Exploration of thioglycosides in photoinduced desulfurative cross-coupling reactions

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Thioglycosides have been a mainstay of *O*-glycosylation chemistry. Here we demonstrate that under mild photochemical conditions, readily synthesized bench-stable electron poor thioglycosides are also useful *C*-glycoside precursors, undergoing desulfurative glycosyl radical generation. Two complementary classes thioglycosides are described. The glycosyl dithioimidocarbonates, undergo radical coupling in the presence of 4CzIPN, a weak acid and Hantzsch ester, under blue light illumination. Alternatively, 4-cyanotetrafluorophenyl or 4-tetrafluropyridyl thioglycosides can be used to generate glycosyl radicals in the presence of a base and Hantzsch ester under blue light irradiation in a catalyst-free approach. These radicals perform well in Geise-like reactions to yield *C*-glycosides with high stereoselectivity. Furthermore, related thioethers bearing 4-cyanotetrafluorophenyl groups are also potent radical precursors.

C-glycosides are found in natural products and recently have become key structures of pharmaceuticals.[1] In comparison with *O*-glycosides, the *C*-glycoside provides metabolic stability towards hydrolytic enzymes, while preserving many of the important protein recognition features.[1-4]

In the synthesis of *C*-glycosides, glycosyl radicals are the simplest and most versatile disconnection. Addition to glycosyl radicals generally leads to excellent anomeric selectivity due to the preferred axial addition[5,6], alternatively equatorial *C*-glycosides can be formed with transition metal-based catalysis[3]. Due to the versatility of glycosyl radicals, significant effort has gone into exploring methods to generate these species (Fig 1.). Classically glycosyl halides provided convenient precursors but these are unstable and are most often used in radical chain based reactions under thermal initiation.[6-9] Methods based on glycosyl xanthates or dithiocarbamates are promising but require multistep synthesis and are most often paired with organotin hydrides.[10-11] Other more complex *C*-glycosyl esters and *C*-glycosyl acids have been explored due to the ability to pair these reagents with photocatalytic approaches, however the *C*-glycosides are challenging to access for many pyranosyl derivatives.[12-15] Glycosyl trifluoroborates have also been explored with similar challenges.[16-17] Glycosyl 1,4-dihydropyridyl esters are promising due to the ease of forming esters and the activity of these esters under photocatalytic conditions.[18-21] We hypothesized that thioglycosides could provide radical precursors that are simple to produce and are stable to many protecting group modifications.[4,22-23] Excellent examples of using oxidized thioglycosides, such as sulfoxides and sulfones, have shown these derivatives to be potent radical precursors under visible light illumination.[2,4,24-28] Here, we sought to further simplify the generation of potent glycosyl radical precursors by directly using readily accessible thioglycoside derivatives to construct *C*-glycosides with Hantzsch esters for blue light photoinduced radical fragmentation.

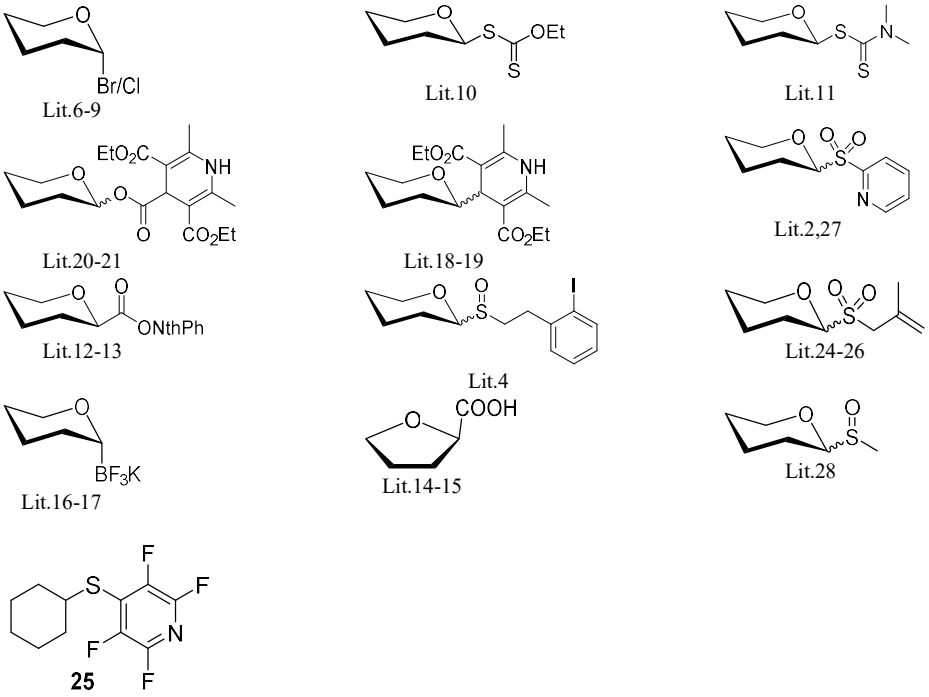


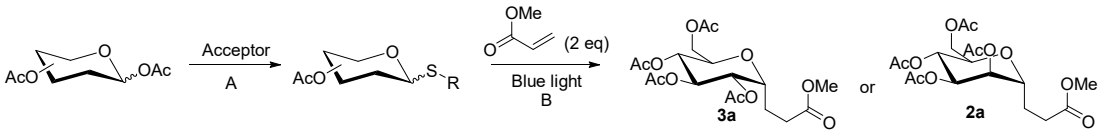
Fig.1 Representative radical precursors

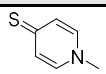
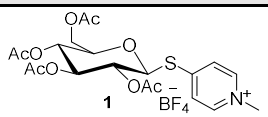
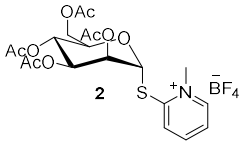
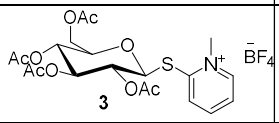
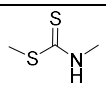
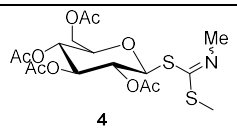
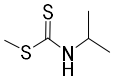
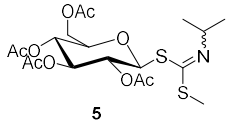
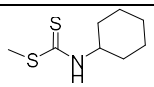
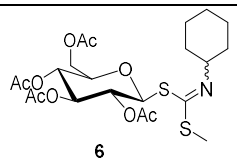
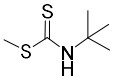
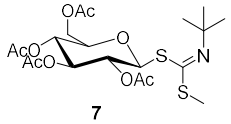
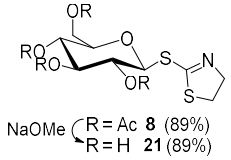
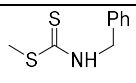
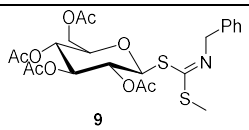
Results and discussion

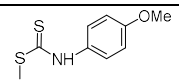
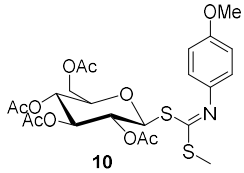
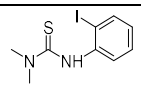
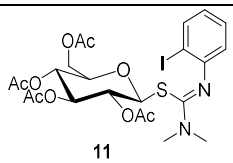
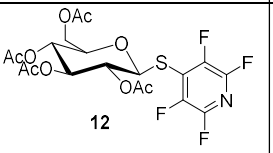
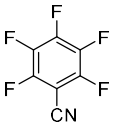
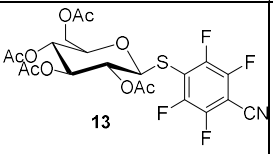
Hantzsch esters (HE) have been successfully used in many photoinduced approaches serving either directly as the visible-light-absorbing species or as electron rich donors in electron donor acceptor complexes.[2,29-31] In most cases HE serves as the reductant in the excited state and as a hydrogen atom donor.[2,29-30] It was envisaged that a readily synthesized thioglycoside derivative may serve as the complementary electron poor acceptor to HE to form glycosyl radicals.

