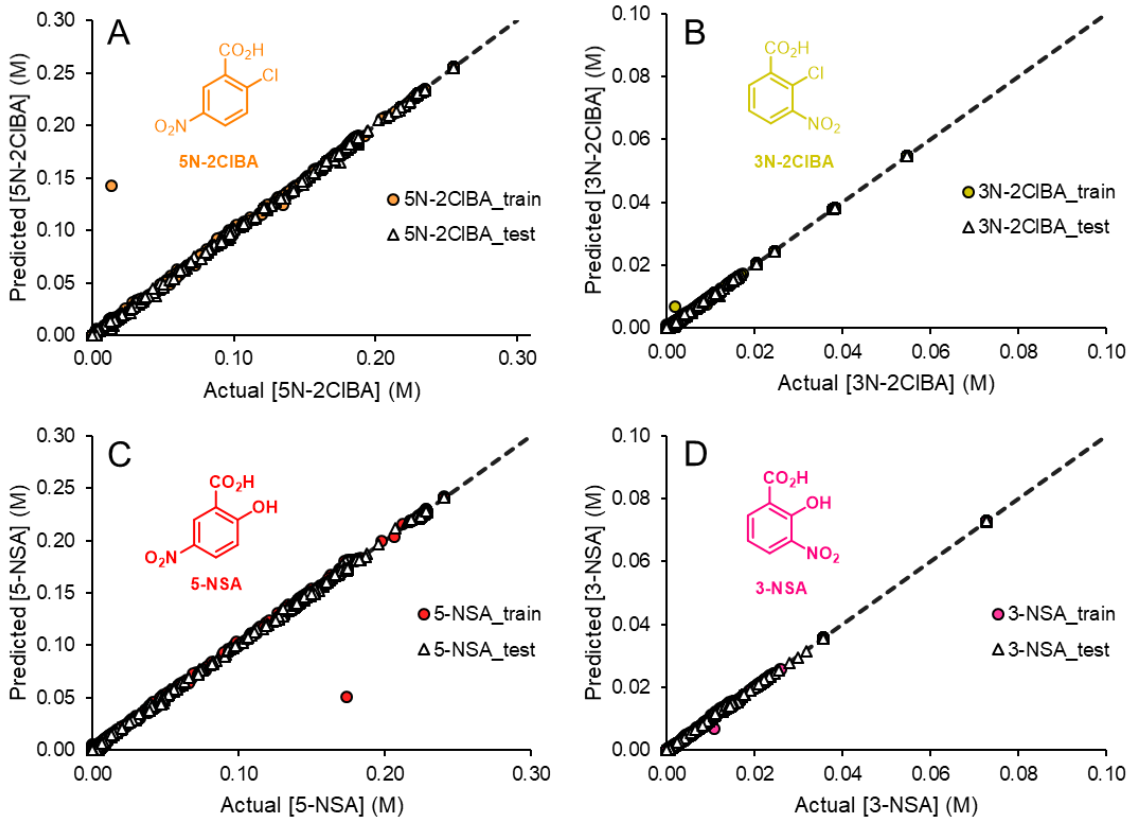


Figure S17. Predicted vs true plots for the NN of each reaction component (A, B, C, D), with the target line (y = x) appended. Colored circles show the training set data, and white triangles show the validation set data.

2.3. Inline IR

2.3.1. General Details

Inline FT-IR spectra were recorded on a ReactIR 15 instrument (Mettler Toledo, ReactIR 15) equipped with an AgX 9.5 mm fiber and a DiComp (Diamond composite) probe. The acquisition time for each data point was 15 s and spectra were recorded between 2500 and 900 cm^{-1} using the maximum resolution of 4 cm^{-1}. Prior to starting the experiments it was ensured that the MCT detector was initially warmed up (>4h), then cooled with liquid nitrogen, the signal to noise ratio was above 5000 and the peak height was between 18000 and 24000.

2.3.2. Process Integration

For inline monitoring of the process stream after the hydrogenation reaction, the IR probe was implemented directly after the atmospheric gas-liquid separator. The gas-liquid separator was constructed from a PTFE T-connector (10.5 mm bore), which was mounted vertically and could be filled with glass wool or PP cones to impede the flow path and reduce the velocity of the liquid phase. The biphasic gas-liquid stream was introduced at the sideward connection, excess hydrogen was allowed to escape through the upper tubing (leading to an extractor), and the liquid stream was allowed to flow downwards into a second PTFE T-connector. This second T-connector (6.5 mm bore) was mounted in a horizontal position, with an inclination of about 10°. The ReactIR probe was inserted at the downward facing end (left in **Figure S18**), and the reaction solution was allowed to overflow through the upper end (bottom right in **Figure S18**). Using this setup the liquid output of the hydrogenation reaction could be continuously monitored without any interfering gas bubbles with a minimal hold-up volume. Additionally, a smaller PTFE tube (0.8 mm o.d., 0.3 mm i.d., 2 × 80 cm length) was used to continuously withdraw a stream for online UHPLC sampling, which is further discussed in section 2.4.2.

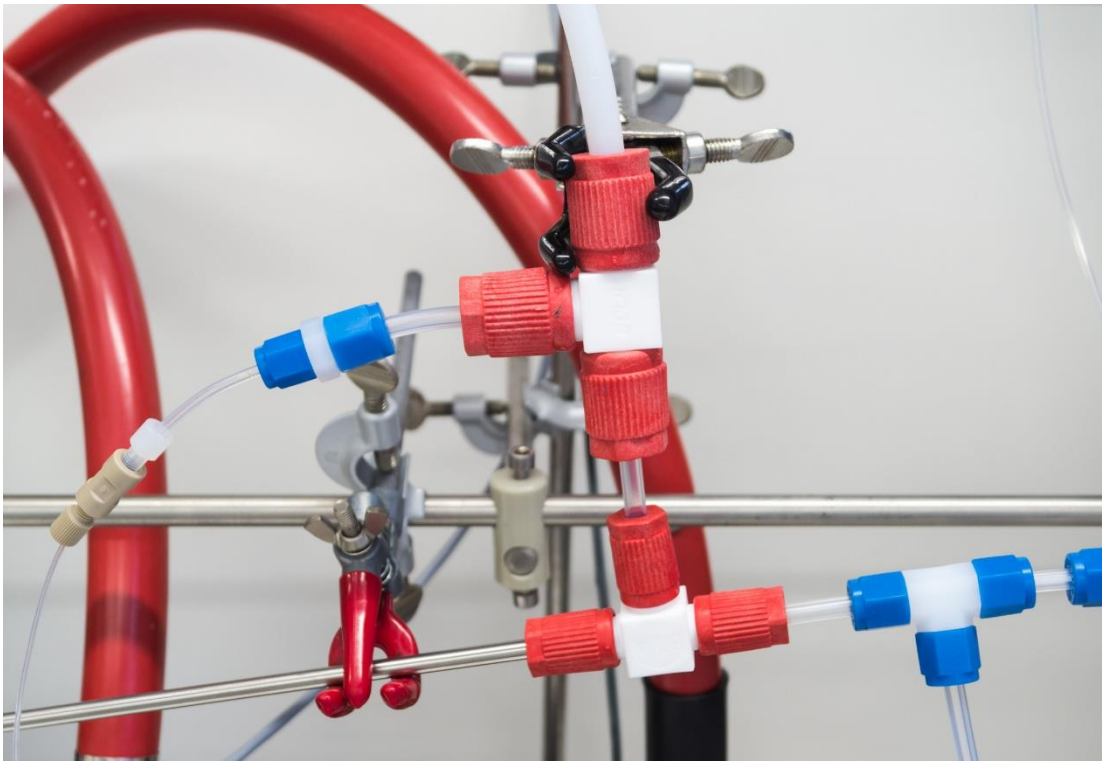


Figure S18. Photograph of the G/L separator with an attached IR probe and the additional UHPLC sampling tubing.

2.3.3. Data Analysis Through Indirect Hard Modeling

Measurements of Training Set and Validation Set Solutions

Training and validation set solutions were prepared by weighing the correct amounts of 2ClBA, 3N-2ClBA, 5N-2ClBA, 3-NSA, 5-NSA, 3A-2ClBA, 5A-2ClBA, 3-ASA, 5-ASA into 10 mL or volumetric flask, with 0.5 M NaOH to the 10 mL mark (**Table S4**). The solutions were typically sonicated and stored in the fridge prior to use. The general measuring parameters (listed above) were used.

Table S4. Overview of the prepared solutions for the training set (pure_5-ASA, pure 3-ASA, pure 5A-2ClBA, pure 3A-2ClBA, pure_5-NSA, pure_3-NSA, pure_5N-2ClBA, pure_3N-2ClBA, pure_2ClBA and Level_0 to Level_7).

Entry	[5-ASA] (M)	[3-ASA] (M)	[5A-2ClBA] (M)	[3A-2ClBA] (M)	[5-NSA] (M)	[3-NSA] (M)	[5N-2ClBA] (M)	[3N-2ClBA] (M)	[2ClBA] (M)
pure_5-ASA	0.146	0	0	0	0	0	0	0	0
pure_3-ASA	0	0.1451	0	0	0	0	0	0	0
pure_5A-2ClBA	0	0	0.143	0	0	0	0	0	0
pure_3A-2ClBA	0	0	0	0.145	0	0	0	0	0
pure_5-NSA	0	0	0	0	0.149	0	0	0	0
pure_3-NSA	0	0	0	0	0	0.149	0	0	0
pure_5N-2ClBA	0	0	0	0	0	0	0.153	0	0
pure_3N-2ClBA	0	0	0	0	0	0	0	0.149	0
pure_2ClBA	0	0	0	0	0	0	0	0	0.166
Level_0	0	0	0	0	0	0	0	0	0
Level_1	0.2975	0.000784	0.01907	0.007693	0.002665	0.004194	0.030423	0.075174	0.009453
Level_2	0.151495	0.001828	0.013615	0.01513	0.004128	0.297641	0.060191	0.037785	0.005263
Level_3	0.076218	0.003657	0.009185	0.030353	0.007798	0.150328	0.001072	0.019309	0.300671
Level_4	0.037299	0.007078	0.298963	0.060124	0.014548	0.076234	0.001985	0.010022	0.151344
Level_5	0.018676	0.014941	0.150274	0.001142	0.029118	0.038314	0.004088	0.00516	0.074829
Level_6	0.010004	0.029489	0.074484	0.001958	0.059961	0.019725	0.007601	0.299742	0.037632
Level_7	0.004493	0.059815	0.037137	0.00394	0.001311	0.01066	0.015201	0.150585	0.01926

Table S5. Overview of the process samples added to the PLS training data, and used for validation. Concentrations were determined at steady state by online UHPLC analysis. Calibration samples were used individually (100 or 200 spectra), whilst validation samples were combined and calculated as a single mean spectrum.

Entry	[5-ASA] (M)	[3-ASA] (M)	[5A-2ClBA] (M)	[3A-2ClBA] (M)	[5-NSA] (M)	[3-NSA] (M)	[5N-2ClBA] (M)	[3N-2ClBA] (M)	[2ClBA] (M)
calibration_1	0	0	0	0	0	0	0	0	0
calibration_2	0.1653	0.00857	0.01171	0	0	0	0	0.00457	0.0139
calibration_3	0	0	0	0	0	0	0	0	0
validation_1	0.18	0.012	0.024	0.002	0	0	0.001	0.004	0
validation_2	0.169	0.011	0.015	0	0	0	0	0.004	0.007
validation_3	0.165	0.008	0.012	0	0	0	0	0.004	0.017
validation_4	0.137	0.008	0.01	0	0	0.027	0	0.003	0.018
validation_5	0.082	0.006	0.058	0.017	0	0	0	0	0.007
validation_6	0.045	0.007	0.008	0	0.001	0.107	0.001	0	0
validation_7	0.147	0.007	0.012	0	0	0	0.001	0.006	0
validation_8	0.16	0.011	0.014	0	0	0	0.001	0.005	0.007
validation_9	0.164	0.009	0.015	0	0	0	0.002	0.003	0.008
validation_10	0.16	0.011	0.015	0	0	0	0.002	0	0.008

Building the Indirect Hard Model

Indirect hard modeling was carried out using the software PEAXACT 5.3 (S-PACT) and the following workflow was used.

1. The acquired training and validation set spectra (roughly 120 spectra per level) were read into PEAXACT as SPC format and a mean average was calculated to provide one representative spectrum for each level.
2. Pretreatment model: All spectra were processed with the same pretreatment conditions. For baseline correction a rubberband subtraction was chosen. The global range was set from 1600 to 1020 cm^{-1}, to avoid processing parts of the spectrum without relevant information.
3. Generation of pure component models: Peaks were added empirically and stepwise (15-25 peaks per pure component) to the model until the residuals were below roughly two order of magnitude (~1-2%) compared to the largest peak. The fitting mode was initially set to minimum interaction, but then increased to medium interaction, allowing a higher flexibility within the model.
4. Generation of mixture model: A weighted sum of each pure component model represents a mixture model, including medium flexibility in the peak parameters. The peak position was allowed to shift by ± 30 wavenumbers.
5. Calibration model and validation: The training set was comprised of the pure component spectra and eight different component mixtures (Level_0 to Level_7). The calibration model provided a performance indicator of model error, the root-mean-square error of calibration ($RMSE_C$). Additionally, to perform cross-validation (CV), the training set was divided into subgroups (k fold = 3) by concentration level. The CV algorithm generates reduced data sets to get a performance indicator of model error, the root-mean-square error of cross validation ($RMSE_{CV}$). To validate the model the root mean square error of validation ($RMSE_V$) was calculated from the validation set. The errors values of the best indirect hard model approach are listed in **Table S6**.

Due to the apparent difficulties for the best indirect hard model to predict some of the analyte concentrations (especially of the target molecule 5-ASA), a Partial Least Squares (PLS) regression model was developed instead.

Table S6. Key statistics for the indirect hard model approach to calculate compound concentrations from IR data. Errors are described for each compound in mM ($RMSE_C$ error of calibration, $RMSE_{CV}$ error of cross validation, $RMSE_V$ error of validation).

Compound	Range (M)	R^2	$RMSE_C$ (mM)	$RMSE_{CV}$ (mM)	$RMSE_V$ (mM)
5-ASA	0-0.297453	0.7857	43.5	45.4	35.4
3-ASA	0-0.161	0.9275	13.3	14.8	9.1
5A-2ClBA	0-0.298963	0.9843	11.7	15.7	13.7
3A-2ClBA	0-0.145	0.7679	21.6	27.8	3.0
3-NSA	0-0.149	0.8920	15.1	16.2	10.8
5-NSA	0-0.297641	0.9981	4.1	7.8	1.1
3N-2ClBA	0-0.149	0.9503	10.2	18.1	13.2
5N-2ClBA	0-0.299742	0.9671	17.2	18.6	4.6
2ClBA	0-0.300671	0.7115	51.8	53.1	8.4

2.3.4. Data Analysis Through Partial Least Squares (PLS) Regression

A PLS model was built in PEAXACT 5.3 software (S-PACT), using the following workflow:

1. The acquired training set spectra (roughly 100 spectra per level) were read into PEAXACT.
2. All spectra were processed with the same pretreatment conditions: baseline correction (rubberband), smoothing/derivative (1st order derivative with a filter length of 5). The global range was set from 1600 to 1020 cm^{-1} to avoid processing parts of the spectrum containing no relevant information, or heavily overlapping signals. Additionally, the following regions were removed, to remove peaks arising from iPrOAc: 1560-1540; 1425-1400; 1100-1130 cm^{-1}.
3. Calibration model: The pure component spectra were found to be detrimental to the model in this case (assumedly due to shifts in the spectra caused by interactions with other components), so were not used. The training set was made up of the seven levels (detailed above), as well as two sets of solvent background spectra and a set of representative process samples taken from previously collected process data (a total of 1750 spectra). The calibration model provided a performance indicator of model error, the root-mean-square error of calibration ($RMSE_C$). Additionally, to perform cross-validation (CV), the training set was divided into subgroups (k fold = 2) by concentration level. The CV algorithm generates reduced data sets to get a performance indicator of model error, the root-mean-square error of cross validation ($RMSE_{CV}$).
4. Validation: Using process data, with a steady state concentration verified by UHPLC analysis, ten mixture levels were created as mean spectra (mean of ~100 spectra). Concentration predictions for these samples were compared with the UHPLC measured (“true”) concentration. To validate the model, the root-mean-square error of validation ($RMSE_V$) was calculated.

The predicted vs. true plots for the finalized models, including validation sets, are shown in **Figure S20** to **Figure S22**, with the relevant statistics appended.

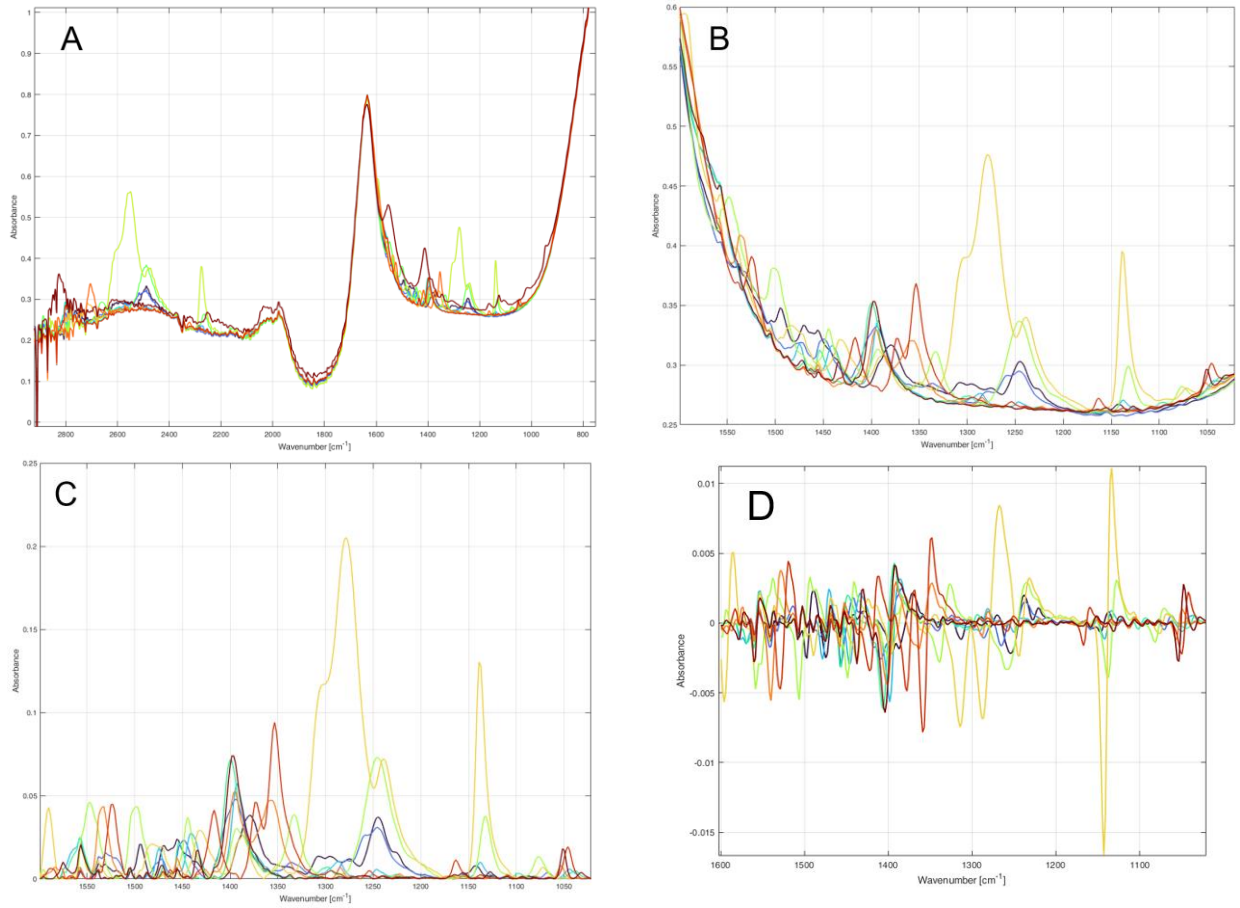


Figure S19. An overview of the pretreatment performed for the construction of IR PLS models, showing all overlaid individual component spectra. **A:** Full spectra with no pretreatment applied. **B:** Spectra after reducing the global range to 1600-1020 cm^{-1}. **C:** Spectra after applying a "rubberband" baseline correction. **D:** Spectra after applying a first derivative transformation.

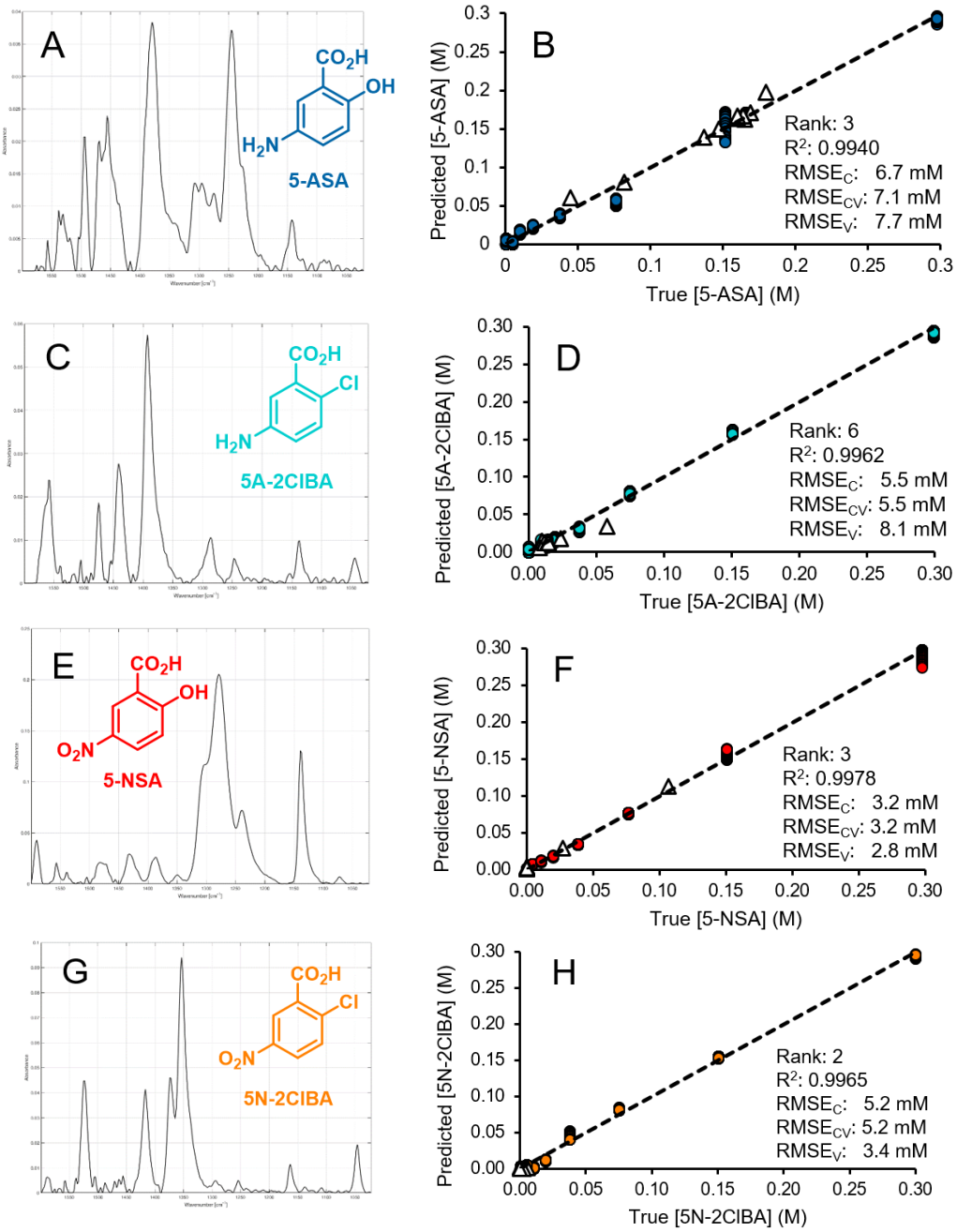


Figure S20. Individual IR spectra of 5-substituted reaction components, after pretreatment (A, C, E, G). Graphs showing the true vs predicted concentrations for the PLS model of each species (B, D, F, H). Colored circles show the training set data, and white triangles show the validation set data. Key statistics are summarized next to each graph, demonstrating the fitting parameters and error ($RMSE_C$ error of calibration, $RMSE_{CV}$ error of cross validation, $RMSE_V$ error of validation).

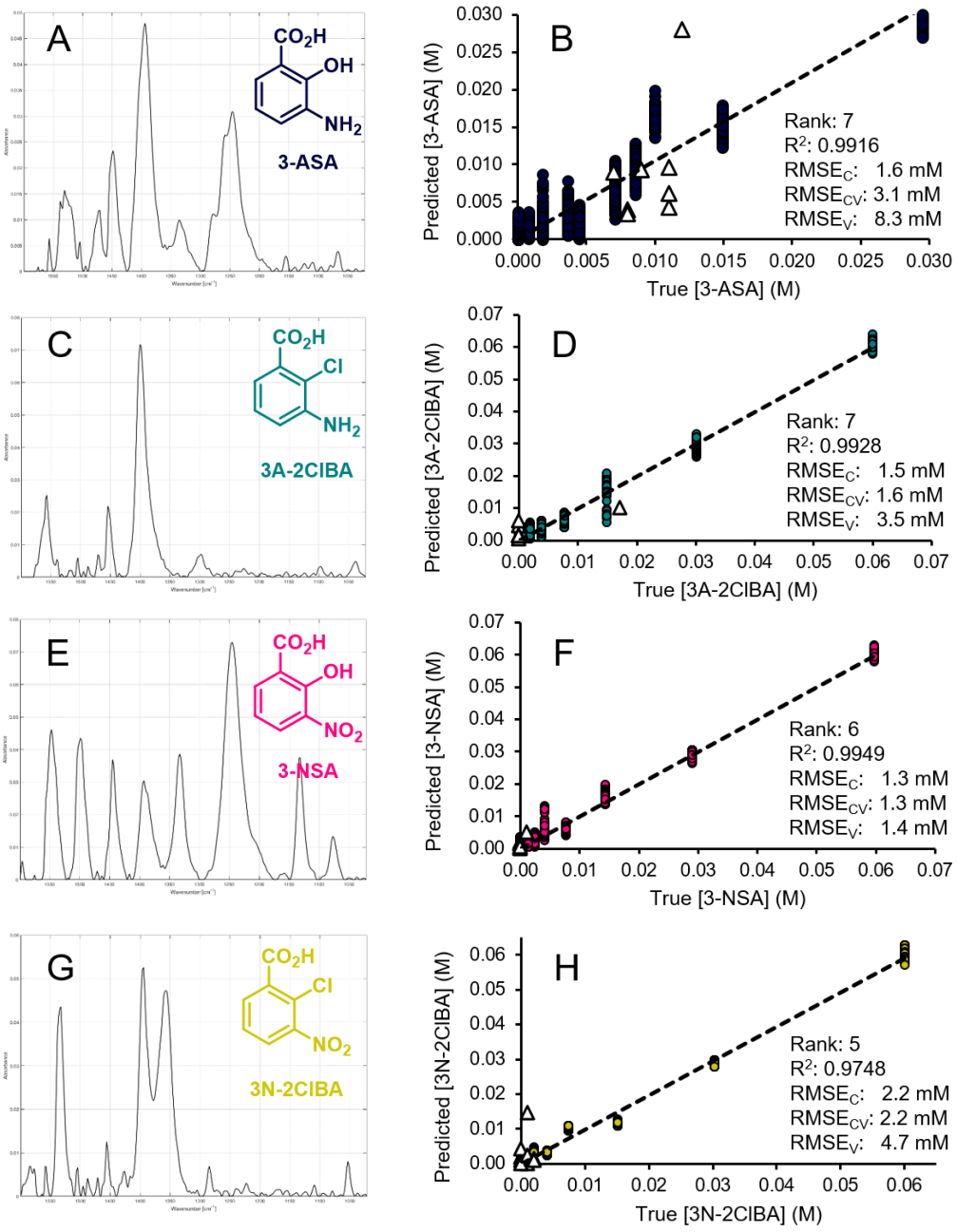


Figure S21. Individual IR spectra of 3-substituted reaction components, after pretreatment (A, C, E, G). Graphs showing the true vs predicted concentrations for the PLS model of each species (B, D, F, H). Colored circles show the training set data, and white triangles show the validation set data. Key statistics are summarized next to each graph, demonstrating the fitting parameters and error ($RMSE_C$ error of calibration, $RMSE_{CV}$ error of cross validation, $RMSE_V$ error of validation).

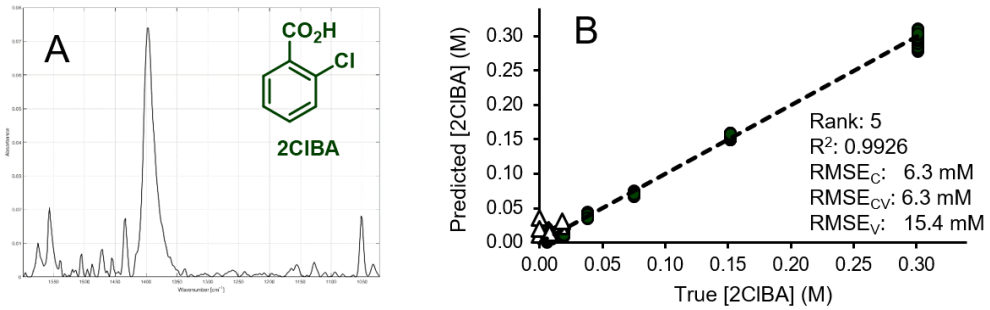


Figure S22. Individual IR spectrum of 2ClBA starting material, after pretreatment (A). Graphs showing the true vs predicted concentration for the PLS model (B). Colored circles show the training set data, and white triangles show the validation set data. Key statistics are summarized next to each graph, demonstrating the fitting parameters and error ($RMSE_C$ error of calibration, $RMSE_{CV}$ error of cross validation, $RMSE_V$ error of validation).

2.4. Online UHPLC

2.4.1. General Details and Final Method

The UHPLC-DAD (Shimadzu Nexera X2) was comprised of a degassing unit (DGU-20A), two solvent delivery units (LC-30AD), a thermostated autosampler (SIL-30AD), thermostated column oven (CTO-20AC), diode array detector (SPD-M30A) and a control unit (CBM-20A). The analysis was carried out on a Phenomenex Kinetex Biphenyl reversed-phase analytical column (100 × 2.1 mm, particle size 1.7 µm, pore size 100 Å) at 45 °C using mobile phase A (H_2O + 5 mM H_3PO_4 + 5 mM KH_2PO_4 + 0.33 mM sodium *n*-octylsulfate) and B (MeOH + H_2O (2 + 1 v/v) + 5 mM H_3PO_4 + 5 mM KH_2PO_4 + 0.33 mM sodium *n*-octyl sulfonate) at a flow rate of 0.5 mL/min. The buffer solution was freshly prepared on a daily basis and filtered through 0.2 µm nylon filters. Compounds were eluted with the following gradient: starting with 3% B, increasing to 45% B over 2.5 min, holding at 45% B for 1.2 min, increasing to 60% B over 0.5 min, holding at 60% B for 0.3 min, decreasing to 3% B over 0.01 min and equilibrating the column with 3 % B for 2.99 min (= 7.5 min total acquisition time). Chromatograms were recorded at a wavelength of 229 nm. Representative chromatograms for online mode is shown in **Figure S23** and for offline mode in **Figure S24**. The online calibration graphs are provided for each compound in **Figure S25** to **Figure S33**.

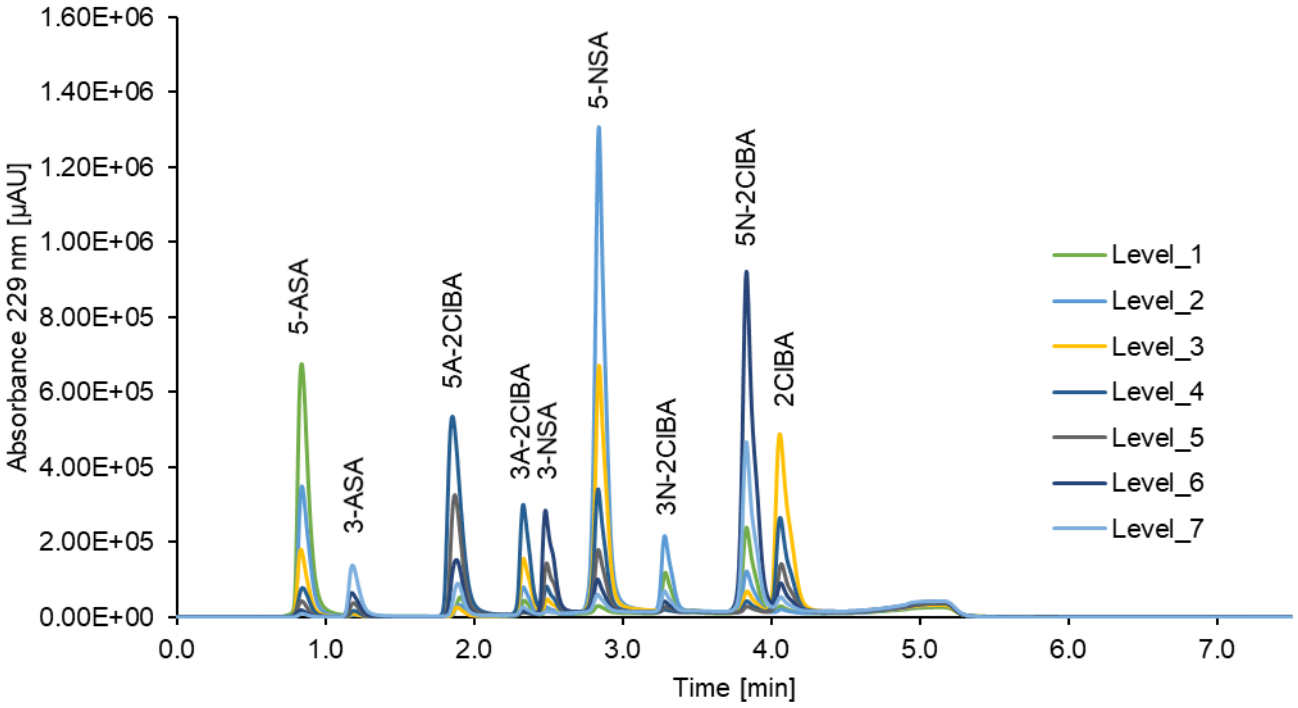


Figure S23. Example chromatograms of 7 different mixtures containing different levels of the 9 target analytes in 0.001 - 0.301 mol/L concentrations. The mixtures were prepared from commercially available samples and were injected without additional dilution using the 10 nL internal sample loop for online analysis.

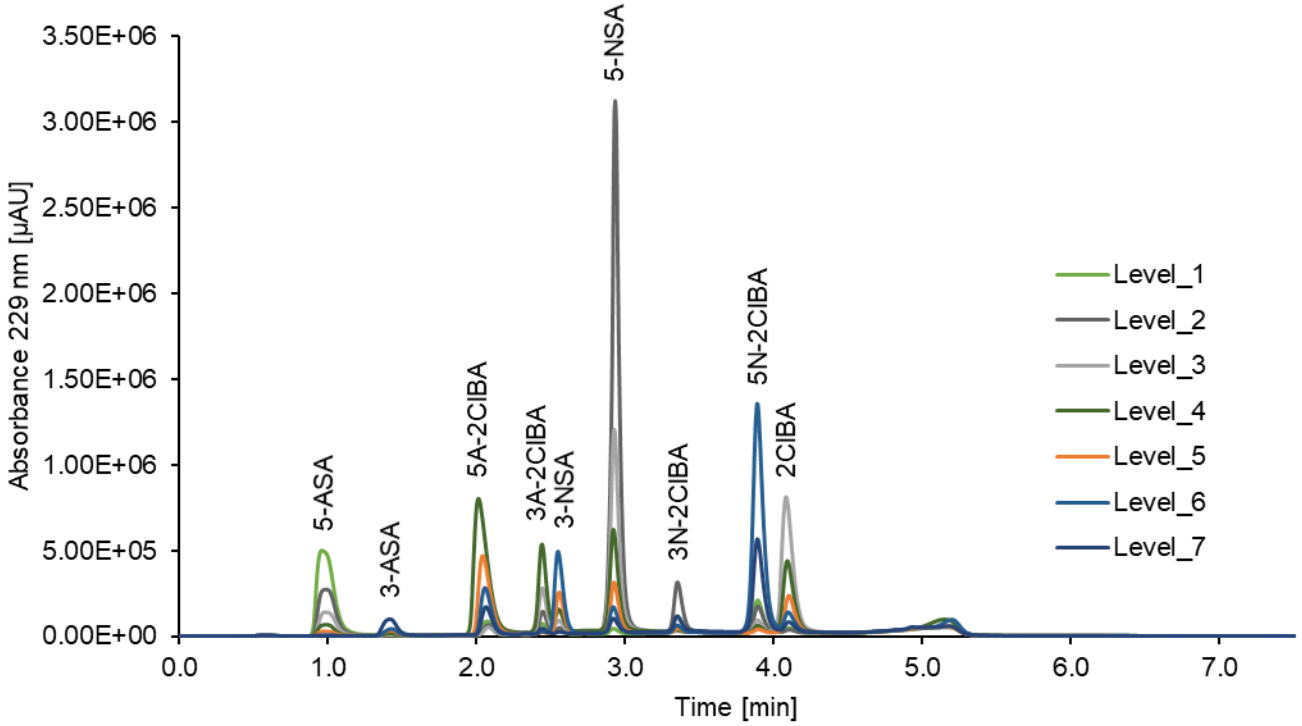


Figure S24. Example chromatograms of 7 different mixtures containing different levels of the 9 target analytes in 0.001 - 0.301 mol/L concentrations. The mixtures were prepared from commercially available samples, diluted 1:20 in MeOH and 0.5 µL were injected using the SIL-30AC autosampler for offline analysis.

