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A compatibility study on the glycosylation of 4,4′-dihydroxyazobenzene†

Jonathan Berry, Guillaume Despras * and Thisbe K. Lindhorst *

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Photoresponsive glycoconjugates based on the azobenzene photoswitch are valuable molecules which can be used as tools for the investigation of carbohydrate–protein interactions or as precursors of shape-switchable molecular architectures, for example. To access such compounds, glycosylation of 4,4′-dihydroxyazobenzene (DHAB) is a critical step, frequently giving heterogeneous results because DHAB is a challenging glycosyl acceptor. Therefore, DHAB glucosylation was studied using nine different glycosyl donors, and reaction conditions were systematically varied in order to find a reliable procedure, especially towards the preparation of azobenzene bis-glucosides. Particular emphasis was put on glucosyl donors which were differentiated at the primary 6-position (N_3, OAc) for further functionalisation. The present study allowed us to identify suitable glycosyl donors and reaction conditions matching with DHAB, affording the bis-glycosylated products in fair yields and good stereocontrol.

Introduction

Since their historical use as dyes,[1] azobenzene derivatives have received great interest as photosensitive molecular switches.[2] This is due to the fact that the azobenzene N=N double bond gives rise to two isomeric forms, a *trans* (*E*) and a *cis* (*Z*) isomer, which can be reversibly interchanged by light of different wavelengths.[2] Moreover, substitution of the phenyl rings allows modification and fine-tuning of the photochromic properties of azobenzene photoswitches.

The phenyl rings of azobenzene derivatives can be further functionalised in order to include the photoswitch into various molecular architectures and probes. Hence, the azobenzene hinge has found applications in liquid crystals,[3] fast information-transmitting materials,[4] photoswitchable catalysts,[5] or actuators.[6] Azobenzene photoswitches were also extensively used in supramolecular chemistry, in particular in light-driven molecular machines,[7] and importantly, they were incorporated into biomolecules,[2b,8] such as peptides[9] and proteins,[10] nucleic acids,[11] lipids,[12] and also carbohydrates[3b–d,13,14,15,16] to enable photocontrol of molecular features and biological activity.

As the distance between the two *para*-positions of azobenzene varies between roughly 9 Å in the *trans* state and 5.5 Å in the *cis* form (Fig. 1a), isomerisation of the N=N double bond offers an opportunity to switch the relative orientation of molecular moieties ligated to both ends of the azobenzene. In glycobiology, this has been employed to study carbohydrate–lectin interactions in relation to the spatial presentation of the connected glyco ligands. In 2002, Jayaraman *et al.* first described the synthesis of azobenzene glycoconjugates and their investigation in lectin binding studies.[17] Since then, azobenzene glycoconjugates have gained increasing interest in the glycosciences. Our group has recently mounted azobenzene glycoconjugates onto gold surfaces in the form of glyco-SAMs (self-assembled monolayers).[18] Here, the azo group was employed as a molecular hinge in order to switch the orientation of α-D-mannoside ligands terminating the SAMs (Fig. 1b). By photoisomerization, the orientation of the sugar ligands on the surface can be altered, allowing for the control of mannose-specific adhesion of bacterial cells.[19] More recently, we have introduced photoresponsive glycoazobenzene macrocycles (Fig. 1c), which are shape-switchable and capable of reversible modification of chiroptical or solubility properties.[20] Along the same lines, J. Xie and colleagues reported the synthesis of azobenzene glycomacrolactones.[21]

In such work, the glycosylation of hydroxy-functionalised azobenzene served as a key step in the direct conjugation of the carbohydrate moiety and the photoswitchable azobenzene unit. We have typically employed *O*-glycosyl trichloroacetimidates as glycosyl donors to achieve azobenzene glycosides in good yields.[18,22] However, the bis-glycosylation of 4,4′-dihydroxyazobenzene (DHAB), as it was used for the preparation of azobenzene glycomacrocycles for example (Fig. 1c), is frequently impaired by poor to moderate yields.[10d,20a] This is due to the decreased nucleophilicity of the hydroxy groups in *para*-positions of the azobenzene, which is based on a tautomerism

