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Site- and Stereoselective *O*-Alkylation of Glycosides by Rh(II)-Catalyzed Carbenoid Insertion

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Supporting Information Placeholder

ABSTRACT: Carbohydrates are synthetically challenging molecules with vital biological roles in all living systems. Selective synthesis and functionalization of carbohydrates provide tremendous opportunities to improve our understanding on the biological functions of this fundamentally important class of molecules. However, selective functionalization of seemingly identical hydroxyl groups in carbohydrates remains a long-standing challenge in chemical synthesis. We herein describe a practical and predictable method for the site- and stereoselective alkylation of carbohydrate hydroxyl groups via Rh(II)-catalyzed insertion of metal carbenoid intermediates. This represents one of the mildest alkylation methods for the systematic modification of carbohydrates. Density functional theory (DFT) calculations suggest that the site-selectivity is determined in the Rh(II)-carbenoid insertion step, which prefers insertion into hydroxyl groups with an adjacent axial substituent. The subsequent intramolecular enolate protonation determines the unexpected high stereoselectivity. The most prevalent *trans*-1,2-diols in various pyranoses can be systematically and predictably differentiated based on the model derived from DFT calculations. We also demonstrated that the selective *O*-alkylation method could significantly improve the efficiency and stereoselectivity of glycosylation reactions. The alkyl groups introduced to carbohydrates by OH insertion reaction can serve as functional groups, protecting groups, and directing groups.

■ INTRODUCTION

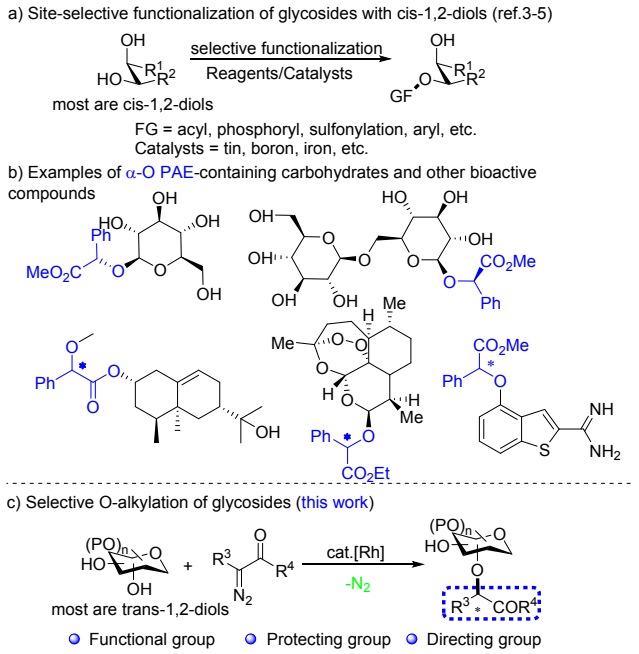
Carbohydrates are essential components of many natural products, medicines, and macromolecular glycoconjugates.[1] It is therefore critical to develop efficient and selective methods for their syntheses and modifications and to probe how structural differences influence their biological functions. However, selective functionalization of the seemingly identical hydroxyl groups in carbohydrates represents a formidable challenge.[2] Although tremendous successes have been achieved for selective functionalization of carbohydrate *cis*-1,2-diols in pyranoses,[3] much less is known about the selective functionalization of the corresponding *trans*-1,2-diols. While the greater intrinsic reactivity of equatorial OHs in comparison to axial OHs can be significantly amplified by catalysts in *cis*-1,2-diols,[4] it is not obvious how to systematically differentiate *trans*-1,2-diols,[5] where both OHs occupy equatorial positions (Scheme 1a).

Recently, we developed a catalytic site-selective acylation method that can systematically differentiate *trans*-1,2-diols in pyranoses.[6] Selective functionalization of carbohydrate *trans*-1,2-diols by other types of reactions, such as alkylation,[7] remains largely unexplored. In fact, alkyl groups that can be readily cleaved are more widely used than acyl groups as the protecting group for the synthesis of carbohydrates. Alkyl groups are also frequently found in bioactive carbohydrate derivatives. For example, α-*O* substituted phenylacetic esters (α-*O* PAE) are present in both carbohydrates and other bioactive compounds (Scheme 1b).[8]

Transition metal-catalyzed insertion of α-diazophenylacetic acid esters into various OH bonds represents a typical strategy for alkylation and has been widely used for the construction of these C-O bonds.[9] However, only a few methods were reported for the stereoselective insertion of metal carbenoids into alcoholic OH bonds.[10] Among them, only one method provided high stereoselectivity for secondary alcohols.[10b] The Yu group investigated the mechanisms of the transition metal-catalyzed carbenoid OH insertions using DFT calculations and rationalized why previous attempts using chiral Rh(II) catalysts failed to afford any appreciable stereoselectivity.[11] To the best of our knowledge, there is no study on the site- or stereoselective functionalization of carbohydrate hydroxyl groups by any transition metal-catalyzed carbenoid insertion reactions, despite the mildness of the conditions compared to other alkylation methods.[12]

We herein report our discovery of a site- and stereoselective *O*-alkylation method for carbohydrate *trans*-1,2-diols by Rh(II)-catalyzed insertion of metal carbenoid into O–H bonds (Scheme 1c). It provides a truly practical solution for the selective alkylation of a variety of carbohydrates systematically and predictably under extremely mild conditions. DFT calculations not only provide the insights on the source of the unexpected site- and stereo selectivity, but also a predictable model for diverse carbohydrate substrates. The utility of the resulting alkyl group as protecting group and also directing groups are demonstrated in efficient and stereoselective glycosylation reactions.

