ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

Gold-Catalyzed Synthesis of 2-Deoxy Glycosides Using *S*-But-3-ynyl Thioglycoside Donors

Surya Adhikari, Kedar N. Baryal, Danyang Zhu, Xiaohua Li, and Jianglong Zhu*

Department of Chemistry and School of Green Chemistry and Engineering, The University of Toledo, 2801 West Bancroft Street, Toledo, Ohio 43606, United States

Supporting Information

ABSTRACT: A mild and atom-economic gold(I)-catalyzed glycosylation for stereoselective synthesis of 2-deoxy α-glycosides using bench-stable 2-deoxy *S*-But-3-ynyl thioglycoside donors has been described. Under optimal conditions, 2-deoxy and 2,6-dideoxy thioglycoside donors were able to react with a variety of primary, secondary, and tertiary alcohol acceptors to afford α-selective glycosides in good to excellent yields.

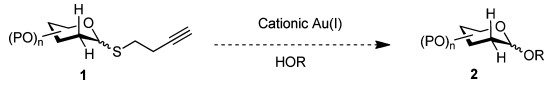
KEYWORDS: *gold, homogeneous catalysis, alkyne, glycosylation, 2-deoxy glycosides*

2-Deoxy sugars exist in a wide range of bioactive natural molecules and have been found to play a critical role in their biological activities.[1−3] Consequently, a great deal of studies for the synthesis of 2-deoxy glycosides have been reported over recent decades.[4−6] Nevertheless, stereoselective construction of a 2-deoxy glycosidic linkage remains challenging because of the absence of a directing group at C-2, despite the availability of numerous glycosylation protocols.[7] A most common strategy for stereoselective preparation of 2-deoxy sugars involves the installation of a directing group at C-2, followed by its removal after glycosylation.[4−6,8−19] In addition, other methods have been developed for stereoselective synthesis of 2-deoxy glycosides using glycosyl phosphites,[20,21] glycosyl halides,[22,23] glycosyl imidates,[24] (2′-carboxy)benzyl-4,6-*O*-benzylidene-2-deoxyglucoside,[25] 3,4-*O*-carbonate-protected thioglycosides,[26] dehydrative glycosylation of lactol,[27] and alkoxy-substituted anomeric radical,[28,29] as well as anomeric O-alkylation.[30]

Recently, transition-metal catalysis has been successfully applied to the stereoselective synthesis of *O*-glycosides including 2-deoxy sugars.[31,32] In general, use of catalytic amounts of transition-metal complex as promoter provided a "green", mild, and orthogonal alternative approach to the traditional glycosylation. In some cases, anomeric selectivity can be controlled by careful selection of the ligand coordinating to the transition metal rather than substrate control or directed by the coordinating ability of the transition metal to the heteroatoms (e.g., oxygen and nitrogen) of glycosyl donors and acceptors. For instance, O'Doherty reported stereoselective synthesis of 2-deoxy sugars using palladium-catalyzed O-glycosylations of 6-*tert*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones followed by functionalization.[33] In 2004, Toste disclosed a rhenium(V)-catalyzed selective formation of 2-deoxy α-glycosides from "armed" glycals.[34] Later, in 2009, Nguyen reported a cationic palladium(II)-catalyzed synthesis of 2-deoxy glycoside using 2-deoxy glycosyl trichloroacetimidate donor.[35] Most recently, Yu developed a gold(I)-catalyzed synthesis of 2-deoxy glycosides using 2-deoxy *ortho*-alkynylbenzoate donors.[36,37]

Given the aforementioned merits, our group has also been interested in developing mild and atom-economic transition-metal-catalyzed O-glycosylations for synthesis of 2-deoxy glycosides using readily available and bench-stable glycosyl donors. Along with this direction, we became enamored of the O-glycosylations via homogeneous cationic gold(I)-catalyzed selective activation of the alkyne functionality reported by Yu group,[36−38] but with an aim of development of 2-deoxy glycosyl donors bearing a simple alkyne-containing leaving group.[39,40] On the basis of the observation from Yu and co-workers,[36,37] we speculated that 2-deoxy *S*-but-3-ynyl thioglycosides (cf. **1**, Scheme 1) bearing a more nucleophilic sulfur[38,41,42] atom may

Scheme 1. Au(I)-Catalyzed Synthesis of 2-Deoxy Glycosides Using *S*-But-3-ynyl Thioglycosides

