Supporting Information

Automated Flow and Real-Time Analytics Approach for Screening Functional Group Tolerance in Heterogeneous Catalytic Reactions

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Contents

1. Continuous Flow Setup

1.1. General details

Solvents and chemicals were all obtained from commercial suppliers and were used without any further purification unless otherwise noted.

1.2. Detailed reaction setup

1.2.1. General

A photograph of the hydrogenation setup can be found below (Figure S1), a schematic representation in Scheme 2. Each component is described in more detail in the subsequent sections. The continuous flow setup has been previously described.[1]

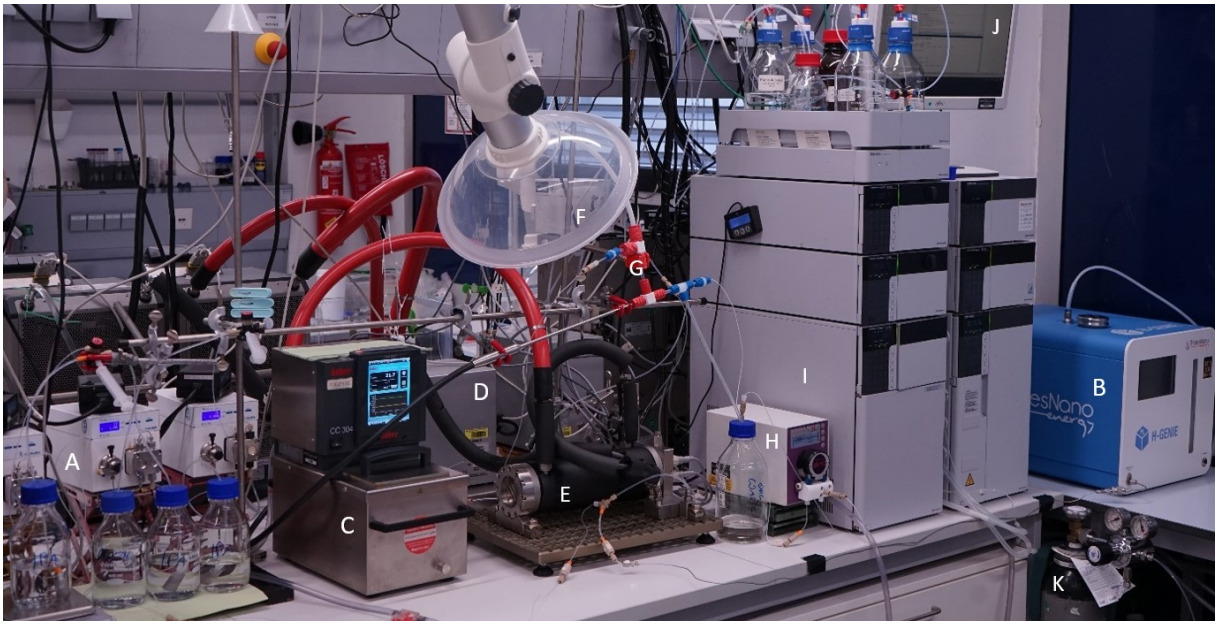

Figure S1. Labelled photograph of the hydrogenation setup; A: HPLC pumps for liquid feed; B: H-Genie; C: thermostat; D: FT-IR; E: Miprowa Lab reactor and MMRS; F: extractor; G: gas/liquid separator mounted on IR probe; H: peristaltic pump for UHPLC sampling; I: UHPLC; J: Computer for controlling and monitoring; K: N_2-bottle leading to backpressure regulator (not visible on the figure).

1.2.2. Pumps and liquid feeds

The liquid feeds were delivered through perfluoro alkoxy alkane (PFA) tubing (inlet i.d. 1.6 mm, 1.2 mL; outlet: i.d. 0.8 mm, 1.8 mL) by three High Performance Liquid Chromatography (HPLC) pumps (Knauer, AZURA P 4.1S) (Figure S2). All of the pumps included an integrated pressure sensor. The feed for the substrate **1** was placed on a balance (Kern, KB 2400-2N) to monitor the actual flow rate by running a script. The liquid feeds were combined within a 4-way connector made from polyether ether ketone (PEEK) (i.d. 0.5 mm) and then passed through PFA tubing (i.d. 0.8 mm, 1.8 mL), a check valve, and another PFA tubing (i.d. 0.8 mm, 0.4 mL) to enter a PEEK Y-connector (i.d. 0.5 mm) for mixing with the hydrogen feed. All valves and connectors were manufactured by IDEX.

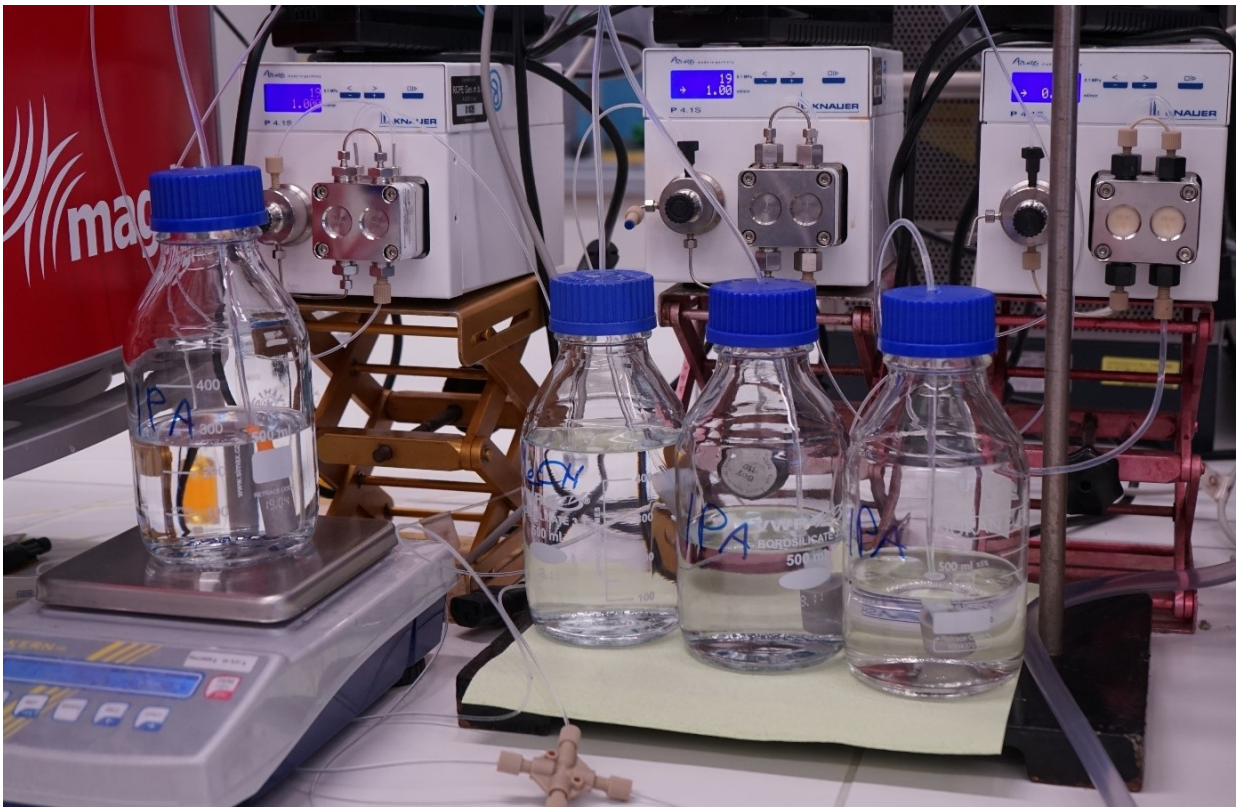

Figure S2. Photograph of the three HPLC pumps used in the flow setup.

1.2.3. Hydrogen generator and mass flow controller

The hydrogen generator with an integrated mass flow controller (MFC) (ThalesNano Energy, H-Genie) was used for the introduction of hydrogen gas (Figure S3). The system was operated using HPLC grade water. The flow rate of H_2 was measured in mL_n/min, where n represents measurement under standard conditions, i.e., T_n = 25 °C, P_n = 1.01 bar. The hydrogen was fed to the reactor via stainless-steel tubing (i.d. 0.8 mm, 2.6 mL), followed by a check valve and PFA tubing (i.d. 1.6 mm, 0.6 mL). The liquid and the hydrogen stream were combined in a Y-connector made from PEEK, which then passed through PFA tubing (i.d. 1.6 mm, 1.6 mL), which enabled observation of the slug flow regime within this section of the flow setup (Figure S4), and then entered the Modular MicroReaction System (Ehrfeld, MMRS) via an 1/16" input connector (0711 2 0124 F, Hastelloy C-276) and a coax heat exchanger (0309-4-0004-F, Hastelloy C-276).

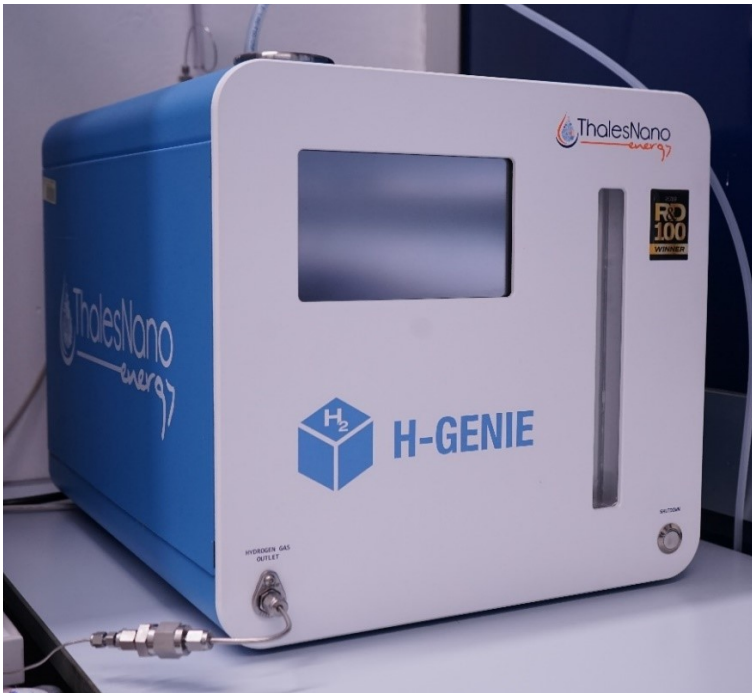

Figure S3. Photograph of the hydrogen generator and mass flow controller.

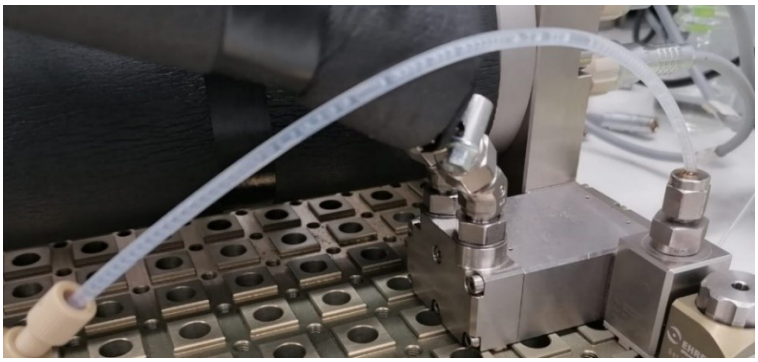

Figure S4. Process medium entering the reactor in slug flow regime.

1.2.4. Reactor

The hydrogenation reaction was performed in a Miprowa Lab reactor (Ehrfeld, 0224-2-2004-F, Hastelloy C-276) (Figure S5). This reactor contains reaction channels with a rectangular cross-section (1.5 mm × 12 mm × 300 mm). The flange (Figure S6) was used to reduce the number of channels from 8 to 4. The first channel was filled with a standard herringbone shaped flow baffle (three layers, 45° angle, strut width 1.0 mm, spacing 2.0 mm, length 300 mm) manufactured from Hastelloy C-276 (6114-1-3244). The second channel was filled with one Catalytic Static Mixer (CSIRO and Precision Plating Australia, CSM) of 150 mm length (see Figure S7). A previous study suggests that within the reactor the flow regime changed from slug flow to stratified flow, with the liquid phase adhering to the catalyst.[2]

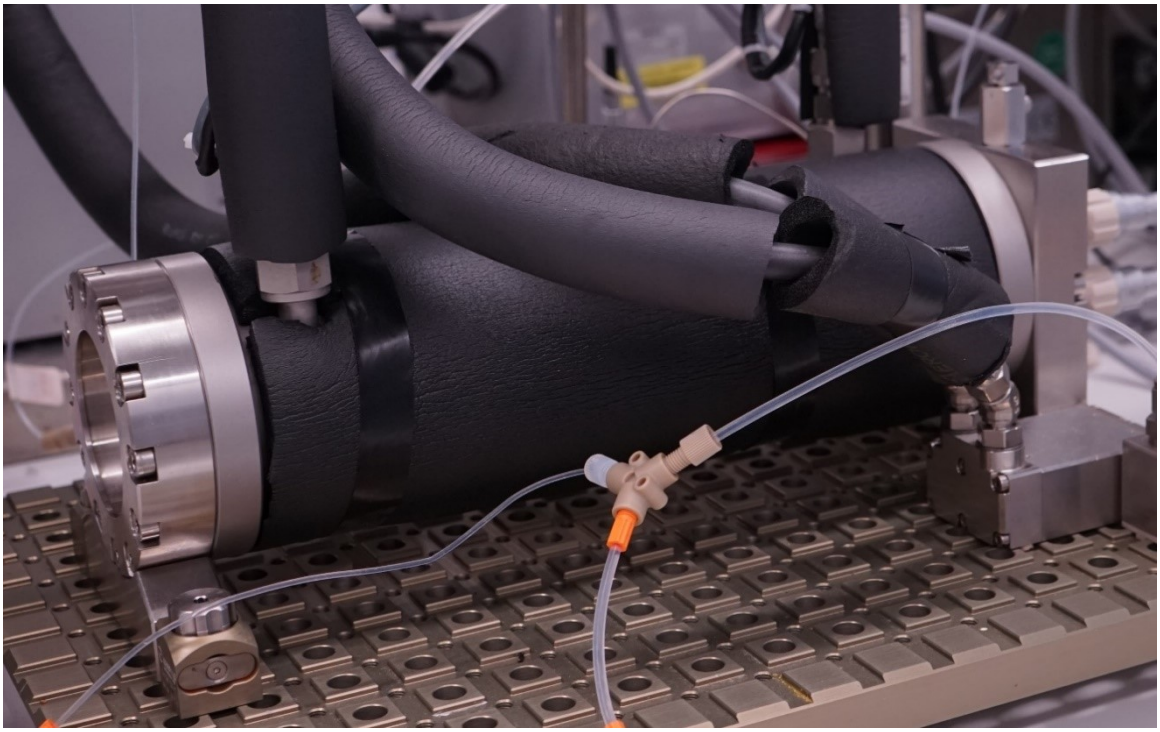

Figure S5. Photograph of the Miprowa Lab reactor and MMRS.

