Novel Fully Organic Water Oxidation Electrocatalysts: A Quest for Simplicity

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⊥Supporting Information

ABSTRACT: Despite the growing need for readily available and inexpensive catalysts for the half-reactions involved in water splitting, water oxidation and reduction electrocatalysts are still traditionally based on noble metals. One long-standing challenge has been the development of an oxygen evolution reaction catalyzed by easily available, structurally simple, and purely organic compounds. Herein, we first generalize the performance of the known N-ethyl-flavinium ion to a number of derivatives. Furthermore, we demonstrate an unprecedented application of different pyridinium and related salts as very simple, inexpensive water oxidation organocatalysts consisting of earth-abundant elements (C, H, O, and N) exclusively. The results establish the prospects of heterocyclic aromatics for further design of new organic electrocatalysts for this challenging oxidation reaction.

1. INTRODUCTION

In the context of renewable energy transformation and storage,¹ the production of hydrogen through water electrolysis is of eminent importance. Although catalytic water reduction is already well investigated,² the water oxidation step has drawn less attention, despite representing the kinetically limiting half-reaction of the water splitting process.³⁴ To date, water oxidation catalysis is performed the most efficiently with molecular complexes and solids based on expensive transition metals, in particular Ru,¹⁻⁵ Ir,⁶ Co,⁷ or Os,⁸ whereas on the technical scale electrolyzers mostly use Ni.

Recently, the N-ethyl-flavinium ion (EtFl¹⁺, Figure 1) was reported by Glusac and co-workers to function as a first organocatalyst for the four-electron electrocatalytic water oxidation.⁹ This seminal piece of work represents an entry into an unexplored class of water oxidation catalysts based on potentially inexpensive and easily available organic heterocycles.¹⁰¹¹ We envision that further developments within this class of compounds might yield improvements in catalytic activity and synthetic availability and perhaps thereby eventually provide an economical and environmentally friendly alternative for the water oxidation reaction. However, another cationic iminium derivative, N-methyl-9-phenyl-acridinium (Acr¹⁺, Figure 1), was found inactive toward the oxidation of water.¹²

In the mechanism proposed,⁹ the EtFl¹⁺ catalyst adsorbed on the glassy carbon electrode surface is oxidized to a radical cationic iminium derivative, N-ethyl-9-phenyl-acridinium (Acr¹⁺, Figure 1), was found inactive toward the oxidation of water.¹²

Received: December 13, 2017
Accepted: February 20, 2018
Published: March 5, 2018
a catalyst. In essence, $\Delta E_{0.5}$ represents the reduction of water oxidation overpotential (and concomitantly, of activation energy) achieved by the catalysts.

2. RESULTS AND DISCUSSION

For the reference compound EtFl$^+$ ClO$_4^−$, we measure an onset potential shift of $\Delta E_{0.5} = 0.385$ V when the catalyst is added to the electrolytic mixture (Figure S1 in the Supporting Information). Another quantification of the catalytic effect is provided by electrochemical impedance spectroscopy (Figure S2), with a 3-fold reduction of charge transfer resistance achieved by the catalyst at +1.94 V on a glassy carbon surface. In energy terms, this corresponds to a reduction of the activation free enthalpy by a modest 2.5 kJ mol$^{-1}$. Appending peripheral functional groups to the EtFl$^+$ backbone is tolerated. The carboxylic acid derivative EtFlCH$_2$ΦCOOH$^+$ ClO$_4^−$ yields an overpotential reduction value $\Delta E_{0.5} = 0.277$ V (Figure S3).

