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A Novel Strategy for Oligosaccharide Synthesis via Temporarily Deactivated *S*-Thiazolyl Glycosides as Glycosyl Acceptors

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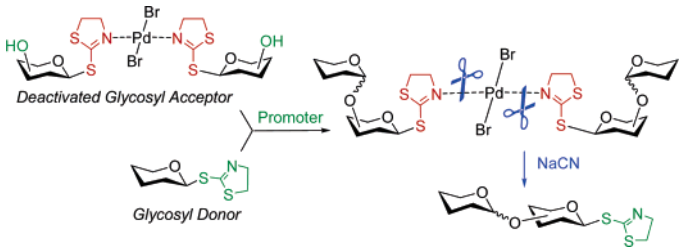
ABSTRACT



A new glycosylation strategy that allows chemoselective activation of the *S*-thiazolyl (STaz) moiety of a glycosyl donor over the temporarily deactivated glycosyl acceptor, bearing the same anomeric group, has been developed. This deactivation is achieved by engaging of the STaz moiety of the glycosyl acceptor into a stable palladium(II) complex. Therefore, obtained disaccharides are then released from the complex by simple ligand exchange.

An explosive growth of the field of glycobiology has stimulated interest in the synthesis of a large number of biologically and therapeutically important glycoconjugates and the improvement of glycosylation methods.[1−4] In recent years, convergent synthetic strategies where one type of leaving group is selectively activated over another have come to the fore.[5] Slightly differently, the armed−disarmed approach allows chemoselective activation of the armed glycosyl donor over the disarmed acceptor, both bearing the same leaving group.[6] The deactivating effect is achieved by the use of appropriate protecting groups: acyl to disarm, and benzyl to arm. Here we report a conceptually novel method for oligosaccharide synthesis that involves temporary disarming of a leaving group in the glycosyl acceptor by its external deactivation.

As a part of a program to develop new methods and strategies for convergent oligosaccharide synthesis, we became interested in glycosyl thioimidates, a class of glycosyl donors with the generic leaving group $SCR^1{=}NR^2$. We have already reported the synthesis of *S*-benzoxazolyl (SBox)[7,8] and *S*-thiazolyl (STaz)[9] glycosides and evaluated them in stereoselective glycosylations and convergent oligosaccharide synthesis. Considering the multifunctional character of the thioimidoyl moiety, and the fact that this leaving

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(2) Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173−200.
(3) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160.
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(8) Demchenko, A. V.; Kamat, M. N.; De Meo, C. *Synlett* **2003**, 1287−1290.
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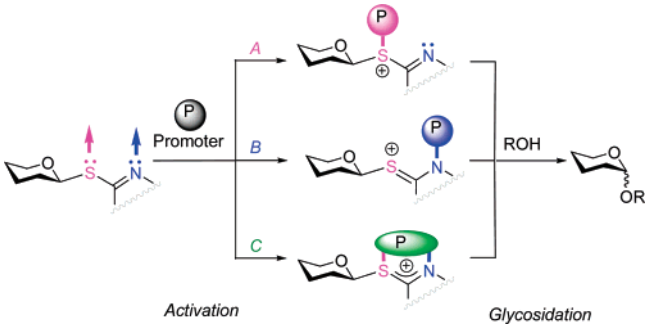
group does not depart on its own, we have developed three major activation pathways for their use in glycosylation reactions (Scheme 1).[7] In the first pathway, thiophilic

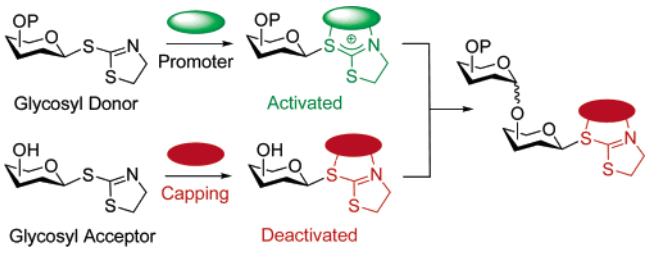
Scheme 1. Activation Pathways for Thioimidate Glycosidation



reagents (NIS/TMSOTf) serve to activate the anomeric leaving group via complexation to the sulfur atom (pathway A). In the second approach, electrophilic promoters such as MeOTf target the thioimidoyl nitrogen (pathway B). Finally, metal salt-based promoters (AgOTf or $Cu(OTf)_2$) can complex to both the sulfur and nitrogen atoms intra- or intermolecularly (pathway C) and bring about anomeric activation. Some of these promoters are already commonly used for thioglycoside activation.[10] However, it is the possibility of using metal-salt-based activation that distinguishes the thioimidates from their *S*-alkyl/aryl counterparts.

