

A "Traceless" Directing Group Enables Catalytic S_N2 Glycosylation toward 1,2-*cis*-Glycopyranosides

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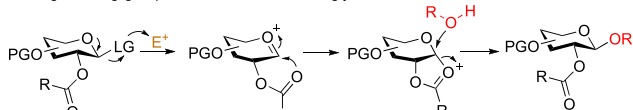


Supporting Information

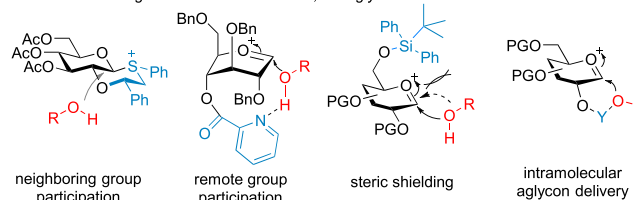
ABSTRACT: Generally applicable and stereoselective formation of 1,2-*cis*-glycopyranosidic linkage remains a long sought after yet unmet goal in carbohydrate chemistry. This work advances a strategy to this challenge via stereoinversion at the anomeric position of 1,2-*trans* glycosyl ester donors. This S_N2 glycosylation is enabled under gold catalysis by an oxazole-based directing group optimally tethered to a leaving group and achieved under mild catalytic conditions, in mostly excellent yields, and with good to outstanding selectivities. The strategy is also applied to the synthesis of oligosaccharides.

The main challenge arising from the construction of glycosidic bonds in oligosaccharide synthesis^{1,2} is how to control the anomeric configuration formed from a diverse array of glycosyl donors and acceptors. Remarkable advances in stereoselective glycosylation reactions have been achieved and especially in the context of the formation of 1,2-*trans* glycosidic bonds via neighboring group participation (Figure 1A). In contrast,

A: Neighbouring group assistance in 1,2-*trans* glycoside formation



B: Selected Strategies for the formation of 1,2-*cis* glycosides



C: The directing-group-on-leaving-group (DGLG) strategy: a conceptually general S_N2 glycosylation

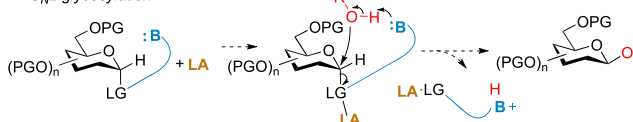


Figure 1. Strategies for stereoselective glycosylation and our design.

the formation of 1,2-*cis* glycosidic bonds remains challenging, and a much-needed strategy that is generally applicable to every sugar donor type has yet to be developed. Some innovative methods^{3–6} partially addressing this challenge are shown in Figure 1B. Due to the need to install a special directing group or protecting group (PG) on the sugar ring, they suffer from limited scope and/or complicated donor synthesis. Moreover, such groups may complicate subsequent glycosylation or requiring additional PG manipulation. Alternative strategies for the synthesis of 1,2-*cis*-glycosides relying on

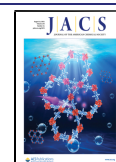
solvent effects^{7,8} or halide ion catalysis⁹ are also limited by applicable scope.

We envisioned an S_N2 glycosylation strategy that features a basic group installed on the glycosyl leaving group (LG) and facilitating acceptor attack (Figure 1C). This strategy allows simultaneous activation of donor and acceptor and mimics glycosyl hydrolases/transferases¹⁰ and would conceptually accommodate any glycosyl donors, regardless of their configurations and protecting group patterns. We term this as directing-group-on-leaving-group (DGLG). Upon glycosylation, this directing group departs along with the leaving group and hence can be considered "traceless" in the glycoside product. This design necessitates S_N2 glycosylation in order to harness the directing effect. By using a 1,2-*trans*-glycosyl donor, this strategy would lead to general access to the challenging 1,2-*cis*-glycosides. Notably, other remarkable catalytic strategies of simultaneous donor and acceptor activation for S_N2-type glycosylation have been reported,^{5,11–14} including Schmidt's acid–base catalysis¹¹ and Jacobsen's macrocyclic bithiourea-catalyzed glycosylation.^{12–14}

