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Catalytic and Regioselective Oxidation of Carbohydrates To Synthesize Keto-Sugars under Mild Conditions

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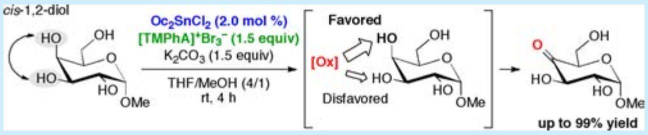
S Supporting Information

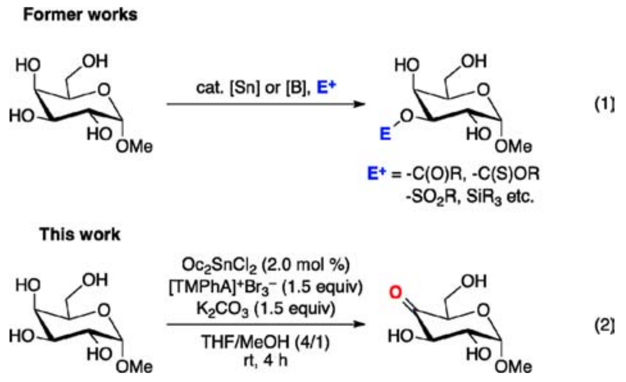
ABSTRACT: A new catalytic and regioselective approach for the synthesis of keto-sugars is described. An organotin catalyst, Oc_2SnCl_2, in the presence of trimethylphenylammonium tribromide ($[TMPhA]^+Br_3^-$) accelerates the regioselective oxidation at the *"axial"*-OH group of 1,2-diol moieties in galactopyranosides. The reaction conditions can also be used for the regioselective oxidation of various carbohydrates.



Carbohydrates remain important targets in various fields, such as synthetic organic chemistry and biochemistry because of their unique and specific bioactivities.[1] Particularly, aminosaccharides have attracted attention for their antibacterial activities against *Helicobacter pylori*, which is considered to be the cause of stomach cancer and gastric ulcer.[2] Thiosaccharides have also proven useful for investigating biological phenomena, including adhesion, proliferation, and apoptosis in the process of carcinogenesis, and recently have attracted much attention as bioprobes and enzyme inhibitors.[3] We are strongly interested in keto-sugars as useful precursors for the synthesis of these pseudosaccharides. Various catalytic methods for the regioselective oxidation of a primary-OH group of unprotected carbohydrates are well-known.[4] Additionally, many known methods for transforming a C═O bond in keto-sugars into C−C, C−N, C−O, and C−S bonds are available.[5,6a] Conversely, catalytic methods for the regioselective oxidation of a particular secondary-OH group of unprotected carbohydrates have been only reported by Minnaard and co-workers.[6] They succeeded in the pioneering regioselective oxidation of D-Glc derivatives with a catalytic amount of $[(neocuproine)PdOAc]_2OTf_2$. However, the catalytic oxidation reaction of carbohydrates except D-Glc derivatives has not been shown.

Over the past decade, various catalytic methods with organotin or borinic acid catalysts for the regioselective functionalization of carbohydrates have been developed.[7] A remarkable advantage of these catalyses is that the catalysts promote several types of functionalization of the *"equatorial"*-OH group in *cis*-1,2-diol moieties (or moieties where equatorial-OH and axial-OR[8] groups are next to one another) in unprotected and partially protected carbohydrates (eq 1 of Scheme 1). Herein, we report a new catalytic approach for the regioselective oxidation of an *"axial"*-OH group in *cis*-1,2-diol moieties in unprotected carbohydrates to straightforwardly synthesize the corresponding keto-sugars under mild conditions (eq 2 of Scheme 1).

Scheme 1. Catalytic and Regioselective Functionalizations of Unprotected Carbohydrates



As part of our efforts on the catalytic regioselective oxidation of unprotected carbohydrates, we first demonstrated the oxidation of Me-α-D-Gal **1** under a variety of conditions (Table 1). Oxidation at C(4)−OH of **1** occurred regioselectively in the presence of Oc_2SnCl_2 (2.0 mol %), trimethylphenylammonium tribromide ($[TMPhA]^+Br_3^-$) as the oxidant (1.5 equiv), and anhydrous K_2CO_3 (1.5 equiv) in THF/MeOH (4/1) (entry 1, 94% yield). The spectroscopic data of **2** agreed well with known data for the keto-sugar.[6f] $[TMPhA]^+Br_3^-$ has been widely used as a more readily handled reagent instead of Br_2 for the bromination reaction at the α-position of carbonyl compounds such as ketones and esters.[9] Recently, Sayama and co-workers found that a combination of $[TMPhA]^+Br_3^-$ (4.0 equiv) and $SbBr_3$ or $CuBr_2$ (20 mol %) was applicable to the oxidation of secondary alcohols.[10]