On the basis of the accepted mechanistic hypothesis of water attack to the iminium carbon of EtFl$^+$, one would expect that a neutral flavin, Fl, in which the imine nitrogen is not quaternized should be electrocatalytically inert. Figure 2a shows that, unexpectedly, neutral Fl furnishes a species highly active for water oxidation as well: when water is added to the electrolytic mixture, the oxidation currents become significantly larger than their reductive counterparts. We measure $\Delta E_{0.5} = 0.420$ V, slightly larger than with EtFl$^+$, and observe larger current densities as well. These results, however, are valid only for the second and subsequent voltammetric cycles. If we start with a fresh electrolytic solution of Fl (and water) near the open-circuit potential and sweep in the anodic direction (light blue curve of Figure 2b), no faradaic current (apart from the small pseudo-capacitive current due to glassy C electrode) is observed at all up to 2.50 V. After the initial voltammetric cycle, subsequent sweeps witness very clear faradaic peaks, which initially increase with each cycle and eventually stabilize. The reason for the appearance of two distinct peaks instead of one could possibly be clarified by spectroelectrochemical methods. If after such a set of voltammetric cycles, the electrolyte is stirred, then left to stand for a few seconds, and measured again in the same manner, the behavior shown on Figure 2b is reproducible. These observations contrast those observed for EtFl$^+$, where the first and subsequent cycles are essentially identical to each other.

A plausible explanation for this behavior is furnished by recollecting the redox-based synthesis of EtFl$^+$ from Fl.$^{9a}$ Indeed, alkylating of the heterocyclic N atom is performed in three steps: reduction by dithionite, electrophilic attack by an alkyl halide, and reoxidation. Thus, under our voltammetric conditions, each cathodic sweep must result in the formation of the intermediary compound, Fl$^-$, which is presumably protonated and subsequently oxidized to HFl$^+$. This metastable species then features a reactivity much akin to that of the alkylated compound. The comparison of cyclic voltammograms recorded with two distinct switching potential values on the cathodic side is consistent with this model (Figure S4). Finally,
functionalized derivatives of neutral flavins may also be active. FIC_{6}\Phi COOH yields \( \Delta E_{0.5} = 0.284 \) V \( \text{Figure S5} \) at the second and subsequent voltammetric cycles.

Let us now turn to simplified structures that still feature a highly electron-deficient heterocycle. Pyridinium salts, among them N-methyl-3,5-dinitropyridinium \( (\text{MePy}^+) \), have recently been reported by Cibulka and co-workers to successfully catalyze the sulfoxidation reaction.\(^{13}\) This mono-oxidation, albeit a two-electron reaction only, is relevant to water oxidation if the proposed mechanism is correct, given the prominent intermediacy of an ortho-carbon-bound peroxide species. Despite their facile access, pyridinium compounds have not been investigated for water oxidation to date.

Figure 3a shows the success of this simplified compound, which we prepared and investigated as a triflate salt,\(^{13}\) and for which both the molecular weight and the synthetic effort are diminished very significantly. The shape of the voltammogram is qualitatively reminiscent of the flavinium family of compounds, with a peaking behavior characteristic of molecular, dissolved catalysts.\(^{14}\) A quantitative comparison, however, reveals that \( \text{MePy}^+ \) is significantly more proficient than \( \text{EtFl}^+ \). The water oxidation onset is further shifted to less positive potentials by approximately \( 0.2 \) V (\( \Delta E_{0.5} = 0.575 \) V). This corresponds to a reduction of the activation free enthalpy on the order of \( 18 \) kJ mol\(^{-1}\).

The demonstration that water is indeed the substrate being oxidized electrocatalytically is provided in Figure 3b. Anodic current densities increase with water concentration, linearly at first, and reach a plateau in highly concentrated media (approximately 10 M). The anodic peak of interest also shifts from about \( 1.68 \) V to near \( 1.46 \) V (vs Ag/AgCl) due to the increasing polarity of the medium upon water addition, which stabilizes charged species. At the highest water concentration, dihydrogen evolution and reoxidation are also observable. Further, the product, \( \text{O}_2 \), is directly measured by optical means \( \text{(Figure 4)} \) during bulk electrolysis at constant potentials. We compare the reference compound, \( \text{EtFl}^+ \text{ClO}_4^- \), at relatively high potential \( E = 1.94 \) V versus Ag/AgCl (green dotted line) with our new \( \text{MePy}^+ \text{OTf}^- \) at much more moderate value \( E = 1.34 \) V (continuous blue line). The gray curves represent the control measurements taken in the absence of a catalyst. The extreme electrocatalytic proficiency of \( \text{MePy}^+ \) toward water oxidation (as compared to that of \( \text{EtFl}^+ \)) is materialized by a similar \( \text{O}_2 \) production rate obtained at \( 600 \) mV lesser overpotential, whereas most water oxidation catalysts increase the electrocatalytic current density by a factor 10 for every \( 60 \) mV overpotential increase (Tafel plot).