Scheme 1. Selective Functionalization of Glycosides



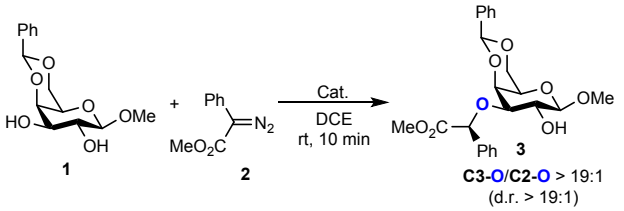
■ RESULTS AND DISCUSSION

Discovery of the Site- and Stereoselective Alkylation, Optimization of the Reaction Conditions, and Determination of the Stereochemistry.

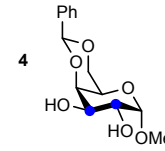
We began our investigation on selective carbohydrate alkylation by examining the reaction between β-galactoside **1** and α-diazo ester **2** in the presence of different transition metal catalysts.[13] Rh(II)-based catalysts showed the highest catalytic efficiency. Although $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ have similar reactivity, the former provided better stereoselectivity than the latter for most substrates. After further optimizing the reaction by screening solvents and reactant concentrations, C(3)-alkylation product **3** could be obtained with high yield and selectivity under the condition indicated in Table 1. We then tested the method in common monosaccharides **4**-**7**. Interestingly, only *trans*-1,2-diol **6** derived from α-glucose underwent highly site-selective C(2)-alkylation to yield product **11**. Surprisingly, high stereoselectivity was observed for all four diols **4**-**7** in Table 1. The C(2)-alkylation products **9** and **12** are separated from the corresponding C(3)-alkylation products **10** and **13**, respectively.

We next determined the configuration of the newly generated stereogenic center (Scheme 2), by preparing chiral diazo compounds **14a** and **14b** from the corresponding chiral secondary alcohols. These diazo compounds were then used as the carbenoid precursors for the Rh(II)-catalyzed OH insertion of substrates **1** and **6**, respectively, to afford four diastereomeric ester products (**15a**, **15b**, **16a**, and **16b**). The configuration of these four products was then determined by ^{1}H NMR, similarly to Mosher or mandelic esters.[13-14] Our NMR studies indicated that the newly generated stereogenic center (C**) in all four products (**15a**, **15b**, **16a**, and **16b**) and several others in the SI[13] has an *S*-configuration. Our analysis was further confirmed by single crystal X-ray diffraction of products **3** (CCDC1908784) and **11** (CCDC1908783).[13]

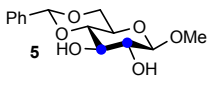
Table 1. Initial Screening of Conditions for Common Glycosides with a 1,2-Diol for Alkylation.[a]



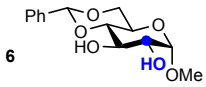
catalyst	$Rh_2(OAc)_4$	$Rh_2(oct)_4$	$Rh_2(esp)_2$	$Pd(OAc)_2$[c]	$Cu(OTf)_2$[d]	$CuCl_2$[d]
3[b]	**78%**	67%	82%	<10%	messy	<10%



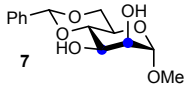
(**C2-O**/**C3-O** = 3:1)
8, 85% (**C2-O** + **C3-O**)
(d.r. of both isomers > 19:1)



(**C2-O**/**C3-O** = 1:2)
9, 36% (**C2-O**, d.r. > 19:1)
10, 60% (**C3-O**, d.r. > 19:1)



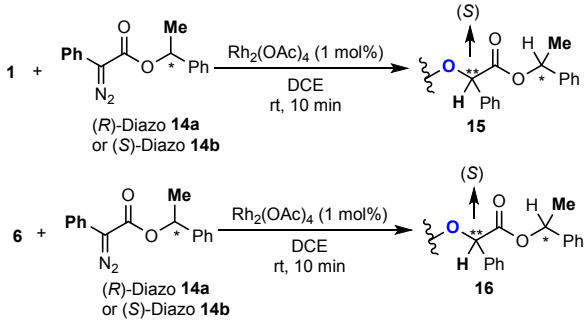
(**C2-O**/**C3-O** > 19:1)
11, 93% (**C2-O**, d.r. = 11:1)

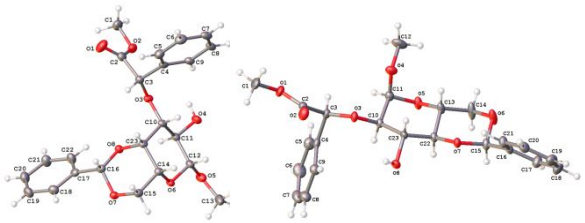


(**C2-O**/**C3-O** = 1.3:1)
12, 44% (**C2-O**, d.r. > 19:1)
13, 36% (**C3-O**, d.r. > 19:1)

[a] Reaction conditions: saccharides (0.2 mmol, 1.0 equiv), α-diazo compounds (0.3 mmol, 1.5 equiv), Cat. (1 mol%), 4Å MS (100 mg) and solvent (1 mL) at room temperature under argon atmosphere for 10 min. [b]Yield of isolated product, ratio of regioisomer (r.r.) and diastereomeric ratio determined by crude NMR. [c]5 mol%. [d]10 mol%. C2-O = C2 O-alkylation product, C3-O = C3 O-alkylation product.

