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

Jiří Svoboda and Burkhard König*

Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, 93053 Regensburg, Germany

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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 homogeneous solutions where molecules behave rather chaotically. Their encounters within the thermal bath of Brownian motion occur with statistical distribution between the possible 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 equalizing power of thermal fluctuations by additional control elements. Bias in the orientation during reaction 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 therefore may exhibit higher selectivity than those in homogeneous solution. Photodimerizations of crystalline aromatic or olefinic compounds belong to the oldest known organic photoreactions. In this type of reaction the crystal lattice locks the relative orientation of the photoreactive groups. If the orientation is favorable 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 the 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 the simple alignment of double bonds. Long-range molecular movements within crystals 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, cocrystals 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. Enantioselective photochemical conversion of chiral crystals into optically active products has been described.[11] Different approaches utilize zeolites as supramolecular hosts for photoreactions.[12] Internal complexation, or intracrystalline 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 cavities 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, cocrystal, or inclusion complex for the desired regio- or stereoselective outcome of a given reaction remains a challenge. Therefore, an attractive strategy is to transfer the topochemical control from the solid state to homogeneous solution using suitable templates. Such reactions are easier to analyze, design, and optimize. We will 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 sensitizer) of various construction (a rational design, cyclodextrin, cucurbituril, DNA, etc.) which reversibly binds a substrate molecule 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 preform a species which undergoes a thermal process are therefore not included. In the ideal scenario the template should act as a catalyst

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Jiří Svoboda, born 1979 in Prague, Czech Republic, received his M.Sc. degree from the Institute of Chemical Technology in Prague, where he worked in the group of Professors Ivan Stibor and Pavel Lhoták on the chemistry of thiacalixarenes. Currently, he is concluding his Ph.D. studies at the University in Regensburg, Germany, under the supervision of Professor Burkhard König. His research focuses on the chemistry of flavins and application of flavin-based molecules as photochemical sensitizers. Apart from chemistry, he likes board games and the art of bonsai.

Burkhard König received his doctorate degree in 1991 from the University of Hamburg under the direction of Professor de Meijere. He continued his scientific education as a postdoctoral fellow with Professor M. A. Bennett, Canberra, and Professor B. M. Trost, Stanford. In 1996 he obtained his "Habilitation" at the University of Braunschweig. Since 1999 he has been Full Professor of Organic Chemistry at the University of Regensburg. His current research interests focus on the development of synthetic receptors.

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 noncatalytic 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, cocrystals, any kind of solids, polymers, solid phase + gas reactions, reactions in zeolites, micelles, membranes, compartmented solutions, aggregates, or reactions 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]

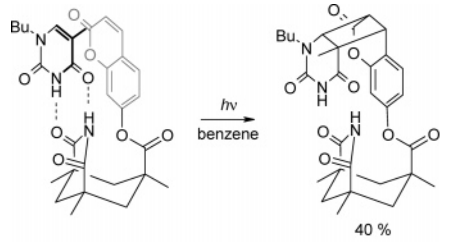
The division of the sections is somewhat artificial as they partly overlap and some of the work could be featured in several of them. However, we tried to divide them in a way to make reading and understanding easier. The survey begins with photoreactions in which selectivity was achieved by shielding 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 noncovalent assemblies where the substrates are preorganized in a defined way by the host molecule. Examples using DNA as a template for selective reactions are followed by contributions featuring a covalently bound sensitizer and a substrate-binding site to enhance the efficiency of energy- or 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 templates which bind a substrate by noncovalent interactions to distinguish between different sides of attack and thus direct the course of a photochemical transformation by the presence of 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 shape and size 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 coumarin group, and 3-butylthymine **2** (Scheme 1).[17,18] 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.

Scheme 1. Stereoselective Cycloaddition of Coumarin and Thymine

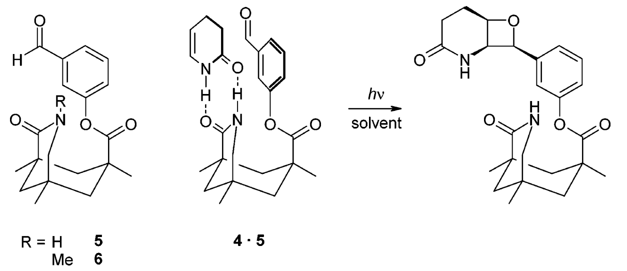


1 · 2 **3**

A similar—still noncatalytic—example from Bach et al. described the stereoselective Paternó−Büchi reaction of 3,4-dihydro-1*H*-pyridin-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 nonpolar solvents such as benzene favored formation of the complex. Diastereomeric ratios up to 95:5 and up to 56% yield were observed (toluene,

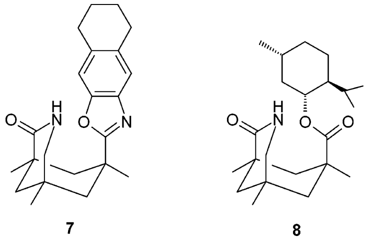
Scheme 2. Stereoselective Paternó−Büchi Reaction and Its Predominant Product



−10 °C). The importance of hydrogen bonding for the stereoselectivity was proved by a control experiment with the *N*-methylated host **6**, which does not allow face discrimination and showed no stereoselectivity.

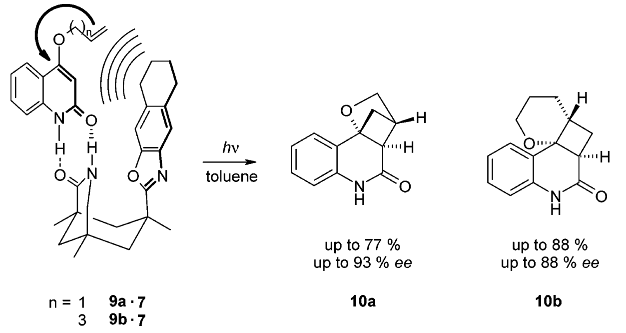
The next steps toward efficient catalytic asymmetric induction were chiral templates containing benzoxazole (host **7**) or menthol (host **8**) as steric shields (Scheme 3).

Scheme 3. Chiral Templates Used for Catalytic Asymmetric Induction



Templates **7** and **8** were used in an intramolecular [2+2] photocycloaddition of substituted 2-quinolones **9** (Scheme 4).[21]

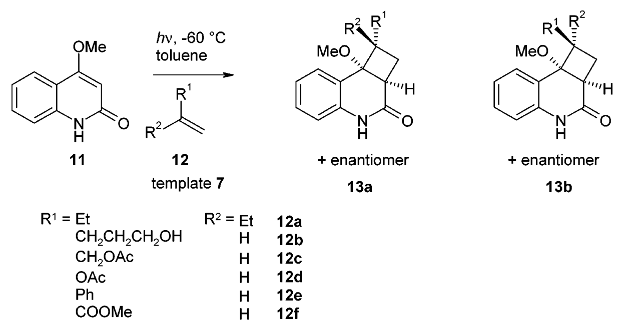
Scheme 4. Intramolecular [2+2] Cycloaddition



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 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 equiv 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 equiv 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). Nonsymmetric olefins **12b**−**f** gave a mixture of two diastereomers **13**. Olefins **12b**−**c**,**f** showed diastereoselectivity in favor of isomer **13a** (ratios **13a**:**13b** were 90:10 or higher, yields 80−84%) with ee values from 81% to 92%. Styrene **12e** favored 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.

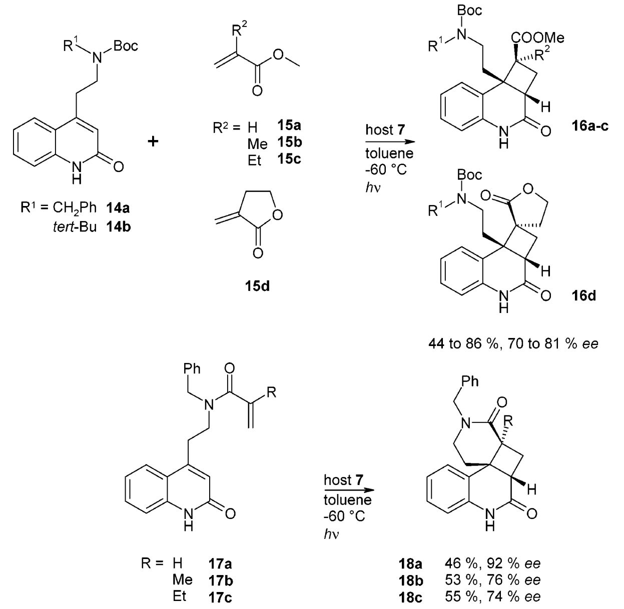
Scheme 5. [2+2] Photocycloaddition of 4-Methoxy-2-quinolones[a]



[a] See text for yields and ee values.