Otto Diels Institute of Organic Chemistry, Christiana Albertina University of Kiel, Otto-Hahn-Platz 3/4, 24118 Kiel, Germany. E-mail: tklind@oc.uni-kiel.de

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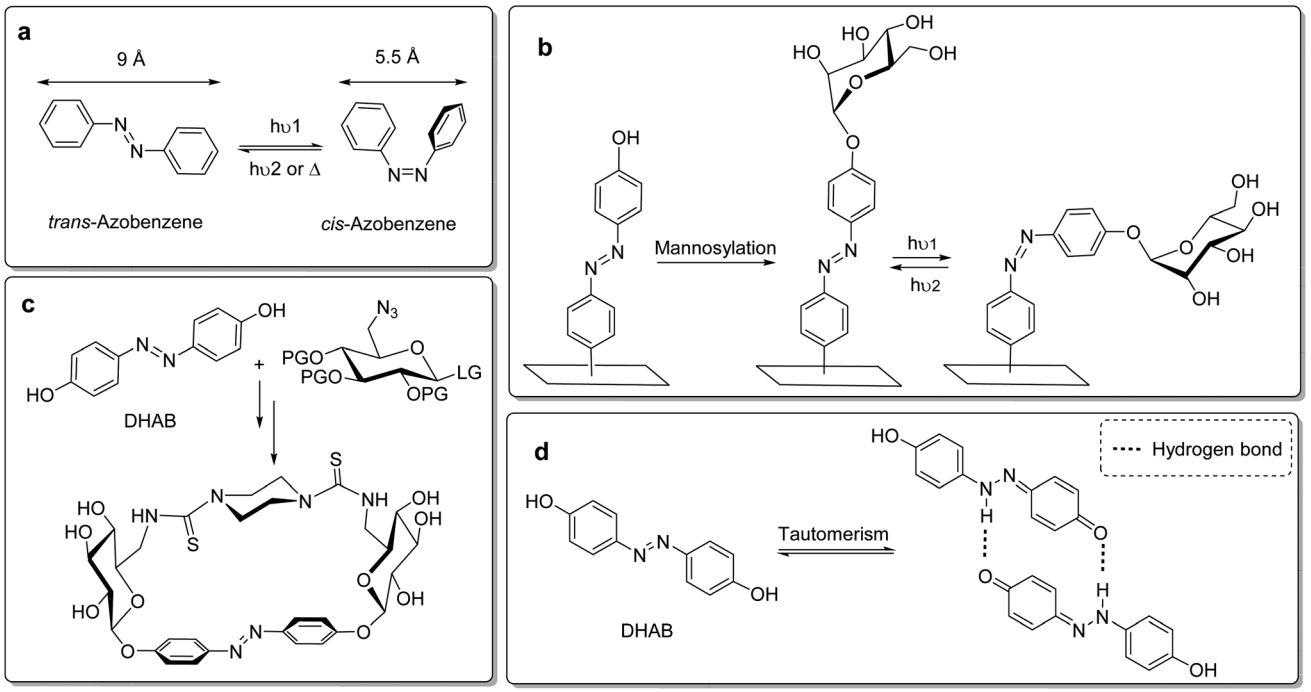


Fig. 1 Photoisomerisation of azobenzene and examples of photoresponsive glycoconjugates. (a) Light or heat-induced isomerisation of azobenzene; (b) mannosylation of hydroxyazobenzene mounted onto a surface leads to glyco-SAMs where glyco ligand orientation can be photoswitched; (c) glycosylation of 4,4′-dihydroxyazobenzene (DHAB) leads to shape-switchable glycoazobenzene macrocycles; (d) tautomeric equilibrium of DHAB with its hydrazoquinone form and possible intermolecular hydrogen bonding promoting the hydrazoquinone tautomer.

with the corresponding hydrazoquinone form, affecting both *para*-OH groups in DHAB (Fig. 1d). This tautomerism is promoted by intermolecular hydrogen bonds.[23]

