β-Selective 2-Deoxy- and 2,6-Dideoxyglucosylations Catalyzed by Bis-Thioureas.

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ABSTRACT: We present methods for β-selective 2-deoxy and 2,6-dideoxyglucosylations of natural products, carbohydrates, and amino acids using bis-thiourea hydrogen-bond-donor catalysts. Disarming ester protecting groups were necessary to counter the high reactivity of 2-deoxyglycosyl electrophiles toward non-stereospecific S_N1 pathways. Alcohol and phenol nucleophiles with both base- and acid-sensitive functionalities were compatible with the catalytic protocol, enabling access to a wide array of 2-deoxy-β-O-glucosides.

β-Configured 2-deoxy glycosides are integral components in various biologically active natural products (**Figure 1A**).[1,2] The most conceptually straightforward approach to the synthesis of β-2-deoxyglycosides involves stereospecific invertive displacement of appropriate and often readily available α-configured glycosyl electrophiles. However, these electrophiles are highly prone to inherently α-selective non-stereospecific S_N1-like pathways due to the electron-rich nature of the site of nucleophilic substitution relative to fully oxygenated analogs (**Figure 1B**).[3–7]

As such, application of otherwise β-selective glycosylation protocols to 2-deoxyglycosylations has proven challenging,[8–10] and the synthesis of 2-deoxy-β-glycosides has remained a long-standing challenge in the field.[11] The Bennett group devised a strategy of in situ generation of α-glycosyl sulfonates and stereospecific displacement by strongly nucleophilic potassium alkoxides, allowing the synthesis of β-linked 2-deoxyoligosaccharides and 2-deoxyglycoside natural products.[12–17] However, the need for strongly basic conditions limited its application with base-sensitive functionalities. Li and coworkers developed a directing-group strategy with trimethylsilyl trifluoromethanesulfonate catalysis.[18,19] Excellent β-selectivities were obtained, but the requirement for a strongly Lewis acidic catalyst renders the method incompatible with Lewis-basic functionalities. An alternative strategy, reported by Niu and coworkers, employs palladium catalysis to achieve stereo- and chemoselective 2-deoxy glycosylations of phenols across a remarkable scope of nucleophiles and electrophiles.[20] This notable advance in functional-group-compatible 2-deoxy glycosylations notwithstanding, a mild and general protocol for the 2-deoxy-β-glycosylation of both phenols and alcohols remains elusive. Other methods, including umpolung strategies,[21–24] C-2 auxiliaries,[25–28] boronic acid catalysis,[29] supramolecular capsules,[30] and acid-catalyzed substitutions at cryogenic temperatures,[31–34] which similarly lack generality in nucleophile scope or require multi-step protocols.

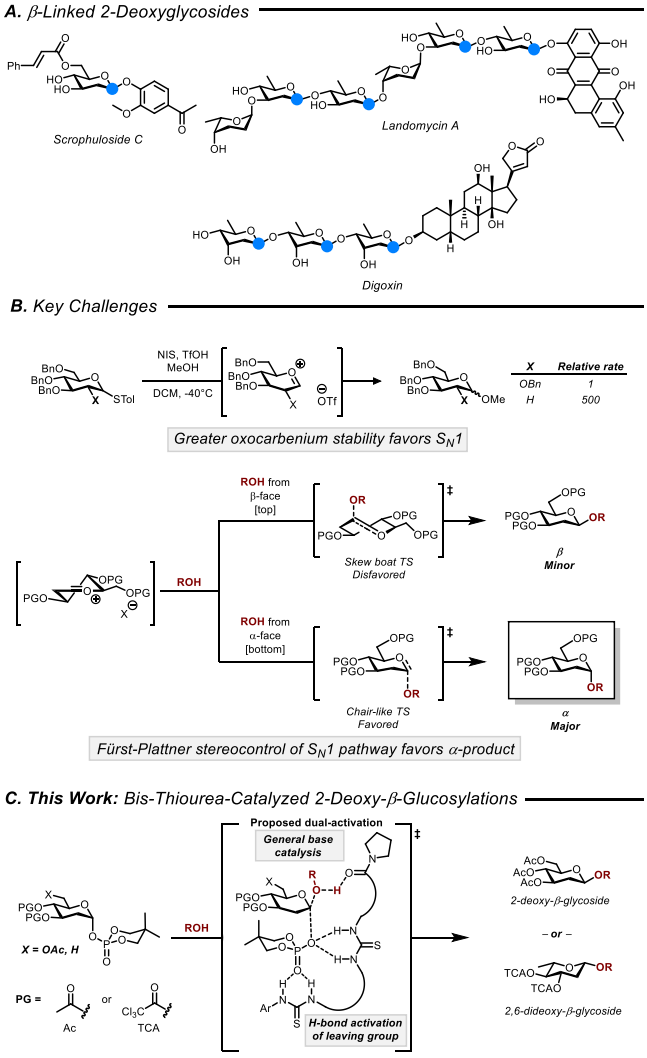

Figure 1. (A) Selected examples of natural products bearing β-linked 2-deoxyglycosides. (B) 2-Deoxyglycosyl electrophiles are highly reactive towards S_N1-like pathways, resulting in inherent bias toward formation of α-glycosides.