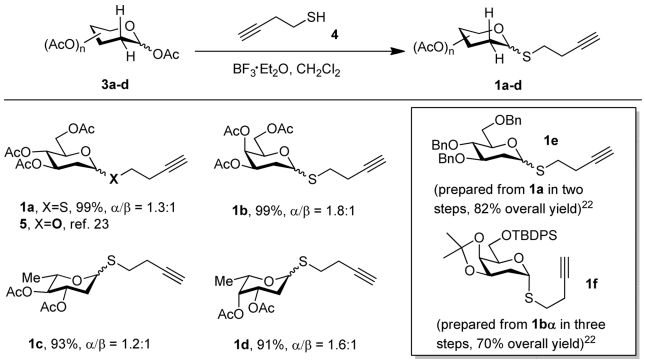


likely attack the activated alkyne for anomeric ionization to facilitate the subsequent glycosylation. In addition, it is well-known that thioglycosides[7] are stable and survive in a variety of transformations, including protecting group manipulations.

Peracetylated 2-deoxy *S*-but-3-ynyl thioglycosides (**1a−d**) can be conveniently prepared as a mixture of anomers in one step from readily available 2-deoxy glycosyl acetates (**3a−d**) and 3-butyn-1-thiol[43] (**4**) in the presence of boron trifluoride diethyl etherate under standard conditions (Table 1).[44] In addition, **1a** was converted to the perbenzylated donor **1e** in

Received: October 13, 2012
Revised: November 26, 2012
Published: November 28, 2012

Table 1. Synthesis of 2-Deoxy- *S*-But-3-ynyl Thioglycosides[a]

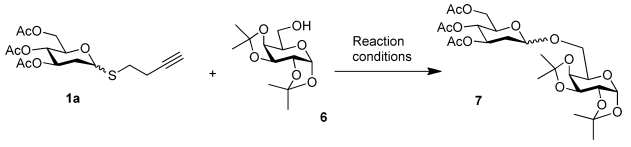


[a]General conditions: peracetate (1.0 equiv), 3-butyn-1-thiol (2.0 equiv), $BF_3{\cdot}Et_2O$ (2.0 equiv), CH_2Cl_2, 0 °C to RT, 30 min.

two steps (82% overall yield), and **1b** was converted to donor **1f** in three steps (70% overall yield).[44] We also prepared an analogous 2-deoxy but-3-ynyl glucoside donor **5**[45] for comparing its reactivity with **1a** toward gold(I) catalysis.

The reaction between 2-deoxy *S*-but-3-ynyl D-thioglucoside, **1a**, and diacetone D-galactose, **6**, was first studied under gold(I) catalysis (Table 2). Initially, it was found that neither Ph_3PAuCl nor $Ph_3PAuNTf_2$ was effective catalyst for this type of O-glycosylation (entries 1−2). Use of 2.5 mol % cationic gold(I) complex $Ph_3PAuOTf$, prepared from Ph_3PAuCl and AgOTf, was able to catalyze this glycosylation and gave 12% conversion in 6 h (entry 3). Variation of phosphine ligand from PPh_3 to $(4\text{-}CF_3{-}Ph)_3P$[46] in the cationic gold(I) complex slightly improved the conversion to 18% (entry 4). Addition of 5 mol % triflic acid in this reaction increased the yield to 47% conversion (entry 5), probably because of facilitation of protodeauration and regeneration of the cationic gold(I) catalyst. Increasing the catalyst loading to 5 mol % led to 95% conversion and 92% isolated yield with 3/1 α/β selectivity (entry 6). This anomeric selectivity was not totally unexpected, provided that there is no participating group present at C-2. It was further found that use of excess AgOTf was able to promote this reaction to completion in 30 min with 99% isolated yield of 2-deoxy disaccharide **7** (entry 7), probably as a result of the silver effect in gold catalysis.[47] It is also possible that excess silver triflate may partially hydrolyze to triflic acid, which facilitates protodeauration and regeneration of the cationic gold(I) catalyst. We also investigated the reaction using pure **1a**α and **1a**β separately and found that they gave comparable experimental outcomes, although **1a**α was found to be a little more reactive than its β counterpart.[48] Therefore, a mixture of **1**α and **1**β was subsequently employed in this type of O-glycosylation reactions.

