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Very Important Publication

Robust Photocatalytic Method Using Ethylene-Bridged Flavinium Salts for the Aerobic Oxidation of Unactivated Benzylic Substrates

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Abstract: 7,8-Dimethoxy-3-methyl-1,10-ethylenealloxazinium chloride (1a) was found to be a superior photooxidation catalyst among substituted ethylene-bridged flavinium salts (R = 7,8-diMeO, 7,8-OCH_2O-, 7,8-diMe, H, 7,8-diCl, 7-CF_3 and 8-CF_3). Selection was carried out based on structure vs catalytic activity and properties relationship investigations. Flavinium salt 1a proved to be robust enough for practical applications in benzylic oxidations/oxygenations, which was demonstrated using a series of substrates with high oxidation potential, i.e., 1-phenylethanol, ethylbenzene, diphenylmethane and diphenylmethanol derivatives substituted with electron-withdrawing groups (Cl or CF_3). The unique capabilities of 1a can be attributed to its high photostability and participation via a relatively long-lived singlet excited state, which was confirmed using spectroscopic studies, electrochemical measurements and TD-DFT calculations. This allows the maximum use of the oxidation power of 1a, which is given by its singlet excited state reduction potential of +2.4 V. 7,8-Dichloro-3-methyl-1,10-ethylenealloxazinium chloride (1 h) can be used as an alternative photocatalyst for even more difficult substrates.

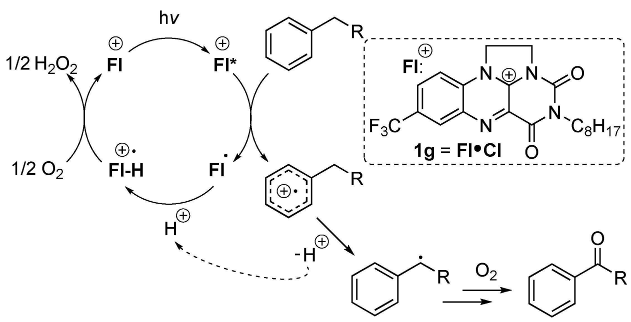
Keywords: Aerobic oxidation; Electron transfer; Photochemistry; Photoredox catalysis; Spectroscopy

Introduction

During the recent rapid development of visible-light photocatalytic oxidative transformations of benzylic C(sp^3)-H group,[1,2] flavins[3] as well as acridinium salts,[4] eosin Y,[5] and other organic dyes[6–8] have been shown as catalysts with the potential to be sustainable alternatives to more expensive iridium,[9,10] and ruthenium[11,12] complexes. The usability of the most common flavin derivative, riboflavin tetraacetate (**RFTA**), in photooxidative systems has limitations in terms of its excited state reduction potential (E^*_{red} = 1.67 V vs SCE).[13] The oxidative power of **RFTA** can be enhanced upon complexation to Sc^{3+}[14] or derivatization of the flavin structure via the introduction of an electron-withdrawing group(s) or positive charge.[15–17] Another improvement of the aerobic flavin photooxidative procedure is the addition of iron complexes to decompose the H_2O_2 by-product,[18] optimizing the flow arrangement with the participation of singlet oxygen,[19] use of the micelle-effect,[20] and the involvement of electrochemistry.[21]

Aerobic benzylic oxidations promoted by ethylene-bridged flavinium salt **1 g** have been recently described by our group,[16] which has introduced this type of flavin derivative in photoredox catalysis (Scheme 1). The procedure is based on the very positive reduction potential of excited **1g*** (E^*_{red} = 2.67 V vs SCE in maximum[22]), which is able to activate a benzylic substrate via single electron transfer (SET). The resulting radical reacts with molecular oxygen to form the appropriate carbonyl compound. Subsequently, **1g** is regenerated by molecular oxygen. Hydrogen peroxide is decomposed by molecular sieves.

This method utilising **1g** has been shown to be useful for a large range of benzylic substrates, i.e., substituted toluene derivatives, alkylbenzenes and benzyl alcohols. However, the practical use of **1g** has some limitations due its low photostability, which was mainly observed in a case of difficult electron-poor substrates that require long reaction times.



