Flavin-Based Photocatalysts

Dissertation

Zur Erlangung
des Doktorgrades der Naturwissenschaft
(Dr. rer. nat.)
an der Fakultät Chemie/Pharmazie
der Universität Regensburg

vorgelegt von
Jiří Svoboda
aus Prag
2007

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"*Nothing is impossible, if you can imagine it. That's what being a scientist is all about.*"

Prof. H. J. Farnsworth

Contents

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Chapter 1

Templated Photochemistry: Toward Catalysts Enhancing the Efficiency and Selectivity of Photoreactions in Homogeneous Solutions*

1. Introduction

Photochemical reactions are an important tool in modern synthetic chemistry. They often lead to products virtually inaccessible by thermal reactions and proceed along the excited-state pathway. However, it is often difficult to predict and control the outcome of photochemical transformations in homogenenous solutions where molecules behave rather chaotically. Their encounters in the thermal bath of Brownian motion occur within statistical distribution between all reaction geometries. Nevertheless, a defined mutual geometry is the origin of regio- or stereoselectivity of a chemical reaction, and improvement of reaction selectivity is therefore an attempt to overcome the equalising power of thermal fluctuations by additional control elements. Bias in the orientation may come from the reacting partners themselves (e.g., the Cram and Felkin–Anh rules of 1,2-stereoinduction),[1] chiral auxiliaries,[2] or selective reagents.[3] Orientation of the reactants can be also influenced by the widely used transition-metal catalysts with sophisticated ligands.[4]

On the other hand, spatial arrangement of molecules and their movement is more or less fixed in the solid state. Reactions in the crystal lattice may

*This Chapter was already published as a review, see: Svoboda, J.; König, B. *Chem. Rev.* **2006**, *106*, 5413–5430. For the ease of reading, structures, schemes and references are numbered separately from the rest of the Dissertation. Some references are therefore given twice, once in Section 8 of this Chapter, and once in Chapter 5 on page 119.

therefore ehibit higher selectivity than those in homogeneous solution. Photodimerisations of crystalline aromatic or olefinic compounds belong to the oldest known organic photoreactions. In this type of reactions, the crystal lattice locks the relative orientation of the photoreactive groups. If the orientation is favourable for reaction, reactivity increases, and vice versa. Unlike the photochemistry in a homogeneous solution, this leads to the selectivity for some of the photoproducts. Schmidt coined the term "topochemical" principle or "topochemistry" for (non)reactivity determined by a limiting distance between the reactive groups.[5–7] Although this model found widespread acceptance, many exceptions violating this concept were known from the very beginning.[8] Later, AFM techniques enabled experimental elucidation of solid-state photochemistry. This showed that the supramolecular arrangement of molecules in the crystal plays a more important role for reaction control than simple alignment of double bonds. Long-range molecular movements within crystal upon photochemical reaction and even, although rare, topotactic single-crystal to single-crystal reactions were found. The work is comprehensively covered by recent reviews.[9] Reactions of inclusion complexes are a variation of the solid-state photochemistry topic.[10] Here, co-crystals of a host compound and the starting materials of a photochemical reaction are used. Supramolecular arrangement may control the regio- and stereoselectivity of the photoprocess. Enantionselective photochemical conversion of chiral crystals into optically active products has been described.[11] Different approaches utilise zeolites as supramolecular hosts for photoreactions.[12] Internal complexation, or intra-crystalline adsorption, occurs by diffusion of the guest into the channels and cavities of the zeolite crystal and is size and shape selective. Complexation of organic compounds may reversibly depend on temperature. The geometry of zeolite restricts conformation and orientation of included guests and their reaction partners, leading to more selective reactions. In the absence of any low-energy electronic states of the zeolite, photoreaction occurs only with the included guest.

The common disadvantage of solid-state photoreactions is the difficult prediction and control of reaction selectivity. Finding the suitable crystal, co-crystal, or inclusion complex for the desired regio- or stereoselective outcome of a given reactions remains a challenge. Therefore, an attractive strategy is to transfer the topochemical control from the solid to homogeneous solution using suitable templates. Such reactions are easier to analyse, design and optimise. We wil discuss recent attempts in this field in the following sections.

The scope of this review is limited to templated reactions in a homogeneous solution which are initiated or mediated by light. By template we mean a host molecule (sometimes containing a sensitiser) of various construction (a rational design, cyclodextrin, cucurbituril, DNA, etc.) which reversibly binds a substrate and typically does not become part of the product. The substrate undergoes a truly photochemical process or at least a

process which is light-mediated. Reactions where light is only required to pre-form a species which undergoes a thermal process are therefore not included. In the ideal scenario the template should act as a catalyst and be present in subequimolar amounts, but this aim could not be always achieved due to (i) low association constants, (ii) undesired photochemical reactions in the unbound state which often competed with the desired reaction, or (iii) inhibition of the template by the reaction product. To illustrate the progress and development in the rapidly advancing field, we extend the discussion of catalytic processes by closely related non-catalytic examples and auxiliary approaches where the template is covalently bound to the substrate but could be easily regenerated. We focus on reactions in true homogeneous solutions only and do not consider any confined media, such as crystals, co-crystals, any kinds of solids, polymers, solid phase + gas reactions, reactions in zeolites, micelles, membranes, compartmented solutions, aggregates, or reaction in and of liquid crystals. We refer the interested reader to reviews and examples discussing the topics exceeding the scope of this review[13] as well as to recent reviews related to the discussed topic.[14]

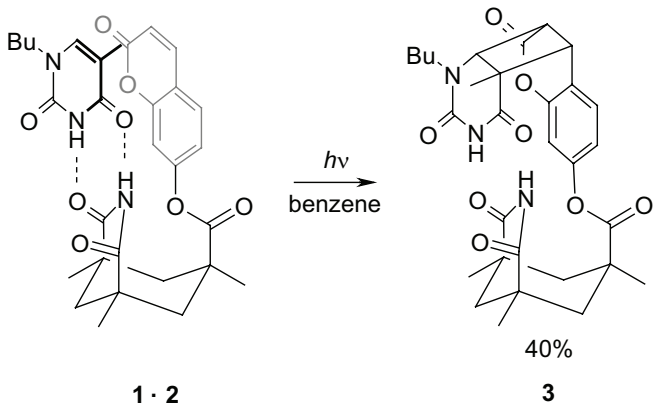
The division of the sections is somewhat artificial as they partly overlap and some of the work could be featured in several of them. However, we tried to divide them in a way to make reading and understanding easier. The survey begins with photoreactions in which selectivity was achieved by shielding one face of a reactant. Not all the discussed examples used a catalytic template, but as we reasoned above, they illustrate the conceptual development over the last years. The next group of examples mimics topochemical reactions in the solid state by non-covalent assemblies where the substrates are pre-organised in a defined way by the host molecule. Examples using DNA as a template are followed by contributions featuring covalently bound sensitiser and a substrate-binding site to enhance the efficiency of energy- and electron-transfer processes. Finally, photoreactions in molecular flasks or soluble cavities establish a relationship to reactions in zeolites or inclusion complexes.

2. Templates Containing a Shield

This section describes those examples which bind a substrate by non-covalent interactions to distinguish between different sides of attack and thus direct the course of a photochemical transformation by the presence of a steric hindrance.[15,16] Some of the reactions are bimolecular and some intramolecular. However, in all cases, direction of the approach is not governed by the size and shape of the substrate itself but by stereodifferentiation of its two faces by the template's shield (stereoexclusive approach).

Pioneering work in this area was carried out by Mori *et al.* who studied a reaction between compound **1**, which contains a covalently bound imide

binding site and a coumaring group, and 3-butylthymine **2** (Scheme 1).[17,18]

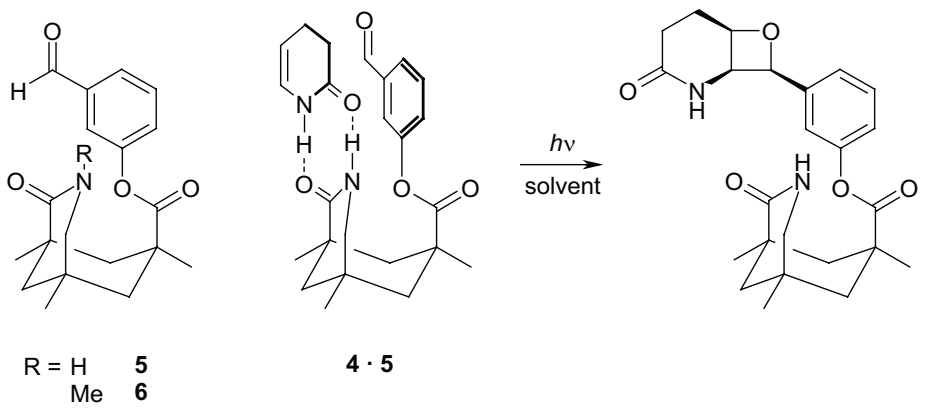


SCHEME 1. Stereoselective cycloaddition of coumarin and thymine

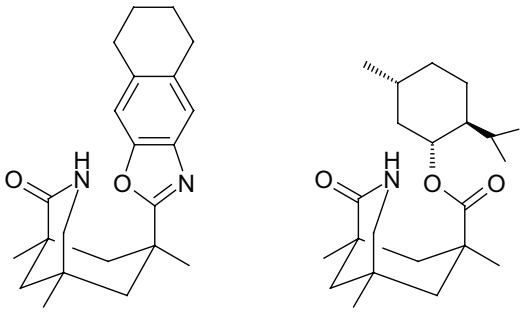
We are aware of the fact that in this example compound **1** did not act as a catalyst because after the photochemical reaction, cycloadduct **3** was covalently bound to the template which could not be reused. However, we wish to include this example for "historical" reasons to illustrate the progress in the field which is dynamic and quickly developing. The presence of the covalently bound recognition site increased the reaction rate and the cis-syn/cis-anti ratio up to 96:4

A similar—still noncatalytic—example from Bach *et al.* described the stereoselective Paternó–Büchi reaction of 3,4-dihydro-1*H*-pyridine-2-one **4** with a covalently host-bound benzaldehyde **5**.[19,20] Substrate **4** was bound to chiral host **5** by two directional hydrogen bonds, and its enantiotopic faces were thus differentiated (Scheme 2). Diastereoselectivity depended on solvent polarity in accordance with the expectation: polar solvents such as acetonitrile disturbed formation of the complex and lowered the diastereomeric ratio, while non-polar solvents such as benzene favoured formation of the complex. Diastereomeric ratios up to 95:5 and up to 56% yield were observed (toluene, $-10\,^{\circ}\mathrm{C}$). The importance of hydrogen bonding for the steroselectivity was proved by a control experiment with the *N*-methylated host **6**, which does not allow face discrimination and showed no stereoselectivity.

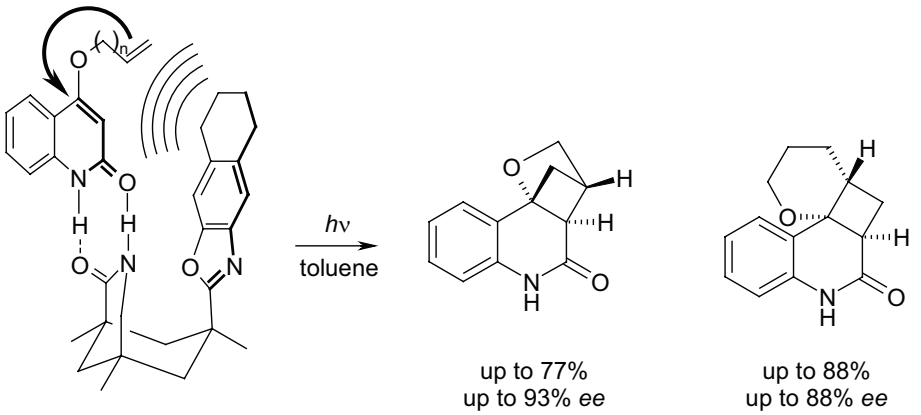
The next steps toward efficient catalytic asymmetric induction were chiral templates containing benzoxazole (host **7**) or menthol (host **8**) as steric shields (Scheme 3). Templates **7** and **8** were used in an intramolecular [2+2] photocycloaddition of substituted 2-quinolones **9** (Scheme 4).[21] The menthol residue did not sufficiently discriminate the two sides of the substrate and the ee values remained low when using the template **8**. The benzoxazole-containing host **7** proved superior, and high yields and ee values could be



SCHEME 2. Stereoselective Paternó–Büchi reaction and its predominant product



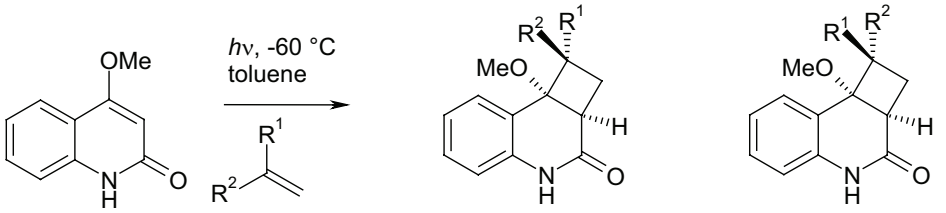
SCHEME 3. Chiral templates used for catalytic asymmetric induction



SCHEME 4. Intramolecular [2+2] cycloaddition

achieved by use of more than one equivalent of the host, thus forcing association with the substrate. The four-membered ring in **10a** was formed with up to 79% yield and 84% ee (77% yield and 93% ee of **ent-10a** is reported for the reaction at −60 °C with 2.6 eq. of host *ent*-**7**) and the six-membered ring in **10b** with up to 88% yield and an 88% ee (−15 °C, toluene, 1.2 eq. of host **7**).

Photocycloaddition of 4-methoxy-2-quinolone **11** with various olefins **12** was studied in detail.[22] Cycloaddition of **11** with symmetric olefin **12a** in the presence of chiral host **7** yielded a single product **13**, which was formed with 61% yield and 92% ee (Scheme 5). Non-symmetric olefins **12b–f** gave

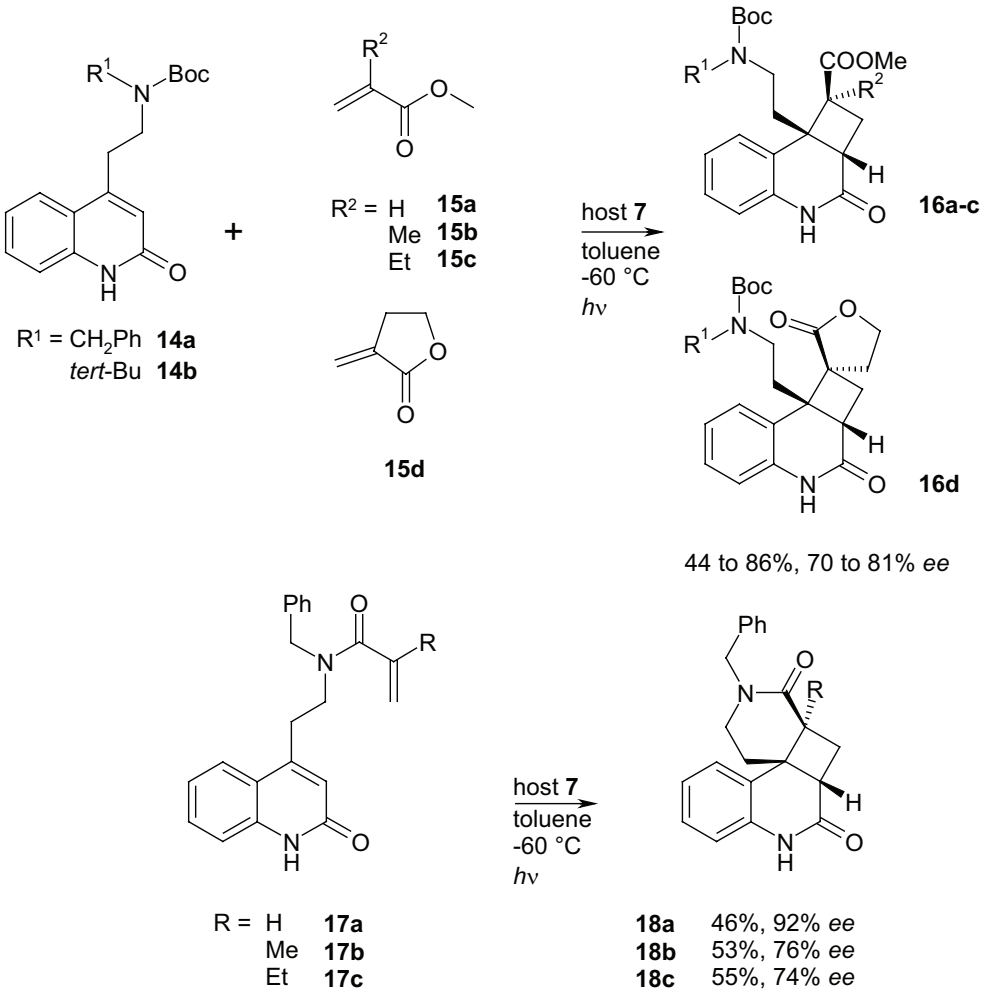


R^1 = Et	R^2 = Et	**12a**
$CH_2CH_2CH_2OH$	H	**12b**
CH_2OAc	H	**12c**
OAc	H	**12d**
Ph	H	**12e**
COOMe	H	**12f**

SCHEME 5. [2+2] Photocycloaddition of 4-methoxy-2-quinolones; See text for yields and ee values

a mixture of two diastereomers **13**. Olefins **12b–c,f** showed diastereoselectivity in favour of isomer **13a** (ratios **13a**:**13b** were 90:10 or higher, yields 80–84%) with ee values from 81% to 92%. Styrene **12e** favoured formation of the corresponding endo-isomer **13b** (ratio **13a**:**13b** was < 5:95, yield 29%) with 83% ee. Olefin **12d** yielded a 63:27 mixture of products **13a** and **13b** (overall yield 89%). However, both of the products were formed highly enantioselectively (**13a** with 93% ee, **13b** with 98% ee). Replacing the chiral host by its enantiomer resulted in product enantioselectivity reversal.

Enantioselectivity of [2+2]-photocycloaddition of protected 4-(2'-aminoethyl)-quinolones **14** with acrylates **15** could also be successfully manipulated by the template **7** (Scheme 6, top).[23] In its presence, the exo products **16** were isolated with 44–86% yield and 70–81% ee. Higher ee values were observed at lower temperatures. Superstoichiometric amounts of the template **7** (2.5 eq. based on the quinolone **14**) had to be employed in order to overcome the self-association of **14** to which the incomplete chirality transfer was attributed. Variation of quinolone **14** or acrylate **15** concentrations

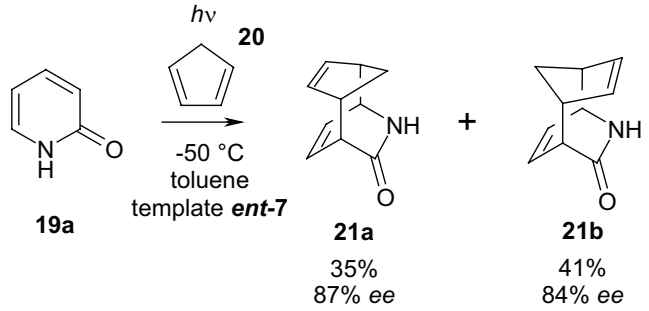


SCHEME 6. Enantioselective inter- and intramolecular cycloaddition of 4-(2'-aminoethyl)-quinolones; See text for individual yields of the intramolecular cycloaddition

had no influence on the observed ee value. At −60 °C, there were no detectable side reactions due to hydrogen abstraction. Compounds **17** cyclised in the presence of the chiral host **7** to render the tetracyclic products **18** in an intramolecular fashion (Scheme 6, bottom). Yields of the reaction were lowered by competing intramolecuar oligomerisation. However, observed ee values were higher than the aforementioned intermolecular reaction because the oligomerisation reduced the extent of racemic intramolecular reactions not templated by the host. This is best illustrated by the reaction of **17a** which gave product **18a** with the lowest yield (46%) but highest ee value (92%).

The template **7** was successfully used for the stereoselective Diels–Alder reaction of photochemically generated (*E*)-*o*-quinodimethane with alkenes[24] and for enantioselective radical cyclisation reaction of 4-(4'-iodobutyl)quinolones.[25]

The chiral host **7** found another application for the stereoselective [4+4] photocycloaddition of 2-pyridone **19a** to cyclopentadiene **20** (Scheme 7).[26] Upon irradiation in the presence of the chiral host *ent*-**7**, a mixture of di-

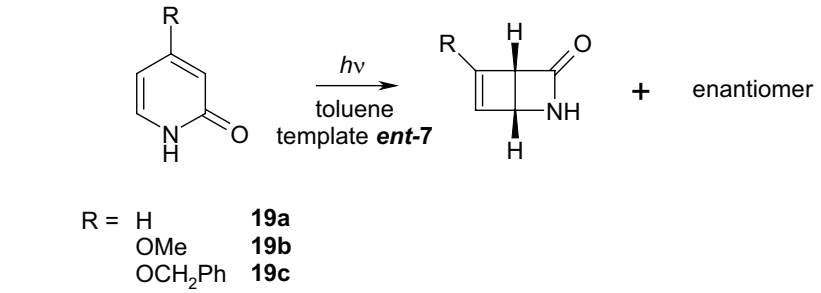


SCHEME 7. [4+4] Photocycloaddition of 2-pyridone to cyclopentadiene

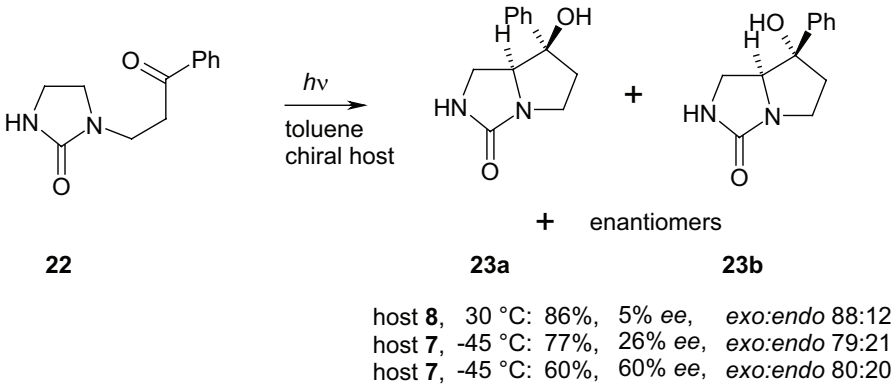
astereomeric products **21**, which were formed with significant ee values, was obtained.

Intramolecular [4π] cyclisation of 2-pyridone **19a** was considered, too.[26] Since the reaction is known to proceed with low yields, 4-substituted pyridones **19b,c**, which undergo cyclisation more readily, were investigated. The reaction rate and yield increased with temperature, but on the other hand, low temperature was required for high association of the substrate with the host. The highest stereoselectivity (23% ee, 51% yield) was observed for 4-benzyloxy-2-pyridone **19c** at −20 °C (Scheme 8).

Another stereoselective photochemical reaction described was the Norrish–Yang cyclisation.[27] Upon irradiation in the presence of chiral host **7** or **8**, imidazolidinones **22** yielded a mixture of stereoisomers **23** (Scheme 9). The exo isomer **23a** prevailed in the reaction mixture with a ratio of about 4:1 without a significant influence of the reaction temperature. The ee values of the exo isomer **23a** depended on temperature and increased at lower



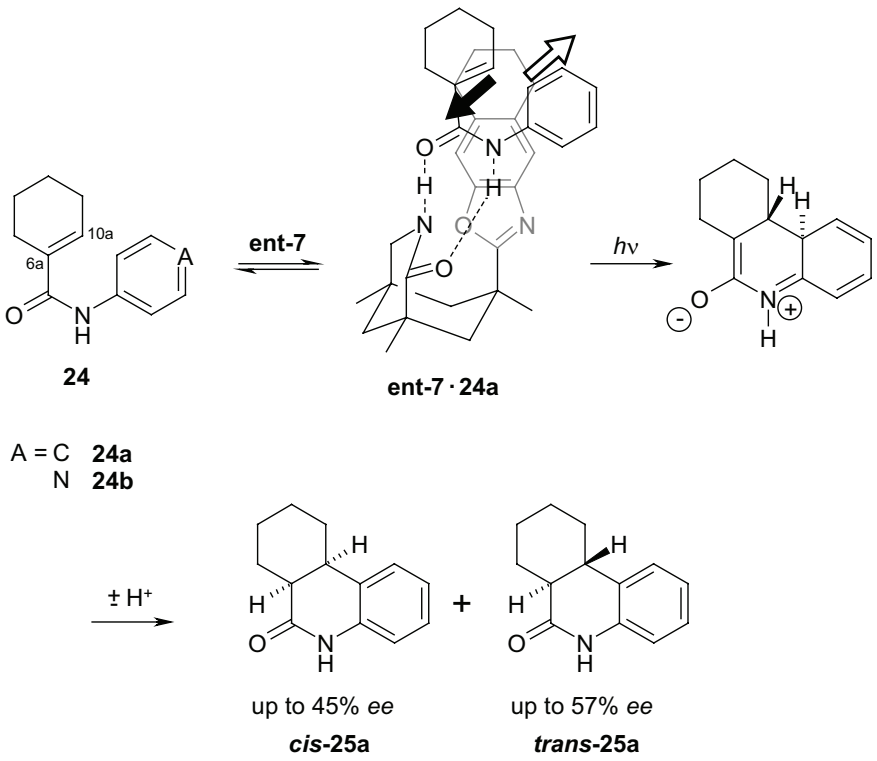
Scheme 8. [4π] Cyclisation of 2-pyridones



Scheme 9. Norrish–Yang cyclisation

temperatures. Similar to the aforementioned example, the benzoxazole-containing host **7** induced higher ee values than its menthol analogue **8** because of better face differentiation. The best results reached 60% ee (toluene, −45 °C). Within the error limit, the enantiomeric chiral host *ent*-**7** delivered the same ee, predominantly giving the product *ent*-**23a**. The ee values of the minor endo diastereomer **23b** were not always determined, but they were usually lower than for the exo isomer **23a**.

The chiral template *ent*-**7** was also used for stereoselective [6π] photocyclisation of compound **24a**.[28] The cyclohexene ring located in the vicinity of the shield preferred turning away from it during the photochemically allowed conrotatory ring closure due to steric reasons (Scheme 10). Therefore, the zwitterionic intermediate was formed stereoselectively in the presence of the template. Upon protonation by the host, which acted as a Brønsted acid, the zwitterionic intermediate tautomerised to yield the products **25a**. Since the configuration at carbon atom C_{10a} was already fixed, protonation of carbon atom C_{6a} could give rise to the cis product *cis*-**25a** or to the trans product *trans*-**25a.** Dissociation of the intermediate from the template, which was required for the protonation, opened its *re* face (with respect to the carbon atom C_{6a}), and preference for the trans product was therefore

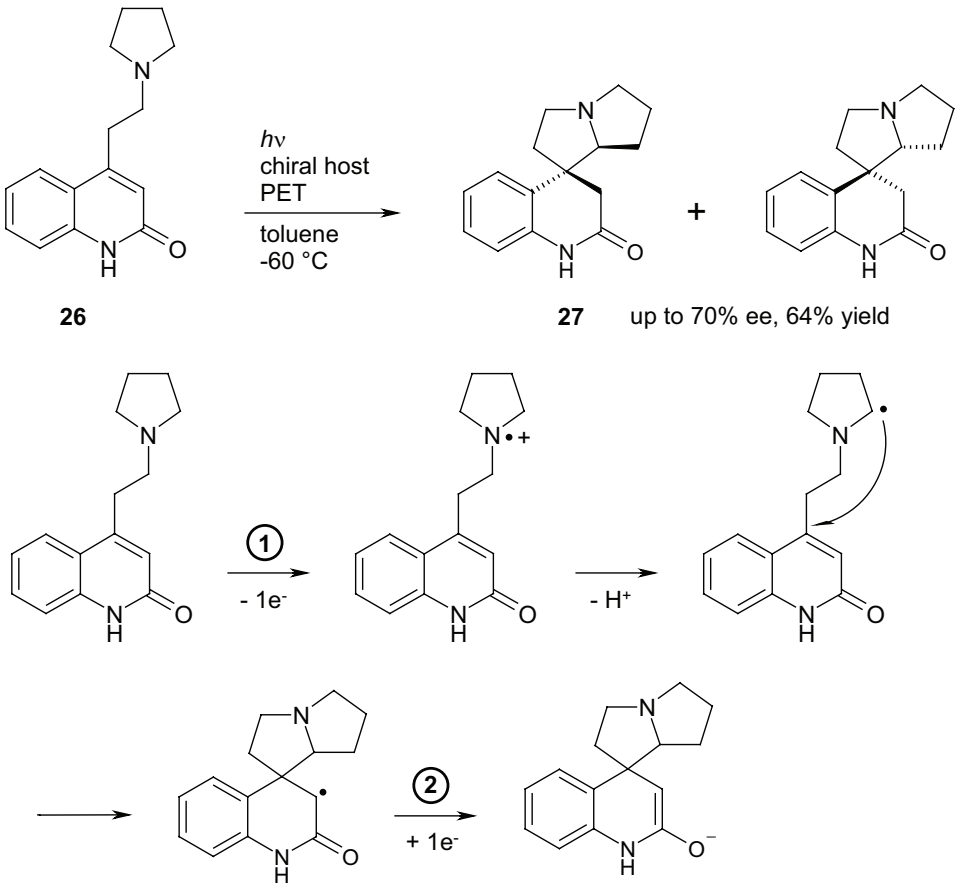


SCHEME 10. Enantioselective [6π] photocyclisation; Yields and ee values depend on conditions of the reaction, see text for discussion

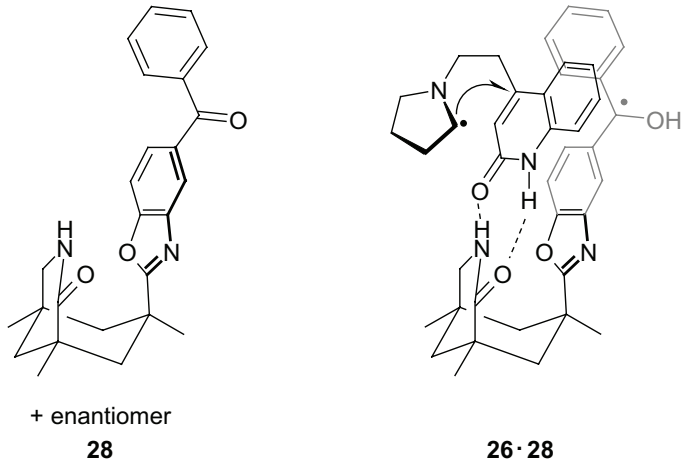
observed. Thus, the major product *trans*-**25a** (trans:cis ratio up to 73:27 in toluene at −55 °C) was obtained with up to 57% ee (toluene, −55 °C). The minor cis product *cis*-**25a** was obtained with up to 45% ee (toluene, 35 °C). Similar experiments with the analogous **24b** rendered very low ee values, and its cyclisation was therefore not studied in detail.

Prochiral quinolone **26** cyclised to a chiral pyrrolizidine **27** by a photoinduced electron-transfer reaction (PET) in the presence of chiral host **28** (Schemes 11 and 12).[29] The chiral host **28** fulfilled three conditions: (i) it contained an efficient sensitiser of the electron-transfer process in close proximity to the substrate, (ii) it bound the substrate by two directional hydrogen bonds, and thus (iii) it differentiated its two enantiotopic faces. The reaction proceeded successfully in the presence of 5–30 mol % of the chiral host **28**, reached ee values up to 70%, and gave yields up to 64% (higher values were observed with higher amounts of template). Again, use of the enantiomeric form of the host led to reversion of the enantiomeric preference. The results were also compared to a reaction where a mixture of the benzoxazole chiral host **7** and *p*-methoxybenzophenone was used, and the importance of sensitiser proximity was thus proved.

The intramolecular enone–olefin [2+2] photocycloaddition of quinolone

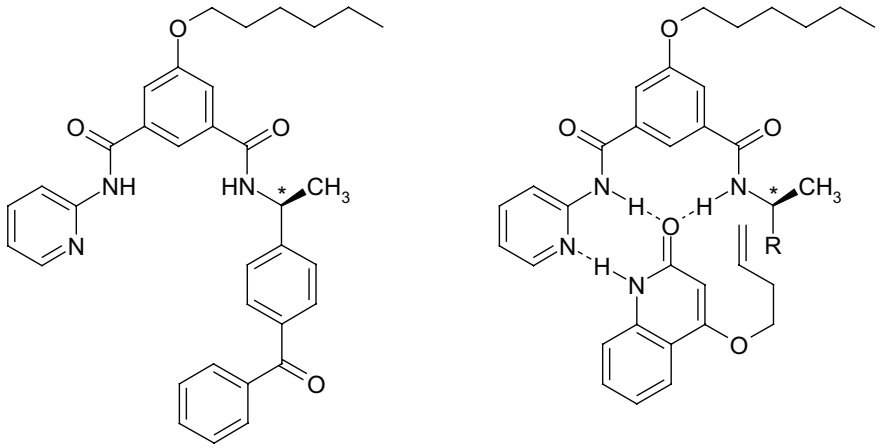


Scheme 11. Enantioselective photochemical formation of pyrrolizidine **27** and its proposed mechanism; Key: (1) photoinduced electron transfer, (2) back electron transfer from template



Scheme 12. Chiral host **28** used for enantioselective cyclisation and its function

29 reported by Cauble *et al.*[30] showed that in the absence of a rigid aromatic shield, some enantioselectivity is still achieved in catalytic templated photochemistry. The "sensitising receptor" **30** contains a complementary hydrogen-bonding pattern to bind the substrate **29** (Scheme 13). The pres-



SCHEME 13. "Sensitising" receptor **30** used for stereoselective [2+2] photocycloaddition of quinolone **29** and its complex with the substrate; R = 4-C_6H_4(C=O)Ph

ence of the receptor **30** increased the efficiency of the cyclisation reaction and allowed for its stereoselective course at lower temperatures upon which the asymmetric induction strongly depended (highest ee values of ca. 20% were achieved at −70 °C). The reaction required only catalytic amounts of the receptor **30**. Experiments with 1:1 and 4:1 substrate **29**:receptor **30** mixtures gave comparable enantiomeric excess, which indicates that the observed level of asymmetric induction indeed results from the intrinsic enantiofacial bias conferred by association of quinolone **29** to the sensitising receptor.

3. Photochemical Reactions in Non-Covalent Assemblies

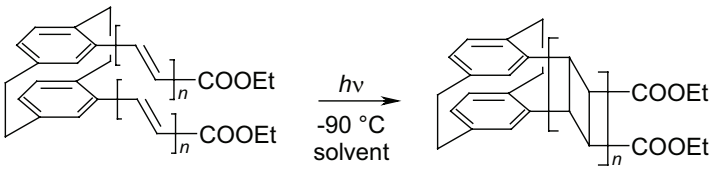
As already stated in the Introduction (page 1), the spatial arrangement of molecules in the crystal is defined by the rigid crystal lattice and selective photochemical reactions could be thus achieved in the solid state. We continue our review with examples where supramolecular templates mimic the spatial fixation in crystals by pre-organisation of the reaction components within a non-covalent assembly in an advantageous and better defined geometry, thus leading to an increase in reaction rate and selectivity.

