Studies of Catalyst-Controlled Regioselective Acetalization and Its Application to Single-Pot Synthesis of Differentially Protected Saccharides.

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ABSTRACT: This article describes the studies on regioselective acetal protection of monosaccharide-based diols using chiral phosphoric acids (CPAs) and their immobilized polymeric variants, (R)-Ad-TRIP-PS and (S)-SPINOL-PS as the catalysts. These catalyst-controlled regioselective acetalizations were found to proceed with high regioselectivities (up to >25:1 rr) on various D-glucose, D-galactose, D-mannose and L-fucose derived 1,2-diols, and could be carried in a regiodivergent fashion depending on the choice of the chiral catalysts. The polymeric catalysts were conveniently recycled and reused multiple times for gram scale functionalizations with catalytic loading as low as 0.1 mol%, and their performance was often found to be superior to the performance of their monomeric variants. These regioselective CPA-catalyzed acetalizations were successfully combined with common hydroxyl group functionalizations as single-pot telescoped procedures to produce 34 regioisomERICALLY pure differentially protected mono- and disaccharide derivatives. To further demonstrate the utility of the polymeric catalysts, the same batch of (R)-Ad-TRIP-PS catalyst was recycled and reused to accomplish single-pot gram-scale syntheses of 6 differentially protected D-glucose derivatives. The subsequent exploration of the reaction mechanism using NMR studies of deuterated and nondeuterated substrates revealed that low-temperature acetalizations happen via syn-addition mechanism, and that the reaction regioselectivity exhibits strong dependence on the temperature. The computational studies indicate complex temperature-dependent interplay of two reaction mechanisms, one involving an anomic phosphate intermediate and another via concerted asynchronous formation of acetal that results in syn-addition products. The computational models also explain the steric factors responsible for the observed C2-selectivities and are consistent with experimentally observed selectivity trends.

1. INTRODUCTION

Carbohydrates are essential molecules that not only serve as immediate energy sources, but are also associated with numerous biological activities. Accordingly, the studies of carbohydrates have been the focus of many ongoing investigation in the fields of organic chemistry, biochemistry, and drug discovery. However, in many instances, gaining access to complex oligosaccharides and glycoconjugates has been the bottleneck for the exploration of their biological and medicinal properties. Complex oligosaccharides are comprised of the simpler monosaccharides, and, not surprisingly, modern synthetic approaches to oligosaccharides strongly rely on the ability to access differentially protected building blocks. Synthesis of such differentially protected monosaccharides often requires multiple step sequences to differentiate numerous hydroxyl groups, and may suffer from low yields and tedious purifications due to the formation of undesirable regioisomers throughout these sequences. To address the challenges associated with the selective functionalization of monosaccharides, numerous methods, including single pot functionalization approach by the Hung group, have been previously developed. However, the majority of such methods rely on the reagents and catalysts that discriminate between the axial and equatorial hydroxyl groups while only few methods exist for the selective differentiation of equatorial hydroxyl groups that are in similar steric and electronic environment (cf. Scheme 1A). While possible with achiral reagents or catalysts, such transformations often exhibit strong electrophile- and substrate structure dependence and lack generality (cf. Scheme S1-1 for compiled representative examples). Pioneered by the Miller group, the approaches based on the use of asymmetric catalysts to achieve site-selective functionalization of sugar-derived polyols have recently gained significant attention. While many efforts, most notoriously by the Kawabata and Tang groups have focused on exploring asymmetric catalysts for the selective acylation reactions, chiral catalyst-controlled site-selective phosphorylation, thiocarbonylation, sulfonation, silylation, acetalization and glycosylation have also been explored in the context of chiral catalyst-controlled functionalization of sugar-derived polyols.

We have long-standing interests in utilizing chiral phosphoric acids as the catalysts leading to regio- and stereoselective acetal formation. As the part of these studies our group...
disclosed selective functionalization of monosaccharides using 1,1'-bi-2-naphth (BINOL)-derived chiral phosphoric acids (CPAs)\textsuperscript{13} as the catalysts to direct regioselective acetalization of carbohydrate-derived 2,3-diols (cf Scheme 1B).\textsuperscript{13} This study demonstrated that (R)-CPA catalyst 1 could promote regioselective protection of D-glucose, D-galactose, D-mannose-derived diols and a L-fucose-derived triol with enol ethers such as dihydropyran (DHP), 2-methoxypropane (2-MP), and 1-methoxy cyclohexene (1-MCH). The reactions of D-glucose and D-galactose derivatives proceeded at the sites that cannot be directly functionalized with achiral reagents such as n-dibutyltin(IV) oxide (cf. Scheme SI-1).\textsuperscript{44} In addition, it was observed that the chirality of the catalyst played an important role as using the (S)-1 or achiral acids such (PhO)\textsubscript{2}P(OMe)\textsubscript{3} resulted in unsatisfactory reactions or selectivity switch. Importantly, these transformations featured mild reaction conditions and the use of easily available and non-toxic substrates and catalysts.

**Scheme 1. Synthetic challenges and summary**

A. Challenge: differentiating equatorial alcohols in carbohydrates:

B. Nagorny group (2013): 

C. Current work:

Building on this approach, the current article expands the substrate scope and demonstrates the use of CPA-catalyzed regioselective acetalizations for the scalable single-pot synthesis\textsuperscript{16} of various differentially protected D-glucose, D-galactose and D-mannose mono- and disaccharides (Scheme 1C). These telescoped single-pot multiple step protocols proceed with high selectivities and efficiencies and require minimum purifications to access valuable protected building blocks from commercially available diol precursors. To address the challenges associated with the accessibility of the catalyst 1, we describe the development of immobilized catalysts 2 and 3 that was found to promote highly selective acetalization reactions and could be recycled and re-used multiple times. The use of catalyst 2 that is structurally equivalent to 1 allowed to achieve substantial reduction of the catalyst loading (0.5 to 0.1 mol%) for gram-scale reactions and significantly improve the selectivity of acetalization for several different substrates. In addition, catalyst 3 allowed regiodivergent protection at positions that cannot be accessed using catalysts 1 or 2.