In the absence of Oc_2SnCl_2, as expected, the catalytic oxidation reaction did not afford **2** at all (entry 2). Moreover, the reaction hardly progressed in the absence of K_2CO_3 (entry 3). When Bu_2SnCl_2 and Dd_2SnCl_2 were employed instead of Oc_2SnCl_2, both oxidation reactions smoothly proceeded (entries 5 and 6, 86% and 88% yields, respectively). On the other hand, when Oc_2SnCl_2 was replaced with other organotin or inorganic tin catalysts, the yields were decreased (entries 4 and 7−12).

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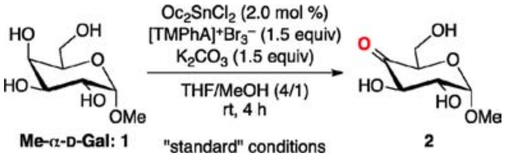
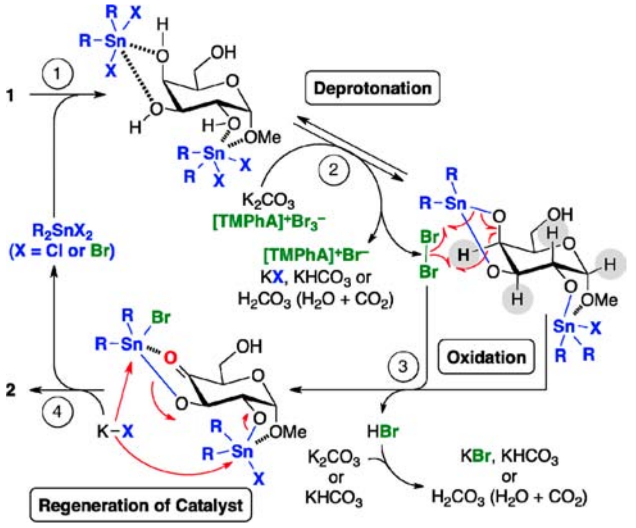
Table 1. Catalytic and Regioselective Oxidation of Methyl-α-D-Galactopyranoside



entry	variation from the "standard" conditions	yield (%)
1	none	94
2	no Oc_2SnCl_2	0
3	no K_2CO_3	0
4	Me_2SnCl_2	45
5	Bu_2SnCl_2	86
6	Dd_2SnCl_2	88
7	Ph_2SnCl_2	62
8	Oc_2SnO	70
9	Bu_2SnO	70
10	$SnCl_4$	48
11	$SnCl_2$	54
12	$SnBr_2$	51
13	$[TMA]^+Br_3^-$	90
14	$[TBA]^+Br_3^-$	–[94][a]
15	$[BnTMA]^+Br_3^-$	18
16	$[BMIm]^+Br_3^-$	92
17	Ph_3BiCl_2	0
18	Br_2	93
19	Li_2CO_3	73
20	Na_2CO_3	88
21	Cs_2CO_3	85
22	$KHCO_3$	70
23	PEMP	0
24	pyridine	0
25	2,4,6-collidine	28
26	THF	76
27	MeOH	78
28	PhMe/MeOH (4/1)	71
29	1,4-dioxane/MeOH (4/1)	85
30	CPME/MeOH (4/1)	68
31	THF/EtOH (4/1)	76
32	THF/H_2O (4/1)	2
33	addition of TEMPO or HQME (1.5 equiv)	0

[a] The yield was determined by ^1H NMR analysis using a calibrated 1,4-bis(trifluoromethyl)benzene as the internal standard. $[TMA]^+Br_3^-$ = tetramethylammonium tribromide. $[TBA]^+Br_3^-$ = tetrabutylammonium tribromide. $[BnTMA]^+Br_3^-$ = benzyltrimethylammonium tribromide. $[BMIm]^+Br_3^-$ = 1-butyl-3-methylimidazolium tribromide. PEMP = 1,2,2,6,6-pentamethylpiperidine. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl. HQME = hydroquinone monomethyl ether.

