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H-bonding, not remote participation, explains the influence of remote substituents on stereoselectivity in α-galactosylations

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The underlying roles of remote substituents in the stereochemical control of the formation of acetals and related reactions have been heavily debated. The competing prevailing theories were inconsistent with some of the trends reported herein. Specifically, electron-poor benzoate groups at the 4-position of a galactosyl donor gave unexpectedly high α-stereoselectivities in galactosylations. A Hammett study and DFT calculations led us to propose that non-classical intramolecular hydrogen-bonding to the β-glycosyl triflate can rationalize the selectivities observed. Using a *para*-nitrobenzoate protecting group at position 4 of galactosyl donors gave high α-selectivities in the synthesis of galactosides. Benzyl, silyl, allyl and carbamate groups were tolerated. The utility of this protocol was demonstrated in >10 examples, including a gram-scale example and a trisaccharide.

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Introduction

The use of substituents remote from a reaction centre to influence the stereochemical outcome of reactions is widespread in chemistry.[1–7] In the case of reactions proposed to proceed *via* oxacarbenium ions, this has been the subject of many studies.[8–16] The role of esters as remote substituents in stereoselective glycosylations has been the topic of much controversy and debate, especially in relation to 4-*O*-ester-mediated synthesis of biologically important 1,2-*cis*-galactosides and -fucosides (Fig. 1).[17–28] Flowers first proposed that "long-range participation", whereby the axial 4-*O*-ester of a fucosyl donor forms a dioxolenium ion intermediate analogous to **1** with an inaccessible β-face, could explain the high 1,2-*cis*-selectivity observed in fucosylations when benzoates were placed at the 4-position.[17,18] Many studies have since invoked this intermediate to rationalize stereoselective 1,2-*cis*-galactosylations and fucosylations.[19,21–23,26–28] Computational studies have been used to support this hypothesis and, indeed, dioxolenium ions have been detected experimentally using infrared ion spectroscopy and cryogenic vibrational spectroscopy.[22,23,29,30] However, these conditions are not representative of experimental conditions in the solution phase. Conversely, Woerpel, Crich and others have advocated for the hypothesis that through-space electrostatic stabilization of ion pairs **2** could explain the high stereoselectivity observed.[13,25,31] Crich and co-workers have provided significant experimental evidence against dioxolenium ion intermediates for 4-*O*-esters,[25,32,33] and concluded that the evidence supports this alternative

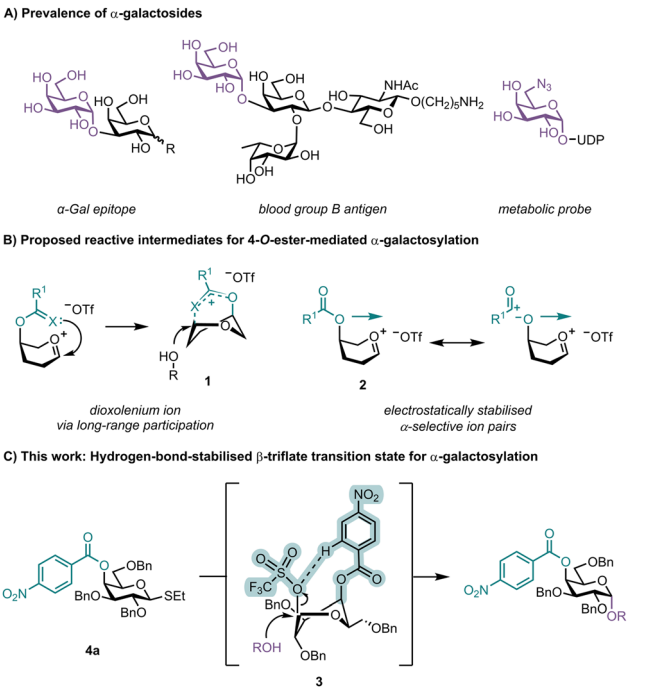

Fig. 1 (A) Prevalence of α-galactosides. (B) Proposed explanations for the effect of 4-*O*-benzoates in influencing stereoselective acetal formation. (C) α-Galactosylation *via* proposed H-bond-stabilized β-triflate transition state **3** (this work).

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electrostatic stabilization hypothesis. They have rationalized selectivities reported elsewhere under their theory (*e.g.*, more electron-rich 4-*O*-pivalates give higher selectivity than 4-*O*-acetates because they can better stabilize the partial positive charge on the anomeric carbon). Crich concluded that formation of a dioxolenium ion was a borderline phenomenon that, although detectable, was not crucial to stereoinduction in galactosylations directed by 4-*O*-esters.[25] Under either of the above theories, the addition of electron-donating groups to the ester would be expected to improve stereoselectivity, while electron-withdrawing groups would be expected to be detrimental to selectivity. Herein we report observation of an unexpected trend in studies of 1,2-*cis*-galactosylations, wherein high α-selectivity is observed using an electron-withdrawing *para*-nitrobenzoate ester at position 4.[34]

Our findings add to other unexplained reports of high α-selectivities observed using galactosyl donors bearing 4-*O*-esters with electron-withdrawing substituents. Lorenço and Ventura reported a marked increase in α-selectivity when the more electron-deficient 4,6-*O*-dichloroacetyl-protected galactosyl donor was used relative to the corresponding 4,6-*O*-acetyl donor.[35] Seeberger and Pagel observed excellent α-selectivity in glycosylations using a 4-*O*-trifluoroacetyl-protected galactosyl donor.[23] Independently, Li, Seeberger and Demchenko have described a requirement for the presence of two ester groups on the galactosyl donor, either at positions 3 and 4 or 4 and 6, to achieve significant α-selectivity relative to the corresponding mono-acetylated donors.[36–38] All of these reports seem contrary to the idea that the 4-*O*-ester is involved in stabilizing positive charge at the anomeric position, or in the formation of a dioxolenium ion. Herein, we detail our investigations towards understanding our observed α-selectivity trends that have led us to a new hypothesis: an S_N2-like transition state **3**, involving a H-bond-interaction with the β-glycosyl triflate. We also detail the usefulness of our findings to practical saccharide synthesis.

