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The influence of acceptor acidity on hydrogen bond mediated aglycone delivery (HAD) through the picoloyl protecting group

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The outcome of glycosylation reactions heavily relies on the specific protecting group patterns employed on both the donor and acceptor molecules. The picoloyl (Pico) protecting group stands out as it can steer the stereoselectivity in a glycosylation reaction through hydrogen bond-mediated aglycone delivery (HAD). This provides *syn*-stereoselectivity, with respect to the stereochemistry of the Pico group, by forming a hydrogen bond between the incoming acceptor and the picoloyl ring nitrogen. We here probe how acceptor acidity influences the stereo-directing effect of the picoloyl protecting group. A set of 3-*O*-functionalized glucosyl and mannosyl donors, each bearing different protecting groups (picolinate, nicotinate, isonicotinate, and benzoate), were synthesized for systematic evaluation. For the 3-*O*-picoloyl-glucose series, the picoloyl group exhibited minimal influence on stereoselectivity, with only weak nucleophiles showing a modest shift in selectivity for the 3-*O*-Pico protected glucosyl donor in comparison to the other C-3-acyl glucosides. In contrast, in the 3-*O*-picoloyl-mannose series a much stronger β-directing effect was observed, wherein more acidic acceptors led to increased β-selectivity. The results provide insights into the complex interplay of acceptor acidity and glycosylation stereoselectivity mediated by the picoloyl protecting group.

Introduction

One of the principal challenges in oligosaccharide synthesis is the stereoselective formation of glycosidic bonds. The stereochemical outcome of glycosylation reactions is highly dependent on the protecting group patterns on both the donor and acceptor molecule.[1] Therefore, steering the reaction towards the desired stereoisomer requires careful selection of protecting groups.[2] In recent years there has been much interest in strategies that employ protecting groups on remote positions (C-3, C-4, or C-6) to influence the stereochemical outcome of glycosylation reactions, when one cannot rely on neighboring group participation (NGP) from C-2.[3] There are two distinct categories of strategies employing remote protecting groups: those that form covalent intermediates and those which act through non-covalent interactions.[4] The first of these includes the long-range participation (LRP) by remote ester groups participate to form a bridged bicyclic intermediate.[5] These bridged bicyclic intermediates direct the stereoselectivity to provide the *anti*-products, with respect to the orientation of the ester moiety, by blocking one side of the carbohydrate ring (Scheme 1a). In the latter category, the most common strategy is the hydrogen-bond-mediated aglycone delivery (HAD) developed by the group of Demchenko.[6] In this methodology, a remote position is functionalized with a protecting group capable of acting as a hydrogen-bond acceptor. The most common protection group used in this category, due to its advantageous installation[7] and deprotection conditions,[8] is the picoloyl ester (Pico). Contrary to the reactions of the dioxanium ions, this protecting group steers the stereoselectivity of glycosylation reactions to provide the *syn*-products with respect to the position of the Pico-group. The picoloyl ester influences the stereochemical outcome of glycosylation reactions by formation of a hydrogen bond between the picoloyl ring nitrogen and the glycosyl acceptor (Scheme 1b). Support for this *modus operandi* has been delivered by a plethora of reactions, involving various donors featuring the picoloyl ester on various carbohydrate positions, providing *syn*-stereoselectivity.[9] While much effort has been devoted to screening the substrate scope and tuning reaction conditions,[6a,10] the role of the acceptor on HAD has not been studied systematically. Generally, stronger *O*-nucleophiles are less acidic and thus exhibit weaker hydrogen bonding.[11] Given the central role of the hydrogen bond within the HAD mechanism, the hydrogen-bonding capacity of the *O*-acceptor is likely to be important.[12]

Here we study the role of acceptor acidity on HAD, through a systematic investigation of 3-*O*-picoloyl-glucosyl and mannosyl donors in combination with a set of acceptors of gradually increasing acidity. To this end, we functionalized the C-3-

