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Directed S_N2 Glycosylation Employing an Amide-Functionalized 1-Naphthoate Platform Featuring a Selectivity-Safeguarding Mechanism

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Abstract

This work implements a catalytic S_N2 glycosylation by employing an amide-functionalized 1-naphthoate platform as a latent glycosyl leaving group. Upon gold-catalyzed activation, the amide group enables the S_N2 process by directing the attack of the glycosyl acceptor via H-bonding interaction, which results in stereoinversion at the anomeric center. Unique in this approach is that the amide group also enables a novel safeguarding mechanism by trapping oxocarbenium intermediates and, hence, minimizing stereorandom S_N1 processes. The strategy is applicable to the synthesis of a broad range of glycosides with high to excellent levels of stereoinversion

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ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c02792.
Detailed experimental procedures, mechanistic studies, X-ray structure, and NMR spectra (PDF)

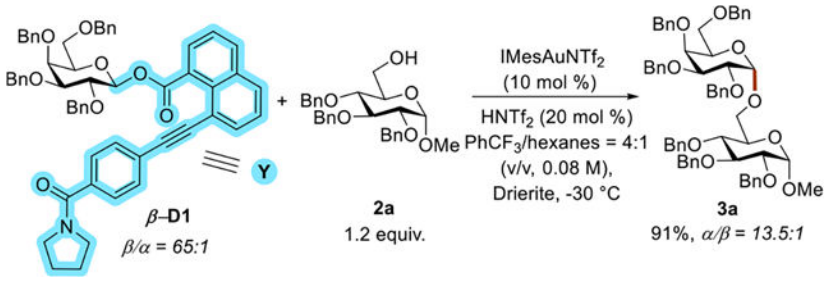
Accession Codes
CCDC 2234653 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

from anomerically pure/enriched glycosyl donors. These reactions are generally high-yielding, and their applications in the synthesis of challenging 1,2-*cis*-linkage-rich oligosaccharides are demonstrated.

Glycans and their conjugated forms, including peptidoglycans, glycoproteins, glycopeptides, glycolipids, and lipopolysaccharides, play key roles in a variety of vital biological processes and many pathological events, including signal transduction, fertilization, metathesis, cell–cell adhesion, viral infection, and immune responses.[1–3] Chemical synthesis of these complex carbohydrate structures hinges on the stereoselective construction of glycosidic bonds.[1,4,5] A variety of creative strategies, including neighboring group participation,[6–10] remote group participation,[11–17] intramolecular aglycon delivery,[18–20] conformational bias,[21,22] solvent participation,[23–26] and halide/nucleophile catalysis[27,28] have been developed to achieve anomeric selectivity. However, they rely on discrete sugar structures and/or protecting group (PG) patterns and, hence, are limited in scope. Moreover, they do not permit stereoselective access to the opposite and disfavored anomeric products. An S_N2 glycosylation strategy that does not rely on sugar ring structure features and/or protecting group patterns would, in theory, offer a long-soughtafter general solution that can deliver every type of glycosidic linkage with stereospecificity. However, such a method remains elusive despite recent developments in S_N2 strategies,[29,30] which include Jacobsen et al.'s bis-thiourea catalysis[31,32] and our earlier directing-group-on-leaving-group (DGLG) approach.[33] In the latter case, we engineered Yu's *ortho*-alkynylbenzoate system to position an oxazole moiety for directing an S_N2 attack at the anomeric position by an incoming acceptor (Scheme 1A).[33] However, this approach still suffers from the lack of inversion with α-glucosyl donors, the moderate S_N2 characteristics with challenging secondary acceptors, and the long synthetic sequence (approximately seven steps) required for the installation of the oxazolefunctionalized benzoate leaving group. In this work, we report a new and general approach to S_N2 glycosylation by employing an amide-directing group that (a) realizes both conversions from α donors to β products and from β donors to α products, (b) accommodates a broad range of sugar types, (c) requires only two linear steps for the installation of a designed leaving group, and (d) achieves exceptional stereoselectivity with challenging secondary acceptors. Our mechanistic studies reveal that the directing group also enables a unique safeguarding mechanism for high levels of stereoinversion.

