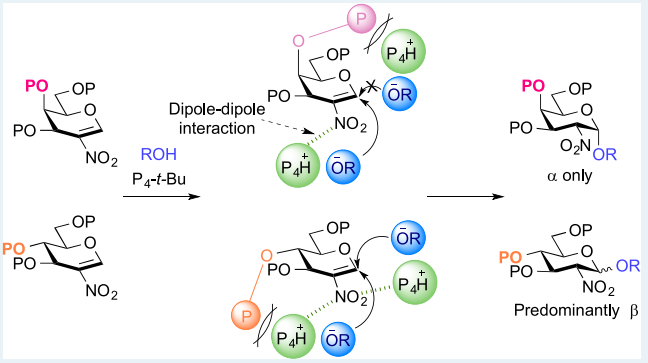
Superbase-Catalyzed Stereo- and Regioselective Glycosylation with 2-Nitroglycals: Facile Access to 2-Amino-2-deoxy-*O*-glycosides

Kumar Bhaskar Pal, Aoxin Guo, Mrinmoy Das, Gábor Báti, and Xue-Wei Liu*

ABSTRACT: An efficient superbase-catalyzed stereo- and regioselective glycosylation of 2-nitroglycals with high functional group compatibility is reported. The ion pair generated from alcohol and a catalytic amount of P_4-*t*-Bu was vital for the successful implementation of this stereoselective glycosylation under mild conditions, producing moderate to good yields. Under reported reaction conditions, 2-nitrogalactals produce α-stereoisomers exclusively, while 2-nitroglucal yielded more β-products. The notable difference between the outcomes was investigated by the density functional theory (DFT) study. In addition, we have synthesized the key intermediate of a mucin-type core-6 glycoconjugate, thus illustrating the synthetic potency of this method.



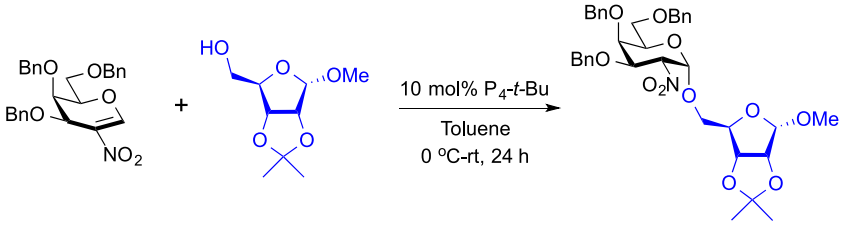
KEYWORDS: *2-nitroglycals, superbase, stereo- and regioselective glycosylation, ion pair, dipole−dipole interaction, mucin-type core 6 glycan*

Characterization, chemical preparation, and investigations into the structure−function relationships of glycans and glycoconjugates are of high practical interest and a discipline to which continued scientific endeavors are devoted.[1] 2-Amino sugars are one of the most significant classes of carbohydrates that can be found in several natural products e.g., TMG-chitotripmycin, tunicamycin V, ribostamicins, streptomycin, gentamicins, and lividomycins.[2] They contribute to extensive diversity of biologically important functions including immune and anti-inflammatory effects, antifungal and antibacterial responses, surface-functionalized nanocarriers for the medication of numerous diseases.[3] Alongside this, a certain number of biologically important polysaccharides e.g., chitosan, heparan sulfate, and peptidoglycans are there in which the 2-amino-2-deoxy-*O*-glycoside structures are imparted. Thus, in the world of carbohydrate chemistry, synthesis of 2-amino-2-deoxy-*O*-glycoside structures has been one of the most fascinating areas to work on in recent days. Since most of the naturally occurring 2-amino-2-deoxy sugars are N-acetylated, glycosylation with the pristine 2-acetamido-2-deoxy glycosyl donor would be preferable to simplify the protection strategy. However, the traditional 1,2-*trans*-glycosylation of 2-acetamido glycosyl donors turned out to be low yielding due to the formation of a stable oxazoline intermediate.[4] Besides that, 1,2-*cis* glycosylation with 2-azido glycosyl is often accompanied by poor stereoselectivity.[5] As an alternative synthetic strategy, switching the donor to 2-nitroglycals would afford us new prospects for both 1,2-*trans* and 1,2-*cis* glycosides stereoselectively.[6] To arrive at the native 2-acetamido-2-deoxy glycosides, the subsequent reduction and acetylation step was easily performed by Galan's group.[6d]

In recent times, developing novel methodologies to prepare stereoselective *O*-glycosidic linkages gained interest in the chemists' society to a great extent.[7−13] Over the past few years, several alluring approaches have been ferreted out on regioselective glycosylation and synchronously performing both stereo- and regioselective glycosylation[7,11b,14−18] providing solutions for the daunting challenges associated with several orthogonal protection and deprotection steps in oligosaccharide synthesis. Despite the efforts that have been made toward stereoselective glycosylation,[4] we have identified an important research gap to be filled, aiming to provide an alternative method toward oligosaccharide and biologically salient natural product synthesis.

Noticeably, in recent years, organic catalysts are making a significant contribution in the stereoselective glycosylation of 2-nitroglycals.[6b−d] In 2009, Yu and his co-workers demonstrated the role of 4-dimethylaminopyridine (DMAP) and 2-phenylpyridine (PPY) in the stereoselective β-glycosylation of 2-nitroglycals.[6b] Schmidt's group reported an exceptional method

Scheme 1. Optimized Reaction Conditions for Stereoselective *O*-Glycosylation of 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-galactal (2a) with Methyl-2,3-*O*-isopropylidene-D-ribofuranoside (3a)[a]



2a **3a** **4a**, α only, 89%

[a]Isolated yield.