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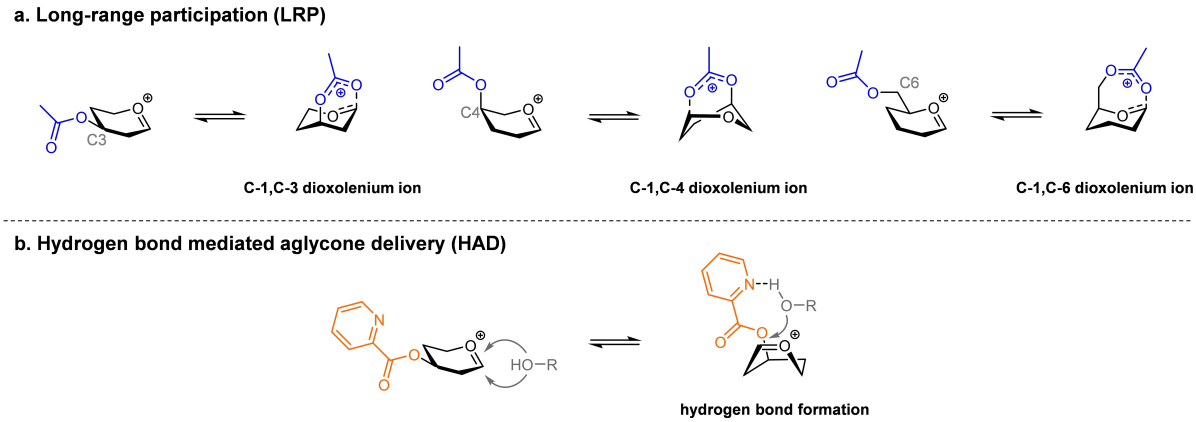

Scheme 1. (a) A schematic representation of the possible reactive intermediates in long range participation (LRP). (b) Hydrogen bond mediated aglycone delivery (HAD) by the picoloyl protecting group, mounted at C-3.

hydroxyl with benzyl, benzoate, picoloyl, and picoloyl-related protecting groups. Subsequently, we examined the effect of acceptor acidity on the stereoselective outcome of glycosylation reactions employing these donors. This study shows that more acidic, *i.e.*, less nucleophilic, *O*-acceptors are better at hydrogen bond mediated aglycone delivery. The results provide insights into how acceptor tuning can be utilized to optimize the stereoselectivity provided by the picoloyl protecting group.

Results and discussion

To investigate the influence of acceptor acidity on the HAD mechanism, we set out to establish acceptor acidity-stereoselectivity trends for a set of glucosyl and mannosyl donors. As model acceptors we used of a set of partially-fluorinated ethanol derivates (*i.e.*, 2,2,2-trifluoroethanol, TFE; 2,2-difluoroethanol, DFE; 2-fluoroethanol, MFE; ethanol, EtOH), which are well-established as model-acceptors. These model acceptors exhibit a gradual increase of acidity along the acceptor series, making this set of alcohols a powerful tool for investigating the acidity-stereoselecivity relationship. As for the donor systems, we employed a set of glucosyl and mannosyl donors, that are protected with benzyl ethers or a benzyl ether and benzylidene acetal to mask the C-2, C-4 and C-6 hydroxyl functions, placing different protecting groups at the C-3-OH. We chose these donor systems because previous research has shown the HAD mechanism to be relevant for mannosyl 3-*O*-picoloyl donors, while playing a less important role for the glucosyl 3-*O*-picoloyl-donors. Furthermore, we have recently investigated the structurally related 3-*O*-benzoyl glucosyl and -mannosyl donors which provide strikingly disparate stereoselectivities in their glycosylation reactions.[13] While LRP plays an important role in the mannosylation reactions (providing the α-products) the benzoyl ester played no major role in the glycosylation reactions of the corresponding glucosyl donors, where the stereoselectivity of the reactions critically depended on the nucleophilicity of the acceptors. This stark contrast in the reaction mechanism that is followed and the resulting stereoselectivity, make the glucosyl and mannosyl 3-*O*-protected donors an excellent system to investigate the acceptor acidity-stereoselectivity trends and establish how they depend on the available reaction paths (Scheme 2b). To verify that any trends arising from the picoloyl protecting group are the result of HAD, we included donors in our experimental set-up which are structurally and electronically similar to the picoloyl protecting group. The nicotinate (Nico, *N* at *meta* position) and *iso*-nicotinate (*i*-Nico, *N* at *para* position) protecting groups are picoloyl-regioisomers having the pyridine nitrogen at different positions in the ring. These protecting groups have similar electron-withdrawing properties as the picoloyl protecting group but are likely less capable of HAD,[6a,14] as hydrogen bonding with these groups would orient the acceptor too far away from the anomeric center of the donor.

