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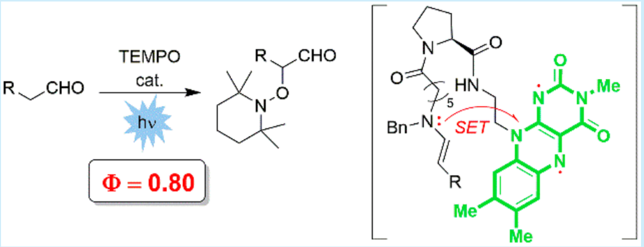
Efficient Use of Photons in Photoredox/Enamine Dual Catalysis with a Peptide-Bridged Flavin−Amine Hybrid

Takuma Tagami,[†] Yukihiro Arakawa,*[,†] Keiji Minagawa,[†,‡] and Yasushi Imada*[,†]

[†]Department of Applied Chemistry, Tokushima University, Minamijosanjima, Tokushima 770-8506, Japan
[‡]Institute of Liberal Arts and Sciences, Tokushima University, Minamijosanjima, Tokushima 770-8502, Japan

Supporting Information

ABSTRACT: An isoalloxazine (flavin) ring system and a secondary amine have been integrated through a short peptide linker with the aim of using photons as efficiently as possible in photoredox/enamine dual catalysis. We herein report a peptide-bridged flavin−amine hybrid that can catalyze α-oxyamination of aldehydes with TEMPO under weak blue light irradiation to achieve an extremely high quantum yield of reaction (Φ = 0.80).



The concept of combining visible-light driven photoredox catalysis with enamine catalysis, pioneered by MacMillan et al. in 2008,[1] has given rise to many unique reactivities that are not accessible with each of them independently. For example, the catalytic C−C bond formation at the α-position of aldehydes with an alkyl halide, which is not trivial to achieve with a solo enamine catalysis, has become feasible in an enantioselective manner.[2] A similar concept was also introduced by Akita et al. in 2009 for the catalytic C−O bond formation at the α-position of aldehydes with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in a nonenantioselective manner.[3] Such a dual catalysis involves a single electron transfer (SET) between an excited photocatalyst and an enamine formed in situ or an α-amino radical derived from the enamine at a point of contact between merged catalytic cycles (Figure 1a, left). Since both are catalytic species and the excited form of photocatalyst is particularly labile, their concentration in solution tends to be too low to make their SET efficient, which can be reflected in a very low quantum yield (Φ) of reaction when any chain process is absent. Indeed, Zeitler et al. reported Φ values of 0.06−0.09 for the enantioselective α-alkylation of aldehydes catalyzed by Eosin Y as a photocatalyst combined with a chiral imidazolidinone cocatalyst.[4] Another recent example was reported by MacMillan et al. for the direct enantioselective α-benzylation of aldehydes with alcohols using an iridium-based photocatalyst and a chiral secondary amine cocatalyst, in which the Φ value was determined to be 0.071.[5] Unfortunately, the α-oxyamination of aldehydes with TEMPO introduced by Akita et al.[3] has been followed by only a limited number of reports so far and their quantum yield has not been determined.[6] Such a Φ value, which represents how many molecules react as desired with a photon absorbed ($\Phi \leq 1$), is typically evaluated only for gaining mechanistic insight, but it would be ideal to be closer to the maximum for economical use of photons concerning the actual reaction efficiency.

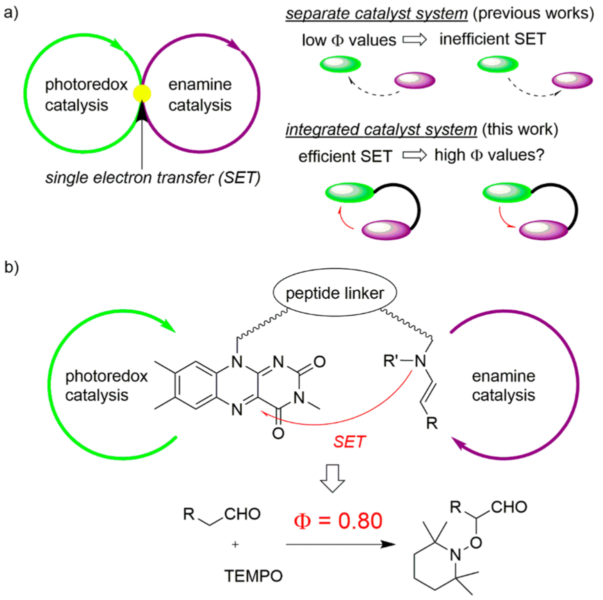


Figure 1. Concept of flavin−amine hybrid catalyst.

