Sulfur and Azobenzenes, a Profitable Liaison: Straightforward Synthesis of Photoswitchable Thioglycosides with Tunable Properties

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Abstract: Azobenzene photoswitches are valuable tools for controlling properties of molecular systems with light. We have been investigating azobenzene glycoconjugates to probe carbohydrate-protein interactions and to design glyco-azobenzene macrocycles with chiroptical and physicochemical properties modulated by light irradiation. To date, direct conjugation of glycosides to azobenzenes was performed by reactions providing target compounds in limited yields. We therefore sought a more effective and reliable coupling method. In this paper, we report on a straightforward thioarylation of azobenzene derivatives with glycosyl thiols as well as other thiols, thereby increasing the scope of azobenzene conjugation. Even challenging unsymmetrical conjugates can be achieved in good yields via sequential or one-pot procedures. Importantly, red-shifted azoswitches, which are addressed with visible light, were easily functionalized. Additionally, by oxidation of the sulfide bridge to the respective sulfones, both the photochromic and the thermal relaxation properties of the core azobenzene can be tuned. Utilizing this option, we realized orthogonal three-state photoswitching in mixtures containing two distinct azobenzene thioglycosides.

Introduction

Controlling properties of biomolecules in a reversible manner is a captivating task that holds formidable potential to study complex processes in living organisms. Light is an excellent external stimulus in such applications because it offers a high degree of spatiotemporal resolution, can be precisely regulated, and is often non-destructive in the visible range. Thus, chemists have developed molecules that can be switched between two forms by means of light irradiation, called photoswitches.[21] Among those, azobenzene has arisen as one of the largest and best studied class of photochromic compounds. Indeed, it exhibits intense UV-visible absorption properties that can be finely tuned by substitution of the azobenzene phenyl rings, and especially undergoes remarkable spatial modification upon trans/cis isomerization of the azo bond.[3]

The combination of carbohydrates with azobenzene to form azobenzene glycoconjugates (ABGs) has emerged as a promising strategy to modulate macroscopic properties of carbohydrate in a spatiotemporally controlled manner.[30] For instance, ABGs have found applications in material sciences as photoswitchable hydrogelators,[31] micellar reactors,[32] and liquid crystals.[33] During the past two decades, they also have gained increasing interest in the field of glycobiology as tools to probe carbohydrate-protein recognition. Jayaraman and co-workers, reported in 2002 the synthesis and photosomerization properties of azobenzene glyoclusters based on lactose and galactose, and they studied their binding behavior towards the high-affinity lectin peanut agglutinin (PNA).[34] Our group reported on the immobilization of photosensitive glycoligands of the bacterial lectin FimH on gold surface, as self-assembled monolayers (glyco-SAMs), and also at the surface of human cells.[35] Hence, the orientation of α-D-mannoside ligands was reversibly switched by photoirradiation, allowing for the control of specific adhesion of live bacterial cells.[36–c] More recently, we introduced photosensitive glycoazobenzene macrocycles, which can change their molecular shape and thus their chiroptical or solubility properties.[37a, b, 10] In the same direction, Xie and colleagues reported azobenzene glycomacroclactones,[31] some of which were stereoselectively cyclized by intramolecular glycosylation.[32]

In order to maximize the transmission of geometrical information from the azo hinge to the sugar as well as the chirality transfer from the sugar to the molecular switch, a direct connection between both moieties is required. For this purpose, glycosylation of hydroxyazobenzene derivatives is undoubtedly the most obvious reaction in comparison to other approaches such as ester or amide bond formation, urea or thiourea bridging and copper-catalyzed azide-alkyne cyclo-
addition (CuAAC). The direct conjugation of azobenzene to carbohydrate derivatives by glycosylation was previously achieved in our group employing glycosyl acetimidate or thioglycoside donors, or Mitsunobu conditions. However, the use of dihydroxyazobenzene (DHAB) as glycosyl acceptor to build azobenzene bis-glycosides resulted in inconsistent results and limited yields. Therefore, we have recently investigated this reaction in detail and concluded that the scope of glycosyl donors and activation methods is very limited. Likewise, the use of the Mitsunobu reaction for the conjugation of DHAB to the anomeric center or primary positions of glycosides was highly substrate-dependent and often led to low to moderate yields. In view of the contrasting results obtained with the aforementioned methods, we sought for a reliable conjugation reaction effective on a wide scope of substrates, also including more sophisticated azoswitches such as ortho-substituted azobenzenes and diazocine, an ortho-ethylened bridge azobenzenes. The latter azo derivatives are important red-shifted switches which can be addressed with visible light and are thereby compatible with biological media. We focused on a strategy based on halogenides (iodide, bromide) of azo derivatives and glycosyl thiols as electrophilic and nucleophilic partners, respectively, in a palladium-catalyzed Buchwald-Hartwig-Migita cross-coupling reaction (Figure 1).

