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Tuning flavin-based photocatalytic systems for application in the mild chemoselective aerobic oxidation of benzylic substrates

Amal Hassan Tolba,[a] František Vávra,[a] Josef Chudoba,[b] and Radek Cibulka*[a]

Dedication ((optional))

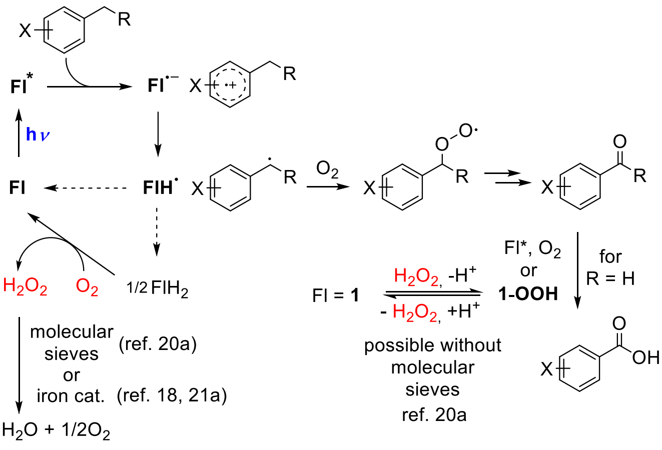
Abstract: New flavin-based photocatalytic systems used for chemoselective aerobic visible-light oxidation have been developed by tuning the flavin structure and reaction conditions. 1,3-Dimethyl-7-trifluoromethylalloxazine (**2**) and 10-butyl-3-methyl-7-trifluoromethylisoalloxazine (**3**) were shown to mediate the selective oxidation of benzyl alcohols to form aldehydes in the presence of Cs_2CO_3. Flavin **3** was superior in the oxidation of toluene derivatives to form aldehydes in the presence of trifluoroacetic acid. On the other hand, photooxidations provided by ethylene-bridged quaternary flavinium salt **1** gave the corresponding carboxylic acids. The usefulness of the developed catalytic systems using **1**–**3** was also demonstrated in the oxidation of secondary benzylic and aliphatic alcohols, and benzylic methylene groups to form the corresponding ketones. The systems have the advantage of a broad substrate scope and metal-free conditions, which distinguish them from the previously reported flavin photooxidation reactions.

Introduction

Aerobic oxidation/oxygenation reactions mediated by photoactive catalysts and visible light have been established as valuable and sustainable alternatives to conventional ground state oxidations based on metal- or halogen atom-containing stoichiometric oxidants.[1] Photooxidation methods utilize light to generate a strong oxidizing agent from a suitable dye via excitation. In an optimal procedure, molecular oxygen is used both as a source of oxygen atoms and a reagent for photocatalyst regeneration.[1a] Some ruthenium- and iridium-containing complexes have been used in photocatalytic oxidations.[1a,2] Nevertheless, various organic photocatalysts have been tested as greener and less expensive alternatives, such as acridinium salts,[1a,3] quinones[4] and fluorenones.[5] One of the most potent class of photocatalysts used for photooxidations and photooxygenations is the flavins.[6] Recently, the versatility of flavin photocatalysts has been demonstrated by a plethora of applications including aerial sulfoxidation,[7] decarboxylative cyanation,[8] coumarin synthesis based on a coupled E/Z-isomerization-oxidation procedure,[9] [2+2] cycloaddition,[10] oxidative cycloelimination,[11] aromatic chlorination,[12] hydrazine and triphenylphosphine oxidation to promote the photocatalytic Mitsunobu reaction,[13] *N*-bromo succinimide activation[14] and the photochemical demethylation or debenzylation reactions.[15]

Herein, we have focused on the chemoselective oxidation of inert benzylic $C(sp^3)$-H bonds and inactivated alcohols to prepare their corresponding carbonyl compounds. The synthesis of these compounds is one of the most important challenges in the pharmaceutical and fine chemical industry.[1f,1g,16] Indeed, riboflavin tetraacetate (**RFTA**) has already been shown to effectively oxidize benzyl alcohols to aldehydes, but the scope of the reaction is limited to electron-rich substrates such as 4-methoxybenzyl alcohol.[17] In the presence of an iron salt at 50 °C in a flow-arrangement, **RFTA** has also been shown to oxidize benzylic methylene groups to their corresponding ketones or methine groups to alcohols.[18] When coordinated to rare-earth metals such as scandium, **RFTA** is able to oxidize non-activated benzyl alcohols[19] and some toluene derivatives to their corresponding aldehydes.[19a] Very recently, to avoid using rare-earth metals, we developed a system using excited flavinium salt **1** which is the strongest biomimetic oxidant reported to date.[20]

