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Electrochemical Hydroxylation of Electron-Rich Arenes in Continuous Flow

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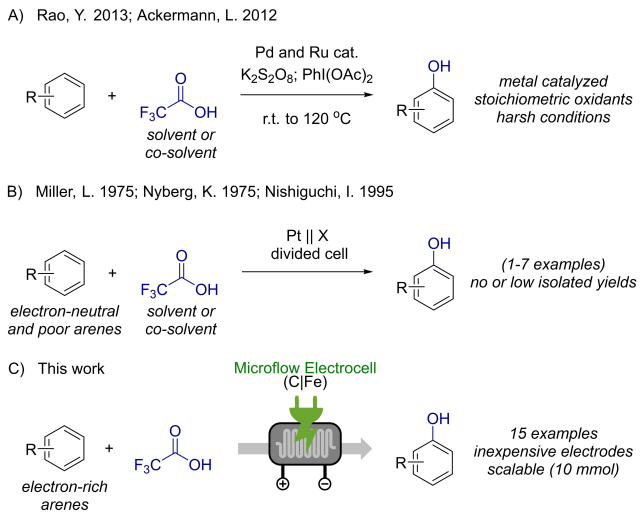
Dedicated to Laura Ošeka, who was born during the preparation of the manuscript for this article and helped to write it.

Electrochemical hydroxylation of arenes by trifluoroacetic acid provides a straightforward access to aryl oxygen compounds under the mild and environmental benign reaction conditions. Harmful and pollutant stoichiometric amounts of oxidation reagents and the use of metal-catalysts can be avoided. Herein, we present a novel method for the synthesis of hydroxylated products from electron-rich arenes that was achieved by the implementation of a continuous-flow setup. The continuous nature of the process allowed to fine-tune the reactions conditions in order to prevent the decomposition of the sensitive products expanding the reaction scope beyond electron-poor and neutral arenes that were previously reported in the batch processes. Thus, synthetically valuable hydroxylated arenes were obtained in good yields with the residence time just over a minute. In order to demonstrate the reliability and the efficiency of the electrochemical flow setup, a scale up experiment was also performed.

Introduction

Aryl oxygen compounds are important precursors for synthesis of valuable polymers, complex bioactive compounds, and are common structural motifs in many natural products.[1–3] Direct synthesis of phenols by oxidative hydroxylation of arenes is the most straightforward yet challenging approach as the products of such transformation are more electron-rich than substrates and are prone to be overoxidized. The traditional methods for arene hydroxylation rely on transition-metal catalysis and often require harsh reaction conditions.[4–6] Out of different possible options to hydroxylate arenes,[7,8] oxygen[9,10] and H_2O_2[11–13] are the most frequently used oxidative hydroxylation agents. Lutz Ackerman and Yu Rao have demonstrated methods in which trifluoroacetic acid was used as a hydroxyl group source in transition-metal catalyzed oxidation of arenes in the presence of stoichiometric oxidants (Scheme 1A).[14,15] Synthetic electrochemistry gathered a significant attention over the last decade since it is a great alternative to the traditional methods that require stoichiometric amounts of toxic and wasteful oxidants and metal catalysts.[16,17] In electrochemical transformations, electrons are used as safe and clean reactants to generate highly reactive radical intermediates under the mild reaction conditions providing access to the previously unapproachable reaction pathways.[18] Therefore, electrochemistry satisfies the principles of green chemistry in many aspects and can be considered sustainable.[19] In the early reported examples of electrochemical hydroxylation of arenes, trifluoroacetic acid was used in high excess, either as a solvent or co-solvent. Additionally, these transformations were carried out in an unfavorable divided electrochemical cell equipped mostly with costly platinum electrodes (Scheme 1B).[20–22] Moreover, these methodologies are limited in their broad reaction applicability with respect to electronic properties of arene substrates. Only seven



Scheme 1. Hydroxylation of arenes using TFA.

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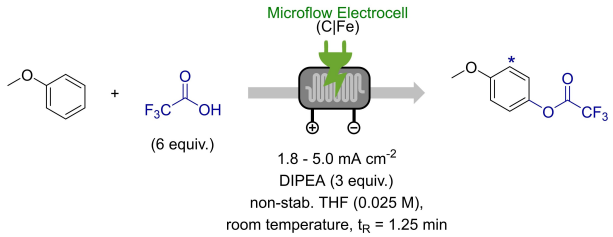
examples in total on the oxidation of electron-poor or neutral arenes with moderate yields are accessible. The more recent work by Nakajama et al. describes electrochemical esterification with TFA in a more feasible undivided cell setup, but this approach is limited only to one aromatic compound, benzene, leaving the scope of electron-rich arenes unexplored.[23] In the transformations described above, the substrate is directly oxidized on the electrode surface. Alternatively, the Ackerman group has recently demonstrated the indirect electrochemical hydroxylation of arenes catalyzed by transition-metals.[24,25]

Selective direct electrochemical hydroxylation of electron-rich arenes is still a difficult task. The desired hydroxylated product is much easier to oxidize than the starting compound, thus overoxidation and polymerization can easily occur leading to deposition on the electrode surface.[26,27] Fouling of electrodes is a common problem for electrochemical batch processes.[18,28] Moreover, such processes can also suffer from emerging local hot-spots and insufficient mixing. However, limitations of the batch-conditions can be overcome by transferring the reaction into a continuous-flow setup. In flow microreactors, the reaction mixture is continuously pumped through narrow channels between the two isolated electrodes (average 250 μm interelectrode gap), which ensures a very efficient mass and heat transfer by diffusion. High electrode surface-to-volume ratio and effective mixing significantly reduce the reaction time (typically 5 min in flow vs. overnight in batch), which helps to prevent degradation of sensitive products under electrochemical conditions and increases the reaction selectivity.[29–31] This knowledge and the previous experience helped us to develop a convenient continuous-flow methodology for the electrochemical hydroxylation of electron-rich aromatic compounds by the use of trifluoroacetic acid as the oxygen source.[32–35] With this procedure we successfully demonstrate a scale-up experiment as well (Scheme 1, C).

