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An efficient glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors under the catalysis of $Ph_3PAuOTf$

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Abstract

A new and powerful glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors and $Ph_3PAuOTf$ as a promoter is disclosed. The donors are readily available and stable; the glycosidic coupling yields are generally excellent; the promotion system is catalytic, neutral, and orthogonal to the known glycosylation conditions.

Keywords: Glycosylation; Gold; Catalyst; Glycosides; *ortho*-Alkynylbenzoates; $Ph_3PAuOTf$

The continuous addition of various glycosylation methods, especially since 1980s, to the historical Koenigs–Knorr protocol has enabled the synthesis of oligosaccharides and glycoconjugates of increasing complexity in unprecedented effectiveness.[1,2] Not only the once formidable glycosylation problems have been addressed satisfactorily, such as the β-mannopyranoside synthesis,[3] but also the assembly of oligosaccharides and glycoconjugates could be achieved in an efficient 'programmable' manner by employing a set of the carefully designed glycosyl donors and acceptors,[4] such as the orthogonal glycosylation.[5] However, those glycosylation methods are mostly variants (e.g., variation in protecting pattern or activating system) of the still limited types of glycosyl donors with functional groups of disparate chemical nature at the anomeric position. The major ones include (1) glycosyl halides, (2) thioglycosides, (3) imidates, (4) phosphate/phosphite derivatives, (5) sulfoxides, (6) glycals, (7) 1-acyl-, 1-carbonate, and variants, (8) 4-pentenyl glycosides, (9) 1-hydroxyl sugars, (10) orthoesters, (11) 1,2-anhydrosugars, and (12) glycosyl diazirines.[2] Among them only glycosyl imidates and phosphate/phosphite derivatives are able to be activated for glycosidation with a catalytic amount of the promoters.[6] Development of new anomeric leaving groups capable of being activated (preferably catalytically) under new mechanisms (thus new glycosylation conditions orthogonal to the present ones) would raise the glycosidic coupling technique to a new height, where automated synthesis of oligosaccharides as efficient as the synthesis of nucleotides and peptides shall be implemented.[7]

In fact, no advantageous properties have been disclosed for glycosyl donors outside the above categories. A recent trial was the activation of propargyl glycosides with $AuCl_3$ for glycosidation.[8a] Unfortunately, acyl protected propargyl glycosides failed to glycosidation, and the coupling of the 'armed' propargyl per-benzylglucoside with a slightly less active acceptor (i.e., cholesterol) led to a low yield (39%) of the coupled product. Nevertheless, use of the C–C triple bond as an activating element to trigger the glycosidation is novel and could find orthogonal conditions to the conventional ones.[8,9] In addition, recent studies have shown that activation of C–C triple bonds could be highly

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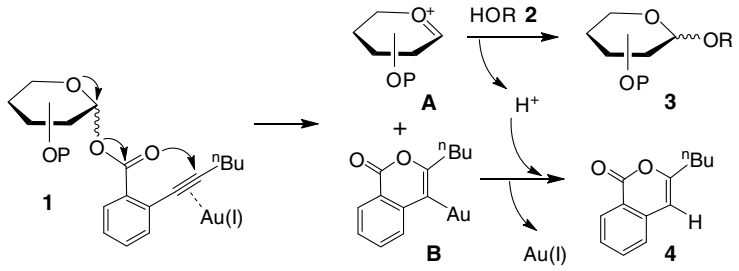


Scheme 1. Glycosylation with glycosyl *ortho*-hexynylbenzoates as donors under the catalysis of Au(I).

