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FOCUS REVIEW

Advanced flavin catalysts elaborated with polymers

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Abstract

A variety of biological redox reactions are mediated by flavoenzymes due to the unique redox activity of isoalloxazine ring systems, which are found in flavin cofactors. In the field of synthetic organic chemistry, the term "flavin" is generally used for not only isoalloxazines but also related molecules including their isomers and some analogs, and those having catalytic activity are called *flavin catalyst*. Flavin catalysts are typically metal-free, and their catalytic activity can be readily accessed using mild terminal oxidants such as H_2O_2 and O_2; therefore, redox reactions with these compounds have great promise as alternatives to reactions with conventional metal catalysts for the sustainable production of important chemicals. We recently became interested in using polymers for the development of flavin catalysts, especially to improve their practicality and advance the field of catalysis. Here, we summarize our recent research on such flavin–polymer collaborations including the development of facile preparation methods for flavin catalysts using polymers, readily reusable polymer-supported flavin catalysts, and flavin–peptide–polymer hybrids that can catalyze the first flavoenzyme-mimetic aerobic oxygenation reactions.

Introduction

Flavoenzymes are composed of flavin cofactors and apoenzymes, and they are responsible for various oxidative metabolic processes in nature [1–9]. The unique redox properties of isoalloxazine ring system **Fl** (Fig. 1a), found in flavin cofactors, allows for diverse oxidation reactions using molecular oxygen (O_2) as a terminal oxidant (aerobic oxidation). For example, flavin monooxygenases (FMOs) are widely distributed in mammalian liver and metabolize xenobiotic substrates through the activation of O_2 followed by the donation of an oxygen atom to the substrate. Although many oxidoreductases such as cytochrome P450 possess metals in their active sites, flavoenzymes are metal-free, which has inspired chemists to use simple **Fl** or its analogs as a molecular catalyst for the development of metal-free catalytic oxidations. In 2003, our group reported the first FMO-mimetic aerobic oxidations catalyzed by **Fl**-like heterocyclic molecules (**FlEt$^+$A$^-$**) bearing an ethyl group at the *N*5 position (Fig. 1b) [10]. **FlEt$^+$A$^-$** is generally called a *flavinium salt* or *cationic flavin* (Fig. 1b), whereas **Fl**, which is equivalent to the active center of a flavoenzyme, is called *neutral flavin* (Fig. 1a). **Fl** and **FlEt$^+$A$^-$** are structurally similar, but their physical and chemical properties are actually quite different. For example, **Fl** has a fluorescent yellow color because of its emission properties, but **FlEt$^+$A$^-$** has a nonfluorescent deep purple color. There have been many reports regarding catalytic oxidation reactions with such isoalloxazines, as well as related molecules including their isomers and some analogs (all called *flavin catalyst*) as seen in some previous reviews [11–16] and recent examples [17–37].

Oxidation is one of the most fundamental reactions in the production of valuable chemical substances. Given that many classical oxidation methods depend on the use of metal oxides, the development of catalytic oxidation reactions that can be carried out in a safe and efficient manner without utilizing scarce resources, such as rare metals, and producing toxic wastes is necessary for our sustainable future. From this point of view, aerobic oxidation systems with flavin catalysts including **Fl** and **FlEt$^+$A$^-$** show great promise as environmentally friendly and clean oxidations because not only do they utilize metal-free organocatalysts

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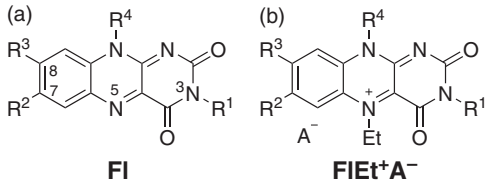


Fig. 1 Neutral flavins **a** and cationic flavins **b**

but also the only waste derived from the terminal oxidant (O_2) is H_2O.

