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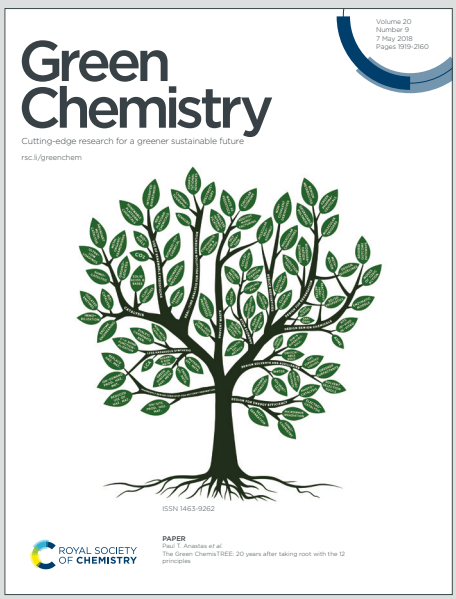

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ARTICLE

Stannous Chloride as a Low-toxic and Extremely Cheap Catalyst for Regio/Site-Selective Acylation with Unusually Broad Substrate Scope

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This work reports stannous chloride ($SnCl_2$)-catalyzed regio/site-selective acylation with unusually broad substrate scope. In addition to 1,2- and 1,3-diols and glycosides containing *cis*-vicinal diol, the substrate scope also includes glycosides without containing *cis*-vicinal diol. For such a substrate scope, usually, only methods using stoichiometric amounts of organotin reagents can lead to the same protection pattern with high selectivities and highly isolated yields (84 – 97% in most cases). Therefore, $SnCl_2$, as a low-toxic and extremely cheap reagent, should be the best catalyst for regio/site-selective acylation compared with any previously reported reagents.

Introduction

Regio/site-selective protection strategies can identify multiple hydroxyl groups with similar activity, avoiding a large number of tedious and time-consuming hydroxyl protection and deprotection processes, thereby reducing the synthetic steps of building blocks in carbohydrate chemistry.[1] Organotin reagents have been playing key roles in selective protection strategies for decades.[2,3] By the use of stoichiometric amounts of organotin reagents, good selectivities could be obtained over a broad substrate scope, including 1,2- and 1,3-diols, glycosides containing *cis*-vicinal diol and glycosides without containing *cis*-vicinal diol.[3] The protection pattern was summarized that the primary and equatorial hydroxyl groups showed good selectivity for substrates containing 1,2-diol, 1,3-diol, and *cis*-diol, and the equatorial hydroxyl groups adjacent to the axial substituents showed good selectivity for substrates containing *trans*-diol, one adjacent substituent being axial and the other being equatorial. However, due to the potentially inherently toxicity of organotins, protection strategies (focusing on acylation) using catalytic amounts of organotin[4] and lower-toxic alternatives, including heavy metal-based complexes,[5] chiral catalysts[6] and other metallic/nonmetallic catalysts[7] and reagents,[8] have been developed in succession. In most cases, researchers have focused on controlling site-selectivities, and been less concerned about whether the used catalysts are cheap and readily available so that these catalysts often have complex structures (Figure 1). In addition, some of these catalysts are applicable to substrates containing *cis*-diol (Figure 1a),[6c,7a,g] another are applicable to substrates containing *trans*-diol (Figure 1b),[6a,b,7c] and even some of them are only applicable to very specific substrates (Figure 1c).[7b,d-f] There are only few catalysts that are applicable to both substrates containing *cis*-diol and substrates containing *trans*-diol (Figure 1d) except for the methods using stoichiometric amounts of organotin reagents.[5a,b,8a] These may be the reasons why toxic organotin reagents are still often used in laboratories to date.[2a-e] Our group has been committed to developing protection strategies where the used reagents are inexpensive and environmental-friendly.[9] Particularly, $[Fe(acac)_3]$ (acac = acetylacetonate), a green and inexpensive catalyst for selective acylation of 1,2-diols, 1,3-diols, and glycosides containing *cis*-vicinal diol, was identified by us recently.[10] After that, it was further found that $FeCl_3$ and acetylacetone could be used as a catalytic system to catalyze selective acylation.[11] These results encouraged us to extensively investigate catalytic systems composed of various metal salts and acylacetone ligands.[12] To our delight, during these investigations, we occasionally found that stannous chloride ($SnCl_2$) was a perfect catalyst for selective acylation (Figure 1e). A systematic investigation on $SnCl_2$-catalyzed selective acylation has been addressed in this study. The results indicated that $SnCl_2$ showed similar/higher catalytic activity to/than organotins in acylation. $SnCl_2$ could not only catalyze the selective acylation of 1,2-diols, 1,3-diols, and glycosides containing *cis*-diol, but also catalyze the selective acylation of glycosides containing *trans*-diol, leading to the same protection pattern with high selectivities and highly isolated yields as that in methods using stoichiometric amounts of organotin reagents. Furthermore, the structure of $SnCl_2$ is simpler than those of organotins so that $SnCl_2$ is more inexpensive and easily acquired. Therefore, for the first time, we have found a low-toxic reagent for acylation, $SnCl_2$, which is not only possibly more inexpensive than organotin reagents, but also comparable

