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# Stereoretentive C($sp^3$)−S Cross-Coupling

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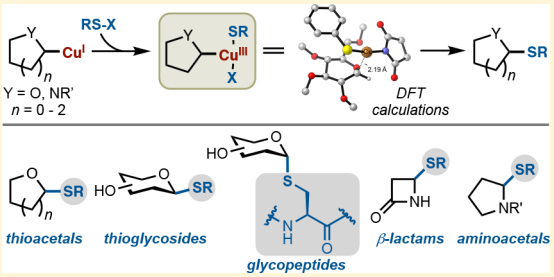
Supporting Information

**ABSTRACT:** We report a stereoretentive cross-coupling reaction of configurationally stable nucleophiles with disulfide and *N*-sulfenylsuccinimide donors promoted by Cu(I). We demonstrate the utility of this method in the synthesis of thioglycosides derived from simple alkyl and aryl thiols, thioglycosides, and in the glycodiversification of cysteine residues in peptides. These reactions operate well with carbohydrate substrates containing common protective groups and reagents with free hydroxyl and secondary amide functionalities under standardized conditions. Competition experiments in combination with computational DFT studies established that the putative anomeric intermediate is an organocopper species that is configurationally stable and resistant to epimerization due to its short lifetime. The subsequent reductive elimination from the Cu(III) intermediate is rapid and stereoretentive. Taken together, the glycosyl cross-coupling is ideally suited for late stage glycodiversification and bioconjugation under highly controlled installation of the aliphatic carbon−sulfur bonds.






## INTRODUCTION

The stereoselective synthesis of carbon−heteroatom bonds constitutes a central goal of synthetic chemistry given their functional importance in the activities of commercial drugs, natural products, and biologics.[1] An example in which the handedness of the saturated carbon plays an imperative role is in the synthesis of bioactive glycosides where the configuration of the anomeric carbon is essential in determining the shape, recognition, localization, and, in general, the biological activities.[2] In addition to *O*-linked glycosides, both synthetic and natural modifications of saccharides frequently involve the introduction of a sulfur atom, and many of the commercially available bioactive thioacetals displaying important biological activities are in the form of thioglycosides (Scheme 1A). Numerous synthetic applications of thioglycosides highlight their utility as versatile glycosyl donors in chemical glycosylation reactions.[3] Thioglycosides are also common glycomimetics (e.g., *S*-linked galactosylceramides) and demonstrate enhanced hydrolytic stabilities relative to their natural *O*-linked congeners while retaining similar conformational preferences.[4] Considering biologics, carbohydrate modifications of cysteine residues in peptides and proteins is of special interest.[5] In addition to the *S*-glycosidic bond found in natural peptides (e.g., sublancin),[6−9] synthetically modified *S*-linked glycopeptides are abundant given their resistance to chemical and enzymatic degradation,[10−12] improved antibacterial activities,[13] and ability to act as stable surrogates of the natural *O*-GlcNAc in proteins and peptides.[4,14] Within the family of $\alpha$-substituted thioethers, aminothioacetals in the form of $\beta$-lactams are one of the most common broad-spectrum antibiotics consisting of penicillins, cephalosporins, and carbapenems.[15] In all of the above examples, the configuration of the C−S linkage is crucial for preserving the relevant physicochemical and biological properties.

Given the significance of glycosyl thioacetals, various methods for their synthesis have been described (Scheme 1B). The preparation of thioglycosides and glycoconjugates starts from a glycosyl donor activated with a Lewis acid in the presence of a thiol nucleophile.[16] Reactions with substrates already equipped with anomeric thiols proceed via displacement of a halide[11,17] or via a thiol−ene reaction with dehydroalanine **4**.[18] However, these processes lack stereochemical control at the anomeric carbon and/or the newly formed amino acid $\alpha$-carbon center.[4,19,20] Davis and coworkers established an alternative protocol that involves a disulfide exchange followed by reductive contraction of the glycosyl disulfide with a phosphine.[21,22] All of the above methods are limited by the nature of the anomeric thiols, which are often available only as the thermodynamic anomer or require multistep syntheses.[4,23] Thus, in order to access both anomers of thioglycosides, an alternative synthetic platform would be necessary, and a complementary approach capitalizes on reversal of polarity at the anomeric carbon. Organolithium[24] and Grignard[25] reagents have been engaged in reactions with sulfur electrophiles; however, this class of reagents is limited only to 2-deoxy sugars due to inherent instability and presents a challenge to bioconjugation due to

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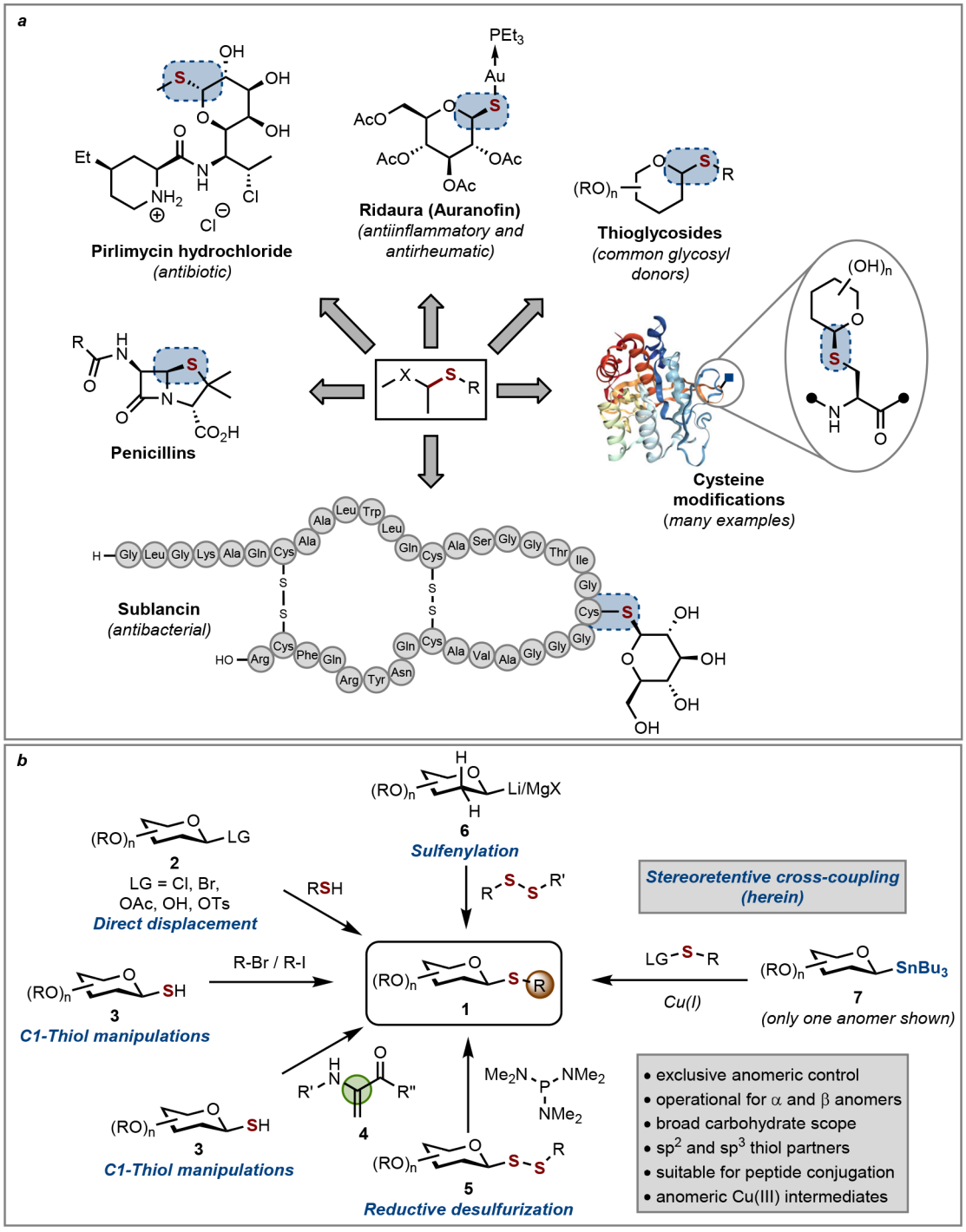
**Scheme 1. (a) Selected Bioactive Thio(amino)acetals; (b) Representative Methods for the Synthesis of *S*-Linked Glycosides and Thioacetals**




their incompatibility with various functional groups commonly found in peptides and proteins.[26,27] The formation of a C($sp^2$)−S bond in small molecules and proteins has been accomplished with various aryl nucleophiles such as boronic acids,[28−31] organopalladium,[32] and organogold[33] reagents. Unlike aryl nucleophiles, the synthesis of C−S bonds with saturated carbons via transition metal-catalyzed reactions is limited. In fact, the cross-coupling of primary and secondary alkyl boronic acids and a trifluoromethylthiol electrophile in the presence of copper(I) and a 2,2′-bipyridine ligand represents the sole example of C($sp^3$)−S bond formation.[34,35]

Curiously, a stereospecific C($sp^3$)−S cross-coupling process has not been reported despite its obvious advantages such as predictable stereochemical outcomes and the myriad of preparative methods for accessing chiral nucleophiles. Here, we report a stereoretentive cross-coupling reaction between configurationally stable nucleophiles and sulfur electrophiles resulting in the formation of thioacetals and thioglycosides. This method represents a conceptually novel approach to C−S bond formation as it signifies a departure from previously established strategies (i.e., nucleophilic substitution). To the best of our knowledge, this work is the first example of a



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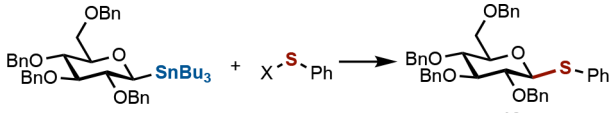
stereospecific metal-catalyzed C($sp^3$)−S cross-coupling reaction characterized by a broad substrate scope with potential applications in high-precision bioconjugation.

