A General Strategy for the Synthesis of Rare Sugars via Ru(II)-catalyzed and Boron-mediated Selective Epimerization of 1,2-*trans*-diols to 1,2-*cis*-diols

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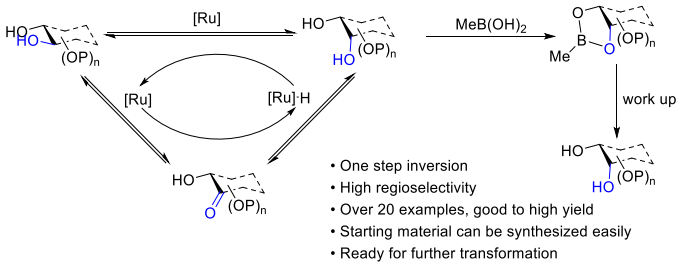
Supporting Information Placeholder

ABSTRACT: Human glycans are primarily composed of nine common sugar building blocks. On the other hand, several hundred monosaccharides have been discovered in bacteria and most of them are not readily available. The ability to access these rare sugars and the corresponding glycoconjugates can facilitate the studies of various fundamentally important biological processes in bacteria, including interactions between microbiota and the human host. Many rare sugars also exist in a variety of natural products and pharmaceutical reagents with significant biological activities. Although methods have been developed for the synthesis of rare monosaccharides, most of them involve lengthy steps. Herein we report an efficient and general strategy that can provide access to rare sugars from commercially available common monosaccharides via a one-step Ru(II)-catalyzed and boron-mediated selective epimerization of 1,2-*trans*-diols to 1,2-*cis*-diols. The formation of boronate esters drives the equilibrium towards 1,2-*cis*-diol products, which can be immediately used for further selective functionalization and glycosylation. The utility of this strategy was demonstrated by the efficient construction of glycoside skeletons in natural products or bioactive compounds.



■ INTRODUCTION

Carbohydrates are vital components of many glycoconjugates, which are ubiquitous in nature and play key roles in different biological processes.[1] Although there are only nine common monosaccharides found in vertebrate glycans[2], over 600 uncommon or rare monosaccharides have been discovered in bacteria. Rare sugars also exist in a variety of bioactive natural products and pharmaceutical reagents (Fig. **1a**).[3] It has been shown that the rare sugar motifs are often essential for their pharmacological activity,[4] as the sugar motif can improve the bioavailability, potency, or other pharmacological properties.[5] Most rare sugar motifs on bacterial glycoconjugates are not present on human cell surface, which help to differentiate pathogens and host cells in drug discovery, especially for the development of vaccines.[5b, 5c] It is therefore significant to develop efficient methods to access diverse ranges of rare sugars and their analogues.

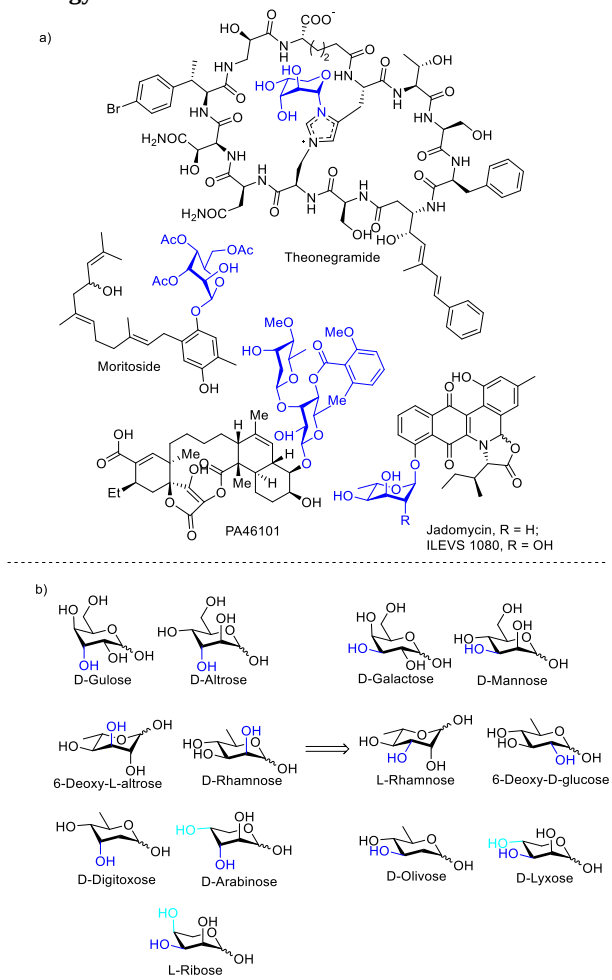
Two main strategies have been actively pursued for the chemical synthesis of rare sugars: 1) synthesis from naturally occurring common monosaccharides and 2) *de novo* synthesis from simple feedstock chemicals.[5c] Most methods reported to date using the first strategy often require extensive functional group manipulations and suffer from low selectivity when the seemingly identical hydroxyl groups in carbohydrates need to be differentiated.[6] Although *de novo* synthesis can avoid the selectivity issue, only certain types of rare sugars can be prepared efficiently.[7] The synthesis of rare sugars is still challenging and strategies that can access a broad range of rare sugars are lacking, albeit significant amount of efforts devoted to this area.[5c, 8] We have been interested in developing novel methods for the preparation of rare sugars and reported strategies for the *de novo* syntheses of a series of deoxy rare sugars recently.[9] We envision that numerous rare sugars can be derived from common sugars if the stereochemistry of the secondary OH groups can be efficiently and selectively manipulated. For example, a systematic strategy can be realized for the synthesis of many rare sugars if 1,2-*trans*-diols in common monosaccharides can be epimerized to 1,2-*cis*-diols, which requires the inversion of one OH group selectively (Fig. **1b**). Since common monosaccharides are considered as renewable non-fossil resources, conversion of the abundant naturally occurring carbohydrates to more valuable chemicals would be more sustainable preparation methods.[10]