Based on the known reactivity of pyridyl thioglyosylsulfones with HE under photoinduced radical formation,[2] we explored glycosyl thiopyridinium salts **1** through **3**. These could be prepared in a single step from the parent glycosyl acetates and methylthiopyridones (Table 1, Entry 1 to 3). The structure of the mannosyl thiopyridinium **2** was confirmed by X-ray crystallography (See SI). Preliminary photochemical experiments under standard conditions using blue light, triethylamine as the base and methyl acrylate as the radical acceptor indicated that compound **3** gave a useful yield of the expected α-*C*-glycoside **3a**. The lack of product formation with compound **1** suggests the pyridinium regioisomer is key to the reactivity of these compounds. The absorbance spectra of **3** with HE was investigated. It was found that an absorbance band tailing into the visible region (>450 nm) was present only in solutions containing both HE and **3**, suggesting the photoreduction may proceed through an EDA complex (Fig S1).[29-31] Emboldened by the potential of using thioglycosides in *C*-glycoside formation we pursued compounds that could be produced in higher yields, that were more stable to storage, and that were amenable to protecting group manipulations.

Table 1. Exploration of thioglycosides as radical precursors



Entry	Acceptor	Conditions A (yield)	Thioglycoside	Conditions B (product)	Yield
1		BF_3•Et_2O, MeCN, reflux (25 %)	 1	HE (3 eq), Et_3N (3 eq), DMAc (0.25 N), 16h (**3a**)	Trace
2		BF_3•Et_2O, MeCN, reflux (22 %)	 2	HE (3 eq), Et_3N (3 eq), DMAc (0.25 N), 16h (**2a**)	42%
3		BF_3•Et_2O, MeCN, reflux (37 %)	 3	HE (3 eq), Et_3N (3 eq), DMAc (0.25 N), 16h HE (2 eq), DMAc (0.25 N), 16h (**3a**)	37% 56%
4		BF_3•Et_2O, DCM (89%)	 4	HE (2 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 16h HE (2 eq), TFA (1.5 eq), DMSO (0.2 N), 16h 4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 2.5 h 4CzIPN (1.9%), HE (1.5 eq), TFA (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	19% 59% 80% 69%
5		BF_3•Et_2O, DCM (82%)	 5	4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	82%
6		BF_3•Et_2O, DCM (99%)	 6	4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	84%
7		BF_3•Et_2O, DCM (84%)	 7	4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 2.5 h 4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DCM (0.2 N), 2.5 h (**3a**)	82% 79%
8		BF_3•Et_2O, DCM (89%)	 NaOMe (R = Ac **8** (89%), R = H **21** (89%))	4CzIPN (1.9%), HE (1.5 eq), C_6H_5COOH (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	81%
9		BF_3•Et_2O, DCM (78%)	 9	4CzIPN (1.9%), HE (1.5 eq), CH_3COOH (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	80%

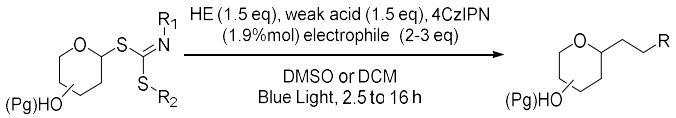
10		$BF_3•Et_2O$, DCM (89%)	 10	4CzIPN (1.9%), HE (1.5 eq), CH_3COOH (1.5 eq), DMSO (0.2 N), 2.5 h 4CzIPN (1.9%), HE (1.5 eq), TFA (1.5 eq), DMSO (0.2 N), 2.5 h (**3a**)	None 74%
11		$BF_3•Et_2O$, DCM (90%)	 11	$Ir(ppy)_3$ (1%), HE (1.5 eq), Cs_2CO_3 (1.5 eq), DMSO (0.1 N), 2.5 h (**3a**)	73%
12		1. Thiourea, $BF_3•Et_2O$, DCM 2. Acceptor, NEt_3, MeCN (75% two steps, one pot)	 12	HE (1.5 eq), K_2CO_3(1.5 eq), DMSO (0.1 N), 6h HE (1.5 eq), KOAc (1.5 eq), DMSO (0.1 N), 6h (**3a**)	86% 73%
13		1. Thiourea, $BF_3•Et_2O$, DCM 2. Acceptor, NEt_3, MeCN (80% two steps, one pot)	 13	HE (1.2 eq), $KHCO_3$ (1.2 eq), DMAc (0.1 N), 1h, (**3a**) HE (1.2 eq), K_2CO_3 (1.2 eq), DMSO (0.1 N), 1h, (**3a**) HE (1.2 eq), KF (1.2 eq), DMSO (0.1 N), 1h, (**3a**) HE (1.2 eq), KAc (1.2 eq), DMSO (0.1 N), 1h, (**3a**) HE (1.2 eq), $KHCO_3$, (1.2 eq), DMSO (0.1 N), 1h, (**3a**) HE (1.2 eq), $KHCO_3$, (1.2 eq), DMSO (0.1 N, 10% dH_2O), 1h no base no HE no light	26% 81% 78% 73% 87% Trace Trace None None

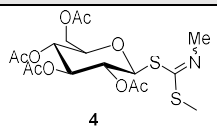
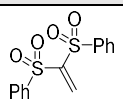
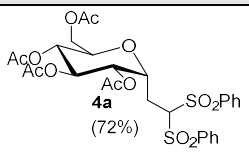
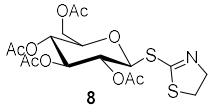
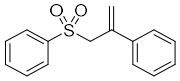
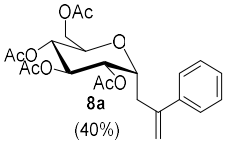
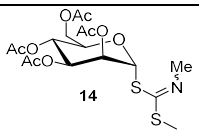
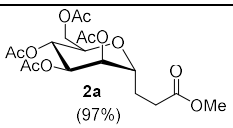
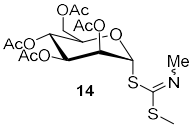
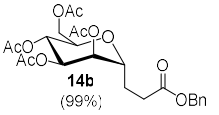
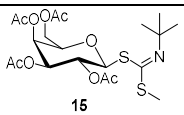
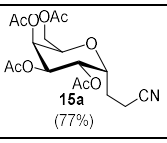
a) all reactions were run at room temperature unless otherwise noted

