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ortho-(Methyltosylaminoethynyl)benzyl glycosides as new glycosyl donors for latent-active glycosylation[†]

Xiaoping Chen,^a Dacheng Shen,^a Qiaoling Wang,^a You Yang^b and Biao Yu*^a

A new glycosylation protocol employing *ortho*-(methyltosylaminoethynyl)benzyl glycosides as glycosyl donors and TMSOTf as the catalyst is disclosed. These donors can be readily prepared from the corresponding 'latent' *ortho*-iodobenzyl glycosides *via* a Sonogashira coupling, thus providing a new approach for the 'latent-active' synthesis of glycans.

New glycosylation methods are continuously developed with efforts to construct the extremely diverse glycosidic linkages occurring in glycans and glycoconjugates in an efficient and economical manner.¹ In the last decade, much interest has been devoted to the investigation of glycosylation protocols based on activation of the $C \equiv C$ triple bonds. Thus, propargyl glycosides and 1,2-orthoesters (under the catalysis of AuX_3),^{2,3} glycosyl alkynoates (under the promotion of Hg(OTf)₂),⁴ dipropargylcyanoacetates (under the catalysis of $AuCl_3/AgSbF_6$),⁵ as well as alkynyl-containing thioglycosides (under the catalysis of Au(1) complexes),⁶ are disclosed to be effective donors in certain glycosylation reactions. Especially, glycosyl ortho-alkynylbenzoates (under the catalysis of a gold(1) complex, such as PPh₃AuNTf₂ and PPh₃AuOTf) have been found to have wide applications in the synthesis of complex glycans and glycoconjugates;^{7,8} and the general mechanism of this glycosylation reaction has been largely elucidated.^{7c-e} During the course of these studies, we tried glycosyl orthoalkynylbenzyl glycosides as donors, which would have the advantage of easy manipulation of the protecting groups, but found no glycosylation took place under similar conditions wherein the corresponding ortho-alkynylbenzoates underwent glycosylation. We envisioned introduction of an electron-rich substituent on the alkyne moiety to facilitate the desired glycosylation pathway. Here we report ortho-(methyltosylaminoethynyl)benzyl glycosides

as a new type of glycosyl donors which can be activated by a catalytic amount of TMSOTf under mild conditions and their applicability in the 'latent-active' synthesis of glycans.

The desired glycosyl ortho-(methyltosylaminoethynyl)benzyl glycosides could be easily prepared from the corresponding ortho-iodobenzyl glycosides via a Sonogashira coupling with ynamide 4.⁹⁻¹¹ Taking the preparation of perbenzoyl glucopyranoside 1a as an example (Scheme 1), ortho-iodobenzyl glucopyranoside 3a was obtained via condensation of perbenzoylated glucose 2a with 2-iodobenzyl alcohol under the action of TMSOTf, which was then subjected to coupling with ynamide 4 in the presence of (PPh₃)₂PdCl₂ and CuI in i-Pr₂NH/DMF to provide the desired ortho-(methyltosylaminoethynyl)benzyl glucoside **1a** in high yield (90%).¹⁰ Manipulation of the protecting groups on the iodobenzyl glycoside 3a followed by Sonogashira coupling would lead to (methyltosylaminoethynyl)benzyl glucopyranosides bearing different protecting group patterns, such as 1c (Table 2). (Methyltosylaminoethynyl)benzyl rhamnopyranoside 1b and 2-deoxy-glucopyranoside 1d were similarly prepared by Sonogashira coupling as the key step (see ESI[†] for details). All these glycosides were found to be stable when stored at room temperature.

With the perbenzoyl glucoside **1a** as a potential donor and cholesterol **5a** as an acceptor, a variety of π -acids and Lewis acids (0.1 eq.) were screened as promoters for the desired



Scheme 1 Preparation of *ortho*-(methyltosylaminoethynyl)benzyl glucopyranoside **1a**.