Chemoenzymatic or enzymatic methods were developed to achieve hydroxyl group inversion, however, they suffer from limited substrate scope and low conversion ratio.[3f, 11] Traditional chemical methods for the inversion of hydroxyl groups, either by stepwise oxidation-reduction process or by S_N2 reactions, have obvious drawbacks (Scheme **1a-b**). In most cases, it requires the prefunctionalization of starting materials, which may involve lengthy functional group manipulations, the use of stoichiometric amount of toxic or sensitive reagents, production of large amount of waste, low yields and low selectivity. To address these issues, significant efforts have been devoted to site-selective oxidation. In addition to the classical methods employing toxic tin reagents[12], transition metal catalyzed site-selective oxidation of the C3-OH of pyranosides was reported by Waymouth [13] and Minnaard[14]. The keto sugar generated from unprotected or partially protected glycoside could undergo further transformation[15] and has been used in OH epimerization[15a] and carbohydrate-based antibiotic synthesis[16]. However, stoichiometric oxidants and reductants are necessary and the scope of the oxidation is limited in terms of the types of substrates that can be employed and the position that can be selectively oxidized. In addition, it is not clear if the selective inversion always happen in the reduction step for carbohydrates with different configuration. Nevertheless, it is one of the most important breakthroughs in the field as evidenced by its applications.

During our investigation, Wendlandt and coworkers reported an elegant photo-catalytic site-selective OH epimerization reaction for the preparation of rare sugars from unprotected or minimally protected common sugars (Scheme **1c**).[17] It provides an efficient practical method to access a series of unprotected rare sugars. The isolated yields are as high as 69% to 82% when α-methylglucoside, β-methylfucoside, α-methylxyloside, and 6-silyl protected α-methylglucoside were employed as the common sugar starting materials, though the yields dropped to 24% to 48% when β-methylgalactoside, β-methylarabinoside, N-acetylglucosamine, and 1,6-anhydro sugars were used as the substrates. Interestingly, completely unprotected reducing sugars including glucose, 6-deoxyglucose, fucose

and 2-deoxyglucose could also participate in the site-selective epimerization reaction with isolated yields ranging from 29% to 55%. Most impressively, OH inversion products were also successfully obtained from disaccharide sucrose and trisaccharide raffinose in 53% and 25% isolated yields, respectively. In most cases, the C3-OH group underwent selective inversion reaction. Given the number of rare sugars from nature and the limited methods available, there are great needs for the development of additional efficient and general reactions based on various mechanisms. We herein report a novel Ru(II)-catalyzed and boron-mediated method for the preparation of rare sugars containing a 1,2-*cis*-diol from common sugars with a 1,2-*trans*-diosl motif (Scheme **1d**). The 1,2-*cis*-diol products can be used immediately for further selective functionalization and glycosylation, while the epimerized products from unprotected sugars may need to be further manipulated for chemical glycosylation.

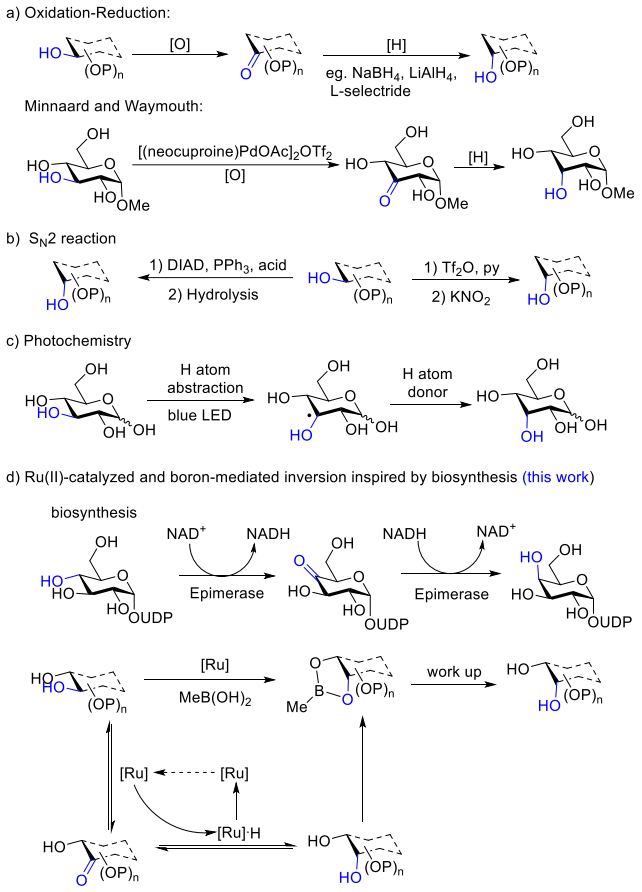
Figure 1. Selected Rare Sugars and Proposed Synthetic Strategy