Electrocatalytic current densities cannot be converted to turnover frequencies (TOFs) directly as in the case of homogeneous catalysis, given that the amount of molecular catalyst at the electrode surface is unknown. The Sáviant diffusion model for “foot-of-the-wave” analysis of the curve shape\(^{14}\) is not applicable to our case due to the adsorption of the electrocatalyst demonstrated by Glusac et al.\(^{9,12}\) To provide a value that can be compared to the homogeneous catalysts nevertheless, we therefore calculate a lower bound of the TOF.
on the basis of the assumption that the electrode surface is covered with a compact monolayer of MePy+. For this, we will use an area of the molecular cation of approximately 50 Å² based on its molecular structure, a value that is consistent with the integrated current of the cyclic voltammograms recorded in the absence of water (≈1 C m⁻²). On the basis of this value, the current density, \( j = 2 \text{ mA cm}^{-2} \) (5 nmol O₂ s⁻¹ cm⁻²), obtained at the voltammetric peak of Figure 3b yields TOF ≥ 16 s⁻¹ or TOF ≥ 56 000 h⁻¹. Any possibly lower surface coverage would yield even larger TOF values.

Further derivatives MePyz⁺ and MePym⁺ give rise to an electrocatalytic proficiency less pronounced than MePy⁺ and practically inexistent, respectively (Figures S6 and S7). A rationale for this behavior can be derived from ¹H NMR spectroscopy. The chemical shifts exhibited by the ortho hydrogens of these three cations follow the same trend as the catalytic activities (Figure S8): MePy⁺ (9.92 ppm) > MePyz⁺ (9.49 ppm) > MePym⁺ (9.28 ppm). Given that these values furnish a measure of the electrophilic character of heterocycles, the contrasting reactivities of the three novel compounds provide strong credence to the crucial mechanistic importance of a highly electrophilic ortho carbon (C2). The combination of two nitro substituents ortho to para to the crucial C2 at which nucleophilic attack by water occurs (see Figure S9 for a sketch of the hypothetical mechanism, based on the published avinium system) seems to be ideal.

3. CONCLUSIONS

The ethylflavinium salt (EtFl⁺), which was initially published as an exceptional case of an organic water oxidation electrocatalyst, now belongs to a broader group of heterocyclic cations, some of which are simplified, more easily accessible, and even more active (Figure 5). Catalytic proficiency scales with the electrophilic character of the heterocycle. This property does not require the complex flavin structure. The much simpler pyridinium framework outperforms the reference compound, EtFl⁺, by a significant amount. The pyridinium compound, MePy⁺, is stable for weeks in solution and under conditions of electrocatalytic turnover and outperforms EtFl⁺ by about 18 kJ mol⁻¹ in activation energy reduction. These results open an avenue toward more insightful mechanistic investigation of the water oxidation mechanism, for example, by time-resolved and potential-dependent spectroelectrochemical experiments and, thereby, toward further improvements in the performance of organic electrocatalysis.

4. METHODS

4.1. Materials. All chemicals used for syntheses and electrochemistry were purchased from commercial sources and were used without further purification. Nitrogen served as protective gas. All solvents were purified by distillation using rotary evaporation or were purchased in HPLC quality. All products were dried in vacuum (10⁻³ bar).

4.2. Electrochemistry Measurements. The glassy carbon working electrode was obtained from Bioanalytical Systems, Inc. (BASi), the Pt mesh counter electrode from ALS Co., Ltd., and the Ag wire as the pseudo-reference electrode from Alfa Aesar. The pseudo-reference was calibrated before and after measurements with respect to a Ag/AgCl (sat)/NaCl (3 M) reference electrode (+0.209 V vs normal hydrogen electrode) from BASi on a K₄[Fe(CN)₆] electrolyte (0.1 M aqueous with 1 M KCl) and lies at a constant +0.04 V versus Ag/AgCl. In the text, all potentials are quoted with respect to Ag/AgCl, that is, they have been corrected by +0.04 V. The electrochemistry data were collected with a CompactStat potentiostat from Ivium Technologies, and the fits were performed by the instrument’s software. O₂ optrode and optical oxygen meter were from Pyro Science. Cyclic voltammetry was performed with a scan rate of 100 mV s⁻¹ in 0.1 M Me₄N BF₄ in MeCN solvent. The concentration of organic substance is 3 mM and that of water (if present) is 0.5 M, unless otherwise mentioned. Impedance spectroscopy measurements were carried out at 1.94 V versus Ag/AgCl. The electrode consists of a disk of 3 mm diameter (area 0.071 cm²). O₂ was measured at the potential mentioned in the text in 0.1 M Me₄N BF₄ in MeCN, with or without the addition of 0.5 M water and/or 3 mM organic substance. Before measurements, the solutions were bubbled with N₂.