We figured that, in order to improve the yields of DHAB bis-glycosides and to broaden the scope of azobenzene glycosides, we would have to study alternative glycosylation methods rather than to modify the azobenzene acceptor diol. Consequently, we commenced a study on the bis-glycosylation of DHAB, employing different glucosyl donors with variation of the anomeric leaving group as well as protecting groups. We were especially interested to improve the yields of DHAB bis-glycosylation with 6-azido-6-deoxy-functionalised glucosyl donors, as 6-functionalisation enables incorporation of the glycoazobenzene switch into larger molecular constructs.[20a]

Results and discussion

Preparation of glucosyl donors

Four common types of glucosyl donors were investigated in the glycosylation of DHAB, thioglucosides, glucosyl bromides, glucosyl sulfoxides, and *O*-glucosyl acetimidates (Chart 1). In most cases, the sugar hydroxy groups were protected as acetyl or benzoyl esters, respectively, to guarantee the stereoselective formation of 1,2-*trans*-glucosides based on the participating effect of the 2-*O*-acyl group. Two of the employed donors were silylated to achieve so-called super-armed glycosyl donors (*vide infra*).[24]

The glucosyl donors **1**, **2**, **4**, **5** and **6** were prepared starting from D-glucose according to standard procedures (*cf.* ESI†).

The preparation of the 6-azido-6-deoxy-modified glucosyl donors **3** and **7** started from levoglucosan (Scheme 1), which was first perbenzoylated with benzoyl chloride in pyridine to give **11** in 92% yield. Subsequent opening of the protected 1,6-anhydroglucose with (phenylthio)trimethylsilane (TMSSPh) in the presence of zinc iodide at 120 °C under microwave heating gave thioglucoside **12** in 98% yield with complete β-selectivity. Then, the free primary hydroxy group was substituted by an azide under Bose-Mitsunobu[25] conditions to afford **3** in 71% yield. Trichlorocyanuric acid (TCCA)-promoted hydrolysis of **3** in an acetone/water mixture yielded the reducing intermediate, which in turn reacted with (*N*-phenyl)trifluoroacetimidoyl chloride under basic conditions to provide the glucosyl donor **7** in 76% yield over two steps.

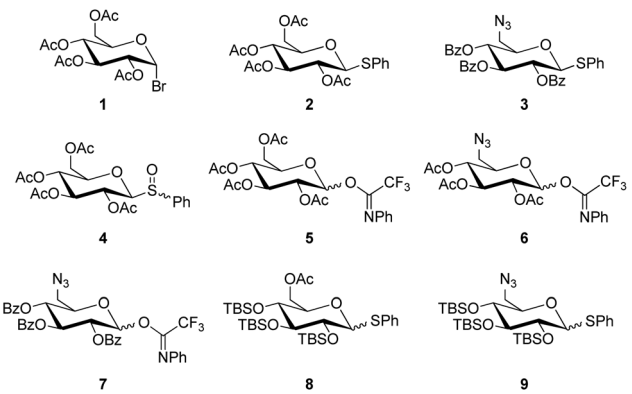
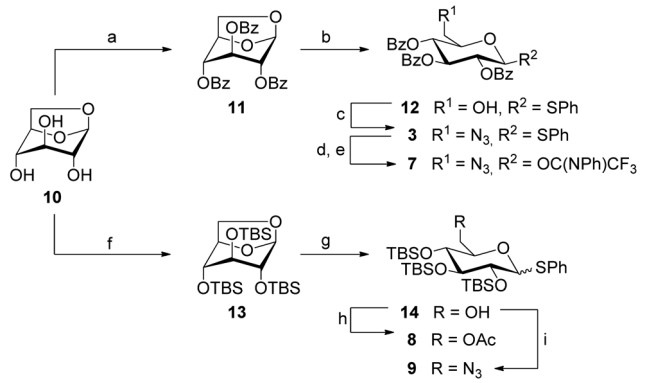


Chart 1 Structures of glycosyl donors used in the present study.



