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Letter

Catalytic Activation of Thioglycosides with Copper-Carbenes for Stereoselective 1,2-*Cis*-Furanosylations

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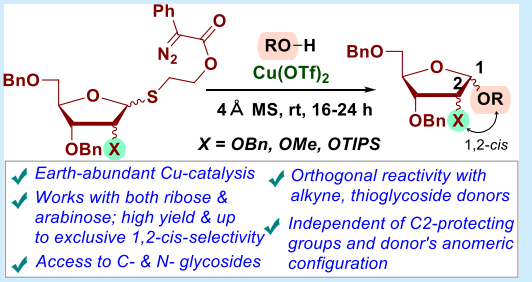
ABSTRACT: Thioglycoside activation, crucial for oligosaccharide synthesis, faces challenges with the need for stoichiometric promoters, additives, and cryogenic conditions, particularly in stereoselective 1,2-*cis*-linkage formation. This study introduces a carbene-based catalytic method using $Cu(OTf)_2$ for thioglycoside activation, enabling efficient 1,2-*cis*-furanosylation in ribose and arabinose. The method is orthogonal to conventional thioglycoside and alkyne donors, accommodates sterically demanding acceptors, and achieves stereoselectivity independent of the donor anomeric configuration and C2-protecting groups, with copper chelation playing a key role.



Thioglycosides have been employed for decades as facile glycosyl donors for synthesizing oligosaccharides and glycoconjugates as they hold excellent thermostability and tunable reactivities.[1] Numerous methods have been developed for activating and selectively functionalizing these thioglycoside donors.[1a,2] While elegant, most methods use stoichiometric amounts of harsh and moisture-sensitive reagents, often resulting in undesired side reactions, especially in substrates bearing reactive functionalities.[1f,3] For example, the activating conditions for substrates bearing alkenes are often incompatible and require low temperatures to avoid side reactions.[4] Thus, developing milder methods for thioglycoside activation has been an area of continuous interest. Additionally, catalytic activation of thioglycosides is limited, with most methods utilizing precious rare-earth metals such as rhodium and gold.[5] Furthermore, no catalytic methods for thioglycoside activation are known for synthesizing 1,2-*cis*-furanosides, key constituents of several biomedically relevant carbohydrates.[6] This is likely because constructing a 1,2-*trans* linkage via anchimeric assistance from a C2-*O*-acyl protecting group is relatively straightforward,[2f,7] while achieving the 1,2-*cis* linkage poses a more formidable challenge due to the absence of C2-*O*-participating groups. Additionally, the higher stability of the oxocarbenium ion in furanosides compared to their pyranoside counterparts further complicates the attainment of 1,2-*cis*-selectivity.[8] Therefore, most glycosylation methods developed for 1,2-*cis* linkages in the pyranoside system are ineffective for furanosides, leading to a mixture of stereoisomers with similar glycosyl donors in furanosylation reactions.[9]

A literature review identified an approach by the Wan group using cooperative catalysis with rhodium(II) and Brønsted acid for carbene-based thioglycoside activation (Figure 1a).[5b] This method generates anomeric sulfonium ylides, followed by protonation to form oxocarbenium ions for glycosylation. However, it struggles with 1,2-*cis*-selectivity, likely due to rhodium's inability to form C2-*O* coordination to direct the nucleophile, and it lacks examples of 1,2-*cis*-furanosylations.

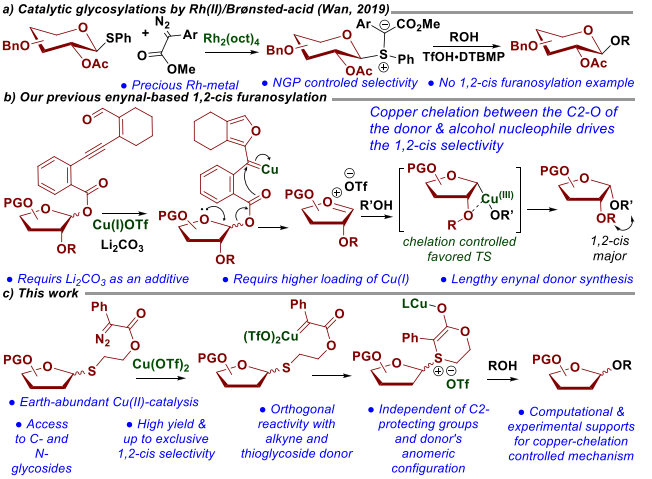


Figure 1. (a) Catalytic glycosylation with Rh-carbene. (b) Enynal derived carbene based 1,2-*cis*-furanosylation. (c) Our approach.

