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Non-covalently dendronized flavins as organocatalysts for aerobic reduction of olefins

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ABSTRACT

A variety of association complexes of synthetic flavin with diaminopyridine and melamine receptors are described in terms of synthesis, association properties, and catalytic activities for aerobic hydrogenation of olefins. The 1:1 association complex of lumiflavin **1** with 2,6-bis(acylamino)pyridine receptor bearing 3,4,5-trialkoxybenzyl ether dendron unit **2** acts as an efficient supramolecular organocatalyst for the aerobic reduction of styrene at ambient temperature under atmospheric air pressure.

1. Introduction

Flavin is a model compound of various flavin-containing oxidases[1] and monooxygenases[2] that has attracted much attention as an environmentally benign organocatalyst for aerobic oxidative organic transformations.[3,4] Fig. 1 shows a common catalytic cycle for aerobic oxidative transformation with flavoenzymes and synthetic flavins. Reduction of oxidized flavin (Fl_{ox}) to the reduced flavin (Fl_{red}) and subsequent O_2 incorporation affords 4a-hydrodioxyflavin (FlOOH). This species undergoes dissociation of H_2O_2 or oxygen transfer to substrates (S) to regenerate Fl_{ox}. Oxidases employ the first dehydrogenation process as a crucial step for oxidative transformation.[1] Simulation of these enzymatic functions with neutral[5] and cationic[6] flavin catalysts provides the dehydrogenative transformation of alcohols,[5a,b,e] amines,[5e,6a] hydrazines,[6b] thiols,[5c,d] NADH model compounds,[5d] and nitroalkanes.[5c] Monooxygenases promote oxygen transfer to the substrate with FlOOH.[2] The aerobic oxygenation of various heteroatom compounds including amines,[7a,c] sulfides,[7a,c] and ketones[7b] can be also performed using this catalytic process with the synthetic flavin catalysts under O_2 atmospheric pressure.

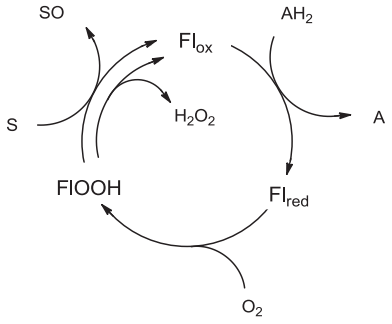

Fig. 1. Catalytic cycle for oxidative transformations with flavoenzymes and synthetic flavins.

In 2005, we reported that a series of synthetic flavins act as efficient catalysts for generation of the reducing agent diimide NH=NH,[8] using these aerobic and anaerobic processes for the oxidation of hydrazine. This principle can be applied to provide a convenient method for the aerobic reduction of olefins that proceeds under mild conditions of 1 atm of molecular oxygen or air (Eq. 1).[9] The catalytic hydrogenation of olefins can be performed with a small amount of hydrazine, 1 atm of O_2 or air, and an organocatalyst, to produce water and nitrogen gas as the sole waste products. This is a useful alternative to transition-metal catalysts and H_2 gas[10] with

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respect to atom efficiency and safety. As part of our program, which is aimed at the formation of new organic functional materials, we have investigated the development of efficient organocatalysts enhanced by molecular association and aggregation. Association complexes of neutral flavins with 2,6-bis(acylamino)pyridines bearing poly(benzyl ether) dendron units act as efficient supramolecular organocatalysts for aerobic reduction.[9c]

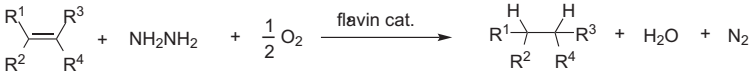
In an attempt to produce novel enzyme-like catalytic functions, we have been investigating the association properties and catalytic activities of new supramolecular flavin complexes with a variety of 2,6-bis(acylamino)pyridine and melamine (1,3,5-triazine-2,4,6-triamine) receptors. This has lead to association complexes of lumiflavin (**1**) with 2,6-bis(acylamino)pyridine doubly-linked to a poly(3,4,5-trisubstituted benzyl ether)dendron unit bearing long alkoxy chains as terminal groups (**2**), which are efficient supramolecular organocatalysts for the aerobic oxidation of olefins. The catalytic activity is much higher than those of non-associated **1** or its association complexes with non-dendronized receptors **3**–**5** (Scheme 1). This is a rare example of an organocatalyst that is enhanced by the hydrogen-bonding association of organic molecules, although a variety of metallic[11] and non-metallic dendrimers[12] have been widely used as catalysts for organic transformation. Rotello and colleagues reported that neutral flavins covalently linked to a benzyl ether dendron unit at the 3-position exhibit high catalytic activity for the aerobic oxidation of 1-benzyl-1,4-dihydronicotinamide in water.[13] The present strategy is an alternative, unique supramolecular approach to the development of next-generation artificial flavoenzymes. In this paper, we describe the full details of the synthesis and characterization of the supramolecular flavin complexes, with focus on the dynamic association behavior and catalytic activity for the aerobic reduction of olefins in air under mild conditions.