**Scheme 2. Site-selective MOC and MOP protection of monosaccharide-derived diols\textsuperscript{a}**

\textsuperscript{a}The reactions with 2-methoxypropane (2-MOP) were performed overnight at \textdegree C and the reactions with 1-methoxycyclohexene (1-MOC) were performed overnight at \textdegree C on 0.056 mmol scale (0.042 M solution) for 18-24 h in the presence of 4 Å MS. The reaction with 4a was performed on 2.78 mmol (1.0 g) scale. These rr values were determined by \textsuperscript{1}H
NMR analysis of the crude reaction mixtures of the products 5
and 6 as well as their acetylated derivatives. The values with
asterisk* represent conversion determined by 1H NMR anal-
ysis, and each entry represents an average of 2 experiments.

Finally, this article summarizes the mechanistic and com-
putational QM/MM studies of the acetalization reaction
mechanism and reveals that this transformation may pro-
cede through an interplay of two different reaction mecha-
nisms with the asynchronous concerted acetalization mecha-
nism being dominant at low temperatures and leading to
the observed selective formation of acetals. These insights
into the reaction mechanism were used to develop a stereo-
chemical model explaining the observed selectivity trends.

2. DISCUSSION

Selective protection of a single alcohol moiety as an acetal
within a sugar-derived diol possessing alcohols in similar
steric and electronic environment represents a challenge.
Acid-catalyzed acetal formation is known to proceed
through the highly reactive intermediates—oxocarbenium
ions, which are known to react with nucleophiles indiscrim-
inately. The resultant acetals are also acid labile, and equili-
bration/isomerization leading to the most thermodynamically
stable product under the reaction conditions is not un-
common. Being very useful in organic synthesis and carbo-
hydrate chemistry, mixed acetal protecting groups such as
1-methoxy cyclohexyl (MOC) and 2-methoxy-2-propyl
(MOP) are very sensitive to acids and may easily hydrolyze
and/or undergo the formation of 1,3-dioxolanes and 1,3-di-
oxanes.17

With these considerations in mind, it was particularly
surprising to observe that (R)-Ad-TRIP (1)-catalyzed for-
mations of MOC and MOP acetals often proceeded with
great levels of regiocontrol and high yields (cf. Scheme 2 and
SI Scheme 2S).13,14 Remarkably, the control experiments
with various achiral phosphoric acids such as DPPA and
BPPA as well as p-TSA and CSA did not lead to selective re-
actions, and approximately equimolar mixtures of the C2
and C3 protected acetals were obtained in each instance in
diminished yields. Similarly, the use of enantiomeric (S)-
Ad-TRIP catalyst 1 often resulted in diminished yields and
selectivities, and in the instance of 5c, 5i, 5m, and 5p the
selectivity was reversed to produce significant amounts of
the C3-regiosomer. Not surprisingly, the use of L- rather
than D-sugars such as L-fucose-derived triol 4k required
(S)- rather than (R)-1 to achieve selective protection of the
C3 position.

Scheme 3. Regioselective single-pot synthesis of the differentially protected mono- and disaccharide derivatives en-
abled by (R)-Ad-TRIP(1)-catalyzed regioselective MOC- and MOP-protections

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4Isolated yield after one-pot sequence leading to 6. The reaction mixtures were concentrated by the stream of N2 prior to each
protection step. Unless noted otherwise, these experiments were carried on 0.056 mmol scale. MOC protection was accomplished as
described in Scheme 2.4Acylations were carried using Ac\textsubscript{2}O (1.1 equiv), DMAP (10 mol\%), Et\textsubscript{3}N (5.0 equiv) or BzCl (1.2 equiv), DMAP
Alkylation was accomplished by addition of NaH (1.2 equiv), alkyl halide (1.1 equiv), TBAI (0.1 equiv) and DMF (cat.). The MOC cleavage was achieved by addition of 0.05 M HCl in CH₂Cl₂ (pH = 5). The final glycosylation step to form 7a and 7b was accomplished with 2.5 equiv of TMSOTf (20 mol%) in DCM at 0 °C in the presence of 4 Å MS. The glycosylations leading to 7c-7f was accomplished in the presence of 1.4 equiv of triis-benzylated L-rhamnose trichloroacetimidate. Compounds 6r-6t were generated using MOP-protected intermediates 5q and 5s. Benzyldiene acetal cleavage was accomplished using Et₃SiH (5 equiv). CF₃CO₂H (5 equiv), DCM, 0 °C, 2 h. The synthesis of 8a was carried out on 1.0 g scale. Please refer to SI for the detailed description of these single-pot protocols.

