Supramolecular Control of the Template-Induced Selective Photodimerization of 4-Methyl-7-*O*-hexylcoumarin

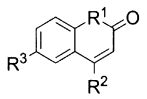
William G. Skene,[a, b] Emilie Couzigné,[a, c] and Jean-Marie Lehn*[a]

Abstract: A symmetric ditopic molecular receptor (**3**), containing two identical hydrogen-bonding recognition subunits, was designed and synthesized. These subunits are capable of binding substrates with complementary donor and acceptor sites to form a supramolecular complex through hydrogen bonding. Receptor **3** was designed to accept two guest molecules, which are held in close proximity within the supramolecular species. The substrate molecule, 4-methyl-7-*O*-hexylcoumarin (**1c**), forms a 2:1 complex with a binding constant of $150\,M^{-1}$ for the second substrate, passing first through a 1:1 complex with an affinity constant of $510\,M^{-1}$. The orientation of two molecules of **1c** when bound to the template leads to the selective formation of the *trans-syn* [2+2] photoproduct **2cB** upon irradiation. Other photoproducts typically produced in the absence of the template are suppressed.

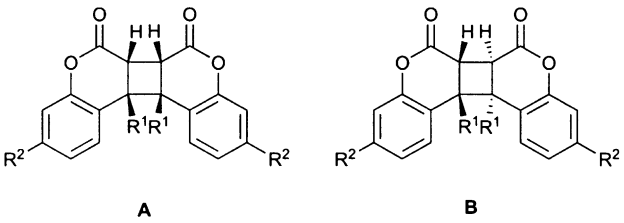
Keywords: coumarins · photochemistry · selective photodimerization · supramolecular chemistry · template effects

Introduction

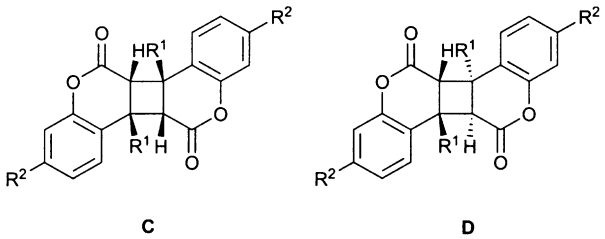
Numerous investigations have been carried out on the subject of [2+2] photodimerizations,[1–3] especially of thymine and uracil, since their products exhibit high biological toxicity.[4–7] Other systems giving rise to [2+2] photoproducts, among them coumarin and its derivatives (**1a–c**), have been actively studied to fully understand the mechanistic pathways of these photoreversible reactions and to ultimately control product distribution.[8–10] Thus, similar to other photodimerization reactions, photoirradiation of **1** can potentially lead to four cycloaddition products; *cis-syn, trans-syn, cis-anti* and *trans-anti* (**2A–D**, respectively). Under typical experimental conditions, however, the two *syn* (**2A** and **2B**) photoproducts are formed predominately, while only trace amounts of the *anti* dimers **2C** and **2D** are observed.[7] The



1a $R^1 = O$; $R^2 = R^3 = H$
1b $R^1 = O$; $R^2 = H$; $R^3 = O\text{-Alkyl}$
1c $R^1 = O$; $R^2 = CH_3$; $R^3 = O\text{-}C_6H_{13}$
1d $R^1 = NH$; $R^2 = R^3 = H$
1e $R^1 = NH$; $R^2 = H$; $R^3 = O\text{-alkyl}$



A **B**



C **D**

2a $R^1 = R^2 = H$
2b $R^1 = H$; $R^2 = O\text{-alkyl}$
2c $R^1 = CH_3$; $R^2 = O\text{-}C_6H_{13}$

