Supporting Information

On-chip integration of organic synthesis and HPLC/MS analysis for monitoring stereoselective transformations at the micro-scale

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1 Chemicals

The following table lists all chemicals used in this work. All chemicals were used as received without further purification.

Table SI-1. Used chemicals, purities and manufacturers.

Chemical	Purity	Source
Methanol	>99%	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
n-Heptane	p. A.	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
Chloroform	p. A.	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
n-Hexane		
Water	purified	Smart2Pure water purifying system (18.2 MΩ·cm, TKA Wasseraufarbeitungssysteme GmbH, Niederelbert, Germany
Acetonitrile	>99%	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
Propan-2-ol	99.5%	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
2-Methylpropan-2-ol	>99%	Fluka, Buchs, Switzerland
2-Methyl-2-Butanol	99%	Sigma Aldrich, Steinheim, Germany
Formic acid(FA)	98%	Carl Roth GmbH + Co. KG, Karlsruhe, Germany
Trifluoroacetic acid (TFA)	>99.8%	Merck, Darmstadt, Germany
Ethylendiaminediacetate (EDDA)	98%	Sigma Aldrich, Steinheim, Germany
2,2-Dimethyl-1,3-dioxane-4,6-dione (**2**)	98%	Sigma Aldrich, Steinheim, Germany
(±)- Citronellal, (±)-3,7-Dimethyl-6-octenal (**1**)	>95%	Sigma Aldrich, Steinheim, Germany
trans–Cinnamaldehyde (**5**)	99%	Sigma Aldrich, Steinheim, Germany
1,3-Butanediol diacrylate	99%	Sigma Aldrich, Steinheim, Germany
Butyl acrylate	>99%	Sigma Aldrich, Steinheim, Germany
3-(Trimethyoxysilyl)propylmethacrylate	98%	Sigma Aldrich, Steinheim, Germany
N-methyl pyrrole (**4**)	99%	Sigma Aldrich, Steinheim, Germany
Chiral imidazolidinone-based organocatalysts (**6** and **8**)	97%	Sigma Aldrich, Steinheim, Germany
2,2-Dimethoxy-2-phenylacetophenone	99%	Sigma Aldrich, Steinheim, Germany

Trichloro(1H,1H,2H,2H-perfluorooctyl)silane	97%	Sigma Aldrich, Steinheim, Germany

2 Materials, equipment and software

The following table lists all instrumental parts and equipment for the microfluidic operation. Furthermore, the software for instrument control and data evaluation is listed below.

Table SI-2. Materials and equipment.

Device, material	Source
ProntoSIL C18 SH, 5 µm and 3 µm	BISCHOFF Analysentechnik u.-geraete GmbH, Leonberg, Germany
Chiralpak IA-5, 5 µm	Chiral Technologies Europe, Daicel Corp., Osaka, Japan
Agilent 1260 infinity binary LC-System	Agilent Technologies Inc., Santa Clara, United States
neMESYS high pressure modules with cetoni 2.5 mL steel syringes	cetoni GmbH, Korbußen, Germany
10-port valve C72MPKH-4670ED	VICI AG International, Schenkon, Switzerland
PEEK capillary tubing (50, 75, and 125 µm inner and 360 µm outer diameter, TPK.102, TPK.103, TPK.105)	VICI AG International, Schenkon, Switzerland
ferrules (N-123-04)	Upchurch Scientific, IDEX Health & Science LLC, United States
headless nuts PEEK-screws (F-123H)	Upchurch Scientific, IDEX Health & Science LLC, United States
home-built steel clamp-system	From collaboration with the Mainz Institute of Microtechnology, Mainz, Germany
fused-silica capillary tubing (20 µm inner and 360 µm outer diameter)	CS-Chromatographie Service GmbH, Langerwehe, Germany
inline HPLC pressure meter	Duratec Analysentechnik GmbH, Hockenheim, Germany
in-linefilters (9085-20-10)	Upchurch Scientific, IDEX Health & Science LLC, United States
bulk-head unions (M-432)	Upchurch Scientific, IDEX Health & Science LLC, United States

tees (P-775)	Upchurch Scientific, IDEX Health & Science LLC, United States
sleeves (F-230)	Upchurch Scientific, IDEX Health & Science LLC, United States
nuts (F-130)	Upchurch Scientific, IDEX Health & Science LLC, United States
Stainless steel tees (JR-ZT1C)	VICI AG International, Schenkon, Switzerland
crosses (JR-ZX1C)	VICI AG International, Schenkon, Switzerland
5-, 10-, 20-, 40-fold magnification objective (LUCPlanFLN)	Olympus Deutschland GmbH, Hamburg, Germany
100 W mecury discharge burner (U-LH100HG)	Olympus, Deutschland GmbH, Hamburg, Germany
band-passfilter (350/50)	AHF Analysentechnik AG, Tübingen, Germany
long-passfilter (>390 nm)	AHF Analysentechnik AG, Tübingen, Germany
Dichroic mirror (380 nm)	AHF Analysentechnik AG, Tübingen, Germany
Bruker micrOTOF III with NanoSprayAdapterset for Apollo II	BrukerDaltonik GmbH, Bremen, Germany
Agilent 6150 Quadrupole with nanoESI spray shield	Agilent Technologies Inc., Santa Clara, United states
XYZ linear translation stages (PY005/M - Compact Five-Axis Platform, Metric and XYZ Three-Axis Miniature Translation Stage, 1/2" Travel, T12XYZ/M)	Thorlabs GmbH Dachau/Munich, Germany
Color bullet camera (19 mm)	KJL Sicherheitssysteme GmbH & Co.KG, Hamburg, Germany

The following table lists the software used for instrument control and data evaluation.

Table SI-3. Software.

Software	Source
Clarity 5.0.5.98	DataApex, Prague, Czech Republic
Origin Pro 8G	OriginLab Corporation, Northampton,

	USA
Microsoft office 2010	Microsoft Corporation, Redmond, USA
OpenLAB A.01.05	Agilent Technologies Inc., Santa Clara, USA
Otof Control 3.4	BrukerDaltonik GmbH, Germany
HyStar 3.2	BrukerDaltonik GmbH, Germany
Data analysis 4.3	BrukerDaltonik GmbH, Germany
neMESYS Use Interface 2.6.0.4	cetoni GmbH, Korbußen, GERMANY

3 Dimensions and modifications of the borosilicate microchips

The glass chips were made out of borosilicate glass (BF33) produced by iX factory (Dortmund, Germany) according to our designs. The chips were made by common photolithography, wet-etching and bonding techniques. The chips were diced with a wafer saw to dimensions of 10 mm to 45 mm with a thickness of 2.2 mm and all the channels are 155 µm wide and 45 µm deep, except for the column outlet channel and two (about 150 µm length) narrowings for better porous polymer frit attachment at both sides of the column compartment which had a channel width of 130 µm at an equal depth of 45 µm. Furthermore, in the cover slide seven powder blasted cones were included for fluidic contacting. The nominal volume of such cones was 2.2 µL, however the homemade steel clamp system was used for direct fluidic interfacing to the etched microchannel structure with negligible band broadening effects (dead volume ~60 nL). The layout of the chip is shown in figure SI-1.

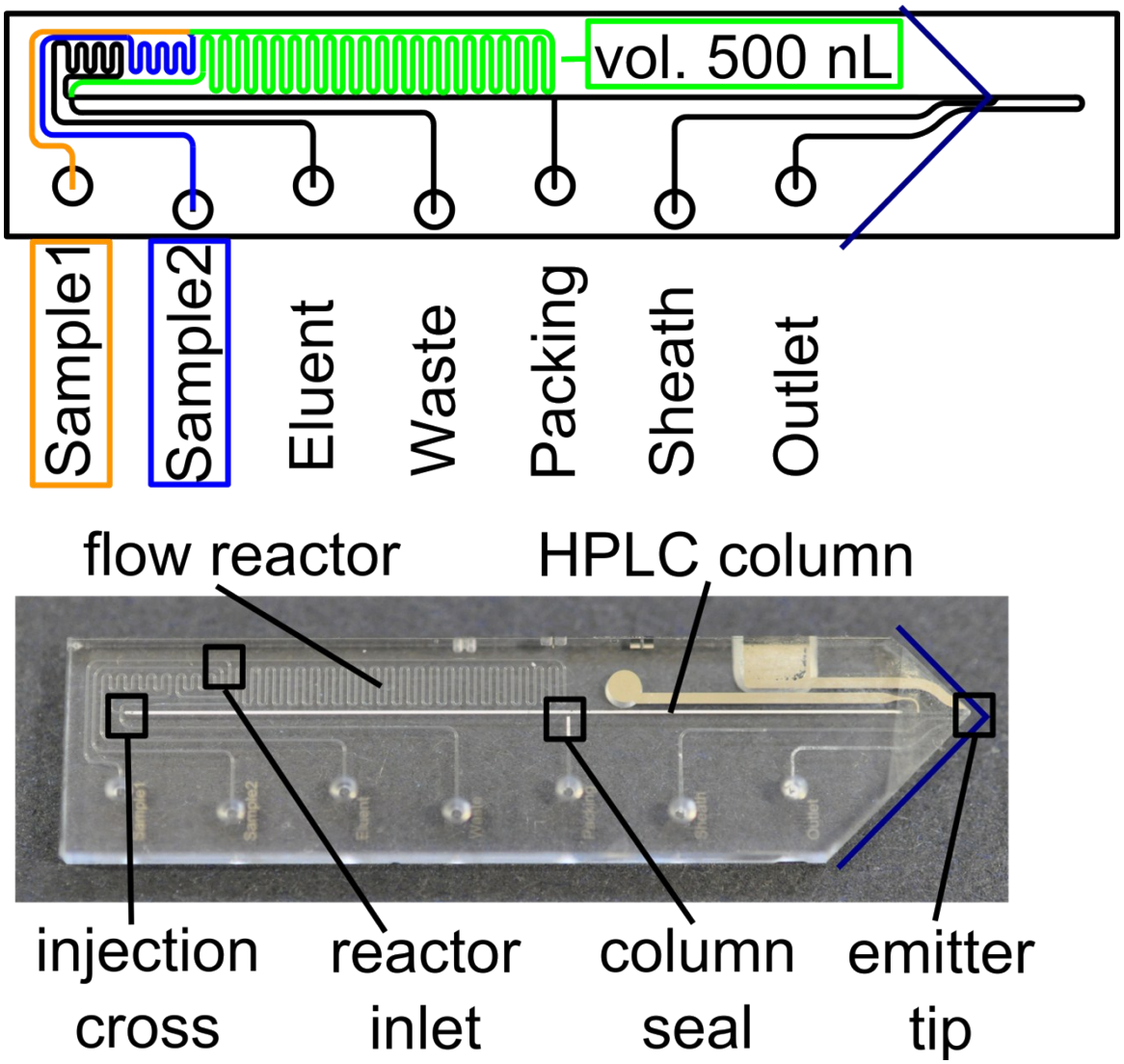


Figure SI-1. General chip layout. *Top* Schematic representation of the chip layout with all seven fluidic connection ports. Sheath and outlet channel are not used in this work. The packing channel is for the column generation process only and is sealed with a photopolymerized polymer plug. *Bottom* Photograph of the packed chip with the grinded and hydrophobized emitter tip.

