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Stereoselective P(III)-Glycosylation for the Preparation of Phosphinated Sugars

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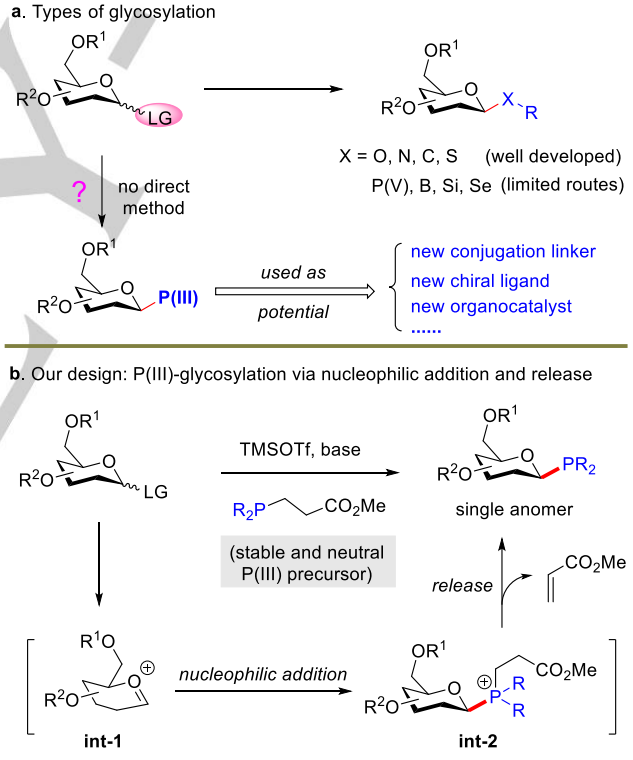
Abstract: Most of the reported work focus on the development of *O*-, *N*-, *C*- and *S*-glycosylation methods. However, no study explores P(III)-glycosylation reaction. Herein we describe a convenient protocol to realize P(III)-glycosylation process. A simple *β*-phosphino ester is adopted as P(III)-transfer reagent for this new type of glycosylation via a nucleophilic substitution and release strategy. Diverse phosphine units are introduced to the anomeric center of various sugars efficiently and with excellent stereoselectivity. The value of this method is showcased by the prepared P(III)-sugars as novel linkers in bioactive molecule conjugation, new chiral ligands in metal-catalyzed asymmetric allylic substitutions and organocatalysts. Preliminary mechanistic studies corroborated the designed P(III)-transfer process.

Glycosylation is a fundamental reaction with carbohydrates and exists in all domains of life. It is estimated that approximately one-fifth of all natural products and 70% of approved or preclinical protein therapeutics are glycosylated.[1] Thus, numerous glycosylation methods have been developed for the efficient construction of various anomeric bonds in the past decades, which represents a longstanding research focus in organic synthesis.[2] In addition to the well-established *O*-glycosylation,[3] several types of related mimics, such as *N*-,[4] *S*-,[5] and *C*-glycosylation[6] have also been extensively studied, due to their potentially distinct physiological and chemical properties from *O*-glycosides (Scheme 1a). Other types of anomeric glycosylation with the introduction of P,[7] B,[8] Si,[9] and Se[10] *etc.* have received comparably limited development. In particular, *P*-glycosylation for the construction of anomeric C-P bond has been seldomly studied, and methods are developed for the introduction of P(V) unit (mainly phosphonate) via Michaelis–Arbuzov reaction or de novo synthesis.[7] Only one case described the reduction of phosphine oxide to prepare anomeric P(III) unit.[7c] Thus, no method is described for the direct P(III)-glycosylation reaction.