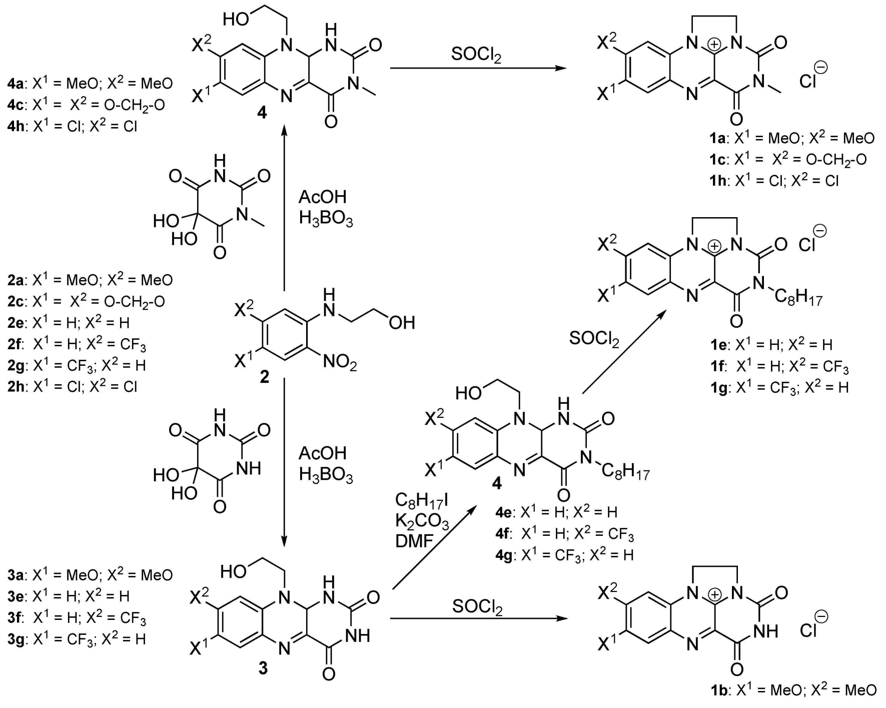
Scheme 1. Simplified mechanism of benzylic photooxidation promoted by flavinium salt **1g**.

To optimize the structure of ethylene bridged flavinium catalysts, we decided to synthesise a series of derivatives **1** bearing various substituents at the 7- and 8-position to study the structure vs properties relationship with a focus on the stability, photochemical and electrochemical properties and reactivity towards model substrates. This approach led us to discover the most suitable derivatives of **1** for the design of robust aerobic photocatalytic oxidation systems. The practical application of these new flavin photocatalysts was verified in terms of the scope of electron-poor benzylic substrates.

Results and Discussion

Synthesis

The synthesis of flavinium salts **1** (Scheme 2, see the Supporting Information S1 for details) was started by the condensation of an appropriate *o*-nitroaniline (**2**) and alloxan in acetic acid in the presence of boric acid to give the corresponding isoalloxazine **3**. We attempted to incorporate an octyl group at the N(3)-position of the isoalloxazine via alkylation using octyl iodide in a presence of potassium carbonate in DMF. However, while the alkylation was successful for isoalloxazines **3e**, **3f** and **3g**, the procedure led to the decomposition of the isoalloxazine structure when using 7,8-dimethoxy and 7,8-dichloro derivatives **3a**



Scheme 2. Synthesis of ethylene-bridged flavinium salts **1**.

and **3 h**, respectively. Therefore, we prepared a series of 3-methyl analogues **4** via the condensation of **2 a**, **2 h** and **2 c** with *N*-methylalloxan (alkyl group was introduced to avoid problems with solubility of the catalyst).[16] The synthesis of salts **1** was accomplished via quaternization of the alkylated isoalloxazines **4** in $SOCl_2$. We also synthesised non-alkylated 7,8-dimethoxy derivative **1 b** to compare its properties with alkylated salt **1 a**. 7,8-Dimethyl derivative **1 d** was prepared from (−)-riboflavin according to a literature procedure.[23]

Spectral and Electrochemical Properties

Electrochemical and spectral properties of the flavinium salts **1** were measured to estimate their behaviour in photocatalytic systems and to obtain the optimal conditions for their application as a photocatalyst (Table 1 and the Supporting Information S2–S4). A bathochromic shift of the absorption maxima identical to the fluorescence maxima occurs for derivatives **1 a–d** bearing electron-donating methyl or alkoxy groups. Moreover, alkoxy groups with a positive resonance effect cause a significant hyperchromic shift in the spectra obtained for **1 a–c**.

The ground state reduction potential was measured using cyclic voltammetry and was in good agreement with the Hammett constants (see the Supporting Information S4). The reduction potential in the singlet excited state $E^*_{red}(S1)$, the value expressing the maximum ability of **1** to transfer an electron from the substrate molecule, was calculated upon the addition of the ground state reduction potential E_{red} and first singlet excited state energy estimated from the intersection between normalized absorbance and emission spectra.[24]

Table 1. Spectral and electrochemical properties of flavinium salts **1**.

Flavinium salt	λ_{max} [nm]	λ_F [nm]	ε [L mol^{-1} cm^{-1}]	E_{red} [V][a]	E^*_{red} [V][b]
1 a	449	520	17500	−0.38	+2.2
1 b	449	520	20500	−0.30	+2.3
1 c	450	500	15000	−0.36	+2.3
1 d	449	500	9000	−0.24	+2.5
1 e	408	490	9000	−0.21	+2.6
1 f	406	490	5500	−0.03	+2.7
1 g[c]	401	480	8000	+0.02	+2.7
1 h	420	500	9000	+0.12	+2.8

[a] Ground state potential of the first reversible wave $E(\mathbf{1}/\mathbf{1}^\bullet)$ vs SCE measured by cyclic voltammetry.
[b] Calculated as $E^*_{red}(S1) = E_{red} + E^{0-0}(S1)$; $E^{0-0}(S1)$ taken from intersection point (see the Supporting Information S2).
[c] Ref. [16].