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 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 equiv based on the quinolone **14**) had to be employed in order to overcome self-association of the quinolones **14** to which the incomplete chirality transfer was attributed. Variation of quinolone **14** or acrylate **15** concentrations had no influence on the observed ee value. At −60 °C, there were no detectable side reactions due to hydrogen abstraction. Compounds **17** cyclized in the presence of the chiral host **7** to render the

Scheme 6. Enantioselective Inter- and Intramolecular Cycloaddition of 4-(2′-Aminoethyl)quinolones[a]



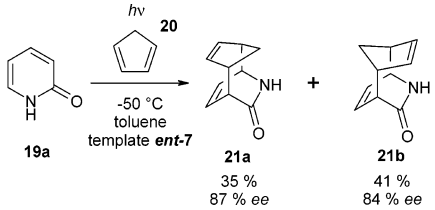
[a] See text for individual yields of the intermolecular cycloaddition.

tetracyclic products **18** in an intramolecular fashion (Scheme 6, bottom). Yields of the reaction were lowered by competing intermolecular oligomerization. However, observed ee values were higher than for the aforementioned intermolecular reaction because the oligomerization 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 a photochemically generated (*E*)-*o*-quinodimethane with alkenes[24] and for an enantioselective radical cyclization reaction of 4-(4′-iodobutyl)-quinolones.[25]

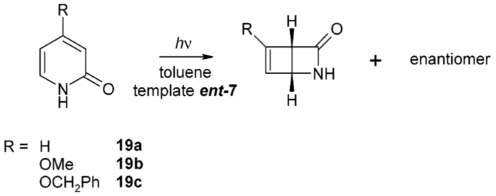
The chiral host **7** found another application for the stereoselective [4+4] photocycloaddition of 2-pyridone **19a** to cyclopentadiene **20** (Scheme 7).[26] Upon irradiation in the presence of the chiral host *ent*-**7**, a mixture of diastereomeric products **21**, which were formed with significant ee value, was obtained.

Scheme 7. [4+4] Photocycloaddition of 2-Pyridone to Cyclopentadiene



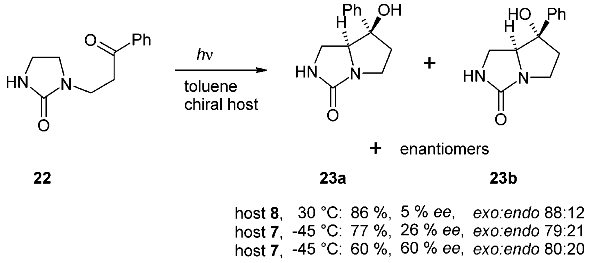
Intramolecular [4π] cyclization of 2-pyridone **19a** was considered too.[26] Since the reaction is known to proceed with low yields, 4-substituted pyridones **19b,c**, which undergo cyclization more readily, were investigated. The reaction rate and yield decreased with temperature, but on the other 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).

Scheme 8. [4π] Cyclization of 2-Pyridones



Another stereoselective photochemical reaction described was the Norrish−Yang cyclization.[27] Upon irradiation in the presence of chiral host **7** or **8**, imidazolidinones **22** yielded a mixture of stereoisomers **23** (Scheme 9).

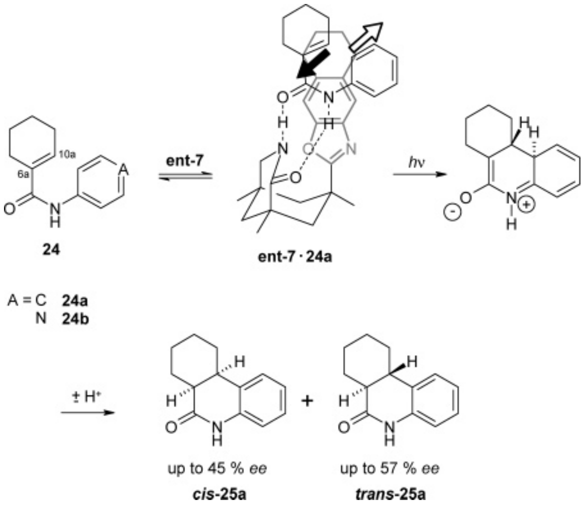
Scheme 9. Norrish−Yang Cyclization



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 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] photocyclization 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 tautomerized 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 carbon atom C_{6a}), and preference for the trans product was therefore observed. Thus, the major trans 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 cyclization was therefore not studied in detail.

Scheme 10. Enantioselective [6π] Photocyclization[a]

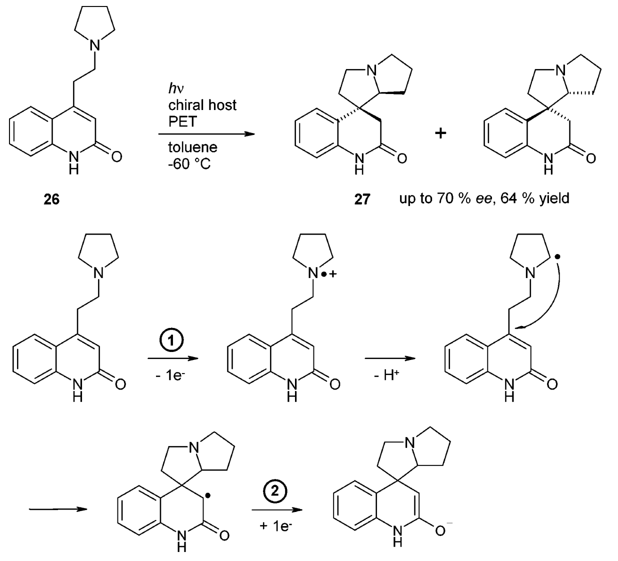


[a] Yields and ee values depend on conditions of the reaction; see text for discussion.

Prochiral quinolone **26** cyclized to a chiral pyrrolizidine **27** by a photoinduced electron-transfer reaction (PET) in the presence of chiral host **28** (Schemes 11 and 12).[29]

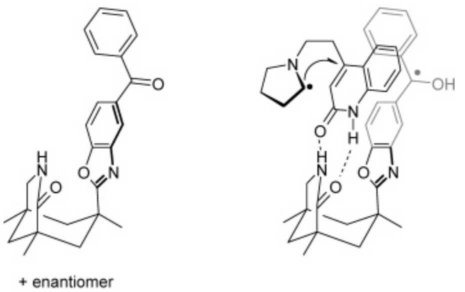
The chiral host **28** fulfilled three conditions: (i) it contained an efficient sensitizer of the electron-transfer process in close proximity to the substrate, (ii) it bound the substrate by two directional hydrogen bonds, and thus (iii) it differentiated its two enantiotopic faces.

Scheme 11. Enantioselective Photochemical Formation of Pyrrolizidine 27 and Its Proposed Mechanism[a]



[a] Key: (1) photoinduced electron transfer, (2) back electron transfer from template.

Scheme 12. Chiral Host 28 Used for Enantioselective Cyclization and Its Function

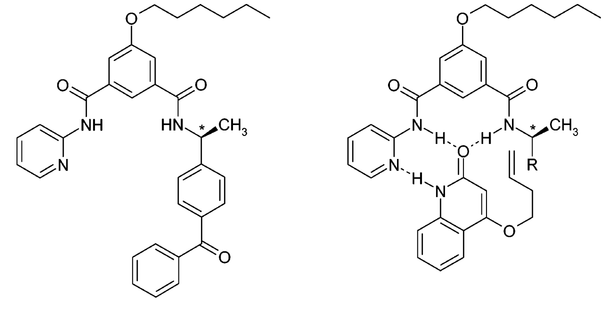


The reaction proceeded successfully in the presence of 5−30 mol % of the chiral host **28**, reached ee values up to 70%, and gave yields up to 64% (higher values were observed with higher amounts of template). Again, use of the enantiomeric form of the host led to reversion of the enantiomeric preference. The results were also compared to a reaction where a mixture of the benzoxazole chiral host **7** and *p*-methoxybenzophenone as a sensitizer was used, and the importance of sensitizer proximity was thus proved.

