# 2-Diphenylphosphinoyl-acetyl as a remote directing group for the highly stereoselective synthesis of β-glycosides

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**Abstract:** The configuration of the anomeric glycosidic linkages is crucial for maintaining the biological functions and activities of carbohydrate molecules. However, their stereochemistry control in glycosylation represents one of the most challenging tasks in carbohydrate chemistry. In this report, the easily accessible 2-diphenylphosphinoyl-acetyl (DPPA) group was developed as a highly stereodirecting group for catalytic glycosylation via hydrogen-bond mediated delivery of the alcoholic acceptors. TMSOTf-catalyzed glycosylation with 6-*O*-DPPA glycosyl imidate donors displayed excellent β-selectivity and broad substrate scope, particularly applicable to synthesize the challenging β-configured 2-deoxy- and 2-azido-2-deoxy-glycosides from electron-deficient or bulky acceptors. Chemoselective removal of the DPPA group could be readily achieved under the mild catalysis of Ni(OTf)$_2$, and further application was demonstrated in the synthesis of biologically important oligosaccharides, uronic acids, and 2,6-dideoxy-glycosides.

Carbohydrates are one of the essential biomolecules in life processes, and are persistently engaged in the occurrence and treatment of many diseases.[1,2] The conformation and bioactivities of carbohydrates are significantly affected by the configuration of the anomeric glycosidic linkages in either α (usually axial for pyranosides) or β (usually equatorial for pyranosides) orientation. However, a typic chemical glycosylation is promoted by acid and proceeds via $S_N1$ pathway, giving a mixture of α- and β-glycosides (Fig. 1a).[3,4] Hence, the stereochemistry control in glycosylation is one of the central topics and difficult tasks in carbohydrate chemistry,[5-7] particularly in the synthesis of β-configured 2-deoxy- and 2-azido-2-deoxy-glycosides,[8-14] which are important structural components or synthetic precursors of numerous drugs and bioactive molecules such as digoxin, landomycin, hyaluronic acid, and lipid A.[15,16] Owing to the anomeric effect, glycosylation with 2-deoxy- or 2-azido-2-deoxy-glycosyl donors tends to give α-glycosides as the major product.[3,4,10] Thus, extensive studies have been devoted into the construction of the more challenging β-glycosides,[8-14] employing α-donors/intermediates via $S_N2/S_N2$-like pathway,[17-20] α-face steric hindrance,[21-24] 2-halo participation,[25,26] β-glycosyl lithium,[27,28] triflate acceptor,[29] 2,3-anhydrosugar,[30] de novo synthesis,[31,32] oxidative activation with $I_2$,[33] etc. However, their application in complex carbohydrate synthesis was usually case by case, hampered by narrow substrate scope, low efficiency, tedious steps, or harsh conditions. Even for the regular non-deoxy-glycosyl (e.g. glucosyl) donors adaptable to the well-developed 2-$O$-acyl participation strategy (Fig. 1b),[34] the glycosylation could encounter the formation of 1,2-orthoester by-products, and the later saponification for removing the acyl group would decompose those base-labile substrates.[35] Hence, the development of new strategies for β-selective glycosylation is still in high demand, particularly for the efficient access to the biologically and synthetically important 2-deoxy- and 2-azido-2-deoxy-β-glycosides.
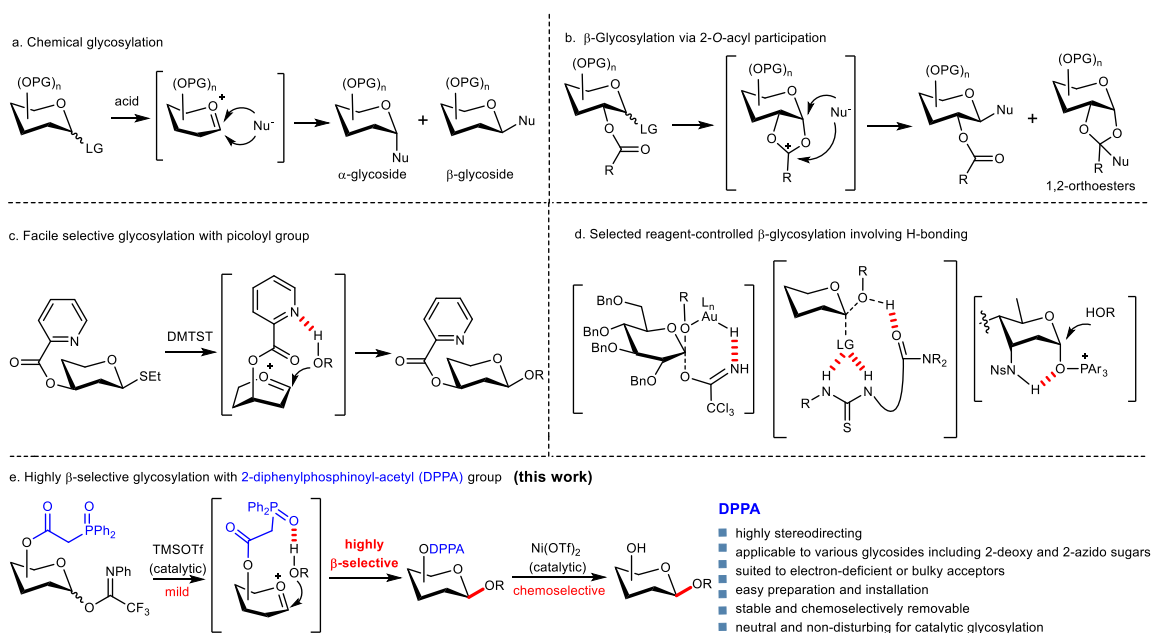


