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Aerobic Reduction of Olefins by In Situ Generation of Diimide with Synthetic Flavin Catalysts

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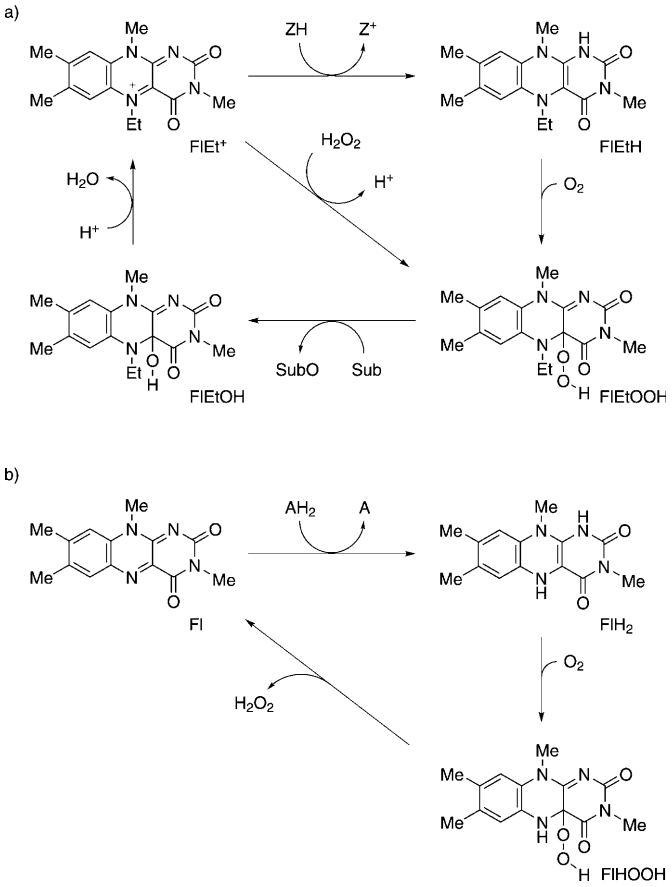
Abstract: A versatile reducing agent, diimide, can be generated efficiently by the aerobic oxidation of hydrazine with neutral and cationic synthetic flavin catalysts **1** and **2**. This technique provides a convenient and safe method for the aerobic reduction of olefins, which proceeds with 1 equiv of hydrazine under an atmosphere of O_2 or air. The synthetic advantage over the conventional gas-based method has been illustrated through high hydrazine efficiency, easy and safe handling, and characteristic chemoselectivity. Vitamin B_2 derivative **6** acts as a highly practical, robust catalyst for this purpose because of its high availability and recyclability. Association complexes of **1b** with dendritic 2,5-bis(acylamino)pyridine **15** exhibit unprecedented catalytic activities, with the reduction of aromatic and hydroxy olefins proceeding significantly faster when a higher-generation dendrimer is used as a host pair for the association catalysts. Contrasting retardation is observed upon similar treatment of non-aromatic or non-hydroxy olefins with the dendrimer catalysts. Control experiments and kinetic studies revealed that these catalytic reactions include two independent, anaerobic and aerobic, processes for the generation of diimide from hydrazine. Positive and negative dendrimer effects on the catalytic reactions have been ascribed to the specific inclusion of hydrazine and olefinic substrates into the enzyme-like reaction cavities of the association complex catalysts.

Keywords: alkenes · dendrimers · host–guest systems · hydrogenation · organocatalysis

Introduction

Flavin-containing oxygenases[1a] and oxidases[1b] catalyze a variety of oxidative organic transformations in biological processes.[2] Simulation of these processes has been studied extensively by using various synthetic flavin organocatalysts.[3,4] Scheme 1a shows a common catalytic cycle for oxygenase model reactions with a representative synthetic flavin, 5-ethyl-3,7,8,10-tetramethylisoalloxazinium salt ($FlEt^+$). A highly reactive flavin hydroperoxide (FlEtOOH) is generated by either direct addition of H_2O_2 (the shunt process) or reduction and subsequent incorporation of O_2.[5] Oxygen atom transfer to the substrate (Sub) and dehydration complete the catalytic cycle.[4] By this catalytic process, various heteroatomic compounds, including amines,[6a,c,d,7a,c] sulfides,[6a,d,f–h,7a,c] and ketones,[6b,7b] undergo oxygenation reactions with H_2O_2[6] or O_2 (1 atm)[7] under mild conditions. Model reactions of flavin-containing oxidases/dehydrogenases have also been extensively studied with cationic $FlEt^+$ and neutral synthetic flavin, 3,7,8,10-tetramethylisoalloxazine (Fl), as catalyst (Scheme 1b). The reaction proceeds by



Scheme 1. Catalytic cycle for typical model reactions of a) flavin monooxygenases and b) flavin dehydrogenases.

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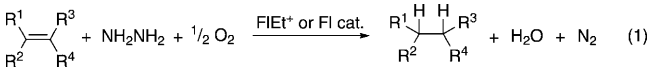
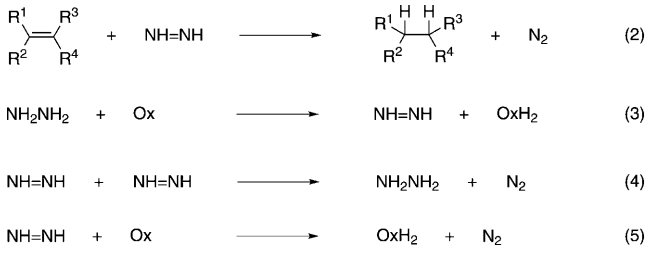
a similar redox process, including anaerobic dehydrogenation of the substrate (AH_2),[3b] O_2 incorporation into the reduced flavin (FlH_2), and elimination of H_2O_2. These processes with neutral[8] and cationic[9] flavin catalysts provide various dehydrogenative transformations of alcohols,[8a,b,e] amines,[8e,9a] hydrazines,[9b] thiols,[8c,d] NADH model compounds,[8d] and nitroalkanes.[8c] During the course of our systematic studies on the simulation of enzymatic functions of flavin monooxygenases with synthetic flavin catalysts,[4b,6a,c,h,7] we found that a series of synthetic flavins act as efficient catalysts for the generation of the reducing agent diimide, NH=NH,[10] by the above aerobic and anaerobic processes for the oxidation of hydrazine. This finding led to the development of a mild and convenient method for the aerobic reduction of olefins that proceeds under an atmosphere of O_2 (1 atm), as depicted in Equation (1).[11]



(1)

Diimide is a powerful reducing agent for various symmetrical unsaturated compounds, as depicted in Equation (2). Because of its low stability, this reagent must be used directly after generation from protected diimide derivatives, such as arylsulfonyl hydrazine,[12] azodiformate salts,[12b,13] and anthracene-9,10-diimine.[14] On the other hand, diimide has been generated by the oxidation of hydrazine [Eq. (3)] with H_2O_2,[13c,15] $NaIO_4$,[16] Se,[17] PhSe(O)OH,[18] $K_3[Fe(CN)_6]$,[12b,19] and O_2 with metal catalysts.[13c,20] These methods generally require an excess amount of hydrazine and oxidants for completion of the reaction[21] because reactive diimide readily undergoes both a self-process [Eq. (4)] and over-oxidation [Eq. (5)]. Despite this limitation, the aerobic oxidation of hydrazine is one of the most promising methods for diimide generation because the method principally provides an environmentally benign process for the hydrogenation of olefins that proceeds in air with the ultimately safe chemical byproducts of nitrogen and water. This method for diimide generation shows extraordinarily high hydrazine efficiency because the catalytic system of flavins can avoid the inevitable disproportionation reaction. Thus, the method provides a highly convenient and safe process for the hydrogenation of olefins that can be performed with 1 equiv of hydrazine, 1 atm of O_2 or air, and an organocatalyst,[22] which is a convenient alternative to transition-metal catalysts and H_2 gas[23] with respect to atom efficiency and safety. In this study, a series of neutral and cationic flavins and their association complexes with various 2,6-bis(acylamino)pyridines have been prepared, characterized, and examined for catalytic behavior in this new type of aerobic reduction.

