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Nonenzymatic and Metal-Free Organocatalysis for in Situ Regeneration of Oxidized Cofactors by Activation and Reduction of Molecular Oxygen

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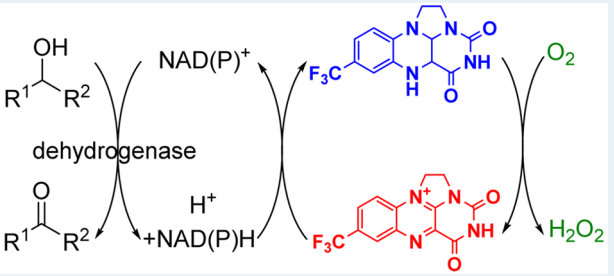
Supporting Information

ABSTRACT: The application of synthetic flavinium organocatalysts for the in situ regeneration of oxidized cofactors $NAD(P)^+$ using O_2 as the terminal oxidant without any special illumination or equipment is reported. With the aid of the highly active bridged flavinium catalyst, the rate of NAD(P)H oxidation is accelerated by 3 orders of magnitude. The results show that the catalytic activity of the bridged flavinium catalyst is not dependent on light but on only oxygen. Furthermore, this catalyst is compatible with various preparative enzymatic oxidation reactions. A hydride transfer mechanism is proposed for the presented system.



KEYWORDS: *cofactor regeneration, flavin, organocatalysis, aerobic oxidation, enzyme catalysis, metal-free catalysis*

1. INTRODUCTION

Enzyme-catalyzed transformations have emerged as an elegant synthetic methodology during the last few decades;[1] oxidoreductases (EC 1.x.x.x) account for the majority of known enzymes and have attracted considerable attention because they can catalyze regio-, chemo-, and stereoselective transformations that cannot be easily achieved by chemical catalysts.[2] However, their broader application has been restricted because of their cofactor dependency. The high cost, widespread usage, and physical instability of the cofactors in particular for nicotinamide cofactors NADH and NADPH [NAD(P) = nicotinamide adenine dinucleotide (phosphate)] necessitate efficient and economical regeneration techniques for multiple reuse cycles. Unfortunately, compared to the well-developed NAD(P)H regeneration system, the corresponding oxidized forms of the $NAD(P)^+$ regeneration systems are relatively less because of the kinetic limitation, insufficient thermodynamic driving force, and low operational stability.[3] Various strategies such as using NAD(P)H oxidases as natural catalyst,[4] substrate coupling,[5] chemoenzymatic,[6] electrochemical,[7] photochemical,[8] and biomimetic catalysis[9] systems have been reported for $NAD(P)^+$ regeneration. Although many of these methods are practical, some still have drawbacks such as high enzyme cost, the need for cosubstrates to serve as terminal electron acceptors or special equipment, formation of additional byproducts, low total turnover number (TTN) and turnover frequency (TOF), and being dependent on a metal mediator. The last one represents a major obstacle for the true preparative applicability; nearly all of the nonenzymatic $NAD(P)^+$ regeneration systems involve the use of a metal mediator, especially for the noble metal catalyst, such as the Rh, Ru, Ir complex.[3] However, mutual inactivation of the metal catalyst and enzyme is frequently observed because of the undesirable bonding between the metal complex and nucleophilic residues of the enzyme.[10]

In this context, the development of an organocatalyst for the nonenzymatic in situ regeneration of $NAD(P)^+$ is useful because it avoids the problem of mutual inactivation of the metal catalyst and enzyme. Furthermore, a small organic molecule can regenerate both NADH and NADPH without discrimination and have pH and temperature ranges broader than those of most enzymatic regeneration systems. From a practical point of view, this method is especially meaningful when molecular oxygen is used as the terminal electron acceptor, and the catalyst is water-soluble, which is more suitable for the real enzyme work environment. As early as 1973, Jones et al. reported the use of natural flavin adenine mononucleotide (FMN) for NAD^+ regeneration;[11] however, its efficiency is limited because of the rather sluggish kinetics of hydride transfer from NADH to the oxidized flavin, and the TOF of FMN lies in the range of a few catalytic cycles per day.[12] This low efficiency required that a large quantity of FMN (usually >2 equiv of FMN with respect to the substrate) be used, and separation of products from the reaction mixture is inconvenient. Kaiser et al. also reported the preparation of semisynthetic enzymes by incorporating flavins in papain,

