Photocatalysis with Flavins

Dissertation

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“…schau hi schau her a Nosnbär!!!”

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Keep on rocking!!!

Contents

Zusammenfassung

Die vorliegende Dissertation stellt neue Anwendungen von Flavinen in Photooxidationsreaktionen für die organische Synthese vor. In Kapitel 1 wird ein kurzer Überblick über die Flavinchemie gegeben. Dabei wird auf deren Redoxchemie und Anwendung in der organischen Synthese eingegangen.

In Kapitel 2 werden die Ergebnisse mechanistischer Untersuchungen der Flavin vermittelten Photooxidation von 4-Methoxybenzylalkohol zu 4-Methoxybenzaldehyd diskutiert. Es wird ein Elektronentransfer von 4-Methoxybenzylalkohol zum Triplett Zustand des Flavins als erster Schritt in der Oxidationsreaktion postuliert. Die Quantenausbeute der Photooxidation nahm mit zunehmender Alkoholkonzentration ab. Bei hohen Konzentrationen wird Flavin im Singulett angeregten Zustand durch einen unproduktiven Elektronen Hin- und Rücktransfer gequencht. Zu sehr niedrigen Alkoholkonzentrationen hin nahm die Quantenausbeute der Oxidationsreaktion ebenfalls ab, da hier die Diffusion der limitierende Faktor wird. Quantenausbeuten wurden mit Hilfe eines von Prof. Dr. Eberhard Riedle und Uwe Megerle, von der Ludwig-Maximilian-Universität München, neu entwickelten Aktinometers gemessen.

Die Anwendung von Flavin katalysierten Photoreaktionen wird in Kapitel 3 berichtet. Es konnte gezeigt werden, dass in wässrigen Lösungen Benzylamine zu Benzaldehyden oxidiert werden. Diese Oxidationsreaktion wurde auf die Spaltung von Benzyl geschützten primären Aminen und Alkoholen angewandt. Unter den Selben photooxidativen Bedingungen waren Carboxybenzoyl geschützte Amine inert.

In Kapitel 4 wird die Erweiterung Flavin katalysierter Photooxidationen auf die Oxidation von benzylischen Positionen von Kohlenwasserstoffen, Alkenen und Carboxylaten diskutiert. Die Elektronendichte am aromatischen System war dabei entscheidend für die Oxidationsrate: elektronenarme und sehr elektronenreiche Arene wurden nicht umgesetzt, wohingegen 4-Methoxytoluol in 58% Ausbeute zum korrespondierenden Aldehyd oxidiert wurde. Die oxidative Spaltung von Stilbenen und Zimtsäuren zu Benzaldeyhden, wie auch die Oxidation von Tolan zu Benzil wurden das erste mal berichtet. Außerdem konnten Bedingungen zur quantitativen oxidativen Decarboxylierung von Phenylessigsäuren gefunden werden. Basierend auf Literaturberichten und den Versuchsergebnissen werden Reaktionsmechanismen

für die Flavin katalysierte Oxidation von Methylbenzenen, Stilbenen, Tolan und Phenylessigsäuren vorgeschlagen.

Im abschließenden Kapitel 5 wird die Synthese eines Flavins das eine polymerisierbare Vinylfunktion trägt beschrieben. Dieses konnte mit Acrylsäure und Styrol copolymerisiert werden, womit ein wasserlösliches und ein in Chloroform lösliches Flavin Copolymer erhalten wurde. Durch Quervernetzung mit Divinylbenzol waren außerdem gänzlich unlösliche Polymere zugänglich. Lösliche Copolymere wurden mittels UV-Vis- und Fluoreszenzspektroskopie charakterisiert.

Summary

The thesis presents the use of flavin photo catalysis in organic synthesis. A short review of flavin chemistry emphasizing the redox chemistry and applications to organic synthesis is given in chapter 1.

The results of mechanistic studies of the flavin mediated photo oxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde are presented in chapter 2: The initial process of the oxidation reaction is an electron transfer from 4-methoxybenzyl alcohol to flavin in its triplet state. The quantum yield of the reaction decreased with increasing concentration of alcohol. It is reasoned that at higher concentrations the flavin singlet excited state is quenched, leading to an unproductive electron transfer from alcohol to flavin and back electron transfer. Diffusion is the limiting factor at low alcohol concentrations and the quantum yield of the oxidation reaction is dropping again. The quantum yields were determined using a newly developed actinometer, which was developed in collaboration with Prof. Dr. Eberhard Riedle and Uwe Megerle from the Ludwig-Maximilian-Universität, Munich.

The application of flavins in photo catalysis is presented in chapter 3. It was shown that benzyl amines can be oxidized to the corresponding aldehydes in aqueous solution. This oxidation reaction was applied to the deprotection of benzyl protected primary amines and alcohols. Carboxybenzoyl protected amines were inert under these conditions.

In chapter 4 the flavin-mediated photo oxidation has been extended to benzylic carbon atoms in hydrocarbons, alkenes, carboxylates. The electron density of the arene moiety was crucial for the rate of oxidation: electron poor and very electron rich arenes were not converted to the corresponding aldehydes, whereas 4-methoxy toluene could be oxidized in 58% to 4-methoxy benzaldehyde. The oxidative cleavage of stilbenes and cinnamic acids to benzaldehydes and the oxidation of tolane to benzil by flavin mediated oxidation were reported for the first time. Conditions to achieve quantitative decarboxylative oxidation of phenylacetic acids have been found. Based on literature evidence and the results presented, reaction mechanisms for the flavin photo catalyzed oxidation of methylbenzenes, stilbenes, tolane and phenyl acetic acids are proposed.

In the closing chapter 5 the synthesis of a polymerizable flavin bearing a vinyl function is described. The monomer was copolymerized with acrylic acid and styrene yielding flavin copolymers that are water soluble or soluble in chloroform, respectively. Upon cross-linking with divinyl benzene insoluble polymers were obtained. The soluble copolymers were characterized by UV-Vis and fluorescence measurements.

Chapter 1: Introduction to Flavin Catalysis

Flavins are ubiquitous in nature. They not only act as redox active prosthetic group in enzymes but also as antennae for light absorption and light emission. The biologically active forms of riboflavin (vitamin B2, **1**) are flavin adenine dinucleotide (FAD, **2**) and flavin mononucleotide (FMN, **3**; Figure 1). Since flavoenzymes exhibit such a chemical versatility and play diverse roles in biology they have been the subject in a variety of studies.[1]

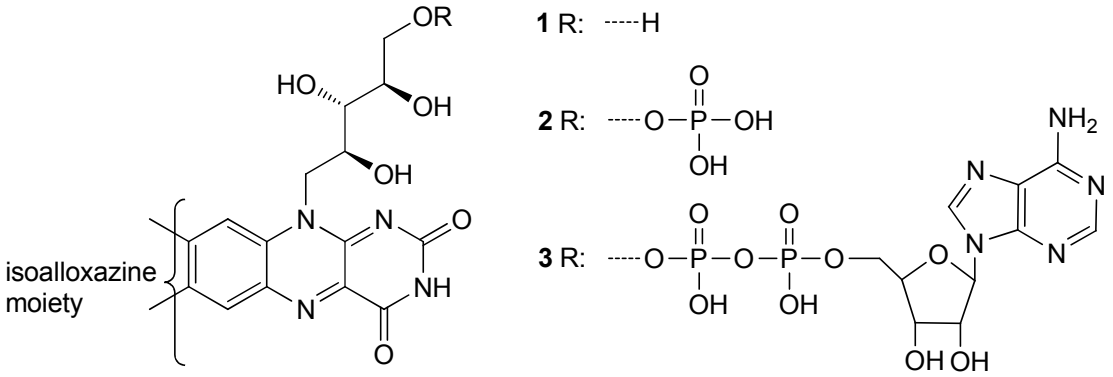
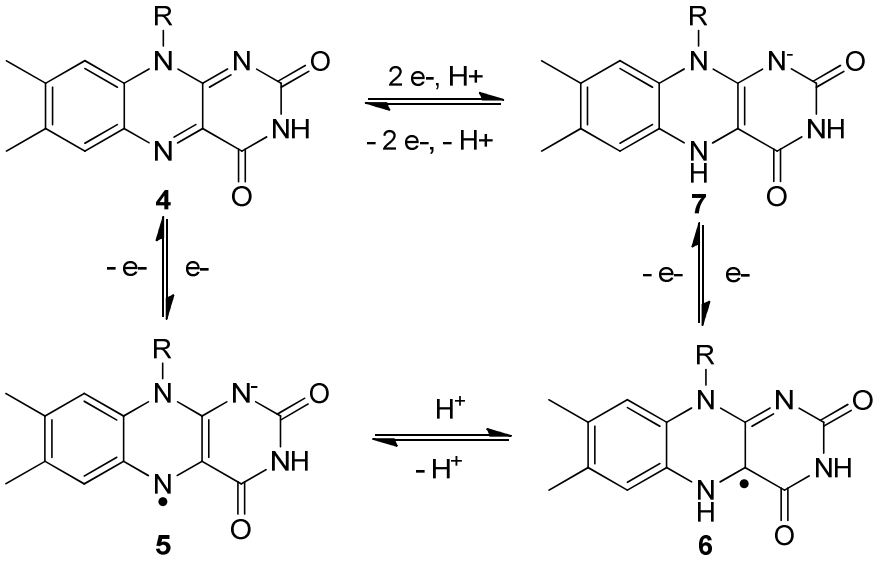


Figure 1: Structures of natural flavins

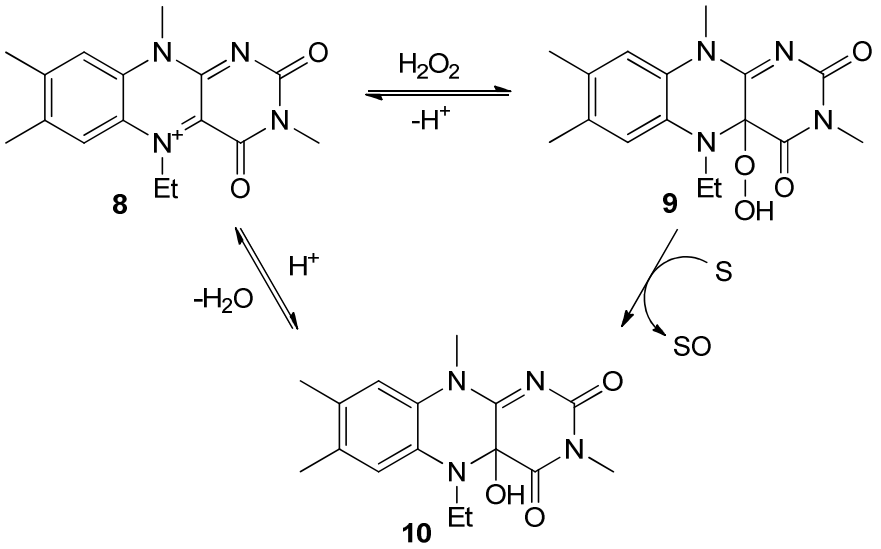
The use of visible light to catalytically mediate a redox reaction is of great interest. Using visible light for substrate activation allows mild reaction conditions and can provide more sustainable chemical processes.[2] Here the intrinsic flavin redox activity has been explored in photo organocatalysis. The use of simple flavins as organocatalysts in non light driven reactions has been studied for some time, whereas the use as photo organocatalyst on preparative scale is not widely elaborated yet. Here a short review of recent flavin-mediated thermal and photo catalytic reactions by means of preparative synthetic chemistry is given.

The redox properties of flavins are depicted in scheme 1. Flavins can undergo sequential electron uptake, yielding three different oxidation states. From the fully oxidized quinone **4** one electron uptake and protonation yields semiquinone **6**, that can take up another electron to yield the fully reduced hydroquinone **7**.[3]



Scheme 1: Different redox states of flavins

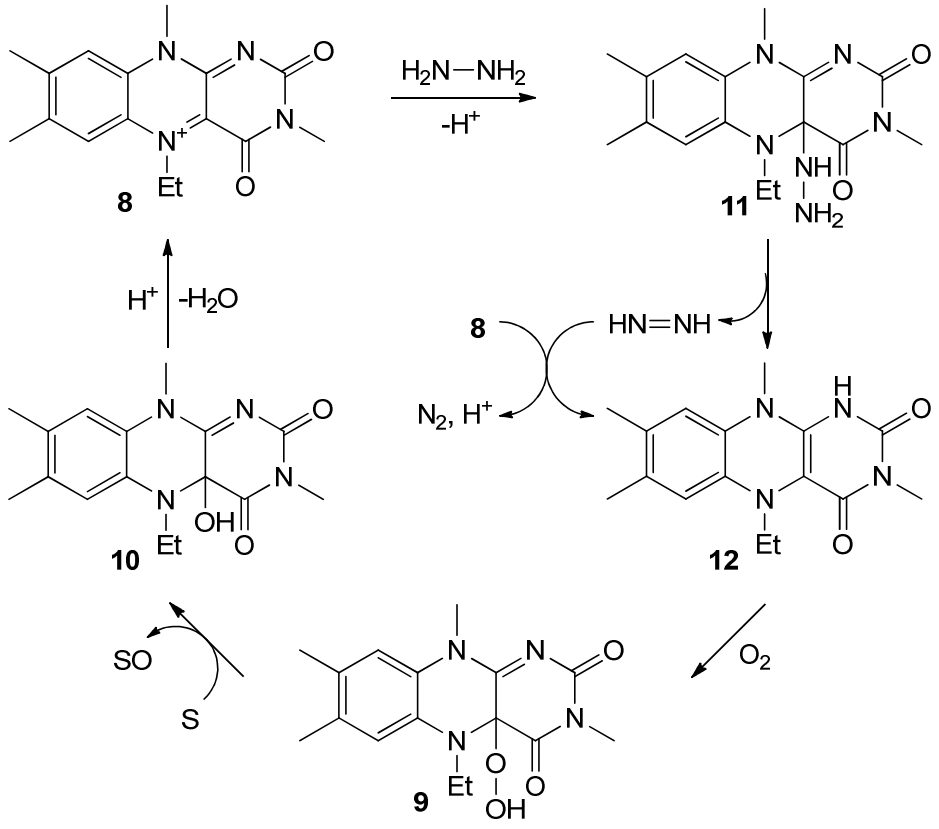
Murahashi et al. used 3N-methyl 5N-ethyl lumiflavin perchlorate salt **8** as catalyst precursor in the anaerobic oxidation of tertiary amines to N-oxides, N-hydroxylamines and secondary amines to nitrones and sulfides to sulfoxides.[4] Flavin peroxide **9** was proposed to be the catalytically active species, giving 4a hydroxy flavin **10**. The catalytic cycle is closed by the regeneration of **9** from **10** by H_2O_2 as the terminal oxidant.



Scheme 2: Catalytic cycle of anaerobic oxidation with N5 alkylated flavins (S: substrate, SO: oxidized substrate)

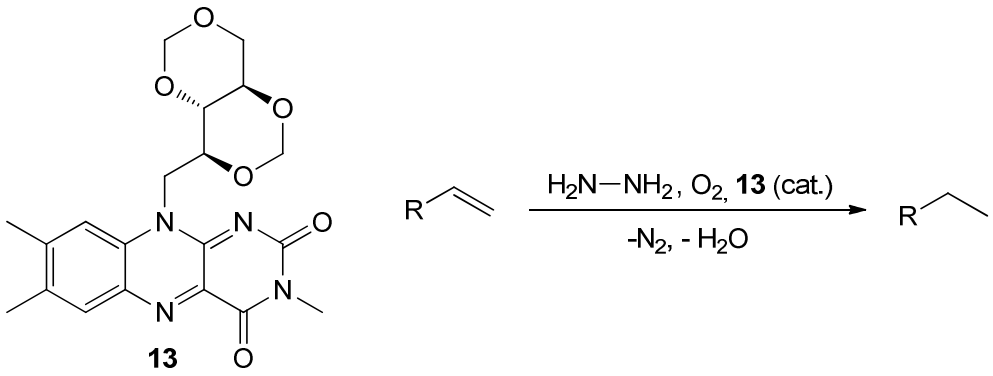
The principle of flavin catalyzed oxidation of sulfides to sulfoxides using H_2O_2 as terminal oxidant was adopted for the oxidation in micellar systems containing amphiphilic flavinium salts. In micellar systems the sulfoxidation rate was higher as compared to homogeneous systems depending on the pH value and type of micelle used. [5]

In a further improvement of the flavinium salt catalyzed oxidation Murahashi et al. reported the oxidation of sulfides, amines and N-hydroxylamies with oxygen.[6] Catalytic active **9** is formed from reduced flavin **12** and oxygen. The reduced flavin is formed by reduction of flavinium salt **8** by hydrazine as shown in scheme 3.[7] Since diimide, that is also capable of reducing **8** to **12**, is formed *in situ* the aerobic oxidation allover only requires 0.5 equivalents of hydrazine.



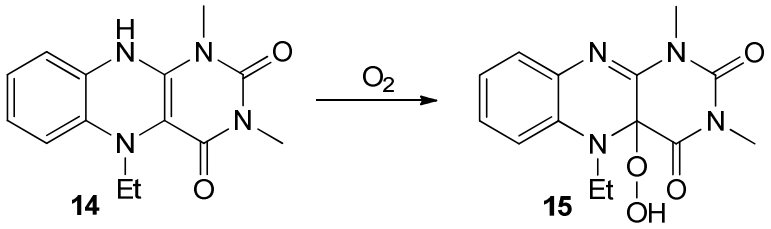
Scheme 3: Catalytic cycle of aerobic oxidation with N5 alkylated flavins using hydrazine as reductant (S: substrate, SO: oxidized substrate)

The principle of in situ generation of diimide by flavin catalysis was also used in the organocatalytic reduction of alkenes under aerobic conditions. The formed diimide is able to reduce alkenes giving nitrogen and water as environmentally benign by-products.[8] Naota et al. improved the aerobic hydrogenation of alkenes by using easy accessible neutral flavin **13** as organocatalyst. By extracting the reaction mixture in MeCN with hexane the product alkanes were obtained quantitatively (scheme 4), leaving catalyst **13** for reuse in the MeCN phase.[9]



Scheme 4: Aerobic hydrogenation of alkenes catalyzed by neutral flavin **13**

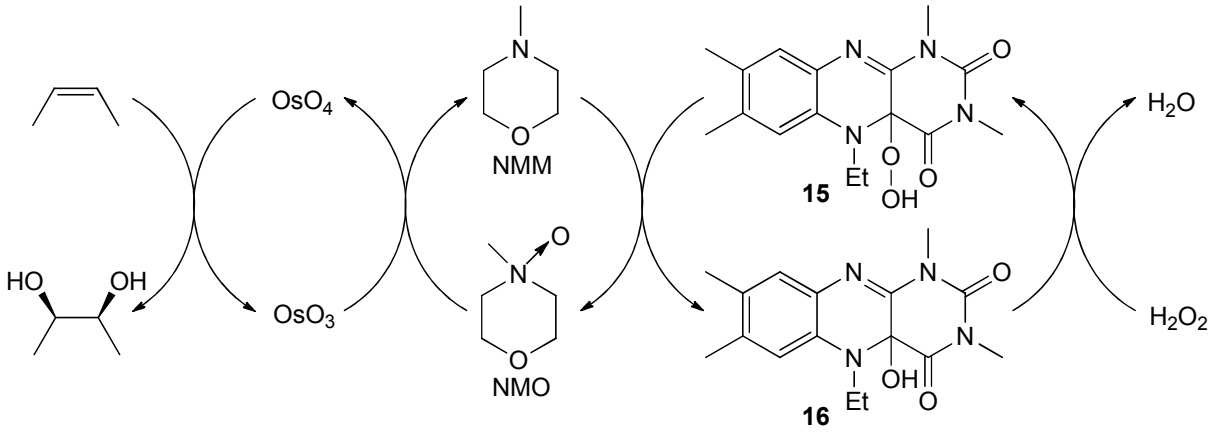
Bäckvall et al. reported the synthesis and use of neutral N1, N3, N5 alkylated dihydroflavin **14** to organocatalysis. Here **14** can be used in aerobic oxidations as precursor for catalytically active flavin peroxide **15** to oxidize tertiary amines to N-oxides[10] and sulfides to sulfoxides[11] with H_2O_2 as terminal oxidant. The catalytic cycle that was proposed is in analogy to the one proposed by Murahashi.[4, 7]



Scheme 5: Formation of catalytically active flavin peroxide **15** from trialkylated neutral flavin **14**

A recyclable neutral trialkylated flavin immobilized in ionic liquid [bmim]PF_6 for the sulfoxidation by hydrogen peroxide has been developed as well.[11a] The catalyst could be recycled up to seven times without loss of activity or selectivity.

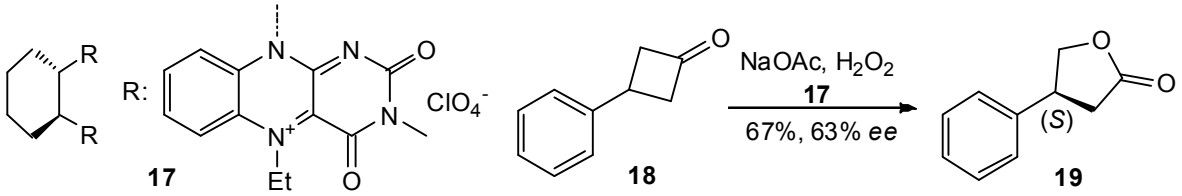
Bäckvall et al. applied the flavin catalyzed nitrogen oxidation on an osmium catalyzed dihydroxylation of olefins.[12] Hereby the reoxidation of NMM to NMO, that reoxidizes itself OsO_3 to OsO_4 as dihydroxylation agent, is realized by flavin peroxide **15**. In the overall dihydroxylation reaction, electrons are transported from the substrate to the terminal oxidant H_2O_2 (scheme 6).



Scheme 6: Catalytic system for osmium catalyzed dihydroxylation of alkenes

Here once again the immobilization of flavin **14**, osmium catalyst and NMM could be realized in an ionic liquid system. The immobilized catalytic system could be reused at least five times without loss of activity.[12b]

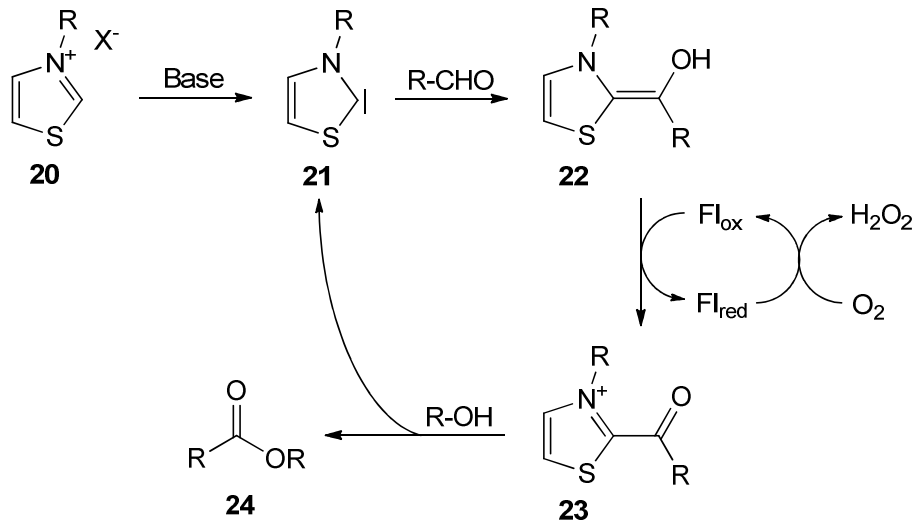
An asymmetric Baeyer-Villiger oxidation reaction with H_2O_2 catalyzed by bisflavin **17** was reported in 2002.[13] The peroxide form of planar-chiral bisflavin **17** derived from **17** and H_2O_2 served as oxidizing agent for the Baeyer-Villiger oxidation. The proposed hydrophobic *π*-*π* stacking between the phenyl ring of flavin and that of the substrate induced the asymmetric induction on the oxidation of the aromatic cyclobutanone **18** to lactone **19** (Scheme 7).