The stability of the flavinium salt is an important issue for its application in photocatalytic systems. Therefore, we compared the stability of salts **1** under conditions similar to a photocatalytic procedure recently described:[16] Irradiation near the absorption maxima in the presence of trifluoroacetic acid in acetonitrile under an oxygen atmosphere. Trifluoroacetic acid was added to avoid the formation of 10a-adducts with nucleophiles, which (i) do not absorb in the visible light region and (ii) accelerate decomposition or allow other (undesired) oxidation processes to occur.[16,25] In Table 2, the stability was expressed using the half-life of the flavinium salts (see the Supporting Information S4 for details).

Dimethoxy flavinium salts **1 a** and **1 b** were found to be extremely stable when compared to other derivatives, whereas methylendioxy derivative **1 c** was unstable due to the oxidative cleavage of the methylene group, which was confirmed using mass spectrometry. Derivative **1 d** with methyl groups had also enhanced stability compared to non-substituted salt **1 e**. 7,8-Dichloro derivative **1 h** exhibited similar stability to **1 e** and both were more stable than trifluoromethyl derivatives **1 f** and **1 g**.

Catalytic Activity in the Model Photooxidation Reaction

The catalytic efficiency of the flavinium salts in a photooxidative system were compared using the benzylic oxidation of model substrates bearing an electron-withdrawing group, 1-chloro-4-ethylbenzene (**5-Cl**) and 1-ethyl-4-(trifluoromethyl)benzene (**5-CF$_3$**), to give their corresponding acetophenones **6** under the previously described optimized conditions.[16] The temperature was set at 40 °C which was found as optimal from the point of view of reaction conversions (see the Supporting Information S6). The conversion of both substrates to **6** after 8 h of irradiation using a 400 or 450 nm diode (close to their absorption

Table 2. Stability of flavinium salts **1** under irradiation.[a]

Flavinium salt	Irradiation wavelength [nm]	Half-life [min]
1 a	450	1100
1 b	450	900
1 c	450	25
1 d	450	300
1 e	400	65
1 f	400	19
1 g	400	7
1 h	400	85

[a] **1** (0.025 mmol), CF_3COOD (1 mmol), CD_3CN (1 mL). Irradiated under O_2 atmosphere at 40 °C and monitored by ^1H NMR.

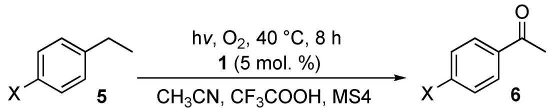
maxima) are displayed in Table 3 (for more data, see the Supporting Information S6).

Borderline catalytic activity can be observed in the ability to mediate the oxidation of highly electron-deficient **5-CF$_3$**. While catalysts bearing electron-donating substituents exhibit low efficacy, the non-substituted catalyst **1 e** and those bearing electron-withdrawing groups show significant conversions with the best performance observed with **1 h**. Chlorinated substrate **5-Cl** was well oxidized in the presence of all the catalysts studied. One should bear in mind that catalysts **1 a** and **1 b** are still present and active after 8 h of reaction according to lifetimes measurements and according to the linear course of conversion vs time dependence for **5-CF$_3$** oxidation mediated by **1 a**. Indeed, a 4-fold extension of the reaction time led to 4-fold increase in the reaction conversion with **1 a**. On the other hand, oxidation of **5-CF$_3$** by **1 g** decelerated during time because of catalysts decomposition (see the Supporting Information S7 for reaction profiles). Interestingly, **1 g** showed some activity even after couple of hours irradiation which can be explained either by positive effect of molecular sieves on stability (molecular sieves were not present in photostability measurements) or by non-zero activity of decomposition products.

Substrate Scope – Preparative Experiments

The high stability of **1 a** combined with the high reduction potential and sufficient stability of **1 h** makes these two catalysts promising candidates to replace **1 g** in the photooxidative protocol used for electron-poor substrates. Furthermore, we demonstrated the usefulness of these two catalysts in preparative experiments performed on a 1-2 mmol scale (Table 4).

Table 3. Photocatalytic activity of flavinium salts **1**.[a]



Catalyst	Irradiation λ [nm]	Conversion to **6**[b,c] [%]	
		5-Cl	**5-CF$_3$**
1 a	450	84	15 (61[d])
1 b	450	86	10
1 c	450	39	2
1 d	450	88	8
1 e	400	89	43
1 f	400	78	47
1 g	400	74	65
1 h	400	74	80

[a] **5** (0.1 mmol), **1** (0.005 mmol; 5 mol. %), MS 4 A (15 mg) and CF$_3$COOH (0.2 mmol) dissolved in CH$_3$CN (0.2 mL). Irradiated under O$_2$ atmosphere at 40 °C for 8 h.
[b] Determined by ^{1}H NMR using dimethylsulfone as a standard.
[c] Traces of benzoic acid were observed.
[d] 32 h.

