Gain of Function Recyclable Photoswitches: Reversible Simultaneous Substitution and Photochromism Generation

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Abstract

The use of molecular photoswitches has spread to virtually every field of pure and applied chemistry because of the extraordinary level of control they provide over the behavior of matter at smallest scales. Photoswitches possess at least two different states with distinct structures and/or electronics and further functionalization of their core chromophore structures is needed to tailor them for a specific application. In this work we present a different concept for the generation and use of molecular photoswitches. It allows not only simultaneous establishment of photochromism and functionalization, but also full recyclability of a non-photochromic precursor material. Using a high-yielding and reversible ammonium salt formation, a functional group is introduced into a symmetric precursor while at the same time a strong electronic push-pull character is established in the structure. The resulting desymmetrization leads to efficient photoswitching capacity and the functional group can be fully removed subsequently by a simple heating step recovering the precursor for another functionalization round. We finally demonstrate feasibility of this concept over two consecutive closed loop functionalization/photoswitching/recovery steps. This concept offers great potential in any chemical research and application driven area but especially for the creation of responsive reprogrammable materials, no-background photoswitch labeling, and sustainable chemistry.

Introduction

Molecular photoswitches are used extensively as high precision tools to introduce light responsiveness to the nanoscopic scale in all chemistry-related areas. At present a plethora of different photoswitch motives are available with distinct particular strengths that can be used rationally for tailored applications.[1, 2] The latter range from light responsive materials,[3-5] chemical biology,[6-9] catalysis,[10, 11] to molecular machines,[12-17] dissipative self-assembly,[18, 19] or energy storage[20, 21] to name a few. Recently, a number of new photoswitch motives have been developed in addition to long-time established azobenzenes, stilbenes, diarylethenes, or spiropyranes.[1, 2] These encompass for example Stenhouse dyes,[22-24] imidazolyl-radicals,[25, 26] hemipiperazines,[27] hydrazones,[28] homoaromatics,[29] or indigoids.[30-35] However, all photoswitches have in common that they alternate between at least two different states, which are distinct in geometry and/or electronic properties. Further, to make a photoswitch effective for an application, substitution with dedicated functional groups is crucial and such introduced functionality then needs to undergo strong and predictable changes upon photoswitching. Because substitutions are leading to covalent modification of photoswitches, a recycling and repurposing of a dedicated synthesized photoswitch itself is not straight forward and no attempts in such direction are currently made to the best of our knowledge. In the context of recycling, photoswitches have instead been used as ready-made outside tools to control recycling processes of a different functional molecule or material.[36, 37]

In this work we present a concept for the simultaneous establishment of photoswitching capability and covalent functionalization in a fully reversible and recyclable fashion (Figure 1). By making use of reversible covalent chemistry a symmetric precursor entity with no discernible photoswitching capacity is turned into a photoswitch via a reversible alkylation reaction. Such reversible alkylation of aniline is known for some time,[38] has been further developed by Lehn in the context of dynamic covalent chemistry,[39] and was used more recently to establish stereo-control over chiral ammonium ions.[40] For the purpose of this work alkylation introduces a functional group of choice and this group can be removed by simple heating recovering the precursor. Subsequently the same precursor can then be turned into a photoswitch for a different purpose by another alkylation with a different functional group, which also can be removed to recover the precursor and so on. Without a functionalization present the chromophore does not act as photoswitch, which eliminates the problem of unwanted background photoisomerization of unfunctionalized precursors. Crucial for the realization of this concept is a symmetric precursor for which we employ a diaryl-hemithioindigo (diaryl-HTI)[41] bearing the same dimethyl-aniline group twice in its diarylmolecular fragment (Figure 1). This precursor shows no photochromism and apparent photoisomerization because a double bond rotation leads to the exact same molecule. Alkylation at one of the two dimethyl-aniline groups however introduces a positive charge in the resulting ammonium ion and at the same time a strong cross-conjugated electronic push-pull system in the diaryl-moiety. As a result, pronounced photochromism and very good photoswitching between the now desymmetrized *Z* and *E* isomers is established using blue and red-light irradiation. A variety of different allylic, benzylic, or propargylic bromides can be used as alkylation reagents, all of which are removed at higher temperatures either in solution or even neat in vacuum. This concept enables a novel access to reversible construction of a photoswitchable functional entity and thus provides an unique opportunity for generating smart, recyclable, and reconfigurable molecules and materials.