2. Results and discussion

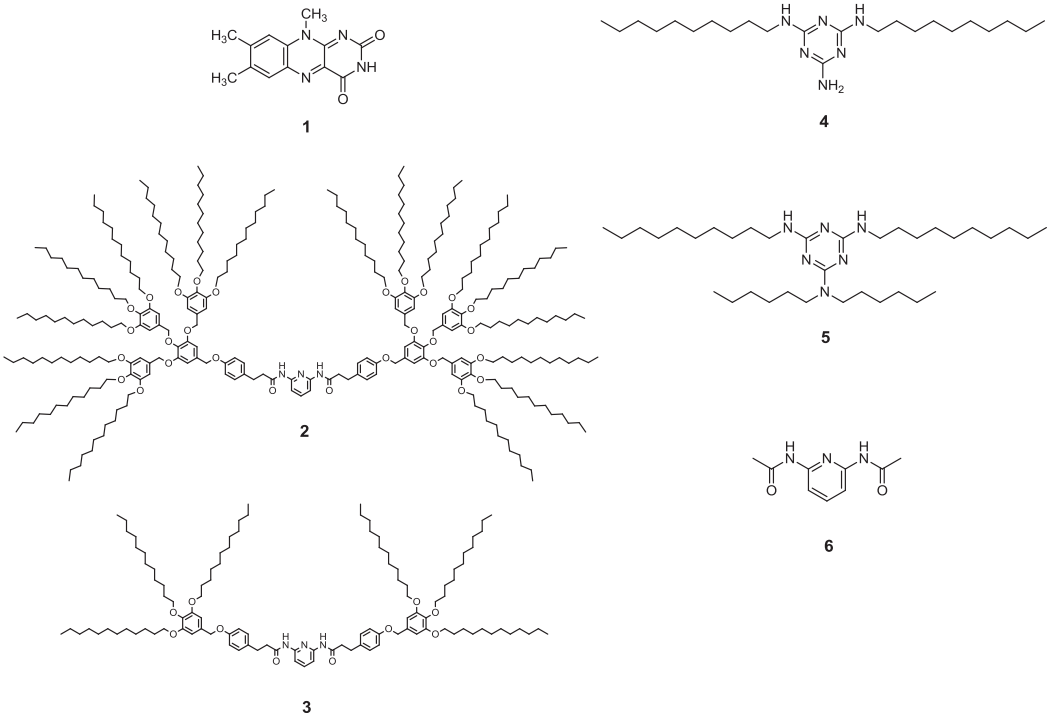
2.1. Synthesis and characterization of association complexes of lumiflavin

The synthetic routes to 2,6-diaminopyridines **2** and **3**, and to melamine derivatives **4** and **5** are shown in Fig. 2. Dendronized bis(acylamino)pyridine **2** and its non-dendronized analogue **3** were prepared by the reaction of 2,6-bis[3-(4-hydroxyphenyl)propanoylamino]pyridine (**9**) with the corresponding dendritic and nondendritic 3,4,5-trisubstituted benzyl halides (**8** and **7**), respectively, in the presence of K_2CO_3 in acetone. N^2,N^4-Didecyl-1,3,5-triazine-2,4,6-triamine (**4**) was prepared by the reaction of 2,4,6-trichloro-1,3,5-triazine (**10**) with decylamine and subsequent amination of the resulting 6-chloro-N^2,N^4-didecyl-1,3,5-triazine-2,4-diamine (**11**) with ammonium hydroxide in aqueous solution. N^2,N^4-Didecyl-N^6,N^6-dihexyl-1,3,5-triazine-2,4,6-triamine (**5**) was prepared by amination of **11** with dihexylamine.

The association properties of lumiflavin **1** with receptors **2**–**5** and 2,6-bis(acetylamino)pyridine (**6**) were examined in $CDCl_3$ using ^{1}H NMR (270 MHz) analysis. Job's plots for the association of **1** with **4** indicated that flavin **1** forms a 1:1 complex with 2,6-diaminopyridine receptors (Fig. 3). The association constants K_a for complexes **1**·**2**, **1**·**3**, **1**·**4**, and **1**·**5** in $CDCl_3$ at 303 K were determined to be 306, 341, and 387, and 30 M^{-1}, respectively, on the basis of the concentration dependence of the ^{1}H NMR chemical shift of the N(3)H proton signal (Fig. 4). The K_a values for receptors **2**–**4** are in the range of 306–387 M^{-1}, which are similar to that with less bulky receptor **6** (437 M^{-1}).[9c] This result strongly suggests that lumiflavin **1** is sufficiently associated with these receptors via typical 3-point hydrogen bonding, as shown in Scheme 2. It is reasonable to assume that asymmetrical didodecylaminotriazine **4**



(1)



Scheme 1. Lumiflavin **1** and receptors **2**–**6**.

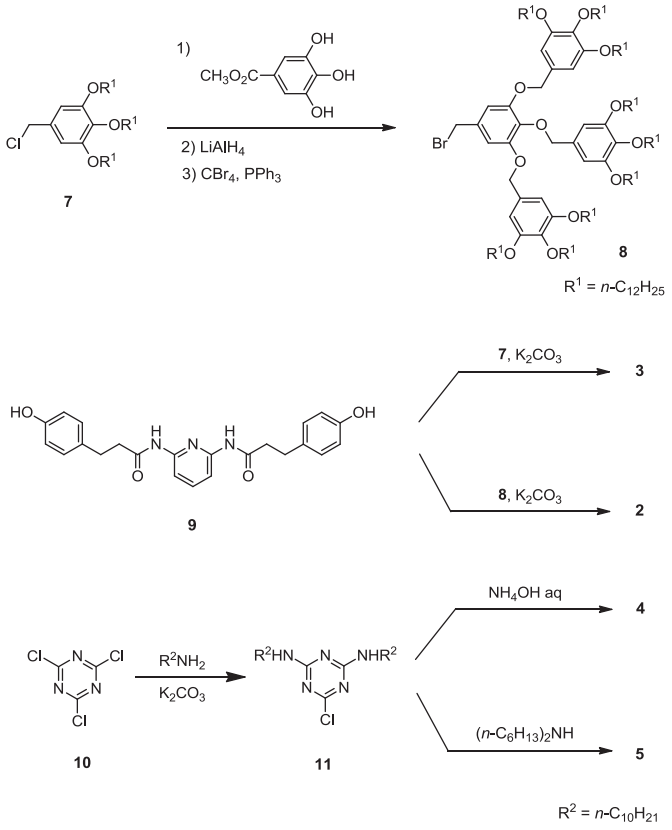


Fig. 2. Synthetic routes for **2**–**5**.

