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# Palladium-Catalyzed C−S Bond Formation as a Tool for Latent−Active Glycosylation

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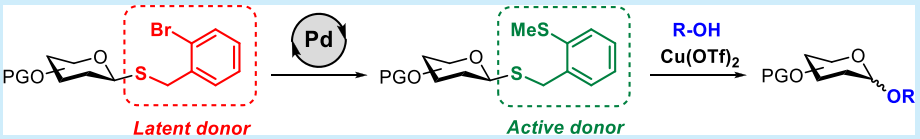


**ABSTRACT:** A high-yielding palladium-catalyzed C−S cross-coupling is presented for utilization in carbohydrate chemistry as a key transformation for attachment of a second chelating sulfur atom that allows the exploitation of a latent−active glycosylation strategy with $Cu(OTf)_2$ as the promoter. The novel approach employs *o*-Br-benzyl thioglycosides as latent glycosyl donors and *o*-SMe-benzyl thioglycosides as the active counterparts.



The transition metal palladium is a highly valued tool element for catalyzing transformations on especially $sp^2$-hybridized centers. It has perhaps mostly been studied for the preparation of C−C as well as C−N/C−O bonds, whereas far fewer examples have been presented for the generation of C−S bonds, which is probably due to deactivation of the metal catalyst.[1] The main driving force for conducting research into C−S bond formation chemistry has arguably been to establish powerful methods for preparing the many sulfur-containing pharmaceuticals, but the C−S bond has additionally found application in materials science.[2−4]

Although carbohydrate chemistry is a subdivision of organic chemistry, palladium has only rarely ventured into this field besides being used as a heterogeneous catalyst for *O*-debenzylation. We have recently made some use of modern homogeneous palladium catalysis for protecting group manipulations[5] and protecting group-mediated reactivity tuning of glycosyl donors.[6,7] In this paper we report on our development of a novel latent−active glycosylation approach using palladium as a central tool and describe how the instalment of a sulfur atom is used to facilitate a subsequent chemoselective step by exploiting the coordinating/chelating ability of a sulfide.

Oligosaccharides are structurally highly diverse and much less straightforward to synthesize compared to other biomolecules such as oligopeptides and oligonucleotides. Furthermore, due to their complexity, natural isolation has not offered a way of obtaining adequate amounts for use in studying their involvement in biological processes.[8−13] Therefore, new methods for the efficient synthesis of complex carbohydrate structures are still needed and are being developed.[14−17]

A powerful strategy used for streamlining oligosaccharide synthesis is the latent−active method, where a glycosyl donor is chemoselectively activated and reacted with a carbohydrate-based glycosyl acceptor, which carries an unreactive (latent) donor functionality that can be converted into an active donor functionality for activation in a later step. The first latent−active glycosylation strategies were published in the 1990s by Roy,[18] Fraser-Reid,[19] and Boons,[20] and later examples include work from the groups of Kim,[21] Huang,[22] Wang,[23] Demchenko,[24] Yu,[25] Wan,[26,27] and Ragains.[28] Various strategies have been applied for the conversion from a latent to active donor, including reduction and subsequent acetylation,[18,22] reductive debromination,[19] Rh/Ir-catalyzed isomerization,[20,23] hydrogenolysis,[21] *N*-deacylation,[24] sulfur oxidation[26,27] and the before-mentioned Pd-catalyzed C−C cross-couplings (Sonogashira and Suzuki couplings, respectively).[25,28] A recent example is given in Scheme 1A.

In oligosaccharide synthesis, the glycosyl donor leaving group determines the mode of activation, which basically refers to the choice of Lewis acid (e.g., halophilic, thiophilic, hard or soft). Based on previous studies with anomeric benzoates as C-1 leaving groups, we have found that a second coordination center (*o*-OMe) significantly increases the glycosyl donor reactivity.[29] We wanted to explore whether a similar trend would be present among one of the most used glycosyl donor types, the thioglycosides.