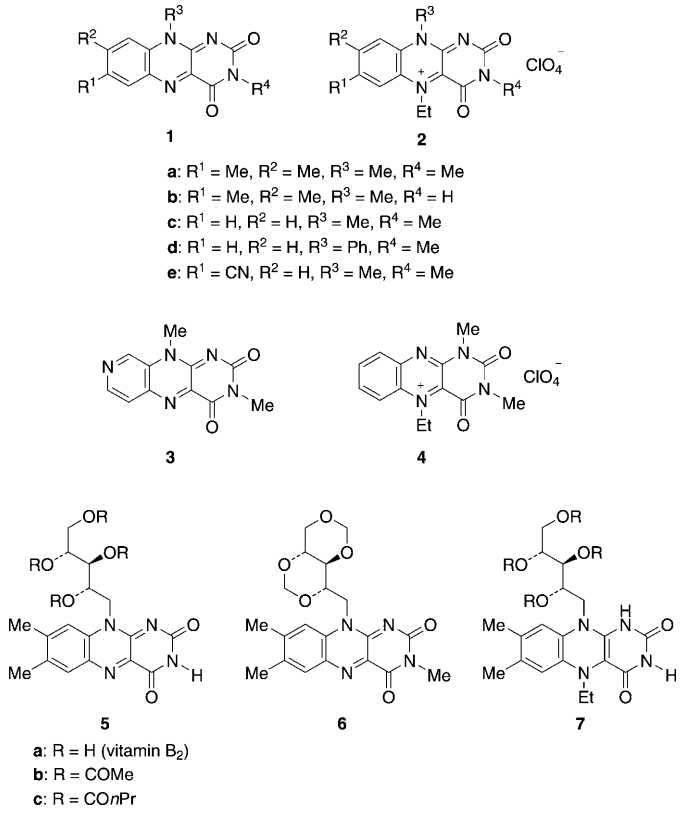
As part of our program to develop new organocatalysts bearing more sophisticated enzymatic functions, such as substrate specificity,[2,24] we continue to study the catalytic activities of new flavin–dendrimer association complexes. Associ-



ation complexes of neutral flavins with 2,6-bis(acylamino)-pyridines[25] bearing poly(benzyl ether) dendron units have been proven to act as efficient supramolecular organocatalysts for the aerobic reduction studied herein.[26] Recently, a variety of dendritic compounds with transition-metal[27] and organic[28] active cores have been studied extensively as catalysts for various molecular transformations.[29] Higher catalytic activities due to various dendrimer effects, including local condensation of the substrate around the reactive core,[28b–e] electrical stabilization of the intermediates,[28a] and inhibition of the formation of inert dimer species,[27b,e–g] have been achieved. Stereochemical congestion by dendron units has sometimes caused valuable size selectivity of substrates[27a,c] and products.[27d] Rotello and co-workers independently reported that neutral flavins covalently linked to a benzyl ether dendron unit at the 3-position showed high catalytic activity in the aerobic dehydrogenation of 1-benzyl-1,4-dihydronicotinamide in water[30] in which strong hydrophilic–hydrophobic interactions generated between the dendrimer and water would give rise to localization of the substrate around the flavin site. This leads to acceleration of the rate-determining dehydrogenation step (Scheme 1b). The flavin–dendrimer association catalysts reported herein show remarkable specificity in their catalytic activity towards aromatic and hydroxy olefins, and they retard the reduction of aliphatic olefins. This is a very rare case of catalytic specificity achieved by the design of artificial reaction cavities.[31] Herein, we describe full details of the aerobic reduction of olefins with a variety of synthetic flavin catalysts from both synthetic and mechanistic viewpoints.

Results and Discussion

Synthesis of flavins: A variety of synthetic flavins were prepared to examine their catalytic activity in the aerobic reduction of olefins (Scheme 2). Neutral flavins, isoalloxazines **1**, were prepared by the condensation of alloxanes with *N*-alkyl-*o*-nitroaniline.[32] Cationic flavins, 5-ethylisoalloxazinium salts **2**, were derived by reductive ethylation of **1** with acetaldehyde and subsequent oxidation with $NaNO_2$.[7c] Related analogues, 3,10-dimethyl-8-azaisoalloxazine (**3**)[8c] and 5-ethyl-1,3-dimethylalloxazinium perchlorate (**4**),[6d] were also prepared according to literature procedures. Compound **6** was derived from commercially available riboflavin **5a** (vitamin B_2) by acetalization and N^5-ethylation.[7b] Although cationic flavins **2** and **4** should be handled carefully under



Scheme 2. Synthetic flavins **1**–**6** used for the aerobic reduction of olefins.

argon, neutral flavins **1**, **3**, **5**, and **6** are easy to prepare and can be stored under air, and even under weak basic and acidic conditions. Recently, a reduced form of protected riboflavin **7** was reported to be an alternative catalyst for the aerobic reduction of olefins.[33] The preparation and handling of **7** should be carried out under strict anaerobic conditions using sophisticated laboratory techniques because reduced flavins have a high reactivity towards O_2, as shown in Scheme 1b.

Catalytic reduction of olefins: The catalytic activities of various flavins (1 mol%) were examined in the reduction of *trans*-5-decene with $NH_2NH_2{\cdot}H_2O$ (1.2 equiv) in CH_3CN at 25°C under O_2. Table 1 shows the turnover frequencies and redox potentials of various flavin catalysts. Cationic flavins **2** generally exhibit higher catalytic activities (entries 1–5) with the flavin analogue **4**[5b–d,f,g] also showing comparable catalytic activity presenting this reduction reaction (entry 6). The activities of various substituted flavins decrease in the order **2a** (R^1, R^2=Me) > **2c** (R^1, R^2=H) > **2e** (R^1=CN, R^2=H) (entries 1, 3, and 5). This tendency is consistent with the redox potentials (**2a**: 306 mV; **2c**: 388 mV; **2e**: 512 mV), which indicates that the rate-determining step of this reaction accelerates with electron-rich flavins. Neutral flavins **1**, **5**, and **6** show moderate activities (entries 7–11 and 13–16). In contrast to the cationic flavins, electron-deficient flavins accelerate the reaction in the order **1a** (R^1, R^2=Me, −809 mV) < **1c** (R^1, R^2=H, −721 mV) < **1e** (R^1=CN, R^2=H, −569 mV) (entries 7, 9, and 11). Also, electron-deficient flavin analogue **3**[8c] (−496 mV) shows a relatively high activity compared with those of the cationic flavins (entry 12). The higher catalytic activities of the electron-deficient neutral flavins strongly suggest that the rate-determining step of the reaction is different to that of the reaction with cationic flavins. As for the solvents, CH_3CN gave the best results. However, the reaction also proceeds in various protic and halogenated solvents, including CF_3CH_2OH, MeOH, EtOH, and $CHCl_3$.

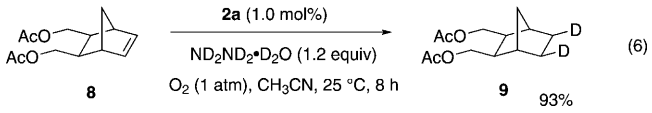
Table 1. Catalytic activities of the synthetic flavins **1**–**6** used for the reduction of *trans*-5-decene.[a]

Entry	Catalyst	$E^{o\prime}$ [mV][b]	TOF [h^{-1}][c]
1	**2a**	306	18
2	**2b**	316	13
3	**2c**	388	8.4
4	**2d**	427	15
5	**2e**	512	4.4
6	**4**	109	15
7	**1a**	−809	4.7
8	**1b**	−761	3.4
9	**1c**	−721	7.6
10	**1d**	−695	6.2
11	**1e**	−569	8.8
12	**3**	−496	14
13	**5a**	–[d]	3.8
14	**5b**	−725	4.9
15	**5c**	−725	6.9
16	**6**	−803	8.2

[a] The reaction of *trans*-5-decene (0.25 M) with $NH_2NH_2{\cdot}H_2O$ (1.2 equiv) in CH_3CN was carried out in the presence of catalyst (1 mol%) at 25°C under an atmosphere of O_2. [b] Determined by cyclic voltammetry (1.0 mM solution in CH_3CN, 0.10 M tetrabutylammonium perchlorate, scan rate 0.1 $V s^{-1}$) based on the relationship $E^{o\prime}=(E_p^c+E_p^a)/2$. [c] Determined by GLC analysis based on the formation of decane. [d] Not determined because of low solubility.