The D-glucose derivatives possessing 4,6-benzyldiene acetal protection and featuring β-configuration in the anomeric position exhibited highest levels of regiocontrol exclusively providing the C2-protected products 5a-5e and 5i. The size and nature of the anomeric substituent with β-configuration seemed to have little effect on the reaction selectivity; however, the changes in the 4,6-acetal moiety seemed to have a significant effect. Thus, the (R)-1-catalyzed 2-MOP protection leading to 2-naphthyl product 5p proceed with the significantly lower C2-selectivity (3:1 rr) than for the corresponding benzylidene acetald derivative 5i (>25:1 rr). In line with this observation, the analogous to 5i acetonide derivative 5m was produced in only 12.1 rr while the MOP-derivative 5o. Similarly, MOC protection leading to the derivatives 5g and 5h lacking the 4,6-benzyldiene acetald moiety were produced with lower C2 selectivities (5:1 and 7:1 rr, correspondingly) than for the benzylidene acetald containing products 5a-5e. Finally, it should be noted that the presence of the axial substitution next to the C2/C3 diol seems to direct the protection to the position furthest away from the axial substitution. Thus, both the MOC and 2-MOP protection of D-galactose derivatives with β-anomeric configuration, 4i and 4j, provided C2-protected products 5i, 5j, 5q and 5r in good-to-excellent selectivities and yields. Following this trend, D-glucose derivative with α-methoxy configuration 4f provided the C3 (rather than the C2) products 5f and 5n in moderately good selectivities (88:1 rr and 6.3:1 rr, correspondingly).

While mixed acetal protecting groups are less common in carbohydrate synthesis than acyl or benzyl protection, their stability to bases and significant lability under the mildly acidic conditions offer excellent opportunities for carrying out the subsequent functionalizations in a single operation. Therefore, our following studies were focused on demonstrating that regioselective products 5a-5s are of great utility for the telescoped preparation of differentially protected monosaccharide derivatives from commercially available building blocks such as 4a. Inspired by the streamline method for the single-pot synthesis of various D-glucose derivatives by the Hung and coworkers,4 we investigated one-pot derivatizations of 5a (cf. Scheme 3). Considering that both the MOC and 2-MOP protecting groups are highly labile in the presence of an acid (vide supra), our single pot protocol included in situ removal of the MOC protection with 0.05 M HCl without deprotecting the 4,6-benzyldiene acetal.17 The high volatility of 0.05 M HCl solution in DCM was also suitable for the overall single-pot functionalization process as it could be removed by passing a nitrogen stream over the reaction mixture without the necessity of carrying the reaction work up.

The one-pot transformations leading to differentially protected C2/C3 products 6a-6t (cf. Scheme 3A) commenced with CPA (1)-directed regioselective acetalization, and the resultant C2-acetal 5a (or 5q and 5s) was successfully obtained in full conversion. At this point, the mixture was dried by sequentially applying a gentle N₂ blow and flask evacuation before the next step. Initially the crude mixture containing compound 5a was subjected to free C3-hydroxyl group protection without affecting the C2-acetal. Since mixed acetals are acid- and heat-labile, acidic conditions and high reaction temperatures were avoided. The regioselective acylations of the C3-OH were accomplished using (RCO)₂O/Py or ROCl/Et₃N in the presence of catalytic DMAP (substrates 6a-6j). Alternatively, the C3-alkylation was accomplished using alkyl halides and sodium hydride as the base in the presence of catalytic TBAI (6k-6t). The C2 MOC (or MOP) acetal was removed by adding excess of HCl solution in DCM to the reaction mixture. The resultant acidic solutions were concentrated by passing N₂ stream to blow out the volatiles and subsequent evacuation of the reaction vessel, and the concentrated crude oils were subjected to the C2-protection to provide products 6a-6t in good yields (49-83% overall yield). In addition to the D-glucose-based derivatives 6a-6q, this method was also successfully applied to generate D-galactose-based substrates 6r and 6s as well as D-mannose-derived substrate 6t using MOP (rather than MOC) protection strategy. Unlike other substrates, D-mannose derivative 5s contained MOP acetal at the C3 position, which required functionalization in a reverse way (C2-benzylation, C3-acetal cleavage, and C3-acylation) to afford compound 6t in good overall yield (77%) and selectivity (>12:1 rr for the first step).

It is noteworthy that while some of the derivatives (i.e. 6k-6q) might be potentially accessible through one-pot glucose functionalization strategy developed by the Hung group, one-pot synthesis of the derivatives 6a-6j featuring the C3 acyl protection has not been previously described and would be challenging to accomplish via Hung’s single-pot protocol in good yields. Similarly, previously published one-pot protection protocols could not be readily adopted to the synthesis of D-galactose and D-mannose derivatives similar to 6r-6t. Finally, the operational simplicity for the deprotection of the MOC and MOP groups allows to expand the scope of the protecting groups (to include substrates...
like 6e) and achieve flexibility in controlling the C2/C3 protection to generate regiosomeric substrates like 6d and 6q in similar yields (60% and 69%, correspondingly).

The aforementioned regioselective manipulations on 4a could be combined with glycosylation to accomplish concomitant protection and glycosylation of the C2 and C3 positions (cf. Scheme 3B). Thus, CPA-catalyzed C2-protection with MOC was followed with acylation (7a and 7b) or alkylation (7c or 7d), subsequent MOC group cleavage, and glycosylation with 2,3,4-OBn L-rhamnopyranoside trichloroacetimidate to provide derivatives 7a-7d in good yields (65-72%) as single regioisomers with the glycosylated C2 position. This protocol was also extended to other sugars such as D-mannose (4s) to provide the protected and glycosylated derivative 7f as the single regioisomer in 63% yield. The inclusion of the additional C2 protection/C3 deprotection sequence also allowed to achieve the reverse glycosylation of the C3 position and resulted in the derivative 7e in moderate yield (39%). Importantly, the C3 hydroxyl group in 4a is more reactive in glycosylation with 2,3,4-OBn L-rhamnopyranoside trichloroacetimidate, and the direct glycosylation of 4a provides ~3:1 mixture of the regiosomeric C3 and C2 products in 79% overall yield. Correspondingly, the described strategy offers advantages for the synthesis of C2 glycosides such as 7a-7d.