Table 1. Reaction Optimization.[a]



Entry	Variation from the standard conditions	Conversion [%][b]	Yield [%][c]
1	TFA (3 equiv.), Bu_3N (2 equiv.), CH_3CN (0.1 M), $t_R = 5$ min	71	31
2	TFA (3 equiv.), Bu_3N (2 equiv.), stab. THF (0.1 M), $t_R = 5$ min	83	68
3	TFA (3 equiv.), Bu_3N (2 equiv.), stab. THF (0.1 M), $t_R = 5$ min graphite anode	85	48
4	TFA (3 equiv.), Bu_3N (2 equiv.), stab. THF	90	74
5	none	88	71
6	no electricity	0	0
7	batch[d]	5	5
8	batch[e]	33	29

[a] Reaction conditions: anisole (1.25 mmol), TFA (6 equiv.), DIPEA (3 equiv.), non-stabilized fresh THF (0.025 M), graphite anode/stainless steel cathode, 1.8–5.0 mA cm^{-2}, room temperature, residence time 1.25 min. [b] Conversion determined by GC-FID with decane as an internal standard. [c] Yield determined by GC-FID with decane as an internal standard. [d] Batch reaction conditions: 0.25 mmol scale, 3.3 mA cm^{-2}, 3.9 F, graphite anode/stainless steel cathode. [e] Batch reaction conditions: 3.3 mA cm^{-2}, 11.8 F, graphite anode/stainless steel cathode, 0.25 mmol scale.

Results and Discussion

We started our investigation of the electrochemical hydroxylation of electron-rich arenes by performing the reaction under the galvanostatic conditions with anisole, as a model substrate, in an electrochemical microflow reactor.[36] In order to keep the reaction setup simple and inexpensive, an undivided-cell reactor equipped with the carbon based anode (graphite) and stainless steel cathode was used alternatively to the previously described methods.[20–22] We have performed an intensive screening for the optimal reaction conditions and the highlights are represented in Table 1 (see *Supporting Information* for the complete screening). First, the preliminary results revealed that TFA ester of cresol **1** forms in low yield, when the reaction is performed in acetonitrile, a typical first-choice solvent for radical transformation (Table 1, entry 1). The optimization experiments showed that the highest yields were achieved with incomplete conversions. Pushing the reactions to the full conversion by increasing the electric current resulted in the degradation of the desired product, as it is more reactive than the starting material. The main detected side products were overoxidized compounds and some arene–arene coupling products.[37,38] Trifluoroacetic acid has to be used in excess in comparison to the amine base to keep it protonated. First, this ensures enough conductivity by forming a salt and second its oxidation potential is thereby substantially elevated. Hence, oxidative deposition/degradation of the amine base can be avoided on the electrode surface, which could subsequently inhibit the electrochemical process. The yield of the reaction increased significantly after the solvent was changed to THF (Table 1, entry 2). Potentially, TFA ester is more stable in THF, while in acetonitrile it undergoes hydrolysis leading to the formation of cresol **1**, which is further overoxidized under the electrochemical conditions. Unfortunately, with the increased yield we have also faced some deposition of the side products on the electrodes over the operation time. To overcome this issue, different electrode combinations were tested. Particularly, we aimed to use graphite for the both electrodes, which would allow to slowly alter the polarity and suppress deposition.[39] However, the graphite cathode proved to be inefficient for the described transformation (Table 1, entry 3). The simultaneous dilution of the reaction mixture and the increase of the flow