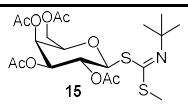
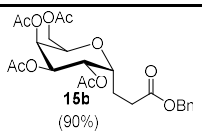
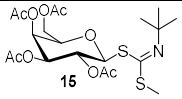
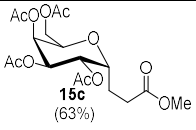
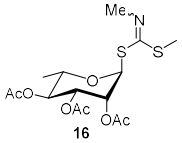
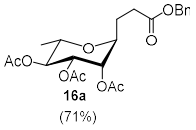
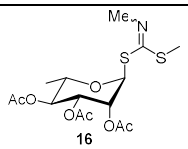
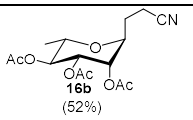
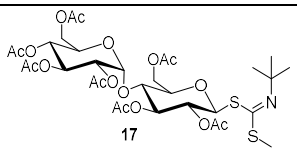
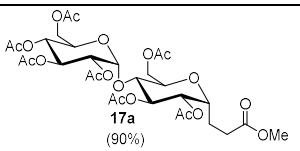
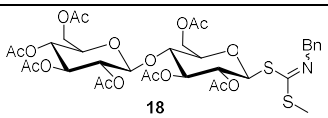
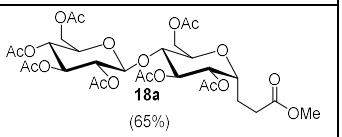
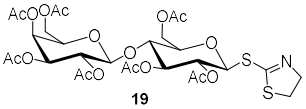
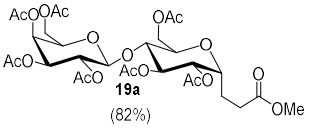
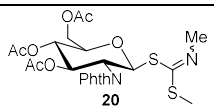
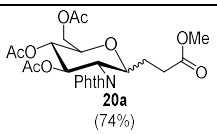
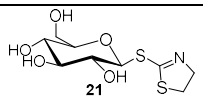
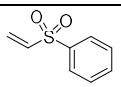
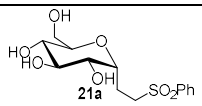
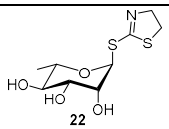
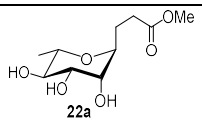
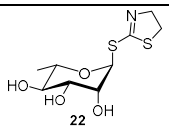
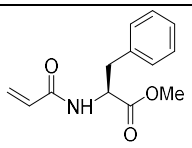
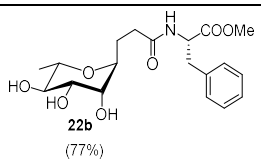
Given the promise of xanthates[10] and dithiocarbmates[11] as radical precursors we next explored the use of the glucosyl dithioimidocarbonates **4** (Table 1. Entry 4). As the structure of dithioimidocarbonates are similar to dithiocarbamates, we speculated that the dithioimidocarbonates may have similar properties and serve as radical precursors. As clearly demonstrated by Demchenko and colleagues, dithioimodocarbonates are useful glycosyl donors in *O*-glycosylation chemistry and can be readily synthesized from peracetylated precursors.[23,24] It was envisaged that the protonated dithioimidocarbonate could undergo photoinduced reduction by HE under blue light irradiation (Fig 2). Preliminary experiments with dithioimidocarbonate **4** in the presence of acid gave moderate yields of the *C*-glycoside **3a**. The yield was dependent on the acid used, with benzoic acid performing more poorly than TFA affording *C*-glycoside **3a** with yields of 19% and 59%, respectively. Investigation of the UV spectra of solutions of **4** with HE in the presence of acid showed a small bathochromic shift in comparison with the individual components, suggesting an EDA complex may be formed under the reaction conditions (Fig S2). In future applications we planned to use glycosides bearing acid sensitive groups and thus explored the possibility of improving the reaction in the presence of the weaker benzoic acid through addition of 4CzIPN as a photocatalyst. The addition of 4CzIPN significantly improved the yield of the reaction with benzoic acid, affording *C*-glycoside **3a** (80% entry 4, table 1). Various thioimidocarbonates (Entries 4-10, Table 1) were subjected to the photocatalyst promoted conditions and all preformed well forming the desired *C*-glycoside **3a** in high yield

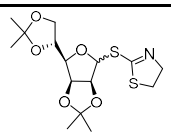
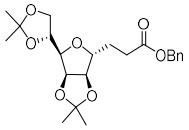
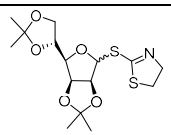
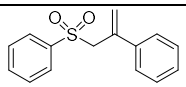
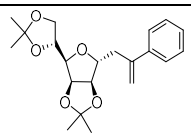
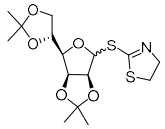
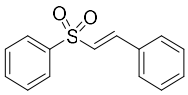
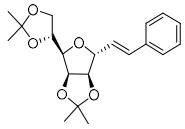
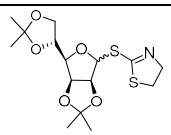
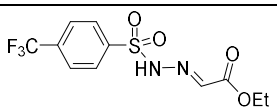
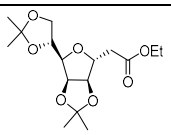
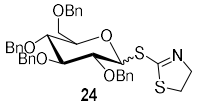
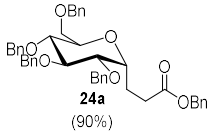
(Table 1). Despite the promising results of these glycosides, it was found that attempts to remove the acetyl protecting groups from **4** under acidic or basic conditions led to compound decomposition, however, the cyclic dithioimidocarbonate **8** (entry 8, table 1) was stable to Zemplen deprotection conditions and afforded the corresponding unprotected glucosyl dithioimidocarbonate **21** (89%). The results from entry 4 to 9 (table 1) suggest that the dithioimidocarbonate alkyl groups do not significantly influence the reaction yield, both acetic acid and benzoic acid can activate the substrates. We further found that with the replacement of an alkyl substituent by a phenyl group on the dithioimidocarbonate resulted in the necessity to use a stronger acid, TFA, for activation of the radical precursor (entry 10, table 1). Inspired by the work of the Niu group[4], we also designed and synthesized glycosyl thioimidate **11** (entry 11, table 1) as the radical precursor. Aryl radical was formed via photoreduction dehalogenation[32] of **11**, follow by intramolecular radical substitution to attack the anomeric C-S bond, generating *N*,*N*-dimethyl-2-benzothiazolamine (see Fig S3 in SI for mechanism and details) and glycosyl radical, which proceeds to form *C*-glycoside **3a**. However, the reaction yield was not significantly improved over simpler substrates.

