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# Ni/Photoredox-Dual-Catalyzed Functionalization of 1-Thiosugars

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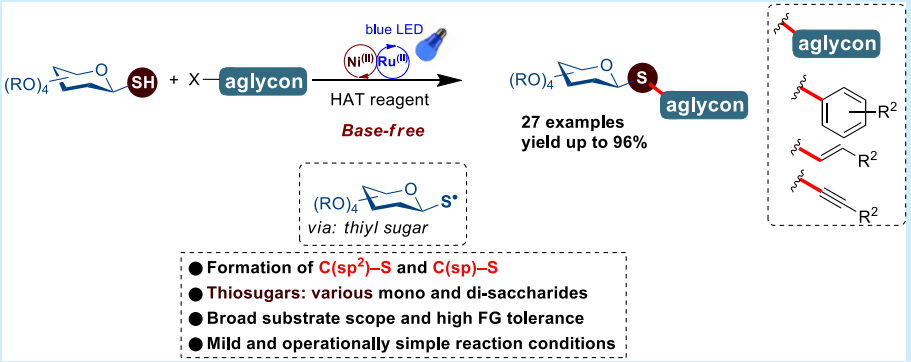
Supporting Information




**ABSTRACT:** A general protocol for functionalization of glycosyl thiols has been reported. This protocol is based on a single-electron Ni/photoredox dual-catalyzed cross coupling between 1-thiosugars and a broad range of aryl bromides and iodides as well as alkenyl and alkynyl halides. This base-free method gives access to a series of functionalized thioglycosides in moderate to excellent yields with a perfect control of the anomeric configuration. Moreover, it has been shown that this methodology may be transposed successfully to the continuous-flow photoredox chemistry.

1-Thioglycosides are of great interest in pharmaceutical science.[1] These derivatives are considered as mimetics of biologically relevant *O*-glycosides as they are known to be resistant toward enzymatic hydrolysis.[2] Some biologically active 1-thioglycosides are represented in Figure 1, including the hSGLT1 inhibitor, ligand of lectine A, cytotoxic Hsp90 inhibitor, galactosidase and glycosidase inhibitors, as well as antimicrobial agents. In addition, thioglycosides are considered as versatile intermediates in organic synthesis.[3]

Despite their potential interest in medicinal chemistry, only few methods report their synthesis. Usually, they are prepared by reaction of thiophenol with per-O-acetylated glycosyl donors in the presence of a Lewis acid.[4] They also could be prepared by substituting the halogen atom at the anomeric position of the sugar by a thiolate anion.[5] These approaches however suffer from the harsh reaction conditions and are limited in substrate scope with thiophenols. Various Pd-,[6] Ni-,[7] or Cu-catalyzed[8] S arylations of glycosyl thiols with aryl iodides were developed independently by Sticha,[8a] Xue,[8c] and our group (Figure 2 Ia,b).[9] However, demanding reaction conditions such as high catalyst loadings (30 mol % in the case of Ni catalysis), specialized phosphine ligands for the Pd catalysis, elevated reaction temperatures (80−120 °C cases of Pd or Cu catalysis), and long reaction times often limit the practicability or the scope of substrates. Moreover, in all these cases the coupling is effective with only aryl iodides; however, the cross coupling with aryl bromides is rather unexplored.

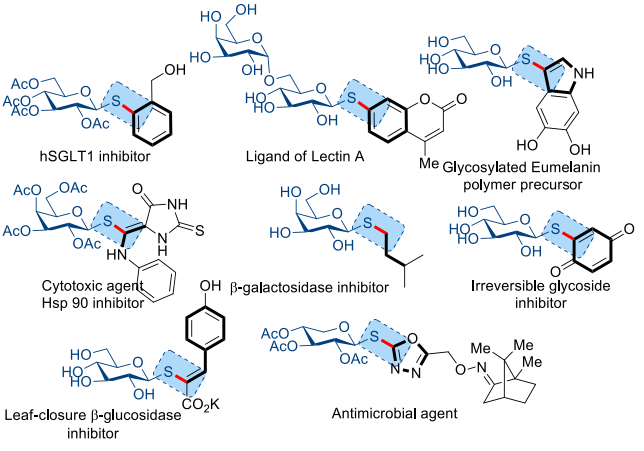



**Figure 1.** Example of biologically active thioglycosides.

Owing to the high importance of thioglycosides, there is a strong impetus to develop mild and general reactions for their efficient synthesis.

