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Highly Stereoselective Synthesis of 2-Azido-2-Deoxyglycosides via Gold-Catalyzed S_N2 Glycosylation

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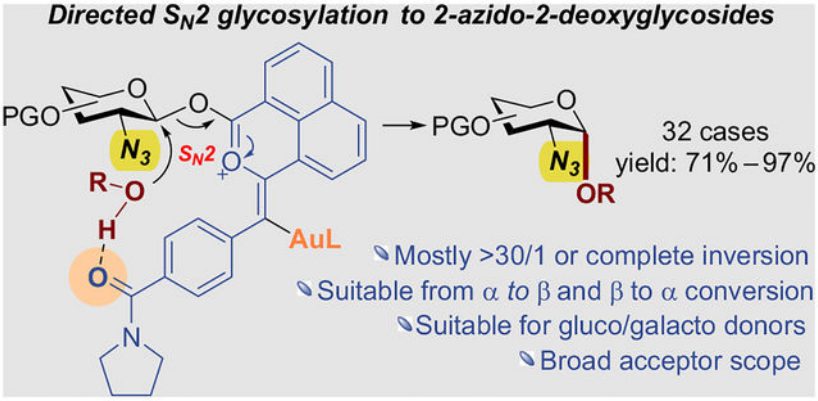
Abstract

Highly stereoselective synthesis of 2-azido-2-deoxyglucosides and 2-azido-2-deoxygalactosides is achieved via a gold-catalyzed S_N2 glycosylation. The glycosyl donors feature a designed 1-naphthoate leaving group containing an amide group. Upon gold activation of the leaving group, the amide group is optimally positioned to direct an S_N2 attack by an acceptor via H-bonding interaction. Both 2-azido-2-deoxyglucosyl/galactosyl donor anomers can undergo stereoinversion at the anomeric position, affording the opposite anomeric glycoside products with excellent levels of stereoselectivity or stereospecificity and in mostly excellent yields. This S_N2 glycosylation accommodates a broad range of acceptors. The utility of this chemistry is demonstrated in the synthesis of a trisaccharide featuring three 1,2-*cis*-2-azido-2-deoxyglycosidic linkages.

Graphical Abstract



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Supporting Information

Supporting Information is available and includes experimental procedures and NMR spectra.

Conflict of Interest

The authors declare no competing financial interest.

Keywords

aminosugar; glycosylation; 1,2-cis-glycosidic linkage; gold catalysis; directing group

Introduction

2-Amido/amino-2-deoxy-D-glycopyranosyl units are found in many biologically important poly-/oligasaccharides, glycoconjugates, and glyco-based antibiotics and medicines (see Scheme 1a for examples).[1–5] Their efficient assembly with high levels of anomeric stereoselectivity[6–11] is essential to glycoscience research and the development of glycomedicine. 1,2-*trans*-2-amido/amino-2-deoxyglycosides can be reliably synthesized through the neighboring group participation of a C(2)-amido/imido/alkoxycarbonylamino group, albeit with drawbacks (Scheme 1b).[10,12–14] In comparison, the stereoselective construction of 1,2-*cis*-counterparts remains challenging.[15] In the 1970s, Paulsen et al.[16] and Lemieux and Ratcliffe[17] pioneered the use of 2-azido-2-deoxyglycosyl donors for stereoselective 1,2-*cis* glycosylation. Despite the 2-azido group serving as an ideal masked amino group due to its relative stability, nonparticipating property, and ease of transformation to the amino/acetamido group, the glycosylation reactions exhibit mostly moderate to poor 1,2-*cis* selectivity[18–20] and low/moderate yields.[21,22] Several innovative solutions have since been documented, including the use of ring-fused 2,3-oxazolidinone thioglycoside donors,[23–25] the Lewis/Brønsted acid-catalyzed α-glycosylation of benzylidene-protected 2-aminoglycosyl trihaloacetimidate donors,[26–29] and the employment of steric shielding or remote participation,[30] but they can be limited in scope,[30,31] afford moderate yields[25] due to side reactions,[31,32] and/or exhibit moderate/varied α/β selectivity. As such, considering the biological significance of aminoglycosides, there is still a great need for developing high-yielding and highly stereoselective synthesis of 1,2-*cis*-2-amido/amino-2-deoxyglycosides that applies to a broad range of acceptors.

