Article

Visible-Light-Mediated Stadler−Ziegler Arylation of Thiosugars with Anilines

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Further functionalizations

- thiosugars
  - monosaccharides
  - polysaccharides
  - protected and unprotected
- Anilines
  - Functional group tolerance: (−CN, −Cl, −Br, −I,−CO$_2$Me, −C(O)Me, −CO$_2$H, −OH...etc)
- Photocatalyst
  - no base
  - rt
- Thioglycosides
  - 31 examples
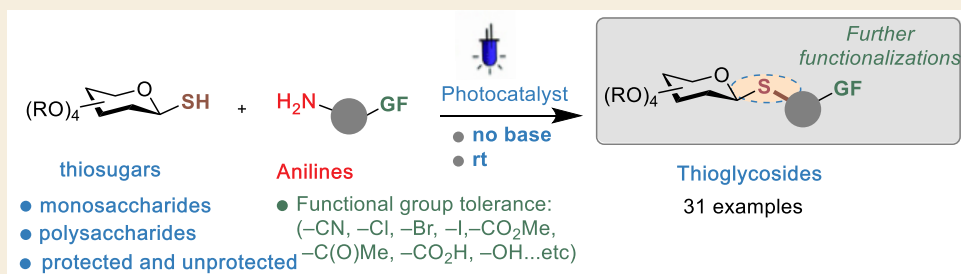
ABSTRACT: Here, we report a one-pot Stadler−Ziegler reaction toward the synthesis of 1-thioglycosides in good yield from commercially available anilines and (un)protected 1-glycosyl thiols. This simple and mild approach employs the photoredox catalyst [Ru(bpy)$_3$](PF$_6$)$_2$ under visible light.

KEYWORDS: photoredox, thiosugars, aryl diazoniums, Stadler−Ziegler reaction, thioglycosides, anilines, C-glycosides

Many glycosides containing a C−S anomeric bond display proprieties offering access to a broad array of fields, including drug discovery and chemical biology.[1−14] These glycomimetics are known to be more resistant to metabolic hydrolysis than their *O*-glycoside congeners under biological conditions.[15−17] Figure 1A displays representative examples of bioactive 1-thioglycosides including FDA-approved antibiotic clindamycin used in the treatment of a variety of serious infections[18] and GB1107, an orally active inhibitor of galectin-3 that reduces lung adenocarcinoma growth and blocks metastasis.[19] Besides, different other biological activities are well explored with thioglycosides including hSGLT1,[20] lectine A,[21] and Hsp90 inhibitions.[22,23] On the other side, thioglycosides are largely used as versatile and reactive intermediates in polysaccharide assembly tactics through iterative glycosylations (Figure 1B).[24−32]

Due to their key role in many biological processes, the development of methods toward an efficient and stereoselective synthesis of 1-arylthioglycosides is considered to be of great importance.[33,34] A well-known strategy largely applied toward these target *S*-arylated glycosides is the cross-coupling reaction typically catalyzed by the Pd,[35−38] Ni,[39] Cu[40−43] transition metals, in which an aryl halide reacts with a glycosyl thiols leading to the desired thioglycoside derivative (Figure 1C). Despite their high interest, these methods required the use of expensive catalysts or a high temperature and a long reaction time, limiting thus the practicability or the scope of substrates. Liao and Yan reported an efficient transition-metal-free protocol for the synthesis of aryl 1-thioglycosides *via* an *in situ* arynes generation (Figure 1C).[44] Although efficient, some

limitations persisted such as a lack of regioselectivity with nonsymmetrical arynes or the limited tolerance for functional groups. Recently, our group developed the first electrochemical method for coupling various glycosyl thiols with aryl iodides and bromides under base-free conditions (Figure 1C).[45] Highly complex thioglycosides could be prepared under this ecofriendly method including unprotected thiosugars. In addition, we developed another protocol for the synthesis of aryl 1-thioglycosides *via* a Ni/Ru photoredox dual-catalyzed cross-coupling of thiosugars with aryl iodides (Figure 1C).[46] Suitable for only protected thiosugars, this method did not also tolerate the more available and less expensive aryl bromides.

