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Regio- and Stereochemical Controlled Koenigs–Knorr-Type Monoglycosylation of Secondary Hydroxy Groups in Carbohydrates Utilizing the High Site Recognition Ability of Organotin Catalysts

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Abstract: The catalytic regio- and stereoselective monoglycosylation of carbohydrates using organotin catalysts is demonstrated. The one-step reaction affords various oligosaccharides linked at the secondary hydroxy group in high chemical yield and good regio- and stereoselectivities. The regioselectivity of the glycosylation is shown to depend on the spatial arrangement of the hydroxy groups in the carbohydrates.

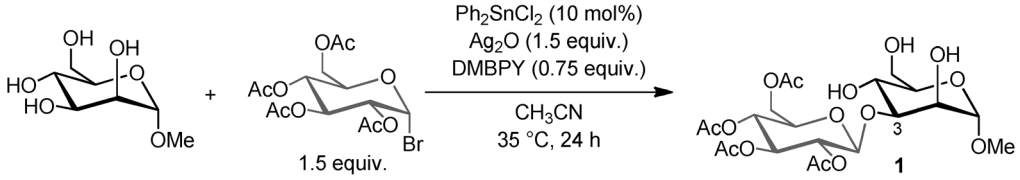
Keywords: glycosylation; oligosaccharides; organotin catalysts; regioselectivity; stereoselectivity

Oligosaccharide-containing glycoconjugates such as glycoproteins, glycolipids, and proteoglycans are ubiquitous in nature and play an important role in a wide range of biological processes, e.g., in modulating the activity, dynamic stability, and intracellular transportation of proteins.[1] Glycoconjugates are major components of the outer membrane of mammalian cells, and the oligosaccharide units play fundamental roles in intercellular processes including infection, cell growth, and cell-cell adhesion, etc.[2] Since the recent identification of the vital roles played by the oligosaccharide units in biologically interesting glycosides such as vancomycin and calicheamicin, there has been increased interest in the synthesis, biomechanism, and biological activities of these glycosides.[3] Carbohydrate-based surfactants with an oligosaccharide as the polar head group are widely used in industry. The amphiphilic surfactants help in the solubilization of membrane proteins by interacting with the hydrophobic sites of the proteins.[4]

Polyols are used as building blocks for the synthesis of natural products and new drugs.[5] However, the selective functionalization of polyols remains one of the most fundamental challenges. The non-enzymatic regioselective functionalization of the secondary hydroxy groups in carbohydrates is of particular interest because of the difficulty in functionalizing one specific hydroxy group from among the multiple groups present. Over the last few decades, various catalytic methods for the regioselective functionalizations including acylation and sulfonylation of carbohydrates have been developed.[6] In the case of glycosylation, Cruzado and a few groups reported the regioselective 6-*O*-glycosylation of carbohydrates by using stoichiometric quantities of Bu_2SnO.[7] However, we feel that the addition of Bu_2SnO is not necessary for 6-*O*-glycosylation because the nucleophilicity of primary hydroxy group is basically higher than that of secondary hydroxy group.[8] Most recently, Taylor reported the regioselective glycosylation of the secondary hydroxy groups in carbohydrates by using borinic acid as the catalyst. The method afforded high regio- and stereoselectivities for the synthesis of oligosaccharides. However, this method is not applicable to those carbohydrates bearing free primary hydroxy groups.[9] To the best of our knowledge, a widely applicable catalytic method for the regioselective glycosylation of secondary hydroxy groups in a variety of carbohydrates has not been reported so far.[7–11] Herein, we present the first catalytic regio- and stereoselective Koenigs–Knorr-type monoglycosylation of secondary hydroxy groups in carbohydrates by using organotin dichloride.

The effects of various reaction parameters and conditions on the efficiency of glycosylation at the C-3 OH of methyl α-D-mannopyranoside are summarized in Table 1. After a series of optimization experiments, we found that selective glycosylation at the C-3 OH of methyl α-D-mannopyranoside proceeded most efficiently in the presence of Ph_2SnCl_2 (10 mol%),

Table 1. Regio- and stereoselective glycosylation of methyl α-D-mannopyranoside catalyzed by Ph_2SnCl_2.