Generally accepted mechanism for photooxidations with flavins **Fl** involves electron transfer from benzylic substrate to an excited flavin **Fl*** followed by an oxygenation reaction (Scheme 1).[17-21] Then, reduced flavin $\mathbf{FlH_2}$ is re-oxidized by oxygen. Aerobic regeneration of the flavin catalyst produces hydrogen peroxide which usually supports catalyst bleaching. To avoid this undesired process, an iron salt[18,21] or molecular sieves[20a] can be added to decompose the formed hydrogen peroxide. Alterna-



Scheme 1. General scheme for benzylic oxidations promoted by flavins **Fl**.

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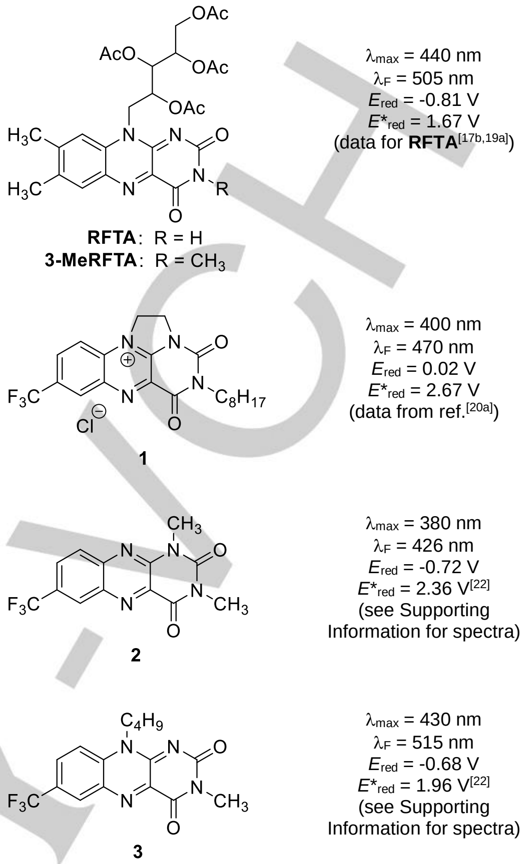
tively, hydrogen peroxide can be consumed in a coupled oxygenation reaction, which was demonstrated when combining **RFTA** with non-heme Fe(II) complex[21a] and by using flavinium salt **1** under specific conditions (see below for details).[20a]

The enormous oxidation power of flavinium salt **1** has been demonstrated in the aerobic photooxidation of deactivated benzylic substrates such as 4-trifluoromethyltoluenes to the corresponding carboxylic acids.[20a] However, it was troublesome to stop the oxidation at the aldehyde stage. The light dependent cycle involving **1** as a photocatalyst carries out the oxidation to give the aldehyde, which is followed by photooxidation to the carboxylic acid (Scheme 1). For substrates with strongly electron-withdrawing groups such as CF_3 or NO_2, the photocatalytic oxidation of toluene to its corresponding aldehyde has been coupled with an organocatalytic cycle involving flavin hydroperoxide **1-OOH** to transform the aldehyde to its carboxylic acid.[20a] This process occurs in the absence of molecular sieves. Under these conditions, hydrogen peroxide remains in the system and it is added to flavinium salt **1** to form **1-OOH** (Scheme 1). In contrast, trifluoroacetic acid was used in fully photocatalytic systems to prevent formation of adducts like **1-OOH** or **1-OH** thus keeping concentration of photocatalyst **1** as high as possible.[20a]

Herein, we have attempted to overcome the above-mentioned limitations by gently tuning the flavin-based catalytic systems via the selection of the most suitable flavin derivative and optimization of the reaction conditions. This has led to photooxidation systems allowing the chemoselective oxidation of benzyl alcohols or toluene derivatives to their corresponding aldehydes or the effective oxidation of inactivated substrates with high oxidation potentials (secondary alcohols/methylene containing compounds) to form ketones.

