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Bifunctional Molecular Photoswitches Based on Overcrowded Alkenes for Dynamic Control of Catalytic Activity in Michael Addition Reactions

Stefano F. Pizzolato, Beatrice S. L. Collins, Thomas van Leeuwen, and Ben L. Feringa^{*[a]}

Abstract: The emerging field of artificial photoswitchable catalysis has recently shown striking examples of functional light-responsive systems allowing for dynamic control of activity and selectivity in organocatalysis and metal-catalysed transformations. While our group has already disclosed systems featuring first generation molecular motors as the switchable central core, a design based on second generation molecular motors is lacking. Here, the syntheses of two bifunctionalised molecular switches based on a photoresponsive tetrasubstituted alkene core are reported. They feature a thiourea substituent as hydrogen-donor moiety in the upper half and a basic dimethylamine group in the lower half. This combination of functional groups offers the possi-

bility for application of these molecules in photoswitchable catalytic processes. The light-responsive central cores were synthesized by a Barton–Kellogg coupling of the prefucationalized upper and lower halves. Derivatization using Buchwald–Hartwig amination and subsequent introduction of the thiourea substituent afforded the target compounds. Control of catalytic activity in the Michael addition reaction between (*E*)-3-bromo- β -nitrostyrene and 2,4-pentanedione is achieved upon irradiation of stable-(*E*) and stable-(*Z*) isomers of the bifunctional catalyst **1**. Both isomers display a decrease in catalytic activity upon irradiation to the metastable state, providing systems with the potential to be applied as ON/OFF catalytic photoswitches.

Introduction

External control of catalytic systems by light is a highly challenging and still underdeveloped field of modern organic chemistry. In the quest for responsive catalytic systems, many advantages arise from the use of light as a clean, non-invasive stimulus, in which judicious choice of irradiation wavelength may allow precise control over catalyst function, activity and selectivity. A number of photoresponsive catalysts have been developed over the last decade, exploiting the established switching properties of azobenzenes, diarylethenes and overcrowded alkenes.^[1–5] Promising results in photochemical control of catalyst activity or selectivity have been achieved through different approaches by harnessing cooperative,^[6–12] steric^[13–20] and electronic effects^[21–25] of the photo-accessible isomers.

For instance, Hecht and co-workers developed a series of photoswitchable catalysts based on a 3,5-disubstituted azobenzene core featuring a piperidine base, in which the modu-

lation of steric shielding was used to control catalytic activity (Scheme 1a).^[16] Upon photoswitching, the basic piperidine nitrogen atom is exposed in the (*Z*)-isomer, allowing enhancement of the rate of the aza-Henry reaction of nitroethane to *p*-

Scheme 1. a) Photoswitchable azobenzene-based piperidine as a light- and heat-triggered catalyst to achieve rate control of the Henry reaction by reversible steric shielding of basic/nucleophilic sites. b) A photoswitchable overcrowded alkene-based light- and heat-triggered thiourea-DMAP bifunctional catalyst to achieve control of rate and enantioselectivity in a Michael addition reaction by reversible *E/Z* photoisomerization and thermal helix inversion.

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nitroanisaldehyde as compared to the (*E*)-isomer ($k_Z/k_E=35.5$). Rebek and co-workers introduced a light-responsive cavitand/piperidinium complex that displayed switchable catalytic activity for the Knoevenagel condensation of aromatic aldehydes with malonitrile.^[17] The cavitand features an azobenzene arm capable of competing with the piperidinium ion for the cavity when irradiated with UV light, allowing reversible control of the guest binding and reactivity. Imahori and co-workers reported a bis(trityl alcohol)-substituted azobenzene as a cooperative bifunctional switchable catalyst capable of reversible activity control when applied to a Morita–Baylis–Hillman reaction of 3-phenylpropanal and 2-cyclopenten-1-one.^[10] The switchable catalyst was able to increase the yield of the reaction after 2 h (background, 27%) from 37%, using the less active state (*E*)-isomer, to 78% yield using the more active (*Z*)-isomer. Pericás and co-workers developed a switchable azobenzene-thiourea organocatalyst, which was used to achieve control of Michael addition reactions through reversible hydrogen-bond shielding of the catalytic unit, enabled by a nitro group as the blocking moiety.^[20] The (*E*)-isomer effectively catalysed the Michael addition of 2,4-pentanedione to (*E*)-3-bromo- β -nitrostyrene (full conversion was achieved after 19 h), whereas the photogenerated (*Z*)-isomer, in which the nitro group engages in hydrogen bonding interactions with the thiourea moiety, led to a significantly lower reaction rate (only 23% conversion after 20 h). Chen and co-workers developed a pseudo-enantiomeric pair of optically switchable helicenes containing a catalytic 4-*N*-methylaminopyridine (MAP).^[26] Successful application was found in the enantiodivergent Steglich rearrangement of *O*- to *C*-carboxylactones, with formation of either enantiomer with up to 91 (*R*) and 94% *ee* (*S*), respectively. Branda and co-workers developed various systems for exploiting the characteristic switching of structural and electronic properties of diarylethenes to allow, for instance, the control of Lewis acidity/basicity,^[27,28] stereoselectivity^[8] and substrate reactivity.^[29–33] Other approaches, including the application of photoresponsive systems for controlling the rate of ring-opening polymerizations,^[24,34–36] are summarized in recent comprehensive reviews.^[1–5]

Our group has demonstrated stimuli-responsive control of the activity and enantioselectivity of a catalyst by dynamic conformational changes of a first generation molecular motor equipped with two functional groups able to cooperatively accelerate a reaction (Scheme 1b; for the switching process of the main core, see Scheme 2a).^[9] The two pseudo-enantiomeric (*Z*)-isomers of the molecular motor during its rotary cycle were shown to control the stereochemical outcome of an organocatalytic thiol 1,4-addition, allowing access to both enantiomers of the product depending on the state of the catalyst. This organocatalyst bears a 2-aminopyridine base and a weakly acidic thiourea functionality, which were proposed to engage in bidentate coordination of the substrates, leading to both accelerated reaction rates and high levels of stereocontrol. Subsequently, we extended the application of this concept to an organocatalysed Henry reaction upon structural modification of the chiral catalyst, improving its versatility and efficiency through a more constrained catalytic pocket.^[12]

Furthermore application of dynamic control of chirality with responsive phosphine ligands for palladium-catalysed enantioselective allylic substitution was demonstrated.^[37] A similar chiral first generation molecular motor scaffold was recently exploited in a light- and heat-responsive bis-urea receptor capable of multi-state regulation of dihydrogen phosphate ion binding affinity.^[38] A major difference in binding affinity of the interchangeable isomers was observed, enabling external control of substrate binding by the dynamic host.

