Visible light flavin photo-oxidation of methylbenzenes, styrenes and phenylacetic acids†

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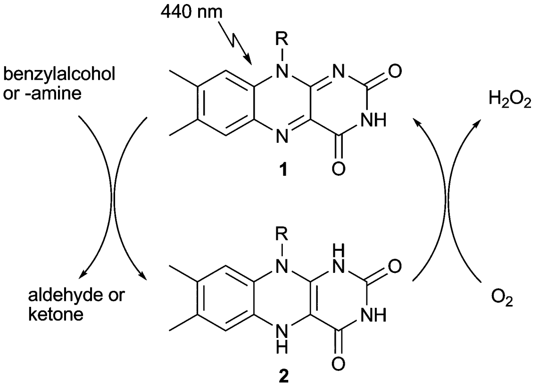
We report the photocatalytic oxidation of benzylic carbon atoms under mild conditions using riboflavin tetraacetate as photocatalyst and blue-emitting LEDs (440 nm) as light source. Oxygen is the terminal oxidant and hydrogen peroxide appears as the only byproduct in most cases. The process oxidizes toluene derivatives, stilbenes, styrenes and phenylacetic acids to their corresponding benzaldehydes. A benzyl methyl ether and acylated benzyl amines are oxidized directly to the corresponding methyl ester or benzylimides. The mechanism of the reactions has been investigated and the results indicate that oxygen addition to benzyl radicals is a key step of the oxidation process in the case of phenylacetic acids.

Introduction

Flavins have attracted much attention since they are involved in a large number of biological processes acting as redox co-factors, such as flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN)[1] and photoreceptors. Besides the application as flavoenzyme models for biochemical processes,[2] synthetic flavin derivatives have been used as organocatalysts in thermal[3] and photochemical[4] oxidation reactions. The latter processes utilize the increased oxidation power of the isoalloxazine chromophore in its oxidized form **1** upon excitation by light.[5] When an electron donor is present, the excited triplet form of **1** can undergo subsequent two electron reduction and protonation to yield dihydroflavin **2**, which is oxidized back to **1** by molecular air oxygen as the terminal oxidant. In this catalytic process hydrogen peroxide is obtained as sole stoichiometric by-product (Scheme 1).[4]



Scheme 1 Catalytic cycle of aerobic riboflavin tetraacetate (RFT: R = $C_{13}H_{19}O_8$) mediated photo-oxidation of benzyl alcohols or benzyl amines.

In previous studies we used flavin-mediated photocatalysis for the oxidation of benzyl alcohols[4b,c,e] and benzyl amines.[4a] The method was used for the selective photocatalytic removal of benzyl protecting groups,[4a] and is now extended to flavin-mediated photocatalytic oxidation to methylbenzenes, styrenes and phenylacetic acids. Riboflavin tetraacetate (RFT, see Scheme 1)[6] is used as a readily available and non-toxic photocatalyst; blue light-emitting high power LEDs serve as a selective and efficient light source.

Oxidation of methylbenzenes

The aerobic photochemical oxidation of methylbenzenes under heterogeneous[7] and homogeneous[8] reaction conditions has been described. Yet the use of purely visible light is still the exception.[8b,c] Quenching of the excited state of flavin by methyl- and methoxybenzenes *via* electron transfer (ET) has been known for some time,[9] but no products of the ET reactions have been described so far. We therefore investigated the reaction as a possible C–H activation pathway to functionalize electron-rich arenes at their benzyl position.

First encouraging results were obtained by subjecting 4-methoxytoluene **3a** to standard flavin photocatalysis conditions: 0.01 mmol of substrate and 10 mol% RFT were dissolved in 1 mL solvent and irradiated with blue light (440 nm, 3 W LED) and the course of the reaction was monitored by GC analysis. Besides 4-methoxybenzaldehyde **3b**, the only side product that could be detected in small amounts by ^{1}H NMR was 4-methoxybenzyl alcohol **5** as a likely intermediate of the benzyl oxidation.

Starting from this initial result, we optimized the reaction conditions by varying the solvent and oxygen content (see Table 1). The oxidation reaction depends heavily on the water content: nearly no conversion was obtained in pure MeCN, whereas the yield of aldehyde **4a** increased with the increasing portion of water to reach a maximum at a 1 : 1 mixture of H_2O–MeCN. At higher water content the yield decreased again.[10]

Complete consumption of **3a** in H_2O–MeCN 1 : 1 required the addition of another 10 mol% RFT after 20 min of irradiation time. After 40 min of irradiation **3a** was consumed completely and aldehyde **4a** was obtained in 58% yield. Since no other side product could be detected in appreciable amounts, a parasitic side reaction, giving products that could not be detected by GC and ^{1}H NMR analysis, is proposed. From earlier studies it is known that phenolic compounds are oxidized to not detectable,[11] presumable polymeric

