Supplementary Information (SI) for Reaction Chemistry & Engineering.

Supporting info

Electrochemical hydrocarboxylation of styrene with CO_2 in continuous flow

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STARTING MATERIALS

Commercially available chemicals

Styrene (distilled prior to use) and 1,3,5-trimethoxybenzene were bought from merck. Bu_4NBF_4, Et_4NBF_4, Me_4NBF_4, $LiClO_4$, Bu_4NClO_4, Bu_4NPF_6, Et_4NI were bought from tci and used as such. N,N-Dimethylformamide (anhydrous), acetonitrile and tetrahydrofuran were bought from Chem-lab and dried with molecular sieves prior to use.

REACTOR DESIGN

To perform the electrochemical carboxylation of styrene, an undivided electrochemical flow cell from Analytical Sales and Services, Inc. is used. The setup consists of two aluminium end plates pushing together two alignment gaskets with the corresponding electrodes. The electrodes that were used for this reaction are an impervious graphite plate electrode (bought at Analytical Sales and Services, Inc.) as cathode, and a magnesium electrode (bought at Evek GmbH) as anode, both with a dimension of 50 x 50 x 3 mm. All electrodes are sonicated for 3 x 10 minutes in acetone and put in an oven of 90°C before use, additionally, the Mg electrode is also scrubbed with sandpaper to remove the MgO layer prior to sonication. The electrodes are separated by a PFA flow channel film (type: simple, thickness: 0.127 mm, surface area: 681 mm^2) resulting in a reactor with an internal diameter of 0.086 ml. Electricity is then supplied by a power supply via spring test probes and pogo pins. **(Fig. S1)**

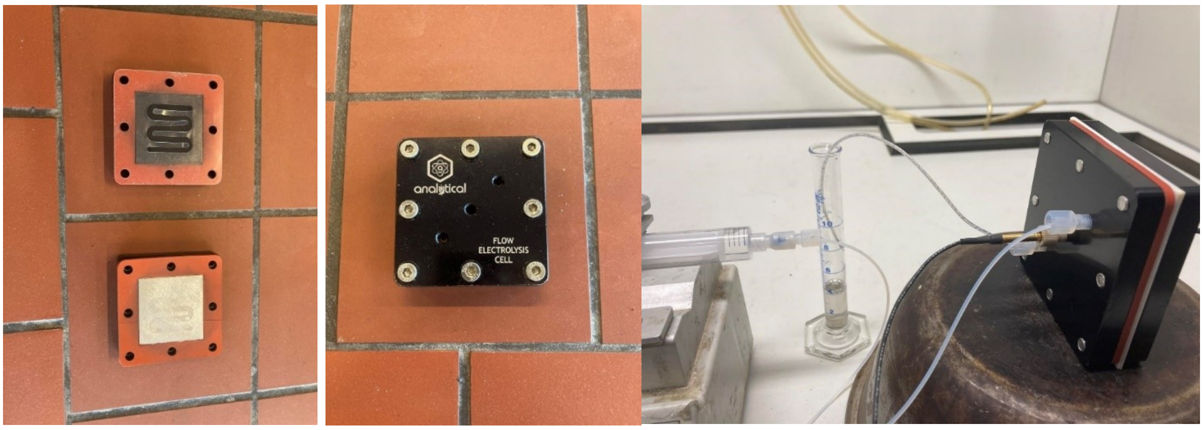


Fig. S1 Internal compartments of the flow cell with two electrodes confined by alignment gaskets and separated by a flow channel (left). View of reaction mixture stream in-and outlet as well as connection hole for pogo pin in the middle in the assembled reactor (middle). Fully connected and functional reactor (right).