Having established the potential of molecular motors^[39–42] as multiple switching elements in dynamic chemical systems for stereoselective catalysis and anion recognition, we engaged in the challenge of developing a prototype for a responsive bifunctional organocatalyst^[43–47] based on the second generation molecular motor core. Unlike the first generation molecular motor (Scheme 2a),^[48] the second generation motor structure features non-identical upper and lower halves, in which the upper half contains the sole stereogenic center of the molecule (Scheme 2b).^[49–54] Upon irradiation with UV light, the central stilbene-type alkene can undergo a photochemical *E/Z* isomerization that yields a metastable (*MS*) diastereoisomer (top/right structures), which holds the opposite helical chirality to the original stable (*St*) diastereoisomer (top/left structures).

Scheme 2. Isomerization processes leading to unidirectional rotation in: (a) first generation molecular motor (four-stage cycle with four distinctive stereoisomers), (b) second generation molecular motor (four-stage cycle with only two distinctive stereoisomers in case of symmetrically substituted lower half). *St* = stable isomer, *MS* = metastable isomer.

The metastable species can subsequently undergo a thermally activated isomerization in which the upper half moves along the lower half, again resulting in an inversion of helicity, namely thermal helix inversion (THI).^[50] In the resulting stable isomer (bottom/right structures), the upper half has undergone a 180° rotation with respect to the lower half.

In our previous study, we combined a 5-membered ring in the lower half (fluorene) with a sulfur-containing 6-membered ring in the upper half (5,8-dimethylthiochromene and benzo[*f*]thiochromene). This resulted in distinctive high-energy activation barriers for the thermal relaxation step in the rotary cycle of the second generation molecular motors and consequently, long half-lives of the metastable species.^[50, 55] More precisely, the THI energy barrier dramatically increased due to the high conformational constraints, resulting in an alternative and predominant thermal relaxation process, known as thermal *E/Z* isomerization (TEZI) [for 5,8-dimethylthiochromene: $\Delta^\ddagger G^\circ_{\text{THI}}$ (100 °C, 1 atm) = 138 kJ mol⁻¹, $\Delta^\ddagger G^\circ_{\text{TEZI}}$ (100 °C, 1 atm) = 129 kJ mol⁻¹, $t_{1/2}$ (20 °C, 1 atm) = 75 years; for benzo[*f*]thiochromene: $\Delta^\ddagger G^\circ_{\text{THI}}$ (100 °C, 1 atm) = 140 kJ mol⁻¹, $\Delta^\ddagger G^\circ_{\text{TEZI}}$ (100 °C, 1 atm) = 129 kJ mol⁻¹, $t_{1/2}$ (20 °C, 1 atm) = 4300 years]. We demonstrated that these overcrowded alkene systems could be used as highly thermally stable and selective photoswitchable bistable systems, both important requirements for reliable photoresponsive catalysts, in which each state should be selectively addressable with a high photostationary state (PSS) ratio while remaining stable over time.

An interesting aspect of the second generation molecular motor scaffold is the possibility of functionalising the otherwise symmetrical lower half with two different catalytically active moieties (depicted as A and B in Scheme 3), which could dynamically cooperate with the single functionality (C) on the upper half. Through this design, two distinct bifunctional catalytic pairs could be accessed. Notably, these two pairs of catalytic functional groups would also be addressed with two opposite helical chirality, *P* or *M*, upon irradiation and thermal relaxation. We envisioned such a design as a feasible future route for stimuli-responsive switchable catalysts in multi-tasking systems and one-pot multi-step diastereo- and enantioselective reactions.^[2-4, 9, 37, 56-60]

Although the ultimate goal remains the syntheses of tri-functionalised bi-stable switches and their use as catalysts in one-pot multistep reactions, initial studies have focused on the feasibility of introducing well-established catalytic functional groups onto the overcrowded alkene scaffold found in second generation molecular motors. Here, we report the first syntheses of two bifunctional molecular switches **1** and **2** based on the second generation molecular motor scaffold (Figure 1a). Featuring catalytic functions, each switch was obtained both as (*E*)- and (*Z*)-stereoisomers [only (*E*)-isomer shown]. These switches are related to analogous examples^[9, 16] and may allow for dynamic control of activity as ON/OFF or OFF/ON catalysts (Figure 1b). Moreover, the present preliminary study is a stepping stone for the future synthesis of more complex trifunctional photoswitchable catalysts in multi-step syntheses (see Scheme 3).

Scheme 3. Proposed design of a trifunctional light- and heat-responsive organocatalyst for diastereo- and enantioselective one-pot multi-step systems. The catalyst is envisioned to be switchable between four different states, each displaying a different combination of active cooperative catalytic pairs (AC or BC) and helicity (*P* or *M*). Depicted are only two of the four possible products accessible by combining three starting components (shown as coloured spheres) in a chemo- and enantioselective fashion (suggested handedness of the newly generated stereogenic centres indicated on the connecting bond). By triggering the proper catalyst states, both enantiomers of each diastereoisomer could be accessed.

Figure 1. (a) Bifunctional molecular switches **1** and **2** [(*Z*)-isomers omitted]. (b) General scheme for photoswitching of the bifunctional catalyst and potential application as an OFF/ON catalyst. (c) Retrosynthetic analysis of **1** and **2**.

