Communication

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Catalytic Site-selective Acylation of Carbohydrates Directed by Cation-*n* Interaction

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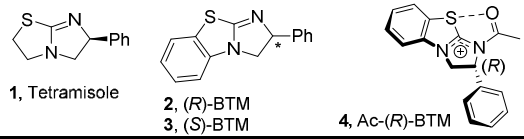
Supporting Information Placeholder

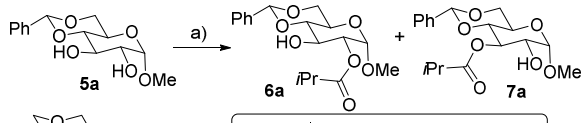
ABSTRACT: Site-selective functionalization of hydroxyl groups in carbohydrates is one of the long-standing challenges in chemistry. Using a pair of chiral catalysts, we now can differentiate the most prevalent *trans*-1,2-diols in pyranoses systematically and predictably. DFT calculations indicate that the key determining factor for the selectivity is the presence or absence of a cation-*n* interaction between the cation in the acylated catalyst and an appropriate lone pair in the substrate. DFT calculations also provided a predictive model for site-selectivity and this model is validated by various substrates.

Efficient and selective chemical methods for the synthesis and modification of carbohydrates are important for the understanding of their functions and the development of effective therapeutic reagents. Numerous methods have been developed for the differentiation of *cis*-1,2-diols in pyranoses.[1] The intrinsic selectivity in *cis*-1,2-diols can be amplified by external reagents or catalysts such as tin[2] or boron.[3] Chiral catalysts[4] and achiral reagents[5] were also developed to override the intrinsic selectivity in *cis*-1,2-diols. A novel chiral catalyst was developed for site-selective acylation of β-glucopyranosides.[6] Other achiral[7] and chiral catalysts[8] reported to date generally enhanced the intrinsic selectivity for the functionalization of a limited number of carbohydrates with few exceptions. The state-of-the-art chemistry lacks a general strategy for catalyst-controlled site-selective functionalization of carbohydrate hydroxyl groups, especially equatorial ones.[1] We herein report our progress towards this challenging task by using a pair of chiral catalysts to control the site-selectivity, primarily through a cation-*n* interaction between the cationic active catalyst and an appropriate oxygen lone pair in the substrates.

Tetramisole **1** and benzotetramisoles (BTMs) **2** and **3** were initially developed by Birman for the resolution of secondary alcohols (Scheme 1).[9] Positively charged intermediate **4** with a non-bonding interaction between the sulfur atom and the carbonyl oxygen is proposed as the actual acylation species.[10] We and others recently applied these catalysts for dynamic kinetic stereoselective acylation of lactols.[11] These three chiral catalysts were selected for site-selective acylation of α-glucose derivative **5** with a free C(2)/C(3)-diol. The details for the screening of conditions are summarized in SI. We obtained C(2)-acylation product **6a** preferentially together with significant amount of diacylation product by using catalyst **1** (Scheme 1A). The C(3)-OH in α-glucoside **5a** could be selectively acylated to form **7a** using catalyst **2**, while the C(2)-OH was selectively acylated to form **6a** using catalyst **3**. In contrast, a 1:1 ratio of **6a**/**7a** was observed using DMAP as the catalyst. The C(2)-OH in **5b** with a methylidene protecting group is intrinsically favored for acylation using DMAP as the catalyst. While catalyst **2** was able to override the intrinsic selectivity to yield **7b** as the major product, catalyst **3** enhanced the intrinsic selectivity to a ratio of over 20:1. When we tried to extend the method to β-glucoside **8a**, we observed equal amount of acylation products **9a** and **10a** by using (*R*)- or (*S*)-BTM catalyst (Scheme 1B).



