

Article

Activation of Thioglycosides with Copper(II) Bromide

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Abstract: Reported herein is a new protocol for glycosidation of alkyl and aryl thioglycosides in the presence of copper(II) bromide. While the activation with CuBr₂ alone was proven suitable for reactive glycosyl donors, the activation of less reactive donors was more efficient in the presence of triflic acid as an additive. A variety of thioglycoside donors in reactions with different glycosyl acceptors were investigated to determine the initial scope of this reaction.

Keywords: glycosylation; synthesis; activation; oligosaccharides; transition metals

1. Introduction

A myriad of approaches have been developed for the chemical synthesis of glycosidic linkages [1–3]. Glycosyl halides [4,5], glycosyl imidates [6], and thioglycosides [7] have become the most prominent glycosyl donors utilized in chemical glycosylation and oligosaccharide synthesis. First synthesized by Fischer in 1909 [8], thioglycosides are stable towards a majority of protecting group manipulations albeit can be readily activated in the presence of mild thiophilic reagents [7,9–12]. Among a plethora of known thiophilic promoters, transition metals have been used for decades. In fact, the first known method for thioglycoside activation makes use of mercury(II) salts [13]. Nevertheless, only recently the activation of conventional thioglycosides through the direct coordination of a metal salt with the anomeric sulfur has been investigated in detail. First reported by Pohl et al., a sub-stoichiometric amount of Ph₃Bi(OTf)₂ was able to activate propylthio glycosides [14,15]. Subsequently, Sureshan et al. [16] performed activation of thioglycosides using a sub-stoichiometric amount of AuCl₃. Zhu et al. [17] also showed that propargylthio glycosyl donors are activated through the direct coordination of Au(III) to the sulfur atom rather than the remote pathway via the alkyne functionality. As a part of our efforts toward the development of novel methods for glycosylation, previously we reported that alkyl/aryl thioglycosides can be activated with palladium(II) bromide (PdBr₂) [18]. It has been found that the activation can be performed in the presence of PdBr₂ only, but an additive (propargyl bromide) accelerates the activation process. A preliminary mechanistic analysis relying on ¹H NMR spectroscopy revealed that propargyl bromide could form a more reactive reaction intermediate and possibly acts as the leaving group scavenger. For example, when thiogalactoside **1** was activated for glycosidation with glycosyl acceptor **2** in the presence of PdBr₂ only, the reaction was slow and disaccharide **3** was obtained in 76% yield in 48 h. However, in the presence of propargyl bromide, disaccharide **3** was obtained in 96% yield within 24 h (Scheme 1A). It was postulated that the reaction proceeds via the intermediacy of complex A. In an effort to identify greener and more accessible transition metal salts, reported herein is our investigation of copper(II)-promoted activation of thioglycosides.



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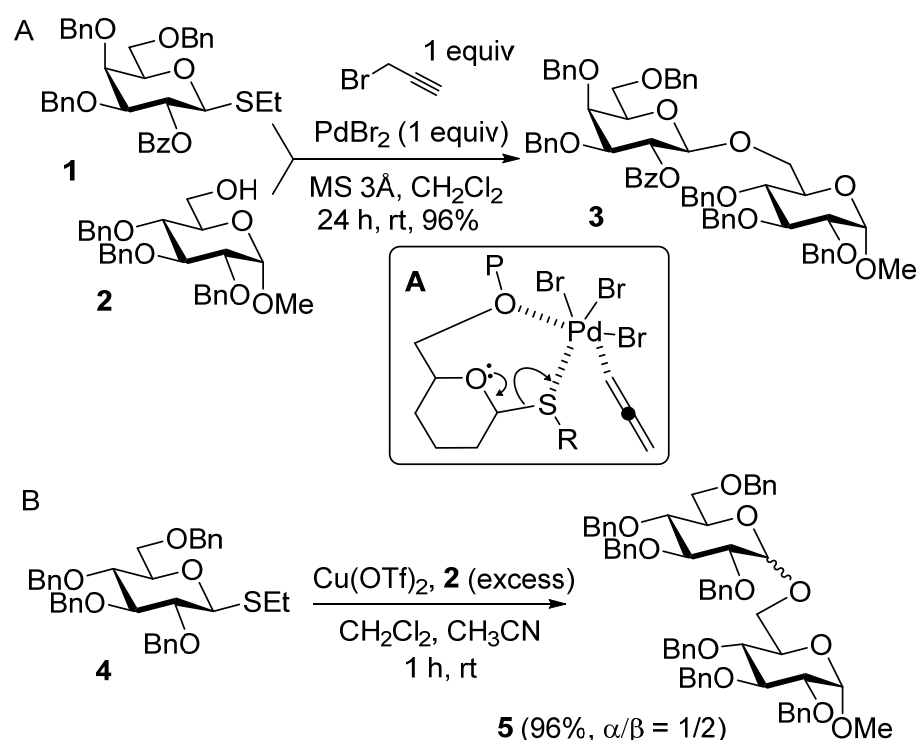
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Scheme 1. Previous examples of ethylthio glycoside activation in the presence of palladium (A) and copper salts (B).