Results and Discussion

Design

To address high switching performance and thermal stability, the aforementioned bi-stable switch core was chosen (thiopyran upper half, fluorene lower half, Figure 1a). Our prototypes feature a thiourea substituent in the upper half, a well-established hydrogen-donor moiety in organocatalysis,^[47,61,62] and a basic dimethylamine group in the lower half. These functionalities were chosen to reflect commonly encountered functional groups within the field of organocatalysis^[47,62–68] and to avoid synthetic compatibility issues associated with the Barton–Kellogg coupling,^[69,70] the signature synthetic step for this family of overcrowded alkenes. The reaction conditions required to synthesize the thioketone and diazo coupling partners (Figure 1c) impose challenges to the synthetic design. For instance, the established methodology commonly adopted to generate the thioketone includes the use of Lawesson's reagent or P_4S_{10} at high temperatures for prolonged reaction times, which may cause problems with other functionalities present in the molecule. In line with these considerations, we chose to install a dimethylamine substituent in the lower half, which is expected to tolerate the conditions for thioketone formation. On the other hand, the more sensitive thiourea motif in the upper half is to be installed after the construction of the tetrasubstituted alkene and amination of the upper half by a Buchwald–Hartwig coupling (Figure 1c).^[71]

Synthesis

The synthesis of (*E*)-1 and (*Z*)-1 is outlined in Schemes 4 and Scheme 5. The lower half coupling partner was synthesized

Scheme 4. Synthesis of the lower half of switches 1 and 2.

from commercially available 2-aminofluorene (Scheme 4). Methylation of the aniline moiety by reductive amination with formaldehyde and sodium cyanoborohydride provided **3** (89%). Oxidation of the fluorene was then achieved under an atmosphere of air using the trialkyl ammonium salt Triton B as a catalyst in pyridine (89%). Fluorenone **4** was converted into the reactive thioketone **5** by thionation with P_4S_{10} in moderate yield (33%), in which experimental observations indicate a subtle balance between conversion of starting material and decomposition of product in this step, both highly dependent on temperature and reaction time.

Scheme 5. Synthesis of the upper half of molecular switch 1.

The synthesis of the upper half started from commercially available 2-bromo-1,4-dimethylbenzene (Scheme 5). By reacting with chlorosulfuric acid, the aryl halide was first converted to the corresponding arylsulfonyl chloride **6** (90%). Subsequent reduction with zinc powder and sulfuric acid provided a 1.0:0.6 mixture of 4-bromo-2,5-dimethylbenzenethiol **7** and the corresponding disulfide, respectively (82% overall), which was converted quantitatively to pure **7** by reduction with sodium borohydride. A 1,4-addition reaction with methacrylic acid afforded the sulfide **8** (38%). The thiopyranone ring was finally constructed using a two-step procedure from acid **8** by converting to the more reactive acyl chloride with oxalyl chloride followed by intramolecular Friedel–Craft acylation to afford **9** (93%). All steps could be performed on gram-scale with an overall yield of 26% over five steps from commercial starting materials.

Ketone **9** was converted to the corresponding hydrazone **10** (42%) by condensation with hydrazine monohydrate (Scheme 6). The hydrazone **10** could be transformed into the required diazo coupling partner **11** for the Barton–Kellogg coupling reaction by rapid in situ oxidation at low temperature with [bis(trifluoroacetoxy)iodo]benzene. Reaction with thioketone **5** yielded a mixture of episulfides, (*E*)-**12** and (*Z*)-**12**, which were readily converted by desulfurisation with triphenylphosphine to the overcrowded alkenes (*E*)-**13** and (*Z*)-**13**. The two isomers could be separated by flash column chromatography to provide (*E*)-**13** and (*Z*)-**13** in 35 and 21% yield, respectively, starting with hydrazone **10**. The geometry of isomers (*E*)-**13** and (*Z*)-**13**, obtained in their stable states only, was assigned on the basis of the 1H NMR chemical shifts of the absorptions corresponding to the dimethylamine substituent and the protons in position 1 or 8 on the fluorenyl lower half (highlighted in Scheme 6), in line with previously reported analogous second generation molecular motor scaffolds [for example: St-(*E*)-**13**, δ (-NMe₂) = 3.07 ppm, St-(*Z*)-**13**, δ (-NMe₂) = 2.69 ppm; St = stable form; see the Supporting Information for further details]. Initial attempts to install the benzophenone imine moiety on bromides **13** by Buchwald–Hartwig amination failed, with no detectable conversion even after prolonged reaction times. A halide exchange to the iodide species before the Buchwald–Hartwig reaction, however, allowed us to suc-

Scheme 6. Synthesis of molecular switches (*E*)-1 and (*Z*)-1. Note: (*E*)-13 and (*Z*)-13 were assigned using the ^1H NMR chemical shifts of the absorption peaks corresponding to the dimethylamine substituent and the protons in position 1 or 8 on the fluorenyl lower half, in line with previously reported analogous second generation molecular motor scaffolds (see the Supporting Information for further details).

cessfully continue the synthesis. Bromides (*E*)-13 and (*Z*)-13 were converted separately by an aromatic Finkelstein reaction to the corresponding iodides (*E*)-14 and (*Z*)-14 using a combination of copper iodide and potassium iodide. High temperatures and long reaction times were required, providing (*E*)-14 in good yield (90%) and (*Z*)-14 as a mixture of product and unconverted bromide starting material [(*Z*)-14:(*Z*)-13 = 8:1, 48%]. The more reactive iodide species were then subjected to the Buchwald–Hartwig amination reaction using a palladium(II) acetate/1,1'-bis(diphenylphosphino)ferrocene catalytic system to install the benzophenone imine moiety [(*E*)-15: 36%, (*Z*)-15: 63%].

After hydrolysis to the free amine 16 [(*E*)-16: 80%, (*Z*)-16: 91%], nucleophilic addition to 3,5-bis(trifluoromethyl)phenyl isothiocyanate afforded the target thiourea-functionalized switches [(*E*)-1: 85%, (*Z*)-1: 90%]. The related switches (*E*)-2 and (*Z*)-2 were synthesized using an analogous route starting from 6-bromo-2-naphthol as shown in Schemes 7 and Scheme 8.

Photoswitching process

The switching properties of (*E*)-1, (*Z*)-1, (*E*)-2 and (*Z*)-2 were monitored by UV/Vis absorption spectroscopy (Figure 2) and ^1H NMR spectroscopy [illustrated for (*E*)-1 in Figure 3 and (*Z*)-1 in Figure 4, vide infra]. Solutions of stable (*E*)-1, (*Z*)-1, (*E*)-2 and (*Z*)-2 in tetrahydrofuran ($1.0\text{--}2.0 \times 10^{-5}\text{ M}$) in 1 cm quartz cuvettes were irradiated at room temperature while stirring for a few minutes towards the metastable state using UV light [(*E*)-1 and (*Z*)-1, 312 nm; (*E*)-2 and (*Z*)-2, 365 nm]. The photochemical *E/Z* isomerisations were found to be characterised by clear isosbestic points, indicating the absence of side reactions. All four switches exhibited a decrease in intensity of the absorption bands at 300–350 nm upon irradiation at 312 nm or 365 nm and the appearance of a new absorption band in the

Scheme 7. Synthesis of the upper half of molecular switch 2 from commercial starting material in 70% yield over five steps.

region 350–480 nm, characteristic of the generated metastable isomers. The metastable isomers were shown to be highly thermally stable, exhibiting no degradation or back-isomerisation upon standing at room temperature for extended periods of time.