**Fig. 1 Chemical glycosylation and selected strategies for β-glycosylation.** PG: protecting group; LG: leaving group;

DMTST: dimethyl(methylthio)sulfonium triflate; Nu: nucleophile; Ns: *p*-nitrobenzenesulfonyl.

Hydrogen bonding (H-bonding) could be utilized for the anomeric stereocontrol in glycosylation.[5,36,37] In 2012, Demchenko and coworkers reported the use of picoloyl (Fig. 1c), a pyridine-containing group, to realize a facial selective glycosylation via the H-bond tethering between the pyridine moiety and the alcoholic acceptors.[38] This process used thioglycosides as donors and a stoichiometric amount of dimethyl(methylthio)sulfonium triflate (DMTST) as promoter. Although they observed decreased stereoselectivity when electron-deficient or bulky acceptors were glycosylated,[39] this elegant strategy has been successfully applied to prepare various glycosides including α-sialic glycosides.[40-48] Another *N*-heterocyclic 2-quinolinecarbonyl group was employed by Yang and coworkers as H-bond-acceptor to effectively construct β-arabinofuranosides and α/β-Kdo glycosides.[49,50] H-bonding also played an important role in several reagent-controlled strategies for β-glycosylation using α-glycosyl donors or intermediates (Fig. 1d).[51-55]