It was accordingly decided to study the activation of *ortho*-(methylthio)benzyl thioglycosides (**I** and **IV**, Scheme 1B), which is a hitherto undescribed glycosyl donor type. A reason for selecting this donor structure for our investigations was the

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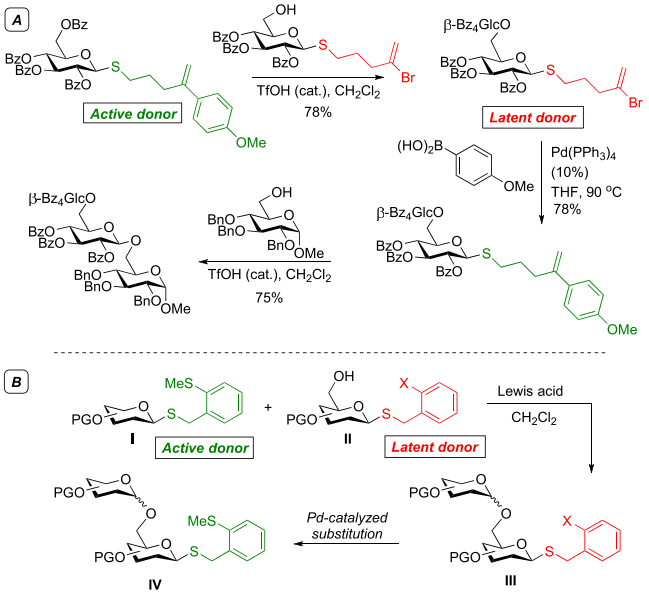
**Scheme 1. (A) Recent Example of a Latent-Active Glycosylation (See Ref 28); (B) This Study Using a Pd-Catalyzed C−S Cross-Coupling for Activation of the Latent Donor**



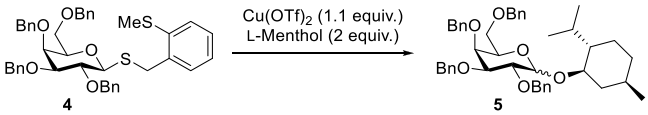

possibility of obtaining such donors from analogous thioglycosides bearing a halide in the *ortho*-position (as in **II** and **III**, Scheme 1B) through a palladium-catalyzed C−S cross-coupling. Additionally, providing conditions would exist where the *o*-SMe bearing glycosyl donor **I** could be activated without affecting the *o*-halide functionalized donor **II**, a potentially useful latent−active approach would be established. In such a way, with reference to Scheme 1B, the donor functionality of the product **III** could subsequent to the first glycosylation be converted into the active *o*-SMe functionality in compound **IV**, and this donor would be set for another glycosylation step.

Initially, to investigate the reactivity of thioglycosides of the type **I**, various glycosyl donors were synthesized by standard methods using *ortho*-(methylthio)benzyl mercaptan and the desired acetylated carbohydrate substrates (see Supporting Information). The reactivity of a per-*O*-benzylated glucosyl donor (**1**) of this type was tested against a per-*O*-benzylated benzyl thioglucoside (**2**) in a competition experiment using NIS/TfOH activation and L-menthol as the acceptor (Conditions A, Scheme 2 and Supporting Information).

Opposite to our expectations, the *ortho*-substituted donor **1** was less reactive (ca. 30%) than the nonsubstituted thiobenzyl donor **2**, possibly due to increased hindrance around the anomeric sulfur atom. We therefore went on to evaluate various metal triflates as potential promoters hoping the presence of two chelating sulfur atoms coordinated by the right metal would facilitate leaving group departure (Conditions B, Scheme 2). We investigated triflates of Cu(II), Fe(III), Bi(III), In(III), Mg(II), Zn(II), Ni(II), Al(III), Sc(III), Ag(I), and Yb(III) and found only Cu(II) and Fe(III) to be suitable for activation in $CH_2Cl_2$ with L-menthol as the acceptor. $Bi(OTf)_3$ also caused some degree of activation of **1**, while the other tested metal triflates only provided less than 10% conversion of the donor or no activation at all. Cu(II) and Fe(III) triflates elicited comparable activity, but since $Fe(OTf)_3$ is highly hygroscopic we chose to proceed with $Cu(OTf)_2$. Only one previous example of $Cu(OTf)_2$ acting as the single activator of thioglycosides (SEt) has previously been reported.[30]