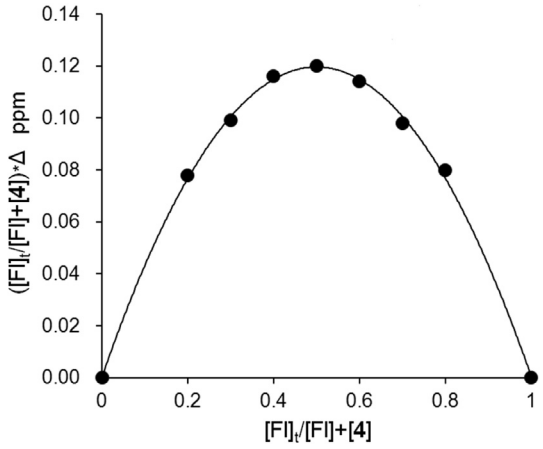


Fig. 3. Continuous variation plot (Job's plot) derived from the ^{1}H NMR data for **1** and receptor **4** in $CDCl_3$ at 303 K. [**1**]+[**4**]=3.13×10^{-4} M.

is bound with **1** at a less bulky binding site including 2-amino and 6-decylamino groups, as depicted in Scheme 2b, because the association at the much more bulky binding site including 2- and 4-decylamino groups generates steric congestion, as clearly evidenced by the low K_a (30 M^{-1}) of the **1**·**5** complex.

Fig. 5 shows the change in the ^{1}H NMR chemical shift of the 7-CH_3 proton signals for **1** with variation in the concentrations of **2**, **3**, and **6**. Nondendritic receptors **3** and **6** exhibit a typical downfield shift of the 7-CH_3 proton signal with increase in the concentration of the receptors. This phenomenon can be ascribed to a decrease in the electron density of the flavin rings by the hydrogen-bonding association. In contrast, a significant upfield shift is observed for similar treatment with dendritic receptor **2**. This unusual upfield shift can be rationalized by assuming a remote shielding effect of the aromatic rings of **2**, which overcomes the original deshielding effect of the hydrogen-bonding associations. Thus, the 7-CH_3 group of associated **1** in complex **1**·**2** is located closely to the 3,4,5-trialkoxyphenyl groups of **2**, as shown in Scheme 2a, which indicates that an enzyme-like, deep cavity for the catalytic reaction is generated in this association complex.

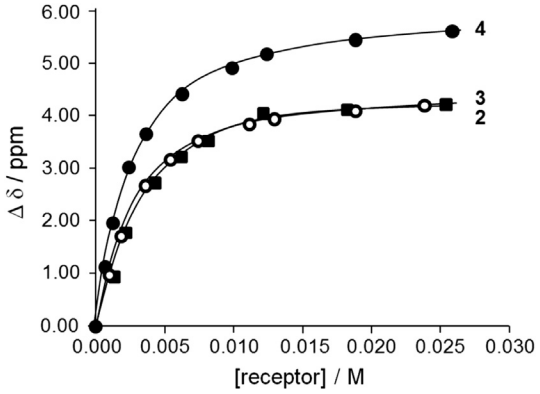
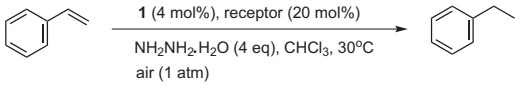


Fig. 4. Change in ^{1}H NMR chemical shift of the N(3)H proton signal for **1** as a function of the receptor concentration; **2** (○), **3** (■), and **4** (●) in $CDCl_3$ at 303 K. [**1**]$_0$=2.09×10^{-4} (for **2**), 2.11×10^{-4} (for **3**), and 1.49×10^{-4} (for **4**) M.

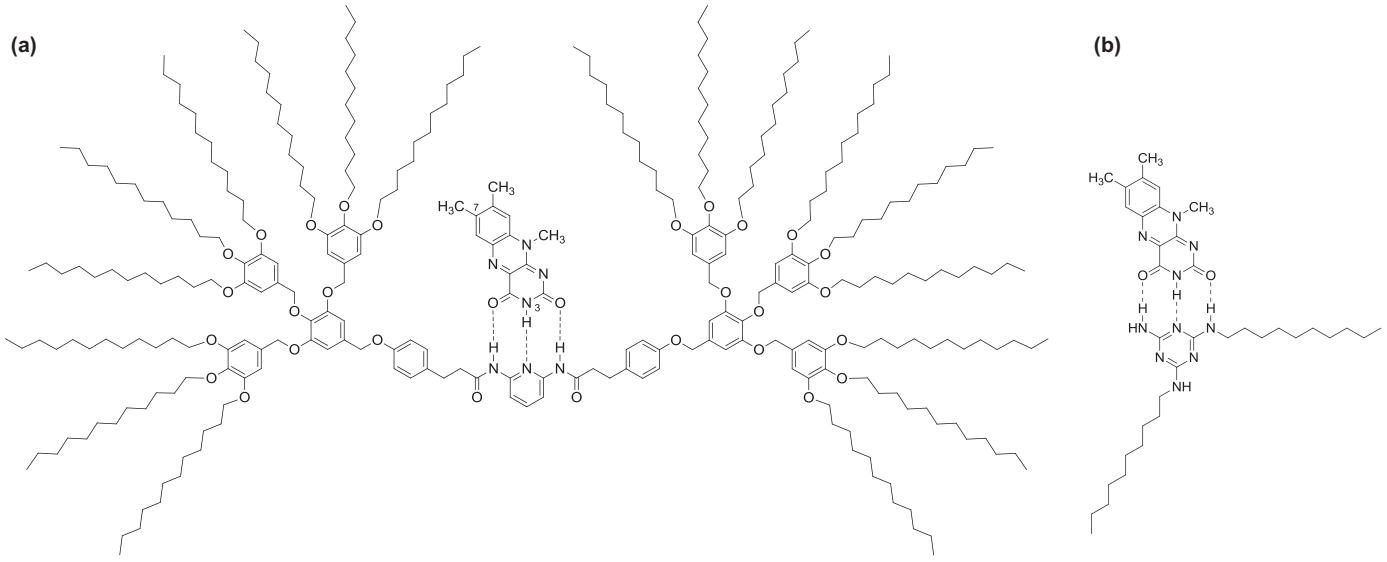
2.2. Aerobic reduction of styrene with supramolecular flavin catalysts