Compared to the basic pyridine and derivatives that could potentially interfere with glycosylation promoters, phosphine oxides are generally considered to be more neutral but stronger H-bond-acceptors.[56] We questioned whether phosphine oxides would lead to better stereoselectivity and yields in catalytic glycosylation, aiming for the efficient preparation of the labile 2-deoxy-β-glycosides requiring mild reaction conditions.[48] Thus, we envisioned several phosphine oxides (e.g. Fig. 1e) coupled to sugars via ester linkages, given the mild and easy formation of ester bonds as well as their good tolerance toward various conditions. Moreover, it would be feasible to selectively remove these phosphine oxide-containing esters by the mild metal chelation instead of the basic saponification.[57] The β-oriented 6-OH of sugars would be selected as the coupling site for quick access to glycosyl donors. Furthermore, late-stage elaboration of a deprotected 6-OH such as glycosylation, oxidation, and dehydroxylation could readily provide (1→6)-linked oligosaccharides, uronic acids, and 6-deoxy sugars, which are widespread in drugs and bioactive molecules (e.g. heparin). The other hydroxyl groups would be protected by benzyl groups rather than acyl groups to exclude the neighboring or remote participation of acyl groups in glycosylation.[48] Herein, we report the development of a highly stereodirecting and chemoselectively removable 2-diphenylphosphinoyl-acetyl (DPPA) group for β-glycosylation (Fig. 1e). TMSOTf-catalyzed glycosylation with DPPA-installed glycosyl *N*-phenyltrifluoroacetimidate (PTFAI) donors displayed excellent β-selectivity and generality for the 2-deoxy/2-deoxy-2-azido sugars, as well as the non-deoxy sugars (e.g. glucose, galactose, mannose) as a good compensation for the conventional 2-*O*-acyl participation strategy to avoid orthoester formation and ester saponification.[34,35]
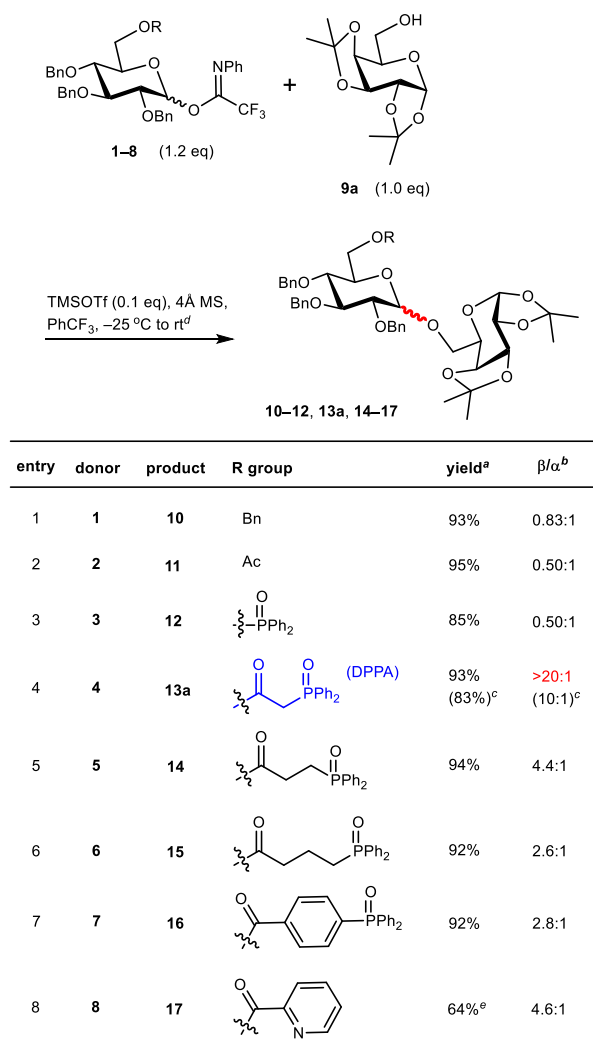
**Results**

**Fig. 2 Glycosylation of 9a with donors 1–8 varied at O6.** [a]Isolated by chromatography. [b]Determined by ^{1}H NMR. [c]The crude of donor **4** was directly used without the standard silica gel column purification. [d]Warmed to rt from –25 °C in 1 h, and stirred for another 1 h at rt. [e]Warmed to rt from –25 °C in 1 h, and stirred overnight.

**Screening for stereodirecting groups.** Our studies commenced with the screening of glycosylation conditions using the easily accessible D-glucosyl donors (see SI for Table S1), giving the optimized conditions (1.2 eq of PTFAI donor,[58-60] 0.1 eq of TMSOTf, PhCF$_3$,[61,62] 4Å MS, –25 °C to rt). PhCF$_3$, an alternative solvent to CH$_2$Cl$_2$,[62] was found to provide the best β-selectivity with high yields. Next, a series of PTFAI donors (**1**–**8**, Fig. 2) bearing different substitutes at O6 were prepared (see SI for details), including five phosphine-oxide-containing acyl groups for H-bonding as well as benzyl/acetyl/picoloyl groups for control reactions.[63-66] Their stereodirecting effects were then evaluated in the glycosylation of relatively hindered alcohol **9a**. As expected, 6-OBn donor **1** was converted into disaccharide **10** with

