doi:10.2533/chimia.2011.202 Chimia 65 (2011) 202–209

Fun with Photons: Selective Light Induced Reactions in Solution and in Water Soluble Nano-containers

Anoklase Ayitou, Barry C. Pemberton, Elango Kumarasamy, Nandini Vallavoju, and J. Sivaguru§*

§Gramaticakis-Neumann Prize Winner 2010

Abstract: Two distinct strategies for controlling selectivity, in particular stereoselectivity in photochemical reactions are reviewed. In the first strategy, supramolecular approach using cucurbituril nano-containers in catalytic amounts is employed to control selectivity during photochemical transformations. In the second approach, a generalized methodology for carrying out light-induced transformations in solution at ambient conditions is detailed where axially chiral motifs are employed to enantiospecifically transfer the axial chirality in the reactant to point chirality in the photoproduct(s).

Keywords: Asymmetric photoreactions · Cucurbiturils · Host–Guest chemistry · Molecular chirality · Supramolecular catalysis

Prof. ***Sivaguru Jayaraman*** (Siva) is a 5th year assistant professor at the Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND, USA. He received his Bachelors degree (1996) from St. Joseph's College (Autonomous), Bharathidasan University, Trichy, India and Masters degree (1998) from IIT-Madras, Chennai, India. He received his PhD degree (2003) in chemistry from Tulane University, New Orleans under the guidance of Prof. V. Ramamurthy. He completed a post-doctoral fellowship (2003–2006) at Columbia University, NY under the mentorship of Prof. Nicholas J. Turro. Siva moved to his current position at NDSU in 2006 and established an independent research program that has gained prominence among his peers within a very short time as evidenced by the CAREER award from the National Science Foundation (2008). At NDSU, his research talents were recognized with the 2010 College of Science and Mathematic Award for Excellence in Research. His current research interests include Photocatalysis (supramolecular and organic photocatalysis), Light induced asymmetric transformations, Photochemistry within organized and confined media, Supramolecular photochemistry, Host–Guest Systems, Molecular recognition in chemical and biological systems and Molecular Self-Assembly.

*Correspondence: Prof. Dr. J. Sivaguru
North Dakota State University
Department of Chemistry and Biochemistry
1231 Albrecht Blvd.,
104H, LADD Hall, P.O. Box 6050, NDSU Dept 2735
Fargo, ND 58108-6050. USA
Tel.: +1 701 231 8923
Fax: +1 701 231 8831
E-mail: sivaguru.jayaraman@ndsu.edu

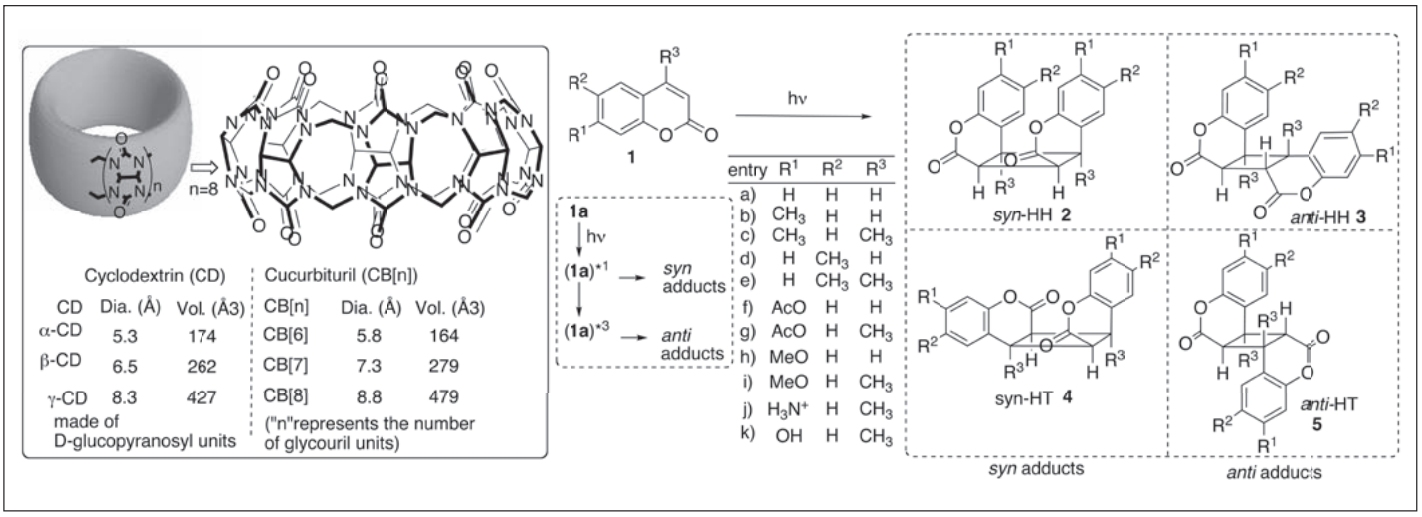
The review article details two distinct ways of controlling selectivity, in particular stereoselectivity in photochemical reactions. The first part uses water-soluble nano-container molecules known as cucurbiturils in catalytic amounts to control selectivity while the second aspect addresses a traditional challenge of enantiocontrol in photoreactions, where molecularly chiral (axially chiral) chromophores are employed for enantiospecific photoreactions.

1. Water-soluble Nano-containers as Supramolecular Photocatalysts

Exploiting supramolecular interactions to alter/improve existing reactivity and/or selectivity has been a topic of interest due to the prospect of using nano-inspired materials for harvesting light induced transformations.[1] Additionally, the nano-confinement imposed by macrocyclic hosts such as cyclodextrins,[2–4] cucurbit[n]urils[5–12] and synthetic capsules[13,14] has shown promise towards the development of efficient enzyme-mimetics[2,3] for various chemical transformations.[12,15–17] Some key factors that have to be considered before employing organized assemblies to control photoreactivity within supramolecular environments[18] are i) available free space, ii) structural rigidity and iii) type of non-bonding interaction that develops between the host and the guest. In our opinion cucurbiturils not only satisfy the above requirements, but also are water-soluble, making them appealing from an environmental perspective.

1.1 *Cucurbit[n]urils*

Cucurbiturils[5–12] are a family of molecular container compounds with shapes similar to that of pumpkins (botanical name *cucurbitaceae*[6]). Cucurbiturils (CBs)[5–12] feature a cavity similar to that of cyclodextrins (Scheme 1). Similar to cyclodextrins that are made of D-glucopyranosyl units, CBs are constructed of glycouril units. The number of glycouril units (denoted by CB6, CB7 and CB8) determines the available volume within cucurbiturils (CBs). The glycouril unit provides a hydrophobic pocket (nano-cavity) in which the portal is made of polar carbonyl groups that allows them to bind to both polar and non-polar organic molecules. Recent efforts by various groups[7–12,19] have opened up new opportunities for using cucurbiturils as 'nano-reaction vessels'. Cucurbit[8]urils



Scheme 1. Left: Structural comparison of cucurbit[n]urils (CBs) and cyclodextris (CDs); Right: Photodimerization of coumarin derivatives.

(CB[8]) attracted our attention as their cavity volume is similar to that of γ-cyclodextrins (γ-CD). We chose to investigate the photodimerization of coumarin derivatives **1** (Scheme 1) within CB[8] as we reasoned that CB[8] with a similar (Scheme 1) cavity volume (479 Å^3) as that of γ-CD (cavity volume 427 Å^3), will be an ideal candidate and will most likely form 1:2 host–guest (HG) complexes, as γ-CD forms a 1:2 complex with various coumarin derivatives and other photochromophores.[20]

1.2 *Supramolecular Catalysis with CBs*

Using 'nano-cavities' to confine reactive photochromophores allows for investigation of photoreactions based on size/shape of the nano-cavity along with the structural rigidity and non-bonding interactions that develop between the host and guest within the nano-cavity. To successfully employ CB[8] as a 'nano-reaction vessel' for synthetic transformations, it is critical to employ them in catalytic amounts in order to overcome a fundamental bottleneck *viz*., solubility of CB[8] in high amounts (>0.2 mM) that is typically employed for synthetic reactions.