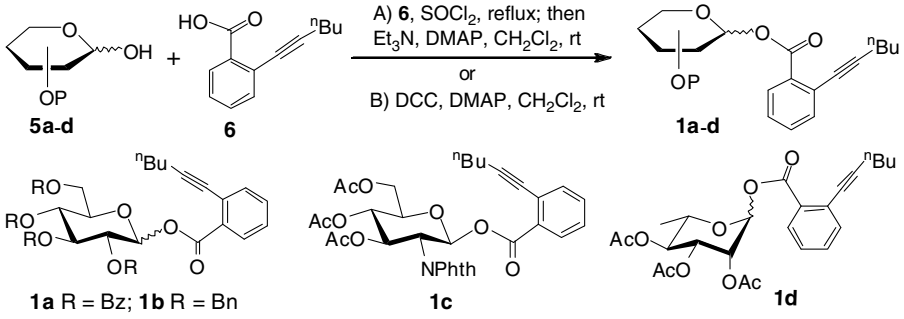
efficient with various cationic gold complexes, and those complexes, particularly Au(I) complexes, possess little oxophilic character, thus displaying good functional group compatibility and low air and moisture sensitivity.[10] We envisioned the position of the C–C triple bond installed in the anomeric group as a key element to determine the leaving property of the group and thus the efficiency of the new glycosylation protocol. Here we report a new and highly efficient glycosylation protocol with glycosyl *ortho*-hexynylbenzoates as donors and $Ph_3PAuOTf$ as a catalyst.

Our earlier studies showed that 4-pentynyl and 5-hexynyl glycosides (in analogy to the 4-pentenyl glycosides under the activation of iodonium species)[11] were almost inert under the action of gold complexes (e.g., $AuCl_3$ and $Ph_3PAuOTf$). Therefore, an inherently more active alkynyl group (toward the action of gold complexes) was desired to serve as the leaving group in the new glycosylation protocol. *o*-Alkynylbenzoate perfectly fits this requirement; and its leaving property (in the presence of $Ph_3PAuCl/AgOTf$) has just been demonstrated by Umetsu et al.[12] Thus, activation of the benzylic triple bond with Au(I) in glycosyl *o*-hexynylbenzoate **1** attracts nucleophilic attack of the proximal carbonyl oxygen, resulting in subsequently the cleavage of the glycosidic bond to give isocoumarin B and the sugar oxocarbenium A, which is the common intermediate for glycosidation (Scheme 1). Protonolysis of the Au–C bond in B regenerates the Au(I) catalyst; an additional merit of this catalytic cycle is the consumption of the proton (from alcohol **2**), leading to inherent neutral conditions for the reaction (to provide cleanly glycoside **3** and isocoumarin **4**).

The representative glycosyl *ortho*-hexynylbenzoates (**1a**–**d**) were readily prepared by condensation of the corresponding lactols (**5a**–**d**) with *o*-hexynylbenzoic acid (**6**)[13] in high yields (Table 1).[14] Depending on the type of lactols and the reaction conditions as well, a varied ratio of the α:β anomers was attained. However, experiments showed little difference (in accord with the glycosylation mechanism shown in Scheme 1) between the pair of anomers in glycosylation (e.g., Table 2, entry 4); thus the anomeric mixtures were not separated but directly used in the glycosylation reactions.

Exhilaratingly, the first trial in the coupling of per-benzoyl-D-glucopyranosyl *o*-hexynylbenzoate (**1a**, 1.2 equiv) with cholesterol (**2b**, 1 equiv) in the presence of $Ph_3PAuOTf$ (0.1 equiv)[15] and 4 Å MS in CH_2Cl_2 at rt has attained a very clean reaction within 2 h, leading to the desired

Table 1
Preparation of glycosyl *ortho*-hexynylbenzoates **1a** –**d**



Entry	Lactol	Ester	Conditions	Yield	β:α
1	**5a**	**1a**	A	80	1:2.2
2			B	95	1.4:1
3	**5b**	**1b**	A	81	1:2.5
4			B	98	1:1.4
5	**5c**	**1c**	A	69	β only
6			B	94	β only
7	**5d**	**1d**	A	83	1:12.4