In 2021, we published a study introducing an S_N2 glycosylation strategy that employs a directing-group-on-leaving-group strategy (DGLG)[33,34] based on Yu's glycosyl *ortho*-alkynylbenzoate system.[35,36] Recently, we reported that a second-gen approach improved upon the original work by replacing the oxazole-functionalized *O*-alkynylbenzoate with a synthetically much more accessible amide-functionalized 1-naphthoate in the glycosyl donor, which exhibited enhanced S_N2 characteristics in the construction of both 1,2-*cis* and 1,2-*trans* glycosidic linkages as well as both 2-deoxyglucoside anomers.[37,38] Based on these results, we speculated that this DGLG strategy could effectively address the long-standing challenges of achieving high stereoselective glycosylation with 2-azido-2-deoxyglycosyl donors. In this work, we disclose the synthesis of 2-azido-2-deoxyglucosides and 2-azido-2-deoxygalactosides based on this consideration. The glycosylation method offers several desirable features, including mild reaction conditions, accommodation of a wide range of acceptors, high yielding, and high levels of S_N2 characteristics (Scheme 1c). Both 1–2-*cis*- and 1,2-*trans*-2-azido-2-deoxyglycosides can be synthesized with high efficiency and high to excellent stereoselectivity.

Experimental Section

General procedure for gold-catalyzed S_N2 glycosylation

A donor (0.06 mmol), an acceptor (2.0 equiv, 0.12 mmol), and 100 mg grounded white drierite were added sequentially to a vial. Trifluorotoluene ($PhCF_3$, 0.45 mL) was then injected. The vial was capped with an open-top screw cap with a silicon liner, sealed with parafilm, shaken, and cooled to the corresponding temperature. Meanwhile, a $PhCF_3$ solution (0.3 mL) of $(PhO)_3PAuCl$ (0.1 equiv, 0.006 mmol, 3.26 mg), $AgNTf_2$ (0.1 equiv, 0.006 mmol, 2.33 mg), and $HNTf_2$ (0.2 equiv, 0.012 mmol, 3.37 mg) was injected into the vial. The reaction progress was monitored by thin-layer chromatography. Upon completion, a dichloromethane (DCM; 0.3 mL) solution of tetrabutylammonium chloride (1.0 equiv, 0.06 mmol, 16.7 mg) and *N*,*N*-diisopropylethylamine (1.0 equiv, 0.06 mmol, 7.8 mg) was used to quench the reaction, and the reaction mixture was filtered through a Celite pad before column chromatography.

Results and Discussion

The desired 2-azido-2-deoxyglycosyl 1-naphthoate donors of type **1** (e.g., **1a** in Table 1) were readily prepared in two steps—alkylation and Sonogashira coupling—from the corresponding 2-azido-2-deoxyglycosyl halides[39–41] and commercially available 8-bromo-1-naphthoic acid (Scheme 2, see the Supporting Information for details). The two-step yields range from 70% to 85%.

We initiated the conditions study by examining the reaction between 2-azido-2-deoxy-D-glucosyl 1-naphthoate donor 1a and the methyl α-D-glycopyranoside A1—a primary acceptor. First, the reaction was conducted using 1.2 equiv of A1 in the presence of 10 mol % IMesAuCl/$AgNTf_2$ and 20 mol % $HNTf_2$, in $PhCF_3$ (0.08 M) at 0 °C. Within 3 h, the reaction was complete, yielding methyl (3,4,6-tri-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **2a** in 75% nuclear magnetic resonance (NMR) yield, with the con-comitant generation of the byproduct **3**.[37] The reaction showed a favorable α/β ratio of 19/1 (Table 1, entry 1). Lowering the reaction temperature to −20 °C and prolonging the reaction time resulted in an improved α/β ratio of >30/1 (Table 1, entry 2). More acidic gold catalysts such as Ph_3PAu^+ and $(PhO)_3PAu^+$ improved the yield slightly and sped up the reaction, notably in the latter case (Table 1, entries 3 and 4). By increasing the amount of **A1** to two equivalents, the reaction yield was substantially improved to 94% while maintaining the excellent α selectivity (entry 5). In the absence of 20% $HNTf_2$, the reaction proceeded much more slowly, requiring 24 h to reach complete consumption of **1a**, and the yield was a lower 76% (entry 6). This outcome is consistent with our previous conclusion[37] as well as that of Zhu and Yu,[42] that is, a strong acid additive facilitates protodeauration and hence catalyst regeneration, there-by speeding up the reaction. A similarly sluggish and lower-yielding reaction was observed when the reaction solvent was DCM (entry 7). This solvent effect was previously observed[37] and rationalized to be due to the much higher solubility of the interfering byproduct **3** in DCM than in $PhCF_3$. For the more hindered and hence more challenging secondary acceptor **A2**, similar trends were observed in the stereoselective formation of the diglucoside product **2b**

under these varied conditions (entries 8–12). Moreover, the reactions exhibited complete α-selectivity, and by using two equivalents of the acceptor, the yield was 85% (entry 12).