Results and Discussion

When designing catalytic systems for aerobic oxidation, we consider the following facts concerning flavin photocatalysts: i) Excited ethylene-bridged flavinium salt **1** (Figure 1) is an extremely strong oxidizing agent,[20a] which disfavours its use in chemoselective (partial) oxidation reactions. Moreover, salt **1** undergoes photo-bleaching and thus, it is not useful under prolonged reaction conditions; ii) corresponding “neutral” analogues of flavinium salts are weaker oxidants because of missing positive charge. Therefore we tested alloxazine **2** which is believed to be milder oxidant then **1** in its excited state according to reduction potentials (E_{red}* = 2.36 V for **2**[22] vs 2.67 V for **1**[20a]); iii) **RFTA** is known to only catalyse the oxidation of electron-rich benzylic substrates.[17] Thus, we tested its 7-trifluoromethyl analogue **3**, which has been proposed to be a more powerful oxidizing agent considering the reduction potential in its excited state (E_{red}* = 1.96 V for **3**[22] vs 1.67 V for **RFTA**[19a]). Flavin derivatives **1** and **2** were prepared as previously reported[20a,23] and flavin **3** was synthesized via the condensation of *N*-butyl-4-trifluoromethylbenzene-1,2-diamine with alloxane followed by methylation (see Experimental).



RFTA: R = H
3-MeRFTA: R = CH_3

λ_{max} = 440 nm
λ_F = 505 nm
E_{red} = -0.81 V
E^*_{red} = 1.67 V
(data for **RFTA**[17b,19a])

1

λ_{max} = 400 nm
λ_F = 470 nm
E_{red} = 0.02 V
E^*_{red} = 2.67 V
(data from ref.[20a])

2

λ_{max} = 380 nm
λ_F = 426 nm
E_{red} = -0.72 V
E^*_{red} = 2.36 V[22]
(see Supporting Information for spectra)

3

λ_{max} = 430 nm
λ_F = 515 nm
E_{red} = -0.68 V
E^*_{red} = 1.96 V[22]
(see Supporting Information for spectra)

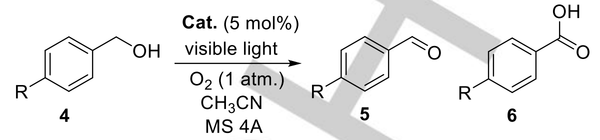
Figure 1. Flavins employed in the study and their spectral and electrochemical data (vs SCE) in acetonitrile.

We first studied the chemoselective photooxidation of benzyl alcohols (**4**) to their corresponding aldehydes (**5**) using 4-chlorobenzyl alcohol (**4-Cl**) as a model substrate. In accordance with our previous results,[20a] the oxidation catalysed by **1** in the presence of trifluoroacetic acid resulted in the exclusive formation of 4-chlorobenzoic acid (**6-Cl**). The same result was obtained regardless of whether the catalytic system was irradiated at the maximum (400 nm) or edge (448 nm) of the absorption of catalyst **1** (Table 1, Entries 1 and 2, respectively). Acid **6-Cl** was also preferably formed using **2** under acidic conditions (Entry 3), while catalyst **2** provided aldehyde **5-Cl** in the presence of Cs_2CO_3 (Entry 4). Similar results were obtained for electron-deficient trifluoromethyl derivative **4-CF$_3$**; we observed the preferred formation of acid **6-CF$_3$** with **2** in the presence of trifluoroacetic acid and selective oxidation toward aldehyde **5-CF$_3$** under basic conditions (Entries 5–7). An even better result was obtained using isoalloxazine **3**, which provided aldehyde **5-CF$_3$** in good yield and selectively under irradiation at 448 nm (close to maximum absorption) (Entry 8). Newly developed procedures using catalysts **2** and **3** were proved in 1 mmol scale experiments, which provided aldehydes **5** in high yield starting from **4-OCH$_3$**, **4-Cl** and **4-CF$_3$** (see Table 2, Entries 1–3).

According to the redox potentials in their excited states (Figure 1), catalyst **2** and **3** should oxidize electron-rich 4-methoxybenzyl alcohol (**4-OMe**; E_{ox} = 1.57 V[3c]). On the other hand, isoalloxazine **3** will not be able to oxidize chloro- (**4-Cl**) and trifluoromethyl (**4-CF$_3$**) derivatives with E_{ox} values 2.16 and 2.70 V, respectively.[20a] This is reflected also in fluorescence quenching experiments. While addition of **4-OMe** causes significant decrease of fluorescence intensity of a solution of isoalloxazine **3** with the Stern-Volmer constant value K_S = 88 L mol^{-1}, a quenching with **4-CF$_3$** is almost undetectable with K_S = 0.9 L mol^{-1} (see Supporting Information). This is why basic conditions are essential in these oxidation reactions, facilitating the formation of alkoxide, which undergoes electron transfer to an excited flavin more easily (Scheme 2A).[24] Fukuzumi have reported that RFTA oxidizes **4-H** and **4-Cl** to their corresponding aldehydes under strongly acidic conditions using perchloric acid.[3c] However, the same system oxidizes neither electron-poor **4-CF$_3$** nor electron-rich **4-OMe** because of the high oxidation potential and back electron transfer, respectively.[3c] Our method with isoalloxazine **3** and Cs_2CO_3 seems to be more general, allowing the oxidation of electron-poor (**4-CF$_3$**), electron-neutral (**4-Cl**) and electron-rich (**4-OMe**) substrates (see Table 1, Entries 8–10 and Table 2).