These transformations could be further combined with benzylidene acetal opening/C4 protection steps to accomplish single-pot generation of differentially protected D-glucose derivatives 8a-8f depicted in Scheme 3B. Thus, the previously developed protocol included regioselective benzylidene acetal reduction with CF₃CO₂H/μ-THF leading to product containing free C4 alcohol that was subsequently protected. These single-pot transformations proceeded in 25-38% overall yield (~85% yield per operation) with high levels of overall regiocontrol. These procedures were scalable, and the derivative 8a was made on 1.0 g scale (31% yield) with the same yield as on 0.056 mmol scale.

The substrates 6a-6t carry a thiophenol moiety at the anomeric position, and, hence, could serve as glycosyl donors (Eq. 1 and 2). Thus, we selected two derivatives of 4a (i.e. 6b and 6q) and demonstrated that the regioselective protection leading to 6b and 6q could be combined with glycosylation using acceptors 9 and 11 and leading to single pot formation of disaccharides 10 and 12. While the yield of 10 (35%) was diminished due to the lability of acetone moieties in 9 and 10 under the acidic conditions (Eq. 1), the single pot synthesis of 12 proceeded in good yield (55%) and selectivity (Eq. 2).

We believe that the aforementioned results demonstrate that CPA-catalyzed regioselective acetalizations are of great use for the single pot protection and glycosylation of monosaccharides. While this method allows to expand the repertoire of sugar derivatives and transformations developed by Hung, it suffers from the obligatory use of expensive chiral acid (R)-Ad-TRIP (2). We surmised that the costs associated with the use of 2 could be dramatically reduced if the catalyst is immobilized on a solid support as numerous recent studies suggest that such catalysts could be readily recovered and recycled or employed for the catalyst in continuous flow.¹⁰

Scheme 4. Synthesis and applications of polystyrene-supported CPA catalyst (R)-Ad-TRIP-PS (2) and (S)-SPINOL-PS (3)

| Cycle number | CPA loading (mmol) | scale (g) | time (h) | conversion (%) | C2/C3 (±)
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<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>1.0</td>
<td>18</td>
<td>99</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>2</td>
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<td>1.0</td>
<td>18</td>
<td>95</td>
<td>23:1</td>
</tr>
<tr>
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<td>18</td>
<td>97</td>
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<tr>
<td>4</td>
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<td>1.0</td>
<td>18</td>
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<tr>
<td>5</td>
<td>0.5</td>
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<td>6</td>
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<tr>
<td>9</td>
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<tr>
<td>10</td>
<td>0.1</td>
<td>5.0</td>
<td>36</td>
<td>99</td>
<td>&gt;25:1</td>
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Scheme 4. Synthesis and applications of polystyrene-supported CPA catalyst (R)-Ad-TRIP-PS (2) and (S)-SPINOL-PS (3)
(a) 13 (1 equiv), Br_2 (2.2 equiv), DCM (0.16 M), −78 °C, 2.5 h, 92%; (b) 4-vinylphenylboronic acid (2.4 equiv), K_2CO_3 (4.0 equiv), EtOH:THF = 1:1 (0.1 M), Ph(PPh_3)_3 (15 mol%), reflux, 12 h, 65%; (c) POCl_3 (2.0 equiv), pyridine (0.1 M), 70 °C, 2 h, then H_2O (0.1 M) 100 °C, 16 h, 57%; (d) 15 (1 equiv), Br_2 (2.2 equiv), DCM (0.16 M), −78 °C, 2.5 h, 97%; (e) 4-vinylphenylboronic acid (5 equiv), K_2CO_3 (5.0 equiv), dioxane:water=2:1 ratio (0.066 M), Ph(PPh_3)_3 (5 mol%), 70 °C, 5 h, 88% yield; (f) POCl_3 (5.0 equiv), pyridine (0.1 M), 70 °C, 12 h, then H_2O (0.1 M) 100 °C, 16 h, 75%.

Therefore, our subsequent efforts were focused on developing a catalytically active immobilized version of 1 (cf. Scheme 4 and SI Scheme 3). Based on the previously developed strategies for TRIP immobilization, we investigated this variant for the synthesis of immobilized on polystyrene support catalyst (R)-Ad-TRIP-PS (2). While the previously published route did not lead to catalytically active in acetalization reactions (R)-Ad-TRIP-PS (2), we were able to modify this approach (cf. Scheme 4A) to produce a viable immobilized catalyst 2. Based on our previous observation that (S)-SPINOL CPA derived from 15 may lead to regiodivergent acetalization, we also pursued preparation of new immobilized (S)-SPINOL-PS (3)°° described in Scheme 4B, using the approach developed for the synthesis of 2. Remarkably, the gram scale syntheses of 3 was accomplished in only 4 steps from 15 that is a commercially available derivative of (S)-SPINOL. Gratifyingly, both immobilized catalysts (R)-Ad-TRIP-PS (2) and (S)-SPINOL-PS (3) were found to efficiently promote the catalytic activity and selectivity in acetalization of 4a and could be conveniently recovered and recycled by filtration and wash (cf. Scheme 4C, and Tables SI-15 and SI-2S). Most importantly, we were able to repeatedly run nine consecutive 1.0 g scale MOP-protections of 4a with only 0.5 mol% (50 mg) of the same batch of catalyst 2 without erosion in yield or selectivity. Then, using the same batch (i.e. 0.1 mol% loading) of 2, a 5.0 g scale acetalization gave 5a in >25:1 rr, and 99% conversion. These results indicate that significant catalyst economy was achieved as the same 50 mg of 2 were used to convert the total of 14.0 g of 4a into 5a. Importantly, parallel evaluation of catalyst 1 at 0.5 mol% loadings indicated that such reactions were also possible; however, it
was required twice as much time as for 2 (i.e. 36 h vs 18 h) to achieve full conversion.