In the first part, development of a covalent substitute for the dimerisation of cinnamic acid is described. In this case, the two components were pre-

organised within a covalent assembly which could be, however, considered temporary and reusable, and we therefore include this work as well. The second part discusses truly non-covalent assemblies and begins with systems which employ the template effect of alkali or alkaline earth metal cations on coronand systems, and concludes with systems which utilise recognition of di- or triaminotriazine by barbiturate and other suitable molecules.

3.1 Temporary Covalent Pre-organisation

In the [2.2]paracyclophane system **31a**, the two reactive parts of the molecule were kept in close proximity (ca. 3 Å), thus resembling the arrangement in the crystal.[31–33] It was shown that the [2π+2π] cycloaddition of this and vinylogous cyclophane systems **31a–c** to cyclobutane derivatives **32** proceeded with excellent yield and stereoselectivity (Scheme 14).



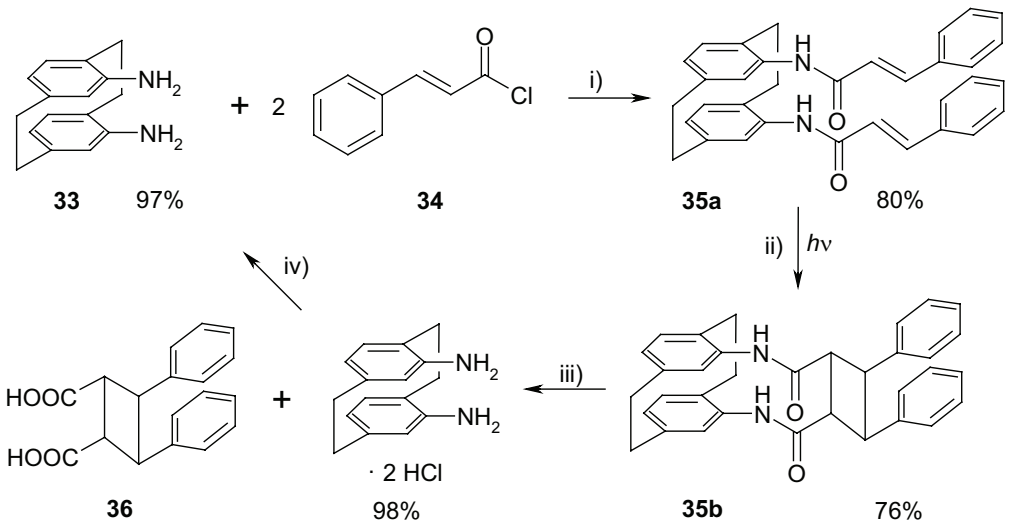
n =	1	**31a**	**32a**	100%
	2	**31b**	**32b**	> 90%
	3	**31c**	**32c**	83%

Scheme 14. Photochemical synthesis of [n]ladderanes

Interestingly, the effect of the pseudolattice extended beyond its immediate vicinity.[34] However, this advantage could not be employed in catalytic reactions nor could the template be regenerated, as the reacting centers were connected by C–C bonds. Therefore, a similar system **33** in which the template served as an auxiliary and could be recycled was prepared.[35] The rigid cyclophane lattice bore two connection points to which the actual reaction substrates **34** bound. Once bound in a conjugate **35a**, they could undergo the desired photochemical reaction yielding **35b**. After removal of the β-truxinic product **36**, which was formed exclusively, the rigid cyclophane space **33** was regenerated. The amide bonds were easy to form and easy to cleave and thus served as a temporary linkage between the template **33** and the substrate **34**. All individual steps of the cycle ran with good to excellent yields (Scheme 15).

3.2 Non-Covalent Intramolecular Pre-Organisation

The efficiency of dimerisation of anthracene, incorporated in a macrocyclic crown ether or tethered by an ethylene glycol chain, was influenced by com-

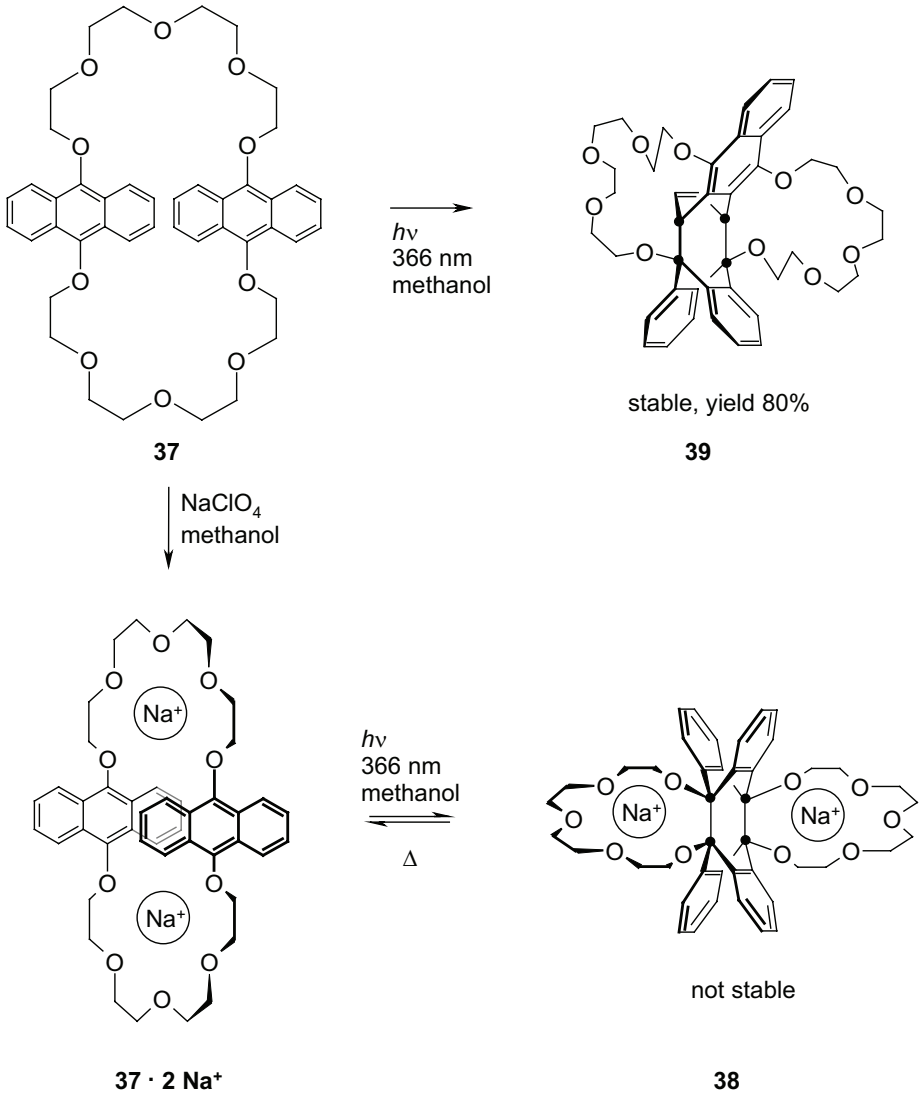


SCHEME 15. Temporary use of the cyclophane unit for topochemical reaction control in solution; Conditions: (i) 1,4-dioxane, r.t., 24 h, (ii) hν, acetone, 7 h, (iii) conc. hydrochloric acid, reflux, 24 h, (iv) solid potassium hydroxide

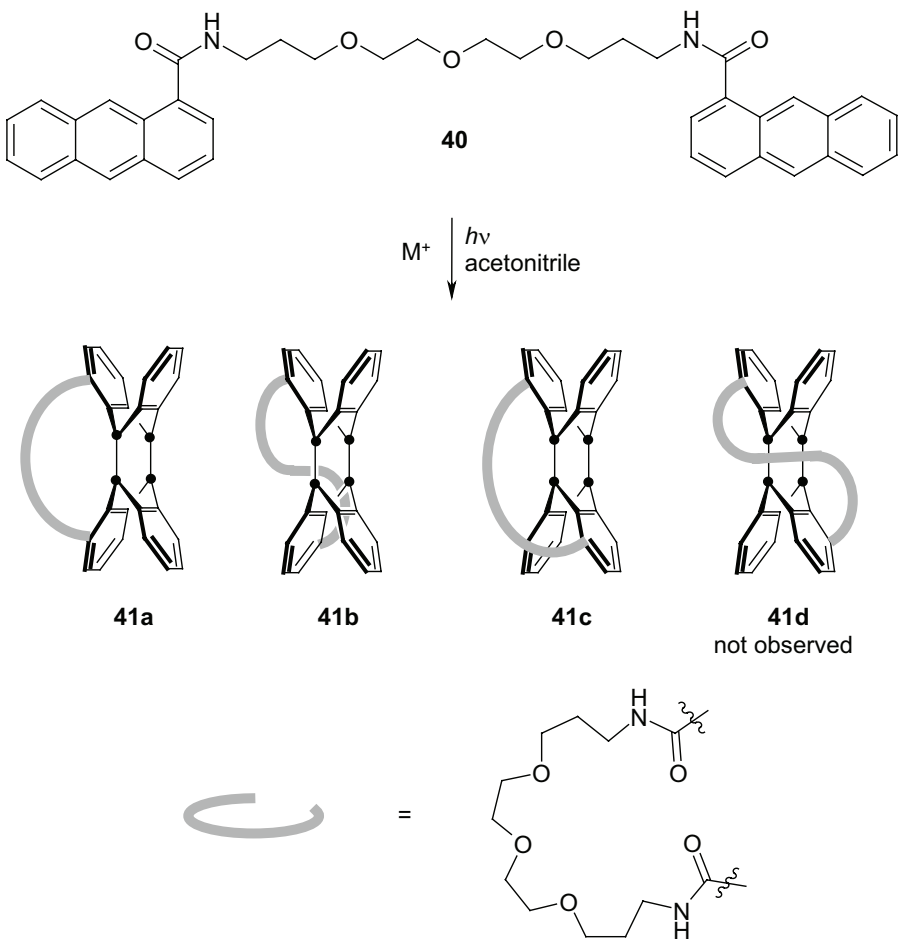
plexation of guest ions.[36–41] In the simpler cases, efficiency and regioselectivity of the cycloaddition responded to only one chemical input: either to the presence of alkali metal cations[38] or to the presence of alkaline earth metal cations.[39]

The regioselectivity of the photocycloaddition of two anthracene units in **37** was subject to the presence of sodium ions.[38] If present, a symmetric product **38** (Scheme 16) was obtained (quantum yield $\Phi_R = 8.3 \times 10^{-3}$ in methanol), while in the absence, a non-symmetric photocycloaddition product **39** was obtained with much lower quantum yield ($\Phi_R = 1.9 \times 10^{-4}$ in methanol). Compound **38** is not thermally stable, slowly reverting to the starting material at room temperature. Potassium ions could also be used to yield the symmetric regioisomer **38**, but the quantum yield of the process ($\Phi_R = 1.8 \times 10^{-3}$ in methanol) is lower.

The regioselectivity of photocycloaddition of bis-anthracene **40** responded to the presence of alkaline earth metal ions.[39] Upon irradiation, three regioisomers were formed; isomer **41d** was not detected (Scheme 17).[42,43] With increasing ion radius of the alkaline earth metal ion present, preference for regioisomer **41c** was observed at the cost of isomer **41a** (the ratio of **41c** increased from 17% with magnesium ions to 46% with barium ions, the ratio of **41a** decreased from 81% with magnesium ions to 54% with barium ions). Formation of isomer **41b** was prohibited in all cases (relative isomer ratio 2% with magnesium ions down to 0.1% in the presence of barium ions). Alkali metal ions did not influence the ratio of the isomers. Identical experiments



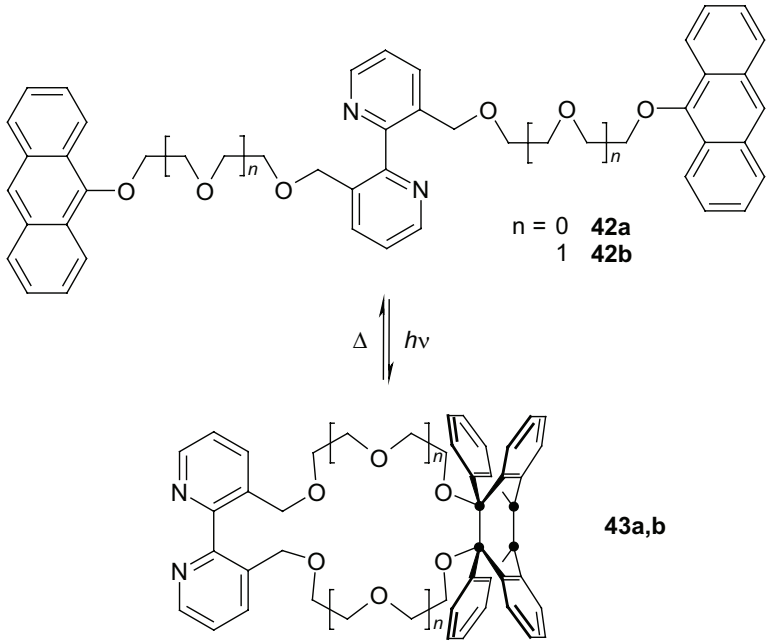
Scheme 16. Cation-templated dimerisation of anthracene



SCHEME 17. Dimerisation of two glycol-linked anthracenes; All possible isomers shown, product ratio depended on metal cation present (see text). Preparative yields were not published

were carried out with anthracenes linked in the 2-position. However, in this case, no effect of alkali or alkaline earth metal ions on the regioisomer distribution was observed.

It was also possible to construct a system which exhibited the logical "OR" operation and responded to two different stimuli.[41] Molecule **42** contained two anthracene units which dimerised upon irradiation, two glycol chains for binding of alkali metal ions, and a 2,2'-bipyridyl unit for binding of transition-metal ions (Scheme 18). Upon irradiation of compound **42** in the presence of sodium or mercury(II) ions, the quantum yield of dimerisation increased 2-fold as opposed to the reaction in the absency of any cation template ($\Phi_R = 0.23$ in the absence of template, 0.37 in the presence of mercury(II) ions, and 0.43 in the presence of sodium ions or both of the cations, measured for compound **42a** in acetonitrile, and $\Phi_R = 0.19$

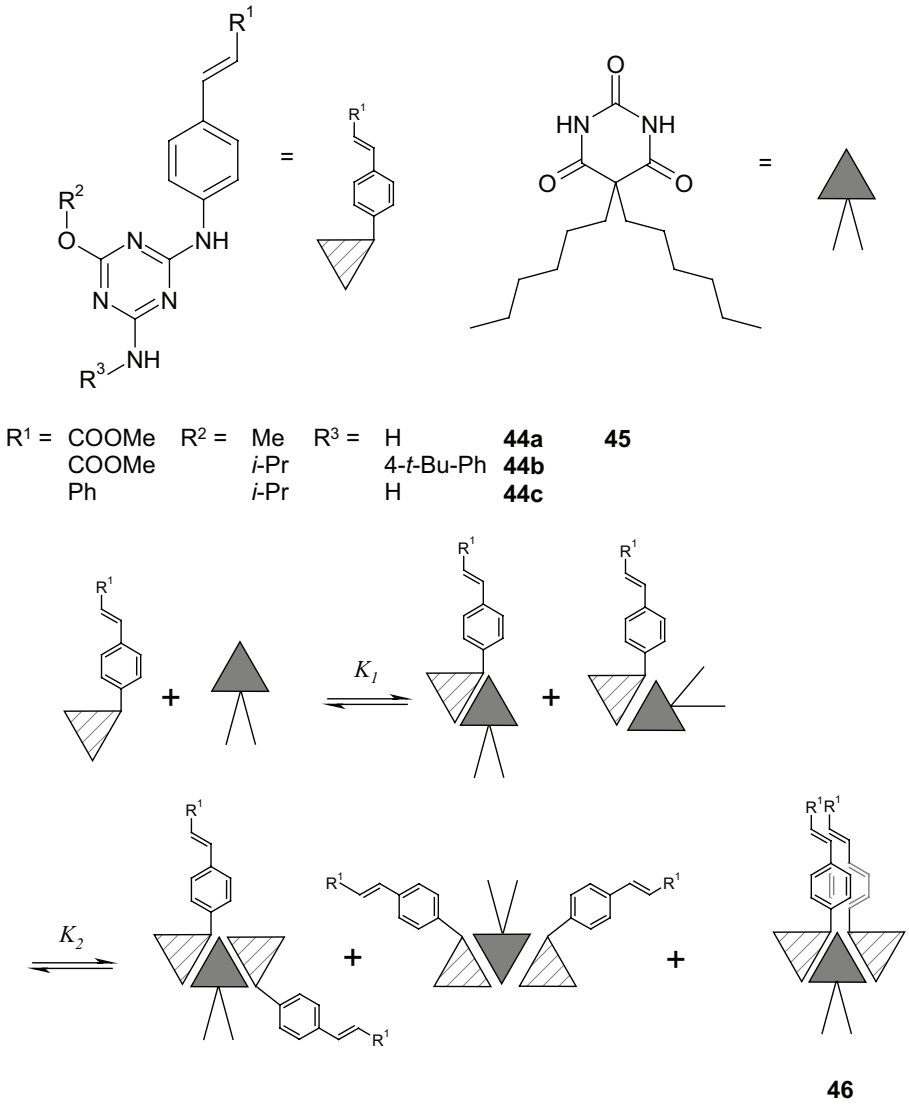


Scheme 18. Dimerisation of anthracene dependent on two different stimuli; The product is not thermally stable, and the efficiency of the photochemical reaction in the presence of metal cations was characterised by quantum yields (see text)

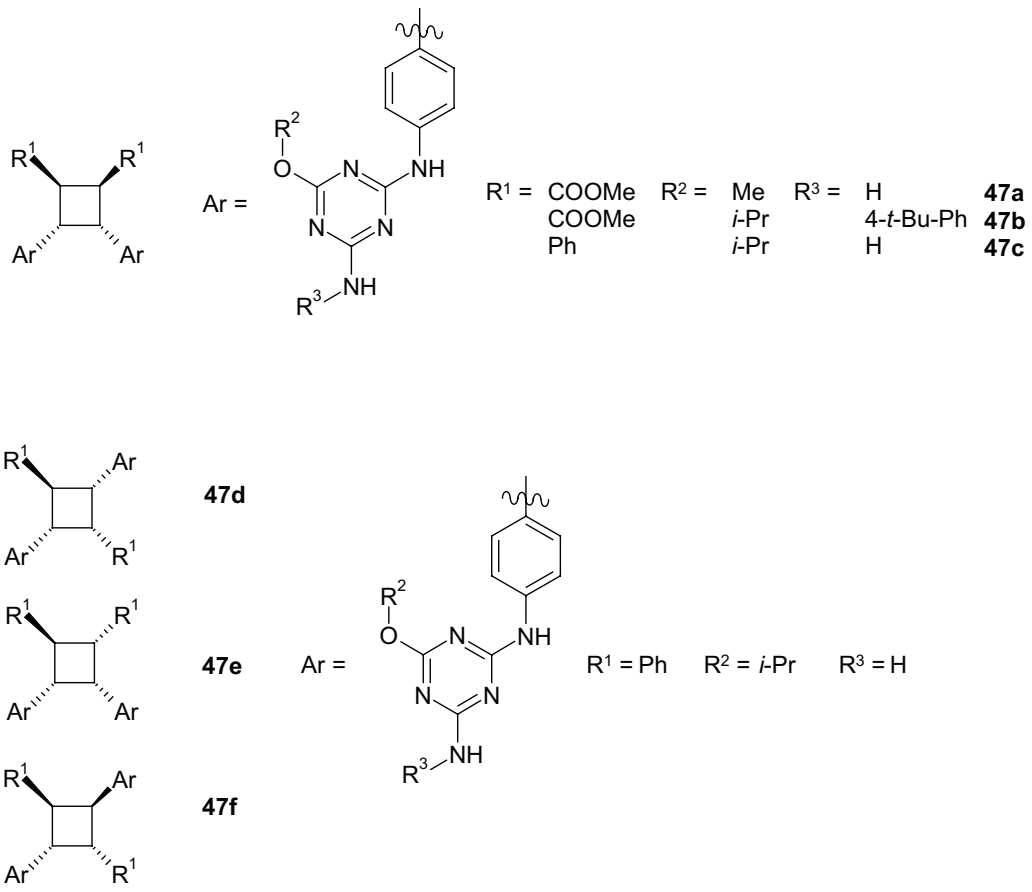
in the absence of templates, 0.26 in the presence of mercury(II) ions, 0.29 in the presence of sodium ions, and 0.32 in the presence of both cations, measured for compound **42b** in acetonitrile). The quantum yield remained high when both stimuli were present, as required for an "OR" gate. The rate of thermal dissociation decreased and the stability of the photoproduct **43** increased in the presence of sodium ions. The dissociation constant dropped from 97×10^{-6} to 29×10^{-6} s^{-1} for compound **43a** and from 202×10^{-6} to 2.9×10^{-6} s^{-1} for compound **43b**. On the other hand, the presence of mercury(II) ions did not significantly influence the product stability.

3.3 Non-Covalent Intermolecular Pre-Organisation

A diaminotriazine–barbiturate-based assembly was successfully used for dimerisation of cinnamates and stilbenes.[44,45] The hydrogen-bonding pattern of the diaminotriazine present in molecules **44** was complementary to that of barbituric acid **45**. In its presence, several hydrogen bonded dimers and trimers can form. However, only one of them (complex **46**) locked the two cinnamates or stilbenes **44** in a suitable geometry for photocycloaddition (Scheme 19). The presence of the barbiturate template **45** increased the reactivity and induced selectivity for some of the product isomers (Scheme 20). For dimerisation of cinnamates **44a** and **44b**, formation of β-truxinate products **47a,b** was preferred (quantum yield increased from



SCHEME 19. Dimerisation of cinnamate and stilbene in a non-covalent assembly

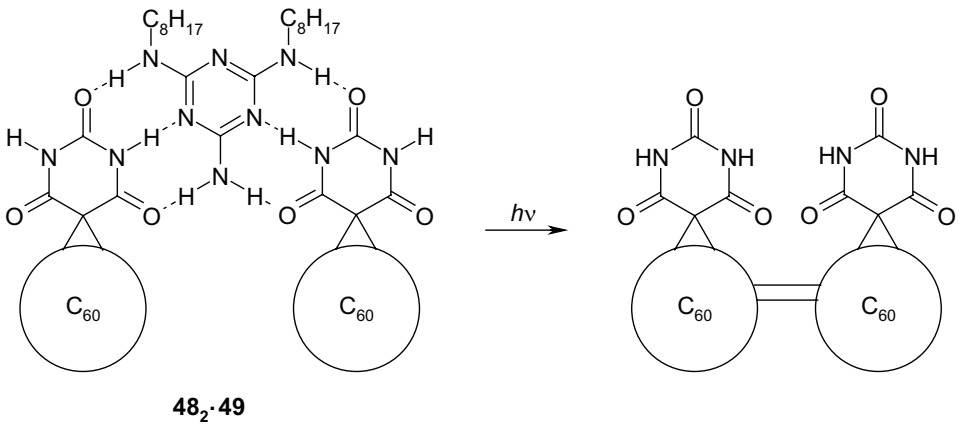


Scheme 20. Products of cinnamates and stilbene **44** photodimerisation; See text for quantum yields of their formation

0.7×10^{-3} to 2.3×10^{-3} for cinnamate **44a**, and from 0.1×10^{-3} to 0.8×10^{-3} for cinnamate **44b**). In the case of the stilbene **44c** dimerisation, formation of all products (**47c–e**) apart from **47f** was enhanced (quantum yield increased from 0.8×10^{-3} to 4.6×10^{-3} for the products **47c–e** altogether but decreased from 0.7×10^{-3} to 0.5×10^{-3} for product **47f**).

A melamine–barbiturate assembly (Scheme 21) was successfully used for dimerisation of fullerenes.[46,47] Two fullerene–barbiturate conjugates **48** were bound by the melamine host **49** and efficiently underwent dimerisation upon irradiation. In the absence of the melamine host **49**, no dimerisation was observed.

The effect of diaminotriazine–barbiturate and glycol–metal cation binding was combined in one molecule **50** (Scheme 22) to further enhance the efficiency of cinnamate dimerisation.[48] Accordingly, the cinnamate was "equipped" with both a diaminotriazine substituent and a polyethylene gly-

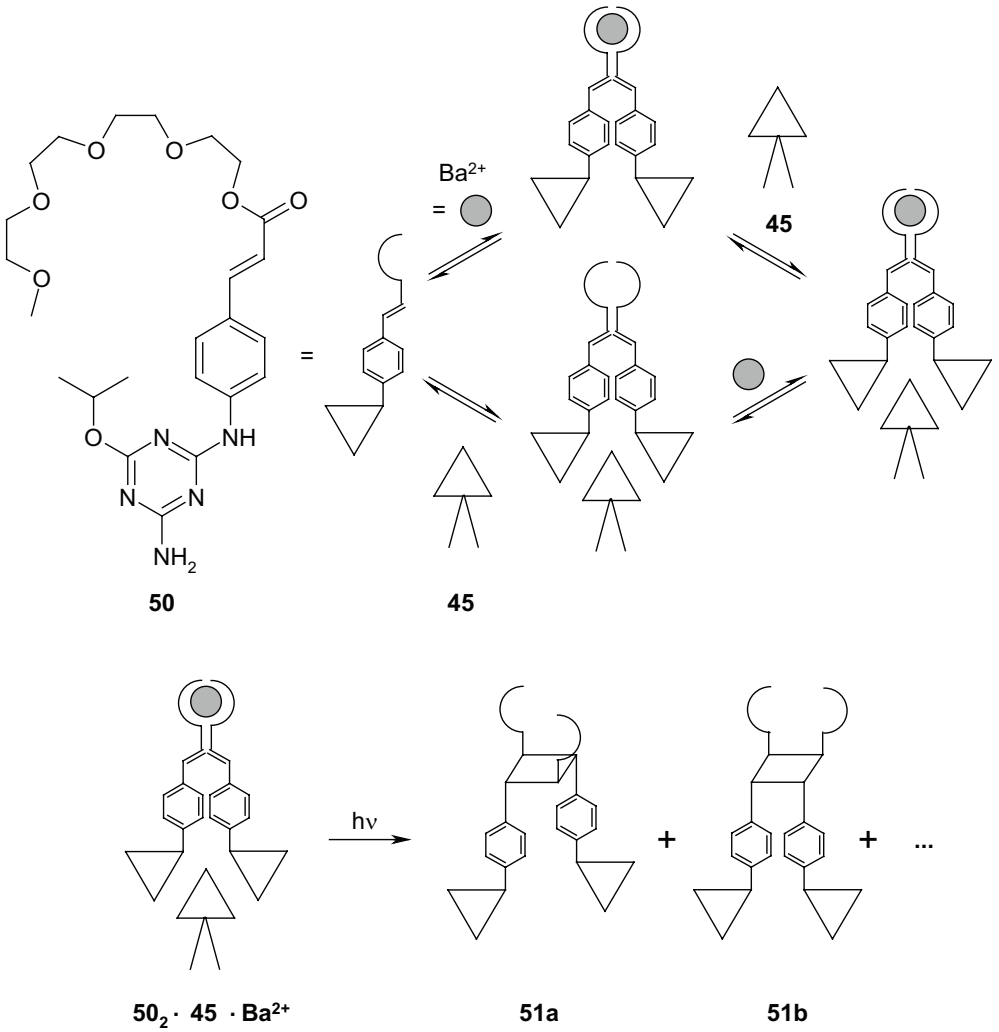


48$_2$·49

SCHEME 21. Dimerisation of fullerenes in a melamine–barbiturate assembly; Yield of the reaction was not given

col chain. Quantum yields of dimerisation and product selectivity were studied in the presence or absence of barbiturate **45** and in the presence of various metal cations. For example, efficiency of dimerisation (taken as yield of dimers after a certain time of irradiation) increased twice in the presence of 0.5 eq. of barbiturate **45** or potassium ions. When both of the templates were present, a 5-fold increase in dimerisation efficiency was observed, which could be explained by co-operative effect of the two templates. The most significant effect was observed in the presence of barium ions. Interestingly, the presence of barium ions during irradiation hardly influenced the selectivity for product **51a** and **51b**, although the quantum efficiency increased ca. 300 times (from 3.6×10^{-5} to 9.1×10^{-3} for product **51a** and from 3.7×10^{-5} to 1.0×10^{-2} for product **51b**). On the other hand, the presence of the barbiturate template **45** increased quantum yield only ca. twice (from 3.6×10^{-5} to 6.4×10^{-5} for product **51a** and from 3.7×10^{-5} to 5.3×10^{-5} for product **51b**) but increased the product ratio **51b**:**51a** from 1:1 to 5:1. This indicated that the main effect of the non-directive ion chelation by polyethylene glycol (as opposed to hydrogen bonding between diaminotriazine and barbiturate) was to increase the local concentration of the reactants. The flexibility of the glycol chain probably prevented transfer of geometrical information from the metal ion coordination site to the photoactive moieties.

Photodimerisation of coumarins **52** was successfully influenced by a symmetric ditopic receptor **53** containing two identical hydrogen-binding recognition sites (Scheme 23).[49] Coumarin **52** forms a 2:1 complex with template **53**. Unlike free coumarin **52**, which yielded a 60:40 mixture of syn and anti coumarin photodimer, irradiation of complex **52**$_2$·**53** led exclusively to formation of trans-syn head-to-head dimer **54**. The preference for the trans



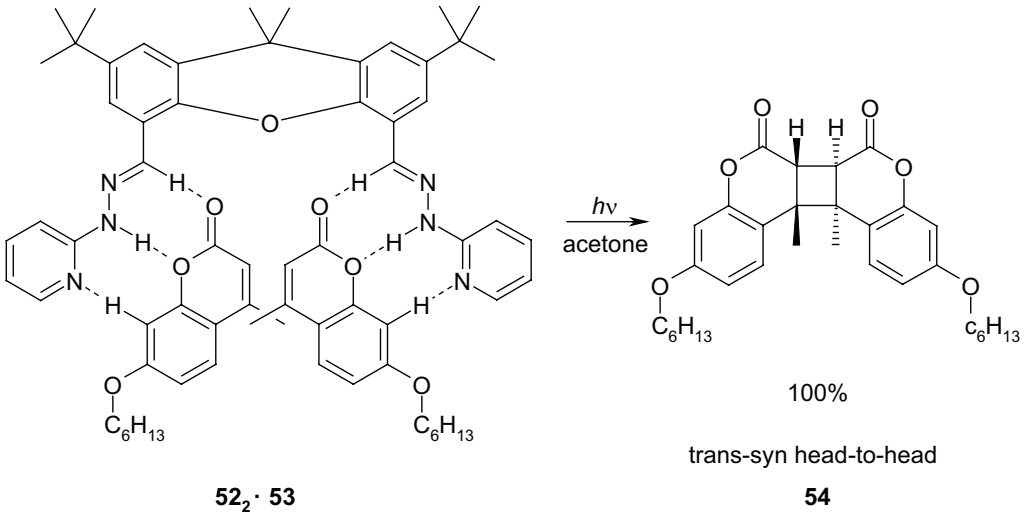
Scheme 22. Dimerisation of cinnamates influenced by two supramolecular interactions; See text for quantum yield of the products

isomer was explained by steric effects. Interestingly, the quantum yield of coumarin **52** dimerisation was lower in the presence of the template **53** ($\Phi = 0.03$, ca. one-half of the quantum yield observed for free coumarin **52**) because of template shielding. However, this shielding effect increased the stability of the dimer, protecting it from the backward reaction. The importance of hydrogen bonding for photodimerisation efficiency was proved by template analogues with missing or methylated recognition units.

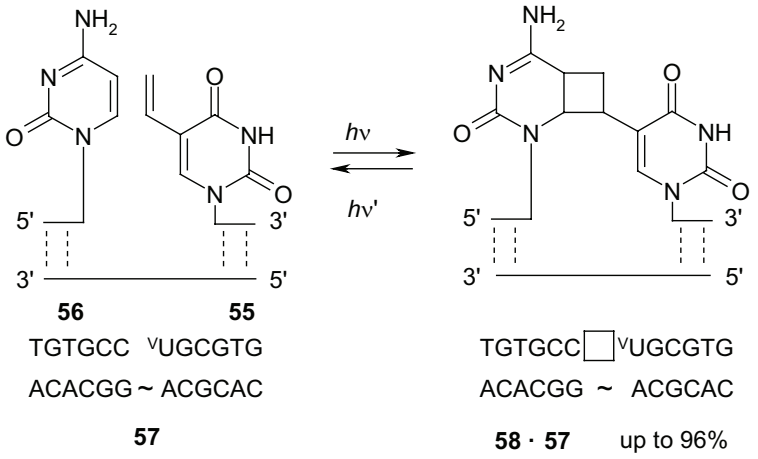
4. Complementary DNA Strands as Templates

In this section we summarise photochemical reactions (ligations of deoxynucleotides) whose reactants required pre-organisation by the complementary DNA strand.

Vinyldeoxyuridine (^{V}U) base was incorporated into the oligodeoxynucleotide strand **55** by automated synthesis, and was connected to another portion of the strand (**56**) by a [2+2] cycloaddition.[50] However, in the absence of the template, represented by the complementary DNA strand **57**, no reaction occurred. In the presence of the complementary oligodeoxynucleotide **57**, both components **55** and **56** bound to the template and underwent clean and efficient reaction upon irradiation at 366 nm to yield the ligated product **58** (Scheme 24). The ligation between the 5'-terminal ^{V}U residue and 3'-terminal C residue is selective. There is no reaction the the 5'-terminal ^{V}U and 3'-terminal A or G residue. The process was found to be reversible and the back reaction proceeded rapidly at 302 nm. Products of the cleavage reaction could be irradiated again, and the cyclobutane product was

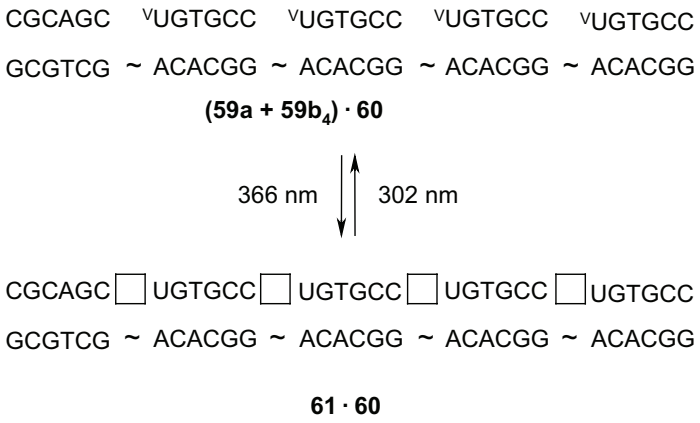


SCHEME 23. Ditopic template-assisted photodimerisation of coumarin



Scheme 24. Oligodeoxynucleotide-directed photoligation

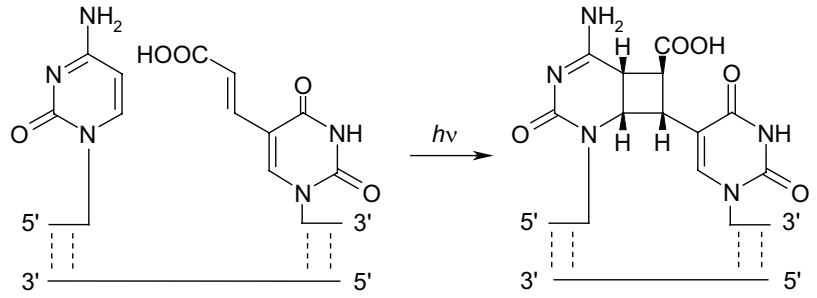
re-formed. Efficiency of the reaction was proven by the simultaneous ligation of five oligodeoxynucleotides **59** (4× ^{V}UGTGCC, **59b**; 1× CGCAGC, **59a**) bound to one template **60** (Scheme 25). Again, the expected ligation product **61** was cleanly formed.