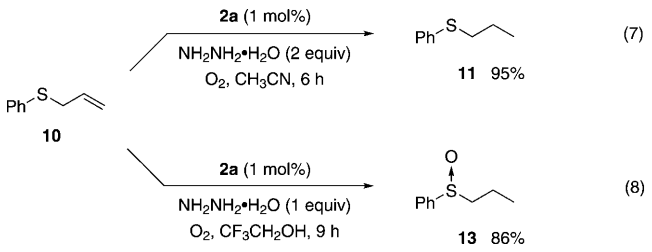
Representative results of the aerobic reduction of olefins with typical flavin catalysts are shown in Table 2. Various olefins were converted into the corresponding hydrogenated products quantitatively when the reactions were carried out with $NH_2NH_2{\cdot}H_2O$ (1.2–2.0 equiv) and **2a** (1 mol%) at 25°C for 5–6 h under O_2 (entries 1, 4, 5, 10, 13, 14, 16, and 17). Although the initial rates of the reactions with neutral flavin catalysts **1a**, **5c**, and **6** were lower than those with the cationic catalyst **2a** (Table 1), most of the reactions with neutral flavins gave rise to the quantitative formation of products after stirring for 24 h (entries 2, 3, 6–9, 11, 12, 15, and 18–21). Vitamin B_2 derivatives **5c** and **6** are especially useful catalysts due to their high availability and stability. Benzyl and benzyloxycarbonyl protecting groups, easily removed by metal-catalyzed hydrogenation,[34] can tolerate the applied reaction conditions (entries 6, 7, and 15). Alkylthio groups, which frequently inhibit the catalytic activity of transition-metal complexes, do not retard the organocatalytic reactions studied herein (entries 17–21).[16a] Terminal olefins are selectively reduced in the presence of trisubstituted olefins (entries 10 and 11).[15] Alkynes undergo consecutive reduction with excess hydrazine to afford the corresponding alkanes chemoselectively (entry 12).[13c] The reduction of

camphene proceeds with higher *endo* selectivity (*endo*/*exo* = 90:10) than the reduction performed by conventional hydrogenation with Pd/C catalyst (68:32; entry 5).[13a] This method provides an alternative, inexpensive strategy for the stereoselective 1,2-dideuteriation of olefins, whereas the conventional methods require expensive D_2 gas[35] or an excess amount of ND_2ND_2.[36] In a typical reaction, selective 1,2-deuteriation of 2-*exo*,3-*exo*-bis(acetoxymethyl)bicyclo-[2.2.1]hept-5-ene (**8**) can be performed with only 1.2 equiv of $ND_2ND_2{\cdot}D_2O$ to afford **9** in a yield of 93% [Eq. (6)].



(6)

Note that the reactivity of inert thioalkyl groups can be enhanced by the addition of protic media. Table 3 shows the product distribution in the catalytic aerobic reduction of phenyl 2-propenyl sulfide (**10**) in the presence of varying amounts of phenol. The reaction of **10** with less than 1 equiv of phenol affords the hydrogenated product, phenyl propyl sulfide (**11**), selectively (Table 3, entry 1), whereas similar treatment with a large amount of phenol affords increasing amounts of the S-oxidation products, phenyl 2-propenyl sulfoxide (**12**) and phenyl propyl sulfoxide (**13**). Such a drastic change in chemoselectivity has previously been observed exclusively with highly acidic alcohols such as phenol (pK_a 9.99) and CF_3CH_2OH (12.4).[37] The use of solvents of low acidity such as CH_3CN, MeOH, EtOH, $CHCl_3$, and CH_2Cl_2 gives rise to the selective formation of **11**. Thus, the hydrogenation and simultaneous S-oxidation can be controlled, as depicted in Equations (7) and (8). The latter is a very rare case of a reduction proceeding simultaneously with an oxygenation process.



(7)

(8)

Bis(methylenedioxy)flavin **6** has been proven to be the most robust, practical catalyst for this purpose. The reusability of various flavin catalysts (2 mol%) was examined for the aerobic reduction of 4-*tert*-butylstyrene (**14**) with $NH_2NH_2{\cdot}H_2O$ (2.0 equiv) at 30°C in CH_3CN. After the reaction, the product alkane was isolated by extraction with hexane. The next runs were performed simply by adding new substrate olefin and hydrazine to the remaining catalyst-containing organic solution. Table 4 shows typical results for the recycling of catalysts **2a**, **5c**, and **6**. Neutral riboflavin derivative **6** did not show any loss of product yield even on the third run (entry 7). Another vitamin B_2 derivative, riboflavin tetrabutyrate **5c**, lost activity on the second run (entry 4) because of hydrolysis of the ester moieties. None of the cationic flavins, including **2a**, were robust, although they exhibited the highest catalytic activities in the first runs (entries 1 and 2).

Catalysis of noncovalently dendronized flavins: With the aim of creating novel enzyme-like catalytic functions, we designed new association complexes of neutral flavins with 2,6-bis(acylamino)pyridine derivatives doubly linked to two benzyl ether dendron units (Scheme 3). Dendronized bis(acylamino)pyridines **15a** (first generation: 2,6-bis(3-{4-[3,5-bis(phenylmethoxy)phenylmethoxy]phenyl}propanoylamino)pyridine, abbreviated as G1PAP), **15b** (second generation: G2PAP), and **15c** (third generation: G3PAP) were prepared by the reaction of 2,6-bis[3-(4-hydroxyphenyl)propanoylamino]pyridine with the corresponding dendritic benzyl bromides.[38] Dendrimer **16** with different branching points (2,6-bis{3,5-bis[3,5-bis(phenylmethoxy)phenylmethoxy]benzoylamino}pyridine, abbreviated as G2BAP) was prepared by the condensation of dendritic methyl benzoate with 2,6-diaminopyridine. The association properties of the dendritic and nondendritic bis(acylamino)pyridines with neutral flavin **1b** were examined in $CDCl_3$ by ^1H NMR (400 MHz) analysis. Job's plots indicated that neutral flavin **1b** forms a 1:1 complex with dendrimer **15a** (see the Supporting Information).[25,39] The association constants K_a for the interaction of **1b** with **15**, **16**, and 2,6-bis(acetylamino)pyridine (**17**, AAP) were determined in $CDCl_3$ at 303 K on the basis of the concentration dependence of the ^1H chemical shift of the N3-H signal (Figure 1 and Table 5). The K_a values for the dendritic bis(acylamino)pyridines **15** at 303 K are in the range of 404–434 M^{-1} (Table 5, entries 1–3), similar to the values determined for **17** (AAP, 437 M^{-1} (entry 5); reported value:[25] 510 M^{-1} at 298 K). These results indicate that the association of **1b** with **15** is not hindered by steric congestion with interior and exterior benzyl ether units. This is in contrast to the much smaller K_a value (11 M^{-1}) determined for the association of **1b** with **16** bearing shorter linkers (entry 4). Thus, it can be said that the high association properties of **15** can be

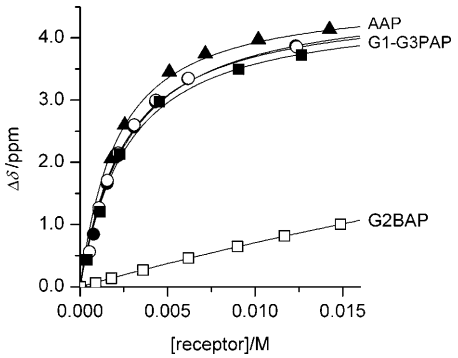
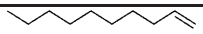
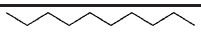
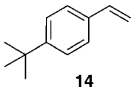
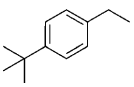
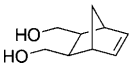
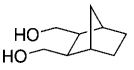
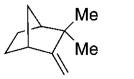
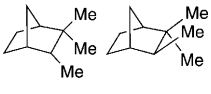
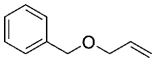
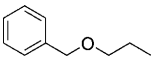
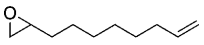
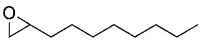
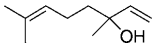
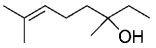
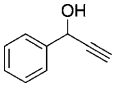
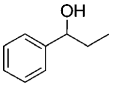
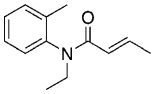
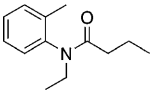
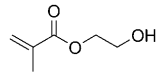
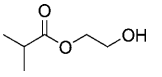
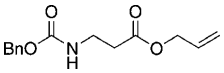
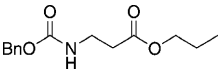
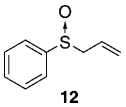
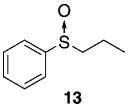
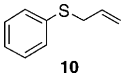
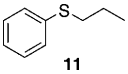
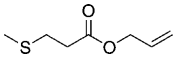
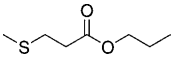
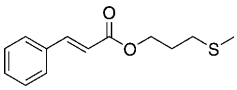
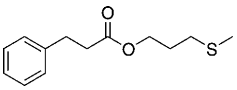


Figure 1. Plot of changes in the ^1H NMR chemical shift of N(3)H proton signal of **1b** versus concentration of bis(acylamino)pyridine receptors **15a** (G1PAP, ●), **15b** (G2PAP, ○), **15c** (G3PAP, ■), **16** (G2BAP, □), and **17** (AAP, ▲) in $CDCl_3$ at 303 K. $[\mathbf{1b}]_0 = 4.00 \times 10^{-4}$ M.

