Electronic Supplementary Information

Autonomous Model-Based Experimental Design for Rapid Reaction Development

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1 Experimental Details

1.1 General Experimental Details

Solvents and chemicals were obtained from commercial suppliers and used without further purification unless otherwise noted. For the S_NAr reaction, 3,4-difluoronitrobenzene (purity >98%) was obtained from TCI. Morpholine (purity >99%) and triethylamine (purity >99.5%), were purchased from Sigma Aldrich. For the benzylic bromination, *N*-bromosuccinimide (purity >99%) was obtained from Sigma Aldrich. 4-Fluorotoluene (purity >99%) was purchased from TCI. Acetic acid (purity >99.8%) and MeCN (HPLC grade) were obtained from VWR.

In the flow setup, standard PFA tubing (0.8 mm or 1.6 mm i.d.), fittings, and T-pieces manufactured from PTFE or PEEK were used.

High field NMR spectra were recorded on a Bruker 300 MHz instrument. ^{1}H spectra were recorded at 300 MHz, with a chemical shift (δ) relative to the methyl group (3.31 ppm) of methanol-d4 expressed in parts per million. The letters s, d, t dd, td, and m indicate singlet, doublet, triplet, doublet of doublets, triplet of doublets, and multiplet, respectively.

Caution: Bromine
During the photochemical benzylic bromination, color indicating the formation of some quantity of molecular bromine (Br_2) was observed. Bromine is a toxic and genotoxic brown liquid with a high vapor pressure. Excess bromine and solutions containing bromine should always be carefully quenched with diluted sodium thiosulfate solution. The quench with sodium thiosulfate is highly exothermic.

Automated modeling and self-optimization experiments were performed using the automated continuous flow chemistry platform at the Kappe Laboratories in Graz. This platform is comprised of Supervisory Control and Data Acquisition (SCADA) software (Evon, XAMControl), which is further connected to a Distributed Control System (DCS) (HiTec Zang, LabVision software and LabManager hardware), which communicates to actuators and sensors. The platform includes several syringe pumps (HiTec Zang, SyrDos2 equipped with high- or low pressure pump heads) and HPLC pumps (Knauer, AZURA P 4.1S with 10 mL or 50 mL pump heads made out of stainless steel, ceramic, or Hastelloy). Additionally, the platform includes thermostats (Huber, Ministat 240, and CC-304), gas and liquid mass flow controllers (Bronkhorst), pressure controllers (Bronkhorst, EL-PRESS), and hydrogen generator (Thales Nano Energy, H-Genie). A modular micro reaction system (Ehrfeld, MMRS), a shell-and-tube reactor 5 (Ehrfeld, Miprowa Lab reactor) provides the flexibility of performing different reaction types in the automated platform. Several real-time PAT instruments such as temperature and pressure sensors, FTIR (Mettler Toledo, ReactIR 15), benchtop NMR (Magritek, Spinsolve Ultra), UV/vis spectrometer (Avantes, AvaSpec ULS2048), and online UHPLC (Shimadzu, Nexera X2) are established within the

platform. The automated data processing is accomplished with PEAXACT and ProcessLink (S-PACT), Matlab, or Python. Advanced Process Control is enabled by communication to Matlab, Python, or DLLs embedded in XAMControl.

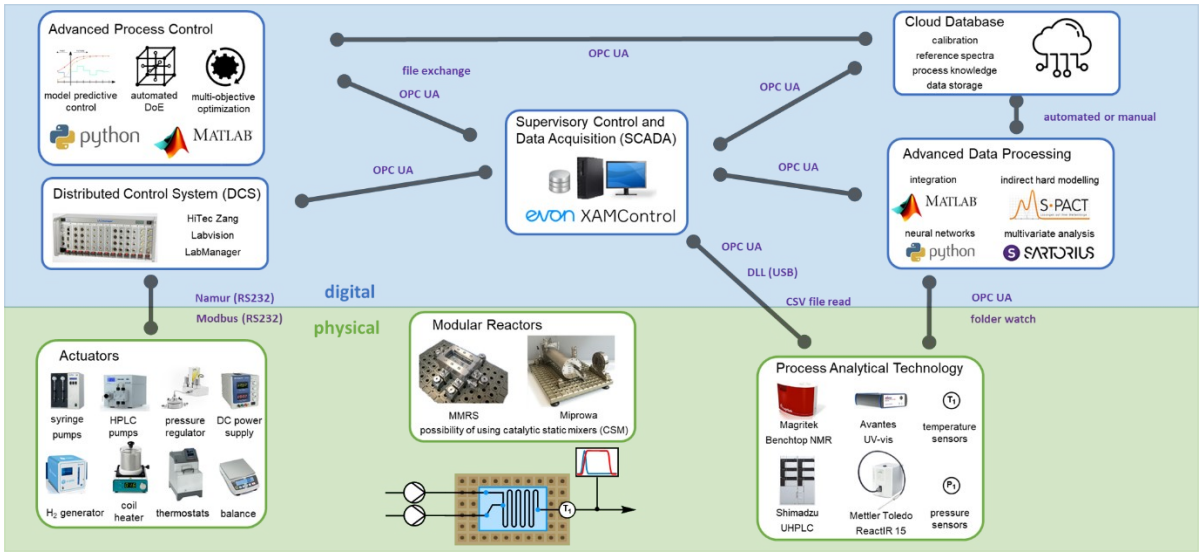


Fig. S1. Schematic overview of the automated modular flow chemistry platform at the Kappe Lab. Green background represents the physical world and blue the digital.

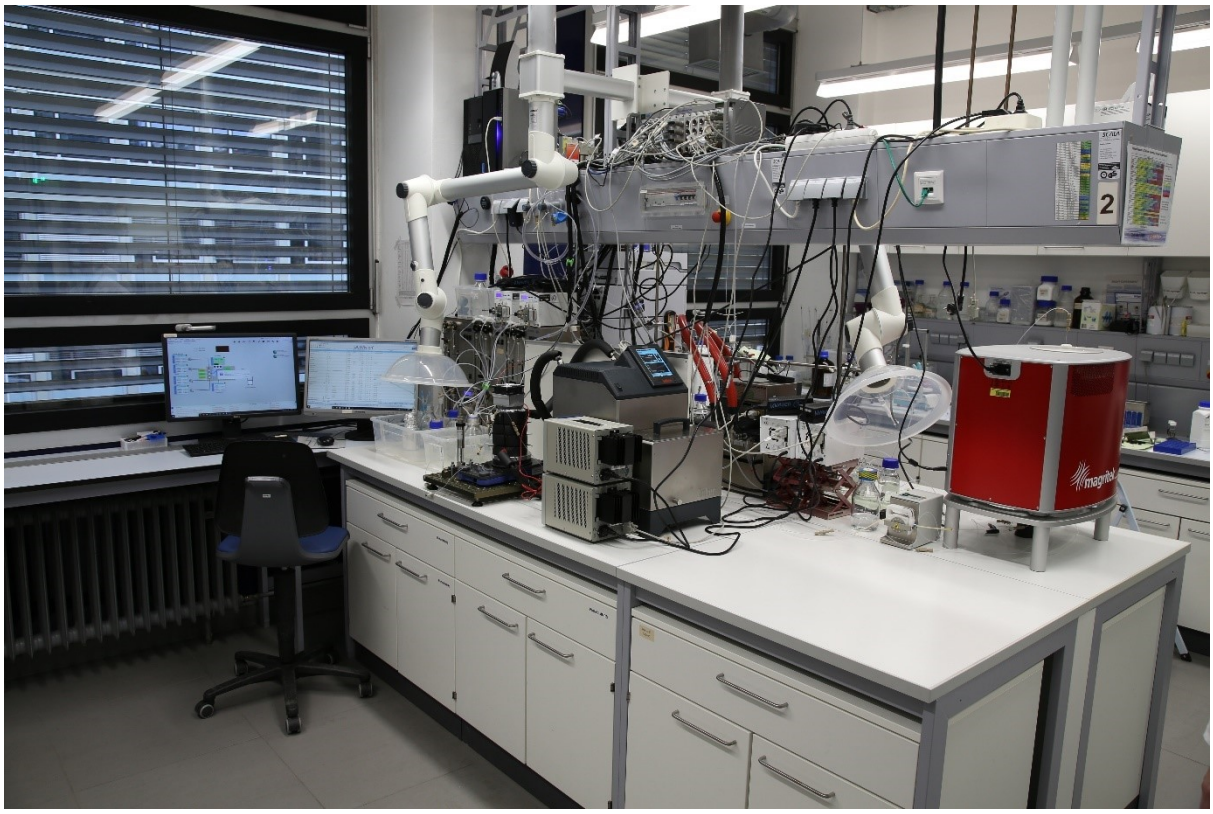


Fig. S2. Picture of the automated modular flow chemistry platform.

2 Optipus Software

Optipus is an open-source software that was developed during the course of this study and is fully available on GitHub. It is written in Python 3.7.9 and uses several freely available Python packages.
https://github.com/SKenb/AutomatedDoE

The main task is to plan, execute and evaluate model-based experimental design (automated DoE) studies. The program finds suitable experiments, communicates with an existing system, scales and transforms measured data, and designs/validates models. Moreover, a graphical user interface (GUI), proper logging, and export/import possibilities are present.

2.1 Main program design

The main program design implements a simple state machine that executes different programs/tasks within an environment of managed error and logging handling. The main functionality of the automated DoE can be programmed within small tasks/programs without dealing with concrete error handling.
This state machine and the main functionality are placed in its own thread, which is controlled via a local web-server. Hence, it is also possible to implement the GUI as a website and use the standard web technologies to realize the GUI.

2.2 Automated DoE

The automation of the model-based experimental design (automated DoE) is implemented within 6 Tasks/States, see Fig. S3, which are executed in the correct order from the mentioned superior state machine.

In the first state ("InitDoE"), the program is initialized, and so everything is reset, and all variables are defined. Thereby, basic objects (like the "factorSet") are directly adopted from the interface/GUI. Moreover, a new directory in the logging-Folder is created, where all essential information of the run is stored.
The logic for finding new experiments is implemented in the following state ("FindNewExperiments"). Thereby the python package "pyDOE2" (1.3.0) is used, which provides a variety of functions to create designs for any number of factors. The default logic uses the 2-level Full-Factorial ("ff2n") function to get a full factorial design for the number of defined factors.
These experiments are not returned all at once. Instead, they are returned in sets to establish several model iterations. In general, each set contains “min(8, 2^((n/2)))” experiments. Thereby, n is the number of factors and each set contains a maximum of eight experiments. On top of those eight experiments, one experiment covering the center point is added to each set. For the first set, two experiments for the center point are added. Additionally, after the full factorial design sets, face center points are considered,

resulting in a central composite face-centered (CCF) design. These face center points result in more design iterations with the possibility of gaining more detailed models, including quadratic effects. Here, each set contains only two experiments.

Subsequently, the state ("ExecuteExperiments") implements the functionality to conduct the experiments. The interface and logic for an existing programmable logic controller (PLC) are implemented in the class XAMControl and used in this state. The PLC forwards the factor/experiment values and returns the measurement values to the program. In this state, all experiments within one design iteration are conducted after proceeding to the next state.

The conducted experiments are evaluated in the fourth state ("EvaluateExperiments"). The data gets scaled to a unit range from -1 to 1. Moreover, the data is transformed (i.e., Box Cox transformation with an offset to allow negative values) to approximate a normal distribution.

Afterward, the prepared data is extended by adding interaction and quadratic factors. Starting with the extended data set, a model is created using multiple linear regression (MLR). Thereby the functionalities from the python package "statsmodel" (0.13.0) are used. Based on the significance and weights of model coefficients, the algorithm starts to remove non-significant terms. Squared terms are removed before interaction terms, and interaction terms are removed before main factor terms. For each model, statistical scores R^2 and Q^2 are stored. This enables the best overall model to be filtered with respect to a definable objective/logic. The default filtering logic attempts to maximize Q^2, minimize the number of model coefficients, and avoid substantial R^2 drops. This logic is realized by searching the model for the maximum Q^2 score and takes all models with a similar Q^2 score ($> 0.95 \times Q^2_{max}$). For this set of models, the R^2 score is determined, and all models showing an R^2 score significantly smaller than the maximum ($< R^2_{max} - 0.1$) are removed. Thus, a higher Q^2 is not accepted at a cost of a substantial drop in R^2. Then, from the remaining models, the most lightweight model (least number of coefficients) is selected. This filtering logic could be adjusted depending on the user requirements.

Based on the center point experiments, RepScore is calculated as a measure of experimental repeatability across the experiment set (Equation S1):

$$RepScore = 1 - \frac{Variance\ in\ center\ point\ results}{Variance\ in\ entire\ data\ set} \quad (1)$$

The best model is used to predict the responses for the conducted experiments and compare them against the measured ones. Thereby it is possible to detect potential experimental outliers. Outliers could result from measurement uncertainties and are handled within the following state ("HandleOutliers").

In the state of outlier detection, the program seeks and deals with outliers. Thereby, an outlier is detected by facing the difference between the measured and predicted value of the responses. The current logic uses the function “outlier_test()” of the python package "statsmodel". The function returns studentized residuals, among other values. Outliers are defined by comparing the studentized residuals with a definable threshold. The default value of this threshold is 4 standard deviations.

After determining the outliers, the corresponding experiments are re-conducted. If the repeated measurement results in the same outcome (relative change of the responses is lower than 10%), the outlier can be verified, and both experiments (original and re-conducted one) are removed from the model. If the repeated measurement shows a different result, the initial measurement is replaced with the new response value.

The final state ("StopDoE") implements a final clean-up and is reached after all experiments are conducted. If there are still experiments, the program starts a new design iteration in the state ("FindNewExperiments"). Additionally, a stop is conceivable if the best model in the design iteration shows no/minimal performance increase compared to older ones. In this final state, the best overall model is determined.

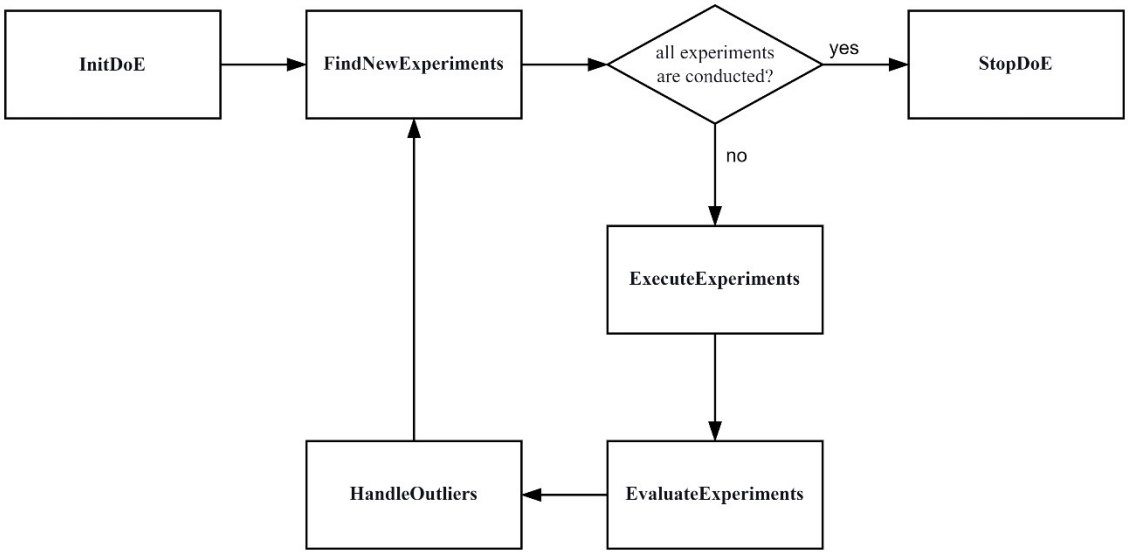


Fig. S3. Illustration of the 6 main Tasks/States of the automation of the Model-Based Experimental Design (Automated DoE).

2.3 Optimization

Besides the automation of the model-based experimental design (automated DoE), the factors are optimized to the maximum response using the best overall model. Here the functionalities for bounded optimization from the Python package "scipy" (1.7.1) are used.

After optimization, an optional robustness test is possible. In this robustness test, the initial factor bounds are adjusted around the optimum, and the automated DoE is started again in a more focused region of the design space, see also Section 4.4. The logging/results are stored within a subfolder in the same folder as the initial run.

2.4 GUI

A local web-server is implemented to realize a graphical user interface (GUI). Thus, it is possible to use the standard web technologies (HTML5, CSS3, JS, ...) for the GUI itself. The GUI is reachable with any

browser under the address/link: "http://localhost:8080/" and can also be accessed by multiple users simultaneously. Five important subpages are provided and these are described below.

In the "Define" section, the user can define the factors (names, bounds, units, symbols) and specify the folder paths for interacting with the existing PLC. It is possible for the user to define network paths, allowing the PLC to be located in a different directory, but within the same network. Moreover, adjustments for a possible OPC UA implementation/alternative could be adopted in this section.

In the "Import" section, one can import exported experiments or entire runs. The normalized format (Table S1) allows measurements to be imported from any other system. The imported measurements are used if the same experiments are requested, instead of conducting the same experiment again.

The section "Automated DoE" allows for controlling of the automated DoE process. One can start/stop and pause/resume the process. Moreover, detailed status information is printed in this section, and export is possible (if the process is pausing).

In the "Result" section, one can directly/live evaluate and investigate the current design models and intermediate results. Also, the investigation of previous runs is possible within this section.

In the last section ("About"), some minor information (Version) can be found.

Table S1. Normalized csv format for exporting/importing experiments.

<FactorName 1>	<FactorName 2>	...	<FactorName N>	Response	Additional
<LowerBound 1>	<LowerBound 2>	...	<LowerBound N>		
<UpperBound 1>	<UpperBound 2>	...	<UpperBound N>		
<Symbol 1>	<Symbol 2>	...	<Symbol N>		
<Unit 1>	<Unit 2>	...	<Unit N>		
<Value Exp. 1>	<Value Exp. 1>	...	<Value Exp. 1>	<Value Exp. 1>	<Value Exp. 1>
<Value Exp. 2>	<Value Exp. 2>	...	<Value Exp. 2>	<Value Exp. 2>	<Value Exp. 2>
...	...	...	...	...	...

2.5 Report

The software provides an automated notification functionality to allow users to focus on other tasks whilst the automated DoE is running. Thereby, the program sends an E-mail (see Fig. S4) to the user(s) after the automated DoE has finished. The E-mail contains all relevant statistics and information about the run. Additionally, there is the possibility of informing the users via SMS.

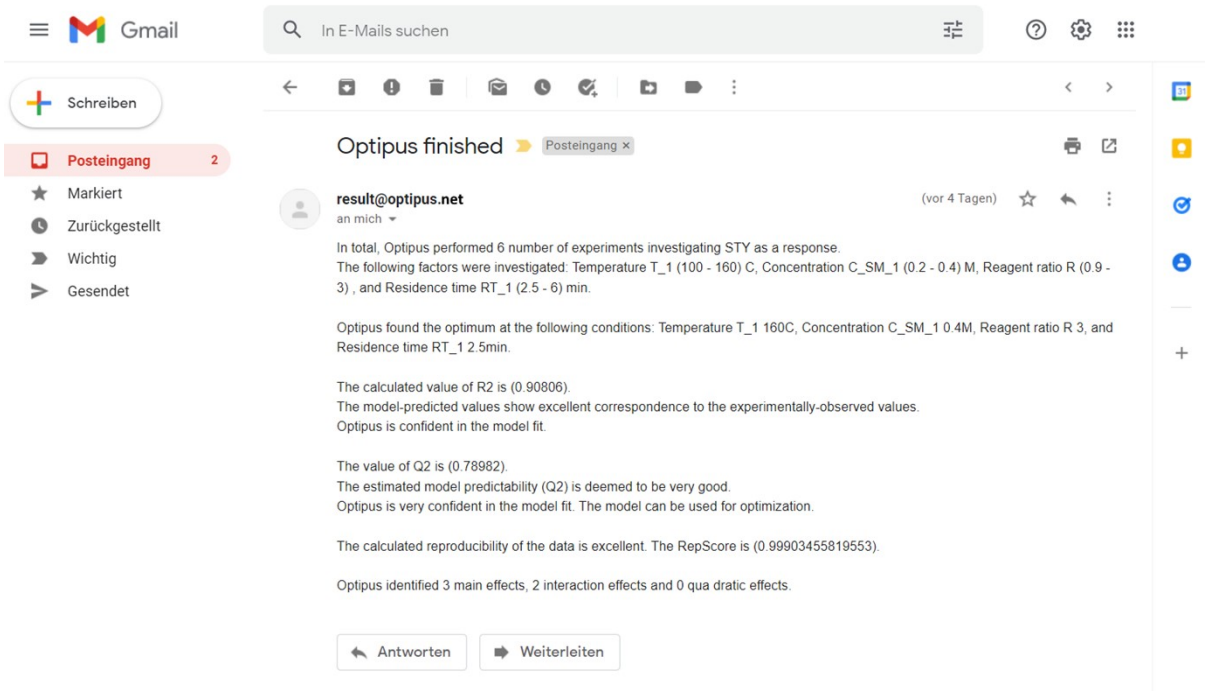


Fig. S4. E-Mail report from Optipus after an automated DoE run.