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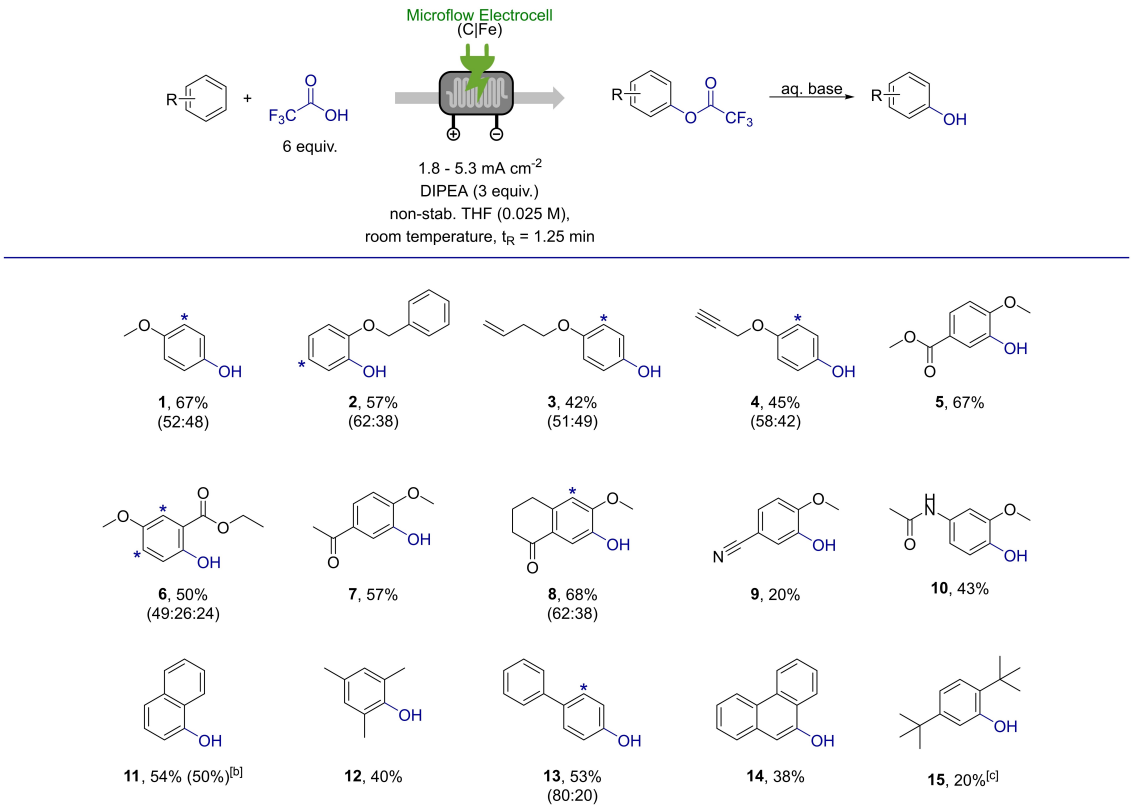
rate enabled stable steady state with high yields while the process productivity remained at the same level. Any deposited materials could thus be flushed out of the active zone of the reactor, while the process remained performing constantly and efficiently. TFA ester of cresol **1** was obtained in 74% yield with the residence time only 1.25 minutes (Table 1, entry 4). To our surprise, these conditions appeared to be completely unproductive when other electron-rich arenes were tested. Further investigation revealed that BHT, used for THF stabilization, also inhibits oxidation of less electron-rich arenes. After reoptimization of the reaction conditions, we have achieved similar to previous results while using an increased amount of TFA and diisopropylethylamine instead of tributylamine and distilled or freshly opened non-stabilized THF (Table 1, entry 5). The newly established conditions were later successfully applied for other substrates in the series. It should be mentioned that the reaction became sensitive to the quality of solvent and amine after BHT was removed. Next, no conversion was observed without electricity confirming the electrochemical nature of the process (Table 1, entry 6). Finally, the reaction performed under the batch conditions provided the product with considerably lower yield comparing to flow (Table 1, entry 7 and 8). High electrode surface-to-volume ratio of the flow microreactor, short interelectrode gap and effective mixing allowed to obtain the product just in 1.25 minutes, whereas the batch process required 10 hours to reach only 33% conversion. Prolonged reaction time causes the decomposition of electron-rich compounds by overoxidation under the electrochemical conditions. Moreover, the Faraday-efficiency of the reaction performed in flow is much higher comparing to that of the batch process (FE_{flow} 49% vs FE_{batch} 5%), making the transformation more sustainable. The productivity of the flow process is 0.64 mmol h^{-1} with 71% yield (0.9 mmol h^{-1} with 100% theoretical yield).

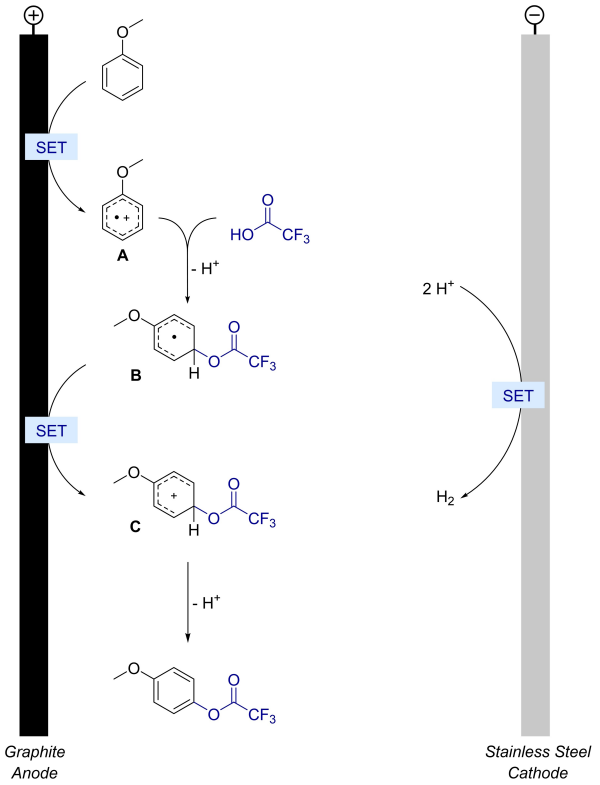
With the optimal reaction conditions in hand, the scope of electrochemical hydroxylation of different electron-rich arenes was investigated (Scheme 2). After completion of the electrochemical reaction, the crude mixture was treated with an aqueous base to yield the hydroxylated product upon TFA ester hydrolysis. Anisole and its derivatives provided a mixture of *ortho*- and *para*-isomers, which are chromatographically separable (Scheme 2, compounds **1**–**4**). However, we kept isomers of cresol **1** unseparated to avoid evaporation of the volatile *ortho*-isomer. Functional groups that might be sensitive towards radical reactions, such as benzyl, propargyl and terminal double bond, stayed intact under our electrochemical conditions. Next, we studied the influence of electron-withdrawing groups on the reactivity of the substrates. Even though these compounds required higher current densities to reach useful conversion rates, the corresponding products were isolated in the highest yields (Scheme 2, compounds **5**–**8**). Both carboxyl and carbonyl groups tolerated the work-up procedure well and did not



Scheme 2. Scope of hydroxylation of electron-rich arenes. [a] Reaction conditions: arene (1 mmol), TFA (6 equiv.), DIPEA (3 equiv.), non-stabilized fresh THF (0.025 M), graphite anode/stainless steel cathode, 1.8–5.3 mA cm^{-2}, room temperature, residence time 1.25 min, collected for 66.6 min. Work-up with saturated $NaHCO_3$. In brackets the ratio of different isomers is shown. The overall isolated yield is given for the chromatographically separated isomers of compounds **2**–**4**, **6** and **8**. [b] 10 mmol scale reaction collected for 66 h 6 min. [c] Residence time 2.5 min, collected for 133.2 min.

