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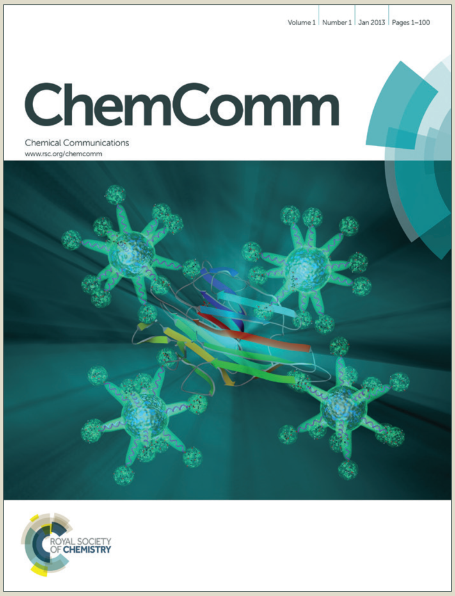

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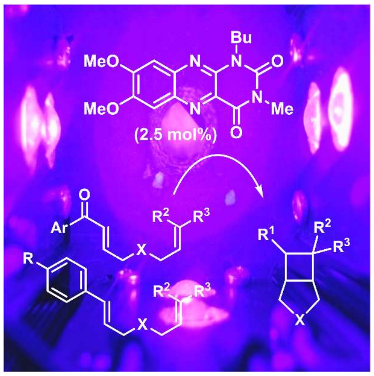
New application of flavins in visible light photocatalysis: excited alloxazine allows fast cycloaddition of both electron-poor and electron rich dienes.



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Tailoring Flavins for Visible Light Photocatalysis: Organocatalytic [2+2] Cycloadditions Mediated by a Flavin Derivative and Visible Light†

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New application of flavin derivatives in visible light photocatalysis was found. 1-Butyl-7,8-dimethoxy-3-methyl-alloxazine, when irradiated by visible light, was shown to allow an efficient cyclobutane ring formation by an intramolecular [2+2] cycloaddition of both styrene dienes, considered as electron-rich substrates, and electron-poor bis(arylenones), presumably proceeding by an energy transfer mechanism.

Rapid development of visible light photocatalysis occurring within the past decade has stimulated a renaissance of organic photochemistry.[1,2] Replacement of high-intensity UV light with visible light in combination with suitable photocatalysts/sensitisers absorbing in the proper region made photochemistry available for most laboratories[3] as it can be performed in common vessels made from borosilicate glass and with conventional light sources, including the current light emitting diodes (LEDs).[4] Photoexcitation, in general, allows several chemical transformations that are not accessible by thermal reactions.[5,6] Use of visible light even improves classical photochemical methodologies by avoiding side reactions of functionalities sensitive to UV light.

The [2+2] cycloaddition of alkenes, producing cyclobutane derivatives, represents a typical challenge for photochemistry as corresponding thermal procedures and four-membered ring cyclisations are disfavoured.[7] Conventional synthetic methods for [2+2] photocycloadditions usually require high-intensity UV light,[8] but recently, new procedures based on visible light photocatalysis have also appeared in this important area. Yoon reported radical [2+2] cycloadditions with a $\mathrm{Ru(bpy)_3^{2+}}$ photocatalyst, which occur after irradiation with visible light in the presence of a sacrificial reducing or oxidising agent in the case of either electron-poor (arylenones) or electron-rich substrates (styrenes), respectively.[9,10] Nicewicz described [2+2] cycloadditions of electron-rich styrenes with tris-(4-methoxyphenyl)pyrylium tetrafluoroborate working in the excited state as a single electron oxidant;[11a] Zeitler showed reductive cyclization of arylenones to take place with Eosin Y.[11b] In contrast to electron transfer processes, [2+2] photocycloadditions involving energy transfer are applicable across a broad substrate scope as they are not limited by the electrochemical properties of the substrates. Nevertheless, such processes utilising visible light are still very rare; an iridium(III) polypyridyl complex (E_T = 255 kJ mol^{-1}) providing an intramolecular [2+2] cycloaddition of substituted styrenes[12] and very recent systems, based on a thioxanthone dye (E_T = 264 kJ mol^{-1}), designed by Bach[13] and Sivaguru[14] for stereoselective [2+2] cycloadditions of a specific group of substrates are the only examples.