1.3 *Coumarin Derivatives as Molecular Probes*

Coumarin has historically been the subject of intense photochemical and spectroscopic interest mainly as a consequence of its significance in biological systems and use in various materials of commercial interest.[21–28] Recently, we have been exploring the role of cucurbit[8]urils (CB[8]) in altering the photoreactivity (Scheme 1) of coumarin derivatives.[29–33] Our investigation revealed that both neutral and cationic coumarins **1a–k** form stable HG complexes with CB[8].[30,31] The HG ratios of **1a–k** with CB[8] were examined using ^{1}H-NMR and UV-Vis spectroscopy (Job plot) and by single crystal XRD (Fig. 1).[29–33]

Current investigations in our laboratory have established that the photoproduct resulting from templating of coumarins within CB[8] cavity is likely dictated by electrostatic/non-bonding interactions as well as by volume restrictions.[30,31] In water/CB[8] media non-polar coumarins **1b–e** preferentially formed *syn*-photoproducts, whereas polar coumarins with the ability to form H-bonds as in **1j–k** preferentially formed the *anti*-dimer (Fig. 2, left). Based on spectroscopic characterization, computational modelling and control studies with coumarin substrates (**1b–i**) we postulated that the H-bonding interaction between the polar functional groups (OH and NH_3^+) and the amide-carbonyl of CB portals is likely responsible for the observed selectivity (Fig. 2, left).

1.4 *Dynamic Supramolecular System in Solution*

Photoreactivity of non-polar coumarins **1a–i** within CB[8] provided an opportunity to enhance their photodimerization efficiency. Additionally, we observed that these non-polar coumarins formed dynamic HG complex in water (Fig. 2, right). For example, **1d** formed a H:G ratio of 1:1.6 indicating a mixture of 1:1 and 1:2 CB[8]:**1d** host–guest complex along with an uncomplexed coumarin in solution. The dimerization efficiency in the case of **1d–e** was higher inside the cavity (Path A; Fig. 2, right), while for coumarins **1a, 1f–i** the dimerization outside the cavity was much higher (Path B; Fig. 2, right). For example, the photodimerization of **1d** is very effi-

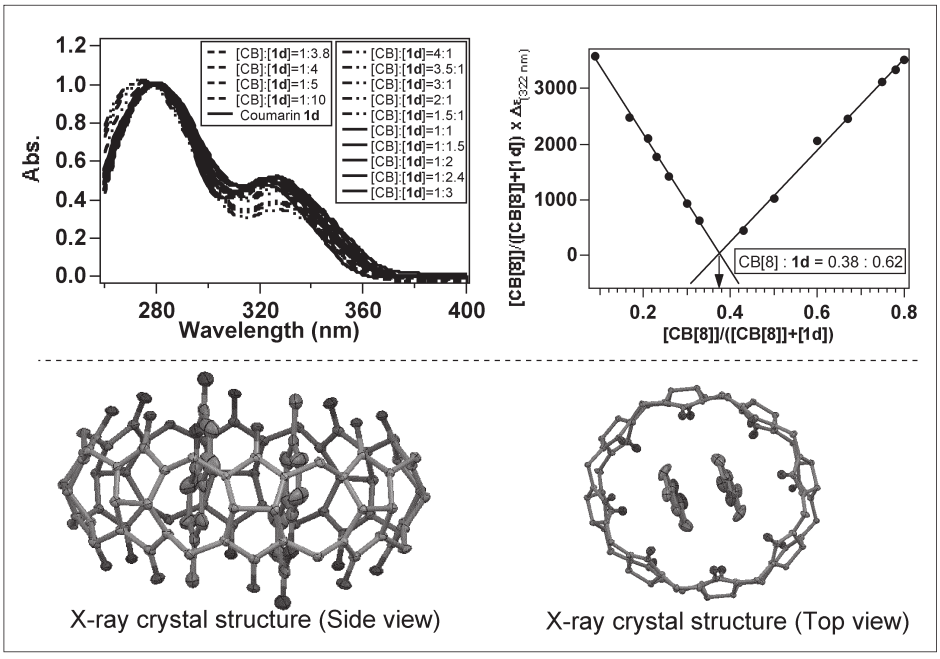


Fig. 1. Characterization of HG complex of **1d**@CB[8] by abs. spectroscopy/Job plot (top) and by single crystal XRD (bottom).

cient within the cavity *viz.,* ~50% conversion in 72 h in isotropic media (benzene) compared to >70% conversion in 60 min in the presence of CB[8] in water. In general, the different stereoisomeric photoproducts are observed in the presence of CB[8] compared to isotropic media. For example, in the case of **1d**, *syn* dimers were observed within CB[8] and *anti* dimers in isotropic media. To understand the supramolecular system in detail we will concentrate on the photochemistry of **1d** as a model chromophore to understand the influence of confinement within CBs.

1.5 *Photophysical Aspects – Effect of Confinement within CBs*

To ascertain the excited state chemistry of **1d** within CB[8], we carried out steady state and time resolved emission fluorescence and phosphorescence measurements (Fig. 3). Photophysical investigations of **1d** within CB[8] not only provided further insights into the nature of the reactive excited state, but also added credibility to our proposed dynamic behavior of CB[8]-**1d** host–guest complex in water. We observed (Fig. 3A) a 40 nm red shift, an increase in the emission quantum yield and an increase in the fluorescence lifetime (Fig. 3B) upon encapsulation of **1d** within CB[8]. The maximum emission intensity was observed for the 1:1 complex and the emission intensity decreased for the 1:2 complex because photodimerization pathway competes with the radiative pathway decreasing the emission quantum yield. Fluorescence lifetime measurements (Fig. 3B) showed three distinct decays with a long-lived component (~3.7 ns) from a 1:1 HG complex, an ~0.7 ns component being the 1:2 HG complex and the <0.1 ns being the uncomplexed form (**1d** is established[34] to have a <0.1 ns component decay in water). In addition, there was also an observable phosphorescence at 77 K (Fig. 3C) in the presence of CB[8]. Thus photophysical studies revealed that the photoreactions could occur from both the excited singlet and excited triplet state.

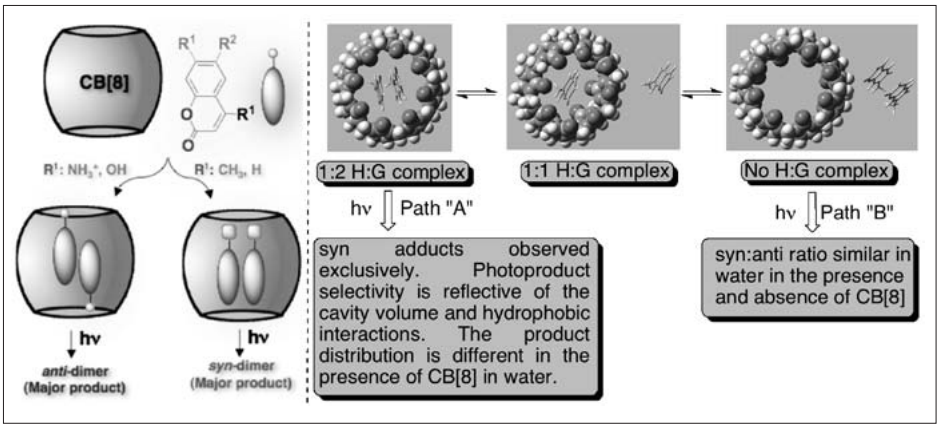


Fig. 2. Left*:* Photoproduct selectivity in polar and non-polar coumarins leading to *anti*- and *syn*-dimers respectively. Right: Host–guest dynamics and its influence on photochemical pathway within CB[8].