(C) The approach to catalytic, β-selective 2-deoxy and 2,6-dideoxyglucosylations presented herein.

Our group previously developed stereospecific β-glycosylations with glycosyl phosphates promoted by bis-thiourea hydrogen-bond-donor (HBD) catalysts.[35–38] Extensive experimental and computational evidence has been advanced consistent with a mechanism of substitution involving dual activation of both the electrophile and nucleophile via general acid/base interactions (**Figure 1C**). Precise geometrical preorganization and matching of the hydrogen-bond-donating and -accepting domains of the catalysts were critical for achieving high levels of stereospecificity. Here, we report the successful extension of this dual activation strategy to β-selective 2-deoxy- and 2,6-dideoxyglucosylations of amino acids, carbohydrates, natural products, and pharmaceuticals. The approach relies on precise tuning of the bis-thiourea catalysts together with utilization of precisely tuned phosphate leaving groups and disarming protecting groups[39,40] to attenuate the inherent reactivity of the deoxy- and dideoxy-glucosyl electrophiles.

Our initial studies found that glycosylations with armed[39,40] 2-deoxyglucosyl chlorides yielded promising results with highly nucleophilic primary and secondary alcohols.[41] However, subsequent efforts to effect glycosylation of complex nucleophiles with 2-deoxyglycosyl chlorides proved unsuccessful, as we found that the HCl byproduct generated could not be trapped efficiently enough to avoid substrate decomposition via Ferrier rearrangements.[42,43] Given the especially successful application of glycosyl phosphates in stereospecific glycosylations promoted by bis-thioureas, we refocused our efforts towards identifying 2-deoxy glucosyl phosphate derivatives with the appropriate balance of stability and reactivity properties.[35–38] Glucosyl phosphates bearing electron-rich arming[39,40] protecting groups such as benzyl ethers were found to undergo immediate decomposition during attempted preparation and/or isolation. Even disarmed 2-deoxyglucose derivatives bearing carboxylate protecting groups proved too unstable in the case of diaryl phosphate derivatives. However, analogous dialkyl phosphate derivatives were synthesized from the corresponding thioglucosides[44] and found to be bench-stable and readily purified. Evaluation of this class of electrophiles in the 2-deoxyglucosylation of threonine derivative **3a** led to identification of glucosyl phosphate **2a** as displaying the most promising levels of reactivity and selectivity for formation of the β-glucoside product. Extensive evaluation of reaction conditions revealed the optimal solvent, concentration, temperature, and reaction time for the model 2-deoxyglucosylation of **3a** and molecular sieves as a crucial additive to sequester the phosphoric acid leaving group and minimize electrophile hydrolysis (see Supporting Information for details).[35–38] Catalyst optimization efforts included extensive variation of the pyrrolidine substituents, as these components had proven to be crucial handles for tuning reactivity and selectivity in previous glycosylation studies.[36,38] In the case of the model 2-deoxyglucosylation reaction, bis-thiourea derivative **1a**, which bears an electron-rich 5-*N*-methyl indolyl substituent in the "northern" fragment and an unsubstituted pyrrolidine in the "southern" fragment, was found to be the most effective with respect to both β-selectivity and yield, the latter feature resulting from minimization of glucal side-product formation arising from elimination.

The scope of suitable nucleophilic partners in 2-deoxy-β-glucosylation reactions with electrophile **2a** promoted with catalyst **1a** was explored (**Figure 2**). Focus was placed on couplings where mild conditions would be advantageous compared to existing protocols that rely on either stoichiometric metal amide base or catalytic strong Lewis acids. Reactions were performed with two equivalents of **2a** to compensate for unproductive consumption of electrophile through elimination and hydrolysis pathways. Alcohols bearing base-sensitive functional groups, such as protected amino acids (**3a**-**3b**) or pleuromutilin (**3e**), which possesses an enolizable stereocenter, underwent reaction with high β-selectivity without erosion of stereopurity. Deoxy-sugar-based acceptors (**3c** and **3d**) were excellent substrates, yielding disaccharides with high selectivity and efficiency. Alcohols with acid-sensitive functionalities, including hemiacetals (**3f** and **3j**), tertiary amines (**3g** and **3i**), and aromatic heterocycles (**3h**), also underwent 2-deoxyglucosylation by the catalytic approach. Basic alumina was required for substrates with basic-nitrogen functionality (**3g-3h, 3m**) to prevent the formation of ammonium phosphate salts, which inhibit thiourea catalysts. The particularly challenging alcohols **3h-3j** possessing both base- and acid-sensitive functionality were also found to be suitable substrates under the catalytic conditions.

