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Acceptor reactivity in glycosylation reactions

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The outcome of a glycosylation reaction critically depends on the reactivity of all reaction partners involved: the donor glycoside (the electrophile), the activator (that generally provides the leaving group on the activated donor species) and the glycosyl acceptor (the nucleophile). The influence of the donor on the outcome of a glycosylation reaction is well appreciated and documented. Differences in donor reactivity have led to the development of chemoselective glycosylation reactions and the reactivity of donor glycosides has been tuned to affect stereoselective glycosylation reactions. The quantification of donor reactivity has enabled the conception of streamlined one-pot glycosylation sequences. In contrast, although it has long been known that the nature and the reactivity of the nucleophile influence the outcome of a glycosylation, the knowledge of acceptor reactivity and insight into the consequences thereof are often circumstantial or anecdotal. This review documents how the reactivity impacts the glycosylation reaction outcome both in terms of chemical yield and stereoselectivity. The effect of acceptor nucleophilicity on the reaction mechanism is described and steric, conformational and electronic influences are outlined. Quantitative and computational approaches to comprehend acceptor nucleophilicity are assessed. The increasing insight into the stereoelectronic effects governing glycoside reactivity will eventually enable the conception of effective stereoselective glycosylation methodology that can be tuned to the reaction partners at hand.

Introduction

Synthetic oligosaccharides and glycoconjugates are extremely valuable research tools for biomedical and biotechnological purposes and synthetic oligosaccharides have made it into the clinic to replace naturally sourced oligosaccharides that are structurally less well-defined and more heterogeneous. Notwithstanding these successes, the assembly of complex oligosaccharides continues to be a time and labor consuming process, as a result of the lack of general glycosylation procedures and the many variables that play a role in a chemical glycosylation reaction.[1–3] In a traditional (Lewis) acid catalyzed reaction, the donor is activated to produce a reactive electrophilic species which then reacts with the incoming nucleophile, the "acceptor". Over the years significant progress has been made in understanding and harnessing the reactivity of the donor glycoside and insight into the effect of the ring substituents and protecting group patterns on the reactivity of the donor building block has allowed the generation of effective chemoselective and orthogonal glycosylation strategies as well as enabled the development of stereoselective glycosylation methodology.[4] The reactivity of the acceptor, on the other hand, is less well studied and often taken for granted.[5] At the same time, it is well appreciated that the nature of the acceptor can have a major influence on the outcome of a glycosylation reaction, both in terms of isolated yield and stereoselectivity. Numerous examples of glycosylation reactions have shown that the reactivity of the acceptor, like that of glycosyl donors, can be manipulated by changing protecting groups.[6] Unfortunately, most studies that report on new glycosylation methods, strategies or mechanisms, employ a rather variable set of acceptors, often chosen because of ease of availability, or used because a target oriented approach is taken. As a result, the acceptors used in these studies differ greatly in steric and electronic properties, making it difficult to establish clear structure–reactivity relationships.[7] Unexpected stereoselectivities and/or poor yields, as a result of ill-understood acceptor reactivity, are continuously being reported,[8–12] and indicate the need for deeper insight into carbohydrate acceptor reactivity and its effect of the outcome of glycosylation reactions. At a time when the mechanism of the glycosylation reaction is understood better than ever before[13] and insight in and control over donor reactivity has taken shape it is clear that understanding and harnessing the reactivity of the glycosyl acceptor is crucial for the development of more general glycosylation methodology and to remedy the need for ill-defined and time consuming reaction optimization procedures, that have thwarted the field

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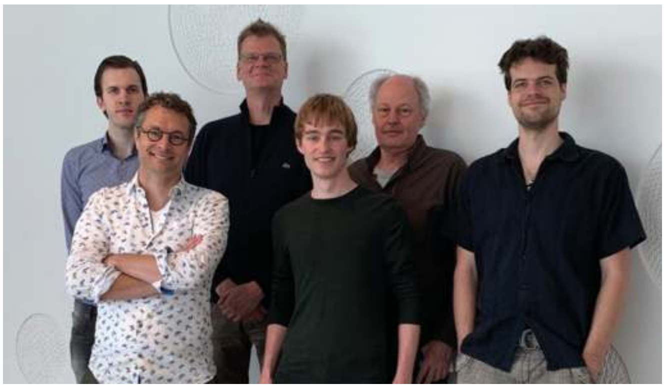
for so long. This review aims to provide an overview of our current understanding of the structural features influencing acceptor reactivity and the effect thereof on the outcome of glycosylation reactions. It will survey the systematic approaches that have been undertaken to probe, analyze and quantify acceptor reactivity.

Observations on acceptor reactivity

In one early example, Sinaÿ and co-workers[14] described the clear influence of the protecting groups of the acceptor on the outcome of glycosylations of galactosyl bromide **1** (Table 1). *N*-Acetyl-glucosamine acceptors **2–5**, with an *O*-benzyl (**2**) or *O*-allyl (**3**, **4**) group at C-3 gave good yields, regardless of the nature of the protecting group at C-6 (*O*-benzyl or *O*-acetyl), but the yield of the condensation dropped to a mere 5% when the acceptor **5**, bearing an *O*-acetyl at C-3 was used.

In 1981 Paulsen and Lockhoff examined a set of donors (**12–14**, Table 2) with two very similar rhamnosyl acceptors, differing only in the anomeric protection (*O*-benzyl in **10** *vs.* *O*-trichloroethyl in **11**).[15] In this set of experiments both the influence of the reactivity of the donor (**12** > **13** > **14**) and acceptor (**10** > **11**) became evident. Formation of the β-linked products was explained by assuming a direct displacement of the anomeric α-bromides, while the α-galactosyl linkages were thought to arise from the corresponding β-bromides, formed by *in situ* anomerization of the α-bromides with $HgBr_2$.



From left to right: Jacob van Hengst, Jeroen Codée, Hermen Overkleeft, Thomas Hansen, Gijs van der Marel and Stefan van der Vorm

Jacob van Hengst obtained his BS degree in Molecular Science and Technology (2014) and a MS degree in Chemistry (2017) from Leiden University. In 2017 he started his PhD research under the guidance of Jeroen Codée and Gijs van der Marel, investigating how the stereochemistry and protecting group pattern of both the donor and acceptor glycoside building blocks affect the course of glycosylation reactions.

Jeroen Codée obtained his PhD degree from Leiden University (2004) under the guidance of Jacques van Boom and Stan van Boeckel investigating thioglycosides in the assembly of heparin and heparan sulfates. After a post-doctoral stay at the ETH Zürich with Peter Seeberger, working on automated and flow synthesis, he returned to Leiden University, where he currently is Associate Professor. He was awarded the Carbohydrate Research Award for Creativity in Carbohydrate Chemistry in 2017 and his research interests include synthetic carbohydrate chemistry, reaction mechanisms, glycobiology and glycoimmunology.

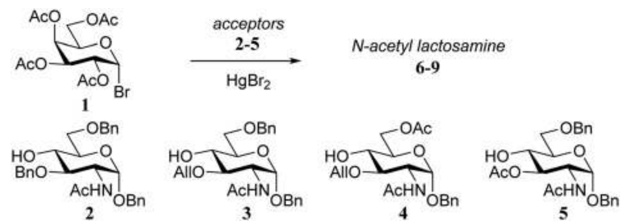
Hermen Overkleeft received his PhD degree from the University of Amsterdam (1997) and, after post-doctoral stays at Leiden University (1997–1999, with Van Boom and Van der Marel) and Harvard Medical School (1999–2001, with Hidde Ploegh) he became Full Professor at Leiden University, where he currently is the director of the Leiden Institute of Chemistry. Trained as an organic chemist, his work centers around the design and development of covalent and competitive glycosidase and peptidase inhibitors for chemical biology research. He is the recipient of the Jeremy Knowles Award of the Royal Society of Chemistry to promote interdisciplinary research between chemistry and the life sciences. He is a Fellow of the Royal Society of Chemistry (UK) and an elected member of the Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen – KNAW).