^a State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,

³⁴⁵ Lingling Road, Shanghai 200032, China. E-mail: byu@mail.sioc.ac.cn ^b Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China

University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

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Table 1Screening of promoters for the glycosylation of ortho-(methyl-
tosylaminoethynyl)benzyl glucoside 1a with cholesterol 5a

BzO BzO BzO BzO BzO BzO OBz 1a (1.2 eq.)) + + + + + + + + + + + + + + + + + + +	romoter MS, CH ₂ Cl ₂ , B2O b B2O OBz B2O OBz 6aa
Entry	Promoter (0.1 eq.)	Isolated yield (%)
1	PPh ₃ AuNTf ₂	43
2	TMSOTf	91
3	Bi(OTf) ₃	83
4	In(OTf) ₃	67
5	$Cu(OTf)_2$	46
6	$Sc(OTf)_3$	17
7	BF_3OEt_2 (1.2 eq.)	21
8	SnCl ₄	26
9	PtCl ₂	16
10	AuBr ₃	Trace
11	CuI or LiOTf	No reaction

glycosylation reaction in the presence of 4 Å MS in CH_2Cl_2 at room temperature (Table 1). Surprisingly, PPh₃AuNTf₂, the effective catalyst for the glycosylation of glycosyl *ortho*-alkynylbenzoates,⁷ could not catalyze the present coupling effectively, providing the desired β-glucoside **6aa** in only 43% yield (entry 1). The major byproduct arose from the nucleophilic addition of cholesterol **5a** onto the ynamide moiety.^{11*a*,*e*} TMSOTf turned out to be the most effective catalyst, wherein the coupled glycoside **6aa** was obtained in a high yield of 91% (entry 2). Bi(OTf)₃, In(OTf)₃, and Cu(OTf)₂ were shown to be better catalysts than PPh₃AuNTf₂, leading to **6aa** in 83%, 67%, and 46% yield, respectively (entries 3–5). Sc(OTf)₃, BF₃OEt₂, SnCl₄, and PtCl₂ were found to be ineffective for this coupling (16–26%) (entries 6–9), whereas the coupling partners stayed inert in the presence of AuBr₃, CuI, and LiOTf (entries 10 and 11).

Next, we investigated briefly the scope of the TMSOTf-catalyzed glycosylation reaction with ortho-(methyltosylaminoethynyl)benzyl glycosides as donors (Table 2). Four representative glycosides 1a-1d and four alcohols 5a-5d were selected as coupling partners, and all the reactions were carried out under fixed conditions (0.1 eq. TMSOTf, 4 Å MS, CH₂Cl₂, rt, 2 h). The couplings of perbenzoyl-glucopyranoside 1a with all the four alcohols led to the coupled glycosides in excellent yields (>91%) and with complete β -selectivity (entries 1–4), testifying the participation of the neighbouring group in the glycosylation.¹ Similarly, the couplings of 2,3,4-tri-O-benzoyl-L-rhamnopyranoside 1b with alcohols 5a–5d provided the corresponding α -L-rhamnosides in a fully stereocontrolled manner in high yields (88-95%; entries 5-8). As expected, the corresponding glycosylation reactions of perbenzylglucopyranoside 1c and 2-deoxy-glucopyranoside 1d, in the absence of a neighboring participating group, led to the coupled glycosides in high yields (83–99%), albeit in a pair of the α - and β -anomers (Table 2, entries 11–16).^{12,13} It was noted that the reactions with the hindered glucose-4-OH derivative 5c as the acceptor were devoid of the addition of alcohol onto the ynamide moiety, therefore the unglycosylated 5c could be fully recovered.

In fact, the addition of alcohol onto the ynamide moiety became a serious problem when the alcohol to be glycosylated
 Table
 2
 Glycosylation
 with
 ortho-(methyltosylaminoethynyl)benzyl
 glycosides
 1a-1d
 as donors under the catalysis of TMSOTf
 Glycosylation
 <t



 a Isolated yield. b The α/β ratio was determined by 1H NMR spectroscopic measurement.

