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

Scheme 1. General procedure for the preparation of monoacylate **3**.

Scheme 2. Regioselective functionalization by organoborinate catalysis.

Scheme 3. Regioselective oxidation of glucosides by palladium catalysis.

Scheme 4. Selectivity switch in copper catalyzed acylation of partially protected carbohydrates.

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)Pd(OAc)₂OTf₂] (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**).

Scheme 5. First example for the regioselective functionalization of partially protected carbohydrates by organotin catalysis.

Scheme 6. First example for the regioselective functionalization of non-protected carbohydrates by organotin catalysis.

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 $\text{Cu}(\text{OTf})_2$ (10 mol%) and N,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 dioxy) 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 $n\text{-Bu}_2\text{SnO}$ afforded, in moderate yields and regioselectivities, monosulfonates **12** and **15** in the sulfonylation of methyl α - and methyl β -D-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 $n\text{-Bu}_2\text{SnCl}_2$ (5 mol%), 3,5-difluorobenzenesulfonyl chloride (1.3 equiv.), and 1,2,2,6,6-pentamethylpiperidine (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 $n\text{-Bu}_2\text{SnCl}_2$ or PEMP as a base, the reaction to afford **16** hardly proceeded (entries 2 and 3). We

Table 1. Regioselective sulfonylation of α -D-glucoside by organotin catalysis.

Entry	[Sn]	Base	R	R'	Product	Yield (%)
1	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-Me	(3,5-F)Ph	16	98
2	None	PEMP	O-Me	(3,5-F)Ph	16	0
3	<i>n</i> -Bu ₂ SnCl ₂	None	O-Me	(3,5-F)Ph	16	Trace
4	Me ₂ SnCl ₂	PEMP	O-Me	(3,5-F)Ph	16 + 17	26 ^a
3	<i>n</i> -Oct ₂ SnCl ₂	PEMP	O-Me	(3,5-F)Ph	16	88
4	Ph ₂ SnCl ₂	PEMP	O-Me	(3,5-F)Ph	16	Trace
5	<i>n</i> -Bu ₂ SnO	PEMP	O-Me	(3,5-F)Ph	16	47
6	<i>n</i> -Bu ₂ SnCl ₂	<i>i</i> -Pr ₂ NEt	O-Me	(3,5-F)Ph	16	70
7	<i>n</i> -Bu ₂ SnCl ₂	Pyridine	O-Me	(3,5-F)Ph	16	Trace
8	<i>n</i> -Bu ₂ SnCl ₂	2,6-Lutidine	O-Me	(3,5-F)Ph	16	Trace
9	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O- <i>n</i> -Oct	(3,5-F)Ph	17	80
10	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-PNP	(3,5-F)Ph	18	90
11	<i>n</i> -Bu ₂ SnCl ₂	PEMP	S-Et	(3,5-F)Ph	19	95
12	<i>n</i> -Bu ₂ SnCl ₂	PEMP	Br	(3,5-F)Ph	20	0
13	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-Me	Me	21	15
14	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-Me	Ph	22	20
15	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-Me	Tf	23	0
16	<i>n</i> -Bu ₂ SnCl ₂	PEMP	O-Me	(3,5-CF ₃)Ph	24	98

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

Scheme 7. Regioselective monosulfonylation of β -D-lactoside by organotin catalysis.

tested several combinations of organotin catalyst and base other than *n*-Bu₂SnCl₂ and PEMP, but no improvement in the yield of **16** was observed (entries 4–8). We then demonstrated regioselective sulfonylation with several α -D-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 α -D-glucoside derivatives bearing *O*-alkyl and *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 D-galactoside and D-mannoside, but also disac-

charides such as β -D-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 a valuable precursor for the synthesis of deoxy carbohydrates, which are generally known as rare

Scheme 8. Regioselective Barton–McCombie deoxygenation of methyl α -D-glucoside by organotin catalysis.

Scheme 9. Gram scale synthesis of colitose thioglycoside **31** via organotin catalysis.

Scheme 10. Regio- and stereoselective glycosylation of methyl α -D-galactoside 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(1)-position of **32** as a glycosyl donor, leading to 90% yield of **33** (Scheme 10). In the case of this reaction, the use of 5,5'-dimethyl-2,2'-bipyridyl (DMBPY) as a bulky base was effective. Furthermore, the catalytic regio- and stereoselective glycosylations of several monosaccharides and natural products such as digoxin, a typical cardiac glycoside, were achieved under the best suitable conditions (Scheme 11). Interestingly, the use of n -Bu₂SnCl₂ and n -Oct₂SnCl₂, which worked effectively in the aforementioned sulfonylation (14) and thiocarbonylation reactions (16), resulted in significantly lower yields of **33**. On the other hand, Ph₂SnCl₂, which was not effective in the aforementioned sulfonylation and thiocarbonylation reactions, accelerated the glycosylation to afford **33**.

We propose a possible rationale for the generation of regioselectivity in these organotin-catalyzed reaction (14, 16, 19), as illustrated in Scheme 12. Using methyl α -D-galactoside as an example, the organotin catalyst, R₂SnCl₂, initially coordinates selectively with *cis*-1,2-diol (or dioxyl) moieties to form complex A. Because

Scheme 11. Regio- and stereoselective glycosylation of digoxin by organotin catalysis.

Scheme 12. Proposal mechanism in organotin catalysis.

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 R_2SnCl_2 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 de-

Scheme 13. Regioselective oxidation of methyl α -D-galactoside by organotin catalysis.

veloped. 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 dioxy) moieties in carbohydrates. After much effort, we found that the oxidation of methyl α -D-galactoside using trimethylphenylammonium tribromide ([TMPhA] $^+$ Br $_3^-$, 1.5 equiv.) (20) in the presence of *n*-

$\text{Oct}_2\text{SnCl}_2$ (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, $n\text{-Oct}_2\text{SnCl}_2$ 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_2CO_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 $[\text{TMPhA}]^+\text{Br}_3^-$ to afford **35**. Finally, $n\text{-Oct}_2\text{SnCl}_2$ 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_2SnCl_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 $n\text{-Bu}_2\text{SnCl}_2$, *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,

Scheme 14. Proposal mechanism in organotin catalyzed oxidation.

Scheme 15. Selectivity switch in organotin catalyzed thiocarbonylation of methyl D-glucoside.

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 -D-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.

Scheme 18. Regioselective acylation of partially protected carbohydrates by using chiral scaffolding 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 β -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 β -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 β -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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