Thomas Hansen obtained his bachelor degree from the Leiden University of Applied Sciences (2013) and his master degree summa cum laude from Leiden University in 2015. Directly after he started his PhD research under guidance of Jeroen Codée and Gijs van der Marel developing computational tools to study the glycosylation reaction mechanism. He has recently introduced a computational strategy to study the conformational behavior and reactivity of glycosyl oxocarbenium ions. His research interests include computational chemistry, synthetic carbohydrate chemistry and unraveling reaction mechanisms.

Gijs van der Marel is Full Professor in Organic Chemistry at Leiden University. He trained with Prof. Jacques van Boom on the development of synthetic methods for oligonucleotides and obtained his PhD degree in 1981. His research has been directed at the development of synthetic chemistry to assemble all types of biopolymers: nucleic acids, peptides and carbohydrates as well as hybrids and analogues thereof to study their role in biology. He has supervised > 100 PhD students and his research interests include synthetic organic chemistry methodology, biopolymer synthesis, glycobiology and chemical biology and immunology.

Stefan van der Vorm obtained his BSc Molecular Science and Technology degree from Leiden University in 2010. In 2013 he completed his Master degree in Chemistry and in the same year he started his PhD research with Jeroen Codée and Gijs van der Marel. In 2018 he completed his PhD thesis "Reactivity and Selectivity in Glycosylation Reactions" which describes the development of tools to study glycosylation reactions mechanisms, and the effect of donor and acceptor reactivity thereon. Reactivity scales have been introduced to map the effect of acceptor nucleophilicity on the stereoselectivity of glycosylation reactions. Currently Stefan is lecturer in organic chemistry at Leiden University.

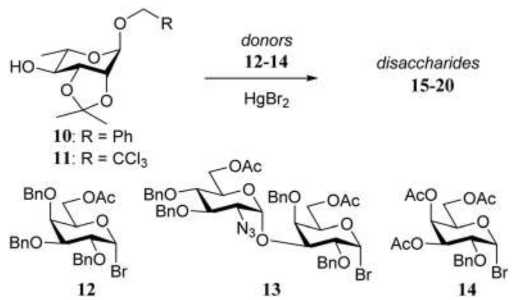
Table 1 Acceptor protecting groups influencing glycosylation yield (Sinaÿ, 1978)[14]



Acceptor	Product	Yield (%)
2	**6**	87
3	**7**	77
4	**8**	78
5	**9**	5

All glycosylations proceeded with exclusive β-selectivity.

Table 2 Decrease in acceptor reactivity leads to increase in α-selectivity (Paulsen and Lockhoff, 1981)[15]



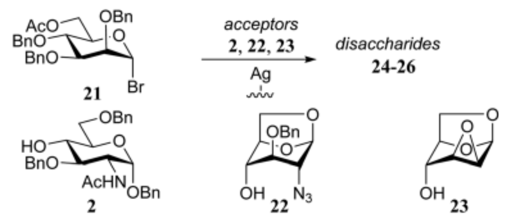
	Acceptor **10**		Acceptor **11**	
Donor	Product	α : β (yield)	Product	α : β (yield)
12	**15**	19 : 81 (75%)	**18**	81 : 19 (82%)
13	**16**	34 : 66 (66%)	**19**	100 : 0 (54%)
14	**17**	100 : 0 (81%)	**20**	100 : 0 (87%)

Yields of combined isolated anomers. Reagents and conditions: donor (1 eq.), acceptor (1 eq.), powdered 4 Å M.S., $HgBr_2$ (0.1 eq.), DCM, room temperature (20), 0 °C (17), or −20 °C (**15**, **16**, **18**, **19**).

Reactive acceptors can take the direct substitution pathway displacing the α-bromide, while less reactive nucleophiles require the more reactive β-bromides for an effective reaction. Following this line of reasoning, the trichloroethyl protected rhamnosyl acceptor **11**, providing more of the α-linked products than its benzyl protected analogue **10**, was found to be significantly less reactive than its benzyl counterpart.

In another example, Paulsen and Lebuhn probed the silver-silicate promoted glycosylation of mannosyl bromide **21** with different glucose and glucosamine acceptors (Table 3). While the conformationally locked glucosamine acceptor **22** and mannose acceptor **23** proved to be capable of direct S_N2-type displacement of activated α-bromide, leading to the synthesis of 1,2-*cis*-linked disaccharides **25** and **26**, the use of *N*-acetyl glucosamine **2** only delivered the undesired α-product, possibly through the intermediacy of an oxocarbenium-like intermediate that is attacked from the α-face.[16]

Table 3 Conformationally restricted acceptors provide more β-product (Paulsen and Lebuhn, 1983)[16]



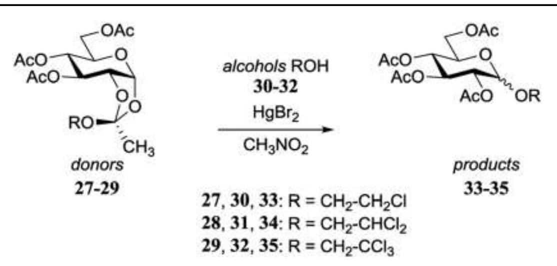
Acceptor	Product	Yield (%)	α : β
2	**24**	75	α only
22	**25**	65	1 : 6
23	**26**	63	1 : 5.5

Yields of the β-anomer. Reagents and conditions: donor (1.1 eq.), acceptor (1 eq.), powdered 4 Å M.S., silver-silicate, DCM, room temperature (or 35 °C for **24**).

Garegg and Kvarnström provided an early example how the stereochemical outcome of a glycosylation reaction can be influenced by the reactivity of the acceptor nucleophile.[17,18] Through a Kochetkov orthoester glycosylation reaction, different orthoesters (**27–29**) were converted in the presence of the corresponding alcohol (**30–32**) under the aegis of 0.33 eq. $HgBr_2$ in refluxing CH_3NO_2, into the α/β-glycosides **33–35** (Table 4). A gradual change in stereoselectivity is observed depending on the orthoester/alcohol functionality. The dichloroethanol system provided an unselective glycosylation, while the more electron rich monochloroethanol showed moderate β-selectivity and the more electron poor trichloroethanol led to a slightly α-selective reaction.