EXPERIMENTAL PROCEDURES

Continuous flow hydrocarboxylation of styrene using a syringe pump and CO_2 presaturation for optimized conditions

Styrene (52 mg, 0.5 mmol), H_2O (63 mg, 3.5 mmol) and Bu_4NBF_4 (329 mg, 1 mmol) are added to a volumetric flask of 10 ml which is filled with DMF until the mark. Afterwards, the solution is flushed with CO_2-filled balloons for 30 minutes. The reaction mixture is sent to an electrochemical microreactor via a syringe pump with a flow rate of 0.208 ml/min where it is electrolyzed under constant current conditions of 50 mA. **(Fig. S2)** The microreactor has an internal volume of 0.086 ml resulting in a total residence time of 25 seconds. After 3 residence times have passed, the mixture is collected. After the reaction has finished, a small aliquot of 100 µl is taken, diluted in acetonitrile and analyzed via quantitative HPLC to calculate the remaining styrene in the mixture. **(See: analysis procedures)** Afterwards, the remaining mixture is acidified with 5 ml 2 M HCl and stirred in room temperature for 10 minutes. 10 ml of H_2O is added whereafter the mixture is then extracted 3 times with 20 ml Et_2O. The resulting organic phase is evaporated under reduced pressure and yield of mono-and dicarboxylated products are determined via quantitative ^{1}H-NMR. **(See: analysis procedures)**

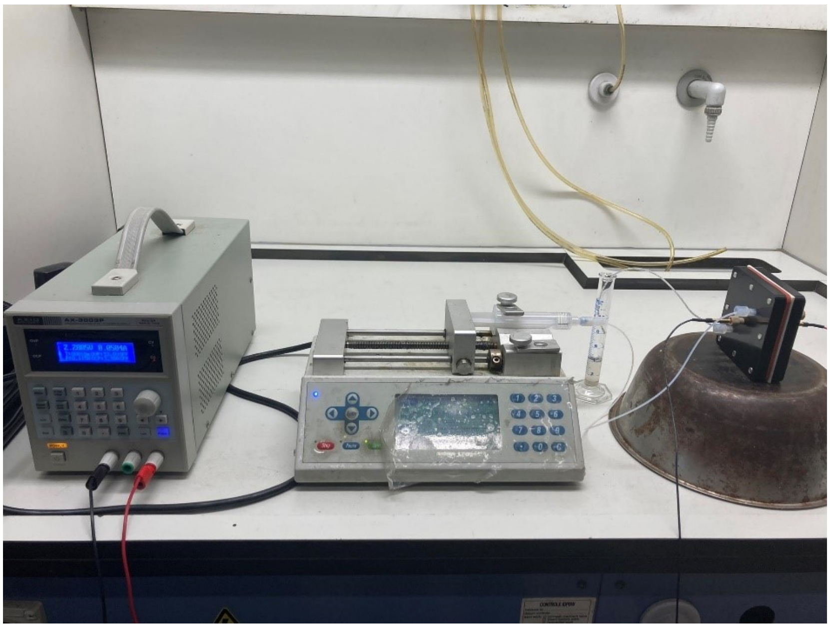


Fig. S2 Setup for the continuous flow hydrocarboxylation of styrene with electrochemical cell (right), syringe pump (middle) and power supply (left).

Fully continuous flow hydrocarboxylation of styrene with CO_2 dosing for optimized conditions

Styrene (130 mg, 1.25 mmol), H_2O (34 mg, 1.88 mmol) and Bu_4NBF_4 (822 mg, 2.5 mmol) are added to a volumetric flask of 25 ml which is filled with DMF until the mark. The reaction mixture is sent to a Y-piece via a dual-piston pump with a flow rate of 0.208 ml/min where it is mixed with a flow of 1.02 ml_N/min CO_2 via a mass flow controller (MFC). The resulting stream is then briefly cooled in an ice bath to promote CO_2 dissolution (it should be noted that the actual reaction stream entering the reactor is already warmed up to room temperature again). To ensure a uniform flow pattern, a back pressure regulator (BPR) is installed after the cooling bath and is set at 1 bar. The BPR is positioned before the reactor because placing it downstream caused the reactor to leak. Subsequently, the mixture is electrolyzed under constant current conditions of 50 mA. **(Fig. S3)** The microreactor has an internal volume of 0.086 ml resulting in a total residence time of 25 seconds. After 3 residence times are passed, around 10 ml of the mixture is collected. After the reaction has finished, a small aliquot of 100 µl is taken, diluted in acetonitrile and analyzed via quantitative HPLC to calculate the remaining styrene in the mixture. **(See: analysis procedures)** Afterwards, the remaining mixture is acidified with 5 ml 2 M HCl and stirred in room temperature for 10 minutes. 10 ml of H_2O is added whereafter the mixture is then extracted 3 times with 20 ml Et_2O. The resulting organic phase is evaporated under reduced pressure and yield of mono-and dicarboxylated products are determined via quantitative ^{1}H-NMR. **(See: analysis procedures)**

