Synthesis of Insoluble Polystyrene-Supported Flavins and Their Catalysis in Aerobic Reducion of Olefins

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((Additional Supporting Information may be found in the online version of this article.))

ABSTRACT

2',4'-*p*-Vinylbenzylideneriboflavin (**2',4'-PVBRFl**) was prepared as a flavin-containing monomer and copolymerized with divinylbenzene and styrene or its *p*-substituted derivatives such as 4-acetoxystyrene, 4-vinylbenzyl alcohol, and 4-vinylbenzoic acid to give the corresponding non-functionalized and functionalized PS-DVB-supported flavins **PS(H)-DVB-Fl**, **PS(OAc)-DVB-Fl**, **PS(CH$_2$OH)-DVB-Fl**, and **PS(COOH)-DVB-Fl**, respectively. **PS(OH)-DVB-Fl** was also prepared by hydrolysis of **PS(OAc)-DVB-Fl** under basic conditions. These novel flavin-containing insoluble polymers exhibited characteristic fluorescence in solid state, except **PS(OH)-DVB-Fl**, and different catalytic activities in aerobic reduction of olefins by in-situ generated diimide from hydrazine depending on their pendant functional group. For example, **PS(H)-DVB-Fl** was found to be particularly effective for neutral hydrophobic substrates, which could be readily recovered by a simple filtration and reused more than 10 times without loss in catalytic activity. On the other hand, **PS(OH)-DVB-Fl** and **PS(COOH)-DVB-Fl** proved to be highly active for phenolic substrates known to be less reactive in the reaction with conventional non-supported flavin catalysts.

KEYWORDS: heterogeneous polymers; catalysis; flavin; aerobic oxidation; fluorescence

INTRODUCTION

Flavoenzymes such as monooxygenase and DNA photolyase containing flavin cofactors play a pivotal role in biological redox systems in nature.[1] Catalytic functions of these flavoenzymes have inspired chemists to use the active center, the isoalloxazine ring of flavin cofactors, for developing simple flavin molecule-catalyzed metal-free redox reactions for organic synthesis.[2] Although various biomimetic flavin-catalyzed organic reactions have been reported, they have not yet reached the stage of practical application. One of the unsolved issues responsible for such limitation is efficient recovery and reuse of the flavin catalysts. In general, immobilizing catalysts on an insoluble support can be highly effective since it allows for not only easy recovery and reusability of the catalysts as well as facile product isolation but also the development of continuous flow synthesis.[3] Nevertheless, it is surprising that the immobilization of flavin catalysts onto an insoluble support via covalent bond has remained unexplored so far, although there have been several reports on the synthesis and application of linear soluble polymer-supported flavins.[4-7] König and co-workers reported that flavin molecules bearing fluorinated or hydrophobic aliphatic chains could be immobilized onto solid supports such as fluorous silica gel, reversed phase silica gel, and polyethylene pellet and used them as reusable heterogeneous photocatalysts for oxidation of benzyl alcohols in water.[8] However, since they are noncovalent immobilizations, it is probably not so easy to apply them to other reactions requiring organic solvents or additional reagents without catalyst leaching. Thus, a readily reusable insoluble polymer-supported flavin catalyst potentially available for comprehensive reactions has so far not been developed.

Reduction of olefins is among the most fundamental molecular transformations in organic synthesis. The most commonly used method for olefin reduction today is arguably that with molecular hydrogen catalyzed by a transition metal such as Pd and Pt because of its high efficiency and reliability, even though noble metal catalysts and risky H_2 gas are required.[9] Meanwhile, olefin reduction by diimide, NH=NH, is known as an alternative method where in principle NH=NH has to be generated in-situ due to its high lability.[10] In this respect, there is no doubt that hydrazine, NH_2NH_2, is the most attractive NH=NH generator, because it is much cheaper than other candidates, such as anthracene diimide and arylsulfonylhydrazide,[10] and H_2O is the sole byproduct of oxidation of NH_2NH_2 by O_2. We previously introduced an efficient way for the generation of NH=NH by the aerobic oxidation of NH_2NH_2 with synthetic flavin catalysts, which led us to the development of a convenient and safe method for the flavin-catalyzed aerobic reduction of olefins.[11] Combination of the inherent chemoselectivity of diimide reduction[10] and the redox catalytic activity of flavin molecules has allowed for efficient reduction of various olefins including those not applicable in typical metal-based hydrogenation under mild conditions, as demonstrated by us[11] and others,[12] which is highly environmentally benign because of utilizing metal-free organocatalyst (flavin) and nonhazardous terminal oxidant (O_2) and producing nontoxic wastes (N_2 and H_2O). The synthetic utility of the flavin-catalyzed olefin reduction further led us to develop readily reusable insoluble polymer-supported flavin catalysts to render it even more practical.

In this article, we present the first insoluble organic polymer-supported flavins and their use as an efficient and reusable catalyst for aerobic reduction of olefins with hydrazine. We have chosen poly(styrene-*co*-divinylbenzene) (PS-DVB) as a support, because the corresponding polymeric catalysts can be designed from comonomers and easily prepared by radical copolymerization.[3] We initially show the synthesis of new flavin-containing styrene monomer, 2′,4′-*O*-*p*-vinylbenzilidene riboflavin (**2′,4′-PVBRFl**), and then its radical copolymerization with divinylbenzene and styrene or *p*-functionalized styrene derivatives to prepare poly(styrene-*co*-divinylbenzene-*co*-**2′,4′-PVBRFl**) (**PS(R)-DVB-Fl**) bearing a different pendant group (R). Finally, we detail the catalytic activities as well as reusability of **PS(R)-DVB-Fl** in aerobic reduction of olefins with hydrazine.

