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A broadly applicable stereospecific glycosylation

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The development of a general strategy for stereospecific construction of every type of glycosidic linkage remains a much sought-after yet unrealized goal. Such a strategy would be particularly useful in the context of complex glycan syntheses. Glycosylations involving an S_N2 mechanism are ideal to ensure stereospecificity but have been challenging to implement in a manner conferring generality across a range of sugars. Here we disclose a stereospecific glycosylation method that accommodates a broad range of monosaccharides, including hexopyranoses (for example, glucose, galactose, mannose, fucose, alluronate, 2-azido-2-deoxyglucose and 2-azido-2-deoxygalactose) and pentofuranoses (for example, arabinose, ribose, xylose and lyxose). Mild activation with an electrophilic bromine reagent results in complete inversion of the anomeric configuration and excellent yields for many glycosylations. The method proved reliable in multistep oligosaccharide syntheses and automated glycan assembly.

The synthesis of pure, well-defined natural and unnatural peptides, oligonucleotides and oligosaccharides[1–3] is key to studying the biological functions of these essential biopolymers. Peptides and oligonucleotides are readily prepared using robust and general methods for the construction of amide and phosphate diester linkages. Automated solid-phase synthesis enables non-experts to gain rapid access to the desired molecules. Oligosaccharides are structurally much more complex than the other two biopolymers owing to anomeric configurations, diverse monosaccharides and branching. The key synthetic challenge is the stereospecific construction of every type of glycosidic bond with defined anomeric stereochemistry by a common approach. Despite a century of research and many methodological advances[4–7], a robust, broadly applicable, high-yielding and stereospecific glycosylation method akin to the effectiveness of peptide bond formation has yet to be developed. Automated glycan assembly (AGA)[8,9] demands robust and general synthetic methods, as oligosaccharides containing certain linkages remain difficult to prepare[10].

Controlling the anomeric configuration is a key challenge in carbohydrate synthesis[11]. While 1,2-*trans* glycosidic linkages benefit from well-established neighbouring group participation, the reliable construction of 1,2-*cis*-glycosidic linkages[12] and control over anomeric configurations of 2-deoxyglycosides remain daunting challenges. Few methods[1,4–7] offer general access to complex oligosaccharides via solution-phase oligosaccharide synthesis or AGA. Ideally, glycosidic bond construction will meet several stringent requirements: (1) stereospecificity across a broad range of monosaccharides to install α and β anomeric linkages, (2) yields routinely exceeding 90%, (3) employing glycosyl acceptors (nucleophiles) as limiting reagents and (4) mild reaction conditions that are compatible with many protecting groups. For AGA, the solvent(s) must swell the resin, reaction times must be short (ideally <1 h) and insoluble catalysts or reagents are to be avoided.

S_N2 glycosylations[13] that are not limited to specific monosaccharides and protecting group patterns could offer stereospecific access to all glycosidic linkages, including challenging 1,2-*cis* and 2-deoxyglycosides. Current state-of-the-art S_N2 glycosylation methods[4,6,14–18] do not meet the stringent requirements outlined above. We previously introduced a directing-group-on-leaving-group (DGLG) strategy to facilitate directed acceptor delivery (Fig. 1a, **A**/**A′**). Divorcing

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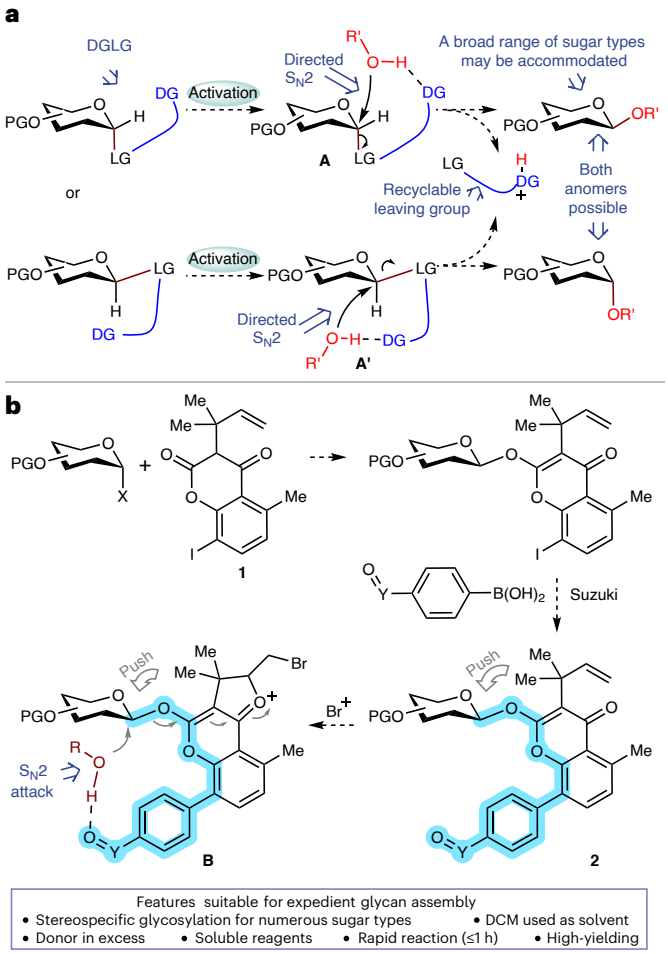