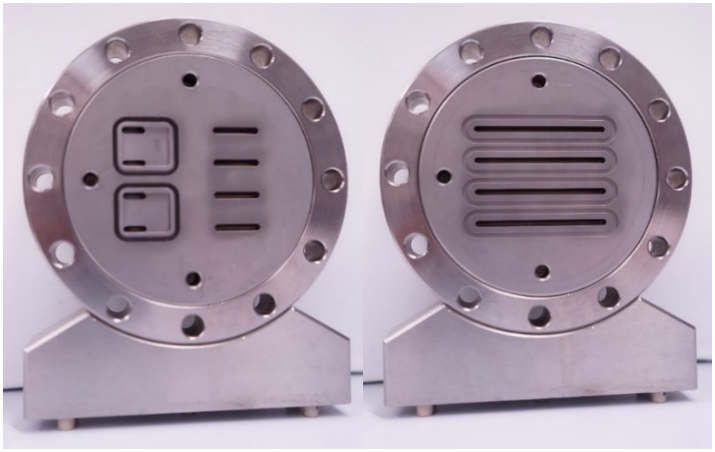

Figure S6. Photograph of the Flange in 4 (left) and 8 (right) channel orientation.

1.2.5. Catalytic Static Mixer

The CSMs were manufactured from 316L stainless steel powder by selective laser melting, according to a design by CSIRO.[2–4] The 3D-printed static mixers were coated with Pd/Al_2O_3 by CSIRO and Precision Plating Australia via a slurry coating technique.[1,5] The average amount of Pd on each CSM was measured to be ~0.24 g. Additionally, reactions for 2-chlorotoluene (**A12**) were performed with an identical static mixer, but coated with (i) Pt/Al_2O_3, and (ii) Pd deposited via electroplating (Pd/EP).[1,3,5]

Throughout the project, 7 Pd/Al_2O_3 CSMs were used. Their performance in the initial reaction without additive ranged between 60% and 80% conversion at 0.5 M substrate **1** concentration (with one outlier, the CSM used in the run including thiophenol, only achieving 50% conversion but this caused deactivation so we selected not to repeat this experiment). Full conversion was always achieved without additive in the case of 0.1 M substrate **1** concentration. The reactor volume is calculated as 2.7 mL for each of the empty sections (one channel having 2 sections), and as 1.7 mL for a section that is filled, giving a contact time of ~51 s for the additive screening experiments, as all of which were carried out using a single CSM and a total flow of 2 mL/min.

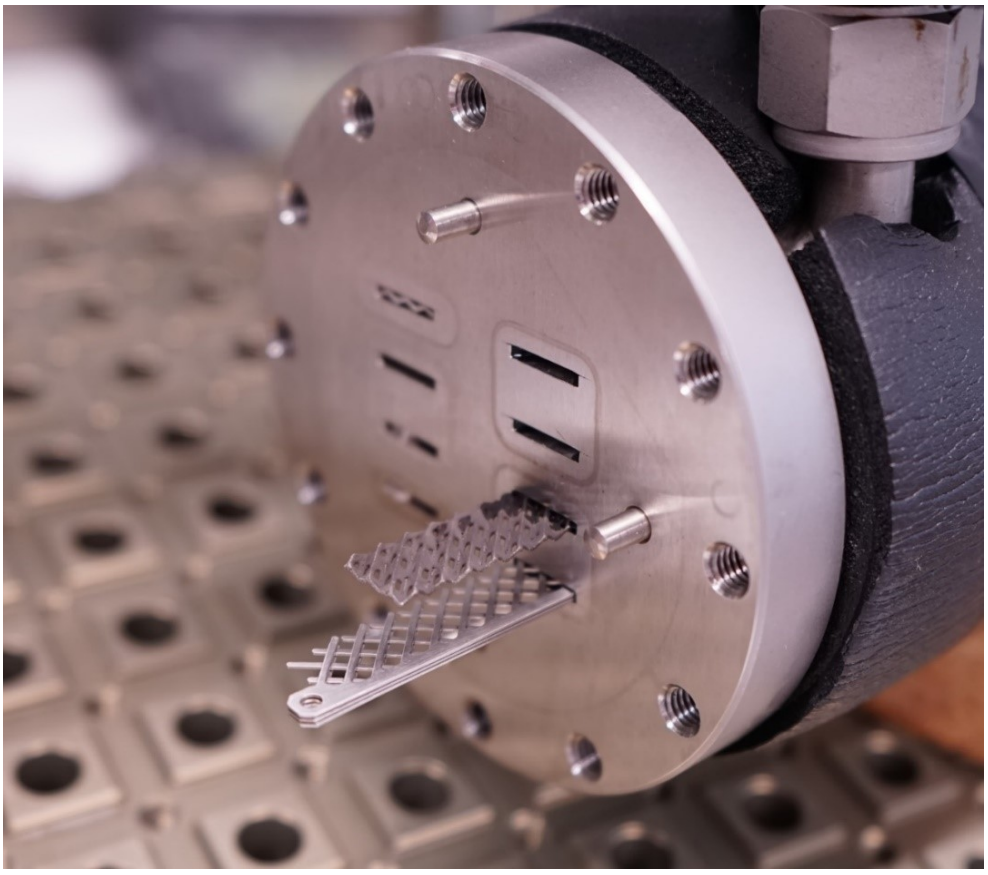

Figure S7. Photograph of the opened Miprowa Lab reactor, showing static mixing element (bottom) and Catalytic Static Mixer (top).

1.2.6. Temperature and pressure control

The temperature of the reactor and heat exchanger was adjusted using a thermostat (Huber, CC-304) (Figure S8) and was monitored at two points for the process stream: 1) process medium input to reactor, 2) process medium output from reactor, and two points for the thermal fluid stream as well: 1) thermostat bath temperature, 2) thermal fluid output from the reactor. Due to alternating gas/liquid slugs, the temperature signal which was measured by the sensors directly contacting the process medium was prone to oscillate depending on the ratio and flow rates of the liquid and gas streams. Additionally, the thermal fluid exiting the reactor was led to a coax heat exchanger (0309-4-0004-F, Hastelloy C-276) just in front of the reactor to preheat the entering process medium before returning to the thermostat.

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 stainless-steel coil (i.d. 0.8 mm, 1 mL), which was submerged in a water bath at ambient temperature to cool the reaction output.

The pressure inside the system was controlled by a nitrogen pressure loaded back pressure regulator (Equilibar, Zero Flow BPR), regulated by a pressure controller (Bronkhorst, EL-PRESS) with attached PFA tubing (i.d. 1.6 mm, 0.8 mL in total) as in- and outlet. At ambient pressure, after passing through PFA tubing (i.d. 0.8 mm, 2 mL) the excess hydrogen was separated by a custom made gas-liquid separator mounted on an inline Fourier Transform Infrared Spectroscopy (FT-IR) probe also containing an inlet tubing for online Ultra High Performance Liquid Chromatography (UHPLC) sampling (pictured in figure S13 in section 3.1.3.).

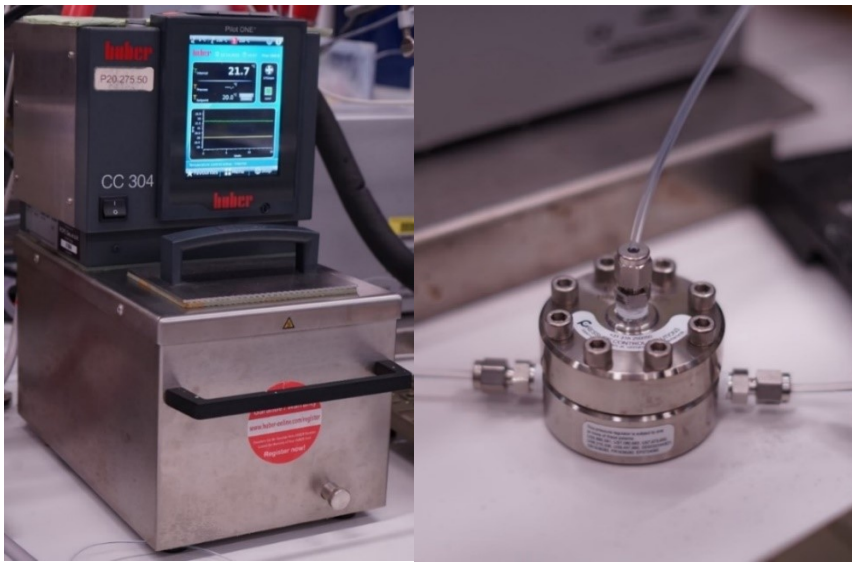

Figure S8. Photographs of the Huber CC-304 thermostat (left) and Bronkhorst EL-PRESS pressure controller (right).

2. Process Analytical Technology

2.1. Inline FT-IR spectroscopy

2.1.1. General

FT-IR measurements were made using a Mettler Toledo ReactIR 15 instrument, equipped with an AgX 9.5 mm fibre and a DiComp (diamond composite) probe. Sampling time was set to 15 s with a measured wavenumber range from 1700 to 800 cm^{-1} using the maximum resolution of 4 cm^{-1}. Prior to starting the experiments, it was ensured that the MCT (mercury cadmium telluride) detector was cooled with liquid nitrogen, so that the signal to noise ratio was above 15000 and the peak height was between 18000 and 24000 counts.

2.1.2. Partial Least Square (PLS) regression and calibration

The reaction was relatively complex to monitor by FT-IR due to the absence of prominent isolated bands with high intensity for the product **2**, and also from the generation of water during the reaction. Therefore, advanced data processing techniques such as Indirect Hard Modelling (IHM) were attempted for FT-IR prediction but was rejected since it did not provide satisfying results. Thus, Partial Least Square (PLS) regression was selected.

PLS regression modelling was performed using the software PEAXACT 5.3 (S-PACT) and the following workflow was used:

Calibration mixtures of five different levels were prepared in 20 mL volumetric flasks, by weighing in pure components and filling up to the mark with MeOH. The weight of each component corresponded to the target concentration shown in Table S1.

Table S1. Target concentration of each compound in the calibration mixture

Mixture #	Substrate [mM]	Product [mM]	Additive [mM]
I	50	550	550
II	100	400	400
III	250	250	250
IV	400	100	100
V	550	50	50

For calibration measurements, the FT-IR probe was carefully readjusted to point downwards (to an angle of about 45°). On this, a cap of a regular 4 mL screw vial was mounted after creating a fitting cavity in it. Samples of about 2 mL were simply screwed on and the measurement was started. After gathering enough spectra, the measurement was paused, the probe cleaned with acetone and dried with Argon, and the next sample was measured. The acquired training set spectra were read into PEAXACT as SPC format. For an even better approximation, the PLS model was refined with process data.

The spectra were processed with the following pretreatment conditions. Baseline correction: rubberband subtraction; smoothing/derivative: smoothing only with a filter length of 5. The global range was set from 1700 to 800 cm^{-1} to avoid processing parts of the spectrum without relevant information. Additionally, the ranges 940 to 1135 cm^{-1} and 1370 to 1505 cm^{-1} were neglected due to very intense signals of solvent. Example spectra are provided in Figure S9.

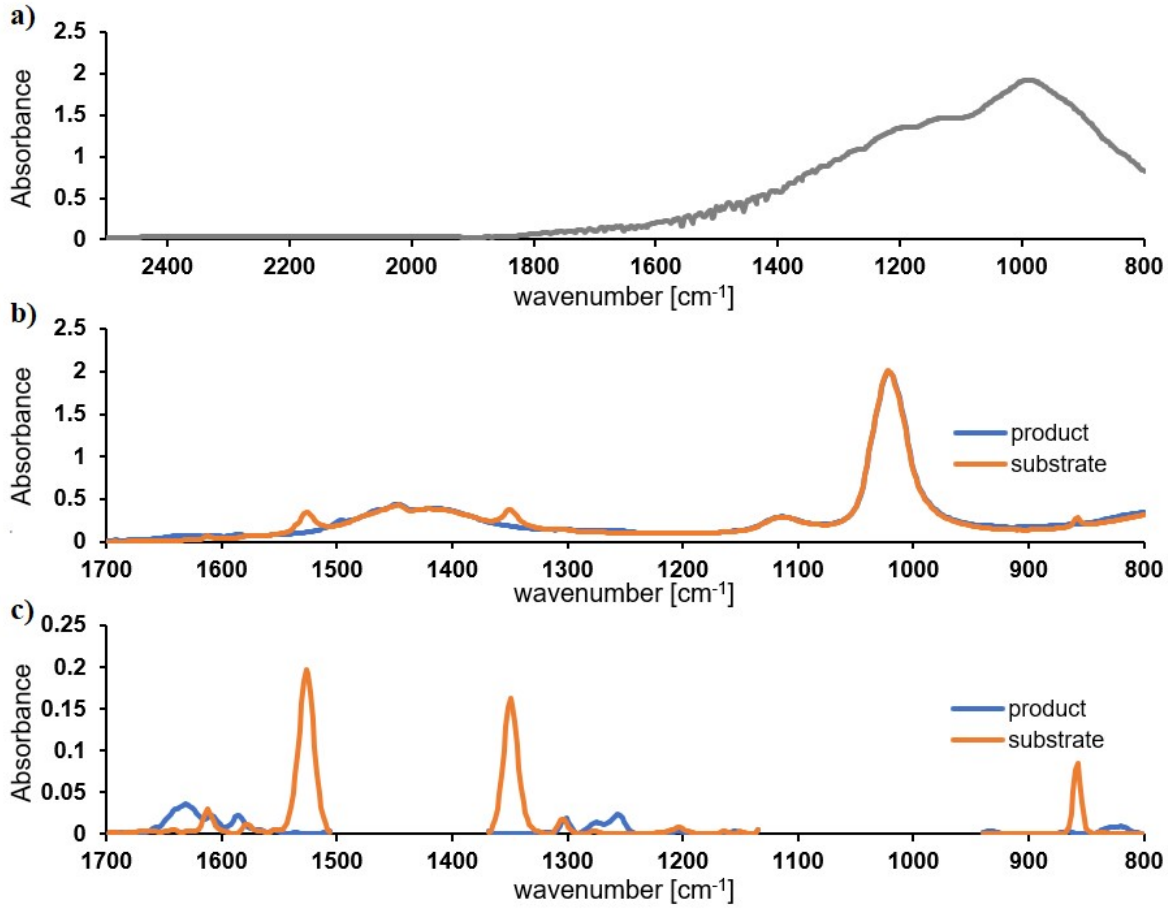

Figure S9. FT-IR spectrum of a) background measurement; substrate **1** and product **2** in same concentration (0.55 mol/L) as b) unprocessed spectrum, c) spectrum including pretreatment.

