Glycosylation

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Mapping the Relationship between Glycosyl Acceptor Reactivity and Glycosylation Stereoselectivity

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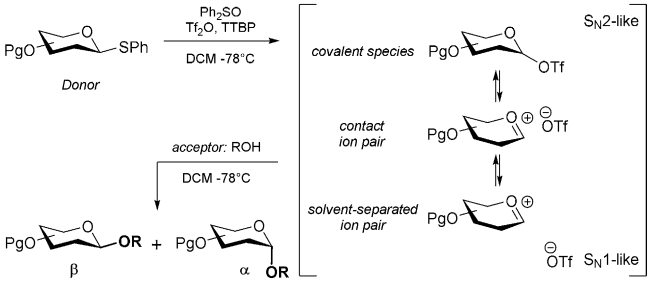
Abstract: *The reactivity of both coupling partners—the glycosyl donor and acceptor—is decisive for the outcome of a glycosylation reaction, in terms of both yield and stereoselectivity. Where the reactivity of glycosyl donors is well understood and can be controlled through manipulation of the functional/protecting-group pattern, the reactivity of glycosyl acceptor alcohols is poorly understood. We here present an operationally simple system to gauge glycosyl acceptor reactivity, which employs two conformationally locked donors with stereoselectivity that critically depends on the reactivity of the nucleophile. A wide array of acceptors was screened and their structure–reactivity/stereoselectivity relationships established. By systematically varying the protecting groups, the reactivity of glycosyl acceptors can be adjusted to attain stereoselective cis-glucosylations.*

The union of two carbohydrates to generate larger oligosaccharides is arguably one of the most important reactions in glycochemistry.[1] Although the glycosylation reaction has been actively studied for more than half a century, many aspects that affect this reaction, in terms of both yield and stereoselectivity, remain enigmatic.[2] The reactivity of the carbohydrate building blocks is one of the most important determinants that influences the outcome of a glycosylation reaction.[3] The reactivity of donor glycosides has been very well documented: the relative reactivity value (RRV) of hundreds of thioglycosides has been established and hundreds of anomeric triflates and other covalent reactive species, key reactive intermediates formed in situ during the reaction, have been characterized.[4] The reactivity of acceptor glycosides is less well understood and systematic studies investigating this important reaction parameter are extremely scarce.[5] At the same time, it is common practice to change protecting groups on the acceptor building block to influence the yield or change the stereoselectivity of a glycosylation reaction.[6] Often, this is done in a time consuming, trial-and-error manner since well-defined guidelines on how to tune the reactivity of an acceptor and how this effects the glycosylation reaction are absent.[7]

Recently, we have shown that the reactivity of the acceptor can have a profound influence on the stereochemical outcome of a glycosylation reaction.[8] Through the use of a panel of partially fluorinated ethanol derivatives (ethanol, mono-, di- and trifluoro ethanol)[5c] we revealed how the stereochemical outcome of a glycosylation depends on acceptor nucleophilicity as a result of a shift mechanism, with weaker nucleophiles requiring a more dissociative reaction mechanism (with more S_N1 character) than reactive acceptors, which can engage more readily in an S_N2-type displacement reaction (Scheme 1).[9] The stereochemical outcome of glycosylation reactions of 4,6-*O*-benzylidene-protected glucose (**A**, Figure 1) and glucosazide (**B**, Figure 1) donors turned out to be especially sensitive to the reactivity of the nucleophile. A gradual change in stereoselectivity was observed for these donors going from near complete β-



Scheme 1. General glycosylation mechanism, showing the equilibrium of reactive species. Pg = protecting group.

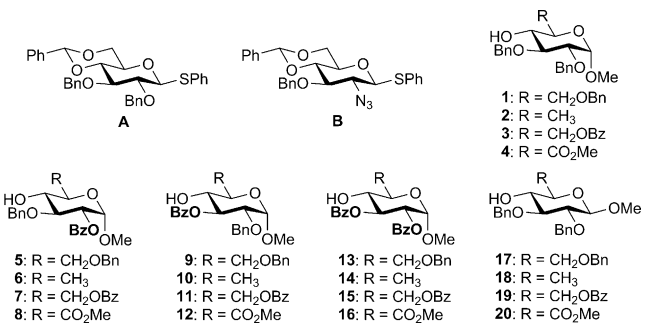


Figure 1. Donors **A** and **B** and C-4-OH glucosyl acceptors **1**–**20**.