Fig. 1 | Design for stereospecific glycosylations. a, The DGLG strategy for S_N2 glycosylations. **b**, DGLG design based on a chromenone platform permits facile activation by an electrophilic bromine reagent. PG, protecting group; LG, leaving group; DG, directing group.

the directing group from the monosaccharide by placing it on the anomeric leaving group provides the basis for stereospecific glycosylations of unparalleled generality. Initial proof-of-concept studies[15,18,19] suffer from limited scope, incomplete anomeric configuration inversion, long reaction times (typically >12 h), the need to use excess acceptor, and solvents ($PhCF_3$, hexanes or cyclohexane) that do not properly swell polystyrene resins used during AGA.

Building on these early studies[15,18,19] a conceptually distinct approach was envisioned (Fig. 1b). Donor **2** with a leaving group based on a 4*H*-chromen-4-one core and featuring a rigid scaffold (highlighted in blue) between the oxygen atom of the directing group Y=O and the anomeric leaving oxygen atom was designed. Its tertiary 1,1-dimethylallyl group enhances the rigidity by sterically compelling its sugar ring to orient towards the directing group. The activation of **2** with an electrophilic bromine reagent occurs distal to the anomeric centre and entails a facile 5-*exo*-*trig* cyclization of its chromenone oxygen to the vinyl group. This cyclization should be further facilitated by the gem-dimethyl groups owing to the Thorpe–Ingold effect. Upon the formation of a strong H-bond between an alcoholic acceptor and the donor directing group oxygen, the conserved rigid scaffold in the activated donor **B** (highlighted in blue) was envisioned to facilitate a backend delivery of the acceptor at the anomeric position because the entropy cost stemming from organizing an S_N2 transition state is minimized and the acceptor is positioned at a proper distance from the anomeric centre of the donor. This approach may enable rapid glycosylations, permit the use of acceptors as limiting reagents and solvents such as dichloromethane (DCM) that swell polymer supports, and tolerate more potent directing groups that may not be compatible with metal catalysis or acid activation but can lead to improved S_N2 reaction characteristics and a broader reaction scope. Here, we reduce this design to practice and achieve rapid and highly efficient glycosylations with an inversion of configuration at the anomeric position across a broad range of monosaccharide scaffolds. The method was applied in the context of solution-phase oligosaccharide synthesis and AGA.

Results

Donor synthesis and reaction optimization

Donor **2** was prepared from chromane-2,4-dione **1** and a glycosyl halide via glycosylation followed by a Suzuki–Miyaura coupling. **1** is readily synthesized in three steps from commercially available 2-hydroxy-6-methylbenzoic acid (see Supplementary Section 2 for details).