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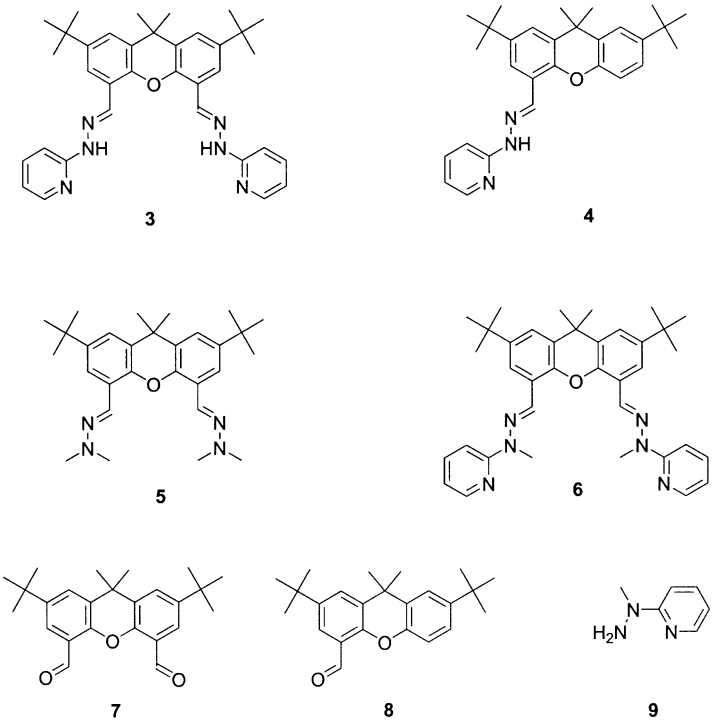
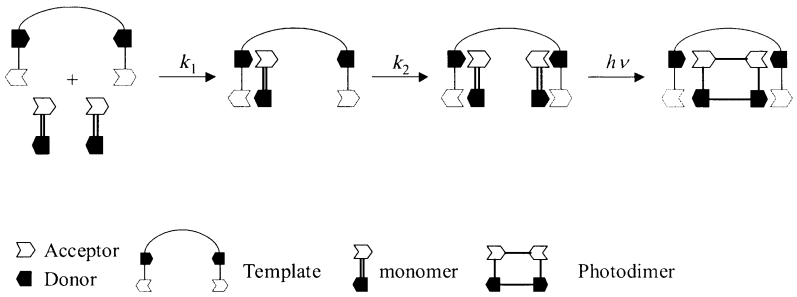
ratio of coumarin photoproducts can significantly be altered through control of the reaction conditions such as solvent choice,[9,11,12] Lewis acid addition,[13,14] micellar environment,[15,16] solid-state irradiation,[13,14] modification of the coumarin precursor,[17,18] use of inclusion complexes[15] and tethered precursors,[17,19–21] or recently with pseudo-rotaxanes.[22] Much effort has been focused on crystal engineering and packing within the solid state to influence the product distribution.[23–27] These various modifications are understood to change the photochemical reaction manifolds of the intermediates by perturbing the transition moment ultimately influencing the product distribution.[8,10,28] In view of obtaining control over photoproduct selectivity, we investigated whether a molecular receptor, capable of forming a specifically oriented supramolecular complex in the ground state with two dimer precursors, could promote such product amplification through the geometry and steric confinement of the supramolecular species, similar to known thermal cycloadditions.[29] The synthesis of such a molecular template and our photochemical findings are described herein.

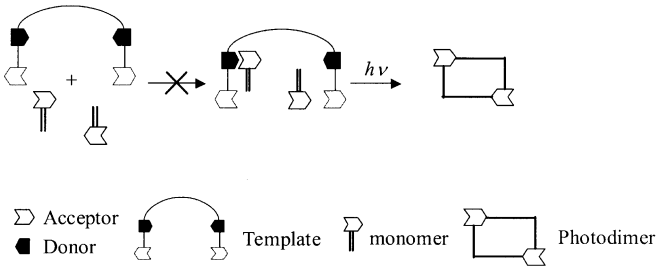


Results and Discussion

The binding of two coumarin units to a ditopic molecular template such as **3** would lead to a symmetric supramolecular structure, whereby the orientation of the two monomers would be expected to favour the exclusive formation of *syn* dimers upon irradiation, as represented in Scheme 1. Photoirradiation of free **1a**, like that of other [2+2] precursors, leads exclusively to *syn* dimers, so that binding of two units of **1a** to the receptor **3** would not drastically alter the ratio among the four potential isomers. For comparison we also prepared three template analogues of **3**, namely compounds **4**–**6**, synthesized from a combination of compounds **7**–**9**; for details see the Experimental Section. We therefore sought out a photodimerizable compound that contained sites capable of forming a supramolecular complex through hydrogen bonding with a template, but whose major photoproducts under normal irradiation conditions would be *anti* dimers. The formation of a 2:1 complex between such a precursor and a template should preferentially yield *syn* dimers, demonstrating template-assisted selective photodimerization. The anticipated *anti* dimers would be suppressed, since, in addition to steric hindrance within the template cleft, the corresponding orientation of the precursors would not be achieved (see Scheme 2). Coumarin derivatives **1b** and **1c** are suitable candidates for such selective photodimerization as they satisfy the necessary criteria. In particular, **1c** predominately forms *anti* dimers upon irradiation[15–17,19,20] and was selected for *syn* product amplification. Substitution at the 4- and 7-coumarin positions creates a weak donation that changes the transition moment, in turn affecting the product distribution.[8] The transition moments can further be influenced by solvent polarity[11] and the use of cyclodextrin or micelles.[12,15,16] With respect to previous reports,[30–34] we set forth the design and subsequent synthesis of a template, which



Scheme 1. Schematic representation of the reaction pathway responsible for selective *syn* photodimer formation within a supramolecular 2:1 species.



Scheme 2. Orientation of the partners within the 2:1 supramolecular complex required for *anti* photodimer formation.

would promote the formation of otherwise minor products upon photodimerization, through template-assisted selective product amplification.

