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Comparison of Riboflavin-Derived Flavinium Salts Applied to Catalytic H_2O_2 Oxidations

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A series of flavinium salts, 5-ethylisoalloxazinium, 5-ethylalloxazinium, and 1,10-ethylene-bridged alloxazinium triflates, were prepared from commercially available riboflavin. This study presents a comparison between their optical and redox properties, and their catalytic activity in H_2O_2 oxidations of sulfide, tertiary amine, and cyclobutanone. Reflecting the difference between the π-conjugated ring structures, the flavinium salts displayed very different redox properties, with reduction potentials in the order of: 5-ethylisoalloxazinium > 5-ethylalloxazinium > 1,10-ethylene-bridged alloxazinium. A comparison of their catalytic activity revealed that 5-ethylisoalloxazinium triflate specifically oxidises sulfide and cyclobutanone, and 5-ethylalloxazinium triflate smoothly oxidises tertiary amine. 1,10-Bridged alloxazinium triflate, which can be readily obtained from riboflavin in large quantities, showed moderate catalytic activity for the H_2O_2 oxidation of sulfide and cyclobutanone.

Introduction

Flavinium salts have previously been developed by mimicking the functions of flavin-dependent monooxygenases.[1] Recently, flavinium salts have drawn much attention for their unique biomimetic organocatalytic properties, which promote various metal-free oxidative transformations.[2] The flavinium catalysts generally require O_2 and H_2O_2 as easily available, inexpensive, and minimally polluting terminal oxidants to carry out chemoselective oxidative reactions under mild conditions, such as the oxidation of sulfides,[3,4] amines,[5,6] ketones,[7] aldehydes,[8,9] boronic acids,[10] thiols,[4a] metal complex,[11] and other functional groups[12,13], as well as asymmetric oxidations.[14] In addition, multiple catalytic systems based on flavinium catalysis have been explored gradually by combining metals,[15] biocatalysts,[16] and organocatalysts.[17] Therefore, the flavinium-catalysed system has emerged as a promising tool for environmentally friendly transformations, and may fulfil the increasing demand for green sustainable chemistry.

Flavinium catalysts are commonly classified into three types: 5-alkylisoalloxaziniums (**1**), 5-alkylalloxaziniums (**2**), and 1,10-bridged alloxaziniums (**3**), based on the difference between their conjugated systems (Fig. 1).[2e,f] Because flavinium cations (**1**–**3**) can be prepared by *N*-alkylation of neutral flavins (**4** and **5**), a series of artificial flavins has been synthesized through a flavin ring formation reaction mainly by using a condensation reaction between 1,2-diaminobenzenes (**6** and **7**) and alloxanes (**8**) (Fig. 1).[3c,4b,8a,14b,f,h,18,19]

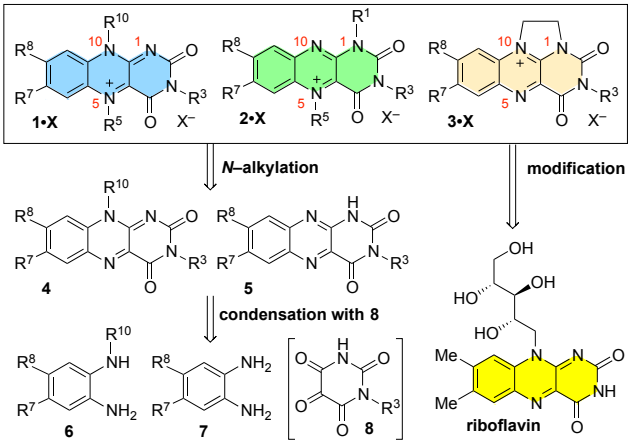

Fig. 1 Three types of flavinium salts; 5-alkylisoalloxaziniums (**1**·**X**), 5-alkylalloxaziniums (**2**·**X**), and 1,10-bridged alloxaziniums (**3**·**X**).

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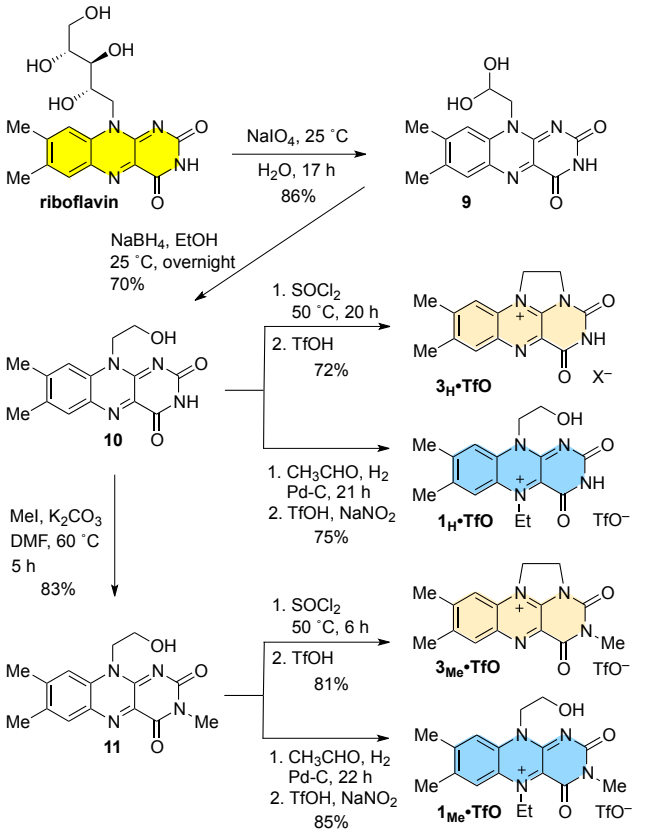
Naturally occurring riboflavin (vitamin B_2), one of the most important bioactive compounds, is synthesised by microbial fermentation, and thus is obtained commercially with low-cost. Because of its abundance and because the use of riboflavin can avoid the multiple synthetic manipulations for the synthesis of the flavin ring skeleton, some chemists have attempted to synthesise semi-synthetic flavinium catalysts by the modification of riboflavin. However, very few examples of riboflavin-derived 7,8-dimethylflavinium catalysts have been reported.[3k,m,7b,13b,d,e] In particular, 1,10-bridged 7,8-dimethylalloxazinium catalysts have not previously been developed except for in our recent reports,[17a] although analogous 1,10-bridged alloxaziniums have recently been applied to various reactions.[3g,h,n,o,6,8b,13c,14h,16,17a,18a,20]

