

Photooxidation of Benzyl Alcohols with Immobilized Flavins

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Abstract: Benzyl alcohols are oxidized cleanly and efficiently to the corresponding aldehydes under irradiation using flavin photocatalysts and aerial oxygen as the terminal oxidant in homogeneous aqueous solution. Turnover frequencies (TOF) of more than 800 h⁻¹ and turnover numbers (TON) of up to 68 were obtained. Several flavin photocatalysts with fluorinated or hydrophobic aliphatic chains were immobilized on solid supports like fluorinated silica gel, reversed phase silica gel or entrapped in polyethylene pellets. The catalytic efficiency of the heterogeneous photocatalysts was studied for the oxidation of different benzyl alcohols in water and compared to the analogous homogeneous reactions. Removal of the

heterogeneous photocatalyst stops the reaction conversion immediately, which shows that the immobilized flavin is the catalytically active species. The immobilized catalysts are stable, retain their reactivity if compared to the corresponding homogeneous systems and are easily removed from the reaction mixture and reused. TOF of up to 26 h⁻¹, TON of 280 and up to 3 reaction cycles without loss of activity are possible with the heterogeneous flavin photocatalysts.

Keywords: catalyst recycling; flavins; fluorinated chemistry; immobilization; photooxidation; redox chemistry

Introduction

Flavin is a prosthetic group of flavoproteins and a versatile electron carrier in biological systems. In nature, flavins occur mostly in the form of flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN) or riboflavin co-factors.^[1] The presence and structure of the surrounding protein, substitutions, and non-covalent interactions significantly alters the redox properties of these compounds. Furthermore, irradiation has a major effect on the reactivity of flavins by increasing their redox power.^[2]

Recently, flavins have received interest as flavoenzyme models^[3] and for applications in chemical catalysis.^[4,5] Photooxidation of alcohols using catalytic amounts of flavin is particularly advantageous due to the low toxicity of the reagent. The flavin-mediated photooxidation of benzyl alcohols is an efficient process using air as terminal oxidant; the reaction was recently investigated and optimized for homogeneous reaction in acetonitrile solution.^[6] High power LEDs serve as a selective and efficient light source for the reaction, which makes applications to synthesis very easy.

Although a typical catalyst loading in the photooxidation reactions is about 1 mol%, it is advantageous to immobilize the catalysts to facilitate its separation from the reaction mixture and a potential reuse. Furthermore, for the synthesis of larger quantities of carbonyl compounds, it would be desirable to accomplish the catalytic oxidation of alcohols in a continuous reaction process which requires catalysts that are immobilized on a suitable surface and are available for a number of reaction cycles.

Only few examples of immobilized flavins have been published. Bäckvall et al. described the catalytic oxidation of sulfides to sulfoxides by H₂O₂ or NMO to NMO in the osmium-catalyzed dihydroxylation with flavin derivatives immobilized in an ionic liquid.^[4a,7] Rotello et al. reported on the development of flavin derivatives appended on polystyrene copolymers to study their redox properties.^[3b] To the best of our knowledge no use of heterogeneously immobilized flavins as catalysts in organic reactions has been reported.

Typical immobilization strategies for catalysts are covalent binding to a solid support, physical or electrostatic adsorption,^[8] and entrapment of catalysts in porous materials. From these methods, electrostatic

and physical adsorption are the most simple to implement; however, both approaches are prone to catalyst leaching. A special case of surface adsorption that partly overcomes this drawback uses perfluorinated alkyl chains as tags to impose fluororous properties on a given molecule. This allows separation of the perfluorinated compound from a complex reaction mixture by fluororous phase extraction or adsorption on fluororous silica or perfluorinated polymers.^[9] Fluororous technology has been applied to catalyst recovery in transition metal^[10] and organocatalysis.^[11]

We have investigated the immobilization of flavin photocatalysts on unmodified, fluororous and reversed phase silica gel, and the flavin entrapment in PE pellets and glue. The catalytic activity of the heterogeneous photocatalysts was determined in benzyl alcohol photooxidations in aqueous solution and compared to the analogous reactions in homogeneous solution. We discuss and compare here the stability of the different immobilized catalysts and their photooxidation efficacy.

Results and Discussion

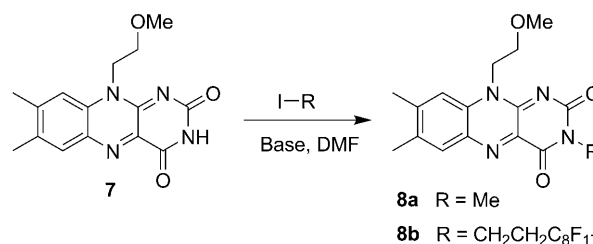
Synthesis

The new flavin derivatives were synthesized according to the Kuhn protocol.^[12] Dinitro compound **1** was obtained in an optimized route from commercially available 4,5-dimethylnitroaniline.^[13] Fluorinated amine **2** was synthesized *via* azide substitution of iodide **5** and subsequent reduction.^[14]

In a nucleophilic aromatic substitution, dinitro compound **1** was reacted with fluorinated amine **2**. After reduction of the remaining nitro group, the resulting amine was instantly used without isolation due to its sensitivity to air. Cyclocondensation with alloxane monohydrate yielded flavin **4** in 38% over two steps. The fluorine mass content of the compound reaches 47%. In order to enhance fluorine interactions, mole-

cules with even higher fluorine content are required. Therefore, flavin **4** was alkylated with iodide **5** and potassium carbonate in dry dimethylformamide to obtain flavin **6** in 62% yield. Flavin **6** exhibits a fluorine mass content of 57% (Scheme 1).

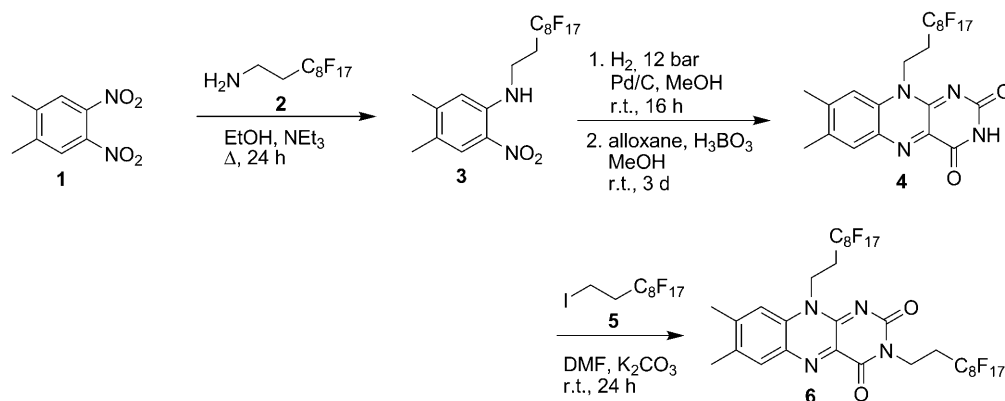
The synthesis and use of flavin **7** was recently reported.^[6] 3-*N*-Methylation of the compound was accomplished in dry dimethylformamide with methyl iodide and caesium carbonate as base yielding 91% of flavin **8a**. The use of a perfluorinated alkylation agent **5** gave flavin **8b** in 23% yield (Scheme 2).



