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Gold(I)-Catalyzed Glycosidation of 1,2-Anhydrosugars

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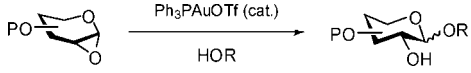

Being able to increase the yield by >20% compared to the conventional use of anhydrous zinc chloride (>1 equiv) as a promoter, $Ph_3PAuOTf$ is disclosed to be a superior catalyst for the well-established glycosylation reaction with 1,2-anhydrosugars as donors.

Driven by the need for various carbohydrates of defined composition to serve as molecular tools for significant biochemical and biological studies, numerous glycosidic coupling methods have been developed.[1] Among these protocols, glycosidation with 1,2-anhydrosugar as donors distinguishable in one characteristic in that it provides the coupling products with a free 2-hydroxyl group.[2,3] This is extremely advantageous in the synthesis of carbohydrates containing a 1 → 2 linkage, which occurs characteristically in many natural glycoconjugates, such as saponins.[4] The glycosidation reaction of 1,2-anhydrosugars and its application in the construction of complex carbohydrates have been well elaborated by Danishefsky and co-workers.[2] Multi equivalents of $ZnCl_2$ is mostly employed as a promoter in coupling with ordinary alcohol acceptors. However, compromised yields or even failure in obtaining the desired coupling products are not uncommon.[5] In some cases, coupling of the 1,2-anhydrosugars with stannyl ethers better generated in situ (under the promotion of $Zn(OTf)_2$) proceeds.[5a,b] A number of other acids (e.g., $BF_3 \cdot OEt_2$,[6a,b,f] AgOTf,[6a,b,f] $TrClO_4$,[6a] $ZnBr_2$,[6c] TfOH,[6d] SiO_2,[6e] and $LiClO_4$[5c]) have been occasionally used as the promoters in the glycosidation with 1,2-anhydrosugars, but no advantageous results are generalized. In principle, sugar 1,2-epoxides are exceedingly sensitive to the opening of the alkoxy-epoxide ring in the presence of acids; therefore, extremely mild Lewis acids would be sufficient to activate the oxirane for a nucleophilic attack of alcohols at the anomeric carbon. Stronger acids would open the oxirane ring prior to glycoside bond formation, thus leading to side reactions and the loss of the stereoselectivity in glycoside formation.[2,7] We envisioned that a Lewis acid weaker than $ZnCl_2$ and devoid of a nucleophilic counteranion to be a better promoter for the glycosidation of 1,2-anhydrosugars. Here, we report that $Ph_3PAuOTf$ has turned out to be the choice.

Tremendous recent examples have shown that cationic gold complexes are highly carbophilic Lewis acids that activate C−C multiple bonds toward nucleophilic attack.[8] Meanwhile, these complexes, particularly Au(I) complexes, possess little oxophilic character, thus displaying good functional oxo-group compatibility and low air and moisture sensitivity.[8,9] In fact, the activation of epoxides with gold complexes has occasionally been encountered.[10] This prompted us to try Au(I) complexes as catalysts for the activation of the exceedingly vulnerable sugar 1,2-epoxides for glycosidation.

Thus, the glycosidation of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**1**)[11] with cholesterol (**2a**) was first set up as a model reaction for examining the action of Au(I) catalysts (Table 1). Following the seminal procedure of Danishefsky and Halcomb,[11] coupling of the newly prepared glucose 1,2-epoxide (**1**) with cholesterol under the promotion of three equivalents of $ZnCl_2$ in THF gave the *β*-glycoside (**3a**) stereoselectively in 47% yield, which is comparable to the yields reported in the literature (52% and 42%).[11,12] Gratifyingly, 0.1 equiv of $Ph_3PAuNTf_2$[13] promoted the glycosidation to a similar extent (entry 2). In a mixed solvent of CH_2Cl_2/THF (3: 2, v/v), the reaction promoted by 0.1 equiv of $Ph_3PAuNTf_2$ was able to provide the glycoside **3a** in 78% (entry 4). $Ph_3PAuOTf$[14] in CH_2Cl_2 gave similar results (entry 6), and the yield of the product was increased to 88% upon increasing the catalyst load to 0.2 equiv (entry 7).

(1) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531. (b) Fügedi, P. In *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds; CRC Press: Boca Raton, FL, 2006; pp 89−179.

(2) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419.

(3) The recently reported C2-hydroxyglycosylation with glycal donors involves the intermediacy of 1,2-anhydrosugars. Honda, E.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 7343–7352.