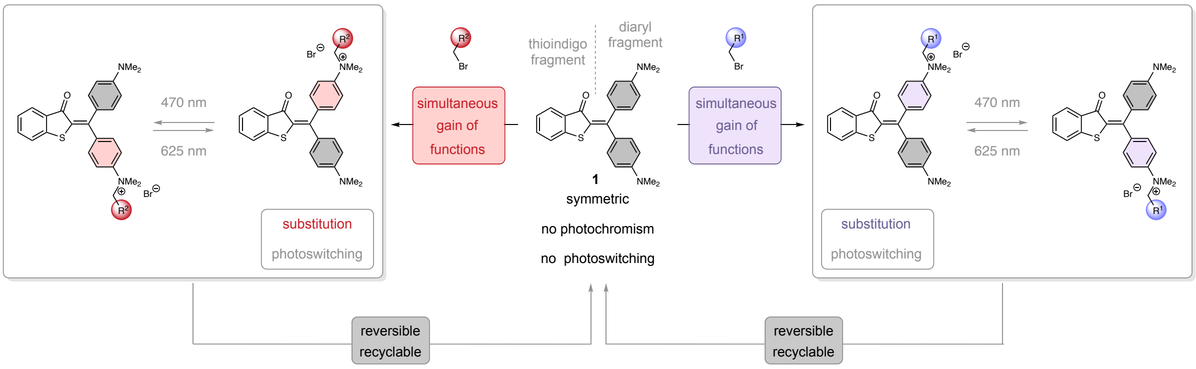
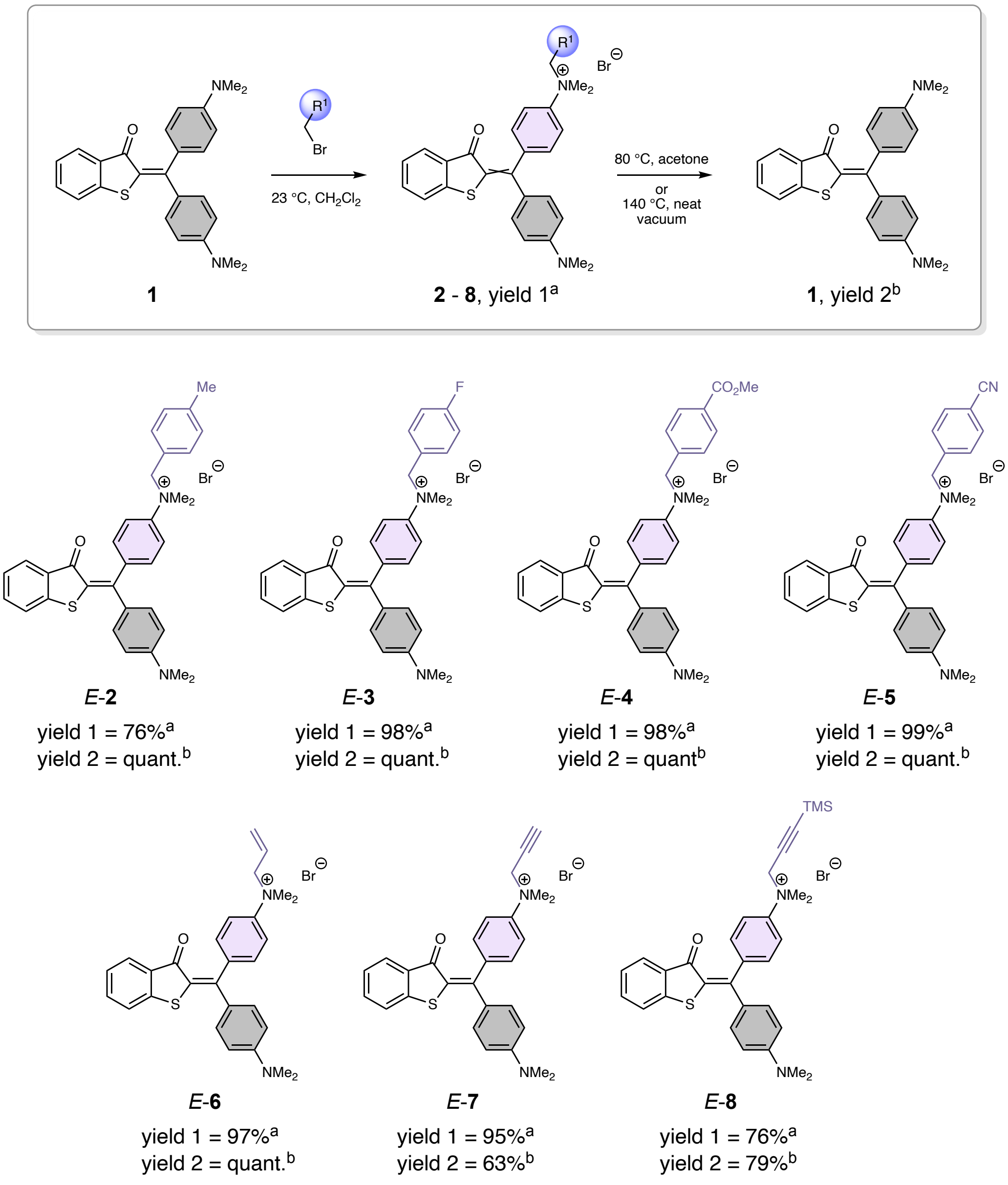