more α-anomer (entry 1), while glycosylation with 6-OAc donor **2** showed even higher α-selectivity (β/α = 0.50:1, entry 2).[67] Gratifyingly, we observed excellent β-selectivity when 6-ODPPA donor **4** was employed (entry 4), and the desired disaccharide **13a** was obtained in a high 93% yield with the β/α ratio of more than 20:1. This β-selectivity could be attributed to an intermolecular aglycone delivery that was mediated by the H-bond tethering between the phosphine oxide on **4** and the 6-OH on **9a** (Fig. 1e).[38] The acetyl-derived linkage in DPPA group proved to be crucial for the high stereoselectivity, as further elongation with more flexible aliphatic (entries 5 and 6) or rigid aromatic linkage (entry 7) resulted in the decrease of β/α ratio. It is noteworthy that PTFAI donor **4** was prepared nearly as a single β-anomer using the standard protocol of $CF_3C(NPh)Cl$ and $K_2CO_3$ in acetone, implying that the high β-selectivity in the glycosylation with **4** was not caused by $S_N2$ or $S_N2$-like attack. To simplify the purification of donor **4**, we collected its crude after a quick filtration and directly applied to glycosylation without the standard silica gel column purification. However, the resulting β/α ratio of disaccharide **13a** decreased to 10:1 (entry 4), presumably due to the trace amount of the remaining $K_2CO_3$ that disturbed the pivotal H-bonding. The effect of picoloyl group was also examined using 6-*O*-picoloyl PTFAI donor **8** in this catalytic glycosylation (entry 8), giving a modest β-selectivity (β/α = 4.6:1) with a dramatically decreased 64% yield, suggesting that the picoloyl group could disturb the TMSOTf-catalyzed glycosylation due to the basic pyridine moiety.
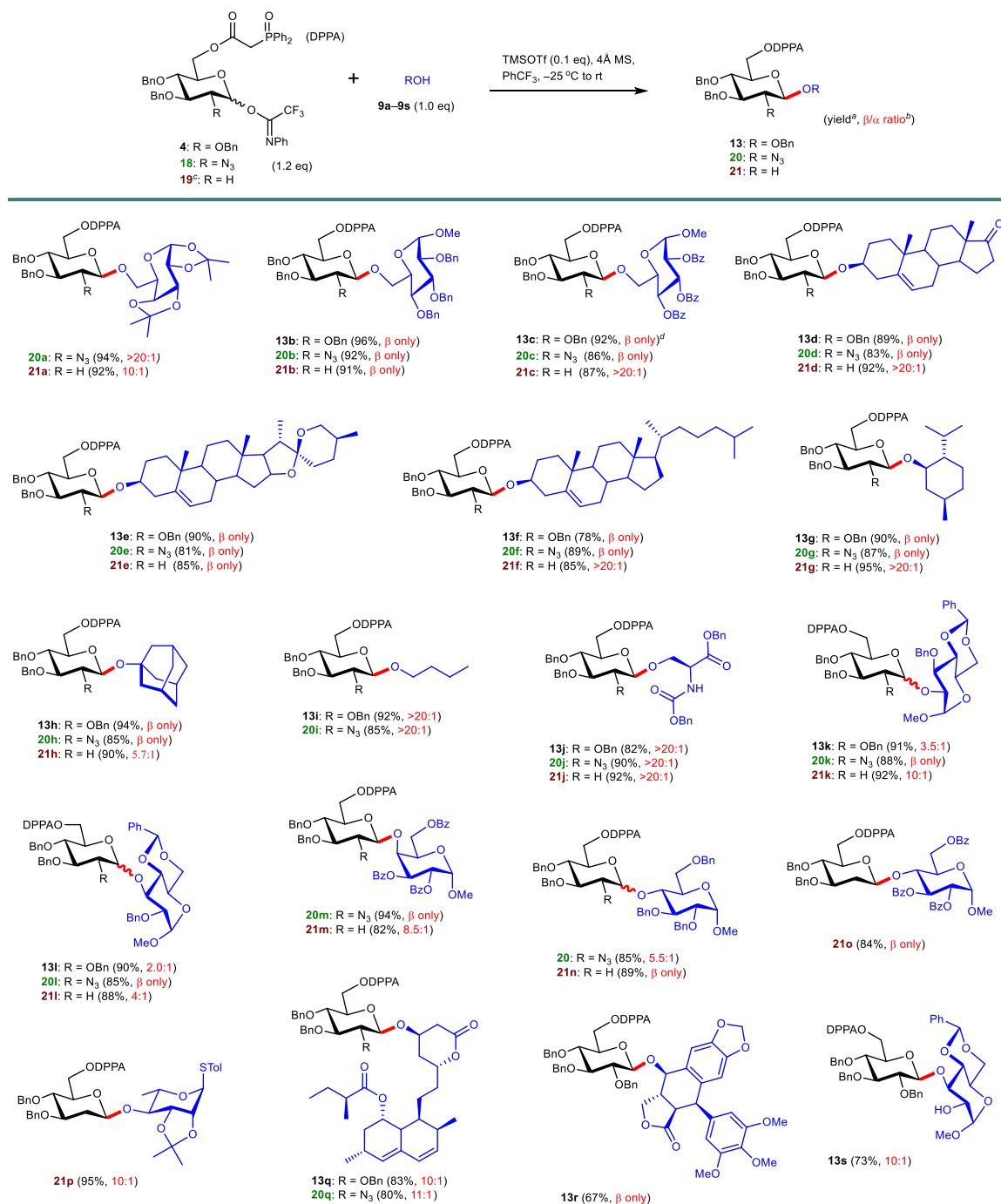
**Fig. 3 Reaction scope with 6-ODPPA glycosyl donors 4, 18, and 19.** [a]Isolated by chromatography. [b]Determined by ^{1}H NMR. [c]Donor **19** was prepared and used without silica gel column purification. [d]Scaled up.