3 Control Software

XAMControl is a SCADA software for industrial automation. It allows direct communication with actuators and sensors via OPC UA to different DCS systems. The process is visualized in XAMControl Iris (Fig. S5 and Fig. S7), which allows the display of real-time process data and manual process control from the operator. The backbone of XAMControl is the designer, which allows PLC integration either with object orientated programming or coding (Fig. S6 and Fig. S8) in C# programming language. All recorded data points are stored in a cloud repository and can be accessed with XAMControl Iris or be exported to csv files. For a detailed insight into the control methods and applied filters for raw concentration data see reference S1.

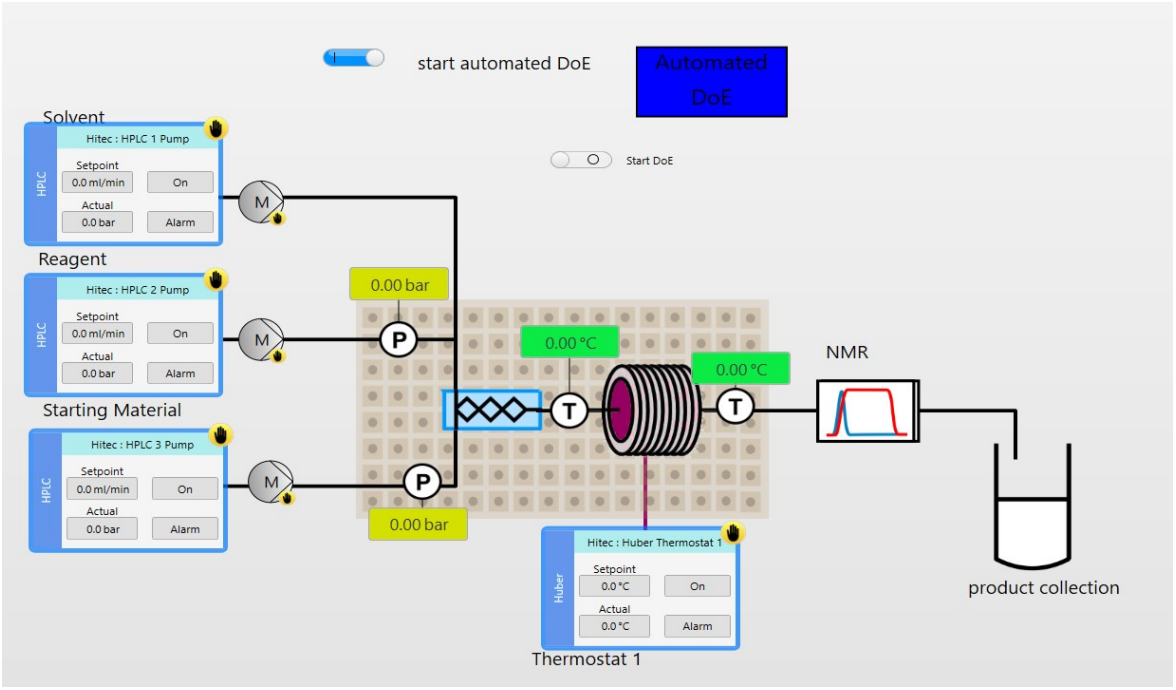


Fig. S5. Process visualization in XAMControl Iris for the S_NAr. The actuators and PAT can be controlled from this view.

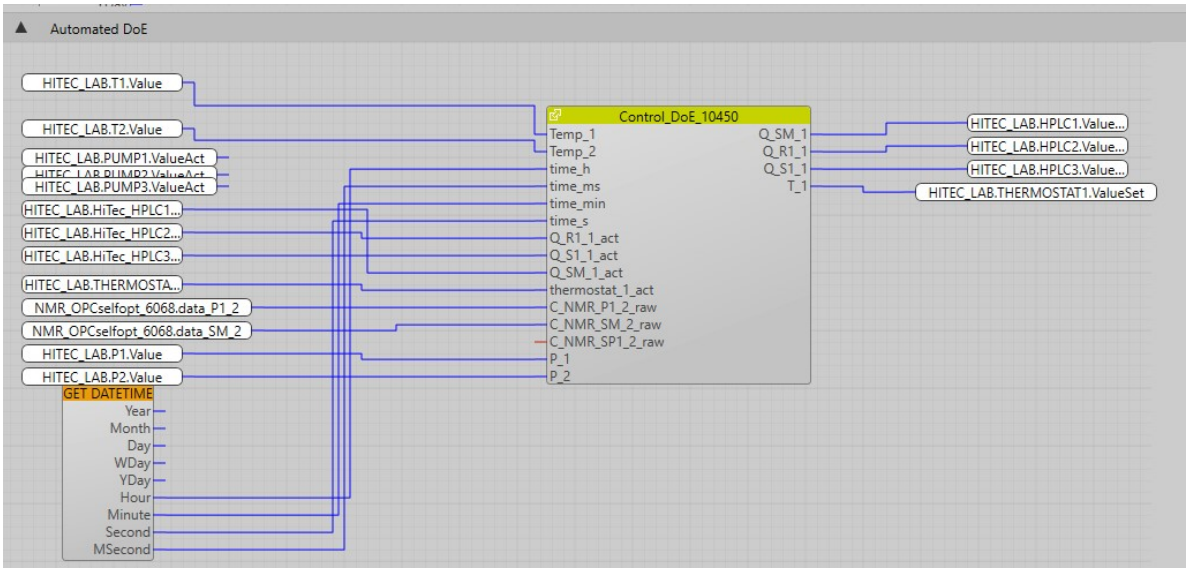


Fig. S6. Object oriented PLC design in XAMControl for the S_NAr. The figure represents all inputs and outputs variables for the PLC.

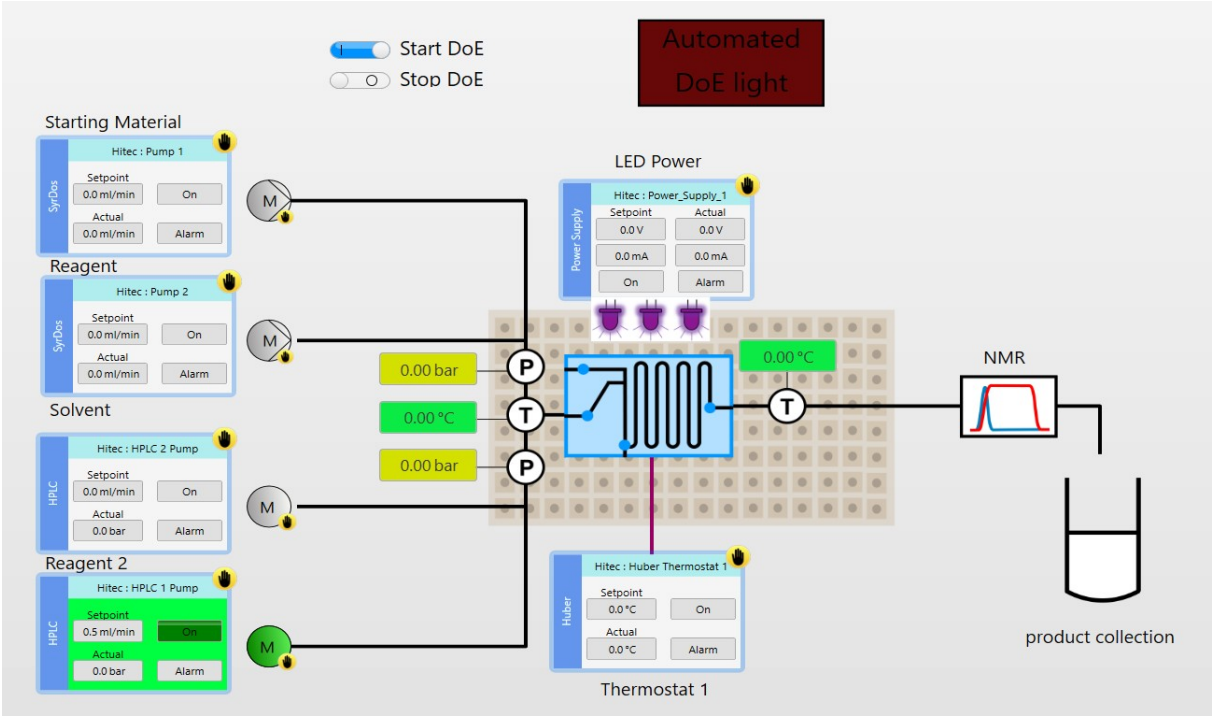


Fig. S7. Process visualization in XAMControl Iris for the benzylic bromination. The actuators and PAT can be controlled from this view.

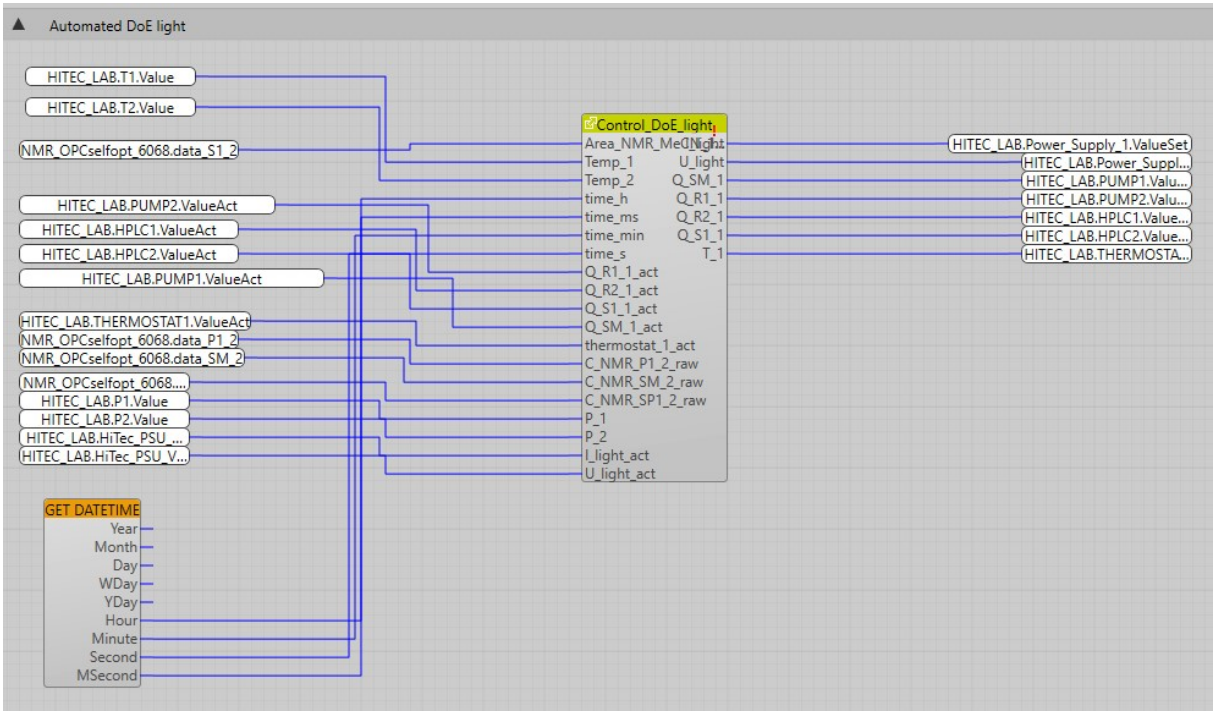
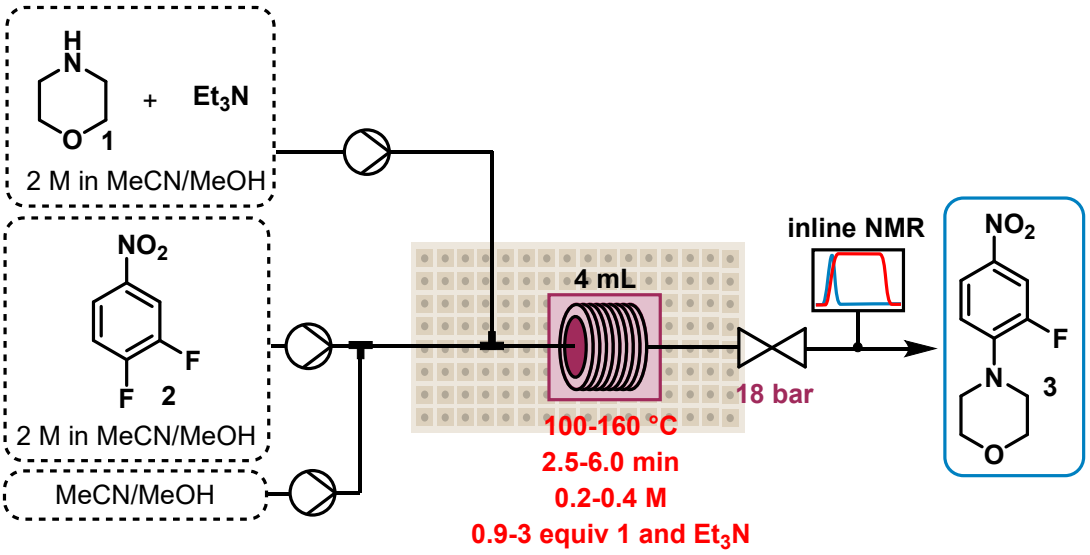


Fig. S8. Object oriented PLC design in XAMControl for the benzylic bromination. The figure represents all inputs and outputs variables for the PLC.

4 S_NAr

4.1 Experimental Setup



The continuous flow setup was slightly modified from a literature procedure.[S1]

Preparation of stock solutions:

2.0 M 3,4-difluoronitrobenzene (**2**) solution: In a 250 mL volumetric flask 3,4-difluoronitrobenzene (**2**) (79.5 g) was dissolved with a mixture of MeCN/MeOH (1+1 v/v).

2.0 M morpholine (**1**) and 2.0 M triethylamine solution: In a 500 mL volumetric flask morpholine (**1**) (87 g) and triethylamine (101.1 g) were diluted with a mixture of MeCN/MeOH (1+1 v/v).

Solvent mixture: In a 2 L Duran bottle, HPLC grade MeCN and HPLC grade MeOH were mixed (1+1 v/v).

The S_NAr reaction was performed in a Modular MicroReaction System (Ehrfeld Mikrotechnik, MMRS). The morpholine (**1**) and triethylamine, and solvent (MeCN/MeOH) streams were delivered with two Knauer AZURA P 4.1S pumps (10 mL/min pump head made of Hastelloy). The two streams were mixed prior to the MMRS system in a T-piece (PEEK, 0.5 mm i.d.) and entered the MMRS system through a 1/16" o.d. in/out connector (0711-2-0124-F, Hastelloy C-276), followed by a pressure sensor module (0518-1-60x4-F, Hastelloy C-276). The substrate feed with 3,4-difluoronitrobenzene (**2**) was delivered with a Knauer AZURA P 4.1S pumps (10 mL/min pump head made of Hastelloy), through PFA tubing, to the MMRS system. The feed entered the system through a 1/16" o.d. in/out connector (0711-2-0124-F, Hastelloy C-276), followed by a pressure sensor module (0518-1-60x4-F, Hastelloy C-276) and was mixed in a T-type connecting module (0723-1-0004, Hastelloy C-276) with the diluted morpholine stream. The reaction mixture passed through a temperature sensor (0501-2-1004-X, Hastelloy C-276), followed by a capillary reactor (0214-1-1004-F, build in connection body of 4.00 mL, Hastelloy C-276) which was temperature controlled by a thermostat (Huber, Ministat 240). After the capillary reactor, the

reaction solution passed through another temperature sensor (0501-2-1004-X, Hastelloy C-276) and exited the MMRS system via a 1/16" o.d. in/out connector (0711-2-0124-F, Hastelloy C-276). The outlet PFA tubing (0.2 mL, 0.8 mm i.d.) from the MMRS system was placed in a water bath and connected to a membrane-based BPR (Zaiput, BPR-10) which was set to 18 bar. The reaction stream was delivered through PFA tubing (0.9 mL, 0.8 mm i.d.) to the benchtop NMR (Magritek, Spinsolve Ultra 43 MHz). A 6-port valve was installed prior to the glass flow cell (800 µL internal volume, 550 mm length) by-passing the NMR allowing the instrument to be shimmed without stopping the reaction pumps. The reaction stream left the NMR through PFA tubing (0.3 mL, 0.8 mm i.d.) and was collected in the receiver vessel.

4.2 PAT Integration and Analytical Model

The details on the integration of the NMR and the data processing model (indirect hard modelling) can be found in reference S1.

4.3 Optipus Run (Design 1)

The Optipus algorithm was allowed to change in four reaction input factors: temperature of the reactor (°C), concentration of starting material **2** in the reactor (mol/L), equivalents of reagent **1**, residence time in the reactor (min). The upper and lower bounds for the input factors are provided in Table S2. The experimental results are provided in Table S3 and figures of the real-time model building are depicted in Fig. S9 to Fig. S14. The history of R^2 and Q^2 values for model evaluation during the experiments is shown in Fig. S15. The scores for the final model are provided in

Table S4 and more detailed results on the model coefficients provided in Table S5.

Table S2. Lower and upper bounds for the input factors during the Optipus run for Design 1 of the S_NAr reaction.

Limits	Temperature (°C)	Conc. starting material **2** (mol/L)	Equiv of **1**	Residence time (min)
Lower	100	0.2	0.9	2.5
Upper	160	0.4	3	6.0

Table S3. Detailed results for the Optipus run for Design 1 of the S_NAr reaction.

Entry	Temperature (°C)	Conc. starting material **2** (mol/L)	Equiv of **1**	Residence time (min)	STY (kg L^{-1} h^{-1})
1	100	0.20	0.90	2.50	0.00
2	100	0.40	0.90	2.50	0.07
3	100	0.40	3.00	6.00	0.52
4	100	0.20	3.00	6.00	0.12
5	130	0.30	1.95	4.25	0.34
6	130	0.30	1.95	4.25	0.34
7	160	0.20	0.90	2.50	0.07
8	160	0.40	0.90	2.50	0.41

Entry	Temperature (°C)	Conc. starting material **2** (mol/L)	Equiv of **1**	Residence time (min)	STY (kg L^{-1} h^{-1})
9	160	0.40	3.00	6.00	0.80
10	160	0.20	3.00	6.00	0.32
11	160	0.20	0.90	6.00	0.14
12	160	0.40	0.90	6.00	0.40
13	160	0.40	3.00	2.50	1.35
14	160	0.20	3.00	2.50	0.32
15	130	0.30	1.95	4.25	0.36
16	100	0.20	0.90	6.00	0.02
17	100	0.40	0.90	6.00	0.12
18	100	0.40	3.00	2.50	0.57
19	100	0.20	3.00	2.50	0.11
20	160	0.30	1.95	4.25	0.51
21	100	0.30	1.95	4.25	0.17
22	130	0.40	1.95	4.25	0.62
23	130	0.20	1.95	4.25	0.15
24	130	0.30	0.90	4.25	0.14
25	130	0.30	3.00	4.25	0.51
26	130	0.30	1.95	6.00	0.34
27	130	0.30	1.95	2.50	0.34

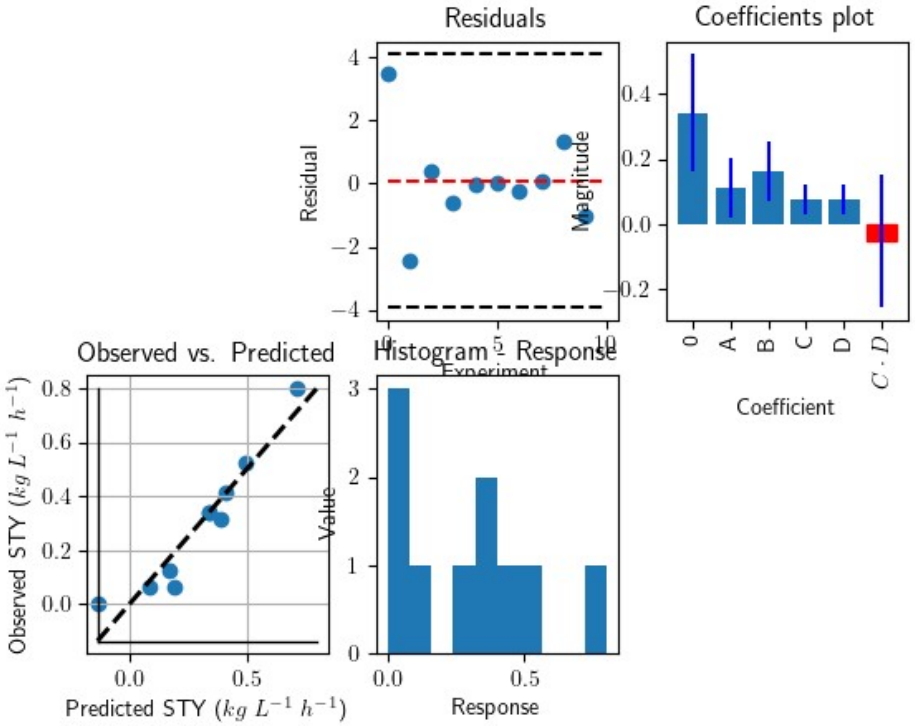


Fig. S9. Model from the Optipus software after 10 experiments for Design 1. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