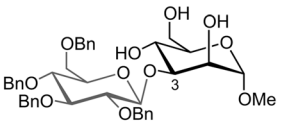
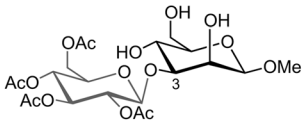
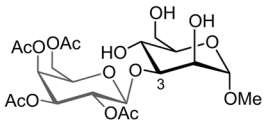
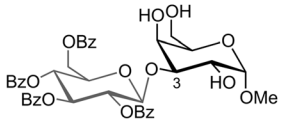
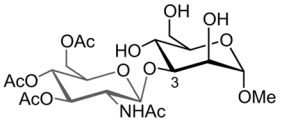
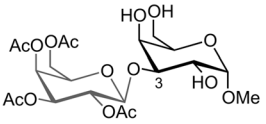
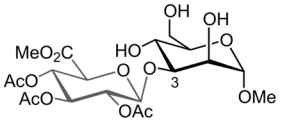
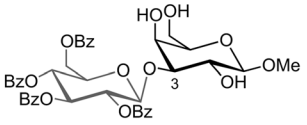
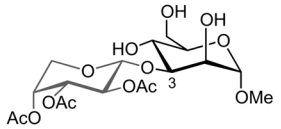
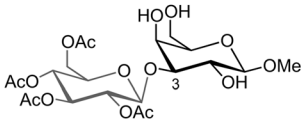
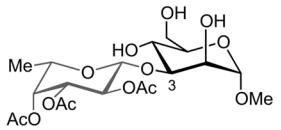
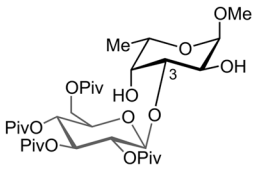
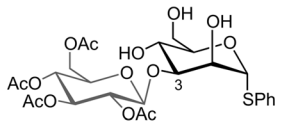
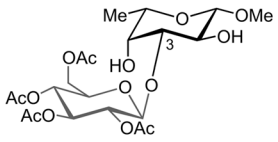
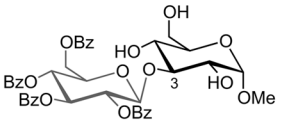
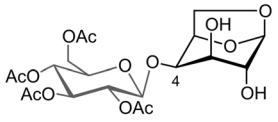
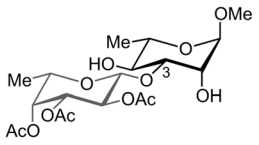
Entry	Variation from the "standard" conditions	Yield [%]
1	none	99
2	10 mmol-scale of α-D-Man	99
3	no Ph_2SnCl_2	0
4	no Ag_2O	0
5	no DMBPY	46 (2)[a]
6	Ph_2SnCl_2 (5 mol%), 48 h	62
7	Me_2SnCl_2, instead of Ph_2SnCl_2	40
8	Bu_2SnCl_2, instead of Ph_2SnCl_2	4
9	Oc_2SnCl_2, instead of Ph_2SnCl_2	5
10	Ph_2SnO, instead of Ph_2SnCl_2	40
11	Ph_2SnS, instead of Ph_2SnCl_2	75
12	$PhSnCl_3$, instead of Ph_2SnCl_2	93
13	Ph_3SnCl, instead of Ph_2SnCl_2	66
14	Ph_4Sn, instead of Ph_2SnCl_2	63
15	AgO, instead of Ag_2O	59
16	Ag_2CO_3, instead of Ag_2O	76
17	AgOTf, instead of Ag_2O	12 (29)[a]
18	$AgClO_4$, instead of Ag_2O	12 (34)[a]
19	AgF, instead of Ag_2O	<1
20	PEMP,[c] instead of DMBPY	71
21	pyridine,[c] instead of DMBPY	74
22	2,4,6-collidine,[c] instead of DMBPY	77
23	toluene, instead of CH_3CN	<1
24	DCM, instead of CH_3CN	26 (2)[a]
25	THF, instead of CH_3CN	60
26	1,4-dioxane, instead of CH_3CN	67
27	H_2O, instead of CH_3CN	15
28	α-D-Glc-F, instead of α-D-Glc-Br	0 (<1)[b]
29	α-D-Glc-Cl, instead of α-D-Glc-Br	0 (53)[b]
30	α-D-Glc-SPh, instead of α-D-Glc-Br	0 (2)[b]

[a] The yield of the orthoester.
[b] The reaction was carried out at 60 °C.
[c] 1.5 equiv. of base was added.