a) Examples of bioactive compounds that contain rare sugar motifs. b) Proposed synthesis of rare sugars from common monosaccharides *via* epimerization of 1,2-*trans*-diols to 1,2-*cis*-diols

Our strategy was inspired by the biosynthesis of carbohydrates mediated by enzymes in short-chain dehydrogenase/reductase (SDR) family.[3f, 18] After oxidation of a specific hydroxyl group in the sugar by NAD^+, the keto sugar can either be reduced by NADH to give epimerized product, or undergo deprotonation/protonation at the α-position and then reduced by NADH to give a rare sugar with both hydroxyl groups epimerized. NAD^+/NADH cycle is crucial during this process. We envision that a [Ru]/[Ru]-H cycle, which has been used in hydrogen borrowing/hydrogen transfer reactions[19] including alcohol isomerization reactions,[20] could be used for the equilibration of hydroxyl groups in carbohydrates. The addition of a boron reagent may then shift the equilibrium to the formation of 1,2-*cis*-diols. However, hydrogen abstraction from sterically hindered secondary alcohols is much more difficult than primary alcohols.[21] It is not clear if secondary alcohols in carbohydrates can participate in the Ru-catalyzed hydrogen abstraction prior to our investigation. In addition, the compatibility of the metal catalyst with the boron adduct and the type of boron reagents are unknown under the hydrogen borrowing/hydrogen transfer reaction conditions.

Scheme 1. Strategies for the Chemical Synthesis of Rare Sugars by OH Inversion Reactions



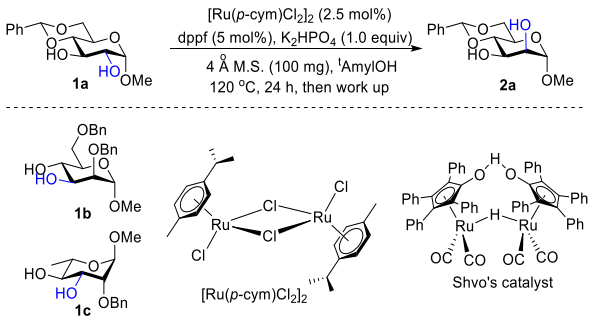
■ RESULTS AND DISCUSSION

Optimization of Reaction Conditions.

We first began our investigation on selective OH inversion using **1a** as the model substrate (Table **1**). A brief summary is depicted in Table **1** (See Supplementary Tables **S1**–**S4** for detailed optimization). After screening various Ru catalysts, $[Ru(p\text{-cym})Cl_2]_2$ was selected and product **2a** was prepared with an NMR yield of 46% (Entry **1**). The inversion occurred selectively on the hydroxyl group adjacent to the axial substituent. Without the dppf ligand, no product was observed (Entry **2**). Almost the same yield was obtained using catalytic amount of K_2HPO_4, while no product was observed in the absence of base (Entry **3**-**4**). Having established the conditions that can equilibrate the starting material and the product, which was further demonstrated later, we started investigating chelating reagents that may promote the formation of more *cis*-diols. It has been shown that boric acid can promote the isomerization between aldose and ketose[11a, 22] and boronic acids or boronate esters can be used for protection and regioselective functionalization of *cis*-diols.[23] Inspired by these reports, we first explored various boronic acids for the OH inversion reactions, though it is not clear if they are compatible with the reaction conditions and can drive

the equilibrium under the reaction conditions. The addition of 1.2 equiv. of $PhB(OH)_2$ completely shut down the reaction (Entry **5**). Considering that the formation of boronate esters usually requires azeotropic removal of water, we decided to change the solvent from ^{t}AmylOH to toluene. Interestingly, while no reaction occurred using $PhB(OH)_2$ and *p*-$MeOPhB(OH)_2$, about 13% product was observed on NMR when ^{n}BuB$(OH)_2$ was employed (Entry **6**-**8**). To our delight and also surprise, the addition of less sterically hindered alkyl boronic acid, $MeB(OH)_2$, led to a 68% yield of the desired product (Entry **9**). The equilibrium can indeed be shifted to the 1,2-*cis*-diol side under the reaction condition. We then further extended the reaction time to 32 h and a slightly higher yield was obtained (Entry **10**). Increasing the amount of $MeB(OH)_2$ to 2.0 equiv. increased the yield to 86% (Entry **11**). Changing the catalyst to $Ru(PPh_3)_3Cl_2$ improved the yield to 95% based on NMR and a 94% isolated yield was obtained (Entry **12**).