Binding of substrate 1c to receptor 3: The synthesis of template **3** was easily achieved in two steps (as compared to the previous strategy involving four steps[35,36]) from the dialdehyde **7** and 2-hydrazinopyridine in good yield. Previous work has shown the capability of this receptor to efficiently bind substrate molecules through hydrogen bonds between the pyridine nitrogen and the adjacent amine with complementary donor and acceptor sites, making it a suitable template for the present study.[35–37]

Carbostyril **1d** was originally investigated as a potential dimerization candidate, as it possesses two sites capable of sustaining such hydrogen bonding with the receptor. The binding isotherm measured by NMR titration allows the determination of the overall association constants for 1:1 and 2:1 complexes with **3** in $CDCl_3$; these were found to be about $860\,M^{-1}$ and $60\,M^{-1}$, respectively. Unfortunately, the photodimerization of this lactam leads exclusively to the *syn* dimer, even in the absence of the template, regardless of the experimental conditions, consistent with previous results.[2,38] Also, the photoproducts precipitate upon formation and can only be solubilized in trifluoroacetic acid, making characterization and subsequent quantification of the products very difficult.

Coumarin **1c** also satisfied our selection criterion and proved a better candidate for selective photoproduct amplification studies. The association constants measured ($510\,M^{-1}$ and $154\,M^{-1}$ for the 1:1 and 2:1 complexes, respectively) were comparable to those found for **1d**, indicating that **1c** binds equally well to the template. These results imply the initial formation of a moderately stable 1:1 complex between the template and **1c**, which thereafter leads to a 2:1 complex upon further addition of coumarin, according to Scheme 1. This stoichiometry was confirmed by Job's method through the use NMR spectrometry (Figure 1), whereby the observed maximum at constant concentration corresponds to a 2:1 complex.[39] The titration method employed followed the changes in chemical shift of the N–H proton of **3** due to hydrogen bonding to the C=O group of **1d** or **1c**. The limitation of this method is that no information concerning binding through the pyridine nitrogen can be obtained. Therefore, it is not surprising that the measured isotherms for **1d** and **1c** are similar, since the centre involved in binding is similar for the two monomers. The slight variances observed reflect the differences in weak binding of the guest's heterocyclic site with the receptor, in line with a recent report concerning weak synthon binding.[40] Even though the measured values are for $CDCl_3$, it was found that the formation of the supramolecular complex between a guest and the template are not dramatically affected by the use of acetone as solvent, the isotherms observed for the two solvents being similar.[35]

The mode of binding of **1c** to receptor **3** is not as straightforward as with previous examples for hydrogen bonding or with **1d**.[31,32] The optimal bonding situation would be observed with carbostyril **1d**, which possesses the conventional hydrogen-bonding pattern involving two hydrogen bonds between its N–H and C=O groups and the complementary pyridine nitrogen and N–H sites of the template **3**. With **1c**, in which the hydrogen bonding donor –NH is not present, the mode of interaction most likely involves a hydrogen-bonding pattern composed of binding between the N–H centre of the template and the lactone oxygen site, together with two weak C–H···X interactions between the imino =C–H and the pyridine nitrogen atom of the template with the carbonyl oxygen atom and the oppositely located aromatic C–H of **1c**, respectively, as schematically represented in compound **10**. Such interactions have previously been observed and are well identified by crystal structures.[40,41] NMR data can provide information about an interaction between the =CH proton and the guest **1c**. Monitoring the change in chemical shift of the =CH proton signal of the template on titration with the guest should result in a deshielding shift, consistent with hydrogen bonding interaction. Titration of **3** with **1c** gives rise to such a change in chemical shift of approximately $\Delta\delta = 0.4$ ppm, indicative of the binding represented in **10**. Moreover, the binding isotherm obtained by this titration experiment agrees with the binding constants obtained from the titration method used to observe the chemical shift of the N–H proton, thus further confirming the formation of a 2:1 supramolecular complex.

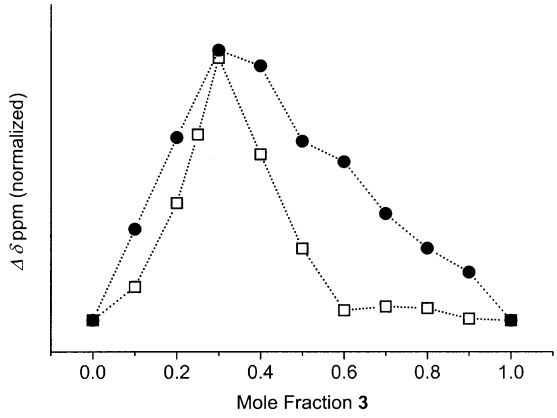
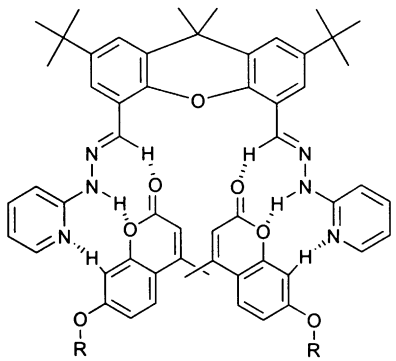


Figure 1. Job plot at constant concentration for the binding of the dimer precursors **1d** (□, 10 mM) and **1c** (●, 100 mM) to the receptor **3** with variation of 9.6–10.5 ppm.