Scheme 7: Asymmetric Baeyer-Villiger Oxidation catalyzed by bisflavin **17**

An asymmetric variant of the flavin catalyzed Baeyer-Villiger oxidation could be achieved as well. Here the chemoselectivity of the lactonization of cyclobutanones over double bond epoxidation and oxidation of sulfides was in the focus of the research.[14]

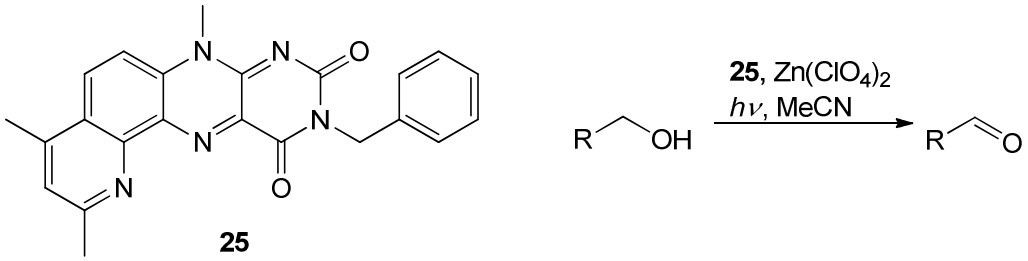
An interesting application of flavin catalysis was explored by Yano et al. and Shinkai et al.: they independently used coupled flavin-thiazolium ion catalysis in micellar systems for the oxidation of aldehydes to their corresponding esters.[15] A reaction mechanism was proposed as follows: deprotonation of thiazolium ion **20** yields carbene **21** that activates an aldehyde to form intermediate enol **22**. Enol **22** can be oxidized by flavin to imine **23** which is hydrolyzed by the solvent alcohol to liberate ester **24** and carbene **21**. The so formed reduced flavin is reoxidized by oxygen present in the solution and can enter the catalytic cycle again.



Scheme 8: Flavin and thiazolium ion catalyzed oxidation of aldehydes to esters

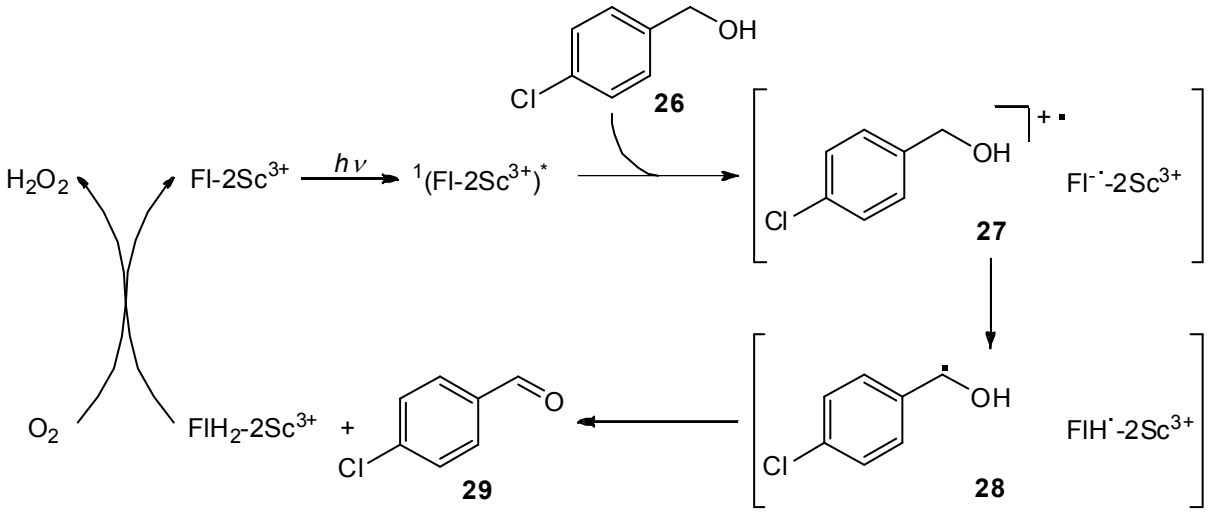
As another example of thermal flavin organocatalysis the hydroxylation of arenes is presented. Phenylalanine could be hydroxylated non regiospecific by using flavinium salt **8** as catalyst and H_2O_2 or O_2 as oxygen source under acidic conditions.[16] Since the proposed mechanism of the reaction is only very speculative it will not be presented here.

Shinkai et al. realized that the oxidation power of flavins increases upon Zr^{4+} ion coordination to the flavin scaffold. This effect was attributed to the electron withdrawing properties of Zr^{4+} ion coordinated to flavin.[17] In a subsequent paper Shinkai et al. exploited the increased oxidation power of oxidized flavins upon excitation by light.[18] As in the case of thermal flavin mediated oxidation, flavin **25** exhibited increased oxidation power in the presence of metal salts. Under aerobic conditions, photo irradiation and the presence of Zn(II) salt flavin **25** was able to oxidize not only benzyl alcohol, but also aliphatic alcohols (Scheme 9). [19]



Scheme 9: Photo oxidation of alcohols with flavin metal complex **25**-Zn^{2+}

Fukuzumi et al. utilized rare earth metal complexes of flavins to study the aerobic photo oxidation of benzyl alcohols in oxygen saturated MeCN in detail.[20] The flavin metal complex is excited to its singlet excited state by light. Electron transfer (ET) from the singlet excited state of flavin metal complex to benzyl alcohol **26** was proposed. In the radical ion pair **27**, besides competing non productive back ET, proton transfer from benzyl radical cation to flavin radical anion takes place. The so formed radical pair **28** collapses via a fast hydrogen transfer to form benzaldehyde **29** and fully reduced flavin that is reoxidized by oxygen present in solution (Scheme 10).



Scheme 10: Proposed reaction mechanism of photo oxidation of p-chloro benzyl alcohol by Fl-2Sc^{3+}

The statement that excited flavin metal complexes react via an ET to benzyl alcohols from their singlet excited state was rationalized as follows: upon complexation of metals to flavin the lowest excited state of the flavin changes from n,π^* triplet state to π,π^* singlet state.[20b] This is in contradiction to the generally accepted fact that photo excitation of flavins (without metal present) leads to their triplet state by intersystem crossing from the singlet state. Quenching of photo excited flavins by electron donors then proceeds from their triplet state.[21]

Since ET is strongly dependent on the distance of donor and acceptor[22] it was proposed that flavin mediated photo oxidation reactions can be improved by tethering a substrate binding site to the redox active flavin. D´Souza et al. realized a binding cavity for substrate benzyl alcohols by tethering β-cyclodextrin to the C7 position of lumiflavin. The authors claimed that the cyclodextrin binding site is responsible for the acceleration factor of 6.5 x 10^2 over riboflavin **1** in the 4-tert-Bu-benzyl alcohol photo oxidation under acidic conditions.[23]

In our working group the flavin mediated photo oxidation of 4-methoxy benzyl alcohol has been studied extensively. Zn(II)-cyclen was used as binding site for alcohols. Flavin **30** has been prepared and tested in photo oxidation reactions. It was shown

that flavin **30** is superior to parent flavins **31** and **32** lacking a binding site in the photo oxidation of 4-methoxy benzyl alcohol in MeCN.[24]

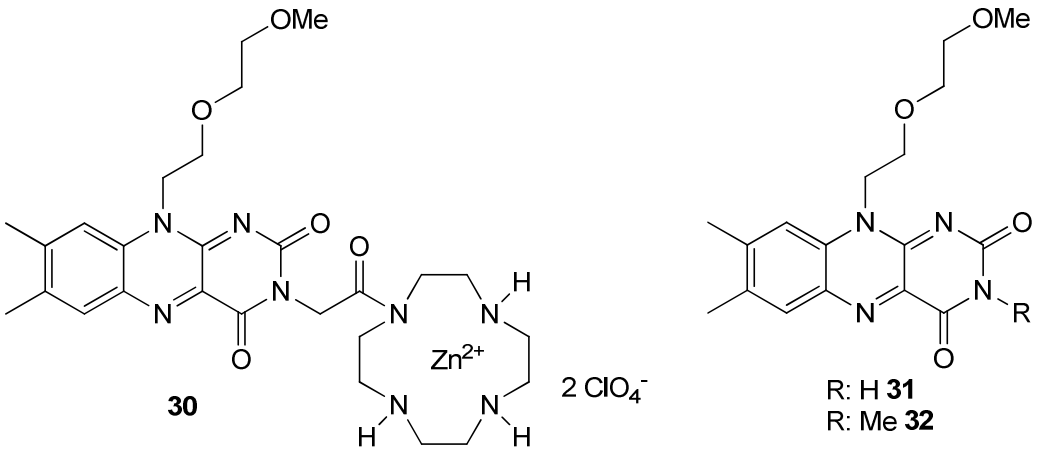
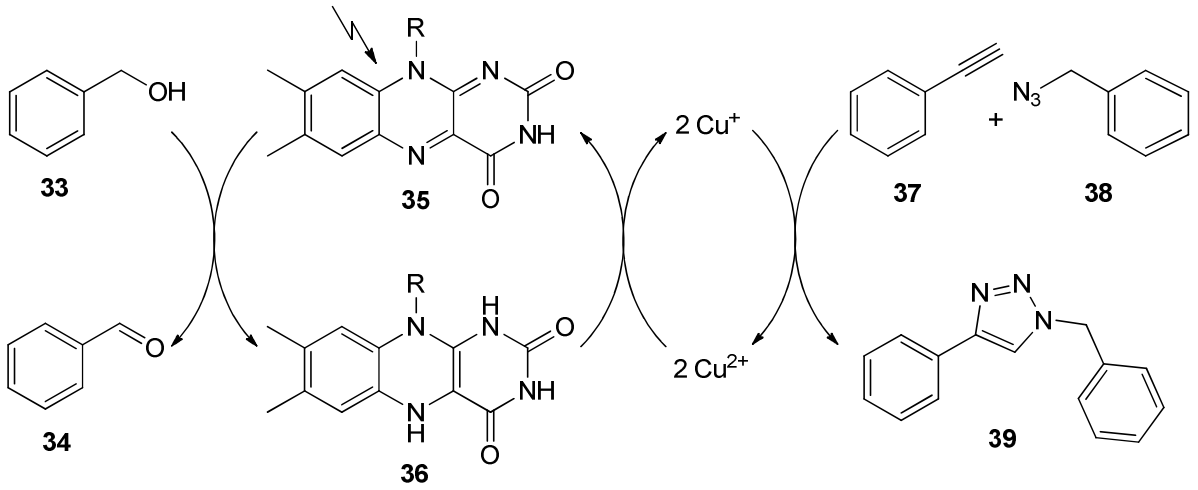


Figure 2: Flavin **30** with tethered Zn(II)-cyclen as binding site and parent flavins **31** and **32**

Further studies revealed that the rate of riboflavin tetraacetate **35** (RFT)[25] mediated aerobic photo oxidation in MeCN can be enhanced by a 30-fold by adding catalytic amounts of thiourea.[26] In these studies blue-light-emitting diodes (LEDs) were used as efficient and selective light source for the first time.
The photo oxidation of benzyl alcohols was even more accelerated when the reaction medium was changed from MeCN to water. With this finding the substrate scope could be extended to electron poor benzyl alcohols. Additionally the immobilization of RFT **35** as photo catalyst on fluorinated silica gel was achieved. [27]

In another application the reductive half cycle of flavin catalysis was used to drive a reaction. Hereby benzyl alcohol **33** was employed as electron source to form reduced RFT **36**. This in turn was able to reduce Cu(II) to Cu(I) that acted as catalyst in a Huisgen cycloaddition of benzyl azide **37** and phenyl acetylene **38** under anaerobic conditions (Scheme 11).[28] Usually these cycloaddition reactions are done in aqueous solution, but Cu(I) as active catalyst is not stable in aqueous solutions and disproportionates. Due to the permanent re-reduction of Cu(II) to Cu(I) by flavin photo catalysis the cycloaddition reaction can proceed further.



Scheme 11: Photo reduction of Cu(II) to Cu(I) to catalyze a Huisgen cycloaddition (R = $C_{13}H_{19}O_8$)

As another example of RFT **35** mediated photo reduction, the photo reduction of 4-nitrophenyl phosphate has been investigated.[29] As electron donor NEt_3 was used under anaerobic conditions. The catalytic cycle can be explained in accordance as it is shown in scheme 11. In this case reduced RFT **36** is reducing 4-nitrophenyl phosphate to its corresponding aniline.

The outstanding redox properties of flavins have been applied to a variety of redox reactions. The application of flavins as organocatalysts in thermally driven reactions has been achieved for the oxidation of amines, sulphides, alcohols and cyclobutanones. Thereby the oxidation properties of flavins have been exploited in the reduction of alkenes as well. The use of flavins as photo catalysts in redox reactions enables the synthetic chemist to do reactions which are thermodynamically not possible in the ground state. The applicability of flavin mediated photo reactions to organic synthesis is still limited, but with a deeper understanding of reaction mechanisms the application to more sophisticated organic synthesis will be realized. The use of light as energy source, as it is present in abundance by the sun, is desirable in terms of environmentally benign organic synthesis.

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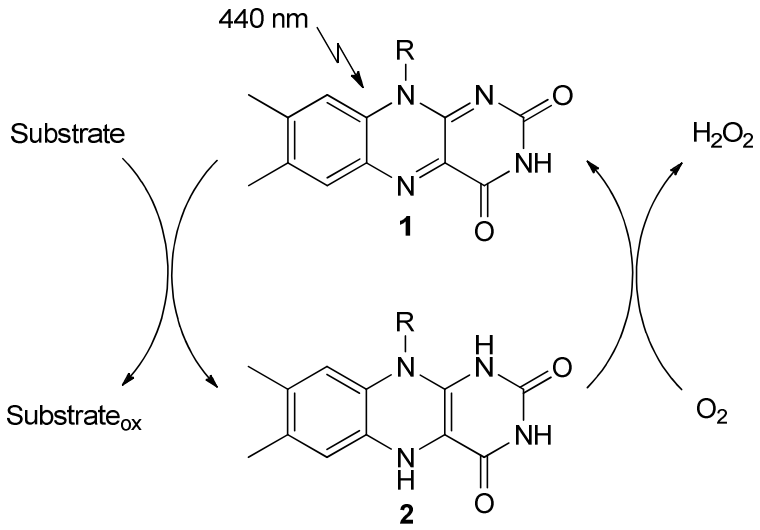
Chapter 2: Mechanistic Studies on the Flavin mediated Photo Oxidation of 4-Methoxybenzyl Alcohol*

Development of an Opto-Electronic Actinometer

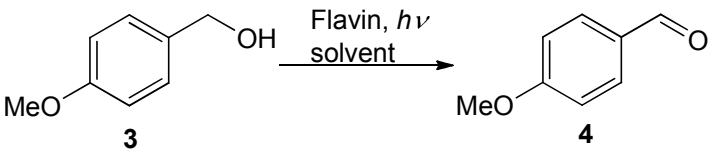
In flavin mediated photooxidations[1] the increased oxidation power of the isoalloxazine chromophore in its oxidized form **1** upon excitation by light[2] is exploited. Subsequent two electron reduction and protonation gives dihydroflavin **2**, which is reoxidized to **1** by molecular air oxygen as the terminal oxidant yielding hydrogen peroxide as sole stoichiometric by-product (Scheme 1).[1]



Scheme 1: Catalytic cycle of aerobic flavin mediated photo oxidation of benzyl alcohols or benzyl amines (riboflavin: R = $C_5H_{11}O_4$ riboflavin tetraacetate (RFT): R = $C_{13}H_{19}O_8$)

* The investigations presented in this chapter were performed in collaboration with Uwe Megerle, Matthias Wenninger and Prof. Dr. Eberhard Riedle at the Ludwig-Maximilian-Universität (LMU) in Munich and Roger J. Kutta and Prof. Dr. Bernhard Dick at the University of Regensburg. U.M., M.W. and Prof. Dr. E.R. developed the LED based actinometer. U.M. and R.J.K. performed all spectroscopic measurements. R.L. carried out all experiments on the LED based actinometer. The experiments to verify the electron transfer mechanism of the photo oxidation have been already published. Schmaderer, H.; Hilgers, P.; Lechner, R.; König, B. *Adv. Synth. Catal.* **2009**, *351*, 163-174.

The flavin mediated photo oxidation of 4-methoxybenzyl alcohol **3** to 4-methoxy benzaldehyde **4** (Scheme 2) has been studied recently in our working group. The oxidation reaction has been optimized with regard to yield and reaction rate.[1a, b, d]



3 **4**

Scheme 2: Flavin mediated photo oxidation of 4-methoxybenzyl alcohol **3** to 4-methoxy benzaldehyde **4**

The optimization of the yield of light used for the photo reaction has previously not been in the focus of the study. The quantum yield (QY) is defined as the number of events occurring per photon absorbed by the system. Strictly this definition applies only for monochromatic excitation. Quantum yields can be used for photo physical processes (e.g. intersystem crossing, fluorescence, phosphorescence) or photochemical reactions.[3] In the case of photo catalysis the quantum yield would be the fraction of light utilized for the conversion of a certain amount of starting material or production of a certain amount of product. Future developments of photo catalytic reactions require the simultaneous optimization of chemical yield and quantum yield to reach the desired overall efficiency for real life applications. Standard actinometric procedures are laborious and often not transferable to visible light irradiation.[4]

For that reason an easy, reproducible actinometer applicable to the whole range of visible light is desirable. Since photo catalytic chromophores absorb only selected parts of the visible spectrum, selective light sources like modern high power light emitting diodes (LEDs) are superior to often used mercury lamps, halogen lamps or energy-saving light bulbs. They can provide high photon fluxes at a variety of well defined wavelength bands which allows the choice of the optimized light source for a given visible light photoreaction. In addition it is easier to image the light of a LED into the sample cell in a defined way.

Megerle and Riedle developed an opto-electronic device for the rapid and facile determination of quantum yields for visible light photoreactions under the conditions

of a chemical synthesis laboratory. A scheme of the actinometer setup is shown in figure 1 together with a photograph of the assembled device. The light from the LED is imaged into the sample cell with a fast photographic lens of f = 50 mm. The large aperture of f / 1.4 together with the high imaging quality of the photographic lens ensures an efficient utilization of the available photons and a high degree of control and reproducibility of the illumination. The light not properly imaged by the lens is blocked by a cylindrical radiation protection between the LED and the lens and a rectangular aperture in front of the cuvette.

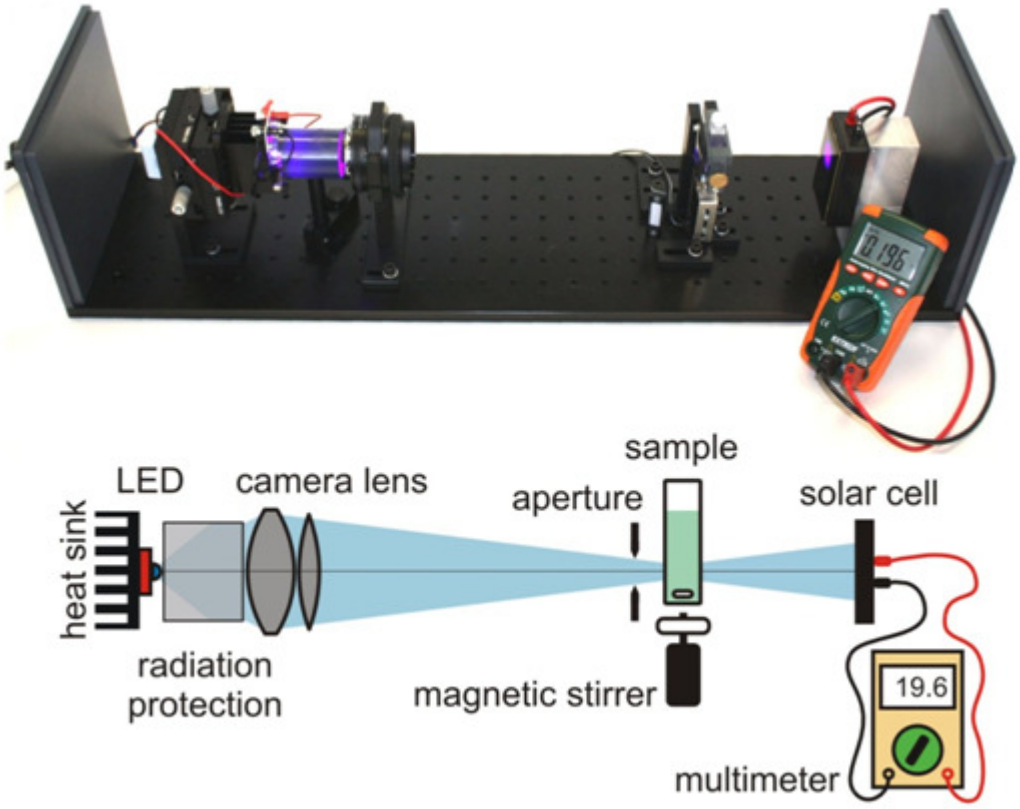


Figure 1: Top: Photograph of the compact and portable actinometer setup; Bottom: Schematic of the actinometer setup with a high-power light emitting diode as light source and a multimeter connected to a solar cell as light detector

The defined, near perpendicular incidence of the radiation on the sample allows for an accurate determination of the number of absorbed photons by measuring the radiant power in the transmitted beam with and without sample. The transmitted power is detected by a commercially available solar cell detector and monitored by a multimeter. The response was found to be linear in the range of 0.2 and 20 mW,

which is in the standard range of the setup, when LEDs with 3 W electrical power are used.

The quantum yield ϕ of the overall photoreaction can be calculated from the number of absorbed photons $N_{ph,abs}$ and the amount of product formed N_{prod}:

$$\Phi = \frac{N_{prod}}{N_{ph,abs}} = N_A \cdot h \cdot c \cdot \frac{c_{prod} \cdot V}{P_{abs} \cdot \Delta t \cdot \lambda_{LED}}. \quad (1)$$

Here, N_A is the Avogadro constant, h is Planck's constant, c is the speed of light, c_{prod} is the product concentration, V is the sample volume, P_{abs} is the absorbed radiant power, Δt is the illumination time and λ_{LED} is the central wavelength of the LED.