4.3. Preparative (Flash) Column Chromatography/Thin-Layer Chromatography (TLC). Preparative (flash) column chromatography was performed on Macherey & Nagel Silica gel 60 M (0.04—0.063 mm) as the stationary phase. Thin-layer chromatography (TLC) was performed on silica TLC cards (Alugramm SIL G, layer thickness 0.20 mm, Fluka) with a fluorescence indicator (lamp wavelengths 254 and 366 nm).

4.4. NMR Spectroscopy. ¹H NMR and ¹³C NMR spectra were recorded at room temperature (rt) on a Bruker Avance or JEOL JNM GX 400 spectrometer operating at 300 MHz or 400 MHz in deuterated solvents as standard (CDCl₃: ¹H 7.24 ppm, ¹³C 77.0 ppm; dimethyl sulfoxide (DMSO)-d₆: ¹H 2.49 ppm, ¹³C 39.5 ppm; MeOH-d₄: ¹H 3.30 ppm, ¹³C 49.0 ppm; acetoned-d₆: ¹H 2.04 ppm, ¹³C 29.8 ppm; benzol-d₈: ¹H 7.15 ppm, ¹³C 118 ppm). Chemical shifts are given in the δ scale in parts per million. To characterize the multiplicities of the signals, the following abbreviations are used: s (singlet), d (doublet), t

Figure 5. Summary of electrocatalytic water oxidation efficiencies (quantified as overpotential reduction) of the compounds investigated in the present study. The originally published ethylflavinium salt is part of a broader family of heterocyclic organocatalysts, some of which are structurally simpler and catalytically even more proficient than it.
(triplet), q (quartet), sex (sextet), m (multiplet), dd (double of a doublet), dspt (double of septet), td (triplet of doublet), dq (double of quartet), and br s (broad singlet).

4.5. Mass Spectrometry. Matrix-assisted laser desorption ionization mass spectra were recorded with a Shimadzu Biotech AXIMA Confidence, electron ionization mass spectra with a Thermo Scientific Finnigan MAT 95 XP, and electrospray ionization mass spectra with a Bruker Daltonik maXis 4G or a Bruker Daltonik micTOF II focus.

4.6. Infrared Spectroscopy. IR spectra of the compounds were recorded as thin films on a Varian IR-660 apparatus.

4.7. Elemental Analysis. Elemental analyses (C, H, N) were carried out with an Elementar vario MICRO cube machine.

4.8. Synthesis Schemes. Schemes S1 and S2 in the Supporting Information summarize the synthetic pathways toward flavins and flavinium derivatives and toward the monoaromatics, respectively. The schemes also provide the compound numbers.

4.9. N-Ethyl-4,5-dimethyl-2-nitroaniline (10). Compound 9 (4.5-dimethyl-2-nitroaniline, 100 mg, 0.62 mmol) was dissolved in 5 mL of MeOH/ AcOH (10:1 v/v) mixture with 3 Å MS. 2-Picoline borane complex (79.6 mg, 0.37 mmol) and acetaldehyde (69.2 μL, 1.24 mmol) were added and stirred for further 6 h. The mixture was evaporated, dissolved in dichloromethane (DCM) (5 mL), filtered, and purified via column chromatography (silica, hexane/DCM 2:1 → 1:1 v/v) to obtain compound 10 as a deep orange solid (106 mg, 0.55 mmol, 88% yield). 1H NMR (300 MHz, CDCl3): δ 1.34 (t, J = 7.5 Hz, 3H), 2.15 (s, 3H), 2.25 (s, 3H), 3.11 (q, J = 7 Hz, 2H, amine peak coincident with q), 4.65 (s, 1H), 6.51 (s, 1H) ppm. 13C NMR (75 MHz, CDCl3): δ 14.4, 18.5, 20.7, 37.7, 114.1, 124.3, 126.2, 129.6, 144.0, 147.2 ppm. HRMS-ESI (m/z): [M + H]+ calcd for C12H11ClN4O6 260.0855, found: 260.0864.