Over the years it has become clear that *N*-acetylglucosamine C-4-OH acceptors are generally very poor nucleophiles.[5] In a detailed study by Crich and co-workers, several glucosamine acceptors, bearing different *N*-protecting groups (**38–42**, Table 5) were used to unearth the underlying reasons why these acceptors behave so poorly in glycosylation reactions.[19] Glycosylations of these acceptors with mannosyl sulfoxide **36** are reported in

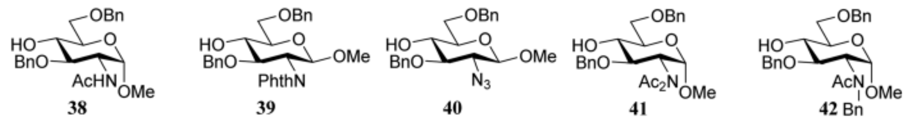
Table 4 The stereoselectivity of orthoester glycosylations are dependent on the orthoester substituent (Garegg and Kvarnström, 1976)[17]

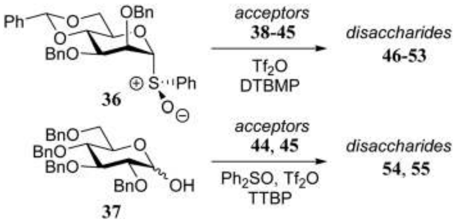


Donor	Alcohol	Product	Yield (%)	α : β
27	**30**	**33**	87	16 : 84
28	**31**	**34**	83	50 : 50
29	**32**	**35**	78	67 : 33

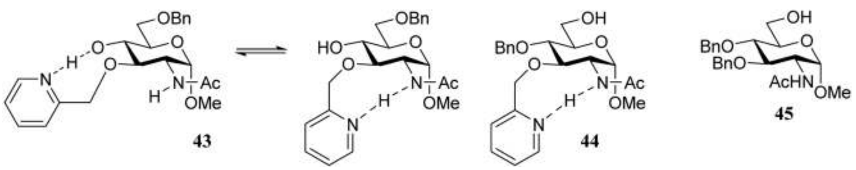
Reagents and conditions: donor (1 eq.), alcohol (2 eq.), $HgBr_2$ (0.33 eq.), CH_3NO_2 reflux, 15 min.

Table 5 Intermolecular hydrogen-bonding is detrimental to acceptor reactivity (Crich and Dudkin, 2001)[19]





Acceptor	Product	Yield (%)	α : β
38	**46**	9	β only
39	**47**	53	β only
40	**48**	70	β only
41	**49**	47	β only
42	**50**	39	β only
43	**51**	8	β only
44	**52**	63	β only
45	**53**	39	β only
44	**54**	87	1 : 1.2
45	**55**	18	1 : 2.4



Reagents and conditions: for **36**: donor (0.2 mmol), DTBMP (0.4 mmol), Tf_2O (0.22 mmol), DCM (8 mL), then acceptor (0.4 mmol, 2 mL DCM), −78 °C to 0 °C; for **37**: donor (0.1 mmol), Ph_2SO (0.28 mmol) Tf_2O (0.15 mmol), toluene/DCM (3/1, 1 mL), −78 °C to −40 °C then TTBP (0.5 mmol, 0.5 mL DCM), acceptor (0.1 mmol, 1 mL DCM), −78 °C to room temperature.

Table 5 and the results showed glucosazide **40** to be superior to the other acceptors, based on the yield of the reactions. Diamides **41** and **39** were found to be more effective nucleophiles than acetamide **38**. In a competition experiments in which **38**, **39**, and **40** competed for the same activated donor, products **46**, **47** and **48** were formed in a 1 : 3 : 10 ratio, corroborating the results of the individual glycosylations.

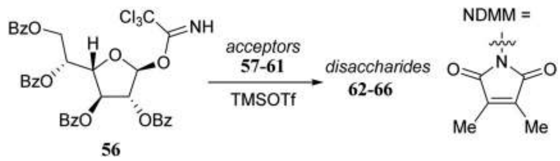
It was reasoned that the poor reactivity of acceptor **38** originated from an intermolecular hydrogen-bonding network involving the amide functionality. To substantiate this assumption, picolyl protected **43** and **44** were prepared to disrupt the intermolecular network by introducing an intramolecular hydrogen-bond between the picolyl nitrogen and the amide hydrogen. Experiments using acceptor **44**, bearing the C-3-*O*-picolyl ether and its C-3-*O*-benzyl counterpart **45**, showed that for the primary alcohol in **44** disruption of the intermolecular hydrogen-bond network is effective, leading to higher glycosylation yields for picolyl acceptor **44** to product **52**. It sorted no effect in increasing the reactivity of the C-4-OH in **43** with respect to acceptor **38** as both glycosylations proceeded with a similarly poor yield. This result was explained by the possibility of the picolyl nitrogen in **43** to form either a hydrogen-bond with the C-4-OH or with the C-2-amide NH. Acceptors **44** and **45** were made to compete in a glycosylation with sulfoxide donor **36** and this experiment resulted in a 2 : 1 mixture of disaccharides **52 : 53**, corroborating the findings of the individual glycosylations. Acceptors **44** and **45** were also used in dehydrative glycosylations with donor **37** to show how the reactivity difference between the two acceptors translates into a large difference in yield between products **55** and **56**.

Rúveda and co-workers investigated the relative reactivities of a series of dimethylmaleimide (DMM) protected glucosamine acceptors (**57**, **59**, and **60**, Table 6) by competition experiments using galactofuranose donor **56**.[20] The reactivity of these nucleophiles was compared to that of *N*-acetyl glucosamine acceptor **61** and cyclic carbamate **58**. The cyclic nature of the 2-*N*-3-*O*-carbamate in the latter glucosamine ties back the group at C-3, rendering the C-4-OH more accessible and thus a better nucleophile.[21–23]

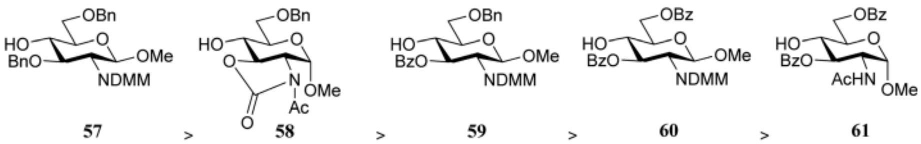
From the results in Table 6 it becomes clear that benzoyl groups in the acceptor have a retarding effect on the glycosylation rate. In this study the poor reactivity of *N*-actyl glucosamine **61** again becomes apparent. In a second set of competition experiments, the reactivity of allosamine and glucosamine acceptors bearing the DMM-protecting group, were assessed in glycosylations with galactopyranosyl donor **67** (Table 7).[24] Allosamine **68** outcompeted the epimeric acceptors **69** and **70**. This relatively high reactivity was related to an activating H-bond that can be formed between the DMM carbonyl and the axial C-3-OH in **68**, which was supported by NMR and computational studies. Notably this reactivity series reveals, that axial-orientated hydroxyl groups are not always poorer nucleophiles; a commonly regarded notion that is primarily based on steric arguments.[25]

Rúveda and co-workers further explored the DMM-glucosamine series in a set of glycosylation reactions in which the relative reactivity of C-3-OH and C-4-OH nucleophiles were tested.[26] The regioselectivity for glycosylation at the C-3-OH over the C-4-OH increased in the order of C-6-OBz > C-6-OTBDPS > C-6-OBn showing that the electron withdrawing benzoyl at C-6 diminishes the reactivity of the proximal C-4-OH with respect to the C-3-OH (C-3/C-4, 1 : 0 for **56**, and 2 : 1 for **67**, Table 8). The bulky TBDPS in acceptor **80** sterically hinders the nucleophilic attack of the C-4-OH, leading to increased

Table 6 Acceptor competitions revealed the effect of protecting groups on the reaction rates (Rúveda, 2006)[20]

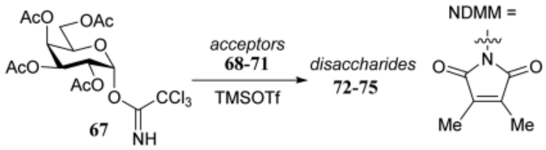


Acceptors	Products	Ratio
58 : 57	**62 : 63**	1 : 4
58 : 59	**62 : 64**	1.5 : 1
58 : 60	**62 : 65**	7 : 1
58 : 61	**62 : 66**	11 : 1

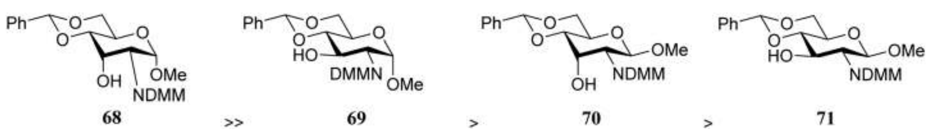


Reagents and conditions: two acceptors (1 eq. each), donor (1.2 eq.), TMSOTf (1.25 eq.), 4 Å M.S., DCM/CH_3CN (29/1, 0.34 M), −30 °C.