Table 1. Initial Screening of Conditions for Common Glycosides with a 1,2-Diol for Alkylation[a]



Entry	S.M.	Solvent	Alterations	Yield [%][a]
1	**1a**	^{t}AmylOH	None	46
2	**1a**	^{t}AmylOH	Without ligand	N.P.
3	**1a**	^{t}AmylOH	Without base	N.P.
4	**1a**	^{t}AmylOH	10 mol% K_2HPO_4 instead of 1.0 equiv. K_2HPO_4	44
5	**1a**	^{t}AmylOH	1.2 equiv. $PhB(OH)_2$	N.P.
6	**1a**	toluene	1.2 equiv. $PhB(OH)_2$	N.P.
7	**1a**	toluene	1.2 equiv. *p*-$OMePhB(OH)_2$	trace
8	**1a**	toluene	1.2 equiv. ^{n}BuB$(OH)_2$	13
9	**1a**	toluene	1.2 equiv. $MeB(OH)_2$	68
10	**1a**	toluene	1.2 equiv. $MeB(OH)_2$, 32 h	76
11	**1a**	toluene	2.0 equiv. $MeB(OH)_2$	86
12[d]	**1a**	toluene	**5 mol% $Ru(PPh_3)_3Cl_2$, 1.2 equiv. $MeB(OH)_2$**	**95(94[b])**
13[d]	**1b**	toluene	5 mol% $Ru(PPh_3)_3Cl_2$, 1.2 equiv. $MeB(OH)_2$	N.P.
14[d]	**1c**	toluene	5 mol% $Ru(PPh_3)_3Cl_2$, 1.2 equiv. $MeB(OH)_2$	N.P.
15[e]	**1b**	toluene	5 mol% Shvo's cat., 1.2 equiv. $MeB(OH)_2$	34/50[c]
16[e]	**1b**	toluene	5 mol% Shvo's cat., 1.2 equiv. $MeB(OH)_2$, 36 h	12/21[c]
17[e]	**1b**	toluene	5 mol% Shvo's cat., 3.0 equiv. $MeB(OH)_2$	35/70[c]
18[e]	**1b**	toluene	5 mol% Shvo's cat., 5.0 equiv. $MeB(OH)_2$	69/8[c]
19[e]	**1b**	toluene	5 mol% Shvo's cat., 5.0 equiv. $MeB(OH)_2$, degas	67/25[c]
20[e]	**1b**	**toluene**	**5 mol% Shvo's cat., 5.0 equiv. $MeB(OH)_2$, degas, 200 mg M.S.**	**85(85[b])/8[c]**

[a] All reactions were carried out in a 25-ml Schlenk tube under argon atmosphere on a scale of 0.1 mmol, and yields were determined by ^{1}H NMR spectroscopy of the crude product by using CH_2Br_2 as internal standard. [b] Isolated yield. [c] Yields of the recovered starting material based on ^{1}H NMR spectroscopy of the crude product by using CH_2Br_2 as internal standard. [d] Without dppf. [e] Without dppf and K_2HPO_4.

With the optimized condition in hand, we next examined the scope of substrates. To our surprise, no product was observed for substrates **1b** or **1c** under the previously optimized condition (Entry **13**-**14**). This is puzzling because the adjacent substituents for the 1,2-*trans*-diols in substrates **1a**, **1b** and **1c** are very similar. The 1,2-*trans*-diols in these substrates are all adjacent to one equatorial substituent and one axial substituent. The main difference between substrates **1a** and **1b** or **1c** is the γ position of the predicted reactive OH group–the blue OH that will undergo inversion. Substrate **1a** has an equatorial substituent on the γ position, while **1b** and **1c** have an axial substituent on the corresponding positions. We then further investigated the reaction conditions for substrates **1b** and **1c**, by using different bases, adding more boronic acid or other additives (see Tables **S6**). However, none of them yielded any product. We then examined different Ru catalysts. We finally obtained a 34% yield of the inversion product and a 50% yield of recovered starting material using Shvo's catalyst (Entry **15**). For comparison, without $MeB(OH)_2$, only a 16% yield of product was observed. A 21% yield product was observed with decreased catalyst loading (Table **S6**). Further prolonging the reaction time to 36 h caused a decrease in both yield and recovery of starting materials (Entry **16**). After carefully analyzing the byproducts from the reactions, we found that some of the starting materials decomposed to tri-ol or tetra-ol, which appeared to be responsible for the low yields of products and recovered starting materials. This indicates that hydrogenolysis can compete with the reduction of the ketone intermediate and consume [Ru]-H in this case, suggesting that shifting the equilibrium more towards the 1,2-*cis*-diol by trapping the product with more boronic acid may reduce the hydrogenolysis byproduct. After increasing the amount of $MeB(OH)_2$ to 3.0 equiv., we obtained more products and more recovered starting materials (Entry **17**). Further increasing the amount of $MeB(OH)_2$ to 5.0 equiv. gave us a 68% yield of product (Entry **18**). It is worth noting that methyl boronic acid is available in bulk quantities and could be recovered from water phase easily with high recovery rate after reaction.[23d] The current condition thus represents one of the most practical and sustainable methods for the epimerization of carbohydrate hydroxyl groups. Since water is generated during the formation of boronate esters, degassing and the addition of molecular sieves improve the yield further to 85% (Entry **19**-**20**).