Dual nickel photocatalysis has emerged as a powerful strategy and a remarkably efficient tool for organic cross-coupling reactions in recent years.[10] Although this approach

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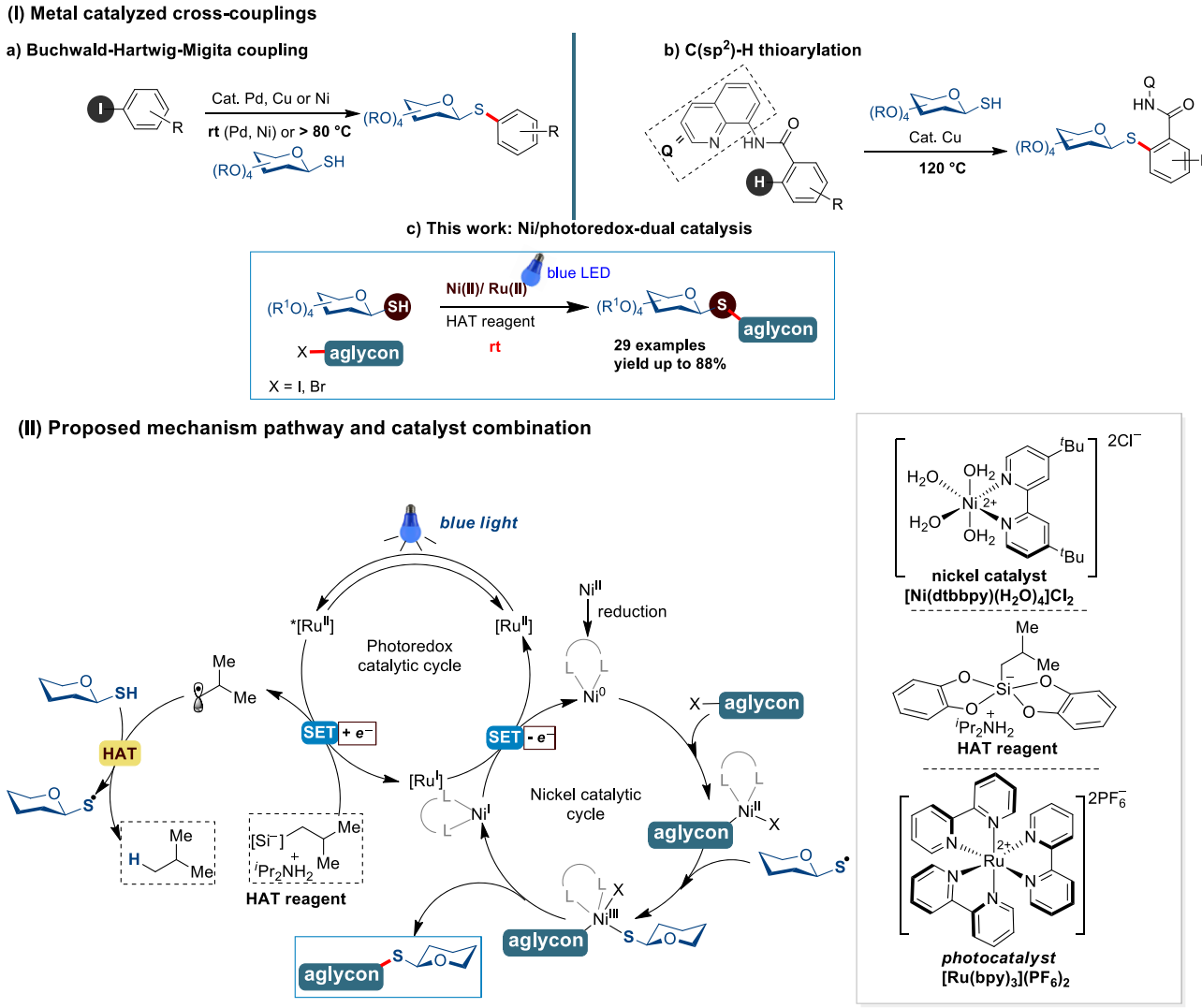