In this study, three types of 7,8-dimethylflavinium catalysts were synthesised from naturally occurring riboflavin: 5-ethyl-7,8-dimethylisoalloxazinium (**1·TfO**), 5-ethylalloxazinium (**2·TfO**), and 1,10-ethylenealloxazinium triflates (**3·TfO**). Their optical and redox properties were investigated, and their catalytic activity was analysed in several oxidations using H_2O_2 as a terminal oxidant to compare the three types of flavinium salts. The results are expected to provide insight into the possibility and application of riboflavin-derived flavinium catalysts. Despite the obvious synthetic advantage of the 7,8-dimethylflavinium skeleton, little attention has been given to the systematic study on the property differences and catalytic activity between **3** and **1**/**2**, although the difference between **1** and **2** has been well examined previously.[2e,3j]

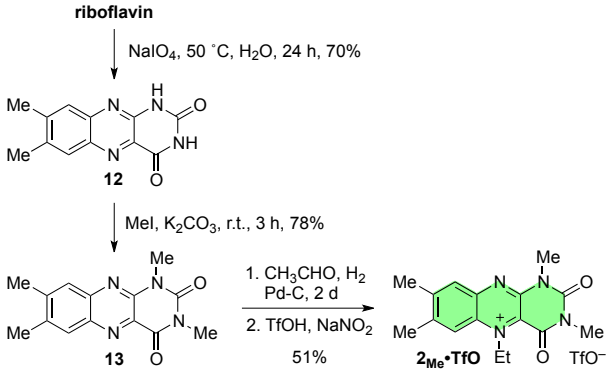
Results and discussion

Synthesis of riboflavin-derived flavinium salts

As shown in Schemes 1 and 2, a series of flavinium triflates (**1**–**3·TfO**s) was synthesized from riboflavin. Through oxidation with $NaIO_4$ at 25 °C followed by the reduction of **9** with $NaBH_4$, 10-(2-hydroxyethyl)-7,8-dimethylisoalloxazine (**10**) can be readily in large quantities (>10 g) obtained from riboflavin.[4d,21] Due to the ease of synthesis and the possibility to obtain **10** in large quantities, it is employed as a key synthetic intermediate of flavinium salts (Scheme 1). Intramolecular cyclisation of **10** with $SOCl_2$ and subsequent treatment with TfOH afforded 1,10-ethylene-bridged alloxazinium triflate (**3_H·TfO**)[17a] in 72% yield. Because of facile intramolecular cyclisation, **3_H·TfO** was readily synthesised and obtained on the gram scale. Reductive N^5-ethylation of **10** with CH_3CHO, followed by oxidation with $NaNO_2$ and TfOH, gave 5-ethylisoalloxazinium triflate (**1_H·TfO**) in 75 yield. To investigate the substitution effect of the N^3-position, 3-methylated 1,10-ethylene-bridged alloxazinium triflate (**3_{Me}·TfO**) and 5-ethylisoalloxazinium triflate (**1_{Me}·TfO**)[4d] were synthesised in 81 and 85% yields, respectively, from 10-(2-hydroxyethyl)-3,7,8-trimethylisoalloxazine (**10**), prepared by the methylation of **9** with MeI. Interestingly, when the oxidation of riboflavin with $NaIO_4$ was carried out at 50 °C, alloxazine (**12**) was obtained in 70% yield (Scheme 2). In contrast, the same oxidation gave **9** in 86% yield at 25 °C (Scheme 1). After N^1- and N^3-dimethylation of **12**, reductive N^5-ethylation of **13** and subsequent oxidation with $NaNO_2$ and TfOH successfully afforded 5-ethylalloxazinium triflate (**2_{Me}·TfO**) in 51% yield. It is noteworthy that 1,10-ethylene-bridged alloxazinium triflates (particularly **3_H·TfO)** could be synthesised through the most facile synthetic pathway through which upscaling can be readily carried out.



Scheme 1 Synthesis of 1,10-ethylene-bridged alloxazinium triflates (**3_H·TfO** and **3_{Me}·TfO**) and 5-ethylisoalloxazinium triflates (**1_H·TfO** and **1_{Me}·TfO**) from riboflavin.



Scheme 2 Synthesis of 5-ethylalloxazinium triflate (**2_{Me}·TfO**) from riboflavin.

Optical properties of flavinium salts

To explore the optical properties of the flavinium salts, their absorption and fluorescence spectra were measured from a CH_3CN-salt solution (Fig. 2 and Table 1). The isoalloxazinium triflates (**1_H·TfO** and **1_{Me}·TfO**) gave rise to the typical absorption signals centred at around 420 and 560 nm, assigned to the π–π^* transitions of the π-conjugated isoalloxazinium ring (Fig. 2A).[22] In comparison with **1_H·TfO** and **1_{Me}·TfO**, **2_{Me}·TfO** presented blue-shifted absorption signals at 395 and 460 nm. The π-conjugated system of the isoalloxazinium ring includes its imide moiety, whereas the π-conjugation of the alloxazinium ring does not extend to the imide moiety. Therefore, the relatively narrow conjugated system of **2_{Me}·TfO** presumably results in the blue-shift. The absorption spectra of **3_H·TfO** and **3_{Me}·TfO** were not equivalent to that of **2_{Me}·TfO**, although they possess the similar alloxazinium ring structure, and the absorption signals were further blue-shifted to around 260 and 380 nm maybe due to the difference of the cation delocalisation within the conjugated ring system. As a result, **1_H·TfO** and **1_{Me}·TfO** were purple, while **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO** appeared yellow. The CH_3CN solution of **1_H·TfO** and **1_{Me}·TfO** exhibited very weak fluorescence (λ_{Fmax} = 648 and 645 nm, respectively) upon excitation at 560 nm (Fig. 2B). In contrast to the isoalloxazinium salts, the alloxazinium salts provided strong fluorescence signals upon excitation at 380 nm; **2_{Me}·TfO** showed blue-shifted, yellow fluorescence (λ_{Fmax} = 545 nm) and **3_H·TfO** and **3_{Me}·TfO** displayed strong yellowish-green fluorescence (λ_{Fmax} = 486 and 485 nm, respectively) (Fig. 2C).