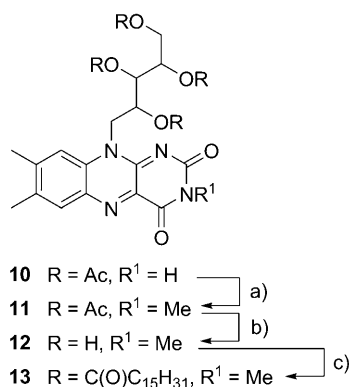
Scheme 2. Preparation of *N*-methylated and fluorinated flavins **8**.

The synthesis of a hydrophobic flavin **13** started from commercially available riboflavin. Riboflavin tetraacetate (**10**), which is easily available in large amounts from riboflavin,^[15] was methylated as described before yielding flavin **11**^[16] in 71% yield. The acetyl groups of the ribityl chain were cleaved by *p*-toluenesulfonic acid to give 3-methylriboflavin (**12**)^[16] (73%). Reaction with palmityl chloride gave 3-methyltetrapalmityl riboflavin (**13**) as an orange soft solid in 52% yield (Scheme 3). This flavin shows high solubility in organic solvents and its hydrophobic properties are desired for immobilization on reversed phase silica gel.

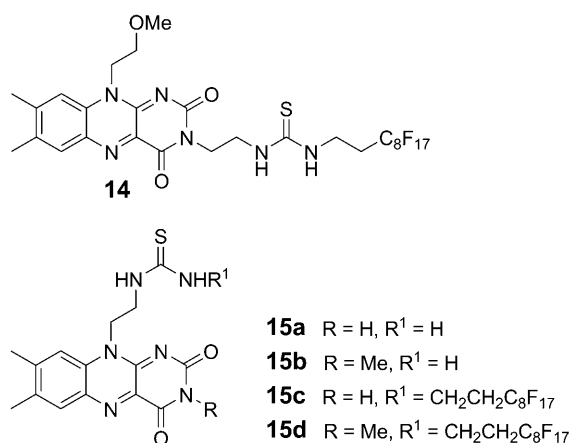
In addition, some previously prepared flavin derivatives,^[6] shown in Scheme 4, were tested for immobilization and as catalysts.



Scheme 1. Synthesis of perfluorinated flavin **6**.



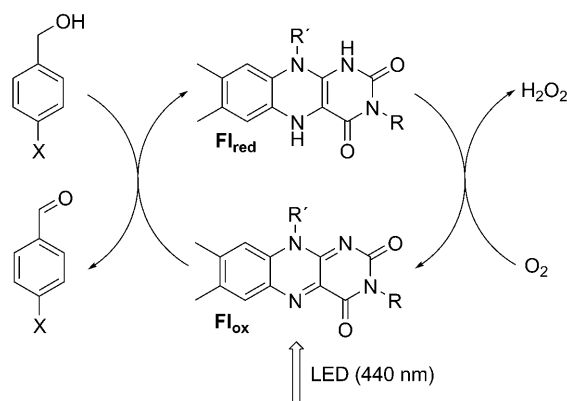
Scheme 3. Synthesis of riboflavin derivatives. *Reaction conditions:* a) MeI, CsCO₃, DMF, room temperature, 16 h; b) *p*-TsOH, EtOH, Δ, 17 h; c) C₁₆H₃₁OCl, pyridine, CHCl₃, room temperature, 24 h



Scheme 4. Thiourea-flavin derivatives investigated for catalytic activity.

Photooxidations in Aqueous Homogeneous Solution

Recently, we studied the photooxidation of *p*-methoxybenzyl alcohol in the presence of various flavin catalysts in acetonitrile solution.^[6] In the catalytic cycle, oxidized flavin (**Fl_{ox}**) is excited by irradiation with light of suitable wavelength. As light source we used commercially available high power LEDs with an emission maximum at 440 nm which matches the longest wavelength absorption maximum of oxidized flavin. After irradiation, the flavin becomes strongly oxidizing and benzyl alcohol is converted into the corresponding aldehyde. If oxygen is present in the reaction mixture, the reduced flavin species (**Fl_{red}**) is instantly reoxidized, forming hydrogen peroxide as the second reaction product.^[4d,6,17,18] Overall, benzyl alcohol is oxidized in a light-driven catalytic cycle by aerial oxygen as terminal oxidant (Scheme 5).^[17–20] In these experiments, we were able to almost completely convert the alcohol starting material in a typical set-



Scheme 5.

up within one hour, corresponding to a TOF of up to 10 h⁻¹.

However, we realized that this reaction is even more efficient in aqueous solution. Figure 1 shows a standard screening set-up (left without irradiation; right with irradiation). The photocatalytic activity of different flavins was tested in solutions of benzyl alcohol in D₂O (for detailed set-up see Experimental Section).

With 10 mol% of riboflavin tetraacetate (**10**) as photocatalyst the reaction was completed within five minutes (Table 1, entry 1). Within one minute, it was possible to convert 58% of the alcohol corresponding to a TOF of 350 h⁻¹ (entry 2) and lower catalyst loadings led to a TOF of more than 800 h⁻¹ (entry 3). If the reaction mixture is not stirred, the TOF drops by a factor of 5, demonstrating the importance of efficient mixing during the course of the reaction, especially for longer irradiation times (entry 4). Our previous investigations in acetonitrile solution showed that the addition of thiourea dramatically accelerates this photooxidation.^[6] Therefore, we also tried to further improve the rates in aqueous solution by the addition of thiourea. However, in water the addition of thiourea decreases the reaction rates (entries 5 and 6). Whereas in acetonitrile electronically activated substrates, such as *p*-methoxybenzyl alcohol were required for the conversion into the aldehyde,^[6] the scope of convertible substrates is significantly extended in water. Alteration of the redox potentials or a tighter catalyst–substrate interaction in the more polar solvent may explain the observation. We were able to convert unsubstituted benzyl alcohol (entry 8) and electron-poor benzyl alcohols in moderate to good yields (entries 9–11). As expected, due to the electronic deactivation, the reaction rates drop compared to *p*-methoxybenzyl alcohol. An experiment with 2.5 mmol of *p*-methoxybenzyl alcohol and a catalyst loading of 1 mol% in 250 mL of water demonstrates the applicability on preparative laboratory scale, as full conversion was obtained after 20 h in a

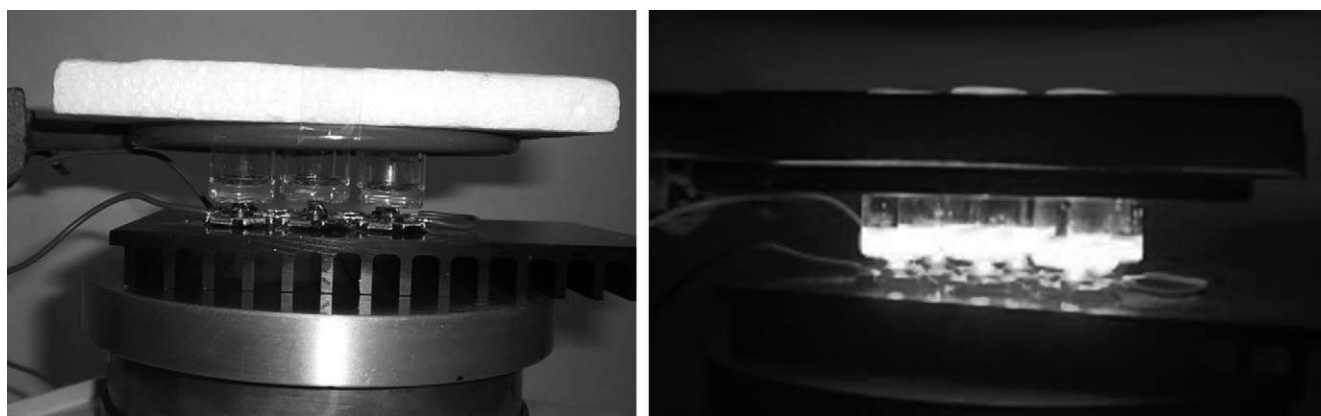


Figure 1. Standard screening setup (*left*: without irradiation; *right*: with irradiation).