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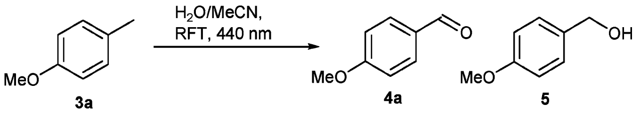
† Electronic supplementary information (ESI) available: UV-Vis absorption spectra of RFT 1 during the photo-oxidation of 4-methoxytoluene **3a**. See DOI: 10.1039/c0pp00202j

Table 1 Photocatalytic oxidation of 4-methoxytoluene **3a**



			Yield (%)[b]		
H_2O–MeCN/mL	Conditions[a]	Irradiation time/min	Aldehyde **4a**	Alcohol **5**	Starting material **3a**
0/1.0		10	2	0	95
0.2/0.8		10	16	0	49
0.4/0.6		10	18	0	9
0.5/0.5		10	28	0	11
0.6/0.4		10	24	4	29
0.7/0.3		10	19	0	49
0.5/0.5		**40**[c]	**58**	**0**	**0**
0.5/0.5	O_2	5	29	4	33
0.5/0.5	O_2	10	21	0	1
0.5/0.5	O_2	20	51	6	0
0.5/0.5	no RFT/O_2	20	0	0	65
0.5/0.5	dark/O_2	20	0	0	69
0.5/0.5	no RFT	20	0	0	88
0.5/0.5	dark	20	0	0	90
0.5/0.5	D_2O/MeCN-d_3/O_2	5	10	0	11

The bold row shows optimized conditions with the best results.[a] O_2: oxygen saturated solution. [b] Determined by GC. [c] 20 mol% RFT.

products under flavin-mediated photo-oxidation conditions.[4a,12] Hence hydroxylation of the aromatic core by water and subsequent oxidation to polymeric compounds is proposed.[13]

The reaction proceeded faster and RFT did not bleach when the photocatalysis was done in an oxygen-saturated system, but there was no beneficial effect on the yield of **4a**.

Without irradiation as well as when the reaction mixture was irradiated in the absence of RFT no benzaldehyde **4a** was formed. In some oxidation reactions, 4-methoxybenzyl alcohol **5** was detected as a side product. Since alcohol **5** is oxidized faster to aldehyde **4a** than toluene **3a**,[4b] alcohol **5** might be an intermediate in the oxidation of toluene **3a**.

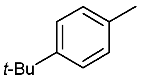
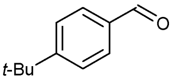
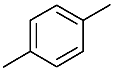
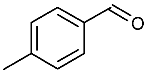
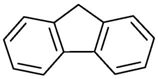
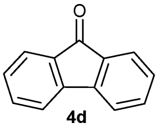
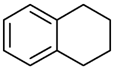
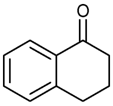
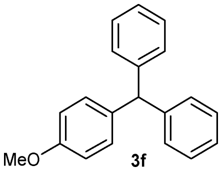
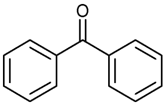
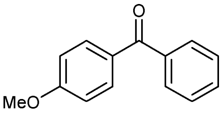
To exclude a singlet oxygen oxidation pathway, which flavins can mediate under photo-irradiation,[14] the photo-oxidation reaction was performed in deuterated solvents. Since the lifetime of singlet oxygen is significantly prolonged in deuterated solvents compared to the same non-deuterated solvents,[15] the photo-oxidation reaction should be accelerated in deuterated solvents, if singlet oxygen formation is involved. The yield of aldehyde **4a** was lower in deuterated compared to non-deuterated solvents at identical irradiation times, disfavouring a singlet oxygen reaction pathway and indicating the role of water as reactant. The change of pK_a by changing from H_2O to D_2O is not decisive since the reaction is not dependent on the pH value in a certain range.[16] The quantum yield of the flavin-mediated photo-oxidation of 4-methoxytoluene **3a** was determined to be 1.1% [$c = 0.01$ mol L^{-1} in 2 mL of H_2O–MeCN 1 : 1, O_2 purged].

We then applied the oxidation conditions to a variety of methylbenzenes. The results are summarized in Table 2. The conversion rate of methylbenzenes depends on the electronic character of the arene: benzene rings bearing electron donating substituents lead to a faster conversion, while more electron poor arenes are not active at all. This is in accordance with previous observations on flavin-mediated photo-oxidation of benzyl alcohols and benzyl amines.[4a,b] Toluene, benzyl bromide and ethyl benzene are not electron rich enough to be oxidized by flavin photo-oxidation. Fluorene **3d** gave fluorenone **4d** as oxidation product in 16% yield. Tetrahydronaphthalene **3e** was oxidized to α-tetralone **4e** in 34% yield. Unreacted starting material was only partly recovered, which indicates competing polymerization processes as described above.