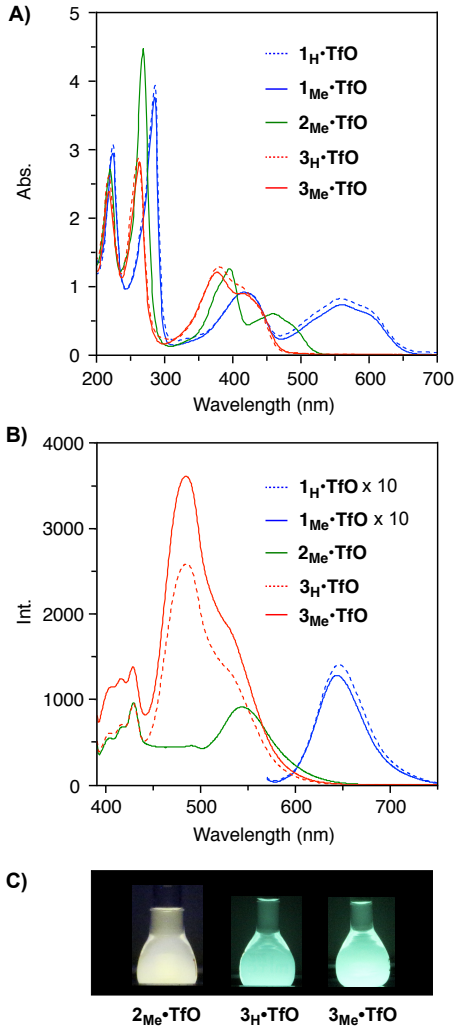


Fig. 2 (A) Absorption spectra of 0.1 mM **1_H·TfO**, **1_{Me}·TfO**, **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO** in CH_3CN measured at 25 °C. (B) Fluorescence spectra of 0.20 μM **1_H·TfO**, **1_{Me}·TfO**, **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO** in CH_3CN measured at 25 °C (**1_H·TfO** and **1_{Me}·TfO**: λ_{Ex} = 560 nm; **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO**: λ_{Ex} = 380 nm). (C) Photographs of 0.1 mM **2_{Me}·TfO**, **2_H·TfO**, and **3·TfO** in CH_3CN under UV light (λ_{Ex} = 365 nm)

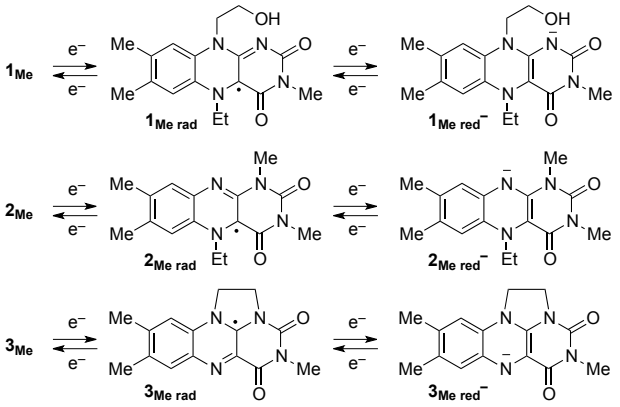
Table 1. Chemical shifts and absorption peaks of flavinium cations[a]

Entry	Flavinium	Absorption	Fluorescence
		λ_{max} (log ε)[a], nm	$\lambda_{F,max}$ [a,b], nm
1	**1_H·TfO**	559 (3.91), 417 (3.96), 286 (4.59), 224 (4.49)	648
2	**1_{Me}·TfO**	560 (3.87), 416 (3.96), 285 (4.58), 224 (4.47)	645
3	**2_{Me}·TfO**	460 (3.78), 395 (4.10), 268 (4.65), 220 (4.44)	545
4	**3_H·TfO**	380 (4.11), 261 (4.46), 218 (4.42)	486
5	**3_{Me}·TfO**	376 (4.09), 263 (4.46), 218 (4.38)	485

[a] In CH_3CN. [b] Excitation wavelength (λ_{Ex}) was 560 nm for **1_H·TfO** and **1_{Me}·TfO**, and 380 nm for **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO**.

Redox property of flavinium salts

To investigate the redox activity, the reduction potentials of



Scheme 3 Redox reactions of flavinium cations.

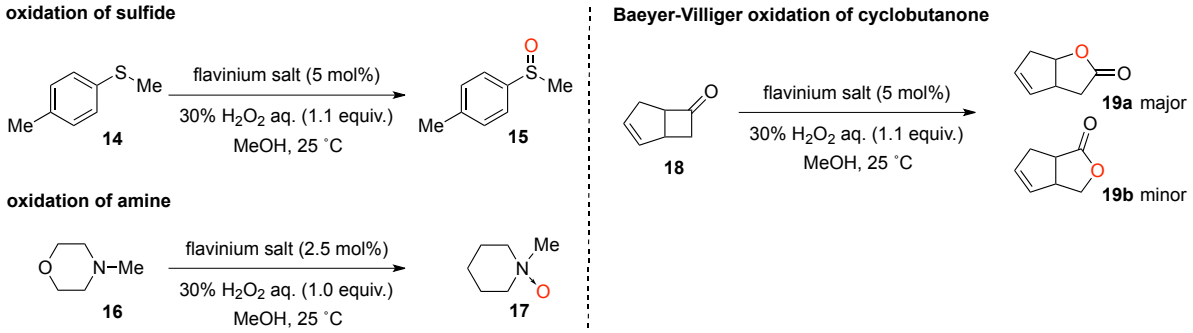
the synthesized flavinium salts were determined by cyclic voltammetry (CV) in a solution of CH_3CN containing Bu_4NClO_4 (0.1 M); the results are summarised in Table 2. The obtained voltammograms exhibit two reversible reduction peaks, which correspond to the two-electron reduction of flavinium salts (Scheme 3).[4b,22] Among the three N^3-substituted flavinium salts, **1_{Me}·TfO** showed the most positive potentials, with reduction potentials (E_1 and E_2) of 0.263 and –0.365 V *vs* SCE, followed in order by **2_{Me}·TfO** and **3_{Me}·TfO** (Table 2, entries 2, 3, and 5, respectively). The first and second reductions of **3_{Me}·TfO** (–0.255 and –1.25 V *vs* SCE) were largely unfavourable in comparison with those of **1_{Me}·TfO**. Therefore, the LUMO orbital of **1_{Me}** seems to be stabilized rather than those of **2_{Me}** and **3_{Me}**, and **1_{Me}·TfO** is more electrophilic than **2_{Me}·TfO** and **3_{Me}·TfO**. The N^3-unsubstituted flavinium salts, **1_H·TfO** and **3_H·TfO,** showed comparatively positive reduction potentials to the corresponding N^3-substituted **1_{Me}·TfO** and **3_{Me}·TfO** because of the lack of an electronegative methyl substituent (entries 1 and 4). Although the two reversible reduction peaks were observed for N^3-substituted flavinium salts,[4b,22] the second reduction peaks of the N^3-unsubstituted **1_H·TfO** and **3_H·TfO** (E_2 = –0.256 and –0.725 V, respectively) were likely irreversible (Fig. S1). The irreversible peaks would result from the complex formation of the flavin radical or reduced forms.[23] These results indicated that the redox activity of the flavinium salts can be significantly regulated by the initial modification of riboflavin.