Obviously, a convenient and straightforward P(III)-glycosylation route should be valuable and may open a new door for the potential use of P(III)-glycosyl compounds (Scheme 1a). First, sugars are naturally chiral skeletons. P(III)-based sugars



Scheme 1. Typical types of glycosylation and our design

have been demonstrated feasible as chiral ligands in a series of catalytic reactions.[11] For these cases, P(III) unit is often linked to the hydroxy group of sugars.[11] Thus, the incorporation of P(III) unit directly to the carbon skeleton of sugar molecules may provide distinct influence on the catalytic process and stereocontrol effect. Second, chiral P(III) units can work as organocatalysts in various asymmetric transformations, such as Morita-Baylis-Hillman (MBH) reaction.[12] However, P(III)-derived sugars as potential chiral organocatalysts have been seldomly explored in such cases. Finally, a P(III) unit may also be used as

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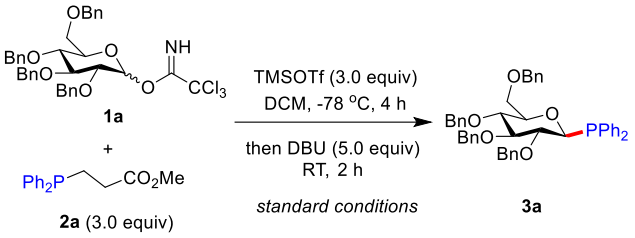
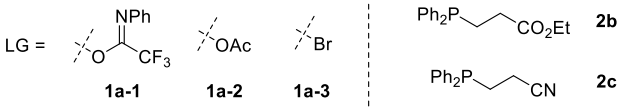
Table 1. Reaction development





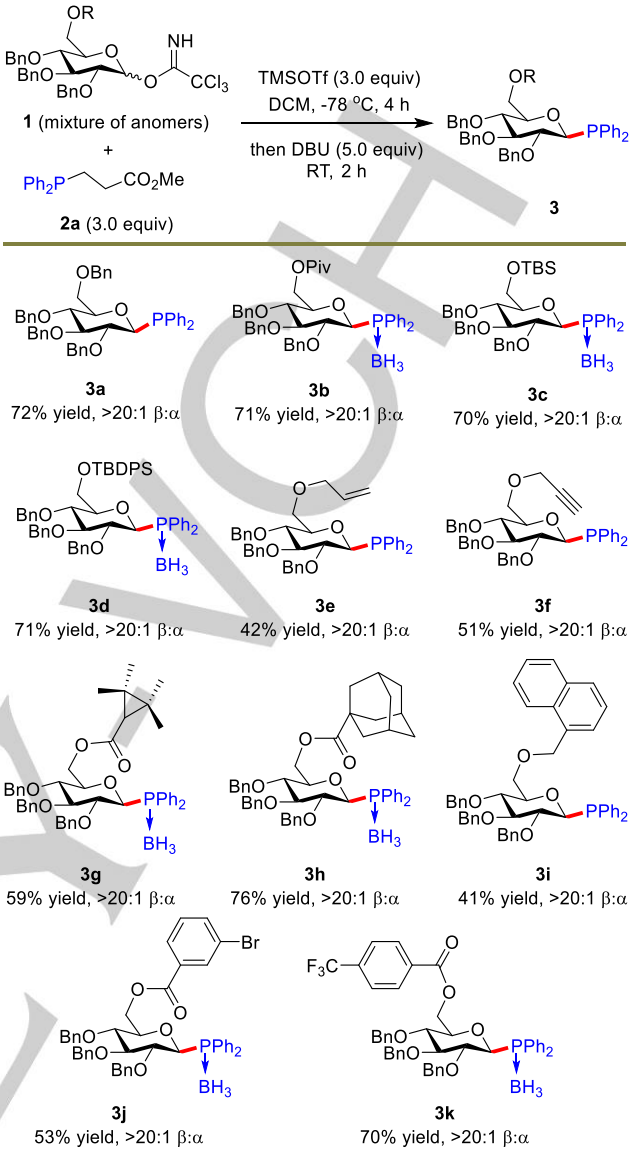
Entry[a]	derivatizations	Yield (%)
1	no	72[b]
2	**1a-1** instead of **1a**	trace
3	**1a-2** instead of **1a**	n.d.
4	**1a-3** instead of **1a**	n.d.
5	**2b** instead of **2a**	58
6	**2c** instead of **2a**	40
7	$BF_3.Et_2O$ as LA	trace
8	TfOH as LA	11
9	TBSOTf as LA	31
10	AgOTf as LA	n.d.
11	Toluene as the solvent	24
12	Et_2O as the solvent	29
13	THF as the solvent	n.d.
14	EtOAc as the solvent	50
15	Et_3N or K_2CO_3 instead of DBU	n.d.