A question has appeared whether the trifluoromethyl group is necessary for the isoalloxazine moiety to be efficient in the photooxidation of electron-deficient benzyl alcohols in the presence of Cs_2CO_3. Thus, we proved the use of RFTA in the oxidation of **4-CF$_3$** under these newly developed conditions. Considering the oxidation properties of **RFTA** can be influenced by deprotonation of the hydrogen atom in the 3-position, we also tested its 3-methyl analogue (**3-MeRFTA**). However, in both cases, only a small amount of product was formed in contrast with the reaction using trifluoromethyl-substituted flavin **3** (Table 1, cf. Entries 8 vs 11 and 12).

Table 1. Optimizing conditions for chemoselective photocatalytic oxidations of benzyl alcohols.[a]

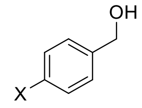
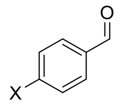


Entry	R	Cat.	Light [nm]	Additive	Yield [%][b]		
					4	5	6
1	Cl	**1**	400	CF_3COOH	33	n.d.[c]	67
2	Cl	**1**	448	CF_3COOH	n.d.[c]	13	73
3	Cl	**2**	400	CF_3COOH	51	n.d. [c]	49
4	Cl	**2**	400	Cs_2CO_3	39	61	n.d.
5	CF_3	**2**	400	CF_3COOH	17	2	81
6	CF_3	**2**	448	CF_3COOH	56	32	12
7	CF_3	**2**	400	Cs_2CO_3	73	27	n.d.[c]
8	CF_3	**3**	448	Cs_2CO_3	29	71	n.d.[c]
9	Cl	**3**	448	Cs_2CO_3	34	66	n.d.[c]
10	OMe	**3**	448	Cs_2CO_3	59	41	n.d.[c]
11	CF_3	**RFTA**	448	Cs_2CO_3	96	4	n.d.[c]
12	CF_3	**3-MeRFTA**	448	Cs_2CO_3	93	7	n.d.[c]

[a] Reaction conditions: **4** (0.14 mmol), catalyst (5 mol%), additive (0.14 mmol), MS 4Å (15 mg), acetonitrile (250 μL), visible light, 45 °C, oxygen (balloon), 8h. [b] Yields determined by ^{1}H NMR. [c] Not detected.

Chemoselective oxidation of toluene derivatives to their corresponding benzaldehydes represents an even more interesting and valuable synthetic task. In our search for a suitable flavin catalytic system we used toluene (**7-H**) as a model substrate (Table 3). As described in our previous paper, flavinium salt **1** catalyses the selective oxidation of 4-chlorotoluene (**7-Cl**) to acid **6-Cl** under acidic conditions. This transformation takes place

Table 2. Preparative experiments on photocatalytic oxidations of benzylalcohols.[a]

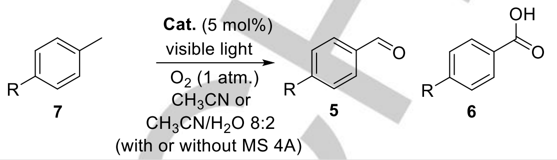
Entry	Substrate	Main product	Catalyst	Wavelength	Additive	Conv.[b] [%]	Yield[c] [%]
							
1	X = Cl (**4-Cl**)	X = Cl (**5-Cl**)	**2**	400	Cs_2CO_3	72	55
2	X = CF_3 (**4-CF$_3$**)	X = CF_3 (**5-CF$_3$**)	**3**	448	Cs_2CO_3	71	63
3	X = OCH_3 (**4-OCH$_3$**)	X = OCH_3 (**5-OCH$_3$**)	**2**	400	Cs_2CO_3	100	87

[a] Conditions: substrate (1 mmol), catalyst (5 mol%), MS 4 Å (125-150 mg), solvent, additive (0.7 mmol), CH_3CN (2 mL), 400 or 448 nm, 45 °C, oxygen (balloon), 24 h. [b] Determined by ^{1}H NMR. [c] Preparative yields.