Table 7 Acceptor competitions revealed the effect of protecting groups on the reaction rates (Rúveda, 2011)[24]



Acceptors	Products	Ratio
68 : 69	**72 : 73**	10 : 1
68 : 70	**72 : 74**	13 : 1
69 : 70	**73 : 74**	2 : 1
69 : 71	**73 : 75**	5 : 1
70 : 71	**74 : 75**	3 : 1



Reagents and conditions: two acceptors (1 eq. each), donor (1.1 eq.), TMSOTf (0.28 eq.), 4 Å M.S., DCM, −25 °C.

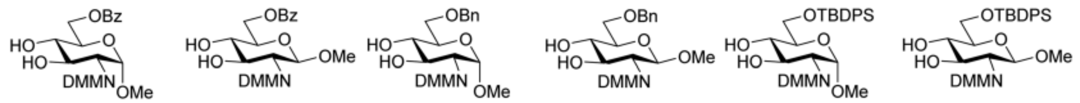
C-3/C-4-regioselectivity with respect to the glycosylation of the C-6-OBn acceptor **78** (compare 5 : 1 for **80** and 3.2 : 1 for **78**, with donor **56**). Notably, the relative reactivity of the acceptors was more similar in glycosylations using donor **67** and the glycosylations of the β-anomeric acceptors (**77**, **79**, **81**) also showed different regioselectivities, favouring the C-4-OH nucleophile, which was attributed to the difference in hydrogen-bonding capacity of the DMM group with the C-3-OH in the different anomers.[27,28]

Steric and conformational effects

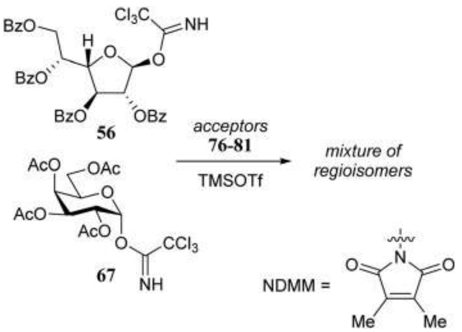
It is difficult to separate individual steric or electronic contributions of the different functional groups on the overall reactivity of a glycosyl acceptor alcohol as these effects are heavily intertwined. In the following section, selected examples of glycosylation reactions are provided, of which the relative stereochemical outcome can be understood to result from changes in steric and conformational effects.

As a first example the model thiodonors **82** and **83** are compared in glycosylation reactions with a set of acceptors (**86–89**) of increasing steric demands.[29] Because donors **82** and **83** only carry a single electronwithdrawing substituent, they are rather reactive and substitution reactions on these donors likely proceed through a dissociative mechanism. Two observations merit attention. First, with increasing steric demand of the acceptor nucleophile more α-product is formed for both donors. Second, the uronic acid donor provides products with a larger degree of β-selectivity than the benzyloxymethyl donor. To account for the observed stereoselectivity of the reactions, the half-chairs **84** and **85** were proposed to be product forming intermediates. Structure **85** with its equatorial substituent is the predominant conformer when R is large, whereas in structure **84**, the smaller carboxylic acid ester can provide better electronic stabilization of the positive charge at the anomeric

Table 8 Stereoelectronic effects of protecting groups influence the regioselectivity of diols (Rúveda, 2007)[26]



76 77 78 79 80 81



Donor	Acceptor	Yield (%)	(1 → 3) : (1 → 4)
56	**76**	68	1 : 0
56	**77**	75	1 : 1
56	**78**	71	3.2 : 1
56	**79**	71	1 : 2.9
56	**80**	73	5 : 1
56	**81**	87	1 : 2.2
67	**76**	91	2 : 1
67	**77**	74	1 : 13
67	**78**	56	1 : 1
67	**79**	88	0 : 1
67	**80**	50	1.6 : 1
67	**81**	88	0 : 1

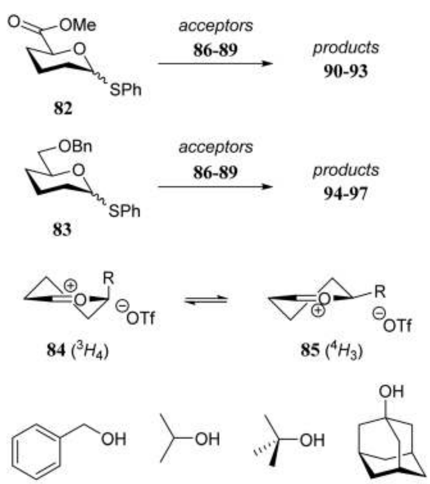
Reagents and conditions: donor (0.11 mmol, 1.1 eq.), acceptor (0.1 mmol, 1 eq.), 4 Å M.S., TMSOTf (0.21 mmol, 2.1 eq.), DCM/CH_3CN (37/1), −25 °C.

center when taking up an axial orientation. Favourable top-face attack then delivers the β-glycoside. With larger acceptors a Curtin–Hammett-type scenario takes place, in which the energetically less favorable conformer contributes more to the final product distribution, because there are less steric interactions in the transition state leading from this oxocarbenium ion. The two half-chairs of the benzyloxymethyl ion are more similar in energy, explaining the higher α-selectivity of donor **83** (Table 9).

In the early 90's Spijker and van Boeckel were the first to report on the concept of double stereodifferentiation[30] in synthetic carbohydrate chemistry.[31] They unambiguously showed how the absolute chirality of the coupling partners can impact the outcome of a glycosylation reaction (Scheme 1). The condensations of the two enantiomeric donors, D-fucosyl bromide **98** and L-fucosyl bromide **99** with D-glucosamine acceptor **100** proceeded with a rather different outcome. The glycosylation of donor **99** and acceptor **100** provided the disaccharide product with the expected *trans*-selectivity (α : β, 1 : 8.4), while the use of the enantiomeric donor **98** led to an anomeric mixture (α : β, 2 : 1). Although neighboring group participation is generally a powerful stereocontrolling tool, here it falls short because of an apparent steric mismatch in the transition state. In the second example, the enantiomeric pairs of D- and L-diacetoneglucose **102**/**103** were condensed with D-glucosyl bromide **101** to show that the 1,2-*cis*-selectivity in these glycosylations also depend, albeit to a lesser extent, on the absolute chirality of the reaction partners.