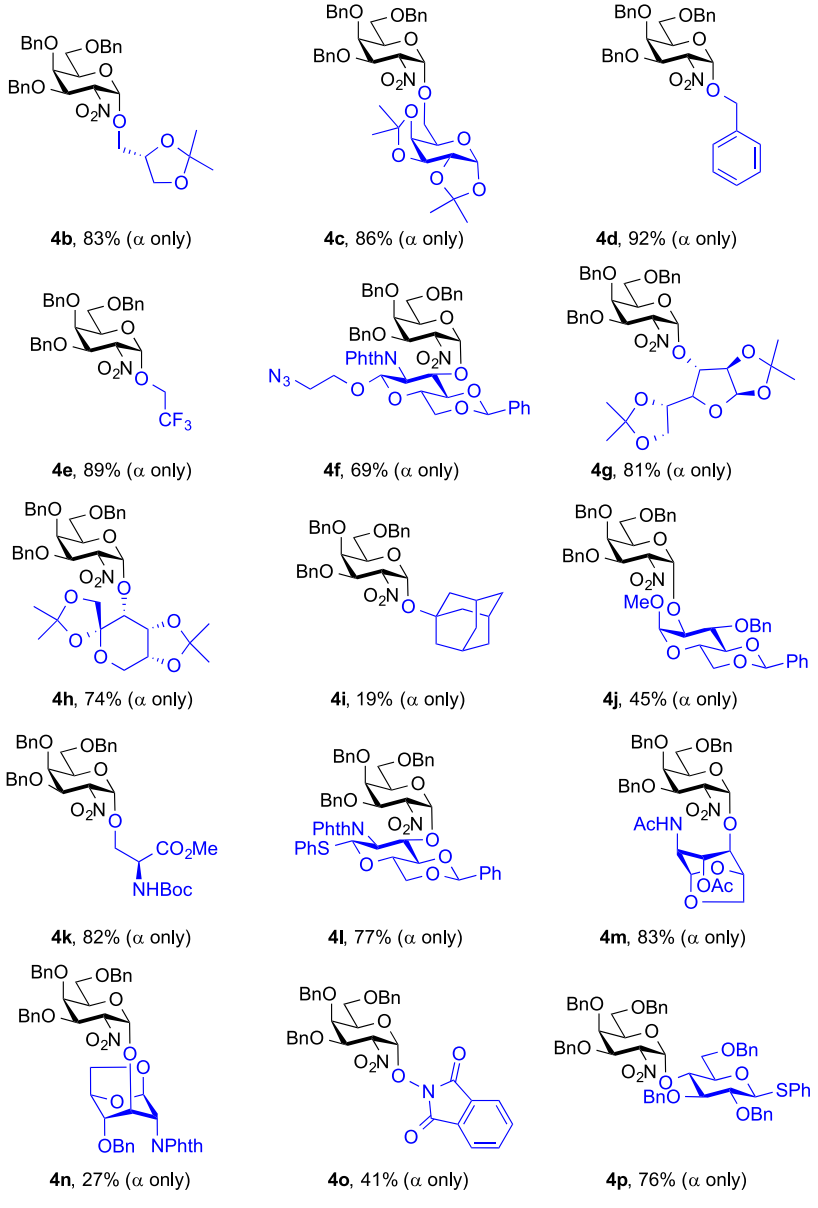


Figure 1. Stereoselective *α*-*O*-glycosylation of **2a** with a range of glycosyl acceptors (**3b**−**3p**). The reactions were carried out under a N_2 atmosphere using 0.075−0.15 mmol of 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**2a**), 0.05−0.1 mmol of the acceptor, and 0.01−0.02 mmol of P_4-*t*-Bu in hexane (10 or 20 mol %) in 2−4 mL of dry toluene for 24 h. Isolated yields.

to equip 2-nitrothioglycosides that act as mediators for the formulation of 1,2-*trans* glycosidic linkages by utilizing chiral thiourea catalysts.[6c] Recently, Galan and her team provided a wonderful approach to furnish 2-nitrogalactosides with *α*-stereoselectivity by employing a bifunctional chiral thiourea catalyst,[6d] but certainly, the detailed mechanistic rationale behind those stereoselective glycosylation reactions are awaiting further empirical and theoretical investigations to be unraveled.

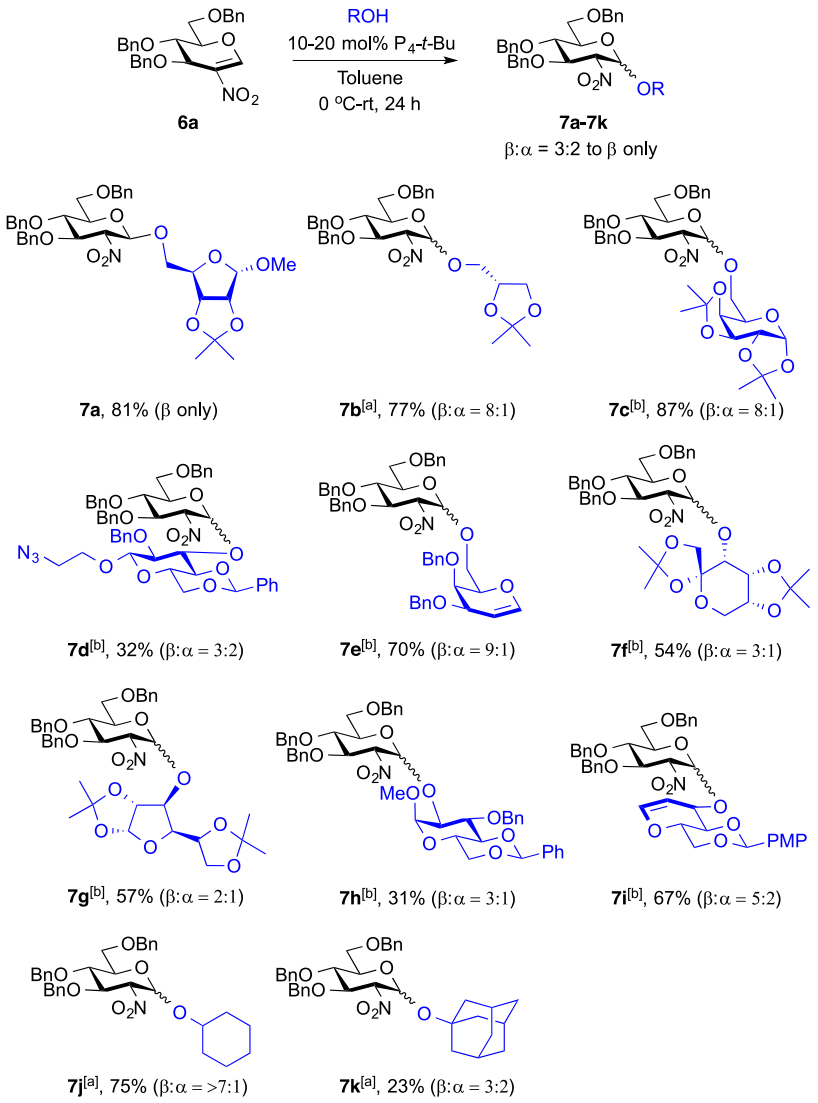


Figure 2. Recent *β*-Selective *O*-glycosylation of **6a** with a variety of glycosyl acceptors. [a] Stereoselectivity determined by ^{1}H NMR. [b] Both anomers were separated by flash column chromatography. Reaction conditions as in Figure 1. Isolated yields.

In the last 2 decades, P_4-*t*-Bu has emerged as an exceedingly valued tool in developing general and versatile synthetic methods. It has received considerable attention for the formation of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds in several organic syntheses.[19] Since the efficiency of the phosphazene bases in carbohydrate chemistry has not been assayed before, and thus, as a part of our ongoing research interest in stereo and regioselective glycosylation,[8b,11] we envisioned that 2-nitroglycal, being an olefinic pyranose, would react with the activated alkoxide ion pair derived from glycosyl acceptors with a catalytic amount of P_4-*t*-Bu to eventually yield *O*-glycosides. On top of that, we assumed that the large protonated P_4-*t*-Bu ion pair could concede the foundation for a stereoselective attack for the approaching alkoxide toward 2-nitroglycal.

At the very outset to optimize the reaction condition, we treated **3a** with 3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-galactal (**2a**)[20] with an array of organic and inorganic bases both in catalytic and stoichiometric amounts (Supporting Information, Table S1). From these results, we have observed that P_4-*t*-Bu worked more efficiently starting the reaction at 0 °C and slowly warming up to room temperature, yielding 89% (Scheme 1). Throughout the catalyst screening, we found the loading crucial, as the reaction provided lower yield when stoichiometric or 5 mol % of P_4-*t*-Bu were introduced into the reaction. Moreover, we have been fascinated by the exclusive *α*-selectivity when P_4-*t*-Bu was applied. Finally, it should be emphasized that we got a decent yield even when we performed the reaction at 70 °C (Supporting Information, Table S1).