4.10. N'-Ethyl-4,5-dimethylbenzene-1,2-diamine (11). Compound 10 (5.44 g, 28.0 mmol) was dissolved in MeOH (250 mL) and cooled to 0 °C. A freshly prepared solution of Na2S2O4 (252 mg, 3.65 mmol) and NaClO4 hydrate (474 mg, 5.44 g, 28.0 mmol) was dissolved in MeOH (229 mg, 0.85 mmol), and K2CO3 (1.18 g, 8.50 mmol), and acetaldehyde (471 μL, 371 mg, 8.50 mmol) was added and stirred for 10 min under N2 atmosphere. The mixture was heated to 75 °C for 90 min. The reaction was allowed to cool to rt and was stirred overnight. The precipitate was filtered and washed with water (2 mL). The mixture was purified using column chromatography (DCM/acetone 2:1 v/v) to obtain a yellow solid (735 mg, 2.59 mmol, 37% yield). 1H NMR (300 MHz, CDCl3): δ 1.47 (t, J = 6.0 Hz, 3H), 2.42 (s, 3H), 2.53 (s, 3H), 3.50 (s, 3H), 4.75 (q, J = 7 Hz, 2H), 7.39 (s, 1H), 8.04 (s, 1H) ppm. 13C NMR (75 MHz, CDCl3): δ 12.4, 19.5, 21.6, 28.7, 40.1, 115.0, 130.7, 132.8, 135.0, 135.6, 136.6, 147.8, 148.2, 156.1, 160.1 ppm. HRMS-ESI (m/z): [M + ClO4−]− calcd for C17H21ClN4O6 385.1870, found: 385.1867.

4.11. 10-Ethyl-7,8-dimethylbenzolpteridine-2,4-(3H,10H)-dione (12). Compound 11 (2.9 g, 17.7 mmol) was dissolved in glacial acetic acid (70 mL). Alloxane (4.24 g, 26.5 mmol) and H2BO3 (1.64 g, 26.5 mmol) were suspended in glacial acetic acid (40 mL) at 40 °C and added within 5 min. The mixture was heated to 50 °C for 90 min. The reaction was allowed to cool to rt and was stirred overnight. The precipitate was filtered and washed with water. The crude product was recrystallized from boiling acetic acid/water mixture (8:2 to 6:4 v/v) to obtain a yellow orange solid (2.83 g, 60% yield). 1H NMR (300 MHz, trifluoroacetic acid (TFA)-d7/CDCl3 (4:1 v/v)): δ 1.52 (t, J = 7.5 Hz, 3H), 2.37 (s, 3H), 2.52 (s, 3H), 4.62 (q, J = 6 Hz, 2H), 7.76 (s, 1H), 8.06 (s, 1H) ppm. 13C NMR (75 MHz, TFA-d7/CDCl3 (4:1 v/v)): δ 11.9, 18.9, 21.6, 46.3, 116.5, 129.8, 130.3, 133.0, 139.9, 140.3, 146.2, 149.5, 158.3, 159.4 ppm. HRMS-ESI (m/z): [M + H]+ calcd for [C23H15N5O4]+ 385.1870, found: 385.1867.