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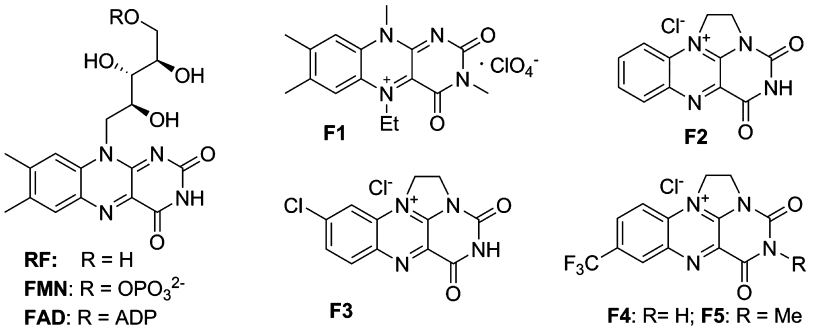

Figure 1. Structures of the flavin catalysts used in this study.

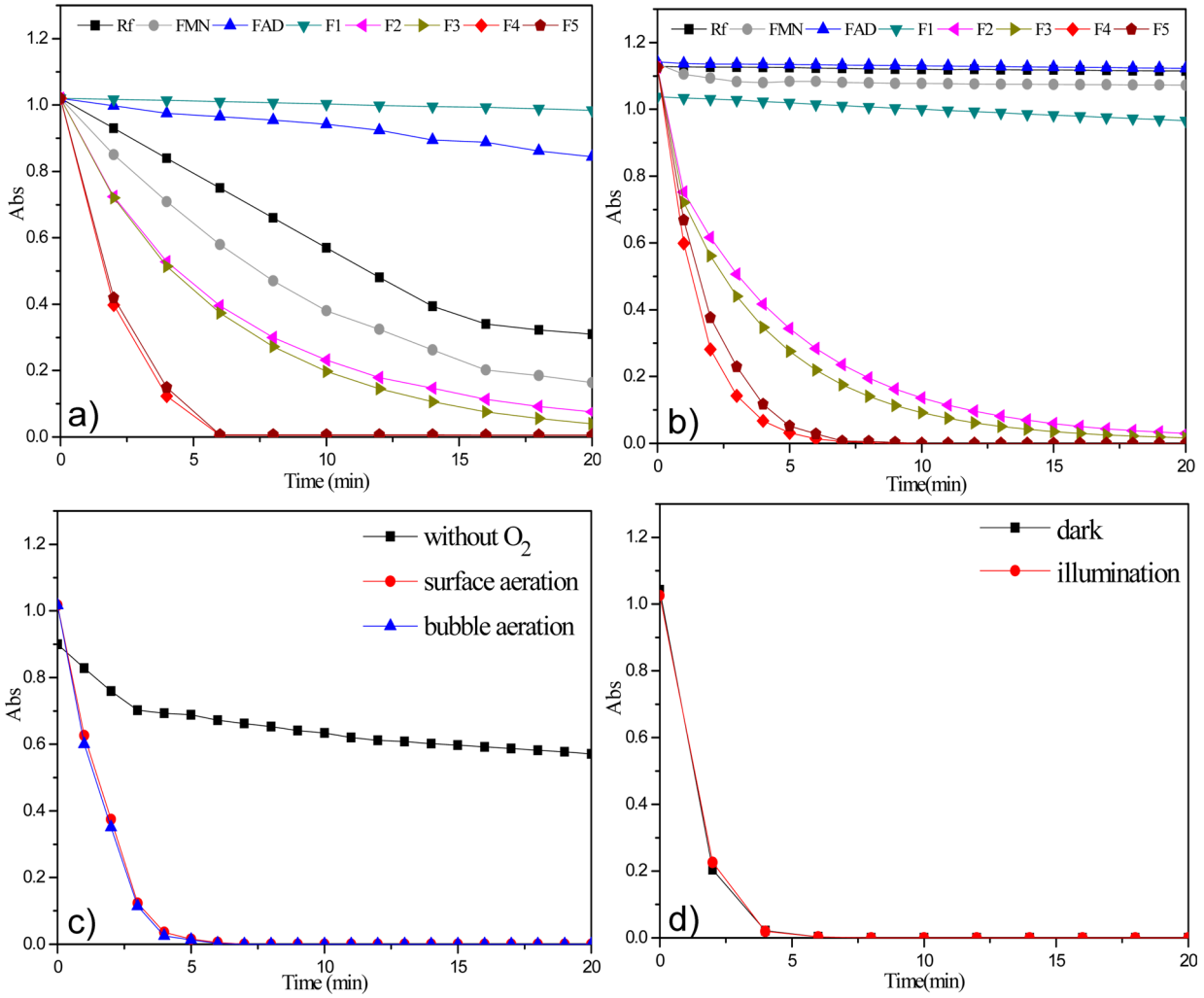

Figure 2. Reaction conditions: 0.2 mM NAD(P)H, 4 μM flavins, and phosphate buffer (pH 7) at 30 °C. (a) The reactions were performed without any special illumination. (b) The reactions were performed in darkness. (c) The reactions were performed under air- or oxygen-free conditions using **F4** as a catalyst. (d) NADPH was used instead of NADH in the reaction using **F4** as a catalyst.

which are capable of catalyzing nicotinamide oxidations; however, this method still suffers from multistep synthesis, and the improvement in catalytic efficiency is not obvious.[13] Inspired by these pioneering works as well as recent significant advances in designing new structures of flavin analogues,[14] we reconsidered the natural FMN catalyst. Herein, we report a simple, mild, and highly efficient method for the aerobic in situ regeneration of NAD(P)$^+$ by using a synthetic, water-soluble bridged flavinium organocatalyst.

2. RESULTS AND DISCUSSION

Initial experiments were performed with NADH as a probe substrate, and after preliminary screening of the flavin analogues, we focused on several potential synthetic flavinium derivatives **F1**−**F5**;[15] the natural flavins RF, FMN, and FAD were also chosen for comparison (Figure 1). The extent of oxidation of the NADH was measured through the change in the characteristic NADH absorbance at 340 nm via the UV spectrum (Figure S1). As shown in Figure 2a, the conversion of

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NADH varies markedly with the change in the structure of flavin catalysts, and the following order of reactivity was observed: **F5** ≈ **F4** > **F3** ≈ **F2** > FMN > RF > FAD > **F1**. This phenomenon may be caused by the different redox potentials of the flavin catalysts; the $E^{o\prime}$ values of these catalysts decrease in the following order: **F5** ≈ **F4** (−72 mV) > **F3** (−103 mV) > **F2** (−167 mV) > FMN (−219 mV).