2,3,4,6-tetraacetyl-α-D-glucopyranosyl bromide (1.5 equiv.), Ag_2O (1.5 equiv.), and 5,5′-dimethyl-2,2′-bipyridyl (DMBPY, 0.75 equiv.) in CH_3CN at 35 °C (entry 1; 99% yield and no regio- and stereoisomers).

When the reaction was carried out on a 10 mmol scale, use of the catalyst for regioselective glycosylation resulted in excellent yield and selectivity (entry 2; 99% yield and no regio- and stereoisomers). In the absence of Ph_2SnCl_2 or Ag_2O, the reaction did not afford any product including the desired disaccharide **1** (entries 3 and 4). In the absence of DMBPY, **1** was obtained in 46% yield and the corresponding orthoester[7c,9,11a] was formed in 2% yield (entry 5). The use of smaller amounts of catalyst afforded **1** in lower yield (entry 6; 62% yield), as did the use of other dialkyltin dichlorides instead of Ph_2SnCl_2 (entries 7–9). When the glycosylation was conducted with 10 mol% of Ph_2SnO, Ph_2SnS or Ph_3SnCl instead of Ph_2SnCl_2, the desired disaccharide **1** was isolated in moderate yields (entries 10, 11 and 13). $PhSnCl_3$ could be employed in place of Ph_2SnCl_2, at the expense of a slight decrease in chemical yield (entry 12; 93% yield). Contrary to our expectations, the use of Ph_4Sn as a catalyst afforded **1** in 63% yield without formation of the regioisomers such as a Ac-β-D-Glc-(1→6)-α-D-Man-OMe (entry 14). The identity of the Ag salt used as the promoter was crucial to the success of this transformation. When Ag_2O was replaced with AgO or Ag_2CO_3, the yield of **1** decreased drastically (entries 15 and 16). On using silver(I) salts

Table 2. Regio- and stereoselective glycosylation of various carbohydrates.[a]

Entry	Product	Entry	Product
1[b,c]	 **2**: 80% (6%)[d]	9	 **10**: 91%
2[c]	 **3**: 95%	10[f,h,j]	 **11**: 60%
3[b,c,f-h]	 **4**: 88%	11[m]	 **12**: 90%
4[h-j]	 **5**: 75% (1%)[c]	12[c,f]	 **13**: 98% (<1%)[d]
5[k]	 **6**: 99%	13[i,m]	 **14**: 98%
6[f]	 **7**: 90% (2%)[d]	14[c,h]	 **15**: 65%
7[f,l]	 **8**: 81%	15[h]	 **16**: 81%
8[h,j]	 **9a**: 80% (<1%)[d]	16	 **17**: 96%
		17[f]	 **18**: >99%

