Highlight Review

Nonenzymatic Regioselective Acylation of Carbohydrates

Takeo Kawabata* and Takumi Furuta

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Abstract

A nonenzymatic one-step procedure for the chemo- and regioselective acylation of carbohydrates has been developed. With 1 mol % of an organocatalyst, acylation of octyl β-D-glucopyranoside took place preferentially on the secondary hydroxy group at C(4) among four hydroxy groups including the primary hydroxy group at C(6) in 99% selectivity and in 98% yield. This could be alternatively achieved by a conventional protection/deprotection procedure via five steps and in 46% overall yield. Thus, development of the present process is expected to contribute to extremely shorten synthetic steps of carbohydrates.

♦ Introduction

Carbohydrates are involved in a wide range of intercellular processes including infection, metastasis, differentiation, and regulation of signaling.[1] In order to clarify the mechanisms of these events and to develop new therapeutics, chemical synthesis of carbohydrates is indispensable. However, synthetic methods of carbohydrates have been relatively unexplored. Multistep protection/deprotection procedures are usually required for their synthesis because of the lack of a direct method for the chemo- and regioselective manipulation of one of the multiple hydroxy groups of carbohydrates.[2] Here we describe an organocatalytic one-step procedure for the chemo- and regioselective acylation of carbohydrates. The present method enables direct functionalization of one of the multiple hydroxy groups of carbohydrates in up to >99% regioselectivity. With 1 mol % of an organocatalyst,[3] acylation of octyl β-D-glucopyranoside took place preferentially on the secondary hydroxy group at C(4) among four hydroxy groups including the primary hydroxy group at C(6) in 99% selectivity and in 98% yield (Figure 1a). This could be alternatively achieved by a conventional protection/deprotection procedure via five steps and in 46% overall yield (Figure 1b). Thus, this catalyst is able to discriminate one out of four hydroxy groups in different microenvironment, and promote acylation exclusively on the intrinsically less reactive hydroxy group, and it enables the performance of conventionally difficult molecular transformation via fine molecular recognition of substrate structure.

♦ Recent Progress on Selective Acylation of Carbohydrates

Selective manipulation of one of the multiple hydroxy groups of carbohydrates has been a fundamental challenge in organic synthesis. For example, selective acylation of a primary hydroxy group in the presence of three secondary hydroxy

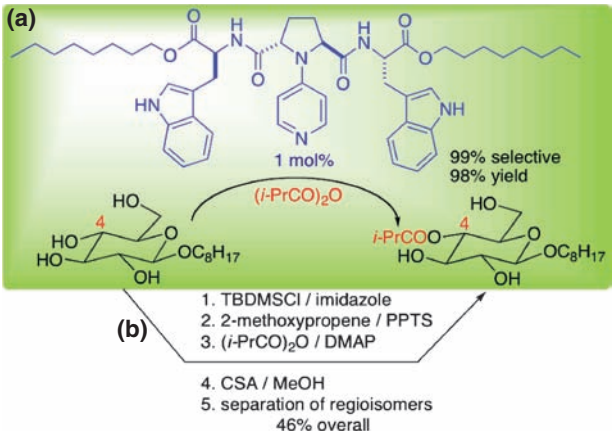
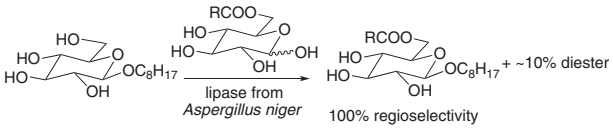


Figure 1. (a) A catalytic one-step process and (b) a conventional five-step procedure for the introduction an acyl group into C(4)–OH of octyl β-D-glucopyranoside.



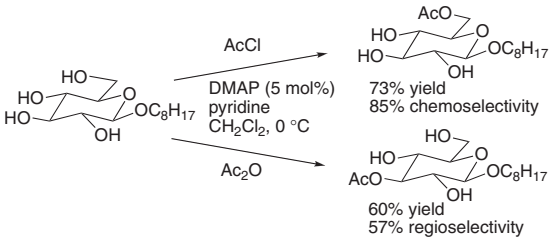
Scheme 1. Selective enzymatic acylation.

groups of octyl β-D-glucopyranoside has been achieved in ca. 100% chemoselectivity by an enzymatic process, however, concomitant diacylation was unavoidable (Scheme 1).[4]

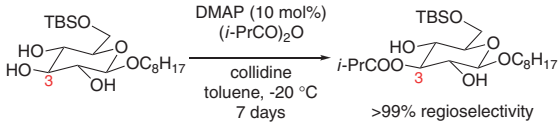
Since the primary hydroxy group at C(6) of glucose derivatives has the highest intrinsic reactivity, the selective introduction of an acyl group at C(6)–OH of carbohydrates is a reasonable consequence. For example, Kattnig and Albert reported regioselective 6-O-acylation of octyl β-D-glucopyranoside in 85% selectivity and in 73% yield simply by treatment with acetyl chloride in the presence of DMAP. Interestingly, they also found that use of acetic anhydride in place of acetyl chloride gave the 3-*O*-acetate in 57% selectivity in 60% yield (Scheme 2).[5]