The apparatus was tested by determining the quantum yield of ferrous production in the classical potassium ferrioxalate actinometry under[5] irradiation with 443 nm light at room temperature. The amount of ferrous produced was measured via spectrophotometric determination of its 1,10-phenanthroline complex at 510 nm. The obtained value of $\phi_{Fe(II)}$ = 0.99 is in perfect agreement with the reported quantum yields.[3b]

As an example from ongoing research the photo catalytic enantioselective alkylation reaction of aldehydes recently reported by MacMillan et al.[6] was measured. They used ruthenium-tris-bipyridine as the redox active photocatalyst and a 15 W energy-saving light bulb for irradiation. So far, no quantum efficiency of the reaction has been reported. With the actinometer setup and an irradiation time of 60 minutes with a 443 nm LED, we could determine the quantum yield of this reaction to 49%.

Studies on the Mechanism of Flavin-mediated Photo Oxidation

The same LED was also used to drive the aerobic photo oxidation of 4-methoxybenzyl alcohol **3** in the presence of RFT acting as photo catalyst. To understand the RFT mediated photo oxidation mechanism better, the quantum yield was determined under different reaction conditions. Thereby the dependencies of the quantum yield on optimum solvent mixture and concentration of 4-methoxybenzyl

alcohol **3** becomes evident. A strong dependence of the reaction quantum yield on the substrate concentration and the solvent was found.

In pure MeCN (20 mM 4-methoxybenzyl alcohol, 2 mM RFT) a quantum yield of 0.004% was measured. Upon addition of water the quantum yield increased drastically by three orders of magnitude to 2.4% (20 mM 4-methoxybenzyl alcohol, 2 mM RFT in MeCN/H_2O = 1/1). This observation is in good agreement to reported earlier experiments in which the reaction rate significantly dependent on the solvent.[1a, b, d]

The quantum yield dependency was then measured over a range of 20 to 80% (v/v) for water in MeCN. As shown in Figure 2 the quantum yield goes through an optimum of 3.0% at a water content of 40%. The critical role of water as a cosolvent is a first hint for an ET mechanism.[7]

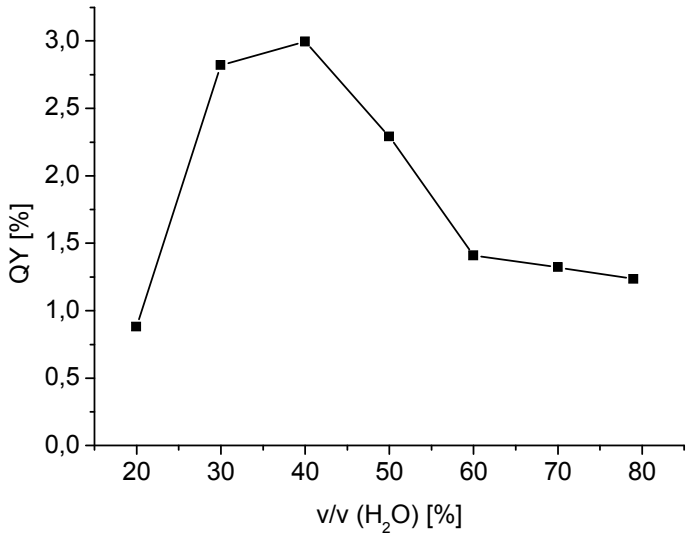


Figure 2: QY of 4-methoxy benzaldehyde **4** production against the water to MeCN ratio as solvent

The 4-methoxybenzyl alcohol **3** concentration was also found to affect the quantum yield of the photo oxidation reaction. Figure 3 shows the dependency of the alcohol **3** oxidation quantum yield from the alcohol **3** concentration. It was shown that the quantum yield has an optimum at a 20 mM concentration (RFT 2 mM, MeCN/H_2O = 1/1). At low alcohol concentrations, the quantum yield is limited by diffusion. At higher concentrations the quantum yield decreases again. Here it is proposed that at higher alcohol concentrations the singlet excited state of RFT is quenched non productively.

This process competes with the intersystem crossing (ISC) to the flavin triplet state. The triplet quantum yield decreases. As the relevant ET is suggested to occur from 4-methoxybenzyl alcohol to ^{3}RFT the alcohol oxidation quantum yield decreases as well.

This finding was further confirmed by transient absorption spectroscopy on picoseconds to microseconds time scale.†

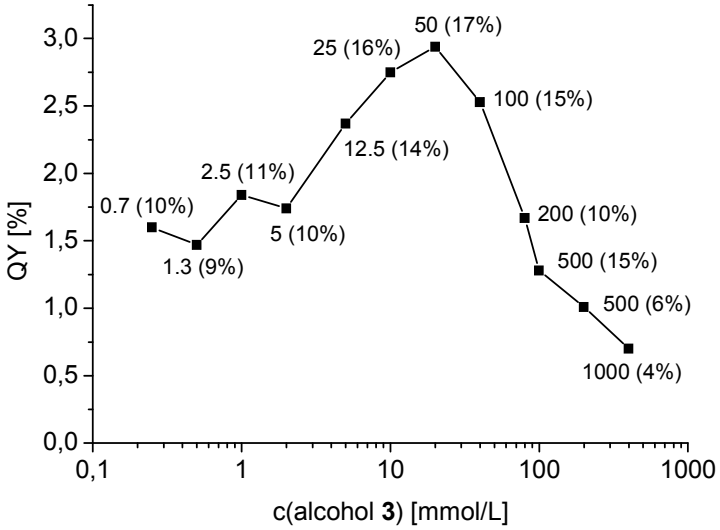
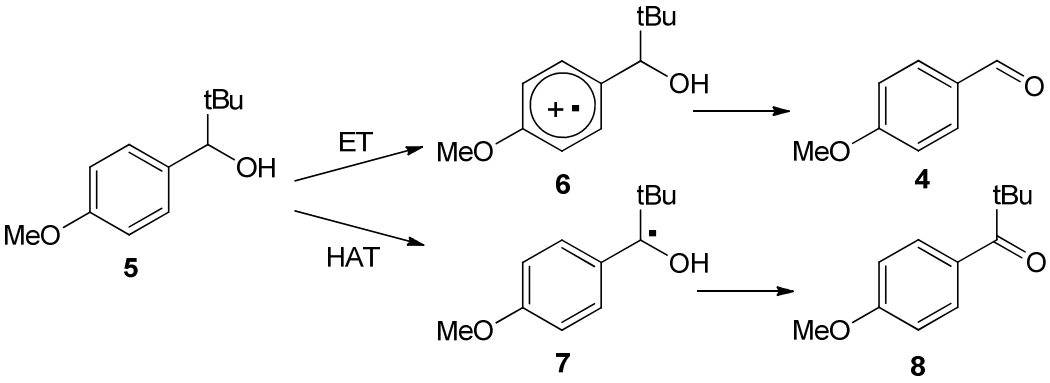


Figure 3: QY of 4-methoxy benzaldehyde **4** production against substrate concentration in MeCN/H_2O using a RFT concentration of 2 mM. The labels indicate the illumination time in minutes with the 443-nm LED and – in parenthesis – the chemical yield of 4-methoxy benzaldehyde **4**

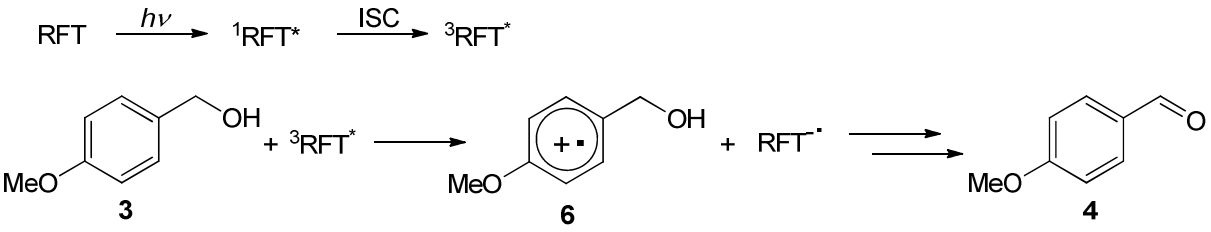
Additional evidence for an initial ET step was provided using 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol[8] **5** as probe in the RFT mediated photo oxidation (Scheme 11). Oxidation of compound **5** allows discriminating between an ET or hydrogen abstraction mechanism (HAT). At the experimental conditions used,[9] the result indicates a mechanism which exclusively proceeds via the ET pathway.[10] Compound **4** was the only product obtained from the oxidation reaction.

† Spectroscopic analysis was performed by Uwe Megerle, Matthias Wenninger and Eberhard Riedle at the Ludwig-Maximilian-Universität in Munich and Roger J. Kutta and Bernhard Dick at the University of Regensburg. Manuscript for publication is in preparation.



Scheme 3: Possible oxidation pathways of probe **5**: ET route to yield 4-methoxy benzaldehyde **4** or HAT route to yield ketone **8**

The results presented in this chapter are in agreement with a postulated primary ET from alcohol **3** to the triplet state of RFT in flavin mediated photo oxidation of benzyl alcohols. In contradiction to the postulated ET of benzyl alcohols to singlet state flavin-metal complexes by Fukuzumi et al.[11] we found that ET from alcohol **1** is only productive to the triplet state of RFT (Scheme 14).



Scheme 4: Initial ET from alcohol **3** to RFT triplet state to form radical ion pair

Conclusion

An easy to handle opto-actinometer was developed and used for studying the RFT mediated photo oxidation of 4-methoxybenzyl alcohol **3** to 4-methoxy benzaldehyde **4**. We have shown that the initial step in the RFT mediated photo oxidation of 4-methoxy benzaldehyde **4** is an electron transfer. Further we have proven that electron transfer occurs from alcohol **3** to the triplet state of RFT. The ET to singlet

excited state is not productive. These findings may have a significant impact on the design of flavin catalysts: it was proposed that tethering of a substrate binding site to the flavin core enhances the photo induced electron transfer and might induce stereoselectivity to photo reactions. But when the substrate is in close vicinity to the excited flavin, no intersystem crossing of the flavin singlet state to the triplet state can occur. The flavin singlet excited state is quenched via electron transfer from the substrate. This may promote non-productive back electron transfer. Therefore precise preliminary considerations have to be made before a flavin with a binding site for a certain substrate is designed.

Experimental

All chemicals were purchased from commercial suppliers and used as received. NMR spectra were recorded on a Bruker spectrometer 300 MHz (^{1}H-NMR) or 75 MHz (^{13}C-NMR) with TMS as the external standard. Luxeon high power royal blue LEDs, 3 W, irradiation maximum 443 nm were used as light sources.
Monitoring of the reaction and product analysis was performed by gas chromatographic analysis (GC 5890 Series II from Hewlett-Packard, capillary column J+W Scientific—DB-5MS/30 m x 0.25 mm/0.25 mm film). The structures of the products were confirmed by comparison with standard samples.

General procedure for QY determination:

Reaction mixtures of 4-methoxybenzyl alcohol and RFT (4.0 µmol) in 2 mL of MeCN/H_2O in a cuvette (d = 10 mm) were irradiated in the LED based actinometer. Samples were withdrawn from the cuvette and the proper amount of toluene as external standard was added. The yield of the reactions was monitored by GC measurements.

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[9] Reaction conditions: $4 \cdot 10^{-3}$ mmol **5**, 10 mol% RFT, D_2O 1mL (2% DMSO-d_6), 10 min irradiation at 443 nm. Aldehyde **4** was formed quantitatively as determined by ^{1}H NMR.

[10] Schmaderer, H.; Hilgers, P.; Lechner, R.; König, B. *Adv. Synth. Catal.* **2009**, *351*, 163-174.

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Chapter 3: Oxidation and Deprotection of Primary Benzyl Amines by Visible Light Flavin Photo Catalysis‡

Introduction

Several methods for the oxidation of amines into their corresponding aldehydes have been reported in the literature. However, the reaction conditions are rather harsh, require the stoichiometric use of metallic reagents or suffer from overoxidation or lack of selectivity towards other functional groups.[1] The use of air oxygen as stoichiometric oxidant is particular desirable from an environmental and economical point of view. Some aerobic catalytic procedures for amine oxidation are available,[2] but examples of visible light photocatalysis accelerating or mediating the process are rare.[3]

The oxidation of amines by flavin in its ground or excited state has been studied extensively to elucidate the mechanism of monoamine oxygenase enzymes and their inhibition.[4] Thermal aerobic oxidation of amines to N-oxides using flavin catalysts has been accomplished,[5] but to the best of our knowledge no application to organic synthesis of flavin-mediated photooxidation of amines to aldehydes has been described so far.

We report the scope and limitations of flavin-mediated aerobic photooxidation of benzyl amines into aldehydes. The reaction is applied to cleave benzyl protecting groups selectively by blue light irradiation. Riboflavin tetraacetate (RFT)[6] is used as readily available and non-toxic photocatalyst; blue light emitting high power LEDs serve as selective and efficient light source.

‡ The investigations presented in this chapter have been already published: Lechner, R.; König, B. *Synthesis* **2010**, *10*, 1712-1720.

Photooxidation of Benzyl Amines

4-Methoxybenzyl amine **3a** was chosen as substrate to optimize the reaction conditions for the RFT mediated photooxidation to **4a**. The course of the reactions was monitored by ^{1}H-NMR. Upon irradiation of a solution of benzyl amine **3a** (c = $4 \cdot 10^{-3}$ mol/L) in 1 mL of D_2O (containing 4% of DMSO-d_6 and 10 mol% of RFT) with blue light (440 nm, 3 W LED) a decrease in intensity of the benzyl amine resonance signals and the appearance of the aldehyde **4a** resonance signals was observed (Figure 1 left). Only traces (< 5%) of a side product, presumable the imine **5**, could be detected.

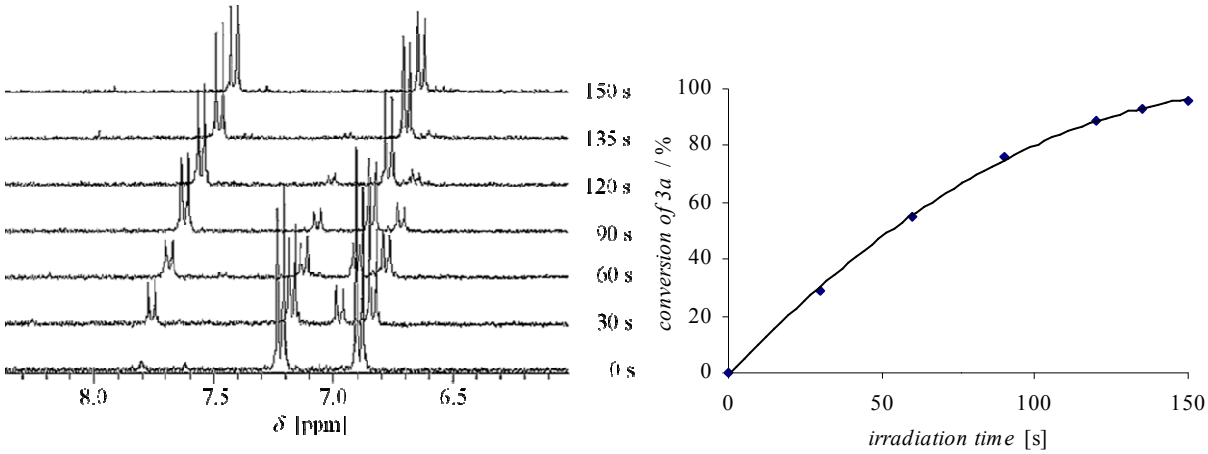


Figure 1: Photooxidation of **3a** ($4 \cdot 10^{-3}$ mmol) to **4a** with RFT (10 mol%) in D_2O (1 mL, 4% DMSO-d_6); left: Stack plot of ^{1}H-NMR spectra of the aromatic region (perspective view of spectra is used; no chemically induced shift of resonance signals is observed); right: reaction kinetic as monitored by NMR

Without irradiation only 6% of aldehyde **4a** was formed, whereas no reaction occurred when the solution was irradiated in the absence of RFT. No catalytic turnover was observed when the reaction was conducted in the absence of air oxygen. These findings confirm the proposed photocatalytic reaction mechanism. The quantum yield of the photocatalytic oxidation of **3a** was determined to be 0.023 [c = 0.01 mol/L in 1 mL of H_2O and 1 mL of MeCN, 10 mol% of RFT, blue light (440 nm) irradiation]. At low catalyst concentrations (0.1 mol%) and prolongation of the reaction time to 60 min a minimal turnover number (TON) of 910 was determined. Imine **5** was formed exclusively, when the reaction was performed in dry acetonitrile.

To demonstrate the use of the photocatalytic oxidation on preparative scale, 1 mmol of **3a** was converted using 1 mol% of RFT. Aldehyde **4a** was isolated in 77% yield.

The optimized reaction conditions were then applied to the photo catalytic conversion of a variety of benzyl amines. All results are summarized in Table 1.

The conversion rate of primary benzyl amines dependents on the electronic character of the arene: Benzene rings bearing electron donating substituents lead to fast and complete conversion, while electron poor arenes decelerate the photooxidation. This is in accordance with previous observations on flavin-mediated photooxidation of benzyl alcohols.[1]

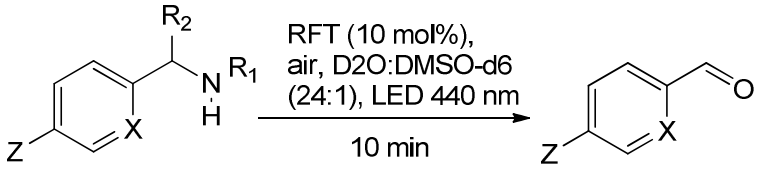
Secondary amine **3e** was photooxidized giving aldehyde **4a**. Branched benzyl amine **3f** was oxidized to the corresponding ketone, but benzyl amine **3g**, having a *t*-butyl group on the benzyl position, was converted into aldehyde **4a** under elimination of the substituent. This observation allows, in analogy to the photooxidation of 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol,[7] to discriminate between an electron transfer and a hydrogen abstraction mechanism for the photooxidation of benzyl amines. Under the applied reaction conditions we exclusively observe the electron transfer pathway. Phenyl glycine methyl ester **3h** was not converted under the reaction conditions.

Compounds **3i** and **3k** were investigated for photooxidation as examples of aliphatic, not benzylic amines. Butyl amine **3i** was not oxidized to butyraldehyde **4i** and rapid bleaching of RFT was observed after 4 min of irradiation. Butyl amine was consumed when the irradiation time was prolonged to 60 min and the catalyst loading enhanced (100 mol% RFT), but no aldehyde formation could be detected by ^{1}H-NMR.

Aliphatic amine **3k** bearing an electron rich aromatic system was photooxidized under the standard conditions giving aldehyde **4a** and a small amount of an unidentified side product. The RFT photocatalyst bleached rapidly converting this substrate and addition of more RFT (two times 10 mol%) was necessary to complete the reaction.

As an example of a cyclic secondary benzyl amine tetrahydro isoquinoline **6** was submitted to the standard photooxidation conditions. Compound **6** was oxidized to the corresponding isoquinoline **7** in nearly quantitative yield. Oxidative ring opening was not observed.

Table 1: Photo catalytic oxidation of benzyl amines



3 **4**

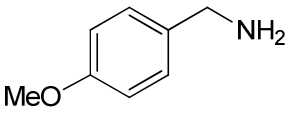
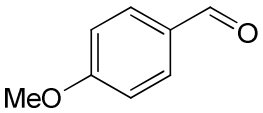
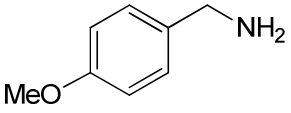
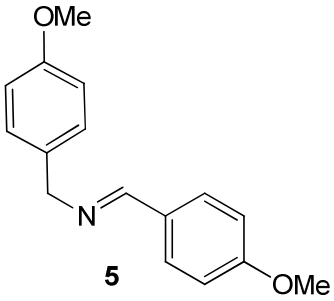
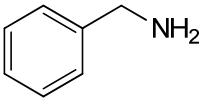
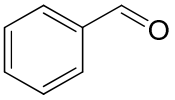
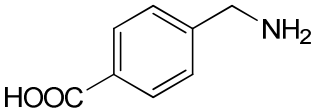
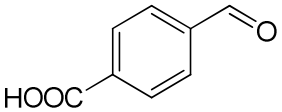
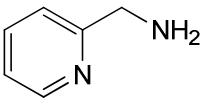
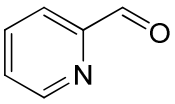
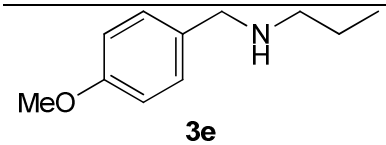
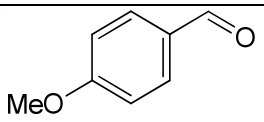
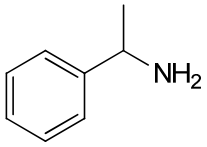
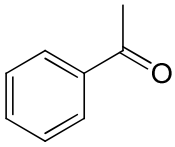
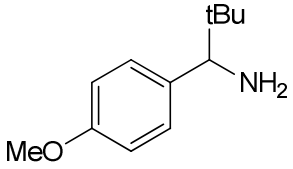
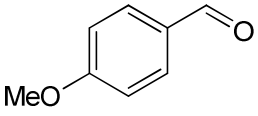
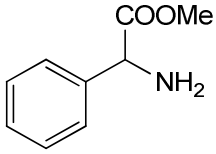
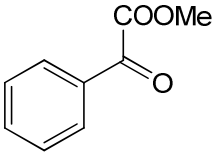
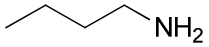
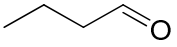
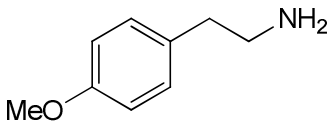
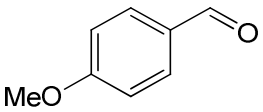
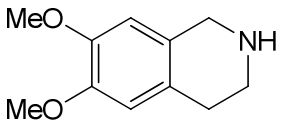
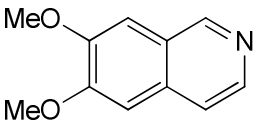
Amine	Product	Conversion[a]
 **3a**	 **4a**	96% 6%[b] 0%[c] 31%[d] 91%[e] 77%[f] 95%[g]
 **3a**	 **5**	
 **3b**	 **4b**	79%
 **3c**	 **4c**	16%
 **3d**	 **4d**	50%

Table 1: Continued

 **3e**	 **4e**	90%
 **3f**	 **4f**	44%
 **3g**	 **4a**	95%
 **3h**	 **4h**	0%
 **3i**	 **4i**	0%[h]
 **3k**	 **4a**	89%[i]
 **6**	 **7**	97%[k]

Reaction conditions: Amine $4 \cdot 10^{-3}$ mmol in 1 mL D_2O (4% DMSO-d_6); 10 mol% RFT; Irradiation for 10 min at 440 nm (LED). (a) Determined by ^{1}H-NMR. (b) Without irradiation. (c) Without catalyst. (d) RFT 0.1 mol%, reaction time 60 min. (e) RFT 30 mol%, 20% DMSO-d_6, deoxygenized solution. (f) Isolated yield, amine 1 mmol, RFT 1 mol%, reaction time 2h. (g) Amine 0.1 mmol, in 1 mL dry MeCN. (h) Reaction time 4 min. (i) RFT 30 mol%, reaction time 15 min. (k) 24% DMSO-d_6.