2. Results and Discussion

Our interest to copper(II) was sparked by a report by Dondoni, Marra, and Massi wherein the synthesis of disaccharides was achieved by the activation of ethylthio glycosides promoted by copper(II) triflate [19]. We were fascinated by these results because Cu(OTf)_2 is a well-known activator for reactive glycosyl donors, such as halides⁵ or thioimides [20–22], but not conventional alkyl/aryl thioglycosides. In accordance with the reported protocol, thioglycoside **4** was reacted with excess of acceptor **2** to afford the corresponding disaccharide **5** in a high yield albeit with poor stereoselectivity (Scheme 1B) [19].

By means of a personal communication with Professor Marra, the authors have learnt that the choice of the reaction solvent is essential. Marra and co-workers observed that the activation of thioglycosides promoted by Cu(OTf)_2 proceeded much faster in acetonitrile (or MeCN/DCM), a solvent in which Cu(OTf)_2 is highly soluble. The solvent was suspected to act as a ligand judged by the color change of the reaction mixture. Marra and co-workers have also suspected that reactions in MeCN proceeded through a single-electron transfer, whereas for reactions in DCM the copper salt acted as a thiophilic metal. It was also noted that these reaction conditions were better suited for the activation of “armed” glycosyl donors such as per-*O*-benzylated thioglycoside **4**. These observations were made in 2005, and to the best of our knowledge no follow-up investigation has yet emerged.

To elaborate on this discovery, for our own study we chose copper(II) bromide (cupric bromide) as a significantly cheaper and less moisture sensitive alternative to Cu(OTf)_2 . For the initial experimentation, we selected a highly reactive galactosyl donor **1** [23] equipped with the superarming protecting group pattern [24], and a conventional primary glycosyl acceptor **2** [25]. When the reaction of glycosyl donor **1** with acceptor **2** was promoted with 0.8 equiv of CuBr_2 in DCM at rt, disaccharide **3** [26] was obtained in 45% in 24 h (Table 1, entry 1). Complete 1,2-*trans* selectivity achieved in this reaction is due to the participation of the neighboring 2-*O*-benzoyl ester group, a well-known effect in carbohydrate chemistry [27]. Encouraged by this promising result, we performed activations in the presence of 1.5, 2.0, and 2.5 equiv of CuBr_2 . As a result, disaccharide **3** was obtained in 70, 75, and 96%

yield, respectively (entries 2–4). Therefore, we chose to conduct all subsequent experiments in the presence of 2.5 equiv of the promoter.

Table 1. CuBr₂-mediated glycosidation of donors **1** and **6** with glycosyl acceptor **2**.