Figure 1 Concept of gain of function recyclable photoswitches. A symmetric precursor diaryl-HTI **1** without photochromism is turned into a capable photoswitch by introduction of a functional group. After alkylation of one of the two anilines, a strong push-pull system is established leading to strong photochromism and pronounced photoisomerization capacity. Depending on the alkylating agent different functionalities can be introduced at the same time, which are removed under heating recovering precursor **1**. The cycle can then be repeated with a different functional alkyl group using the very same recycled precursor.

Results and Discussion

The dianiline-HTI **1** precursor is a derivative of recently established double-bond substituted hemiindigoids[42, 43] and was synthesized according to a protocol published earlier.[41] Reversible introduction of an alkyl-substituent at one aniline nitrogen required a suitable reactive group and a variety of benzyl, allyl, or propargyl bromides were chosen for this purpose. After mixing **1** with different alkyl bromides in CH_2Cl_2 solution the corresponding push-pull photoswitches

2 – **8** were obtained in very good yields of >94% except for derivatives **2** and **8**, which were isolated in 76%. Crucial for high yields is the use of 2-20 equivalents of the respective alkyl bromide to minimize both, double alkylation and incomplete conversion. Because of the pronounced polarity differences between non, mono- and dialkylated products, isolation of the desired mono-alkylated ones is facilitated by normal phase column chromatography. The synthetic scheme and all reversibly functionalized derivatives **2** – **8** are shown in Figure 2.



1 **2 - 8**, yield 1[a] **1**, yield 2[b]

E-**2**
yield 1 = 76%[a]
yield 2 = quant.[b]

E-**3**
yield 1 = 98%[a]
yield 2 = quant.[b]

E-**4**
yield 1 = 98%[a]
yield 2 = quant[b]

E-**5**
yield 1 = 99%[a]
yield 2 = quant.[b]

E-**6**
yield 1 = 97%[a]
yield 2 = quant.[b]

E-**7**
yield 1 = 95%[a]
yield 2 = 63%[b]

E-**8**
yield 1 = 76%[a]
yield 2 = 79%[b]

Figure 2 Reversible synthesis of photoswitchable functionalized diaryl-HTIs **2** – **8** and recovery of the symmetric precursor **1**. The structures of diaryl-HTIs **2** – **8** are shown schematically. [a] isolated yields; [b] yields determined by *in-situ* heating experiments via ^{1}H NMR spectroscopy.