Scheme 2. Determination of the Stereochemistry[a]





X-ray structure of **3**
(CCDC1908784)

X-ray structure of **11**
(CCDC1908783)

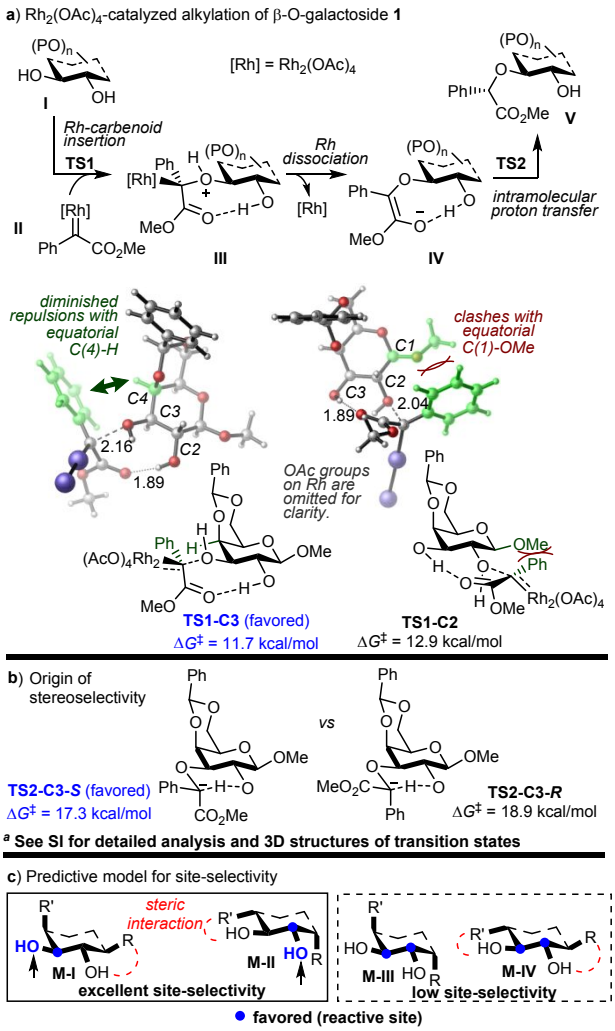
[a] Reaction conditions: See Table 1 for conditions. α-diazo compounds **14a** or **14b** (0.3 mmol, 1.5 equiv) was used.

Mechanistic Studies by DFT Calculations.

It is not obvious how to rationalize the high site- and stereoselectivity observed for the OH insertion of β-galactoside **1** and α-glucoside **6**. We surmised that an unrecognized mode of interaction may govern these high selectivities. To gain additional

mechanistic insights, DFT calculations were performed to explore the origin of the selectivity in the alkylation of β-galactoside **1** using $Rh_2(OAc)_4$ as the catalyst (Scheme 3a). The computational results revealed that the site-selectivity is governed by steric repulsions with adjacent equatorial substituents in the insertion of the Rh-carbenoid (**II**) to the equatorial OH groups (**TS1**). Due to the hydrogen bonding interaction between the ester group of **II** and the *trans*-1,2-diol on the glycoside, the Ph group of **II** is nearly coplanar with the equatorial substituent on the other vicinal carbon. Therefore, in the C(3)-OH insertion transition state (**TS1-C3**), the Ph group of **II** points towards the C(4)-H, whereas in the C(2)-OH insertion (**TS1-C2**), the same Ph points towards the equatorial C(1)-OMe. Due to the *syn*-pentane-type repulsion with the equatorial OMe substituent on C(1), the C(2) insertion is disfavored, in agreement with the experimentally observed C(3)-selectivity. Our computational studies also indicated that the Rh-carbenoid insertion with α-glucoside **6** is C(2)-selective due to similar steric effects of the equatorial C(4) substituent in **6** that block the C(3)-OH insertion.[13]

Scheme 3. DFT Calculations and Working Model for Site-selective Alkylation



Our calculations indicated the dissociation of $Rh_2(OAc)_4$ from **III** to generate ester enolate **IV** was very facile, consistent with previous calculations.[11] This suggested that the unexpected high stereoselectivity was determined in the subsequent enolate *C*-protonation step (**TS2**). Indeed, based on our calculations, the intramolecular protonation by the adjacent equatorial OH group is stereoselective and forms the experimentally observed (*S*)-alkylation product (Scheme 3b). In transition state **TS2-C3-S**, the sterically hindered phenyl group (with an A-value of 3.0 kcal/mol) is placed at the equatorial position and the smaller ester group (with an A-value of 1.27 kcal/mol) is placed at the axial position.