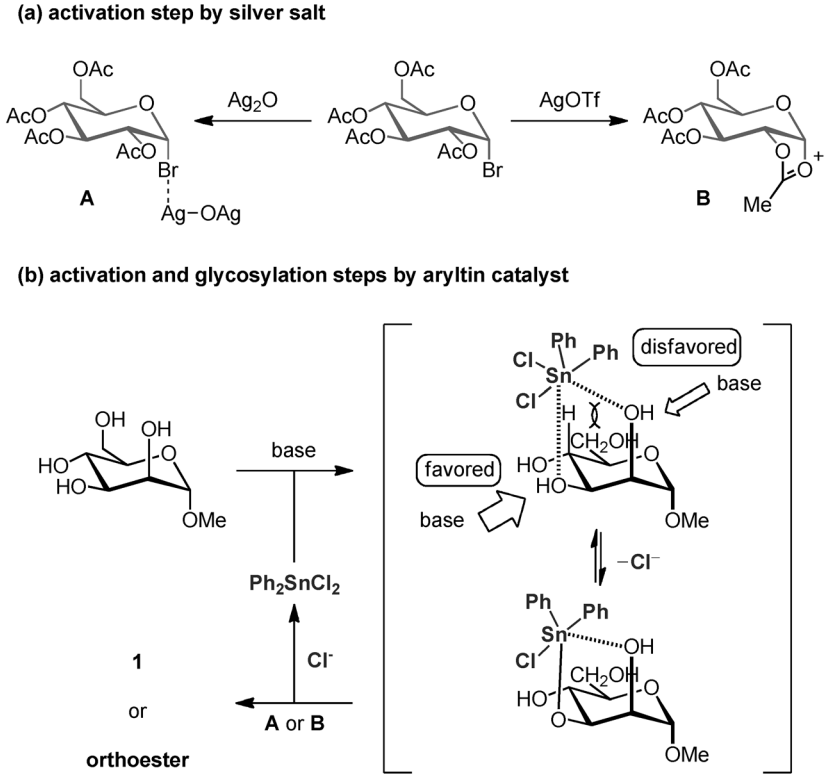
with stronger Lewis acidity, such as AgOTf and $AgClO_4$, **1** was obtained in only 12% yield, while the major product was the corresponding orthoester with yields of 29–34% (entries 17 and 18). AgF did not act as a promoter under these reaction conditions (entry 19). The use of 1,2,2,6,6-pentamethylpiperidine (PEMP), which we previously used in the regioselective functionalization of carbohydrates,[6d,e] instead of DMBPY gave **1** in 71% yield (entry 20). The reactions with pyridine and 2,4,6-collidine also afforded the product in good yield (entries 21 and 22). The reactivity of these bases was comparable to that of DMBPY. However, DMBPY by virtue of its bulkiness prevented the formation of trisaccharides. In less polar solvents such as toluene and DCM, the yields of **1** were markedly decreased (entries 23 and 24). On the other hand, the use of THF and 1,4-dioxane as the solvent in place of CH_3CN resulted in only a slight decrease in chemical yield (entries 25 and 26). Surprisingly, the catalytic reaction in H_2O afforded **1** in 15% yield along with deacylated **1** (entry 27). However, the formation of non-negligible amounts of trisaccharides (3–47% yield) could not be avoided when these silver salts, bases, and solvents under the present conditions (entries 17, 18, and 20–25). Next, we examined the scope of the catalytic regioselective monoglycosylation for various leaving groups of the glycosyl donor and attempted to find the best reaction conditions. Unfortunately, in the case of α-D-glucopyranosyl fluoride and α-D-thioglucopyranoside as the glycosyl donor, the glycosylation did not give any products including the desired disaccharide **1** under the conditions (entries 28 and 30). In contrast, α-D-glucopyranosyl chloride could act as good substitute for α-D-glucopyranosyl bromide (entry 29).

Based on the optimization studies, the functional group tolerance of the glycosyl donor is discussed below. Galactopyranosyl, arabinopyranosyl and fucopyranosyl halides underwent regio- and stereoselective glycosylation (entries 2 and 5–6, Table 2). Furthermore, substrates bearing benzyl, amino and ester groups were tolerated in the glycosylation reaction (entries 1 and 3–4). When phenyl α-D-thiomannopyranoside was used as the glycosyl acceptor, the reaction afforded the corresponding disaccharide **8** in 81% yield (entry 7). Based on these results, this catalytic system was used to differentiate between the primary and secondary hydroxy groups for a wide range of carbohydrates acting as a glycosyl acceptor. Monoglycosylation was observed only at *cis*-1,2-diol moieties, with an equatorial OH in derivatives of mannopyranoside (entry 9), galactopyranoside (entries 10–13 and 16), fucopyranoside (entries 14–15) and arabinopyranoside (entry 17) in high yield and excellent regioselectivity.