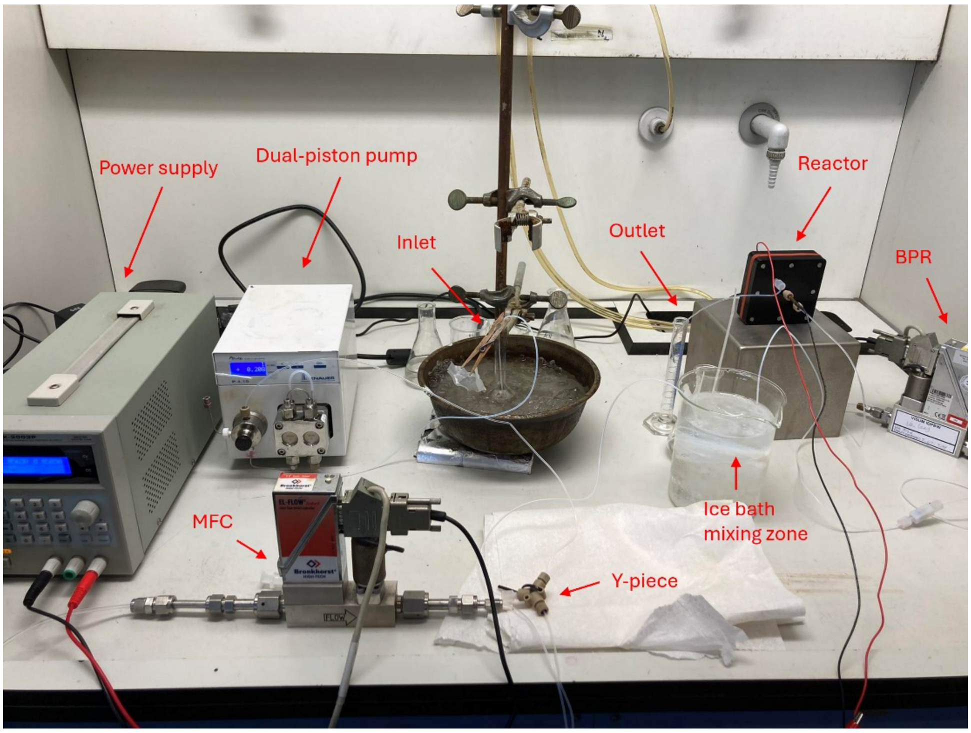


Fig. S3 Setup for the fully continuous flow carboxylation of styrene with CO_2 dosing

ANALYSIS PROCEDURES

Quantitative HPLC analysis of unreacted styrene

To quantify unreacted styrene after reaction, 100 µl of the reaction mixture prior to acidification is diluted 10-fold in acetonitrile and analyzed using quantitative HPLC, employing a calibration curve. **(Fig. S4)** To reduce equipment variability, the sample was analyzed three times, and the average value was recorded. The spectra were analyzed at a wavelength of 280,8 nm with an elution pattern of 90/10-0/100 H_2O/MeCN (C18 column).