Lastly, in our experimental design we used Ph_2SO/Tf_2O[15] mediated pre-activation conditions which transform the parent donors into the corresponding glycosyl triflates prior to the addition of the acceptor.[16] This method of activation is well suited for this study, as it generates well-defined reactive intermediates without the use of a Brønsted acid. The non-acidic conditions are essential to study the influence of acceptor acidity, as protonation of the picoloyl group can preclude HAD.[14,17] To scavenge the TfOH, released in the glycosylation reactions upon attack of the alcohol on the activated glycosyl donors, we included a non-nucleophilic base in the reaction mixtures. To confirm that protonation of the Pico group does not affect the stereochemical outcome of the glycosylation reactions,[18] we briefly explored the use of different equivalents (2.5 or 10) of 2,4,6-tri-*tert*-butylpyrimidine (TTBP), 2,6-di-*tert*-butylpyrimidine, and 2,4,6-tri-*tert*-butylpyridine, having pK_aH values of 1.02, 3.58 and 4.02. No effect of these bases was observed on the stereoselectivity (See Supplementary Table 1) and therefore we continued with the use of the commonly used TTBP in the study.

Based on this experimental design, we generated the set of 3-*O*-protected phenyl 2,4,6-*O*-benzyl-1-thio-glucosyl **1–5** and mannosyl donors **6–10** (See Table 1 and 2), on which the following 3-*O* protecting groups were installed: benzyl (**1** and

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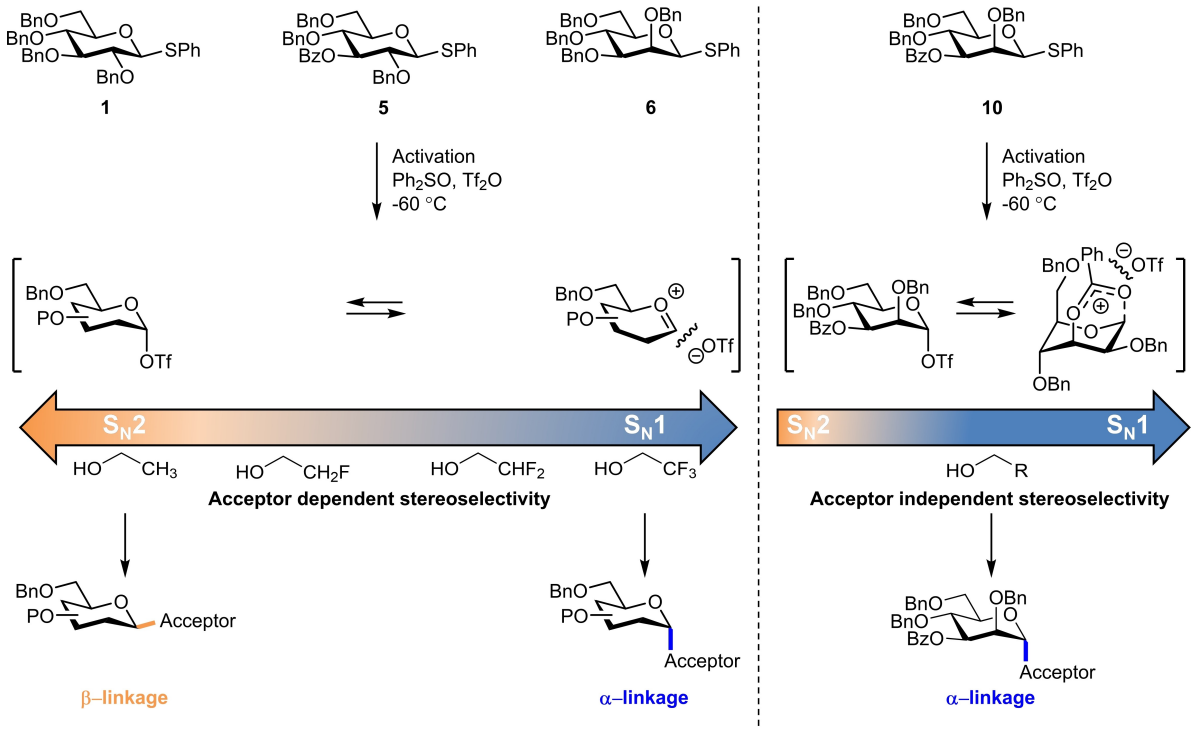

Scheme 2. General mechanism of glycosylations employing the Ph_2SO/Tf_2O mediated pre-activation conditions.