Although azobenzene derivatives bearing sulfide motifs have already been reported, direct thioarylation of azoswitches, to the best of our knowledge, has never been disclosed. Moreover, systematic studies on the influence of sulfur-based substituents on photochromic and thermal relaxation properties of azobenzene derivatives are lacking.

The use of isoelectronic sulfur instead of oxygen has several advantages. First, glycosyl thiols are stable towards mutarotation allowing a complete stereocontrol of the anomeric configuration. In addition, thiosaccharides are known to be resistant towards enzyme-catalyzed glycosidic bond cleavage. Furthermore, our synthetic approach allows for facile derivatization of ortho-substituted azobenzene or diazocine derivatives, that otherwise requires tedious synthetic sequences. Also, azobenzene conjugates with a sulfide bridge in para position may have similar photochromic behavior than their para-oxygenated counterparts. Importantly, the sulfur atom can be oxidized to yield the respective sulfones, resulting in a modified electron density of the azobenzene unit and thus allowing to modulate photochromic properties.

In this account, we demonstrate the full potential of S-azobenzene conjugates through their direct synthesis and their tunable photochromic properties. The scope of the palladium-catalyzed coupling was studied using a wide range of azobenzene and thiol substrates, especially glycosyl thiols. In particular, we achieved the functionalization of valuable red-shifted azo-switches and the one-pot synthesis of unsymmetrical conjugates. After converting sulfide bridges into sulfones, we investigated the influence of sulfur oxidation on photochromic and thermal relaxation properties. Last but not least, orthogonal three-state photoswitching of two distinct derivatives mixed in solution was shown by NMR spectroscopy.

Results and Discussion

**Bis-functionalization of p,p'-diiodoazobenzene derivatives with glycosyl thiols**

Since azobenzene bis-glycosides are key intermediates in the synthesis of photoswitchable glycomacrocycles, we started our investigation by studying the conjugation of p,p'-diiodoazobenzene derivatives with glycosyl thiols (Scheme 1). As electrophiles of the Buchwald-Hartwig-Migita cross-coupling, the azobenzene 1 was chosen as a reference besides tetra-ortho-fluoroazobenzene 5 and diazocine 6. Tetra-ortho-fluoroazobenzene derivatives present two main special features, a red shift of the trans $\pi\rightarrow\pi^*$ absorption band, thus allowing trans $\rightarrow$ cis switching with visible light irradiation, and a high thermal stability of the metastable cis isomer. However, to date, only a few functionalized tetra-ortho-fluoroazobenzenes have been reported, due to multi-step and low yielding syntheses. Also the functionalization of diazocine is demanding. Hence, this photoswitch has rarely found applications, which is unfortunate.

**Figure 1.** Palladium-catalyzed S-arylation of azobenzene derivatives (depicted here with glycosyl thiols) for the preparation of photoswitchable conjugates and subsequent sulfur oxidation enabling the modulation of the photochromic properties.
as it represents a cyclic azoswitch with reverse thermodynamic stability and addressability with visible light in comparison to azobenzene,[22] as nucleophiles, three differently substituted glucosyl thiols, 7–9, were used together with the thiglycoside 10 carrying a primary SH functional group.