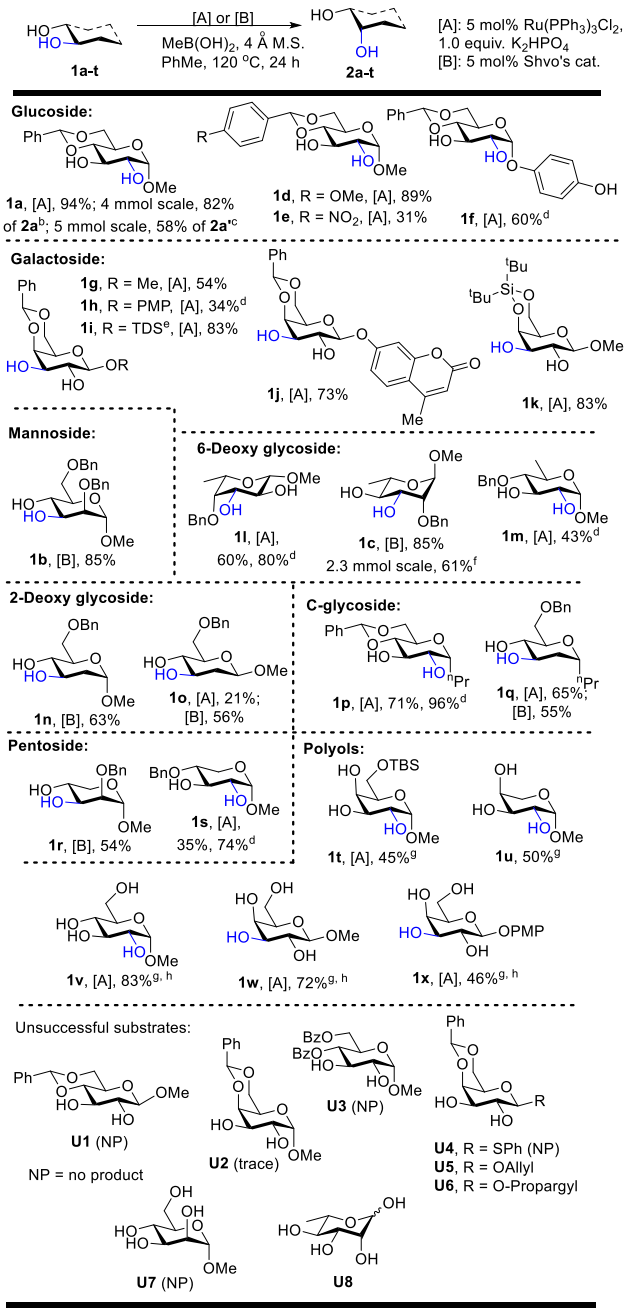
Scope of Substrates.

Based on the above optimized reaction conditions, a series of carbohydrate substrates were prepared and examined for the OH inversion reaction (Table **2**). Substrates with a *trans*-diol were synthesized by adapting literature reports with good to high yields (See Supplementary Information for detailed procedure). The OH inversion product derived from our model substrate **1a** can be isolated in a 94% yield. A gram scale reaction was carried out for model substrate **1a**. Desired OH inversion product **2a** could be isolated in a 82% yield. Methyl boronate ester **2a'** could also be isolated in a 58% yield in a gram scale reaction without working up the reaction. The lower yield of the boronate ester is due to its hydrolysis on the silica gel column. Electron rich benzylidene protecting group (**1d**)