6), picolinate (**2** and **7**), nicotinate (**3** and **8**), isonicotinate (**4** and **9**) and benzoyl (**5** and **10**). Each donor was reacted with the four model acceptors (TFE, DFE, MFE and EtOH), and the stereoselective outcome was recorded (Tables 1–4). Results from the 3-*O*-benzyl and 3-*O*-benzoyl donors were taken from previous work, and are provided for comparison.[5d] The results of the glycosylations with the 3-*O*-benzyl donors **1** and **5** show the 'intrinsic' stereoselectivity of the donors under the used glycosylation conditions, while the glycosylations with the 3-*O*-benzoyl donors **6** and **10** show the influence of acyl groups on this selectivity.

First, we explored the acceptor acidity-stereoselectivity relationship for glucosyl donors **1**–**5**. As previously described,[19] the stereoselectivity of the glycosylation reactions of the 2,4,6-tri-*O*-benzyl glucose **1** and **5** gradually shifts from α- to β-stereoselectivity as the nucleophilicity of the acceptor increases.[20] The 3-*O*-Pico-glucosyl donor **2**, and the Nico and *i*-Nico stereoisomer counterparts **3** and **4**, show identical trends. The lack of stereochemical steering of the Pico-type esters is in line with the observations of the group of Demchenko.[21] They have shown that β-selective glycosylations can be achieved using 3-*O*-picoloyl-glucosyl donors by protonation of the picoloyl nitrogen using an excess of acid, which serves to stabilize a covalent α-triflate intermediate.[14,17] Thus, under the essentially neutral pre-activation reaction conditions used here, no β-directing effect would be expected.

Next, we examined the reactivity-stereoselectivity trends for the mannosyl donors **6**–**10** (Table 2). The stereoselectivity of the glycosylations with the 3-*O*-benzyl-mannosyl donor **6** gradually shifts from α- to β-stereoselectivity as the nucleophilicity of the acceptor increases, while the 3-*O*-benzoyl-mannosyl donor **10** solely provides the α-linked products. These can originate from a 1,3-dioxanium ion intermediate, formed by a long-range participation mechanism.[5d,22] The introduction of a nitrogen atom in the benzoyl ring on either the *meta* (Nico donor **8**) or the *para*-position (*i*-Nico donor **9**), leads to a slightly decreased stereoselectivity in the reactions. In contrast to donors **8** and **9**, the 3-*O*-picoloyl mannose donor **7** provides product mixtures with both anomers in approximately similar amounts for ethanol, MFE and DFE. TFE, the most acidic acceptor of the series, provides a modestly β-selective glycosylation, which in light of the benchmark results obtained for this acceptor with benzyl donor **6** and benzoyl mannoside **10**, stands out (Table 2). The increased β-selectivity in the reactions of the 3-*O*-Pico donor **7** can be explained by a HAD mechanism, with the most acidic acceptor experiencing the strongest stereochemical guidance.

Finally, we considered the 4,6-*O*-benzylidene-mannosyl and glucosyl donor systems. The 4,6-*O*-benzylidene mannose system has been introduced for the generation of β-mannosidic linkages (i.e. the β-Crich-mannosylation).[23] This preference of 4,6-*O*-benzylidene mannosyl donors in forming the β-product is generally considered to be the result of a S_N2-like attack on the anomeric α-triflate, which is stabilized for these donors due to the conformational tethering of C-4 and C-6. However, LRP by C-3-acyl groups can completely overturn the β-selectivity in this system.[5b,20,24] In the corresponding glucose case, the α- and β-triflates play a role, with the latter becoming the more important reactive intermediate in the reaction with decreasing nucleophilicity of the acceptor.[19,20] In contrast to the mannosyl