[15c] There seems to be a linear relationship between the catalytic activity and the redox potential of the catalysts. However, if we compared only **F1** (280 mV) and **F4** (−72 mV), the order of catalytic activity is nearly the opposite of the earlier observation. We speculate that this phenomenon may be due to the conformation of **F1**, which would change from planar to bent during the process that is common in natural flavin reduction,[16] whereas this is not allowed in the case of **F4** because of the hindering effect of the N^1,N^{10}-ethylene bridge bond, which is obvious beneficial for accepting hydride from NADH (vide infra). To evaluate the effect of light irradiation, the same reactions were further performed in darkness. To our delight, **F2**−**F5** showed activities similar to those of the former condition (Figure 2b), which is an advantage for an enzyme catalysis system or a fermentation system. However, under the same conditions, the conversion of NADH was much slower or null when using RF, FMN, FAD, and **F1** as the catalysts. These results showed that the light has little influence on the catalytic activity of the ethylene-bridged flavin catalysts. Thus, we speculated that another factor that affects the catalytic activity is probably due to the oxygen. To check this point, the control experiments were conducted under oxygen-free conditions using **F4** as a catalyst. As shown in Figure 2c, a sharply decreased catalytic activity of **F4** was observed when the reaction was performed under oxygen-free conditions. The different modes of O_2 supply (surface or bubble aeration) were also studied and appeared to have little effect on the reaction, which demonstrates its superior catalytic activity for the activation of O_2. On the basis of these results, we believe that the catalytic activity of the ethylene-birdged flavin catalyst is not dependent on light but on only oxygen.