Having these optimized reaction conditions in hand, we then explored the substrate scope of this stereoselective Michael-type addition reaction of 2-nitrogalactals. As carbohydrate synthesis often employs a wide range of protecting groups, we set out to explore their tolerance in our transformation. Throughout our studies, we have investigated the glycosylation of model 2-nitrogalactal donor, **2a** with a range of alcohols, ornamented by electron-withdrawing, and electron-donating protecting-groups (Figure 1). In each case, the reaction provided the corresponding glycosylated products with entirely *α*-selectivity in low to high yields. It must be mentioned that we pulled out better yield when we have used 20 mol % P_4-*t*-Bu while conducting glycosylations with secondary alcohols (Figure 1). Sterically hindered alcohols **3i** and **3n** (see the Supporting Information) afforded lower yield (19% **4i** and 27% **4n**,

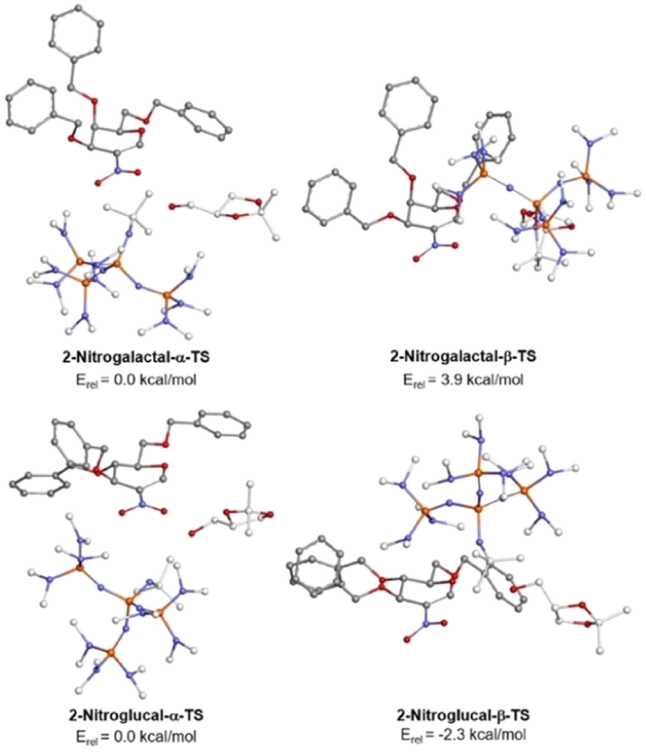


Figure 3. Calculated structures and relative energies of plausible 2-nitroglycal-P_4-*t*-Bu ion-pair intermediates.

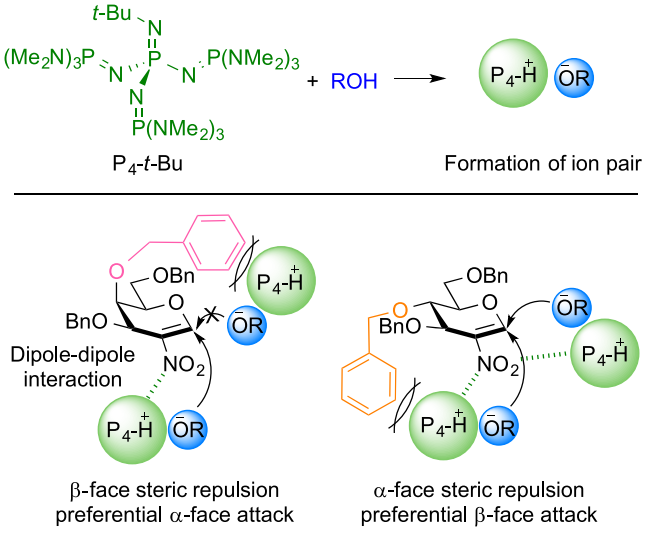
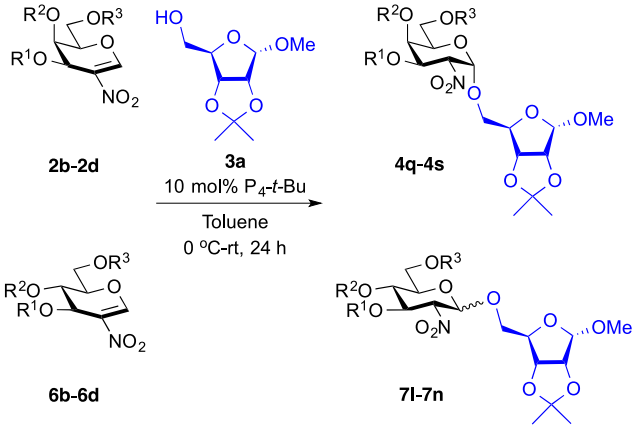


Figure 4. Schematic representation of the proposed mechanism giving rise to different stereoselectivities in P_4-*t*-Bu base-catalyzed glycosylation.

respectively, Figure 1) as expected. Furthermore, in cases of alcohols **3j** and **3o** (see the Supporting Information), the yields were moderate (45% **4j** and 41% **4o**, respectively, Figure 1), but each case providing exclusive α-selectivity.

To investigate whether this method is extendable to 2-nitroglucal derivatives, we turned our attention to exploring the scope of P_4-*t*-Bu catalyzed glycosylation on known donor *O*-benzyl protected 2-nitroglucal (**6a**).[20] Repeating the glycosylation with an array of sugar acceptors, including a series of common carbohydrate protecting building blocks, we were surprised by the completely reversed selectivity at the anomeric

Table 1. Reaction of Various 2-Nitroglycal 2b−2d and 6b−6d Donors with Glycoside Acceptor 3a[a]



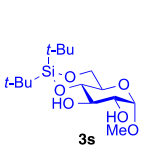
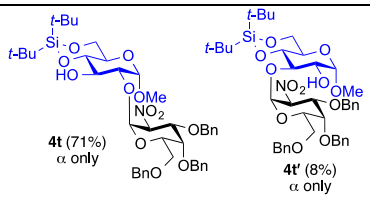
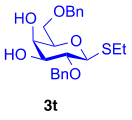
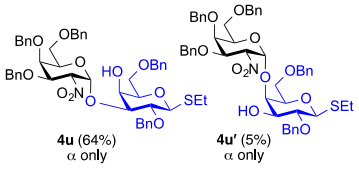
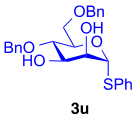
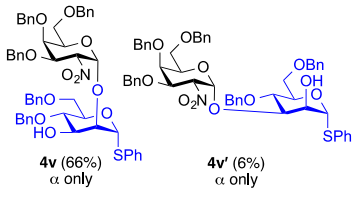
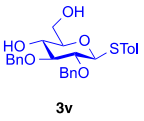
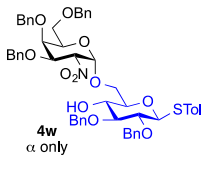
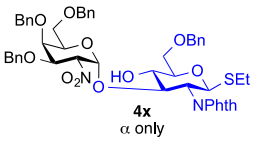
entry	donor	R^1	R^2	R^3	product	yield (%)[b]	α/β
1	**2b**	Bn	Ac	Bn	**4q**	60	1:0
2	**2c**	Bn	Bn	Ac	**4r**	64	1:0
3	**2d**	Allyl	Allyl	Allyl	**4s**	76	1:0
4	**6b**	Bn	Ac	Bn	**7l**	42	0:1
5	**6c**	Bn	Bn	Ac	**7m**	51	0:1
6	**6d**	Bn	Bn	TBDPS	**7n**	63	1:8