Table 2. diverse glycosyl dithioimidocarbonates and their radical reaction



Entry	Thioglycoside	Coupling partner (condition)	*C*-glycoside (isolated yield)
1	 **4**	 A	 **4a** (72%)
2	 **8**	 A	 **8a** (40%)
3	 **14**	 B	 **2a** (97%)
4	 **14**	 B	 **14b** (99%)
5	 **15**	 B	 **15a** (77%)

6	 **15**	 B	 **15b** (90%)
7	 **15**	 C	 **15c** (63%)
8	 **16**	 B	 **16a** (71%)
9	 **16**	 B	 **16b** (52%)
10	 **17**	 B	 **17a** (90%)
11	 **18**	 C	 **18a** (65%)
12	 **19**	 B	 **19a** (82%)
13	 **20**	 C	 **20a** (74%)
14	 **21**	 B	 **21a** (41%)
15	 **22**	 B	 **22a** (85%)
16	 **22**	 B	 **22b** (77%)

17	 23	 B	 **23a** (88%)
18	 23	 B	 **23b** (24%)
19	 23	 B	 **23c** (40%)
20	 23	 D	 **23d** (29%)
21	 24	 B	 **24a** (90%)

A) 4CzIPN, HE, benzoic acid, DCM; B) 4CzIPN, HE, acetic acid, DMSO; C) 4CzIPN, HE, benzoic acid, DMSO; D) 1. 4CzIPN, HE, acetic acid, DCM, 2. NEt_3, EtOH, 80℃.

A series of diverse glycosyl dithioimidocarbonates were synthesized (Table 2). All the substrates were successfully converted to the corresponding *C*-glycosides with addition of various radical acceptors. Protecting groups including acetyl (entry 1 to 13, table 2), benzyl (entry 21, table 2) and isopropylidene (entry 17 to 20, table 2) are well tolerated. Furthermore, unprotected substrates (entry 14 to 16, table 2) also gave the desired *C*-glycosides under these reaction conditions. The isolated yields for *C*-glycosides **23b** and **23c** (entry 18 and 19, table 2) are lower than desired due to challenging purifications requiring two chromatography steps. The synthesis of *C*-glycoside **23d** (entry 20, table 2) used a radical acceptor recently reported in literature.[33] The hydrazide intermediate was carried forward without purification and treated with base to promote sulfinate and dinitrogen extrusion, affording **23d**. All the glycosyl dithioimidocarbonates listed in table 2 are bench stable and can be stored under ambient conditions for extended periods (>1 year) without decomposition, with the exception of glycosyl **21** which required storage at -20 °C when kept for extended periods.

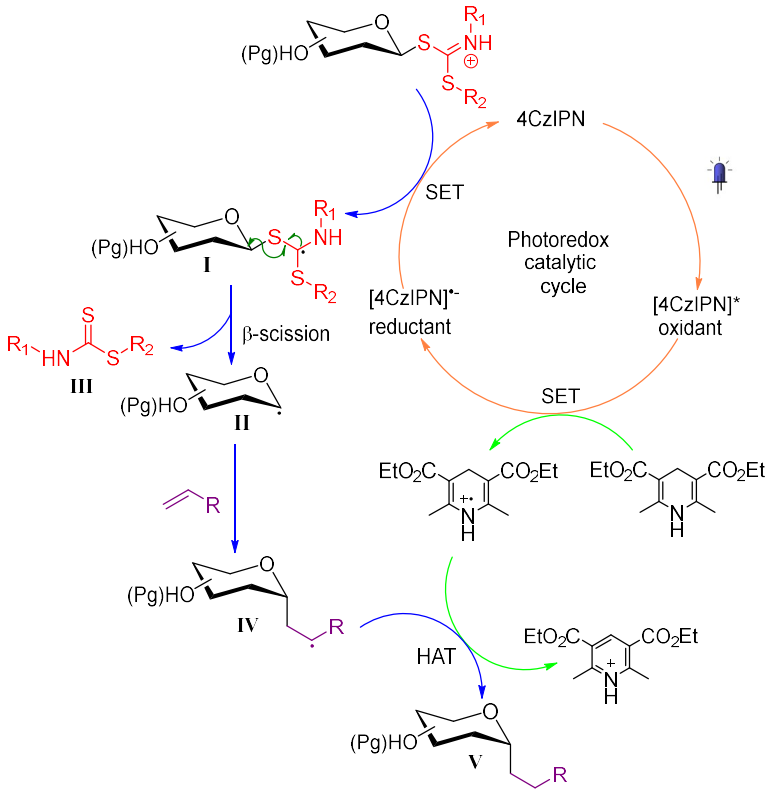


Fig 2. Proposed mechanism for photoinduced desulfurative radical coupling C-glycoside formation from glycosyl dithioimidocarbonates

The proposed mechanism for photoinduce desulfurative radical coupling of the glycosyl dithioimidocarbonates is shown in Fig 2. Upon photoexcitation of 4CzIPN the excited state can readily oxidize HE via a single electron transfer mechanism.[33] The protonated glycosyl dithioimidocarbonate, undergoes electrochemical reduction by the reduced photocatalyst. This reduction would yield the α-amino radical **I**. Its β-scission follows to give thiocarbamate **III** (confirmed by Mass spectroscopy) and glycosyl radical **II**.[34, 35] Glycosyl radical can subsequently add to the acceptor to give rise to radical intermediate **IV**. **IV** then undergoes hydrogen atom transfer (HAT) with dihydropyridine radical cation to deliver *C*-glycoside product **V** in high axial selectivity.

Despite the utility of dithioimidocarbonates there were limitations for the storage of some of these glycosides. Particularly, GlcNAc derivatives decomposed to oxazolines on storage. Phthalimido protected GlcN derivatives were stable but gave poor stereoselectivity in the radical couplings (table 2, entry 13). To avoid these complications we explored alternative electron poor thioglycosides.

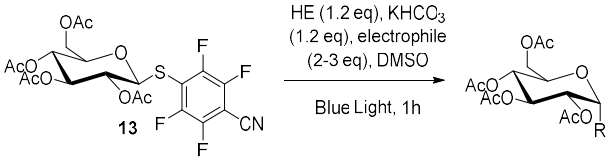
In 2021, Dilman's group developed a series of alkyl sulfides bearing perfluorinated pyridines as the radical precursors to forge C-C bonds.[36] In this report, sulfide **25** (Fig 1) is activated under blue illumination (455 nm) at 90 – 100 °C in the presence of Hantzsch ester, triethylamine and photocatalyst $Ir(ppy)_3$ to generate a cyclohexyl radical, which is subsequently trapped by the radical acceptor *tert*-butyl acrylate, to afford *tert*-butyl 3-cyclohexylpropanoate (42%). Building on this report, we hypothesized that thioglycosides bearing fluorinated aryls may undergo radical formation in the presence of HE, without requiring a photocatalyst. Thioglycosides **12** and **13** (table 1) were prepared in two-step, one pot protocols proceeding

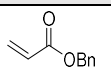
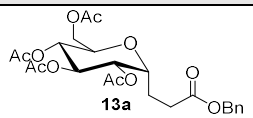
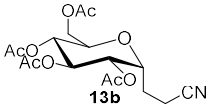
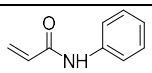
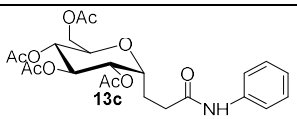
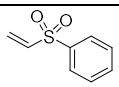
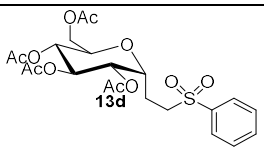
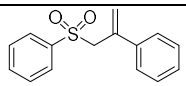
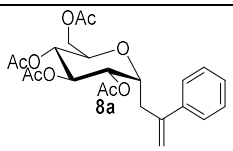
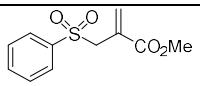
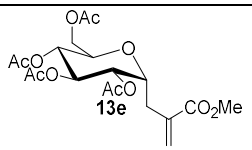
through the corresponding glycosyl thiouronium salt followed by an S_NAr reaction with the desired pentafluoroaryls.