Table 2. Reduction potentials of flavinium triflates[a]

Entry	Flavinium	E^{p}_{c} (V *vs* SCE) [b]	E^{p}_{a} (V *vs* SCE) [b]	E_1 (V *vs* SCE) [b]	E_2 (V *vs* SCE) [b]
1	**1_H·TfO**	0.246, -0.372	0.315, -0.140	0.281	-0.256
2	**1_{Me}·TfO**	0.231, -0.397	0.295, -0.332	0.263	-0.365
3	**2_{Me}·TfO**	-0.058, -0.818	0.007, -0.755	-0.026	-0.787
4	**3_H·TfO**	-0.236, -0.748	-0.170, -0.702	-0.203	-0.725
5	**3_{Me}·TfO**	-0.291, -1.28	-0.219, -1.23	-0.255	-1.25

[a] The redox potentials of the flavins were measured by cyclic voltammetry at a scan rate of 100 mV/s in tetrabutylammonium perchlorate (0.1 M) containing CH_3CN. [b] The electrochemical potentials (E_1 and E_2) of each flavinium were determined by the relationship $E = (E^{c}_{p}+E^{a}_{p})/2$ relative to SCE.

Table 3. Catalytic activities of flavinium salts for H_2O_2 oxidation of various substrates[a]



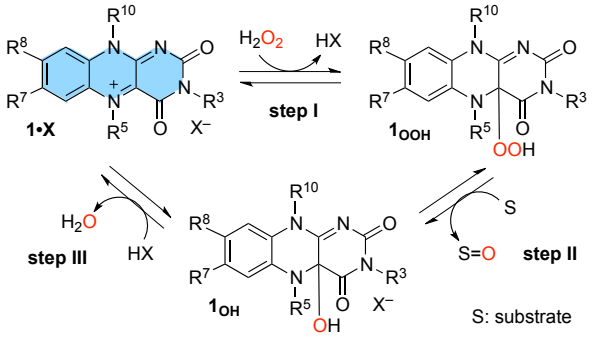
		Sulfide [a]		Tertiary amine [b]		Cyclobutanone [c]	
Entry	Catalyst	v_{obs} (μmol/h)	v_{obs}/v_0	v_{obs} (μmol/h)	v_{obs}/v_0	v_{obs} (μmol/h)	v_{obs}/v_0
1	None	2.3 [d] (= v_0)	–	6.2 (= v_0)	–	0.80 [a] (= v_0)	–
2	**1_H·TfO**	>1.9 x 10^2 [d]	>83				
3	**1_{Me}·TfO**	>2.2 x 10^2 [d]	>98	56 [d]	9.1	>1.2 x 10^2	>1.5 x 10^2
4	**2_{Me}·TfO**	4.7 [d]	2.1	5.8 x 10^2	94	5.3	8.6
5	**3_H·TfO**	13 [d]	5.6	10	1.7	13	16
6	**3_{Me}·TfO**	4.8 [d]	2.2	(>93) [e]	(>15) [e]		

[a] Conditions: **14** (0.1 M), flavinium salt (5 mol%), diethylene glycol diethyl ether (0.5 equiv, internal standard), 30% H_2O_2 aq. (1.1 equiv), and MeOH at 25 °C. [b] Conditions: **16** (0.5 M), flavinium salt (2.5 mol%), mesitylene (0.5 equiv, internal standard), 30% H_2O_2 aq. (1.0 equiv), and CD_3OD at 25 °C. [c] Conditions: **18** (0.1 M), flavinium salt (5 mol%), 1,1,2,2-tetrachloroethane (0.5 equiv, internal standard), 30% H_2O_2 aq. (1.1 equiv), and MeOH at 25 °C. [d] Average of two runs. [e] Decomposition of the catalyst presumably occurred.

