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COMMUNICATION

An Uncommon Use of Irradiated Flavins: Brønsted Acid Catalysis

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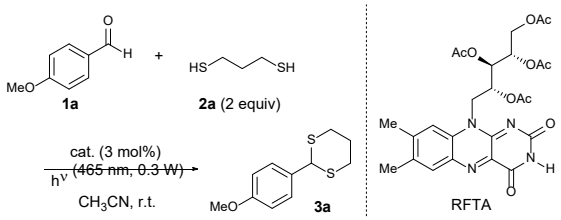
We present that thioacetalization of aldehydes can be induced by blue light irradiation in the presence of a catalytic amount of riboflavin tetraacetate (RFTA) under aerobic conditions. Several control experiments have suggested that the reaction is more likely to be catalyzed by acidic species generated in situ during the light irradiation. We have proposed that single electron transfer from a thiol (RSH) to the excited state of RFTA can take place to give a one-electron oxidized thiol ($RSH^{+\bullet}$) and the one-electron reduced RFTA ($RFTA^{-\bullet}$), which can be trapped by molecular oxygen to be stabilized as Brønsted acids including the protonated $RFTA^{-\bullet}$ ($RFTAH^{\bullet}$). Finally, we have demonstrated that such acidic species can be prepared in advance as a solution and used as Brønsted acid catalysts for not only the thioacetalization but also Mannich-type reactions.

Flavin molecules, such as riboflavin and its derivatives, have attracted increasing attentions as versatile photoredox /photosensitizing catalysts over a decade,[1] which are generally utilized under consecutive irradiation with visible light. Our research group has recently joined this seminal field by introducing the first photoredox/enamine dual catalysis with a peptide-bridged flavin–amine hybrid,[2] in addition to continuously contributing to the development of flavin-catalyzed thermal reactions under non-irradiation conditions.[3] In this article, we introduce a new aspect of such flavin molecules for organic synthesis, which uncommonly allows for the use of a flavin molecule like a Brønsted acid catalyst after short time irradiation in the presence of a thiol and molecular oxygen (O_2).

During our research on the development of flavin catalysis,[2,3] we serendipitously found that 4-methoxybenzaldehyde (**1a**) reacted smoothly with 1,3-propanedithiol (**2a**, 2 equiv) in the presence of riboflavin tetraacetate (RFTA, 3 mol%)[1d–1f,1h–1k,1m,1s–1u,2] in acetonitrile under consecutive blue LED irradiation (465 nm, 0.3 W) and air at room temperature to afford the corresponding dithiane derivative **3a** in quantitative yield within 6 hours (Table 1, entry 1). No desired reaction occurred in the absence of either RFTA, light, or O_2, indicating that all of them could be essential for the reaction (entries 2–4). Although increasing the partial pressure of O_2 made the reaction more efficient (entry 5), reaction conditions under air were used for further studies because they are efficient enough. To understand the effectiveness of RFTA, other organic dyes including 3-methyllumiflavin (MFl), 1,3-

Table 1 Catalytic thioacetalization of **1a** with **2a**[a]



entry	cat.	hν	atmos.	time (h)	yield (%)[b]
1	RFTA	on	air	6	99
2	–	on	air	6	0
3	RFTA	off	air	6	0
4	RFTA	on	N_2	6	0
5	RFTA	on	O_2	3	100
6	MFl	on	air	1 [6]	30 [88]
7	DMA	on	air	1	15
8[c]	Eosin Y	on	air	1	0
9	MB	on	air	1	0
10[d]	$Ir(ppy)_3$	on	air	1	0

[a]Reactions were performed with 0.735 mmol of **1a** and 1.47 mmol of **2a** in 3.5 mL of acetonitrile under defined conditions. [b]Determined by ^1H NMR spectroscopy using 1,4-dioxane as an internal standard. [c]Performed in acetonitrile/DMF (6/1) with green LED light (525 nm). [d]Performed in DMF.