## RESULTS AND DISCUSSION

Motivated by the importance of C($sp^3$)−S linkages, we set out to identify conditions that would establish a C−S bond in high stereoselectivity. Our previous work involving the stereospecific transformations of anomeric stannanes[36−39] led us to hypothesize that the controlled formation of new C($sp^3$)−S bonds would result from a stereoretentive cross-coupling process of anomeric nucleophiles. Configurationally stable glycosyl stannanes were elected for their excellent stability, availability as either anomer, as well as their amenability toward the preparation of glycoconjugates and protein bioconjugation. For optimization of the reaction conditions, we chose 2,3,4,6-tetra-*O*-benzyl-$\beta$-D-glucopyranosylstannane **8** and phenyl disulfide **9a** as the model substrates (Table 1).

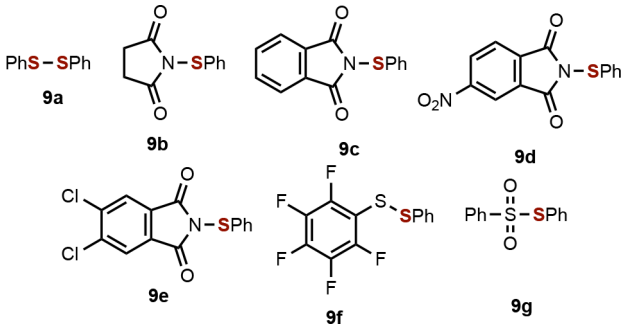
**Table 1. Identification of Glycosyl Cross-Coupling Conditions**[a]




8 9 10

| entry | solvent | El | time (h) | $\alpha$:$\beta$[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | *m*-xylene | **9a** | 24 | $\beta$ only | 20 |
| 2 | $(CH_2Cl)_2$ | **9a** | 24 | $\beta$ only | 42 |
| 3 | 1,4-dioxane | **9a** | 24 | 1.0:2.1 | 28 |
| 4 | $(CH_2Cl)_2$ | **9a** | 72 | $\beta$ only | 45 |
| 5 | *m*-xylene | **9a** | 72 | $\beta$ only | 62 |
| 6 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9a** | 72 | $\beta$ only | 68 |
| 7 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9a** | 96 | $\beta$ only | 72 |
| 8 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9b** | 72 | $\beta$ only | 52 |
| 9 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9c** | 72 | $\beta$ only | 50 |
| 10 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9d** | 72 | $\beta$ only | 30 |
| 11 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9e** | 72 | $\beta$ only | 49 |
| 12 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9f** | 72 | $\beta$ only | 71 |
| 13 | *m*-xylene:$(CH_2Cl)_2$ (2:1) | **9g** | 72 | 1.0:2.9 | 39 |
| 14[d] | 1,4-dioxane | **9a** | 72 | $\beta$ only | 15 |
| 15[d] | 1,4-dioxane | **9b** | 72 | $\beta$ only | 58 |

[a]Reaction conditions: sulfide **9a**−**9g** (0.100 mmol, 1.0 equiv), **8** (1.5 equiv), CuCl (3.0 equiv), and dry solvent (3.0 mL) under $N_2$, 130 °C. [b]Anomeric selectivities determined by $^1$H NMR using unpurified reactions mixtures. [c]Isolated yields. [d]CuCl (50 mol %), JackiePhos (55 mol %) in 1,4-dioxane (3.0 mL).




First, various solvents were assayed using CuCl (3 equiv) at 130 °C. Although *m*-xylene and 1,2-dicholoroethane produced the desired product **10** in 20% and 42% yield, respectively, with exclusive $\beta$ selectivity, the reaction in 1,4-dioxane afforded **10** in 28% yield as an $\alpha$:$\beta$ (1:2.1) mixture of anomers (entries 1−3). The latter case was intriguing as it represented the first instance in which we observed an erosion of stereoselectivity when running the glycosyl cross-coupling in an ethereal solvent. We rationalized this result by the coordinating ability of 1,4-dioxane and its propensity to stabilize copper in high oxidation states, which presumably led to the erosion of anomeric configuration. Exclusive selectivity was restored by extending the reaction time to 72 h and changing the solvent to either 1,2-dicholoroethane or *m*-xylene, which afforded thioglycoside **10** in 45% and 62% yield, respectively (entry 4 and 5). We further improved the yield by using a 2:1 mixture of *m*-xylene and 1,2-dicholoroethane, furnishing **10** in up to 72% yield (entry 6 and 7).

Having established the feasibility of the sulfenylation reaction with symmetrical disulfides, we next tested various unsymmetrical sulfide donors equipped with competent leaving groups (entries 8−13). Our investigation of these electrophiles stemmed from the hypothesis that, in order to access a diverse selection of *S*-linked glycans, the various sulfide donors might require a suitable leaving group to facilitate the coupling. We discovered that succinimide-containing thiophenol **9b** was less effective than disulfide **9a** and provided **10** in only 52% yield. Additional studies with phthalimide-containing thiophenols, regardless of their electronic nature (e.g., **9c**; electron-deficient phthalimides with 4-$NO_2$ in **9d** and 4,5-$Cl_2$ in **9e**), resulted in no improvement to the yield. When testing the reaction with unsymmetrical sulfide donors, we had to consider the competition for transfer to the C1 position introduced by the liberated leaving group. With the understanding that optimal results would only be viable if the leaving group's nucleophilicity was relatively low, we employed pentafluorophenyl disulfide **9f** and, to our delight, isolated 71% of the desired product **10** (entry 12). Finally, *S*-phenyl benzenethiosulfonate **9g** was coupled with $\beta$-stannane **8** to afford **10** in a moderate yield (39%, entry 13) and only a slight preference for the $\beta$-anomer ($\alpha$:$\beta$ 1:2.9). Again, we reasoned that the destabilizing effects exerted by poorly coordinating ligands, such as sulfonates, on highly oxidized copper species generated a configurationally labile intermediate, which ultimately led to the observed scrambling of stereochemistry.

When we assessed the reaction's performance using substoichiometric amounts of CuCl, we found that *N*-phenylsulfenylsuccinimide **9b** was more effective than symmetrical disulfide **9a** (entries 14 and 15) at 50 mol % of CuCl. The catalyst loading of CuCl could be reduced as low as 20 mol %, but this resulted in ∼10% decrease in the yield, albeit with no change in diastereoselectivity (data not shown). It is also interesting to note that, under these conditions, only the $\beta$ anomer was detected in 1,4-dioxane when JackiePhos (55 mol %) was included as an external phosphine ligand.[40] The bulky phosphine ligand prevents anomerization of the organocopper intermediate(s) and ensures substrate compatibility with coordinating solvents. Having found these conditions, the sulfenylation was now amenable to the coupling of unsymmetrical donors and could provide entry into the glycodiversification of complex substrates, which might be otherwise challenging to access in the form of symmetrical disulfides.