Noble metal complexes still dominate as photoactive species in visible light photocatalysis.[1] Because of the price of the dye, as well as environmental aspects representing important issues, looking for a new, simple photoactive organocatalyst and its application in photocatalysis represents an important goal.[2] One of the most prominent natural chromophores is represented by flavin cofactors[15] (Figure 1), which are involved in several light-dependent processes, for example, in light generation by bacterial luciferase,[16] in plant phototropism[17] and in photolyases in the cleavage of cyclobutane-pyrimidine dimers to repair DNA damage.[18] Due to interesting photochemical properties, flavins (e.g., riboflavin tetraacetate **1**) have been tested in photocatalysis;[19,20] nevertheless, their applications, except of photolyase models,[21] are still limited to photooxidations of benzylic derivatives, amines and sulfides.

Our idea to apply flavins to sensitised visible light [2+2] cycloadditions led us to consider their triplet energy, which is too low in the case of blue light-absorbing isoalloxazines (λ_max = 450 nm; E_T = 209 kJ mol^{-1} for riboflavin[22]) to excite substituted styrenes usually used as substrates for this reaction (E_T = 249 and 259 kJ mol^{-1} for β-methylstyrene[23a] and 1-phenylbut-2-en-1-one[23b], respectively). Indeed, our attempt to use **1** as photocatalyst of **3a** cycloaddition did not lead to cyclobutane product. Therefore, we turned our attention to isomeric alloxazines (Figure 1) absorbing light on the border of the visible region with triplet energies expected to be above those of isoalloxazines (E_T = 245 kJ mol^{-1} for 1,3,7,8-tetramethyl-alloxazine).[24] Moreover, alloxazines are known to exhibit high intersystem crossing (ISC) yield (e.g. Φ_ISC = 0.71 for 7,8-dimethylalloxazine in acetonitrile).[24b,25] For our purpose, we tuned the alloxazine structure by introducing

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methoxy groups to the benzene ring to adjust the absorption maximum to approximately 400 nm and added a butyl chain on the N(1) nitrogen to provide sufficient solubility for the catalyst (for synthesis of **2**, see ESI).

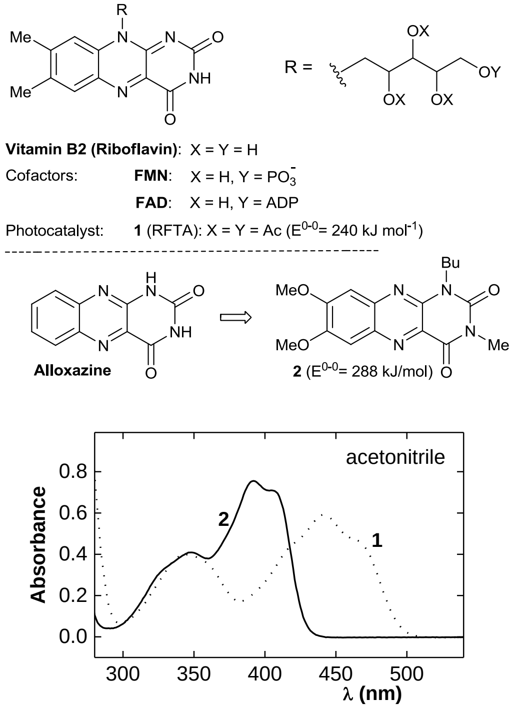
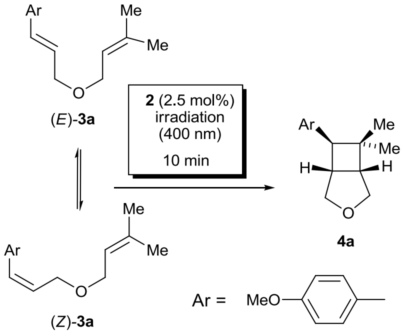


Figure 1. Flavins involved in natural and artificial photochemical processes, design of photocatalyst **2** and UV-VIS spectra of **1** and **2** (c = 5×10^{-5} mol L^{-1}).

To our delight, irradiation of a solution of diene (E)-**3a** in the presence of 2.5 mol% of **2** with a 400 nm LED led to the formation of the [2+2] cycloadduct **4a** within a short time (Table 1). The conversion to the [2+2] cycloadduct after 10 minutes of irradiation did not differ in most types of solvents (Entries 1 – 7). Nevertheless, in alcohols (Entries 8 and 9) and mainly in acetonitrile (Entry 10), it still increased. Additionally, we detected the formation of (Z)-**3a**, providing evidence that a triplet state E/Z photoisomerisation of the styrene double bond occurs. The rate of isomerisation is faster than the rate of cycloaddition, as demonstrated by the composition of the reaction mixtures in acetonitrile after 1 and 10 minutes irradiation (cf. Entries 10 and 12, see ESI for kinetic profile). It is noteworthy that irradiation of (Z)-**3a** led to a mixture of the same composition as that of (E)-**3a** (cf. Entries 10 and 11); the cycloadduct of the same relative configuration was formed as the major product, regardless of the configuration of the starting styrene.