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dimethylalloxazine (DMA), Eosin Y, and methylene blue (MB) as well as a transition metal complex, Ir(ppy)$_3$, which could be excited by absorbing visible lights, were also tested as a photocatalyst for the present reaction. Interestingly, the flavin type molecules RFTA, MFl, and DMA were specifically effective, while the non-flavin type dyes Eosin Y, MB, and Ir(ppy)$_3$ showed no catalytic activity (entries 6–10). Particularly effective was RFTA, probably because of its higher reduction potential compared to that of MFl in their ground state (RFTA: $E_{1/2}^{red}$ = –725 mV, MFl: $E_{1/2}^{red}$ = –809 mV, vs Ag/AgCl)[3e] and its higher absorption efficiency compared to that of DMA at 465 nm (RFTA: λ_{max}^{abs} ≈ 450 nm, DMA: λ_{max}^{abs} ≈ 400 nm).[1f] Further optimization of the reaction parameters showed that acetonitrile as a solvent, 465 nm as a LED wavelength, and 0.3 W as an electric power of the blue LED could be the best choice (see supporting information).

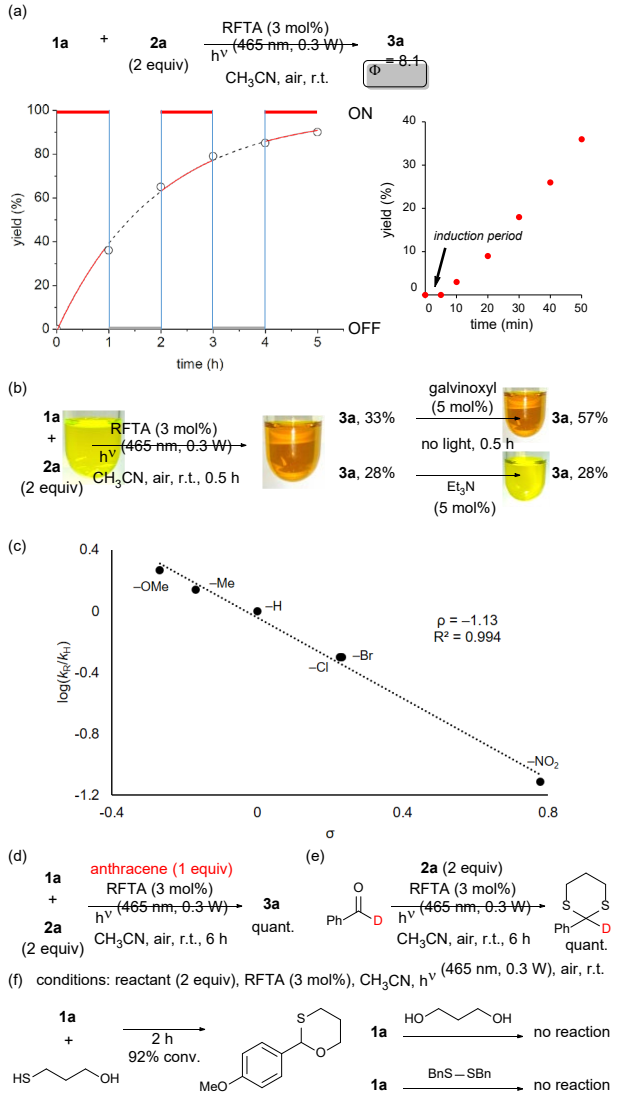


Fig 1. Control experiments.