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

to organotin reagents in other aspects, including selectivity, substrate scope, and reaction efficiency.

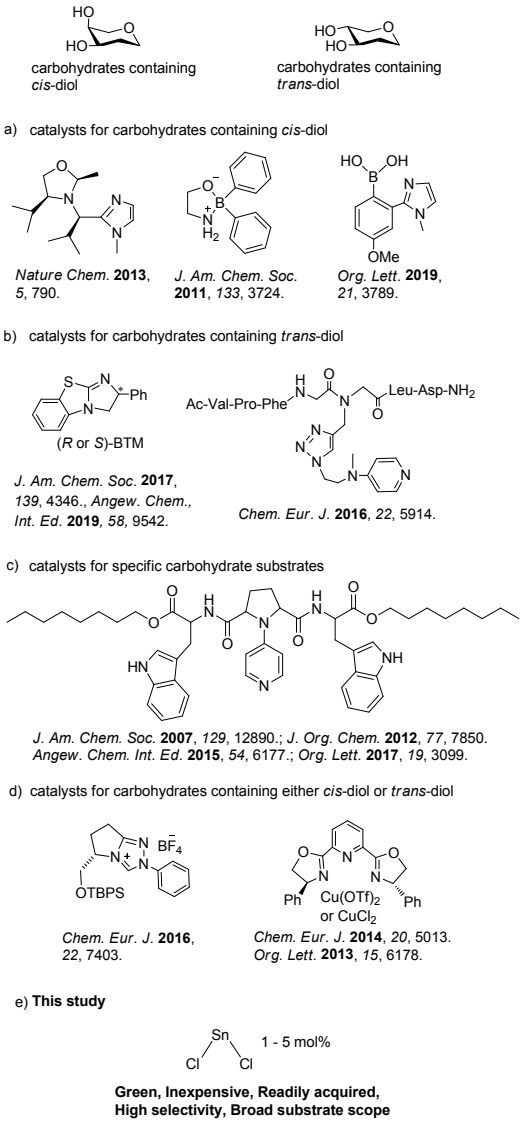


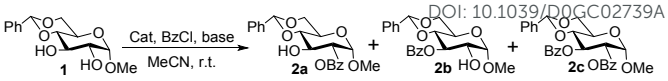
Figure 1 Comparison of various methods for selective acylation.

Results and discussion

Optimization of reaction conditions.

Based on the investigation of catalytic systems composed of various metal salts and acetylacetone, we tried to screen out a catalytic system that can catalyze the selective acylation of substrates containing *trans*-diol. For this purpose, the methyl-4,6-benzylidene-α-D-glucopyranoside **1** which contains *trans*-diol was used as a substrate in benzoylation to explore feasible reaction conditions (Table 1). The ratio of 2-benzoylated product **2a**, 3-benzoylated product **2b**, 2,3-di-benzoylated product **2c** and residual starting material **1** indicates the selectivity and the reactivity of this benzoylation (Figure S1 in SI).

Table 1 Comparison of results achieved under various conditions[a]