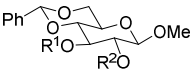
A) Acylation of α-*O*-glucosides 5a and 5b



5b, $R^1 = R^2 = H$
6b, $R^1 = H$, $R^2 = i$PrC(O)
7b, $R^1 = i$PrC(O), $R^2 = H$

catalyst	1	2	3	DMAP
6a / 7a	7:1 [100%]	< 1:20 (92%)	17:1 (94%)	1:1 (98%)
6b / 7b		1:7 (70%)	> 20:1 (91%)	3:1 [86%]

B) Acylation of β-*O*-glucoside 8a



8a, $R^1 = R^2 = H$
9a, $R^1 = H$, $R^2 = i$PrC(O)
10a, $R^1 = i$PrC(O), $R^2 = H$

catalyst	2	3
9a / 10a [conversion]	1:1 [100%]	1:1 [70%]

Conditions: a) catalyst (10 mol%), $(i\text{PrCO})_2O$ (2.5 equiv), $i\text{Pr}_2\text{NEt}$, rt, unless noted otherwise.

Notes: Yields in ( ) are isolated yield of the major isomer. Conversions of substrates in [ ] and ratios of major isomer *vs* minor isomer were determined by ^{1}H NMR of crude products.

Scheme 1. Acylation of C(2)/C(3)-Diols in Glucosides

We suspect that an unrecognized mode of interaction with the catalyst governs the dramatically different selectivity between *O*-glucosides **5a** and **8a**. We performed density functional theory (DFT) calculations to explore the origin of the site-selectivity in the acylation of α-glucosides **5a** and **5b** using (*R*)- and (*S*)-BTM catalysts (Schemes 2A-2C). The most favorable conformers of the

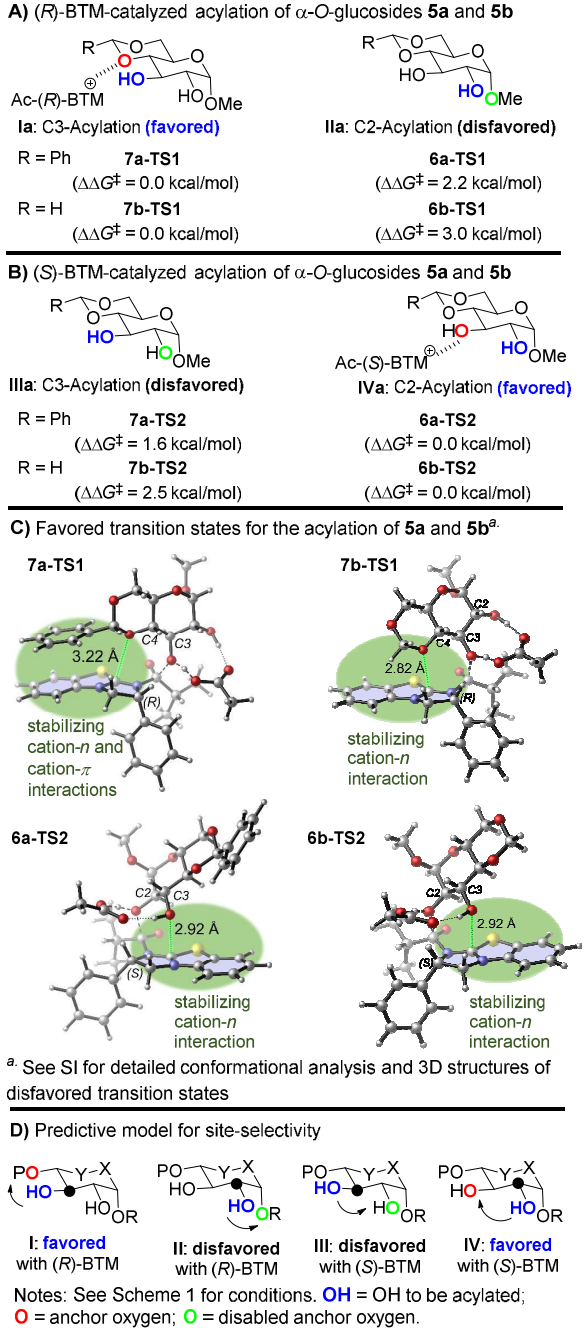
acylation transition states revealed a fundamentally different origin of stereochemical control from that in the previous experimental systems, which is dominated by the cation-π interaction with aromatic substituents on the substrate.[12] Instead, the transition states (TSs) for the acylation of **5a** and **5b** feature a stabilizing cation-*n* interaction between the positively charged acylated catalyst and a lone pair on an OR or OH group of the substrate (e.g. **Ia/IVa**, Schemes 2A/2B), defined as the "anchor" oxygen (shown in red). The nature of this cation-*n* interaction is expected to be a charge-diploe type electrostatic interaction.[13] Detailed analysis of interactions in all favored and disfavored TSs for the acylation of **5a** and **5b** is shown in SI.