[a] The reaction was carried out in 0.10 mmol scale. The yield was estimated by ^{31}P NMR with CH_2Br_2 as the internal standard. LA, Lewis acid. n.d., not detected. [b] Isolated yield.

a linker to connect a sugar molecule and another intriguing unit, and thus find possible applications in the exploration of new bioactive molecules, especially considering the wide existence of anomeric C-P bond in bioactive molecules[13] and the renaissance of sugar-based drugs.[14]

As P(III) has a strong nucleophilicity, we envisioned that a neutral P(III) unit bearing a removable group might attack an electrophilic glycosyl species **int-1** to form a quaternary phosphonium salt **int-2** which has a strong tendency to cleave one unit to regenerate a new neutral P(III) unit[15] (Scheme 1b). The readily available β-phosphino ester bearing an easily removable propionate under weak base might be a suitable and stable P(III)-transfer reagent to realize the unprecedented P(III)-glycosylation.

Based on this hypothesis and after a series of trials, we established the P(III)-glycosylation reaction between glucose **1a** bearing a Schmidt leaving group and β-phosphino methylester **2a** with TMSOTf as the Lewis acid and DBU as the base (Table 1). Under these standard conditions, the P(III)-glycosylation product **3a** was isolated in 72% yield as a single β-anomer (entry 1). Other widely used leaving groups in glucose, including *N*-(phenyl)trifluoroacetimidate developed by Yu (**1a-1**), OAc (**1a-2**) and Br (**1a-3**), failed to exhibit reasonable reactivity (entries 2-4). In comparison, Ph_2P skeletons bearing different removable units



Scheme 2. Scope for P(III)-glycosylation of substituted pyranoses.[a] [a] Isolated yield. All the products were observed as corresponding single anomer. The anomer ratio was estimated by both ^1H NMR and ^{31}P NMR. For **3b**-**3d**, **3g**, **3h**, **3j** and **3k**, the product was stabilized with $BH_3{\cdot}SMe_2$.

as P(III)-transfer reagents (**2b**, **2c**) seem to have less influence on the transformation. Both cases generated product **3a** in 40-58% yield (entries 5-6). Next, a set of Lewis acids, such as $BF_3{\cdot}Et_2O$, TfOH, TBSOTf and AgOTf as activators for the formation of electrophilic sugar oxonium intermediate were evaluated, but all led to obvious erosion of reaction yields (entries 7-10). The use of 3.0 equivalents of TMSOTf was necessary to guarantee the high yield of **3a** (see SI for the related evaluations). In addition, several other solvents instead of DCM were tested (entries 11-14). No reasonable trend was shown and only low yield of **3a** was observed for all cases. Weak organic and inorganic bases instead of DBU were unfavorable for the present transformation (entry 15).

Next, the scope of various glucose derivatives was checked and the results are summarized in Scheme 2. When the sugar molecule bearing an ester, silyl, alkene, alkyne, small ring, bulky bridged ring or aryl unit as the substrate, all these glycosylation