We reported highly selective 3-O-acylation of 6-O-protected glucose derivatives.[6] Treatment of octyl 6-*O*-TBS-β-D-glucopyranoside with isobutyric anhydride in the presence of 10 mol % of DMAP and 2,4,6-collidine in toluene at −20 °C for 7 days gave octyl 3-*O*-isobutyryl-6-*O*-TBS-β-D-glucopyranoside in a perfect regioselectivity (>99%) and in 89% yield for monoacylation (Scheme 3). We assume that observed regioselectivity is the result of the intrinsically high reactivity of C(3)–OH result-

Prof. Takeo Kawabata, Dr. Takumi Furuta*
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011
E-mail: kawabata@scl.kyoto-u.ac.jp



Scheme 2. Acylating agent-dependent selective acylation.



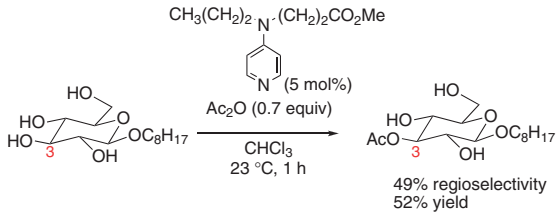
Scheme 3. Selective acylation of a protected glucopyranoside.

ing from intramolecular H-bonding networks of octyl 6-*O*-TBS-β-D-glucopyranosides. The success in achieving extremely high regioselectivity may rely on the proper choice of a substrate and an acid anhydride. Substrates with high solubility in less polar solvents should enhance their own intramolecular H-bonding networks in the solvents. Isobutyric anhydride works effectively in the discrimination of hydroxy groups in different microenvironments because of its steric effects as well as its high k_{cat}/k_{uncat} ratio.[7]

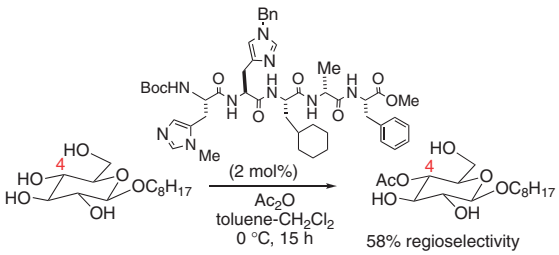
Hu and Vesella also reported regioselective benzoylation of methyl 6-*O*-TBDPS-β-D-glucopyranoside with Oriyama's catalyst[8] and benzoyl chloride in 84% selectivity.[9] Moitessier and co-workers have also reported highly selective 3-O-acetylation of 6-O-protected methyl α-D-glucopyranoside in up to 93% regioselectivity.[10]

On the other hand, chemoselective acylation of a secondary hydroxy group in the presence of a free primary hydroxy group is much more difficult. Kurahasi, Mizutani, and Yoshida reported a pioneering example of chemoselective acylation of a secondary hydroxy group at C(4) of octyl α-D-glucopyranoside in 61% selectivity with an acetic anhydride–DMAP system, where diacylation was minimized by the use of less (0.70 equiv) acetic anhydride.[11a] They also reported regioselective acylation of octyl β-D-glucopyranoside with functionalized DMAP derivatives, which gave the 3-*O*-acetate in 49% regioselectivity (Scheme 4).[11b]

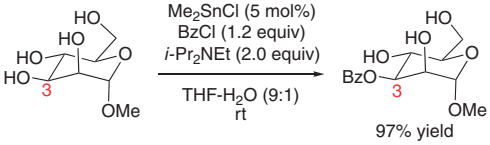
Recently, Griswold and Miller reported an excellent approach to the selective introduction of an acetyl group at a secondary hydroxy group of octyl β-D-glucopyranoside by using peptide-based chiral catalysts.[12] Moderately selective 4-O-



Scheme 4. Selective acylation of a secondary hydroxy group by functionalized DMAP.



Scheme 5. Selective acylation of a secondary hydroxy group by a peptide-based catalyst.



Scheme 6. Tin-mediated highly regioselective benzoylation of carbohydrates.

acylation has been achieved in a ratio of 22:58:11:9 for 6-*O*-, 4-*O*-, 3-*O*-, and 2-*O*-acylate, respectively, without the formation of diacylates (Scheme 5).