The inevitable loss of one thiol moiety in the reaction of symmetrical donors presented an opportunity for further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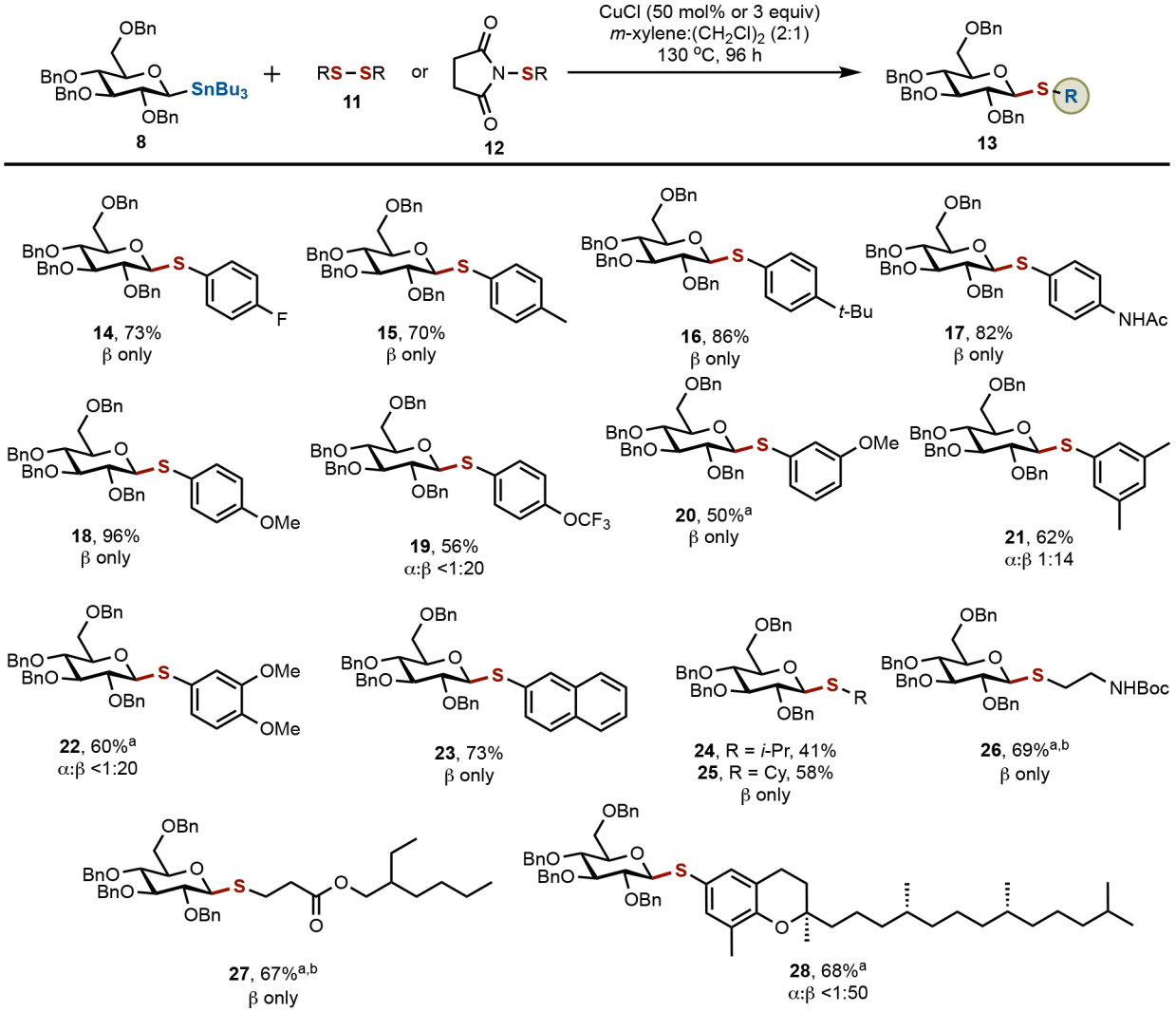
**Scheme 2. Scope of C($sp^3$)−S Cross-Coupling of β-D-Glucose Stannane 8 with Aryl and Alkyl Sulfur Electrophiles**




[a]CuCl (50 mol %), JackiePhos (55 mol %), 1,4-dioxane (3.0 mL), 130 °C, 96 h. [b]110 °C. Compounds **14**−**19**, **21**, and **23** were prepared with **11**; compounds **20**, **22**, and **24**−**28** were prepared with **12**. General reaction conditions: β-D-glucose **8** (1.5 equiv), sulfur electrophile (1 equiv), CuCl (3 equiv), anh. *m*-xylene:$(CH_2Cl)_2$ (2:1, 3.0 mL) under $N_2$, 130 °C, 96 h.

reaction improvement and led us to focus our concluding optimization studies on finding the ideal stoichiometry of the coupling partners. We reasoned that, under oxidative conditions, the thiol byproduct generated over the course of the reaction could be recycled into a disulfide, which would allow for only 0.5 equiv of the sulfide electrophile to be used. Thus, when we attempted the cross-coupling reaction in an open flask using **9a** (0.50 equiv), CuCl (3 equiv), and **8** (1 equiv), **10** was isolated in 58% (data not shown). The sole role of air in this process was to dimerize a thiol into a disulfide, and because these conditions also afforded exclusive anomeric control, we excluded the possible intermediacy of a radical organocopper species. This protocol ensures full consumption of the thiol and offers an alternative to reactions where modifications of the thiol with another leaving group could be problematic.

The optimized conditions were applied to reactions with β-D-glucose stannane **8** and various disulfides **11** and succinimides **12** (Scheme 2). For simple and commercially available thiol substrates, disulfides **11** were used with 3 equiv of CuCl in a mixture of *m*-xylene and 1,2-dichloroethane. These conditions afforded aryl glycosides containing electron-withdrawing (**14**) and electron-donating (**15**−**20**) groups on the aromatic ring, along with polysubstituted (**21**, **22**) and polycyclic (**23**) aryls. For the reactions forming alkyl glycosides **24**−**27**, we found that *N*-sulfenylsuccinimides **12** were better suited based on the improved yields, the ability to use catalytic amounts of copper, and the ease of preparation of complex substrates (e.g., **27**). We also found that the addition of a bulky phosphine ligand (JackiePhos) helped to stabilize the putative anomeric organocopper intermediate by preventing elimination of the C2 substituent, which allowed for an increase in the reaction yields. Additionally, the reaction of a succinimide derived from δ-tocopherol furnished the *S*-linked glycoside **28**, demonstrating the potential value of the cross-coupling method for late-stage functionalization.

Further studies were aimed at establishing the generality of the cross-coupling method with different saccharides (Scheme 3). A series of monosaccharide nucleophiles was prepared for each anomer and subjected to the optimized conditions from Table 1 using *p*-methoxyphenyl disulfide **30** or succinimide **31** as the common electrophile. We were pleased to find that the



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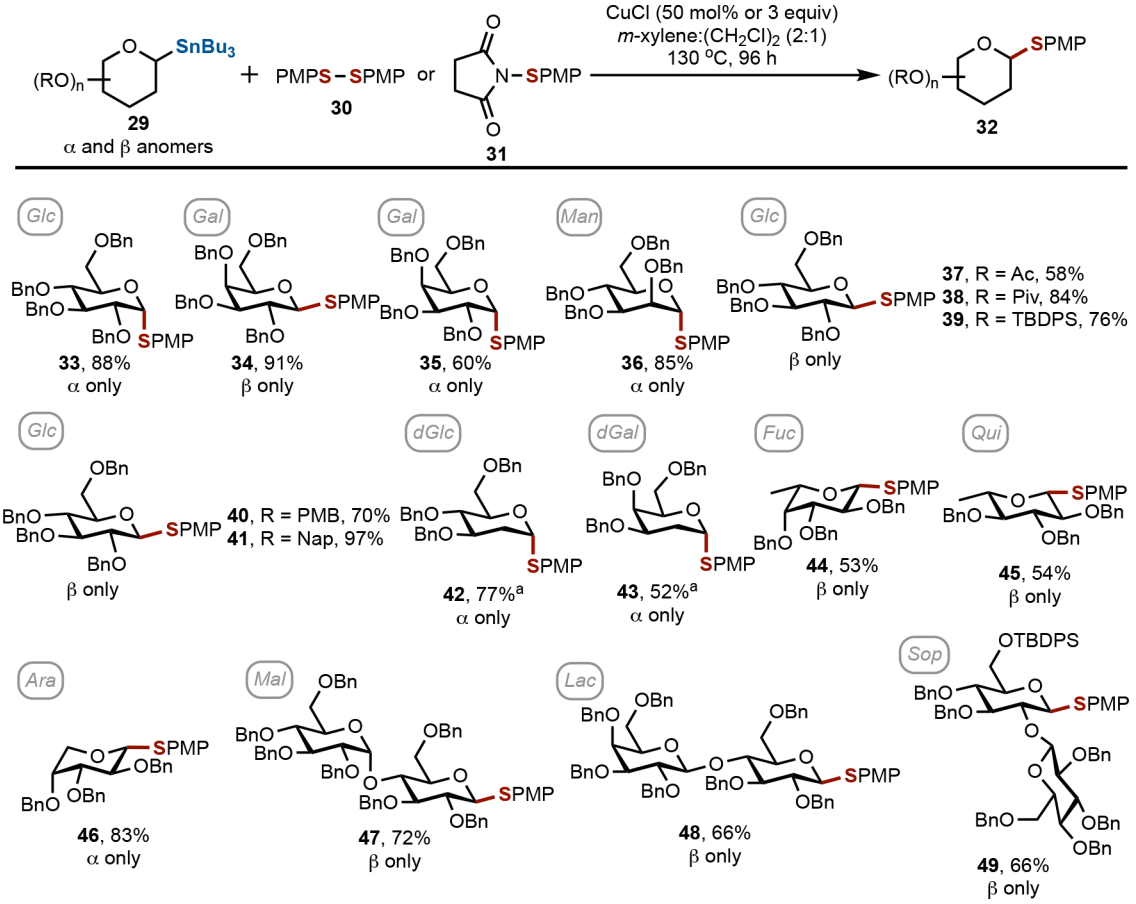
**Scheme 3. Reaction Scope of Mono- and Disaccharides: Carbohydrate Diversity Explored with $(PMPS)_2$ or *N*-(4-Methoxyphenyl)sulfenylsuccinimide as the Sulfur Electrophiles**