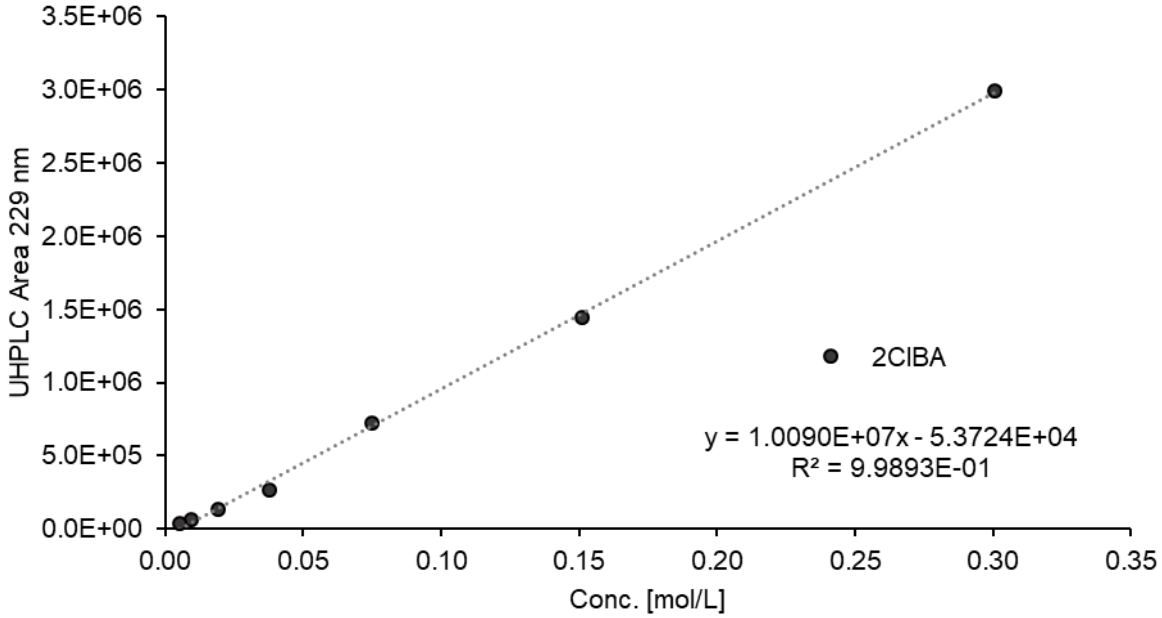


Figure S25. Calibration curve for online UHPLC analysis of 2ClBA at a wavelength of 229 nm

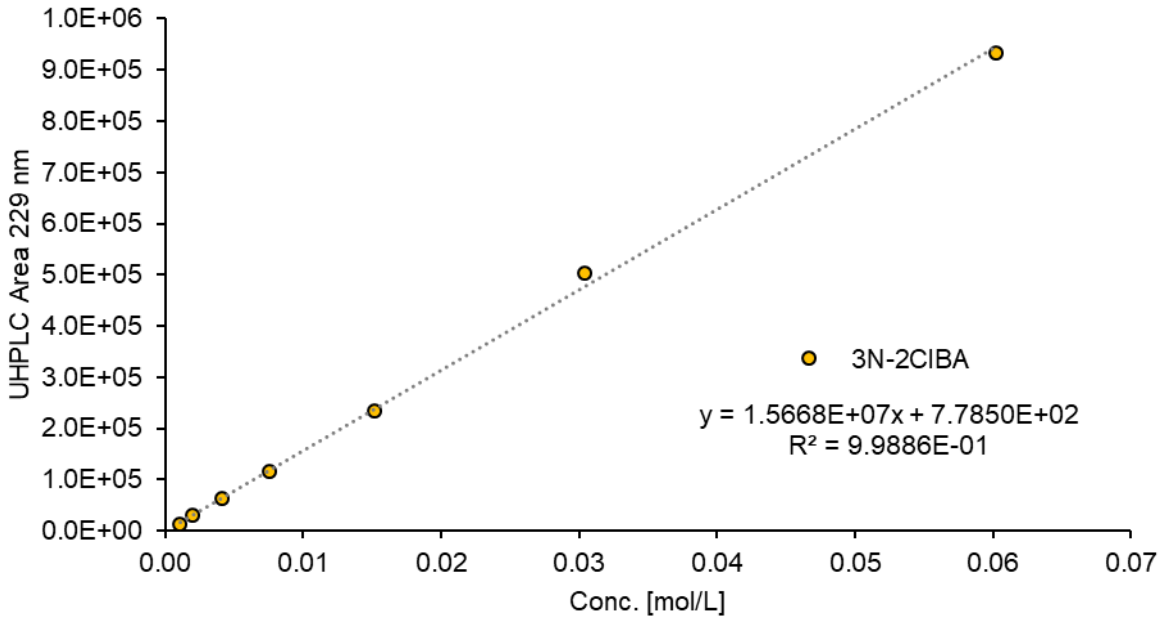


Figure S26. Calibration curve for online UHPLC analysis of 3N-2ClBA at a wavelength of 229 nm

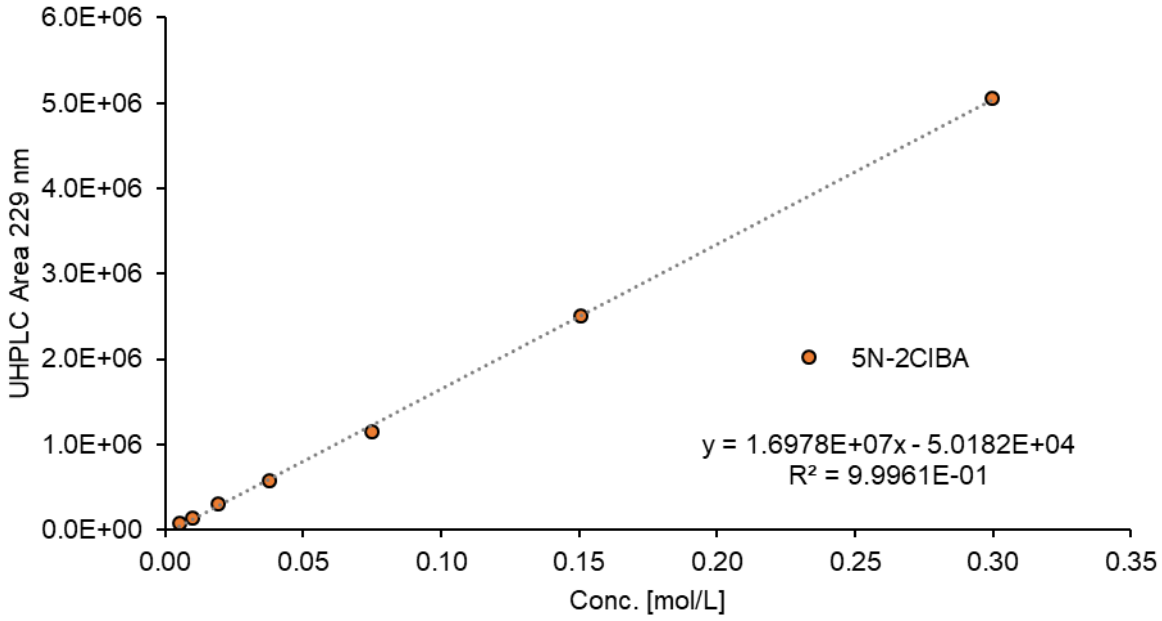


Figure S27. Calibration curve for online UHPLC analysis of 5N-2ClBA at a wavelength of 229 nm.

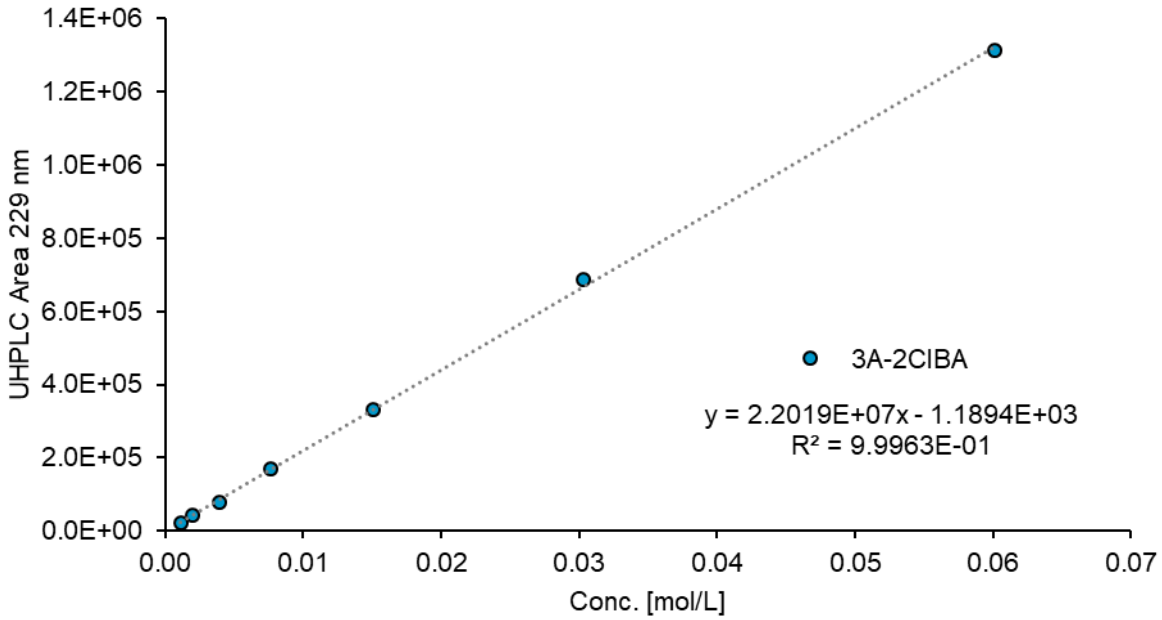


Figure S28. Calibration curve for online UHPLC analysis of 3A-2ClBA at a wavelength of 229 nm.

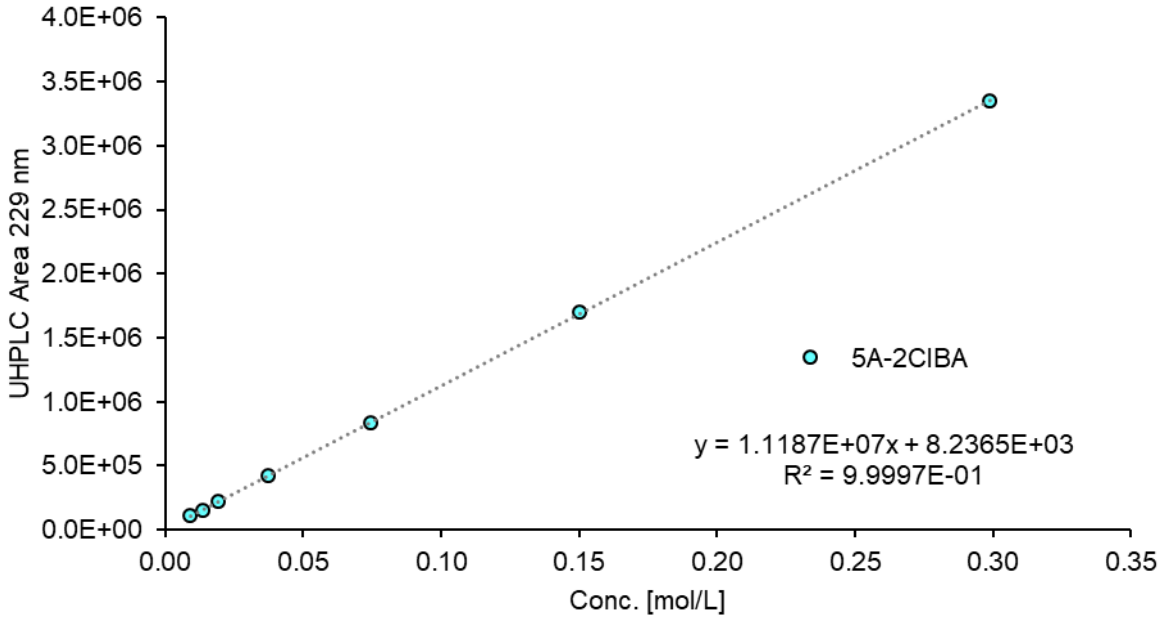


Figure S29. Calibration curve for online UHPLC analysis of 5A-2ClBA at a wavelength of 229 nm.

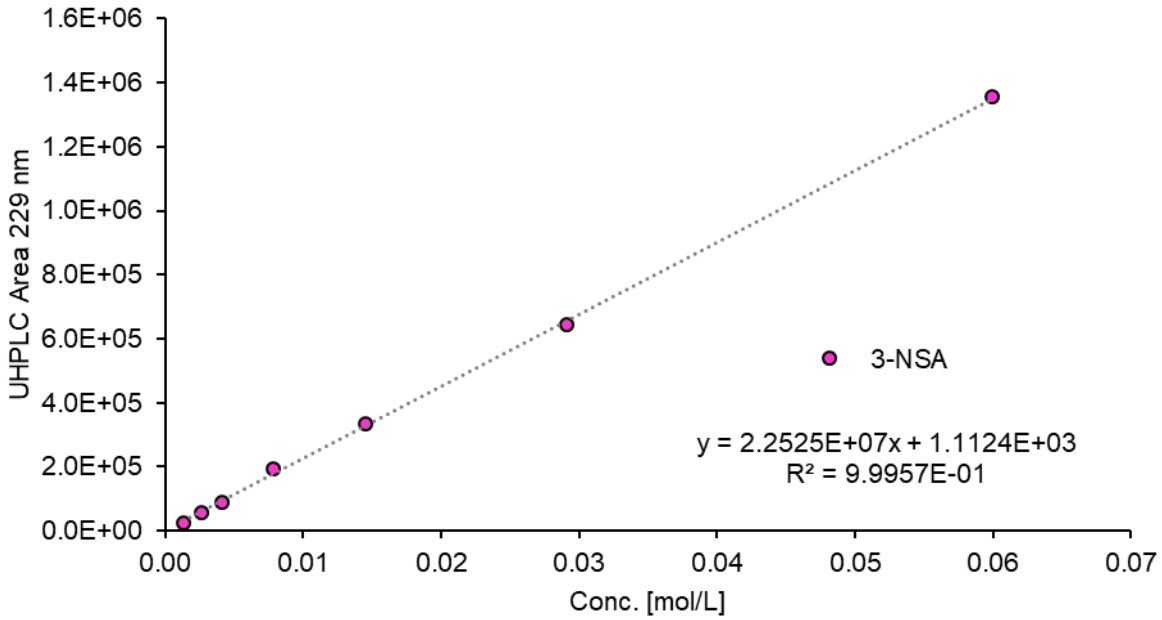


Figure S30. Calibration curve for online UHPLC analysis of 3-NSA at a wavelength of 229 nm.

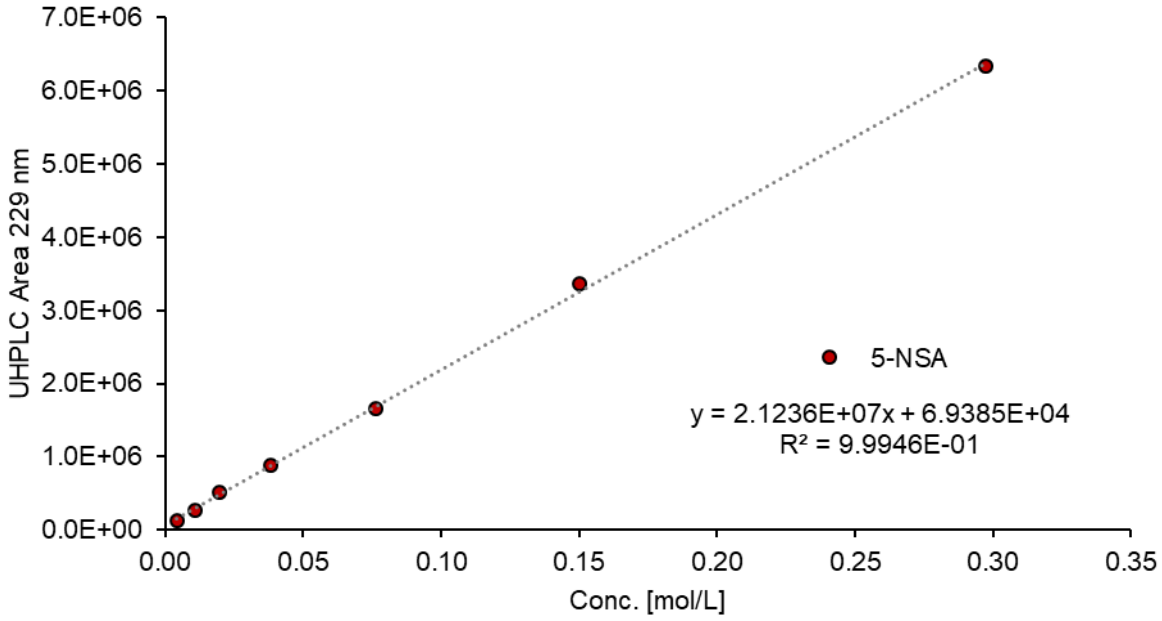


Figure S31. Calibration curve for online UHPLC analysis of 5-NSA at a wavelength of 229 nm.

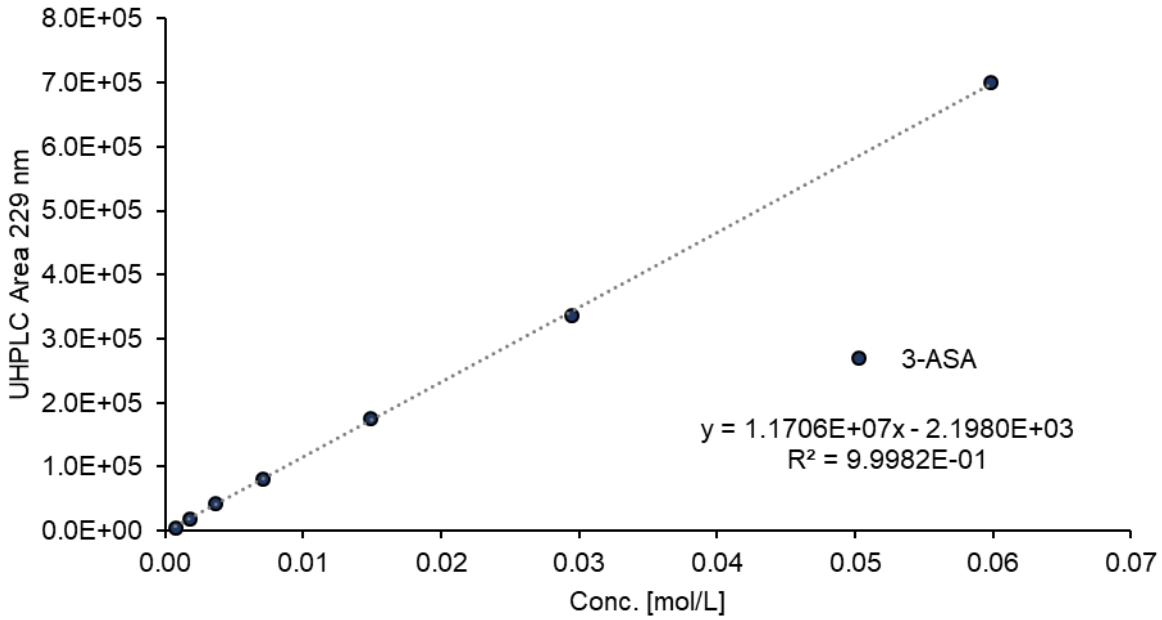


Figure S32. Calibration curve for online UHPLC analysis of 3-ASA at a wavelength of 229 nm.

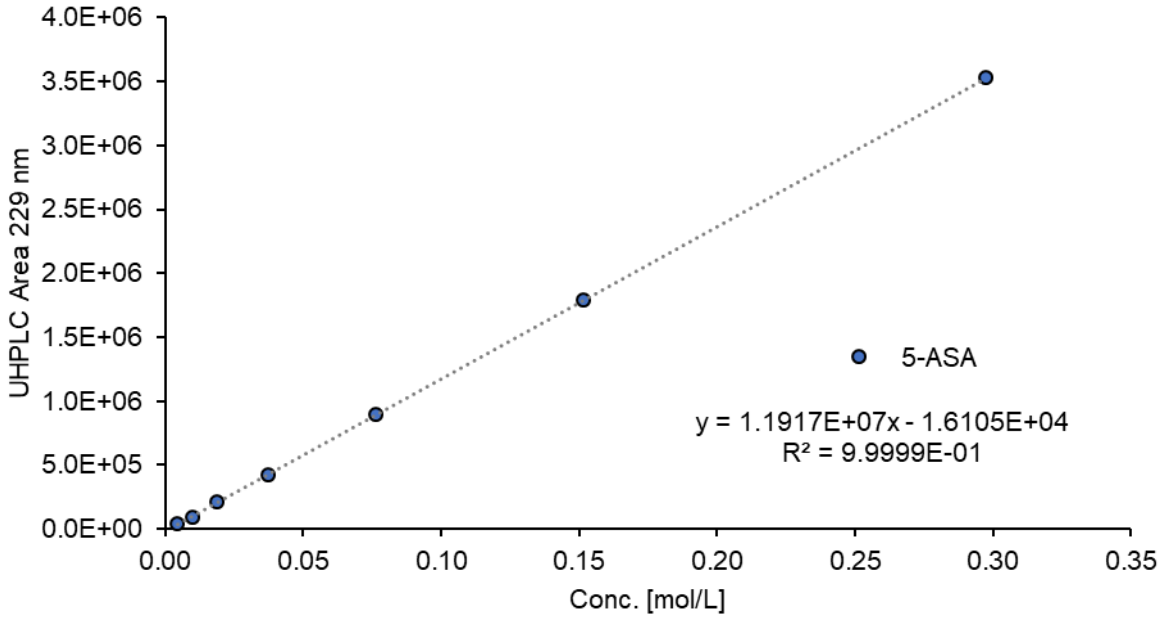


Figure S33. Calibration curve for online UHPLC analysis of 5-ASA at a wavelength of 229 nm.

2.4.2. Process Integration

Online UHPLC integration was accomplished by using an UHPLC internal sample injector (10 nL, 20000 psi, Cheminert Nanovolume, Part# C84U-6674-.01EUH) (**Figure S34** & **Figure S35**), which was controlled by the Shimadzu LabSolutions software. The injection valve was triggered according to the following pattern, defined within the acquisition method: 0.01 min inject; 6.00 min load. Samples were continuously withdrawn as a bypass directly in front of the IR probe and pumped through the injection valve using PTFE tubing

(0.3 mm i.d.) with a total volume of 112 µL. A peristaltic pump (Vapourtec SF-10) was used to pump the bypass stream with a constant flow rate of 500 µL/min, causing a retention of about 30 s. After each analysis, the processed UHPLC data was automatically exported into a csv file (LabSolutions v5.93) and read into XAMControl, containing information about the retention times, areas, analyte concentrations and the chromatogram at 229 nm.

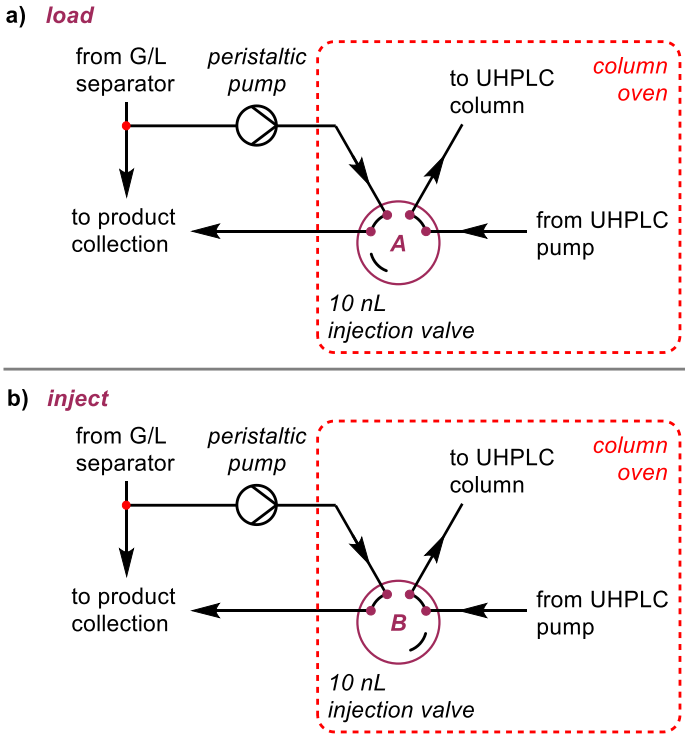


Figure S34. Configuration of 10 nL injection valve inside column oven for online UHPLC measurements. a) load. b) inject by 90° rotation of injection valve.

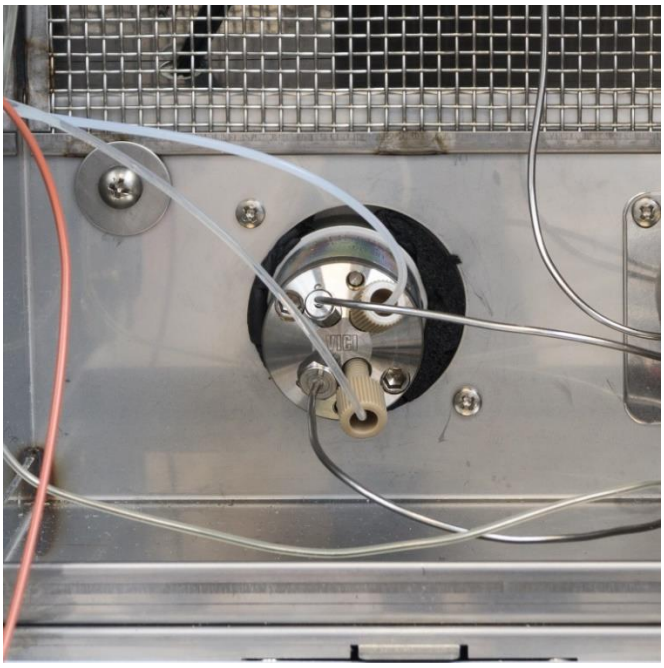


Figure S35. Photograph of the 10 nL injection valve inside the column oven for online UHPLC analysis.

2.4.3. Method Development

To establish a suitable online UHPLC analysis for this process, a method was required with good reproducibility, fast analysis time, good sensitivity and sufficient separation of the process analytes.

Based on a literature-known UHPLC method for the separation of 5-ASA from six potential impurities within the final drug product,[1] we initiated method development with the evaluation of an aq. phosphate buffer/MeOH system. With a total analysis time of 15 min and a different impurity profile,[1] the main objectives were adapting this method for the main analytes occurring within the three-step synthesis, while simultaneously minimizing the analysis time.

Throughout the method optimization process, solvents A and B were prepared according to the following general procedure:

Stock Solution: In a 500 mL or 1000 mL volumetric flask, defined amounts of H_3PO_4, KH_2PO_4 or K_2HPO_4 were dissolved in HPLC grade water to give the desired pH phosphate buffers, with a total phosphate ion concentration of 30 mM. Optional, as an ion pair reagent, sodium *n*-octyl sulfonate (nOSA) was added to the stock solution to result in final concentrations between 0.25 mM and 20.00 mM. The solvent system was optimized by varying the ratio of different phosphate ions and the nOSA concentration within the stock solution.

Solvent A: 50 mL stock solution were diluted to 150 mL with HPLC grade water.

Solvent B: 50 mL stock solution were diluted to 150 mL with HPLC grade MeOH.

Solvents A and B were filtered through 0.2 µm nylon filters prior to use and prepared on a daily basis.

A Phenomenex Kinetex 1.7µm biphenyl 100 Å, LC column with 100 mm x 2.1 mm heated to 45 °C, was used with a total liquid flow rate of 0.5 mL/min, resulting in an approximate system pressure between 500 bar and 850 bar. The detection wavelength of 229 nm was chosen due to the good response of all analytes, and maintained throughout the entire method development. A mixture containing approximately 5 mM of 5-ASA, 3-ASA, 5A-2ClBA, 5-NSA, 3-NSA, 5N-2ClBA, 3N-2ClBA and 2ClBA was used for development.

For an initial screen, two 30 mM phosphate buffer stock solutions with a pH of 6.7 and 2.3 respectively were prepared, resulting in a final buffer concentration of 10 mM in solvent A and B. Six different isocratic levels between 3% and 45% solvent B were evaluated for 8 minutes (followed by a purge at 50% solvent B for 1.8 min). For the pH 6.7 buffer isocratic measurements, early elution of multiple target analytes was observed, even at low levels of solvent B (**Figure S36**). This can be explained by deprotonation of the carboxylic acid moiety which is present in all analytes, permitting minimal interaction of the ionic species with the reversed phase column.

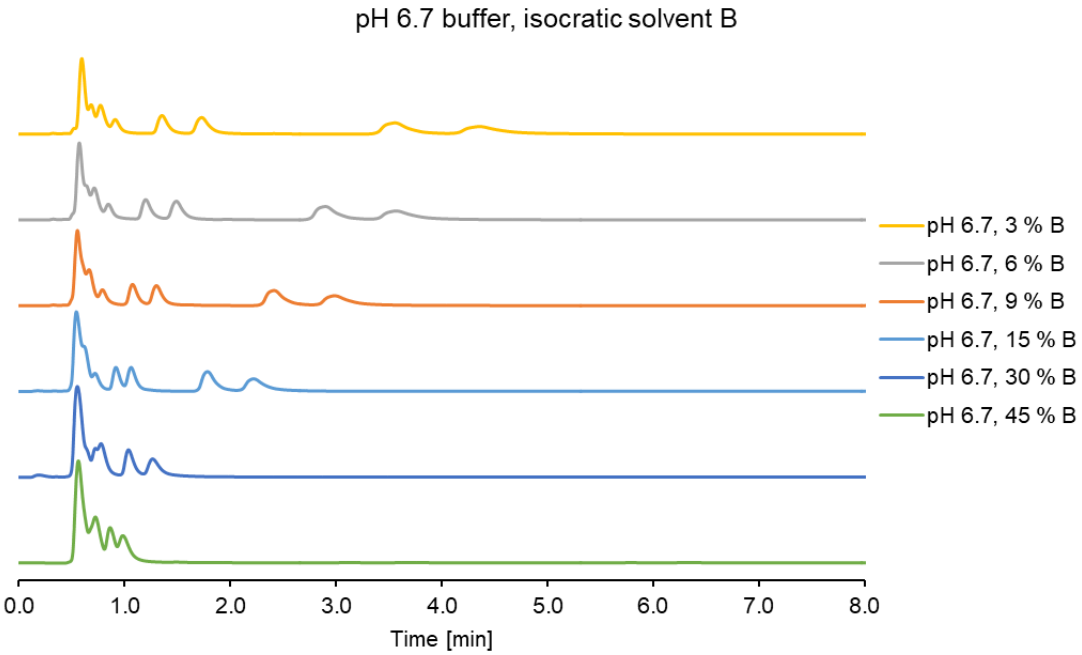


Figure S36. Isocratic levels for 8 min for pH 6.7 buffer.

When the pH of the stock solution was adjusted to 2.3 by using larger proportions of H_3PO_4, better separation of the analytes was observed (**Figure S37**). The retention time of the three amine containing species 5-ASA, 3-ASA and 5A-2ClBA (which eluted first) was affected less by the changing levels of solvent B, due to their protonated nature at this low pH.

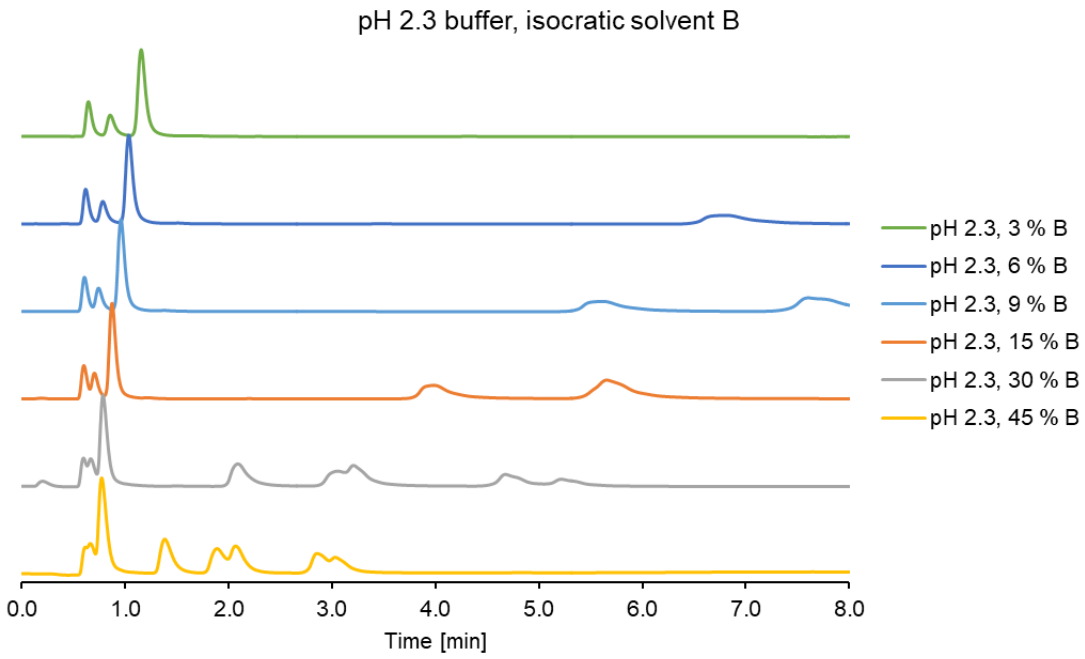


Figure S37. Isocratic levels for 8 min for pH 2.3 buffer.

Based on these results, the gradient depicted in **Figure S38** was used for further optimization. Starting from 3%, the content of solvent B was increased to 50% over 5 min and held constant for 1 min, followed by an equilibration phase of 3 min at 3%.

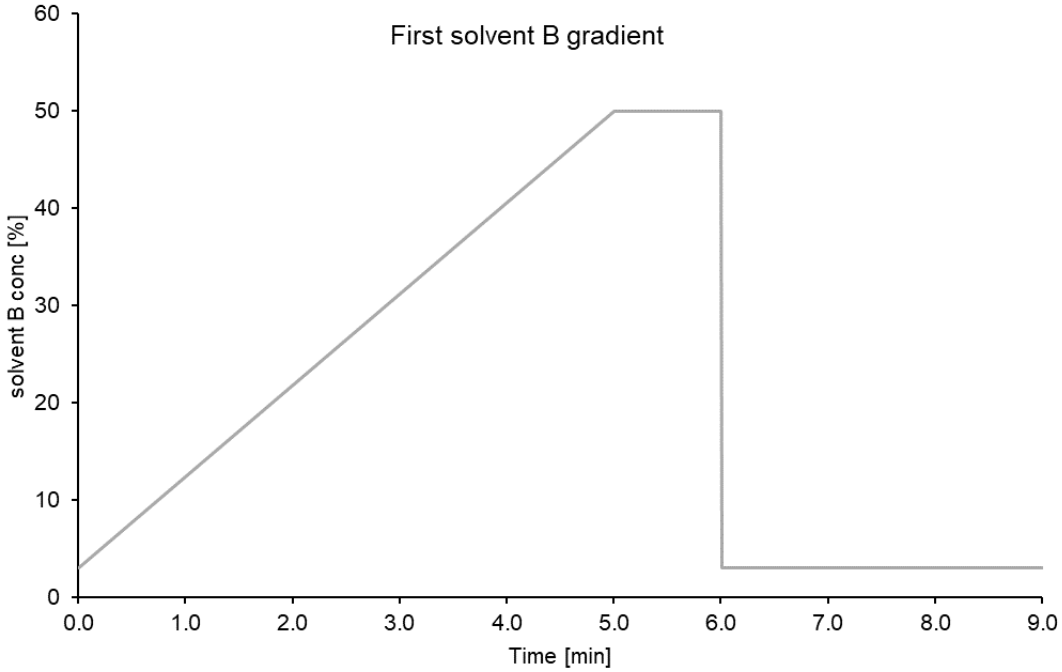


Figure S38. First gradient used during UHPLC method optimization: 3% to 50% solvent B over 5 min.

The gradient ramp (**Figure S38**) was used to directly compare the effect of both pH 2.3 and pH 6.7 buffer stock solutions (**Figure S39**), confirming the previous observations during the isocratic methods: at pH 6.7 the nonpolar nitro-containing species and the 2ClBA were better resolved, whereas the pH 2.3 buffer stock solution showed promising separation of the polar amine species.

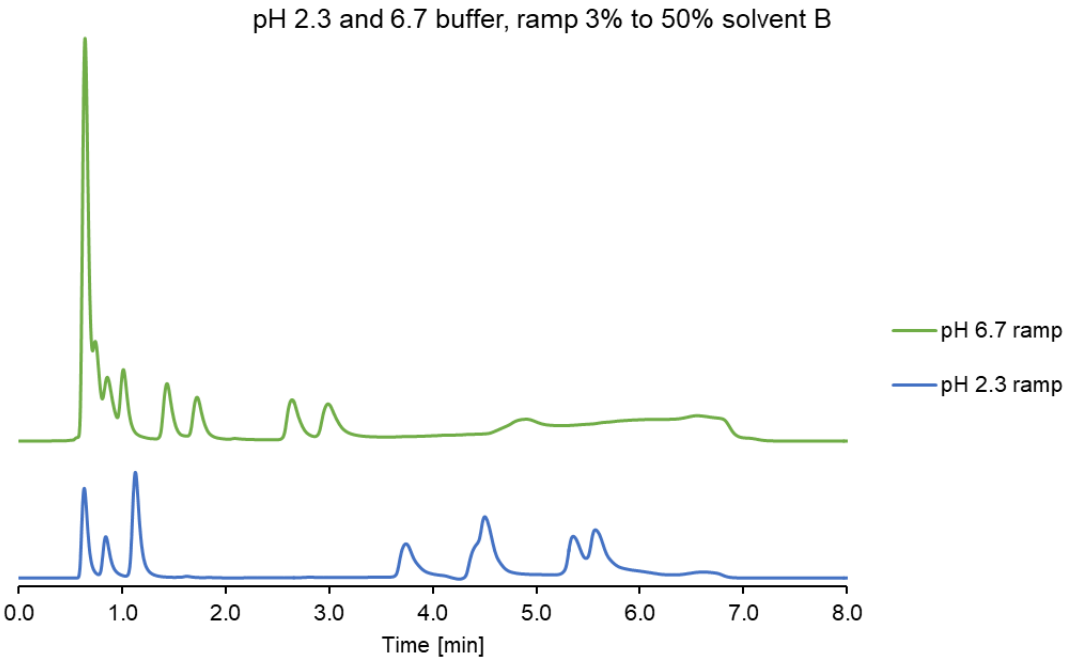


Figure S39. Comparison between pH 2.3 and pH 6.7 stock solution during the first gradient ramp.

Despite the improved separation of the amine species at pH 2.3, the first analyte (5-ASA, 0.6 min) was considered to overlap with the injection solvent front (0.5 min). Therefore, sodium *n*-octyl sulfonate was introduced as an ion pair reagent. Initial concentrations between 5 mM and 20 mM (**Figure S40**) showed strong additional retention of the polar amine species, resulting in an overlap with the more nonpolar analytes.

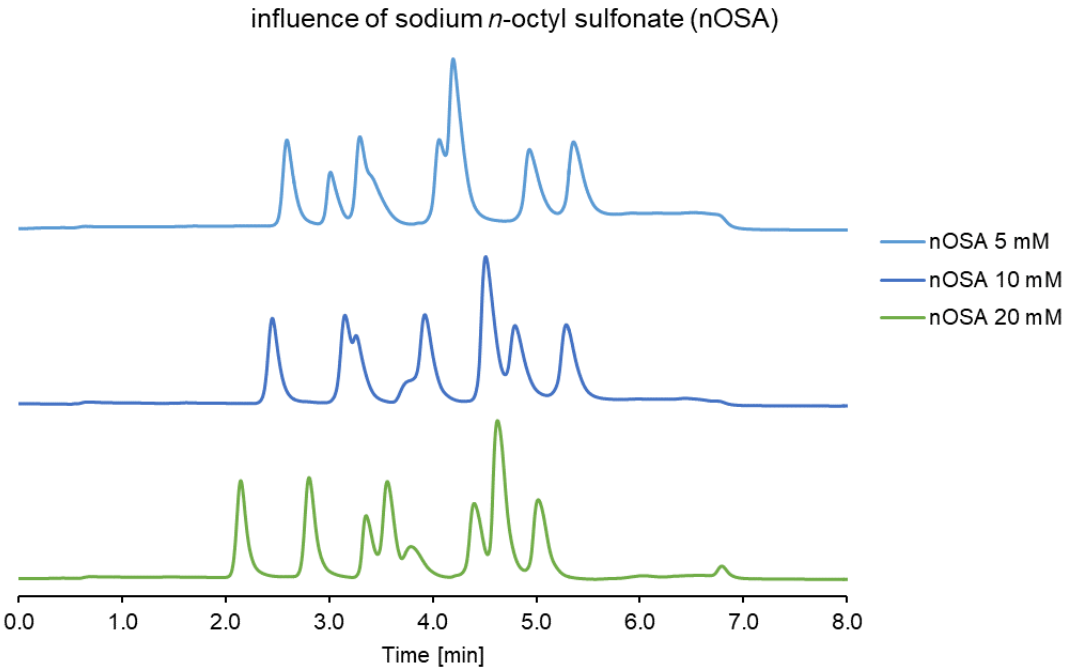


Figure S40. Initial evaluation of nOSA as ion pair reagent.

Therefore, lower concentrations of nOSA, in particular below 1 mM, were evaluated (**Figure S41**). Satisfying resolution of the analytes was observed, when solvents A and B were prepared with a 0.33 mM nOSA concentration. The analytes eluted in the following order: 5-ASA (0.964 min), 3-ASA (1.345 min), 5A-2ClBA (2.074 min), 3-NSA (2.893 min), 5-NSA (3.426 min), 3N-2ClBA (4.087 min), 5N-2ClBA (4.881 min) and 2ClBA (5.182 min).

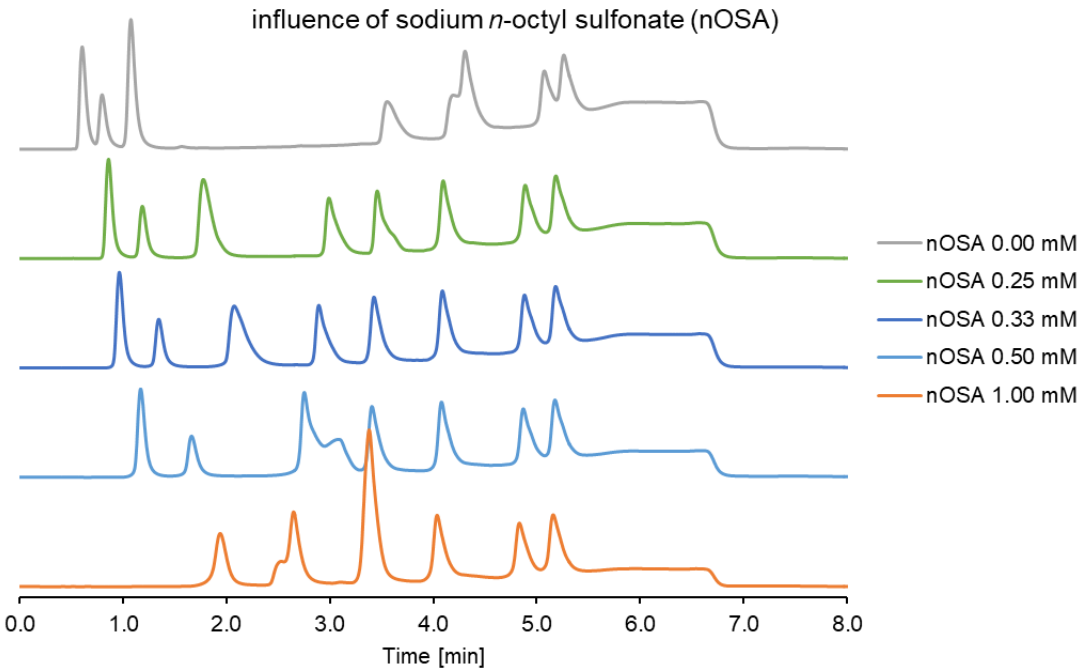


Figure S41. Optimization of nOSA concentration below 1 mM.