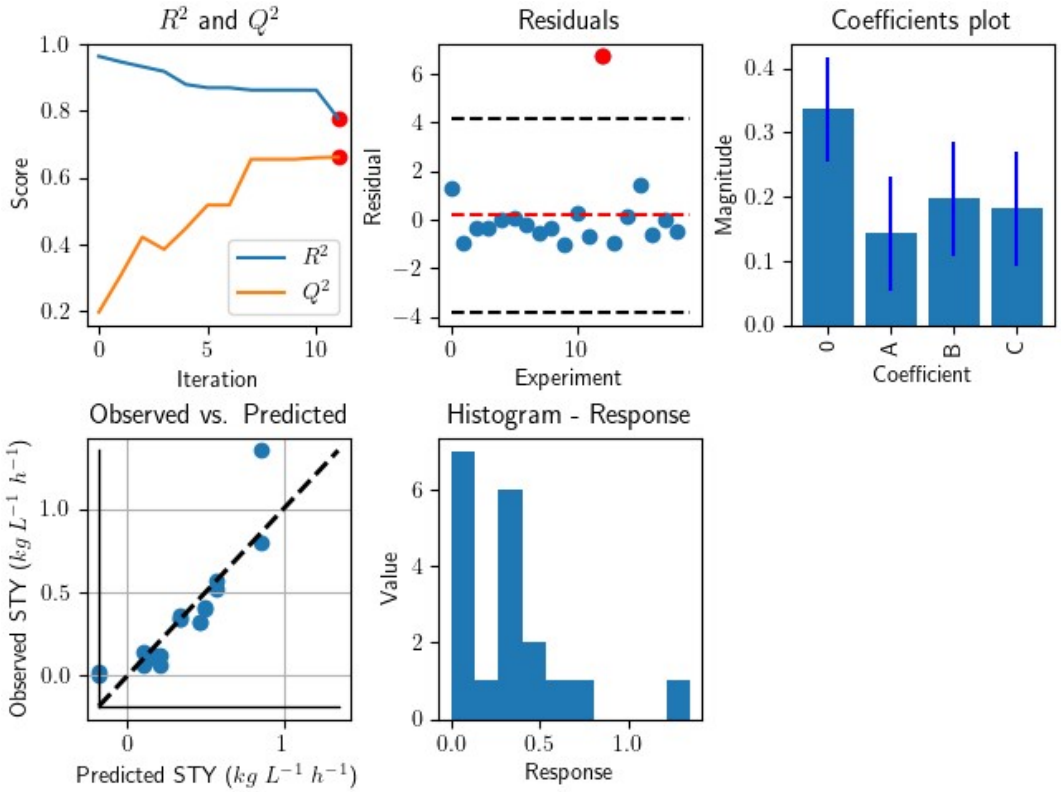


Fig. S10. Selected model from the Optipus software after 19 experiments for Design 1. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

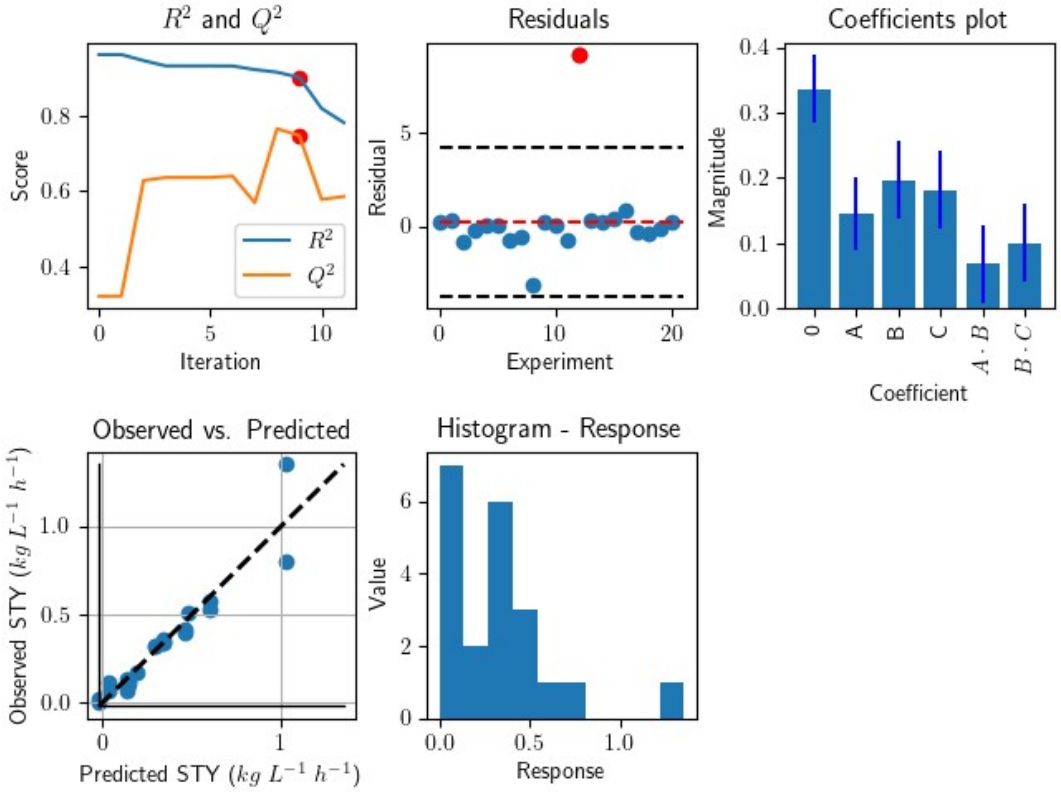


Fig. S11. Selected model from the Optipus software after 21 experiments for Design 1. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

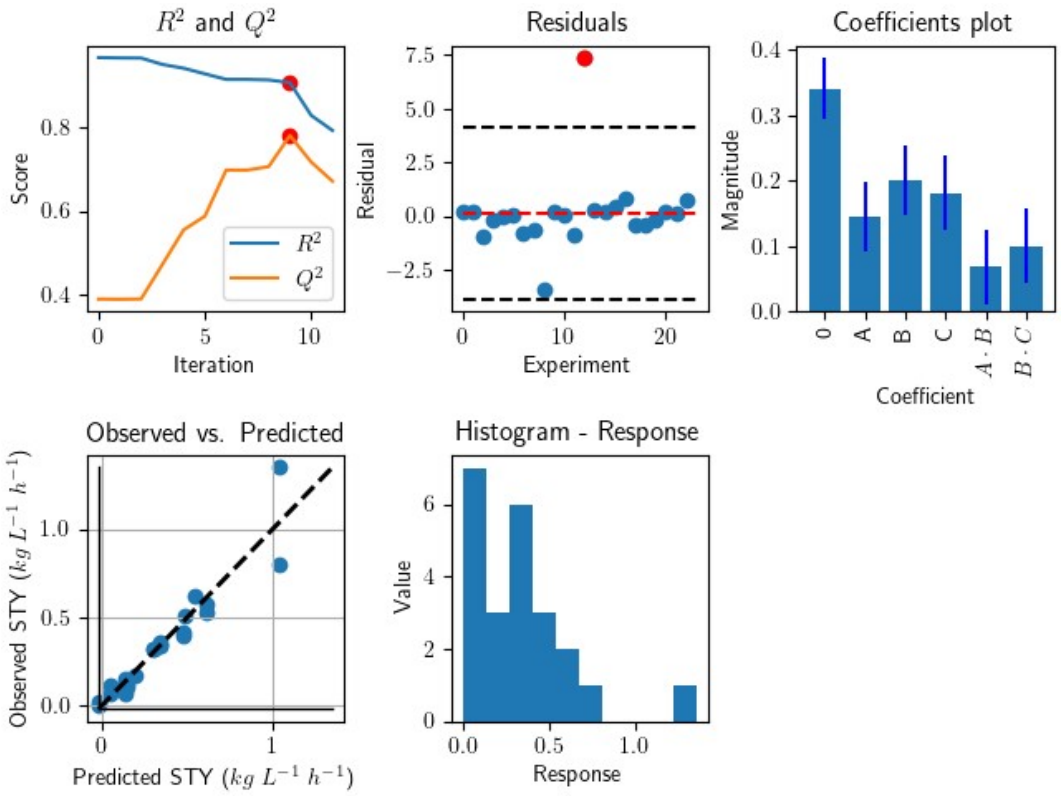


Fig. S12. Selected model from the Optipus software after 23 experiments for Design 1. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

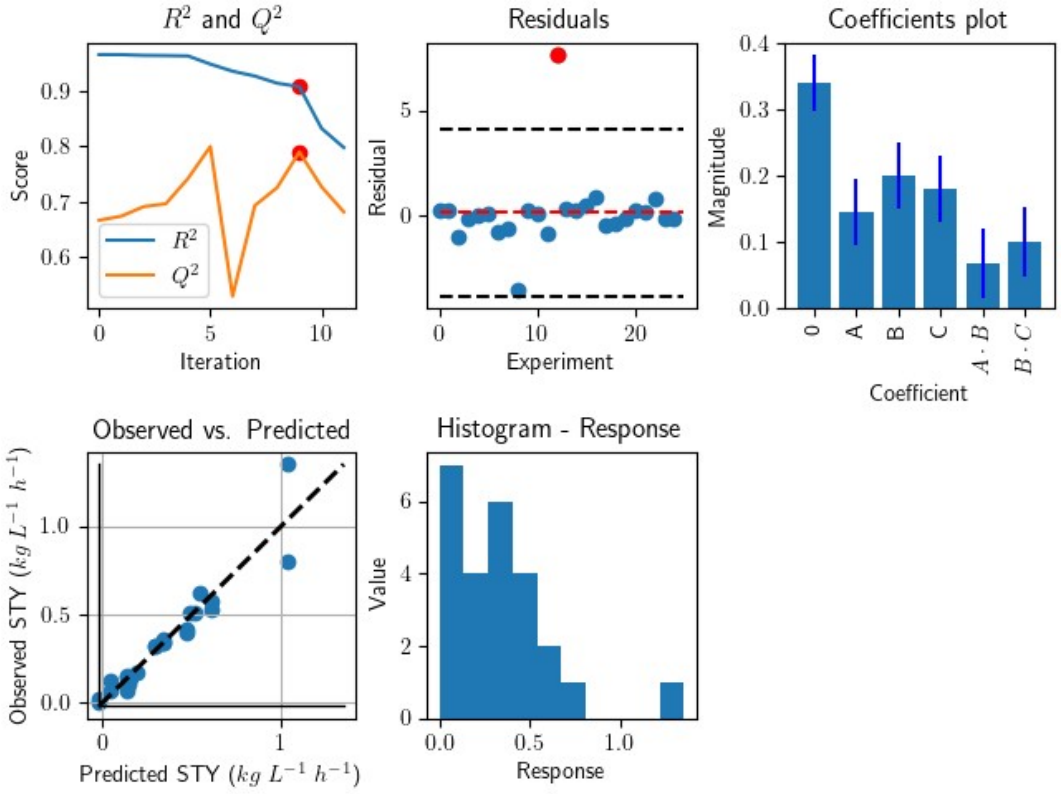


Fig. S13. Selected model from the Optipus software after 25 experiments for Design 1. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

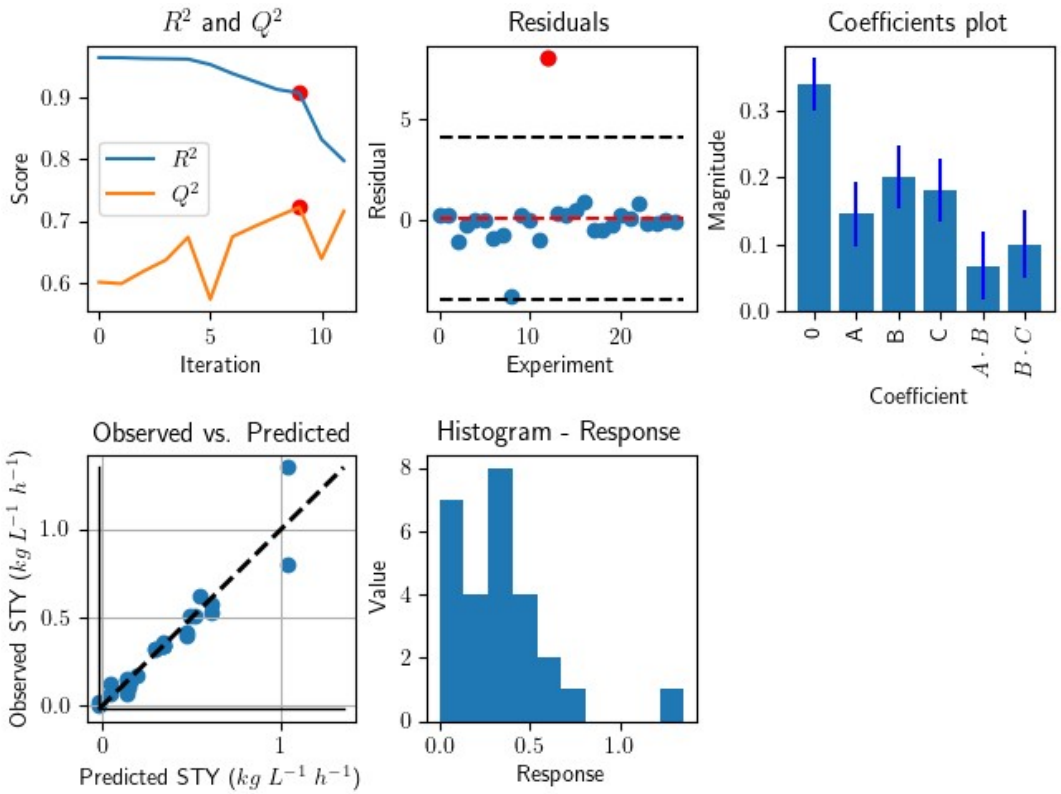


Fig. S14. Selected model from the Optipus software after 27 experiments for Design 1. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

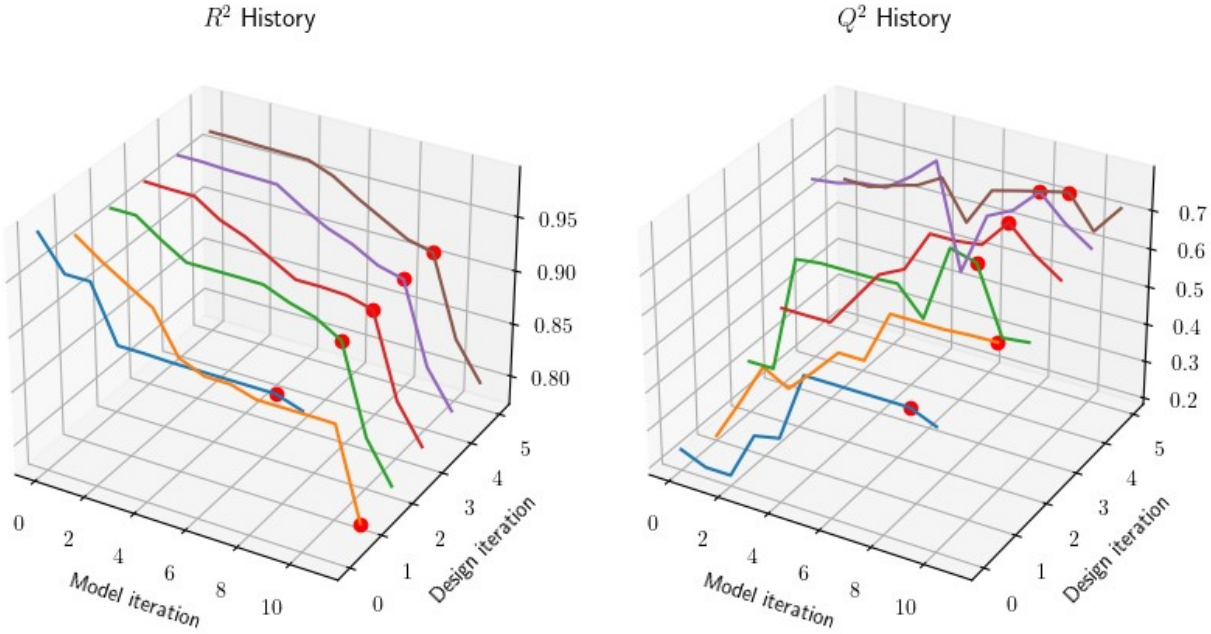


Fig. S15. History of R^2 and Q^2 values for different model evaluation during the experiments of Design 1.

Table S4. Scores for the final model for Design 1 of the S_NAr reaction. 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. RepScore is a measure of the repeatability of the center points.

R^2	Q^2	RepScore
0.96548	0.72219	0.99999028

Table S5. Model coefficients and scaled model coefficients for the final model final model for Design 1 of the S_NAr reaction. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

Factors	Model Coefficients	Scaled Model Coefficients
0	0.2117145	0.3391203
A	-0.00194967	0.14507661
B	-2.79144945	0.20072152
C	-0.11348835	0.18101748
A * B	0.02261851	0.06785552
B * C	0.95295317	0.10006008

4.4 Optipus Run (Design 2)

The Optipus algorithm was allowed to change four input factors: temperature of the reactor (°C), concentration of starting material **2** in the reactor (mol/L), equivalents of reagent **1**, residence time in the reactor (min). The upper and lower bounds for the input factors are provided in Table S6 and were chosen based on the optimum of the first design and Equation S2. The experimental results are provided in Table S7 and figures of the real-time model building are depicted in Fig. S16 to Fig. S21. The history of R^2 and Q^2 values for different model evaluation during the experiments are shown in Fig. S22. The scores for the final model are provided in Table S8 and more detailed results on the model coefficients are provided in Table S9.

$$Boundary_{Design2} = Optimum_{Design1} \pm \left[\left(max.\,Boundary_{Design1} - \; min.\,Boundary_{Design1}\right) \times 0.05\right] \quad (2)$$

Table S6. Lower and upper bounds for the input factors during the Optipus run for Design 2 of the S_NAr reaction

Limits	Temperature (°C)	Conc. starting material **2** (mol/L)	Equiv of **1**	Residence time (min)
Lower	157	0.39	2.85	2.325
Upper	163	0.41	3.11	2.675

Table S7. Detailed results for the Optipus run for Design 2 of the S_NAr reaction

Entry	Temperature (°C)	Conc. starting material **2** (mol/L)	Equiv of **1**	Residence time (min)	STY (kg L^{-1} h^{-1})
1	157	0.39	2.90	2.33	1.51
2	157	0.41	2.90	2.33	1.61
3	157	0.41	3.11	2.68	1.59
4	157	0.39	3.11	2.68	1.50
5	160	0.40	3.00	2.50	1.59
6	160	0.40	3.00	2.50	1.59
7	163	0.39	2.90	2.33	1.59
8	163	0.41	2.90	2.33	1.91
9	163	0.41	3.11	2.68	1.66
10	163	0.39	3.11	2.68	1.54
11	163	0.39	2.90	2.68	1.50
12	163	0.41	2.90	2.68	1.59
13	163	0.41	3.11	2.33	1.78
14	163	0.39	3.11	2.33	1.70
15	160	0.40	3.00	2.50	1.58
16	157	0.39	2.90	2.68	1.40
17	157	0.41	2.90	2.68	1.53
18	157	0.41	3.11	2.33	1.69
19	157	0.39	3.11	2.33	1.63
20	157	0.40	3.00	2.50	1.55
21	163	0.40	3.00	2.50	1.66
22	160	0.39	3.00	2.50	1.52
23	160	0.41	3.00	2.50	1.65
24	160	0.40	3.11	2.50	1.62
25	160	0.40	2.90	2.50	1.55
26	160	0.40	3.00	2.33	1.67
27	160	0.40	3.00	2.68	1.51

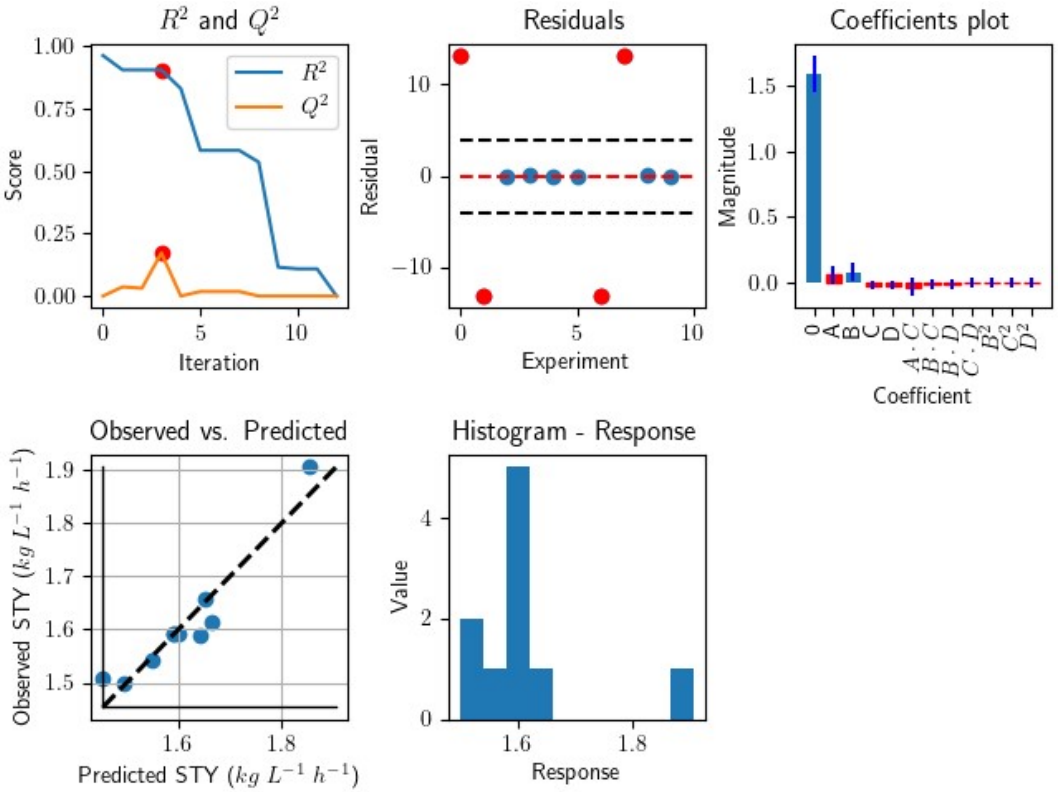


Fig. S16. Selected model from the Optipus software for Design 2 after 10 experiments. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

