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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 glycoazobenzene 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.[1] 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.[2]

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The combination of carbohydrates with azobenzene to form azobenzene glycoconjugates (ABGs) has emerged as a promising strategy to modulate macroscopic properties of carbohydrates in a spatiotemporally controlled manner.[3] For instance, ABGs have found applications in material sciences as photoswitchable hydrogelators,[4] micellar reactors[5] and liquid crystals.[6] 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 photoisomerization properties of azobenzene glycoclusters based on lactose and galactose, and they studied their binding behavior towards the high-affinity lectin peanut agglutinin (PNA).[7] Our group reported on the immobilization of photoresponsive glycoligands of the bacterial lectin FimH on gold surface, as self-assembled monolayers (glyco-SAMs), and also at the surface of human cells.[8] Hence, the orientation of α-D-mannoside ligands was reversibly switched by photoirradiation, allowing for the control of specific adhesion of live bacterial cells.[8a–c] More recently, we introduced photoresponsive glycoazobenzene macrocycles, which can change their molecular shape and thus their chiroptical or solubility properties.[9a,b,10] In the same direction, Xie and colleagues reported azobenzene glycomacrolactones,[11] some of which were stereoselectively cyclized by intramolecular glycosylation.[12]

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,[8,9a,13] or Mitsunobu conditions.[9b,14] However, especially 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.[13] 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.[13] 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[15] and diazocine, an *ortho*-ethylene bridged azobenzene.[16] 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).[17] Although azobenzene derivatives bearing sulfide motifs have already been reported,[18,19] 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.[20] Furthermore, our synthetic approach allows for facile derivatization of *ortho*-substituted azobenzene or diazocine derivatives, that otherwise requires tedious synthetic sequences.[15,21,22] 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,[23] besides tetra-*ortho*-fluoroazobenzene **5**,[23] and diazocine **6**.[16c] Tetra-*ortho*-fluoroazobenzene derivatives present two main special features, a red shift of the *trans* n→π* absorption band, thus allowing *trans*→*cis* switching with visible light irradiation, and a high thermal stability of the metastable *cis* isomer.[15] However, to date, only a few functionalized tetra-*ortho*-fluoroazobenzenes have been reported, due to multi-step and low yielding syntheses.[21] Also the functionalization of diazocine is demanding. Hence, this photoswitch has rarely found applications, which is unfortunate