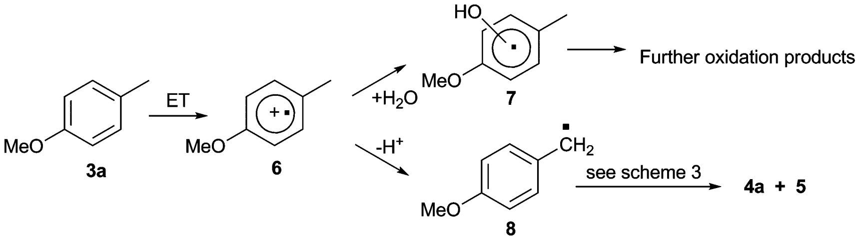
Treating of triphenylmethane as well as triphenylmethanol with these oxidation conditions did not yield any oxidation products, whereas more electron rich 4-methoxytriphenylmethane **3f** underwent oxidative degradation to benzophenone **4f** in 24% and 4-methoxybenzophenone **4g** in 35% yield. This kind of oxidative degradation is known from triphenylmethane radicals derived from triphenylmethyl halides[17] or triphenylmethane.[18] It was proposed that the triphenylmethane radical cation that is formed after initial ET to excited flavin loses a proton to form a triphenylmethyl radical. This is quenched by oxygen to form a peroxy radical that collapses into benzophenone and phenol.[18]

To gain more data on possible intermediates formed during the flavin-mediated photo-oxidation of **3a**, we followed the course of the UV-Vis absorption of RFT under aerobic, oxygen saturated and anaerobic conditions (see ESI†). Strong bleaching of the RFT **1** absorption in the visible region with elongated irradiation times was observed. A 50% bleach of the absorption band at 446 nm is obtained after about 90 s of irradiation. No recovery of the bleached signals was obtained when the system was purged with air after the irradiation. Therefore the obtained flavin species is not reduced RFT **2**. The same course of RFT **1** bleaching was observed when the reaction was followed in an oxygen saturated system, besides bleaching of RFT **1** slowing down. The 50% bleach of RFT **1** was retarded to roughly 150 s irradiation time. The irradiation of the reaction mixture under anaerobic conditions showed a fast bleaching of RFT **1**. When the mixture then was purged with air a blue flavin species developed, exhibiting two absorption maxima at 601 nm and 629 nm. We assign this spectrum to a neutral N5

Table 2 Photocatalytic oxidation of methylbenzenes in MeCN–H_2O 1 : 1

Entry	Irradiation time[a]/min	Starting material	Product(s)	Yield (%)[b]
1	165	 **3b**	 **4b**	40[c]
2	270	 **3c**	 **4c**	43[c]
3	100	 **3d**	 **4d**	16
4	100	 **3e**	 **4e**	34
5	60	 **3f**	 **4f**	24[c,d]
			 **4g**	35

[a] The reaction mixtures were irradiated until RFT was completely bleached. [b] Determination of yield by GC. [c] 20 mol% RFT. [d] MeCN–H_2O 3 : 2.



Scheme 2 Proposed mechanism for flavin-mediated photo-oxidation of methylbenzenes.

alkyl flavin radical.[19] This radical was stable in the dark at least for some minutes, but decayed quickly under irradiation.

Scheme 2 and 3 show possible pathways of flavin-mediated methylbenzene photo-oxidation by considering the presented results.

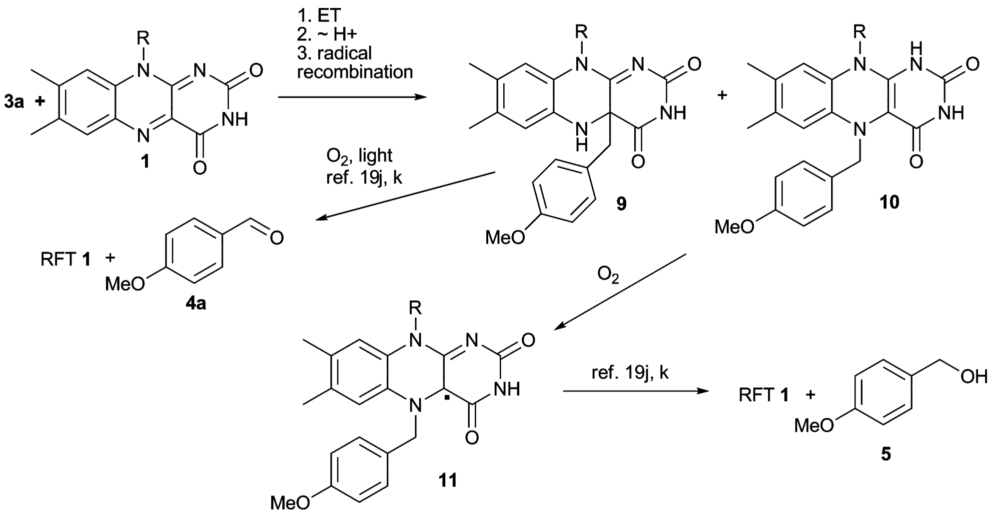
The initial step in the photo-oxidation process is an ET from methylbenzene **3a** to RFT in the triplet excited state.[9] The so-formed radical ion pair of radical cation **6** and $RFT^{\bullet-}$ can either collapse *via* back ET to **3a** and RFT **1** or follow two different productive pathways: Either the attack of water on the radical cation **6** to give phenol **7** that is further oxidized by flavin to presumable polymeric compounds or the radical cation **6** that is a strong acid (pK_a of toluene radical cation in MeCN was estimated by Arnold[20a] to be −13 and −12 by Green[20b]) loses a proton to give benzyl radical **8** (Scheme 2). Benzyl radical **8** and $RFT^{-\bullet}$ can recombine to form covalent intermediates.[19] The C4a adduct **9** collapses under irradiation and oxygen present to aldehyde **4a** and RFT.[19j,k] The N5 adduct **10** is oxidized by oxygen in a dark reaction to form the observed neutral radical **11**. The radical is undergoing an ET and subsequently fragments to RFT **1** and benzyl alcohol **5** (Scheme 3).[19j,k] Whether benzyl alcohol **5** is the outcome of an intermediate benzyl cation that is trapped by water or generated *via* a concerted mechanism is not known.

