**Electrosynthesis in Extended Channel Length, Microfluidic Electrolysis Cells**

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# **General Experimental**

A variety of microfluidic electrochemical cells were used throughout this work, which have been reported elsewhere.1–3 The procedures described below state which reactor was used (Syrris Flux, Ammonite 8 or Ammonite 15) for each specific example, although it is important to note that the procedures are applicable in each reactor, as long as adequate adjustments are made to current, flow rate and/or concentration. Either a carbon PVDF blend (SIGRACET BMA 5, Eisenhuth) or platinum sheet (99.9%, 0.1 mm thick, Johnson Matthey) was used as the anode as stated in the experimental. For the cathode a recessed stainless steel (grade 316L) or recessed carbon PVDF blend was used as stated in the experimental. A Rapid Electronics switching mode power supply (85-1903) or TTi 35 V/10A power supply (type TSX3510P) was used to provide constant current during the experimentation. Either a HPLC style pump (Syrris FRX) or a peristaltic pump (Ismatec Reglo Digital) was used to flow the solutions through the electrochemical cells.

TLC was performed on aluminium plates precoated with silica gel 60 with an F254 indicator; visualised under UV light (254 nm) and/or by staining with potassium permanganate. Flash column chromatography was performed using; high purity silica gel, Geduran®, pore size 60 Å, 230–400 mesh particle size.

1H NMR and 13C NMR spectra were recorded in CDCl3 solutions at 298 K at 400 MHz and 100 MHz respectively. Chemical shifts are reported in δ units using CHCl3 as an internal standard (δ 7.27 ppm 1H, δ 77.00 ppm 13C). Coupling constants (*J*) were recorded in Hz and are corrected. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), td (triplet of doublets) and m (multiplet). Electrospray (ESI) resolution mass spectra were recorded on a Waters ZMD quadrupole spectrometer. Electron impact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC-MS.

Experimental procedures for the anodic methoxylation of *N*-formylpyrrolidine, anodic TEMPO mediated alcohol oxidation and anodic NHC mediated esterification and amidation reactions have been reported elsewhere.3–6

# **Procedure for the Benzylic Methoxylation of 4-*t*-butyltoluene**



A 0.20 M solution of 4-*tert*-butyltoluene (1.78 g, 2.07 mL, 12.0 mmol 1.00 equiv.) with 0.05 M of tetraethylammonium tetrafluoroborate (0.65 g, 3.00 mmol 0.25 equiv.) was made in methanol (60 mL) and the solution was sonicated for 5 min. The solution was flowed through the electrochemical flow cell (Ammonite 8, fitted with a carbon/PVDF anode and stainless steel cathode) at 0.50 mL min–1 with 1.00 A of current applied for 2 h (60 mL total volume of solution). The collected solution was then stirred in water (100 mL) acidified with 2.0 M HCl and stirred for 1 h. The solution was then neutralised with sat. NaHCO3. The organic solution was then extracted with EtOAc (3 x 100 mL), and the combined solutions dried (MgSO4), filtered and the solvent removed to give the crude product as an oil (2.02 g). NMR and EI-MS showed the consumption of starting material and the formation of the 4-*t*-butylbenzaldehyde as the major product. Purification of the crude was achieved by column chromatography in 10% EtOAc in hexanes to give 4-*t*-butylbenzaldehyde (1.13 g, 58%) as a colourless oil. Current efficiency based on isolated yield was 37%.

Spectroscopic and physical data are consistent with reported data.7

**1H NMR** (400 MHz, CDCl3): δ (ppm) 9.99 (1H, s), 7.83 (2H, d, *J* = 8.4 Hz), 7.56 (2H, d, *J* = 8.4 Hz), 1.36 (9H, s). **13C NMR** (100 MHz, CDCl3): δ (ppm) 192.2, 157.6, 134.0, 130.1, 125.5, 35.2, 31.1.