To gain the calibration model, imported spectra (15 of each level) were tagged with the "true" concentration values of each compound in the mixture. For all compounds in every model a rank had to be chosen, reflecting the "degree of fitting" that is applied. The ranks were adjusted considering two factors, namely the observation of the parity plot and minimizing the RMSEc (root mean square errors of calibration) and RMSEcv (root mean square error of cross-validation). Typically, the number of ranks used in the models varied between 3 and 8, however, in certain instances the value was increased up to 12.

Additionally, cross validation (CV) was executed. In this, the N original training samples are divided into two subsets, one training set to fit the calibration model and one test set to compute a validation error. These sets are re-divided and validated until every sample has been used for testing exactly once. The validation errors are averaged over the partitions to give the cross-validation error, which reflects the predictive performance of the model. Due to N being very low in this set, the method "Leave-1-out" was chosen, in which, as the name suggests, only one sample is taken out and used as test set.

The ranges for $RMSE_{CV}$ found result in 1.3 – 4.8 mM, 2.9 – 11.3 mM and 1.2 – 13.7 mM for substrate **1**, product **2**, and additives, respectively. This equals an error of less than 3% when referring to a maximum expected concentration of 500 mM. The results for toluene (**A11**) were not included in this range of $RMSE_{CV}$ because of its very unsteady prediction due to its chemical structure. The errors found for this compound are 15.3 mM for substrate **1**, 2.6 mM for product **2** and 28.6 mM for additive.

Table S2. FT-IR limit of quantification (LOQ) and limit of detection (LOD) for the additives.

Additive	LOQ [mM]	LOD [mM]
Morpholine (**A1**)	7	2
N-methylmorpholine (**A2**)	36	11
Piperazine (**A3**)	27	8
DABCO (**A4**)	17	5
DBU (**A5**)	26	8
N-methylimidazole (**A7**)	71	21
Lutidine (**A8**)	18	5
Thiophenol (**A9**)	96	29
Thioanisole (**A10**)	69	21
Toluene (**A11**)	357	107
2-Chlorotoluene (**A12**)	170	50

2.1.3. Process integration

For inline monitoring of the process stream after the hydrogenation reaction, the FT-IR probe was implemented directly after the atmospheric gas-liquid separator. The gas-liquid separator was constructed from a polytetrafluoroethylene (PTFE) T-connector (10.5 mm bore), which was mounted vertically. 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 FT-IR probe was inserted at the downward facing end (left in Figure S10), and the reaction solution was allowed to overflow through the upper end (bottom right in Figure S10). 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 2.2.3.

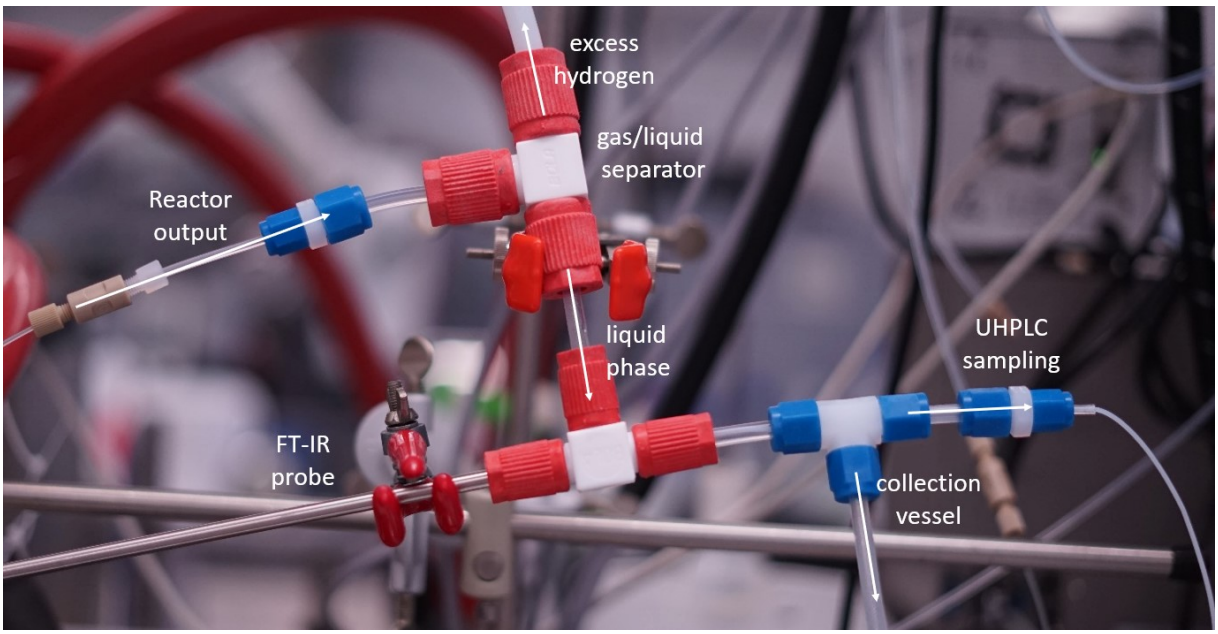

Figure S10. Gas-liquid separator mounted on FT-IR probe, including tubing for UHPLC sampling.

2.2. Online UHPLC analysis

2.2.1. General

The UHPLC-DAD was comprised of a degassing unit (DGU-20A), two solvent delivery units (LC-30AD), a thermoregulated autosampler (SIL-30AD), thermoregulated column oven (CTO-20AC), diode array detector (SPD-M30A) and a control unit (CBM-20A).

Analysis was performed using a Phenomenex Luna Omega C18 column (50 × 2.1 mm, particle size 1.6 µm, pore size 100 Å) at 45 °C using mobile phase A (H_2O + 0.02% HCOOH) and B (MeCN + 0.02% HCOOH at a total flow rate of 1 mL/min.

The mobile phases A and B were prepared from HPLC grade solvents.

Compounds (apart from the exceptions mentioned below) were eluted with the following gradient:

Method A: starting with 1% B for 0.5 min, increasing to 20 % B over 1 min, increasing to 100 % B over another 1.5 min, holding 100 % B for 1 min and equilibrating the column with 1 % B for 2.99 min (= 7 min total acquisition time).

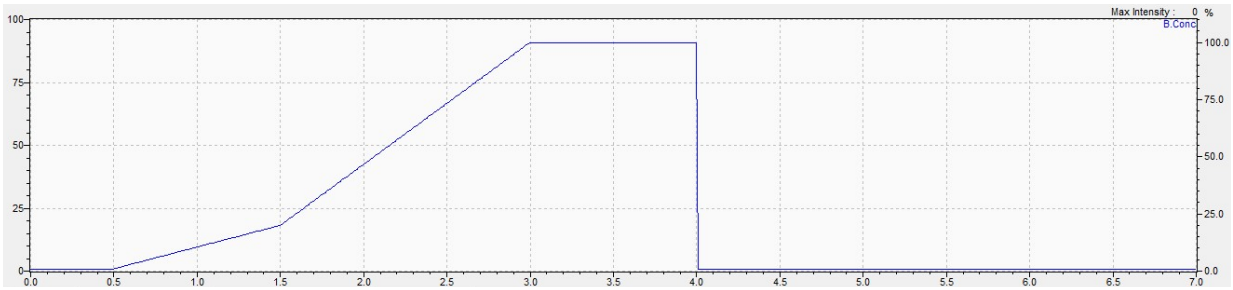

Figure S11. UHPLC Method A.

For toluene (**A11**) and 2-chlorotoluene (**A12**), the gradient method was modified to give improved separation of the peaks. This method was also used on thiophenol (**A9**), but satisfying separation was not achieved. Following method was used:

Method B: starting with 1 % B for 0.5 min, increasing to 35 % B over 1 min, holding at 35 % B for 0.7 min, increasing to 100 % B over 3.8 min and holding 100% B for 1 min and equilibrating the column with 1 % B for 2.99 min (= 10 min total acquisition time).

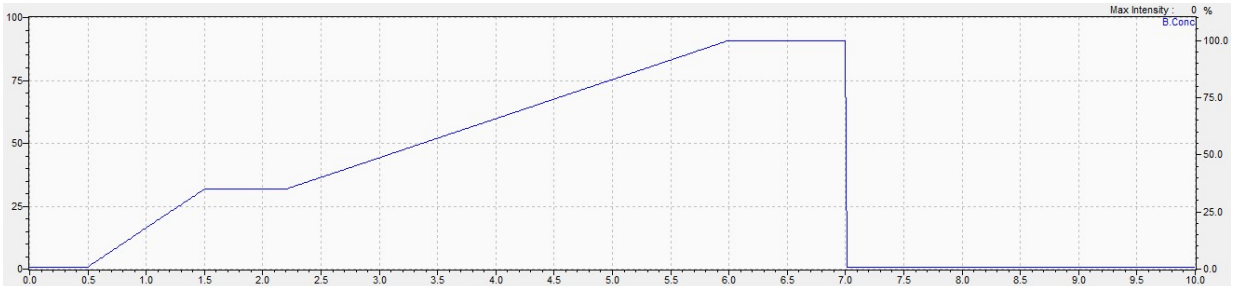

Figure 12. UHPLC Method B.

Chromatograms were integrated at a wavelength of 210 nm. Representative chromatograms are shown in Figure S13 – S16.

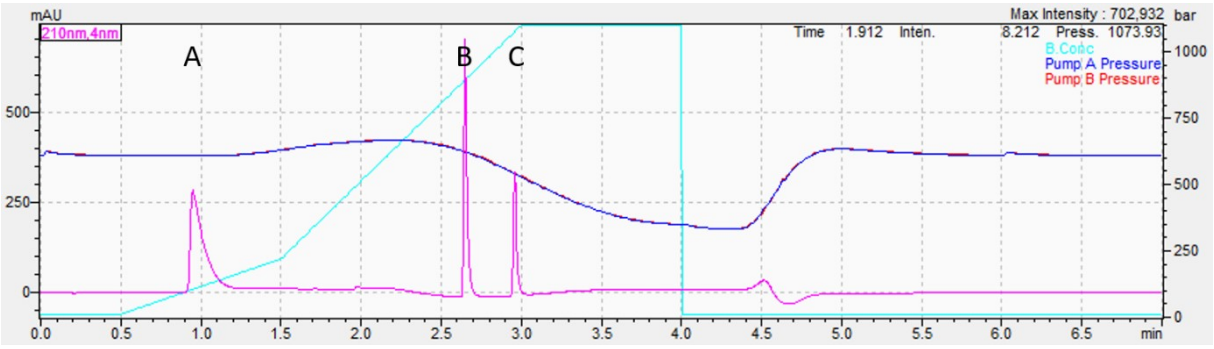

Figure S13. Example of UHPLC chromatogram; showing A: product **2** at rt = 0.95 min, B: substrate **1** at rt = 2.65 min**,** C: ITSD at rt = 2.95 min using Method A

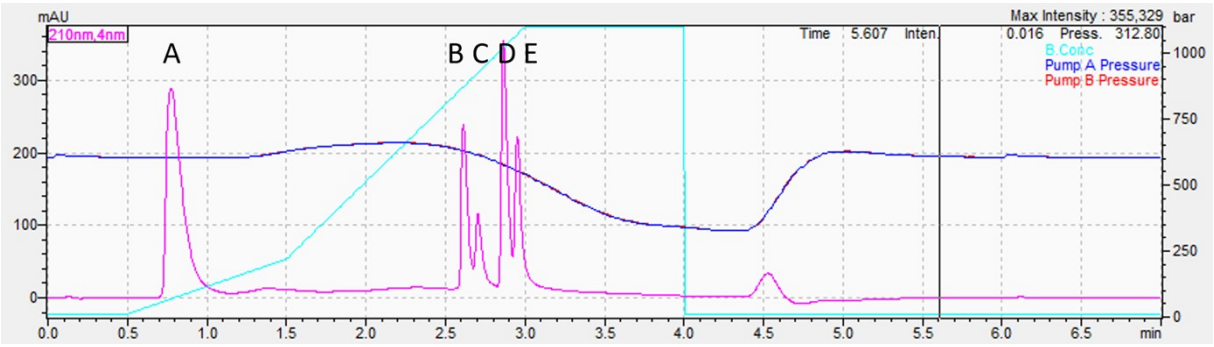

Figure S14. Example of UHPLC chromatogram, showing unsatisfying separation of A: product **2** at rt = 0.8 min, B: substrate **1** at rt = 2.65 min**,** C: toluene (**A11**) at rt = 2.7, D: 2-chlorotoluene (**A12**) at rt = 2.9 min, E: ITSD at rt = 2.95 min using Method A.

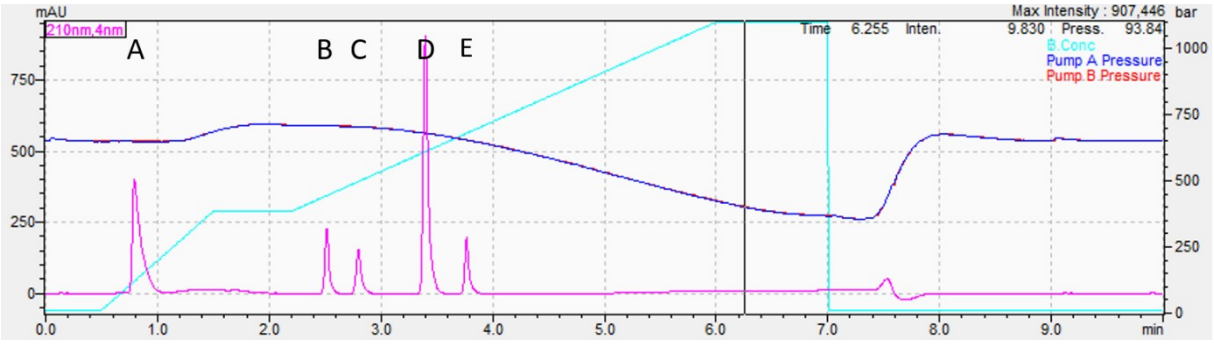

Figure S15. Example of UHPLC chromatogram, showing unsatisfying separation of A: product **2** at rt = 0.8 min, B: substrate **1** at rt = 2.5 min**,** C: toluene (**A11**) at rt = 2.8 min, D: 2-chlorotoluene (**A12**) at rt = 3.4 min, E: ITSD at rt = 3.8 min using Method B.