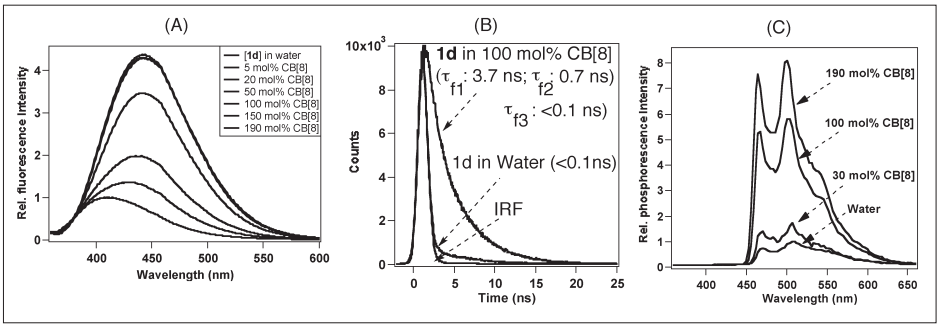


Fig. 3. Photophysical aspects of 6-methylcoumarin **1d** in water. (A) Room temperature fluorescence, (B) fluorescence lifetime at room temperature, (C) phosphorescence at 77K.

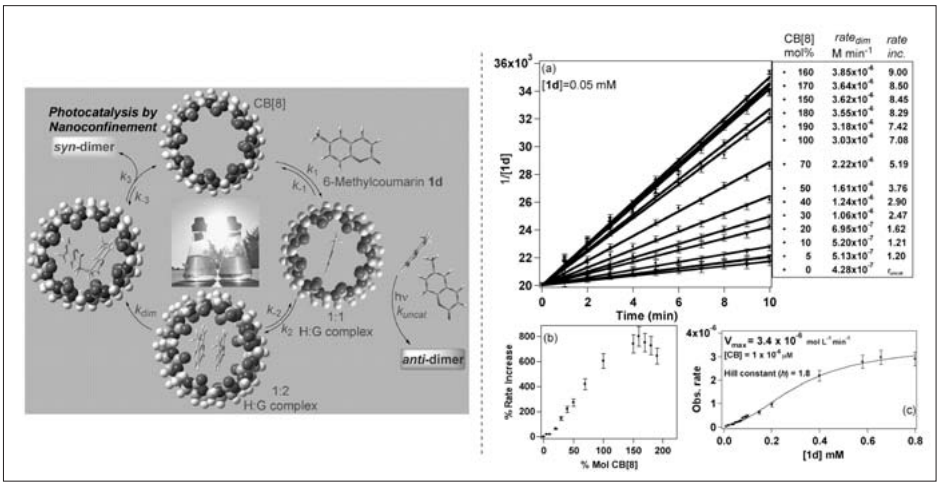


Fig. 4. Left: CB[8] mediated catalytic cycle for photodimerization of coumarins. Right: (a) Kinetics of photodimerization of **1d** at various mol% of CB[8]; (b) Rate increase with various mol% of CB[8]. (c) Saturation kinetics; Error bars represent a 10% error in the values.

1.6 *Supramolecular Photocatalysis by Confinement within CB[8] Nano-cavity*

In principle, photochemical transformations with catalytic amounts of CB[8] are quite feasible, as our investigations have revealed that non-polar coumarins form dynamic host–guest (HG) complexes (Fig. 2; Path A) and react very efficiently in water. We employed **1d** as a model system to investigate the feasibility of employing CB[8] as a catalytic supramolecular nano-reaction vessel. Our results point to a likely catalytic cycle (Fig. 4, left) involving CB[8] where the photodimerization of **1d** results in the exclusive formation of *syn*-dimers. A closer look at the catalytic cycle reveals that the photodimerization process occurs in the presence of catalytic amounts of CB[8] presumably due to the high photodimerization rate within the cavity. The photodimerization in water outside the CB[8] cavity (background reaction) determines the efficiency of the catalytic cycle and the selectivity in the photodimerization process (*syn–anti* ratio). The extent of background reaction compared to the reaction within the cavity can easily be understood based on the photoproduct distribution as the *anti* dimer is formed outside the cavity (in water) while *syn* dimer is observed within the cavity.

In the present case, the *anti*-dimer is formed only outside the cavity whereas the *syn* isomers are formed within the cavity. Thus the ratios of *syn–anti* isomer not only reflect the selectivity within the confined environment of CB[8] but also the efficiency of the catalytic cycle. As the reaction in water has been postulated to occur from a

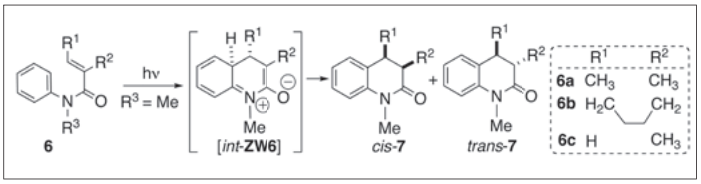
triplet state, the background reaction can be completely quenched in the presence of oxygen. Thus, the catalytic efficiency can be enhanced by carrying out the reaction in O_2 saturated solution as the photodimerization outside the cavity is lowered in the presence of O_2 leading (O_2 acting as a triplet quencher) to a pronounced *syn–anti* ratio even at low mol% of CB[8]. Saturation kinetics (Fig. 4c) gave a turnover number of 3.4 min^{-1}. The maximum rate of photodimerization (Fig. 4a,b) occurred at 160 mol% of CB[8]. This is a reflection of the dynamic nature of the system indicating that the maximum concentration of 1:2 HG complex occurs at 160 mol% of CB[8]. Additionally, the sigmoidal dependence on coumarin concentration (with constant CB[8] concentration) implies that the overall catalytic process is cooperative in nature (Fig. 4c). A Hill plot gave a Hill constant of 1.8, ascertaining a positive allosteric effect. The positive allosterism could be envisioned based on the single crystal XRD of CB[8]-**1d** (Fig. 1) HG complex that showed a guest-induced shape change.[33] The symmetrical CB[8] cavity becomes elliptical upon inclusion of the guest. We believe that the first coumarin binding with CB[8] induces a slight alteration of the shape of the cavity to accommodate the second coumarin facilitating the enhancement of photo-dimerization. This is reflected in the positive allosteric effect. We were successful in performing photodimerization of **1d** with catalytic amounts of CB[8] under sunlight (8 h exposure) in water that resulted in complete conversion of **1d** to *syn* photodimers highlighting a greener approach for synthetic manipulation.[29]

1.7 *Outlook*

Our results clearly show that cucurbiturils can be effectively employed in catalytic amounts to control light induced transformations. The effect of confinement and the enhanced reactivity within CBs is reflected in the photoproduct selectivity.

