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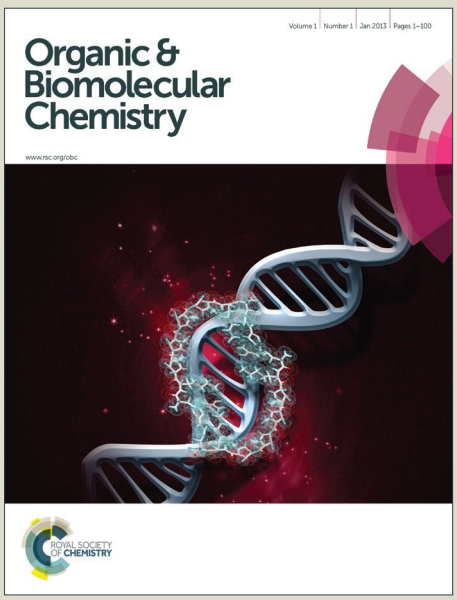

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Direct Synthesis of C-Glycosides from Unprotected 2-*N*-Acyl-Aldohexoses via Aldol Condensation-oxa-Michael Reactions with Unactivated Ketones

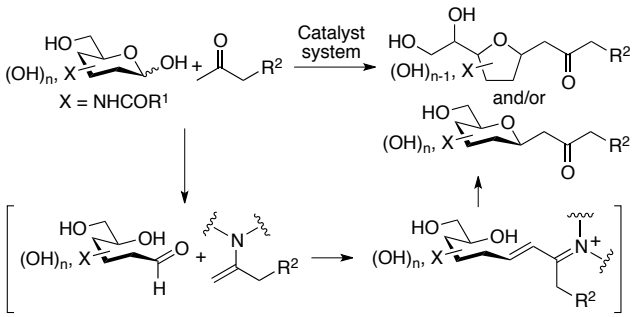
Sherida Johnson[a] and Fujie Tanaka*[a]

C-glycosides are important compounds as they are used as bioactive molecules and building blocks. We have developed methods to concisely synthesize C-glycosides from unprotected 2-*N*-acyl-aldohexose and unactivated ketones; we designed aldol-condensation-oxa-Michael addition reactions catalyzed by amine-based catalysts with the use of additives. Depending on the conditions used, C-glycosides were stereoselectively obtained. Our methods allowed the C-C bond formations at the anomeric centers of unprotected carbohydrates under mild conditions to lead the C-glycosides in atom- and step-economical ways.

Introduction

Methods for the C-C bond formation at the anomeric centers of unprotected carbohydrates are necessary to provide concise access to C-glycosides, glycoconjugates, carbon chain-elongated carbohydrates, and related compounds.[1-3] These molecules are used as therapeutics, bioactives, bioactive candidates, probes, synthons, and building blocks.[1-3] Some pioneering chemical (i.e., non-enzymatic) methods for the C-C bond formation at the anomeric carbons or hemiacetal carbons of unprotected carbohydrates have been reported; these include reactions of unprotected carbohydrates, directly or via in situ-formed imines/iminium ions, with nucleophiles.[4,5] However, the reactions are relatively limited.[4-6] The reactions of unprotected aldohexoses that form 6-membered hemiacetals have been less demonstrated.[2,4-6] Especially, reactions of 2-*N*-acyl-substituted C6-carbohydrates (such as *N*-acetyl-D-mannosamine and *N*-acetyl-D-glucosamine) have rarely been included in the reported examples in spite of the importance of the products. Here we report direct C-C bond formation at the anomeric carbon of unprotected 2-*N*-acyl-C6-aldopyranoses with unactivated ketones to give C-glycosides (Scheme 1).

Our design to generate the C-glycosides involves aldol condensations of unprotected carbohydrates with simple ketones such as acetone, followed by oxa-Michael cyclization. To prepare this type of C-glycosides, reactions were previously performed with 1,3-diketones via Knoevenagel condensation followed by elimination of the acyl group.[5d-i] There have been no reports of direct, non-enzymatic reactions of unprotected aldohexoses, that form 6-membered cyclic hemiacetals, with unactivated ketones.[5j] Note that 6-membered hemiacetals are usually stable; usually no reactions on the anomeric centers proceed.[7] To perform the reactions of unmodified 2-*N*-acyl-aldopyranoses with unactivated ketones, we designed strategies that use amine-based catalysts to generate enamines of the ketones and simultaneously that provide interactions for the carbohydrates to open the cyclic hemiacetals to generate the aldehyde groups, by mimicking enzyme strategies.