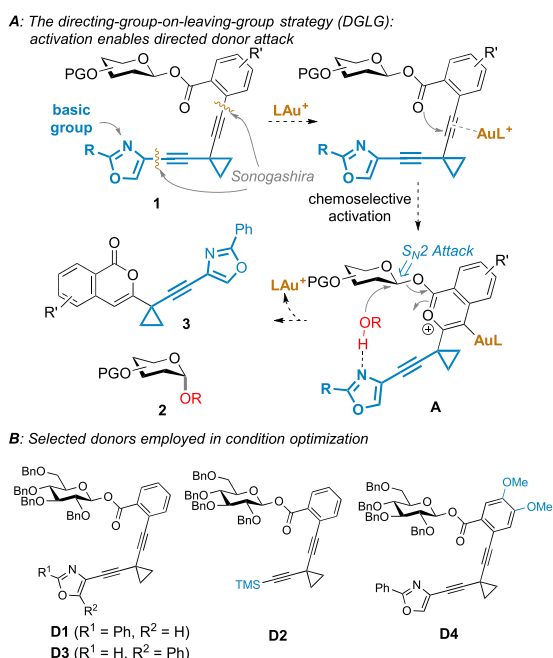
In practice, we engineered the LG based on the *ortho*-alkynylbenzoates used in Yu's glycosylation chemistry.¹⁵ As shown in Scheme 1A, in the designed donor 1, the *ortho* C–C triple bond is terminated by an alkynylcyclopropyl group, which features a mildly basic oxazole ring. It is anticipated that its gold-promoted cyclization would deliver isochromenylium intermediate A,¹⁶ which has its side arm oxazole ring positioned to direct an alcohol acceptor to attack at the backend of the activated anomeric C–O bond. Such delivery of the acceptor would afford glycoside 2 with the inverted configuration at the anomeric carbon and hence realize the desired S_N2 glycosylation.

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Scheme 1. Implementing the “Traceless” Directing Group Design



The designed donors can be prepared straightforwardly via two consecutive Sonogashira couplings (see the [Supporting Information](#) for details), and some representative ones are shown in [Scheme 1B](#). [Table 1](#) outlines the condition optimization for the synthesis of methyl D-glucopyranosyl-(1 → 6)-α-D-glucopyranoside **5a** from the β-D-glucopyranosyl donors ([Scheme 1B](#)) and the acceptor methyl α-D-glucopyranoside **4a**. To our delight, with **D1** as the donor, **5a** was obtained with a respectable α/β ratio of 11:1 in the presence of 20 mol % $\text{PPh}_3\text{AuNTf}_2$ in CH_2Cl_2 (DCM) at -35°C (entry 1). In comparison, donor **D2** devoid of oxazole led to little stereoselectivity (entry 2), revealing the critical role of the basic heterocycle in enabling anomeric configuration inversion. By increasing the gold catalyst loading to 0.5 and 1.0 equiv, the α/β ratio was lowered to 2.8:1 (entry 3) and 1.5:1 (entry 4), respectively. These results are consistent with the directing role played by the oxazole nitrogen as the cationic gold(I) increasingly binds to it and hence diminishes its designed function. This detrimental binding of oxazole to Au(I) is even more pronounced with donor **D3**, of which the oxazole is devoid of substitution at its C2 position and hence presents an unhindered ring nitrogen for coordination. In this case, the gold catalyst appeared to be largely sequestered (entry 5). Upon further donor and conditions optimization, we discovered that donor **D4** bearing two methoxy groups on its benzoate permits a faster reaction while maintaining similar α selectivity (entry 6). With $\text{IMesAu}^+\text{BARF}^-$ generated from $\text{IMesAuCl}/[\text{Ag}(\text{MeCN})_2]^+\text{BARF}^-$ as the catalyst in 5 mol %, the reaction was sluggish at 0°C . With 62% conversion after 16 h, the α/β selectivity was, however, improved to >20:1 (entry 7). Changing the reaction solvent from DCM to PhCF_3 led to near quantitative yield while maintaining excellent α selectivity (entry 8). Lowering the reaction temperature led to an even better selectivity but at the cost of conversion (entry 9). The solvent effect, as evident from entries 7 and 8, was further examined. We discovered that isochroman-1-one byproduct **3** ($R' = 3,4\text{-(MeO)}_2$) is crystalline and has significantly higher solubility in DCM (>0.02 M at -15°C)