Stereochemical control in glycosylation reactions is a significant objective due to the importance of oligosaccharides in Nature,[39] and in the development of vaccines and therapeutics.[40] For example, the α-galactoside motif is of pivotal importance in the blood group B antigen and in the manifestation of diseases such as Chagas and Fabry disease (Fig. 1A).[41–45] Thus, α-galactosides are important as targets in the pharmaceutical industry and as tools for biological research.[46,47] In spite of their significance, access to α-galactoside-containing compounds is limited. Enzymatic methods can be limited by a low substrate promiscuity,[48,49] and methods for the isolation of α-galactosides from natural sources tend to be low-yielding.[50–52] Thus the chemical synthesis of galactosides is the principal way to access a broad range of compounds.

The 1,2-*cis*-glycosidic linkage central to these compounds renders their syntheses challenging; current methods for 1,2-*cis*-galactosylation are imperfect, in either the breadth of scope, the cost of reagents for their synthesis, or the restrictions they place on downstream uses.[53] The exploitation of donor protecting groups to control the stereochemical outcome of α-galactosylations, for example the use of esters described above, is a widely used approach. However, further investigation of this mode of stereoselectivity is crucial to improving our understanding of 1,2-*cis*-galactosylation so that efficient and selective methodologies for the synthesis of complex carbohydrates can be advanced.

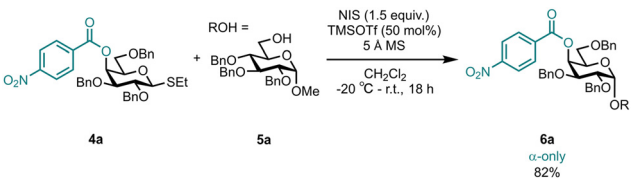
A serendipitous discovery prompted us to re-examine the potential of a single benzoate protecting group to control the stereochemical outcome of α-galactosylations. Thiogalactoside donor **4a**, featuring a *para*-nitrobenzoate group at position four, was observed to afford exclusive α-selectivity in a glycosylation with acceptor **5a** (Scheme 1). This result, featuring an electron-deficient 4-*O*-ester moiety, was unexpected as it diverged from hypotheses outlined above involving α-galactosylation *via* a cationic dioxolenium or oxacarbenium ion intermediate. Re-examination of the literature highlighted the aforementioned reports of enhanced α-selectivities with depleted electron densities of the donor.[23,35–38] To the best of our knowledge, other than suggestions of S_N2-type reaction *via* β-glycosyl triflate intermediates, the mode of stereoselectivity of α-galactosylations using electron-poor donors has not been investigated in-depth.

Results and discussion

In order to probe the mode of stereoselectivity in our galactosylation system, we performed a Hammett study.[54,55] The electronic effect of the *para*-substituent of the 4-*O*-benzoate group on the α-selectivity of glycosylation was investigated. The effect of acceptor nucleophilicity on the stereochemical outcome was also studied, inspired by experiments designed by Codée and Boltje (Table 1).[22] Donors **4a–g** were prepared and tested in glycosylations using ethanol (**7**) and 2-fluoroethanol (**8**) as model acceptors. Ethanol is commonly used as a test acceptor, but it is a stronger nucleophile than most carbohydrate acceptors.[56] Thus, the weaker nucleophile, 2-fluoroethanol, was chosen to better represent carbohydrate acceptor nucleophilicity. The results are shown in Table 1, and the corresponding Hammett plots are shown in Fig. 2 and 3.

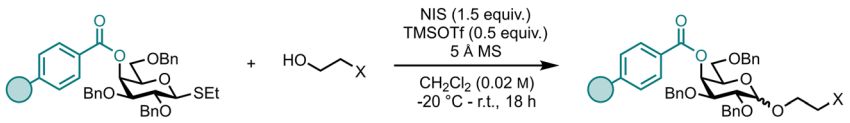
Our primary observation was that opposing trends were observed depending on the nucleophile used, suggesting a change in mechanism or selectivity-determining step with a change in nucleophilicity.

The trend observed for the ethanol series (Fig. 2) for substituents with σ_p values in the range −0.83 to 0 was consistent with what might be expected under existing proposals for



Scheme 1 α-Glycosylation of acceptor **5a** using donor **4a**.

Table 1 Hammett study on the effect of *para*-substituent (blue ball) and acceptor nucleophilicity on glycosylation selectivity



Entry	Donor	R	Acceptor	Product	Yield[a] (%)	$\alpha:\beta$ [b]	Entry	Donor	R	Acceptor	Product	Yield[a] (%)	$\alpha:\beta$ [b]
1	**4a**	NO_2	7	**9a**	52	74 : 26	8	**4a**	NO_2	**8**	**9h**	42	88 : 12
2	**4b**	CF_3	7	**9b**	48	75 : 25	9	**4b**	CF_3	**8**	**9i**	35	85 : 15
3	**4c**	Br	7	**9c**	51	73 : 27	10	**4c**	Br	**8**	**9j**	30	84 : 16
4	**4d**	H	7	**9d**	55	64 : 36	11	**4d**	H	**8**	**9k**	46	79 : 21
5	**4e**	Me	7	**9e**	44	70 : 30	12	**4e**	Me	**8**	**9l**	39	78 : 22
6	**4f**	OMe	7	**9f**	41	77 : 23	13	**4f**	OMe	**8**	**9m**	44	86 : 14
7	**4g**	NMe_2	7	**9g**	57	88 : 12	14	**4g**	NMe_2	**8**	**9n**	29	77 : 23

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy before purification by column chromatography. Results shown are an average of those obtained from duplicate experiments.