2. Enantiospecific Photoreactions in Solution

Asymmetric photoreactions have not enjoyed the same level of success as thermal reactions. Conventional chiral inductors employed in thermal reactions alter the relative activation energy in the ground state and therefore are not effective in inducing stereoselection during phototransformation.[35] Chiral discrimination during phototransformation has to occur in the excited state within the short lifetime of the excited molecules/intermediates and/or transition states.[35] Photochemists have successfully employed various organized assemblies[36–41] to carry out asymmetric photoreactions and have achieved varying degrees of success. To achieve stereoselection during phototransformation of prochiral reactants in solution, the chiral discrimination must transpire within the substrate, unlike in organized assemblies[36–41] that provide the chiral discrimination, leading to noticeable stereoselectivity/specificity. Organized assemblies like crystals could provide a chiral environment if the prochiral substrate(s) crystallizes in one of the chiral space groups (molecular chirality), the process being inherently unpredictable. These molecularly chiral crystals could be transformed to chiral photoproducts with very high stereoselectivity/stereospecificity.[42–44] It would be ideal to have a similar methodology of transferring molecular chirality from the reactant to point chirality in the product in solution during phototransformations.[45]



Scheme 2. Conrotatory 6π-photocyclization of acrylanilides.

2.1 *Methodology*

Our approach is to make use of built-in molecular constraints within a reactant and transform them to chirally enriched photoproducts with high stereospecificity. The constraints make the reactants axially chiral and are based on the well-established concept of rotamer control *via* restricted bond rotation that has been successfully employed for various transformations.[8a,46–49] The methodology of employing axially chiral rotamers draws inspiration from Havinga's NEER principle (Non-Equilibrating Excited Rotamers),[50] where conformer-based product control during photochemical reactions is well documented. The axially chiral chromophores were synthesized with relative ease using established literature procedures.[46–49] Due to space limitations, we will detail the photochemistry of molecularly chiral (axially chiral) acrylanilides.[51–53] We have also employed the above methodology to other photochemical reactions (γ-hydrogen abstraction, [2+2]-cycloaddition, 4π-cyclization).[54–57]

2.2 *6π-Photocyclization of Molecularly Chiral (Axially Chiral) Acrylanilides*

We chose to investigate 6π-photocyclization of molecularly chiral acrylanilides as model system to test our methodology because i) the photochemical pathway is well established in literature;[58–62] ii) it is well known that bulky (*tert*-butyl) *ortho* substituents in N,N'-disubstituted anilides are molecularly chiral (axially chiral) due to restricted rotation of the N–C(Aryl) bond and are fairly stable at ambient conditions; iii) synthesis (three steps) and chromatographic separation are well documented in literature.[46–49] Mechanistically,[58–62] 6π-photocyclization of achiral acrylanilides **6** (Scheme 2) upon direct irradiation occurs *via* a conrotatory ring closure (Scheme 2) from a singlet ππ* excited state leading to the zwitterionic intermediate *int*-**ZW6**.[58–62] Depending on the substituents on the double bond (R^1 and/or R^2), photocyclization of acrylanilides **6** yields a mixture of *cis*-**7** and *trans*-**7** 3,4-dihydroquinolin-2-one photoproducts (Scheme 2). The *cis*-:*trans*- (*c*-**7**:*t*-**7**) ratio in the photoproduct was found to be dependent on the nature of the solvent employed (Table 1, entries 17–19). It is well established in literature that in an aprotic solvent, H-transfer to the zwitterionic intermediate formed from acrylanilides (without *o-tert*-butyl substituent) occurred to a large extent *via* a thermally allowed intramolecular suprafacial [1,5]-H shift, while in protic solvents or in the presence of Brønsted acids, the proton was delivered intermolecularly.[58–62]

2.3 *Regioselectivity in the 6π-Photocyclization of Molecularly Chiral Acrylanilides*

Atropisomeric mixtures of *o-tert*-butylacrylanilides with N-methyl substitution **8a–g** were synthesized and irradiated using a 450 W medium pressure Hg-lamp with Pyrex cutoff in various solvents (Table 1, Scheme 3). The photoproducts were characterized by NMR spectroscopy, ESI-MS and chromatographic analysis that confirmed the formation of *cis*-**9** and *trans*-**9** 3,4-dihydroquinolin-2-ones without the *tert*-butyl group (Scheme 3, top). Irradiation of the corresponding N-H derivatives **10a–c** under identical conditions gave the cyclized products *cis*-**11** and *trans*-**11** (Scheme 3, middle), with the *o-tert*-butyl group intact on the phenyl ring.[58–62] It is striking to note that substitution at the amide nitrogen (H *vs*. Me) was able to dictate the regiochemistry of cyclization on the phenyl ring. Based on the behaviour of the parent acrylanilide **6** (Scheme 2), one would expect the cyclization of **8** to occur at the unsubstituted *ortho*-position on the phenyl ring and not at the *ortho*-carbon bearing the *tert*-butyl group, leading to *cis*-**9** and *trans*-**9** as observed. On the other

Table 1. Enantioselectivity and *cis/trans ratio* during photocyclization[a-c] of acrylanilides.

Entry	Solvent	Substrate	*c*-**9**:*t*-**9**	[%] ee *cis*-**9**		[%] ee *trans*-**9**	
	α,β-substituted axially chiral acrylanilides			(+)-**8**	(–)-**8**	(+)-**8**	(–)-**8**
1)	1:2 THF-C_6H_6	**8a**	62:38	– [e]	– [e]	95 (A)	89 (B)
2)	Acetone		55:45	– [e]	– [e]	94 (A)	90 (B)
3)	1:2 THF-C_6H_6	**8b**[d]	22:78	93 *(S, R)*	80 *(R, S)*	94 *(S, S)*	–
4)	MeOH		65:35	99 *(S, R)*	*85 (R, S)*	99 *(S, S)*	
5)	Acetone		67:33	92 *(S, R)*	92 *(R, S)*	88 *(S, S)*	–
6)	1:2 THF-C_6H_6	**8d**	42:58	– [e]	– [e]	88 (A)	91 (B)
7)	Acetone		46:54	– [e]	– [e]	91 (A)	94 (B)
8)	1:2 THF-C_6H_6	**8e**	52:48	90 (B)	91 (A)	99 (B)	93 (A)
9)	$CHCl_3$		41:59	91 (B)	98 (A)	95 (B)	99 (A)
10)	MeOH		70:30	99 (B)	99 (A)	99 (B)	99 (A)
11)	Acetone		63:37	87 (B)	90 (A)	90(B)	91 (A)
	α-substituted axially chiral acrylanilides			(+)-**8**		(–)-**8**	
12)	TFE	**8f**	- [f]	0		0	
13)	1:2 THF-C_6H_6		- [f]	0		0	
14)	Acetone		- [f]	92 (A)		94 (B)	
15)	TFE	**8g**	- [f]	0		0	
16)	Acetone		- [f]	94 (A)		92 (B)	

cis/trans ratio during photocyclization[a-c] of achiral acrylanilides with **6a-b** and **10a-b** [h]

Entry	Solvent	*c*-**7a**:*t*-**7a** (from **6a**)[g]	*c*-**7b**:*t*-**7b** (from **6a**)[g]	*c*-**11a**:*t*-**11a** (from **10a**)[g]	*c*-**11b**:*t*-**11b** (from **10b**)[g]
17)	1:2 THF-C_6H_6	52:48	11:89	72:28	82:18
18)	$CHCl_3$	49:51	41:59	70:30	90:10
19)	MeOH	18:82	83:17	80:20	-

[a]Irradiations were performed with 450 W medium pressure Hg-lamp under a constant flow of nitrogen (time varies based on the solvent between 90 min to 5 h). Conversion varied between 5–70% depending on the solvent. Increasing the irradiation time (>5 h) resulted in higher conversion, but uncharacterized additional side products were observed. In acetone, conversion was 50–60%. Isolated yields were 49 and 51% in acetone for **8e** and **8f** respectively. [b]A and B refers to the first and second peak that elutes out on the HPLC for a given pair of enantiomers; values are average of 3 runs with ±5% error; reaction temperature 0-3 °C; (+) and (–) represents the sign of their CD signals at 240 nm in methanol (**8a–c**) and methylcyclohexane (**8g**). Similarly for **8d–f**, (+) and (-) represents the sign of optical rotation in $CHCl_3$. Regis-(RR)-WHELK-01 chiral stationary phase employed for separation of *cis* and *trans* enantiomers. [c]*cis:trans* Ratio and conversion based on relative integration of corresponding peaks in NMR and HPLC/GC. TFE=trifluoroethanol. [d]Absolute configuration assigned based on comparison of optical rotation values from literature (ref. [63]). In the case of **8d** photoproducts, chromatographic separation is necessary prior to HPLC analysis as HPLC retention times of *trans*-**8d** overlaps with the reactant **8d**. [e]*cis*-**9** Enantiomers were not separable on chiral stationary phase employed in our laboratory. [f]*cis* and *trans* Isomers not feasible in photoproducts from methacryloyl derivatives **8c**, **8f** and **8g** as they are α-substituted derivatives. [g]Photocyclization of various derivatives of parent acrylanilide **6a-b** already reported in literature (refs [58–62]). [h]Only *cis/trans* selectivity was studied as the substrates are not axially chiral.