**Figure 2.** (Ia and b) Traditional metal-catalyzed cross-coupling methods for the synthesis of thioglycosides. (Ic) Dual nickel photocatalyzed approach. (II) Proposed mechanism.

was used successfully for the C−C bond construction, the formation of a C−heteroatom bond through Ni-photoredox processes is less explored. Moreover, methods which use photoredox dual catalysis to form a thiyl radical and promote it through cross coupling with aryl halides to form C−S bonds are rare. Johannes and co-workers developed an Ir/Ni dual-photoredox-mediated cross-coupling reaction of thiols with aryl iodides.[11] Very recently, Molander et al. reported the first Ni/photoredox cross-coupling reaction for the S-arylation of cysteine-containing unprotected peptides.[12] The authors showed elegantly that the mildness of this approach allows late-stage functionalization of complex biomolecules. However, the S-arylation of the anomeric bond of thiosugars under Ni-photoredox dual catalysis has never been examined, probably due to the inherent complexity of carbohydrates.

In continuation of our study on the reactivity of thiosugars under transition metal catalysis, we became interested in whether the S-(hetero)arylation of 1-thiosugars could be realized by the single-electron dual Ni/photocatalysis (Figure 2Ic). We considered that 1-thiosugars may be suitable substrates for such a strategy, keeping in mind that a practical synthetic method should work not only with aryl iodides but also with aryl bromides as well as alkenyl- and alkynyl-bromides. We could assume that the catalytic cycle may be initiated by photon absorption, generating excited state Ru photocatalyst, followed by oxidation of the HAT reagent via single electron transfer (SET) (Figure 2, II). In this context, ammonium bis(catechol)alkylsilicates were recently found to be effective hydrogen atom transfer (HAT) reagents for $Csp^2$−S coupling under the Ni/photoredox processes.[13] Rapid H atom abstraction from the glycosyl sulfhydryl group generates a glycosyl thiyl radical. This later adds to Ni(II) which arises from Ni(0) oxidative addition with the aglycon halide. In a possible alternative of the catalytic cycle, Molander, Kozlowski, and co-workers reported that the thiyl radical metalation may precede the oxidative addition step.[14] Reductive elimination from Ni(III) affords the desired thioglycoside, and the dual catalytic cycles are closed by a final SET.

In the first set of experiments, we examined the coupling of tetra-*O*-acetylated 1-thio-*β*-D-glucopyranose **1a** with 1-bromo-benzonitrile **2a** as a model study under various reaction conditions. Representative results from this study are summarized in Table 1. The reaction of **1a** (1 equiv) with **2a** (1 equiv) was first investigated under Molander's conditions



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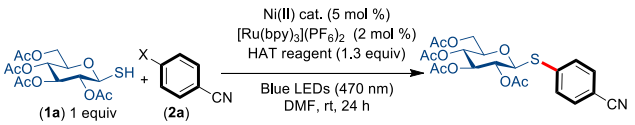
**Table 1. Optimization of the Coupling Reaction of 1a with 2a**[a]




| entry | X | equiv of 2a | solvent | 3a (%)[b] |
|---|---|---|---|---|
| 1 | Br | 1 | DMF | 59 |
| 2 | Br | 1.3 | DMF | 79 |
| **3** | **Br** | **1.5** | **DMF** | **85**[c] |
| 4 | Br | 2 | DMF | 81 |
| 5 | Br | 2 | DMA | 32 |
| 6 | Br | 2 | DMSO | 54 |
| 7 | Br | 2 | MeCN | 40 |
| 8 | Br | 2 | THF | 19 |
| 9 | I | 1.5 | DMF | 90 |
| **10** | **I** | **1.5** | **DMF** | **95**[d] |