Table 1. Reaction Discovery and Optimization

entry	donor	catalyst (equiv) ^a	solvent (conc.)	temp./time	yield (α/β) ^b
1	D1	A	DCM	$-35^\circ\text{C}/24\text{ h}$	95% (11:1)
2	D2	A	DCM	$-35^\circ\text{C}/24\text{ h}$	95% (1.5:1)
3	D1	A ^c	DCM	$-35^\circ\text{C}/12\text{ h}$	95% (2.8:1)
4	D1	A ^d	DCM	$-35^\circ\text{C}/12\text{ h}$	96% (1.5:1)
5	D3	A	DCM	$-35^\circ\text{C}/24\text{ h}$	<5% (N/A) ^e
6	D4	A	DCM	$-35^\circ\text{C}/5\text{ h}$	96% (11:1)
7	D4	B	DCM	$0^\circ\text{C}/16\text{ h}$	62% (>20:1) ^e
8	D4	B	PhCF_3	$0^\circ\text{C}/16\text{ h}$	>99% (>20:1)
9	D4	B	PhCF_3	$-15^\circ\text{C}/24\text{ h}$	41% (30:1) ^e
10	D4	B	<i>f</i>	$-15^\circ\text{C}/15\text{ h}$	>99% ^g (27:1)
11	D2	B	<i>f</i>	$-15^\circ\text{C}/10\text{ h}$	92% ^h (3.1:1)

^aA: $\text{Ph}_3\text{PAuNTf}_2$ (20 mol %); B: IMesAuCl (6 mol %)/ $[\text{Ag}(\text{MeCN})_2]^+\text{BARF}^-$ (5 mol %). ^bCombined NMR yield and anomeric ratio determined by NMR. ^cUsing 50 mol % catalyst instead. ^dUsing 1 equiv of catalyst instead. ^eConversion is nearly the same as yield. ^f PhCF_3 and cyclohexane ($v/v = 4:1$) were used as the solvent and the initial substrate concentration is 0.08 M. ^g97% isolated yield. ^h93% conversion.

than in PhCF_3 ($\sim 0.0056\text{ M}$ at -15°C). It is reasoned that the slower reaction rate in DCM is partly due to the coordination of Au(I) by oxazole nitrogen of **3**. In contrast, in PhCF_3 , most of **3** precipitates out from the reaction. To this end, with a mixture of PhCF_3 and even less dissolving cyclohexane ($v/v = 4:1$) and at an increased concentration (0.08 M), the reaction was substantially accelerated and proceeded to completion in 15 h at -15°C (entry 10). The reaction was again quantitative in yield and highly α-selective. In comparison, under these optimized conditions, **D2** again resulted in a poor α/β ratio of 3.1:1 (entry 11).

The optimized conditions (i.e., [Table 1](#), entry 10) were applied to a range of acceptors using **D4** as the donor. As shown in [Figure 2](#), chiral alcohols like (*R*)-1-phenylethanol and *L*-menthol proceed with excellent yields and nearly exclusive α selectivity (**5b** and **5c**). *L*-Serine esters and cholesterol were running in different solvents due to their poor solubility in the mixed solvent system, but the yields and α selectivities remained high (**5d** and **5e**). The reaction of the galactopyranose-based primary alcohol acceptor proceeded in 90% yield and with >30:1 α/β ratios (**5f**). With methyl groups replacing the benzyl groups in **D4**, the selectivity was diminished to 13.5:1 (**5g**). We attribute this to the fact that methyl is less inductively electron-withdrawing than benzyl; consequently, the methylated donor has a higher tendency of participating in the $\text{S}_{\text{N}}1$ pathway. We then examined tri-*O*-benzyl-D-glucopyranoside acceptors with a secondary hydroxy group at 2-, 3-, or 4-position (**5h–5j**). While the yields are all high, the α/β selectivity ranges from >20:1 for the 1 → 2 linkage to 11:1 for the 1 → 4 linkage and 6:1 for the 1 → 3 linkage. We also prepared the 4-*t*-butylbenzyl counterpart of donor **D4**, which shall be more soluble in nonpolar solvents, but the improvement was marginal (**5k**). The D-glucofuranose- and L-rhamnopyranose-derived acceptors also reacted well, exhibiting excellent yields and selectivities (**5l** and **5m**), while