Table 1. Catalytic photooxidations with flavins in homogeneous aqueous solution.^[a]

Entry	Flavin	X	<i>t</i> [min]	Aldehyde [%]	TON	TOF [1/h]
1	10	OMe	5	100	10	–
2	10	OMe	1	58	5.8	348
3 ^[b]	10	OMe	5	68	68	816
4 ^[c]	10	OMe	5	59	5.9	71
5 ^[c,d]	10	OMe	15	79	7.9	32
6 ^[c,d,e]	10	OMe	15	48	4.8	19
7 ^[c,d]	11	OMe	15	48	4.8	19
8	10	H	25	75	7.5	18
9	10	COONa	25	74	7.4	18
10	10	COOMe	25	58	5.8	14
11	10	COOH	25	47	4.7	11

^[a] Conditions: *V* = 1 mL, 2% DMSO-*d*₆ in D₂O, alcohol: 0.002 M, 10 mol% of catalyst.

^[b] 1 mol% of catalyst.

^[c] Without stirring.

^[d] Reaction in an NMR tube instead of a small glass vial.

^[e] Addition of thiourea (0.2 mM).

very clean reaction (see Supporting Information for details).

Earlier, Fukuzumi et al. presented a mechanism for this reaction starting with an initial electron transfer from the alcohol substrate to the oxidized flavin catalyst, leading to the aldehyde and hydrogen peroxide as products.^[17,19] Later, this mechanism was supported by calculations^[20] and we observed stoichiometric hydrogen peroxide formation in previous studies.^[4d,6] 1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-ol was used as probe to discriminate between an electron transfer and a hydrogen abstraction mechanism for the photooxidation of benzyl alcohols.^[21] At the conditions of our experiments, we exclusively observe the electron transfer pathway (see Supporting Information for details).

Photooxidation with Silica Gel-Immobilized Flavins

After the optimization of the photooxidation conditions in homogeneous solution, heterogeneous flavin catalysts immobilized on silica gel were investigated. Initially, flash silica gel particles with diameters of 35–70 μm were used as solid support for immobilization due to their large surface areas. Immobilization of the catalysts was accomplished by soaking flash silica gel with solutions of flavins in chloroform and evaporation of the solvent, which gave homogeneous yellow powders of flavin-coated silica gel (Figure 2).

Fluorinated flavins **4**, **6** and **8b** and non-fluorinated flavins **7**, **8a**, **13**, **14** and **15** were immobilized on silica gel and fluorinated silica gel. The nature of the support has a dramatic effect on the stability of the immobilized catalyst in aqueous solution. Fluorinated flash silica gel turned out to be a more suitable support for all flavins compared to standard flash silica gel. In water, considerable amounts of the chromophores were washed off from not fluorinated flash silica gel, giving yellow and fluorescing solutions. No leaching of flavins was observed from the fluorinated support in aqueous media and in toluene, even if flavins without fluorine tags were applied. It was also checked whether riboflavin tetraacetate (**10**) was washed off from the support in a reaction mixture containing *p*-methoxybenzyl alcohol. After stirring for 30 min under standard conditions, the characteristic absorption of flavin was not detectable in a UV/Vis spectrum, an indication of a flavin concentration in solution smaller than $c = 10^{-7}$ mol/L (see Supporting Information for details).

The photocatalytic activity of immobilized flavins on silica supports (1% per mass) was tested in solutions of benzyl alcohol in D₂O (for detailed set-up see Experimental Section).

With riboflavin tetraacetate (**10**) as catalyst, the system retains its activity compared to homogeneous solution and *p*-methoxybenzyl alcohol was completely converted within one hour (Table 2, entries 1 and 2).

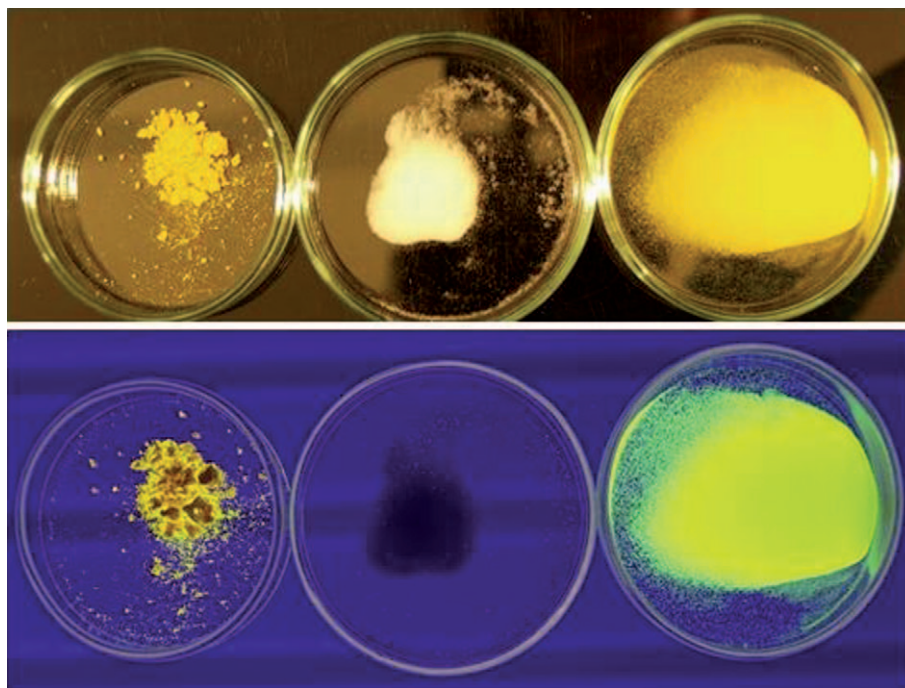


Figure 2. Top: Normal light irradiation; bottom: UV blue light irradiation. Left: solid flavin **10**, middle: non-modified silica gel, right: immobilized catalyst.

However, in some reactions, oxidation to minor amounts of *p*-methoxybenzoic acid occurs. Shorter reaction times of 30 or 15 min, respectively, suppress the undesired acid by-product (entries 3 and 4).

Oxygen is the terminal oxidant of this reaction. Therefore, it was investigated whether the photooxidation is accelerated under an oxygen atmosphere (entries 5–7). However, the conversion drops by a factor of two compared to the standard experiments in aerial environment (entries 2–4). The adverse effect of high oxygen concentrations may be due to the quenching of the flavin excited state by oxygen.