The gradient ramp was further optimized in several iterations to decrease the overall method time from 9.0 min to 7.5 min, including a final equilibration of 3.0 min (**Figure S42**). To prevent column degradation over time, flow rates higher than 0.5 mL/min were not considered, as the maximum pressure during the method reached 850 bar (manufacturer recommendation for column longevity: < 1.034 bar).

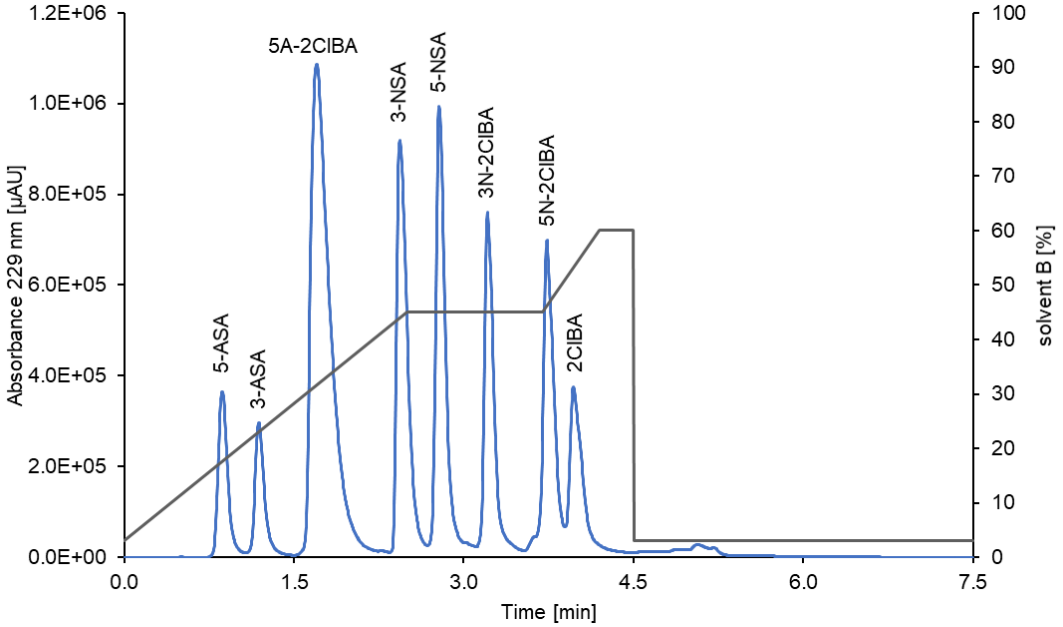


Figure S42. Final method for UHPLC analysis: 3% B to 45% B over 2.5 min, hold 45% B for 1.2 min, increase to 60% B over 0.5 min, hold 60% B for 0.3 min, decrease to 3% B over 0.01 min, equilibration at 3% B for 2.99 min.

3. Nitration Reaction Optimization Data

3.5. Detailed Setup

Input solutions were made up with conc. H_2SO_4 in 500 mL volumetric flasks.
0.5 M 2ClBA: In a 500 mL volumetric flask 39.1518 g of 2ClBA was diluted in conc. H_2SO_4.
0.6 M HNO_3: A 500 mL volumetric flask was placed in an ice bath and filled with 400 mL conc. H_2SO_4, then 19.2 mL of conc. HNO_3 (15.6 M, 68%) was slowly added. After the addition, the volumetric flask was removed from the ice bath, allowed to reach room temperature, and filled up to the 500 mL mark with conc. H_2SO_4.
2.5 M HNO_3: A 500 mL volumetric flask was placed in an ice bath and filled with 400 mL conc. H_2SO_4, then 80.0 mL of conc. HNO_3 (15.6 M, 68%) was slowly added. After the addition, the volumetric flask was removed from the ice bath, allowed to reach room temperature, and filled up to the 500 mL mark with conc. H_2SO_4.

A picture of the flow setup is depicted in **Figure S43**. The MMRS platform is shown in **Figure S44**. For a detailed description of each experiment see the individual sections.

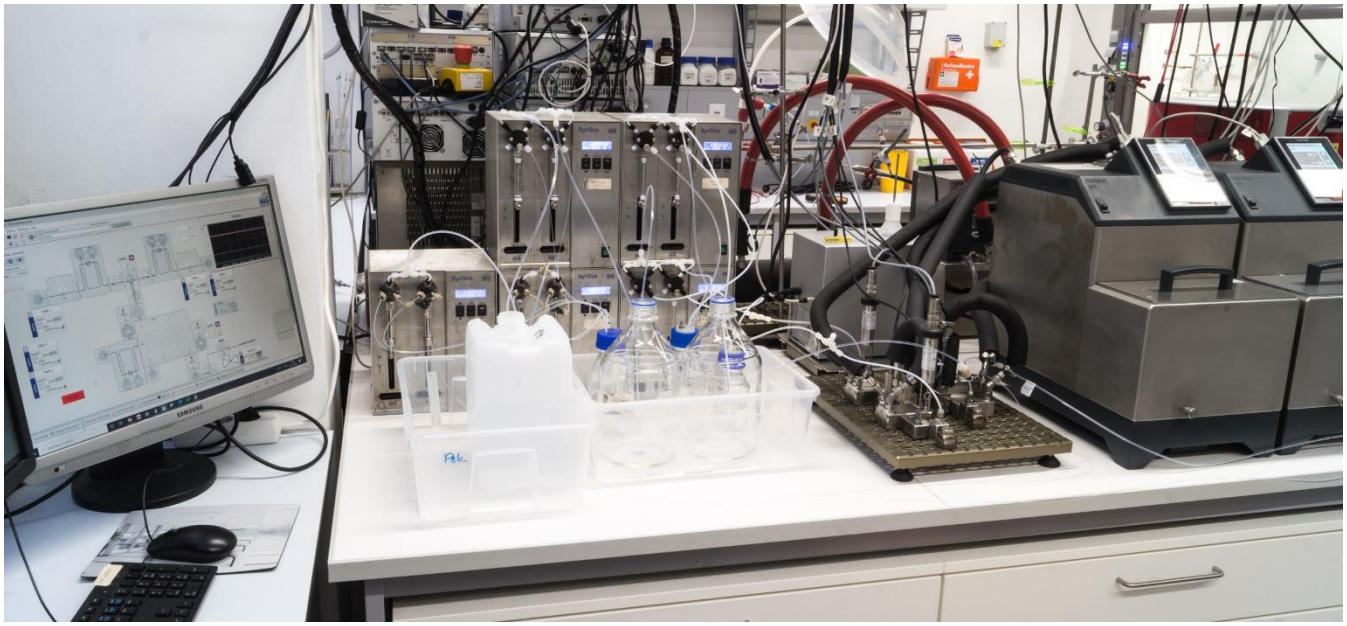


Figure S43. Photograph of the nitration setup.

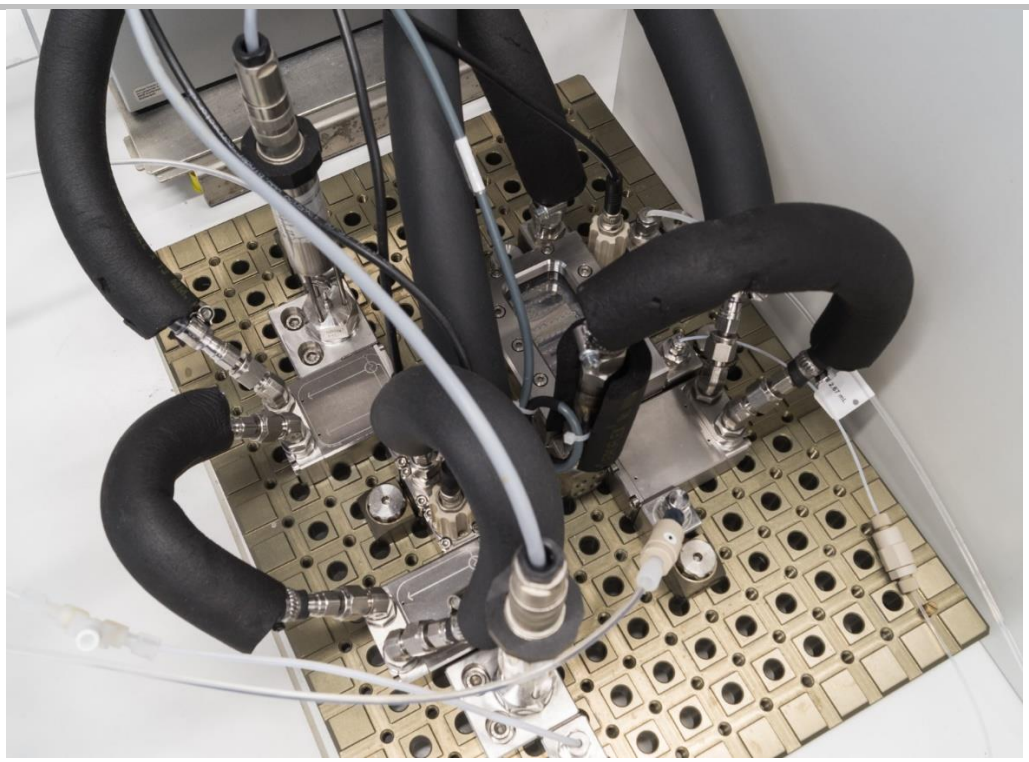


Figure S44. Photograph of the MMRS system in the final configuration for the nitration reaction.

3.1. Initial Optimization

3.1.1. Batch Experiments

The feasibility study was carried out in batch to investigate concentration, nitrating agent and solvent selection (**Table S8**). In these experiments 2ClBA was dissolved in 1 mL solvent in a 4 mL screw cap vial. The vial was placed in a metal block and was either heated or cooled. The nitrating agent was added in one portion to the stirred substrate solution. In the case of NH_4NO_3 as nitrating agent, NH_4NO_3 was dissolved in 0.5 mL solvent and added to the substrate dissolved in 0.5 mL solvent. A sample was taken after 1 min and analyzed with UHPLC. It was observed that reaction mixtures containing >20% of water formed a white precipitate. As a starting point for the flow optimization a 0.5 M substrate concentration was chosen, HNO_3 was selected as nitrating agent, and H_2SO_4 as solvent.

Table S7. Batch optimization table and observed results.

Concentration	Solvent	Nitrating agent	Temperature	Conversion	Observation
0.25 M	H_2SO_4	1.2 equiv. NH_4NO_3	0°C	>99%	-
0.25 M	H_2SO_4/AcOH	1.2 equiv. NH_4NO_3	25°C	20%	Precipitate
0.25 M	H_2SO_4	1.2 equiv. 15.6 M HNO_3	25°C	>99%	-
0.5 M	H_2SO_4	1.2 equiv. 15.6 M HNO_3	25°C	>99%	-
0.5 M	H_2SO_4/H_2O	1.2 equiv. 1 M HNO_3	25°C	-	Precipitate
0.5 M	H_2SO_4/H_2O	1.2 equiv. 5 M HNO_3	25°C	>99%	-
0.5 M	H_2SO_4/H_2O	3 equiv. 5 M HNO_3	25°C	>99%	Precipitate
0.5 M	H_2SO_4/H_2O	6 equiv. 5 M HNO_3	25°C	>99%	Precipitate
0.5 M	H_2SO_4	1.2 equiv. 5 M HNO_3	25°C	>99%	-

3.1.2. Initial Flow Experiments

Initial continuous flow optimization data was collected using the FlowPlate lab with an LL design process plate (**Figure S50**). First, HNO_3 loadings between 1.0 and 3.0 equiv, at a total flow rate of 2.5 mL/min were screened (**Figure S45**, light blue). The yield of 5N-2ClBA reached a maximum of 78% with 3.0 equivalents of HNO_3, however, the reaction did not go to completion (92% conversion). To reach full conversion the equivalents of HNO_3 were further increased and a lower flow rate was chosen (**Figure S45**, orange). The obtained results were not satisfying when compared to the batch results, where 1.2 equivalents of HNO_3 provided full conversion. Screening different flow rates and temperatures (**Figure S45**, red, green, blue) revealed that the reaction outcome is limited by mixing performance, as evidenced by an increase in yield at higher flow rate (i.e. shorter residence time, clearly visible in **Figure S45**). This is thought to be caused by the high reaction mixture viscosity (dynamic viscosity of 95% H_2SO_4 = 17.6 mPa s at 25 °C).[2] The mixing behavior of fast reactions in microreactors has already been extensively studied.[3,4] Switching to a TG design process plate, which is designed to have better mixing in a single phase, compared to the LL design, resulted in a consistent increase in yield of 6-13% compared to the LL design (**Figure S46**). The use of high flow rates in the nitration process was limited by the downstream processing, because large quantities of water are required to dilute acidic stream (5:1 flow rate ratio). Therefore, the flow rate of the reaction mixture was limited to <2 mL/min.

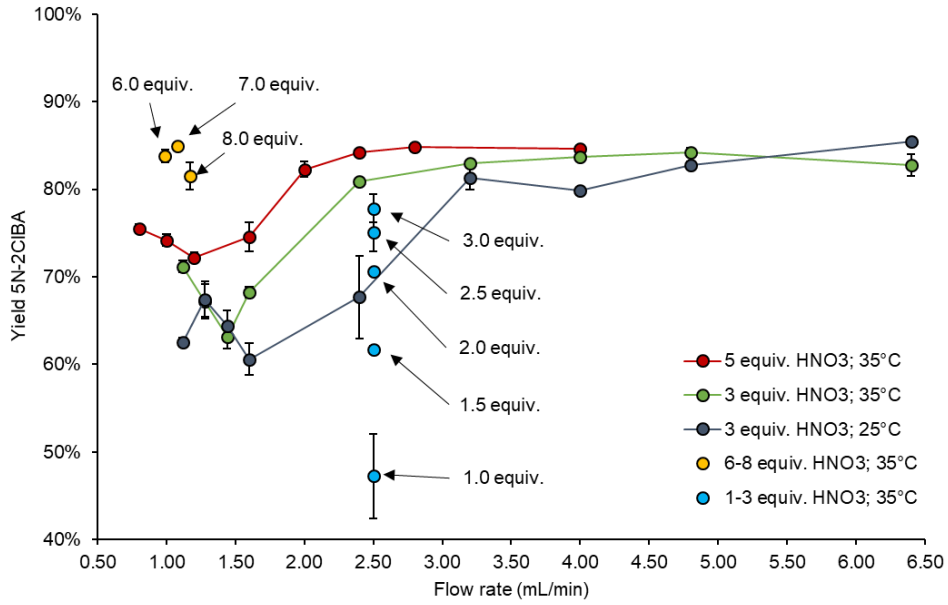


Figure S45. Comparison of different experimental results for the nitration in the FlowPlate Lab to different flowrates, equivalents of HNO_3 and temperatures.

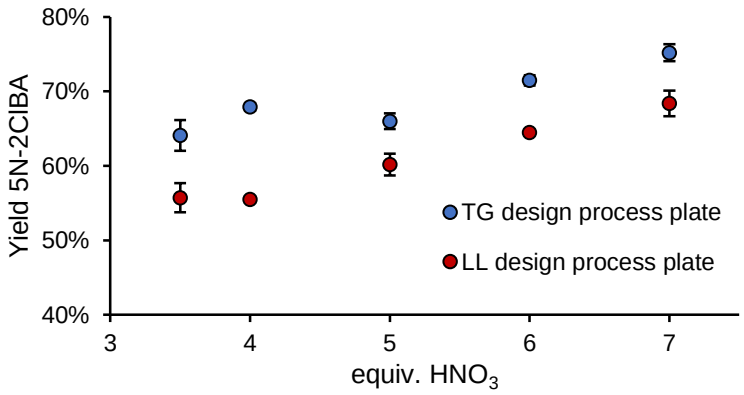


Figure S46. Comparison different process plate designs in the FlowPlate Lab for the nitration reaction.

Further investigation found that a mixer based on a split-and-recombine mixing principle (Cascade Mixer 06, Ehrfeld, **Figure S47**) provided effective mixing over a broad range of flow rates (**Figure S48A**). The cascade mixer provided superior performance compared to the FlowPlate Lab reactor, particularly at low flow rates (<3 mL/min). Using this reactor, the excess of HNO_3 could be significantly reduced, to stoichiometric amounts (**Figure S48B**). To decide on the final reactor volume (i.e. whether an additional residence time unit would be required), experiments with different residence times and temperatures were conducted. For the final process a reactor volume of 0.343 mL was chosen, which corresponds to a residence time of 20.6 s at a flow rate of 1 mL/min.

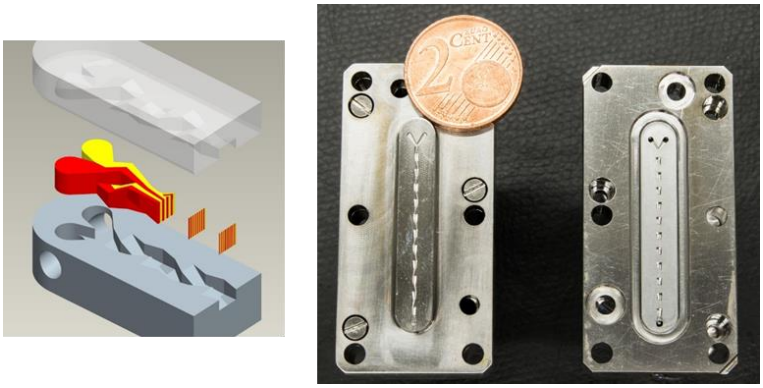


Figure S47. Left) A CAD picture of the split-and-recombine mixing principle. Right) The split-and-recombine mixer (Cascade Mixer 06, Ehrfeld)

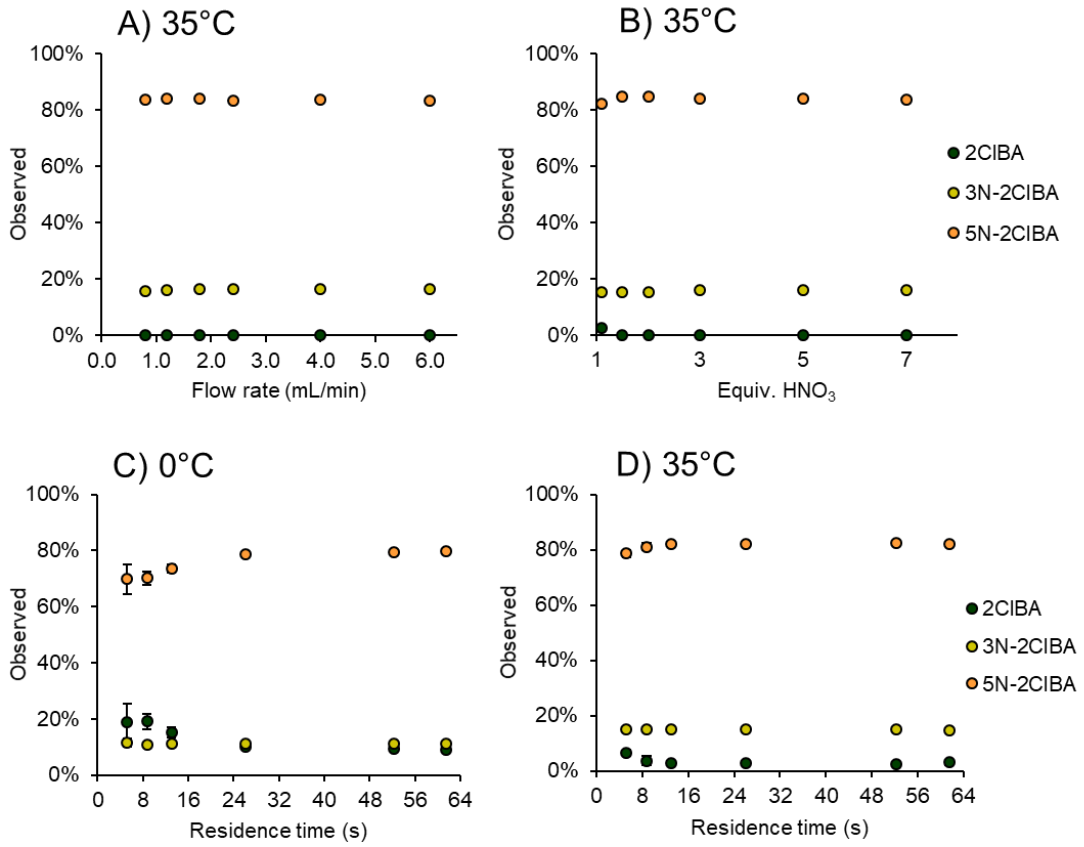


Figure S48. The reaction progress using the cascade mixer at different temperatures and residence times.

3.1.3. Setup and Results of Nitration in FlowPlate Lab

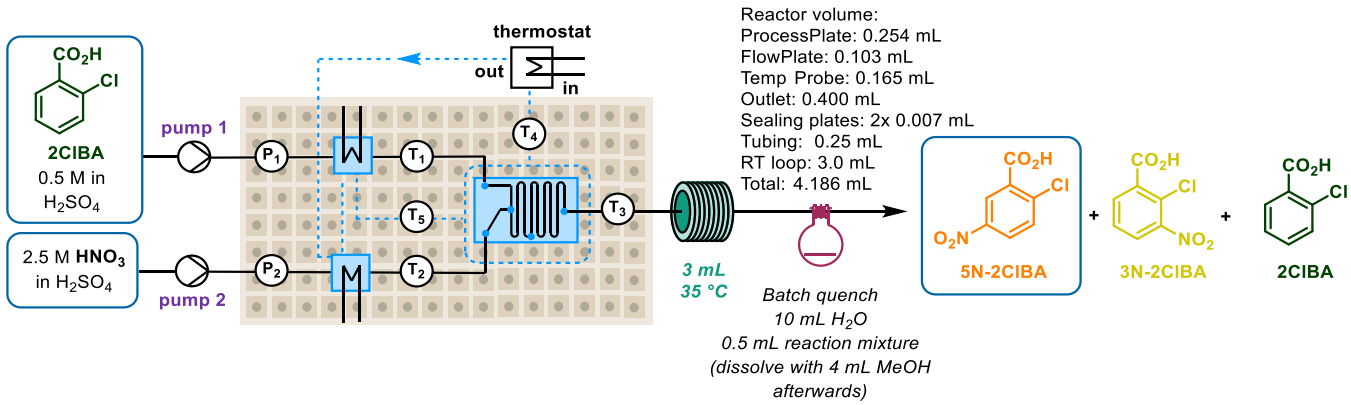


Figure S49. Process scheme for the nitration in the FlowPlate Lab.

The HNO_3 and 2ClBA feeds were delivered with two SyrDos2 pumps (30 bar valve, 5 mL syringes, pump 1 for 2ClBA feed and pump 2 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the system through 1/8" input connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276), then temperature sensors (0501-2-1004-X, Hastelloy C-276) the MMRS system. The two streams were mixed in a temperature controlled FlowPlate Lab (1701-3-0004-F, Hastelloy C-276) equipped with either an LL design process plate (1701-4682-HC, LL-Mixer, Nominal Width 0.2 mm, Hastelloy C-22). The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the FlowPlate Lab was controlled by a thermostat (Huber, Ministat 240). The nitration mixture left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), 1/8" input connector (0711-2-0224-F, Hastelloy C-276) and a 3 mL PFA coil which was placed in a temperature controlled water bath. Samples were collected by quenching 0.5 mL of the reaction mixture into 10 mL of H_2O. Addition of 4 mL of MeOH dissolved the formed precipitate and samples were analyzed offline by UHPLC.

SUPPORTING INFORMATION

Table S8 Results from the initial optimization experiments, measuring the distribution of 2ClBA, 3N-2ClBA and 5N-2ClBA with UHPLC. Each percentage value is the mean of 3 measured points.

Entry	Pump 1 (mL/min)	Pump 2 (mL/min)	Thermostat (°C)	Equiv. HNO_3	2ClBA UHPLC	3N-2ClBA UHPLC	5N-2ClBA UHPLC
1	0.40	0.40	35	5.0	11.2 ± 0.7%	13.3 ± 0.1%	75.5 ± 0.5%
2	0.50	0.50	35	5.0	12.7 ± 0.7%	13.1 ± 0.1%	74.2 ± 0.7%
3	0.60	0.60	35	5.0	14.8 ± 0.7%	13.0 ± 0.1%	72.2 ± 0.5%
4	0.80	0.80	35	5.0	11.9 ± 2.0%	13.5 ± 0.3%	74.6 ± 1.7%
5	1.00	1.00	35	5.0	2.9 ± 0.9%	14.8 ± 0.1%	82.3 ± 0.9%
6	1.20	1.20	35	5.0	0.7 ± 0.2%	15.1 ± 0.1%	84.2 ± 0.2%
7	1.40	1.40	35	5.0	0.0 ± 0.1%	15.2 ± 0.1%	84.8 ± 0.1%
8	2.00	2.00	35	5.0	0.0 ± 0.1%	15.4 ± 0.1%	84.6 ± 0.1%
9	0.45	0.54	35	6.0	1.3 ± 0.9%	14.9 ± 0.2%	83.8 ± 0.7%
10	0.45	0.63	35	7.0	0.1 ± 0.1%	15.0 ± 0.1%	84.9 ± 0.1%
11	0.45	0.72	35	8.0	4.1 ± 1.8%	14.4 ± 0.3%	81.5 ± 1.6%
12	2.08	0.42	35	1.0	44.0 ± 5.9%	8.8 ± 1.1%	47.2 ± 4.8%
13	1.92	0.58	35	1.5	26.8 ± 0.6%	11.4 ± 0.2%	61.7 ± 0.4%
14	1.79	0.71	35	2.0	16.3 ± 0.2%	13.1 ± 0.1%	70.6 ± 0.2%
15	1.67	0.83	35	2.5	11.2 ± 2.6%	13.6 ± 0.4%	75.1 ± 2.2%
16	1.56	0.94	35	3.0	8.1 ± 1.9%	14.0 ± 0.3%	77.8 ± 1.6%
17	0.70	0.42	35	3.0	16.2 ± 0.8%	12.6 ± 0.1%	71.2 ± 0.7%
18	0.80	0.48	35	3.0	20.8 ± 2.4%	12.1 ± 0.4%	67.2 ± 2.0%
19	0.90	0.54	35	3.0	25.5 ± 1.6%	11.3 ± 0.3%	63.1 ± 1.3%
20	1.00	0.60	35	3.0	19.4 ± 0.7%	12.3 ± 0.2%	68.3 ± 0.6%
21	1.50	0.90	35	3.0	4.6 ± 0.4%	14.5 ± 0.1%	80.8 ± 0.4%
22	2.00	1.20	35	3.0	2.1 ± 0.1%	14.9 ± 0.1%	83.0 ± 0.1%
23	2.50	1.50	35	3.0	1.2 ± 0.1%	15.1 ± 0.4%	83.7 ± 0.4%
24	3.00	1.80	35	3.0	0.0 ± 0.1%	15.7 ± 0.4%	84.3 ± 0.4%
25	4.00	2.40	35	3.0	0.0 ± 0.1%	17.2 ± 1.2%	82.8 ± 1.2%
26	0.70	0.42	25	3.0	27.1 ± 0.6%	10.4 ± 0.1%	62.5 ± 0.5%
27	0.80	0.48	25	3.0	21.4 ± 2.4%	11.2 ± 0.3%	67.5 ± 2.1%
28	0.90	0.54	25	3.0	24.8 ± 2.1%	10.8 ± 0.4%	64.4 ± 1.7%
29	1.00	0.6	25	3.0	29.2 ± 2.2%	10.2 ± 0.4%	60.6 ± 1.8%
30	1.50	0.9	25	3.0	20.9 ± 5.4%	11.5 ± 0.7%	67.7 ± 4.7%
31	2.00	1.2	25	3.0	4.9 ± 1.3%	13.8 ± 0.1%	81.3 ± 1.3%
32	2.50	1.5	25	3.0	6.6 ± 0.5%	13.5 ± 0.1%	79.9 ± 0.4%
33	3.00	1.80	25	3.0	3.4 ± 0.5%	13.8 ± 0.1%	82.8 ± 0.4%
34	4.00	2.40	25	3.0	0.0 ± 0.1%	14.6 ± 0.1%	85.4 ± 0.1%

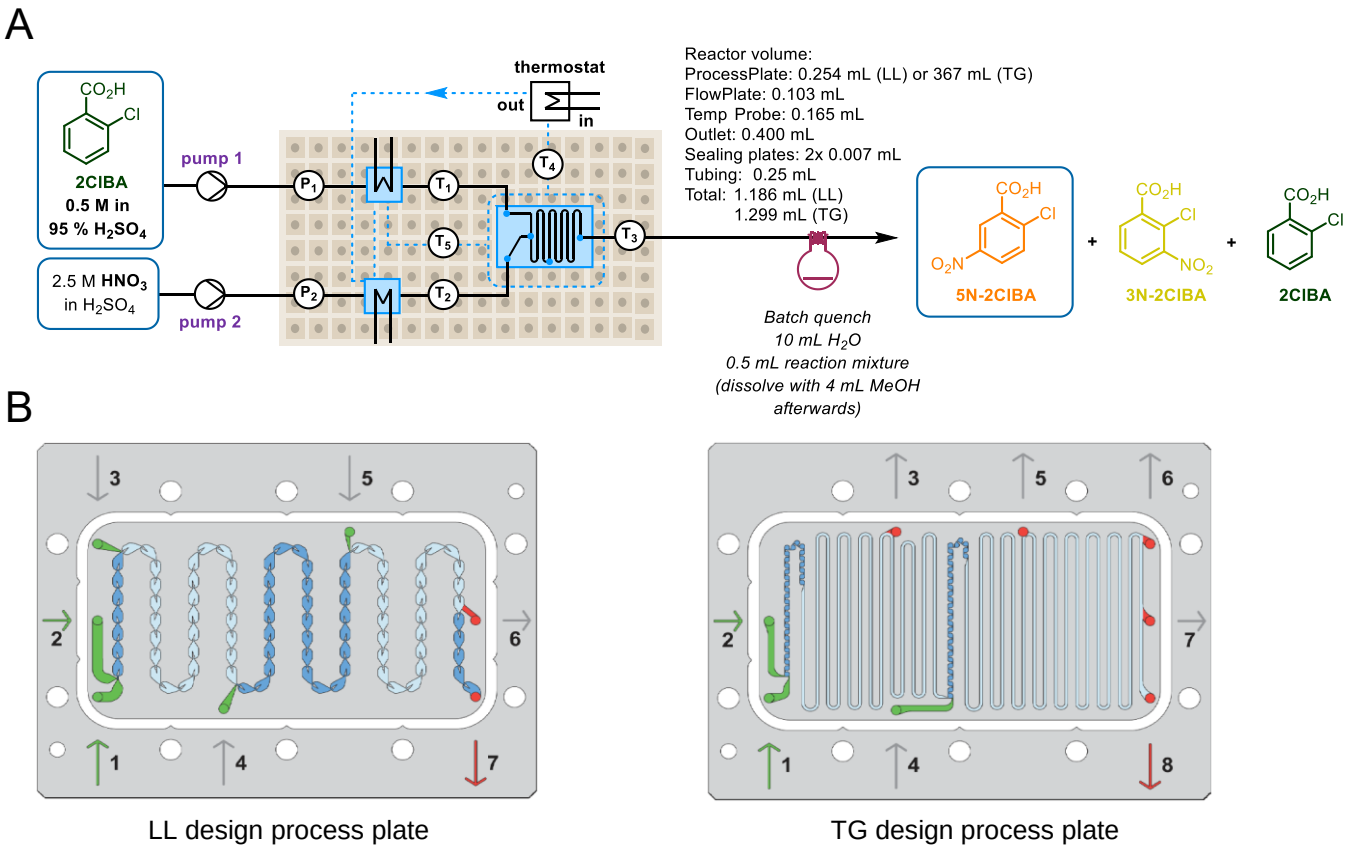


Figure S50. A) Process scheme for the nitration in the FlowPlate Lab. B) design of the different process plates for the FlowPlate Lab reactor.

The HNO_3 and 2ClBA feeds were delivered with two SyrDos2 pumps (30 bar valve, 5 mL syringes, pump 1 for 2ClBA feed and pump 2 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the system through 1/8" input connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276), then temperature sensors (0501-2-1004-X, Hastelloy C-276) the MMRS system. The two streams were mixed in a temperature controlled FlowPlate Lab (1701-3-0004-F, Hastelloy C-276) equipped with either a LL design process plate (1701-4682-HC, LL-Mixer, Nominal Width 0.2 mm, Hastelloy C-22) or a TG design process plate (1701-2643-HC, TG-Mixer, Nominal Width 0.2 mm, Hastelloy C-22). The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the FlowPlate Lab was controlled by a thermostat (Huber, Ministat 240). The nitration mixture left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), 1/8" input connector (0711-2-0224-F, Hastelloy C-276) and a small PFA tube. Samples were collected by quenching 0.5 mL of the reaction mixture into 10 mL of H_2O. Addition of 4 mL of MeOH dissolved the formed precipitate and samples were analyzed offline by UHPLC.

Table S9. Results for the initial optimization measuring the distribution of 2ClBA, 3N-2ClBA and 5N-2ClBA with UHPLC. Each percentage value is the mean of 3 measured points. [a]experiment performed in the LL design process plate. [b]experiment performed in the TG design process plate

Entry	Pump 1 (mL/min)	Pump 2 (mL/min)	Thermostat (°C)	Equiv. HNO_3	2ClBA UHPLC	3N-2ClBA UHPLC	5N-2ClBA UHPLC
1[a]	0.59	0.41	35	3.5	34.0 ± 2.5%	10.2 ± 0.5%	55.7 ± 2.0%
2[a]	0.56	0.44	35	4.0	34.2 ± 0.3%	10.3 ± 0.1%	55.5 ± 0.3%
3[a]	0.50	0.50	35	5.0	28.7 ± 1.7%	11.2 ± 0.3%	60.2 ± 1.5%
4[a]	0.45	0.55	35	6.0	23.6 ± 0.2%	11.9 ± 0.2%	64.5 ± 0.1%
5[a]	0.42	0.58	35	7.0	19.1 ± 2.1%	12.5 ± 0.4%	68.4 ± 1.7%
6[b]	0.59	0.41	35	3.5	24.2 ± 2.4%	11.7 ± 0.4%	64.1 ± 2.1%
7[b]	0.56	0.44	35	4.0	19.7 ± 0.6%	12.4 ± 0.1%	67.9 ± 0.5%
8[b]	0.50	0.50	35	5.0	22.0 ± 1.3%	12.0 ± 0.2%	66.0 ± 1.1%
9[b]	0.45	0.55	35	6.0	15.5 ± 0.8%	13.0 ± 0.1%	71.5 ± 0.7%
10[b]	0.42	0.58	35	7.0	11.2 ± 1.3%	13.6 ± 0.2%	75.2 ± 1.1%

3.1.4. Setup and Results of Nitration in Cascade Mixer

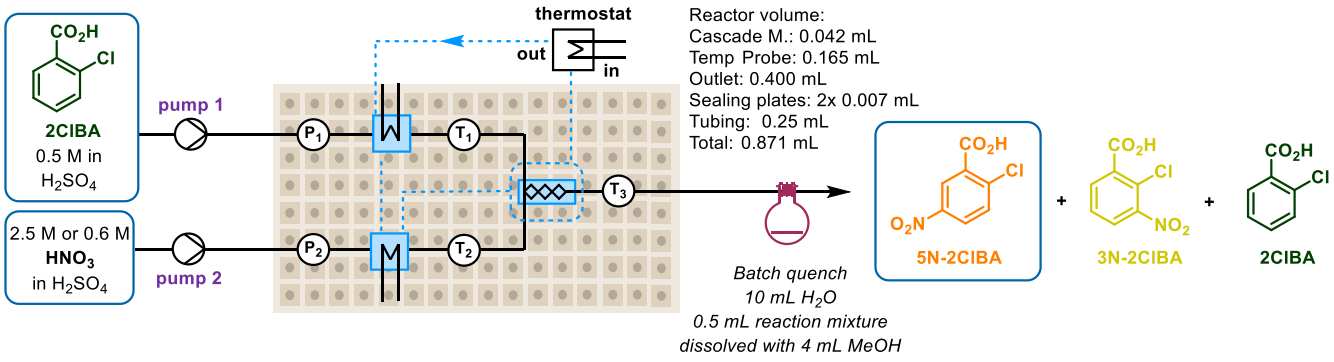


Figure S51. Process scheme for the nitration in the cascade mixer.

The HNO_3 and 2ClBA feeds were delivered with two SyrDos2 pumps (30 bar valve, 5 mL syringes, pump 1 for 2ClBA feed and pump 2 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the system through 1/8" input connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276), then temperature sensors (0501-2-1004-X, Hastelloy C-276) the MMRS system. The two streams were mixed in a temperature controlled cascade mixer 06 (0216-3-0014-F, mixing structure 10 µL, Hastelloy C-276). The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the cascade reactor was controlled by thermostat (Huber, Ministat 240). The nitration mixture left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), 1/8" input connector (0711-2-0224-F, Hastelloy C-276) and a PFA tubing. Samples were collected by quenching 0.5 mL of the reaction mixture into 10 mL of H_2O. Addition of 4 mL of MeOH dissolved the formed precipitate and samples were analyzed offline by UHPLC.

SUPPORTING INFORMATION

Table S10. Results for the initial optimization measuring the distribution of 2ClBA, 3N-2ClBA and 5N-2ClBA with UHPLC. Each percentage value is the mean of 3 measuring points. [a]For these experiments a 2.5 M stock solution of HNO_3 was used. [b]For these experiments a 0.6 M stock solution of HNO_3 was used.

Entry	Pump 1 (mL/min)	Pump 2 (mL/min)	Residence time (s)	Thermostat (°C)	Equiv. HNO_3	2ClBA UHPLC	3N-2ClBA UHPLC	5N-2ClBA UHPLC
1[a]	0.75	0.45	43.6	35	3.0	0.0 ± 0.0%	15.9 ± 0.1%	84.1 ± 0.1%
2[a]	0.60	0.60	43.6	35	5.0	0.0 ± 0.0%	16.0 ± 0.1%	84.0 ± 0.1%
3[a]	0.50	0.70	43.6	35	7.0	0.0 ± 0.0%	16.1 ± 0.2%	83.9 ± 0.2%
4[a]	0.40	0.40	65.3	35	5.0	0.0 ± 0.0%	15.7 ± 0.1%	84.3 ± 0.1%
5[a]	0.90	0.90	29.0	35	5.0	0.0 ± 0.0%	16.6 ± 0.2%	83.4 ± 0.2%
6[a]	1.20	1.20	21.8	35	5.0	0.0 ± 0.0%	16.3 ± 0.2%	83.7 ± 0.2%
7[a]	2.00	2.00	13.1	35	5.0	0.0 ± 0.0%	16.5 ± 0.2%	83.5 ± 0.2%
8[a]	3.00	3.00	8.7	35	5.0	0.0 ± 0.0%	16.5 ± 0.2%	83.5 ± 0.2%
9[b]	0.44	0.41	61.5	0	1.1	9.0 ± 0.7%	11.1 ± 0.1%	79.9 ± 0.6%
10[b]	0.52	0.48	52.3	0	1.1	9.3 ± 0.5%	11.1 ± 0.1%	79.5 ± 0.5%
11[b]	1.04	0.96	26.1	0	1.1	9.9 ± 0.7%	11.3 ± 0.1%	78.8 ± 0.6%
12[b]	2.09	1.91	13.1	0	1.1	15.3 ± 1.8%	11.0 ± 0.3%	73.7 ± 1.5%
13[b]	3.13	2.87	8.7	0	1.1	19.1 ± 2.8%	10.7 ± 0.4%	70.2 ± 2.4%
14[b]	5.22	4.78	5.2	0	1.1	18.7 ± 6.8%	11.5 ± 1.5%	69.8 ± 5.4%
15[b]	0.44	0.41	61.5	35	1.1	3.0 ± 0.9%	14.8 ± 0.2%	82.2 ± 0.7%
16[b]	0.52	0.48	52.3	35	1.1	2.6 ± 0.1%	15.1 ± 0.1%	82.3 ± 0.1%
17[b]	1.04	0.96	26.1	35	1.1	2.9 ± 0.2%	15.0 ± 0.1%	82.1 ± 0.1%
18[b]	2.09	1.91	13.1	35	1.1	2.9 ± 0.7%	15.1 ± 0.2%	82.1 ± 0.5%
19[b]	3.13	2.87	8.7	35	1.1	3.7 ± 1.5%	15.2 ± 0.3%	81.0 ± 1.2%
20[b]	5.22	4.78	5.2	35	1.1	6.5 ± 0.9%	14.9 ± 0.3%	78.6 ± 1.2%
21[b]	0.49	0.61	47.5	35	1.5	0.0 ± 0.0%	15.1 ± 0.1%	84.9 ± 0.1%
22[b]	0.41	0.69	47.5	35	2	0.0 ± 0.0%	15.1 ± 0.1%	84.9 ± 0.1%

3.2. Quench and First Separation

Initial attempts to perform the quench in a simple 4-way connector (in an ice bath) were compromised due to solid formation either in the 4-way connector or directly after it (**Figure S52**).