undergo hydrolysis nor aldol reaction. Unfortunately, 4-methoxybenzonitrile showed low conversion even at high current giving the product in rather low yield (Scheme 2, compound **9**). When acetyl protected 4-methoxyaniline was submitted to the electrochemical reaction, the obtained hydroxylated product contained methoxy group at the *meta*-position (Scheme 2, compound **10**). Potentially, the methyl group migrated from one oxygen-atom to another during the basic work-up procedure. Finally, we have turned our attention to other electron-rich arenes that do not contain methoxy group in the structure (Scheme 2, compounds **11**–**15**). Naphthalene reacted smoothly under the standard reaction conditions and 1-naphthol **11** was obtained exclusively in good yield. In order to demonstrate the usefulness of the developed method and the reliability of the flow process, we performed the scale up experiment (10 mmol) without any additional optimization by pumping the reaction mixture for a prolonged time.[30,31,40] Further, the electrochemical hydroxylation of mesitylene and biphenyl proceeded similarly to other electron-rich arenes and products were isolated in good yields and high regioselectivity for the latter (Scheme 2, compounds **12** and **13**). Although in the reaction with phenanthrene the preliminary experiments demonstrated very promising results, isolation of phenanthrol **14** proved challenging, as it was prone to the partial decomposition during the work-up. Moreover, electrochemical oxidation of anthracene in the presence of trifluoroacetic acid proceeded very efficiently providing the corresponding ester as a single isomer with the highest NMR yield (85%) in the series. However, despite the stability of the corresponding TFA ester under the electrochemical conditions, 9-anthracenol was oxidized by atmospheric oxygen and formed dimeric compound upon the work-up leading to the complete loss of the desired product (for more information see *Supporting Information*). An attempt to isolate TFA ester of anthracenol resulted in sluggish yield, as it readily hydrolyzed on silica gel and decomposed. On the contrary, 1,4-di-*tert*-butylbenzene stayed almost unreactive under the standard reaction condition, probably due to the steric hindrance from two *tert*-butyl groups, and only a small amount of compound **15** was obtained, when the reaction was performed at lower flow rate. Finally, it is worth mentioning that the highest possible yields for all the substrates were obtained without reaching the full conversion making it possible to recover unreacted starting material.

We propose that the electrochemical transformation is initiated by a single electron transfer (SET) oxidation of an electron-rich arene on the surface of anode (Scheme 3). Being a strong electrophile, radical cation **A** is trapped by trifluoroacetic acid leading to the formation of the neutral radical **B**, which further undergoes second oxidation event. Finally, the aromatic system is restored upon deprotonation of cation **C** by the base. Simultaneously with oxidative processes, hydrogen reduction occurs as a cathodic half-reaction. After completion of the electrochemical part of the reaction sequence, TFA ester is hydrolyzed by aqueous base during the work-up procedure to yield the corresponding hydroxylated product. Comparing our experimental results to the previously published data,[41,42] it can be assumed that the working oxidation potential window for



Scheme 3. Proposed mechanism.

the developed method is approximately 1.6–2.1 V *vs* SCE with anisole in the middle. For the substrates with higher E_{OX} only traces of products were observed, while solvent oxidation was prevalent. On the contrary, it was challenging to perform mono hydroxylation of very electron-rich arenes with E_{OX} lower than 1.6 volts, as they tend to be overoxidized or/and form arene–arene coupling products.[26,27]

Conclusion

In conclusion, we have reported the electrochemical hydroxylation of electron-rich arenes. The developed transformation is performed under the continuous-flow conditions that allowed to obtain sensitive products in only 1.25 minutes residence time. The method can be straightforwardly scaled up to the synthetically useful scale. Valuable hydroxylated arenes were obtained in good yields without the use of harmful stoichiometric oxidants or metal-catalysts, demonstrating the sustainability of this presented electrochemical procedure.

Experimental Section

General information. All capillary tubing and microfluidic fittings were purchased from IDEX Health & Science. Disposable syringes were from BD Discardit II®, NORM-JECT® purchased from VWR Scientific. Syringe pumps used: Chemix Inc. Fusion 200 Touch and KD Scientific Inc. KDS-200-CE. Reagents and dry solvents were

bought from Sigma Aldrich, TCI, Honeywell and Fluorochem and are used as received. Technical solvents were bought from VWR International, Keemiakaubandus AS and Biosolve, and are used as received. THF refers to tetrahydrofuran, when needed THF was distilled over $LiAlH_4$, PE refers to petroleum ether b.p 40–60 °C, EtOAc refers to ethyl acetate, DCM refers to dichloromethane. ^1H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument or Bruker-Avance 400 at 400 MHz for ^1H, 377 MHz for ^{19}F and 100 MHz for ^{13}C. ^1H NMR spectra are reported in parts per million (ppm) downfield relative to CD_3OD (3.31 ppm), DMSO-d_6 (2.50 ppm) or $CDCl_3$ (7.26 ppm) and ^{13}C NMR spectra are reported in ppm relative to CD_3OD (49.00 ppm), DMSO-d_6 (39.52 ppm) or $CDCl_3$ (77.16 ppm) unless stated otherwise. GC analyses were performed on a GC-MS combination (Shimadzu GC-2010 Plus coupled to a Mass Spectrometer; Shimadzu GCMS-QP 2010 Ultra) with an auto sampler unit (AOC-20i, Shimadzu) and GC-FID (Shimadzu GC-2010) with an auto sampler unit (AOC-20i, Shimadzu). Precoated silica gel plates (Merck 60 F254 or F254, Supelco Sigma-Aldrich™) were used for TLC. Flash column chromatography was performed on a Biotage® Isolera Prime with silica gel Kieselgel 63–200 μm.

