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$Hg(OTf)_2$-catalyzed glycosylation using alkynoate as the leaving group

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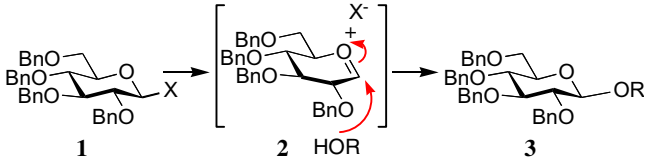
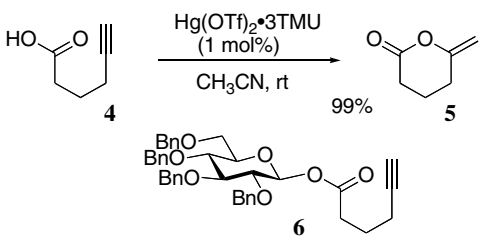
Abstract—A novel $Hg(OTf)_2$-catalyzed glycosylation procedure has developed using alkynoic acid residues as the leaving group under mild reaction conditions and efficient catalytic turnover. The process is particularly useful for the glycosylation of hindered alcohols.

Much attention has been focused on development of efficient glycosylation methodologies due to the biological significance of a lot of complex oligosaccharides and glycoconjugates.[1] After introduction of the Koenigs–Knorr method, the classic glycosylation using stoichiometric amounts of mercuric salt,[2] many modern glycosylation reactions have been developed.[3] Lewis acids have been employed to activate leaving groups such as glycosyl trichloroacetimidate,[4] thioglycoside,[5] *n*-pentenyl glycoside,[6] glycosyl fluoride,[7] and glycosyl phosphate.[8] Recently, Ferrier type catalytic glycosylation reaction has been developed using glycal as the glycosylation donor and a variety of metal-salts as catalysts.[9] Mukaiyama also developed unique catalytic glycosylation procedures.[10] Most of these glycosylation reactions involve oxonium cation **2** as the common intermediate, and generation the of **2** under a milder condition is critical to achieving efficient glycosylation. Herein, we describe a novel mercuric triflate [$Hg(OTf)_2$]-catalyzed glycosylation using alkynoate as the leaving group, a reaction that is particularly useful for the glycosylation of hindered alcohols. This procedure is the first example of a mercuric salt-catalyzed glycosylation reactions at least to our knowledge, and corresponds to the catalytic version of pentenyl ether and ester glycosylations reported by Frase-Reid and Kunz, respectively,[6] Scheme 1.



Scheme 1.

Recently, we found that mercury(II) trifluoromethanesulfonate (mercuric triflate),[11,12] and its tetramethylurea (hereafter TMU) complex showed highly efficient catalytic activity for hydration of terminal alkynes leading to methyl ketones,[13] hydroxylative 1,6-enyne cyclization to give *exo*-methylene five-membered ring products,[14] arylalkyne cyclization leading to dihydronaphthalenes,[15] cyclization of 1-alkyn-5-one leading to 2-methylfuranes,[16] and aryl-ene-yne cyclization affording polycarbocycles.[17] We also disclosed a reaction of ω-alkynoic acids **4** with catalytic amount of $Hg(OTf)_2 \cdot 3TMU$ to afford δ-methylene-δ-lactones **5** in quantitative yield[18] (Scheme 2).



Scheme 2.

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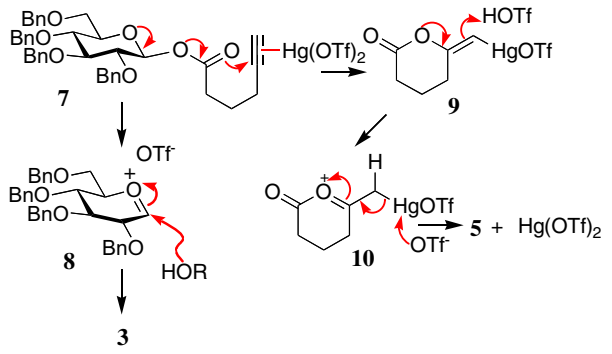
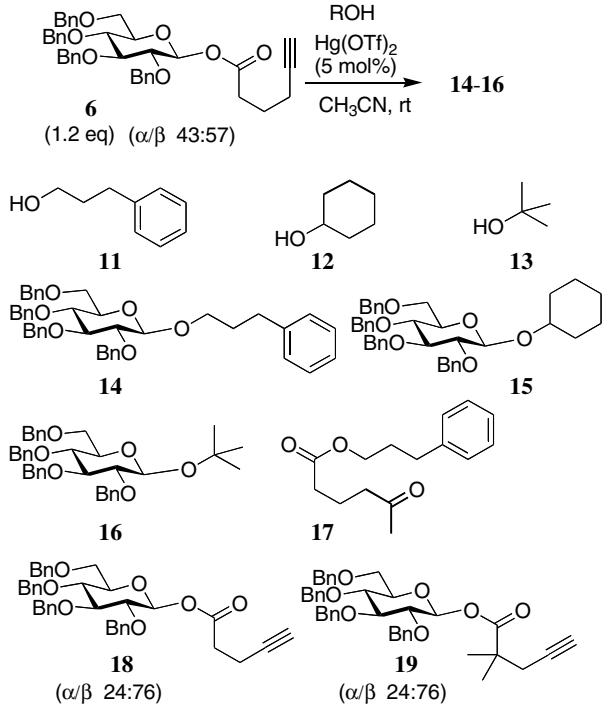


Scheme 3.