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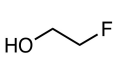
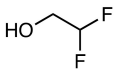
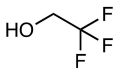
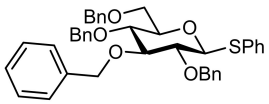
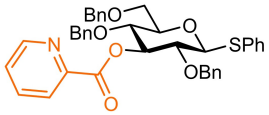
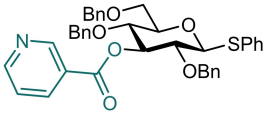
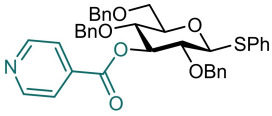
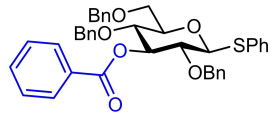
Table 1. Experimentally found stereoselectivities for model glycosylation reactions with the phenyl 2,4,6-tri-*O*-benzyl-1-thio glucosyl donors **1–5**; Experimental conditions: pre-activation-based glycosylation conditions; nucleophile (2 eq.), Tf_2O (1.3 eq.), Ph_2SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), −80 to −60 °C. The stereoselectivity of the reaction is expressed as α:β and based on ^{1}H-NMR of the purified compounds. In all cases, the NMR spectra for both the crude and purified compounds were compared to analyze whether the measured stereoselectivity did not alter upon purification.

	Donor	Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)
1		15:85[a] (70%)	36:64[a] (75%)	48:52[a] (58%)	72:28[a] (80%)
2		28:72 (43%)	36:64 (39%)	46:54 (50%)	49:51 (55%)
3		20:80 (48%)	40:60 (50%)	41:59 (47%)	47:53 (51%)
4		19:81 (46%)	32:68 (50%)	50:50 (52%)	65:35 (31%)
5		15:85[a] (76%)	34:66[a] (82%)	48:52[a] (70%)	79:21[a] (76%)

>90:10	>80:20	>60:40	50:50	<40:60	20:80	<90:10	(α:β)

[a] Results from Hansen *et al.* (2020),[5d] identical glycosylation conditions were used.

system, LRP has been shown not to play a significant role in the glycosylations of the C-3-*O*-acyl donors.[13] We were therefore very interested, whether the introduction of a 3-*O*-picoloyl protecting group would provide a stereoselectivity trend consistent with either a LRP, HAD or β-Crich-mannosylation mechanism.[24] We thus generated the set of phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-glucosyl donors, carrying a 3-*O*-benzyl (**11**), picolinate (**12**), nicolinate (**13**), isonicolinate (**14**) or benzoate (**15**) at C-3 and the corresponding mannosides **16**—**21**. Table 3 reports the stereochemical outcome of the model glycosylations with the glucosyl donors, while the results of the mannosylation reactions are reported in Table 4. The data for 3-*O*-benzyl and 3-*O*-benzoyl donors **11**, **15**, **16** and **21** have previously been reported.[18,24] In line with the results displayed in Table 1, the nature of the C-3-*O*-protecting group has relatively little influence on the stereoselectivity of the reactions of the 4,6-*O*-benzylidene glucosyl donors **11**—**15**, although the formation of the β-products slightly increases when the picoloyl, nicoloyl and *i*-nicoloyl groups are used (Table 3).

In contrast to the benzylidene glucose series, the benzylidene mannose series shows different stereoselectivity for the C-3-acyl donors in comparison to the C-3-benzylated donor (Table 4). 3-*O*-Benzyl donor **16** provides β-selective glycosylations, while installation of a 3-*O*-benzoyl group (donor **20**) completely overturns this stereoselectivity, leading to complete α-selectivity for all acceptors.[26] In contrast, the donors with the Pico- (donor **17**), Nico (donor **18**) and *i*-Nico (donor **19**) groups provide anomeric mixtures in which the amount of β-product increases with increasing acidity/lower nucleophilicity of the acceptors, indicating that LRP in these latter systems is less effective. We also note the contrast with the results in Table 2, where the effect of the different C-3-acyl

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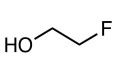
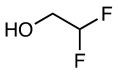
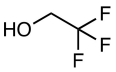
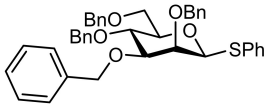
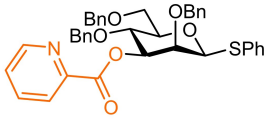
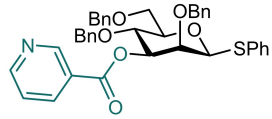
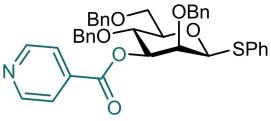
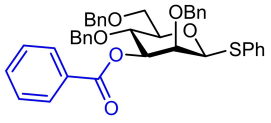
Table 2. Experimentally found stereoselectivities for model glycosylation reactions with the phenyl 2,4,6-tri-*O*-benzyl-1-thio mannosyl donors **6–10**; Experimental conditions: pre-activation-based glycosylation conditions; nucleophile (2 eq.), Tf_2O (1.3 eq.), Ph_2SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), −80 to −60 °C. The stereoselectivity of the reaction is expressed as α:β and based on ^{1}H-NMR of the purified compounds. In all cases, the NMR spectra for both the crude and purified compounds were compared to analyze whether the measured stereoselectivity did not alter upon purification.