10

Photodimerization of coumarin 1c: The use of authentic samples was required to compare HPLC retention times of the template-assisted photoproducts of **1c** with those obtained in its absence. Therefore, irradiation of **1c** and subsequent isolation of its photodimers was required. Only two photoproducts were observed at conversions below 30%; they were easily separated by column chromatography and characterized by 2D NMR spectroscopy and were found to be 60% *syn* and 40% *anti* dimers. No other products were detected with the analytical methods used. Determination of the dimer configuration was difficult based on simple ^{1}H NMR spectroscopy without authentic samples. The difference between the two *cis* and *trans* isomers is relatively small and the *trans* cyclobutyl protons give a NMR signal 0.1 ppm upfield from their *cis* counterparts, due to the shielding effects of the carbonyl and phenyl groups.[15] Through the use of a chiral shift reagent and 2D proton NMR spectroscopy, complete characterization of the isolated photoproducts was possible and led to the assignment of the *trans* form to both the s*yn* and *anti* dimers (**2cB** and **2cD**). The configuration of the observed photodimers is consistent with previous reports for sensitized dimerization.[15,16,19,20] No appreciable change was observed when performing either direct irradiation in chloroform or sensitized irradiation with acetone. Since the experimental conditions employed are relatively dilute, direct excitation of the precursor undergoes intersystem crossing forming the triplet state before quenching occurs. This manifold leads exclusively to the *trans* isomers; conversely the *cis* isomers arise from singlet excimer formation at higher concentrations, whereby two monomers can be in close proximity required for promoting such an interaction.[21]

Photodimerization of coumarin 1c in presence of receptor 3: Irradiation of **1c** in the presence of 0.5 equivalents of the template **3** led exclusively to the head-to-head *trans-syn* dimer **2cB**. The production of this dimer can be rationalized through the pathway described in Scheme 1 further supported by the 2:1 binding constant measured. The complete suppression of the head-to-tail *anti* dimers can result only if the coumarin precursors are prevented from adopting the corresponding arrangement (Scheme 2), further supporting the orientation of the two monomer substrates **1c** as represented in **10**. The preferential formation of the *trans* isomer stems from steric effects and has previously been observed for hydrogen-bonded complexes in photodimerization.[1] Correct molecular overlap for dimerization to proceed occurs with the two unsaturated groups in a separated yet stacked arrangement, but not within the same plane. Such an arrangement can be achieved through a rotation around the C–CH= bonds in the side chains of the template and avoids steric interaction between the 4-methyl groups within the 2:1 complex of **1c** with **3**. The results obtained represent a successful demonstration of light-induced, selective product amplification arising from a template-induced, modified supramolecular complex.

In the presence of the template **3**, the observed quantum yield ($\Phi = 0.03$) of photodimerization of **1c** was roughly half that observed in its absence.[42] A higher value is anticipated due to a higher local concentration of the precursor as a result of two molecules of **1c** being held in close proximity within the template. A higher probability of encounter is induced by the 2:1 complex formation, leading to an increase in quantum yield relative to the native dimerization. Since the measured triplet value of **3** is about 22 kJ mol^{-1} higher than that of **1c** in ethanol, and even greater in apolar solvents, quenching of the coumarin triplet state by the template cannot be responsible for the decreased quantum yield. Even though endergonic triplet quenching is possible, it is not present to a high degree in this case, owing to low concentrations of the reagents. Therefore, the lower quantum yield may arise predominately from a screening effect of the template, as there is a large spectral overlap between the two partners. Moreover, the screening effect benefits photoproduct stability by decreasing photodecomposition of the dimers to regenerate the reagents, which is known to occur under UV irradiation. The relatively low concentration used further ensures that dimerization proceeds from within the supramolecular complex and not between adjacent complexes or via aggregates.

Control irradiation experiments: To confirm the role of hydrogen bonding in the irradiation of coumarin **1c** leading to controlled product formation, the phenyl hydrazone analogue of **3** would be a suitable reference. It would lack the pyridine nitrogen and the eventual formation of the *anti* isomer by irradiation in the presence of **1c** would confirm, a contrario, the bonding scheme depicted in **10**. However, attempts to prepare this compound were unsuccessful due to its thermal and photochemical instability. Starting reagents involving phenyl hydrazine or its salt systematically resulted in the formation of benzene and nitrogen as decomposition products in addition to unreacted dialdehyde **7**. Alternatively, protonation should disrupt the hydrogen bonding, consequently leading to an anticipated different photoproduct distribution, confirming the role of the templated supramolecular complex. Indeed, the addition of such trace amounts of acid to **3** gave rise to an equal amount of the two photodimers upon irradiation (Figure 2), indicating the destruction of the template effect. As a control, the photoreaction of **1c** alone in the presence of acid gave nearly the same product distribution.