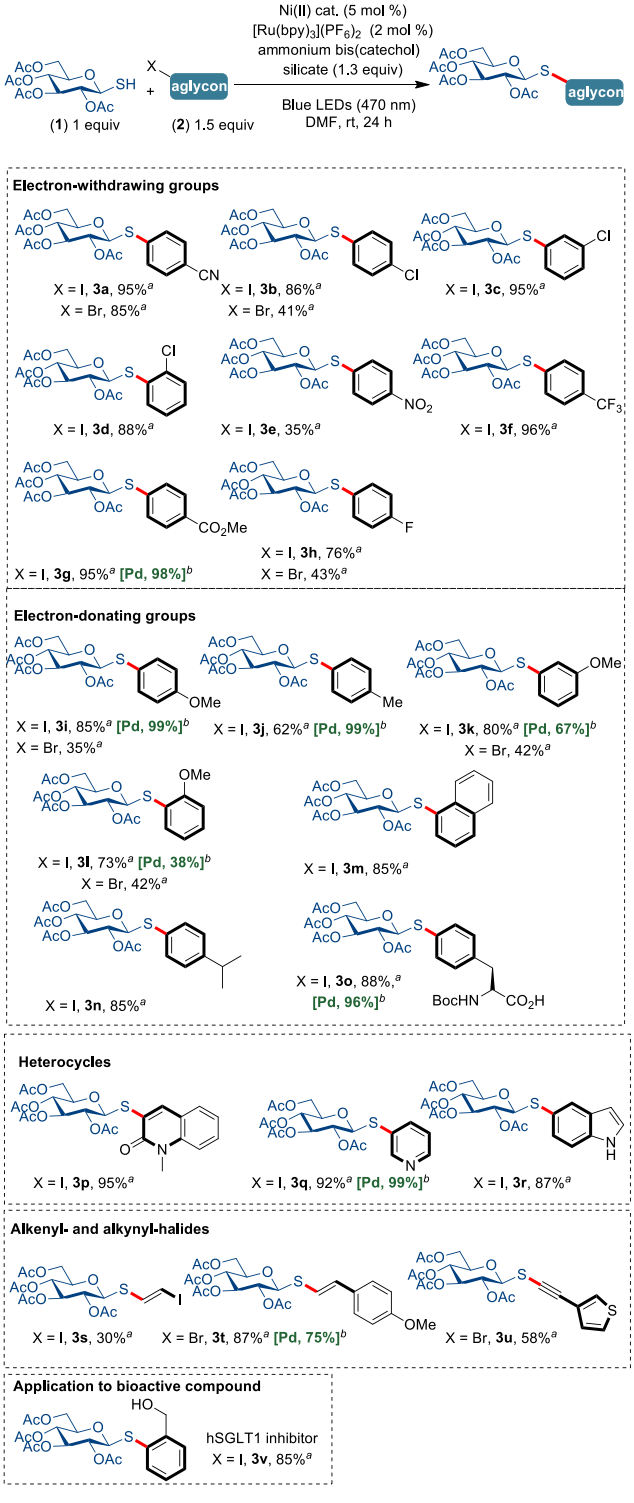
[a]A sealable tube was charged with thiosugar **1a** (1 equiv, 0.2 mmol), 1-bromo-4-benzonitrile **2a** (*xx* equiv), $[Ni(dtbbpy)(H_2O)_4]Cl_2$ precatalyst (5 mol %), $[Ru(bpy)_3](PF_6)_2$ (2 mol %), and HAT reagent (diisopropylammonium bis(catechol)isobutylsilicate) (1.3 equiv) in dry and degassed DMF (1.0 mL). [b]Yield of isolated product. [c]70% of **3a** when 3 mol % of Ni catalyst was used. [d]150 mg of molecular sieves was added.

using 5 mol % of $[Ni(dtbbpy)(H_2O)_4]Cl_2$ and 2 mol % of a commercially available $[Ru(bpy)_3(PF_6)_2]$ photocatalyst in the presence of ammonium bis(catechol)alkyl silicate (1.3 equiv) as a HAT reagent under blue-light-emitting diode (LED) irradiation (Table 1, entry 1). Pleasingly, this protocol afforded the desired thioglycoside **3a** in a moderate 59% yield as a single $\beta$-anomer ($J_{1,2}$ = 9 Hz). Increasing the amount of the bromide partner **2a** from 1 equiv to 1.3 equiv furnished **3a** in a good 79% yield (entry 2). Moreover, the yield was increased up to 85% when 1.5 equiv of **2a** was used (entry 3). The optimization of the reaction conditions was continued with respect to solvent; however, no significant improvement of the yield of **3a** was observed with DMA, DMSO, MeCN, and THF (entries 5−8). Finally, performing the coupling reaction with the iodobenzonitrile instead of the bromide led to **3a** in 90% yield (entry 9). Extensive examinations of the other reaction parameters revealed that the use of molecular sieves plays an important role in this reaction. The yield of **3a** was improved up to 95% with complete retention of the anomeric configuration when the reaction was conducted in the presence of molecular sieves (entry 10). A control experiment showed that all parameters (Ni catalyst, Ru photocatalyst, HAT reagent, and light) were essential for the reaction to proceed. Without one of them, the reaction do not occur.