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selectivity for the most reactive acceptor (ethanol) to complete α-selectivity for the weakest nucleophiles (trifluoroethanol, hexafluoro-*iso*-propanol, see Table 1, Entries 1–4). It follows from this established relationship that the stereoselectivity of a glycosylation between a benzylidene glucose donor and a given acceptor provides a direct indication of the reactivity of the acceptor alcohol. We therefore reasoned that the benzylidene glucose/glucosazide glycosylation system would be ideal to "measure" the reactivity of acceptor alcohols in a glycosylation reaction setting. In this work, we conceptualized this hypothesis and we used the system to systematically map the reactivity of a panel of carbohydrate acceptors to show how functional and protecting groups influence the nucleophilicity of the alcohols to provide a scale of relative acceptor reactivities against which any desired acceptor can be measured to reveal its potential stereoselectivity in glycosylations.

Table 1: Glycosylations with model acceptors and 2,3-di-*O*-benzyl acceptors **1**–**4**.[a]

Acceptor	Donor **A** α/β (yield)	Donor **B** α/β (yield)	Acceptor	Donor **A** α/β (yield)	Donor **B** α/β (yield)
	1:10 (68%)	<1:20 (83%)	**1**	**1A** 1:1 (82%)	**1B** 1:7 (88%)
	1:2.8 (70%)	1:6.7 (90%)	**2**	**2A** 2:1 (85%)	**2B** 1:5 (69%)
	5:1 (70%)	2.9:1 (64%)	**3**	**3A** 4:1 (92%)	**3B** 1:1.1 (67%)
	>20:1 (64%)	>20:1 (94%)	**4**	**4A** 5:1 (90%)	**4B** 1.1:1 (93%)

[a] Data for acceptor **1** and **4**, and the four ethanol derivatives has been published in Ref. [8a,b].

To probe the effect of different functional and protecting groups on the reactivity of a carbohydrate acceptor alcohol, we used two thioglycoside donors, benzylidene glucose **A** and benzylidene glucosazide **B**, in combination with a preactivation procedure[10] in which the donor glycoside is activated prior to the addition of the acceptor. This gives a simpler reaction mechanism manifold than an in situ activation approach, which makes it easier to analyze the effects of changing the reactivity of the building blocks used. For both donors, we previously established a strong relationship between acceptor reactivity and glycosylation stereoselectivity, and across the board, glycosylations of donor **B** provided more β-product than the glycosylations of donor **A**.[8a,b] This effect was accounted for by the greater tendency of donor **B** to partake in S_N2-type reactions as a result of the electron-withdrawing effect of the C-2 azide and the greater stability of the anomeric triflate that is formed as a reactive intermediate. In effect, the combination of the two donor systems should allow mapping of the reactivity of acceptors of widely varying reactivity. As a first objective, we focused on mapping the stereoselectivity–reactivity relationship for a diverse set of C-4-OH glucosyl acceptors (Figure 1, **1**–**20**). To keep steric and other structural effects to a minimum, we compared the effect of O-benzyl or O-benzoyl groups since these groups are of a similar size but differ significantly in their electronic properties. We investigated all possible positional benzyl/benzoyl permutations. We also probed the effect of different chemical functionalities at the C-6 position, where we installed a 6-deoxy and carboxylic acid ester functionality in addition to the benzyl- and benzoyl- protected primary alcohol functionalities. The effect of the anomeric configuration was also analyzed.[11]