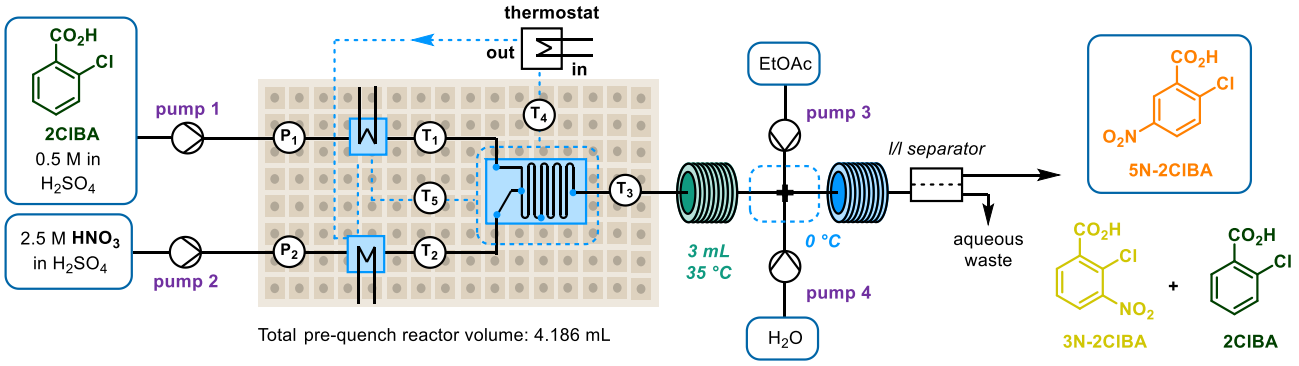


Figure S52. Process scheme for implementing the quench in a 4-way connector.

In the next stage, the quench was evaluated in a temperature controlled FlowPlate Lab reactor (**Figure S54**). The LL process plate allowed the organic and aqueous streams (port 1 and port 2) to be premixed in the first mixing zone, quench the reaction mixture in the second mixing zone (port 3) (**Figure S50B**). This aforementioned configuration overcame the limitation of solid formation during the quench. In addition, the FlowPlate has enhanced heat transfer properties compared to a simple 4-way connector. Preliminary data on the quench suggested to use either EtOAc or iPrOAc as organic solvent for the extraction, as both solvents provided >90% recovery of the organic phase. iPrOAc was favored over EtOAc, since it was expected to be less prone to saponification after the addition of NaOH, which might negatively affect phase separation performance during longer term processing. To evaluate the stability of the system a nitration run was performed for 6 h (**Figure S53**). The recovery of the organic phase after the L/L separator was between 91% and 94%, with no decrease observed over time.

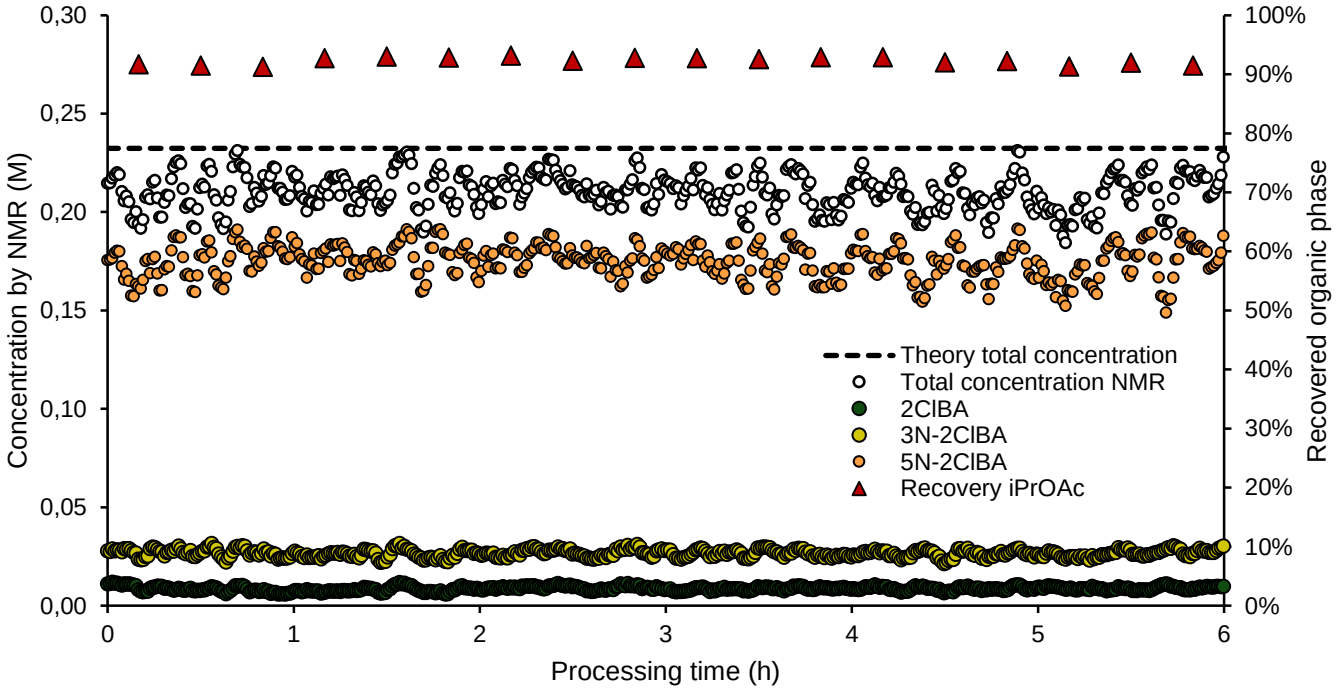


Figure S53. Experimental results for the stability run of the telescoped nitration, quench and separation.

SUPPORTING INFORMATION

Experimental Details: Stability of Extraction and Separation

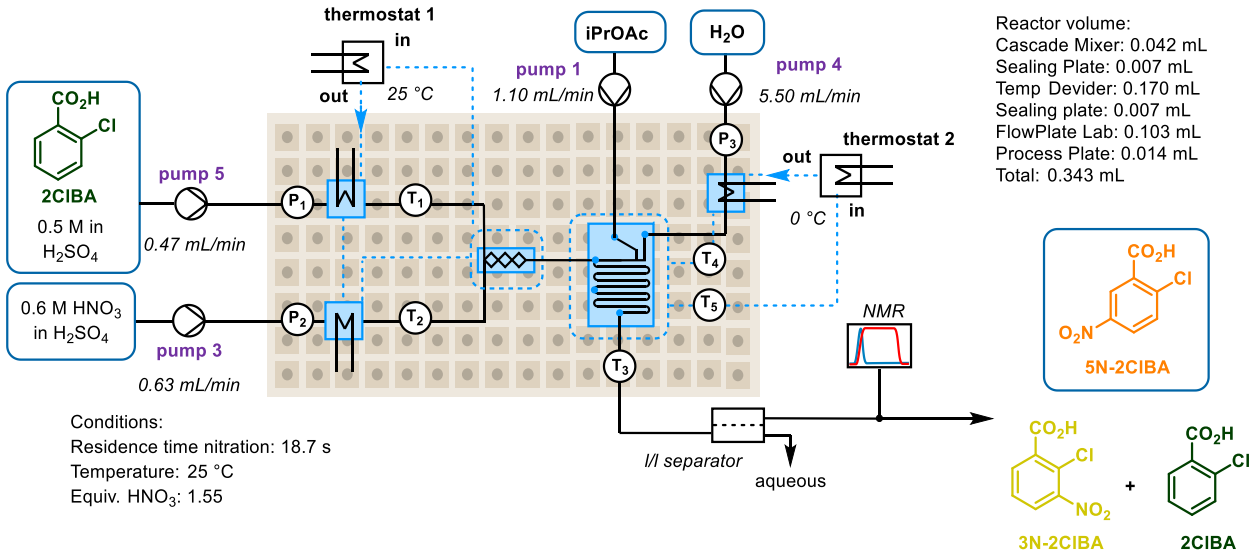


Figure S54. Process scheme for the nitration, quench and separation experiment.

The HNO_3 (0.63 mL/min) and 2ClBA (0.47 mL/min) feeds were delivered with two SyrDos2 pumps (30 bar valve, 2.5 mL syringes, pump 5 for 2ClBA feed and pump 3 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the system through 1/8" in/out connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276), then temperature sensors (0501-2-1004-X, Hastelloy C-276) the MMRS system. The two streams were mixed in a temperature controlled cascade mixer 06 (0216-3-0014-F, mixing structure 10 µL, Hastelloy C-276) and delivered through a temperature dividing block to the FlowPlate Lab (1701-3-0004-F, Hastelloy C-276) where the reaction solution was quenched with premixed water and iPrOAc. The total reactor volume for the nitration was 343 µL. The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the cascade reactor were controlled by thermostat 1 (Huber, Ministat 240). The water feed (5.5 mL/min) was pumped with a SyrDos2 pump (pump 4, 30 bar valve, 5 mL syringes) through PFA tubing (1.6 mm i.d.) and a check valve (Upchurch, CV-3321) to the MMRS system where it entered through a 1/8" in/out connector (0711-2-0224-F, Hastelloy C-276), pressure sensor module (0518-1-60x4-F, Hastelloy C-276) and coax heat exchanger (0309-4-0004-F, Hastelloy C-276) into the FlowPlate Lab. The iPrOAc feed (1.1 mL/min) was delivered with a SyrDos2 pump (pump 1, 90 bar valve, 2.5 mL syringes) through PFA tubing (0.8 mm i.d.) and a check valve (Upchurch, CV-3321) to the MMRS system where it was connected with a 1/16" in/out connector (0711-2-0124-F, Hastelloy C-276) to the FlowPlate Lab. The temperature in heat exchanger and the FlowPlate Lab was controlled by thermostat 2 (Huber, Ministat 240). The FlowPlate Lab was equipped with a LL design Process Plate (1701-4682-HC, LL-Mixer, Nominal Width 0.2 mm, Hastelloy C-22). The iPrOAc stream entered at port 1, the water stream at port 2 and the process stream from the nitration at port 3 and the quenched stream exit the process plate at port 7 (**Figure S50B**).

The quenched stream left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), 1/8" in/out connector (0711-2-0224-F, Hastelloy C-276) and a short PFA tube (150 mm length, 3.2 mm i.d.) connected to the Zaiput separator (SEP-10) equipped with a hydrophobic PFA membrane (0.4 µm, OB-400-S10). The aqueous stream was diverted to a waste bottle and the organic phase stream was delivered through PFA tubing (0.8 mm i.d.) to the benchtop NMR. A back pressure regulator (Upchurch cartridge holder (P-465) equipped with a 2.8 bar (blue, P-761) cartridge) was installed in a bypass prior the glass flow cell (800 µL internal volume, 550 mm length) for the NMR for safety reasons. Fractions for calculating the iPrOAc recovery were collected in 50 mL polypropylene tubes.

3.3. Reaction Progress Study of Nitration

The results of the reaction progress experiments are shown in **Figure S55**. The process plate for the quench was changed to the SZ design with broader reaction channels to reduce the back pressure at a total flow rate of 45 mL/min.

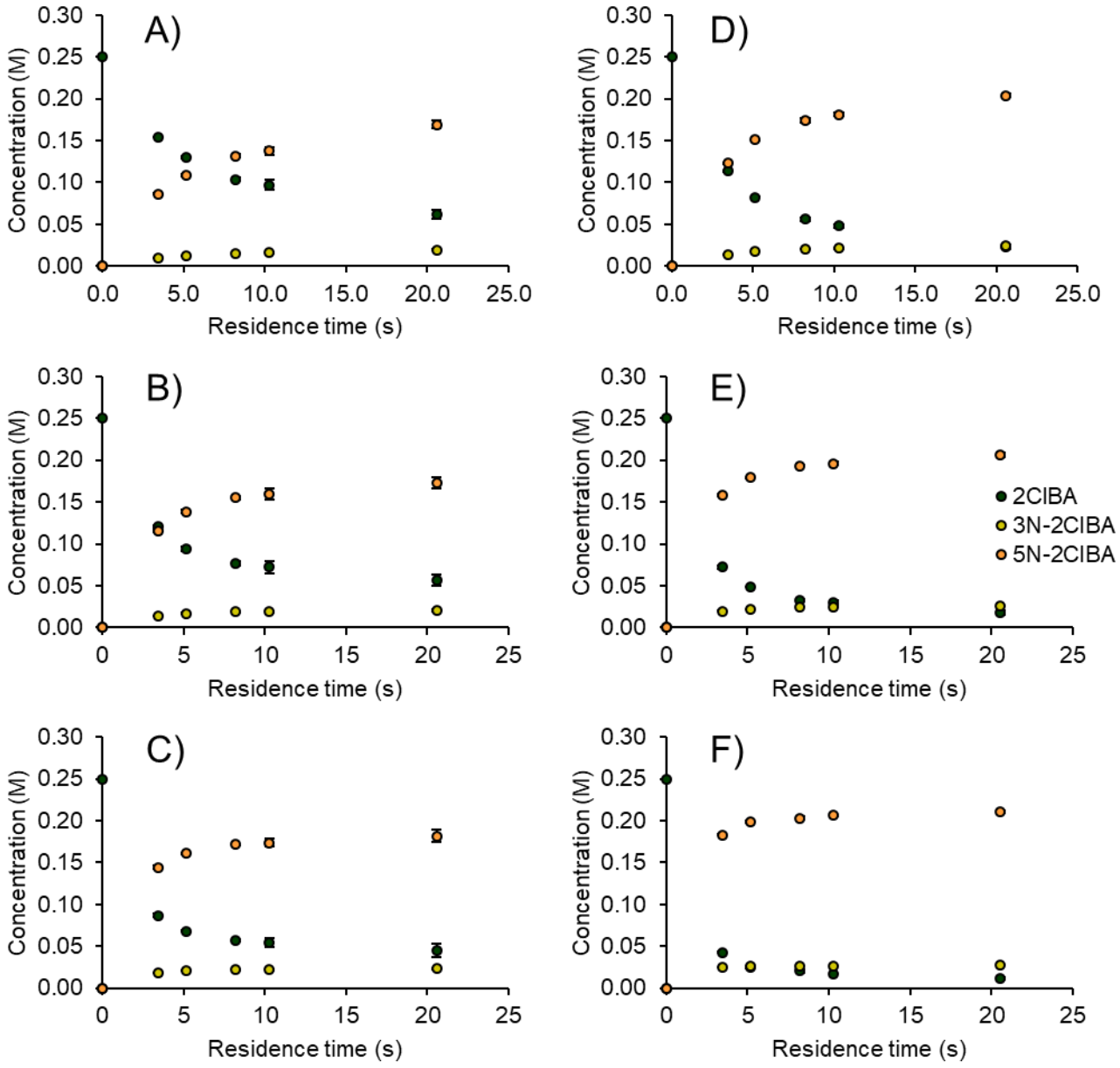


Figure S55. Results from the reaction progress experiments of the nitration. The following conditions for **A)** 1.0 equivalent of HNO_3 and 0 °C reaction temperature, **B)** 1.0 equivalent of HNO_3 and 7.5 °C reaction temperature, **C)** 1.0 equivalent of HNO_3 and 15 °C reaction temperature, **D)** 1.5 equivalent of HNO_3 and 0 °C reaction temperature, **E)** 1.5 equivalent of HNO_3 and 7.5 °C reaction temperature and **F)** 1.5 equivalent of HNO_3 and 15 °C reaction temperature were used.

SUPPORTING INFORMATION

Experimental Details: Nitration Kinetics

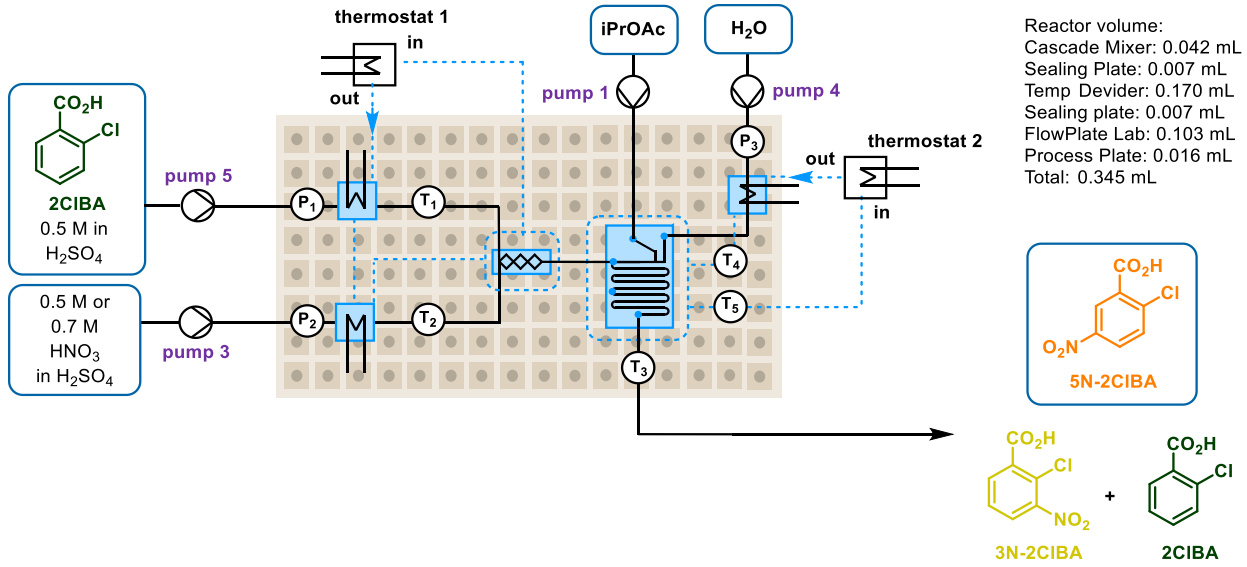


Figure S56. Process scheme for the reaction progress experiments.

The HNO_3 and 2ClBA feeds were delivered with two SyrDos2 pumps (30 bar valve, 5 mL syringes, pump 1 for 2ClBA feed and pump 2 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the system through 1/8" input connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276), then temperature sensors (0501-2-1004-X, Hastelloy C-276) the MMRS system. The two streams were mixed in a temperature controlled FlowPlate Lab (1701-3-0004-F, Hastelloy C-276) equipped with either an LL design process plate (1701-4682-HC, LL-Mixer, Nominal Width 0.2 mm, Hastelloy C-22) or a TG. The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the FlowPlate Lab was controlled by a thermostat (Huber, Ministat 240). The nitration mixture left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), 1/8" input connector (0711-2-0224-F, Hastelloy C-276) and a 3 mL PFA coil which was placed in a temperature controlled water bath. Samples were collected by quenching 0.5 mL of the reaction mixture into 10 mL of H_2O. Addition of 4 mL of MeOH dissolved the formed precipitate and samples were analyzed offline by UHPLC.

Table S11. Results for the initial optimization measuring the distribution of 2ClBA, 3N-2ClBA and 5N-2ClBA with UHPLC. Each percentage value is the mean of 3 measuring points. [a]For these experiments a 0.5 M stock solution of HNO_3 was used. [b]For these experiments a 0.7 M stock solution of HNO_3 was used.

Entry	Pump 5 (substrate) (mL/min)	Pump 3 (HNO_3) (mL/min)	Pump 1 iPrOAc (mL/min)	Pump 4 water (mL/min)	Equiv. HNO_3	Residence time (s)	Thermostat 1 (°C)	2ClBA UHPLC (M)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)
1[a]	0.50	0.50	1.50	5.00	1.0	20.6	0.0	0.062 ± 0.005	0.019 ± 0.001	0.169 ± 0.005
2[a]	1.00	1.00	3.00	10.00	1.0	10.3	0.0	0.097 ± 0.006	0.016 ± 0.001	0.137 ± 0.005
3[a]	1.25	1.25	3.75	12.50	1.0	8.2	0.0	0.103 ± 0.002	0.015 ± 0.001	0.131 ± 0.002
4[a]	2.00	2.00	6.00	20.00	1.0	5.1	0.0	0.129 ± 0.001	0.012 ± 0.001	0.108 ± 0.001
5[a]	3.00	3.00	9.00	30.00	1.0	3.4	0.0	0.154 ± 0.007	0.010 ± 0.001	0.086 ± 0.006
6[a]	0.50	0.50	1.50	5.00	1.0	20.6	7.5	0.056 ± 0.007	0.021 ± 0.001	0.173 ± 0.006
7[a]	1.00	1.00	3.00	10.00	1.0	10.3	7.5	0.072 ± 0.002	0.019 ± 0.001	0.159 ± 0.002

SUPPORTING INFORMATION

Table S12. Results for the initial optimization measuring the distribution of 2ClBA, 3N-2ClBA and 5N-2ClBA with UHPLC. Each percentage value is the mean of 3 measuring points. [a]For these experiments a 0.5 M stock solution of HNO_3 was used. [b]For these experiments a 0.7 M stock solution of HNO_3 was used.

Entry	Pump 5 (substrate) (mL/min)	Pump 3 (HNO_3) (mL/min)	Pump 1 iPrOAc (mL/min)	Pump 4 water (mL/min)	Equiv. HNO_3	Residence time (s)	Thermostat 1 (°C)	2ClBA UHPLC (M)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)
8 [a]	1.25	1.25	3.75	12.50	1.0	8.2	7.5	0.076 ± 0.003	0.019 ± 0.001	0.155 ± 0.002
9 [a]	2.00	2.00	6.00	20.00	1.0	5.1	7.5	0.094 ± 0.001	0.017 ± 0.001	0.139 ± 0.001
10 [a]	3.00	3.00	9.00	30.00	1.0	3.4	7.5	0.121 ± 0.008	0.014 ± 0.001	0.115 ± 0.007
11 [a]	0.50	0.50	1.50	5.00	1.0	20.6	15.0	0.045 ± 0.005	0.023 ± 0.001	0.182 ± 0.005
12 [a]	1.00	1.00	3.00	10.00	1.0	10.3	15.0	0.054 ± 0.001	0.022 ± 0.001	0.174 ± 0.001
13 [a]	1.25	1.25	3.75	12.50	1.0	8.2	15.0	0.057 ± 0.001	0.022 ± 0.001	0.172 ± 0.001
14 [a]	2.00	2.00	6.00	20.00	1.0	5.1	15.0	0.068 ± 0.001	0.021 ± 0.001	0.161 ± 0.002
15 [a]	3.00	3.00	9.00	30.00	1.0	3.4	15.0	0.087 ± 0.002	0.019 ± 0.001	0.144 ± 0.002
16 [b]	0.50	0.50	1.50	5.00	1.5	20.6	0.0	0.023 ± 0.002	0.024 ± 0.001	0.204 ± 0.002
17 [b]	1.00	1.00	3.00	10.00	1.5	10.3	0.0	0.048 ± 0.002	0.021 ± 0.001	0.181 ± 0.002
18 [b]	1.25	1.25	3.75	12.50	1.5	8.2	0.0	0.056 ± 0.002	0.020 ± 0.001	0.174 ± 0.001
19 [b]	2.00	2.00	6.00	20.00	1.5	5.1	0.0	0.082 ± 0.001	0.017 ± 0.001	0.151 ± 0.001
20 [b]	3.00	3.00	9.00	30.00	1.5	3.4	0.0	0.113 ± 0.001	0.014 ± 0.001	0.123 ± 0.003
21 [b]	0.50	0.50	1.50	5.00	1.5	20.6	7.5	0.018 ± 0.003	0.026 ± 0.001	0.207 ± 0.002
22 [b]	1.00	1.00	3.00	10.00	1.5	10.3	7.5	0.030 ± 0.003	0.024 ± 0.001	0.196 ± 0.001
23 [b]	1.25	1.25	3.75	12.50	1.5	8.2	7.5	0.032 ± 0.001	0.024 ± 0.001	0.193 ± 0.001
24 [b]	2.00	2.00	6.00	20.00	1.5	5.1	7.5	0.048 ± 0.001	0.022 ± 0.001	0.179 ± 0.001
25 [b]	3.00	3.00	9.00	30.00	1.5	3.4	7.5	0.072 ± 0.002	0.020 ± 0.001	0.158 ± 0.001
26 [b]	0.50	0.50	1.50	5.00	1.5	20.6	15.0	0.011 ± 0.001	0.028 ± 0.001	0.211 ± 0.001
27 [b]	1.00	1.00	3.00	10.00	1.5	10.3	15.0	0.017 ± 0.001	0.027 ± 0.001	0.206 ± 0.001
28 [b]	1.25	1.25	3.75	12.50	1.5	8.2	15.0	0.021 ± 0.002	0.026 ± 0.001	0.203 ± 0.002
29 [b]	2.00	2.00	6.00	20.00	1.5	5.1	15.0	0.025 ± 0.001	0.027 ± 0.001	0.199 ± 0.001
30 [b]	3.00	3.00	9.00	30.00	1.5	3.4	15.0	0.043 ± 0.001	0.024 ± 0.001	0.183 ± 0.001

3.4. Design Space Definition

For the detailed experimental description see section 3.1.4. The detailed flow rates and temperature setting for the experiments are listed in **Table S16** and **Table S17**. Samples for the individual experiments were collected in 15 mL polypropylene vials as triplicates, directly after the MMRS platform. The design space was limited to the temperature of 0 °C to 35 °C, the equivalents of HNO_3 from 1 to 2, and the residence time 8 s to 25 s. The experimental results from the UHPLC were imported from excel and fitted in MODDE (v12.1 Sartorius). The models were fit by using main, square, and interaction terms. The histogram plots for 2ClBA, 3N-2ClBA, and 5N-2ClBA did not show a "bell shaped" distribution, therefore the response were transformed: logarithmic (10Log(Y+1), negative logarithmic (-10Log(100-6*Y), and negative logarithmic (-10Log(90-Y), respectively. Entry 43 was excluded for the 2ClBA model because it had a standard deviation greater than 4 in the residuals normal probability plot.

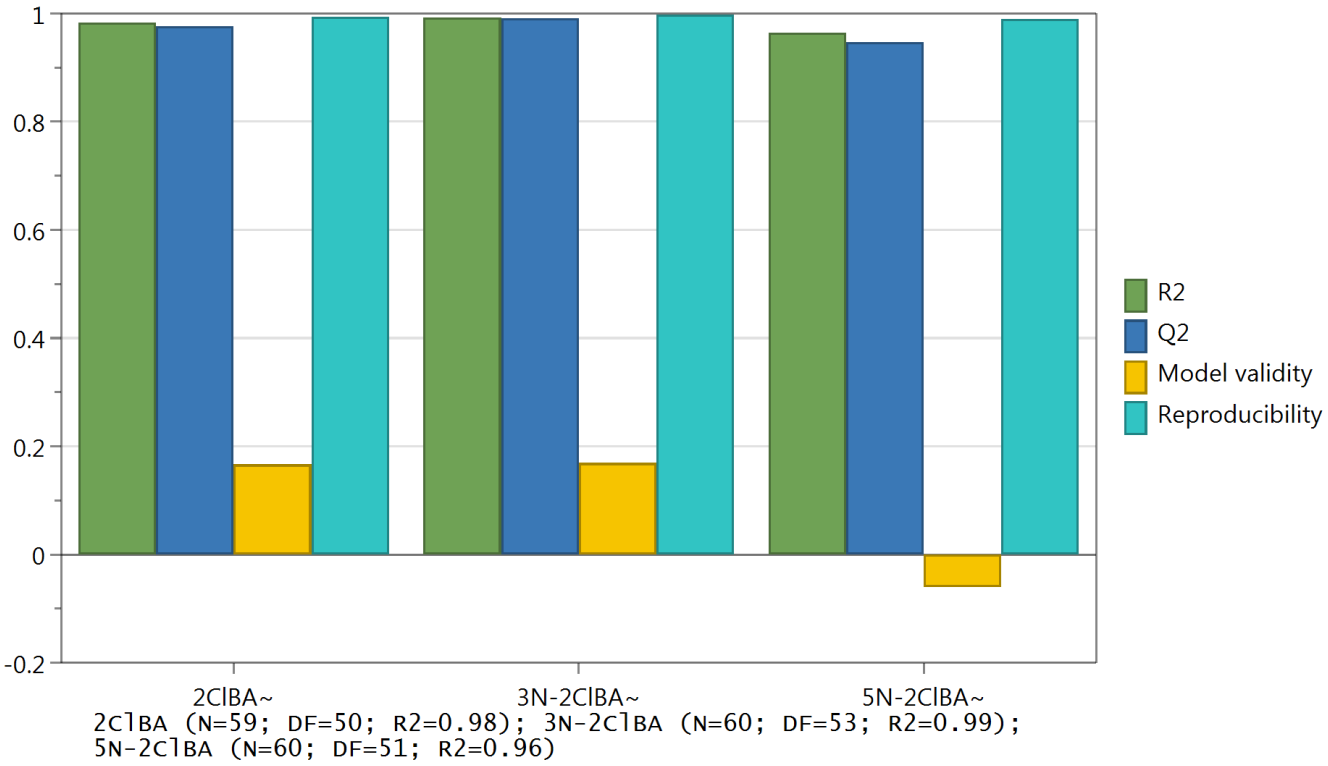


Figure S57. Summary of fit for all models. R^2 is a measure of how well the model fits the experimental data points. Q^2 measures how well the model predicts future data (should be greater than 0.1 for a significant model and greater than 0.5 for a good model). Reproducibility is a measure of experimental error. Model validity can be low (negative) in good models due to very good replicates.

3.4.1. 2ClBA Model

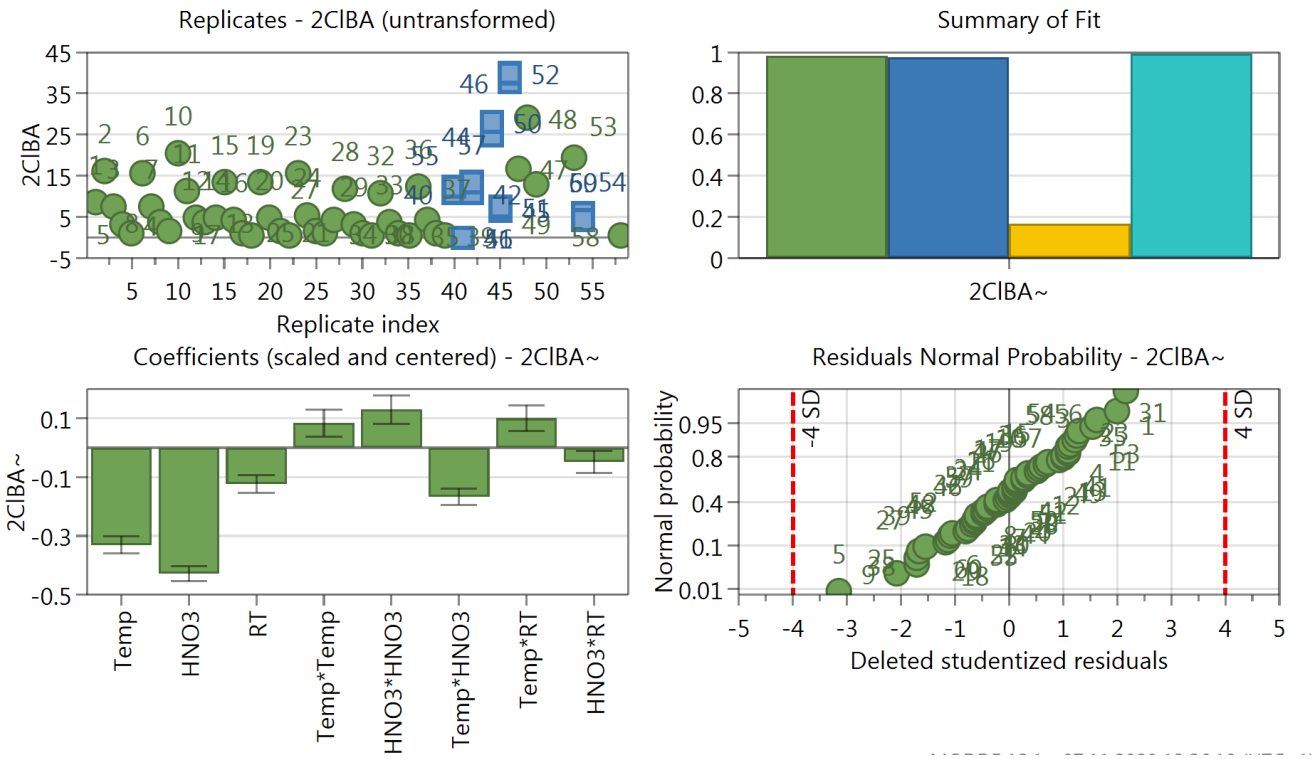


Figure S58. Summary of the design space for 2ClBA.

Table S13. ANOVA of the design space model for 2ClBA.

2CLBA	DF	SS	MS (VARIANCE)	F	P	SD
TOTAL	59	48.1659	0.816372			
CONSTANT	1	37.275	37.275			
TOTAL CORRECTED	58	10.8909	0.187775			0.43333
REGRESSION	8	10.7109	1.33886	371.779	0.000	1.15709
RESIDUAL	50	0.180061	0.00360122			0.0600102
LACK OF FIT	42	0.170516	0.0040599	3.40271	0.036	0.0637174
(MODEL ERROR)						
PURE ERROR	8	0.00954511	0.00119314			0.0345418
(REPLICATE ERROR)						
	N = 59	Q2 =	0.976	Cond. no. =	5.019	
	DF = 50	R2 =	0.983	RSD =	0.06001	
		R2 adj. =	0.981			

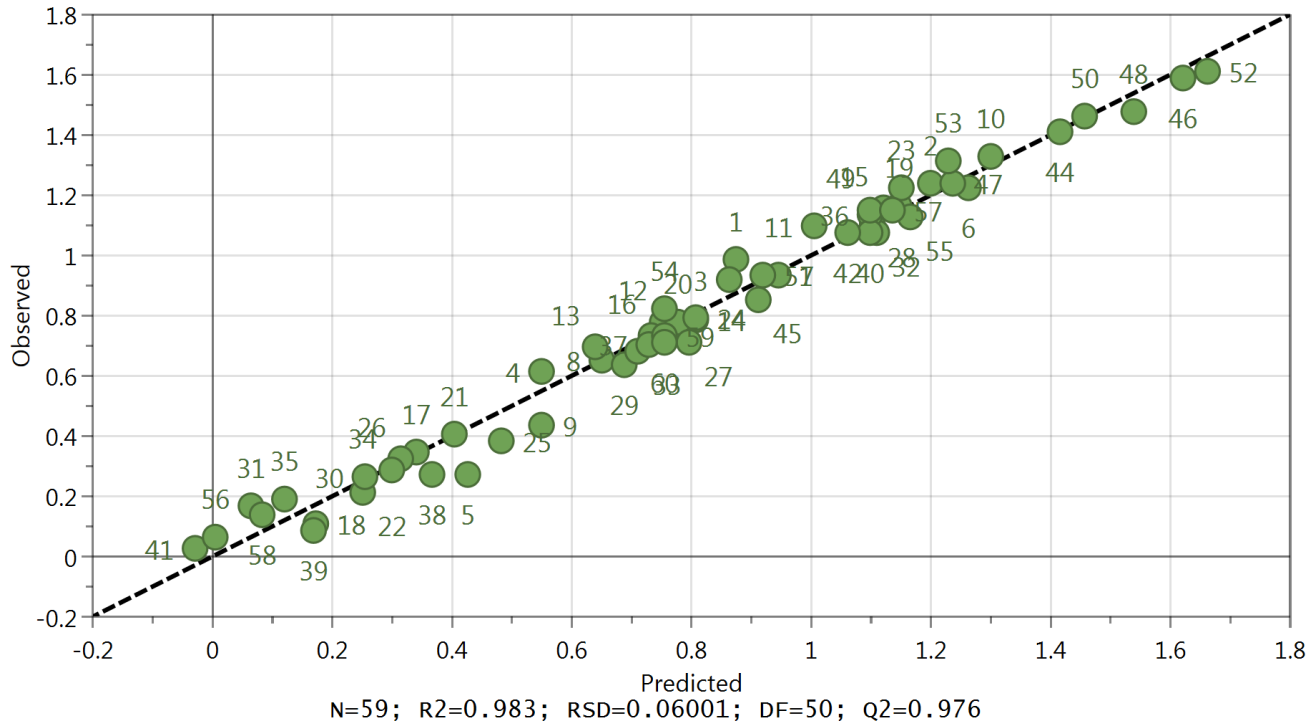


Figure S59. Predicted vs actual results from design space model for 2ClBA.

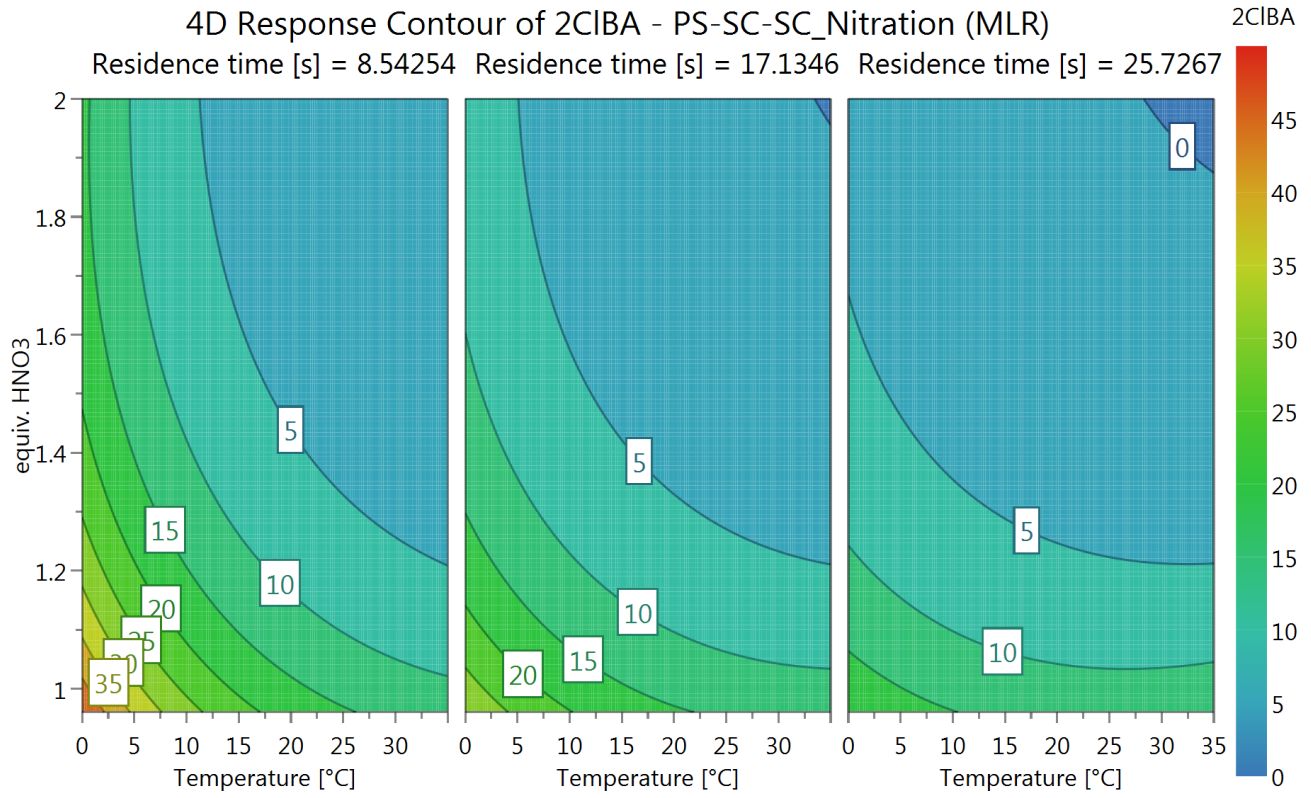


Figure S60. Contour plot showing results from the design space model for 2ClBA.