[a]**31** (1.5. equiv), CuCl (50 mol %), JackiePhos (55 mol %), KF (3 equiv), 1,4-dioxane (3.0 mL), 130 °C, 96 h. General reaction conditions: **29** (1.5 equiv), $(PMPS)_2$ **30** (1 equiv), CuCl (3 equiv), anh. *m*-xylene:$(CH_2Cl)_2$ (2:1, 3.0 mL) under $N_2$, 130 °C, 96 h.

general conditions were operational for both anomers of D-glucose (**33**), D-galactose (**34**, **35**), as well as the $\alpha$-anomer of D-mannose (**36**), all proceeding with retention of configuration for each substrate. Moreover, the nature of the protective group had no impact on the selectivity, and groups commonly used in preparative carbohydrate chemistry such as esters (**37**, **38**), and silyl (**39**) and benzyl ethers (**40**, **41**) were also tolerated. We ultimately employed benzyl groups in many of our examples because they are highly convenient for the preparation and manipulation of anomeric nucleophiles. Historically, the removal of benzyl ethers has required harsh conditions, potentially rendering their use incompatible with sensitive groups such as the C−S linkage. Cognizant of this restraint, we were able to demonstrate that benzyl groups in the thioglycosides (e.g., **10**) could be removed without cleavage of the C−S bond and concomitant C1-epimerization using a strong Lewis acid ($BCl_3$) in the presence of a carbocation scavenger (mesitylene) in 71% (for details, see the SI). This protocol, in addition to other known methods for the debenzylation of thioglycosides,[41] could be easily extended to other *S*-linked glycans.

2-Deoxy glycosides, notorious for their reluctance toward stereocontrolled manipulations,[42,43] were easily prepared from the corresponding stannanes **42** and **43** in synthetically useful yields. Similarly, other electron-rich monosaccharides such as L-fucose (**44**), L-quinovose (**45**), and even a pentose (D-arabinose **46**) furnished the corresponding thioglycosides with a complete transfer of anomeric configuration. Encouraged by these results, we also tested reactions with disaccharides. In addition to maltose **47** and lactose **48**, which were viable substrates in this coupling, the C2-linked disaccharide sophorose also underwent smooth conversion into *S*-linked disaccharide **49** despite possessing a heavily congested anomeric position. We believe the preparation of **49** strongly highlights the utility of the presented glycosyl thiol coupling since other methods frequently used to install glycosidic linkages in high selectivities often rely on neighboring-group participation and, considering the poor anomeric preferences exerted by 1,2-linked disaccharides together with the lack of participating group at C2, this particular synthesis would present them with a formidable challenge.

*S*-linked glycosides are frequently employed as surrogates of *O*-linked glycans due to their increased hydrolytic stability[44] and retention of conformational preferences similar to the natural cognates.[12] We found consistently high anomeric selectivities in reactions using 6-thio-6-deoxy-D-glucose, modified at C6 with a succinimide group, which resulted in the formation of $\alpha$- and $\beta$-linked glycosides **51**−**56** (Scheme 4a). We reasoned that the synthetic endeavor might be unnecessarily complicated by the preparation of symmetrical disulfide glycosyl donors, and oxidative conditions under air or oxygen to regenerate the disulfide might produce suboptimal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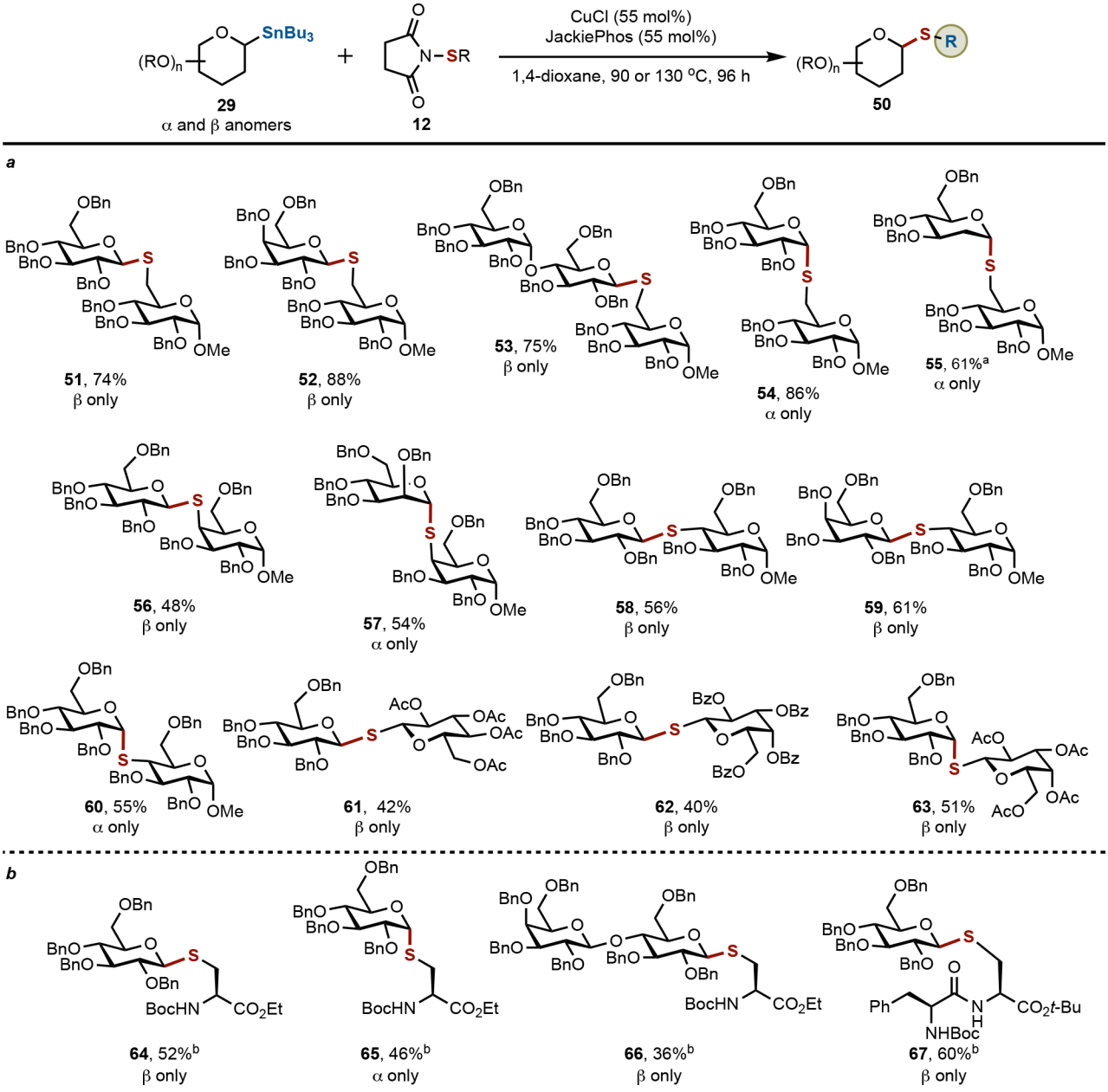
**Scheme 4. (a) Scope of Reactions with Various Mono- and Disaccharides; (b) Conjugation of Saccharides via Sulfur in Cysteine**




[a]KF (3 equiv). [b]**29** (1.0 equiv), **12** (1.5 equiv), CuCl (50 mol %), JackiePhos (55 mol %), 1,4-dioxane (3.0 mL), 90 °C, 96 h. General reaction conditions: **29** (1.5 equiv), **12** (1.0 equiv), CuCl (50 mol %), JackiePhos (55 mol %), 1,4-dioxane (3.0 mL), 130 °C, 96 h.