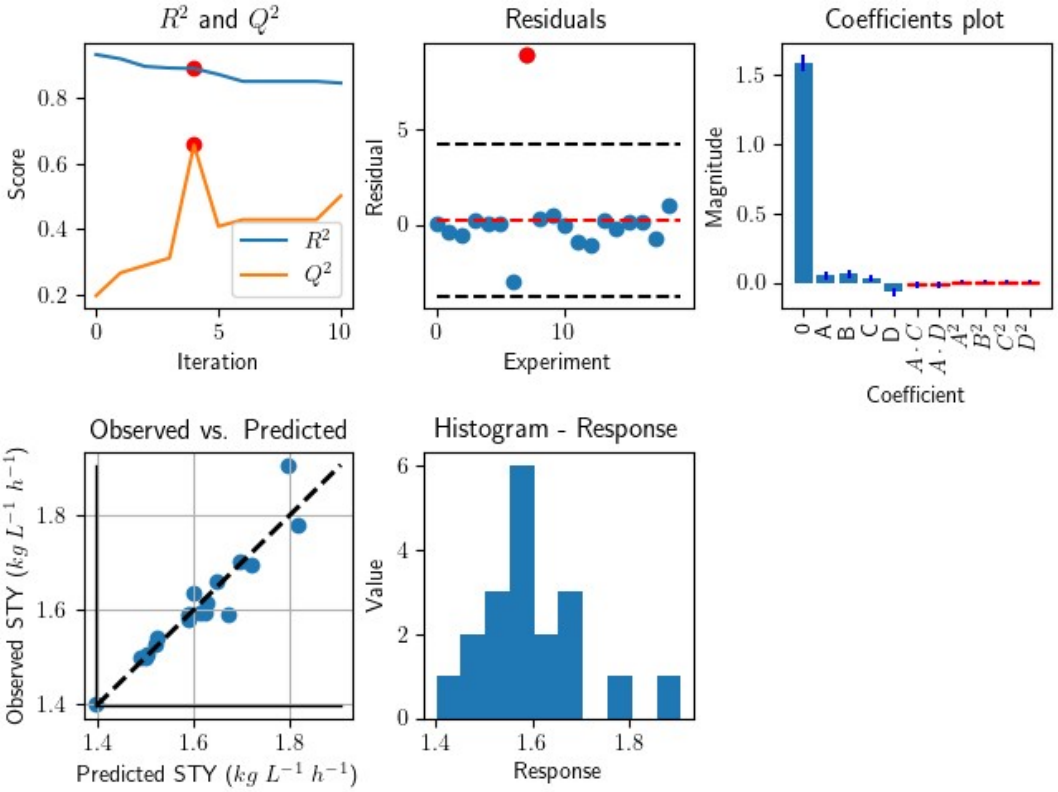


Fig. S17. Selected model from the Optipus software for Design 2 after 19 experiments. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

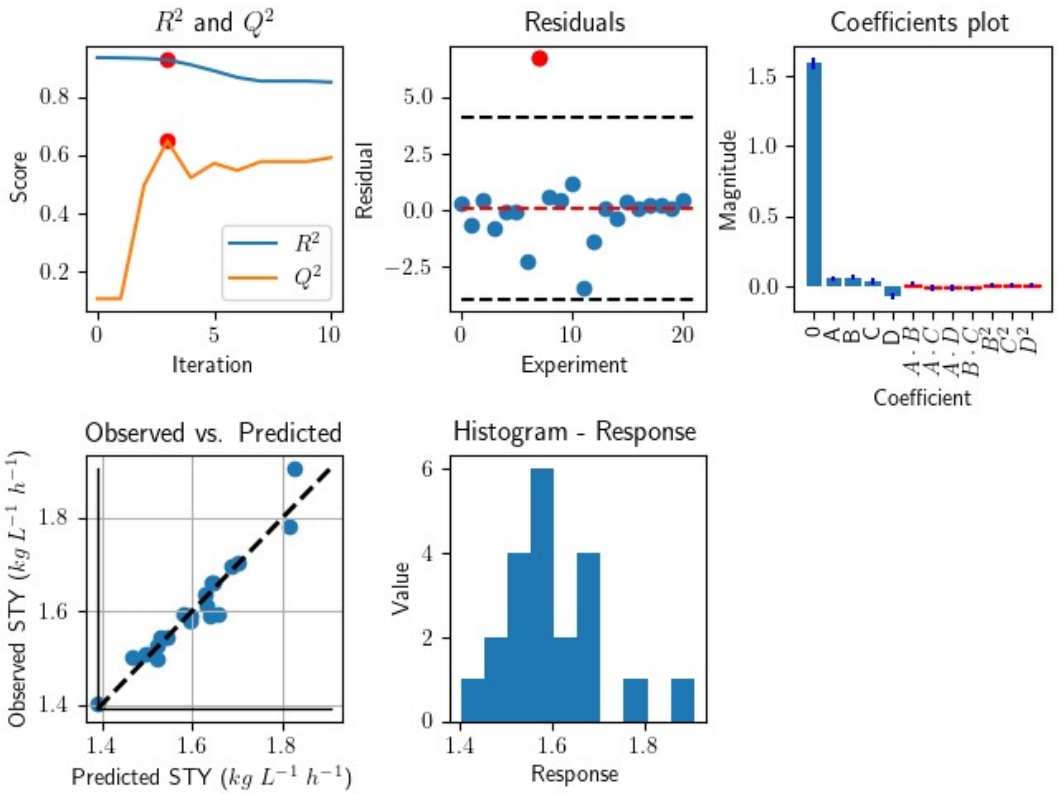


Fig. S18. Selected model from the Optipus software for Design 2 after 21 experiments. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

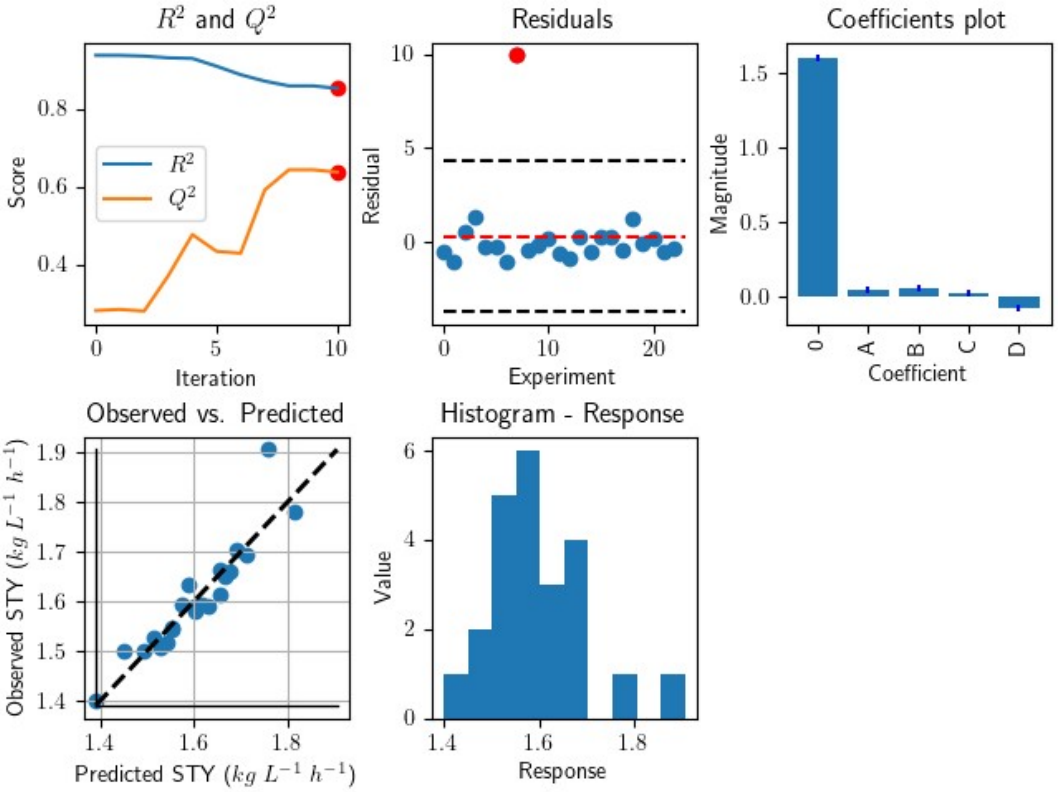


Fig. S19. Selected model from the Optipus software for Design 2 after 23 experiments. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

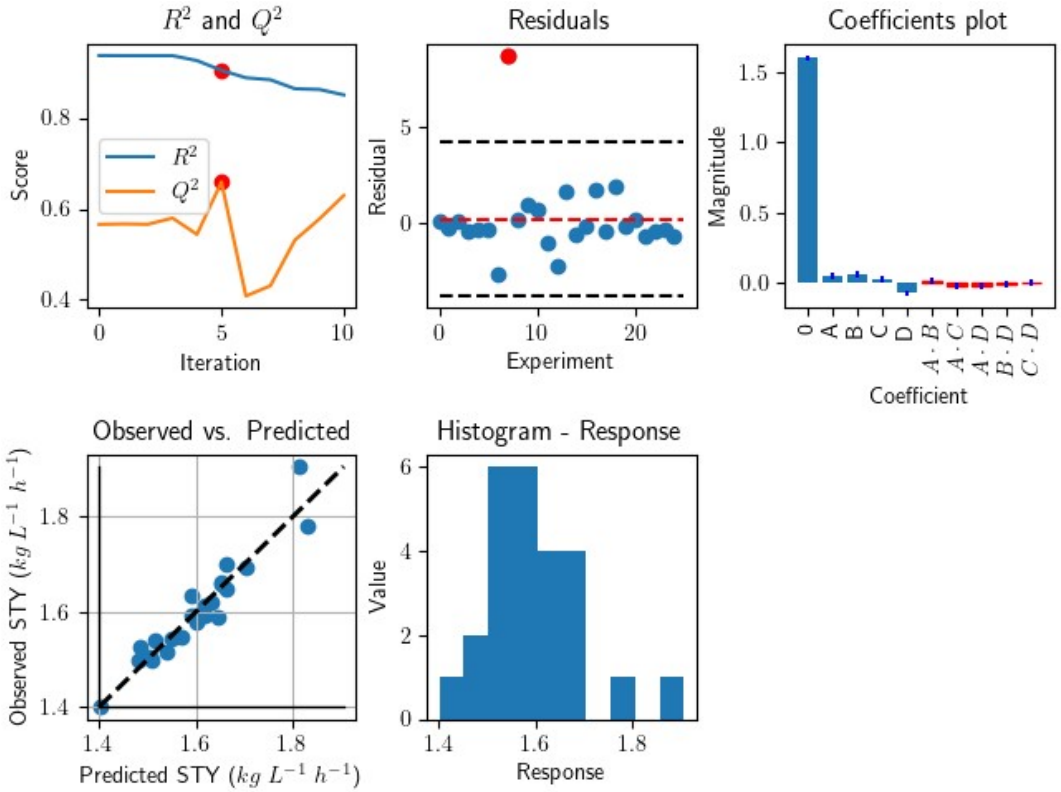


Fig. S20. Selected model from the Optipus software for Design 2 after 25 experiments In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

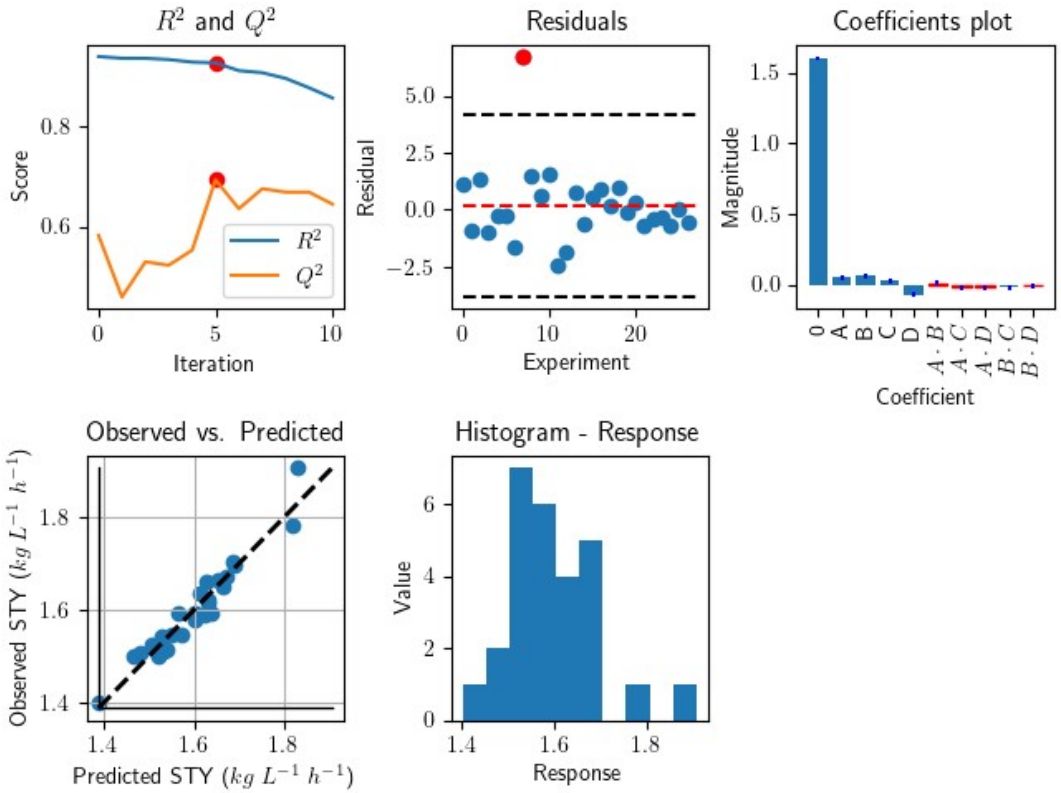


Fig. S21. Selected model from the Optipus software for Design 2 after 27 experiments. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

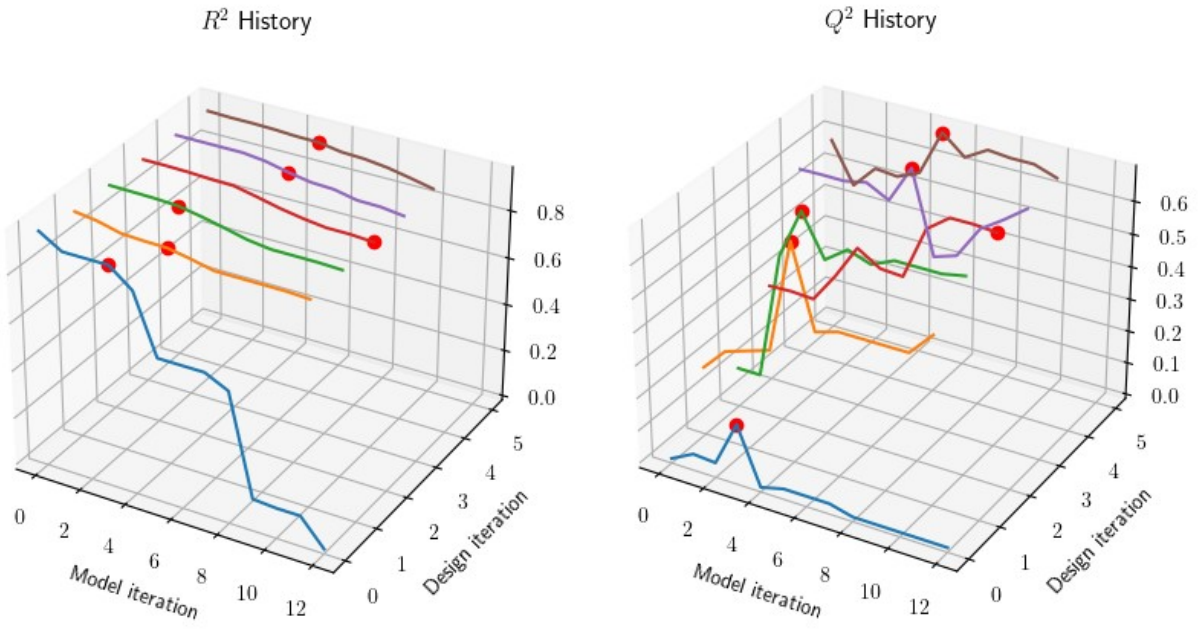


Fig. S22. History of R^2 and Q^2 values for model evaluation during the experiments of Design 2.

Table S8. Scores for the final model final model for Design 2 of the S_NAr reaction. 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. RepScore is a measure of the repeatability of the center points.

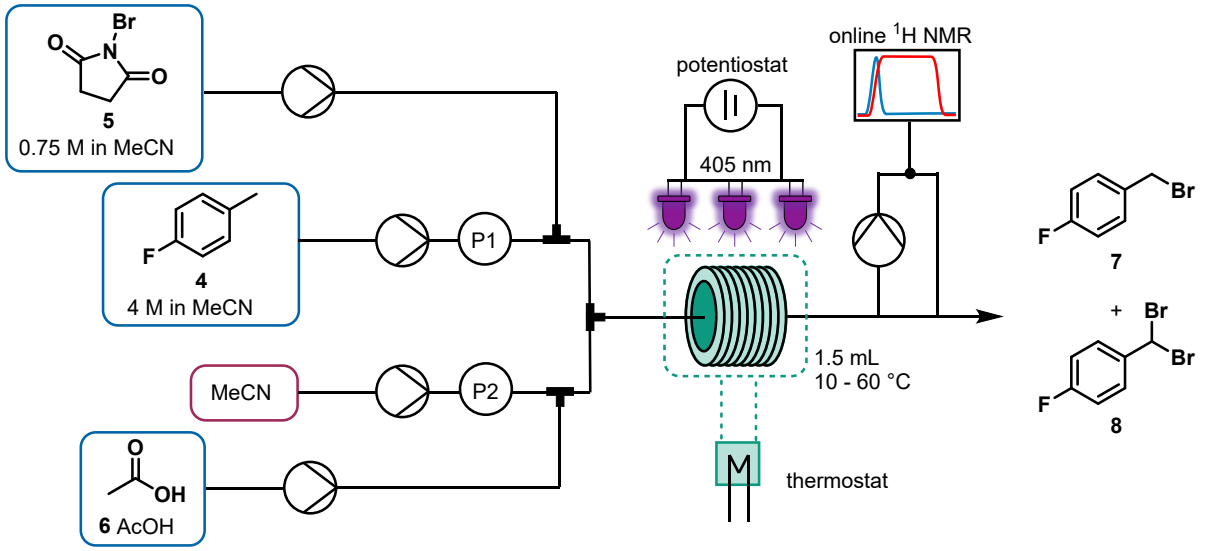
R^2	Q^2	RepScore
0.93974	0.69327	0.99999991

Table S9. Model coefficients and scaled model coefficients for the final model for Design 2 of the S_NAr reaction. The factor set is the constant (**0**), the temperature of the reactor (**A**), concentration of starting material **2** (**B**), equivalents of reagent 1 (**C**), residence time in the reactor (**D**).

Factors	Model Coefficients	Scaled Model Coefficients
0	-38.7035814	1.60075611
A	0.07786759	0.05108248
B	-2.58678363	0.06228266
C	16.1036804	0.03014471
D	6.32273042	-0.07071934
A * B	0.45358179	0.01360745
A * C	-0.05549375	-0.01748053
A * D	-0.03031662	-0.01591623
B * C	-17.3439688	-0.01821117
B * D	-4.69045236	-0.00820829

5 Benzylic Bromination

5.1 Experimental Setup



Preparation of stock solutions:

0.75 M *N*-bromosuccinimide (**5**) solution: *N*-bromosuccinimide (**5**) (33.7 g) was dissolved in MeCN (HPLC grade, 250 mL).

4 M 4-fluorotoluene (**4**) solution: 4-fluorotoluene (**4**) (110.1 g) was dissolved in MeCN (HPLC grade, 250 mL).

The photoinduced benzylic bromination reaction was performed in a custom-built coil photoreactor, making use of a Modular MicroReaction System (Ehrfeld Mikrotechnik, MMRS) for reagent introduction/mixing and pressure sensors. The streams of the *N*-bromosuccinimide (**5**) and 4-fluorotoluene (**4**) solutions were delivered by two SyrDos2 pumps (90 bar valve, 1.0 mL syringes). The MeCN and AcOH (**6**) stream were delivered by two Knauer AZURA P 4.1S pumps (10 mL/min pump head made of Hastelloy) connected to cartridge BPRs (IDEX, green 34 bar) to ensure sufficient back pressure for the pumps. The feeds of 4-fluorotoluene and MeCN were led through a 1/16" o.d. in/out connector (0711-2-0124-F, Hastelloy C-276) and a pressure sensor module (0518-1-60x4-F, Hastelloy C-276). The remaining streams (NBS solution and AcOH) were directly connected to the respective mixing units.