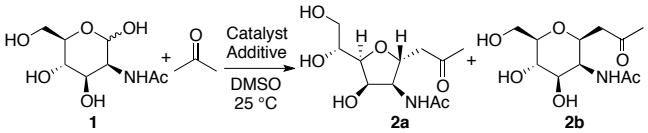


Scheme 1. C-C Bond forming reactions at the anomeric carbon of unmodified aldopyranoses to lead to C-glycosides.

Results and discussion

We first investigated reactions of *N*-acetyl-D-mannosamine (**1**) with acetone. Before testing enzyme-mimicking strategies, we started to perform the reaction under commonly used enamine-based catalysis conditions. Selected reaction conditions tested and the results are shown in Table 1. When L-proline was used as the catalyst,[8] product **2a** was obtained although the yield was very low (entry 1). On the other hand, in the presence of D-proline as the catalyst, **2** was not obtained (entry 2). For these reactions, carbohydrate **1** was mostly remained as unreacted. The proline catalysis conditions,[8] widely used for aldol reactions of aldehydes and acetone, did not efficiently catalyze the reactions of **1**. When amines were used as additives to the L-proline-catalyzed reaction, depending on amine additive, reaction rates and product stereoselectivities varied (entries 3-6). We expected the amine additives to act as a base in the formation of the enamines with the proline. In addition, the amine additives may be protonated and act as acids. We also expected that addition of amines would make the reaction conditions more basic to promote the formation of the aldehyde from the hemiacetal.[9] With *N*,*N*-diisopropylethylamine (DIPEA) additive, 5-membered C-glycoside **2a** was obtained in reasonable yield (62%) with an excellent diastereoselectivity (>10:1) after 4 days (entry 6). The structure of C-glycoside **2a** was confirmed by X-ray crystal structure analysis.[10]

Table 1. Reaction of *N*-acetyl-D-mannosamine (**1**) with acetone to afford **2**.[a]

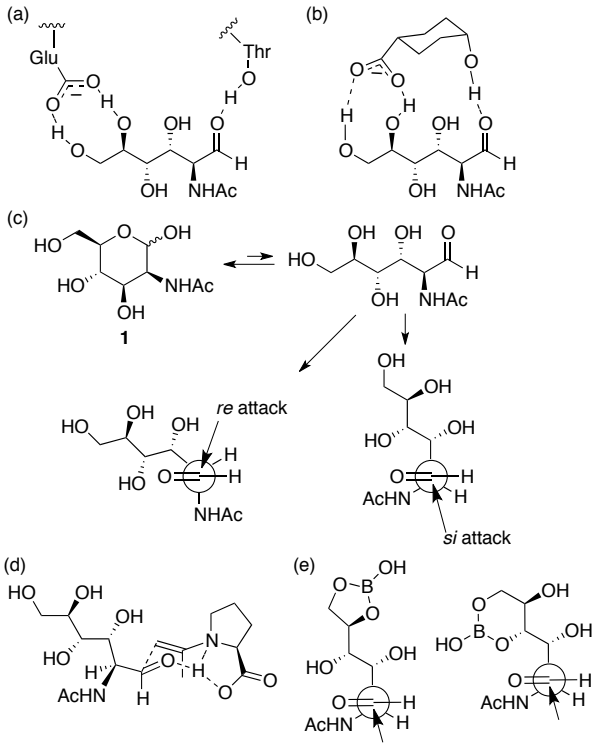


Entry	Catalyst	Additive[b]	Time (h)	Yield (%)[c]	Ratio **2a**:**2b**
1	L-Proline	none	24	6	>10:1
2	D-Proline	none	24	nd	-
3	L-Proline	Et_3N	96	31	3:1
4	L-Proline	EDA	96	54	3:1
5	L-Proline	TMEDA	120	28	9:1
6	**L-Proline**	**DIPEA**	**96**	**62**	**>10:1**
7	D-Proline	DIPEA	96	nd	-
8	Pyrrolidine + CH_3COOH	DIPEA	96	nd	-
9	none	DIPEA	96	nd	-
10	L-Proline	DIPEA	48	27	>10:1
11[d]	L-Proline	DIPEA	48	82	1:1
12[e]	**L-Proline**	**DIPEA + 3**	**48**	**44**	**>10:1**
13[e]	D-Proline	DIPEA + **3**	48	nd	-
14[e]	L-Proline	DIPEA + **4**	48	12	>10:1
15[e]	L-Proline	DIPEA + CH_3COOH	96	29	2:1
16[e]	L-Proline	DIPEA + H_3BO_3	48	29	1:>10
17	L-Proline	DBU	96	59	1:>10
18[f]	**Pyrrolidine**	**H_3BO_3**	**24**	**57**	**1:>10**
19	Pyrrolidine	DBU	96	13	-
20	Pyrrolidine	none	24	nd	-
21[f]	none	H_3BO_3	24	nd	-