With the aim of using photons as efficiently as possible in the photoredox/enamine dual catalysis, we focused attention toward covalently linked donor−acceptor molecules found in the chemistry of artificial photosynthesis.[7] It is known that the rate of photoinduced intramolecular electron transfers from an excited donor moiety to an acceptor moiety highly depends on their distance and orientation. We envisioned that this knowledge could be applied for developing a new type of photoredox catalysts that integrated an amine functionality and a photoactive functionality within a molecule, which might

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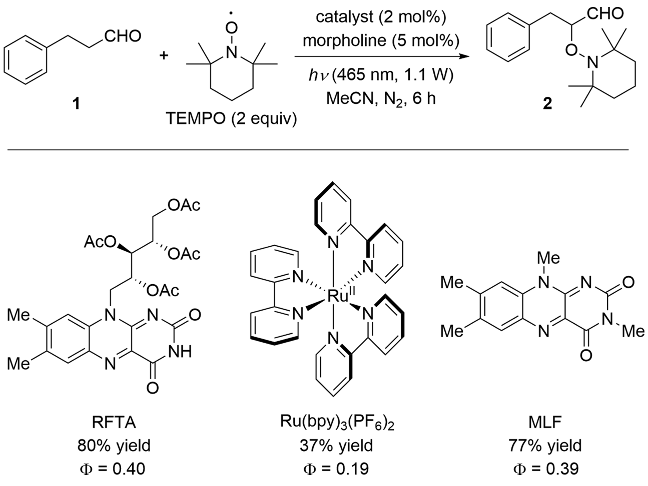
render SET from/to an enamine-related species to/from an excited photocatalyst more efficiently to provide not only high quantum efficiency but also unusual reactivity (Figure 1a, right). Only recently, Alemán et al. reported such a bifunctional photoaminocatalyst consisting of imidazolidinone and thioxanthone for the α-alkylation of aldehydes, which involved a chain propagation pathway ($\Phi > 1$).[8]

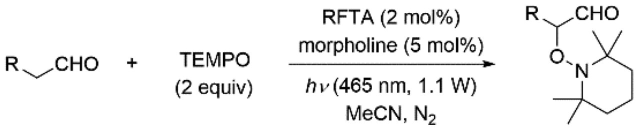
To externalize our own idea that targets a chain process-free photoredox/enamine dual catalysis ($\Phi < 1$), we focused on riboflavin, namely vitamin B_2, which is a naturally occurring photoactive organic molecule easily functionalizable at its N3 and N10 positions without affecting its optical properties such as absorbance and fluorescence. For example, riboflavin tetraacetate (RFTA, Scheme 1) is one of the readily accessible riboflavin derivatives well soluble in organic solvents, which absorbs purple and blue light to emit green/yellow light (for the UV−vis absorbance, emission, and excitation spectra of RFTA, see Supporting Information). Although there have been a number of reports on such flavin molecules as a photoredox catalyst for visible-light induced reactions,[9] their catalytic activity in any dual photoredox/enamine catalysis has never been reported so far. In addition, our research group has much experience in using flavin molecules through the developments of their thermal catalysis,[10] which are the reason for choosing them as a chromophore in this study. On the other hand, we selected light emitting diodes (LED) as a visible-light source possessing a rather narrow emission band to realize the efficient use of photons. Herein, we first present that flavin molecules including RFTA can efficiently promote the α-oxyamination of aldehydes with TEMPO by cooperating with a secondary amine cocatalyst under visible-light irradiation through a chain process-free photoredox/enamine dual catalysis. Then, we introduce a new type of photoredox hybrid catalysts consisting of a flavin ring system and a secondary amino group bridged by a peptide linker, in which extremely high Φ values up to 0.80 are achieved (Figure 1b).

Scheme 1. Comparison of Photoredox Activity between RFTA, $Ru(bpy)_3(PF_6)_2$, and MLF in the Visible-Light Induced α-Oxyamination of 1 with TEMPO Cocatalyzed by Morpholine