In preliminary experiments, we compared Pd(OAc)₂/Xantphos and the precatalyst Xantphos-PdG₃ as catalytic systems for the cross-coupling reaction, and observed that the latter was superior, in accordance with previous studies on S-arylation with glycosyl thiols.[17] Therefore, in this account, we focused on the use of Xantphos-PdG₃ to obtain the cross-coupling products 11–16 at room temperature in 5 to 20 min with only 2 mol% of catalyst used. The azobenzene derivatives 1 and 5 showed excellent conversions in this reaction. Neither the bulky 6-silylether in 8 nor the demanding N-Troc protecting group of the glucosamine derivative 9 impaired the coupling reaction. Products 11–15 were obtained in 69% to 92% isolated yield while 16 was obtained quantitatively. Conversion of the diazobenzene diiodide 6 required a higher temperature (80°C) and thus we performed the corresponding coupling reactions in 1,4-dioxane to isolate 17 and 18 in 75% and 59% yield, respectively. Given the excellent results obtained in the preparation of symmetrical thio-ligated glyco-azoswitches, we next explored the synthesis of unsymmetrical azobenzene conjugates.

**Monofunctionalization of unsymmetrical azobenzenes with different thiols**

In order to assess the scope of the Buchwald-Hartwig-Migita cross-coupling with respect to the nature of the thiol substrate, we studied the monofunctionalization of differently substituted p-iodoazobenzenes with various thiols (Scheme 2). The mono-substituted azobenzene 2 was used as a reference compound and coupled with the glucosyl thiol 7, affording the expected coupling product 23 within minutes in 90% yield. The reaction of the azobenzene derivative 3 with 7 gave product 24 in 87% yield. We were delighted to observe an excellent chemoselectivity between iodine and bromine substituents in 3 as reported by Messaoudi et al.[17b] hence allowing for a subsequent substitution of the bromine substituent.

The azobenzene 4 showed a good compatibility of the cross-coupling reaction with hydroxy groups while providing phenolic conjugates such as 25 (in 93%), which can be functionalized further by alkylation or glycosylation, for instance. Also, thiophenol 19 smoothly reacted with the hydroxyazobenzene 4 to give product 26 in 86% yield. The N-Boc-protected cysteine methyl ester 20 was also readily ligated with 4, although a longer reaction time was required, affording product 27 in 68% yield. Finally, aliphatic thiols bearing competitive hydroxy (21) or amino (22) groups were coupled with 4, providing products 28 and 29 in 81% and 47% yield, respectively. In case of cysteamine (22), however, the reaction required a higher temperature (70°C) and a lower isolated yield was obtained due to incomplete conversion. This might be explained with the amino group acting as an ancillary ligand of the cross-coupling catalyst and thus impairing the reaction. Importantly, no side-product was observed in the reaction of 4 and 22, indicating that N-arylation did not occur. Very interestingly, the tetra-ortho-fluoroazobenzene 5 could be effectively mono-functionalized to afford product 30 in 81% yield, while the bis-conjugated product was isolated in 14% yield. This was achieved by using an excess of azobenzene (2 equiv.) at 0°C under dilute conditions. These conditions allow

**Scheme 1.** Preparation of symmetrical azobenzene bis-thio-glycosides via thioarylation catalyzed by Xantphos-PdG₃ (2 mol%) with thiol (2 equiv.) and Et₃N (2 equiv.) Conditions A: THF, RT; conditions B: 1,4-dioxane, 80°C; compounds 11–16 were prepared according to conditions A whereas compounds 17 and 18 were achieved according to conditions B; TBDPS: tert-butyldiphenylsilyl; Troc: trichloroethoxycarbonyl.
for the sequential preparation of unsymmetrical azobenzene glycoconjugates based on the azobenzene diiodide 5.

Encouraged by these excellent results, we investigated the preparation of hetero-bis-azobenzene conjugates, especially focusing on one-pot procedures.

**Hetero-bis-functionalization of azobenzenes with glycosyl thiols**

Before undertaking the one-pot synthesis of unsymmetrical cross-coupling products, the sequential synthesis of bis-azobenzene glycosides starting from 3 and 4 (cf. Scheme 2) was studied. Hence, starting from the previously synthesized unsymmetrical azobenzene monothioglycosides 24 and 25, respectively, we prepared the corresponding hetero-bis-azobenzene glycosides 31 and 32 (Scheme 3). Conjugate 31 was obtained in good yield (73 %) by substitution of the para-bromide group in 24, in the presence of Xantphos-PdG3 at 60 °C. On the other hand, the phenolic glycosyl acceptor 25 was reacted with the glycosyl thioimidate donor 33 (prepared in one step from thiol 7), using BF₃-etherate as glycosylation promoter, to provide compound 32 in 65 % yield.