Our design is shown in Scheme 1B. The donor **D** is a glycosyl 1-naphthoate featuring a *para*-amide-functionalized phenylethynyl group at C8. It is anticipated that upon gold-promoted cyclization, donor **D** is converted into the activated intermediate **A**, in which the amide group is positioned to deliver an acceptor for a backend attack at the anomeric position via H-bonding interaction. It is noteworthy that this donor-activation strategy is not previously known.[34] The key features in this design are that, compared with the oxazole approach,[33] the activated leaving group in **A** is much more rigid, and the amide group directing group is sterically less demanding than the oxazole moiety. In addition, the donor synthesis can be accomplished in two linear steps from glycosyl halides and commercial reagents, i.e., the glycosylation with 8-bromo-1-naphthoic acid (<$6/g) and the Sonogashira coupling with 4-ethynylbenzamide, which was prepared from the corresponding acid (<$5/g).

We began the study by examining the reaction of the galactosyl donor *β*-**D1** with the methyl *α*-D-glycopyranoside acceptor **2a** (eq 1). Under the optimized reaction conditions (see the Supporting Information for details), the disaccharide product **3a** was formed in 91% yield and with a good *α*/*β* selectivity (13.5/1). Lower levels of stereoinversion at the anomeric position were observed when donors without the amide group or with other *N*,*N*-dialkylamide groups were used. The addition of $HNTf_2$ (20 mol %) improved reaction conversion.



Eq. 1

The scope of this S_N2-type glycosylation is shown in Figure 1. First, a range of carbohydrate acceptors was glycosylated by the galactosyl 1-naphthoate *β*-**D1** with excellent stereoselectivity and in good to excellent yields. For example, the reaction of the galactopyranose-based primary alcohol acceptor afforded the disaccharide **3b** in 98% yield and with a 19:1 *α*/*β* ratio, and the reactions of tri-*O*-benzyl-D-glucopyranoside acceptors with a sterically hindered secondary hydroxy group at the 4-, 2-, or 3-position (**3c–3e**) exhibited high levels of S_N2 characteristics with *α*/*β* ratios > 20:1 and yields that were good to excellent. With a removable acetyl replacing the *O*-6-benzyl as the protecting group in *β*-**D1**, a better *α*/*β* ratio of >20:1 was realized with primary acceptor **2a**. Next, we turned our attention to the *β*-D-glucopyranosyl donors; the reactions of a range of primary or secondary alcohol acceptors again exhibited excellent *α* selectivity and good to excellent yields (**3g–3r**). Notably, this approach performed substantially better than our previous oxazole approach with hindered secondary glucose-based acceptors. In the cases of **3i** and **3j**, the 1,2-*cis*-diglucosides were formed with >30:1 selectivity and exclusivity, respectively. In contrast, they were formed in 11:1 and 6:1 selectivity, respectively, with the oxazole approach.[33] Methyl 2,3,6-tri-*O*-benzoyl-D-glucopyranoside, which possesses a hindered and electronically deactivated secondary hydroxy group at the 4-position, was also a suitable acceptor, and the *α*-glucoside **3m** was formed with exclusive *α* selectivity and in 85% yield. *β*-Glucopyranosyl donors bearing removable protecting groups, such as 6-*O*-acetyl, 6-*O*-Fmoc, and 3-*O*-Lev, were also allowed, which afforded **3n–3r** in good yields and with high *α* selectivities. We then explored this S_N2 glycosylation chemistry using a fucose-derived donor, and the *α*-fucoside **3s** was formed with almost complete anomeric inversion and in excellent yield.

This S_N2 glycosylation also permits highly stereoinvertive conversion of *α*-donors to *β*-1,2-*trans*-disaccharides. For example, the reactions of the galactose donor *α*-**D1** with glucoside acceptors at the 6-*O* and 4-*O* positions afforded 3t and **3u**, respectively, with excellent

β-selectivities and in good to excellent yields. In these cases, two equivalents of acceptors were employed, and the reactions were performed in DCM and at −40 °C. Similarly, high levels of stereoinversion at the anomeric position were observed with α-glucoside donors, and the β-disaccharides **3v–3x** were formed in good to excellent yields and with high stereoselectivity. 1,2-*trans*-Glycosidic linkages are invariably prepared by harnessing the participation of a neighboring 2-acyloxy group. Our approach circumvents that and permits 2-*O*-benzyl protection, which—unlike acyl groups—is stable under basic conditions. However, with a 2-acyloxy group, our approach could not outcompete the anchimeric effect for the construction of 1,2-*cis*-glycosidic linkages.