**Substrate scope.** With 6-ODPPA confirmed as a promising β-directing group for glycosylation, the corresponding 2-deoxy- and 2-azido-2-deoxy-glycosyl PTFAI donors **19** and **18** were prepared (see SI for details), respectively. Together with glucosyl donor **4**, they were employed to glycosylate various alcohols as substrate scope examination (Fig. 3). The

intrinsic high-reactivity of deoxy sugars made 2-deoxy imidate **19** not shelf-stable, and we used its crude for glycosylation without silica gel column purification. Nevertheless, all three donors generally led to excellent β-selectivity (β only or β/α>20:1) and high yields in the glycosylation of reactive and moderately reactive alcohols **9a**–**9j**, including electron-rich/electron-deficient glycosides **9b/9c**, sterols **9d**–**9f**, menthol **9g**, adamantanol **9h**, butanol **9i** and serine **9j**. The β-specific glycosylation of sapogenin aglycone **9d**–**9f** showed a practical synthetic route to those β-linked 3-*O*-glycosyl saponins possessing diverse bioactivities (e.g. ginsenosides, polyphyllins, dioscin).[68] It is particularly noteworthy that complete β-selectivity could be obtained when electron-deficient acceptor **9c** was glycosylated, compared to the previously reported β/α ratio of 2.9:1 using the 6-*O*-picoloyl thioglycoside counterpart of donor **4**.[39] Additionally, this reaction could be readily scaled up, as demonstrated by the preparation of disaccharide **13c** (β only, 0.94 g, 92%). 2-Deoxy donor **19** was found to be slightly less β-directing than **18** and **4** presumably owing to the lack of silica gel purification, but it still led to excellent β-selectivity in most cases, except in the preparation of **21a** (β/α = 10:1) and **21h** (β/α = 5.7:1) from structurally rigid alcohols **9a** and **9h**. Further application to synthesize more complex and sophisticated glycoconjugates was successfully demonstrated in the conversion of antitumor podophyllotoxin (**9r**) and cholesterol-lowering drug lovastatin (**9q**) into glycosides **13r**, **13q**, and **20q** with high β-selectivity and yields.

It has been well recognized that acceptors with poor reactivity, such as **9k**–**9p**, tend to give poor β-selectivity in glycosylation as a consequence of the steric hindrance or electron-withdrawing groups.[38,39,49,51,69,70] Thus, we examined their performance in this DPPA-directed β-glycosylation (Fig. 3). As expected, the β-selectivity dropped to a modest range when benzylidene-tethered glucosides **9k** and **9l** were glycosylated with glucosyl donor **4**, and **9l** bearing the less reactive 3-OH resulted in a lower β/α ratio (2.0:1 for **13l**) than that of 2-OH **9k** (3.5:1 for **13k**).[51] However, an unexpected regio- and stereo-selectivity was observed when 2,3-diol **9s** was glycosylated with 1.2 eq of donor **4**. Instead of the anticipative (1→2)-linked disaccharide as the major product, we only obtained (1→3)-linked disaccharide **13s** in 73% yield with a dramatically improved β/α ratio of 10:1, in comparison to the ratio of 2.0:1 for **13l**. The structure of the β-anomer of **13s** was carefully characterized by 2D NMR spectra including COSY, HSQC, and HMBC, wherein the correlation between H3 and C1' as well as the $J_{H1',H2'}$ coupling constant of 7.8 Hz indicated the β-(1→3)-glycosidic linkage unambiguously. This interesting result might be related to a selective activation of 3-OH by H-bonding, giving a promising way to realize the regio- and stereo-selective glycosylation of the less reactive 3-OH without shielding 2-OH.

