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

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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-nitroglactals 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-chitotriptymycin, tunicamycin V, ribostamycin, 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 α -Glycosylation of 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-galactal (2a) with Methyl-2,3-*O*-isopropylidene-D-ribofuranoside (3a)^a

^aIsolated 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 ¹H 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-nitroalactals. 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-nitroalactal 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-nitroglucal- 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-Nitroglucal **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

^aThe 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. ^bIsolated 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		 4t (71%) α only 4t' (8%) α only	79
2		 4u (64%) α only 4u' (5%) α only	69
3		 4v (66%) α only 4v' (6%) α only	72
4		 4w α only	84
5		 4x α only	63

^aAll of the reactions afforded the α -stereoisomer. ^bIsolated yields. ^cReaction 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 phosphazanium 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 co-workers,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 non-reversible 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-nitroglucal substrates. The computational results agree with our observations from ^1H NMR experiments (Supporting Information, Figures S3 and S4). The H1 and H3 peaks of 2-nitroglactal (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 $\text{P}_4\text{-}t\text{-Bu}$ and alcohol were added to 2-nitroglactal (2a). Lower electron density is experienced by C1 and C3 carbons when the phosphazanium-alkoxide ion pair forms.

Afterward, we attempted to explore the donor scope with both 2-nitroglactal and glucal derivatives having varying protecting groups. Pleasingly, this glycosylation method proceeded smoothly with a range of 2-nitroglactal (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-nitroglactal, 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 $\text{P}_4\text{-}t\text{-Bu}$

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-phosphazanium 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 phosphazanium 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 phosphazanium 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 phosphazanium 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 P₄-*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 P₄-*t*-Bu. A wide range of 2-nitroalactals 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-nitroalactals 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 (P₄-*t*-BuH⁺RO[−]) between the P₄-*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 P₄-*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)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

DMAP, 4-dimethylaminopyridine; PPY, 2-phenylpyridine

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