# **Procedure for Paired Electrosynthesis**



A 0.10 M solution of 4-*tert*-butyltoluene (73.8 mg, 0.50 mmol, 1.0 equiv.) with dimethyl phthalate (**1**) (97.6 mg, 0.50 mmol, 1.0 equiv.) and tetraethylammonium tetrafluoroborate (54.0 mg, 0.25 mmol, 0.5 equiv.) in Methanol (5.0 mL) was made up in a volumetric flask and sonicated. The solution was flowed through the electrochemical flow cell (Syrris Flux reactor, fitted with a carbon/PVDF anode and carbon/PVDF cathode) at 0.10 mL min–1 with 80 mA of current applied for 50 min (5.0 mL of solution). On completion the solvent was removed and the crude product was treated with EtOAc (10 mL), upon which a white precipitate was generated (Et4NBF4), which was removed by filtration (the Et4NBF4 can be reused after recrystallization from hot methanol). The solvent was removed to give an oil, which was purified by column chromatography in 20% EtOAc in hexanes. Phthalide (**2**) (40 mg, 0.33 mmol, 67%, (76% BRSM)) was collected as a white solid, and 4-*t*-butylbenzaldeyhde was collected as an oil with mono-methoxylated *t*-butyl toluene as an inseparable impurity. Current efficiency based in the isolated yield of phthalide (**2**) is 54%.

Spectroscopic and physical data for **2** are consistent with reported data.8

**1H NMR** (400 MHz, CDCl3): δ (ppm) 7.94 (1H, d, *J* = 7.6 Hz), 7.70 (1H, td, *J* = 7.6, 1.0 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.51 (1H, d, *J* = 7.6 Hz), 5.33 (2H, s). **13C NMR** (100 MHz, CDCl3): δ (ppm) 171.1, 146.4, 134.0, 129.0, 125.8, 122.1, 69.6.

# **Procedure for the Anodic formation of Quinone Ketals**



A 0.20 M solution of hydroquinone diether **3** (198 mg, 1.0 mmol, 1.0 equiv.) with 0.02 M KOH (1.00 mL of a 0.10 M solution, 0.10 mmol, 0.10 equiv.) was made in methanol (5.00 mL) in a volumetric flask and sonicated. The solution was flowed through the electrochemical flow cell (Syrris Flux, fitted with a Carbon/PVDF anode and stainless steel cathode) at 0.10 mL min–1 with 80 mA of current applied for 50 min (5 mL of solution). On completion, the solvent was removed to give a mixture of the quinone *bis*- and monoketals **4** and **5** (~4:1) as an oil, which was purified by column chromatography in 75% EtOAc in hexanes. Quinone *bis*-ketal **4** (159 mg, 0.81 mmol, 81%) was collected as a colourless oil. Current efficiency based on isolated yield of **4** is 65%.

Spectroscopic and physical data of **4** are consistent with the literature.9

**1H NMR** (400 MHz, CDCl3): δ (ppm) 5.92 (4H, s), 4.05 (8H, s). **13C NMR** (100 MHz, CDCl3): δ (ppm) 130.3, 96.4, 65.2. **LRMS** (ESI+): 197.2 [M+H]+.

# **Procedure for Anodic Fluorination**



Glassware was flame dried and placed under an inert atmosphere. A 0.10 M solution of ethyl (phenylthio)acetate (**6**) (98.1 mg, 0.50 mmol 1.00 equiv.) with triethylamine trihydrofluoride (80.6 mg, 80 µL, 0.50 mmol 1.00 equiv.) and tetrabutylammonium tetrafluoroborate (82.3 mg, 0.25 mmol, 0.5 equiv.) was made up in DME (5 mL) in a volumetric flask and sonicated. 5.00 mL of the reaction solution was flowed through the electrochemical flow cell (Syrris Flux reactor, fitted with a carbon/PVDF or platinum electrode anode and stainless steel cathode) at 0.10 mL min–1 with 70 mA of current applied for 50 min (5.00 mL of solution). On completion, the reaction mixture was diluted with Et2O (30 mL) and quenched with a solution of sat. NaHCO3 (30 mL). The organic solution was separated and washed with brine (2 x 25 mL), dried (MgSO4), filtered and the solvent removed to give a mixture of mono- and difluorinated products as a yellow oil (82%:2%, 19F NMR). The crude product was analysed by 19F NMR to determine the yields of **7** and **8**, by comparing integration of the product signals against a known amount of hexafluorobenzene added to the NMR sample as an internal calibration standard. Current efficiency is 37% based on NMR yield of **7** (82%).