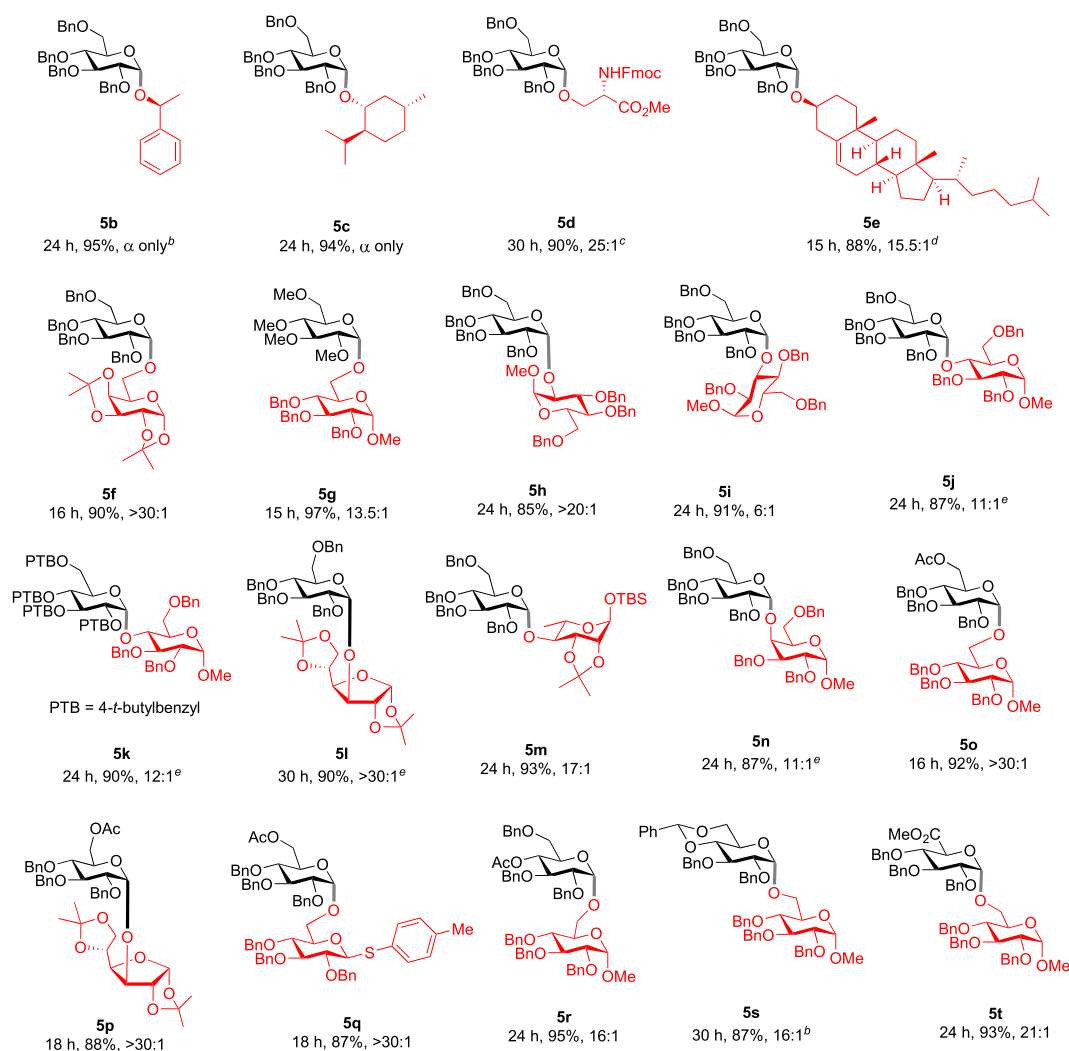


Figure 2. Reaction scope with β -D-glucopyranosyl donors. ^aStandard condition. ^bConcentration: 0.02 M. Reaction was stirred at 0 °C with 12% IMesAuCl and 10% [Ag(MeCN)₂]⁺BARF[−]. ^cConcentration: 0.08 M. DCM and cyclohexane ($\nu/\nu = 1:1$) were used as the solvent. Reaction was run at 0 °C. ^dConcentration: 0.04 M. Reaction was stirred at −15 °C with 12% IMesAuCl and 10% [Ag(MeCN)₂]⁺BARF[−]. PhCF₃ and cyclohexane ($\nu/\nu = 1:1$) were used as the solvent. ^eUsing 2.0 equiv of acceptors.

the reaction of methyl α -2,3,6-tri-*O*-benzylgalactopyranoside exhibited a respectable 11:1 preference for the α -glycosidic linkage (**5n**). With readily removable acetyl replacing the *O*-6-benzyl group in **D4**, generally higher selectivities were observed (**5o**–**5q**). This gold catalysis also tolerates a thioglycoside as the acceptor (**5q**). In addition, modifying **D4** by replacing the 4-*O*-benzyl group with acetyl, by installing 4,6-*O*-benzylidene, or by oxidizing it into methyl glucuronate was inconsequential, as the product from reacting with **1a** (i.e., **5r**, **5s**, or **5t**, respectively) was obtained in an excellent yield and with high α selectivity.

We then applied this design to the synthesis of other 1,2-*cis*-pyranosides (Figure 3). The reaction of the corresponding β -D-galactopyranosyl donor with a primary or secondary alcohol donor also exhibited excellent α selectivity, affording 1,2-*cis*-galactosides **5u** or **5v** in excellent yield (Figure 3A). The reaction of the xylopyranosyl donor was also highly α -selective and efficient (Figure 3B). We