We then turned our attention to one-pot procedures for preparing unsymmetrical azobenzene conjugates (Scheme 4). First of all, we exploited the sharp difference in reactivity between the para-iodo and para'-bromo substituents in 3 to perform sequential S-arylation reactions in one-pot. In order to guarantee a proper coupling in the second step, we systematically added the same amount of catalyst as the initial load (1 mol %). Thus 3 was first substituted by thiol 8 at room temperature and then by thiol 7 at 60 °C to provide product 31 in a good yield of 73 %. According to an analogous procedure, 3 was successfully coupled to both 7 and the cysteine derivative 20 to give conjugate 34 in 70 % yield.

Next, based on the good result obtained in preparing the mono-functionalized conjugate 30 (Scheme 2), we conducted a one-pot synthesis in which stoichiometric amounts of 5 and thiol 7 were reacted at −10 °C, followed by addition of an excess of thiol 8, affording 35 in a fair yield of 51 %. Finally, we prepared the conjugate 36, bearing a thioacetate-terminated linker, suitable for the fabrication of glyco-SAMs on a gold substrate.
Azobenzene 4 was first coupled with thiol 7 at room temperature and then, the alkylation of the phenol with the tosylated spacer 37 in DMF at 80 °C followed to yield 57% of the desired product 36.

With this collection of azobenzene S-glycosides in hand, the oxidation of the sulfur atom was studied next.

Oxidations at sulfur atom

The oxidation of the ligating sulfur atoms in the prepared glyco-azoswitches to obtain the respective sulfones is relevant because electron withdrawing substituents in para-positions of azobenzenes such as sulfonyl groups influence both π →π* and n →π* transitions. We therefore expected a hypsochromic shift of the π →π* band, compared to the parent sulfide derivative and also an increased separation of the n →π* bands of each isomer as reported in case of ortho-substituted azobenzenes. In addition, altered relaxation kinetics of the sulfone cis isomer were expected. For the oxidation of the monosubstituted compound 23, meta-chloroperbenzoic acid (mCPBA) was used. A slight excess of mCPBA in dichloromethane afforded a mixture of sulfoxide 38a and sulfone 38b which were isolated in 43% and 53% yield, respectively (Scheme 5). Since we were also interested in studying sulfoxides, the mixture 38a/38b was formed on purpose because the two species were easy to separate and thus, we could obtain both from a single reaction. On the other hand, sulfoxide derivatives of the bis-glycosides were not considered as prime target molecules as the configuration of the stereogenic sulfur center of the sulfoxide groups is difficult to control and hence diastereomeric mixtures would be obtained, which are complicated to analyze. Mixed conjugates having a sulfone and a sulfide at each end of the azobenzene moiety were prepared following a two-step sequence. Hence, oxidation of compound 24 was achieved, affording sulfone 39 in 87% yield, and subsequent coupling with thiol 7 afforded compound 40 in 46% yield. In the same manner, the sulfone 41 was obtained in 68% yield from 30 and next reacted with thiol 7 to provide 42 in 59% yield. Finally, the complete oxidation of molecules 11 and 12 afforded the disulfone derivatives 43 and 44 in 79% and 78% yield, respectively.