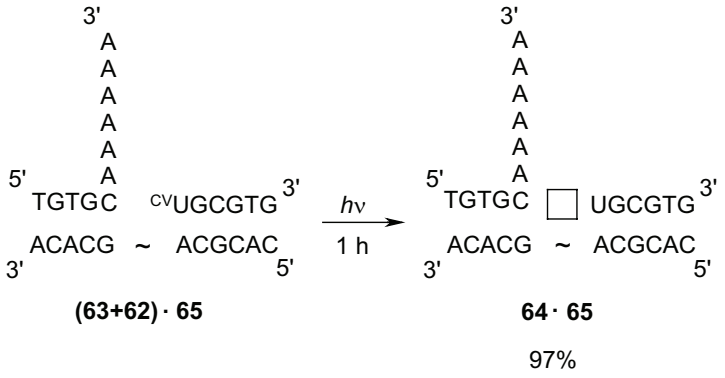
Scheme 25. Simultaneous ligation of five vinyldeoxyuridine-containing oligodeoxynucleotides; Conversion and reversion are quantitative

Later, the idea was extended to the synthesis of branched oligonucleotides.[51,52] A new, more reactive nucleotide—5-carboxyvinyldeoxyuridine (^{CV}U)—was employed (Scheme 26) which enabled shorter irradiation time during the ligation reaction. Similarly to the previous example, the ^{CV}U-containing oligoeoxynucleotide **62** was efficiently ligated to a C residue modified by a polyA chain **63** to yield product **64** (Scheme 27) while bound to the complementary oligodeoxynucleotide strand template **65**.

The ^{CV}U residue was also used for efficient photoligation to a 3'-terminal



SCHEME 26. Structure of the 5'-terminal ^{CV}U residue and the photocycloaddition product with a 3'-terminal C residue



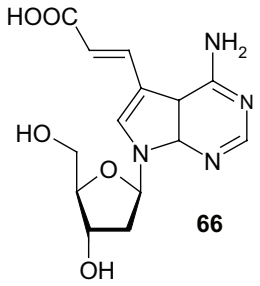
SCHEME 27. Synthesis of a branched oligodeoxynucleotide strand

C or T residue in the presence of the complementary RNA strand, thus forming a hybrid duplex.[53] Sensitivity of the photoligation efficiency to mismatches in the sequence of the complementary RNA strands was then successfully used for detection of RNA single-point mutations.

The DNA photoligation methods were extended by the use of α-5-(cyanovinyl)deoxyuridine at the 3' terminus,[54] contrary to previous examples where the modified base was always located at the 5' terminus. It was predicted by molecular modelling methods that the α anomer would interact better with the 5'-terminal T residue better than the β anomer. Again, irradiation at 366 nm quickly and efficiently yielded the ligated oligodeoxynucleotides in the presence of the complementary DNA strand. The photoligation efficiency depended on sequence specificity; in the case of single mismatched oligodeoxynucleotides, conversion after identical time periods reached only 9–15%. The method was verified by synthesis of a branched nucleotide with T residue at the ligation point modified by a polyA chain, similar to the previous example.

It was also possible to prepare a photoreactive nucleotide based on adenosine instead of uridine.[55] In this case, 7-carboxyvinyl-modified 7-deaza-2'-deoxyadenosine **66** (Scheme 28) located at the 5' terminus reacted with a

3'-terminal T or C residue in the presence of a complementary DNA strand. Photoligation was extremely rapid (93% yield within 5 min) and selective



66

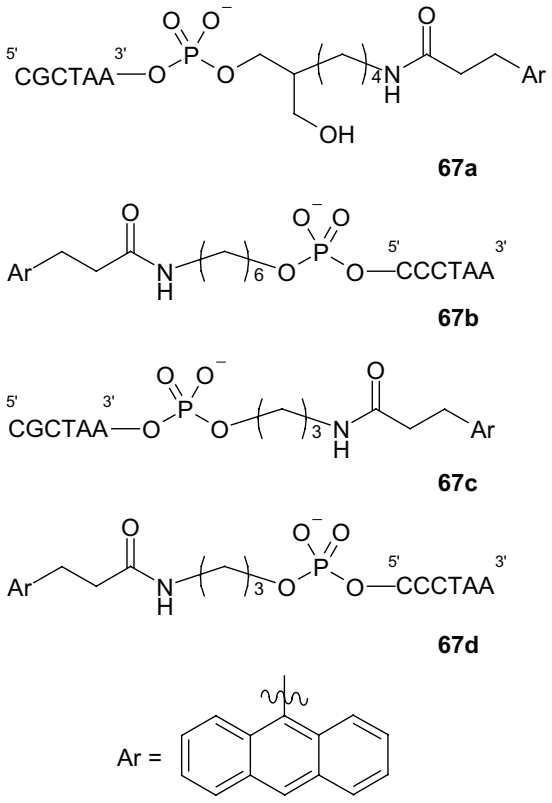
Scheme 28. Structure of 7-carboxyvinyl-7-deaza-2'-deoxyadenosine

for the 3'-terminal C or T residues. A or G residues did not undergo reaction. The photoreversibility of the process was similar to the aforementioned example.

Another option is connecting two DNA strands by photocycloaddition of anthracenes.[56] Anthracene units were linked to the 5' or 3' termini of the strands by a hexamethylene or trimethylene chain (Scheme 29, compounds **67**). The sequences were designed to stack the anthracene units in the presence of the complementary DNA strand **68a**. Upon irradiation, the asembled anthracene units undergo photodimerisation and connect the two strands. The relative yields of the anthracene photodimer after 30 min were **67d**+**67a** (1.46) > **67b** + **67a** (1.00) > **67b** + **67c** (0.33) > **67d** + **67c** (0.24).[57] Photoligation efficiency of **67b** with **67a** was studied in the presence of several longer (**68b**–**d**) or mutated (**68e**–**g**) templates. Although a one-residue-long gap (template **68b**) was tolerated (relative yield 1.1), the ligation efficiency rapidly decreased with increasing length of the gap (relative yield 0.16 with template **68c** and 0.06 with template **68d**). The process is sensitive to one-base displacement in a position-dependent manner. Efficiency decreased in the order **68a** (1.00) > **68e** (0.35) > **68f** (0.19) > **68g** (0.00), which shows that a base pair mismatch in the binding site region (**68g**) reduces the efficiency more than mismatches between the two binding sites. No ligation was observed with a half-scrambled sequence template. The order of ligation efficiency co-incided with the duplex thermal stability order.

5. Templates with a Covalently Bound Chromophore and Recognition Site

The efficiency of a photochemical reaction can be often enhanced by a suitable sensitiser as an additive. The idea to covalently attach the sensitiser to a substrate-binding site was sucessfully used for efficient oxidation of ben-

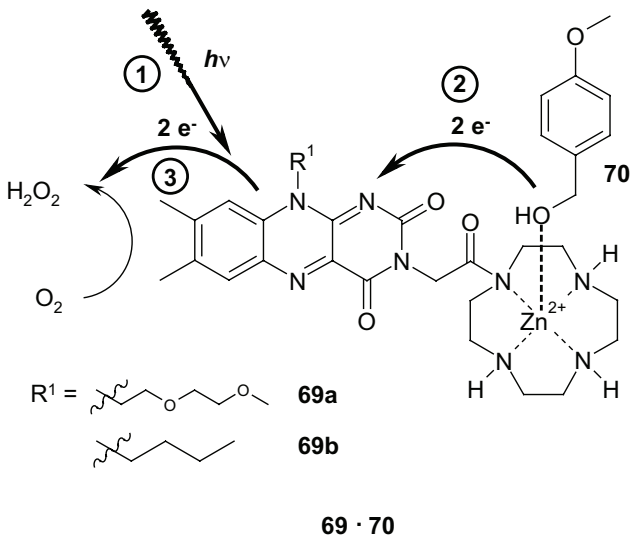


TTAGGGTTAGCG	**68a**
TTAGGG**T**TTAGCG	**68b**
TTAGGG**TT**TTAGCG	**68c**
TTAGGG**TTT**TTAGCG	**68d**
TTAGGG**A**TAGCG	**68e**
TTAGGGT**A**AGCG	**68f**
TTAGGGTTA**T**CG	**68g**

SCHEME 29. Ligation of oligodeoxynucleotides by photocycloaddition of anthracenes

zylalcohol and photorepair of thymine dimers. Contrary to the previous sections, there is no shielding effect or pre-organisation of reaction components. Selectivity and efficiency were achieved by conducting the desired photoreaction only in the vicinity of the sensitiser and thus by conversion of the diffusion-controlled process to an intramolecular reaction.[58]

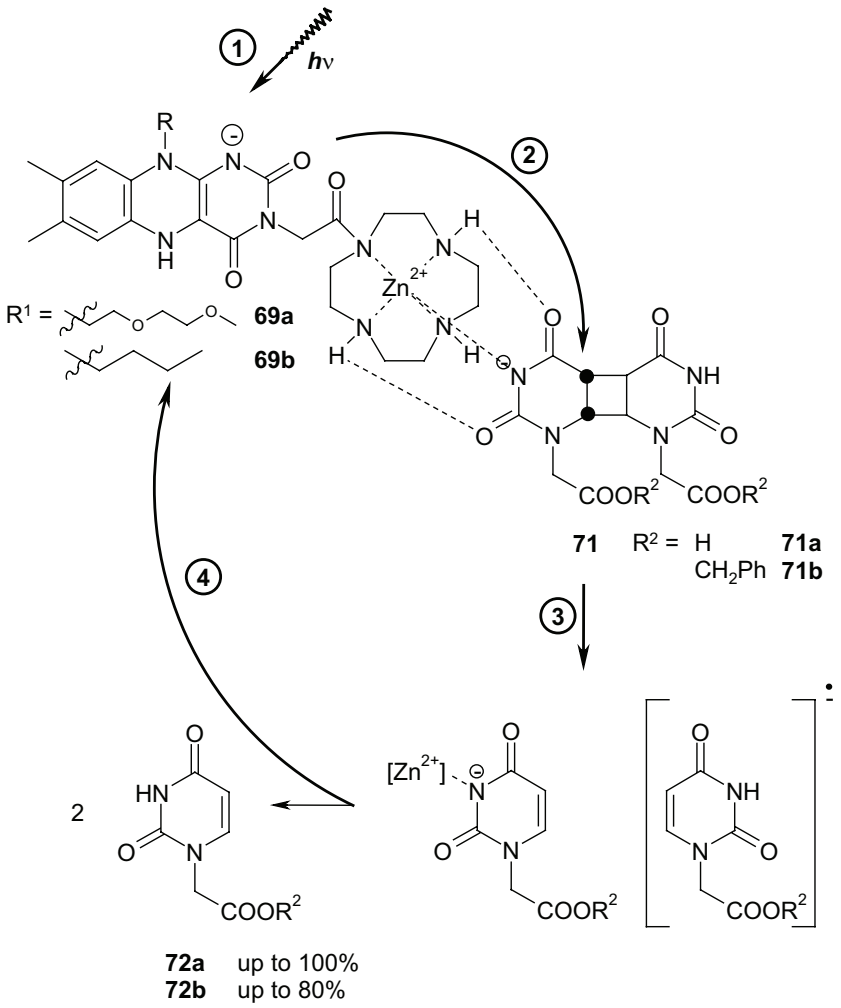
The first such system reported (compound **69a**) used a flavin group as the photomediator and Lews-acidic zinc(II)–cyclene as the binding site.[59–61] The zinc(II)–cyclene bound 4-methoxybenzyl alcohol **70**, and upon irradiation, the excited flavin chromophore oxidised the alcohol to the corresponding aldehyde (Scheme 30).[62] After the reaction, the flavin skeleton was in its reduced state and required re-oxidation before the next turn of the cycle. Aerial oxygen rapidly re-oxidised the flavin unit and the reaction went forth. Thus, the net reaction was ocidation of 4-methoxybenzylalcohol **70** to the corresponding aldehyde by oxygen; however, in the absence of the template **69a** or light, the reaction did not proceed. The importance of the proximity of the substrate and the sensitiser was proved by experiments with flavin which did not contain the zinc(II)–cyclene binding site or with equimolar mixtures of flavin and zinc(II)-cyclene perchlorate. Only the complete sensitiser **69a** which contained covalently bound zinc(II)-cyclene exhibited high



SCHEME 30. Schematic representation of the catalytic oxidation of 4-methoxybezyl alcohol by a flavin unit; Key: (1) irradiation, (2) oxidation of substrate,(3) reoxidation of flavin

conversion and turnover number (yield 90% after 2 hrs of irradiation). The sensitiser acted as a true catalyst: 10 mol % of the sensitiser was sufficient for efficient oxidation of the substrate. Oxidation was possible both in acetonitrile and aqueous buffer solution due to the good solubility of the sensitiser **69a** and high association constant.

The sensitisers **69** were also found to act as an artificial functional model of a photolyase.[63] A major environmental damage to DNA is the UV-radiation-induced [2+2] cycloaddition between two adjacent thymine residues on one strand of DNA, leading to formation of a cis-syn thymine cyclobutane dimer. DNA lyase selectively recognises the thymine dimers and repairs them by photinduced electron transfer using a non-covalently bound reduced flavin as the electron donor, excited by visible light. The described photolyase model **69** selectively bound to the thymine dimers **71** both in organic solvents (compound **69b** with thymine dimer **71b**) and aqueous environment (compound **69a** with thymine dimer **71a**), and upon irradiation by visible light induced electron-transfer-catalysed cycloreversion, thus cleaving the cyclobutane ring (Scheme 31). Analysis of the reaction mixture showed a fast and clean conversion of the thymine dimer **71b** to the monomers **72b**. The reaction was carried out in acetonitrile (completion time 120 min) or methanol (completion time 60 min). High hydrophilicity of the glycol-substituted flavin sensitiser **69a** allowed for efficient repair of the thymine dimer **71a** in water. The reaction in water was faster than that in organic solvents (78% conversion after 10 s of irradiation). This observation was explained by higher polarity of water and thus by better stacking of the flavin unit and the thymine dimer facilitating the electron-transfer

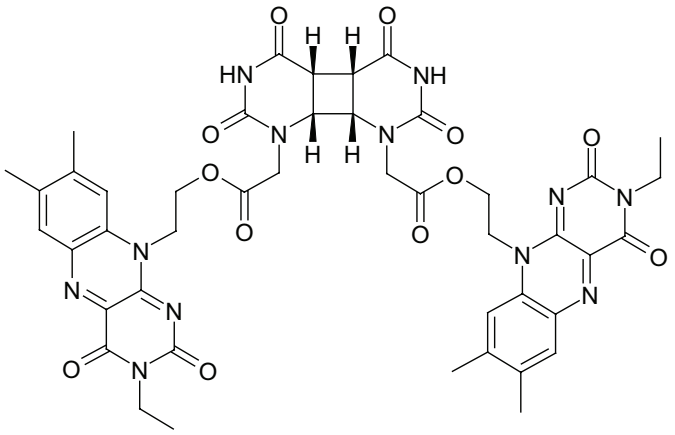


SCHEME 31. Functional model of photolyase; Key: (1) irradiation, (2) electron transfer, (3) cycloreversion, (4) back electron transfer

step.

Flavin-based artificial photolyase models were studied in great detail. Most of the examples featured flavin units covalently linked to the pyridimine dimers, such as in compound **73** (Scheme 32).[64–66]

The efficiency of the cycloreversion was, apart from a covalent linkage, also enhanced by incorporation of flavin into an oligopeptide strand.[67] The synthesis made use of an artificial flavin-containing amino acid **74** (Scheme 33), leading to flavin-containing oligopeptides **75** and **76**. To mimic a helix–loop–helix protein and enhance binding to DNA, two flavin-containing peptides were linked by a bis(bromoacetyl)benzene template to yield compound **76** (Scheme 34). In solution, the oligopeptides **75** and **76** bound to a lesion-containing synthetic oligonucleotide **77**, presumably by



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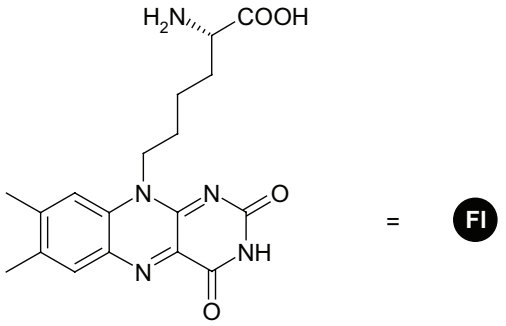
SCHEME 32. Example of a photolyase model with covalently attached flavin units[64f]



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SCHEME 33. Artificial flavin-containing amino acid and its schematic representation

interaction of the phosphodiester and arginine or lysine residues. Upon irradiation by daylight or 366 nm light, the flavin unit was reduced in the presence of ethylene diamine tetraacetic acid and the excited reduced chromophore then cleanly repaired the DNA damage (Scheme 35).

Thymine dimer could be efficiently cleaved by a carbazole nucleoside incorporated into a complementary DNA strand.[68] Upon irradiation, cyclorеversion of the thymine dimer occured, and the repaired oligodeoxynucleotide was isolated with 92% yield. Templates with an additional carbazole nucleoside or adenosine residue in the active site worked with comparable yields (94% and 93%, respectively). When mismatched bases were present in the damaged strand, no repair was observed.

Thymine dimer was also selectively recognised by a compound containing two 2,6-bis(acylamino)pyridine binding sites and an anthraquinone chromophore.[69] It was also possible to prevent formation of thymine dimer by

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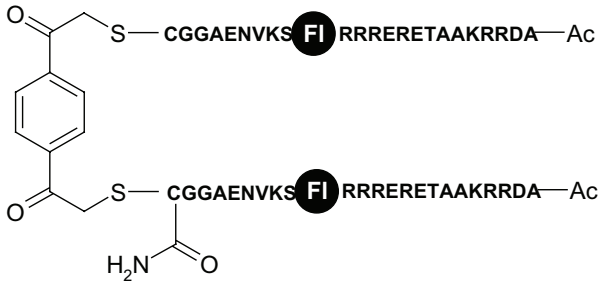

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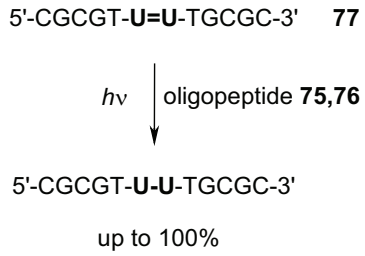
SCHEME 34. Flavin-containing oligopeptides



SCHEME 35. Photorepair of DNA damage by a flavin-containing oligopeptide

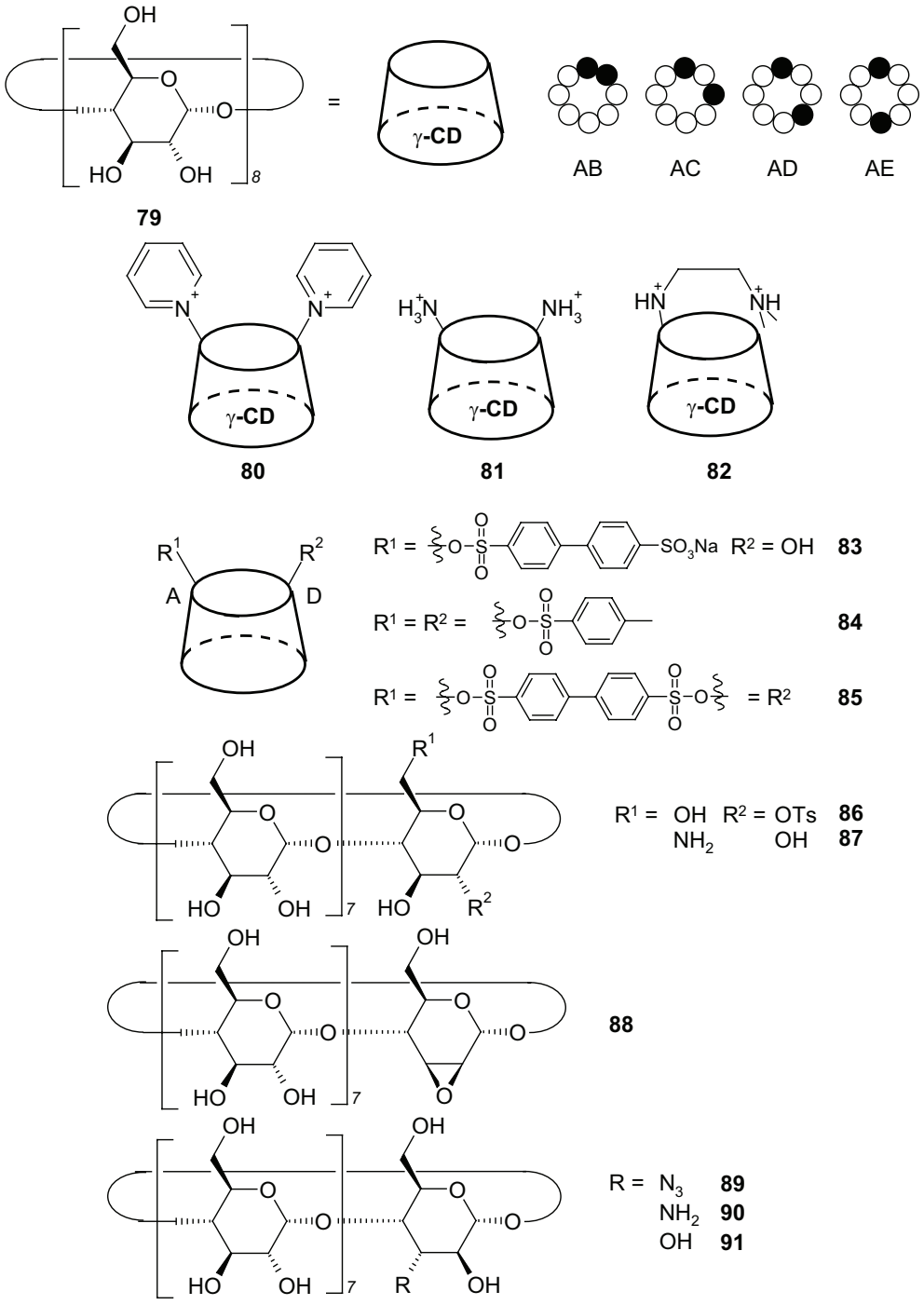
binding the two thymine bases to a dinuclear complex so far apart from each other that they could not undergo the photocycloaddition reaction.[70] However, this is an example of efficient reaction blocking, not enhancement, and the work is therefore not discussed in detail.

6. Photochemical Reactions in a Molecular Flask

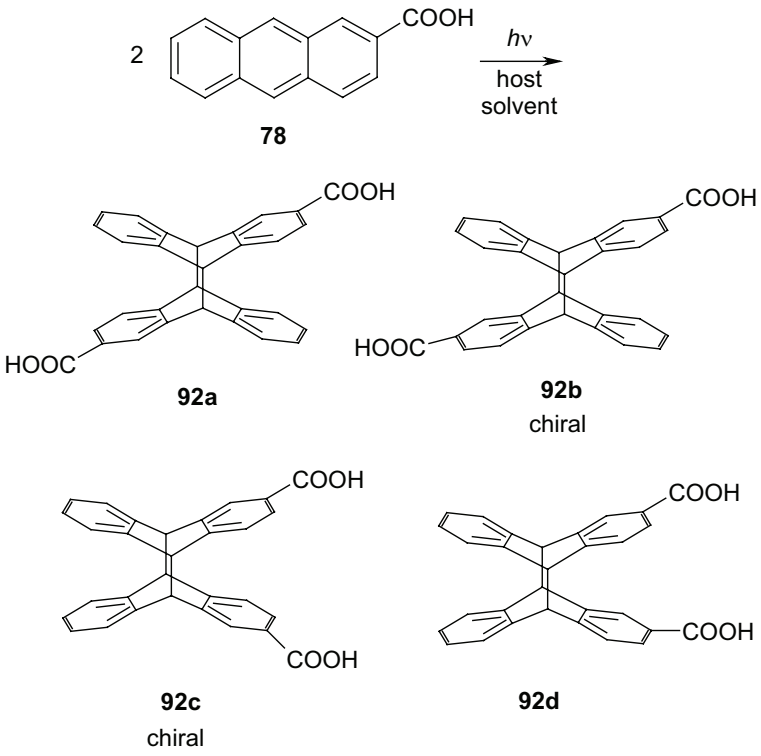
A variety of photochemical transformations are influenced and enhanced by the presence of a molecular flask, i.e., a large template molecule which includes the guest or guests, thus pre-organising them advantageously for a desired photochemical reaction. These premises are similar to those outlined in Section 3, where photochemistry within non-covalent assemblies was described. In this section we discuss examples where the host, or template molecule, is significantly larger than the guest and can be therefore described as a true molecular flask which protects substrates from the surrounding environment and thus controls the course of a photochemical reaction.

The spectrum of reactions enhanced in this manner is wide and ranges from dimerisations of aromatic and olefinic systems to selective photochemical cleavage or transport of a host-bound sensitiser toward a light beam. The molecular flasks used are known from other supramolecular applications. Cyclodextrins are favourite template scaffolds because of their good availability, various sizes, and inherent chirality, a property which was used for enantioselective photochemical rections.[71–74] Other examples include self-assembled cage and bowl, cucurbiturils, and a self-assembled cavitand. In this section, we describe photodimerisations and photocycloaddition reactions first, and continue with selective photochemical cleavage reactions and systems with transport function.

The best studied photochemical reaction in a molecular flask is probably the dimerisation of anthracene carboxylate **78**.[75–83] γ-Cyclodextrin (**79**) and modified (**80**–**91**) cyclodextrins were used to manipulate yield and stereochemical outcome of the dimerisation reaction (Scheme 36). Two of the possible four isomers **92a**–**d** are chiral (Scheme 37), which stimulated investigations on the asymmetric induction by the inherently chiral cyclodextrin.[43] Different experimental conditions disallow for direct comparison of the individual results, but effects of the host geometry on the selectivity of the dimerisation reaction are definitely observed. Overall, the results from photodimerisation of anthracene carboxylic acid in the presence of γ-cyclodextrin-based templates can be summarised in the following way: The presence of any γ-cyclodextrin derivative accelerates the reaction by an increase of the local concentration of anthracene molecules. The structure of the cycloadduct necessarily reflects the structure of the precursor ground-state assembly because within the excited singlet state lifetime (ca. 10 ns) the orientation of the aggregate does not change by dissociation and no reaction of free anthracene-2-carboxylic acid with the 1:1 inclusion complex occurs. Therefore, better control of the relative geometry leads to higher selectivity of the photodimerisation. With γ-cyclodextrin **79**, irradiation of anthracene-2-carboxylate **78** led preferentially to formation of isomers **92a** (up to 43% yield) and **92b** (up to 46% yield and 41% ee).[77] With bis-pyridinio-γ-cyclodextrins **80AB**–**AE**, the electrostatic repulsion of the two carboxylate groups was partly overcome and the two molecules aligned to the pyridinium units.[78] Preference for isomers **92a** (up to 43% yield) and **92c** (up to 32% yield and ca. 10% ee) was observed. Diamino-modified γ-cyclodextrins **81AB-AE** led to an increased formation of isomers **92c** (up to 32% yield, 27% ee) and **92d** (up to 21% yield) in comparison to the isomer distribution in the presence of γ-cyclodextrin **79**.[79] γ-Cyclodextrin **85**, bearing a dicationic substituent, was selective for the formation of isomers **92c** (up to 42% yield, 41% ee) and **92d** (up to 41% yield).[80] γ-Cyclodextrin with flexible hydrophobic caps **83** and **84** did not significantly influence the product distribution or enantioselectivity of the dimerisation when compared to γ-cyclodextrin **79**.[81] However, γ-cyclodextrin **82** with a rigid hydropho-



SCHEME 36. γ-Cyclodextrins used as hosts for the photodimerisation of anthracene carboxylate **78**



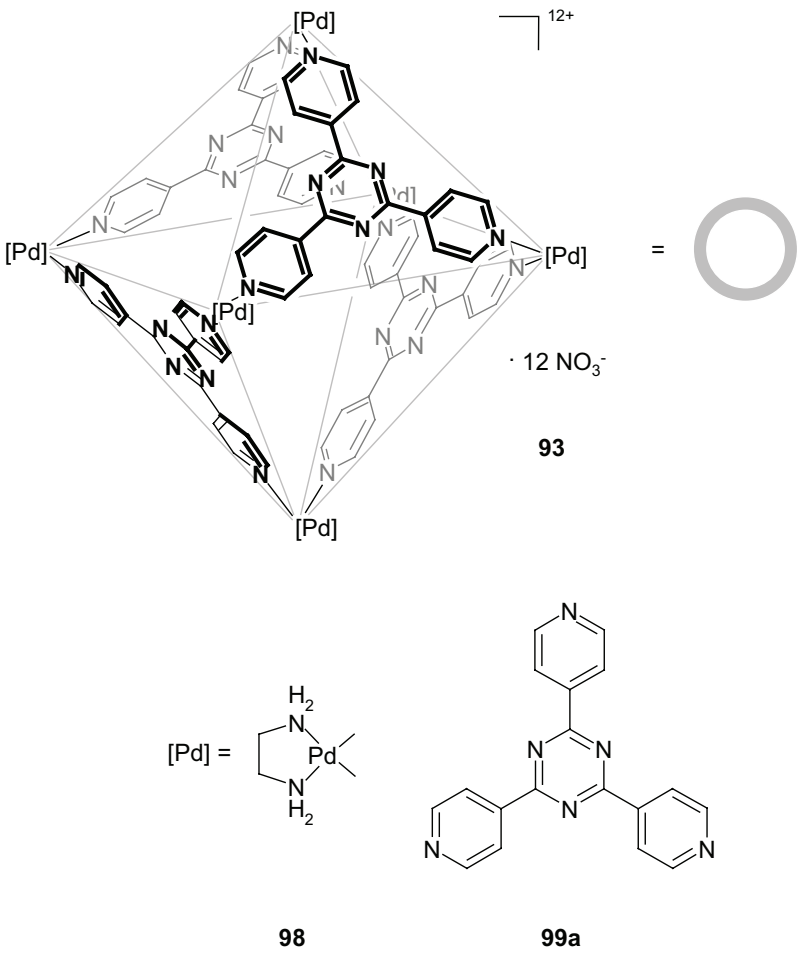
SCHEME 37. Yields and ee values depend on host and conditions employed and are discussed in text

bic cap enabled formation of product **92b** with up to 58% ee, although the yield was lower than with γ-cyclodextrin **79**. A series of secondary face[84] modified γ-cyclodextrins **86**–**91** did not influence the relative yields of cyclodimers **92a**–**d** either.[82] However, the enantioselectivity of the reaction was significantly enhanced with some derivatives. Isomer **92b** was obtained with 47% yield and 53% ee at 0 °C and 0.1 MPa and with 53% yield and 71% ee at −21.5 °C and 210 MPa when using the modified γ-cyclodextrin **90** as template.

Other investigations have concerned photodimerisation of anthracene-2-carboxylate **78** in the binding pocket of the protein bovine serum albumin, which leads to selective formation of isomers **92c** (up to 38% yield, 41% ee) and **92d** (up to 43% yield).[83]

A self-asembled cage-like molecule **93** (Scheme 38) was used for highly selective photochemical dimerisation of acenaphthylenes **94** and **95**,[85,86] naphthoquinone (**96**)[86] and antracene-9-carbaldehyde (**97**),[85] which adopted a well defined geometry in the stringent environment. The self-assembled cage **93** was composed out of six metal complexes **98** and four tridentate ligands **99a**.

Irradiation of the acenapthylene molecules **94** and **95** (Scheme 39) acco-

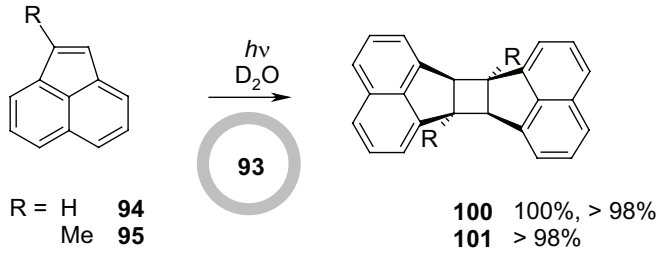


SCHEME 38. Self-assembled molecular cage

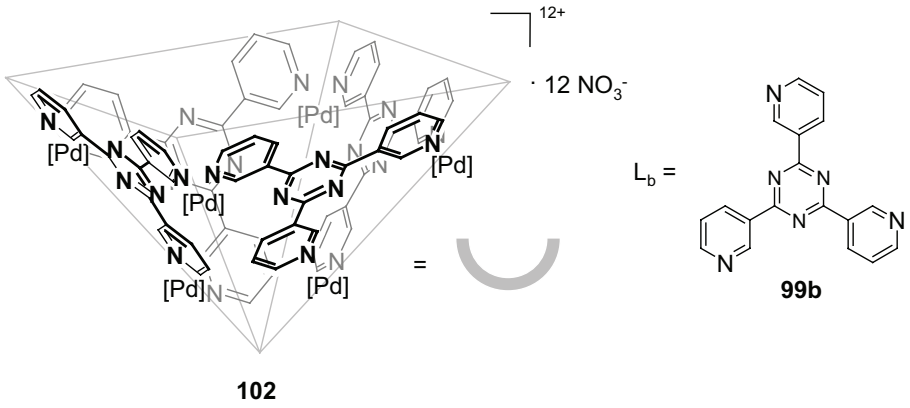
modated inside the cage **93** led to selective formation of the syn dimer **100** and **101** in more than 98% yield and without any other regio- or stereoisomers.[85,86]

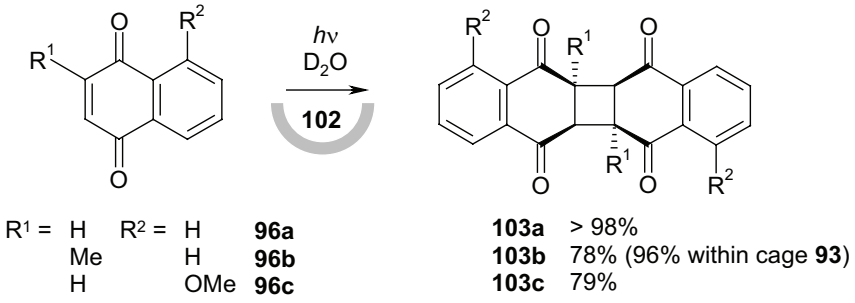
Similarly, photodimerisation of naphthoquinone **96a** inside a self-assembled bowl-like molecule **102** consisting of six units of **98** and four units of **99b** led selectively to the formation of the syn dimer **103a** (Scheme 40).[86] The regioselectivity of the photodimerisation of 2-methylnaphthoquinone **96b** was very high (96% head-to-tail dimer **103b**) with molecular cage **93** but only moderate (78% head-to-tail dimer **103b**) with molecular bowl **102**. Dimerisation of 5-methoxynaphthoquinone **96c** led to formation of isomer **103c** in 79% yield in the presence of molecular bowl **102**. Irradiation of **96b** without the cage (50 mM, 3 hrs, benzene) did not afford any dimerisation product, while that of **96c** gave the anti dimer in 21% yield.