Entry	Various Conditions Base and Catalyst (equiv)	[b] Ratio (**2a**/**2b**/**2c**/**1**)
1	DIPEA (1.9), $FeCl_3$/Hacac (1/3, 0.1), 4h	48/6/2/44
2	DIPEA (1.9), $BiCl_3$/Hacac (1/3, 0.1), 4h	79/15/0/6
3	DIPEA (1.9), $MnCl_2$/Hacac (1/2, 0.1), 4h	78/5/3/14
4	DIPEA (1.9), $SnCl_2$/Hacac (1/2, 0.1), 4h	92/3/0/5
5	DIPEA (1.9), $SnCl_2$ (0.1), 1h	96/4/0/0
6	DIPEA (1.9), Hacac (0.2), 4h	29/4/0/67
7	DIPEA (1.9), 4h	31/4/0/65
8	DIPEA (1.5), $SnCl_2$ (0.05), 1h	95/4/0/1
9	DIPEA (1.2), $SnCl_2$ (0.05), 4h	89/5/0/6
10	DIPEA (1.5), $SnCl_2$▪$2H_2O$ (0.05), 1h	84/3/0/13
11[c]	DIPEA (1.8), $SnCl_2$▪$2H_2O$ (0.05), 1h	84/4/0/12
12	TEA (1.5), $SnCl_2$ (0.05), 4h	84/4/6/6
13	Pyridine (1.5), $SnCl_2$ (0.05), 4h	43/6/38/13
14	DABCO (1.5), $SnCl_2$ (0.05), 4h	61/2/15/22
15	DBU (1.5), $SnCl_2$ (0.05), 4h	14/4/2/80
16	K_2CO_3 (1.5), $SnCl_2$ (0.05), 4h	63/7/0/30
17[d]	DIPEA (1.5), $SnCl_2$ (0.05), 8h	58/21/9/12
18[d]	DIPEA (1.5), 8h	55/27/9/9

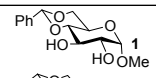
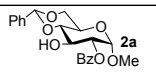
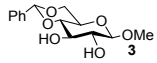
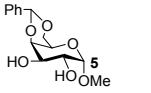
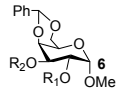
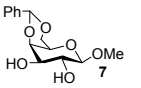
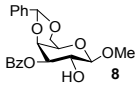
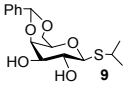
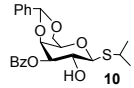
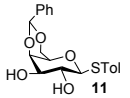
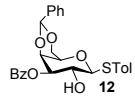
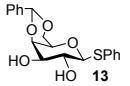
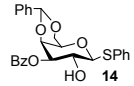
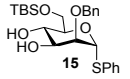
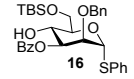
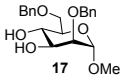
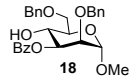
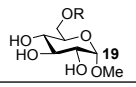
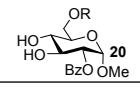
[a] Reaction conditions: substrate **1** (0.1mmol), BzCl (1.2 equiv), CH_3CN (0.5 mL), rt. [b] Ratios determined by ^1H NMR. [c] BzCl (1.4 equiv). [d] Bz_2O (1.2 equiv), 40 ℃.

We initially tested the system composed of 0.1 equiv of $FeCl_3$ and 0.3 equiv of acetylaceton in the presence of 1.9 equiv of DIPEA and 1.2 equiv of BzCl (Entry 1). Although the result showed a good selectivity (**2a/2b/2c**: 48/6/2), a large amount of **1** (44%) indicated low or no catalytic activity of this system. Interestingly, when $BiCl_3$ was used instead of $FeCl_3$, the conversion rate was greatly improved (94%) at the cost of selectivity (**2a/2b/2c**: 79/15/0, Entry 2). When $MnCl_2$ was used, a good selectivity (**2a/2b/2c**: 78/5/3) but still an unsatisfactory conversion rate (86%) was obtained (Entry 3). Encouragingly, when $SnCl_2$ was used, an excellent selectivity (**2a/2b/2c**: 92/3/0) and a satisfactory conversion rate (95%) were observed (Entry 4). To our surprise, a better result was obtained in the absence of the acetylacetone ligand (**2a/2b/2c/1**: 96/4/0/0, Entry 5). As expected, the absence of $SnCl_2$ led to low reactivity of the benzoylation (Entries 6 and 7). These results indicated that acetylacetone used as the ligand was superfluous while $SnCl_2$ was used as the catalyst. The excellent result was maintained when 0.05 equiv of $SnCl_2$ and 1.5 equiv of DIPEA were used (**2a/2b/2c/1**: 95/4/0/1, Entry 8). The use of 1.2 equiv of DIPEA led to a slight decrease in the conversion rate (89/5/0/6), and prolonging the reaction time (4 h in Entry 9) could not further increase this conversion rate. We wondered if the stannous chloride dihydrate ($SnCl_2$▪$2H_2O$) could be used instead of the stannous chloride. The result indicated that the conversion rate was reduced from 99% (Entry 8) to 87% (Entry 10), but the selectivity still remained (95/4 in Entry 8, 84/3 in