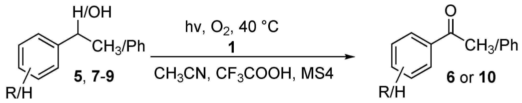
The conditions used for the preparative experiments were analogous to those used on an analytical scale. We used a large dilution as it was found to be beneficial for the reaction rate (see the Supporting Information S6). In terms of the substrate scope, we mainly focused on electron-deficient compounds bearing chloro or trifluoromethyl groups. We studied the oxidation of the benzylic CH$_2$ group as well as the corresponding secondary benzylic hydroxyl function. The reaction mixtures were irradiated until the substrate/product ratio changed (monitored by ^{1}H NMR spectroscopy) or catalyst decomposed (loss of colour and fluorescence).

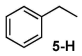
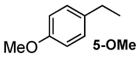
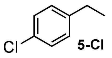
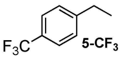
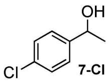
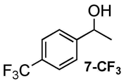
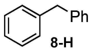
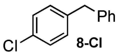
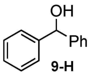
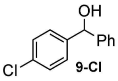
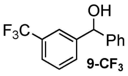
To our delight, **1 a** was shown to oxidize almost all of the substrates studied on preparative scale: Non-substituted or chloro substituted ethylbenzene derivatives **5-H** and **5-Cl** (Entries 1 and 3), 1-(4-chlorophenyl)ethanol (**7-Cl**) (Entry 7), diphenylmethanes **8** (Entries 10–13) and carbinols **9** (Entries 14–16), with high conversion and yield to their corresponding ketones **6** and **10**, even when using 1.5 mol% catalyst (Entry 12). With 0.5 mol% of **1 a**, moderate conversion was achieved (Entry 13). Oxidation of electron rich methoxyderivative **5-OMe** (Entry 2) provided ketone **6-OMe** containing small amount (5%) of benzoic acid (product of overoxidation) and traces of alcohol intermediate. Similarly, traces of the corresponding benzoic acid were observed in oxidations of **5-Cl** and **7-Cl** (Entries 3 and 7). Flavin **1 a** even oxidized very difficult substrate, alcohol **7-CF$_3$**, with high yield (Entry 8), albeit for the longer reaction time and catalyst loading required. Conversion of **5-CF$_3$** to **6-CF$_3$** with **1 a** was rather small on preparative scale (Entry 4) in contrast to analytical scale (see Table 3, Entry 1).

For substrates **5-CF$_3$** and **7-CF$_3$** with high oxidation potential, **1 h** was applied as an alternative and potentially stronger oxidation catalyst considering its excited state reduction potential. The oxidations using **1 h** occurred with good conversions, which were higher than those obtained using the original catalyst **1 g** (cf Entries 5 and 6).

In general, comparing photocatalysts **1 a** and **1 h**, **1 a** is superior. The high stability of catalyst **1 a** allows long-term oxidation to be carried out. Moreover, the reaction using **1 a** is very simple with no need of temperature control (it should be noted that the reaction mixture reaches up to 45 °C during irradiation). To demonstrate usefulness of **1 a** on large scale, we performed oxidations starting from 2.02 g of **8-Cl** and 2.19 g of **9-Cl** (10 mmol) obtaining product **10-Cl** in preparative yields 74 and 85%, respectively, after 12 h irradiation.

Table 4. Preparative experiments on photooxidations.



Entry	Substrate	Catalyst/ Time [h]	Conv.[f] [%]	Yield.[g] [%]
1[a]	 **5-H**	**1a**/16	84	69
2[a]	 **5-OMe**	**1a**/40	90[h]	53
3[a]	 **5-Cl**	**1a**/12	98[h]	55
4[a][c]	 **5-CF$_3$**	**1a**/96	26	n.d.[i]
5[b]	**5-CF$_3$**	**1h**/2	51	24
6[b]	**5-CF$_3$**	**1g**/2	30	n.d.[i]
7[a]	 **7-Cl**	**1a**/16	90[h]	57
8[a][c]	 **7-CF$_3$**	**1a**/96	87	66
9[b]	**7-CF$_3$**	**1h**/2	57	53
10[a]	 **8-H**	**1a**/16	90	67
11[a]	 **8-Cl**	**1a**/12	92	85
12[a][d]	**8-Cl**	**1a**/12	67	62
13[a][e]	**8-Cl**	**1a**/12	40	n.d.[i]
14[a]	 **9-H**	**1a**/24	90	78
15[a]	 **9-Cl**	**1a**/24	83	81
16[a]	 **9-CF$_3$**	**1a**/24	75	68

[a] Substrate (2 mmol), catalyst **1** (5 mol. %), MS 4 A (300 mg) and CF_3COOH (2 eq.) dissolved in CH_3CN (16 mL). Irradiated under O_2 atmosphere. No temperature control.
[b] Substrate (1 mmol), catalyst **1** (5 mol. %), MS 4 A (150 mg) and CF_3COOH (2 eq.) dissolved in CH_3CN (12 mL). Irradiated under O_2 atmosphere at 20 °C.
[c] 10 mol. % of **1 a**.
[d] 1.5 mol. % of **1 a**.
[e] 0.5 mol. % of **1 a**.
[f] NMR conversion.
[g] Preparative yield.
[h] Benzoic acid (≤5%) formed.
[i] Not determined.