Photochromic properties of the synthesized azobenzene glycoconjugates

Nine compounds of the synthesized glycoconjugates were selected (Table 1) in order to investigate their photochromic properties and the relaxation of the metastable isomers. This specific selection was made to evaluate the influence of substitution patterns in para- and ortho-positions of the azobenzene core as well as the impact of the sulfur oxidation state. The main spectroscopic data are listed in Table 1. Figure 2 shows the absorption spectra of the assessed molecules in DMSO.
provided a good basis to evaluate the influence of sulfur oxidation on the photochromic behaviour of the respective conjugates. In line with a previous study on O-glycoside analogues,\textsuperscript{[26]} \(23\) in the ground state shows two absorption maxima at 351 nm and 441 nm, respectively corresponding to \(\pi\rightarrow\pi^*\) and \(n\rightarrow\pi^*\) transitions (Table 1, entry 1, Figure 2a). Increasing the oxidation state of the sulfur atom resulted in a hypsochromic shift of the \(\pi\rightarrow\pi^*\) band in case of \(\text{trans}\) isomers, the effect being stronger for the sulfone derivative (Table 1, entries 2 and 3, Figure 2a). Photostationary states (PSS) containing high amounts of \(\text{cis}\) isomer were reached upon irradiation with UV light (365 nm) for \(23\) and \(38\) a. In contrast, 68\% of \(\text{cis}\)-38 b was obtained after photoisomerization at the same wavelength. In addition, sulfur oxidation leads to a bathochromic shift of the \(n\rightarrow\pi^*\) transition in the \(\text{trans}\) isomer whereas it gets slightly shifted to lower wavelengths in the \(\text{cis}\) form (Figure 2d).

**Table 1.** Spectroscopic data of selected azobenzene thioglycosides: maxima (\(\lambda_{\text{max}}\)) of \(\pi\rightarrow\pi^*\) and \(n\rightarrow\pi^*\) transitions of \(\text{trans}\) and \(\text{cis}\) isomers,\textsuperscript{[a]} with the corresponding separation of the \(n\rightarrow\pi^*\) bands (\(\Delta\lambda_{n\rightarrow\pi^*}\)) in each isomeric state, composition of the photostationary state (PSS) mixtures at different wavelengths of irradiation\textsuperscript{[b]} and half-lives of thermal relaxation.\textsuperscript{[c,d]}

| Entry | Compound | \(\lambda_{\text{max}}\) \(\pi\rightarrow\pi^*\) trans [nm] | \(\lambda_{\text{max}}\) \(n\rightarrow\pi^*\) trans [nm] | \(\lambda_{\text{max}}\) \(n\rightarrow\pi^*\) cis [nm] | \(\Delta\lambda_{n\rightarrow\pi^*}\) [nm] | PSS 365 nm\textsuperscript{h} | PSS 435 nm\textsuperscript{h} | PSS 520 nm\textsuperscript{h} | PSS 590 nm\textsuperscript{h} | \(t_{1/2}\) \(\text{cis}\) |
|-------|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1     | 23       | 351             | 441             | 439             | 2               | 5/95            | 78/22           | –               | –               | 10 h            |
| 2     | 38a      | 334             | 451             | 434             | 17              | 10/90           | 84/16           | –               | –               | 20 h            |
| 3     | 38b      | 327             | 453             | 432             | 21              | 32/68           | 87/13           | –               | –               | 2.1 h           |
| 4     | 11       | 374             | ND              | 445             | –               | 14/86           | 74/26           | 82/18           | 95/5\textsuperscript{d} | 3.0 h           |
| 5     | 40       | 366             | ND              | ND              | –               | 31/69           | 86/14           | 60/20           | 86/14\textsuperscript{e} | 1.4 h           |
| 6     | 43       | 317             | 464             | 432             | 21              | 32/68           | 87/13           | –               | –               | –               |
| 7     | 12       | 369             | 460             | 433             | 27              | 20/80           | 80/20           | 30/70           | 16/84\textsuperscript{d} | 100 h           |
| 8     | 42       | 358             | 464             | 429             | 35              | 32/68           | 86/14           | 32/68           | 8/92\textsuperscript{d} | 93 h            |
| 9     | 44\textsuperscript{f} | 310             | 472             | 423             | 49              | 97/3            | 91/9            | 28/72           | 9/91\textsuperscript{d} | 31 min         |