Recently, a one-pot method for regioselective deprotection of fully TMS-protected glucose derivatives has been developed.[13] More recently, Onomura and co-workers reported an excellent catalytic method for regioselective benzoylation of carbohydrates (Scheme 6).[14]

♦ *A Working Hypothesis for Selective Acylation of a Certain Secondary Hydroxy Group in the Presence of a Free Primary Hydroxy Group*

We chose 4-pyrrolidinopyridine (PPY) as a catalytic center for acylation because PPY is known to be the most powerful catalyst for the acylation of alcohols.[15] It has been well established that the reactive intermediates generated from PPY derivatives and acid anhydrides are acylpyridinium ions.[16] A hypothetical picture of transition-state molecular assembly between the acylpyridinium ion generated from a functionalized PPY derivative and a carbohydrate substrate is show in Figure 2, which enables the selective acylation of a secondary hydroxy group in the presence of a primary hydroxy group. Since the primary hydroxy group at C(6) of carbohydrates is the most reactive, it would

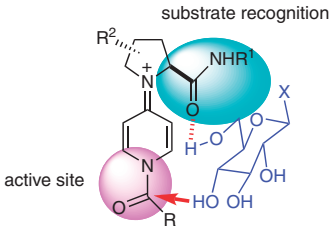


Figure 2. A working hypothesis for selective acylation of a certain secondary hydroxy group in the presence of a free primary hydroxy group.

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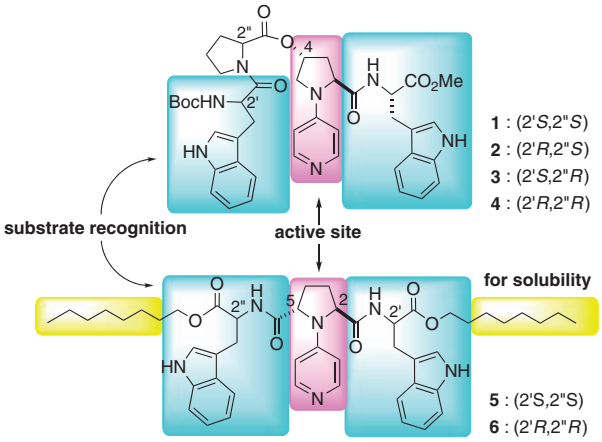


Figure 3. Design and structure of catalysts.

preferentially form a H-bond with H-bond acceptor(s). If an amide carbonyl group of the catalyst forms a H-bond with the primary hydroxy group at C(6), the hydroxy group at C(4) is in close proximity to the reactive acyl group of the acyl pyridinium ion, so that it would selectively be acylated. If additional interactions of the hydroxy groups at C(2) and/or C(3) with a functionality (R^1) of the catalyst are operative, the combined effects of these attractive interactions would fix the substrate conformation, which would further facilitate the selective acylation of the hydroxy group at C(4).

We chose tryptophan as a functional side chain (NHR[1] in Figure 2) of the catalyst because its indole substructure is expected to be suitable for H-bonding as well as for CH–π interaction with carbohydrates. It has been also reported that pyrrole units, similar to indole units, were effectively used as recognition sites for carbohydrates.[17] The notion that tryptophan can be used as a carbohydrate recognition site is also suggested by the facts that two tryptophan moieties are highly preserved in the substrate-recognition site of a family of β-glucosidases.[18] Based on these backgrounds, catalysts **1**–**4**[19] and **5** and **6**[20] with dual functional side chains consisting of two tryptophan substructures were prepared from *trans*-4-hydroxy-L-proline and L-pyroglutamic acid, respectively (Figure 3).[21,22]

Catalysts **1**–**4** were designed with an expectation that the indole unit of the C(4)–side chain of catalysts would be located in proximity to the pyridine nitrogen due to the turn structure caused by proline. Since the relative orientation of two indole units was supposed to be concerned with recognition of the substrate, all possible stereoisomers of dipeptides consisting of proline and tryptophan were introduced at C(4) of the pyrrolidine ring. Molecular modeling of acylpyridinium ion **7**[23] generated from **1** and isobutyric anhydride was performed by MacroModel (V. 9.0)/MCMM conformational search with the AMBER* force field (Figure 4). The calculated structure indicated that the indole unit in the C(4)–side chain of **7** was in close proximity to the reactive acyl group.

C_2-symmetric chiral PPYs **5** and **6** with two identical side chains consisting of L- and D-tryptophan, respectively, at C(2) and C(5) of the pyrroridine ring were also prepared. Octyl esters in **5** and **6** are employed to enhance the solubility of catalysts in less polar solvents where H-bonding works more effectively. Molecular modeling of acylpyridinium ion **8**[23] generated from **5** and isobutyric anhydride was also performed by MacroModel

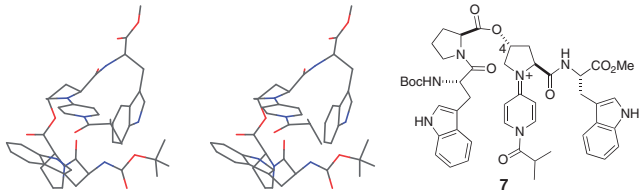


Figure 4. The most stable structure (stereo view) of acylpyridinium ion **7** generated by MocroModel (V. 9.0) with the AMBER* force field.