In contrast to **1 a**, there is no potential to enhance the yield of the photooxidation reactions using **1 h** upon prolonging the reaction time because of relatively fast bleaching. The reaction temperature used in the large-scale experiments using **1 h** had to be controlled at 20 °C to decelerate the decomposition of the catalyst. On the other hand, as a powerful alternative to **1 a**, **1 h** seems to be more useful than original derivative **1 g**.

Mechanistic Investigations

Our previous mechanistic studies using mass spectrometry and EPR on benzylic oxidations using **1 g** confirmed that the reaction occurs via a benzylic radical and that protonated flavin radical $FlH^{\bullet +}$ was a product of electron and proton transfer from the substrate.[16,17] Herein, we also found that radical chain mechanism is not involved as evident from the measured quantum yields $\Phi = 0.0047$ and 0.055 of **5-Cl** photooxidation mediated by **1 a** and **1 h**, respectively (see the Supporting Information S13). Nevertheless, a question appeared in regard the excited state of the flavinium species and whether singlet oxygen was involved in the reaction. Therefore, we performed a series of photophysical measurements on **1 a** or **1 h** using a chlorotoluene (**CT**) model substrate utilising steady-state and transient absorption spectroscopy as well as TD-DFT calculations.

Singlet and triplet excitation energies were calculated employing the TD-DFT/6-31++G(d,p) level of theory (see Experimental and the Supporting Information S14 and S17). Figure 1 shows the singlet excitation energies compared with the experimental absorption spectra. Table 5 summarises the theoretical

Table 5. Important data for electron transfer with **1 a** and **1 h**.

	Data for **1 a**	Data for **1 h**
$E^{0\text{–}0}$(S1) [eV]	2.80[a] (2.6[b])	2.84[a] (2.7[b])
$E^{0\text{–}0}$(T1) [eV]	1.79[a]	2.10[a]
E^*_{red}(S1) [V]	2.42[a] (2.2[b])	2.96[a] (2.8[b])
E^*_{red}(T1) [V]	1.41[a]	2.22[a]
τ_F [ns]	6.10	0.46
Φ_F	0.31	0.079
Φ_Δ	0.69	0.82
singlet excited state quenching under argon		
k(**CT**) [$M^{-1}s^{-1}$]	3.1×10^{10}	14×10^{10}
k(**MB**) [$M^{-1}s^{-1}$]	0.9×10^{10}	3.4×10^{10}
k(**DMB**) [$M^{-1}s^{-1}$]	1.5×10^{10}	1.9×10^{10}
triplet state quenching		
k(**CT**) [$M^{-1}s^{-1}$]	1.8×10^{8}	4.1×10^{10}
k(**EDTA**) [$M^{-1}s^{-1}$]	1.9×10^{10}	n.d.

[a] Value from calculated data.
[b] Value based on spectral measurements.
τ_F: fluorescence lifetime; Φ_F: fluorescence quantum yield; Φ_Δ: singlet oxygen quantum yield.

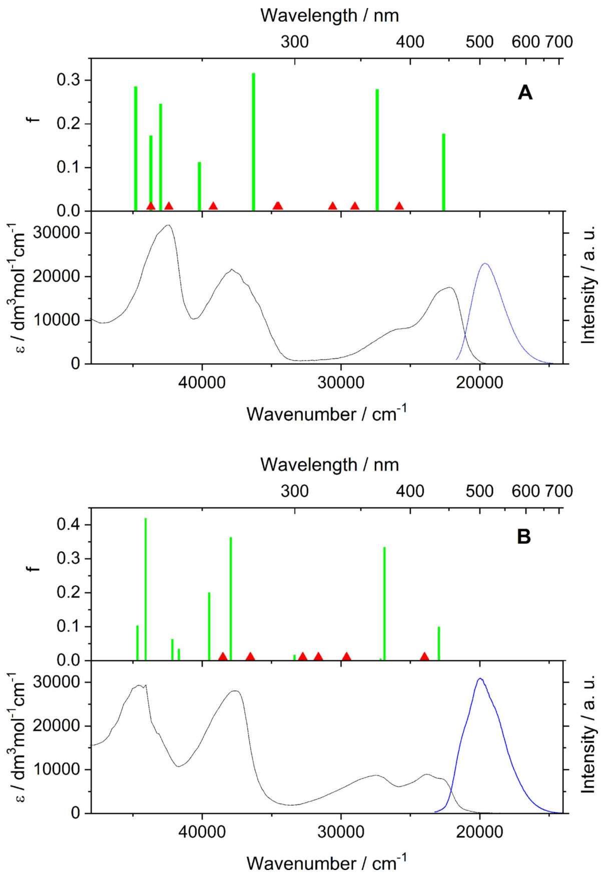


Figure 1. The predicted lowest-energy singlet-singlet π,π* transitions for **1 a** (A) and **1 h** (B) – upper panels – compared to the experimental absorption spectra in acetonitrile – bottom panels. Red triangles represent the weak n,π* transitions. The experimental fluorescence spectra in acetonitrile are also shown (in blue).

