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Alternating Current Electrolysis for Organic Electrosynthesis: Trifluoromethylation of (Hetero)arenes

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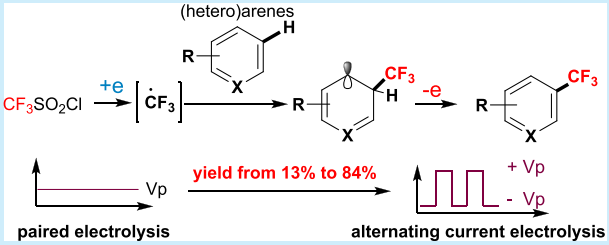
ABSTRACT: Paired electrolysis has a limited reaction scope for organic synthesis because it is often not compatible with reactions involving short-lived intermediates. We addressed this limitation using alternating current electrolysis (ACE). Using trifluoromethylation of (hetero)arenes as a model reaction, we showed that the yield was improved from 13% using paired electrolysis to 84% using ACE. We have also developed a theory for guiding the rational design of reaction parameters for future applications of ACE.



Organic electrosynthesis has recently attracted much attention from synthetic chemists because it is sustainable and can provide unique reactivity.[1−5] In typical organic electrosynthetic reactions, only one electrode is utilized to transform substrates of interest, while the other entails the redox transformation of sacrificial species, making these processes less sustainable than desired. Paired electrolysis, in which two desirable half-reactions are performed simultaneously at the two electrodes, is mostly unexplored. As summarized by Baran et al.,[6] only ∼20 out of ∼900 organic electrosynthetic methods developed between 2000 and 2017 were based on paired electrolysis. Paired electrolysis is attractive because it not only improves the energy efficiency by using both electrodes but also provides a unique reaction environment where two redox-opposite reactions of substrates take place in the same pot.[7] The limited reaction scope of paired electrolysis is because the slow mass transfer of intermediates between two electrodes requires stable intermediates.[8−16] For reactions involving short-lived intermediates, paired electrolysis generally leads to low yields due to the loss of the intermediates during mass transfer (Figure 1a).

To overcome this inherent limitation of paired electrolysis, Mo et al. closely spaced the electrodes in a microfluidics platform to reduce the mass transfer time.[17] However, this approach requires complicated device fabrication, and the smallest interelectrode distance they examined (25 μm) can only handle reactions with intermediates having a subsecond or longer lifetime (estimated from the interelectrode diffusion time). Here, we propose a more straightforward approach: alternating current electrolysis (ACE). During ACE, an alternating voltage ($\pm V$) is applied to drive the redox transformations of the substrates sequentially at the *same* electrode (Figure 1b). ACE has been largely underexplored for organic synthesis.[18−22] In this work, we hypothesize that, in this reaction scheme, the intermediates do not have to migrate between the two electrodes, enabling short-lived intermediates to react immediately upon the electrode polarity reversal.

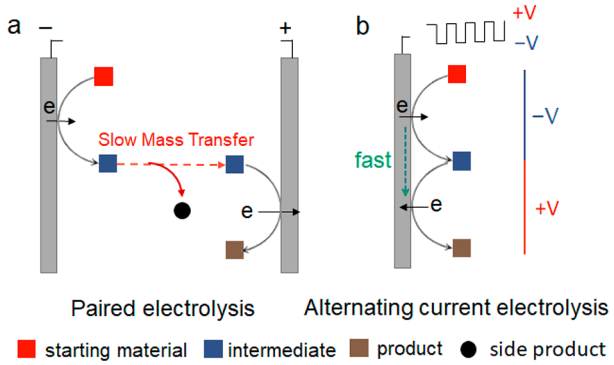


Figure 1. Schematics of (a) paired electrolysis and (b) proposed alternating current electrolysis (ACE) for a sequential reaction that includes two redox-opposite steps.

To test this proposed idea, we chose trifluoromethylation of (hetero)arenes as the model reaction.[23−27] Direct trifluoromethylation is of great importance for pharmaceuticals.[28] The trifluoromethylation reaction, developed by MacMillan et al.,[29] proceeds via a sequential reaction mechanism: triflyl chloride (**1**) is first reduced to form CF_3 radical, then the reactive CF_3

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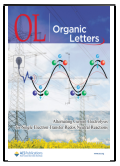

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radical combines with aromatic systems; finally, the resultant radical undergoes oxidation to form the product. In principle, the same chemical transformations could be accomplished electrochemically by performing the redox events at the cathode and anode sequentially. Because the radical intermediates formed by CF_3 radical addition to (hetreo)-arenes lost the aromaticity, they are unstable[30,31] and can cause low yields of trifluoromethylated products using the paired electrolysis setup, which we hypothesize will be addressed by ACE.

