Recent Advances in the Regioselective Functionalization of Carbohydrates Using Non-Enzymatic Catalysts

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Abstract
Protection–deprotection strategies are one of the most essential techniques in the synthesis of complex compounds. However, if a functional group can be freely introduced onto a particular position of a compound without interference from other functionalities, some protection–deprotection steps in the synthesis can be eliminated. Though some advances have been recently reported for the removal of these steps in natural product synthesis by groups such as Baran et al. (1), the use of protecting groups is still necessary in the synthesis of polyols such as glycosides and polysaccharides. Additionally, no non-enzymatic methods are available to directly functionalize these polyols because methods to selectively recognize a particular OH group in polyols or monosaccharides, which is a unit of polyols, have not been sufficiently developed. In this review, we report recent advances in this field from the literature and our own approaches for the regioselective functionalization of carbohydrates employing non-enzymatic catalysts.

A. Introduction
When we attempt to functionalize a particular OH group in carbohydrates, protection of all of other OH groups is usually necessary as many unwanted byproducts are obtained from the direct functionalization of non-protected carbohydrates. However, multistep synthetic protocols employing protection–deprotection sequences are not always efficient. For example, for the preparation of 3, shown in Scheme 1, the direct acylation of octyl β-D-glucoside afforded various monoacylates in an unpredictable ratio and in 47% total yield, with 22% yield of diacylates. Conversely, the multistep synthetic protocol required five steps to afford 3 in only 46% overall yield (2). As a result, non-enzymatic catalytic methods for the direct and regioselective functionalization of polyols such as carbohydrates have recently attracted much attention in the synthetic community.

B. Regioselective Functionalization of Carbohydrates by Organoborinate Catalysis
It is well known that, in the absence of non-protected primary OH groups in carbohydrates, organoboronic acids selectively recognize cis-1,2-diol moieties to form 5-membered cyclic boronic ester intermediates (3). In 2011, as a result of the catalyst screening, Taylor and Lee presented the catalytic regioselective acylation of partially protected carbohydrates via these intermediates. 2-Aminoethyl diphenylborinate 5 gave the best result in this acylation reaction (Scheme 2) (4). Subsequently, the authors reported the catalytic regioselective alkylation, sulfonylation, glycosylation, and silylation of carbohydrates with 5 (5). However, these methods...
with 5 cannot be applied to regioselective monofunctionalizations of carbohydrates bearing a non-protected primary C(6)-OH group because multiple products are produced via both 5- and 6-membered cyclic boronic ester intermediates (3a, 3b).

C. Regioselective Functionalization of Carbohydrates by Palladium Catalysis

In 2013, de Vries and Minnaard reported a regioselective oxidation of glucosides using a palladium catalyst (6). It was the first report of the catalytic and regioselective oxidation of secondary OH groups in non-protected carbohydrates. Oxidation of methyl α-D-glucoside with 2,6-dichloro-1,4-benzoquinone (DCBQ) in the presence of [(neocuproine)PdOAc]OTf2 (2.5 mol%) gave ketosaccharide 6 in 96% yield (Scheme 3). Ketosaccharides are extremely useful precursors for synthesizing various pseudosaccharides such as amino sugars. Therefore, many methods for the transformation of ketosaccharides have been reported (7). The authors reported that the reaction of 6 with H2NOMe, followed by the hydrogenation of the imine using PtO2, gave aminosaccharide 7, and they proposed that the regioselectivity was caused by a kinetically controlled coordination between the palladium catalyst and the C(3)-OH group. This proposal was supported by investigations into the pK_a values of OH groups in carbohydrates (8).
D. Regioselective Functionalization of Carbohydrates by Copper Catalysis

Miller and Dong independently reported the regioselective functionalization of partially protected carbohydrates using copper catalysts (9, 10). An advantage common to both catalyses is that the choice of ligand can switch the site of the OH group to be functionalized. For example, Dong et al. reported that, in the presence of Cu(OTf)₂ (10 mol%) and N,N,N′-tetramethylethylenediamine (TMEDA, 12 mol%) as the ligand, the acylation of C(6)–O-protected-α-D-galactoside 8 proceeded preferentially at the C(2)–OH group to afford 9 without the formation of C(4)–O-acylate. Conversely, in the presence of (S,S)-Ph-Box (10 mol%), the acylation proceeded preferentially at the C(3)–OH group of 8 to afford 10 without the formation of C(4)–O-acylate as well (Scheme 4).