With the aim of developing and defining the scope of the presented method, **F4** was then tested for the oxidation of NADPH. As expected for an organocatalyst, it did not distinguish between nonphosphorylated NADH and phosphorylated NADPH and also exhibited high activity even in the dark (Figure 2d). The TOFs of **F4**-catalyzed NADH and NADPH oxidation were calculated to be 21.1 and 21.9 min^{-1}, respectively (corresponding to activities of 61.3 and 63.6 U mg^{-1}, respectively), according to the conversion of NAD(P)H during the first minute of the reaction. Although this value is much lower than that of NADH oxidase, it is high enough among the nonenzymatic aerobic NAD^+ regeneration systems (Table 1). Encouraged by these results, we then checked the effect of pH, temperature, and buffers for the presented system (Figure S2); as expected for the advantage of an organocatalyst, **F4** showed high stability and activity over broader pH and temperature ranges than those of most enzymatic regeneration systems, which demonstrates the robustness of the presented method.

On the basis of these results, we proposed that **F4** could be used as a novel and efficient organocatalyst for aerobic $NAD(P)^+$ regeneration; we then coupled it to enzymatic oxidation to check its applicability. In further experiments, H_2O_2 is generated as the reduction product of oxygen, and catalase was used to dismutate H_2O_2. To be able to compare the efficiency of **F4** with those of previously reported systems, we typically applied reaction conditions analogous to those used in previous studies. Horse liver alcohol dehydrogenase (HLADH)-catalyzed oxidative lactonization of diols was first chosen for this purpose; such oxidations are of preparative interest as they give access to enantiopure lactones through oxidation of the corresponding cyclic hemiacetal intermediates, which are important building blocks for the synthesis of natural products and drug intermediates.[12a,17] We were pleased to find that in the presence of 0.25 mol % **F4** and 0.5 mol % NAD^+, cofactor regeneration proceeded successfully, and the desired chiral lactone (1*R*,6*S*)-(+)-*cis*-8-oxabicyclo[4.3.0]nonan-7-one (**1b**) was obtained in 93% yield and >99% enantiomeric excess (Table 2, entry 1), which indicates that *cis*-1,2-bis(hydroxymethyl)cyclohexane (**1a**) is exclusively oxidized by HLADH because otherwise the product should be racemic. To exclude the possibility that commercial HLADH might contain contaminants such as cofactors, two confirmatory experiments were performed. (1) HLADH was denatured by boiling or addition of trichloroacetic acid, and the soluble fraction was then recovered and analyzed using high-performance liquid chromatography by comparing it with the standard cofactor compounds.[18] (2) Experiment 1 was repeated using FMN instead of **F4** as the catalyst under the same reaction conditions (Table 2, entry 1, and Figure S5). Both results showed that such a possibility can be excluded. Further control experiments also proved that the direct oxidation of the substrate through mediator **F4** can be ruled out. Notably, replacing NAD^+ with its reductive form, NADH, had little influence on the reaction (Table 2, entry 1). Under these nonoptimized conditions, the calculated TOF of **F4** over the total reaction time is ∼16 h^{-1}, which is much more efficient by ∼3 orders of magnitude than the TOF of the same reaction catalyzed by the FMN/O_2 system (∼0.01 h^{-1}).[12a] However, this value is far from the TOF of the catalytic aerobic NADH oxidation (Table 1) and even lower than the number calculated according to the conversion after reaction for 1 h [TOF ∼ 80 h^{-1} (Figure S3)], which indicates that the potential of this catalyst was not fully exploited. This phenomenon may be due to the reaction between the substrate and the enzyme being the rate-limiting step. To check this point, the concentration of HLADH was doubled in the subsequent contrast experiment, and the result showed that the rate of reaction accelerated remarkably and the reaction was completed in 8 h (Table 2, entry 1). The oxidative desymmetrization of 3-methyl-1,5-pentanediol (**2a**) also

Table 1. Comparison of Catalytic Performances of the Reported Aerobic NAD^+ Regeneration Systems

entry	regeneration system	TOF (min^{-1})	ref
1[a]	$[Ru(PDon)_3](ClO_4)_2/O_2$	3.4	7a
2	$[Ru(TPA)(PDon)](Cl_2)/O_2$	2.1	7a
3[b]	$[Co(TPA)(PDon)](BF_4)_2/O_2$	0.6	7a
4[c]	$Fe(TSPP)/O_2$	6.6	9a
5	FMN/O_2	0.03	7a
6	$FMN/h\nu/O_2$	5.8	8
7[d]	**F4**/O_2	21.1	this study
8[e]	NADH oxidase	1926	4a