Scheme 1 Preparation of glucosyl donors **3** and **7–9**. Reagents and conditions: (a) BzCl (6 eq.), pyridine, rt, 92%; (b) ZnI_2 (4 eq.), TMSSPh (2.5 eq.), CH_2Cl_2, μW (150 W), 120 °C, 25 min, 98%; (c) PPh_3 (1.5 eq.), DIAD (2.5 eq.), DPPA (1.5 eq.), THF, −15 °C to rt, 71%; (d) TCCA (1 eq.), acetone/H_2O (9 : 1), rt; (e) $ClC(NPh)CF_3$ (1.5 eq.), Cs_2CO_3 (1.5 eq.), CH_2Cl_2, rt, 76% over 2 steps; (f) TBSCl (6 eq.), NMI (7 eq.), I_2 (2.5 eq.), pyridine, rt, 80%; (g) ZnI_2 (4 eq.), TMSSPh (2.5 eq.), CH_2Cl_2, rt, 96%; (h) Ac_2O (1.5 eq.), DMAP (0.2 eq.), pyridine, rt, 95%; (i) PPh_3 (1.5 eq.), DIAD (2.5 eq.), DPPA (1.5 eq.), THF, −15 °C to rt, 85%; DIAD = diisopropyl azodicarboxylate; DPPA = diphenylphosphorylazide; TCCA = trichlorocyanuric acid; TBSCl = *t*-butyldimethylchlorosilane; NMI = *N*-methylimidazole; TMSSPh = (phenylthio)trimethylsilane.

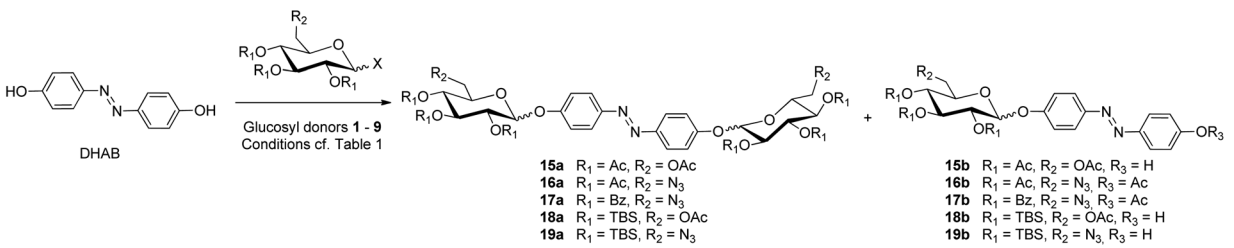
In analogy to the preparation of **11**, persilylation of levoglucosan was envisaged for the synthesis of the silylated glucosyl donors **8** and **9**. However, this reaction step required an optimization (*cf.* ESI†) to avoid the formation of the undesired 2,4-disilyated levoglucosan derivative. Finally, the persilylated levoglucosan derivative **13** was obtained in 80% yield by the addition of iodine to a mixture of **10**, TBSCl and *N*-methylimidazole in pyridine.[26]

When the following ring opening step with **13** was performed under microwave heating as employed for the acyl-protected analogue **11**, degradation was observed. Lowering the reaction temperature to 80 °C only slightly improved the reaction, but when the reaction was carried out at room temperature, it afforded the desired 6-OH-free thioglucoside **14** in 96% yield as an anomeric mixture ($\alpha : \beta = 1 : 4$). This result complies with the higher reactivity of the armed silylated sugar derivatives in comparison to disarmed acylated analogues. The primary alcohol function in **14** was then acetylated to afford the glucosyl donor **8** in 95% yield, and the targeted 6-azido-6-deoxy glucosyl donor **9** was obtained in 85% under Bose-Mitsunobu conditions.