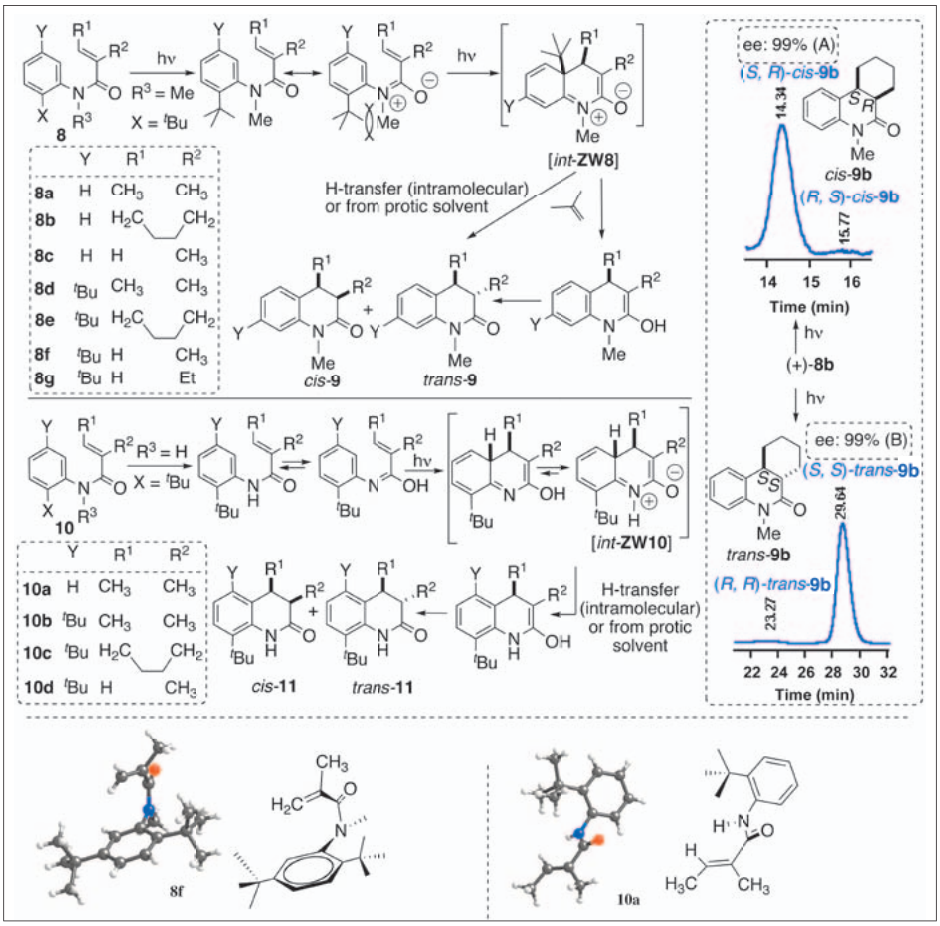
hand, in the corresponding N-H derivatives **10**, photocyclization occurred at the expected unsubstituted *ortho* carbon (similar to the parent acrylanilide **6**)**.** A mechanistic understanding for the difference in behaviour between the N-methyl acrylanilide **8** and the corresponding N-H acrylanilide **10** is crucial if one is to employ the system for studying molecular chiral (axial chiral) transfer during phototransformations.[51–57]

To enable a detailed mechanistic rationalization for the observed difference in the photocyclization between the N-Me *o-tert*-butylacrylanilides **8** and the corresponding N-H derivatives **10**, structural parameters must be reliably known. Fortunately, we succeeded in crystallizing the N-Me derivative **8f** and the N-H derivative **10a** and obtained their solid-state structure by X-ray crystallography (Scheme 3 bottom). It should be emphasized that the rigid conformation in the solid state is taken as a starting point to rationalize the observed photobehavior in solution where dynamic movements (rotational, translational, *etc*.) are prevalent. Based on the analysis of the crystal structure, it is plausible that the conformation that is observed in the crystalline state (Scheme 3 bottom) is reflective of the diminished steric impediments between the *o-tert*-butyl and the N-Me groups. Examination of the crystal structure of axially chiral acrylanilides **8f** (Scheme 3 bottom) revealed that the dihedral angle is almost 90 degrees between the plane formed by the aromatic ring and the plane formed by the N-methyl-amide carbonyl unit. The likely reason for this orientation is to minimize the 1,3-allylic strain ($A^{1,3}$-strain) between the *ortho-tert*-butyl and the N-methyl substituents. On the other hand, in the case of N-H derivatives as in **10**, the amide N-H can tautomerize to the corresponding enol form in solution eliminating the A-strain (Scheme 3). The tautomerization of the N-H derivatives orient them in a conformation that is optimal for photocyclization at the unsubstituted *ortho*-carbon on the phenyl ring (Scheme 3, middle).

Based on the established mechanistic pathway for 6π-photocyclization, direct irradiation of N-methyl substituted *ortho-tert*-butylacrylanilides **8** in methanol, TFE or 1:2 THF-benzene results in the singlet state reactivity. This likely results in a zwitterionic intermediate *int*-**ZW8** to avoid the 1,3-allylic strain between the *ortho-tert*-butyl and N-methyl substituents. The zwitterionic intermediate *int*-**ZW8** subsequently undergoes either an H shift from the *o-tert*-butyl substituent or a H-transfer from the protic solvent leading to *cis*-**9** and *trans*-**9**, with the loss of 2-methylpropene (Scheme 3). The intramolecular or intermolecular H-transfer depends on the solvent employed.[58–62] Photocyclization in methanol-*d* confirmed the H-shift from protic solvents based on deuterium incorporation.[53] On the other hand, 6π-photocyclization of the N-H derivatives **10** likely occurs from the amide enol form that is oriented ideally for photocyclization at the unsubstituted *ortho*-carbon on the phenyl ring resulting in the zwitterionic intermediate *int*-**ZW10** (Scheme 3). The zwitterionic intermediate *int*-**ZW10** subsequently undergoes an intramolecular-shift or H-shift from the solvent to *cis*-**11** and *trans*-**11**.[58–62] Thus, photocyclization of N-H *ortho-tert*-butyl acrylanilides **10** is similar to that reported for the parent acrylanilides **6** without an *o-*^{t}Bu group (Scheme 2).[58–62]

2.4 *Enantiospecific 6π-Photocyclization of Molecularly Chiral Acrylanilides*

To ascertain the transfer of axial chirality to point chirality during 6π-photocyclization



Scheme 3. 6π-photocyclization of axially chiral acrylanilides **8** (top) and NH-acrylanilides **10** (middle). Bottom: X-ray crystal structure of **8f** (left), and **10a** (right). Insert: HPLC analysis of *cis*- and *trans*-photoproducts upon irradiation of (+)**8b**.

molecularly chiral acrylanilides **8**, we examined the enantiomeric excess in the 3,4-dihydroquinolin-2-ones photoproducts *cis*-**9** and *trans*-**9** (Table 1). In the case of α,β-substituted axially chiral **8a–b** and **8d–e**, very high enantiomeric excess (~90%) was observed in photoproducts in both direct irradiation (in solvents methanol, $CHCl_3$ and 1:2 THF-C_6H_6) and sensitized irradiations (acetone as solvent and sensitizer). The optical antipodes of **1** gave the opposite enantiomers in the photocyclized product indicating that the system was well behaved (Table 1; entries 1–11).