Another clear manifestation of the effect of the shape of the acceptor on the outcome of a glycosylation reaction can be observed when carbohydrate acceptors are locked in 'inverted' chair conformations. As was shown above, conformationally locking a glucose/glucosamine acceptor in a $^1C_4$ chair places the C-4-OH in a position that is well accessible, thereby increasing its nucleophilicity.[16,32] A well-established phenomenon in heparin synthesis is the excellent α-selectivity, generally

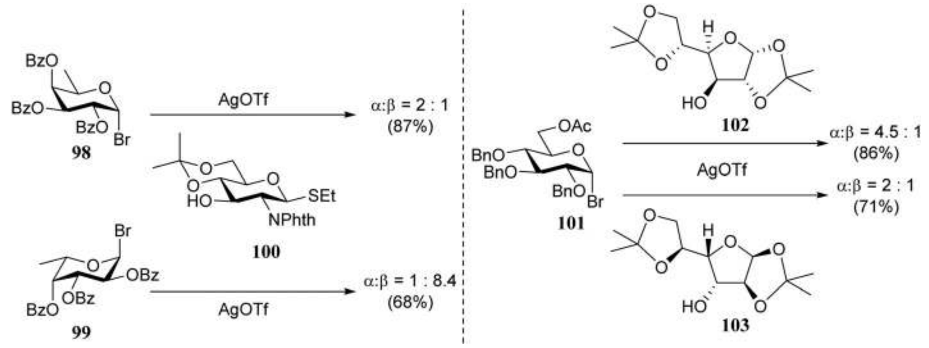
Table 9 Stripped glycosides provide a model system to study donor and acceptor steric hindrance (Codée, 2009)[29]



Donor	Acceptor	Product	Yield (%)	α : β
82	**86**	**90**	67	1 : 7.7
82	**87**	**91**	48	1 : 3.8
82	**88**	**92**	52	1 : 2.9
82	**89**	**93**	52	1 : 1.2
83	**86**	**94**	82	1 : 1.4
83	**87**	**95**	61	1.7 : 1
83	**88**	**96**	60	2.6 : 1
83	**89**	**97**	74	3 : 1

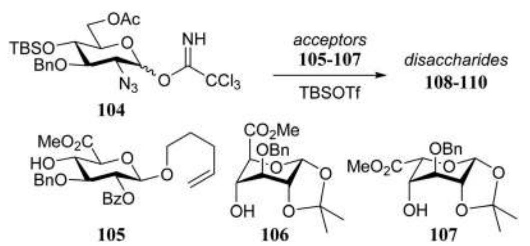
Reagents and conditions: donor (1 eq.), Ph_2SO (1.2 eq.), TTBP (3 eq.), Tf_2O (1.1 eq.), 3 Å M.S., DCM (0.05 M), −78 °C, then acceptor (4 eq.) in DCM (5 M) −78 °C, 15 min.

observed in glycosylations of glucosazide donors with L-idose/L-iduronic acid acceptors taking up an $^1C_4$ chair conformation. This important manifestation of double stereodifferentiation has been of great assistance in the assembly of synthetic



Scheme 1 Double stereodifferentiation in glycosylation reactions. (Spijker and van Boeckel, 1991).[31] *Reagents and conditions*: AgOTf, 2,6-di-*tert*-butylpyridine (0.8 eq.), 4 Å M.S., DCM, −50 °C.

Table 10 Conformational restriction leads to higher yields and α-selectivities (Seeberger, 2002)[35]



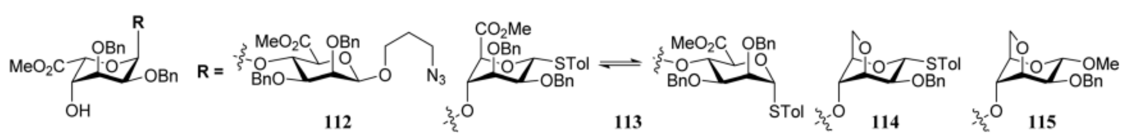
Acceptor	Product	Yield (%)	α : β
105	**108**	57	3 : 1
106	**109**	86	α only
107	**110**	91	α only

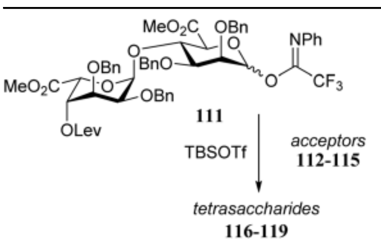
Reagents and conditions: donor (1.25 eq.), acceptor (1 eq.), TBSOTf (0.125 eq.), 4 Å M.S., DCM, −78 °C to room temperature, 2.5 h.

heparin and heparan sulfate fragments.[33,34] To transpose this stereodifferentiation to glycosylations involving D-glucuronic acid ester acceptors, Seeberger and co-workers locked these acceptors in a similar $^1C_4$ chair conformation (Table 10).[35] While the condensation of glucosazide donor **104** with D-glucuronic acid acceptor **105** provided an anomeric mixture (**108**; α : β, 3 : 1) in a relatively low yield, the glycosylation of the glucuronate acceptor in the $^1C_4$ conformation (**109**), proceeded in high yield with excellent α-selectivity, in analogy to reaction of the L-iduronic acid acceptor **110**.

Conformational changes further away from the reacting alcohol may also impact the reactivity of the nucleophile.[36–38] In the assembly of L-guluronic acid–D-mannuronic acid alginates Zhang *et al.* observed that the condensation of disaccharide acceptor **112** with mannuronic acid donor **111** proceeded in moderate yield (Table 11).[39] When this condensation was performed with acceptor **113**, having an α-*S*-tolyl group instead of the β-*O*-(azidopropyl) functionality at the 'reducing' end of the acceptor, a 91% yield was obtained. It was reasoned that the conformational flexibility of acceptor **113** was responsible for this large difference in reactivity.[40,41] The use of model disaccharide acceptors having a conformationally locked $^1C_4$ reducing end saccharide (as in **114** and **115**) confirmed that the 'ring inverted' acceptors were apt nucleophiles. This study has shown that conformational flexibility of the reaction partners can be key to accommodate the stringent steric requirements in the crowded glycosylation reaction transition states.

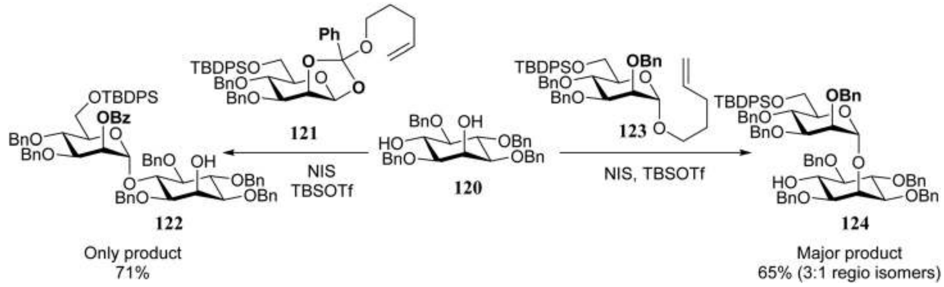
Table 11 Conformational flexibility of acceptor **112** dramatically increased glycosylation yield (Codée, 2015)[39]





Acceptor	Product	Yield (%)
112	**116**	45
113	**117**	91
114	**118**	71
115	**119**	95

All glycosylations proceeded with exclusive β-selectivity. Reagents and conditions: donor (3 eq.), acceptor (1 eq.), TBSOTf (0.6 eq.), 4 Å M.S., DCM, −78 °C to −45 °C.



Scheme 2 Donor–acceptor match and mismatch, led to the formulation of reciprocal donor–acceptor selectivity. (Fraser-Reid, 2000).[42,43] *Reagents and conditions*: donor (1.3 eq.), acceptor (1 eq.), NIS (1.3 eq.), TBSOTf (cat), DCM, room temperature.

It has been observed by Fraser-Reid and co-workers that the different hydroxyl groups in diol acceptors react with different specificity for a given donor system. Diol **120** can be regioselectively glycosylated at the equatorial hydroxyl with pentenyl orthoester donor **121**, while the axial alcohol in **120** reacts selectively with pentenyl mannoside **123** (Scheme 2).[42–45] Building on Paulsen notion that the reactivity of both reaction partners should be "matched" for an optimal glycosylation reaction,[46–49] Fraser-Reid coined the concept of reciprocal donor acceptor selectivity (RDAS), to account for these observations.[50–53] Although the concept still awaits a proper mechanistic explanation, the counter-intuitive outcome of several recent reactions have been related to this phenomenon.[54–58] To provide a satisfactory explanation for these observations, more insight is required into the intrinsic reactivity of (carbohydrate) acceptors and better (computational) methodology should be developed to assess the transition states of glycosylation reactions.

