Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information for

In-Situ FTIR Spectroscopic Monitoring for Electrochemically Controlled Organic Reactions in a Recycle Reactor

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1. Materials and general procedures.

Reagents: Solvents or reagents were used without further purification unless otherwise stated. HPLC-grade DMSO and *n*-tetradecane were purchased from Alfa Aesar, while pyridine (Chromasolv for HPLC), lithium perchlorate (99.99%) and (S)-*cis*-Verbenol were purchased from Sigma Aldrich. Tetraethylammonium perchlorate was purchased from Alfa Aesar as a wet solid containing ca. 10% water. Prior to use, water was removed under reduced pressure by toluene azeotrope and the dry solid was stored in a desiccator. TBHP was purchased as a 70% w/w solution in H_2O from Alfa Aesar, and its concentration was determined by iodometric titration. Zinc trifluoromethanesulfinate (TFMS) was prepared according to literature procedures.[1] The compound is also commercially available from Aldrich. The sulfinate salts was freed of $ZnCl_2$ by washing with 1:1 DCM–EtOAc (3 x 30 mL per gram of salt). The purity of the zinc salt was determined by ^{19}F-NMR using NaF as internal standard, according to the following procedure: Known quantities (ca. 15 mg) of the zinc salt and NaF (oven-dried) were weighed into a 1-dram vial. The solids were dissolved in D_2O (1 mL) and sonicated for 5 min. The resulting solution was analyzed by ^{19}F-NMR (d1 = 20 s, 128 scans) to determine the concentration of the zinc sulfinate in the sample. Samples of varying purity performed equally in the reaction, provided the amount of salt added was adjusted appropriately.

For characterization of reaction products: NMR spectra were recorded on Bruker DRX-600, DRX-500 and AMX-400 instruments and were calibrated using residual undeuterated solvent or TMS as an internal reference. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, heptet = heptet, m = multiplet, br = broad. ^{19}F-NMR are referenced to trichlorofluoromethane; high-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight reflection experiments. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material, unless otherwise stated. ATR-IR spectra of the reaction product were recorded on a Perkin

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[1] O'Hara, F.; Baxter, R. D.; O'Brien, A. G.; Collins, M. R.; Dixon, J. A.; Fujiwara, Y.; Ishihara, Y.; Baran, P. S. *Nat. Protoc.* **2013**, *8*, 1042

Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher Johns 12144 melting point apparatus and are uncorrected.

Reaction Analysis: GC data was obtained on an Agilent 7890A GC-FID instrument with a Durabond DB-5 column with H_2 and He as carrier gases. HPLC data were obtained using an Agilent 1100 series system fitted with an Agilent Eclipse XDB-C18 column (5 μm particle size), using MeCN/H_2O (0.1 % formic acid) as eluent. FT-IR kinetics were obtained using a Nicolet 7600 FT-IR spectrometer fitted with a liquid nitrogen-cooled MCT detector and a Harrick demountable liquid flow cell (model number TFC-S13-3).

More details of the system are given in Sections S2 and S3.

Electrochemical experiments: Bulk electrolysis experiments were carried out using a NuVant EZ-StatPro potentiostat/galvanostat and a Pine Instruments WaveNow WC50 Potentiostat/galvanostat. ELAT hydrophobic carbon cloth (purchased from NuVant) was used as the working and auxiliary electrodes. A BASi Ag/AgCl reference electrode was also used for bulk electrolysis experiments with Zn sulfinates. The verbenol oxidation experiments (Scheme 1) were performed at constant current without a reference electrode. A further practical description of the electrochemical system is given in Section S2 and S3.

2. Standard procedures for electrochemically-initiated verbenol oxidation (Scheme 1 in paper)

A known amount of *n*-tetradecane (34 mg, 17 mmol) was added to the test tube via pipette and weighed. Verbenol was then added (48 mg, 0.32 mmol, 1.0 equiv) followed by 8 mL pyridine-$LiClO_4$ (0.5M), and *tert*-butyl hydroperoxide (212 μL of a 70% w/w solution in H_2O, 1.6 mmol, 5 equiv) via pipette in a single portion. After stirring for 3 minutes, the reaction mixture was recirculated through the Harrick cell in the FT-IR setup. The reaction vessel was then equipped with the cloth electrodes at the desired immersion level. The reaction progress was monitored by IR (1680 cm^{-1} for the verbenone carbonyl stretch). The IR monitoring method was validated by concomitant GC monitoring.