For *trans*-1,2-diols, our computational analysis indicated that an equatorial OH that was not blocked by an adjacent equatorial substituent, the favored OH group, could preferentially undergo the site-selective alkylation reaction over the equatorial OH that was blocked by an adjacent equatorial substituent, the disfavored OH group. This is rather counter intuitive, as the OH group adjacent to equatorial substituent is often considered more sterically accessible than the OH group adjacent to an axial substituent in most alkylation reactions. In the case of Rh(II)-catalyzed OH alkylation, the interaction between the ligand on the metal and the substrate dictates the site-selectivity, while the selectivity in most other OH alkylation reactions are determined by the interactions between the substrate and the alkylation reagent. The stereoselectivity was determined by the different A-values of Ph and ester groups in the chair-like transition state.

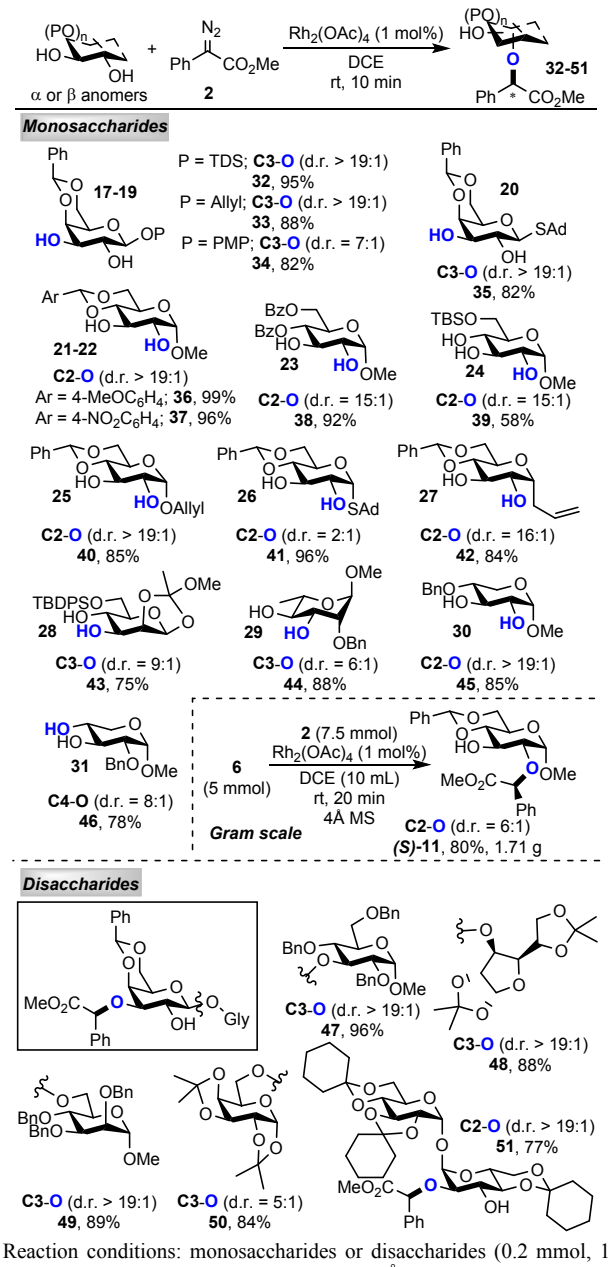
Taken together, DFT calculation offered us a working model to predict the site- and stereoselectivity for the Rh(II)-catalyzed alkylation of many other glycosides. In a *trans*-1,2-diol, the OH with an adjacent axial substituent (R or R' in Scheme 3c) is favored for $Rh_2(OAc)_4$-catalyzed insertion, while the OH with an adjacent equatorial substituent (R or R' in Scheme 3c) is disfavored for $Rh_2(OAc)_4$-catalyzed insertion. High site-selectivity was observed for **M-I** and **M-II** because one OH is favored while the other is not. Low site-selectivity was observed for **M-III** and **M-IV**, because both OHs are favored in the former case while both OHs are disfavored for the latter. As discussed before, the reactivity of OH alkylation through Rh(II)-catalyzed insertion of carbene is determined by the interaction between the ligand on the metal and the carbohydrate substrate. Highly site- and stereoselective alkylation of an equatorial OH group between an axial and an equatorial substituents becomes possible for the first time.

Scope of Substrates.

Having established optimal reaction conditions and a predictive model, a series of carbohydrate substrates were then prepared and examined for the site- and stereoselectivity of the OH insertion reaction (Table 2). In all cases, the experimental observations are consistent with our working model. We first changed the anomeric OMe group in β-galactoside to OTDS in **17**, OAllyl in **18**, OPMP in **19**, and *S* adamantyl (SAd) in **20**. The reactions afforded the corresponding C(3)-*O*-alkylation products **32**-**35** in good yields with high selectivities. We then tested the electronic effect of the protecting group in α-glucosides and found high selectivity for the alkylation of substrates **21**-**23**. We were pleased to find that triol **24** derived from α-glucose also underwent highly site- and stereoselective C(2)-OH insertion to afford product **39**. High site-selectivity was retained when we replaced the anomeric OMe by OAllyl, SAd (Ad = adamantyl), and Allyl groups in α-glucoside **25**-**27**. High stereoselectivity was observed for *O*- and *C*-glucosides **25** and **27** but not **26**.

We next examined *trans*-1,2-diols derived from other types of glycosides, such as mannoside (product **43**), rhamnoside (product **44**), and xyloside (products **45** and **46**). As expected, alkylation products were obtained in good yields with high selectivities. Results from substrates **28** and **31** suggest that the scope is not limited to C(2)/C(3)-*trans*-1,2-diols. To evaluate the scalability, a gram-scale reaction was performed, yielding the corresponding major stereoisomer (*S*)-**11** in 80% yield (1.71 g).