then explored this S_N2 glycosylation using α -mannosyl donors. As shown in Figure 3C, only a moderate inversion of the anomeric configuration was detected in the case of **5x** when a tetra-*O*-benzylated version was employed. This result suggests that this DGLG strategy may be of limited utility for the synthesis of 1,2-*cis*-rhamnosides.

To our delight, with a 4,6-benzylidene-protected α -mannosyl donor,¹⁷ the reactions exhibited exclusive S_N2 characteristics regardless of the nature of the acceptor, and both **5y** and **5z** were formed in only β -forms. In comparison, with a donor without the oxazole group, **5y** was formed with an α/β ratio of 1:13, and **5z** was formed in a literature report¹⁸ of 1:12, revealing the beneficial directing effect in addition to the inherent selectivity. A reported drawback¹⁹ of employing 4,6-*O*-benzylidenemannosyl donors²⁰ is the substantially diminished selectivities caused by adverse steric buttressing of bulky *O*3 groups. Despite subsequent improvements via using sterically minimal propargyl as the *O*2 protecting group²¹ or employing Yu's *o*-alkynylbenzoate system,¹⁸ the issue remains with bulky acceptors. For example, mannoside **5ab** containing a bulky 3'-*O*-TBS group formed from the sterically demanding secondary glucoside acceptor exhibited $\leq 7:1$ β/α ratios. Using our strategy, **5ab** was formed with an improved β/α ratio of 13:1. Remarkably, the reaction was run at ambient temperature, which is advantageous over literature cryogenic conditions (e.g., −20 °C¹⁸ and −78 °C²¹). This strategy was also successfully applied to the synthesis of **5aa**.