results, especially for those disulfides derived from congested (e.g., C4) thiols. A more challenging reaction with the succinimide at the axial position resulted in a diminished but synthetically useful yield of **57** (54%). An accessible C4 equatorial *N*-sulfenylsuccinimidate of D-glucose was coupled with $\beta$ and $\alpha$ anomers of D-glucose and D-galactose to smoothly furnish disaccharides **58**–**60** in improved yields (55–61%). With this protocol we were able to prepare a precursor to thiocellobiose (**58**), an inducer of cellulose-degrading enzymes.[45] Finally, reactions with sensitive thiol electrophiles at C1 are particularly interesting and allow for access to 1,1-*S*-linked glycans with exclusive selectivities for both anomers (**61**–**63**). The synthesis of this unique class of disaccharides demonstrates yet another important feature of the glycosyl cross-coupling platform; the electronic effects of various protective groups in either the glycosyl donor (i.e., stannane) and the acceptor (i.e., (di)sulfide) do not bear any impact on the yield or selectivities. This observation stands in striking contrast to more classical glycosylation reactions where reactivity differences form the conceptual basis for armed-disarmed reactivities of various glycosyl donors.[46]

Next, we expanded the cross-coupling protocol to reactions with amino acids and peptides (Scheme 4b). In addition to natural *S*-linked glycopeptides, cysteine glycosylation is an established method for the glycodiversification of peptides and proteins, providing entry into wide scope of glycoconjugates with improved stabilities and activities.[14] While many methods are available for glycopeptide and glycoprotein synthesis, their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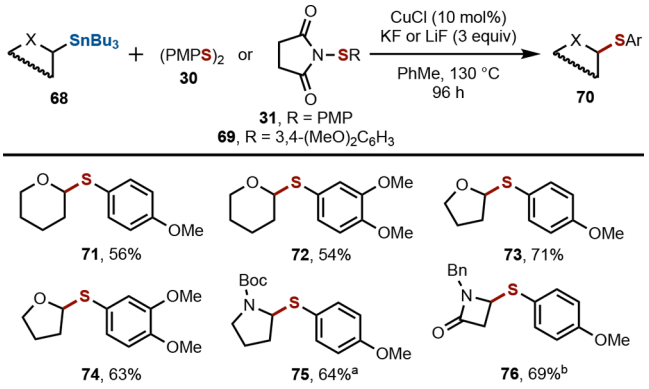
scope is often limited to reactions with the $\beta$-anomers of C1-thiols.[21] With the newly developed glycosyl thiol coupling, access to both configurations is possible as exhibited in the synthesis of $\alpha$- and $\beta$-linked cysteine derivatives **64** and **65**. Furthermore, we demonstrated that disaccharide **66** and dipeptide **67** underwent smooth conversion into the corresponding $\beta$-linked cysteine glycoconjugates in 36−62% yield. Our concerns that the peptide substrates could be incompatible with elevated reaction temperatures causing epimerization at the $\alpha$-carbonyl through the probable elimination of the anomeric thiol followed by addition to the $\alpha,\beta$-unsaturated system were unwarranted. This undesired pathway was completely suppressed by lowering the reaction temperature to 90 °C, allowing for glycoconjugates **64**−**67** to be isolated as a single diastereomer in each case. On the basis of these encouraging results, we believe the developed method is suitable for the late-stage coupling of fully assembled oligopeptide chains, thus providing an unprecedented opportunity to pursue bioconjugation of therapeutics and biologics.

To further highlight our method's potential in general biodiversification, we pursued the synthesis of thioacetals and thioaminoacetals derived from unfunctionalized heterocyclic building blocks (Scheme 5). The general conditions optimized for complex substrates were successfully translated to oxygen-bearing saturated heterocycles **71**−**74**. We were also able to demonstrate that these conditions were compatible with *N*-heterocyclic substrates and successfully merged pyrrolidine- and azetidine-derived $\alpha$-aminostannanes **75** and **76** with disulfide **30**. Thioaminoacetal **76** is a noteworthy example given the presence of this structural element in $\beta$-lactam antibiotics. In these reactions, addition of KF (3 equiv) was critical to achieve high yields despite being unnecessary in the correlative reaction using saccharides. We postulated that the fluoride source must play an important role in activating the C1-tin, as it is comparatively less reactive in simple tetrahydropyran and tetrahydrofuran substrates, which lack oxygen substitution and are thus considered more electron-rich in nature. Additionally, the ability of the benzyl groups at the neighboring positions in protected saccharides to stabilize the anomeric organocopper cannot be ruled out.[47]

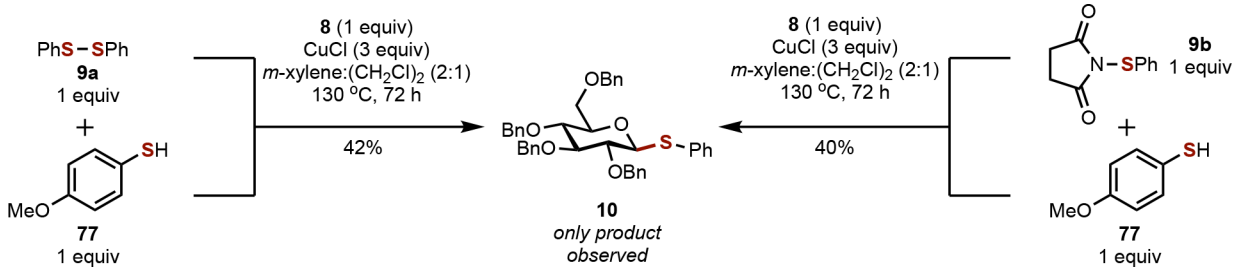
**Scheme 5. Cross-Coupling with Unfunctionalized Heterocycles**[c]




[a]**68** (1.0 equiv), **30** (1.5 equiv). [b]**68** (1.0 equiv), **30** (2.0 equiv), CuI (10 mol %), LiF (3 equiv), 1,4-dioxane (2.0 mL). [c]General reaction conditions: **68** (2.0 equiv), **31** or **69** (1.0 equiv), CuCl (10 mol %), KF (55 mol %), KF (3 equiv), toluene (2.0 mL), 130 °C, 96 h.

The high anomeric selectivities produced by the C−S cross-coupling reactions prompted us to undertake mechanistic and computational studies summarized in Schemes 6−9. From the outset of the investigations, we excluded the possibility that, under the optimized conditions with either a disulfide or *N*-sulfenylsuccinimide donor, the cross-coupling proceeds via radical intermediates.[48−50] The consistently high diastereoselectivities observed for both anomers suggested no intercession of radical species and control studies of the reactions involving **8** with disulfide **9a** or succinimide **9b** in the presence of a radical scavenger (1,1-diphenylethylene, 1 equiv; for details, see the SI) had no impact on yield or selectivity, confirming our initial assumption. Additional experimental results lead us to propose that the C−S bond-forming step occurs intramolecularly. We base this assertion on the cross-coupling reaction of disulfide **9a** or succinimide **9b** in the presence of thiol **77**, which resulted in the exclusive formation of **10**. This result indicates that (a) the sulfur ligands at the copper center do not undergo exchange with external thiols; (b) the formation of a C−S bond occurs via reductive elimination from the copper intermediate as opposed to substitution at C1; and (c) under the reaction conditions, disulfide **77** does not partake in a thiol exchange with **9a** or **9b** to form mixed disulfide 4-MeOC$_6$H$_4$S-SC$_6$H$_5$ (Scheme 6). We also established that weakly coordinating solvents (e.g., 1,4-dioxane, *t*-BuOH) diminish the anomeric selectivity by facilitating the dissociation of copper from C1. This result stands in contrast to the C−C cross-coupling process in which no scrambling of stereochemistry was observed regardless of the solvent used.[37] The loss of stereochemical integrity could be averted by inclusion of JackiePhos, which, in addition to suppressing the elimination of the C2 group (e.g., OBn), restores high anomeric selectivities for reactions involving either anomer and functions to stabilize Cu(III) species. This beneficial effect is likely caused by facilitating the reductive elimination step from a short-lived anomeric Cu(III) intermediate (vide infra).