Importantly, the result corresponding to entry 1 clearly proved that this catalysis proceeded with excellent stereochemical control *via* an direct S_N2-type inversion mechanism, and not by neighboring group participation. On the other hand, the catalytic regioselective glycosylation of methyl α-D-glucopyranoside with 2,3,4,6-tetrabenzoyl-α-D-glucopyranosyl bromide selectively afforded Bz-β-D-Glc-(1→3)-α-D-Glc-OMe **9a** as the major product (entry 8)[12] and not the expected disaccharide, Bz-β-D-Glc-(1→2)-α-D-Glc-OMe **9b**.[10c] Furthermore, all the physical and spectroscopic data pertaining to disaccharide **19**, formed by deprotection of the Bz groups in **9a**, were in perfect accord with those of the previously reported methyl α-D-laminarabioside.[13] Then, when **9b** was treated under the same reaction conditions, we observed 1,2-shift of the glycosyl donor to transform **9b** into **9a**. It seems that **9a** is maybe thermodynamically more stable. However, the mechanism of 1,2-shift is still unclear.

The regio- and stereoselectivity of these glycosyl acceptors in this catalytic glycosylation can be explained as follows (Scheme 1). Coordination of Ph_2SnCl_2 with the *cis*-diol moieties in these glycosyl acceptors is favored after moving freely among diol moieties. As the coordination of metal ions increases the acidity of the hydroxy groups, even a weak base such as DMBPY is sufficient to induce deprotonation. Then, the an axial-H adjacent to the reacting axial-OH in the *cis*-1,2-diol moiety restricts the approach of

[a] For the reaction conditions as a standard, see Table 1.
[b] The reaction was carried out using the glycosyl chloride as a donor.
[c] The reaction was carried out at 60 °C.
[d] Isolated yield of the regioisomer.
[e] In THF/1,4-dioxane (1:2).
[f] In 1,4-dioxane.
[g] Ag_2O (2.0 equiv.) was used.
[h] The glycosyl acceptor was recovered in 6–31% yield.
[i] In THF.
[j] The reaction was carried out at 50 °C.
[k] DMBPY (0.65 equiv.) was used.
[l] Glycosyl donor (1.0 equiv.) and glycosyl acceptor (1.5 equiv.) were used.
[m] The reaction was carried out at 45 °C.

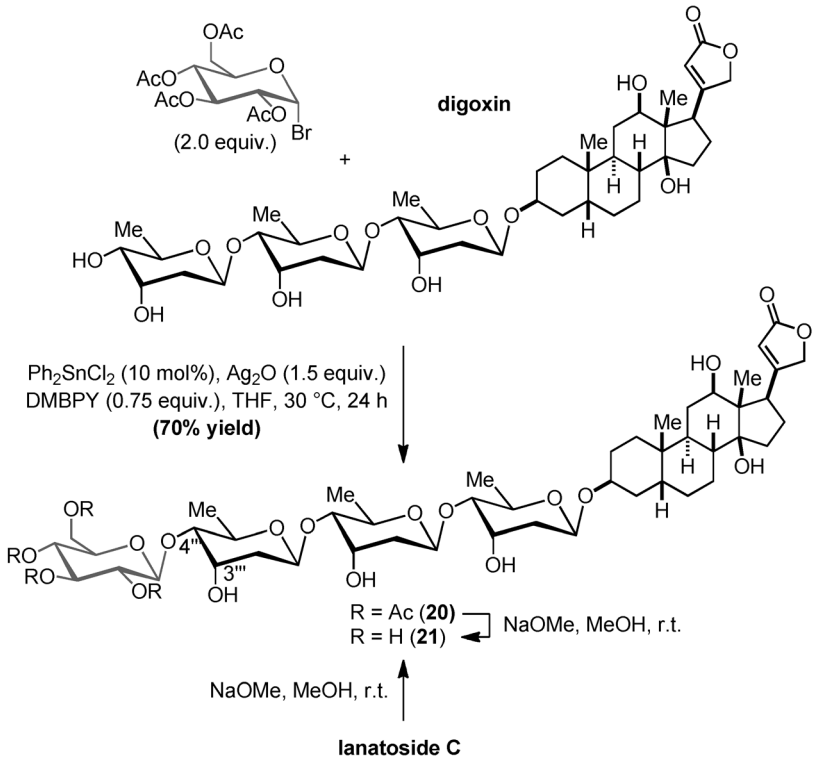


Scheme 1. Plausible explanation of the regio- and stereoselective glycosylation of carbohydrates.