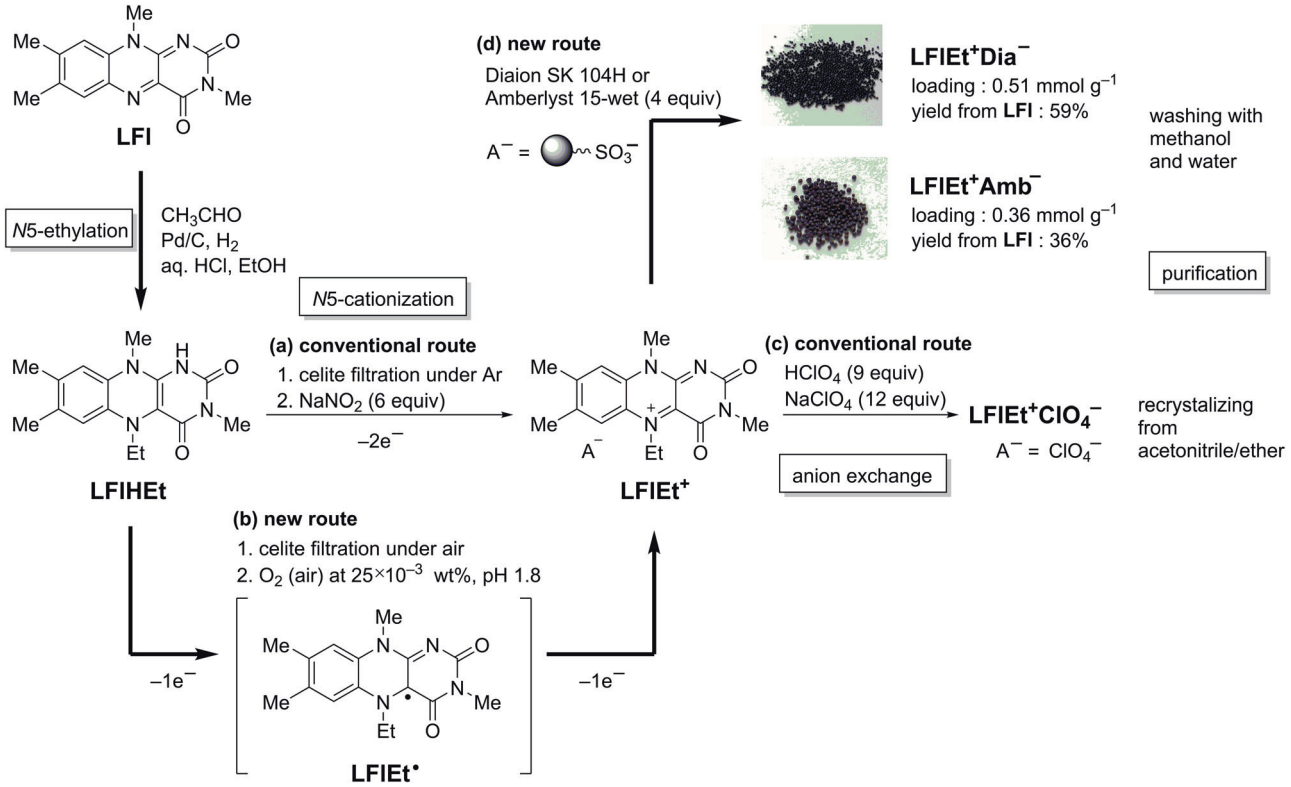
Organic reactions in living organisms usually involve naturally occurring polymers such as proteins, sugars, and nucleic acids. Synthetic organic chemistry has also effectively incorporated synthetic polymers for various applications, such as solid-phase organic synthesis [38, 39] and polymer-supported reagents and catalysts [40, 41]. We recently became interested in using polymers for the development of flavin catalysts, especially for improving their practicality and advancing the field of catalysis. In this article, some recent advances in such flavin–polymer collaboration reported by our group are summarized [35–37].

Practical synthesis of FlEt$^+$A$^-$ catalysts utilizing cation-exchange resins

The catalytic activity of **FlEt$^+$A$^-$** for oxidation was first discovered by Murahashi et al. in 1989 for the oxidation of amines and sulfides with hydrogen peroxide (H_2O_2) [42]. Although various oxidation reactions catalyzed by **FlEt$^+$A$^-$**, generally perchlorate salts ($A^- = ClO_4^-$), with H_2O_2 or O_2 as the terminal oxidant have been developed to date, their laboratorial, as well as industrial applications are still limited compared with traditional metal-based oxidation reactions [43, 44]. One of the reasons for such limitations is that the conventional preparation method for **FlEt$^+$ClO$_4^-$** requires careful operation under an inert atmosphere, product purification and analysis steps with intricate experimental techniques, and most problematically, a large excess of hazardous reagents, such as toxic $NaNO_2$ and explosive $NaClO_4$ [45, 46]. For example, 5-ethyl-3-methyllumiflavinium perchlorate (**LFlEt$^+$ClO$_4^-$**), one of the most commonly used **FlEt$^+$A$^-$**-type catalysts, is typically prepared from 3-methyllumiflavin (**LFl**) through *N*(5)-ethylation using acetoaldehyde and hydrogen gas in the presence of Pd/C catalyst under acidic aqueous-alcoholic conditions. The *N*(5)-cationization step requires the removal of Pd/C by filtration with Celite under argon, which is followed by an oxidation with 6 equivalents of $NaNO_2$ (Scheme 1a), anion exchange using 9 equivalents of $HClO_4$ and 12 equivalents of $NaClO_4$ (Scheme 1c), and purification by recrystallization. It should be noted that **FlEt$^+$A$^-$** catalysts are so labile under basic and nucleophilic conditions that it is difficult to employ ordinary extractions and column chromatographic separations for their purification. Therefore, ClO_4^- or other expensive non-coordinating anions, such as TfO^-, BF_4^-, and PF_6^- [47], had to be used to generate isolable, crystalline **FlEt$^+$A$^-$**.