1 or 6 (1.0 equiv) + 2 (0.80 equiv) $\xrightarrow[\text{MS 3Å}]{\text{Conditions, see Table}}$ 3 or 7

1 and 3: R₃ = R₄ = R₆ = Bn
6 and 7: R₃ = R₄ = R₆ = Bz

Entry	Donor	Conditions	Product, Yield
1	1	CuBr ₂ (0.8 equiv), DCM, rt, 24 h	3, 45%
2	1	CuBr ₂ (1.5 equiv), DCM, rt, 24 h	3, 70%
3	1	CuBr ₂ (2.0 equiv), DCM, rt, 24 h	3, 75%
4	1	CuBr ₂ (2.5 equiv), DCM, rt, 24 h	3, 96%
5	1	CuBr ₂ (2.5 equiv), DCM, 40 °C, 4 h	3, 84%
6	1	CuBr ₂ (2.5 equiv), DCE, rt, 22 h	3, 98%
7	1	CuBr ₂ (2.5 equiv), DCE, 80 °C, 3 h	3, 85%
8	1	CuBr ₂ (2.5 equiv), DCE/MeCN (1/1, v/v), rt, 6 h	3, 70%
9	1	CuBr ₂ (2.5 equiv), MeCN, rt, 1.5 h	3, 80%
10	1	Cu(OTf) ₂ (2.5 equiv), DCE, rt, 24 h	3, 24%
11	1	CuCl ₂ (2.5 equiv), DCE, rt, 24 h	3, 16%
12	1	CuBr (2.5 equiv), DCE, rt, 24 h	NR
13	6	CuBr ₂ (2.5 equiv), DCE, rt, 24 h	7, 36%
14	6	CuBr ₂ (2.5 equiv), MeCN, rt, 6 h	7, 50%
15	6	CuBr ₂ (2.5 equiv), DCE, 80 °C, 4 h	7, 70%
16	6	CuBr ₂ (2.5 equiv), TfOH (0.5 equiv), DCE, rt, 24 h	7, 96%
17	1	CuBr ₂ (2.5 equiv), TfOH (0.5 equiv), DCE, rt, 3 h	3, 73%

These reactions were not swift and required 24 h to complete, and to enhance the reaction rates, we investigated the effect of the reaction temperature. When the reaction was performed at 40 °C, it was completed within 4 h. However, the shorter reaction time has also translated into a reduced yield of 84% for disaccharide **3** (entry 5). We then investigated the effect of the reaction solvent. When the reaction was carried out in 1,2-DCE at rt, disaccharide **3** was produced in an excellent yield of 98% and the reaction time was slightly reduced to 22 h (entry 6). Like in the case of reactions in DCM, increasing the reaction temperature (to 80 °C in this case) led to a decreased reaction time to 3 h, but also a decreased yield of 85% for disaccharide **3** (entry 7). Further investigation of the reaction solvent did not result in the anticipated gains. Although reactions in MeCN/1,2-DCE or neat MeCN were significantly faster at rt, 6 h or 1.5 h, the yields of disaccharide **3** were also reduced to 70 or 80%, respectively (entries 8 and 9). As a result of this optimization study, we identified reaction conditions listed in entry 6, CuBr₂ (2.5 equiv) in 1,2-DCE at rt, as the most suitable conditions for the activation of donor **2**. It should be noted that other copper(II) salts such as Cu(OTf)₂ or CuCl₂ gave inferior results under these reaction conditions. Thus, disaccharide **3** was obtained in 24 or 16% yield, respectively, in 24 h (entries 10 and 11). An attempt to perform the activation in the presence of copper(I) bromide resulted in no reaction after 24 h (entry 12).

When the developed reaction conditions comprising 2.5 equiv CuBr₂ in 1,2-DCE at rt were applied to the activation of per-*O*-benzoylated glycosyl donor **6** [28,29] for reaction with acceptor **2**, the corresponding disaccharide **7** [30] was obtained in a disappointing yield of 36% after 24 h (entry 13). This result was not totally unexpected due to a significantly lower reactivity of donor **6** due to its disarming protecting group pattern [31] (all esters) in comparison with the superarmed donor **1**. Hence, we conducted further optimization