On the other hand, 2-azido-2-deoxy donor **18** remained highly β-directing even in the glycosylation of the poor acceptors **9k** and **9l**, leading to the β-configured **20k** and **20l** in a stereospecific manner (Fig. 3). This could be attributed to the

electron deficiency of azido group that could slow down the reaction and allow the sufficient formation of H-bond, implying that other electron-withdrawing groups such as acetyl and benzoyl on donors could also benefit the stereoselectivity.[20] Moreover, it was particularly interesting to obtain **20m** as a single β-anomer in the glycosylation of 4-OH galactoside **9m**, one of the most electron-deficient and sterically hindered glycosyl acceptors. This complete β-selectivity could be a consequence of the enhancement of H-bonding due to the multiple electron-withdrawing benzoyl groups that made **9m** a better H-bond-donor.[71] Meanwhile, the enhanced H-bonding could also make the H-bonded **9m** more nucleophilic to compete with the free **9m** in glycosylation. This hypothesis was supported by the decreased β/α ratio of 5.1:1 when another bulky 4-OH glucoside **9n** was glycosylated with donor **18**, although **9n** is usually considered to be more reactive than **9m** and supposed to give better stereoselectivity because of its equatorial orientation of 4-OH and multiple electron-donating benzyl groups.

In terms of the more challenging glycosylation of these poor acceptors with highly reactive 2-deoxy donor **19**, it was gratifying to find that the 6-ODPPA group still led to excellent or good β-selectivity, and the corresponding disaccharides **21k**–**21p** were afforded in high yields (Fig. 3). Notably, complete β-selectivity was obtained in the glycosylation of bulky acceptor **9n** or **9o** bearing glucosyl 4-OH, no matter electron-rich or electron-deficient. This could be attributed to the high flexibility of sugar ring that could quickly change the conformation to benefit the intermolecular H-bonding. Flexible galactoside **9m** bearing the even more bulky 4-OH could also be successfully converted into disaccharide **21m** with a satisfactory β/α ratio of 8.5:1. Replacement of **9m** with more reactive acceptors **9k**, **9l**, and **9p** did not significantly improve the β-selectivity presumably due to their rigid skeleton restrained by benzylidene or isopropylidene, but still giving disaccharides **21k**, **21l**, and **21p** in high yields. This detrimental effect of rigidity on β-selectivity was also consistent with the decreased β/α ratio obtained in the preparation of **21a** and **21h** above.
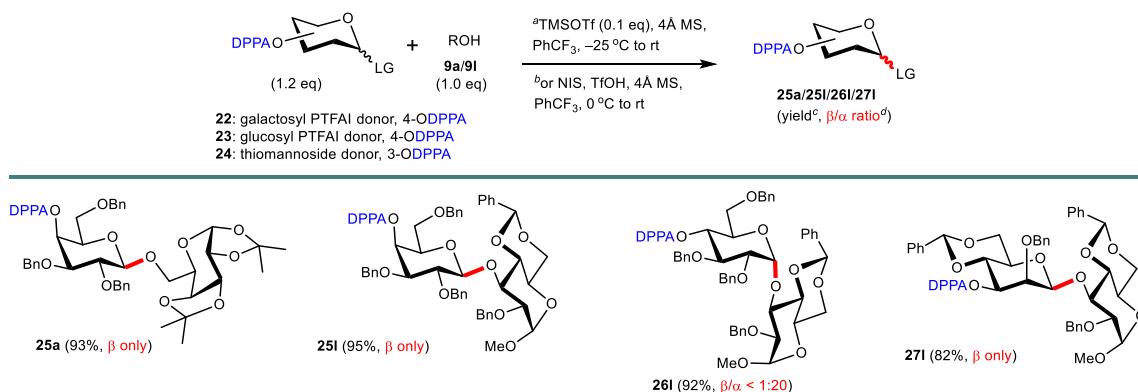


**Fig. 4 Stereoselective glycosylation with galactosyl, glucosyl, and mannosyl donors 22–24 bearing 3- or 4-ODPPA**

**group.** [a]For PTFAI donor **22** and **23**. [b]For thiomannoside donor **24**. [c]Isolated by chromatography. [d]Determined by ^{1}H NMR.