In Table 1, the results of the glycosylation reactions of donors **A** and **B**, previously obtained with the fluorinated model alcohols, are listed alongside the reactions of 2,3-di-*O*-benzyl acceptors **1**–**4**. A clear transition from β- to α-selectivity, following the electron-withdrawing tendency of the protecting/functional group at the C-6 position, arises. Uronic acid **4**, which features a strongly electron-withdrawing carbonyl group in close proximity to the nucleophilic center of the acceptor, provides the most α-product, thus indicating that this is the least reactive of the four acceptors studied.[12] It is also clearly apparent that the C6-O-benzoyl has a disarming effect on the reactivity of the acceptor since glucoside **3** is more α-selective than its C6-O-benzyl counterpart **1**. The configuration at the anomeric center does not affect the reactivity of the C4-OH acceptors as judged from the identical stereoselectivities of α-anomers **1**–**4** and β-anomers **17**–**20** (Table 2). The relatively remote protecting group at the C-2 position also has no apparent effect on the glycosylation stereoselectivity (compare **1A**–**4A**, Table 1, to **5A**–**8A**, Table 2).

However, the nature of the protecting group at the C-3 position has a dramatic effect on the stereoselectivity. A significant shift in the α/β-selectivity is observed in favor of the *cis* glycosides upon exchanging the C-3-O-benzyl group for a benzoyl functionality. Where acceptors **1**–**4** showed poor α-selectivity with donor **A** and β-selectivity when paired with donor **B** (Table 1, products **1A/B**–**4A/B**), the introduction of a strategically positioned benzoate turns these acceptors in highly (or even completely) α-selective acceptors (Table 2, products **9A/B**–**12A/B**). These results show that merely the exchange of two C−H bonds for a C=O bond can have a tremendous impact on the stereoselectivity of a glycosylation reaction. The only glycosylation in the latter series that was not completely α-selective, namely, the condensation of glucosazide **B** and acceptor **9** (product **9B**, $\alpha/\beta = 6.7:1$), could be rendered fully α-selective by changing the C-6-O-benzyl for a benzoyl, thereby further disarming this acceptor building block (product **11B**).

To further examine whether reactivity tuning can be achieved by using more electron-withdrawing protecting groups, we probed a series of nitrobenzoyl ester protected acceptors (**21**–**24**; Table 3 and Figure 2). Placing a single nitro group on the C-6-benzoate (at the *ortho*, *meta*, or *para* position) of the acceptor does not have a significant effect on the stereoselectivity of the condensation reactions (see products **21A**–**23A**, Table 3 vs. product **3A**, Table 1). However, the introduction of two *ortho* nitro groups on the

Table 2: Glycosylation results for β-glucoside acceptors **17**–**20**, 2-*O*-benzoyl acceptors **5**–**8**, 3-*O*-benzoyl acceptors **9**–**10**, and 2,3-di-*O*-benzoyl acceptors **13**–**16**.

Acceptor functional group C6	Acceptor (2,3-OBn, β-OMe)	Donor **A** α/β (yield)	Donor **B** α/β (yield)	Acceptor (2-OBz, 3-OBn)	Donor **A** α/β (yield)	Donor **B** α/β (yield)	Acceptor (2-OBn, 3-OBz)	Donor **A** α : β (yield)	Donor **B** α : β (yield)	Acceptor (2,3-OBz)	Donor **A** α : β (yield)	Donor **B** α : β (yield)
(6-OBn)	**17**	**17A** 1:1 (79%)	**17B** 1:7 (80%)	**5**	**5A** 1:1.1 (81%)	**5B** 1:6 (88%)	**9**	**9A** >20:1 (95%)	**9B** 6.7:1 (77%)	**13**	**13A** >20:1 (90%)	**13B** 10:1 (93%)
(6-deoxy)	**18**	**18A** 1.1:1 (87%)	**18B** 1:5.6 (86%)	**6**	**6A** 1.1:1 (86%)	**6B** 1:5 (88%)	**10**	**10A** >20:1 (93%)	**10B** 14:1 (81%)	**14**	**14A** >20:1 (83%)	**14B** 20:1 (96%)
(6-OBz)	**19**	**19A** 3.3:1 (73%)	**19B** 1:1.2 (70%)	**7**	**7A** 3.5:1 (88%)	**7B** 1.3:1 (87%)	**11**	**11A** >20:1 (95%)	**11B** >20:1 (85%)	**15**	**15A** >20:1 (91%)	**15B** >20:1 (69%)
(5-CO_2Me)	**20**	**20A** 5:1 (83%)	**20B** 1.2:1 (85%)	**8**	**8A** 4.8:1 (96%)	**8B** 1.2:1 (82%)	**12**	**12A** >20:1 (86%)	**12B** >20:1 (93%)	**16**	**16A** >20:1 (84%)	**16B** >20:1 (99%)