of reaction conditions to enhance glycosylations with donor **6**. This included varying all major factors, solvent, temperature, and additives, while keeping the amount of CuBr₂ constant. Pilot investigation of the reaction solvent and temperature led to only marginal improvements. Thus, reaction in MeCN produced disaccharide **7** in 50% yield in 6 h (entry 14). Reaction in 1,2-DCE performed at 80 °C led to the formation of **7** in 70% in 4 h (entry 15). The desired solution was found by implementing TfOH as an additive for this reaction, and the optimal amount was found to be 0.5 equiv. Thus, glycosidation of donor **6** with acceptor **2** in the presence of CuBr₂ (2.5 equiv) and TfOH (0.5 equiv) in DCE at rt led to the formation of disaccharide **7** in 96% yield in 24 h (entry 16)! A control experiment performed with the reactive glycosyl donor **1** in the presence of CuBr₂ (2.5 equiv) and TfOH (0.5 equiv) in DCE at rt led to disaccharide **3** in a reduced yield of 73% (entry 17). This result was rationalized by the enhanced rate of hydrolysis of the glycosyl donor that is taking place in the presence of TfOH (see the SI for NMR monitoring experiments). Also observed was that in the absence of glycosyl acceptor, the glycosyl bromide will be slowly produced in the presence of CuBr₂ alone. Traces were present between 4 and 20 h. In the presence of CuBr₂ and TfOH, hemiacetal, the product of donor hydrolysis is produced first (2–4 h), and then slow production of the glycosyl bromide begins (20 h).

Therefore, as a result of these optimization studies, we concluded that reactive glycosyl donors are best activated in the presence of CuBr₂ (2.5 equiv) only, whereas unreactive donors may require TfOH (0.5 equiv) as an additive. With these considerations in mind, we applied the developed reaction conditions to glycosidation of acceptor **2** with a variety of thioglycosides of different sugar series equipped with various protecting and leaving groups. All reactions have been performed using Conditions A (CuBr₂ only) and the least reactive glycosyl donors have also been activated using Conditions B (CuBr₂/TfOH). This study is summarized in Table 2.

Table 2. Broadening the scope of the CuBr₂-assisted glycosylation to other glycosyl donors.

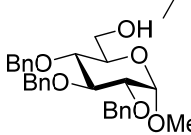
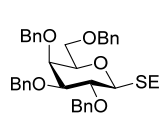
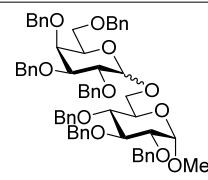
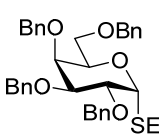
Glycosyl donor (1.0 equiv, see Table)  2 (0.80 equiv) Conditions: A. CuBr₂ (2.5 equiv) B. CuBr₂ (2.5 equiv) and TfOH (0.5 equiv) DCE, MS 3Å, rt PGO-OR' disaccharide products			
Entry	Donor	Conditions	Product, Yield, Ratio α/β
1	 8	A	 9, 72%, $\alpha/\beta = 1/1.5$
2	 10	A	9, 61%, $\alpha/\beta = 1/1.8$

Table 2. Cont.

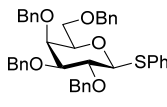
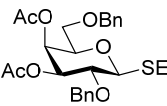
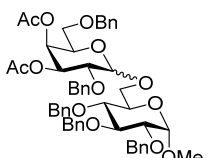
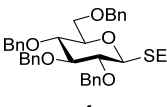
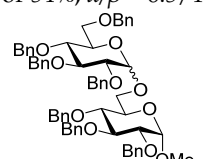
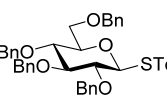
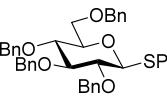
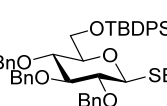
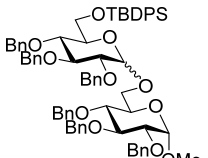
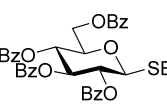
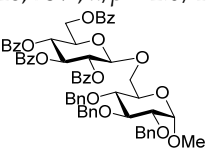
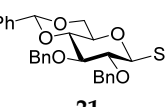
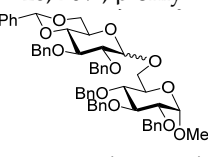
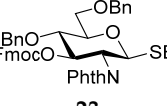
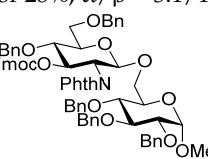
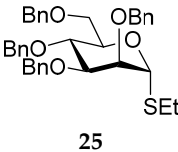
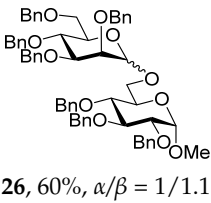
3	 11	A	9, 45%, $\alpha/\beta = 1/1.5$
4	 12	A or B	 13, 35%, $\alpha/\beta = 6.5/1$ or 54%, $\alpha/\beta = 6.5/1$
5	 4	A	 14, 82%, $\alpha/\beta = 1.1/1$
6	 15	A	14, 79%, $\alpha/\beta = 1/1.4$
7	 16	A	14, 60%, $\alpha/\beta = 1/1.1$
8	 17	A	 18, 73%, $\alpha/\beta = 2.0/1$
9	 19	A	 20, 70%, β only
10	 21	A or B	 22, 15%, $\alpha/\beta = 3.1/1$ or 28%, $\alpha/\beta = 3.1/1$
11	 23	A	 24, 76%, β only