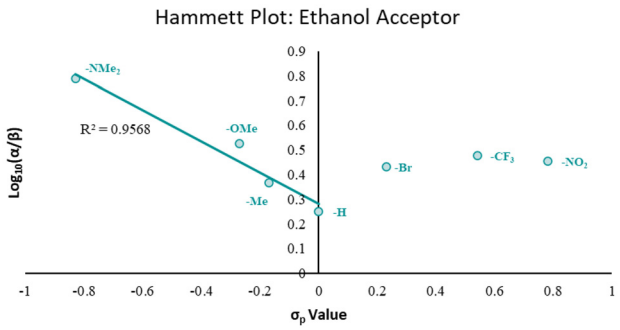


Fig. 2 Hammett plot of the change in galactosylation stereoselectivity *vs.* the electronic effect of the *para*-benzoate substituent using ethanol as the acceptor (see Table 1 for reaction conditions). A line of best fit for σ_p values from −0.83 to 0 is shown (R^2 = 0.9568). See SI for a plot of σ_p^+ with a line of best fit of $\sigma_p^+ \leq 0$ (R^2 = 0.9964) and alternative plots.

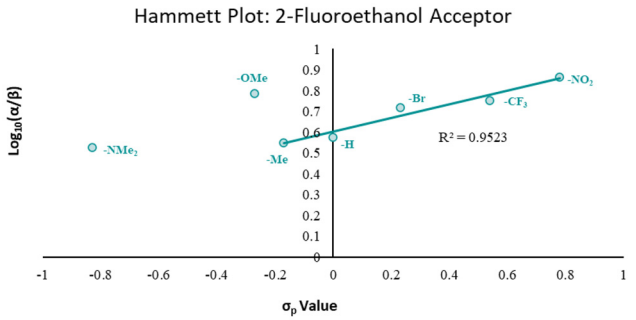


Fig. 3 Hammett plot of the change in galactosylation stereoselectivity *vs.* the electronic effect of the *para*-benzoate substituent using 2-fluoroethanol as the acceptor (see Table 1 for reaction conditions). A line of best fit for σ_p values from −0.17 to 0.78 is shown (R^2 = 0.9523).

α-galactosylations using donors bearing 4-*O*-esters (*vide supra*), with the most electron-donating *para*-dimethylamino substituent affording the highest α-selectivity. However, the substituents with $\sigma_p > 0$ do not fit this trend. An excellent correlation (R^2 = 0.9964) was also observed with σ_p^+ for substituents with $\sigma_p^+ < 0$ (see SI for alternative data treatments).

In contrast, for the more carbohydrate acceptor-representative 2-fluoroethanol series, there is a trend with a slope of opposite sign for substituents with σ_p in the range −0.17 to 0.78 (Fig. 3). In this series, strongly electron-donating substituents with $\sigma_p < -0.2$ are outliers. Notably, *para*-nitro-substituted donor **4a** afforded the highest α-selectivity. This result, and the trend shown in Fig. 3, seemed inconsistent with current rationalizations of the role of 4-*O*-esters and has both theoretical and practical implications discussed herein.[57]

We turned to computational chemistry to seek an understanding of the surprising α-selectivity afforded by the electron-poor 4-*O*-esters presented above.[58] Potential pathways involving S_N2-type reactions *via* α- and β-glycosyl triflate intermediates were considered for donor **4d** (Fig. 4). α-Glycosylations *via* reactive β-triflate intermediates have been reported previously and, in recent years, the characterisation of β-glycosyl triflates has been reported.[59–61]

We acknowledge that this system is governed by a fine balance of multiple variables, such as reaction conditions and substrates. For instance, the introduction of a single fluorine atom to the acceptor appears to change the selectivity-determining step. Consequently, energy differences observed were relatively small. Thus, the aim of this computational investigation was not to find a definitive answer, but rather to explore mechanistic possibilities. A key question was whether the computational investigations could suggest a rationale for the LFER observed using 2-fluoroethanol.

The reaction of donor **4d** in glycosylations of ethanol and 2-fluoroethanol was investigated starting from the α-glycosyl triflate intermediate (Fig. 4). Benzyl groups were replaced by methyl groups for computational feasibility. As expected, the α-triflate (0 kcal mol^{-1}) was more stable than the β-triflate (2.5 kcal mol^{-1}), and the latter was more reactive. Consistent