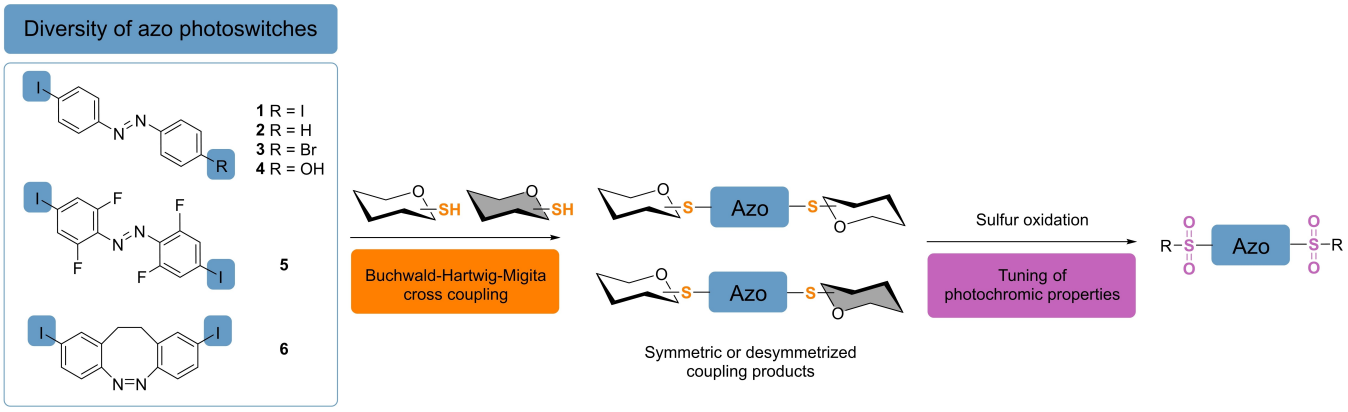
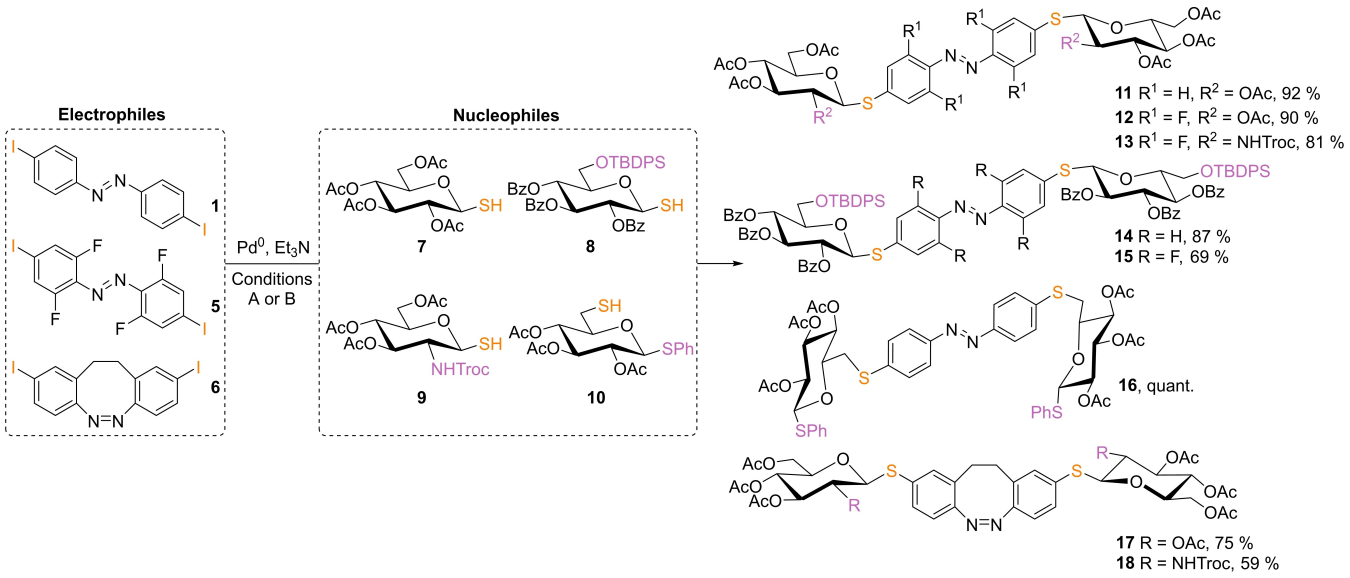


Figure 1. Palladium-catalyzed *S*-arylation of azobenzene derivatives (depicted here with glycosyl thiols) for the preparation of photoswitchable conjugates and subsequent sulfur oxidation enabling the modulation of the photochromic properties.



Scheme 1. Preparation of symmetrical azobenzene bis-thioglycosides via thioarylation catalyzed by Xantphos-PdG3 (2 mol%) with thiol (2 equiv.) and Et_3N (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.