Donor	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)
6 	33:67[a] (70%)	60:40[a] (75%)	80:20[a] (65%)	>98:2[a] (84%)
7 	55:45 (58%)	55:45 (32%)	50:50 (48%)	31:69 (59%)
8 	85:15 (53%)	85:15 (60%)	85:15 (69%)	86:14 (60%)
9 	90:10 (73%)	88:12 (94%)	86:14 (72%)	84:16 (83%)
10 	>98:2[a] (94%)	>98:2[a] (87%)	>98:2[a] (87%)	>98:2[a] (79%)

>90:10	>80:20	>60:40	50:50	<40:60	20:80	<90:10	(α:β)

[a] Results from Hansen *et al.* (2020),[5d] identical glycosylation conditions were used.

groups seems to differ significantly less. We hypothesize that these differences can be explained by destabilization of the intermediate 1,3-dioxanium ion formed from the different donors. The 1,3-dioxanium ions of the benzylidene-protected donors are less stable because of the increased ring strain in these ions,[13] forcing the dioxanium ion to take up a $B_{2,5}$-type conformation, instead of the more favorable $^1C_4$ conformation that can be attained by the 4,6-di-*O*-benzyl donors. The results indicate that the stability of the 1,3-dioxanium ions (as gauged by the α-selectivity of the reactions) further decreases with the introduction of a ring nitrogen in the acyl groups, with the destabilizing inductive effect of the ring nitrogen increasing with diminishing the distance to the dioxanium ion (Pico > Nico > *i*-Nico, as seen from Supplementary Table 2). The Pico-group shows the strongest β-directing effect, with β-selectivity increasing with increasing acceptor acidity. This trend is consistent with a scenario in which there is competition between LRP and HAD mechanisms, in which the most acidic nucleophiles prefer the latter.

Conclusions

To conclude, we studied the role of acceptor acidity in the β-directing effect of the C-3-*O*-picoloyl protecting group in glucosyl and mannosyl donors. For the 3-*O*-picoloyl-glucose series, we observed, in line with previous studies, no significant influence of the picoloyl group on the stereoselectivity of the glycosylation reactions. Only for acidic, and thus weak nucleophiles, a modest shift in stereoselectivity was observed. The 3-*O*-picoloyl-mannose series exhibit a much stronger β-directing effect, with more acidic acceptors providing more β-selective

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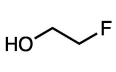
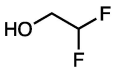
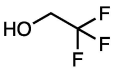
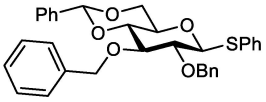
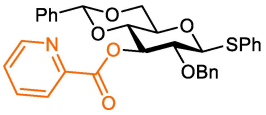
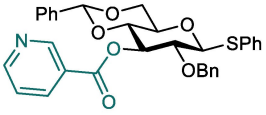
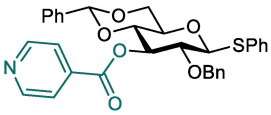
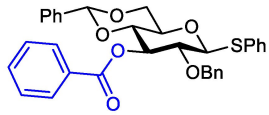
Table 3. Experimentally found stereoselectivities for model glycosylation reactions with the phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-mannosyl donors **11–15**; Experimental conditions: pre-activation-based glycosylation conditions; nucleophile (2 eq.), Tf_2O (1.3 eq.), Ph_2SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), −80 to −60 °C. The stereoselectivity of the reaction is expressed as α:β and based on ^{1}H-NMR of the purified compounds. In all cases, the NMR spectra for both the crude and purified compounds were compared to analyze whether the measured stereoselectivity did not alter upon purification.