Table 2. Optimization of Gold(I)-Catalyzed O-Glycosylation[a]



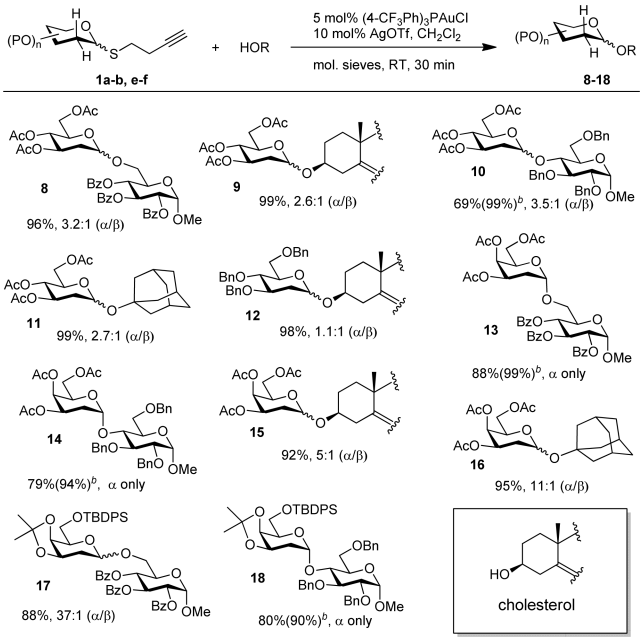
entry	reaction conditions	yield[b] (α/β)[c]
1	2.5 mol % Ph_3PAuCl	<1%
2	2.5 mol % $Ph_3PAuNTf_2$	<1%
3	2.5 mol % Ph_3PAuCl, 2.5 mol % AgOTf	12% conv
4	2.5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 2.5 mol % AgOTf	18% conv
5[d]	2.5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 2.5 mol % AgOTf	47% conv
6[e]	5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 5 mol % AgOTf	92% (3:1)
7[f]	5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 10 mol % AgOTf	99% (3:1)
8[g]	2.5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 10 mol % AgOTf	99% (3:1)
9	10 mol % AgOTf, RT, 48 h	no reaction
10[h]	5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, 10 mol % AgOTf	no reaction

[a]Reactions were performed using 0.1 mmol of **6**, 0.12 mmol of **1a** (1.2 equiv), gold and/or silver catalyst in 1 mL of anhydrous CH_2Cl_2 in the presence of 4 Å molecular sieves at room temperature for 6 h unless otherwise noted. [b]Isolated yield. [c]α/β ratio was determined by ^1H NMR analysis. [d]Addition of 5 mol % triflic acid. [e]95% conversion was observed. [f]Reaction was complete in 30 min. [g]Reaction required 22 h to complete. [h]2-Deoxy-3-butynyl-D-glucoside donor **5** was used, reaction was performed at room temperature or 40 °C.

Lowering gold catalyst loading to 2.5 mol % required a much longer reaction time to achieve comparable results (entry 8). This gold(I)-catalyzed reaction seemed to be fast initially and sluggish after some time. It was not surprising to us that no reaction occurred without gold(I) catalyst (entry 9). In contrast, use of 2-deoxy-but-3-ynyl D-glucoside donor (**5**) under optimal conditions did not afford any desired product (entry 10), which was consistent with the observation by Yu and co-workers.[36] These experiments demonstrate the higher reactivity of thioglycoside, probably due to the more nucleophilic nature of the sulfur atom over oxygen.

With this optimal condition developed, we next investigated the reaction scope using 2-deoxy *S*-but-3-ynyl thioglycosides (**1a**−**b**, **e**−**f**) and a variety of alcohol acceptors. As shown in Table 3, both peracetylated and perbenzylated 2-deoxy *S*-but-3-ynyl D-thioglucosides (**1a** and **1e**) reacted with primary,

Table 3. Gold(I)-Catalyzed Synthesis of 2-Deoxy Glycosides[a]



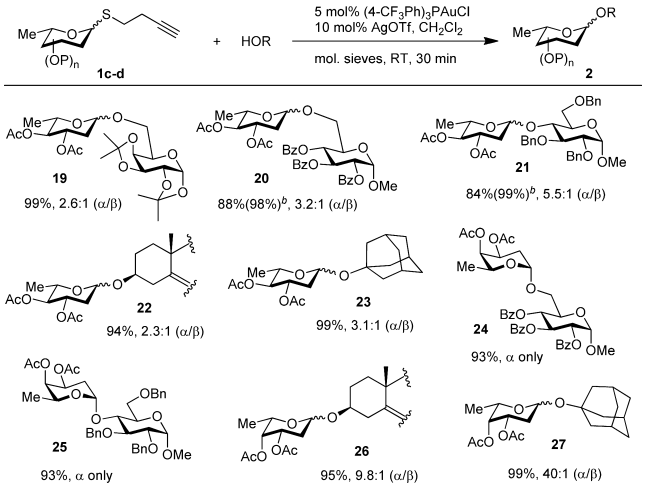
[a]General conditions: a mixture of 0.1 mmol of alcohol acceptor, 0.12 mmol of thioglycoside donor **1** (1.2 equiv), 5 mol % $(4\text{-}CF_3{-}Ph)_3PAuCl$, and 10 mol % AgOTf, and 4 Å molecular sieves in 1 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 30 min. [b]Yields based on recovered acceptors are reported in the parentheses.