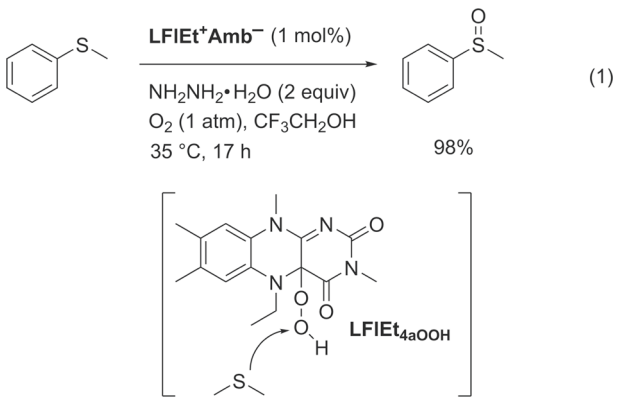
We developed a much safer, easier, and less expensive alternative route utilizing air instead of $NaNO_2$ for the *N*(5)-cationization step (Scheme 1b) and commercially available cation-exchange resins instead of $HClO_4$ and $NaClO_4$ for the anion exchange and purification steps (Scheme 1d) [35]. After the full conversion of **LFl** (24 mM, 674×10^{-3} wt%) into 5-ethyl-3-methyl-1,5-dihydrolumiflavin (**LFlHEt**) according to the literature protocol [46], the subsequent Celite filtration was carried out under air by using water for rinsing and gave a reddish brown-colored solution containing 5-ethyl-3-methyllumiflavosemiquinone (**LFlEt$^\bullet$**) and **LFlEt$^+$** in a ratio of 75:25 (225×10^{-3} wt%, pH 0.6). It was found that the remaining **LFlEt$^\bullet$** could be fully converted to **LFlEt$^+$** by diluting the reddish brown-colored solution nine times with deionized water followed by exposing the resulting mixture (25×10^{-3} wt%, pH 1.8) to air with vigorous stirring for 2 h (Scheme 1b). To the resulting crude purple solution of **LFlEt$^+$** was then added four equivalents of a sulfonic acid cation-exchange resin, such as Diaion SK104H (Mitsubishi) and Amberlyst 15-wet (Organo), and the resulting heterogeneous mixture was shaken at room temperature for 3 h to fully transfer **LFlEt$^+$** onto the solid phase (Scheme 1d). Finally, the resulting dark resin was simply washed with methanol and water and then freeze-dried to give the flavinium salt immobilized on Diaion SK104H (**LFlEt$^+$Dia$^-$**, 59%, 0.51 mmol g^{-1}) or Amberlyst 15-wet (**LFlEt$^+$Amb$^-$**, 36%, 0.36 mmol g^{-1}). It should be emphasized that the syntheses of these lumiflavinium resins from **LFl** require neither hazardous chemicals nor an inert atmosphere and is feasible on a gram scale.

LFlEt$^+$Dia$^-$ and **LFlEt$^+$Amb$^-$** were demonstrated to be effective catalysts for the aerobic oxidation reactions [35] originally developed by our group with **LFlEt$^+$ClO$_4^-$** [10]. For example, thioanisole was smoothly oxidized in the presence of 1 mol% of **LFlEt$^+$Amb$^-$**, two equivalents of hydrazine monohydrate, and 1 atm of O_2 in 2,2,2-trifluoroethanol (TFE) at 35 °C to give methyl phenyl sulfoxide in 98% yield in 17 h (Eq. 1). Comparable catalytic activity was also observed with less expensive **LFlEt$^+$Dia$^-$**; however, the catalyst had to be pre-swelled with a small amount of acetonitrile. We believed that the present sulfoxidation would occur via the same principle as that with **LFlEt$^+$ClO$_4^-$** involving the catalytic generation of 5-ethyl-4a-hydroperoxy-3-methyllumiflavin (**LFlEt$_{4aOOH}$**) as an active electrophilic



Scheme 1 Preparation of 5-ethyl-3-methyllumiflavinium salt; **a** and **c** conventional route, **b** and **d** new route

species (Eq. 1), although the role of the resins in the catalysis remains unclear.