In an effort to expand the scope of the oligosaccharide synthesis in general and the STaz method in particular, we wondered whether it would be possible to temporarily nullify the reactivity of the thioimidoyl derivatives toward glycosylation by reversible blocking of one or both of the activation centers. For example, if the lone pair on the nitrogen were temporarily deactivated (capped), this would make promoter-assisted thioimidate activation via any of the pathways shown in Scheme 1 a very unlikely process. One possible way in which this could be achieved is if we were to engage the STaz moiety in a stable, nonionizing metal complex. Overall, this should allow chemoselective activation of a "free" STaz leaving group (glycosyl donor) over a deactivated (complexed, capped) STaz moiety (glycosyl acceptor); the concepts are illustrated in Scheme 2. If such an approach were successful, it might prove possible to chemoselectively glycosylate without the necessity for

Scheme 2. Outline of the Temporary Deactivation Concept

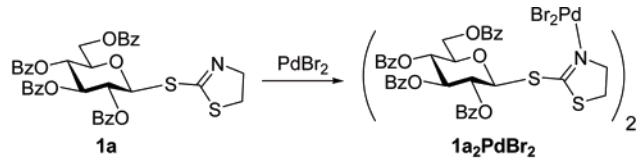


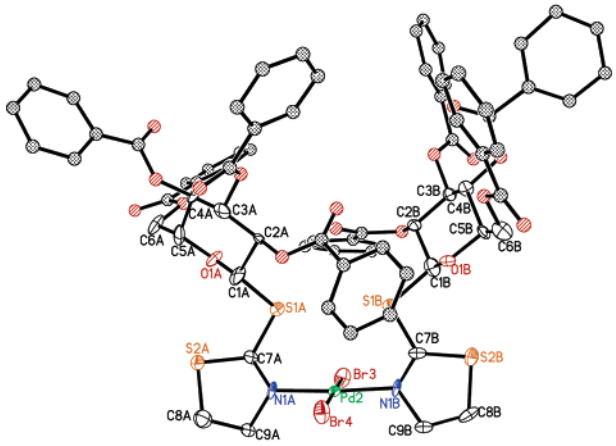
activating or deactivating the anomeric moiety through changing the electronic environment around the anomeric center. This would also provide an alternative to the previously explored armed−disarmed[6] and active−latent glycosylation strategies.[11,12]

After glycosylation, a number of synthetic scenarios can be envisaged. For example, the disaccharide could be cleaved from the complex by ligand exchange and used in a subsequent glycosylation as a glycosyl donor. Alternatively, a temporary protecting group (P, Scheme 2) could be removed and the resulting glycosyl acceptor unit used for chain elongation.

To establish whether chemically stable transition metal complexes could be formed from STaz glycosides, we chose to examine the reaction of the per-benzoylated STaz glycoside **1a**[9] with $PdBr_2$ (1−2 mol equiv) in the presence of 3 Å molecular sieves in dry $(CH_2Cl)_2$. A very stable complex **1a$_2$PdBr$_2$**, containing two sugar ligands, was formed quantitatively after 2 h at room temperature (Scheme 3). To

Scheme 3. Synthesis and X-ray Crystal Structure of a Representative Palladium(II) Complex **1a$_2$PdBr$_2$**





1a$_2$PdBr$_2$

elucidate how the metal was attached to the sugar units, the structure of **1a$_2$PdBr$_2$** was determined by X-ray crystallography. It was found that attachment occurs via the nitrogen atoms of the thiazoline rings (Pd−N (av) =2.009 (8) Å).[13] In like fashion, the partially protected STaz glycosides **1c−g**