Flavins including alloxazines are known to sensitise the formation of singlet oxygen.[20a,25] Therefore, standard experiments were performed in Schlenck tubes under an argon atmosphere, not allowing singlet oxygen chemistry to proceed. Nevertheless, no side products were observed after irradiation under an air atmosphere, showing that the reaction could be performed simply in a flask without the exclusion of oxygen. Of course, it took place more slowly under air as the excited catalyst was partially quenched by oxygen (cf. Entries 10 and 13). As expected, with RFTA, either isomerization or cycloaddition did not proceed even under optimized conditions (Entry 14). In acetonitrile, several blank experiments were performed to exclude spontaneous formation of the cycloadduct, but cycloaddition or isomerisation of **3a** did not occur without light or a photocatalyst. Our effort to study substrate scope led us to blank experiments with dienes **3**, **5**, **7**, **9** and **11,** which did not form a cycloadduct in the absence of **2**. The only exception was the 4-nitroderivative **3e** (R = NO_2, in Table 2), which formed a cyclobutane spontaneously after irradiation as it has low but still sufficient absorption at 400 nm (see ESI).

Table 1. [2+2] Photocycloaddition of **3a** mediated by **2** and visible light performed on analytical scale.[a]

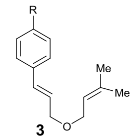
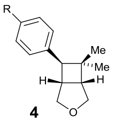
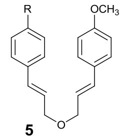
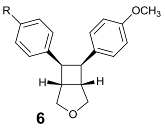
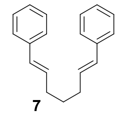
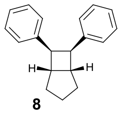
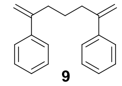
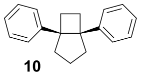
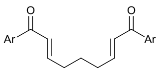
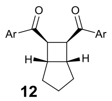


Entry	Diene	Solvent	Conversion[b] [%]		
			(Z)-**3a**	(E)-**3a**	**4a**
1	(E)-**3a**	CD_2Cl_2	19	24	57
2	(E)-**3a**	$CDCl_3$	23	23	54
3	(E)-**3a**	THF-d^8	18	28	54
4	(E)-**3a**	Toluene-d^8	18	28	54
5	(E)-**3a**	Acetone-d^6	20	23	57
6	(E)-**3a**	DMF-d^7	23	23	54
7	(E)-**3a**	DMSO-d^6	28	12	60
8	(E)-**3a**	CD_3OD	15	7	78
9	(E)-**3a**	Ethanol-d^6	15	7	78
10	(E)-**3a**	CD_3CN	6	7	87
11	(Z)-**3a**	CD_3CN	7	7	86
12[c]	(E)-**3a**	CD_3CN	59	28	13
13[d]	(E)-**3a**	CD_3CN	15	23	62
14[e]	(E)-**3a**	CD_3CN	n.d.[f]	100	n.d.[f]

[a] Reaction was performed in Schlenck tube in 1 mL of solvent under argon atmosphere; c(**2**) = 5×10^{-4} mol L^{-1}, c(**3a**) = 2×10^{-2} mol L^{-1}; [b] Relative conversion determined by ^{1}H NMR; total conversion was proved not to drop under 95% using calibrated internal standard; [c] Reaction time: 1 min.; [d] Under air; [e] With **1** as catalyst; [f] Not detected.

