Published in final edited form as:
Chem Commun (Camb). 2008 November 21; (43): 5633–5635. doi:10.1039/b810569c.

4-(Pyridin-2-yl)thiazol-2-yl thioglycosides as bidentate ligands for oligosaccharide synthesis *via* temporary deactivation†

Papapida Pornsuriyasak, **Nigam P. Rath**, and **Alexei V. Demchenko**
Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121, USA

Alexei V. Demchenko: demchenkoa@umsl.edu

Abstract

This study focusses on a new concept for oligosaccharide synthesis based on 4-(pyridin-2-yl)thiazol-2-yl thioglycosides that can either act as effective glycosyl donors or can be deactivated by stable bidentate complexation with palladium(II) bromide.

Traditional linear approaches for oligosaccharide assembly are cumbersome, and consequently the availability of complex glycostructures remains insufficient to address the challenges of modern glycosciences.[1–4] Recent improvements for oligosaccharide synthesis, *i.e.* selective activation of one leaving group over another[5–9] or chemoselective activation of building blocks wherein reactivity is dictated by the nature of protecting groups,[10–13] significantly shorten oligosaccharide assembly. Nevertheless, these expeditious approaches[14] and even high-throughput automated[15,16] or one-pot technologies[17,18] are still far from being comprehensively applicable.

We have already reported a temporary deactivation concept for oligosaccharide synthesis based on the ability of *S*-thiazolinyl (STaz) glycosides to be engaged in stable non-ionizing transition metal complexes.[19] As depicted in Scheme 1, this strategy allows chemoselective activation of the “free” STaz (or other) moiety on the glycosyl donor **B** over the deactivated (capped) STaz moiety on the glycosyl acceptor **A**. Upon glycosylation, the disaccharide **C** is released from the complex to provide “free” disaccharide **D**, which can be directly used as a glycosyl donor for subsequent transformations.

What remained unexplored is the ability to carry out the multistep synthesis—it would be advantageous if upon glycosidation, **C** could be converted into an acceptor **E** by removing a strategically placed substituent (P). The latter could then couple with the donor **B** to form the trisaccharide and consequently higher oligosaccharides upon reiteration of the deprotection–glycosylation sequence. Indeed, the possibility of achieving a desired oligosaccharide employing only one class of a leaving group, irrespective of the nature of the protective groups, would be very attractive. This approach should also allow for bidirectional[20,21] (*e.g.* **D** + **A**) and convergent[22,23] (*e.g.* **D** + **E**) couplings. Unfortunately, our attempts to apply this idea to STaz glycosides have failed due to the marginal stability of the monodentate Pd(II)STaz complex and its propensity to decomplex.

†Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of all new compounds and their ^{1}H and ^{13}C NMR spectra, as well as the structure and geometrical parameters for **6**. CCDC reference number 693543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810569c

Correspondence to: Alexei V. Demchenko, demchenkoa@umsl.edu.

To address this challenge, we investigated a series of novel anomeric moieties that would be capable of forming more stable bidentate complexes, as depicted in Fig. 1. Herein we report our preliminary investigation of this concept, focusing primarily on 4-(pyridin-2-yl)thiazol-2-yl (PT) thioglycosides as glycosyl donors and as complexed glycosyl acceptors.

We found that bromide **1** serves as a suitable precursor for the synthesis of SPT glycosides upon reaction with readily accessible thiolate **2** (Scheme 2). The requisite SPT glycoside **3**, obtained in 99% yield, was then converted into benzylated glycosyl donor **4**. This transformation clearly demonstrated the compatibility of the SPT moiety with strongly basic reaction conditions (MeONa or NaH). The peracetate **3** was also converted into a glycosyl acceptor *via* intermediate **5**, as shown in Scheme 2.

The complexation of **5** with $PdBr^2$ took place quantitatively and the resulting complex was sufficiently stable to detritylation conditions to afford acceptor **6** (see Fig. 2 for crystal structure). We believe that this observation alone may serve as a viable proof of the bidentate concept, since the first generation monodentate STaz ligands were found to be unstable to detritylation. The glycosyl acceptor **6** was then glycosylated with glycosyl donor **4** in the presence of silver triflate. Upon subsequent decomplexation with NaCN, the requisite disaccharide **7** was obtained in 90% yield. It should be noted that yields achieved with the STaz mediated temporary deactivation were significantly lower.[19]

To explore the scope of our concept, we investigated major aspects of the SPT methodology. First, we determined that the SPT–$PdBr^2$ complex is also stable under standard conditions for silyl group introduction/cleavage, tritylation, acylation/deacylation, and acetal formation, reductive opening and cleavage.[24] Second, we determined the applicability of this concept to other classes of glycosyl donors including trichloroacetimidates, thioimidates, and alkyl/aryl thioglycosides.[25] Third, both primary and secondary glycosyl acceptors bearing the complexed SPT moiety were obtained and tested accordingly (see ESI[†]).