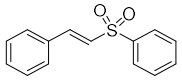
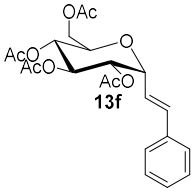
Subjecting **12** and **13** to a photoredox Geise reaction with addition of HE and K_2CO_3 under blue LED activation gave *C*-glycoside **3a** in 86% and 81% yields, respectively. We further optimized the reaction with compound **13** by altering the base used. We also confirmed the necessity of light, base, and HE (Table 1).

Pleased with the scalable synthesis, and the fact that compounds **12** and **13** were stable to bench-top storage, we explored the scope of this transformation with a variety of radical acceptors. Using thioglycoside **13**, *α,β*-unsaturated esters, nitriles and sulfones proved to be excellent coupling partners under the photoredox conditions. Addition-elimination reactions also afforded the desired products (entry 5, 6 and 7, table 3), even with a more challenging radical acceptor (*E*)-(2-(phenylsulfonyl)vinyl)benzene, albeit with lower yield (Entry 7, table 3).

Table 3. Photocatalyzed reactions of thioglycoside 13

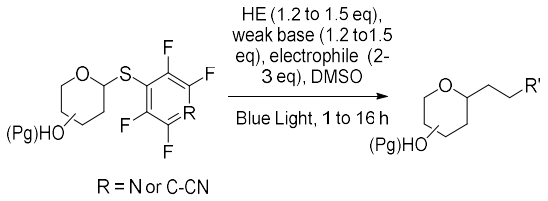


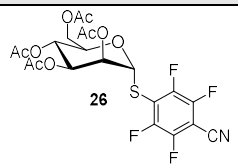
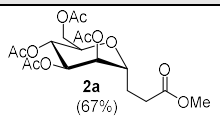
Entry	Acceptor	*C*-glycoside	Yield (%)
1			97%
2			70%
3			75%
4			93%
5			58%
6			70%

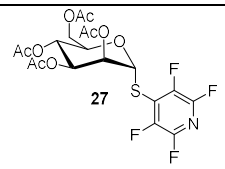
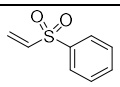
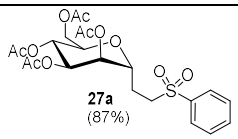
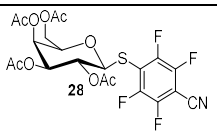
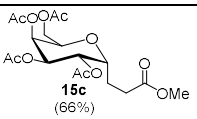
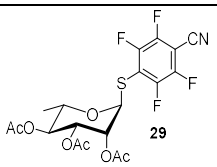
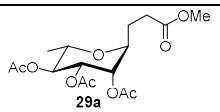
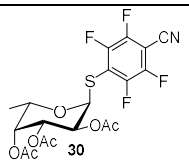
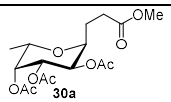
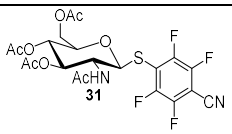
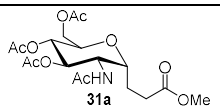
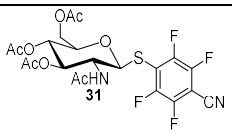
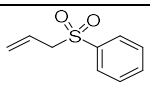
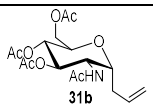
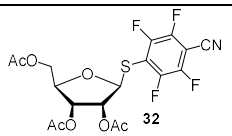
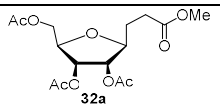
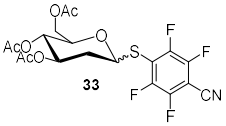
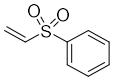
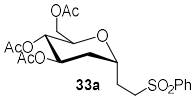
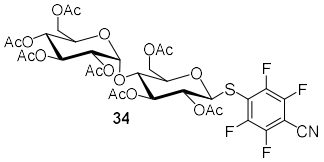
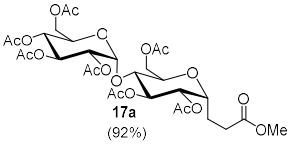
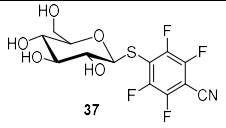
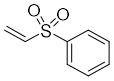
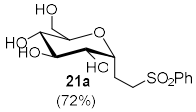
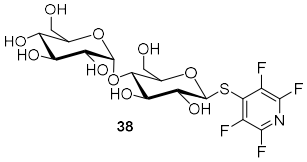
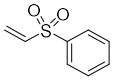
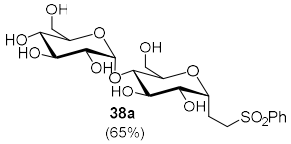
7			20%

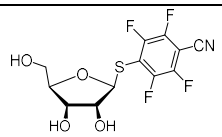
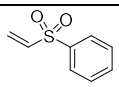
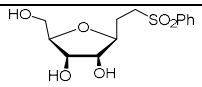
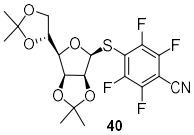
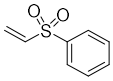
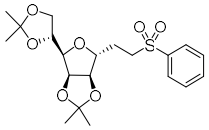
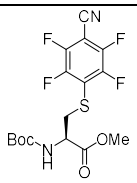
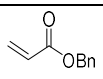
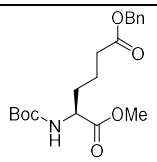
Given the promise of compounds **12** and **13** as radical precursors, we explored the glycosyl donor scope by synthesizing and testing various structurally diverse tetrafluorinated aryl thioglycosides (Table 4). These thioglycosides could be conveniently prepared from the peracetylated sugars in a single pot as described above, with the exception of GlcNAc derivative **31**, where it was necessary to synthesize the thiouronium salt from thiourea and the glycosyl chloride to avoid oxazoline formation. The 4-cyano-tetrafluorophenyl thioglycosides proved to be sufficiently stable to be deacetylated under mildly acidic conditions, suggesting further protecting-group-free manipulations would be possible if required. The 4-tetrafluoropyridyl thioglycosides were stable to deacetylation under mildly basic conditions. Importantly, both protected and unprotected thioglycosides (**26**-**40**, please see SI for **35** and **36**) exhibit excellent stability. Storage under ambient conditions (benchtop, room temperature, clear vial) over several months is possible without decomposition for all the radical precursors including the GlcNAc derivative **31**. This range of thioglycosides underwent the same catalyst-free desulfurative coupling to afford *C*-glycosylation products (entry 1 to 14, table 4) in good to excellent yields. Given the synthetic route to these radical precursors proceeds via an S_NAr reaction we explored generation of other thioethers from thiols as radical precursors. The synthesis of a 4-cyano-tetrafluorophenyl cysteine derivative (**41**) proceeded smoothly, and was an excellent substrate for the desulfurative cross-coupling reaction (entry 15, table 4). These results suggests that this operationally simple reaction will be useful in the generation of amino acid derivatives may have be useful for modification of other thiol-containing biomolecules.[37]