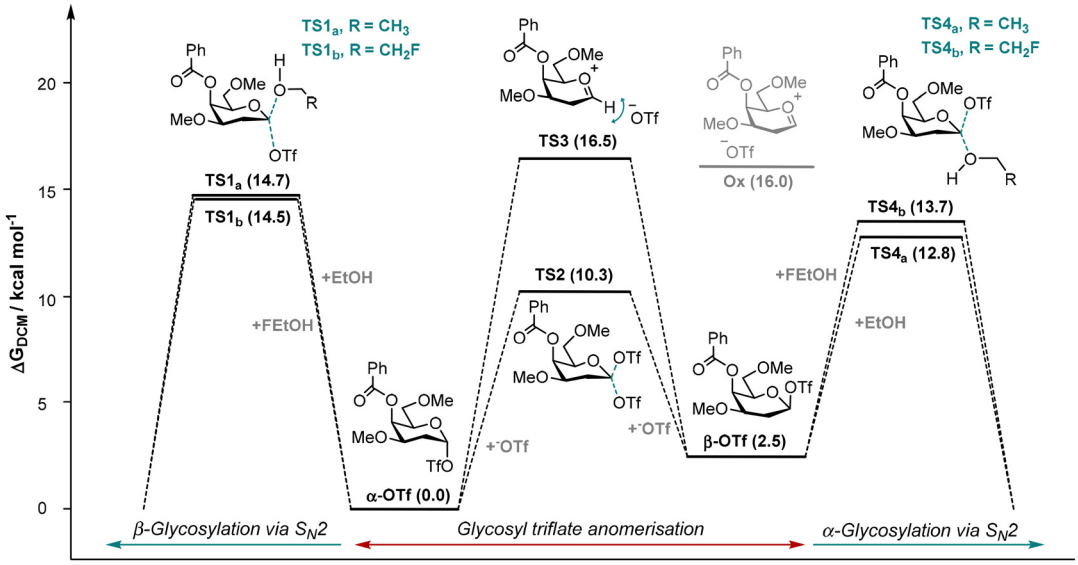


Fig. 4 Reaction energy diagram *via* glycosyl triflate intermediates for the glycosylation of ethanol and 2-fluoroethanol using donor **4d**. Gibbs free energies (kcal mol^{-1}) are given relative to the anomeric α-OTf intermediate. Computed at the SMD(CH_2Cl_2)-(TightPNO)DLPNO-CCSD(T)/aug-cc-pVTZ//SMD(CH_2Cl_2)-PBE0-D3/def2-TZVP level of theory, thermochemical corrections were applied at 253.15 K (−20 °C). The C-2 substituent is omitted from all structures for clarity.

with experimental results, a preference for α-glycoside is predicted. The barrier for S_N2 anomerization between α- and β-triflates was found to be relatively low (**TS2**, 10.3 kcal mol^{-1}).[61] Anomerization *via* an S_N1-like mechanism was also considered, and found to be higher in energy (**TS3**, 16.5 kcal mol^{-1}). Transition state energies for S_N2 glycosylations from both α- and β-triflates were higher than that of triflate anomerization for glycosylations of both ethanol and 2-fluoroethanol. Transition states leading to α-product (**TS4a**, 12.8 kcal mol^{-1} and **TS4b**, 13.7 kcal mol^{-1}) were lower in energy than those leading to β-product (**TS1a**, 14.7 kcal mol^{-1} and **TS1b**, 14.5 kcal mol^{-1}). Thus, the favourable formation of α-product would be predicted in an S_N2-like glycosylation.

Our calculations indicate that the energy of the oxacarbenium ion intermediates tend to be higher than the glycosylation barriers (see SI), but not high enough to exclude entirely their involvement or that of a competing S_N1 pathway. These findings support the idea that the stereoselectivity afforded by this donor type may hinge on a continuum of S_N1- and S_N2-type mechanisms. The mechanistic preference likely shifts with changes in the donor ester substituents and the nucleophilicity of the acceptor, providing a plausible explanation for the outliers observed in the Hammett study.

We also investigated the possibility of reaction *via* a dioxolenium ion intermediate (SI Fig. 2). In this case, we found that the energy barriers to rotation of the 4-*O*-ester into the required geometry for long-range participation (18.7 and 20.2 kcal mol^{-1}) were the highest of this pathway. This was consistent with Crich's proposal that rotation to an unfavourable antiperiplanar geometry between the ester carbonyl bond and the α-C–H bond would prevent dioxolenium ion formation.[24,33,62,63] Thus, contrary to the gas phase calculations of Seeberger and Pagel,[23] our calculations do not support the intermediacy of a dioxolenium ion (but the fine balance of the system does not allow us to be definitive).

Subsequent examination of transition state images derived from **4d** for triflate anomerization (**TS2**) and α- and β-glycosylation (**TS4b** and **TS1b**, respectively) revealed a possible explanation for the LFER observed using 4-*O*-esters bearing electron-withdrawing substituents (Fig. 5). We noted that the β-triflate shows a considerable distortion away from a chair conformation in the ground state. It was noted that the *ortho*-proton of the benzoate was close in space to the anomeric oxygen of the triflate group. Aided by non-covalent interaction images (SI Table 2), a non-classical H-bonding interaction between these atoms was observed computationally. This type of non-classical H-bonding from a C–H donor has been reported previously in various contexts.[64–68] When the triflate group was in the β-configuration, the interaction was observed for both the triflate anomerization (**TS2**, 2.39 Å) and the α-glycosylation (**TS4b**, 2.39 Å) steps. However, the interaction was not observed when the triflate group was in the α-configuration. Importantly, this non-classical H-bond would be impacted by the seemingly remote *para*-substituent of the benzoate. The presence of an electron-withdrawing substituent, such as a nitro-group, should enhance the H-bond donating ability of the *ortho*-proton, thus affording a stronger interaction. Indeed, TS modelling of the corresponding triflate derived from nitrobenzoate donor **4a** revealed a shorter H-bonding distance of 2.28 Å in the triflate anomerization step (Fig. 6). We propose that using 2-fluoroethanol as the acceptor (and related carbohydrate-based acceptors), this stabilizing non-classical H-bond shifts the fine balance between reaction pathways, facilitating an S_N2-like reaction of a β-triflate as the

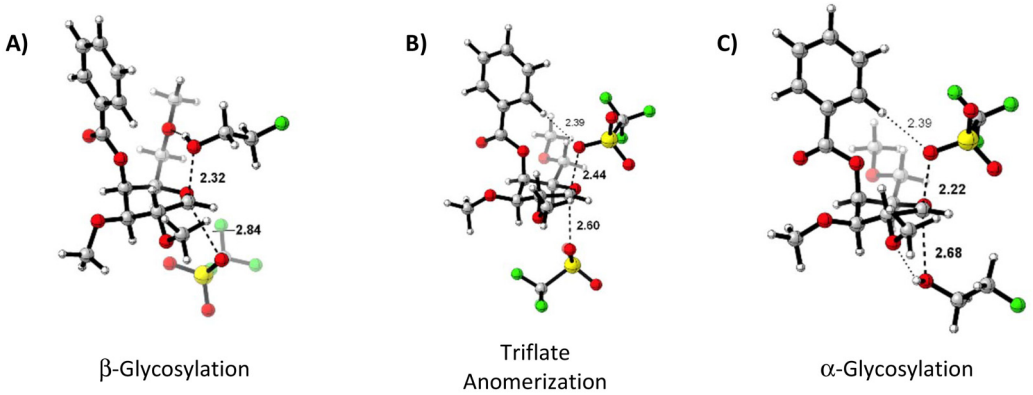


Fig. 5 Transition state images for (A) β-glycosylation, (B) triflate anomerization and (C) α-glycosylation of donor **4d** with 2-fluoroethanol.