DMBPY (1,3-diaxial interaction). Hence, the most accessible hydroxy group, which is the equatorial-OH, can be attacked by DMBPY. The glycosylation reaction, which proceeds *via* intermediate **A** generated from the coordination of the glycosyl donor with Ag_2O, results in **1** with stereoinversion at the anomeric position of the glycosyl donor. In contrast, the use of Ag(I) salts with stronger Lewis acidity such as AgOTf yields the orthoester *via* the intermediate **B**. Another possible mechanism is *via* concerted reaction. The result obtained when using Ph_4Sn as the catalyst (entry 14, Table 1) indicates that the nucleophilic substitution by the equatorial OH and the deprotonation at the equatorial-OH may occur concertedly. A similar mechanism for the S_N2-type glycosylation was proposed by Taylor.[9]

Catalytic regioselective functionalization of natural products containing multiple hydroxy groups has attracted much interest in recent years. For instance, Kawabata and Taylor recently reported regioselective acylation and glycosylation of cardiac glycosides, respectively, with excellent yields and selectivities.[5d,f] Therefore, we applied our protocol to the regio- and stereoselective monoglycosylation of a naturally occurring compound containing five secondary hydroxy groups and one tertiary hydroxy group. Treatment of digoxin with 2,3,4,6-tetraacetyl-α-D-glucopyranosyl bromide (2.0 equiv.), Ag_2O (1.5 equiv.), and DMBPY (0.75 equiv.) in the presence of Ph_2SnCl_2 (10 mol%) in THF at 30 °C for 24 h gave the oligosaccharide **20** in 70% yield. Then deprotection of the Ac groups in **20** was accomplished upon treatment with NaOMe in MeOH to provide compound **21** in 89% yield. The compound **21** showed mp 228–231 °C, $[\alpha]_D^{19}$: +12.6 (*c* 0.51, EtOH) {lit[14a] mp 220–231 °C, lit[14b] $[\alpha]_D^{20}$: +12 (*c* 1.08, EtOH)}. Additionally, the physical and spectroscopic data for **21** agreed well with those for the bioactive cardiac glycoside, deslanoside (deacetyl-lanatoside C),[15] obtained by methanolysis[16] of an Ac group at C-3‴ in commercially available lanatoside C (Scheme 2).

In conclusion, a catalytic one-step process for the monoglycosylation of secondary hydroxy group in carbohydrates with high yield and excellent regioselectivity was developed. This facile methodology can be applied to a wide range of carbohydrates, including those containing highly reactive free primary hydroxy groups. This significantly expands the scope of this reaction to include a great variety of oligosaccharides without the formation of regioisomers in the minimum number of steps. The regio- and stereoselectivity of the glycosylation depend on the spatial arrangement of the hydroxy groups in the carbohydrate. The proposed reaction allows for the direct functionalization of natural products including carbohydrates and provides new insight into polyol-metal ion interaction and its activation process. The scope, applications,



Scheme 2. Regio- and stereoselective glycosylation of digoxin.

and mechanism of this reaction are currently under investigation.

Experimental Section

Typical Procedure

After stirring the mixture of methyl α-D-mannopyranoside (97.1 mg, 0.5 mmol) and diphenyltin dichloride (17.2 mg, 0.05 mmol) in CH_3CN (10 mL) in a brown vial at room temperature for 10 min, silver oxide (173.8 mg, 0.75 mmol), 5,5′-dimethyl-2,2′-bipyridyl (69.1 mg, 0.375 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (308.4 mg, 0.75 mmol) were added to the suspension at room temperature. After stirring vigorously for 24 h at 35 °C, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with a few drops of saturated aqueous NH_4Cl, diluted with chloroform/acetone (1/1), and then filtered to remove insoluble salts. After the solution was evaporated, the residue was purified by SiO_2 column chromatography (chloroform/methanol 99/1–90/10) to give methyl 3-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranoside **1** as a white solid; yield: 259.2 mg (99%).

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