The catalytic activities of various supramolecular flavin catalysts for the reduction of styrene with $NH_2NH_2\cdot H_2O$ (4 equiv) in the presence of flavin catalyst (4 mol %) and various 2,6-diaminopyridine receptors (20 mol %) in $CHCl_3$ were examined at 30 °C and under air at atmospheric pressure (Eq. 2). The yields of the ethylbenzene product were periodically determined by gas–liquid chromatography (GLC) analysis using an internal standard (decane). Fig. 6 shows the reaction profiles for the aerobic reduction of styrene with supramolecular lumiflavin catalyst with various dendritic and nondendritic receptors **2**–**5**. The flavin–dendrimer association complex **1**·**2** exhibits a significant acceleration effect, while the nondendritic analogue **1**·**3** also shows better catalytic activity than non-associated lumiflavin **1**. However, the positive effect of receptors **2** and **3** is not observed for reduction with receptors **4** and **5**.



(2)

The present flavin-catalyzed aerobic reduction can be rationalized by the consecutive anaerobic and aerobic processes shown in Scheme 3. Lumiflavin **1** undergoes nucleophilic attack and a subsequent 1,3-hydrogen shift to give the reduced flavin–diimide complex **12**. The active diimide in **12** reacts with styrene to afford ethylbenzene as the product with the liberation of nitrogen gas and reduced flavin **13**. The incorporation of O_2 into **13** gives 4a-hydrodioxyflavin **14**, which performs oxygen transfer to a second NH_2NH_2 molecule to afford the flavin–diimide complex **15**. Diimide reduction of the second olefin with **15** regenerates **1** to complete the catalytic cycle. Kinetic studies on the reduction of 5-decene with catalyst **1** revealed that the nucleophilic attack of NH_2NH_2 to **1** is the rate-determining step for the overall process.[9c]



Scheme 2. Proposed major binding mode of the (a) **1**·**2** and (b) **1**·**4** complexes.

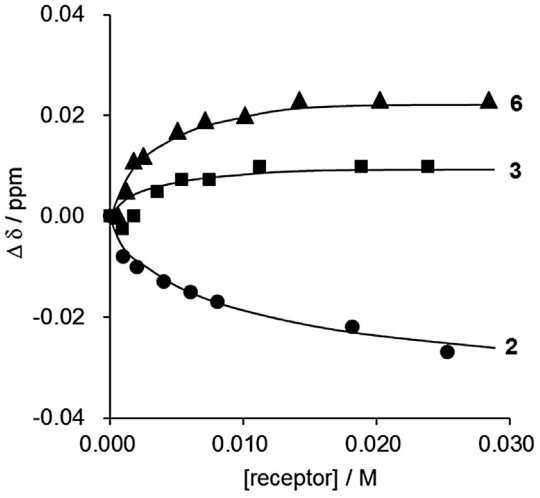


Fig. 5. Change in the ^{1}H NMR chemical shift of the 7-CH_3 signals for lumiflavin **1** as a function of the receptor concentration; **2** (●), **3** (■), and **6** (▲) in $CDCl_3$ at 303 K. $[\mathbf{1}]_0=4.00\times10^{-4}$ M.

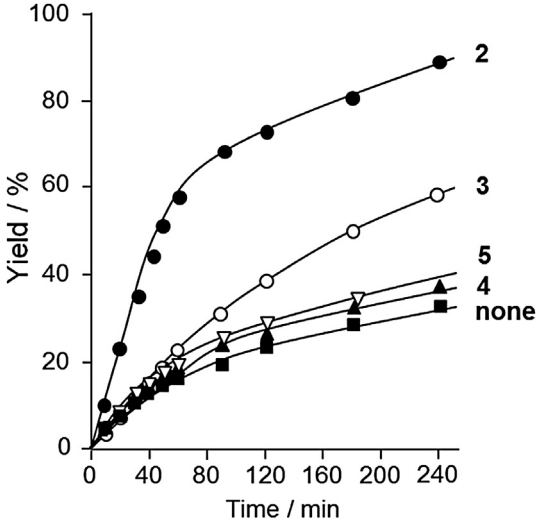
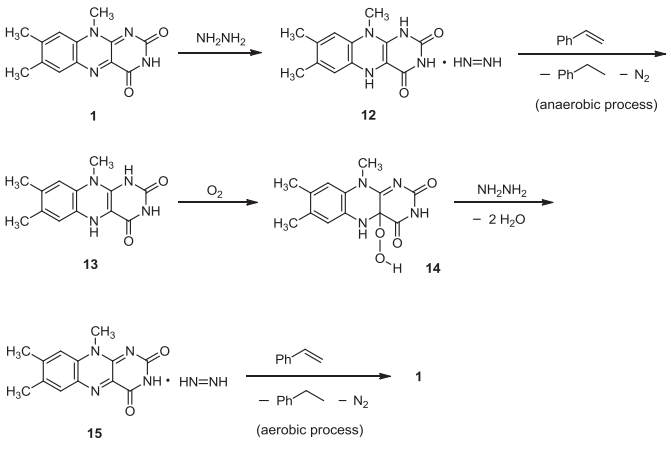


Fig. 6. Time dependence of the product yields for the flavin-catalyzed aerobic reduction of styrene. Conditions: styrene (6.3×10^{-2} M), $NH_2NH_2\cdot H_2O$ (2.5×10^{-1} M), flavin catalyst **1** (2.5×10^{-3} M), additional receptor **2**–**5** (1.25×10^{-2} M), $CHCl_3$, 30 °C. Product yields were determined by GLC analysis based on an internal standard (decane).