Based on these promising results for the regioselective acetalization of 4a using immobilized catalysts 2 and 3, our subsequent studies focused on investigating these polymeric catalysts in the acetalizations of other substrates and comparing them to the monomeric catalysts 1 and 16 (cf. Scheme 5A and 5B). Gratifyingly, (R)-Ad-TRIP-PS catalyst 2 demonstrated a great selectivity profile for the generation of the corresponding 2-MOP protected derivatives, and with the exception of one case (5n), the resultant products were obtained in excellent C2-selectivity (cf. Scheme 5A). It is noteworthy that the selectivities and yields for substrates 5l, 5r, and 5s obtained with the immobilized catalyst 2 matched the corresponding results previously obtained for CPA 1. Remarkably, in three instances (5m, 5o, and 5p), PS-supported CPA 2 provided significantly higher regioselectivities than the monomeric acid 1 (25:1 rr vs 3:1 rr for 5p, 25:1 rr vs 6:1 rr for 5o, and 19:1 rr vs 12:1 rr for 5m). Finally, in instances of 5n and 5q, the selectivities obtained with 2 were lower than the selectivities obtained with 1 (1:1 rr vs 6:1 rr for 5n and 20:1 rr vs 15:1 rr for 5q).

The subsequent evaluation of (S)-SPINOL-PS catalyst (3) resulted in regiodivergent acetalization of substrates 4a, 4j, 4m, and 4p, leading to the regioisomeric C3 acetals 17a–17f in good to excellent selectivities; however, in the case of substrates 4f and 4h, the same regioisomers as with (R)-Ad-TRIP (1) and (R)-Ad-TRIP-PS (2) were observed. The selectivities improved with increasing steric size of the O4/O6 acetal (from 6:1 to 8:1 to 10:1 rr for 17c, 17a, and 17b). Similarly, increasing the steric size of electrophile (i.e. 1-MOC vs. 2-MOP) consistently resulted in an improvement of the reaction selectivities (from 10:1 for 17b to 14:1 for 17f and from 8:1 for 17a to 9:1 for 17e). To demonstrate the scalability of the process, the synthesis of 17a with (S)-3 was successfully carried on 1.0 g (2.78 mmol) scale with improved 94% yield and 8:1 rr.

It is noteworthy that in the case of the (R)-Ad-TRIP-PS (2), the use of (S)-SPINOL-PS(3) may lead to significant improvement in the reaction selectivity in comparison to the monomeric catalyst 16. Such improvements in selectivity were observed for substrates 17a–17c, 17e, 17f, and 5o although for 17d polymeric catalyst was inferior to 16. Remarkably, complete switch in selectivity was observed in the case of substrate 4f, and while polymeric (S)-3 resulted in moderately selective formation of the C3-protected product 5n (3:1 rr), monomeric (S)-16 resulted in the formation of the C2 regiosomer of 5n (1:3 rr). These observations suggest that the additional structural features present in 2 and 3 that are not present in 1 and 16 such as the linker and polystyrene matrix may impact the steric interactions between the CPA and substrate. This could have both positive or negative consequences for the reaction outcome although in the majority of cases presented in Schemes 5A and 5B improvements in the selectivity were observed.

Scheme 6. A. Selectivity versus temperature profile for the MOC and 2-MOP protection of 4a, and theoretically predicted selectivity profile for a reaction with no mechanism switch using Arrhenius model with ΔΔG° = 1.2 kcal/mol.a
B. Control equilibration experiment.b C. Potential reaction mechanisms for the CPA-catalyzed acetalization reaction.

aThe reactions with 2-methoxy-2-propene (2-MOP) and 1-methoxy-1-cyclohexene (1-MOC) were performed overnight at the specified temperature on 0.056 mmol scale (0.042 M solution) in the presence of 4Å MS. The C2/C3 ratio was determined by 1H NMR.
To demonstrate the utility of the immobilized CPAs for the gram scale synthesis of differentially protected mono-saccharide derivatives, we performed series of 1.0 g scale functionalizations of 4a using the same batch (50 mg or 0.5 mol%) of (R)-Ad-TRIP-PS 3 (cf. Scheme 5C). The selective MOP-protections of 4a were followed by filtration, and the filtrate was subjected to the previously developed one-pot derivatizations (cf. Scheme 3). The recovered and recycled catalyst 3 was then reused to accomplish subsequent cycles of regioselective functionalization of 4a. This protocol allowed consecutive one-pot syntheses of 6a (0.96 g), 6b (1.2 g), 6f (1.1 g), 6k (0.98 g), 6p (1.2 g), and 8e (0.67 g) using the same batch of catalyst 3 (50 mg). It is also noteworthy that the single-pot procedures leading to 6a, 6b, 6f, 6k, 6p, and 8e were readily scalable and proceeded with improved overall yields. Altogether, these studies suggest that immobilized CPA-catalysts 2 and 3 hold great potential for the regioselective preparation of differentially protected monosaccharide derivatives, and that the use of the regioselective CPA-catalyzed acetalization allows the expansion of the single-pot methods previously developed by Hung and others.4,5