[a] Reaction conditions: *N*-Acetyl-D-mannosamine (**1**) (0.4 mmol, 1.0 equiv), acetone (0.6 mL, 8 mmol, 20 equiv), catalyst (0.2 mmol, 0.5 equiv), and amine additive (if added, 0.2 mmol, 0.5 equiv) in DMSO (1.0 mL), at 25 °C, except noted. [b] Additives: EDA = ethylenediamine, TMEDA = tetramethylethylenediamine, DIPEA = *N*,*N*-diisopropylethylamine, compound **3** = *cis*-4-hydroxycyclohexanecarboxylic acid, compound **4** = *trans*-4-hydroxycyclohexanecarboxylic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [c] Isolated yield; nd = formation of **2** was not detected. [d]

Reaction at 40 °C. [e] DIPEA (0.6 mmol, 1.5 equiv) and acid additive (0.4 mmol, 1.0 equiv). [f] H_3BO_3 (0.4 mmol).

Both the L-proline and DIPEA were essential for the catalysis: Use of D-proline or pyrrolidine-acetic acid instead of L-proline or no pyrrolidine-based catalyst in the presence of DIPEA did not give the aldol product (entries 7-9). Whereas the L-proline catalyzed reaction with DIPEA afforded **2a**, the reaction needed 4 days to give the product in a reasonable yield; the reaction for 48 h only gave the product in a low yield (entry 10). Heating at 40 °C resulted faster reaction than the reaction at 25 °C, but the stereoselectivity was eroded (entry 11).



Scheme 2. (a) A schematic representation of interactions, observed in an X-ray crystal structure, between the aldehyde form of *N*-acetyl-D-mannosamine (**1**) and enzyme *N*-acetylneuraminic acid lyase (a mutant with low catalytic activity to obtain the ligand complex) that catalyzes reversible condensation between pyruvates and **1**.[11] (b) A proposed interactions between the aldehyde form of **1** and additive acid **3**. (c) *Re*- and *si*-attacks on the aldehyde generated from carbohydrate **1**. (d) A plausible transition state catalyzed by L-proline for the C-C bond forming step, in which the enamine attacks *re*-face of the aldehyde. (e) Proposed role of boric acid in the reaction.

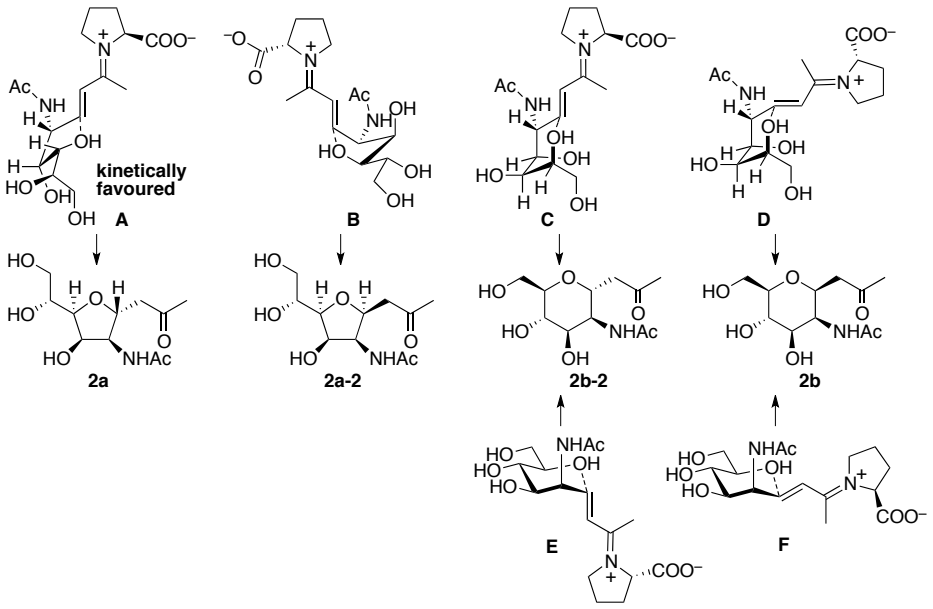
It has been suggested that an enzyme that catalyzes the aldol reaction of **1** (and the retro-aldol reaction of *N*-acetylneuraminic acid) binds the aldehyde form of **1** using the carboxylate of a glutamic acid residue and a threonine hydroxy group during the catalysis (Scheme 2a).[11] Although the complex structure has been discussed as the result of the retro-aldol reaction and has not been explained for the corresponding aldol reaction, we interpret that the aldehyde-bound crystal structure suggests that formation of the aldehyde form is one of the factors for accelerating the aldol reaction by the enzyme. Based on this consideration, we tested additives to provide similar interactions to those observed in the enzyme complex for increasing the formation of the aldehyde to accelerate the reaction (Scheme 2b). The reaction using L-proline as the catalyst in the presence of DIPEA and *cis*-4-hydroxycyclohexanecarboxylic acid (**3**) gave product **2a** in reasonable yield in shorter reaction time than that in the absence of additive **3** (entry 12 versus entry 10). The reaction in the presence of L-proline, DIPEA, and acid **3** was faster at the initial stage of the reaction than