Table 2. Flavin-catalyzed aerobic reduction of olefins.[a]

Entry	Substrate	Product[b]	Hydrazine hydrate [equiv]	Catalyst	t [h]	Isolated yield [%]
1			1.2	**2a**	4	99
2			2.0	**5c**[b]	24	94
3	**14**		2.0	**6**[b]	24	93
4			1.2	**2a**	5	96
5		 *endo*/*exo* 90:10	1.2	**2a**	8	54[c]
6			2.0	**5b**[b]	24	91
7			2.0	**5c**[b]	24	93
8			2.0	**5b**[b]	24	90
9			2.0	**5c**[b]	24	85
10			2.0	**2a**	5	96
11			1.5	**5c**[b]	24	87
12			5.0[d]	**5c**[b]	30	92
13[e]			2.0	**2a**	5	98
14[e]			2.0	**2a**	5	90
15			2.0	**5c**[b]	24	86
16	 **12**	 **13**	2.0	**2a**	6	92
17			2.0	**2a**	6	95
18			2.0	**5c**[b]	24	90
19	**10**	**11**	2.0	**6**[b]	24	91
20			2.0	**5c**[b]	24	89
21[e]			2.4	**5c**[b]	24	94

[a] The reaction of olefin (2.5×10^{-1} M) with $NH_2NH_2{\cdot}H_2O$ in CH_3CN was carried out in the presence of catalyst (1.0 mol%) at room temperature (25–30 °C) under an atmosphere of O_2. [b] 2.0 mol%. [c] GLC yield. [d] The reaction was carried out with 4.0 equiv $NH_2NH_2{\cdot}H_2O$ and a further 1.0 equiv $NH_2NH_2{\cdot}H_2O$ was added after 24 h. [e] The reaction was carried out at 50 °C.

Table 3. Product distribution in the reaction of **10**.[a]

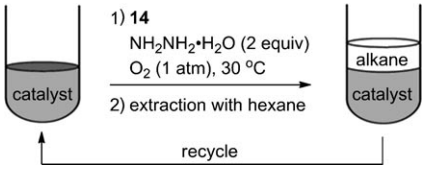
Entry	PhOH [equiv]	Product ratio[b] [%]		
		11	**12**	**13**
1	0.2	100	0	0
2	1	94	0	6
3	5	40	5	55
4	20	22	4	74

[a] The reaction of **10** (2.5×10^{-1} M) in CH_3CN was carried out in the presence of flavin catalyst **2a** (1.0 mol%), phenol, and $NH_2NH_2{\cdot}H_2O$ (1.0 equiv) at 25 °C for 24 h under an atmosphere of O_2. [b] The ratios of the three products, **11**, **12**, and **13**, were determined by GLC analysis.

attributed to its long phenylethyl linkers, which provide a distance of approximately 25 Å between the two branching points of the dendron units. This characteristic molecular structure gives rise to the smooth association of **1b** without any significant steric hindrance from bulky benzyl ether moieties. The association constants K_a observed for **1b** with **15a–c** at 298–313 K fit well ($R^2=0.998$–0.999) with the van't Hoff relationship of $\ln K_a$ versus $1/T$, from which thermodynamic parameters $\Delta H°$ and $\Delta S°$ were determined, as shown in Table 5. None of the thermodynamic parameters for the complexation of **1b·15** show any significant difference, which indicates that the association behavior of **1b** is not influenced by varying the steric and electronic effects of dendrimers **15**.

Figure 2 shows the changes in the ^{1}H NMR chemical shifts of the 7-CH_3 and 8-CH_3 proton signals of **1b** upon varying the concentration of receptors **15** and **17**. Increasing the concentration of nondendritic **17** gives rise to a slight downfield shift in the 7- and 8-CH_3 proton signals. This can be attributed to the decrease in the electron density in the flavin rings of **1b** as a result of the hydrogen-bonding association with **17**. In contrast, a remarkable upfield shift was observed upon similar treatment with the dendritic bis(acylamino)pyridines **15**. Note that the extent of these shifts increases significantly when a dendrimer of higher generation is employed as the receptor [G3PAP (**15c**) > G2PAP (**15b**) > G1PAP (**15a**)]. This phenomenon can be ascribed to the remote shielding effect of the benzene rings of **15**, which appears to significantly overcome the ordinary deshielding effects of hydrogen-bonding association. The remarkable upfield shift that is observed upon association of **1b** with **15c** indicates that specific aromatic protons of the dendrimer are located very close to the methyl protons of **1b**. In other words, an artificial deep cavity has been created in the association complex **1b·15c** in which even the outside circumferences of the 7- and 8-methyl groups of the flavin experience some shielding effect by the benzyl ether moieties of the dendrimer. This deep cavity provides an artificial

Table 4. Recycling of flavin catalysts in the aerobic reduction of **14**.[a]



Entry	Catalyst	Run[b]	Isolated yield [%]
1	**2a**	1	95
2	**2a**	2	34
3	**5c**	1	93
4	**5c**	2	64
5	**6**	1	93
6	**6**	2	94
7	**6**	3	94

[a] The reaction of 4-*tert*-butylstyrene (**14**; 1.25×10^{-1} M) with $NH_2NH_2{\cdot}H_2O$ (2.0 equiv) in CH_3CN was carried out in the presence of flavin catalyst (2.0 mol%) at 30°C for 24 h under an atmosphere of O_2. [b] Extraction with hexane gave the alkane product and the CH_3CN solution from the previous run was reused instead of recharging the catalyst.

Table 5. Association constants and thermodynamic parameters for the complexation of **1b** with bis(acylamino)pyridine receptors in $CDCl_3$.

Entry	Receptor	K_a[a] [M^{-1}]	ΔG^{o}[b] [kJ mol^{-1}]	ΔH^{o}[b] [kJ mol^{-1}]	$T\Delta H^{o}$[b] [kJ mol^{-1}]
1	**15a** (G1PAP)	404±20	−15.1	−29.3	−14.1
2	**15b** (G2PAP)	434±27	−15.3	−28.8	−13.6
3	**15c** (G3PAP)	411±35	−15.2	−29.1	−13.9
4	**16** (G2BAP)	11±1			
5	**17** (AAP)	437±60	−15.3	−32.9	−17.6

[a] Evaluated by nonlinear least-squares curve fitting of the data process assuming 1:1 complexation by ^{1}H NMR analysis in $CDCl_3$ at 303 K, as shown in Figure 1. [b] Determined on the basis of the van't Hoff relationship using association constants estimated at 298–313 K (see the Supporting Information).

enzyme-like reaction pocket that shows unprecedented substrate specificity, as described in detail in the next section.

The flavin–dendrimer complex catalysts **1b·15** exhibit characteristic acceleration effects in the reduction of specific olefins. Figure 3 shows the time-dependence of the product yield in the aerobic reduction of various olefins with association and nonassociation catalysts. Dendrimers **15a–c** (G1–G3PAP) activate the reduction of aromatic olefins such as 4-phenyl-1-butene (**18**), with the higher-generation dendrimers exhibiting higher catalytic activities, as shown in Figure 3a. This dendrimer effect appears more prominently in the reduction of *o*-allylphenol (**19**; Figure 3b). In contrast, the dendrimers act as a retardant in the reduction of aliphatic olefins such as 1-dodecene (**20**; Figure 3c), although a slight acceleration effect by the hydroxy group has been observed, as shown in the reduction of 11-undecen-1-ol (**21**; Figure 3d). Such remarkable positive and negative effects are not observed in any reaction with nonassociative dendrimer **16** (G2BAP) and nondendritic **17** (AAP), although these receptors slightly accelerate the reactions on account of their moderate Lewis acidity. This is unprecedented enzyme-like catalytic activity, with aromatic or hydroxy olefins being accelerated and aliphatic olefins deactivated with high specificity.