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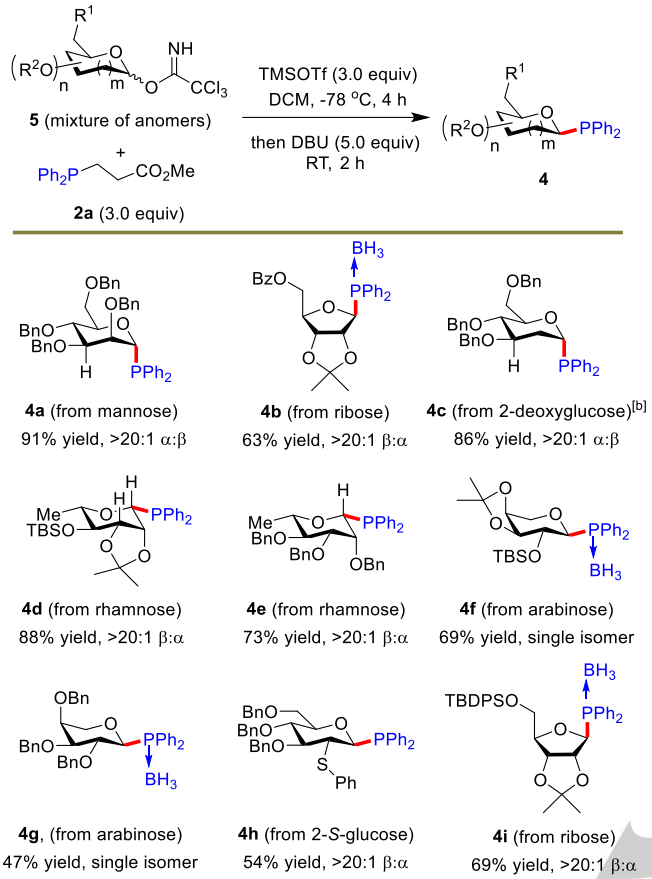
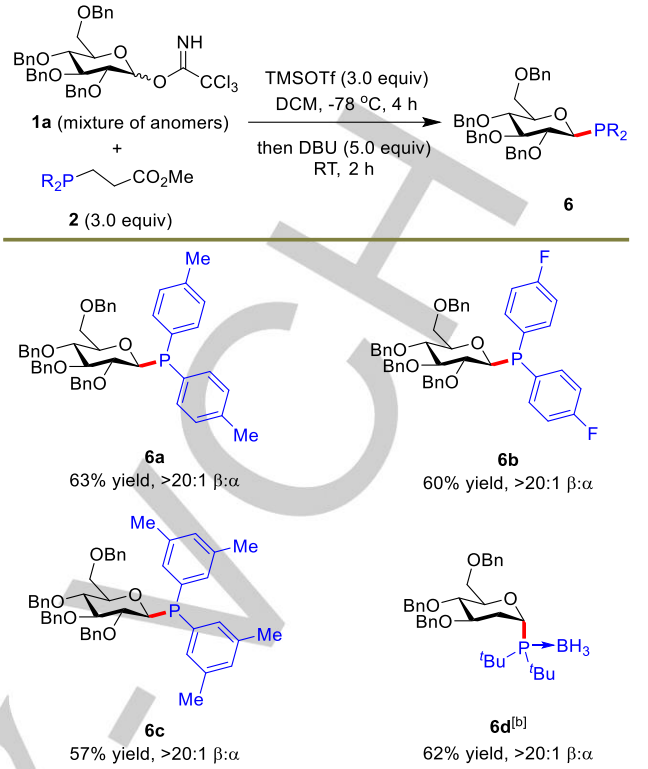


Scheme 3. Scope for P(III)-glycosylation of different saccharides.[a] [a] Isolated yield. All the products were observed as corresponding single anomer. The anomer ratio was estimated by both ^{1}H NMR and ^{31}P NMR. For some cases, the product was stabilized with BH_3·SMe_2. [b] OAc as the leaving group in the corresponding substrate **5**.

processes performed well, providing P(III)-sugars in 41-76% yield as exclusively β-anomers (**3a**-**3k**). In particular, the retained functional group such as alkyne was a versatile unit for further modifications. It should be noted that for some cases, the formed P(III) products were not very stable during purification and needed to be stabilized by borane for easy purification. All the products were observed with >20:1 β:α anomeric selectivity.