Owing to the high importance of thioglycosides, there is a strong impetus to develop a mild and general photoredox reaction for their efficient synthesis. We wish to identify more suitable partners than bromides, and iodides able to react efficiently with thiosugars under a simple photoredox protocol to generate the desired thioglycoside. Specifically, we focused our attention on the introduction of an approach that tolerates reactive functions on the aryl partners such as halogens, carboxylic acids, or alcohols, which may be subjected to further functionalization. Since aryl amines are usually more readily
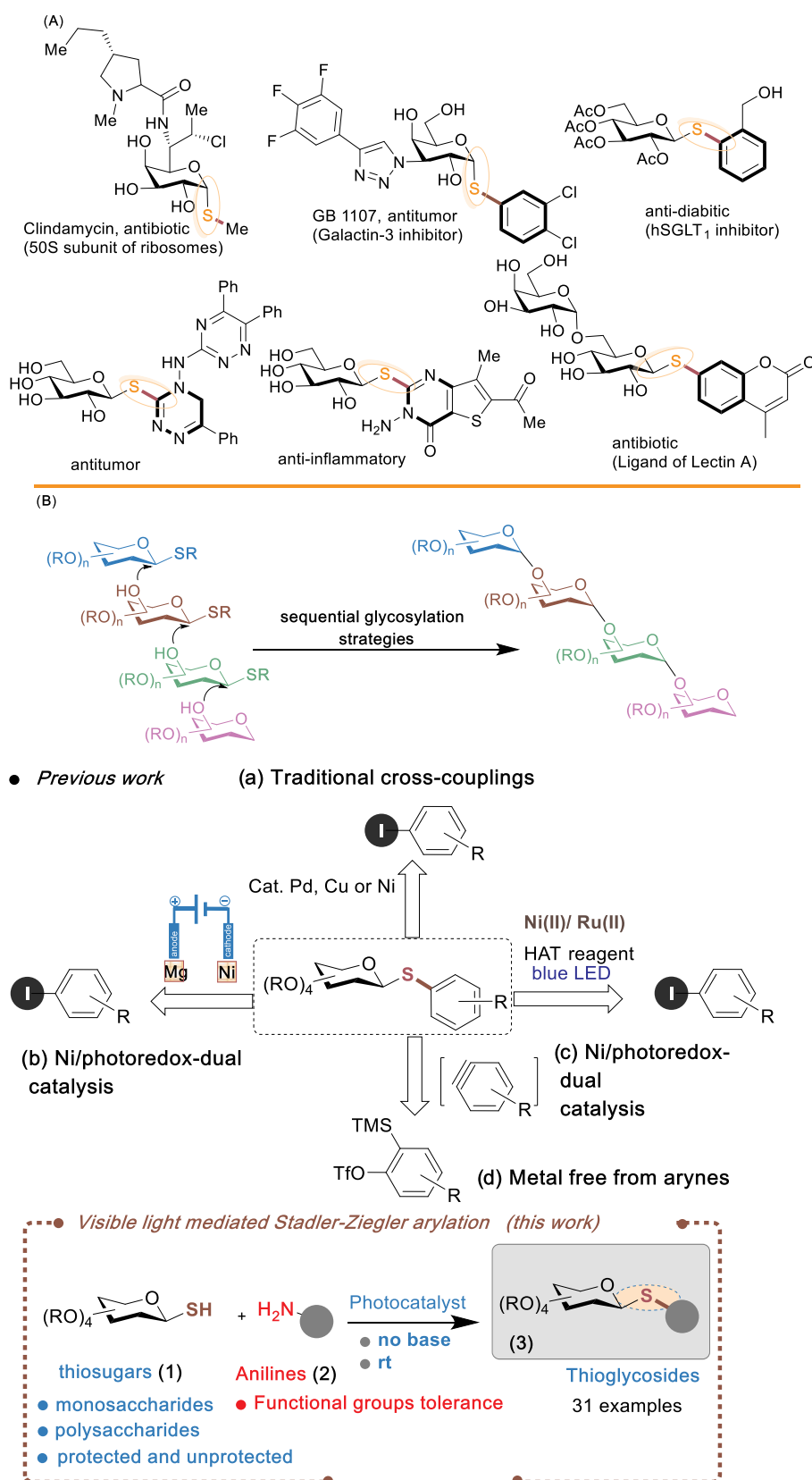
Figure 1. (A) Examples of bioactive thioglycosides, (B) utility of thioglycosides in sequential glycosylation reaction, and (C) catalytic strategies to access to thioglycosides **3**.