Phenolic nucleophiles were also demonstrated to be useful partners in the catalytic couplings, albeit under a slightly modified reaction protocol. Increased dilution relative to the glucosylation of alcohols ($[\mathbf{4}]_0$ = 0.025 M vs. $[\mathbf{3}]_0$ = 0.2 M), and addition of basic alumina were found to enhance β-selectivity (**Figures S9**, **S12**). Phenols bearing functionality such as amides (**4a**) and indoles (**4b**) proved to be effective coupling partners. In addition, tertiary-amine-containing (**4c**) and sterically hindered (**4d**) phenols underwent 2-deoxyglucosylation with good levels of β-selectivity, albeit in modest yields. Finally, glucosylation of β-estradiol **4e** was observed to occur with moderate selectivity for the phenolic position.

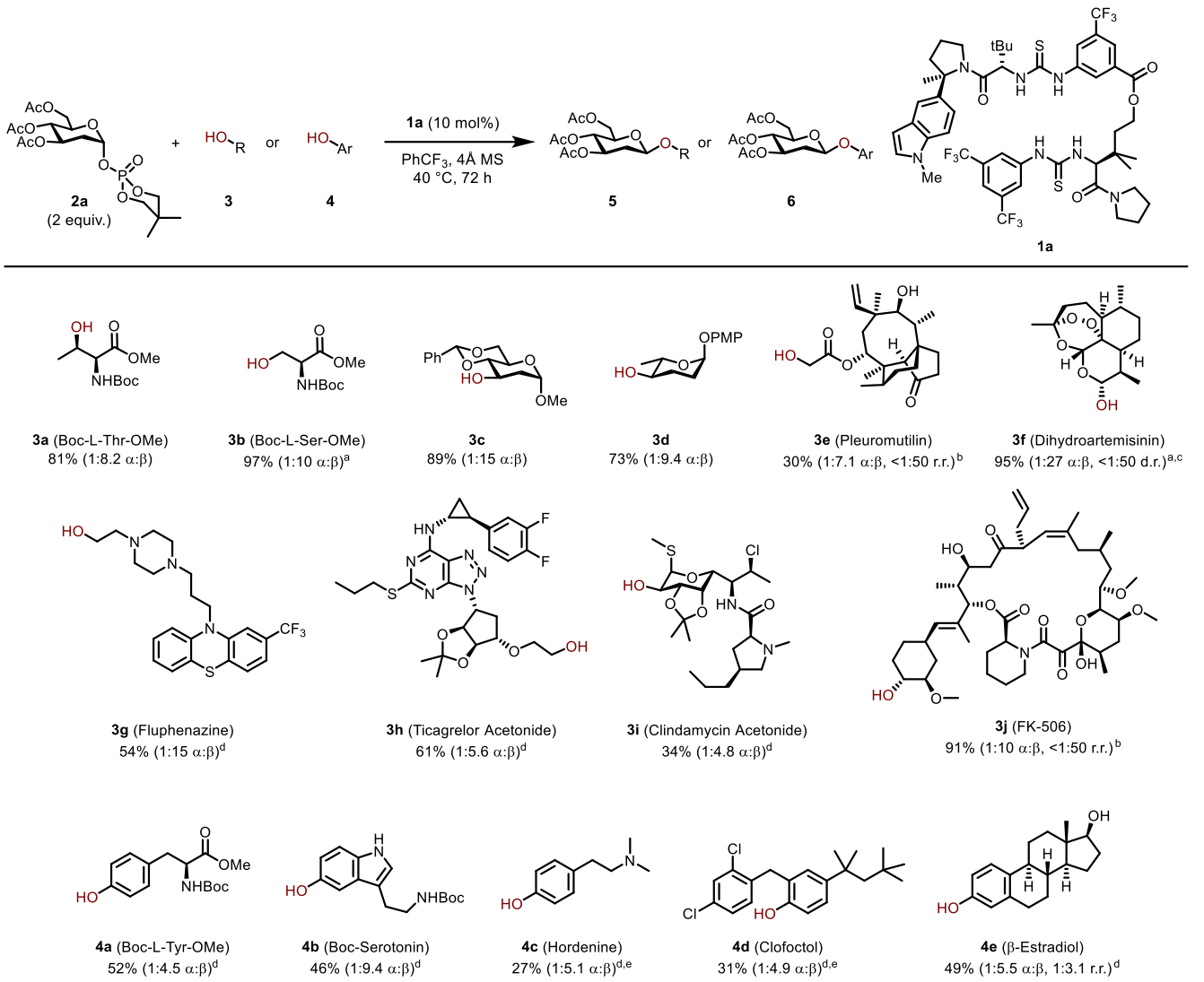

Figure 2. Scope of nucleophiles for 2-deoxy-β-glucosylation. Reactions were performed on a 0.15 mmol scale. Selectivities were determined by ^{1}H NMR analysis of crude product mixtures except **5e** (see SI for details). [a]48 h reaction time. [b]Regioselectivity was defined as the measured signal-to-noise ratio of the anomeric signal peak in the crude spectrum as only one regioisomer was detected by ^{1}H-NMR spectroscopy of the crude reaction mixture. [c]Diastereomer ratio with respect to the acetal stereocenter derived from hemiacetal of **3f**, which is prone to epimerization in organic solvent (ref. 45, see SI for details). [d]With Al_2O_3 (Brockmann Activity I, basic). [e]96 h reaction time.