Hydrogen peroxide, the second product of the reaction, is not able to oxidize *p*-methoxybenzyl alcohol.^[4d] A standard reaction mixture with 10 equivalents of hydrogen peroxide instead of a flavin catalyst does not show any conversion after stirring for 30 min (see Supporting Information).

Like in homogeneous solution (Table 1), the addition of thiourea decelerates the conversion (entries 8 and 9),^[6] but a larger scope of possible substrates is observed. Electronically not activated benzyl alcohols were oxidized with the catalysts on fluorinated silica gel with reasonable TOFs and good overall conversions (entries 10–13).

A surprising correlation arises from the analysis of the catalytic activity of different immobilized flavins (entries 1, 16–24). All 3-*N*-substituted flavins show a reduced catalytic activity in the photooxidation of *p*-methoxybenzyl alcohol in aqueous solution when immobilized on silica support. In homogeneous reaction

conditions the catalytic activity of 3-*N*-alkylated and 3-*N*-H flavins is comparable (Table 1, entries 5 and 7), indicating that this difference has to be attributed to the immobilization. Neither the redox potentials^[4d] nor the shape of HOMO and LUMO^[22] of the flavin chromophore are significantly influenced by 3-*N*-alkylation. A different orientation of the flavin chromophore on the support surface may be envisaged to cause the differences in reactivity.

Flavins **7** and **15a** showed considerably higher TOFs of 4.7 and 4.9 h^{−1}, respectively, compared to all other tested derivatives, exceeding riboflavin tetraacetate (**10**) as catalyst (3.6 h^{−1} under comparable conditions).

In general, the TOF of the photoreaction with immobilized flavins drops compared to experiments in homogeneous solution by a factor of 8–20, while TON and aldehyde yields remain comparable (Table 3, entries 1–6).

Recycling of the immobilized photocatalysts was demonstrated by placing a reaction mixture into a syringe with a filter. After each 15 min of irradiation and stirring, the reaction mixture was removed and the conversion was monitored by ¹H NMR. To the remaining immobilized catalyst in the syringe, a fresh benzyl alcohol solution was added and the procedure was repeated (see Supporting Information for details). The activity of the immobilized photocatalyst remained almost unchanged for three cycles with high TOFs of 10 h^{−1} and then dropped by 30% in the next two cycles (Table 4, entries 1–5). These results con-

Table 2. Catalytic photooxidations with flavins immobilized on silica gel.^[a]

Entry	Flavin	X	<i>t</i> [h]	Aldehyde [%]	Acid [%]	TON	TOF [1/h]
1	10	OMe	2	71	29	7.1	3.6
2	10	OMe	1	83	17	8.3	8.3
3	10	OMe	0.5	78	3	7.8	16
4	10	OMe	0.25	65	3	6.5	26
5 ^[b]	10	OMe	1	46	0	4.6	4.6
6 ^[b]	10	OMe	0.5	33	0	3.3	6.6
7 ^[b]	10	OMe	0.25	29	0	2.9	12
8 ^[c]	10	OMe	2	52	8	5.2	2.6
9 ^[d]	10	OMe	2	55	12	5.5	2.8
10	10	Me	2	41	9	4.1	2.1
11	10	H	2	44	0	4.4	2.2
12	10	COOMe	2	36	0	3.6	1.8
13	10	COOH	2	24	0	2.4	1.2
14	10	COONa	2	<3	0	<0.3	<0.15
15	4	OMe	2	61	9	6.1	3.1
16	7	OMe	2	93	4	9.3	4.7
17	8a	OMe	2	46	3	4.6	2.3
18	8b	OMe	2	10	0	1.0	0.5
19	11	OMe	2	54	1	5.4	2.7
20	14	OMe	2	10	0	5.0	2.5
21	15a	OMe	2	97	3	9.7	4.9
22	15b	OMe	2	77	8	7.7	3.9
23	15c	OMe	2	59	4	5.9	3.0
24	15d	OMe	2	18	3	1.8	0.9
25 ^[e]	13	OMe	15.5	2.8	–	280	18
26 ^[f]	6	OMe	4	<3	–	–	–

^[a] Conditions: *V* = 1 mL; 1% per mass flavin on fluorinated silica gel; 10 mol% of catalyst; alcohol: 0.002 M.^[b] Oxygen atmosphere.^[c] Addition of thiourea (0.002 M).^[d] Addition of thiourea (0.001 M).^[e] Reversed phase silica gel instead of fluorinated, pure alcohol solution.^[f] Immobilized on fluorinated glass instead of fluorinated silica gel, *V* = 7 mL, alcohol: 0.01 M, without stirring**Table 3.** Comparison of homogeneous, silica gel and polyethylene based catalysis.^[a]

Entry	X	System	<i>t</i> [min]	Aldehyde [%]	TON	TOF [1/h]
1	OMe	in solution	1	58	5.8	348
2	OMe	on silica gel	30	78	7.8	16
3	H	in solution	25	75	7.5	18
4	H	on silica gel	120	44	4.4	2.2
5	COOMe	in solution	25	58	5.8	14
6	COOMe	on silica gel	120	36	3.6	1.8
7 ^[b]	OMe	in solution	5	59	–	–
8 ^[b,c]	OMe	PE-pellet	240	65	–	–

^[a] Conditions: *V* = 1 mL, D₂O, tetraacetyl riboflavin (**10**) as catalyst, alcohol: 0.002 M.^[b] Without stirring.^[c] Alcohol: 0.01 M.

firm that the immobilized flavins are catalytically active and not chromophore molecules that are leaching from the support. As an additional experiment, we removed the immobilized catalyst from a reaction mixture that was irradiated for 30 min (yield: 72% of aldehyde). Continued irradiation of the same solution without the catalyst under identical conditions for

30 min did not result in further reaction conversion (see Supporting Information). The photooxidation proceeds only in the presence of the heterogeneous photocatalyst.

To show the applicability of the photooxidation to the preparative laboratory scale we used *p*-methoxybenzyl alcohol as substrate and solvent. 3-Methyl-

Table 4. Recycling experiments with immobilized catalysts.^[a]

Entry	Alcohol [M]	Immobilization	<i>t</i> [min]	Aldehyde [%]	Run	TON	TOF [1/h]
1 ^[b]	0.002	on SiO ₂	15	22	1	2.2	8.8
2 ^[b]	0.002	on SiO ₂	15	25	2	2.5	10
3 ^[b]	0.002	on SiO ₂	15	24	3	2.4	9.6
4 ^[b]	0.002	on SiO ₂	15	15	4	1.5	6.0
5 ^[b]	0.002	on SiO ₂	15	8	5	0.8	3.2
6	0.01	PE	240	46	1	–	–
7	0.01	PE	240	29	2	–	–

^[a] Conditions: *V* = 1 mL, D₂O, tetraacetylriboflavin (**10**) as catalyst, *p*-methoxybenzyl alcohol as substrate.

^[b] 10 mol% of catalyst.

trapalmitylriboflavin (**13**), which is a very low melting oily solid and completely insoluble in water was immobilized on reversed phase silica gel, comprising C₁₈-alkyl chains and was used as catalyst. Preparation of the supported catalyst was carried out in the same way as for fluorinated silica gel. The photooxidation in neat *p*-methoxybenzyl alcohol allows an overall conversion of 2.8% to the aldehyde with a TOF of 18 h^{−1} and high TON of 280 (Table 2, entry 25).