\(\text{[a]}\) UV-Vis spectra were recorded in DMSO (50 \(\mu\)M) at 25 °C; ND: not determined because of the overlap between the \(\pi\rightarrow\pi^*\) and \(n\rightarrow\pi^*\) transition bands;\(\text{[b]}\) composition at the PSS were measured by NMR in DMSO-d6 (1 mM), after 2 min irradiation at the appropriate wavelength; mixtures at the PSS are given as \(\%\text{(trans)}\)/\(\%\text{(cis)}\);\(\text{[c]}\) the half-lives of \(\text{cis}\) isomers were measured by UV-Vis spectroscopy in DMSO (50 \(\mu\)M) at 40 °C;\(\text{[d]}\) For compounds 12 and 42, thermal relaxation parameters were measured at 65, 70, 75 and 80 °C, then an Arrhenius plot provided the corresponding rate constant and half-life at 40 °C;\(\text{[e]}\) after 2 min irradiation with UV (365 nm) or green (520 nm) light, the sample was irradiated for 5–20 min with orange (590 nm) light;\(\text{[f]}\) PSS were measured by NMR in MeCN-d3 (1 mM) after 2 min irradiation at the appropriate wavelength.
isomers of homo bis-thioglucosides trans and cis afforded conjugates: upon sulfur oxidation, the 
zenes decreases moderately for mixed sulfide/sulfone conjugates (Figure 2b and 2c), the corresponding similar trend as for monosubstituted derivatives. Whereas the impacts the thermal relaxation rate of the sufficient to achieve separation is greater in the oxidized counterparts although not arising from the azo bond improve the separation of IRRADIATION OF

Figure 2. Overlays of absorption spectra and corresponding expansions in the area of the n−π* transitions for compounds 23, 38a, and 38b (a, d), 11, 40, and 43 (b, e), 12, 42, and 44 (c, f); inset: expansion in the 500–600 nm area for spectra of 12, 42 and 44; solid lines: trans isomers, dotted lines: cis-rich PSS after irradiation for 2–20 min at an appropriate wavelength; spectra were recorded in DMSO (50 μM) at 25°C.

In fact, effective conversion to the cis isomer (72% in the PSS) was achieved by illumination of 44 with green light (Table 1, entry 9) and 97% and 91% trans-44 were obtained, respectively, upon UV- and blue light irradiation.

We also looked at the possibility to affect the isomerization with orange light (590 nm), which is beneficial for using azobenzene conjugates in biological studies. Although the molar extinction in the near red range is quite weak (see inset in Figure 2f), such effective photoisomerization performed by addressing the tail of the n−π* band has been already reported in case of ortho-substituted azobenzenes.19d,27,28 Strikingly, trans–cis switching was indeed effective upon irradiation of compounds 12, 42 and 44 at 590 nm. In addition, the amount of cis isomer obtained in the PSS at 590 nm was larger (84–92%) than after photoisomerization with light of separation is greater in the oxidized counterparts although not sufficient to achieve trans–cis isomerization with visible light.

The increase of the sulfur oxidation state also strongly impacts the thermal relaxation rate of the cis isomer as the half-life drops by a factor of 5 from the sulfide 23 (10 h) to the sulfone 38b (2.1 h) while it is 20 h in case of the sulfone 38a (Table 1, entries 1–3). The absorption spectra of the p,p'-difunctionalized compounds 11, 40, 43 and 12, 42, 44 show a similar trend as for monosubstituted derivatives. Whereas the trans isomers of homo bis-thioglucosides 11 and 12 exhibit absorption maxima around 370 nm for the π−π* band (Table 1, entries 4 and 7, Figure 2b and 2c), the corresponding λmax decreases moderately for mixed sulfide/sulfone conjugates 40 and 42 (Table 1, entries 5 and 8). Oxidation of both sulfide bridges to sulfones (compounds 43 and 44) causes a dramatic hypsochromic shift (over 50 nm compared to 11 and 12, respectively) of the π* transition (Table 1, entries 6 and 9). Variation of the n−π* band cannot be properly observed with molecules 11 and 40 due to a strong overlap with the π−π* bands in trans isomers undergoes a red shift while it is blue-shifted in cis isomers. As a consequence, the gap between the two bands arising from the ortho-fluoro groups gets further increased up to 49 nm after sulfur oxidation. This result is not surprising as it was reported that electron withdrawing groups in para-position to the azo bond improve the separation of n−π* bands.16d,17b Irradiation of 11, 40, 12 and 42 with light of 365 nm afforded cis-rich mixtures in the PSS, however with lower amounts of cis isomer in case of mixed sulfide/sulfone 40 and 42. The overlap between the respective trans and cis π−π* bands in 40 and 42 may result from the observed moderate blue shift of trans π−π* as well as a likely red shift of the cis π−π* transition (Figure 2b and c). When compounds 11, 12, 40 and 42 were exposed to blue light (435 nm), the trans isomer dominated in the PSS mixture (74%–86%). Addressing 12 and 42 with green light (520 nm) afforded 70% and 68% of cis isomer in the equilibrium mixture whereas 11 and 40 were mostly converted into trans at the same wavelength. Due to the strong blue shift of the π−π* band, it was not possible to isomerize the disulfone 43 using UV (365 nm) nor visible light and we observed a scarce change in the absorption spectrum after minutes of exposure to UV-B (280–315 nm). Nevertheless, the ortho-fluoro-substituted disulfone compound 44 presents interesting photochromic features.
lower wavelengths (see Table 1). We observed that the time needed to reach the PSS at 590 nm is dependent on the trans/cis composition of the starting mixture: the higher the amount of trans, the longer the irradiation time (see Supporting Information). Exposure to orange light was also carried out with compounds 11 and 40, and in both cases, the extent of trans isomer was significantly increased after irradiation times in the same range than those needed for the fluorinated derivatives.