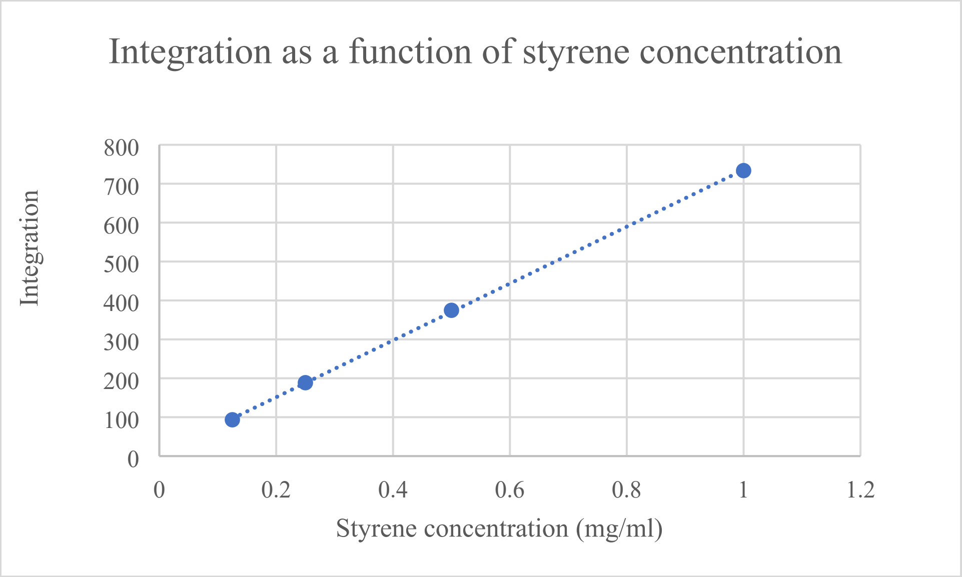


Fig. S4 HPLC calibration curve to quantify the conversion of styrene **1**

Quantitative ^{1}H-NMR analysis of carboxylation products

To quantify the yield of the monocarboxylated product **2** and dicarboxylated product **3**, 1,3,5-trimethoxybenzene is added to the crude reaction mixture after work-up whereafter the mixture is redissolved in acetonitrile. To calculate the yield of 3-phenylpropionic acid **2**, a fraction of the mixture is evaporated and analyzed via ^{1}H-NMR in d_6-DMSO. **(Fig. S5, Fig. S6)** To calculate the yield of phenylsuccinic acid **3**, the same procedure is followed but $CDCl_3$ is used as solvent to avoid signal overlap. **(Fig. S7, Fig. S8)** All observed carboxylic acid signals are consistent with previous literature and were also confirmed by spiking experiments. [1,2]

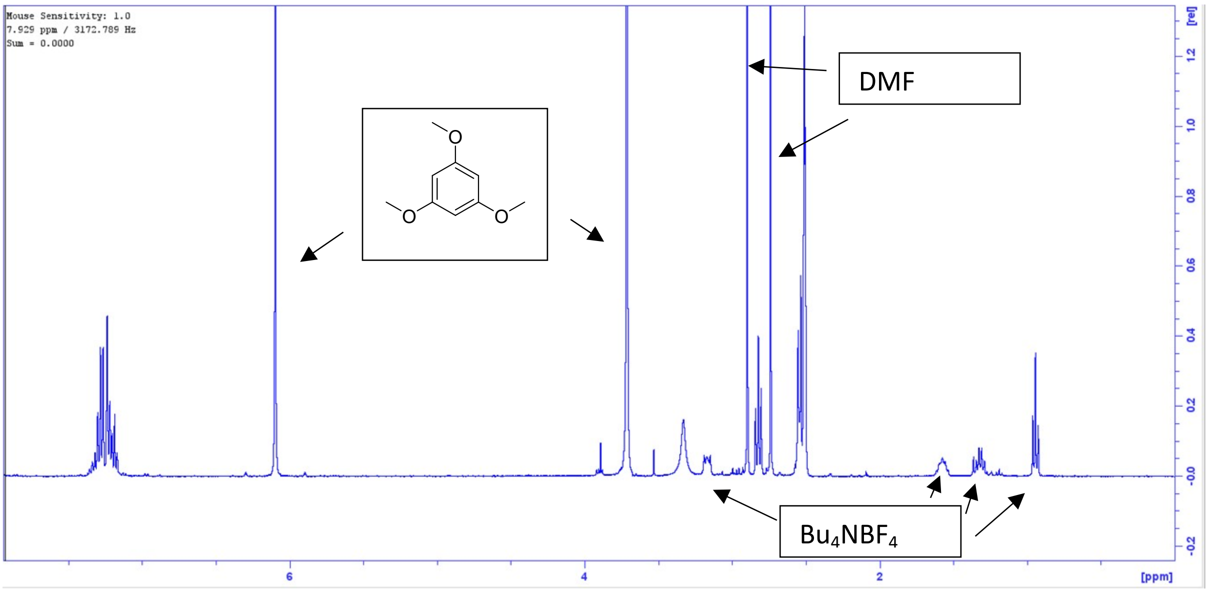


Fig. S5 Typical ^{1}H-NMR spectrum (0-8 ppm) of reaction products + internal standard in d_6-DMSO