Based on our mechanistic analysis we postulated that the photocyclization occurred at the *ortho* carbon *via* '*int*-**ZW8**' (Scheme 3) with the eventual loss of the *o*-*tert*-butyl substituent. If this holds true, the enantiomeric excess in the photoproducts (*cis*-**9** and *trans*-**9**) must be identical, as the resulting zwitterionic intermediate '*int*-**ZW8**' (Scheme 3) has a defined chiral center at the benzylic position formed by stereospecific ring closure. The second proton transfer step is non-stereospecific leading to *cis* and *trans* photoproducts with identical *ee* values. Fortunately, we were successful in separating the enantiomers of both the *cis*-**9b** and the *trans*-**9b** in the case of cyclohexyl derivatives **8b** (Scheme 3; HPLC insert). Inspection of Table 1 indicates that similar enantiomeric excess was observed in both *cis*-**9** and *trans*-**9** photoproducts. Additionally, the benzylic carbon in the *cis* and *trans* photoproducts has the same absolute stereochemistry adding credibility to our proposed mechanism (Scheme 3; HPLC insert). For example in the case of (+)-**8b**, photocyclization in methanol gives (*S, R*)-*cis*-**9b** and (*S, S*)-*trans*-**9b** with the same absolute stereochemistry (*S*) at the benzylic position.

Inspection of Table 1 reveals that the β-substituent in the alkene is crucial for achieving the high enantiomeric excess under direct irradiation conditions (singlet spin state reactivity). For example, in 1:2 THF-C_6H_6 as solvent the *ee* value of >90% was observed for (+)-**8d** with β-CH_3 substituent, where as 0% *ee* value is observed for the corresponding methacryloyl derivative (+)-**8f** with β-H substituent (Table 1; compare entries 6 and 13).

2.5 *Reactive Spin-state Dependent Enantiospecific 6π-Photocyclization of Axially Chiral Acrylanilides*

While the excited singlet-state reactivity (*via* direct irradiation) led to a racemic mixture in the photoproducts for α-substituted axially chiral acrylanilides **8f** and **8g**, the corresponding triplet reactivity (*via* triplet sensitization with acetone acting as the solvent and sensitizer) led to enantiomeric ratios (*e.r.* values) >95:05 in the 3,4-dihydroquinolin-2-one photoproduct **9** at ambient conditions. To examine the role of reactive spin state (S_1 or T_1) dependent photocyclization of axially chiral α-substituted acrylanilides **8f–g** (**8f**: α-methyl and **8g**: α-ethyl) to the corresponding 3,4-dihydroquinolin-2-one photoproduct **9**, we carried out detailed photophysical studies with α-substituted axially chiral substrates **8f–g** and the N-H *o*-*tert*-butyl derivative **10d** and N-Me derivative **6c** without the *o*-*tert*-butyl group. Both **8f–g** showed fluorescence (Fig. 5A) at room temperature in methylcyclohexane (MCH). The emission maxima shifted bathochromically upon changing the solvent from non-polar MCH to polar solvents like ethanol or acetonitrile, similar to the fluorescence emission behaviour of other methacrylanilides that are reported in literature.[59] Additionally, for **8f–g** we observed phosphorescence (Fig. 5A) at 77 K in MCH glass with a triplet energy (E_T) of ~77.3 kcal·mol^{-1} and a lifetime (τ_p) of ~1.58 s (Fig. 5B). Based on the emission studies,[64] it is clear that the lowest excited singlet and triplet state have a ππ* configuration in **8f–g**.

Based on the established paradigm[64] for photochemical reactions *viz* photocyclization, a zwitterionic intermediate is expected for the photocyclization from the ππ* singlet excited-state $S_1(\pi\pi^*)$ and a diradicaloid intermediate is likely from the corresponding ππ* triplet excited-state $T_1(\pi\pi^*)$.[64] This prompted Ogata and coworkers[59,60] to propose a zwitterionic intermediate originating from the singlet ππ* (S_1 ππ*) excited-state for the 6π-photocyclization of achiral acrylanilide (N-H substituted derivative without *ortho*-*tert*-butyl group on the phenyl ring). In the case of **8f–g**, we believe that the restricted N–C(aryl) bond rotation not only imparts axial chirality (molecular chirality) to the system but also enables us to access the triplet state (as we observe phosphorescence) at 77 K in MCH glass. While in the case of achiral N-H acrylanilide (*viz.*, *ortho*-*tert*-butyl N-H acrylanilide **10d**) we failed to observe any phosphorescence at 77 K, both achiral and axially chiral N-methyl derivatives **8f–g** (molecular chiral **8f–g** and achiral **6c**) gave observable phosphorescence at 77 K in MCH glass. Thus the presence of N-Me substituent is crucial to accessing the triplet-excited manifold. We believe that the enolization of the N-H acrylanilides (as in **10d**; Fig. 5C) to the enol form enables it to cyclize only from the singlet-excited state, as it is oriented optimally for 6π-photocyclization. On the other hand,

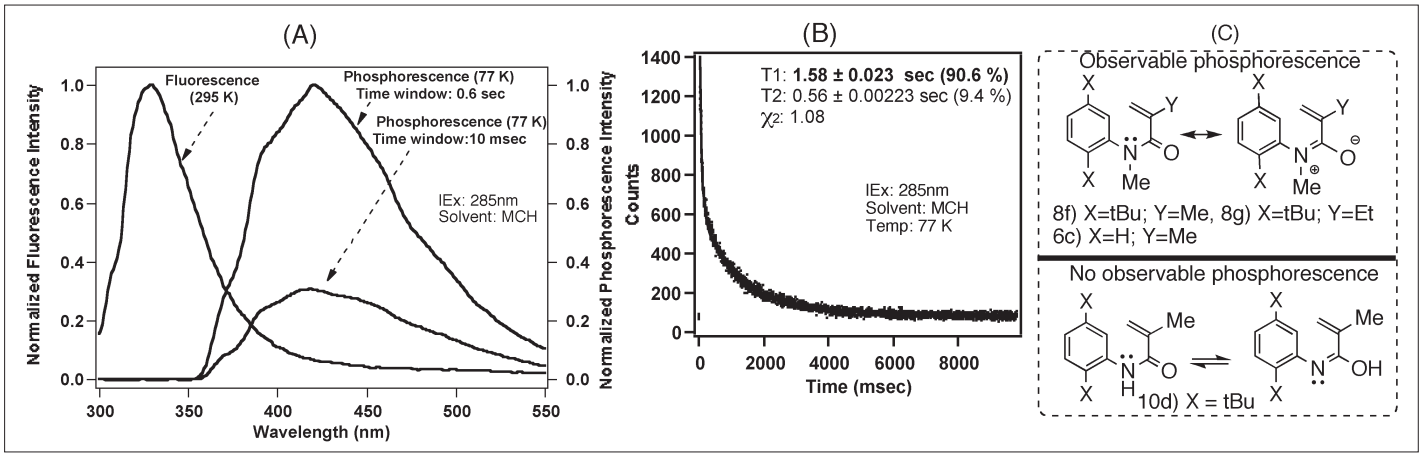
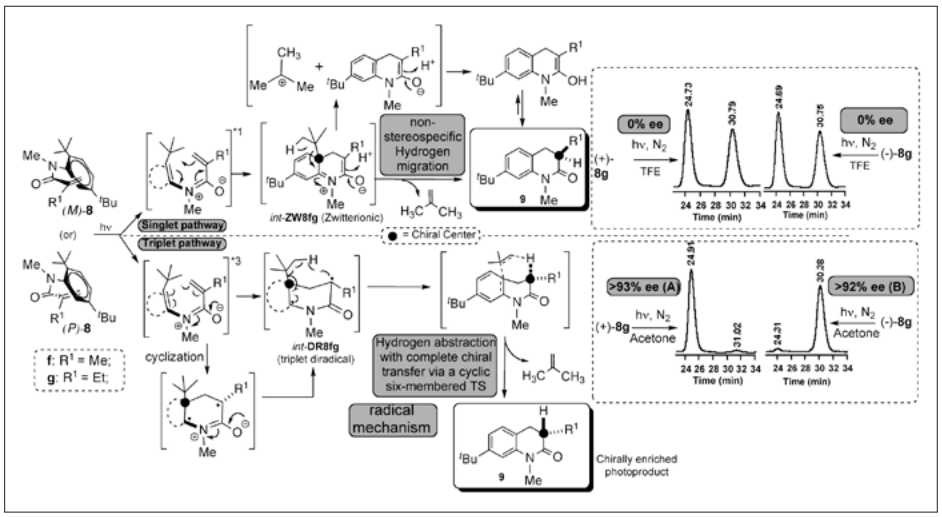