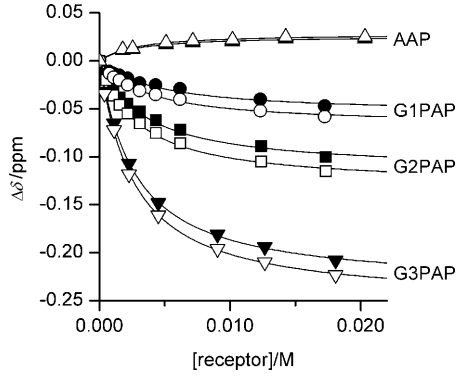
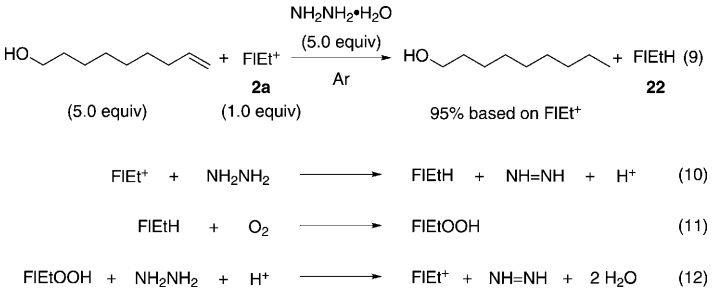
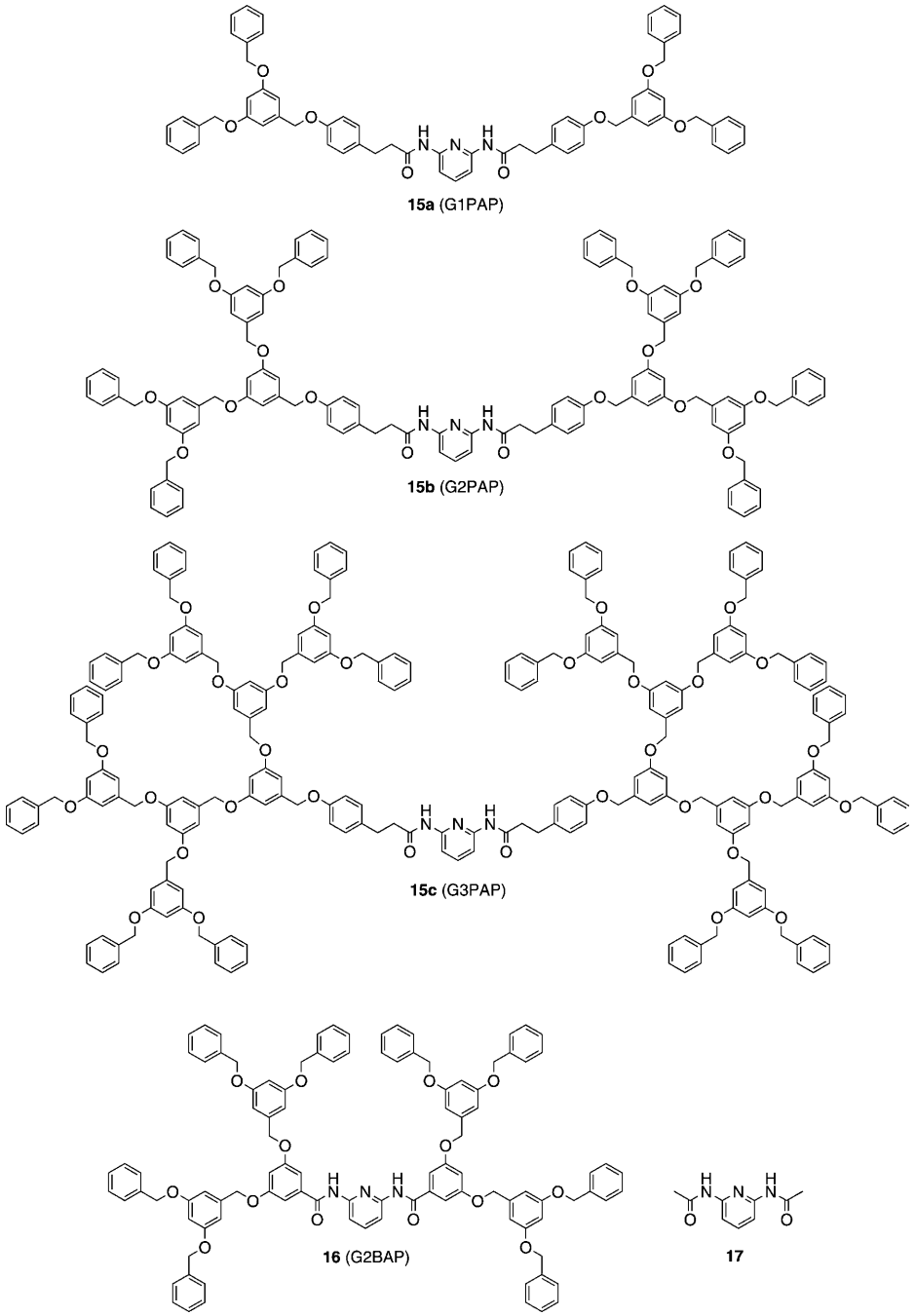


Figure 2. Plot of changes in the ^{1}H NMR chemical shifts of the 7-CH_3 (closed symbols) and 8-CH_3 (open symbols) signals of flavin **1b** versus concentration of 2,6-bis(acylamino)pyridine receptors **15a** (●, ○), **15b** (■, □), **15c** (▼, ▽), and **17** (▲, △) in $CDCl_3$ at 303 K. $[\mathbf{1b}]_0=4.00\times10^{-4}$ M.

Mechanistic investigation: The stoichiometry of the aerobic reduction was examined in the reaction of 9-decen-1-ol with $NH_2NH_2{\cdot}H_2O$ (1.0 equiv) in the presence of neutral flavin catalyst **6** (1.0 mol%) in CH_3CN at 25°C under air. When 27 mol% of O_2 was consumed after stirring for 22 h, the conversion of 9-decen-1-ol was determined to be 58 mol%, which is almost 2 mol equiv of O_2. Given that 1 equiv of $NH_2NH_2{\cdot}H_2O$ is sufficient for the completion of the reaction in many cases (Table 2, entries 1 and 4), the stoichiometry of the reaction can be rationally expressed as depicted in Equation (1). The stoichiometric reaction of cationic flavin **2a** with an excess of $NH_2NH_2{\cdot}H_2O$ (5.0 equiv) and 9-decen-1-ol (5.0 equiv) was examined at 25°C in CH_3CN under anaerobic conditions (argon). UV analysis of the reaction mixture showed that $FlEt^+$ (**2a**; $\lambda_{max}=400$ and 558 nm) was converted quantitatively into reduced flavin FlEtH (**22**; 344 nm) with a sharp isosbestic point (see the Supporting Information). GLC analysis showed that decan-1-ol was formed in 96% yield based on **2a** during this anaerobic process [Eq. (9)]. These results strongly suggest that the catalytic reduction studied herein includes the anaerobic dehydrogenation of hydrazine. On the basis that 2 mol of olefin can be reduced with 1 mol of O_2, the catalytic reduction can be rationalized by a mechanism that includes two independent steps for the generation of diimide, that is, anaerobic [Eq. (10)][9b] and aerobic processes [Eqs. (11) and (12)].[5]





Scheme 3. Bis(acylamino)pyridine dendritic receptors examined for supramolecular flavin catalysts.

To gain further insight into the mechanism, the concentration dependence on the initial rates of the catalytic reactions was examined in the reduction of *trans*-5-decene ($2.50–5.00\times10^{-1}$ M) with $NH_2NH_2{\cdot}H_2O$ ($2.50–5.00\times10^{-1}$ M) in the presence of a flavin catalyst (**2a** or **1a**, 2.50×10^{-3} M) in CH_3CN at 30 °C under an atmosphere of O_2 or air. Figures 4–6 show initial reaction profiles with varying concentrations of *trans*-5-decene (Figure 4), $NH_2NH_2{\cdot}H_2O$ (Figure 5), and O_2 (Figure 6). The reaction profiles in Figure 4a and b indicate that the olefin concentration did not have a significant influence on the initial rates of the reactions with catalyst **2a** or **1a**. A clear dependence on the concentration of hydrazine was observed in the reaction with catalyst **1a** (Figure 5b), whereas the reaction under similar conditions with catalyst **2a** showed much weaker hydrazine dependence (Figure 5a). In contrast, O_2 dependence was observed exclusively in the reaction with catalyst **2a** (Figure 6a). These results strongly suggest that the rate-determining step of the reaction with catalyst **2a** is the incorporation of O_2 [Eq. (11)], whereas the rate-determining step of the reaction with catalyst **1a** is the dehydrogenation or oxygenation of hydrazine [Eqs. (10) or (12)].

The initial reaction rates with association catalysts **1b·15c** and **1b·17** were also examined in the aerobic reduction of 4-phenyl-1-butene (**18**) in $CHCl_3$ at 30 °C under similar conditions. Similar to nonassociation catalyst **1a** (Figures 4b and 6b), no significant dependence on concentration of either olefins or O_2 was observed in the reduction reactions with **1b·15c** and **1b·17** (see the Supporting Information). In contrast, a clear dependence on the concentration of hydrazine was observed in the reduction reactions with these two association catalysts (Figure 7). Thus, it can be concluded that all the systems with neutral flavin catalysts exhibit a clear dependence exclusively on the concentration of hydrazine. These results indicate that the rate-determining step of the reduction with all neutral flavin catalysts is the oxidation of hydrazine. Note that the degree of hydrazine dependence increases in the order of **1a** < **1b·17** < **1b·15c**, as shown in Figures 5b and 7. Thus, we can be fairly certain that the rate-determining step of this catalytic reaction is accelerated by both an increase in Lewis acidity by hydrogen-bonding complexation and the remote cavity effect of the dendron units. This is consistent with the fact that the reactions of **18** and **19** are accelerated in the order **1a** < **1b·17** < **1b·15c**, as mentioned in Figure 3a and b.