[a]The reactions were carried out under an inert atmosphere (N_2) using 0.15−0.3 mmol of 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**2a**), 0.1−0.2 mmol of the acceptor, and 0.01−0.02 mmol of P_4-*t*-Bu in hexane (10 mol %) in 2−4 mL of dry toluene for 24 h [b]Isolated yields.

position, while still maintaining a high yield (Figure 2). This observation was later thoroughly investigated by density functional theory (DFT) calculation with **6a** donor and **3b** acceptor (Figure 3). Gratifyingly, this method proceeded with moderate to excellent yields, which demonstrates that the reaction condition tolerates a variety of common carbohydrate protecting groups. This method performed exceptionally well on primary alcohols, yielding a glycosidic product in favor of the β-anomer (**7a**, **7b**, **7c**, and **7e**, Figure 2). On the contrary, most of the secondary alcohols brought forth corresponding glycosides (**7d**, **7f**, **7g**, **7h**, and **7i**, Figure 2) with a 3:2 to 3:1 β/α stereoselectivity. The reaction of cyclohexanol **3x** with **6a** also proceeded to provide **7j** in 75% yield with β-stereoselectivity (Figure 2, >7:1 β/α). The use of the sterically hindered tertiary alcohol 1-adamantol **3i** led to the formation of **7k** in 23% yield with relatively weak β-selectivity when allowed to react with **6a** (Figure 2, 3:2 β/α).

DFT calculations were performed to explicate the mechanism leading to the stereoselectivity of the glycosylation. The results indicated that for glycosylation of both 3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-galactal (**2a**) and 3,4,6-tri-*O*-benzyl-2-deoxy-2-nitroglucal (**6a**), the α-glycoside product is thermodynamically favored over the β-stereoisomer, with an energy difference between α- and β-stereoisomers $\Delta E_{\alpha-\beta} = -2.3$ kcal/mol for **2a** and $\Delta E_{\alpha-\beta} = -2.1$ kcal/mol for **6a** (Figure 3). Nevertheless, the identification of transition states (TSs) arising from the reaction routes of P_4-*t*-Bu base-catalyzed glycosylation, leading to different anomeric isomers (α- or β-face attack) revealed disparate thermokinetics of glycosylation of **2a** and **6a**. For glycosylation of **2a**, the TS of the reaction route leading to α-glycoside is lower in energy level by 3.9 kcal/mol with respect to the TS of the reaction route leading to β-glycoside (Figure 3).

Table 2. Regio- and Stereoselective Glycosylation of 2a with Various Glycoside Diol Acceptors (3s−3w)[c]

Entry	Acceptor	Product[a]	Yield (%)[b]
1	 **3s**	 **4t** (71%) α only; **4t′** (8%) α only	79
2	 **3t**	 **4u** (64%) α only; **4u′** (5%) α only	69
3	 **3u**	 **4v** (66%) α only; **4v′** (6%) α only	72
4	 **3v**	 **4w** α only	84
5	 **3w**	 **4x** α only	63

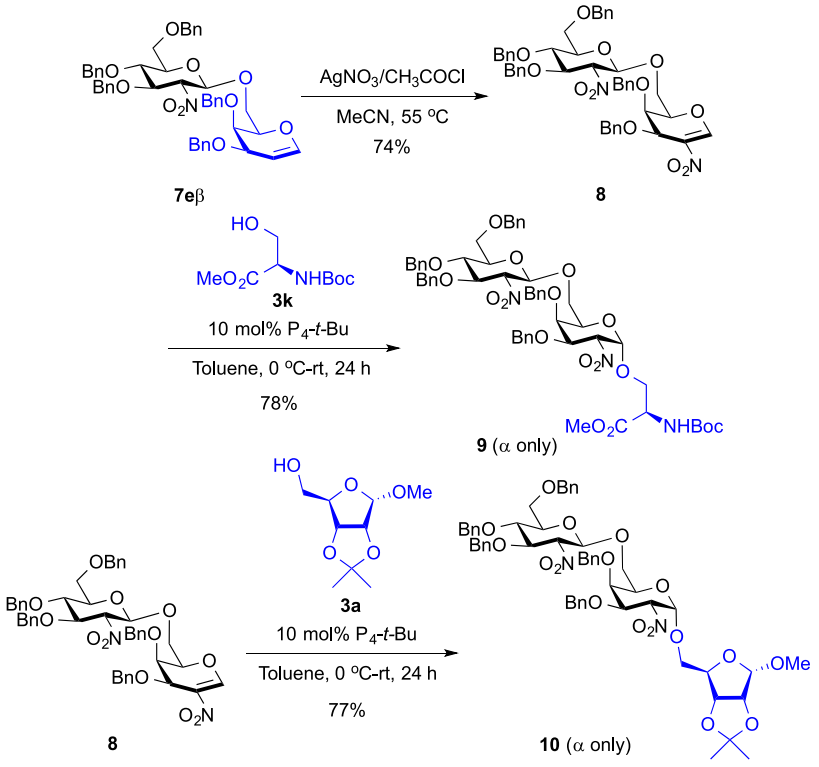
[a]All of the reactions afforded the α-stereoisomer. [b]Isolated yields. [c]Reaction conditions as in Table 1, and all of the reactions were carried out at 0 °C for 12 h.

Contrarily, for the glycosylation of **6a**, TS of the reaction route leading to α-glycoside is higher in energy level by 2.3 kcal/mol with respect to the TS of the β-face reaction route (Figure 3). Hence, while the formation of α-glycoside is both thermodynamically and thermokinetically favored for **2a**, the formation of β-glycoside is thermokinetically favored for **6a**. Presumably, the contrast in the relative energy level of α- and β-TSs for **2a** and **6a** can be ascribed to the steric repulsion between the alkyl groups on the bulky phosphazenium cation (P_4-*t*-BuH^+) accompanying the alkoxide nucleophile and the benzyl protecting groups on the glycal substrate: In **2a**, the C4 benzyl group sticks at the axial position and pointing away from α-face, leaving the α-face of the pyranose ring accessible, while repelling bulky nucleophiles approaching from the β-face (Figure 4), whereas in **6a**, the C4 substituent lies at the equatorial position and points away from the β-face, leaving β-face exposed, while repelling bulky P_4-*t*-BuH^+RO^- approaching from the α-face (Figure 4).

It is worth mentioning that the P_4-*t*-Bu base-catalyzed alcohol addition to aryl alkenes reported by Bandar and his coworkers,[21] which closely resembles our glycosylation reaction, is reversible under optimal conditions, while DFT computations and experimental observations indicate that the P_4-*t*-Bu base-catalyzed alcohol glycosylation reaction is virtually nonreversible under the optimal conditions. The disparity in reversibility can be explained by fact that the reaction outcome of alcohol addition to aryl−alkene reaction is governed by thermodynamics, while thermokinetics plays a more decisive role in determining the outcome of the P_4-*t*-Bu base-catalyzed glycosylation reaction (see the Supporting Information for a detailed discussion).