4 Chip CF/stop-flow-HPLC-ESI-MS experiments

4.1 Experimental setup

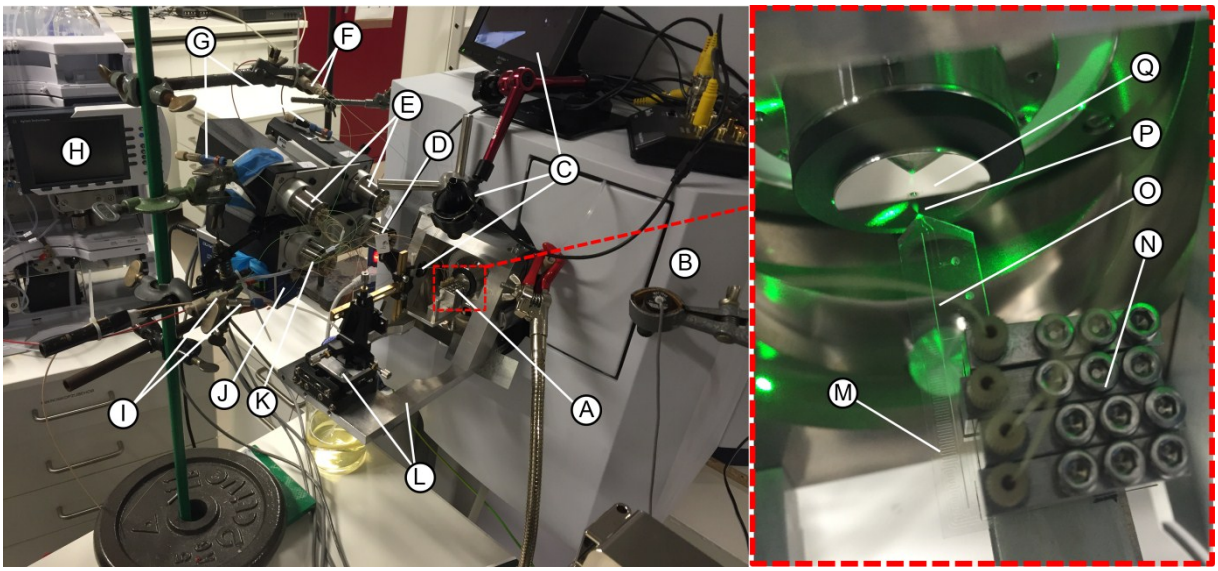


Figure SI-2. Photograph of the experimental setup in front of the mass spectrometer. A) Chip with home-built steel connection clamps and capillary PEEK-tubing, B) mass spectrometer micrOTOF III with NanoSpray adapter set, C) cameras and monitor for chip positioning, D) optional 10-port valve for the stop-flow-mode (valve "A" in schematic stop-flow overview), E) both injection valves for sample 1 and sample 2 (loop dimensions: 3.68 µL, 300 mm length, 125 µm inner diameter (ID), 360 µm outer diameter (OD) PEEK capillary tubing), F) sample pump inlets (high-pressure syringe pumps with 2.5 mL steel syringes), G) needleports for sample injection into each loop, H) elution pump (binary HPLC pump with degasser), I) pinch (high-pressure syringe pump with 2.5 mL steel syringes) and eluent pump inlets, J) pressure meter, K) main 10-port valve (valve "B" in schematic all drawings), L) multiaxis translational microstages and homebuilt instrumental platform. Insert on the right with a closer look on part (A): M) reaction structure, N) home-built high-pressure steel connection claps, O) microfabricated HPLC column, P) grinded and hydrophobized emitter tip, Q) MS inlet with nanoESI spray shield. The nano-ESI spray was illuminated with a laser pointer (523±10 nm;<5 mW) for visualization purposes.

4.2 Chip-MS interfacing

Experimental conditions:

For positioning of the chip in front of the spray shield two XYZ linear translation stages (PY005/M - Compact Five-Axis Platform, Metric and XYZ Three-Axis Miniature Translation Stage, 1/2" Travel, T12XYZ/M - Thorlabs) and two cameras (KJL Sicherheitssysteme GmbH & Co.KG, Hamburg, Germany) were used. The on-chip emitter was held at ground potential over liquid contact at the metal parts of the valves, while the orifice of the Bruker MicrOTOF III mass spectrometer (or the Agilent 6150 Quadrupole mass spectrometer) was set to a capillary voltage of 4000 V (3000 V for the Agilent mass spec). The chip-to-spray shield distance was approximately 2 mm. The MS was used in TOF-only mode (for the Bruker MS), with 4 $L \cdot min^{-1}$ drying gas, 350°C dry gas temperature, 50 to 600 m/z (50-500 m/z – Agilent) mass range and an acquisition rate of 3 spectra per second.

Emitter integration:
To hyphenate the microchip LC a sheathless nano electrospray emitter was integrated at the column outlet by grinding open the outlet channel after the column from both sides until the outlet of the separation channel was in the middle of the tip. After that the tip was also flattened by grinding off the top and the bottom slide, to generate a pyramidal emitter tip. To reduce wetting of the glass emitter surface and hence reduce extra-column swept volumes for the nanoESI coupling, the emitter tip was hydrophobized. To do that, the tip surface was first activated with 1 M NaOH for 30 min while pumping MeOH through the column at a very low flowrate to protect the phase material from the basic solution. Afterwards, the tip was washed with H_2O, isopropanol (IPA) and hexane prior to hydrophobization by immersion of the tip in a silanization reagent consisting of 10 vol% trichloro(1H,1H,2H,2H-perfluoro-octyl)silane in 80/20 vol% heptane/chloroform for 10 min. During this process hexane was pumped continuously through the chip to avoid a silanization inside the chip. With this technique a hydrophobization was achieved with a contact angle for aqueous solutions of around 90° (visually evaluated) at the grinded emitter tip.

4.3 Microfluidic setup continuous flow mode

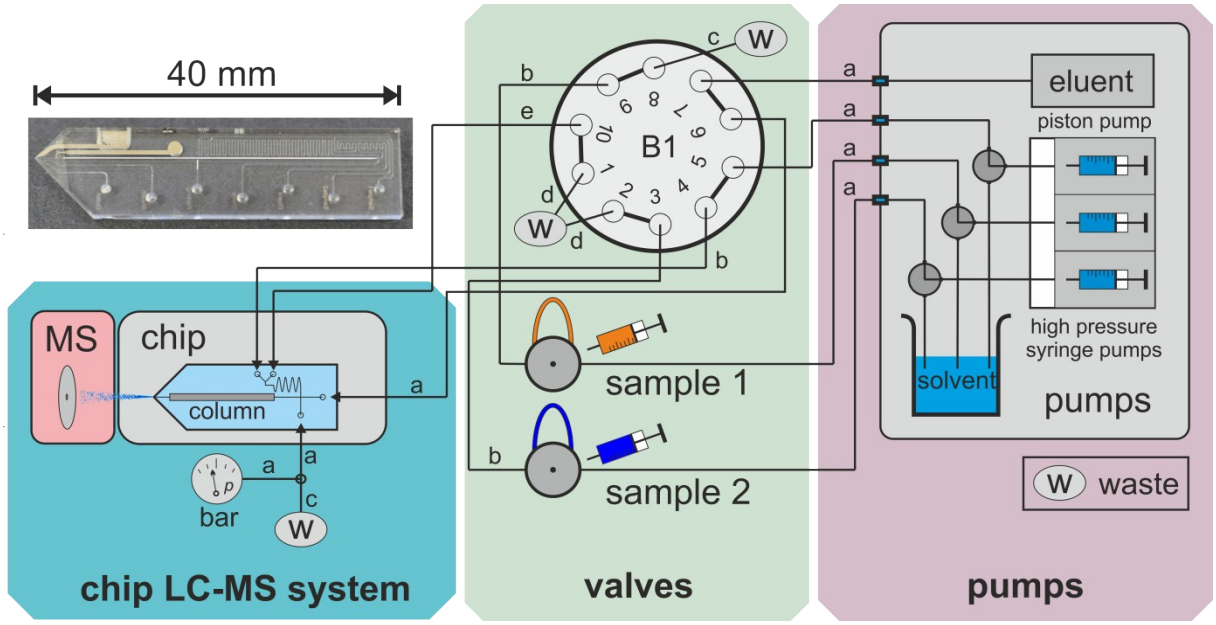


Figure SI-3. Schematic overview of the microfluidic setup for the continuous flow mode. The main 10-port valve is in elution mode (Valve B in Position 1 – "B1"), where the elution pump is delivering elution solvent to the column head. The high-pressure syringe pumps were connected to the microfluidic circuitry with 1/16" PEEK tubing with 120 µm ID, inline filters (2 µm SST frit) and adapters to fit 360 µm OD PEEK capillary tubing (all in grey box on the right). The remaining microfluidic setup consisted of 360 µm OD PEEK capillary tubing of differing IDs and lengths: a) 75 µm, 20 cm; b) 50 µm 15 cm; c) 50 µm 60 cm; d) 50 µm 30 cm; e) 50 µm 13.5 cm. The injection loops each had a volume of 3.68 µL.

A typical injection in continuous flow mode is based on a time profile. Starting the data acquisition at time point t = 0s, the two injection valves are switched to inject at t = 5s. At t = 10 s, the main valve is switched to *injection mode* (valve B in Position 2, connecting port 1 and 2) and transferring the sample solutions to and through the reactor and infusing the reactor outlet onto the column head. At t = 15 s the main valve is switched back to *elution mode* (Valve B in Position 1 – "B1"), the flow reactor is flushed backwards and the sample plug is eluted over the column.