To gain insights into the mechanism of this unexpected catalysis, additional experiments were carried out using **1a** as a substrate, **2a** as a reactant, and RFTA as a catalyst unless otherwise noted (Fig. 1). First of all, an intermittent irradiation experiment was performed, in which irradiation (ON) /non-irradiation (OFF) of the blue light was switched every one hour, started from the ON state. There was no difference in overall reaction profiles between the reaction irradiated continuously and that irradiated intermittently, showing that the irradiation could be required only for initiating the reaction (Fig. 1a). The quantum yield of reaction (Φ) was determined to be 8.1 by chemical actinometry with potassium ferrioxalate,[4] which also implied that chain propagation pathways could be involved (Fig. 1a). However, the reaction was not prevented at all by the addition of galvinoxyl free radical after 0.5 h reaction, which led us to exclude radical chain mechanisms (Fig. 1b, upper). On the other hand, the addition of a catalytic amount of triethylamine completely suppressed the reaction with a change of color of the reaction mixture from yellowish brown to fluorescence yellow that is characteristic of RFTA (Fig. 1b, lower), which suggested that the present reaction could be catalyzed by less-fluorescence RFTA-related acidic species, recoverable with a base, generated *in situ* under the visible light irradiation. Indeed, an obvious induction period within 10 minutes was observed by closely pursuing the reaction under optimized conditions (Fig. 1a). In addition, a Hammett plot was constructed with different *p*-substituted benzaldehydes to determine the ρ value of –1.13 (Fig. 1c), indicating substituent effects for stabilization of ionic intermediates. The involvement of singlet oxygen was ruled out since the reaction was not affected by the addition of anthracene (Fig. 1d). A deuterium labeling experiment revealed that acyl radical formation was not involved (Fig. 1e). A similar cyclization took place using 3-mercapto-1-propanol instead of **2a** as a reactant to afford the corresponding *S*,*O*-acetal, while 1,3-propanediol and dibenzyl disulfide were totally unreactive (Fig. 1f), showing that catalytically active species could be formed only in the presence of mercapto functionality (RSH). Quenching experiments by fluorescence spectroscopy suggested that there was a high possibility of photochemical electron transfer (PET) between the excited state of RFTA and RSH to give the one-electron reduced RFTA, RFTA$^{-\bullet}$, and a one-electron oxidized RSH, RSH$^{+\bullet}$ (see supporting information). Although the aerobic atmosphere was essential for the reaction (Table 1, entry 4), no consumption of O_2 was apparently observed by a gas burette and no formation of **2a**-derived stable oxoacids such as sulfinic acid and sulfonic acid was observed by ^{1}H NMR analysis of the reaction mixture. To ensure that such sulfur oxoacids should not be involved, we exposed thiols including 1-dodecanethiol and benzyl mercaptan under the reaction conditions in the absence of any aldehydes, which afforded only the corresponding disulfides in very low yields (see supporting information).[5] Although RFTA$^{-\bullet}$ has a reducing ability that can readily react with even O_2 in air,[2] it must be much less reducing and more stable under acidic conditions due to undergoing protonation.[3f] It should also be noted that only a trace amount of hydrogen peroxide was recognized from the mixture of **2a** and RFTA after 30 min irradiation (see supporting information). As a consequence, we are currently proposing that, after the PET process, a proton transfer (PT) takes place from RSH$^{+\bullet}$ to RFTA$^{-\bullet}$ to give RS$^\bullet$ and RFTAH$^\bullet$, and the RFTAH$^\bullet$

(p*K*a~8)[6] can cause the present Brønsted acid catalysis (Fig 2). On one hand, the RS• may be stabilized through its O_2 adduct RSOO• in equilibrium[7] or stored as the corresponding disulfide, although it is not clear at the moment.

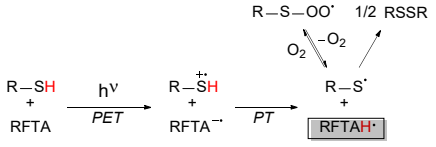
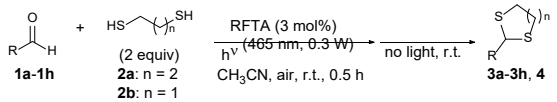
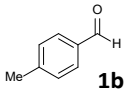
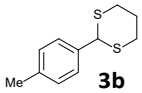
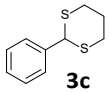
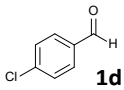
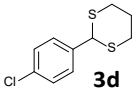
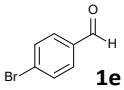
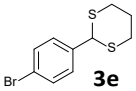
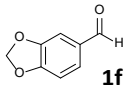
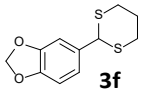
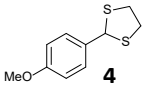


Fig 2. Plausible mechanism for the *in situ* generation of Brønsted acidic species.

Table 2 Scope of catalytic thioacetalization[a]



entry	substrate	time (h)	product	yield (%)[b]
1	**1a**	10	**3a**	85
2	 **1b**	8	 **3b**	82
3	 **1c**	9	 **3c**	84
4	 **1d**	15	 **3d**	86
5	 **1e**	15	 **3e**	73
6	 **1f**	12	 **3f**	74
7	 **1g**	12	 **3g**	59
8	 **1h**	6	 **3h**	100[c]
9	**1a**	10	 **4**	85

[a]Reactions were performed with 0.735 mmol of **1** and 1.47 mmol of **2** in 3.5 mL of acetonitrile in the presence of 3 mol% of RFTA under air at room temperature, which was irradiated by blue LED light only for the initial 30 minutes. [b]Isolated yields. [c]Conversion of **1** determined by ^{1}H NMR spectroscopy.