After synthesis the thermal stabilities of the isomers and photoswitching properties of **2** – **8** were investigated (Figure 3). Assignment of isomers could be made by an ROE NMR experiment for derivative **2** directly, which could be transferred to all other photoswitches because of their very similar structural and electronic properties. In all cases the *Z* configured isomers are metastable and revert to the stable *E* isomers in the dark, typically within hours to days at 23 °C in polar aprotic solvents like DMSO or DMF. Protic solvents like MeOH accelerate the thermal isomerization and an extrapolated half-life of 10 s at 23 °C was found for *Z*-**4**. In all cases, a thermal equilibrium is reached with both isomers being present and the *E* isomer strongly favored. The corresponding free enthalpy differences ΔG as well as the Gibbs energies of activation for the thermal isomerizations $\Delta G^{\ddagger}$ could be obtained from equilibrium and kinetic analyses. All determined values are summarized in Table S2 in the Supporting Information. With established thermal stabilities in the min-h time range photoswitching could be investigated conveniently at 23 °C to omit interference of thermally induced isomerizations. Photoswitches **2** – **8** undergo efficient photoswitching in polar solvents and DMSO and DMF were chosen because they solubilize the highly polar compounds well enough to allow for NMR analysis (see Figure 3 for selected examples). As the push-pull system generated during functionalization is essentially the same for all derivatives the molar absorptions, photochromism, and isomer accumulation in the photostationary state (pss) are very similar for all photoswitches **2** – **8** (see Table 1 for all measured values). Absorptions are quite distinct for *E* and *Z* isomers, with the former possessing a long-wavelength maximum at around 490 nm and the latter one at around 520 nm. This ca. 30 nm difference between absorption maxima establishes a pronounced photochromism, which is visible to the naked eye and is comparable to the one observed earlier for cross-conjugated push-pull diaryl-HTIs.[41] It can be explained by the strong electron acceptor moiety of the ammonium ion paired with a very strong aniline donor. Photoisomerization from the *E* to the *Z* isomers is affected most effectively by 470 nm light leading to enrichment of the *Z* isomer in 71%-79% in the pss. Conversely, the *Z* to *E* photoisomerization proceeds under 625 nm irradiation and 90%-quant. of the *E* isomer is obtained. Thus, proper photoswitching is established as a result of mono-alkylation, which is well competitive with state-of-the-art performances, especially for visible and red-light responsive, photoswitches.