Fig. 5. (A) Fluorescence (at 298 K) and phosphorescence (at 77 K) of **8f** in methylcyclohexane (MCH). (B) Phosphorescence decay kinetics of **8f** at 77 K in MCH glass. (C) Role of N-methyl (**8f–g** and **6c**) and N-H substitution (**10d**).

in case of the N-methyl derivatives (as in **8f**–**g**; Fig. 5C), the nitrogen lone pair is part of the 6π-backbone leading to photoreactivity from the ππ* excited state. Based on the phosphorescence, the triplet ππ* state of **8f–g** lies at ~77 kcal•mol^{-1}. Hence triplet energy transfer from acetone (E_T ~79 kcal·mol^{-1})[65] is quite likely. The involvement of triplet spin state *viz.*, T_1(ππ*) in the reaction pathway was ascertained by carrying out the reaction under O_2 saturated conditions that resulted in <5% conversion.[53] Thus 6π-photocyclization of **8f–g** could possibly occur from either the singlet (S_1) or the triplet (T_1) spin-state depending on the reaction conditions.[66]

Similar to the photocyclization (direct irradiation) of α,β-substituted axially chiral acrylanilides that occurred *via* zwitterionic intermediate '*int*-**ZW8**' (Scheme 3), direct irradiation (singlet chemistry) in the case of *ortho*-*tert*-butyl α-substituted axially chiral acrylanilides **8f–g** led to photocyclization that occurred at the *ortho* carbon *via* an analogous zwitterionic intermediate '*int*-**ZW8fg**' (Scheme 4, top) followed by a non-stereospecific hydrogen migration with the eventual loss of the *o*-*tert*-butyl substituent. As the photocyclization occurred from the S_1(ππ*) excited state upon direct irradiation in the case of **8f–g**, the formation of a zwitterionic intermediate ('*int*-**ZW8fg**') was expected.[58–62] Similarly, triplet sensitized irradiation of **8f–g** led to photocyclization from T_1(ππ*) excited state resulting in a diradical (triplet diradical) intermediate '*int*-**DR8fg**' (Scheme 4, bottom). This triplet diradical '*int*-**DR8fg**' subsequently abstracts a hydrogen atom from *o*-*tert*-butyl substituent leading to 3,4-dihydroquinolin-2-one photoproduct **9**. The high enantiomeric ratio (Table 1) in the photoproduct **2** under sensitized irradiation (acetone as solvent and sensitizer) points out to a stereospecific hydrogen abstraction *via* a cyclic six-membered transition (Scheme 4, bottom) state from triplet diradical intermediate (*int*-**DR8fg**).



Scheme 4. Photocyclization of axially chiral α-substituted acrylanilides **8f–g** and under direct (singlet) and sensitized (triplet) irradiations.

Thus the excited spin state S_1(ππ*) or T_1 (ππ*) not only leads to the formation of same photoproduct *via* two different reactive intermediates and/or transition states, but also determines the *e.r.* values in the photoproduct in the case of α-substituted axially chiral acrylanilides **8f–g**.

2.6 *Outlook*

Our strategy of employing axially chiral chromophores has opened up the possibility of achieving very high enantiomeric excess in phototransformations in solution, a traditionally difficult task. Employing axially chiral chromophores that equilibrate very slowly in the ground state leading to very high enantioselectivity in the photoproducts draws inspiration from Havinga's NEER principle (Non-Equilibrating Excited Rotamers), where conformer-based product control is well documented.[50] We have also been very successful in employing this methodology of using axially chiral chromophores in various photochemical transformations. Axially chiral chromophores in conjunction with their corresponding achiral counterparts offer rich and divergent photoreactivity that helps us to better understand mechanisms of light-induced stereospecific transformations.

3. Conclusion

The ongoing investigations in our lab have uncovered two methodologies to achieve high selectivity in solution during photochemical transformations. Using a supramolecular approach, we have employed cucurbiturils in catalytic amounts to control selectivity during photochemical transformations. To tackle the traditional challenge of controlling enantioselectivity we have employed axially chiral motifs to enantiospecifically transfer the axial chirality in the reactant to point chirality in the photoproduct. This methodology was found to be efficient for various photoreactions thus presenting itself as a generalized methodology to perform light-induced transformations in solution at ambient conditions.

Acknowledgment

The authors thank the Swiss Chemical Society for the 2010 SCS Grammaticakis-Neumann Prize and for the hospitality during the award ceremony at ETH-Zürich. The work was performed with generous funding from the National Science Foundation (NSF-CAREER: CHE-0748525). The authors thank the NSF ND-EPSCoR program for a doctoral dissertation fellowship to BCP (Grant EPS-0814442). AJA thanks a Graduate Student Fellowship from NSF and UNCF/MERCK science initiative research grant. The start-up fund to establish the research program was with generous funding from the Department of Chemistry and Biochemistry, North Dakota State University, Fargo ND. The authors also thank the ND-EPSCoR program for seed grants (2006-2007: Grant EPS-0447679 and 2010-2011: Grant EPS-0814442). The authors would like to thank Dr. Nilotpal Barooah and Dr. Josepha Jesuraj for their contributions.