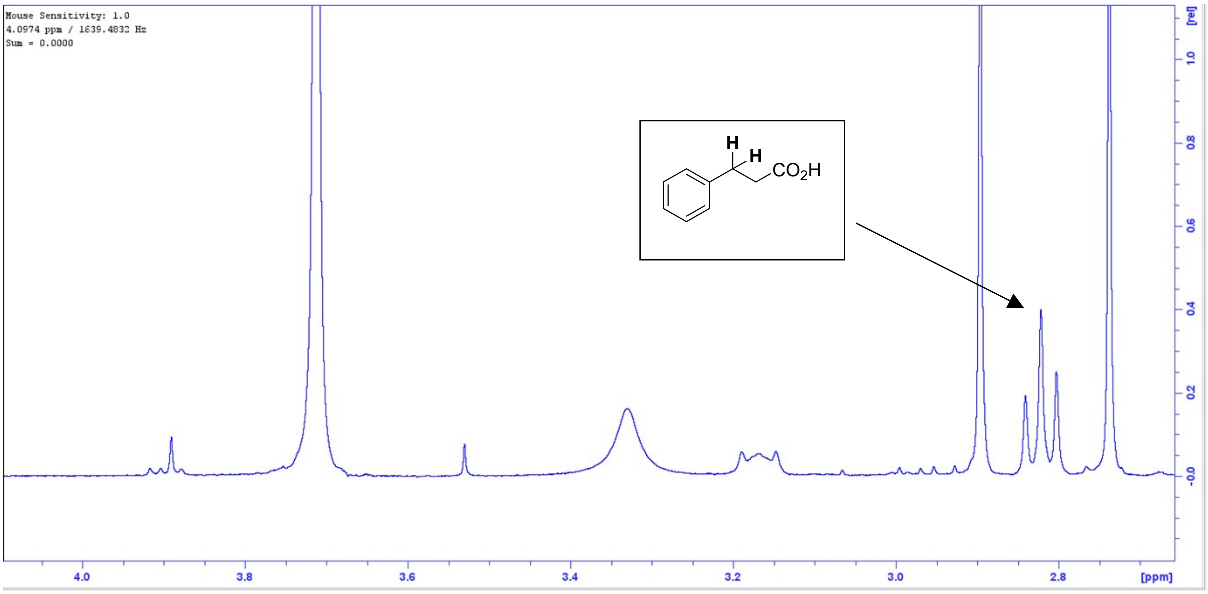


Fig. S6 Zoom in (2.65-4.10 ppm) of typical ^{1}H-NMR spectrum on signal used to quantify 3-phenylpropionic acid in d_6-DMSO. Signals are assigned to the hydrogen atoms in bold.