Figure 2a shows our experimental setup. The power supply was a waveform generator, which can supply either a constant

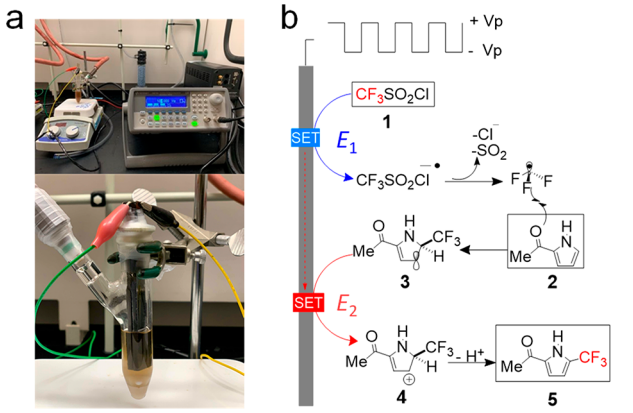
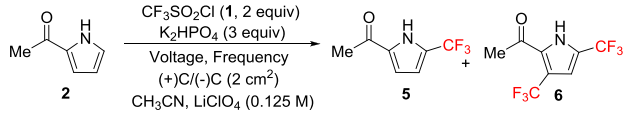


Figure 2. (a) Photographs of the experimental setup for ACE. A square waveform was applied between two glassy carbon plate electrodes by a waveform generator. (b) Proposed mechanism for electrochemical trifluoromethylation of 2-acetylpyrrole (**2**) using ACE.

voltage bias (DC) to perform paired electrolysis or an oscillating square waveform (AC) to perform ACE. During ACE, the reaction was initiated by reducing **1** to CF_3 radicals when the potential of an electrode was negative (Figure 2b). The generation of CF_3 radicals was confirmed by a radical trapping experiment using TEMPO (Figure S1). CF_3 radicals then combined with 2-acetylpyrrole (**2**) to form the radical intermediate **3**. Upon the voltage polarity reversal, **3** was oxidized to the allylic cation **4** at the *same* electrode. Subsequent deprotonation of **4** was rapid, generating the final product **5**. During ACE, the same chemical transformations were also taking place on the other electrode.

During reaction optimization (Table 1), we varied the frequency f and amplitude V_p of the square waveform. We found that trifluoromethylation of **2** at 100 Hz and 4.4 V (entry 5) afforded the desired product **5** in 84% yield. The mono/bistrifluoromethylated product ratio (**5**/**6**) was found to be 19:1. Both f and V_p strongly affected the yield and selectivity. At 100 Hz, **5** was predominantly formed with a **5**/**6** ratio of >20:1 (entries 4 and 6). In contrast, **6** became more favorable at 10 Hz (entry 7). At 1000 Hz, no reaction took place (entry 8). If V_p was set greater or less than 4.4 V, the yield of **5** decreased. At V_p < 4.4 V, there was a significant amount of unreacted **2** recovered after 24 h (entries 2−4). At V_p = 4.8 V, although **2** was completely consumed, a chlorinated side product was isolated in 16% yield (entry 6). Importantly, the use of 60 Hz sine waveform (entry 9), the same waveform as the household power supply, afforded the desired product **5** in 40% NMR conversion. The application to a large scale was explored utilizing 1 mmol of 2-acetylpyrrole (**2**), and the

Table 1. Reaction Development[a]



entry	V_p (V)	f (Hz)	conversion[b] (%)	yield[c] (%)	**5**/**6** ratio[d]
1	0	n/a	<1		
2	3.3 (AC)	100	6		
3	3.6 (AC)	100	27		
4	4.0 (AC)	100	48	44	24:1
5	**4.4 (AC)**	**100**	**100**	**84**	**19:1**
6	4.8 (AC)	100	44		44:1
7	4.4 (AC)	10	21		0.75:1
8	4.4 (AC)	1000	<1		
9	4.4 (AC, sine)	60	40		
10	4.4 (AC)[e]	100	66	64	
11	**4.4 (DC)**	**n/a**	**13**		

[a]Reaction scale: 0.5 mmol of **2** (1 equiv) in 4 mL of acetonitrile. [b]Conversion and ratio of **5**/**6** were determined by ^{19}F NMR. [c]Isolated yield of **5**. [d]Chlorinated product was isolated in 16% yield. [e]1 mmol of **2**.

desired product **5** was obtained in a comparable yield (64%, entry 10). To compare, the paired electrolysis condition only gave a 13% yield of **5** using *identical* chemical reagents at a constant voltage of 4.4 (entry 11). The control experiment established that, when no voltage was applied, there was no reaction (entry 1). Overall, the results in Table 1 confirmed our hypothesis that the ACE significantly improved the yield compared to the paired electrolysis.