The versatility of the approach developed was illustrated by the synthesis of medicinally relevant oligosaccharides of *Streptococcus pneumoniae* serotype 14 (SPn14), the most prevalent cause of invasive pneumococcal disease worldwide.[26] The bacterial isolate of SPn14 polysaccharide is poorly immunogenic due to the abundance of similar sequences in mammalian tissues.[27] This complicates its use as vaccine, and as a result, scientists throughout the world have already turned their attention to the chemical synthesis of SPn14 oligosaccharides and derivatives thereof.[28–31] The branched tetrasaccharide repeating unit of SPn14 consists of lactose linked to the C-6 of lactosamine.

To perform this synthesis, we obtained the key building blocks **8**,[32] **9**, and **11** (Scheme 3). The synthesis of **9** was performed starting from known triacetyl-*N*-phthalimido bromide,[33] whereas lactose donor **11** was obtained from the corresponding ethyl thioglycoside.[31] The STaz donor **8** was then coupled with the complexed acceptor **9** in the presence of AgOTf followed by desilylation with TBAF to allow the disaccharide acceptor **10**. The latter was then coupled with the lactose donor **11** to afford the SPn14 tetrasaccharide repeat unit **12**.

For the subsequent convergent elongation, one portion of tetrasaccharide **12** was treated with NaCN to afford glycosyl donor **13**, whereas another portion of **12** was treated with 10% TFA to afford glycosyl acceptor **14**. The coupling of **13** and **14** followed by decomplexation under the standard reaction conditions afforded octasaccharide **15**.

[†]Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of all new compounds and their ^1H and ^{13}C NMR spectra, as well as the structure and geometrical parameters for **6**. CCDC reference number 693543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810569c

In conclusion, we have developed a new approach to expeditious oligosaccharide assembly. This method complements the advantageous features that made effective strategies such as orthogonal, armed–disarmed, bidirectional, and convergent, very attractive. In addition, as illustrated by the synthesis of oligosaccharide **15**, the SPT-mediated approach allows for the flexible operation (and the interchange) of the different strategies upon demand. Thus, selective activation is executed for the synthesis of **10** and **12**, whereas fundamentals of chemoselective, convergent, and bi-directional strategies are executed during the transformation of **12** into **15**. It is to be expected that the efficient synthesis of pneumococcal oligosaccharide **15** reported herein will significantly contribute to the international scientific effort dealing with the synthesis of fully synthetic vaccines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank NIGMS (GM077170) for financial support of this work and NSF for grants to purchase equipment (CHE-9974801, CHE-9708640, CHE-9309690, CHE-0420497). Dr R. E. K. Winter and Mr J. Kramer (UM—St. Louis) are thanked for HRMS determinations.