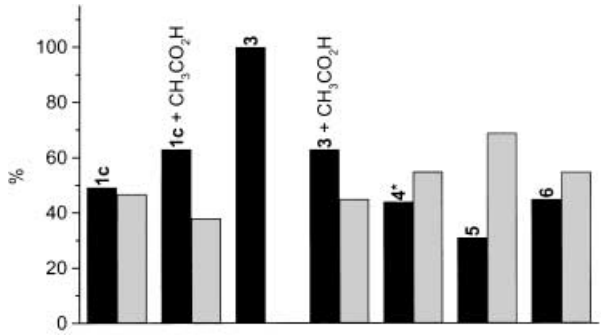


Figure 2. Photoproduct distribution resulting from photodimerization of **1c** under various conditions in acetone: dark grey *syn*, and light grey *anti* isomers. *Only trace amounts detected.

To further ascertain the importance of supramolecular and steric effects for controlled photodimerization, the analogues **4** (synthesized from **8** and **9**), **5** and **6** of receptor **3** were synthesized.[43] The single-arm template analogue **4** contains a donor and acceptor site capable of binding only one coumarin monomer, in contrast to **3**. Under stoichiometric conditions of one monomer equivalent, no controlled photodimer production should be observed with this asymmetric template. Indeed, the irradiation of **4** in acetone led only to trace amounts of photoproducts with no control over the product distribution.

Two other template analogues, **5** and **6**, were investigated, as they do not possess the –NH donor sites capable of sustaining the pre-irradiation arrangement necessary for *syn* photoproduct formation. Furthermore, they both have a cleft similar to **3** in which two monomers could potentially fit. The photoproduct distribution obtained upon irradiation of the two donor-free templates **5** and **6** in the presence of **1c** was roughly identical to those observed in the absence of the templates within experimental error. These results, combined with the photoirradiation in presence of **4**, confirm that a templating effect of **3** with **1c** through supramolecular control is responsible for the selective photoproduct formation. The orientation of two coumarin monomers within the template controlled by the complex is such that only the *syn* products can be formed. Furthermore, the bulk of the template ensures that photodimerization occurs solely between two molecules of **1c** located within the cleft.

Conclusion

Irradiation of the 2:1 supramolecular complex **10** formed by the symmetric ditopic receptor **3** with 4-methyl-7-*O*-hexylcoumarin **5** displays formation and selective amplification of the otherwise minor head-to-head *syn* [2+2] **2cB** photoproduct. This outcome may be rationalized in terms of the pre-irradiation orientation of the two coumarin substrate molecules within the supramolecular species. Relative disposition and steric effects within the complex as well as triplet-based dimerization may be considered responsible for the preferential formation of the observed *trans* isomer rather than the *cis* form, while light absorption by the receptor may account for a reduction in the [2+2] dimer quantum yield. The results obtained illustrate the ability to control the regio- and/or stereoselectivity of chemical reactions between molecular species, by proper design of supramolecular entities and represent a process of supramolecular structure selective catalysis.

Experimental Section

All reagents were used as received from Aldrich without further purification unless otherwise stated. HPLC analyses were performed on an HP 1100 series HPLC equipped with a diode array detector and an Eclipse™ XDB-C18 reverse phase column. A mobile phase of 85% methanol/15% water was used and the retention times monitored at 210 nm; the absorption spectra and retention times were compared to authentic samples (vide infra). The binding constants were measured by an NMR titration method in $CDCl_3$ and the isotherm data subsequently fitted with the Chemequi program.[44] NOE and COSY 2D NMR spectra were recorded on a Bruker 300 MHz spectrometer, whereby the absolute configuration of the [2+2] photodimers was determined by using an optically active chemical shift reagent, europium(III)-*tris*-(3-trifluoromethylhydroxymethylene-(+)-camphorate).

7-Hexyloxy-4-methylchromen-2-one (1c): 7-Hydroxy-4-methylcoumarin (2.01 g, 11.4 mmol) was added to dimethylformamide (125 mL), followed by sodium carbonate (1.45 g, 13.9 mmol). The slurry was stirred at room temperature for 20 minutes, after which 1-bromohexane (1.92 mL, 13.5 mmol) was then added and the mixture was subsequently refluxed for 16 h after the addition of a catalytic amount of potassium iodide. The solvent was removed under vacuo, whereby the paste was taken up in dichloromethane and washed with water. The organic phase was separated and the solvent removed followed by flash chromatography (SiO_2) with 10% ethyl acetate/90% dichloromethane. Compound **1c** was isolated as a colourless oil (2.85 g, 96%). ^{1}H NMR (200 MHz, [D]chloroform): δ = 7.16 (d, J = 8.9 Hz, 1H; Aryl), 6.56 (dd, J = 2.4 Hz, 1H; Aryl), 6.42 (d, J = 2.4 Hz, 1H; Aryl), 5.79 (s, 1H; Aryl), 3.72 (t, 2H; CH_2), 2.11 (s, 2H; CH_2), 1.51 (m, 2H; CH_2), 1.12 (m, 4H; CH_2), 0.69 ppm (t, 3H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 161.9, 160.7, 155.0, 152.4, 125.4, 113.1, 112.2, 111.4, 101.0, 68.4, 31.4, 28.9, 25.5, 22.5, 18.3, 13.9 ppm; MS (70 eV): m/z (%): 260.3 (30) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{20}O_3$ (260.33): C 73.82, H 7.74; found: C 73.30, H 8.32.