available and less expensive than the corresponding aryl halides, we were interested in using them as coupling partners in the famous Stadler−Ziegler reaction.[47−50] We hypothesized

that highly reactive aryl diazonium salts generated from aryl amines would be suitable as arylating agents, able to easily generate aryl radicals which could then be trapped by the

Table 1. Optimization of the Coupling Reaction of 1a with 2a[a]
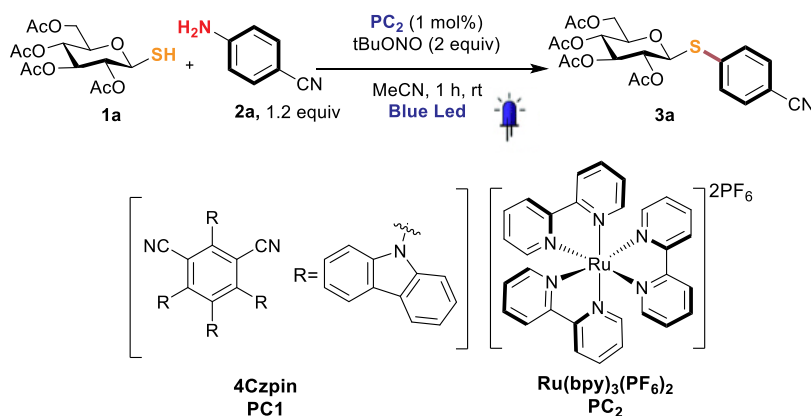
| entry	deviation from the standard conditions	yield 3a (%)[b]
1	none	77
2	PC1 instead PC2	66
3	PC2 0.5 mol %	70
4	+ molecular sevies 4 Å	trace
5	DMSO or DMF or DMA or MeOH instead of MeCN	traces
6	Dioxane instead of MeCN	43
7	No photocatalyst PC1	17
8	No LED	17
9	No photocatalyst PC1 and LED	17

[a]Reactions conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), *t*BuONO (0.6 mmol), MeCN (2.0 mL), blue LEDs (4.5 W, irradiation). [b]Isolated yield.

Scheme 1. Scope and Limitation of the Coupling of 1a with Alkylamines 2[a]
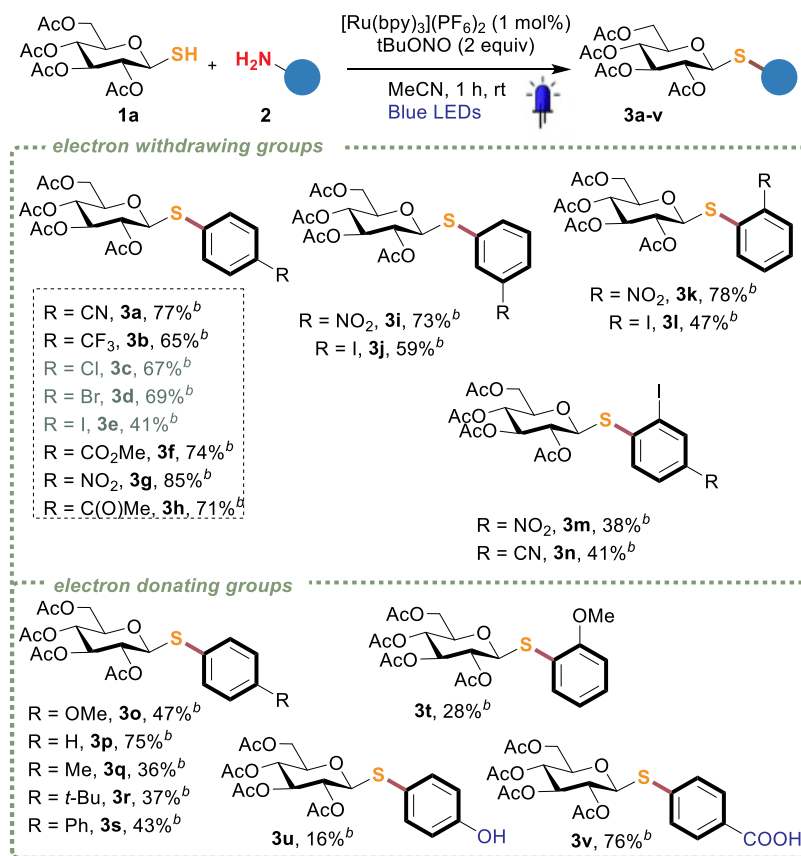
[a]See SI for the reaction conditions. [b]Yield of the isolated product.