Initially, the formation of methyl D-glucopyranosyl-(1→6)-α-D-glucopyranoside **4a** from β-D-glucopyranosyl donors **2a**–**2d** and the primary acceptor methyl α-D-glycopyranoside **3** was explored. $(Coll)_2Br^+NTf_2^-$ (bis(*sym*-collidine)bromine(I) bis(trifluoromethanesulfonyl)imide, 1.8 equiv.)—a stable electrophilic bromine reagent that dissolves readily in DCM—promoted complete glycosylation in DCM within 1 h at a temperature of −40 °C (Table 1, entries 1–4). The donor directing group plays a key role in achieving S_N2 glycosylations. Donor **2a** featuring the pyrrolidine-derived amide afforded a moderate α/β ratio of 8.8/1 (entry 1). Replacing the amide group with stronger H-bond acceptors[20] such as diphenylphosphinoyl[21,22] (**2b**, entry 2), dimethylphosphinoyl (**2c**, entry 3) and diisopropylphosphinoyl (**2d-1**) led to a steady improvement of stereoselectivity to α-glycoside formation only (entry 4). Raising the reaction temperature to 0 °C in the case of the best donor **2d-1** (entry 5) led to a slightly diminished α/β ratio (35/1), as some **3** (~5%) remained unreacted. By replacing all benzyl groups in **2d-1** with less-arming 4-CF_3Bn groups in **2d-2** (ref. 23), **3** was completely consumed at 0 °C while the α/β ratio of the diglucoside product **4b** did not change (entry 6). This trifluoromethylated benzyl group facilitated the separation of donor anomeric mixtures during the preparation of α-glucosyl and α-galactosyl donors. Lowering the reaction temperature to −40 °C (entry 7) with **2d-2** also led to complete S_N2 transformation (cf. entry 4). During all reactions using donors **2d**, the cyclized bromo by-product **5d** was formed quantitatively and was isolated and fully characterized. This by-product can be recycled and converted back to donor **2d-2** in two steps—the regeneration of the vinyl group upon Zn reduction of the C–Br bond and the Koenigs–Knorr glycosylation—in 60% overall yield. In the absence of a directing group, donor **2e** exhibited little stereoselectivity (entry 8), further confirming the essential role of the directing group in this S_N2 glycosylation. *N*-bromosuccinimide (NBS), a weaker brominating reagent with limited solubility at low temperatures, led to a sluggish and less selective reaction at elevated temperatures (entry 9). Lastly, switching the counteranion of the electrophilic bromine reagent from non-nucleophilic NTf_2^- to nucleophilic OTf^- (entry 10) and ClO_4^- (entry 11) led to poor stereoselectivities, suggesting that the nucleophilic attack at the activated donor by these counteranions was facile. Additional conditions optimizations can be found in Supplementary Section 6.3.

Reaction scopes

This S_N2 glycosylation strategy is generally applicable to various pyranosyl and furanosyl donors and a host of acceptors (Fig. 2). The construction of 1,2-*cis* glucosidic linkages (**4a**–**4o**) was stereospecific, with primary and secondary acceptors resulting in the exclusive formation of α-anomers from pure β-donors in excellent yields. The mild reactions were completed at −40 °C in 1 h and tolerated thioglycosides (**4i**) and temporary protecting groups such as Fmoc (**4n** and **4o**). This stereospecific glycosylation also worked well for the conversion of

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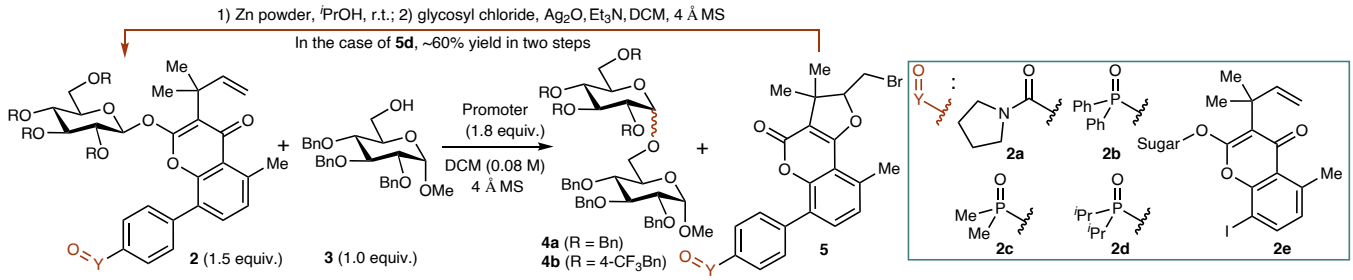
Table 1 | Optimization of glycosylation conditions[a]



Entry	Donor	Promoter	Conditions	Yield[b]	α/β[b]
1	**2a** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	99%	8.8:1
2	**2b** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	99%	21:1
3	**2c** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	85%[c]	32:1
4	**2d-1** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	99%	α only
5	**2d-1** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	0 °C, 0.5 h	95%[d]	35:1
6	**2d-2** (R=4-CF_3Bn)	$(Coll)_2Br^+NTf_2^-$	0 °C, 0.5 h	99%	35:1
7	**2d-2** (R=4-CF_3Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	99%	α only
8	**2e** (R=Bn)	$(Coll)_2Br^+NTf_2^-$	−40 °C, 1 h	99%	1.3:1
9	**2d-2** (R=4-CF_3Bn)	NBS	0 °C to r.t., 12 h	45%	4.5:1
10	**2d-2** (R=4-CF_3Bn)	$(Coll)_2Br^+OTf^-$	−40 °C, 1 h	84%	1:2.1
11	**2d-2** (R=4-CF_3Bn)	$(Coll)_2Br^+ClO_4^-$	−40 °C, 1 h	87%	1:2.0

[a]Standard reaction conditions: donor **2** (0.060 mmol, 1.5 equiv.), acceptor **3** (0.040 mmol, 1.0 equiv.), promoter (0.072 mmol, 1.8 equiv.) and 100 mg of 4 Å MS in anhydrous DCM (0.75 ml) in a cooling bath. [b]Yield and anomeric ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c]15% of **3** remained. [d]5% of **3** remained. r.t., room temperature; MS, molecular sieves; Bn, benzyl.