EXPERIMENTAL

General

Melting points were measured on an AS ONE ATM-01. NMR spectra were recorded using a JEOL JNM-ECX-400 (^{1}H, 400 MHz) and JNM-ECA-400 spectrometers (^{1}H, 400 MHz) or a Varian Unity-Inova 600 spectrometer (^{1}H, 600 MHz and ^{13}C, 151 MHz). The chemical shifts of ^{1}H NMR and ^{13}C NMR signals are quoted relative to tetramethylsilane. IR spectra were recorded on a JASCO IR-460 spectrometer with ATR unit. UV spectra were recorded on JASCO V-550 spectrometer. Steady-state emission and excitation spectra were recorded using a Hitachi F-7000 spectrometer. The solid state emission quantum yield was measured using a $BaSO_4$-coated integrating sphere (69 mm internal diameter) with an exit port (20 mm diameter) connected to a polychromator (Photal MCPD-1000), image intensifier (Hamamatsu Photonics, C7039-02), and dual-cooled CCD camera (Hamamatsu Photonics, C4880-17). Excitation ray for solid state emission was a diode laser (Coherent, Radius 405) or a high stability mercury xenon lamp (Hamamatsu Photonics, L2422) coupled with a monochromator (Photon Technology International, Model 101). All emission spectra were corrected for the spectral response of the optical system using quinine bisulfate and *N,N*-dimethylaminonitrobenzene as a standard[13]. GC analyses were carried out on a Shimazu GC-2010 by using a DB-1 glass capillary column (0.25 mm×30 m).

Materials

Riboflavin (Kanto Chemical), hydroquinone (nacalai tesque), *p*-toluenesulfonic acid monohydrate ($TsOH•H_2O$, TCI), dimethyl 2,2'-azobis(2-methylpropionate) (MAIB, Wako Chemical), hydrazine monohydrate (Wako Chemical, nacalai tesque), 4-phenyl-1-butene (Kanto Chemical), *o*-allylphenol (Kanto Chemical), DMF (nacalai tesque), and acetonitrile (nacalai tesque) were commercially available and used without further purification. 2,2'-Azobis(isobutyronitrile) (AIBN, Wako Chemical) and 4-vinylbenzoic acid (TCI) were purified by recrystallization from methanol. 4-Acetoxystyrene (Sigma Aldrich, Japan) was purified by washing with 0.1 N sodium hydride and water. Styrene (nacalai tesque) and divinylbenzene (DVB, Wako Chemical) were purified by distillation under reduced pressure. 4-Vinylbenzaldehyde diethyl acetal[14] and 4-vinylbenzyl alcohol[15] were prepared according to the reported procedure.

Synthesis of 2',4'-PVBRFl

Riboflavin (225 mg, 0.60 mmol), *p*-$TsOH•H_2O$ (114 mg, 0.60 mmol), and hydroquinone (0.4 mg, 3.6 μmol) were placed in a heat-gun-dried 50 mL round bottom flask under a nitrogen atmosphere. DMF (12 mL) and 4-vinylbenzaldehyde diethyl acetal (309 mg, 1.5 mmol) were added, and the solution was stirred for 3 h at 80 °C. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (3×30 mL). The aqueous layer was extracted with ethyl acetate (3×30 mL), and the combined organic layers were dried over $MgSO_4$, which was filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a mixture of MeOH:EtOAc 6:94 as eluent to afford 163 mg of **2',4'-PVBRFl** as yellow powder (56%): M.p. 180 °C (decomp.); ^1H NMR (600 MHz, DMSO-d_6, δ): 2.38 (s, 3H, 7-CH_3), 2.45 (s, 3H, 8-CH_3), 3.45-3.53 (m, 1H, 3'-CH), 3.55 (dt, *J* = 11.6 Hz, 1H, 5'-CH), 3.64 (ddd, *J* = 9.6, 6, 1.6 Hz, 1H, 4'-CH), 3.75 (ddd, *J* = 11, 6, 1.5 Hz, 1H, 5'-CH), 4.16 (ddd, *J* = 9.6, 7.5, 2.6 Hz, 1H, 2'-CH), 4.68 (t, *J* = 6 Hz, 1H, 5'-OH), 4.76-4.94 (br, 1H, 1'-CH), 5.11-5.23 (br, 1H, 1'-CH), 5.23 (dd, *J* = 10.8, 0.6 Hz, 1H, -C=CH), 5.50 (s, 1H, -OCHO-), 5.64 (d, *J* = 5.4 Hz, 1H, 3'-OH), 5.81 (dd, *J* = 18, 0.6 Hz, 1H, -C=CH), 6.68 (dd, *J* = 10.8, 17.4 Hz, 1H,-CH=C), 7.21 (d, *J* = 8.4 Hz, 2H, *m*-H), 7.35 (d, *J* = 7.8 Hz, 2H, *o*-H), 7.81 (s, 1H, 6-ArH), 8.01 (s, 1H, 9-ArH), 11.35 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6, δ): 18.7, 20.6, 46.2, 60.7, 63.3, 78.5, 81.8, 99.0, 114.7, 118.1, 125.4, 126.3, 130.4, 132.0, 133.7, 135.7, 136.1, 137.1, 137.2, 137.4, 145.6, 150.6, 155.3, 159.8 ppm; IR (ATR): v = 3491, 3322, 3162, 3012, 2829, 1716, 1650, 1574, 1532, 1497, 1421, 1402, 1349, 1259, 1226, 1180, 1132, 1082, 1011, 833 cm^{-1}; UV-Vis (ethanol): λ_{max} (ε) = 264 (34344), 360 (6351), 444 nm (8898); Fluorescence emission : λ_{max} (solid) = 556 nm (λ_{ex} = 442 nm), λ_{max} (ethanol) = 516 nm (λ_{ex} = 442 nm); MS (DART): *m/z* 491.1

([M+H]$^+$); Anal. calcd. for $C_{26}H_{26}N_4O_6$: C 61.41, H 5.55, N 11.02; found: C 61.58, H 5.42, N 11.09.