The PSS ratios for all four switches were determined using ^1H and ^{19}F NMR spectroscopy. In a general procedure, the compound (approximately 0.5 mg) was dissolved in CD_2Cl_2 (0.7 mL) and the sample was irradiated in an NMR tube at 312 nm at room temperature. The isomerization process was monitored over time by means of ^1H NMR spectroscopy (see Figure 3 for

Scheme 8. Synthesis of molecular switches (*E*)-2 and (*Z*)-2.

Figure 2. UV/Vis spectra of the switching process of **1** and **2**. Experimental UV/Vis absorption spectra in black of stable forms of (*E*)-1, (*Z*)-1, (*E*)-2 and (*Z*)-2 (THF, $1.0\text{--}2.5 \times 10^{-5}$ M). Irradiation of (*E*)-1 (312 nm), (*Z*)-1 (312 nm), (*E*)-2 (365 nm) and (*Z*)-2 (365 nm) to the metastable isomers affords a PSS shown in blue with five intermediate moments in the process (total irradiation time: 5–10 min) shown in red (St:MS ratio = (*E*)-1, 18:82; (*Z*)-1, 10:90; (*E*)-2, 20:80; (*Z*)-2, 16:84, ratios as determined by ^1H and ^{19}F NMR spectroscopy in CD_2Cl_2 , vide infra). Similar results were also obtained when CH_2Cl_2 , toluene or acetonitrile were used as solvent.

St-(*E*)-1). No further changes were observed after 15 min of irradiation. Both isomers, St-(*E*)-1 and MS-(*Z*)-1 were assigned using two dimensional COSY and NOESY NMR experiments (see the Supporting Information for further details). The relative integration of the absorptions of the two isomers revealed a PSS ratio (312 nm) in CD_2Cl_2 of St-(*E*)-1:MS-(*Z*)-1 = 18:82. An analogous experiment with St-(*Z*)-1 was performed (Figure 4). A PSS ratio of St-(*Z*)-1:MS-(*E*)-1 = 10:90 was achieved after irradiation at 312 nm in CD_2Cl_2 for 15 min.

Figure 3. (a) ^1H NMR spectra of St-(*E*)-1 (approximately 0.5 mg in CD_2Cl_2 , 0.7 mL), with magnification of corresponding ^{19}F NMR spectra as inserts. (b) ^1H NMR spectra after irradiation with 312 nm light of St-(*E*)-1 to the metastable state MS-(*Z*)-1 affords a PSS mixture of St-(*E*)-1:MS-(*Z*)-1 = 18:82, with magnification of the corresponding ^{19}F NMR spectra. Spectral region of the solvent residual peak (5.30–5.10 ppm) omitted for clarity.

Comparable results were obtained for St-(*E*)-2 and St-(*Z*)-2, affording, upon irradiation with 365 nm light, a PSS ratio of St-(*E*)-2:MS-(*Z*)-2 = 20:80 and St-(*Z*)-2:MS-(*E*)-2 = 16:84, respectively (see the Supporting Information for further details). Interestingly, irradiation at longer wavelength (395 nm for **1** and 420 nm for **2**) gave PSS mixtures consisting mostly of the metastable isomer,^[72] even though this isomer absorbs more strongly at these wavelengths, and led to no, or minimal, change in the UV/Vis spectra.^[73] Similar results were also obtained when dichloromethane, toluene or acetonitrile were used as solvent. Notably, the corresponding unfunctionalised molecular switches constituting the light-responsive core of **1** and **2** have been shown to undergo efficient reversible switching with 312/365 nm and 420/450 nm light over multiple cycles with no

Figure 4. (a) ^1H NMR spectra of St-(Z)-1 (approximately 0.5 mg in CD_2Cl_2 , 0.7 mL), with magnification of corresponding ^{19}F NMR spectra as inserts. (b) ^1H NMR spectra after irradiation with 312 nm light of (Z)-1 to the meta-stable state MS-(E)-1 affords a PSS mixture of St-(Z)-1:MS-(E)-1 = 10:90, with magnification of corresponding ^{19}F NMR spectra. Arrows indicate absorption peaks of corresponding hydrogen atoms in St-(Z)-1 and MS-(E)-1.

evidence of fatigue.^[55] Moreover, the thiourea moiety was present in our previous successful examples of functionalised molecular motors employed in photo-responsive catalytic and anion binding systems.^[9,12,38] From a parallel series of irradiation tests performed on compounds **13**, **16** and **28** (an analogous compound of **13** lacking the amine moiety in the lower half; Figure 5), the reduced photoswitching behaviour appears to arise due to the detrimental influence of the dimethylamine substituent. Compound **28** was in fact the only compound in this study that displayed efficient reversible photo-isomerization (see the Supporting Information for further details).

This lack of reversible switching considerably mitigates the possibility of using these switches as efficient reversible ON/OFF catalysts and future studies will aim to discern what functional groups, specifically those with potentially catalytic capabilities, are compatible with efficient reversible photoisomerization.

Figure 5. The different intermediates or substructures of target compound **1** studied to investigate the role of the amine substituents in the reversibility of the photoswitching process.

It was hypothesized that the lone pair of the dimethylamine substituent might be responsible for the deactivation of the switching process, originating from a detrimental difference between the absorbance values and quantum yields of the stable and metastable isomers. Hence, the addition of a Brønsted acid may result in a recovery of the reversible switching properties, providing the possibility for a pH-gated photo-responsive system. Solutions of St-(E)-1 and St-(Z)-1 (THF, $1.0\text{--}2.5 \times 10^{-5}\text{ M}$) were irradiated with UV light (365 nm and 395 nm) before and after the addition of excess acid or base (respective aliquots of 2 M aq. HCl and 2 M aq. NaOH) (see the Supporting Information for further details). Large changes in the UV/Vis spectra profiles and shift of the isosbestic points during irradiation cycles were observed upon addition of aliquots of both base and acid (365 nm in presence of base, 395 nm in presence of acid). This observation could be explained by activation of the backward switching path upon protonation of the dimethylamine substituent. However, degradation could not be excluded as alternative reasoning for the observed change in the UV/Vis spectra during the backward irradiation, as the original spectra could not be recovered upon multiple irradiation cycles. Nevertheless, such observation opens new insights for future development of pH-gated photo-responsive systems based on molecular motors/switches.