Table 2. Cont.

12		A	
	25		26, 60%, $\alpha/\beta = 1/1.1$

We first investigated a series of other galactosyl donors; and these reactions showed a decline in the product yields that was clearly correlated with the predicted general trends for relative reactivity of glycosyl donors [32–39]. Per-*O*-benzylated galactosyl donor **8** [40,41] produced the corresponding disaccharide **9** [42] in 72% yield as a mixture of anomers ($\alpha/\beta = 1/1.5$, entry 1, Table 2). A similar reaction outcome was achieved with α -thioglycoside **10** [43] and disaccharide **9** was obtained in 61% ($\alpha/\beta = 1/1.8$, entry 2). The lower yield was rationalized by lower reactivity of α -thioglycosides than their β -linked counterparts [37]. Glycosidation of phenylthio glycoside **11** [44] produced disaccharide **9** in 45% yield ($\alpha/\beta = 1/1.5$, entry 3). This lower yield was rationalized by general lower reactivity of arylthio glycosides versus their alkylthio counterparts [45]. Glycosylation of partially acylated donor **12** [46] using conditions A produced disaccharide **13** [47] in a modest yield of 35% (entry 4). Expectedly, this result with partially disarmed glycosyl donor **12** could be enhanced when the reaction was repeated using Conditions B. In this case, disaccharide **13** was obtained in an improved yield of 54% (entry 4). These reactions were relatively α -selective [47], $\alpha/\beta = 6.5/1$ for both Conditions A and Conditions B. A similar enhancement of stereoselectivity was recently observed for 3,4-di-*O*-benzoylated galactosyl donors [48].

We then investigated a series of glucosyl donors, which provided comparable results under reaction conditions A. Thus, per-*O*-benzylated ethyl, tolyl, and phenyl thioglycosides **4** [49], **15** [50], and **16** [51] produced disaccharide **14** [42] in 60–82% yield (α/β from 1.1/1 to 1/1.4, entries 5–7). Similarly to that observed in the D-galacto series, SPh donor was the least reactive in this case. 6-*O*-TBDPS-protected donor **17** [52] produced disaccharide **18** [53] in 73% yield ($\alpha/\beta = 2.0/1$, entry 8). Even per-*O*-benzoylated donor **19** [29] reacted well under conditions A and the corresponding disaccharide **20** [54] was isolated in 70% yield (entry 9). Only one example in this series wherein torsionally deactivated [55,56] glycosyl donor **21** have failed to produce good yields. Thus, under conditions A or B, disaccharide **22** [57] was obtained in 15 or 28% yield, respectively ($\alpha/\beta = 3.1/1$ in both cases, entry 10). Glycosidation of glucosamine-derived donor **23** [58] afforded disaccharide **24** [18] in a respectable yield of 76% (entry 11). Glycosylation of per-benzylated mannosyl donor **25** [59] was also possible, and the corresponding disaccharide **26** [60,61] was obtained in 60% yield with no selectivity (entry 12).