We then applied our approach to the synthesis of 2-deoxy glucosyl donors. From the β-per-*O*-benzoylated donor, the α-2-deoxy glucosides **3y** and **3z** were formed from the β-donor with ≥15/1 stereoselectivities and in excellent yields. Moreover, the β counterparts of these products, i.e., **3af** and **3ag**, were prepared from the α-donor in excellent yields and with ≥10/1 stereoselectivities. Our approach is also applicable to the stereoselective construction of both α- and β-mannosidic and -rhamnosidic linkages. To this end, our mannosyl donors possess 2,3- and 4,6-*O*-acetonide protecting groups, and the rhamosyl donors possess a 2,3-acetonide protecting group.[35–37] Stereoinversion was realized with each mannose and rhamnose donor anomer, and the reactions exhibited good to excellent stereoselectivities and high yields.

Besides the broad applicability, this chemistry represents improvement over literature reports in the construction of some specific glycosidic linkages, and the comparison is shown in the Supporting Information.

To demonstrate the utility of this strategy, we applied it in the synthesis of challenging 1,2-*cis*-oligosaccharides. As shown in Scheme 2A, methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **2c** reacted with the glucose donor **β-D6** chemoselectively at the more accessible 6-OH group to afford disaccharide **4a** with excellent α selectivity and in 94% yield within 3 h. Subsequent glycosylation with β-D1 afforded the branched trisaccharide 4b in 87% yield and with an α/β ratio of >30:1. Scheme 2B illustrates the versatility of our approach in the synthesis of the pentasaccharide **4f**, the skeleton of which resembles an α-glucan pentasaccharide repeating unit found in *Aconitum carmichaeli*.[8] Initially, the primary acceptor **2a** was glucosylated by **β-D7** to afford the α-diglucoside **4c** upon subsequent removal of the Nap group by DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) in 87% yield and with 20:1 stereoselectivity. The trisaccharide **4d** was prepared with an excellent α selectivity from **4c** upon glycosylation with **β-D1** and subsequent acetyl removal. Finally, **4d** underwent two iterative α-glucosylations, which are intertwined by basic hydrolysis, to afford the pentasaccharide **4f** featuring all 1,2-*cis* glycosidic linkages in 53% combined yield.

To gain insights into the reaction mechanism, we monitored the reaction shown in eq 1 by running a series of crude ^{1}H NMR (for details, see the Supporting Information). In addition to the yellow byproduct **5a**, we observed the formation of a new naphthoate-containing byproduct showing a doublet at 9.52 ppm (J = 7.4 Hz, Scheme 3A). We propose its structure as **5b**, which is the aurated precursor to **5a**, and attribute the downfield resonance

to the naphthalene C7–H by the deshielding alkenyl gold moiety. This consideration is supported by the isolation and characterization of the dimethylated counterpart of **5b**, i.e., **5c**, by NMR analysis and X-ray diffraction studies. Compound **5c** has a similarly downfield-shifted doublet (9.65 ppm, J = 7.4 Hz), along with other closely related ^{1}H NMR resonances. The formation of **5c** and **5b** supports the proposed gold-catalyzed activation of the donor for ensuing glycosylation. Furthermore, VT-NMR experiments from −35 °C to room temperature revealed two intermediates (Scheme 3B). We assigned them as the amide-attacked structures **B** and **C**, of which the former is the aurated precursor of the latter. With 20% $HNTf_2$ added, less **B** and more **C** were observed during the course of the reaction. Moreover, **B** has a downfield doublet at 9.49 ppm with J = 7.5 Hz, which is very similar to the ones observed in **5b** and **5c**. The small coupling constants of 3.4 and 3.5 Hz for the anomeric signals of **B** and **C** at 5.66 and 5.52 ppm, respectively, suggest they are α-anomers. To support their structural assignment, per-*O*-benzylgalactosyl chloride was treated with 1.0 equiv of $AgNTf_2$ in the presence of phenyl(pyrrolidin-1-yl)methanone (1.2 equiv) in anhydrous CD_2Cl_2 (Scheme 3B). Delightfully, the related intermediate, i.e., **C′**, was formed nearly quantitatively at rt as soon as the halogen abstractor was added. Its α configuration was established by the anomeric $^1J_{C–H}$ (177 Hz), and the anomeric proton signals are similar to those of **B** and **C**. About half of **C′** decomposed after 4 h at rt, which suggests **B** and **C** formed under cryogenic conditions can be stable and slow to react with acceptors.