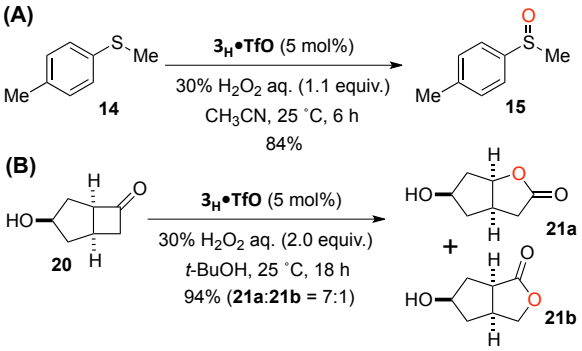
Catalytic activity

To gain insight into the influence of structural difference of the riboflavin-derived flavinium salts on their catalytic activity, the flavinium triflates were compared on the basis of flavinium-catalysed oxidations of sulfide, amine, and cyclobutanone in the presence of H_2O_2 (Table 3). The initial rates of these reactions were determined both with and without the catalyst (v_{obs} and v_0, respectively). The enhancement in the reaction rate in the presence of a flavinium catalyst, relative to that of the non-catalysed process (v_{obs}/v_0), was calculated for each of the flavinium triflates. In the oxidation of sulfide (**14**), the isoalloxazinium salts (**1_H·TfO** and **1_{Me}·TfO**) showed significantly higher activities than that of the alloxazinium salts (**2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO**). The reaction mechanism of flavinium-catalysed H_2O_2 oxidation is shown in Scheme 4.[2,3a] The flavinium salt (**Fl^+·X**) undergoes a reaction with H_2O_2 to form HX and oxidatively active hydroperoxyflavin (**Fl_{OOH}**) (step I), which is responsible for the oxygenation of various substrates. Through the transfer of oxygen to the substrates, **Fl_{OOH}** is converted to a hydroxy adduct (**Fl_{OH}**) (step II), and then H_2O elimination of **Fl_{OH}** with HX affords **Fl^+·X** (step III), which is the rate-limiting step of the 5-alkylated isoalloxazinium catalysts (**1_H·TfO** and **1_{Me}·TfO**).[3a] As revealed by the electrochemical measurements, **1_H·TfO** and **1_{Me}·TfO** were more electrophilic than **2_{Me}·TfO**, **3_H·TfO** and **3_{Me}·TfO**. The relatively higher activity of **1_H·TfO** and **1_{Me}·TfO** can be explained by their electrophilic character which enhances the smooth generation of the oxidatively active **Fl_{OOH}** from **Fl^+** in the presence of H_2O_2. As Cibulka and coworkers reported,[2e,3j] the alloxazinium salts are less electrophilic than the isoalloxazinium salts, and much more difficult to react with H_2O_2. Therefore, H_2O_2 addition seems to be the rate-limiting step of **2_{Me}·TfO**, **3_H·TfO**, and **3_{Me}·TfO** (step I). This is supported by the revelation of a slightly lower activity of the more electronegative *N*^{3}-methylated **3_{Me}·TfO** than that of the corresponding *N*^{3}-unsubstituted **3_H·TfO**.

In the *N*-oxidation of tertiary amine (**16**), the most efficient catalyst was **2_{Me}·TfO**, followed in order by **3_{Me}·TfO**, **1_{Me}·TfO**, and **3_H·TfO**, because the basic condition can accelerate the rate-limiting H_2O_2 addition step of **2_{Me}** (step I).[2e,3j] *N*-Oxidation with **3_{Me}·TfO** rapidly decelerated before reaching the 10% yield, presumably owing to the decomposition of the catalyst under basic conditions.[3h] The Baeyer-Villiger oxidation of cyclobutanone (**18**) was also conducted using **1_{Me}·TfO**, **2_{Me}·TfO**, and **3_H·TfO**. Because the reaction conditions were neutral like that of sulfoxidation, the order of the most efficient catalyst (**1_{Me}·TfO** > **3_H·TfO** > **2_{Me}·TfO**) was identical to that of the sulfoxidation of **14**. In conclusion, **1·TfO** displayed outstanding activity for oxidation under neutral conditions, while **2·TfO** favoured oxidation under basic conditions. Contrary to **1·TfO**



Scheme 4. Catalytic cycle of the flavinium-catalysed H_2O_2 oxidation, illustrated using simple **1·X**.



Scheme 5 (A) Sulfoxidation of **14** and (B) Bayer-Villiger oxidation of **20,** catalysed by **3_H·TfO** in the presence of H_2O_2.

and **2·TfO**, **3·TfO** showed moderate catalytic activity for H_2O_2 oxidations tested in this study. However, **3_H·TfO** is more readily synthesised on a large scale from riboflavin. Therefore, we confirmed the availability of **3_H·TfO** in the catalytic sulfoxidation and Bayer-Villiger reactions with H_2O_2 (Scheme 5). Although **3_H·TfO** showed a lower catalytic activity than **1·TfO**, the chemoselective sulfoxidation of **14** was efficiently performed by 5 mol% of **3_H·TfO**, yielding the corresponding sulfoxide without overoxidation to sulfone (Scheme 5A). The Baeyer-Villiger oxidation of **20** was also promoted to give the corresponding lactones (**21a** and **21b**) in good yield (Scheme 5B).

Conclusions

We synthesized 5-ethylisoalloxazinium (**1·TfO**), 5-ethylalloxazinium (**2·TfO**), and 1,10-ethylene alloxazinium triflates (**3·TfO**) from commercially available riboflavin in three or four steps. Their redox properties and catalytic activity were largely different from each other depending on the π-conjugated ring structures, although these flavinium salts possess the same 7,8-dimethyl substituents originating from riboflavin. These results indicated that simple modification of riboflavin can provide unique flavin compounds with diverse functionalities, which are useful in a wide variety of applications. This information would be useful for designing further efficient

redox organocatalysts with high accessibility, as well as for developing novel riboflavin-containing functional materials.[24]

Experimental

Large scale synthesis of 9. Sodium periodate (159 g, 0.74 mol) was added to a suspension of riboflavin (100 g, 0.27 mol) in water (4.0 L) in five portions, and the mixture was stirred at ca. 25 ˚C for 17 h. The yellow precipitate was collected by filtration, washed with water (700 mL), MeOH (700 mL), and diethyl ether (400 mL), and dried under reduced pressure to give **9** (69.0 g, 86%) as a yellow powder. IR (KBr): ν_{max}/cm^{-1} 3180br (OH), 1723s (NCO), 1656s (NCO), 1578s (NCO), 1546s (NCO). δH (500 MHz; TFA-*d*; r.t.) 8.49 (s,1H, ArH), 8.04 (s, 1H, ArH), 7.16 (dd, 1H, J =3.0, 7.0 Hz, CH), 5.68 (dd, *J* =7.0, 15 Hz, 1H, C*H*H), 5.44 (dd, *J* = 2.5, 15 Hz, 1H, C*H*H), 2.90 (s, 3H, CH_3), 2.79 (s, 3H, CH_3). The spectral properties of **9** were in good agreement with the reported data.[4d]