Next, we investigated the critical role of V_p and f in the ACE method. We measured the standard reduction potential (E_1) of **1** and the oxidation potential (E_2) of **3**, which determines the voltage required for trifluoromethylation to proceed. The cyclic voltammogram of **1** (Figure 3a) showed an onset potential for **1** reduction of approximately −0.7 V vs Ag/AgCl. We estimated E_1 to be −0.97 V using the inflection points of the cathodic wave.[32] To detect the oxidation of the unstable intermediate **3**, we used fast-scan linear sweep voltammetry.[33] We first held the electrode potential at −1.2 V to reduce **1** and generate a pool of radical **3**. Subsequent scanning the electrode potential positively at a high scan rate of 20 V/s enabled the oxidation of **3** before it proceeded through other pathways. At low scan rates, the electrochemical signal from the oxidation of **3** significantly diminished (Figure S2), confirming the instability of **3**. We observed an anodic wave starting from 0 V with a major peak at ∼0.7 V (Figure 3b). When the potential was held at −0.4 V, wherein no CF_3 radical was generated, no anodic wave was observed, suggesting the anodic wave results from the oxidation of **3**. To further confirm this result, we carried out two additional experiments. First, we elongated the holding time at −1.2 V to generate more CF_3 radicals. Second, we increased the concentration of **2** in the reaction mixture. In both cases, we observed a significantly increased current (Figure 3), confirming the anodic wave arose from the oxidation of **3**. Accordingly, we estimated E_2 to be 0.5 V using the inflection points of the anodic wave.[32] Based on these results, we estimated the thermodynamic voltage for electrochemical trifluoromethylation, $|E_1 - E_2|$, is ∼1.5 V. It is worth noting that the current took off after ∼0.85 V for all experiments due to direct electro-oxidation of **2**.[34−36]

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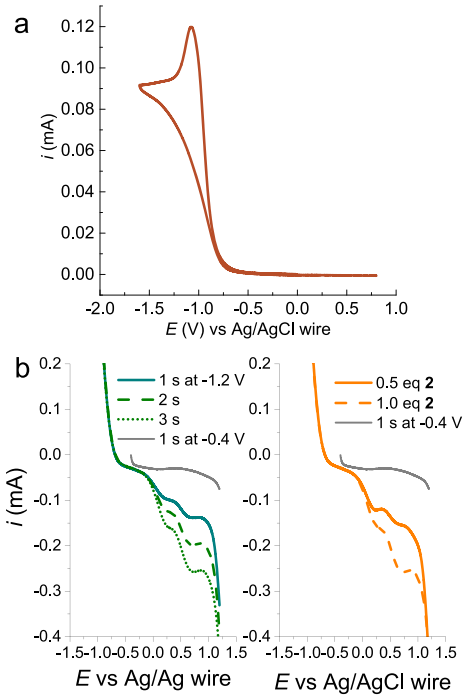

Figure 3. (a) Cyclic voltammograms of **1** in MeCN. A Ag/AgCl wire was used as the quasi-reference electrode. Scan rate: 50 mV/s. (b) Fast-scan linear sweep voltammograms of a mixture of **1** and **2**. Left panel: Electrode potential was held at −1.2 V for 1, 2, and 3 s followed by sweeping the potential positively to 1.2 at 20 V/s. Concentrations of **1** and **2** were both 0.25 M. Right panel: Different equivalents of **2** to **1** were added, and the holding time at −1.2 V was 3 s. Gray curve: Electrode potential was held at −0.4 V for 1 s before the potential sweep.

We continued investigating why our optimal voltage (4.4 V) was much higher than the thermodynamic value of 1.5 V. We identified two reasons.