predominantly via excited **1**, which is strong enough to oxidize aldehyde **5-Cl** to acid **6-Cl**. This is not the case for the trifluoromethyl substrate. The photoinduced electron transfer from aldehyde **5-CF_3** to **1*** is rather endergonic and the oxidation of **5-CF_3** to **6-CF_3** is mainly catalysed by the flavin-hydroperoxide generated from **1** upon the addition of H_2O_2, which is formed during the reaction in the absence of MS or by its reaction with oxygen.[20] Overoxidation to the acid using photocatalyst **1** was also observed for toluene (Table 3, Entries 1 and 2) and benzoic acid was selectively formed with **2** under acidic conditions (Entry 3). On the other hand, the aldehyde product was formed preferably using **3** in acetonitrile (Entry 4). Oxidation using **3** was even more efficient in acetonitrile/water, which is known to avoid the aggregation of flavins (Entry 5).[17b] Flavin **3** seems to be a good choice also for chloro-derivatives (Entries 6–8). The developed reaction conditions were successfully proven on a 1 mmol scale for toluene (**7-H**), 4-chlorotoluene (**7-Cl**) and 1-bromo-2-methylnaphthalene **8** (Table 4, Entries 1–3). Unfortunately, electron-poor 4-trifluoromethyltoluene (**7-CF_3**) was oxidized with low conversion (Table 3, Entry 9). Our attempts to further vary the reaction conditions and the catalyst led to either overoxidations to acid **6** (Table 3, Entry 10) or gave aldehyde **5** in very low conversion.

According to its redox potential (Figure 1), excited isoalloxazine **3** is not strong enough to take an electron from toluene (**7-H**; E_{ox} = 2.20 V[25]). Nevertheless under acidic conditions, neutral flavin is transformed into its flavinium salt, which is a more powerful oxidizing agent (Scheme 2B).[3c] It should be noted that trifluoroacetic acid is able to protonate flavin **3**, which has been confirmed using UV-VIS spectroscopy (see Supporting Information). Fluorescence quenching experiments confirmed that photoinduced electron transfer from toluene to protonated flavin **3** is feasible (K_S = 23 L mol^{-1}) while to "neutral" **3** not (K_S < 1 L mol^{-1}; see Supporting Information). The fact that the catalytic system using **3** and CF_3COOH does not oxidize 4-trifluoromethyl toluene (**7-CF_3**; E_{ox} = 2.61 V[20a]) corresponds to the previous observation by Fukuzumi, in which the **RFTA**-HBr system was not effective for the oxidation of 4-trifluoromethylbenzyl alcohol **4-CF_3** because of its high oxidation potential (E_{ox} = 2.70 V[20a]).

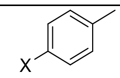
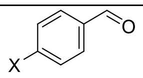
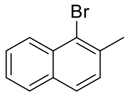
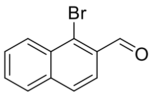
Table 3. Optimizing conditions for chemoselective photocatalytic oxidations of toluenes.[a]



Entry	R	Cat.	Light [nm]	Additive	Yield [%][b]		
					7	**5**	**6**
1	H	**1**	400	CF_3COOH	0	9	91
2	H	**1**	448	CF_3COOH	81	15	4
3	H	**2**	400	CF_3COOH	0	0	100
4	H	**3**	448	CF_3COOH	77	23	traces
5	H	**3**	448	CF_3COOH[c]	58	42	traces
6	Cl	**2**	400	CF_3COOH	56	32	12
7	Cl	**2**	400	-[c]	83	17	n.d.[d]
8	Cl	**3**	448	CF_3COOH[c]	31	69	n.d.[d]
9	CF_3	**3**	448	CF_3COOH[c]	95	5	n.d.[d]
10[e][f]	CF_3	**1**	400	CF_3COOH[c]	47	26	18

[a] Reaction conditions: **4** (0.14 mmol), catalyst (5 mol%), CF_3COOH (0.14 mmol) only if mentioned, MS 4Å (15 mg), acetonitrile (250 uL), visible light, 45 °C, oxygen (balloon), 8h. [b] Yields determined by ^1H NMR. [c] Mixture acetonitrile-water (8:2) used as solvent. [e] ref.[20a]; [f] 9% of alcohol detected.

Table 4. Preparative experiments on photocatalytic oxidations.[a]

Entry	Substrate	Main product	Catalyst	Wavelength	Additive	Conv.[b] [%]	Yield[c] [%]
							
1[d]	X = H (**7-H**)	X = H (**5-H**)	**3**	448	CF_3COOH	40	37
2[d]	X = Cl (**7-Cl**)	X = Cl (**5-Cl**)	**3**	448	CF_3COOH	25	18
3	 **8**	 **9**	**3**	448	CF_3COOH	71	57

[a]Conditions: substrate (1 mmol), catalyst (5 mol%), MS 4 Å (125-150 mg), solvent, additive (0.7 mmol), CH_3CN (2 mL), 400 or 448 nm, 45 °C, oxygen (balloon), 24 h. [b] Determined by ^1H NMR. [c] Preparative yields. [d] 10 mol% cat., In the absence of MS, CH_3CN:H_2O (80:20) (2 mL).