SUPPORTING INFORMATION

3.4.2. 3N-2ClBA Model

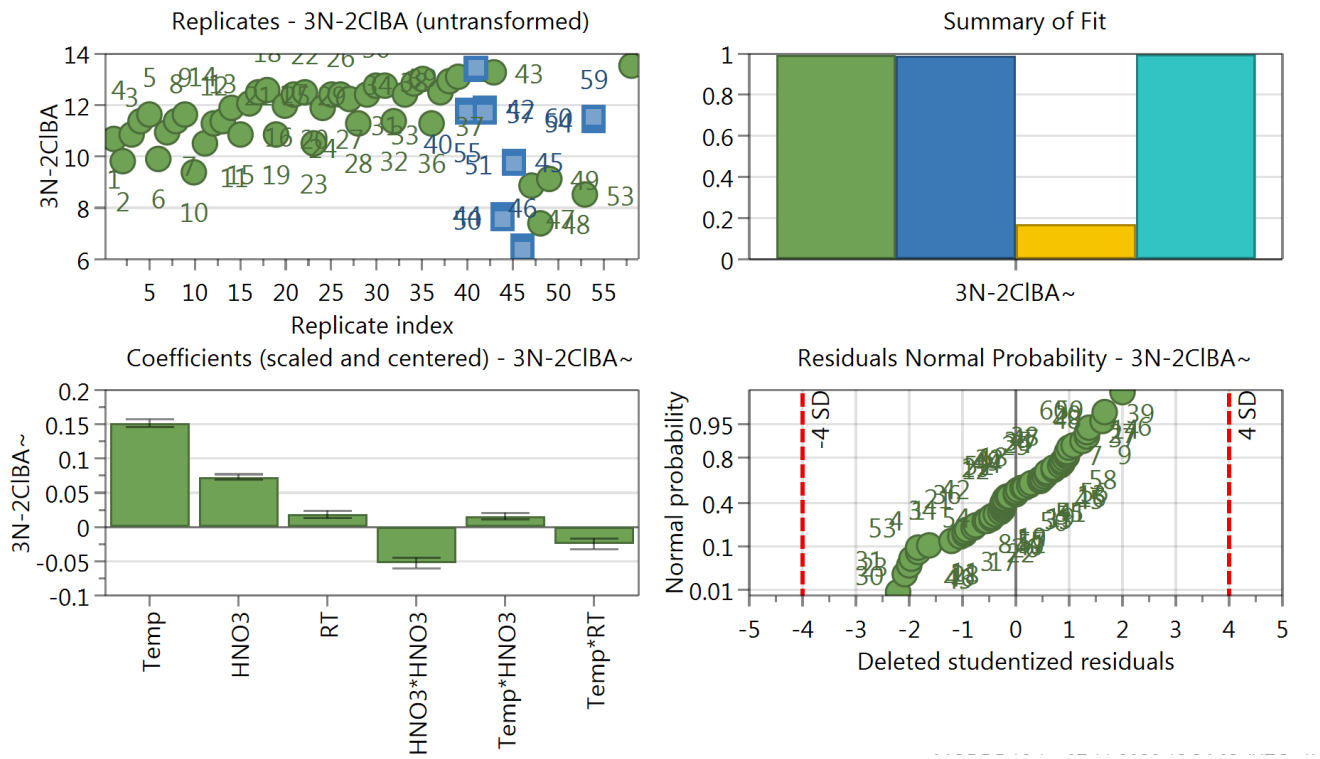


Figure S61. Summary of the design space model for **3N-2ClBA**.

Table S14. ANOVA of the design space model for **3N-2ClBA**.

3N-2CLBA	DF	SS	MS (VARIANCE)	F	P	SD
TOTAL	60	135.107	2.25178			
CONSTANT	1	134.186	134.186			
TOTAL CORRECTED	59	0.920884	0.0156082			0.124933
REGRESSION	6	0.914404	0.152401	1246.47	0.000	0.390385
RESIDUAL	53	0.00648011	0.000122266			0.0110574
LACK OF FIT	45	0.00615652	0.000136811	3.38235	0.036	0.0116966
(MODEL ERROR)						
PURE ERROR	8	0.000323589	4.04486e-05			0.00635992
(REPLICATE ERROR)						
	N = 60	Q2 =	0.991	Cond. no. =	4.238	
	DF = 53	R2 =	0.993	RSD =	0.01106	
		R2 adj. =	0.992			

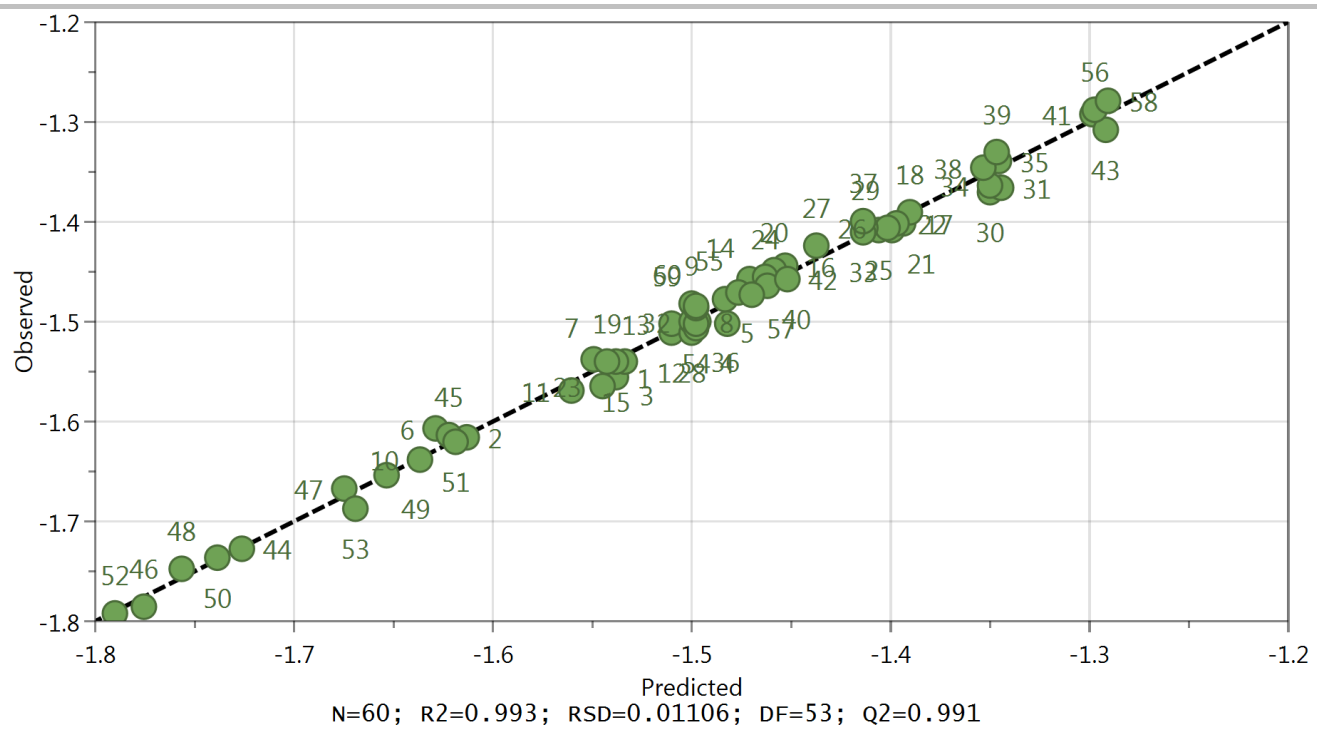


Figure S62. Predicted vs actual results from design space model for 3N-2ClBA.

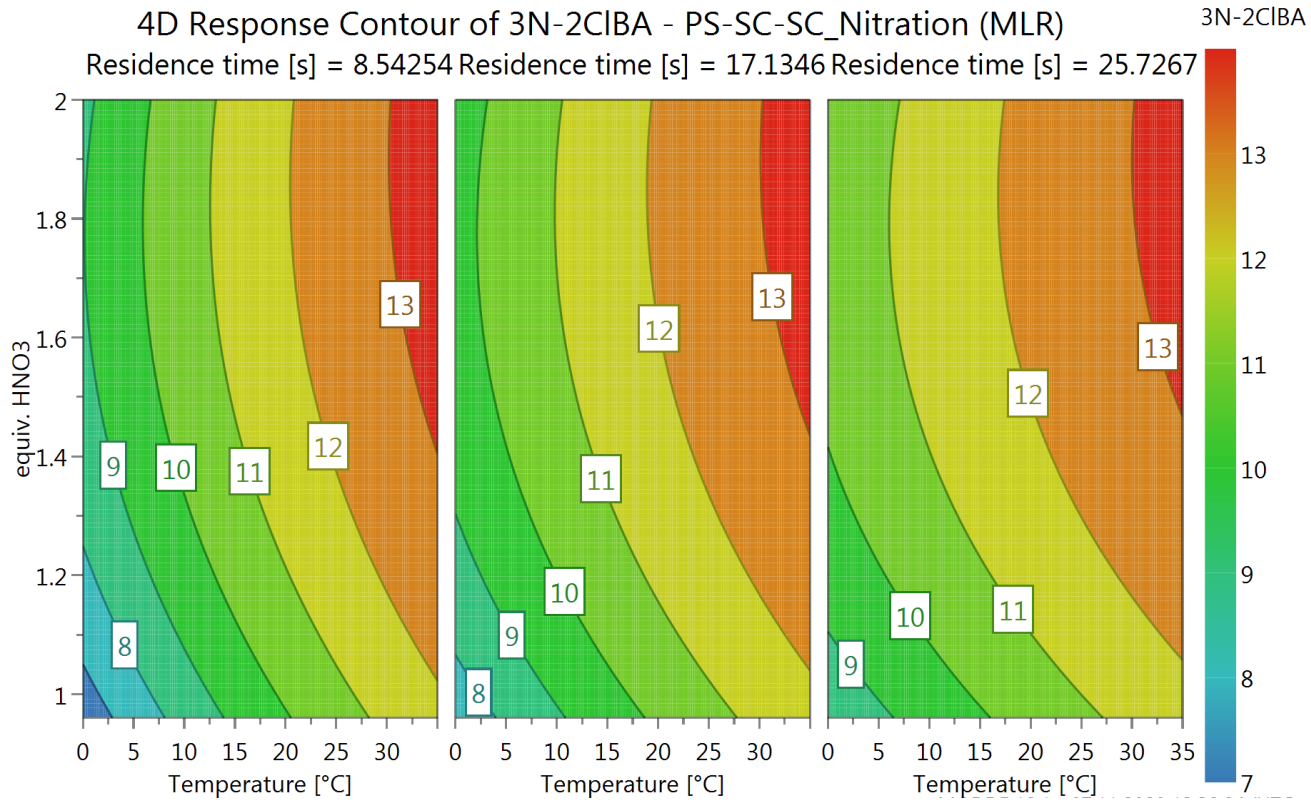


Figure S63. Contour plot showing results from the design space model for 3N-2ClBA.

3.4.3. 5N-2ClBA Model

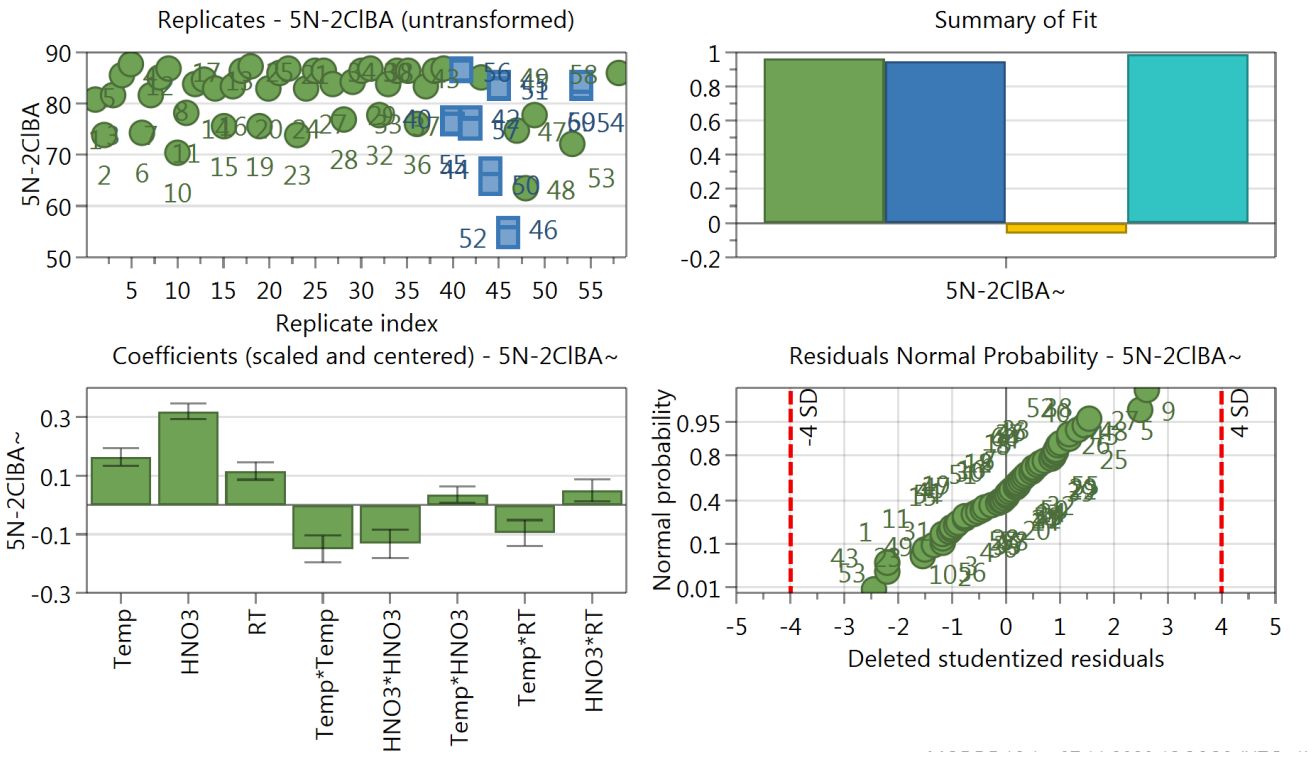


Figure S64. Summary of the design space model for 5N-2ClBA.

Table S15. ANOVA of the design space model for 5N-2ClBA.

5N-2CLBA	DF	SS	MS (VARIANCE)	F	P	SD
TOTAL	60	52.2576	0.87096			
CONSTANT	1	46.887	46.887			
TOTAL CORRECTED	59	5.37056	0.0910265			0.301706
REGRESSION	8	5.17951	0.647438	172.826	0.000	0.804636
RESIDUAL	51	0.191056	0.00374619			0.0612062
LACK OF FIT	43	0.183552	0.00426866	4.55097	0.014	0.0653349
(MODEL ERROR)						
PURE ERROR	8	0.00750373	0.000937966			0.0306262
(REPLICATE ERROR)						
	N = 60	Q2 =	0.947	Cond. no. =	5.115	
	DF = 51	R2 =	0.964	RSD =	0.06121	
		R2 adj. =	0.959			

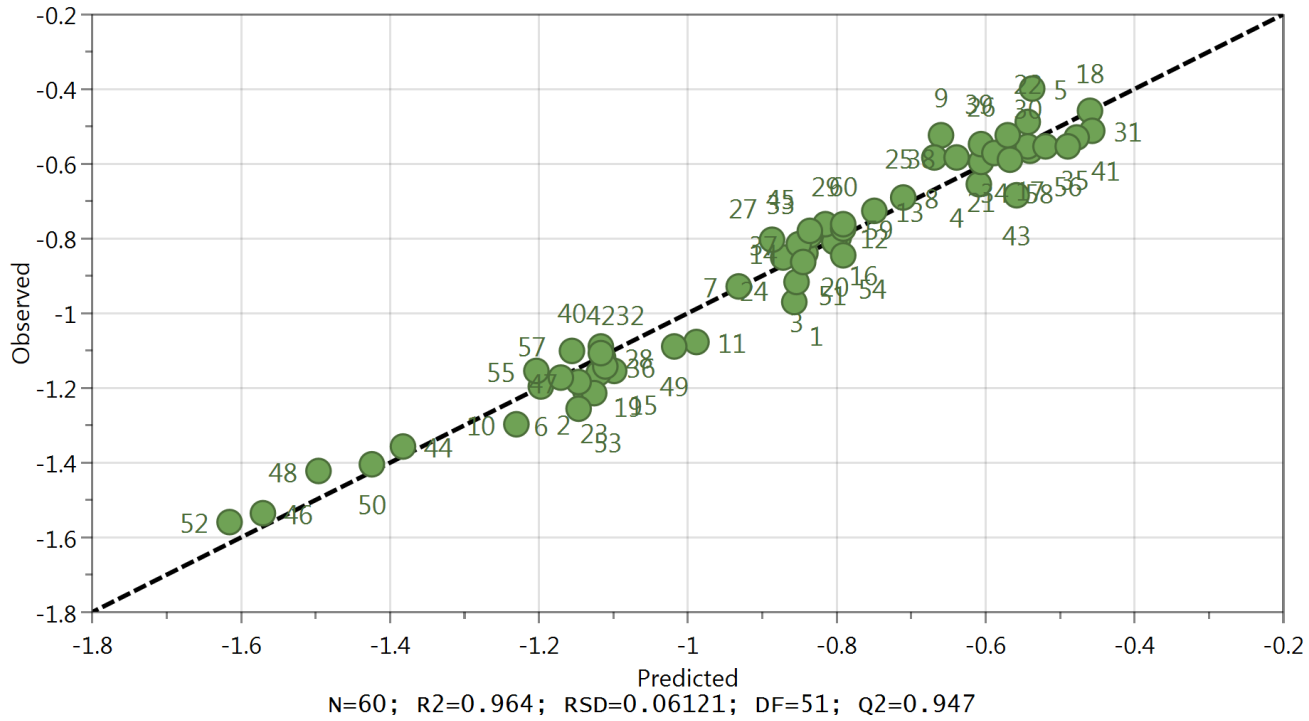


Figure S65. Predicted vs actual results from design space model for 5N-2ClBA.

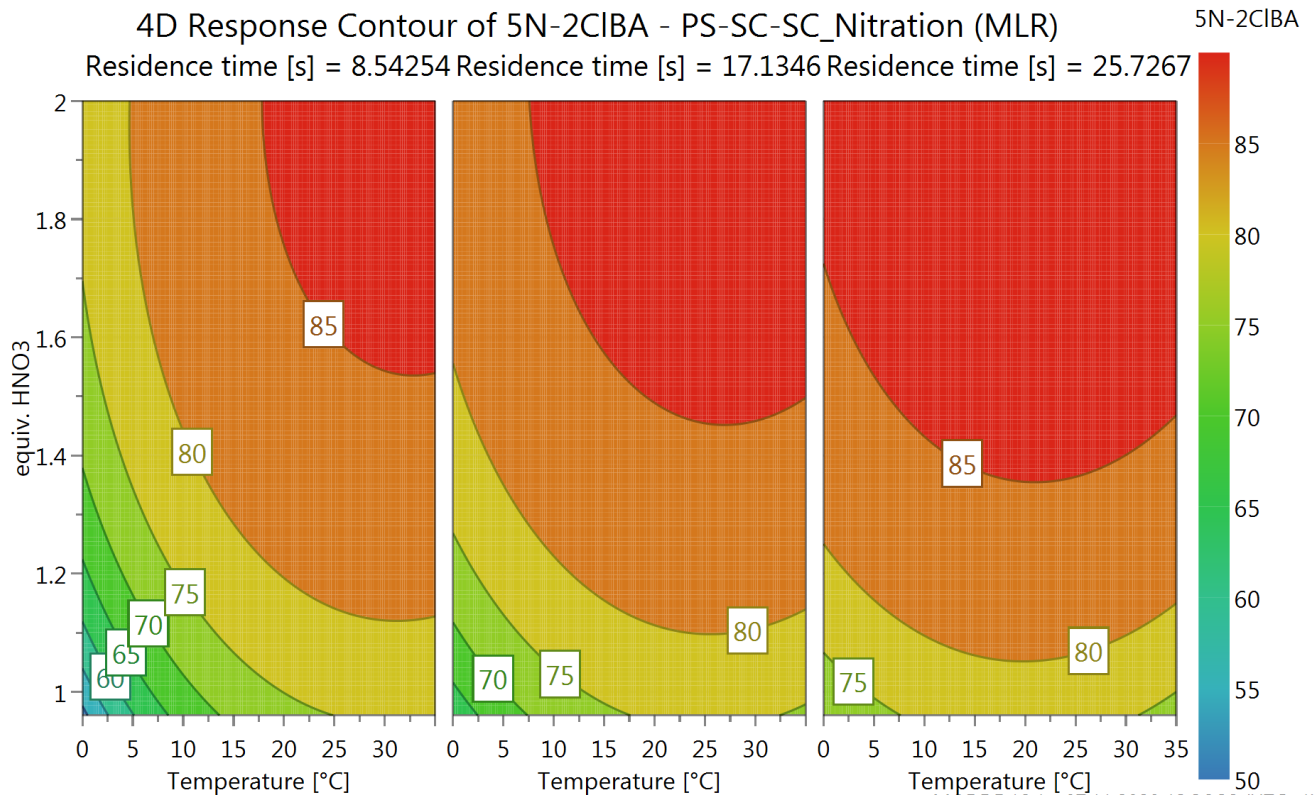


Figure S66. Contour plot showing results from the design space for 5N-2ClBA.

3.4.4. Experimental data

Table S16. Experimental conditions for the design space screen. Measuring the distribution of 2ClBA, 3N-2ClBA, and 5N-2ClBA with UHPLC. Each data point is a mean values of 3 measuring points.

Entry	Pump 5 (substrate) (mL/min)	Pump 3 (HNO_3) (mL/min)	Pump 1 iPrOAc (mL/min)	Pump 4 water (mL/min)	Equiv. HNO_3	Residence time (s)	Thermostat 1 (°C)	2ClBA UHPLC	3N-2ClBA UHPLC	5N-2ClBA UHPLC
1	0.40	0.40	0.80	4.00	1.2	25.7	15	8.7 ± 0.1%	10.7 ± 0.1%	80.6 ± 0.1%
2	0.60	0.50	1.10	5.50	1.0	18.7	15	16.3 ± 0.1%	9.8 ± 0.1%	73.9 ± 0.1%
3	0.53	0.57	1.10	5.50	1.3	18.7	15	7.4 ± 0.2%	10.9 ± 0.1%	81.8 ± 0.2%
4	0.46	0.65	1.10	5.50	1.7	18.6	15	3.1 ± 0.8%	11.4 ± 0.1%	85.5 ± 0.7%
5	0.41	0.68	1.10	5.50	2.0	18.8	15	0.9 ± 0.1%	11.7 ± 0.1%	87.5 ± 0.1%
6	0.87	0.73	1.60	8.00	1.0	12.9	15	15.7 ± 0.6%	9.9 ± 0.1%	74.4 ± 0.5%
7	0.77	0.83	1.60	8.00	1.3	12.9	15	7.6 ± 0.2%	10.9 ± 0.1%	81.5 ± 0.2%
8	0.66	0.95	1.60	8.00	1.7	12.8	15	3.5 ± 0.1%	11.4 ± 0.1%	85.1 ± 0.1%
9	0.60	1.00	1.60	8.00	2.0	12.9	15	1.7 ± 0.1%	11.6 ± 0.1%	86.7 ± 0.1%
10	1.31	1.10	2.40	12.00	1.0	8.5	15	20.4 ± 0.1%	9.4 ± 0.1%	70.2 ± 0.1%
11	1.15	1.25	2.40	12.00	1.3	8.6	15	11.4 ± 1.4%	10.5 ± 0.2%	78.1 ± 1.2%
12	1.00	1.40	2.40	12.00	1.7	8.6	15	5.0 ± 0.8%	11.2 ± 0.1%	83.7 ± 0.7%
13	0.90	1.50	2.40	12.00	2.0	8.6	15	4.0 ± 1.0%	11.4 ± 0.1%	84.7 ± 0.9%
14	0.40	0.40	0.80	4.00	1.2	25.7	25	5.1 ± 1.0%	11.9 ± 0.1%	83.0 ± 0.8%
15	0.60	0.50	1.10	5.50	1.0	18.7	25	13.4 ± 0.6%	10.9 ± 0.1%	75.7 ± 0.5%
16	0.53	0.57	1.10	5.50	1.3	18.7	25	4.4 ± 0.2%	12.0 ± 0.1%	83.5 ± 0.2%
17	0.46	0.65	1.10	5.50	1.7	18.6	25	1.2 ± 0.2%	12.5 ± 0.1%	86.3 ± 0.2%
18	0.41	0.68	1.10	5.50	2.0	18.8	25	0.3 ± 0.1%	12.6 ± 0.1%	87.1 ± 0.1%
19	0.87	0.73	1.60	8.00	1.0	12.9	25	13.7 ± 0.6%	10.9 ± 0.1%	75.5 ± 0.5%
20	0.77	0.83	1.60	8.00	1.3	12.9	25	4.9 ± 0.3%	12.0 ± 0.1%	83.1 ± 0.2%
21	0.66	0.95	1.60	8.00	1.7	12.8	25	1.5 ± 0.2%	12.4 ± 0.1%	86.1 ± 0.2%
22	0.60	1.00	1.60	8.00	2.0	12.9	25	0.6 ± 0.2%	12.5 ± 0.1%	86.9 ± 0.2%
23	1.31	1.10	2.40	12.00	1.0	8.5	25	15.8 ± 1.2%	10.5 ± 0.2%	73.7 ± 1.0%
24	1.15	1.25	2.40	12.00	1.3	8.6	25	5.2 ± 0.1%	11.9 ± 0.1%	82.9 ± 0.1%
25	1.00	1.40	2.40	12.00	1.7	8.6	25	1.4 ± 0.2%	12.4 ± 0.1%	86.2 ± 0.2%
26	0.90	1.50	2.40	12.00	2.0	8.6	25	1.1 ± 0.1%	12.4 ± 0.1%	86.5 ± 0.1%
27	0.40	0.40	0.80	4.00	1.2	25.7	30	4.1 ± 0.1%	12.2 ± 0.1%	83.6 ± 0.1%
28	0.60	0.50	1.10	5.50	1.0	18.7	30	11.8 ± 0.4%	11.3 ± 0.1%	76.9 ± 0.4%
29	0.53	0.57	1.10	5.50	1.3	18.7	30	3.4 ± 0.1%	12.4 ± 0.1%	84.2 ± 0.1%
30	0.46	0.65	1.10	5.50	1.7	18.6	30	0.8 ± 0.1%	12.7 ± 0.1%	86.4 ± 0.1%
31	0.41	0.68	1.10	5.50	2.0	18.8	30	0.5 ± 0.2%	12.8 ± 0.1%	86.7 ± 0.1%
32	0.87	0.73	1.60	8.00	1.0	12.9	30	10.9 ± 0.4%	11.4 ± 0.1%	77.7 ± 0.3%

SUPPORTING INFORMATION

Table S17. Experimental conditions for the design space screen. Measuring the distribution of 2ClBA, 3N-2ClBA, and 5N-2ClBA with UHPLC. Each data point is a mean values of 3 measuring points.

Entry	Pump 5 (substrate) (mL/min)	Pump 3 (HNO_3) (mL/min)	Pump 1 iPrOAc (mL/min)	Pump 4 water (mL/min)	Equiv. HNO_3	Residence time (s)	Thermostat 1 (°C)	2ClBA UHPLC	3N-2ClBA UHPLC	5N-2ClBA UHPLC
33	0.77	0.83	1.60	8.00	1.3	12.9	30	3.8 ± 0.3%	12.4 ± 0.1%	83.8 ± 0.2%
34	0.66	0.95	1.60	8.00	1.7	12.8	30	0.9 ± 0.2%	12.8 ± 0.1%	86.2 ± 0.2%
35	0.60	1.00	1.60	8.00	2.0	12.9	30	0.6 ± 0.5%	13.0 ± 0.1%	86.4 ± 0.4%
36	1.31	1.10	2.40	12.00	1.0	8.5	30	12.6 ± 0.1%	11.3 ± 0.1%	76.1 ± 0.1%
37	1.15	1.25	2.40	12.00	1.3	8.6	30	4.1 ± 0.1%	12.5 ± 0.1%	83.4 ± 0.1%
38	1.00	1.40	2.40	12.00	1.7	8.6	30	0.9 ± 0.2%	13.0 ± 0.1%	86.2 ± 0.2%
39	0.90	1.50	2.40	12.00	2.0	8.6	30	0.2 ± 0.1%	13.1 ± 0.1%	86.7 ± 0.1%
40	0.60	0.50	1.10	5.50	1.0	18.7	35	10.9 ± 0.2%	11.8 ± 0.1%	77.3 ± 0.2%
41	0.41	0.68	1.10	5.50	2.0	18.8	35	0.1 ± 0.1%	13.4 ± 0.1%	86.6 ± 0.1%
42	1.31	1.10	2.40	12.00	1.0	8.5	35	10.9 ± 0.5%	11.9 ± 0.1%	77.2 ± 0.4%
43	0.90	1.50	2.40	12.00	2.0	8.6	35	1.6 ± 2.1%	13.3 ± 0.3%	85.2 ± 1.8%
44	0.60	0.50	1.10	5.50	1.0	18.7	0	24.9 ± 0.2%	7.8 ± 0.1%	67.3 ± 0.1%
45	0.41	0.68	1.10	5.50	2.0	18.8	0	6.2 ± 0.4%	9.8 ± 0.1%	84.0 ± 0.3%
46	1.31	1.10	2.40	12.00	1.0	8.5	0	38.0 ± 0.2%	6.5 ± 0.1%	55.5 ± 0.2%
47	0.90	1.50	2.40	12.00	2.0	8.6	0	16.5 ± 1.3%	8.9 ± 0.2%	74.6 ± 1.1%
48	0.87	0.73	1.60	8.00	1.0	12.9	0	29.2 ± 1.1%	7.4 ± 0.1%	63.5 ± 1.0%
49	0.60	1.00	1.60	8.00	2.0	12.9	0	13.1 ± 3.9%	9.2 ± 0.4%	77.7 ± 3.5%
51	0.60	0.50	1.10	5.50	1.0	18.7	0	27.6 ± 0.1%	8.8 ± 0.1%	63.6 ± 0.1%
52	0.41	0.69	1.10	5.50	1.9	18.7	0	7.4 ± 0.5%	11.2 ± 0.1%	81.4 ± 0.4%
53	1.31	1.09	2.40	12.00	1.0	8.6	0	39.3 ± 0.1%	7.4 ± 0.1%	53.3 ± 0.1%
54	0.90	1.50	2.40	12.00	1.9	8.6	0	19.2 ± 0.5%	9.9 ± 0.1%	70.9 ± 0.4%
55	0.67	0.84	1.51	7.55	1.5	13.6	17.5	5.5 ± 0.1%	13.1 ± 0.1%	81.4 ± 0.1%
56	0.60	0.50	1.10	5.50	1.0	18.7	35	12.2 ± 0.1%	13.5 ± 0.1%	74.2 ± 0.1%
57	0.41	0.69	1.10	5.50	1.9	18.7	35	0.2 ± 0.1%	15.4 ± 0.1%	84.4 ± 0.1%
58	1.31	1.09	2.40	12.00	1.0	8.6	35	12.9 ± 0.2%	13.5 ± 0.1%	73.5 ± 0.1%
59	0.90	1.50	2.40	12.00	1.9	8.6	35	0.4 ± 0.1%	15.5 ± 0.1%	84.1 ± 0.1%
60	0.67	0.84	1.51	7.55	1.5	13.6	17.5	4.3 ± 0.1%	13.3 ± 0.1%	82.3 ± 0.1%
61	0.67	0.84	1.51	7.55	1.5	13.6	17.5	4.1 ± 0.2%	13.4 ± 0.1%	82.6 ± 0.2%

4. Hydrolysis Reaction Optimization Data

4.1. Detailed Setup

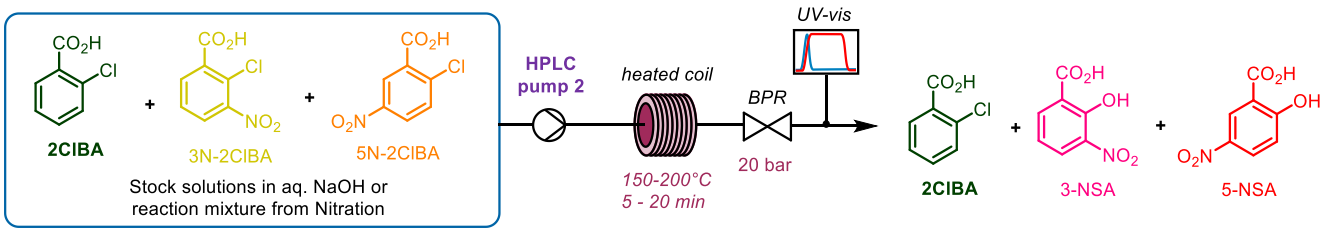


Figure S67. Process scheme for the continuous flow hydrolysis experiment.

The input solution were either prepared from pure substances or from a reaction mixture obtained from the nitration. The substrate feed was pump with a Knauer AZURA P 4.1S HPLC pump (10 mL/min pump head made of Hastelloy C and an integrated pressure sensor) through a 10 mL stainless steel coil which was placed on a coil heater (Uniqsis, HotCoil UQ1025-1). A Swagelok KCB series backpressure regulator (KCB1H0A2B5P60000, 25.8 bar max pressure) was used to maintain 20 bar in the reactor. The reaction outlet was collected in polyethylene vials and analyzed with offline UHPLC.

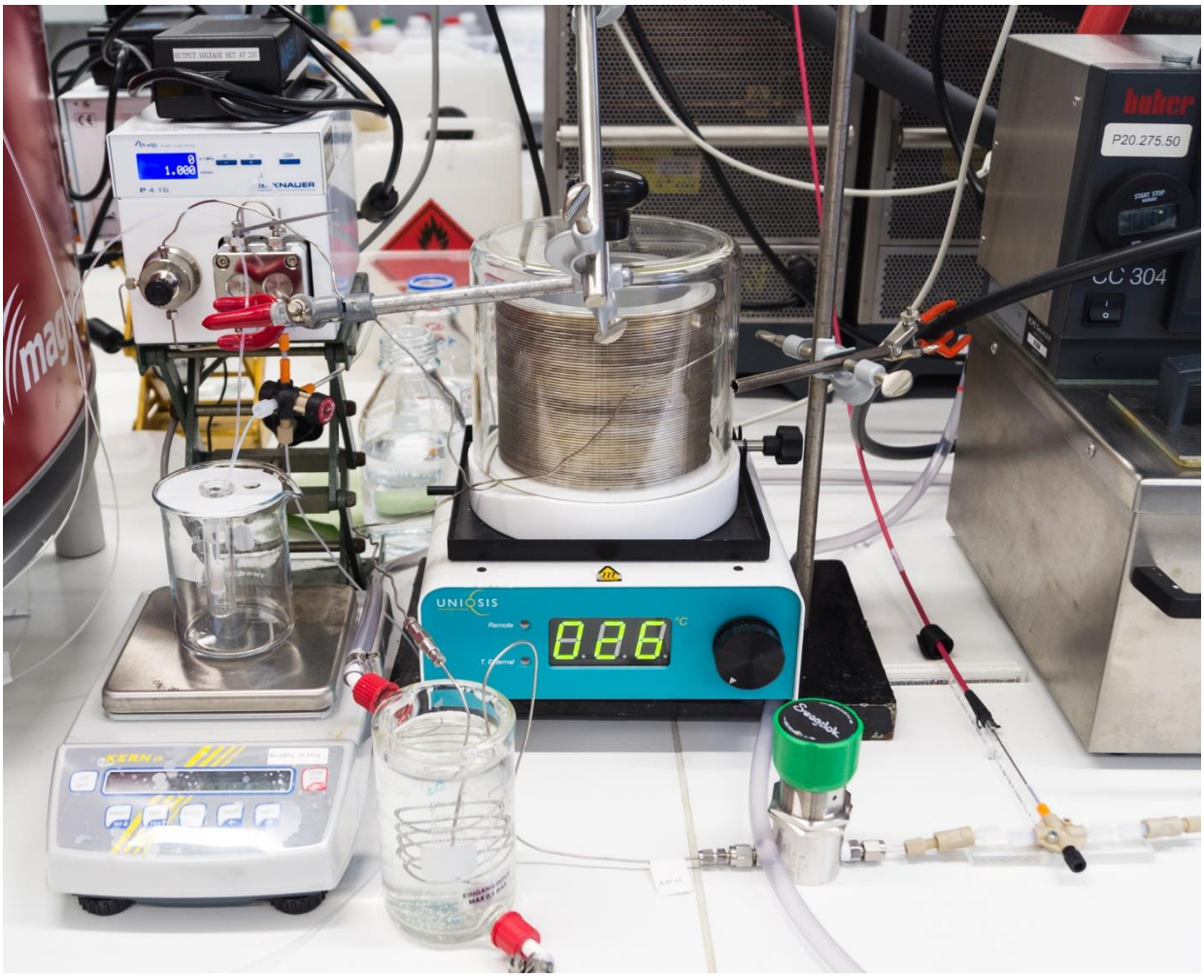


Figure S68. Photograph of the setup used for the hydrolysis reaction.

4.2. Initial Optimization

4.2.1. Batch Optimization

Preliminary data for the hydrolysis step was collected in batch by performing a fractional factorial design plan including 4 factors: concentration of the substrate (5N-2ClBA), temperature, time, and the equivalents of NaOH. The experimental conditions and results are provided in **Table S19**. The obtained results were fitted in MODDE (v12.1, Sartorius). The hydrolysis of 2ClBA to salicylic acid at 210 °C and 5.0 equivalents of NaOH did not occur. It was observed that reaction solution with a concentration >0.25 M predominantly formed an orange precipitate. Additionally, a 0.25 M solution of pure intermediate 5-NSA prepared in a 1.25 M aqueous NaOH solution immediately forms a precipitate.

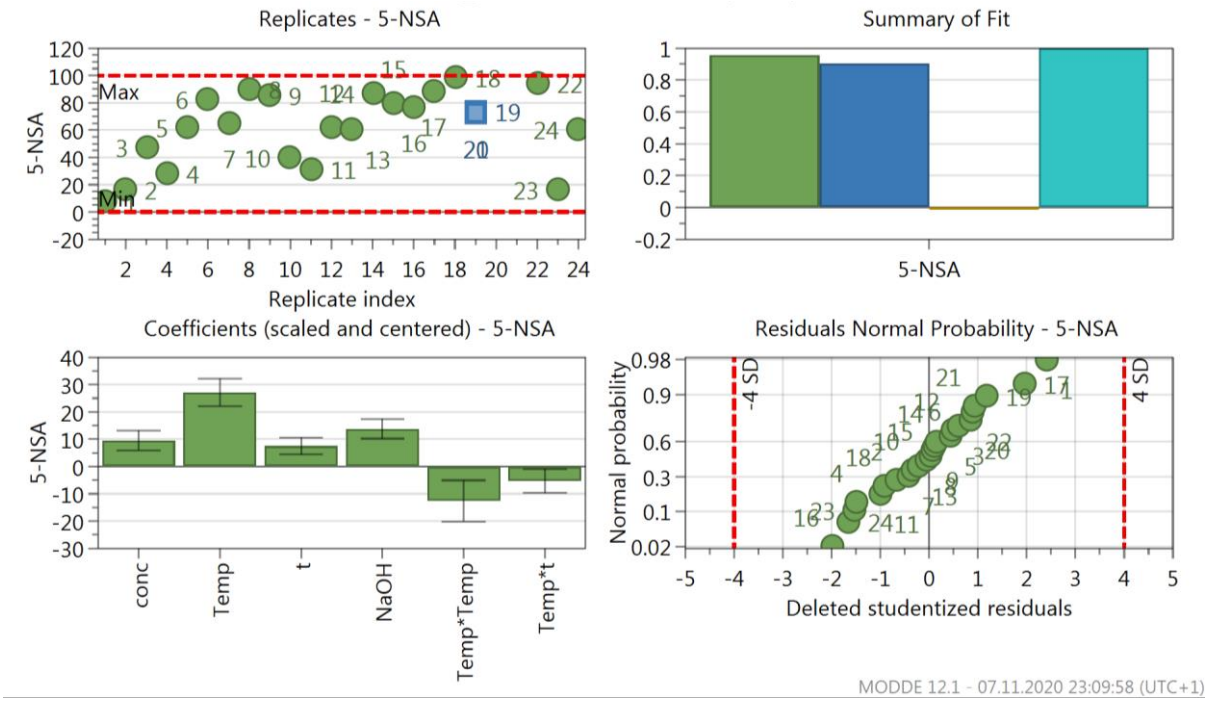


Figure S 69. Summary of the DoE model for 5-NSA.

Table S18. ANOVA of the DoE model for 5-NSA.