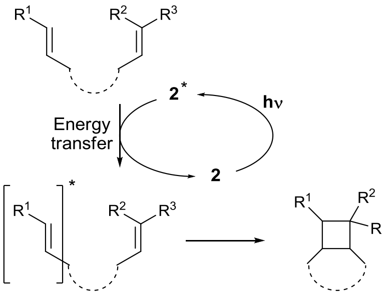
A substrate scope investigation performed on a semipreparative scale under optimised conditions showed our photocatalytic system based on **2** to be a versatile tool for intramolecular [2+2] cycloadditions of various types of dienes (Table 2), including styrenes **3** with both electron-donating and electron-withdrawing substituents, symmetrical and non-symmetrical bis(styrenes) **5**, **7** and **9**, and, interestingly, bis(arylenones) **11**, which belong among the electron-poor substrates that are usually the subject of visible light photocycloadditions by a reductive radical pathway taking place in the presence of Lewis acid (lithium salt) only even with strong reductants such as excited Ru(bpy)$_3$ or Eosin Y.[9,10,11b] In the [2+2] photocycloaddition mediated by **2**, there is indirect evidence that it occurs presumably via an energy transfer mechanism (Scheme 1) which could be allowed (despite it seems to be slightly endothermic[26]) by high Φ_{ISC} of **2** and/or by nonvertical energy transfer[27]: (i) substrates **3c**, **3d**, **9** and **11** are too electron-poor to be oxidised with excited alloxazines (see ESI), (ii) triplet state *E*/*Z*-photoisomerization occur after irradiation of 1-phenylpropene, 1-(*p*-methoxyphenyl)propene as well as of 1-(4-methoxyphenyl)but-2-en-1-one in the presence of alloxazine **2** (see ESI), (iii) irradiation of (*Z*)-**3a** led to a mixture of the same composition as that of (*E*)-**3a** and (iv) cyclization of (Z,Z)-**11a** gave almost the same mixture of cyclobutane products preferentially with *cis* configuration of arylcarbonyl groups as we observed with (*E*,*E*)-**11a** (cf. Entries 10 and 13). On the other hand, reductive mechanism cannot be excluded for strongly electron-poor **11c**.

Table 2. Substrate scope investigation for [2+2] photocycloadditions mediated by **2** and visible light.[a]

Entry	Substrate	Cyclobutane	Time [min]	Yield[b] [%]	d.r.[c]
	 **3**	 **4**			
1	R = MeO (**3a**)	**4a**	10	82	>10:1
2	R = H (**3b**)	**4b**	10	87	>10:1
3	R = Br (**3c**)	**4c**	45	76	>10:1
4	R = CF$_3$ (**3d**)	**4d**	30	81	>10:1
5	(*Z*)-**3a**	**4a**	10	65	>10:1
	 **5**	 **6**			
6	R = H (**5a**)	**6a**	10	61	7:3
7	R = CF$_3$ (**5b**)	**6b**	10	97	5:1
8	 **7**	 **8**	90	42	7:1
9	 **9**	 **10**	25	80	–
	 **11**	 **12**			
10	Ar = Ph (**11a**)	**12a**	45	70	5:1
11	Ar = 4-MeOPh (**11b**)	**12b**	45	67	4:1
12	Ar = 4-CF$_3$Ph (**11c**)	**12c**	45	58	1:1
13	(*Z*,*Z*)-**11a**	**12a**	45	57	4.5:1

[a] Reaction mixtures containing substrate (2×10^{-4} mol) and **2** (5×10^{-6} mol) in acetonitrile (20 mL) under argon atmosphere were irradiated (LED, 400 nm) until complete conversion was achieved; [b] Preparative yields; [c] Diastereoisomeric ratio determined by ^{1}H NMR spectra of the reaction mixture.

It is noteworthy that quantitative conversions were achieved in all cases and that cycloadditions with electron-rich styrenes were faster than with other substrates. Irradiation of 1-phenylpropene and 1-(*p*-methoxyphenyl)propene led to only photoisomerisation (see ESI), most likely because of the extremely short lifetime[23] of the triplet state of styrenes, disfavouring intermolecular cyclisation. Concerning stereochemistry, our results correspond to those from photocatalytic radical processes:[9,10] i) *exo* diastereoisomers were formed as major products with excellent diastereoselectivity for **3**, and ii) cycloadditions of **5**, **7**, **9** and **11** yielded predominantly products with *cis* configurations of aryl and arylcarbonyl substituents.



Scheme 1. Proposed mechanism of [2+2] photocycloaddition mediated by **2** and visible light.

In summary, we demonstrated the first application of a flavin derivative for photocatalytic C-C bond formation thus opening a completely new application area for flavin photocatalysts, which have been used solely in photooxidations. The use of alloxazine instead of isoalloxazine allowed us to perform an intramolecular visible light [2+2] photocycloaddition, which is still considered the domain of noble metal complex photocatalysts. Photocycloaddition with organocatalyst **2** was shown to take place with a broad spectrum of dienes. Thanks to its versatility and its utilisation of a combination of photoactive organocatalyst and visible light, the system with flavin **2** distinguishes itself from those already published for visible light [2+2] photocycloadditions. Some other flavin derivatives are expected to be able to promote similar reactivity, which offers the possibility for further enhancement of the photocatalytic system presented.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of NMR and UV-VIS spectra. See DOI: 10.1039/b000000x/

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