the reaction in the presence of only L-proline and DIPEA (entry 12 versus entry 10). The high stereoselectivity to give **2a** was retained in the reaction. In contrast, use of *trans*-4-hydroxycyclohexanecarboxylic acid (**4**) or acetic acid instead of **3** was not effective to give **2** (entry 12 versus entries 14 and 15). These results indicate that compound **3** provide specific interactions with **1** to enhance the reaction, although exact roles of **3** needs to be determined.

The stereochemistry of product **2** may be determined at the oxa-Michael step, but, the reaction rate of the formation of product **2** may be affected by the rate of the initial nucleophilic attack of the enamine on the aldehyde group. Proline stereochemistry was also important to accelerate the reaction under the conditions with **3** (entry 12 versus entry 13); the most favoured transition state for the C-C bond formation at the aldol step may be involved in the re-attack to the aldehyde by the acetone enamine with L-proline[8] (Scheme 2c, d). Addition of **3** may increase the aldehyde form of carbohydrate **1** without altering the transition state of the C-C bond-forming reaction on the aldehyde group. The aldol condensation product, an intermediate that affords **2**, may also be generated by a Mannich route; in this case, the aldehyde generated from the hemiacetal may form an iminium ion with proline before the C-C bond formation.[12]

We also tested boric acid as an additive in the L-proline catalysis with DIPEA. In this case, the major product was altered; 6-membered β-C-glycoside **2b** was obtained as the major product (entry 16). Boron derivatives have been used to form B-O covalent bonds with unprotected carbohydrates.[13] We propose that the B-O bond formation also mimics the enzyme's role to generate the aldehyde group from the hemiacetal (Scheme 2e). The reaction catalyzed by pyrrolidine-boric acid also afforded **2b** as the major product isomer (entry 18). Reactions using pyrrolidine alone or boric acid alone as catalyst did not give **2** nor the corresponding aldol product (entries 20 and 21). When the amine additive was DBU in the L-proline catalysis, the major product was also **2b** (entry 17).

For the reaction of **1** to generate **2a**, the best conditions tested include the catalysis by L-proline with DIPEA at 25 °C when 4 days reaction time is acceptable (entry 6). To obtain **2a** in reasonable yield in 2 days, the best condition was the catalysis by L-proline with DIPEA and **3** at 25 °C (entry 12). To obtain **2b**, the best condition was the catalysis by pyrrolidine-boric acid at 25 °C (entry 18).

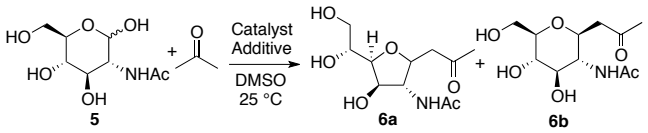


Scheme 3. Plausible transition states to afford **2** via oxa-Michael reactions. Under the catalysis by the proline-DIPEA (with or without **3**), transition state **A** may be most favoured.