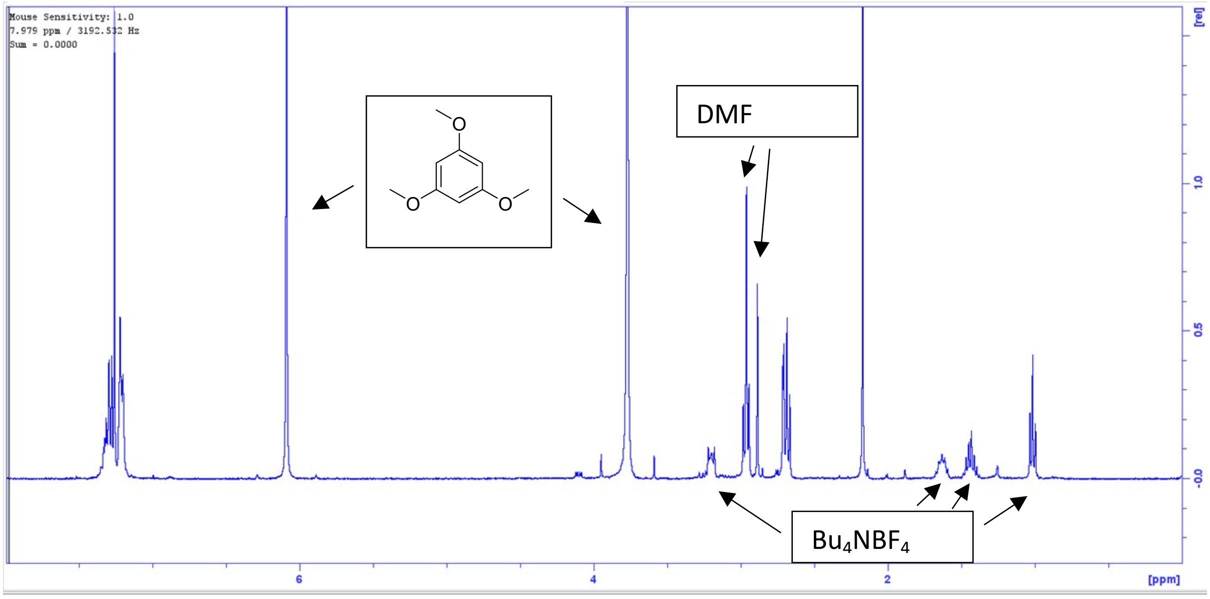


Fig. S7 Typical ^{1}H-NMR spectrum (0-8 ppm) of reaction products + internal standard in $CDCl_3$

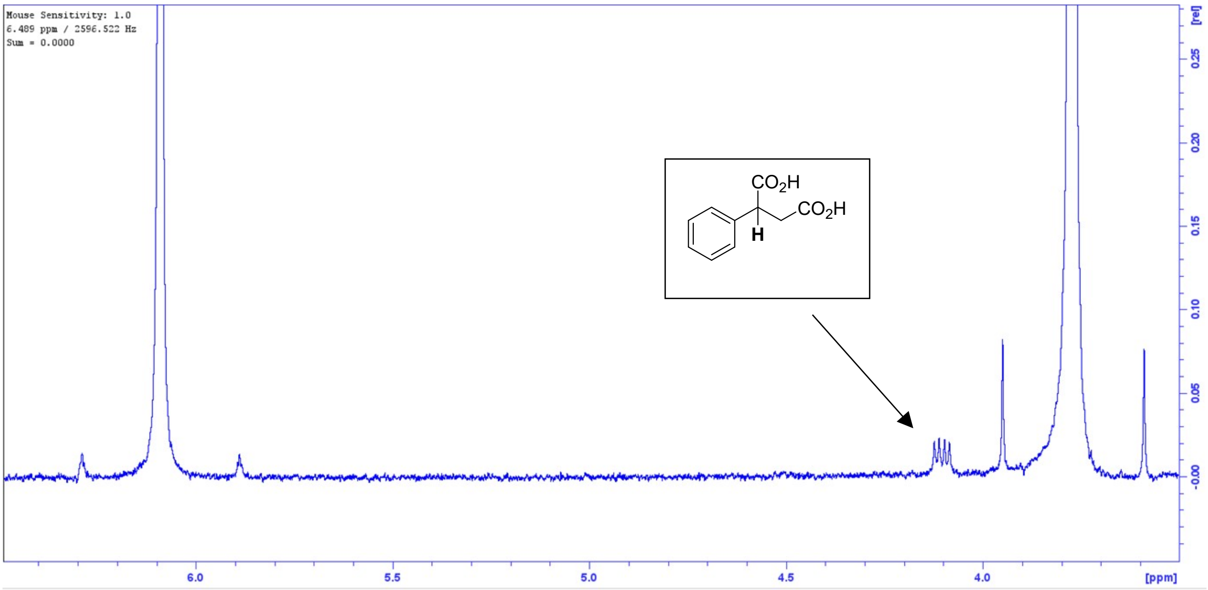
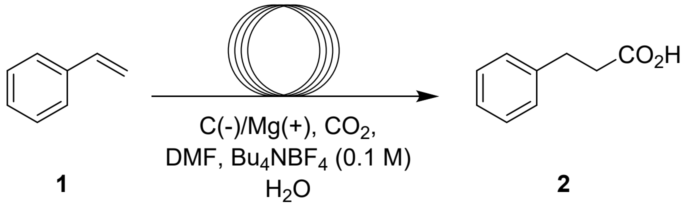