Large scale synthesis of 10. To a suspension of **9** (25.0 g, 83 mmol) in Solmix AP-7 (8.7 L, 85:5:10 EtOH/2-propanol/1-propanol), $NaBH_4$ (5.15 g, 0.14 mol) was added in five portions, and the mixture was stirred at 25 °C overnight. After adding water (1.7 L), the resulting precipitate was collected by filtration, washed with methanol (1.7 L) and diethyl ether (0.8 L), and then suspended in MeOH (280 mL). After evaporation of the solvents, the residue was washed with water (0.3 L) and dried in vacuo to afford **10** (16.7 g, 70%) as a yellow powder. IR (KBr): ν_{max}/cm^{-1} 3225br (OH), 1712s (NCO), 1672s (NCO), 1578s (NCO), 1547s (NCO). δH (400 MHz; DMSO-d_6; r.t.) 11.33 (s, 1H, -CON*H*CO-), 7.89 (s, 2H, ArH), 4.95 (t, *J*=5.8 Hz, 1H, OH), 4.69 (t, *J*=5.8 Hz, 2H, CH_2), 3.80 (m, 2H, CH_2), 2.53-2.45 (3H, CH_3, overlapped with DMSO-d_5), 2.40 (s, 3H, CH_3). The spectral properties of **10** were in good agreement with the reported data.[4d]

Large scale synthesis of $\mathbf{3_H}$•TfO. A mixture of **10** (7.08 g, 25 mmol) and $SOCl_2$ (43.0 mL, 0.59 mol) was stirred at 50 ˚C for 20 h under molecular nitrogen. The resulting yellow precipitate was collected by filtration, washed with CH_2Cl_2 (350 mL), and purified by reprecipitation from formic acid (42 mL) by diethyl ether (800 mL). After a collection by filtration, the crude product was washed with 6% aqueous HCl (14 mL x 2) and dissolved into 1.5% aqueous HCl (640 mL). After solvent evaporation under reduced pressure, the resulting residue was redissolved into 1.5% aqueous HCl (640 mL) and lyophilized to obtain the chloride salt of $\mathbf{3_H}$ ($\mathbf{3_H}$•**Cl**, 5.80 g) as a yellow powder. To exchange the counter anion, TfOH (479 µL, 5.4 mmol) was added to a solution of $\mathbf{3_H}$•**Cl** (1.50 g, 4.9 mmol) in MeOH (500 mL), and the resulting mixture was dried by evaporation. The residue was then washed with diethyl ether (250 mL) and dried in vacuo to obtain $\mathbf{3_H}$•**TfO** (1.92 g, 72%) as a yellow powder. IR (KBr): ν_{max}/cm^{-1} 1744br (NCO), 1629s (NCO), 1602s (NCO). δH (500 MHz; DMSO-d_6; r.t.) 12.75 (s, 1H, NH), 8.38 (s, 1H, ArH), 8.12 (s, 1H, ArH), 5.31 (t, *J* = 9.5 Hz, 2H, CH_2), 4.64 (t, *J* = 9.3 Hz, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). The spectral properties of $\mathbf{3_H}$•**TfO** were in good agreement with the reported data.[17a]

Synthesis of $\mathbf{1_H}$•TfO. Acetaldehyde (3.00 mL, 54 mmol) was added to a mixture of **10** (552 mg, 1.9 mmol), 10% Pd-C (41.2 mg, 0.039 mmol), conc. HCl (3.0 mL), EtOH (32 mL), and water (32 mL), and the mixture was stirred at room temperature for 21 h under molecular hydrogen. The reaction mixture was filtered through a pad of Celite under nitrogen, and the filtrate solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous TfOH (4.00 mL, 8.0 mmol), $NaNO_2$ (612 mg, 8.9 mmol), and NaOTf (3.10 g, 19 mmol), the mixture was stirred at room temperature for 30 min. The resulting purple precipitate was collected by filtration, washed with cold water (40 mL) and diethyl ether (40 mL x 2) to give $\mathbf{1_H}$•**TfO** (672 mg, 75%) as a purple powder. mp 195.9-196.7 °C. Elemental analysis: Found: C, 43.7; H, 4.2; N, 11.9. Calc. for $C_{17}H_{19}F_3N_4O_6S$: C, 44.0; H, 4.1; N, 12.1%. IR (KBr): ν_{max}/cm^{-1} 1702s (NCO), 1675s (NCO), 1597s (NCO), 1545vs (NCO). δH (400 MHz; CD_3CN; r.t.) 9.96 (br s, 1H, NH), 8.17 (s, 1H, ArH), 8.12 (s, 1H, ArH), 6.08 (br s, 2H, CH_2), 4.94 (t, *J* = 5.4 Hz, 2H, CH_2), 4.04 (t, *J* = 5.5 Hz, 2H, CH_2), 2.62 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 1.75 (t, *J* = 7.1 Hz, 3H, CH_3). δC (126 MHz; CD_3CN; r.t.) 156.90, 153.94, 153.28, 152.12, 143.52, 138.01, 132.19, 127.27, 124.84 (q, *J* = 353 Hz, CF_3), 121.31, 120.20, 58.88, 53.34, 51.10, 21.54, 20.26, 15.35. The corresponding molecular ion peak was not detected in the HRMS spectrum for $\mathbf{1_H}$•**TfO**.