We then turned our attention on investigating glycosylation of other glycosyl acceptors using glycosyl donor **1** under conditions A. Glycosylation of secondary glycosyl acceptors **27** [25] or **29** [25] was very effective, and the respective disaccharides **28** [18] and **30** [26] were obtained in 93–95% yield (entries 1 and 2, Table 3). Glycosylation of hindered 4-OH acceptor **31** [25] was less efficient, nevertheless disaccharide **32** [26] was obtained in a respectable yield of 70% (entry 1). Finally, glycosylation of electronically deactivated benzoylated 6-OH acceptor **33** [62] produced disaccharide **34** [63] in 95% yield (entry 4).

Table 3. Extending the scope of the CuBr₂-promoted glycosylation to other glycosyl acceptors.

Acceptor (see table, 0.80 equiv) CuBr₂ (2.5 equiv) DCE, MS 3 Å, rt 1 (1.0 equiv) → disaccharide products (see table)		
Entry	Acceptor	Product, Yield
1	27	28, 93%
2	29	30, 95%
3	31	32, 70%
4	33	34, 95%

3. Experimental

General. All chemicals used were reagent grade and used as supplied. The ACS grade solvents used for reactions were purified and dried in accordance with standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F₂₅₄. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH₂Cl₂ and ClCH₂CH₂Cl were distilled from CaH₂ directly prior to the application. Molecular sieves (3 Å), used for reactions, were crushed and activated in *vacuo* at 390 °C during 8 h in the first instance and then for 2–3 h at 390 °C directly prior to application. ¹H NMR spectra were recorded at 400 MHz, ¹³C NMR spectra were recorded at 100 MHz. The ¹H NMR chemical shifts are referenced to tetramethylsilane (δ_H = 0 ppm) or CHCl₃ (δ_H = 7.26 ppm) for ¹H NMR spectra for solutions in CDCl₃. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ¹H NMR spectra (see the Supplementary Material).

3.1. Synthesis of Building Blocks

Ethyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio-β-D-galactopyranoside (1) was synthesized as reported previously and its analytical data was in accordance with that previously described [23].

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (2) was synthesized as reported previously and its analytical data was in accordance with that previously described [25].

Ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (4) was synthesized as reported previously and its analytical data was in accordance with that previously described [49].

Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- β -D-galactopyranoside (6) was synthesized as reported previously and its analytical data was in accordance with that previously described [28,29].

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-galactopyranoside (8) was synthesized as reported previously and its analytical data was in accordance with that previously described [40,41].

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio- α -D-galactopyranoside (10) was synthesized as reported previously and its analytical data was in accordance with that previously described [43].

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-galactopyranoside (11) was synthesized as reported previously and its analytical data was in accordance with that previously described [44].

Ethyl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-1-thio- β -D-galactopyranoside (12) was synthesized as reported previously and its analytical data was in accordance with that previously described [46].

Tolyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside (15) was synthesized as reported previously and its analytical data was in accordance with that previously described [50,51].

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside (16) was synthesized as reported previously and its analytical data was in accordance with that previously described [51].

Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio- β -D-glucopyranoside (17) was synthesized as reported previously and its analytical data was in accordance with that previously described [52].

Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- β -D-glucopyranoside (19) was synthesized as reported previously and its analytical data was in accordance with that previously described [29].

Ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio- β -D-glucopyranoside (21) was synthesized as reported previously and its analytical data was in accordance with that previously described [64].

Ethyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-fluorenylmethoxycarbonyl-2-phthalimido-1-thio- β -D-glucopyranoside (23) was synthesized as reported previously and its analytical data was in accordance with that previously described [58].

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio- α -D-mannopyranoside (25) was synthesized as reported previously and its analytical data was in accordance with that previously described [59].

Methyl 3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (27) was synthesized as reported previously and its analytical data was in accordance with that previously described [25].

Methyl 2,4,6-tri-*O*-benzyl- α -D-glucopyranoside (29) was synthesized as reported previously and its analytical data was in accordance with that previously described [25,65].

Methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (31) was synthesized as reported previously and its analytical data was in accordance with that previously described [25].

Methyl 2,3,4-tri-*O*-benzoyl- α -D-glucopyranoside (33) was synthesized as reported previously and its analytical data was in accordance with that previously described [62].

3.2. Synthesis of Disaccharides

3.2.1. Method A—General Procedure for Glycosidation of Thioglycosides in the Presence of CuBr₂

A mixture containing thioglycoside donor (30 mg, 0.040–0.050 mmol), glycosyl acceptor (0.030–0.040 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in dry 1,2-dichloroethane (C₂H₄Cl₂, DCE, 1.0 mL) was stirred under argon for 1 h at rt. After that, copper bromide (CuBr₂, 2.5 equiv to donor, 0.100–0.125 mmol) was added and the reaction mixture was stirred for 24 h at rt. The solids were filtered off through a pad of Celite and rinsed successively with DCM. The combined filtrate (~20 mL) was washed with

H₂O (2 × 5 mL). The organic phase was separated, dried with MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution) to afford a disaccharide derivative in yields listed in tables and below.

3.2.2. Method B—General Procedure for Glycosidation of Thioglycosides in the Presence of CuBr₂ and TfOH

A mixture containing thioglycoside donor (30 mg, 0.040–0.050 mmol), glycosyl acceptor (0.030–0.040 mmol), and freshly activated molecular sieves (3 Å, 90 mg) in dry 1,2-dichloroethane (C₂H₄Cl₂, DCE, 1.0 mL) was stirred under argon for 1 h at rt. After that, copper bromide (CuBr₂, 2.5 equiv to donor, 0.100–0.125 mmol) and TfOH (0.50 equiv to donor, 0.020–0.025) was added and the reaction mixture was stirred for 24 h at rt. The solids were filtered off through a pad of Celite and rinsed successively with DCM. The combined filtrate (~20 mL) was washed with H₂O (2 × 5 mL). The organic phase was separated, dried with MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution) to afford a disaccharide derivative in yields listed in tables and below.

Methyl 6-O-(2-O-benzoyl-3,4,6-tri-O-benzyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (3) was obtained from thioglycoside 1 and glycosyl acceptor 2 by Method A in up to 98% yield as a clear film. Analytical data for 3 was in accordance with that reported previously [26].

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (7) was obtained from thioglycoside 6 and glycosyl acceptor 2 by Method B in up to 96% yield as a white amorphous solid. Analytical data for 7 was in accordance with that reported previously [30].

Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-galactopyranosyl)-α-D-glucopyranoside (9) was obtained from thioglycosides 8, 10 or 11 and glycosyl acceptor 2 by Method A in 72, 62, or 45% yield, respectively (α/β = 1/1.5–1.8) as a colorless syrup. Analytical data for 9 was in accordance with that reported previously [42].

Methyl 6-O-(3,4-di-O-acetyl-2,6-di-O-benzyl-α/β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (13) was obtained from thioglycoside 12 and glycosyl acceptor 2 by Method A or Method B in 35 or 54% yield, respectively (α/β = 6.5/1) as a colorless syrup. Analytical data for 13 was in accordance with that reported previously [47].

Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (14) was obtained from thioglycosides 4, 15 or 16 and glycosyl acceptor 2 by Method A in 82, 79 or 60% yield, respectively (α/β = from 1.1/1 to 1/1.4) as a colorless syrup. Analytical data for 14 was in accordance with that reported previously [42].

Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4-tri-O-benzyl-6-O-*tert*-butyldiphenylsilyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (18) was obtained from thioglycoside 17 and glycosyl acceptor 2 by Method A in 73% yield (α/β = 2.0/1) as a colorless syrup. Analytical data for 18 was in accordance with that reported previously [53].

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (20) was obtained from thioglycoside 19 and glycosyl acceptor 2 by Method A in 70% yield as a clear film. Analytical data for 20 was in accordance with that reported previously [54].