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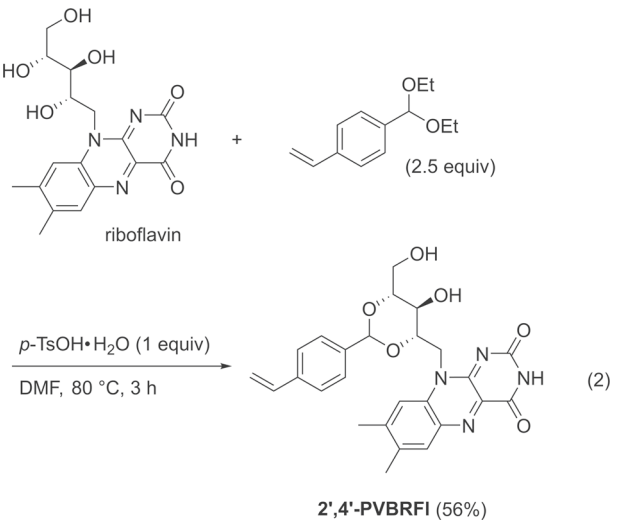
Synthesis of insoluble polymer-supported Fl by polymerization and their catalytic activity

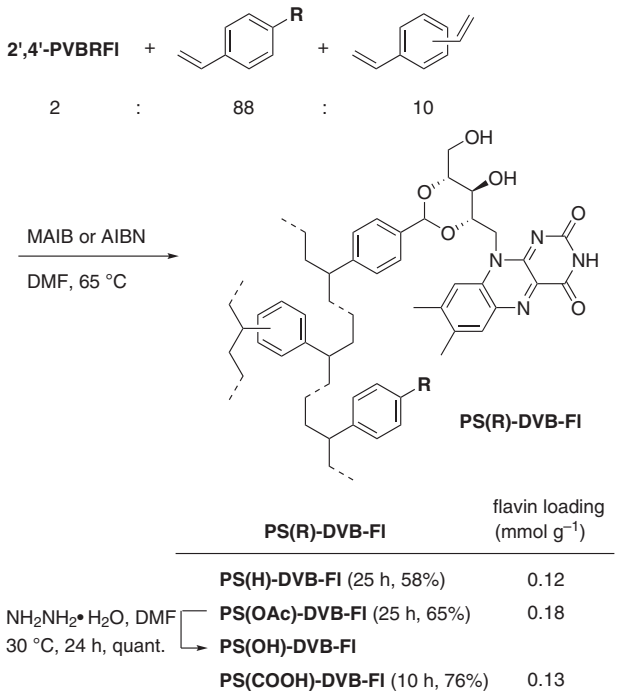
Neutral flavins (**Fl**, Fig. 1a) and their catalysis have recently received much attention as they are generally inexpensive, nontoxic, readily available, and easy to handle. The current mainstream methodology is to develop photoredox or photosensitizing reactions with visible light irradiation utilizing the optical emission properties of **Fl**, which are of great importance for its unique applications [17–29]. On the other hand, our group has been interested in light-independent catalytic systems [48, 49], which are much less developed, and we have previously introduced a method for hydrogenating olefins with in situ-generated diimide (NH = NH) through the aerobic oxidation of hydrazine (NH_2NH_2) catalyzed by **Fl** under metal-free and hydrogen gas-free conditions [50]. Although environmentally benign and synthetically useful, the original reaction system is homogeneous, so efficient recovery and reuse of the **Fl** catalysts are not trivial. In addition, acidic substrates, such as those bearing phenolic hydroxyl groups, are much less reactive because they significantly diminish the nucleophilicity of NH_2NH_2, which is involved in the rate-determining step as a nucleophilic reductant [51].

To overcome such limitations, we designed a novel flavin-containing vinyl monomer, 2′,4′-*O*-*p*-vinylbenzylidene riboflavin (**2',4'-PVBRFl**), and its copolymers, poly(styrene-*co*-divinylbenzene-*co*-**2′,4′-PVBRFl**) (**PS(R)-DVB-Fl**) bearing different pendant groups (R), as efficient and reusable heterogeneous catalysts for the aerobic reduction of olefins with hydrazine [36]. The monomer (**2',4'-PVBRFl**) was easily synthesized from riboflavin (vitamin B_2) through treatment with 2.5

equivalents of 4-vinylbenzaldehyde diethyl acetal and one equivalent of *p*-toluenesulfonic acid monohydrate in DMF at 80 °C for 3 h in 56% yield (Eq. 2), and it was subsequently used for the preparation of flavin-containing polymers (**PS(R)-DVB-Fl**) by free-radical polymerization. Styrene or 4-vinylbenzoic acid was copolymerized with divinylbenzene and **2′,4′-PVBRFl** in a molar ratio of 88:10:2 under typical radical polymerization conditions to afford **PS(H)-DVB-Fl** and **PS(COOH)-DVB-Fl**, respectively, whereas **PS(OH)-DVB-Fl** was prepared via a similar copolymerization method with 4-acetoxystyrene as the major comonomer followed by hydrolysis of the resulting polymer (**PS(OAc)-DVB-Fl**) with an excess of hydrazine (Scheme 2).