Donor	Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)
11 	30:70[a] (80%)	50:50[a] (65%)	82:18[a] (95%)	>98:2[a] (74%)
12 	<2:98 (39%)	24:76 (49%)	58:42 (31%)	74:26 (28%)
13 	<2:98 (47%)	26:74 (69%)	65:35 (42%)	>98:2 (60%)
14 	16:84 (51%)	28:72 (37%)	80:20 (57%)	97:3 (53%)
15 	25:75[a] (quant.)	45:55[a] (quant.)	85:15[a] (74%)	>98:2[a] (84%)

>90:10	>80:20	>60:40	50:50	<40:60	20:80	<90:10	(α:β)

[a] Results from Remmerswaal *et al.* (2024),[13] identical glycosylation conditions were used.

glycosylation reactions. This dichotomy between the glucose and mannose series is reminiscent of the directing effect of the C-3-*O*-acyl groups, which in the mannose series have a strong effect, while hardly affecting glucosylation reactions. This is likely because the HAD pathway takes place through a more dissociated mechanism. The stereoselectivity in the glucosylation reactions is dictated primarily by the competition of the substitution reactions of the α- and β-triflates, which are in equilibrium through an *in situ* anomerisation scheme. The outcome of mannosylation reactions can be rationalized with the equilibrium of the anomeric α-triflate with oxocarbenium[5k,26] or dioxanium ion intermediates.[13] The observed trends in the mannose series are consistent with a scenario in which there is competition between LRP and HAD mechanisms, in which more acidic acceptors show stronger direction by the HAD mechanism.

Supporting Information

Procedures for synthesis and analytical data of all donors and precursors; computational details for calculations of reactive intermediates.

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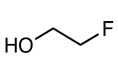
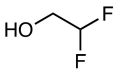
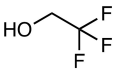
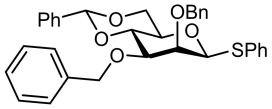
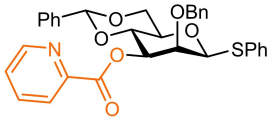
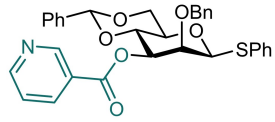
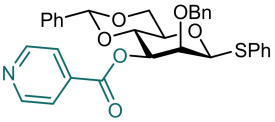
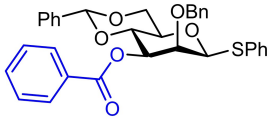
Table 4. Experimentally found stereoselectivities for model glycosylation reactions with the phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-mannosyl donors **16–20**; Experimental conditions: pre-activation-based glycosylation conditions; nucleophile (2 eq.), Tf_2O (1.3 eq.), Ph_2SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), −80 to −60 °C. The stereoselectivity of the reaction is expressed as α:β and based on ^{1}H-NMR of the purified compounds. In all cases, the NMR spectra for both the crude and purified compounds were compared to analyze whether the measured stereoselectivity did not alter upon purification.

Donor	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)	 Product α:β (yield)
16 	23:77[a] (51%)	18:82[a] (59%)	17:83[a] (61%)	19:81[a] (55%)
17 	73:27 (71%)	69:31 (51%)	55:45 (64%)	32:68 (64%)
18 	80:20 (48%)	72:28 (38%)	68:32 (50%)	58:42 (54%)
19 	>98:2 (54%)	83:17 (59%)	73:27 (61%)	50:50 (36%)
20 	>98:2[a] (73%)	>98:2[a] (94%)	>98:2[a] (72%)	>98:2[a] (83%)

>90:10	>80:20	>60:40	50:50	<40:60	20:80	<90:10	(α:β)

[a] Results from Remmerswaal *et al.* (2024),[13] identical glycosylation conditions were used.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[18] For the picoloyl group, to our knowledge, no pK_aH values are available. Therefore, to provide us with reference values, we computed the solution-phase basicity ($\Delta G_{basicity} = \Delta G_N - \Delta G_{NH^+}$) of the ring nitrogen of donors **1–3** and the proton scavengers. As expected, the trends of the solution-phase basicities of the proton scavengers closely follow the pKaH values (262.8, 266.8, 268.7 kcal mol^{-1} for respecively 2,4,6-tri-*tert*-butylpyrimidine, 2,6-di-tert-butylpyrimidine and 2,4,6-tri-*tert*-butylpyridine). The computed solution-phase basicity of donors **1–3** were much lower, regardless of donor approximately ~258.8 kcal mol^{-1}, than that of the proton scavenger.

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