4.4 Conversion in relation to reactor residence time

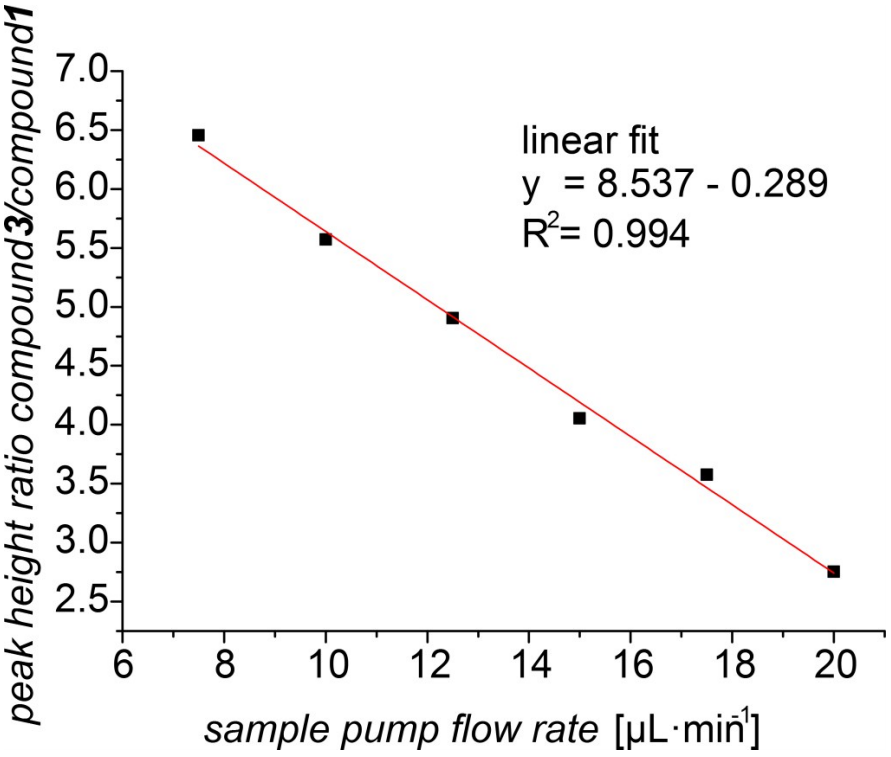


Figure SI-4. Evaluation of conversation of reaction A (scheme 1) by the EIC peak height ratio of product **3** to starting material **1** at varying sample pump flow rates for continuous flow mode(on-chip reaction and separation). Column: BISCHOFF ProntoSIL C18 SH, 5 µm, 35 mm. Mobile phase: 300 µL/min, MeOH/H_2O (70/30) with 0.1% formic acid. Sample pumps: 7.5-20 µL/min, MeOH/H_2O (80/20 vol%). Pinch: 7.5-20 µL/min, MeOH/H_2O (50/50 vol%).

4.5 Catalyst screening experiments

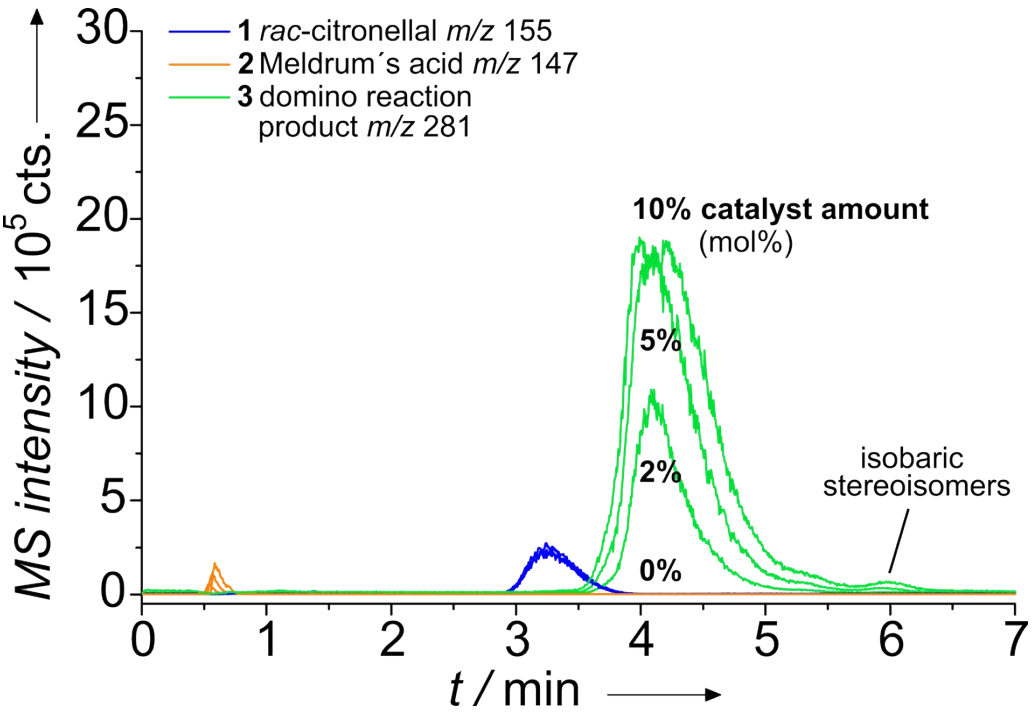


Figure SI-5. Overlaid extracted ion chromatograms for the catalyst activity screening (domino reaction - reaction time each 10.0 s, reactor volume approx. 500 nl). Column: ProntoSIL C18 SH, particle diameter 5 µm, length 35 mm. Mobile phase: 200 µl·min^{-1}, MeOH/H_2O (70/30vol% with 0.1% formic acid), sample pumps: 10 µl·min^{-1}, MeOH/H_2O (80/20 vol%), pinch: 10 µl·min^{-1}, MeOH/H_2O (50/50 vol% with 0.1% formic acid). 13 bar elution pressure at the injection cross at a linear flow rate of 1.18 mm·s^{-1} over the column. Reactant inlet A: **1** (0.1 mol·l^{-1}), reactant inlet B: **2** (0.12 mol·l^{-1}), 0-10 mol% (in relation to **2**) EDDA each in MeOH/H_2O (80/20 vol%).

4.6 Microfluidic setup stop-flow mode

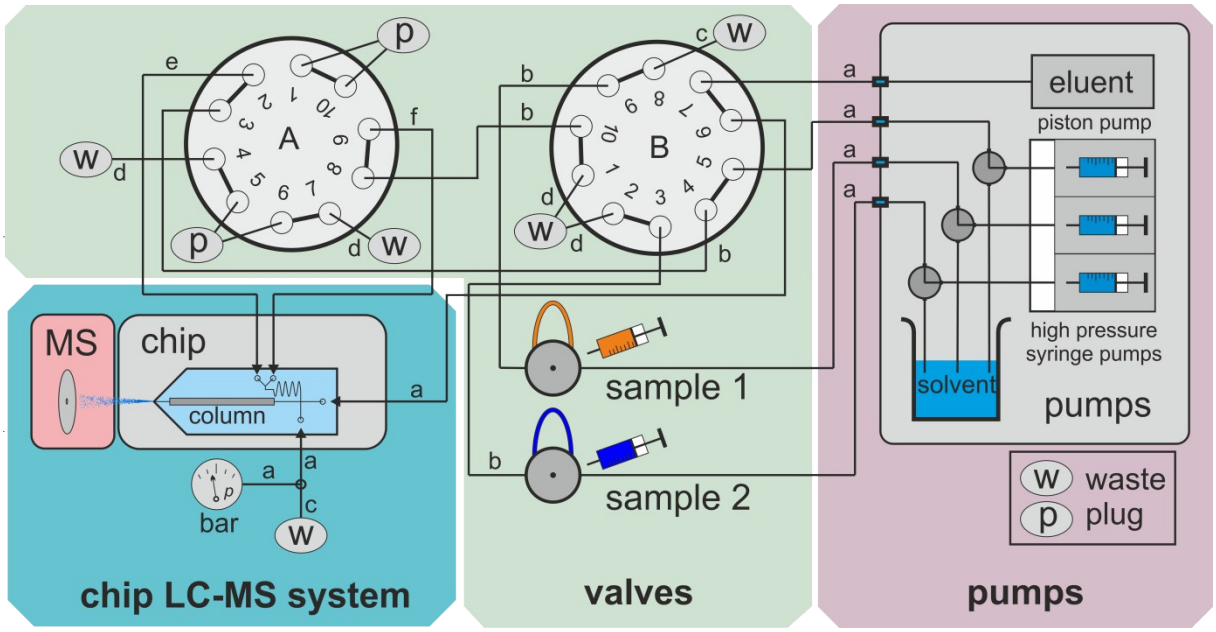


Figure SI-6. Schematic overview of the microfluidic setup for the stop-flow mode. The high-pressure syringe pumps were connected to the microfluidic circuitry with 1/16" PEEK tubing with 120 µm ID, inline filters (2 µm SST frit) and adapters to fit 360 µm OD PEEK capillary tubing (all in grey box on the right). The remaining microfluidic setup consisted of 360 µm OD PEEK capillary tubing of differing IDs and lengths: a) 75 µm, 20 cm; b) 50 µm 15 cm; c) 50 µm 60 cm; d) 50 µm 30 cm; e) 50 µm 13 cm; f) 50 µm 14.5 cm. The injection loops each had a volume of 3.68 µL.