Exploring the catalytic activities of **PS(R)-DVB-Fl** (3 mol%) in the aerobic reduction of olefins with hydrazine monohydrate (3 equiv) in acetonitrile under air at 30 °C revealed that **PS(H)-DVB-Fl** is particularly effective for aprotic substrates, whereas **PS(OH)-DVB-Fl** and **PS (COOH)-DVB-Fl** efficiently catalyze the reduction of phenolic hydroxyl group-containing olefins, which are less reactive in the conventional homogeneous system. For example, when 4-phenyl-1-butene was used as an aprotic substrate, **PS(H)-DVB-Fl** was considerably more active than **PS(OH)-DVB-Fl** and **PS(COOH)-DVB-Fl** in providing the corresponding hydrogenated product because its strong hydrophobicity prevents its self-aggregation during the reaction (Fig. 2a). On the other hand, the opposite trends in catalytic activity were observed when *p*-vinylphenol was used as an acidic substrate (Fig. 2b), which could be explained by the high affinity of **PS(OH)-DVB-Fl** and **PS (COOH)-DVB-Fl** for hydrazine via acid–base interactions, rendering the concentration of hydrazine on solid-phase higher and that in solution phase lower, and as a result, the



Scheme 2 Synthesis of **PS(R)-DVB-Fl**

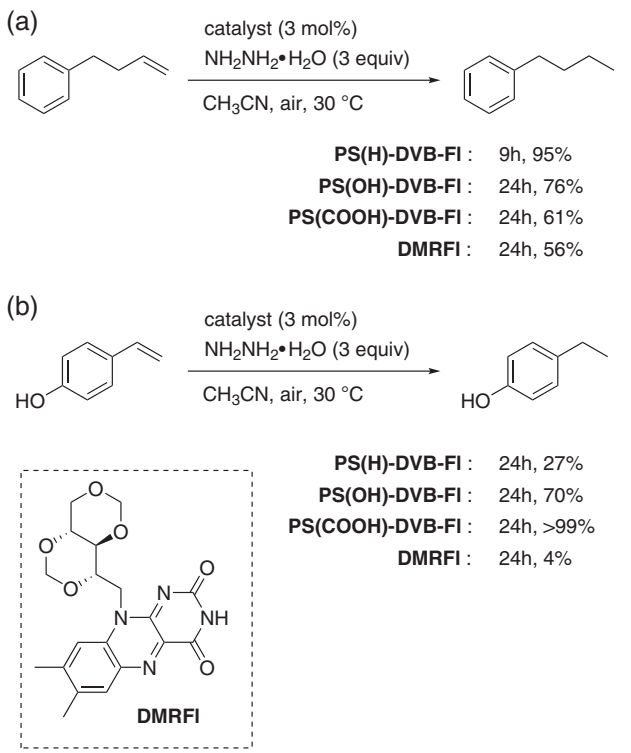


Fig. 2 Flavin-catalyzed aerobic reduction of 4-phenyl-1-butene **a** and *p*-vinylphenol **b**

rate-determining nucleophilic addition of hydrazine to flavin is more favorable. It should be noted that the catalytic activities of **PS(R)-DVB-Fl** were generally higher than that

of 2′,4′:3′,5′-di-*O*-methyleneriboflavin (**DMRFl**), a known low-molecular-weight **Fl** catalyst (Fig. 2). Furthermore, efficient catalyst recovery and reuse were demonstrated with **PS(H)-DVB-Fl** and **PS(COOH)-DVB-Fl**; these compounds could be readily recovered by a simple filtration and reused without loss in activity for at least 13 and 4 cycles, respectively.

These results showed that the catalytic activity of **Fl** could be controlled by tuning the reaction environment created in the polymer network. We therefore expected that $\mathbf{Fl_{4aOOH}}$ in **PS(R)-DVB-Fl** might be effective for FMO-mimetic aerobic oxygenations, but such catalytic activity was not observed.