Table 4. Reactions of diverse glycosides



Entry	Thioglycoside	Coupling partner (condition)	*C*-glycoside (isolated yield)
1		 A	

2	 **27**	 B	 **27a** (87%)
3	 **28**	 A	 **15c** (66%)
4	 **29**	 A	 **29a** (82%)
5	 **30**	 A	 **30a** (72%)
6	 **31**	 A	 **31a** (85%)
7	 **31**	 A	 **31b** (30%)
8	 **32**	 A	 **32a** (61%)
9	 **33**	 A	 **33a** (86%)
10	 **34**	 A	 **17a** (92%)
11	 **37**	 A	 **21a** (72%)
12	 **38**	 B	 **38a** (65%)

13	 **39**	 A	 **39a** (56%)
14	 **40**	 A	 **40a** (90%)
15	 **41**	 A	 **41a** (57%)

A) HE, $KHCO_3$, DMSO; B) HE, K_2CO_3, DMSO;

To shed light on the mechanism of this catalyst-free photoinduced desulfurative cross-coupling reaction, UV-vis absorption spectra of the reaction components were analyzed (Fig 3). DMSO solutions at concentrations equivalent to the reaction conditions were analyzed. Thioglycoside **12** alone and K_2CO_3 alone (light blue and deep cyan dashed traces) were both weakly absorbing in the visible region (> 400 nm) but when mixed (yellow doted trace) the solution produces an absorbing species that tails into the visible region. This band is consistent with an anion-π complex being formed between the electron poor aryl and base.[38] The solution of HE (green dashed trace) shows the expected absorbance spectra, and in the presence of K_2CO_3 (green doted trace), gives a strongly absorbing species above 450 nm consistent with deprotonation of the HE.[29] Interestingly, a solution containing all the reaction components (dark blue solid trace) showed the loss of the deprotonated HE band and an overall bathochromic shift in the absorbance of the solution (Fig 3A). Assignment of the species present is speculative, but the spectra may arise from formation of an EDA complex between **12** and the HE anion. Similarly, analysis of glycoside **13** shows a potential anion-π complex with bicarbonate (yellow doted trace). The weaker base in this solution only leads to partial deprotonation of the HE (green doted trace) but similarly addition of **13** to this solution (dark blue solid trace) results in loss of the band indicative of the HE anion and an overall bathochromic shift in the spectra (Fig 3B). Inspection of the spectra of **12** and **13** in the presence of HE without base (deep blue dashed trace) shows differences between these thioglycosides. A solution of HE and thioglycoside **12** appears like that of the HE alone, while with glycoside **13** there is a clear bathochromic shift in the spectra (Fig 2A and 2B). The difference is consistent with the reduction potential of these two glycosides with compound **13** being a stronger oxidant, and more likely to form an EDA complex with HE. Cyclic voltammetry of these compounds shows compound **13** (-1.74 V) to be more readily reduced than compound **12** (-1.84 V) (See SI).

A tentative mechanism for these catalyst-free desulfurative cross-coupling reactions involves the Hantzsch ester anion forming in the presence of the inorganic base (Fig 3C). Subsequent photoinduced single electron transfer from $*HE^-$ to 4-cyano-2,3,5,6-tetrafluorophenyl thioglycosides leads to dihydropyridine radical and the radical anion of the thioglycoside which

undergoes desulfurative fragmentation to produce the glycosyl radical. Finally, addition of the glycosyl radical to an alkene generates alkyl radical which is reduced by the dihydropyridine radical to form the *C*-glycoside.