Glycosylations

Then, with nine different glucosyl donors in hand (*cf.* Chart 1), the bis-glycosylation of DHAB[27] was investigated (Scheme 2). The results are summarized in Table 1. In previous work, *O*-glycosyl trichloroacetimidates were used for DHAB bis-glycosylation giving rise to yields between 30 and maximal 50%.[10d,20a] In order to improve the bis-glycosylation of DHAB, we first assessed glucosyl bromide **1**, as silver salts, which are employed to activate Koenigs–Knorr-type glycosyl donors, should be compatible with an azobenzene acceptor. However, regardless of whether silver carbonate or silver oxide was used as promoter,[28] only hydrolysis of the glucosyl donor occurred while the acceptor was nearly fully recovered (Table 1, entry 1). Next, we employed thioglucosides, as these donors present several great advantages; indeed thioglycosides are bench-stable, can be easily prepared in high yields and are compatible with a wide range of reaction conditions. When the acetyl-protected donor **2** was reacted under standard *N*-iodosuccinimide (NIS)/triflic acid (TfOH) activation,[29] complete donor hydrolysis was observed (entry 2). When NIS was replaced by NBS (*N*-bromosuccinimide) a similar result was observed (entry 3). In both cases various DHAB-derived side products were formed, including the *N*-dehydro-*N*-iodohydrazoquinone tautomer (*cf.* ESI†). These results indicate that, the azophenol/hydrazoquinone tautomerism of DHAB (*cf.* Fig. 1d) not only effects a decreased oxygen nucleophilicity but also increases the nucleophilicity of the nitrogen atoms of the azo group. Hence, especially with soft electrophiles such as iodonium ions, *N*-halogenation of the azo group competes with the activation of the glycosyl donor and inhibits the reactivity of the acceptor.

As it was not possible to activate thioglycosides with halogenium-donating promoters, the benzoylated thioglucoside **3** was activated with methyl triflate (MeOTf)[30] or dimethyl(methylthio)sulfonium triflate (DMTST).[31] Bearing the azophenol/hydrazoquinone tautomerism in mind, we figured that acidic media may favor the formation of the hydrazoquinone tautomer. Therefore, we buffered the following glycosylation reactions with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), which is known as an effective proton scavenger. Unfortunately, glycosylation of DHAB with **3** under these conditions (entries 4 and 5) failed. While the glucosyl donor was hydrolyzed or remained unreacted, again a number of DHAB-derived by-products were formed, presumably including *O*-methylated derivatives. The disappointing results with the thioglycosides led us to consider the glucosyl sulfoxide **4** as glycosyl donor, as it should be effective for the glycosylation of



Scheme 2 Glycosylation of DHAB with different glycosyl donors. The desired bis-glucosylated products are numbered with "**a**", the mono-glycosylated by-products with "**b**".

Table 1 Glycosylation of DHAB with donors **1–9** under various conditions[a]

Entry	Donor[b]	Promoter (eq./donor)	Base (eq./DHAB)	Solvent	Temp.	Bis-glycoside, yield, αβ : ββ, monoglycoside, yield, α : β
1	**1**	Ag_2CO_3 (1.1) or Ag_2O (2)	—	MeCN	rt	Donor hydrolysis
2	**2**	NIS/TfOH (1.5/0.05)	—	MeCN	0 °C	Donor hydrolysis
3	**2**	NBS/TfOH (1.5/0.1)	—	MeCN	rt	Donor hydrolysis
4	**3**	MeOTf (3.0)	DTBMP (2.2)	CH_2Cl_2	rt	Donor hydrolysis
5	**3**	DMTST (1.5)	DTBMP (2.2)	CH_2Cl_2	−30 °C	No activation
6	**4**[c]	Tf_2O (1.0)	DTBMP (3)	CH_2Cl_2	−78 °C	Donor hydrolysis
7	**5**	$BF_3{\cdot}OEt_2$ (1.1)	—	MeCN	rt	**15a**, 68%, 0 : 1, **15b**, not observed
8	**6**	$BF_3{\cdot}OEt_2$ (1.1)	—	MeCN	rt	**16a**, 48%, 0 : 1, **16b**, 14%, 0 : 1
9	**7**	$BF_3{\cdot}OEt_2$ (1.1)	—	MeCN	rt	**17a**, 38%, 0 : 1, **17b**, 25%, 0 : 1
10	**8**	MeOTf (3.0)	DTBMP (2.2)	CH_2Cl_2	rt	**18a**, 50%, 1 : 5, **18b**, 20%, 1 : 10
11	**8**	MeOTf (3)	DTBMP (2.2)	MeCN	rt	**18b**, 17%, 1 : 5
12	**8**	MeOTf (3)	DTBMP (2.2)	CH_2Cl_2/[bmim][OTf] (10 : 1)	rt	**18a**, 7%, 1 : 6, **18b**, 31%, 1 : 12
13[d]	**8**	BSP/Tf_2O (2.2/2.2)	DTBMP (2.2)	CH_2Cl_2/[bmim][OTf] (9 : 1)	−90 °C	**18a**, 18% 1 : 10, **18b**, 12% 1 : 5
14	**9**	MeOTf (3.0)	DTBMP (2.2)	CH_2Cl_2	rt	**19a**, 10%, 1 : 4, **19b**, 14%, 1 : 8