Entry 10). We then tried to eliminate the adverse effects caused by crystal water of $SnCl_2$▪$2H_2O$ by increasing the amount of DIPEA and BzCl simultaneously, but failed (Entry 11). We gave up studying the application of $SnCl_2$▪$2H_2O$ since the prices of $SnCl_2$▪$2H_2O$ and $SnCl_2$ are almost the same. Various bases, including TEA, pyridine, DABCO, DBU and K_2CO_3, were also tested in this benzoylation with 0.05 equiv of $SnCl_2$ (Entries 12 - 16). A relatively good result was also obtained with TEA as the base (**2a/2b/2c/1**: 84/4/6/6, Entry 12). The other results showed poor selectivities and/or poor conversion rates. When Bz_2O was used as the acylation reagent instead of BzCl, the reaction had to proceed at 40℃ due to the low activity of Bz_2O, but the poor selectivity was obtained regardless of the presence of $SnCl_2$, indicating that $SnCl_2$ did not show significant catalytic activity in this reaction (Entries 17 and 18). We also screened several commonly used solvents and identified acetonitrile (MeCN) as the optimal solvent under the catalyst loading (Table S1 and Figure S2 in SI).

Evaluation of this method using various substrates.

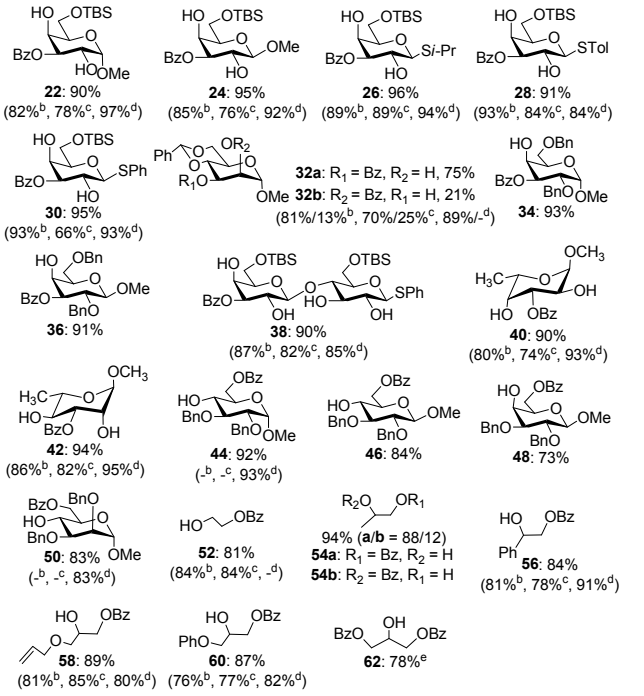
Table 2 $SnCl_2$-catalyzed regioselective benzoylation of substrates containing *trans*-diol[a]

Entry	Substrate	Product	Isolated Yields %
1	 **1**	 **2a**	92 (85[5b], 83[5a])
2	 **3**	No or poor selectivity	Low conversion rate[b]
3	 **5**	 **6**	**6a**: R_1=Bz R_2=H **6b**: R2=Bz R_1=H 95 (**6a/6b** = 65/35)
4	 **7**	 **8**	86 (81[5b])
5	 **9**	 **10**	93
6	 **11**	 **12**	87
7	 **13**	 **14**	90
8	 **15**	 **16**	89
9	 **17**	 **18**	85
10	 **19**	 **20**	**20a**: R=TBS 83 (84[5a]) **20b**: R=TBDPS 87

[a] Reaction conditions: substrate (0.1 - 0.2 mmol), $SnCl_2$ (0.05 equiv), DIPEA (1.5 equiv), BzCl (1.2 - 1.5 equiv), MeCN (0.5 - 1.0 mL), 1 - 2 h, rt. [b] No or low catalytic activity.

With the optimal condition (Entry 8 in Table 1) in hand, we further evaluated this method using glycoside substrates containing a *trans*-diol moiety in this benzoylation (Table 2). The results showed a protection pattern that is identical to the protection pattern when using stoichiometric amounts of organotin reagents: an axial group and an equatorial group are adjacent to the *trans*-diol moiety, which is the key to selectivity, and the hydroxyl group adjacent to the axial group is selectively protected.[3] It can be seen, benzoylation of substrates **1**, **7**, **9**, **11**, **13**, **15**, **17** and **19** by this method led to excellent yields of the selectively benzoylated products **2a**, **8**, **10**, **12**, **14**, **16**, **18** and **20** (83 - 93%, entries 1, 4 -10 in Table 2), and benzoylation of substrates **3** and **5** led to poor selectivies since two equatorial or axial groups are adjacent to their *trans*-diol moieties (Entries 2 and 3 in Table 2). However, an interesting result was that $SnCl_2$ showed no or low catalytic activity for the acylation of **3**, but showed high catalytic activity for the acylation of **5**, indicating that the adjacent axial group plays a key role for the catalytic activity. It is worth mentioning that these satisfactory selective acylation results for substrates containing a *trans*-diol have never been achieved using iron-based catalytic systems.[10-12a] Compared with organotins and catalysts shown in Figure 1d, this method has advantages in terms of substrate scope, product yield and reaction efficiency (Table S2 in SI).[4,5a,b,8a]