To demonstrate the utility of this strategy, we applied it to oligosaccharide synthesis. As shown in Scheme 2A, using

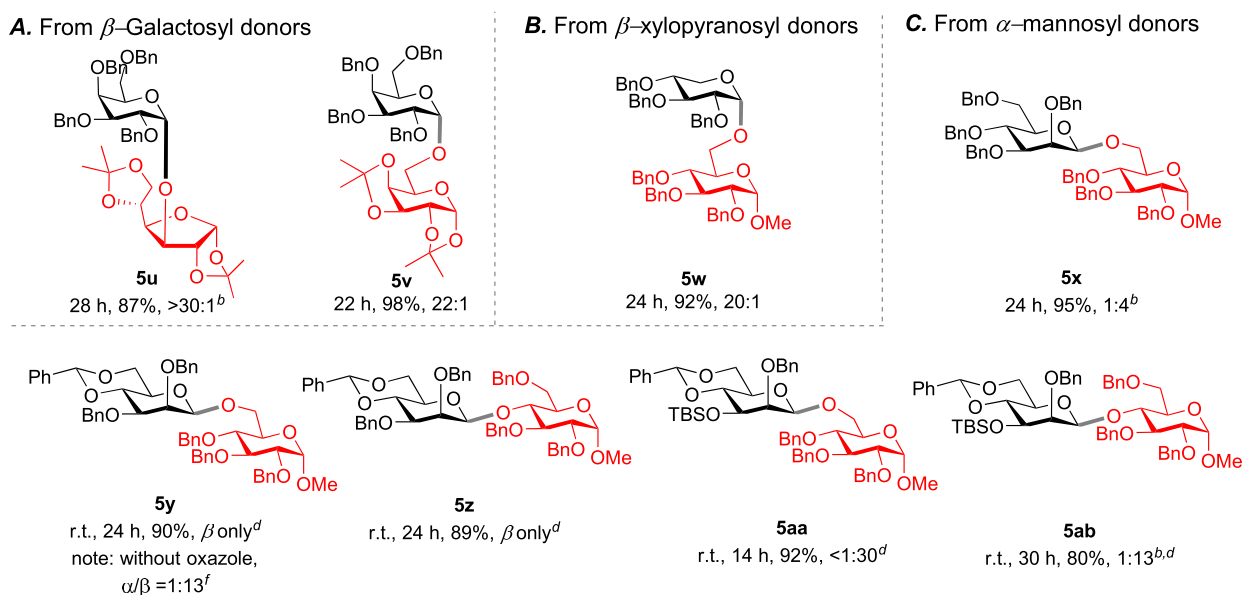
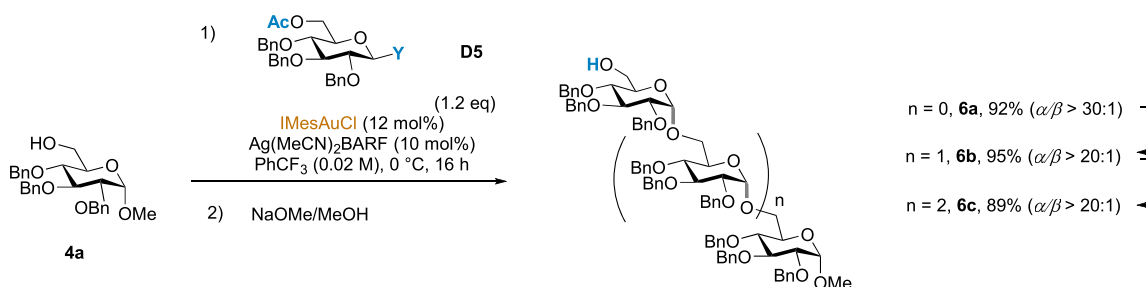


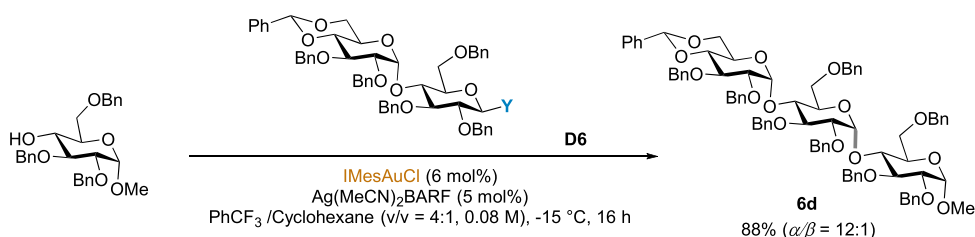
Figure 3. Reaction scope with other 1,2-*trans*-monosaccharide donors. ^aStandard conditions. ^bUsing 2.0 equiv of acceptors. ^cReaction was run in 0.02 M PhCF₃, with 1.2 equiv of acceptor, using 10% PPh₃AuNTf₂ as catalyst and at -25 °C. ^dReaction was run at room temperature. ^eNMR yield. ^fSee the Supporting Information for details.