values obtained for $E^{0\text{–}0}$(S1) and $E^{0\text{–}0}$(T1), which give the most information in regard electron transfer in the photooxidation reactions. The $E^{0\text{–}0}$(S1) values calculated from the experimental data based on UV-VIS-fluorescence spectra intersection point are slightly lower (see values in parenthesis). From the values obtained for the excitation energies and ground state reduction potentials, the corresponding excited state reduction potentials, E^*_{red}(S1) and E^*_{red}(T1), were calculated. Upon comparing the excited state reduction potentials of **1 a** and **1 h** with the ground state oxidation potential of chlorotoluene ($E_{\mathrm{ox}} = 2.21$ V vs SCE), electron transfer from the triplet excited state seems to be endergonic for **1 a** and with a ΔG value close to zero for **1 h**. On the other hand, electron transfer is markedly exergonic for both catalysts in their singlet excited states.

Measuring the bimolecular quenching rate constant of **1 a** and **1 h** in the singlet excited state with **CT** was performed using static and dynamic fluorescence measurements. Triplet state quenching was studied using laser-flash photolysis (see Table 5 and the Supporting Information S9 and S11). Interestingly, the fluorescence quenching rate constants for **CT** are higher when compared to the diffusion limit of acetonitrile and the quenching rate constant of methoxybenzene (**MB**, $E_{\mathrm{ox}} = 1.73$ V vs SCE) and 1,3-dimethoxybenzene (**DMB**, $E_{\mathrm{ox}} = 1.50$ V vs SCE), which are better electron donors. This observation can be explained by the formation of a complex between **1** and **CT** accelerating the electron transfer process. The interaction between **1 a** and **CT** was confirmed using a titration study monitored using UV-VIS or ^{1}H NMR spectroscopy (see the Supporting Information S9). Analogous interaction between **1 h** and **MB** is proposed which is manifested by unexpected higher quenching rate constant of **1 h** fluorescence with **MB** compared to **DMB**.

The triplet state quenching rate constant for **1 a** with **CT** was lower by two orders of magnitude when compared to that obtained for the singlet excited state and the value is also significantly lower than that with EDTA, which is known as a good quencher of flavins (see the Supporting Information S11). The data obtained for the quenching rates together with the thermodynamic values for the photoinduced electron transfer and relatively long lifetime of the singlet excited state of **1 a** (6.1 ns in the presence of oxygen) support the idea that the oxygenation reaction occurs via the singlet excited state of **1 a**. On the other hand, the participation of **1 h** triplet excited state during the photooxidation process is expected because of the very short lifetime of its singlet excited state.

The presence of chlorotoluene (**CT**) significantly decreases the efficiency of singlet oxygen sensitization by both **1 a** and **1 h** as evident from the singlet oxygen quantum yield vs **CT** concentration relationships (see the Supporting Information S12). While singlet oxygen quantum yield Φ_Δ is 0.69 and 0.82 for **1 a** and **1 h**, respectively in the absence of **CT**, it decreases to 0.18 and 0.15 at a concentration of 20 mM for this substrate. Keeping in mind that the concentration of the substrate is even higher (> 0.1 M) in standard photooxidations, singlet oxygen participation for this reaction is unlikely.

Conclusions

We have described a new photocatalytic procedure for the aerobic oxidation/oxygenation of benzylic substrates mediated by ethylene-bridged flavinium salt **1 a** and blue light. Use of dimethoxyflavinium salt **1 a** instead of trifluoromethyl derivative **1 g**, mentioned in a preliminary report[16] is advantageous because of its substantially higher photostability allowing a simple reaction arrangement without temperature control. The method seems to be unique among flavin-based photooxidation systems as it is both metal-free and robust and allows the oxidation of highly electron-deficient substrates. In this aspect, the method exceeds other photooxidation methodologies performed using organic dyes and it is comparable with a method using a sub-stoichiometric amount of sodium trifluoromethanesulfinate.[26] Our mechanistic investigations show that the reaction starts via electron transfer from the benzylic substrate to the singlet excited state of **1 a**, which offers the maximum oxidizing power. Alternatively, **1 h** can be used instead of **1 a** for substrates with extremely high oxidation potential.

Some ethylene-bridged flavinium salts **1** have been previously studied in organocatalysis or biocatalysis.[25b,27] Attempts to achieve the high efficiency of **1** in oxidation reactions have often led to derivatives bearing electron-withdrawing group(s). In photocatalysis, too electron-deficient flavinium salts seem to be disadvantageous. However, methoxy functionalities have a positive effect on the properties of the flavin photocatalyst causing its high stability, while maintaining its highly positive excited state reduction potential. A similar effect has already been described among the neutral alloxazines used in energy transfer cycloadditions,[28] 5-ethylalloxazinium salts used in [2+2] cycloelimination,[29] and acridinium salts used in various photooxidative processes.[30] We plan to further investigate this effect among flavin derivatives and to evaluate the performance of stable and powerful salt **1 a** in other photooxidative processes.