We then investigated whether principles used in 2-deoxy-β-glucosylations could be applied to the more challenging 2,6-dideoxy-β-glucosylations. Disarmed diacetoxy-substituted derivatives were too unstable for isolation and application in the catalytic reaction, so we evaluated a series of 2,6-dideoxy-L-glucose derivatives with various protecting group schemes and phosphate leaving groups. Bis-trichloroacetyl (TCA) derivative **7a** was identified as displaying the best compromise between reactivity and stability. Threonine derivative **3a** displayed poor reactivity as a nucleophile, so tyrosine derivative **4a** was used as the model substrate in catalyst optimization studies to enable accurate determination of α/β-selectivities by ^{1}H-NMR analysis of crude reaction mixtures. In a survey of bis-thioureas with different arylpyrrolidine substituents, the 2-naphthyl substituted ***ent*-1b,** previously effective in site-selective glycosylations,[38] provided the best yields and β-selectivity (**Figures S14-S15**). As observed in prior studies, the absolute stereochemistry of the catalyst influenced reaction outcomes (**Figure S16A**).).[35–37] ***ent*-1** catalysts induced improved yield and β-selectivity with 2,6-dideoxy-L-glucose derivatives (**7**), whereas the enantiomeric **1** catalysts were more effective with the pseudo-enantiomeric 2-deoxy-D-glucose derivatives (**2**).

The scope of nucleophiles in 2,6-dideoxyglucosylation reactions is shown in **Figure 3**. It was observed that unavoidable yield losses attributable to partial loss of the TCA protecting groups were occurring during product isolation, so a quantitative deprotection procedure was developed, isolating products as unprotected 2,6-dideoxyglucosides (**8** or **9**). Alcohols and phenols generally reacted with moderate β-selectivity, including functionally rich amino acids (**3a-b**, **4a**), natural products (**3e**, **4e**-**4g**), and synthetic pharmaceuticals (**3h**, **3d**). β-Estradiol (**4e**) reacted with modest chemoselectivity for the phenol, yielding the phenolic

glucoside with good β-selectivity. The *N*-heterocycle-containing substrate **3h** was glucosylated in good yield, however substrates with strongly basic and nucleophilic amines were incompatible with the 2,6-dideoxyglucosylation protocol, unlike in 2-deoxyglucosylations.