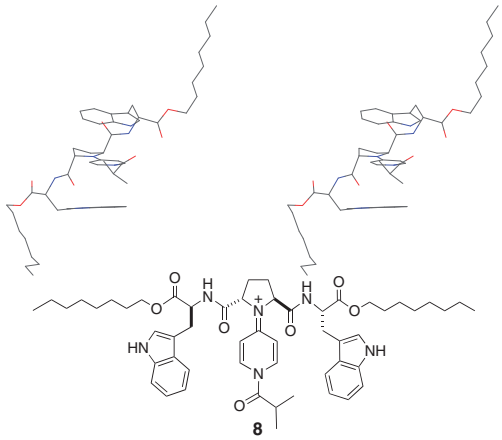


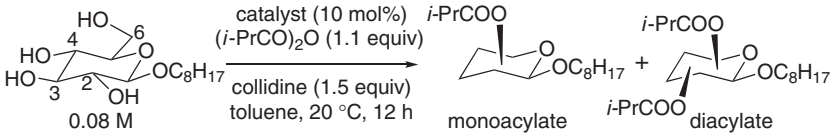
Figure 5. The most stable structure (stereo view) of acylpyridinium ion **8** generated by MocroModel (V. 9.0) with the AMBER* force field.

(V. 9.0)/MCMM conformational search with the AMBER* force field (Figure 5). The calculated structure indicated that the indole units in the C(2)– and C(5)–side chains of **8** were also in close proximity to the reactive acyl group.

♦ *Regioselective Acylation of Octyl β-D-Glucopyranoside with Functionalized PPYs*

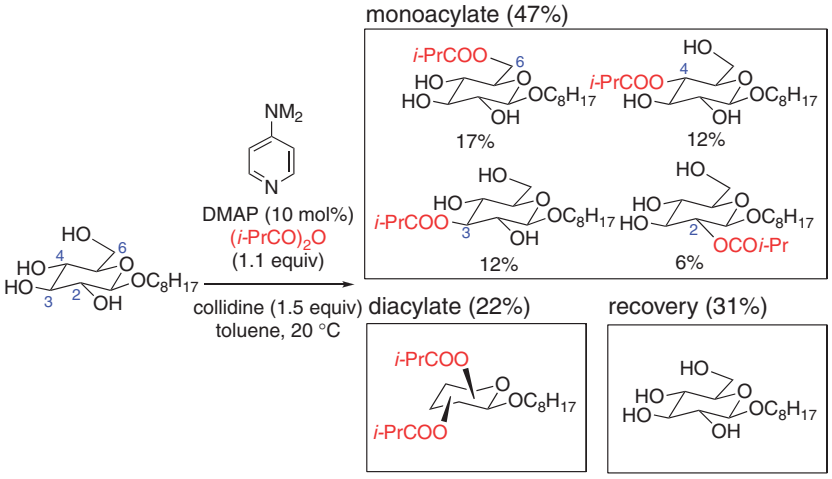
Regioselectivity of acylation of octyl β-D-glucopyranoside was investigated with functionalized PPY derivatives **1**–**6**. Isobutyric anhydride was employed as an acylating agent because it has been known to show high selectivity in acylative kinetic resolution of racemic alcohols,[21] probably due to the high k_{cat}/k_{uncat} ratio.[7] Effects of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside were investigated (Table 1). A solution of octyl β-D-glucopyranoside in toluene was treated with 1.1 mol equiv of isobutyric anhydride in the presence of 10 mol % of a catalyst and 1.5 equiv of collidine at 20 °C for 12 h (Table 1). Analysis of the products was unambiguously performed by the comparison with authentic samples of 6-*O*-, 4-*O*-, 3-*O*-, and 2-*O*-isobutyryl octyl β-D-glucopyranosides, which were independently prepared via conventional protection/deprotection sequences. With DMAP as a catalyst, four monoacylates, 6-*O*-, 4-*O*-, 3-*O*-, and 2-*O*-isobutyryl octyl β-D-glucopyranosides, were obtained in a ratio of 36:26:26:12 in a combined yield of 47% together with 22% of the diacylates and 31% recovery (Table 1, Entry 1 and Scheme 7). Thus, totally random acylation took place by DMAP-catalysis.

Table 1. Effects of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside



Entry	Catalyst	Monoacylate /%	Regioselectivity[a] 6-O : 4-O : 3-O : 2-O	Diacylate /%	Recovery /%
1	DMAP	47	**36** : 26 : 26 : 12	22	31
2	**1**	66	30 : **60** : 10 : 0	16	16
3	**2**	65	**46** : 40 : 11 : 3	20	12
4	**3**	67	**55** : 33 : 10 : 1	19	14
5	**4**	62	**49** : 39 : 11 : 1	24	10
6	**5**	84	11 : **86** : 3 : 0	12	2
7	**6**	71	20 : **73** : 7 : 0	17	9

[a]% Regioselectivity among four monoacylates.