Irradiation of the complex of anthracene-9-carbaldehyde (**97**) and cage



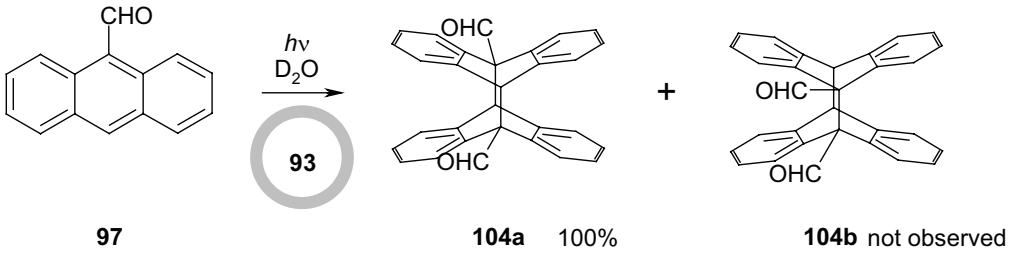
Scheme 39. Photodimerisation of acenaphthylenes in the molecular cage **93**





Scheme 40. Photodimerisation of naphthoquinones in a molecular bowl **102**

93 in a ratio 2:1 led to selective formation of the photodimerisation product **104a** (Scheme 41).[85] The cage **93** accomodated the two guest in a geometry



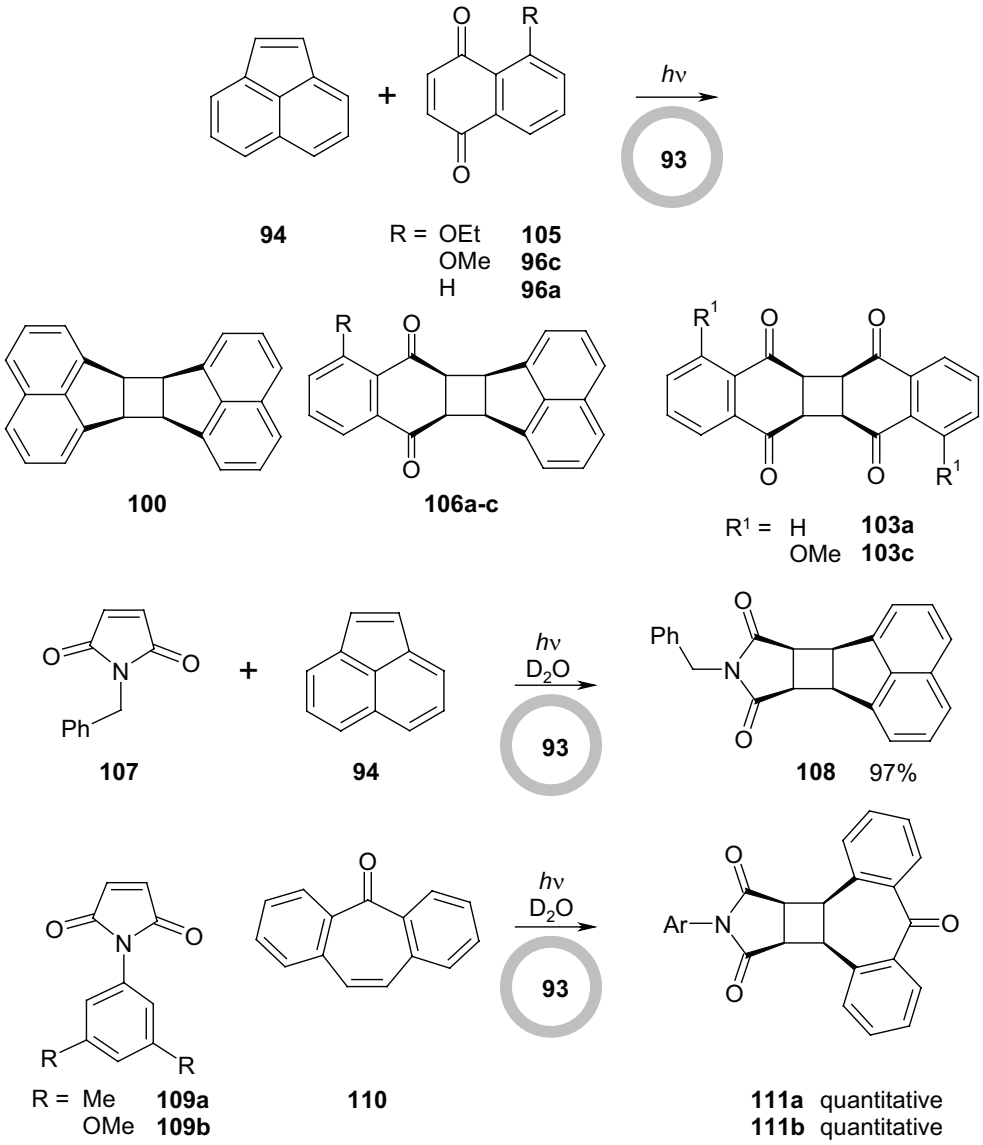
SCHEME 41. Photodimerisation of anthracene-9-carbaldehyde in molecular cage

leading to exclusive formation of the isomer shown; formation of the other possible isomer **104b** was not observed. Other 9-substituted anthracenes were photoinactive inside the cage.

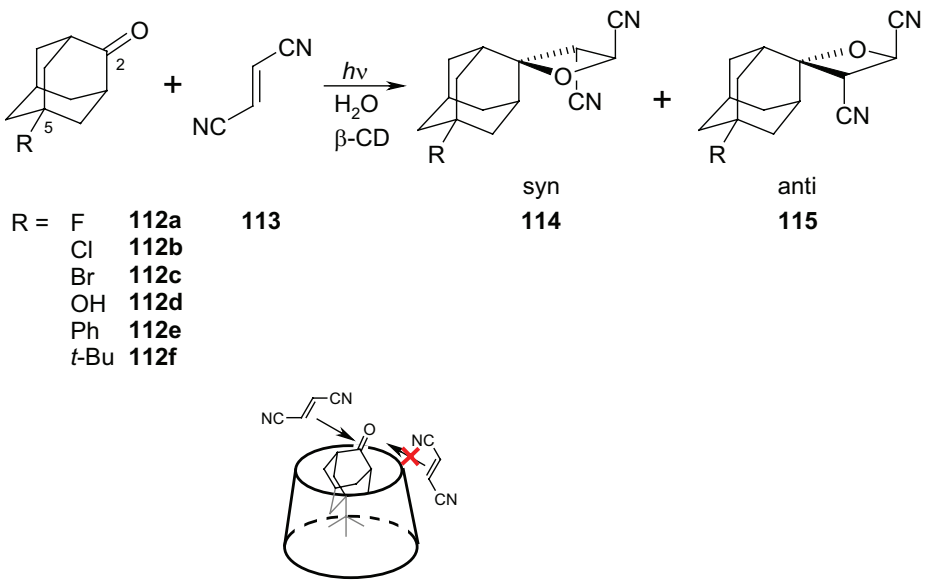
Acenaphthylene **94** undergoes efficient cycloaddition with 5-ethoxynaphthoquinone **105** using cage **93** (Scheme 42, top).[87–89] Irradiation of the 1:1:1 complex (acenaphthylene **94**:naphthoquinone **105**:cage **93**) led to selective formation of cis-syn cycloadduct **106a** in 92% yield. Formation of the ternary complex and hence the resulting photoproduct was governed by the bulkiness of the naphthoquinone guest: when 5-methoxynaphthoquinone **96c** was used, the same isomer **106b** was still the major product (yield 44%), but the reaction mixture contained **100** (6%) and **103c** (22%) as side products. With naphthoquinone (**96a**), selectivity was impaired even further (**100**, 21%; **106c**, 35%; **103a**, 14%). The cage was also successfully used for cycloaddition reactions of otherwise photoinactive guests (Scheme 42, bottom). *N*-Benzylmaleimide (**107**), a photochemically inert substrate, efficiently undergoes cycloaddition with acenaphthylene (**94**) when inside the molecular cage **93** and yields the syn cycloadduct **108** exclusively in 97% yield. Similar efficiency was observed for reaction of *N*-arylmaleimides **109a** and **109b** with dibenzosuberenone **110**. The syn cycloadducts **111a** and **111b** were both isolated in quantitative yield.

The cage **93** and related molecular capsules were successfully used for stabilisation of photochemically generated reactive intermediates which then underwent desired reactions.[90] However, in these cases, irradiation by light was only used to generate the intermediate, while the reactions of interest were thermal, and these reactions are therefore not discussed in detail.

A reversal of the syn:anti selectivity of the Paternó–Büchi reaction of adamantan-2-one **112** with fumaronitrile **113** was achieved by use of β-cyclodextrin.[91] A series of adamantan-2-ones **112** reacted with fumaronitrile **113** to yields the corresponding syn and anti oxetanes **114** and **115** (Scheme 43) with some preference for the syn isomer. The syn:anti ratio largely depends on the 5-substituent of the adamantanone **112**. During



Scheme 42. Cross-photocycloadditions of substrates in the molecular cage **93**; See text for the yields of acenaphthylene (**94**)–naphthoquinone (**96a,c**, **105**) cycloadditions

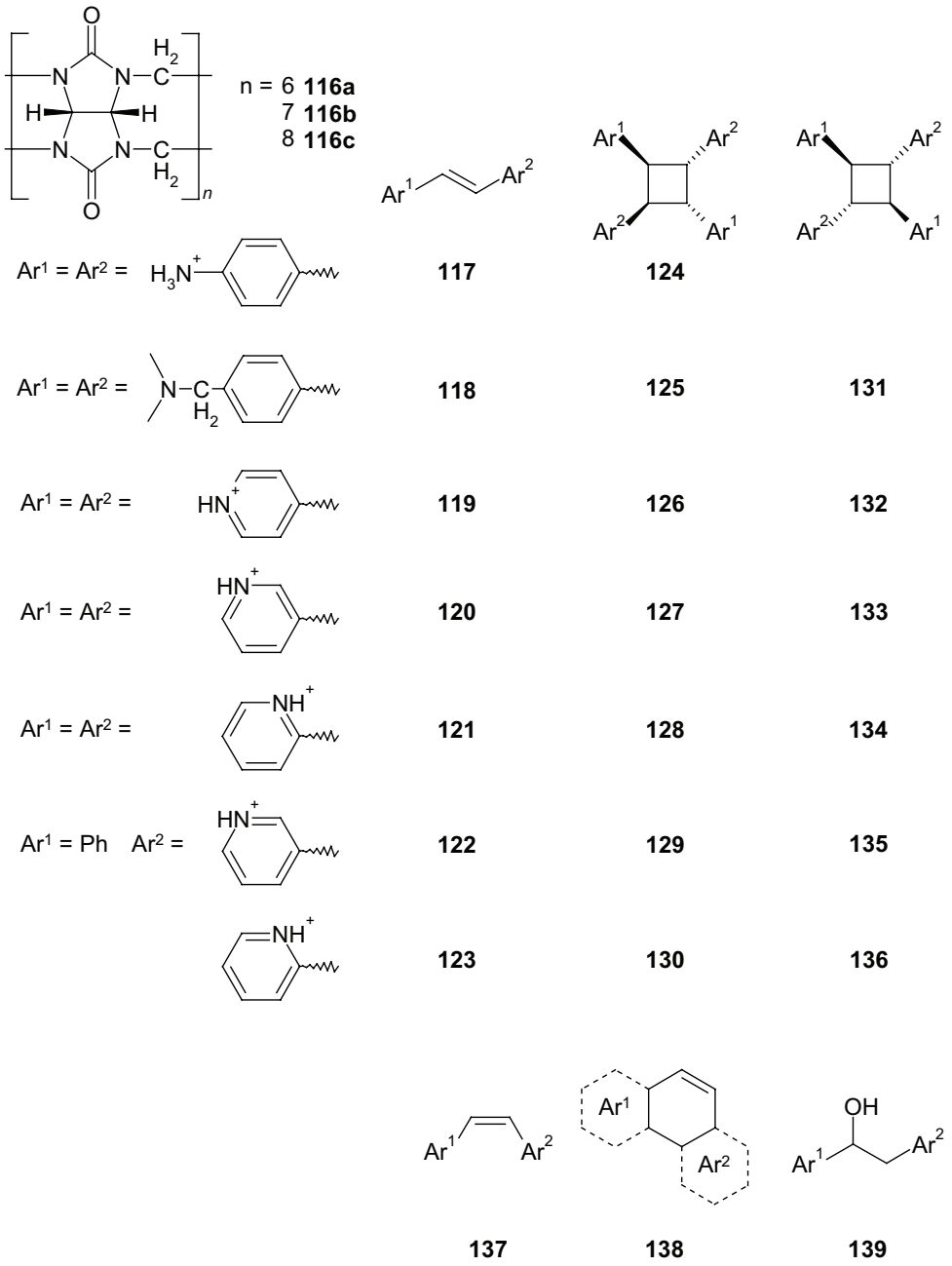


SCHEME 43. Paternó–Büchi reaction of adamantan-2-ones with fumaronitrile in the presence of β-cyclodextrin (β-CD) favouring formation of the syn isomer **114**

the reaction the substrate is firmly anchored in the β-cyclodextrin cavity, thus blocking approach of fumaronitrile from one face of the carbonyl group. Better fitting substituents such as phenyl (**112e**) or *tert*-butyl (**112f**) lead preferentially to the syn cycloadduct **114** with ratios up to 86:14. In the absence of β-cyclodextrin, selectivity for the anti isomer **115** (e.g. R = Cl, syn:anti, 43:57; R = *t*-Bu, syn:anti, 36:82) is observed in aqueous solution. The presence of α- or γ-cyclodextrin does not change this preference significantly.[92]

6-(5-Cyanonaphthyl-1-carboamido)-6-deoxy-β-cyclodextrin was found to manipulate the anti-Markovnikov addition of methanol to 1,1-diphenylpropene.[93] In 50% aqueous methanol, 2-methoxy-1,1-diphenylpropane was obtained with up to 61% yield and 6% ee (1 eq. of the template, $-40\,^{\circ}$C). In pure methanol, conversion below 1% was observed. In 25% aqueous methanol, the isolated yields were 15–18% with ee values of up to 11%.

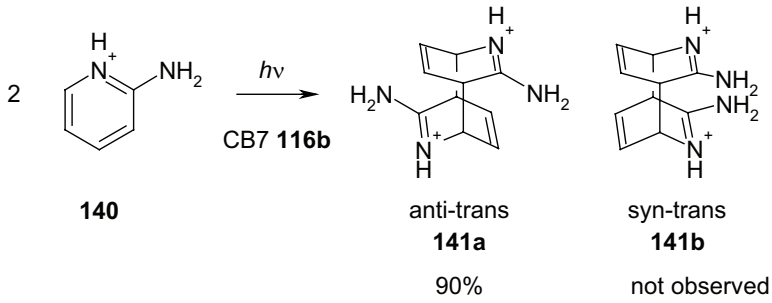
Photocycloaddition of double bonds in stilbenes[94–96] and its nitrogen-containing analogues,[97] 2-aminopyridine,[98] and cinnamates[99,100] was studied in the presence of cyclodextrins or cucurbiturils **116** (Scheme 44). When cucurbituril **116** of the correct size was used, the guest molecules coordinated to the portal oxygens atoms in a defined geometry, leading to high selectivity for some of the products. In the case of diaminostilbenes **117**, photodimerisation in the cavity of cucurbit[8]uril **116c** occured and syn cycloadduct **124** was selectively formed with a syn:anti ratio higher than 95:5.[95] In the absence of the template **116c**, the main reaction pathway was the isomerisation to the corresponding *Z*-isomer **137**. In case of dimethylaminomethyl-



Scheme 44. Photodimerisation of stilbene and its nitrogen-containing analogues in the cavity of cucurbit[8]uril **116c** or cyclodextrins

substituted stilbene **118**, irradiation in the presence of γ-cyclodextrin led to selective formation of the trans dimer **131** (yield 79%, minor cis dimer **125** 19% yield).[101] In the presence of the smaller α- or β-cyclodextrins or in the absence of any template, the photodimerisation reaction was prohibited. Similar enhancement was observed for the nitrogen-containing stilbene analogues **119** to **123**.[97] Irradiation in the absence of any template yielded the corresponding cis isomers **137**, an intramolecular cyclisation product **138**, and the hydration product **139**, while in the presence of cucurbit[8]uril **116c** a mixture of the corresponding syn dimers **126**–**130** (81–90% yield) and anti dimers **132**–**136** (0–6% yield) was obtained. The cavity of cucurbit[7]uril **116b** was too small to accommodate two molecules of the guest, and its presence did not enhance dimerisation selectivity.

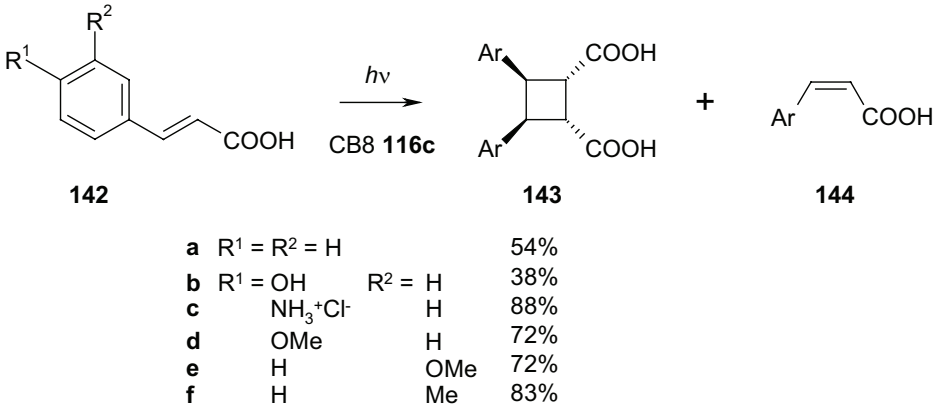
The [4+4] photocycloaddition of 2-aminopyridine hydrochloride **140** inside the cavity of cucurbit[7]uril **116b** gives an increased selectivity for the anti-trans dimer **141a** (yield up to 90% without any side products).[98] In the absence of the template, both anti-trans **141a** and syn-trans **141b** dimers were formed in a ratio of ca. 4:1 (Scheme 45). The template also protected the protonated form from thermal dissociation to the starting materials.



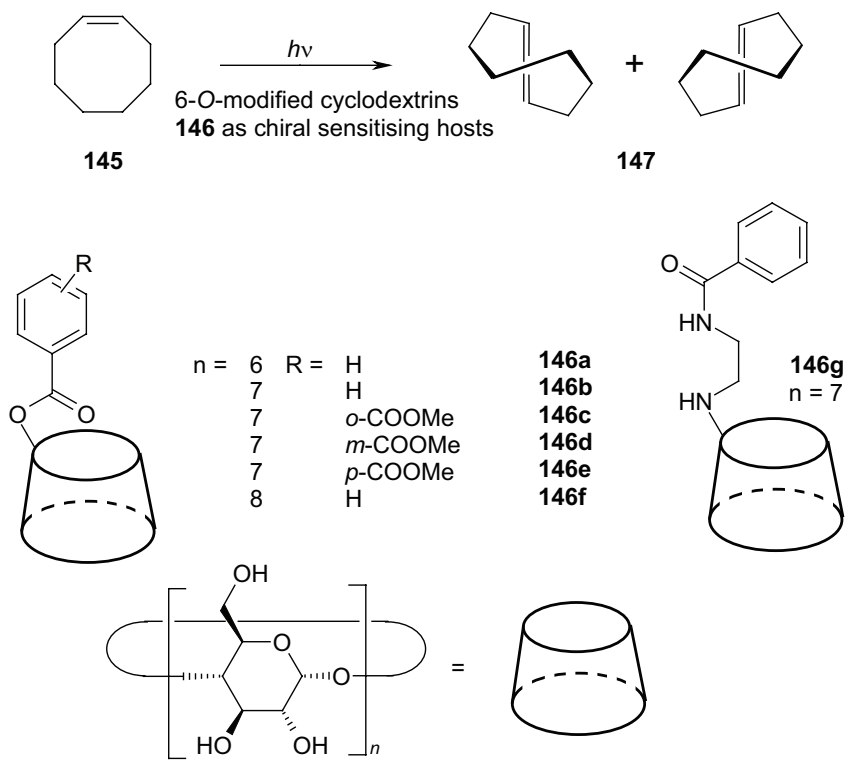
SCHEME 45. Photodimerisation of 2-aminopyridine hydrochloride in the cavity of cucurbit[7]uril **116b**

Irradiation of *trans*-cinnamic acid **142** included in the cavity of cucurbit[8]uril **116c** led to selective formation of the cyclic dimer **143** together with the corresponding cis isomer **144** (Scheme 46).[99] Best results were observed for 4-amino-*trans*-cinnamic acid hydrochloride **142c**, which yielded 88% of the corresponding dimer **143c**.

Enantiodifferentiating photoisomerisation of *Z*-cyclooctene **145** to chiral *E*-cyclooctene **147** (Scheme 47) was achieved in the cavity of 6-*O*-substituted cyclodextrins **146a**–**g**.[102–104] Host compound **146b** gave the best results with E/Z ratio of 0.29 and ee of 24% after irradiation at $-40\,^{\circ}\mathrm{C}$ in 50% aqueous methanol. With the other cyclodextrin derviatives **146a,c**–**g**, higher E/Z ratios were observed but the ee values remained low. Photoisomerisation of *Z*-cyclooctene **145** in the presence of a permethylated 6-*O*-benzoyl-β-cyclodextrin was recently described.[105] This host is more



Scheme 46. Photodimerisation of cinnamic acid in the cavity of cucurbit[8]uril **116c**



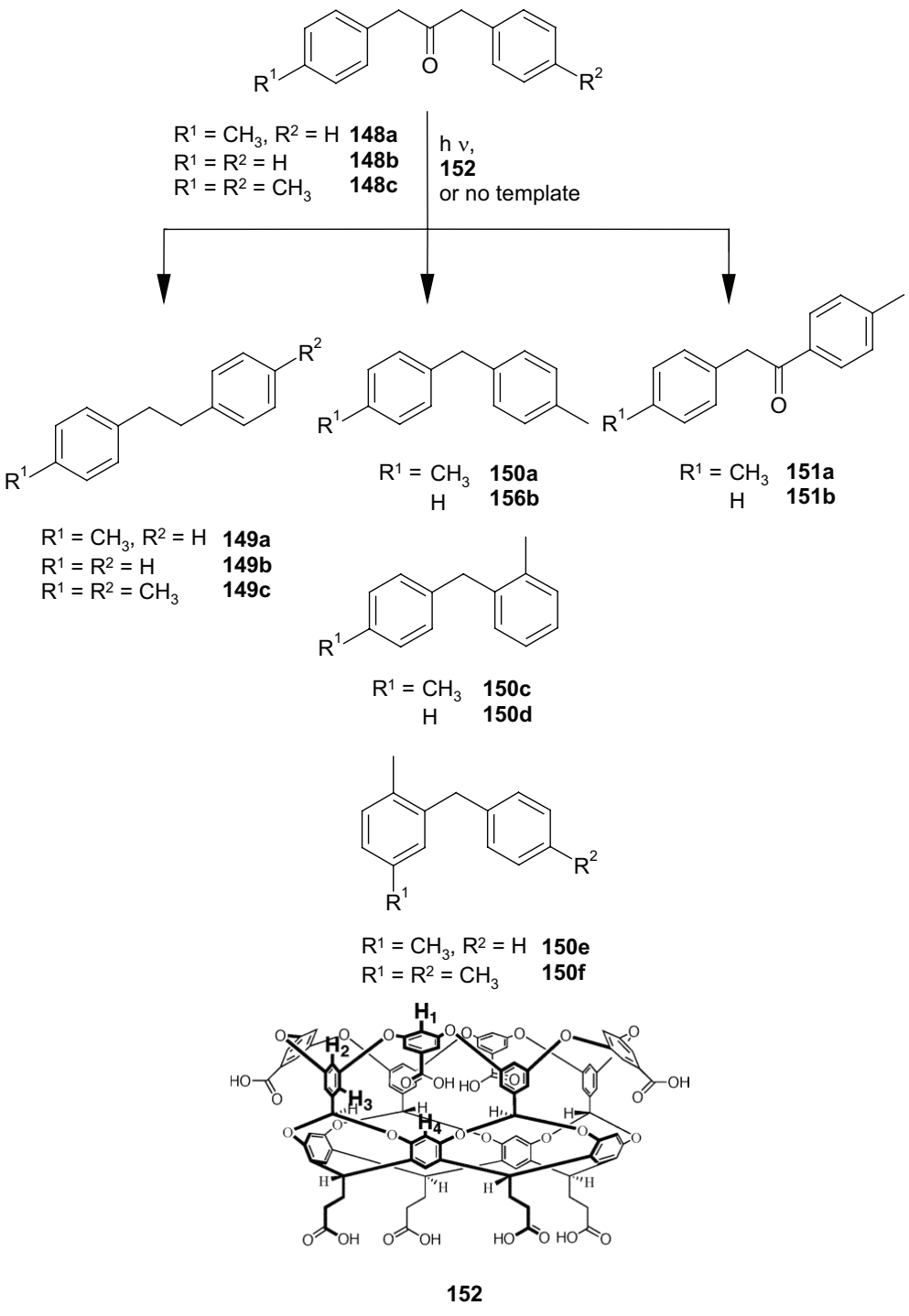
Scheme 47. Enantiodifferentiating photoisomerisation of *Z*-cyclooctene; *E/Z* ratios and ee values depend on the chiral host **146** and conditions (see text)

flexible due to the absence of the hydrogen-bond network on the secondary face[84] of the cyclodextrin. The E/Z ratios and ee values critically depend on the temperature and composition of the solvent. In pure methanol, the E/Z ratio remained low with no significant asymmetric induction since practically no complexation of the *Z*-cyclooctene **145** by the host occurred and all photochemistry took place "outside" the cavity, in the bulk media. In aqueous solutions containing 50% or 25% of methanol, the chiral sense of the photoproduct **147** could be switched by temperature. The best results reached 9% ee for for *(R)*-(−)-**147** (obtained in 50% aqueous methanol at −40 °C) and 4% ee for *(S)*-(+)-**147** (obtained in 25% aqueous methanol at 40 °C).

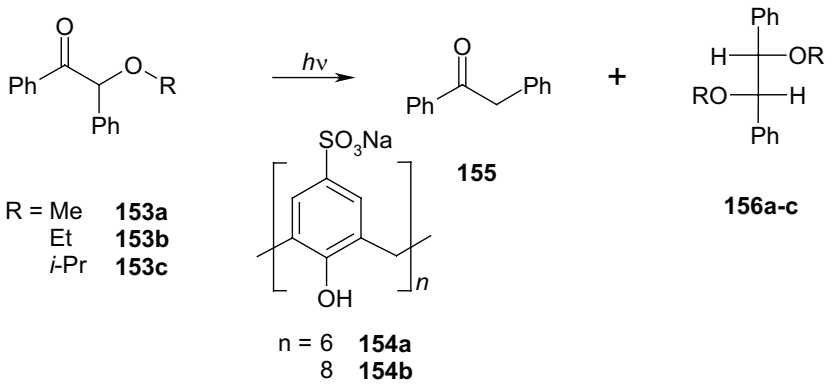
The selectivity of photochemical cleavage reactions was successfully manipulated by inclusion of the starting material in a self-assembled cavitand[106] or in a water-soluble calixarene.[107] In the absence of a template, photochemical cleavage of 1-phenyl-3-*p*-tolylacetone **148a** yielded a mixture of decarbonylation products **149a**–**c** (Scheme 48).[106] When included in a self-assembled cavitand $\mathbf{152}_2$, ketone **148a** gave a mixture of the decarbonylated product **149a** (41%), rearranged decarbonylated products **150a,c,e** (15%), and rearranged product **151a** (44%). 1,3-Diphenylacetone **148b** rendered similar results (decarbonylated product **149b** in 38% yield, rearranged decarbonylated products **150b,d** in 13% yield, and rearranged product **151b** in 49% yield) unlike 1,3-bis-(*p*-tolyl)-acetone **148c** whose geometry in the cavity favoured formation of the decaronylated product **149c** in 96% yield along with minute amounts of side products.

Benzoin alkyl ethers **153** (Scheme 49) preferentially undergo Norrish Type II cleavage when encapsulated in the cavity of *p*-sulphonatocalixarenes **154**.[107] The substrate was locked by the cavity in a conformation which favoured the γ-hydrogen abstraction (yielding deoxybenzoin as the major product) rather than the cleavage of the C–C bond (yielding pinacol ether as the major product). Higher yields of the Norrish Type II reaction were observed with the larger calixarene **154b**: benzoines **153a**–**b** yielded up to 96% of deoxybenzoin **155** and benzoin **153c** up to 85% of deoxybenzoin **155** together with minor amounts of the corresponding pinacol ethers **156a**–**c**. The smaller cavity of calixarene **154a** allowed cage escape, and observed yields of the the Type II product were therefore lower. Compound **153a** gave up to 70% of deoxybenzoin **155** and 30% of pinacol ether **156a**. Compound **153b** yielded up to 67% of **155** and 32% of **156b**, and **153c** gave up to 65% of **155** and 35% of **156c**.

Compound **158** is able to transport sensitiser **157** and release the phthalocyanine upon irradiation.[108,109] Two cyclodextrin units are linked in **158** by a tether containing a central C=C double bond (Scheme 50). The *tert*-butyl groups of the phthalocyanine sensitiser **157** bind into the cyclodextrin cavities, making complex **157**·**158** water-soluble. Upon irradiation, sensitiser **157** effected formation of singlet oxygen[110,111] and thus cleavage of



SCHEME 48. Photochemical cleavages of substituted acetones; See text for yields of individual products. Structure of compound **152** reproduced from ref. 106



SCHEME 49. Selective Norrish type II cleavage in the cavity of a calixarene; See text for yields of individual products

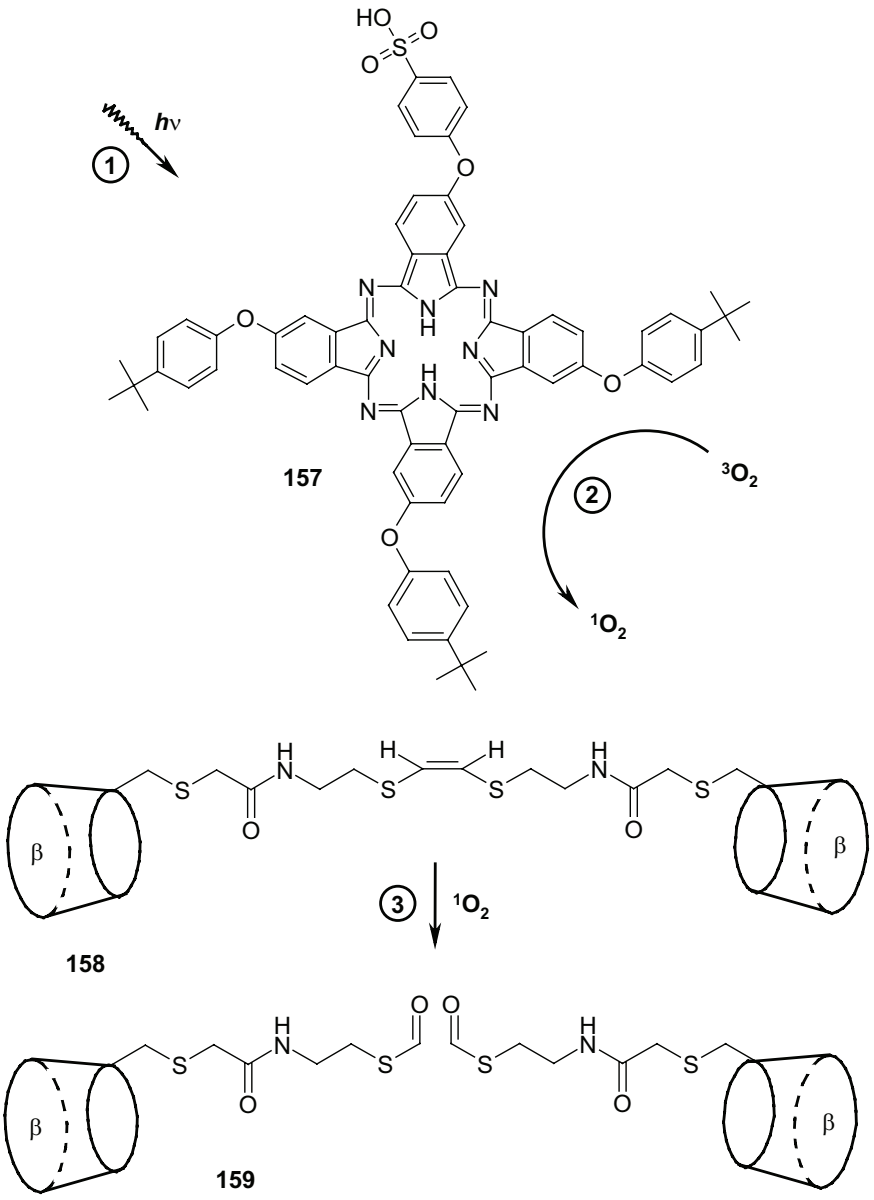
the C=C double bond yielding **159**. Once the two cyclodextrin units were disconnected, the binding affinity for the sensitiser **157** decreased. The cooperative effect of the two cyclodextrins is lost, and the loose linker chains compete for binding into the cyclodextrin cavity. The complex therefore dissociates, leading to precipitation of the now insoluble phthalocyanine sensitiser. Eventually, the sensitiser concentrated in a directed light beam, as shown by an experiment with a reaction irradiated through a small hole in a shield surrounding the reaction vessel. Binding to the cyclodextrin dimer and rate of the cleavage reaction was improved in a series of zinc phthalocyanines.[112]

7. Conclusion

The concept of reaction control in homogeneous solutions by templates is clearly established in photochemistry. Shielding of prochiral faces, topochemical reaction control, templation, and aggregate or inclusion complex formation are strategies found to enhance and control reaction efficiency, regio- or stereoselectivity. However, the number of truly catalytic examples and their efficiency remain limited. Development of catalytic templates controlling the stereochemistry of photoreactions with high precision and activity will be therefore a future challenge in the field.