The intramolecular enone−olefin [2+2] photocycloaddition of quinolone **29**[30] reported by Cauble et al. showed that in the absence of a rigid aromatic shield some enantioselectivity is still achieved in catalytic templated photochemistry. The ‘sensitizing receptor’ **30** contains a complementary hydrogen-bonding pattern to bind the substrate **29** (Scheme 13).

The presence of the receptor **30** increased the efficiency of the cyclization 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 sensitizing receptor.

Scheme 13. ‘Sensitizing Receptor’ 30 Used for Stereoselective [2+2] Photocycloaddition of Quinolone 29 and Its Complex with the Substrate; R = 4-$C_6H_4(C{=}O)Ph$



3. Photochemical Reactions in Noncovalent Assemblies

As already stated in the Introduction, 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 preorganization of the reaction components within a noncovalent assembly in an advantageous and better defined geometry, thus leading to an increase in reaction rate and selectivity.

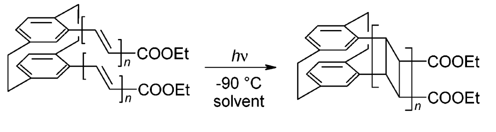
In the first part, development of a covalent substitute for the dimerization of cinnamic acid is described. In this case, the two components were preorganized within a covalent assembly which could be, however, considered temporary and reusable, and we therefore include this work as well. The second part discusses truly noncovalent assemblies and begins with systems that employ the template effect of alkali or alkaline earth metal cations on coronand systems and concludes with systems that utilize recognition of di- or triaminotriazine by barbiturate and other suitable molecules.

3.1. Temporary Covalent Preorganization

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).

Scheme 14. Photochemical Synthesis of [*n*]Ladderanes

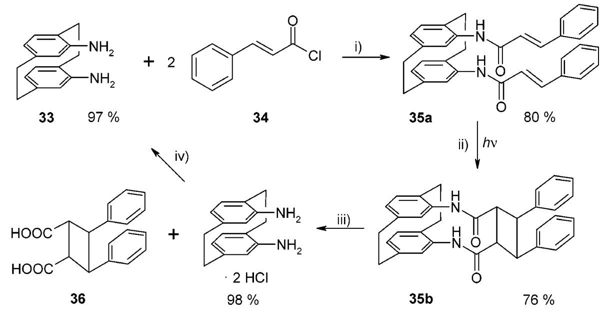


n =			
1	**31a**	**32a**	100 %
2	**31b**	**32b**	> 90 %
3	**31c**	**32c**	83 %

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 system 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 spacer **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).

Scheme 15. Temporary Use of the Cyclophane Unit for Topochemical Reaction Control in Solution[a]



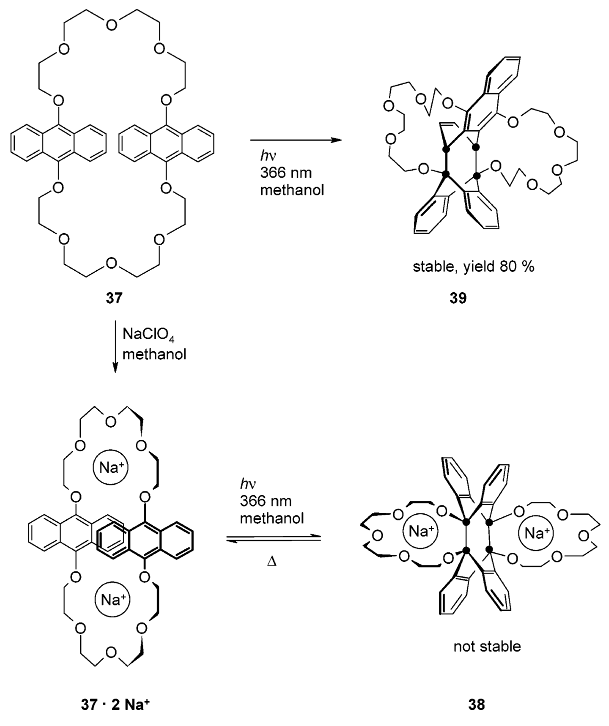
[a] (i) 1,4-Dioxane, room temperature, 24 h; (ii) *hν*, acetone, 7 h; (iii) concentrated HCl, reflux, 24 h; (iv) solid KOH.

3.2. Noncovalent Intramolecular Preorganization

The efficiency of dimerization of anthracene, incorporated in a macrocyclic crown ether or tethered by an ethylene glycol chain, was influenced by complexation 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]

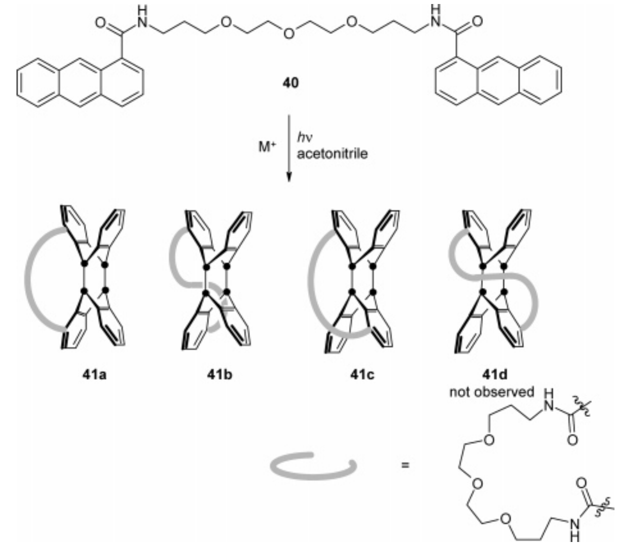
The regioselectivity of the photocycloaddition of two anthracene units in **37** was subject to the presence of sodium ions.[38] If present, a symmetric product **38** (Scheme 16) was obtained (quantum yield $\Phi_R = 8.3 \times 10^{-3}$ in methanol), while in the absence of sodium ions, a nonsymmetric 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.

Scheme 16. Cation-Templated Dimerization of Anthracene



The regioselectivity of photocycloaddition of bis-anthracene **40** responded to the presence of alkaline earth metal ions.[39] Upon irradiation, three regioisomers **41a−c** 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 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.

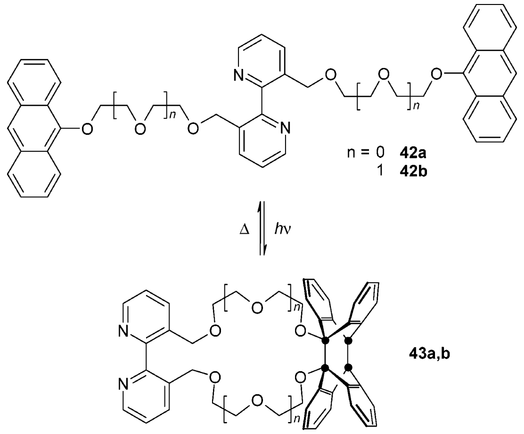
Scheme 17. Dimerization of Two Glycol-Linked Anthracenes[a]



[a] All possible regioisomers shown. Product ratio depended on metal cation present (see text). Preparative yields were not published.

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 dimerized 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 ions or mercury(II) ions, the quantum yield of dimerization increased 2-fold as opposed to the reaction in the absence 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 $\Phi_R = 0.19$ 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.

Scheme 18. Dimerization of Anthracene Dependent on Two Different Stimuli[a]



[a] The product is not thermally stable, and the efficiency of the photochemical reaction in the presence of metal cations was characterized by quantum yields (see text).

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.

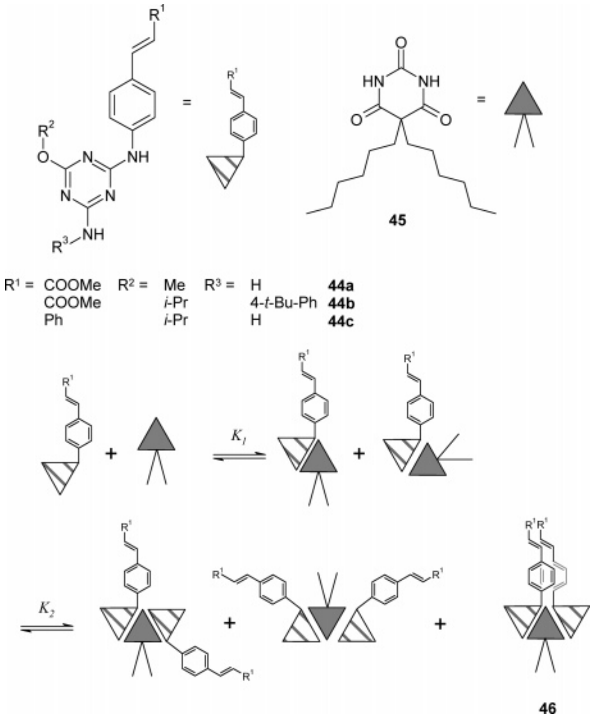
3.3. Noncovalent Intermolecular Preorganization

A diaminotriazine−barbiturate-based assembly was successfully used for dimerization 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 (**46**) locked the two cinnamates or stilbenes **44** in a suitable geometry for photocycloaddition (Scheme 19).