(4) Yu, B.; Zhang, Y.; Tang, P. *Eur. J. Org. Chem.* **2007**, 5145–5161.

(5) (a) For example, see Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693–5700. (b) Liu, K. K.-C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 4933–4934. (c) Schmid, U.; Waldmann, H. *Chem. Eur. J.* **1998**, *4*, 494–501.

(6) (a) Yang, G.; Kong, F.; Fraser, R. R. *Carbohydr. Res.* **1994**, *258*, 49–58. (b) Du, Y.; Kong, F. *J. Carbohydr. Chem.* **1995**, *14*, 341–352. (c) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Griffith, D. A.; Oriyama, T.; Marsden, S. *J. Am. Chem. Soc.* **1995**, *117*, 1940–1953. (d) Lu, P.-P.; Hindsgaul, O.; Li, H.; Palcic, M. M. *Can. J. Chem.* **1997**, *75*, 790–800. (e) Matsushita, Y.-i.; Sugamoto, K.; Kita, Y.; Matsui, T. *Tetrahedron Lett.* **1997**, *38*, 8709–8712. (f) Ding, X.; Kong, F. *J. Carbohydr. Chem.* **1999**, *18*, 775–787.

(7) (a) Timmers, C. M.; van der Marel, G. A.; van Boom, J. H. *Chem. Eur. J.* **1995**, *1*, 161–164. (b) Chiappe, C.; Lo Moro, G.; Munforte, P. *Tetrahedron* **1997**, *53*, 10471–10478.

(8) For a recent review, see Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211.

(9) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563.

(10) (a) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965. (b) Zhao, P.-Q.; Xu, L -W.; Xia, C.-G. *Synlett* **2004**, 846–850. (c) Dai, L-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191–3194.

(11) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

(12) Schimmel, J.; Eleuterio, M. I. P.; Ritter, G.; Schmidt, R. R. *Eur. J. Org. Chem.* **2006**, 1701–1702.

(13) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(14) (a) Komiya, S.; Kochi, J. K. *J. Organomet. Chem.* **1977**, *135*, 65–72. (b) Canales, S.; Crespo, O.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; Mendizabal, F. *Organometallics* **2000**, *19*, 4985–4994. (c) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966–6967.

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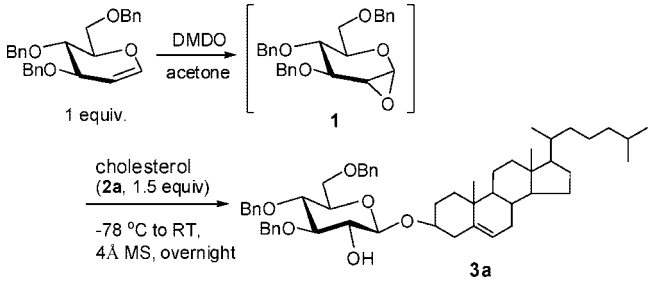
TABLE 1. Au(I)-Catalyzed Glycosidation of 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (1) with Cholesterol (2a)[a]



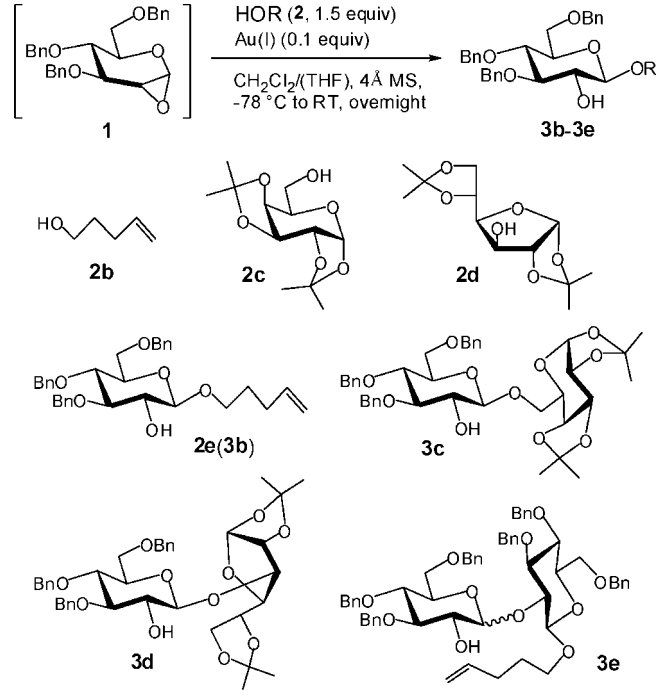
entry	catalyst (equiv)	solvent	yield (%)[b]
1	$ZnCl_2$ (3.0)	THF	47; 52;[11] 42;[12]
2	$Ph_3PAuNTf_2$ (0.1)	THF	50
3	$Ph_3PAuNTf_2$ (0.1)	CH_2Cl_2	47
4	$Ph_3PAuNTf_2$ (0.1)	CH_2Cl_2/THF (3:2)	78
5	$Ph_3PAuNTf_2$ (0.05)	CH_2Cl_2/THF (3:2)	66
6	$Ph_3PAuOTf$ (0.1)	CH_2Cl_2	78
7	$Ph_3PAuOTf$ (0.2)	CH_2Cl_2	88
8	Ph_3PAuCl (0.1)	CH_2Cl_2	trace
9	AgOTf (0.1)	CH_2Cl_2	trace