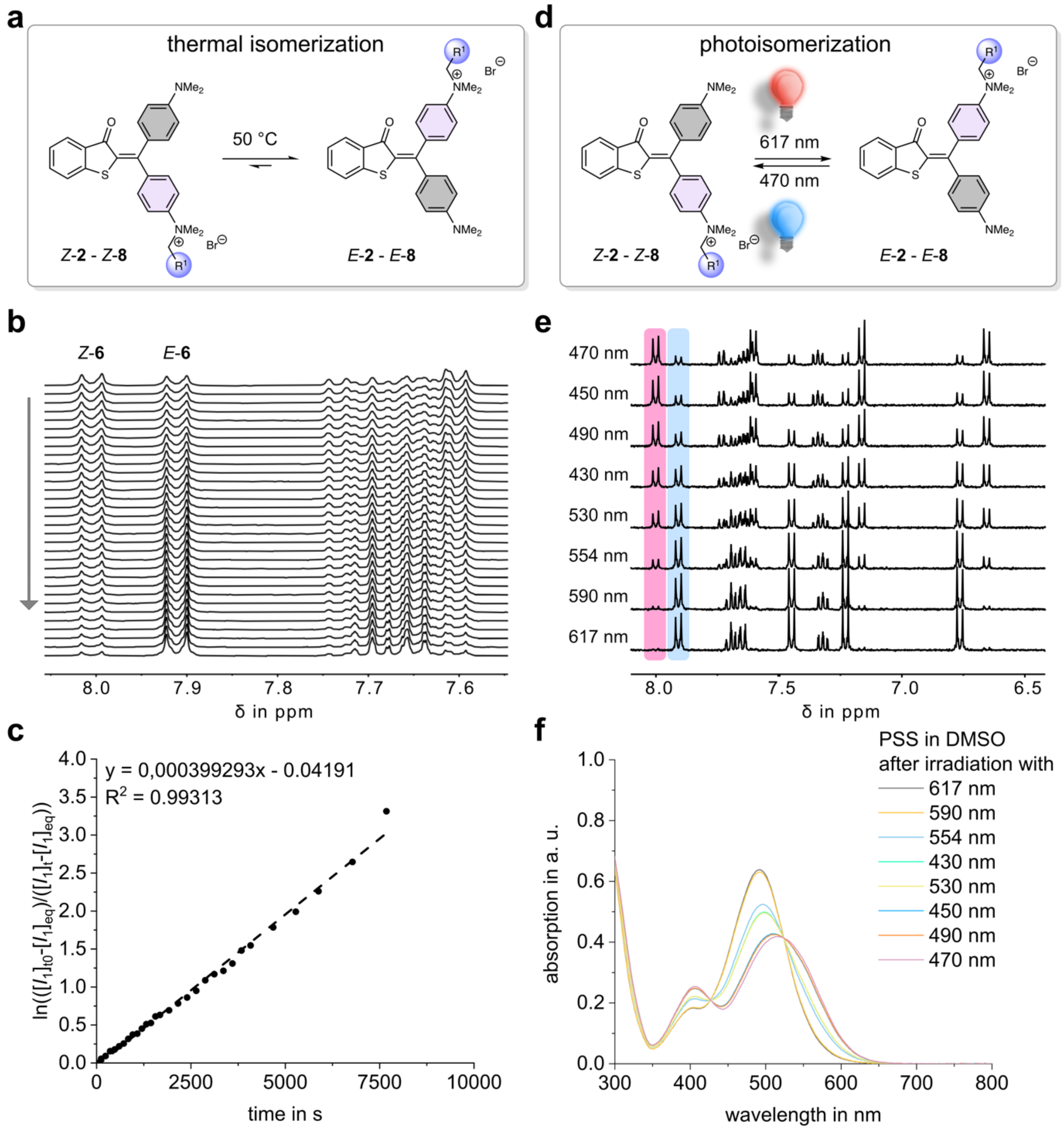


Figure 3 Thermal stability and photoswitching properties of functionalized diaryl-HTIs. All derivatives **2** to **8** behave very similar, therefore data are shown exemplarily for derivative **6**. **a** Thermal isomerization of functionalized diaryl-HTIs. **b** Thermal isomerization of **6** in DMSO solution at 22 °C in the dark. A thermal equilibrium is reached with 85% *E*-**6** as the dominant isomer. **c** Kinetic analysis of thermal *Z*-**6** to *E*-**6** isomerization. **d** Photoisomerization behavior of functionalized diaryl-HTIs. **e** ^{1}H NMR spectra of **6** in DMSO-d_6 at 22 °C recorded after irradiation with different indicated wavelengths to the pss. **f** UV/Vis absorption spectra of **6** in DMSO at 22 °C after irradiation with different indicated wavelengths to the pss.