Table 2. Scope of Glycosides[a]

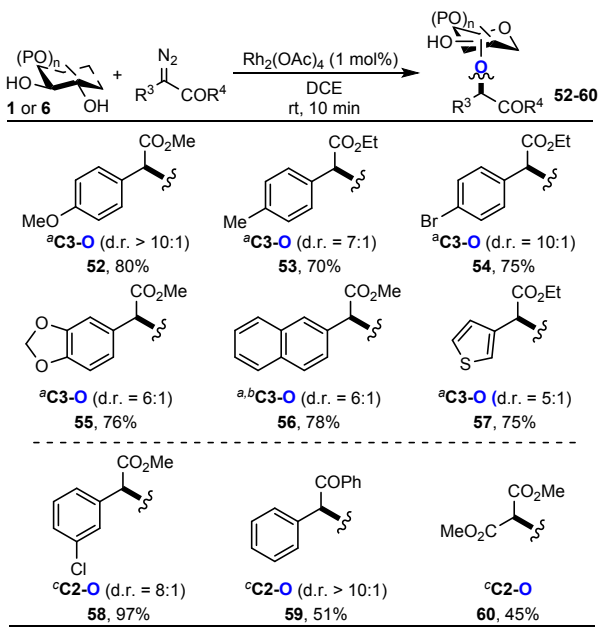


[a] Reaction conditions: monosaccharides or disaccharides (0.2 mmol, 1.0 equiv), **2** (1.5 equiv), $[Rh_2(OAc)_4]$ (1 mol%), 4Å MS (100 mg) and DCE (1 mL) at room temperature under argon atmosphere for 10 min. Yield of isolated product, ratio of regioisomer (r.r.) > 19:1 and diastereomeric ratio (d.r.) determined by crude NMR. Ad = adamantyl. C2-O = C2 O-alkylation product, C3-O = C3 O-alkylation product.

To further explore the scope of the selective alkylation reaction, we next examined the OH insertion reaction in more complex disaccharides. The C(3)-alkylation products **47-50** were prepared site- and stereoselectively from the corresponding galactose-containing disaccharides. Notably, we also selectively alkylated the OHs in *trans*-1,2-diols derived from trehalose to afford product **51**.

We next examined the scope of the Rh(II)-catalyzed alkylation method with respect to the α-diazo compounds (Table 3). A wide variety of substituents on the aryl moiety of α-diazo esters could be tolerated, although their electronic properties and positions slightly affected the diastereoselectivity. In addition to phenyldiazoacetate esters, α-diazo ketone and α-diazomalonate could also participate in the reaction to afford products **59** and **60**, respectively.

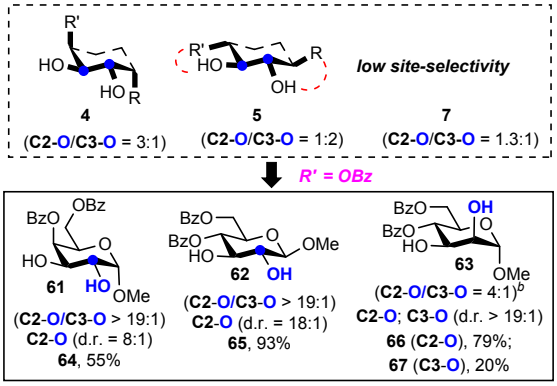
Table 3. Scope of α-Diazo Compounds[a]



[a] Reaction conditions: **1** (4,6-*O*-benzylidene methyl-β-D-galactopyranoside, 0.2 mmol, 1.0 equiv), α-diazo compounds (1.5 equiv), $[Rh_2(OAc)_4]$ (1 mol%), 4Å MS (100 mg) and DCE (1 mL) at room temperature under argon atmosphere for 10 min. Yield of isolated product, ratio of regioisomer (r.r.) > 19:1 and diastereomeric ratio (d.r.) determined by crude NMR. [b] $[Rh_2(esp)_2]$ (1 mol%) was used. [c] **6** (4,6-*O*-benzylidene methyl-α-D-glucopyranoside, 0.2 mmol, 1.0 equiv) was used. C2-O = C2 O-alkylation product, C3-O = C3 O-alkylation product.

The above results indicate that we are able to differentiate *trans*-1,2-diols in a variety of different settings. However, low site-selectivity was observed in some *trans*-1,2-diols, such as α-galactoside **4**, where both OHs are favored, and β-glucoside **5**, where both OHs are disfavored (Table 1). Because the rate of Rh-carbenoid insertion in the site-selectivity determining step is highly dependent on the nucleophilicity of the OH oxygen, we envisioned that highly site-selective OH insertion may be possible in these cases by tuning the electronic nature of the surrounding protecting groups. Indeed, much higher site-selectivity was observed for substrates **61** and **62** than that of **4** and **5**, respectively (Scheme 4), because the electronic withdrawing Bz-groups disfavor the alkylation of C3-OH group. We are also able to extend this strategy to α-mannoside **63** with a *cis*-1,2-diol. The Bz-group in **63** again improved the site-selectivity over the benzylidene group in **7**. The diastereoselectivity remained high in most cases.