Preparation of PS(H)-DVB-Fl

2',4'-PVBRFl (39 mg, 0.08 mmol), styrene (367 mg, 3.52 mmol), DVB (52 mg, 0.40 mmol) and MAIB (18 mg, 0.08 mmol) was dissolved in DMF (2 mL) in a screw tube (18 mmID). The mixture was bubbled with nitrogen for 1 min and stirred at 65 °C for 25 h under nitrogen atmosphere. The resulting yellow gel was poured into ether and crushed, then washed with ether, THF, and methanol by means of Soxhlet extractor and dried in *vacuo* to give 214 mg of poly(2',4'-PVBRFl-*co*-St-*co*-DVB) (**PS(H)-DVB-Fl**) as yellow solid (58%). The content of flavin unit in polymer was calculated to be 0.12 mmol g^{-1} based on the elemental analysis data: Anal. Found: C 88.82, H 7.81, N 0.69; M.p. 180 °C (decomp.); Fluorescence emission (solid): λ_{max} = 539 nm (λ_{ex} = 405 nm); IR (ATR): v = 3060, 3026, 2921, 2852, 1601, 1584, 1547, 1493, 1451, 756, 696, 541 cm^{-1}. Particle size of the polymer was controlled by grinding and sieving prior to use as catalyst.

Preparation of PS(OAc)-DVB-Fl

2',4'-PVBRFl (78 mg, 0.16 mmol), 4-acetoxystyrene (1.14 g, 7.04 mmol), DVB (104 mg, 0.80 mmol) and AIBN (26 mg, 0.16 mmol) was dissolved in DMF (4 mL) in a screw tube (18 mmID). The mixture was bubbled with nitrogen for 1 min and stirred at 65 °C for 18 h under nitrogen atmosphere. The resulting yellow gel was poured into ether and crushed, then washed with ether, THF, and methanol by means of Soxhlet extractor and dried in *vacuo* to give 869 mg of poly(2',4'-PVBRFl-*co*-4-acetoxystyrene-*co*-DVB) (**PS(OAc)-DVB-Fl**) as yellow solid (65%). The content of flavin unit in polymer was calculated to be 0.18 mmol g^{-1} based on the elemental analysis data: Anal. Found: C 74.73, H 6.46, N 0.98; Fluorescence emission (solid): λ_{max} = 537 nm (λ_{ex} = 405 nm); IR (ATR): v = 2923, 2849, 1754, 1505, 1367, 1130, 1186, 1164, 1014, 909, 844, 552 cm^{-1}.

Preparation of PS(OH)-DVB-Fl

A mixture of **PS(OAc)-DVB-Fl** (900 mg) and $NH_2NH_2 \bullet H_2O$ (1.02 g, 20.3 mmol) in DMF (20 mL) was stirred at 30 °C for 3 h in a screw tube (18 mmID). The resulting orange gel was poured into water and crushed, then washed with water, methanol, and ether by means of Soxhlet extractor and dried in *vacuo* to give 321 mg of poly(2',4'-PVBRFl-*co*-4-hydroxystyrene-*co*-DVB) (**PS(OH)-DVB-Fl**) as orange solid. The content of flavin unit in polymer was estimated to be 0.18 mmol g^{-1} because of quantitative conversion judged by FT-IR analysis: IR (ATR): v = 3329, 3024, 2915, 1611, 1540, 1509, 1444, 1363, 1225, 1171, 1013, 905, 825 cm^{-1}. Particle size of the polymer was controlled by grinding and sieving prior to use as catalyst.

Preparation of PS(CH$_2$OH)-DVB-Fl

2',4'-PVBRFl (39 mg, 0.08 mmol), 4-vinylbenzyl alcohol (477 mg, 3.56 mmol), DVB (52 mg, 0.40 mmol) and MAIB (18 mg, 0.08 mmol) was dissolved in DMF (2 mL) in a screw tube (18 mmID). The mixture was bubbled with nitrogen for 1 min and stirred at 65 °C for 36 h under nitrogen atmosphere. The resulting yellow gel was poured into ether and crushed, then washed with ether, THF, and methanol by means of Soxhlet extractor and dried in *vacuo* to give 207 mg of poly(2',4'-PVBRFl-*co*-4-vinylbenzyl alcohol-*co*-DVB) (**PS(CH$_2$OH)-DVB-Fl**) as yellow solid (48%). The content of flavin unit in polymer was calculated to be 0.15 mmol g^{-1} based on the elemental analysis data: Anal. Found: C 77.36, H 7.40, N 0.85; Fluorescence emission (solid): λ_{max} = 553 nm (λ_{ex} = 405 nm); IR (ATR): v =3322, 2921, 1540, 1511, 1419, 1211, 1011, 806 cm^{-1}. Particle size of the polymer was controlled by grinding and sieving prior to use as catalyst.