4.7 Mixing efficiency

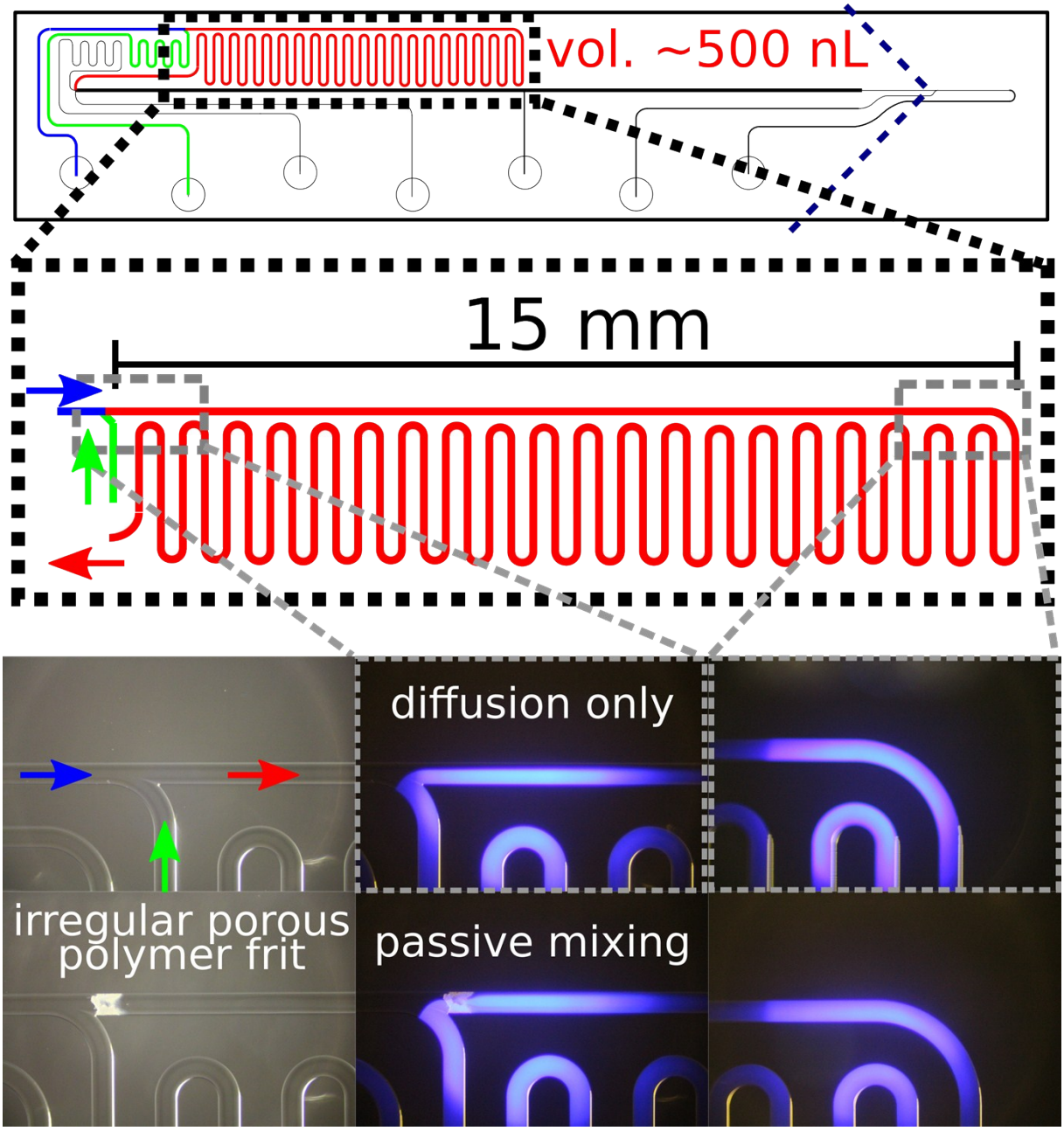
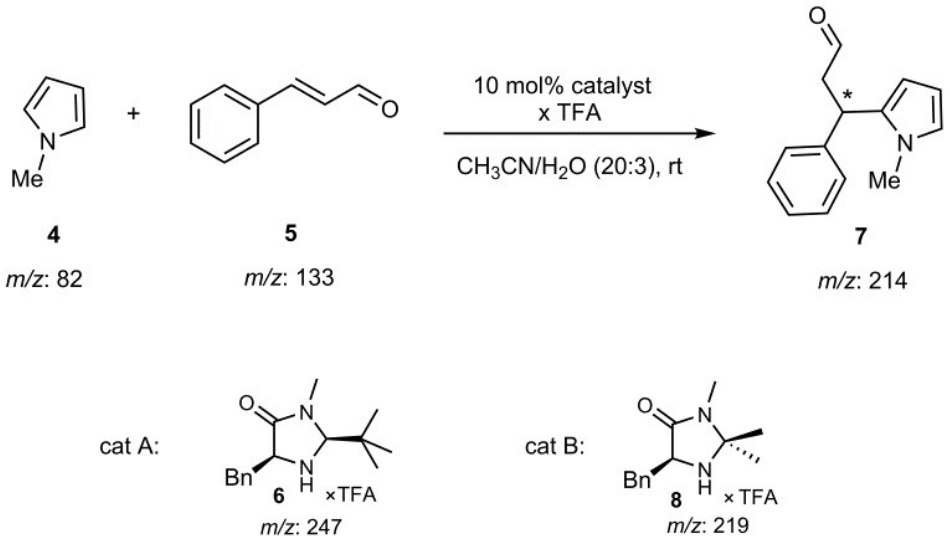


Figure SI-7. Examination of the mixing efficiency in the meandering reactor compartment. A schematic layout of the chip with both sample inlets (blue and green) and the reactor compartment (red) is shown in the top. A close up of the reactor part with directions of flow at the reactor inlet and outlet is shown in the middle. At the bottom two rows of micrographs compare the mixing efficiency of diffusion based (upper row) and passive (lower row) mixing at the reactor inlet and the first turn structure after about 15 mm of straight channel. For this experiments, sample 1 consisted of pure ACN whereas sample 2 was a 100 µg·ml^{-1} solution of Coumarin 120 in ACN. Both sample pumps were set to 10 µl·min^{-1}. While the passive mixing structure accelerates mixing, the diffusion based approach also ensures a rapid homogeneous distribution of sample within the whole channel due to short diffusive lengths even in a straight channel (in accordance with Stokes-Einstein-equation). Furthermore, the reactor design features 40 sharp U-turns to ensure complete mixing also for high molecular weight compounds like proteins.

4.8 Optical setup for fluorescence microscopy

5-, 10-, 20-, and 40-fold magnification objectives (Olympus Deutschland GmbH) were used for imaging at an inverted microscope (X71, Olympus). For excitation a high pressure mercury vapor lamp, a band-pass filter (350/50, AHF Analysentechnik AG, Tübingen, Germany) and a dichroic mirror (380 nm, AHF Analysentechnik AG) were used. The fluorescent light was filtered by a long-pass filter (>390 nm, AHF Analysentechnik AG).

4.9 Enantioselective iminium-catalyzed Friedel-Crafts alkylation



Scheme SI-1. Enantioselective iminium-catalyzed Friedel-Crafts alkylation of methyl pyrrole 4 and cinnamaldehyde (5) with imidazolidinone-based MacMillan catalysts 6 or 8 to generate a β-pyrrolyl aldehyde 7.

4.10 Column generation

To generate a particulate separation column inside a microfluidic glass chip (iX-factory GmbH, Dortmund, Germany) a protocol published by Thurmann et al.2014[1] for slurry packing stationary phase materials was applied. Briefly, the channels were flushed with 1 M NaOH for 30 min, with H_2O for 10 min and with EtOH for 10 min in that order to activate the silanole groups on the glass surface. After activation, 3-methacryloxylpropyltrimethoxysilane (γ-MAPS) was flushed through the chip for 30 min, prior to a 24 h silanization step. Then, the solution was removed from the chip by flushing with EtOH and then nitrogen. After flushing with casting solvent (20 vol% ethanol/ 60 vol% acetonitrile/ 20 vol% 5 mM phosphate buffer, pH 6.8), the pre-polymer solution (composition see table below) was introduced to the microchip and two porous polymer frits were photopolymerized into the microchannel by laser-induced polymerization at 355 nm (355 nm diode, Microtime 200, Picoquant GmbH, Germany, focused into the microchannel with a 40-fold objective (Olympus LUCPlanFLN 40x, Olympus Europa Holding GmbH, Germany) to define the column compartment. These frits, one in the beginning of the separation channel at the injection cross and one at the column outlet in the end of the separation channel, are keeping the porous particles inside the separation column. For the introduction of the frits, the chip was placed on a X-Y-table of an inverted microscope (X71, Olympus).
The following table lists the composition of the pre-polymer solution for the porous polymer monolithic (PPM) frits.

Table SI-4. Chemicals used for polymer monoliths

Substances
67 vol% casting solvent (20 vol% ethanol/ 60 vol% acetonitrile/ 20 vol% 5 mM phosphate buffer, pH 6.8)
16 vol% n-butyl acrylate
16.5 vol% 1,3-butandiol diacrylate
0.5 vol% 3-methacryloxylpropyltrimethoxysilane
2 wt% 2,2-dimethoxy-2-phenylacetophenone (DMPA)

After completion of the frits, the leftover monomer-slurry was thoroughly flushed out with casting solvent and EtOH, subsequently. In the next step, the microchip separation column was generated by a slurry packing procedure. For this reason the packing channel was connected to a six port valve with a loop (~3 mL) filled with a suspension (~10 $mg \cdot mL^{-1}$ in MeOH) containing particulate material e.g. ProntoSIL120-5-C18 SH (5 µm mean diameter, BISCHOFF Analysentechnik u.-geraete GmbH, Leonberg, Germany) or ChiralPak IA-5 (5 µm mean diameter, Daicel Corp., Osaka, Japan), respectively. The slurry was packed and compressed into the column compartment of the microchip during ultrasonication, applying a maximum pressure of 90 bar (170 bar for the 3 µm C18 material). After the stationary phase was compressed for 45 min and the system relaxed again, the packing channel was sealed *via* laser assisted photo polymerization. Here, the used monomer-slurry was slightly different compared to the one for the frit preparation (0.5 vol% 3-methacryloxylpropyltrimethoxysilane, 87.5 vol% ~~1,3-butandiol diacrylate, 12~~ vol% methanol and 2 wt% DMPA). The chip was flushed

[1] a) S. Thurmann, A. Dittmar, D. Belder, *J. Chromatogr. A* **2014**, *1340*, 59–67.

b) S. Thurmann, L. Mauritz, C. Heck, D. Belder, *J. Chromatogr. A* **2014**, *1370*, 33–39.

with the pre-polymer solution at 100 bar for 2 min (180 bar for the 3 µm C18 material). After relaxation the desired spots were irradiated with the pulsed 355 nm laser to immobilize the chip column without any dead volume by an in-situ generated polymer plug. The excess of monomer solution was removed by flushing with methanol.