The positive effect of dendritic receptor **2** on this catalytic reaction can be ascribed to the acceleration of the rate-determining NH_2NH_2 addition, as shown in Fig. 7. Complex **1**·**2** could include several NH_2NH_2 molecules inside the cavity of 3,4,5-trialkoxyphenyl units through hydrogen bonding interaction. This induces a high concentration of NH_2NH_2 around the reactive 4a-position of associated **1**, which leads to an acceleration of the second-order addition of NH_2NH_2. Such an equilibrated inclusion–addition process of NH_2NH_2 would be much faster than the ordinary nucleophilic addition of free NH_2NH_2 to non-associated **1**. The slight acceleration effect of non-dendritic receptor **3** (Fig. 6) is also attributed to the significant inclusion abilities of trialkoxyphenyl groups. Therefore, the effect of the dendritic receptor is the result of collaborative effects of outer and inner alkoxides toward the capture, penetration, and holding of NH_2NH_2 in the reactive cavity of the catalytically active species. Internal alkenes, such as more bulky stilbene do not react under the present conditions. This would arise from specific catalytic activities of the dendrimer–flavin supramolecular catalysts, which can discriminate the bulky substrate with high shape selectivity.



Scheme 3. Mechanism for the aerobic reduction of styrene with catalyst **1**.

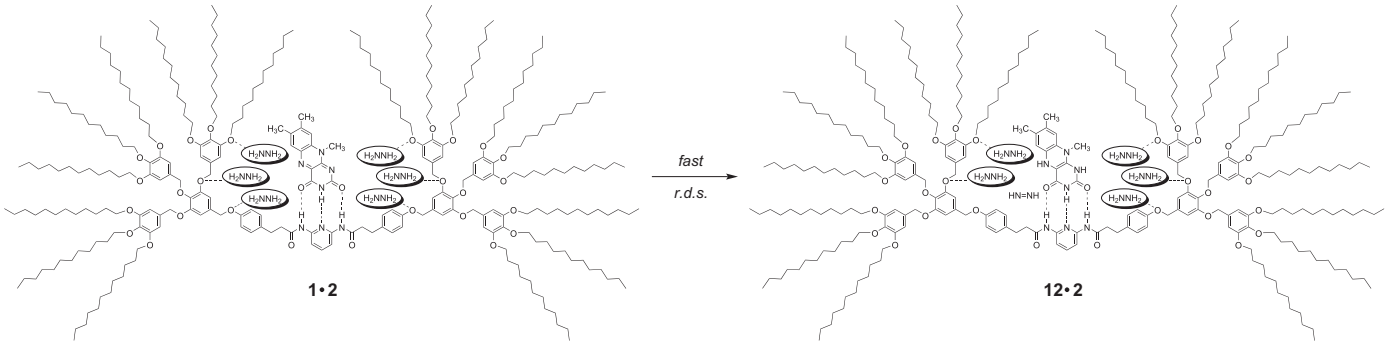


Fig. 7. Schematic representation of the effect of NH_2NH_2 concentration on the rate-determining formation of flavin–diimide active intermediates.

3. Conclusions

We have found that the association complex of lumiflavin **1** with dendritic 2,6-bis(acylamino)pyridine receptor **2** bearing 3,4,5-trialkoxybenzyl dendron units act as a highly efficient supramolecular organocatalyst for the aerobic reduction of olefins at ambient temperature under atmospheric pressure. Systematic studies on the association properties and catalytic effects of various receptors revealed that 3,4,5-tribenzyloxy unit and its dendritic structure is the key to enhancing catalytic activity. This is a rare case of a supramolecular organocatalyst that provides significant enhancement of the catalytic activity by association with enzyme-like receptors bearing high inclusion properties.

4. Experimental section

4.1. General

NMR spectra were obtained on Jeol JNM-GSX270 and Varian Unity-Inova 500 spectrometers. IR spectra were recorded on a Bruker EQUINOX 55/s. Mass spectra were obtained on a Jeol JMS-DX303HF mass spectrometer. Elemental analyses were carried out on a J-Science Lab JM10 micro corder. GLC analyses were conducted on a Shimadzu GC-18A using a DB-1 glass capillary column (0.25 mm×30 m).

4.2. Materials

Commercially available methyl 3,4,5-trihydroxybenzoate, 1-bromododecane, 2,6-diaminopyridine, 2,4,6-trichloro-1,3,5-triazine (**9**), decylamine, dihexylamine, and $NH_2NH_2·H_2O$ were used without further purification. 7,8,10-Trimethylisoalloxazine (lumiflavin, **1**)[7c] and 2,6-bis[3-(4-hydroxyphenyl)propanoylamino]pyridine (**9**)[9c] were prepared according to procedures given in the literature.

4.2.1. Preparation of methyl 3,4,5-tridodecyloxybenzoate.[14] A mixture of methyl 3,4,5-trihydroxybenzoate (1.84 g, 10.0 mmol), 1-bromododecane (7.44 mL, 31.0 mmol), and K_2CO_3 (13.4 g, 97.0 mmol) was stirred in DMF (60 mL) for 5 h at 70 °C. After the reaction mixture was poured into water, the resulting precipitate was collected by filtration and subjected to column chromatography (SiO_2, $CHCl_3$) to afford the product ester (6.28 g, 91%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 9H, CH_3), 1.20–1.40 (m, 48H), 1.43–1.53 (m, 6H), 1.74 (tt, J=7.2, 7.2 Hz, 2H, $-OCH_2CH_2-$), 1.81 (tt, J=7.2, 7.2 Hz, 4H, $-OCH_2CH_2-$), 3.89 (s, 3H, OCH_3), 4.007 (t, J=7.2 Hz, 4H, $-OCH_2-$), 4.014 (t, J=7.2 Hz, 2H, $-OCH_2-$), 7.25 (s, 2H, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 22.7, 26.04, 26.07, 29.30, 29.35, 29.38, 29.55, 29.62, 29.65, 29.68, 29.71, 29.74, 30.3, 31.91, 31.93, 52.1, 69.2, 73.5, 108.0, 124.6, 152.8, 166.9; MS (FAB) m/z 689 [M^+].