An attempt to create an active photocatalyst by immobilization of flavin **6** on commercially available fluorinated glass^[23] failed due to the small amount of deposited photoactive compound. No significant conversion was observed with this catalyst even after 4 h of irradiation (Table 2, entry 26).

Flavin Immobilization by Entrapment in PE Pellets or Glues

In some solvents, the catalysts were washed off from the silica gel support. Therefore, an entrapment of flavins in polymer pellets and in simple glue was tried. As water is the best solvent for the photocatalytic oxidation completely insoluble polyethylene (PE) was selected as material for the entrapment. The preparation of flavin containing PE pellets is simple: The flavin chromophore and commercially available PE powder are mixed in a ratio of 1:100 by weight. This mixture is compressed to 125 MPa at 80 °C yielding yellow, fluorescing pellets (Figure 3).

To determine the catalytic activity, the flavin-PE pellets were placed at the top of 1 mL of an aqueous

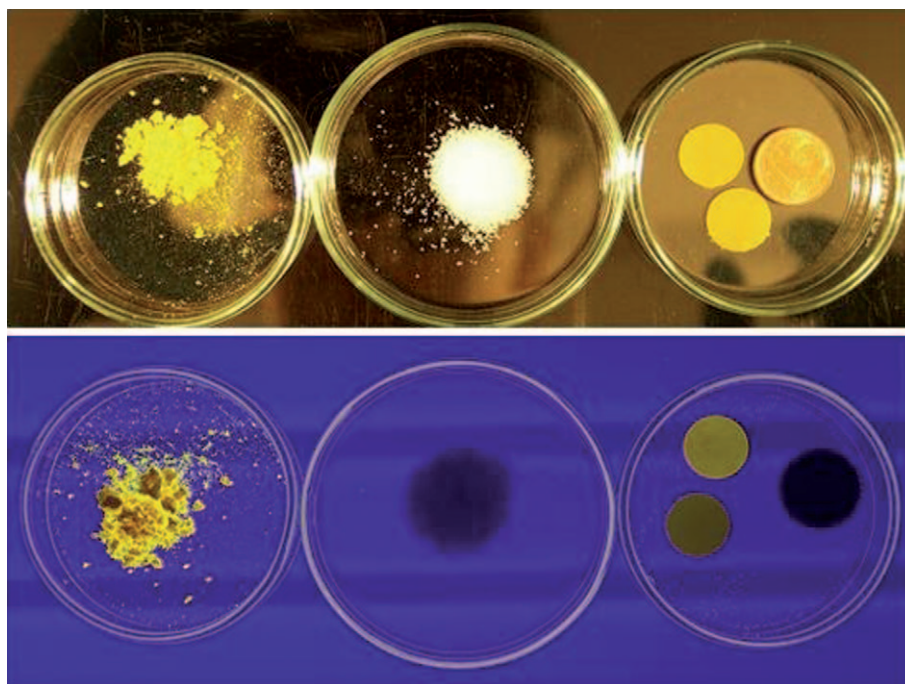


Figure 3. Top: Normal light, bottom: UV light. Left: solid flavin **10**, middle: PE powder, right: immobilized catalyst + 1 cent coin for comparison.

Table 5. Catalytic photooxidations with entrapped flavins.^[a]

Entry	Flavin	Alcohol [mM]	<i>t</i> [h]	Immobilization method	Aldehyde [%]
1	10	10	4	PE	65
2	11	10	4	PE	55
3	8a	10	4	PE	14
4	7	10	4	PE	n.s.c. ^[b]
5	–	10	4	pure PE	n.s.c. ^[b]
6	13	2	1	coated on glass	29
7	10	2	12	superglue	n.s.c. ^[b]

^[a] Conditions: *V* = 1 mL, D₂O.^[b] n.s.c. = no significant conversion.^[24]

p-methoxybenzyl alcohol solution (0.01 M in D₂O) in a small glass reaction vessel, which was irradiated from the bottom by an LED (440 nm) without stirring. The reaction conversion was monitored by ¹H NMR.

Riboflavin tetraacetates **10** and **11** were found to be the most active catalysts if immobilized in PE pellets. A conversion of the benzyl alcohol to the aldehyde in 55–65% yield was observed after 4 h (Table 5, entries 1 and 2). In absolute numbers, 5.5–6.5 μmol were converted in such a reaction. However, compared to the reaction in homogeneous aqueous solution which reaches under identical conditions the same conversion after 5 min (Table 1, entry 4), the efficiency is drastically reduced by a factor of 50. In addition, one pellet contains about 4.6 μmol of flavin, which means that the catalyst loading is 45%. Obviously, not all flavin molecules are accessible for the photocatalytic reaction as they are trapped in the bulk of the pellet leading to a lower effective loading. Other entrapped flavins **7** and **8a** (entries 3 and 4) showed only low or no significant photooxidation activity. As expected, no conversion was obtained if a PE pellet without flavin was used. Recycling of flavin catalyst pellets is limited; the activity drops by 50% in the second run (Table 4, entries 6 and 7).

In order to obtain stable immobilized flavin layers, we entrapped riboflavin tetraacetate (**10**) by mixing a chloroform solution with superglue^[25] and evaporating the mixture. This yielded a stable polymer layer containing the chromophore in a glass, which unfortunately showed no conversion when irradiated in the presence of substrate solution for 12 h (entry 7). Simple evaporation of a chloroform solution of tetrapalmitylriboflavin (**13**) without adding glue yielded a stable chromophore layer in a glass vial. This layer is stable in aqueous solution, but is destroyed by stirring. Therefore, the photooxidation was investigated by irradiation of the flavin layer with a solution of *p*-methoxybenzyl alcohol that was not stirred. Within 1 h, 29% of the substrate was converted into the corresponding aldehyde (entry 6).

Conclusions

The photooxidation of benzyl alcohols to the corresponding aldehydes with flavin catalysts using oxygen as the terminal oxidizing agent proceeds very rapidly and efficiently in aqueous solution. A TOF of more than 800 h^{−1} and a TON of up to 68,800 were observed. It was possible to oxidize benzyl alcohols which are electronically not activated for this reaction.

To create heterogeneous photocatalysts, several new flavin derivatives were prepared and immobilized on solid supports (fluorous silica gel, reversed phase silica gel, PE pellets). The immobilized photocatalysts retained their catalytic activity for benzyl alcohol oxidation. In comparison to the analogous homogeneous reactions, the reaction rates decrease by a factor of 8–20 for immobilization on silica gel and by a factor of 50 for the catalyst entrapment in polyethylene pellets.

The highest catalytic activity (TOF 26 h^{−1}), best stability (TON 280) and up to 3 reaction cycles without loss of performance are possible with flavins **7**, **10** and **13** immobilized on fluorous silica gel and reversed phase silica gel, respectively.

In summary, we have shown that heterogeneous photocatalysts can be derived from functionalized flavins by physical adsorption on a fluorinated silica gel support or by mechanical entrapment. The immobilized chromophores are the catalytically active species, as the photooxidation reaction stops immediately when the heterogeneous catalyst is removed. The heterogeneous catalysts significantly facilitate product isolation and catalyst recycling. Flavin-catalyzed photooxidations are suited for preparative laboratory scale conversions. The introduced heterogeneous catalysts facilitate the use of flavin photooxidation catalysts in synthesis and pave the way to applications in energy efficient transformations in continuous flow reactions.