E. Regioselective Functionalization of Carbohydrates by Organotin Catalysis

Regioselective functionalization of non-protected carbohydrates employing organotin was enthusiastically investigated by many researchers in the latter part of the 20th century. In particular, Tsuda et al. reported several methods for functionalizing carbohydrates (11). The advantage of using organotin is that it enables the regioselective functionalization of equatorial OH groups in cis-1,2-diol (or dioxyl) moieties among the multiple OH groups in carbohydrates. Additionally, even though a non-protected primary OH group exists in carbohydrates, the regioselectivity does not normally decrease. Thus, organotin has, potentially, higher site-recognition ability than organoboronic acid (or borinic acid). However, these reactions require a stoichiometric amount of organotin and harsh conditions in order to form stannylene acetal intermediates. Furthermore, because of its human and environmental toxicity, decreasing the use of organotin has recently become a concern in chemical research.

To the best of our knowledge, the acylation reaction reported by Herradón et al. in 1994 was the first example of the regioselective functionalization of carbohydrates employing a catalytic amount of organotin (Scheme 5) (12). Subsequently, Martinelli et al. achieved the first organotin-catalyzed regioselective functionalization of non-protected carbohydrates (13). They reported that catalytic n-Bu₂SnO afforded, in moderate yields and regioselectivities, monosulfonates 12 and 15 in the sulfonylation of methyl α- and methyl β-xyloside (Scheme 6). However, the application of this method to carbohydrates containing non-protected primary OH groups. Further, the transformations of the resultant monosulfates have not been reported. Both these methods have plenty of scope for improvement in terms of yield and regioselectivity.

E-1. Regioselective Sulfonylation of Carbohydrates by Organotin Catalysis

We investigated the catalytic sulfonylation of the C(2)–OH group of α-D-glucoside with high yield and regioselectivity. After conducting a series of optimization studies, we found that regioselective sulfonylation employing n-Bu₂SnCl₂ (5 mol%), 3,5-difluorobenzenesulfonyl chloride (1.3 equiv.), and 1,2,2,6,6-pentamethyldipiperidine (PEMP, 2.0 equiv.) proceeded at the C(2)–OH group of methyl α-D-glucoside, affording monosulfate 16 in 98% yield (14). In this reaction, multisulfonates were not produced (entry 1 of Table 1). In the absence of either n-Bu₂SnCl₂ or PEMP as a base, the reaction to afford 16 hardly proceeded (entries 2 and 3). We
tested several combinations of organotin catalyst and base other than \( n\text{-Bu}_2\text{SnC}_2 \) and PEMP, but no improvement in the yield of 16 was observed (entries 4–8). We then demonstrated regioselective sulfonylation with several \( \alpha\text{-D}-\text{glucoside} \) derivatives under the reaction conditions of entry 1 (entries 9–12). Consequently, we found that the reaction conditions can be applied to not only \( \alpha\text{-D}-\text{glucoside} \) derivatives bearing \( \text{O-alkyl} \) and \( \text{O-aryl} \) as the R group (entries 9 and 10), but also to thioglucoside, which is valuable as a glycosyl acceptor in glycosylation (entry 11). However, the reaction with electrophiles such as MsCl or TfCl did not afford satisfactory yields (entries 13–16).

This organotin-catalyzed reaction with not only monosaccharides such as \( \text{D-galactoside} \) and \( \text{D-mannoside} \), but also disaccharides such as \( \beta\text{-D}-\text{lactoside} \) afforded the corresponding monosulfoxides in high yields with high regioselectivities (Scheme 7). However, we could not achieve the transformation of the resultant monosulfates in good yields because of the effects of Richardson–Hough rules (15).