Table 3: Glycosylation results for C-6-nitrobenzoate glucosyl acceptors **21**–**24**, C-3-OH glucosyl acceptors **25** and **26**, and C-2-OH glucosyl acceptors **27** and **28**.

Acceptor	Donor **A** α/β (yield)	Acceptor	Donor **A** α/β (yield)	Donor **B** α/β (yield)
21	**21A** 3:1 (92%)	**25**	**25A** 1:2.7 (78%)	**25B** <1:20 (70%)
22	**22A** 3.3:1 (49%)	**26**	**26A** >20:1 (100%)	**26B** 11:1 (83%)
23	**23A** 3.5:1 (83%)	**27**	**27A** 9:1 (76%)	**27B** 1.6:1 (66%)
24	**24A** 5.6:1 (83%)	**28**	**28A** >20:1 (85%)	**28B** 13:1 (92%)

benzoate, as in acceptor **24**, does lead to a slight change in stereoselectivity towards the α product.[13]

We next examined the reactivity of C-3-OH and C-2-OH glucosyl acceptors and here too probed the influence of benzoyl versus benzyl protecting groups. Table 3 lists the results obtained with acceptors **25**–**28** (Figure 2). From these results, it becomes apparent that, in line with the results described above, the reactivity of the C-2- and C-3-OH acceptors can be tuned, and thus the stereoselectivity of the glycosylations controlled, by changing the nature of the protecting groups. Clearly, the steric effects that play a role in the transition state of the reactions of the C-2, C-3, and C-4-hydroxy groups will differ, and this must be born in mind when comparing the reactivity of these alcohols. However, based on the stereoselectivity of the glycosylations listed in Tables 1 and 3, the order of reactivity of the different hydroxy groups on the glucose ring, in combination with the benzylidene glucose donors studied, appears to be: C-3-OH > C-4-OH > C2-OH.[14]

Finally, we extended our study to *manno*- and *galacto*-configured acceptors (**29**–**36**, Table 4 and Figure 2). From the stereoselectivity with which products **29 A/B**–**31 A/B** are formed, the reactivity order for the galactose alcohols appears to be C-3-OH > C-2-OH > C4-OH, with the axial C-4-OH clearly being the least reactive of the series. As noted above, the steric requirements for each of these alcohols will be different and this may be an important factor in the relatively low reactivity of the latter alcohol. Here too, the introduction of benzoate esters instead of benzyl groups turns poorly/moderately α-selective acceptors into highly α-selective nucleophiles (see products **32 A/B** vs. products **30 A/B**, Table 4). For the mannose acceptors (**33**–**35**), the following reactivity trend observed: C-4-OH > C-3-OH > C-2-OH. In line with the galactose series, the axial OH is the least reactive and provides the highest α-stereoselectivity. Reactivity tuning through protecting-group alteration is equally effective in this

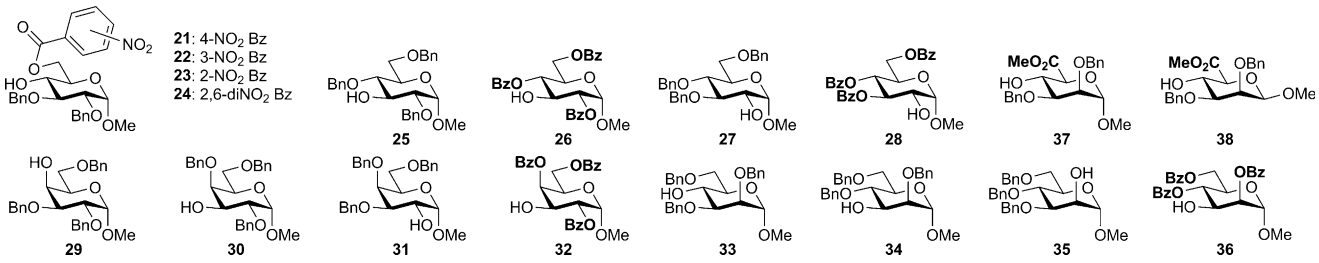

Figure 2. Structures of nitrobenzoyl acceptors **21**–**24**, and *gluco*-, *galacto*-, *manno*-configured acceptors **25**–**38**.