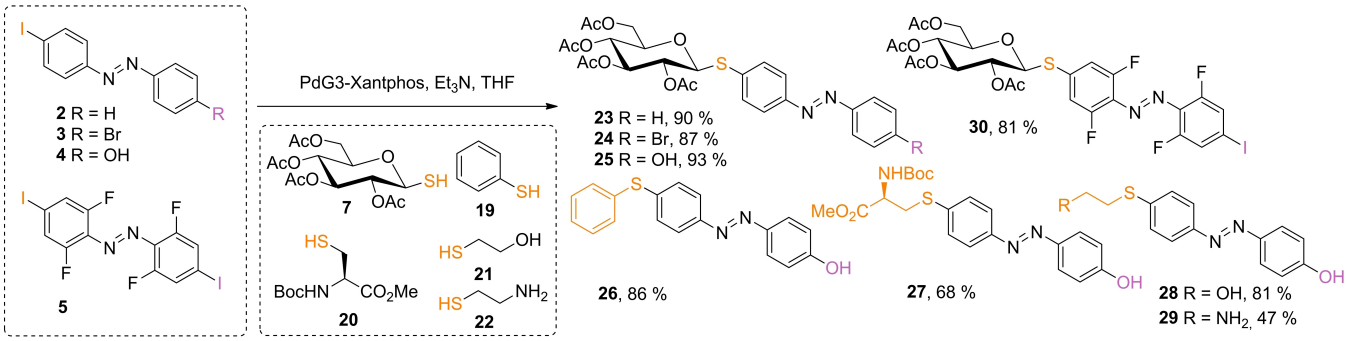
as it represents a cyclic azoswitch with reverse thermodynamic stability and addressability with visible light in comparison to azobenzene.[22] As nucleophiles, three differently substituted glucosyl thiols, **7**–**9**, were used together with the thioglycoside **10** carrying a primary SH functional 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 NTroc 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 diazocine 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 2. Monofunctionalization of differently substituted *p*-iodoazobenzene derivatives with various thiols. Conditions for preparation of compounds **23**–**29**: the thiol (1–1.2 equiv.) and the azobenzene (1–1.2 equiv.) were stirred in THF in presence of PdG3-Xantphos (1–5 mol%) and Et_3N (1–1.4 equiv.) at RT except for **29** which was obtained after heating at 70 °C; conditions for preparation of **30**: the thiol and an excess of the azobenzene (2 equiv.) were stirred at 0 °C in the presence of 1 mol% catalyst and Et_3N (1 equiv.).

for the sequential preparation of unsymmetrical azobenzene glycoconjugates based on the azobenzene diiodide **5**.

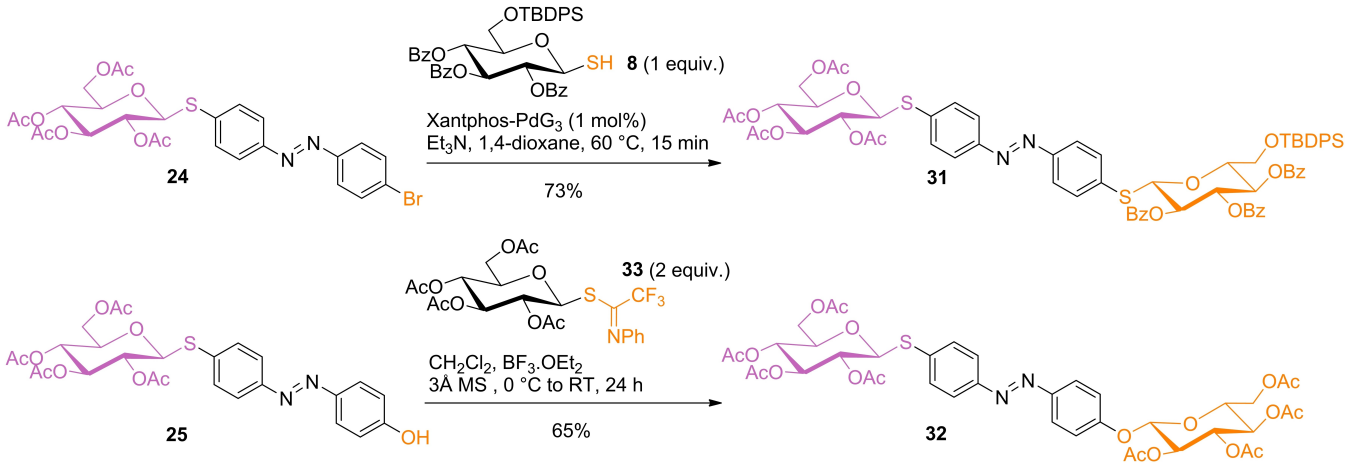
Encouraged by these excellent results, we investigated the preparation of hetero-bis-azobenzene conjugates, especially focusing on one-pot procedures.