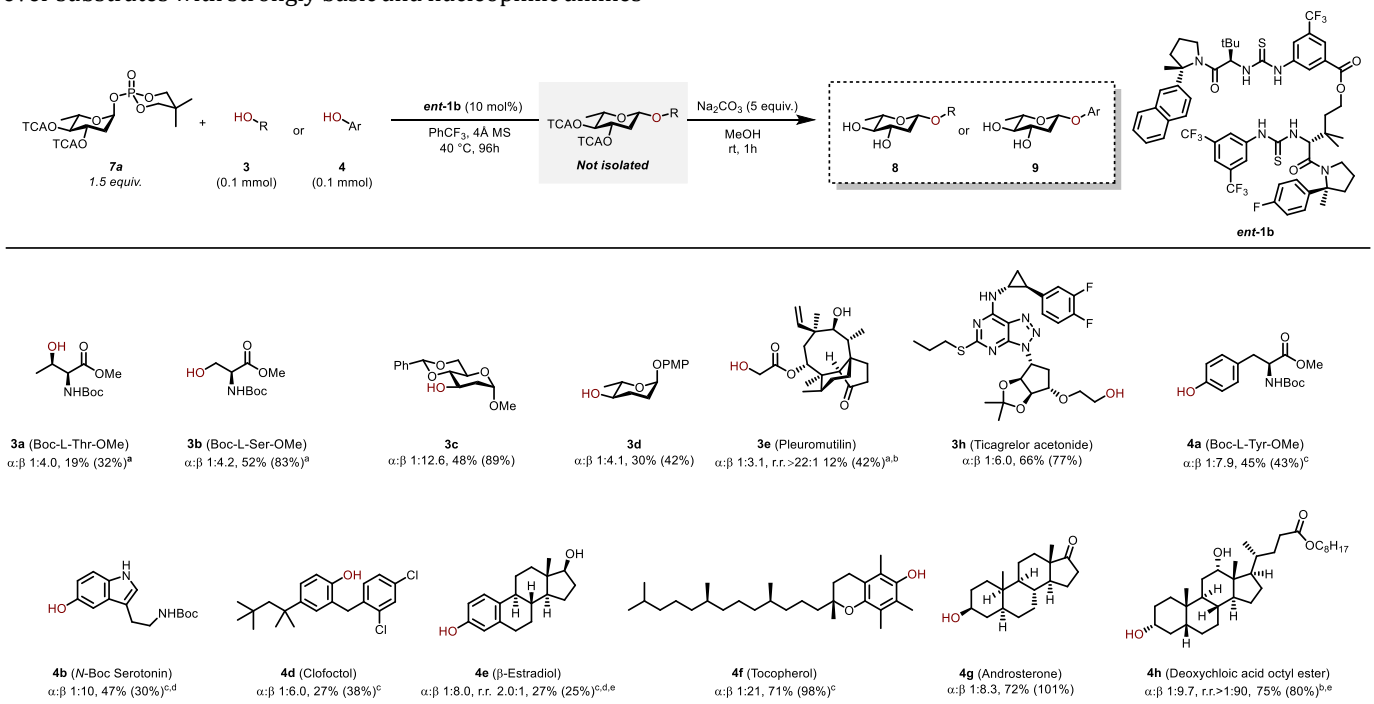

Figure 1. Scope of nucleophiles for 2,6-dideoxyglucosylation. Reactions were performed on a 0.10 mmol scale. Crude yields (in parenthesis) were determined using 1,3,5-trimethoxybenzene as an internal standard. Selectivities were determined by ^{1}H NMR analysis of crude product mixtures. The difference between crude and isolated yield was caused by difficulties with chromatographical separation of methyl glucosides formed during deprotection of the crude glycosylation mixtures. [a]128 h reaction time. [b]Regioselectivity was defined as the measured signal-to-noise ratio of the anomeric signal peak in the crude spectrum as only one regioisomer was detected by ^{1}H-NMR spectroscopy of the crude reaction mixture. [c]With Al_2O_3 (Brockmann Activity I, basic). [d]Crude yield was likely underestimated due to low solubility of product in NMR solvent. [e]1.0 equiv. electrophile.

Previous studies on glycosylation reactions of fully oxygenated α-glycosyl donors promoted by bis-thiourea HBD catalysts have provided evidence that β-selectivity arises from predominant stereoinvertive substitution at the anomeric position.[35–38,41] However, and as noted above, 2-deoxyglycosyl donors are far more prone to undergo epimerization or substitution via S_N1 pathways (**Figure 1B**). To probe the origin of β-selectivity in 2-deoxyglucosylations promoted by **1a**, compound **2a** was prepared in two different levels of anomeric purity (α:β = >20:1 and 3.3:1) and subjected to the optimized reaction conditions for glucosylation of **3a** and **4a**. Very similar β-selectivities were observed regardless of the anomeric purity of **2a** (**Figure 4A**). These results are consistent with product distribution governed by either Curtin-Hammett control over rapidly equilibrating anomers of **2a**, stereospecific reaction via a single anomer of **2a**, or stereoselective nucleophilic substitution through a common reactive intermediate. To distinguish these two scenarios, the glycosylation of **3b** with different anomeric mixtures of **2a** (α:β = >20:1 and 2.5:1) was halted at low conversion and the anomeric composition of unconsumed **2a** in each reaction was determined (**Figure 4B)**. The observed lack of convergence in the anomeric ratio of **2a**, despite a significant degree of product formation, is inconsistent with the rapid equilibration reflective of Curtin-Hammett control. In contrast to the findings depicted in **Figure 4A**, an analogous set of experiments with the 2,6-dideoxyglucosyl phosphate revealed different levels of β-selectivity are obtained using **2b** with different initial levels of anomeric purity (**Figure 2C**). Thus, the two different classes of deoxyglucosyl phosphates appear to undergo substitution with different levels of stereospecificity.

Heterogenous additives play a critical role in the deoxyglucosylation reactions described above. As in previously studied HBD-catalyzed glycosylations with glycosyl phosphates,[35–38] added 4Å molecular sieves are required to sequester the phosphoric acid byproduct formed during the glycosylation. Our present study has further shown that use of basic alumina improves the β-selectivity of phenolic 2-deoxyglucosylations. In the absence of both 4Å molecular sieves and basic alumina, α-enriched 2,6-dideoxyglucosyl phosphate **7a** was observed by NMR to undergo anomerization to approximately 6:1 α:β mixtures, followed by rapid decomposition (**Figure 4D**). Anomerization was not observed in the presence of 4Å molecular sieves, indicating that small amounts of phosphoric acid likely promotes the anomerization process. In addition, the combination of basic alumina and 4Å molecular sieves was found to improve the efficiency of sequestering soluble phosphoric acid (**Figure S24**). We propose that such efficient sequestration is needed for reaching optimal levels of β-selectivity in phenolic glucosylations by suppressing both undesired,

phosphoric acid-catalyzed background reactions as well as *in situ* anomerization to β-phosphates. However, low concentrations of soluble phosphoric acid do not appear to have the same deleterious effect on glucosylations of alcohols.