With these developments in hand, our subsequent studies were focused on experimental and computational exploration of the mechanism for the regioselective acetalizations and development of a stereochemical model explaining the observed selectivity trends. Both MOC and MOP acetalizations demonstrated unusual selectivity versus temperature profiles (cf. Scheme 6A). Thus, both types of acetalization were unselective at the temperatures above ~30 °C, but demonstrated significant jump in selectivity once cooled below ~50 °C. These unusual temperature vs. selectivity profiles are not consistent with the theoretically predicted using Arrhenius model regioselectivity on temperature dependence computed for ΔG°=1.2 kcal/mol (cf. Scheme 6A and SI Figure 2S). The regioselectivity should be exponentially dependent on temperature, and the profiles in Scheme 6A should not involve abrupt increase of selectivity at some threshold temperature. The observed temperature dependence suggests that the acetalization may happen through competing mechanisms, and that the mechanism prevailing at the temperatures below ~50 °C might be different from the reaction mechanism at higher temperatures. To test whether the product is stable at higher temperatures, regioisomerically enriched product 5a was re-subjected to acid 1 at room temperature (Scheme 6B) for 12 h. This result is in significant isomerization of 5a into the regioisomeric product 17g, and the crude reaction mixture contained ~1:7:1 ratio of 5a:17g. The significant amounts of diol 4a were also present in the mixture and suggested that the formation of 17g proceeded through 4a and that the overall acetal formation is reversible at room temperature.

With these observations in mind, three different reaction mechanisms depicted in Scheme 6C were proposed. These involved the conventional mechanism proceeding through the oxocarbenium ion (option A), as well as direct synchronous or asynchronous concerted addition, as previously proposed by us for CPA-catalyzed spiroketalizations (option B). Alternatively, the catalyst may react with the MOC or 2-MOP enol ethers to form a phosphate intermediate, which then proceeds through Sₐ1 or Sₐ₈ mechanisms that were observed by us for CPA-catalyzed glycosylation of 6-deB (option C). Differentiating these mechanistic options computationally represents a challenging task as it requires finding and optimizing conformationally flexible transition states structures. To address some of these challenges, our computational studies used the reaction-path and transition-state search tool called the Growing String Method (GSM).3,4 The large size of the system (207 atoms) motivated a Quantum Mechanics/Molecular Mechanics (QM/MM) approach to make the reaction path analysis feasible. The QM/MM borders were set on the C-C bond at the 3,3′-positions of the chiral catalyst (R)-2 placing bulky hydrocarbon moieties in the MM region (cf. Scheme 75-SI).

Reaction pathways were determined using GSM for the 20 lowest energy conformers for each path (C2 and C3 in each mechanism, cf. SI). The concerted mechanism was investigated first, beginning from the complex involving the substrate N-bonded to (R)-2 (Figure 1A). The reaction pathway shows an asynchronous concerted transformation: the CPA protonates the enol ether (PG) to generate an oxocarbenium cation that then reacts with the OH-group of the sugar substrate 4a (TS₁ for C2-path and TS₂ for C3-path). The resultant CPA anion deprotonates the OH-group synchronously with oxygen nucleophilic attack on the oxocarbenium cation. The lowest energy activation barriers among the 20 conformers of each TS favour C2-protected product 5a formation at 223K (ΔΔG°273 = −1.2 kcal/mol) and 273K (ΔΔG°273 = −1.0 kcal/mol) (Table 6S-SI). Activation energies (ΔG°, kcal/mol) for this mechanism (21.1 and 22.3 kcal/mol for C2- and C3-paths respectively) are slightly higher than expected from the experimental data (18-19 kcal/mol for overnight reaction at ~50 °C). This concerted mechanism, which does not show an oxocarbenium intermediate (Scheme 6C, Path A), does bear similarities with the oxocarbenium mechanism. In particular, the oxocarbenium ion appears along the reaction path at the transition state structure, which identifies the concerted mechanism as asynchronous (Scheme 6C, Path B).

The two-elementary-step phosphate-mediated mechanism (Scheme 6C, Path C) was investigated next. To do so, 20 conformationally distinct reaction pathways involving (R)-(2) and 1-methoxycyclohexene (PG) were examined. The phosphate intermediate is reached via asynchronous protonation of the enol ether PG followed by nucleophilic
attack with the same phosphoric acid oxygen that participated in substrate protonation. The activation energy for the lowest barrier phosphate formation step is 14.7 kcal/mol. Unlike our previous studies of the CPA-catalyzed glycosylations, the covalent phosphate intermediate formation was not directly observed by low temperature $^{31}P$, $^{13}C$ or $^1H$ NMR studies (cf. Scheme SI-S4). This is not surprising, however, as the computational studies indicate that covalent phosphate is 4.4 kcal/mol less stable than the reactant complex. Keeping in mind the low energy barrier for its formation and dissociation back, this step should be considered as being in equilibrium. During the reaction, the phosphate acetal would be formed only in trace quantities and exist as a steady-state intermediate, which could be observed in deuterium-exchange experiment with deuterium-labelled phosphoric acid (cf. SI-XVIII, Part C).

The second step of the phosphate-mediate pathway (Path C) has a reaction energy profile more consistent with a concerted $S_{11}$ mechanism rather than an $S_{12}$ mechanism, as no stable carbocation intermediates were detected (cf. Figure 2A). In this step the OH-group of 2,3-diol 4a attacks the carbon atom of the methoxy cyclohexane fragment of the phosphate intermediate at the same time as the C-O phosphate bond cleaves. This second step is rate-limiting and shows the opposite regioselectivity compared to the concerted mechanism. That is, at both temperatures of interest the C3-protection was favored over the C2-protection ($\Delta \Delta G_{273}^\circ = 1.5$ kcal/mol and $\Delta \Delta G_{273}^\circ = -1.6$ kcal/mol, Table 65-S1). Surprisingly, the activation energies of the rate-limiting step were also close to the ones computed for the concerted mechanism (Figure 2A).