3,10-Bishexyloxy-12b,12c-dimethyl-6a,6b,12b,12c-tetrahydro-5,8-dioxadibenzo[a,i]biphenylene-6,7-dione (2cB): Coumarin **1c** (503 mg, 1.93 mmol) was dissolved in acetone (25 mL) in a Pyrex test tube, which was then sealed and the oxygen removed through a stream of argon for 30 minutes. The solution was irradiated for 12 h with a 400 W lamp then the solvent removed. The crude oil was purified by chromatography (SiO_2) with 10% ethyl acetate/90% dichloromethane to yield **2cB** as a white solid. ^{1}H NMR (200 MHz, [D]chloroform): δ = 7.07 (d, J = 8.7 Hz, 2H; Aryl), 6.61 (dd, J = 6.0 Hz, 2H; Aryl), 6.03 (d, J = 3.0 Hz, 2H; Aryl), 3.77 (m, 4H; CH_2), 3.40 (s, 2H; CH), 1.67 (m, 10H; CH_2), 1.30 (m, 12H; CH_2), 0.89 ppm (t, 6H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 164.9, 159.8, 150.3, 127.4, 113.6, 112.4, 102.3, 68.3, 55.3, 41.1, 31.7, 31.5, 28.9, 25.6, 22.6, 14.0 ppm; MS-FAB: m/z (%): 521.3 (100) $[M+H]^+$; HRMS-FAB: m/z calcd for $C_{32}H_{41}O_6$: 521.2910; found: 521.2903.

3,9-Bishexyloxy-6b,12b-dimethyl-6a,6b,12a,12b-tetrahydro-5,11-dioxadibenzo[a,b]biphenylene-6,12-dione (2cD): Isolated as a white solid after column chromatography (SiO_2) with 10% ethyl acetate/90% dichloromethane. ^{1}H NMR (200 MHz, [D]chloroform): δ = 7.04 (d, J = 8.7 Hz, 2H; Aryl), 6.77 (dd, J = 6.0 Hz, 2H; Aryl), 6.61 (d, J = 3.0 Hz, 2H; Aryl), 3.95 (t, 4H; CH_2), 3.36 (s, 2H; CH), 1.79 (m, 4H; CH_2), 1.64 (m, 18H; CH_2), 0.89 ppm (t, 6H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 166.1, 159.9, 151.6, 128.0, 114.8, 112.4, 102.9, 68.5, 46.6, 45.0, 31.6, 29.1, 26.4, 25.7, 22.6, 14.0 ppm.

(2,7-Di-*tert*-butyl-9,9-dimethyl)-9H-xanthene-4,5-dicarbaldehyde (7): 4,5-Dibromo-2,7-di-*tert*-butyl-9,9-dimethyl-9H-xanthene (438 mg, 0.91 mmol) was added to anhydrous diethyl ether (50 mL) and the mixture was cooled to −78 °C under an argon atmosphere. A solution of *n*-butyllithium (7 mL, 11.2 mmol) was slowly added. The reaction was stirred at the low temperature for 60 minutes, after which dimethylformamide (2 mL, 25.8 mmol) was added and the temperature was raised to room temperature. The mixture was stirred for 60 minutes then 2 M HCl (5 mL) was added and stirring continued for a further 30 minutes. Diethyl ether was removed under vacuum then the residue was extracted with ethyl acetate. The solid was purified by chromatography (SiO_2) with 10% ethyl acetate/90% hexane to yield the product as a white solid (206 mg, 60%). M.p. 248–249 °C; ^{1}H NMR (200 MHz, [D]chloroform): δ = 10.68 (s, 2H; CH), 7.83 (d, J = 2.4 Hz, 2H; Aryl), 7.72 (d, J = 2.4 Hz, 2H; Aryl), 1.70 (s, 6H; CH_3), 1.37 ppm (s, 18H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 188.9, 149.6, 146.7, 130.6, 129.5, 124.1, 123.5, 62.2, 34.8, 32.5, 31.4, 29.7 ppm; MS-FAB: m/z (%): 379.3 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{30}O_3$ (378.50): C 79.33, H 7.99; found: C 79.59, H 8.14.