Scheme 1 $SnCl_2$-catalyzed regioselective benzoylation of substrates containing *cis*-, 1,2-, or 1,3-diol[a]

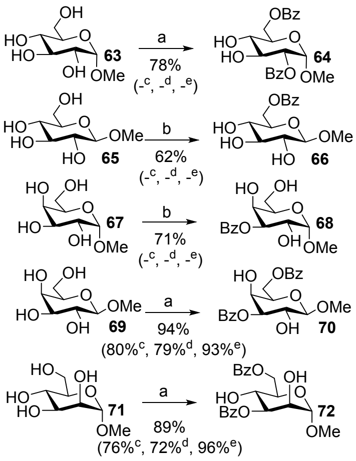


[a] Reaction conditions: substrates **21**, **23**, ··· **59**, **61** (0.1 - 0.2 mmol), $SnCl_2$ (0.05 equiv), DIPEA (1.2 -1.5 equiv), BzCl (1.2 - 1.5 equiv), MeCN (0.5 - 1.0 mL), 1 - 2 h, rt. [b] $Fe(acac)_3$ (0.1 equiv), DIPEA (1.2 equiv), BzCl (1.2 equiv), 2 – 8 h, rt (ref 10). [c] $FeCl_3$ (0.1 equiv), acetylacetone [Hacac] (0.31 equiv), DIPEA (1.9 equiv), BzCl (1.5 equiv), 4 – 12 h, rt (ref 11). [d] $FeCl_3$ (0.1 equiv), benzoyltrifluoroacetone [Hbtfa] (0.2 equiv), K_2CO_3 or DIPEA (1.9 equiv), BzCl (1.5 equiv), 1 – 12 h, rt (ref 12a). [e] DIPEA (2.5 equiv) and BzCl (2.5 equiv) were used.

This method was further applied to the selective benzoylation of substrates containing a *cis*-, 1,2-, or 1,3-diol moiety (scheme 1). The results are better/similar than/to those we previously reported in methods using iron (III)-catalysts.[10-12a] Furthermore, $SnCl_2$ showed the highest catalytic activity and this method

showed the highest reaction efficiency. For almost all substrates containing a *cis*-diol moiety, the products in which the equatorial hydroxyl group of the *cis*-diol moiety is benzoylated were obtained in 90 - 96% yields. For the substrates containing 1,2-, or 1,3-diol, the primary hydroxyl groups were selectively benzoylated. The manno-type substrate showed a relatively poor selectivity (**32a/32b**: 75/21%) in this method, which is likely due to acyl group migration, the benzoate group migrating from the equatorial position to the axial position.[13] Glycerol containing two primary hydroxyl groups produced a mixture of mono- and di-substituted products under the above conditions. Therefore, we used 2.5 equiv of DIPEA and 2.5 equiv of BzCl in this reaction, obtaining dibenzoylated product **62** in 78% yield.

Scheme 2 $SnCl_2$-catalyzed site-selective benzoylation of unprotected methyl glycosides

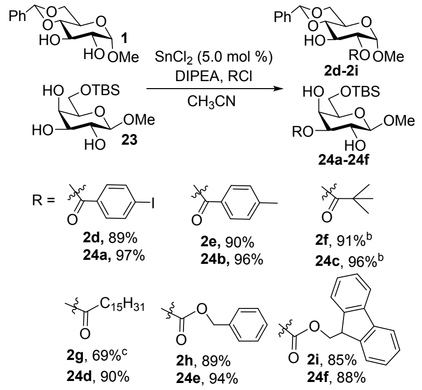


Reaction conditions: [a] Substrate (0.2 mmol), $SnCl_2$ (0.05 equiv), DIPEA (2.5 equiv), BzCl (2.5 equiv), MeCN (1.0 mL), 1 h, rt. [b] Substrate (0.2 mmol), $SnCl_2$ (0.05 equiv), DIPEA (1.5 equiv), BzCl (1.5 equiv), MeCN (1.0 mL), 0.5 - 1 h, rt. [c] $Fe(acac)_3$ (0.1 equiv), DIPEA (4 equiv), BzCl (4 equiv), MeCN (1.0 mL), 2 - 8 h, rt (ref 10). [d] $FeCl_3$ (0.1 equiv), Hacac (0.31 equiv), DIPEA (4.6 equiv), BzCl (4.0 equiv), 4 – 8 h, rt (ref 11). [e] $FeCl_3$ (0.1 equiv), Hbtfa (0.2 equiv), DIPEA (4.0 equiv), BzCl (3.0 equiv), 3 h, rt (ref 12a).