With the optimized conditions in Table 1, entries **5** and **12** in hand, we further examined the reaction of donor **1a** with a range of additional acceptors. As shown in Table 2, remarkably, all the cases, i.e., **2c**–**2l** exhibited exclusive α selectivities. For these cases employing primary acceptors (**2f**, **2g**, and **2k**), the reaction yields are above 90%, as is the case in **2a**. For the cases using challenging secondary acceptors (**2d**, **2e**, **2i**, and **2l**), the reaction yields (71–85%) are comparatively lower. On the other hand, both the yields of **2h** and **2j** were 94%. With *tert*-butanol as the acceptor, the product was obtained in 84% yield (**2c**). The acceptors included nonsugar alcohols *tert*-butanol (**2c**), L-menthol (**2d**) and cholesterol (**2e**), primary glycosyl acceptors derived from galactose (**2f**), glucose (**2g**), and arabinose (**2k**), and secondary acceptors derived from glucose (**2h**, **2i**), rhamnose (**2j**), and xylose (**2l**). Of note is that the benzoyl-protecting groups in the cases of **2g** and **2h** did not affect the outstanding reaction outcomes, suggesting that these acceptors are sufficiently nucleophilic despite inductive deactivation.

We also prepared the 2-azido-2-deoxy donor variants of **1a** with the benzyl groups at 6-*O* and 4-*O* positions replaced by acetyl groups, respectively. As shown in the cases of **2m**–**2q**, the glycosylation reactions again exhibited exclusive α-selectivities with both primary and secondary glycoside acceptors, and the reaction yields ranged from 76% to 94%.

We then applied our methodology to the synthesis of 1,2-*cis*-2-azido-2-deoxygalactosides. However, the reactions of per-benzylated 2-azido-2-deoxy-β-D-galactopyranosyl donors **1b** were surprisingly slow at −20 °C. Elevating the reaction temperature to 0 °C led to a complete reaction in 3–24 h. As shown in Table 3a, the glycosylation reactions proceeded with mostly excellent levels of stereoinversion, affording 1,2-*cis*-2-azido-2-deoxygalactosides **2r**, **2s**, and **2u**–**2y** exclusively or with >20:1 α/β selectivities and in mostly excellent yields. The exception was the case of **2t** with an α/β ratio of 12/1. Similar to the 2-azido-2-deoxyglucoside cases, a variety of acceptors including secondary (**2u**–**2w** and **2y**) and electronically deactivated (**2t** and **2v**) were readily tolerated. However, this strategy is not suitable for the synthesis of β−2-azido-2-deoxymannosides.

In addition to these conversions of β-donors to 1,2-*cis*-α−2-azido-2-deoxyglycosides, we wondered whether this strategy would permit the stereoselective synthesis of 1,2-*trans*-2-azido-2-deoxyglycosides[43–45] by using the corresponding 1,2-*cis*-2-azido-2-deoxy donors. Despite the synthesis of 1,2-*trans*-2-amido-2-deoxyglycosides, as discussed previously, can be achieved reliably via neighboring group participation, the multiple steps needed for converting a suitable participating group to the often-desired acetamido and the harsh reaction conditions employed therein often lead to diminished synthetic efficiency. The stereoselective synthesis of 1,2-*trans*-2-azido-2-deoxyglycosides via this S_N2 glycosylation strategy represents a valuable and unified approach to stereoselective access to both anomers of 2-azido-2-deoxyglycosides. As shown in Table 3b, the 2-azido-2-deoxymannoside **2z** was formed with exclusive stereoinversion and in 78% yield. The α-counterpart of glucosyl donor **1a** was prepared with an α/β ratio of 15/1. As shown in Table 3c, its reaction with the primary acceptor **A1** resulted in near inversion of the α/β ratio of the product

2aa at 1:16, suggesting high levels of S_N2 glycosylation. With the challenging **A2** as the acceptor, the α/β ratio of the product **2ab** is 1/8, which amounts to an estimated α/β ratio of 1:18 if the pure α-donor is used. In addition, its reaction with an arabinose-derived acceptor afforded the product **2ac** in 95% yield and with an α/β ratio of 1/12. In the cases of the α-galactosyl donor (α/β = 22/1, Table 3d), the reactions with primary acceptors were also highly stereoinvertive, affording **2ad**–**2af** in excellent yields and with ≥20:1 β/α selectivities.