(10) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205.
(11) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053−6056.
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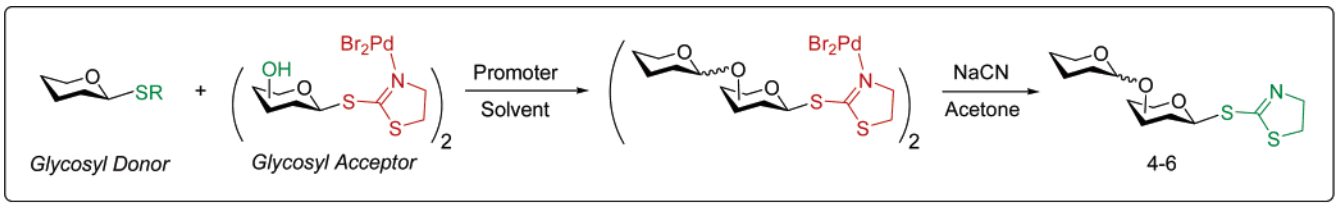
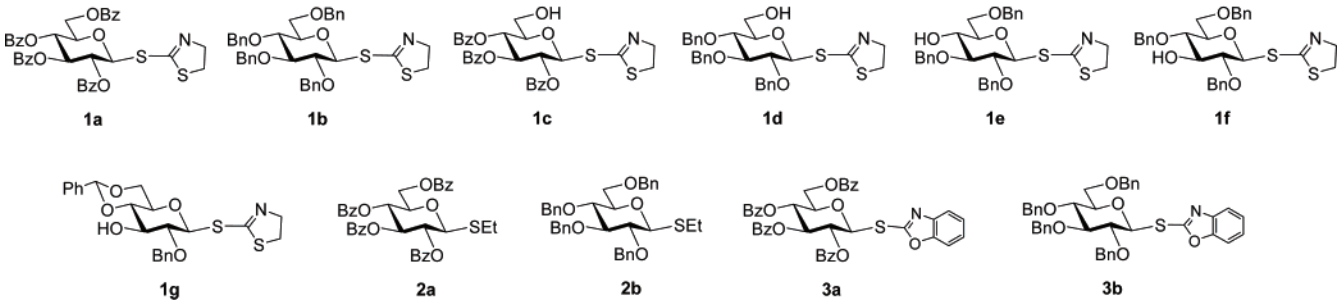
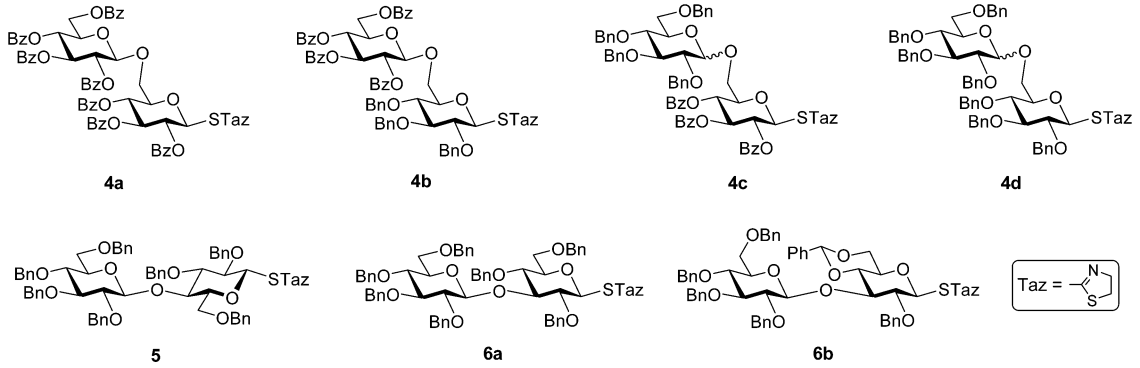
Table 1. Synthesis of the Disaccharide Derivatives **4**−**6** via a New Strategy Based on the Temporary Deactivation Concept