α-glucosyl donors into β-glucosides (**4p**–**4r**). For primary acceptors, complete anomeric inversion (**4p** and **4q**) was realized. The construction of 1,2-*cis* galactosidic linkages was also stereospecific with various acceptors, and **4s**–**4y** were formed in pure α-form from β-galactosyl donors in high yields. The enhanced reactivity of an α-galactosyl donor required a lower reaction temperature (−60 °C) for an efficient conversion to β-galactoside **4z**, achieving excellent stereoinversion with the primary acceptor **3**. Challenging β-mannosides **4aa** and **4ab** were obtained in excellent yields and with complete stereochemical inversion using a 2,3-di-*O*-methyl-4,6-*O*-benzylidene-α-D-mannosyl donor. Replacing the *O*-methyl ethers with *O*-benzyl ethers maintained the stereospecificity but resulted in lower conversions. The reactions of doubly acetonide-protected mannosyl donors[24] with both **3** and a secondary acceptor resulted in nearly complete anomeric stereochemical inversion and high yields en route to both β-mannosides (**4ac** and **4ad**) and α-mannosides (**4ae** and **4af**). Excellent stereoselectivities (**4ag** and **4ah**) and complete anomeric configuration inversion (**4ai** and **4aj**) were also achieved with L-rhamnosyl α- and β-donors, respectively.

1,2-*cis* glycosidic linkages in α-D-2-azido-2-deoxyglucosides (**4ak**–**4al**), α-D-2-azido-2-deoxygalactosides (**4am**–**4ao**), α-L-fucosides (**4ap** and **4aq**) and α-D-alluronates (**4r** and **4s**) were readily installed with complete stereochemical inversion and in excellent yields. The reaction affording the protected Tn antigen **4ao** demonstrated superior efficiency compared with literature examples4[25,26].

Stereoselective construction of α- or β-2-deoxyglycosides is synthetically challenging[27]. Both α-2-deoxyglucosides (**4at** and **4au**) and β-2-deoxyglucosides (**4av**–**4ax**) were produced in sterically pure form or >20:1 anomeric selectivities. In the cases of **4aw** and **4ax**, the donor is per-*O*-[3,5-bis(trifluoromethyl)benzyl]-protected, and pyrrolidin-1-ylcarbonyl as the directing group performed better than diisopropylphosphinoyl.

The S_N2 glycosylation strategy was successful in the construction of all four types of 1,2-*cis* pentofuranoside[19,28,29]: β-D-arabinosides **6a** and **6b**, α-D-xylosides **6e** and **6f**, α-D-ribosides **6g** and **6h**, and β-D-lyxosides **6i** and **6j**. The reactions with primary and less reactive secondary acceptors were high-yielding and exhibited high or complete stereoinversion. Challenging β-lyxosides **6i** and **6j** are produced with high stereoselectivities[19,28,29]. 1,2-*trans* α-D-arabinosides **6c** and **6d** were also readily prepared from a β-donor using the S_N2 strategy.

These stereospecific or highly stereoselective glycosylation reactions used acceptors as limiting reagents and proceeded to completion mostly in 1 h at −40 °C and in DCM. They surpassed previous findings in our[15,18,19] and other laboratories[11,12] and are attractive for use in AGA.

Oligosaccharide synthesis

α-Glucan pentasaccharide **7**, the repeating unit of an immunostimulating glycan isolated from *Aconitum carmichaeli*[30] and composed exclusively of 1,2-*cis* glycosidic linkages, was prepared to illustrate the utility of the approach. Each glycosidic linkage was installed using 1.2–1.5 equiv. donor, with complete α-selectivity, in good-to-excellent yield, and within 1 h (Fig. 3a).

6-*O*-Fmoc donor **BB3**, previously used in the synthesis of **4n** and **4o**, was used as a building block during AGA. Resin equipped with a photocleavable linker was reacted with thioglucoside donor **BB1**, followed by three successive glycosylations with excess of **BB3**. Subsequent photocleavage delivered tetraglucoside **8** in 15% yield over eight steps (Fig. 3b). $^1J_{C-H}$ coupling constants in the ^{1}H–^{13}C coupled heteronuclear single quantum coherence spectrum confirm the α-configuration of each glycosidic linkage. Similarly, tetraglucoside **9** containing two glucosyl-1,4-α-glucosidic linkages was synthesized in 21% yield over eight steps using **BB3** and 4-*O*-Fmoc donor **BB2**.