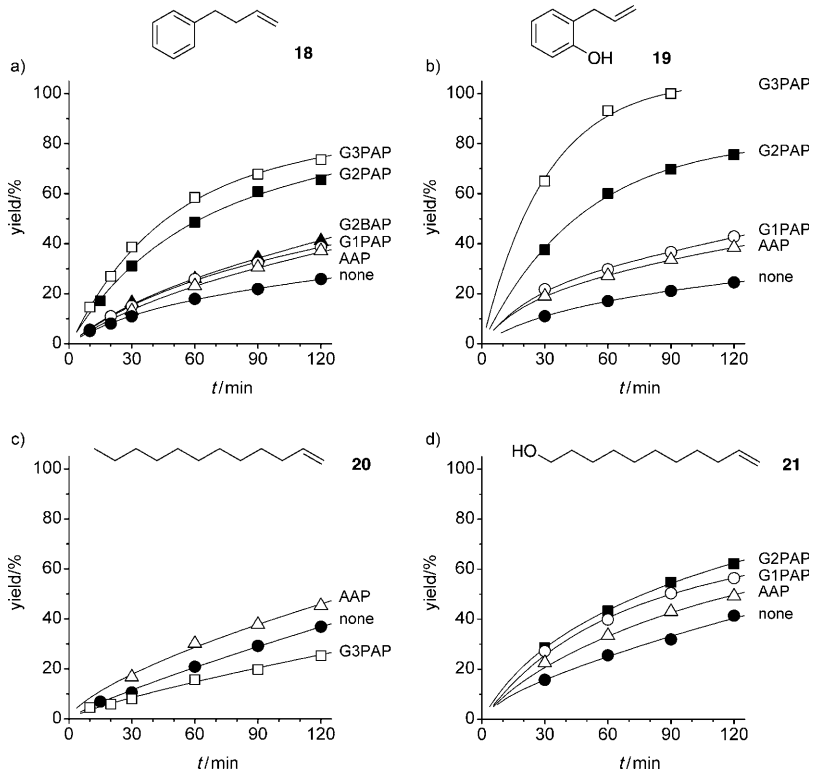


Figure 3. Reaction profiles for the flavin-catalyzed aerobic reduction of a) 4-phenyl-1-butene (**18**), b) *o*-allylphenol (**19**), c) 1-dodecene (**20**), and d) 10-undecen-1-ol (**21**). Conditions: olefin (6.3×10^{-2} M), $NH_2NH_2{\cdot}H_2O$ (2.5×10^{-1} M), flavin catalyst **1b** (2.5×10^{-3} M), additional receptor **15a** (G1PAP, 1.25×10^{-2} M; ○), **15b** (G2PAP, 1.25×10^{-2} M; ■), **15c** (G3PAP, 1.25×10^{-2} M; □), **16** (G2BAP, 1.25×10^{-2} M; ▲), **17** (AAP, 1.25×10^{-2} M; △), none (●), $CHCl_3$, 30 °C in air. Product yields were determined by GLC analysis based on an internal standard (decane).

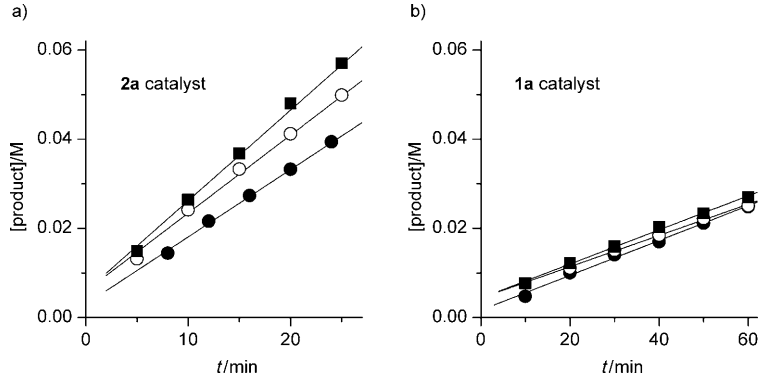


Figure 4. Concentration dependence of $[trans\text{-5-decene}]_0$ in the aerobic reduction of *trans*-5-decene with hydrazine in CH_3CN at 30 °C. Conditions: a) $[\mathbf{2a}]=2.50\times10^{-3}$ M, b) $[\mathbf{1a}]=2.50\times10^{-3}$ M, $[trans\text{-5-decene}]_0=2.50\times10^{-1}$ M (●), 3.75×10^{-1} M (○), 5.00×10^{-1} M (■), $[NH_2NH_2{\cdot}H_2O]_0=2.50\times10^{-1}$ M, O_2 (1 atm).

Mechanism of the aerobic reduction of olefins: The aerobic reduction of olefins with cationic flavin catalyst **2a** can be rationalized by the mechanism shown in Scheme 4. Nucleophilic attack of NH_2NH_2 at the 4a-position of **2a** gives adduct 4a-NH_2NHFlEt (**23**), which undergoes elimination of diimide by a 1,3-hydrogen shift to afford reduced flavin–diimide association complex **24**. Dehydrogenation of *N*-alkylhydrazine to afford benzene and nitrogen has been reported to proceed by similar anaerobic processes with a flavin catalyst.[9b] The olefin is reduced with the associated diimide in **24** to give the alkane product, molecular nitrogen, and reduced flavin **22**. This anaerobic process has been confirmed by control experiments on the stoichiometric reduction of 9-decen-1-ol with NH_2NH_2 and **2a**, which afforded decan-1-ol and reduced flavin **22** under argon [Eq. (9)]. The high hydrazine efficiency observed in this catalytic process can be ascribed to the strong hydrogen-bonding association properties of the flavin species, which protects the diimide from self-disproportionation [Eq. (4)] by tight complexation. Reduced flavin **22** reacts with O_2 to afford hydroperoxyflavin **25**.[5] Oxygen transfer to NH_2NH_2 and subsequent dehydration give the second flavin–diimide association complex **26**, which performs a similar reduction of the second olefin to afford the alkane product, molecular nitrogen, and hydroxyflavin **27**. Dehydration of hydroxyflavin **27** gives **2a** to complete the catalytic cycle. Given that (1) the aerobic reduction gives 2 equiv of olefin per 1 equiv of O_2 and (2) various amino compounds are known to undergo N-oxygenation with flavin catalysts under aerobic conditions,[7a,c] one can safely state that this aerobic reduction includes first an anaerobic process followed by an aerobic process to generate the diimide, although the second aerobic process must still be confirmed by direct evidence to make a definitive mechanistic conclusion. High O_2 dependence, observed exclusively in the reaction with catalyst **2a** (Figures 4a, 5a, and 6a), strongly suggests that the rate-determining step of the **2a**-catalyzed reaction is the incorporation of O_2 into the reduced flavin **22** to form flavin hydroperoxide **25**. This is consistent with the experimental results that show that electron-rich flavins accelerate the reactions (Table 1) if we assume that the incorporation of O_2 proceeds by rate-determining

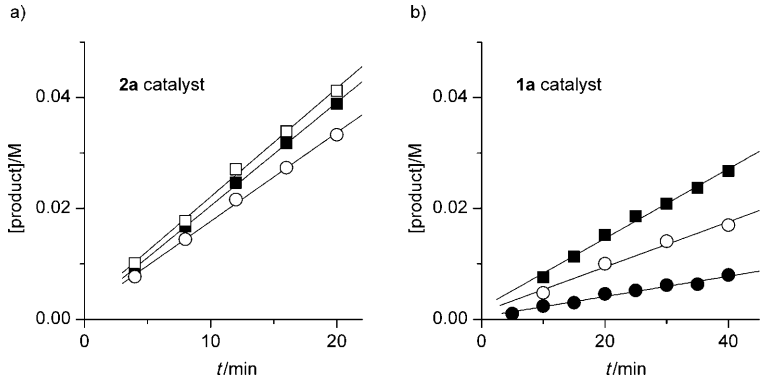


Figure 5. Concentration dependence of $[NH_2NH_2{\cdot}H_2O]_0$ in the aerobic reduction of *trans*-5-decene with hydrazine in CH_3CN at 30°C. Conditions: a) $[\mathbf{2a}]=2.50\times10^{-3}$ M, b) $[\mathbf{1a}]=2.50\times10^{-3}$ M, $[trans\text{-5-decene}]_0=2.50\times10^{-1}$ M, $[NH_2NH_2{\cdot}H_2O]_0=1.25\times10^{-1}$ M (●), 2.50×10^{-1} M (○), 3.75×10^{-1} M (■), 5.00×10^{-1} M (□), O_2 (1 atm).