Synthesis of 11. To a mixture of **10** (2.99 g, 11 mmol), K_2CO_3 (7.41 g, 58 mmol), and DMF (300 mL) was added MeI (3.40 mL, 55 mmol), and the mixture was stirred at 60 ˚C for 5 h under molecular nitrogen. After most of the solvents was removed under reduced pressure, 0.3 M aqueous HCl (0.30 L) was added to the residue and the mixture was stirred for 30 min. The resulting powder was collected by filtration and washed with hexane (100 mL). A part of the crude product (558 mg/2.78 g) was washed with water (50 mL) and dried in vacuo to give **11** (527 mg, 83%) as a yellow powder. IR (KBr): ν_{max}/cm^{-1} 3422br (OH), 1698s (NCO), 1644s (NCO), 1582s (NCO), 1550s (NCO). δH (500 MHz; DMSO-d_6; r.t.) 7.94 (s, 1H, ArH), 7.92 (s, 1H, ArH), 4.97 (t, *J* = 6.0 Hz, 1H, OH), 4.71 (t, *J* = 6.0 Hz, 2H, CH_2), 3.81 (m, 2H, CH_2), 3.27 (s, 3H, CH_3), 2.54-2.45 (3H, CH_3, overlapped with DMSO-d_5), 2.40 (s, 3H, CH_3). The spectral properties of **11** were in good agreement with the reported data.[4d]

Synthesis of $\mathbf{1_{Me}}$•TfO. Acetaldehyde (2.80 mL, 50 mmol) was added to a mixture of **11** (507 mg, 1.7 mmol), 10% Pd/C (73.5 mg, 0.069 mmol), conc. HCl (2.7 mL), EtOH (32 mL), and H_2O (32 mL), and the mixture was stirred at room temperature for 22 h under molecular hydrogen. The reaction mixture was filtered

through a pad of Celite under nitrogen, and the filtrate solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous TfOH (2.50 mL, 5.0 mmol), TfONa (2.70 g, 16 mmol), and $NaNO_2$ (574 mg, 8.3 mmol) at 0 ˚C, the mixture was stirred for 15 min. An additional 2 M aqueous TfOH (2.50 mL, 5.0 mmol) was added to this, and the resulting purple precipitate was collected by filtration, washed with cold water (10 mL x 2) and diethyl ether (20 mL x 3), and dried under reduced pressure to give **1_{Me}•TfO** (687 mg, 85%) as a purple powder. IR (KBr): ν_{max}/cm^{-1} 1712s (NCO), 1650vs (NCO), 1600s (NCO), 1559vs (NCO). δH (400 MHz; CD_3CN; r.t.) 8.19 (s, 1H, ArH), 8.12 (s, 1H, ArH), 6.08 (br, 2H, CH_2), 4.96 (br, 2H, CH_2), 4.04 (t, *J* = 5.6 Hz, 2H, CH_2), 3.42 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.79 (t, *J* = 7.2 Hz, 3H, CH_3). The spectral properties of **1_{Me}•TfO** were in good agreement with the reported data.[4d]

Synthesis of 3_{Me}•TfO. A mixture of **11** (700 mg, 2.3 mmol) and $SOCl_2$ (4.20 mL, 58 mmol) was stirred at 50 ˚C for 6 h. The solvent was removed under reduced pressure, and the residue was washed with diethyl ether (50 mL x 4) and dried in vacuo to afford orange powder (796 mg). After some of the crude product (529 mg) was dissolved in water (300 mL), the aqueous layer was washed with $CHCl_3$ (150 mL x 3) and lyophilized to obtain the chloride salt of **3_{Me}** (**3_{Me}•Cl**, 457 mg) as an orange powder. To exchange the counter anion, TfOH (22.9 µL, 0.26 mmol) was added to a solution of **3_{Me}•Cl** (74.5 mg, 0.23 mmol) in MeOH (47 mL), and the resulting mixture was dried by evaporation. The resulting residue was washed with diethyl ether (47 mL), dried in vacuo, and dissolved in water (10 mL), and lyophilized to obtain **3_{Me}•TfO** (88.1 mg, 81%) as a yellow powder. mp 164˚C (dec). IR (KBr): ν_{max}/cm^{-1} 1747s (NCO), 1703s (NCO), 1636s (NCO), 1610s (NCO). δH (500 MHz; DMSO-d_6; r.t.) 8.43 (s, 1H, ArH), 8.15 (s, 1H, ArH), 5.34 (t, *J* = 9.3 Hz, 2H, CH_2), 4.71 (t, *J* = 9.3 Hz, 2H, CH_2), 3.41 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). δC (126 MHz; DMSO-d_6; r.t.) 157.91, 152.49, 147.15, 142.56, 142.49, 139.13, 131.74, 131.19, 127.81, 121.06 (q, *J* = 317 Hz, CF_3) 117.26, 50.62, 45.81, 28.95, 21.27, 19.76. HRMS (ESI+): m/z calcd for $C_{15}H_{15}N_4O_2$ (M - TfO^-), 283.1190; found, 283.1192.

Synthesis of 12.[17b] Sodium periodate (4.77 g, 22 mmol) was added to a suspension of riboflavin (3.00 g, 8.0 mmol) in water (120 mL), and the mixture was stirred at 50 ˚C for 24 h. The brown precipitate was collected by filtration, washed with water (180 mL), MeOH (130 mL), and diethyl ether (20 mL), and dried in vacuo to give **12** (1.34 g, 70%) as a yellow powder. IR (KBr): ν_{max}/cm^{-1} 1699br (NCO), 1577s (NCO), 1485s (NCO). δH (500 MHz; DMSO-d_6; r.t.) 11.82 (s, 1H, -CONHCO-), 11.66 (s, 1H, -CONHC-), 7.91 (s, 1H, ArH), 7.70 (s, 1H, ArH), 2.49 (s, 3H, $ArCH_3$), 2.46 (s, 3H, $ArCH_3$). The spectral properties of **12** were in good agreement with the reported data.[3i]

Synthesis of 13.[17b] A mixture of **12** (4.00 g, 17 mmol), K_2CO_3 (11.8 g, 86 mmol), and methyl iodide (2.40 mL, 39 mmol) in dry DMF (150 mL) was stirred for 3 h at room temperature. After most of the solvent was evaporated under reduced pressure at 50 ˚C, water (200 mL) was added to the residue, and the crude mixture was extracted with $CHCl_3$ (700 mL). The organic layer was washed with brine (200 mL) and dried over $MgSO_4$, filtrated, and evaporated to dryness. No further purification was required in order to obtain **13** (3.48 g, 78%) as a yellow solid. IR (KBr): ν_{max}/cm^{-1} 1720s (NCO), 1677s (NCO), 1556s (NCO). δH (400 MHz; $CDCl_3$; r.t.) 8.07 (s, 1H, ArH), 7.79 (s, 1H, ArH), 3.81 (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 2.54 (s, 3H, $ArCH_3$), 2.51 (s, 3H, $ArCH_3$). The spectral properties of **12** were in good agreement with the reported data.[8a]