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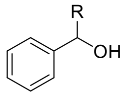
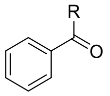
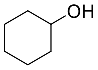
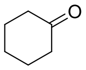
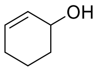
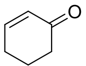
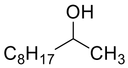
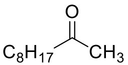
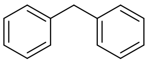
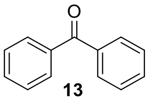
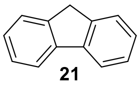
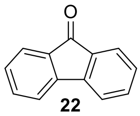
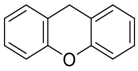
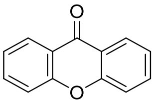
There is usually no problem in terms of the chemoselectivity in the oxidation of secondary alcohols and methylene groups to their corresponding ketones. Nevertheless, there is still a lack of metal-free, environmentally friendly methods for this transformation. In our preliminary study, we have shown that flavinium salt **1** can oxidize substituted 1-phenylethanols to their corresponding ketones in the presence of CF_3COOH in moderate yield.[20a] A similar result (46% conversion) was also observed for 1-phenylethanol (**10**). Herein, we found basic conditions using Cs_2CO_3 (analogously to the method used for the oxidation of benzyl alcohol) are beneficial, giving an almost quantitative yield of 1-phenylethanone (**11**) starting from 1-phenylethanol (**10**) (Table 5, Entry 1). We also found this oxidation occurs using **2** and **3,** but with lower efficacy (Table 5, Entries 2 and 3). Analogous results were obtained for the oxidation of diphenylmethanol (**12**) (Table 5, Entries 4 and 5).

In accordance with the results obtained for toluene derivatives, we found acidic conditions to be necessary for the efficient oxidation of the methylene to the carbonyl group. Using diphenylmethane (**20**) as a substrate, we demonstrated that the oxidation occurs with both flavinium salt **1** and alloxazine **2** in the presence of an acid (see Supporting Information). Nevertheless, the use of strong trifluoroacetic acid lead to oxidation to benzaldehyde (**5-H**) as a side reaction and thus, acetic acid was used to give ketone **13** as the sole product (Table 5, Entry 9). Presence of trifluoroacetic acid causes significant amount of benzaldehyde (**5-H**) formed also during diphenylmethanol (**12**) oxidation (see Supporting Information). Thus, we propose that this relatively strong acid can initiate dehydration of **12** to form carbocation undergoing further oxidative transformation resulting into C-C bond cleavage. Singlet oxygen produced by flavin sensitization[26] might be involved in this side reaction. The

Table 5. Preparative experiments on photocatalytic oxidations of secondary alcohols and methylene-containing compounds.[a]

Entry	Substrate	Main product	Catalyst	Wavelength	Additive	Conv.[b] [%]	Yield[c] [%]
							
1	R = CH_3 (**10**)	R = CH_3 (**11**)	**1**	448	Cs_2CO_3	97	94
2	R = CH_3 (**10**)	R = CH_3 (**11**)	**2**	400	Cs_2CO_3	47	n.d.[d]
3	R = CH_3 (**10**)	R = CH_3 (**11**)	**3**	448	Cs_2CO_3	71	n.d.[d]
4	R = Ph (**12**)	R = Ph (**13**)	**1**	448	Cs_2CO_3	99	72
5	R = Ph (**12**)	R = Ph (**13**)	**2**	400	Cs_2CO_3	66	n.d.[d]
6[e]	 **14**	 **15**	**2**	400	Cs_2CO_3	40	22
7[e]	 **16**	 **17**	**2**	400	Cs_2CO_3	56	18
8[e]	 **18**	 **19**	**2**	400	Cs_2CO_3	36	15
9[f]	 **20**	 **13**	**2**	400	CH_3COOH	75	70
10[f]	 **21**	 **22**	**1**	400	CF_3COOH	57	51
11	 **23**	 **24**	**1**	448	CF_3COOH	100	99

[a]Conditions: substrate (1 mmol), catalyst (5 mol%), MS 4 Å (125-150 mg), solvent, additive (0.7 mmol), CH_3CN (2 mL), 400 or 448 nm, 45 °C, oxygen (balloon), 24 h. [b] Determined by ^1H NMR. [c] Preparative yields. [d] Not determined. [e] 10 mol% cat., 48h. [f] 10 mol% cat.