To this end, a mechanism was proposed in Scheme 3C using β-**D1** as the donor. The donor initially undergoes LAu^+-promoted cyclization to afford the activated glycosyl donor **D**. The proper alignment of the directing amide group facilitates the backside attack at the anomeric carbon by an acceptor alcohol via the formation of an H-bond, therefore realizing S_N2 glycosylation and delivering the stereoinverted glycoside α-**3**, along with the byproduct **5b′**. The protodeauration of **5b′** forms the yellowish byproduct **5a**. Alternatively, **D** could undergo minor anomeric fragmentation to form the oxocarbenium intermediate E and be attacked by **5b** or **5c**, which are stronger nucleophiles than alcoholic acceptors, to form the cationic imidate intermediates **B** or **C**. The α-anomers of these two intermediates are thermodynamically favored and should be predominant, as we observed in Scheme 3B. As alluded before, the likely low reactivities of **B** and **C** at the reaction temperature (i.e., −30 °C) should render them only susceptible to attack by good nucleophiles. For primary alcohol acceptors, their glycosylation via **B** or **C** might occur, albeit slowly, and lead to the formation of the undesired β-**3**. However, hindered secondary alcohol acceptors, which are weaker nucleophiles, cannot attack B or C to form glycosidic bonds. This consideration is consistent with the surprising observations that less nucleophilic secondary alcohol acceptors could lead to better stereoinversion than primary alcohol acceptors (e.g., **3c**/**3d**/**3e** vs **3a**; **3i**/**3j** vs **3h**) and reveals that the amide directing group also plays a unique yet critical role of safeguarding the stereoinversion by effectively removing the oxocarbenium intermediate **E** from the reaction. The accelerating effect of $HNTf_2$ can also be explained by regenerating the gold catalyst upon protonation of the unreactive intermediate **B**.

In conclusion, we have developed a catalytic S_N2 glycosylation that permits the construction of a broad range of glycosidic linkages with high to excellent levels of stereoinversion from anomerically pure/enriched glycosyl donors. Both α- and β-anomers of D-glucosides,