In the (*R*)-BTM-catalyzed reaction of **5a**, this favorable cation-*n* interaction is augmented by a cation-π interaction that significantly stabilizes the C(3)-acylation TS **7a-TS1** compared to the C(2)-acylation TS **6a-TS1**, where the cation-*n* interaction is disrupted by the axial α-OMe group (defined as "disabled anchor" **O** in **IIa**). In the reaction with the (*S*)-BTM catalyst, the site-selectivity is completely reversed to favor the C(2)-acylation, due to a stronger cation-*n* interaction with the C(3)-OH in **6a-TS2**. In the (*S*)-BTM-catalyzed C(3)-acylation, the cation-*n* interaction with C(2)-OH is disfavored due to steric repulsions with the adjacent axial α-OMe group (disabled anchor **O** in **IIIa**). In the reactions of **5b** with a methylene protecting group, no cation-π interaction is available, and thus the selectivity is completely dictated by cation-*n* interactions. Taken together, the computational analysis indicated the cation-*n* interaction is sensitive to the stereochemical environment around the O lone pair. Such interaction is only possible with equatorial OH and OR groups that are not blocked by an adjacent axial substituent. This allowed us to predict site-selectivity based on the presence or the absence of the cation-*n* interaction.

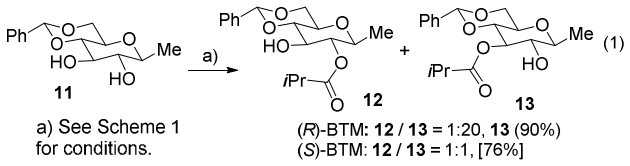
We generalized the above analysis to a predictive working model that can be easily applied to other monosaccharides (Scheme 2D). We can use our right hand to predict the site-selectivity of (*R*)-BTM-catalyzed acylation, and our left hand to predict the site-selectivity of (*S*)-BTM-catalyzed acylation. If the thumb aligns with the C-H bond on the dotted carbon and points to the hydrogen atom, the rest of fingers will curve towards the adjacent anchor OH or OR that is supposed to interact with the acylated catalyst. If the anchor OH or OR is on the equatorial position and there is no adjacent axial substituent, it is a favored situation (e.g. **I** and **IV**). If the anchor OH or OR is on the axial position (e.g. **II**) or on the equatorial position with an adjacent axial substituent (e.g. **III**), the anchor is not able to interact with the catalyst (defined as disabled **O**). It is therefore a disfavored situation. It is also a disfavored situation if the anchor OH or OR is replaced by a group without any lone pair, such as a C(1)-carbon atom in *C*-glycosides. One would also expect a disabled anchor if the oxygen is attached to an electron-withdrawing or sterically demanding group.

If the C(1)-OR group in **II** and **III** is changed to β-configuration, such as β-*O*-glucoside **8a**, they will become favored. Strong cation-*n* interactions are predicted to be present in all four TSs as favored situations for β-*O*-glucoside **8a**. Thus, no selectivity is expected for the acylation of **8a** using either (*R*)- or (*S*)-BTM catalyst, which is consistent with experimental results in Scheme 1B.

Based on the above analysis for *O*-glucosides, if we replace the β-OMe anchor on the C(1)-position in **8a** with a methyl group in β-*C*-glucoside **11** (Eq. 1), we will remove the cation-*n* interaction that directs the (*R*)-BTM-catalyzed acylation of C(2)-OH in **11**, while the rest of situations remain the same. We predict that high selectivity for the acylation of C(3)-OH of **11** can be achieved by using (*R*)-BTM as the catalyst, while no selectivity is expected for the (*S*)-BTM-catalyzed acylation of **11**. Indeed, a ratio of 1:20 for products **12**/**13** was observed in (*R*)-BTM-catalyzed acylation of **11**, while a ratio of 1:1 was obtained by using (*S*)-BTM catalyst!