8. Notes and References

[1] Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
[2] For examples, see: (a) Natarajan, A.; Mague, J. T.; Ramamurthy, V. *Crystal Growth & Design* **2005**, *5*, 2348–2355. (b) Natarajan, A.; Mague, J. T.; Ramamurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 3568–3576. (c) Alam, M. M. *Synlett* **2003**, 1755–1756.



SCHEME 50. Cyclodextrin-based photosensitiser carrier **158**; Yield of the reaction was not given. Key: (1) irradiation, (2) sensitisation of oxygen, (3) cleavage of C=C double bond

[3] For an example, see: Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219–235.

[4] For an example, see: Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.

[5] Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647–678.

[6] In the classical example, photodimerisation of cinnamic acid in the crystal, a limiting distance of 0.42 nm was defined. If groups are closer, they react. If groups are further apart, no reaction is observed.

[7] For recent reviews on solid-state control of photoreactivity, see: (a) Ito, Y. *Synthesis* **1998**, 1–32. (b) Feldman, K. S.; Campbell, R. F.; Saunders, J. C.; Ahn, C.; Masters, K. M. *J. Org. Chem.* **1997**, *62*, 8814–8820.

[8] One example is the photodimerisation of crystalline anthracene, which occurs at a "topochemically forbidden" distance of the reaction groups of 0.6 nm. See: Kaupp, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 595–598 and references therein.

[9] (a) Ramamurthy, V.; Schanze, K. S. *Photochemistry of Organic Molecules in Isotropic and Anisotropic Media*; Marcel Dekker, Inc.: New York, 2003. (b) Kaupp, G. In *Comprehensive Supramolecular Chemistry*; Davies, J. E., Ripmeester, J. A., Eds.; Elsevier: Oxford, UK, 1996; Vol. 6, p 381. (c) Kaupp, G. *Adv. Photochem.* **1995**, *19*, 119.

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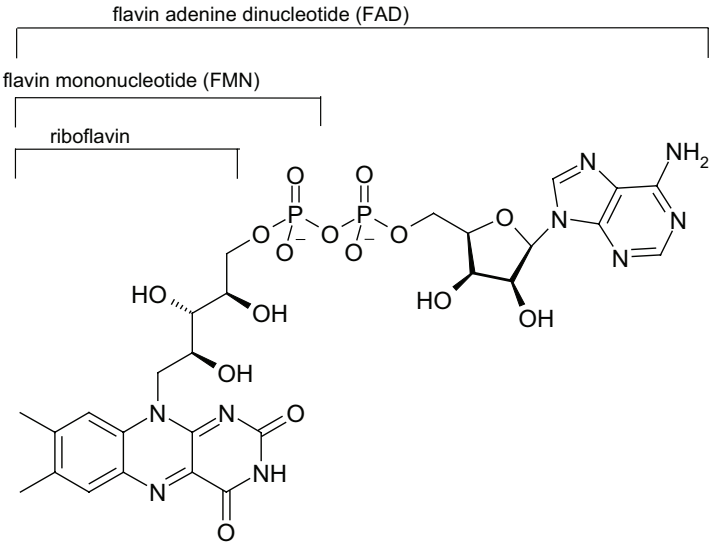
Chapter 2

2'-Oxoethyl Flavin Revisited*

1. Introduction

The flavin (7,8-dimethylbenzo[g]pteridin-2,4-dione) unit is the functional component of many redox enzymes,[1,2] often in the form of flavin mononucleotide (FMN) or flavin adenine dincucleotide (FAD) co-factor (Scheme 1), and is responsible for a variety of biochemical redox transformations. For



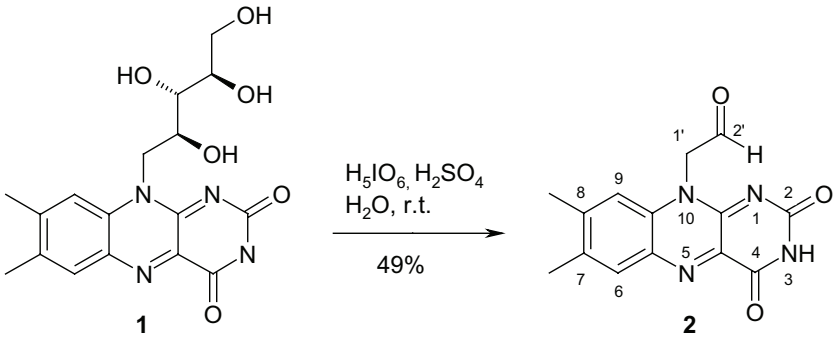
Scheme 1. Riboflavin and flavin-based co-factors FAD and FMN

humans, it is an essential compound, and must be acquired from the nutri-

*The investigations described in this Chapter have already been submitted for publication (Svoboda, J.; König, B.; Sadeghian, K.; Schütz, M. *Z. Naturforsch*). Theoretical computations (see pages 58–60 and 84) have been carried out by K. Sadeghian and Prof. M. Schütz from the Institute of Physical and Theoretical Chemistry, Universität Regensburg.

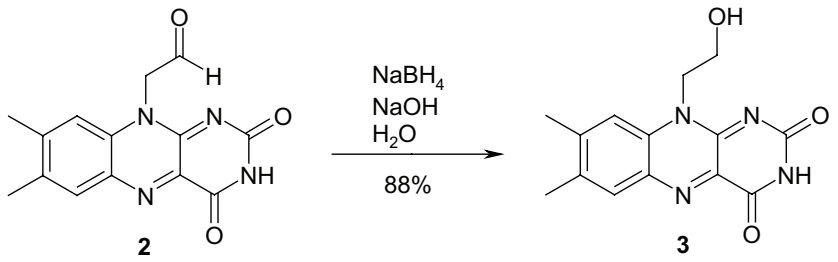
tion in the form of riboflavin **1**, vitamin B_2. Redox activity of the flavin unit, even enhanced upon irradiation, was studied in flavoenzyme models and applied for the construction of *de novo* functional molecules.[3–26] In organic synthesis, they are usually accessed *via* the Kuhn synthesis[27] which is a multi-step procedure to be repeated every time a change in the design is required, and there is a logical interest to prepare flavin-based molecules in a quicker and modular fashion from an easily available common intermediate.

Therefore, our objective was to investigate the reactivity of 2'-oxoethyl flavin **2**, known product of riboflavin **1** oxidative degradation (Scheme 2).[28] Not much is known about the chemical behaviour of this intermediate, al-



SCHEME 2. Oxidative degradation of riboflavin **1** to 2'-oxoethyl flavin **2**

though described more than five decades ago and easily accessible from commercially available riboflavin **1**[29] at multi-gram scale. Apart from several examples of its use for the modification of amino-group-containing polymers[30,31] and surface-bound monolayers,[32,33] 2'-oxoethyl flavin **2** has been mostly considered a product of riboflavin **1** photodegradation.[34,35] Reduction of 2'-oxoethyl flavin **2** to the corresponding alcohol **3** has been described (Scheme 3),[36] but to the best of our knowledge, no synthetic application



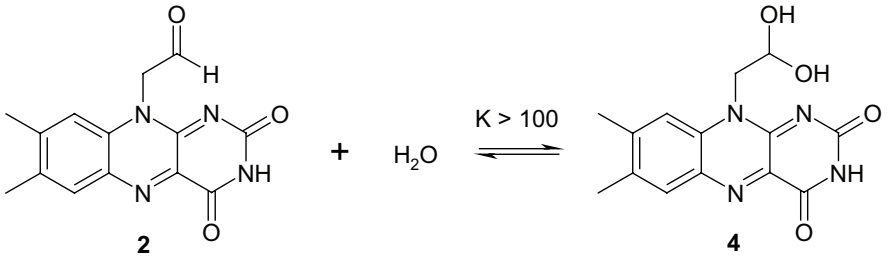
SCHEME 3. Reduction of 2'-oxoethyl flavin **2**

thereof—apart from simple acetylation[36]—has been reported. We reasoned whether 2'-oxoethyl flavin **2**, containing the versatile aldehyde functional group, can be used to establish a route to more complicated flavin-based molecules using nucleophilic addition to the aldehyde. We have therefore

accomplished a synthetic study on 2'-oxoethyl flavin **2**, extended its original characterisation by modern spectroscopic methods, and prepared a new derivative.

2. Results and Discussion

2'-Oxoethyl flavin **2** was prepared according to the known procedure.[28] Starting from commercially available riboflavin **1**, oxidative degradation by periodic acid[37] yielded up to 5 g of 2'-oxoethyl flavin **2** in one batch. Additionally, we have clarified structure of the hydrate, mentioned first by Petering,[38] using ^{1}H NMR spectrometry. We observed that the raw product spectrum contains two sets of resonance signals: the first belongs to the desired aldehyde product **2**, while the second, more intensive set of signals does not include the typical aldehyde proton resonance and its side chain resonance signals exhibit higher multiplicity than expected. The second set of signals was assigned to geminal diol **4**, formed by an equilibrium hydration reaction of the aldehyde **2** (Scheme 4). Chemical shifts of these signals



Scheme 4. Equilibrium hydration of 2'-oxoethyl flavin **2**

were in accordance with the generally observed pattern:[39] resonance of the protons in position 2' (see Scheme 2 for numbering) is observed at 5.31 ppm in the *gem*-diol **4**, shifted 4.43 ppm upfield from the aldehyde resonance at 9.74 ppm (generally −4.6 to −5.0 ppm), and the resonance of α-protons is observed at 6.27 ppm in the *gem*-diol form **4**, shifted 0.63 ppm downfield from the resonance of α-protons at 5.64 ppm in the aldehyde form (generally +0.7 to 0.9 ppm). Interestingly, even the resonance of aromatic protons in position 6 and 9 is influenced by the hydration reaction, although rather distant. On hydration, resonance of proton 9, observed at 7.71 ppm, shifts 0.16 ppm downfield to 7.87 ppm, while resonance of proton 6, observed at 7.94 ppm, shifts 0.03 ppm upfield to 7.91 ppm. This observation suggests an interaction between the aldehyde–*gem*-diol group and the conjugate flavin system. The azeotropic drying of crude product with toluene (see Chapter 4, page 86) forces the equilibrium to the aldehyde **2**, and only the corresponding signal set can be observed in the ^{1}H NMR spectrum after this treatment.

To probe this unexpected tendency to prefer the *gem*-diol form **4** rather

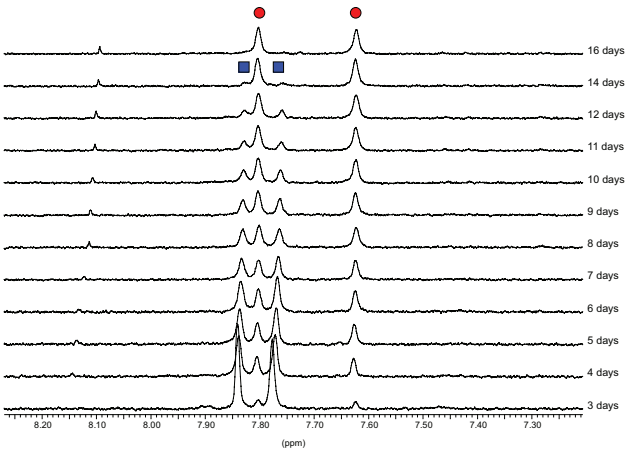


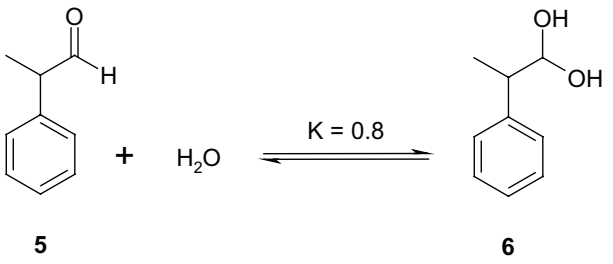
FIGURE 1. The equilibrium of aldehyde **2** and *gem*-diol **4** favours the *gem*-diol form. ■ aldehyde **2**, ● *gem*-diol **4**. Signals of aromatic protons in position 6 and 9 are shown. Aldehyde **2** 2×10^{-3} M (initial concentration), trifluoroacetic acid 2×10^{-4} M, deuterium oxide:dimethylsulphoxide-d_6 = 1:1 (v/v) 762 μL, ambient temperature. Measured on a Bruker spectrometer with working frequency 300 MHz using 64 transitions

then the aldehyde form **2**, the equilibrium constant of hydration was determined. A sample of the azeotropically dried aldehyde **2** in a mixture of dimethylsulphoxide-d_6 and deuterium oxide (1:1 v/v) was prepared, and changes of the *gem*-diol **4**:aldehyde **2** ratio were monitored by ^{1}H NMR spectroscopy (Figure 1). Intensity of the aldehyde **2** set of resonance signals steadily decreased, accompanied by an increase in the *gem*-diol **4** signals intensity.[40]

After 16 days of standing at ambient temperature, the concentration of aldehyde fell under the detection level, and the ratio *gem*-diol **4**:aldehyde **2** must have therefore reached at least 100.[39] This is highly unusual: typical examples of aldehydes or ketones which form hydrates of such stability, are those which contain electronegative substituents in the α-position increasing the polarisation of the aldehyde group, such as trichloroacetaldehyde (equilibrium constant of hydration 2000), and those where hydration releases deviation from "ideal" geometry, such as cyclopropanone.[41] However, in the case of 2'-oxoethyl flavin **2**, there are no electronegative substituents in the α-position nor geometry strain to be released.

For comparison, similar experiment was carried out with structurally related 2-phenylpropionic aldehyde **5** (Scheme 5). Again, increase of the *gem*-diol **6** signals intensity at the expense of aldehyde **5** signals intensity was observed, but in this case, the mixture equilibrated at 45:55 *gem*-diol **6**:aldehyde **5** ratio which corresponds to an equilibrium constant of 0.8, as expected for a general aldehyde.

In order to understand the preference of the *gem*-diol over the aldehyde form, *ab initio* electronic structure calculations at the level of second-order



SCHEME 5. Equilibrium hydration of 2-phenylpropionic aldehyde **5**

Møller-Plesset perturbation theory (MP2) were performed. Basis Set Superposition Error (BSSE) contaminations of the interaction energy (which in the context of an intramolecular hydrogen bond cannot be corrected for with the counterpoise procedure of Boys and Bernardi[42]) were to large extent avoided by performing *local* MP2 (LMP2) calculations. Correlation energies obtained from local correlation methods like LMP2 are much less affected by BSSE effects than the energies of the corresponding canonical methods, as was demonstrated before.[43] Geometry optimisations of the 2'-oxoethyl flavin and its *gem*-diol form were carried out with the efficient analytic LMP2 energy gradient method described previously[44] using the aug-cc-PVDZ AO basis set of Dunning.[45] Single point energy calculations at these geometries were performed employing the more extended aug-cc-PVTZ and aug-cc-PVQZ sets, respectively, which were used to extrapolate the correlation energy at the basis set limit (two-point extrapolation formula).[46] Analogous calculations were also performed for the 2-phenylpropionic aldehyde **5** and its *gem*-diol form **6** to have a reference system an aldehyde with "normal" chemical behaviour. The parameters specifying the calculations in detail are given in Chapter 4, page 84.

For the *gem*-diol form **2** of 2'-oxoethyl flavin molecule the calculations predict the formation of an intramolecular hydrogen bond between one of the hydroxy groups of the diol and the nitrogen atom in position 1 of the flavin skeleton. The length of this hydrogen bond is comparatively short, i.e., 1.96 Å vs. 2.05 and 2.07 Å for the water dimer and the water ammonia complex, respectively, calculated at the same level of theory. In order to assess the strength of this hydrogen bond additional *constrained geometry* optimizations were performed for a sequence of different C-1'–C-2'–OH dihedral angles. A barrier height of 8.34 kcal/mol at the basis set limit was so obtained for the rotation about this dihedral angle breaking the hydrogen bond. Due to the absence of sterical hindrance this barrier height appears to be a reasonable estimate for the strength of the intramolecular hydrogen bond, which is substatially stronger than the hydrogen bond of the water dimer (4.94 kcal/mol) or even of the water–ammonia dimer (6.48 kcal/mol).

For the electronic contribution to the hydration reaction energy of 2'-

oxoethyl flavin **2** a value of −47.2 kcal/mol (extrapolated to the basis set limit, −46.8 kcal/mol for the aug-cc-pVQZ basis alone) was obtained. This is −5.5 kcal/mol more than for the reference system, again reflecting the enhanced stability of the former due to intramolecular hydrogen bond formation. Based on these electronic reaction energies the related free energy differences at room temperature were assessed using harmonic vibrational frequencies calculated at the level of density functional theory (B3-LYP hybrid functional, TZVP basis set).[47] The free energy differences for the hydration reactions so obtained amount to −38.2 kcal/mol and −26.9 kcal/mol for 2'-oxoethyl flavin **2** and the 2-phenylpropionic aldehyde **5**, respectively. Due to the underlying approximation of an ideal solution these two values certainly have to be taken with care. However, the error imposed by this model is likely to cancel to large extent in the difference between these two free energy differences, which amounts to −11.3 kcal/mol. Thus we can infer from these free energy calculations that (i) the free reaction energies are smaller (absolute value) than the corresponding pure electronic reaction energies, and (ii) zero point energy corrections and finite temperature entropic effects disfavour the *gem*-diol form to lesser extent for 2'-oxoethyl flavin **2** than for the 2-phenylpropionic aldehyde reference system.

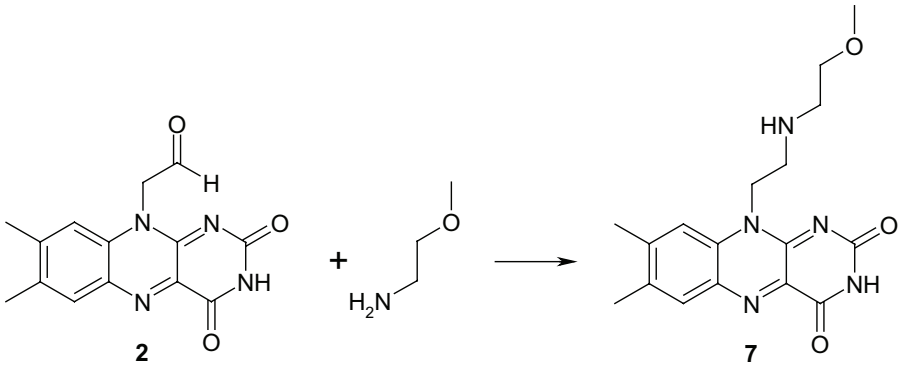
To summarise, we conclude from our calculations and experimental findings, that the intramolecular hydrogen bond occurring in the *gem*-diol form **2** of the 2'-oxoethyl flavin **4** leads to a stabilisation of the diol over the aldehyde to such an extent that the aldehyde form **4** can barely be observed by the spectrometric methods applied in this work.

To explore the use of 2'-oxoethyl flavin **2** in synthetic flavin chemistry, a range of reactions were attempted. Unfortunately, the poor solubility (lower than 2 g/L in dimethylsulphoxide, < 305 mg/L in dichloromethane, < 200 mg/L in ethanol, and < 30 mg/L in tetrahydrofurane) and lability to base[48,49] severely limit the synthetic use of aldehyde **2**.

Reductive alkylation, for example by 2-methoxyethanol, would be among synthetically interesting transformations, because it directly furnishes 10-(3',6'-dioxahept-1'-yl) flavin, derivative of good solubility in organic and aqueous solvent.[7,8] Unfortunately, neither the conditions used by Doyle *et al.*[50] nor by Bethmont *et al.*[51] led to the desired product. Knövenagel or Wittig reactions which would introduce a synthetically versatile carboxylic acid function[52,53] failed, too. The first, carried out in the presence of pyridine and piperidine under reflux,[54] yielded a complex reaction mixture, while the latter, using an ylide pre-formed from triethyl phosphoacetate and sodium hydride, did not convert to products. Surprisingly, even the formation of acyclic and cyclic acetals failed in our hands, and the starting material remained intact under the reaction conditions. On the other hand, reaction with highly basic butyl lithium yielded a complex reaction mixture, indicating decomposition of the flavin skeleton.

Reductive amination under catalytic hydrogenation conditions yielded

the expected secondary amine **7** (Scheme 6). The amine **7** was the only



Scheme 6. Reductive amination of 2'-oxoethyl flavin **2**; Conditions: ethanol, hydrogen (10 bar), 10% palladium on charcoal, r.t., 28%, or (ii) ethanol, hydrogen (40 bar), 10% palladium on charcoal, 60 °C, 80%

organic product of the reaction, and the yield could be increased up to 80% either by increasing the reaction temperature or using neat 2-methoxyethyl amine as solvent. It was not possible to reduce the intermediate imine by sodium cyanoborohydride,[55] sodium triacetoxyborohydride,[56] or sodium borohydride[57]—these reducing agents were too basic and similar to the aforementioned examples, the reaction yielded a palette of flavin decomposition products. Secondary amine **7** is better soluble in organic solvents than the starting material, and the amino group may be a target of subsequent derivatisation for example by acylation.

3. Conclusion

In conclusion, we have extended the characterisation of 2'-oxoethyl flavin **2** and clarified the structure of its *gem*-diol form **4**. In solutions containing water, the *gem*-diol form **4** is highly favoured and the equilibrium constant of aldehyde **2** and hydrated form **4** was found higher than 100, far from the range typical for general aldehydes. We have shown by theoretical calculations that the *gem*-diol **4** is stabilised by a hydrogen bond between one of the hydroxyl group and the nitrogen atom in position 1 of the flavin skeleton. A variety of nucleophilic addition reactions were attempted to employ 2'-oxoethyl flavin **2** as a building block for the construction of more complicated flavin-based molecules. However, the reactivity of the aldehyde group is influenced by the flavin skeleton, as the unusual stability of the *gem*-diol **4** indicates. Reductive amination under hydrogenation conditions was the only successful chemical transformation of the aldehyde **2** giving the secondary amine **7** in good yield.

Chapter 3

Thiourea-Enhanced Flavin Photooxidation of Benzyl Alcohol*

1. Introduction

Flavins are Nature's beloved redox co-factors.[1,2] They occur ubiquitously in a number of enzymes that bring the most essential biochemical processes about, mostly in the form of flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) co-factors. Their redox properties, reactivity and selectivity for the desired process are fine-tuned by substitution, non-covalent interactions and the presence of the surrounding protein, and their function can therefore be tailored to the task required. Their reactivity even increases upon irradiation, making them strong oxidising agents.[58–61]

A large number of flavoenzyme models which try to simulate a particular feature of the protein in a minimised system have been studied in the past.[5,9–20,22,23,25,26,62–68] Most of them focus on the changes of the flavin chromophore redox potentials caused by non-covalent interactions. However, examples where the modification of flavin reactivity was applied to chemical catalysis are less common.[6–8,21,69–74]

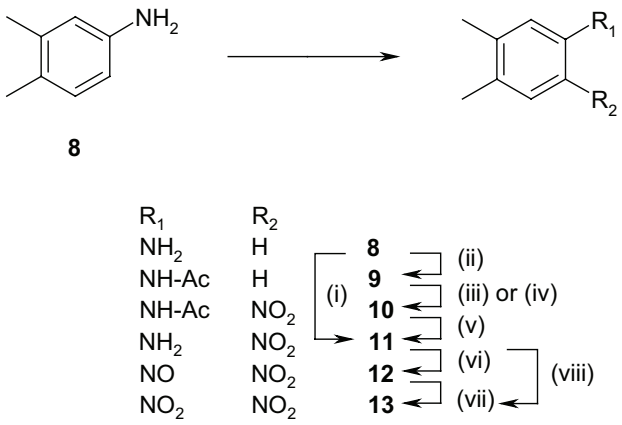
In this work, we report flavin molecules functionalised with a thiourea group[24,75–77] which was supposed to bind reversibly substrates of photooxidation reactions to keep them in the vicinity of the excited chromophore. This should increase the electron transfer efficiency by making the process intramolecular rather then diffusion-controlled.[7,8,24] To investigate possible

*The investigations described in this Chapter have already been submitted for publication (Svoboda, J.; Schmaderer, H.; König, B. *Chem. Eur. J.*). Synthesis and characterisation of compounds **33**, **34**, **36**, **38**–**40**, **44** and **45** was carried out by H. Schmaderer from the Institute of Organic Chemistry, Universität Regensburg. J. Svoboda and H. Schmaderer contributed equally to the kinetic experiments.

effects of thiourea functionalisation, the activity of the new flavin molecules was studied on the photooxidation of 4-methoxybenzyl alcohol in air.[78]

2. Synthesis

The synthesis of the new compounds follows the Kuhn synthesis.[27] The preparation of 4,5-dimethyl-1,2-dinitrobenzene **13** was optimised to obtain the starting material in sufficient quantities. The simple nitration of 4,5-dimethylaniline **8**[79] (Scheme 7, method i) was found unreliable, and the



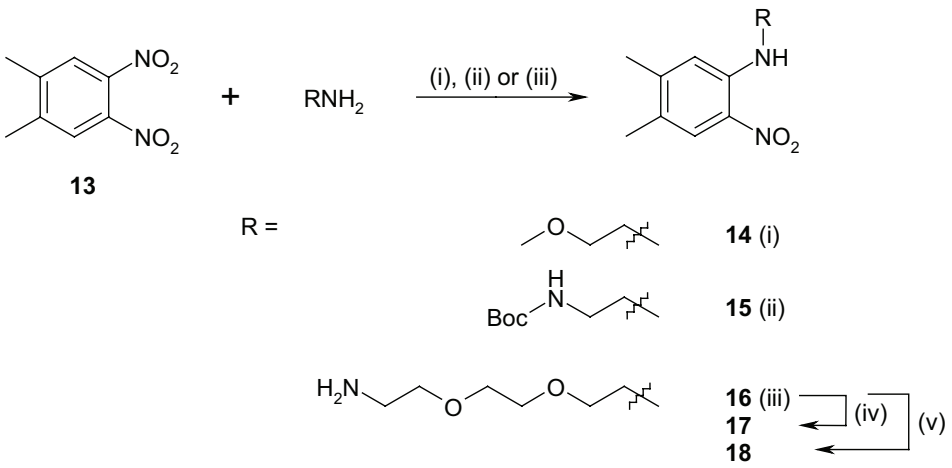
SCHEME 7. Synthesis of 4,5-dimethyl-1,2-dinitrobenzene **13** from 3,4-dimethylaniline **8**; Conditions: (i) 65% nitric acid, 98% sulphuric acid, $< 0\,^{\circ}C$, (ii) acetic anhydride, acetic acid, reflux, 15 min, (iii) 65% nitric acid, 98% sulphuric acid, $< 0\,^{\circ}C$, (iv) 65% nitric acid, acetic acid, 10–15 °C, 1 hr, (v) 98% sulphuric acid, 100 °C, 25 min, (vi) potassium peroxodisulphate, sulphuric acid, water, r.t., (vii) 30% hydrogen peroxide, sulphuric acid, r.t., (viii) 30% hydrogen peroxide, acetic acid, 50 °C, 16 hrs. See text for yields

amino group was therefore protected by acetylation before the nitration took place (method ii).[80] Nitration of acetanilide **9** described by Monge *et al.*[80] (method iii) was too energetic and significant amounts of undesired 2,6-dinitro product were obtained. Milder method of Sugaya *et al.* (method iv) was therefore employed.[81] 2-Nitroacetanilide **10** was then cleaved by hot sulphuric acid to yield the corresponding 2-nitroaniline **11** (method v) with overall yield 46%. Although the two-step method for the oxidation of 2-nitroaniline **11** *via* 1-nitro-2-nitroso intermediate **12** rendered fair results (methods vi–vii),[7,82] it was not very elegant due to low solubility of the starting material and product in the aqueous reaction mixture. Far older one-step approach[83] using hydrogen peroxide in acetic acid was therefore used with 46% yield of the dinitro product **13** (method viii).

Reactivity of the electron-deficient dinitro derivative **13** towards nucleophilic aromatic substitution makes the introduction of the desired substituent possible. Although corresponding 2-fluoronitro derivative was the

intermediate of choice in some cases,[4,11,84–87] we found the substitution reactions using the dinitro derivative **13** quite straightforward and easy-going.

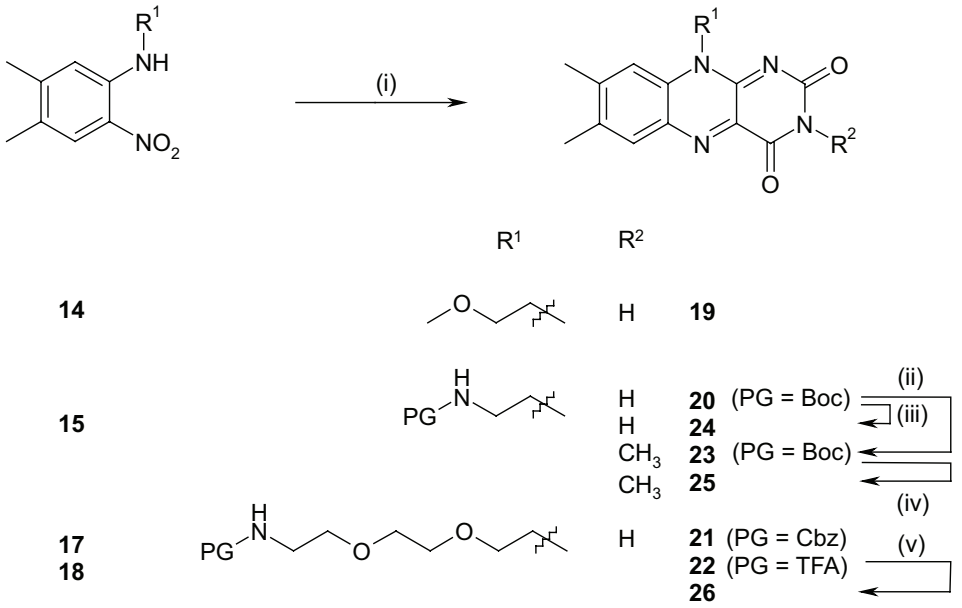
Heating the dinitro compound **13** with 3-oxabut-1-yl amine, 2-(*tert*-butyloxycarbonylamino)ethyl amine or symmetrical 3,6-dioxaoctyl-1,8-diyl diamine led to *N*-substituted 2-nitroanilines **14**–**16** (Scheme 8). The glycol



Scheme 8. *ipso*-Substitution of dinitro compound **13** with amines and protection of the side chain amino group; Conditions: (i) 3-oxabut-1-yl amine (neat), 80 °C, 6 hrs, 99%, (ii) pyridine, 24 hrs, 90 °C, 46%, (iii) ethanol, reflux, 62 hrs, 51%, (iv) Cbz-Cl, TEA, dichloromethane, r.t., 30 min, 64%, (v) ethyl trifluoroacetate, TEA, methanol, r.t., 24 hrs, 83%

chains increase the solubility of the target molecules in polar solvents, and the amino groups were converted to thiourea moieties later on. Although 3,6-dioxaoct-1,8-diyl diamine was not mono-protected, two fold substitution was not observed. However, the side chain amino group disturbs the course of the cyclocondensation reaction of the phenylene diamine intermediate with alloxane hydrate, and had to be protected before completion of the flavin synthesis. The flavin skeleton is sensitive to bases,[48,49] and protective groups which require removal by base are therefore not suitable. Suitable protective groups were benzyloxycarbonyl and trifluoroacetyl protective group.

The synthesis of the flavin skeleton was completed by reduction of the remaining nitro group and cyclocondensation of the resulting phenylene diamine intermediates with alloxane hydrate in the presence of boric acid to yield flavins **19**–**22** (Scheme 9). Flavin **20** was *N*-methylated by dimethyl sulphate to give the corresponding analogue **23**. *tert*-Butyl carbamates **20** and **23** were cleaved by hydrogen chloride and yielded 10-(2'-aminoethyl) flavins **24**·**HCl** and **25**·**HCl**. Unfortunately, the benzyloxycarbonyl protective group of flavin **21** could not be removed by any of the usual methods.[88,89] Cleavage of the trifluoroacetamide **22** in strongly acidic environ-



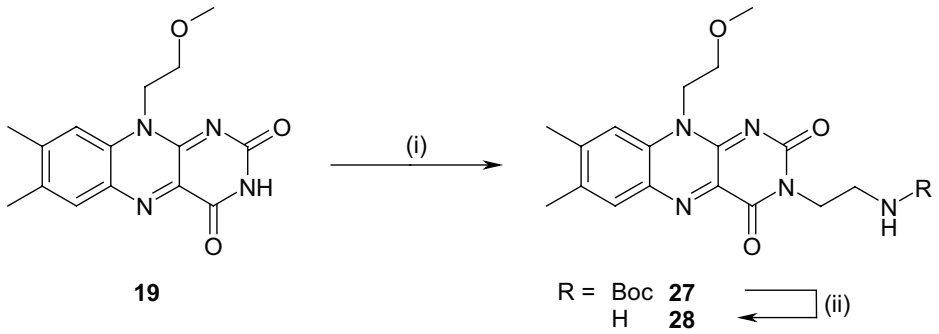
SCHEME 9. Completion of flavin synthesis; Conditions: (i) 1. Dihydrogen (g), 10% palladium on activated charcoal, acetic acid (compounds **14**, **15**, and **18**), or tin(II) chloride, ethanol, reflux, 72 hrs (compound **17**), 2. alloxane hydrate, boric acid, acetic acid, r.t., 50% (**19**), 47% (**20**), 71% (**21**), 48% (**22**), (ii) dimethyl sulphate, caesium carbonate, DMF (dry), r.t., overnight, 53%, (iii) hydrogen chloride, diethyl ether, chloroform, r.t., overnight, 83%, (iv) hydrogen chloride, diethyl ether, chloroform, r.t., overnight, 100%, (v) aqueous hydrochloric acid (6 M), 95–100 °C, 90 min, 100%

ment[90] led to the quantitative formation of aminoglycol flavin **26·HCl**.