To further elucidate the compatibility of the present protocol, different types of sugars were evaluated (Scheme 3). The P(III)-glycosylation process indeed had broad application scope and a series of pyranose derivatives, such as mannose, 2-deoxyglucose, rhamnose, arabinose and 2-*S*-glucose, underwent the transformation smoothly, furnishing **4a** and **4c**-**4h** in 47-91% yield. It seemed that the absolute configuration of achieved *P*-anomer varied with corresponding sugar molecule, but all were observed with >20:1 anomeric selectivity. The observed high stereochemical control for the present method might be attributed to the large steric hindrance of P(III) nucleophile which favored a *trans*-nucleophilic attack at the anomeric position relative to neighboring substituents in sugar skeletons.[16] In addition, the protocol could be extended to the P(III)-glycosylation of furanoses. For example, ribose derivative underwent the glycosylation in good yield and with excellent anomeric selectivity (**4b**, **4i**).



Scheme 4. Scope for P(III)-glycosylation with different phosphine sources.[a] [a] Isolated yield. All the products were observed as corresponding single anomer. The anomer ratio was estimated by both ^{1}H NMR and ^{31}P NMR. For some cases, the product was stabilized with BH_3·SMe_2. [b] **5c** was used instead of **1a**.

To explore the scope of introduced disubstituted phosphine, a couple of β-phosphino methylesters **2** were checked next (Scheme 4). When the aryl unit in the phosphine center containing an electron-donating or -withdrawing group, no discernible influence on the glycosylation was observed (**6a**, **6b**). For both cases, the substituted P(III)-glycosylated sugars were prepared in around 60% yield. Polysubstituted aryl in the *P*-transfer reagent **2** also reacted smoothly with **1a**, furnishing the corresponding phosphinated sugar **6c** in a moderate yield. In addition, dialkylphosphine could be introduced to the anomeric center in a reasonable yield (**6d**), suggesting the modification potential and diversity when utilizing these chiral P(III) compounds as catalysts or ligands.

The reliability of the present methodology was highlighted by a gram-scale test with model reaction (Scheme 5a). **3a** was achieved in 1.4 gram in 66% yield, comparable to that on a 0.1 mmol scale. The prepared P(III)-sugars can be easily transformed into various P(V)-sugars (Scheme 5b). For example, with **3a** as a substrate, the corresponding phosphanimine, phosphine oxide, phosphine sulfide and phosphine selenide were synthesized in one-step with high yields and retained stereoselectivities (**7**-**10**). Among them, phosphine oxide **8** is a known compound[7b,7c] and provides support for the stereoselectivity determination of **3a** as a β-anomer. In addition, the introduced anomeric P(III) unit can function as an efficient linker to connect two different bioactive molecules under mild conditions, which might find applications in lead compound discovery area (Scheme 5c). For example, drug molecules including Zidovudine,[17] Indometacin,[18] Naproxen[19] and Paracetamol[20] were easily conjugated with the prepared