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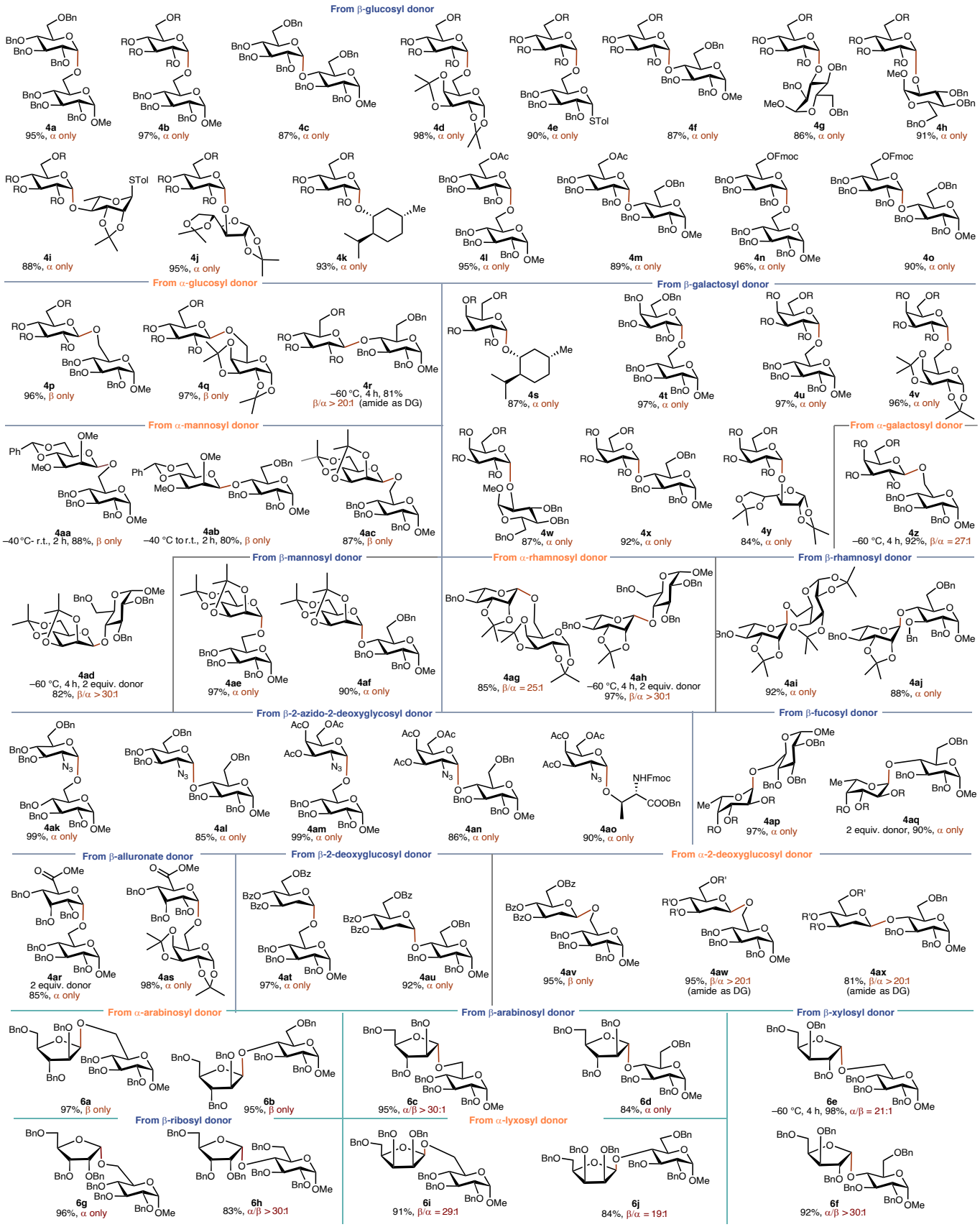

Fig. 2 | Glycosylation scope with pyranose and furanose donors. Representative examples using 1.5 equiv. donor, 1.0 equiv. acceptor, 1.8 equiv. $(Coll)_2Br^+NTf_2^-$, 4 Å MS in anhydrous DCM, at −40 °C, 1 h. R = 4-CF_3Bn, R′ = 3,5-$(CF_3)_2$Bn. Fmoc, 9-fluorenylmethyloxycarbonyl group; Tol, *p*-tolyl group; Bz, benzoyl group.