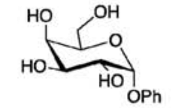
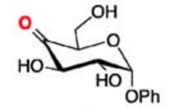
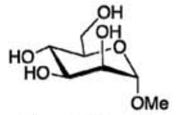
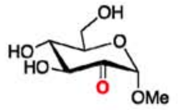
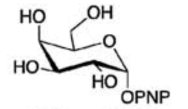
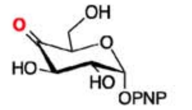
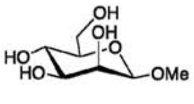
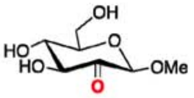
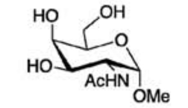
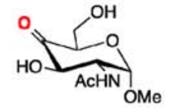
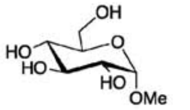
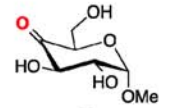
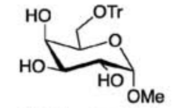
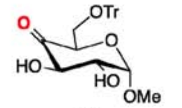
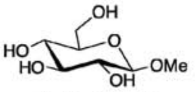
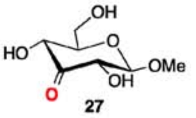
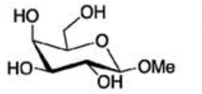
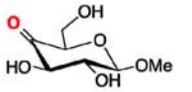
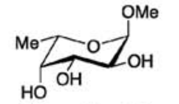
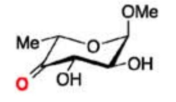
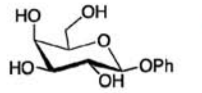
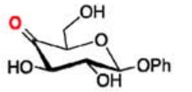
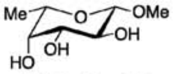
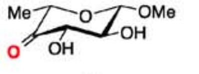
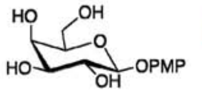
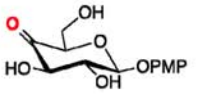
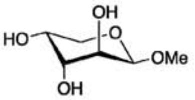
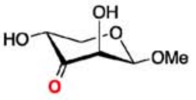
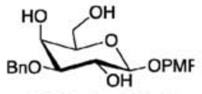
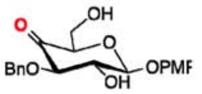
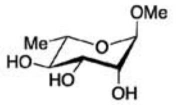
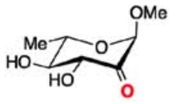
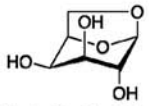
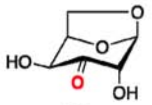
Scheme 2. Plausible Mechanism for the Catalytic and Regioselective Oxidation of Carbohydrates



Although several organic and organometallic oxidants were examined instead of $[TMPhA]^+Br_3^-$, they did not lead to an improvement in yield (entries 13 and 15–18). When tetrabutylammonium tribromide ($[TBA]^+Br_3^-$) was used as the oxidant, the oxidation reaction was successfully accomplished. However, we could not isolate **2** as a pure product because of the difficulty of removing the residue derived from the oxidant by silica gel chromatography (entry 14). When 1,2,2,6,6-pentamethylpiperidine (PEMP), which we often used in previous studies,[7d−f] was employed instead of K_2CO_3, contrary to our expectations, the oxidation reaction did not occur (entry 23). Although several bases and solvents were tested instead of K_2CO_3 and THF/MeOH, respectively, satisfactory results were not obtained (entries 19–22, 24–32). Typical radical scavengers were tested to help clarify the oxidation mechanism. Consequently, the progress of the catalytic reaction was completely halted in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or hydroquinone monomethyl ether (HQME) (entry 33).

Next, we applied the best suitable conditions to various unprotected carbohydrates (Table 2). When α-D-Gal **3** and **5** were used as the reactants, desirable yields of **4** and **6** were obtained (entries 1 and 3, 92% and 98% yields, respectively). In the case of the oxidation of **7**, the keto-sugar **8** was obtained in 97% yield without bromination at the α-position of the Ac-group (entry 3). A carbohydrate bearing a bulky protective group at the C(6)-position was also oxidized to afford the desired keto-sugar **10** in good yield (entry 4, 89% yield). In addition, the catalytic oxidation of β-D-Gal **11**, **13**, **19** and L-Fuc **28**, **30** proceeded smoothly in 94–99% yields (entries 5, 6, 9, 14, and 15).[11] Under the optimized conditions, the keto-sugar **16** was selectively obtained in 69% yield (entry 7).[12] When the oxidation of α-D-Man **21**, β-D-Man **23**, and α-L-Rhm **34** with 10 mol % of Oc_2SnCl_2 was attempted, unfortunately, high yields were not obtained (entries 10, 11, and 17, 47%, 44%, and 52% yields, respectively).[12,13] Taking our previous studies into consideration,[7d−g] these unsatisfactory yields may be caused by the insufficient reactivity of $[TMPhA]^+Br_3^-$ rather than the interaction between Oc_2SnCl_2 and a *cis*-1,2-diol moiety in **21**, **23**, and **34**. On the other hand, protected-β-D-Gal **17**, a carbohydrate with a protective group at the equatorial-OH group of the *cis*-1,2-diol moiety, was not oxidized at all (entry 8). This is because $[TMPhA]^+Br_3^-$ might not be able to approach equatorial-H at the C(4)-position of **17** by the steric hindrance of the Bn-group. Moreover, the oxidation of α-D-Glc **25** and β-D-Glc **26**, which are unprotected carbohydrates without *cis*-1,2-diol moieties, selectively afforded the corresponding keto-sugar **2** and **27**, respectively. However, the yields were far from satisfactory because of the low reactivities of **25** and **26** (entries 12 and 13, 39% and 28% yields, respectively). Although increasing the amount of Oc_2SnCl_2 provided better yields (58% and 49% yields, respectively),[12] extension of the reaction time or a higher reaction temperature was not effective for improving the yields. In the case of the oxidation of β-D-Ara **32**, a mixture of plural