Although $Cu(OTf)_2$ provided a large degree of donor activation of **4** with L-menthol as the acceptor (Table 1),

**Table 1. Results for $Cu(OTf)_2$-Promoted Glycosylation with Donor 4 with Isolated Yields**

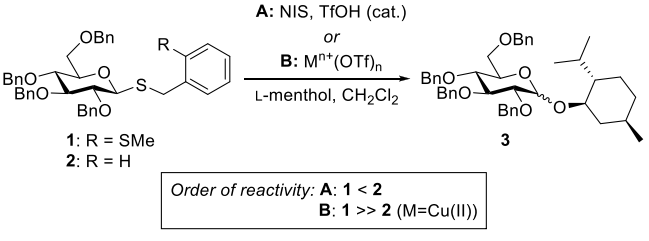



| Entry | Solvent | Additive | Conditions | Yield ($\alpha/\beta$) |
|---|---|---|---|---|
| 1 | MeCN | – | rt, 15 min | 75% (1.7:1) |
| 2 | MeCN | – | 0 °C, 80 min | 80% (1.4:1) |
| 3 | MeCN | TTBP, MS | rt, 7 min | 94% (1:2.3) |
| 4 | $CH_2Cl_2$/MeCN 2:1 | TTBP, MS | rt, 8 min | 92% (1:2.0) |
| 5 | $CH_2Cl_2$/MeCN 4:1 | TTBP, MS | rt, 10 min | 94% (1:1.4) |

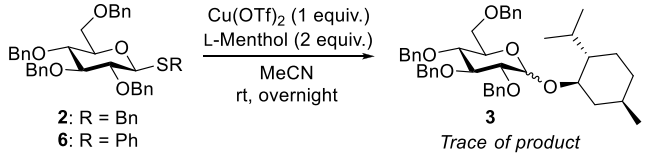
conversion was never complete in $CH_2Cl_2$. Switching to MeCN, which is known to dissolve $Cu(OTf)_2$, resulted in full conversion in only minutes at ambient temperature and formation of 75% of the L-menthyl glycoside **5** (entry 1, Table 1). The yield was improved to 80% by performing the reaction at 0 °C (entry 2), while addition of the hindered base tri-*tert*-butylpyrimidine (TTBP)[31] and molecular sieves (MS) further increased the yield to 94% in just minutes at ambient temperature (entry 3). Mixtures of $CH_2Cl_2$ and MeCN also provided glycosidic product in high yields with a slightly altered anomeric ratio (entries 4 and 5). Despite these promising results in terms of yield and reaction rate, activation was found to require a stoichiometric amount of Lewis acid.

$Cu(OTf)_2$ was found to activate neither benzyl or phenyl thioglycosides **2** and **6** (Scheme 3) in MeCN at ambient temperature with L-menthol as the acceptor on the same time scale as in Table 1. Only a trace of glycosidic product was observed when the reactions was left overnight, suggesting the importance of a metal chelating effect of the two sulfur atoms in the *ortho*-substituted donor, activating the algycon and making this donor a privileged substrate under these activation