To demonstrate the synthetic utility of this chemistry, we set out to prepare the synthetically challenging trisazidoglucoside **6** containing three 1,2-*cis*-2-azido-2-deoxy glycosidic linkages. The pseudoiterative synthesis sequence is shown in Scheme 3: the first such glycosidic linkage in **4** was formed with exclusive α-selectivity and in 92% overall yield upon coupling the 6-*O*-acetyl donor **1c** with pent-4-en-1-ol (2.0 equiv), followed by basic methanolysis. Subsequent glycosylations using the 4-*O*-acetyl donor **1d** and the per-*O*-benzylated donor **1a**, respectively, again exhibited complete anomeric configuration inversion and high reaction efficiency. In both cases, two equivalents of the acceptor (i.e., **4** or **5**) were employed. After the reaction, the excess acceptor in the case of **5** was recovered.

The high level of stereoinversions observed in most of the cases, that is, the conversion of β donors to α glycosides and vice versa, is consistent with the directed S_N2 glycosylation mechanism. As shown in Scheme 4a, the directed S_N2 reaction of the cyclized and hence activated intermediate β-**A**-**Au** generated from a β-donor (i.e., β−**1**) should afford the stereo-inverted 2-azido-2-deoxyglycoside product α−**2**. A minor S_N1 pathway leading to the oxocarbenium intermediate **B** may occur, which is trapped by the stoichiometric and more nucleophilic amide moiety from species bearing this functional group to form the trapped intermediate α-**C**-**Au**/α-**C**. Intermediate **C** favors the α configuration due to the anomeric effect. In addition, α-**C**-**Au** can be generated directly from β-**A**-**Au** via intramolecular stereoinvertive amide attack. In the presence of a good nucleophile, for example, a primary alcohol donor, this intermediate undergoes further glycosylation to deliver β−**2**. In contrast, with a poor nucleophilic acceptor such as a secondary alcohol, this glycosylation does not occur. Consequently, when using β donors, employing a primary alcohol acceptor results in compromised α/β selectivity but increased yield. When reacting with secondary alcohols, complete stereo inversion is maintained, but the yield can be compromised. In the case of **2t**, the α/β ratio of 12/1 is much lower than that of **2r**. We attributed the moderate stereoselectivity to the decreased nucleophilicity of the tri-*O*-benzoyl-protected acceptor, which leads to increased formation of α-**C**-**Au**/α-**C**. The acceptor, despite being inductively deactivated, is a primary alcohol and hence sterically viable to attack α-**C**-**Au**/α-**C**. As such, a significant amount of β−**2t** is formed.

We noticed that the β/α ratio of **2aa** (16/1) is higher than that of **2ab**. The former is formed from an α-glucosyl naphthoate donor and the primary acceptor **A1**, and the latter is formed from the same donor and the secondary acceptor **A2**. These results are contrary to the trend observed using β-donors and not consistent with the rationale put forth in Scheme 4a but can be rationalized in Scheme 4b. In this case, β-**C**-**Au** was generated from the cyclized intermediate α-**C**-**Au** via intramolecular stereoinvertive amide attack and should exhibit

increased electrophilicity compared to its α-counterpart. As a result, it can glycosylate secondary acceptors. In comparison to using **A1** as the acceptor, the glycosylation of **A2** led to the increased formation of β-**C-Au** due to a comparably slow S_N2 process. As such, more α−**2** can be formed via β-**C-Au**, resulting in a lower β/α ratio in the case of **2ab**.