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To address the challenge of 1,2-*cis*-furanosylations, our group recently developed benzoate donors activated by enynal-derived copper carbenes (Figure 1b).[10] However, the need for higher loadings of copper(I) trifluoromethanesulfonate, the use of a base additive (Li_2CO_3), and the lengthy synthesis required for benzoate donors prompted us to shift our focus to more stable and versatile thioglycoside donors. Drawing inspiration from our previous work and expertise in using earth-abundant metal carbenes,[10,11] we hypothesized that copper carbenes could effectively activate thioglycosides and direct alcohol nucleophiles by coordinating with the C2-ether protecting group, thereby achieving 1,2-*cis*-furanosylation with high stereoselectivity (Figure 1c).

Our approach commences with the activation of a simple thioglycoside donor using an external diazo compound under copper-catalyzed conditions, exploiting the ability of copper to coordinate with furanose C2-*O* and incoming alcohol nucleophiles to achieve 1,2-*cis*-selectivity.[10] The reaction of thioglycoside donor **1a** with diazo compound **2a** and methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose acceptor **3a** under copper(I) trifluoromethanesulfonate conditions produced the desired disaccharide **4a** with excellent 1,2-*cis*-stereoselectivity but a low yield (Table 1a, 15%, α/β = 7/1), with most starting materials unreacted. Using copper(II) trifluoromethanesulfonate slightly improved the yield to 20%, though unreacted materials persisted. Stoichiometric copper further improved the yield to 55%, but it also generated multiple byproducts, including carbene dimer, direct alcohol insertion, and other unidentified compounds.

Aiming for an additive-free thioglycoside activation method and addressing the competitive direct attack of the acceptor nucleophile on the diazo-derived carbene, we focused on enhancing the reactivity of the sulfur atom in thioglycosides toward the diazo moiety. To this end, we devised an intramolecular thioglycoside diazo donor, anticipating that the proximity and intrinsic reactivity of the sulfur atom would overcome the competitive reactivity issues observed in intermolecular reactions.

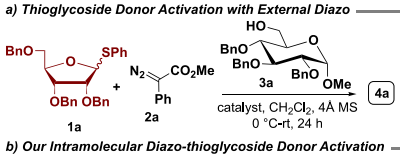
Intramolecular diazo thioglycoside donors can be synthesized in two steps using commercially available starting materials and remain stable for months (see Supporting Information (SI) for details). Optimization of our intramolecular diazo thioglycoside activation began with the 2,3,5-tri-*O*-benzyl-D-ribofuranosyl donor **1b** and the glucopyranose acceptor **3a** (Table 1b). Replicating Rh(II)-catalyzed conditions yielded the desired disaccharide **4a** at ~10% with the formation of major byproduct **5** (entry 1).[5b] Switching to copper salts, 10 mol % copper(I) triflate improved the yield to 37% with excellent 1,2-*cis*-selectivity (9/1) (entry 2). However, using other copper(I) counteranions reduced both yield and selectivity (entries 3, 4). Remarkably, with 10 mol % of copper(II) triflate, the reaction provided an excellent yield (88%) with an α-*cis*-selectivity of 9/1 at room temperature in 20 h (entry 5). Under the reaction conditions, a minor degree of byproduct formation was observed, specifically byproduct **5**, which likely results from the interaction between the oxocarbenium ion and the released oxathian counterpart (see SI page S31 for details).[5b] Since some of the donors followed an unproductive pathway, an increased amount of donor (1.4 equiv) was necessary to fully consume the acceptor. At lower temperatures, the decomposition of diazo compounds slows, which is a critical step in forming copper carbenes. The subsequent reaction steps depend on the successful completion of this initial process. Although byproduct formation decreased, the reaction resulted in a similar yield and selectivity of the desired product **4a** (entries 6, 7). Testing other metal triflates, $Zn(OTf)_2$ gave only the rearrangement byproduct **5**, while $Fe(OTf)_2$ required 50 °C for diazo decomposition with no stereoselectivity (entries 8, 9). Without molecular sieves, both yield and selectivity decreased, leading to increased byproduct formation (entry 10).