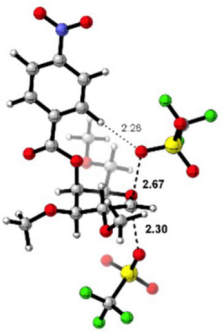
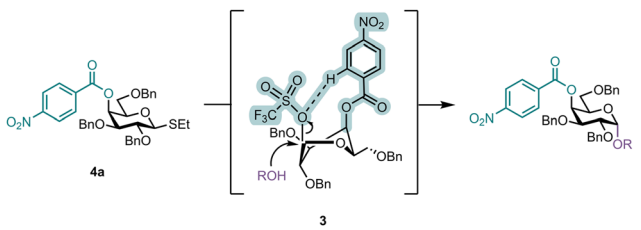


Fig. 6 Transition state image for triflate anomerization derived from *para*-nitrobenzoate donor **4a**.

dominant pathway to afford α-product (Scheme 2). The change in reaction pathways detected here for 4-*O*-esters bearing electron-withdrawing substituents might also explain some of the anomalous results reported by Ventura, Seeberger and Demchenko among others, mentioned previously.[23,35–38]

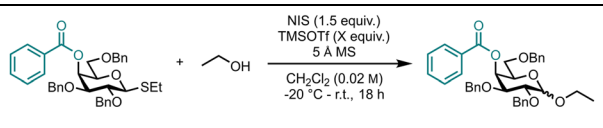
To probe this hypothesis experimentally, we first turned our attention to the energy barrier for anomerization from α-triflate to β-triflate necessary for α-galactosylation to occur (**TS2**, 10.3 kcal mol^{-1}). We postulated that an increase in triflate concentration should help to encourage the S_N2 reaction *via* the β-triflate, and thus increase the stereoselectivity of our reaction. The effect of the equivalents of TMSOTf used in the glycosylation of donor **4d** and ethanol on the stereochemical outcome was studied (Table 2). These reaction partners were chosen as this would provide a direct comparison with a reaction studied computationally (Fig. 4). The low selectivity observed previously in this reaction would also prove useful, as there was ample room available to observe improvement in the stereochemical outcome. As shown in Table 2, the concentration of TMSOTf did indeed affect the stereoselectivity of glycosylation. The most significant change in selectivity was observed from entry 2 to entry 3, with a change from 50 mol% to a stoichiometric amount of TMSOTf reflecting an increase from α/β = 64 : 36 to 79 : 21. A further increase in concentration to 1.5 equivalents of TMSOTf did not provide any further significant increase in α-selectivity. These results supported our hypothesis that a triflate intermediate is important for stereoinduction in our galactosylation system.

Next, we examined the stereoselectivity of glycosylation when protons around the 4-*O*-benzoate ring, proposed to be involved in the H-bonding interaction, were replaced with fluorine (Table 3). Glycosylation of non-substituted donor **4d** was chosen as a control for comparison. In comparison with non-substituted compound **9k**, a drop in stereoselectivity from α/β = 79 : 21 to α/β = 70 : 30 was observed when di-*ortho*-fluoro-substituted **10b** was subjected to glycosylation with 2-fluor-



Scheme 2 Proposed H-bond-stabilized α-glycosyl triflate transition state **3**.

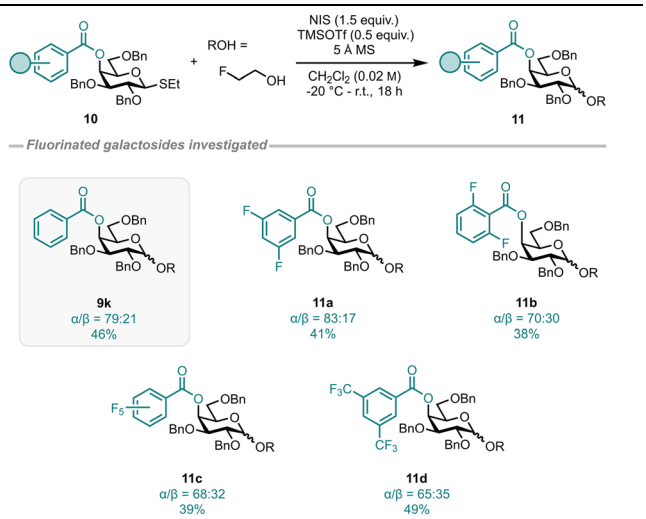
Table 2 Effect of TMSOTf concentration on glycosylation stereoselectivity



Entry	TMSOTf equiv.	$\alpha:\beta$ [a]
1	0.25	66 : 34
2	0.5	64 : 36
3	1.0	79 : 21
4	1.5	80 : 20

[a] Determined by ^{1}H NMR spectroscopy before purification by column chromatography.

Table 3 Changes in galactosylation selectivity observed when benzoate protons were replaced with F atoms



α/β-Selectivities were determined by ^{1}H NMR spectroscopy before purification by column chromatography. Yields indicate isolated yields.

oethanol. This offers evidence supporting the involvement of the *ortho*-protons in a H-bonding interaction with the β-triflate (Fig. 7). This was further reinforced by the drop in selectivity observed for pentafluorinated compound **11c** (α/β = 68 : 32) relative to **9k**.