5-NSA	DF	SS	MS (variance)	F	p	SD
Total	24	110429	4601.21			
Constant	1	94300.8	94300.8			
Total corrected	23	16128.1	701.223			26.4806
Regression	6	15447	2574.5	64.2543	0.000	50.7395
Residual	17	681.144	40.0673			6.32988
Lack of Fit	15	679.564	45.3043	57.3469	0.017	6.73085
(Model error)						
Pure error	2	1.58001	0.790004			0.888822
(Replicate error)						
	N = 24	Q2 =	0.905	Cond. no. =	3.768	
	DF = 17	R2 =	0.958	RSD =	6.33	
		R2 adj. =	0.943			

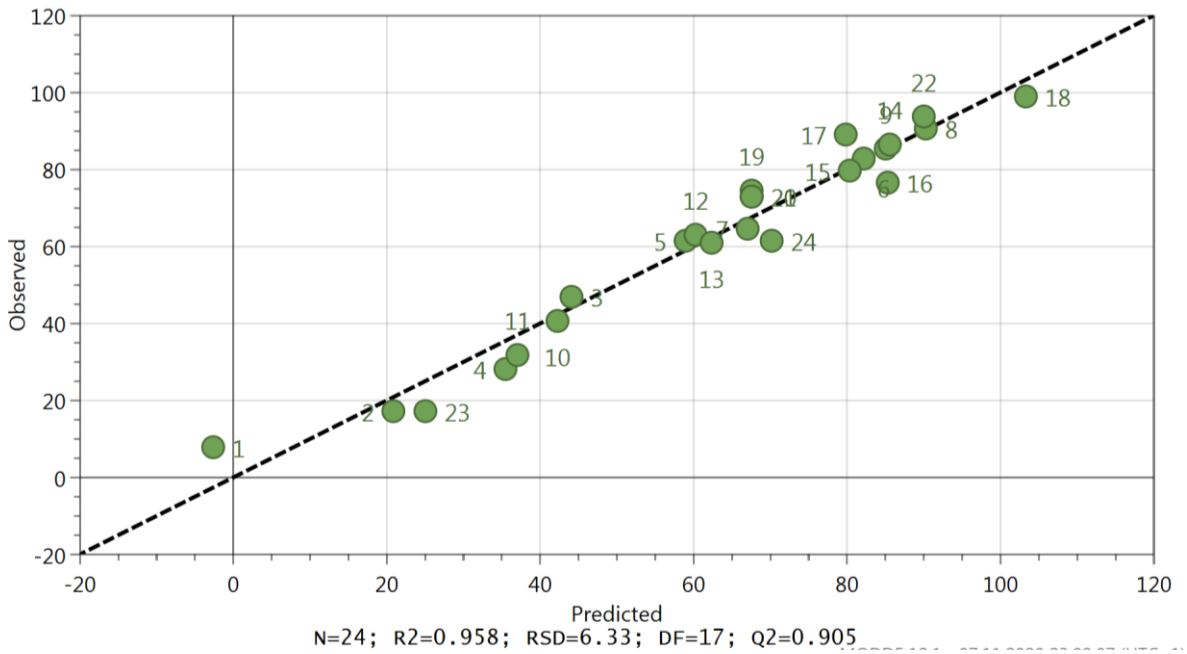


Figure S70. Predicted vs actual results from the DoE model for 5-NSA.

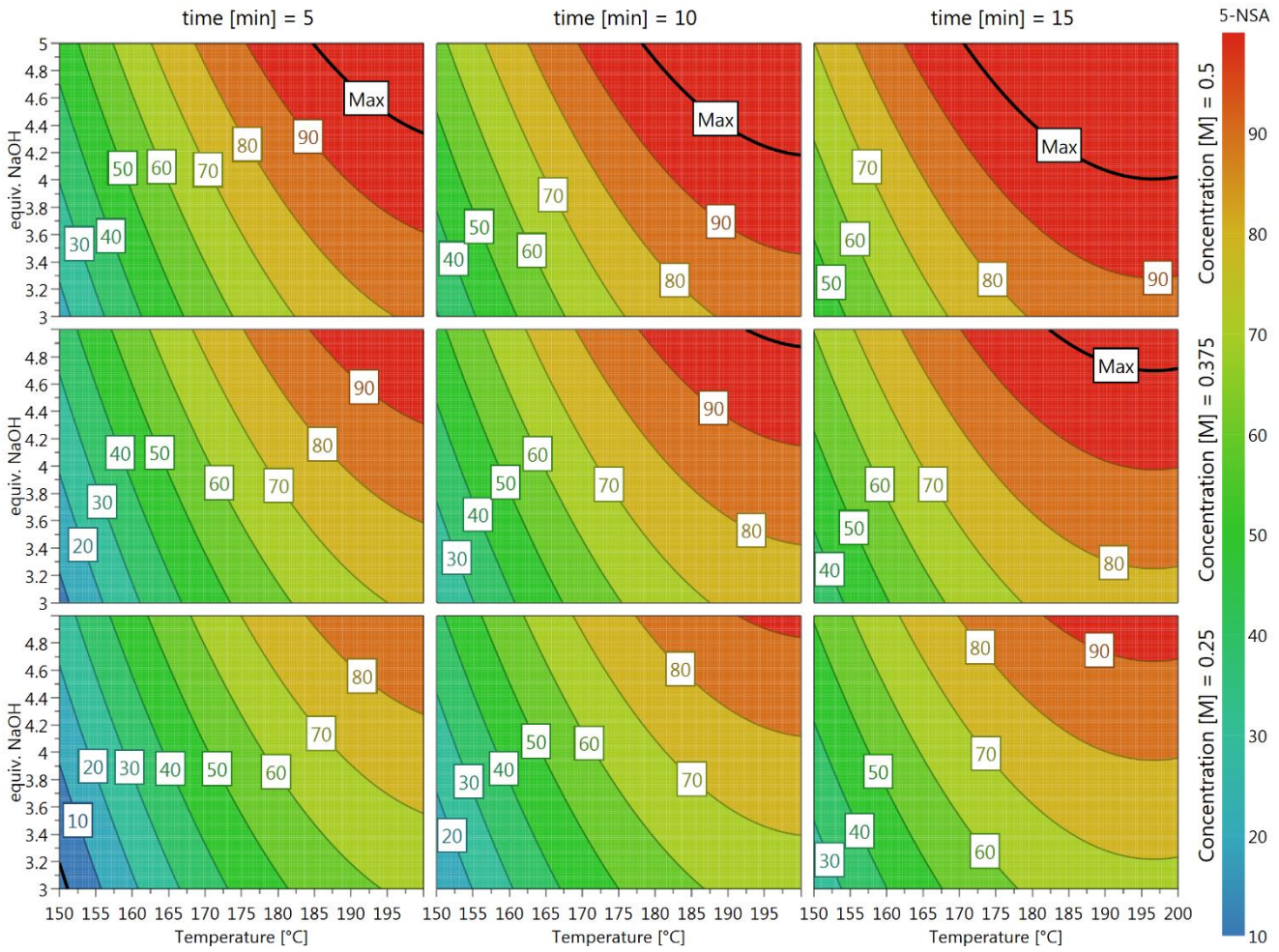
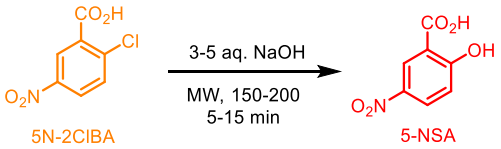


Figure S71. Contour plot showing results from the DoE model for 5-NSA.

Experimental Details: Initial Microwave optimization



A microwave vial was equipped with a stirrer bar and the desired amount of 5N-2ClBA was diluted to a volume of 2 mL with the correct concentration of an aqueous NaOH solution (prepared by diluting a 2.5 M NaOH solution with water). After microwave irradiation, the reaction was analyzed by HPLC at a wavelength of 215 nm.

Table S19. Experimental conditions and results for the initial optimization of the hydrolysis in the microwave.

Entry	Concentration (M)	Temperature (°C)	Time (min)	Equiv. NaOH	5N-2ClBA HPLC	5-NSA HPLC	Observation
1	0.250	150	5	3	92.2%	7.8%	
2	0.375	150	5	4	83.0%	17.0%	
3	0.500	150	5	5	52.9%	47.1%	orange precipitate
4	0.250	170	5	3	72.1%	27.9%	
5	0.375	170	5	4	38.4%	61.6%	
6	0.500	170	5	5	17.1%	82.9%	orange precipitate
7	0.375	190	5	3	35.2%	64.8%	
8	0.500	190	5	4	9.6%	90.4%	orange precipitate
9	0.250	190	5	5	14.5%	85.5%	
10	0.500	150	15	3	59.4%	40.6%	
11	0.250	150	15	4	68.1%	31.9%	
12	0.375	150	15	5	37.2%	62.8%	orange precipitate
13	0.375	170	15	3	39.1%	60.9%	
14	0.500	170	15	4	13.5%	86.5%	orange precipitate
15	0.250	170	15	5	20.1%	79.9%	
16	0.500	190	15	3	23.5%	76.5%	
17	0.250	190	15	4	10.9%	89.1%	
18	0.375	190	15	5	1.3%	98.7%	orange precipitate
19	0.375	170	10	4	25.6%	74.4%	orange precipitate
20	0.375	170	10	4	27.3%	72.7%	orange precipitate
21	0.375	170	10	4	26.9%	73.1%	orange precipitate
22	0.250	200	5	5	6.2%	93.8%	
23	0.250	150	5	5	82.8%	17.2%	
24	0.250	175	5	5	38.7%	61.3%	

4.2.2. Flow Optimization

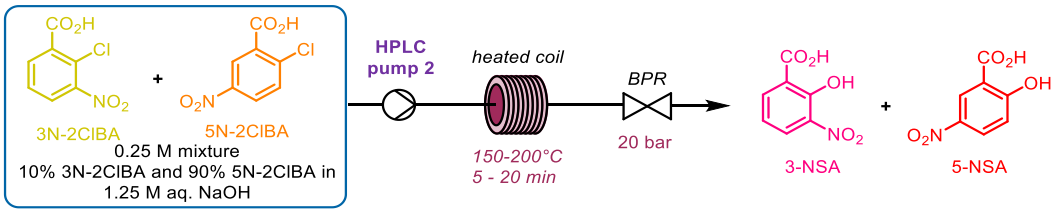


Figure S72. Process scheme for the continuous flow hydrolysis experiment.

The input solution for the experiment was prepared by dissolving 10.0589 g of a mixture of 10 wt% 3N-2ClBA and 90 wt% 5N-2ClBA with 9.9924 g of NaOH in a 200 mL volumetric flask filled up to the mark with H_2O. The feed was pump with a Knauer AZURA P 4.1S HPLC pump (10 mL/min pump head made of Hastelloy C and an integrated pressure sensor) through a 10 mL stainless steel coil which was placed on a coil heater coil heater (Uniqsis, HotCoil UQ1025-1). A Swagelok KCB series backpressure regulator (KCB1H0A2B5P60000, 25.8 bar) was used to maintain 20 bar in the reactor. The reaction outlet was collected in polyethylene vials and analyzed with offline UHPLC.

Table S20. Experimental conditions and results for the initial optimization in flow.

Entry	Concentration (M)	Temperature (°C)	Time (min)	Equiv. NaOH	3N-2ClBA UHPLC	3-NSA UHPLC	5N-2ClBA UHPLC	5-NSA UHPLC
1	0.250	200	5	5.0	0.1 ± 0.1%	9.4 ± 0.1%	1.1 ± 0.1%	89.3 ± 0.1%
2	0.250	200	10	5.0	0.1 ± 0.1%	10.1 ± 0.1%	0.0 ± 0.1%	89.8 ± 0.1%
3	0.250	200	20	5.0	0.1 ± 0.1%	9.8 ± 0.1%	0.0 ± 0.1%	90.1 ± 0.1%
4	0.250	180	5	5.0	0.6 ± 0.1%	5.5 ± 0.1%	19.0 ± 0.1%	74.9 ± 0.1%
5	0.250	180	10	5.0	0.3 ± 0.1%	7.4 ± 0.1%	5.8 ± 0.1%	86.4 ± 0.1%
6	0.250	180	20	5.0	0.1 ± 0.1%	8.9 ± 0.1%	0.7 ± 0.1%	90.3 ± 0.1%

4.3. Reaction Progress Study of Hydrolysis

4.3.1. Reaction Progress Study in Batch

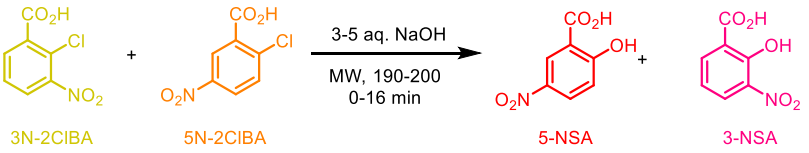


Figure S73. Reaction scheme of the reaction progress experiments in batch.

A microwave vial was equipped with a stirring bar and the desired amount of a mixture of 10 wt% 3N-2ClBA and 90 wt% 5N-2ClBA and diluted to a volume of 2 mL with the right concentration of an aqueous. NaOH solution (prepared by diluting a 2.5 M NaOH solution with water). After microwave irradiation the reaction was analyzed by UHPLC. Selected examples for the reaction progress experiments are shown in **Figure S74** for the detailed results see **Table S21** to **Table S24**.

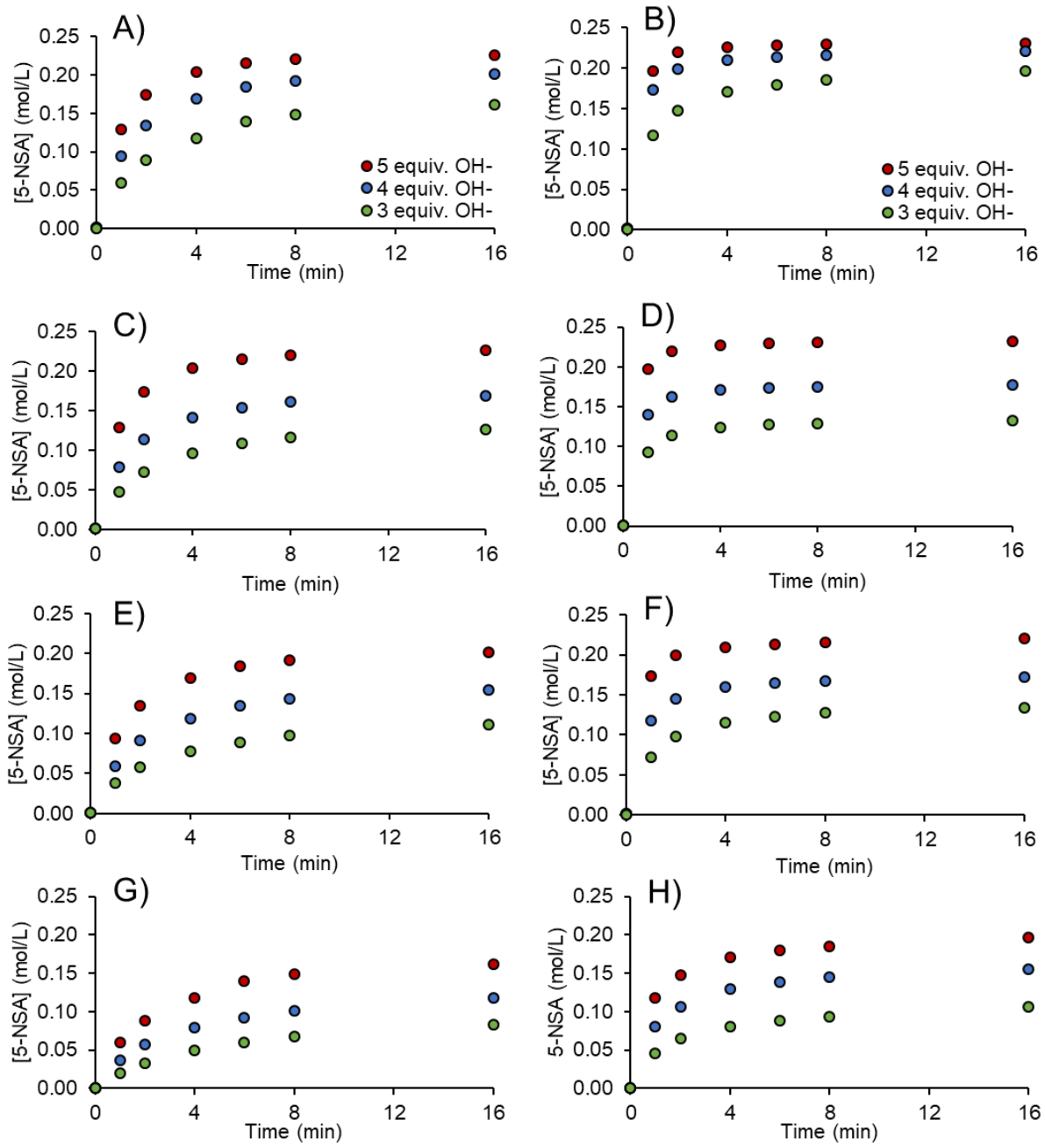


Figure S74. Selected results from the reaction progress experiments. **A)** Initial concentration of 5N-2ClBA 0.236 M and different equivalents of OH^- at 190 °C, **B)** Initial concentration of 5N-2ClBA of 0.235 M and different equivalents of OH^- at 210 °C**, C)** Concentration dependency 0.236 M (red), 0.183 M (blue) and 0.139 M (green) of 5N-2ClBA, 5 equivalents of OH^- at 190 °C, **D)** Concentration dependency 0.235 M (red), 0.183 M (blue) and 0.140 M (green) of 5N-2ClBA, 5 equivalents of OH^- at 210 °C, **E)** Concentration dependency 0.236 M (red), 0.184 M (blue) and 0.142 M (green) of 5N-2ClBA, 4 equivalents of OH^- at 190 °C, **F)** Concentration dependency 0.234 M (red), 0.184 M (blue) and 0.140 M (green) of 5N-2ClBA, 4 equivalents of OH^- at 210 °C, **G)** Concentration dependency 0.237 M (red), 0.186 M (blue) and 0.141 M (green) of 5N-2ClBA, 3 equivalents of OH^- at 190 °C, **H)** Concentration dependency 0.240 M (red), 0.186 M (blue) and 0.141 M (green) of 5N-2ClBA, 3 equivalents of OH^- at 210 °C,

SUPPORTING INFORMATION

Table S21. Experimental conditions and results for the reaction progress experiments in batch.

Entry	Equiv. NaOH	Initial [NaOH] (M)	Temperature (°C)	Time (min)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)	3-NSA UHPLC (M)	5-NSA UHPLC (M)
1	3.1	0.810	190	0	0.026	0.237	0.000	0.000
				1	0.021	0.180	0.002	0.060
				2	0.020	0.151	0.004	0.089
				4	0.019	0.121	0.006	0.117
				6	0.017	0.100	0.007	0.139
				8	0.016	0.091	0.008	0.148
				16	0.015	0.077	0.009	0.162
2	3.1	0.630	190	0	0.019	0.186	0.000	0.000
				1	0.018	0.149	0.001	0.037
				2	0.017	0.129	0.003	0.057
				4	0.016	0.107	0.004	0.079
				6	0.015	0.094	0.005	0.092
				8	0.015	0.085	0.006	0.101
				16	0.013	0.068	0.007	0.117
3	3.1	0.480	190	0	0.015	0.141	0.000	0.000
				1	0.014	0.121	0.001	0.020
				2	0.014	0.108	0.001	0.033
				4	0.013	0.091	0.002	0.049
				6	0.012	0.081	0.003	0.060
				8	0.012	0.073	0.004	0.067
				16	0.011	0.058	0.005	0.083
4	3.1	0.810	210	0	0.024	0.240	0.000	0.000
				1	0.018	0.121	0.006	0.117
				2	0.016	0.091	0.009	0.148
				4	0.014	0.068	0.011	0.171
				6	0.014	0.058	0.012	0.180
				8	0.013	0.053	0.012	0.185
				16	0.012	0.041	0.014	0.196
5	3.1	0.630	210	0	0.018	0.186	0.000	0.000
				1	0.015	0.104	0.004	0.081
				2	0.013	0.078	0.006	0.107
				4	0.011	0.056	0.007	0.129
				6	0.011	0.046	0.008	0.139
				8	0.010	0.040	0.009	0.144
				16	0.009	0.029	0.010	0.155

Table S22. Experimental conditions and results for the reaction progress experiments in batch.

Entry	Equiv. NaOH	Initial [NaOH] (M)	Temperature (°C)	Time (min)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)	3-NSA UHPLC (M)	5-NSA UHPLC (M)
6	3.1	0.480	210	0	0.014	0.141	0.000	0.000
				1	0.012	0.095	0.002	0.046
				2	0.011	0.076	0.003	0.064
				4	0.010	0.060	0.004	0.080
				6	0.010	0.052	0.005	0.088
				8	0.009	0.046	0.005	0.094
				16	0.008	0.034	0.006	0.106
7	4.1	1.080	190	0	0.025	0.236	0.000	0.001
				1	0.020	0.143	0.005	0.094
				2	0.018	0.102	0.007	0.135
				4	0.015	0.067	0.010	0.169
				6	0.013	0.052	0.012	0.185
				8	0.013	0.044	0.013	0.192
				16	0.011	0.035	0.014	0.201
8	4.1	0.840	190	0	0.020	0.184	0.000	0.001
				1	0.017	0.125	0.003	0.060
				2	0.016	0.094	0.005	0.091
				4	0.014	0.066	0.007	0.119
				6	0.012	0.050	0.009	0.134
				8	0.011	0.041	0.010	0.143
				16	0.010	0.029	0.011	0.154
9	4.1	0.640	190	0	0.015	0.142	0.000	0.001
				1	0.013	0.104	0.002	0.038
				2	0.012	0.084	0.003	0.058
				4	0.011	0.065	0.004	0.077
				6	0.010	0.053	0.005	0.089
				8	0.010	0.045	0.006	0.097
				16	0.008	0.030	0.007	0.111
10	4.1	1.080	210	0	0.026	0.234	0.000	0.001
				1	0.015	0.061	0.011	0.173
				2	0.012	0.034	0.015	0.199
				4	0.010	0.023	0.017	0.210
				6	0.009	0.019	0.018	0.214
				8	0.009	0.017	0.018	0.216
				16	0.008	0.012	0.019	0.221

Table S23. Experimental conditions and results for the reaction progress experiments in batch.

Entry	Equiv. NaOH	Initial [NaOH] (M)	Temperature (°C)	Time (min)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)	3-NSA UHPLC (M)	5-NSA UHPLC (M)
11	4.1	0.840	210	0	0.019	0.184	0.000	0.001
				1	0.013	0.067	0.007	0.118
				2	0.011	0.039	0.009	0.145
				4	0.009	0.024	0.012	0.160
				6	0.008	0.019	0.012	0.165
				8	0.007	0.016	0.013	0.168
				16	0.006	0.011	0.014	0.173
12	4.1	0.640	210	0	0.016	0.140	0.000	0.001
				1	0.012	0.068	0.004	0.073
				2	0.010	0.042	0.007	0.098
				4	0.008	0.025	0.009	0.116
				6	0.007	0.017	0.010	0.123
				8	0.006	0.012	0.011	0.128
				16	0.005	0.007	0.012	0.133
13	5.1	1.350	190	0	0.026	0.236	0.000	0.001
				1	0.018	0.107	0.008	0.130
				2	0.014	0.062	0.013	0.174
				4	0.011	0.032	0.016	0.204
				6	0.009	0.020	0.019	0.216
				8	0.008	0.014	0.020	0.221
				16	0.006	0.009	0.021	0.226
14	5.1	1.050	190	0	0.021	0.183	0.000	0.001
				1	0.017	0.105	0.004	0.079
				2	0.014	0.070	0.007	0.114
				4	0.011	0.041	0.010	0.142
				6	0.010	0.028	0.012	0.155
				8	0.009	0.022	0.013	0.161
				16	0.007	0.014	0.014	0.169
15	5.1	0.800	190	0	0.017	0.139	0.000	0.001
				1	0.014	0.091	0.003	0.048
				2	0.013	0.066	0.004	0.073
				4	0.011	0.043	0.007	0.096
				6	0.009	0.030	0.008	0.109
				8	0.008	0.022	0.009	0.117
				16	0.006	0.012	0.011	0.127

Table S24. Experimental conditions and results for the reaction progress experiments in batch.

Entry	Equiv. NaOH	Initial [NaOH] (M)	Temperature (°C)	Time (min)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)	3-NSA UHPLC (M)	5-NSA UHPLC (M)
16	5.1	1.350	210	0	0.027	0.235	0.000	0.001
				1	0.013	0.038	0.016	0.197
				2	0.008	0.014	0.020	0.220
				4	0.005	0.007	0.022	0.228
				6	0.005	0.006	0.023	0.229
				8	0.004	0.005	0.023	0.231
				16	0.003	0.003	0.024	0.232
17	5.1	1.050	210	0	0.022	0.183	0.000	0.001
				1	0.012	0.042	0.011	0.140
				2	0.009	0.020	0.014	0.163
				4	0.007	0.012	0.016	0.171
				6	0.007	0.009	0.017	0.173
				8	0.006	0.008	0.017	0.175
				16	0.005	0.005	0.018	0.177
18	5.1	0.800	210	0	0.016	0.140	0.000	0.001
				1	0.011	0.048	0.006	0.092
				2	0.009	0.026	0.009	0.114
				4	0.007	0.016	0.010	0.124
				6	0.006	0.012	0.011	0.127
				8	0.006	0.011	0.011	0.129
				16	0.005	0.007	0.012	0.132

4.3.2. Confirmatory Experiments in Flow

The results from the reaction progress in batch were validated with continuous flow experiments. The process scheme is shown in **Figure S72**. Results for the experiments are depicted in **Table S25**.

The input solution for entry 1 was prepared by dissolving 10.0814 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA with 6.0709 g of NaOH in a 250 mL volumetric flask filled up to the mark with H_2O. The input solution for entry 2 was prepared by dissolving 10.0813 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA with 9.9466 g of NaOH in a 250 mL volumetric flask filled up to the mark with H_2O.

Table S25. Continuous flow results for the reaction progress of the hydrolysis step.

Entry	Equiv. NaOH	Initial [NaOH] (M)	Temperature (°C)	Flow rate (mL/min)	Time (min)	3N-2ClBA UHPLC (M)	5N-2ClBA UHPLC (M)	3-NSA UHPLC (M)	5-NSA UHPLC (M)
1	3.0	0.607	210	0.000	0.0	0.011	0.188	0.000	0.000
				8.000	1.25	0.006	0.072	0.005	0.116
				5.000	2.0	0.005	0.052	0.007	0.136
				2.500	4.0	0.004	0.028	0.009	0.159
				1.250	8.0	0.002	0.014	0.011	0.173
				1.000	10.0	0.002	0.012	0.011	0.175
				0.625	16.0	0.001	0.007	0.012	0.180
2	5.0	1.000	210	0.000	0.0	0.011	0.188	0.000	0.000
				8.000	1.25	0.003	0.023	0.010	0.164
				5.000	2.0	0.002	0.011	0.012	0.175
				2.500	4.0	0.000	0.002	0.014	0.183
				1.250	8.0	0.000	0.001	0.015	0.184
				1.000	10.0	0.000	0.002	0.014	0.183
				0.625	16.0	0.000	0.002	0.014	0.185

4.4. Design Space Definition

Dynamic experiments were executed to screen the design space for the hydrolysis reaction. The process scheme is depicted in **Figure S72**. The input solution for the first dynamic experiment was prepared by dissolving 10.0814 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA with 6.0709 g of NaOH in a 250 mL volumetric flask filled up to the mark with H_2O. The input solution for the second dynamic experiment was prepared by dissolving 10.0813 g of a mixture of 6 wt% 3N-2ClBA and 94 wt% 5N-2ClBA with 9.9466 g of NaOH in a 250 mL volumetric flask filled up to the mark with H_2O. The reactor was heated to 210 °C over a time period of 60 min and a flow rate of 1.0 mL/min was used. The reaction mixture was monitored by inline UV/vis spectrometry and offline UHPLC.

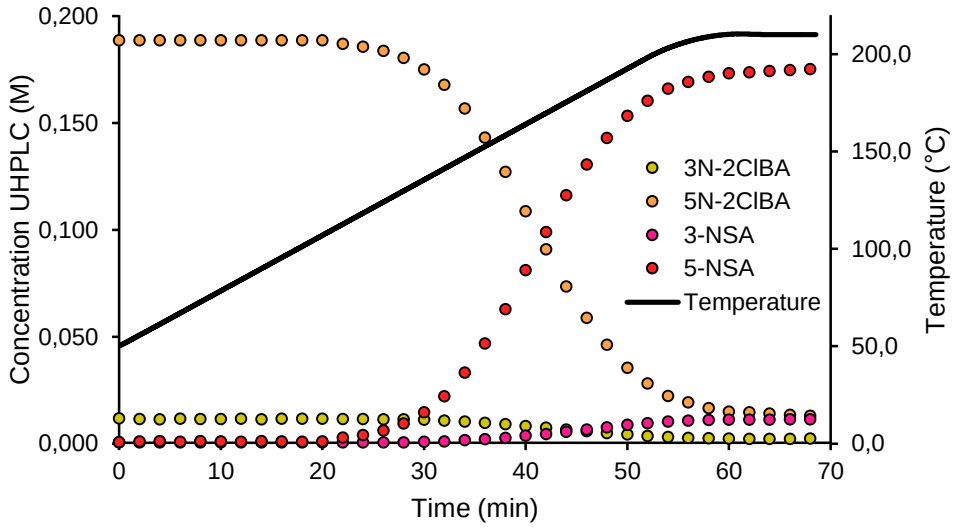


Figure S75. Dynamic experiment of the hydrolysis step using 3.0 equivalents of NaOH. Increasing the temperature from 50 °C to 210 °C over a time period of 1 h.

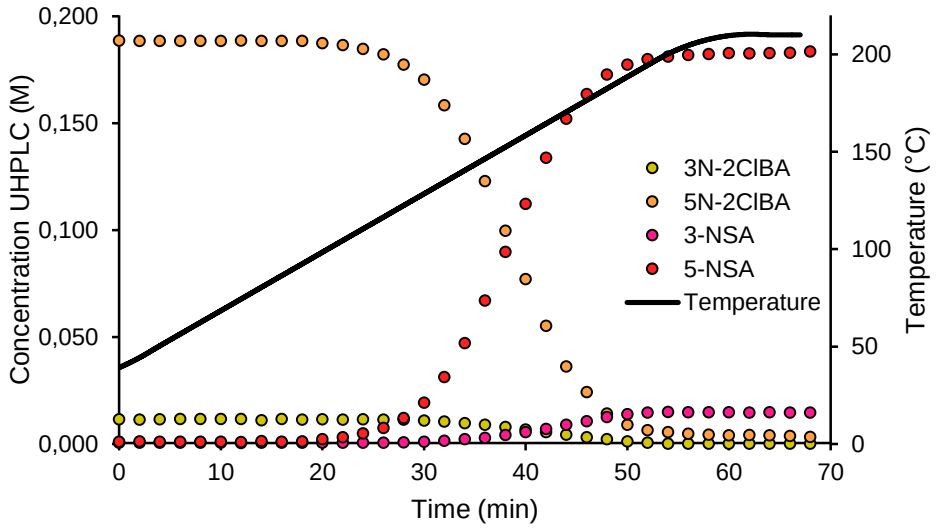


Figure S76. Dynamic experiment of the hydrolysis step using 5.0 equivalents of NaOH. Increasing the temperature from 39 °C to 210 °C over a time period of 1 h.

4.5. Telescoped Nitration and Hydrolysis

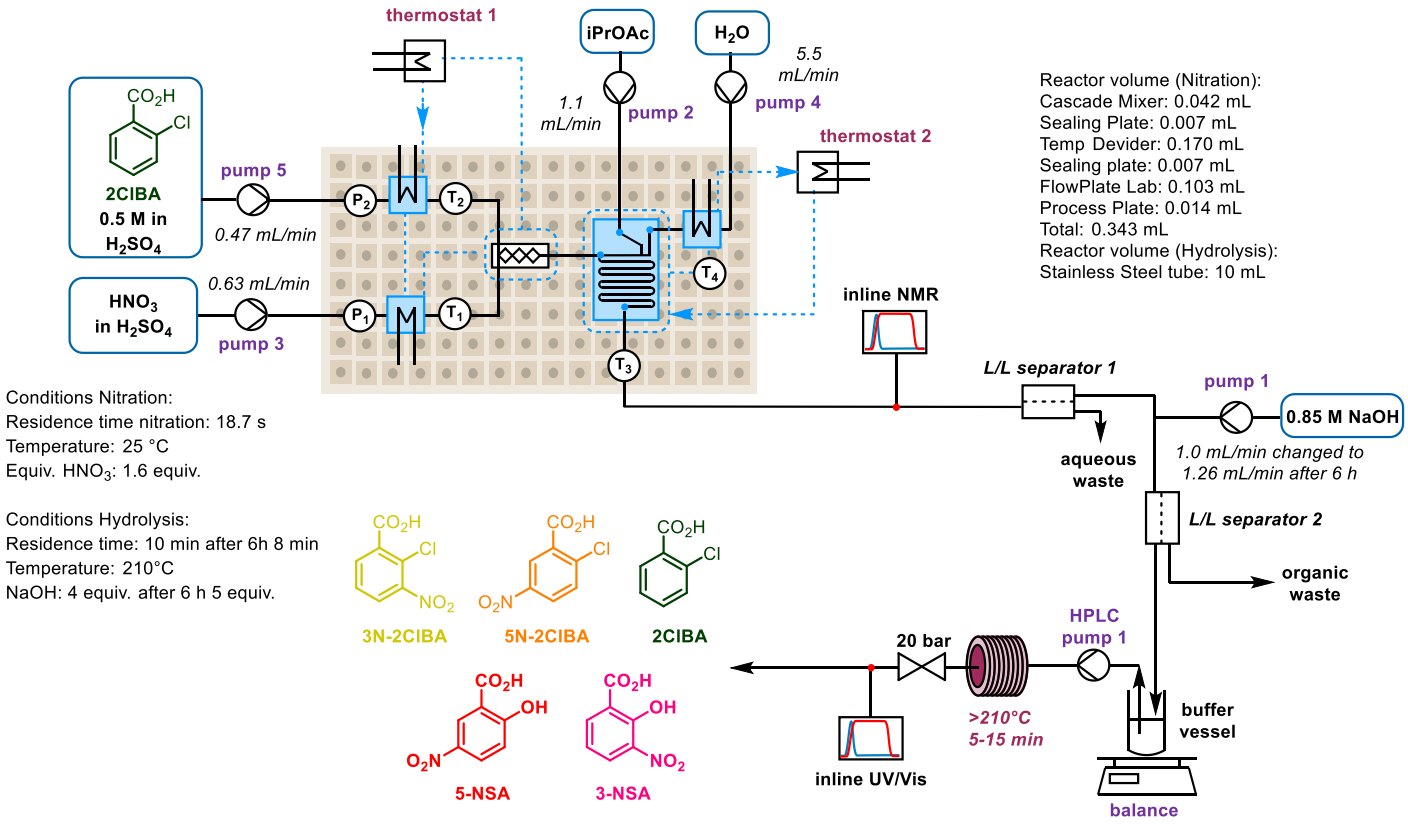


Figure S77. Process scheme of the telescoped process for the nitration and substitution.

Input solutions:

0.5 M 2ClBA: In a 250 mL volumetric flask 19.5731 g of 2ClBA was diluted in conc. H_2SO_4.

0.6 M HNO_3: A 500 mL volumetric flask was placed in an ice bath and filled with 400 mL conc. H_2SO_4, then 19.2 mL of conc. HNO_3 (15.6 M, 68%) was slowly added. After the addition, the volumetric flask was removed from the ice bath, allowed to reach room temperature, and filled up to the 500 mL mark with conc. H_2SO_4.

0.85 M NaOH: In a 1 L volumetric flask 34.0046 g of NaOH was diluted in deionized H_2O.

Offline samples for UHPLC analysis were taking at the reactor outlet and at the buffer vessel. The results for the telescoped run are depicted in **Figure S78** and **Figure S79**.

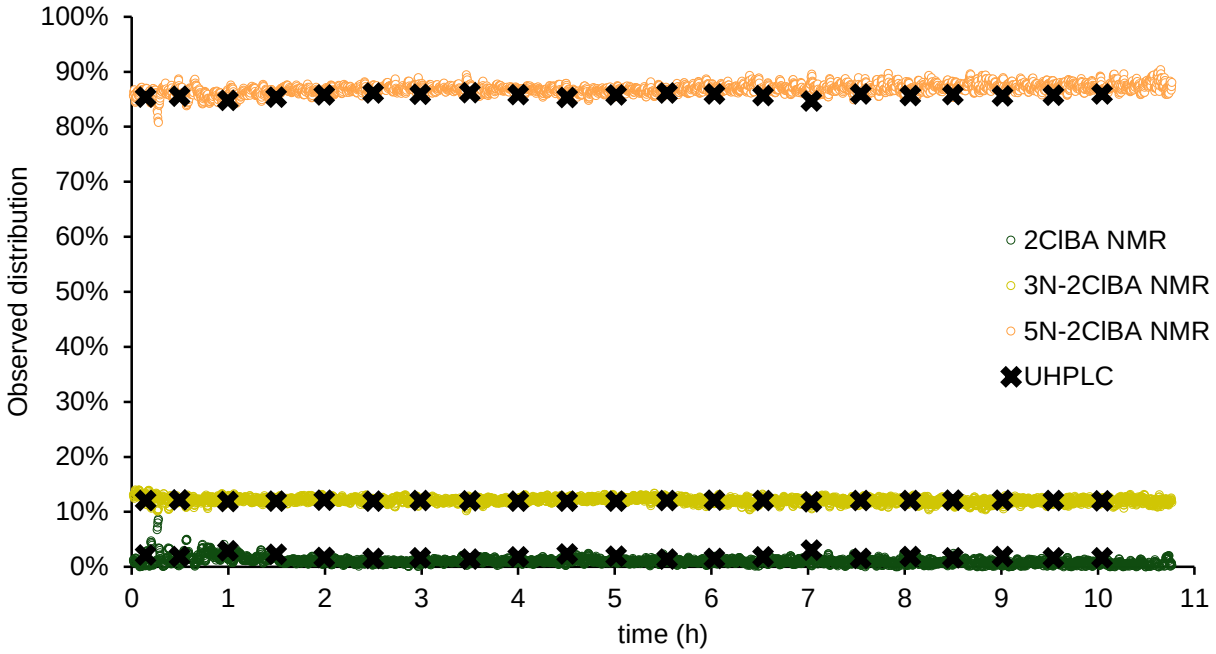


Figure S78. NMR results from the telescoped process.

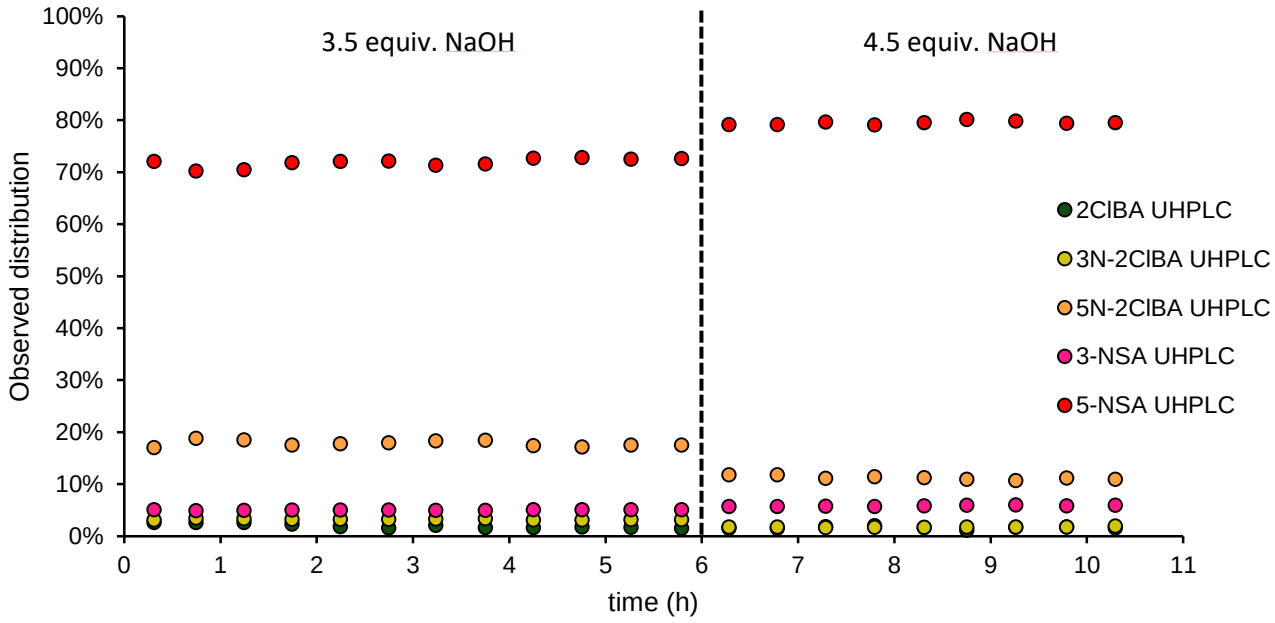


Figure S79. Offline UHPLC results for the telescoped process at the reactor outlet.