Methyl 2,3,4-tri-O-benzyl-6-O-(2,3-di-O-benzyl-4,6-O-benzylidene-α/β-D-glucopyranosyl)-α-D-glucopyranoside (22) was obtained from thioglycoside 21 and glycosyl acceptor 2 by Method A or Method B in 15 or 28% yield, respectively (α/β = 3.1/1) as a colorless syrup. Analytical data for 22 was in accordance with that reported previously [57].

Methyl 2,3,4-tri-O-benzyl-6-O-(4,6-di-O-benzyl-2-deoxy-3-O-fluorenylmethoxycarbonyl-2-phthalimido-β-D-glucopyranosyl)-α-D-glucopyranoside (24) was obtained from thioglycoside 23 and glycosyl acceptor 2 by Method A in 76% yield as a clear film. Analytical data for 24 was in accordance with that reported previously [18].

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-mannopyranosyl)- α -D-glucopyranoside (26) was obtained from thioglycoside 25 and glycosyl acceptor 2 by Method A in 60% yield ($\alpha/\beta = 1/1.1$) as a colorless syrup. Analytical data for 26 was in accordance with that reported previously [60,61].

Methyl 2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-galactopyranosyl)-3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (28) was obtained from thioglycoside 1 and glycosyl acceptor 27 by Method A in 93% yield as a colorless syrup. Analytical data for 28 was in accordance with that reported previously [18].

Methyl 3-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-galactopyranosyl)-2,4,6-tri-*O*-benzyl- α -D-glucopyranoside (30) was obtained from thioglycoside 1 and glycosyl acceptor 29 by Method A in 95% yield as a clear film. Analytical data for 30 was in accordance with that reported previously [26].

Methyl 4-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-galactopyranosyl)-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (32) was obtained from thioglycoside 1 and glycosyl acceptor 31 by Method A in 70% yield as a clear film. Analytical data for 32 was in accordance with that reported previously [26].

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl- β -D-galactopyranosyl)- α -D-glucopyranoside (34) was obtained from thioglycoside 1 and glycosyl acceptor 33 by Method A in 95% yield as a white amorphous solid. Analytical data for 34 was in accordance with that reported previously [63].

4. Conclusions

A new method for the activation of thioglycosides has been developed. The activation with CuBr₂ can be sluggish with unreactive thioglycoside donors. In these cases, the outcome can be improved in the presence of triflic acid additive. Upon standardizing the basic reaction conditions for both reactive and unreactive glycosyl donors, further examination of various thioglycosides has been performed. In most cases, our activation system was effective and predictable, but the product yields were largely dependent on the reactivity of the glycosyl donor. We believe that this study will fundamentally contribute to other developments of copper-catalyzed reactions with carbohydrates [66–75]. Further optimization of the reaction conditions, investigation of the reaction mechanism, and its application in automated synthesis of glycans are currently underway in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27217354/s1>, Figure S1: NMR Monitoring to Understand Mechanistic Aspects of the Reaction; Figure S2: ¹H NMR Spectra of Known Compounds; Figure S3: ¹H NMR (CDCl₃ 400 MHz) of compound 3; Figure S4: ¹H NMR (CDCl₃ 400 MHz) of compound 7; Figure S5: ¹H NMR (CDCl₃ 400 MHz) of compound 9; Figure S6: ¹H NMR (CDCl₃ 400 MHz) of compound 13; Figure S7: ¹H NMR (CDCl₃ 400 MHz) of compound 14; Figure S8: ¹H NMR (CDCl₃ 400 MHz) of compound 18; Figure S9: ¹H NMR (CDCl₃ 400 MHz) of compound 20; Figure S10: ¹H NMR (CDCl₃ 400 MHz) of compound 22; Figure S11: ¹H NMR (CDCl₃ 400 MHz) of compound 24; Figure S12: ¹H NMR (CDCl₃ 400 MHz) of compound 26; Figure S13: ¹H NMR (CDCl₃ 400 MHz) of compound 28; Figure S14: ¹H NMR (CDCl₃ 400 MHz) of compound 30; Figure S15: ¹H NMR (CDCl₃ 400 MHz) of compound 32; Figure S16: ¹H NMR (CDCl₃ 400 MHz) of compound 34.

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