2.2.2. Calibration

Substrate **1**, product **2**, 3,5-lutidine (**A8**), toluene (**A11**) and 2-chlorotoluene (**A12**) were calibrated against biphenyl as an internal standard (ISTD) by UHPLC. All other additives were either not visible by UHPLC or badly separated (DBU (**A5**), thiophenol (**A9**)) by the UHPLC methods. For these calibrations, 5 mixtures of varying compound concentrations were prepared by the following procedure:

A 0.025 mol/L ISTD stock solution was prepared by weighing in the appropriate amount of ISTD in a 250 mL volumetric flask. The flask was filled up with MeOH to the mark. Then, the compounds to be calibrated were weighed in (for the same target concentrations as in the FT-IR calibration, see Table S1) in a 20 mL volumetric flask and filled to the mark with the ISTD stock solution. The resulting 5 calibration mixtures were then diluted with MeOH (1+9) for offline UHPLC analysis to be in the same concentration range as for online analysis.

The resulting chromatograms were integrated and measured against ITSD at 210 nm after separation with UHPLC method A (7 min) for substrate **1**, product **2** and 3,5-lutidine (**A8**) or UHPLC method B (10 min) for toluene (**A11**) and 2-chlorotoluene (**A12**). The calibration functions can be found in Figure S16 below. For the observed intermediate, the value was assumed based on the mean value for the response factors of substrate **1** and product **2**. Unfortunately, we did not have access to reference standards for the intermediates, which is the reason for taking an average response factor of the substrate and product as a reasonable estimate. Even if the response factor was incorrectly estimated, the influence to the mass balance is relatively small, since by area% of the intermediate at the maximum of 10-11 area% (in the case of piperazine) was seen. When observed, i.e. morpholine (**A1**), DABCO (**A4**), thiophenol (**A9**) and thioanisole (**A10**), the intermediate accounted for ~4 area%.

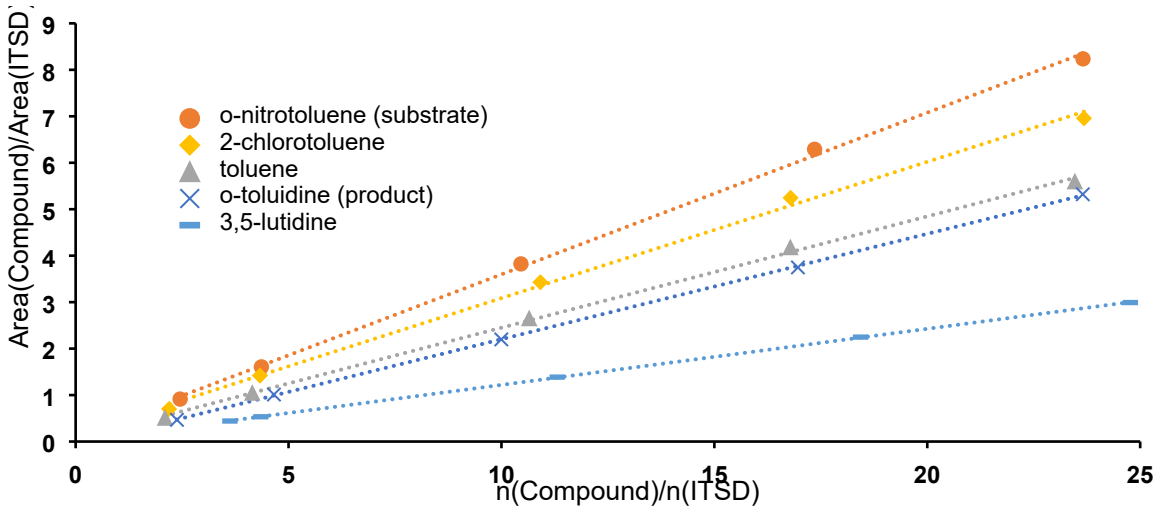

Figure S16. UHPLC calibration for substrate **1**, product **2**, 3,5-lutidine (**A8**), toluene (**A11**) and 2-chlorotoluene (**A12**).

To evaluate the error of the UHPLC analysis, a sample taken during a reaction was measured and analysed 9 times, which resulted in an analytical error of less than 2% for both substrate **1** and product **2**.

2.2.3. Process integration

Online UHPLC integration was accomplished by using an UHPLC internal sample injector (10 nL, 20000 psi, Cheminert Nanovolume, Part# C84U-6674-.01EUH), 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 (9.00 min load for exceptions). Samples were continuously withdrawn as a bypass directly in front of the FT-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 product stream with a constant flow rate of 500 µL/min.

2.3. GC-MS analysis

GC-MS was performed using a Shimadzu GCMS-QP2010 SE, using a Rtx-5MS column (30 m × 0.25 mm × 0.25 µm) and helium as carrier gas with a linear velocity of 40 cm/sec. The injector temperature was set to 280 °C. After 1 min at 50 °C, the oven temperature was increased by 25 °C/min to 300 °C and then kept at 300 °C for 3 min. The mass detector was a quadrupole with pre-rods and electron impact ionization. The following settings were used in the detector: ion source temperature 200 °C, interface temperature 310 °C, solvent cut time 2 min 30 sec, acquisition mode scan, mass range m/z = 50 till m/z = 400.

From the reaction including piperazine (**A3**) as additive, a sample was taken during additive introduction and measured via GC-MS. The resulting GC spectrum and the associated structures based on the mass detection is shown in Figure S17.

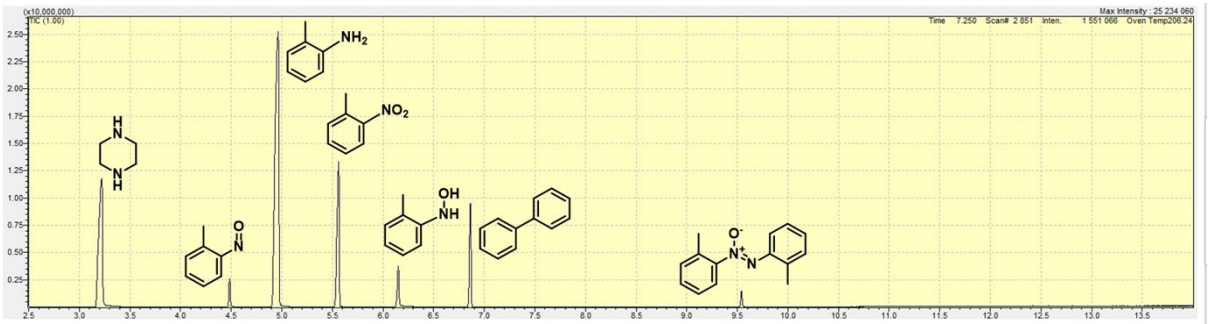

Figure S17. Measured GC-MS spectrum when using piperazine (**A3**) as additive.

2.4. ICP-MS analysis

To investigate any possible leaching of Pd and Al from the CSM, Inductively Coupled Plasma - Mass Spectrometry (ICP-MS) analysis was performed.

For ICP-MS, samples (10 mL) were reduced under low pressure to remove most of the solvent. After mixing an aliquot (100 µL) of the remaining liquid with nitric acid (5 mL), microwave-assisted acid digestion was carried out in an MLS UltraClave instrument. The temperature was ramped up to 250 °C in 40 min and kept at this temperature for another 30 min. These samples were diluted further for the subsequent ICP-MS measurement. For the reactions analyzed by ICP-MS, the procedure above was performed for 4 samples: one for the substrate feed, one for the additive feed, and two for the collected product stream during additive introduction. For the reaction including piperazine (**A3**), Pd and Al contents were measured using an Agilent 7900 ICP-MS instrument, for the one including thiophenol (**A9**), an Agilent 7700 ICP-MS instrument was used. For both Al and Pd, contents in all samples were determined to be below 50 ppb.

3. Experimental Details

3.1. Standard reaction conditions

Since the deactivation of catalyst / rate retardation could go unobserved at quantitative conversion, the aim of the initial experiments was to establish conditions to achieve partial conversion (between 60% and 80%). We were also interested in running the screening experiments at conditions that provide full conversion. The preliminary reaction condition screening (Section 5.1) resulted in the following conditions for the flow ramp (section 4.4.2.).

Fixed parameter for all runs. The flow system was operated at a total flow rate of 2 mL/min (~51 s contact time), a jacket temperature of 100 °C and a backpressure of 20 bar.

Partial conversion. Substrate concentration of 0.5 mol/L within the reactor using 3.3 eq. (74 mL/min) of hydrogen.

Full conversion. Substrate concentration of 0.1 mol/L within the reactor using 4.5 eq. (20 mL/min) of hydrogen.

3.2. Preparation of feed solutions

Feed solutions were freshly prepared before every flow ramp experiment.

The feed solution of *o*-nitrotoluene (**1**) (1 mol/L) was prepared in a 500 mL volumetric flask. Biphenyl (5 mol%) as internal standard was added. The flask was filled to the mark with MeOH.

The feed solution of additive (1 mol/L) was prepared in a 200 mL volumetric flask. The flask was filled to the mark with MeOH. Both feed solutions were sonicated for at least 5 minutes to ensure a homogeneous solution. Neat MeOH was used as the third liquid feed.

3.3. Reactor start-up

The following procedure was executed:

1. Flush the reactor with MeOH.
2. Set the back-pressure regulator to the desired reaction pressure.
3. Set H-Genie to desired pressure and flow, pause flow when pressure is reached
4. Turn off liquid pump briefly to switch input to substrate solution (using a valve).
5. Start pump, UHPLC injections, FT-IR measurement and the flow ramp protocol
6. Perform reaction at set conditions according to the flow ramp.
7. Cut H_2 flow, decrease pressure in steps of 3 bar, cool reactor to room temperature.
8. Wash reactor with MeOH and iPrOH (minimum 3 times the reactor volume).

9. Store pumps and reactor in iPrOH until next use.

3.4. Process control

3.4.1. Software

The entire platform (but the peristaltic pump leading to the UHPLC) was monitored and controlled using a HiTec Zang LabManager and LabVision software (Figure S18). Actuators were automated according to Table S2.

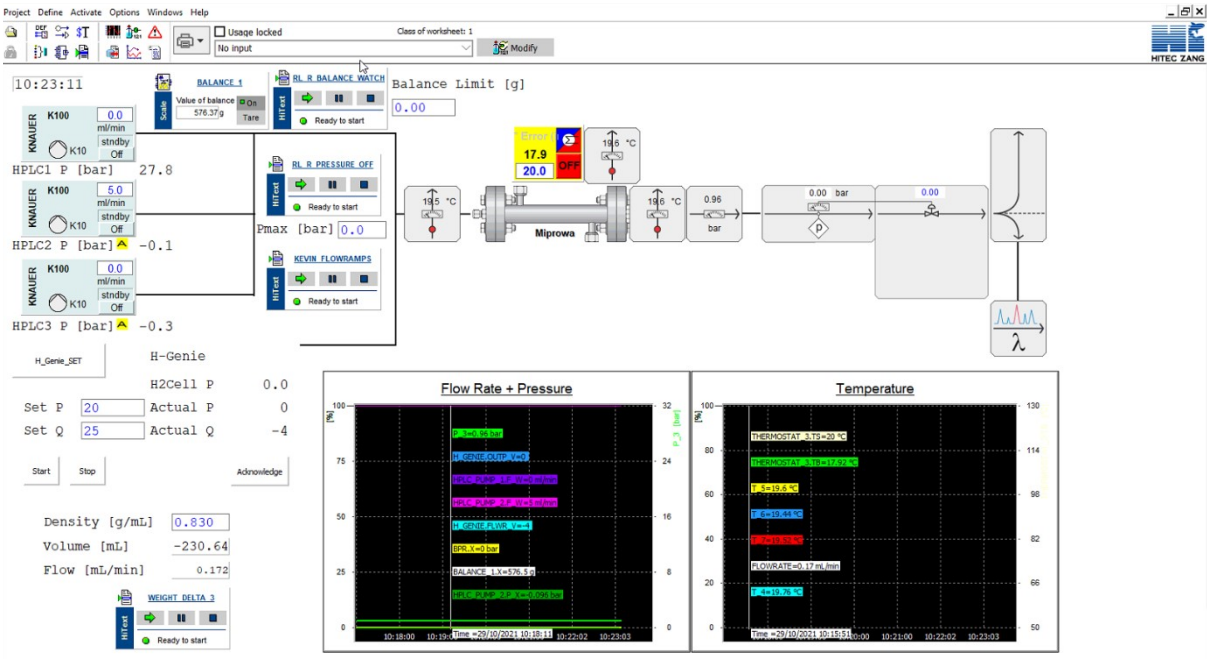

Figure S18. Screenshot of the LabVision software used to control the flow platform.

Table S3. List of equipment that was used in the study and its interface to LabVision.