Hetero-bis-functionalization of azobenzenes with glycosyl thiols

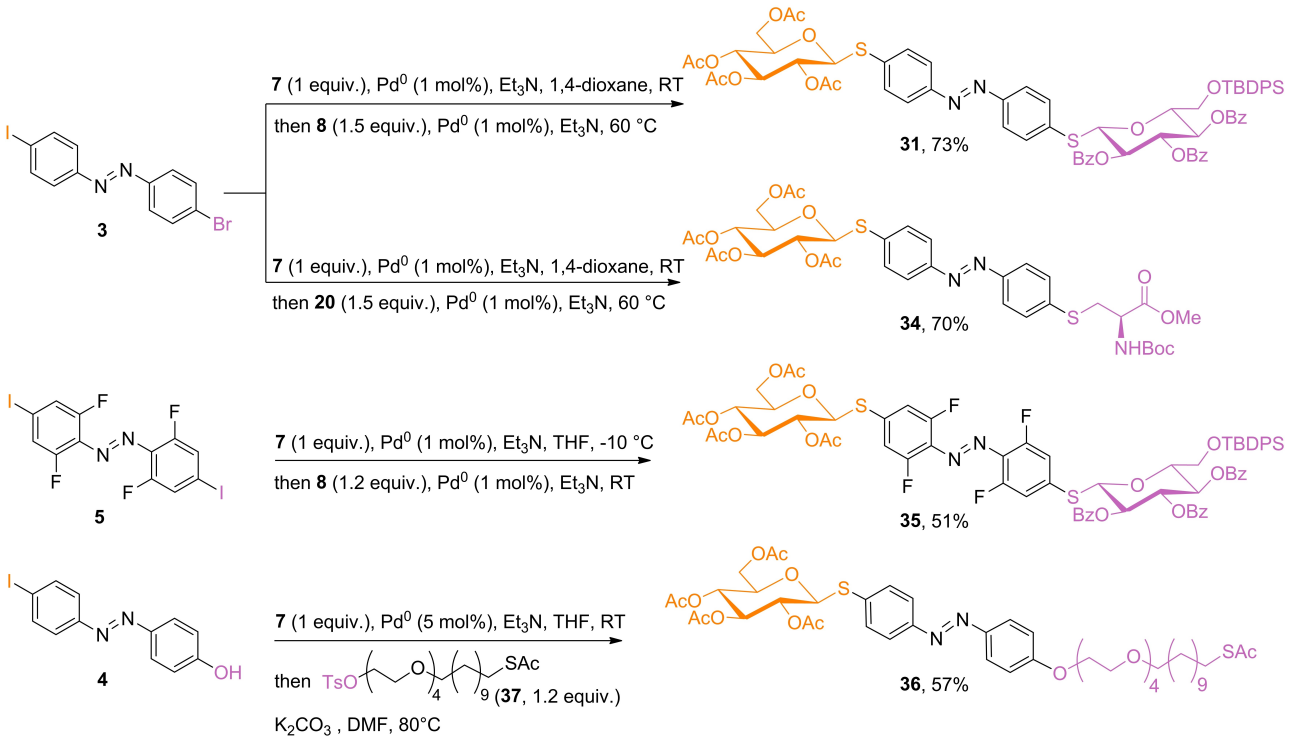
Before undertaking the one-pot synthesis of unsymmetrical cross-coupling products, the sequential synthesis of bis-azobenzene glycosides starting from **3** and **4** (cf. Scheme 2) was studied. Hence, starting from the previously synthesized unsymmetrical azobenzene monothioglycosides **24** and **25**, 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**),[24] using BF_3-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 **7** at room temperature and then by thiol **8** 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



Scheme 3. Preparation of unsymmetrical azobenzene bis-glycoconjugates according to two sequential conjugation reactions (two sequential cross-coupling reactions or cross-coupling followed by glycosylation, respectively).