can be well tolerated, while electron poor benzylidene protecting group (**1e**) deteriorated the yield. A phenol substituent on the anomeric position (**1f**) can be tolerated. Different substituents on the anomeric position including alkyl, aryl, or silyl group were tested in galactosides **1g** to **1i** to give different gulosides. Over 50% yields were obtained for most substrates. Interestingly, substrate **1j** bearing a fluorescence group, which was usually used as a probe for galactosidase, can also undergo inversion to generate a potential probe for gulosidase. The silyl protecting group in substrate **1k** can also be tolerated and give corresponding guloside in an 83% yield. D-altroside **2b**, which was found in many bioactive pharmaceuticals or natural products, can be easily prepared from D-mannoside **1b**. Several deoxy sugars were also tested for the epimerization reaction. 6-Deoxy sugars, including D-fucoside **1l**, D-rhamnoside **1c** and 6-deoxy glucoside **1m** can be converted into 6-deoxy-L-guloside **2l**, 6-deoxy-L-altroside **2c** and D-rhamnoside **2m**, respectively. It is worth to mention that the scale up reaction can also give a satisfying yield for substrate **1c** when the reaction was carried out under 2.3 mmol scale. 2-Deoxy-α-D-*ribo*-hexoside **2n**/**2o** can be easily synthesized using our OH inversion strategy starting from 2-deoxy glucosides **1n**/**1o**. *C*-Mannoside can be generated from *C*-glucoside **1p** with a 71% yield under the standard condition, and it can be further improved to 96% when 10 mol% catalyst was employed. The C3 OH group within 2-deoxy-*C*-glucoside **1q** can be inverted with moderate 55-65% yields as well. The scope of the substrates can be further expanded to pentosides. D-xyloside **1s** can be converted to the corresponding D-lyxoside **2s** with a 74% yield, while D-lyxoside **1r** can be converted to corresponding D-arabinoside **2r** and L-riboside **2r'**. We also tested more challenging triol and tetraol glycosides. Interestingly, the inversion of C2 OH was observed in triol susbtrates **1t** and **1u** and the corresponding D-taloside **2t** and L-riboside **2u**, where all three OH groups end up on the same side of the pyranose ring, were prepared successfully. We hypothesize that the formation of more stable tetra- coordinated boronate ester with all three OHs in the product may dictates the selectivity in these two cases. Since boronic acids were reported as a transient protecting group previously,[23d] we also tested tetraol substrates **1v, 1w** and **1x**, and excellent yields of OH inversion tetraol products can be obtained.

We also tested β-glucoside, α-galactoside, and substrates with benzoyl, SPh, allyl or propargyl groups. No reaction occurred or only trace amount of product was observed for substrates **U1**-**U4**. Isomerization of alkene was observed for substrate **U5** and decomposition occurred for substrate **U6**. α-Methyl mannoside **U7** gave no desired product because the *cis*-diol motif forms boronate ester first, which shuts down the OH inversion reaction. Application of current method to reducing monosaccharide **U8** was not successful because of the oxidation of anomeric OH to lactone and reduction of anomeric OH.

Table 2. Scope of Ru-catalyzed Regioselective OH Inversion[a]

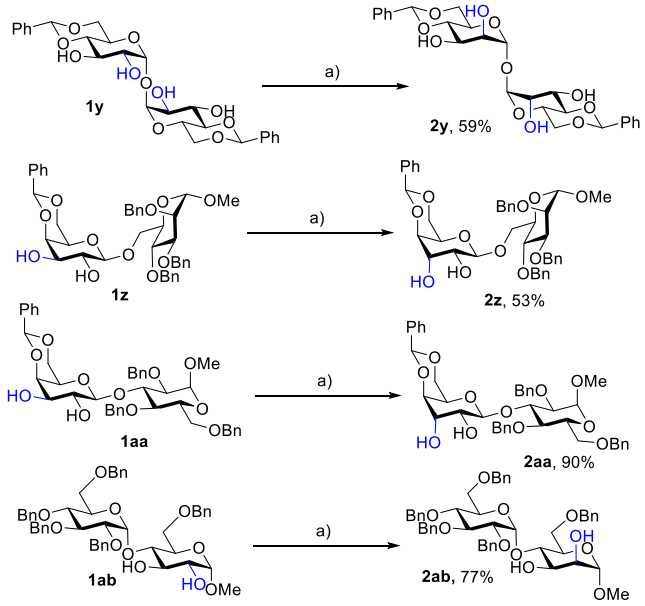


[a]Reaction conditions: **[A]**: Glycoside (0.1 mmol, 1.0 equiv), $Ru(PPh_3)_3Cl_2$ (5 mol%), K_2HPO_4 (1.0 eq.), $MeB(OH)_2$ (5.0 eq.), 4Å MS (100 mg), and toluene (0.5 mL) at 120 °C under argon atmosphere for 24 h. **[B]** Glycoside (0.1 mmol, 1.0 equiv), Shvo's cat. (5 mol%), $MeB(OH)_2$ (5.0 eq.), 4Å MS (100 mg), and toluene (0.5 mL) at 120 °C under argon atmosphere for 24 h. [b]Glycoside (4 mmol, 1.0 equiv), $Ru(PPh_3)_3Cl_2$ (5 mol%), K_2HPO_4 (1.0 eq.), $MeB(OH)_2$ (5.0 eq.), 4Å MS (5.0 g), and toluene (20 mL) at 120 °C under argon atmosphere for 24 h. [c]Without workup. Methyl boronate **2a'** was obtained as the product from **1a**.[d]$Ru(PPh_3)_3Cl_2$ (10 mol%) was used. [e]TDS = Thexyldimethylsilyl. [f]Glycoside (2.3 mmol, 1.0 equiv), Shvo's cat. (5 mol%), $MeB(OH)_2$ (5.0 eq.), 4Å MS (2.3 g), and toluene (15 mL) at 120 °C under argon atmosphere for 24 h. [g]10.0 eq. $MeB(OH)_2$ were used. [h]Product was peracetylated for the convenient of separation.