[a] See the Experimental Section for a typical procedure. [b] Isolated yield based on glucal; yields based on recovered cholesterol are >98%.

We then examined the glycosidation of 1,2-anhydrosugar (**1**) with a set of alcohols (**2b**−**e**) under the influence of 0.1 equiv of $Ph_3PAuNTf_2$ (in CH_2Cl_2/THF (3:2)) or $Ph_3PAuOTf$ (in CH_2Cl_2) (Table 2). The reactions with the primary alcohols (**2b** and **2c**) in the presence of both Au(I) catalysts gave the desired β-glycosides (**3b** and **3c**) in excellent yields (82−89%, entries 1−4), which is remarkably higher than that with $ZnCl_2$ as the promoter (<63%).[11,15] However, $Ph_3PAuNTf_2$ (and $ZnCl_2$ as well) hardly promoted the glycosidation with hindered sugar alcohols (**2d** and **2e**, entries 5 and 7). Nevertheless, the same reactions in the presence of $Ph_3PAuOTf$ proceeded well, providing the desired glycosides **3d** and **3e** in good yields (62% and 59%, respectively). In the latter case (entry 8), the α-anomer (**3e**-α) was also formed as a minor product, suggesting that a portion of the sugar oxocarbenium was being formed prior to the S_N2-type opening of the oxirane ring.[7]

3,4,6-Tri-*O*-acetyl- and 3,4,6-tri-*O*-benzyl-1,2-anhydro-α-D-galactopyranose (**4**[16] and **6**[5b,17]) were readily prepared but rarely used as glycosyl donors for the glycosylation of alcohols in the literature. The glycosidation of these two 1,2-anhydrogalactoses with alcohols (**2a**−**2e**) proceeded well under the influence of 0.1 equiv of $Ph_3PAuOTf$, providing the corresponding coupling products (**5a**−**5e** and **7a**−**7e**) in satisfactory yields (38−96%, Table 3). However, a significant amount of the α-anomer was formed in each case (β:α < 7:1). Especially, the coupling of **4** with **2e**, which gave the lowest yield of the product (38%, entry 5), formed equal amounts of the β:α anomers, while the coupling of **6** with **2d** led to the α-anomer only and in 41% yield (entry 9). These results reflect the ease of opening of the 1,2-oxiranes in the 1,2-anhydrogalactoses **4** and **6**, and this problem of a lack of stereoselectivity has been addressed by Danishefsky and co-workers by using galactal epoxides with cyclic carbonate engaging the C3 and C4 oxygens.[2,18]

TABLE 2. Au(I)-Catalyzed Glycosidation of 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (1)[a]



entry	Au(I)	HOR	product	yield (%)[b]
1	$Ph_3PAuNTf_2$	**2b**	**3b**	83; 63[15]
2	$Ph_3PAuOTf$	**2b**	**3b**	82
3	$Ph_3PAuNTf_2$	**2c**	**3c**	89; 58[11]
4	$Ph_3PAuOTf$	**2c**	**3c**	82
5	$Ph_3PAuNTf_2$	**2d**	**3d**	0
6	$Ph_3PAuOTf$	**2d**	**3d**	62
7	$Ph_3PAuNTf_2$	**2e**(**3b**)	**3e**	<10
8	$Ph_3PAuOTf$	**2e**	**3e**	59 (β:α =2.5)

[a] See the Experimental Section for a typical procedure. [b] Isolated yield based on glucal; yields based on recovered acceptors are >98%.