Regarding the thermal back isomerization of metastable cis isomers at 40 °C, cis-40 relaxes nearly two-fold faster than cis-11, with respective half-lives of 3 h and 1.4 h. As expected, cis-12 is highly thermally stable (t1/2 = 100 h) whereas the cis-disulfone 44 relaxes over 190-fold quicker (t1/2 = 31 min).[28] The half-life of the hetero conjugate cis-42 was found to be in same range as the one of cis-12 with a value of 93 h.

Finally, the diazocine bis-glycoconjugate 17 was evaluated, also in DMSO. Figure 3 shows representative absorption spectra and Table 2 lists the main photochromic features of the diazocine conjugate. Irradiation of 17 at 400 nm (Figure 3), yielded 71% of the trans isomer in the PSS while cis-17 was quantitatively recovered upon exposure to green or orange light. Moreover, a half-life of 22 min (40°C) was measured for trans-17. Interestingly, the trans—cis isomerization process can also be achieved quantitatively in the red area (660 nm, Figure 3) and even with far-red light (690 nm), although longer irradiation time was required in the last case.[30] To the best of our knowledge, only red-shifted diazocines containing a heteroatom in the bridging part showed similar features.[16d] Hence, our thioarylation approach allows for facile preparation of functional and red light-switchable diazocines in only three steps.

Orthogonal photoswitching in mixtures

Based on the photoisomerization results described above, we anticipated the possibility to achieve orthogonal switching by irradiating mixtures of two distinct conjugates in solution. Orthogonal photoswitching is of great interest for controlling two distinct parameters in complex light-responsive molecular systems.[22,31] In fact, it may be difficult to orthogonally achieve each of the four possible isomers using light stimuli only,14b due to overlaps between the absorption bands of the respective switches, and systems solely fueled by light require fine-tuning of irradiation conditions.27b,31 Hence, we selected two pairs of relevant molecules that may be addressed at least with light of three different wavelengths. We investigated by NMR spectroscopy equimolar mixtures of compounds 11 and 44, on the one hand, and of 17 and 44, on the other hand (Figure 4). We expected to observe switching between trans/trans, cis/trans and trans/cis mixtures in case of the pair 11/44. In an alternative fashion, the pair 17/44 would allow a selection between cis/trans, cis/cis and trans/trans states. By operating with light in the near UV – green range, it was possible to reach PSS mixtures with over 70% of the major isomer for each of the two compounds present in solution, thus achieving the purposes described above (see Table 3). The cis/trans ratios observed in each PSS in case of the mixtures were found to be very similar to those measured with the single molecules. This indicates that, at the concentration chosen for these experiments, the photoswitchable conjugates may not disturb photochromic properties of each other.