With these encouraging results, we investigated next the scope for this dual Ni/photocatalysis process by systematically varying the nature of the electrophile partner **2** and the thiosugar substrates **1a−e** (Scheme 1). All the couplings proceeded cleanly and selectively in good yields. As shown in Scheme 1, various electron-deficient and electron-rich aryl iodides having *para*- and *meta*-substitution effectively underwent reaction with *tetra*-*O*-acetylated 1-thio-$\beta$-D-glucopyranose **1a** in yields up to 96% (products **3a−o**).

Various reactive functional groups were tolerated, such as nitrile (**3a**), ester (**3g**), halogens (**3b−d**, **3h**), isopropyl (**3n**), and amino acid (**3o**). In addition, the presence of an *ortho* substitution at the aromatic ring of the coupling partner does

**Scheme 1. Scope of Coupling of Thioglucose 1a with Halo(hetero)arenes, Alkenyl Halides, and Alkynyl Bromides 2**[c]




[a]Yield of isolated product. [b]Comparison with results obtained by Pd catalysis reported in refs 8a, 8b, and 8c. [c]Reaction conditions: A sealable tube was charged with thiosugar **1a** (1 equiv, 0.2 mmol), aryl, alkenyl, or alkynyl halides **2** (1.5 equiv), $[Ni(dtbbpy)(H_2O)_4]Cl_2$ precatalyst (5 mol %), $[Ru(bpy)_3](PF_6)_2$ (2 mol %), and HAT reagent (diisopropylammonium bis(catechol)isobutylsilicate) (1.3 equiv) in dry and degassed DMF (1.0 mL).



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not affect the coupling process as compounds **3d**, **3l** , and **3m** having *ortho* substituent groups were obtained in 88%, 73%, and 85% yields, respectively.

Aside from aryl iodides, aryl bromides can also serve as coupling partners under Ni photocatalysis. For example, cross coupling of aryl bromides bearing various functions (−CN, −Cl, −F, and − OMe) have been successfully achieved under room temperature to afford the corresponding thioglycosides (**3a−b**, **3h**, **3i**, **3k**,**l**) in moderate to good yields with no changes to the standard reaction conditions. However, we can note that aryl bromides are less reactive than their iodide congeners in this cross-coupling protocol. Interestingly, couplings with heteroaryl halides derived from quinolinone, pyridine, and indole have also been successful, furnishing **3p−r** in excellent yields (87%−95%). In addition, *para*-iodophenylalanine (NHBoc) can be employed as a coupling partner (compound **3o**).

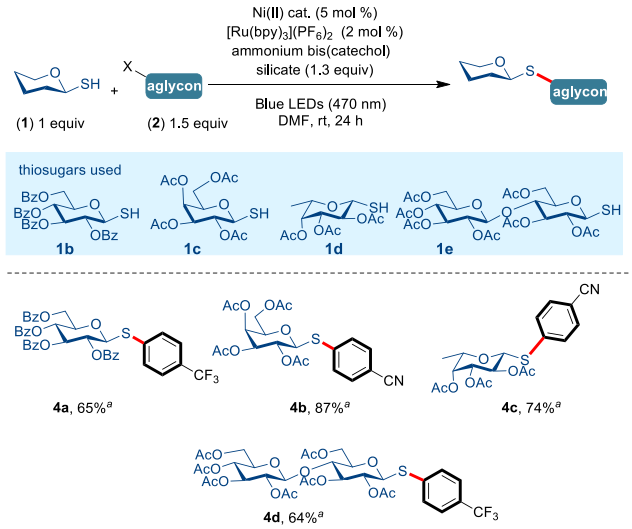
One can be note that across a number of substrates coupling products were afforded in comparable yields to those obtained under palladium-catalyzed (thermal) conditions.