# **Procedure for Kolbe Electrolysis**



A 1.00 M solution of mono-methyl succinate (**9**) (661 mg, 5.00 mmol, 1.00 equiv.) with 10 mol % of KOH (28 mg, 0.50 mmol, 0.10 equiv.) was made in methanol (5.00 mL) in a volumetric flask and sonicated. The solution was then flowed through an electrochemical flow cell (Syrris Flux reactor, fitted with a Pt electrode and stainless steel cathode) at 0.10 mL min–1 with 1.00 A of current passing for 50 min (5.00 mL of solution). On completion the sample was diluted with EtOAc and analysed by GC. The GC was calibrated by running standard solutions of known concentration of starting materials and products to generate calibration curves. From the calibration curve the conversion (always 100%) and the yield was determined. Current efficiency based on GC yield of **10** (60%) is 10%.

# **Procedure for Titration of Electrochemically Generated CeIV**

A 0.10 M solution of Ce(MeSO3)3 was made by treating Ce2(CO3)3∙xH2O (315 mg), with an excess of methane sulfonic acid (720 mg, 0.49 mL) in water (5.00 mL). The 0.10 M Ce(MeSO3)3 solution was flowed through the electrochemical flow cell (Syrris Flux Reactor, fitted with a Pt anode and stainless steel cathode) at 1.00 mL min–1 with 300 mA of current passing for 5 min (5.00 mL of solution). A bright yellow solution was collected which is consistent with the CeIV being generated (CeIV – bright yellow. CeIII – colourless).

On completion, the yellow solution was titrated with a 0.2 M solution of FeIISO4, under an inert atmosphere. The titration indicated 0.48 mmol of CeIV to be present in the solution (96%).

# **Procedure for 4-*t*-butyl Benzaldehyde Mediated by Electrochemically Generated CeIV**



A 0.20 M solution of Ce(MeSO3)3 was made by treating Ce2(CO3)3∙xH2O (1.36 g) with methane sulfonic acid (5.77 g, 3.9 mL) in water (10.0 mL). The 0.20 M Ce(MeSO3)3 solution was flowed through the electrochemical flow cell (Syrris Flux Reactor, fitted with a Pt anode and stainless steel cathode) at 1.0 mL min–1 with 600 mA of current passing for 10 min (10.0 mL of solution). Colour change to a yellow/orange solution was observed. The oxidised solution, containing the CeIV solution was flowed into an RBF containing 4-*t*-butyltoluene (430 mg, 0.50 mL, 2.9 mmol, 5.81 equiv.) in methanesulfonic acid (2.00 mL). The reaction mixture was stirred rapidly at 85 °C under Ar atmosphere for 10 min. After 10 min of stirring the reaction had become colourless, signalling the end of the reaction. The reaction mixture was then allowed to cool. The organic product was extracted with CH2Cl2 (3 x 10 mL, combined, dried (MgSO4), filtered and the solvent removed to give a crude oil. The crude was purified by column chromatography in 15% EtOAc in hexanes. 4-*t­*-butylbenzaldehyde (78.0 mg, 0.48 mmol, 96% (based on CeIV generated)) was collected as a colourless oil. Current efficiency based on isolated yield of 4-*t­*-butylbenzaldehyde is 52%.

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