3. Standard procedure for the electrochemical trifluoromethylation (Scheme 2 in paper)

A solution of the heterocycle (1.80 mmol, 1.0 equiv), tetraethylammonium perchlorate (1.1 g, 4.8 mmol) and zinc sulfinate salt (2.52 mmol, 1.4 equiv) in DMSO (32.5 mL) was placed in a 50 mL beaker containing a carbon working electrode (ELAT carbon cloth, 6 cm x 8 cm), a stirrer bar, and a Ag/AgCl reference electrode. A fritted chamber containing H_2SO_4–DMSO (7.5 mL of a 0.5 M solution) and a carbon auxiliary electrode (5 cm x 3 cm) was placed in the center of the beaker. The electrodes were connected to a potentiostat/galvanostat and current of 25 mA was applied to the stirred cell for 8 h (1.62 F/mol passed). The cell potential drifted from +0.7 to +1.3 V during the course of the electrolysis. Following electrolysis, the auxiliary compartment was removed and the reaction mixture was poured onto saturated $NaHCO_3$–EDTA solution (100 mL – caution, gas evolved). The aqueous phase was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with water (2 x 100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by chromatography over silica gel or recrystallization afforded the fluoroalkylated heterocycle.

4. Practical notes on setup of the electrochemical cells.

No specialized glassware was used. A description of the experimental setup used in the verbenol oxidation is given below.

<u>For verbenol oxidation (Scheme 1):</u>

Part A. Solution. In a 15 mL glass test tube cut to 10 cm height, verbenol (**2**) is added along with a weighed amount of *n*-tetradecane. After adding 8 mL of pyridine (0.5M $LiClO_4$), the reaction mixture was vigorously stirred for 3 minutes. The TBHP solution

(212 µL) was then added in one aliquot via pipette immediately prior to the electrochemical experiments.

Part B. Dual syringe recirculating system.

The system was assembled by using two syringe pumps (Model NE-1000, New Era Pump Systems Inc) programmed as reciprocating units. Unidirectional flow is maintained by using a series of check valves (IDEX CV Inlet Asy 3psi 1/4–28) as shown below in Fig S1.

With a viscous 0.5M $LiClO_4$ solution, we addressed differences in the wetting of the IR cell under different flow conditions. The data in Figure 2 allowed us to choose flow rates to ensure that well-mixed conditions continued to prevail as the stream flowed through the FT-IR cell. Mixing for reaction homogeneity is carried out in the electrochemical cell with a magnetic stirrer. The reaction proceeds in the electrochemical reactor, as the [O^{-}] are generated at the electrode. The recycle flow through the FT-IR cell allows us to monitor in real time with minimal lag the reaction progress as it occurs in the electrochemical reactor.

The flow rates for withdrawal and infusion with two 10 mL Hamilton syringes were 6 mL/min and 8mL/min respectively unless otherwise stated.

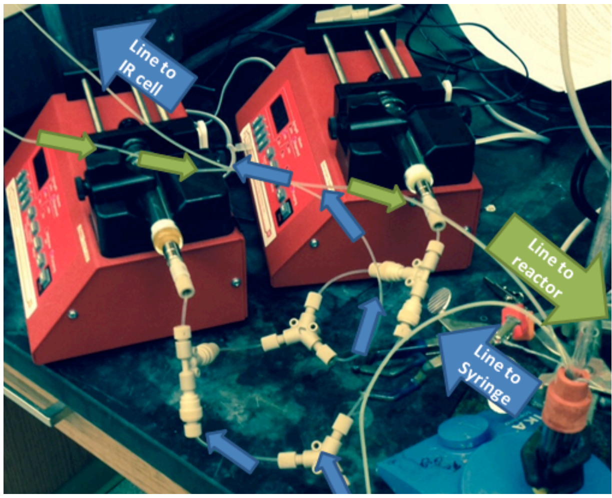

Figure S1.

Part C. Electrode setup for undivided cell. 15 cm by 1 cm Elat C cloth strips were immobilized in the body of 1 mL syringes and pushed through a septum cap as shown in

Fig S2. This setup allowed us to perform the electrolyses while avoiding electrode contact.

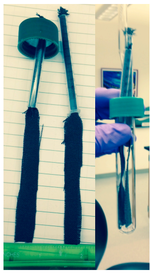
Figure S2.

Part D. Cell assembly. The cell was assembled in the test tube at the desired immersion level as shown in Fig S3. The cell was interfaced with 1/16” PFA Tubing (IDEX) connected to the dual syringe system and the Harrick IR cell.

Part E. Electrolysis. Current was applied (10 mA unless otherwise noted) with a Pine Instruments WaveNow potentiostat after connecting the electrode alligator clips to the stirred reaction solution (Fig S3). The electrolysis is performed without a separator between working and counter electrode. GC samples are taken in the beginning and end of the reaction and are passed through a $Na_2S_2O_8$ plug prior to GC analysis. GC analysis is used to determine the analyte concentration and corroborate the IR response.