4.12. 10-Ethyl-3,7,8-trimethylbenzolpteridine-2,4-(3H,10H)-dione (2). Compound 12 (922 mg, 3.41 mmol) was dissolved in dimethylformamide (DMF) (45 mL); K2CO3 (4.71 g, 34.1 mmol) was added, followed by dropwise addition of MeI (4.84 g, 2.16 mL, 34.1 equiv). The mixture was stirred overnight (18 h). Brine was added, and the mixture was extracted with DCM (4× 50 mL). The solvent was dried over MgSO4 and removed under reduced pressure. The crude product was purified using column chromatography (DCM/acetone 2:1 v/v) to obtain a yellow solid (735 mg, 2.59 mmol, 76% yield). 1H NMR (300 MHz, CDCl3): δ 1.47 (t, J = 6.0 Hz, 3H), 2.42 (s, 3H), 2.53 (s, 3H), 3.50 (s, 3H), 4.75 (q, J = 7 Hz, 2H), 7.39 (s, 1H), 8.04 (s, 1H) ppm. 13C NMR (75 MHz, CDCl3): δ 12.4, 19.5, 21.6, 28.7, 40.1, 115.0, 130.7, 132.8, 135.0, 135.6, 136.6, 147.8, 148.2, 156.1, 160.1 ppm. HRMS-ESI (m/z): [M + ClO4−]− calcd for C17H21ClN4O6 385.1870, found: 385.1867.
4.15. 4-(10-Ethyl-7,8-dimethyl-2,4-dioxo-4,10-dihydro-benzolpteridin-3(2H)-yl)butanoic Acid (3). Compound 13 (154 mg, 0.40 mmol) was dissolved in concd HCl (5 mL) and heated to 85–90 °C for 45 min. The mixture was cooled to 0 °C, and ice water (30 mL) was added. The yellow precipitate was filtered and washed with water, and the residue was recrystallized from boiling glacial acetic acid/water (7:3 v/v) to give orange needles (103 mg, 0.29 mmol, 73% yield). 1H NMR (400 MHz, TFA-d8): δ: 1.50 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 2.99 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 4.10 (t, J = 6 Hz, 2H), 7.74 (s, 1H), 8.04 (s, 1H) ppm. 13C NMR (100 MHz, TFA-d8): δ: 1.18, 18.8, 21.2, 22.0, 30.9, 42.8, 46.0, 129.7, 130.0, 132.9, 136.8, 140.4, 146.1, 150.2, 158.1, 159.7, 180.6 ppm. HRMS-ESI (m/z) [M + H]+ calc for [C14H13NO5]+ 260.0845, found: 260.0847. 1H and 13C NMR spectra are not provided due to the radical character of the flavinum salt and the corresponding signal broadening. EA (C8H7N3O4): C: 54.10; H: 4.83; N: 10.15; found: C: 53.72; H: 4.60; N: 10.27. HRMS-ESI (m/z) [M + ClO4−]− calc for [C14H13NO4ClO4]−: 433.1870, found: 433.1870.

4.16. Methyl 4-(10-ethyl-7,8-dimethyl-2,4-dioxo-4,10-di-hydrobenzolpteridin-3(2H)-yl)methyl Benzoate (14). Compound 12 (300 mg, 1.10 mmol) was suspended in dry DMF (30 mL) under N2 atmosphere; methyl 4-(bromomethyl)benzoate (731 mg, 3.19 mmol) and then K2CO3 (1.53 g, 11.0 mmol) were added, and the mixture was heated to 90 °C for 100 min. The mixture was cooled to rt, and DCM (60 mL) was added. The crude was filtered, washed with little water and MeOH, and dried under vacuum to obtain 2-hydrazinyl-3,5-dinitropyridine (3.72 g, 18.7 mmol, 95% yield) as intermediate compound 16, which was directly used without further purification. 2-Hydrazinyl-3,5-dinitropyridine (3.00 g, 15.1 mmol) was suspended in H2O (100 mL), silver acetate (9.00 g, 53.9 mmol) was added at room temperature, and the mixture was heated to reflux for 2 h. The crude mixture was filtered, washed with little water and MeOH, and dried under vacuum. The isolated crude was recrystallized from boiling acetonitrile and precipitated from diethyl ether.