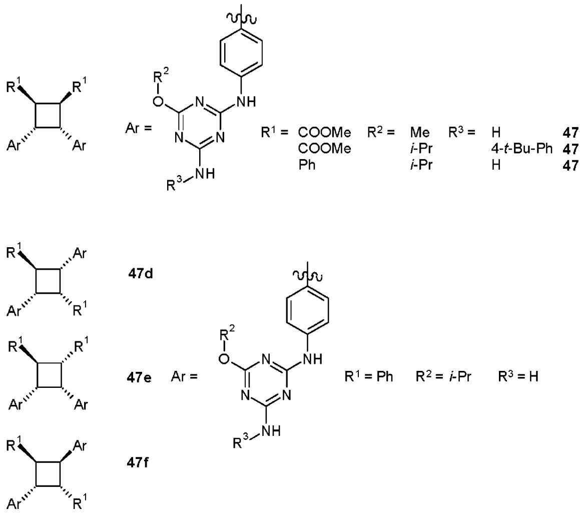
The presence of the barbiturate template **45** increased the reactivity and induced selectivity for some of the product isomers (Scheme 20). For dimerization of cinnamates **44a** and **44b**, formation of *β*-truxinate products **47a,b** was preferred (quantum yield increased from 0.7 × 10^{-3} to 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** dimerization, 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 was successfully used for dimerization of fullerenes (Scheme 21).[46,47] Two fullerene−barbiturate conjugates **48** were bound by the melamine host **49** and efficiently underwent dimerization upon irradiation. In the absence of the melamine host **49**, no dimerization was observed.

Scheme 19. Dimerization of Cinnamate and Stilbene in a Noncovalent Assembly



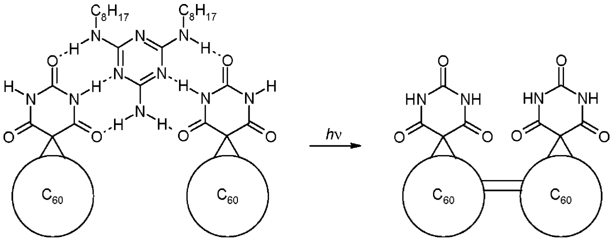
Scheme 20. Products of Cinnamates and Stilbene 44 Photodimerization[a]



[a] See text for quantum yields of their formation.

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 dimerization.[48] Accordingly, the cinnamate was 'equipped' with both a diaminotriazine substituent and a polyethylene glycol chain. Quantum yields of dimerization 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 dimerization (taken as yield of dimers after a certain time of irradiation) increased twice in the presence of 0.5 equiv of barbiturate **45** or potassium ions. When both of the templates were present, a 5-fold increase in dimerization efficiency was observed, which could be explained by a 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 the 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:**

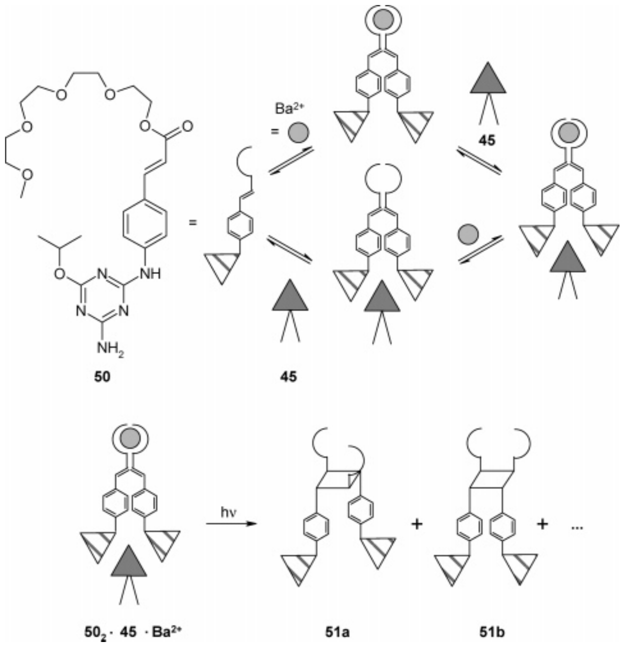
Scheme 21. Dimerization of Fullerenes in a Melamine−Barbiturate Assembly[a]



48_2·49

[a] Yield of the reaction was not given.

Scheme 22. Dimerization of Cinnamates Influenced by Two Supramolecular Interactions[a]

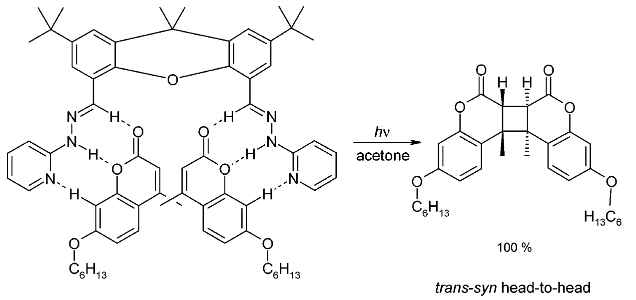


[a] See text for quantum yields of the products.

51a from 1:1 to 5:1. This indicated that the main effect of the nondirective 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.

Photodimerization 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 the 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 the trans-syn head-to-head dimer **54**. The preference for the trans isomer was explained by steric effects. Interestingly, the quantum yield of coumarin **52** dimerization 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 photodimerization efficiency was proved by template analogues whose recognition units were either missing or altered by methylation.

Scheme 23. Ditopic Template-Assisted Photodimerization of Coumarin



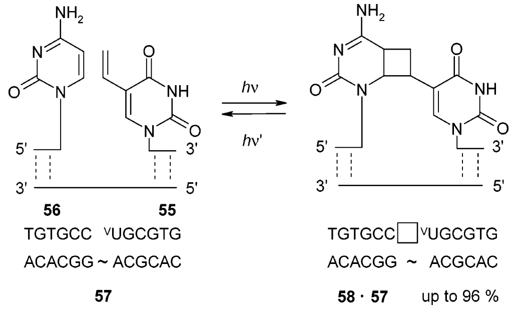
52_2· 53 **54**

4. Complementary DNA Strands as Templates

In this section we summarize photochemical reactions (ligations of deoxynucleotides) whose reactants required preorganization by the complementary DNA strand.

Vinyldeoxyuridine (^{V}U), incorporated into the oligodeoxynucleotide strand **55** by automated synthesis, 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).

Scheme 24. Oligodeoxynucleotide-Directed Photoligation

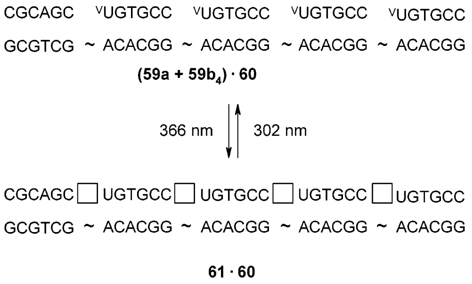


The ligation reaction between the 5′-terminal ^{V}U residue and 3′-terminal C residue is selective. There is no reaction between the 5′-terminal ^{V}U and a 3′-terminal A or G residue. The process was found to be reversible and the back reaction proceeded rapidly at 302 nm. Products of the cleavage reaction could be irradiated again, and the cyclobutane product was thus reformed. 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.

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 nucleotide **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**.

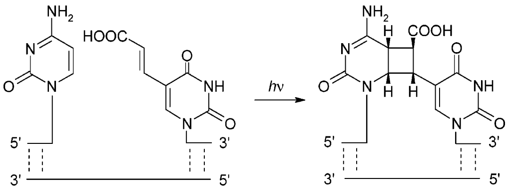
The ^{CV}U residue was also used for efficient photoligation to a 3′-terminal C or T residue in the presence of the

Scheme 25. Simultaneous Ligation of Five Vinyldeoxyuridine-Containing Oligodeoxynucleotides[a]

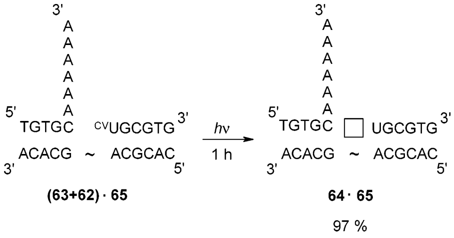


[a] Conversion and reversion are quantitative.