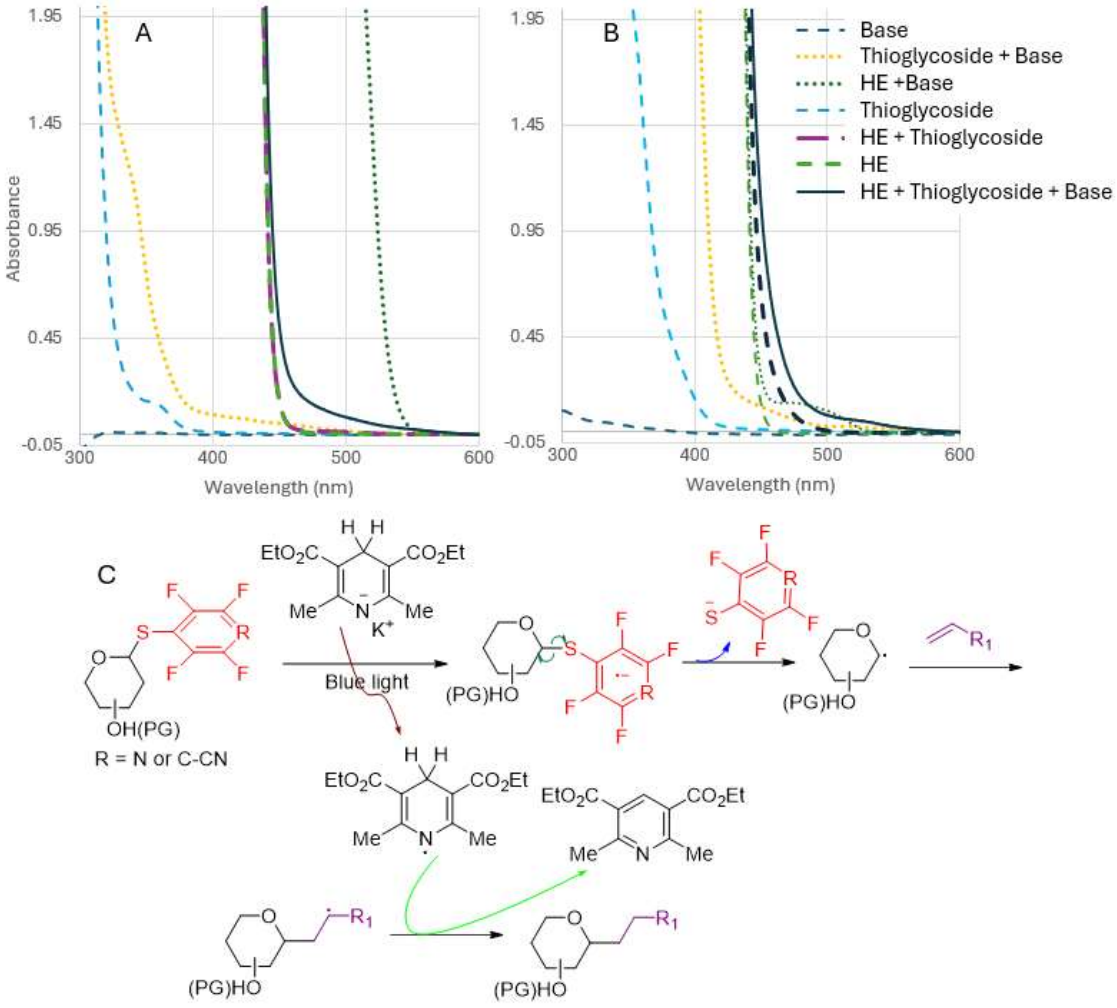


Figure 3. Absorbance spectra and proposed mechanism of photoinduced desulfurative radical coupling. A. Thioglycoside **12**, Base K_2CO_3, B. Thioglycoside **13**, Base $KHCO_3$. C. Proposed mechanism

Conclusions

In conclusion, we have developed a class of glycosyl dithioimidocarbonate and tetrafluorinated aryl thioglycosides that can be readily synthesized from commercial peracetylated sugars. We have demonstrated these bench stable species generate corresponding glycosyl radicals under photoinduced conditions in the presence of HE. The conditions are mild and avoid the use of toxic regents. The reactions can easily be carried out on the benchtop with minimal precautions against water and oxygen. This novel glycosylation method complements the current methodology to access *C*-glycosides. Ongoing research exploring reactions with

similar sulfides are being carried out to investigate the generality of this approach to the generation of radicals in other contexts.

Data availability

Experiment procedures, useful information, NMR spectrum and mass spectrometry data are available in Supplementary Information. Crystallographic data for the reported structures in this article have been deposited with the Cambridge Crystallographic Data Centre, accession numbers CCDC 2307380 and 2307381 respectively.

References

1. Ghosh, T. & Nokami, T. Recent development of stereoselective *C*-glycosylation via generation of glycosyl radical. *Carbohydr. Res.* **522**, 108677 (2022).
2. Wang, Q. *et al*. Visible light activation enables desulfonylative cross-coupling of glycosyl sulfones. *Nature Synthesis* **1**, 967-974 (2022).
3. Jiang, Y., Zhang, Y., Lee, B. C. & Koh, M. J. Diversification of Glycosyl Compounds via Glycosyl Radicals. *Angew. Chem. Int. Ed.* **62**, e202305138 (2023).
4. Shang, W., *Su S.-N., Shi, R., Mou Z.-D., Yu,G.-Q., Zhang, X., Niu D.*. Generation of Glycosyl Radicals from Glycosyl Sulfoxides and Its Use in the Synthesis of *C*-linked Glycoconjugates. *Angew. Chem. Int. Ed.* **60**, 385-390 (2021).
5. Chen, A. *et al.* Stereoselective alkyl *C*-glycosylation of glycosyl esters via anomeric C–O bond homolysis: efficient access to *C*-glycosyl amino acids and C-glycosyl peptides. *Chem. Sci.* **14**, 7569-7580 (2023).
6. Giese, B. & Dupuis, J. Diastereoselective Syntheses of *C*-Glycopyranosides. *Angew. Chem. Int. Ed.* **22**, 622-623 (1983).
7. Wang, Q. *et al.* Iron-catalysed reductive cross-coupling of glycosyl radicals for the stereoselective synthesis of C-glycosides. *Nature Synthesis* **1**, 235-244 (2022).
8. Jiang, Y., Wang, Q., Zhang, X. & Koh, M. J. Synthesis of *C*-glycosides by Ti-catalyzed stereoselective glycosyl radical functionalization. *Chem* **7**, 3377-3392 (2021).
9. Mou, Z.-D., Wang, J.-X., Zhang, X. & Niu, D. Stereoselective Preparation of *C*-Aryl Glycosides via Visible-Light-Induced Nickel-Catalyzed Reductive Cross-Coupling of Glycosyl Chlorides and Aryl Bromides. *Adv. Synth. Cat.* **363**, 3025-3029 (2021).
10. Kiya, N., Hidaka, Y., Usui, K. & Hirai, G. Synthesis of CH_2-Linked α(1,6)-Disaccharide Analogues by α-Selective Radical Coupling *C*-Glycosylation. *Org. Lett.* **21**, 1588-1592 (2019).
11. Li, G., Noguchi, M., Arisaka, G., Tanaka, Y. & Shoda, S.-i. A protecting group–free approach for synthesizing *C*-glycosides through glycosyl dithiocarbamates. *Org. Biomol. Chem.* **19**, 3134-3138 (2021).
12. Ji, P. *et al.* Visible-Light-Mediated, Chemo- and Stereoselective Radical Process for the Synthesis of *C*-Glycoamino Acids. *Org. Lett.* **21**, 3086-3092 (2019).
13. Wan, I. C. S., Witte, M. D. & Minnaard, A. J. From D- to L-Monosaccharide Derivatives via Photodecarboxylation–Alkylation. *Org. Lett.* **21**, 7669-7673 (2019).
14. Ma, Y. *et al.* Highly stereoselective synthesis of aryl/heteroaryl-*C*-nucleosides via the merger