4.17. 4-(10-Ethyl-7,8-dimethyl-2,4-dioxo-4,10-dihydro-benzolpteridin-3(2H)-yl)methyl Benzoic Acid (4). Compound 14 (183 mg, 0.44 mmol) was synthesized according to the procedure of compound 3. The crude mixture was recrystallized from boiling acetic acid/water mixture (8:2 v/v) to obtain a yellow/orange powder (158 mg, 0.39 mmol, 89% yield). 1H NMR (400 MHz, CDCl3): δ: 1.47 (t, J = 8 Hz, 3H), 2.42 (s, 3H), 2.53 (s, 3H), 3.86 (s, 3H), 4.75 (q, J = 8 Hz, 2H), 5.32 (s, 2H), 7.39 (s, 1H), 7.62 (d, J = 8 Hz, 2H) ppm. 13C NMR (100 MHz, CDCl3): δ: 12.4, 19.5, 21.6, 40.2, 44.8, 52.0, 115.0, 129.3, 129.31, 129.7, 130.8, 132.9, 135.1, 135.7, 136.7, 142.0, 148.0, 148.3, 155.5, 159.9, 166.9 ppm. HRMS-ESI (m/z) [M + H]+ calc for [C14H13NO4]+ 249.0981, found: 249.1074.

4.18. 3-(4-Carboxybenzyl)-5,10-diethyl-7,8-dimethyl-2,4-dioxo-2,3,4,10-tetrahydrobenzolpteridin-5-ium Perchlorate (5). Synthesis using 2-picoline borane complex. Compound 4 (860 mg, 0.21 mmol) was added to a mixture of N2 purged DMF (5 mL) and Na2S2O3 (146 mg, 0.84 mmol) under N2 atmosphere at rt. The reaction was stirred for 10 min. Picolin–borane complex (29.2 mg, 0.27 mmol), glacial acetic acid (60.0 μL, 1.05 mmol), and acetaldehyde (351 μL, 277 mg, 6.30 mmol) were added at room temperature and then heated to 60 °C for 2.5 h. The reaction was cooled to room temperature, filtered, and the filtrate was evaporated to receive an either orange or greenish mixture. HClO4 (2 M, 4 mL) was added and stirred for 10 min under N2 atmosphere. NaNO2 (173 mg, 2.51 mmol) and NaClO4 hydrate (383 mg, 2.73 mmol) were added at rt within 30 min. After addition, the reaction was stirred for 1 h. The mixture was filtered and washed with water (4 mL), DCM (4 mL), and EtO (5 mL). The dark residue was recrystallized from CH3CN/EtO. The product was collected by filtration, then washed again with DCM (2 mL) and EtO to obtain compound 5 as a dark purple compound (87.0 mg, 0.16 mmol, 76% yield). 1H and 13C NMR spectra are not provided due to the radical character of the flavinum salt and the corresponding signal broadening. EA (C8H7N3O4): C: 54.10; H: 4.83; N: 10.15; found: C: 53.72; H: 4.60; N: 10.27. HRMS-ESI (m/z) [M – ClO4−]− calc for [C14H13NO4ClO4]−: 433.1870, found: 433.1870.

4.19. General Procedure for Alkylation of the Heterocycles. The corresponding heterocycle (1 equiv) was dissolved in diethyl ether under N2 atmosphere. Methyl trifluoromethanesulfonate (1.5–2.0 equiv) was added at room temperature and stirred between 2 and 16 h. The solvent was removed, and the residue was dissolved in acetonitrile and recrystallized from diethyl ether.

4.20. 3,5-Dinitropyridine (17). Hydrazine hydrate (4.92 g, 98 mmol) was dissolved in MeOH (50 mL) and cooled using ice bath. 2-Chloro-3,5-dinitropyridine (4 g, 19.65 mmol) was dissolved in MeOH (150 mL) and added dropwise to the mixture. After complete addition, the ice bath was removed and the mixture was stirred overnight. The dark brown precipitate was filtered, washed with little water and MeOH, and dried under vacuum to obtain 2-hydrazinyl-3,5-dinitropyridine (3.72 g, 18.7 mmol, 95% yield) as intermediate compound 16, which was directly used without further purification. 2-Hydrazinyl-3,5-dinitropyridine (3.00 g, 15.1 mmol) was suspended in H2O (100 mL), silver acetate (9.00 g, 53.9 mmol) was added at room temperature, and the mixture was heated to reflux for 2 h. The crude mixture was filtered, washed with little water and MeOH, and dried under vacuum. The isolated crude was recrystallized from boiling acetonitrile and precipitated from diethyl ether.