### E-2. Regioselective Thiocarbonylation and Glycosylation of Carbohydrates by Organotin Catalysis

In this section, we report our catalytic approach to the regioselective thiocarbonylation and glycosylation of carbohydrates, and propose a reaction mechanism to rationalize the regioselectivity observed in the reactions.

Thiocarbonated sugar is an valuable precursor for the synthesis of deoxy carbohydrates, which are generally known as rare Table 1. Regioselective sulfonylation of \( \alpha\text{-D}-\text{glucoside} \) by organotin catalysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>([\text{Sn}])</th>
<th>Base</th>
<th>R</th>
<th>R'</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>None</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>Me(_2)SnCl(_2)</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16 (+17)</td>
<td>26(^a)</td>
</tr>
<tr>
<td>5</td>
<td>Ph(_2)SnCl(_2)</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>( n\text{-Bu}_2\text{SnO} )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>i-Pr(_2)NEt</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>Pyridine</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>Trace</td>
</tr>
<tr>
<td>9</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>2,6-Lutidine</td>
<td>O–Me</td>
<td>(3,5-F)Ph</td>
<td>16</td>
<td>Trace</td>
</tr>
<tr>
<td>10</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–n-Oct</td>
<td>(3,5-F)Ph</td>
<td>17</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>S–Et</td>
<td>(3,5-F)Ph</td>
<td>19</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>Br</td>
<td>(3,5-F)Ph</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>Me</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>Ph</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>Tf</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>( n\text{-Bu}_2\text{SnCl}_2 )</td>
<td>PEMP</td>
<td>O–Me</td>
<td>(3,5-CF(_3))Ph</td>
<td>24</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^a\) A 49:51 mixture of 2-O-sulfonate (16) and 6-O-sulfonate (17) was observed in 53% overall yield.

Scheme 7. Regioselective monosulfonylation of \( \beta\text{-D}-\text{lactoside} \) by organotin catalysis.
or unnatural sugars. We investigated the sulfonylation of methyl α-D-glucoside with phenyl chlorothionoformate (1.5 equiv.) in the presence of catalytic n-Oct₂SnCl₂ (10 mol%) and tetrabutylammonium iodide (TBAI, 10 mol%) for a short step synthesis of deoxy carbohydrates with high yields, and found that monothiocarbonate 26, which was regioselectively thiocarbonylated at the C(2)–OH group of α-D-glucoside, was isolated in 98% yield (Scheme 8).

Subsequently, deoxygenation of 26 under radical conditions gave 27 in 97% yield over two steps. Furthermore, these catalytic reaction conditions were applied to the regioselective thiocarbonylation of several monosaccharides and disaccharides and good yields were obtained (16).

Very recently, Bennett and Lloyd achieved a short step synthesis of colitose thioglycoside 31, which has been used as a glycosyl donor in the development of antimicrobial vaccines of E. coli O111 (17), via the organotin-catalyzed regioselective thiocarbonylation developed by us as a key step (Scheme 9) (18).

The organotin-catalyzed method was applied to the regioselective glycosylation of carbohydrates (19). Using Ag₂O (1.5 equiv.) as a promoter in the presence of catalytic Ph₂SnCl₂ (10 mol%), it was found that the C(3)–OH group of methyl α-D-galactoside was linked, both regio- and stereoselectively, to the C(2)–OH group of α-D-glucoside, was isolated in 98% yield (Scheme 8). Subsequently, deoxygenation of 26 under radical conditions gave 27 in 97% yield over two steps. Furthermore, these catalytic reaction conditions were applied to the regioselective thiocarbonylation of several monosaccharides and disaccharides and good yields were obtained (16).

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of this coordination, the acidity of the C(2)-, C(3)-, and C(4)-OH groups is increased. Consequently, deprotonation of the C(3)-OH group, which is the least sterically hindered of the three OH groups, may occur regioselectively to form complex B by using a suitable base, as the deprotonation on the C(2)- and C(4)-OH groups is sterically hindered by the neighboring OMe group, and by 1,3-diaxial repulsion, respectively. Finally, the C(3)-OH group in methyl α-D-galactoside reacts with an electrophile E+ to form product C, and R2SnCl2 is regenerated, thus completing the catalytic cycle.