Conclusion

In summary, a gold-catalyzed S_N2 glycosylation method was achieved for highly stereoselective synthesis of 2-azido-2-deoxyglucosides and 2-azido-2-deoxygalactosides. This method employs a 1-naphthoate leaving group featuring an amide directing group. Upon gold activation of the leaving group, the amide is optimally positioned to direct an S_N2 attack by an acceptor via H-bonding interaction. From 1,2-*trans*-2-azido-2-deoxyglycosyl donors, this chemistry provides highly stereoselective and efficient construction of 1,2-*cis*-2-azido-2-deoxyglycosidic linkages. In most cases, exclusive 1,2-*cis* stereochemistry is achieved. This approach is also applicable to the stereoselective construction of 1,2-*trans*-2-azido-2-deoxyglycosides. A broad range of acceptors is allowed. The utility of this chemistry was demonstrated in the synthesis of a trisaccharide featuring three 1,2-*cis*-2-azido-2-deoxyglycosidic linkages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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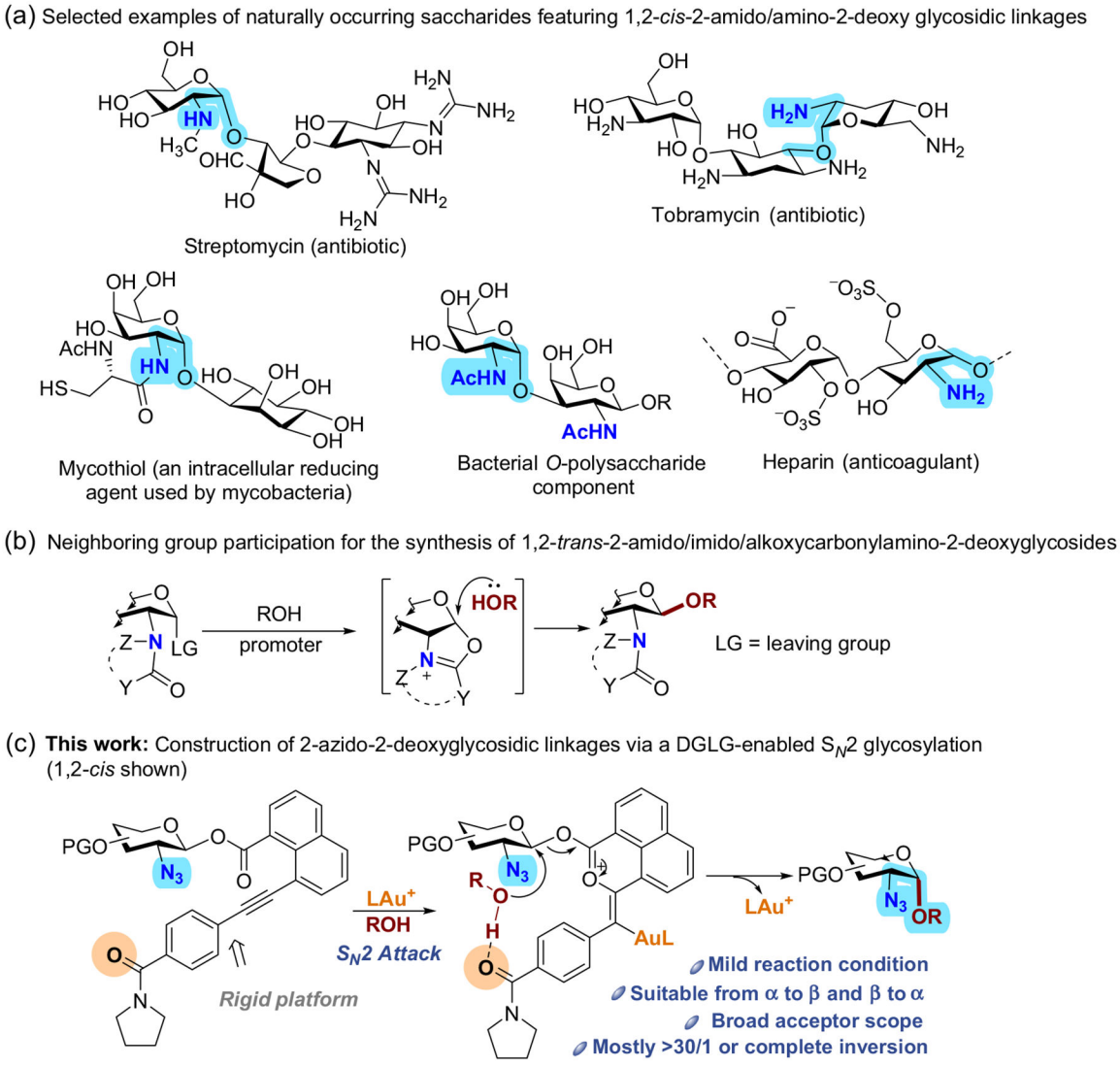
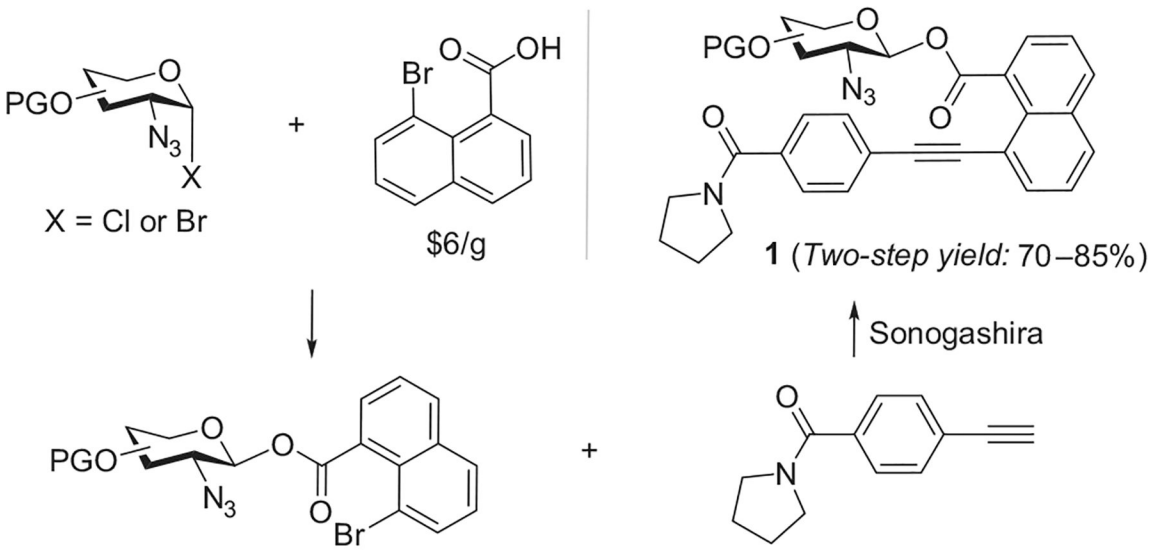
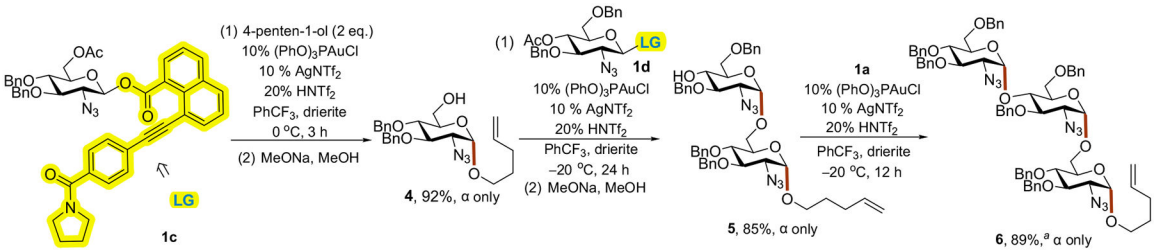