entry	donor	acceptor	promoter	solvent	temperature	time	product	yield, %	α/β ratio
1	**1a**	**1c$_2$PdBr$_2$**	MeOTf	DCE	−20 °C → rt	16 h	**4a**	63	β only
2	**1a**	**1d$_2$PdBr$_2$**	MeOTf	DCE	−40 °C → rt	20 h	**4b**	56	β only
3	**1b**	**1c$_2$PdBr$_2$**	Cu(OTf)$_2$	DCE	−20 °C → rt	19 h	**4c**	72	2.0/1
4	**1b**	**1d$_2$PdBr$_2$**	NIS/TfOH	DCE	−40 °C → rt	16 h	**4d**	61	1.8/1
5	**1b**	**1e$_2$PdBr$_2$**	MeOTf	DCE	−40 °C → rt	6 h	**5**	52	2.2/1
6	**1b**	**1f$_2$PdBr$_2$**	MeOTf	DCE	−40 °C → rt	20 h	**6a**	48	2.5/1
7	**2a**	**1c$_2$PdBr$_2$**	NIS/TfOH	DCE	−20 °C	2 h	**4a**	86	β only
8	**2b**	**1c$_2$PdBr$_2$**	NIS/TfOH	DCE	−20 °C	5 min	**4c**	72	1.3/1
9	**2b**	**1c$_2$PdBr$_2$**	NIS/TfOH	MeCN	−20 °C	5 min	**4c**	69	β only
10	**2b**	**1g$_2$PdBr$_2$**	NIS/TfOH	DCE	rt	20 min	**6b**	63	2.0/1
11	**3a**	**1c$_2$PdBr$_2$**	Cu(OTf)$_2$	DCE	rt	40 min	**4a**	76	β only
12	**3b**	**1c$_2$PdBr$_2$**	Cu(OTf)$_2$	DCE	rt	30 min	**4c**	78	1/3.6



were employed for the synthesis of glycosyl acceptors **1c$_2$PdBr$_2$**−**1g$_2$PdBr$_2$**. These were found to be of sufficient purity to be used in subsequent glycosylation without any adverse effects.[14]

Having synthesized these palladium(II) complexes, we performed a number of coupling experiments (Table 1). First of all, we demonstrated that either benzoylated (**1a**) or benzylated STaz glycosyl donor (**1b**) could be activated over temporarily deactivated benzoylated or benzylated 6-hydroxyl glycosyl acceptors (**1c$_2$PdBr$_2$** and **1d$_2$PdBr$_2$**, respectively). Upon glycosylation, the obtained disaccharides were released from the complex by treatment with NaCN in acetone. As a result, a range of (1→6)-linked disaccharides **4a**−**d** were isolated in moderate to good yield (entries 1−4,

(13) Single-crystal structure was solved and refined in monoclinic space group C_2. Cell parameters: a = 43.8030(8) Å, b = 14.8246(3) Å, c = 26.4865(5) Å, β = 108.874(1)°, V = 16274.6(5) Å^3, z = 8, R(F) = 0.095, wR(F^2) = 0.200 for 28628 independent reflections, 1687 parameters and 10 restraints. A Bruker SMART 1K CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) was used for data collection at 160(2) K.

(14) Palladium(II) complexes have an extended shelf life and are of sufficient stability to be purified by chromatography or crystallization.

Table 1). Our results provide encouraging support for the temporary deactivation effect.

We next set about examining whether it would be possible to activate an electronically "disarmed" (benzoylated) glycosyl donor **1a** over an otherwise "armed" (benzylated) glycosyl acceptor $\mathbf{1d_2PdBr_2}$ (entry 2).[15] In this case, the complexed, Pd-deactivated *S*-thiazolyl leaving group was found to be entirely inert. Each coupling experiment was performed in the presence of different promoters, most commonly AgOTf, MeOTf, $Cu(OTf)_2$, or NIS/TfOH. However, only those resulting in better yields are listed. Similarly, (1→4)- and (1→3)-linked disaccharides **5** and **6a** were obtained (entries 5 and 6).[16]

(15) As anticipated, the attempted coupling of **1a** with uncomplexed **1d** resulted in the formation of the 1,6-anhydro derivative, a product of the intramolecular self-condensation of **1d**. Similar precedents were previously reported; for example, see: Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V.; Makarova, Z. G.; Zhulin, V. M.; Kochetkov, N. K. *Dokl. Akad. Nauk* **1989**, *309*, 110−114.

(16) In some cases the yields were compromised due to the trans-ligation (partial donor−acceptor exchange) that occurs prior to glycosylation. Most typically, the highest ligand exchange rates were achieved with electronically activated (benzylated) acceptors in the presence of AgOTf.

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(18) Steinborn, D.; Junicke, H. *Chem. Rev.* **2000**, *100*, 4283−4317.

Clearly, our results provide solid evidence for the preferential activation of one leaving group over another without the requirement for altering the protecting group pattern. An attractive feature of this strategy is that it does not rely on protecting groups to control the leaving group ability and, thus, glycosyl donor reactivity. Since protecting groups also control the anomeric stereoselectivity of glycosylation, the new approach offers more flexibility in this respect.

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Supporting Information Available: Experimental procedures for the synthesis of **1c**−**f**, **4a**−**d**, **5**, and **6a** and their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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