**Scheme 6. Competition Experiments between Disulfide 9a and *N*-Sulfenylsuccinimide 9b in the Presence of External Thiol 77**



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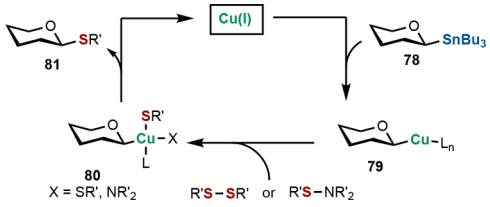
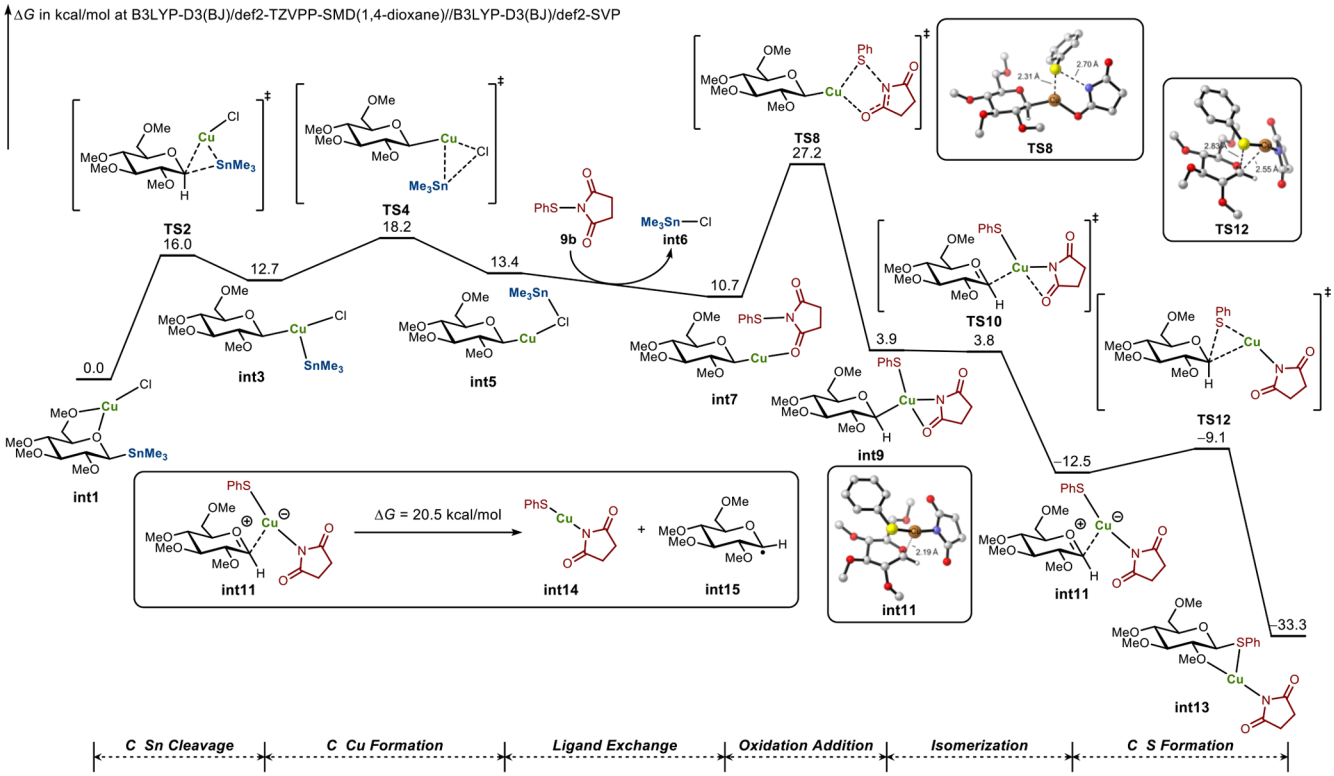
Taken together, we propose that the Cu(I)-mediated stereoretentive C($sp^3$)−S cross coupling proceeds via an oxidative addition of anomeric organocopper species **78** across the S−S or S−N bond leading to the formation of Cu(III) species, **79** (Scheme 7).[51] Intermediate **79** then undergoes a reductive elimination to form the new C−S bond in **80**,[52] which releases a thiol or imide byproduct and restores a Cu(I) catalyst. In the presence of an external oxidant, such as $O_2$, the thiol generated is dimerized into a disulfide that can reenter the catalytic cycle. This mechanistic proposal is consistent with in silico studies,[53] and the free energy diagrams describing the most favorable pathways for the Cu(I)-catalyzed C($sp^3$)−S cross coupling of $\beta$- and $\alpha$-D-glucosyl stannanes with *N*-phenylsulfenylsuccinimide **9b** are shown in Scheme 8 and 9. With the $\beta$-stannane (Scheme 8), the initial glucose-CuCl complex **int1** undergoes a sequential oxidative addition via **TS2** to give **int3** followed by a reductive elimination via **TS4** to achieve the overall transmetalation and furnish glycosyl cuprous intermediate **int5**. The formation of this organocopper species is endergonic, with a Gibbs free energy difference of +13.4 kcal/mol between **int1** and **int5**. Despite extensive efforts, the cyclic concerted transmetalation transition state could not be located. Subsequent transformations of intermediate **int5** involve a ligand exchange with **9b** to form succinimide-coordinated intermediate **int7** followed by an oxidative addition via five-centered transition state **TS8**, which results in the cleavage of the S−N bond and the formation of **int9**. The imide carbonyl assists the oxidative transformation of Cu(I) into Cu(III), presumably by its ability to stabilize copper centers in high oxidation states. The structural instability of **int9**—due to the highly oxidized Cu center—causes a rapid, heterolytic dissociation of the C−Cu bond via **TS10** and, facilitated by a charge transfer concurrent with bond cleavage, results in equatorial organocopper **int11** with a reduced Cu(I) center. While complex **int11** displayed noticeable ion-pair character, we presumed the overall likelihood of full separation between the glycosyl moiety and metal—which would result in loss of anomeric configuration—was small.[54] Results from additional studies on the dissociation of **int11** and **int26** into neutral radical species **int15** and copper complex **int14** supported this hypothesis; the transformations from **int9** and **int26** required +20.5 and +16.8 kcal/mol, respectively, to generate the corresponding products—an endergonicity that seemed too high to make such pathways feasible (Schemes 8 and 9). Furthermore, we determined that the dissociations of **int11** and **int26** into two, separated ions were equally as improbable given that they were even more endergonic and significantly less favorable (for details, see the SI). The subsequent three-centered C−S bond formation proceeds through an early transition state **TS12**, which has a shallow barrier of only 3.4 kcal/mol and also precludes the anomerization of **int11**. The rapid conversion of **int9** into **int13** is reminiscent of a *C*-heteroatom reductive elimination with well-defined aryl-Cu(III) complexes studied

**Scheme 7. Proposed Mechanism of Stereoretentive C($sp^3$)−S Cross-Coupling**




**Scheme 8. DFT-Computed Free Energy Profile of Cu(I)-Catalyzed C($sp^3$)−S Cross-Coupling of $\beta$-Glycosyl-stannanes**



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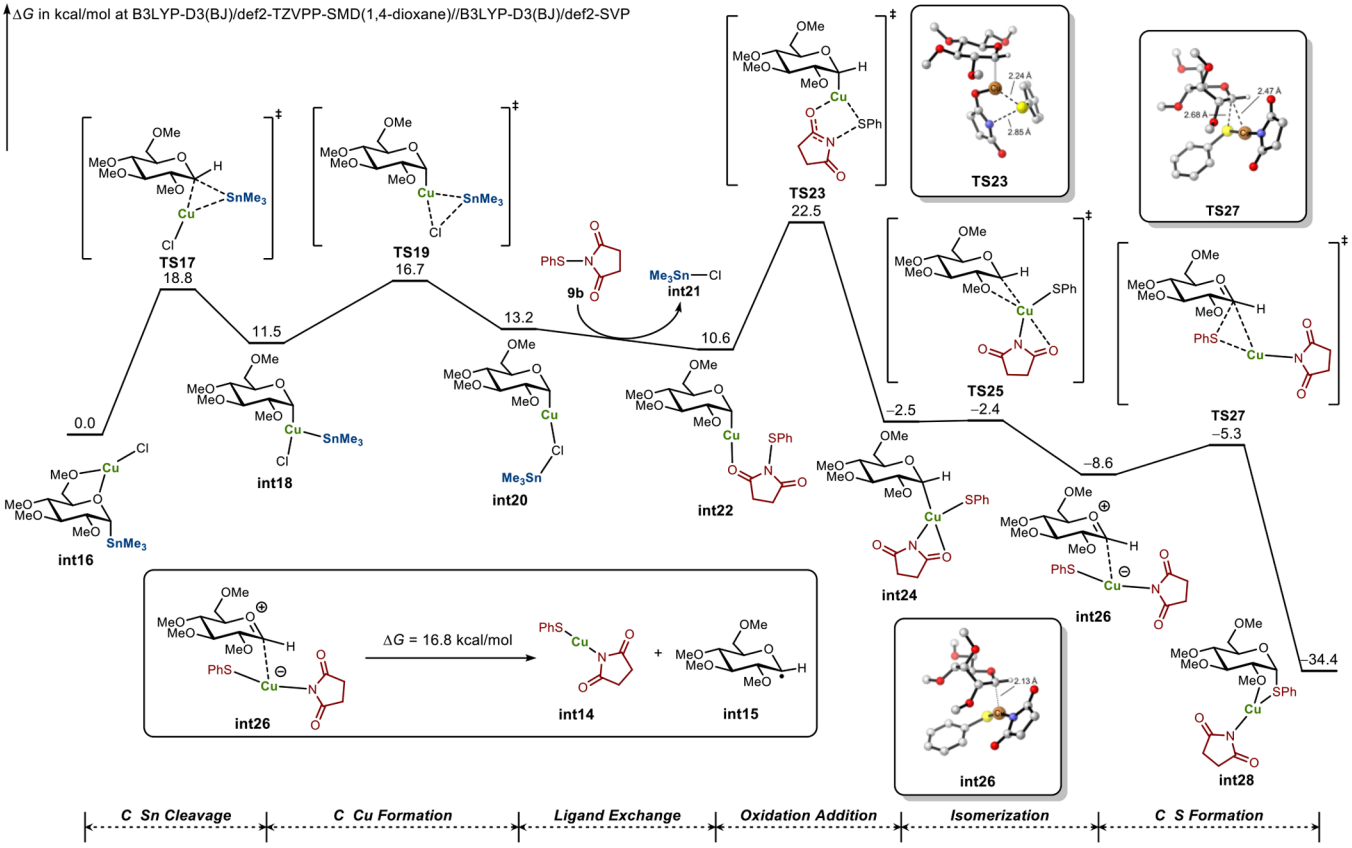
**Scheme 9. DFT-Computed Free Energy Profile of Cu(I)-Catalyzed C($sp^3$)−S Cross-Coupling of $\alpha$-Glycosyl-stannanes**