Table 2. Catalytic and Regioselective Oxidation of Carbohydrates[a]

entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	 Ph-α-D-Gal: 3	 4	79^{b} $[92]^{b,c}$	10	 Me-α-D-Man: 21	 22	31 $[47]^{c}$
2	 PNP-α-D-Gal: 5	 6	98	11	 Me-β-D-Man: 23	 24	28 $[44]^{c}$
3	 Me-(2-*N*-Ac)-α-D-Gal: 7	 8	97	12	 Me-α-D-Glc: 25	 2	39 $[58]^{c}$
4	 6-*O*-Tr-α-D-Gal: 9	 10	79 $[89]^{c}$	13	 Me-β-D-Glc: 26	 27	28 $[49]^{c}$
5	 Me-β-D-Gal: 11	 12	94	14	 Me-α-L-Fuc: 28	 29	94 $[94]^{b}$
6	 Ph-β-D-Gal: 13	 14	81^{b} $[96]^{b,c}$	15	 Me-β-L-Fuc: 30	 31	98 $[98]^{b}$
7	 PMP-β-D-Gal: 15	 16	41 $[69]^{c}$	16	 Me-β-D-Ara: 32	 33	$–^{d}$
8	 3-*O*-Bn-β-D-Gal: 17	 18	0 $[0]^{c}$	17	 Me-α-L-Rhm: 34	 35	39 $[52]^{c}$
9	 1,6-Anhydro-β-D-Gal: 1	 20	99 $[98]^{b}$				

[a] Reaction conditions as a standard: Oc_2SnCl_2 (2.0 mol %), $[TMPhA]^{+}Br_3^{-}$ (1.5 equiv), and K_2CO_3 (1.5 equiv) in THF/MeOH (4/1) at room temperature for 4 h. [b] The oxidation was carried out in THF. [c] 10 mol % of Oc_2SnCl_2 was used. [d] A mixture of three keto-sugars was isolated without remarkable regioselectivity. PNP = *p*-nitrophenyl. Ac = acetyl. TBS = *tert*-butyldimethylsilyl. Bz = benzoyl. Bn = benzyl.

keto-sugars was isolated without remarkable regioselectivity because of the presence of two axial-OH groups (C(2)− and C(3)−OH groups) of a *cis*-1,2-diol moiety and a moiety where an equatorial-OMe and an axial-OH group are next to one another, as in **32** (entry 16).

Mechanistic studies on the oxidation of alcohols using trimethylphenylammonium tribromide have been unclear.[9] On the basis of some relevant studies[14] and based on our results shown in Tables 1 and 2, we propose the following as a plausible reaction mechanism for this catalysis (Scheme 2). First, selective coordination of the organotin catalyst with *cis*-1,2-diol moieties (or moieties where equatorial-OR[8] and axial-OH groups are next to one another) in carbohydrates increases the acidity of both hydroxy groups (step 1). Then, both hydroxy groups are deprotonated by K_2CO_3 (step 2). Next, Br_2 generated from $[TMPhA]^{+}Br_3^{-}$ approaches the less hindered C−H bond, and the bromo radical may abstract the equatorial-H atom to afford the desired keto-sugar with high regioselectivity (step 3). Finally, the organotin catalyst is regenerated, thus completing the catalytic cycle (step 4).

In summary, we have developed a new catalytic method for the regioselective oxidation of unprotected carbohydrates using $[TMPhA]^{+}Br_3^{-}$ and K_2CO_3 to produce keto-sugars in a single step. The oxidation reaction can be run with 2.0 mol % of Oc_2SnCl_2 in high yield and excellent regioselectivity under mild conditions. In addition, this catalytic method is now applicable to the regioselective oxidation of a wide range of unprotected carbohydrates. More examples, such as the oxidation of polysaccharides, or natural glycosides containing multiple hydroxy groups, are under investigation.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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