4-Fluorotoluene (**4**) and NBS (**5**) solutions as well as the MeCN and AcOH streams respectively were mixed prior to the reactor system in T-pieces (PEEK, 0.5 mm i.d.). The resulting streams were then mixed in another T-piece (PTFE, 0.5 mm i.d.) before entering the reactor. The photoreactor coil consisted of 1/16" o.d. PFA tubing (reactor volume 1.492 mL) in a double-walled beaker filled with silicon oil for heat exchange. A 405 nm LED wafer (50 W maximum input power) was mounted on top of the reactor. The LED was powered by two benchtop power supplies connected in series (BK Precision, Model 1739. Note: this setup of two benchtop power supplies in series was required in order

to reach sufficient voltage to power the LEDs). The reaction stream was delivered through PFA tubing (0.58 mL, 0.8 mm i.d.) to a T-piece (PEEK, 0.5 mm i.d.) diverting the stream partially for online sampling. Online sampling was performed by a peristaltic pump (Ismatec, ISM834C), which was set to 10 rpm corresponding to a flow rate of approximately 1 mL/min. The sampling stream was pumped through a glass flow cell in a benchtop NMR spectrometer (Magritek, Spinsolve Ultra 43 MHz). The sampling stream left the NMR spectrometer through PFA tubing (0.5 mL, 0.8 mm i.d.) and was recombined with the process stream in a batch quench vessel filled with saturated. aq. sodium thiosulfate pentahydrate solution.

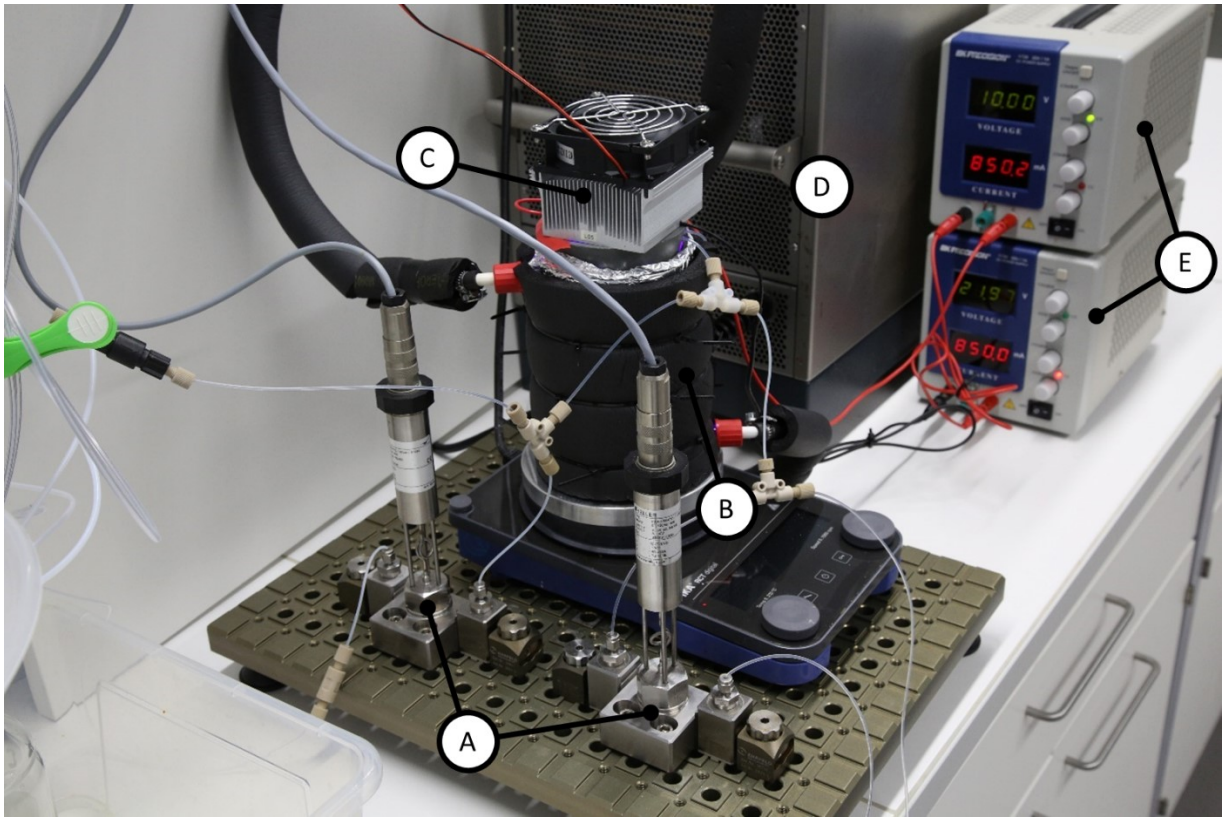
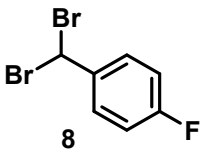


Fig. S23. Reaction setup for the benzylic bromination. (A) pressure sensors, (B) photo reactor, (C) 405 nm LED with cooling fan, (D) thermostat, (E) benchtop power supplies.

1-(Dibromomethyl)-4-fluorobenzene



8

A microwave vial was charged with 4-fluorotoluene (0.5009 g, 4.55 mmol) and *N*-bromosuccinimide (2.4553 g, 13.79 mmol, 3 equiv) was suspended in MeCN (10 mL, HPLC-grade) in a vial. The vial was capped and irradiated under stirring using a 50 W (input power) LED wafer (405 nm, distance: 7 cm) for 16 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL) and EtOAc (20 mL) was added. Subsequently, the organic phase was separated and washed using brine (10

mL) and 0.1 M aqueous HCl solution (3 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residuals were redissolved in petroleum ether (20 mL) and the solution was filtered through a plug of silica (frit 3 cm diameter, 1.5 cm silica in the frit). The solvent was removed under reduced pressure, yielding the desired product as a colorless oil (0.5802 g, 47%).

^{1}H NMR (300 MHz, Chloroform-*d*, δ): 7.65 – 7.48 (m, 2H), 7.13 – 6.98 (m, 2H), 6.64 (s, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*, δ): 163.2 (d, *J* = 250.4 Hz), 138.2 (d, *J* = 3.4 Hz), 128.7 (d, *J* = 8.7 Hz), 115.8 (d, *J* = 22.2 Hz), 39.8.

^{19}F NMR (471 MHz, Chloroform-*d*, δ): -110.44 – -110.54 (m).

5.2 PAT Integration and Analytical Model

Inline reaction monitoring by ^{1}H-NMR was accomplished by using a benchtop 43.795 MHz spectrometer (Magritek, Spinsolve Ultra 43 MHz). The benchtop NMR was typically shimmed on a regular basis with a mixture of deionized H_2O (10%) and D_2O (90%) ("QUICKSHIM ALL", linewidth at 50%: <0.4 Hz, linewidth at 0.55%: <8.0 Hz, signal to noise ratio: >20,000). Additionally, shims were directly performed with the flow cell for the S_NAr and benzylic bromination reactions on MeCN or the reaction mixture ("QUICKSHIM ALL", linewidth at 50%:<0.6 Hz, linewidth at 0.55%: <9.0 Hz, signal to noise ratio: >16,000).

5.2.1 Solutions prepared for indirect hard model

Preparation of training and validation solutions was performed by weighing the corresponding amount of 4-fluorotoluene (**4**), 1-(bromomethyl)-4-fluorobenzene (**7**), and 1-(dibromomethyl)-4-fluorobenzene (**8**) in 10 mL volumetric flasks (Table S10). The flasks were then filled up to the 10 mL mark with MeCN. The prepared solutions were stored at room temperature until the start of the measurement and were pumped with a peristaltic pump (Ismatec, ISM834C) through the benchtop NMR. The pump was set to 10 rpm, which corresponds to a flow rate of approximately 1 mL/min. The tubing and NMR flow cell were flushed first with air, then with MeCN and with air again to avoid cross-contamination. For each training and validation level, 100 spectra were acquired (number of scans: 1, repetition time: 10 s, pulse angle: 90 °, acquisition time: 6.4 s).

Table S10. Overview of the prepared training and validation sample to build the indirect hard model.

Entry	4-fluorotoluene **4** (mol/L)	1-(bromomethyl)-4-fluorobenzene **7** (mol/L)	1-(dibromomethyl)-4-fluorobenzene **8** (mol/L)
Train_1	0	0.01	0.501
Train_2	0	0.484	0
Train_3	0.499	0	0
Train_4	0.398	0.291	0.195
Train_5	0.099	0.395	0.301
Val_1	0.2	0.112	0.399

Val_2	0.3	0.193	0.098

5.2.2 Development of an IHM model

The acquired training and validation spectra were loaded into PEAXACT (S-PACT), assigned concentration labels, and grouped into different levels. A representative spectrum for each level was obtained by calculating the mean of the individual spectra.

Pretreatment model: All spectra underwent the same pretreatment conditions: base line correction (Straight Line Subtraction), phasing (Auto, Negative Peak Penalization), and spectral alignment of the highest peak (MeCN) to 1.98 ppm. The global range was from 0 ppm to 15 ppm.

Generation of pure component models: Peaks were added empirically and stepwise to the model (24 – 30 peaks per model) until the residuals were roughly two orders of magnitude lower than the largest peak (Fig. S24, A, B, and C). The fitting mode was set to maximal interactions, allowing the greatest flexibility within the model.

Generation of mixture model: A weighted sum of each pure component model represents the mixture model, including flexible but constrained peak parameters.

Calibration model and validation: The training set was comprised of the pure component spectra and five different component mixtures (Train_1 to Train_5). 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 (leave group out) 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 (Val_1 and Val_2). The calibration model and RMSE are depicted in Fig. S24 (D, E, and F).

The concentration values from the IHM during reaction monitoring were corrected using the ^{13}C satellite peak of the solvent (MeCN) by Equation S3.

$$C_{corrected} = C_{raw} * \frac{Area_{MeCN_{13C}\,pure} * C_{MeCN_{13C}\,pure}}{Area_{MeCN_{13C}\,actual} * C_{MeCN_{13C}\,actual}} \quad (3)$$

$Area_{MeCN_{13C}\,pure}$:9.9337

$C_{MeCN_{13C}\,pure}$: 19.146 mol/L

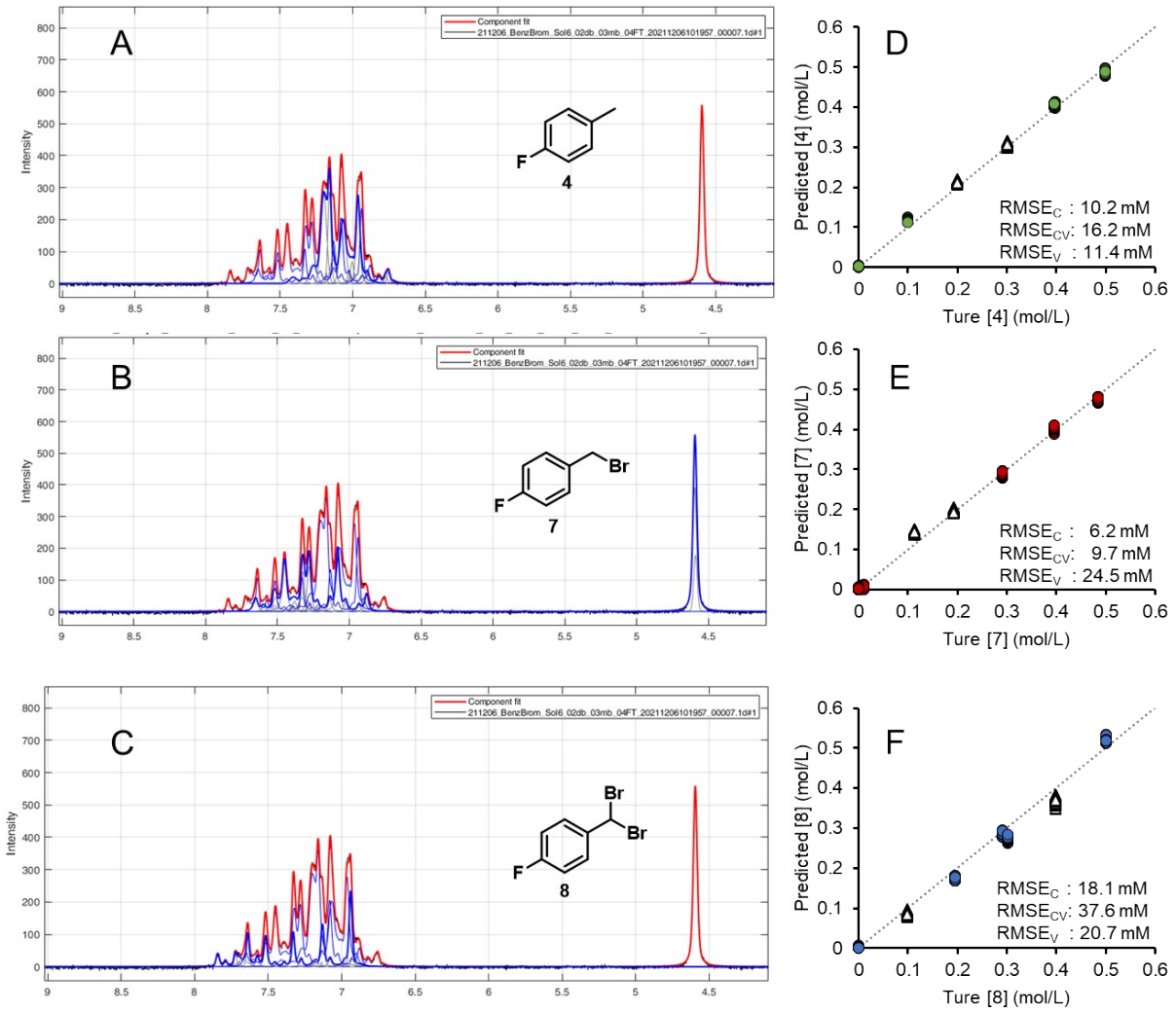


Fig. S24. The fitted mixture model is highlighted in red in spectra A, B, and C. The pure component spectrum for each individual compound is highlighted in blue in spectra A, B, and C. The parity plots are shown in D, E, F with the target line (y = x). The colored circles display the training data and the triangles the validation data. Relevant statistical data is provided in the parity plots (RMSE$_c$: root mean square error of calibration, RMSE$_{CV}$: root mean square error of cross validation, RMSE$_V$: root mean square error of validation).

5.3 Self-Optimization

In the self-optimization experiments of the benzylic bromination, the optimization algorithm could adjust in total six different variables: ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene), concentration of starting material, residence time in the reactor (min), the temperature of the reactor (°C), the light intensity (mA), and ratio of reagent **6** (acetic acid) to starting material **4**. The input factors had their upper and lower bounds set (Table S11). The objective of the optimization was to simultaneously maximize the STY, conversion, and selectivity, as defined by Equation S4. Hyperparameters resulting from the Gaussian process (GP) models generated in the self-optimization experiment are displayed in Table S13. The lower the hyperparameter for a variable, the higher its influence on the optimization objective.

Table S11. Lower and upper bounds for the six input factors in the self-optimization experiments for the benzylic bromination.

Limits	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv of 6 (AcOH)
Lower	0.8	0.25	0.333	20	100	0
Upper	1.3	0.45	1.167	60	950	0.1

$$minimize\ [-\ln\ (STY),\ -\ln\ (Conversion),\ -\ln\ (Selectivity)] \quad (4)$$

Table S12. Experimental results for the self-optimization experiment using TSEMO algorithm.

Entry	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv AcOH	STY (kg L^{-1} h^{-1})	Conv	Selectivity
I_1	1.30	0.43	0.96	22.8	504	0.047	0.15	20%	14%
I_2	1.00	0.40	0.90	25.6	150	0.088	0.00	20%	0%
I_3	1.02	0.34	0.34	26.8	576	0.032	0.35	0%	-777%
I_4	1.15	0.44	0.44	32.3	873	0.058	0.20	3%	60%
I_5	1.09	0.31	0.51	36.0	795	0.066	0.01	21%	1%
I_6	0.80	0.42	0.84	37.9	691	0.081	0.57	27%	37%
I_7	1.08	0.25	0.55	42.8	608	0.074	0.18	7%	52%
I_8	0.86	0.35	0.65	44.2	192	0.094	0.01	18%	1%
I_9	1.24	0.30	1.14	49.7	898	0.016	2.14	102%	71%
I_10	0.96	0.38	1.07	51.9	353	0.036	0.00	17%	1%
I_11	0.89	0.32	0.79	53.4	257	0.024	0.01	1%	23%
I_12	1.21	0.27	0.71	58.2	413	0.006	0.01	8%	2%
S_1	1.30	0.35	1.16	57.3	890	0.039	2.55	102%	74%
S_2	1.01	0.38	1.16	43.8	949	0.052	3.41	102%	90%
S_3	1.18	0.41	1.08	44.4	943	0.052	4.00	102%	92%
S_4	1.06	0.41	1.13	43.9	861	0.100	3.87	101%	93%
S_5	1.15	0.39	1.15	54.2	808	0.042	3.53	95%	98%
S_6	1.24	0.43	1.10	52.4	895	0.032	3.66	100%	83%
S_7	1.13	0.43	1.02	47.1	852	0.010	4.20	101%	86%
S_8	1.17	0.44	1.14	54.2	836	0.069	3.84	101%	87%
S_9	1.11	0.45	1.17	55.4	902	0.100	4.05	101%	92%
S_10	1.03	0.42	1.17	53.6	936	0.074	3.75	101%	92%
S_11	1.24	0.39	1.17	45.0	620	0.100	3.49	102%	92%
S_12	1.07	0.32	1.03	55.3	940	0.079	3.23	102%	91%
S_13	0.90	0.28	1.17	57.3	584	0.094	2.29	100%	85%
S_14	1.30	0.43	1.15	56.4	779	0.088	3.42	102%	79%
S_15	1.16	0.41	1.09	53.7	865	0.097	3.82	102%	87%
S_16	1.24	0.44	1.01	59.2	950	0.088	4.19	101%	85%
S_17	1.06	0.45	1.08	44.2	697	0.021	4.44	102%	93%
S_18	1.05	0.40	1.17	51.7	610	0.024	3.44	102%	87%
S_19	1.03	0.43	1.03	53.7	850	0.044	4.12	101%	86%
S_20	0.87	0.34	1.01	59.6	674	0.071	3.19	91%	93%
S_21	0.80	0.44	0.99	53.9	915	0.100	4.21	101%	84%
S_22	0.80	0.44	1.15	52.4	761	0.099	3.48	87%	93%
S_23	0.90	0.43	1.17	45.4	652	0.042	3.60	93%	93%
S_24	1.17	0.41	1.17	55.3	767	0.014	3.60	102%	88%
S_25	0.88	0.45	1.17	51.0	712	0.066	3.78	95%	92%
S_26	0.85	0.43	0.98	58.2	692	0.069	4.22	93%	91%

Entry	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv AcOH	STY (kg L^{-1} h^{-1})	Conv	Selectivity
S_27	1.09	0.45	1.12	43.2	892	0.086	4.17	101%	91%
S_28	0.89	0.45	1.09	46.0	632	0.079	4.31	99%	93%
S_29	0.97	0.45	1.08	58.6	844	0.001	4.51	94%	102%
S_30	1.06	0.45	1.12	58.2	793	0.047	4.11	96%	93%

Table S13. Hyperparameters resulting from the GPs generated in the self-optimization experiment.

Variable	STY	Conversion	Selectivity
$\theta_{\text{Equiv of } \mathbf{5}}$	63.2456	63.2456	63.2456
$\theta_{\text{Conc. of } \mathbf{4}}$	77.0600	158.1139	158.1139
$\theta_{\text{Residence time}}$	1.9158	1.2288	1.7736
$\theta_{\text{Temperature}}$	0.1635	0.6085	0.0477
$\theta_{\text{Intensity}}$	0.0018	0.0010	0.0018
$\theta_{\text{Equiv. of } \mathbf{6} \text{ (AcOH)}}$	316.2278	316.2278	316.2278

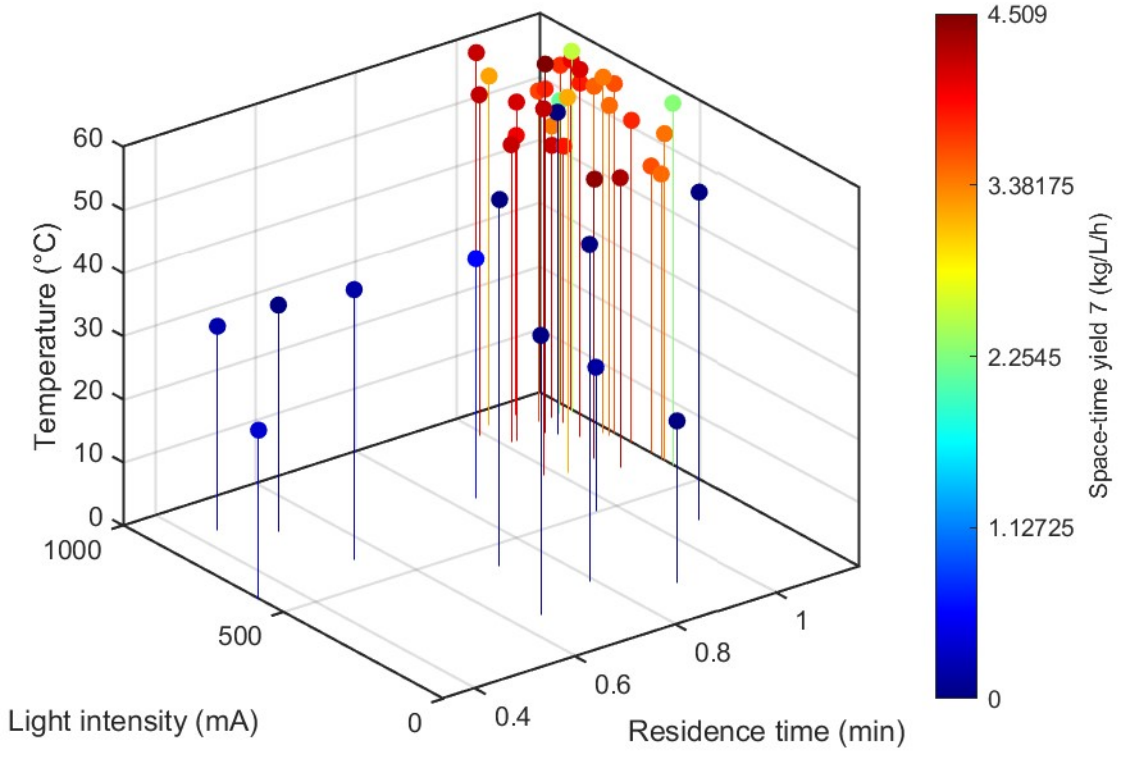


Fig. S25. Results from the self-optimization for the benzylic bromination.