Inspections on the geometry of the TS species arising in thermokinetically favored reaction routes reveal that the distance between the P_4-*t*-Bu quaternary ammonium nitrogen and glycal 2-nitro group oxygen is 5.78 Å for the glucal-TS and 5.81 Å for the galactal-TS, both falling within the typical length range of attractive dipole−dipole interactions. The computational results suggest that in TS species for both **2a** and **6a**, attractive interactions between the permanent dipoles of the P_4-*t*-Bu quaternary ammonium group and the glycal nitro group may be present. The plausible dipole−dipole interaction in the TS species is expected to moderately shift the electron density on the 2-nitroglycal substrate further toward the electron-withdrawing nitro group, lowering the electron density on adjacent carbons and enhancing the electrophilicity of the

Scheme 2. Synthesis of the Key Disaccharide Intermediate of Mucin-Type Core 6 Glycan and a Model Trisaccharide



anomeric center. This inference is further corroborated by the computed Mulliken charges of C1 and C3 on the glycal ring (Supporting Information, Table S8). In both 2-nitroglucal and galactal, the Mulliken charges of C1 and C3 are slightly more positive in the TS species with respect to the free 2-nitroglycal substrates. The computational results agree with our observations from ^{1}H NMR experiments (Supporting Information, Figures S3 and S4). The H1 and H3 peaks of 2-nitrogalactal (**2a**) endured a weak yet appreciable downfield shift (7.643−7.649 ppm for H1 and 4.569−4.580 ppm for H3, Figure S4) when P_4-*t*-Bu and alcohol were added to 2-nitrogalactal (**2a**). Lower electron density is experienced by C1 and C3 carbons when the phosphazenium-alkoxide ion pair forms.

Afterward, we attempted to explore the donor scope with both 2-nitrogalactal and glucal derivatives having varying protecting groups. Pleasingly, this glycosylation method proceeded smoothly with a range of 2-nitrogalactal (α selective, **4q**−**4s**, Table 1, entries 1, 2, and 3) and 2-nitroglucal donors (β selective, **7l**−**7n**, Table 1, entries 4, 5 and 6). Having established the stereoselective transformation, we turned our attention to regioselective glycosylation (Table 2, entry 1). We began our studies with the known diol **3s** and *O*-benzyl-protected 2-nitrogalactal, **2a** (Table 2, entry 1). To our satisfaction, we obtained 66% α-anomer of 2-*O*-glycoside (**4t**) and 6% of 3-*O*-α-glycosidic product (**4t′**). It is worth mentioning that when we have performed the reaction at 0 °C and slowly warming up to room temperature we obtained a trace amount (9%) of β anomer of the 2-*O*-glycosidic product (**4t**β). Therefore, we maintained the temperature at 0 °C throughout the reaction, omitting the formation of the β-anomer of the 2-*O*-glycosylated product. Furthermore, we obtained improved yield for 2-*O*-α-glycoside **4t** (71%) over 3-*O*-α-glycoside **4t′** (8%) when we carried out the reaction at 0 °C (Table 2, entry 1). Encouraged by the regioselective glycosidic bond formation using P_4-*t*-Bu catalyst, a few more reactions were attempted with a range of diols. Galactoside diol **3t** afforded the less-hindered 3-*O*-α-glycosidic product (4u, 64%) alongside with other 4-*O*-regioisomer in 5% (**4u′**), perhaps credited to the steric hindrance around the axial hydroxyl groups (Table 2, entry 2).[22] However, surprisingly, intrinsic site selectivity[22,23] has been reversed in the case of mannoside diol **3u** (Table 2, entry 3), drafting a greater extent of axial the 2-*O*-glycosidic product **4v** (66%) over the less-hindered 3-*O*-glycoside **4v′** (6%). Glycosylation with the glucoside diol **3v** afforded 6-*O*-glycoside **4w** (84%) with an absolute α-stereoselectivity, explicitly proving that 6-*O*-glycosylation advances much quicker than 4-*O*-glycosylation (Table 2, entry 4). However, it is worth noting that the glucoside diol **3w** solely furnished 3-*O*-α-glycoside (**4x**, 63%) with complete regioselectivity (Table 2, entry 5).

DFT computations of the relative stability of ion pairs formed at different positions of the sugar acceptor have been performed to rationalize the experimentally observed regioselectivity of the reaction. The results from the optimized alkoxide-phosphazenium ion pair structures (Supporting Information, Table S6 and Figure S6) suggest that, for the fused ring glucose acceptor **3s**, 2-position ion pair is favored over the 3-position ion pair by ∼11.9 kcal/mol, probably resulting from a stronger steric interaction between the bulky phosphazenium and the silyl-di-*tert*-butyl group on the fused ring in 3-position ion pair (Supporting Information, Table S6 and Figure S6). For the mannose acceptor **3u**, 2-position ion pair is favored over its 3-position counterpart by ∼7.4 kcal/mol, presumably stabilized by the hydrogen bond between the pyranose ring oxygen and the protonated phosphazenium cation (Supporting Information, Table S6 and Figure S6). For the 2-phthalimido glucose acceptor **3w**, the 3-position ion pair is favored over its 4-position counterpart by ∼9.8 kcal/mol, presumably stabilized by the hydrogen bond between the protonated phosphazenium cation

and the C2-phthalimide group, which stabilizes the 3-position ion pair (Supporting Information, Table S6 and Figure S6).

To showcase the applicability of our method, we then turned our focus to synthesize the precursor for the disaccharide core of mucin-type Core 6 glycan (Scheme 2).[6c,24,25] Therefore, we started with selective nitration at the C2 position of **7eβ**, which afforded our desired disaccharide donor **8** in 74% yield. Glycosylation of Boc-functionalized serine (**3k**) employing 10 mol % of P_4-*t*-Bu proceeded smoothly to give the corresponding glycoconjugate **9** as a sole isolated product with absolute α-stereoselectivity (Scheme 2). Thereafter, we applied this method effectively to furnish trisaccharide **10** with a complete α-selectivity from disaccharide donor **8**, which demonstrates that we can certainly employ this method to prepare higher analogues of *N*-glycans and 2-amino-2-deoxy sugar-containing oligosaccharides (Scheme 2).