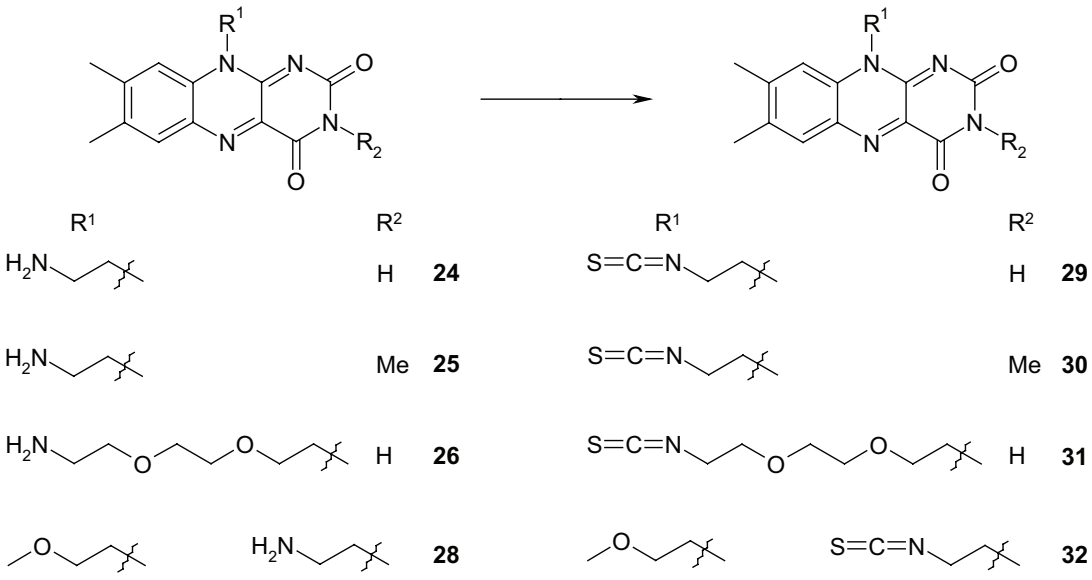
Flavin **19** was *N*-alkylated by 2-(*tert*-butyloxycarbonylamino)ethyl bromide (Scheme 10). Cleavage of *tert*-butylcarbamate **27** by hydrogen chloride yielded the corresponding 3-(2'-aminoeth-1'-yl) flavin **28·HCl**. Amines **24**–**28** were then converted to the corresponding isothiocyanates **29**–**32** by reaction with thiophosgene in a two-phase solvent mixture (Scheme 11). The reactions were clean, rapid and very good yields of the isothiocyanates were obtained.

The reaction of isothiocyanates with amines leads to the formation of substituted thioureas.[75,91] Flavin isothiocyanates **29**–**32** show high reactivity, and corresponding thioureas are obtained with excellent yields. Passing gaseous ammonia through the solution of a given isothiocyanate leads to mono-substituted thioureas **33**–**36** (Scheme 12) which are less soluble than the starting materials and were isolated by filtration or trituration in 44–100% yield. Reaction with secondary amines led to *N,N'*-substituted thioureas **37**–**40**. A hydrophilic chain (thiourea **37**) or fluorophilic chain (thioureas **38**–**40**) were introduced to increase the solubility of the molecules in hydrophilic or fluorophilic solvents, respectively.

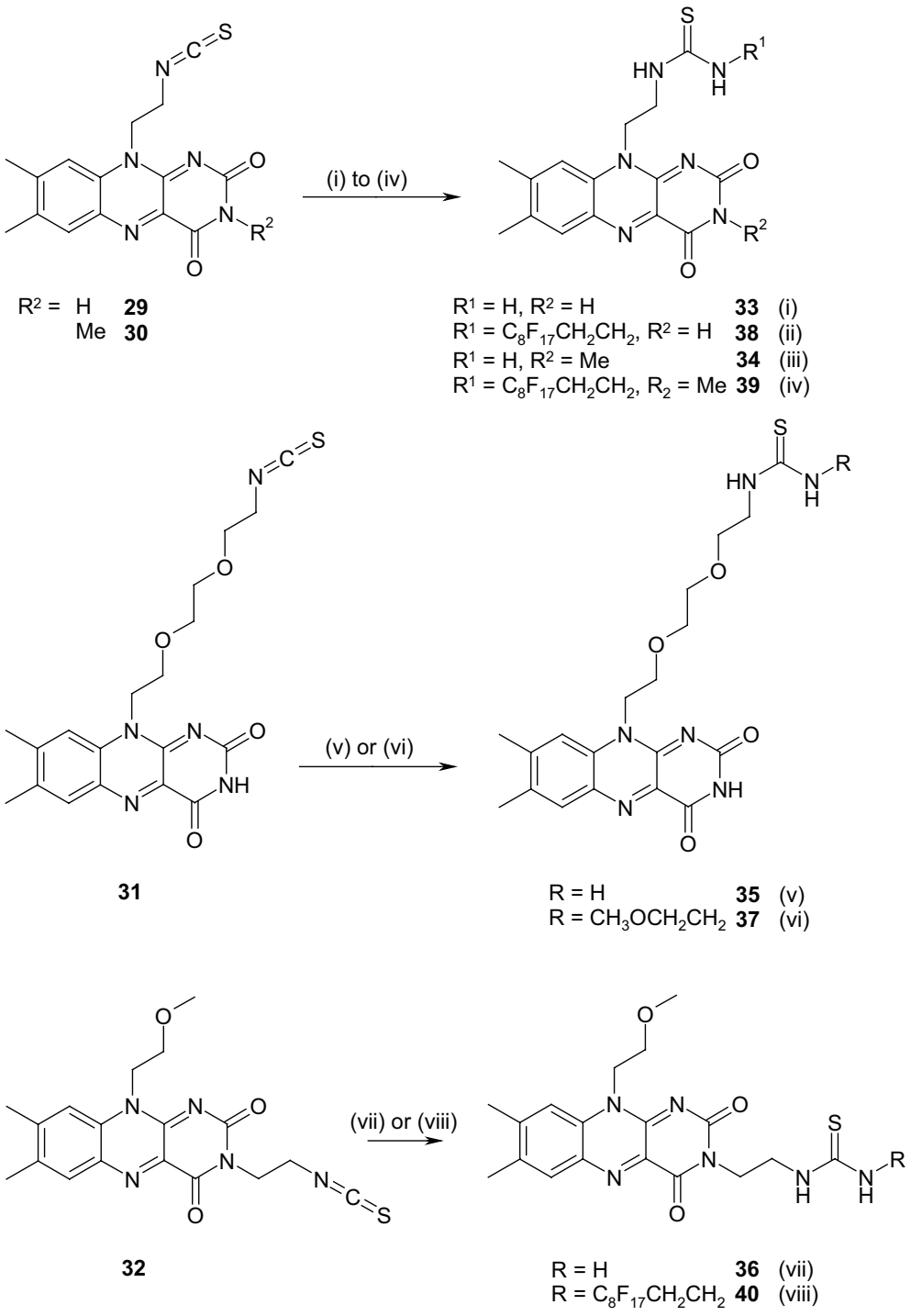
Flavins containing two thiourea groups were prepared starting from fla-



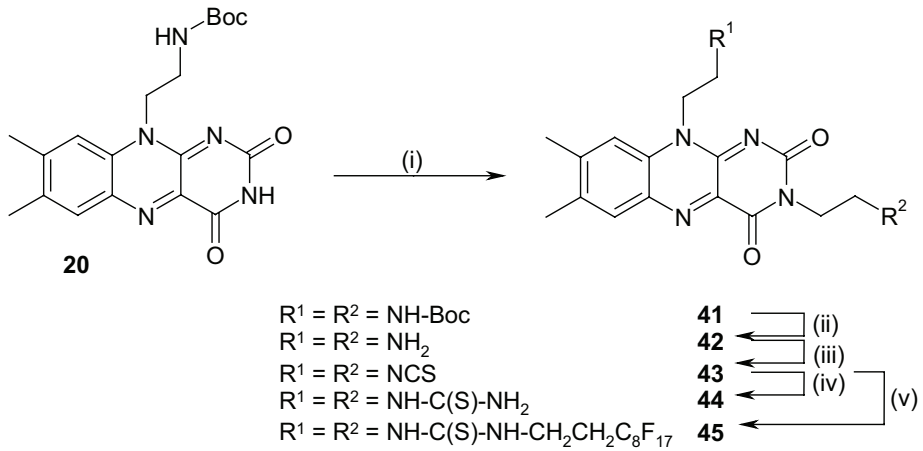
SCHEME 10. Synthesis of 3-(2'-aminoeth-1'-yl) flavin **28**; Conditions: (i) 2-(*tert*-butyloxycarbonylamino)eth-1-yl bromide, potassium carbonate, sodium iodide, DMF (dry), r.t., 3 d, 54%, (ii) hydrogen chloride, diethyl ether, r.t., 95%



SCHEME 11. Synthesis of isothiocyanates **29**–**32**; Conditions: thiophosgene, dichloromethane, calcium carbonate, water, r.t., 87% (**29**), 79% (**30**), 97% (**31**), 89% (**32**)



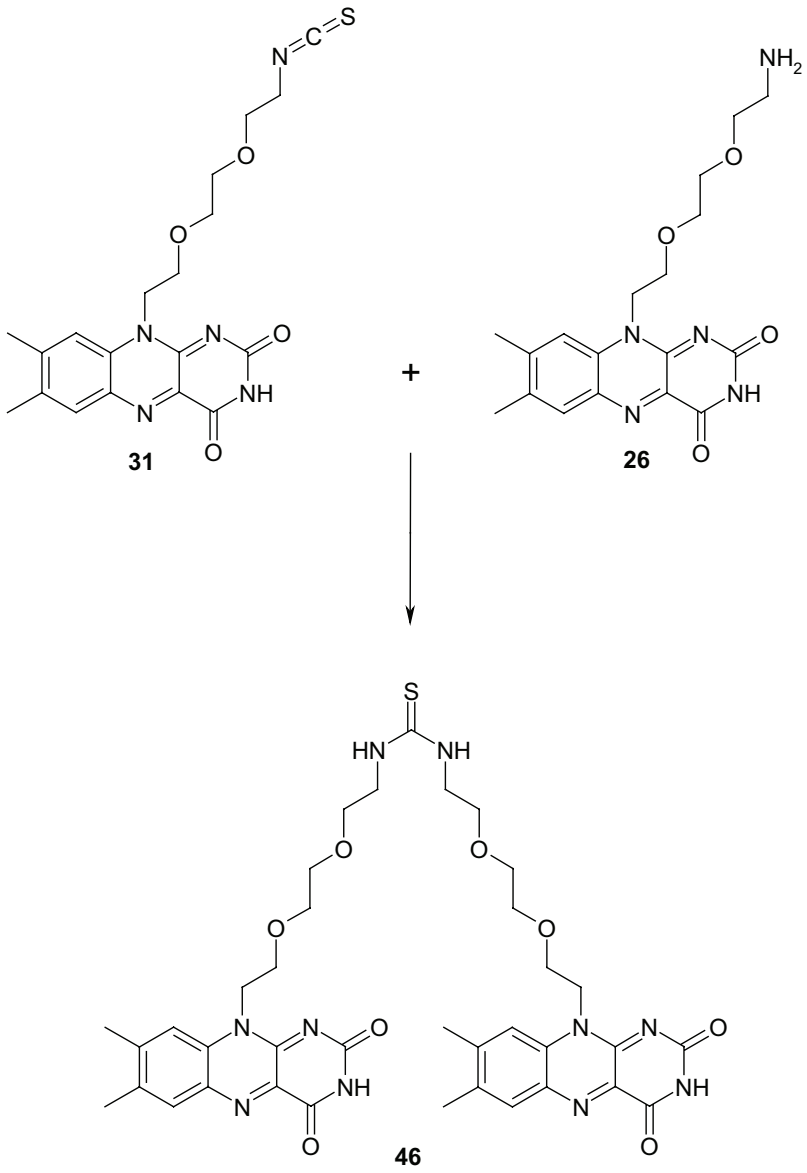
SCHEME 12. Synthesis of thioureas **33**–**40** from isothiocyanates **29**–**32**; Conditions: (i) ammonia (g), methanol, r.t., 3 hrs, 76%, (ii) perfluorooctylethyl amine, TEA, chloroform, reflux, overnight, 68%. (iii) ammonia (g), chloroform, r.t., 2 hrs, 68%, (iv) perfluorooctylethyl amine, TEA, chloroform, reflux, overnight, 79%, (v) ammonia (g), chloroform, r.t., 3 hrs, 44%, (vi) 3-oxabut-1-yl amine, chloroform, reflux, 2.5 hrs, 100%, (vii) ammonia (g), chloroform, r.t., 3 hrs, 100%. (viii) perfluorooctylethyl ammonium chloride, TEA, reflux, 18 hrs, 67%



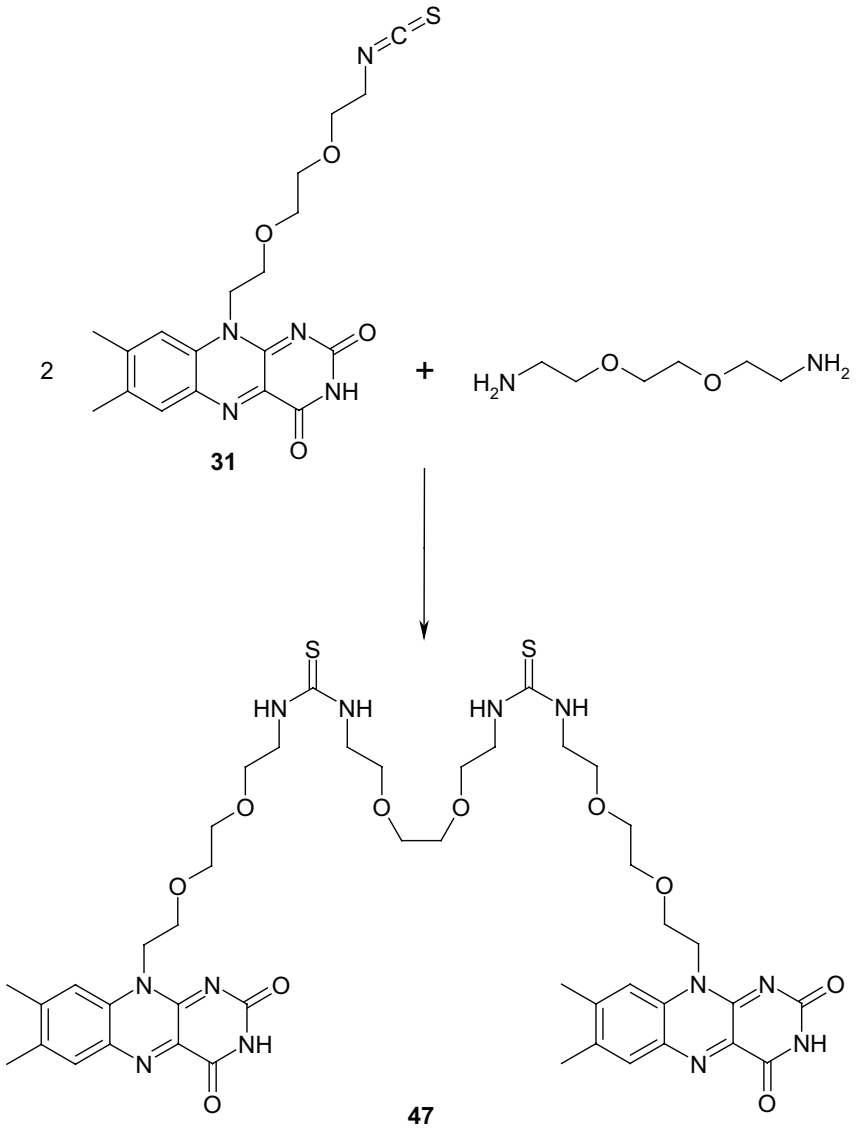
SCHEME 13. Synthesis of flavin–bis(thiourea) compounds **44** and **45**; Conditions: (i) 2-(*tert*-butyloxycarbonylamino)eth-1-yl bromide, potassium carbonate, sodium iodide, DMF (dry), 3 d, 52%, (ii) hydrogen chloride, diethyl ether, methanol, r.t., overnight, 100%, (iii) thiophosgene, dichloromethane, calcium carbonate, water, overnight, 81%, (iv) ammonia (g), methanol, chloroform, 100%, r.t., 1 hr, (v) perfluorooctylethyl amine, TEA, chloroform, reflux, 51%

vin **20** which was alkylated with 2-(*tert*-butyloxycarbonylamino)ethyl bromide yielding flavin **41** (Scheme 13). Removal of both Boc protective groups led to bis(2'-aminoethyl) flavin dihydrochloride **42·2 HCl** in quantitative yield. Two-fold reaction with thiophosgene under the conditions mentioned above led to bis(isothiocyanatoethyl) flavin **43**. Reaction of both isothiocyanate groups with ammonia gave compound **44** containing two monosubstituted thiourea groups, and reaction with perfluorooctylethyl amine yielded compound **45** containing two *N,N'*-substituted thiourea groups.

The reaction of isothiocyanate **31** with aminoglycol flavin **26** (Scheme 14), and two-fold reaction of isothiocyanate **31** with 3,6-dioxaoct-1,8-diyl diamine (Scheme 15) yielded bis-flavins **46** and **47**, respectively, containing one or two thiourea groups and a glycol linker of varying length.[19,68,73] Both reactions gave high yields of the bis-flavins **46** and **47**.



SCHEME 14. Synthesis of bis-flavin **46**; Conditions: TEA, chloroform, reflux, 22 hrs, 100%



SCHEME 15. Synthesis of bis-flavin **47**; Conditions: chloroform, reflux, 8 hrs, 93%

3. Catalytic Properties

Flavin-mediated photo-oxidation of 4-methoxybenzyl alcohol to the corresponding aldehyde using air as terminal oxidant was chosen as the model reaction to study the catalytic activity of the new flavin-thiourea compounds. Other photocatalysts, such as titanium dioxide, can mediate this oxidation as well, but they require intense UV irradiation.[92] The catalytic flavin cycle starts with the oxidised form of flavin which is irradiated by visible light (λ = 440 nm, absorption maximum of flavins in the visible region). The excited chromophore is a strong oxidising agent,[58–61] and accepts stepwise electrons and protons from the benzyl alcohol substrate. The aldehyde is formed, along with the reduced flavin which reacts rapidly with oxygen dissolved in the reaction mixture to yield the hydroperoxide intermediate. The hydroperoxide intermediate then instantaneously releases hydrogen peroxide and regenerates the oxidised flavin, thus completing the catalytic cycle.[93,94] The oxidation of benzyl alcohol to benzaldehyde by oxygen is an exothermic process, but it does not proceed in the absence of flavin or light. The efficiency of the flavin photooxidation increases, if substrate binding sites are present at the chromophore,[7,8,16] and the experiments we describe in the following aim to clarify the effect of thiourea substituents on the photoxidation process. The reaction was monitored in a mixture of acetonitrile-d_3 and dimethylsulphoxide-d_6 (98:2 v/v) by ^{1}H NMR.[95] Upon irradiation, the intensity of the resonance signals corresponding to the benzyl alcohol decreased, while benzaldehyde resonance signals appeared in a very clean conversion (Figures 1–2, Table 1). At the concentrations used (flavin 2×10^{-4} M, 4-methoxybenzyl alcohol 2×10^{-3} M), the resonance signals of the photocatalysts are only observed as minor peaks in the baseline noise. Hydrogen peroxide was not detected by NMR, presumably due to fast deuterium exchange with the solvent.[96]

In the absence of flavin, light, or oxygen, or in the presence of thiourea alone, the reaction did not proceed (Table 1, entries 17–20).[97] Using simple flavins **49**, **19**, and **50** (Scheme 16) which do not contain the thiourea group, some amount of the product was formed, but the conversion remained very low (entries 11, 12 and 16). Bis-flavins **46** and **47** (entries 13 and 14) were not very efficient either, presumably due to steric reasons or unproductive excimer formation.[18] Thiourea groups connected to the 3- or 10-position lead to similar rate enhancements: 3-(2'-thioureidoethyl) flavin **36** oxidised 64% of the alcohol within 60 min, while 10-(2'-thioureidoethyl) flavin **33** oxidised 47% (entries 2 vs. 4). The distance of the thiourea group to the chromophore plays a significant role:[98] With the thiourea group located at the end of the dioxaoctyl chain (catalyst **35**), the conversion reached 92%, while with a short ethylene spacer (catalyst **33**), only 47% was observed (entries 1 vs. 4).

The flavin-thiourea photocatalysts remain active for several subsequent

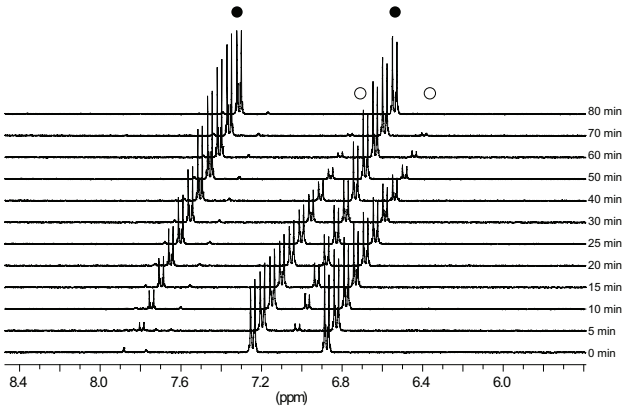


FIGURE 1. Stack plot of the aromatic region of the ^{1}H NMR spectra recorded during the irradiation of 4-methoxybenzyl alcohol in the presence of 10-thioureidoglycol flavin **35**. Perspective view of the spectra is used (no change of the chemical shift of the signals). ● 4-Methoxybenzyl alcohol aromatic signals, ○ 4-methoxybenzaldehyde aromatic signals. Resonance signals in the baseline noise belong to flavins. Initial concentration of 4-methoxybenzyl alcohol 2×10^{-3} M, concentration of flavin catalyst 2×10^{-4} M. Recorded at a Bruker spectrometer with working frequency 400 MHz using 64 transitions

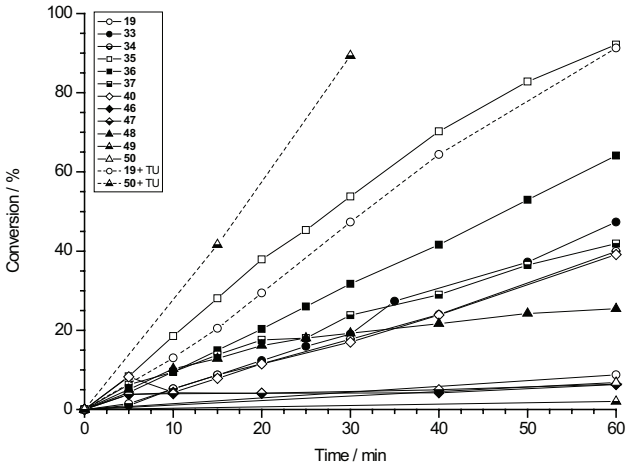
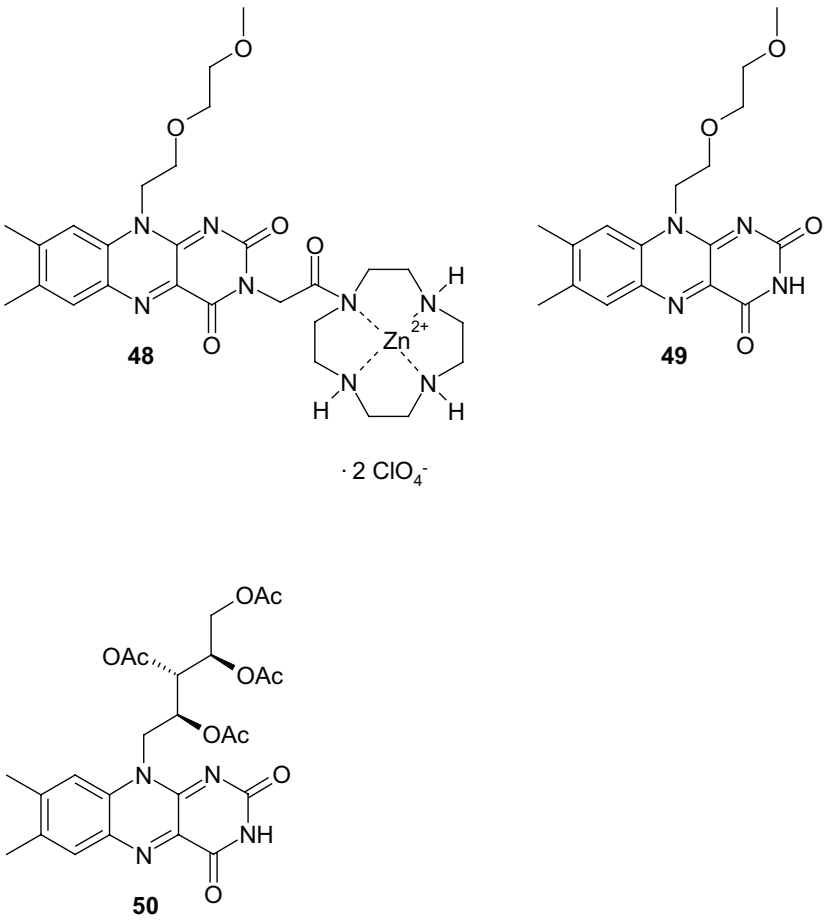


FIGURE 2. Flavin-mediated photo-oxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde. Conditions: Initial concentration of 4-methoxybenzyl alcohol 2×10^{-3} M, concentration of flavin catalyst 2×10^{-4} M. 'TU' denotes the addition of thiourea to the reaction mixture (2×10^{-4} M). The conversion was calculated from the ratio of areas under the aromatic signals in 1H NMR spectra recorded during the experiment

TABLE 1. Results of flavin-mediated photooxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde

	Catalyst mol×L^{-1}	Alcohol mol×L^{-1}	Substrate catalyst	Time h	Conversion %	TON	TOF h^{-1}	QY %
Flavin-catalysed photooxidations								
1	**35** (2×10^{-4})	2×10^{-3}	10:1	1	92	9.2	9.2	0.93
2	**36** (2×10^{-4})	2×10^{-3}	10:1	1	64	6.4	6.4	0.65
3	**38** (3×10^{-5})	2×10^{-3}	70:1	1	64	45	45	0.65
4	**33** (2×10^{-4})	2×10^{-3}	10:1	1	47	4.7	4.7	0.48
5	**37** (2×10^{-4})	2×10^{-3}	10:1	1	41	4.1	4.1	0.42
6	**34** (2×10^{-4})	2×10^{-3}	10:1	1	40	4.0	4.0	0.41
7	**40** (2×10^{-4})	2×10^{-3}	10:1	1	39	3.9	3.9	0.40
8	**44** (5×10^{-5})	2×10^{-3}	40:1	1	27	11	11	0.27
9	**48** (2×10^{-4})	2×10^{-3}	10:1	1	25	2.5	2.5	0.25
10	**39** (2×10^{-5})	2×10^{-3}	100:1	1	20	20	20	0.20
11	**19** (2×10^{-4})	2×10^{-3}	10:1	1	9	0.9	0.9	0.09
12	**50** (2×10^{-4})	2×10^{-3}	10:1	1	7	0.7	0.7	0.07
13	**46** (2×10^{-4})	2×10^{-3}	10:1	1	6	0.6	0.6	0.06
14	**47** (2×10^{-4})	2×10^{-3}	10:1	1	6	0.6	0.6	0.06
15	**45** (1×10^{-5})	2×10^{-3}	200:1	1	3	6	6	0.03
16	**49** (2×10^{-4})	2×10^{-3}	10:1	1	2	0.2	0.2	0.02
Experiments without light, oxygen or flavin								
17	**35** (2×10^{-4})	2×10^{-3}	10:1	1[a]	5	0.5	0.5	0.05
18	**35** (2×10^{-4})	2×10^{-3}	10:1	1[b]	0	–	–	–
19	None	2×10^{-3}	N/A	1	0	–	–	–
20	None[c]	2×10^{-3}	N/A	1	0	–	–	–
Experiments with lower catalyst loading								
21	**35** (2×10^{-4})	2×10^{-2}	100:1	16	84[d]	87	5.4	0.55
22	**35** (2×10^{-5})	2×10^{-3}	100:1	156	61	61	0.4	0.004
23	**35** (2×10^{-4})	2×10^{-1}	1000:1	96	50[e]	580	6.0	0.006
Stoichiometric mixtures of flavin and thiourea and miscellaneous experiments								
24	**19** (2×10^{-4})[c]	2×10^{-3}	10:1	1	91	9.1	9.1	0.92
25	**49** (2×10^{-4})[c]	2×10^{-3}	10:1	1	95	9.5	9.5	0.97
26	**50** (2×10^{-4})[c]	2×10^{-3}	10:1	0.5	89	8.9	18	1.81
27	**49** (2×10^{-4})[f]	2×10^{-3}	10:1	1	99	9.9	9.9	1.01
28	**19** (2×10^{-4})[g]	2×10^{-3}	10:1	1	3	0.3	0.3	0.03

[a] Reaction mixture was thoroughly purged by argon prior to irradiation.
[b] Instead of irradiation, the reaction mixture was left standing in the dark.
[c] Thiourea (2×10^{-4} M) was added to the reaction mixture.
[d] Mixture of 4-methoxybenzaldehyde (81%) and *p*-anisic acid (3%).
[e] Mixture of 4-methoxybenzaldehyde (42%) and *p*-anisic acid (8%).
[f] *N,N,N',N'*-Tetramethylthiourea (2×10^{-4} M) was added to the reaction mixture.
[g] Urea (2×10^{-4} M) was added to the reaction mixture.



SCHEME 16. Flavin molecules, which do not contain a thiourea group, used for comparison

cycles (Figure 3). After every hour, the conversion of 4-methoxybenzyl alcohol to the aldehyde was determined by ^{1}H NMR, and an aliquot of concentrated alcohol stock solution was added to restore the initial alcohol-to-catalyst ratio. While high conversion within 1 h was observed in the first cycles, the activity of the photocatalyst then decayed due to bleaching of the flavin chromophore.

To probe the activity of the most efficient compound **35** further, experiments with higher substrate-to-photocatalyst ratios were carried out (Table 1, entries 21–23). Regardless of whether the concentration of the substrate was higher or concentration of the flavin catalyst lower to reach the higher ratio, the reaction was significantly slower and longer irradiation times were therefore required. Nevertheless, unprecedented turnovers were observed: using mere 0.1 mol % of the flavin photocatalyst, a total conversion of 50% after 4 days of irradiation was observed. 4-Methoxybenzyl alcohol (42%) was in this case accompanied by *p*-anisic acid (8%), the

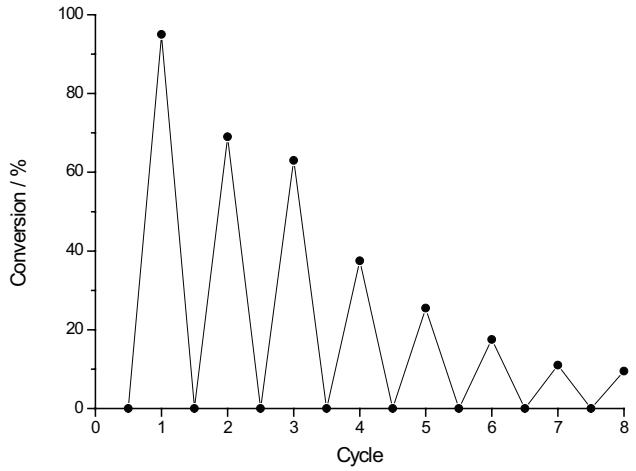


FIGURE 3. Repeated oxidation of 4-methoxybenzyl alcohol; Conditions: flavin-thiourea 16 2×10^{-4} M, 4-methoxybenzyl alcohol 2×10^{-3} M before every cycle (1 h). Products accumulated in the reaction mixture

product of a subsequent oxidation which was not observed in the experiments with 10 mol % of flavin catalysts even upon prolonged irradiation of the fully converted reaction mixtures or mixtures with authentic 4-methoxybenzaldehyde. This result corresponds to TON 580, significantly exceeding the highest turnover reported for this reaction.[7] Fluorophilic catalysts **38** and **39** and bis-thiourea catalysts **44** and **45** (entries 3, 8, 10 and 15) were not sufficiently soluble to test their efficiency at 2×10^{-4} M. However, they were highly active even at lower concentrations, especially compound **38** which was able to oxidise 64% of the substrate while present at 1.5 mol %, thus achieving a TOF of 45 h^{-1}.

Surprisingly, the covalent linkage between the flavin chromophore and the thiourea group was not decisive for the catalytic activity. Mixtures of related flavin molecules which do not contain the covalently-linked thiourea group, and stoichiometric amounts of thiourea worked comparably well (Table 1, entries 24–26). This made us revise the hypothesis of reversible non-covalent binding of substrate to the thiourea group. Indeed, addition of 4-methoxybenzyl alcohol to the most active catalyst **35** did not cause any quenching of flavin fluorescence and induced no changes in the UV/VIS spectra, suggesting no direct binding between the substrate and the thiourea group. This assumption was supported by ^{19}F NMR titration of flavin–thiourea **35** and 2-fluorobenzyl alcohol. Upon addition of the flavin–thiourea, no change in the chemical shift of the fluorine atom was observed, again indicating no direct interaction.

To assess whether the presence of thiourea influences the flavin redox potential by hydrogen binding, as observed in natural flavoenzymes and their models,[14,17,25,67,68,99–105] the reduction potentials of flavin **35** and

10-(3',6'-dioxahept-1'-yl) flavin **49** was determined by cyclic voltammetry (Figure 4). The measurement revealed a shift of the reduction potential by

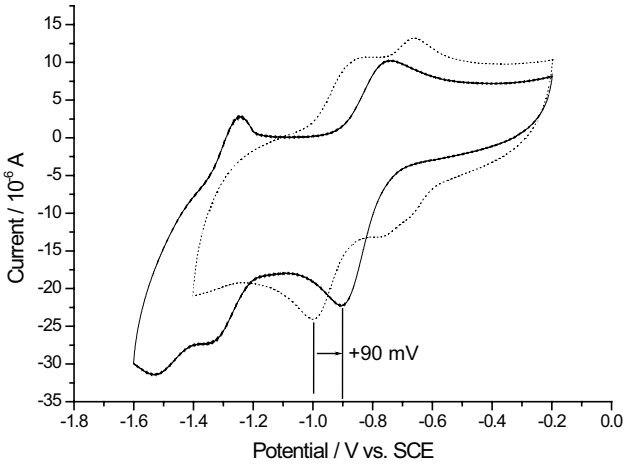
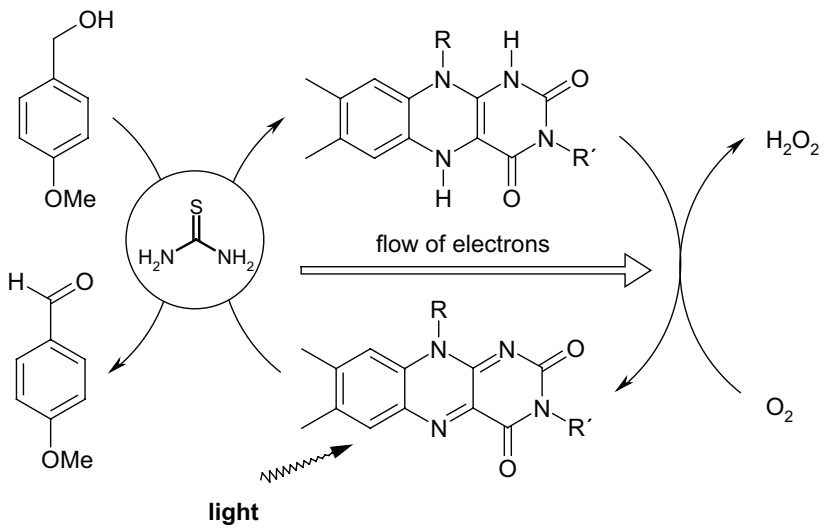


FIGURE 4. Cyclic voltammograms of flavin-thiourea **35** (solid line) and 10-(3',6'-dioxahept-1'-yl) flavin **49** (dashed line). See Experimental Section for the conditions of the measurement

+90 mV for flavin thiourea **35** compared to **49**. However, this shift is not as pronounced as in related flavin molecules which catalyse the oxidation of 4-methoxybenzyl alcohol less efficiently (e.g., compound **48**, reduction potential shifted by +200 mV compared to compound **49**),[7] and cannot justify the high activity in the oxidation reactions. To disprove a hydrogen-bond-mediated change of the flavin redox potential as the source of reactivity increase in alcohol photooxidation, experiments with a mixture of flavin **49** and either thiourea or *N,N,N',N'*-tetramethylthiourea were carried out giving comparable results (Table 1, entries 25 vs. 27).