In the aim to further push the limit of this Ni-photocatalysis protocol, we examined the coupling of **1a** with halogenated alkenes and alkynes. Delightfully, when *E*-*β*-styryl bromide was employed, the coupling with **1a** afforded stereoselectively the desired alkenyl thioglycoside derivative **3t** in 87% yield. In addition, reaction of 4-(bromoethynyl)thiophene with **1a** furnished the desired alkynyl-thioether **3u** in 58% yield. Interestingly, when (*E*)-1,2-diiodoethene was used, the coupling reaction with **1a** furnished selectively the monocoupling product **3s** in a moderate 30% yield, while the formation of dicoupling product has never been observed. Finally, this methodology was applied with success to the synthesis of the compound **3v** (85% yield), an hSGLT1 inhibitor used for the control of hyperglycemia in patients with diabetes.

In a next step, we examined the scope of this method with respect to the glycosyl thiols. As depicted in Scheme 2, this coupling reaction tolerates different glycosylthiols **1b−e**: *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**, all coupled with the 4-iodobenzonitrile **2a** to give thioglycosides **4a−c** in good yields. In addition, this coupling could be applied to the complex disaccharide 1-thio-*β*-D-cellobiose **1e** which was efficiently reacted with **2a** to give **4d** in 64% yield.

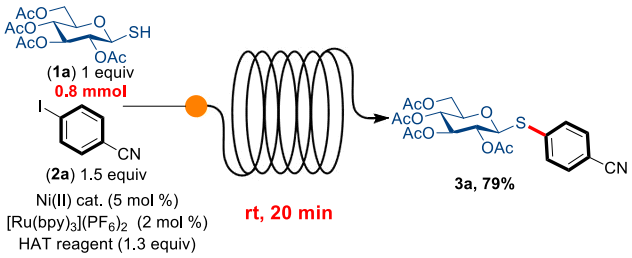
Recently, continuous-flow synthetic methodologies combined to photochemistry have become an emerging field.[15] This combination could allow the development of a fully automated process with an increased efficiency and, in many cases, improved sustainability. The great peculiarity of a flow photoredox system is a very efficient irradiation that allows us to speed the reaction rate up so that productivity is generally greatly improved with respect to the batch system. Indeed, reaction scale up is usually easy to perform with high yields. In order to accelerate our coupling process, we attempted to transport the continuous-flow techniques to our reaction. We were pleased to see that the thioarylation of **1a** with **2a** in a large-scale version (0.8 mmol scale, 4-fold), could be carried out under the same conditions at a residence time of 20 min at 25 °C. Remarkably, the reaction runs smoothly with complete conversion, and the desired product was isolated in 79% yield (Scheme 3).

**Scheme 2. Scope of Thiosugars 1b−e Coupling with Iodoarenes**[b]




[a]Yield of isolated product. [b]Reaction conditions: A sealable tube was charged with thiosugar **1b−e** (1 equiv, 0.2 mmol), aryl halides **2** (1.5 equiv), $[Ni(dtbbpy)(H_2O)_4]Cl_2$ precatalyst (5 mol %), $[Ru(bpy)_3](PF_6)_2$ (2 mol %), and HAT reagent (diisopropylammonium bis(catechol)isobutylsilicate) (1.3 equiv) in dry and degassed DMF (1.0 mL).

**Scheme 3. Continuous-Flow Coupling of Thioglucose 1a with 2a**




In summary, we have shown that 1-thiosugars are competent nucleophile partners in the Ni/photoredox-dual-catalyzed cross-coupling reactions and developed a general method for the synthesis of thioglycosides in batch or in flow. The method tolerates a wide range of functional groups such as aryl, heteroaryl, alkenyl, and alkynyl bromides and iodides. In addition, a variety of glycosyl thiols could be used. This method opens news opportunities for using thiosugars in synthetic methodology.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01730.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

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## Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

In memory of Professor François COUTY.

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