To summarize, a highly stereo- and regioselective *O*-glycosylation of 2-nitroglycals with various types of alcohols has been accomplished in the presence of a catalytic amount of organic superbase P_4-*t*-Bu. A wide range of 2-nitrogalactals and 2-nitroglucals underwent *O*-glycosylation and provided synthetically useful 2-deoxy-2-nitro-*O*-glycosides in good to excellent yields. Throughout our studies, we observed that 2-nitrogalactals produce α-stereoisomers as the sole isolated product, whereas 2-nitroglucals furnished more β-products. We have investigated the reason behind these varying results with the aid of DFT studies. Mechanistically, the reaction proceeds via the formation of an ion pair (P_4-*t*-BuH^+RO^-) between the P_4-*t*-Bu and alcohol (ROH), which activates the alcohol for the nucleophilic addition with 2-nitroglycals. From these results, we suggest a probable dipole−dipole interaction amongst the nitro group of the 2-nitroglycals and the P_4-*t*-BuH^+ (cationic part of the ion pair), which triggers the catalytic reaction process by enhancing the electrophilicity of the anomeric carbon. Apart from that, we profited from our method to regioselectively perform glycosylation as well. This method has been effectively used to synthesize the disaccharide precursor of mucin-type Core 6 glycan that demonstrates the applicability of this procedure. In the end, to illustrate the efficacy of our method, we have synthesized a trisaccharide which shows that our method can be applied to furnish higher analogues of *N*-glycans and 2-amino-2-deoxy glycoside-containing oligosaccharides. We would like to emphasize that a simple step of reduction of the 2-deoxy-2-nitro-glycosides provides facile access to the corresponding 2-deoxy-2-amino-glycosides,[6c] which further can be transformed into 2-acetamido-, 2-*N*-phthalimido-, 2-*N*-trichloroethoxycarbamido-, or 2-azido-functionalized glycosides as required.[26] Hence, our methodology provides a more efficient alternative for the chemical synthesis of this family of biologically important oligosaccharides. With this straightforward method toward various 2-nitro-2-deoxy-*O*-glycosides, we hope to provide a handy tool for carbohydrate synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c00753.

Experimental procedures and full characterization of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xue-Wei Liu − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371;* orcid.org/0000-0002-8327-6664; Email: xuewei@ntu.edu.sg

Authors

Kumar Bhaskar Pal − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371;* orcid.org/0000-0002-1892-1890

Aoxin Guo − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371;* orcid.org/0000-0002-7072-4106

Mrinmoy Das − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371;* orcid.org/0000-0002-9955-9044

Gábor Báti − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c00753

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Nanyang Technological University (RG120/18), the Ministry of Education (MOE 2013-T3-1-002), and the National Research Foundation (NRF2016NRF-NSFC002-005), Singapore, for their financial support. This work is dedicated to Professor Charles E. Mckenna on his 75th birthday.

■ ABBREVIATIONS USED

DMAP, 4-dimethylaminopyridine; PPY, 2-phenylpyridine

■ REFERENCES

(1) Jelinek, R.; Kolusheva, S. Carbohydrate Biosensors. *Chem. Rev.* **2004**, *104*, 5987−6016.

(2) (a) Takatsuki, A.; Arima, K.; Tamura, G. J. New Antibiotic. I: Isolation and Characterization of Tunicamycin. *J. Antibiot.* **1971**, *24*, 215. (b) Usuki, H.; Nitoda, T.; Ichikawa, M.; Yamaji, N.; Iwashita, T.; Komura, H.; Kanzaki, H. TMG-chitotriomycin, an Enzyme Inhibitor Specific for Insect and Fungal β-*N*-Acetylglucosaminidases, Produced by Actinomycete *Streptomyces anulatus* NBRC 13369. *J. Am. Chem. Soc.* **2008**, *130*, 4146−4152. (c) Hainrichson, M.; Nudelman, I.; Baasov, T. Designer Aminoglycosides: The Race to Develop Improved Antibiotics and Compounds for the Treatment of Human Genetic Diseases. *Org. Biomol. Chem.* **2008**, *6*, 227−239.

(3) (a) Kang, B.; Opatz, T.; Landfester, K.; Wurm, F. R. Carbohydrate Nanocarriers in Biomedical Applications: Functionalization and Construction. *Chem. Soc. Rev.* **2015**, *44*, 8301−8325. (b) Li, Y.; Chen, L.; Liu, Y.; Zhang, Y.; Liang, Y.; Mei, Y. Anti-inflammatory Effects in a Mouse Osteoarthritis Model of a Mixture of Glucosamine and Chitooligosaccharides Produced by Bi-Enzyme Single-Step Hydrolysis. *Sci. Rep.* **2018**, *8*, No. 5624. (c) Liu, W.; Qin, Y.; Liu, S.; Xing, R.; Yu, H.; Chen, X.; Li, K.; Li, P. Synthesis of *C*-Coordinated *O*-Carboxymethyl Chitosan Metal Complexes and Evaluation of their Antifungal Activity. *Sci. Rep.* **2018**, *8*, No. 4845.