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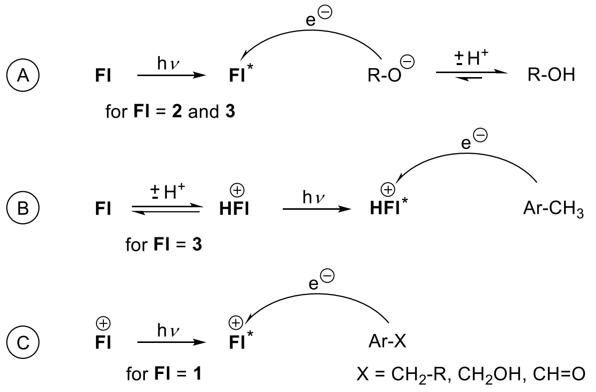
reactions using fluorene **21** and xanthene **23** selectively gave the desired products **22** and **24**, respectively (Table 5, Entries 10 and 11). It should be noted that **21** with relatively rigid central ring is more difficult substrate being oxidized efficiently only with **1** while **23** is transformed to the corresponding ketone **24** quantitatively with all tested flavins **1**-**3** (see Supporting information).

Finally, we showed the possible application of our flavin-based method for the oxidation of non-activated (non-benzylic) alcohols. Similar to benzylic alcohols **4**, basic conditions were beneficial for the oxidation of cyclohexanol (**14**), cyclohex-2-enol (**16**) and dodecan-2-ol (**18**) (Table 5, Entries 6–8). Nevertheless, a longer reaction time and higher catalyst loading were required to achieve a significant conversion.



Scheme 2. Proposed activation modes being involved in photooxidations with flavin derivatives presented in the work; activation by alcohol deprotonation (A), by flavin protonation (B) and by using flavinium salt instead of "neutral" flavin (C).

Conclusions

We have demonstrated that gentle tuning of the flavin catalyst structure and reaction conditions can lead to effective chemoselective aerobic photooxidation methodologies. The method using "neutral" alloxazine **2** or isoalloxazine **3** in either acidic or basic medium provides the chemoselective transformation of toluene derivatives and benzyl alcohols to their corresponding aldehydes. These methods utilize the "activation" of either the alcohol substrate (by deprotonation) or flavin catalyst **3** (by protonation) to allow electron transfer to occur (Scheme 2A and 1B). On the other hand, excited flavinium salt **1**, as a representative of a very strong oxidation agent, is suitable for the oxidation of substrates with high oxidation potentials to give their products in the highest oxidation states, carboxylic acids or ketones (Scheme 2C). Our methodologies conducted under metal-free conditions and are thus distinguishable from the previously reported chemoselective flavin-based oxidation methods, which require rare earth or transition metal ions. Considering the substrate scope and redox potential, newly developed flavin **3** is a more versatile and more powerful oxidizing agent when compared to the conventionally used **RFTA** catalyst, which only allows the oxidation of electron-rich substrates. Thus, trifluoromethyl derivative **3** can act as suitable alternative to RFTA when designing flavin-based systems for the other photocatalytic transformations.

Experimental Section

General. 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, 100.58 MHz for ^{13}C and 376.29 MHz for ^{19}F) at 298 K unless otherwise indicated. Chemical shifts δ are given in ppm, using residual solvent as an internal standard. ^{19}F NMR chemical shifts were measured relative to CCl_3F. Coupling constants *J* are reported in Hz. High-resolution mass spectra were obtained on LTQ Orbitrap Velos (Thermo Scientific), equipped with a linear ion trap and orbitrap analyzers. UV/Vis and fluorescence spectra were recorded on Varian Cary 50 Bio and Varian Eclipse spectrometers. 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). Melting points were measured on a Boetius melting point apparatus and are uncorrected.

Starting materials, reagents and substrates were obtained from commercial suppliers and used without further purification. The solvents were purified and dried using standard procedures. Flavinium salt **1** and alloxazine **2** were prepared according to the described procedures.[20a,23] For the synthesis of precursors for **3**, see Supporting Information.