We next evaluated the scope of the thioacetalization and reacted a range of different aldehydes **1a**–**1h** and dithiols **2a**–**2b** in the presence of 3 mol% of RFTA, which were irradiated for initial 30 minutes prior to leaving them under non-irradiation conditions for 9–15 hours (Table 2). Various aromatic aldehydes **1a**–**1f** with both electron-donating and electron-withdrawing substituents (entries 1–6) as well as aliphatic aldehydes **1g**–**1h** (entries 7 and 8) reacted smoothly with **2a** to give the corresponding 1,3-dithianes **3a**–**3h** in good yields. It should be noted that piperonal **1f** bearing an acetal functional group that are typically acid-labile was tolerated to afford **3f** (entry 6). The use of **2b** instead of **2a** allowed for the formation of 1,3-dithiolane such as **4** (entry 9).

Finally, we preliminarily explored whether such photo-induced Brønsted acid catalysts could be prepared in advance and used for other reactions. To a solution of 1-dodecanethiol (4.7 mM, 3 mol%) and RFTA (4.7 mM, 3 mol%) in acetonitrile pre-irradiated by blue LED light (465 nm, 0.3 W) for 1 h under O_2 (1 atm) (Fig. 3a) was added *trans*-benzylideneaniline (1 equiv) and the trimethylsilyl (TMS) enol ether derived from acetophenone (**5**, 3 equiv), which was stirred for 1 h under dark and nitrogen atmosphere and evaluated by ^{1}H NMR spectroscopy. The desired Mannich-type reaction[8] proceeded smoothly to give the corresponding β-amino ketone **6a** in 99% yield (Fig. 3b), while the same reaction performed without the pre-irradiation afforded **6a** only in 19% yield. These results indicated that catalytically active species was prepared by irradiating the initial RFTA–thiol–O_2 mixture as expected. The feasibility of this catalytic system was also demonstrated with other imines and silyl enol ethers as substrates under the same procedure and conditions, providing various β-amino ketones **6b**–**6e** in high NMR yields (Fig. 3b). Moreover, the prepared catalyst was found to be effective for promoting three-component Mannich-type reactions using different *p*-substituted benzaldehydes, aniline, and **5**, which efficiently afforded the adducts **6a** and **6f**–**6i** without aldol by-products (Fig. 3c).

In conclusion, we have found that visible light irradiation to a RFTA-thiol-O_2 mixture can generate Brønsted acidic species that can be used as efficient catalysts for thioacetalization of aldehydes as well as Mannich-type reactions under non-irradiation and mild conditions. To our knowledge, this is the first example of Brønsted acid catalysis with flavin molecules, which have so far been typically used for redox catalysis and energy transfer catalysis, and distinct from previous photochemical strategies.[9,10] Since RFTA and its analogues are inexpensive, metal-free, and versatile as catalysts,[1] we believe that the present method should open wide application in organic synthesis—as a catalyst that plays multiple roles in one-pot synthesis, for example.

Conflicts of interest

There are no conflicts to declare.

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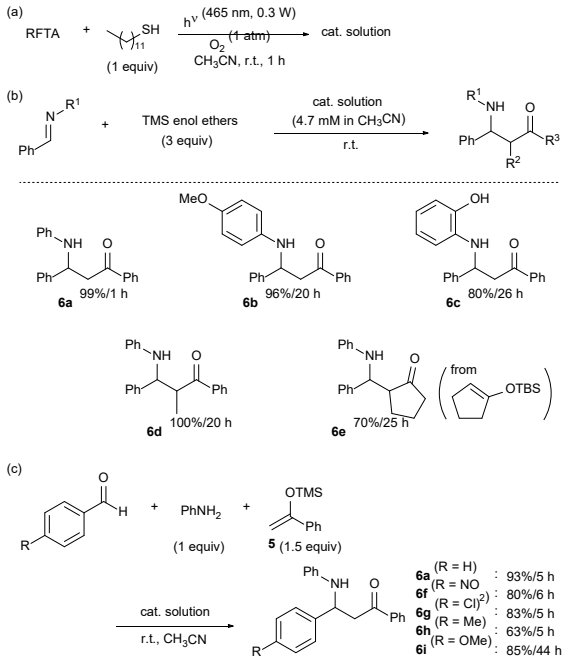

Fig. 3 Catalytic Mannich-type reactions.

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