As mentioned above, flavin molecules have never been found to be a photoredox catalyst in the dual catalytic system merged with enamine catalysis despite their potential especially as an alternative to conventional transition-metal-based photocatalysts. We chose the α-oxyamination of aldehydes with TEMPO as a benchmark reaction, which previously require tris(bipyridyl)ruthenium(II) complex $[Ru(bpy)_3(PF_6)_2]$ as a photoredox catalyst along with morpholine as an amine cocatalyst,[3] and explored whether RFTA could commute $Ru(bpy)_3(PF_6)_2$ for this reaction (Scheme 1). Using blue LED light (465 nm, 1.1 W) that was shed to a tubular reactor with a diameter of 5 mm at a distance of 1 cm, 3-phenylpropanal (**1**) was fully consumed within 6 h in the presence of 2 mol % of RFTA and 5 mol % of morpholine and 2 equiv of TEMPO in acetonitrile under a nitrogen (N_2) atmosphere and the desired α-oxyaminated product **2** was obtained in 80% yield along with 20% of unclear byproducts. $Ru(bpy)_3(PF_6)_2$ instead of RFTA was less active under the same conditions, and a similar level of selectivity was observed. Other organic dyes including 1,3-dimethylalloxazine and Eosin Y were also considerably less effective (see Supporting Information). The Φ values obtained with RFTA and $Ru(bpy)_3(PF_6)_2$ have been determined to be 0.40 and 0.19, respectively, by chemical actinometry with potassium ferrioxalate,[11] indicating that no radical chain pathway is involved. The superior photoredox activity of RFTA may be explained by its excited-state reduction potential (E^*_{red} = 1.67 V vs SCE)[12] higher than that of $Ru(bpy)_3(PF_6)_2$ (E^*_{red} = 0.77 V vs SCE).[2a] In fact, 3-methyllumiflavin (MLF), which is known to be slightly less oxidizing than RFTA in their ground state (RFTA: $E_{\mathrm{red}} = -0.73$ V, MFl: $E_{\mathrm{red}} = -0.81$ V), showed comparable photocatalytic activity under identical conditions. The RFTA catalytic system was demonstrated to be applicable for other aldehydes such as *n*-butanal, isovaleraldehyde, *n*-octanal, and phenylacetaldehyde as a substrate with a similar level of efficiency (Table 1, entries 2−5). It should be noted that the lack of any one of flavin, morpholine, and LED light did not allow for the present reaction with **1**, which led us to propose the photoredox/enamine dual catalysis (Scheme 2) involving SET from the enamine **D** to the excited flavin **Fl*** for generating the enamine radical cation $\mathbf{D}^{+\bullet}$ that reacts with TEMPO and then undergoes hydrolysis to regenerate the amine cocatalyst by releasing the adduct. Although a nitrogen atmosphere was required for the efficient catalysis (see Supporting Information), a trace amount of unremoved oxygen might act as a terminal oxidant[2a] that could receive an electron from the flavin radical anion $\mathbf{Fl}^{-\bullet}$ to regenerate **Fl**.

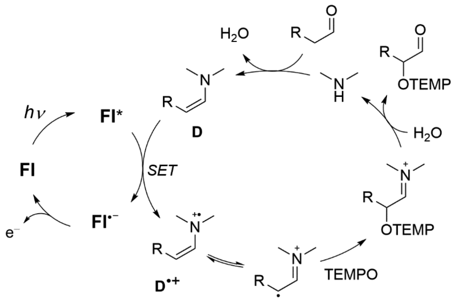
Table 1. Scope of α-Oxyamination with TEMPO in RFTA/Morpholine Catalyst System[a]



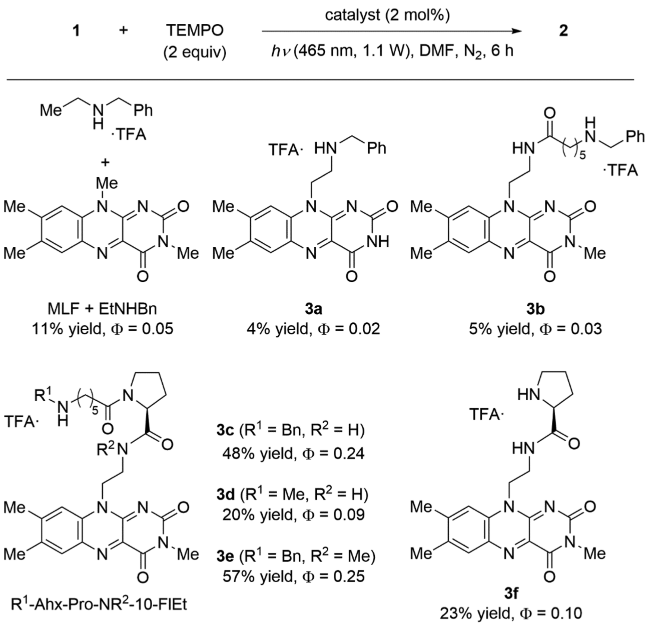
entry	R	time (h)	yield (%)[b]
1	Bn	6	80
2	Et	4	71
3	*i*-Pr	8	79
4	*n*-C_6H_{13}	8	78
5	Ph	4	52

[a] Reactions were performed with 50 μmol of aldehyde and 100 μmol of TEMPO in 0.5 mL of acetonitrile in the presence of 17 μmol of 1,3,5-trimethoxybenzene as an NMR internal standard, 2 mol % of RFTA, and 5 mol % of morpholine and under a nitrogen atmosphere and blue LED light irradiation. [b] NMR yields.