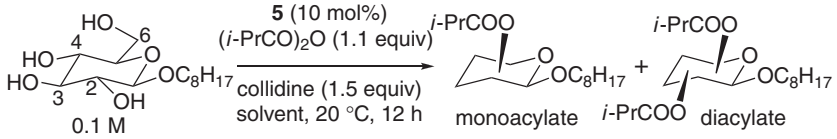
Scheme 7. Random acylation by DMAP catalysis.

The 6-*O*-acylate was the major product in the acylation promoted by catalysts **2**–**4** as well as DMAP (Entries 1 and 3–5). On the other hand, the secondary hydroxy group at C(4) was predominantly acylated (60%) even in the presence of a free primary hydroxy group at C(6) in the acylation with catalyst **1** (Entry 2). These observations indicate that the relative orientation of two indole units of these catalysts is critically involved in the selective acylation of octyl β-D-glucopyranosides. Regioselectivity of acylation of octyl β-D-glucopyranoside was further investigated with C_2-symmteric catalysts **5** and **6**. Selectivity for 4-O-acylation was significantly increased in up to 86% and 73% when catalyst **5** and **6** were employed, respectively (Entries 6 and 7).

Table 2 shows solvent effects on the regioselectivity of acylation of octyl β-D-glucopyranoside with catalyst **5**. The polarity of the solvents roughly correlated with the chemo- and regioselectivity of acylation. The highest selectivity (91%) for acylation of the secondary hydroxy group at C(4) was observed in $CHCl_3$ (Entry 1), whereas acylation of the primary hydroxy group was predominant (63%) in DMF (Entry 4). The observed solvent effects suggest that H-bonding rather than CH–π interaction between a substrate and a catalyst may be significantly involved in the driving force for the selective 4-O-acylation. Another interesting phenomenon is that the higher ratio of 4-O-acylation is associated with the higher yield for monoacylation and the lower the yield for diacylation (Entries 1–4). This phenomenon suggests that the 4-O-acylation would proceed in an accelerative manner.

Temperature dependence of regioselectivity of acylation is shown in Table 3. A decrease in the reaction temperature to 0 °C increased the regioselectivity for 4-O-acylation to 98% (Entry 2). Only 1 mol % of catalyst was effective for controlling the regioselectivity of acylation at −20 °C, and gave the 4-*O*-acylate and the 3-*O*-acylate in a 99:1 ratio in a combined yield of 98% (Entry 4). The reaction at −50 °C with 10 mol % of **5** showed perfect chemo- and regioselectivity, and gave the 4-*O*-acylate as a sole product in 98% yield (Entry 5). These strong temperature effects may indicate the contribution of a large negative $\Delta S^{\neq}$ term for regioselective acylation, which may suggest multiple H-bonding at the transition state of acylation. Use of acid anhydride is critical for the regioselectivity because use of acid chloride loses the selectivity of acylation even in the presence of catalyst **5** (Entries 6 vs. 2).

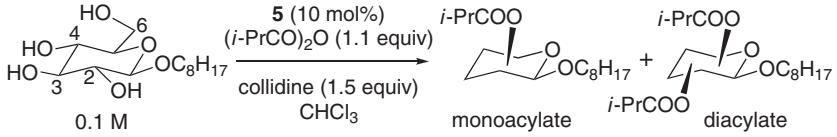
Table 2. Solvent effects on regioselectivity of acylation of octyl β-D-glucopyranoside



Entry	Solvent	Monoacylate /%	Regioselectivity[a] 6-O : 4-O : 3-O : 2-O	Diacylate /%	Recovery /%
1	$CHCl_3$	**90**	4 : **91** : 5 : 0	4	3
2[b]	Toluene	84	11 : 86 : 3 : 0	12	2
3	THF	51	27 : 51 : 22 : 0	28	16
4	DMF	46	**63** : 12 : 24 : 1	26	21

[a]% Regioselectivity among four monoacylates. [b]The reaction was carried out with a substrate concentration of 0.08 M.

Table 3. Effects of temperature on regioselectivity of acylation of octyl β-D-glucopyranoside with catalyst **5** in $CHCl_3$



Entry	Temp. /°C	Time /h	Monoacylate /%	Regioselectivity[a] 6-O : 4-O : 3-O : 2-O	Diacylate /%	Recovery /%
1	20	12	90	4 : 91 : 5 : 0	4	3
2	0	12	97	0 : 98 : 2 : 0	2	0
3	−20	12	98	0 : 99 : 1 : 0	0	0
4[b]	−20	24	**98**	**0 : 99 : 1 : 0**	**0**	**0**
5	−50	38	**98**	**0 : >99 : <1 : 0**	**0**	**0**
6[c]	0	48	47	60 : 35 : 5 : 0	13	19

[a]% Regioselectivity among four monoacylates. [b]1 mol % of catalysts **5** was used. [c]*i*-PrCOCl was used in place of $(i\text{-PrCO})_2O$.