Catalytic activity

Having investigated the photoresponsive dynamic motion of bifunctionalised switches **1–2**, we next studied their ability as photoswitchable cooperative catalysts. Wang and co-workers reported a BINAM-based catalyst bearing a combination of an aromatic dimethylamine substituent as the active nucleophilic group and a thiourea as the H-bond donor moiety displaying promising activity as a catalyst for the Morita–Baylis–Hillman (MBH) reaction.^[67] Despite the literature claims, our attempts to catalyse the reaction between 2-cyclohexen-1-one and 3-phenylpropionaldehyde using either (E)-1, (Z)-1, (E)-2, (Z)-2 or the original literature catalyst did not lead to any conversion to the desired Michael adduct as determined by ^1H NMR spectroscopy (Scheme 9). We postulate that these disappointing results are due to the limited catalytic activity of the dimethylaniline moiety, both in terms of the low nucleophilicity of the aryl amine and the structurally constrained nature of the tertiary amine within the catalyst. Future studies will focus on the introduction of alternative, more nucleophilic, aliphatic amine functionalities (e.g., aliphatic amine) into the lower half, in line

Scheme 9. Attempted catalysis of the Morita–Baylis–Hillman reaction between 2-cyclohexen-1-one and 3-phenylpropionaldehyde using either (E)-1, (Z)-1, (E)-2 or (Z)-2; no conversion to the desired Michael adduct was observed by ^1H NMR spectroscopy.

with the majority of successful catalysts reported for the asymmetric organocatalysed MBH reaction.^[74–78]

Although our initial model of cooperative catalysis induced by photocontrolled geometrical changes appears to be completely unsuccessful, other recent reports led us to reassess the molecular photoswitches (*E*-1, (*Z*)-1, (*E*)-2 and (*Z*)-2. Studies by both Hecht and Pericás has addressed the possibility of shielding a catalytic moiety, in one photoaccessible isomer, either by simple steric interactions (Hecht) or through hydrogen bonding interactions (Pericás).^[16,20] Analysis of the photoswitches (*E*-1, (*Z*)-1, (*E*)-2 and (*Z*)-2 suggests that the catalytically active hydrogen bonding thiourea moiety could be analogously deactivated in both the *St*-(*Z*) or *MS*-(*Z*) isomers either through steric shielding of the thiourea moiety by the dimethylamine group or through hydrogen-bonding interactions. To investigate these ideas further, we tested our system in the Michael addition reaction (as described by Pericás) between (*E*)-3-bromo- β -nitrostyrene and 2,4-pentanedione, in which we postulated that the thiourea moiety in the upper half could engage in hydrogen bonding with the nitro-substituent of the substrate, activating it towards nucleophilic attack. The dimethylaniline moiety in the lower half was anticipated to allow control on the activity of the thiourea moiety by steric hindrance or hydrogen bonding interactions, thus causing a difference in catalytic activity between the more accessible (*E*)-iso-

mers [either *St*-(*E*) or *MS*-(*E*)] and the corresponding blocked (*Z*)-isomers [either *MS*-(*Z*) or *St*-(*Z*)]. Each distinct case could then represent a successful example of ON/OFF [*St*-(*E*) to *MS*-(*Z*)] or OFF/ON [*St*-(*Z*) to *MS*-(*E*)] catalytic switches, respectively. Figure 6 illustrates the progress of the conversion, monitored by ¹H NMR spectroscopy, of the Michael reaction between (*E*)-3-bromo- β -nitrostyrene and 2,4-pentanedione, mediated by different forms of the thiourea catalysts in combination with trimethylamine. When the reaction was conducted in the absence of catalyst, only 10% conversion was observed after 18 h ($v_0 = 5.56 \times 10^{-4} \text{ M h}^{-1}$), in line with the results reported by Pericás and co-workers. In the presence of 3 mol% of *St*-(*E*)-1, a clear acceleration of the reaction was observed, with 60% conversion reached after 18 h ($v_0 = 5.33 \times 10^{-3} \text{ M h}^{-1}$). Interestingly, when the reaction was performed under the same conditions with a PSS mixture (312 nm) of *St*-(*E*)-1:*MS*-(*Z*)-1 = 20:80 as catalyst, the rate of the reaction was substantially decreased, reaching only 19% conversion after 18 h ($v_0 = 1.08 \times 10^{-3} \text{ M h}^{-1}$). These results are highly supportive of a model similar to those described by Hecht and Pericás, in which shielding in one geometric isomer inhibits the activating abilities of a key catalytic functionality in the molecule. Additionally, the catalyst *St*-(*E*)-1 could be switched to the less active state *MS*-(*Z*)-1 during the course of the reaction by irradiation of the sample after 4 h. In the presence of 3 mol% of *St*-(*Z*)-1, an in-

Figure 6. (a) Photoswitching of catalytic activity of (*E*)-1 in Michael addition: background blank reaction, no catalyst (black); catalysed by *St*-(*E*)-1 (red); catalysed by PSS mixture of *St*-(*E*)-1:*MS*-(*Z*)-1 = 18:82 upon UV irradiation (312 nm) of *St*-(*E*)-1 (green); catalysed by *St*-(*E*)-1 upon intermediate irradiation (indicated with orange bar) after 4 h (blue). (b) Photoswitching of catalytic activity of (*Z*)-1 in Michael addition: background blank reaction, no catalyst (black); catalysed by *St*-(*Z*)-1 (red); catalysed by PSS mixture of *St*-(*Z*)-1:*MS*-(*E*)-1 = 10:90 upon UV irradiation (312 nm) of *St*-(*Z*)-1 (green); catalysed by *St*-(*Z*)-1 upon intermediate irradiation (indicated with orange bar) after 4 h (blue). (c) Reaction scheme of Michael addition. (d) Comparison between the net activity (yield, [%] indicated above the corresponding bar, contribution of background reaction subtracted) of (*E*)-1 and (*Z*)-1 as not irradiated (blue) and pre-irradiated mixture (red). For reaction conditions, irradiation and monitoring procedure, see the Supporting Information.