Photo catalytic cleavage of Benzyl Protecting Groups

Benzyl protecting groups are widely used in organic synthesis for the protection of amines, carboxylic acids, and alcohols. For their cleavage various conditions are used, e.g. reduction, acetylation or oxidation, depending on the electron density on the benzyl protecting group.[8] However, benzyl deprotection in the presence of other easy to oxidize or reduce functional groups can be difficult. One option to circumvent these problems is the use of photo chemical methods for removing benzyl protecting groups.[9]

I investigated the use of the described flavin-mediated photooxidation of benzyl amines to remove benzyl protecting groups under mild conditions to extend the scope of photo cleavage methods.

Several benzyl protected compounds were submitted to flavin-mediated photo deprotection on an analytical scale (c = 0.01 mol/L, 10 mol% of RFT in MeCN:H_2O; 0.5mL:0.5mL; LED irradiation). Each sample was irradiated by two LEDs (440 nm, 3 W) under stirring in capped sample vials for the time given in Table 2.

As expected from the results of benzyl amine oxidations, the non-substituted benzyl protecting group (Bzl) was cleaved slower from primary amines than the 4-methoxy benzyl (Mob) group: The Mob protecting group was cleaved within 15 min giving only amines **10** and **13**, aldehyde **4a** and RFT as indicated by HPLC (entries 1 - 3). Protected prolines **14** and **16** (entry 4 and 5) gave complex product mixtures upon photo catalytic flavin oxidation. In these cases the deprotected secondary amine may act as an electron donor for flavin yielding unwanted amine oxidation side products. The allylic double bond was not affected by flavin mediated photo deprotection of allyl amine **17** (entry 6) which was deprotected without any detectable side products within 15 min. At pH 3 (adjusted by 0.1 N HCl) Mob protected nitroaniline **19** (entry 7) was deprotected in a clean reaction, whereas a complex product mixture was obtained in a H_2O/MeCN mixture. This might be the result of overoxidation of the product of the deprotection reaction, aniline (**20**), as in the case of secondary amines. The Mob protected carboxylic acid **21** (entry 8) was partly deprotected under the applied conditions, whereas no conversion was obtained for the Bzl protected acid **23** (entry 9).

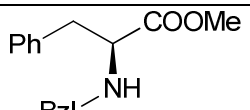
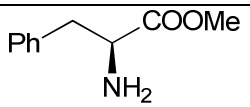
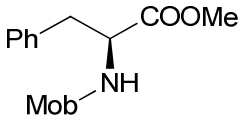
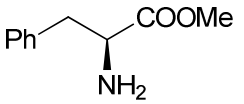
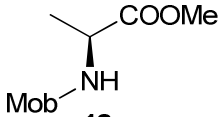
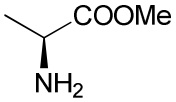
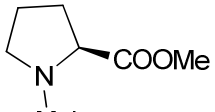
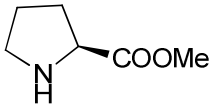
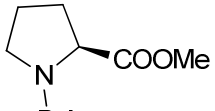
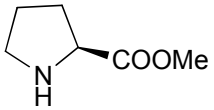
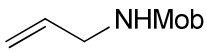
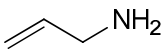
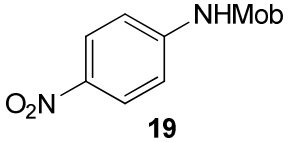
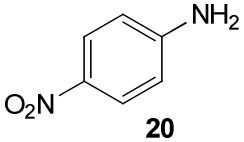
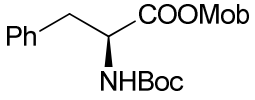
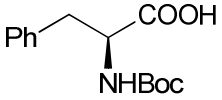
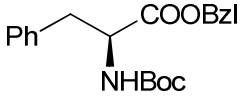
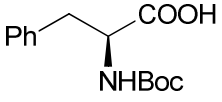
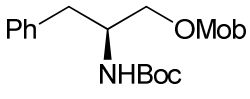
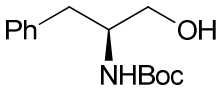
The protected alcohols **25** and **27** behaved similar: Only the Mob group was partly cleaved under photo catalytic oxidation conditions (entry 10) within 15 min, whereas the Bzl protecting group showed no reactivity at all. Mob protected phenol **29** was deprotected (aldehyde **4a** was detected), but phenol **30** was immediately further oxidized to non identified products under the photo oxidative conditions.

The carboxy benzoyl (Cbz) protected amines in compounds **31** and **33** were not affected under the reaction conditions (entry 13 and 14), which should allow the selective deprotection of benzyl protected amines in the presence of a Cbz protected amine.

Sodium dibenzyl phosphonate **35** (entry 16) did not react under the applied reaction conditions. The solvent mixture of water and acetonitrile used for the deprotection reaction is of importance, as no deprotection of compounds in entries 2, 8, 10 was observed using acetonitrile without addition of water. No reactions were observed when solutions of compound **11** and **25** were irradiated in the absence of RFT or when the samples were stirred in the dark in the presence of 10 mol% RFT at pH 3. The presence of RFT and blue light irradiation is therefore essential for the benzyl photo deprotection.

Compounds **11** and **25** were photo deprotected on a 1 mmol scale (entries 2 and 10). For the ease of purification only 1 mol% of RFT was used as photocatalyst and the reactions were done under acidic conditions (pH 3 adjusted by 0.1 N HCl)[9] in 250 mL Erlenmeyer flasks under irradiation with 12 LEDs (3 W each).[10] The hydrochloride salt of phenylalanine methyl ester was isolated in 90% yield after 60 min irradiation of compound **11** by extraction and crystallization. The deprotected alcohol **26** was isolated via column chromatography after 60 min of irradiation in 65% yield. All analytical data including optical rotation of phenylalanine methyl ester hydrochloride and alcohol **26** were consistent with the analytical data of authentic samples.

Table 2: Photo catalytic deprotection of benzyl compounds

Entry	Benzyl protected compound	Product	Conversion[a] Time
1	 **9**	 **10**	81% 60 min
2	 **11**	 **10**	91% 15 min 90%[b]
3	 **12**	 **13**	99% 15 min
4	 **14**	 **15**	Product mixture[c] 15 min
5	 **16**	 **15**	Product mixture[c] 15 min
6	 **17**	 **18**	99% 15 min
7	 **19**	 **20**	98%[d] 30 min
8	 **21**	 **22**	9% 30 min
9	 23	 **24**	0% 30 min
10	 **25**	 **26**	45% 30 min 65%b

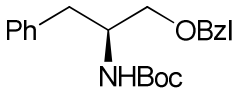
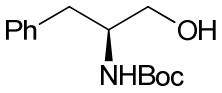
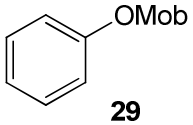
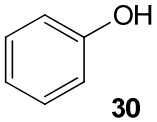
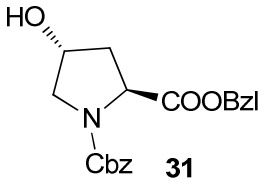
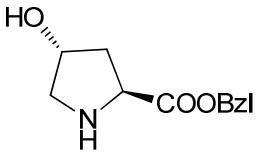
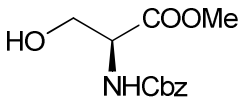
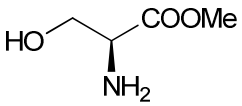
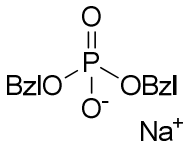
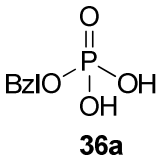
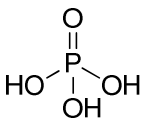
11	 **27**	 **28**	0% 30 min

Table 2: Continued

12	 **29**	 **30**	0%c 30min
13	 **31**	 **32**	0% 60 min
14	 **33**	 **34**	0% 60 min
15	 **35**	 **36a**  **36b**	0% 240 min

Reaction conditions: 0.01 mmol substrate in H_2O:MeCN = 0.5mL:0.5 mL; 10 mol% RFT, irradiation at 440 nm with two LEDs (3 W each) for the time indicated. (a) Calculated from crude HPLC data of reaction mixtures. (b) Isolated Yield, substrate 1.0 mmol, RFT 1 mol%, pH = 3 adjusted by 0.1 N HCl, reaction time 60 min. (c) Starting material was consumed. (d) pH = 3 adjusted by 0.1 N HCl.

Conclusion

Photo catalytic oxidation of benzyl amines to their corresponding aldehydes under mild conditions without overoxidation has been accomplished using RFT as photocatalyst. The use of LEDs emitting in the visible region at 440 nm as light source for RFT excitation avoids undesired non-sensitized photo processes. Oxygen is employed as the terminal oxidant and H_2O_2 and NH_3 appear as sole side products

of the oxidation of primary benzyl amines. The protocol is limited to benzylic amines bearing an electron rich arene group.

Furthermore, I have developed a photo catalytic protocol for Mob group deprotection of primary amines and alcohols. Double bonds, benzyl protected esters and alcohols are tolerated under the applied conditions. Mob esters react much slower and Cbz-protected amines and benzyl phosphate ester are inert under the photodeprotection conditions. The deprotection of protected secondary amines is not applicable presumable due to the oxidation of the electron rich secondary amines by excited RFT.

The procedures are easy to perform and robust on laboratory scale. The photocatalyst and the light sources are readily available and the application limits of the process are well defined, which facilitate their use in organic synthesis.

Experimental

Riboflavin tetraacetate,[6] N-propyl 4-methoxy benzyl amine **3e**,[11] 2-(4-methoxyphenyl)ethanamine **3k**,[12] Bzl-Phe-OMe **9**, Mob-Phe-OMe **11**, Mob-Ala-OMe **12**,[13] Mob-Pro-OMe **14**,[14] Bzl-Pro-OMe **16**,[15] Boc-Phe-OMob **21**,[16] Boc-Phe-OBzl **23**,[17] tert-butyl 1-(benzyloxy)-3-phenylpropan-2-ylcarbamate **27**,[18] Cbz-(OH)-Pro-OBzl **31**,[19] were prepared as previously reported. All other chemicals were purchased from commercial suppliers and used as received. Anhydrous DMF was purchased from Fluka. TLC was done on silica gel 60 F254 aluminium sheet (Merck), with detection under 254 nm or 333 nm UV light. Flash column chromatography was carried out on silica gel 0.035-0.070 mm, 60 Å from Acros. NMR spectra were recorded on a Bruker spectrometer 300 MHz (^{1}H-NMR) or 75 MHz (^{13}C-NMR) with TMS as the external standard. Electron-impact (EI) and chemical ionization (CI) mass spectra were recorded on a Finnigan TSQ 710 spectrometer. Electrospray ionization (ES) mass spectra were recorded on a ThermoQuest Finnigan MAT 9595 spectrometer. IR spectra were recorded on a Biorad Spectrometer Excalibur FTS 3000 spectrometer. Optical rotation was recorded on a Perkin Elmer 241 Polarimeter. Melting points were determined on a Lambda Photometrics OptiMelt MPA 100. Luxeon high power royal blue LEDs, 3 W, irradiation maximum 440 nm (+/- 10 nm)

were used as light sources. PE means petrol ether of a boiling range of 60 to 80 ^{o}C; EA means ethyl acetate.

General procedure for photooxidation of benzyl amines on an analytical scale:

Reaction mixtures of the amine ($4 \cdot 10^{-3}$ mmol) and RFT (10 mol%) in 1 mL of MeCN-d_3 containing 4% DMSO-d_6 were irradiated by one LED (3 W; 440 nm) in capped sample vials. The course of the reaction was monitored by ^{1}H-NMR.

Benzyl amine photooxidation on 1 mmol scale:

4-Methoxy benzyl amine (**3a**, 1.0 mmol) and RFT (0.01 mmol) were dissolved in MeCN/H_2O (4 mL/96 mL). The mixture was irradiated at 440nm over 12 LEDs (3 W each) in a 250 mL Erlenmeyer flask open to air for 2h. The pH was adjusted to 1 by addition of 1 N HCl and the product was extracted by Et_2O. The organic layer was dried over $MgSO_4$, concentrated and the residue was taken up in PE and filtered. Concentration of the filtrate gave aldehyde **4a** as colourless oil (105 mg, 0.77 mmol 77%).

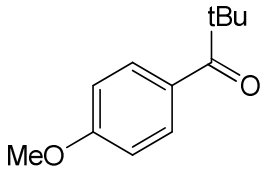
General procedure for benzyl amine photo deprotection reaction on an analytical scale:

The reaction mixture of the benzyl protected compound (0.01 mmol) and RFT (10 mol%) in 0.5 mL of MeCN and 0.5 mL of H_2O) was irradiated at 440 nm over two LEDs (3 W each) in a capped sample vial under air. When anaerobic or dry conditions were used for comparison, the reaction mixtures were irradiated under inert atmosphere in sample vials capped with septa or vials mounted with $CaCl_2$ filled syringes. Degassing of solutions was achieved by three freeze-pump-thaw cycles.

General procedure for photo deprotection reaction on 1 mmol scale:

The reaction mixture containing the benzyl protected amine (1.0 mmol) and RFT (1 mol%) in 50 mL of MeCN and 50 mL of H_2O at pH = 3, adjusted by 0.1 N HCl, was irradiated at 440 nm over 12 LEDs (3 W each) in a 250 mL Erlenmeyer flask open to air. The conversion was monitored by TLC until completion of the reaction, acetonitrile was removed in vaccuo and the residue was washed with Et_2O. Concentration of the aqueous layer by lyophilization gave the crude product, that was crystallized from acetone/Et_2O in the case of hydrochloride salt of phenylalanine methyl ester or purified over silica (PE:EA) in the case of compound **26**.

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one[20]



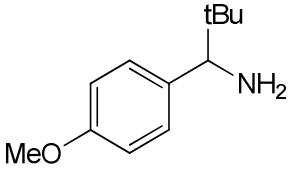
Anisole (2.16 g, 20 mmol) and pivaloyl chloride (1.21 g, 10 mmol) were dissolved in toluene (6 mL) and $AlCl_3$ (1.33 g, 20 mmol) was added. The mixture was stirred at 70°C for 20 min, cooled and 1 N HCl was added. The product was extracted into PE, the organic layer was washed with sat. $NaHCO_3$-sol. and dried over $MgSO_4$. Removing of the solvent and Kugelrohr distillation gave the title compound as colourless oil (1.56 g, 81%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.06 Hz, 2 H, Aryl), 6.90 (d, *J* = 9.06 Hz, 2 H, Aryl), 3.85 (s, 3 H, CH_3), 1.37 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.3 (quat, 1C), 162.0 (quat, 1 C), 131.0 (+, 2 C), 130.1 (quat, 1 C), 113.2 (+, 2 C), 55.4 (+, 1 C), 43.9 (quat, 1 C), 28.4 (+, 3 C).

MS (EI): *m/z* (%) = 192.1 (4) $[M]^{+\cdot}$, 135.0 (100).

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-amine (**3g**)



1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one (580 mg, 3.0 mmol) was dissolved in formamide (6 ml) and formic acid (3 ml) and the mixture was refluxed for 2h. Water

and Et_2O were added, the organic layer was separated and washed with brine, dried over $MgSO_4$ and the solvent was removed. The residue was dissolved in 1 N HCl (15 ml) and the mixture was refluxed for 1h. The mixture was diluted with water and a pH > 10 was set by solid NaOH. The product was extracted into Et_2O, the organic layer was dried over $MgSO_4$ and the solvent was removed to yield a pale yellow oil, that solidified upon cooling (480 mg, 83 %).

Mp 44-45 °C; R_f = 0.2 ($CHCl_3$-MeOH, 9:1).

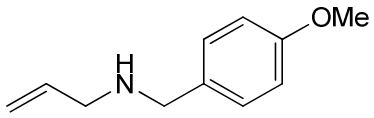
IR (ATR) : 3374, 3011, 2957, 2867, 1612, 1584, 1515, 1247, 1192, 1032, 818 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.78 Hz, 2 H, Aryl), 6.83 (d, *J* = 8.78 Hz, 2 H, Aryl), 3.80 (s, 3 H, CH_3), 3.67 (s, 1 H, CH), 1.74 (bs, 2 H, NH_2), 0.89 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4 (quat, 1 C), 135.7 (quat, 1 C), 129.2 (+, 2 C), 112.9 (+, 2 C), 64.7 (+, 1 C), 55.2 (+, 1 C), 35.1 (quat, 1 C), 26.8 (+, 1 C), 26.5 (+, 1 C), 26.4 (+, 1 C).

MS (CI (NH_3)): *m/z* (%) = 194.2 (17) $[M + H]^+$, 177.1 (100).

***N*-(4-Methoxybenzyl)prop-2-en-1-amine** (**17**)[21]



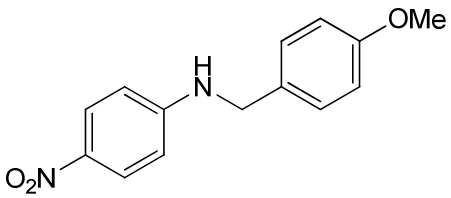
Allyl amine (428 mg, 7.5 mmol) and 4-methoxy benzaldehyde (**4a**, 1.36 g, 10 mmol) were dissolved in EtOH (15 ml) and the solution was stirred at room temp. for 18h. $NaBH_4$ (709 mg, 18.7 mmol) was added and the mixture was stirred until gas evolution had ceased. 0.5 N H_3PO_4 (10 ml) was added to the mixture and further stirred until gas evolution had ceased. The product was extracted into CH_2Cl_2, dried over $MgSO_4$ and the solvent was removed. The residue was purified by Kugelrohr distillation to yield the title compound as colourless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.76 Hz, 2 H, Aryl), 6.88 (d, *J* = 8.76 Hz, 2 H, Aryl), 5.98-5.86 (m, 1 H, CH), 5.22-5.15 (m, 1 H, CH_2), 5.13-5.08 (m, 1 H, CH_2), 3.79 (s, 3 H, CH_3), 3.73 (s, 2 H, CH_2), 3.27 (d, *J* = 6.03 Hz, 2 H, CH_2), 1.44 (bs, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6 (quat, 1 C), 136.9 (+, 1 C), 132.4 (quat, 1 C), 129.4 (+, 2 C), 116 (-, 1 C), 113.8 (+, 2 C), 55.3 (+, 1 C), 52.7 (-, 1 C), 51.7 (-, 1 C).

MS (CI (NH_3)): *m/z* (%) = 178.1 (100) $[M + H]^+$.

_N_-(4-Methoxybenzyl)-4-nitrobenzenamine (**19**)[22]



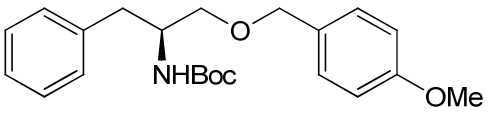
4-Nitro aniline (1.04 g, 7.5 mmol) and 4-methoxy benzaldehyde (4**a**, 1.02 g, 7.5 mmol) were dissolved in MeOH (15 ml) and the solution was stirred at room temp. for 18h. $NaBH_4$ (709 mg, 18.75 mmol) was added and the mixture was stirred until gas evolution had ceased. Water was added to the mixture and the product was extracted into EA. The org. layer was washed with 1 N HCl, sat. $NaHCO_3$-sol., dried over $MgSO_4$ and the solvent was removed. Purification over silica ($CHCl_3$) gave the title compound as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.33 Hz, 2 H, Aryl), 7.26 (d, *J* = 8.78 Hz, 2 H, Aryl), 6.90 (d, *J* = 8.78 Hz, 2 H, Aryl), 6.56 (d, *J* = 9.33 Hz, 2 H, Aryl), 4.83 (bs, 1 H, NH), 4.35 (d, *J* = 5.49 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (quat, 1 C), 153.1 (quat, 1 C), 138.2 (quat, 1 C), 129.3 (quat, 1 C), 128.8 (+, 2 C), 126.4 (+, 2 C), 114.3 (+, 2 C), 11.3 (+, 2 C), 55.4 (+, 1 C), 47.2 (-, 1 C).

MS (CI (NH_3)): *m/z* (%) = 276.2 (100) $[M + NH_4]^+$, 259.2 (14) $[M + H]^+$.

Tert-butyl 1-(4-methoxybenzyloxy)-3-phenylpropan-2-ylcarbamate (**25**)[23]



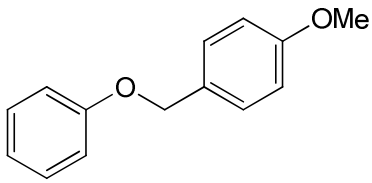
Boc-phenylalaninol (1.5 g, 6.0 mmol) was dissolved in dry DMF (12 ml) under nitrogen atmosphere. The solution was cooled to 0°C and NaH (60%, 552 mg, 13.8 mmol) was added portion wise. The mixture was stirred for 60 min at 0°C and 4-methoxybenzyl bromide (1.33 g, 6.6 mmol) was added. The mixture was allowed to warm to room temp. and stirred for additional 18h. The reaction was quenched with sat. NH_4Cl-sol. and water was added. The product was extracted into Et_2O, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification over silica (PE/EA) gave the title compound as colourless solid (1.44 g, 3.86 mmol, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.51 Hz, 2 H, Aryl), 7.25-7.15 (m, 5 H, Aryl), 6.90 (d, *J* = 8.51 Hz, 2 H, Aryl), 4.93-4.87 (m, 1 H), 4.48 (d, *J* = 11.52 Hz, 1 H, CH_2), 4.39 (d, *J* = 11.52 Hz, 1 H, CH_2), 3.93 (bs, 1 H), 3.82 (s, 3 H, CH_3), 3.40-3.31 (m, 2 H, CH_2), 2.94-2.80 (m, 2 H, CH_2), 1.42 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (quat, 1 C), 155.4 (quat, 1 C), 138.3 (quat, 1 C), 130.2 (quat, 1 C), 129.5 (+, 2 C), 129.5 (+, 2 C), 128.4 (+, 2 C), 126.3 (+, 2 C), 79.3 (quat, 1 C), 72.9 (-, 1 C), 69.7 (-, 1 C), 55.3 (+, 1 C), 51.7 (+, 1 C), 37.9 (-, 1 C), 28.4 (+, 3 C).

MS (ESI): *m/z* (%) = 372.0 (100) $[M + H]^+$.