For all electrochemical continuous-flow reactions, a homemade flow cell was used, together with a Velleman LABPS3005D power supply (for more information see *Supporting information*). The cell consists of a working electrode and a counter electrode, with a PTFE (polytetrafluoroethylene) gasket containing micro-channels in between. The material used for the electrodes were stainless steel electrode (316 L) and Graphite AC-K800 premium Grade (purchased by AgieCharmilles). The active reactor volume is 700 μL. This results in an undivided electrochemical cell. In the cell, direct contact between the electrode surface and the reaction mixture is established. The reaction mixture is pumped through the system via syringe pump, and is collected in a glass vial. All the technical data of the electrochemical microreactor are reported elsewhere.[36]

Voltammograms. Arene (1.0 equiv., 1.25 mmol) together with trifluoroacetic acid (6 equiv., 7.50 mmol, 0.57 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 3.75 mmol, 0.65 mL) were charged to 50 mL volumetric flask and filled with freshly distilled THF (0.025 M) until the bar. The mixture was swirled until homogeneous and taken up into a 50 mL disposable syringe. The solution was pumped through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the current was increased from 50 mA to 150 mA with increments of 10 mA. After steady reaction state was reached (10 minutes at 0.6 mL/min), the corresponding potential was noted and a sample (0.1 mL) was collected in a vial for each data point. The samples were diluted with DCM and analyzed using GC-MS with decane or dodecane as an internal standard.

General procedure. Arene (1.0 equiv., 1.25 mmol) together with trifluoroacetic acid (6 equiv., 7.50 mmol, 0.57 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 3.75 mmol, 0.65 mL) were charged to 50 mL volumetric flask and filled with freshly distilled THF (0.025 M) until the bar. The mixture was swirled until homogeneous and taken up into a 50 mL disposable syringe. The solution was pumped through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the constant current (selected on the basis of the voltammograms recorded) was applied and the system was stabilized for 10minutes. After steady state was reached, the reaction mixture was collected to a 100 mL round-bottom flask for 66.6 min, which corresponds to 1.0 mmol scale. The crude mixture was concentrated under vacuum and saturated aq. $NaHCO_3$ (25 mL) was added to the flask. The reaction mixture was vigorously stirred overnight at room temperature to achieve full hydrolysis of TFA ester. Next, the reaction mixture was extracted with DCM (4×15 mL) first from $NaHCO_3$ solution and then from 1 M HCl solution (25 mL). The organic layers were combined, dried using a phase separator and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel and analyzed by TLC, GS-MS, ^{19}F-NMR, ^1H-NMR and ^{13}C-NMR.

4-Methoxyphenol (1 a) and 2-methoxyphenol (1 b).[43] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–50 % of Et_2O in pentane) to give mixture of isomers **1 a** and **1 b** as a colorless oil in 67 % yield (83 mg, 0.67 mmol) and isomer ratio 52 : 48. ^1H NMR of **1 a** (399 MHz, MeOD) δ 6.75 (d, J = 9.1 Hz, 2H, Ar–H), 6.70 (d, J = 9.0 Hz, 2H, Ar–H), 3.71 (s, 3H, OCH_3). ^{13}C NMR of **1 a** (100 MHz, MeOD) δ = 154.5, 149.0, 116.8, 115.7, 56.2. MS of **1 a** (70 eV) *m/z*: 124 (96) $[M]^+$, 109 (100), 81 (48). ^1H NMR of **1 b** (399 MHz, MeOD) δ 6.95–6.85 (m, 1H, Ar–H), 6.81–6.75 (m, 3H, Ar–H), 3.83 (s, 3H, OCH_3). ^{13}C NMR of **1 b** (100 MHz, MeOD) δ = 152.2, 147.6, 122.2, 120.8, 116.3, 112.8, 56.3. MS of **1 b** (70 eV) *m/z*: 124 (89) $[M]^+$, 109 (100), 81 (58).

2-(Benzyloxy)phenol (2 a)[44] **and 4-(benzyloxy)phenol (2 b).**[45] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica (5–50 % of Et_2O in PE) to give **2 a** as a yellow oil and **2 b** as a white solid in 57 % combined yield (113 mg, 0.56 mmol) and isomer ratio 62 : 38. ^1H NMR of **2 a** (400 MHz, $CDCl_3$) δ 7.48–7.35 (m, 5H, Ar–H), 7.01–6.82 (m, 4H, Ar–H), 5.72 (s, 1H, OH), 5.12 (s, 2H, OCH_2). ^{13}C NMR of **2 a** (101 MHz, $CDCl_3$) δ = 146.1, 145.9, 136.5, 128.8, 128.5, 127.9, 122.0, 120.2, 114.9, 112.4, 71.2. 2-orto MS of **2 a** (70 eV) *m/z*: 200 (6) $[M]^+$, 92 (9), 91 (100). ^1H NMR of 2b (400 MHz, $CDCl_3$) δ 7.46–7.35 (m, 4H, Ar–H), 7.35–7.29 (m, 1H, Ar–H), 6.86 (d, J = 9.0 Hz, 2H, Ar–H), 6.76 (d, J = 9.0 Hz, 2H, Ar–H), 5.01 (s, 2H, OCH_2), 4.51 (s, 1H, OH). ^{13}C NMR of **2 b** (101 MHz, $CDCl_3$) δ = 153.2, 149.8, 137.4, 128.7, 128.0, 127.6, 116.20, 116.18, 70.9. MS of **2 b** (70 eV) *m/z*: 200 (11) $[M]^+$, 92 (8), 91 (100).