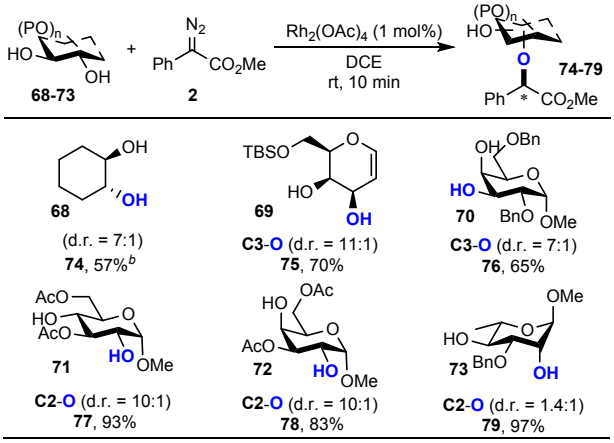
Scheme 4. Tuning the Site-selectivity by Protecting Groups[a]



[a] See Table 1 for conditions, α-diazo compound **2** (0.3 mmol, 1.5 equiv) was used. [b] $Rh_2(oct)_4$ (1 mol%) was used.

Taken together, the above results indicate that both steric and electronic factors could affect the reactivity of the OH group towards carbene insertion reactions. One can take advantage of this to improve the site-selectivity of the carbohydrate alkylation reaction. To further demonstrate the generality and practicability of this selective alkylation reaction, we also examined diols other than *trans*-1,2-diols in carbohydrates (Table 4). The alkylation of simple *trans*-1,2-cyclohexanediol **68** proceeded well to afford the monoalkylation product **74** with a 7:1 diastereomeric ratio. The scope of substrates could also be expanded to carbohydrates containing a *cis*-1,2-diol, such as **69** and **70**. Monoalkylation products **75** and **76** were prepared with 11:1 and 7:1 diastereomeric ratios, respectively. Notably, carbohydrates with a 1,3-diol (e.g. **71-73**) also yield monoalkylation products with high stereoselectivity when the alkylation occurred on the equatorial OH group. Low diastereoselectivity was observed for product **79** when the alkylation occurred on the much less hindered axial OH group. However, as shown in the application later, the diastereoselectivity in this case is inconsequential when the alkyl group was simply used as a protecting group.

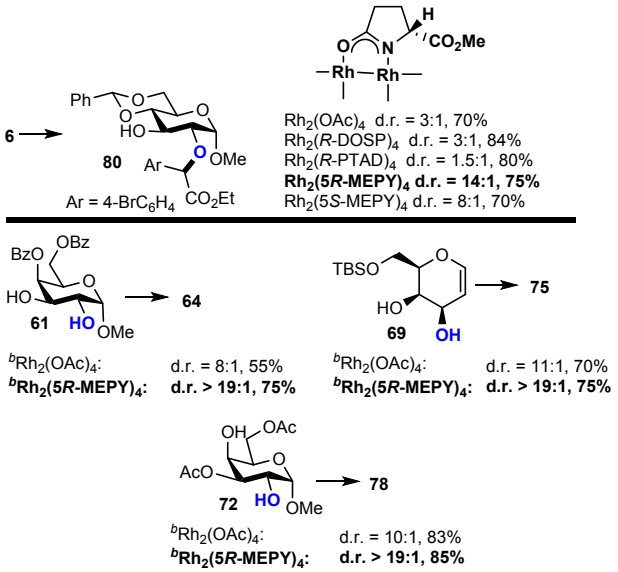
Table 4. Scope of Other Diols[a]



[a] Reaction conditions: diols (0.2 mmol, 1.0 equiv), **2** (1.5 equiv), [$Rh_2(OAc)_4$] (1 mol%), 4Å MS (100 mg) and DCE (1 mL) at room temperature under argon atmosphere for 10 min. Yield of isolated product, ratio of regioisomer (r.r.) > 19:1 and diastereomeric ratio (d.r.) determined by crude NMR. C2-O = C2 O-alkylation product, C3-O = C3 O-alkylation product. [b] methyl 2-diazo-2-(naphthalen-2-yl)acetate (1.0 equiv) was used.

Although high site-selectivity and diastereoselectiviey were observed for most of the achiral Rh(II) catalyst-mediated OH insertion reaction, low to moderate diastereoselectivities were observed in several cases. For example, only a 3:1 d.r. was obtained for product **80** derived from $Rh_2(OAc)_4$-catalyzed carbene insertion to C2-OH of substrate **6** (Scheme 5), when Ar was a para-bromophenyl ring. To further improve the stereoselectivity of this alkylation reaction, we examined several commercially available chiral Rh(II) catalysts. We found that reactions catalyzed by $Rh_2(5R\text{-MEPY})_4$ were much slower than achiral Rh(II) catalysts (120 min *vs* 10 min) and this chiral catalyst afforded the highest stereoselectivity for the formation of product **80**. We then examined the chiral catalyst-mediated carbene OH insertion reaction for several representative diols. We were pleased to find that higher d.r. was observed for *trans*-1,2-diol **61**, *cis*-1,2-diol **69** and *trans*-1,3-diol **72** than the achiral $Rh_2(OAc)_4$-mediated reactions. In all three cases, good yields and excellent regioselectivity were obtained.