4.11 Detailed stop-flow-principle for injection and elution

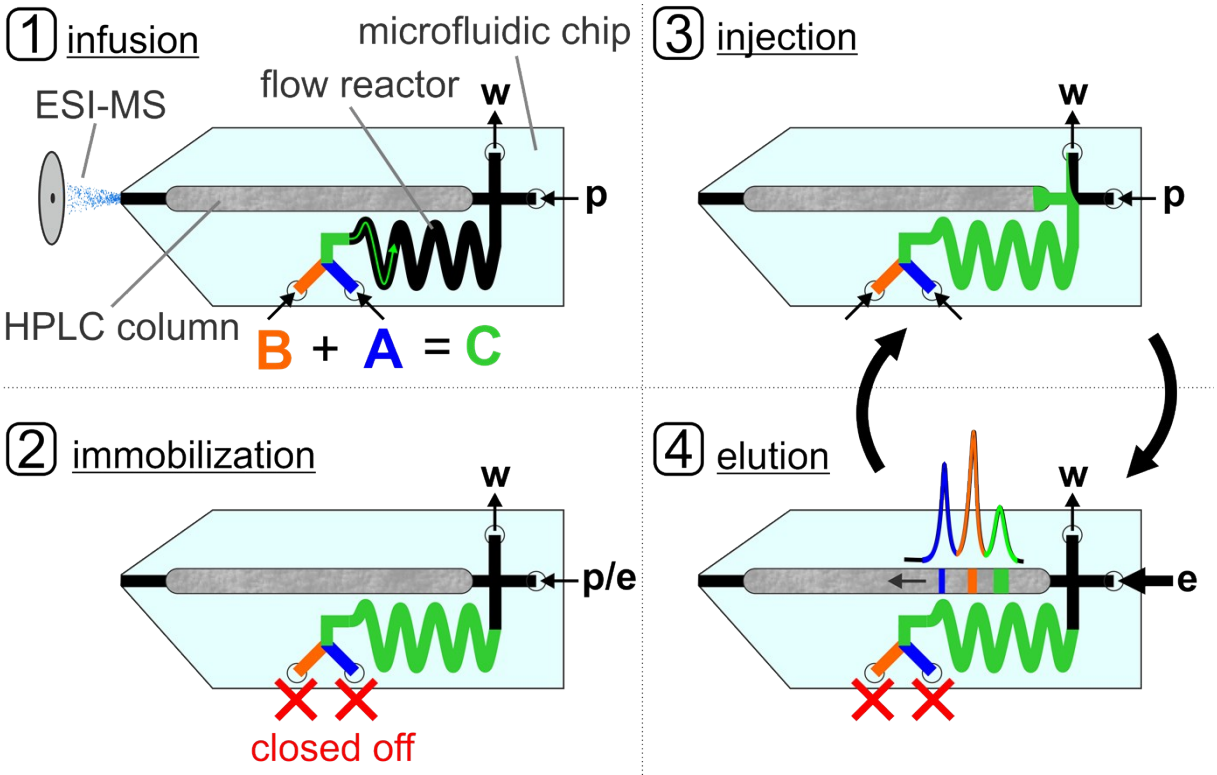


Figure SI-8. Operation principle of the *stop-flow* fluid handling. A detailed walk-through is presented in figures SI-9 to SI-14.

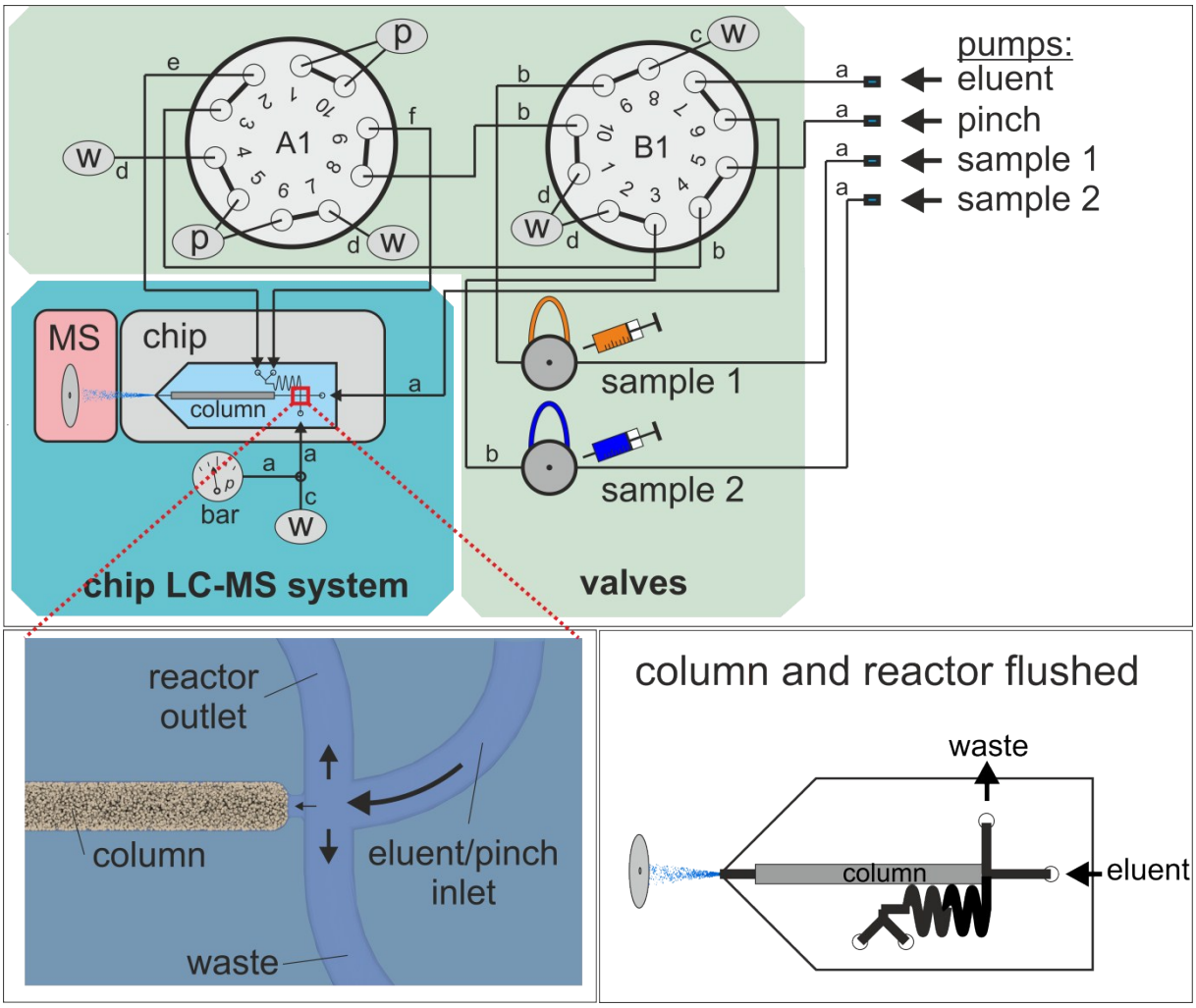


Figure SI-9. Operation principle of the stop-flow setup – staring point: *column and reactor flushing*. The box on the *top* describes the schematic microfluidic setup analogous to figure SI-4. The *bottom left* insert displays magnified illustration of the injection cross to visualize the injection process. The *bottom right* gives a simplified illustration of the current microfluidic situation in relation to the brief schematic in the main article (see figure 4). In this idle mode, the reactor and the column are flushed by both the elution and the pinch pump. The two sample solutions are loaded into the sample loops.

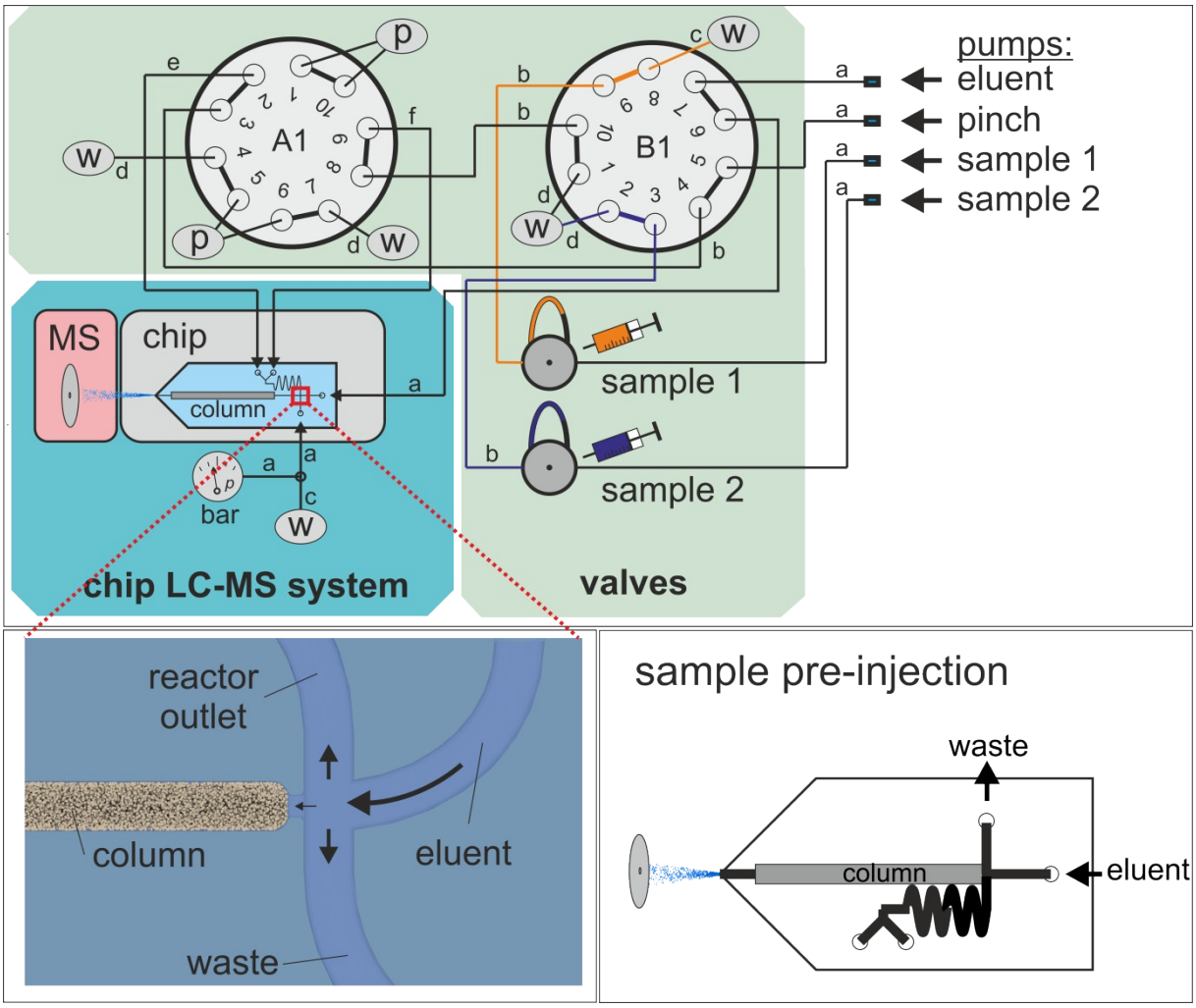


Figure SI-10. Operation principle of the stop-flow setup – step 2: *sample pre-injection or pre-infusion*. The two injection valves (sample1 and sample 2) are switched to inject mode simultaneously by electrical actuators. Meanwhile, the column and the reactor are still flushed since the main valve (B) and the auxiliary stop-flow-valve (A) each still remain in position 1.