Scheme 4. Preparation of unsymmetrical azobenzene hetero-bis-conjugates in a one-pot fashion. Pd^0: Xantphos-PdG3.

surface. 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

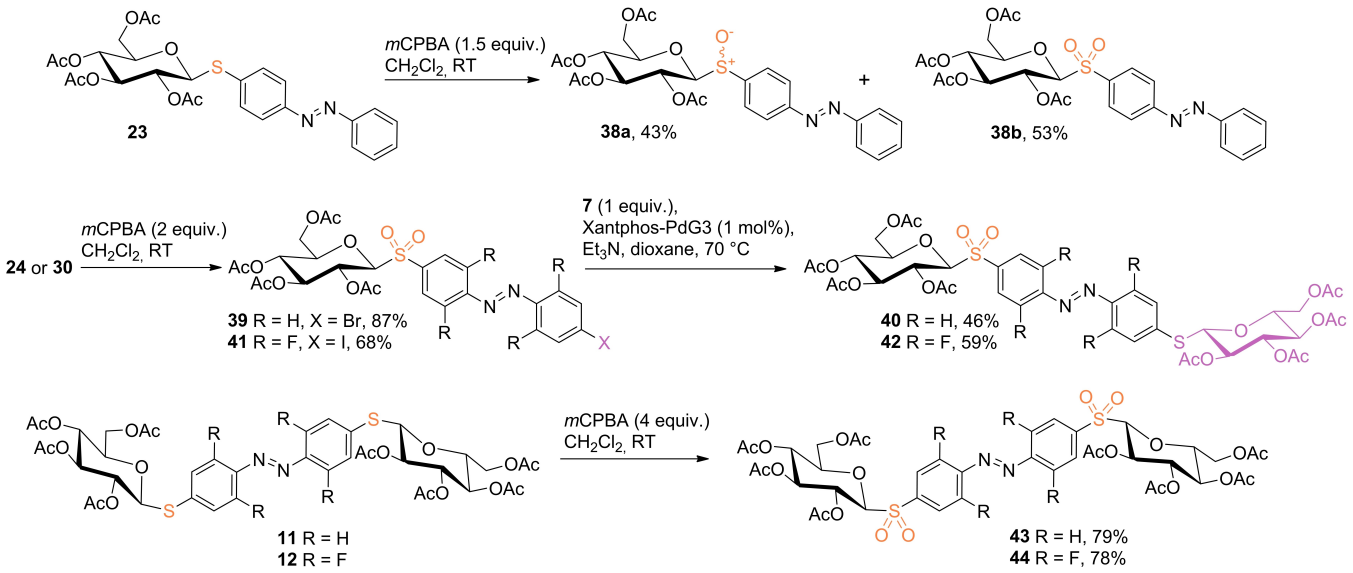
The oxidation of the ligating sulfur atoms in the prepared glyco-azoswitches to obtain the respective sulfones is relevant because electron withdrawing substituents in *para*-positions of azobenzenes such as sulfonyl groups influence both π→π* and n→π* transitions.[15d,19d,25] We therefore expected a 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.[15] In addition, altered relaxation kinetics of the sulfone *cis* isomer were expected.[25]

For the oxidation of the monosubstituted compound **23**, *meta*-chloroperbenzoic acid (*m*CPBA) was used. A slight excess of *m*CPBA 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

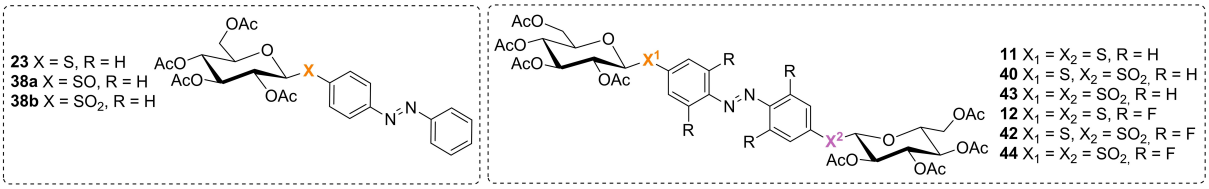
Nine compounds of the synthesized glycoconjugates were selected (Table 1) in order to investigate their photochromic properties and the relaxation of the metastable isomers. This specific selection was made to evaluate the influence of substitution patterns in *para*- and *ortho*-positions of the azobenzene 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.