Scheme 5. Evaluation of Chiral Rh(II) Catalysts[a]

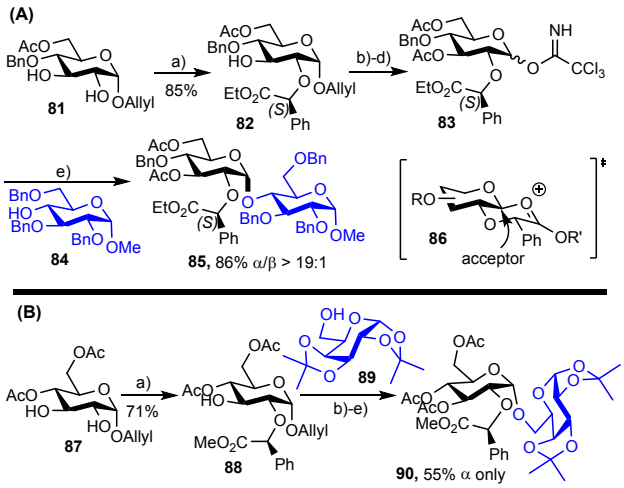


[a] See Table 1 for conditions, α-diazo compound (0.3 mmol, 1.5 equiv) was used, 10 min - 2 h. [b] α-diazo compound **2** was used, 10 min - 2 h. $Rh_2(R\text{-DOSP})_4$: dirhodium(II) tetrakis[(*R*)-*N*-(*p*-dodecylphenylsulfonyl)prolinate]. $Rh_2(R\text{-PTAD})_4$: dirhodium(II) tetrakis[(*R*)-(-)-(1-adamantyl)-(*N*-phthalimido)acetato]. $Rh_2(5R\text{-MEPY})_4$: dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*R*)-carboxylate].

Applications.

We next demonstrated the synthetic utilities of the Rh(II)-catalyzed site- and stereoselective carbene OH insertion in complex settings (Schemes 6-8). The carbene OH insertion reaction provided an efficient and mild way to modify many glycosides by alkyl groups, which can serve as a directing group, protecting group, and functional groups. For example, one of the most remarkable discoveries in stereoselective glycosylation is the chiral auxiliary-directed α-glycosylation from the Boons group, as shown in **86** (Scheme 6A).[15] However, the chiral auxiliary on the C(2)-position was generally introduced by multiple steps involving a S_N2 alkylation reaction. Using our newly developed method, we could prepare C(2)-*O*-alkylation product **82** with a (*S*)-configuration on the newly generated stereogenic center from diol **81** site- and stereoselectively in just one step. We then converted **82** to known trichloroacetimidate glycosyl donor **83** following standard procedures. The glycosylation reaction between known donor **83** and acceptor **84** proceeded highly stereoselectively to yield disaccharide **85** (α/β > 19:1) as reported.[15a] Using the same strategy, we also prepared disaccharide **90** with high α stereoselectivity from glycosyl acceptor **89** and glycosyl donor **88**, which was directly derived from Rh(II)-catalyzed site- and stereoselective alkylation of diol **87** (Scheme 6B). This highly efficient sequence for stereoselective glycosylation becomes possible because of the unexpected highly stereoselective OH carbene insertion through a well-organized intramolecular protonation transition state.

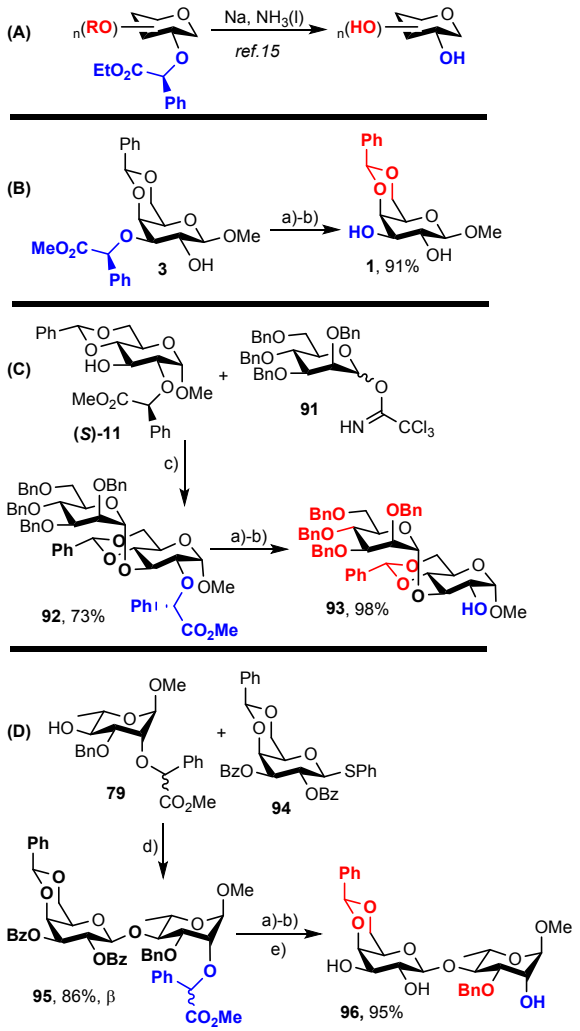
Scheme 6. Alkyl Group as the Directing Group for Stereoselective Glycosylation Reactions



Conditions: a) See Table 1 for standard conditions. b) DMAP, NEt_3, Piv_2O, AcOH, DCM, rt. c) $PdCl_2$, NaOAc/AcOH/H_2O, rt. d) CCl_3CN, DBU, DCM, rt. e) TMSOTf, 4Å MS, DCM, -78 °C - rt.