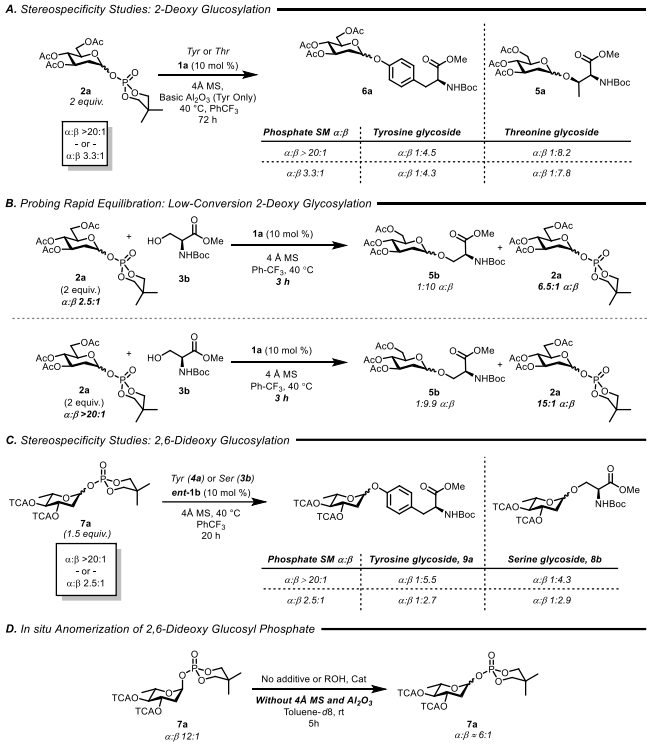

Figure 2. (A) Stereoselectivity of 2-deoxyglucosylation as a function of the α:β ratio of phosphate electrophile. **(B)** Comparison of unconsumed glycosyl phosphate stereopurity as a function of its starting α:β ratio at low conversion. **(C)** Stereoselectivity of 2,6-dideoxyglucosylation as a function of the α:β ratio of phosphate electrophile. **(D)** *In situ* anomerization in absence of 4Å molecular sieves.

In summary, we have developed catalytic and β-selective 2-deoxy and 2,6-dideoxyglucosylations, providing a viable new approach to these longstanding challenges in glycosylation chemistry. The versatility of these methods is demonstrated by the successful synthesis of 2-deoxyglucosides with various nucleophiles featuring both acid- and base-sensitive functionalities. Successful glucosylations with both 2-deoxy and 2,6-dideoxysugars necessitated specific modifications to electrophiles and catalysts. Together with the observation of different degrees of stereospecificity between these two systems, our results underscore the challenges of stereoselective glycosylations with deoxy sugars. We are hopeful that the strategies applied in this work will help spur further advances in selective glycosylation with different classes of deoxysugars.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for catalyst synthesis, substrate synthesis and glycosylations. Procedures and data for mechanistic studies and additional substrates not shown in scope figures.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Li, K.; Cai, J.; Su, Z.; Yang, B.; Liu, Y.; Zhou, X.; Huang, J.; Tao, H. Glycosylated Natural Products From Marine Microbes. *Front. Chem.* **2020**, *7*.

(2) Elshahawi, S. I.; Shaaban, K. A.; Kharel, M. K.; Thorson, J. S. A Comprehensive Review of Glycosylated Bacterial Natural Products. *Chem. Soc. Rev.* **2015**, *44*, 7591–7697.

(3) Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M. α-Selective Organocatalytic Synthesis of 2-Deoxygalactosides. *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155.

(4) 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.

(5) Palo-Nieto, C.; Sau, A.; Williams, R.; Galan, M. C. Cooperative Brønsted Acid-Type Organocatalysis for the Stereoselective Synthesis of Deoxyglycosides. *J. Org. Chem.* **2017**, *82*, 407–414.

(6) 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.

(7) Beaver, M. G.; Woerpel, K. A. Erosion of Stereochemical Control with Increasing Nucleophilicity: O-Glycosylation at the Diffusion Limit. *J. Org. Chem.* **2010**, *75*, 1107–1118.

(8) Crich, D.; Vinogradova, O. On the Influence of the C2–O2 and C3–O3 Bonds in 4,6-O-Benzylidene-Directed β-Mannopyranosylation and α-Glucopyranosylation. *J. Org. Chem.* **2006**, *71*, 8473–8480.

(9) Nielsen, M. M.; Mała, P.; Baldursson, E. Þ.; Pedersen, C. M. Self-Promoted and Stereospecific Formation of N-Glycosides. *Chem. Sci.* **2019**, *10*, 5299–5307.

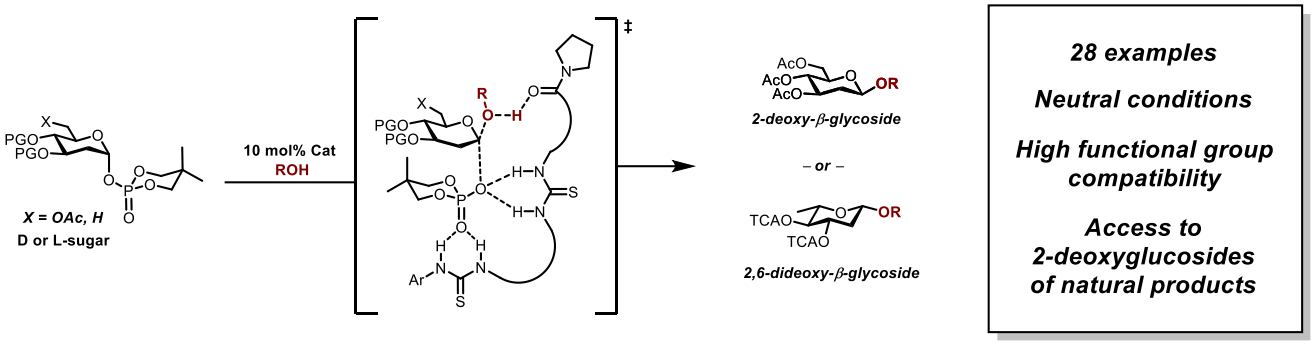
(10) Nielsen, M. M.; Holmstrøm, T.; Pedersen, C. M. Stereoselective O-Glycosylations by Pyrylium Salt Organocatalysis. *Angew. Chem. Int. Ed.* **2022**, *61*, e202115394.