In the next step, dealkylation and recycling of the precursor diaryl-HTI **1** was tested for all derivatives (see Figure 2 for individual yields). Benzyl-derivatives **2** – **8** can be dealkylated under prolonged heating in acetone solution at 50 °C while in DMSO solution the stability is much higher and only minimal dealkylation was found (which in turn enabled the study of thermal double bond isomerizations in the dark as described above). After heating for several hours precursor **1** was reformed quantitatively as judged by *in situ* ^{1}H NMR spectroscopy. For allyl-derivative **6** and fluoro-benzyl derivative **3** dealkylation can also be achieved by heating the neat substance to 140 °C in vacuum (ca. $5 \cdot 10^{-2}$ mbar) leading to convenient recovery of **1** in nearly quantitative isolated yield in both cases. Therefore, the recovery of precursor **1** is highly effective from the corresponding alkylated photoswitches **2** – **8** and isolation is straight forward by simple column chromatography. Depending on the temperature tolerance of introduced functionalities, lower temperatures can be used for the dealkylation in solution or higher temperatures neat.

A closed-loop experiment was performed (Figure 4) in which precursor **1** was converted into the corresponding photoswitch **6** using allyl-bromide in 90% yield in CH_2Cl_2 solution. The obtained **6** was subsequently photoisomerized reversibly between the *Z* (78% in the pss at 470 nm irradiation) and the *E* isomer (96% in the pss at 625 nm irradiation) showcasing proper photoswitch function. Afterwards a heating step at 140 °C under vacuum ($5.8 \cdot 10^{-2}$ mbar) allowed recovery of **1** in 97% yield. The recovered material of **1** was then alkylated with 4-fluorobenzyl bromide and the resulting photoswitch **3** was also reversibly photoisomerized between the *Z* (78% in the pss at 470 nm irradiation) and the *E* isomer (97% in the pss at 625 nm irradiation) in DMF solution. Afterwards precursor **1** was recovered from **3** again in 93%. The closed loop cyclic experiment establishes successful recycling of a photoswitch using the concept of simultaneous gain of function and substitution. A very good overall yield of 73% recovery of precursor **1** was achieved over two different and successive functionalization/photoswitching/defunctionalization steps.