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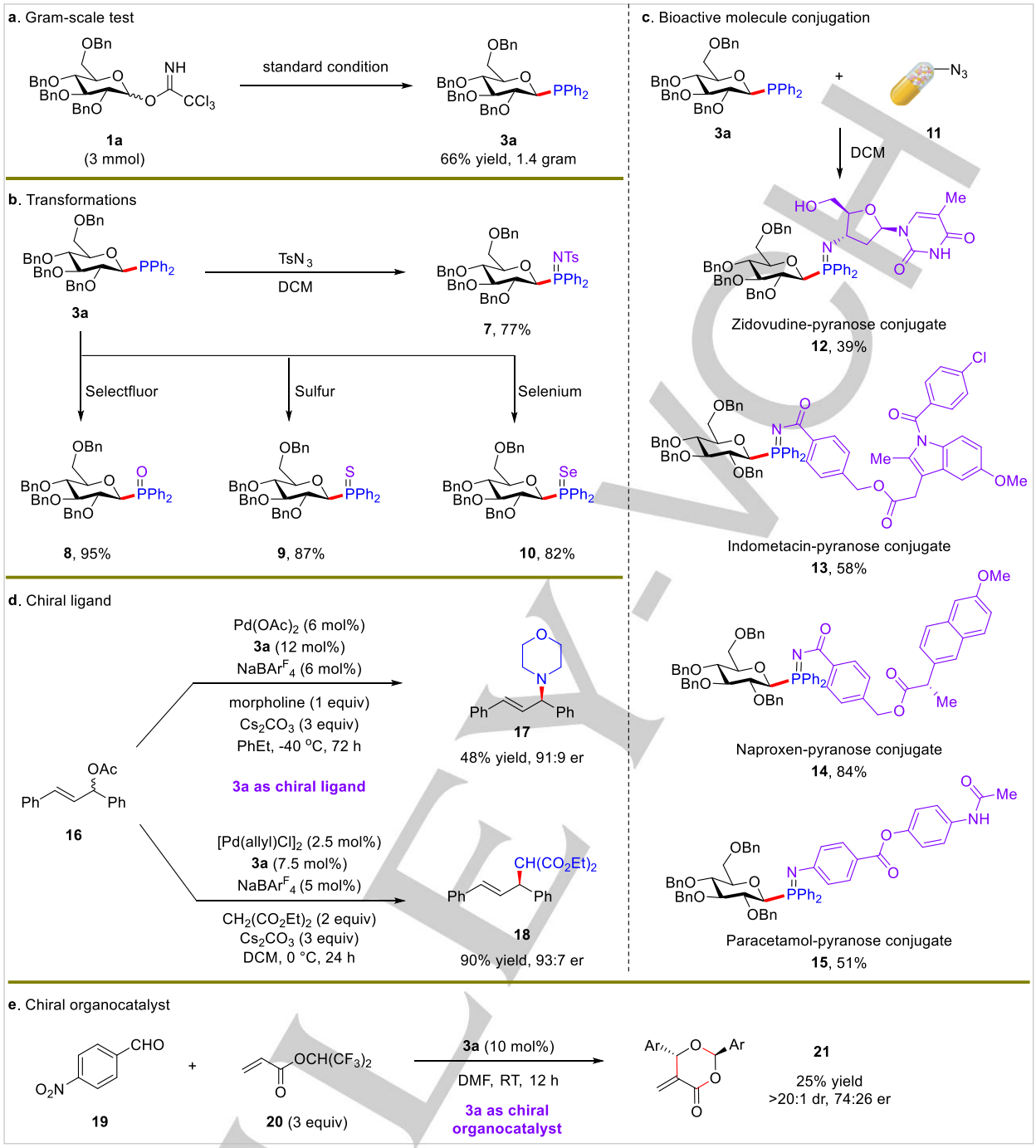

Scheme 5. Gram-scale test, transformations and applications

pyranose skeleton through Staudinger reactions, providing corresponding conjugation products **12**-**15** in 39-84% yield.

Considering the ready availability of sugars and their inherent features as chiral pool, we imagined that a scenario involving P(III)-glycosylated sugars as chiral ligands or catalysts might be feasible. Indeed, with model product **3a** directly as a chiral monophosphine ligand, both Pd-catalyzed asymmetric allylic aminaiton and alkylation were realized smoothly. The corresponding products **17** and **18** were formed in reasonable yields and with good enantioselectivities, highlighting the value of this type of chiral phosphinated sugars (Scheme 5d). In addition, **3a** as a chiral organocatalyst also showed promising stereocontrol in a MBH reaction (Scheme 5e). We hypothesized that further screening of sugar skeletons and the substituents in phosphine center might facilitate the discovery of more efficient ligands and catalysts for related applications.

A set of experiments were conducted to shed light on the possible reaction mechanism (Scheme 6). As the glycosylation is generally considered to involve S_N1 and S_N2 processes,[21] convergent experiments with the use of pure β-**1a** and α-**1a** independently as the substrate were carried out. In this context, the same product **3a** as a β-anomer was obtained in similar yields