Scheme 1 |.
Background of this work.

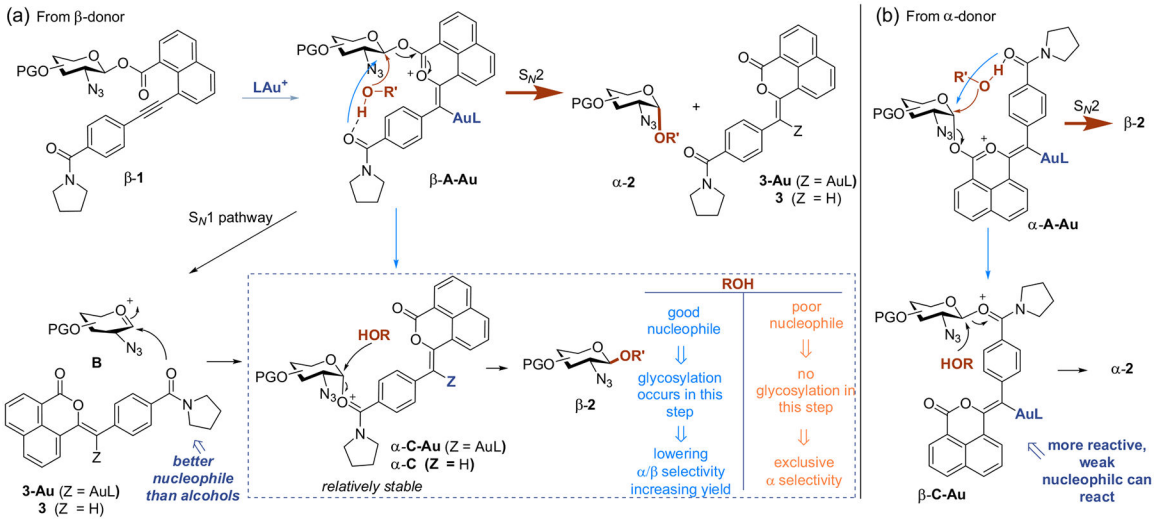


Scheme 2 |.
Synthesis of 2-azido-2-deoxyglycosyl 1-naphthoate donors.



Scheme 3 |.

Synthesis of the trisazidoaccharide 6. Two equivalents of acceptors were used, and the yields were calculated based on the donor. [a]1.0 equiv **5** was recovered after the reaction.

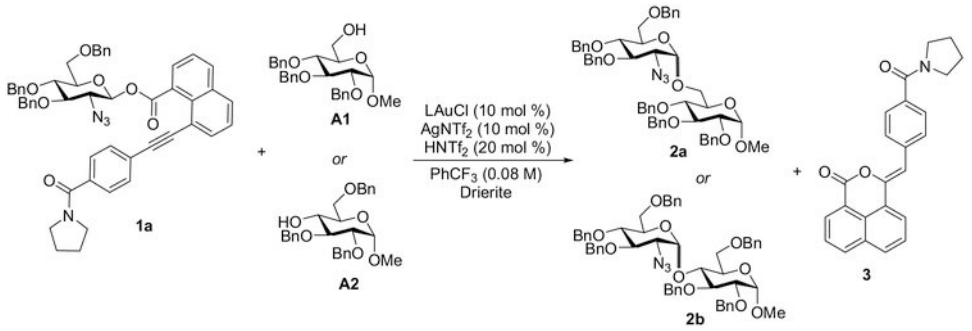


Scheme 4 |.