crease of the reaction rate compared to the blank reaction was observed, with 40% conversion reached after 18 h ($v_0 = 2.94 \times 10^{-3} \text{ M h}^{-1}$). Remarkably, when the reaction was performed under the same conditions with a PSS mixture (312 nm) of St-(Z)-1:MS-(E)-1 = 12:88 as catalyst, the rate of the reaction decreased, reaching less than 16% conversion after 18 h ($v_0 = 1.02 \times 10^{-3} \text{ M h}^{-1}$). Contrary to expectations, the deactivated isomer St-(Z)-1 showed moderate catalytic activity, whereas the expected active isomer MS-(E)-1 provided only minimal increase in reaction rate beyond the observed background reaction. Similar to St-(E)-1, St-(Z)-1 could also be switched to the less active state during the course of the reaction by irradiation of the sample after 4 h. It should be noted that no degradation of the catalyst occurred during the irradiation process, as well as no thermal decay of the metastable species was detected, as determined by ^1H NMR spectroscopy throughout the kinetic experiments.

Due to the limited activity displayed by the catalysts, the background blank reaction may still play an important role in the conversion of the substrate. Assuming that the background blank reaction still affords 10% conversion over 18 h ($v_0 = 5.56 \times 10^{-4} \text{ M h}^{-1}$), even in the presence of the catalyst, the sole contribution of the catalysts can then be calculated as follows in terms of conversion (*Conv.*, Eq. 1), initial reaction rate (v_0 , q. 2), and turnover frequency (*TOF*, Eq. 3):

$$\text{Conv.}_{\text{catalyzed}} = \text{Conv.}_{\text{TOT}} - \text{Conv.}_{\text{blank}} \quad (1)$$

$$v_{0\text{catalyzed}} = v_{0\text{TOT}} - v_{0\text{blank}} \quad (2)$$

$$\text{TOF} = v_{0\text{catalyzed}} / \text{conc.}_{\text{catalyst}} \quad (3)$$

In the case of St-(E)-1, by subtracting the contribution of the background reaction, a 50% conversion ($v_0 = 5.33 \times 10^{-3} \text{ M h}^{-1} - 0.56 \times 10^{-3} \text{ M h}^{-1} = 4.77 \times 10^{-3} \text{ M h}^{-1}$, $\text{TOF} = 1.59 \text{ h}^{-1}$) can be attributed to the sole catalyst action. In the case of the corresponding PSS mixture of St-(E)-1:MS-(Z)-1 = 20:80, a mere 9% conversion ($v_0 = 1.08 \times 10^{-3} \text{ M h}^{-1} - 0.56 \times 10^{-3} \text{ M h}^{-1} = 0.52 \times$

10^{-3} M h^{-1} , $\text{TOF} = 0.173 \text{ h}^{-1}$) can be attributed to the catalyst mixture. Notably, this value appears to be proportional to the fraction of St-(E)-1 present in the catalyst mixture (stable-(E)-1 = 20%), if compared to the former not-irradiated sample (i.e., St-(E)-1 = 100%). Similar behaviour is encountered in the second set of experiments involving St-(Z)-1 and MS-(E)-1. By subtracting the background reaction contribution, pure St-(Z)-1 appears to give 30% conversion after 18 h ($v_0 = 2.94 \times 10^{-3} \text{ M h}^{-1} - 0.56 \times 10^{-3} \text{ M h}^{-1} = 2.38 \times 10^{-3} \text{ M h}^{-1}$, $\text{TOF} = 0.793 \text{ h}^{-1}$), whereas the PSS mixture of St-(Z)-1:MS-(E)-1 = 12:88, afforded only 6% conversion ($v_0 = 1.02 \times 10^{-3} \text{ M h}^{-1} - 0.56 \times 10^{-3} \text{ M h}^{-1} = 0.46 \times 10^{-3} \text{ M h}^{-1}$, $\text{TOF} = 0.153 \text{ h}^{-1}$).

As shown by the experimental results, both stable isomers displayed significant loss of catalytic activity upon irradiation to the metastable state. In contrast to our assumption, this behaviour does not seem predominantly regulated by shielding of the thiourea moiety by the amine substituent, either through steric or hydrogen bonding interactions (vide infra, Computational study), but apparently other veiled parameters play a key role.

Computational study

Although the exact reason for the observed decrease in catalytic activity upon irradiation remains elusive, DFT calculations on various conformations of all four isomers, St-(E)-1, MS-(Z)-1, St-(Z)-1 and MS-(E)-1, allowed us to gather further information to help interpret the results. Conformational analysis on all four isomers allowed us to identify the most stable *cis* and *trans* conformations of all the possible ground state isomers of **1** (Figure 7), in which *cis* and *trans* describes the conformation of the thiourea motif.

It was found in accordance with a previous study that the presumably less catalytically active *anti* conformation of the thiourea unit for each stable and metastable isomers of **1** lies lower in energy.^[79] However, the Gibbs free energy difference ($\Delta G \approx 4 \text{ kcal mol}^{-1}$) is the same for all isomers of **1**. The calcula-

Figure 7. DFT optimized structures of the *cis* (top) and *trans* (bottom) conformations adopted by the thiourea substituent for each stable and metastable isomer of **1** (from left to right, the order follows the switching cycle for second generation molecular motor as depicted in Scheme 2 b: St-(E)-1, MS-(Z)-1, St-(Z)-1 and MS-(E)-1).

tions also allow us to rule out the possibility of intramolecular hydrogen bonding interactions between the thiourea and dimethylaniline moieties, in which the distances are too large in all four isomers for hydrogen bonding. Future research will focus on the investigation of a possible substantial alteration of the electronic properties upon switching to the metastable states, which could provide a plausible explanation for the detrimental impact on the catalytic activity.

Conclusion

We have described the design and synthesis of two photo-responsive bifunctionalised catalysts based on an overcrowded alkene core. The compounds show switching upon irradiation with 312 nm light, forming the corresponding metastable states with good photostationary states. Interestingly, they do not exhibit reversible switching and further investigations are required to determine the influence of the dimethylamine group on the reversibility of the switching processes of bistable switches based on overcrowded alkenes.