The increase in selectivity observed for *meta*-substituted **11a** (α/β = 83 : 17) is consistent with our hypothesis and suggests that the *meta*-protons of the benzoate group are not needed for H-bonding with the β-triflate. The inductive electron-withdrawing effect of the fluorines should strengthen the proposed H-bonding interaction from the *ortho*-protons and thus explain the increase in selectivity observed. The drop in stereoselectivity for **11d** (α/β = 65 : 35) was a surprise initially, however examination of the proposed transition state **TS3** suggested a rationale. While the *ortho*-protons are not disrupted in compound **11d**, the decrease in selectivity may be caused by the introduction of a clash between the trifluoromethyl group and the triflate leaving group (through examination of 3D-model of **TS3**). The experimental results described in Table 3 lend significant support to the argument that the benzoate *ortho*-protons are involved in H-bonding to β-triflate in the transition state for α-galactosylation.

Fig. 7 Loss of H-bonding interaction as a proposed rationalization for the drop in α-selectivity observed using *ortho*-fluorine-substituted 4-*O*-benzoate protecting groups.

Given that the hydrogens proposed to be involved in H-bonding are positioned *meta* to the benzoate substituent, a new Hammet plot using σ_m with the data from 2-fluoroethanol as acceptor was examined (Fig. 8). Consistent with our hypothesis, the plot showed better agreement with the data ($R^2 > 0.99$, excluding *para*-methoxy-substituted benzoate **4f** which remained an outlier; **4f** appears to be a special case and this should be the subject of future investigations). The corresponding plot with EtOH as acceptor did not show an improved correlation, consistent with differences in factors influencing selectivity between the acceptors.

Next, it was hypothesized that the importance of a glycosyl triflate intermediate in our galactosylation could be demonstrated by exclusion of a triflate-based promoter system. Glycosylation of acceptor **5a** with either nitro-substituted donor **4a** or methoxy-substituted donor **4f** was performed using two different promoter systems (Table 4). The standard NIS/TMSOTf promoter system described previously was compared to the use of $CuBr_2$, following a modified procedure to that reported by Demchenko and colleagues.[69]

Using nitro-substituted donor **4a**, a drop in stereoselectivity occurred from α-only using the standard NIS/TMSOTf promo-

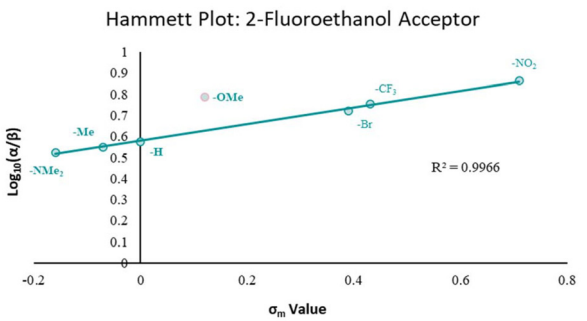
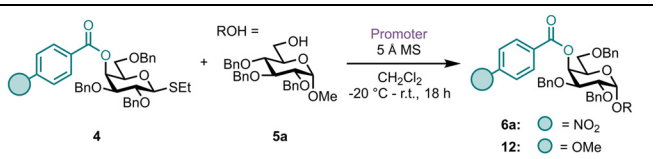


Fig. 8 Hammett plot of the change in galactosylation stereoselectivity *vs.* the electronic effect of the benzoate substituent using 2-fluoroethanol as the acceptor (see Table 1 for reaction conditions). A line of best fit for σ_m values from −0.16 to 0.71 excluding the *para*-OMe substituent is shown (R^2 = 0.9966).

Table 4 Effect of triflate *vs.* non-triflate promoter systems on the stereoselectivity of galactosylations of acceptor **5a** with donors **4a** or **4f**



Entry	Donor		Promoter	$\alpha:\beta$ [a]
1	**4a**	NO_2	NIS TMSOTf	α-only
2	**4a**	NO_2	$CuBr_2$	67 : 33
3	**4f**	OMe	NIS TMSOTf	α-only
4	**4f**	OMe	$CuBr_2$	α-only

[a] α/β-Selectivities were determined by ^{1}H NMR spectroscopic analysis before purification by column chromatography.

ter system (entry 1) to α/β = 67 : 33 using non-triflate promoter $CuBr_2$ (entry 2). However, for methoxy-substituted **4f**, no change in selectivity from α-only was observed for either promoter system (entries 3 and 4). These results suggest again that there are different stereo-determining mechanisms at play in the galactosylations described, with the predominant mechanism determined by the electronic nature of the benzoate *para*-substituent. The stereoselectivity of galactosylations involving electron-poor substituents appears to involve a glycosyl triflate intermediate, as evidenced by the drop in selectivity observed in entry 2 upon exclusion of a triflate promoter. However, for the donor bearing the *para*-OMe substituent, the promoter system does not seem as crucial to stereoselectivity (entries 3 and 4) and it is likely that the stereochemistry of these glycosylations is influenced by other factors.

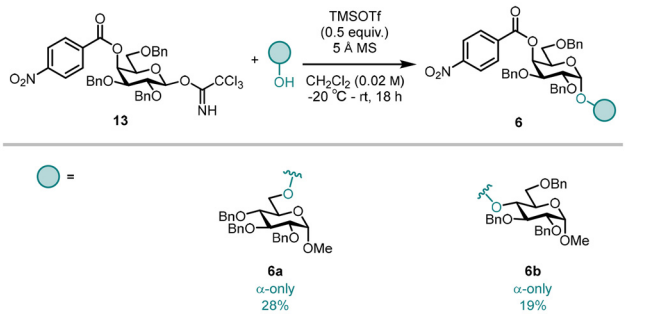
The significance of triflate transition state **3** was scrutinized further using a 4-*O*-nitrobenzoate-protected galactosyl trichloroacetimidate *in lieu* of a thiogalactoside donor (Table 5). It was anticipated that the α-selectivity of trichloroacetimidate galactosylations, typically promoted by triflate-based systems, should not deviate from that recorded using thiogalactosides. This was because a glycosyl triflate was hypothesized to be a common intermediate to both reactions, and the availability of the required triflate counterion would remain intact.[70] Trichloroacetimidate donor **13** was tested in glycosylation with primary alcohol acceptor **5a** and secondary alcohol acceptor **5b**, following a procedure adapted from that reported by Pohl (Table 5).[71] In both cases, exclusive α-selectivity was recorded. Although the spectroscopic yields (unoptimized) of both **6a** and **6b** in these experiments were poor, this demonstrated that α-selectivity is achievable under triflate-based promotion conditions *via* **3**, regardless of the anomeric leaving group. This 4-*O*-nitrobenzoate-mediated α-galactosylation can be carried out catalytically in the promoter, whereas previously, stochiometric quantities of promoter were required.