[a]PDon, 1,10-phenanthroline-5,6-dione. [b]TPA, *N*,*N*,*N*-tris(2-pyridylmethyl)amine. [c]TSPP, meso-tetrakis(4-sulfonatophenyl)-porphyrin. [d]Averaged data of three experiments. [e]Calculated from the reported enzyme activity (39.3 U/mg) and molecular mass (48.8 kDa) of NADH oxidase in ref 4a.

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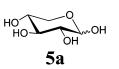
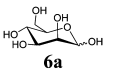
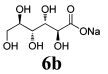
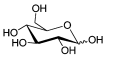
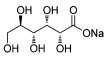
Table 2. F4-Catalyzed in Situ Aerobic Cofactor Regeneration for the Enzymatic Oxidations

Entry	Substrate	Product	Catalyst	t [h]	Yield (%)[b]	TOF (h^{-1})[c]
1[a]	 **1a**	 **1b**	F4	24	93 (> 99% *ee*)	16
				24	94 (> 99% *ee*)[d]	16
				8	98 (> 99% *ee*)[e]	49
			FMN[12a]	60	79 (> 99% *ee*)	0.01
				24	30 (> 99% *ee*)[f]	5.1
2[a]	 **2a**	 **2b**	F4	13	97 (> 99% *ee*)	30
			FMN[12b]	24	70 (90% *ee*)	0.02
				24	52 (97% *ee*)[f]	8.6
3[a]	 **3a**	 **3b**	F4	6	95	63
			FMN/*hν*[8]	8	85	43
4[a]	 **4a**	 **4b**	F4	24	93	16
			$[Ru(PDon)_3]^{+}$ [7a]	3	38	--[g]
5[h]	 **5a**	 **5b**	F4	24	> 99	2.1
			Fe(TSPP)[9a]	66	95	0.7
6[h]	 **6a**	 **6b**	F4	24	92	1.9
			Fe(TSPP)[9a]	113	73	0.3
7[h]	 **7a**	 **7b**	F4	2	> 99	25
				6	> 99[i]	83
				6	97[j]	81
			Fe(TSPP)[9a]	24	95	1.9

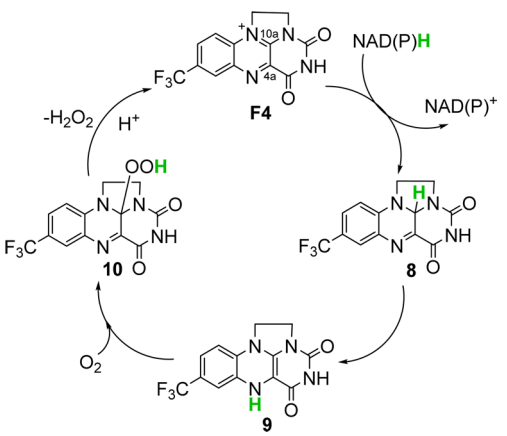
[a]Reaction conditions: substrate (20 mM), NAD^+ (0.1 mM), **F4** (0.05 mM), HLADH (20 U/mL), and catalase (50 U/mL) in 10 mL (50 mM) of aqueous phosphate buffer (pH 8) at room temperature. [b]Isolated yield unless otherwise noted. [c]TOF of **F4** over the total reaction time. [d]NADH was used instead of NAD^+. [e]HLADH (40 U/mL) was used in the reaction. [f]The experiment was repeated using FMN instead of **F4** as the catalyst under the same reaction conditions. [g]The reaction was stopped at a conversion of 38% because of product inhibition. [h]Reaction conditions: monosaccharide (25 mM), $NADP^+$ (0.5 mM), F4 (0.5 mM), GDH (3 U/mL), and catalase (50 U/mL) in 10 mL (50 mM) of an aqueous sodium chloride solution at pH 7 and room temperature, and the yield was determined by ^1H NMR using maleic acid as an internal standard. [i]**F4** at 0.2 mol % was used instead of **F4** at 2 mol %. [j]Glucose (2.25 g) was used.