Scheme 2. Proposed Dual Catalysis with Separate Flavin and Amine



Scheme 3. Catalytic Performance of Flavin−Amine Hybrids 3a−3f



Encouraged by the results of the separate catalyst system, we turned our attention to flavin−amine hybrids initially envisioned (Figure 1b). First of all, flavin derivatives **3a** and **3b** containing an *N*-alkylbenzylamino moiety tethered to a N10 position via different kinds of spacers were prepared and their catalytic activity was compared in the visible-light induced α-oxyamination of **1**. Reactions were carried out with 2 equiv of TEMPO and 2 mol % of a trifluoroacetic acid (TFA) salt[13] of the flavin-amine hybrid catalysts in DMF[14] under a N_2 atmosphere and blue LED irradiation (465 nm, 1.1 W) for 6 h (Scheme 3). Although bifunctional catalytic behaviors of **3a** and **3b** were observed, the corresponding Φ values (0.02 and 0.03, respectively) were unremarkable and even less than that of a separate catalyst system (0.05) catalyzed by the combination of MLF and *N*-benzylethylamine TFA salt (EtNHBn·TFA). However, these initial results were still within our anticipation because the distance between a flavin ring and an assuming enamine moiety in **3a** and **3b** could be too far from each other in their stable conformation. We then relied on our intuition to determine the subsequent candidate, Bn-Ahx-Pro-NH-10-FlEt (**3c**, Bn = benzyl, Ahx = 6-aminohexanoic acid, Pro = proline, 10-FlEt = 2′-(3,7,8-trimethyl-10-isoalloxazyl)ethyl) featuring a prolyl linker that could force the amino group and the flavin ring to get close to each other, as prolyl-containing flavopeptides we previously introduced.[10g,i,j] As expected, a remarkable quantum yield of reaction (48% yield, Φ = 0.24) was attained when the TFA salt of **3c** was used as a catalyst, while it was almost halved by replacing either Bn with a methyl group (Me-Ahx-Pro-NH-10-FlEt, **3d**, 20% yield, Φ = 0.09) or Bn-Ahx with a hydrogen atom (**3f**, 23% yield, Φ = 0.10). These results indicated that the Bn-Ahx-Pro moiety in **3c** is responsible for its catalytic activity.[15] On the contrary, a comparable performance to **3c** was observed with its analogue Bn-Ahx-Pro-NMe-10-FlEt (**3e**, 57% yield, Φ = 0.25), showing that the amide hydrogen of N-terminus in **3c** could be less important. Unfortunately, the moderate yield (48%) obtained with **3c** was not improved with prolonged reaction times due to its own decomposition during the reaction as clearly shown in reaction profiles with the yield of **2** (Figure 2, blue solid line, plateaued) and the absorbance of **3c** at 447 nm (Figure 2, blue dotted line, disappeared). In fact, 7,8-dimethylalloxazine (**4**) possibly derived from **3c** via its photoactivation was observed from the reaction mixture, which had almost no catalytic activity under identical conditions. Thus we sought to optimize reaction conditions to suppress such catalyst decomposition, and as a result, reducing the electric power of LED light was found to be effective. For example, when an electric power of 0.09 W was used, the decomposition of **3c** was considerably suppressed (Figure 2, red dotted line) to afford **2** more slowly but in a higher yield of 64% in 24 h (Figure 2, red solid line).[16] Particularly notable is its Φ value which was determined to be 0.80, which is to the best of our knowledge the highest value ever reported for photoredox/enamine dual catalysis. It should also be noted that any separate catalyst system with EtNHBn·TFA and typical photocatalysts including MLF, $Ru(bpy)_3(PF_6)_2$, tris(2-phenylpyridinato)iridium(III) $[Ir(ppy)_3]$, and Eosin Y resulted in no reaction under identical conditions (see Supporting Information), showing that the present activity and quantum efficiency are unique to the hybrid catalyst.