To further understand the stereodirecting effect of DPPA group installed at O3 and O4 rather than O6, we prepared 4-ODPPA galactosyl donor **22**, 4-ODPPA glucosyl donor **23**, and 3-ODPPA mannosyl donor **24** (see SI for details) to investigate their performance, particularly in the challenging α-glucosylation and β-mannosylation. As depicted in Fig. 4, galactosyl PTFAI donor **22** was first condensed with alcohol **9a** under the standard conditions (0.1 eq of TMSOTf, PhCF$_3$, 4Å MS, –25 °C to rt), and disaccharide **25a** was afforded in 93% yield with complete β-selectivity. For acceptor **9l** that led to the poorest β-selectivity in the aforementioned studies (e.g. **13l** and **20l**), the glycosylation with donor **22** still displayed complete β-selectivity and gave disaccharide **25l** in 95% yield. On the contrary, a high α-selectivity (α/β>20:1) was observed when **9l** was glycosylated with glucosyl donor **23** bearing the α-oriented 4-ODPPA group, and the desired disaccharide **26l** was obtained in 92% yield. Even the more challenging β-mannosylation of **9l** with 3-ODPPA thiomannoside **24** was found to provide the desired **27l** with complete β-selectivity, in contrast to the previously reported β/α ratio of 1.7:1 obtained with **9l** and the 3-OBn counterpart of donor **24** under the similar conditions of NIS and TfOH.[72] These results suggested that DPPA group installed at O3 and O4 was even more stereodirecting in glycosylation.
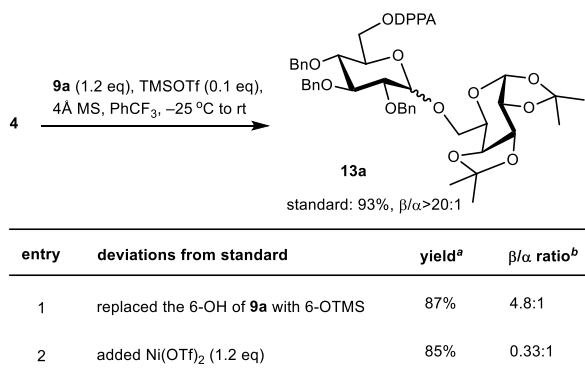


| entry | deviations from standard | yield[a] | β/α ratio[b] |
|---|---|---|---|
| 1 | replaced the 6-OH of **9a** with 6-OTMS | 87% | 4.8:1 |
| 2 | added Ni(OTf)$_2$ (1.2 eq) | 85% | 0.33:1 |

**Fig. 5 Control reactions to verify the H-bonding.** [a]Isolated by chromatography. [b]Determined by ^{1}H NMR.

**H-bonding verification.** The pivotal role of H-bonding in this stereoselective glycosylation was further verified with two more control reactions (Fig. 5), wherein the H-bonding would be interrupted by blocking either H-bond-donor or -acceptor. Thus, the 6-OH of **9a** was shielded by TMS and then applied to the condensation with donor **4** under the standard conditions (entry 1), and disaccharide **13a** was obtained with the expected decreased β/α ratio of 4.8:1 compared to the original ratio of more than 20:1. In fact, the remaining β-selectivity could be caused by the partial TMS-

deprotection during glycosylation, releasing the free 6-OH for H-bonding.[38] The other control reaction was conducted with **9a** and **4** but in the presence of 1.2 eq of Ni(OTf)$_2$ that was envisaged to coordinate the phosphine oxide and block the H-bond-acceptor. Indeed, a reversed stereoselectivity was observed with the β/α ratio of 0.33:1.
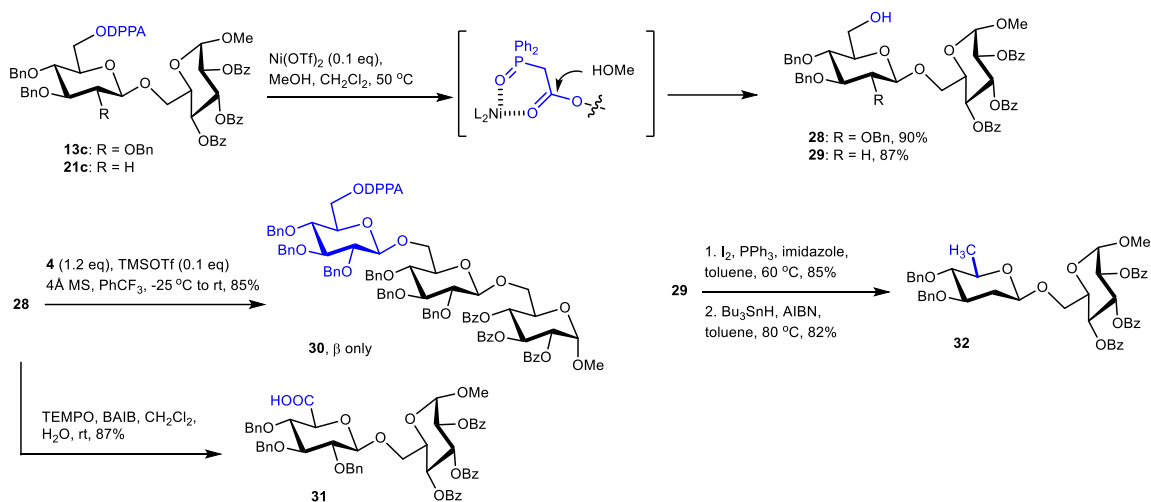