Experimental Section

Dinitrobenzene **1**,^[13] fluorinated amine **2**,^[14] 10-(2-methoxyethyl)-7,8-dimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (**7**)^[6] and riboflavin tetraacetate (**10**)^[15] were prepared by known methods. All other chemicals were purchased from commercial suppliers, checked by ¹H NMR spectrometry and then used as received. Before use, solvents were distilled. Dry *N,N*-dimethylformamide was purchased from Fluka. Fluorinated silica gel with a particle size of 35–70 μm and reversed phase silica gel (40–63 μm) were purchased from Fluka. Thin layer chromatography was carried out on silica gel 60 F254 aluminium sheets (Merck) or on precoated plastic sheets Polygram SIL G/UV254 (Macherey–Nagel, Düren, Germany), with detection under 254 nm or 333 nm UV light or by naked eye (flavins are intensively yellow-coloured). Flash column chromatography was carried out on

silica gel 35–70 μm , 60 Å from Acros. NMR spectra were recorded with a Bruker spectrometer equipped with a robotic sampler at 300 MHz (^1H NMR) or 75 MHz (^{13}C NMR). Tetramethylsilane (TMS) was used as an external standard. Electrospray ionization (ES-MS) mass spectra were recorded on a ThermoQuest Finnigan TSQ 7000 spectrometer. High resolution mass spectrometry (HR-MS) was performed with a ThermoQuest Finnigan MAT 95 spectrometer. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were measured on a Biorad Spectrometer Excalibur FTS 3000.

General Procedure for the Immobilization of Flavins on Fluorous Silica Gel

Flavins (2–5 mg) were dissolved in chloroform (20–30 mL) in a flask (50 mL) and the appropriate amount of silica gel (200–500 mg) was added. The solvent was slowly evaporated. Drying under vacuum gave flavin catalysts on fluorous silica with a loading of 1% per mass as yellow powders. In the case of tetraacetylriflavin (**10**) which was mainly used in our experiments, this represents 18 μmol flavin/g silica gel.

General Procedure for the Immobilization of Flavins in Polyethylene Pellets

Flavin (2.5 mg) and polyethylene powder (247.5 mg) were mixed and brought into a press. A pressure of 125 MPa was adjusted and the pressing tool was heated to 80–100°C until the pressure decreased. The apparatus was allowed to cool down to room temperature and the yellow pellets (1–2 mm thick, 1.3 cm diameter) were removed. To remove traces of flavin that was not completely incorporated, the pellets were washed with water three times.

General Procedure for Testing of the Photocatalytic Activity of Flavins

The photocatalytic activity of flavins was tested in solutions of different benzyl alcohols (0.002 M) in D_2O ($V=1$ mL). Flavins (10 mol%) were added as DMSO- d_6 stock solution (0.01 M) for the experiments in homogeneous solution or as immobilized flavins on silica gel (1% per mass) for heterogeneous experiments. The reaction mixture was stirred and irradiated at room temperature with an array of six LEDs (440 nm, 5 W) in small glass vials (see Figure 1). The progress of the reaction was monitored by ^1H NMR. Heterogeneous catalysts were removed by filtration before the measurement. The ^1H NMR resonance signals of the alcohol and the aldehyde are well separated and were assigned unambiguously. The clean conversion allows the quantitative monitoring of the reaction progress by integration of the aromatic resonance signals (see also Supporting Information).

N-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl)-4,5-dimethyl-2-nitroaniline (**3**)

Dinitro-*o*-xylene **1** (392 mg, 2.0 mmol) was dissolved in ethanol (50 mL). Subsequently, triethylamine (416 μL , 3.0 mmol) and the fluorinated amine **2** (1.31 g, 2.83 mmol) in ethanol (3 mL) were added and the mixture was refluxed for one day. Another portion of amine **2** (300 mg, 648 μmol) was

added. After refluxing for five more days, the solvent was evaporated yielding a yellow-orange solid. Flash column chromatography ($R_f=0.25$; petrol ether:chloroform, 4:1) gave an orange solid; yield: 294 mg (480 μmol , 24%); mp 85°C; IR (ATR): $\nu=3348, 1633, 1578, 1505, 1333, 1242, 1193, 1146, 1007$ cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): $\delta=2.20$ (s, 3 H, Ar- CH_3), 2.30 (s, 3 H, Ar- CH_3), 2.42–2.59 (m, 2 H, $\text{CH}_2\text{C}_8\text{F}_{17}$), 3.65–3.72 (m, 2 H, NH- CH_2), 6.61 (s, 1 H, Ar- H), 7.96 (s, 1 H, Ar- H), 8.02 (tr, $J=5.49$ Hz, 1 H, NH); ^{13}C NMR (75 MHz, CDCl_3): $\delta=18.7$ (Ar- CH_3), 20.9 (Ar- CH_3), 30.8 ($\text{CH}_2\text{C}_8\text{F}_{17}$), 35.1 (N- CH_2), 113.5, 125.5, 127.0, 130.7, 143.1, 147.7 (6 $\times$ Ar-C); ^{19}F NMR (75 MHz, CDCl_3): $\delta=-126.6$ (m, 2 F, CF_2), -123.8 (m, 2 F, CF_2), -123.2 (m, 2 F, CF_2), -122.4 (m, 4 F, 2 $\times$ CF_2), -122.1 (m, 2 F, CF_2), -114.3 (quin, $J=15.3$ Hz, 2 F, CH_2CF_2), -81.2 (tr, $J=9.82$ Hz, 3 F, CF_3); ES-MS: m/z (%) = 613.2 (MH^+ , 100); HR-MS-EI: $m/z=612.0714$ [$\text{M}]^+$, calcd. for $\text{C}_{18}\text{H}_{13}\text{F}_{17}\text{N}_2\text{O}_2$: 612.0706 [$\delta=1.38$ ppm].

10-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl)flavin (**4**)

Nitro compound **3** was dissolved in methanol (30 mL) and chloroform (5 mL). Palladium on activated charcoal (28 mg) was added and the mixture was hydrogenated with 12 bar at room temperature for 16 h. After filtration, alloxane monohydrate (365 mg, 2.57 mmol) and boric acid (700 mg, 11.3 mmol) were added and the mixture was stirred at room temperature for three days in the dark. After evaporation of the solvents, chloroform (300 mL) was added and the organic phase was washed with water and brine. The organic phase was dried over magnesium sulfate and evaporated. The crude product was purified by flash column chromatography ($R_f=0.3$; chloroform:ethyl acetate:methanol, 20:10:3); yield: 118 mg (171 μmol , 38%); yellow solid; mp 310°C (decomp.); IR (ATR): $\nu=3182, 3069, 1724, 1672, 1581, 1538, 1509, 1196, 1141, 824$ cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): $\delta=2.47$ (s, 3 H, Ar- CH_3), 2.58 (s, 3 H, Ar- CH_3), 2.68–2.85 (m, 2 H, $\text{CH}_2\text{C}_8\text{F}_{17}$), 4.99 (tr, $J=7.55$ Hz, 2 H, N- CH_2), 7.42 (s, 1 H, Ar- H), 8.10 (s, 1 H, Ar- H), 8.43 (br s, 1 H, NH); ^{13}C NMR: not measured due to low solubility; ^{19}F NMR (75 MHz, CDCl_3): $\delta=-126.6$ (m, 2 F, CF_2), -123.4 (m, 2 F, CF_2), -123.1 (m, 2 F, CF_2), -122.3 (m, 4 F, 2 $\times$ CF_2), -122.0 (m, 2 F, CF_2), -113.9 (tr, $J=13.2$ Hz, 2 F, CH_2CF_2), -81.2 (tr, $J=9.82$ Hz, 3 F, CF_3); ES-MS: m/z (%) = 689.2 (MH^+ , 100). HR-MS-EI: $m/z=688.0767$ [$\text{M}]^+$, calcd. for $\text{C}_{22}\text{H}_{13}\text{F}_{17}\text{N}_4\text{O}_2$: 688.0767 [$\delta=0.00$ ppm].