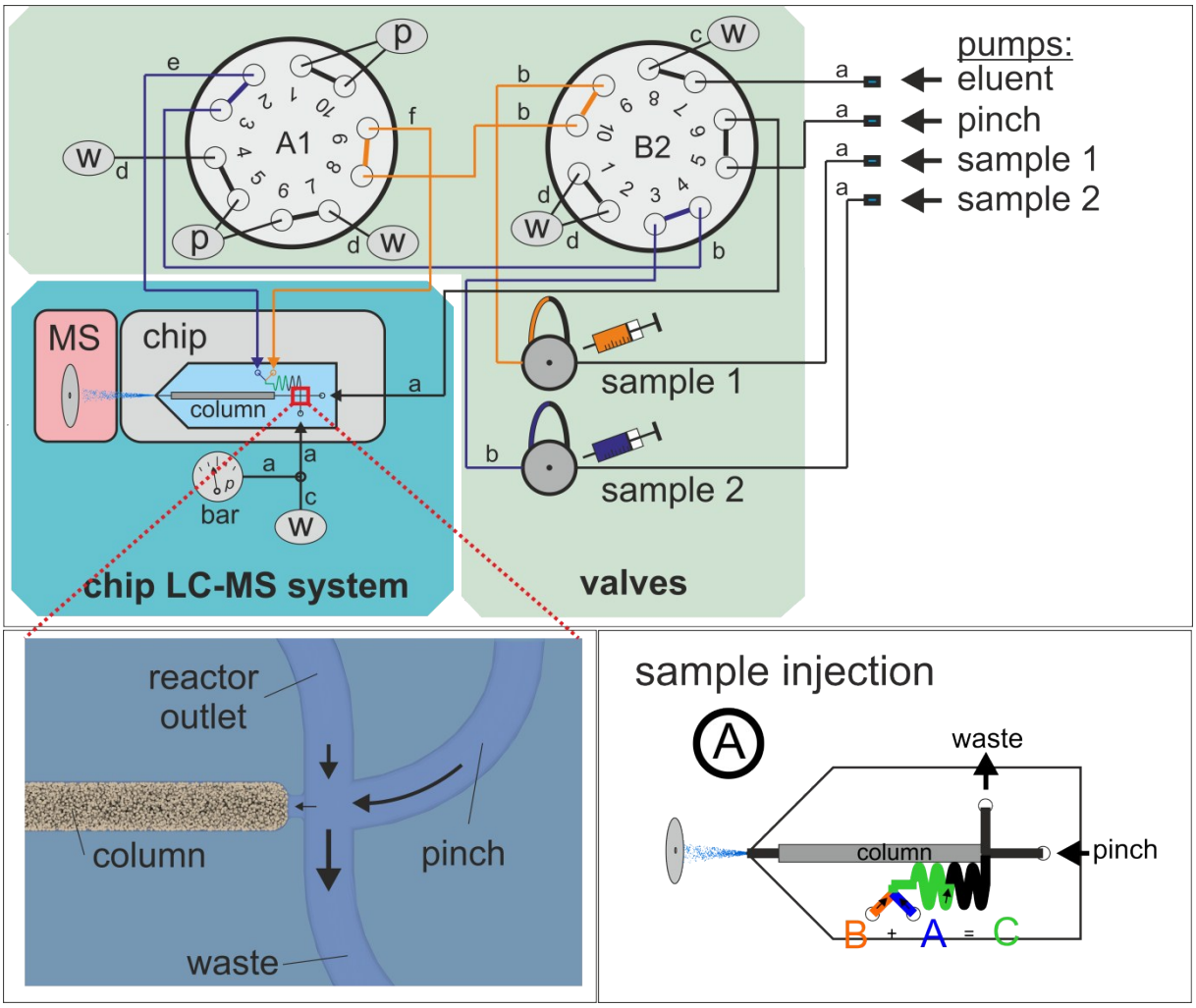


Figure SI-11. Operation principle of the stop-flow setup – step 3: *sample injection*. The main valve (B) is switched to position 2 and both sample streams are directed to the reactor. The slightly different swept volumes of the microfluidic channels for sample 1 and sample 2 are compensated for with differing capillary lengths (e) and (f). The adjustment checked by optical evaluation at the reactor inlet of injections of fluorescent sample solutions (1 µg·ml^{-1} Coumarin120 in 80/20 vol% MeOH/H_2O) independently from each sample loop as well as simultaneous injections from both loops.

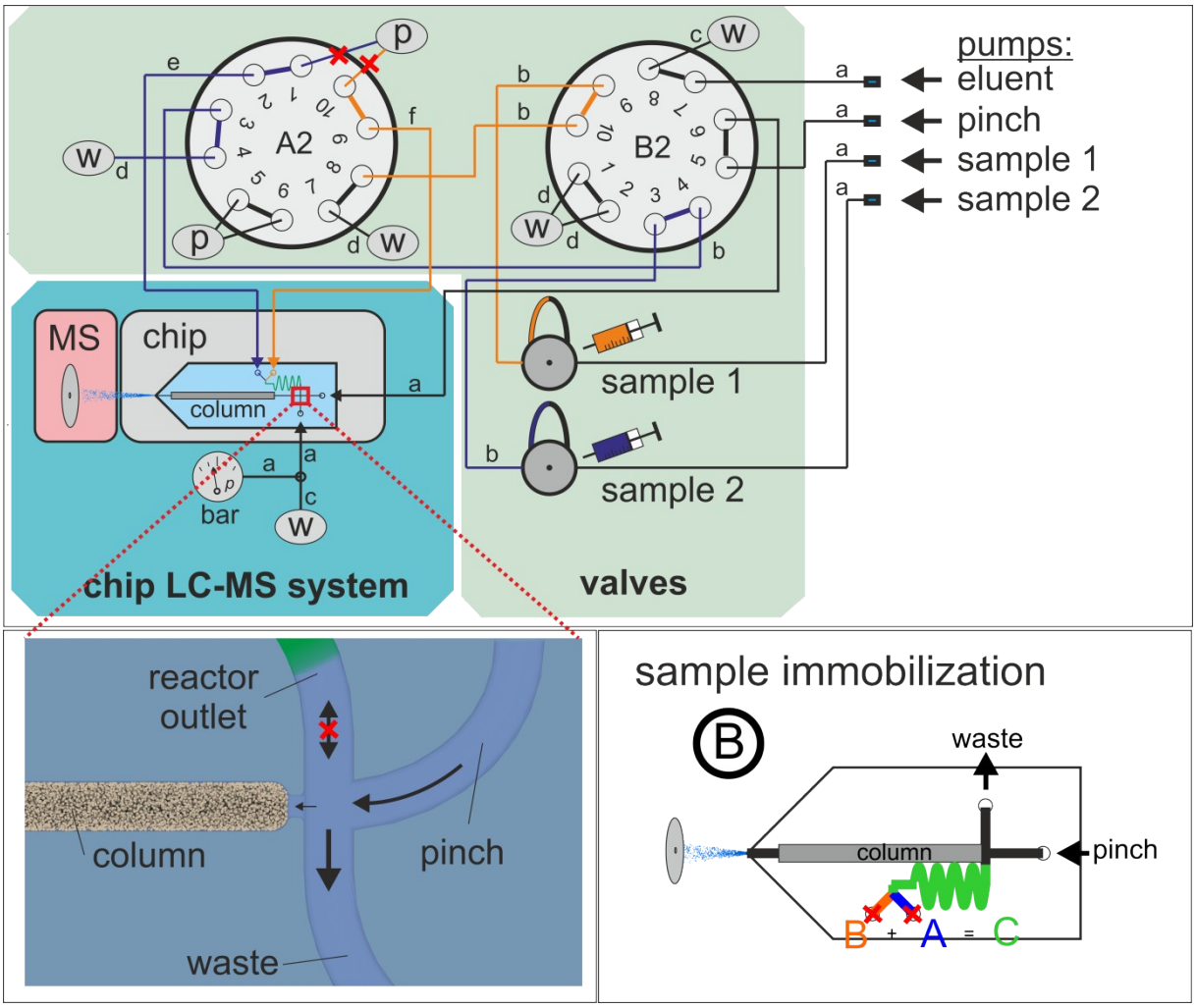


Figure SI-12. Operation principle of the stop-flow setup – step 4: *sample immobilization*. The auxiliary valve (A) is switched to position 2 and both sample inlets to the microchip are sealed off with microplugs. The pinch stream immobilizes the sample solution in the reactor, while flushing the column.