**Scheme 2. General Scheme for Activation of *Ortho*-Substituted Benzyl Thioglycosides and Benzyl Thioglycosides**




**Scheme 3. Sluggish Activation of SBn and SPh Donors with $Cu(OTf)_2$**



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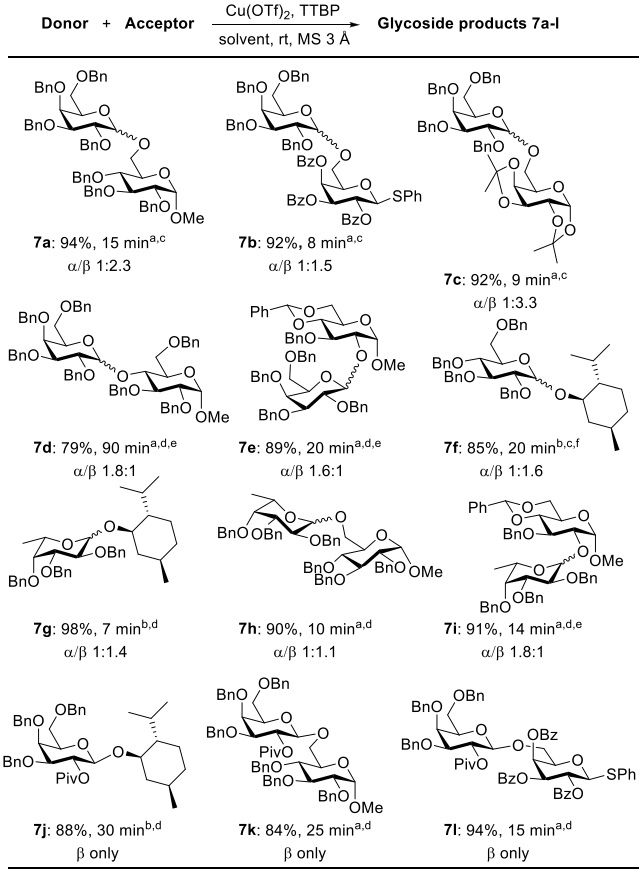
conditions. Interestingly, the analogous *o*-SMe phenyl functionalized donor possessing a $CH_2$-group less than **1** showed a different activation profile where $Bi(OTf)_3$ was found to be a far more active promoter than $Cu(OTf)_2$ (data not shown). This fact underscores the importance of matching the metal ion size and S−S distance.

Post glycosylation with donor **1**, the aglycon could be isolated as the corresponding disulfide. It has, however, not been possible to determine whether the formation of disulfide occurs during glycosylation or following the addition of triethylamine during the workup procedure.

Turning to more relevant carbohydrate-based alcohols in the context of oligosaccharide synthesis established that these more demanding acceptors also lead to excellent glycosylation yields in the time scale of minutes (Scheme 4). The D-galactosyl donor **4** provided good yields with primary alcohol acceptors (yielding glycosides **7a**, **7b**, and **7c**), but also with more hindered secondary acceptors (yielding glycosides **7d** and **7e**). The highest yields of the latter two were, however, obtained at 0 °C. D-Glucosyl, L-fucosyl, and 2-*O*-Piv-protected D-galactosyl donors also provided high yields with L-menthol as the acceptor (**7f**, **7g**, and **7j**), and glycosylations with the L-fucosyl and 2-*O*-Piv-protected D-galactosyl donors were achieved with carbohydrate-based glycosyl acceptors in high yields (**7h**, **7i**, **7k**, and **7l**). Noticeably, the results in Scheme 4 demonstrate the compatibility of the $Cu(OTf)_2$/TTBP promoter system with various protecting groups such as esters (**7b** and **7l**) and acid-labile acetals (**7c**, **7e**, and **7i**). Acetylated donors, however, proved too unstable for $Cu(OTf)_2$ activation, which is in accordance with previous results by us[29] and Yu and co-workers[32] using similar promoter systems.

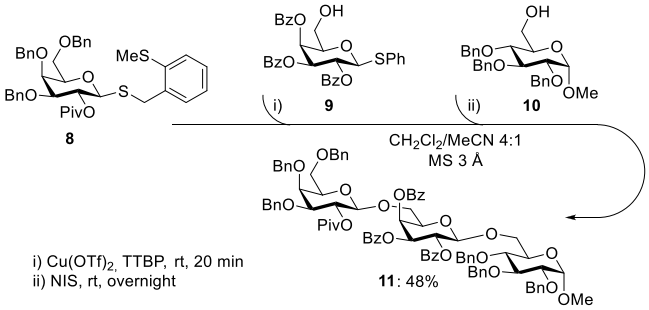
**Scheme 4. Glycosylations with Carbohydrate-Based Acceptors**




[a]Donor/acceptor 1:0.8. [b]Donor/acceptor 1:2. [c]MeCN. [d]$CH_2Cl_2$/MeCN 4:1. [e]0 °C. [f]No TTBP.