Synthesis of 2_{Me}•TfO.[17b] Acetaldehyde (8.50 mL, 0.15 mol) was added to a mixture of **13** (1.02 g, 3.7 mmol), 10% Pd-C (400 mg), H_2O (12.5 mL), and acetic acid (125 mL), and the mixture was stirred for 2 days under molecular hydrogen. The reaction mixture was filtered through a pad of Celite under molecular nitrogen, and the filtrate solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous TfOH solution (10 mL, 20 mmol), TfONa (5.07 g, 30 mmol), and $NaNO_2$ (1.07 g, 16 mmol), the mixture was stirred under air at 0 ˚C for 30 min. The resulting purple precipitate was collected by filtration, washed with cold water (10 mL) and diethyl ether (200 mL) to give the crude product (1.11 g). The product (680 mg) was then purified by the reprecipitation from CH_3Cl to diethyl ether to give **2•TfO** (533 mg, 51%) as a yellow powder. mp 171 ˚C (dec). IR (KBr): ν_{max}/cm^{-1} 1728s (NCO), 1685s (NCO), 1666s (NCO). δH (500 MHz; $CDCl_3$; r.t.) 8.10 (s, 1H, ArH), 8.05 (s, 1H, ArH), 6.12 (br, 1H, N^+CHHCH_3), 5.34 (br, 1H, N^+CHHCH_3), 3.85 (s, 3H, 1-NCH_3), 3.57 (s, 3H, 3-NCH_3), 2.68 (s, 3H, $ArCH_3$), 2.61(s, 3H, $ArCH_3$), 1.85 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3). δC (126 MHz; $CDCl_3$; r.t.) 155.27, 149.25, 148.70, 148.62, 147.25, 146.10, 129.13, 128.95, 120.01 (q, *J* = 320 Hz, CF_3), 119.63, 117.40, 51.57, 30.88, 30.01, 21.76, 20.65, 15.23. HRMS (ESI-TOF) m/z: $[M - TfO^-]^+$ calcd for $C_{17}H_{19}F_3N_4O_5S$, 299.1503, found, 299.1503.

Cyclic voltammetry. Cyclic voltammograms were collected using an electrochemical analyzer model 1210B (BAS, Tokyo, Japan) with a conventional three-electrode cell employing a Pt working electrode, a Pt counter electrode, and a Ag/Ag^+ reference electrode (BAS, Tokyo, Japan). The electrochemical analysis of flavinium salts were carried out in acetonitrile (1.0 mM) containing Bu_4NClO_4 (0.1 M) at a sweep rate of 100 mV/s at 25 ˚C under nitrogen atmosphere. The electrochemical potentials were converted into values relative to SCE using standard redox couple Fc/Fc^+ according to the previously reported method,[12c] and were calculated as the mean of cathodic and anodic peak potentials [$E = (E^c_p + E^a_p)/2$].

Comparison of flavinium catalysts in sulfoxidation of 14. A 30% aqueous H_2O_2 solution (24.9 mg, 0.22 mmol) was added to a mixture of **14** (27.6 mg, 0.20 mmol), flavinium salt (0.01 mmol), and diethylene glycol diethyl ether (16.2 mg, 0.10 mmol, internal standard) in MeOH (2.0 mL), and the reaction mixture was stirred at 25 ˚C. The reaction was monitored by GC, and the yield of **15** was calculated based on the calibration curves using diethylene glycol diethyl ether as an internal standard. These results are summarised in Fig. S2 and Table 3.

Comparison of flavinium catalysts in *N*-oxidation of 16. A 30% aqueous H_2O_2 solution (45.3 mg, 0.40 mmol) was added to a mixture of **16** (40.5 mg, 0.40 mmol), flavinium salt (0.01 mmol), and mesitylene (24.0 mg, 0.20 mmol, internal standard) in CD_3OD (0.8 mL), and the reaction mixture was stirred at 25 ˚C. The reaction was monitored by ^{1}H NMR, and the yield of **17** was calculated using an internal standard. These results are summarised in Fig. S3 and Table 3.

Comparison of flavinium catalysts in Baeyer-Villiger oxidation of 18. A 30% aqueous H_2O_2 solution (45.3 mg, 0.40 mmol) was added to a mixture of **18** (21.6 mg, 0.20 mmol), flavinium salt (0.01 mmol), and 1,1,2,2-tetrachloroethane (16.8 mg, 0.10 mmol, internal standard) in MeOH (2.0 mL), and the reaction mixture was stirred at 25 ˚C. The reaction was monitored by GC, and the total yield of **19a** and **19b** was calculated based on the calibration curves using 1,1,2,2-tetrachloroethane as an internal standard. These results are summarised in Fig. S4 and Table 3.

Sulfoxidation of 14 catalyzed by 3_H•TfO. A 30% aqueous H_2O_2 solution (112 µL, 1.1 mmol) was added to a mixture of **14** (138 mg, 1.0 mmol), **3_H•TfO** (21.0 mg, 0.050 mmol) in MeCN (1.0 mL), and the reaction mixture was stirred at 25 ˚C for 6 h. After an addition of sat. aqueous $NaSO_3$ (1.0 mL) and $CHCl_3$ (20 mL), the organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over $MgSO_4$, and filtered. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 4/1 to 1/3, v/v) to give to give **15** (130 mg, 84%) as a white solid. The spectral properties of **15** were in good agreement with the reported data.[4d]

Baeyer-Villiger oxidation of 20 catalyzed by 3_H•TfO. A 30% aqueous H_2O_2 solution (102 µL, 1.0 mmol) was added to a mixture of **20** (63.1 mg, 0.50 mmol), **3_H•TfO** (10.5 mg, 0.026 mmol) in *t*-BuOH (0.5 mL), and the reaction mixture was stirred at 25 ˚C for 18 h. The yields of **21a** and **21b** were determined to be 82 and 12%, respectively, by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The spectral properties of **21a**[25a] and **21b**[25b] were in good agreement with the reported data.

Conflicts of interest

There are no conflicts to declare.

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