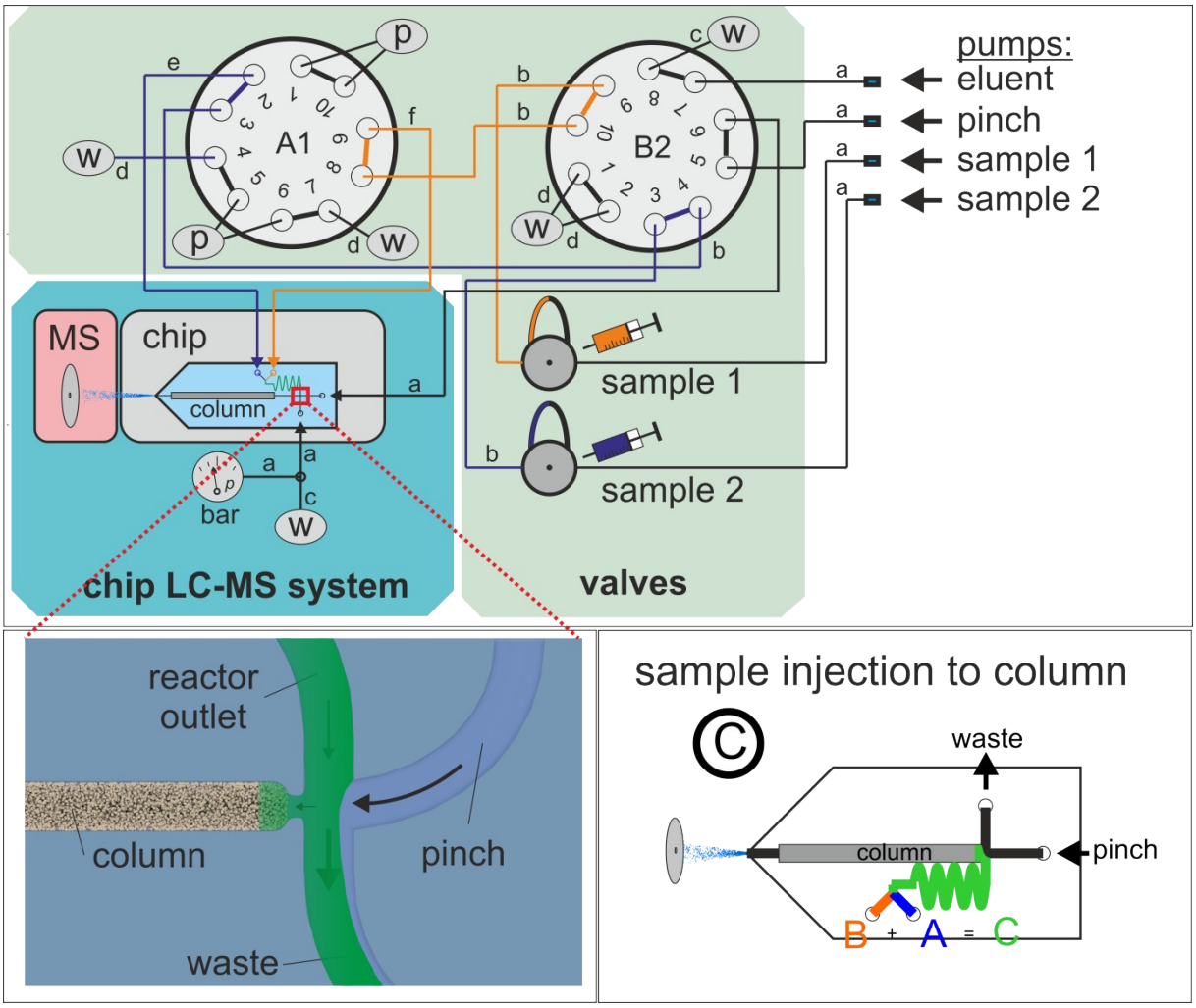


Figure SI-13. Operation principle of the stop-flow setup – step 5: *sample injection or infusion to the column*. The auxiliary valve (A) is briefly switched to position 1and a small sample plug is formed in the column head by infusion, whilst the pinch stream keeps the eluent/pinch inlet path free of sample. By optical determination of epifluorescence micrographs, the split ratio for the injection between infusion onto the column head and waste was adjusted to be about 1 via different restriction capillary dimensions, in order to minimize sample loss.

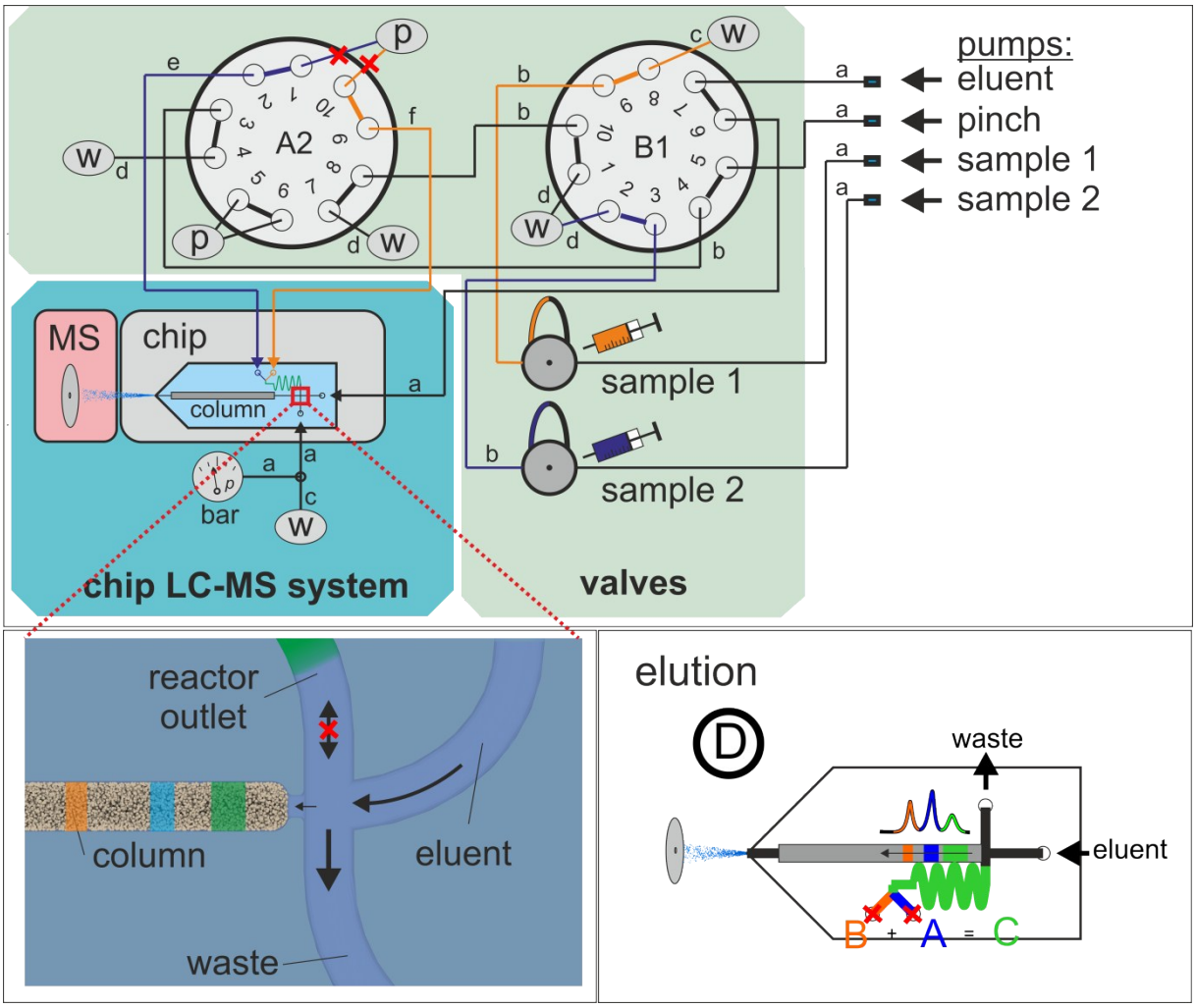


Figure SI-14. Operation principle of the stop-flow setup – step 6: *elution*. Both valves are switched back simultaneously, to immobilize the sample volume again in the reactor and to elute the sampled plug over the column.

Step 5 and 6 may be repeated (as depicted in figure 2) to inject another sample plug. Depending on the sample pump flow rates in relation to the reactor volume, either a fraction of the reactor is injected onto the column each cycle or the whole reactor content is flushed out an replaced by new sample solution. At the end of the run, valve A is back to position 1 to reverse flush the reactor while the column is being re-conditioned.

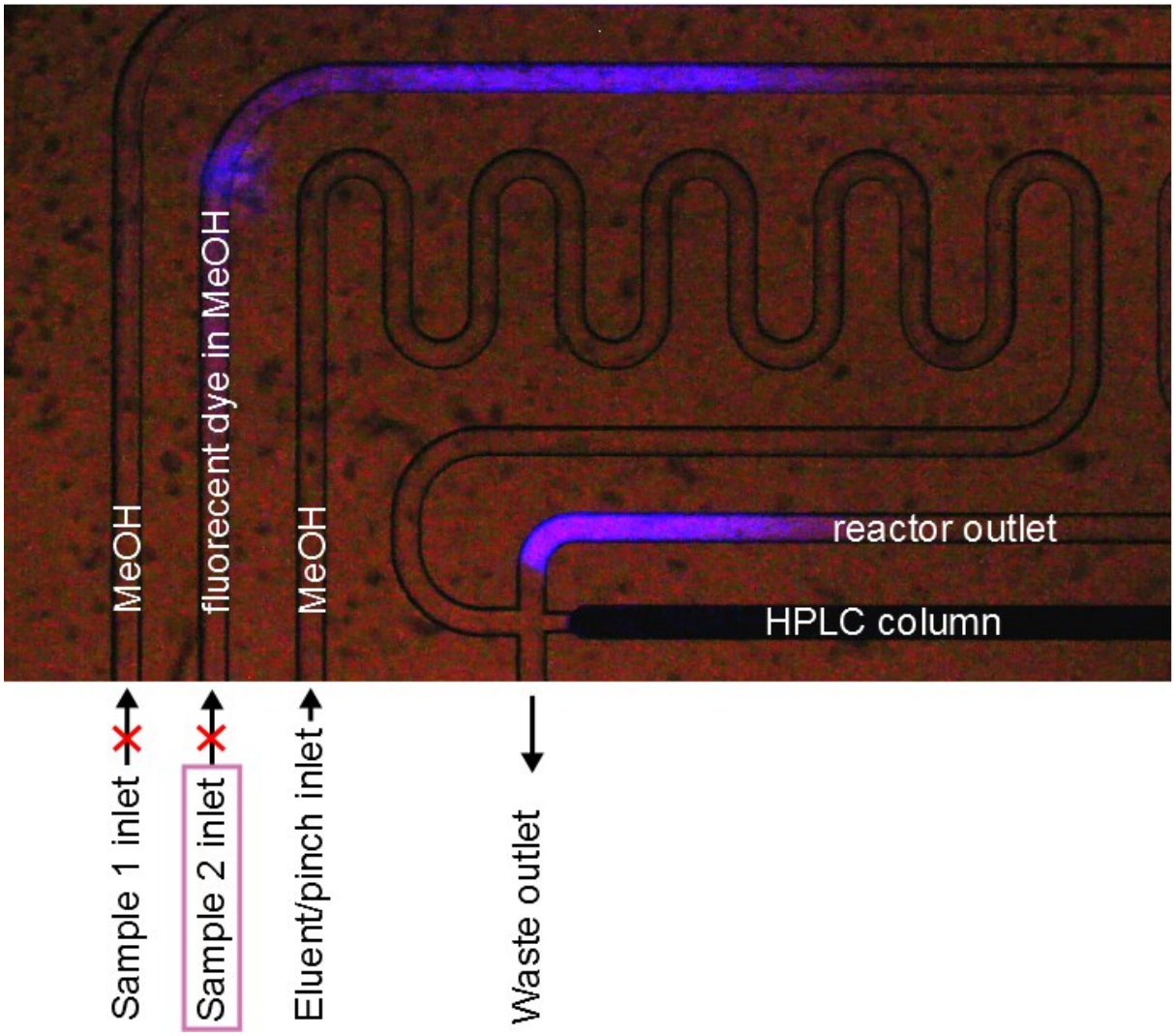


Figure SI-15. Fluorescence micrograph of the injection cross area of the microchip (5-fold magnification) at the *sample immobilization* step (see figure SI-12). From the sample 2 valve a 10 µg·mL^{-1} coumarin120 in 60/40 vol% MeOH/H_2O solution was injected to the chip. Valve positions A2, B1. The sample plug is immobilized by the pinch stream and compressed back into the reaction structure.