(11) Bennett, C. S.; Galan, M. C. Methods for 2-Deoxyglycoside Synthesis. *Chem. Rev.* **2018**, *118*, 7931–7985.

(12) Issa, J. P.; Lloyd, D.; Steliotes, E.; Bennett, C. S. Reagent Controlled β-Specific Dehydrative Glycosylation Reactions with 2-Deoxy-Sugars. *Org. Lett.* **2013**, *15*, 4170–4173.

(13) Issa, J. P.; Bennett, C. S. A Reagent-Controlled SN2-Glycosylation for the Direct Synthesis of β-Linked 2-Deoxy-Sugars. *J. Am. Chem. Soc.* **2014**, *136*, 5740–5744.
(14) Lloyd, D.; Bennett, C. S. An Improved Approach to the Direct Construction of 2-Deoxy-β-Linked Sugars: Applications to Oligosaccharide Synthesis. *Chem. – Eur. J.* **2018**, *24*, 7610–7614.
(15) Jana, M.; Bennett, C. S. Synthesis of the Non-Reducing Hexasaccharide Fragment of Saccharomicin B. *Org. Lett.* **2018**, *20*, 7598–7602.
(16) Mizia, J. C.; Bennett, C. S. Reagent Controlled Direct Dehydrative Glycosylation with 2-Deoxy Sugars: Construction of the Saquayamycin Z Pentasaccharide. *Org. Lett.* **2019**, *21*, 5922–5927.
(17) Yalamanchili, S.; Lloyd, D.; Bennett, C. S. Synthesis of the Hexasaccharide Fragment of Landomycin A Using a Mild, Reagent-Controlled Approach. *Org. Lett.* **2019**, *21*, 3674–3677.
(18) Liu, X.; Lin, Y.; Liu, A.; Sun, Q.; Sun, H.; Xu, P.; Li, G.; Song, Y.; Xie, W.; Sun, H.; Yu, B.; Li, W. 2-Diphenylphosphinoyl-Acetyl as a Remote Directing Group for the Highly Stereoselective Synthesis of β-Glycosides. *Chin. J. Chem.* **2022**, *40*, 443–452.
(19) Liu, X.; Lin, Y.; Peng, W.; Zhang, Z.; Gao, L.; Zhou, Y.; Song, Z.; Wang, Y.; Xu, P.; Yu, B.; Sun, H.; Xie, W.; Li, W. Direct Synthesis of 2,6-Dideoxy-β-Glycosides and β-Rhamnosides with a Stereodirecting 2-(Diphenylphosphinoyl)Acetyl Group. *Angew. Chem. Int. Ed.* **2022**, *61*, e202206128.
(20) Deng, L.-F.; Wang, Y.; Xu, S.; Shen, A.; Zhu, H.; Zhang, S.; Zhang, X.; Niu, D. Palladium Catalysis Enables Cross-Coupling–like SN2-Glycosylation of Phenols. *Science* **2023**, *382*, 928–935.
(21) Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. Umpolung Reactivity in the Stereoselective Synthesis of S-Linked 2-Deoxyglycosides. *Angew. Chem. Int. Ed.* **2013**, *52*, 8012–8016.
(22) Baryal, K. N.; Zhu, J. Stereoselective Synthesis of S-Linked Hexasaccharide of Landomycin A via Umpolung S-Glycosylation. *Org. Lett.* **2015**, *17*, 4530–4533.
(23) Hoang, K. M.; Lees, N. R.; Herzon, S. B. Programmable Synthesis of 2-Deoxyglycosides. *J. Am. Chem. Soc.* **2019**, *141*, 8098–8103.
(24) Hoang, K. M.; Lees, N. R.; Herzon, S. B. General Method for the Synthesis of α- or β-Deoxyaminoglycosides Bearing Basic Nitrogen. *J. Am. Chem. Soc.* **2021**, *143*, 2777–2783.
(25) Roush, W. R.; Bennett, C. E. A Highly Stereoselective Synthesis of 2-Deoxy-β-Glycosides Using 2-Deoxy-2-Iodo-Glucopyranosyl Acetate Donors. *J. Am. Chem. Soc.* **1999**, *121*, 3541–3542.
(26) Roush, W. R.; Narayan, S. 2-Deoxy-2-Iodo-α-Mannopyranosyl and -Talopyranosyl Acetates: Highly Stereoselective Glycosyl Donors for the Synthesis of 2-Deoxy-α-Glycosides. *Org. Lett.* **1999**, *1*, 899–902.
(27) Roush, W. R.; Bennett, C. E. A Highly Stereoselective Synthesis of the Landomycin A Hexasaccharide Unit. *J. Am. Chem. Soc.* **2000**, *122*, 6124–6125.
(28) Chong, P. Y.; Roush, W. R. Concerning the Origin of the High β-Selectivity of Glycosidation Reactions of 2-Deoxy-2-Iodo-Glucopyranosyl Trichloroacetimidates. *Org. Lett.* **2002**, *4*, 4523–4526.