5. Hydrogenation Reaction Optimization Data

5.1. Detailed Setup

The hydrogenation reaction was performed in an Ehrfeld Miprowa Lab reactor (0224-2-2004-F, Hastelloy C-22), as part of the Ehrfeld Modular MicroReaction System (MMRS). Using a designated flange for channel number reduction, four of the eight rectangular reaction channels (1.5 mm × 12 mm × 300 mm) were connected in series. The first two channels were filled with standard herringbone shaped flow baffles (three layers, 45° angle, strut width 1.0 mm, spacing 2.0 mm, length 300 mm) made of Hastelloy C-276 (6114-1-3244). The last two channels were filled with four Catalytic Static Mixers (CSMs) of 150 mm length each. The CSMs were manufactured from 316L stainless steel powder by selective laser melting, according to a design by CSIRO.[5–8] The 3D-printed static mixers were coated with Pd via electroplating technique by CSIRO and Precision Plating Australia.[9]

The liquid feed was delivered by a Knauer AZURA P 4.1S HPLC pump with a 10 mL/min pump head made of Hastelloy C and an integrated pressure sensor. An H-Genie hydrogen generator from ThalesNano Energy, operated with HPLC grade water, was used as hydrogen source with an integrated mass flow controller (MFC). Both streams were combined in a Y-connector (PEEK), immediately before entering the MMRS system via a 1/16" input connector (0711 2 0124 F, Hastelloy C-276), through transparent tubing (PFA 0.8 mm i.d.). This allowed visualization of the resulting biphasic slug flow regime. The temperature of the reactor was adjusted using a Huber CC-304 thermostat, and was monitored at four different points: reaction medium input, reaction medium output, thermostat bath temperature and the thermal fluid output of the reactor. Due to alternating gas-liquid slugs, the temperature signal which was measured by the sensors directly contacting the reaction medium was prone to oscillate depending on the ratio and flow rates of the liquid and gas streams.

After the Miprowa Lab reactor, the reaction stream passed through a pressure sensor module (0518-1-60x4-F, Hastelloy C 276), a 1/16" output connector (0711 2 0124 F, Hastelloy C-276) and a 1 mL stainless steel coil (0.8 mm i.d.) which was submerged in a water bath at ambient temperature. The pressure inside the system was either adjusted by a Swagelok KCB series back pressure regulator (BPR) (KCB1H0A2B5P60000, 25.8 bar) for manual control, or an argon pressure loaded Equilibar Zero Flow BPR, regulated by a Bronkhorst EL-PRESS pressure controller. At ambient pressure, the excess hydrogen was separated by a custom made gas-liquid separator with an attached inline FT-IR probe and an inlet tubing for online UHPLC sampling (**Figure S18**). FT-IR measurements were done using a Mettler Toledo ReactIR 15 instrument, equipped with an AgX 9.5 mm diamond probe. Sampling time was set to 15 s with a wavenumber range from 2500 to 900 cm^{-1}. For UHPLC online sampling, a Vapourtec SF-10 peristaltic pump (withdrawing from directly after the FT-IR probe) delivered a constant flow rate of 500 µL/min through the integrated 10 nL injection valve, via PTFE tubing (0.3 mm i.d., 160 cm total length, 112 µL volume). After the injection valve, the excess sample stream from the online measurement was reunited with the liquid output stream of the gas-liquid separator, causing only minimal loss of material. The setup is depicted in **Figure S80** and a photograph of the described hydrogenation setup can be found in **Figure S81**.

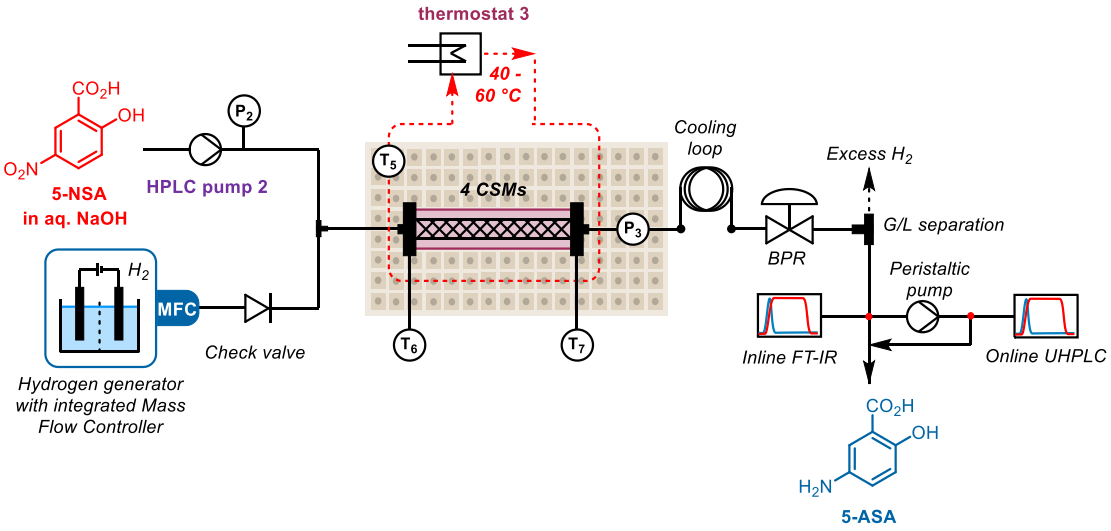


Figure S80. Detailed process diagram of the setup used for the hydrogenation step.

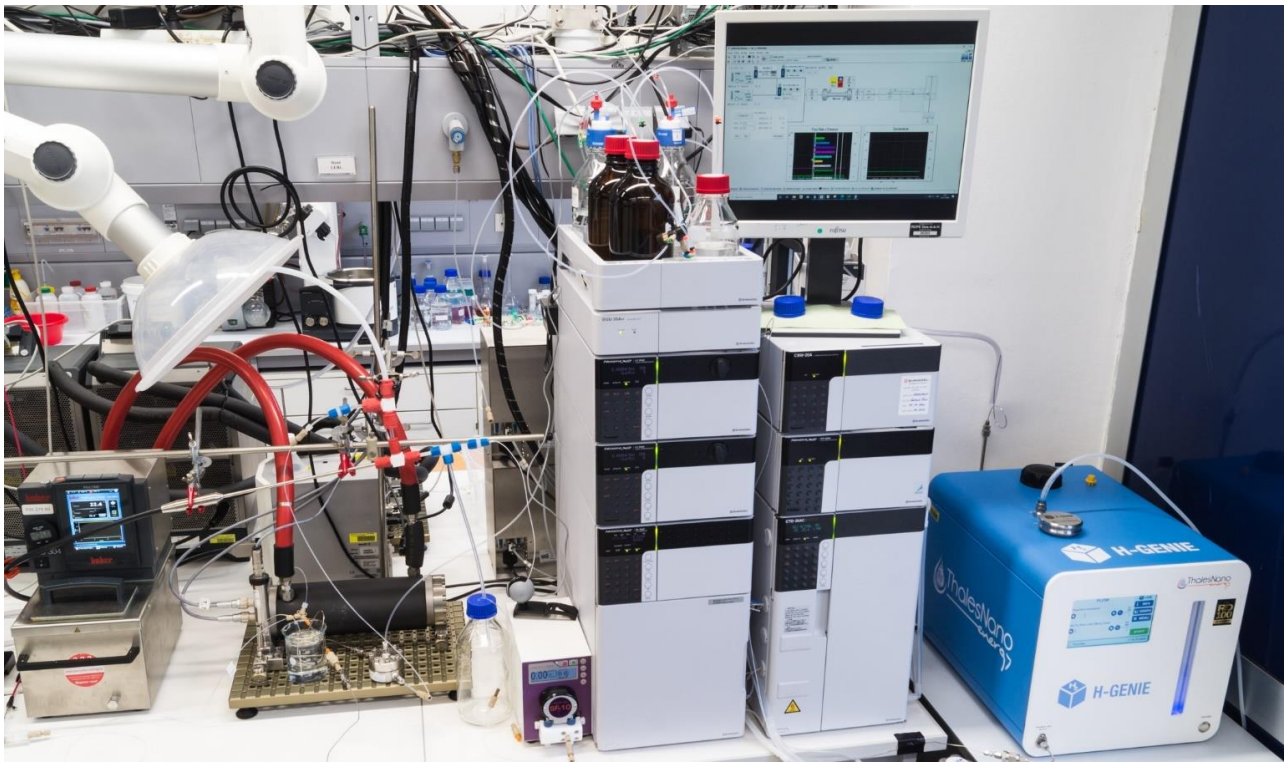


Figure S81. Photograph of hydrogenation setup.

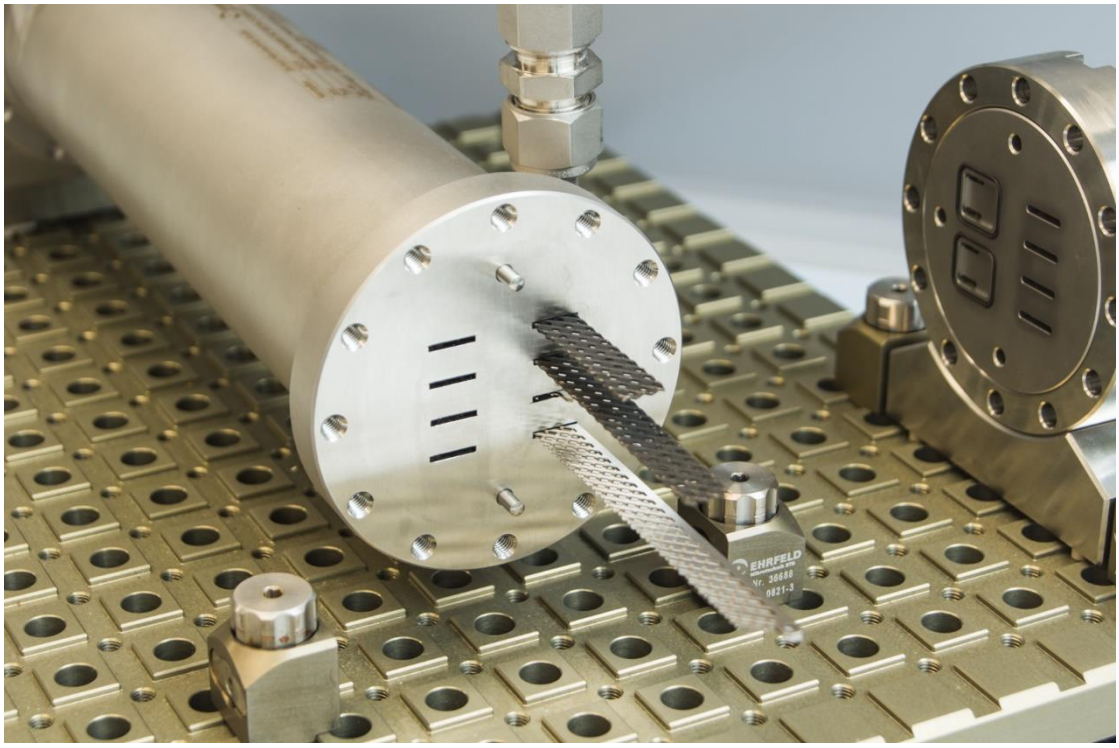


Figure S82. Photograph of opened hydrogenation Reactor with CSMs (top right) and standard herringbone mixing elements (bottom).

5.2. Design Space Definition

Initial process data for the hydrogenation was collected according to a fractional factorial design plan including 5 factors: liquid flow rate (Q_L), hydrogen flow rate (Q_G) temperature, pressure and concentration of starting material (5-NSA was selected as main substrate of interest for the hydrogenation). A combination of 16 experiments according to the lower and upper limits described in **Table S26** was generated, based on the Design of Experiment software Modde (v12.1, Sartorius), with an additional triplicate experiment for the center point. The selective conversion of 5-NSA to 5-ASA determined by offline UHPLC measurements at 229 nm (based on external calibration) was used as response for fitting the model. The results are depicted in **Figure S83** to **Figure S86**.

Table S26. Ranges for hydrogenation optimization, evaluated during the DoE.

Factor	Unit	lower limit	upper limit	center point
Q_L	[mL/min]	1.0	3.0	2.0
Q_G	[mL_N/min]	25	75	50
Temp.	[°C]	40	80	60
Pres.	[bar g]	6	12	9
Conc.	[mol/L]	0.15	0.25	0.20

Table S27. Experimental plan and results for hydrogenation DoE.

Entry	Q_liquid [mL/min]	Q_gas [mL_N/min]	Temperature [°C]	Pressure [bar g]	Conc 5-NSA [mol/L]	cal UHPLC Conv. 229 nm
1[a]	2.0	50	60	9	0.20	69.1
2[a]	1.0	25	80	12	0.25	99.6
3[a]	3.0	25	80	12	0.15	70.6
4[a]	1.0	75	80	12	0.15	99.3
5[a]	3.0	75	80	12	0.25	85.0
6[a]	1.0	25	80	6	0.15	99.3
7[a]	2.0	50	60	9	0.20	78.9
8[a]	3.0	25	80	6	0.25	43.1
9[b]	1.0	75	80	6	0.25	99.6
10[b]	3.0	75	80	6	0.15	89.5
11[b]	1.0	25	40	12	0.15	98.8
12[b]	3.0	25	40	12	0.25	19.6
13[b]	3.0	75	40	12	0.15	56.1
14[b]	1.0	25	40	6	0.25	64.4
15[b]	3.0	25	40	6	0.15	32.8
16[b]	1.0	75	40	6	0.15	98.0
17[b]	3.0	75	40	6	0.25	21.4
18[b]	1.0	75	40	12	0.25	89.8
19[b]	2.0	50	60	9	0.20	76.0

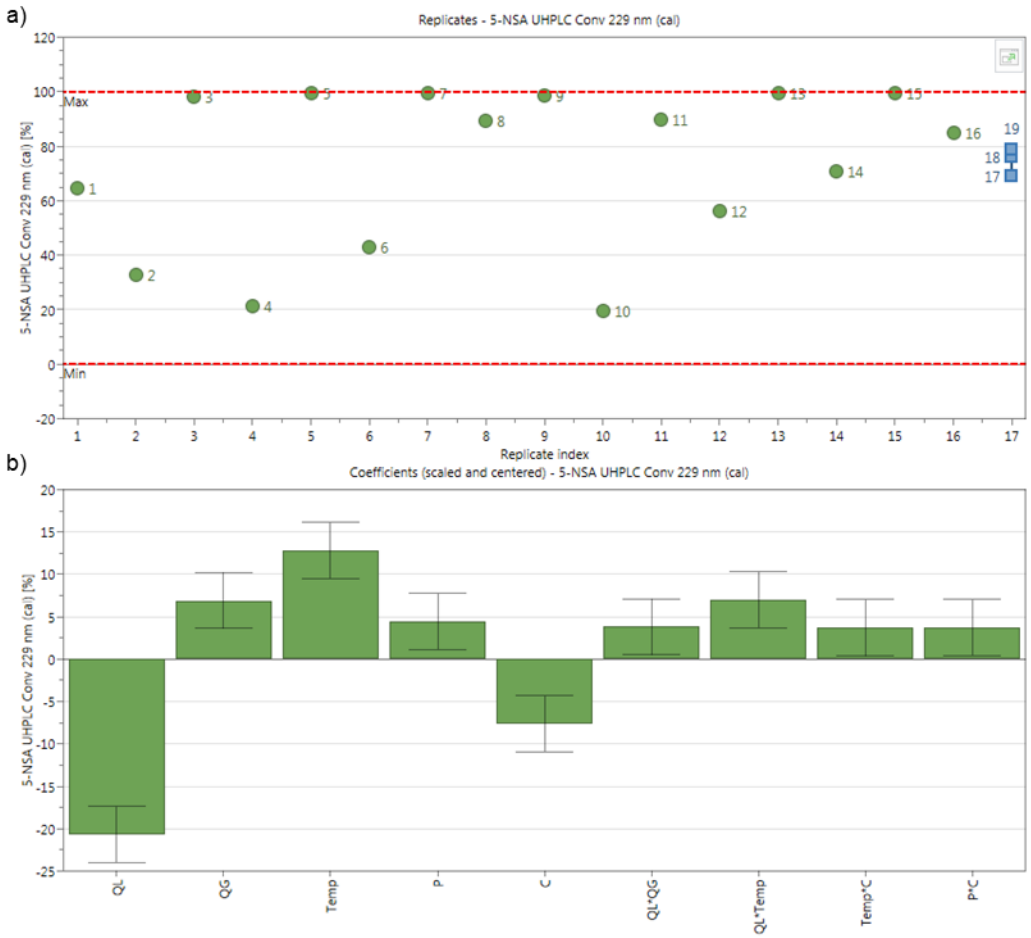


Figure S83. a) Replicate plot shows variability within the design space, compared to the variability of the three replicates. b) Coefficient plot, after non-significant model terms have been removed.

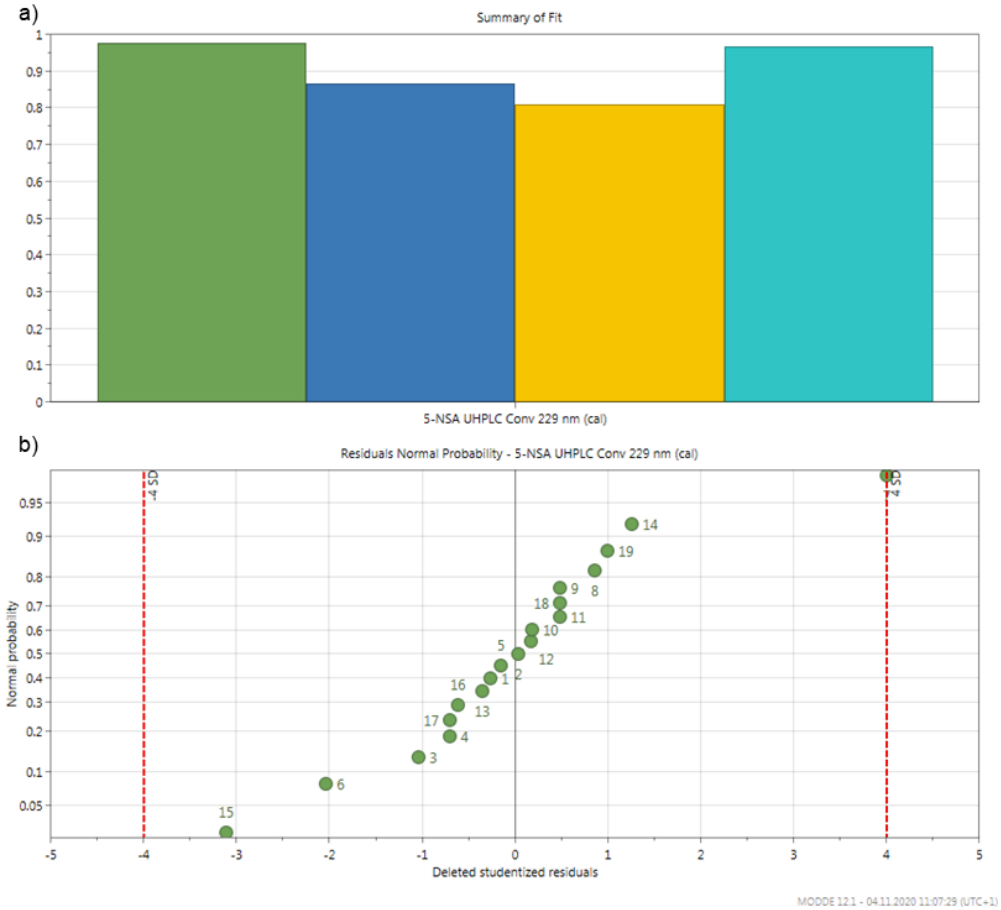


Figure S84. a) Summary of fit shows R^2 = 0.977, Q^2 = 0.867, model validity = 0.808, model reproducibility = 0.966. b) Residuals normal probability plot.

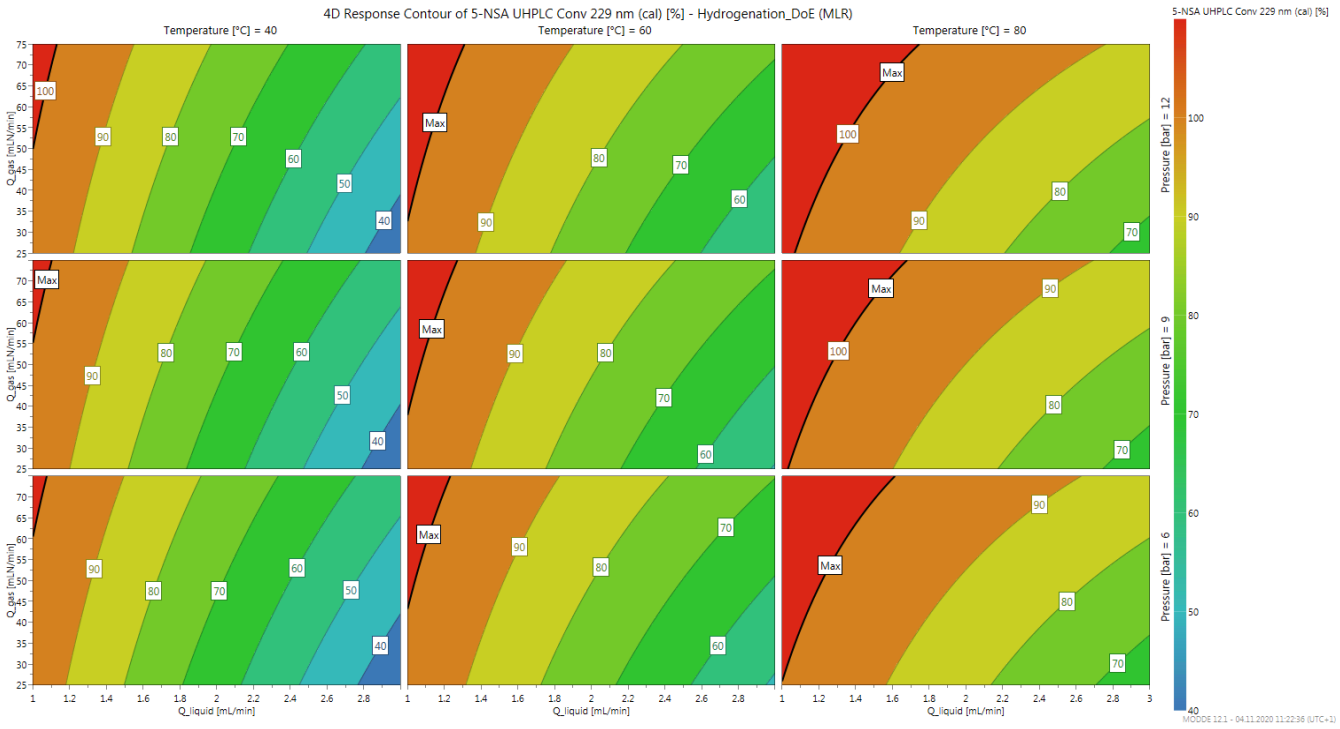


Figure S85. 4D Response contour plot for the conversion of 5-NSA to 5-ASA based on UHPLC analysis. Substrate concentration c(5-NSA) = 0.15 mol/L.

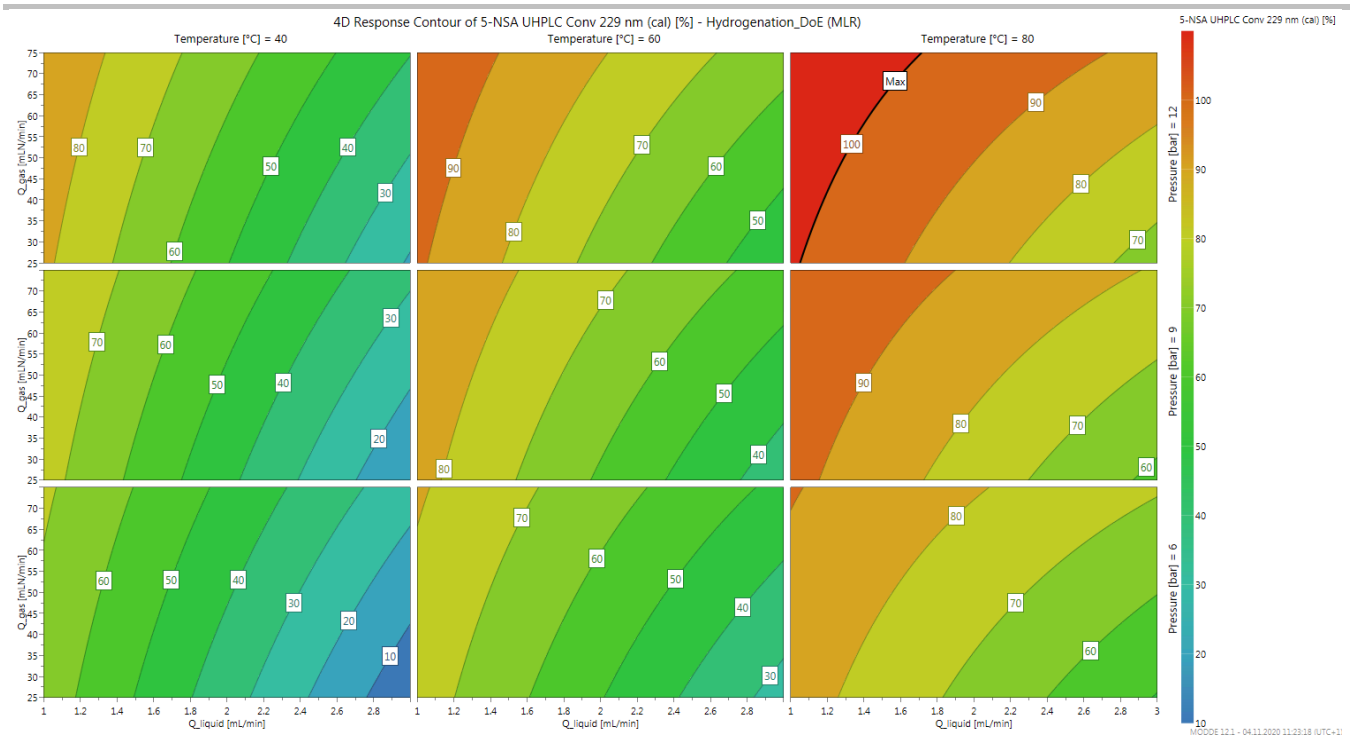


Figure S86. 4D Response contour plot for the conversion of 5-NSA to 5-ASA based on UHPLC analysis. Substrate concentration c(5-NSA) = 0.25 mol/L.

6. Telescoped Process

6.1. Detailed Setup

Input solutions: 0.5 M 2ClBA: In a 500 mL volumetric flask 39.1518 g of 2ClBA was diluted in conc. H_2SO_4.
0.6 M HNO_3: A 500 mL volumetric flask was placed in an ice bath and filled with 400 mL conc. H_2SO_4, then 19.2 mL of conc. HNO_3 (15.6 M, 68%) was slowly added. After the addition, the volumetric flask was removed from the ice bath, allowed to reach room temperature, and filled up to the 500 mL mark with conc. H_2SO_4.
1.5 M NaOH: In a 1000 mL volumetric flask 60.0 g of NaOH was diluted in deionized H_2O.

The flow setup is shown in **Figure S1**. The HNO_3 and 2ClBA feeds were delivered with two SyrDos2 pumps (30 bar valve, 2.5 mL syringes, pump 5 for 2ClBA feed and pump 3 for HNO_3 feed) through PFA tubing (1.6 mm i.d.) to the MMRS system. Both feeds entered the MMRS system through 1/8" input connectors (0711-2-0224-F, Hastelloy C-276), followed by pressure sensor modules (0518-1-60x4-F, Hastelloy C-276), coax heat exchangers (0309-4-0004-F, Hastelloy C-276) and temperature sensors (0501-2-1004-X, Hastelloy C-276). The two streams were mixed in a temperature controlled cascade mixer 06 (0216-3-0014-F, mixing structure 10 µL, Hastelloy C-276) and delivered through a temperature dividing block to the FlowPlate Lab (1701-3-0004-F, Hastelloy C-276) where the reaction solution was quenched with premixed water and iPrOAc. The total reactor volume for the nitration was 343 µL. The temperature in the heat exchangers (2ClBA and HNO_3 feeds) and the cascade reactor was controlled by thermostat 1 (Huber, Ministat 240). The water feed was pumped with a SyrDos2 pump (pump 4, 30 bar valve, 5 mL syringes) through PFA tubing (1.6 mm i.d.) and a check valve (Upchurch, CV-3321) to the MMRS system where it entered through a 1/8" input connector (0711-2-0224-F, Hastelloy C-276), pressure sensor module (0518-1-60x4-F, Hastelloy C-276) and coax heat exchanger (0309-4-0004-F, Hastelloy C-276) into the FlowPlate Lab. The iPrOAc feed was delivered with a SyrDos2 pump (pump 2, 90 bar valve, 2.5 mL syringes) through PFA tubing (0.8 mm i.d.) and a check valve (Upchurch, CV-3321) to the MMRS system where it was connected with a 1/16" input connector (0711-2-0124-F, Hastelloy C-276) to the FlowPlate Lab. The temperature in heat exchanger and the FlowPlate Lab was controlled by thermostat 2 (Huber, Ministat 240). The FlowPlate Lab was equipped with a LL design Process Plate (1701-4682-HC, LL-Mixer, Nominal Width 0.2 mm, Hastelloy C-22). The iPrOAc stream entered at port 1, the water stream at port 2 and the process stream from the nitration at port 3 and the quenched stream exit the process plate at port 7 (**Figure S50B**).

The quenched stream left the MMRS system through a temperature sensor module (0501-2-1004-X, Hastelloy C-276), a 1/8" input connector (0711-2-0224-F, Hastelloy C-276) and a PFA tube (2.67 mL, 1.6 mm i.d.). The aforementioned PFA tube was connected with a two way connector to a lager inner diameter PFA tube (1.66 mL, 3.2 mm i.d.) to ensure slug flow before the Zaiput separator (SEP-10) equipped with a hydrophobic PTFE membrane (0.4 µm, OB-400-SEP10). The aqueous stream was diverted to a waste bottle. The organic phase stream was mixed with an aqueous NaOH stream immediately after the separator in a T-piece (PTFE). The aqueous NaOH stream was a combination of an water stream delivered from SyrDos2 pump (pump 1, 90 bar valve, 1.0 mL syringes) and an aqueous 1.5 M NaOH stream delivered by a Knauer AZURA P 4.1S HPLC pump with a 10 mL/min pump head made of Hastelloy C (HPLC pump 1). A residence time coil made of PFA tubing (3.60 mL, 1.6 mm i.d.) was used for phase separation and extraction prior to phase separation with another Zaiput separator (SEP-10) equipped with a hydrophobic PTFE membrane (0.4 µm, OB-400-SEP10). The organic stream was diverted to a waste bottle and the aqueous phase stream was delivered through PFA tubing (0.72 mL, 0.8 mm i.d.) to the benchtop NMR. A 6-port valve was installed prior the glass flow cell (800 µL internal volume, 550 mm length) to allow for bypassing of the flow cell and for re-shimming of the instrument in case of a failure during a telescoped experiment (Section 2.1.2). The reaction stream left the NMR through PFA tubing (0.36 mL, 0.8 mm i.d.) and was collected in a buffer vessel. The buffer vessel was placed on a balance (Kern, KB 2400-2N) and used as a feed for a second Knauer AZURA P 4.1S HPLC pump with a 10 mL/min pump head made of Hastelloy C (HPLC pump 2).

The hydrolysis step took place in a 20 mL stainless steel coil which was placed on a coil heater (Uniqsis, HotCoil UQ1025-1). The reaction mixture was cooled to room temperature in an additional stainless steel tube (0.9 mL,0.8 mm i.d.) which was placed in an

actively cooled water bath. A Swagelok KCB series backpressure regulator (KCB1H0A2B5P60000, 25.8 bar max pressure) was used to maintain 20 bar in the reactor. The outlet stream of the backpressure regulator was connected to a UV/vis flow cell (Section 2.2.2) and PFA tubing (0.55 mL, 0.8 mm i.d.) to Y-connector (PEEK) where the stream was mixed with a hydrogen stream. The hydrogen was produced in the H-Genie hydrogen generator from ThalesNano Energy, operated with HPLC grade water, with an integrated mass flow controller (MFC). The combined gas-liquid stream entered via a 1/16" input connector (0711 2 0124 F, Hastelloy C-276) the Miprowa Lab reactor placed on an MMRS plate. A channel number reduction flange on the Miprowa Lab reactor was used to connect four of the eight rectangular reaction channels (1.5 mm × 12 mm × 300 mm) in series. The first two channels were filled with standard herringbone shaped mixers (three layers, 45° angle, strut width 1.0 mm, spacing 2.0 mm, length 300 mm) made of Hastelloy C-276 (6114-1-3244). The last two channels were filled with four Catalytic Static Mixers (CSMs) of 150 mm length each. The CSMs were manufactured from 316L stainless steel powder by selective laser melting, according to a design by CSIRO. The 3D-printed static mixers were coated with Pd via an electroplating technique by CSIRO and Precision Plating Australia. The temperature of the reactor was adjusted using a Huber CC-304 thermostat, and was monitored at four different points: reaction medium input, reaction medium output, thermostat bath temperature and the thermal fluid output of the reactor. Due to alternating gas-liquid slugs, the temperature signal which was measured by the Pt100 temperature sensors directly contacting the reaction medium, was prone to oscillate depending on the ratio and flow rates of the liquid and gaseous stream.

After the Miprowa Lab reactor, the reaction stream passed through a pressure sensor module (0518-1-60x4-F, Hastelloy C 276), a 1/16" output connector (0711 2 0124 F, Hastelloy C-276) and a 1 mL stainless steel coil (0.8 mm i.d.) which was submerged in a water bath at ambient temperature. The pressure inside the system was adjusted by an argon pressure loaded Equilibar Zero Flow BPR, regulated by a Bronkhorst EL-PRESS pressure controller. At ambient pressure, the excess hydrogen was separated by a custom made gas-liquid separator with an attached inline FT-IR probe and an inlet tubing for online UHPLC sampling. FT-IR measurements were done using a Mettler Toledo ReactIR 15 instrument, equipped with an AgX 9.5 mm diamond probe. For UHPLC online sampling a Vapourtec SF-10 peristaltic pump equipped with PTFE tubing (112 µL, 0.3 mm i.d.) was used. The samples were continuously taken in front of the FT-IR probe with a constant flow rate of 500 µL/min and pumped through the integrated 10 nL injection valve. After the injection valve, the excess sample stream from the online measurement was reunited with the liquid output stream of the gas-liquid separator, causing only minimal loss of material.

Optimized Start-up Procedure

The start-up was performed with the following workflow:

Step 1.) Flush pump 1, 3, 4, 5, HPLC pump 1 and HPLC pump 2 with H_2O, flush pump 2 with iPrOAc

Step 2.) Prepare the feed solutions and buffer solutions for UHPLC

Step 3.) Flush HPLC pump 1 with 1.5 M NaOH, pump 3 and pump 5 with 3.0 M H_2SO_4

Step 4.) Switch on analytical instruments (warm up) and thermostats. Start hydrogen generator, adjust back pressure regulators and pre-heat reactors

Step 5.) Flush pump 3 and pump 5 with conc. H_2SO_4, record blank and reference measurements (UHPLC, IR, UV/vis)

Step 6.) Shim the NMR, adjust the flow rates for the experiment, switch HPLC pump 2 input feed to process media, allow hydrogen pressure to build up inside hydrogenation reactor.

Step 7.) Start the experiment by switching input feed for pump 3 to 0.6 M HNO_3 and input feed for pump 5 to 0.5 M 2ClBA

Optimized Shutdown Procedure

Step 1.) Switch the input feed of pump 3 and pump 5 to conc. H_2SO_4

Step 2.) Flush pump 3 and pump 5 with 3.0 M H_2SO_4

Step 3.) Flush pump 1, 3, 4, 5, HPLC pump 1 and HPLC pump 2 with H_2O, stop hydrogen input

Step 4.) Stop measurements of the analytical devices and allow for heated reactors to cool down, slowly reduce pressure

Step 5.) Switch pump 2 to H_2O, disconnect liquid-liquid separators, flush thoroughly with water and iPrOAc, and store membrane in toluene

Step 6.) Flush reactors and pumps with isopropanol

6.2. Long Run Data

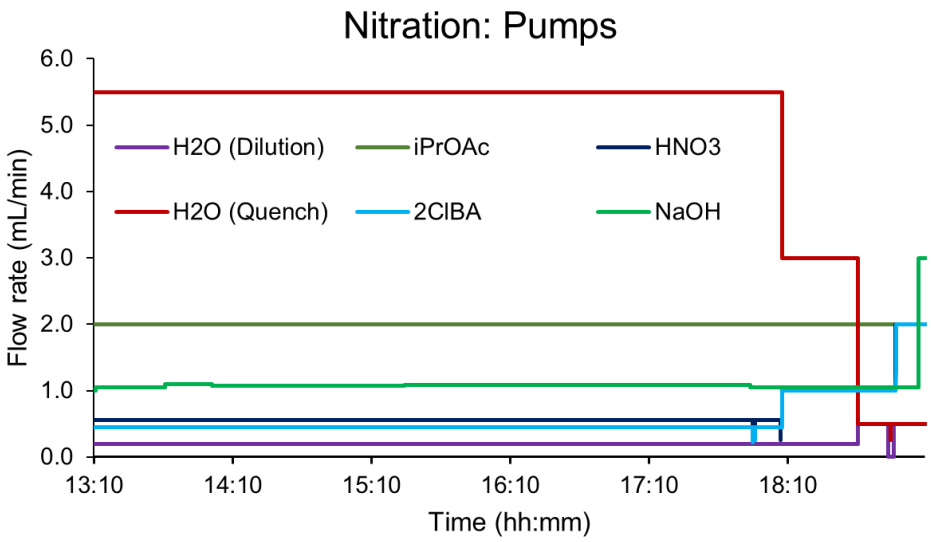


Figure S87. Set points of pumps for the nitration step, during the long run experiment.

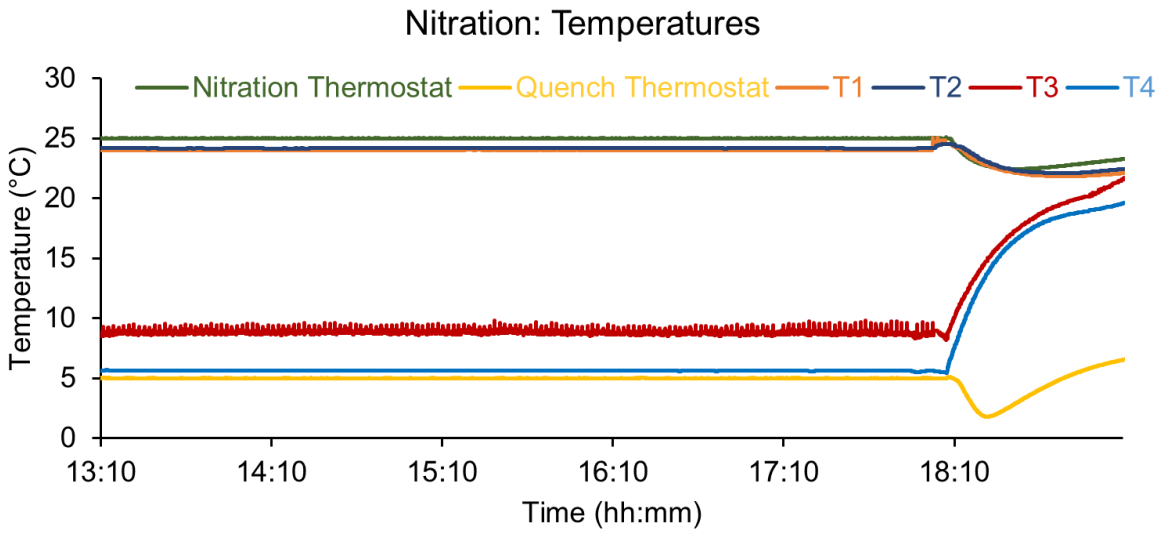


Figure S88. Temperature data from the nitration step, during the long run experiment.

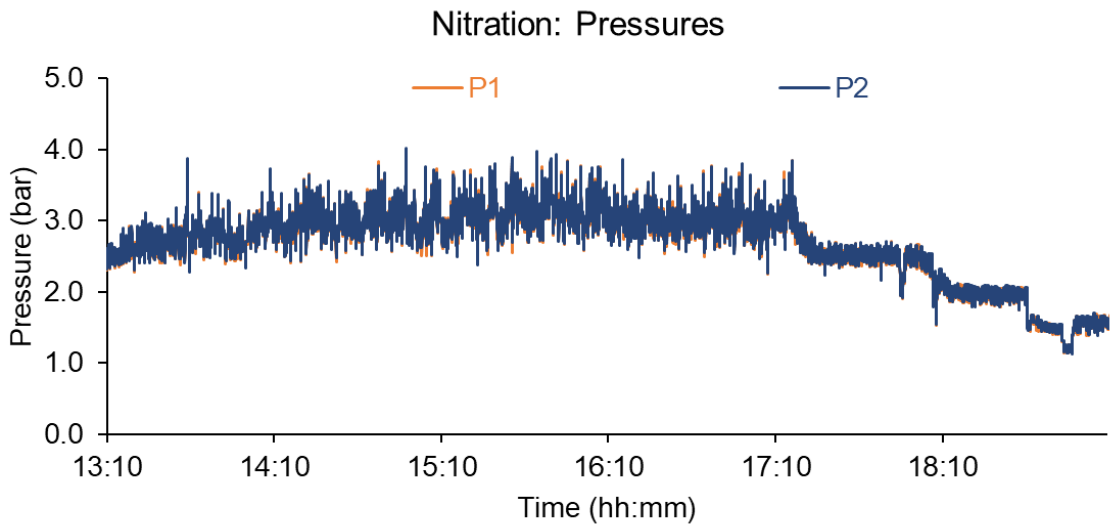


Figure S89. Pressure data from the nitration step, during the long run experiment.