Alkyl groups are arguably the most frequently used protecting groups in carbohydrate synthesis. It is important to remove the alkyl groups efficiently and selectively when they are used as protecting groups. However, there are very limited number of options to remove alkyl groups under mild conditions. Although benzyl or related alkyl groups can be removed by Birch reduction (Scheme 7A),[15] a milder condition would be much more synthetically useful. After surveying various conditions, we found that the alkyl group derived from our selective OH insertion reaction could be removed smoothly and selectively under oxidative conditions to afford product **1** in 91% yield (Scheme 7B).[16] Product (*S*)-**11** could also directly react with **91** to yield disaccharide **92**, which was converted to **93** in nearly quantitative yield under the oxidative conditions (Scheme 7C). In addition, *O*-alkylation product **79** could react with the glycosyl donor **94** to yield disaccharides **95**, which was deprotected under mild conditions to afford product **96** in a 95% yield (Scheme 7D). In all of these examples, the protecting groups that can be removed by Birch reduction or hydrogenolysis, such as benzylidene and benzyl groups highlighted in red, were retained. On the other hand, this chiral ether protecting group is stable under hydrogenolysis conditions.

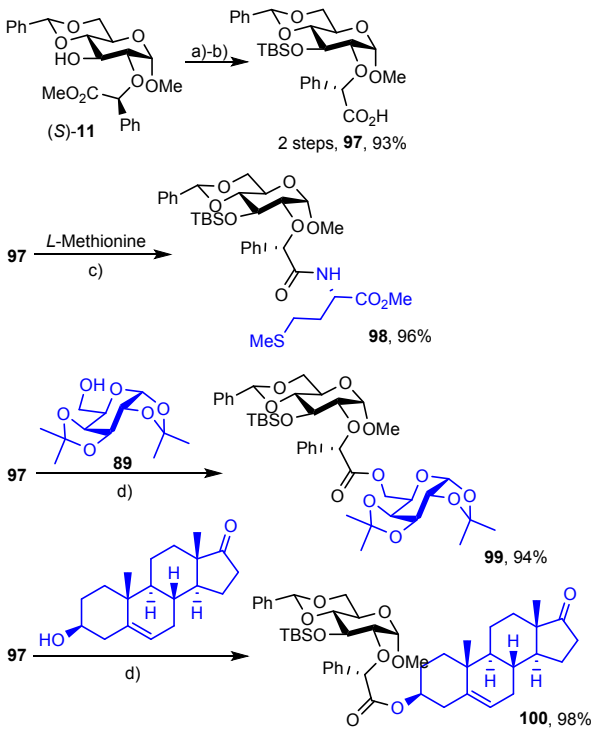
Scheme 7. Alkyl Group as the Protecting Group for Glycosylation Reactions



Conditions: a) KHMDS, -78 °C, THF, 30 min. b) Oxaziridine, -78 °C, 1 - 3 h; r.t., 45 min. c) TMSOTf, DCM, -78 °C - rt. d) NIS, TMSOf, DCM, -78 °C - rt, 4 Å MS. e) NaOMe, MeOH, rt.

The *O*-substituted phenylacetic esters introduced by the Rh(II)-catalyzed selective carbene OH insertion reaction can be further elaborated to more complex functional groups (Scheme 8). For example, the *O*-substituted phenylacetic acid derived from saponification of (*S*)-**11** can react with *L*-methionine to form amino acid derivative **98** and undergo esterification to afford disaccharide analogue **99** and steroid derivative **100**.

Scheme 8: Alkyl Group as the Functional Group



Conditions: a) TBSCl, imidazole, DMF, rt, 6 h. b) LiOH·H_2O, THF/H_2O (v/v, 5:1), rt, 4 h. c) HATU, DIPEA, DCM, rt, 5 h. d) DMAP, DCC, DCM, rt, 5 h.

■ CONCLUSIONS

In summary, we have developed a highly site- and stereoselective *O*-alkylation method for many glycosides that contain a *trans*-1,2-diol including triols by a Rh(II)-catalyzed OH insertion reaction under extremely mild conditions. DFT calculations indicated that the site-selectivity was determined in the Rh-carbenoid insertion step, while the unexpected high stereoselectivity was determined in the subsequent enolate protonation step. The combination of steric and electronic effects further expanded the scope of the site- and stereoselective alkylation reaction to more diols including *cis*-1,2-, *cis*-1,3-, and *trans*-1,3-diols. The site-selectivity for the sterically less accessible OH group is dictated by the interactions between the ligand on the metal catalyst and the substrate, while the selectivity in traditional OH alkylation reactions is influenced by the relative acidity of the OH groups and also the interactions between the substrate and the alkylation reagent. The utility of the selective *O*-alkylation method was demonstrated in several efficient and stereoselective glycosylation and functionalization reactions. The sequence of Rh-catalyzed site- and stereoselective alkylation, glycosylation, and chemo-selective deprotection under mild conditions reported here has the potential to streamline the chemical synthesis of many oligosaccharides. The steric and electronic interactions that govern the site- and stereoselective carbenoid OH insertion may have broad implications in other reactions.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, X-ray structural reports, spectra (^{1}H, ^{13}C NMR and HRMS), and computational details. 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. + These two authors contributed equally.

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