Instrument Type	Make/Model	Quantity	Interface to LabVision
T sensor	Ehrfeld, 0518-2-1004-X	2	M8
T sensor	Huber, Pt100 M16x1 HUB-6352	1	M8
P sensor	Ehrfeld, 0518-1-60x4-F	1	DIN 5-pin
Pump (HPLC)	Knauer, Azura P 4.1S	3	RS232, NAMUR
Pressure regulator	Bronkhorst, EL-PRESS	1	RS232, NAMUR
H_2 generator	Thales Nano Energy, H-Genie	1	RS232, NAMUR
Thermostat	Huber, CC-304	1	RS232, NAMUR
Balance	Kern, KB 2400-2N	1	RS232, NAMUR

3.4.2. Flow ramp

Full automation of the process and the individual steps to the reaction was achieved using an automated flow ramp protocol. The script written in HiText communicates with the HiTec Zang LabManager and enabled automated switching of the flow rates (Figure S19). The run time selected for the individual steps of each step was chosen to be a multiple of the UHPLC measurement time, so 7 minutes (flow ramp A, Figure 3 in the main manuscript) and 10 minutes (flow ramp B, Figure S19) for exceptions mentioned in section 2.2.1. The profile was separated into following steps:

1. Check feed solution
2. Solvent only (implemented to ensure that the temperature is fully reached, to enrich reactor with H_2, and save on substrate consumption during this step)
3. Carry out reaction without additive
4. Carry out reaction with additive
5. Control step without additive
6. Repeat last 3 steps at a dilution of 1:5 to achieve full conversion (with a slight excess of H_2 due to the minimal flowrate of 20 mL/min of the H-Genie)
7. Flush reactor with solvent and cool down system.

```
;setpoint 1.1 solvent only
!HPLC_PUMP_1.F_W = 0
!HPLC_PUMP_2.F_W = 0
!HPLC_PUMP_3.F_W = 2
wait 1260 sec

;setpoint 1.2 substrate + solvent
!HPLC_PUMP_1.F_W = 1
!HPLC_PUMP_2.F_W = 0
!HPLC_PUMP_3.F_W = 1
wait 2940 sec

;setpoint 1.3 substrate + additive
!HPLC_PUMP_1.F_W = 1
!HPLC_PUMP_2.F_W = 1
!HPLC_PUMP_3.F_W = 0
wait 2520 sec

;setpoint 1.4 substrate + solvent
!HPLC_PUMP_1.F_W = 1
!HPLC_PUMP_2.F_W = 0
!HPLC_PUMP_3.F_W = 1
wait 2520 sec

;setpoint 3.1 full conversion
!HG_SET_Q=20
!HG_SET_P=30
start H_GENIE_SETPOINT

!HPLC_PUMP_1.F_W = 0.2
!HPLC_PUMP_2.F_W = 0
!HPLC_PUMP_3.F_W = 1.8
wait 2520 sec
```

Figure S19. Part of flow ramp A written in HiText

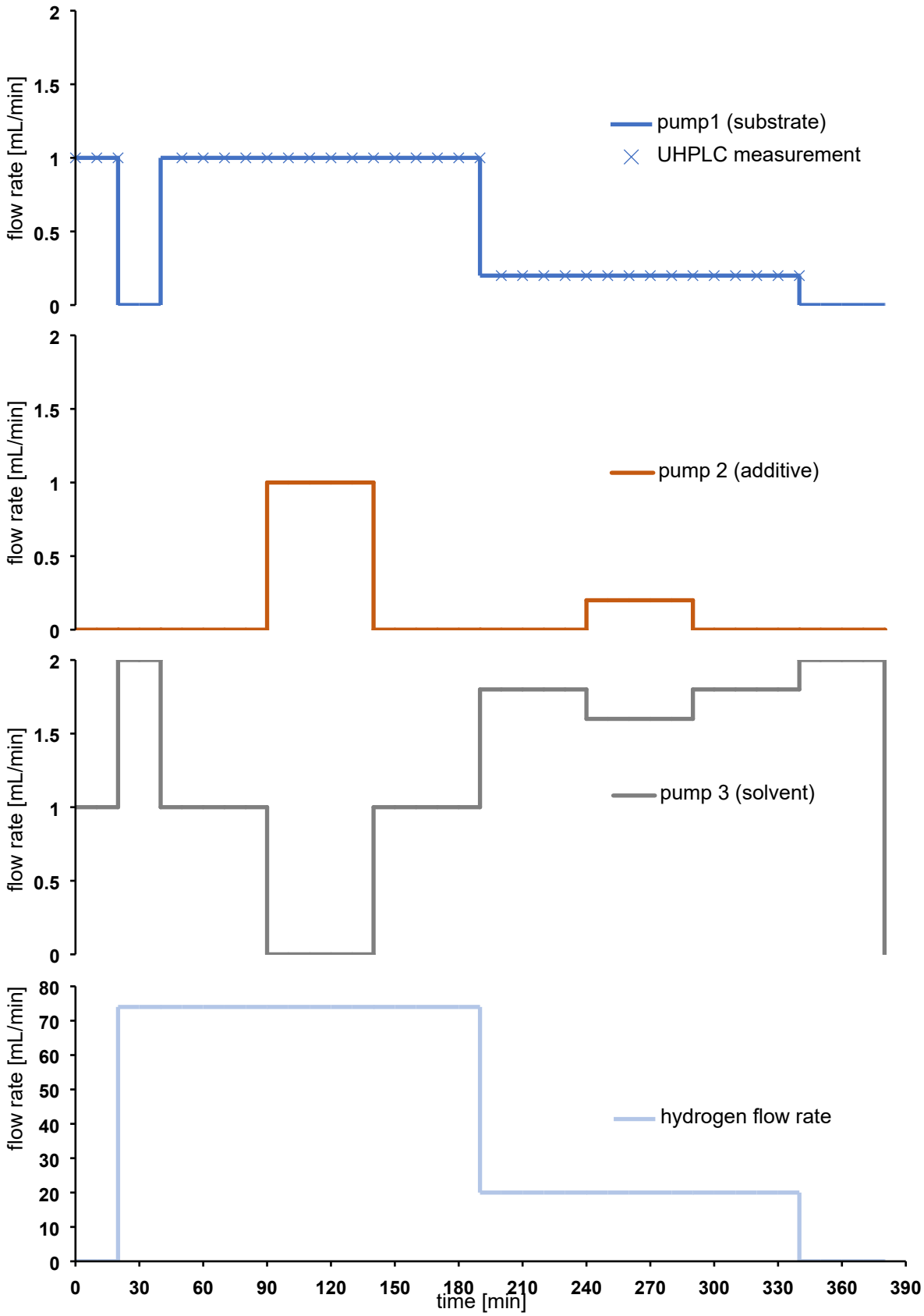

Figure S20. Flow ramp B (UHPLC measurements acquired at 10 min intervals), all steps carried out at a jacket temperature of 100 °C, and a backpressure of 20 bar.

3.4.3. Visualization of FT-IR data in real-time

The recorded FT-IR spectra were automatically read and processed with the PLS model (for PLS model see section 2.1.2) using ProcessLink (S-PACT). This allowed the operator to observe the results of the flow ramp in real-time (Figure S21).

Figure S21. Example of real-time data displayed in ProcessLink.

4. Results

4.1. Parameter screenings

4.1.1. H_2 flow rate screening

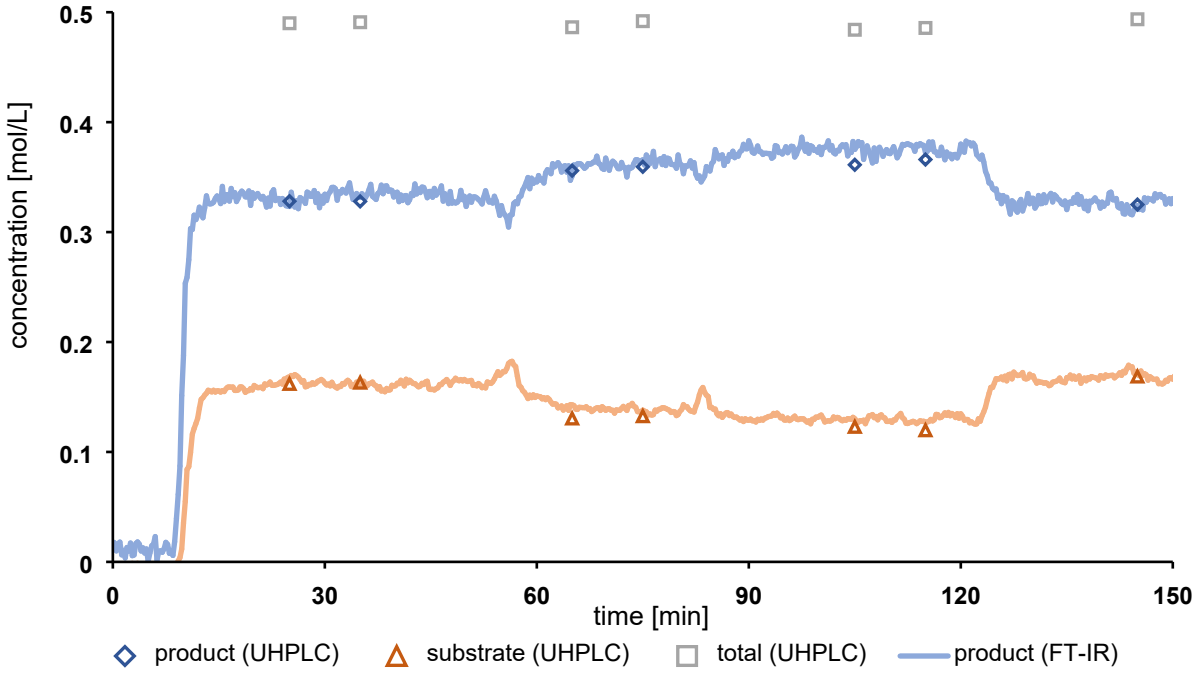

Figure S22. Screening of the influence of H_2 equivalents (3.3, 4.95, 6.6 and then returning to 3.3 equivalents, corresponding to flow rates of 74, 111, 148, and 74 mL/min) at 100 °C jacket temperature, 20 bar backpressure; UHPLC measurements by offline analysis.

4.1.2. Temperature screening

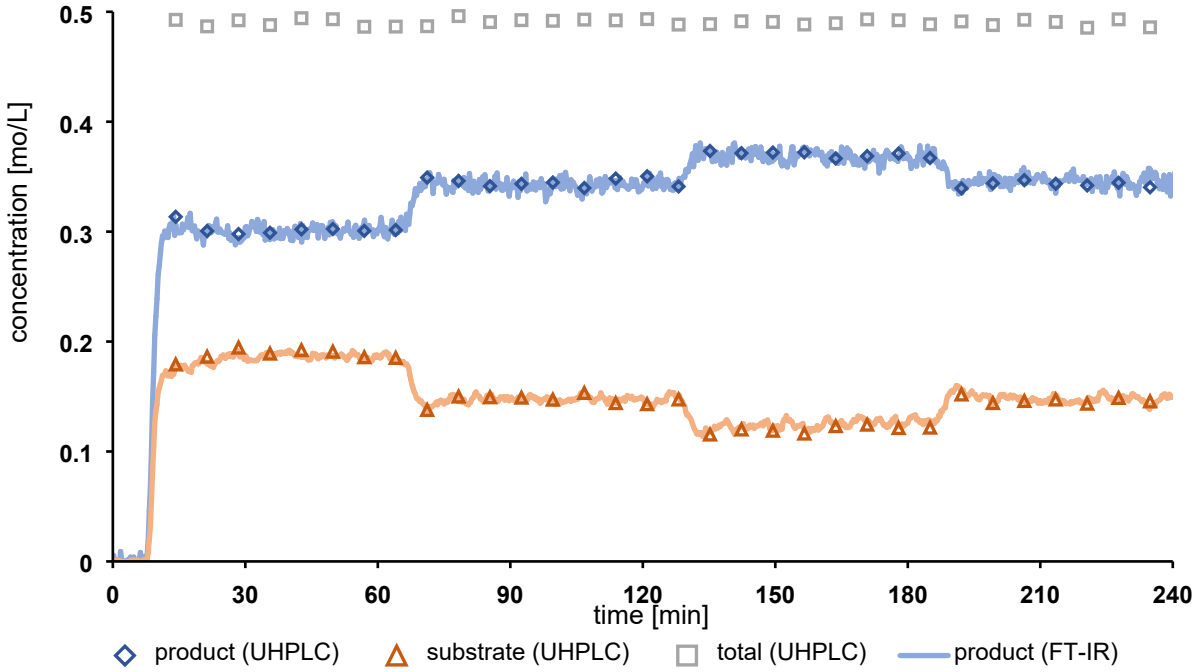

Figure S23. Screening the influence of jacket temperature (80, 100, 120, and 100 °C) at 20 bar backpressure; 3.3 eq. H_2.

4.2. Additives

4.2.1. Morpholine

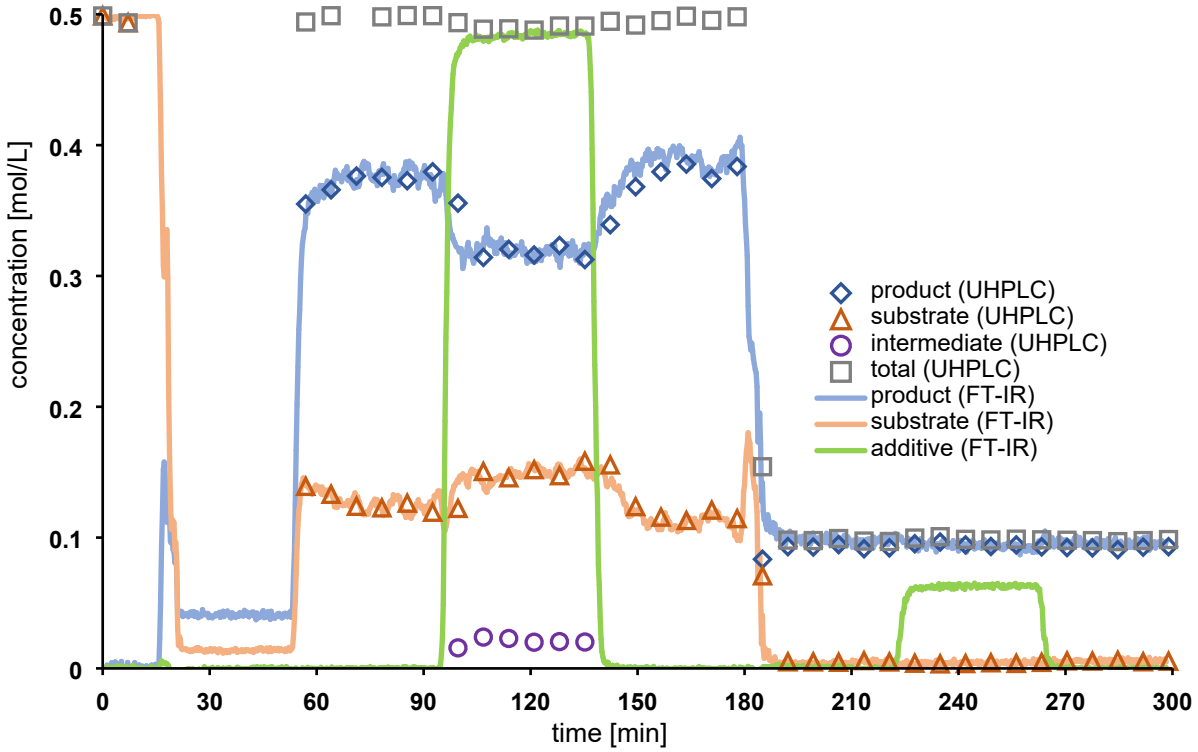

Figure S24. Screening of morpholine (**A1**); flow ramp A.