D-galactosides, D-mannosides, L-rhamnosides, 2-deoxo-D-glucosides,and α-L-fucosides are synthesized with good to excellent stereoselectivities. This generally applicable strategy is achieved by employing an amide-functionalized 1-naphthoate as a latent glycosyl leaving group. Upon its gold activation, the amide group is optimally positioned to direct a backend attack at the anomeric position by an acceptor via H-bonding interaction. Of high significance is that the amide group also safeguards the high stereoselectivity by trapping oxocarbenium intermediates and, hence, minimizing S_N1 processes. This chemistry works particularly well with sterically demanding and, hence, challenging secondary acceptors and is applied successfully in the synthesis of a pentasaccharide with all of its glycosidic linkages being 1,2-*cis*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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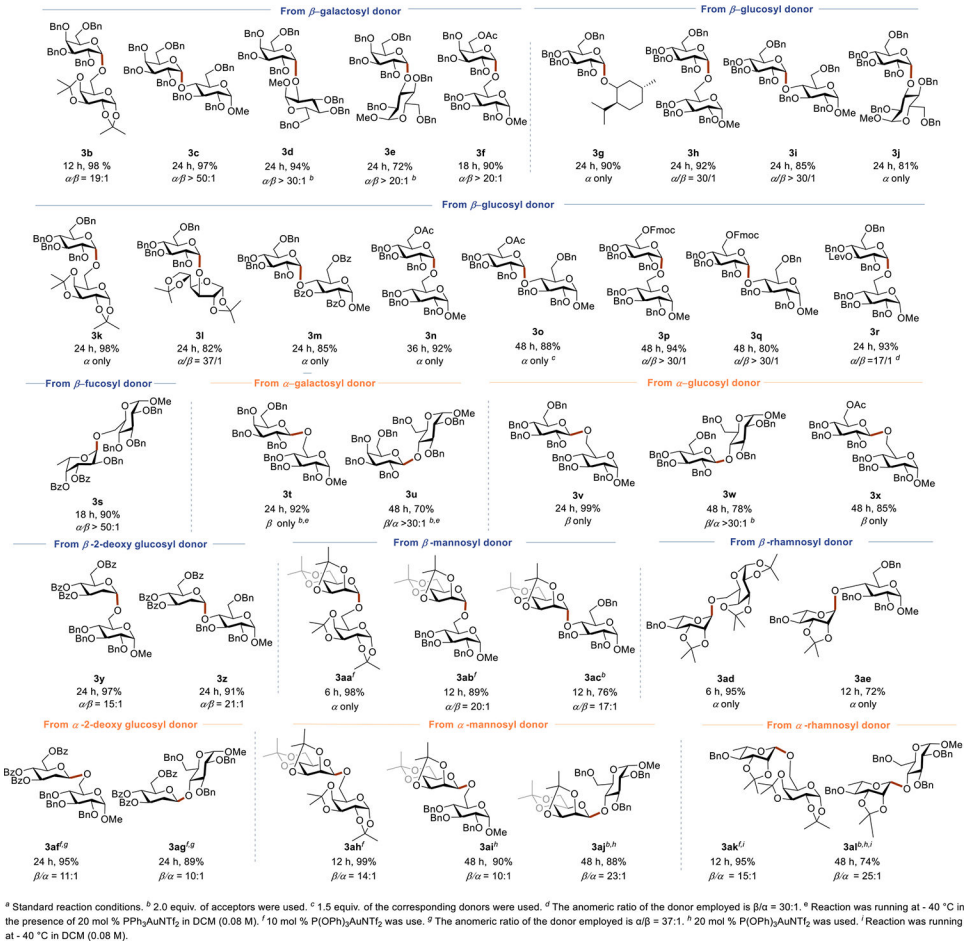
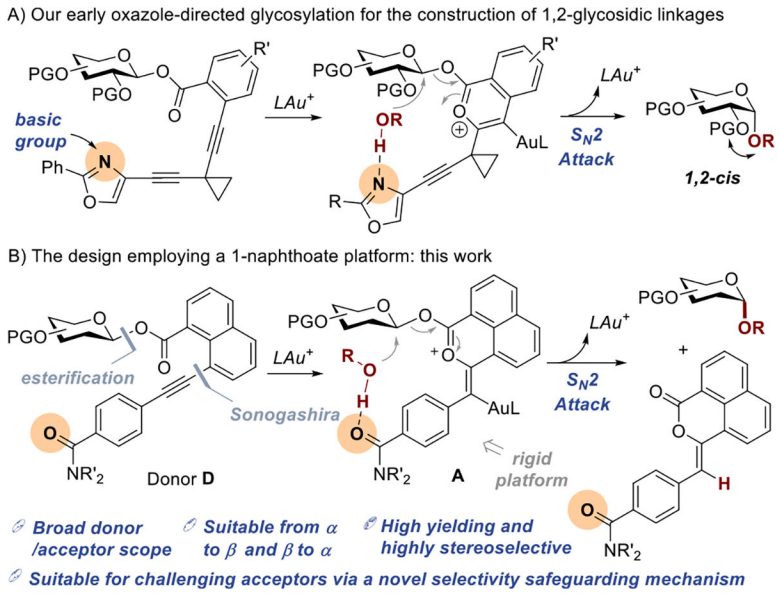