dx.doi.org/10.1021/cs300670k | ACS Catal. 2013, 3, 57−60

secondary, and tertiary alcohol acceptors to afford desired disaccharides and glycoconjugates **8**–**12** in moderate α-selectivity and good to excellent yields. Use of peracetylated 2-deoxy *S*-but-3-ynyl D-thiogalactoside donor **1b** and related donor **1f** in this cationic gold(I)-catalyzed glycosylation provided the desired disaccharides and glycosconjugates **13**–**18** in good to excellent α-selectivity and yields.

We also investigated 2,6-dideoxy *S*-but-3-ynyl thioglycosides in this cationic gold(I) catalysis because of their presence in a variety of bioactive natural molecules.[1−3] As depicted in Table 4, under optimal conditions, peracetylated *S*-but-3-ynyl L-olioside **1c** was able to react with various alcohol acceptors to afford the desired disaccharides and glycoconjugates **19**–**23** in moderate to good α-selectivity and excellent yields. Similarly, peracetylated *S*-but-3-ynyl L-olioside **1d** reacted with these alcohol acceptors to provide the desired disaccharides and glycoconjugates **24**–**27** in good to excellent α-selectivity and yields.

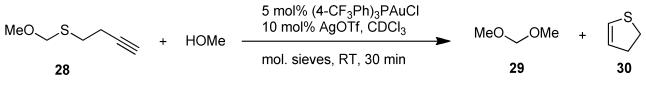
Table 4. Gold(I)-Catalyzed Synthesis of 2,6-Dideoxy Glycosides[a]



[a]General conditions: a mixture of 0.1 mmol of alcohol acceptor, 0.12 mmol of thioglycoside donor **1** (1.2 equiv), 5 mol % (4-CF_3–Ph)$_3$PAuCl, and 10 mol % AgOTf, and 4 Å molecular sieves in 1 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 30 min. [b]Yields based on recovered acceptors are reported in the parentheses.

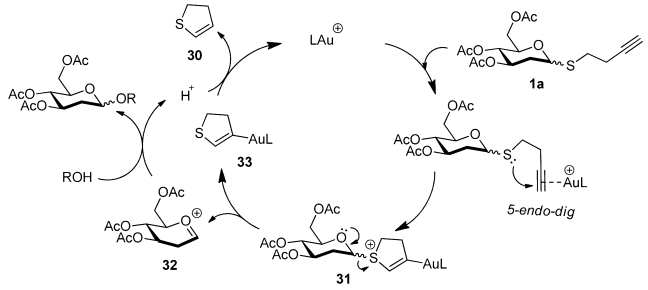
Because of the difficulty in characterizing the volatile byproduct 2,3-dihydrothiophene **30** in the glycosylation reactions, methoxymethyl 3-butynylthioether **28** was prepared[44] and subjected to our optimal cationic gold(I) catalysis in deuterated chloroform ($CDCl_3$) in the presence of a slight excess of methanol (Scheme 2). The reaction was monitored using ^{1}H NMR and found to cleanly afford the desired product dimethoxymethane **29** and byproduct 2,3-dihydrothiophene **30**. 2,3-Dihydrothiophene **30** was unambiguously characterized through analysis of the ^{1}H and ^{13}C NMR, HSQC, and mass spectra.[44]

Scheme 2. Identification of Byproduct 2,3-Dihydrothiophene



On the basis of the fact that 2,3-dihydrothiophene was identified as the byproduct,[44] a plausible mechanism is proposed for this cationic gold(I)-catalyzed glycosylation. As shown in Scheme 3, activation of the alkyne functionality of *S*-but-3-ynyl thioglycoside **1a** by cationic gold(I) catalyst followed by attack of an exo sulfur atom provides sulfonium ion **31**.[38] Subsequent cleavage of the glycosidic bond of **31** results in the formation of oxocarbenium ion **32** and 2,3-dihydrothiophene-4-yl-gold(I) complex **33**. Glycosylation of **32** with an alcohol acceptor furnishes the desired 2-deoxy glycoside and a molecule of triflic acid. Protodenauration of 2,3-dihydrothiophen-4-yl-gold(I) complex **33** leads to the formation of 2,3-dihydrothiophene **30** and regeneration of the cationic gold(I) catalyst.