♦ *Scope of Regioselective Acylation of Various Monosaccharides*

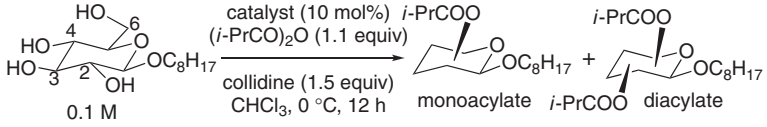
The regioselectivity profile of acylation of various monosaccharides was investigated (Figure 6). Acetylation of octyl β-D-glucopyranoside gave the 4-*O*-acetate in 96% regioselectivity and in 96% yield for monoacylation (Figure 6a), when it was treated with 10 mol % of catalyst **5** in the presence of 1.1 equiv of Ac_2O and 1.5 equiv of collidine in $CHCl_3$ at −20 °C for 24 h. Acylation of octyl β-D-thioglucopyranoside with isobutyric anhydride or acetic anhydride at −60 °C gave the 4-*O*-isobutyrate in 97% regioselectivity (92% yield for monoacylation) or the 4-*O*-acetate in 95% regioselectivity (99% yield for monoacylation), respectively (Figure 6b). The acylated thioglycosides are expected to be used directly for glycosylation because thioglycosides can be used as glycosyl donors.[24] Acylation of octyl α-D-glucopyranoside with isobutyric anhydride at 20 °C gave the 4-*O*-isobutyrate as a major product but with a largely diminished selectivity (54% regioselectivity) (Figure 6c). Acylation of octyl β-D-mannopyranoside with isobutyric anhydride at −50 °C gave the 4-*O*-isobutyrate in 85% regioselectivity (Figure 6d). Acylation took place predominantly at C(4)–OH in glucopyranosides and a mannopyranoside whose C(4)–OH is equatorially oriented. On the other hand, acylation of octyl β-D-galactopyranoside, whose C(4)–OH is axially oriented, took place preferentially at the primary hydroxy group at C(6) (Figure 6e). These observations suggest that equatorial orientation is crucial for the selective acylation of C(4)–OH.

♦ *Mechanistic Aspects of Regioselective Acylation*

Perfect chemo- and regioselectivity was observed in the acylation of the secondary hydroxy group at C(4) of octyl β-D-glucopyranoside in the presence of catalyst **5**. The selective acylation at C(4)–OH, however, might be the result of migration of the 6-*O*-acylate into the 4-*O*-acylate (Figure 7). To examine this possibility, the 6-*O*-isobutyrate of octyl β-D-glucopyranoside was independently prepared and treated under the reaction conditions similar to those of Entry 2 in Table 3, except that isobutyric anhydride was absent. The 6-*O*-isobutyrate was recovered in 99% yield and migration into the 4-*O*-isobutyrate was not observed at all.[25] This indicates that acylation of secondary alcohol at C(4)–OH took place directly under the influence of catalyst **5**.

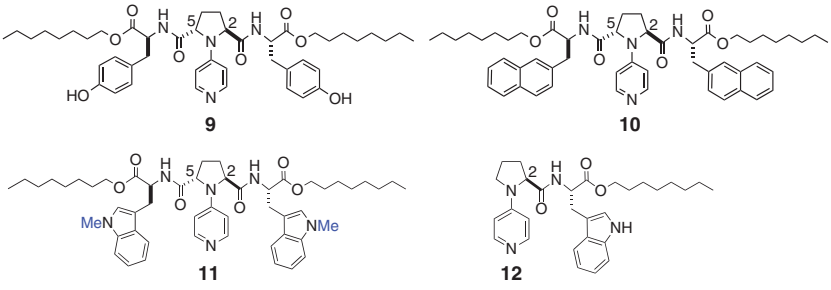
What then is the origin of the regioselectivity in the catalyst **5**-promoted acylation? The hypothesis of H-bonding between primary hydroxy group at C(6) of a carbohydrate with a catalyst (Figure 2) was examined with the 6-O-protected derivative. The 6-OMe derivative of octyl β-D-glucopyranoside was treated under reaction conditions similar to those in Entry 3 in Table 3. The 4-*O*-, 3-*O*-, and 2-*O*-isobutyrates were obtained in a ratio of

Table 4. Effects of functionality of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside



Entry	Catalyst	Monoacylate /%	Regioselectivity[a] 6-O : 4-O : 3-O : 2-O	Diacylate /%	Recovery /%
1	**5**	97	0 : **98** : 2 : 0	2	0
2[b]	**9**	60	23 : **58** : 19 : 0	21	14
3	**10**	74	7 : **65** : 28 : 0	15	4
4	**11**	69	14 : **60** : 26 : 0	20	8
5	**12**	62	13 : **66** : 20 : 1	13	22
6	DMAP	61	33 : 24 : 43 : 0	21	14

[a]% Regioselectivity among four monoacylates. [b]Run at 20 °C for 12 h.