Systematic studies on acceptor reactivity

Although it is clear that the nature of the protecting groups on the acceptor glycosides has an influence on the glycosylation outcome it is often difficult to dissect electronic, steric and conformational effects.[59] Woerpel and co-workers have reported a systematic study relating the effect of the nucleophilicity of the acceptor on the outcome of a glycosylation reaction, using both *C*- and *O*-nucleophiles.[60–64] Table 12 lists the results of glycosylation of both sets of nucleophiles, using 2-deoxyglucosyl acetate or ethanethiol donors **133** and **134**. The nucleophilicity of the acceptor is assessed from the nucleophilicity parameter N,[65–70] introduced by Mayr to quantitatively compare different nucleophiles. Following a logarithmic scale, stronger nucleophiles are characterized by a higher number N, obtained using a large set of kinetic experiments employing benzhydrilium ion electrophiles. Table 12 also reports the field inductive parameter F,[71,72] a measure for the inductive electron-withdrawing power of the substituent (higher numbers indicating a stronger inductive effect). The trend that becomes apparent from the results in Table 12 is that weaker nucleophiles provide more α-product. To account for these results, it was reasoned that the weakest *C*- and *O*-nucleophiles **125** and **129**, react in a stereoselective manner with the glucosyl oxocarbenium ion, taking up a $^4H_3$ conformation (**144**). Increasing acceptor nucleophilicity leads to a decrease in α-selectivity. This erosion of stereoselectivity (from **135** to **138**, and from **139** to **142**) is caused by alternative reaction pathways becoming accessible for the stronger nucleophiles: either non-selective S_N1 reactions in which both sides of oxocarbenium ion **144** are attacked, or S_N2-type substitutions.

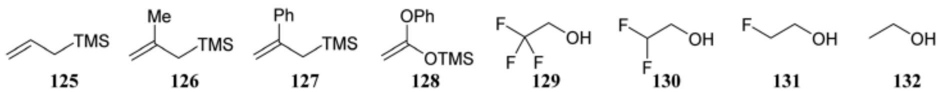
In an earlier study, Garegg *et al.*[73] studied the stereoselectivity of Könings-Knorr reactions of bromide donor **145** with a series of chlorine containing alcohols **30–32** (see also Table 3). Table 13 shows a similar reactivity–stereoselectivity trend, as reported by Woerpel and co-workers, when a polar solvent (CH_3CN) is used in combination with $Hg(CN)_2$ as activator. Despite the fact there was a participating group present on the C-2 of donor **145**, a substantial amount of the product α-anomer **148** was formed in the reaction with acceptor **32**. In a more apolar solvent, DCM, employing AgOTf as activator, the pathway proceeding through the dioxolenium ion prevailed and the β-products were mainly formed for all three acceptors with only a slight shift in stereoselectivity.

In a subsequent study by the same group,[74] the permethylated glucosyl bromide **152** (Scheme 3) was used. In a series of competition reactions monochloroethanol **30** was shown to react faster than trichloroethanol **32**. The weaker nucleophile provided slightly more α-product than the stronger nucleophile. Based on kinetic studies the authors proposed an ion pair mechanism to account for the observed reactivity and stereoselectivity.

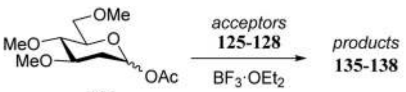
In line with the above described results, Seeberger and co-workers found that the stereoselectivity of condensations of donor **155** with linkers **156** and **157** strongly depended on the reactivity of the nucleophile. While the reactive primary alcohol **156** provided a β-selective reaction, the weaker nucleophile **157** mainly provided the α-product (Scheme 4).[75] By tweaking the reaction temperature and solvent, nearly complete α- or β-stereoselectivity could be obtained.[76] A variety of different donors provided a similar reactivity–stereoselectivity trend.

Le Mai Hoang and Liu introduced donors equipped with a 2-cyanobenzyl group at the C-2-OH and investigated these donors, in a pre-activation glycosylation scheme, with a panel of acceptors (Table 14).[77] Next to the model acceptors *n*-butanol **160** and trifluoroethanol **129**, this study also included carbohydrate acceptors bearing either benzyl ether of acetyl ester

Table 12 Model *C*- and *O*-nucleophilic acceptors in glycosylations correlating nucleophilicity to stereoselectivity (Woerpel, 2008–2010)[60–62]

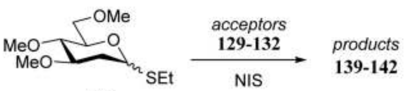


125 126 127 128 129 130 131 132



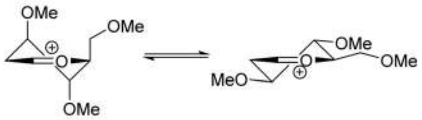
133

Acceptor	N^a	Product	Yield (%)	α : β
125	1.7	**135**	80	89 : 11
126	4.4	**136**	79	43 : 57
127	6.2	**137**	83	61 : 39
128	8.2	**138**	83	45 : 55



134

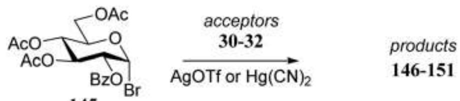
Acceptor	F^b	Product	Yield (%)	α : β
129	0.38	**139**	80	83 : 17
130	0.29	**140**	78	67 : 33
131	0.15	**141**	69	56 : 44
132	0.0	**142**	82	51 : 49



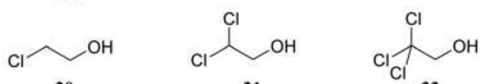
143 ($^3H_4$) **144** ($^4H_3$)

[a] Mayr's nucleophilicity parameter. [b] Field inductive parameter.[71] Reagents and conditions for acetyl donors: donor (1 eq.), acceptor (4 eq.), BF_3OEt_2 (1.5 eq.), DCM, −42 °C to 0 °C. Reagents and conditions for thiodonors: donor (1 eq.), acceptor (4 eq.), NIS (2 eq.), CH_3CN, 0 °C.

Table 13 Stereoselectivity of glycosylations of partially chlorinated ethanols (Garegg, 1985)[73]



145



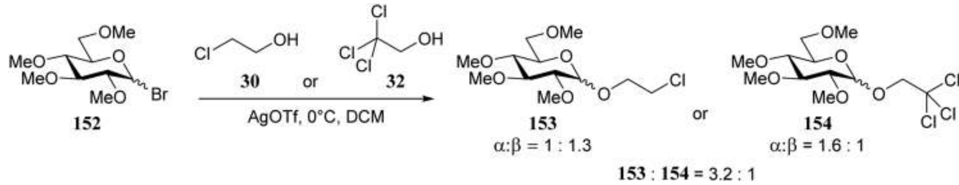
30 31 32

Acceptor	Product	Activator	Solvent	Yield (%)	α : β
30	**146**	$Hg(CN)_2$	CH_3CN	88	5 : 95
31	**147**	$Hg(CN)_2$	CH_3CN	83	17 : 83
32	**148**	$Hg(CN)_2$	CH_3CN	74	67 : 33
30	**149**	AgOTf	DCM	89	0 : 100
31	**150**	AgOTf	DCM	89	1 : 99
32	**151**	AgOTf	DCM	81	4 : 96