Scheme 3. Proposed Mechanism



In conclusion, we have developed a mild and atom-economic cationic gold(I)-catalyzed O-glycosylation for selective synthesis of 2-deoxy and 2,6-dideoxy α-glycosides using 2-deoxy *S*-but-3-ynyl thioglycoside donors. This glycosylation is amenable to a variety of aliphatic alcohol acceptors, including carbohydrate-derived primary and secondary hydroxyl groups. Experimental results indicated that 2,3-dihydrothiophene was formed as a byproduct in this cationic gold(I)-catalyzed O-glycosylation. Studies toward stereoselective synthesis of other types of oligosaccharides via gold catalysis using *S*-but-3-ynyl thioglycoside donors are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Jianglong.Zhu@Utoledo.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Start-up funding from The University of Toledo is gratefully acknowledged. This work was presented in part at the 244th American Chemical Society National Meeting, Philadelphia, PA, United States, August 19–23, 2012, CARB-15.

■ REFERENCES

(1) De Lederkremer, R. M.; Marino, C. *Adv. Carbohydr. Chem. Biochem.* **2008**, *61*, 143–216.

(2) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84.
(3) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99−110.
(4) Borovika, A.; Nagorny, P. *J. Carbohydr. Chem.* **2012**, *31*, 255−283.
(5) Hou, D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911−1940.
(6) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385−8417.
(7) Demchenko, A. V., Ed. *Handbook of chemical glycosylation; Advances in stereoselectivity and therapeutic relevance*; Wiley-VCH: Weinheim, 2008.
(8) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, *5*, 81−84.
(9) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541−3542.
(10) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197−2208.
(11) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084−2092.
(12) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448−5451.
(13) Tavecchia, P.; Trumtel, M.; Veyrieres, A.; Sinay, P. *Tetrahedron Lett.* **1989**, *30*, 2533−2536.
(14) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75−78.
(15) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694−697.
(16) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723−2726.
(17) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466−2467.
(18) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954−958.
(19) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300−314.
(20) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523−3525.
(21) Hashimoto, S.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511−1514.
(22) (a) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577−3581.
(23) Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1989**, *30*, 6417−6420.
(24) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 2505−2507.
(25) Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 459−462.
(26) Lu, Y.-S.; Li, Q.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2008**, *10*, 3445−3448.
(27) Nogueira, J. M.; Nguyen, S. H.; Bennett, C. S. *Org. Lett.* **2011**, *13*, 2814−2817.
(28) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 945−954.
(29) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716−8717.
(30) Morris, W. J.; Shair, M. D. *Org. Lett.* **2009**, *11*, 9−12.
(31) Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2012**, *31*, 284−324.
(32) McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012**, *2*, 1563−1595.
(33) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485−2493.
(34) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510−4511.
(35) Mensah, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650−1657.
(36) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem.—Eur. J.* **2010**, *16*, 1871−1882.
(37) Yu, B.; Sun, J.; Yang, X. *Acc. Chem. Res.* **2012**, *45*, 1227−1236.
(38) During the preparation of our manuscript, Yu and co-workers reported the use of *ortho*-alkynylphenyl thioglycosides as a new type of glycosylation donors under the catalysis of Au(I) complexes. See: Yang, F.; Wang, Q.; Yu, B. *Tetrahedron Lett.* **2012**, *53*, 5231−5234.
(39) Recently, Hotha and co-workers reported Au(III)-catalyzed O-glycosylations employing "armed" substituted propargyl glycoside donors at ambient temperature. See: Kayastha, A. K.; Hotha, S. *Chem. Commun.* **2012**, *48*, 7161−7163.
(40) Previously, Hotha and co-workers disclosed Au(III)-catalyzed O-glycosylations employing "armed" propargyl glycoside donors at elevated temperature. See: Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620−9621.
(41) Previously, Kunz and co-workers reported that (*S*)-pent-4-enyl thioglycosides can be activated by a stoichiometric amount of NIS/TfOH. See: Leuck, M.; Kunz, H. *Carbohydr. Res.* **1998**, *312*, 33−44.
(42) Leuck, M.; Kunz, H. *J. Prakt. Chem.* **1997**, *339*, 322−334.
(43) Journet, M.; Rouillard, A.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **1997**, *62*, 8630−8631.
(44) See the Supporting Information for experimental details.
(45) Yadav, J. S.; Reddy, B. V. S.; Bhaskar Reddy, K.; Satyanarayana, M. *Tetrahedron Lett.* **2002**, *43*, 7009−7012.
(46) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062−12063.
(47) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.
(48) Under identical conditions, **1a**α was found to be more reactive than **1a**β; however, they afforded the 2-deoxy glycosides in comparable α/β selectivity.