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



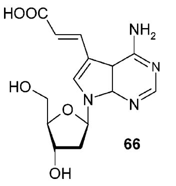
complementary RNA strand, thus forming a hybrid duplex.[53] Sensitivity of the photoligation efficiency to mismatches in the sequence of the complementary RNA strand was then successfully used for detection of RNA single-point mutations.

The DNA photoligation methods were extended by 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 modeling that the α anomer would interact better with the 5′-terminal T residue 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 was only 9−15%. The method was verified by synthesis of a branched oligodeoxynucleotide with T residue at the ligation point modified by a polyA chain, similar to the previous example (Scheme 27).

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.

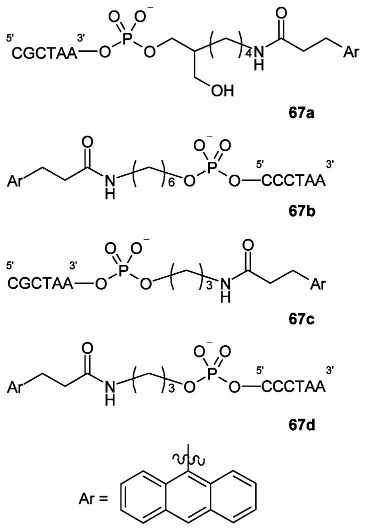
Photoligation was extremely rapid (93% yield within 5 min) and selective for the 3′-terminal C or T residues. A or G residues did not undergo reaction. The photoreversibility of the process was identical to the aforementioned example.

Scheme 28. Structure of 7-Carboxyvinyl-7-deaza-2′-deoxyadenosine



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**).

Scheme 29. Ligation of Oligodeoxynucleotides by Photocycloaddition of Anthracenes



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

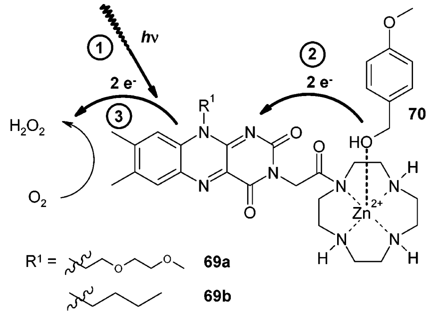
The sequences were designed to stack the anthracene units in the presence of the complementary DNA strand **68a**. Upon irradiation, the assembled anthracene units undergo photodimerization and connect the two strands. The relative yields of the anthracene photodimer after 30 min of irradiation were 1.46 (**67d** + **67a**) > 1.00 (**67b** + **67a**) > 0.33 (**67b** + **67c**) > 0.24 (**67d** + **67c**).[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 in the region between the two binding sites. No ligation was observed with a half-scrambled sequence template. The order of ligation efficiency coincided 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 sensitizer as an additive. The idea to covalently attach the sensitizer to a substrate-binding site was successfully used for efficient oxidation of benzylalcohol and photorepair of thymine dimers. Contrary to the previous sections, there is no shielding effect or preorganization of reaction components. Selectivity and efficiency were achieved by conducting the desired photoreaction only in the vicinity of the sensitizer and thus by conversion of the diffusion-controlled process to an intramolecular interaction.[58]

The first such system reported (compound **69a**) used a flavin group as the photomediator and Lewis-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 oxidized the alcohol to the corresponding aldehyde (Scheme 30).[62]

Scheme 30. Schematic Representation of the Catalytic Oxidation of 4-Methoxybenzyl Alcohol by a Flavin Unit[a]



69 · 70

[a] Key: (1) irradiation, (2) oxidation of substrate, (3) reoxidation of flavin.

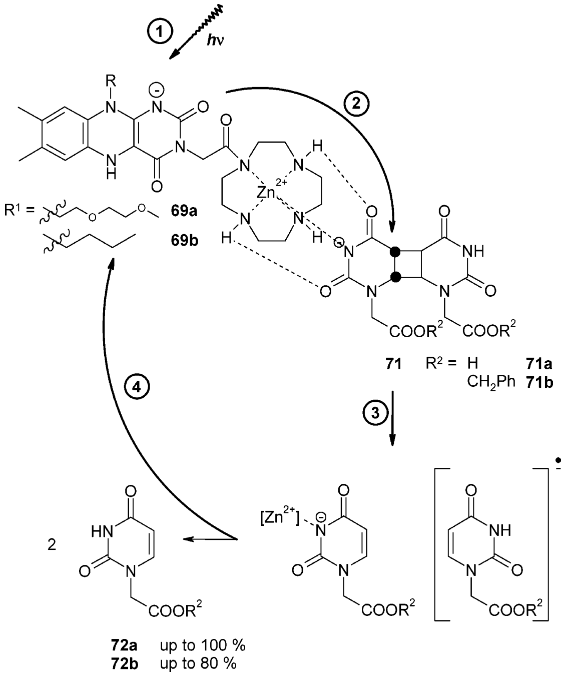
After reaction the flavin skeleton was in its reduced state and required reoxidation before the next turn of the cycle. Aerial oxygen rapidly reoxidized the flavin unit and the reaction went forth. Thus, the net reaction was oxidation of 4-methoxybenzylalcohol to the corresponding aldehyde by oxygen; 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 sensitizer was proved by experiments with flavin which did not contain the zinc(II)−cyclen binding unit or with equimolar mixtures of flavin and zinc(II)−cyclen perchlorate. Only the complete sensitizer **69a** which contained covalently bound zinc(II)−cyclen exhibited high conversion and turnover number (yield 90% after 2 h of irradiation). The sensitizer acted as a true catalyst: 10 mol % of the sensitizer was sufficient for efficient oxidation of the substrate. Oxidation was possible in both acetonitrile and aqueous buffer solution due to the good solubility of the sensitizer **69a** and high association constant.

The sensitizers **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 recognizes the thymine dimers and repairs them by photoinduced electron transfer using a noncovalently 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-catalyzed 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**.

Scheme 31. Functional Model of Photolyase[a]

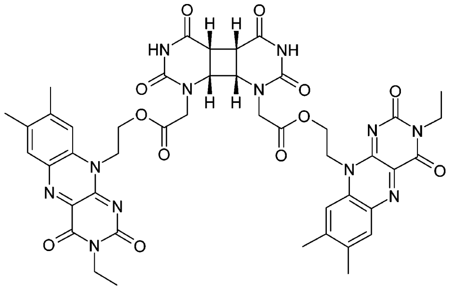


[a] Key: (1) irradiation, (2) electron transfer, (3) cycloreversion, (4) back electron transfer.

The reaction was carried out in acetonitrile or methanol and complete after 120 min of irradiation in acetonitrile or after 60 min in methanol. High hydrophilicity of the glycol-substituted flavin sensitizer **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 the higher polarity of water and thus by better stacking of the flavin unit and the thymine dimer facilitating the electron-transfer step.

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

Scheme 32. Example of a Photolyase Model with Covalently Attached Flavin Units[64f]

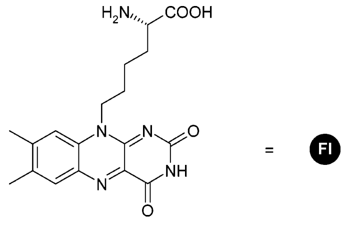


73

The efficiency of the cycloreversion was, apart from a covalent linkage, also enhanced by incorporation of flavin into an oligopeptide strain.[67] The synthesis made use of an artificial flavin-containing amino acid **74** (Scheme 33), leading to flavin-containing oligopeptides **75** and **76.**

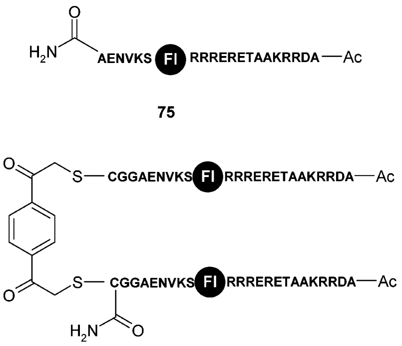
To mimic a helix−loop−helix protein and enhance binding to DNA, two flavin-containing peptides were linked by a bis(bromoacetyl)benzene template to yield **76** (Scheme 34).