Preparation of PS(COOH)-DVB-Fl

2',4'-PVBRFl (39 mg, 0.08 mmol), 4-vinylbenzoic acid (527 mg, 3.56 mmol), DVB (52 mg, 0.40 mmol) and MAIB (18 mg, 0.08 mmol) was dissolved in DMF (2 mL) in a screw tube (18 mmID). The mixture was bubbled with nitrogen for 1 min and stirred at 65 °C for 10 h under nitrogen atmosphere. The resulting yellow gel was poured into ether and crushed, then washed with ether, THF, and methanol by means of Soxhlet extractor and dried in *vacuo* to give 466 mg of poly(2’,4’-PVBRFl-*co*-4-vinylbenzoic acid-*co*-DVB) (**PS(COOH)-DVB-Fl**) as yellow solid (76%). The content of flavin unit in polymer was calculated to be 0.13 mmol g^{-1} based on the elemental analysis data: Anal. Found: C 68.92, H 6.03, N 0.74; Fluorescence emission (solid): λ_{max} = 555 nm (λ_{ex} = 405 nm); IR (ATR): v =2921, 1684, 1608, 1576, 1540, 1507, 1419, 1240, 1177, 1105, 1017, 853, 803, 775, 705 cm^{-1}. Particle size of the polymer was controlled by grinding and sieving prior to use as catalyst.

Typical procedure for aerobic reduction of olefins catalyzed by PS(R)-DVB-Fl

Hydrazine monohydrate (19 mg, 375 μmol) and acetonitrile (0.7 mL) was mixed for 1 min under vigorous stirring. To the mixture was added **PS(R)-DVB-Fl** (3.75 μmol, 3 mol%), an olefin (125 μmol), and acetonitrile (0.3 mL), which was stirred at 30 °C for 14 h under air. The reaction yield was determined by either GC analysis with absolute calibration or NMR measurement using 1,3,5-trimethoxybenzene as an internal standard.

Reuse test of PS(H)-DVB-Fl in aerobic reduction of 4-phenyl-1-butene

A glass reactor with Teflon filter (MultiSynTech, V050TF118) equipped with a Luer stopper (MultiSynTech, V000LS100) was charged with **PS(H)-DVB-Fl** (61 mg, 7.4 μmol), 4-phenyl-1-butene (33 mg, 0.25 mmol), $NH_2NH_2 \cdot H_2O$ (38 mg, 0.75 mmol), and acetonitrile (2 mL). The mixture was agitated using a shaker (125 rpm) at 30 °C under air. The reaction was monitored by GC analysis. The reaction mixture was directly filtered from the glass reactor and the remaining **PS(H)-DVB-Fl** was washed with acetonitrile, THF, and ether, which was reused for the next reaction.

RESULTS AND DISCUSSION

Synthesis of Flavin-Containing Styrene Monomer

Riboflavin (Vitamin B_2) is readily available in commerce and its diacetalized derivatives, such as 2’,4’:3’,5’-di-*O*-methyleneriboflavin (**DMRFl**), have previously proven to be an active catalyst for aerobic reduction of olefins with hydrazine (Figure 1).[11b,11c] Taking this into account, we decided to use riboflavin as a starting material and introduce a styrene moiety to its ribityl group through the 2’,4’- or 3’,5’-acetal linkage.

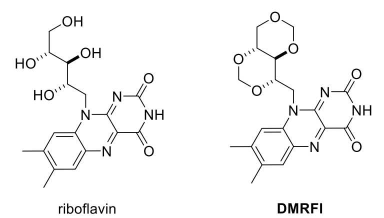
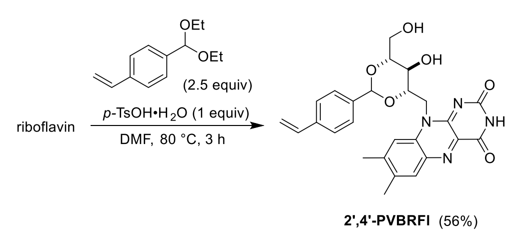


FIGURE 1 Structures of riboflavin and **DMRFl**.

Such partial acetalization of the ribityl group often encounters a synthetic problem even through its protection and deprotection. For example, Yashima and coworkers synthesized 2’,4’-*O*-*p*-ethynylbenzilidene riboflavin as a monomer by the reaction of 5’-*O*-trityl riboflavin and 4-ethynylbenzaldehyde dimethyl acetal followed by the deprotection of the trityl group in 11% yield.[7] By contrast, we found that riboflavin could be readily converted into **2’,4’-PVBRFl** and its 3’,5’-analogue in a ratio of approximately 2:1 with a trace amount of diacetalized product by treating with 2.5 equivalents of 4-vinylbenzaldehyde diethyl acetal and 1 equivalent of $TsOH \cdot H_2O$ in DMF at 80 °C for 3 hours, which could be separated by a column purification to give **2’,4’-PVBRFl** in 56% yield (equation 1). The selective formation of **2’,4’-PVBRFl** can be probably explained by



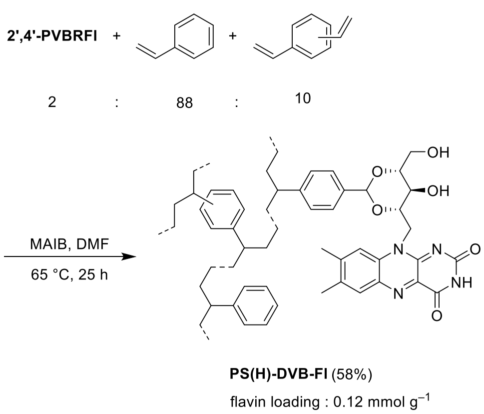
(1)

transacetalization—hydrolysis equilibria that results in thermodynamically more stable **2',4'-PVBRFl** having a freely rotatable primary alcohol group. The structure of **2',4'-PVBRFl** was fully characterized by NMR (^{1}H, ^{13}C, COSY, HMBC, HMQC, ROESY), FT-IR, mass spectroscopy, and elemental analysis.