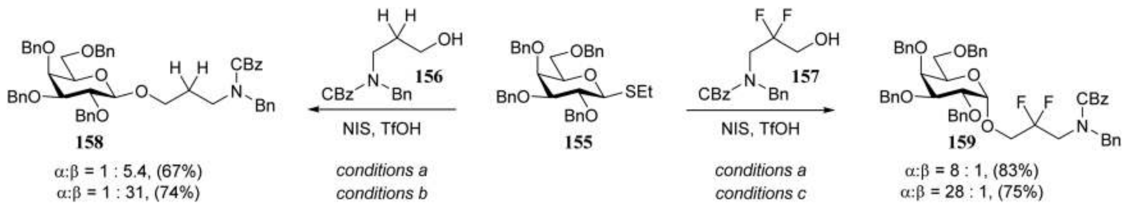
Reagents and conditions: donor (1 eq.), alcohol (1 eq.), activator AgOTf or $Hg(CN)_2$ (1 eq.), solvent CH_3CN or DCM. Glycosylations with $Hg(CN)_2$ were conducted at room temperature, glycosylations with AgOTf at −25 °C with 4 Å M.S.

protection groups. It was observed that the stronger nucleophiles stereoselectively provided the β-linked product, while the use of the weaker nucleophiles led to the generation of the α-linked products in a fully stereoselective manner.[78] The authors reasoned that the stronger nucleophiles (**23**, **160–162**) can partake in an S_N2-like substitution of the intermediate α-nitrilium ion **166**, to selectively provide the β-products. S_N2-like substitution of the intermediate α-triflate, or a closely related contact ion pair, will provide a similar outcome. The α-selectivity of the weaker, acetyl bearing acceptors **163** and **164** and trifluoroethanol **129** was accounted for by a assuming a hydrogen-bond with the cyano functionality on the C-2-*O*-protecting group, guiding the acceptor to the α-face of the donor (as in **167**). An alternative explanation can be found in the diastereoselective attack of the weaker acceptors on the intermediate oxocarbenium ion.

The systematic study described above lay bare the intrinsic dependence of the stereoselectivity of glycosylation reactions on the nature of the nucleophile. To relate the reactivity of carbohydrate acceptors to the set of partially fluorinated ethanol model acceptors, we have investigated a set of glycosyl donors in combination with both the model ethanol acceptors (**129–132**) as well as a set of carbohydrate alcohols.[79] We investigated benzylidene mannose and benzylidene glucose donors, **175** and **177**, because the reaction pathways of these donors have been well characterized.[80] In addition, mannuronic acid donor **176** was probed, as previous results indicated this donor to provide highly selective 1,2-*cis*-glycosylations through reaction pathways, likely involving oxocarbenium ion intermediates.[81] Scheme 5 displays the general pre-activation glycosylation protocol used for glycosylations described in Tables 15–17. Table 15 summarizes the results of the condensation reactions and it shows that the stereoselectivity of the reactions of the benzylidene glucose donor strongly depend on the nucleophilicity of the acceptor alcohol. Glucosylations with the most reactive acceptor, ethanol **132**, provides product **195** with high β-selectivity. Going down the table with decreasing nucleophilicity of acceptors **131**, **130**, **129** and **180**, the glucosylation selectivity gradually changes to exclusively form the α-anomers of **198** and **199**. In contrast, the reactions of the benzylidene mannose **175** and mannuronic acid **176** donors are less sensitive to the reactivity of the nucleophiles and a smaller change in selectivity is observed for donors **175** and **176**, (**185–189**, from 1 : 5 to 3 : 1, α : β; and **190–194**, from 1 : 8 to 1 : 1, α : β) when moving down the

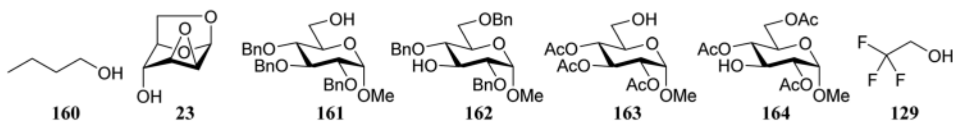


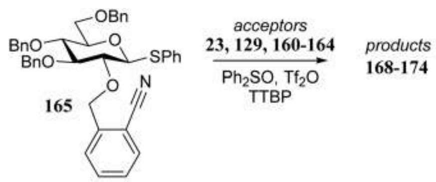
Scheme 3 Competition reactions of different nucleophiles. (Konradsson, 2000).[74]



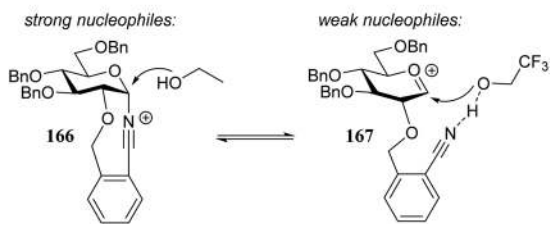
Scheme 4 Linkers of varying nucleophilicity gave opposite glycosylation stereoselectivity. (Seeberger, 2016).[75] *Reagents and conditions*: donor (1.5 eq.), acceptor (1 eq.), NIS (1.5 eq.), TfOH (0.2 eq.); (a) DCM, −20 °C; (b) CH_3CN −40 °C; (c) toluene/dioxane (3/1), room temperature.

Table 14 Reactive acceptors give pure β-selectivity, weak acceptors pure α-selectivity (Le Mai Hoang, 2014)[77]

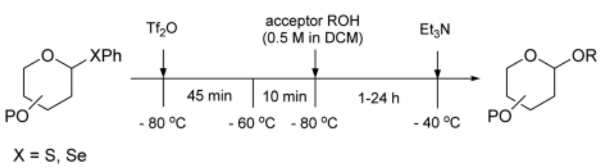




Acceptor	Product	Yield (%)	α : β
160	**168**	90	β only
23	**169**	86	β only
161	**170**	89	β only
162	**171**	86	β only
163[a]	**172**	87	α only
164	**173**	81	α only
129a	**174**	71	α only



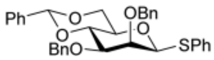
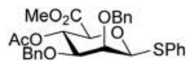
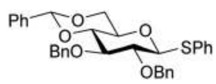
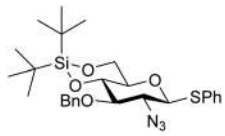
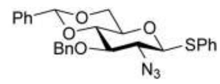
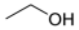
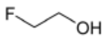
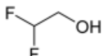
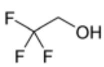
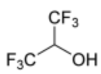
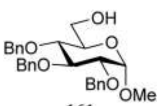
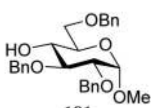
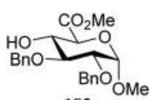
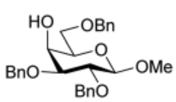
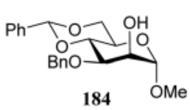
Reagents and conditions: donor (1 eq.), acceptor (1.3 eq.), Ph_2SO (1.4 eq.), TTBP (3 eq.), Tf_2O (2.8 eq.), toluene −60 °C.[a] Et_2O was used as solvent.