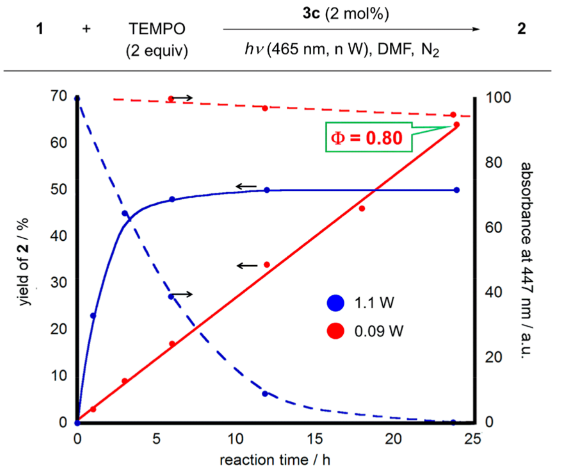
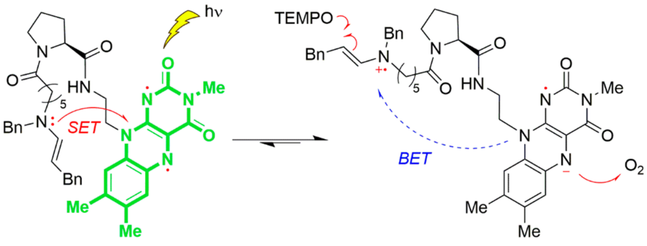


Figure 2. Profiles of the α-oxyamination of **1** and the decomposition of **3c** under blue light irradiation with different electric powers: the left vertical axis shows the yield of **2** obtained with an electric power of 1.1 W (blue solid line) or 0.09 W (red solid line), while the right vertical axis shows the absorbance at 447 nm obtained with that of 1.1 W (blue dotted line) or 0.09 W (red dotted line).

The dual catalytic behavior of **3c** for the α-oxyamination of aldehydes with TEMPO may be explained by considering an efficient intramolecular SET process enabled by its balanced conformational rigidity and flexibility with the key peptide linker. A certain rigidity of the Pro residue could bring the enamine moiety and the excited flavin ring system close to make their SET efficient (Scheme 4, left),[15] while a certain flexibility of the Ahx residue could entropically favor an open conformation within which the resulting free radical cation and anion are liberated to rapidly react with TEMPO and probably the remaining oxygen, respectively, accordingly suppressing back electron transfer (BET) (Scheme 4, right). The undesired decomposition of **3c** into **4** (Figure 2), probably triggered by the β-hydrogen abstraction with N1 nitrogen of the flavin ring system in **3c** through a six-membered transition state (see Supporting Information), could be minimized by making the concentration of enamine sufficiently higher than that of the excited flavin ring under the slow photon irradiation, which brought about the unprecedented quantum yield of reaction.

Scheme 4. A Plausible Explanation for the Catalytic Performance of 3c



In summary, we have demonstrated that simple flavin molecules such as RFTA and MLF can be used as a photoredox catalyst for α-oxyamination of aldehydes with TEMPO under blue LED light irradiation, which are chain-process-free (Φ < 1) and much more efficient compared to $Ru(bpy)_3(PF_6)_2$ previously reported under identical conditions. Furthermore, we have introduced the peptide-bridged flavin−amine hybrid **3c**, Bn-Ahx-Pro-NH-10-FlEt, which can promote the same reaction as a dual functional catalyst with an extremely high quantum yield of reaction (Φ = 0.80) under suitable conditions. This study will provide a guide for the design of new photoredox/enamine dual catalysis that allows for efficient use of photons in a useful molecular transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02567.

Experimantal protocols and selected NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: arakawa.yukihiro@tokushima-u.ac.jp.
*E-mail: imada@tokushima-u.ac.jp.

ORCID

Yukihiro Arakawa: 0000-0003-1000-5799
Yasushi Imada: 0000-0002-4844-5418

Notes

The authors declare no competing financial interest.

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(14) DMF was used as a solvent to fully solubilize the hybrid catalysts, since no significant difference in reaction efficiency between DMF and acetonitrile was found in the separate catalyst system using RFTA and morpholine as catalysts. For details, see Supporting Information.

(15) The role of the Bn group remains unclear. We estimated lowest energy conformations of flavin–enamine hybrid species derived from **3c** and **3d**, respectively, by DFT calculation at the B3LYP/6-31G* level in the ground state and found that the distance between the N5 of flavin ring and the nitrogen atom of enamine in the **3c**-derived model was relatively shorter (4.55 Å) than that in the **3d**-derived model (5.92 Å), which may explain the higher quantum efficiency of **3c**. Such a strained conformation may be explained by the observed intramolecular hydrogen bond between the C=O neighboring the nitrogen atom of Pro and NH of 10-FlEt as well as the observed gauche conformation of ethylene moiety of 10-FlEt residue. For details, see Supporting Information.

(16) The reaction was not enantioselective despite the chirality of **3c**.