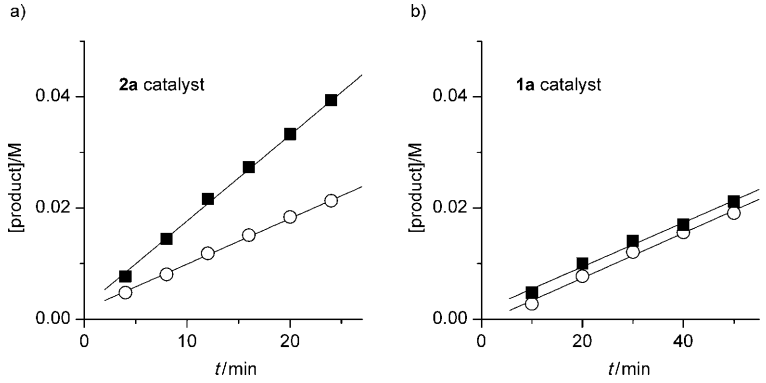


Figure 6. Dependence of the partial pressure of O_2 in the aerobic reduction of *trans*-5-decene with hydrazine in CH_3CN at 30°C. Conditions: a) $[\mathbf{2a}]=2.50\times10^{-3}$ M, b) $[\mathbf{1a}]=2.50\times10^{-3}$ M, $[trans\text{-5-decene}]_0=2.50\times10^{-1}$ M, $[NH_2NH_2{\cdot}H_2O]_0=2.50\times10^{-1}$ M, O_2 (1 atm, ■), air (1 atm, ○).

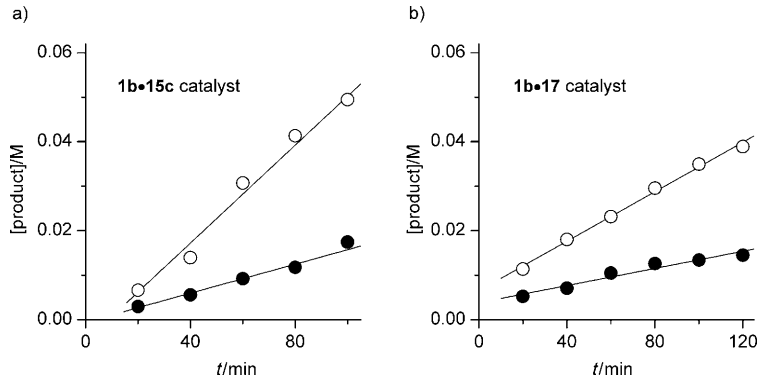
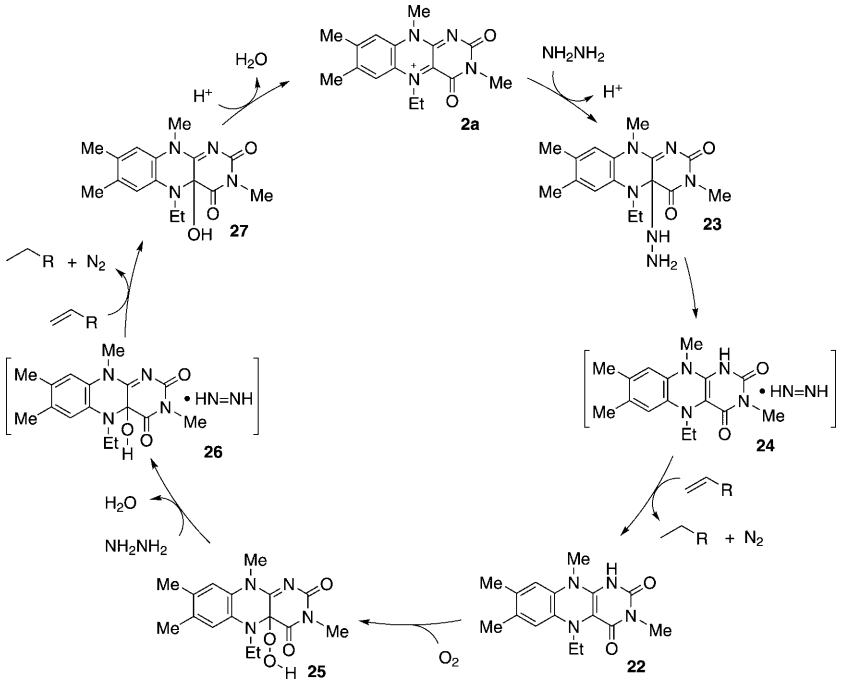


Figure 7. Concentration dependence of $[NH_2NH_2{\cdot}H_2O]_0$ in the aerobic reduction of 4-phenyl-1-butene (**18**) with hydrazine in $CHCl_3$ at 30°C in the presence of associated flavin catalysts. Conditions: $[\mathbf{1b}]=2.50\times10^{-3}$ M, $[\mathbf{15c}]=1.25\times10^{-2}$ M (a), $[\mathbf{17}]=1.25\times10^{-2}$ M (b), $[\mathbf{18}]_0=2.50\times10^{-1}$ M, $[NH_2NH_2{\cdot}H_2O]_0=1.00\times10^{-1}$ M (●), 5.00×10^{-1} M (○), air (1 atm).

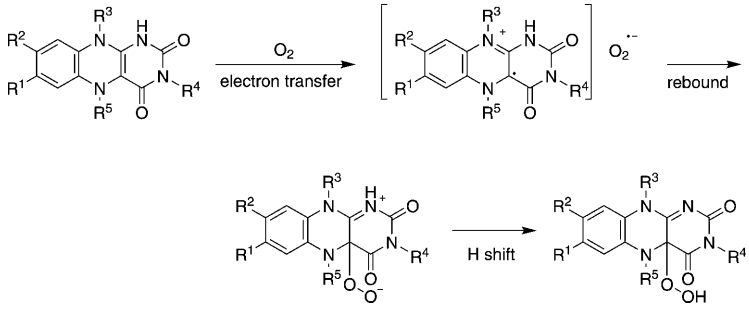
electron transfer from reduced flavin to O_2 as a crucial step (Scheme 5).[5]

Catalytic reduction with neutral flavin 1a proceeds by a similar mechanism (Scheme 6). After the redox sequence involving the anaerobic dehydrogenation of NH_2NH_2, the first reduction of olefin, and O_2 incorporation, the resulting flavin hydroperoxide **28** undergoes elimination of H_2O_2 to afford flavin–H_2O_2 association complex **29**. Oxygen transfer from H_2O_2 in complex **29** to NH_2NH_2 gives rise to the formation of flavin–diimide complex **30**, which performs the second olefin reduction. The high concentration dependence of NH_2NH_2, observed exclusively in the reduction with neutral flavin **1a**, strongly suggests that the rate-determining step is the nucleophilic addition of NH_2NH_2 to **1a** or the oxygenation of NH_2NH_2 with the associated H_2O_2. It is rare that the rate-determining step can be changed by the neutrality of the catalyst. Considering that electron-deficient neutral flavins accelerate the reactions, as shown in Table 1, one can safely state that the rate-determining step of the reduction with a neutral flavin catalyst is the nucleophilic addition of NH_2NH_2 to **1a**. The acceleration with association catalyst **1b·17** (Figure 5b (**1a**) and 7b (**1b·17**)) is attributed to the high Lewis acidity of **17**, which enhances the rate-determining nucleophilic addition of NH_2NH_2 to **1a** upon hydrogen-bonding association.[26]

The positive generation effect of the dendrimer complex catalyst, observed specifically in the reduction of aromatic and hydroxy olefins (Figure 3), can be ascribed to the acceleration of the rate-determining addition of NH_2NH_2. As shown in Scheme 7, mixing dendritic association complex **31** with hydrazine would give rise to an equilibrium with the NH_2NH_2-included complex **32**. Nucleophilic attack of the included NH_2NH_2 on the flavin core affords diimide-included complex **33**. Base on the assumption that the association constant (K_a) of **31** with NH_2NH_2 increases with a higher generation of the dendrimer unit, the rate-determining, anaerobic dehydrogenation of NH_2NH_2 would be rationally accelerated according to the rate equation $d[\mathbf{33}]/dt=kK_a[\mathbf{31}][NH_2NH_2]$. Increasing K_a



Scheme 4. Proposed catalytic cycle for the aerobic reduction of olefins with cationic flavin catalyst **2a**.