**Fig. 6 Selective removal of DPPA group and further conversion to oligosaccharide, uronic acid, and 2,6-dideoxy sugar.**

**Chemoselective removal and further derivatization.** Although the DPPA group could be easily removed under the regular saponification conditions such as MeONa in MeOH, a chemoselective and mild removal without affecting other esters is highly desirable for those base-labile target products. Moreover, derivatization of the resulting alcohol could realize a convenient preparation of many biologically important molecules, such as (1→6)-linked oligosaccharides, uronic acids, and 2,6-dideoxy-β-glycosides. Thus, we conducted a screening (see SI for Table S2) and found that a catalytic amount of Ni(OTf)$_2$ could sufficiently remove the DPPA group in a mixture of MeOH and CH$_2$Cl$_2$ at 50 °C (Fig. 6). This chemoselective deprotection could be attributed to the putative chelation of Ni with the phosphine oxide and carbonyl group, making the carbonyl group electron-deficient and ready for the attack of methanol.[57,73] Accordingly, disaccharides **13c** and **21c** bearing multiple base-labile benzoyl groups and acid-labile glycosidic linkages were smoothly converted into the corresponding alcohols **28** and **29** in around 90% yields. A further elongation was then carried out to glycosylate the resulting disaccharide **28** with another portion of donor **4**, giving trisaccharide **30** in 85% yield with complete β-selectivity. Treatment of **28** with TEMPO and BAIB led to the desired uronic acid **31** in 87% yield. We also demonstrated an efficient conversion of 2-deoxy **29** into 2,6-dideoxy **32** via iodination and subsequent dehalogenation.

## Discussion

As a strong H-bond-acceptor, phosphine oxides were found neutral and non-disturbing for the catalytic glycosylation. We have developed 2-diphenylphosphinoyl-acetyl (DPPA) group as a remote stereodirecting group for TMSOTf-catalyzed glycosylation via the H-bonding between the phosphine oxide and alcoholic acceptors. This DPPA group could be readily prepared and introduced to the O6 of glycosyl donors, directing excellent β-selectivity towards a wide range of acceptors including those with high steric hindrance and electron-deficiency. It is particularly practical for the stereoselective construction of the biologically and synthetically important 2-deoxy- and 2-azido-2-deoxy-β-glycosides, which represent one of the most difficult tasks in carbohydrate chemistry. DPPA group installed at O3 or O4 was also found highly stereodirecting in the challenging β-mannosylation and α-glucosylation. As a temporary protecting group, the DPPA group could be chemoselectively removed with a catalytic amount of Ni(OTf)$_2$ without affecting other acid- or base-labile groups. Further elaboration of the resulting 6-OH provides easy access to (1→6)-linked oligosaccharides, uronic acids and 2,6-dideoxy-β-glycosides, which are important types of glycosides with diverse biological activities. We believe that this work would provide an alternative and inspiring strategy for the more concise and efficient synthesis of bioactive carbohydrate molecules.

## Author contributions

W.L. designed the research and wrote the manuscript. X.L., Y.L., Q.S., G.L. and Y.S. conducted the synthetic work. H.S. contributed computational assistant. P.X., W.X., H.S. and B.Y. revised the manuscript and fully engaged in discussion.

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