[a] All reactions were performed under dry conditions with addition of 3 Å molecular sieves (MS) and with [DHAB] = 0.05 mol × L^{-1} unless otherwise stated. [b] 2.2 eq. of donor were used unless otherwise stated. [c] 4 eq. of donor were used. [d] A solution of the acceptor was added to a mixture of donor and promoter; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; DMTST = dimethyl(methylthio)sulfonium trifluoromethanesulfonate; [bmim][OTf] = 1-butyl-3-methylimidazolium trifluoromethanesulfonate; BSP = 1-benzenesulfinyl piperidine; NIS = *N*-iodosuccinimide; NBS = *N*-bromosuccinimide.

unreactive alcohols according to Kahne.[32] When DHAB was treated with **4** in the presence of triflic anhydride (Tf_2O) and DTBMP at −78 °C, the donor was completely consumed after 1 h, presumably transformed into the corresponding triflate, while DHAB remained unreacted (entry 6). Prolonging the reaction time and increasing the temperature led to the hydrolyzed donor and the unreacted acceptor. Even though Kahne *et al.* have described the successful glycosylation of sterically hindered and electronically deactivated phenols with sulfoxides, this method was not successful with DHAB, again underlining the limited reactivity of this azobenzene diol.

Next, we turned our attention to the *O*-(glucosyl)-*N*-phenyltrifluoroacetimidate donors. Indeed, the acetylated donor **5** under BF_3-etherate activation afforded satisfying 68% of the desired bis-glycosylated compound **15a** as a single ββ-anomer (entry 7). The monoglycosylated product **15b** was not formed.

After this encouraging result, the same method was employed to introduce a 6-azido function into the azobenzene glycoside using the 6-azido-6-deoxy-functionalised glucosyl donor **6** (entry 8). This reaction was again successful, however with lower yields, 48% of **16a** and 14% of the monoglycosylated **16b**, again under complete β-selectivity. The benzoyl-protected analogue of **6**, the acetimidate **7**, under the same conditions led to slightly lower yields, affording the pure ββ-anomer **17a** in 38% along with 25% of pure β-monoglycosylated **17b** (entry 9).

At this stage of the study, the armed thioglycosides **8** and **9** were assessed for the bis-glycosylation of DHAB. As a conclusion from the results obtained with the disarmed thioglucosides (entries 2–5), MeOTf was chosen for the activation. In addition, in order to avoid acid-mediated intermolecular silyl transfer, the reaction medium was buffered with DTBMP. Satisfyingly, when DHAB was reacted with the armed donor **8** under these conditions (entry 10), 50% of the bis-glycosylated product **18a** (αβ : ββ = 1 : 5) and 20% of the monoglycosylated compound **18b** (α : β = 1 : 10) were obtained, however as anomeric mixtures. As DHAB is only partially soluble in CH_2Cl_2, **8** was employed under identical conditions but in acetonitrile (entry 11), and this reaction furnished the monoglycosylated product **19b** in 17% yield as the sole glycoside along with methylated DHAB derivatives.[33] This result indicates that the low solubility of DHAB in CH_2Cl_2 favors glycosylation over methylation of the phenol OH group as well as bis-glycosylation over monoglycosylation. Compared to the glycosylation in CH_2Cl_2, the α : β ratio of **19b** which was obtained in acetonitrile is somewhat unexpected. As acetonitrile is known as a participating solvent, an α-nitrilium intermediate should occur, favoring the formation of the β-anomer.