4.2.2. *N*-Methylmorpholine

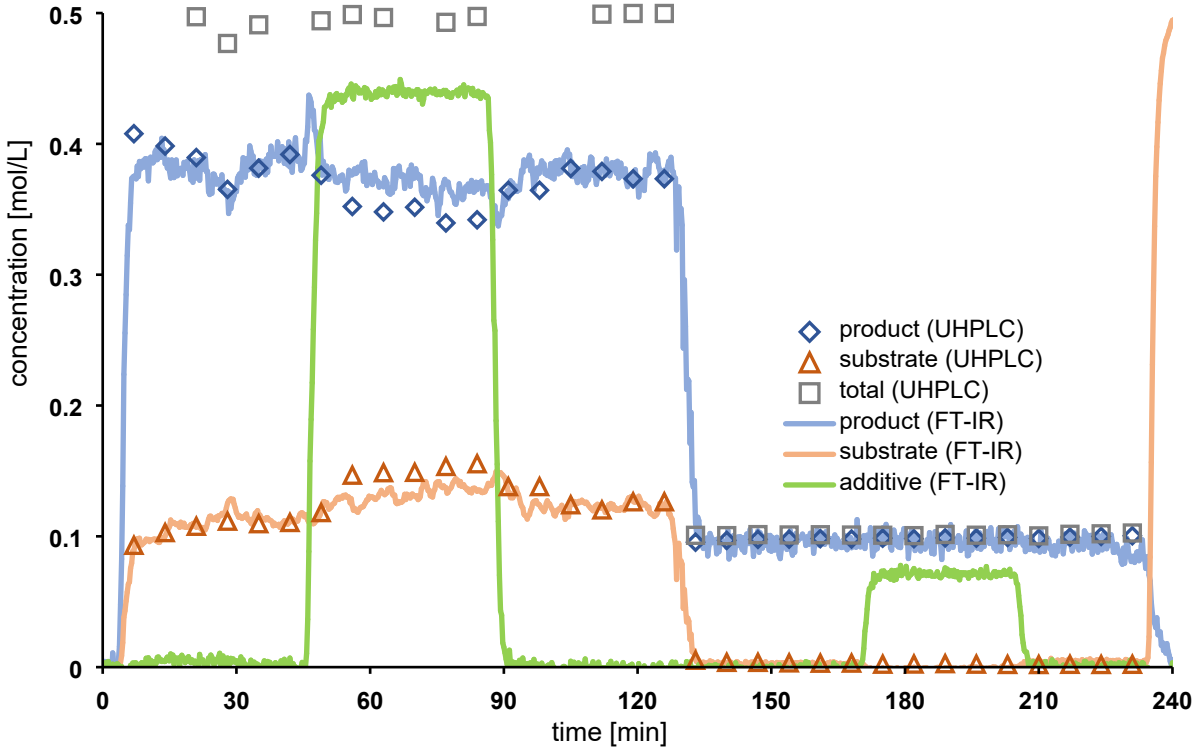

Figure S25. Screening of *N*-methylmorpholine (**A2**); flow ramp A (substrate feed concentration measured at the end).

4.2.3. Piperazine

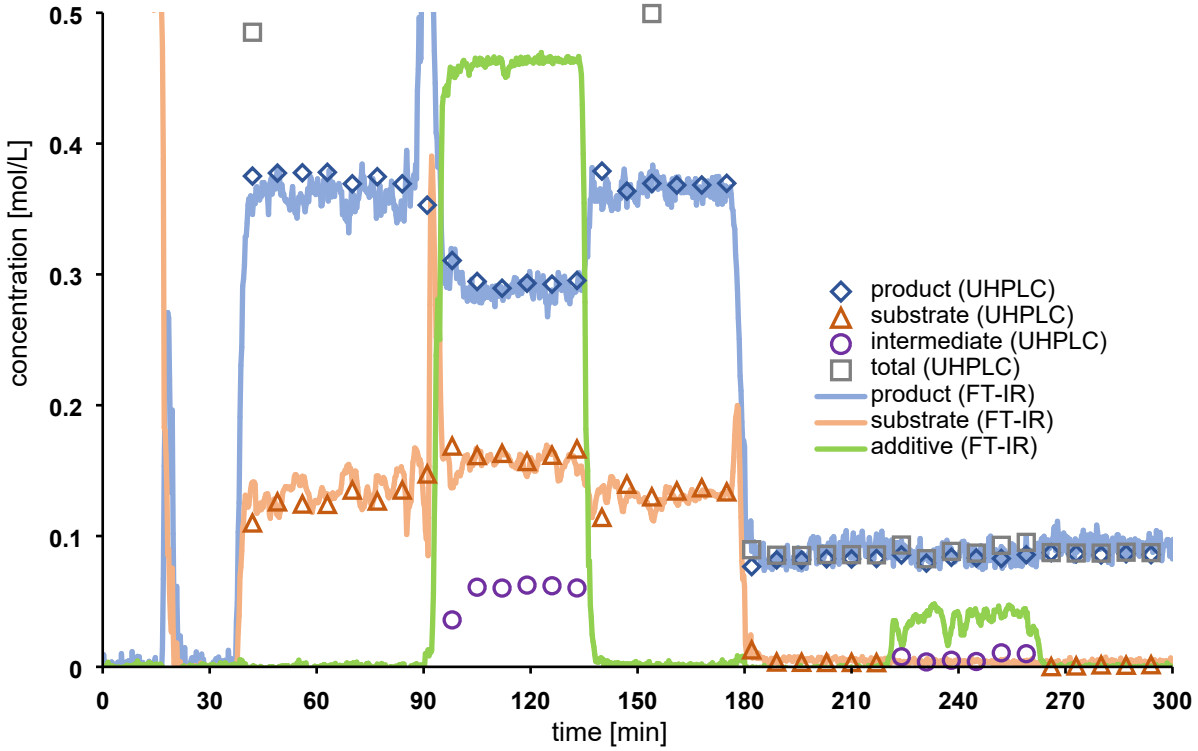

Figure 26 Screening of piperazine (**A3**); flow ramp A, manually lengthened by 7 min due to pump error.

4.2.4. DABCO

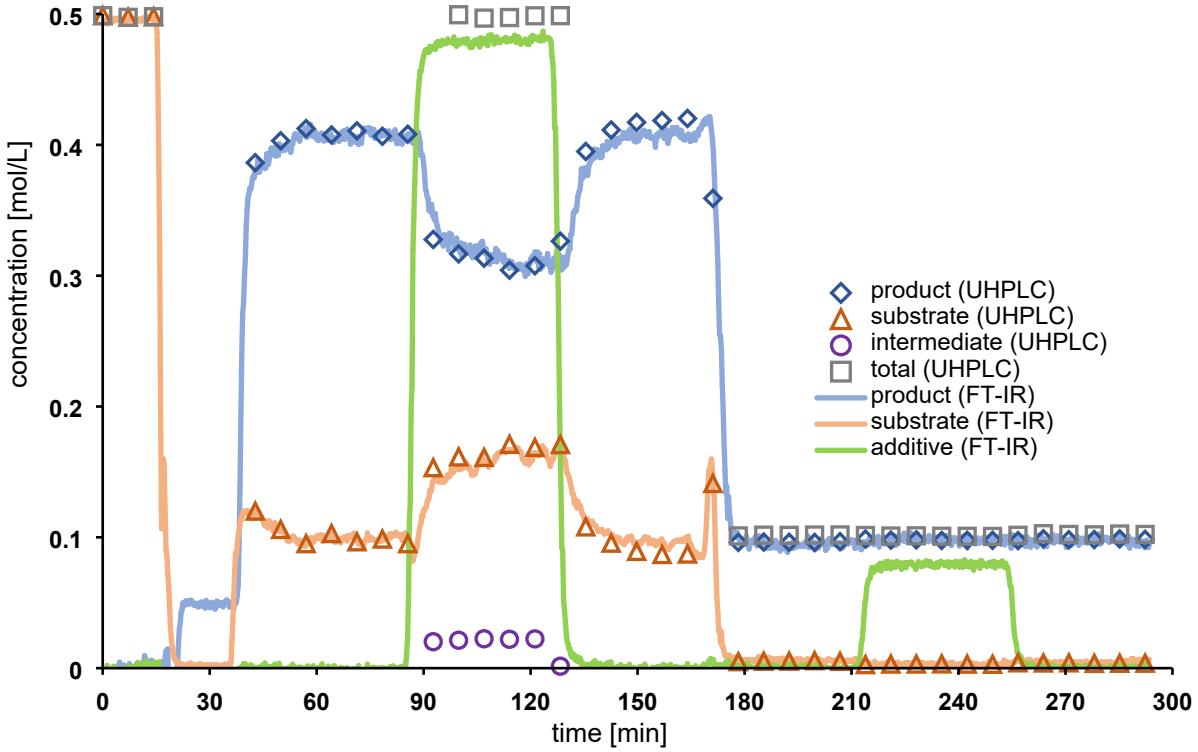

Figure 27. Screening of DABCO (**A4**); flow ramp A, last UHPLC measurement missing.

4.2.5. DBU

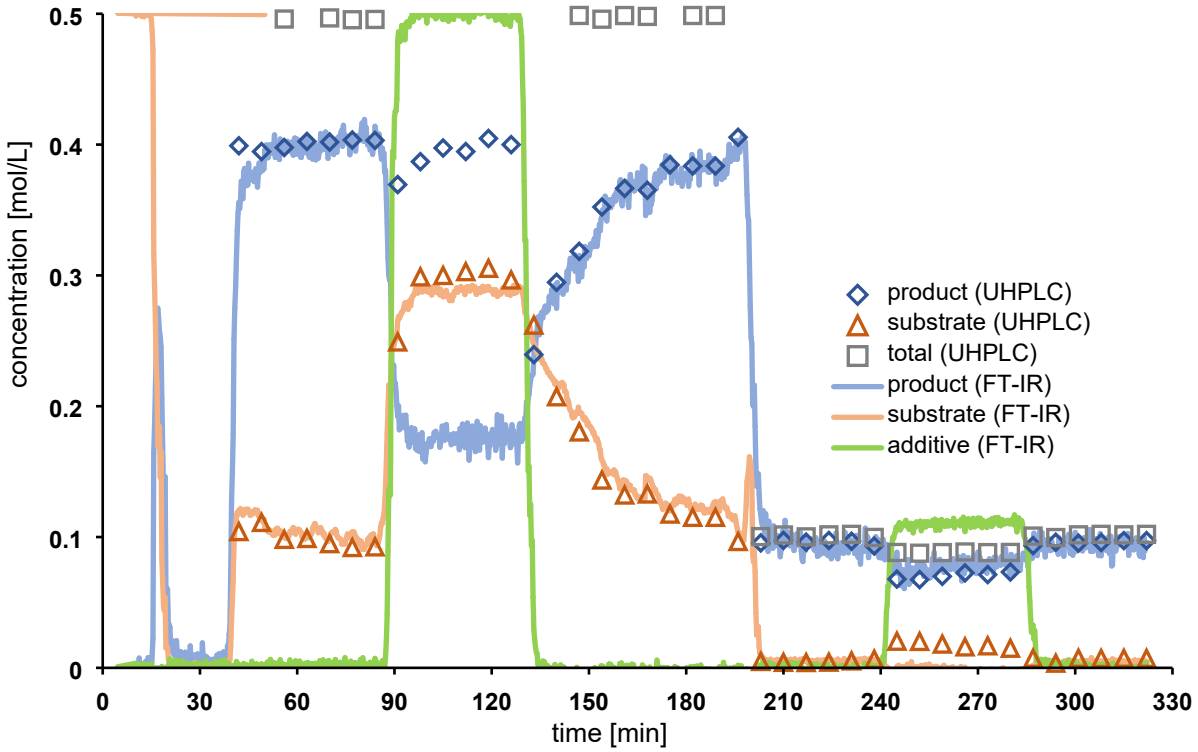

Figure S28. Screening of DBU (**A5**); flow ramp A, control reaction lengthened by 4 UHPLC measurement points.

4.2.6. o-Toluidine (product)

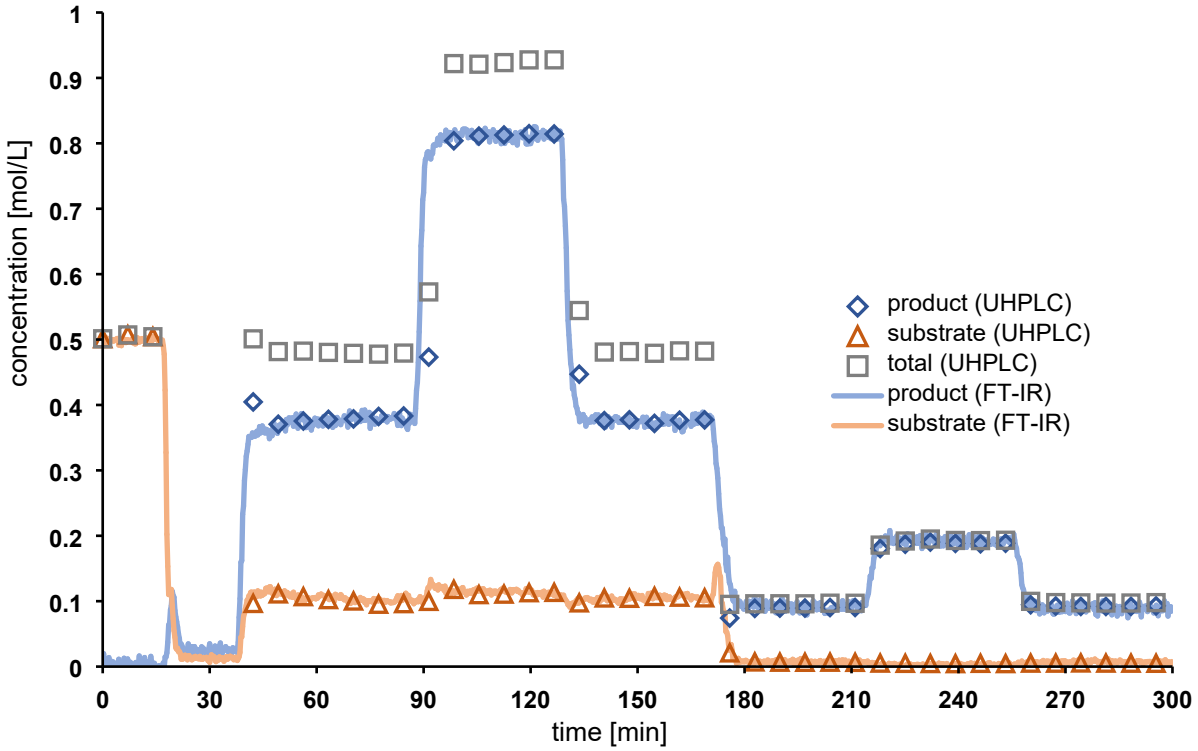

Figure S29. screening of o-toluidine (**A6, 2**); flow ramp A.