(29) Manhas, S.; Taylor, M. S. Dehydrative Glycosidations of 2-Deoxysugar Derivatives Catalyzed by an Arylboronic Ester. *Carbohydr. Res.* **2018**, *470*, 42–49.
(30) Li, T.-R.; Huck, F.; Piccini, G.; Tiefenbacher, K. Mimicry of the Proton Wire Mechanism of Enzymes inside a Supramolecular Capsule Enables β-Selective O-Glycosylations. *Nat. Chem.* **2022**, *14*, 985–994.
(31) Hashimoto, S.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. An Attempt at the Direct Construction of 2-Deoxy-β-Glycosidic Linkages Capitalizing on 2-Deoxyglycopyranosyl Diethyl Phosphites as Glycosyl Donors. *Synlett* **1995**, 1271–1273.
(32) Guo, Y.; Sulikowski, G. A. Synthesis of the Hexasaccharide Fragment of Landomycin A: Application of Glycosyl Tetrazoles and Phosphites in the Synthesis of a Deoxyoligosaccharide. *J. Am. Chem. Soc.* **1998**, *120*, 1392–1397.
(33) Pongdee, R.; Wu, B.; Sulikowski, G. A. One-Pot Synthesis of 2-Deoxy-β-Oligosaccharides. *Org. Lett.* **2001**, *3*, 3523–3525.
(34) Kaneko, M.; Herzon, S. B. Scope and Limitations of 2-Deoxy- and 2,6-Dideoxyglycosyl Bromides as Donors for the Synthesis of β-2-Deoxy- and β-2,6-Dideoxyglycosides. *Org. Lett.* **2014**, *16*, 2776–2779.
(35) Levi, S. M.; Li, Q.; Rötheli, A. R.; Jacobsen, E. N. Catalytic Activation of Glycosyl Phosphates for Stereoselective Coupling Reactions. *Proc. Natl. Acad. Sci.* **2019**, *116*, 35–39.
(36) Mayfield, A. B.; Metternich, J. B.; Trotta, A. H.; Jacobsen, E. N. Stereospecific Furanosylations Catalyzed by Bis-Thiourea Hydrogen-Bond Donors. *J. Am. Chem. Soc.* **2020**, *142*, 4061–4069.
(37) Li, Q.; Levi, S. M.; Jacobsen, E. N. Highly Selective β-Mannosylations and β-Rhamnosylations Catalyzed by Bis-Thiourea. *J. Am. Chem. Soc.* **2020**, *142*, 11865–11872.
(38) Li, Q.; Levi, S. M.; Wagen, C. C.; Wendlandt, A. E.; Jacobsen, E. N. Site-Selective, Stereocontrolled Glycosylation of Minimally Protected Sugars. *Nature* **2022**, *608*, 74–79.
(39) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, Bert. Armed and Disarmed N-Pentenyl Glycosides in Saccharide Couplings Leading to Oligosaccharides. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.
(40) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. Armed/Disarmed Effects in Glycosyl Donors: Rationalization and Sidetracking. *J. Org. Chem.* **1990**, *55*, 6068–6070.
(41) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. Macrocyclic Bis-Thioureas Catalyze Stereospecific Glycosylation Reactions. *Science* **2017**, *355*, 162–166.
(42) Ferrier, R. J.; Overend, W. G.; Ryan, A. E. 712. The Reaction between 3,4,6-Tri-O-Acetyl-D-Glucal and p-Nitrophenol. *J. Chem. Soc. Resumed* **1962**, No. 0, 3667–3670.
(43) Ferrier, R. J.; Prasad, N. Unsaturated Carbohydrates. Part IX. Synthesis of 2,3-Dideoxy-α-D-Erythro-Hex-2-Enopyranosides from Tri-O-Acetyl-D-Glucal. *J. Chem. Soc. C Org.* **1969**, 570–575.
(44) Jiang, J.; Biggins, J. B.; Thorson, J. S. A General Enzymatic Method for the Synthesis of Natural and "Unnatural" UDP- and TDP-Nucleotide Sugars. *J. Am. Chem. Soc.* **2000**, *122*, 6803–6804.
(45) O'Neill, P. M.; Scheinmann, F.; Stachulski, A. V.; Maggs, J. L.; Park, B. K. Efficient Preparations of the β-Glucuronides of Dihydroartemisinin and Structural Confirmation of the Human Glucuronide Metabolite. *J. Med. Chem.* **2001**, *44*, 1467–1470.

Hydrogen-bond-donor-catalyzed, β-selective 2-deoxy- and 2,6-dideoxyglucosylation



28 examples

Neutral conditions

High functional group compatibility

Access to 2-deoxyglucosides of natural products