2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-bis-(pyridin-2-yl-hydrazonomethyl)-9H-xanthene (3): Compound **7** (0.30 g, 0.793 mmol) was dissolved in chloroform (10 mL) and 2-hydrazinopyridine (0.19 g, 1.74 mmol) was added as a solid. The solution was stirred overnight at room temperature. The mix-

ture was then evaporated and subjected to chromatography (SiO_2) with a gradient of 40% ethyl acetate/dichloromethane and increased to 60% ethyl acetate/dichloromethane. The product was obtained (0.41 g, 93%) as a yellowish powder, which decomposed above 184°C. ^{1}H NMR (200 MHz, [D]chloroform): δ = 9.33 (br s, 2H, NH), 8.36 (s, 2H; CH), 8.14 (d, J = 4.9 Hz, 2H; Aryl), 7.83 (d, J = 2.3 Hz, 2H; Aryl), 7.57 (td, J = 7.8 Hz, J = 1.8 Hz, 2H; Aryl), 7.44 (d, J = 2.2 Hz, 2H; Aryl), 7.42 (d, J = 8.4 Hz, 2H; Aryl), 6.74 (t, J = 7.8 Hz, 2H; Aryl), 1.68 (s, 6H; CH_3), 1.40 ppm (s, 18H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 157.6, 146.5, 146.1, 145.4, 138.4, 136.2, 130.1, 123.1, 122.5, 122.4, 114.4, 107.2, 32.4, 31.5, 22.6, 14.1 ppm; MS-FAB: *m/z* (%): 561.2 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{35}H_{40}N_6O$ (560.73): C 74.97, H 7.19, N 14.99; found: C 75.26, H 7.38, N 15.09.

2,7-Di-*tert*-butyl-9,9-dimethyl-9H-xanthene-4-carbaldehyde (8): Trifluoroacetic acid (TFA; 5 mL) followed by hexamethylenetetramine (95.5 mg, 0.68 mmol) was added all at once to 2,7-di-*tert*-butyl-9,9-dimethyl-9H-xanthene (212 mg, 0.66 mmol). The white heterogeneous solution was refluxed for 18 h eventually giving rise to a deep red homogenous solution. The TFA was removed by distillation from the resulting red solution. The red oil was taken up in ethyl acetate (5 mL), after which 2 M aqueous HCl (20 mL) was added and then the solution heated to 80°C for 12 h. The biphasic system was cooled then separated with ethyl acetate and then concentrated in vacuo. The yellow oil was purified by chromatography (SiO_2) with 70% ethyl acetate/30% hexane and the product was isolated as a white solid (44 mg, 13%). M.p. 155–160°C; ^{1}H NMR (200 MHz, [D]chloroform): δ = 10.71 (br s, 1H; NH), 7.78 (d, J = 2.6 Hz, 1H; Aryl), 7.70 (d, J = 2.1 Hz, 1H; Aryl), 7.45 (d, J = 2.6 Hz, 1H; Aryl), 7.29 (d, J = 2.6 Hz, 1H; Aryl), 7.07 (d, J = 8.7 Hz, 1H; Aryl), 1.68 (s, 6H; CH_3), 1.35 ppm (s, 18H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 189.7, 147.5, 129.7, 128.9, 124.8, 123.9, 122.8, 122.7, 115.9, 34.7, 34.5, 32.5, 31.6, 31.4 ppm; MS-FAB: *m/z* (%): 351.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{24}H_{30}O_2$ (350.2): C 82.24, H 8.63; found: C 82.05, H 9.18. Alternatively, compound **8** can be isolated from the reaction mixture of **7** (104 mg, 33%).

***N*-(2,7-Di-*tert*-butyl-9,9-dimethyl-9H-xanthen-4-ylmethylene)-*N'*-pyridin-2-yl-hydrazine (4)**: Compound **8** (20 mg, 0.06 mmol) was dissolved chloroform (10 mL) to which was added (15 mg, 0.14 mmol) 2-hydrazinopyridine; the mixture was then stirred at room temperature for 24 h. The solvent was removed and then subjected to chromatography (SiO_2) with a gradient of 5% ethyl acetate/95% hexane to 50% ethyl acetate/50% hexane. The product was isolated as a white solid (17 mg, 69%). M.p. 155–160°C; ^{1}H NMR (200 MHz, [D]chloroform): δ = 8.95 (s, 1H; NH), 8.41 (s, 1H; CH), 8.21 (d, J = 5.1 Hz, 1H; Aryl), 7.91 (d, J = 2.1 Hz, 1H; Aryl), 7.64 (t, 1H; Aryl), 7.42 (d, J = 7.7 Hz, 1H; Aryl), 7.28 (s, 1H; CH), 7.22 (d, J = 2.6 Hz, 2H; Aryl), 7.05 (d, J = 8.7 Hz, 1H; Aryl), 6.81 (t, 1H; Aryl), 1.66 (s, 6H; CH_3), 1.39 (s, 9H; CH_3), 1.35 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 147.7, 146.6, 145.9, 145.3, 138.1, 135.4, 130.2, 129.4, 124.5, 123.8, 122,6, 121.4, 120.5, 115.7, 107.6, 34.6, 32.3, 31.6 ppm; MS-FAB: *m/z* (%): 441.6 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{29}H_{35}N_3O$ (441.3): C 78.87, H 7.99, N 9.52; found: C 79.01, H 8.04, N 9.58.