Next several buffering bases were assessed (*cf.* ESI†). While none of the investigated bases led to a convincing improvement of the yields or anomeric selectivities, DTBMP was the base of choice to avoid the undesired *O*-methylation of DHAB. We also examined the use of the ionic liquid 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([bmim][OTf]) as a co-solvent in CH_2Cl_2.[34] In this solvent mixture, DHAB is completely dissolved and the activation of the thioglycoside **8** with MeOTf in the presence of DTBMP (entry 12) again favored the monoglycosylated product **19b** (31%) with a good anomeric selectivity (α : β = 1 : 12), while **19a** was isolated in only 7% yield. As observed for the reaction in acetonitrile, *O*-methylated derivatives of DHAB were formed. Interestingly, the promoter system 1-benzenesulfinyl piperidine (BSP)/Tf_2O[35] could efficiently activate donor **8** without reacting with the DHAB acceptor (entry 13). This reaction provided **19a** in 18% yield (αβ : ββ = 1 : 10) and **19b** in 12% (α : β = 1 : 5).

Then, the 6-azido-functionalised donor **9** was assessed under the glycosylation conditions which were found optimal for the armed donor **8** (entry 10). This reaction afforded the bis-

glycoside **20a** in 10% yield ($\alpha\beta : \beta\beta = 1 : 4$) and the mono-glycosylated compound **20b** in 14% yield ($\alpha : \beta = 1 : 8$) (entry 14). When the BSP/Tf_2O system was applied with donor **9** only hydrolysis was observed. As observed with the acylated donors **6** and **7**, the 6-azido group seems to have a detrimental effect on the glycosylation of DHAB. This is consistent with previous reports of glycosylations involving 6-azido-6-deoxy-glycosyl donors and different kinds of phenolic acceptors, yielding the products in low to moderate yields.[10c,d,20a,36,37]

Conclusions

We carefully investigated the glycosylation of 4,4′-dihydroxyazobenzene with a range of glycosyl donors displaying different reactivities. Our study provided useful data to delineate the scope and limitations of this glycosylation reaction and allows to foresee mismatch cases for DHAB. Four main features are underpinned by our results. First, DHAB is a poorly reactive acceptor, mainly because the nucleophilicity of the phenolic hydroxy groups is lowered by a tautomeric equilibrium between the azophenol and the hydrazoquinone form. Second, this tautomerism may increase the nucleophilicity of the nitrogen atoms in the azo bond, which leads to *N*-halogenation when halogenium-providing promoters are used. Third, when glycosylations are carried out in a buffered medium with electrophilic activators such as MeOTf or DMTST, the choice of the base is crucial to prevent competing *O*-methylation of DHAB. Fourth, the solubility of DHAB is an important parameter to control the degree of DHAB glycosylation. The lower the solubility of DHAB, the higher the yield of bis-glycosylated product.

In conclusion, we believe our work reveals a new facet of the complexity of glycosylation reactions. Here, the azobenzene derivative DHAB was in the focus of our work and although glycosylation of DHAB remains challenging, we have identified glycosyl donors and activation methods compatible for the bis-glycosylation of this important photoswitch. In particular, the use of silyl-protected thioglycosides which are differentiated at the primary 6-position of the sugar ring is promising for the preparation of photoswitchable glycoconjugates and macrocycles. Efforts will be made for improving the glycosylation efficiency, regarding both stereoselectivity and degree of substitution, by varying the silyl protecting groups, the nature of the functional group at position 6 and further finely tune the reaction conditions.

Conflicts of interest

There are no conflicts of interest to declare about the authors.

Acknowledgements

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