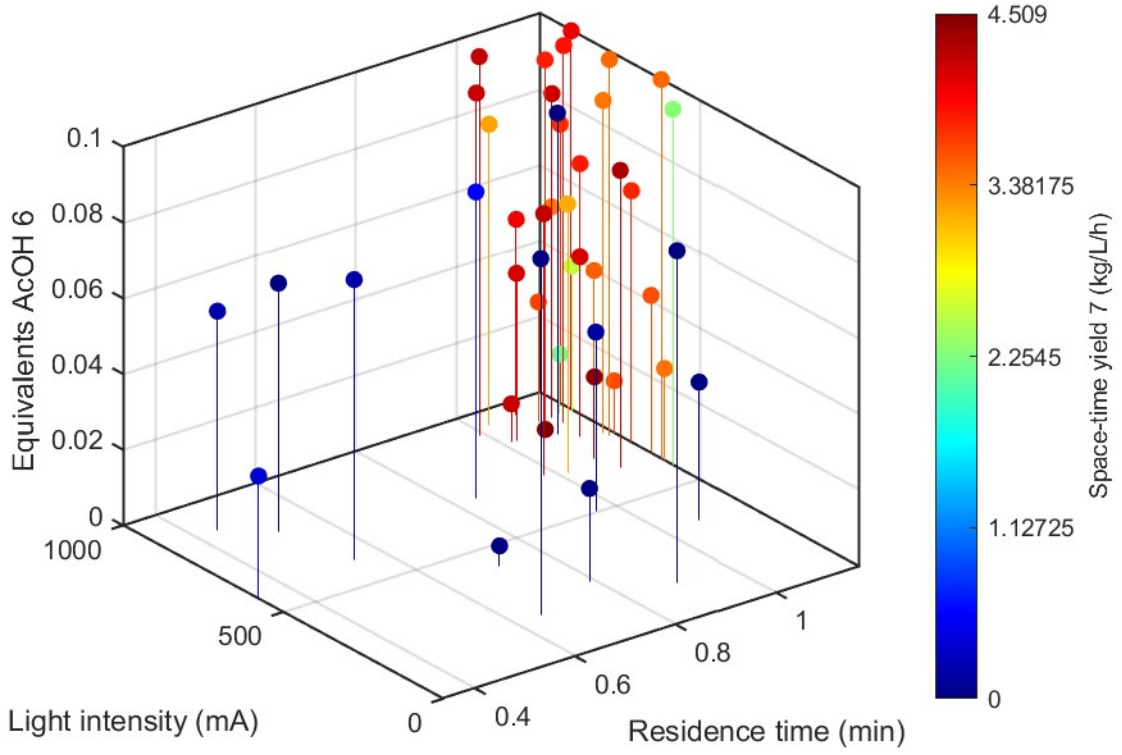


Fig. S26. Results from the self-optimization for the benzylic bromination.

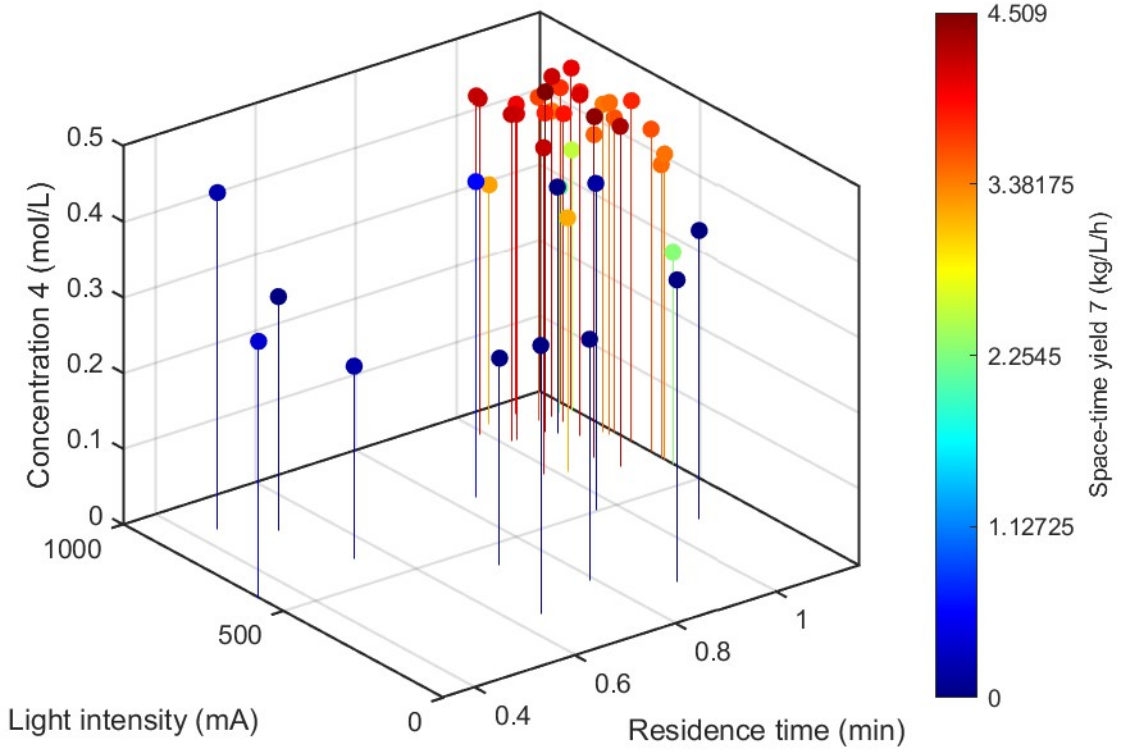


Fig. S27. Results from the self-optimization for the benzylic bromination.

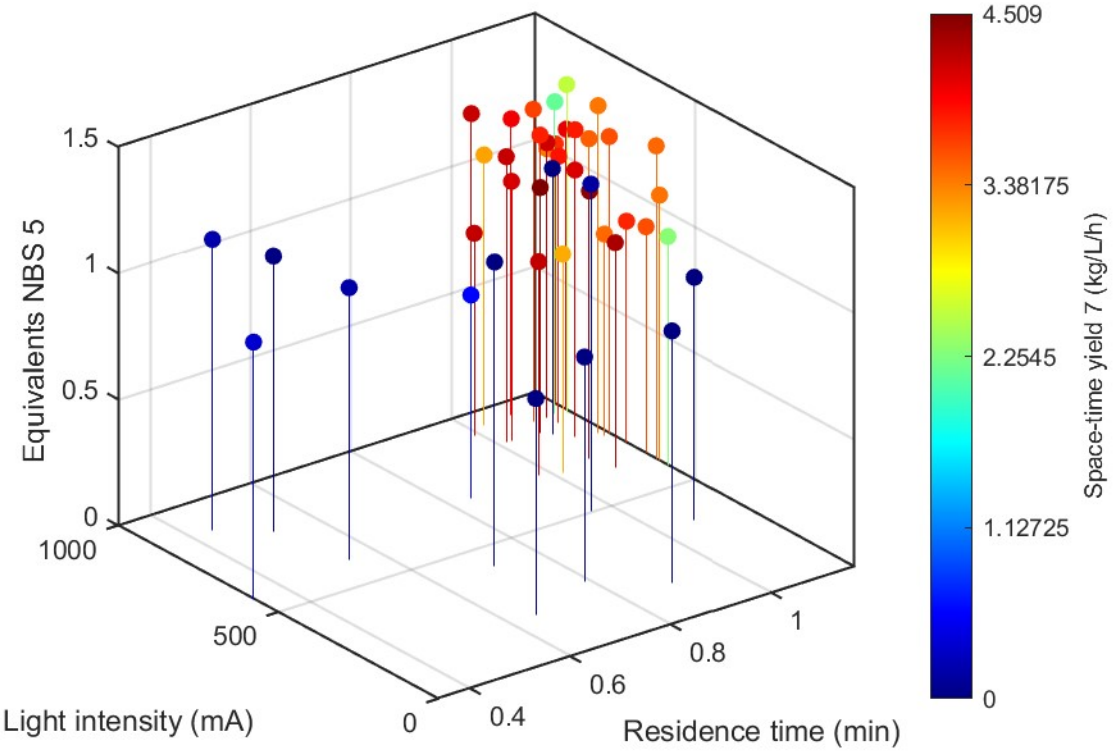


Fig. S28. Results from the self-optimization for the benzylic bromination.

5.4 Optipus Run

The Optipus algorithm was allowed to vary six input factors: ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene), concentration of starting material, residence time in the reactor (min), the temperature of the reactor (°C), the light intensity (mA), and ratio of reagent **6** (acetic acid) to starting material **4**. The upper and lower bounds for the input factors are provided in Table S14. The experimental results are provided in Table S15 and figures of the real-time model building are depicted in Fig. S29 to Fig. S42. The scores for the final model are provided in In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (0), temperature of the reactor (A), ratio of reagent **5** (*N*-bromosuccinimide) to starting material 4 (4-fluorotoluene) (B), concentration of starting material (C), residence time in the reactor (D), light intensity (E), and ratio of reagent **6** (acetic acid) to starting material (F).

Table S16 and more detailed results on the model coefficients are provided in Table S17.

Table S14. Lower and upper bounds for the input factors during the Optipus run for the benzylic bromination.

Limits	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv of 6 (AcOH)

Lower	0.9	0.4	0.8	40	750	0.01
Upper	1.1	0.45	1.2	50	950	0.05

Table S15. Experimental results for the optimization of the benzylic bromination using Optipus.

Entry	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv AcOH	STY (kg L^{-1} h^{-1})	Conv	Selectivity
1	0.90	0.400	0.80	40	750	0.010	0.04	8%	10%
2	0.90	0.450	0.80	40	750	0.010	0.05	5%	14%
3	1.10	0.450	1.20	40	950	0.050	3.93	99%	93%
4	1.10	0.400	1.20	40	950	0.050	3.22	100%	85%
5	1.00	0.425	1.00	45	850	0.030	4.08	98%	86%
6	1.00	0.425	1.00	45	850	0.030	4.06	99%	85%
7	0.90	0.400	0.80	50	750	0.010	0.07	8%	16%
8	0.90	0.450	0.80	50	750	0.010	0.09	7%	21%
9	1.10	0.450	1.20	50	950	0.050	3.78	100%	89%
10	1.10	0.400	1.20	50	950	0.050	3.08	99%	82%
11	1.10	0.400	0.80	50	950	0.050	4.08	86%	83%
12	1.10	0.450	0.80	50	950	0.050	4.83	84%	90%
13	0.90	0.450	1.20	50	750	0.010	3.54	93%	89%
14	0.90	0.400	1.20	50	750	0.010	3.28	90%	97%
15	1.00	0.425	1.00	45	850	0.030	4.07	99%	85%
16	1.10	0.400	0.80	40	950	0.050	1.79	44%	72%
17	1.10	0.450	0.80	40	950	0.050	2.44	47%	82%
18	0.90	0.450	1.20	40	750	0.010	3.63	90%	95%
19	0.90	0.400	1.20	40	750	0.010	3.06	90%	90%
20	1.10	0.400	0.80	40	750	0.010	0.07	6%	19%
21	1.10	0.450	0.80	40	750	0.010	0.06	3%	28%
22	0.90	0.450	1.20	40	950	0.050	3.51	92%	89%
23	0.90	0.400	1.20	40	950	0.050	3.04	94%	86%
24	1.00	0.425	1.00	45	850	0.030	4.02	98%	85%
25	1.10	0.400	0.80	50	750	0.010	0.12	9%	23%
26	1.10	0.450	0.80	50	750	0.010	0.21	9%	37%
27	0.90	0.450	1.20	50	950	0.050	3.53	91%	91%
28	0.90	0.400	1.20	50	950	0.050	3.05	91%	88%
29	0.90	0.400	0.80	50	950	0.050	4.43	90%	87%
30	0.90	0.450	0.80	50	950	0.050	5.18	88%	92%
31	1.10	0.450	1.20	50	750	0.010	3.78	98%	90%
32	1.10	0.400	1.20	50	750	0.010	3.26	96%	90%
33	1.00	0.425	1.00	45	850	0.030	4.19	91%	95%
34	0.90	0.400	0.80	40	950	0.050	0.39	16%	42%
35	0.90	0.450	0.80	40	950	0.050	0.73	18%	64%
36	1.10	0.450	1.20	40	750	0.010	4.05	98%	97%
37	1.10	0.400	1.20	40	750	0.010	3.42	97%	93%
38	0.90	0.400	0.80	40	950	0.010	0.07	11%	11%
39	0.90	0.450	0.80	40	950	0.010	0.08	7%	16%
40	1.10	0.450	1.20	40	750	0.050	4.03	98%	96%
41	1.10	0.400	1.20	40	750	0.050	3.45	100%	92%
42	1.00	0.425	1.00	45	850	0.030	4.14	97%	89%
43	0.90	0.400	0.80	50	950	0.010	0.41	26%	28%
44	0.90	0.450	0.80	50	950	0.010	1.30	34%	59%
45	1.10	0.450	1.20	50	750	0.050	4.07	99%	96%

Entry	Equiv of **5**	Conc. SM **4** (mol/L)	Residence time (min)	Temperature (°C)	Intensity (mA)	Equiv AcOH	STY (kg L^{-1} h^{-1})	Conv	Selectivity
46	1.10	0.400	1.20	50	750	0.050	3.45	100%	91%
47	1.10	0.400	0.80	50	750	0.050	0.51	21%	42%
48	1.10	0.450	0.80	50	750	0.050	1.01	24%	66%
49	0.90	0.450	1.20	50	950	0.010	3.68	91%	95%
50	0.90	0.400	1.20	50	950	0.010	3.21	94%	90%
51	1.00	0.425	1.00	45	850	0.030	4.31	99%	90%
52	1.10	0.400	0.80	40	750	0.050	0.16	11%	25%
53	1.10	0.450	0.80	40	750	0.050	0.26	9%	43%
54	0.90	0.450	1.20	40	950	0.010	3.68	88%	98%
55	0.90	0.400	1.20	40	950	0.010	3.24	93%	93%
56	1.10	0.400	0.80	40	950	0.010	0.70	30%	42%
57	1.10	0.450	0.80	40	950	0.010	1.50	36%	65%
58	0.90	0.450	1.20	40	750	0.050	3.60	90%	94%
59	0.90	0.400	1.20	40	750	0.050	3.27	93%	93%
60	1.00	0.425	1.00	45	850	0.030	4.28	98%	91%
61	1.10	0.400	0.80	50	950	0.010	2.76	62%	78%
62	1.10	0.450	0.80	50	950	0.010	4.59	78%	92%
63	0.90	0.450	1.20	50	750	0.050	3.57	90%	93%
64	0.90	0.400	1.20	50	750	0.050	3.22	93%	91%
65	0.90	0.400	0.80	50	750	0.050	0.21	14%	26%
66	0.90	0.450	0.80	50	750	0.050	0.36	14%	41%
67	1.10	0.450	1.20	50	950	0.010	4.13	100%	97%
68	1.10	0.400	1.20	50	950	0.010	3.48	100%	92%
69	1.00	0.425	1.00	45	850	0.030	4.28	99%	90%
70	0.90	0.400	0.80	40	750	0.050	0.05	9%	10%
71	0.90	0.450	0.80	40	750	0.050	0.09	7%	20%
72	1.10	0.450	1.20	40	950	0.010	4.12	100%	97%
73	1.10	0.400	1.20	40	950	0.010	3.60	100%	95%
74	1.00	0.425	1.00	40	850	0.030	3.11	78%	83%
75	1.00	0.425	1.00	50	850	0.030	4.01	93%	89%
76	1.00	0.425	1.00	45	750	0.030	3.03	76%	83%
77	1.00	0.425	1.00	45	950	0.030	4.18	99%	88%
78	1.00	0.425	1.00	45	850	0.050	3.89	89%	90%
79	1.00	0.425	1.00	45	850	0.010	3.76	87%	89%
80	0.90	0.425	1.00	45	850	0.030	3.72	89%	87%
81	1.10	0.425	1.00	45	850	0.030	4.20	97%	90%
82	1.00	0.450	1.00	45	850	0.030	4.41	96%	90%
83	1.00	0.400	1.00	45	850	0.030	3.92	91%	95%
84	1.00	0.425	0.80	45	850	0.030	0.75	24%	51%
85	1.00	0.425	1.20	45	850	0.030	3.70	98%	94%

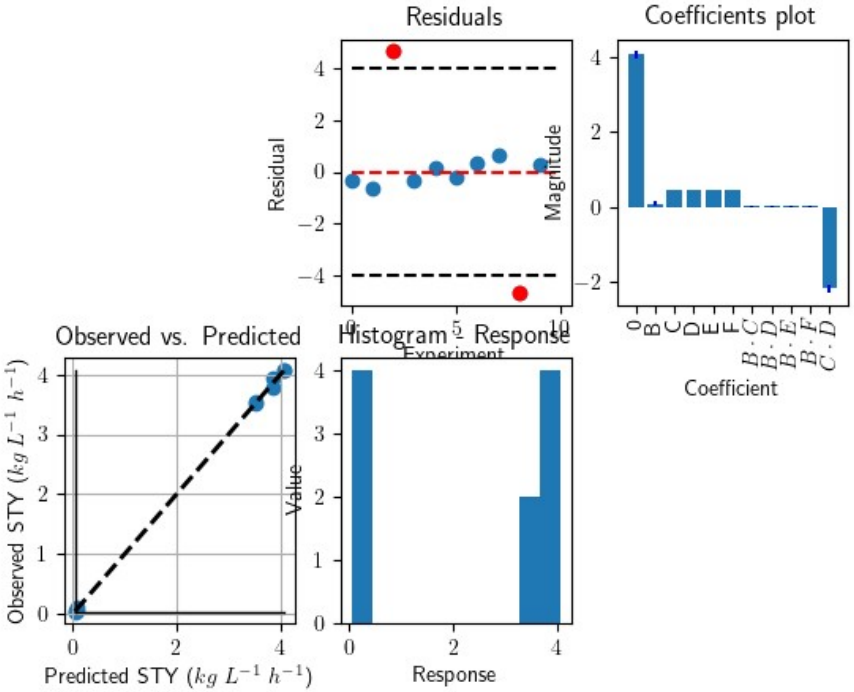


Fig. S29. Model from the Optipus software after 10 experiments for the benzylic bromination. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

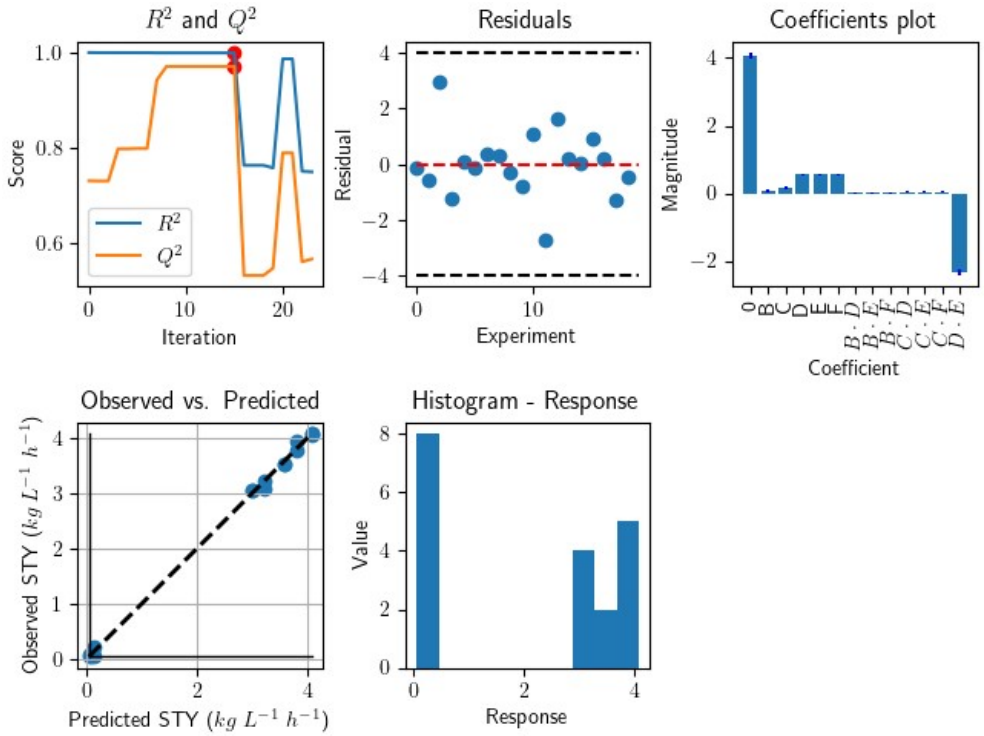


Fig. S30. Model from the Optipus software after 19 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