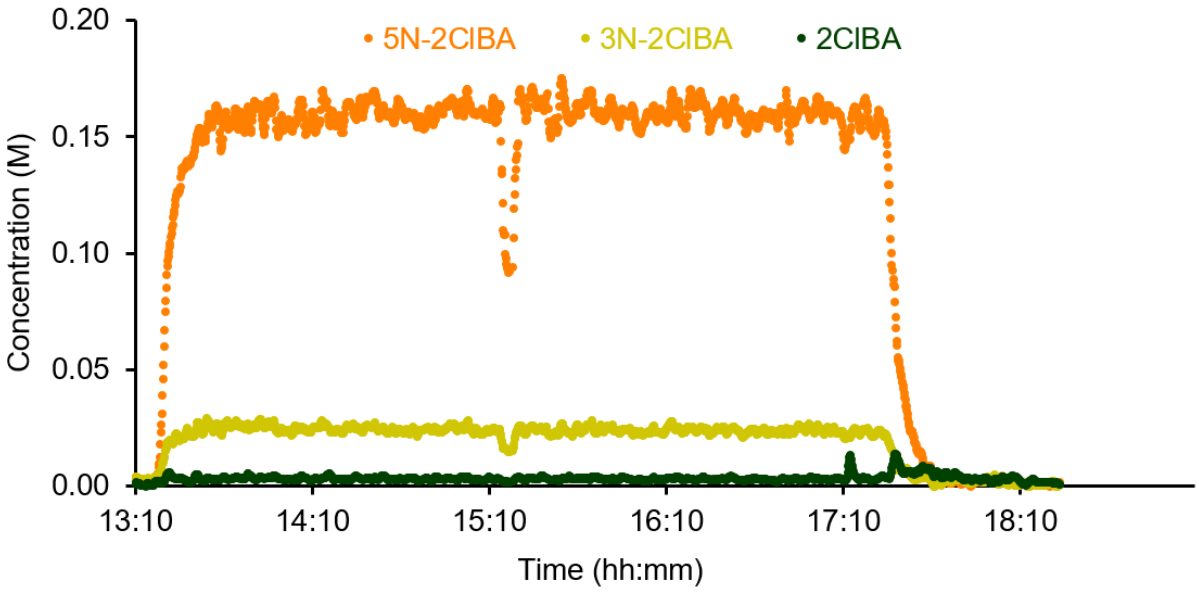


Figure S90. NMR data from the long run experiment.

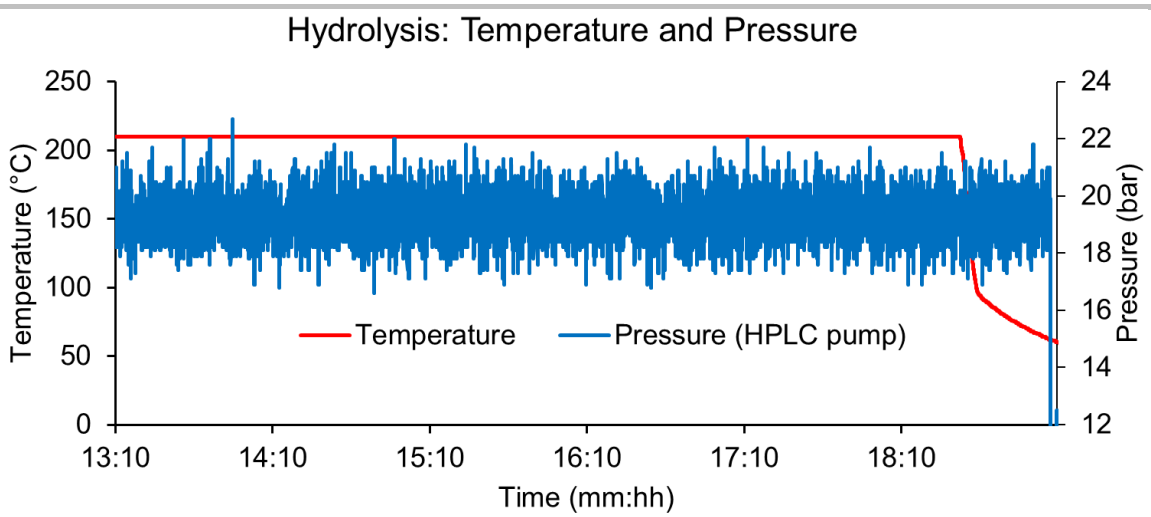


Figure S91. Temperature and pressure data from the hydrolysis step, during the long run experiment.

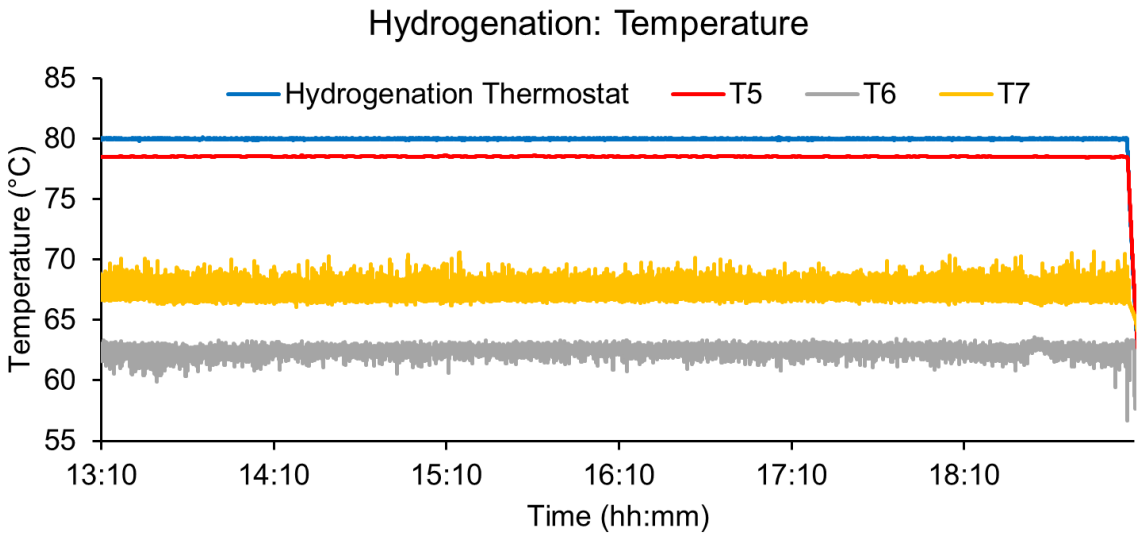


Figure S92. Temperature data from the hydrogenation step, during the long run experiment.

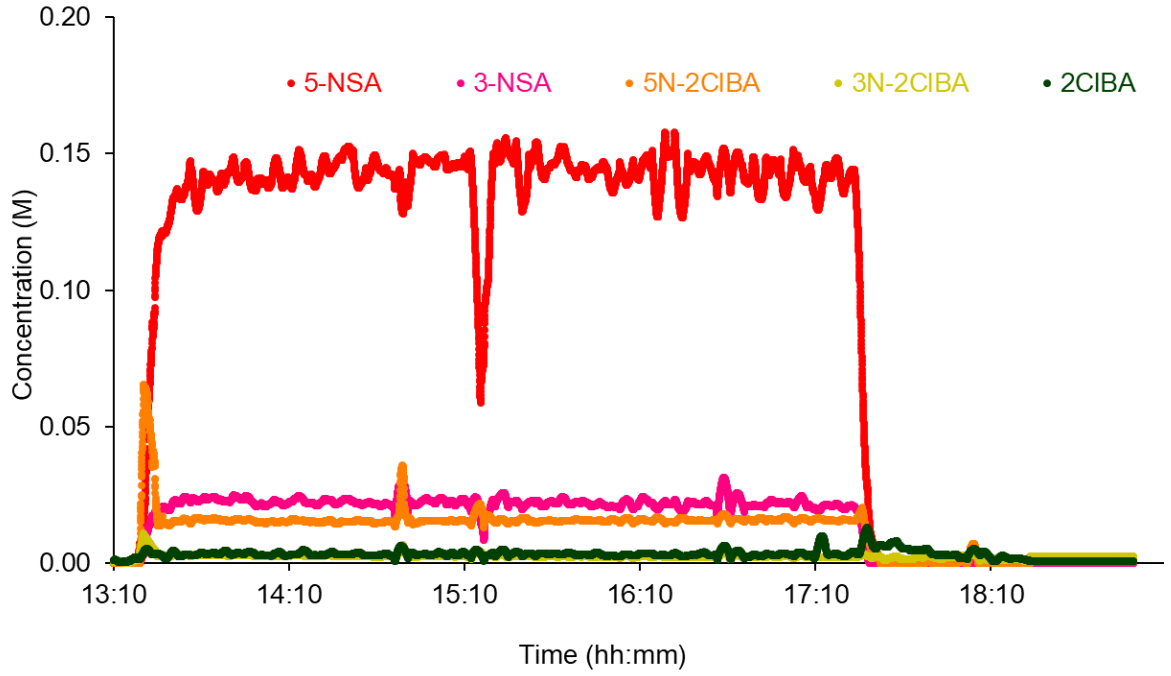


Figure S93. UV/vis data from the long run experiment.

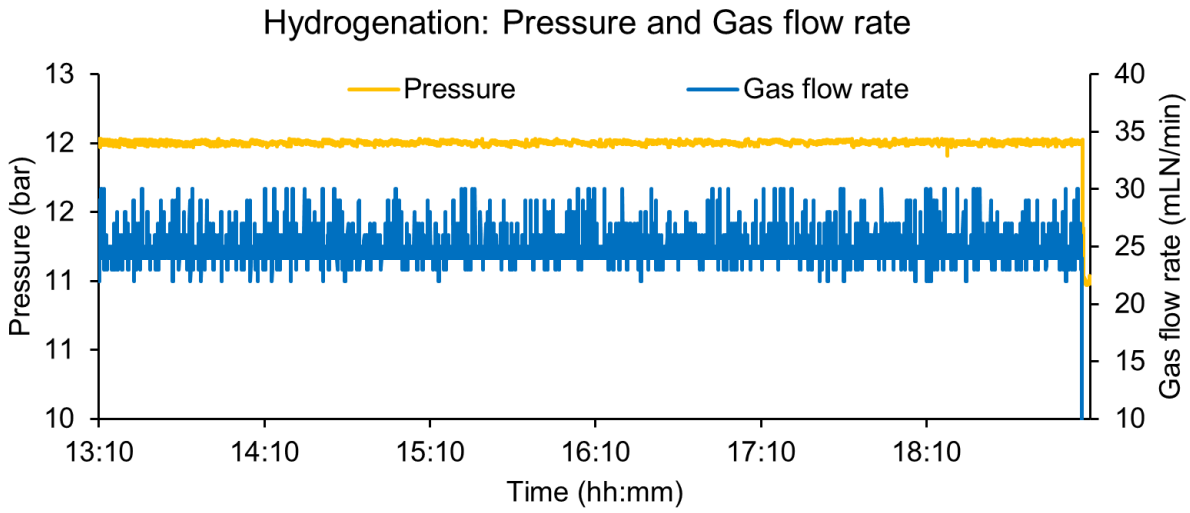


Figure S94. Pressure and gas flow rate data from the hydrogenation step, during the long run experiment.

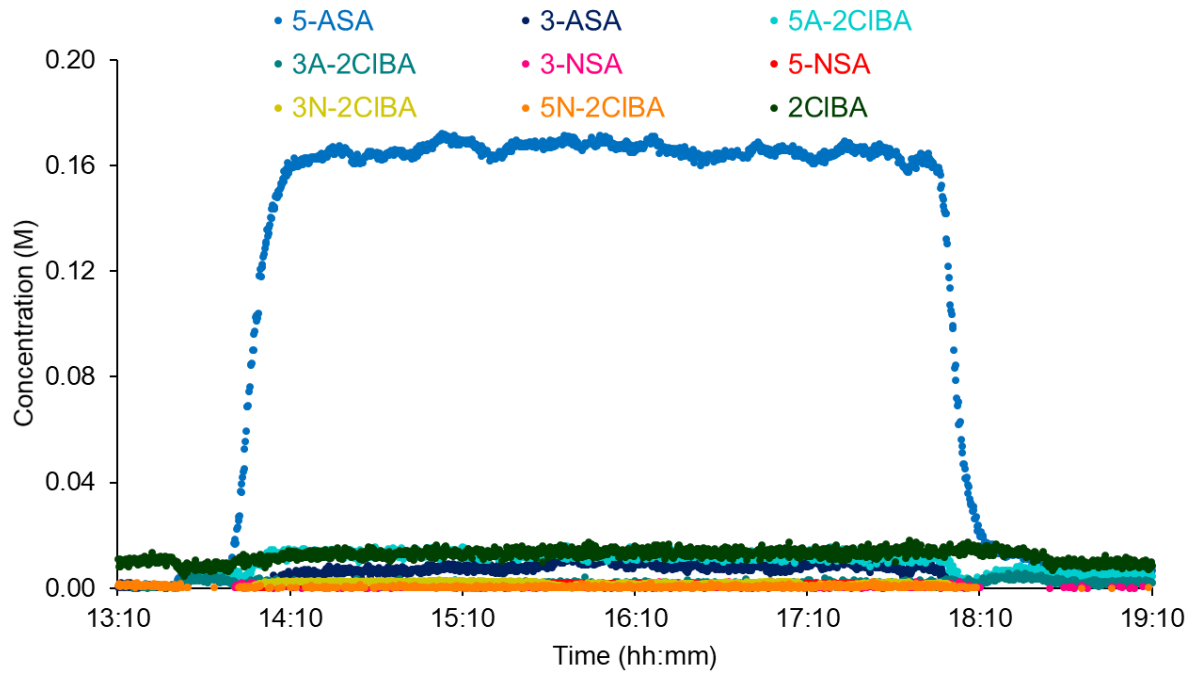


Figure S95. IR data from the long run experiment.

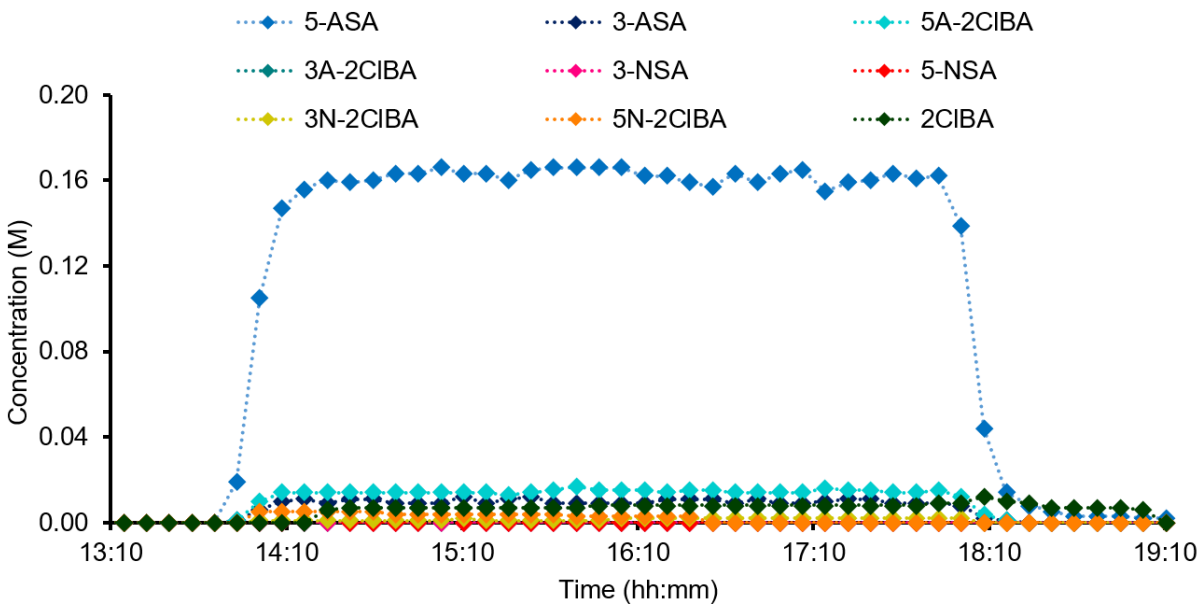


Figure S96. UHPLC data from the long run experiment.

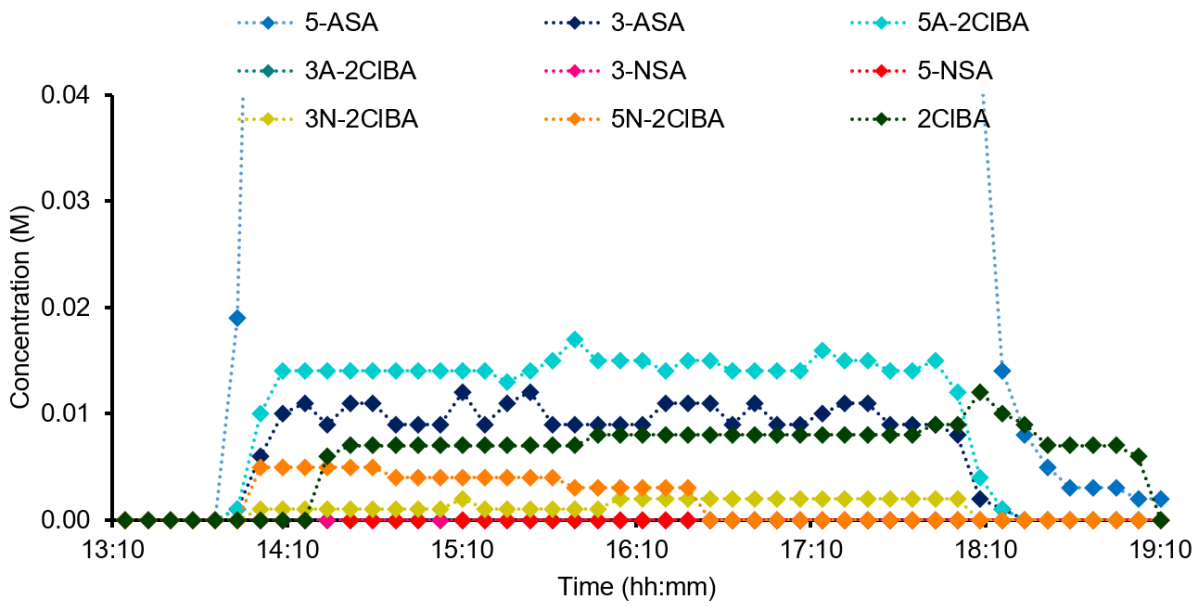


Figure S97. UHPLC data from the long run experiment, showing lower concentration impurities.

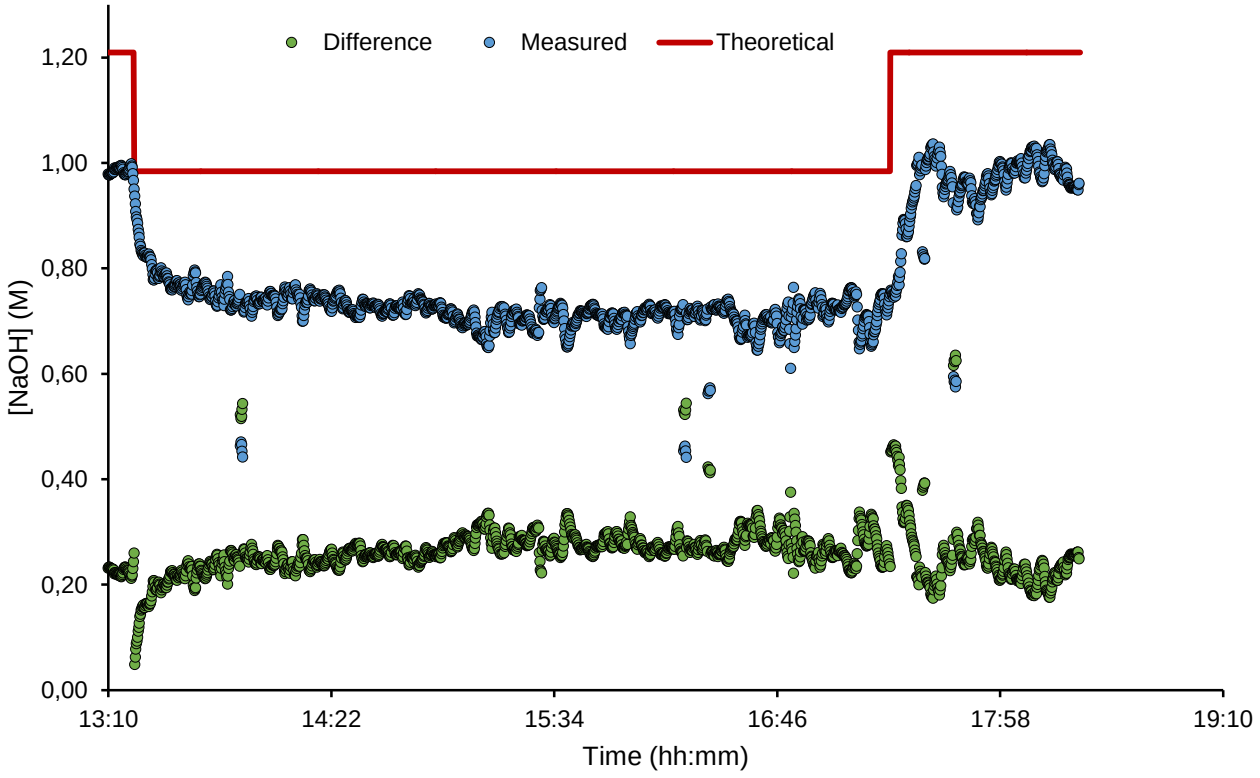


Figure S98. Determination of hydroxide concentration by NMR. The measured concentration is shown in blue points, whilst the expected concentration is shown as a red line. The difference between the two is represented in green.

6.3. Dynamic Operation Data

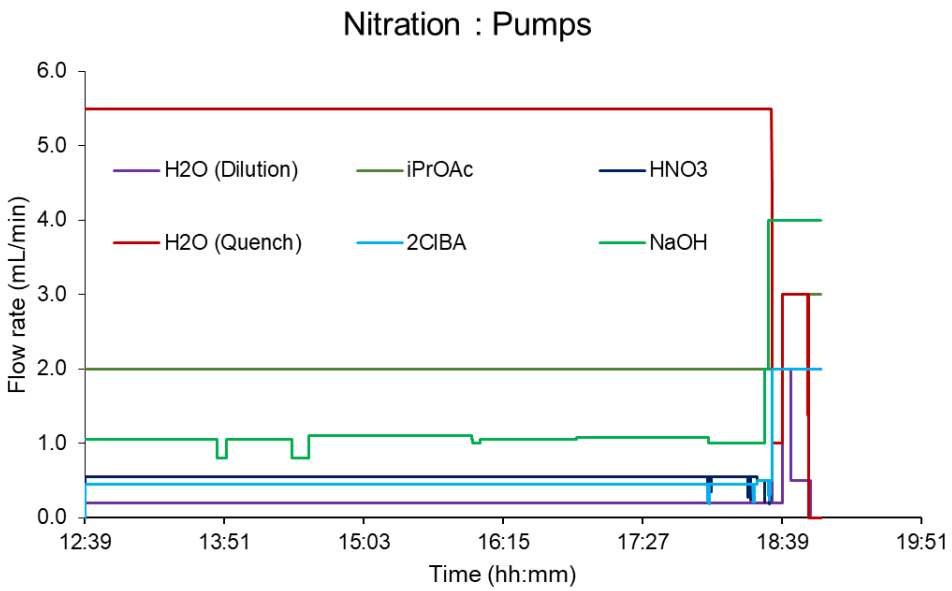


Figure S99. Set points of pumps for the nitration step, during the dynamic experiment.

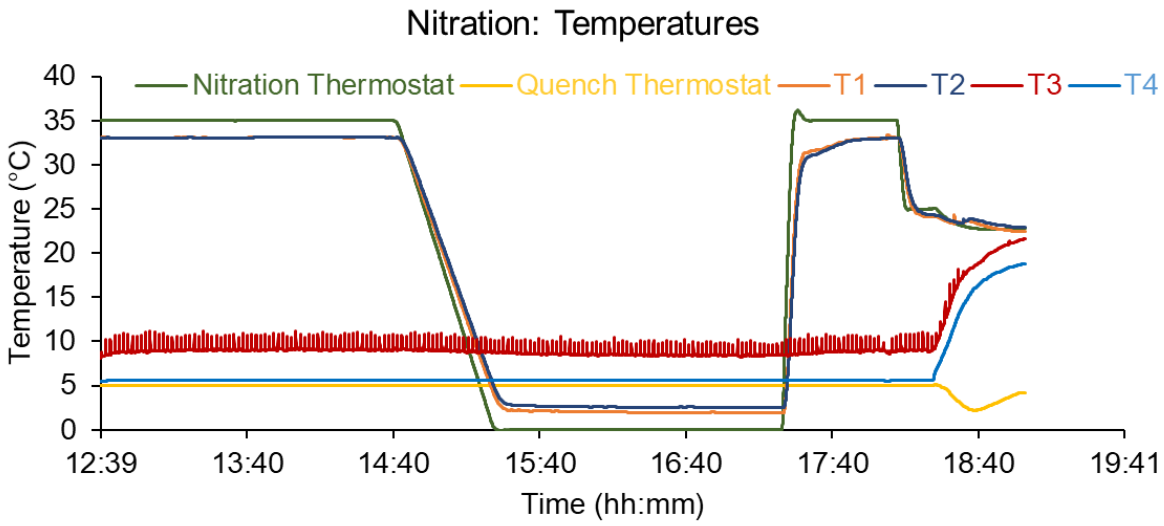


Figure S100. Temperature data for the nitration step, during the dynamic experiment.

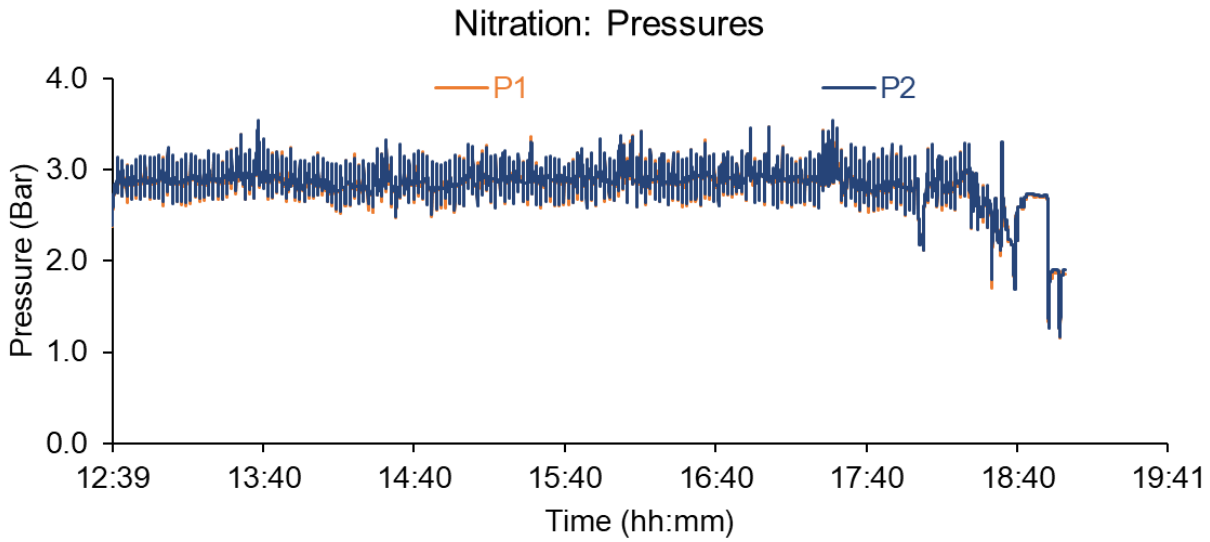


Figure S101. Pressure data for the nitration step, during the dynamic experiment.

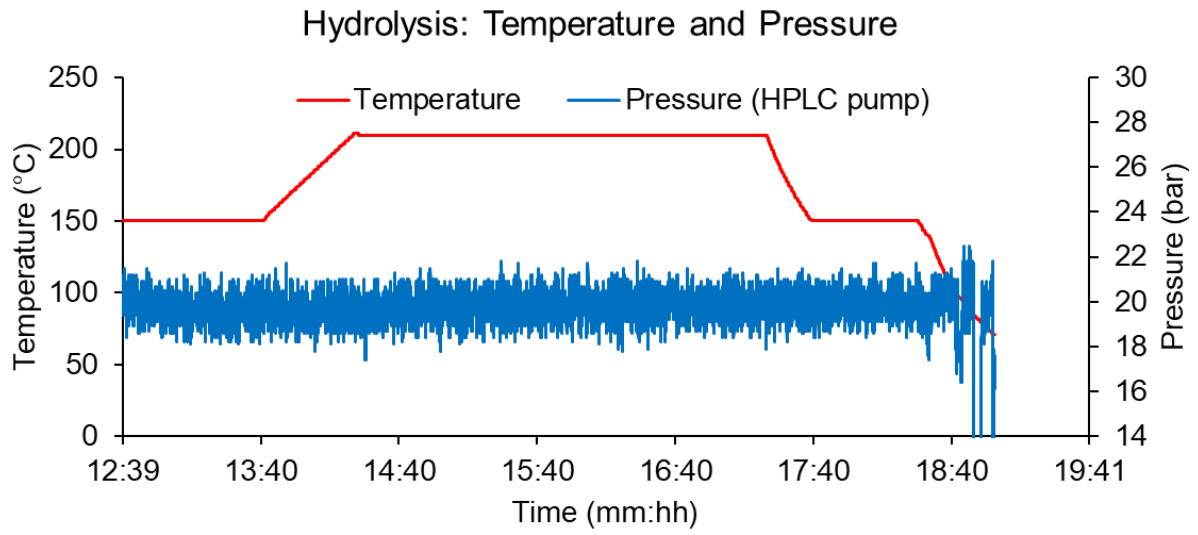


Figure S102. Temperature and pressure data for the hydrolysis step, during the dynamic experiment.

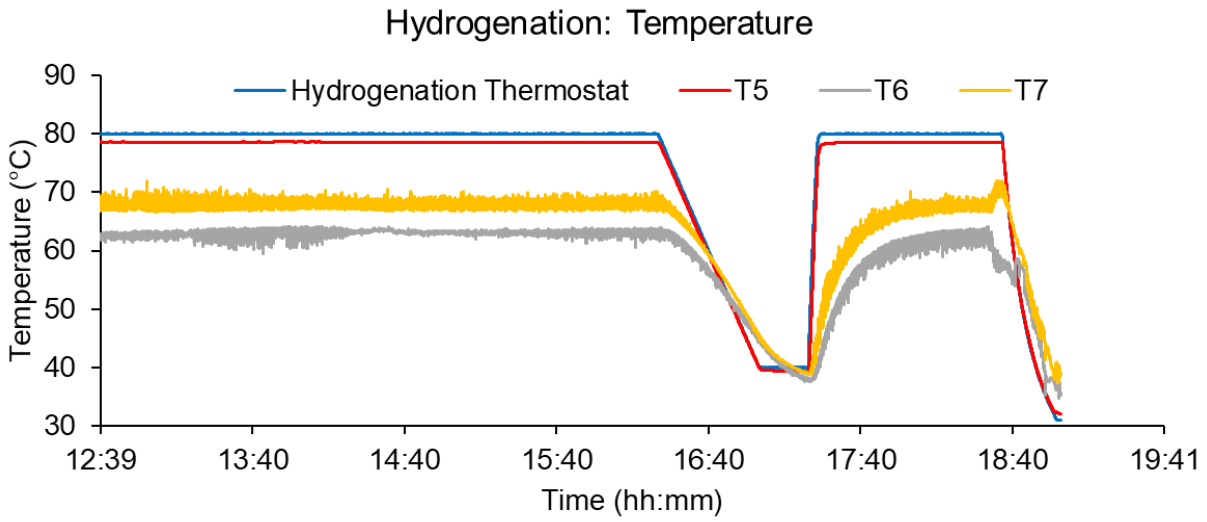


Figure S103. Temperature data for the hydrogenation step, during the dynamic experiment.

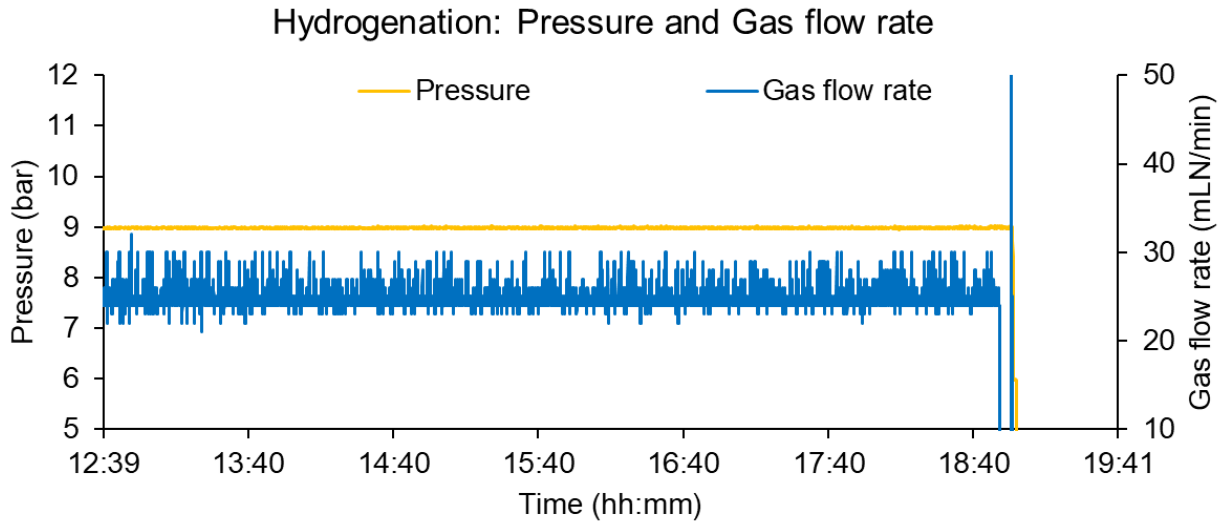


Figure S104. Pressure and gas flow data for the hydrogenation step, during the dynamic experiment.

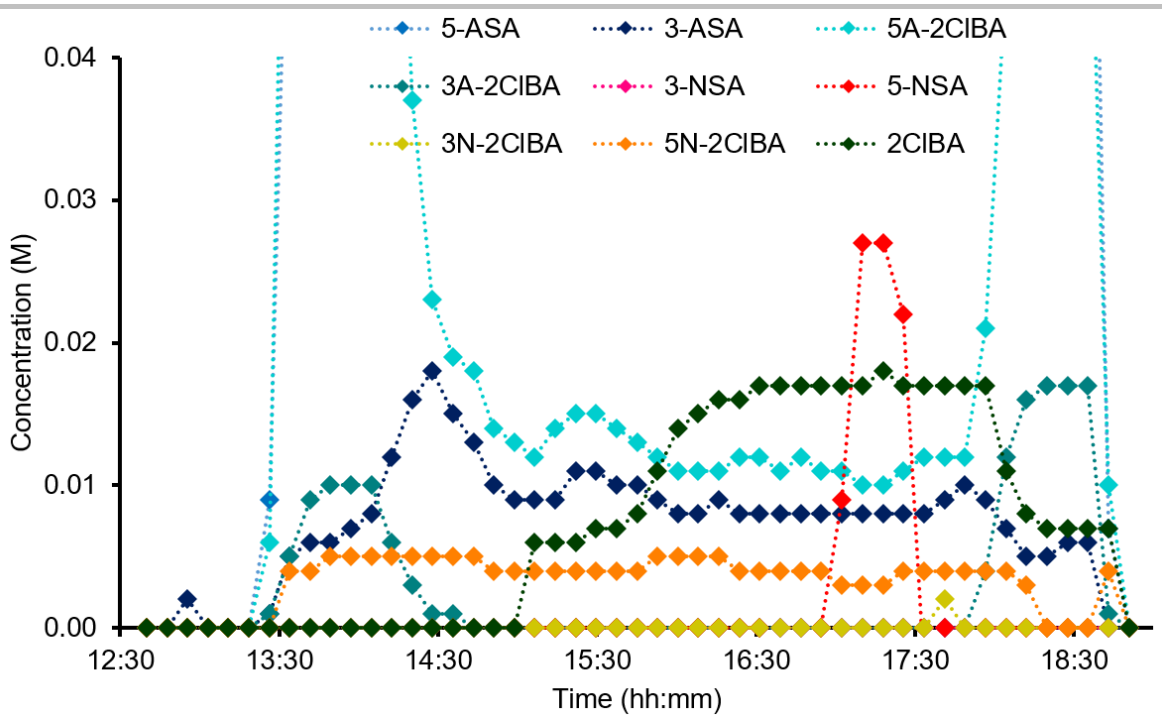


Figure S105. UHPLC data from the dynamic experiment, showing lower concentration impurities.

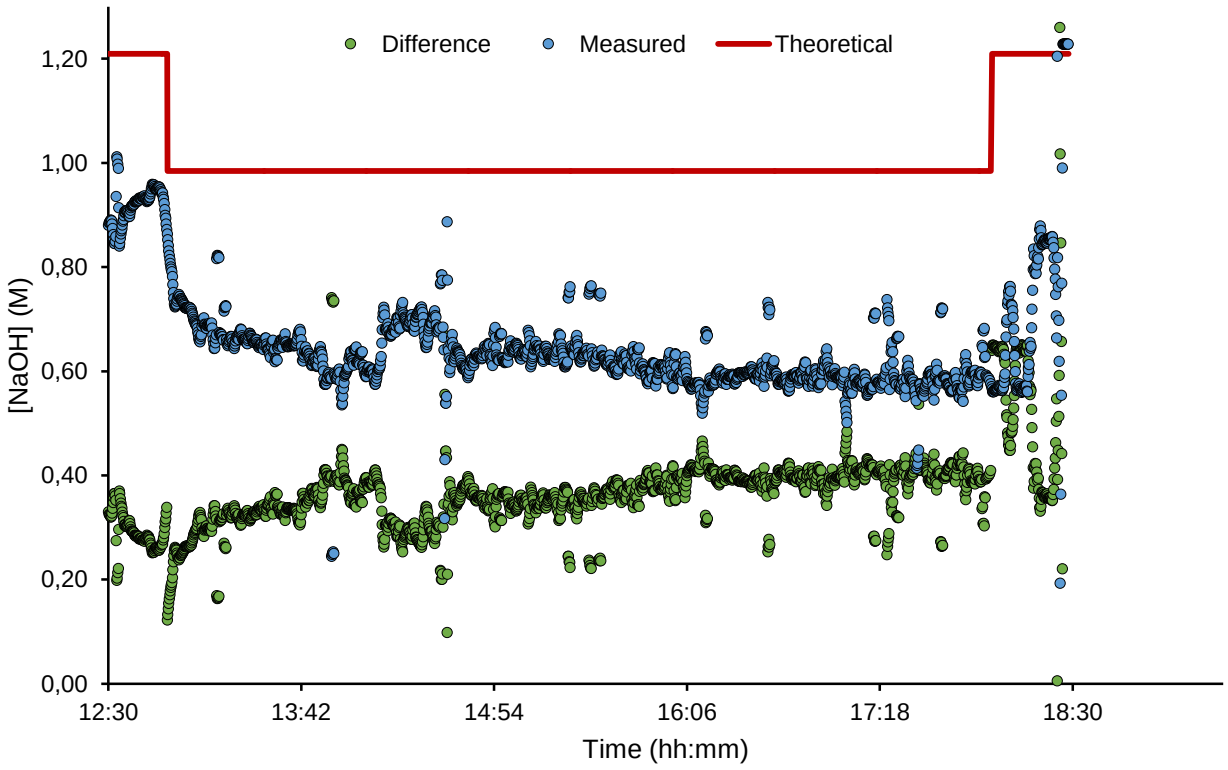


Figure S106. Determination of hydroxide concentration by NMR. The measured concentration is shown in blue points, whilst the expected concentration is shown as a red line. The difference between the two is represented in green.

7. References

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[9] “Precision Plating (Aust) Pty Ltd.,” can be found under http://www.precisionplating.com.au/, **2020**.