A new glycosylation protocol employing ortho-(methyltosylamino-ethynyl)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. In the last decade, much interest has been devoted to the investigation of glycosylation protocols based on activation of the C=C triple bonds. Thus, propargyl glycosides and 1,2-orthoesters (under the catalysis of AuX3), glycosyl alkynoates (under the promotion of Hg(OTf)2), dipropargylglycanoacetates (under the catalysis of AuCl3/AgSbF6), as well as alkynyl-containing thioglycosides (under the catalysis of Au(i) complexes), are disclosed to be effective donors in certain glycosylation reactions. Especially, glycosyl ortho-alkynylbenzoates (under the catalysis of a gold(i) complex, such as PPh3AuNTf2 and PPh3AuOTf) have been found to have wide applications in the synthesis of complex glycans and glycoconjugates; and the general mechanism of this glycosylation reaction has been largely elucidated.

During the course of these studies, we tried glycosyl ortho-alkynylbenzyl 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. 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 glucosyl 1a in high yield (90%). Manipulation of the protecting groups on the iodobenzyl glucoside 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 glucose 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
glycosylation reaction in the presence of 4 Å MS in CH2Cl2 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 by-product arose from the nucleophilic addition of cholesterol 5a onto the ynamide moiety.10 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, BF3·OEt2, SnCl4, and PCl3 were found to be ineffective for this coupling (16–26%) (entries 6–9), whereas the coupling partners stayed inert in the presence of AuBr3, Cul, and LiOTf (entries 10 and 11).

Next, we investigated briefly the scope of the TMSOTf-catalyzed glycosylation reaction with ortho-(methyltosylaminoethynyl)benzyl glucosides 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%) with complete β-selectivity (entries 1–4), testifying the participation of the neighbouring group in the glycosylation.14 Similarly, the couplings of 2,3,4-tri-O-benzoyl-l-rhamnopyranoside 1b with alcohols 5a–5d provided the corresponding α- and β-anomers in a fully stereoccontrolled manner in high yields (88–95%); entries 5–8). As expected, the corresponding glycosylation reactions of perbenzyl-glucopyranoside 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 5e as the acceptor were devoid of the addition of alcohol onto the ynamide moiety, therefore the unglycosylated 5e could be fully recovered.

In fact, the addition of alcohol onto the ynamide moiety became a serious problem when the alcohol to be glycosylated is highly reactive. Thus, the condensation of 1a with 4-penten-1-ol 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 glucosides 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
the keteniminium led to sugar oxocarbenium ion C and 1H-isochromene D which was indeed characterized (path a). Sugar oxocarbenium ion C underwent glycosylation in the presence of ROH to provide glycoside E. 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-(methyltosylaminoethyl)-benzyl glycoside donors are readily prepared from the ortho-iodobenzyl glycosides, which are inactive in the glycosylation reactions of the former, these donors could be applied to the expedient synthesis of oligosaccharides based on the ‘latent-active’ strategy. The previous donors applicable in the ‘latent-active’ synthesis of glycans include p-acetamidophenyl thioglycosides (vs. p-nitrophenyl thioglycosides), n-pentenyl glycosides (vs. 4,5-dibromopentyl glycosides), vinyl glycoside (vs. 1-methyl-2-propenyl glycosides), 2-(hydroxycarboxyl)benzyl glycosides (vs. 2-(benzoxycarboxyl)benzyl glycosides), and S-benzimidazolyl glycosides (vs. N-anisoylated S-benzimidazolyl glycosides). To demonstrate the feasibility of applying the present glycosylation protocol to the ‘latent-active’ assembly of glycans, the ‘active’ ortho-(methyltosylaminoethyl)-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→6)-disaccharide 9 (97%), which was then converted into the ‘active’ ortho-(methyltosylaminoethyl)benzyl disaccharide 10 via Sonogashira coupling with ynamide 4 (88%) (Scheme 4). Subsequent glycosylation of disaccharide 10 with cholesterol 5a or glucose-4-0H 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’ ortho-iodobenzyl glucoside acceptor 8 provided the ‘latent’ ortho-iodobenzyl 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-(methyltosylaminoethyl)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 expedient assembly of glycans via the ‘latent-active’ strategy using the present protocol has been demonstrated promising preliminary results shall warrant further elaboration and application of this new glycosylation method.

Financial support from the Ministry of Science and Technology of China (2012ZX09502-002), the National Natural Science Foundation of China (21432012), the Fundamental Research Funds for the Central Universities (WY1514052), and the Shanghai Pujiang Program (15PJ1401500) is gratefully acknowledged.

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