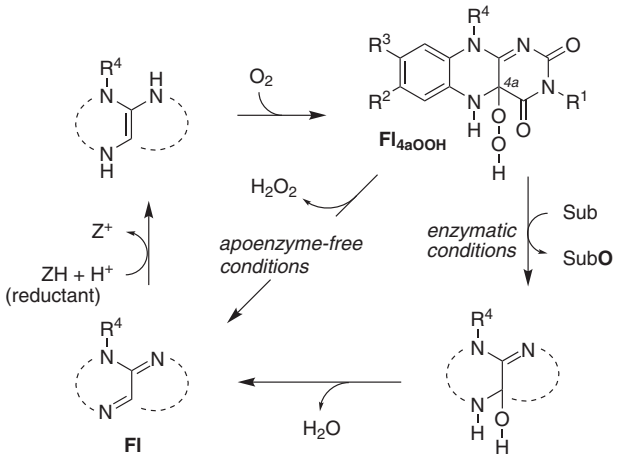


Fig. 3 General understanding of the mechanism of **Fl**-catalyzed aerobic oxygenation under enzymatic conditions and apoenzyme-free conditions

Resin-supported flavopeptides that catalyze FMO-mimetic aerobic oxygenations

The specific functions of FMO originate from the fact that 4a-hydroperoxyflavin ($\mathbf{Fl_{4aOOH}}$, Fig. 3), a key active species for monooxygenation, is derived from the **Fl** of the flavin cofactors and can be appropriately stabilized under enzymatic conditions [52–54]. In other words, it is not trivial to simulate it using simple **Fl** due to the lability of the corresponding $\mathbf{Fl_{4aOOH}}$, which readily decomposes into **Fl** and H_2O_2 under apoenzyme-free conditions (Fig. 3). By contrast, similar 4a-hydroperoxy species derived from $\mathbf{FlEt^+A^-}$, such as $\mathbf{LFlEt_{4aOOH}}$ (Eq. 1), can be sufficiently stable even under apoenzyme-free conditions but are much more active than H_2O_2 as oxidants [55–57], explaining why $\mathbf{FlEt^+A^-}$ has been exclusively used as molecular catalysts for FMO-mimetic oxidation reactions.

4a-Hydroperoxyflavin ($\mathbf{Fl_{4aOOH}}$), a key active species for FMO, had never been utilized for catalytic aerobic oxidations under apoenzyme-free conditions due to its lability (Fig. 3). Recently, this long-standing challenge was finally overcome using our designed catalyst consisting of **Fl**, a peptide, and polystyrene (PS) resin [37]. We calculated that $\mathbf{Fl_{4aOOH}}$ could be stabilized by a conjugated peptide through intramolecular hydrogen bonds, and we demonstrated that specific **Fl**-peptide conjugates, *flavopeptides*, immobilized on PS resins such as 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS could efficiently catalyze aerobic sulfoxidations, as well as Baeyer–Villiger oxidation in the same manner as an FMO, and the resin played a crucial role involving forming a hydrophobic microenvironment to stabilize the $\mathbf{Fl_{4aOOH}}$.

The flavopeptides were designed based on the following hypotheses: (i) a peptide chain should be connected to the *N*3 position of **Fl** relatively close to the active site of 4a; (ii) readily available lumiflavin-3-acetic acid (3-FlC2) [58] should be used as the **Fl** and incorporated to the N terminus of the peptide; (iii) a simple dipeptide (3-FlC2-AA1-AA2) or tripeptide (3-FlC2-AA1-AA2-AA3) should be designed using inexpensive L-amino acids; (iv) an L-proline residue should be placed at AA1 to induce a constrained γ-turn structure and make the active site and AA2-AA3 spatially close; (v) AA2 and/or AA3 should be filled with acidic amino-acid residues that can be expected to interact with the active site by intramolecular hydrogen bonds. In accordance with these design policies, we proposed 3-FlC2-Pro-AA2 and 3-FlC2-Pro-AA2-AA3 as the frameworks for the flavopeptide. To estimate appropriate structures for AA2 and AA3, lowest energy conformations of some 3-FlC2-Pro-AA2 and 3-FlC2-Pro-AA2-AA3 derivatives in their $\mathbf{Fl_{4aOOH}}$ form under vacuum were explored by density functional theory (DFT) calculations at the B3LYP/6-31G* level. As a result, it was found that 3-FlC$2_{4a(R)OOH}$-Pro-Tyr-Glu-NHMe and 3-FlC$2_{4a(R)OOH}$-Pro-Tyr-Asp-NHMe could be stabilized with ideal intramolecular hydrogen bonds between the CO adjacent to the nitrogen atom of Pro and the NH of Tyr (γ-turn), between the C(4)O of 3-FlC2 and the OH in the side chain of Tyr, and between the 4aOOH of 3-FlC2 and the COOH in the side chain of Glu/Asp, and these are graphically represented for the Asp-derivative (Fig. 4).

Various flavopeptides were then prepared by a standard solid-phase peptide synthesis method following a Fmoc/*t*Bu protocol using an amine-functionalized PS resin (NH_2-PS) and used as resin-supported variants for evaluating their catalytic activity in FMO-mimetic aerobic oxygenation reactions.