thiosugar nucleus. Since the pioneering work by Stadler[47] and by Ziegler,[48] this process has been used in various applications

for the synthesis of arylsulfides including industrial manufacturing.[51−59] Recently, various groups reported modifications of

Scheme 2. Scope and Limitation of the Coupling of Glycosyl Thiols 1b−h with the Aniline 2g[a]
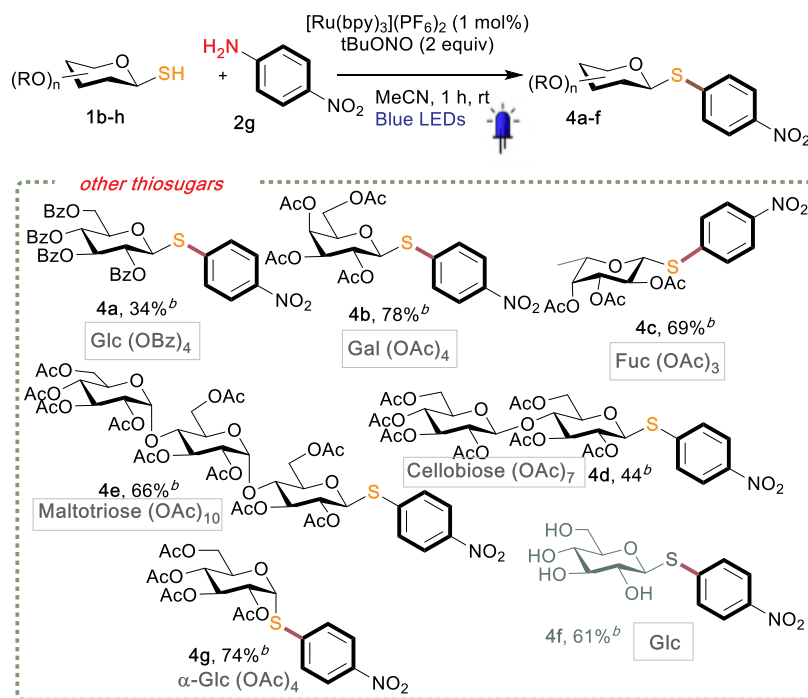
[a]See SI for the reaction conditions. [b]Yield of the isolated product.

this protocol to achieve improved yields and milder reaction conditions. Among them, the group of Noël reported a mild procedure for the synthesis of arylsulfides using photoredox catalysis.[60−62] To avoid the isolation of diazonium salts and to enhance the reaction efficiency, the authors established an elegant one-pot protocol from aryl amines combining the diazotization and coupling steps.[60,61]

Based on these recent achievements, and on our ongoing interests in metal-catalyzed functionalization of thiosugars,[63−67] we propose herein a catalytic photoredox method for the arylation of protected and unprotected thiosugars with various anilines (Figure 1C). If successful, this approach would provide not only an excellent complementary pathway to the established S-arylation methods but also immediate access to a reactive platform that can be engaged in numerous postfunctionalizations.

To examine the feasibility of this study, we chose the coupling of tetra-O-acetylated 1-thio-β-D-glucopyranose **1a** with a commercially available 4-cyanoaniline **2a** as a model study under various reaction conditions (Tables 1 and S1 in the Supporting Information). The reaction of **1a** (1 equiv) with **2a** (1.2 equiv) was first investigated using 1 mol % of a commercially available Ru(bpy)$_2$PF$_6$ photocatalyst in the presence of tBuONO (2 equiv) as a diazotization reagent in acetonitrile under a white light-emitting diode (LED) irradiation at room temperature for 24 h (Table S1, entry 1, SI). Accordingly, these conditions afforded the expected product **3a** in an encouraging 67% yield as a single β-anomer ($J_{1,2}$ = 9.0 Hz) (see SI). Increasing the amount of the aniline partner **2a** from 1.2 to 2 equiv furnished **3a** in a slightly lower yield (57%, Table S1, entry 2, SI). Pleasantly, switching from white to blue light furnished **3a** in 77% yield (Table S1, entry 3, SI). Interestingly, reducing the reaction time to only 1 h instead of 24 h led to the thioglucoside **3a** in a good 77% yield (Table 1, entry 1). The reaction time was fixed at 1 h, and we