10-Butyl-7-(trifluoromethyl)isoalloxazine. *N*-Butyl-2-nitro-4-(trifluoromethyl)aniline (11.34 g, 43.24 mmol) was dissolved in methanol (100 ml), palladium on carbon (10%, 250 mg) was added and the mixture was stirred 10 hours under hydrogen atmosphere. After filtration of palladium through celite and evaporation solvent, *N*-butyl-4-trifluoromethylbenzene-1,2-diamine (9.60 g, 96 %) was obtained which was immediately dissolved in acetic acid (30 ml). To this mixture hot solution of alloxane (7.10 g, 49.98 mmol) and boric acid (3.20 g, 51.75 mmol) in acetic acid (180 ml) was added and the mixture was stirred at 70 °C for 3 hours. After cooling to the room temperature and standing for 3 days, precipitated crystals was filtrated, washed with acetic acid (10 ml), methanol (15 ml) and ether (15 ml). Filtrate was evaporated, dissolved in methanol and precipitate with ether. Collected crystalline compound was dried in vacuo to obtained 5.40 g (39 %) of 10-butyl-7-(trifluoromethyl)isoalloxazine. M. p. 263 – 266 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.52 (s, 1H), 8.48 (d, *J* = 1.8 Hz, 1H), 8.26 – 8.00 (m, 2H), 4.58 (t, *J* = 7.8 Hz, 2H), 1.70 (q, *J* = 7.9 Hz, 2H), 1.48 (q, *J* = 7.4 Hz, 2H), 1.03 – 0.85 (m, 3H). ^{19}F NMR (282 MHz, DMSO-*d*$_6$) δ -60.72. HRMS-ESI+ m/z for $C_{15}H_{13}F_3N_4O_2+H^+$ $[M+H]^+$ calculated: 339.10634, found 339.10649.

10-Butyl-3-methyl-7-trifluoromethylisoalloxazine (3). 10-butyl-7-(trifluoromethyl)isoalloxazine (0.50 g, 1.47 mmol) was dissolved in DMF (50 ml), potassium carbonate (0.60 g,4.34 mmol) and methyl iodide (1.20 g, 8.46 mmol) were added. Reaction mixture was stirred at 65°C overnight, then diluted with water (500 ml) and extracted into dichloromethane (3 x 100 ml). Organic phase was washed with water (3 x 100 ml) and dried over magnesium sulphate. After evaporation of solvent, 0.36 g (70 %) of **3** was obtained. M. p. 141 – 146 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.61 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.11 – 8.04 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 4.70 (t, *J* = 8.1 Hz, 2H), 3.54 (s, 3H), 1.94 – 1.79 (m, 2H), 1.66 – 1.46 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.22, 155.67, 149.21, 138.57, 135.01, 134.71, 131.42 (q, *J* = 3.3 Hz), 130.95 (q, *J* = 3.9 Hz), 128.81 (q, *J* = 34.5 Hz), 121.76, 116.29, 45.14, 29.26, 29.08, 20.30, 13.90. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.69. HRMS-ESI+

m/z for $C_{16}H_{15}F_3N_4O_2+Na^+$ $[M+Na]^+$ calculated: 375.10393, found 375.10421.

Preparative photooxidations – general method. A mixture of a substrate (1 mmol), catalyst (0.05 or 0.10 mmol), additive (0.7 mmol; CF_3COOH or Cs_2CO_3) and activated MS 4 Å (125-150 mg) in CH_3CN (2 mL) was bubbled with oxygen (2 min) and then was stirred at 45 °C under irradiation by Luxeon LED diodes under O_2 atmosphere (balloon) for 24 hours (if not otherwise mentioned). The solids were filtered off and the solvent was evaporated. The crude product was purified by column chromatography on silica gel.

Acknowledgments

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Keywords: Oxidation • Photocatalysis • Aldehydes • Ketones • Chemoselectivity

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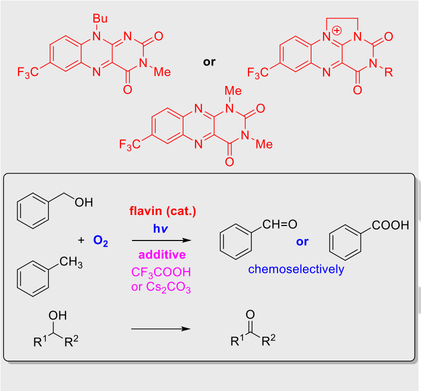
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Chemoselective oxidation of substituted benzyl alcohols and toluenes using a flavin photocatalyst, visible light and a suitable additive has been developed. Depending on the flavin and the additive, oxidation takes place selectively to the corresponding aldehyde or carboxylic acid. Procedure is useful also for oxidation of secondary alcohols or benzylic methylene-containing compounds to ketones.



Chemoselective photooxidation*

*A. H. Tolba, F. Vávra, J. Chudoba, R. Cibulka**

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Tuning flavin-based photocatalytic systems for application in the mild chemoselective aerobic oxidation of benzylic substrates