Scheme 33. Artificial Flavin-Containing Amino Acid and Its Schematic Representation



74

Scheme 34. Flavin-Containing Oligopeptides

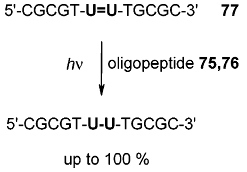


75

76

In solution, the oligopeptides **75** and **76** bound to a lesion-containing synthetic oligonucleotide **77**, presumably by 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 flavin chromophore then cleanly repaired the DNA damage (Scheme 35).

Scheme 35. Photorepair of DNA Damage by a Flavin-Containing Oligopeptide



A thymine dimer could be efficiently cleaved by a carbazole nucleoside incorporated into a complementary DNA strand.[68] Upon irradiation, cycloreversion of the thymine dimer occurred, 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 recognized by a compound containing two 2,6-bis(acylamino)pyridine binding sites and an anthraquinone chromophore.[69] The example is not discussed in detail because the catalytic properties of the template are still under investigation.

It was also possible to prevent formation of thymine dimer by binding the two thymines to a dinuclear complex so far apart from each other that it 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

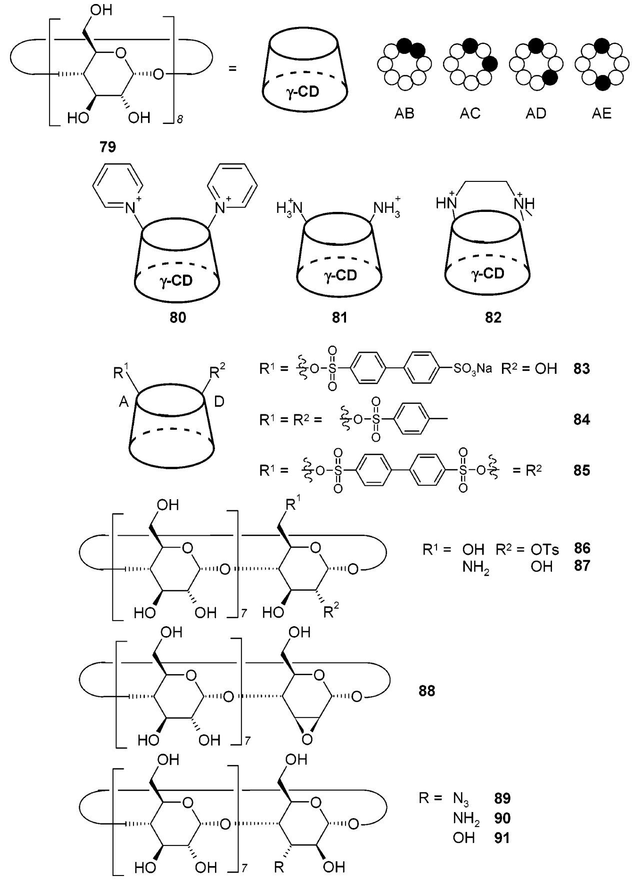
A variety of photochemical transformations is influenced and enhanced by the presence of a molecular flask, i.e., a large template molecule which includes the guest or guests, thus preorganizing them advantageously for a desired photochemical reaction. These premises are similar to those outlined in 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 that 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 dimerizations of aromatic and olefinic systems to selective photochemical cleavage or transport of a host-bound sensitizer toward a light beam. The molecular flasks used are known from other supramolecular applications. Cyclodextrins are favorite template scaffolds because of their good availability, various sizes, and inherent chirality, a property which was used for enantioselective photochemical reactions.[71−74] Other examples include self-assembled cage and bowl, cucurbiturils, and a self-assembled cavitand.

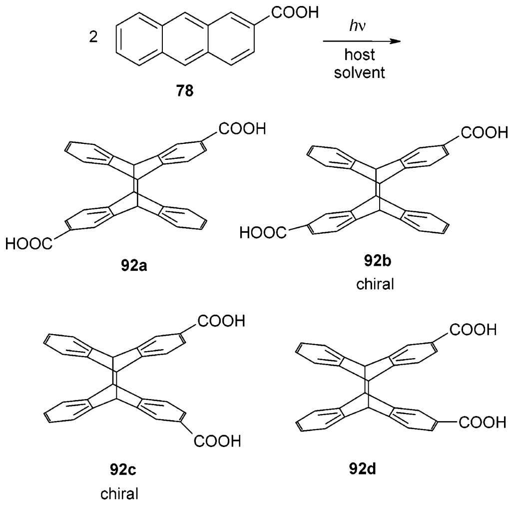
We describe in this section first photodimerization and photocycloaddition reactions within molecular flasks and continue with selective photochemical cleavage reactions and systems with transport function.

The best studied photochemical reaction in a molecular flask is probably dimerization of anthracene carboxylate **78**.[75−83] γ-Cyclodextrin (**79**) and modified (**80**−**91**) cyclodextrins were used to manipulate the yield and stereochemical outcome of the dimerization reaction (Scheme 36). Different experimental conditions disallow for direct comparison of the individual results, but effects of the host geometry on the selectivity of the dimerization reaction are observed. 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] Overall, the results from photodimerization of anthracene carboxylic acid in the presence of γ-cyclodextrin can be summarized 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 photodimerization. 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 carboxylates 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 formation of isomers **92c** (up to 42% yield, 41%

Scheme 36. γ-Cyclodextrins Used as Hosts for the Photodimerization of Anthracene Carboxylate 78



Scheme 37. Possible Isomers of Anthracene Carboxylate Photodimerization[a]



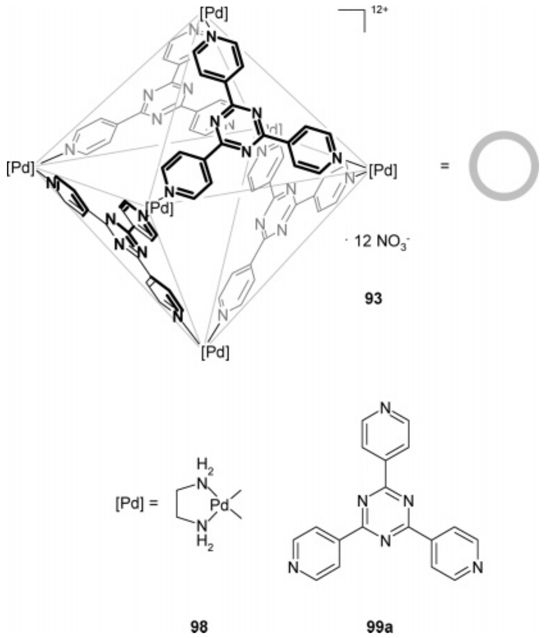
[a] Yields and ee values depend on host and conditions employed and are discussed in the text.

ee) and **92d** (up to 41% yield).[80] γ-Cyclodextrins with flexible hydrophobic caps **83** and **84** did not significantly influence the product distribution or enantioselectivity of the dimerization when compared to γ-cyclodextrin **79**.[81] However, γ-cyclodextrin **82** with a rigid hydrophobic cap enabled formation of product **92b** with up to 58% ee, although the yield was lower than with the γ-cyclodextrin **79**. A series of secondary face[84] modified γ-cyclodextrins **86**−**91** did not significantly 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 studied photodimerization 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-assembled cage-like molecule **93** (Scheme 38) was used for the highly selective photochemical dimerization of acenaphthylenes **94** and **95**,[85,86] naphthoquinone (**96**),[86] and anthracene-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**.