4-(But-3-en-1-yloxy)phenol (3 a)[46] **and 2-(but-3-en-1-yloxy)phenol (3 b).**[47] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–30 % of Et_2O in PE) to give **3 a** as a yellow solid and **3 b** as a yellow oil in 42 % combined yield (69 mg, 0.42 mmol) and isomer ratio 51 : 49. ^1H NMR of **3 a** (400 MHz, $CDCl_3$) δ 6.80 (d, J = 9.4 Hz, 2H, Ar–H), 6.75 (d, J = 9.4 Hz, 2H, Ar–H), 5.90 (ddt, J = 17.1, 10.3, 6.7 Hz, 1H, $CH{=}CH_2$), 5.16 (dq, J = 17.2, 1.6 Hz, 1H, $=CH_2$), 5.10 (dq, J = 10.3, 1.3 Hz, 1H, $=CH_2$), 4.91 (s, 1H, OH), 3.96 (t, J = 6.7 Hz, 2H, OCH_2), 2.52 (qt, J = 6.8, 1.4 Hz, 2H, $CH{-}CH_2{-}CH_2$). ^{13}C NMR of **3 a** (101 MHz, $CDCl_3$) δ = 153.1, 149.7, 134.7, 117.1, 116.2, 116.0, 68.2, 33.9. MS of **3 a** (70 eV) *m/z*: 164 (25) $[M]^+$, 110 (100), 55 (40). ^1H NMR of **3 b** (400 MHz, $CDCl_3$) δ 6.97–6.92 (m, 1H, Ar–H), 6.91–6.80 (m, 3H, Ar–H), 5.90 (ddt, J = 17.1, 10.3, 6.7 Hz, 1H, $CH{=}CH_2$), 5.69 (s, 1H, OH), 5.20 (dq, J = 17.2, 1.6 Hz, 1H, $=CH_2$), 5.15 (dq, J = 10.2, 1.4 Hz, 1H, $=CH_2$), 4.11 (t, J = 6.5 Hz, 2H, OCH_2), 2.57 (qt, J = 6.6, 1.4 Hz, 2H, $CH{-}CH_2{-}CH_2$). ^{13}C NMR of **3 b** (101 MHz, $CDCl_3$) δ = 146.1, 145.9, 134.3, 121.8, 120.2, 117.6, 114.7, 112.2, 68.2, 33.8. MS of **3 b** (70 eV) *m/z*: 164 (31) $[M]^+$, 110 (78), 55 (100).

4-(Prop-2-yn-1-yloxy)phenol (4 a)[48] **and 2-(prop-2-yn-1-yloxy)phenol (4 b).**[49] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–50 % of Et_2O in PE) to give **4 a** as a yellow oil and **4 b** as a yellow oil in 45 % combined yield (67 mg, 0.45 mmol) and isomer ratio 58 : 42. ^1H NMR of **4 a** (400 MHz, $CDCl_3$) δ 6.90–6.84 (m, 2H, Ar–H), 6.80–6.75 (m, 2H, Ar–H), 4.76 (s, 1H, OH), 4.63 (d, J = 2.4 Hz, 2H, OCH_2), 2.51 (t, J = 2.4 Hz, 1H, ≡CH). ^{13}C NMR of **4 a** (101 MHz, $CDCl_3$) δ = 151.9, 150.4,

116.5, 116.2, 79.0, 75.5, 56.8. MS of **4a** (70 eV) *m/z*: 148 (31) $[M]^+$, 109 (100). ^{1}H NMR of **4b** (400 MHz, $CDCl_3$) δ 7.01–6.90 (m, 3H, Ar–H), 6.88–6.83 (m, 1H, Ar–H), 5.63 (s, 1H, OH), 4.76 (d, *J* = 2.4 Hz, 2H, OCH_2), 2.56 (t, *J* = 2.4 Hz, 1H, ≡CH). ^{13}C NMR of **4b** (101 MHz, $CDCl_3$) δ = 146.3, 144.8, 122.9, 120.3, 115.3, 113.0, 78.2, 76.3, 57.2. MS of **4b** (70 eV) *m/z*: 148 (40) $[M]^+$, 109 (100).

Methyl 3-hydroxy-4-methoxybenzoate (5).[50] Reaction was performed following the general procedure at 130 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–35% of EtOAc in PE) to give **5** as a colorless oil in 67% yield (122 mg, 0.67 mmol). ^{1}H NMR of **5** (400 MHz, MeOD) δ 7.53 (dd, J = 8.5, 2.1 Hz, 1H, Ar–H), 7.42 (d, J = 2.1 Hz, 1H, Ar–H), 6.98 (d, J = 8.5 Hz, 1H, Ar–H), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH3). ^{13}C NMR of **5** (101 MHz, MeOD) δ = 168.6, 153.4, 147.5, 123.9, 123.4, 117.0, 111.8, 56.4, 52.4. MS of **5** (70 eV) *m/z*: 182 (51) $[M]^+$, 167 (4), 151 (100), 123 (24), 108 (10).