Notes and references

1. Seeberger PH, Werz DB. Nature. 2007; 446:1046–1051. [PubMed: 17460666]
2. Galonic DP, Gin DY. Nature. 2007; 446:1000–1007. [PubMed: 17460660]
3. Prescher JA, Bertozzi CR. Nat Chem Biol. 2005; 1:13–21. [PubMed: 16407987]
4. Dube DH, Bertozzi CR. Nat Rev Mol Cell Biol. 2005; 4:477–488.
5. Nicolaou KC, Dolle RE, Papahatjis DP, Randall JL. J Am Chem Soc. 1984; 106:4189–4192.
6. Roy R, Andersson FO, Letellier M. Tetrahedron Lett. 1992; 33:6053–6056.
7. Kanie O, Ito Y, Ogawa T. J Am Chem Soc. 1994; 116:12073–12074.
8. Deshpande PP, Kim HM, Zatorski A, Park TK, Ragupathi G, Livingston PO, Live D, Danishefsky SJ. J Am Chem Soc. 1998; 120:1600–1614.
9. Demchenko AV, Pornsuriyasak P, De Meo C, Malysheva NN. Angew Chem, Int Ed. 2004; 43:3069–3072.
10. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B. J Am Chem Soc. 1988; 110:5583–5584.
11. Douglas NL, Ley SV, Lucking U, Warriner SL. J Chem Soc, Perkin Trans 1. 1998:51–65.
12. Zhang Z, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH. J Am Chem Soc. 1999; 121:734–753.
13. Smoot JT, Pornsuriyasak P, Demchenko AV. Angew Chem, Int Ed. 2005; 44:7123–7126.
14. Demchenko AV. Lett Org Chem. 2005; 2:580–589.
15. Seeberger PH, Werz DB. Nat Rev Mol Cell Biol. 2005; 4:751–763.
16. Seeberger PH. Chem Soc Rev. 2008; 37:19–28. [PubMed: 18197330]
17. Wang Y, Ye XS, Zhang LH. Org Biomol Chem. 2007; 5:2189–2200. [PubMed: 17609746]
18. Wang CC, Lee JC, Luo SY, Kulkarni SS, Huang YW, Lee CC, Chang KL, Hung SC. Nature. 2007; 446:896–899. [PubMed: 17443183]
19. Pornsuriyasak P, Gangadharmath UB, Rath NP, Demchenko AV. Org Lett. 2004; 6:4515–4518. [PubMed: 15548064]
20. Zhu T, Boons GJ. Angew Chem, Int Ed. 1998; 37:1898–1900.
21. Zhu T, Boons GJ. Angew Chem, Int Ed. 1999; 38:3495–3497.
22. Paulsen H. Angew Chem, Int Ed Engl. 1982; 21:155–173.
23. Ogawa T, Yamamoto H, Nukada T, Kitajima T, Sugimoto M. Pure Appl Chem. 1984; 56:779–795.

24. Wuts, PGM.; Greene, TW. Greene's Protective Groups in Organic Synthesis. 4. Wiley-Interscience; Hoboken, New Jersey: 2007.
25. Demchenko, AV., editor. Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance. Wiley-VCH; Weinheim: 2008.
26. Babl FE, Pelton SI, Theodore S, Klein JO. Clin Infect Dis. 2001; 32:1155–1161. [PubMed: 11283804]
27. Schneerson R, Levi L, Robbins JB, Bryla DM, Schiffman G, Lagergard T. Infect Immun. 1992; 60:3528–3532. [PubMed: 1500160]
28. Kochetkov NK, Nifant'ev NE, Backinowsky LV. Tetrahedron. 1987; 43:3109–3121.
29. Michalik D, Vliegenthart JFG, Kamerling JP. J Chem Soc, Perkin Trans 1. 2002; 17:1973–1981.
30. Joosten JAF, Kamerling JP, Vliegenthart JFG. Carbohydr Res. 2003; 338:2611–2627. [PubMed: 14670721]
31. Sundgren A, Lahmann M, Oscarson S. J Carbohydr Chem. 2005; 24:379–391.
32. Pornsuriyasak P, Demchenko AV. Chem Eur J. 2006; 12:6630–6646.
33. Kochetkov NK, Byramova NE, Tsvetkov YE, Backinowsky LV. Tetrahedron. 1985; 41:3363–3375.

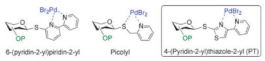


Fig. 1.
Anomeric thiomoieties for bidentate ligation.