decided to examine the other reaction parameters. The reaction with the organophotocatalyst 4CzIPN ($E_{(PC*/PC−)}$ = +1.43 V) instead of Ru(bpy)$_2$PF$_6$ was less efficient and gave **3a** in a 66% yield (entry 2). Decreasing amounts of the photocatalyst to 0.5 mol % gave **3a** in a still good yield of 70% (entry 3). However, tentative to remove traces of water from the reaction medium by adding molecular sieves (4 Å) led to complete inhibition of any reactivity (entry 4). The influence of the solvent was also examined and revealed that MeCN was the solvent of choice since the other solvents such as dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), N,N-dimethylformamide (DMF), and MeOH were completely incompatible with this coupling (entry 5) or less efficient in the case of dioxane (43%, entry 6). Negative controlling experiments demonstrated that both the Ru photocatalyst and light are crucial for this reaction (entries 7−9).

With these encouraging results, we investigated next the scope and limitations for this Stadler−Ziegler reaction using a series of commercially available aryl amines **2** bearing different functional groups. As showed in Scheme 1, cross-couplings of tetra-O-acetylated 1-thio-β-D-glucopyranose **1a** with aryl amines bearing various functions (−CN, −Cl, −Br −I, −CF$_3$, −NO$_2$, −CO$_2$Me, −C(O)Me, −OMe, −Me, −tBu, −Ph) at para or meta positions have been successfully achieved to afford the corresponding thioglycosides (**3a−j** and **3o−s**) in yields up to 85%. Interestingly, reactive C-halogen bonds (e.g., I, Br, Cl) were tolerated in this photoredox reaction affording compounds **3c−e**, **3j**, **3l**, **3m**, **n** in acceptable yields. The presence of halogen substituents in these products provided a handle for further structural diversifications using metal-catalyzed cross-coupling reactions. In addition, the presence of an ortho substitution at the aromatic ring of the aniline partner affects slightly but does not inhibit the coupling process completely, as compounds **3k−n** were obtained in