We then used free methyl glycosides **63**, **65**, **67**, **69** and **71** as substrates to evaluate this method (Scheme 2). These substrates firstly reacted with 1.5 equiv of BzCl in the method. For substrates **65** and **67**, 6-OBz-β-glucopyranoside **66** and 3-OBz-α-galactopyranoside **68** were obtained in moderate yields (62% and 71%, respectively). For substrates **63**, **69** and **71**, once their mono-benzoylated products were formed, these mono-benzoylated products were further benzoylated to form di-benzoylated products immediately. Therefore, substrates **63**, **69** and **71** were used to react with 2.5 equiv of DIPEA and 2.5 equiv of BzCl. Consequently, di-benzoylated products **64**, **70** and **72** were obtained in 78%, 94% and 89% yields respectively. For iron-based catalysts,[10-12a] only the di-benzoylation of substrates containing cis-diol (**69**, **71**) was feasible, which required more DIPEA and BzCl, and longer reaction time.

We then evaluated the scope of this method with various acylation reagents. Methyl-4,6-benzylidene-α-D-glucoside **1** containing *trans*-diol and methyl-6-OTBS-β-D-galactoside **23** containing *cis*-diol were used to test with various acylation reagents (Scheme 3), including *p*-I-BzCl, *p*-M-BzCl, PivCl, a long-chain aliphatic carboxylic acid chloride ($C_{15}H_{31}COCl$) and two chloroformates (CbzCl and FmocCl). In almost all cases, the desired products were obtained in high yields (85 - 97%). Only the reaction of substrate **1** with the long-chain aliphatic carboxylic acid chloride led to a relatively poor yield of 2-acylated product **2g** (69%). The reaction of substrates **1** or **23** with PivCl required 2.0 equiv of DIPEA and 2.0 equiv of PivCl for a highly efficient acylation.

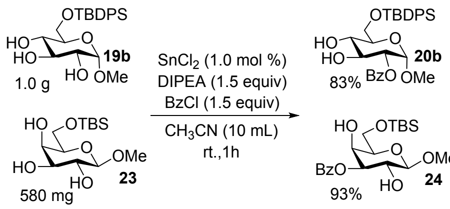
Scheme 3 $SnCl_2$-catalyzed selective acylation of **1** and **23** with various acylation reagents[a]



[a] Reaction conditions: substrate (0.1 mmol), $SnCl_2$ (0.05 equiv), DIPEA (1.5 equiv), RCl (1.5 equiv), MeCN (0.5 - 1.0 mL), 0.5 - 1 h, rt. [b] substrate (0.1 mmol), $SnCl_2$ (0.05 equiv), DIPEA (2.0 equiv), PivCl (2.0 equiv), MeCN (0.5 mL), 0.5 h, rt. [c] 3-acylated product was isolated in 26% yield.

This method was also tested in large-scale reactions where the amount of catalyst was reduced to 0.01 equivalent. Methyl 6-*O*-TBDPS-α-D-glucopyranoside **19b** (1.0 g) and methyl 6-*O*-TBS-β-D-galactopyranoside **23** (580 mg) were reacted with 1.5 equiv of BzCl in the presence of 0.01 equiv of $SnCl_2$ and 1.5 equiv of DIPEA in acetonitrile (10 mL) at room temperature for 1 h, giving expected monobenzoylated products **20b** and **24** in 83% and 93% yields respectively (Scheme 4). The reason why the 0.05 equiv of $SnCl_2$ was used above is that the amount of catalyst is too small to accurately weigh. However, this result indicated that even the use of 0.01 equiv of $SnCl_2$ was effective in catalyzing this regio/site-selective acylation.

Scheme 4 $SnCl_2$-catalyzed selective acylation in a large-scale

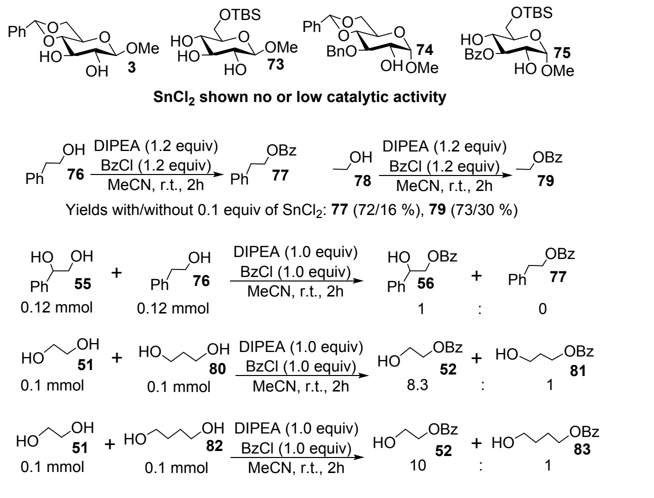


Mechanism studies.