To further expand the scope of the selective OH inversion reaction, we next examined the reaction in more complex disaccharides. Starting from trehalose derivative **1y**, product with two inverted -OH group can be isolated in a 59% yield. The galactose unit in disaccharides **1z** and **1aa** can be converted to the corresponding rare sugar-containing disaccharides **2z** and **2aa** in good yields. The

glucose motif in disaccharide **1ab** can also be converted to mannose through this one-step OH inversion method. These examples demonstrate that the selective OH inversion method can be applied to the synthesis or modification of more complex carbohydrates. Moreover, the successful inversion of one OH group in polyol substrates **1t**-**1x** and **1y**, shows the potential of this site-selective epimerization method in complex carbohydrates.

Table 3. Scope of Disaccharides for Ru-catalyzed Regioselective OH Inversion



Conditions: a) $Ru(PPh_3)_3Cl_2$ (10 mol%), K_2HPO_4 (1-2.0 equiv), $MeB(OH)_2$ (5-10.0 equiv.), 4 A M.S. (200 mg), PhMe (1.0 mL), 120 °C, 24 h.

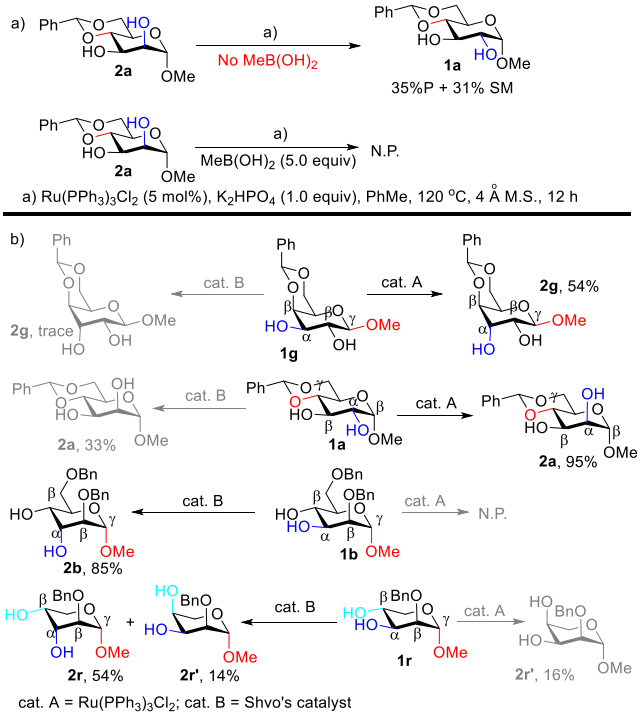
Mechanistic investigations.

We performed several experiments to confirm the proposed mechanism of the selective epimerization reaction. By resubjecting product **2a** to the reaction condition in the absence of boronic acid, a mixture of product and starting material was obtained with a ratio about 1:1 (Scheme 2**a**). This unequivocally demonstrates that the ruthenium catalyst can promote the interconversion between the two epimeric secondary alcohols, likely through a ketone intermediate based on previous relevant reports.[24] On the other hand, when resubjecting product **2a** to the reaction condition in the presence of boronic acid, **1a** was not observed. This indicates that boronic acid can drive the equilibrium to form 1,2-*cis*-diols and trap the products through the formation of boronate ester.

Based on the experiment data, the OH inversion reaction occurs selectively on the OH with an adjacent axial substituent. This could be rationalized by different steric hindrance around the two reaction sites. Previous study showed that hydrogen transfer reaction for secondary alcohols with two β-substituents was sluggish.[21d] The axial bond adjacent to the reaction site may create an open space and allow Ru catalyst to approach carbohydrate substrates to mediate the inversion reaction through oxidation followed by reduction.

We also observed that different sugar skeletons have different preferences for the Ru catalysts (Scheme 2**b**). For substrates with an equatorial substitution at the γ position of the reaction site, $Ru(PPh_3)_3Cl_2$ usually gave better yields. While substrates with an axial substitution at the γ position of the reaction site usually require Shvo's catalyst to invert the OH group. This phenomenon may originate from different hydrogen abstraction mechanism of these Ru catalysts.[20a, 24-25] In the case of $Ru(PPh_3)_3Cl_2$, the isomerization was promoted by a sequence of elimination of HCl in the presence of base, oxidation via β-hydride elimination, reduction via migratory insertion, and protonation. For Shvo's catalyst, direct removal of 2H from alcohol and addition of 2H to ketone was proposed in literature. The detailed reason that is responsible for the different substrate scope of these two Ru catalysts will be further investigated in the future.