Scheme 3. Further Functionalizations[a]
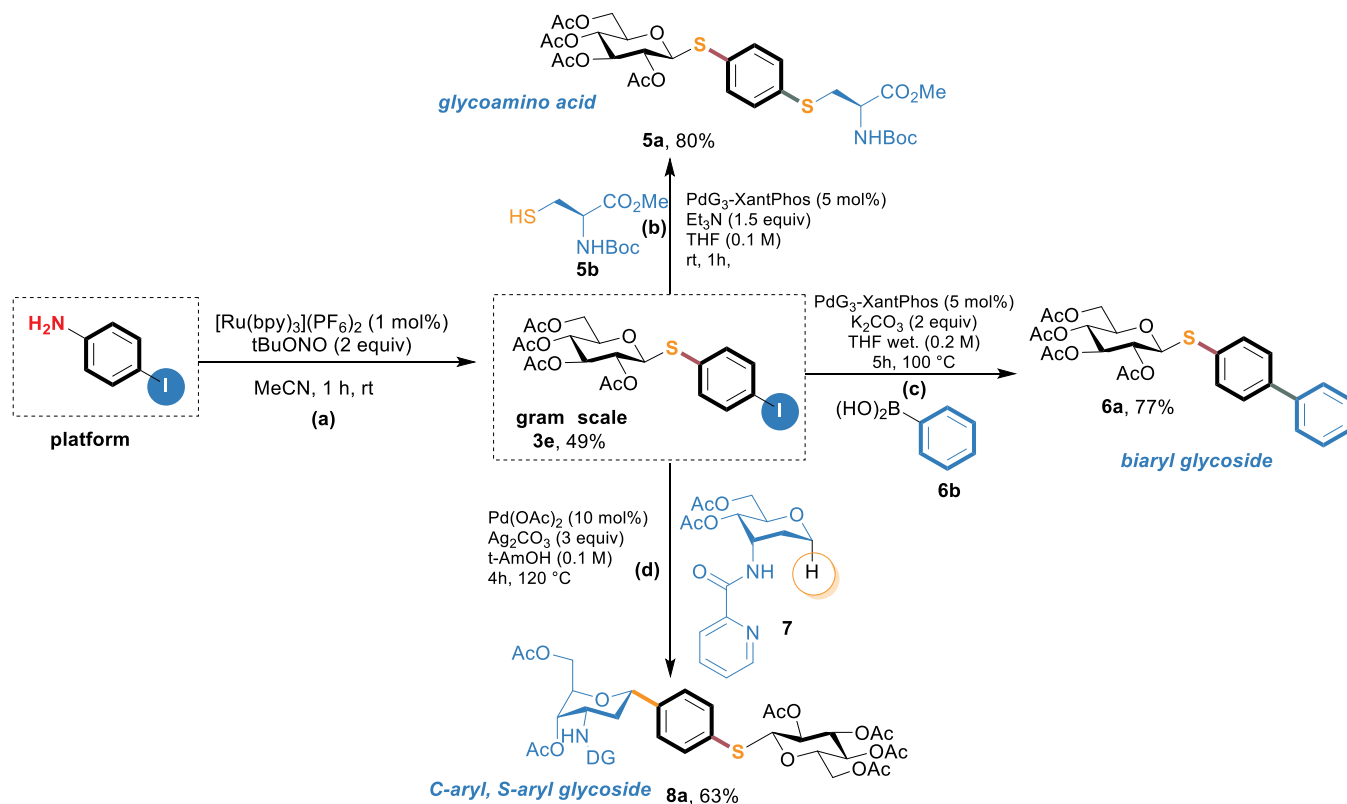
*[a]*Reactions conditions: (a) **1a** (3 mmol), **2e** (1.2 equiv), [Ru(bpy)₃](PF₆)₂ (1 mol %), MeCN 20 mL, *t*BuONO (2 equiv), Blue led, rt, 1 h. (b) **3e** (0.1 mmol), **5b** (0.1 mmol), PdG3 XantPhos (5 mol %), Et₃N (1.5 equiv), in THF (0.1 M) at rt for 1 h. (c) **3e** (0.1 mmol), **6b** (0.2 mmol), PdG3 XantPhos (5 mol %), K₂CO₃ (2 equiv), in wet THF (0.2 M) at 100 °C for 5 h. (d) **3e** (0.4 mmol), **7** (0.2 mmol), Pd(OAc)₂ (10 mol %), Ag₂CO₃ (3 equiv), in *t*-AmOH (0.1 M) at 120 °C for 4 h.
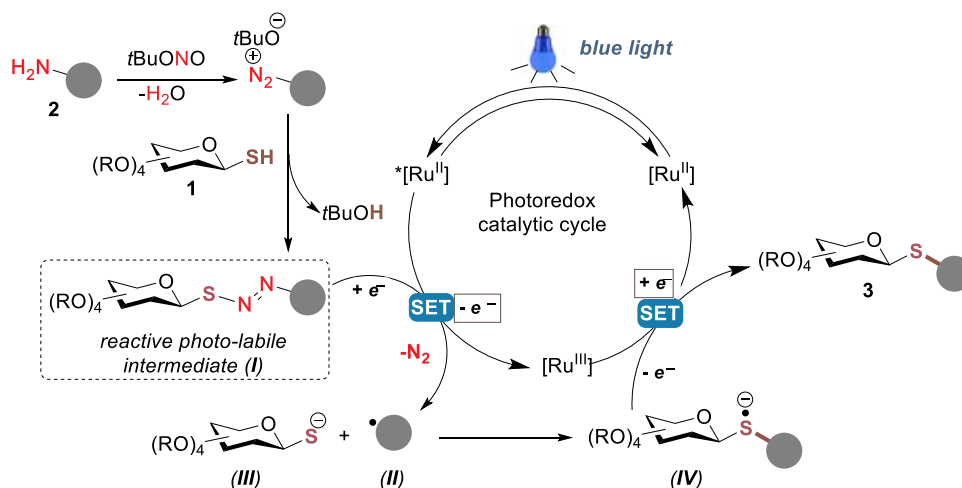

Figure 2. Proposed mechanism.

yields ranging between 38% and 78%, depending on the electronic effect of the functional group.