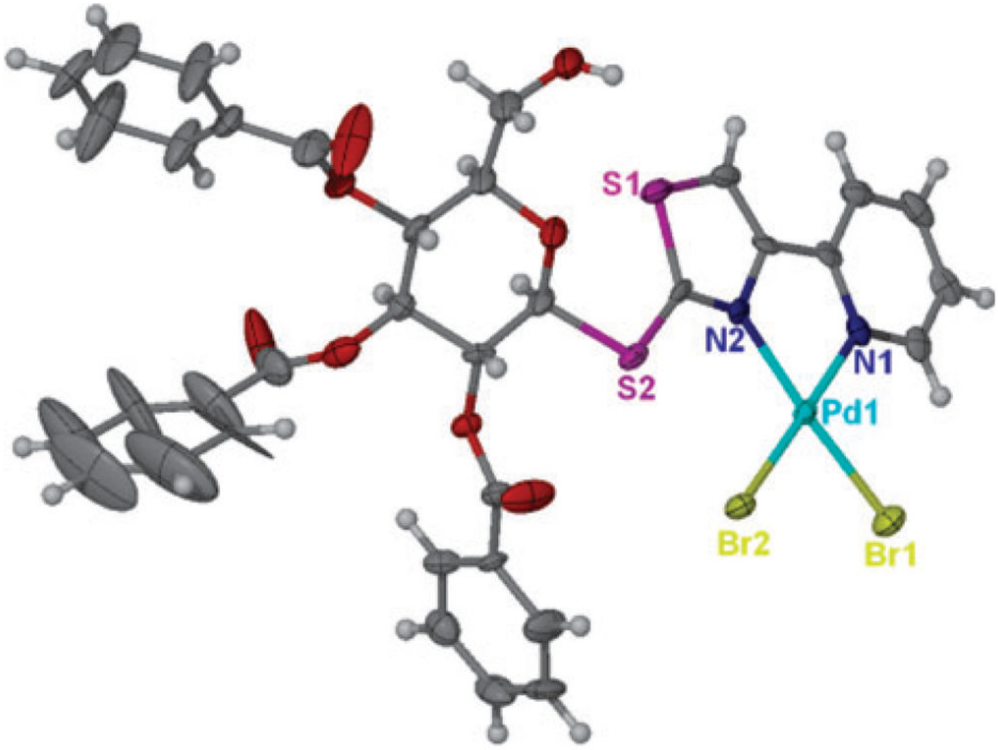
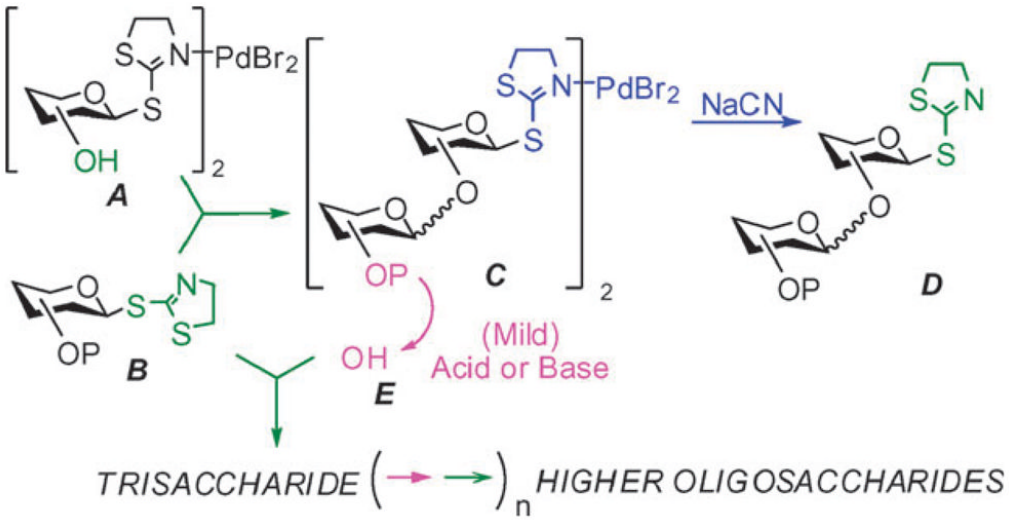
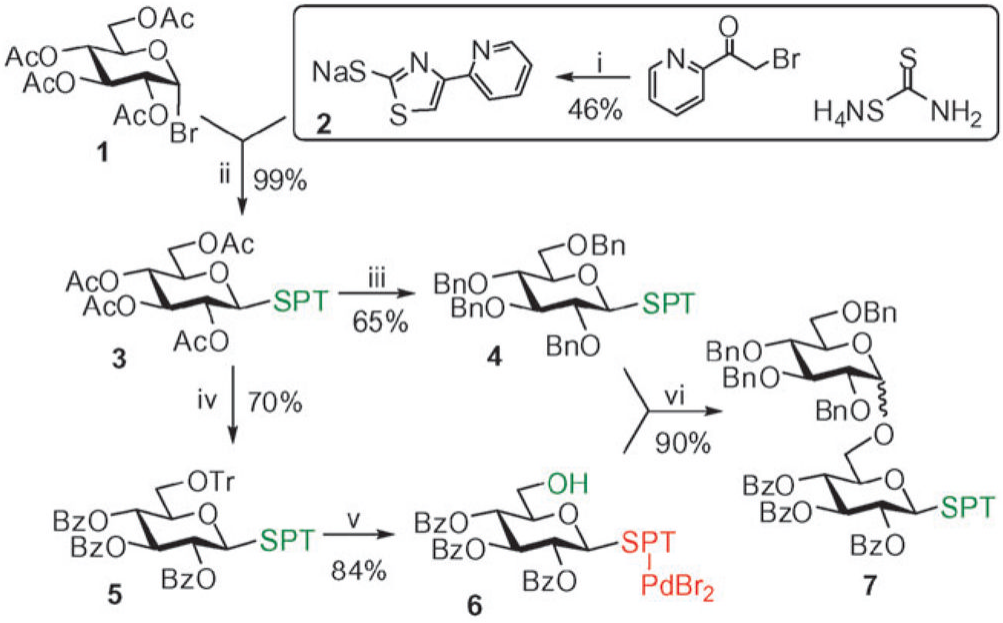