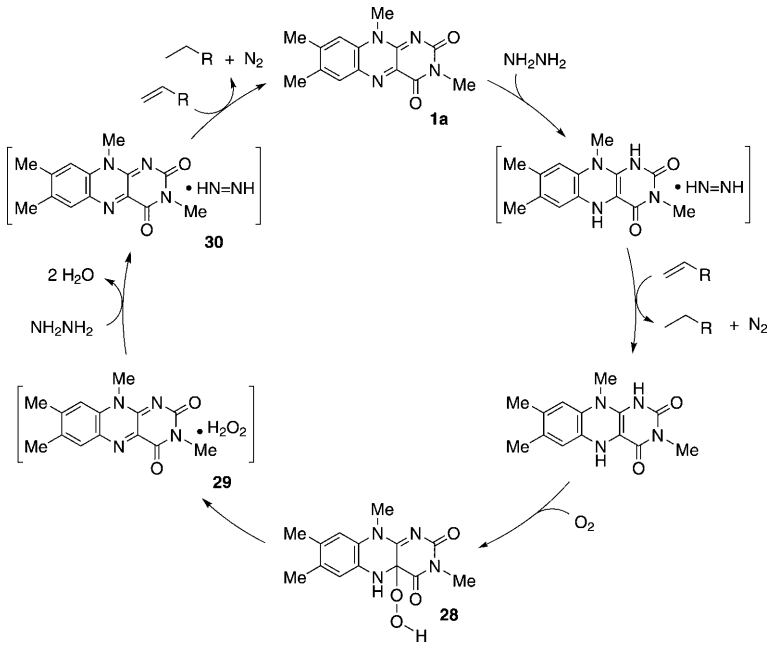
Scheme 5. Reaction of reduced flavin with molecular oxygen.

values in higher-generation dendrimers may be the result of an increasing number of benzyl ether moieties, which would capture much more NH_2NH_2 inside the cavity of the dendrimers. Note also that the dendrimers do not influence the O_2 incorporation process significantly: No O_2 dependence was observed in the reduction with the flavin–dendrimer complex catalysts.

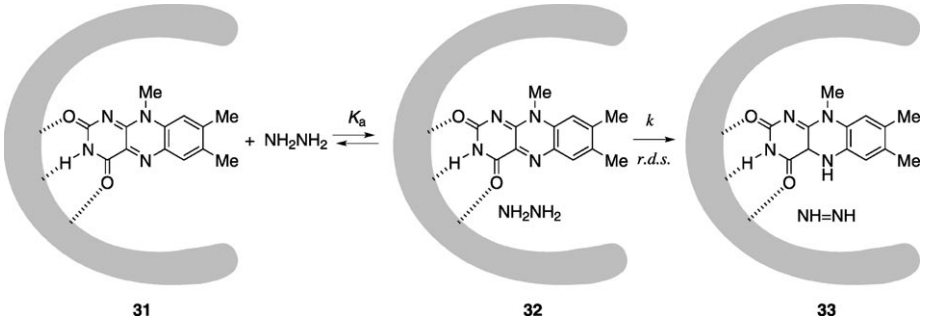
The specific reactivity of aromatic and hydroxy olefins observed in the reduction with dendrimer–flavin catalysts might be explained by the localization of the olefins inside the dendrimer cavity. This would be quite reasonable if the rate-determining step of the catalytic reaction is the reduction of the olefins with diimide. However, kinetic studies revealed that the initial rates of the reduction are independent of the concentration of olefins, as shown in Figure 4. To rationalize this substrate specificity, we assume the self-disproportionation of diimide, occurring locally inside the dendritic cavity, and its effective avoidance in the case of specific olefins. Differing from the proposed 1:1 association of flavin with diimide in CH_3CN, the reaction with flavin–dendrimer catalysts would have the possibility of generating intermediates **34**, which include more than 2 mol equiv of diimide inside the cavity due to the enhanced hydrogen-bonding properties caused by the benzyl ether dendron unit (Scheme 8). This would cause significant disproportionation of the diimide and subsequent decay in the concentration of NH_2NH_2 during the reaction. Assuming that the overall rate of the catalytic reaction is controlled by the rate-determining dehydrogenation of NH_2NH_2, we can suggest that this undesirable decrease in concentration of NH_2NH_2 would give rise to a gradual decrease in the reaction rate. Aromatic and hydroxy olefins would undergo faster inclusion inside the dendritic cavity because of their strong stacking or hydrogen-bonding properties. Thus, these substrates can consume the included diimide efficiently for proper reduction. Scheme 9 shows a schematic representation of the inclusion of *o*-allylphenol inside the dendritic cavity. Higher generation dendrimers would provide much better opportunities for the inclusion and reduction of olefins, which leads to a positive generation gap in the efficiency of the reduction (Figure 3a, b, and d). In contrast, the negative effect of the dendrimer observed in the reduction of aliphatic olefins (Figure 3c) can be attributed to the low inclusion properties of dendrimers towards aliphatic olefins, which allows the disproportionation of the included diimide before the reduction.

Conclusion

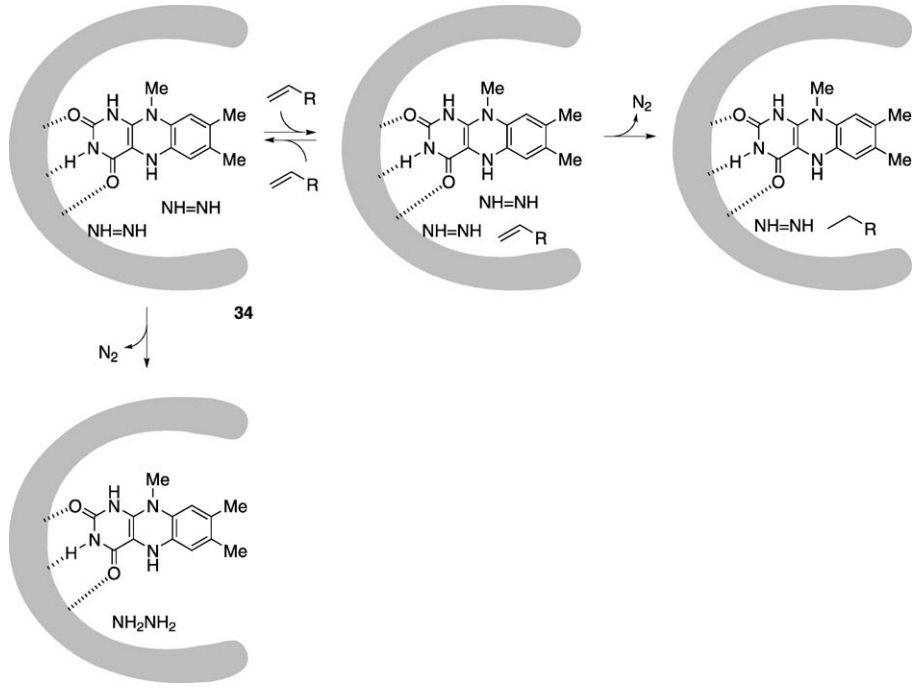
We have developed an efficient method for the generation of a powerful reducing agent, diimide, by the anaerobic and aerobic oxidation of NH_2NH_2 with synthetic flavin catalysts. This method provides an efficient and convenient approach to the aerobic reduction of olefins under mild conditions. Neutral flavin derived from riboflavin acts as a practical catalyst because of its high availability, stability, and reusability, although a series of cationic flavins exhibit higher catalytic activities. Unprecedented enzyme-type substrate specificity has been observed in the reduction with association complex catalysts of neutral flavin with dendritic 2,6-bis(acylamino)-pyridines. A remarkable enhancement of catalytic activity is exhibited exclusively in the reduction of aromatic and/or hydroxy olefins, whereas a contrasting negative dendrimer effect is observed upon similar treatment of aliphatic olefins.



Scheme 6. Proposed catalytic cycle for the aerobic reduction of olefins with neutral flavin catalyst **1a**.



Scheme 7. Plausible rate-determining step for flavin–dendrimer complex catalysis.



Scheme 8. Competitive disproportionation of diimide occurring inside the dendritic cavity.

Control experiments and kinetic studies have revealed that the catalytic reduction described herein can proceed by two independent processes, anaerobic and aerobic, for the generation of diimide, with an unprecedented and significant change in the rate-determining step being observed by changing the neutrality of the flavin catalyst. A positive dendrimer effect, observed specifically with aromatic or hydroxy olefins, is a result of specific inclusion properties of the interior benzyl ether dendron units of the flavin–dendrimer association complexes.

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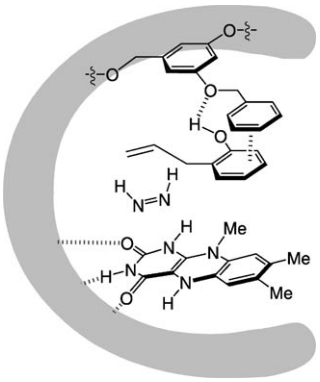

Scheme 9. Schematic representation for the association of *o*-allylphenol with dendrimer–flavin complex catalyst.

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[21] 10 equiv/H_2O_2 (7 equiv),[15] 40 equiv/$NaIO_4$ (6.5 equiv),[16a] 85 equiv/$NaIO_4$ (20 equiv),[16b] 1.3 equiv/Se (2 equiv),[17] 10 equiv/PhSe(O)OH (2 equiv),[18] 17 equiv/$K_3[Fe(CN)_6]$ (5.5 equiv).[19] 11 equiv/CuCl (0.2 equiv)/air,[20a] 400 equiv/$CuSO_4$ (0.09 equiv)/O_2,[20a] and 200 equiv/$Cu(OAc)_2$ (0.27 equiv)/air.[20c]

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