**E-3. Regioselective Oxidation of Carbohydrates by Organotin Catalysis**

Following a report by Minnaard et al. (6), we began to investigate a new catalytic method for the regioselective oxidation of carbohydrates. Though the regioselective oxidation of carbohydrates with a stoichiometric amount of organotin was reported by Tsuda et al. (11), an organotin-catalyzed system has never been developed. Therefore, an efficient catalytic method for the synthesis of ketosaccharides had been eagerly awaited for some time.

At the beginning, we expected that the application of the organotin-catalyzed methods developed by us (14, 16, 19) to the oxidation of carbohydrates would enable us to regioselectively oxidize equatorial OH groups in the cis-1,2-diol (or dioxyl) moieties in carbohydrates. After much effort, we found that the oxidation of methyl α-D-galactoside using trimethylphenylammonium tribromide ([TMPPhA]+Br3–, 1.5 equiv.) (20) in the presence of n-
Oct$_2$SnCl$_2$ (2 mol%) gave ketosaccharide 35, in which the axial C(4)–OH group of methyl α-D-galactoside was regioselectively oxidized in 94% yield (Scheme 13) (21). Although the result contradicted our expectations, it did not contradict the result reported by Tsuda et al. (11). We applied this catalytic method to several monosaccharides, and good results were obtained.

Our proposed catalytic oxidation reaction mechanism is illustrated in Scheme 14. Using methyl α-D-galactoside as an example, n-Oct$_2$SnCl$_2$ initially coordinates selectively with cis-1,2-diol (or dioxyl) moieties to form complex D. The selective coordination increases the acidity of the C(2)–, C(3)–, and C(4)–OH groups. Consequently, these OH groups may be deprotonated by K$_2$CO$_3$ to form complex E. Next, regioselective radical cleavage of the least sterically hindered equatorial C(4)–H bond proceeds via the six-membered transition state F through Br$_2$ generated from [TMPhA]$^+\cdot$Br$^-$. Finally, n-Oct$_2$SnCl$_2$ is regenerated, thus completing the catalytic cycle.

F. Selectivity Switch in the Regioselective Functionalization of Carbohydrates

In the process of developing organotin catalysis, we observed an interesting relationship between the length of alkyl chains in the catalysts and their selectivity, the details of which are shown in Scheme 15. When a 1:1 mixture of methyl α- and β-D-glucoside was reacted with Me$_2$SnCl$_2$, i.e., a catalyst bearing shorter alkyl groups, 36, in which the C(6)–OH group of β-D-glucoside was functionalized, was selectively obtained. Conversely, with n-Bu$_2$SnCl$_2$, i.e., the catalyst bearing longer alkyl groups, 37, in which the C(2)–OH group of α-D-glucoside was functionalized, was selectively obtained (Scheme 15). Similar phenomena were also observed in several combinations of carbohydrates (22). It should be noted that the chemoselectivity can be switched by regulating only the length of the alkyl chains in the catalysts. Molecular recognition like this has been reported in enzymatic reactions (23), but we accomplished it by using a non-enzymatic catalyst. This is,
to our knowledge, the first report of this kind of non-enzymatic selectivity.

G. Regioselective Functionalization of Carbohydrates by Organocatalysis

Studies on the regioselective functionalization of carbohydrates using organocatalysts have been occasionally reported. Among these studies, the approaches by Miller, Kawabata, and Tan for the regio- (or site-) selective functionalization of carbohydrates, as well as glycosides, have recently attracted much attention in the synthetic organic community.