Synthesis of Flavin-Containing Cross-Linked Polystyrenes

PS-DVB-Supported Flavin

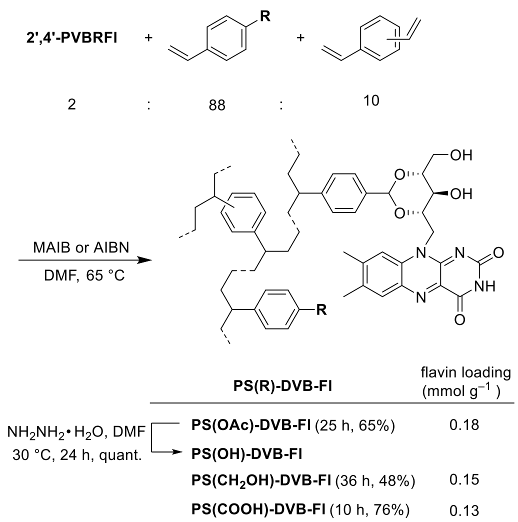
We carried out radical copolymerization of styrene, divinylbenzene, and **2',4'-PVBRFl** in the molar ratio of 88:10:2 using MAIB as an initiator under heating and inert conditions (Scheme 1). The copolymerization proceeded successfully, which was recognized by gelation of the reaction mixture, to give PS-DVB-supported flavin (**PS(H)-DVB-Fl**) in 58% yield after washing with ether, THF, and methanol, followed by drying in *vacuo*. The flavin loading of **PS(H)-DVB-Fl** was calculated to be 0.12 mmol g^{-1} from its nitrogen content determined by elemental analysis. In addition, the actual CHN content of **PS(H)-DVB-Fl** was in good agreement with the theoretical value, indicating that the present copolymerization took place according to the feed molar ratio.



SCHEME 1 Synthesis of **PS(H)-DVB-Fl**.

Functionalized PS-DVB-Supported Flavins

The choice of support polymer is crucial for developing efficient polymer-supported



SCHEME 2 Synthesis of **PS(OAc)-DVB-Fl**, **PS(OH)-DVB-Fl**, **PS(CH$_2$OH)-DVB-Fl**, and **PS(COOH)-DVB-Fl**.

catalysts since the catalytic reactions take place in microenvironment created in the polymer network.[3] In view of the fact that the catalysis of neutral flavin for the aerobic reduction of olefins involves the nucleophilic reduction of a flavin molecule with hydrazine as a rate-determining step,[11c] PS-DVB was supposed to be too hydrophobic as a support for the target reaction because of the strong hydrophilicity of hydrazine. Thus, we designed additional three polymeric flavins **PS(CH$_2$OH)-DVB-Fl**, **PS(OH)-DVB-Fl**, and **PS(COOH)-DVB-Fl** containing different hydrophilic pendant groups in PS-DVB. 4-Vinylbenzyl alcohol, 4-acetoxystyrene or 4-vinylbenzoic acid was copolymerized with divinylbenzene and **2',4'-PVBRFl** in the molar ratio of 88:10:2 under radical conditions to afford **PS(CH$_2$OH)-DVB-Fl**, **PS(OAc)-DVB-Fl**, and **PS(COOH)-DVB-Fl**, respectively, in moderate to high yields (Scheme 2). The acetyl groups in **PS(OAc)-DVB-Fl** were quantitatively hydrolyzed by a treatment with an excess of hydrazine in DMF to give **PS(OH)-DVB-Fl**, which was confirmed by IR spectroscopic data that showed the disappearance of C=O absorbance at 1754 cm^{-1} and the appearance of –OH absorbance at 3329 cm^{-1}. The flavin loadings of **PS(CH$_2$OH)-DVB-Fl**, **PS(OAc)-DVB-Fl**, and **PS(COOH)-DVB-Fl** were estimated to be 0.15, 0.18, and 0.13 mmol g^{-1}, respectively, through elemental analyses.