***N'*-[2,7-Di-*tert*-butyl-5-(dimethylhydrazonomethyl)-9,9-dimethyl-8a,10a-dihydro-9H-xanthen-4-ylmethylene]-*N,N*-dimethylhydrazine (5)**: *N,N*-Dimethyl hydrazine (50 μL, 0.65 mL) was added to a solution of dialdehyde **7** (23 mg, 0.06 mmol) in ethanol (10 mL), solubilized by heating; the mixture was then refluxed for 8 h. The solvent was removed under reduced pressure and the white solid was further dried under vacuum to quantatively afford compound **5**. ^{1}H NMR (200 MHz, [D]chloroform): δ = 7.8 (d, J = 2.6 Hz, 4H; Aryl), 7.34 (d, J = 2.1 Hz, 2H; CH), 3.02 (s, 12H; CH_3), 1.36 (s, 6H; CH_3), 1.36 ppm (s, 18H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 145.8, 130.0, 128.4, 123.3, 122.0, 119.8, 42.9, 34.7, 31.9, 31.6 ppm; MS-FAB: *m/z* (%): 464.7 (100) $[M+H]^+$.

***N*-Methyl-*N*-pyridin-2-ylhydrazine (9)**: *N*-methylhydrazine (20 mL, 360 mmol) was added to 2-bromopyridine (5 mL, 5 mmol) and the mixture was refluxed under an argon atmosphere for 2 h. The residual solvent was distilled off and the oil fully dried under vacuum. This residual oil was purified by chromatography (SiO_2) in dichloromethane with a gradient to 3% methanol to yield the product as a slightly yellow oil (4.86 g, 79%). ^{1}H NMR (200 MHz, [D]chloroform): δ = 8.14 (dd, J = 3.1 Hz, 2H; NH), 7.43 (t, 2H; Aryl), 6.95 (d, J = 7.7 Hz, 2H; Aryl), 6.55 (t, 2H; Aryl), 4.09 (br s, 2H; NH), 3.19 ppm (s, 6H; CH_3) ^{13}C NMR (50 MHz, [D]chloroform): δ = 161.2, 147.3, 137.0, 112.8, 107.3, 41.0 ppm; MS (70 eV): *m/z* (%): 123.2 (100) $[M]^+$; elemental analysis calcd (%) for $C_6H_9N_3$ (123.2): C 58.51, H 7.37;N 34.12 found: C 59.01, H 7.42, N 34.21.

***N*-(2,7-Di-*tert*-butyl-9,9-dimethyl-9H-xanthen-4-ylmethylene)-*N'*-pyridin-2-yl-1,1'-dimethylhydrazine (6)**: Hydrazine **9** (264 mg, 0.21 mmol) was added to dialdehyde **7** (29 mg, 0.077 mmol) in a 9:1 mixture of ethanol/chloroform (35 mL) and then refluxed for 24 h. The solvent was removed under reduced pressure and compound **6** was quantatively isolated as a white solid upon drying under vacuum. Decomposition above 207°C; ^{1}H NMR (200 MHz, [D]chloroform): δ = 8.24 (s, 4H; NH), 7.97 (d, J = 2.1 Hz, 2H; Aryl), 7.74 (s, 2H; CH), 7.65 (t, J = 2.1 Hz, 2H; Aryl), 7.44 (d, J = 2.6, 2H; Aryl), 6.79 (t, J = 6.2 Hz, 2H; Aryl), 3.77 (s, 6H; CH_3), 1.69 (s, 6H; CH_3), 1.34 ppm (s, 18H; CH_3); ^{13}C NMR (50 MHz, [D]chloroform): δ = 157.9, 147.1, 145.7, 137.7, 130.3, 129.4, 122.9, 120.5, 115.6, 109.9, 34.7, 32.0, 31.6, 29.3 ppm; MS-FAB: *m/z* (%): 590.8 (100) $[M+H]^+$.

Template-mediated photodimerization: A Pyrex NMR tube was charged with the template **3** (6.57 mg, 2.4×10^{-2} mmol) and coumarin **1c** (6.13 mg, 1.3×10^{-2} mmol), which were then dissolved in acetone (2 mL). The oxygen from the homogeneous solution was removed by a stream of argon and the tube subsequently sealed. The sample was exposed to a 400 W lamp for 12 h and the product distribution determined by HPLC analysis. In the case of the asymmetric template, **4** (2.4 mg, 1.2×10^{-3} mmol) was dissolved in acetone (1 mL) along with **1c** (1.5 mg, 2.4×10^{-3} mmol) in a Young NMR tube, subjected to four cycles of purge-pump-thaw, and then irradiated in the sealed tube. The same irradiation procedure was adopted for the stoichiometric irradiation of template analogues **5** and **6**.

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