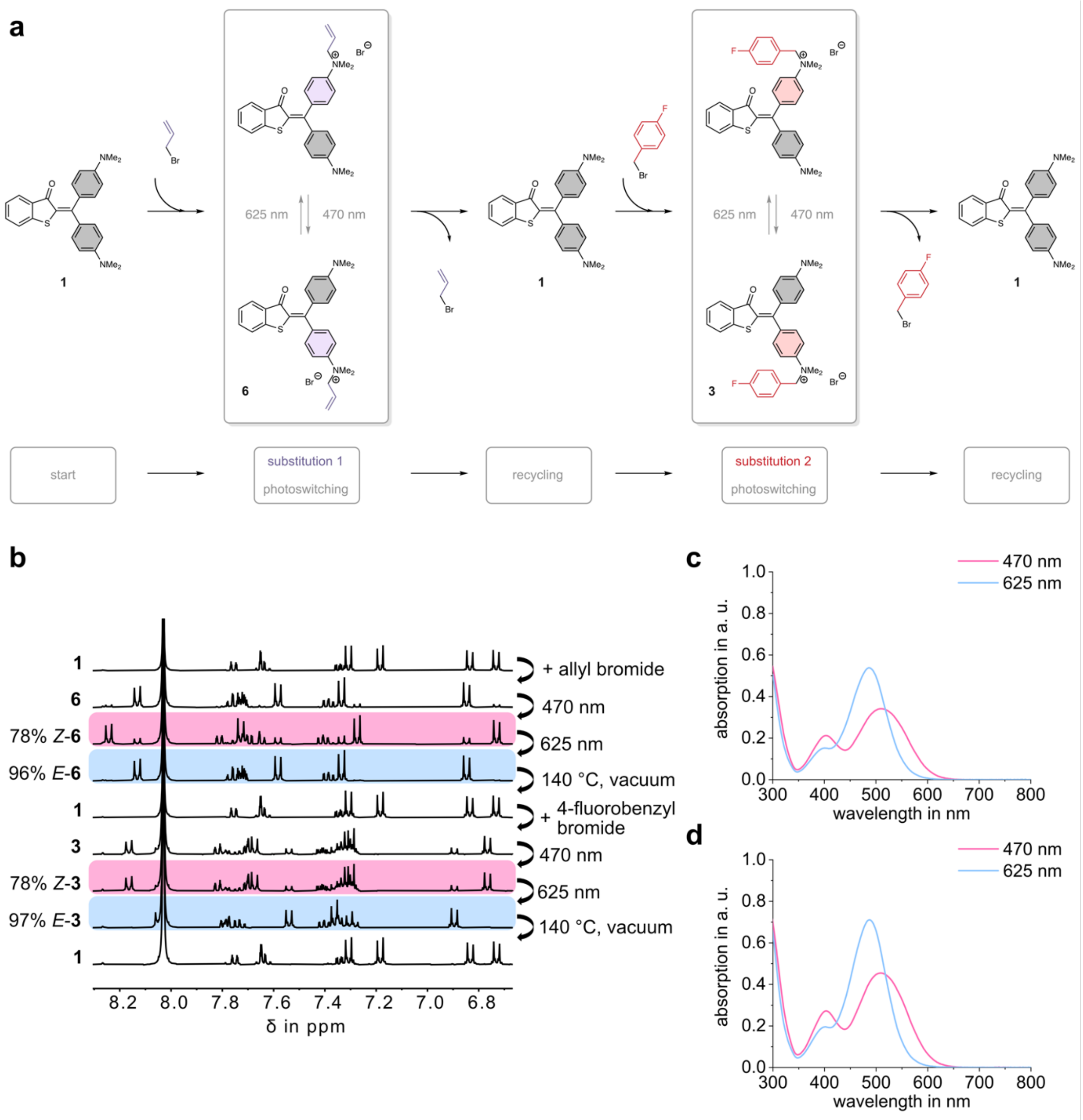


Figure 4 Cyclic experiment consisting of transforming precursor **1** first into allyl-functionalized photoswitch **6** with viable reversible photoisomerization capacity, subsequent recycling of precursor **1**, followed by a second transformation to 4-fluorobenzyl-functionlized photoswitch **3**, and a final recycling step recovering precursor **1** again. **a** Schematic representation of the close loop cyclic experiment. **b** ^{1}H NMR spectra (400 MHz, DMF-*d*$_7$, 22 °C) recorded after each individual step of the cycle allowing to additionally quantify the individual efficiencies *in situ*. Photoisomerization steps are highlighted with pink and blue colors. **c** UV/Vis spectra recorded after *E* to *Z* and *Z* to *E* photoisomerization of **6** in DMF solution at 22 °C. **d** UV/Vis spectra recorded after *E* to *Z* and *Z* to *E* photoisomerization of **3** in DMF solution at 22 °C.

In conclusion, we demonstrate a concept for the simultaneous establishment of substitution and photoswitching in a versatile molecular precursor. The precursor itself possesses no photochromism because of its symmetry, which eliminates unwanted background photoswitching of unfunctionalized remaining starting material. The substitution reaction leads to a symmetry braking and introduction of a powerful electronic push-pull character in the molecule endowing it with efficient photoisomerization capacity. The functionalization can be fully reversed and the precursor molecule is recovered in a simple heating step establishing its recyclability for multiple different functionalizations and photoswitching purposes. This was demonstrated by a closed loop cyclic experiment with two sequential functionalization/photoswitching/recovery steps to recycle the precursor in high yield. With this concept we establish reversible gain of photoswitching simultaneously with functionalization and a potent recycling approach for photochromes that can be transferred to many chromophore motives. It will open up a plethora of novel applications for photoswitches especially in the context of reprogrammable smart molecules and materials research, sustainable functional chemistry, as well as chemical biology. We also foresee great use as an efficient photoswitch labeling strategy and for the purpose of high-throughput screenings because of the ease of functionalization, the resulting robust and constant photoresponse, and facile precursor recovery. Our future efforts are headed in these directions.

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