1-Methoxy-4-(phenoxymethyl)benzene (**29**)[24]



4-Methoxy benzyl chloride (320 mg, 2.05 mmol) was added to a mixture of phenol (565 mg, 6.0 mmol) and K_2CO_3 (1000 mg) in dry acetone (10 ml) under nitrogen. The mixture was refluxed for 18h, cooled and filtered. After removing of the solvent, the crude product was purified over silica to yield the title compound as colourless solid (360 mg, 1.98 mmol, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.78 Hz, 2 H, Aryl), 7.33-7.27 (m, 2 H, Aryl), 7.00-6.97 (m, 3 H, Aryl), 6.93 (d, *J* = 8.78 Hz, 2 H, Aryl), 5.00 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (quat, 1 C), 158.9 (quat, 1 C), 129.5 (+, 2 C), 129.3 (+, 2 C), 129.1 (quat, 1 C), 120.9 (+, 1 C), 114.9 (+, 2 C), 114.0 (+, 2 C), 69.7 (-, 1 C), 55.3 (+, 1 C).

MS (EI): *m/z* (%) = 214.1 (2) $M]^{+\cdot}$, 121.1 (100).

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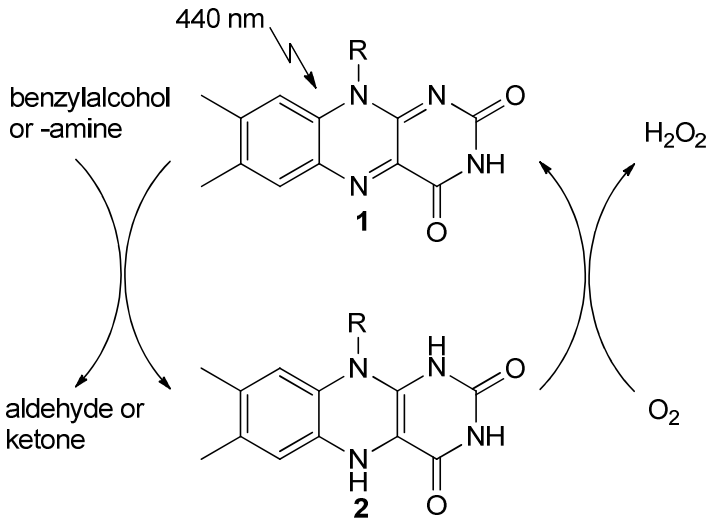
Chapter 4: Visible Light Flavin Photooxidation of Methylbenzenes, Phenylenes and Phenylacetic Acids

Introduction

In the previous chapters the use of flavin-mediated photo catalysis for the oxidation of benzyl alcohols and benzyl amines has been described. The method was used for the selective photo catalytic removal of benzyl protecting groups, and is now extended to flavin-mediated photo catalytic oxidation to methylbenzenes, styrenes and phenylacetic acids.



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

Oxidation of Methylbenzenes

The aerobic photochemical oxidation of methylbenzenes under heterogeneous[1] and homogeneous[2] reaction conditions has been described. Yet the use of purely visible light is still the exception.[2b, c] Quenching of the excited state of flavin by methyl- and methoxybenzenes via electron transfer (ET) is known for some time,[3] but no products

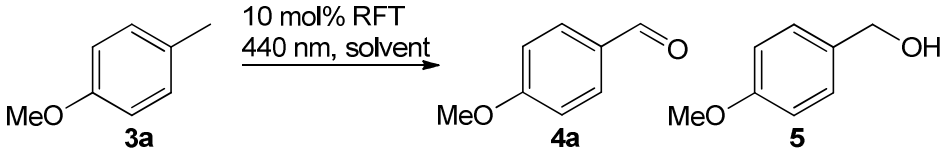
of the ET reactions have been described so far. Therefore the reaction was investigated as a possible C-H activation pathway to functionalize electron rich arenes at their benzyl position.

First encouraging results were obtained by subjecting 4-methoxy toluene **3a** to standard flavin photo catalysis conditions. Besides 4-methoxy benzaldehyde **3b**, the only side product that could be detected in small amounts by ^{1}H NMR was 4-methoxy benzyl alcohol **5** as a likely intermediate of the benzyl oxidation.

Starting from this initial result, the reaction conditions were optimized by varying the solvent and oxygen content. Solutions of 4-methoxy toluene **3a** (c = 0.01 mol/L) in 1 mL of solvent and 10 mol% of RFT were irradiated with blue light (443 nm, 3 W LED) and the course of the reaction was monitored by GC analysis. 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.[4]

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,[5] presumable polymeric products under flavin mediated photo oxidation conditions.[6] Hence hydroxylation of the aromatic core by water and subsequent oxidation to polymeric compounds is proposed.[7]

Table 1: Photo catalytic oxidation of 4-methoxy toluene **3a**



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

Reaction condition: 4-Methoxy toluene **3a** (0.01 mmol), solvent 1 mL, RFT 10 mol%, irradiation time as depicted; a) O_2: oxygen saturated solution; b) Determined by GC; c) 20 mol% RFT.

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

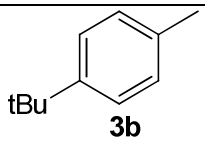
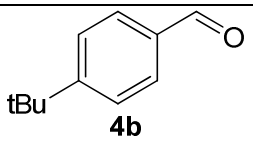
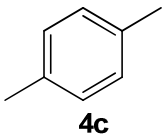
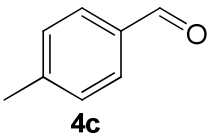
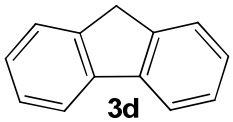
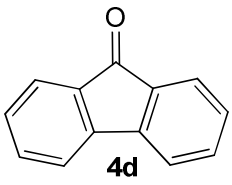
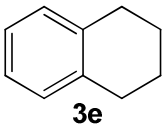
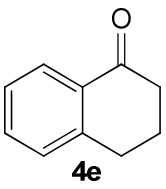
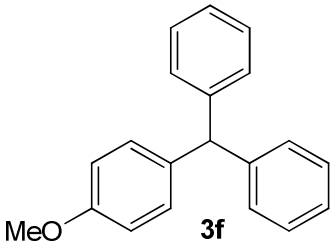
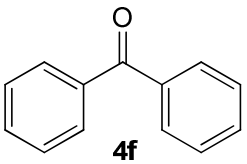
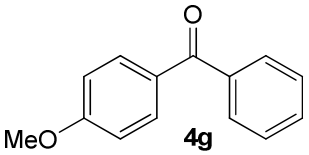
Without irradiation as well as when the reaction mixture was irradiated in the absence of RFT no benzaldehyde **4a** was formed. In some oxidation reactions, 4-methoxy benzyl alcohol **5** was detected as a side product. Since alcohol **5** is oxidized faster to aldehyde **4a** than toluene **3a**, alcohol **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,[8] 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,[9] 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. This negative solvent isotope effect (SIE) is also indicative for the participation 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.[10] The quantum yield of the flavin-mediated photo oxidation of 4-methoxy toluene **3a** was determined to be 0.011 [1.1%; c = 0.01 mol/L in 1 mL of H_2O and 1 mL of MeCN, O_2 purged, 10 mol% RFT, blue light (440 nm) irradiation].

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 photooxidation of benzyl alcohols and benzyl amines. 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 *alpha*-tetralone **4e** in 34% yield. Unreacted starting material was only partly recovered, which indicates competing polymerization processes as described above.

Table 2: Photo catalytic oxidation of methylbenzenes

Entry	Irradiation time[a]	Starting material	Product(s)	Yield (%)[b]
1	2.75 h	 **3b**	 **4b**	40[c]
2	3.5 h	 **4c**	 **4c**	43[c]
3	100 min	 **3d**	 **4d**	16
4	100 min	 **3e**	 **4e**	34
5	60 min	 **3f**	 **4f**  **4g**	24[c, d] 35

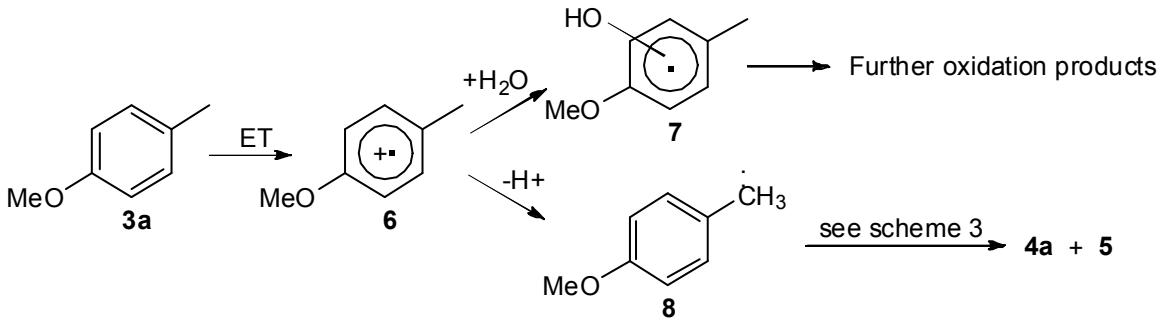
Reaction conditions: Methylbenzene (0.01 mmol), solvent 0.5 mL MeCN, 0.5 mL H_2O, RFT 10 mol%, irradiation time as depicted; a) The reaction mixtures were irradiated until RFT was completely bleached; b) Determination of yield by GC; c) 20 mol% RFT; d) 0.6 mL MeCN, 0.4 mL H_2O.

Treating of triphenylmethane as well as triphenylmethanol with standard oxidation conditions did not yield any oxidation products, whereas more electron rich 4-methoxy triphenylmethane **3f** underwent oxidative degradation to benzophenone **4f** in 24% and 4-methoxy benzophenone **4g** in 35% yield. This kind of oxidative degradation is known from triphenylmethane radicals derived from triphenylmethyl halides[11] or triphenylmethane.[12] It was proposed that the triphenylmethane radical cation that is formed after initial ET to excited flavin loses a proton to form a

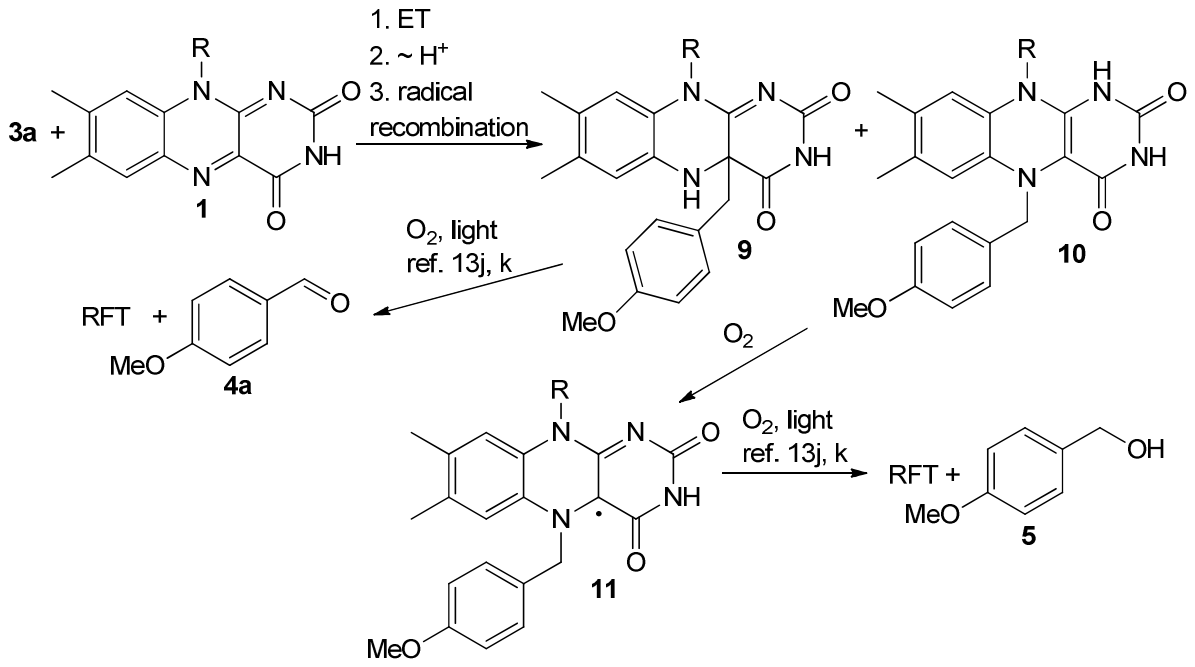
triphenylmethyl radical. This is quenched by oxygen to form a peroxy radical that collapses into benzophenone and phenol.[12]

To gain more data on possible intermediates formed during the flavin-mediated photo oxidation of **3a**, the course was followed of the UV-Vis absorption of RFT under aerobic, oxygen saturated and anaerobic conditions (see Appendix). 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 90s 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 that bleaching of RFT **1** was slowed down. The 50% bleach of RFT **1** was retarded to roughly 150s 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. this spectrum was assigned to a neutral N5 alkyl flavin radical.[13] 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:



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



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

The initial step in the photo oxidation process is an ET from methylbenzene **3a** to RFT in the triplet excited state (see ref. 3 and discussion in chapter 2). The so formed radical ion pair of radical cation **6** and $RFT^{\cdot -}$ 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 formation of radical cation **6** that is a strong acid (pK_a of toluene radical cation in MeCN was estimated by Arnold[14a] to be -13 and -12 by Green[14b]) looses a proton to give benzyl radical **8** (Scheme 2). Benzyl radical **8** and $RFT^{\cdot -}$ can recombine to form covalent intermediates.[13] The C4a adduct **9** collapses under irradiation and oxygen present to aldehyde **4a** and RFT.[13j, k] The N5 adduct **10** is oxidized by oxygen in a dark reaction to form the observed neutral radical **11**. The radical is undergoing a photo induced ET and subsequently fragments to RFT **1** and benzyl alcohol **5** (Scheme 3).[13j, 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. Both routes would explain the observed SIE since water is participating as reactant.

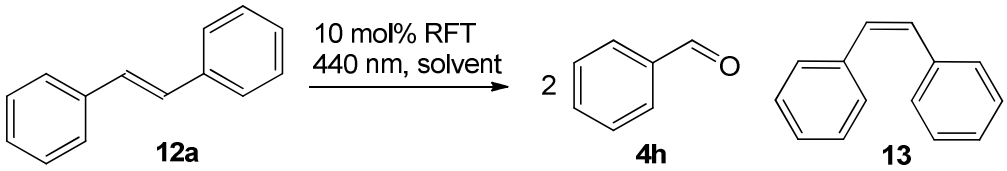
The electron donating methoxy group on the arene in the case of 4-methoxy toluene **3a** stabilizes the initially formed radical cation **6**.[2c, 3, 15, 16] The proposed ET pathway

is further supported by the 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 $RFT^{\cdot -}$.[17] Secondly, when the proton is not directly transferred from radical cation **6** to $RFT^{\cdot -}$, water is acting as a base or proton relay, promoting the rate limiting deprotonation step of radical cation **6** to form benzyl radical **8**.[16a, b] Additional the reoxidation of flavin from its reduced state **2** to its oxidized state **1** is faster in water compared to MeCN.[18]

Oxidation of Phenylenes

The photo oxidative cleavage of stilbenes and styrenes has been of great interest for some time.[19] Studies towards the flavin-photosensitization of stilbene have been undertaken, but only the *trans*-*cis* isomerisation of stilbene has been observed.[20] An example of double bond oxidation by flavin sensitization is the oxidation of unsaturated fatty acids in MeCN that yielded the hydroperoxides of the fatty acids. It was proposed that the oxidation proceeds by a type II (singlet oxygen) mechanism.[21] To our delight, applying flavin photo oxidation conditions (0.01 mmol substrate, 10 mol% RFT, 0.4 mL H_2O, 0.6 mL MeCN) to *trans*-stilbene **12a**, we obtained benzaldehyde **4h** in 69 % yield (considering the production of 2 eq. of benzaldehyde **4h** for 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).

Table 3: Photo catalytic oxidation of *trans*-stilbene **12a**



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

Reaction conditions: Stilbene **12a** (0.01 mmol), solvent 1 mL, RFT 10 mol%, irradiation time as depicted; a) O_2: oxygen saturated solution; b) Determination of yield by GC.

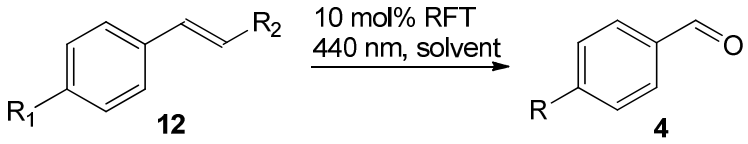
When the oxidation was performed in pure MeCN only 5% of benzaldehyde **4h** was detected within 5 min irradiation time, but 42% of *cis*-stilbene **13** was observed after 5 min irradiation. The formation of 10% *cis*-stilbene **13** already after 1 min irradiation time is indicative that *cis*-stilbene **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 high SIE 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 0.011 [1.1%; c = 0.01 mol/L in 0.8 mL of H_2O and 1.2 mL of MeCN, 10 mol% RFT, blue light (440 nm) irradiation].

Next, we applied flavin-mediated photo catalytic oxidation reaction conditions to electron rich symmetrical stilbene **12b** and unsymmetrical stilbene **12c** (Table 4). As

expected, the symmetrical stilbene **12b** was oxidized to 4-methoxy benzaldehyde **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 irradiation time to 4-methoxy benzaldehyde **4a** in 69% and 4-NO_2 benzaldehyde **4i** in 64% yield.

Table 4: Photo catalytic oxidation of phenylenes



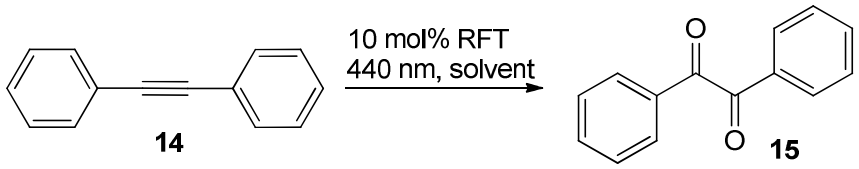
Entry	Irradiation time	Starting material	Product(s)	Yield (%)[a]
1	80 min	R_1: OMe, R_2: C_6H_4-4-OMe **12b**	R: OMe **4a**	36[b]
2	80 min	R_1:NO_2, R_2: C_6H_4-4-OMe **12c**	R: OMe **4a**	69[c]
			R: NO_2 **4i**	64
3	80 min	R_1: H, R_2: COOH **12d**	R: H **4h**	68[d]

Reaction conditions: Starting material (0.01 mmol), solvent 0.5 mL MeCN, 0.5 mL H_2O, RFT 10 mol%, irradiation time as depicted; a) Determination of yield by GC; b) 2.4 mL MeCN and 0.1 mL H_2O; c) 1.0 mL MeCN, 0.6 mL H_2O; d) 20 mol% RFT.

Styrene, alpha methyl styrene and 4-methoxy styrene 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 beta nitro styrenes were subjected to the photo catalytic oxidation conditions, oxidative cleavage did not take place.

Photo catalytic oxidation reaction of tolane **14**[22] gave benzil **15** as sole oxidation product in 28% yield leaving 2% of starting tolane **14** (Table 5). 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**.

Table 5: Photo catalytic oxidation of tolane **14**

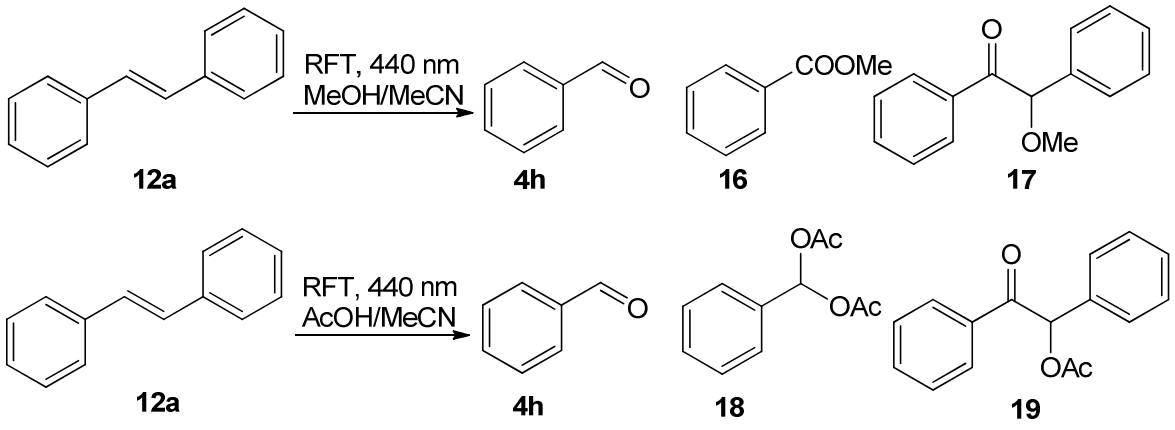


14 **15**

Entry	Irradiation time	Starting material	Product(s)	Yield (%)[a]
1	100 min	Tolane **14**	Benzil **15**	28
2	100 min	Tolane **14**	Benzil **15**	^{18}O labelled[b]

Reaction conditions: Tolane **14** (0.01 mmol), solvent 0.6 mL MeCN, 0.4 mL H_2O, RFT 10 mol%, irradiation time as depicted; a) Determination of yield by GC; b) 0.6 mL MeCN, 0.4 mL $H_2{}^{18}O$ (10.5%), ^{18}O was incorporated into benzil **15**.

Oxidation of stilbene **12a** in a MeOH/MeCN mixture yielded benzaldehyde **4h** as main product, but benzoic acid methyl ester **16** and O-methyl benzoin **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-acetyl benzoin **19** were formed as well (Scheme 4). These results clearly indicate the role of the solvent acting as a nucleophile in the course of the oxidation reactions.