by Rivas and Stahl.[52,55] On the basis of the Gibbs free energy profile, the rate-determining step of the stereoretentive glycosyl C($sp^3$)−S cross-coupling is the oxidative addition of *N*-sulfenylsuccinimide with an overall barrier of 27.2 kcal/mol.

The mechanism of the C($sp^3$)−S cross-coupling with $\alpha$-glucosyl substrate is similar to the reaction pathway computed for the $\beta$ anomer (Scheme 9). The initial transformations of Cu-succinimide complex **int16** into **int22** are comparable in profile to the equatorial stannane. However, the rearrangement of **int22** into unstable **int24** is more facile than the analogous step with the $\beta$ glucoside, with a calculated activation barrier 4.7 kcal/mol less than the corresponding value for the $\beta$ pathway. The lower barrier for this conversion, which is also the rate-determining step, could be attributed to the destabilizing interactions in **int22** originating from a 1,2-*cis* arrangement of the C2-OMe group and the anomeric copper center. Finally, to complement the studies on the redox pathway, we also considered an alternative mechanism in which anomeric organocopper intermediates **int7** and **int22** form the C−S bond through a nucleophilic substitution at the sulfur center without a change in oxidation state of the metal. However, a relevant transition state could not be located despite extensive efforts.

The C−S cross-coupling with disulfide donors was also investigated computationally, and the overall reaction profiles are strikingly similar to the computed pathway with *N*-sulfenylsuccinimide with the oxidative addition step across a S−S bond in intermediates **int5** and **int20** being the rate-determining step (data not shown).

## CONCLUSIONS

In conclusion, we have presented a stereoretentive method for the formation of a C($sp^3$)−S bond and its applications in the synthesis of chiral thioacetals and thioglycosides. This novel reaction is characterized by a uniformly high transfer of configuration from the glycosyl donor to the product under standardized conditions and is compatible with a multitude of functional groups. The electrophilic sulfur component, in the form of a disulfide or succinimide, can be installed into a wide range of small molecules, including various saccharides and a selection of peptides, making this method suitable for late-stage glycodiversification. Furthermore, the availability of anomeric nucleophiles in either configuration offers unprecedented access to a chemical glycosylation platform that accommodates the predictable and programmable preparation of both anomers. A combination of experimental and theoretical studies established that the transfer of anomeric configuration and the generation of glycosyl copper species involves sequential oxidative addition and reductive elimination steps, which are both stereoretentive in nature. Once the glycosyl copper intermediate undergoes the oxidative addition, the lifetime of the anomeric organocopper(III) species is too short for epimerization at the anomeric center due to the low barriers of C−Cu bond cleavage and C−S bond formation. Taken together, the C($sp^3$)−S cross-coupling method establishes a novel mechanistic platform for the discovery of stereoretentive reactions in preparative carbohydrate chemistry and beyond.



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## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11211.

Detailed experimental procedures, copies of NMR spectra for all new compounds (PDF)

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§F.Z. and E.M. contributed equally.


### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832−2842.

(2) Rodriguez, J.; O'Neill, S.; Walczak, M. A. Constrained saccharides: a review of structure, biology, and synthesis. *Nat. Prod. Rep.* **2018**, *35*, 220−229.

(3) Demchenko, A. V. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH Verlag: Weinheim, Germany, 2008.

(4) Aydillo, C.; Compañón, I.; Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. S-Michael Additions to Chiral Dehydroalanines as an Entry to Glycosylated Cysteines and a Sulfa-Tn Antigen Mimic. *J. Am. Chem. Soc.* **2014**, *136*, 789−800.

(5) Bédard, F.; Biron, E. Recent Progress in the Chemical Synthesis of Class II and S-Glycosylated Bacteriocins. *Front. Microbiol.* **2018**, DOI: 10.3389/fmicb.2018.01048.

(6) Taylor, C. M. Glycopeptides and glycoproteins: Focus on the glycosidic linkage. *Tetrahedron* **1998**, *54*, 11317−11362.

(7) Oman, T. J.; Boettcher, J. M.; Wang, H.; Okalibe, X. N.; van der Donk, W. A. Sublancin is not a lantibiotic but an S-linked glycopeptide. *Nat. Chem. Biol.* **2011**, *7*, 78−80.

(8) Hsieh, Y. S. Y.; Wilkinson, B. L.; O'Connell, M. R.; Mackay, J. P.; Matthews, J. M.; Payne, R. J. Synthesis of the Bacteriocin Glycopeptide Sublancin 168 and S-Glycosylated Variants. *Org. Lett.* **2012**, *14*, 1910−1913.

(9) Biswas, S.; Garcia De Gonzalo, C. V.; Repka, L. M.; van der Donk, W. A. Structure−Activity Relationships of the S-Linked Glycocin Sublancin. *ACS Chem. Biol.* **2017**, *12*, 2965−2969.

(10) Zhu, X.; Pachamuthu, K.; Schmidt, R. R. Synthesis of Novel S-Neoglycopeptides from Glycosylthiomethyl Derivatives. *Org. Lett.* **2004**, *6*, 1083−1085.

(11) Thayer, D. A.; Yu, H. N.; Galan, M. C.; Wong, C.-H. A General Strategy toward S-Linked Glycopeptides. *Angew. Chem., Int. Ed.* **2005**, *44*, 4596−4599.

(12) Pachamuthu, K.; Schmidt, R. R. Synthetic Routes to Thiooligosaccharides and Thioglycopeptides. *Chem. Rev.* **2006**, *106*, 160−187.

(13) Amso, Z.; Bisset, S. W.; Yang, S.-H.; Harris, P. W. R.; Wright, T. H.; Navo, C. D.; Patchett, M. L.; Norris, G. E.; Brimble, M. A. Total chemical synthesis of glycocin F and analogues: S-glycosylation confers improved antimicrobial activity. *Chem. Sci.* **2018**, *9*, 1686−1691.

(14) De Leon, C. A.; Levine, P. M.; Craven, T. W.; Pratt, M. R. The Sulfur-Linked Analogue of O-GlcNAc (S-GlcNAc) Is an Enzymatically Stable and Reasonable Structural Surrogate for O-GlcNAc at the Peptide and Protein Levels. *Biochemistry* **2017**, *56*, 3507−3517.

(15) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. Bacterial Resistance to β-Lactam Antibiotics: Compelling Opportunism, Compelling Opportunity. *Chem. Rev.* **2005**, *105*, 395−424.

(16) Calce, E.; Digilio, G.; Menchise, V.; Saviano, M.; De Luca, S. Chemoselective Glycosylation of Peptides through S-Alkylation Reaction. *Chem. - Eur. J.* **2018**, *24*, 6231−6238.

(17) Dere, R. T.; Zhu, X. The First Synthesis of a Thioglycoside Analogue of the Immunostimulant KRN7000. *Org. Lett.* **2008**, *10*, 4641−4644.

(18) Dadová, J.; Galan, S. R. G.; Davis, B. G. Synthesis of modified proteins via functionalization of dehydroalanine. *Curr. Opin. Chem. Biol.* **2018**, *46*, 71−81.

(19) Bernardes, G. J. L.; Chalker, J. M.; Errey, J. C.; Davis, B. G. Facile Conversion of Cysteine and Alkyl Cysteines to Dehydroalanine on Protein Surfaces: Versatile and Switchable Access to Functionalized Proteins. *J. Am. Chem. Soc.* **2008**, *130*, 5052−5053.

(20) Gutiérrez-Jiménez, M. I.; Aydillo, C.; Navo, C. D.; Avenoza, A.; Corzana, F.; Jiménez-Osés, G.; Zurbano, M. M.; Busto, J. H.; Peregrina, J. M. Bifunctional Chiral Dehydroalanines for Peptide Coupling and Stereoselective S-Michael Addition. *Org. Lett.* **2016**, *18*, 2796−2799.