4.2.7. *N*-Methylimidazole

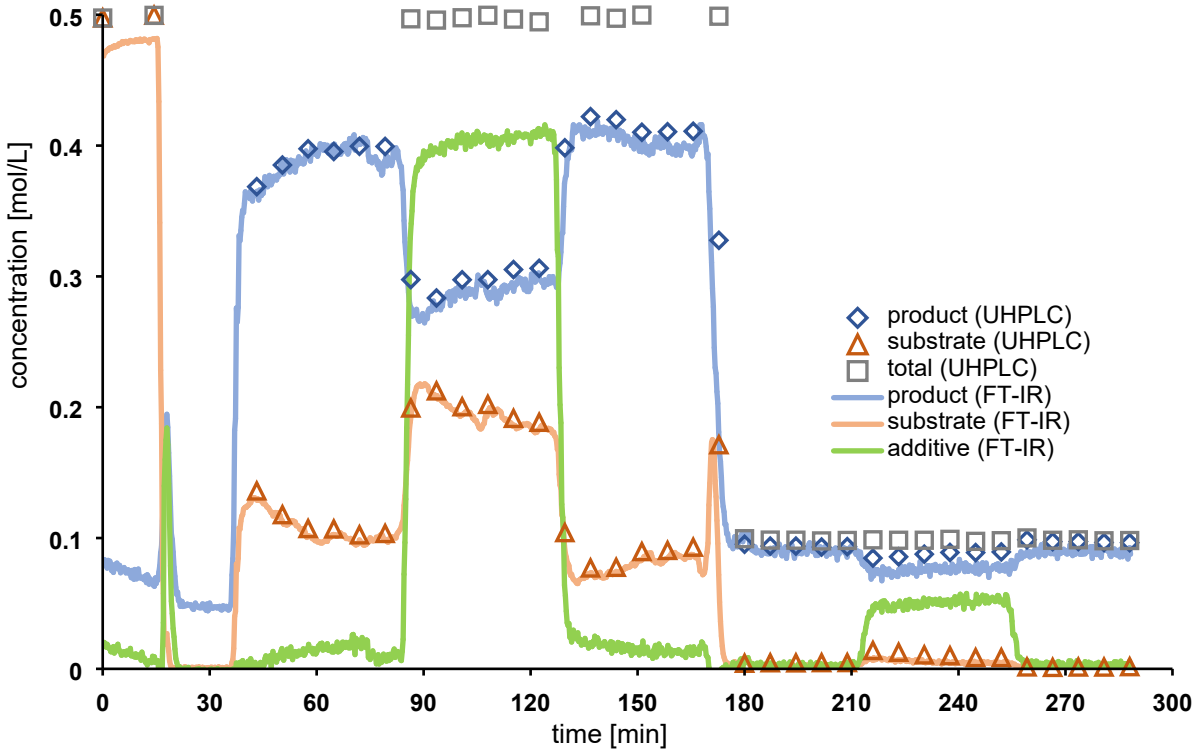

Figure S30. Screening of *N*-methylimidazole (**A7**), flow ramp A, last measurement missing.

4.2.8. 3,5-Lutidine

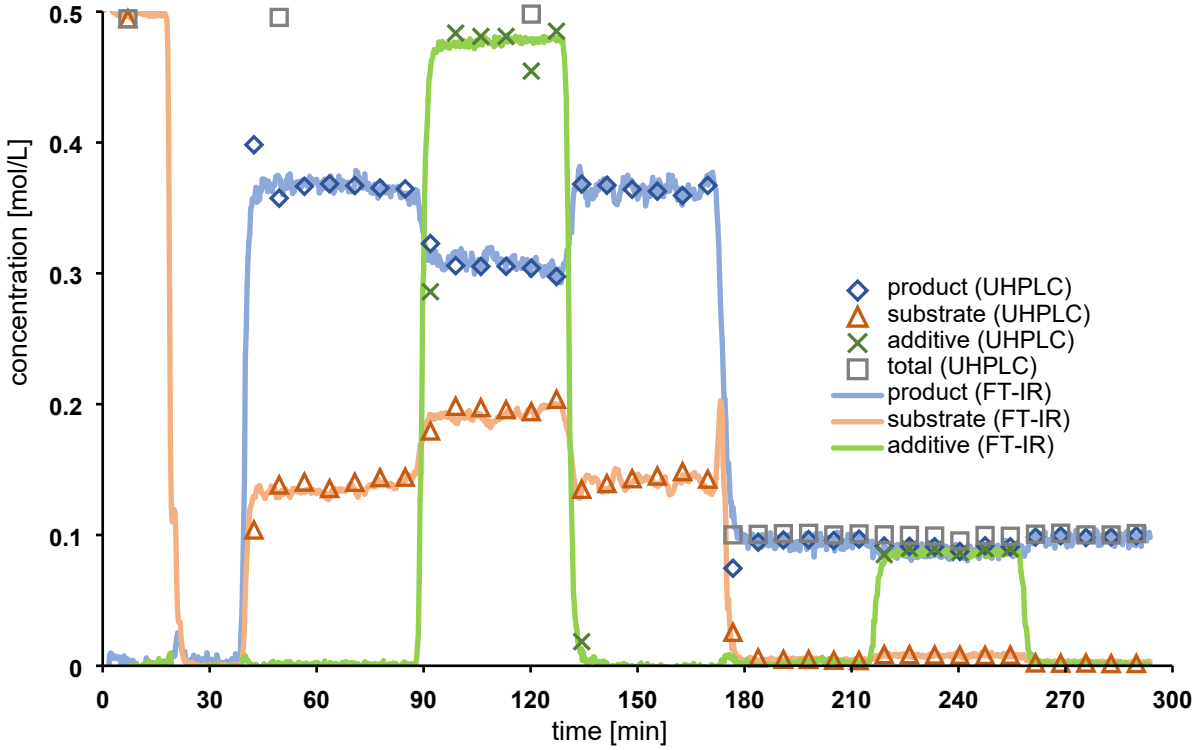

Figure S31. Screening of 3,5-lutidine (**A8**); flow ramp A, last UHPLC measurement missing.

4.2.9. Thiophenol

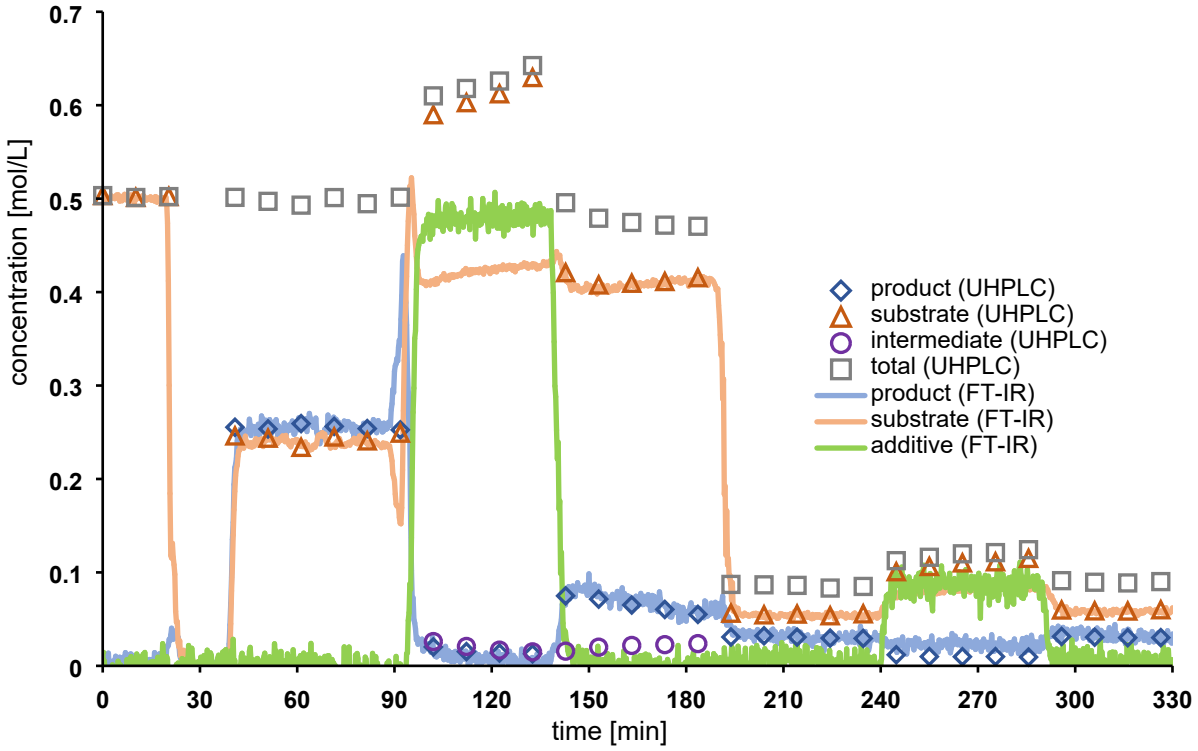

Figure S32. Screening of thiophenol (**A9**); flow ramp B.

4.2.10. Thioanisole

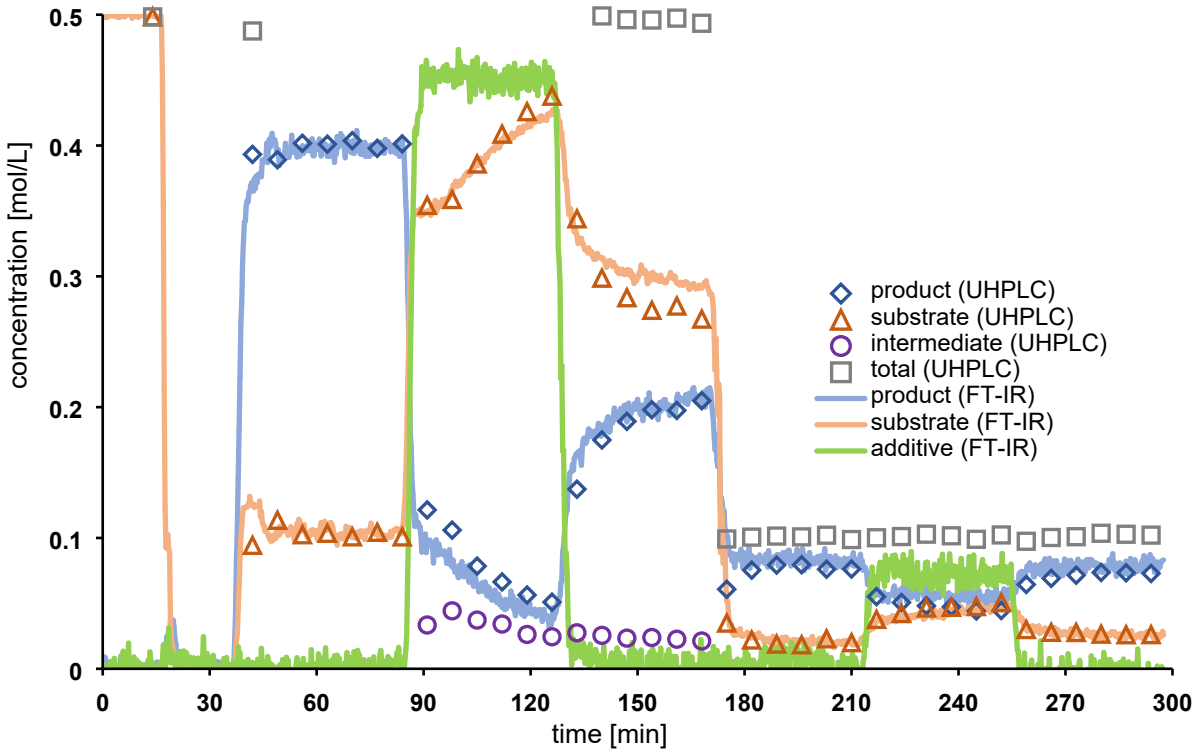

Figure S33. Screening of thioanisole (**A10**); flow ramp A.

4.2.11. Toluene

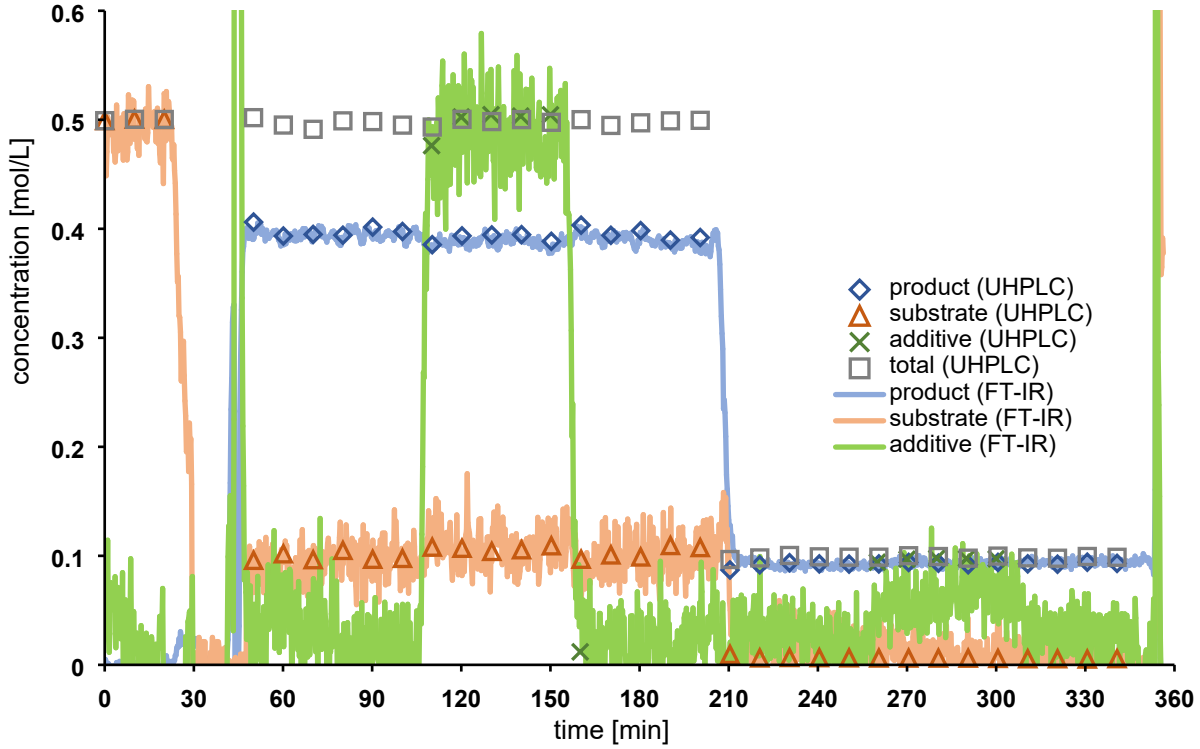

Figure S34. Screening of toluene (**A11**); flow ramp B, last UHPLC measurement point missing.