(4) Beau, J.-M.; Boyer, F.-D.; Norsikian, S.; Urban, D.; Vauzeilles, B.; Xolin, A. Glycosylation: The Direct Synthesis of 2-Acetamido-2-deoxy-Sugar Glycosides. *Eur. J. Org. Chem.* **2018**, *2018*, 5795−5814.
(5) (a) Ngoje, G.; Li, Z. Study of the Stereoselectivity of 2-Azido-2-deoxyglucosyl Donors: Protecting Group Effects. *Org. Biomol. Chem.* **2013**, *11*, 1879−1886. (b) Banou, J.; Boullanger, P.; Lafont, D. Synthesis of Oligosaccharides of 2-Amino-2-deoxy sugars. *Chem. Rev.* **1992**, *92*, 1167−1195.
(6) (a) Schmidt, R. R.; Vankar, Y. D. 2-Nitroglycals as Powerful Glycosyl Donors: Application in the Synthesis of Biologically Important Molecules. *Acc. Chem. Res.* **2008**, *41*, 1059−1073. (b) Xue, W.; Sun, J.; Yu, B. An Efficient Route toward 2-Amino-β-d-galacto- and -glucopyranosides *via* Stereoselective Michael-Type Addition of 2-Nitroglycals. *J. Org. Chem.* **2009**, *74*, 5079−5082. (c) Peng, P.; Geng, Y.; Göttker-Schnetmann, I.; Schmidt, R. R. 2-Nitro-thioglycosides: α- and β-Selective Generation and Their Potential as β-Selective Glycosyl Donors. *Org. Lett.* **2015**, *17*, 1421−1424. (d) Medina, S.; Harper, M. J.; Balmond, E. I.; Miranda, S.; Crisenza, G. E. M.; Coe, D. M.; McGarrigle, E. M.; Galan, M. C. Stereoselective Glycosylation of 2-Nitrogalactals Catalyzed by a Bifunctional Organocatalyst. *Org. Lett.* **2016**, *18*, 4222−4225.
(7) Kumagai, D.; Miyazaki, M.; Nishimura, S.-I. Cyclic Di-*t*-butylsilylenediyl Ether Group as a Convenient Protective Group for the Glycoconjugate Synthesis. *Tetrahedron Lett.* **2001**, *42*, 1953−1956.
(8) (a) Xiang, S.; Lu, Z.; He, J.-X.; MaiHoang, K. L.; Zeng, J.; Liu, X.-W. β-Type Glycosidic Bond Formation by Palladium-Catalyzed Decarboxylative Allylation. *Chem. - Eur. J.* **2013**, *19*, 14047−14051. (b) Xiang, S.; Hoang, K. L. M.; He, J.-X.; Tan, Y. J.; Liu, X.-W. Reversing the Stereoselectivity of a Palladium-Catalyzed *O*-Glycosylation through an Inner-Sphere or Outer-Sphere Pathway. *Angew. Chem., Int. Ed.* **2015**, *127*, 614−617. (c) Yao, H.; Zhang, S.; Leng, W.-L.; Leow, M.-L.; Xiang, S.; He, J.-X.; Liao, H.; Hoang, K. L. M.; Liu, X.-W. Catalyst-Controlled Stereoselective *O*-Glycosylation: Pd(0) vs Pd(II). *ACS Catal.* **2017**, *7*, 5456−5460. (d) Sau, A.; Williams, R.; Palo-Nieto, C.; Franconetti, A.; Medina, S.; Galan, M. C. Palladium-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals. *Angew. Chem., Int. Ed.* **2017**, *129*, 3694−3698.
(9) (a) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. Cooperative Catalysis in Glycosidation Reactions with *O*-Glycosyl Trichloroacetimidates as Glycosyl Donors. *Angew. Chem., Int. Ed.* **2013**, *52*, 10089−10092. (b) Balmond, E. I.; Benito-Alifonso, D.; Coe, D. M.; Alder, R. W.; McGarrigle, E. M.; Galan, M. C. A 3,4-*trans*-Fused Cyclic Protecting Group Facilitates α-Selective Catalytic Synthesis of 2-Deoxyglycosides. *Angew. Chem., Int. Ed.* **2014**, *53*, 8190−8194. (c) Das, S.; Pekel, D.; Neudörfl, J.-M.; Berkessel, A. Organocatalytic Glycosylation by Using Electron-Deficient Pyridinium Salts. *Angew. Chem., Int. Ed.* **2015**, *54*, 12479−12483. (d) Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. Stereocontrolled Photoinduced Glycosylation Using an Aryl Thiourea as an Organo Photoacid. *Org. Lett.* **2016**, *18*, 3190−3193.
(10) Cox, D. J.; Smith, M. D.; Fairbanks, A. J. Glycosylation Catalyzed by a Chiral Brønsted Acid. *Org. Lett.* **2010**, *12*, 1452−1455.
(11) (a) Hoang, K. L. M.; Liu, X.-L. The Intriguing Dual-Directing Effect of 2-Cyanobenzyl Ether for a Highly Stereospecific Glycosylation Reaction. *Nat. Commun.* **2014**, *5*, No. 5051. (b) Hoang, K. L. M.; He, J.-x.; Báti, G.; Chan-Park, M. B.; Liu, X.-W. A Minimalist Approach to Stereoselective Glycosylation with Unprotected Donors. *Nat. Commun.* **2017**, *8*, No. 1146. (c) Báti, G.; He, J.-X.; Pal, K. B.; Liu, X.-W. Stereo- and Regioselective Glycosylation with Protection-less Sugar Derivatives: An Alluring Strategy to Access Glycans and Natural Products. *Chem. Soc. Rev.* **2019**, *48*, 4006−4018.
(12) (a) Nguyen, H.; Zhu, D.; Li, X.; Zhu, J. Stereoselective Construction of β-Mannopyranosides by Anomeric *O*-Alkylation: Synthesis of the Trisaccharide Core of *N*-linked Glycans. *Angew. Chem., Int. Ed.* **2016**, *55*, 4767−4771. (b) Palo-Nieto, C.; Sau, A.; Galan, M. C. Gold(I)-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals. *J. Am. Chem. Soc.* **2017**, *139*, 14041−14044. (c) Huang, N.; Liao, H.; Yao, H.; Xie, T.; Zhang, S.; Zou, K.; Liu, X.-W. Diastereoselective Synthesis of *C*-Vinyl Glycosides *via* Gold(I)-Catalyzed Tandem 1,3-Acyloxy Migration/Ferrier Rearrangement. *Org. Lett.* **2018**, *20*, 16−19.
(13) Zhao, G.; Wang, T. Stereoselective Synthesis of 2-Deoxyglycosides from Glycals by Visible-Light-Induced Photoacid Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 6120−6124.
(14) (a) Augé, C.; Veyrières, A. Stannylene Derivatives in Glycoside Synthesis. Application to the Synthesis of the Blood-Group B Antigenic Determinant. *J. Chem. Soc., Perkin Trans. 1* **1979**, *1*, 1825−1832. (b) Murase, T.; Kartha, K. P. R.; Kiso, M.; Hasegawa, A. Synthesis of the α-Neu5Ac-(2→6)-Gal Structure. Facile 6-*O*-Sialylation Following Stannylene Activation of an Unprotected D-Galactopyranoside. *Carbohydr. Res.* **1989**, *195*, 134−137. (c) Cruzado, C.; Bernabe, M.; Martin-Lomas, M. Regioselective Glycosylation of Mono- and Disaccharides *via* Organotin Derivatives. *Carbohydr. Res.* **1990**, *203*, 296−301. (d) Wu, B.; Li, M.; O'Doherty, G. A. Synthesis of Several Cleistrioside and Cleistetroside Natural Products *via* a Divergent *De Novo* Asymmetric Approach. *Org. Lett.* **2010**, *12*, 5466−5469. (e) Bajaj, S. O.; Sharif, E. U.; Akhmedov, N. G.; O'Doherty, G. A. *Denovo* Asymmetric Synthesis of the Mezzettiaside Family of Natural Products *via* the Iterative Use of a Dual B-/Pd-Catalyzed Glycosylation. *Chem. Sci.* **2014**, *5*, 2230−2234.
(15) Evans, P. G.; Osborn, H. M. I.; Suthers, W. G. The Utility of Glycoside Copper Chelates for Effecting Regioselective Glycosidation. *Tetrahedron Lett.* **2002**, *43*, 7855−7857.
(16) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. Iterative One-Pot Synthesis of Oligosaccharides. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221−5224.
(17) (a) Oshima, K.; Aoyama, Y. Regiospecific Glycosidation of Unprotected Sugars via Arylboronic Activation. *J. Am. Chem. Soc.* **1999**, *121*, 2315−2316. (b) Oshima, K.; Yamauchi, T.; Shimomura, M.; Miyauchi, S.; Aoyama, Y. Selective 3-*O*- and/or 6-*O*-Glycosidation of Unprotected *O*- and *S*-Glycosides Promoted by an Intramolecularly Coordinated Arylboronic Compound. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1319−1324. (c) Kaji, E.; Nishino, T.; Ishige, K.; Ohya, Y.; Shirai, Y. Regioselective Glycosylation of Fully Unprotected Methyl Hexopyranosides by Means of Transient Masking of Hydroxy Groups with Arylboronic Acids. *Tetrahedron Lett.* **2010**, *51*, 1570−1573. (d) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. Regioselective Activation of Glycosyl Acceptors by a Diarylborinic Acid-Derived Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 13926−13929. (e) Beale, T. M.; Taylor, M. S. Synthesis of Cardiac Glycoside Analogs by Catalyst-Controlled, Regioselective Glycosylation of Digitoxin. *Org. Lett.* **2013**, *15*, 1358−1361. (f) Fenger, T. H.; Madsen, R. Regioselective Glycosylation of Unprotected Phenyl 1-Thioglycopyranosides with Phenylboronic Acid as a Transient Masking Group. *Eur. J. Org. Chem.* **2013**, *2013*, 5923−5933. (g) Beale, T. M.; Moon, P. J.; Taylor, M. S. Organoboron-Catalyzed Regio- and Stereoselective Formation of β-2-Deoxyglycosidic Linkages. *Org. Lett.* **2014**, *16*, 3604−3607. (h) Nakagawa, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. Regioselective and 1,2-*cis*-α-Stereoselective Glycosylation Utilizing Glycosyl-Acceptor-Derived Boronic Ester Catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 10935−10939. (i) Nishi, N.; Nashida, J.; Kaji, E.; Takahashi, D.; Toshima, K. Regio- and Stereoselective β-Mannosylation Using a Boronic Acid Catalyst and its Application in the Synthesis of a Tetrasaccharide Repeating Unit of Lipopolysaccharide Derived from *E. coliO75,*. *Chem. Commun.* **2017**, *53*, 3018−3021. (j) Takahashi, D.; Tanaka, M.; Nishi, N.; Toshima, K. Novel 1,2-*cis*-Stereoselective Glycosylations Utilizing Organoboron Reagents and their Application to Natural Products and Complex Oligosaccharide Synthesis. *Carbohydr. Res.* **2017**, *452*, 64−77. (k) Dimakos, V.; Taylor, M. S. Site-Selective Functionalization of Hydroxyl Groups in Carbohydrate Derivatives. *Chem. Rev.* **2018**, *118*, 11457−11517. (l) Dimakos, V.; Su, H. Y.; Garrett, G. E.; Taylor, M. S. Site-Selective and Stereoselective C−H Alkylations of Carbohydrates via Combined Diarylborinic Acid and Photoredox Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 5149−5153.
(18) Muramatsu, W.; Yoshimatsu, H. Regio- and Stereochemical Controlled Koenigs-Knorr-Type Monoglycosylation of Secondary Hydroxy Groups in Carbohydrates Utilizing the High Site Recognition