Scheme 38. Self-Assembled Molecular Cage

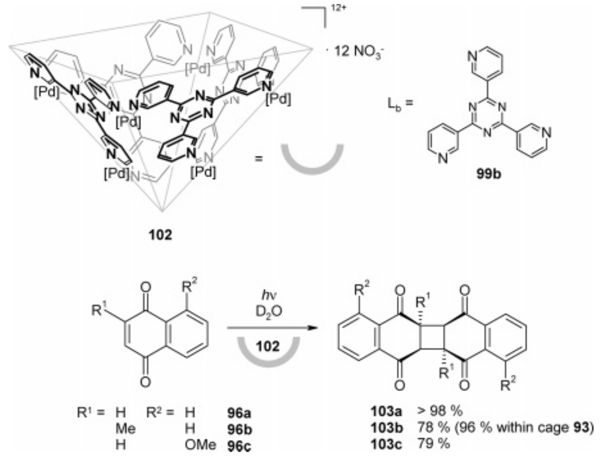


Irradiation of two acenaphthylene molecules **94** and **95** accommodated inside the cage **93** led to selective formation of the syn dimer **100** and **101** in more than 98% yield and without any other regio- or stereoisomers (Scheme 39).[85,86]

Scheme 39. Photodimerization of Acenaphthylenes in the Molecular Cage 93

Similarly, photodimerization 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 formation of the syn dimer **103a** (Scheme 40).[86] The regioselectivity of the photodimerization 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**. Dimerization of 5-methoxynaph-

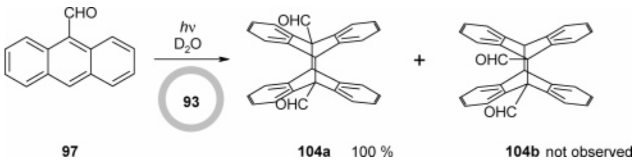
Scheme 40. Photodimerization of Naphthoquinones in a Molecular Bowl 102



thoquinone **96c** led to formation of isomer **103c** in 79% yield in the presence of molecular bowl **102**. Irradiation of **96b** without the cages (50 mM, 3 h, benzene) did not afford any dimerization product, while that of **96c** gave the anti dimer in 21% yield.

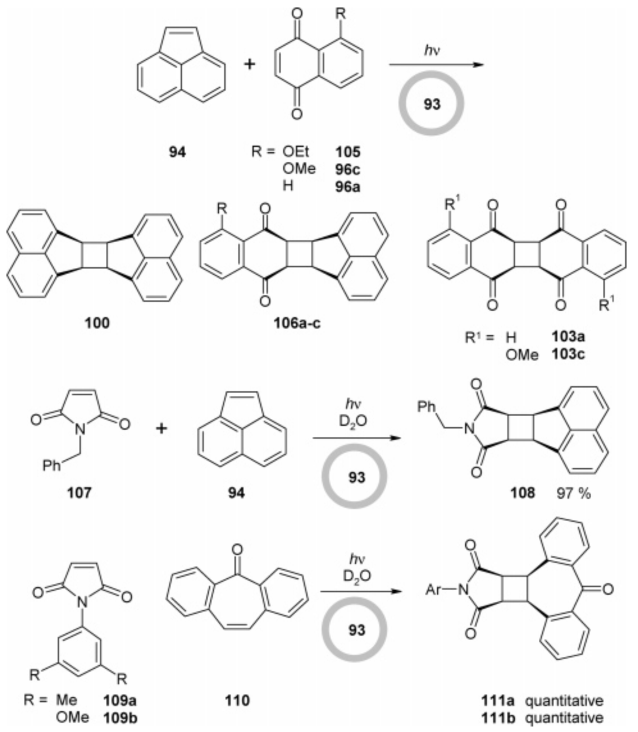
Irradiation of the complex of anthracene-9-carbaldehyde (**97**) and cage **93** in a ratio 2:1 led to selective formation of the photodimerization product **104a** (Scheme 41).[85] The cage **93** accommodated the two guests in a geometry leading to exclusive formation of the isomer shown; formation of the other possible isomer **104b** was not observed. Other 9-substituted anthracenes were photoinactive inside the cage.

Scheme 41. Photodimerization of Anthracene-9-carbaldehyde in Molecular 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 of the resulting photoproduct was governed by the bulkiness of the naphthoquinone guest: when 5-methoxynaphthquinone **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%. A 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.

Scheme 42. Cross-Photocycloaddition of Substrates in the Molecular Cage 93[a]

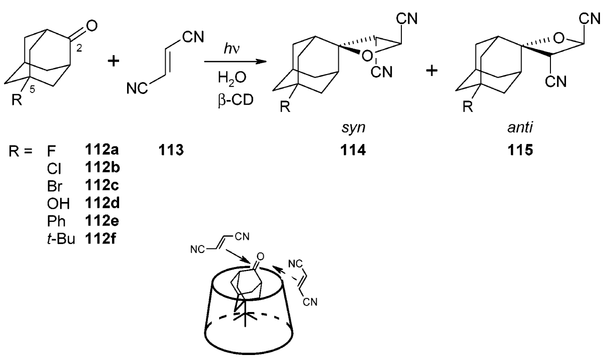


[a] See text for the yields of acenaphthylene (**94**)−naphthoquinone (**96a,c**, **105**) cycloadditions.

The cage **93** and related molecular capsules were successfully used for stabilization 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 reaction of interest was thermal, and these examples 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 yield 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 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 of up to 86:14.

Scheme 43. Paternó−Büchi Reaction of Adamantan-2-ones with Fumaronitrile in the Presence of *β*-Cyclodextrin (*β*-CD) Favoring Formation of the Syn Isomer 114

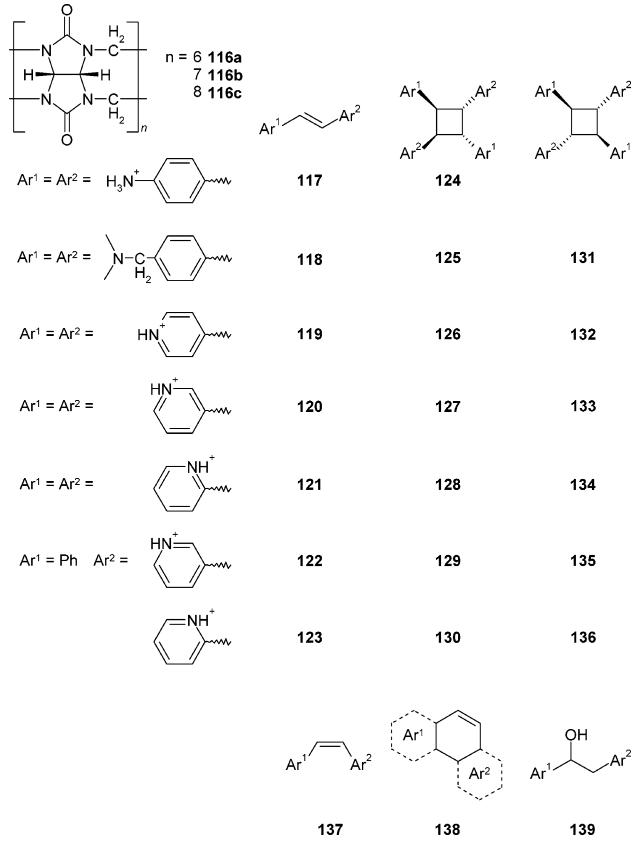


In the absence of β-cyclodextrin, typical selectivities in aqueous solution favor the anti isomer **115** (e.g., R = Cl, syn:anti, 43:57; R = *t*-Bu, syn:anti, 38:62). The presence of α- or γ-cyclodextrin does not change this preference significantly.[92]

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 equiv of the template, −40 °C). In pure methanol, a conversion below 1% was observed. In 25% aqueous methanol, the isolated yields were 15−18% with ee values of up to 11%.

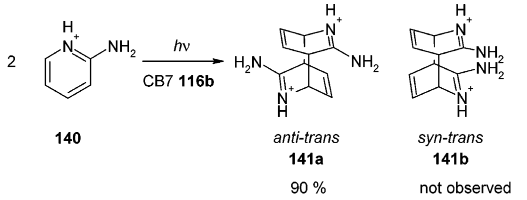
Photocycloaddition of double bonds in stilbenes[94−96] and its nitrogen-containing analogues,[97] 2-aminopyridine[98] and cinnamates,[99,100] was studied in the presence of cyclodextrins or cucurbiturils **116** (Scheme 44). When cucurbituril **116** of the correct size was used, the guest molecules coordinated to the portal oxygen atoms in a defined geometry, leading to high selectivity for some of the products. In the case of diaminostilbenes **117**, photodimerization in the cavity of cucurbit[8]uril **116c** occurred 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 isomerization to the corresponding *Z*-isomer **137**. In case of the dimethylaminomethyl-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 photodimerization reaction was prohibited. A 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 cyclization 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 dimerization selectivity.