Fig. S8 Zoom in (3.5-6.5 ppm) of typical ^{1}H-NMR spectrum on signal used to quantify phenylsuccinic acid in $CDCl_3$. Signals are assigned to the hydrogen atom in bold.

ADDITIONAL EXPERIMENTS



Varying current

To increase productivity, it was examined how higher current affected the conversion rate of styrene. It was seen that when current increased, conversion of styrene dropped significantly. At higher currents, more F/mol is needed to reach the same conversion while yield of monocarboxylated product **2** dropped significantly. **(Table S1, entry 4)** A current of 200 mA or higher resulted in a gel-like reaction mixture, suggesting polymerization.

Table S1 Varying current for the electrochemical hydrocarboxylation of styrene towards 3-phenylpropionic acid

Entry[a]	Current (mA)	Residence time	F/mol	Conversion 1 (%)[b]	Yield 2 (%)[c]
1	50	25s	3	87	72
2	100	12s	3	70	n.d.
		16s	4	73	n.d.
3	200	6s	3	51	n.d.[d]
		10s	5	65	n.d.[d]
4	400	3s	3	38	n.d.[d]
		6s	6	83	13[d]

[a] Reactions were performed after flushing the reaction mixture with CO_2 for 30 minutes, with a styrene starting concentration of 0.05 M and 7 eq. H_2O, under constant current conditions (50 mA, 3 F/mol, 25s residence time)

[b] Conversion determined via quantitative HPLC analysis

[c] Yield determined via quantitative ^{1}H-NMR analysis

[d] Resulting reaction mixture formed a gel

n.d.: not determined

Reaction stability over time

During the constant current reaction, a small but steadily increasing reaction potential was observed. This increase is attributed to minor fouling build-up at the electrodes that will increase the overall cell resistance. To assess the decline in styrene conversion due to fouling buildup over time, three different samples were taken over the course of the reaction. **(Table S2)**

Table S2 Follow-up of the electrochemical hydrocarboxylation of styrene towards 3-phenylpropionic acid

Time[a]	Conversion 1 (%)[b]	Cell potential
0 min	93	1.4 V
20 min	87	1.6 V
40 min	81	1.8 V

[a] Reaction was performed after flushing the reaction mixture with CO_2 for 30 minutes, with a styrene starting concentration of 0.05 M and 3 eq. H_2O, under constant current conditions (50 mA, 3 F/mol, 25s residence time). After three internal volumes of reaction mixture had passed through the reactor to ensure equilibration, the first sample was taken and considered the starting point (0 min).
[b] Conversion determined via quantitative HPLC analysis

CO_2 SOLUBILITY IN ORGANIC SOLVENTS

The solubility of CO_2 for the different organic solvents that were used are given below. **(Table S3)** It should be noted that solubility is both dependent on temperature and pressure, solubility is given here at standard conditions.[3]

Table S3

Solvent	CO_2 solubility (M)
DMF	0.199
THF	0.205
MeCN	0.279

ELECTROCHEMICAL & PRODUCTIVITY PARAMETERS

The key electrochemical performance metrics—Faradaic efficiency, current density, and space–time yield—for the most critical optimization reactions are summarized below. **(Table S4)**

Current density (mA/cm^2) was calculated via:

$$current\ density = \frac{I}{A}$$

where I is the applied current in milliamperes and A = 6.81 cm^2 is the electrode surface area in the reactor.