(21) Bernardes, G. J. L.; Gamblin, D. P.; Davis, B. G. The Direct Formation of Glycosyl Thiols from Reducing Sugars Allows One-Pot Protein Glycoconjugation. *Angew. Chem., Int. Ed.* **2006**, *45*, 4007−4011.

(22) Bernardes, G. J. L.; Grayson, E. J.; Thompson, S.; Chalker, J. M.; Errey, J. C.; El Oualid, F.; Claridge, T. D. W.; Davis, B. G. From Disulfide- to Thioether-Linked Glycoproteins. *Angew. Chem., Int. Ed.* **2008**, *47*, 2244−2247.

(23) Dere, R. T.; Wang, Y.; Zhu, X. A direct and stereospecific approach to the synthesis of α-glycosyl thiols. *Org. Biomol. Chem.* **2008**, *6*, 2061−2063.

(24) Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. Umpolung Reactivity in the Stereoselective Synthesis of S-Linked 2-Deoxyglycosides. *Angew. Chem., Int. Ed.* **2013**, *52*, 8012−8016.

(25) Reeves, J. T.; Camara, K.; Han, Z. S.; Xu, Y.; Lee, H.; Busacca, C. A.; Senanayake, C. H. The Reaction of Grignard Reagents with Bunte Salts: A Thiol-Free Synthesis of Sulfides. *Org. Lett.* **2014**, *16*, 1196−1199.

(26) Boutureira, O.; Bernardes, G. J. L. Advances in Chemical Protein Modification. *Chem. Rev.* **2015**, *115*, 2174−2195.

(27) Gunnoo, S. B.; Madder, A. Chemical Protein Modification through Cysteine. *ChemBioChem* **2016**, *17*, 529−553.

(28) Herradura, P. S.; Pendola, K. A.; Guy, R. K. Copper-Mediated Cross-Coupling of Aryl Boronic Acids and Alkyl Thiols. *Org. Lett.* **2000**, *2*, 2019−2022.

(29) Taniguchi, N. Convenient Synthesis of Unsymmetrical Organochalcogenides Using Organoboronic Acids with Dichalcogenides via Cleavage of the S−S, Se−Se, or Te−Te Bond by a Copper Catalyst. *J. Org. Chem.* **2007**, *72*, 1241−1245.

(30) Xu, H.-J.; Zhao, Y.-Q.; Feng, T.; Feng, Y.-S. Chan−Lam-Type S-Arylation of Thiols with Boronic Acids at Room Temperature. *J. Org. Chem.* **2012**, *77*, 2878−2884.

(31) Qiao, Z.; Ge, N.; Jiang, X. $CO_2$-promoted oxidative cross-coupling reaction for C-S bond formation via masked strategy in an odourless way. *Chem. Commun.* **2015**, *51*, 10295−10298.
(32) Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. Organometallic palladium reagents for cysteine bioconjugation. *Nature* **2015**, *526*, 687.
(33) Messina, M. S.; Stauber, J. M.; Waddington, M. A.; Rheingold, A. L.; Maynard, H. D.; Spokoyny, A. M. Organometallic Gold(III) Reagents for Cysteine Arylation. *J. Am. Chem. Soc.* **2018**, *140*, 7065−7069.
(34) Beletskaya, I. P.; Ananikov, V. P. Transition-Metal-Catalyzed C−S, C−Se, and C−Te Bond Formation via Cross-Coupling and Atom-Economic Addition Reactions. *Chem. Rev.* **2011**, *111*, 1596−1636.
(35) Shao, X.; Liu, T.; Lu, L.; Shen, Q. Copper-Catalyzed Trifluoromethylthiolation of Primary and Secondary Alkylboronic Acids. *Org. Lett.* **2014**, *16*, 4738−4741.
(36) Zhu, F.; Rourke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A. Highly stereospecific cross-coupling reactions of anomeric stannanes for the synthesis of C-aryl glycosides. *J. Am. Chem. Soc.* **2016**, *138*, 12049−12052.
(37) Zhu, F.; Rodriguez, J.; Yang, T.; Kevlishvili, I.; Miller, E.; Yi, D.; O'Neill, S.; Rourke, M. J.; Liu, P.; Walczak, M. A. Glycosyl Cross-Coupling of Anomeric Nucleophiles: Scope, Mechanism, and Applications in the Synthesis of Aryl C-Glycosides. *J. Am. Chem. Soc.* **2017**, *139*, 17908−17922.
(38) Zhu, F.; O'Neill, S.; Rodriguez, J.; Walczak, M. A. Stereoretentive Reactions at the Anomeric Position: Applications in the Synthesis of Selenoglycosides. *Angew. Chem., Int. Ed.* **2018**, *57*, 7091−7095.
(39) Yang, T.; Zhu, F.; Walczak, M. A. Stereoselective oxidative glycosylation of anomeric nucleophiles with alcohols and carboxylic acids. *Nat. Commun.* **2018**, *9*, 3650.
(40) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. Pd-Catalyzed N-Arylation of Secondary Acyclic Amides: Catalyst Development, Scope, and Computational Study. *J. Am. Chem. Soc.* **2009**, *131*, 16720−16734.
(41) Ané, A.; Josse, S.; Naud, S.; Lacône, V.; Vidot, S.; Fournial, A.; Kar, A.; Pipelier, M.; Dubreuil, D. Unusual anomeric rearrangement of para-nitrobenzoylxanthate d-glycosides: a new direct stereoselective access to $\alpha$-thioglycosides from pyranose sugars. *Tetrahedron* **2006**, *62*, 4784−4794.
(42) Bennett, C. S.; Galan, M. C. Methods for 2-Deoxyglycoside Synthesis. *Chem. Rev.* **2018**, *118*, 7931−7985.
(43) Issa, J. P.; Lloyd, D.; Steliotes, E.; Bennett, C. S. Reagent Controlled $\beta$-Specific Dehydrative Glycosylation Reactions with 2-Deoxy-Sugars. *Org. Lett.* **2013**, *15*, 4170−4173.
(44) Sylla, B.; Legentil, L.; Saraswat-Ohri, S.; Vashishta, A.; Daniellou, R.; Wang, H.-W.; Vetvicka, V.; Ferrières, V. Oligo-$\beta$-(1→3)-glucans: Impact of Thio-Bridges on Immunostimulating Activities and the Development of Cancer Stem Cells. *J. Med. Chem.* **2014**, *57*, 8280−8292.
(45) Rho, D.; Desrochers, M.; Jurasek, L.; Driguez, H.; Defaye, J. Induction of cellulose in Schizophyllum commune: thiocellobiose as a new inducer. *J. Bacteriol.* **1982**, *149*, 47−53.
(46) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. Armed and disarmed n-pentenyl glycosides in saccharide couplings leading to oligosaccharides. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
(47) Molander, G. A.; Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012**, *134*, 16856−16868.
(48) Gong, H.; Sinisi, R.; Gagné, M. R. A Room Temperature Negishi Cross-Coupling Approach to C-Alkyl Glycosides. *J. Am. Chem. Soc.* **2007**, *129*, 1908−1909.
(49) Gong, H.; Gagné, M. R. Diastereoselective Ni-Catalyzed Negishi Cross-Coupling Approach to Saturated, Fully Oxygenated C-Alkyl and C-Aryl Glycosides. *J. Am. Chem. Soc.* **2008**, *130*, 12177−12183.
(50) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896−4899.
(51) Casitas, A.; Ribas, X. The role of organometallic copper(III) complexes in homogeneous catalysis. *Chem. Sci.* **2013**, *4*, 2301−2318.
(52) Font, M.; Parella, T.; Costas, M.; Ribas, X. Catalytic C−S, C−Se, and C−P Cross-Coupling Reactions Mediated by a CuI/CuIII Redox Cycle. *Organometallics* **2012**, *31*, 7976−7982.
(53) Lefèvre, G.; Franc, G.; Tlili, A.; Adamo, C.; Taillefer, M.; Ciofini, I.; Jutand, A. Contribution to the Mechanism of Copper-Catalyzed C−N and C−O Bond Formation. *Organometallics* **2012**, *31*, 7694−7707.
(54) Hosoya, T.; Takano, T.; Kosma, P.; Rosenau, T. Theoretical Foundation for the Presence of Oxacarbenium Ions in Chemical Glycoside Synthesis. *J. Org. Chem.* **2014**, *79*, 7889−7894.
(55) Huffman, L. M.; Casitas, A.; Font, M.; Canta, M.; Costas, M.; Ribas, X.; Stahl, S. S. Observation and Mechanistic Study of Facile C-O Bond Formation between a Well-Defined Aryl−Copper(III) Complex and Oxygen Nucleophiles. *Chem. - Eur. J.* **2011**, *17*, 10643−10650.


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