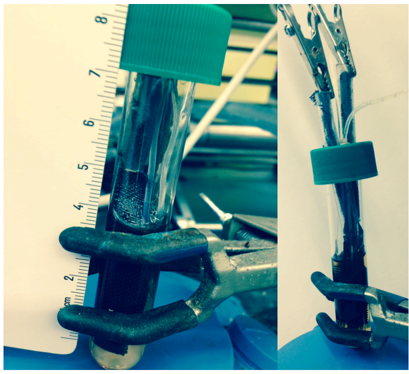
Figure S3.

<u>For trifluoromethylation reaction (Scheme 2):</u> A detailed procedure for the trifluoromethylation experiments is described in: Blackmond *et al* Angew. Chemie Int. Ed. 2014, 53, 12062.

4. Procedures for FT-IR kinetics.

Instrumentation: FT-IR kinetics were obtained using a Nicolet 7600 FT-IR spectrometer fitted with a liquid nitrogen-cooled MCT detector and a Harrick demountable liquid flow cell (model number TFC-S13-3). The flow cell was constructed using Ge windows (spaced by a. three layers of spacers for the verbenol oxidation were necessary to avoid cell wetting issues with the rather viscous pyridine solvent mixture :12 μm, 6 μm and 25 μm- and b. 12 μm spacers for trifluoromethylation), and was angled away from the beam path by 25° to eliminate the interference pattern.

The IR signatures used in this work are listed in the table below

Compound	**IR Frequency (cm^{-1})**
Verbenone (**2**)	1680
Zn TFMS	1722
4	1145

The alcohol oxidation mixture was pumped through the IR cell and returned to the reaction vessel at a 6 mL/min rate of withdrawal with 8 mL/min infusion rates on the reciprocating syringe pump systems (Scheme 1). The trifluoromethylation reaction mixture was pumped through the cell and returned to the reaction vessel at 8 mL/min (Scheme 2).

The height of peaks at 1722 cm^{-1} and 1145 cm^{-1} in the second derivative of the absorbance spectrum was used to monitor consumption of TFMS and formation of **4**, respectively. Formation of **2** was monitored using the peak height at 1680 cm^{-1} of the absorbance spectrum. A Savitzky–Golay filter (7 points, 3rd order polynomial) was applied to smooth the individual spectra for trifluoromethylation. 64 spectra obtained at 4 cm^{-1} resolution and taken over a 25 s interval were co-added to obtain each data point. For the alcohol oxidation, the reaction mixture was circulated for 5 minutes through the setup to allow for cell equilibration. A background was collected of the entire reaction contents.

Alcohol oxidation (Scheme 1): at the end of the reaction, the reaction content was sampled using a glass capillary, pushed through a $Na_2S_2O_8$ plug, diluted by 200 µL chloroform and analysed by GC using *n*-tetradecane as internal standard (calibration for retention time 5.2 min, **2 s**hown in Fig S5).

Trifluoromethylation (Scheme 2): a background spectrum of DMSO–NEt_4ClO_4 was taken prior to the experiment. At the end of the reaction, a sample was taken and analyzed by HPLC and NMR to obtain the final conversion. To determine [**4**], 50 µL aliquots of the reaction mixture were taken, diluted with MeCN (400 µL), and analysed by HPLC (using the peak area at 254 nm. Peak area was calibrated to concentration (Figure S4).

[TFMS] was determined by ^{19}F-NMR in d_6-DMSO using $PhOCF_3$ as an internal standard (d1 = 20.6 s).

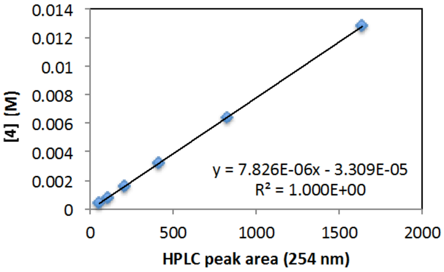

Figure S4 – HPLC calibration curve for 4 at 254 nm.

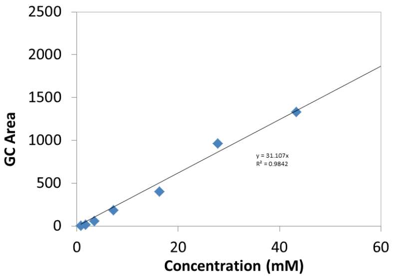

Figure S5. GC calibration curve for 2 at 5.2 min ret time.