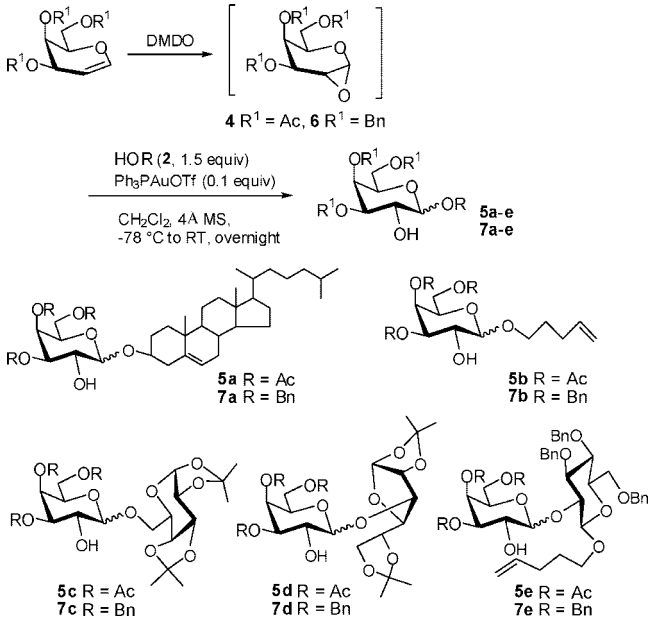
This point was validated by the glycosidation of 3,4-*O*-carbonyl-6-*O*-*tert*-butyldimethylsilyl-1,2-anhydro-α-D-galactopyranose (**8**[6c]) with alcohols **2a** and **2b** (Table 4). Under the action of $Ph_3PAuOTf$ (0.1 equiv.) in CH_2Cl_2, only the β-glycosides **9a** and **9b** were obtained in excellent yields of 96% and 94%, respectively.

To further confirm the superior properties of $Ph_3PAuOTf$ in catalyzing the glycosidation of 1,2-anhydrosugars, glucosamine derivative **2f**[5c] was employed as an acceptor (Table 5). The coupling of this hindered sugar alcohol (**2f**) with the glucose 1,2-epoxide **1** in the presence of $LiClO_4$ provided the coupled disaccharide **3f** in only 13% yield with a β:α ratio of 2:1.[5c] The use of $Ph_3PAuOTf$ (0.1 equiv) greatly increased the yield of **3f** (59%) and improved the β selectivity as well (β:α > 5:1, entry 1). The coupling of **2f** with the galactose 1,2-epoxide **6** in the presence of $LiClO_4$, $ZnCl_2$, or $Zn(OTf)_2$ provided the α-disaccharide **7f** as the sole coupling product and in a low 5−11% yield;[5c] the use of $Ph_3PAuOTf$ (0.1 equiv) was again able to increase the yield of **7f** to 30% (entry 2).

In summary, $Ph_3PAuOTf$ has been disclosed to be an effective catalyst for the glycosidation of 1,2-anhydrosugars. In the

(15) Gordon, D.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361–366.
(16) Cavicchioli, M.; Mele, A.; Montanari, V.; Resnati, G. *J. Chem. Soc., Chem. Commun.* **1995**, 901–902.
(17) (a) Bellucci, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron: Asymmetry* **1995**, *6*, 221–230. (b) Tanaka, H.; Matoba, N.; Takahashi, T. *Chem. Lett.* **2005**, *34*, 400–401. (c) Bosse, F.; Marcaurelle, L. A.; Seeberger, P. H. *J. Org. Chem.* **2002**, *67*, 6659–6670.
(18) Gervay, J.; Peterson, J. M.; Oriyama, T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 5465–5468.

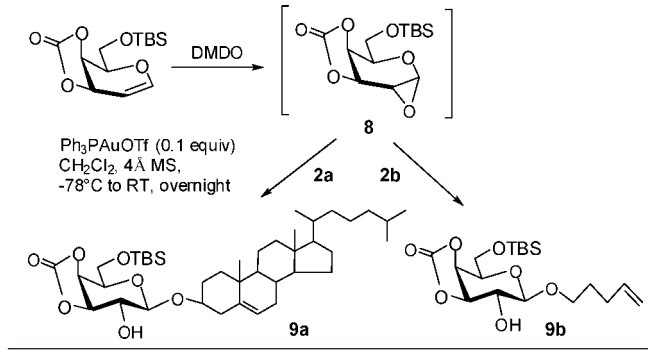
TABLE 3. $Ph_3PAuOTf$-Catalyzed Glycosidation of 1,2-Anhydro-α-D-galactopyranoses (4 and 6)[a]