4.21. 1-Methyl-3,5-dinitropyridin-1-ium Trifluoromethanesulfonate (6). The compound was synthesized according to general procedure. Chemicals used: 3,5-dinitropyridine (17) (264 mg, 1.561 mmol), diethyl ether (7 mL), and methyl trifluoromethanesulfonate (480 mg, 320 μL, 2.93 mmol). Reaction time: overnight. Slight yellow solid (494 mg, 1.48 mmol, 95%), 1H NMR (300 MHz, DMSO-d6): δ: 9.12 (t, J = 3 Hz, 1H), 9.72 (d, J = 3 Hz, 2H) ppm.

4.22. 4-(Trifluoromethyl)pyrimidine (19). 2-Hydrazinyl-3,5-(trifluoromethyl)pyrimidine (18) (200 mg, 1.12 mmol) was suspended in water (15 mL) and CuSO4 5H2O (700 mg, 2.8 mmol) and heated to 80 °C for 3 h. The mixture was filtered, cooled to room temperature, and extracted using ethyl acetate (3×10 mL). The mixture was concentrated and purified via column chromatography (silica, ethyl acetate). The isolated product was isolated as a colorless oil (40 mg, 0.26 mmol, 24%). 1H NMR (300 MHz, CDCl3): δ: 7.66 (d, J = 1.5 Hz, J2 = 5 Hz, 1H), 9.01 (d, J = 3 Hz, 1H), 9.40 (s, 1H) ppm.
4.23. 1-Methyl-4-(trifluoromethyl)pyrimidin-1-ium Trifluoromethanesulfonate (7). The compound was synthesized according to the general procedure. Chemicals used: 4-(trifluoromethyl)pyrimidine (19 mg, 0.13 mmol), methyl trifluoromethanesulfonate (43 mg, 28.4 μL, 0.26 mmol), and diethyl ether (1 mL). Reaction time: overnight. The product was obtained as a white solid (33 mg, 0.11 mmol, 81%).

H NMR (300 MHz, CD3CN): δ: 4.37 (s, 1H), 8.50 (d, 6.5 Hz), 9.28 (d, 6.6 Hz), 9.58 (s, 1H) ppm. 15N NMR (282 MHz, CD3CN): δ: −70.43 (3F), −79.03 (3F) ppm. HRMS-ESI (m/z) [M − TIO]+ calcd for [C6H4F3N3]+ 200.0556, found: 200.0557.

4.24. 3-Cyano-1-methylpyrazin-1-ium trifluoromethylpyrimidin-1-ium trifluoromethanesulfonate (8). The compound was synthesized according to the general procedure. Chemicals used: pyrazine-2-carbonitrile (20) (200 mg, 1.90 mmol), methyl trifluoromethanesulfonate (2.85 mmol, 468 mg, 312 μL), and diethyl ether (6 mL). Reaction time: 2 h. The product was obtained as a white solid (427 mg, 1.59 mmol, 83%).

H NMR (300 MHz, CD3CN): δ: 4.44 (s, 3H), 9.00 (d, J = 3.3 Hz, 1H), 9.24 (s, 1H), 9.48−9.50 (m, 1H) ppm. 13C NMR (100 MHz, CD3CN): δ: 50.8−50.9 (m), 113.9, 117.2−126.8 (m), 135.9, 142.5−142.7 (m), 143.1−143.3 (m), 152.9 ppm. 19F NMR (282 MHz, CD3CN): δ: −79.81 (3F) ppm. HRMS-ESI (m/z) [M − TIO]+ calcd for [C6H5F3N3]+ 163.04778, found: 163.04778.

**ASSOCIATED CONTENT**

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01982.

Synthesis schemes (Schemes S1 and S2); additional electrochemical data (Figures S1−S7); quantification of electrophilic character (Figure S8); hypothetic reaction mechanism (Figure S9) (PDF)

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**Notes**

The authors declare no competing financial interest. The manuscript was written through contributions of all authors.

**ACKNOWLEDGMENTS**

This work was supported by the Interdisciplinary Center for Molecular Materials (ICMM), the Research Network “Solar Technologies go Hybrid” (SoT-Techn)—an initiative of the Bavarian State Ministry for Science, Research and Art, and the European Research Council (ERC) under the European Union’s Horizon 2020 program (Grant Agreement 647281, Solaclyl). We thank S. Schlicht and S. Haschke for the preparation of various oxide surfaces as electrodes by atomic-layer deposition.

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