4.2.2. Preparation of 3,4,5-tridodecyloxybenzyl alcohol.[14] A mixture of methyl 3,4,5-tridodecyloxybenzoate (6.15 g, 8.92 mmol) and $LiAlH_4$ (0.406 g, 10.7 mmol) was stirred in dry THF (20 mL) for 1 h at room temperature. After the reaction was quenched with excess $Na_2SO_4·10H_2O$, the resulting mixture was filtered, dried over $MgSO_4$, and evaporated under reduced pressure to give the product alcohol (5.49 g, 93%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 9H, CH_3), 1.17–1.39 (m, 48H), 1.39–1.54 (m, 6H), 1.69–1.84 (m, 6H, $-OCH_2CH_2-$), 3.93 (t, J=6.6 Hz, 2H, $-OCH_2-$), 3.97 (t, J=6.6 Hz, 4H, $-OCH_2-$), 4.59 (s, 2H, CH_2OH), 6.56 (s, 2H, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 22.7, 26.09, 26.13, 29.35, 29.38, 29.41, 29.61, 29.65, 29.69, 29.72, 29.74, 30.32, 31.91, 31.93, 65.7, 69.1, 73.4, 105.4, 136.0, 137.6, 153.3.

*4.2.3. Preparation of 3,4,5-tridodecyloxybenzyl chloride (**7**).*[14] A mixture of 3,4,5-tridodecyloxybenzyl alcohol (5.49 g, 8.30 mmol), thionyl chloride (0.844 mL, 11.6 mmol), and DMF (0.10 mL) was stirred in CH_2Cl_2 (55 mL) for 30 min at room temperature. Removal of the solvent and excess thionyl chloride under reduced pressure gave **7** (5.20 g, 92%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 9H, CH_3), 1.15–1.40 (m, 48H), 1.40–1.54 (m, 6H, $-O(CH_2)_2CH_2-$), 1.73 (tt, J=7.2, 7.2 Hz, 2H, $-OCH_2CH_2-$), 1.79 (tt, J=7.2, 7.2 Hz, 4H, $-OCH_2CH_2-$), 3.94 (t, J=7.2 Hz, 2H, $-OCH_2-$), 3.97 (t, J=7.2 Hz, 4H, $-OCH_2-$), 4.51 (s, 2H, CH_2Cl), 6.56 (s, 2H, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1, 22.7, 26.08, 26.11, 29.35, 29.37, 29.39, 29.60, 29.63, 29.65, 29.69, 29.72, 29.74, 30.32, 31.92, 31.94, 47.0, 69.1, 73.4, 107.1, 132.3, 153.2.

4.2.4. Preparation of methyl 3,4,5-tris(3,4,5-tridodecyloxybenzyloxy) benzoate.[15] A mixture of methyl 3,4,5-trihydroxybenzoate (1.03 g, 5.59 mmol), **7** (11.4 g, 16.8 mmol), and K_2CO_3 (6.95 g, 50.3 mmol) was stirred in DMF (80 mL) for 5 h at 70 °C. After the reaction mixture was poured into water, the resulting precipitate was collected by filtration and subjected to column chromatography (SiO_2, $CHCl_3$) to afford the product ester (10.7 g, 91%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 27H, CH_3), 1.17–1.52 (m, 162H), 1.62–1.82 (m, 18H), 3.75 (t, J=6.6 Hz, 4H, $-OCH_2-$), 3.88 (s, 3H, $-OCH_3$), 3.88 (t, J=6.6 Hz, 10H, $-OCH_2-$), 3.93 (t, J=6.6 Hz, 4H, $-OCH_2-$), 5.03 (s, 4H, ArCH_2OR), 5.04 (s, 2H, ArCH_2OR), 6.60 (s, 2H, ArH), 6.63 (s, 4H), 7.38 (s, 2H, ArH).

4.2.5. Preparation of 3,4,5-tris(3,4,5-tridodecyloxybenzyloxy)benzyl alcohol.[15] A mixture of methyl 3,4,5-tris(3,4,5-tridodecyloxybenzyloxy)benzoate (10.7 g, 5.06 mmol) and $LiAlH_4$ (1.77 g, 46.6 mmol) was stirred in dry THF (100 mL) for 2 h at room temperature. After the reaction was quenched by the addition of aqueous NaOH solution, the

resulting mixture was filtered, dried over $MgSO_4$, and evaporated under reduced pressure to give the product alcohol (9.06 g, 85%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 27H, CH_3), 1.16–1.52 (m, 162H), 1.65–1.80 (m, 18H), 3.77 (t, J=6.4 Hz, 4H, −OCH_2−), 3.87 (t, J=6.4 Hz, 8H, −OCH_2−), 3.88 (t, J=6.4 Hz, 2H, −OCH_2−), 3.92 (t, J=6.4 Hz, 4H, −OCH_2−), 4.57 (s, 2H, ArCH_2OR), 4.97 (s, 2H, ArCH_2O), 5.01 (s, 4H, ArCH_2OR), 6.61 (s, 4H, ArH), 6.63 (s, 2H), 6.66 (s, 2H, ArH); MS (FAB) m/z 2084 [M^+].