Switches St-(E)-1 and St-(Z)-1 display properties of photo-switchable catalytic activity control in the Michael addition reaction between (E)-3-bromo- β -nitrostyrene and 2,4-pentanedione. From the experimental results, both isomers displayed a decrease in catalytic activity upon irradiation to the metastable state, which could not be accredited to any detectable decomposition of the catalysts. As opposed to our initial assumption of controlling the activity of the thiourea moiety by steric hindrance or hydrogen bonding interactions, both E- and Z-isomers behave comparably as ON/OFF catalytic switches upon photoisomerization with clear changes in reaction rate and turnover frequency, regardless of the catalyst geometry. Therefore, such behaviour does not seem predominantly regulated by the steric hindrance exerted by the amine substituent around the thiourea moiety. As demonstrated in this work, an aromatic amine substituent was shown to be detrimental for the photochemical reversibility of the switching process and a poorly active catalytic moiety. These studies provide valuable insight into the requirements for the design of more effective and complex trifunctional molecular switches, which may allow the photocontrol of catalyst activity and selectivity in multicomponent reactions. Key to the successful development of these future catalysts will be a deeper understanding of the effect of ancillary functional groups on reversible photoswitching and the introduction of more active catalytic groups to ensure higher catalyst performance.

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- [1] R. S. Stoll, S. Hecht, *Angew. Chem. Int. Ed.* **2010**, *49*, 5054–5075; *Angew. Chem.* **2010**, *122*, 5176–5200.
- [2] R. Göstl, A. Senf, S. Hecht, *Chem. Soc. Rev.* **2014**, *43*, 1982–1996.
- [3] T. Imahori, S. Kurihara, *Chem. Lett.* **2014**, *43*, 1524–1531.
- [4] V. Blanco, D. A. Leigh, V. Marcos, *Chem. Soc. Rev.* **2015**, *44*, 5341–5370.
- [5] M. Vlatković, B. S. L. Collins, B. L. Feringa, *Chem. Eur. J.* **2016**, *22*, 17080–17111.
- [6] F. Würthner, J. Rebek, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 446–448; *Angew. Chem.* **1995**, *107*, 503–505.
- [7] R. Cacciapaglia, S. Di Stefano, L. Mandolini, *J. Am. Chem. Soc.* **2003**, *125*, 2224–2227.
- [8] D. Sud, T. B. Norsten, N. R. Branda, *Angew. Chem. Int. Ed.* **2005**, *44*, 2019–2021; *Angew. Chem.* **2005**, *117*, 2055–2057.
- [9] J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429–1432.
- [10] T. Imahori, R. Yamaguchi, S. Kurihara, *Chem. Eur. J.* **2012**, *18*, 10802–10807.
- [11] M. Samanta, V. Siva Rama Krishna, S. Bandyopadhyay, *Chem. Commun.* **2014**, *50*, 10577–10579.
- [12] M. Vlatković, L. Bernardi, E. Otten, B. L. Feringa, *Chem. Commun.* **2014**, *50*, 7773–7775.
- [13] A. Ueno, K. Takahashi, T. Osa, *J. Chem. Soc. Chem. Commun.* **1980**, 837–838.
- [14] W.-S. Lee, A. Ueno, *Macromol. Rapid Commun.* **2001**, *22*, 448–450.
- [15] H. Sugimoto, T. Kimura, S. Inoue, *J. Am. Chem. Soc.* **1999**, *121*, 2325–2326.
- [16] M. V. Peters, R. S. Stoll, A. Kühn, S. Hecht, *Angew. Chem. Int. Ed.* **2008**, *47*, 5968–5972; *Angew. Chem.* **2008**, *120*, 6056–6060.
- [17] O. B. Berryman, A. C. Sather, A. Lledó, J. Rebek, *Angew. Chem. Int. Ed.* **2011**, *50*, 9400–9403; *Angew. Chem.* **2011**, *123*, 9572–9575.
- [18] R. S. Stoll, M. V. Peters, A. Kuhn, S. Heiles, R. Goddard, M. Bühl, C. M. Thiele, S. Hecht, *J. Am. Chem. Soc.* **2009**, *131*, 357–367.
- [19] R. S. Stoll, S. Hecht, *Org. Lett.* **2009**, *11*, 4790–4793.
- [20] L. Osorio-Planes, C. Rodríguez-Esrich, M. A. Pericàs, *Org. Lett.* **2014**, *16*, 1704–1707.
- [21] T. Niazov, B. Shlyahovsky, I. Willner, *J. Am. Chem. Soc.* **2007**, *129*, 6374–6375.
- [22] D. Wilson, N. R. Branda, *Angew. Chem. Int. Ed.* **2012**, *51*, 5431–5434; *Angew. Chem.* **2012**, *124*, 5527–5530.
- [23] B. M. Neilson, C. W. Bielawski, *J. Am. Chem. Soc.* **2012**, *134*, 12693–12699.
- [24] B. M. Neilson, C. W. Bielawski, *Chem. Commun.* **2013**, *49*, 5453–5455.
- [25] B. M. Neilson, C. W. Bielawski, *Organometallics* **2013**, *32*, 3121–3128.
- [26] C.-T. Chen, C.-C. Tsai, P.-K. Tsou, G.-T. Huang, C.-H. Yu, *Chem. Sci.* **2017**, *8*, 524–529.
- [27] V. Lemieux, M. D. Spantulescu, K. K. Baldrige, N. R. Branda, *Angew. Chem.* **2008**, *120*, 5112–5115.
- [28] H. D. Samachetty, N. R. Branda, *Chem. Commun.* **2005**, *100*, 2840–2842.
- [29] D. Sud, R. McDonald, N. R. Branda, *Inorg. Chem.* **2005**, *44*, 5960–5962.
- [30] V. Lemieux, S. Gauthier, N. R. Branda, *Angew. Chem. Int. Ed.* **2006**, *45*, 6820–6824; *Angew. Chem.* **2006**, *118*, 6974–6978.
- [31] M. Shi, G.-N. Ma, J. Gao, *J. Org. Chem.* **2007**, *72*, 9779–9781.
- [32] Z. Erno, A. M. Asadirad, V. Lemieux, N. R. Branda, *Org. Biomol. Chem.* **2012**, *10*, 2787–2792.
- [33] D. Sud, T. J. Wigglesworth, N. R. Branda, *Angew. Chem. Int. Ed.* **2007**, *46*, 8017–8019; *Angew. Chem.* **2007**, *119*, 8163–8165.
- [34] J. Dai, Zhongran; Cui, Yaqin; Chen, Changjuan; Wu, *Chem. Commun.* **2016**, *52*, 8826–8829; Cui, Yaqin; Chen, Changjuan; Wu, *Chem. Commun.* **2016**, *52*, 8826–8829.
- [35] V. Sashuk, O. Danylyuk, *Chem. Eur. J.* **2016**, *22*, 6528–6531.