Sulfoxidation is one of the most common aerobic oxygenation reactions that flavoenzymes efficiently catalyze in nature. The aerobic oxidation of thioanisole was used as a test reaction to evaluate the catalytic activities of the flavopeptides under the conditions that were previously developed by our group for reactions with $\mathbf{FlEt^+A^-}$ [10]. As theoretically expected, 3-FlC2-Pro-Tyr-Glu-Ado-NH-PS and 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS (10 mol%) smoothly

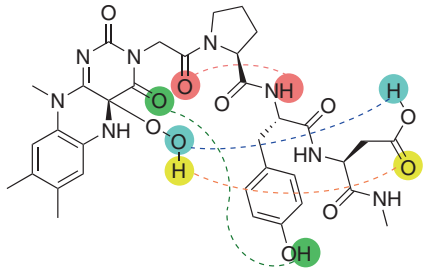


Fig. 4 Graphical representation of the notable hydrogen bonds found in the lowest energy structure of 3-FlC2$_{4a(R)OOH}$-Pro-Tyr-Asp-NHMe estimated by DFT calculations

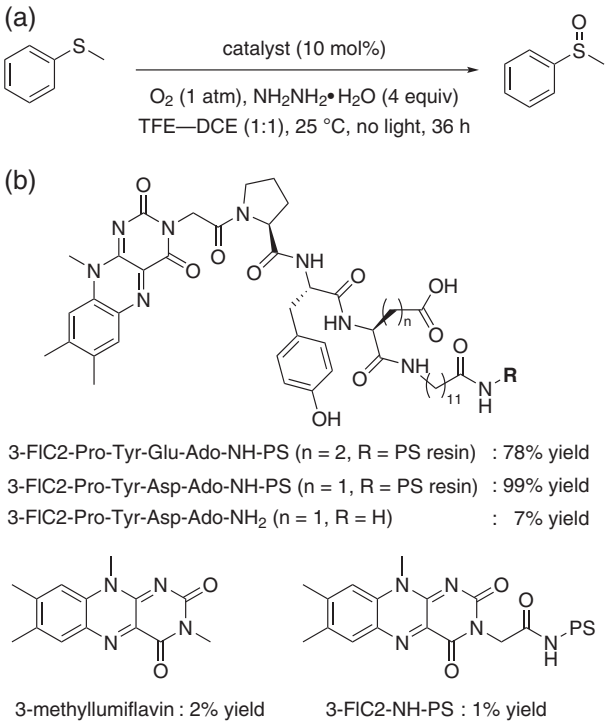


Fig. 5 Flavin-catalyzed aerobic oxidation of thioanisole: **a** reaction conditions, **b** catalysts used and the corresponding yields of methyl phenyl sulfoxide

catalyzed the desired sulfoxidation in the presence of four equivalents of hydrazine monohydrate and 1 atm of O_2 in a 1:1 mixture of TFE and 1,2-dichloroethane (DCE) at 25 °C to give methyl phenyl sulfoxide in 78% yield and 99% yield, respectively, in 36 h without overoxidation to the corresponding sulfone. No significant reactivity was observed when 3-methyllumiflavin or 3-FlC2-NH-PS was used as the catalyst under otherwise identical conditions (Fig. 5). These results, as well as the results of control experiments with various flavopeptides revealed that the Pro-Tyr-Glu and Pro-Tyr-Asp sequences are responsible for the catalytic activity. Notably, 3-FlC2-Pro-Tyr-Asp-Ado-NH_2 exhibited a much lower catalytic activity than 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS (Fig. 5), showing the importance of the hydrophobic PS resin, which causes the flavopeptide to take on an effective conformation. It should also be noted that no reaction occurred in the absence of either TFE, O_2, hydrazine, or flavopeptide, which indicated that all of these components were essential. In addition, successful reactions were conducted while protected from light, so the involvement of singlet oxygen can be ruled out [23, 26]. Moreover, the excellent chemoselectivity, which is one of the features of flavin catalysts, could exclude the participation of a peracid and suggested that $\mathbf{Fl_{4aOOH}}$ served as the major oxidant. A Hammett study for the present aerobic sulfoxidation using 3-FlC2-Pro-Tyr-Glu-βAla-NH-PS gave a ρ value of –1.54, which is similar to that of the stoichiometric oxidation of sulfides with 5-ethyl-4a-hydroperoxy-3-methyllumiflavin ($\mathbf{LFlEt_{4aOOH}}$, $\rho = -1.47$) [59], suggesting that the present oxidation of sulfides took place electrophilically, and the conjugated peptide-stabilized $\mathbf{Fl_{4aOOH}}$ served as the active species (Fig. 4).