The result led us to generate oxonium cation **2** in a catalytic manner, and we designed novel glycosyl donor molecule **6** that has an alkynoate as the leaving group. The proposed reaction mechanism is shown in Scheme 3. A π complexation of $Hg(OTf)_2$ with alkyne as shown in **7** should generate oxonium cation **8** as well as vinylmercuric lactone **9**. Cation **8** will be attacked by ROH leading to glycoside **3** and TfOH, and the latter protonates **9** generating alternative oxonium cation **10**. Subsequent demercuration provides lactone **5** and meanwhile regenerates the catalyst $Hg(OTf)_2$.

Therefore, we examined the reaction of glycosylation donor **6** with alcohols **11**, **12** and **13** by using 5 mol % of $Hg(OTf)_2$ in CH_3CN at room temperature (Scheme 4). The glycosylation of primary alcohol **11** resulted in the lowest yield affording **14** in 70% yield, while the glycosylation of *sec*-alcohol **12** and *tert*-alcohol **13** produced **15** and **16** in 85% and 91% yields, respectively, as seen in Table 1 (entries 1–3). By-product **17**, generated during the reaction of **6** and **11**, resulted from the acid-catalyzed condensation of lactone **5** and alcohol **11**. Thus, the yield of **14** was reduced to 70%. Hindered *sec*-and *tert*-alcohols did not induce the side reaction. When $Hg(OTf)_2{\cdot}3TMU$ was employed as the catalyst, the yield of the reaction from **11** to give **14** was dramatically improved to 94%, though longer reaction period was required. Alcohols **12** and **13** were also converted to **15** and **16** by the reaction with $Hg(OTf)_2{\cdot}3TMU$, respectively, in reasonable yields (entries 4–6).



Scheme 4.

Table 1. $Hg(OTf)_2$ catalyzed glycosylation

Entry	ROH	Additive	Time (min)	Glycoside	Yield[a]	(α/β)[b]
1	**11**	None	30	**14**	70	(24:76)
2	**12**	None	30	**15**	85	(25:75)
3	**13**	None	30	**16**	91	(31:69)
4	**11**	TMU[c]	240	**14**	94	(25:75)
5	**12**	TMU[c]	240	**15**	90	(26:74)
6	**13**	TMU[c]	240	**16**	89	(31:69)

[a] Isolated yield.
[b] Determined by HPLC.
[c] TMU (15 mol %) was employed.

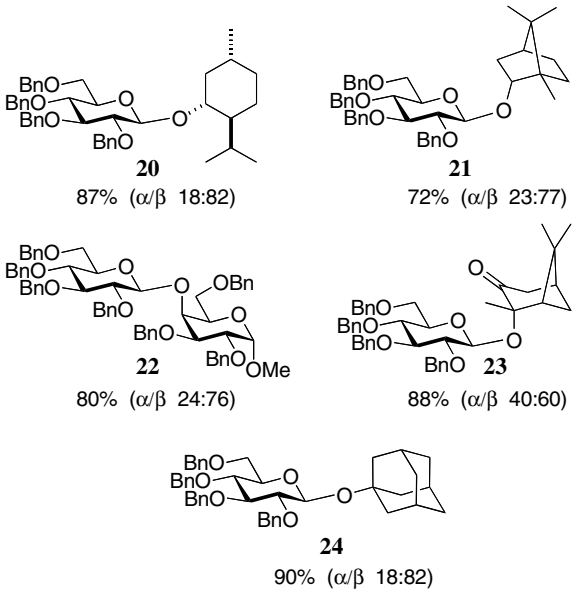
Next, we examined glycosylations of donors 4-pentynoate **18** and 2,2-dimethyl-4-pentynoate **19** with **11** using 5 mol % of $Hg(OTf)_2{\cdot}3TMU$ in CH_3CN at room temperature for 4 h. Since an insignificant difference was observed between these esters 94% yield (α/β 24:76) from **18** and 99% yield (α/β 24:76) from **19**, we decided to use commercially available 5-hexynoic acid residue as the leaving group for further reactions. The solvent and temperature effects were investigated for the reaction of **6** with *tert*-butyl alcohol **13** (Table 2). As seen in entry 3 of Table 1, the reaction in CH_3CN afforded glycoside **16** in 91% yield in α/β 31:69.[19] The reaction in CH_3NO_2 and CH_2Cl_2 afforded **16** in almost 1:1 mixture of stereoisomers in lower yields (Table 2, entries 1 and 2), but the reaction in diethyl ether and toluene afforded the α-isomer predominantly (entries 3 and 4). A reaction at lower temperature (0 °C) in CH_3CN resulted increased β-stereoselectivity α/β 22:78 (entry 5) in 90% yield after 4 h.