The first subset of molecules, which comprises the monosubstituted derivatives **23**, **38a** and **38b** (Table 1, entries 1–3)



Scheme 5. *m*CPBA-mediated oxidations of the sulfur linkages to afford sulfoxide (**38 a**) or sulfone (**38 b**, **43**, **44**) derivatives. Mixed products bearing both sulfide and sulfone functions (**40**, **42**) were synthesized in a sequential fashion.

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



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

[a] UV-Vis spectra were recorded in DMSO (50 μM) at 25 °C; ND: not determined because of the overlap between the π→π* and n→π* transition bands; [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-lives of *cis* isomers were measured by UV-Vis spectroscopy in DMSO (50 μM) at 40 °C; [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; [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; [f] PSS were measured by NMR in MeCN-d3 (1 mM) after 2 min irradiation at the appropriate wavelength.

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,[26] **23** in the ground state shows two absorption maxima at 351 nm and 441 nm, respectively corresponding to π→π* and *n*→π* transitions (Table 1, entry 1, Figure 2a). Increasing the oxidation state of the sulfur atom resulted in a hypsochromic shift of the π→π* band in case of *trans* isomers, the effect being stronger for the sulfone derivative (Table 1, entry 2 and 3, Figure 2a). Photostationary states (PSS) containing high amounts of *cis* isomer were reached upon irradiation with UV light (365 nm) for **23** and **38 a**. In contrast, 68% of *cis*-**38 b** was obtained after photoisomerization at the same wavelength. In addition, sulfur oxidation leads to a bathochromic shift of the *n*→π* transition in the *trans* isomer whereas it gets slightly shifted to lower wavelengths in the *cis* form (Figure 2d). Consequently, compared to the sulfide **23**, the *n*→π* band