The energy diagram summarizing our computational studies is provided in Figure 2A. Even though there was a slight preference for the phosphate mechanism, an obvious assignment of operating mechanism is not possible due to the energy difference being within the errors of the model. This situation, however, allows us to postulate that the concerted mechanism is preferred at low T, and the phosphate mechanism at high T. Invoking this switch in mechanism comes with a change in regioselectivity that nicely explains the experimental results depicted in Scheme 10. At low temperatures, the concerted mechanism (Path B) would therefore give rise to high C2-selectivity ($\Delta \Delta G^\circ (C2-C3) = -1.2$ kcal/mol). At higher temperatures the phosphate mechanism (Path C) likely results in increased amounts of the C3 acetalization product ($\Delta \Delta G^\circ (C2-C3) = 1.5$ kcal/mol).

Figure 1. Probing the reaction mechanism and stereochemistry of acetalization using deuterium-labeled d$_3$-1-methoxy-cyclohexene

A. Probing the syn/anti-stereoselectivity of (R)-Ad-TRIP (1) acetalization using deuterated 1-MOC (d$_3$-1-MOC) at $-78^\circ$C and r.t.

B. $^{1}H-^{13}C$ HSQC spectrum of d$_3$-5a obtained through acetalization with 1 at $-78^\circ$C

C. $^{1}H-^{13}C$ HSQC spectrum of syn/anti-d$_3$-5a obtained through acetalization at r.t.

To experimentally probe our mechanistic hypothesis, a series of experiments with deuterium-labeled d$_3$-methoxycyclohexene (d$_3$-MOC) was executed next (cf. Figure 1 and SI-XVIII, part D). Considering that our computational analysis (vide supra) suggested the concerted mechanism is operative
at −78 °C, monosaccharide hydroxyl group and hydrogen addition to MOC double bond should be exclusively syn-specific. In contrast, the reaction proceeding through a phosphate intermediate should lead to both syn- and anti-addition of the hydroxyl group to the double bond due to fast equilibration though covalent phosphate. Using d5-MOC as the electrophile, acetalization of 4a was performed under the standard reaction conditions and resulted in the formation of deuterated acetals syn-d5-5a1 and syn-d5-5a2 (Figure 1A). The initial stereochemical assignment of syn-d5-5a5 was hindered by the conformational flexibility of the MOC acetal moiety, which resulted in significant overlap of the MOC group signals. This coupled to the fact that two syn- and two anti-diastereomers might be formed by adding ROH to two different faces of MOC prompted us to carry additional NMR studies at −80 °C. The NMR assignments were guided by computational analysis of the d5-5a conformational space and their theoretically predicted 1H and 13C NMR shifts (cf. SI-X). The experiments at −80 °C slowed the interconversion of the chair forms of syn-d5-5a1 and syn-d5-5a2, and we observed four sets of 13C signals present in the NMR spectrum of d5-5a. Each of the diastereomeric syn-products syn-d5-5a1 and syn-d5-5a2 contributed a set of two conformers containing the MOC methoxy group in either an axial or an equatorial position in the cyclohexane ring (cf. Figure 1B, proton pairs 2′-2′ and 4′-4′). The assignment of 1H and 13C NMR signals of syn-d5-5a1 and syn-d5-5a2 was carried using 1H/13C HSQC and EXCY-NOESY. This analysis was consistent with the calculated NMR shifts for the axial and equatorial conformers for these stereoisomers (cf. Scheme SI-X). Most importantly, significant magnetic anisotropy effects exhibited by the PhS-group on the top face of MOC are expected for the syn-rather than the anti-conformers, and that is indeed what is observed in low-temperature NMR spectra of syn-d5-5a1 and syn-d5-5a2 (cf. Figure 1B and 1C).

To further validate this assignment, we independently synthesized and investigated a mixture of syn- and anti-diastereomers of 5a (i.e. syn-d5-5a1, syn-d5-5a2, anti-d5-5a1 and anti-d5-5a1) by running acetalation with d5-MOC at room temperature (cf. Figure 1A and 1C and Scheme X-SI). As expected, the mixture of syn-d5-5a1, syn-d5-5a2, anti-d5-5a1 and anti-d5-5a1 obtained by d5-MOC acetalization at room temperature featured 8 HSQC cross peaks (cf. Figure 1C, proton pairs 1′-1′, 2′-2′, 3′-3′, 4′-4′) due to the additional equatorial and axial conformers for each of 4 diastereomers. These additional signals due to anti-d5-5a isomers are consistent with the computed NMR data as well as the observed 1H/13C signals obtained for 5a containing a nondeuterated MOC group. Altogether, these studies indicate that MOC protection at −78 °C proceeds stereospecifically and results in syn-isomers while the same reaction results in the mixture of syn- and anti-isomers at room temperature. This is in good agreement with our other experimental and theoretical studies that predict a concerted asynchronous acetalation resulting in syn-product at −78 °C. It is also consistent with the predictions that acetalization at higher temperature may proceed through a competitive mechanism involving acetal phosphate-intermediate that is in equilibrium with (R)-Ad-TRIP (1) and 1-MOC at room temperature (cf. SI-X).