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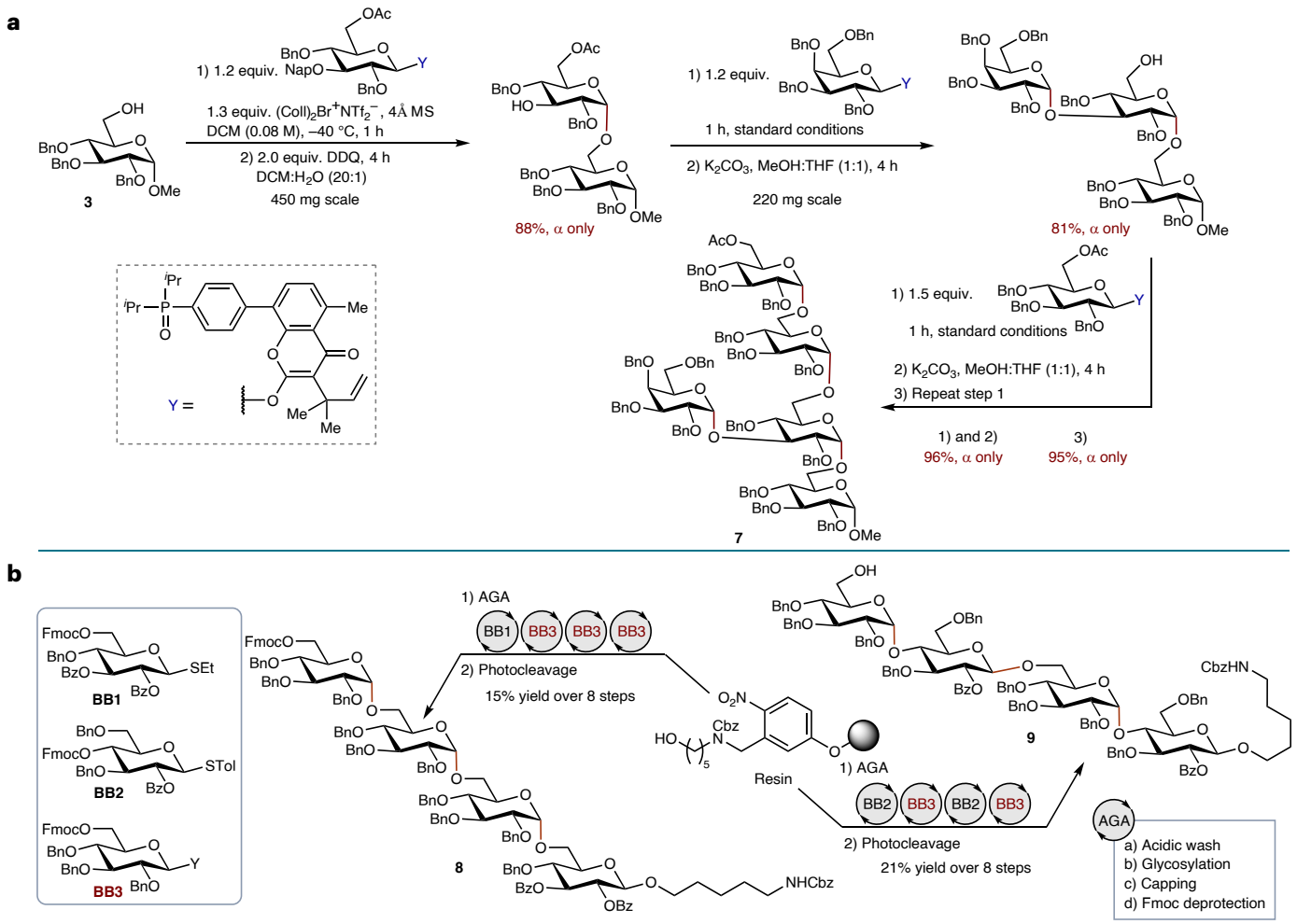

Fig. 3 | Synthesis of oligasaccharides. a, Solution-phase synthesis of pentasaccharide with all 1,2-*cis* glycosidic linkages. **b**, AGA constructing 1,2-*cis* glycosidic linkages. Nap, 2-naphthylmethyl group; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; THF, tetrahydrofuran; Cbz, benzyloxycarbonyl group.