6db

6dc

6dd

99

83

89

2.5:1

10:1

3:1

5b

5c

5d

14

15

16

is highly reactive. Thus, the condensation of 1a with 4-penten-1ol 5e under the catalysis of TMSOTf delivered the coupled glycoside 6ae in only 62% yield, while ester 7, which was derived from the corresponding adduct during workup, was isolated in 34% yield (Scheme 2).¹¹

Based on these experimental findings and the nature of ynamides,^{9,11} a plausible mechanism for the present TMSOTF catalyzed glycosylation reaction with *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors was proposed (Scheme 3). Thus, keteniminium cation **B** was generated from *ortho*-(methyltosylaminoethynyl)benzyl glycoside **A** in the presence of ROH and TMSOTF (wherein HOTf¹⁴ was produced *in situ*).¹⁵ An intramolecular nucleophilic addition of the anomeric oxygen onto



Scheme 2 The coupling of *ortho*-(methyltosylaminoethynyl)benzyl glucopyranoside **1a** with 4-penten-1-ol (**5e**).



Scheme 3 A plausible mechanism for the glycosylation with *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors under the catalysis of TMSOTF.

the keteniminium led to sugar oxocarbenium ion **C** and 1*H*-isochromene **D** which was indeed characterized (path a). Sugar oxocarbenium ion **C** underwent glycosylation in the presence of ROH to provide glycoside \mathbf{E} .^{1e} Alternatively, keteniminium cation **B** could be attacked by the alcohol ROH, giving rise to alkoxy-substituted enamine intermediate **F** (path b). Hydrolysis of the enamine **F** during workup provided ester **G**.

Given the fact that the ortho-(methyltosylaminoethynyl)benzyl glycoside donors are readily prepared from the orthoiodobenzyl glycosides, which are inactive in the glycosylation reactions of the former, these donors could be applied to the expeditious synthesis of oligosaccharides based on the 'latent-active' strategy.¹⁶ The previous donors applicable in the 'latent-active' synthesis of glycans include p-acetamidophenyl thioglycosides (vs. p-nitrophenyl thioglycosides),17 n-pentenyl glycosides (vs. 4,5-dibromopentyl glycosides),18 vinyl glycoside (vs. 1-methyl-2-propenyl glycosides),19 2-(hydroxycarbonyl)benzyl glycosides (vs. 2-(benzyloxycarbonyl)benzyl glycosides),²⁰ and S-benzimidazolyl glycosides (vs. N-anisoylated S-benzimidazolyl glycosides).²¹ To demonstrate the feasibility of applying the present glycosylation protocol to the 'latent-active' assembly of glycans, the 'active' ortho-(methyltosylaminoethynyl)benzyl glycoside 1a was coupled with the 'latent' ortho-iodobenzyl glucoside derivative 8 in the presence of TMSOTf (0.1 eq.) to provide β -(1 \rightarrow 6)-disaccharide 9 (97%), which was then converted into the 'active' ortho-(methyltosylaminoethynyl)benzyl disaccharide 10 via Sonogashira coupling with ynamide 4 (88%) (Scheme 4). Subsequent glycosylation of disaccharide 10 with cholesterol 5a or glucose-4-OH derivative 5c under similar glycosylation conditions furnished cholesterol 3-O-β-disaccharide 11 and β -trisaccharide 12 in 87% and 86% yields, respectively. In addition, glycosylation of disaccharide 10 with the 'latent' orthoiodobenzyl glucoside acceptor 8 provided the 'latent' orthoiodobenzyl trisaccharide 13 in 97% yield, which could be used for further elongation of the glycans via the iterative Sonogashira coupling/glycosylation sequence.

In conclusion, *ortho*-(methyltosylaminoethynyl)benzyl glycosides have been disclosed as a new type of glycosyl donors under the catalysis of TMSOTf. These shelf-stable donors are readily prepared from the corresponding *ortho*-iodobenzyl glycosides *via* Sonogashira coupling with ynamide **4**. The expeditious assembly of glycans *via* the 'latent-active' strategy using the present protocol has been demonstrated. These



Scheme 4 Assembly of oligosaccharides **11–13** by the 'latent-active' strategy using *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors and *ortho*-iodobenzyl glycosides as acceptors.

promising preliminary results shall warrant further elaboration and application of this new glycosylation method.