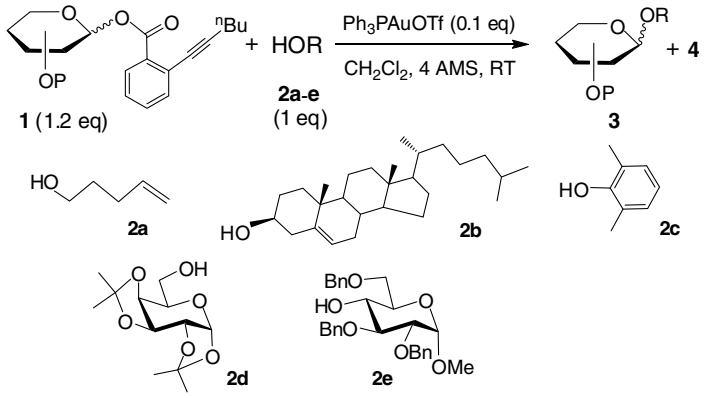
glycoside **3ab** and isocoumarin **4** in nearly quantitative yields (Table 2, entry 2). Thus, we were eager to see a scope of the present glycosylation protocol; the coupling results of the glucose-type donors **1a**–**c** with a panel of alcohols (**2a**–**e**) were listed in Table 1. Worth noting is that (1) the reactions were fast, those with the armed donor **1b** completed at ~0.5 h, and with the disarmed donors **1a** and **1c** completed within 3 h; (2) the reactions were clean; even in the cases of the glycosylation of the hindered 4-hydroxyl sugar derivative **2e** (entries 5, 10, and 15) where only good yields (63–81%) of the coupling products were obtained, the remaining acceptors could be largely recovered; (3) thioglycosides and 4-pentenyl glycosides remained intact; (4) a hindered phenol (**2c**)[16] as well as the aliphatic and sugar alcohols could be glycosylated in nearly quantitative yields (Scheme 2).

The utility of the present protocol was further demonstrated by the synthesis of a representative cytotoxic steroidal saponin, dioscin (Scheme 3).[17] Without modifying the reaction conditions, both the glycosidic coupling between **1a** and diosgenin (**7**) and the bis-glycosylation of the hindered glucopyranoside 2,4-diol **9** with per-acetyl-L-rhamnopyranosyl donor **1d** afforded the corresponding glycosides (**8** and **10**, respectively) in nearly quantitative yields.

Exploiting the new activation conditions that are orthogonal to the activation of the many known glycosyl donors, new versions of the one-pot synthesis of glycoconjugates shall be realized easily. An example is shown in Scheme 3, whereupon addition of the second acceptor (**7**) and promoter NIS to the coupling system of **1a** and thioglycoside **11** led to the steroidal disaccharide **12** in a good 70% yield. The combination of NIS and $Ph_3PAuOTf$ was shown (for the first time) to be effective for the promotion of the glycosidation of thioglycosides.

Summarizing, a glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors and $Ph_3PAuOTf$ as a promoter is disclosed. This new method has significant merits that chemists have been seeking after for a glycosylation reaction: (1) the glycosidic coupling yields are generally excellent; (2) the donors are readily available and stable; (3) the promotion is catalytic; (4) the promotion conditions are orthogonal to the others; (5) the reaction

Table 2
Glycosidic coupling of glycosyl *ortho*-hexynylbenzoates (**1**) with alcohols (**2**) under the catalysis of $Ph_3PAuOTf$[a]