12a **4h** **16** **17**

12a **4h** **18** **19**

Scheme 4: Photo catalytic oxidation of stilbene **12a** in organic solvents

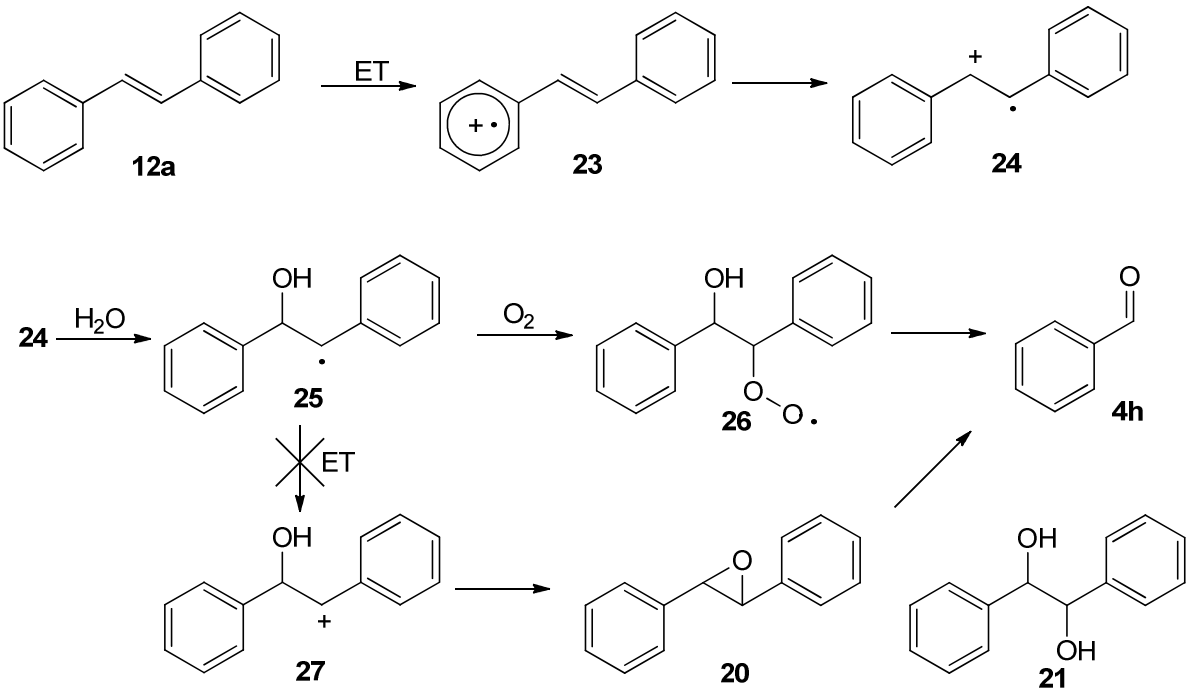
To gain more insight into the mechanism of the oxidative cleavage of stilbenes, *trans*-stilbene oxide **20**, *meso*-hydrobenzoin **21** and benzoin **22** as potential intermediates,

were subjected to the standard photo catalytic oxidation reaction conditions. All three compounds did not yield benzaldehyde **4d** as oxidation product within 1 min irradiation time, excluding the compounds as possible intermediates. In the case of *trans*-stilbene oxide **20** no benzaldehyde **4h** was formed even after 60 min irradiation, whereas *meso*-hydrobenzoin **21** was oxidatively cleaved in 60% to benzaldehyde **4h** within the same irradiation time. Benzoin **22** did not react even after 60 min irradiation as judged by TLC. Since *meso*-hydrobenzoin **21** is not a likely intermediate in the flavin-mediated photo oxidation of stilbene **12a**, the proposed mechanism by Fry *et al.*[23] for anodic cleavage of stilbenes is not valid for our system.

A singlet oxygen reaction pathway can excluded, since it is known that stilbene is not oxidized by singlet oxygen.[19j, k]

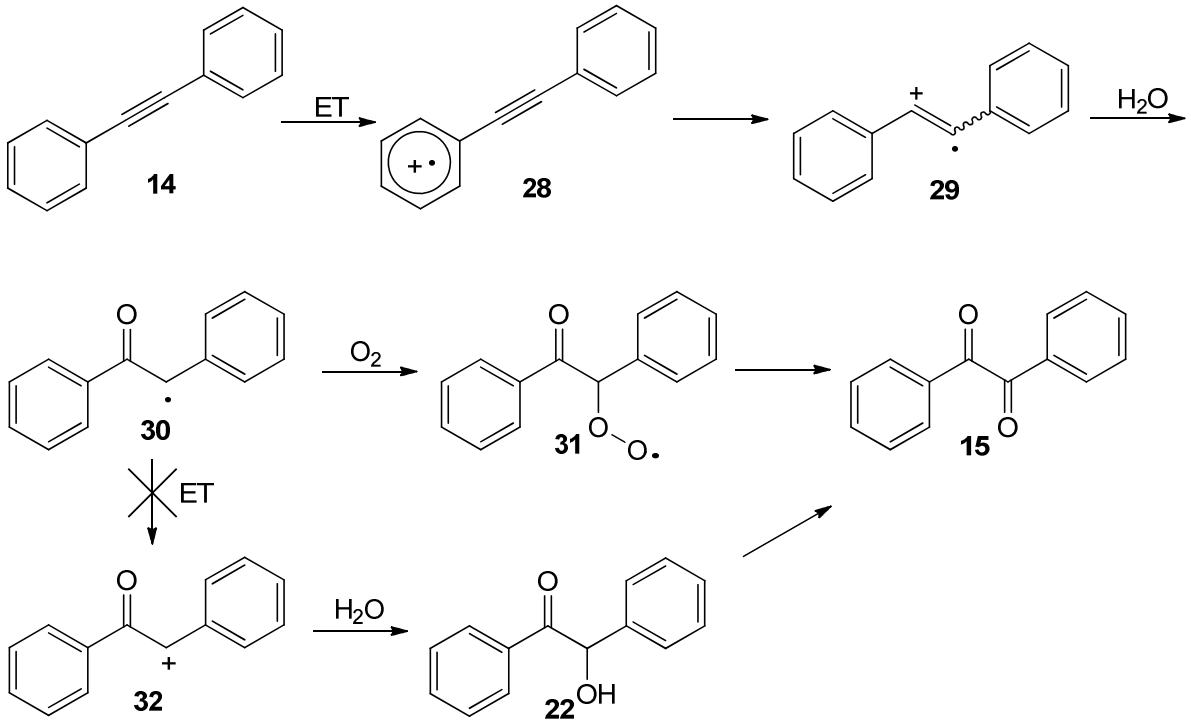
Quenching of the radical cation **24** of unsubstituted stilbene **12a** is not likely since oxygen hardly reacts with radical cations of aromatic olefins.[24] It has been shown that alkene radical cations behave as cations when reacting with nucleophiles,[25] which are in our case water, MeOH or acetic acid. The so formed benzyl radical **25** can now react with oxygen yielding peroxy radical **26**, which undergoes fragmentation to benzaldehyde **4h** (Scheme 5). 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.[26]

A second ET from benzyl radical **25** to flavin seems not likely since the so formed carbocation **26** would give stilbene oxide **20** or *meso*-hydrobenzoin **21** upon reaction with water that could be excluded as intermediates.



Scheme 5: Proposed mechanism for flavin mediated photo oxidation of stilbene **12a**

For the oxidation of tolane **14** to benzil **15**, *trans*-stilbene oxide **20** and *meso*-hydrobenzoin **21** were excluded as intermediates, since submitting these compounds to standard flavin-mediated oxidation conditions as described above did not yield benzil **15**. From these results a reaction pathway in analogy to stilbene oxidation is proposed (Scheme 6). Here, peroxy radical ketone **31** instead of the benzoin **22** is formed, which collapses to benzil **15**.



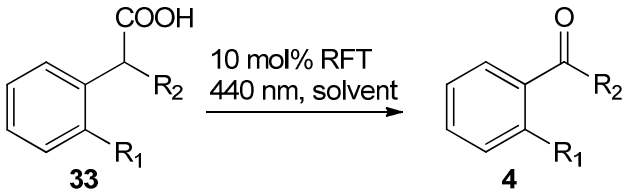
Scheme 6: Proposed mechanism for flavin-mediated photo oxidation of tolane **14**

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

Diphenylacetic acid **33a** was photo oxidized (0.01 mmol substrate, 10 mol% RFT, 0.5 mL H_2O, 0.5 mL MeCN) yielding aldehyde **4h**. This decarboxylative photo oxidation reaction of phenylacetic acids is known.[27] Anaerobic photo-decarboxylation of phenylacetate by excited flavin with accompanying benzylation of the flavin core[13j, k, 28] and oxidative decarboxylation of dihydrophthalates[29] has been described. Photo decarboxylation of *alpha*-hetero carboxylic acids by flavin has been reported as well.[30] We have optimized the reaction conditions of this flavin-mediated decarboxylation for synthetic preparative use.

Table 5: Oxidation of phenylacetic acids



33 **4**

Starting material	H_2O/MeCN (mL)	Conditions[a]	Irradiation time	Yield (%)[b]
R_1: H , R_2:Ph **33a**	0 / 1.0		5 min	2
	0.25 / 0.75		5 min	4
	0.5 / 0.5		5 min	24
	0.7 / 0.3		5 min	34
	0.5 / 0.5	O_2	5 min	11
	0.5 / 0.5	HCl	5 min	8
	0.5 / 0.5	NaOH	5 mins	22
	0.5 / 0.5	open to air	5 min	32
	0.5 / 0.5	open to air	20 min	>99
	0.5 / 0.5	$H_2{}^{18}O$ (10.5%)	20 min	no ^{18}O labelled **4f**[c)]
	0.5 / 0.5	D_2O/MeCN-d_3	5 min	31
R_1: H , R_2:H **33b**	0.5 / 0.5	open to air	30 min	45
R_1: OMe,R_2:H **33c**	0.5 / 0.5	open to air	10 min	43

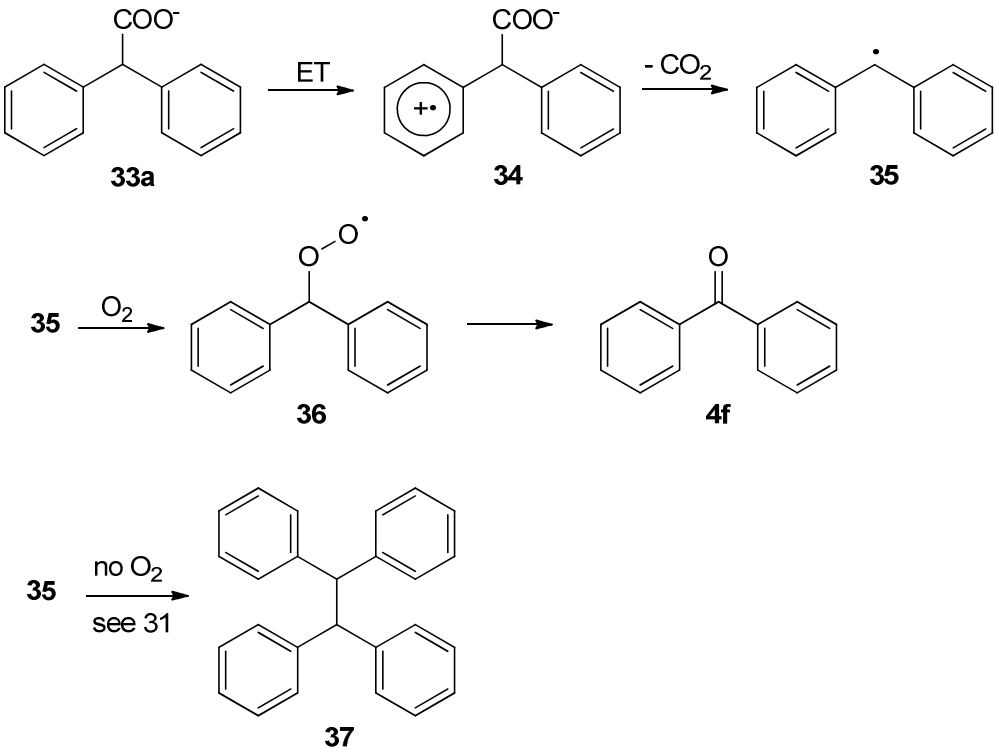
Reaction conditions: Phenylacetic acid (0.01 mmol), solvent 1 mL, RFT 10 mol%, irradiation time as depicted; a) O_2: oxygen saturated solution, HCl: 0.001 N HCl instead of H_2O, NaOH: 0.001 N NaOH instead of H_2O; b) Determination of yield by GC; c) ^{18}O was not incorporated into benzophenone **4f**.

As in the case of flavin-mediated photo oxidation of methylbenzenes and styrenes, the oxidation of diphenylacetic acid **33a** 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 6).

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 **33a** 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 **14** and indicate that dissolved oxygen is acting as oxygen source in the flavin-mediated photo oxidation of diphenylacetic acid **33a**.

With the same protocol phenylacetic acid **33b** was oxidized to benzaldehyde **4h** in 45% yield within 30 min. The more electron rich 2-methoxy phenylacetic acid **33c** 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 7. The deprotonated diphenylacetic acid **33a** 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 the 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 **14** was observed.



Scheme 7: Proposed mechanism for flavin-mediated photo oxidation of diphenylacetic acid **33a**

The occurrence of intermediate benzyl radical **35** is supported by the anaerobic photo oxidation of diphenyl acetic acid in dry MeCN (Scheme 7).[31] As main oxidation product tetraphenyl ethane **37** was identified that is most likely the outcome of the dimerization of two diphenylmethyl radicals **35**. Therefore the same reaction path from intermediate benzyl radical **35** formed as in the case of 4-methoxy toluene **3a** oxidation cannot be excluded completely. The formation of covalent flavin adducts may be affected by the sterical demand of the intermediate benzyl radical.

Conclusion

The flavin-mediated photo oxidation of benzylic carbon atoms in hydrocarbons, alkenes and carboxylates 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-methoxy toluene **3a** could be oxidized in 58% to 4-methoxy benzaldehyde **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 photo catalyzed 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 substitution.

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.

Experimental

Monitoring of the reaction and product analysis was performed by gas chromatographic analysis (GC 5890 Series II from Hewlett-Packard, capillary column J+W Scientific—DB-5MS/30 m x 0.25 mm/0.25 mm film). The structures of the products were confirmed by comparison with standard samples.

General procedure for flavin-mediated photo oxidations:

Starting material (0.01 mmol) and RFT (0.001 mmol) were dissolved in MeCN/H_2O mixtures 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 x 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 x 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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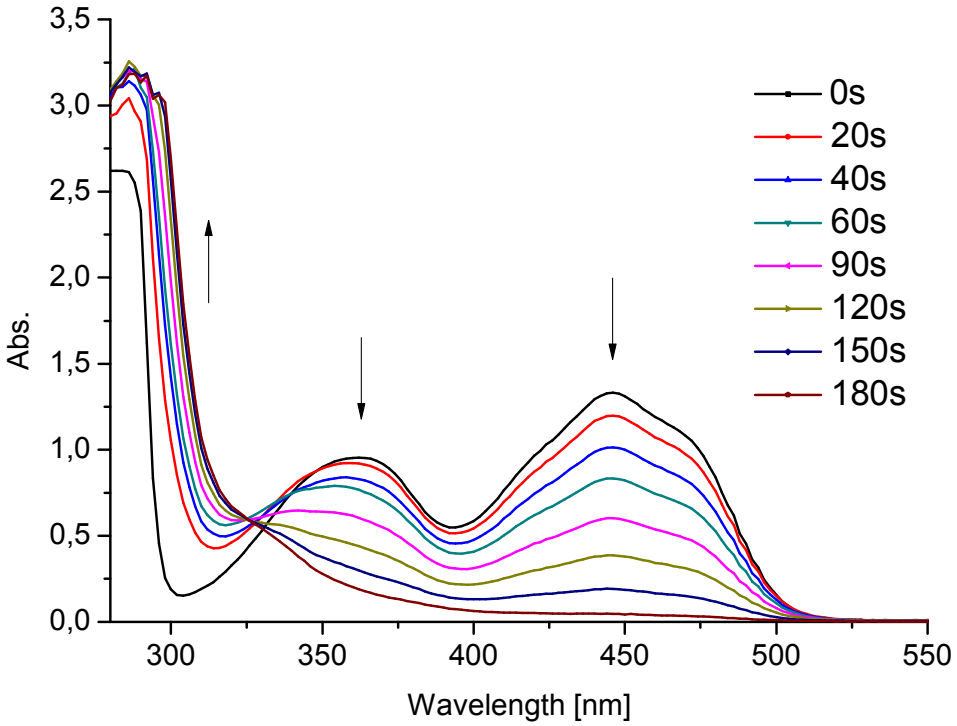
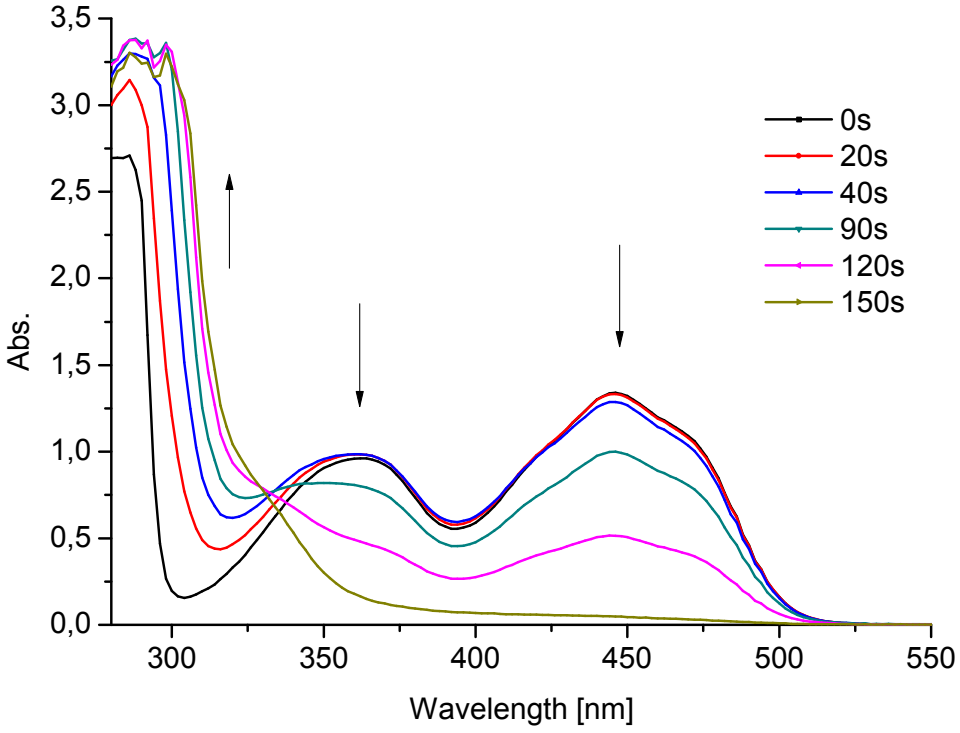
[31] Diphenylacetic acid (0.03 mmol), RFT (0.03 mmol), dry MeCN (3 mL) under N_2, irradiation with LED for 30 min (440 nm, 3 W).

Appendix

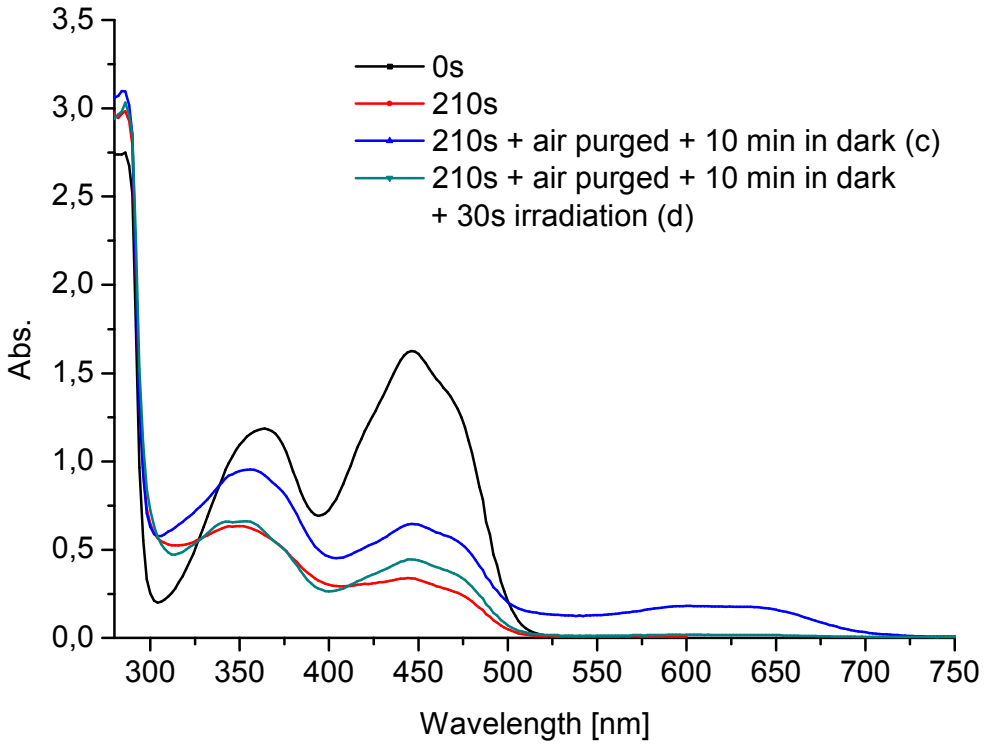
Course of absorption of mixture containing 4-methoxy toluene **3a** (0.02 mmol) and RFT (0.5 µmol) upon irradiation with blue light (443 nm) under air. A 50% bleach of the absorption band at 446 nm was obtained after about 90s of irradiation. No recovery of the bleached signals was obtained when the system was purged with air after the irradiation.



Course of absorption of mixture containing 4-methoxy toluene **3a** (0.02 mmol) and RFT (0.5 µmol) upon irradiation with blue light (443 nm) in oxygen saturated solution. A 50% bleach of the absorption band at 446 nm was obtained after about 150s of irradiation.



Course of absorption of mixture containing 4-methoxy toluene **3a** (0.02 mmol) and RFT (0.5 µmol) upon irradiation with blue light (443 nm) in nitrogen purged (30 min) solution. A 50% bleach of the absorption band at 446 nm was obtained after about 90s of irradiation (not shown). After 210s of irradiation the solution was purged with air for 10s. A blue flavin species developed that was stable in the dark for some minutes (c), but decayed under irradiation (d).



Chapter 5: Synthesis and optical Properties of new Flavin Copolymers

Introduction

Since flavins have been used as organocatalysts in thermal[1] and photo[2] oxidation reactions, the immobilization of flavins as recyclable catalysts is of great interest. The immobilization of flavins on insoluble inorganic,[2b, 3] soluble organic[4] and insoluble organic[5] support has been achieved. To best of my knowledge only two examples of a flavin monomer that has been used in a copolymerization reaction have been reported.[4b,f] A flavin polymer reported by Rotello *et al.* was formed via an atom transfer radical polymerization yielding a polymer with good solubility in a range of solvents.[4b] Challa *et al.* reported the synthesis of polyanionic flavin copolymers and a flavin homopolymer from polymerizable flavin derivatives by radical copolymerization.[2f]

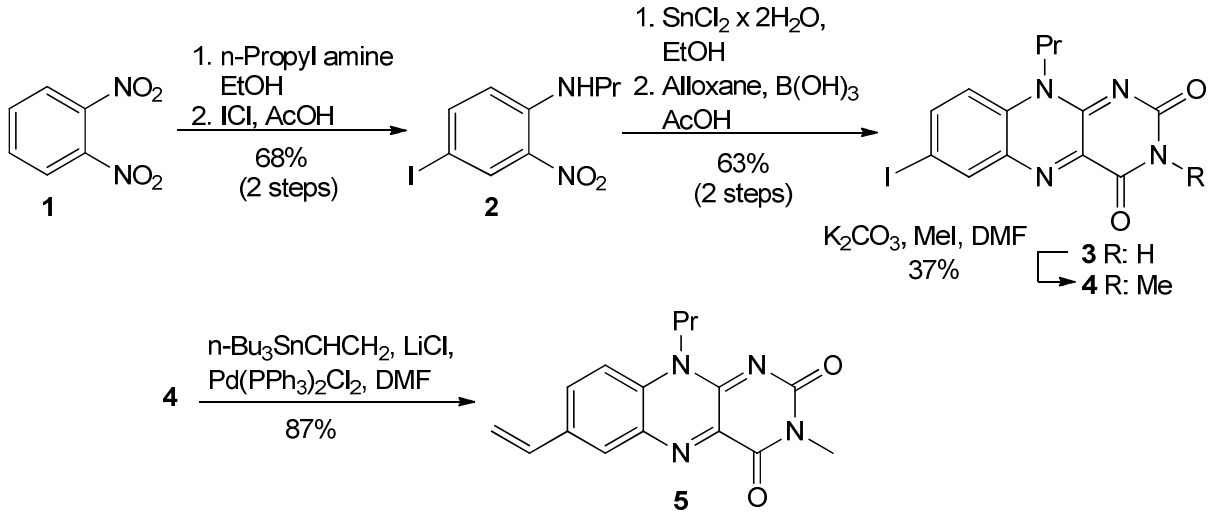
Herein the synthesis is presented of a new and readily accessible polymerizable vinyl flavin, its incorporation in styrene and acrylate copolymers and the optical properties of the resulting materials.