*4.2.6. Preparation of 3,4,5-tris(3,4,5-tridodecyloxybenzyloxy)benzyl bromide (**8**).* A mixture of 3,4,5-tris(3,4,5-tridodecyloxybenzyloxy) benzyl alcohol (1.04 g, 0.499 mmol), CBr_4 (0.413 g, 1.25 mmol), and PPh_3 (0.327 g, 1.25 mmol) was stirred in dry THF (8 mL) for 3.5 h at room temperature under an argon atmosphere. The reaction mixture was extracted with CH_2Cl_2 and water, and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography (SiO_2, hexane/EtOAc=10:1) to afford **8** (0.637 g, 60%) as a colorless solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 27H, CH_3), 1.17–1.52 (m, 162H), 1.65–1.80 (m, 18H), 3.76 (t, J=6.4 Hz, 4H, −OCH_2−), 3.88 (t, J=6.4 Hz, 8H, −OCH_2−), 3.92 (t, J=6.4 Hz, 6H, −OCH_2−), 4.38 (s, 2H, −CH_2Br), 4.96 (s, 2H, 4-(ArCH_2O)Ar), 4.99 (s, 4H, 3,5-(ArCH_2O)$_2$Ar), 6.60 (s, 4H, ArH), 6.67 (s, 2H, ArH), 7.26 (s, 2H, ArH); MS (FAB) m/z 2146 [M^+].

*4.2.7. Preparation of 2,6-bis(3-{4-[3,4,5-tris(3,4,5-tridodecyloxybenzyloxy)benzyloxy]phenyl}propanoylamino)pyridine (**2**).* A mixture of **8** (430 mg, 0.200 mmol), **9** (38.6 mg, 0.095 mmol), and K_2CO_3 (79.0 mg, 0.572 mmol) was refluxed in acetone (7 mL) for 24 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$ and water, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography (Al_2O_3, CH_2Cl_2) gave **2** (351 mg, 81%) as a colorless solid. Mp 75–76 °C; IR (KBr) 2954, 2924, 2851, 1681, 1591, 1505, 1465, 1436, 1368, 1336, 1237, 1117, 996, 810 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.90 (m, 54H, CH_3), 1.20–1.50 (m, 324H), 1.66–1.77 (m, 36H), 2.64 (t, J=7.7 Hz, 4H, CH_2CH_2CONH), 2.99 (t, J=7.7 Hz, 4H, CH_2CH_2CONH), 3.77 (t, J=6.4 Hz, 8H), 3.84–3.90 (m, 40H), 3.92 (t, J=6.4 Hz, 8H), 4.89 (s, 4H), 4.97 (s, 4H), 5.00 (s, 8H), 6.61 (s, 8H, ArH), 6.62 (s, 4H, ArH), 6.72 (s, 4H, ArH), 6.87 (d, J=8.6 Hz, 4H, ArH), 7.14 (d, J=8.6 Hz, 4H, ArH), 7.52 (br, 2H, NH), 7.70 (dd, J=8.3, 8.3 Hz, 1H, PyH), 7.90 (d, J=8.3 Hz, 2H, PyH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.7, 26.15, 26.16, 26.19, 26.20, 26.21, 29.36, 29.37, 29.38, 29.44, 29.48, 29.49, 29.68, 29.72, 29.75, 30.2, 30.38, 30.41, 31.9, 39.5, 68.9, 69.0, 70.2, 71.7, 73.28, 73.36, 75.2, 105.57, 105.63, 106.3, 107.7, 109.5, 115.0, 129.2, 132.1, 132.7, 132.8, 132.9, 137.7, 137.8, 138.3, 149.3, 153.00, 153.02, 153.2, 157.3, 170.4. Anal. Calcd for $C_{295}H_{503}N_3O_{28}$: C, 78.04; H, 11.17; N, 0.93. Found: C, 77.88; H, 11.04; N, 0.88.

*4.2.8. Preparation of 2,6-bis{3-[4-(3,4,5-tridodecyloxybenzyloxy) phenyl]propanoylamino}pyridine (**3**).* A mixture of **7** (143 mg, 0.210 mmol), **9** (40.5 mg, 0.100 mmol), and K_2CO_3 (82.9 mg, 0.600 mmol) was refluxed in acetone (4.0 mL) for 24 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$ and water, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography (Al_2O_3, CH_2Cl_2) gave **3** (74.7 mg, 44%) as a colorless solid. Mp 53–54 °C; IR (KBr) 2955, 2923, 2851, 1685, 1591, 1512, 1458, 1379, 1334, 1299, 1244, 1117, 1015 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 18H, CH_3), 1.15–1.50 (m, 96H), 1.41–1.51 (m, 12H), 1.66–1.87 (m, 12H), 2.66 (t, J=7.7 Hz, 4H, CH_2CH_2CONH), 2.99 (t, J=7.7 Hz, 4H, CH_2CH_2CONH), 3.94 (t, J=6.6 Hz, 4H), 3.96 (t, J=6.6 Hz, 8H), 4.90 (s, 4H), 6.60 (s, 4H, ArH), 6.90 (d, J=8.8 Hz, 4H, ArH), 7.14 (t, J=8.8 Hz, 4H, ArH), 7.52 (br, 2H, NH), 7.69 (dd, J=8.3, 8.3 Hz, 1H, PyH), 7.87 (br, 2H, PyH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.68, 22.69, 29.36, 29.39, 29.4, 29.64, 29.69, 29.73, 29.75, 30.27, 30.34, 31.9, 39.6, 69.2, 70.5, 73.4, 106.16, 106.21, 109.4, 115.0, 129.3, 131.9, 132.7, 138.0, 149.2, 153.3, 157.5, 170.6; Anal. Calcd for $C_{109}H_{179}N_3O_{10}$: C, 77.39; H, 10.67; N, 2.48. Found: C, 77.07; H, 10.81; N, 2.37.