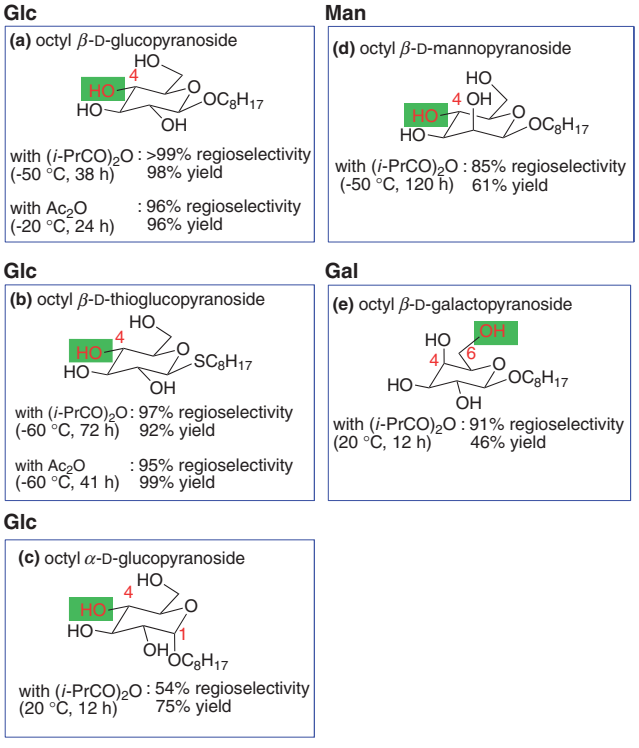


Figure 6. The hydroxy group to be acylated under the conditions of 10 mol % of catalyst **5**/$(RCO)_2O$/collidine/$CHCl_3$ is shown as OH in red color with green square. The regioselectivity is shown as percentage among four monoacylates. Yields are those for monoacylation. The reactions were performed at the temperature and for the time indicated in the parentheses.

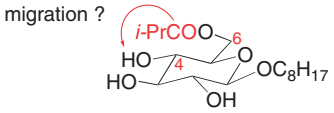
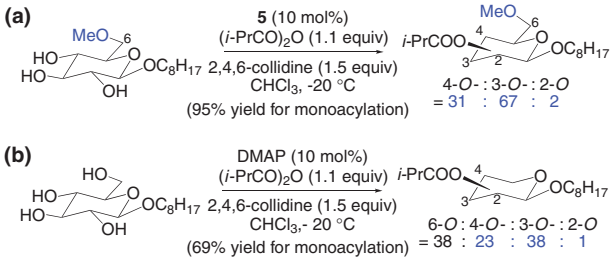


Figure 7. Is acyl migration the origin of 4-O-acylation?



Scheme 8. Nonselective acylations of (a) octyl 6-*O*-methyl-β-D-glucopyranoside promoted by catalyst **5** and (b) octyl β-D-glucopyranoside promoted by DMAP.

31:67:2 in a combined yield of 95% (Scheme 8a). The observed ratio was comparable to the ratio observed in nonselective acylation by DMAP catalysis (Scheme 8b). Thus, H-bonding between primary hydroxy group at C(6) of the substrate and the catalyst seems crucial for regioselective acylation promoted by catalyst **5**.

Effects of the functionality of catalysts on the regioselectivity of acylation were investigated (Table 4). With catalyst **9** and **10** in which the indole substructure of **5** was replaced by *p*-phenol and 2-naphthalene, respectively, acylation took place at the secondary hydroxy group at C(4) predominantly (58–65%), but with decreased regioselectivity (Entries 2 and 3). This indi-

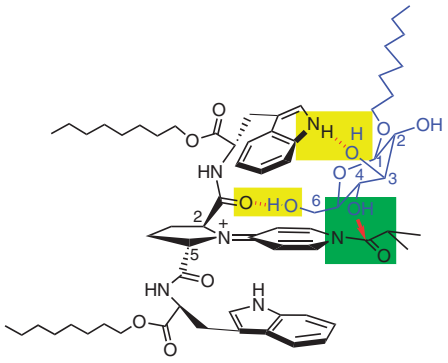
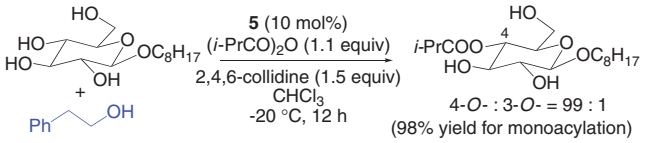


Figure 8. A possible transition state model for selective acylation of octyl β-D-glucopyranoside promoted by **5**.

cates that the indole substructure is not indispensable for the selective acylation at C(4)–OH, but amide carbonyl groups both at C(2) and C(5) of the pyrrolidine ring, common in the catalysts **5**, **9**, and **10**, seems essential for selective acylation at C(4)–OH. With catalyst **11** in which the indole substructure of **5** was replaced by an *N*-methylindole, acylation at the secondary hydroxy group at C(4) was still predominant, but the regioselecitivity was decreased (60%, Entry 4). The observation may suggest that indole NH of catalyst **5** would participate in further increasing the regioselectivity of acylation at C(4)–OH.