The electron donating methoxy group on the arene in the case of 4-methoxytoluene **3a** stabilizes the initially formed radical cation **6**.[8c,9,21,22] The proposed ET pathway is further supported by the

Table 3 Photocatalytic oxidation of *trans*-stilbene

			Yield (%)[b]		
H_2O–MeCN/mL	Conditions[a]	Irradiation time/min	Benzaldehyde **4h**	*cis*-Stilbene **13**	*trans*-Stilbene **12a**
0/1.0		5	5	42	38
0.4/0.6		5	69	2	2
0.4/0.6		1	19	10	72
0.4/0.6	no RFT	5	0	Traces	98
0.4/0.6	in dark	5	Traces	5	88
0.4/0.6	O_2	1	13	11	70
0.4/0.6	D_2O/MeCN-d_3	1	Traces	28	70

[a] O_2: oxygen saturated solution. [b] Determination of yield by GC.



Scheme 3 Formation of covalent intermediates and decomposition to products in the photo-oxidation of methylbenzenes.

critical role of water as solvent: the triplet reduction of flavin proceeds *via* a dipolar intermediate. The degree of ET product formation depends on the extent of solvent interaction. With its high dielectric constant, water is stabilizing the formed separated radical cations **6** and $RFT^{\bullet-}$.[23] Secondly, when the proton is not directly transferred from radical cation **6** to $RFT^{\bullet-}$, water acts as a base or proton relay, promoting the rate limiting deprotonation step of radical cation **6** to form benzyl radical **8**.[22a,b] Additional the reoxidation of flavin from its reduced state **2** to its oxidized state **1** is faster in water compared to MeCN.[24]

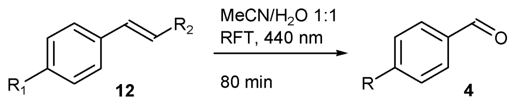
Oxidation of phenylenes

The photo-oxidative cleavage of stilbenes and styrenes has been of great interest for some time.[25] Studies towards the flavin-photosensitization of stilbene have been undertaken, but only the *trans*-*cis* isomerisation of stilbene has been observed.[26] An example of double bond oxidation by flavin sensitization is the oxidation of unsaturated fatty acids in MeCN that yielded hydroperoxides of fatty acids. It was proposed that the oxidation proceeds by a type II (singlet oxygen) mechanism.[27] To our delight, applying flavin photo-oxidation conditions to *trans*-stilbene **12a**, we obtained benzaldehyde **4h** in 69% yield (considering the production of 2 eq. of benzaldehyde **4h** from the oxidation of 1 eq. stilbene **12a**) within 5 min of irradiation time, leaving only 2% of starting material **12a** and 2% of *cis*-stilbene **12b** (Table 3).

When the oxidation was performed in pure MeCN only 5% of benzaldehyde **4h** was detected within 5 min irradiation time, but 42% of *cis*-stilbene **13** was observed. The formation of 10% *cis*-stilbene **13** already after 1 min is indicative that *trans*-stilbene **12a** is oxidized to benzaldehyde **4h** as well. Whether *cis*-stilbene **13** is a general intermediate in the photo-oxidation process cannot be concluded from this data. No reaction was observed when the reaction mixture was irradiated without RFT and only traces of benzaldehyde **4h** were formed when the reaction mixture was stirred in the dark. Oxygen saturation of the solution had no beneficial effect on the reaction rate of the photo-oxidation and only traces of benzaldehyde **4h** were formed when the reaction was done in deuterated solvents for 1 min. The non-dependency on the oxygen content and the large effect of the solvent are indicative that water, but not oxygen is participating in the rate determining step.

The quantum yield of the flavin-mediated photo-oxidative cleavage of *trans*-stilbene **12a** was determined to be 1.1% [c = 0.01 mol L^{-1} in MeCN–H_2O 4 : 3].