In this method, $SnCl_2$ showed no or low catalytic activity for glycosides **3** and **73**, containing a *trans*-diol moiety without an adjacent axial group, for the glycoside **74**, containing a hydroxyl group adjacent to an axial group, and for the glycoside **75**, containing two spaced hydroxyl groups, one of which is adjacent to an axial group. This indicated that both the vicinal-diol moiety and the adjacent axial group played key roles for the catalytic activity of $SnCl_2$. In order to explore how $SnCl_2$ played a catalytic role (Scheme 5), we further compared the benzoylation of mono-hydroxyl substrates **76** and **78** with and without the catalysis of $SnCl_2$. It was observed that generation

rates of benzoylated products **77** and **79** were increased with the addition of 0.1 equiv of $SnCl_2$, indicating that $SnCl_2$ still played a catalytic role in the cases. We then used **76** and its corresponding diol substrate **55** for a competitive reaction. It was observed that only the product **56** starting from **55** was produced, indicating that an adjacent secondary hydroxyl group assists the catalysis of $SnCl_2$ to the benzoylation of the primary hydroxyl group of **55**. Competitive benzoylations in the presence of the equimolar amounts of 1,2-diol **51** and 1,3-diol **80** and the equimolar amounts of **51** and 1,4-diol **82** were also evaluated. The ratios of the products **52** and **81,** and the products **52** and **83** were 8.3/1 and 10/1 respectively. The results may indicate that the formation of a five-membered/six-membered ring intermediate between a tin atom and two hydroxyl groups is also a source of catalytic activity.

Scheme 5 Control experiments[a]



[a] The yields and ratio were determined by ^{1}H-NMR of crude mixture.

In order to explore the interaction between $SnCl_2$, DIPEA and diol, we added $SnCl_2$, DIPEA and 1,2-diol **55** into acetonitrile in sequence (Figure S3). It could be observed that, $SnCl_2$ was not able to be dissolved in acetonitrile (Figure S3a); the aggregated $SnCl_2$ rapidly dispersed into the solvent with the addition of DIPEA (Figure S3b), and then changed from white to yellow (Figure S3c); the formed milky suspension by $SnCl_2$ and DIPEA in acetonitrile could be stable for a long time at room temperature (Figure S3d); and this milky suspension became a clear and transparent solution with the addition of **55** (Figure S3e). This phenomenon should support the coordination of DIPEA to $SnCl_2$, and the coordination of **55** to $SnCl_2$ in the presence of DIPEA. We also explored the interaction between $SnCl_2$, DIPEA and 1,2-diol **55** (Figure S4) or *cis*-diol **35** (Figure S5) by ^{1}H NMR study. $SnCl_2$ could be dissolved into acetonitrile in the presence of DIPEA and **55** or **35.** It was observed that a proton connecting C-1° of **55** and the proton connecting C-3 of **35** shifted to upfield, and the other proton connecting C-1°, the proton connecting C-2° of **55,** and the proton connecting C-4 of **35** shifted to downfield slightly with the addition of $SnCl_2$. This might support the formation of a five-membered ring intermediate between a tin atom and the hydroxyl groups at 1°- and 2°-positions of **55** or 3- and 4-positions of **35**. In light of these studies, a catalytic mechanism was proposed in Figure 2. $SnCl_2$ can form Sn-O bond with a hydroxyl group in the presence of DIPEA (Figure 2a). Only slightly higher benzoylation catalytic activity is shown since the Sn-O bond is slightly easier to break than the H-O bond in this case. However, a hydroxyl group adjancent to this Sn-O species is prone to form a five-membered/six-membered ring intermediate with the tin atom in the presence of DIPEA, consequently leading to the more easily cleaved Sn-O bond and the much higher benzoylation catalytic activity (Figure 2b). Thus, the mechanism for benzoylation catalyzed by $SnCl_2$ is analogous to the proposed mechanism of organotin-mediated protection (Figure 2c).[3c] In the presence of DIPEA, a cyclic dioxolane/dioxane intermediate **C** forms between a diol **A** and a $SnCl_2$ molecule. Then, the intermediate further reacts with a acylating reagent to form the intermediate **D**, where one hydroxyl group is acylated and the other one is occupied by the Sn species. The intermediate **D** subsequently undergoes ligand exchange with the substrate diol to regenerate the cyclic intermediate **C** and the selective acylated product **E**. The regioselectivity is controlled by the steric and stereoelectronic which has been previously discussed.[3c] The possible acyl group migration under the basic condition may decrease the selectivity of acylation.[13]