Photophysical Properties of PS(R)-DVB-Fl

Flavins exhibit a characteristic absorption at ~440 nm with high molar absorptivities as well as an intense fluorescence emission at ~520 nm in solution state.[1g] Indeed, 0.1 mM solution of **2',4'-PVBRFl** in ethanol emitted a bright light under irradiation by a range of UV/Vis lights less than ~500 nm, and its fluorescence spectrum measured with an excitation wavelength of 442 nm showed the maximum emission peak (λ_{max}) at 516 nm (see Supporting Information, Figure S9). Not surprisingly, the fluorescence peak of **2',4'-PVBRFl** in solid state appeared at a slightly longer wavelength (λ_{max} = 556 nm) with much lower intensity, due to concentration quenching (Figure S9). On the other hand, the flavin-containing polymers including **PS(H)-DVB-Fl**, **PS(OAc)-DVB-Fl**, and **PS(COOH)-DVB-Fl** were found to emit light apparently in solid state under 365 nm UV light, except **PS(OH)-DVB-Fl** (Figure 2), which led us to explore their emission properties in more detail. We carried out fluorescence measurements for all kinds of **PS(R)-DVB-Fl** in solid state and determined their solid-state fluorescence quantum yield (ϕ). As expected, a distinct fluorescence emission at ~550 nm was observed for **PS(H)-DVB-Fl** (λ_{max} =542 nm, ϕ = 10.6%), **PS(OAc)-DVB-Fl** (λ_{max} = 542 nm, ϕ = 16.5%), **PS(CH$_2$OH)-DVB-Fl** (λ_{max} = 552 nm, ϕ = 10.1%), and **PS(COOH)-DVB-Fl** (λ_{max} = 552 nm, ϕ = 9.3%) using a 405 nm excitation wavelength (Figure 3), which would indicate that the immobilized flavin molecules were distributed to the polymer network rather homogeneously. By contrast, **PS(OH)-DVB-Fl** exhibited almost no fluorescence emission. This is at least not due to heterogeneous dispersion of flavins into the polymer, given the fact that **PS(OAc)-DVB-Fl** showed the intense fluorescence as mentioned above. Although a clear explanation for the non-fluorescence of **PS(OH)-DVB-Fl** is not available at the moment, we find it interesting because it may be caused by some interactions between the immobilized flavin molecule and phenolic hydroxyl groups, just like the situation in flavoenzyme.[16]

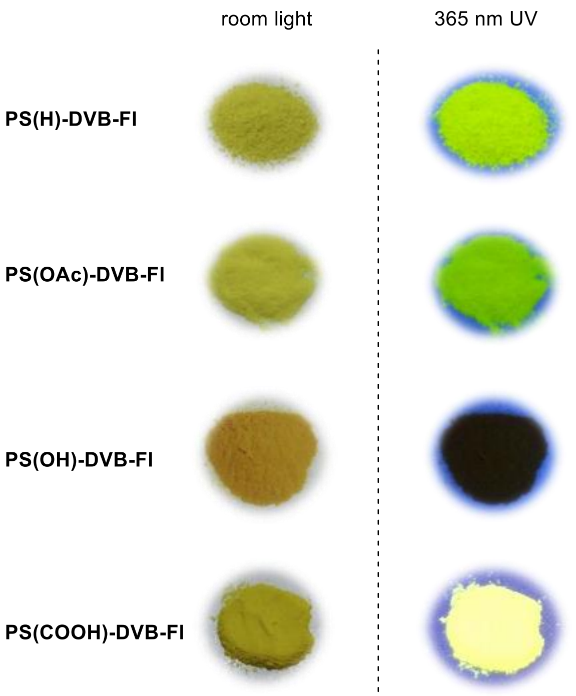


FIGURE 2 Photographs of **PS(R)-DVB-Fl** under room light or UV irradiation (365 nm).

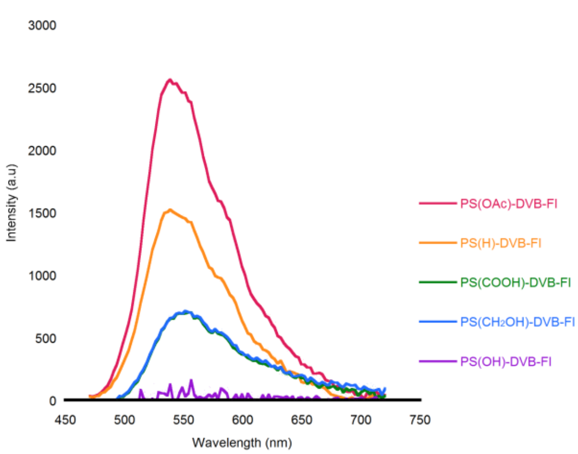
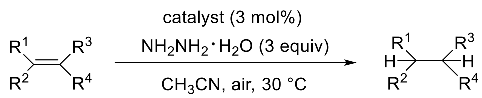


FIGURE 3 Solid-state fluoresence spectra of **PS(R)-DVB-Fl** (λ_{ex} = 405 nm).

Flavin-Catalyzed Aerobic Reduction of Olefins

Aerobic reductions of olefins were carried out with 3 equivalents of hydrazine monohydrate in acetonitrile under air at 30 °C in the presence of 3 mol% of **PS(R)-DVB-Fl** under heterogeneous conditions to evaluate their catalytic activity, in which the polymeric catalysts were ground and sieved to a defined range of particle size prior to use (equation 2).



(2)

The reduction of 4-phenyl-1-butene (**1a**) using **PS(H)-DVB-Fl** with particle size of 53–100 μm proceeded smoothly to give butylbenzene (**2a**)