Finally, a competition experiment was carried out to probe the reactivity of thiogalactoside **4a** relative to 4-*O*-benzoyl donor **4d**. This was to investigate the extent of the stabilizing effect of the proposed H-bonding interaction between the benzoate *ortho*-proton and the β-triflate leaving group. According to Fraser-Reid's armed-disarmed theory[72–74] and stereoelectronic effects,[75] it would be expected that benzoate donor **4a**, bearing an electron-withdrawing nitro substituent, should be more disarmed than non-substituted benzoate **4d** and, thus, less reactive. However, it was hypothesized that the proposed H-bonding interaction in transition state **3** might be stabilizing enough to improve the reactivity of **4a** relative to traditionally more armed donor **4d** in competition for galactosylation of acceptor **5a** (Scheme 3). Significantly, it was found that the ratio of disaccharides **6a** to **14** was 58 : 42, indicating that *para*-nitrobenzoate donor **4a** was more reactive in this experiment than benzoate **4d**. This apparent contradiction of the armed-disarmed theory suggests that the proposed H-bonding in transition state **3** is stabilizing enough to overcome the disarming nature of the electron-poor *para*-nitrobenzoate protecting group. This work provided further evidence to support our proposed transition state **3**. In addition, the experimental outcome is contrary to predicted RRVs using Wong's AutoCHO software and hopefully will enable an adjustment to improve its prediction and make such substrates more amenable for use in one-pot glycosylations.[76] Finally, we note that the proposed H-Bonding interaction might play a role in other glycosylations, *e.g.*, Liang's proposal involving an *N*-benzylcarbamoyl group stabilizing a triflate intermediate.[77]

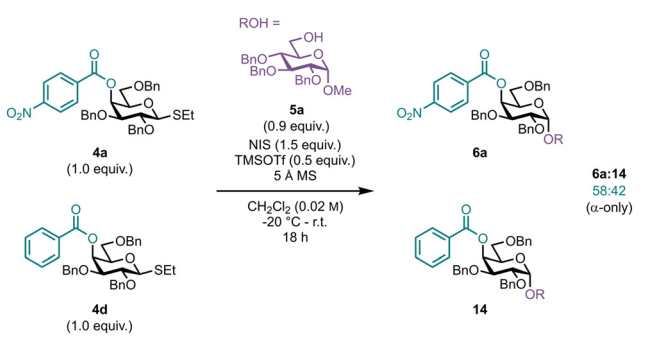
With a plausible explanation for the excellent α-selectivity observed in hand, we explored the consequent practical implications for synthetic carbohydrate chemists. To-date, many solutions involving galactose donors bearing esters have involved use of multiple esters,[38,78] limiting options for regioselective deprotection towards further glycosylation, or are restricted to specific esters which have limitations in either subsequent removal, or cost.[79] The ability to install a cheap *para*-nitrobenzoate group at a single position offers greater synthetic flexibility and a simple way to control glycosylation selectivity.

We demonstrated that our α-galactosylation methodology can be reduced to practice with a range of carbohydrate acceptors (Table 6). We chose *para*-nitro-substituted **4a** as the model donor for surveys of acceptor scope due to its high perform-

Table 5 Glycosylation of primary alcohol acceptor **5a** and secondary alcohol acceptor **5b** using trichloroacetimidate donor **13**

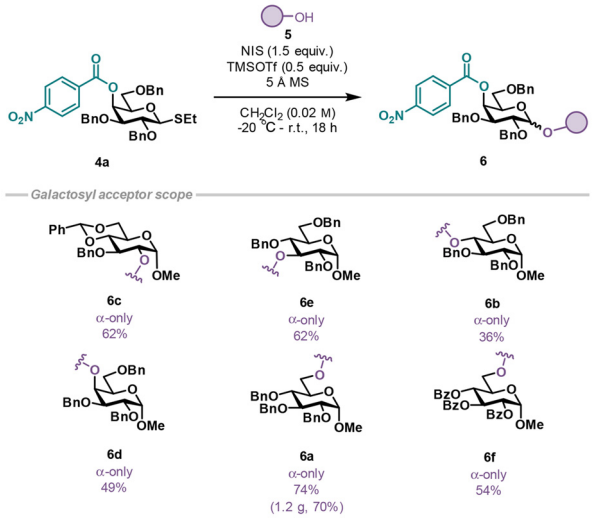


α/β-Selectivities were determined by ^{1}H NMR spectroscopy before purification by column chromatography. NMR spectroscopic yields were calculated from the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.