*4.2.9. Preparation of 6-chloro-N^2,N^4-didecyl-1,3,5-triazine-2,4-diamine (**11**).*[16] A mixture of **10** (0.555 g, 3.01 mmol), decylamine (0.944 g, 6.00 mmol), and K_2CO_3 (1.00 g, 7.26 mmol) was stirred in acetone (4.1 mL) for 15 h at 60 °C. The reaction mixture was extracted with $CHCl_3$ and water, and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was washed with a small portion of acetone to afford **11** (0.629 g, 49%) as a colorless solid. IR (KBr) 3254, 3120, 2957, 2920, 2851, 1641, 1557, 1468, 1410, 1363, 1107 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 6H, CH_3), 1.19–1.41 (m, 28H), 1.50–1.63 (m, 4H, NCH_2CH_2−), 3.27–3.43 (m, 4H, −CH_2N−), 5.87 (br, 2H, −NH); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 14.7, 23.3, 27.4, 29.90, 29.96, 30.2, 32.5, 41.5, 165.5, 167.9; MS (FAB) m/z 426 [(M+H)$^+$].

*4.2.10. Preparation of N^2,N^4-didecyl-1,3,5-triazine-2,4,6-triamine (**4**).*[17] A mixture of **11** (159 mg, 0.374 mmol) and 30% ammonium hydroxide (3 mL) was stirred in 1,4-dioxane and water (2:1 v/v, 8 mL) for 24 h at 150 °C in an autoclave. After the addition of water (150 mL), the reaction mixture was stirred for 24 h at room temperature. The resulting precipitate was collected by filtration to give **4** (99.8 mg, 66%) as a colorless solid. IR (KBr) 3489, 3385, 3355, 3134, 2955, 2918, 2849, 1679, 1608, 1582, 1526, 1480, 1367 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 6H, CH_3), 1.21–1.39 (m, 28H), 1.54 (tt, J=6.6, 6.6 Hz, 4H, NCH_2CH_2−), 3.24–3.44 (m, 4H, −CH_2N−), 4.70 (br, 4H, −NH); FAB–HRMS (m/z): [M+H]$^+$ calcd for $C_{23}H_{47}N_6$, 407.3862; found 407.3833.

*4.2.11. Preparation of N^2,N^4-didecyl-N^6,N^6-dihexyl-1,3,5-triazine-2,4,6-triamine (**5**).* A mixture of **11** (94 mg, 0.221 mmol) and dihexylamine (0.5 mL, 2 mmol) was refluxed in THF (4 mL) for 24 h. The reaction mixture was extracted with $CHCl_3$ and water, and the organic layer was dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (SiO_2, hexane/EtOAc=4:1) gave **5** (77 mg, 61%) as a colorless solid. IR (KBr) 3342, 2956, 2872, 1542, 1466, 1234, 1167, 1162, 1109, 1076 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.6 Hz, 6H, CH_3), 0.89 (t, J=6.6 Hz, 6H, CH_3), 1.20–1.40 (m, 40H, $CH_3(CH_2)_7$−), 1.45–1.65 (m, 8H, NCH_2CH_2−), 3.32 (dt, J=6.6, 6.6 Hz, 4H, −CH_2N−), 3.45 (t, J=6.6 Hz, 4H, −CH_2N−), 4.66 (br, 2H, −NH); MS (FAB) m/z 575 [(M+H)$^+$].

4.3. Determination of binding stoichiometry for the complexation of 1 with 4

Nine ^{1}H NMR samples were prepared by mixing solutions of **1** (3.13×10^{-4} M) and **4** (3.13×10^{-4} M) in $CDCl_3$ in various ratios of 0:1, 0.2:0.8, 0.3:0.7, 0.4:0.6, 0.5:0.5, 0.6:0.4, 0.7:0.3, 0.8:0.2, and 1:0. The ^{1}H NMR (270 MHz) spectrum of each sample was recorded at 303 K. The change in the chemical shift of N(3)H for the flavin ($\Delta\delta$) was plotted against the mole fraction of the flavin [X=[**1**]/([**1**]+[**4**])], as shown in Fig. 3. A maximum was observed at X=0.5, which indicated the formation of a 1:1 complex.

4.4. Determination of association constants (K_a)

The titration experiment of **1** with dendritic 2,6-diacylaminopyridine receptor **2** is described as a typical example. A solution of **1** in $CDCl_3$ (2.09×10^{-4} M) was titrated in an NMR tube with a solution of **2** in $CDCl_3$ (0–2.53×10^{-2} M) at 303 K. The N(3)H signals of **1** were monitored as a function of the concentration of **2**

to the point at which the change in chemical shift reached saturation, as shown in Fig. 4. The association constant K_a, was calculated to be 306±25 M^{-1} (R^2=0.995) from the obtained isotherms ($\Delta\delta$ N(3)H vs [**2**]) by nonlinear regression analysis using Origin 8.6 based on the following equation:

$$\Delta\delta_{obs} = \frac{\Delta\delta_{max}}{2K_a[\mathbf{1}]_0}\left[1 + K_a[\mathbf{2}]_0 + K_a[\mathbf{1}]_0 - \sqrt{(1 + K_a[\mathbf{2}]_0 + K_a[\mathbf{1}]_0)^2 - 4{K_a}^2[\mathbf{2}]_0[\mathbf{1}]_0}\right]$$

The association constants K_a for complexes **1**·**3**, **1**·**4**, and **1**·**5** in $CDCl_3$ at 303 K were determined to be 341±21 M^{-1} (R^2=0.997), 387±7 M^{-1} (R^2=0.998), and 30±8 M^{-1} (R^2=0.989), respectively, by the same method.

4.5. Aerobic reduction of styrene with supramolecular flavin catalyst

A solution of styrene (0.063 mmol), **1** (0.0025 mmol), receptors **2**–**5** (0.0125 mmol), $NH_2NH_2{\cdot}H_2O$ (0.25 mmol), and decane (internal standard) was stirred in CH_3CN (0.4 mL) at 30 °C in a sealed tube containing 3.14 mL of air. The yields of ethylbenzene were determined by GLC analysis using an internal standard. The reaction profiles are shown in Fig. 6.

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