Fig. 2.

X-Ray crystal structure of the acceptor complex **6**. Projection view of the molecule with 50% thermal ellipsoids—the disordered component and solvent have been omitted for clarity. Selected crystallographic parameters for **6**: Empirical formula $C_{38}H_{36}Br_2N_2O_{10}PdS_2$; formula weight 1011.03; monoclinic; space group *C*2, *Z* = 4. Unit cell dimensions: *a* = 26.134(2), *b* = 6.6651(5), *c* = 26.550(3) Å, β = 118.580(4)°, volume 4061.1(7) $Å^3$; number of reflections collected 41 064; independent reflections 7012 [*R*(int) = 0.064]; final *R* indices: *R*1 [*I* 4 2σ(*I*)] = 0.0431, *wR*2 (all data) = 0.0951. CCDC # 693543.

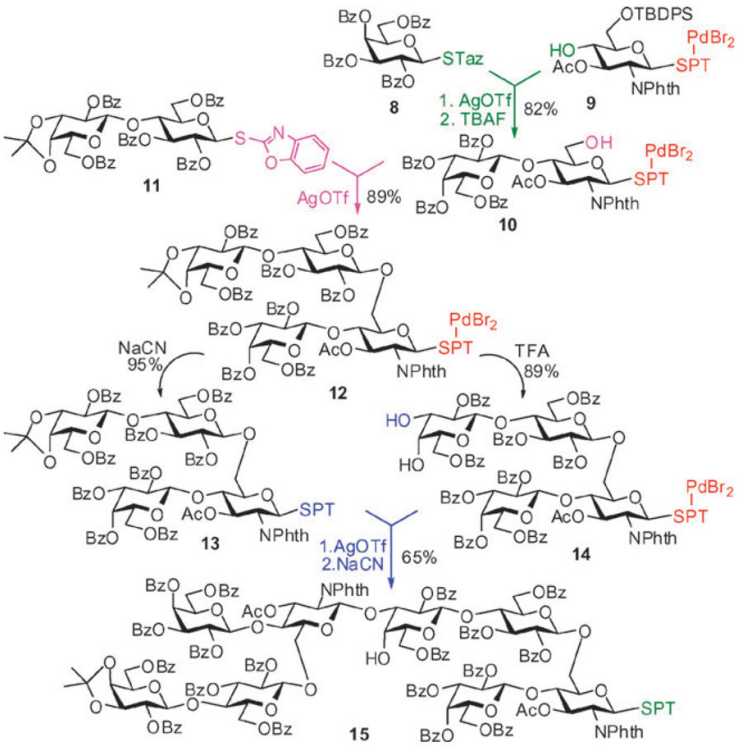


Scheme 1.
Temporary deactivation concept.



Scheme 2.

Synthesis/evaluation of SPT donor **4** and acceptor **6**. *Reagents and conditions*: (i) Na/MeOH; (ii) MeCN; (iii) 1. MeONa/MeOH, 2. BnBr/NaH, DMF; (iv) 1. NaOMe/MeOH, 2. TrCl, C_5H_5N, 3. BzCl; (v) 1. $PdBr_2$, 3 Å MS, 1,2-DCE, 2. 10% TFA/wet DCM, 0 °C; (vi) 1. AgOTf, 3 Å MS, DCM, 2. NaCN, acetone.



Scheme 3.
Synthesis of pneumococcal oligosaccharides.