With optimized conditions, we explored the substrate scope with the benzyl-protected D-ribofuranosyl donor **1b** (Table 2a). Primary alcohols featuring terminal alkene and alkyne functionalities underwent smooth reactions, providing high yields and α-*cis*-selectivity (**4b**, **4c**). Secondary and tertiary alcohols including chiral alcohol acceptors also afforded corresponding furanosylation products with high yields and α-*cis*-selectivity (**4d**–**4h**). Encouragingly, reaction yields and selectivity with carbohydrate alcohol acceptors were unaffected by protecting groups including acetonide, benzyl, and benzoyl (**4i**–**4l**). Notably, hindered carbohydrate acceptors, which are typically less reactive toward glycosylation, performed equally well with high yields and excellent 1,2-*cis*-selectivity (**4m**, **4n**). A protected amino acid alcohol acceptor also showed high *cis*-selectivity (**4o**). Additionally, our system was successfully applied to synthesize *C*- and *N*-glycosides, achieving high yields and excellent *cis*-selectivity (**4p**, **4q**).

Following this, we expanded the substrate scope using arabinose donor **1c** (Table 2b.) Primary, secondary, and bulkier tertiary alcohol acceptors reacted effectively, producing the desired disaccharides in good yields with excellent β-*cis*-stereoselectivity (**6a**–**6e**). Remarkably, acetonide-protected galactose-, benzyl-, benzoyl-, and acetyl-protected glucose

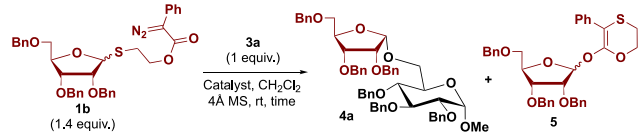
Table 1. Optimization of the Reaction Conditions[a]

a) Thioglycoside Donor Activation with External Diazo



catalyst (mol%)	% yield[b] 4a	α/β ratio[c]
[CuOTf]$_2$·tol (10)	15%	7/1
Cu(OTf)$_2$ (10)	20%	7/1
Cu(OTf)$_2$ (100)	55%	7/1

b) Our Intramolecular Diazo-thioglycoside Donor Activation



Entry	Catalyst (mol %)	Time	% Yield (**4a**)[b]	α/β ratio	% Yield (**5**)[b]
1.	$Rh_2(OAc)_4$ (5%), TfOH·DTBMP	16 h	10%	n.d.	80%
2.	[CuOTf]$_2$·tol (10%)	24 h	37%	9/1	45%
3.	$Cu(MeCN)_4PF_6$ (10%)	24 h	20%	4/1	55%
4.	$Cu(MeCN)_4BF_4$ (10%)	24 h	0%	n.d.	65%
5.	**Cu(OTf)$_2$ (10%)**	20 h	**88%**	9/1	**20%**
6.	Cu(OTf)$_2$ (10%), 0 °C	36 h	65%	9/1	<10%
7.	Cu(OTf)$_2$ (10%), 10 °C	36 h	88%	9/1	20%
8.	Zn(OTf)$_2$ (10%)	36 h	n.r.	n.d.	60%
9.	Fe(OTf)$_2$ (10%), 50 °C	16 h	56%	1/1	40%
10.	Cu(OTf)$_2$ (10%), no 4 Å MS	20 h	58%	7/1	45%

[a]All furanosylations were conducted with acceptor **3a** (0.05 mmol), donor **1b** (0.07 mmol), and CH_2Cl_2 (0.04 M) at 23 °C. [b]Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard, with respective to the acceptor **3a**. [c]Diastereoselectivity was determined by ^{1}H NMR.