First, waveform generators are not an ideal power source.[37] As a result, the actual voltage output from a waveform generator (V_{real}) was lower than the set value of V_p during the ACE reaction.[38] We found V_{real} oscillated between ±2 V at V_p = 4.4 V (Figure 4a). The peak value of V_{real} ($V_{real,peak}$) gradually increased from 1.8 to 2.5 V and then stayed constant until the reaction completion at 24 h (Figure 4b).

Second, there was a substantial *iR* drop in the electrolyte solution between the two electrodes. Figure 4c shows the equivalent circuit of our electrochemical system. The electrodes are represented as an electrical double layer capacitor (C_{EDL}) and an electrochemical resistor (R_{ec}) in parallel, whereas the electrolyte solution between the two electrodes is treated as a constant resistance, $R_{electrolyte}$.[39] During the ACE, positive and negative voltage pulses alternated. Upon one voltage pulse, the voltage available for the electrochemical reactions (V_{ec}) can be described by the following equation (see the derivation in the Supporting Information):

$$V_{ec} = V_{real,peak}(1 - \exp(-2t/R_{electrolyte}C_{EDL}))$$

where $R_{electrolyte}$ and C_{EDL} were estimated to be 5 Ω and 2 mF, respectively (Figure S5). For a 100 Hz square wave with V_p = 4.4 V, V_{ec} is predicted to increase from 0 V at t = 0 to 1.57 V at 5 ms. Because the onset potentials for reducing **1** and oxidizing **3** were measured to be −0.7 and 0 V, the minimum voltage required for electrochemical trifluoromethylation is 0.7 V.

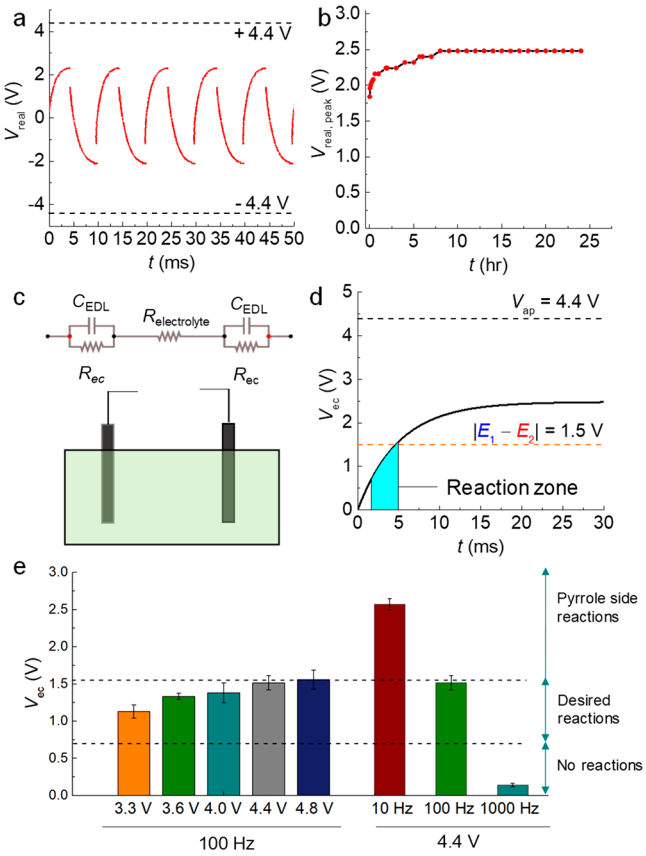

Figure 4. (a) Measured voltage (V_{real}) between two glassy carbon electrodes during the ACE when V_p was set as 4.4 V. (b) Peak value of V_{real} vs reaction time. (c) Equivalent circuit of the electrochemical system for ACE. (d) Theoretical modeling of the voltage available for electrochemical reactions (V_{ec}) vs the voltage pulse duration, t, at V_p = 4.4 V. The region highlighted in blue indicates the reaction zone during a 5 ms voltage pulse of a 100 Hz square wave. (e) Predicted ranges of V_{ec} at different V_p and f. The error bars were calculated from the variations in $V_{real,peak}$ during the reactions.

Therefore, trifluoromethylation only occurred between 1.7 and 5 ms in a single voltage pulse (Figure 4d).