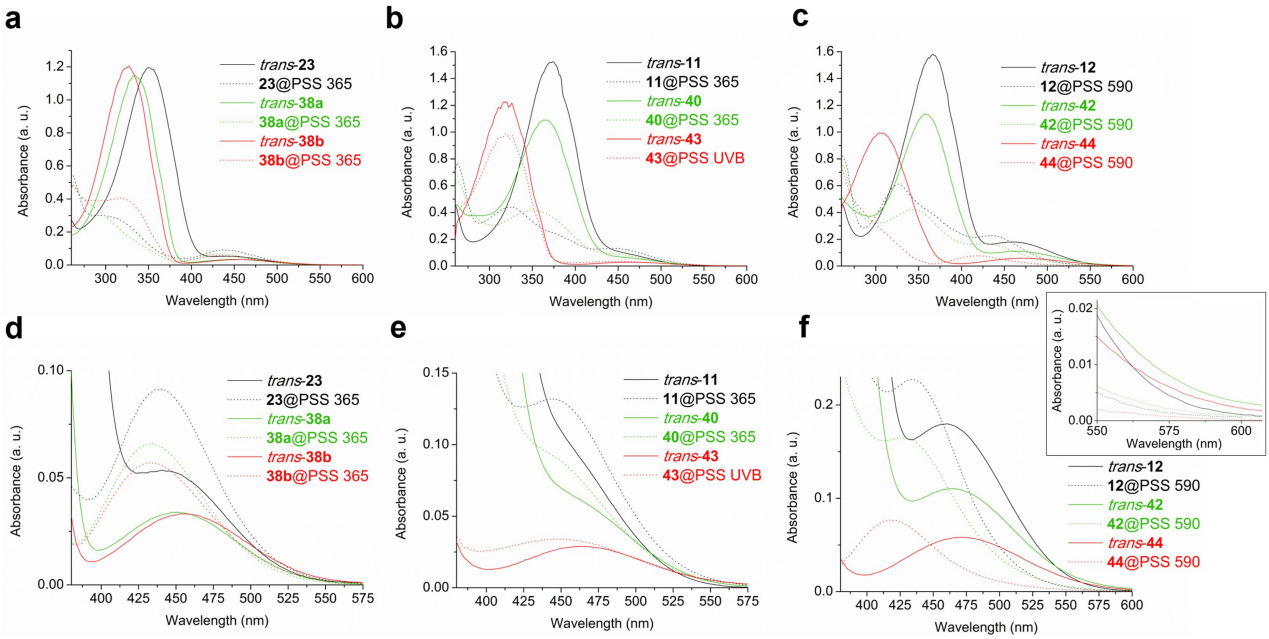


Figure 2. Overlays of absorption spectra and corresponding expansions in the area of the $n\rightarrow\pi^*$ transitions for compounds **23**, **38 a**, and **38 b** (a, d), **11**, **40**, and **43** (b, e), **12**, **42**, and **44** (c, f); inset: expansion in the 500–600 nm area for spectra of **12**, **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.

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 **38 b** (2.1 h) while it is 20 h in case of the sulfoxide **38 a** (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 $\pi\rightarrow\pi^*$ band (Table 1, entries 4 and 7, Figure 2b and 2c), the corresponding λ_{max} 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 $\pi\rightarrow\pi^*$ transition (Table 1, entries 6 and 9). Variation of the $n\rightarrow\pi^*$ band cannot be properly observed with molecules **11** and **40** due to a strong overlap with the $\pi\rightarrow\pi^*$ (Figure 2e). However, examination of the *ortho*-fluoroazobenzenes **12**, **42**, **44** (Figure 2f) provides information which complies with what was observed for the monosubstituted conjugates: upon sulfur oxidation, the $n\rightarrow\pi^*$ band 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 $n\rightarrow\pi^*$ bands.[16a,b]

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* $\pi\rightarrow\pi^*$ bands in **40** and **42** may result from the observed moderate blue shift of *trans* $\pi\rightarrow\pi^*$ as well as a likely red shift of the *cis* $\pi\rightarrow\pi^*$ 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 $\pi\rightarrow\pi^*$ 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.

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 $n\rightarrow\pi^*$ 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

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 ($t_{1/2}$ = 100 h) whereas the *cis*-disulfone **44** relaxes over 190-fold quicker ($t_{1/2}$ = 31 min).[29] 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.[16b] Hence, our thioarylation approach allows for facile preparation of functional and red light-switchable diazocines in only three steps.

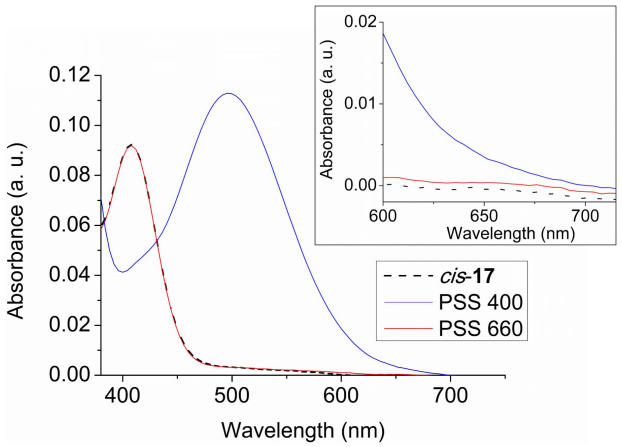


Figure 3. Representative absorption spectra in the area of the $n\rightarrow\pi^*$ transitions for diazocine conjugate **17**; inset: expansion in the 600–700 nm area; dashed black line: ground state, blue line: PSS after 2 min irradiation at 400 nm, red line: PSS after 30 s irradiation at 660 nm; spectra were recorded in DMSO (100 μM) at 25 °C.

Table 2. Spectroscopic data of diazocine conjugate **17**: maxima (λ_{max}) of $n\rightarrow\pi^*$ transitions of *trans* and *cis* isomers,[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[b] and half-life of thermal relaxation.[c]

λ_{max} $n\rightarrow\pi^*$ *cis* [nm]	λ_{max} $n\rightarrow\pi^*$ *trans* [nm]	$\Delta\lambda_{n\rightarrow\pi^*}$ [nm]	PSS 400 nm	PSS >500 nm[d]	$t_{1/2}$ *trans*
407	497	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.