Received: January 25, 2011

[1] N. J. Turro, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10766.
[2] 'Artificial Enzymes', Ed. R. Breslow, Wiley-VCH, Weinheim, **2005**.
[3] I. Tabushi, *Acc. Chem. Res*. **1982**, *15*, 66.
[4] S. A. Nepogodiev, J. F. Stoddart, *J. Am. Chem. Soc.* **1998**, *98*, 1959.
[5] R. Behrend, E. Meyer, F. Rusche, *Liebigs Ann. Chem.* **1905**, *339*, 1.
[6] W. A. Freeman, W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 7367.
[7] J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res*. **2003**, *36*, 621.
[8] W. S. Jeon, K. Moon, S. H. Park, H. Chun, Y. H. Ko, J. Y. Lee, E. S. Lee, S. Samal, N. Selvapalam, M. V. Rekharsky, V. Sindelar, D. Sobransingh, Y. Inoue, A. E. Kaifer, K. Kim, *J. Am. Chem. Soc.* **2005**, *127*, 12984.
[9] A. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094.
[10] J. Lagona, J. C. Fettinger, L. Isaacs, *J. Org. Chem*. **2005**, *70*, 10381.
[11] W. Ong, M. G.-. Kaifer, A. E. Kaifer, *Org. Lett.* **2002**, *4*, 1791.
[12] C. Klock, R. N. Dsouza, W. M. Nau, *Org. Lett.* **2009**, *11*, 2595.
[13] J. Rebek, *Acc. Chem. Res.* **1990**, *23*, 399.
[14] C. L. D. Gibb, A. K. Sundaresan, V. Ramamurthy, B. C. Gibb, *J. Am. Chem. Soc*. **2008**, *130*, 4069.
[15] W. L. Mock, T. A. Irra, J. P. Wepsiec, T. L. Manimaran, *J. Org. Chem.* **1983**, *48*, 3619.
[16] W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302.
[17] J. Kang, G. Hilmersson, J. Santamaria, J. J. Rebek, *J. Am. Chem. Soc.* **1998**, *120*, 3650.
[18] 'Photochemistry in Organized and Constrained Media', Ed. V. Ramamurthy, Wiley-VCH, New York, **1991**.
[19] R. Wang, L. Yuan, D. H. Macartney, *J. Org. Chem.* **2006**, *71*, 1237.
[20] J. N. Moorthy, K. Venkatesan, R. G. Weiss, *J. Org. Chem.* **1992**, *57*, 3292.
[21] G. S. Hammond, C. A. Stout, A. A. Lamola, *J. Am. Chem. Soc*. **1964**, *86*, 3103.
[22] R. Hoffman, P. Wells, H. Morrison, *J. Org. Chem.* **1971**, *36*, 102.
[23] K. Muthuramu, V. Ramamurthy, *J. Org. Chem.* **1982**, *47*, 3976.
[24] W. W. Mantulin, P.-S. Song, *J. Am. Chem. Soc.* **1973**, *95*, 5122.
[25] S. S. J. de Melo, R. S. Becker, A. L. Maqanita, *J. Phys. Chem.* **1994**, *98*, 6054.
[26] R. S. Becker, S. Chakravorti, C. A. Gartner, M. d. G. Miguel, *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 1007.
[27] G. F. Fedorin, V. P. Georgievskii, *J. Appl. Spectros.* **1974**, *20*, 122.
[28] S. K. Allen, A. Todd, J. M. Allen, *Biochem. Biophys. Res. Commun.* **1997**, *235*, 615.
[29] B. C. Pemberton, N. Barooah, D. K. Srivatsava, J. Sivaguru, *Chem. Commun.* **2010**, *46*, 225.
[30] N. Barooah, B. Pemberton, A. C. Johnson, J. Sivaguru, *Photochem. Photobiol. Sci.* **2008**, *7*, 1473.
[31] N. Barooah, B. Pemberton, J. Sivaguru, *Org. Lett*. **2008**, *10*, 3339.
[32] B. Pemberton, E. Kumarasamy, S. Jockusch, D. K. Srivatsava, J. Sivaguru, *Can. J. Chem.* **2011**, DOI: 10.1139/v10.
[33] B. C. Pemberton, R. K. Singh, S. Jockusch, J. P. Da Silva, A. Ugrinov, N. J. Turro, D. K. Srivatsava, J. Sivaguru, *Chem. Commun*. **2011**, submitted.
[34] T. Wolff, H. Goerner, *Phys. Chem. Chem. Phys.* **2004**, *6*, 368.
[35] Y. Inoue, in 'Chiral Photochemistry', Eds. Y. Inoue, V. Ramamurthy, Marcel Dekker, New York, **2004**, pp. 129.
[36] V. Ramamurthy, in 'Photochemistry in Organized and Constrained Media', Wiley-VCH, New York, **1991**, p. 429.
[37] N. J. Turro, M. Garcia-Garibay, in 'Photochemistry in Organized and Constrained Media', Ed. V. Ramamurthy, Wiley-VCH, New York, **1991**, p. 1.
[38] G. M. J. Schmidt, *Pure Appl. Chem.* **1971**, *27*, 647.
[39] J. N. Gamlin, R. Jones, M. Leibovitch, B. Patrick, J. R. Scheffer, J. Trotter, *Acc. Chem. Res.* **1996**, *29*, 203.
[40] T. Mori, R. G. Weiss, Y. Inoue, *J. Am. Chem. Soc.* **2004**, *126*, 8961.
[41] A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139.
[42] F. Toda, *Acc. Chem. Res*. **1995**, *28*, 480.
[43] M. Sakamoto, M. Kato, Y. Aida, K. Fujita, T. Mino, T. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 1132.
[44] M. Veerman, M. J. E. Resendiz, M. A. Garcia-Garibay, *Org. Lett.* **2006**, *8*, 2615.
[45] T. Bach, J. Schröder, K. Harms, *Tetrahedron Lett.* **1999**, *40*, 9003.
[46] D. P. Curran, H. Qi, S. J. Geib, N. C. DeMello, *J. Am. Chem. Soc*. **1994**, *116*, 3131.
[47] D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. l. Cass, A. L. G. Degani, M. Z. Hernandes, L. C. G. Freitas, *Tetrahedron: Asymm.* **1997**, *8*, 3955.
[48] J. Clayden, *Chem. Commun*. **2004**, 127.
[49] A. Honda, K. M. Waltz, P. J. Carroll, P. J. Walsh, *Chirality* **2003**, *15*, 615.
[50] E. Havinga, J. L. M. A. Schlatmann, *Tetrahedron* **1961**, *16*, 146.
[51] A. J.-L. Ayitou, S. J., *J. Am. Chem. Soc.* **2009**, *131*, 5036.
[52] A. J.-L. Ayitou, J. Sivaguru, *Chem. Commun.* **2010**, ASAP. DOI:10.1039/C0CC04416D.
[53] A. J.-L. Ayitou, J. Sivaguru, A. Ugrinov, *Photochem. Photobiol. Sci.* **2009**, *8*, 751.
[54] A. J.-L. Ayitou, J. L. Jesuraj, N. Barooah, A. Ugrinov, J. Sivaguru, *J. Am. Chem. Soc.* **2009**, *131*, 11314.
[55] J. L. Jesuraj, J. Sivaguru, *Chem. Commun.* **2010**, *46*, 4791.
[56] N. Vallavoju, J. Sivaguru, unpublished results.
[57] E. Kumarasamy, J. Sivaguru, unpublished results.
[58] O. L. Chapman, W. R. Adams, *J. Am. Chem. Soc.* **1968**, *90*, 2333.
[59] Y. Ogata, K. Takagi, I. Ishino, *J. Org. Chem*. **1971**, *36*, 3975.
[60] I. Ninomiya, S. Yamauchi, T. Kiguschi, A. Shinobara, T. Naito, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1747.
[61] T. Bach, B. Grosch, T. Strassner, E. Herdtweck, *J. Org. Chem.* **2003**, *68*, 1107.
[62] G. R. Lenz, *J. Org. Chem.* **1976**, *41*, 2201.
[63] T. Naito, Y. Tada, I. Ninomiya, *Heterocycles* **1984**, *22*, 237.
[64] N. J. Turro, 'Modern Molecular Photochemistry', University Science Books, New York, **1991**, 228–230 and 264–266.
[65] S. L. Murov, I. Carmichael, G. L. Hug, 'Handbook of Photochemistry', Marcel Dekker, New York, **1993**, 54–98.
[66] R. Lapouyade, C. Manigand, A. Nourmamod, *Can. J. Chem.* **1985**, *63*, 2192.