Proposed mechanism rationalizing the observed selectivity.

Table 1 |

Conditions Optimizations[a]



Entry	Acceptor	Ligand	Temp./time	Yield[b] (a/β)[c]
1	1.2 equiv **A1**	IMes	0 °C/3 h	75% (19/1)
2	1.2 equiv **A1**	IMes	−20 °C/24 h	78% (>30/1)
3	1.2 equiv **A1**	Ph_3P	−20 °C/12 h	80% (>30/1)
4	1.2 equiv **A1**	$P(OPh)_3$	−20 °C/8 h	84% (>30/1)
5	2.0 equiv **A1**	$P(OPh)_3$	−20 °C/5 h	94% (>30/1)
6[d]	2.0 equiv **A1**	$P(OPh)_3$	−20 °C/24 h	76% (>30/1)
7[e]	2.0 equiv **A1**	$P(OPh)_3$	−20 °C/24 h	74% (>30/1)
8	1.2 equiv **A2**	IMes	0 °C/5 h	70% (α only)
9	1.2 equiv **A2**	IMes	−20 °C/24 h	72% (α only)
10	1.2 equiv **A2**	Ph_3P	−20 °C/12 h	70% (α only)
11	1.2 equiv **A2**	$P(OPh)_3$	−20 °C 9 h	77% (α only)
12	2.0 equiv **A2**	$P(OPh)_3$	−20 °C/6 h	85% (α only)

[a]Reaction was stirred in a cooling bath before being quenched by 1.2 equiv $^{n}Bu_4NCl$ and *N,N*-diisopropylethylamine.

[b]The yield was based on the donor.

[c]Anomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture.

[d]Without $HNTf_2$.

[e] $\varepsilon_{DCM\ (0.08\ M)}$ as the solvent.

Table 2 |

Reaction Scope with 2-Azido-2-Deoxy-β-d-Glucopyranosyl Donors. Reaction Conditions: Donor 1 (0.06 mmol), Acceptor (0.12 mmol), $(PhO)_3PAuCl$/$AgNTf_2$ (0.006 mmol), $HNTf_2$ (0.012 mmol), $PhCF_3$ (0.08 M), Drierite, −20 °C