The Baeyer–Villiger reaction, a synthetically useful oxygenation that converts a ketone into an ester, is also involved in biological processes and can be catalyzed by FMOs known as Baeyer–Villiger monooxygenases [6]. The Baeyer–Villiger oxidation of 3-phenylcyclobutanone into β-phenyl-γ-butyrolactone was used as a test reaction under conditions that were previously developed by our group for the reaction catalyzed by $\mathbf{FlEt^+A^-}$ [60]. In the presence of 5 mol% of 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS, 1 atm of O_2, 20 equivalents of H_2O, and 3.5 equivalents of zinc dust in a mixed solvent of acetonitrile, toluene, and ethyl acetate (8:4:1), the desired oxidation proceeded smoothly to afford the target product in 72% yield in 7 h (Fig. 6). As expected, 3-methyllumiflavin and 3-FlC2-NH-PS were completely inactive under the same reaction conditions (Fig. 6).

The Baeyer–Villiger oxidation with 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS was found to be highly chemoselective, similar to the reaction with FMO. We carried out the reaction with 3-phenylcyclobutanone as a substrate in the presence of an equimolar amount of another reactive substrate such as an olefin or a sulfide. When used as a competitor, cyclooctene remained intact during the desired conversion of the ketone, whereas the preferential formation of cyclooctene oxide does occur under *m*CPBA-based conditions (Fig. 7). Such excellent chemoselectivity was also observed in a competitive oxygenation of the ketone and thioanisole. These results strongly suggested that a peracid did not participate in the reaction.

As a consequence, the first **Fl**-catalyzed aerobic oxygenation reactions under apoenzyme-free conditions were realized using the resin-supported flavopeptide, 3-FlC2-Pro-Tyr-Asp-Ado-NH-PS. The reactivities of the corresponding $\mathbf{Fl_{4aOOH}}$ could be orthogonally controlled by reductants and reaction conditions, and electrophilic sulfoxidations, as well

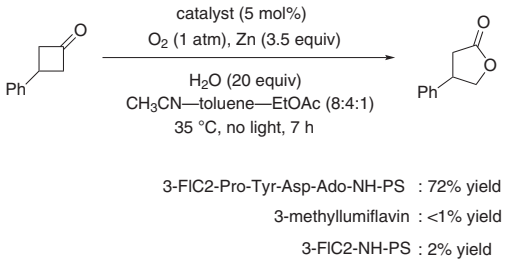


Fig. 6 Flavin-catalyzed Baeyer–Villiger oxidation

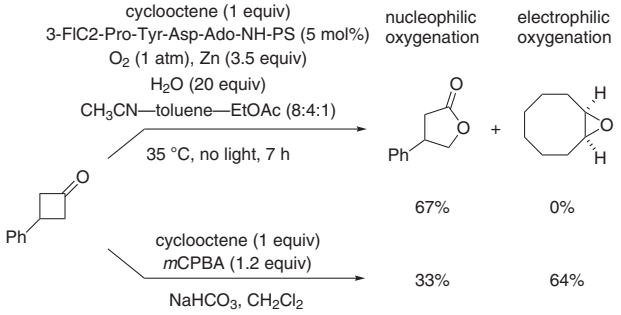


Fig. 7 Evaluation of the chemoselectivity in the Baeyer–Villiger oxidation

as nucleophilic Baeyer–Villiger oxidations could be achieved in a highly chemoselective manner. However, these reactions were not enantioselective despite the chirality of the peptide. The development of asymmetric oxygenation reactions with flavopeptidic catalysts designed in a more elaborated manner is currently underway in our laboratory.

Conclusion

Some challenging issues in the development of flavin catalysts were solved with our simple but elaborated strategies that utilize polymers as a key tool. First, the preparation of **FlEt$^+$A$^-$** catalysts from **Fl**, which previously required inert conditions and hazardous or expensive chemicals, was dramatically simplified by utilizing commercially available cation-exchange resins to install counter anion A^- [35]. Next, a series of insoluble polystyrene-supported **Fl** species bearing different pendant groups were readily prepared from a novel **Fl**-containing vinyl monomer, and these compounds exhibited higher catalytic activities than the conventional homogeneous **Fl** catalyst and excellent reusability in the aerobic reduction of olefins with the in situ-generated diimide from hydrazine [36]. Finally, the first **Fl**-catalyzed aerobic oxygenation reactions under nonenzymatic conditions were achieved by means of the resin-supported flavopeptide catalyst that was designed theoretically [37]. Studies based on such interactions between flavin catalysts and polymers are currently being further expanded toward new developments in both fundamental catalysis and practical applications.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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