Synthesis of a Vinyl Flavin and its use in Copolymerization

As polymerizable flavin monomer flavin **5** with an appending vinyl moiety was synthesized. Precursor **3** was derived by the Kuhn synthesis protocol[6] within four steps: starting from o-nitro benzene **1**, ipso substitution with *n*-propyl amine gave 2-nitro-N-propyl aniline that was iodated with ICl to aniline **2** in 68% yield over two steps. Reduction of compound **2** with $SnCl_2$ and subsequent condensation with alloxane monohydrate gave flavin **3** in 63% yield over two steps. No column chromatography was needed to obtain flavin **3** over four steps in a reasonable yield of 43% from o-nitro benzene **1**. N-3 methylation of **3** gave the better soluble flavin **4**

bearing iodine at C7 position in 37% yield. The polymerizable vinyl group was introduced by a Stille coupling at C7 to obtain flavin **5** in 87% yield.

Scheme 1: Synthesis of flavin monomer **5**



Radical copolymerization of flavin **5** in neat acrylic acid gave copolymer **6** as yellow powder. Copolymer **6** was soluble in water and insoluble in organic solvents as MeOH, $CHCl_3$ and acetone. When flavin **5** was radical copolymerized with styrene and o-divinylbenzene [1% (v/v)] as a cross-linker, a yellow powder **7**, insoluble in water, MeCN, MeOH but soluble in $CHCl_3$ and acetone was obtained. The suspensibility of **7** was very poor in aqueous media. Due to the high surface tension copolymer **7** floated on the water surface. On the other hand it tended to coagulate in pure MeCN. A satisfactory suspensibility of copolymer **7** was obtained in a 1:1 mixture of water and MeCN.

To yield insoluble copolymers, the content of o-divinylbenzene was raised to 10% (v/v). Copolymerization of flavin **5** with styrene and o-divinylbenzene [10% (v/v)] yielded a yellow orange powder **8** that was not soluble in water or any common organic solvent. The suspensibility properties of copolymer **8** in water and MeCN were comparable to the one of copolymer **7**.

When styrene was substituted by acrylic acid methyl ester in the copolymerization reaction [o-divinylbenzene 10% (v/v)] a yellow powder **9** was obtained. As expected, copolymer **9** was not soluble in water or any common organic solvent. The suspensibility of **9** was very poor in water wherein coagulation of **9** could be

observed. On the contrary, copolymer **9** showed good swelling properties in MeCN and aqueous MeCN.

UV-Vis and Fluorescent Spectra

Flavin **4** and **5** showed typical absorption spectra for isoalloxazines, whereby the absorption maxima for **5** appeared red shifted by 8 nm for all three maxima in the analysed spectral window (Figure 1). This indicates an electronic coupling of the double bond at C7 to the isoalloxazine scaffold.

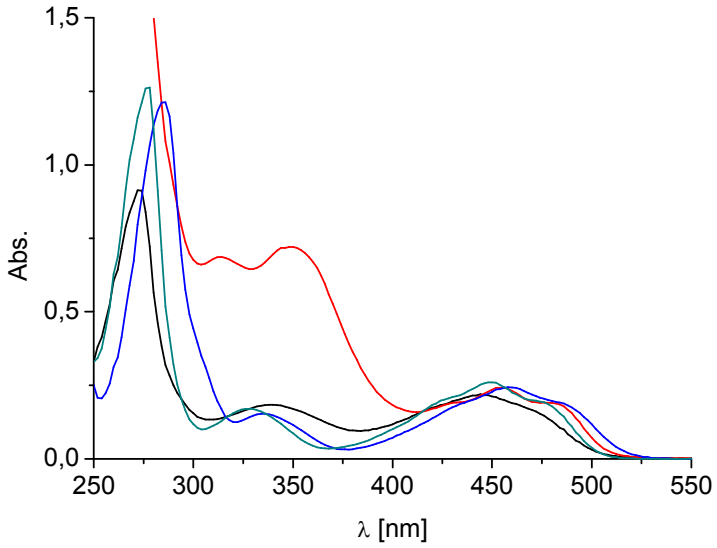


Figure 1: UV-Vis spectra of flavins **4** (green, $2.5 \cdot 10^{-5}$ M in MeCN with 1.5% DMSO), **5** (blue, $2.5 \cdot 10^{-5}$ M in MeCN with 1.5% DMSO) and flavin copolymers **6** (black, $2.5 \cdot 10^{-5}$ M in MeCN with 1.5% H_2O with respect to flavin), **7** (red, $2.5 \cdot 10^{-5}$ M in $CHCl_3$ with respect to flavin)

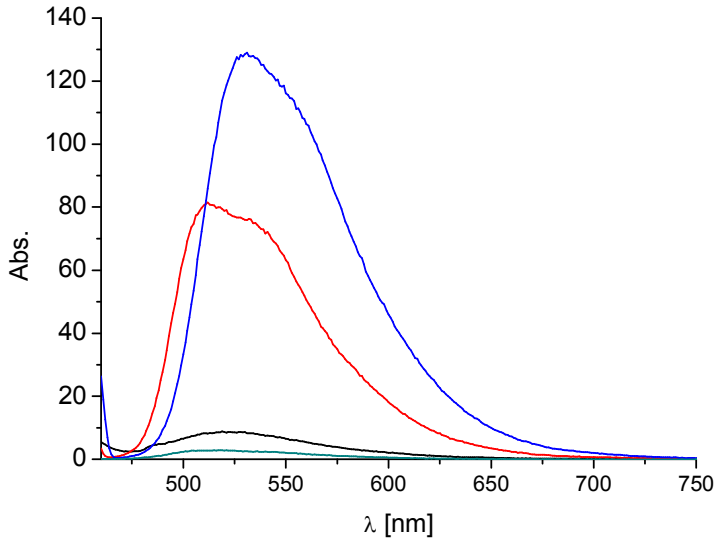


Figure 2: Fluorescence spectra of flavins **4** (green, $2.5 \cdot 10^{-6}$ M in MeCN with 1.5% DMSO), **5** (blue, $2.5 \cdot 10^{-6}$ M in MeCN with 1.5% DMSO) and flavin copolymers **6** (black, $2.5 \cdot 10^{-6}$ M in H_2O with respect to flavin), **7** (red, $2.5 \cdot 10^{-6}$ M in $CHCl_3$ with respect to flavin)

Assuming that the extinction coefficient of flavin **5** is not affected by the embedding in the copolymer, we calculated a flavin loading of $3.6 \cdot 10^{-4}$ mmol/mg for copolymer **6** and $7.6 \cdot 10^{-5}$ mmol/mg for copolymer **7** (spectral data not shown). By knowing the flavin loading, solutions of **6** and **7** containing $2.5 \cdot 10^{-4}$ M flavin were prepared and UV-Vis spectra were recorded (Figure 1).

The UV-Vis spectrum of copolymer **6** in MeCN (1.5% H_2O) is not structured. The absorption band in the visible region is slightly blue shifted by 6 nm to 444 nm as compared to the parent compound **4**. The S_o–S_2 transition of flavins is known to be very sensitive towards solvent polarity.[7] Bathochromic shifts changing from non-polar to polar media have been observed.[4] Therefore the red shift of the S_0-S_2 transition of copolymer **6** from 328 nm for compound **4** to 339 nm was attributed to the influence of the carboxylic backbone of copolymer **6** on the flavin chromophore.

Due to the insolubility of copolymer **7** in MeCN it was only possible to record an UV-Vis spectrum in $CHCl_3$. The longest wavelength absorption maximum at 445 nm is nearly at the same position as for copolymer **6**. The striking difference that we observed is the strong absorption at 314 and 349 nm. Since there should be no appreciable absorption of polystyrene over 300 nm,[8] these absorption maxima arise from the flavin chromophore embedded in the polystyrene matrix.

Fluorescence spectra for compounds **4**, **5** and copolymers **6** and **7** are shown in figure 2. The parent compound **4** showed only a very weak fluorescence with a maximum of emission at 518 nm. The poor emission of **4** is attributed to the heavy atom effect of the iodine on the C7 position.[9] Flavin monomer **5** exhibits a strong fluorescence with a maximum of emission at 531 nm, whereas copolymer **6** with an acrylic acid backbone shows only very weak emission at 522 nm. Polystyrene based copolymer **7** showed moderate fluorescence at 512 nm.

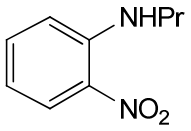
Conclusion

The synthesis of a polymerizable flavin monomer **5** bearing a vinylic group is presented. The synthesis of the isoalloxazine core **3** is straight forward from commercial available starting materials. Subsequent N3 methylation yielded flavin **4** bearing iodine at the C7 position. Compound **4** is an interesting intermediate, since it opens the possibility of diversification at the C7 position via known cross coupling procedures. The longest wavelength absorption of flavin monomer **5** is slightly red shifted due to electronic coupling of the vinyl group into the isoalloxazine skeleton.
Copolymerization of flavin monomer **5** was achieved via radical polymerization with styrene, acrylic acid and methacrylate. Thereby flavin copolymers soluble in water (**6**) and organic solvents (**7**) could be obtained. By cross-linking of the copolymers with divinylbenzene, insoluble polymers (**8**, **9**) could be generated as well. This approach of immobilization might give rise to a new generation of recyclable heterogeneous flavin photo catalysts. Virtually any radical polymerizable comonomer could be used in the copolymerization reaction. The use of trimeric comonomer mixtures with one comonomer bearing a substrate binding site could give rise to recyclable, substrate specific flavin photo catalysts.

Experimental

All chemicals were purchased from commercial suppliers and used as received. Anhydrous DMF was purchased from Fluka. Styrene, o-divinylbenzene, acrylic acid methyl ester were washed with 1 N NaOH to remove added stabilizer prior polymerization. TLC was performed on silica gel 60 F254 aluminum sheets (Merck), with detection under 254 nm or 333 nm UV light. Flash column chromatography was carried out on silica gel (0.035–0.070 mm, 60 Å), obtained from Acros. NMR spectra were recorded with a Bruker spectrometer operating at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) and one operating at 600 MHz (^{1}H NMR) or 150 MHz (^{13}C NMR) with TMS as the external standard. Electron-impact (EI) and chemical ionization (CI) mass spectra were recorded with a Finnigan TSQ 710 spectrometer. Electrospray ionization (ESI) mass spectra were recorded with a ThermoQuest Finnigan MAT 9595 spectrometer. High-resolution mass spectrometry (HRMS) was performed on a ThermoQuest Finnigan MAT 95 spectrometer. IR spectra were recorded with a Biorad Spectrometer Excalibur FTS 3000. Melting points were determined with a Lambda Photometrics OptiMelt MPA 100. UV-Vis spectra were recorded on a Varian Cary 50 Bio UV-Vis spectrometer. Fluorescence spectra were recorded on a Varian Cary Eclipse spectrometer.

2-Nitro-N-propylbenzenamine[10]



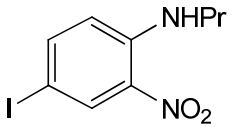
Dinitro benzene **1** (1681 mg, 10 mmol) was dissolved in dry EtOH (10 mL) under nitrogen and n-propyl amine (4.1 mL, 50 mmol) was added. The mixture was refluxed for 16 h. Water was added (50 mL) and the product was extracted into Et_2O (3 x 40 mL). The organic layer was washed with saturated NH_4Cl-sol. (2 x 40 mL), dried over $MgSO_4$. The solvent was removed to give the title compound as red oil that was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, J = 8.6 Hz, J = 1.5 Hz, 1 H, Aryl), 8.05 (bs, 1 H, NH), 7.43-7.37 (m, 1 H, Aryl), 6.82 (dd, J = 8.5 Hz, J = 0.5 Hz, 1 H, Aryl), 6.62-

6.57 (m, 1 H, Aryl), 3.25 (td, *J* = 7.1 Hz, *J* = 5.3 Hz, 2 H, CH_2), 1.80-1.68 (m, 2 H, CH_2), 1.04 (t, *J* = 7.6 Hz, 3 H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): *δ* = 145.7 (quat, 1 C), 136.2 (+, 1 C), 131.7 (quat, 1 C), 127.2 (+, 1 C), 115.0 (+, 1 C), 113.8 (+, 1 C), 44.8 (-, 1 C), 22.3 (-, 1 C), 11.6 (+, 1 C).

4-Iodo-2-nitro-N-propylbenzenamine (2)



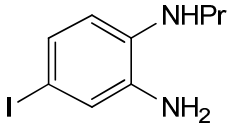
Crude 2-nitro-N-propylbenzenamine, and KOAc (1080 mg, 11 mmol) were suspended in AcOH (10 mL) and ICl (0.58 mL, 11 mmol) was added. The mixture was heated to 80°C for 30 min, poured into water and extracted with Et_2O (3 x 40 mL). The organic layer was washed with 10% Na_2SO_3 (2 x 30 mL), dried over $MgSO_4$ and the solvent was removed to yield **2** as red oil (2090 mg, 6.83 mmol, 68% over two steps).

^{1}H-NMR (300 MHz, $CDCl_3$): *δ* = 8.45 (d, *J* = 1.9 Hz, 1 H, Aryl), 8.05 (bs, 1 H, NH), 7.60 (dd, *J* = 9.1 Hz, *J* = 2.2 Hz, 1 H, Aryl), 6.63 (d, *J* = 9.1 Hz, 1 H, Aryl), 3.25 (td, *J* = 7.0 Hz, *J* = 5.2 Hz, 2 H, CH_2), 1.81-1.69 (m, 2 H, CH_2), 1.04 (t, *J* = 7.6 Hz, 3 H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): *δ* = 145.0 (quat, 1 C), 144.1 (+, 1 C), 134.9 (+, 1 C), 132.7 (quat, 1 C), 115.0 (+, 1 C), 74.1 (quat, 1 C), 44.8 (-, 1 C), 22.2 (-, 1 C), 11.6 (+, 1 C).

MS (ES-MS): m/z (%) = 306.0 (84) $[M]^{-\cdot}$, 126.9 (100) I^-. $C_9H_{11}IN_2O_2$ (306.0).

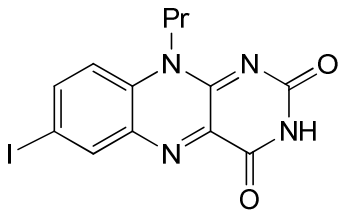
4-Iodo-N1-propylbenzene-1,2-diamine



Compound **2** (2050 mg, 6.70 mmol) and $SnCl_2$ x 2 H_2O (7550 mg, 33.49 mmol) were suspended in dry EtOH (10 mL) under nitrogen. The mixture was refluxed for 30 min, water was added (200 mL) and the pH was set to 9 by 2 N Na_2CO_3. The product was extracted into Et_2O (5 x 80 mL) and the organic layer was treated with activated charcoal. Drying over $MgSO_4$ and removing of the solvent yielded the title compound

as yellow oil (1520 mg, 5.50 mmol, 82%). The oxygen sensitive compound was used without further purification.

7-Iodo-10-propylbenzo[g]pteridine-2,4(3H,10H)-dione (3)



Crude 4-iodo-N1-propylbenzene-1,2-diamine (1520 mg, 5.50 mmol), $B(OH)_3$ (3400 mg, 55 mmol), alloxane mono hydrate (2650 mg, 16.5 mmol) were suspended in AcOH (20 mL) under nitrogen. The mixture was stirred in the dark for 16 h and poured on water. The mixture was cooled and the precipitate was collected on a Buchner funnel and washed with water and Et_2O. Drying of the residue gave **3** (1600 mg, 4.19 mmol, 76%) as orange solid, that was clean enough to be used in the next steps without further purification.

Mp 305°C (dec.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.42 (s, 1 H, NH), 8.47 (d, J = 2.0 Hz, 1 H, Aryl), 8.15 (dd, J = 9.0 Hz, J = 2.1 Hz, 1 H, Aryl), 7.77 (d, J = 9.1 Hz, 1 H, Aryl), 4.50-4.46 (m, 2 H, CH_2), 1.75-1.68 (m, 2 H, CH_2), 1.00 (t, J = 7.4 Hz, 3 H, CH_3).

^{13}C-NMR (150 MHz, DMSO-d_6): δ = 159.5 (quat, 1 C), 155.6 (quat, 1 C), 150.4 (quat, 1 C), 142.5 (+, 1C), 139.5 (+, 1 C), 139.4 (quat, 1 C), 135.9 (quat, 1 C), 132.3 (quat, 1 C), 118.4 (+, 1 C), 90.0 (quat, 1 C), 45.6 (-, 1 C), 19.8 (-, 1 C), 11.0 (+, 1 C).

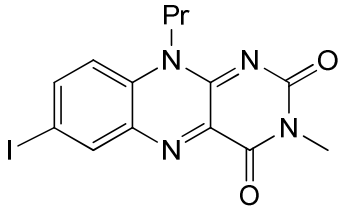
MS (ESI-MS (DCM/MeOH + 10 mmol·l^{-1} NH_4Ac)): m/z (%) = 382.9 (100) $[M + H]^+$, 423.9 (30) $[M + MeCN + H]^+$, 765.0 (32) $[2M + H]^+$.

HRMS (EI-MS 70 eV): m/z calcd for $C_{13}H_{11}IN_4O_2$ $[M]^{+\cdot}$: 381.99268; found: 381.9927 (Δ -0.08 ppm).

IR (ATR): $\tilde{\nu}$ = 3165, 3112, 3028, 2844, 1713, 1661, 1597, 1544, 1399, 1262, 835, 450 cm^{-1}.

UV/Vis (MeCN + 1.5% (v/v) DMSO): λ_{max} (ε) = 275 (42360), 328 (5400), 446 nm (9920).

7-Iodo-3-methyl-10-propylbenzo[g]pteridine-2,4(3H,10H)-dione (4)



Compound **3** (1146 mg, 3.0 mmol) was dissolved in dry DMF (25 mL) at 80°C under nitrogen. The solution was allowed to come to room temperature and K_2CO_3 (622 mg, 4.5 mmol) was added. After stirring the mixture for 30 min in the dark, MeI (0.94 ml, 15 mmol) was added. The mixture was stirred for additionally 24 h. After the addition of water (100 mL) and DCM (50 mL) the organic layer was washed with saturated NH_4Cl-sol. (2 x 20 mL) and water (20 mL). Drying over $MgSO_4$ and removing of the solvent gave crude **4** which was purified over silica (EA, R_f = 0.33) to give pure **4** (466 mg, 1.12 mmol, 37%) as orange solid.

Mp 275°C (dec.)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, 1 H, J = 2.0 Hz, Aryl), 8.10 (dd, J = 2.0 Hz, J = 9.0 Hz, 1 H, Aryl), 7.36 (d, J = 9.1 Hz, 1 H, Aryl), 4.65-4.59 (m, 2 H, CH_2), 3,51 (s, 3 H, CH_3), 1.95-1.82 (m, 2 H, CH_2), 1.11 (t, J = 7.4 Hz, 3 H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.4 (quat, 1 C), 155.7 (quat, 1 C), 148.6 (quat, 1 C), 143.8 (+, 1C), 141.7 (+, 1 C), 137.6 (quat, 1 C), 136.6 (quat, 1 C), 132.3 (quat, 1 C), 116.6 (+, 1 C), 89.5 (quat, 1 C), 46.3 (-, 1 C), 28.9 (+, 1 C), 20.5 (-, 1 C), 11.2 (+, 1 C).

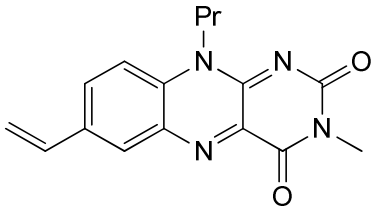
MS (ESI-MS (DCM/MeOH + 10 mmol·l^{-1} NH_4Ac)): m/z (%) = 396.9 (100) $[M + H]^+$.

HRMS (EI-MS 70 eV): m/z calcd for $C_{14}H_{13}IN_4O_2$ $[M]^{+\cdot}$: 396.00833; found: 396.0083 (Δ +0.05 ppm).

IR (ATR): $\tilde{\nu}$ = 3101, 2965, 1702, 1654, 1600, 1546, 1416, 1271, 1188, 971, 814, 410 cm^{-1}.

UV/Vis (MeCN + 1.5% (v/v) DMSO): λ_{max} (ε) = 277 (50440), 328 (6840), 450 nm (10400).

3-Methyl-10-propyl-7-vinylbenzo[g]pteridine-2,4(3H,10H)-dione (5)



Compound **4** (396 mg, 1.0 mmol), LiCl (170 mg, 4.0 mmol), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol) were added to a dry schlenk tube under nitrogen. Dry DMF (15 mL) and tributyl(vinyl)stannane (0.28 mL, 1.3 mmol) were added and the mixture was stirred in the dark for 40h. Saturated NH_4Cl-sol. (100 mL) was added and the mixture was extracted with DCM (3 x 25 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed. Column chromatography over silica ($CHCl_3$:MeOH = 50:1, R_f = 0.4) gave **5** as red solid (257 mg, 0.87 mmol, 87%).

Mp 227°C (dec.)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 2.0 Hz, 1 H, Aryl), 7.89 (dd, J = 9.0 Hz, J = 2.1 Hz, 1 H, Aryl), 7.53 (d, J = 9.0 Hz, 1 H, Aryl), 6.76 (dd, J = 17.6 Hz, J = 10.9 Hz, 1 H, CH), 5.86 (d, J = 17.6 Hz, 1 H, CH_2), 5.42 (d, J = 10.9 Hz, 1 H, CH_2), 4.63-4.57 (m, 2 H, CH_2), 3.445 (s, 3 H, CH_3), 1.91-1.78 (m, 2 H, CH_2), 1.05 (t, J = 7.4 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.7 (quat, 1 C), 155.9 (quat, 1 C), 148.5 (quat, 1 C), 137.1 (quat, 1 C), 136.1 (quat, 1 C), 136.0 (quat, 1 C), 134.1 (+, 1 C), 133.5 (+, 1 C), 132.0 (quat, 1 C), 130.1 (+, 1 C), 117.2 (-, 1 C), 115.4 (+, 1 C), 64.3 (-, 1 C), 28.8 (+, 1 C), 20.6 (-, 1 C), 11.2 (+, 1 C).