Faradaic efficiency (%) was determined using the formula:

$$Faradeic\ efficiency = \frac{n * F * moles\ of\ product}{Qtotal} * 100$$

where n is the number of electrons required per molecule of product, F is the Faraday constant (96,485 C/mol), and Qtotal=I*t is the total charge passed during electrolysis.

Space-time yield ($gL^{-1}h^{-1}$) was calculated as:

$$Space\ time\ yield = \frac{Mass\ of\ product\ formed\ during\ residence\ time}{Reactor\ volume * residence\ time}$$

These metrics provide a comprehensive assessment of both the electrochemical efficiency and the productivity of the reactor system.

Table S4 Faradaic efficiency, current density and productivity of various (pre-)optimized hydrocarboxylation reactions

Entry	Current density (mA/cm^2)	Space-time yield (gL^{-1}h^{-1})	Faradaic efficiency compound 2 (%)
Table 4, entry 1 (3 F/mol)	7.34	735	45
Table 4, entry 1 (3.5 F/mol)	7.34	559	34
Table 4, entry 2 (3 F/mol)	7.34	680	42
Table 4, entry 2 (3.5 F/mol)	7.34	614	38
Table 4, entry 3 (3 F/mol)	7.34	777	48
Table 4, entry 3 (3.5 F/mol)	7.34	633	39
Table 4, entry 4 (3 F/mol)	7.34	540	33
Table 4, entry 4 (3.5 F/mol)	7.34	540	33
Table 6, entry 1	7.34	637	39
Table 6, entry 2 4	7.34	604	37

MATERIALS AND METHODS

High-Performance Liquid Chromatography (HPLC)

To quantify styrene conversion, high-performance liquid chromatography was used with a calibration curve. The 1200 Series LC/MSD SL consists of a Supelco ascentis express C18 column with an internal diameter of 4.6 mm. Additionally, the instrument is equipped with a UV-DAD detector and an Agilent 1100 Series MSD SL mass spectrometer with electrospray ionisation (ESI, 4000 V, 70 eV) coupled with a single quadrupole detector. To elute the components, an acetonitrile/water mixture is used in different ratios.

Nuclear Magnetic Resonance Spectroscopy (NMR)

The spectra were taken by a Bruker Avance Nanobay III NMR spectrometer with a 1H/BB z-gradient high resolution probe. ^{1}H-NMR were recorded at 400 MHz. The software used to process and display the spectra was TOPSPIN version 3.6.4. To prepare the samples for usage, the compounds were dissolved in $CDCl_3$.

Continuous flow pump

The fully continuous flow reactions were carried out using a Knauer AZURA P 4.1S pump, equipped with a pressure sensor and a stainless steel pump head. The pump can deliver a maximum flow rate of 10 mL/min and operating at pressures as high as 200 bar.

Syringe pump

For the presaturation experiments, a Chemyx Fusion 101 Syringe Pump was used

Mass flow controller (MFC)

An EL-FLOW metal-sealed F-201 CM mass flow controller from Bronkhorst® was employed to regulate the oxygen flow to the continuous flow reactor. This controller is capable of handling gas pressures up to 30 bar and allows for precise control of oxygen flow, with a maximum setpoint of 80 mL_N/min .

Continuous flow tubing

To build the continuous flow setup, PFA (polyfluoroalkoxy) tubing with an internal/external diameter of 0.8/1.6 mm was used.

Back pressure regulator

To carefully control the pressure exerted on the reaction mixture, a Bronkhorst® back pressure regulator with model number P-702CV-M10A-AGD-11-K is used. This pressure controller works in the range of 20 mbar to 64 bar and is controlled via FLOW-BUS digital communication software

Power supply

The electrolysis process was powered by an Axiomet AX-3003P power supply, which offers both constant current and constant voltage operation modes.

REFERENCES

[1] J. Malineni, H. Keul, M. Möller, *Dalton Transactions* **2015**, *44*, 17409–17414.

[2] G.-Q. Yuan, H.-F. Jiang, C. Lin, *Tetrahedron* **2008**, *64*, 5866–5872.

[3] M. Jitaru, *Journal of the University of Chemical Technology and Metallurgy* **2007**, *42*, 333–344.