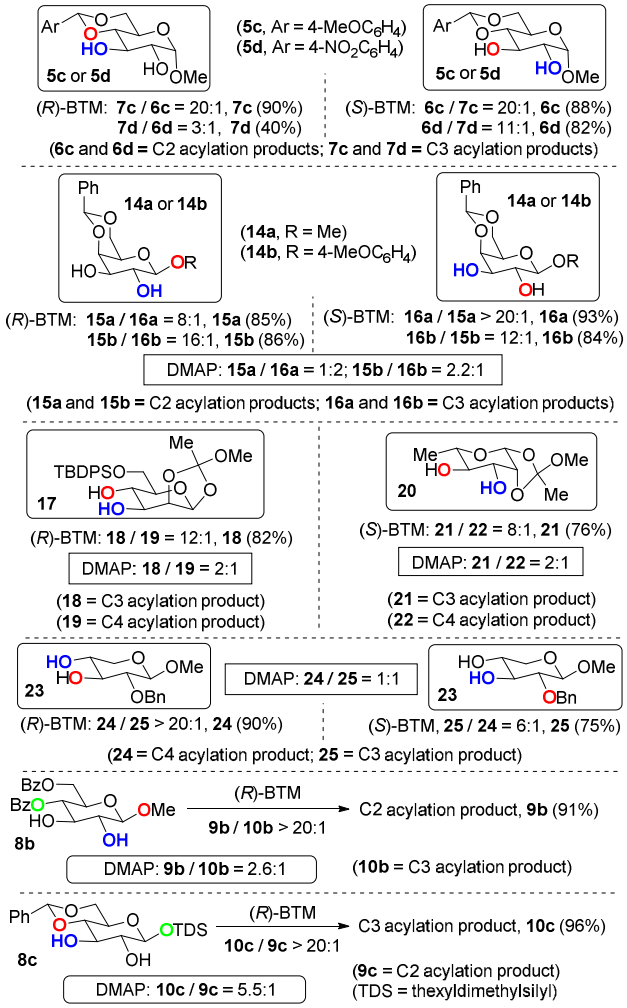


Scheme 2. Working Model for Site-selective Acylation (DFT calculations were performed using the M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d) level of theory.)



Our working model is also supported by experimental data in Schemes 3 and 4. The red anchor "**O**" in each structure is predicted to interact with the catalyst by a cation-*n* interaction for the acylation of blue **OH**. We first examined the electronic effect of

the protecting group in α-glucosides **5c** and **5d**. Results for the acylation of substrate **5c** are almost the same as those for **5a**. The selectivity for the acylation of C(3)-OH in **5d** dropped significantly due to the decreased cation-*n* and cation-π interactions with the more electron-deficient phenyl ring when (*R*)-BTM was employed as the catalyst. We then investigated the site-selectivity for other monosaccharides. For β-galactosides **14a** and **14b**, **15a** and **15b** were the major products using (*R*)-BTM catalyst, while **16a** and **16b** were the major products using (*S*)-BTM catalyst. For D-mannoside **17** and L-rhamnoside **20**, the anomeric OH can be protected together with the C(2)-OH as an orthoester. As expected, while the C(3)-OH in **17** was selectively acylated using (*R*)-BTM catalyst, the C(3)-OH in **20** was selectively acylated using (*S*)-BTM catalyst.



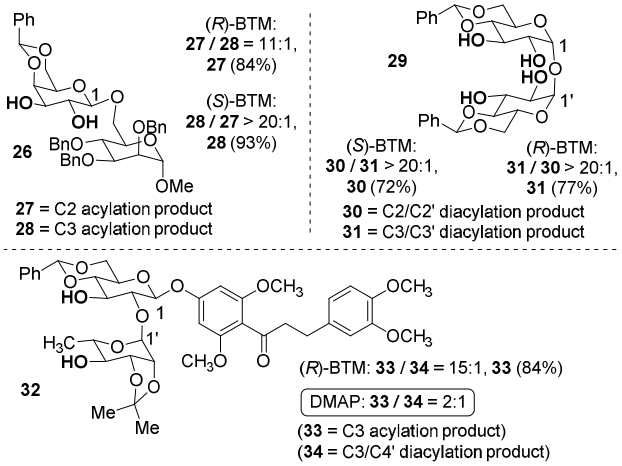
Notes: See Scheme 1 for conditions. **OH** = OH to be acylated; **O** = anchor O that donates its lone pair; **O** = disabled anchor oxygen.