3,10-Bis-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)flavin (**6**)

Flavin **4** (68 mg, 100 μmol) was dissolved in dry dimethylformamide (15 mL) and subsequently, potassium carbonate (72 mg, 521 μmol) and fluorinated iodide **5** (1.30 g, 2.26 mmol) were added and the mixture was stirred for 24 h at room temperature in the dark. The suspension was diluted with chloroform and washed with water (5 $\times$ 100 mL) and brine (2 $\times$ 100 mL). The organic phase was dried over magnesium sulfate and the solvents were evaporated. The crude product was purified by flash column chromatography ($R_f=0.2$; dichloromethane:methanol, 100:1); yield: 71 mg (62 μmol , 62%); yellow solid; mp 155°C; IR (ATR): $\nu=1664, 1585, 1546, 1196, 1144, 656$ cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): $\delta=2.45$ (s, 3 H, Ar- CH_3), 2.46–2.83 (m, 7 H, Ar- CH_3 + $\text{CH}_2\text{C}_8\text{F}_{17}$), 4.43 (tr, $J=7.14$ Hz, 2 H, N- CH_2), 4.96 (tr, $J=$

7.00 Hz, 2H, N-CH₂), 7.41 (s, 1H, Ar-H), 8.07 (s, 1H, Ar-H); ¹³C NMR: not measured due to low solubility; ¹⁹F NMR (75 MHz, CDCl₃): δ = -126.6 (m, 4 F, 2 × CF₂), -124.0 (m, 2 F, CF₂), -123.5 (m, 2 F, CF₂), -123.2 (m, 4 F, 2 × CF₂), -122.3 to -122.1 (m, 12 F, 6 × CF₂), -114.8 (tr, *J* = 12.9 Hz, 2 F, CH₂CF₂), -113.9 (tr, *J* = 13.5 Hz, 2 F, CH₂CF₂), -81.3 to -81.2 (m, 6 F, CF₃); ES-MS: *m/z* (%) = 1135.2 (MH⁺, 100); HR-MS-EI: *m/z* = 1134.0722, [M]⁺, calcd. for C₃₂H₁₆F₃₄N₄O₂: 1134.0730 [delta 0.73 ppm].

10-Methoxyethyl-3-methylflavin (8a)^[16]

Flavin **7** (306 mg, 1.02 mmol) was dissolved in dry dimethylformamide (40 mL) and subsequently, caesium carbonate (488 mg, 1.50 mmol) and methyl iodide (1.37 g, 9.64 mmol) were added and the mixture was stirred for 18 h at room temperature in the dark. The suspension was diluted with chloroform and washed with water (3 × 100 mL) and brine. The organic phase was dried over magnesium sulfate and the solvents were evaporated. The crude product was purified by flash column chromatography (*R*_f = 0.2; chloroform:methanol, 100:1); yield: 293 mg (930 μmol, 91%); yellow solid; mp 255 °C (decomp.). IR (ATR): ν = 2921, 1703, 1651, 1582, 1540, 1451, 1231, 1110, 1014, 970 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.41 (s, 3H, Ar-CH₃), 2.51 (s, 3H, Ar-CH₃), 3.26 (s, 3H, O-CH₃), 3.49 (s, 3H, N-CH₃), 3.88 (tr, *J* = 5.21 Hz, 2H, O-CH₂), 4.87 (tr, *J* = 5.08 Hz, 2H, N-CH₂), 7.62 (s, 1H, Ar-H), 7.99 (s, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.6 (Ar-CH₃), 21.6 (Ar-CH₃), 45.4 (N-CH₂), 59.3 (O-CH₃), 69.6 (O-CH₂), 116.7 (C-9), 132.2 (C-9a), 132.3 (C-6), 135.0 (C-5a), 135.5 (C-4a), 136.7 (C-7), 147.6 (C-8), 148.7 (C-10a), 156.0 (C-2), 160.2 (C-4); ES-MS: *m/z* (%) = 315.0 (MH⁺, 100); HR-MS-EI: *m/z* = 314.1374 [M]⁺, calcd. for C₁₆H₁₈N₄O₃: 314.1379 [delta 1.56 ppm].

3-(1H,1H,2H,2H-Perfluorodecyl)-10-methoxyethyl-flavin (8b)

Flavin **7** (109 mg, 363 μmol) was dissolved in dry dimethylformamide (15 mL) and potassium carbonate (251 mg, 1.81 mmol) was added. After stirring for 20 min, fluorinated iodide **5** (625 mg, 1.09 mmol) in dry dimethylformamide (5 mL) was added. After one day, another portion of iodide **5** (417 mg, 726 μmol) was added and the mixture was stirred for three days at room temperature in the dark. The mixture was diluted with chloroform and washed with water (3 × 100 mL) and brine (100 mL). The organic phase was dried over magnesium sulfate and the solvents were evaporated. The crude brown solid was purified by flash column chromatography (*R*_f = 0.2; chloroform:methanol, 20:1); yield: 63 mg (84 μmol, 23%); yellow solid; mp 175 °C; IR (ATR): ν = 2952, 1708, 1663, 1585, 1552, 1197, 1144, 1111, 1003, 958, 719, 657 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.44 (s, 3H, Ar-CH₃), 2.49–2.67 (m, 5H, Ar-CH₃ + 3-N-CH₂), 3.29 (s, 3H, O-CH₃), 3.91 (tr, *J* = 5.08 Hz, 2H, 10-N-CH₂), 4.45 (tr, *J* = 7.55 Hz, 2H, CH₂C₈F₁₇), 4.89 (tr, *J* = 5.21 Hz, 2H, O-CH₂), 7.67 (s, 1H, Ar-H), 8.03 (s, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.6 (Ar-CH₃), 21.7 (Ar-CH₃), 29.8 (CH₂C₈F₁₇), 34.3 (N-CH₂), 45.6 (N-CH₂), 59.4 (O-CH₃), 69.6 (O-CH₂), 116.8 (C-9), 132.4 (C-9a, C-6, C-5a), 135.3 (C-4a), 137.0 (C-7), 148.1 (C-8), 148.9 (C-10a), 155.1 (C-2), 159.9 (C-4); ¹⁹F NMR (75 MHz, CDCl₃): δ = -126.6 (m, 2 F, CF₂), -124.0 (m, 2 F, CF₂), -123.2 (m, 2 F, CF₂), -122.4 (m, 4 F,

2 × CF₂), -122.2 (m, 2 F, CF₂), -114.8 (quin, *J* = 16.6 Hz, 2 F, CH₂CF₂), -81.2 (tr, *J* = 10.1 Hz, 3 F, CF₃); ES-MS: *m/z* (%) = 747.3 (MH⁺, 100), 769.3 (MN⁺, 16); HR-MS-EI: *m/z* = 746.1178 [M]⁺, calcd. for C₂₅H₁₉F₁₇N₄O₃: 746.1186 [delta 1.03 ppm].