Plausible transition states to afford **2a** and **2b** from the aldol condensation product via oxa-Michael reactions[14] are shown in Scheme 3. In transition states **A**, **B**, **C**, and **D**, the C-N bond of the CNHAc overlaps with the C-C double bond π-system; this may favour the oxygen nucleophilic attack stereoelectronically. In transition states **E** and **F**, there is no such overlap. In proline catalysis with DIPEA (with or without **3**), transition state **A** that leads to **2a** may be stereoelectronically and sterically more favoured than transition state **B** leading to **2a-2** and other transition states leading to 6-membered products **2b** and **2b-2**. Transition state **B** may be less favoured than **A** because of the pseudo axial positions of the C-C double bond and of a hydroxy group. Under the pyrrolidine-boric acid conditions, **2b** may be formed by thermodynamic control by isomerization of **2a** through a reversible ring opening and closing. In fact, when **2a** was treated with the pyrrolidine-boric acid catalysis conditions, **2a** was completely converted to **2b**.

Next, the reaction of *N*-acetyl-D-glucosamine (**5**) with acetone was investigated. Selected results are shown in Table 2. Whereas the reaction of **1** with acetone worked with L-proline catalysis to afford product **2** (Table 1, entry 1 versus entry 2), reaction of **5** to give product **6** worked under D-proline catalysis (Table 2, entry 2 versus entry 1). The reaction of glucosamine derivative **5** with acetone under the D-proline-DIPEA catalysis gave product **6a** and **6b**, but was difficult compared to the reaction of mannosamine derivative **1** using L-proline-DIPEA catalysis (Table 2, entry 4 versus Table 1, entry 6). Addition of additive acid **3** was not effective for the reaction of **5** (Table 2, entry 5). Depending on the stereochemistry of the reactant carbohydrate, suitable additive molecules that generate the aldehyde group may be different. Gluco-type carbohydrates may be more difficult to open the cyclic hemiacetal to generate the aldehyde group than manno- and other types of carbohydrates.[15] On the other hand, pyrrolidine-boric acid catalysis worked well to afford product **6b** (Table 2, entries 6-7). The structure of **6b** was confirmed by X-ray crystal structure analysis.[10]

Table 2. Reaction of *N*-acetyl-D-glucosamine (**5**) with acetone to afford **6**.[a]



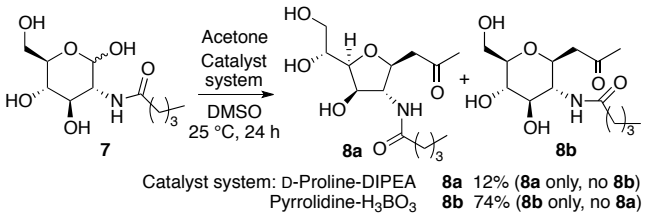
Entry	Catalyst	Additive	Time (h)	Yield (%)[b]	Ratio **6a**: **6b**
1	L-Proline	none	24	nd	-
2	D-Proline	none	24	4	-
3	L-Proline	DIPEA	96	nd	-
4[c]	D-Proline	DIPEA	96	2	-
5[d]	D-Proline	DIPEA + **3**	96	nd	-
6[e]	Pyrrolidine	H_3BO_3	24	22[f]	>10:1
7[g]	Pyrrolidine	H_3BO_3	24	68	1:>10
8[g]	none	H_3BO_3	24	nd	-

[a] Reaction conditions: *N*-Acetyl-D-glucosamine (**5**) (0.45 mmol, 1.0 equiv), acetone (0.66 mL, 9.0 mmol, 20 equiv), catalyst (0.23 mmol, 0.5 equiv), and amine additive (if added, 0.23 mmol) in DMSO (1.0 mL), at 25 °C, except noted. [b] Isolated yield; nd = formation of **6** was not detected. [c] Three times-scale reaction. [d] DIPEA (1.5 equiv to **5**) and **3** (1 equiv to **5**). [e] H_3BO_3 (1 equiv to **5**). [f] Six times-scale reaction. [g] H_3BO_3 (2 equiv to **5**).

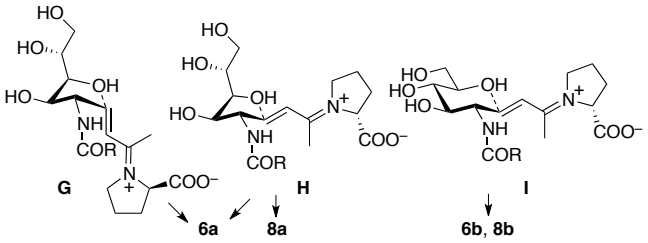
When *N*-valeryl-D-glucosamine (**7**) was used for the D-proline-catalyzed reaction in the presence of DIPEA, product **8a** was obtained as a single diastereomer, and the reaction of **7** under pyrrolidine-boric acid condition selectively gave **8b**.