Table 4 Photocatalytic oxidation of phenylenes



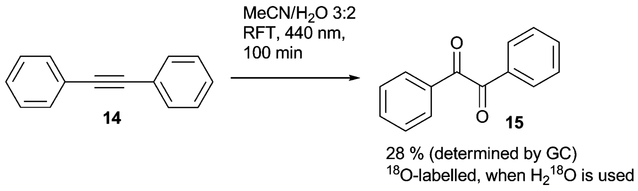
Entry	Starting material	Product/s	Yield (%)[a]
1	R_1: OMe, R_2: C_6H_4-4-OMe **12b**	R: OMe **4a**	36[b]
2	R_1:NO_2, R_2: C_6H_4-4-OMe **12c**	R: OMe **4a**	69[c]
		R: NO_2 **4i**	64
3	R_1: H, R_2: COOH **12d**	R: H **4h**	68[d]

[a] Determination of yield by GC. [b] MeCN–H_2O 24 : 1. [c] MeCN–H_2O 5 : 3. [d] 20 mol% RFT.

Next, we applied flavin-mediated photocatalytic oxidation to electron rich symmetrical stilbene **12b** and unsymmetrical stilbene **12c** (Table 4). As expected, the symmetrical stilbene **12b** was oxidized to 4-methoxybenzaldehyde **4a** in 36% yield within 80 min irradiation time. The slow conversion and the low yield might be attributed to the poor solubility of **12b** and hence the low water content of the reaction mixture. The unsymmetrical stilbene **12c** was oxidized within the same time to 4-methoxybenzaldehyde **4a** in 69% and 4-NO_2 benzaldehyde **4i** in 64% yield.

Styrene, α-methyl styrene and 4-methoxystyrene did not yield the desired benzaldehydes. No products or starting material could be detected with GC-MS, due to polymerization of the starting compounds under the experimental conditions. When β-nitro styrenes were subjected to the photocatalytic oxidation conditions, oxidative cleavage did not take place.

Photocatalytic oxidation reaction of tolane **14**[28] gave benzil **15** as sole oxidation product in 28% yield leaving 2% of starting tolane **14** (Scheme 4). When the oxidation of tolane **14** was done in ^{18}O labelled water (10.5% ^{18}O content), the isotope peak with m/z = 212.1 (benzil m/z = 210.1) was found in a relative abundance of a factor 5.8 higher compared to a sample obtained from non-labelled water as confirmed by EI-MS. This indicates that water is acting, at least partially, as oxygen atom source in the flavin-mediated oxidation of tolane **14** to benzil **15**.



Scheme 4 Photocatalytic oxidation of tolane **14**.

Oxidation of stilbene **12a** in a MeOH–MeCN mixture yielded benzaldehyde **4h** as main product, but benzoic acid methyl ester **16** and *O*-methylbenzoin **17** could be detected by GC-MS as well. A comparable reactivity was observed when the reaction was performed in an AcOH–MeCN mixture: benzaldehyde **4h** was obtained as the main product, but diester **18** and *O*-acetylbenzoin **19** were formed as well (Scheme 5). These results clearly indicate the role of the solvent acting as a nucleophile in the course of the oxidation reactions.

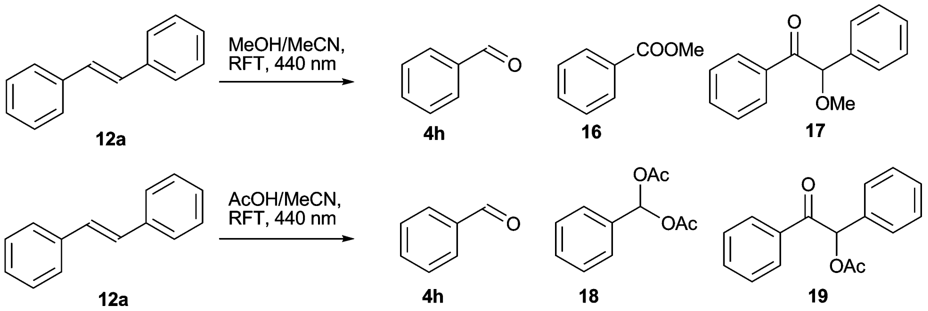
To gain more insight into the mechanism of the oxidative cleavage of stilbenes, *trans*-stilbene oxide, *meso*-hydrobenzoin **25** and benzoin **31** as potential intermediates, were subjected to the standard reaction conditions. All three compounds did not yield benzaldehyde **4h** as oxidation product within 1 min irradiation time, excluding the compounds as possible intermediates. In the case of *trans*-stilbene oxide no benzaldehyde **4h** was formed even after 60 min irradiation, whereas *meso*-hydrobenzoin **25** was oxidatively cleaved in 60% to benzaldehyde **4h** within the same irradiation time. Benzoin **31** did not react even after 60 min irradiation as judged by TLC. Since *meso*-hydrobenzoin **25** is not a likely intermediate in the flavin-mediated photo-oxidation of stilbene **12a**, the proposed mechanism by Fry *et al.*[29] for anodic cleavage of stilbenes is not valid for our system.