of photoredox and nickel catalysis. *Chem. Commun.* **55**, 14657-14660 (2019).
15. Zhu, M. & Messaoudi, S. Diastereoselective Decarboxylative Alkynylation of Anomeric Carboxylic Acids Using Cu/Photoredox Dual Catalysis. *ACS Cat.* **11**, 6334-6342 (2021).
16. Miller, E. M. & Walczak, M. A. Light-Mediated Cross-Coupling of Anomeric Trifluoroborates. *Org. Lett.* **23**, 4289-4293 (2021).
17. Takeda, D. *et al.* β-Glycosyl Trifluoroborates as Precursors for Direct α-*C*-Glycosylation: Synthesis of 2-Deoxy-α-*C*-glycosides. *Org. Lett.* **23**, 1940-1944 (2021).
18. Dumoulin, A., Matsui, J. K., Gutiérrez-Bonet, Á. & Molander, G. A. Synthesis of Non-Classical Arylated *C*-Saccharides through Nickel/Photoredox Dual Catalysis. *Angew. Chem. Int. Ed.* **57**, 6614-6618 (2018).
19. Badir, S. O., Dumoulin, A., Matsui, J. K. & Molander, G. A. Synthesis of Reversed *C*-Acyl Glycosides through Ni/Photoredox Dual Catalysis. *Angew. Chem. Int. Ed.* **57**, 6610-6613 (2018).
20. Wei, Y., Lam, J. & Diao, T. Synthesis of *C*-acyl furanosides via the cross-coupling of glycosyl esters with carboxylic acids. *Chem. Sci.* **12**, 11414-11419 (2021).
21. Wei, Y., Ben-zvi, B. & Diao, T. Diastereoselective Synthesis of Aryl *C*-Glycosides from Glycosyl Esters via C−O Bond Homolysis. *Angew. Chem. Int. Ed.* **60**, 9433-9438 (2021).
22. a) Ramakrishnan, A., Pornsuriyasak, P. & Demchenko, A. V. Synthesis, Glycosidation, and Hydrolytic Stability of Novel Glycosyl Thioimidates. *J. Carbohydr. Chem.* **24**, 649-663 (2005). b) Demchenko A.V., Pornsuriyasak, P., Meo, C.D., Malysheva N.N., Potent, Versatile, and Stable: Thiazolyl Thioglycosides as Glycosyl Donors, *Angew. Chem. Int. Ed.* **43**, 3069 –3072, (2004)
23. Ranade, S. C., Hasty, S. J. & Demchenko, A. V. A Comparative Study of Glycosyl Thioimidates as Building Blocks for Chemical Glycosylation. *J. Carbohydr. Chem.* **32**, 360-379 (2013).
24. Wan, L.-Q. *et al.* Nonenzymatic Stereoselective *S*-Glycosylation of Polypeptides and Proteins. *J. Am. Chem. Soc.* **143**, 11919-11926 (2021).
25. Zhang, C. *et al.* Halogen-bond-assisted radical activation of glycosyl donors enables mild and stereoconvergent 1,2-cis-glycosylation. *Nature Chem.* **14**, 686-694 (2022).
26. Zhang, C. *et al.* Direct synthesis of unprotected aryl *C*-glycosides by photoredox Ni-catalysed cross-coupling. *Nature Synthesis* **2**, 251-260 (2023).
27. Wang, Q., Lee, B. C., Song, N. & Koh, M. J. Stereoselective *C*-Aryl Glycosylation by Catalytic Cross-Coupling of Heteroaryl Glycosyl Sulfones. *Angew. Chem. Int. Ed.* **62**, e202301081 (2023).
28. Xie, D., Wang, Y., Zhang, X., Fu, Z. & Niu, D. Alkyl/Glycosyl Sulfoxides as Radical Precursors and Their Use in the Synthesis of Pyridine Derivatives. *Angew. Chem. Int. Ed.* **61**, e202204922 (2022).
29. Heredia, M. D. *et al.* Transition-Metal-Free and Visible-Light-Mediated Desulfonylation and Dehalogenation Reactions: Hantzsch Ester Anion as Electron and Hydrogen Atom Donor. *J. Org. Chem.* **85**, 13481-13494 (2020).
30. Wu, J., Grant, P. S., Li, X., Noble, A. & Aggarwal, V. K. Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single-Electron Transfer. *Angew. Chem. Int. Ed.* **58**, 5697-5701 (2019).
31. Zhu, D.-L., Wu, Q., Li, H.-Y., Li, H.-X. & Lang, J.-P. Hantzsch Ester as a Visible-Light Photoredox Catalyst for Transition-Metal-Free Coupling of Arylhalides and Arylsulfinates. *Chem. Eur. J.* **26**, 3484-3488 (2020).

32. Nguyen, J. D., D'Amato, E. M., Narayanam, J. M. R. & Stephenson, C. R. J. Engaging unactivated alkyl, alkenyl and aryl iodides in visible-light-mediated free radical reactions. *Nature Chemistry* **4**, 854-859 (2012).
33. X. Zhu , H. Li , Q. Li , T. Ai , J. Lu , Y. Yang and J. Cheng , Determination of the C4H Bond Dissociation Energies of NADH Models and Their Radical Cations in Acetonitrile *Chem. Eur. J.*, 9, 871-880 (2003).
34. Yedase, G. S., John, M. & Yatham, V. R. Organophotoredox-Catalyzed Switchable Selective Transformation of Aromatic Aldehydes into Pinacols and Benzyl alcohols. *Asian J. Org. Chem.* **10**, 2916-2920 (2021).
35. McMaster, C., Bream, R. N. Grainger, R. S. Radical-mediated reduction of the dithiocarbamate group under tin-free conditions. *Org. Biomol. Chem.* **10**, 4752-4758 (2012).
36. Panferova, L. I., Zubkov, M. O., Kokorekin, V. A., Levin, V. V. & Dilman, A. D. Using the Thiyl Radical for Aliphatic Hydrogen-Atom Transfer: Thiolation of Unactivated C−H Bonds. *Angew. Chem. Int. Ed.* **60**, 2849-2854 (2021).
37. a) Wang Y, Deng LF, Zhang X, Mou ZD, Niu D. A Radical Approach to Making Unnatural Amino Acids: Conversion of C-S Bonds in Cysteine Derivatives into C-C Bonds. *Angew Chem. Int. Ed.*. **60,** 2155-2159 (2021). b) Miao, P., Zhang, M., Ni, Z., Chen, Q., Sun, Z., Application of the LADA Strategy for the Synthesis of Unnatural Amino Acids through 1,2-Aryl Migration of Allylic Alcohols, *J. Org. Chem*. **89**, 1543–1551, (2024).
38. Buglioni, L., Mastandrea, M. M., Frontera, A. & Pericàs, M. A. Anion–π Interactions in Light-Induced Reactions: Role in the Amidation of (Hetero)aromatic Systems with Activated N-Aryloxyamides. *Chem. Eur. J.* **25**, 11785-11790 (2019).

Methods

General procedure for photoinduced cross-coupling of glycosyl sulfides

General Method 1 (4CzlPN, Acid, HE)

A dry vial (5 mL) was charged with glycosyl dithioimidocarbonate (0.2 mmol), Hantzsch ester (0.3 mmol), 4CzIPN (3 mg, 1.9%mol), Acid (0.3 mmol) and radical acceptor (0.4 mmol). DMSO or DCM (1 mL) was added, and the vial was sealed with a rubber septum. The reaction mixture was then frozen in a liquid N_2 bath and degassed under vacuum (274 mbar) for 3 minutes. The vial was warmed to room temperature and then placed under a N_2 atmosphere. The vial was stirred under blue LED irradiation for indicated time. The reaction mixture was diluted with EtOAc (50 mL), washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The crude was then purified by column chromatography.

General Method 2 (HE, Base)

A dry vial (5 mL) was charged with thioglycoside (0.2 mmol), Hantzsch ester (0.24 mmol or 0.3 mmol), Base (0.24 mmol or 0.3 mmol) and radical acceptor (0.4 mmol). DMSO (2 mL) was added, and the vial was sealed with a rubber septum. The reaction mixture was then frozen in a liquid N_2 bath and degassed under vacuum (274 mbar) for 3 minutes. The vial was warmed to room temperature and then placed under a N_2 atmosphere. The reaction was stirred under blue LED irradiation for indicated time. The reaction mixture was diluted with EtOAc (50 mL), washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude was then purified by column chromatography.

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Author contributions

J.Z., A.L., A.C., S.M.C. developed the cross-coupling method and conducted the mechanistic studies. M.N. directed the investigations. J.Z and A.L. wrote the manuscript with revisions made by M.N.

Competing interests

The authors declare no competing interests.