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**Table 2. Spectroscopic data of diazocine conjugate 17: maxima (λmax) of n→π* transitions for diazocine conjugate 17; inset: expansion in the 600–700 nm area; dashed black line: ground state, blue line: PSS after 2 min irradiation at 400 nm, red line: PSS after 30 s irradiation at 600 nm; spectra were recorded in DMSO (100 μM) at 25 °C.**

| Compound | λmax n→π* cis [nm] | λmax n→π* trans [nm] | Δλmax cis/ trans [nm] | λ1/2 trans [nm] | PSS 400 nm | PSS > 500 nm [%] | t1/2 trans [min] |
|----------|---------------------|----------------------|------------------------|-----------------|------------|-----------------|-----------------|
| cis-40   | 407                 | 90                   | 71:29                  | > 1:99          | 22 min     |                 |                 |
| cis-12   | 407                 | 90                   | 71:29                  | > 1:99          | 22 min     |                 |                 |
| cis-11   | 407                 | 90                   | 71:29                  | > 1:99          | 22 min     |                 |                 |
| cis-44   | 407                 | 90                   | 71:29                  | > 1:99          | 22 min     |                 |                 |

[a] UV-Vis spectra were recorded in DMSO (50–100 μM) at 25 °C.
[b] Composition at the PSS were measured by NMR in DMSO-d6 (1 mM), after 2 min irradiation at the appropriate wavelength; mixtures at the PSS are given as %trans/%cis; [c] the half-life of trans-17 was measured by UV-Vis spectroscopy in DMSO (50 μM) at 40 °C; [d] irradiations at 520, 590, 630, 660 and 690 nm were achieved, leading to a quantitative recovery of cis-17 in each case.

**Table 3. Isomer ratios measured by 1H NMR spectroscopy of equimolar mixtures of 11/44 and 17/44, respectively, in d2-MeCN (1 mM, 300 K), after irradiation with light of 365 nm, 400 nm, 435 nm or 520 nm.**

| Mixture | 365 nm trans: cis | 400 nm trans: cis | 435 nm trans: cis | 520 nm trans: cis |
|---------|--------------------|--------------------|--------------------|-------------------|
| 11      | 17:83              | 78:22              | 78:22              |                   |
| 44      | 97:3               | 90:10              | 27:73              |                   |
| 17      | –                  | 72:28              | 29:71              | > 1:99            |
| 44      | –                  | 97:3               | 91:9               | 27:73             |

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Conclusion

In conclusion, we disclosed a straightforward and effective preparation of sulfur-based azobenzene conjugates, based on a Buchwald-Hartwig-Migita cross-coupling reaction. This synthetic approach serves the dual purpose of a direct functionalization of azoswitches including red-shifted derivatives and of photochromic tuning of the ligation products. We demonstrated the high modularity of this approach by the synthesis of a wide scope of conjugates including especially challenging unsymmetrical compounds via one-pot procedures. Although we mostly focused on the use of glycosyl thiols, we showed that the coupling is compatible with other kind of thiols and also tolerates other unprotected functional groups. Importantly, we could easily functionalize valuable ortho-fluorinated azobenzene and diazocine, without the need of long and tedious reaction sequences. The photochromic and thermal relaxation properties of mono- and disubstituted ABGs and the influence of sulfur oxidation on these features were investigated in great detail showing that the presence of sulfur-containing groups (sulfide, sulfoxide and sulfone) in para-position of the azobenzene moiety imparts favorable photoisomerization behavior with efficient switching in both cis/trans directions upon exposure to light of appropriate wavelength. Especially, the ortho-fluorinated conjugates can be effectively addressed with visible light, including trans—cis isomerization by irradiation with light of 590 nm. In addition, increasing sulfur oxidation state allows for tuning absorption maxima and increasing the separation of $n\rightarrow\pi^*$ bands, as well as it affects the thermal relaxation rate of the metastable cis isomer. Finally, we demonstrated the orthogonal photoisomerization in solutions containing mixtures of two distinct ABGs.

With this efficient functionalization method in hand, our next efforts will be focused on the preparation of photoresponsive carbohydrate ligands for lectin recognition and also on the synthesis of azobenzene glycomacrocycles. The modularity of our approach will allow the elaboration of complex molecular systems, comprising several distinct photoswitches, in which more than one parameter can be controlled with light. We believe that this work provides a new useful synthetic methodology for the design of photoswitchable molecules used in chemical, material and biological sciences.

Experimental Section

Experimental procedures for the synthesis of new compounds and related characterization data as well as procedures and data for photochromic irradiation experiments and relaxation measurements are given in the Electronic Supporting Information file.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: azobenzene · glycoconjugate · photoswitching · thioarylation · visible light

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