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Notes and references

- (a) X. Zhu and R. R. Schmidt, Angew. Chem., Int. Ed., 2009, 48, 1900–1934; (b) M. J. McKay and H. M. Nguyen, ACS Catal., 2012, 2, 1563–1595; (c) B. Yu, J. Sun and X. Yang, Acc. Chem. Res., 2012, 45, 1227–1236; (d) S. S. Nigudkar and A. V. Demchenko, Chem. Sci., 2015, 6, 2687–2704; (e) L. Bohe and D. Crich, Carbohydr. Res., 2015, 403, 48–59; (f) Y. Yang, X. Zhang and B. Yu, Nat. Prod. Rep., 2015, DOI: 10.1039/C5NP00033E.
- 2 (a) S. Hotha and S. Kashyap, J. Am. Chem. Soc., 2006, 128, 9620–9621;
 (b) S. K. Mamidyala and M. G. Finn, J. Org. Chem., 2009, 74, 8417–8420;
 (c) S. R. Vidadala, S. A. Thadke and S. Hotha, J. Org. Chem., 2009, 74, 9233–9236;
 (d) S. R. Vidadala, G. Gayatri, G. N. Sastry and S. Hotha, Chem. Commun., 2011, 47, 9906–9908;
 (e) A. K. Kayastha and S. Hotha, Chem. Commun., 2012, 48, 7161–7163;
 (f) A. K. Kayastha and S. Hotha, Beilstein J. Org. Chem., 2013, 9, 2147–2155.
- 3 (a) G. Sureshkumar and S. Hotha, Tetrahedron Lett., 2007, 48, 6564–6568; (b) G. Sureshkumara and S. Hotha, Chem. Commun., 2008, 4282–4284; (c) A. Y. Shaikh, G. Sureshkumar, D. Pati, S. S. Guptab and S. Hotha, Org. Biomol. Chem., 2011, 9, 5951–5959; (d) S. A. Thadke, B. Mishra and S. Hotha, Org. Lett., 2013, 15, 2466–2469; (e) S. A. Thadke, B. Mishra and S. Hotha, J. Org. Chem., 2014, 79, 7358–7371; (f) B. V. Rao, S. Manmode and S. Hotha, J. Org. Chem., 2015, 80, 1499–1505.
- 4 H. Imagawa, A. Kinoshita, T. Fukuyama, H. Yamamoto and M. Nishizawa, *Tetrahedron Lett.*, 2006, 47, 4729–4731.
- 5 S. R. Koppolu, R. Niddana and R. Balamurugan, *Org. Biomol. Chem.*, 2015, **13**, 5094–5097.
- 6 (a) F. Yang, Q. Wang and B. Yu, *Tetrahedron Lett.*, 2012, 53, 5231–5234; (b) S. Adhikari, K. N. Baryal, D. Zhu, X. Li and J. Zhu, *ACS Catal.*, 2013, 3, 57–60.
- 7 (a) Y. Li, Y. Yang and B. Yu, *Tetrahedron Lett.*, 2008, 49, 3604–3608;
 (b) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang and B. Yu, *Chem. Eur. J.*, 2010, 16, 1871–1882; (c) Y. Zhu and B. Yu, *Angew. Chem., Int. Ed.*, 2011, 50, 8329–8332; (d) Y. Tang, J. Li, Y. Zhu, Y. Li and B. Yu, *J. Am.*

Chem. Soc., 2013, 135, 18396–18405; (e) Y. Zhu and B. Yu, Chem. – Eur. J., 2015, 21, 8771–8780.