entry	donors	HOR	product	yield[b]	β:α
1	**4**	**2a**	**5a**	83%	3:1[c]
2	**4**	**2b**	**5b**	96%	2.6:1[c]
3	**4**	**2c**	**5c**	78%	4:1[d]
4	**4**	**2d**	**5d**	56%	3:2[c]
5	**4**	**2e**	**5e**	38%	1:1[c]
6	**6**	**2a**	**7a**	82%	7:1[d]
7	**6**	**2b**	**7b**	80%	4.5:1[d]
8	**6**	**2c**	**7c**	81%	2:1[d]
9	**6**	**2d**	**7d**	41%	α only
10	**6**	**2e**	**7e**	56%	2:1[c]

[a] Reaction conditions as described in Table 2 were applied. [b] Isolated yield based on glycal; yields based on recovered alcohols are >98%. [c] Isolated ratio. [d] Ratio determined by ^1H NMR.

TABLE 4. Glycosidation of 3,4-*O*-Carbonyl-1,2-anhydro-α-D-galactopyranose (8)[a]

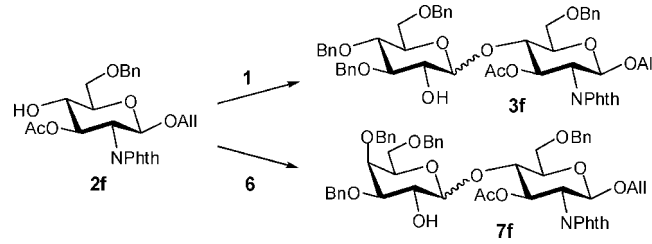


entry	donor	HOR	product	yield (β only)[b]
1	**8**	**2a**	**9a**	96%
2	**8**	**2b**	**9b**	94%

[a] Reaction conditions as described in Table 2 were applied. [b] Isolated yield based on glycal.

comparable examples, the glycosidation catalyzed by $Ph_3PAuOTf$ (0.1 equiv) provided the coupling products in remarkably higher yields (>20%) than those obtained under the promotion of the conventional zinc chloride (~3 equiv). Thus, the $Ph_3PAuOTf$ catalyst shall find applications in the well-established glycosidation protocol with 1,2-anhydrosugars as donors.

TABLE 5. Glycosidation of 1,2-Anhydrosugars (1 and 6) with the Glucosamine Derivative 2f[a]



entry	donor	HOR	product	yield (β:α)[b]
1	**1**	**2f**	**3f**	13% (2:1)[5c] 59% (>5:1)
2	**6**	**2f**	**7f**	5−11% (α)[5c] 30% (α)

[a] Reaction conditions as in Table 2 were applied. [b] Isolated yield based on the glycal; yields based on recovered alcohols are >98%.

Experimental Section

General Procedure for the Glycosidation of 1,2-Anhydrosugars (Table 1, entry 6). 3,4,6-Tri-*O*-benzyl-D-glucal (60 mg, 0.145 mmol) was dissolved in dry CH_2Cl_2 (1 mL), and the solution was cooled to 0 °C under the protection of argon. A solution of dimethyldioxirane (DMDO) in acetone (1.2 equiv, ca. 0.08 M), prepared accordingly,[19] was added. The resulting mixture was stirred at 0 °C for 30 min. The 1,2-anhydroglucose **1** thus obtained was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 30 min, and the residue was then dissolved in cold dry CH_2Cl_2 (2 mL). To a stirred mixture of cholesterol (**2a**, 84 mg, 0.217 mmol) and newly activated 4 Å MS in dry CH_2Cl_2 (2 mL), was added a newly prepared CH_2Cl_2 solution of PPh_3AuOTf (0.0145 M, 1 mL, 0.0145 mmol).[14c] The mixture was stirred at RT for 30 min and was then cooled to −78 °C; the previously prepared solution of 1,2-anhydrosugar **1** was added slowly. The resulting mixture was allowed to warm up naturally to RT and was left overnight. The reaction mixture was then diluted with saturated brine and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, then filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane/ethyl acetate 10:1) to provide **3a** as a white solid (93 mg, 78% based on tri-*O*-benzyl-glucal).

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Supporting Information Available: Full experimental details, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50–51.