After reporting the regioselective acylation of β-ᴅ-glucoside by employing peptide-based chiral catalysts in 2003 (24), Miller et al. have reported excellent catalytic methods for the site-selective functionalization of glycosides such as erythromycin A and vancomycin. First study of the site-selective acylation of erythromycin A employing 38 was reported in 2006, in which diacylate 40 was obtained in preference to diacylate 39 (Scheme 16) (25). Conversely,

Scheme 16. Site-selective acylation of erythromycin A by using peptide-based chiral catalysts.

Scheme 17. Regioselective acylation of carbohydrates by using chiral PPY catalysts.
the use of \(N\)-methylimidazole (or pyridine as solvent) instead of 38 afforded 39 as the major product. Though it seems that the site selectivity is related to both the intermolecular hydrogen bonding in erythromycin A (26) and intramolecular interactions between erythromycin A and catalyst 38 (27), the full mechanistic details are not yet clear.

In 2007, Kawabata et al. developed the \(C_2\)-symmetric chiral nucleophilic catalyst 41, and then achieved regioselective acylation of carbohydrates on the C(4)–OH group (Scheme 17) (2). Catalyst 41 comprises three parts. 4-Pyrrolidinopyridine (PPY), which shows powerful nucleophilicity in acylation reactions, is located on the catalytic center (28), and l-tryptophan, which is suggested to be a carbohydrate recognition agent for a family of \(\beta\)-glucosidases, is located on the side chain (29). Additionally, long alkyl groups are employed on the side chain to increase its solubility in less polar solvents. The authors offer a possible rationale for the generation of regioselectivity in this organocatalytic acylation as follows: Initially, the primary C(6)–OH group, which is most reactive in \(\beta\)-D-glucoside, forms a hydrogen bond with an amide carbonyl moiety on the side chain of 41. Because of this hydrogen bonding, an auxiliary hydrogen bond is formed between the indole NH moiety and the nearby C(3)–OH group of \(\beta\)-D-glucoside. Through both hydrogen bonding interactions, a transition state \(G\) is formed. Finally, the C(4)–OH group approaches the nearby reactive carbonyl group of the acylpyridinium ion, and then acylate 42 is selectively produced. This suggestion is supported by the results of several experiments (2). The organocatalytic method can be used for not only the site-selective acylation of lanatoside C(30) but also the efficient synthesis of monools derived from carbohydrates (31).

In 2013, Tan et al. developed novel organocatalysts that enable not only the regioselective functionalization of partially protected carbohydrates, like the organoborinate-catalyzed reactions reported by Taylor (4, 5), but also the switching of the regioselectivity by choosing a catalyst, like the copper-catalyzed reactions reported by Miller and Dong (9, 10). For example, treatment of \(N\)-methylimidazole (NMI) as a catalyst in the regioselective acylation of 42 afforded monoacylates 44 and 45 in a 42 : 58 ratio, while the use of the chiral scaffolding catalyst 43 afforded 45, in which the equatorial C(3)–OH group in cis-1,2-diol moieties in 42 was acylated with high regioselectivity (Scheme 18) (32). Moreover, in some cases the regioselectivity can be switched by using another similar organocatalyst.

H. Summary

Regioselectivity (or site selectivity) has been one of the challenges in synthetic organic chemistry for a long time. Since the beginning of the 21st century, an increase in the research focus and effort in this field has led to the development of several novel and effective catalysts. In this review, we focused on non-enzymatic catalysts, and reported the regioselective (or site-selective) functionalization of carbohydrates and glycosides using such catalysts. We greatly hope that these approaches will contribute for not only academic investigations such as the efficient syntheses of natural products and polysaccharides, but also the development of new drugs and materials in industries.

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Wataru Muramatsu received his Ph.D. degree from Kyoto University in 2008 under the supervision of Professor Takeo Kawabata. His Ph.D. thesis featured organocatalytic regioselective acylation of carbohydrates. As a Uehara Memorial Foundation postdoctoral fellow, he pursued training in organometallic chemistry with Professor Gregory C. Fu at Massachusetts Institute of Technology, USA (2008–2010). He began his independent studies at Nagasaki University, Japan, as an assistant professor. His research interests are new reaction methods in the fields of carbohydrates and organocatalysis.