Table 4: Glycosylation results for galactosyl acceptors **29**–**32**, mannosyl acceptors **33**–**36**, and mannuronic acid acceptors **37** and **38**.

Acceptor	Donor **A** α/β (yield)	Donor **B** α/β (yield)	Acceptor	Donor **A** α/β (yield)	Donor **B** α/β (yield)
29	**29A** 12:1 (72%)	**29B** 3:1 (86%)	**33**	**33A** 1:2 (76%)	**33B** <1:20 (72%)
30	**30A** 6:1 (85%)	**30B** 1:1.3 (88%)	**34**	**34A** 8:1 (82%)	**34B** 1.1:1 (70%)
31	**31A** 10:1 (87%)	**31B** 1:1.3 (73%)	**35**	**35A** >20:1 (95%)	**35B** 7:1 (65%)
32	**32A** >20:1 (83%)	**32B** 11:1 (90%)	**36**	**36A** >20:1 (100%)	**36B** >20:1 (92%)
37	**37A** 2.5:1 (100%)	**37B** 1:5 (61%)	**38**	**38A** 2.2:1 (64%)	**38B** 1:4.8 (60%)

series (see products **36A/B** vs. products **34A/B**, Table 4). In this series, we finally probed mannuronic acid acceptors **37** and **38**. The C-5-carboxylate in these acceptors has a similar disarming effect on the reactivity of the C-4-OH to that observed in the corresponding glucose acceptors **1** and **17** and glucuronic acid acceptors **4** and **20**.

Overall, the relationship between acceptor reactivity glycosylation stereoselectivity that was established with a set of fluorinated model nucleophiles can be directly translated to carbohydrate acceptors. Just like the reactivity of glycosyl donors, the reactivity of carbohydrate acceptors can be tuned through manipulation of their protecting groups, and their reactivity can be exploited to skew the stereoselectivity of glycosylations in the desired direction.[8a] This adds a powerful tool for the stereoselective construction of glycosidic linkages. Commonly used protecting and functional groups can be used to moderate the reactivity of the glycosyl acceptors, and the protecting groups can be further fine-tuned by changing their electron-withdrawing properties. It is shown that the strategic replacement of a single benzyl group with a benzoyl ester (in effect only exchanging two hydrogen atoms for an oxygen atom) can turn a non-selective condensation into a highly selective *cis*-glycosylation. The concept of acceptor reactivity tuning holds for a variety of acceptor configurations and nucleophilic sites in the acceptor. By using the two model donors **A** and **B**, the reactivity of any other relevant acceptor can be gauged in simple test reactions, through comparison to the reactivity/selectivity of the current set of acceptors. The reactivity can then be appropriately adjusted through the installation of an appropriate functional/protecting-group pattern.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acceptor reactivity · enzyme mechanisms · glycosylation · reactivity tuning · stereoselectivity

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[12] The C-6-OBn has the possibility to hydrogen bond with the 4-OH, thereby rendering the acceptor more nucleophilic. This effect is seen for 6-OBn-protected acceptor **1** versus acceptor **2**, which based on the absence of the electronegative oxygen atom at C-6 should be a more reactive acceptor than **1**. The hydrogen bond may also be the contribution that prevents donor **B** from providing full α-selective condensations (Table 2; **9B**, **13B**).
[13] The addition of a third nitro group on the benzoate did not lead to a further increase in α-selectivity. In fact, slightly more β-product was obtained with the C-6-trinitrobenzoate acceptor **39** (**39A**, $\alpha/\beta = 2.1{:}1$; See the Supporting Information).
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