We then investigated further glycosylation of a variety of hindered alcohols with **6** (Scheme 5). The reaction of less reactive *sec*-alcohols such as menthol, (−)-borneol and methyl 2,3,6-*O*-benzyl-α-D-galactopyranoside at 0 °C for 4 h in CH_3CN afforded the corresponding glycosides **20**, **21**, and **22**, respectively, in good yield.

Table 2. $Hg(OTf)_2$-catalyzed glycosylation of **13** with **6** leading **16**

Entry	Temperature	Solvent	Time (min)	Yield[a]	(α/β)[b]
1	rt	CH_3NO_2	30	74	(49:51)
2	rt	CH_3Cl_2	15	81	(60:40)
3	rt	Diethylether	30	68	(74:26)
4	rt	Toluene	30	52	(70:30)
5	0 °C	CH_3CN	240	90	(22:78)

[a] Isolated yield.
[b] Determined by HPLC.



Scheme 5.

Reaction of even more sterically hindered *tert*-alcohols such as (1*s*,2*s*,5*s*)-(−)-2-hydroxy-3-pinanone and 1-adamantanol at 0 °C for 4 h provided **23** and **24**, respectively, in excellent yields.[19]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.114.

References and notes

1. (a) Esko, J.; Freeze, H.; Hart, G.; Marth, J. *Essentials of Glycobiology*; Cold Spring Harbor: New York, 1999; (b) Dwek, R. A.; Butters, T. A. *Chem. Rev.* **2002**, *102*, 283–284.
2. Koening, W.; Knorr, E. *Ber.* **1901**, *34*, 957.
3. (a) Demchenko, A. V. *Synlett* **2003**, 1225–1240; (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 2947–2993; (c) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624; (d) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160; (e) *Preperative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; Reviews for recent glycosylation see: (f) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095–1121; (g) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.
4. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
5. Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.
6. (a) Fraser-Reid, B.; Konradsson, P.; Mootoo, D.; Udodong, U. *J. Chem. Soc. Chem. Commun.* **1988**, 823–825; (b) Kunz, H.; Werning, P.; Schultz, M. *Synlett* **1990**, 631–632.
7. (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431–432; (b) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192; (c) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382; (d) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571–3574.
8. Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1989**, 685–687.
9. (a) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271–1274; (b) Rafiee, E.; Tangestaninejad, S.; Habibi, M. H.; Mirkhani, V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3611–3614; (c) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429; (d) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337; (e) Hotha, S.; Tripathi, A. *Tetrahedron Lett.* **2005**, *46*, 4555–4558; (f) Lin, H. C.; Du, W. P.; Chang, C. C.; Lin, C. H. *Tetrahedron Lett.* **2005**, *46*, 5071–5076.
10. (a) Takeuchi, K.; Higuchi, S.; Mukaiyama, T. *Chem. Lett.* **1997**, 969–970; (b) Mukaiyama, T.; Wakiyama, Y.; Miyazaki, K.; Takeuchi, K. *Chem. Lett.* **1999**, 933–934; (c) Takeuchi, K.; Tamura, T.; Mukaiyama, T. *Chem. Lett.* **2000**, *29*, 122–123; (d) Takeuchi, K.; Tamura, T.; Mukaiyama, T. *Chem. Lett.* **2000**, *29*, 124–125; (e) Jona, H.; Takeuchi, K.; Mukaiyama, T. *Chem. Lett.* **2000**, *29*, 1278–1279; (f) Jona, H.; Maeshima, H.; Mukaiyama, T. *Chem. Lett.* **2001**, *30*, 726–727; (g) Mukaiyama, T.; Chiba, H.; Funasaka, S. *Chem. Lett.* **2002**, *32*, 392–393; (h) Hashihayata, T.; Mandai, H.; Mukaiyama, T. *Bull, Chem. Soc. Jpn.* **2004**, *77*, 169–178; (i) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523–3525; (j) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979–3981; (k) Colinas, P. A.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2002**, *43*, 9065–9068; (l) Suzuki, T.; Watanabe, S.; Yamada, T.; Hiroi, K. *Tetrahedron Lett.* **2003**, *44*, 2561–2563.
11. Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169–170.
12. Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581–2584.
13. Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12–13.
14. Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609–1611.
15. Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679–3681.
16. Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563–4565.
17. (a) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703–705; (b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451–452.
18. Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, M. *Synlett* **2006**, 639–640.
19. Typical experimental procedure is as follows: a solution of 1-adamantanol (22.3 mg, 0.146 mmol) and glycoside **6** (110 mg, 0.173 mmol) in CH_3CN (2.9 mL) was azeotropically dried through molecular sieves 4 Å using a dropping funnel. To this was added 0.1 M CH_3CN solution of $Hg(OTf)_2$ (72 μL, 0.0072 mmol) at 0 °C. After stirring for 4 h at the same temperature, Et_3N (1 mL), and then aqueous $NaHCO_3$ solution were added, and the mixture was extracted with ether. The dried and concentrated organic material was subjected to column chromatography on ODS (CH_3CN/H_2O 10:1/100:1) to give **24** (α/β 18:82, 88.9 mg, 90% yield).