- [36] A. J. Teator, D. N. Lastovickova, C. W. Bielawski, *Chem. Rev.* **2016**, *116*, 1969–1992.
- [37] D. Zhao, T. M. Neubauer, B. L. Feringa, *Nat. Commun.* **2015**, *6*, 6652.
- [38] S. J. Wezenberg, M. Vlatković, J. C. M. Kistemaker, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 16784–16787.
- [39] M. Schliwa, G. Woehlke, *Nature* **2003**, *422*, 759–765.
- [40] W. M. Horspool, F. Lenci, *CRC Handbook of Organic Photochemistry and Photobiology*, Vols. 1, 2, 2nd Ed., CRC Press, Boca Raton, **2003**.
- [41] G. S. Kottas, L. I. Clarke, D. Horinek, J. Michl, *Chem. Rev.* **2005**, *105*, 1281–1376.
- [42] B. L. Feringa, *J. Org. Chem.* **2007**, *72*, 6635–6652.
- [43] T. Ikariya, M. Shibasaki, *Bifunctional Molecular Catalysis*, Springer, Berlin, **2011**.
- [44] W.-Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298–1310.
- [45] O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051–7071.
- [46] A. E. Allen, D. W. C. Macmillan, *Chem. Sci.* **2012**, *3*, 633–658.
- [47] A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.
- [48] N. Koumura, R. W. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **1999**, *401*, 152–155.
- [49] N. Koumura, E. M. Geertsema, M. B. van Gelder, A. Meetsma, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 5037–5051.
- [50] M. Klok, M. Walko, E. M. Geertsema, N. Ruangsapichat, J. C. M. Kistemaker, A. Meetsma, B. L. Feringa, *Chem. Eur. J.* **2008**, *14*, 11183–11193.
- [51] E. M. Geertsema, S. J. van der Molen, M. Martens, B. L. Feringa, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 16919–16924.
- [52] N. Ruangsapichat, M. M. Pollard, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 53–60.
- [53] T. Kudernac, N. Ruangsapichat, M. Parschau, B. Maciá, N. Katsonis, S. R. Harutyunyan, K.-H. Ernst, B. L. Feringa, *Nature* **2011**, *479*, 208–211.
- [54] J. Bauer, L. Hou, J. C. M. Kistemaker, B. L. Feringa, *J. Org. Chem.* **2014**, *79*, 4446–4455.
- [55] J. C. M. Kistemaker, S. F. Pizzolato, T. van Leeuwen, T. C. Pijper, B. L. Feringa, *Chem. Eur. J.* **2016**, *22*, 13478–13487.
- [56] V. Blanco, A. Carlone, K. D. Hänni, D. A. Leigh, B. Lewandowski, *Angew. Chem. Int. Ed.* **2012**, *51*, 5166–5169; *Angew. Chem.* **2012**, *124*, 5256–5259.
- [57] V. Blanco, D. A. Leigh, U. Lewandowska, B. Lewandowski, V. Marcos, *J. Am. Chem. Soc.* **2014**, *136*, 15775–15780.
- [58] B. Lewandowski, G. De Bo, J. W. Ward, M. Papmeyer, S. Kuschel, M. J. Aldegunde, P. M. E. Gramlich, D. Heckmann, S. M. Goldup, D. M. D'Souza, A. E. Fernandes, D. A. Leigh, *Science* **2013**, *339*, 189–193.
- [59] J. Beswick, V. Blanco, G. De Bo, D. A. Leigh, U. Lewandowska, B. Lewandowski, K. Mishi, *Chem. Sci.* **2015**, *6*, 140–143.
- [60] Y. Cakmak, S. Erbas-Cakmak, D. A. Leigh, *J. Am. Chem. Soc.* **2016**, *138*, 1749–1751.
- [61] M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; *Angew. Chem.* **2006**, *118*, 1550–1573.
- [62] Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601.
- [63] Y. Gao, Q. Ren, L. Wang, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13068–13071.
- [64] C. Yu, Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* **2011**, *17*, 770–774.
- [65] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919–5927.
- [66] X. Li, X.-S. Xue, C. Liu, B. Wang, B.-X. Tan, J.-L. Jin, Y.-Y. Zhang, N. Dong, J.-P. Cheng, *Org. Biomol. Chem.* **2012**, *10*, 413–420.
- [67] J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296.
- [68] D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.
- [69] D. H. R. Barton, B. J. Willis, *J. Chem. Soc. D* **1970**, 1225–1226.
- [70] R. M. Kellogg, S. Wassenaar, *Tetrahedron Lett.* **1970**, *11*, 1987–1990.
- [71] Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, Wiley, Hoboken, **2010**, pp. 575–581.
- [72] This atypical behaviour can be attributed to the presence of the dimethylamino group, because the non-functionalized scaffolds did not exhibit this behaviour. Also, it was observed that a longer irradiation time was required to reach PSS compared to systems without the dimethylamino group, suggesting that this moiety quenches the photoisomerization, possibly by Photoinduced electron transfer (PET). The reason why the dimethylamino group inhibits the backwards photoisomerization to a greater extent than the forward photoisomerization is not fully understood.
- [73] A photoequilibrium is established; in fact a small change in isomer ratio was observed upon irradiation at longer wavelength ($\lambda > 390$ nm), for example, for stable-(Z)-2 to metastable-(E)-2 isomers ratios: 7:93 at 365 nm to 14:86 at 420 nm (by ¹H NMR in CD₃CN).
- [74] Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659–6690.
- [75] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5592.
- [76] A. Berkessel, K. Roland, J. M. Neudörfl, *Org. Lett.* **2006**, *8*, 4195–4198.
- [77] G. Masson, C. Housseman, J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 4614–4628; *Angew. Chem.* **2007**, *119*, 4698–4712.
- [78] V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1–48.
- [79] V. S. Bryantsev, B. P. Hay, *J. Phys. Chem. A* **2006**, *110*, 4678–4688.

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