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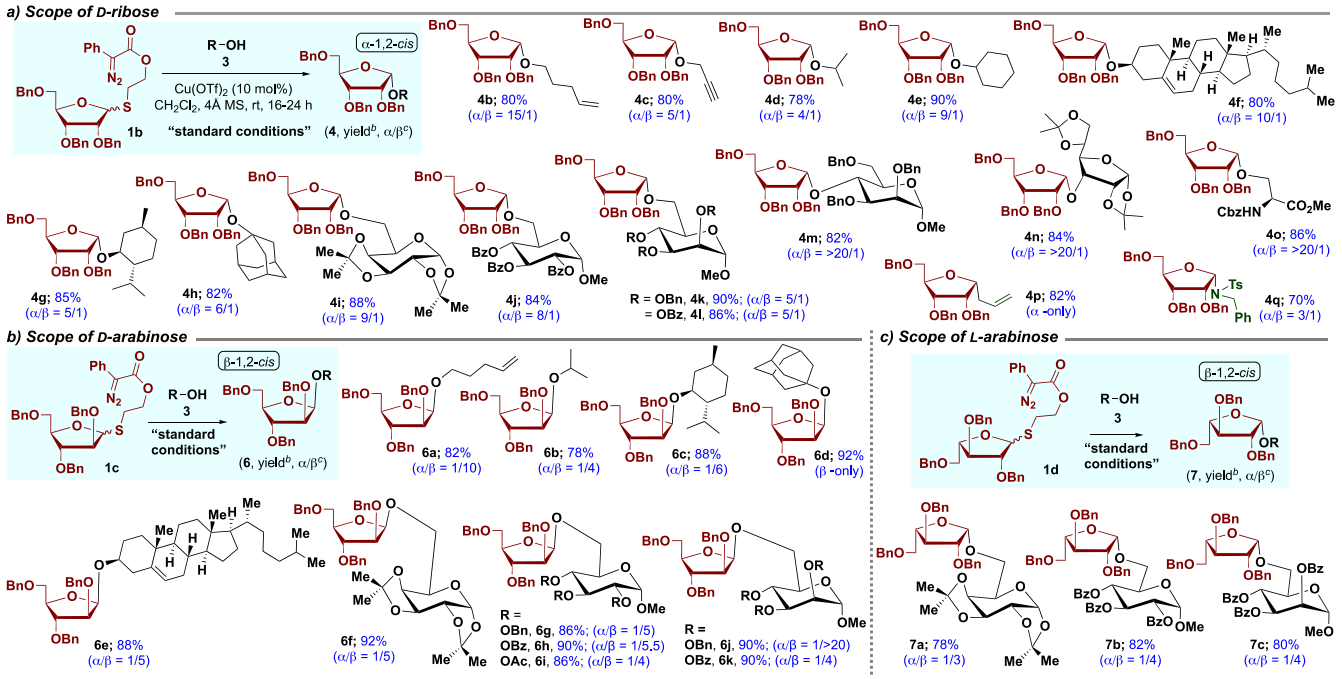
Table 2. Scope of 1,2-*cis*-Furanosylations[a]



[a]All furanosylations were conducted with acceptor **3** (0.05 mmol), donor **1b**/**1c**/**1d** (0.07 mmol), and CH_2Cl_2 (0.04 M). [b]Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]Diastereoselectivity was determined by ^1H NMR.

acceptors demonstrated facile reactivity, furnishing products with good *β-cis*-selectivity and high yields (**6f**–**6i**). Notably, acceptors derived from mannose were unreactive with the Jacobsen bis-thiourea furanosylation protocol.[12] Our method achieved the intended product with high yields and selectivity, adding to the versatility of our approach (**6j**, **6k**).

To demonstrate compatibility with the opposite enantiomer, L-arabinofuranoside donor **1d** was also tested (Table 2c). Reactions with this donor also exhibited *β-cis*-selectivity, likewise D-arabinofuranoside. The acetonide- and benzoyl-protected glucopyranoside acceptors, as well as the benzoyl-protected mannopyranoside acceptor, afforded corresponding products in good yields and *β-cis*-selectivity (**7a**–**7c**).

Recent studies by Jacobsen[12] and Zhang[13] groups showed that donor anomeric composition affects 1,2-*cis*-furanosylation stereoselectivity. We investigated the correlation between the initial anomeric ratio of our diazo thioglycoside donor and the final product's stereoselectivity using both a racemic mixture and an enantiopure ribose donor **1b** (Figure 2a). To our delight, we observed the same yield and stereoselectivity in each trial, suggesting the anomeric composition of the starting diazo donor does not influence the stereoselectivity outcome. Furthermore, testing for potential epimerization of the *α*/*β*-furanoside products under the same conditions revealed no epimerization, demonstrating the mild nature of our protocol.

Next, we investigated the effect of the electronic properties of diazo donors on the reaction kinetics (Figure 2b). Under standard conditions with acceptor **3a**, the *para*-methoxy ribose donor (**1e**) reacted more quickly but produced mainly byproducts, yielding only 34% of the desired product. In contrast, parent donor **1b** provided an 88% yield with minimal byproduct. The *para*-nitro donor (**1f**) was unreactive under the optimized conditions, likely due to the increased stability of the acceptor/acceptor diazo complex.

To investigate the impact of the C2-group, we synthesized donors with various C2 modifications (Figure 2c). We tested whether *cis*-selectivity was driven by copper *π*-aryl coordination or C2 oxygen using a C2 methoxy donor (**1g**), which yielded 92% product with high *α-cis*-selectivity (**8**). Encouraged by this, a C2-OTIPS donor (**1h**), which is suitable for iterative and solid-phase syntheses due to their facile deprotection,[1d,14] provided an excellent yield and *α-cis*-selectivity (**9**). In contrast, the C2 deoxyribose donor (**1i**) decomposed unproductively, indicating that a coordinating group at C2 is crucial for smooth and selective reactivity. Furthermore, to investigate the role of copper in driving *α-cis*-selectivity, we tested the reaction of traditional C2-OTIPS thioglycoside donor (**1h**) under literature-reported NIS/TMSOTf[2n] and NIS/AgOTf[2m] reaction conditions. The reaction produced disaccharides in good yields but without stereoselectivity (Figure 2c). This indicates that copper is likely crucial for achieving the high 1,2-*cis*-selectivity observed in our method.