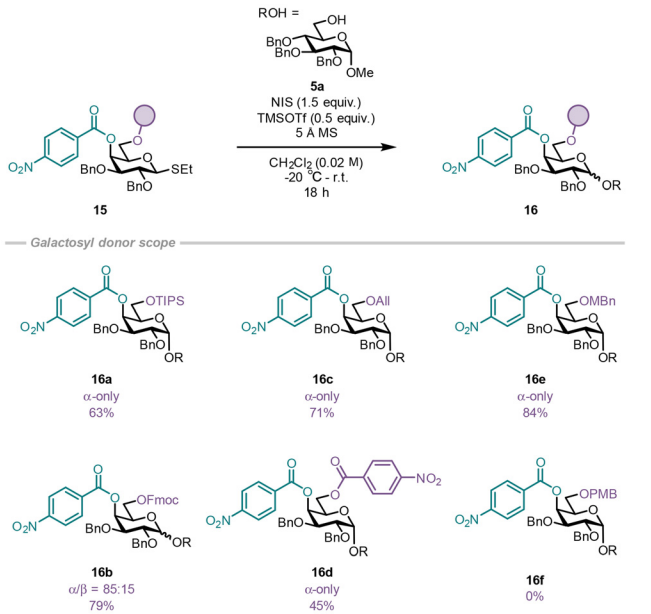
Scheme 3 Competition experiment between donors **4a** and **4d** for galactosylation of acceptor **5a**. Results shown are the average of duplicate experiments.

Table 6 Investigation of glycosyl acceptor scope using model donor **4a**



α/β-Ratios were determined by ^{1}H NMR spectroscopic analysis before purification by column chromatography. Yields indicate isolated yields.

Table 7 Investigation of glycosyl donor scope using model acceptor **5a**



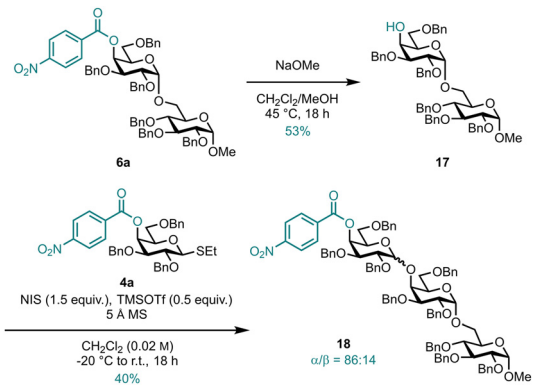
α/β-Ratios were determined by ^{1}H NMR spectroscopic analysis before purification by column chromatography. Yields indicate isolated yields.

ance in glycosylation with carbohydrate acceptor-like 2-fluoroethanol during our Hammett study. Glycosylations of acceptors **5a–f** showed that galactosyl α-1,2-, -1,3-, -1,4- and -1,6-linkages could be formed in exclusive α-selectivities and moderate to high yields. Benzyl, benzylidene and benzoyl protecting groups were well-tolerated in the acceptor.

The synthesis of highest-yielding disaccharide **6a** was chosen for the advancement of this glycosylation to gram-scale. Gram-scale glycosylation between donor **4a** and primary alcohol acceptor **5a** afforded a 70% yield of disaccharide **6a** (1.2 g). Crucially, exclusive α-selectivity was maintained in this experiment. The success of this reaction on gram scale demonstrates the practicality of this methodology, particularly in terms of multi-step complex oligosaccharide syntheses.

Next, the donor scope of our α-galactosylation was investigated (Table 7). It is important that the orthogonal protecting group pattern on the galactosyl donor could be varied, enabling the donor to become a branching point for further oligosaccharide synthesis. A variety of orthogonal protecting groups were installed at position 6 of the donor. Primary glycosyl acceptor **5a** was chosen as the model acceptor for these glycosylations due to its efficient and accessible 3-step synthesis. Exclusive α-selectivities and high yields were observed using a 6-*O*-TIPS-, -allyl- and -(*para*-methylbenzyl)-protecting group. 4,6-Di-*O*-benzoate **16d** was prepared in exclusive α-selectivity, demonstrating the potential for α-selectivity using significantly disarmed donors. The use of a 6-*O*-Fmoc group resulted in slightly lower selectivity, α/β = 85 : 15, for disaccharide **16b** but it remained satisfactorily high. Galactosylation using a 6-*O*-(*para*-methoxybenzyl)-protected donor presented a limitation of this methodology (complex mixtures were obtained).

To further present the utility of our α-galactosylation, disaccharide **6a** was subjected to orthogonal deprotection of the 4-*O*-benzoate group to unmask a new glycosyl acceptor **17** under basic conditions (Scheme 4). Subsequent glycosylation with donor **4a** afforded trisaccharide **18** in α/β = 86 : 14. While the stereoselectivity of this glycosylation was lower than the exclusive α-selectivity obtained for other examples in this work, we feel that the high selectivity was still significant in the broader context of this report.



Scheme 4 Synthesis of galactosyl trisaccharide **18**.

Conclusions

In conclusion, a rationale has been developed to explain why the use of a 4-*O*-(*para*-nitrobenzoate)-protected galactosyl donor afforded up to exclusive α-selectivities in a range of galactosylations. The excellent α-selectivity observed using this

electron-poor 4-*O*-benzoate was inconsistent with existing literature hypotheses involving α-galactosylation *via* cationic dioxolenium ion intermediates. Computational and experimental analyses have led to the proposal of stabilized β-triflate transition state **3** to explain the α-selectivity, which features a stabilizing H-bonding interaction between the *ortho*-proton of the 4-*O*-benzoate group and the anomeric β-triflate. The utility of this methodology has been demonstrated through a gram-scale example, the synthesis of a trisaccharide, as well as reaction with a range of acceptors, to form galactosyl 1,2-, 1,3-, 1,4- and 1,6-linkages in exclusive α-selectivities. We anticipate that the excellent selectivity and tolerance to a range of widely used protecting groups should enable this methodology to be used in the synthesis of branched oligosaccharides containing α-galactosidic linkages. The capacity of H-bonding interactions to influence the stereochemical outcomes of reactions will continue to be of interest to our laboratory and others into the future.[80–85]

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures, ^{1}H, ^{13}C and 2D NMR spectra for all new compounds, and details of computational work. See DOI: https://doi.org/10.1039/d5ob01495f.

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