4.2.12. 2-Chlorotoluene (Pd/Al_2O_3)

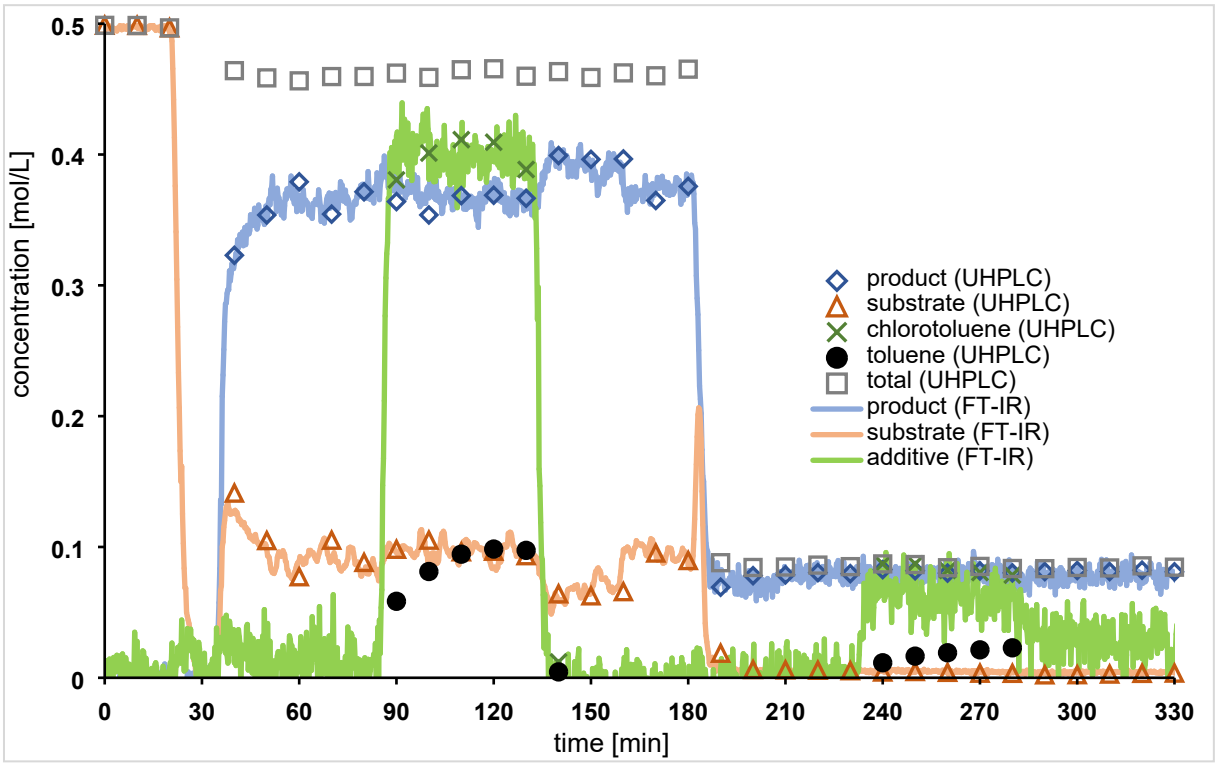

Figure S35. Screening of 2-chlorotoluene (**A12**) with Pd/Al_2O_3 CSM; flow ramp B.

4.2.13. 2-Chlorotoluene (Pt/Al_2O_3)

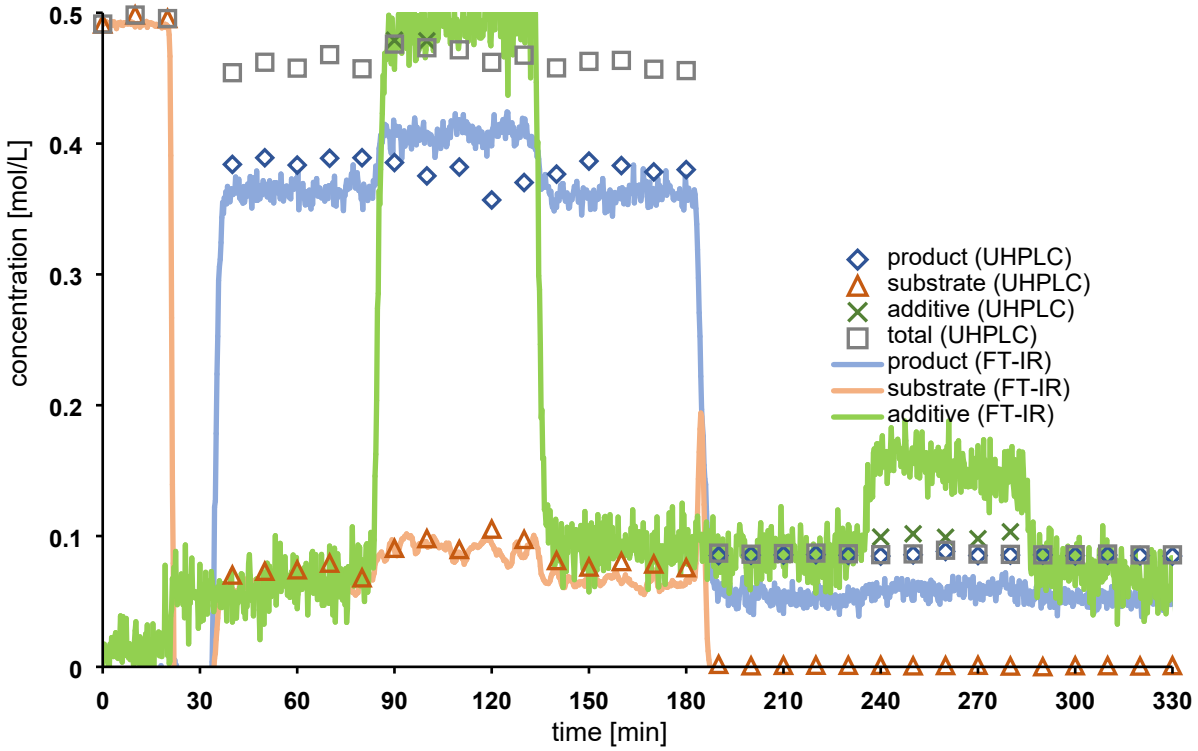

Figure S36. Screening of 2-chlorotoluene (**A12**) with Pt/Al_2O_3 CSM; flow ramp B.

4.2.14. Water

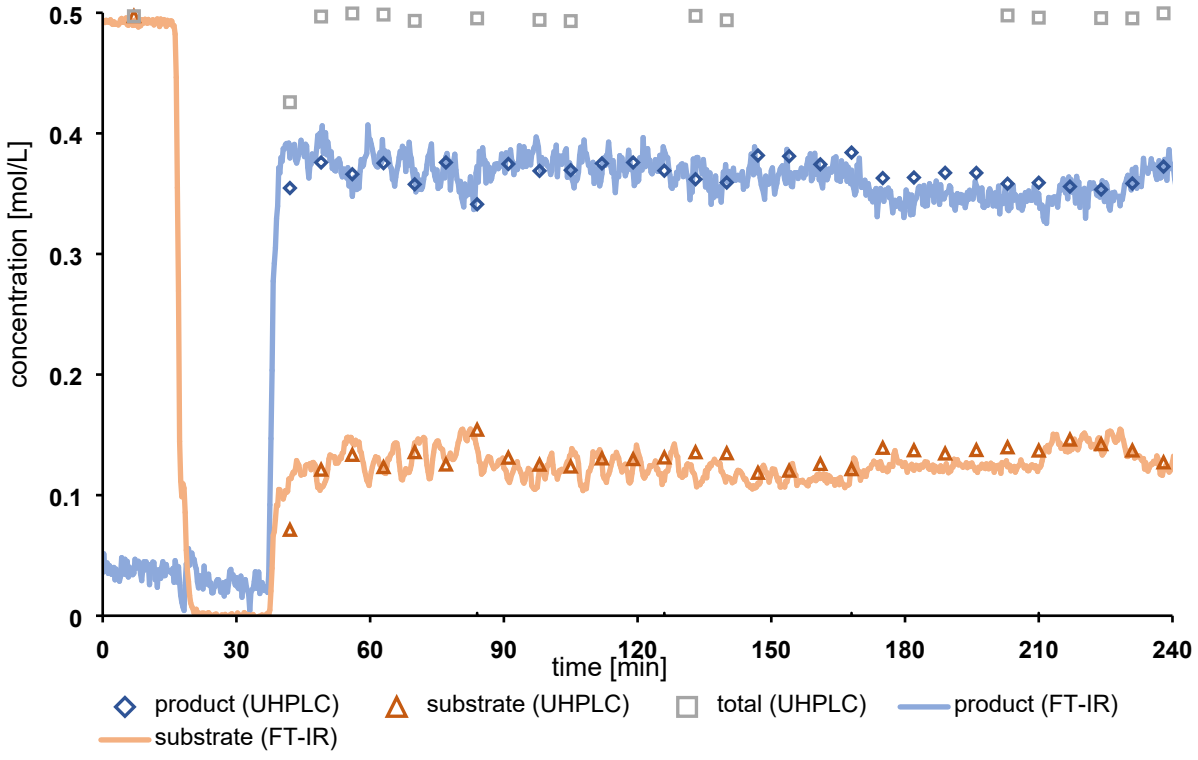

Figure S37. Screening of reaction using water as an additive at 0, 1, 3, 5, 0 equivalents.

4.3. Summarized results

4.3.1. Comparison dehalogenation

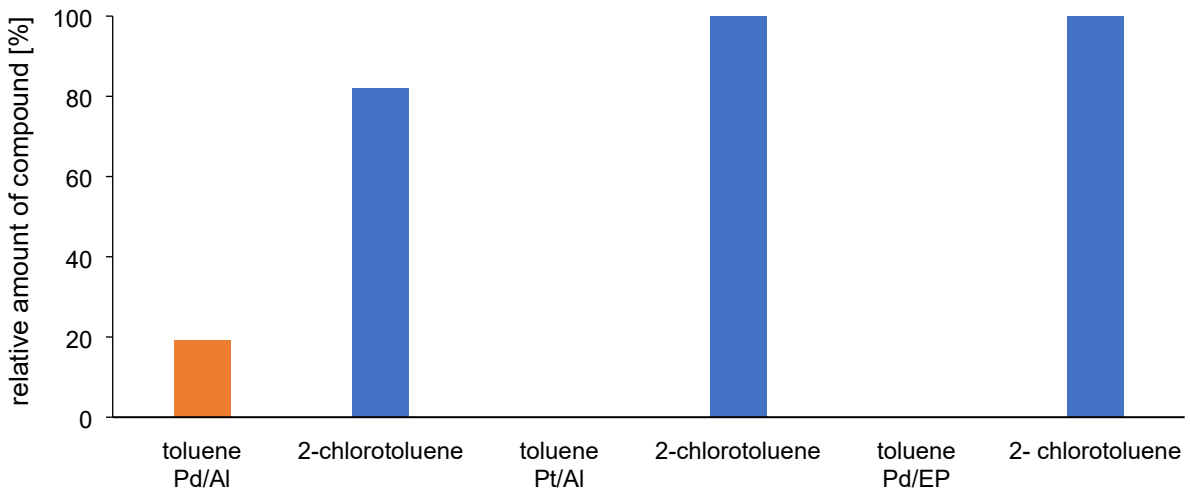

Figure S38. Relative amount of toluene and 2-chlorotoluene detected when using 2-chlorotoluene as additive with different catalysts (Pd/Al_2O_3, Pt/Al_2O_3 and Pd/EP).

5. References

(1) Hornung, C. H.; Nguyen, X.; Carafa, A.; Gardiner, J.; Urban, A.; Fraser, D.; Horne, M. D.; Gunasegaram, D. R.; Tsanaktsidis, J. Use of Catalytic Static Mixers for Continuous Flow Gas-Liquid and Transfer Hydrogenations in Organic Synthesis. *Organic Process Research and Development* **2017**, *21*, 1311–1319. https://doi.org/10.1021/acs.oprd.7b00180.

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(3) Avril, A.; Hornung, C. H.; Urban, A.; Fraser, D.; Horne, M.; Veder, J. P.; Tsanaktsidis, J.; Rodopoulos, T.; Henry, C.; Gunasegaram, D. R. Continuous Flow Hydrogenations Using Novel Catalytic Static Mixers inside a Tubular Reactor. *Reaction Chemistry and Engineering* **2017**, *2*, 180–188. https://doi.org/10.1039/c6re00188b.

(4) Hornung, C. H.; Singh, S.; Saubern, S. Additive Layer Manufacturing of Catalytic Static Mixers for Continuous Flow Reactors. *Johnson Matthey Technology Review* **2018**, *62*, 350–360. https://doi.org/10.1595/205651318X696846.

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(6) Nguyen, X.; Carafa, A.; Hornung, C. H. Hydrogenation of Vinyl Acetate Using a Continuous Flow Tubular Reactor with Catalytic Static Mixers. *Chemical Engineering and Processing: Process Intensification* **2018**, *124*, 215–221. https://doi.org/10.1016/j.cep.2017.12.007.