Experimental Section

General Comments to the Starting Material and Synthesis

Starting materials and reagents were obtained from commercial suppliers and used without further purification. The solvents were purified and dried using standard procedures. Flavinium salts **1**, were prepared and characterized as described in the the Supporting Information S1, S15 and S16. **NMR spectra** were recorded on a Varian Mercury Plus 300 (299.97 MHz for ^{1}H, 75.44 MHz for ^{13}C, and 282.23 MHz for ^{19}F) or Agilent 400-MR DDR2 (399.94 MHz for ^{1}H and 100.58 MHz for ^{13}C) at 298 K unless otherwise indicated. Chemical shifts δ are given in ppm, using residual solvent or tetramethylsilane as an internal standard. Coupling constants *J* are reported in Hz. High-resolution **mass spectra** were obtained on Q-Tof Micro (Waters), equipped with a quadrupole and time-of-flight (TOF) analyser and subsequent a multichannel plate (MCP) detector. Thin layer chromatography (TLC) analyses were carried out on a DC Alufolien Kieselgel 60 F254 (Merck). Preparative column chromatography separations were performed on a silica gel Kieselgel 60 0.040–0.063 mm (Merck). Flash chromatography was performed at Büchi Pure C-810 at Silica 40 µm irregular column. **Melting points** were measured on a Boetius melting point apparatus and are uncorrected.

General Procedures for Photocatalytical Oxidations

Experiments on analytical scale. 5-Cl or **5-CF$_3$** (0.1 mmol) and flavinium salt **1** (0.005 mmol, 5 mol. %) were dissolved in acetonitrile (200 uL) in a vial. CF_3COOH (15.3 µL, 2 eq.) and molecular sieves 4 (15 mg) were added. The reaction mixture was bubbled with oxygen from balloon through a septum for 2 minutes and then, stirred and irradiated (Luxeon STAR/0, 4x1030 mW@700 mA, 450 or 400 nm) for 8 h under oxygen (balloon) at 40 °C. After irradiation, 800 µL of deuterated DMSO with dimethylsulfone as an inert standard was added. Mixture was filtrated by syringe frit into a cuvette and ^{1}H NMR spectrum was measured.

Experiments on preparative scale using 1 a. 1 a (36 mg; 0.1 mmol; 5 mol. %) or (11 mg; 0.03 mmol; 1.5 mol. %) or (3.5 mg; 0.01 mmol; 0.5 mol. %), substrate (2 mmol) and trifluoroacetic acid (306 µL; 4 mmol) were dissolved in anhydrous acetonitrile (16 mL) in 50 mL Erlenmeyer flask equipped with balloon filled with oxygen. Molecular sieves 4 A (300 mg) were added. The reaction mixture was bubbled with oxygen from balloon through a septum for 2 minutes and then, stirred and irradiated (4x Luxeon STAR/0, 4x1030 mW@700 mA, 450 nm) under oxygen atmosphere. Temperature was not adjusted (orientation measurements showed temperature around 40 °C under abovementioned conditions). Reaction was monitored by ^{1}H NMR. Silica gel (~ 3 g) was added and solvent evaporated. Crude reaction mixture was purified by flash chromatography (hexane:EtAc). See the Supporting Information S8 for details.

Experiments on preparative scale using 1 h or 1 g. 1 h (18 mg; 0.05 mmol; 5 mol. %) or **1 g** (23 mg; 0.05 mmol; 5 mol. %), substrate (1 mmol) and trifluoroacetic acid (0.153 mL; 2 mmol) were dissolved in anhydrous acetonitrile (12 mL) in 20 mL double-walled reactor equipped with balloon filled with oxygen. Molecular sieves 4 A (150 mg) were added. The reaction mixture was bubbled by oxygen from balloon through a septum for 2 minutes and then, the reaction mixture was stirred and irradiated (6x Luxeon STAR/0, 4x1030 mW@700 mA, 400 nm) under oxygen atmosphere. Temperature (20 °C) was controlled by thermostat. Reaction was monitored by ^{1}H NMR. Silica gel (~3 g) was added and solvent evaporated. Crude reaction mixture was purified by flash chromatography (hexane:EtAc). See the Supporting Information S8 for details.

Experiments on gram-scale. 1 a (90 mg; 0.25 mmol; 2.5 mol. %), substrate (10 mmol) and trifluoroacetic acid (1.5 mL; 20 mmol) were dissolved in anhydrous acetonitrile (160 mL) in photoreactor equipped by water-cooled 460 nm light source (novaLIGHT TLED100, 100 W). Molecular sieves 4 A (1.5 g) were added. The reaction mixture was bubbled with oxygen via cannula through a septum, stirred and irradiated. Temperature was adjusted by lamp-cooling system to approx. 30 °C. After 6 h of irradiation, the second dose of **1 a** (90 mg; 0.25 mmol; 2.5 mol. %) was added and the reaction mixture was irradiated for another 6 h (monitoring by ^{1}H NMR). Silica gel (~6 g) was added and solvent was evaporated. Crude reaction mixture was purified by flash chromatography (hexane:EtAc). See the Supporting Information S8 for details.