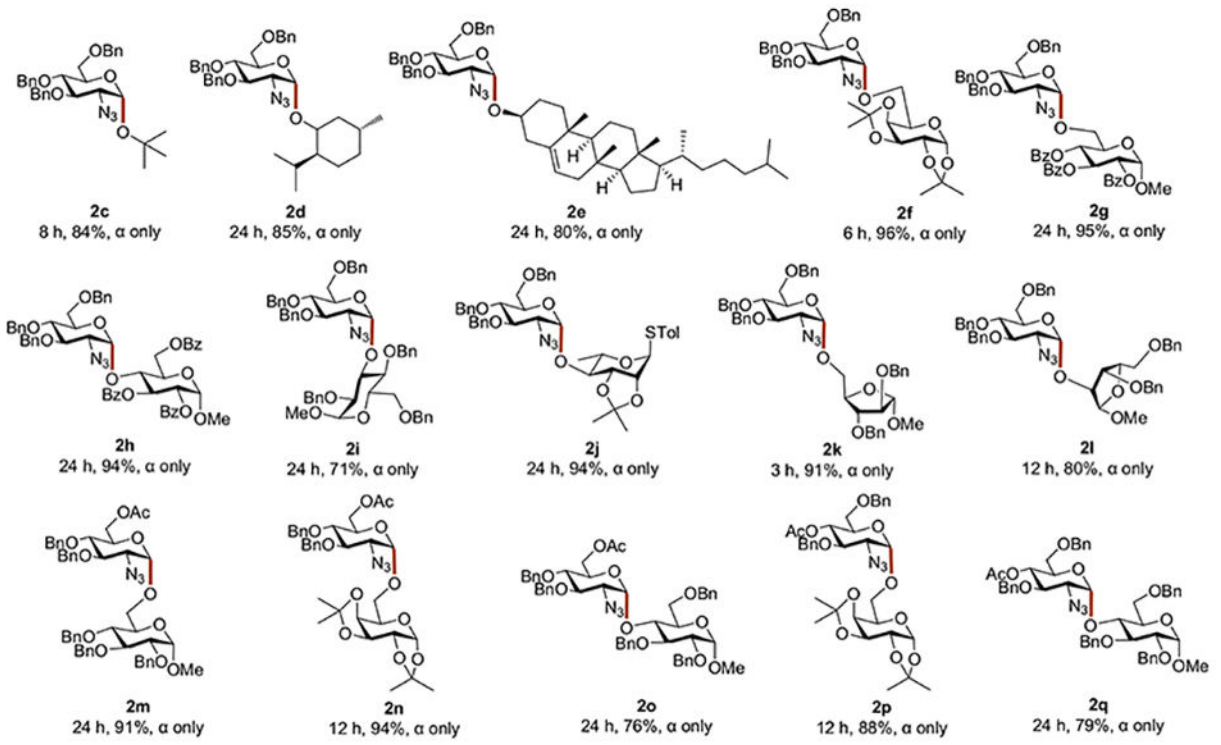
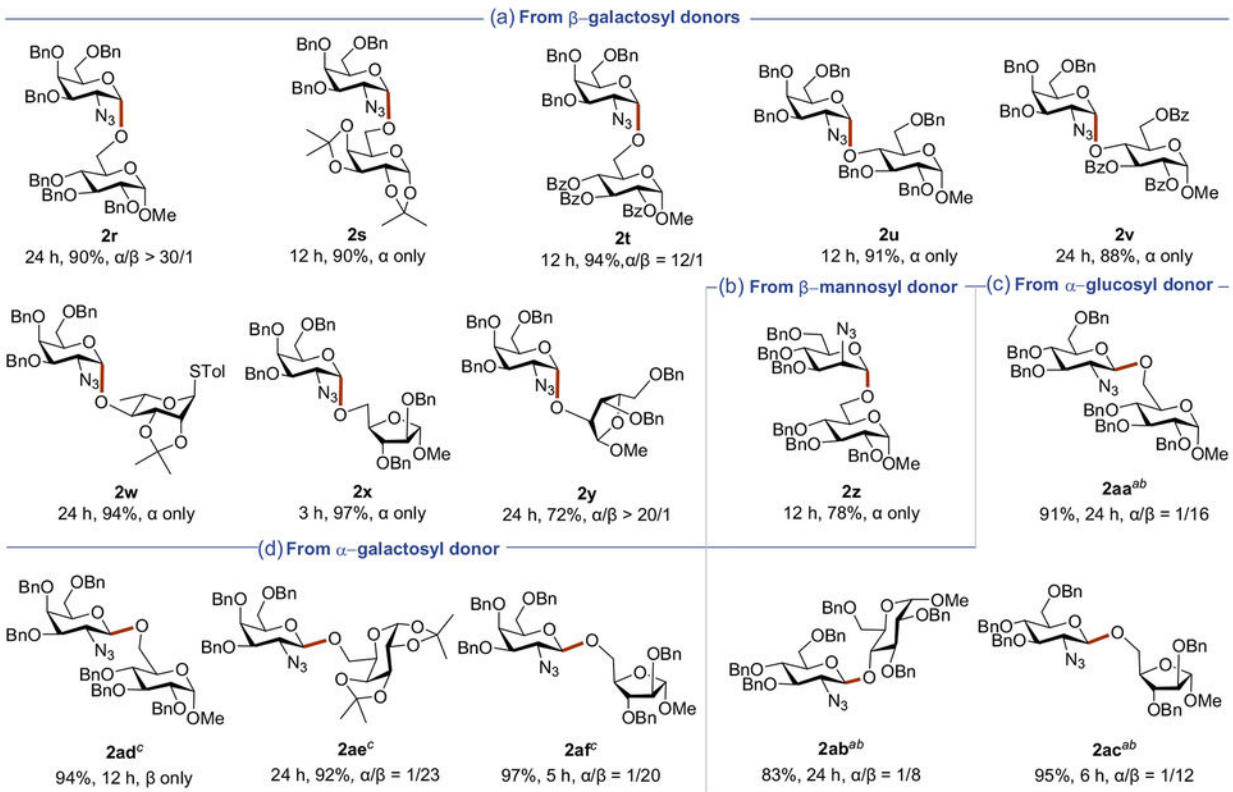


Table 3 |

Reaction Scope with Additional Donors. Reaction Conditions: Donor 1 (0.06 mmol), Acceptor (0.12 mmol), $(PhO)_3PAuCl/AgNTf_2$ (0.006 mmol), $HNTf_2$ (0.012 mmol), $PhCF_3$ (0.08 M), Drierite, 0 °C.



[a] Starting from the donor with a 15/1 α/β ratio.

[b] −20 °C.

[c] Starting from the donor with a 22/1 α/β ratio.