A singlet oxygen reaction pathway can be excluded, since it is known that stilbene is not oxidized by singlet oxygen.[25j,k]

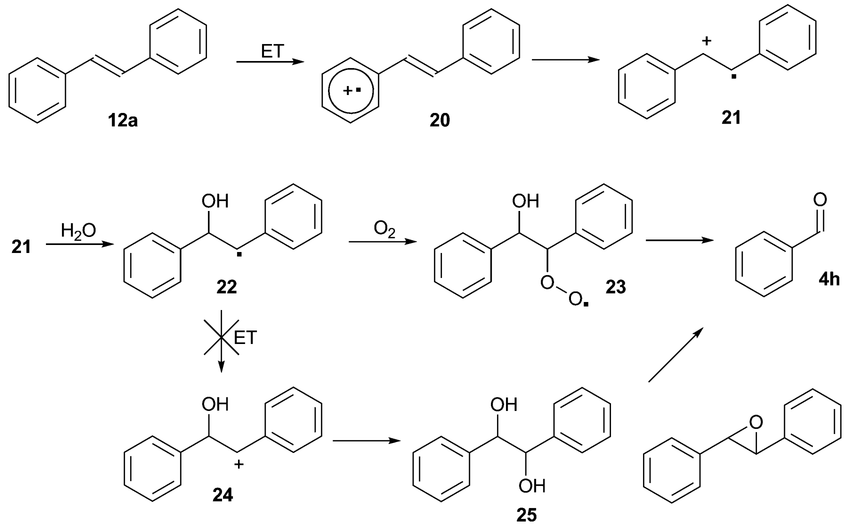
Quenching of the radical cation **21** of stilbene radical cation **20** is not likely since oxygen hardly reacts with radical cations of aromatic olefins.[30] It has been shown that alkene radical cations behave as cations when reacting with nucleophiles,[31] which are in our case water, MeOH or acetic acid. The so-formed benzyl radical **22** can now react with oxygen yielding peroxy radical **23**, which undergoes fragmentation to benzaldehyde **4h** (Scheme 6). The reaction mechanism is in accordance to the proposed mechanism of Velasco *et al.* for the oxidative cleavage of stilbene in aqueous solution under aerobic conditions.[32]

A second ET from benzyl radical **22** to flavin seems not likely since the so-formed carbocation **24** would give *meso*-hydrobenzoin **25** upon reaction with water or stilbene oxide which were excluded as intermediates.

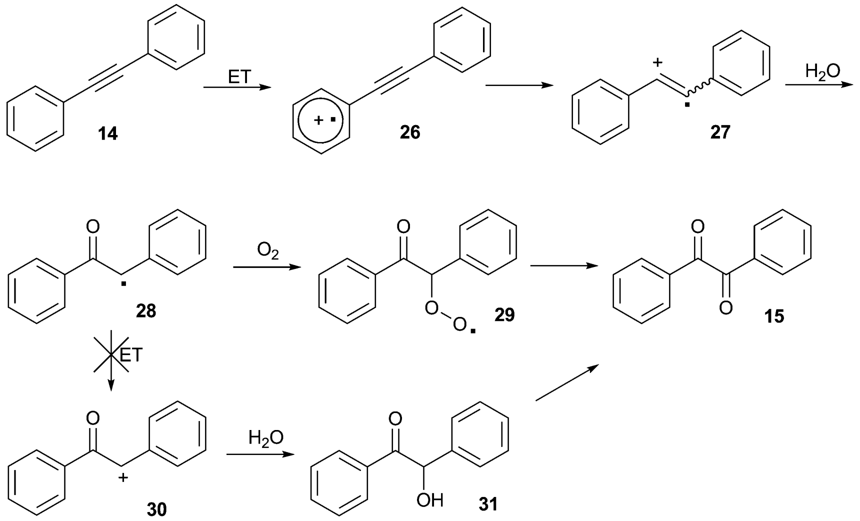
For the oxidation of tolane **14** to benzil **15**, *meso*-hydrobenzoin **25** and *trans*-stilbene oxide were excluded as intermediates, since submitting these compounds to our oxidation conditions did not yield benzil **15**. From these results a reaction pathway in analogy to stilbene oxidation is proposed (Scheme 7). Here, peroxy radical



Scheme 5 Photocatalytic oxidation of stilbene **12a** in organic solvents.



Scheme 6 Proposed mechanism for flavin-mediated photo-oxidation of stilbene **12a**.



Scheme 7 Proposed mechanism for flavin-mediated photo-oxidation of tolane **14**.

ketone **29** instead of the alcohol **23** is formed, which collapses to benzil **15**.

The parasitic side reaction of hydroxylation of intermediate radical cations as it was proposed for the oxidation of methylbenzenes (Scheme 2) seems to be true for the flavin mediated oxidation of phenylenes and tolane as well. These reaction pathways are not shown in the Schemes.

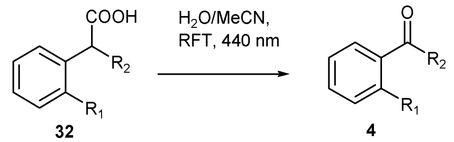
Oxidation of phenylacetic acids

Phenylacetic acid **32b** was photo-oxidized yielding aldehyde **4h**. This decarboxylative photo-oxidation reaction of phenylacetic acids is known.[33] Anaerobic photo-decarboxylation of phenylacetate by excited flavin with accompanying benzylation of the flavin core[19j,k,34] and oxidative decarboxylation of dihydrophthalates[35] has been described. Photo-decarboxylation of α-hetero carboxylic acids by flavin has been reported as well.[36] We have optimized the reaction conditions of this flavin-mediated decarboxylation for synthetic preparative use.