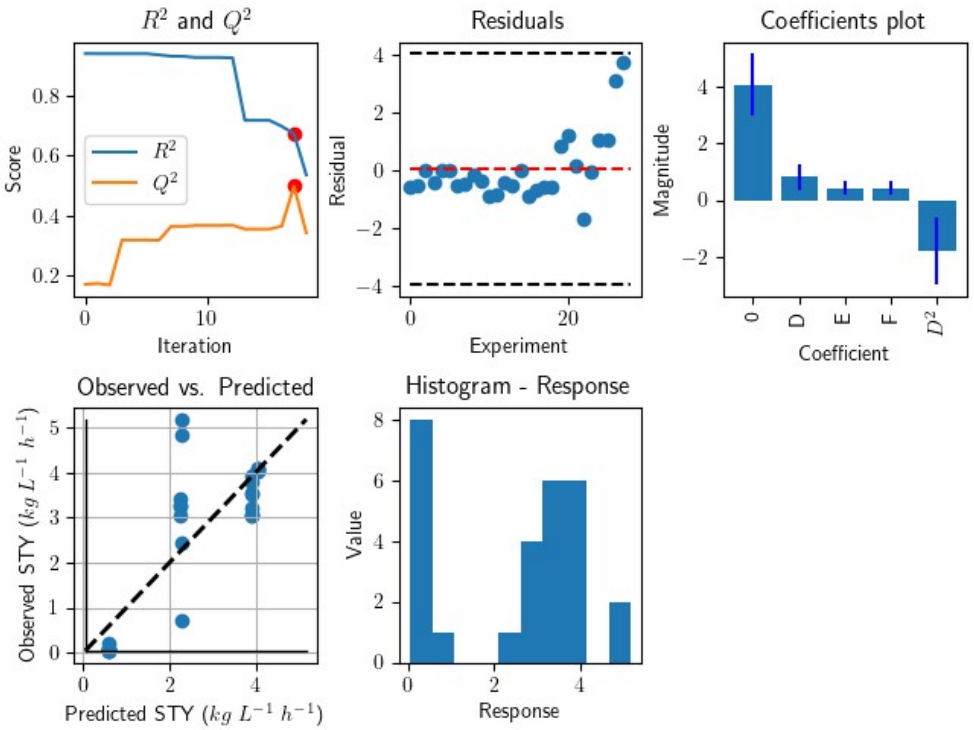


Fig. S31. Model from the Optipus software after 28 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

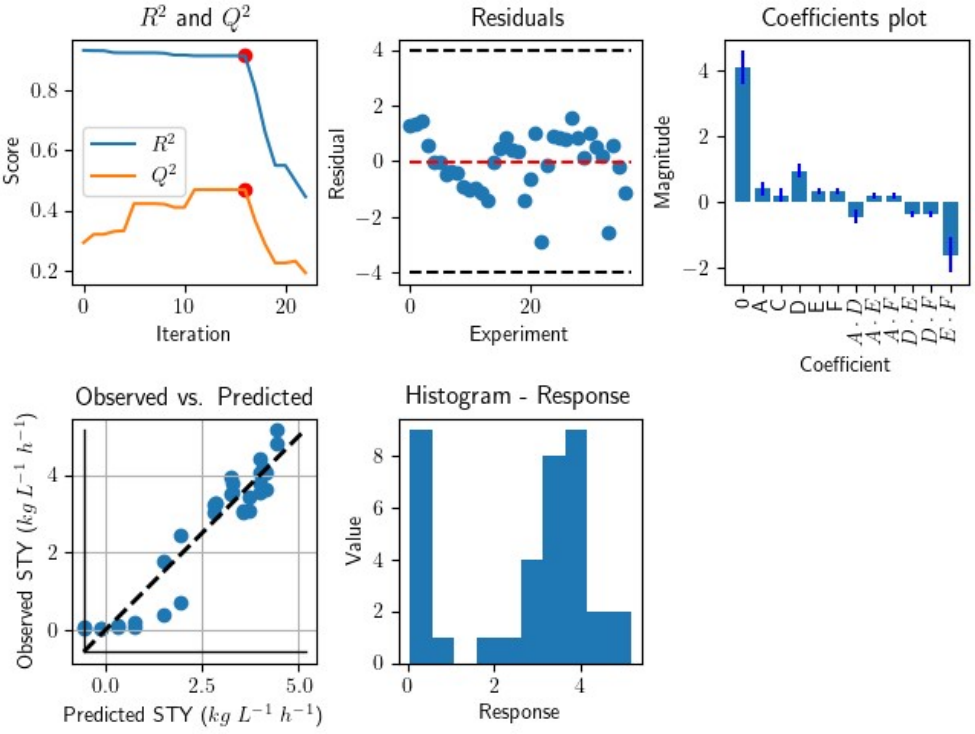


Fig. S32. Model from the Optipus software after 37 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

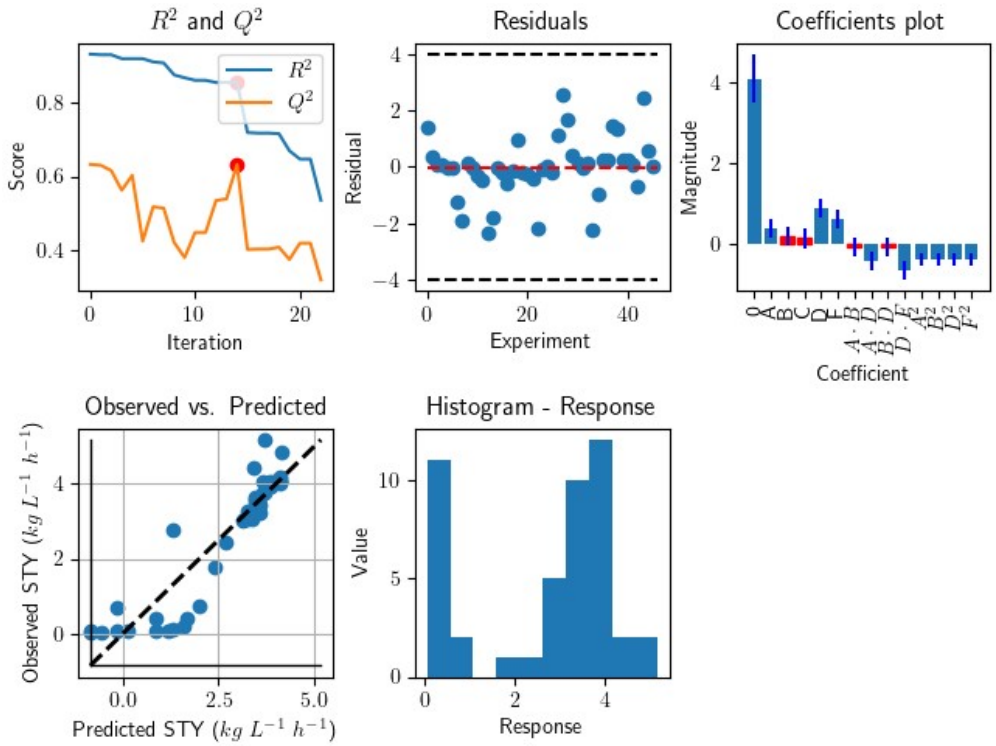


Fig. S33. Model from the Optipus software after 46 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

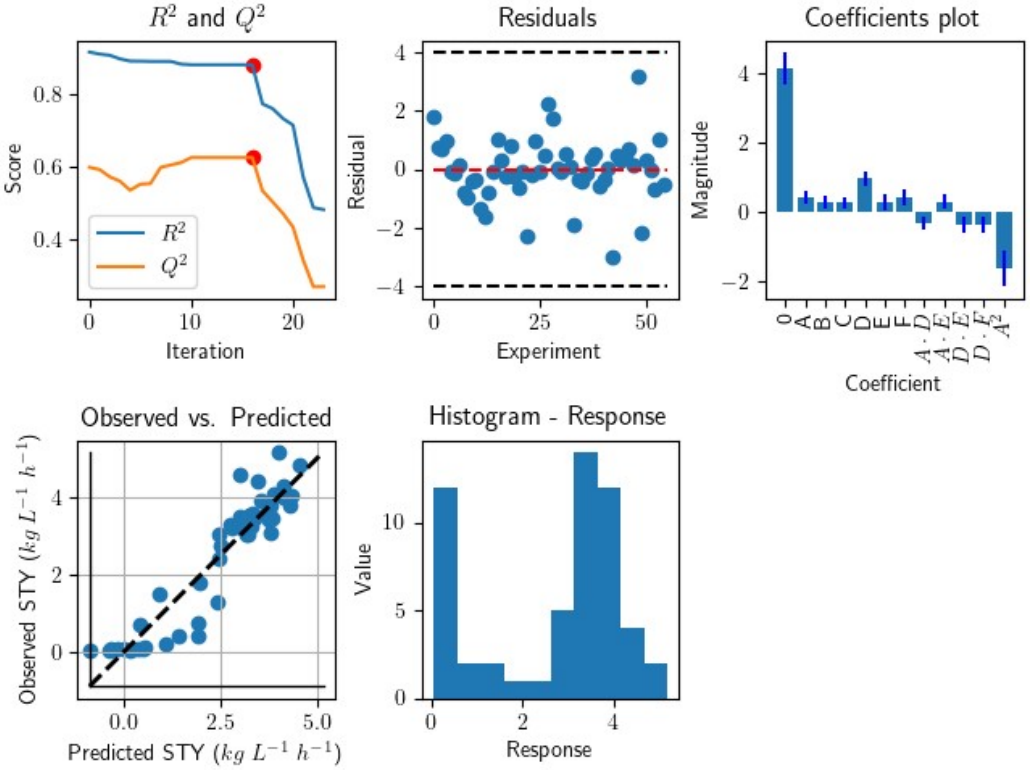


Fig. S34. Model from the Optipus software after 55 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

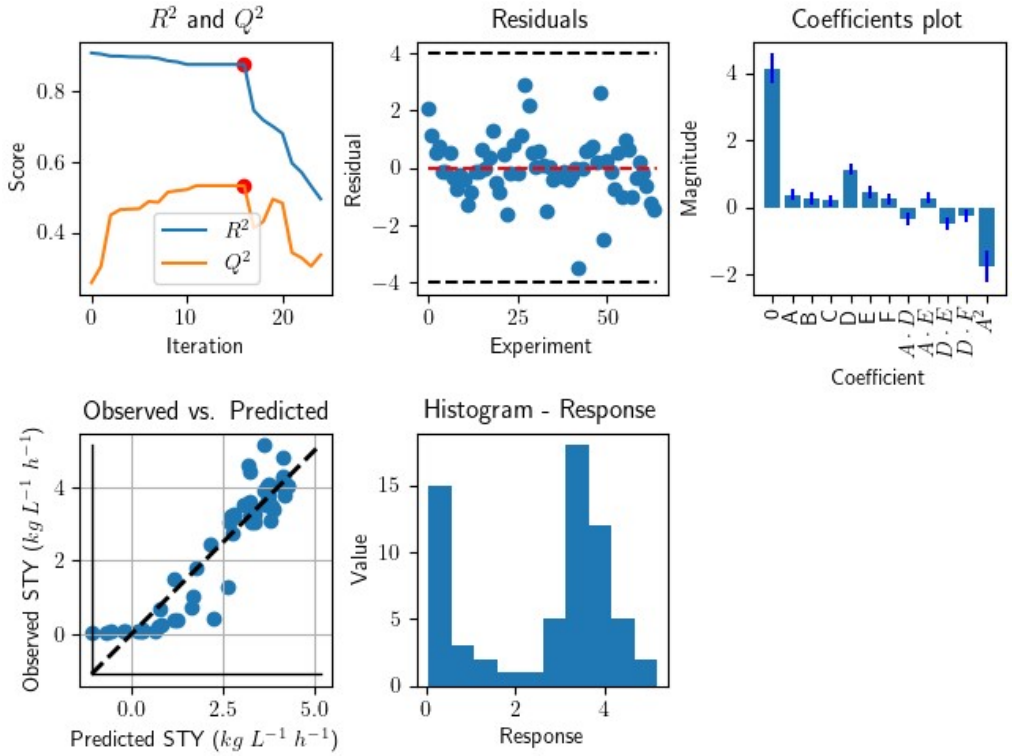


Fig. S35. Model from the Optipus software after 64 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

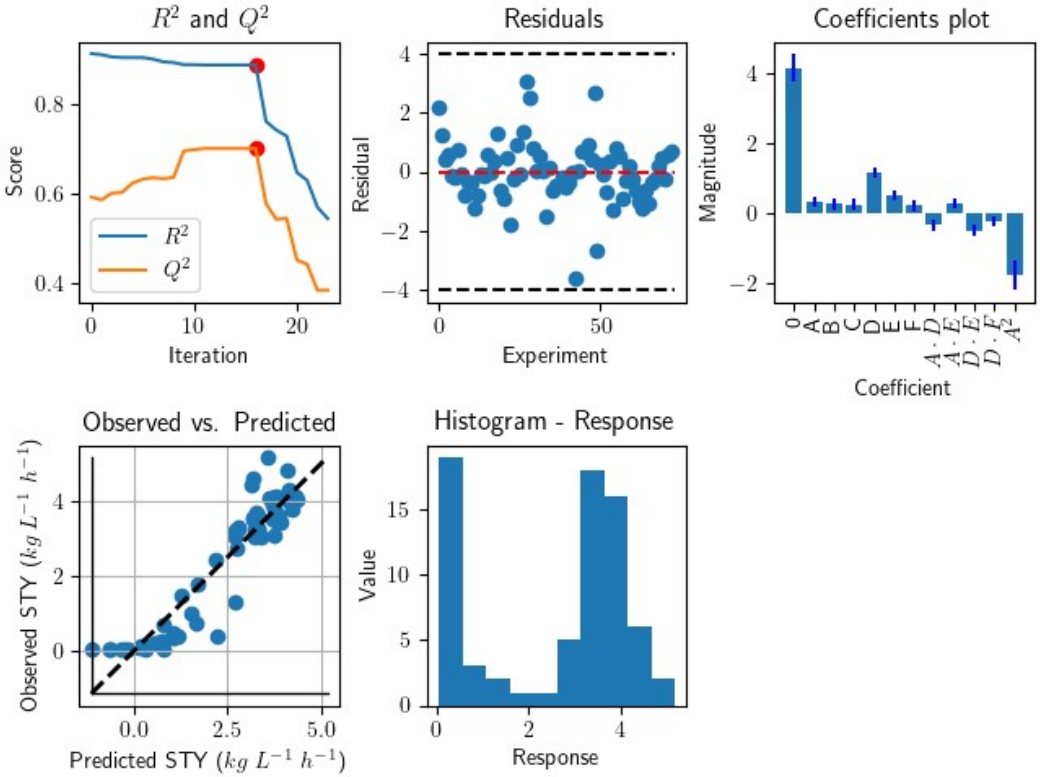


Fig. S36. Model from the Optipus software after 73 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

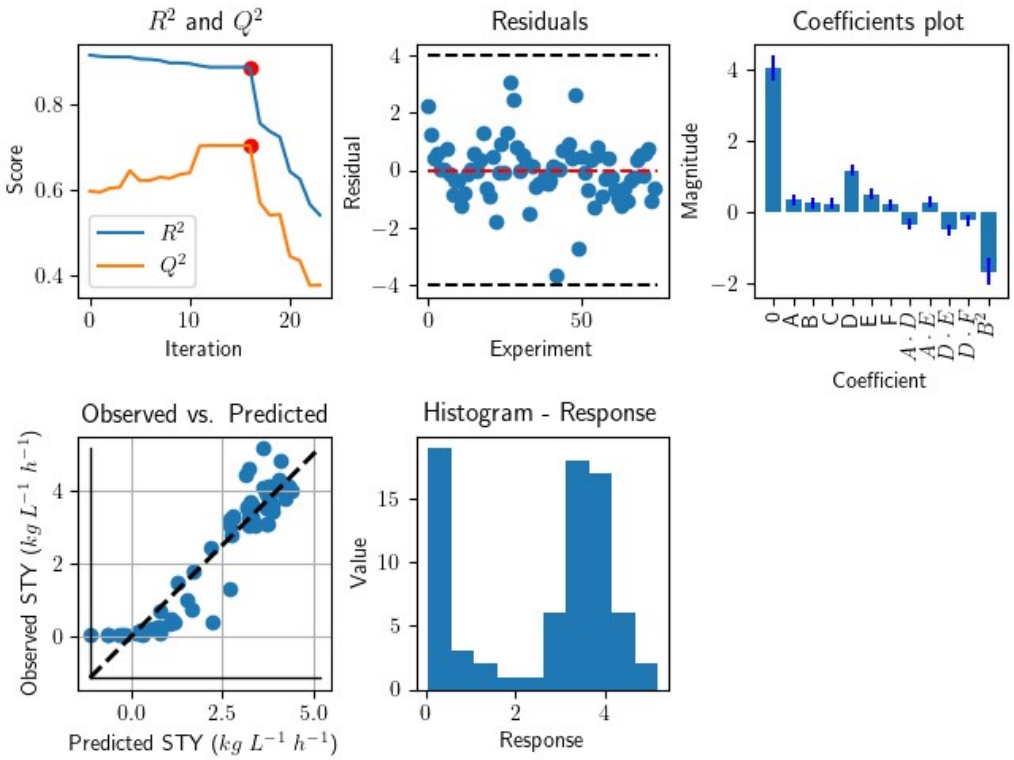


Fig. S37. Model from the Optipus software after 75 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent 6 (acetic acid) to starting material (**F**).