Another potential effect of thiourea which is a mild organic base is the deprotonation of the alcohol, making it more electron-rich and facilitating its oxidation. Although thiourea is more basic than alcohols in aqueous environment, the situation changes in organic media due to less effective solvation of the alcoholate anion, making deprotonation by thiourea virtually impossible.[106,107]

Having disproved the hypotheses described above, we turned our attention to the possibility that thiourea works as an electron mediator between the substrate and the flavin moiety, and assists the chromophore in bringing the oxidation about (Scheme 17). To assess whether electron transfer between the flavin unit and thiourea and other entities participating in the system are thermodynamically feasible, their redox potentials were determined by cyclic voltammetry and ΔG of the electron-transfer reactions was



SCHEME 17. Revised catalytic cycle of the reaction and flow of electrons

TABLE 2. Redox potentials of species participating in the catalytic cycle

Redox process	$E_{\frac{1}{2}}$ vs. SCE [V]	$E_{\frac{1}{2}}$ vs. Fc/Fc^+ [V]
4-Methoxybenzylalcohol ox.	+1.547	+1.086
Flavin **49** red.	−0.717	−1.178
Fl_{red} **49** ox.	−1.234	−1.695
Oxygen red.	−0.923	−1.384
Thiourea ox.	+0.800	+0.339
Thiourea red.	−0.720	−1.181

calculated using the Rehm–Weller equation

$$\Delta G = 96.4 \times (E^{ox}_{\frac{1}{2}} - E^{red}_{\frac{1}{2}}) - \frac{e^2}{\epsilon \times a} - E^{O-O}$$

using typical values for the Coulombic ($\frac{e^2}{\epsilon \times a}$ = 5.4 kJ/mol) and flavin excitation term (E^{O-O} = 241 kJ/mol, neglecting entropy changes from the ground to the excited state).[108,109] Indeed, the excited flavin can oxidise either the alcohol (ΔG = −29 kJ/mol) or thiourea (ΔG = −100 kJ/mol, Tables 2 and 3). The reduced form of flavin may also reduce thiourea (ΔG = −55 kJ/mol) or be re-oxidised by oxygen (ΔG = −35 kJ/mol); however, the rate-determining step is the oxidation of the substrate, not the re-oxidation of the reduced flavin form, as only the oxidised form can be observed in UV spectra recorded during the reaction. Thiourea must there-

Table 3. ΔG of redox processes

ΔG [kJ/mol]		Oxidised species		
		Alcohol	Thiourea	Fl_{red}
Reduced species	Flavin	212	141	
	Flavin*	−29	−100	
	Thiourea	213		−55
	Oxygen	232	160	−35

fore exert its positive effect on the oxidation of the substrate. The ability of thiourea to enhance the reactivity of flavin may stem from its ability to undergo oxidation to highly reactive (radical) intermediates.[110–112] In accordance, urea which cannot tautomerise to the isourea form,[113] which is necessary to undergo the oxidation,[114] does not increase the efficiency of the flavin photocatalyst (Table 1, entry 28). The situation may be analogous to certain oxidases, which contain a stabilised sulphenic acid based on the cysteine side chain in the vicinity of the flavin-dependent active site.[115–120]

The effect of thiourea is a diffusion-controlled process rather than a photochemical reaction within a non-covalent assembly. Firstly, when excess of thiourea with respect to flavin is used, the oxidation proceeds significantly faster compared to stoichiometric mixtures of flavin and thiourea. Secondly, the difference in photocatalyst efficiency with covalently tethered thiourea and stoichiometric mixtures of flavin and thiourea is small.

4. Conclusion

Flavin–thioureas **33**–**40** and **44**–**47** were prepared by the Kuhn synthesis and the application of isothiocyanate chemistry. The photocatalysts were successfully applied to the oxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde using oxygen as the terminal oxidising agent. The activity of some of the catalysts exceeded known systems and high TONs of up to 580 have been observed. The presence of thiourea, either covalently bound to a flavin derivative or added stoichiometrically, led to a 30-fold increase of the reactions quantum yield in some examples. Our investigations revealed that thiourea presumably acts as an efficient electron mediator between the photoactive flavin chromophore and the substrate.

Summary

The presented Dissertation deals with the synthesis and flavin-based catalysts of photochemical processes, and the study of their activity on model examples. In Chapter 1, related supramolecular systems which enhance the efficiency of photochemical reaction in homogeneous solutions are comprehensively reviewed.

First attempts to prepare the flavin-based molecules begun by oxidation of riboflavin **1** to 2'-oxoethyl flavin **2**. However, 2'-oxoethyl flavin **2**, product of the oxidative cleavage, was found to be an untypical aldehyde. In solutions containing water, the *gem*-diol form **4** is highly favoured and the equilibrium constant of aldehyde **2** and hydrated form **4** was found higher than 100, far from the range typical for general aldehydes. We have shown by theoretical calculations that the *gem*-diol **4** is stabilised by a hydrogen bond between one of the hydroxyl group and the nitrogen atom in position 1 of the flavin skeleton. A variety of nucleophilic addition reactions were attempted to employ 2'-oxoethyl flavin **2** as a building block for the construction of more complicated flavin-based molecules. However, the reactivity of the aldehyde group is influenced by the flavin skeleton, as the unusual stability of the *gem*-diol **4** indicates. Reductive amination under hydrogenation conditions was the only successful chemical transformation of the aldehyde **2** giving the secondary amine **7** in good yield.

Flavin–thioureas **33**–**40** and **44**–**47** were prepared by the Kuhn synthesis and the application of isothiocyanate chemistry. The photocatalysts were successfully applied to the oxidation of 4-methoxybenzyl alcohol to 4-methoxybenzaldehyde using oxygen as the terminal oxidising agent. The activity of some of the catalysts exceeded known systems and high TONs of up to 580 have been observed. The presence of thiourea, either covalently bound to a flavin derivative or added stoichiometrically, led to a 30-fold increase of the reactions quantum yield in some examples. Our investigations revealed that thiourea presumably acts as an efficient electron mediator between the photoactive flavin chromophore and the substrate.

Chapter 4

Experimental Procedures

1. General

Flavin **19**,[121] flavin **20**,[65] flavin **24**,[65] 2-perfluorooctylethyl amine,[122–124] 2-(*tert*-butyloxycarbonylamino)ethyl bromide,[125] and flavin **49**[7] were prepared by known methods. Flavin–zinc(II)–cyclene was a gift from Dr. Radek Cibulka. All other chemicals were purchased from commercial suppliers, checked by ^{1}H NMR spectrometry and then used as received. Solvents were distilled, and dried by usual methods if required by the experimental procedure. Dry *N,N*-dimethyl formamide was purchased from Fluka. Thin layer chromatography (TLC) was carried out on Silica gel 60 F_{254} aluminium sheets (Merck) or on pre-coated plastic sheets Polygram SIL G/UV_{254} (Macherey-Nagel, Düren, Germany). Preparative TLC was carried out on home-made glass plates (20×20 cm) coated with silica gel 60 GF_{254} (20 g, Merck). Compounds were detected by UV light (λ = 254 nm, 333 nm) and intensively yellow-coloured flavins were often detected by naked eye. Column chromatography was carried out on silica gel Geduran 60 (Merck) or silica gel 60 M (Macherey-Nagel). Flash chromatography was carried out on silica gel 0.035–0.070, 60 A from Acros.

Nuclear magnetic resonance spectra were recorded at Bruker spectrometer equipped with a robotic sampler at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR), unless otherwise indicated. Tetramethylsilane (TMS) was used as an external standard.

Electron-impact (EI-MS) and chemical ionisation (CI-MS) mass spectra were measured on Finnigan TSQ 710 spectrometer, and electrospray ionisation (ES-MS) mass spectra were measured on ThermoQuest Finnigan TSQ 7000 spectrometer. All methods of high resolution mass spectrometry (HR-MS) were measured on ThermoQuest Finnigan MAT 95 spectrometer.

Elemental composition of new compounds was determined either by HR-MS which was the preferred method, or by combustion elementary analysis (EA).

Melting points were measured on a melting point apparatus Büchi SMP-20 using a glass capillary tube immersed in heated silicon oil, and are uncorrected.

UV/VIS spectra were recorded at Varian Cary 50 Bio UV/VIS spectrometer against air. Fluorescence spectra were recorded at Varian Cary Eclipse.

2. Equilibration Experiments

A solution of aldehyde **2** or **5** (2×10^{-3} M) and trifluoroacetic acid (2×10^{-4} M) in a mixture of deuterium oxide and dimethylsulphoxide-d_6 (1:1 v/v) was prepared, let stand at ambient temperature, and regularly monitored by ^{1}H NMR spectrometry on a Bruker spectrometer with working frequency 300 MHz, using 64 transitions. Contents of the aldehyde and *gem*-diol form was calculated from the integrals of protons 6 and 9 (aldehyde **2**) or β-protons (aldehyde **5**).

3. Theoretical Computations

The *ab initio* calculations were performed with the local MP2 method as implemented in the `MOLPRO`[126] application package, employing the density fitting approximation for the electron repulsion integrals.[44,127] The augmented correlation consistent AO basis sets aug-cc-pVXZ of Dunning[45,128] were used (X=D for geometry optimizations, X=T,Q for single point energies), along with the related fitting basis sets optimized for DF-MP2.[129] For the Hartree-Fock energy and the related component of the LMP2 gradient the JK-fitting basis sets of Weigend[130] related to the cc-pV(X+1)Z AO basis, respectively, were employed. Local orbitals were generated according to the Pipek-Mezey localisation scheme.[131] Pair domains were constructed with the Boughton-Pulay procedure[133] using a completeness criterion of 0.98. The BP domains then were extended by all next nearest neighbour centers. The occupied orbital pair list remained un-truncated in all calculations. The density functional calculations were carried out by using the `TURBOMOLE` application package.[132]

4. Kinetic Experiments

The kinetic experiments were carried out in a mixture of acetonitrile-d_3 and dimethylsulphoxide-d_6. The latter was required to improve solubility of the generally poorly soluble favin–thiourea sensitisers. A typical reaction mixture, prepared in an NMR tube,[134] contained flavin sensitiser (2×10^{-4} M) and 4-methoxybenzyl alcohol (2×10^{-3} M) and had a total volume of 1 mL.

The reaction mixture was prepared under aerobic conditions, but the solution was not additionally saturated by oxygen.[135] The reaction mixture was irradiated by a light-emitting diode (LED) with emission wavelength 440 nm and power of 6 W. The NMR tube was placed vertically above the aperture of the LED. Optical path using this setup was ca. 73 mm. The reaction mixture was irradiated for desired time, and ^{1}H NMR spectrum was then recorded using a Bruker spectrometer with working frequency 400 or 300 MHz using 64 transitions to achieve better signal-to-noise ratio and hence more accurate integration. Sodium 3-(trimethylsilyl)-2,2,3,3-tetradeuteropropionate (2×10^{-3} M) was used as an internal standard. Concentration of the substrate and the product was derived from the are under the peaks of the aromatic doublets (see Figure 1, page 73) and comparison to the integral value of the trimethylsilyl peak of the TSP internal standard. Quantum yields were determined using the standard ferrioxalate actinometry measurement.[135]

5. Cyclic Voltammetry

The cyclic voltammograms were recorded on an Autolab potentiostat using glassy carbon working electrode, platinum auxiliary electrode and saturated calomel reference electrode (SCE). Tetrabutylammonium tetrafluoroborate (0.1 M) was used as an auxiliary electrolyte. The measurement was carried out in a mixture of acetonitrile and dimethylsulphoxide (90:10 v/v) as solvent at 1 mM concentration of analytes. The solution was degassed before the measurement by a stream of argon, and left under a gentle stream of argon during the measurement. Step potential of 0.1 V/s was used.

6. 2'-Oxoethyl Flavin (2)

Riboflavin **1** (5.60 g, 14.9 mmol, 1 eq.) was suspended in dilute sulphuric acid (4 mL acid in 140 mL distilled water) and the suspension was cooled to 0–5 °C using ice bath. A solution of periodic acid (12.50 g, 54.8 mmol, 3.7 eq.) in water (90 mL) was added dropwise, keeping the temperature between 0 and 5 °C. Once the addition was complete, the cooling bath was removed, and the temperature was allowed to rise to ambient temperature. During ca. 60 min of stirring at ambient temperature, all solids dissolved. Active charcoal was added to the reaction mixture and the suspension was gently stirred for 30 min. The solid was filtered off and pH of the filtrate was adjusted to 3.9 by the addition of concentrated sodium hydroxide solution, keeping the temperature between 20 and 25 °C. The mixture was cooled to +1.5 °C using an ice bath. The product precipitated and was separated by filtration using a Büchner funnel. The filtration cake was thoroughly washed with ice-cold water and dried on the vacuum pump. The product was checked by ^{1}H NMR in DMSO-d_6. The spectrum showed presence of the product as a mixture of aldehyde **2** and *gem*-diol **4**. The mixture was therefore azeotropically dried with toluene: The solid was suspended in toluene (200 mL), the suspension was heated to reflux and small portions of the distillate were removed using the Dean–Stark trap. Once the suspension was concentrated to ca. 50 mL (ca. 6 hrs), it was evaporated to dryness *in vacuo* and dried on the pump. Yield 2.08 g (49%).

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.40	s	3 H	CH_3-7
2.46	s	3 H	CH_3-8
5.64	s	2 H	CH_2
7.71	s	1 H	H-9
7.94	s	1 H	H-6
9.74	s	1 H	CHO
11.39	br	1 H	H-3

^{13}C NMR (DMSO-d_6, 150 MHz) δ/ppm: 18.5 (CH_3-7), 20.4 (CH_3-8), 53.7 (CH_2-1'), 116.2 (C-9), 130.6 (C-6), 130.9 (C-6a), 149.9 (C-10a), 195.1 (CHO). The resonance signals of the remaining carbon atoms could not be detected.[136]

ES-MS $\frac{m}{z}$: 284.9 (6%, M+H^+), 303.0 (38%, M + H_2O + H^+), 317.0 (100%, M + CH_3OH + H^+), 605.3 (1%, 2 M + 2 H_2O + H^+), 633.3 (2%, 2 M + 2 CH_3OH + H^+), 655.3 (6%, 2 M + 2 CH_3OH + Na^+).

ES-MS $\frac{m}{z}$: 282.7 (100%, M − H^+), 300.8 (23%, M + H_2O − H^+), 314.7

(52%, M + CH_3OH − H^+).

IR (KBr disc) $\frac{\nu}{cm^{-1}}$: 3436 (broad signal, O-H), 3148 (aromatic C-H), 3025 (aromatic C-H), 2819 (C-H aldehyde), 2361, 1705 (C4=O and N3 wagging, reported at 1703,[137] C4=O and C2=O, reported at 1712[32]), 1652 (C2=O and N3 wagging, reported at 1646,[137] C2=O, N3-H bending and C4=O, reported at 1677[32]), 1577 (C4a-N5, reported at 1578,[137] C4a-N5 and in-phase C10a-N1, reported at 1574[32]), 1539 (C10a-N1, reported at 1546,[137] C4a-N5 and out-of-phase C10a-N1, reported at 1548[32]), 1456 (aromatic C=C), 1398 (CH_3), 1349, 1275 (CH_3), 1244, complex fingerprint area.[138]

MP: > 271 °C (methanol, decomposition).[139]

R_F: 0.57 (ethyl acetate:methanol = 5:2).

7. 10-(3'-Aza-6'-oxahept-1'-yl) Flavin (7)

7.1 Method I

2'-Oxoethyl flavin (256 mg, 0.9 mmol, 1 eq.), 2-methoxyethyl amine (275 mg, 3.7 mmol, 4 eq.) and palladium on activated charcoal (10%, 1 spatula tip) were suspended in ethanol (200 mL) in an autoclave. The autoclave was flushed five times with hydrogen and then filled with hydrogen up to the pressure of 10 bar. The reaction mixture was stirred for 17 hrs at ambient temperature. The suspension was filtered over celite, and filtrate was evaporated in vacuo. Mixture of product and starting material was separated by column chromatography using silica gel as stationary and a mixture of ethyl acetate and methanol (5:2) as mobile phase. Yield 86 mg (28%).

7.2 Method II

2'-Oxoethyl flavin (50 mg, 0.18 mmol, 1 eq.), 2-methoxyethyl amine (52 mg, 0.69 mmol, 3.8 eq) and palladium on activated charcoal (10%, 55 mg) were suspended in ethanol (60 mL) in an autoclave. The autoclave was flushed five times with hydrogen and the filled with hydrogen up to the pressure of 10 bar and placed in 60 °C oil bath. The reaction mixture was stirred for 19 hrs. After cooling, the reaction mixture was filtered over celite, and the filtrate was evaporated *in vacuo*. The product was purified by preparative thin-layer chromatography using a mixture of ethyl acetate and methanol (5:2) as mobile phase. The corresponding zone (R_F 0.05) was extracted by methanol. The extract was filtered and the filtrate was evaporated *in vacuo*.

Yield 48 mg (80%).

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.40	s	3 H	CH_3-7)
2.51	br	3 H	CH_3-8)
2.37	t, J = 5.4 Hz	2 H	CH_2-3')
2.90	t, J = 6.6 Hz	2 H	CH_2-2')
3.23	s	3 H	OMe
3.35	br	2 H	CH_2-4'
4.65	t, J = 6.6 Hz	2 H	CH_2-1'
7.89	s	3 H	H-9
7.91	s	3 H	H-6
11.32	br	1 H	H-3)

^{13}C NMR (DMSO-d_6, 100 MHz) δ/ppm: 18.7 (CH_3-7), 20.5 (CH_3-8), 44.2 (C-1'), 45.8, 48.4, 58.0, 71.9 (C-2',4',5',7'), 116.4 (C-9), 130.8 (C-9a), 131.2 (C-6), 133.8 (C-5a), 135.7 (C-7 or 8), 137.1 (C-4a), 146.4 (C-7 or 8), 150.2 (C-10a), 155.6, 159.9 (C-2,4).

ES-MS $\frac{m}{z}$: 344.1 (100%, M + H^+), 687.5 (4%, 2 M + H^+).

HR-MS (LSI-MS) calcd. for $C_{17}H_{21}N_5O_3$ (M + H^+): 343.1644; found: 343.1640 (delta 1.28 ppm).

MP: > 232 °C (methanol, decomposition).

R_F: 0.05 (ethyl acetate:methanol = 5:2).

8. 4,5-Dimethyl-2-nitroaniline (11)

3,4-Dimethylaniline **8** (20.0 g, 165 mmol) was dissolved in acetic acid (25 mL) and acetic anhydride (25 mL, 27 g, 0.26 mol, 1.6 eq.) was added. The reaction mixture was heated to reflux for 15 min, and then added dropwise to water (300 mL) with ice (*ad necesitam*) and the pink precipitate was filtered off using a Büchner funnel. A mixture of 65% nitric (95 mL, 1.36 mol, 8.2 eq.) and acetic acid (35 mL) was cooled to 10–15 °C. The filtration cake from the previous step was dissolved in acetic acid (50 mL) and the solution was added dropwise to the mixture of acids. Once the addition was complete, the reaction mixture was stirred for additional 60 min at 10–20 °C. The reaction mixture was poured into water (ca. 1 L) and the resulting yellow precipitate was filtered off using a Büchner funnel, and washed well with water. The filtration cake was dissolved in concentrated sulphuric acid (125 mL) and heated to ca. 90 °C for 20 min. The reaction mixture was al-

lowed to cool to ambient temperature, added dropwise to ice (*ad necesitam*), the resulting orange precipitate was filtered off using a Büchner funnel and dried. Yield 12.7 g (46%).

The resonance signals were assigned with the help of a NOESY experiment, and NMR spectra of related *N*-substituted compounds were solved *per analogiam*.

^{1}H NMR ($CDCl_3$) δ/ppm: 2.14 (s, 3 H, Me-4), 2.18 (s, 3 H, Me-5), 6.54 (s, 1 H, H-6), 7.83 (s, 1 H, H-3).

EI-MS $\frac{m}{z}$:166.1 (100%, $M^{+\bullet}$).

9. 4,5-Dimethyl-1,2-dinitrobenzene (13)

4,5-Dimethyl-2-nitroaniline **35** (12.7 g, 76 mmol) was suspended in acetic acid (300 mL) and 30% aqueous hydrogen peroxide (60 mL, ca. 0.66 mol, 8.6 eq.) was added. The reaction mixture was heated to 45–55 °C for 16 h, and was added dropwise to water (750 mL) with ice (*ad necesitam*). The resulting orange precipitate was filtered off using a Büchner funnel, washed and dried. Yield 6.910 g (46%).

^{1}H NMR ($CDCl_3$) δ/ppm: 2.42 (s, 6 H, Me-4,5), 7.68 (s, 2 H, H-3,6).

CI-MS $\frac{m}{z}$: 214.2 (100%, M + $NH_4{}^+$)→184.1 (15%, $-NO^{\bullet}$), 231.2 (43%,M + NH_4^++NH_3).

10. *N*-(3'-Oxabut-1'-yl)-4,5-dimethyl-2-nitro aniline (14)

The product has been described in the literature,[121] but was prepared by a different method back then. Dinitrobenzene **13** (2.94 g, 15 mmol) was dissolved in 3-oxabut-1-yl amine (25 mL) and the reaction mixture was heated to 80 °C for 6 hrs. The mixture was diluted with dichloromethane (100 mL) and then washed with water (2×100 mL) and brine (100 mL). Organic phase was dried over magnesium sulphate and evaporated *in vacuo*. The product (brown oil) partially solified upon drying. Yield 3.35 g (99%).

^{1}H NMR ($CDCl_3$) δ/ppm: 2.14 (s, 3 H, CH_3-4), 2.23 (s, 3 H, CH_3-5), 3.40 (s, 3 H, CH_3-4'), 3.42–3.47 (m, 2 H, CH_2-1'), 3.65 (m, 2 H, CH_2-2'), 6.60 (s, 1 H, H-6), 7.87 (s, 1 H, H-3), 8.07 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$) δ/ppm: 18.4, 20.6 (2×CH_3), 42.6 (CH_2), 58.9 (CH_3), 70.4 (2×CH_2), 114.0 (CH), 124.4 (quaternary C), 126.3 (CH), 129.8, 143.9, 147.1 (3×quaternary C).

11. *N*-(8'-Amino-3',6'-dioxaoct-1'-yl)-4,5-dimethyl-2-nitroaniline (16)

The procedure is analogous to the one described by Sawhney *et al.*[140] Thus, dinitro compound **13** (6.0 g, 30 mmol) was dissolved in ethanol (3 L). 1,8-Diamino-3,6-dioxaoctane (23.8 g, 160 mmol, 5.3 eq.) was added and the reaction mixture was heated to reflux for 62 h. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in dichloromethane, extracted by diluted hydrochloric acid, aqueous phase was separated and neutralised by dilute sodium hydroxide solution. The solution was extracted by dichloromethane, organic phase was separated and evaporated *in vacuo*, the residue was co-evaporated with toluene and dried. Yield 4.6 g (51%) of a red oil.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.15	s	3 H	CH_3-4
2.24	s	3 H	CH_3-5
2.86 3.52 3.66 3.77	4×m	12 H	6×CH_2 glycol
6.61	s	1 H	H-6
7.90	s	1 H	H-3
8.13	br s	1 H	Ar-N*H*-

^{13}C NMR ($CDCl_3$) δ/ppm: 18.6, 20.7 (2×CH_3), 41.1, 42.7, 69.1, 70.3, 70.6, 71.7 (6×CH_2), 114.2 (CH) , 117.8, 124.6 (2×quaternary C), 126.5 (CH), 144.1, 147.3 (2×quaternary C).

ES-MS $\frac{m}{z}$: 298.2 (100%, M + H^+).

HR-MS (EI-MS) $\frac{m}{z}$: calcd. for $C_{14}H_{23}N_3O_4$ ($M^{+\bullet}$): 297.1689; found: 297.1689 (delta 0.00 ppm).

R_F: 0.17 (CH_2Cl_2:MeOH:TEA = 50:2:1).

12. *N*-(8'-Benzyloxycarbonylamino-3',6'-dioxa-oct-1'-yl)-4,5-dimethyl-2-nitroaniline (17)

The procedure is analogous to the one described by Nicola *et al.*[141] Thus, free amine **16** (650 mg, 2.2 mmol) was dissolved in dry dichloromethane (100 mL). A solution of benzyl chloroformate (380 mg, 2.2 mmol, 1 eq.) in dry dichloromethane (50 mL) was added dropwise. Triethylamine (0.75 mL) was added to the reaction mixture and the reaction was monitored by TLC (mobile phase CH_2Cl_2:MeOH:TEA = 50:2:1, staining with ninhydrin). After 30 min, the starting material spot (R_F 0.17) disappeared. The reaction mixture was evaporated in vacuo, the residue was dissolved in a minimal amount of methanol and the solution was applied to four PTLC plates. The mixture was separated using the aforementioned mobile phase, and the corresponding zone (R_F 0.58) was thoroughly extracted with chloroform. The extract was evaporated *in vacuo* and the residue was dried to yield 610 mg (64%) of a red oil.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.13	s	3 H	Me-4
2.22	s	3 H	Me-5
3.41 3.55 3.63 3.73	4×m	12 H	6×CH_2 glycol
5.05	s	2 H	–CH_2Ph
5.44	br s	1 H	H-8'
6.57	s	1 H	H-6
7.30	m	5 H	Ph
7.86	s	1 H	H-3
8.13	s	1 H	NH aniline

^{13}C NMR ($CDCl_3$): 18.6, 20.7, 42.7, 65.1, 66.6, 69.1, 70.2, 70.3, 70.5, 124.5, 126.4, 128.0, 128.5, 130.0, 137.7, 144.0, 147.25, 156.5.

EI-MS (70 eV) $\frac{m}{z}$: 91.1 (100%, $C_7H_7^+$), 179.1 (62%, $[ArNH{=}CH_2]^+$), 431.2 (5%, $M^{+\bullet}$).

EA: calcd. (%) for $C_{22}H_{29}N_3O_6$: C 61.24, H 6.77, N 9.74, O 22.25; found: C 61.44, H 6.91, N 9.65.

R_F: 0.58 (CH_2Cl_2:MeOH:TEA = 50:2:1).

13. *N*-(8'-Trifluoroacetamido-3',6'-dioxaoct-1'-yl)-4,5-dimethyl-2-nitroaniline (18)

Free amine **16** (5.8 g, 20 mmol) was dissolved in methanol (200 mL) and ethyl trifluoroacetate (13 g, 92 mmol, 4.6 eq.) and triethylamine (11 g, 0.11 mol, 5.4 eq.) were added to the solution. The reaction mixture was stirred at ambient temperature and monitored by TLC (mobile phase CH_2Cl_2:MeOH:TEA = 50:2:1). After 24 h, the starting material spot (R_F 0.17) disappeared. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in dichloromethane (100 mL) and the solution was washed with water (3×100 mL). The organic phase was separated, evaporated *in vacuo* and the residue was dried. Yield 6.5 g (83%) of a red oil.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.10	s	3 H	Me-4
2.20	s	3 H	Me-5
3.43 3.53 3.60 3.63 3.72	5×m	12 H	6×CH_2 glycol
6.57	s	1 H	H-6
7.42	br s	1 H	–*NH*–CO–
7.81	s	1 H	H-3
8.15	br	1 H	Ar–*NH*–

^{19}F NMR $CDCl_3$ δ/ppm: −76.4.

ES-MS $\frac{m}{z}$: 394.2 (100%, M+H$^+$).

EI-MS $\frac{m}{z}$: 393.3 (100%, M$^{+\bullet}$).

HR-MS $\frac{m}{z}$: calcd. for $C_{16}H_{22}F_3N_3O_5$ (M$^{+\bullet}$): 393.1512; found: 393.1509 (delta −0.76 ppm).

R_F: 0.46 (CH_2Cl_2:MeOH:TEA = 50:2:1).

14. 10-(8'-Benzyloxycarbonylamino-3',6'-dioxaoct-1'-yl) Flavin (21)

The reduction procedure is analogous to the literature.[142,143] Thus, *o*-nitroaniline **17** (430 mg, 1 mmol) was dissolved in ethanol (100 mL), and tin(II) chloride dihydrate (1.7 g, 7.5 mmol, 7.5 eq.) was added. The reaction mixture was heated to reflux and monitored by TLC (CH_2Cl_2:MeOH:TEA = 50:2:1). After 72 h, the starting material spot (R_F 0.58) disappeared. The reaction mixture was evaporated *in vacuo* and the residue was re-dissolved in ethyl acetate. The solution was washed with a 2 M sodium hydroxide solution, the organic phase was separated, dried over magnesium sulphate, evaporated *in vacuo* and the residue was dried. The crude reduction product was dissolved in acetic acid (25 mL), and alloxane hydrate (1.1 g, 6.9 mmol, 6.9 eq.) and boric acid (1 g, 16 mmol, 16 eq.) were added. The flask was wrapped in aluminium foil and the mixture was stirred at ambient temperature for 22 h, diluted with water (25 mL) and extracted with dichloromethane (50 mL). The organic phase was evaporated *in vacuo* and the residue was co-evaporated with toluene to remove traces of water and acetic acid. The crude product was dissolved in a minimal amount of methanol and separated on four PTLC plates (CH_2Cl_2:MeOH:TEA = 50:2:1, eluting twice). The corresponding zone (R_F 0.43) was extracted by methanol, the extract was evaporated in vacuo and the residue dried. Yield 360 mg (71%) of an orange solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.41	s	3 H	Me-7
2.50	s	3 H	Me-8
3.31 3.47 3.55 3.97	4×m	8 H	CH_2-4',5',7',8'
4.86	br	2 H	CH_2-2'
5.06	s	2 H	PhCH_2
5.30	br	2 H	CH_2-1'
7.15–7.38	m	5 H	Ph
7.66	s	1 H	H-9
7.97	s	1 H	H-6

^{13}C NMR spectrum could not be recorded due to extremely low solubility of the title compound.

EI-MS $\frac{m}{z}$: 242.0 (100%, [M − side chain]$^{+\bullet}$), 507.2 (5%, M$^{+\bullet}$).[144]

MP: 232 °C (decomposition).

EA: calcd. (%) for $C_{26}H_{29}N_5O_6$: C 61.53, H 5.76, N 13.80, O 18.91; found: C 61.33, H 5.84, N 13.85.

R_F: 0.43 (CH_2Cl_2:MeOH:TEA = 50:2:1)

15. 10-(8'-Trifluoroacetamido-3',6'-dioxaoct-1'-yl) Flavin (22)

Trifluoroacetamide **18** (2 g, 5 mmol) was dissolved in acetic acid (60 mL), and palladium on activated charcoal (10% Pd/C, 1 spatula tip) was added. The reaction mixture was placed in an autoclave which was flushed 3× with hydrogen and then filled up to 50 bar. The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was filtered over celite to remove the catalyst, and the filtrate was transferred to a round-bottom flask. Alloxane hydrate (2.1 g, 13 mmol, 2.6 eq.) and boric acid (7 g, 0.11 mol, 22 eq.) were added to the filtrate. The flask was wrapped in aluminium foil and the reaction mixture was stirred at ambient temperature for 6 d. The reaction mixture was evaporated in vacuo, the residue was dissolved in water (300 mL), and the solution was extracted with dichloromethane (2×250 mL). The organic phase was separated, dried over anhydrous magnesium sulphate, evaporated *in vacuo* and dried. Yield 1.13 g (48%) of orange crystals.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.40	s	3 H	CH_3-7
2.50	br s	3 H	CH_3-8
3.25–3.46	m	8 H	CH_2-4',5',7',8'
3.81	t, J = 5.9 Hz	2 H	CH_2-2'
4.78	t, J = 5.9 Hz	2 H	CH_2-1'
7.85	s	1 H	H-9
7.88	s	1 H	H-6
9.47 11.33	2×br s	2×1 H	2×NH

^{13}C NMR could not be recorded due to very limited solubility of the title product.

ES-MS $\frac{m}{z}$: 470.3 (100%, M+H$^+$).

MP: 215 °C (decomposition).

EA: calcd. (%) for $C_{20}H_{22}F_3N_5O_5$: C 51.17, H 4.72, F 12.14, N 14.92, O 17.04; found: C 51.34, H 4.87, N 14.83.

R_F: 0.27 (CH_2Cl_2:MeOH:TEA = 50:2:1),
0.65 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

16. 10-[2'-(*tert*-Butyloxycarbonylamino)eth-1'-yl]-3-methyl Flavin (23)

Flavin **20** (0.8 g, 2.1 mmol) was dissolved in dry DMF (80 mL). Caesium carbonate (0.9 g, 2.8 mmol, 1.3 eq.) and dimethyl sulphate (2.7 g, 2 mL, 21 mmol, 10 eq.) were added, and the mixture was stirred at ambient temperature in the dark overnight. The suspension was diluted with chloroform (250 mL) and washed with water (3×100 mL), 5% aqueous ammonia (100 mL) and water (100 mL). The organic phase was separated, dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by column chromatography ($CHCl_3$:MeOH = 20:1) to yield 0.44 g (53%) of an orange solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
1.21	s	9 H	Boc
2.41	s	3 H	CH_3-7
2.51	s	3 H	CH_3-8
3.28	s	3 H	CH_3-3
3.41	m	2 H	CH_2-1'
4.67	t, J = 5.8 Hz	2 H	CH_2-2'
6.99	t, J = 5.8 Hz	1 H	NH
7.87	s	1 H	H-9
7.95	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.9, 28.0, 28.2 (4×CH_3), 37.0, 44.1 (2×CH_2), 77.9 (quaternary C), 116.2, 131.0 (CH), 131.5, 134.2, 135.8, 135.9, 146.5, 148.9, 155.1, 155.8, 159.7 (9×quaternary C).

ES-MS $\frac{m}{z}$: 300.1 (55%, M + H^+ - Boc), 344.1 (65%, M + H^+ − C_4H_8), 400.2 (100%, M + H^+), 422.2 (20%, M + NH_4^+), 438.2 (15%, M + K^+).

MP: 232 °C (decomposition).

R_F: 0.38 ($CHCl_3$:MeOH = 20:1).