As in the case of photo-oxidation of methylbenzenes and styrenes, the oxidation of diphenylacetic acid **32a** to benzophenone **4f** was dependent on the water content: the higher the water content, the higher the reaction rate. Oxygen saturation of the system had an inhibitory effect and the yield of benzophenone **4f** decreased (Table 5).

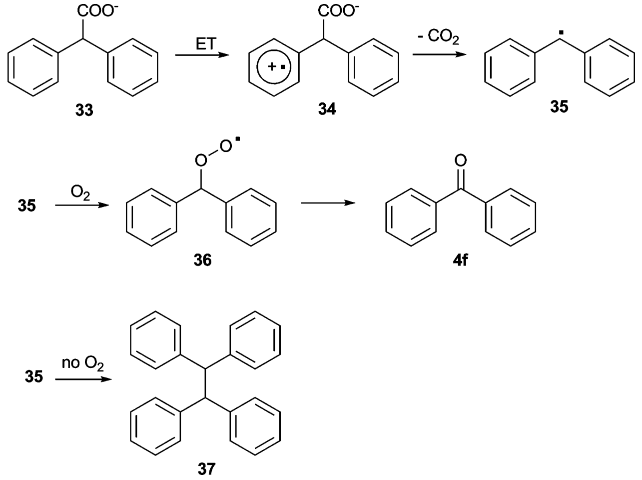
The reaction was accelerated when it was performed open to air in a non-closed sample vial as compared to the closed system. Full conversion of diphenylacetic acid **32a** to benzophenone **4f** in an open reaction system was achieved within 20 min irradiation time. Whether the oxygen availability or the rising partial pressure of CO_2 in the head space upon expelling of CO_2 from the substrate is the limiting factor cannot be concluded from the collected data. No incorporation of ^{18}O was observed when the reaction was done in ^{18}O labelled water (10.5% ^{18}O content). Deuteration of the solvents did not have any impact on the photo-oxidation. These findings are different to the observations on the flavin-mediated oxidations of methylbenzenes, styrenes and tolane and indicate that dissolved oxygen is acting as oxygen

Table 5 Oxidation of phenylacetic acids



Starting material	H_2O–MeCN/mL	Conditions[a]	Irradiation time/min	Yield (%)[b]
R_1: H, R_2:Ph **32a**	0/1.0		5	2
	0.25/0.75		5	4
	0.5/0.5		5	24
	0.7/0.3		5	34
	0.5/0.5	O_2	5	11
	0.5/0.5	HCl	5	8
	0.5/0.5	NaOH	5	22
	0.5/0.5	open to air	5	32
	0.5/0.5	**open to air**	**20**	**>99**
	0.5/0.5	$H_2{}^{18}O$ (10.5%)	20	no ^{18}O labelled **4f**[c]
	0.5/0.5	D_2O/MeCN-d_3	5	31
R_1: H, R_2:H **32b**	0.5/0.5	open to air	30	45
R_1: OMe, R_2:H **32c**	0.5/0.5	open to air	10	43

[a] O_2: oxygen saturated solution, HCl: 0.001 N HCl instead of H_2O, NaOH: 0.001 N NaOH instead of H_2O. [b] Determination of yield by GC. [c] ^{18}O was not incorporated into benzophenone **4f**.



Scheme 8 Proposed mechanism for flavin-mediated photo-oxidation of diphenylacetic acid **33**.

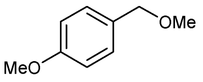
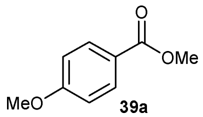
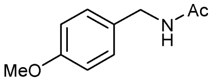
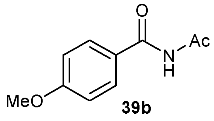
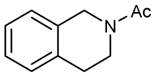
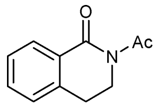
source in the flavin-mediated photo-oxidation of diphenylacetic acid **32a**.

With the same protocol phenylacetic acid **32b** was oxidized to benzaldehyde **4h** in 45% yield within 30 min. The more electron rich 2-methoxyphenylacetic acid **32c** was oxidized to the corresponding aldehyde **4j** in 43% yield already within 10 min of irradiation.

From the obtained data, a reaction pathway for the decarboxylative oxidation of phenylacetic acid is proposed as shown in Scheme 8. The deprotonated diphenylacetic acid **33** undergoes an ET to excited flavin. The so-formed radical cation **34** decarboxylates to give benzyl radical **35** that is trapped by oxygen present in solution yielding peroxy radical **36**, which yields benzophenone **4f** under these reaction conditions. The decarboxylation is very efficient and the yield of the reaction is nearly quantitative. No parasitic side reaction as described for the oxidation of methylbenzenes, phenylenes and tolane was observed. The occurrence of intermediate benzyl radical **35** is supported by the anaerobic photo-oxidation of diphenyl acetic acid in dry MeCN (Scheme 8).[37] Tetraphenyl ethane **37** was identified as main product that most likely results from the dimerization of two diphenylmethyl radicals **35**.