VT ^{1}H NMR spectroscopy studies

The reaction kinetics were probed by variable temperature (VT) nuclear magnetic resonance (NMR) spectroscopy of the reaction of **2d-2** with water as the acceptor. **2d-2** was completely consumed in 1 min at −36 °C in CD_2Cl_2, revealing that $(Coll)_2Br^+NTf_2^-$ rapidly activates the donor even at this low temperature (Fig. 4a). The exclusive formation of α-D-glucose **10** in quantitative yield illustrates that the reaction with water is completely stereoinvertive. Attempts to observe the activated donor of type **B** used VT NMR spectroscopy of the reactions of both anomers of galactosyl donor **2f** under anhydrous conditions (Fig. 4b; for details, see Supplementary Section 7). When β-**2f** was treated by $(Coll)_2Br^+NTf_2^-$ at −40 °C, little substrate remained after 5 min, and the initially activated intermediate β-**C** was not detected. Instead, roughly equal quantities of a triplet at ~5.1 ppm and an unresolved multiplet at 5.8 ppm were formed and assigned to be the β- and α-anomers of the oxyphosphonium salt **D**, respectively. Their structures were assigned with the help of ^{31}P-decoupled ^{1}H NMR spectroscopy and ^{1}H–^{31}P heteronuclear multiple bond correlation. Moreover, α-**D** was prepared from the corresponding galactosyl chloride to confirm its identity. In addition, both anomers of the collidinium species **E** were formed. Their structures were confirmed by the reaction of the corresponding galactosyl bromide with collidine. β-**D** is much less stable than α-**D** and disappeared completely at −10 °C, while the latter only underwent slow conversion to **E** at 25 °C. The detection of both anomers of **D** and **E** in substantial amounts and the apparent absence of β-**C** at −40 °C suggest that the nascent β-**C** undergoes facile S_N1 pathways in the absence of an alcohol acceptor. By stark contrast, all glycosylation reactions using β-**2f** as donor and yielding **4s**–**4y** exhibited complete stereoinversion at the anomeric centre. These results highlight that the directing strategy can thoroughly outcompete the S_N1 pathway. When α-**2f** was treated by $(Coll)_2Br^+NTf_2^-$ at −40 °C, the initially activated intermediate α-**C** was detected. Some α-**2f** remained due to insufficient Br^+ in the reaction. The fact that α-**C** is much more stable than β-**C** is consistent with Lemieux's observation that β-glucosyl bromide is more reactive than its α counterpart[31]. α-**C** gradually disappeared in 50 min at −40 °C and was mostly converted to β-**D** along with a minor amount of α-**D** and **E**. The predominant formation of β-**D** from α-**C** suggests an S_N2-like substitution, which is consistent with the more stable nature of α-**C**. Finally, the critical H-bonding interaction in this stereospecific glycosylation was confirmed by the observation of increasing downfield shift of the ^{1}H signal of the acceptor **3** hydroxyl group in the presence of the donor **2d-2** as the temperature was lowered from 25 °C to −40 °C (for details, see Supplementary Section 7).

Conclusion

A distinct DGLG strategy enables broadly applicable stereospecific glycosylations. Anomerically pure donors featuring a chromenone-based leaving group are activated efficiently under mild conditions. Complete stereochemical inversion at the anomeric position and excellent yields were achieved across many types of monosaccharide. This chemistry offers a unifying strategy for installing challenging 1,2-*cis* glycosidic linkages with excellent stereoselectivity or stereospecificity. 1,2-*trans*