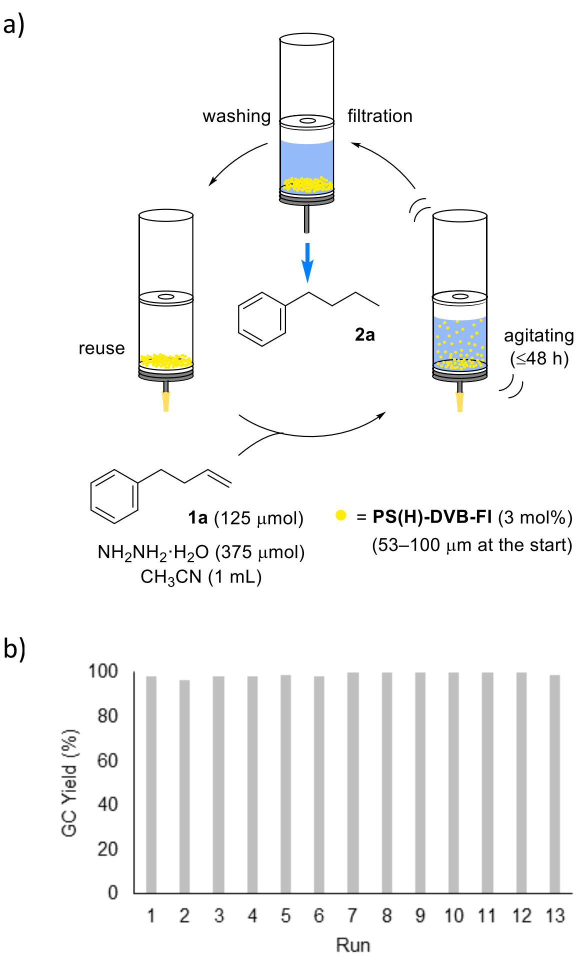
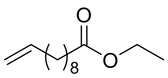
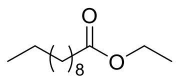
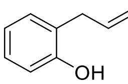
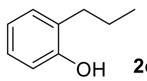
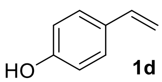
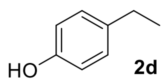


FIGURE 4 Aerobic reduction of **1a** catalyzed by **PS(H)-DVB-Fl**: (a) reaction and recycling protocol, (b) reusability of **1a** (run 1–11, 48 h; run 12, 24 h; run 13, 8 h).

in 86% yield and 98% yield after 24 h and 48 h, respectively (Figure 4b, run 1), in which a filter-equipped glass reactor was used to operate the following catalyst recycling process as efficient as possible (Figure 4a).[17] Solution phase of the reaction mixture was filtered out and analyzed by GC, whereas the residual solid catalyst was washed with acetonitrile, THF, and ether, and dried *in vacuo*, and reused (Figure 4a). Using this simple protocol, the excellent chemical robustness and reusability of **PS(H)-DVB-Fl** could be demonstrated (Figure 4b). Reactions from the 1st run to the 6th run were carried out successively, in which quantitative yields of **2a** were observed without exception. After the 6th run, the reused polymeric flavin catalyst was preserved in a UV-shielding amber desiccator for 3 months, and then the reuse test was restarted to evaluate the storage stability of **PS(H)-DVB-Fl**. The 7th run demonstrated that the catalytic activity was not affected by the storage, which led us to further continue the reuse test until the 11th run under the same conditions. In the 12th run we were finally aware of complete conversion of **1a** to **2a** within 24 h, which was much faster than the reaction using a fresh catalyst in the 1st run. Earlier monitoring of the reaction in the 13th run revealed that the reaction was completed already in 8 h. We supposed that this considerable enhancement of the catalytic activity could be attributed to increasing in the surface area of the solid catalyst as the reactions were repeated. To confirm this assumption, we freshly prepared **PS(H)-DVB-Fl** with particle size of ≤53 μm by careful grinding and sieving, and used it as a catalyst for the same reaction under identical conditions. As expected, nearly quantitative yield was observed in 9 h (Table 1, entry 1), verifying the effectiveness of **PS(H)-DVB-Fl** as a readily reusable as well as highly active catalyst for the present reaction.

Next, we explored the catalytic functions of **PS(CH_2OH)-DVB-Fl**, **PS(OH)-DVB-Fl**, and **PS(COOH)-DVB-Fl**, which were expected to be more effective than **PS(H)-DVB-Fl** as a catalyst

TABLE 1 Flavin-catalyzed aerobic reduction of olefins[a]

Entry	Substrate	Product	Catalyst[b]	Time (h)	Yield (%)[c]
1	**1a**	**2a**	**PS(H)-DVB-Fl**	9	95
2	**1a**	**2a**	**PS(CH_2OH)-DVB-Fl**	24	68
3	**1a**	**2a**	**PS(OH)-DVB-Fl**	24	76
4	**1a**	**2a**	**PS(COOH)-DVB-Fl**	24	61
5	**1a**	**2a**	**DMRFl**	24	56
6	 **1b**	 **2b**	**PS(H)-DVB-Fl**	14	96
7	**1b**	**2b**	**PS(OH)-DVB-Fl**	14	61
8	 **1c**	 **2c**	**PS(H)-DVB-Fl**	36	42
9	**1c**	**2c**	**PS(OH)-DVB-Fl**	36	72
10	**1c**	**2c**	**PS(COOH)-DVB-Fl**	36	76
11	**1c**	**2c**	**DMRFl**	36	19
12	 **1d**	 **2d**	**PS(H)-DVB-Fl**	24	27
13	**1d**	**2d**	**PS(OH)-DVB-Fl**	24	70
14	**1d**	**2d**	**PS(COOH)-DVB-Fl**	24	>99
15	**1d**	**2d**	**DMRFl**	24	4

a Reactions were performed using 125 μmol of the olefin and 375 μmol of hydrazine monohydrate in 1 mL of acetonitrile in the presence of 3 mol% of the catalyst under air at 30 °C.
b Polymeric catalysts with particle size of ≤53 μm were used.
c Determined by GC analysis (entries 1–5) or ^{1}H NMR measurement (entries 6–15) with internal standard.