MS (ESI-MS (DCM/MeOH + 10 mmol·l^{-1} NH_4Ac)): m/z (%) = 297.0 (48) $[M + H]^+$, 593.2 (100) $[2M + H]^+$. (296.13).

HRMS (EI-MS 70 eV): m/z calcd for $C_{16}H_{16}N_4O_2$ $[M]^{+\cdot}$: 296.1273; found: 296.1279 (Δ -1.94 ppm).

IR (ATR): $\tilde{\nu}$ = 3088, 2965, 2876, 1702, 1639, 1586, 1546, 1510, 1427, 1280, 1189, 980, 768, 414 cm^{-1}.

UV/Vis (MeCN + 1.5% (v/v) DMSO): λ_{max} (ε) = 285 (48520), 336 (6160), 458 nm (9760).

Acrylic acid flavin copolymer 6

Flavin **5** (20 mg, 0.0675 mmol) was dissolved in acrylic acid (0.550 mL, 3.37 mmol). The mixture was degassed by passing nitrogen via a cannula through the solution for 15 min. AIBN (5 mg, 0.030 mmol) was added and the mixture was heated to 90°C under nitrogen. After 1h another portion of AIBN (5 mg, 0.030 mmol) was added. Heating was continued for another 3h. After cooling to room temperature $CHCl_3$ (5 mL) was added. The precipitate was filtered of and washed with $CHCl_3$. The residue was taken up in D_2O and freeze dried to yield **6** as yellow powder (20 mg). A flavin loading of $3.6 \cdot 10^{-4}$ mmol/mg copolymer was calculated from UV measurements.

IR (ATR): $\tilde{\nu}$ = 1707, 1554, 1452, 1229, 1173, 821, 603, 461 cm^{-1}.

UV/Vis (H_2O): λ_{max} = 222, 270, 344, 444 nm.

Styrene flavin copolymers 7 and 8

Flavin **5** (14.8 mg, 0.05 mmol), styrene (0.288 mL, 2.5 mmol) and divinylbenzene (2.8 µL/28.0 µL, 0.02 mmol/0.2 mmol) were dissolved in DMSO (2 mL). The mixture was degassed by three freeze-pump-thaw cycles. AIBN (5 mg, 0.030 mmol) was added and the mixture was heated to 60°C under nitrogen. After 1h another portion of AIBN (5 mg, 0.030 mmol) was added. Heating was continued for another 2h. At that time a yellow precipitate could be observed. After cooling to room temperature MeOH (5 mL) was added. The precipitate was filtered of, washed thoroughly with MeOH and dried. Copolymers **7** and **8** were obtained as yellow powders.

Copolymer 7

148 mg as yellow powder.

From UV measurements a flavin loading of $7.6 \cdot 10^{-5}$ mmol/mg copolymer was calculated.

IR (ATR): $\tilde{\nu}$ = 3026, 2922, 1671, 1601, 1556, 1493, 1452, 1064, 1028, 908, 756, 696, 542 cm^{-1}.

UV/Vis ($CHCl_3$): λ_{max} = 262, 314, 349, 455 nm.

Copolymer 8

170 mg of yellow powder.

IR (ATR): $\tilde{\nu}$ = 3025, 2921, 1673, 1601, 1557, 1493, 1452, 1028, 905, 756, 696, 544 cm^{-1}.

Methacrylate flavin copolymer 9

Flavin **5** (14.8 mg, 0.05 mmol), styrene (0.227 mL, 2.5 mmol) and divinylbenzene (22.7 µL, 0.16 mmol) were dissolved in DMSO (2 mL). The mixture was degassed by three freeze-pump-thaw cycles. AIBN (5 mg, 0.030 mmol) was added and the mixture was heated to 60°C under nitrogen. After 1h another portion of AIBN (5 mg, 0.030 mmol) was added. Heating was continued for another 2h. At that time a yellow precipitate could be observed. After cooling to room temperature MeOH (5 mL) was added. The precipitate was filtered of, washed thoroughly with MeOH and dried. Copolymer **9** (58 mg) was obtained as yellow powder.

IR (ATR): $\tilde{\nu}$ = 2949, 1728, 1666, 1592, 1556, 1435, 1265, 1159, 1045, 827, 710, 452 cm^{-1}.

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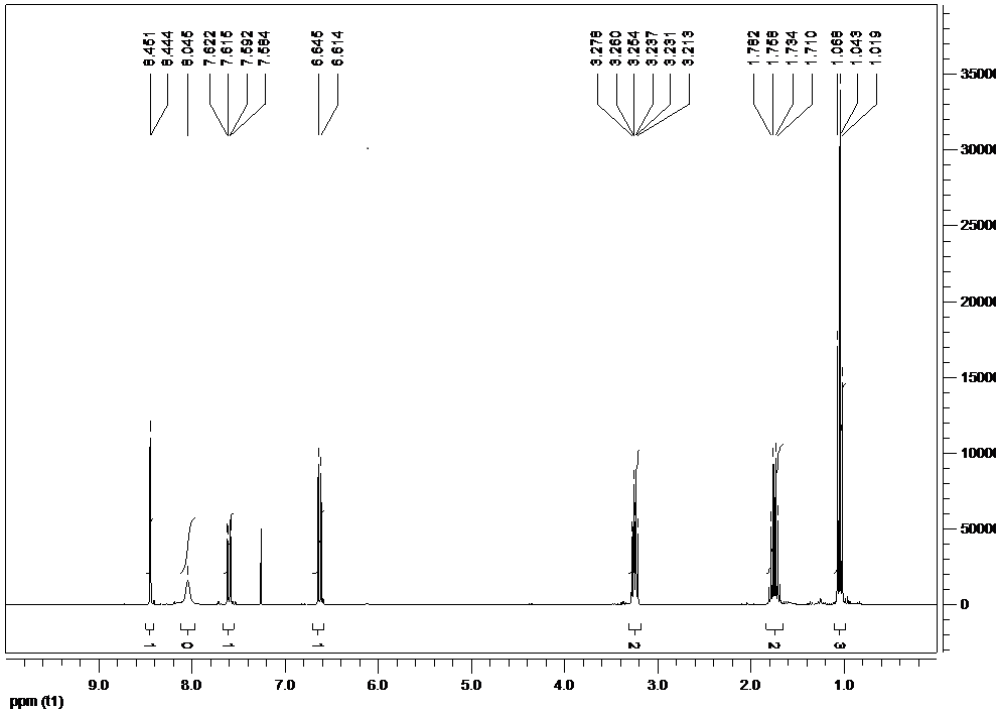
Appendix

1 H NMR of 4-Iodo-2-nitro-N-propylbenzenamine (2)



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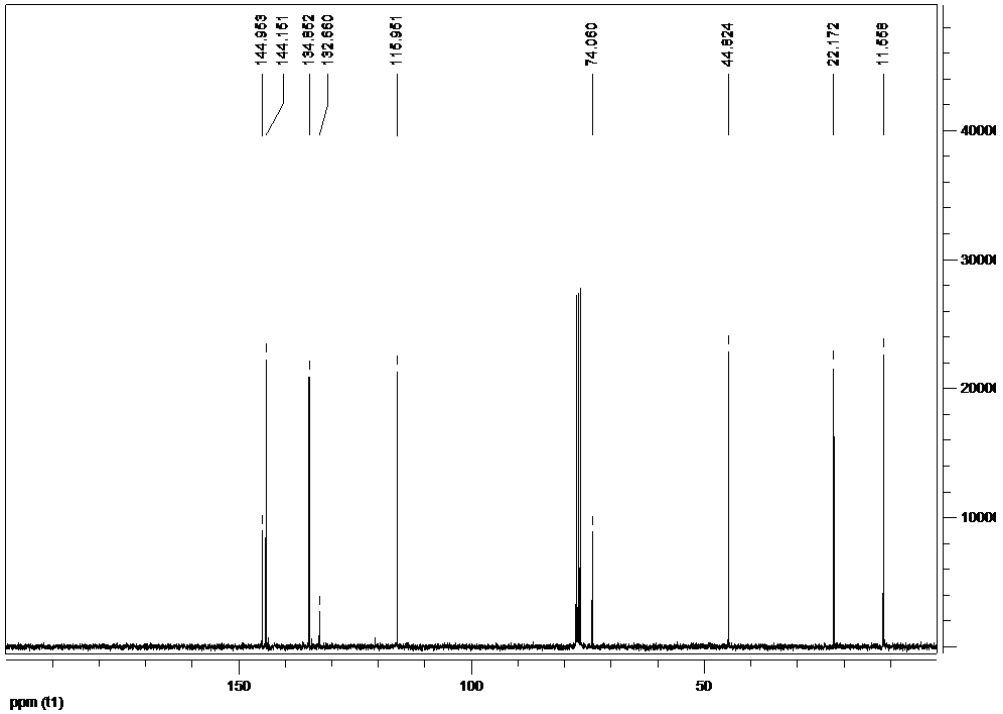

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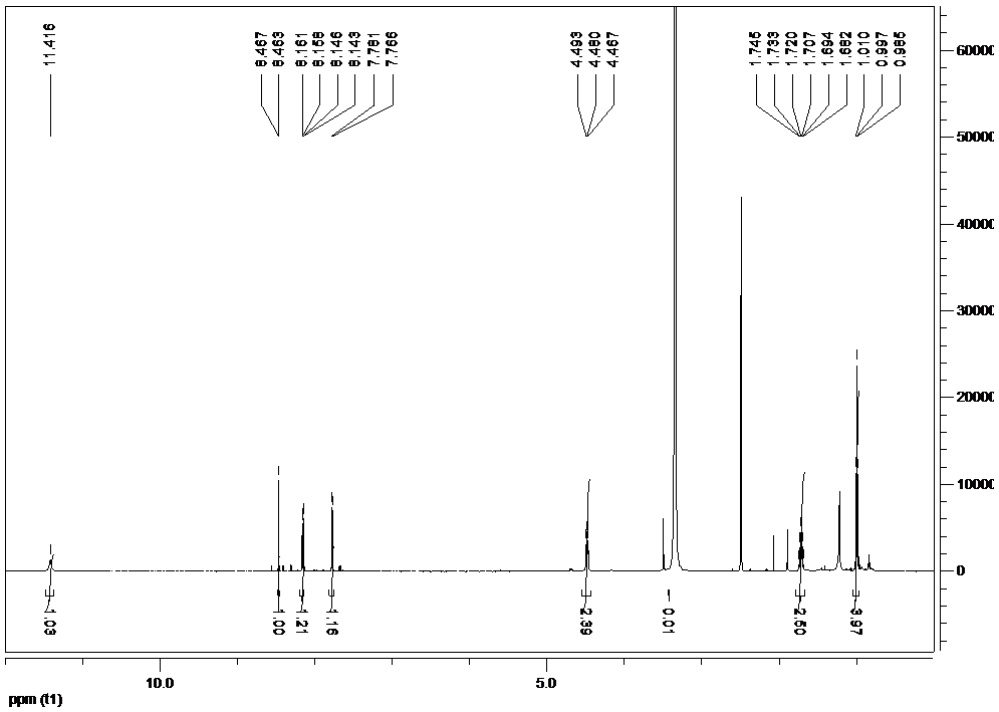

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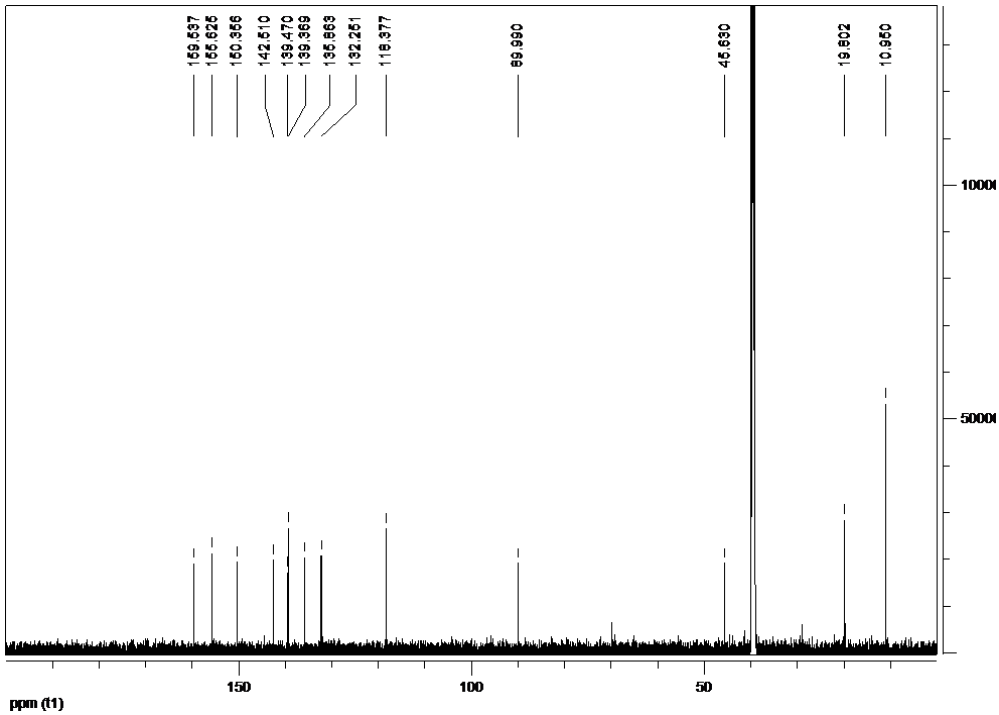

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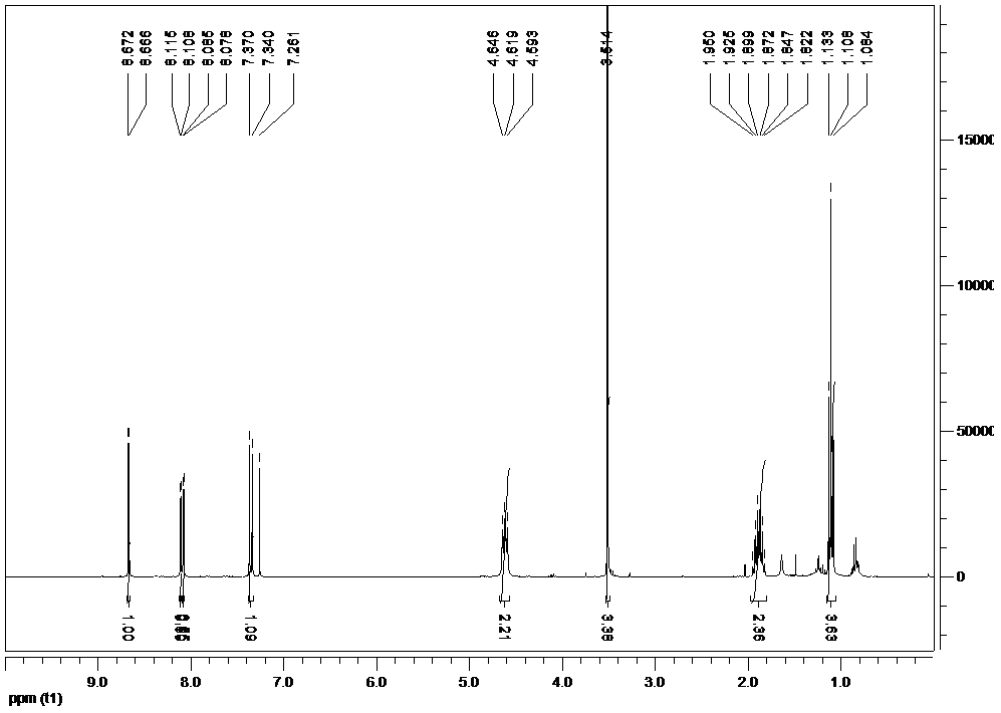

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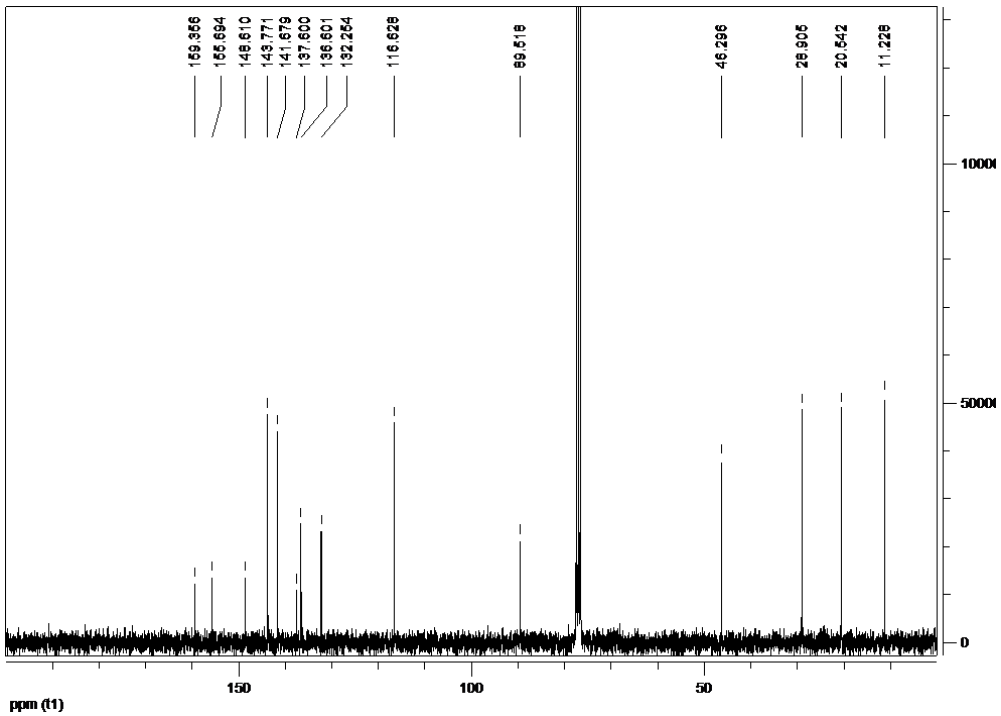

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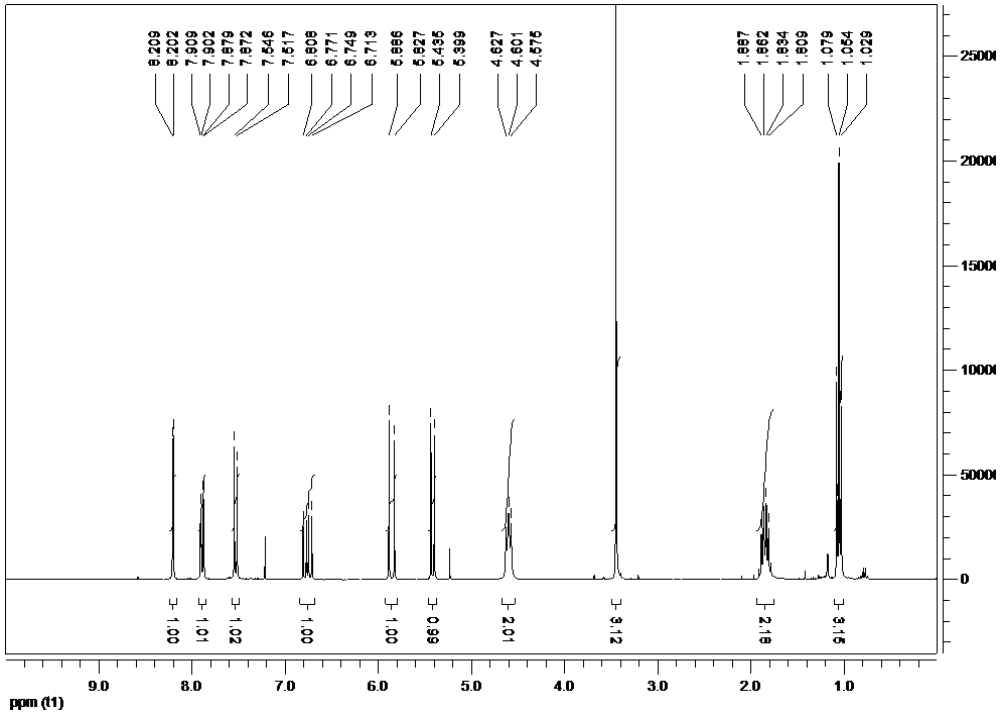
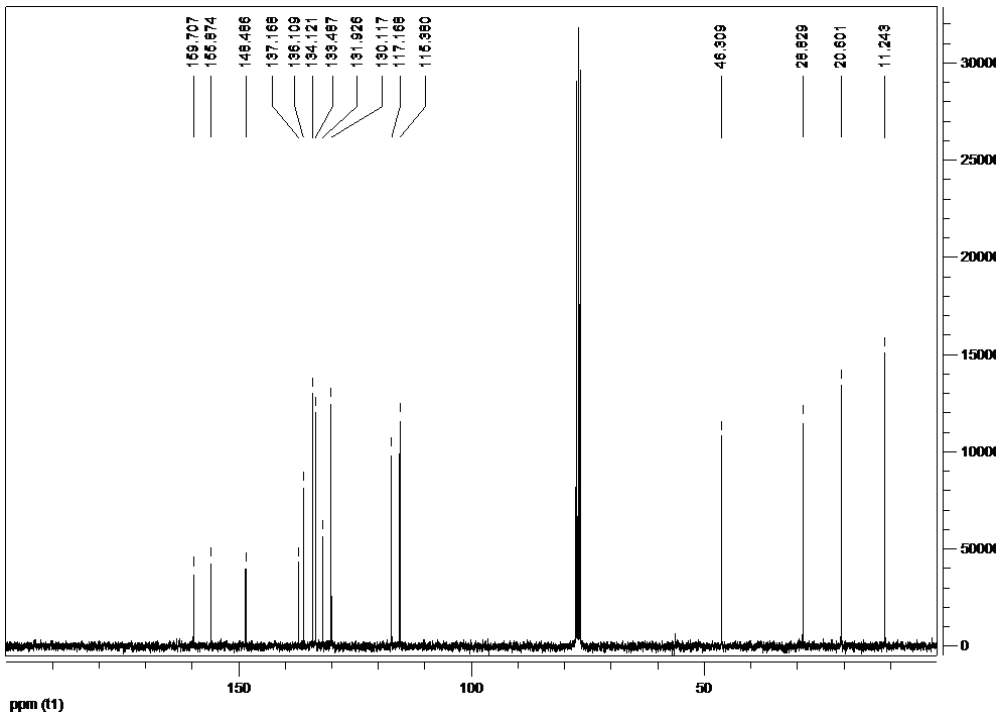


13 C NMR of 3-Methyl-10-propyl-7-vinylbenzo[g]pteridine-2,4(3H,10H)-dione (5)



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