Scheme 3. Site-selectivity for Monosaccharides

Xyloside **23** lacks a C(5)-substituent, which makes the C(4)-OH much more accessible than previously discussed monosaccharides. Indeed, we observed a 20:1 ratio favoring product **24** using (*R*)-BTM catalyst, even though strong cation-*n* interactions are present in the acylation of both C(3)- and C-4 OHs as shown by DFT calculations (see SI). We predicted that (S)-BTM catalyst would selectively acylate the more hindered C(3)-OH group in xyloside **23**, which was then confirmed by the observed 6:1 ratio favoring the formation of **25**. This moderate selectivity again reflects the less sterically hindered nature of C(4)-OH.

Unselective substrates such as β-*O*-glucosides can also be turned into selective ones by tuning the electronic and steric properties of the anchoring oxygen as shown in **8b** and **8c**. We observed an over 20:1 ratio favoring product **9b** for (*R*)-BTM-catalyzed acylation of **8b** and an over 20:1 ratio favoring product **10c** for (*R*)-BTM-catalyzed acylation of **8c**. These results are in sharp contrast to the 1:1 ratio for the formation of **9a** and **10a** from **8a** using the same catalysts (Scheme 1B). Clearly, the electron-withdrawing Bz-group on the C(4)-position of **8b** disabled the anchor oxygen on C(4), while the sterically demanding TDS-group in **8c** disabled the anchoring ability of the oxygen on the anomeric position.

We next examined the site-selective acylation of OHs in more complex settings (Scheme 4). When the β-galactoside unit was placed in disaccharide **26**, the observed site-selectivity was similar to monosaccharide **14a** or **14b**. The C(2)-acylation product **27** and C(3)-acylation product **28** were prepared selectively using (*R*)- or (*S*)-BTM catalyst, respectively. Using chiral BTM catalysts, we were also able to differentiate the OHs in tetra-ol **29** derived from trehalose. We synthesized diacylation products **30** and **31** by selectively acylating the C(2)-/C(2')-OHs or C(3)/C(3')-OHs in **29** using (*S*)-and (*R*)-BTM catalysts, respectively. Substrate **32** was derived from natural product neohesperidin dihydrochalcone. Hydroxyl groups in two different sugar units in **32** could also be differentiated using (*R*)-BTM catalyst as predicted by our model.



Notes: See Scheme 1 for conditions. $(n\mathrm{PrCO})_2\mathrm{O}$ (3.0 equiv) was employed for **29**; Ac_2O (1.5 equiv) was employed for **32**.

Scheme 4. Site-selectivity for Disaccharides

Acylation of **5a** by other carboxylic acids including palmitic acid and levulinic acid could also be realized with high selectivity by generating mixed anhydrides in-situ from the corresponding free carboxylic acid and pivalate anhydride as shown in the SI.

Just based on the cation-*n* interaction alone, we are able to differentiate hydroxyl groups in a variety of different pyranoses. The combination of the cation-*n* interaction with other factors can further expand the scope of the site-selective acylation (e.g. **8b** and **8c**). The recognition of cation-*n* interaction as one of the determining factors for selectivity will also have broad implications in other related site-selective reactions.[14]

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, spectra (IR, ^{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 financial interests.

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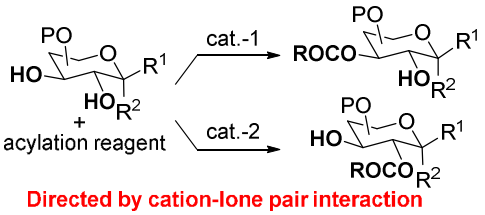
PO
O
R1
HO
HO
R2
+
acylation reagent
cat.-1
cat.-2
ROCO
Directed by cation-lone pair interaction