The predicted ranges of V_{ec} at different V_p and f using the equation above and the measured $V_{real,peak}$ (Figure S7) are summarized in Figure 4e. At all V_p, V_{ec} passed the minimum voltage of 0.7 V required by electrochemical trifluoromethylation. At V_p = 4.8 V, V_{ec} was also enough to oxidize **2** and reduce **1** at the same time (>1.55 V). These results are consistent with the experimental findings that (1) the desired product **5** was observed at $V_p \geq 3.3$ V; (2) the product yield increased, and the unreacted **2** decreased until V_p reached 4.4 V; and (3) the chlorination product was observed at 4.8 V due to the direct oxidation of **2**.[40] A similar analysis was conducted for different f at V_p = 4.4 V. At 1000 Hz, V_{ec} was always below 0.7 V and thus unable to drive the reactions. At 10 Hz, V_{ec} went beyond the voltage for direct oxidation of pyrrole, causing significant side reactions.

Finally, we evaluated the substrate scope. As outlined in Scheme 1, we kept the frequency at 100 Hz and varied the voltage between 2.8 and 4.8 V to obtain the highest yields for different substrates. The trifluoromethylation of pyrroles proceeded smoothly to provide the trifluoromethylated products **7**−**13** in good yield (42−61%) and high regioselectivity. In the presence of a methyl group,

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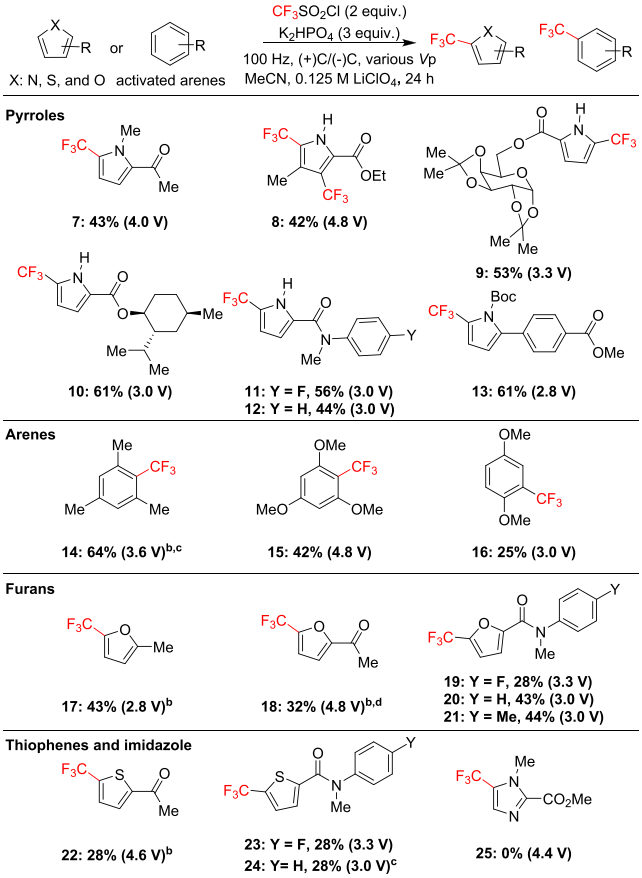
Org. Lett. 2020, 22, 6719−6723

Scheme 1. Scope of Selective Trifluoromethylation[a]



[a]0.25−0.5 mmol scale. [b]Yields were determined by ^{19}F NMR. [c,d]The reaction time was 48 and 72 h, respectively.

bistrifluoromethylated product **8** was observed as the only major product under the optimized reaction condition. The ACE method is also applicable to electron-rich arenes to afford the trifluoromethyl products **14**−**16** in synthetically useful yield (25−64%). Importantly, the preferential trifluoromethylation of pyrroles over arenes enables the selective CF_3 functionalization of pyrroles in substrates containing both aromatic systems such as **11**, **12**, and **13**. For furans and thiophenes, the desired products **17**−**24** were obtained in moderate yields (28−44%). The reduced yield is because furans and thiophenes are more prone to undergo oxidation than pyrroles (Figure S6). A current limitation of the reaction is that highly electron-deficient heterocycles, such as imidazole, were not compatible (**25**) because of inefficient CF_3 radical addition to the imidazole ring (Figure S3). The same mechanism accounts for the different yields for activated arenes (Figure S4).

In conclusion, we have presented a new electrochemical approach using underdeveloped alternating current electrolysis for trifluoromethylation of (hetero)arenes. We have also established a theory for understanding the optimal reaction conditions, essential for guiding the rational design for future applications. This method is significant because it addresses the long-standing limitation of paired electrolysis and will significantly expand the library of electrosynthetic reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01906.

Experimental details, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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