proceeded smoothly with excellent stereoselectivity (Table 2, entry 2) and afforded (*S*)-3-methyl-*δ*-valerolactone (**2b**) as an important synthon for the total synthesis of tulearin C[19] or neopeltolide macrolactone.[20] When the substrate was changed to an achiral diol such as 1,4-butanediol (**3a**), the corresponding butyrolactone (**3b**) could be obtained with excellent yield in a shorter reaction time (Table 2, entry 3). It is noteworthy that cyclohexanol (**4a**), which usually suffers from the product inhibition effect as described previously,[7a,8] also underwent a smooth transformation under the presented system to give cyclohexanone (**4b**) in 93% yield without using a two-liquid-phase system (Table 2, entry 4).

Encouraged by the results obtained from NAD^+ regeneration, we further evaluated the presented method for $NADP^+$ regeneration. Glucose dehydrogenase-catalyzed oxidations of D-xylose (**5a**), D-mannose (**6a**), and D-glucose (**7a**) were selected using Gröger's method;[9a] similar to regeneration of NAD^+, regeneration of $NADP^+$ proceeded successfully under the presented system, and the substrates were smoothly converted into sodium salts in almost quantitative yields (Table 2, entries 5–7, respectively). Notably, all reaction rates increased significantly, and the overall TOFs of oxidation of **5a**, **6a**, and **7a** were 2.1, 1.9, and 25 h^{-1}, respectively, which are much higher than that of iron(III) porphyrin-catalyzed $NADP^+$ regeneration for the same reaction under the same conditions (TOFs of ~0.7, ~0.3, and ~1.9 h^{-1}, respectively).[9a] Encouraged by these results, we further reduced the dosage of **F4** for the oxidation of **7a**, and it was possible to decrease the amount of **F4** from 2 mol % to as low as 0.2 mol % without a significant loss of catalytic efficiency (TOF ~ 83 h^{-1}). To test the feasibility of the presented method on a preparative scale, the gram-scale catalytic system was then examined for this reaction. Similar to the smaller-scale case, the reaction also proceeded smoothly, and the desired product **7b** was obtained in 97% isolated yield (Table 2, entry 7).

For NAD(P)H with strong hydride donor capacity and detection of H_2O_2, a hydride transfer mechanism is proposed for the presented system (Scheme 1). NAD(P)H was first

Scheme 1. Postulated Reaction Mechanism



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oxidized by transferring a hydride from C^4 of the dihydronicotinamide to C^{10a} of **F4** via imine reduction. The generated intermediate **8** then isomerized into the reduced flavin **9** through imine−enamine tautomerization. The isolation of intermediate **9** as an air-sensitive compound (Figures S22 and S27) provided strong support for this mechanism. There are two possible routes for the regeneration of **F4**, one in which the reduced flavin **9** is reoxidized via a sequence of disproportionations and two successive single-electron transfers to O_2 through a C^{4a}-flavin hydroperoxide adduct, as usually known for natural flavin reacting with O_2.[21] However, according to a recent study,[22] another route (as illustrated in Scheme 1) is also possible; following activation of O_2 that resulted in the formation of a transient pseudobase **10** that carries the −OOH group at the C^{10a} position, the catalytic cycle is finally completed by protonation of **10** with a concomitant elimination to produce the starting flavinium cation **F4** and H_2O_2.

3. CONCLUSION

In conclusion, a simple, clean, and highly efficient oxidized cofactor regeneration system using a water-soluble artificial flavinium organocatalyst is presented. It has the following advantages. (1) It avoids the use of a metal or irritant organic cocatalyst. (2) It does not rely on any special illumination or equipment. (3) The water solubility of the catalyst makes a fully homogeneous system, thereby circumventing diffusion limitations, which is an obvious advantage for the real enzyme catalysis system. (4) The regeneration efficiency is high, as evidenced by TOFs for various biotransformations. (5) Mild reaction conditions are used (air atmosphere, more adaptable pH, and temperature tolerant range). Moreover, the presented system provides an easy scale-up protocol. Hence, we believe that it will find wide applications in organic synthesis as well as in industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01261.

All reaction details and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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