Benzyl ether **38a** and the acylated benzyl amines **38b** and **38c** were investigated for comparison. They are photo-oxidized to yield the ester or imides as summarized in Table 6. The acylated benzylamine **38b** was converted in an acetonitrile–water mixture into imide **39b** in 83% yield, while the methyl ether **38a** and the tetrahydroisoquinoline derivative **38c** showed less conversion and lower yields under these conditions. Using methanol as solvent and

Table 6 Oxidation of 4-methoxybenzyl methyl ether and acylated benzylamines

Starting material	Product	Solvent	Irradiation time/min	Conversion (%)[a]	Yield (%)[a]
 **38a**		CH_3CN–H_2O 1 : 1 MeOH (abs.) MeOH	30 180 3 d	95 100 100	55 76[b] 86[c]
 **38b**		CH_3CN–H_2O 1 : 1 MeOH (abs.)	30 180	100 95	83 69
 **38c**		CH_3CN–H_2O 1 : 1 MeOH (abs.)	30 180	49 100	28 70

[a] Determination of conversion and yield by GCMS. [b] 6% 4-methoxybenzyldehyde dimethylacetal as side product. [c] 7 times 10 mol% additional RFT, side product: 14% 4-methoxybenzyldehyde dimethylacetal.

applying longer irradiation times the conversion of the substrates was complete and product yields increased significantly. However, the conversion and yield of **38b** decreased under these conditions. We noticed a rapid fading of flavin in the methyl ether **38a** photo-oxidation in methanol and the reaction was performed adding eight times RFT. This improves the yield of the reaction to 86%.

Conclusions

The flavin-mediated photo-oxidation of benzylic carbon atoms in hydrocarbons, alkenes, carboxylates, ethers and amines was investigated. The potential of methylbenzenes as quenchers for excited flavins has been observed before, but the formation of aldehydes or ketones as oxidation products has not been described so far. The electron density of the arene moiety is crucial for the rate of oxidation: electron poor and very electron rich arenes are not converted to the corresponding aldehydes, whereas 4-methoxytoluene **3a** could be oxidized in 58% to anis aldehyde **4a**.

The oxidative cleavage of stilbene **12a** and cinnamic acid **12d** to benzaldehyde **4h** and the oxidation of tolane **14** to benzil **15** by flavin mediated oxidation are reported for the first time. However, the moderate yields of the photocatalytic oxidations due to competing polymerization limit their synthetic application.

The photo-oxidative decarboxylation of phenyl acetic acids by flavin has been known to produce aldehydes. Conditions to achieve quantitative product yields have been found.

Based on literature evidence and the results presented here, reaction mechanisms for the flavin photocatalyzed oxidation of methylbenzenes, stilbenes, tolane and phenyl acetic acids are proposed. For all compound classes reported here, the initial step is ET from the substrate to the excited flavin. The experimental data do not indicate an oxidation *via* singlet oxygen (Type II oxidation).

Other reaction mechanism after the initial ET step than the suggested one cannot completely be excluded on the basis of our data. In addition, it is likely that different reaction pathways compete and ratios vary with changes in reaction conditions and substrate.

While some of the described conversions may already find application in organic synthesis, the majority is currently limited by narrow applicability or moderate product yields. The use of flavin photocatalysts with substrate binding sites may increase the selectivity and efficiency of some of the photo-oxidations.

Experimental

Quantum yields were determined with the following setup: Light from a 440 nm LED was focused in the cuvette with a lens and the power of the light was measured behind with a calibrated solar cell. A reference measurement with pure solvent provided then the determination of the amount of light that is absorbed by the probe. The chemical yield is determined *via* GC and the quantum yield can be calculated.

General procedure for flavin-mediated photo-oxidations

Starting material (0.01 mmol) and RFT (0.001 mmol) were dissolved in 1 mL solvent in a sample vial. If necessary, the vial was capped with a septa and the solution was purged with oxygen for 30 s through a canula. The capped vial was irradiated at 440 nm (3 W LED).

For GC analysis the sample was diluted with water (1 mL) and extracted with ethyl acetate (3 × 1.5 mL). The organic layer was subjected to GC measurements.

General procedure for flavin-mediated photo-oxidations in $H_2{}^{18}O$ (10.5% ^{18}O)

The sample was prepared as described above using $H_2{}^{18}O$ (10.5% ^{18}O) instead of H_2O. After irradiation, MeCN was removed under a stream of nitrogen. The residue was diluted with water (1 mL) and extracted with ethyl acetate (3 × 1.5 mL). The organic layer was dried over $MgSO_4$ and filtered. The concentrated filtrate was subjected to EI-MS measurements.

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