Scheme 44. Photodimerization of Stilbene and Its Nitrogen-Containing Analogues in the Cavity of Cucurbit[8]uril 116c or Cyclodextrins



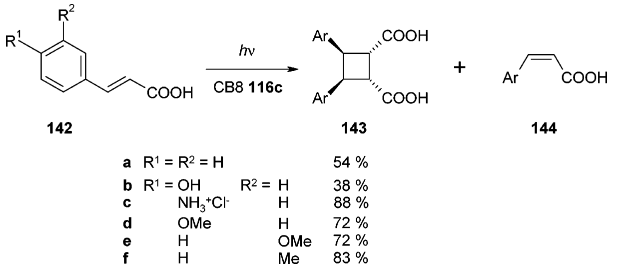
The [4+4] photocycloaddition of 2-aminopyridine hydrochloride **140** inside the cavity of cucurbit[7]uril **116b** gives an increased selectivity for the anti-trans dimer **141a** (yield up to 90% without any side products).[98] In the absence of the template, both anti-trans **141a** and syn-trans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

Scheme 45. Photodimerization of 2-Aminopyridine Hydrochloride in the Cavity of Cucurbit[7]uril 116b



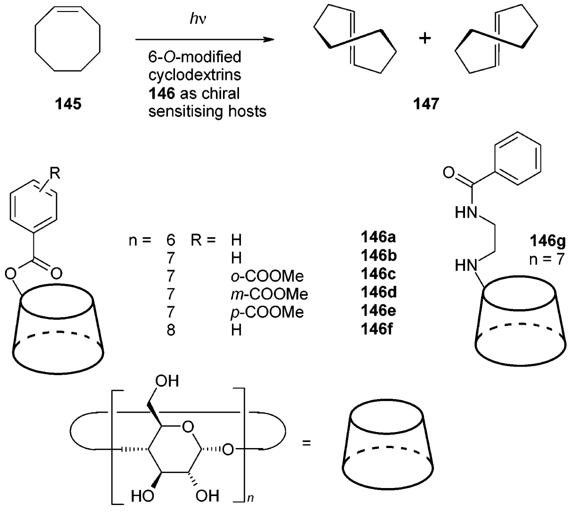
Irradiation of *trans*-cinnamic acids **142** included in the cavity of cucurbit[8]uril **116c** led to selective formation of the cyclic dimer **143** together with the corresponding cis isomer **144** (Scheme 46).[99] Best results were observed for 4-amino-*trans*-cinnamic acid hydrochloride **142c**,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

Scheme 46. Photodimerization of Cinnamic Acid in the Cavity of Cucurbit[8]uril 116c



Enantiodifferentiating photoisomerization 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 an *E/Z* ratio of 0.29 and an ee of 24% after irradiation at −40 °C in 50% aqueous methanol. With the other cyclodextrin derivatives **146a,c**−**g**, higher *E/Z* ratios were observed but the ee values remained low. Photoisomerization of *Z*-cyclooctene **145** in the presence of a permethylated 6-*O*-benzoyl-β-cyclodextrin was recently described.[105] This host is more 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

Scheme 47. Enantiodifferentiating Photoisomerization of *Z*-Cyclooctene[a]



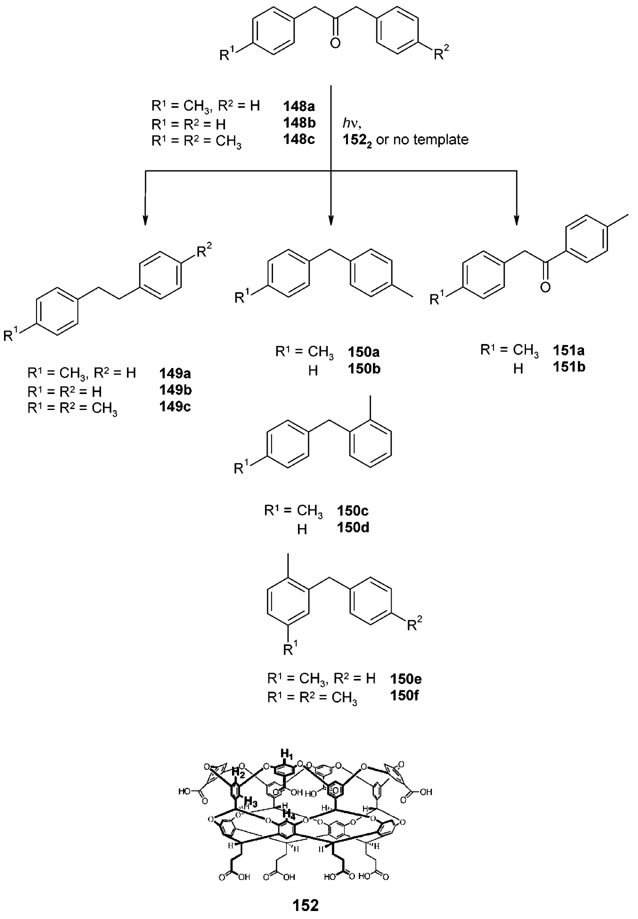
[a] *E*/*Z* Ratios and ee values depend on the chiral host **146** and conditions (see text).

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 (*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 favored formation of the decarbonylated product **149c** in 96% yield along with minute amounts of side products.

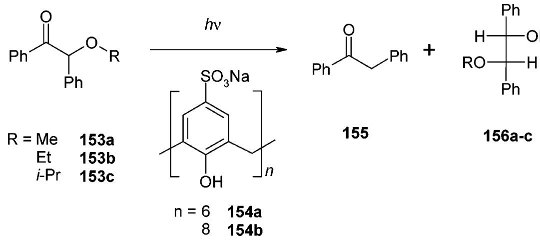
Benzoin alkyl ethers **153** preferentially undergo Norrish Type II cleavage when encapsulated in the cavity of *p*-sulfonatocalixarenes **154** (Scheme 49).[107] The substrate was locked by the cavity in a conformation which favored the γ-hydrogen atom abstraction (yielding deoxybenzoin as the major product) rather than 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 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**.

Scheme 48. Photochemical Cleavages of Substituted Acetones[a]



[a] See text for yields of the individual products. Structure of compound **152** reprinted with permission from ref 106. Copyright 2004 American Chemical Society.

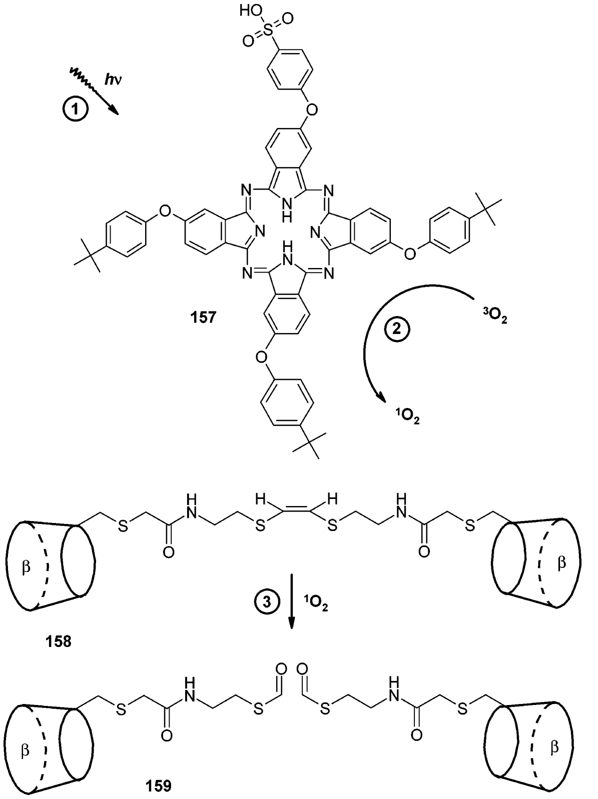
Scheme 49. Selective Norrish Type II Cleavage in the Cavity of a Calixarene[a]



[a] See text for yields of the individual products.

Compound **158**[108] is able to transport sensitizer **157** and release the phthalocyanine upon irradiation.[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 sensitizer **157** bind into the cyclodextrin cavities, making complex **157·58** water-soluble. Upon irradiation, sensitizer **157** effected formation of singlet oxygen[110−111] and thus cleavage of the C=C double bond yielding **159**. Once the two cyclodextrin units were disconnected, the binding affinity for the sensitizer **157** decreased. The co-operative effect of the two cyclodextrins was lost, and the loose linker chains compete for binding into the cyclodextrin cavity. The complex therefore dissociated, leading to precipitation of the now insoluble phthalocyanine sensitizer. Eventually, the sensitizer concentrated in a directed light beam, as shown by an experiment with a reaction irradiated through a small hole in a shield surrounding the

Scheme 50. Cyclodextrin-Based Photosensitiser Carrier 158[a]



157

158

159

[a] Yield of the cleavage reaction was not given. Key: (1) irradiation, (2) sensitization of dioxygen, (3) cleavage of C=C double bond.

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, templating, 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.

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