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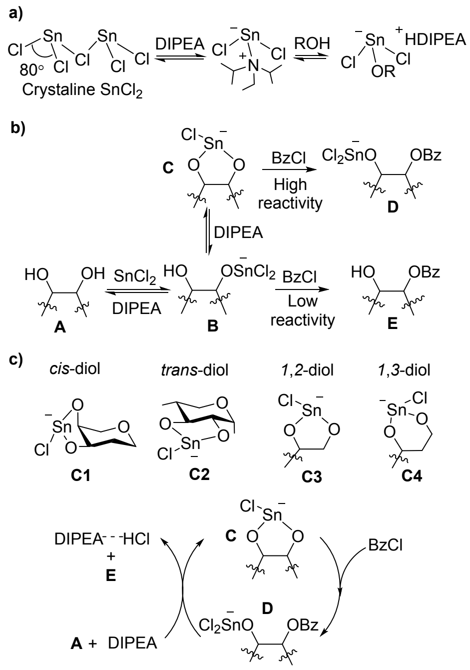

Figure 2 Proposed catalytic mechanism.

Conclusions

Researchers have been trying to find low- or non-toxic reagents that can replace organotin reagents in carbohydrate protection strategies for decades. However, all of these previously reported reagents are inferior to organotin reagents in one or more of the aspects, including selectivity, substrate scope, reaction efficiency and cost. For the first time, we find a low-toxic reagent for acylation, $SnCl_2$, which is superior or comparable to organotin reagents in all of these aspects. $SnCl_2$ still showed high catalytic activity when its used amount was as low as 1 mole%. The substrate scope is as broad as that in methods using stoichiometric amounts of organotin reagents, including 1,2-diols, 1,3-diols, glycosides containing *cis*-diol, and

glycosides containing *trans*-diol. The catalytic activity and selectivity were proposed to originate from the formation of a cyclic dioxolane/dioxane-type intermediate between a diol and Sn species in the presence of DIPEA. The resulting selectivities are high, and the product pattern can be predicted, which is the same as that of traditional organotin-mediated approaches. Usually, the simpler the molecular structure of a reagent, the cheaper and more readily available the reagent is. Therefore, among all the reagents previously reported, Taylor's reagent, iron-based catalysts, and organotins are more practical due to their simple molecule structure. The structure of $SnCl_2$ is the simplest so that $SnCl_2$ is even cheaper than dibutyltin oxide. We compared these reagents with $SnCl_2$ in table 3. It can be seen, the acylation using $SnCl_2$ showed the highest reaction efficiency. Neither Taylor's reagent nor iron-based catalysts showed catalytic activity on *trans*-diol substrates. Thus, $SnCl_2$ as a green and extremely cheap reagent, should be the best catalyst in regio/site-selective acylation. However, it has not been found that $SnCl_2$ exhibited catalytic activity for sulfonylation. Though $SnCl_2$ exhibits high catalytic activity for acetylation, the resulting selectivity is relatively poor likely due to acetyl group migration. Therefore, the use of $FeCl_3$ and Hbtfa should be the best choice for sulfonylation, while the use of $Fe(acac)_3$ should be the best choice for acetylation.

Table 3 Comparison of various acylation methods in practicability.

Catalysts	[a]Used amount	[a,b] Cost (USD/mol)	Sulfon-ylation	*Trans*-diols	Acyla-tion
Taylor's reagent	5-10%	178-356	Y	N	rt., 4-12h
$Fe(acac)_3$	10%	53	N	N	rt., 2-8 h
Hacac	30%	13	N	N	rt., 4-12 h
Hbtfa	2-20%	13-130	Y	N	rt., 1-12 h
Bu_2SnO	100%	130	Y	Y	[c]-
(toxic)	1-10%	1-13	Y	Y	rt., 12 h
$SnCl_2$	1-5%	1-5	N	Y	rt., 1-2 h

[a] Relative to substrates (1 mol). [b] The same grade in the same company. [c] Two steps' operation.

Conflicts of interest

There are no conflicts to declare.

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