Ability of Organotin Catalysts. *Adv. Synth. Catal.* **2013**, *355*, 2518−2524.

(19) (a) Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. Deprotonation of Benzylic Ethers Using a Hindered Phosphazene Base. A Synthesis of Benzofurans from *Ortho*-Substituted Benzaldehydes. *Org. Lett.* **2000**, *2*, 2409−2410. (b) Imahori, T.; Hori, C.; Kondo, Y. Functionalization of Alkynes Catalyzed by *t*-Bu-P4 Base. *Adv. Synth. Catal.* **2004**, *346*, 1090−1092. (c) Suzawa, K.; Ueno, M.; Wheatley, A. E. H.; Kondo, Y. Phosphazene Base-Promoted Functionalization of Aryltrimethylsilanes. *Chem. Commun.* **2006**, 4850−4852. (d) Kharchafi, G.; Jérôme, F.; Douliezb, J.-P.; Barrault, J. Facile and Regioselective Mono- or Diesterification of Glycerol Derivatives over Recyclable Phosphazene Organocatalyst. *Green Chem.* **2006**, *8*, 710−716. (e) Zhang, L.; Nederberg, F.; Messman, J. M.; Pratt, R. C.; Hedrick, J. L.; Wade, C. G. Organocatalytic Stereoselective Ring-Opening Polymerization of Lactide with Dimeric Phosphazene Bases. *J. Am. Chem. Soc.* **2007**, *129*, 12610−12611. (f) Kanazawa, C.; Goto, K.; Terada, M. Phosphazene Base-Catalyzed Intramolecular Cyclization for Efficient Synthesis of Benzofurans *via* Carbon-Carbon Bond Formation. *Chem. Commun.* **2009**, 5248−5250. (g) Hirono, Y.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. Metal-Free Deprotonative Functionalization of Heteroaromatics Using Organic Superbase Catalyst. *Chem. Commun.* **2010**, *46*, 7623−7624. (h) Nacsa, E. D.; Lambert, T. H. Higher-Order Cyclopropenimine Superbases: Direct Neutral Brønsted Base Catalyzed Michael Reactions with α-Aryl Esters. *J. Am. Chem. Soc.* **2015**, *137*, 10246−10253. (i) Zhao, N.; Ren, C.; Li, H.; Li, Y.; Liu, S.; Li, Z. Selective Ring-Opening Polymerization of Non-Strained γ-Butyrolactone Catalyzed by a Cyclic Trimeric Phosphazene Base. *Angew. Chem., Int. Ed.* **2017**, *56*, 12987−12990. (j) Luo, C.; Bandar, J. S. Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 3547−3550. (k) Shigeno, M.; Hayashi, K.; Nozawa-Kumada, K.; Kondo, Y. Phosphazene Base *t*Bu-P4 Catalyzed Methoxy−Alkoxy Exchange Reaction on (Hetero)Arenes. *Chem. - Eur. J.* **2019**, *25*, 6077−6081. (l) Shigeno, M.; Nakamura, R.; Hayashi, K.; Nozawa-Kumada, K.; Kondo, Y. Catalytic Amination of β-(Hetero)arylethyl Ethers by Phosphazene Base *t*-Bu-P4. *Org. Lett.* **2019**, *21*, 6695−6699.

(20) Pachamuthu, K.; Gupta, A.; Das, J.; Schmidt, R. R.; Vankar, Y. D. An Easy Route to 2-Amino-β-*C*-Glycosides by Conjugate Addition to 2-Nitroglycals. *Eur. J. Org. Chem.* **2002**, 1479−1483.

(21) Puleo, T. R.; Strong, A. J.; Bandar, J. S. Catalytic α-Selective Deuteration of Styrene Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 1467−1472.

(22) (a) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. Regioselective Activation of Glycosyl Acceptors by a Diarylborinic Acid-Derived Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 13926−13929. (b) Peng, P.; Schmidt, R. R. An Alternative Reaction Course in *O*-Glycosidation with *O*-Glycosyl Trichloroacetimidates as Glycosyl Donors and Lewis Acidic Metal Salts as Catalyst: Acid−Base Catalysis with Gold Chloride-Glycosyl Acceptor Adducts. *J. Am. Chem. Soc.* **2015**, *137*, 12653−12659. (c) D'Angelo, K. A.; Taylor, M. S. Borinic Acid Catalyzed Stereo- and Regioselective Couplings of Glycosyl Methanesulfonates. *J. Am. Chem. Soc.* **2016**, *138*, 11058−11066.

(23) (a) Cmoch, P.; Pakulski, Z. Comparative Investigations on the Regioselective Mannosylation of 2,3,4-Triols of Mannose. *Tetrahedron: Asymmetry* **2008**, *19*, 1494−1503. (b) Uriel, C.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. Ready Access to a Branched Man_5 Oligosaccharide Based on Regioselective Glycosylations of a Mannose-Tetraol with *n*-Pentenyl Orthoesters. *Org. Biomol. Chem.* **2012**, *10*, 8361−8370.

(24) Winterfeld, G. A.; Schmidt, R. R. Nitroglycal Concatenation: A Broadly Applicable and Efficient Approach to the Synthesis of Complex *O*-Glycans. *Angew. Chem., Int. Ed.* **2001**, *40*, 2654−2657.

(25) Reddy, B. G.; Schmidt, R. R. 2-Nitroglycals: Versatile Intermediates for Efficient and Highly Stereoselective Base-Catalyzed Glycoside Bond Formations. *Nat. Protoc.* **2008**, *3*, 114−121.

(26) Bongat, A. F. G.; Demchenko, A. V. Recent Trends in the Synthesis of *O*-Glycosides of 2-Amino-2-deoxysugars. *Carbohydr. Res.* **2007**, *342*, 374−406.