With the mechanistic picture in hand, transition state analysis was performed to identify the key structural features leading to different selectivities in each mechanism. The non-covalent interactions (NCIs) are known to be crucial in stabilizing or destabilizing the transition states when changes in energy by 1-2 kcal/mol can dramatically change the reaction selectivity. The graphical analysis delineates NCIs into three categories: blue, strong attraction; green, weak interaction; and red, strong repulsion. For the concerted mechanism (Figure 1B) there are two common regions of non-covalent interactions: (1) C-H van-der-Waals interactions of sugar backbone with catalyst adamantyl group and (2) enol other C-H interaction with π-system of catalyst 3-aryl system. The most important interaction (3) is between the 4,6-benzylidine group and CPA isopropyl groups (circled for TS1). The presence of such interaction can destabilize the transition state and make the C3-protection less favorable than the corresponding C2-pathway that lacks such steric repulsion (3). Remarkably, during the C2-protection via the phosphate-mediated mechanism, reactants and catalyst in TS1 are aligned almost in the same ways as for the concerted reaction (TSs). There are some weak π...H-C interactions (4) that appear between the substrate 4a and the MOC protecting group PG, but interactions (1) and (2) with the catalyst skeleton also are present. These similarities in NCI patterns for the TS1 and TSs are in good agreement with almost identical TS energies for the C2-acetylation for both mechanisms. In contrast, the molecular alignment in TSs (C3-protection) is significantly different from the concerted mechanism. The reactants are aligned in a more compact way and positioned further away from the catalytic pocket. The NCIs (1) and (2) arising from the 2,3-diol 4a, MOC enol ether PG and the catalyst are minimized, and only interaction (4) between the reactants are clearly present. The absence of these NCIs in TS2 leads to its higher stability and, thus, the C3-protection prevails for the phosphate-mediated mechanism. Identified interactions and reactants alignment in catalytic cavity can be extrapolated and proved by looking at other substrates. First, using less bulky acetonide-protected compound 4m gives only 1:2:1 regioselectivity favoring the C2-protected product. Two methyl groups in transition state TS2-C3 should cause fewer destabilizing interactions with isopropyl groups reducing selectivity. Bulky C1-subsitutuents in β-configuration (−SC6H5 δBu and −SNaph) shouldn’t impact selectivity as they are positioned far away from catalyst and it is also in agreement with experimental data (substrates 4b and 4d also gives high 25:1 selectivity). Transition state TS1-C2 reveals potential interactions of catalyst backbone with
Figure 2. Computational exploration of the reaction mechanism and stereochemical model for the regioselectivity

A. Energy diagram depicting potential reaction mechanisms at 223 K

B. Noncovalent interaction analysis for regiocontrolling transition states TS$_1$ and TS$_2$ for concerted mechanism at 223 K

C. Noncovalent interaction analysis for regiocontrolling transition states TS$_4$ and TS$_5$ for phosphate-mediated mechanism at 223 K
C1-substituent in α-configuration leading to its destabilization and to C3-selectivity as it was observed in case with D-glucose derivative 4f.

In summary, the concerted asynchronous (Path B) and phosphate intermediate (Path C) mechanisms feature similar interactions in the transition states and molecular positions for the formation of the C2 isomer, which are reflected in negligible energy differences between these two pathways. Thus, the regioselectivity for the CPA-catalyzed acetal formation is determined by the steric interactions in the TS for the C3-protection. At low temperatures these results are consistent with the concerted mechanism being operative, where the sugar substrate alignment leading to the C3 product suffers from the interactions of 4,6-benzylidene acetal moiety with the catalyst. Considering the small difference in the RDS energy barriers for both pathways, the temperature can be an important factor in favoring one mechanism—and therefore one regioselectivity—over another.

3. CONCLUSION

In conclusion, this article describes the utility of regioselective acetalization reactions catalyzed by chiral phosphoric acids 1-3 for single-pot synthesis of 34 regiosomerically pure differentially functionalized mono- and disaccharide derivatives. To further improve the practicality of this approach, we developed two immobilized chiral phosphoric acids (R)-Ad TRIP (2) and (S)-SPINOL (3) that could be used to accomplish regiodivergent acetal protection of monosaccharide-based diols in good-to-excellent selectivities. Unlike their achiral counterparts, catalysts 2 and 3 allow to differentiate equatorial hydroxy groups and selectively produce regiosomeric products. In particular, (R)-Ad TRIP (2) demonstrated superior to monomeric 1 catalytic performance and selectivity, could be readily recycled by filtration and wash, and reused multiple times on 1.0 to 5.0 g scale acetalizations with loadings as low as 0.5 to 0.1 mol%. This enabled achieving significant catalyst economy, and regioselective one-pot gram scale syntheses of 6 differentially protected D-glucose derivatives 6a, 6b, 6f, 6k, 6p, and 8e were accomplished with the same 50 mg batch of catalyst 2. The computational and mechanistic studies indicate complex temperature-dependent interplay of two reaction mechanisms. The dominant at low temperatures concerted asynchronous mechanism favors the formation of the C2 isomer due to destabilizing the TS leading to the C3 isomer interactions between the benzylidene acetal moiety of 4a and catalyst 2. This mechanism should lead to stereospecific addition of ROH resulting in syn-product, which is confirmed through the reaction of 4a with deuterium labeled d3-1-methoxycyclohexene (d3-MOC). The developed stereochemical models allow expanding the scope of this transformation, and further studies focused on exploring more complex substrates and applying these transformations in continuous flow are the subjects of ongoing studies by our groups.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, 1H and 13C NMR spectra, and more detailed description of computational studies, are available free of charge via the Internet.

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