4.12 Typical valve switching profile for stop-flow experiments

A typical valve switching profile for the stop-flow experiments (for 5 min reaction time and a sequential injection at 10 min, with a reset at 60 min time) was as follows:

Table SI-5. Typical valve switching profile for the stop-flow experiments.

Time / min	Valve	Position
0.00	A	A1
0.00	B	B1
0.00	Sample 1	Load
0.00	Sample 2	Load
0.20	Sample 1	Inject
0.20	Sample 2	Inject
0.30	B	B2
0.60	B	B1
0.60	A	A2
5.55	B	B2
5.56	A	A1
5.60	B	B1
5.60	A	A2
10.55	B	B2
10.56	A	A1
10.60	B	B1
10.60	A	A2
…	…	…
60.00	B	B1
60.00	A	A1
60.00	Sample 1	Load
60.00	Sample 2	Load

The automatic valve switching was performed and programmed via RS-232 communication and the Bruker HyStar 3.2 software.

4.13 Catalyst impact on product formation over time

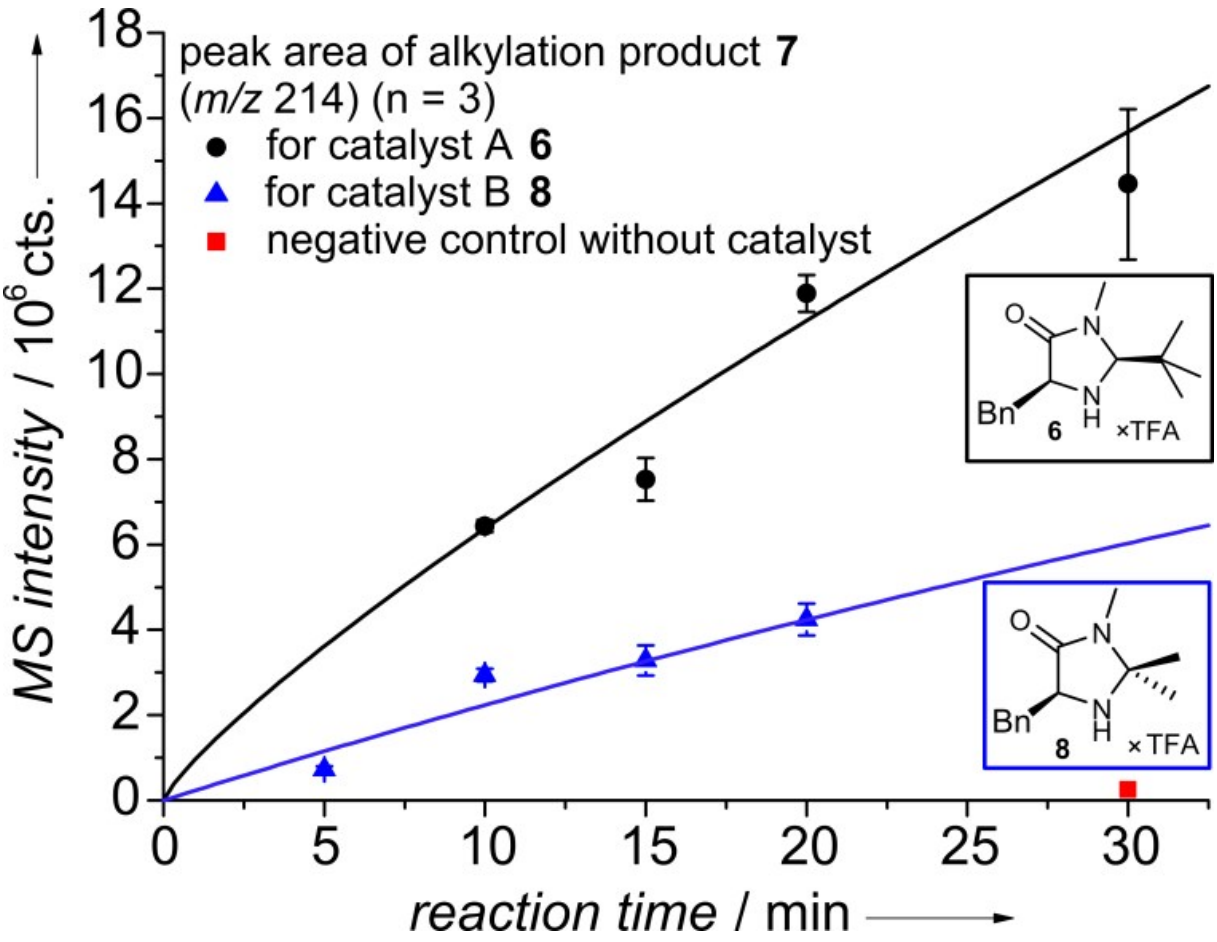
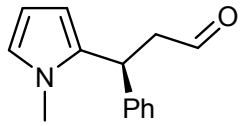


Figure SI-16. Formation of the alkylation product 7 from the iminium-catalyzed Friedel-Crafts alkylation (see scheme 2) based on the peak areas (EIC m/z 214). Two different iminium-based organocatalysts and the negative control without catalyst were investigated after reactions times between 5 and 30 min using stop-flow liquid trapping. Column: ProntoSIL C18 SH, particle diameter 3 µm, length 35 mm. Mobile phase: 100 µl·min-1, MeOH/H2O (60/40 vol%) with 0.1% formic acid. Sample pumps: 10 µl·min-1, MeOH/H2O (80/20 vol%), pinch: 10 µl·min-1, MeOH/H2O (50/50 vol%). 19 bar elution pressure at the injection cross with immobilized sample plug at a linear flow rate of 1.09 mm·s-1 over the column. Reactant inlet A: 4 (0.1 mol·l-1) 20 mol% 6 or 8 (in relation to 5), reactant inlet B: 5 (0.05 mol·l-1), each in ACN/H2O (87/13 vol%).

4.14 Batch synthesis of the alkylation product 7

For peak identification the product was synthesized in batch according to a literature protocol and the sample solutions for the chip experiments were spiked with the synthesized product. For this experiment no catalyst was added to the chip reactor samples.

(*S*)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylpropanal (7)

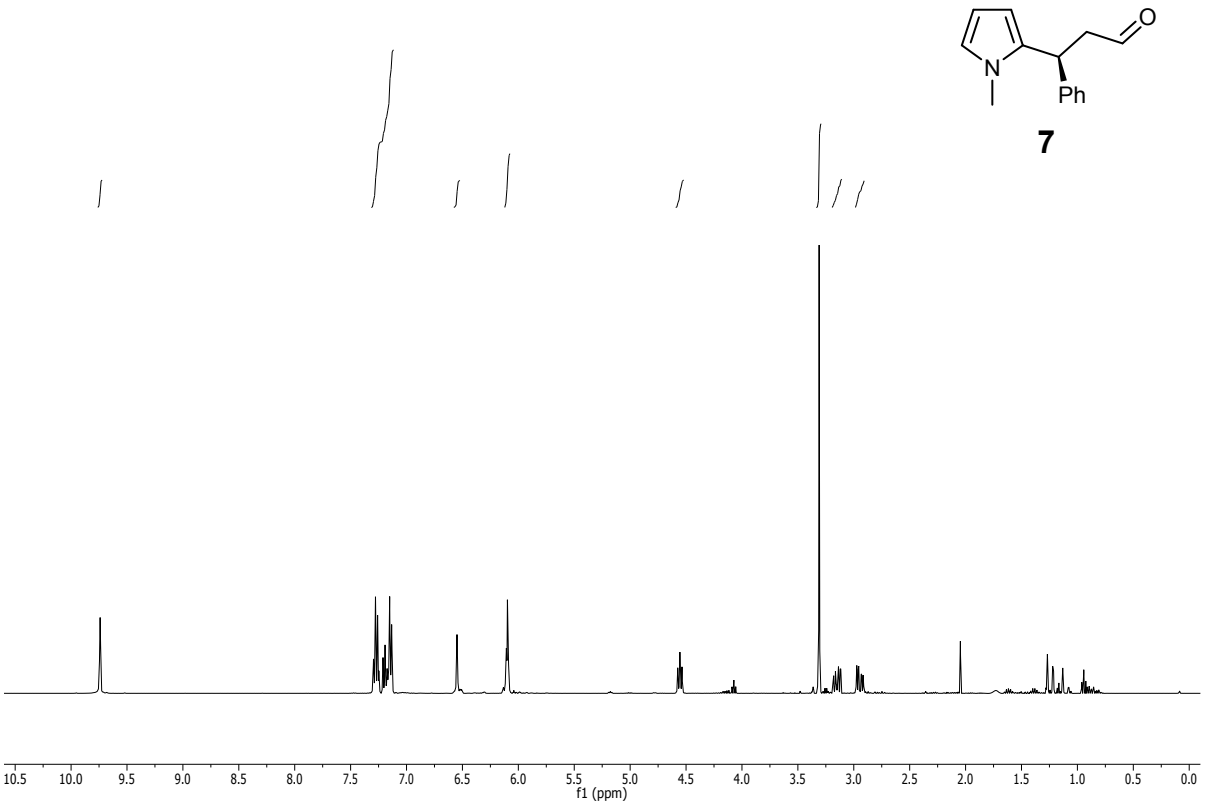


$C_{14}H_{15}NO$
213.28 g/mol

Following a literature procedure[2] using 264 mg 2-propenal (2 mmol, 1.0 equiv) and 811 mg *N*-methylpyrrole (10 mmol, 5.0 equiv) affords compound **7** after column column chromatography (flash gel; hexanes/EtOAc 25/1 to 3/1) as 130 mg of a yellowish oil (0.61 mmol, 31%).

R_f (hexanes/EtOAc 4/1): 0.49. Spectral data are in agreement with the corresponding literature:[2]

^{1}H NMR (400 MHz, $CDCl_3$): 9.74 (t, *J* = 1.8 Hz, 1H), 7.31 – 7.12 (m, 5H), 6.55 (t, *J* = 2.3 Hz, 1H), 6.12 – 6.08 (m, 2H), 4.56 (t, *J* = 7.6 Hz, 1H), 3.31 (s, 3H), 3.15 (ddd, *J* = 17.1, 8.2, 2.1 Hz, 1H), 2.94 (ddd, *J* = 17.1, 6.9, 1.5 Hz, 1H).



[2] Paras, N. A.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.