A possible transition-state assembly for regioselective acylation of octyl β-D-glucopyranoside promoted by catalyst **5** is shown in Figure 8. Since the primary hydroxy group at C(6) is the most reactive in the substrate, it would preferentially form H-bonding with an amide carbonyl that is likely to be the strongest H-bonding acceptor in the acylpyridinium ion generated from **5**. As the result of the H-bonding interaction, the indole NH locates in the proximity of C(3)–OH, resulting in the formation of an additional H-bonding between them. The cooperative effects of two hydrogen bonds would fix the conformation of the substrate at the transition state for acylation, where the C(4)–OH is in close proximity to the reactive carbonyl group of the acyl pyridinium ion, resulting in the selective acylation at C(4)–OH. The C_2-symmetric structure of catalyst **5** seems to be important. An approach of the carbohydrate substrate is possible from either the face of the C(2)–side chain of the acylpyridinium ion or that of C(5)–side chain. The former would lead to the transition state structure shown in Figure 8, which is expected to be identical with the latter due to C_2-symmetric nature of the catalyst. This notion was supported by the results of the corresponding reaction with non-C_2-symmetric catalyst **12** (Table 4, Entry 5). Acylation of octyl β-D-glucopyranoside in the presence of **12** gave the 4-*O*-acylate as the major product, but in decreased regioselectivity of 66% (Entries 1 vs. 5). A substrate approaching from the β-face (the face of the C(2)–side chain) of the acylpyridinium ion generated from **12** would undergo selective acylation at C(4)–OH, while a substrate approaching from the less-hindered α-face (C(5)–side chain is absent in **12**) would undergo nonselective acylation. As a combined result, the 4-O-acylation proceeded preferentially, but in diminished regioselectivity in the acylation with **12**.

The transition state model suggests that acylation of C(4)–OH may proceed in a accelerative manner due to the stabilization of the transition state by dual H-bonding. This expectation



Scheme 9. Competitive acylation in the presence of catalyst **5**.

is consistent with the results shown in Table 2. The notion of accelerative acylation is also supported by the competitive acylation between octyl β-D-glucopyranoside and a primary alcohol (Scheme 9). When a 1:1 mixture of octyl β-D-glucopyranoside and 2-phenylethanol was treated under conditions similar to those in Entry 3 in Table 3, octyl 4-*O*-isobutyryl-β-D-glucopyranoside was obtained in 99% regioselectivity and in 98% yield. The existence of the primary alcohol did not affect the selective acylation of the carbohydrate at all, indicating that acylation of the secondary hydroxy group at C(4) of the carbohydrate proceeds in an accelerative manner in the presence of **5**.

The difference in the regioselectivity of acylation of various monosaccharides shown in Figure 6 may be understood by the transition state model shown in Figure 8. A difference between octyl β-D-glucopyranoside (Figure 6a) and octyl β-D-mannopyranoside (Figure 6d) is the orientation of the hydroxy group at C(2). Since the orientation of the hydroxy group at C(2) does not seem significantly to affect the transition state assembly shown in Figure 8, selective 4-O-acylation is also expected for the mannose derivative (85% regioselectivity). On the other hand, a transition state assembly shown in Figure 8 is not possible with carbohydrates that have an axial hydroxy group at C(4). Accordingly, acylation of the galactose derivative proceeded in a totally different manner, and gave the 6-*O*-acylate as a major product (Figure 6e), because of the intrinsically high reactivity of the primary hydroxy group. In the case of octyl α-D-glucopyranoside (Figure 6c), a transition state assembly shown in Figure 8 may be possible, however, it is somewhat disfavored by the unfavorable interaction between an α-octyloxy substituent at C(1) of the carbohydrate with the acyl group of the acylpyridinium ion. Accordingly, acylation of C(4)–OH of octyl α-D-glucopyranoside took place predominantly, but in the diminished regioselectivity of 54%.

♦ Conclusion

An organocatalytic one-step procedure for highly chemo- and regioselective acylation of carbohydrates has been developed. The catalyst-promoted acylation proceeded in an accelerative manner. The present method enables direct functionalization of one of the multiple hydroxy groups of polyol substrates. Thus, development of the present process is expected to contribute to extremely shorten synthetic routes for carbohydrates.

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This paper is dedicated to Professor Kaoru Fuji on the occasion of his 70th birthday.

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