Ethyl 2-hydroxy-5-methoxybenzoate (6a),[51] **ethyl 4-hydroxy-3-methoxybenzoate (6b),**[52] **and ethyl 2-hydroxy-3-methoxybenzoate (6c).**[51] Reaction was performed following the general procedure at 90 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (10–30% of Et_2O in PE) to give **6a** as a colorless oil, **6b** as a beige solid and **6c** as a colorless oil in 50% combined yield (99 mg, 0.5 mmol) and isomer ratio 49:26:24. ^{1}H NMR of **6a** (400 MHz, $CDCl_3$) δ 10.45 (s, 1H, OH), 7.29 (d, *J* = 3.2 Hz, 1H, Ar–H), 7.07 (dd, *J* = 9.1, 3.2 Hz, 1H, Ar–H), 6.90 (d, *J* = 9.0 Hz, 1H, Ar–H), 4.41 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 1.41 (t, *J* = 7.1 Hz, 3H, CH_2–CH_3). ^{13}C NMR of **6a** (101 MHz, $CDCl_3$) δ = 170.0, 156.2, 152.1, 123.8, 118.6, 112.3, 112.2, 61.6, 56.0, 14.3. MS of **6a** (70 eV) *m/z*: 196 (36) $[M]^+$, 150 (57), 122 (100), 107 (17), 92 (10). ^{1}H NMR of **6b** (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.3, 1.9 Hz, 1H, Ar–H), 7.55 (d, *J* = 2.0 Hz, 1H, Ar–H), 6.94 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.98 (s, 1H, OH), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 1.38 (t, *J* = 7.1 Hz, 3H, CH_2–CH_3). ^{13}C NMR of **6b** (101 MHz, $CDCl_3$) δ = 166.6, 150.0, 146.3, 124.3, 122.8, 114.1, 111.8, 60.9, 56.3, 14.5. MS of **6b** (70 eV) *m/z*: 196 (28) $[M]^+$, 150 (100), 122 (17), 107 (25). ^{1}H NMR of **6c** (400 MHz, $CDCl_3$) δ 11.09 (bs, 1H, OH), 7.44 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar–H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar–H), 6.81 (t, *J* = 8.0 Hz, 1H, Ar–H), 4.40 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 1.41 (t, *J* = 7.1 Hz, 3H, CH_2–CH_3). ^{13}C NMR of **6c** (101 MHz, $CDCl_3$) δ = 170.6, 152.2, 148.6, 121.2, 118.5, 116.5, 112.9, 61.7, 56.3, 14.3. MS of **6c** (70 eV) *m/z*: 196 (44) $[M]^+$, 151 (100), 123 (22), 108 (8).

1-(3-Hydroxy-4-methoxyphenyl)ethan-1-one (7).[53] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of Et_2O in DCM) to give **7** as a yellowish solid in 57% yield (94 mg, 0.56 mmol). ^{1}H NMR of **7** (400 MHz, MeOD) δ 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar–H), 7.41 (d, *J* = 2.2 Hz, 1H, Ar–H), 6.99 (d, *J* = 8.5 Hz, 1H, Ar–H), 3.92 (s, 3H, OCH_3), 2.52 (s, 3H, C=OCH_3). ^{13}C NMR of **7** (101 MHz, MeOD) δ = 199.6, 153.8, 147.6, 131.7, 123.1, 115.7, 111.7, 56.4, 26.3. MS of **7** (70 eV) *m/z*: 166 (47) $[M]^+$, 151 (100), 123 (33), 108 (11).

7-Hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (8a) and 5-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (8b).[54–56] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (1–30% of EtOAc in PE) to give **8a** as a white and **8b** as an orange solid in 67% combined yield (129 mg, 0.67 mmol) and isomer ratio 62:38. ^{1}H NMR of **8a** (400 MHz, MeOD) δ = 7.34 (s, 1H, Ar–H), 6.80 (s, 1H, Ar–H), 3.91 (s, 3H, OCH_3), 2.89 (t, *J* = 6.1, 2H, Ar–CH_2), 2.54 (dd, *J* = 7.2, 5.8, 2H, C=OCH_2), 2.07 (p, *J* = 6.5, 2H, CH_2–CH_2–CH_2). ^{13}C NMR of **8a** (101 MHz, MeOD) δ = 200.1, 154.4, 146.5, 140.4, 126.9, 113.3, 111.6, 56.4, 39.5, 30.3, 24.9. MS of **8a** (70 eV) *m/z*: 192 (81) $[M]^+$, 177 (12), 164 (47), 136 (100). ^{1}H NMR of **8b** (400 MHz, MeOD) δ 7.55 (d, *J* = 8.7 Hz, 1H, Ar–H), 6.93 (d, *J* = 8.6 Hz, 1H, Ar–H), 3.93 (s, 3H, OCH_3), 2.91 (t, *J* = 6.2 Hz, 2H, Ar–CH_2), 2.56 (dd, *J* = 7.3, 5.7 Hz, 2H, C=OCH_2), 2.07 (p, *J* = 6.6 Hz, 2H, CH_2–CH_2–CH_2). ^{13}C NMR of **8b** (101 MHz, MeOD) δ = 200.7, 153.0, 144.1, 132.9, 127.4, 120.5, 109.9, 56.4, 39.7, 24.00, 23.97. MS of **8b** (70 eV) *m/z*: 192 (100) $[M]^+$, 177 (28), 164 (86), 136 (76).

3-Hydroxy-4-methoxybenzonitrile (9).[57] Reaction was performed following the general procedure at 150 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–15% of EtOAc in 1:1 PE:DCM) to give **9** as a white solid in 20% yield (30 mg, 0.2 mmol). ^{1}H NMR of **9** (400 MHz, MeOD) δ 7.17 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar–H), 7.05 (d, *J* = 2.1 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.4 Hz, 1H, Ar–H), 3.90 (s, 3H, OCH_3). ^{13}C NMR of **9** (101 MHz, MeOD) δ = 153.3, 148.4, 126.1, 120.2, 119.0, 112.9, 104.7, 56.5. MS of **9** (70 eV) *m/z*: 149 (71) $[M]^+$, 134 (100), 106 (66).

***N*-(4-Hydroxy-3-methoxyphenyl)acetamide (10).**[58] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–45% of EtOAc in DCM) to give **10** as an orange solid in 43% yield (77 mg, 0.42 mmol). ^{1}H NMR of **10** (400 MHz, DMSO) δ 9.77 (s, 1H, NH), 9.27 (s, 1H, OH), 7.39 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.42 (d, *J* = 2.8 Hz, 1H, Ar–H), 6.35 (dd, *J* = 8.8, 2.8 Hz, 1H, Ar–H), 3.67 (s, 3H, OCH_3), 2.04 (s, 3H, C=OCH_3). ^{13}C NMR of **10** (101 MHz, DMSO) δ = 168.8, 156.9, 149.7, 123.9, 119.6, 104.2, 102.1, 55.0, 23.3. MS of **10** (70 eV) *m/z*: 181 (25) $[M]^+$, 139 (79), 124 (100).