Scheme 2. Synthesis of Oligosaccharides^a

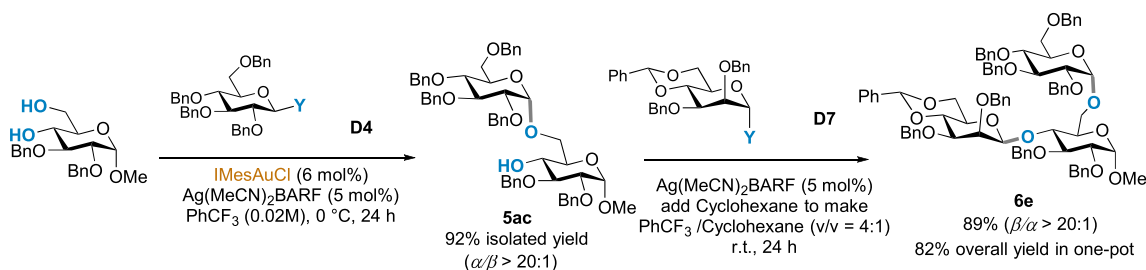
A. Iterative synthesis of isomaltotetraose



B. Disaccharide donor



C. One-pot chemoselective synthesis



^aY = the oxazole-functionalized leaving group.

methyl 2,3,4-tri-O-benzyl-D-glucopyranoside (**4a**) as the initial acceptor and the 6-acetate analog of **D4** (i.e., **D5**) as the

donor, an iterative process consisting of glycosylation and basic hydrolysis delivered protected isomaltotetraose **6c** in 78%

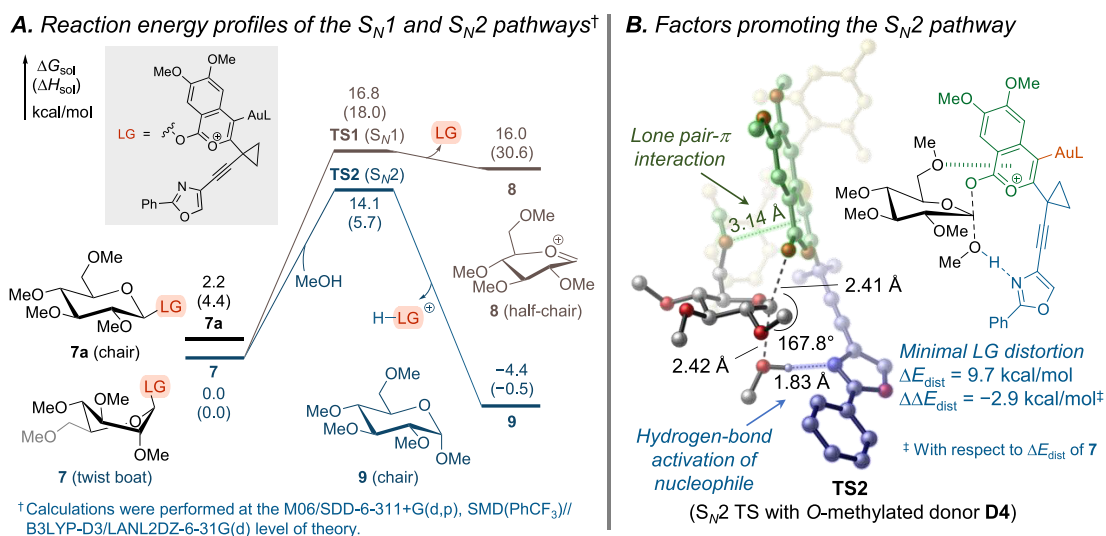


Figure 4. Computational mechanistic studies.