Scheme 2. Mechanistic Investigations.

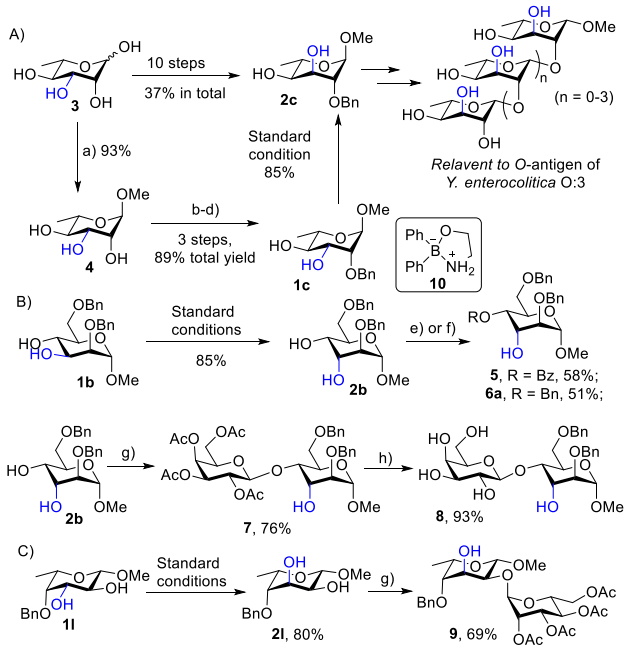


a) Resubjecting products to the OH inversion reaction conditions in the absence or presence of boronic acid. b) Summary of substrate structures and catalysts.

Synthetic Applications.

The OH inversion method we developed not only provides an efficient way for the preparation of rare sugars but also offers a method for the selective functionalization of carbohydrates. Lengthy protecting and deprotecting steps can be avoided in many cases by using the one-step selective OH inversion reaction. In 2017, Yu *et al* synthesized a series of the 6-deoxy-L-Alt*p* oligosaccharides in order to study their potential biological functions in the bacteria−host interaction, after the disclosure of this homopolysaccharide as the *O*-antigen of *Y. enterocolitica* O:3.6.[26] Starting from L-rhamnose, **2c** was prepared in 10 steps. Using the OH inversion method, the synthetic route can be shortened to 5 steps starting from L-rhamnose with a 70% overall yield (Scheme 3**A**). After OH inversion reaction, the resulting *cis*-diol is ready for further functionalization,[23a-c] which can streamline the oligosaccharide synthesis. For example, using boron catalyst, the equatorial OH group can be selectively acylated and glycosylated (Scheme 3**B**). Heating was required for the alkylation of **2b** and a lower yield was obtained for product **6**. These applications showcased the OH inversion method and many other oligosaccharides or natural products can be prepared similarly with high efficiency.[27] As another example, the glycoside skeleton of Zorbamycin, which facilitates the uptake of the drug by cancer cells and plays an important role in the DNA cleavage activity,[28] can be constructed quickly using the selective OH inversion reaction (Scheme 3**C**).

Scheme 3. Synthetic applications.



Conditions: a) MeOH, Dowex X8-200 ion-exchange resin (H^+), reflux[29]; b) butane-2,3-dione, $HC(OMe)_3$, CSA, MeOH reflux; c) NaH, DMF, then BnBr; d) TFA/H_2O = 4:1, 2 h; e) **10**, BzCl, DIPEA, MeCN, r.t.; f) **10**, BnBr, Ag_2O, MeCN, 40 °C; g) **10**, Glycosyl bromide, Ag_2O, MeCN, r.t.; h) NaOMe, MeOH.

CONCLUSIONS

In summary, we have developed a ruthenium-catalyzed and boron-mediated highly selective OH epimerization method for the preparation of *cis*-1,2-diols from *trans*-1,2-diols in various carbohydrates. A number of rare sugars can be synthesized with high yields using this method. The epimerization reaction can also be extended to the selective modification of disaccharides. In all cases, the OH group adjacent to an axial substituent in 1,2-*trans*-diols selectively underwent the inversion reaction. The utility of the OH inversion method was demonstrated by short syntheses of the monosaccharide building block in *Y. enterocolitica* O:3.6 and the glycan of Zorbamycin. The resulting 1,2-*cis*-diol products can be further selectively functionalized following well established methods to differentiate the 1,2-*cis*-diol or directly used in glycosylation to construct glycoside skeleton in natural products and bioactive compounds. Extension of this method to other types of polyols in more complex settings is ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed reaction condition optimization, experimental procedures, characterization data and spectra (^1H, ^{13}C NMR and HRMS). 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 interests.

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