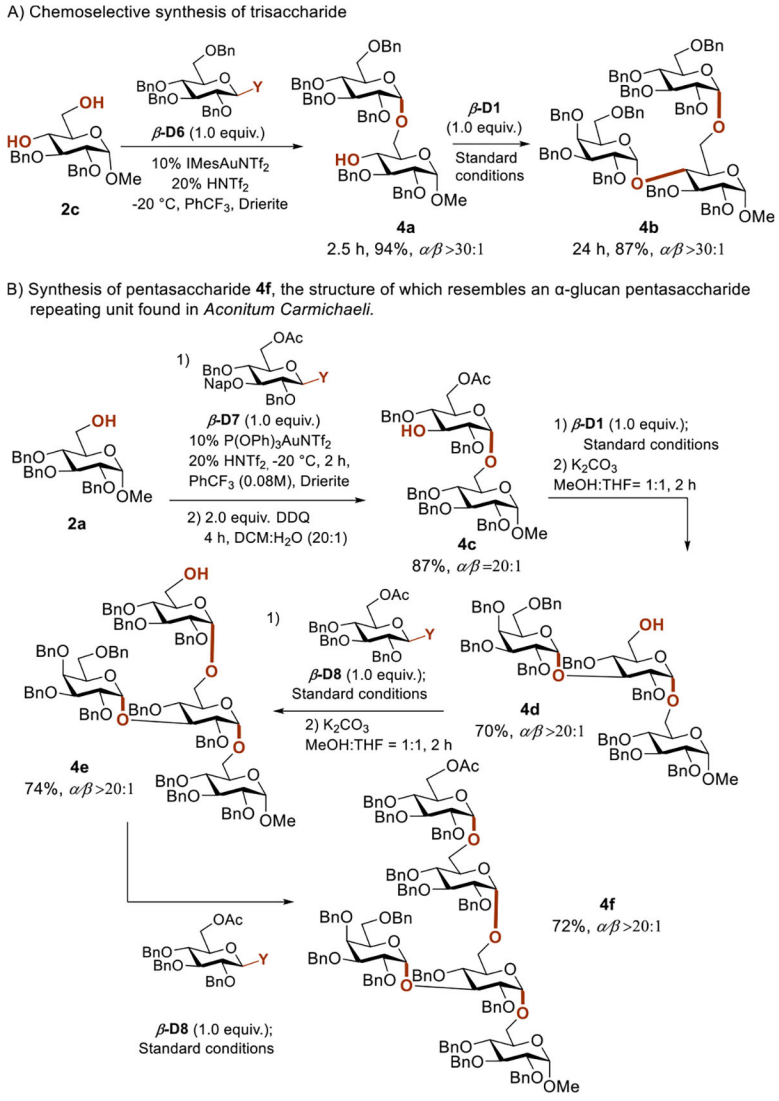
[a] Standard reaction conditions. [b] 2.0 equiv. of acceptors were used. [c] 1.5 equiv. of the corresponding donors were used. [d] The anomeric ratio of the donor employed is β/α = 30:1. [e] Reaction was running at - 40 °C in the presence of 20 mol % PPh_3AuNTf_2 in DCM (0.08 M). [f] 10 mol % $P(OPh)_3AuNTf_2$ was use. [g] The anomeric ratio of the donor employed is α/β = 37:1. [h] 20 mol % $P(OPh)_3AuNTf_2$ was used. [i] Reaction was running at - 40 °C in DCM (0.08 M).

Figure 1.
Reaction scope with various donor types.



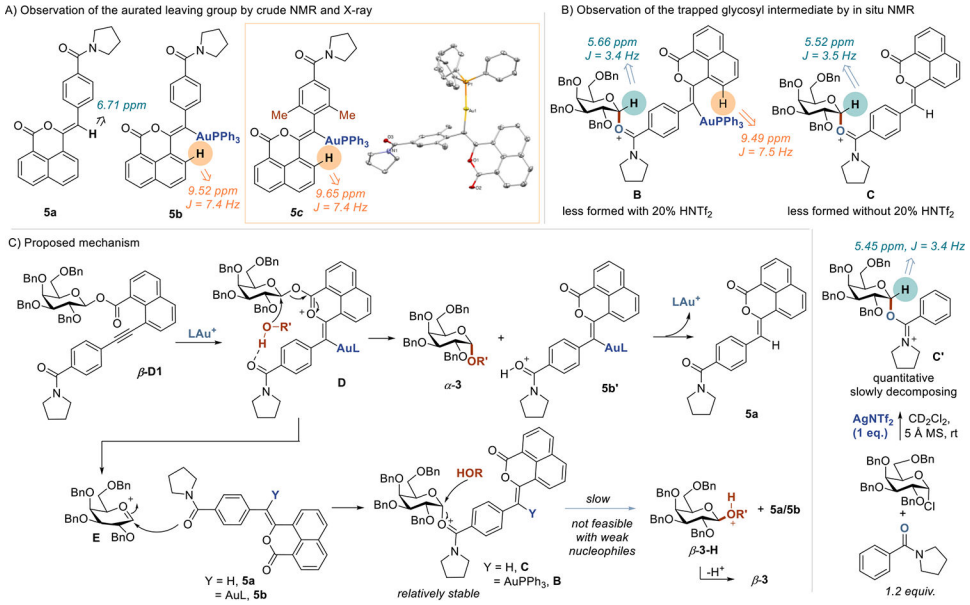
Scheme 1.

Selected Approaches to S_N2 Glycosylation Not Relying on Sugar Ring Structure and/or Protecting Group Patterns



Scheme 2.

Highly Stereoselective Synthesis of Oligosaccharides



Scheme 3.
Mechanistic Studies and the Proposed Mechanism