- 8 (a) Y. Yang, Y. Li and B. Yu, J. Am. Chem. Soc., 2009, 131, 12076-12077; (b) Y. Li and B. Yu, Chem. Commun., 2010, 46, 6060-6062; (c) W. Yang, J. Sun, W. Lu, Y. Li, L. Shan, W. Han, W.-D. Zhang and B. Yu, J. Org. Chem., 2010, 75, 6879-6888; (d) Y. Ma, Z. Li, H. Shi, J. Zhang and B. Yu, J. Org. Chem., 2011, 76, 9748-9756; (e) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, Angew. Chem., Int. Ed., 2011, 50, 4933-4936; (f) Y. Li, J. Sun and B. Yu, Org. Lett., 2011, 13, 5508-5511; (g) J. Yu, J. Sun and B. Yu, Org. Lett., 2012, 14, 4022-4025; (h) J. Zhang, H. Shi, Y. Ma and B. Yu, Chem. Commun., 2012, 48, 8679-8681; (i) J. Yu, J. Sun, Y. Niu, R. Li, J. Liao, F. Zhang and B. Yu, Chem. Sci., 2013, 4, 3899-3905; (j) G. Xiao and B. Yu, Chem. Soc., 2014, 136, 4157-4160; (l) J. Li and B. Yu, Angew. Chem., Int. Ed., 2015, 54, 6618-6621; (m) X. Zhang, Y. Zhou, J. Zuo and B. Yu, Nat. Commun., 2015, 6, 5879, DOI: 10.1038/ncomms6879.
- 9 (a) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar and L.-L. Wei, *Tetrahedron*, 2001, 57, 7575–7606; (b) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, 49, 2840–2859.
- 10 (a) Y.-P. Wang and R. L. Danheis, *Tetrahedron Lett.*, 2011, 52, 2111–2114; (b) M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder and R. P. Hsung, *Org. Lett.*, 2011, 13, 5508–5511.
- (a) M. C. B. Jaimes, V. Weingand, F. Rominger and A. S. K. Hashmi, *Chem. - Eur. J.*, 2013, **19**, 12504–12511; (b) Y. Kong, K. Jiang, J. Cao, L. Fu, L. Yu, G. Lai, Y. Cui, Z. Hu and G. Wang, *Org. Lett.*, 2013, **15**, 422–425; (c) T. Okitsu, K. Nakata, K. Nishigaki, N. Michioka,

M. Karatani and A. Wada, *J. Org. Chem.*, 2014, **79**, 5914–5920; (*d*) D. Fujino, H. Yorimitsu and A. Osuka, *J. Am. Chem. Soc.*, 2014, **136**, 6255–6258; (*e*) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208–4211.

- 12 D. Hou and T. L. Lowary, Carbohydr. Res., 2009, 344, 1911-1940.
- 13 E. Juaristi and G. Cuevas, *The Anomeric Effect*, CRC Press, 1994, pp. 183-194.
- 14 T. T. Dang, F. Boeck and L. Hintermann, J. Org. Chem., 2011, 76, 9353–9361.
- 15 Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, 7, 1047–1050.
- 16 (a) T. C. Shiao and R. Roy, *Top. Curr. Chem.*, 2011, 301, 69–108;
 (b) J. T. Smoot and A. V. Demchenko, *Adv. Carbohydr. Chem. Biochem.*, 2009, 62, 161–250; (c) G. J. Boons, *Tetrahedron*, 1996, 52, 1095–1121.
- (a) R. Roy, F. O. Andersson and M. Letellier, *Tetrahedron Lett.*, 1992, 33, 6053–6056; (b) L. Huang, Z. Wang and X. Huang, *Chem. Commun.*, 2004, 1960–1961.
- 18 B. Fraser-Reid, U. E. Udodong, Z. F. Wu, H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts and R. Madsen, *Synlett*, 1992, 927–942.
- (a) G.-J. Boons and S. Isles, *Tetrahedron Lett.*, 1994, 35, 3593–3596;
 (b) P. Wang, P. Haldar, Y. Wang and H. Hu, *J. Org. Chem.*, 2007, 72, 5870–5873.
- 20 K. S. Kim, J. H. Kim, Y. J. Lee, Y. J. Lee and J. Park, *J. Am. Chem. Soc.*, 2001, **123**, 8477–8481.
- 21 S. J. Hasty, M. A. Kleine and A. V. Demchenko, *Angew. Chem., Int. Ed.*, 2011, **50**, 4197–4201.