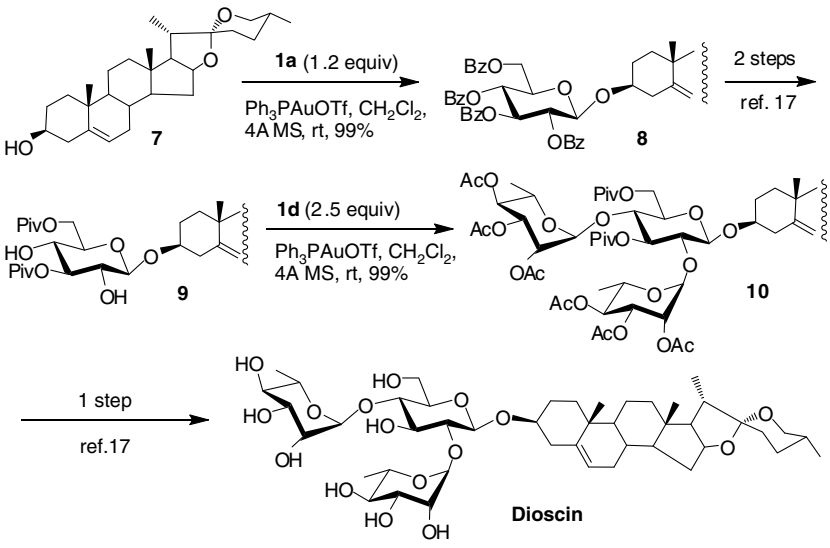


Entry	Donor	Acceptor	Product	Yield	β:α
1	**1a**	**2a**	**3aa**	98	β only
2		**2b**	**3ab**	98	β only
3		**2c**	**3ac**	97	β only
4[b]		**2d**	**3ad**	99	β only
5		**2e**	**3ae**	81 (98)[c]	β only
6	**1b**	**2a**	**3ba**	98	1:1.2
7		**2b**	**3bb**	98	1:1
8		**2c**	**3bc**	92	1:1.2
9		**2d**	**3bd**	99	1:1.4
10		**2e**	**3be**	71 (95)[c]	1:2
11	**1c**	**2a**	**3ca**	99	β only
12		**2b**	**3cb**	99	β only
13		**2c**	**3cc**	91	β only
14		**2d**	**3cd**	99	β only
15		**2e**	**3ce**	63 (93)[c]	β only

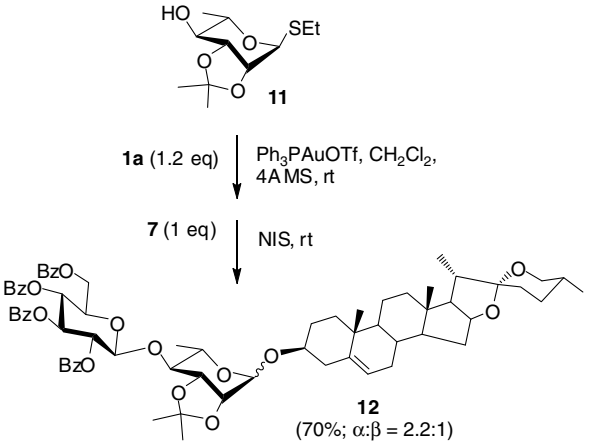
[a] For a typical procedure: To a stirred mixture of the glycosyl benzoate **1a** (94 mg, 0.12 mmol), cholesterol **2b** (39 mg, 0.1 mmol), and 4 Å MS in CH_2Cl_2 (2.5 mL) at rt was added a newly prepared $Ph_3PAuOTf$ in CH_2Cl_2 (0.02 M, 0.5 mL). After stirring at rt for 0.5–3 h (as monitored by TLC), the mixture was filtered through Celite, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc/CH_2Cl_2 12:1:1) to provide glycoside **3ab** as a white solid (96 mg, 98%).

[b] Using the pure α or β-anomer of **1a** in the reaction led to similar results.

[c] Yields based on the consumed acceptors.



Scheme 2. Synthesis of dioscin with glycosyl *ortho*-hexynylbenzoates as glycosylation donors.



Scheme 3. A 'one-pot' orthogonal glycosylation with glycosyl *ortho*-hexynylbenzoate and thioglycoside as donors.

conditions are mild and neutral; thus (6) side reactions are minimal. These excellent preliminary results shall warrant further elaboration and application of this new glycosylation technique.