overall yield and excellent α selectivities after three iterations. Alternatively, related maltotriose derivative **6d** can be accessed in one step from α -maltose-derived donor **D6** in 88% yield and with good α selectivity (Scheme 2B). In addition, as shown in Scheme 2C, we examined chemoselectivity by employing methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside as the acceptor. Its reaction with **D4** indeed selectively glycosylated the more accessible 6-OH group to afford disaccharide **5ac** with excellent α selectivity and in 92% yield. It was then reacted with mannose-derived donor **D7** to afford branched trisaccharide **6e** in 89% yield and with an β/α ratio of >20:1. This two-step sequence was also run successfully in one pot.

To offer insight into the high levels of stereospecificity in the formation of 1,2-*cis* glycosidic bonds, we performed density functional theory (DFT) calculations to study the S_N1 and S_N2 pathways of the glycosylation of *O*-methylated analog of **D4** using MeOH as a model acceptor (Figure 4). The overall catalytic cycle (Figure S3) involves a facile Au(I)-catalyzed cyclization of the *ortho*-alkynylbenzoate to form isochromenylium intermediate **7** with the twisted-boat conformation, which is 2.2 kcal/mol more stable than its chair conformation, **7a**, followed by a rate- and stereoselectivity-determining glycosylation step (Figure 4A). Glycosylation via the concerted S_N2 -transition state (**TS2**) requires lower activation free energy than the leaving group dissociation (**TS1**) in the unimolecular S_N1 pathway ($\Delta G^\ddagger = 14.1$ and 16.8 kcal/mol, respectively).²² These results suggest that the stereospecific S_N2 reaction with the β -donor is faster than the formation of oxocarbenium ion in an S_N1 -type process. To support this finding experimentally, the reaction of the per-methylated counterpart of **D4** with MeOH under the computed reaction conditions (i.e., Table 1, entry 9) yielded permethylated glucose **9** with $\alpha/\beta > 50:1$.

We then analyzed factors that promote S_N2 -like transition state **TS2** (Figure 4B). **TS2** features a loose structure with relatively long C¹–O^{LG} and C¹–O^{Nu} distances (2.41 and 2.42 Å, respectively), which alleviate the 1,2-*cis* steric repulsion between C²–OMe and the alcohol acceptor. The isochromenylium leaving group (LG) requires a relatively small distortion energy ($\Delta E_{\text{dist}} = 9.7$ kcal/mol with respect to the dissociated leaving group and -2.9 kcal/mol with respect to the LG in **7**) to orient the oxazole ring in the side arm to form a strong hydrogen bond with the alcohol acceptor ($d(\text{N}–\text{H}) = 1.83$ Å). In addition,

the isochromenylium ring is oriented perpendicular to the C6 oxygen lone pair. This geometry enables stabilizing lone pair/ π interactions with the positively charged isochromenylium ring [see Figure S5 for the NCI (noncovalent interaction) plot visualization of the stabilizing interactions]. Finally, the lone pair/ π interactions between the C6 oxygen and the isochromenylium promote the pyranose ring in the ground state of **7** to adopt a twisted-boat conformation, which minimizes the distortion of the pyranose ring to achieve the half-chair conformation (⁴H₃) in the S_N2 transition state.

In conclusion, a gold-catalyzed S_N2 glycosylation is developed to achieve access to challenging 1,2-*cis*-glycosidic linkages. This chemistry is enabled by a unique directing-group-on-leaving-group strategy, in which a “traceless” basic oxazole moiety is appended to the anomeric leaving group and engineered to direct the back-end attack at the anomeric center by a glycosyl acceptor. Under exceptionally mild conditions, the reactions exhibit mostly excellent yields and good to outstanding 1,2-*cis* selectivities. Notably, sterically demanding secondary glycosyl acceptors are readily allowed. The utilities of this strategy in oligosaccharide synthesis are successfully demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c04584>.

Experimental procedures and characterization data, computational study results, Cartesian coordinates, and spectral data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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