because of their amphiphilic properties. However, the reduction of **1a** to **2a** catalyzed by any one of these functionalized polymers with particle size of ≤53 μm was not completed even after 24 h (Table 1, entries 2–4), while **PS(H)-DVB-Fl** could efficiently catalyze the reaction (entry 1) as mentioned. Similar tendency in catalytic activity was observed in the reduction of another simple olefin, ethyl 10-undecanoate (**1b**), using **PS(H)-DVB-Fl** (entry 6, 14 h, 96%) and **PS(OH)-DVB-Fl** (ently 7, 14 h, 61%). The amphiphilicity of the acid-functionalized polymers could actually be recognized by apparent aggregation of the polymer particles in the reaction mixtures containing an excess of hydrophilic hydrazine. Nevertheless, only **PS(H)-DVB-Fl**, which is strongly hydrophobic and therefore not aggregated, showed extremely high activity, indicating that particle size is a more crucial factor for reaction efficiency in this case. It is important to note that, at least for the reduction of **1a**, the catalytic functions of **PS(CH_2OH)-DVB-Fl**, **PS(OH)-DVB-Fl**, and **PS(COOH)-DVB-Fl** are not as excellent as **PS(H)-DVB-Fl**, but still comparable with a homogeneous flavin catalyst, **DMRFl** (entry 5), despite their heterogeneity. This fact may be explained by site-isolation effect of the flavin-containing insoluble polymers in which each flavin molecule is isolated from others, that is to say, redoxes of them do not affect each other.

To use the acid-functionalized PS-DVB-supported flavins effectively, we turned our attention to substrates bearing a phenolic hydroxyl group. Given the fact that the rate-determining step of the neutral flavin-catalyzed aerobic reduction is the nucleophilic addition of hydrazine to flavin,[11c] one can expect that such acidic substrates can be unfavorable to the reaction system due to acid-base interaction that lowers the nucleophilicity of hydrazine. Indeed, in homogeneous reaction system with **DMRFl** as a catalyst, *o*-allylphenol (**1c**) and *p*-vinylphenol (**1d**) underwent reduction very slowly to give *o*-propylphenol (**2c**) and *p*-ethylphenol (**2d**) in 19% yield (36 h, entry 11) and in 4% yield (24 h, entry 15), respectively. On the other hand, our polymer-supported flavin catalysts were found to exhibit significantly higher activity for these acidic olefins than **DMRFl**. Particularly effective were **PS(OH)-DVB-Fl** as well as **PS(COOH)-DVB-Fl** over **PS(H)-DVB-Fl**. For example, the reduction of **1c** was catalyzed to furnish **2c** in 42% (**PS(H)-DVB-Fl**, entry 8), 72% (**PS(OH)-DVB-Fl**, entry 9), and 76% yield (**PS(COOH)-DVB-Fl**, entry 10), respectively, after 36 h. An even more distinct advantage of these acid-functionalized polymeric flavins was observed in the reduction of **1d**, which was converted to **2d** in 27% (**PS(H)-DVB-Fl**, entry 12), 70% (**PS(OH)-DVB-Fl**, entry 13), and >99% yield (**PS(COOH)-DVB-Fl**, entry 14), respectively, after 24 h. These results demonstrate that the acid-functionalized polymeric flavins are highly effective catalysts for the present aerobic reduction of olefins bearing a phenolic hydroxy group. This finding can be explained by the high affinity of these flavin polymers for hydrazine via acid-base interaction, which can make the concentration of hydrazine on solid phase higher and that in solution phase lower, and as a result, the rate-determining nucleophilic addition of hydrazine to flavin favorable. Finally, it should also be noted that, in the reduction of **1d** to **2d**, **PS(COOH)-DVB-Fl** could be reused without loss in the activity at least 3 times (see Supporting Information).

CONCLUSIONS

We introduced a novel flavin-containing vinyl monomer, **2’,4’-PVBRFl**, and its copolymers, **PS(R)-DVB-Fl**, as efficient and reusable heterogeneous catalysts for aerobic reduction of olefins with hydrazine. The monomer was easily synthesized from commercially available riboflavin in one step, and the polymeric catalysts were readily prepared by free radical solution copolymerization. Exploring the catalytic activities of **PS(R)-DVB-Fl** in aerobic reduction of olefins with hydrazine revealed that (i) **PS(R)-DVB-Fl** exhibit comparable activities to the non-supported counterpart **DMRFl**, possibly because of flavin molecules dispersedly immobilized onto supports as demonstrated by their characteristic solid state fluorescence, (ii) the non-functionalized PS-DVB-supported flavin, **PS(H)-DVB-Fl**, is particularly effective for aprotic substrates, which can be attributed to its strong hydrophobicity not allowing for aggregation of itself during the reaction unlike with the acid-functionalized PS-DVB-supported flavins, (iii) the acid functionalized PS-DVB-supported flavins such as **PS(OH)-DVB-Fl** and **PS(COOH)-DVB-Fl** have an enhanced affinity for hydrazine, which allows for efficiently catalyzing the reduction of phenolic hydroxyl group-containing olefins known as less reactive substrates in conventional homogeneous system. Efficient catalyst recovery and reuse were demonstrated with **PS(H)-DVB-Fl** that could be readily recovered by a simple filtration and reused without loss in activity at least until 13th run. The results are currently leading us to the synthesis of morphology-controlled flavin-containing insoluble polymers, such as microspheres and mesoporous network polymers, using other polymerization techniques, and their application to the development of a continuous flow system for the present aerobic reduction.

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