3-Methylriboflavin Tetraacetate (11)^[16,26]

Riboflavin tetraacetate **10** (1.63 g, 3.0 mmol) was dissolved in dry dimethylformamide (20 mL) and subsequently, caesium carbonate (1.47 g, 4.50 mmol) and methyl iodide (1.8 mL, 29.0 mmol) were added. After stirring for 16 h at room temperature in the dark, water (5 mL) was added and the solvents were evaporated. The crude product was dissolved in chloroform (250 mL) and washed with water (2 × 100 mL) and brine. The organic phase was dried over magnesium sulfate and the solvents were evaporated. Purification was done by flash column chromatography (*R*_f = 0.15; chloroform:methanol, 50:1); yield: 1.19 g (2.13 mmol, 71%); orange solid; mp 183 °C; IR (ATR): ν = 2920, 1737, 1709, 1659, 1532, 1373, 1209, 1034 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.70 (s, 3H, Ac-CH₃), 2.05 (s, 3H, Ac-CH₃), 2.20 (s, 3H, Ac-CH₃), 2.27 (s, 3H, Ac-CH₃), 2.40 (s, 3H, Ar-CH₃), 2.52 (s, 3H, Ar-CH₃), 3.45 (s, 3H, N-CH₃), 4.22 (dd, *J* = 12.35 Hz, *J* = 5.76 Hz, 1H, CH), 4.40 (dd, *J* = 12.21 Hz, *J* = 2.61 Hz, 1H, CH), 4.59–5.26 (m, 2H, CH), 5.35–5.45 (m, 2H, CH), 5.62–5.65 (m, 1H, CH), 7.51 (s, 1H, Ar-H), 7.97 (s, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.5 (Ar-CH₃), 20.4 (Ac-CH₃), 20.8 (Ac-CH₃), 20.9 (Ac-CH₃), 21.1 (Ac-CH₃), 21.5 (Ar-CH₃), 28.7 (N-CH₃), 44.6 (CH₂), 61.9 (CH₂), 69.0 (CH), 69.4 (CH), 70.4 (CH), 115.4 (C-9), 131.2 (C-9a), 132.9 (C-6), 134.7 (C-5a), 135.6 (C-4a), 136.7 (C-7), 147.6 (C-8), 149.1 (C-10a), 155.3 (C-2), 160.0 (C-4), 169.7 (CO), 169.9 (CO), 170.4 (CO), 170.7 (CO); ES-MS: *m/z* (%) = 559.2 (MH⁺, 100); HR-MS-EI: *m/z* = 558.1962 [M]⁺, calcd. for C₂₆H₃₀N₄O₁₀: 558.1962 [delta -0.01 ppm].

3-Methylriboflavin (12)^[16,27]

3-Methylriboflavin tetraacetate **11** (280 mg, 501 μmol) was dissolved in ethanol (50 mL) and *p*-toluenesulfonic acid (98 mg, 569 μmol) was added. After refluxing for 17 h, another portion of *p*-toluenesulfonic acid (49 mg, 285 μmol) was added and the mixture was refluxed for 3 h. After cooling to room temperature, the solution was stored in the refrigerator overnight and a yellow solid precipitated that was filtered off and dried; yield: 142 mg (364 μmol, 73%); yellow solid; mp 275 °C (decomp.); IR (ATR): ν = 3230, 1716, 1617, 1579, 1532, 1235 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.38 (s, 3H, Ar-CH₃), 2.47 (s, 3H, Ar-CH₃), 3.27 (s, 3H, N-CH₃), 3.44–3.48 (m, 1H, OH), 3.64 (br s, 3H, 3 × OH), 4.23–4.26 (m, 1H, CH), 4.51 (tr, *J* = 5.63 Hz, 1H, CH), 4.58–4.62 (m, 1H, CH), 4.77 (d, *J* = 5.49 Hz, 1H, CH), 4.88–5.00 (m, 2H, CH), 5.13 (d, *J* = 4.67 Hz, 1H, CH), 7.89 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 18.8 (Ar-CH₃), 20.8 (Ar-CH₃), 28.0 (N-CH₃), 47.1 (CH₂), 63.4 (CH₂), 68.8 (CH), 72.8 (CH), 73.6 (CH), 117.4 (C-9), 130.7 (C-6), 132.0 (C-9a), 134.2 (C-5a), 135.7 (C-4a), 135.9 (C-7), 146.2 (C-8), 149.3 (C-10a), 155.0 (C-2), 159.7 (C-4); ES-MS: *m/z* (%) = 391.0 (MH⁺, 100); HR-MS-LSI: *m/z* = 391.1621 [M + H]⁺, calcd. for C₁₈H₂₃N₄O₆: 391.1618 [delta -0.87 ppm].

3-Methyltetrapalmitylriboflavin (13)

3-Methylriboflavin **12** (280 mg, 501 μmol) was suspended in a mixture of dry chloroform (15 mL) and pyridine (15 mL). A solution of palmityl chloride (1.55 mL, 5.13 mmol) in dry chloroform (5 mL) was added dropwise within 1 h at 0°C. Afterwards, the mixture was stirred for 24 h at room temperature. After addition of water (5 mL), the suspension was heated to 60°C for 1 h and the solvents were evaporated afterwards. The crude product was dissolved in chloroform (30 mL) and was washed with sodium hydrogen carbonate solution (2 $\times$ 100 mL) and brine (2 $\times$ 100 mL). The organic phase was dried over magnesium sulfate and the solvents were evaporated. The orange solid was purified by flash column chromatography (R_f = 0.2; petrol ether:ethyl acetate, 2:1); yield: 173 mg (129 μmol , 52%); orange solid; mp 50–53°C; IR (ATR): ν = 2917, 2850, 1741, 1664, 1584, 1545, 1466, 1151, 721 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 0.86–2.53 (m, 130H, 2 $\times$ Ar-CH₃ + 4 $\times$ C₁₅H₃₁), 3.48 (s, 3H, N-CH₃), 4.17–4.23 (m, 1H, CH), 4.43–4.48 (m, 1H, CH), 4.92 (br s, 2H, CH), 5.39–5.49 (m, 2H, CH), 5.67–5.69 (m, 1H, CH), 7.54 (s, 1H, Ar-H), 8.02 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, CDCl_3): δ = 14.2 (CH₃), 19.5 (Ar-CH₃), 21.5 (Ar-CH₃), 28.8 (N-CH₃), 44.6 (CH₂), 61.9 (CH₂), 69.1 (CH), 70.4 (2 $\times$ CH), 115.6 (C-9), 131.4 (C-9a), 133.0 (C-6), 134.7 (C-5a), 135.7 (C-4a), 136.5 (C-7), 147.4 (C-8), 149.2 (C-10a), 155.3 (C-2), 160.0 (C-4), 172.5 (CO), 172.6 (CO), 173.1 (CO), 173.5 (CO), C₁₅H₃₁ (signals not assigned); ES-MS: m/z (%) = 1344.4 (MH⁺, 100).

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