Acknowledgments

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14. Compound **1a**-β: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–7.22 (m, 24H), 6.35 (d, 1H, $J = 7.8$ Hz), 6.03 (t, 1H, $J = 9.3$ Hz), 5.84 (m, 2H), 4.69 (dd, 1H, $J = 12.3$, 2.1 Hz), 4.53 (dd, 1H, $J = 12.0$, 4.2 Hz), 4.44 (m, 1H), 2.46 (t, 2H, $J = 6.6$ Hz), 1.61 (m, 2H), 1.49 (m, 2H), 0.94 (t, 1H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.00, 165.58, 165.04, 165.00, 163.29, 134.49, 133.43, 133.35, 133.24, 133.35, 133.00, 132.42,

130.76, 129.72, 129.68, 129.39, 129.04, 128.59, 128.54, 128.34, 128.31, 128.23, 127.13, 125.76, 97.26, 92.39, 78.89, 73.01, 72.83, 70.79, 68.90, 62.56, 30.54, 21.95, 19.42, 13.60. MALDI-HRMS: m/z $C_{47}H_{40}O_{11}$ $[M+Na]^+$ calcd 803.2463, found 803.2479. Compound **1b**-β: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.12 (m, 24H), 5.89 (d, 1H, $J = 6.6$ Hz), 4.91–4.76 (m, 5H), 4.60–4.44 (m, 3H), 3.84–3.62 (m, 6H), 2.47 (t, 2H, $J = 6.0$ Hz), 1.65–1.41 (m, 4H), 0.93 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.89, 138.36, 137.97, 137.88, 137.79, 134.59, 132.10, 130.59, 130.23, 128.38, 128.30, 128.01, 127.89, 127.88, 127.83, 127.76, 127.69, 127.65, 127.60, 127.00, 125.57, 97.02, 94.50, 84.85, 80.94, 79.15, 77.21, 75.69, 75.53, 75.00, 74.95, 73.42, 68.03, 30.65, 22.06, 19.55, 13.68. MALDI-HRMS: m/z $C_{47}H_{48}O_7$ $[M+Na]^+$ calcd 747.3292, found 747.3283. Compound **1c**-β: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.85 (m, 3H),7.69–7.73 (m, 2H), 7.36–7.46 (m, 2H), 7.22–7.27 (m, 1H), 6.72 (d, 1H, $J = 9.0$ Hz), 6.00 (dd, 1H, $J = 9.3$, 10.5 Hz), 5.27 (t, 1H, $J = 9.3$ Hz), 4.65 (dd, 1H, $J = 8.7$, 10.5Hz), 4.41 (dd, 1H, $J = 3.6$, 12.0 Hz), 4.09–4.18 (m, 2H), 2.45 (t, 2H, $J = 6.9$ Hz), 2.11 (s, 3H), 2.06 (s, 3H), 1.89 (s, 3H), 1.53–1.65 (m, 2H), 1.41–1.51 (m, 2H), 0.94 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.0, 169.5, 167.3, 162.9, 134.6, 134.3, 132.4, 131.1, 130.7, 129.0, 127.1, 125.8, 123.7, 97.4, 90.1, 78.8, 72.5, 70.4, 68.3, 61.5, 53.5, 30.5, 22.0, 20.7, 20.6, 20.4, 19.4, 13.6. MALDI-HRMS: m/z $C_{33}H_{33}NO_{11}$ $[M+Na]^+$ calcd 642.1941, found 642.1946. Compound **1d**-α: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.33 (m, 4H), 6.28 (d, 1H, $J = 1.5$ Hz), 5.47 (dd, 1H, $J = 10.5$, 3.6 Hz), 5.41 (m, 1H), 5.20 (t, 1H, $J = 9.9$ Hz), 4.12 (m, 1H), 2.51 (t, 1H, $J = 6.9$ Hz), 2.20 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.62 (m, 2H), 1.50 (m, 2H), 1.64 (d, 1H, $J = 6.0$ Hz), 0.95 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.65, 163.74, 134.83, 132.22, 130.62, 129.85, 127.20, 124.91, 96.82, 91.29, 79.40, 70.48, 68.84, 68.70, 68.61, 30.53, 21.96, 20.65, 20.53, 19.33, 17.33, 13.53. MALDI-HRMS: m/z $C_{25}H_{30}O_9$ $[M+Na]^+$ calcd 497.1782, found 497.1792.

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