In line with the results from Scheme 3, *S*-phenyl functionalized thioglycosides could furthermore be used as glycosyl acceptors without any activation of these observed (**7b** and **7l**). It was therefore investigated whether the observed chemoselectivity could be exploited to obtain a trisaccharide in a one-pot fashion (Scheme 5). After full conversion of **8** was observed in the first step, the acceptor **10** and NIS were added to the mixture at rt. There was no need for the addition of any additional acid for activation of NIS due to the Lewis acid $Cu(OTf)_2$ already present.[33] The trisaccharide was obtained in a yield of 48% based on the amount of **8**, and an even higher yield would expectedly have been achieved, had it not been for the troublesome purification of **11**.

**Scheme 5. Synthesis of Trisaccharide 11 in a One-Pot Fashion**




The key conversion from a latent to the active *o*-SMe functionalized glycosyl donor was subsequently explored through a Pd-catalyzed substitution of an *ortho*-halide substituent by SMe. Since an *S*-benzyl glycosyl donor has previously proven unreactive toward $Cu(OTf)_2$ activation, we expected the *ortho*-halide functionalized donor to be as well given the bulk and electron-withdrawing nature of the halide.

Literature reveals that bidentate ligands generally are the ligands of choice for Pd-catalyzed C−S bond formations[34−37] and such ligands were therefore explored. After initial investigations, it was found that *ortho*-bromo analogues of the active donor and reaction conditions by Okauchi and co-workers using $Pd_2(dba)_3$ as catalyst, DPPF as ligand, and DIPEA as base in refluxing toluene with NaSMe as the source of sulfur would allow the desired transformation (Scheme 6).[36]

Satisfyingly, the conditions involving both cheap ligand and catalyst as well as an easily handled protocol without metal/ligand premixing resulted in the desired transformations in almost quantitative yields. Furthermore, donors carrying various protecting groups including ethers, acetals, and silyl ethers as well as free alcohols were evaluated as substrates. Other procedures tested included, e.g., the conditions by Hartwig and co-workers using the Josiphos ligand CyPF-*t*Bu and $Pd(OAc)_2$ as catalyst together with NaO*t*Bu as base and octanethiol as the source of sulfur.[35] Even though this procedure has proved successful on simpler chloroarenes, no reaction was observed on an *ortho*-chloro analogue of **12**.

In addition to the substitutions with NaSMe, we also established that the reaction could be achieved using NaS*i*Pr as the source of sulfur providing an alternative access to the analogous sulfide **13d** being a latent donor functionality with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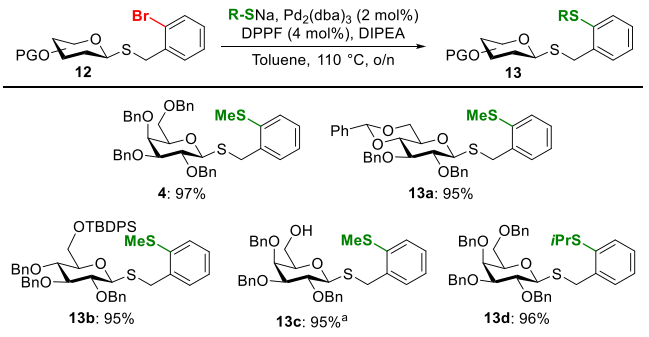
**Scheme 6. Pd-Catalyzed C−S Cross-Coupling (Yields Given Are Isolated Yields after Column Chromatography)**




[a]4 mol% $Pd_2(dba)_3$ and 8 mol% DPPF.

respect to activation by $Tf_2O$ as recently described by Wan and co-workers.[26,27] The *o*-S*i*Pr functionalized galactosyl donor **13d** was found to undergo activation at a similar rate as the analogous *o*-SMe counterpart in the presence of $Cu(OTf)_2$/TTBP. With L-menthol as the acceptor, the *o*-S*i*Pr functionalized donor provided the *O*-menthyl glycoside **5** in 96% yield under the conditions optimized for the *o*-SMe donor. This offers another option for reactivity tuning during oligosaccharide synthesis as our latent donor has the possibility of being converted into another active donor (*o*-S*i*Pr), which is however inert under the reactions conditions developed by Wan an co-workers, and can, if desired, be transformed into an active donor under their glycosylation system.[26,27]