Of note, the presence of a polar function on the aniline such as a carboxylic acid **2v** is well tolerated, furnishing the desired compound **3v** in 76% yield. However, the yield drops down to only 16% when the coupling of **1a** was conducted with a *p*-hydroxy aniline (compound **3u**).

This successful study with the tetra-*O*-acetylated 1-thio-*β*-D-glucopyranose **1a** encouraged us to examine the feasibility of this coupling with different other glycosyl thiols **1b–h**. As

depicted in Scheme 2, this coupling reaction tolerates different glycosyl thiols such as *O*-benzoylated 1-thio-*β*- D -glucopyranose **1b**, *O*-acetylated 1-thio-*β*-D-galactopyranose **1c**, and *O*-acetylated 1-thio-*β*-D-fucopyranose **1d**, which react smoothly with the *p*-nitro aniline **2g** to lead to thioglycosides **4a–c** in yields up to 78%. In addition, this protocol could be extended to more complex and biologically relevant saccharide derivatives such as thio-*β*-D-cellobiose disaccharide **1e** and thio-*β*-D-maltotriose trisaccharide **1f** delivering **4d** and **4e** in 44 and 66% yields, respectively. More interestingly, we observed

that our protocol is compatible with unprotected thiosugars since the reaction of unprotected thio-β-D-glucose **1g** with **2g** yielded the thioglycoside **4f** in a good 61% yield, and no side products arising from the *O*-arylation were observed (Scheme 1). This is another important input compared to our previously reported photoredox approach to functionalize thiosugars with aryl halides. Finally, besides β-glycosyl thiols, α-anomers are also effective coupling partners for this photoredox coupling as α-thioglucose furnishes the α-thioglycoside **4g** in 74% yield.

To further show the synthetic utility of our protocol, we carried out studies on whether the iodinated substrate **3e** could be used as a platform to access more complex thioglycosides through metal-catalyzed transformations of the C−I bond (Scheme 2). To this end, **3e** was first prepared on a gram scale with a slightly higher yield demonstrating the scalability of our protocol. Thus, with substantial amounts of **3e** in hand, we examined next its coupling with the cysteine substrate under our previously reported Pd-catalyzed methodology.[68] When PdG3 XantPhos was used as a catalyst in the presence of Et$_3$N, the glycoamino acid **5a** was isolated in an excellent yield. This later may be used as a building block in the solid-phase peptide synthesis (SPPS) (Scheme 3). In addition, **3e** was converted to the biaryl **5b** in good yield through a Suzuki−Miyaura cross-coupling with the phenylboronic[69] (Scheme 3). Finally, **3e** was engaged in a Csp^3−H activation process of the anomeric C−H bond of substrate **7** under our recently reported protocol.[70] The diglycoside **8a** bearing two different sugars linked through C−C and C−S bonds was obtained in 63% yield (Scheme 3).

From the point of view of mechanistic considerations, based on the literature reports, we may assume that the reaction starts with the *in situ* formation of the diazo salt from aniline and *t*BuONO reagent, followed by the formation of the diazosulfide (**I**) (Figure 2). Noël and co-workers suggested in their early mechanistic studies that this intermediate is the reactive photolabile species in the photocatalytic cycle of the photocatalyzed Stadler−Ziegler process.[60] A single electron transfer (SET) from the excited-state Ru photocatalyst to diazosulfide (**I**) leads to N$_2$ extrusion and the formation of thiolate (**III**) and aryl radical (**II**). These two intermediates evolve into the formation of the thioether radical anion (**IV**), which produces the final thioglycoside and closes Ru-catalytic cycles by a final SET.

In summary, we reported here a new approach for the *S*-arylation of anomeric glycosyl thiols with various aryl amines *via* a cooperative photoredox strategy. This method provides unprecedented access to functionalized thioglycosides under mild conditions with high efficiency and selectivity. We anticipate that this mild synthetic protocol will find numerous applications in organic synthesis as well as in medicinal chemistry.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.2c00006.

Experimental procedures and analytical data; condition selection; characterization data for products; and NMR spectras (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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