In the reaction of **5** to yield **6** (Table 2, entry 4), transition states **G**, **H**, and **I** may be used. In transition states **G** and **H**, the $CH(OH)CH_2OH$ group is at the pseudo-axial position;

because of this, transition states **G** and **H** leading to 5-membered product **6a** may not be as kinetically favoured than transition state **I** leading to 6-membered product **6b**. In the reaction of **7**, which has a bulkier acyl group than **5**, hemiacetal ring opening may be faster than for **5**, resulting the formation of product **8a** from **7** in better yield than the formation of **6a** from **5**. Because of the bulky acyl group of **7**, for the reaction of **7**, transition state **H** may be more favoured than transition state **G**. Under the pyrrolidine-boric acid catalysis in which boric acid was sufficiently used, the reaction of **5** or of **7** gave thermodynamically stable 6-membered product **6b** or **8b**, respectively.

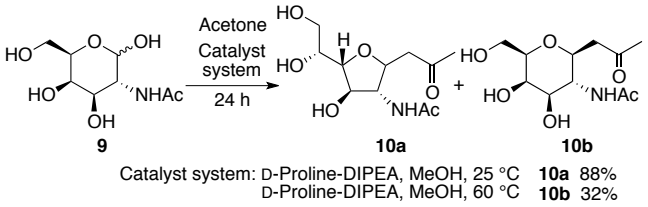


Scheme 4. Reactions of *N*-valeryl-D-glucosamine (**7**) to afford **8**.



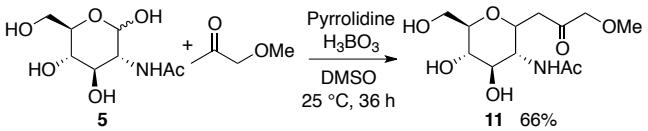
Scheme 5. Plausible transition states for the formation of **6** and **8**.

Reaction of *N*-acetyl-D-galactosamine (**9**) with acetone also provided product **10a** under the D-proline-DIPEA catalysis at 25 °C, and product **10b** was formed when the reaction was performed at 60 °C (Scheme 6).



Scheme 6. Reaction of *N*-acetyl-D-galactosamine (**9**) to afford **10**.

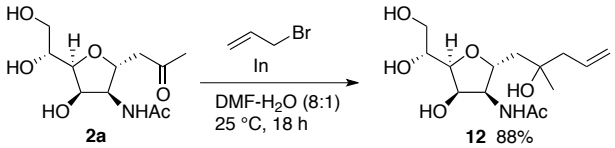
Reactions with ketones other than acetone also gave the corresponding C-glycosides. For example, C-glycoside **11** was synthesized from **5** and methoxyacetone (Scheme 7).



Scheme 7. Reaction of **5** with methoxyacetone to afford **11**.

Further, C-glycosides were transformed with retaining the C-glycoside structures. For example, compound **12** was synthesized by allylation of **2a** (Scheme 8) (See Supporting Information for additional transformations). As ketone-moiety-bearing C-glycosides have been used for syntheses of many C-glycoside derivatives and related molecules,[16] our

methods to synthesize C-glycosides reported here can aid to provide easy access to those molecules and related molecules.



Scheme 8. Transformation of **2a**.

Conclusions

We have developed methods to synthesize C-glycosides from unprotected carbohydrates and unactivated ketones under mild conditions via the C-C bond formation at the anomeric carbon of the carbohydrates. These reactions are atom- and step-economical. Depending on the carbohydrate and the conditions used, 5- and 6-membered C-glycosides were synthesized in highly stereoselective manners. Our strategies allowed access to C-glycosides that were unable to be synthesized by the previously reported methods. We are investigating the roles of the components of the catalyst systems used for the reactions. We are also expanding our strategies to synthesize a series of C-glycosides from unprotected carbohydrates. These results will be reported in due course.

Acknowledgements

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Notes and references

[a] Chemistry and Chemical Bioengineeing Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan.
E-mail: ftanaka@oist.jp

† Electronic Supplementary Information (ESI) available: Synthesis and characterization of compounds, X-ray crystal structures of compounds **2a** and **6b**. See DOI: 10.1039/x0xx00000x

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