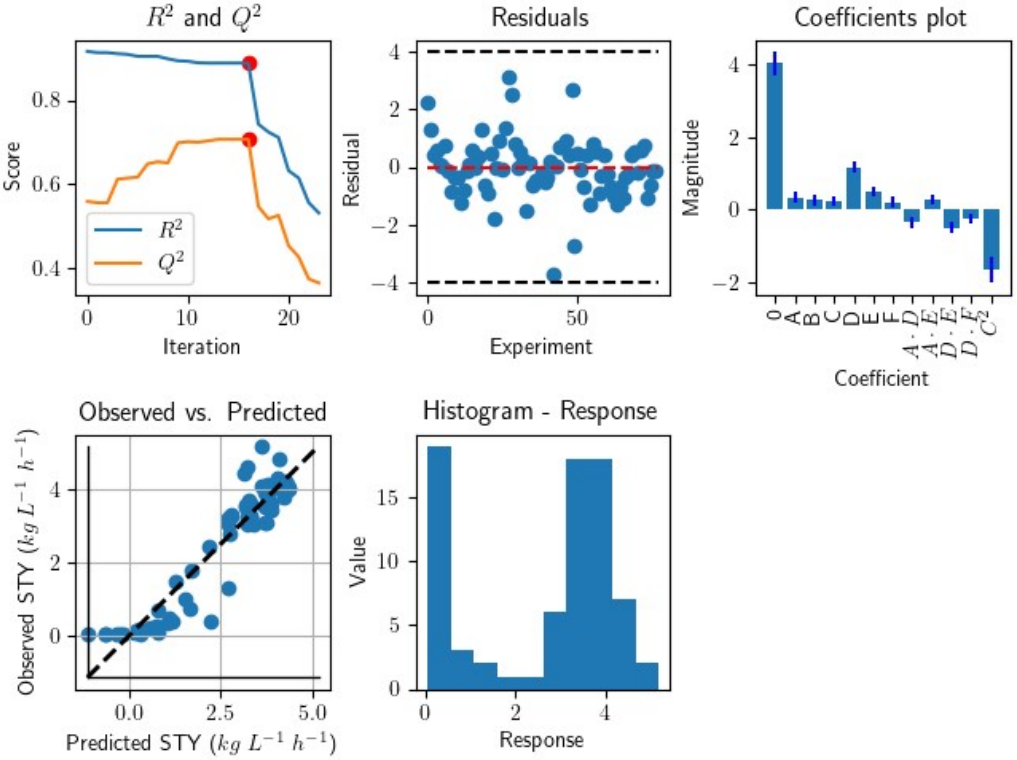


Fig. S38. Model from the Optipus software after 77 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

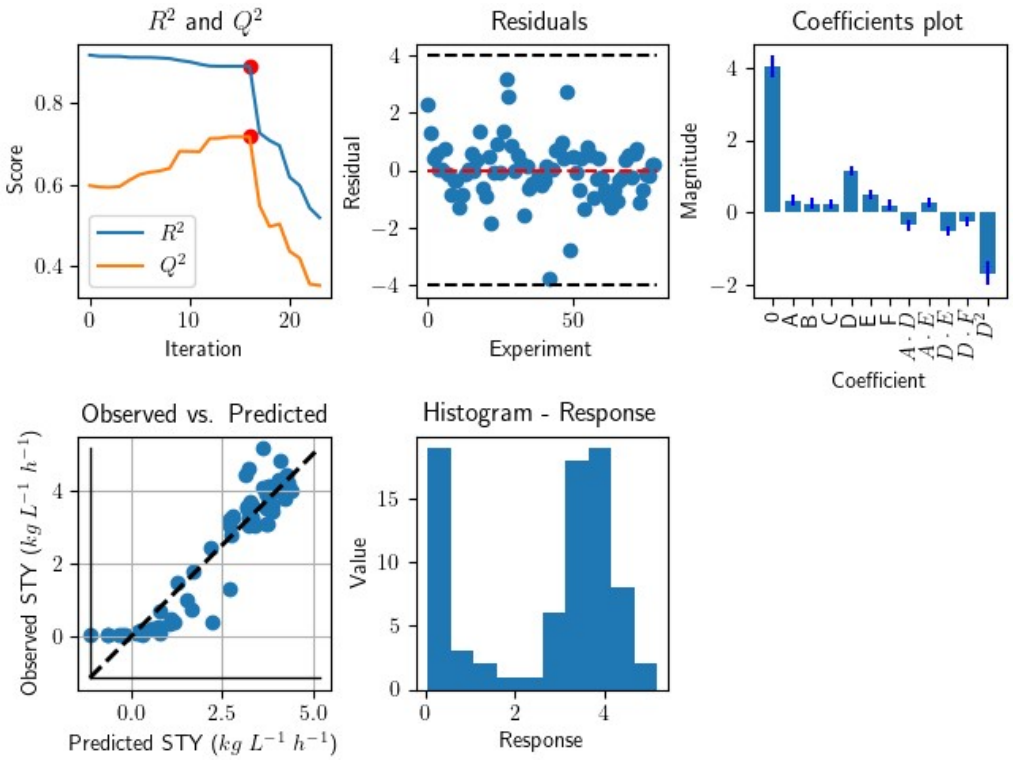


Fig. S39. Model from the Optipus software after 79 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

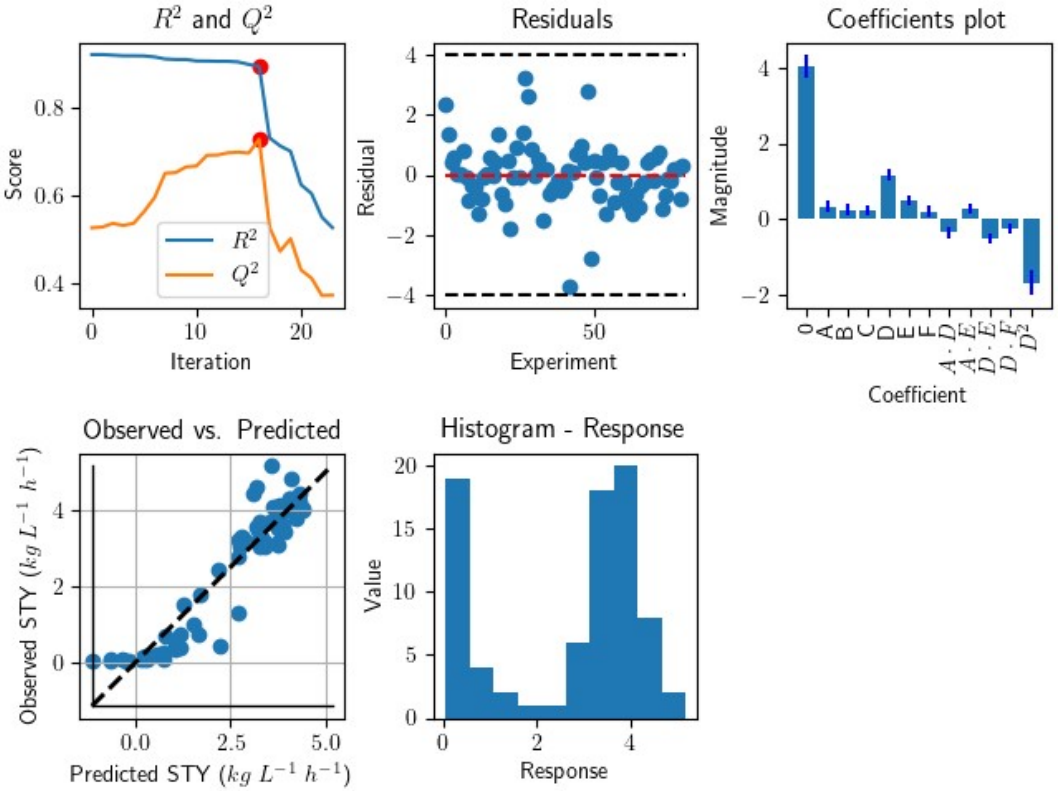


Fig. S40. Model from the Optipus software after 81 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent 6 (acetic acid) to starting material (**F**).

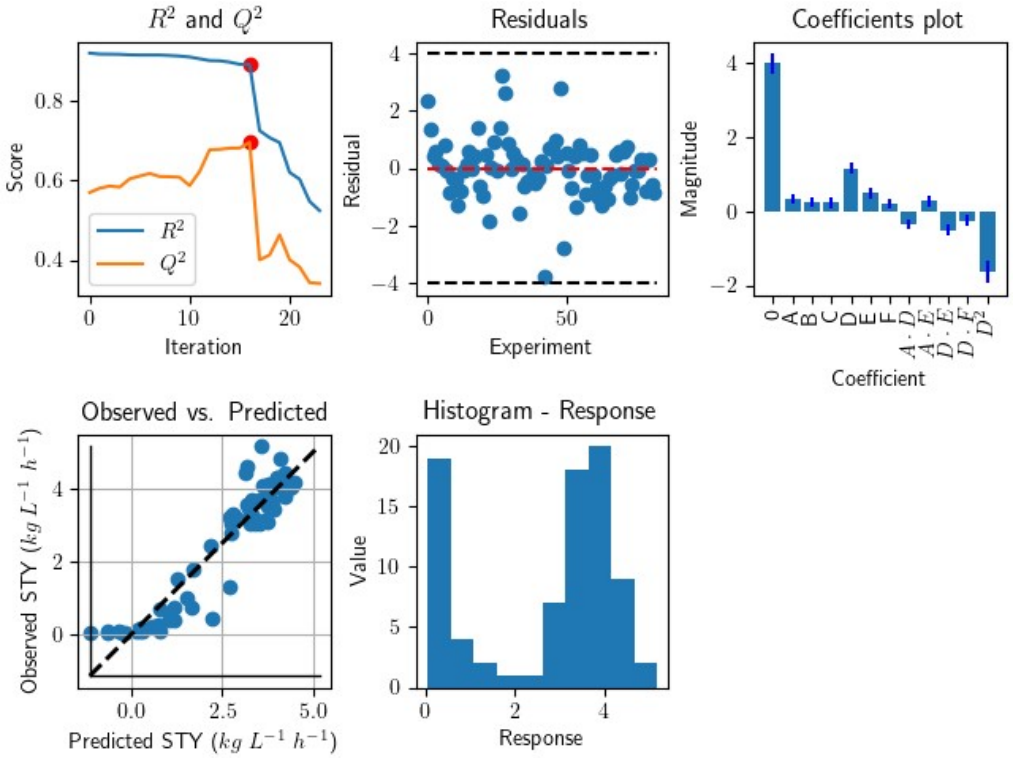


Fig. S41. Model from the Optipus software after 83 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

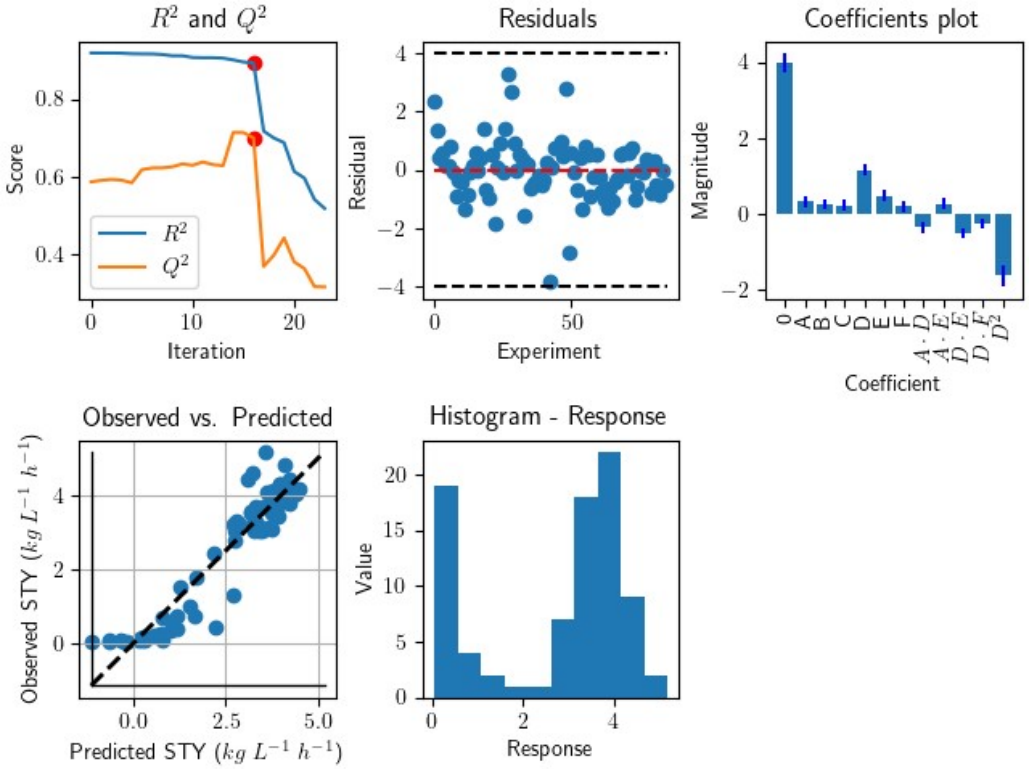


Fig. S42. Model from the Optipus software after 85 experiments for the benzylic bromination. In the R^2 and Q^2 plot the red dot indicates the selected model. A red dot in the residuals plot indicates an outlier The factor set is the constant (**0**), temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

Table S16. Scores for the final model for the benzylic bromination. 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. RepScore is a measure of the repeatability of the center points.

R^2	Q^2	RepScore
0.91874	0.71398	0.99998695

Table S17. Model coefficients and scaled model coefficients for the final model for the benzylic bromination. The factor set are the constant (**0**), the temperature of the reactor (**A**), ratio of reagent **5** (*N*-bromosuccinimide) to starting material **4** (4-fluorotoluene) (**B**), concentration of starting material (**C**), residence time in the reactor (**D**), light intensity (**E**), and ratio of reagent **6** (acetic acid) to starting material (**F**).

Factors	Model Coefficients	Scaled Model Coefficients
0	-73.9166812	3.98240145
A	-0.0617083	0.33164425
B	2.53814454	0.25381445
C	9.49619274	0.23740482
D	125.81783	1.17052613
E	0.00484891	0.49494635
F	71.4487573	0.19976341
A * D	-0.35040978	-0.35040978
A * E	0.00056288	0.28143937
D * E	-0.02522899	-0.50457984
D * F	-61.4605869	-0.24584235
D^2	-40.454149	-1.61816596

5.5 Comparison of DoE model to self-optimization data points

All of the experimental points from the self-optimization experiment were out of the *Optipus'* boundaries for at least one variable. The predicted experiments with one factor out of the boundary had the lowest standard error (s_y) of 0.367 kg/L/h compared to 0.833 and 1.192 kg/L/h for two or three factors out of the boundaries, respectively (see Fig. S43).

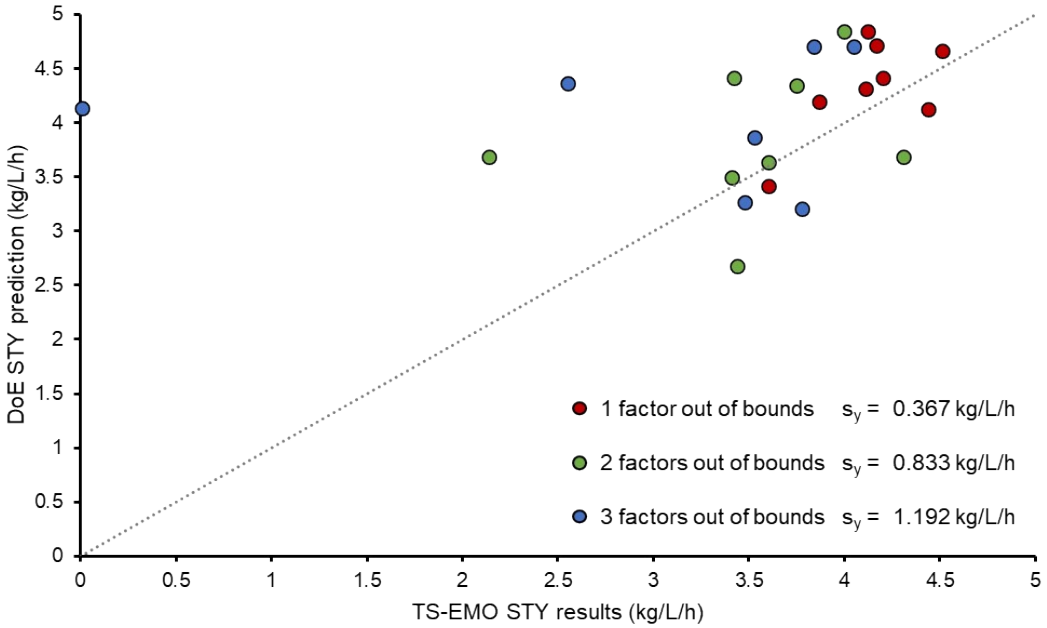
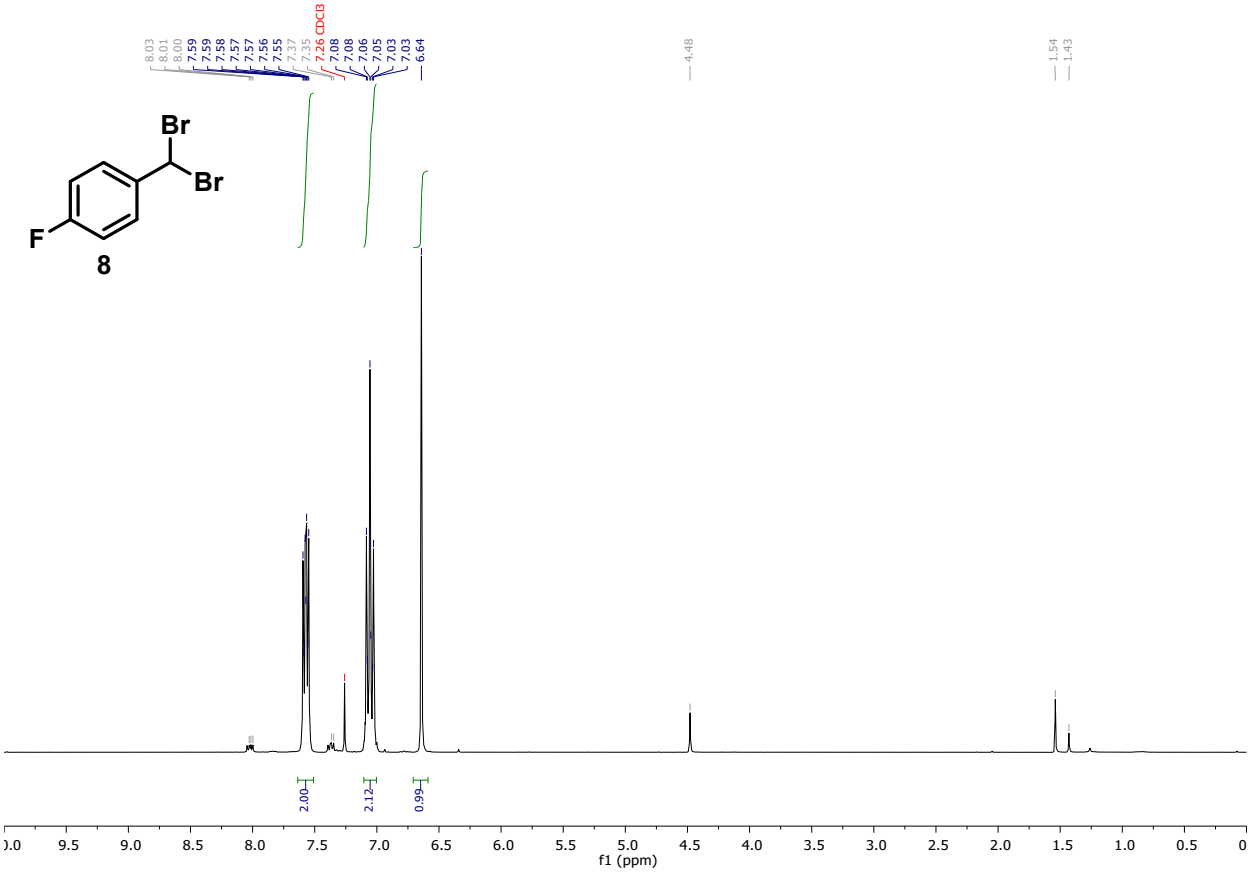


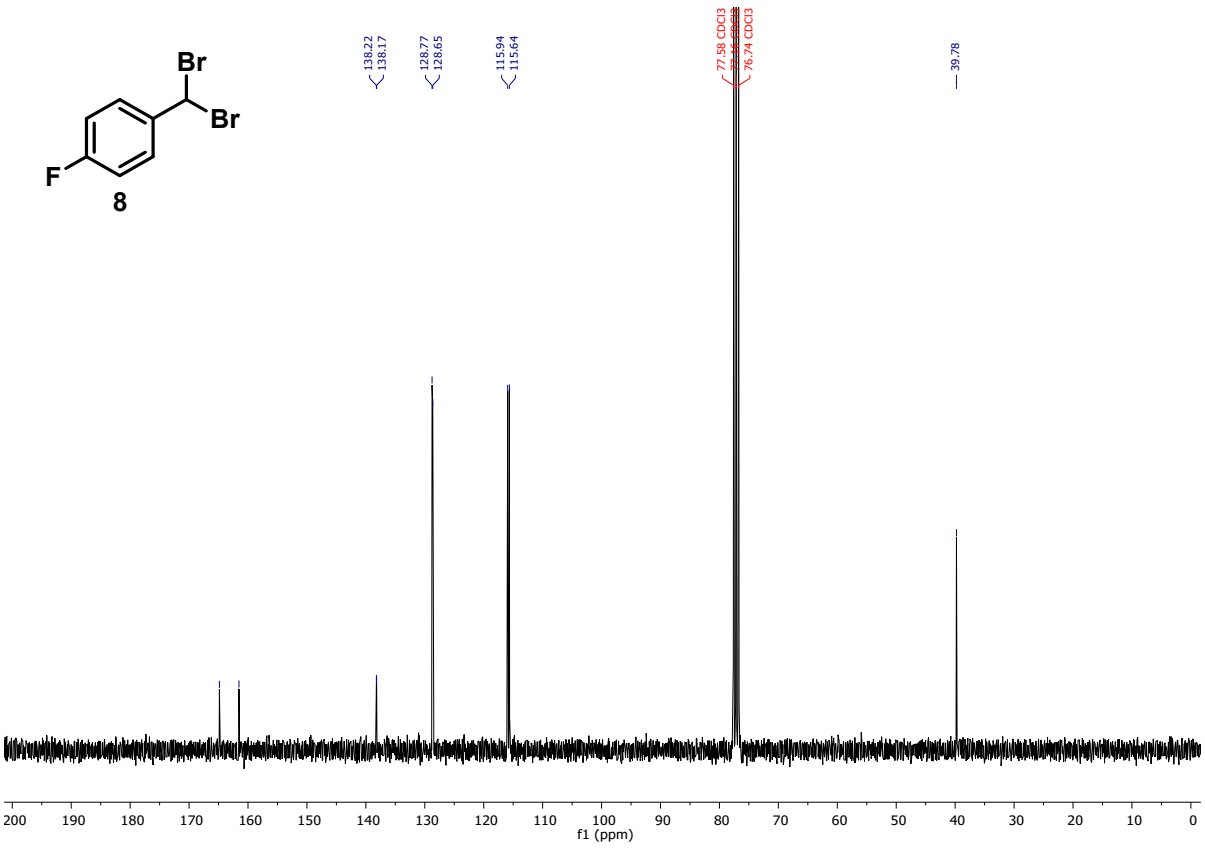
Fig. S43. Parity plot of predicted STY values from the DoE model compared to experimental points from the self-optimization experiment. The standard error (s_y) is provided calculated for the experimental points.

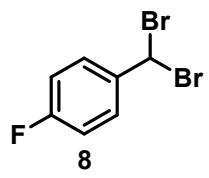
6 References

S1 P. Sagmeister, F. F. Ort, C. E. Jusner, D. Hebrault, T. Tampone, F. G. Buono, J. D. Williams and C. O. Kappe, *Adv. Sci.* 2022, **9***,* 2105547.

7 NMR Spectra






Br
Br
F

8

-110.47
-110.48
-110.49
-110.50
-110.50
-110.50
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
f1 (ppm)