Building on the success of the C2-TIPS protecting group, we explored furanosylation with various alcohol acceptors, achieving good to excellent yields and exclusive 1,2-*cis*-selectivity (Figure 2d). The method efficiently synthesized phenolic glycosides (**9b**) and showed high yield and exclusive *α-cis*-selectivity with benzoyl-protected glucose and benzyl-protected mannose acceptors (**9c**, **9d**). Furthermore, the donor exhibited orthogonal reactivity with alkynyl and thioglycoside donors (**9e**–**9g**), ideal for iterative oligosaccharide synthesis. We then applied our donor in an iterative synthesis for 1,2-*cis*-selective trisaccharide formation. Using C2-OTIPS donor **1h** with acceptor **3a**, we achieved a 90% yield of the 1,2-*cis* product. Subsequent TBAF deprotection of the C2 silyl group and reaction with additional donor **1h** produced the trisaccharide in 74% yield with *α*-only selectivity.

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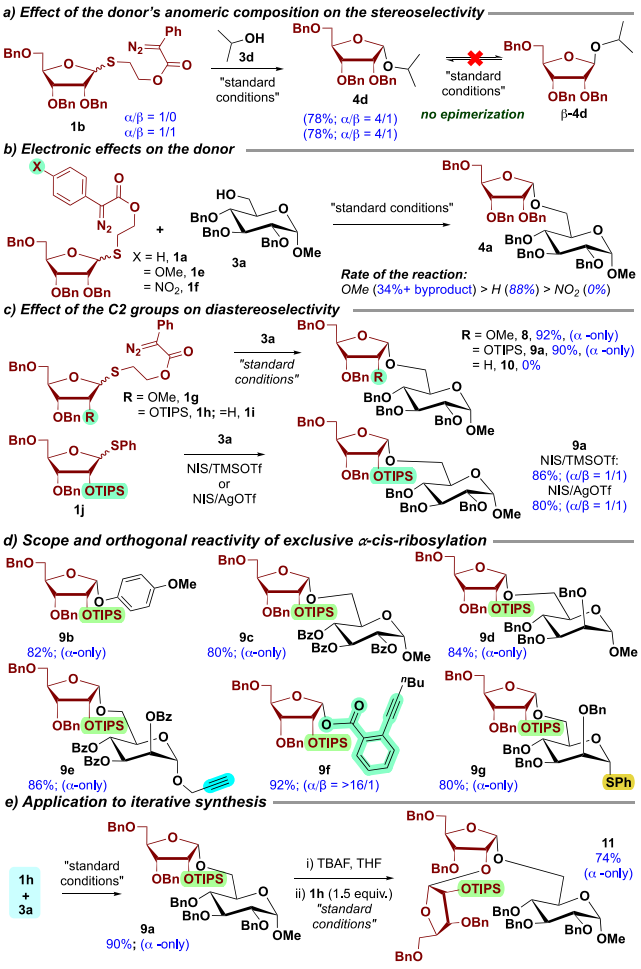

Figure 2. (a) Effect of donor's anomeric configuration on reaction stereoselectivity. (b) Effect of donor's electronics. (c) Effect of the C2-group on reaction diastereoselectivity. (d) Scope and orthogonal reactivity of exclusive 1,2-*cis*-ribosylation. (e) Application to *cis*-selective iterative synthesis.

Mechanistically, the reaction proceeds through an oxocarbenium ion, and the desired 1,2-*cis*-stereoselectivity stems from chelation between the C2-oxygen of the furanose donor and the incoming copper alkoxide nucleophile (see SI page S31 for detailed mechanism and S32 for computational calculations).

In summary, we developed an additive-free, copper(II)-catalyzed 1,2-*cis*-furanosylation, achieving high yields and diastereoselectivity at room temperature. Using benchtop-stable diazo-derived thiofuranosyl donors, the method accommodates diverse alcohol acceptors and furanose donors. Influence of C2 group investigations revealed a very high 1,2-*cis*-selectivity, which was applied in the iterative synthesis of a *cis*-selective trisaccharide. The approach offers stereoselectivity independent of donor anomeric configuration and exhibits orthogonal reactivity with alkyne and thioglycoside donors, broadening its applicability in iterative oligosaccharide synthesis.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03281.

Experimental procedures, computational studies, NMR spectroscopic and analytical data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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