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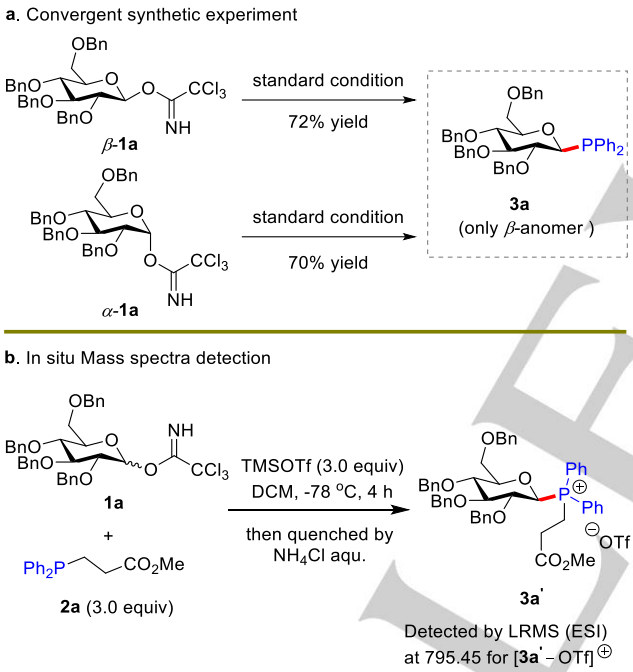
for both cases (Scheme 6a). This result suggested that the transformation might undergo the formation of a same oxonium intermediate. The intermediate would then receive nucleophilic attack from **2a** to generate a quaternary phosphonium salt and finally released the target neutral phosphinated sugar under basic conditions. To further support this mechanistic proposal, a *m/z* value corresponding to the phosphonium cation [**3a'** – OTf] was detected, which provided proof for the deduced formation of a phosphonium salt aforementioned (Scheme 6b).[22] In addition, a set of model reactions were conducted at varying temperatures from -78 °C to room temperature (see SI for details). The yield of **3a** decreased along with the elevation of reaction temperature, but **3a** was always observed as a single β-anomer. The unchanged high stereoselectivity during this process indicated that the steric hindrance might be the major selectivity-control factor due to the introduced bulky PPh_2 unit. The decreased yield along with increased temperature might be because the formed oxonium intermediate is not stable under excessive Lewis acid at high temperature. The product **3a** also showed high stability and was recovered in >99% yield under standard reaction conditions (see SI for details).



Scheme 6. Preliminary mechanistic studies

Conclusion

In conclusion, a stereoselective P(III)-glycosylation protocol is established. With β-phosphino ester as a P(III)-transfer reagent, a series of phosphinated sugars are prepared through a nucleophilic addition and release strategy. The method features simple operation, mild reaction conditions, broad substrate scope and excellent anomeric selectivity. Gram-scale test and a series of downstream transformations show the robustness and application potential of the protocol. The practical value of the methodology is further highlighted by the application of phosphinated sugars as promising conjugation linkers for bioactive molecules, new type of chiral monophosphine ligands for metal catalysis, and novel organocatalysts for asymmetric transformation. Preliminary mechanistic studies suggest that the reaction may undergo sequential formation of oxonium and phosphonium intermediates. We believe the present work will inspire the exploration of seldom studied phosphinated sugar-based bioconjugation process, chiral ligands and catalysts.

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Keywords: Glycosylation • Stereoselectivity • Phosphinated sugars • Chiral ligands • Organocatalysts

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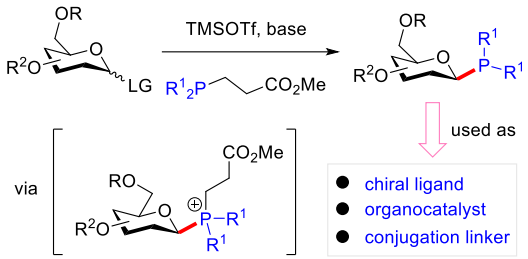

A highly stereoselective P(III)-glycosylation reaction is established, proceeding by a nucleophilic addition and release strategy. With simple a β-phosphino ester as the P(III)-transfer reagent, a series of anomeric phosphinated sugars are prepared efficiently and stereoselectively, and can be used in bioactive molecule conjugation, as chiral phosphine ligands or organocatalysts.