Finally, to demonstrate our novel latent−active glycosylation strategy for oligosaccharide synthesis we aimed at the preparation of trisaccharide **18** (Scheme 7). First, L-fucosyl donor **14** was used in a glycosylation reaction with the acceptor/latent D-galactosyl donor **15** providing the disaccharide **16** in 83% yield. The two resulting anomers were completely separated by flash chromatography, and only the $\alpha$-anomer ($\alpha$-**16**) was used further. $\alpha$-**16** was then converted into the active donor **17** through the established reaction conditions from Scheme 6 in 88% yield. Noticeably, the ester group remains stable under the reaction conditions. To obtain the trisaccharide, **17** was subsequently coupled with acceptor **10**, providing trisaccharide **18** as a single anomer due to the participating 2-*O*-Piv group.

To conclude on our studies, we have shown how palladium catalyzed C−S bond formation can be used as a tool for the installation of a chelating site that allows for later chemical manipulations via chemoselective reactions. We have specifically shown that *o*-SMe functionalized benzyl thioglycosides can be activated by $Cu(OTf)_2$ and that this Lewis acid leaves thiophenyl, thiobenzyl, and *o*-Br-benzyl thioglycosides untouched. It was also demonstrated that *o*-SMe/*o*-Br benzyl thioglycosides is a novel latent−active glycosyl donor pair for obtaining oligosaccharides of biological relevance. Two trisaccharides were prepared in the course of our studies. One of these demonstrate the use of our novel protocol in latent−active glycosylation, and the other shows how our approach can be used in combination with existing methods for thioglycoside activation in a one-pot two-step fashion. We believe our present approach is a powerful alternative to already existing glycosylation methodology, and it will prove useful in the synthesis of complex oligosaccharides. Potentially, transition metal catalysis can also be used in other contexts than glycosylation chemistry for conversion of an unreactive moiety into a reactive moiety.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02090.

Synthetic experimental procedure and full characterizations including NMR spectra (PDF)

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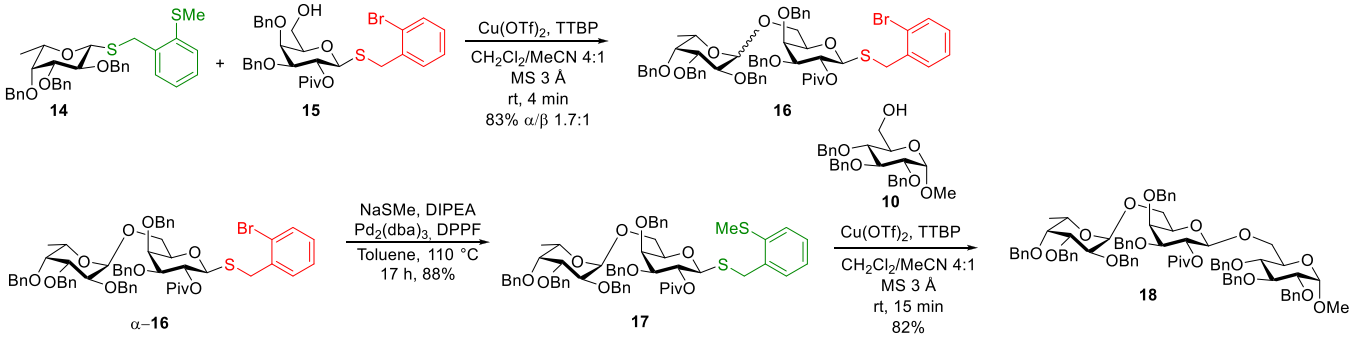
### Notes

The authors declare no competing financial interest.

**Scheme 7. Synthesis of a Trisaccharide Using the Latent−Active Glycosylation Strategy**



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## ■ ACKNOWLEDGMENTS

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