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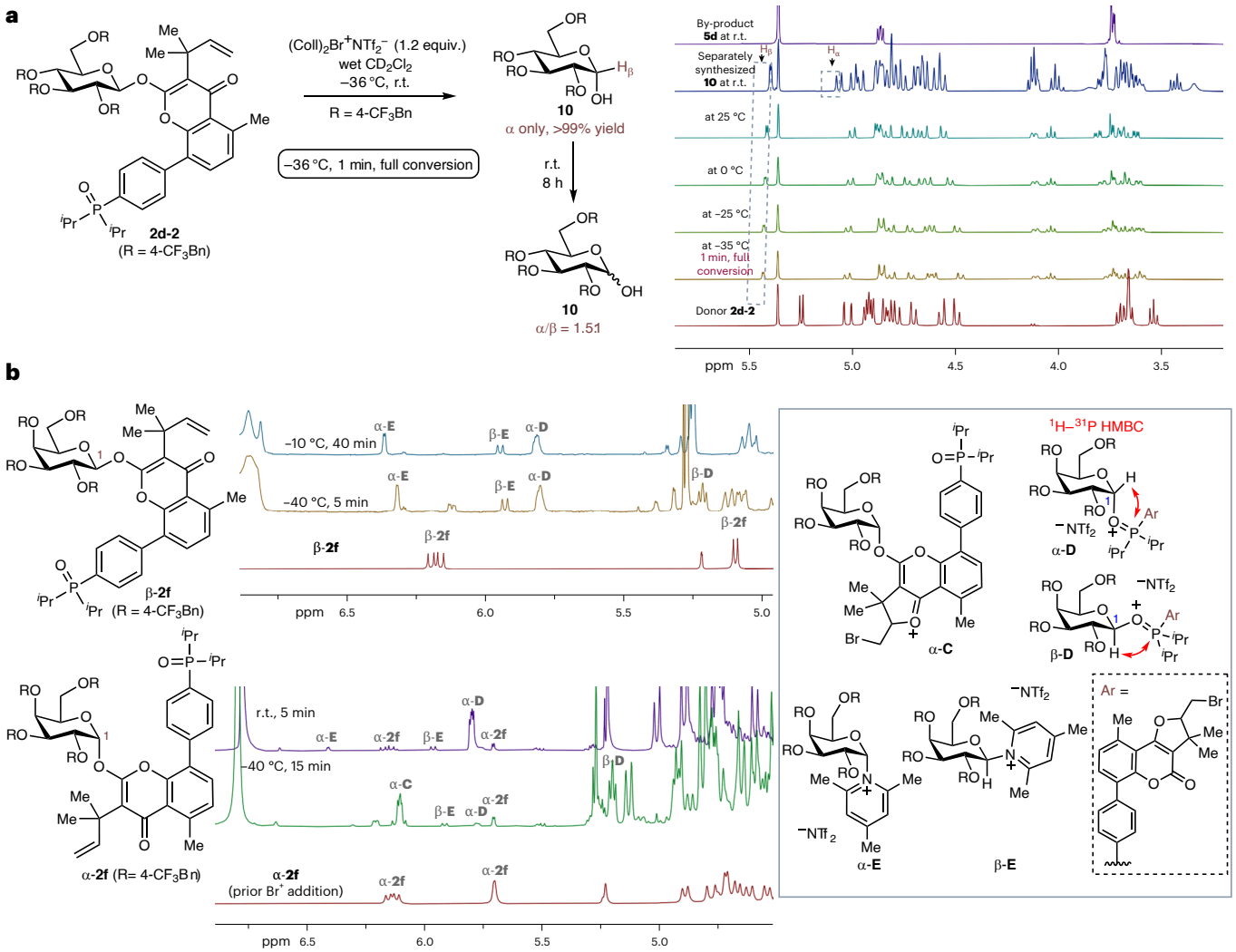

Fig. 4 | Probing the reaction kinetics by VT ^{1}H NMR spectroscopy experiments. a, Using water as an acceptor. **b**, In the absence of an acceptor. Reaction conditions: ~1.0 equiv. $(Coll)_2Br^+NTf_2^-$, CD_2Cl_2, 4 Å MS, −40 °C. HMBC, heteronuclear multiple bond correlation.

glycosides and both anomers of 2-deoxyglucosides can be synthesized with high efficiency and excellent stereoselectivities. The method is readily applicable to multistep oligosaccharide synthesis and AGA in excellent yields and with exceptional stereochemical control.

Methods

General procedure for solution-phase glycosylation

Donor **2** (0.060 mmol, 1.5 equiv.), acceptor **3** (0.040 mmol) and activated 4 Å molecular sieves (100 mg) were added to a glass vial. The vial was capped and sealed with parafilm. Under an argon atmosphere, anhydrous CH_2Cl_2 (0.60 ml) was added, and the mixture was stirred for 2–3 min before being cooled to −40 °C. A solution of $(Coll)_2Br^+NTf_2^-$ (0.072 mmol, 1.8 equiv.) in anhydrous CH_2Cl_2 (0.15 ml) was added dropwise along the inner wall of the vial. The reaction mixture was further stirred for 1 h. The reaction was then quenched by MeOH (5.0 equiv.) at −40 °C. After stirring for 10 min, the mixture was allowed to warm to room temperature. It was then diluted with ethyl acetate and filtered through Celite or a syringe filter to remove the molecular sieves. The filtrate was concentrated under reduced pressure, and ^{1}H NMR spectroscopic analysis of the crude mixture was performed to assess the anomeric selectivity and yield, using 1,3,5-trimethoxybenzene as the internal standard. The crude mixture was then purified by column chromatography on silica gel to yield the desired product **4**.

Data availability

Experimental procedures and characterization data are provided in the Supplementary Information. Correspondence and requests for materials should be addressed to L.Z. and P.H.S.

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Author contributions

The solution-phase studies and the data analysis were mostly performed by Q.Z. and partially by Y.Z. and further assisted by J.Y. and P.K. L.Z. conceived the design and directed the solution-phase studies. The solid-phase studies and data analysis were directed by P.H.S. and performed by N.J.F., J.D.-F. and E.T.S. The paper was prepared by L.Z., P.H.S., Q.Z., Y.Z., N.J.F. and E.T.S. All authors contributed to discussions.

Competing interests

The authors declare no competing interests.

Additional information

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