1-Naphthol (11).[59] Reaction was performed following the general procedure at 75 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in PE) to give **11** as a pale pink solid in 54% yield (78 mg, 0.54 mmol). ^{1}H NMR of **11** (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 1H, Ar–H), 7.86–7.78 (m, 1H, Ar–H), 7.53–7.47 (m, 2H, Ar–H), 7.45 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.31 (dd, *J* = 8.3, 7.4 Hz, 1H, Ar–H), 6.82 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar–H), 5.28 (s, 1H, OH). ^{13}C NMR of **11** (101 MHz, $CDCl_3$) δ = 151.5, 134.9, 127.8, 126.6, 126.0, 125.4, 124.5, 121.7, 120.8, 108.7. MS of **11** (70 eV) *m/z*: 144 (95) $[M]^+$, 115 (100).

2,4,6-Trimethylphenol (12).[60] Reaction was performed following the general procedure at 100 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in hexane) to give **12** as a light-yellow solid in 40% yield (55 mg, 0.4 mmol). ^{1}H NMR of **12** δ 6.80 (s, 2H, Ar–H), 4.38 (bs, 1H, OH), 2.22 (s, 9H, 3xCH_3). ^{13}C NMR of **12** (100 MHz, $CDCl_3$) δ = 150.0, 129.4, 129.2, 122.9, 20.5, 16.0. MS of **12** (70 eV) *m/z*: 136 (71) $[M]^+$, 121 (100), 91 (29).

[1,1′-Biphenyl]-4-ol (13).[61] Reaction was performed following the general procedure at 70 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (5–20% of EtOAc in hexane) to give **13** as a mixture of isomers (80:20) in 53% yield (91 mg, 0.53 mmol). ^{1}H NMR of **13** the main *para*-isomer (400 MHz, MeOD) δ 7.59–7.48 (m, 2H, Ar–H), 7.44 (d, *J* = 8.6 Hz, 2H, Ar–H), 7.40–7.33 (m, 2H, Ar–H), 7.27–7.20 (m, 1H, Ar–H), 6.85 (d, *J* = 8.6 Hz, 2H, Ar–H). ^{13}C NMR of **13** the main *para*-isomer (101 MHz, MeOD) δ = 158.2, 142.4, 133.9, 129.7, 129.0, 127.4, 127.4, 116.6. MS of **13** (70 eV) *m/z*: 170 (100) $[M]^+$, 141 (24).

Phenanthren-9-ol (14).[62] Reaction was performed following the general procedure at 50 mA for 66.6 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in PE) to give **14** as a yellow oil in 38% yield (74 mg, 0.38 mmol). ^{1}H NMR of **14** (400 MHz, MeOD) δ 8.68 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.1 Hz, 1H, Ar–H), 8.32 (dd, *J* = 8.1, 1.6 Hz, 1H, Ar–H), 7.69–7.55 (m, 3H, Ar–H), 7.49–7.38 (m, 2H, Ar–H), 7.01 (s, 1H, Ar–H). ^{13}C NMR of **14** (101 MHz, MeOD) δ = 152.5, 134.9, 132.8, 127.9, 127.77, 127.75, 127.6, 127.4, 127.0, 124.6, 123.8, 123.6, 123.5, 105.9. MS of **14** (70 eV) *m/z*: 194 (100) $[M]^+$, 165 (89).

2,5-Di-*tert*-butylphenol (15).[63] Reaction was performed following the general procedure at 90 mA and 0.3 mL/min flowrate for 133.2 minutes. Purified by flash column chromatography on silica gel (2–10% of EtOAc in cyclohexane) to give **15** as a light-yellow solid in 20% yield (42 mg, 0.2 mmol). ^{1}H NMR of **15** (399 MHz, MeOD) δ 7.07 (d, J = 8.1 Hz, 1H, Ar–H), 6.77 (d, J = 1.9 Hz, 1H, Ar–H), 6.74 (dd, J = 8.1, 2.0 Hz, 1H, Ar–H), 1.36 (s, 9H, 3xCH_3), 1.27 (s, 9H, 3xCH_3). ^{13}C NMR of **15** (100 MHz, MeOD) δ = 156.8, 150.9, 134.0, 127.0, 116.8, 114.3, 35.1, 34.9, 31.8, 30.1. MS of **15** (70 eV) *m/z*: 206 (18) $[M]^+$, 191 (100).

Procedure for scale-up experiment. Naphthalene (1.0 equiv., 12.5 mmol, 1.6 g) together with trifluoroacetic acid (6 equiv., 75.5 mmol, 5.74 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 3.0 equiv., 37.5 mmol, 6.73 mL) were charged to 500 mL volumetric flask and filled with fresh non-stabilized HPLC-grade THF (0.025 M) until the bar. The mixture was stirred until the solution was homogeneous and placed into a 500 mL round-bottom flask. The solution was pumped using ThalesNano Micro HPLC pump through the electrochemical setup with a fixed flowrate of 0.6 mL/min to give a residence time of 1.25 minutes in the active part of the reactor, equipped with a graphite anode, steel cathode divided by a 0.25 mm thick Teflon gasket. Next, the constant current of 80 mA was applied and the system was stabilized for 10minutes. After steady state was reached, the reaction mixture was collected to a 500 mL round-bottom flask for 666 min, which corresponds to 10 mmol scale. The crude mixture was concentrated under vacuum and saturated aq. $NaHCO_3$ (100 mL) was added to the flask. The reaction mixture was vigorously stirred overnight at room temperature to achieve full hydrolysis of TFA ester. Next, the reaction mixture was extracted with DCM (4×150 mL) first from $NaHCO_3$ solution and then from 1 M HCl solution (100 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (5–20% of Et_2O in PE) to give **1-naphthol (11)** as a pinkish solid in 50% yield (720 mg, 5.0 mmol).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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