17. 10-(8'-Amino-3',6'-dioxaoct-1'-yl) Flavin (26)

Trifluoroacetamide **22** (1.1 g, 2.3 mmol) was dissolved in 6 M aqueous solution of hydrochloric acid (200 mL, ca. 1.2 mol, ca. 520 eq.), and the reaction mixture was heated to 90–95 °C and monitored by TLC (mobile phase $CHCl_3$:MeOH:AcOH = 77.5:15:7.5). After 90 min, the starting material spot (R_F 0.65) disappeared. The reaction mixture was evaporated *in vacuo* and the residue was dried (dark brown oil). Yield 940 mg (100%) of compound **26**·**HCl**.

^{1}H NMR (methanol-d_4):

δ/ppm	Multiplicity	Intensity	Assignment
2.46	s	3 H	Me-7
2.58	s	3 H	Me-8
3.06	t, J = 4.9 Hz	2 H	CH_2-8'
3.60–3.68	m	6 H	CH_2-4',5',7'
4.00	t, J = 5.6 Hz	2 H	CH_2-2'
5.00	t, J = 5.6 Hz	2 H	CH_2-1'
7.86	s	1 H	H-9
7.91	s	1 H	H-6

^{13}C NMR (methanol-d_4) δ/ppm: 19.5, 21.4 (2×CH_3), 40.7, 46.3, 68.0, 68.7, 71.3, 71.8 (6×CH_2), 118.1 (CH), 132.5, 133.3, 138.9, 139.0, 141.3, 149.7, 151.7, 158.4 (8×quaternary C), 172.8 (CH).

ES-MS $\frac{m}{z}$: 374.3 (100%, M+H^+).

HR-MS (EI-MS): calcd. for $C_{18}H_{23}N_5O_4$ $[M]^{+\bullet}$: 374.1828; found: 374.1834 (delta 1.69 ppm).

R_F: 0.04 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

18. 3-[2'-(*tert*-Butyloxycarbonylamino)eth-1'-yl]-7,8-dimethyl-10-(3"-oxabut-1"-yl) Flavin (27)

Flavin **19** (1.2 g, 4 mmol, 1 eq.) was dissolved in dry DMF (150 mL) at 80 °C. After cooling to ambient temperature, potassium carbonate (2.8 g, 20 mmol, 5 eq.) was added and the mixture was stirred for 30 min. 2-(*tert*-Butyloxycarbonylamino)ethyl bromide (2.3 g, 10 mmol, 2.5 eq.) in DMF (5 mL) was added dropwise. Sodium iodide (0.9 g, 6 mmol, 1.5 eq.) was added. The reaction mixture was stirred at ambient temperature for one day. Another portion of the bromide (2.3 g, 10 mmol, 2.5 eq.) was added, and the reaction mixture was stirred for two more days at ambient temperature, evaporated *in vacuo*, the residue was dissolved in dichloromethane (400 mL) and the solution was washed with aqueous sodium hydrogen carbonate (250 mL), water (250 mL) and brine (250 mL). The organic phase was separated, dried over magnesium sulphate and evaporated *in vacuo*. The remaining dark oil was purified by column chromatography (AcOEt:MeOH = 20:1), giving the title product as a yellow solid. Yield 950 mg (54%).

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
1.32	s	9 H	Boc
2.40	s	3 H	CH_3-7
2.51	s	3 H	CH_3-8
3.19–3.21	m	2 H	CH_2-2'
3.24	s	3 H	CH_3-4"
3.76	t, J = 5.6 Hz	2 H	CH_2-1"
3.96	t, J = 5.9 Hz	2 H	CH_2-1'
4.83	t, J = 5.6 Hz	2 H	CH_2-2"
6.82	t, J = 5.9 Hz	1 H	NH
7.89	s	1 H	H-9
7.95	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.7, 28.2 (3×CH_3), 37.7, 40.9, 43.8 (3×CH_2), 58.5 (CH_3), 68.4 (CH_2), 77.6 (quaternary C), 116.8, 130.8 (2×CH), 131.4, 133.9, 136.0, 136.4, 146.5, 148.8, 154.8, 155.7, 159.7 (9×quaternary C).

ES-MS $\frac{m}{z}$: 388.1 (65%, M + H^+ − C_4H_8), 444.2 (100%, M + H^+).

MP: 176 °C (decomposition).

R_F: 0.42 (AcOEt:MeOH 10:1).

19. 3-(2'-Aminoeth-1'-yl)-10-(3"-oxabut-1"-yl) Flavin (28)

Flavin **27** (0.85 g, 1.9 mmol) was dissolved in dichloromethane (150 mL) and hydrogen chloride in diethyl ether (10 mL) was added dropwise. The reaction mixture was stirred for 15 h at ambient temperature. The brown precipitate was filtered off and dried. Yield 0.69 mg (95%) of the title product hydrochloride **28**·**HCl**.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.41	s	3 H	CH_3-7
2.51	s	3 H	CH_3-8
3.07–3.09	m	2 H	CH_2-2'
3.24	s	3 H	CH_3-4"
3.79	t, J = 5.5 Hz	2 H	CH_2-1"
4.16	t, J = 5.9 Hz	2 H	CH_2-1'
4.87	t, J = 5.8 Hz	2 H	CH_2-2"
7.94	s	1 H	H-9
7.94–7.96	br	3 H	NH_3^+
7.96	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.7 (2×CH_3), 37.3, 39.9, 44.0 (3×CH_2), 58.5 (CH_3), 68.4 (CH_2), 117.0, 130.8 (CH), 131.4, 133.9, 136.3, 136.4, 146.8, 148.9, 154.9, 160.2 (8×quaternary C).

ES-MS $\frac{m}{z}$: 344.1 (100%, M + H^+).

MP: 150 °C (decomposition).

R_F: 0.00 (AcOEt:MeOH = 10:1).

20. General Procedure 1 for the Preparation of Isothiocyanates 29–32 and 43

Flavin was dissolved in water and calcium carbonate (2.5 eq.) was added. The solution was then added to a rapidly stirred solution of thiophosgene, prepared by the dilution of 0.1 M stock solution in dichloromethane (2 eq.) with dichloromethane, cooled to 0 °C. The reaction mixture was stirred overnight at ambient temperature, diluted with dichloromethane, the organic phase was separated, washed with water, dried over magnesium sulphate and evaporated *in vacuo*. The crude product was purified by chromatography if required.

21. 10-(2'-Isothiocyanatoeth-1'-yl) Flavin (29)

Prepared according to General Procedure 1 from **24** (150 mg) to yield 130 mg (87%) of an orange solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.41	s	3 H	CH_3-7
2.50	s	3 H	CH_3-8
4.14	t, J = 5.8 Hz	2 H	CH_2-2'
4.95	t, J = 5.8 Hz	2 H	CH_2-1'
7.92	s	1 H	H-9
8.00	s	1 H	H-6
11.37	s	1 H	NH

ES-MS $\frac{m}{z}$: 328 (100%, M + H^+).

MP: 182 °C (decomposition).

R_F: 0.39 (AcOEt:MeOH = 10:1).

22. 10-(2'-Isothiocyanatoeth-1'-yl)-3-methyl Flavin (30)

Prepared according to General Procedure 1 from **25·HCl** (109 mg) to yield 80 mg (79%) of an orange solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.46	s	3 H	CH_3-7
2.59	s	3 H	CH_3-8
3.52	s	3 H	CH_3-3
4.17	t, J = 5.8 Hz	2 H	CH_2-2'
4.97	t, J = 5.6 Hz	2 H	CH_2-1'
7.55	s	1 H	H-9
8.09	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.6, 30.0 (3×CH_3), 41.9, 42.8 (2×CH_2), 116.3 (CH), 130.8 (quaternary C), 131.1 (CH), 133.9, 136.0, 136.3, 146.9, 148.9, 155.0, 159.6 (7×quaternary C). Signal of the isothiocyanate group was not observed, presumably due to long relaxation time.

ES-MS $\frac{m}{z}$: 342.1 (100%, M + H^+).

MP: 195 °C (decomposition).

R_F: 0.35 ($CHCl_3$:MeOH = 20:1).

23. 10-(8'-Isothiocyanato-3',6'-dioxaoct-1'-yl) Flavin (31)

Prepared according to General Procedure 1 from **26·HCl** (100 mg) to yield 98 mg (97%) of an orange solid. NMR signals were completely assigned with the help of 2D experiments (NOESY, HMBC, HSQC).

^{1}H NMR ($CDCl_3$, 600 MHz):

δ/ppm	Multiplicity	Intensity	Assignment
2.45	s	3 H	Me-7
2.56	s	3 H	Me-8
3.57–3.62	m	8 H	CH_2-4',5',7',8'
4.04	t, J = 5.5 Hz	2 H	CH_2-2'
4.95	t, J = 5.5 Hz	2 H	CH_2-1'
7.73	s	1 H	H-9
8.03	s	1 H	H-6
8.58	s	1 H	H-3

^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm: 19.5 (Me-7), 21.5 (Me-8), 45.3 (C-4'), 45.6 (C-1'), 67.9 (C-2'), 69.2, 70.6, 70.8 (C-5', 7', 8'), 132.1 (C-9a), 132.4 (C-6), 133.0 (N**C**S), 135.0 (C-5a), 136.0 (C-4a), 137.1, 148.1 (C-7, 8), 150.4 (C-10a), 155.1, 159.6 (C-2, 4), 166.78 (C-9).

EI-MS $\frac{m}{z}$: 91.2 (100%, $C_7H_7^+$), 242.2 (98%, [M − side chain]$^{+\bullet}$), 415.3 (5%, [M]$^{+\bullet}$).[144]

ES-MS $\frac{m}{z}$: 461.1 (100%, M + H^+).

HR-MS (ES-MS): calcd. for $C_{19}H_{21}N_5O_4S$: 415.1314; found: 415.1320 (delta −1.39 ppm).

MP: 178 °C (CH_2Cl_2, decomposition).

R_F: 0.84 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

24. 3-(2'-Isothiocyanatoeth-1'-yl)-10-(3"-oxabut-1"-yl) Flavin (32)

Prepared according to General Procedure 1 from **28·HCl** (0.6 g) to yield 0.54 g (89%) of a yellow solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.41	s	3 H	CH_3-7
2.51	s	3 H	CH_3-8
3.24	s	3 H	CH_3-4"
3.77	t, J = 5.8 Hz	2 H	CH_2-1"
3.95	t, J = 5.9 Hz	2 H	CH_2-1'
4.20	t, J = 5.8 Hz	2 H	CH_2-2'
4.84	t, J = 5.6 Hz	2 H	CH_2-2"
7.91	s	1 H	H-9
7.96	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.7 (2×CH_3), 40.0, 42.8, 44.0 (3×CH_2), 58.5 (CH_3), 68.3 (CH_2), 116.9, 130.8 (2×CH), 131.5, 134.1, 136.0, 136.2, 146.8, 149.0, 154.4, 159.6 (8×quaternary C). The signal of the isothiocyanate group was not observed, presumably due to long relaxation time.

EI-MS $\frac{m}{z}$: 242.2 (100%, [M − CH_2OCH2CH2 − CH_2CH_2NCS]$^{+\bullet}$), 385.2 (5%, [M]$^{+\bullet}$).[144]

MP: 190–193 °C.

R_F: 0.33 (AcOEt).

25. General Procedure 2 for the Preparation of Flavin Photocatalysts with Primary Thiourea Group (33–36 and 44)

Flavin was dissolved in chloroform and gaseous ammonia was passed through the solution for 3 h. The precipitate was filtered off and purified by trituration or chromatography if required.

26. 10-(2'-Thioureidoeth-1'-yl) Flavin (33)

Prepared according to General Procedure 2 from **29** (60 mg) to yield 48 mg (76%) of a yellow solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.40	s	3 H	CH_3-7
2.48	s	3 H	CH_3-8
3.78	m	2 H	CH_2-2'
4.71	m	2 H	CH_2-1'
7.16	br s	2 H	NH_2
7.72	m	1 H	NH
7.87	s	1 H	H-9
8.14	s	1 H	H-6
11.27	s	1 H	H-3

^{13}C NMR (DMSO-d6) δ/ppm: 18.8, 20.6 (2×CH_3), 39.5, 43.6 (2×CH_2), 116.5, 130.8 (2×CH), 131.5, 133.7, 135.8, 136.8, 146.5, 150.3, 155.6, 159.9, 183.8 (9×quaternary C).

ES-MS $\frac{m}{z}$: 345.0 (100%, M + H^+).

EA: calcd. (%) for $C_{15}H_{16}N_6O_2S$: C 52.31, H 4.68, N 24.40, O 9.29, S 9.31; found: C 52.55, H 4.53, N 24.51, S 9.20.

MP: 178 °C (decomposition).

27. 3-Methyl-10-(2'-Thioureidoeth-1'-yl) Flavin (34)

Prepared according to General Procedure 2 from **30** (50 mg) to yield 36 mg (68%) of a yellow solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.38	s	3 H	CH_3-7
2.47	s	3 H	CH_3-8
3.29	s	3 H	CH_3-3
3.77	m	2 H	CH_2-2'
4.70	m	2 H	CH_2-1'
7.18	m	2 H	NH_2
7.75	m	1 H	NH
7.87	s	1 H	H-9
8.14	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.7, 28.0 (3×CH_3), 39.5, 43.6 (2×CH_2), 116.5, 130.8 (2×CH), 131.5, 133.7, 135.8, 136.8, 146.5, 150.3, 155.6, 159.9, 183.8 (9×quaternary C).

ES-MS $\frac{m}{z}$: 357.1 (100%, M − H^+), 417.2 (65%, M + AcO^-), 471.1 (55%, M + CF_3COO^-).

HR-MS (EI-MS): calcd. for $C_{16}H_{19}N_6O_2S$ $[M]^{+\bullet}$: 359.1290; found: 359.1297 (delta −1.89 ppm).

MP: 252 °C (decomposition).

R_F: 0.70 ($CHCl_3$:MeOH = 7:1).

28. 10-(3',6'-Dioxa-8'-thioureidooct-1'-yl) Flavin (35)

Prepared according to General Procedure 2 from **31** (0.5 g) to yield 230 mg (44%) of a brown solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.40	s	3 H	CH_3-7
2.50	s	3 H	CH_3-8
3.35–3.56	m	8 H	CH_2-4',5',7',8'
3.81	t, J = 5.9 Hz	2 H	CH_2-2'
4.80	t, J = 5.5 Hz	2 H	CH_2-1'
7.01	br s	2 H	NH_2
7.54	br s	1 H	*NH*–C(S)NH_2
7.88	s	2 H	CH-6,9)
11.33	s	1 H	H-3

^{13}C NMR (150 MHz, DMSO-d_6) δ/ppm: 18.8, 20.6 (2×CH_3), 43.8 (CH_2), 44.0 (CH_2-1'), 66.7 (CH_2-2'), 69.0, 69.5, 70.1 (3×CH_2), 116.8, 130.7 (2 ×CH), 131.4 (C-9a), 133.7 (C-5a), 135.8, 136.0, 137.1, 146.2, 155.6, 159.9 (6×quaternary C), 182.9 (C=S).

ES-MS $\frac{m}{z}$: 433.1 (100%, M + H^+).

ES-MS $\frac{m}{z}$: 431.1 (100%, M − H^+), 467.1 (50%, M + Cl^-), 491.3 (24%, M + AcO^-).

HR-MS (EI-MS): calcd. for $C_{19}H_{24}N_6O_4S$ $[M]^{+\bullet}$: 432.1580; found: 432.1575 (delta 1.10 ppm).

MP: 170 °C (decomposition).

R_F: 0.60 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

29. 3-(2'-Thioureidoeth-1'-yl)-10-(3"-oxabut-1"-yl) Flavin (36)

Prepared according to General Procedure 2 from **32** (100 mg) to yield 104 mg (100%) of an orange solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.39	s	3 H	CH_3-7
2.49	s	3 H	CH_3-8
3.24	s	3 H	CH_3-4"
3.66	br	2 H	CH_2-1'
3.76	t, J = 5.6 Hz	2 H	CH_2-1"
4.03	br	2 H	CH_2-2'
4.82	t, J = 5.5 Hz	2 H	CH_2-2"
6.98	2×s	3 H	NH groups
7.62			
7.88	s	1 H	H-9
7.90	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.7 (2×CH_3), 39.5, 42.1, 43.9 (3×CH_2), 58.5 (CH_3), 68.3 (CH_2), 116.8, 130.8 (2×CH), 131.4, 133.9, 136.1, 136.2, 146.6, 148.8, 154.9, 159.7, 183.5 (9×quaternary C).

ES-MS $\frac{m}{z}$: 403.1 (100%, M + H^+).

HR-MS (EI-MS): calcd. for $C_{18}H_{22}N_6O_3S$ $[M]^{+\bullet}$: 402.1474; found: 402.1479 (delta −1.22 ppm).

MP: 171 °C (decomposition).

R_F: 0.30 (AcOEt:MeOH = 10:1).

30. General Procedure 3 for the Preparation of Compounds 37–40 and 45–47

Flavin isothiocyanates was dissolved in chloroform, and the corresponding amine (2.5 eq.) and TEA (2 eq.) were added. The reaction mixture was heated to reflux until monitoring by TLC indicated complete conversion. The reaction mixture was then evaporated *in vacuo* and the crude product was purified by chromatography if required.

31. 10-(9',11'-Diaza-3',6',14'-trioxa-10'-thioxo pentadec-1'-yl) Flavin (37)

Prepared according to General Procedure 3 from **31** (20 mg) to yield 24 mg (100%) of an orange solid. NMR signals were assigned *per analogiam* to the isothiocyanate **31** and with the help of HMBC and HSQC experiments.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.43	s	3 H	Me-7
2.54	s	3 H	Me-8
3.14–3.72	m	15 H	CH_2-4',5',7',8',12',13', CH_3-15'
4.05	br	2 H	CH_2-2'
4.99	br	2 H	CH_2-1'
7.59	s	1 H	H-9
8.01	s	1 H	H-6

^{13}C NMR ($CDCl_3$, 100 MHz) δ/ppm: 19.5 (Me-7), 21.6 (Me-8), 44.3 (C-4'), 44.9 (C-1'), 58.5 (C-15'), 70.1, 70.3, 70.6, 70.9, 71.5, 71.5 (C-5',7',8',12',13'), 116.0 (C-9), 131.5 (C-9a), 132.6 (C-6), 135.1 (C-5a), 136.0 (C-4a), 137.3, 148.3 (C-7,8), 150.5 (C-10a), 156.5, 159.7 (C-2,4), 183.1 (C=S).

ES-MS $\frac{m}{z}$: 491.3 (100%, M + H^+).

HR-MS (LSI-MS): calcd. for $C_{22}H_{31}N_6O_5S$: 491.2077; found: 491.2086 (delta −1.90 ppm).

MP: 178 °C (decomposition).

R_F: 0.69 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

32. 10-(3',5'-Diaza-8',8',9',9',10',10',11',11',12',12',13',13',14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl) Flavin (38)

Prepared according to General Procedure 3 from isothiocyanate **29** (50 mg) to yield 82 mg (68%) of a yellow solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.38	s	3 H	CH_3-7
2.46	br	5 H	CH_3-8, CH_2
3.50–4.00	m	4 H	2×CH_2
4.72	m	2 H	CH_2
7.78	t, J = 5.4 Hz	1 H	NH
7.88	s	1 H	H-9
8.03	s	1 H	H-6
11.37	s	1 H	H-3

^{13}C NMR spectrum could not be measured to extremely low solubility of the title compound.

^{19}F NMR (DMSO-d_6) δ/ppm: −125.2 (m, 2 F), −122.6 (m, 2 F), −121.9 (m, 2 F), −121.2 (m, 6 F), −112.7 (m, 2 F), −79.7 (t, J = 9.5 Hz, 3 F, CF_3).

ES-MS $\frac{m}{z}$: 791.2 (100%, M + H^+).

HR-MS (LSI-MS) $\frac{m}{z}$: calcd. for $C_{25}H_{20}F_{17}N_6O_2S$ (M + H^+): 791.1097; found: 791.1102 (delta 0.64 ppm).

MP: 237 °C (decomposition).

33. 10-(3',5'-Diaza-8',8',9',9',10',10',11',11',12',12',13',13',14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-3-methyl Flavin (39)

Prepared according to General Procedure 3 from isothiocyanate **30** (15 mg) to yield 28 mg (79%) of an orange solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.37	s	3 H	CH_3-7
2.45	br	5 H	CH_3-8, CH_2
3.30	s	3 H	CH_3-3
3.52–3.98	m	4 H	2×CH_2
4.69	m	2 H	CH_2
7.79	t, J = 5.4 Hz	1 H	NH
7.89	s	1 H	H-9
8.05	s	1 H	H-6

^{13}C NMR spectrum could not be measured due to extremely low solubility of the title compound.

^{19}F NMR ($CDCl_3$) δ/ppm: −126.6 (m, 2 F), −123.9 (m, 2 F), −123.2 (m, 2 F), −122.4 (m, 2 F), −122.1 (m, 2 F), −114.2 (m, 2 F), −81.2 (t, J = 9.8 Hz, 3 F).

ES-MS $\frac{m}{z}$: 805.2 (100%, M + H^+).

HR-MS (LSI-MS): calcd. for $C_{26}H_{22}F_{17}N_6O_2S$ (M + H^+): 805.1253; found: 805.1281 (delta −3.42 ppm).

MP: 208 °C (decomposition).

34. 3-(3',5'-Diaza-8',8',9',9',10',10',11',11',12',12',13',13',14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-10-(3"-oxabut-1"-yl) Flavin (40)

Prepared according to General Procedure 3 from isothiocyanate **32** (40 mg) to yield 59 mg (67%) of an orange solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.45	s	3 H	CH_3-7
2.55	m	5 H	CH_3-8, CH_2-6'
3.27	s	3 H	CH_3-4"
3.65	m	2 H	CH_2-2'
3.91	t, J = 5.1 Hz	2 H	CH_2-1"
3.99	m	2 H	CH_2-7'
4.30	t, J = 6.2 Hz	2 H	CH_2-1'
4.91	t, J = 5.1 Hz	2 H	CH_2-2"
7.71	s	1 H	H-9
8.04	s	1 H	H-6

^{13}C NMR ($CDCl_3$): δ/ppm: 19.6, 21.8 (2×CH_3), 30.6, 40.6, 40.7, 45.6, 45.7 (5×CH_2), 59.3 (CH_3), 69.5 (CH_2), 117.0, 132.1 (2×CH), 132.2, 134.9, 135.4, 137.6, 137.6, 148.6, 148.8, 156.5, 160.5 (9×quaternary C).

^{19}F NMR ($CDCl_3$) δ/ppm: −126.7 (m, 2 F), −124.0 (m, 2 F), −123.3 (m, 2 F), −122.5 (m, 4 F), −122.2 (m, 2 F), −114.3 (t, J = 13.5 Hz, 2 F, CF_2-8'), −81.3 (t, J = 9.8 Hz, 3 F).

ES-MS $\frac{m}{z}$: 849.3 (100%, M + H^+).

HR-MS (EI-MS): calcd. for $C_{28}H_{25}F_{17}N_6O_6S$ $[M]^{+\bullet}$: 848.1437; found: 848.1438 (delta −0.07 ppm).

MP: 186 °C (decomposition).

R_F: 0.63 (CH_2Cl_2:MeOH = 10:1).

35. 3,10-Bis[2'-(*tert*-butyloxycarbonylamino)eth-1'-yl] Flavin (41)

Flavin **20** (300 mg, 0.78 mmol, 1 eq.) was dissolved in dry DMF (40 mL) at 80 °C. The solution was allowed cool to ambient temperature, potassium carbonate (540 mg, 3.9 mmol, 5 eq.) was added and the mixture was stirred for 30 min. 2-(*tert*-Butyloxycarbonylamino)ethyl bromide (520 mg, 2.3 mmol, 3 eq.) and sodium iodide (180 mg, 1.2 mmol, 1.5 eq.) were added, and the reaction mixture was stirred at ambient temperature. After the first and second day of stirring, another portions of the bromide (520 mg, 2.3 mmol, 3 eq. each portion) were added. After 3 d, the reaction mixture was diluted with chloroform (300 mL), washed with aqueous sodium hydrogen carbonate (100 mL), water (3×100 mL), and brine (100 mL), and the organic phase was evaporated in vacuo. Compound **41** was isolated by flash chromatography ($CHCl_3$:MeOH = 15:1). Yield 210 mg (52%) of an orange solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
1.24	s	9 H	*tert*-Bu
1.34	s	9 H	*tert*-Bu
2.41	s	3 H	CH_3-7
2.50	s	3 H	CH_3-8
3.19	d, J = 6.0 Hz	2 H	CH_2-2'
3.40	d, J = 5.8 Hz	2 H	CH_2-2'
3.96	t, J = 6.0 Hz	2 H	CH_2-1'
4.66	t, J = 5.6 Hz	2 H	CH_2-1'
6.83	t, J = 5.8 Hz	1 H	NH
7.03	t, J = 5.8 Hz	1 H	NH
7.89	s	1 H	H-9
7.95	s	1 H	H-6

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.8, 27.9, 28.1 (4×CH_3), 36.9, 37.8, 40.8, 43.9 (4×CH_2), 77.5, 77.8 (2×quaternary C), 116.1, 130.9 (2× CH), 131.9, 134.0, 135.7, 135.8, 146.5, 148.7, 154.7, 155.6, 155.8, 159.6 (10×quaternary C).

ES-MS $\frac{m}{z}$: 429.2 (25%, M + H^+ − Boc), 473.3 (35%, M + H^+ − Bu), 529.3 (100%, M + H^+), 551.4 (40%, M + Na^+).

MP: 136 °C (decomposition).

R_F: 0.34 ($CHCl_3$:MeOH = 15:1).

36. 3,10-Bis(2'-aminoeth-1'-yl) Flavin (42)

Flavin **41** (150 mg, 0.29 mmol) was dissolved in methanol (30 mL) and hydrogen chloride in ether (3 mL) was added dropwise. The reaction mixture was stirred overnight at ambient temperature. The mixture was evaporated *in vacuo* and the yellow-brownish residue dried. Yield 114 mg (100%) of the dihydrochloride **42**·**HCl**.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.42	s	3 H	CH_3-7
2.55	s	3 H	CH_3-8
3.07	d, J = 5.5 Hz	2 H	CH_2-2'
3.18	d, J = 5.2 Hz	2 H	CH_2-2'
4.18	t, J = 5.9 Hz	2 H	CH_2-1'
4.97	t, J = 6.6 Hz	2 H	CH_2-1'
7.97	s	1 H	H-9
8.13	br s	3 H	NH_3^+
8.30	s	1 H	H-6
8.57	br s	3 H	NH_3^+

^{13}C NMR (DMSO-d_6) δ/ppm: 18.8, 20.5 (2×CH_3), 35.8, 37.1, 38.5, 41.2 (4×CH_2), 116.3 (CH), 130.5 (quaternary C), 131.2 (CH), 134.2, 136.4, 136.5, 147.6, 149.4, 154.9, 160.0 (7×quaternary C).

ES-MS $\frac{m}{z}$: 329.1 (100%, M + H^+).

MP: 268 °C (decomposition).

R_F: 0.00 ($CHCl_3$:MeOH = 15:1).

37. 3,10-Bis(2'-Isothiocyanatoeth-1'-yl) Flavin (43)

Prepared according to General Procedure 1 from **42·2 HCl** (114 mg) to yield 95 mg (81%) of a yellow solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.47	s	3 H	CH_3-7
2.60	s	3 H	CH_3-8
3.91	t, J = 6.3 Hz	2 H	CH_2-2'
4.19	t, J = 5.6 Hz Hz	2 H	CH_2-2'
4.43	t, J = 6.3 Hz	2 H	CH_2-1'
4.99	t, J = 5.9 Hz	2 H	CH_2-1'
7.57	s	1 H	H-9
8.10	s	1 H	H-6

^{13}C NMR ($CDCl_3$) δ/ppm: 18.8, 20.9 (2×CH_3), 40.4, 42.0, 42.3, 43.8 (4×CH_2), 115.6 (CH), 131.1 (quaternary C), 132.0 (CH), 134.6, 135.0, 137.6, 148.6, 149.4, 155.4, 159.9 (7×quaternary C). The resonance signals of the isothiocyanate groups were not observed, presumably due to long relaxation time.

ES-MS $\frac{m}{z}$: 413.1 (100%, M + H^+).

MP: 140 °C (decomposition).

R_F: 0.35 ($CHCl_3$:MeOH = 25:1).

38. 3,10-Bis(2'-Thioureidoeth-1'-yl) Flavin (44)

Prepared according to General Procedure 2 from isothiocyanate **43** (60 mg) to yield 65 mg (100%) of an orange-red solid.

^{1}H NMR (DMSO-d_6):

δ/ppm	Multiplicity	Intensity	Assignment
2.42	s	3 H	CH_3-7
2.50	s	3 H	CH_3-8
3.67–3.69	m	4 H	2×CH_2
4.06	m	2 H	CH_2-2'
4.76	m	2 H	CH_2-1'
6.98–7.77	m	6 H	NH and NH_2 groups
7.95	s	1 H	H-9
8.21	s	1 H	H-6

^{13}C NMR spectrum could not be measured due to extremely low solubility of the title compound.

ES-MS $\frac{m}{z}$: 447.2 (100%, M + H^+).

HR-MS (LSI-MS) $\frac{m}{z}$: calcd. for $C_{18}H_{23}N_8O_2S_2$ (M + H^+): 447.1385; found: 447.1372 (delta −3.00 ppm).

MP: 235 °C (decompobissition).

R_F: 0.30 ($CHCl_3$:MeOH = 10:1).

39. 3,10-Bis[2'-(3',5'-diaza-8',8',9',9',10',10',11',11',12',12',13',13',14',14',15',15',15'-heptadecafluoro-4'-thioxopentadec-1'-yl)-eth-1'-yl] Flavin (45)

Prepared according to General Procedure 3 from isothiocyanate **43** (60 mg) to yield 99 mg (51%) of a red solid.

^{1}H NMR and **^{13}C NMR** spectra could not be measured due to extremely low solubility of the title compound.

^{19}F NMR (DMSO-d_6) δ/ppm = −125.4 (m, 4 F), −122.6 (m, 4 F), −122.0 (m, 4 F), −121.2 (m, 12 F), −112.8 (m, 4 F), −79.7 (m, 6 F).

ES-MS $\frac{m}{z}$: 1339.2 (100%, M + H^+), 1361.2 (15%, M + Na^+).

EA: calcd. (%) for $C_{38}H_{28}F_{34}N_8O_2S_2$: C 34.09, H 2.11, F 48.25, N 8.37, O 2.39, S 4.79; found: C 34.31, H 1.95, N 8.24, S 4.91.

MP: 211 °C (decomposition).

R_F: 0.50 ($CHCl_3$:MeOH = 10:1).

40. Bis-Flavin 46

Prepared according to General Procedure 3 from isothiocyanate **31** (60 mg) and flavin **26·HCl** (120 mg) to yield 99 mg (51%) of a red solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.44	s	6 H	Me-7
2.56	s	6 H	Me-8
3.59 3.72	} 2×m	2×8 H	CH_2-4',5',7',8',12',13',15',16'
4.05	t, J = 5.1 Hz	4 H	CH_2-2',18'
4.11	t, J = 5.1 Hz	4 H	CH_2-1',19'
7.02	br s	2 H	H-9',11'
7.64	s	2 H	H-9
7.99	s	2 H	H-6
9.38	br s	2 H	H-3

^{13}C NMR spectrum could not be measured due to extremely low solubility of the title compound.

ES-MS $\frac{m}{z}$: 395.3 (14%, M + 2 H^+), 414.3 (21%, M + H^+ + K^+), 798.4 (100%, M + H^+), 811.4 (47%, M + Na^+), 827.3 (4%, M + K^+).

EA: calcd. (%) for $C_{37}H_{44}N_{10}O_8S$: C 56.33, H 5.62, N 17.75, O 16.22, S 4.06; found: C 56.47, H 5.42, N 17.91, S 4.05.

MP: 165 °C ($CHCl_3$, decomposition).

R_F: 0.62 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

41. Bis-Flavin 47

Prepared according to General Procedure 3 from isothiocyanate **31** (60 mg) and 3,6-dioxaoct-1,8-diyl diamine (15 mg) to yield 66 mg (93%) of an orange solid.

^{1}H NMR ($CDCl_3$):

δ/ppm	Multiplicity	Intensity	Assignment
2.42	s	6 H	Me-7
2.55	s	6 H	Me-8
3.54–3.87	m	28 H	glycol CH_2's
4.05	br	4 H	CH_2-2'
4.95	br	4 H	CH_2-1'
7.07	br	2 H	H-3
7.66	s	2 H	H-9
7.95	s	2 H	H-6
8.39	br	4 H	H-9',11',20',22'

^{13}C NMR ($CDCl_3$, 150 MHz) δ/ppm: 19.4, 21.5, 45.3, 67.7, 69–72 (unresolved glycol CH_2 groups), 132.2, 136.3, 138.8, 148.2. Due to low solubility of the compound, ^{13}C NMR was reconstructed from HSQC and HMBC experiments. Signals of the remaining carbon atoms could not be therefore observed.

ES-MS $\frac{m}{z}$: 490.5 (100%, M + 2 H^+), 491.5 (22%, M + H^+ + Na^+), 979.5 (72%, M + H^+), 1001.5 (23%, M + Na^+).

HR-MS (EI-MS): calcd. for $C_{44}H_{59}N_{12}O_{10}S_2$: 979.3919; found: 979.3882 (delta 3.73 ppm).

MP: 117 °C (decomposition).

R_F: 0.55 ($CHCl_3$:MeOH:AcOH = 77.5:15:7.5).

Chapter 5

Notes and References

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are 1900 cm^{-1} and 1902 cm^{-1}, respectively, i.e., they differ by merely 2 cm^{-1}. In such a situation Fermi resonance between these two modes is likely to occur, making the situation even more complicated.

[139] This value coincides with the one reported[28] for the *gem*-diol **4** (270.5 °C). This presumably indicates that the *gem*-diol **4** dehydrates at elevated temperature before melting/decomposition begins, and the melting point attributed to the *gem*-diol **4** is actually melting point of the aldehyde **2**.

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Appendix A

List of Abbreviations

ACN Acetonitrile

Boc Benzyloxycarbonyl

CI-MS Chemical ionisation mass spectrometry

DMF *N,N*-dimethylformamide

DMSO Dimethylsulphoxide

EA Combustion elementary analysis

EI-MS Electron-impact mass spectrometry

ES-MS Electrospray ionisation mass spectrometry

HMBC Heteronuclear multiple bond correlation

(RP)-HPLC (Reverse-phase) high-performance liquid chromatography

HR-MS High-resolution mass spectrometry

HSQC Heteronuclear single quantum correlation

LC Liquid chromatography

LED Light-emitting diode

MS Mass spectroscopy

NMR Nuclear atomic resonance

PTLC Preparative thin layer chromatography

QY Quantum yield

$\mathbf{R_F}$ Retention factor

r.t. Room temperature, ambient temperature

TLC Thin layer chromatography

TEA Triethylamine

TFA Trifluoroacetyl