Electrochemical Measurements

Cyclic voltammograms were recorded using Metrohm Autolab PGSTAT128 N, in a 25 mL cell of Metrohm type, in dry acetonitrile, sample concentration was 5×10^{-3} mol/L. Tetrabutylammonium hexafluorophosphate, $[Bu_4N][PF_6]$, puriss., electrochemical grade, Fluka, was used as supporting electrolyte in concentration 0.1 mol/L. The sample solution was prepared directly in the cell, it was deareated by a stream of argon before measurement. A glassy carbon working electrode was used, together with Pt wire auxiliary electrode and Ag wire pseudo-reference electrode. Scan rate was 50, 100, 200, 300 mV/s. Data were referenced to SCE (ferrocene was used as inner standard). E_{red} values were calculated as an average of upper and bottom wave and as an average of results from measurement by scan rate 50, 100, 200, 300 mV/s. See the Supporting Information S4 for details.

Photophysical Measurements

Absorption spectra for flavinium salts **1** were performed on Shimadzu UV-vis spectrophotometer (UV-2550) using quartz cells of 1 cm. **The emission spectra** were measured using Horiba Jobin Yvon Fluorolog-3 spectrofluorometer and the optical density in each case was less than 0.1 nm. The excitation wavelengths were 449, 449, 450, 449, 408, 406 and 420 nm for **1 a**, **1 b**, **1 c**, **1 d**, **1 e**, **1 f** and **1 h**, respectively. See the Supporting Information S2 for details

Fluorescence quantum yields of flavinium salts **1** were determined by preparing series of dilution ranging in absorption from 0.02 to 0.10 and excited at their respective absorption maxima. Lumichrome (LC) has been used as a standard. See the Supporting Information S3 for details.

The fluorescence quenching experiments for **1 a** and **1 h** were carried out using chlorotoluene (**CT**), methoxybenzene (**MB**) and dimethoxybenzene (**DMB**) in the concentration range of 0.5–20 mM using FluoTime 300 Fluorescence Lifetime Spectrometer (PicoQuant). The excitation/emission wavelength for **1 a** and **1 h** were 440/520 nm and 440/500 nm, respectively. See the Supporting Information S9 for details

Transient absorption spectra of **1 a** and **1 h** were measured using laser flash photolysis system build in our lab. All the measurements have been performed using 1 × 0.4 cm quartz cells in the presence and absence of oxygen and quenchers (**CT**, EDTA). The 3ω 2ω Q-smart 450 Quantel laser of 355 nm was used with the energy of 2 mJ/pulse and the signals were detected through PDA detector. The optical density for each sample was around 0.50 at 355 nm and the 1 cm face of cuvette is facing toward laser and 0.4 cm towards lamp. See the Supporting Information S11 for details

Singlet oxygen generation measurements. The characteristic steady-state emission spectra of singlet oxygen were recorded on the Jobin Yvon-Spex Fluorolog 3–221 spectrofluorometer with an H10330B-75 NIR-PMT module, sensitive in the 950 to 1700 nm NIR range. Xenon lamp with a monochromator was used as an excitation source for the steady-state spectra. Phosphorescence decays were measured with SpectraLed diode ($\lambda_{exc}=371$ nm; $\lambda_{em}=1270$ nm) on the same spectrofluorometer. The solutions were studied in 1×1 cm^2 quartz cuvette in equilibrium with ambient air. Quantum yield of singlet oxygen and lifetime of singlet oxygen measurements for **1** was determined by preparing the series of dilutions ranging from 0.02 to 0.10 nm and excited at their respective absorption maxima with detection at 1270 nm using. Perinepthenone (PNF) was used as standard to determine the quantum yield of singlet oxygen by exciting it at 356 nm (see the Supporting Information S12 for details).

DFT Calculations

The equilibrium structures and energies of the positively charged cations from **1 a** and **1 h** were determined by employing the Density Functional Theory (DFT) with Becke's Three Parameter Hybrid Method with the LYP (Lee-Yang-Parr) correlation functional (B3LYP)[31] together with the 6-31++G(d,p)[32] basis sets. Electronic excitation energies for singlet and triplet states of these systems and the corresponding oscillator strengths were obtained from the TD-DFT technique[33] using the same B3LYP functional and 6-31++G(d,p) basis set and at the equilibrium geometry of the absorbing species. The harmonic vibrational frequencies (unscaled) and the energies of the triplet states of **1 a** and **1 h** cations at their equilibrium structures were obtained at the same TD-DFT 6-31++G(d,p) theory level to assure consistency. All of the calculations were performed with the Gaussian16 program suite.[34] See the Supporting Information S14 and S17 for details.

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FULL PAPER

Robust Photocatalytic Method Using Ethylene-Bridged Flavinium Salts for the Aerobic Oxidation of Unactivated Benzylic Substrates

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