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.[27,31] In fact, it may be difficult to orthogonally achieve each of the four possible isomers using light stimuli only,[32] due to overlaps between the absorption bands of the respective switches, and systems solely fueled by light require fine-tuning of irradiation conditions.[27,31] 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 purpose described above (see Table 3). The *trans*/*cis* 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.

Table 3. Isomer ratios measured by ^{1}H NMR spectroscopy of equimolar mixtures of **11**/**44** and **17**/**44**, respectively, in d_3-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

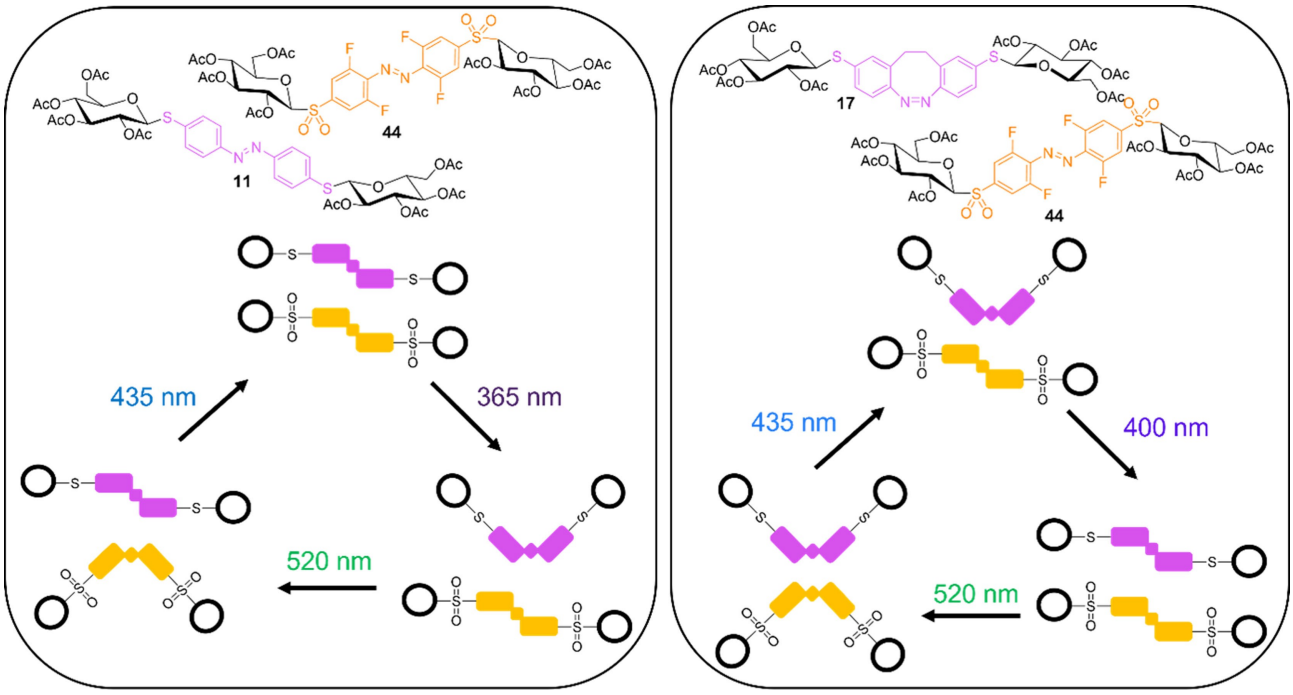


Figure 4. Orthogonal photoisomerization of azobenzene or diazocine glycoconjugates in solution mixtures with light of three distinct wavelengths. Two pairs of conjugates were investigated: **11**/**44** and **17**/**44**.

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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[29] Please note that due to the faster relaxation kinetics of *cis*-**44**, the thermal relaxation process may not be negligible in the *trans→cis* photoisomerization at 590 nm, which requires 20 min of irradiation time.
[30] Due to the longer irradiation time needed to achieve a quantitative *trans→cis* isomerization of **17** with light of 690 nm (20 min), the effect of the thermal relaxation process may not be negligible in this case.
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