Scheme 5 Glycosylation protocol for the reactions described in Tables 15–17. *Reagents and conditions*: donor (1 eq.), Ph_2SO (1.3 eq.), TTBP (2.5 eq.), Tf_2O (1.3 eq.), 3 Å M.S., DCM (0.05 M), −80 °C to −60 °C, then acceptor (2 eq.) in DCM (0.5 M) −80 °C to −40 °C.

nucleophilicity scale in Table 15. It can be reasoned that the most important pathway for substitutions of the strong nucleophiles follows an S_N2-like itinerary, displacing the anomic triflates of the donor glycosides. The weaker nucleophiles require a stronger electrophile bearing more oxocarbenium ion character. The benzylidene glucose oxocarbenium ion will preferentially take up a $^4H_3$-like half-chair conformation that is preferentially attacked on the α-face.[82] This accounts for the gradually shifting stereoselectivity from the β-side to the α-side when the nucleophilicity of the acceptor alcohols decreases. The benzylidene mannose oxocarbenium ion on the other hand may take up a $B_{2,5}$ conformation,[83,84] that can be attacked form the β-face. The mannuronic acid oxocarbenium ion will adopt a $^3H_4$-like half-chair structure, that preferentially follows a reaction itinerary through attack on its β-face. The stereoselectivity of the reactions of the latter two oxocarbenium ions will therefore be similar to the stereoselectivity of the S_N2-type displacement of the intermediate α-triflates and the reactions thus

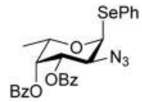
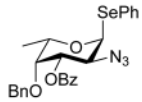
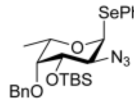
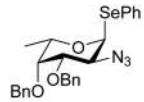
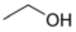
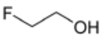
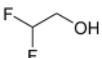
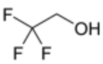
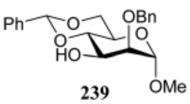
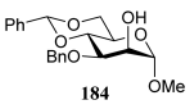
Table 15 Model glycosylation with a range of donors, reacting differently to a set of model acceptors (Codée, 2017)[82]

Acceptor	 175 Product α : β (yield)	 176 Product α : β (yield)	 177 Product α : β (yield)	 178 Product α : β (yield)	 179 Product α : β (yield)
 **132**	**185** 1 : 5 (70%)	**190** 1 : 8 (95%)	**195** 1 : 10 (68%)	**200** < 1 : 20 (65%)	**205** < 1 : 20 (83%)
 **131**	**186** 1 : 5 (86%)	**191** 1 : 6 (70%)	**196** 1 : 3 (70%)	**201** 1 : 5 (79%)	**206** 1 : 6.7 (90%)
 **130**	**187** 1 : 5 (90%)	**192** 1 : 5 (87%)	**197** 5 : 1 (70%)	**202** 2.7 : 1 (76%)	**207** 2.9 : 1 (64%)
 **129**	**188** 1 : 4 (78%)	**193** 1 : 2.5 (85%)	**198** > 20 : 1 (64%)	**203** > 20 : 1 (82%)	**208** > 20 : 1 (94%)
 **180**	**189** 3 : 1 (56%)	**194** 1 : 1 (52%)	**199** > 20 : 1 (65%)	**204** > 20 : 1 (34%)	**209** > 20 : 1 (53%)
 **161**	**210** 1 : 10 (97%)	**215** < 1 : 20 (71%)	**220** 1 : 3 (81%)	**225** 1 : 14 (92%)	**230** < 1 : 20 (89%)
 **181**	**211** 1 : 9 (75%)	**216** < 1 : 20 (61%)	**221** 1 : 1 (79%)	**226** 1 : 3 (81%)	**231** 1 : 7 (88%)
 **182**	**212** 1 : 10 (87%)	**217** 1 : 10 (71%)	**222** 5 : 1 (90%)	**227** 3.3 : 1 (84%)	**232** 1.1 : 1 (93%)
 **183**	**213** < 1 : 20 (70%)	**218** < 1 : 20 (76%)	**223** > 20 : 1 (83%)	**228** 7 : 1 (52%)	**233** 9 : 1 (75%)
 **184**	**214** < 1 : 20 (87%)	**219** 1 : 7 (80%)	**224** > 20 : 1 (80%)	**229** > 20 : 1 (85%)	**234** 9 : 1 (74%)

relatively insensitive to the nucleophilicity of the acceptors. The parallels that can be found in the stereoselectivity of the reactions of the carbohydrate acceptors and those of the model ethanol acceptors shows that the reactivity of the carbohydrate alcohols falls somewhere in between the reactivity of mono-fluoro- and trifluoro-ethanol.

The reactivity–stereoselectivity trends observed for the glycosylation reactions of the benzylidene glucose donor also became apparent in the condensations of the analogous benzylidene glucosamine donors (**178** and **179**, Table 16). The presence of the azide at C-2 shifted the reaction mechanism balance towards the S_N2-side as the electron-withdrawing azide stabilizes the covalent triflate with respect to the intermediate oxocarbenium ion. Glucosazide donors **178** and **179** provide relatively more β-product (disaccharides **200–204** and **205–209**) than their glucose counterpart. The relatively weak nucleophiles **129** and **180** still only provided the α-products **203, 204, 208** and **209.** The increased reactivity of silylidene donor **178** in comparison to that

Table 16 Fucosazide model glycosylations. Donor and acceptor reactivity can be combined to provide high α-selectivity (Codée, 2017)[82]

Acceptor	 **235** Product α : β (yield)	 **236** Product α : β (yield)	 **237** Product α : β (yield)	 **238** Product α : β (yield)
 **132**	**240** 1 : 3 (59%)	**244** 1 : 3 (58%)	**248** 1 : 1 (81%)	**252** 1 : 1 (88%)
 **131**	**241** 1 : 2 (34%)	**245** 1 : 1.5 (60%)	**249** 1 : 1 (80%)	**253** 1 : 1 (72%)
 **130**	**242** 1.5 : 1 (74%)	**246** 1 : 1 (80%)	**250** 2 : 1 (87%)	**254** 2 : 1 (81%)
 **129**	**243** 10 : 1 (50%)	**247** > 20 : 1 (45%)	**251** > 20 : 1 (90%)	**255** > 20 : 1 (80%)
 **239**	**256** 4 : 1 (38%)	**258** 4 : 1 (68%)	**260** > 20 : 1 (74%)	**262** > 20 : 1 (68%)
 **184**	**257** > 20 : 1 (64%)	**259** 10 : 1 (64%)	**261** 9 : 1 (64%)	**263** > 20 : 1 (72%)

of benzylidene donor **179** translates to the formation of more of the S_N1-product. A similar reactivity–stereoselectivity relationship was revealed for a set of fucosazide donors, that were studied in the context of the assembly of complex bacterial glycans.[85,86] As Table 17 reveals, the 1,2-*cis* : 1,2-*trans*-product ratio increases with increasing reactivity of the donor (**237**, **238** > **235**, **236**) and decreasing acceptor reactivity. This can be accounted for with a shift in product forming reaction pathways form a 1,2-*trans*-selective S_N2-like reaction of the reactive nucleophiles and the anomeric α-fucosazide triflates to 1,2-*cis*-selective S_N1-type reactions of the weaker nucleophiles, involving the $^3H_4$-like half-chair L-fucosazide oxocarbenium ions as product forming intermediates.

The gradually changing stereoselectivity of glycosylations of the benzylidene glucose/glucosazide donors as a function of acceptor nucleophilicity, opened up the possibility to use this system as a measure for the reactivity of carbohydrate alcohol acceptors.[87] We have used this set-up to establish structure-stereoselectivity relationships for a large set of glycosyl acceptors, of which the structure in terms of functional and protecting group pattern was systematically changed. We initially investigated C-4-OH glucose acceptors with all possible permutations of benzyl and benzoyl protecting groups of which a selection of the results is given in Table 17. These groups differ significantly in their electronic properties while being sterically very similar. A clear dependence of the reactivity/stereoselectivity on the functional/protecting group pattern was uncovered, with the less-reactive, benzoyl protected acceptors generally providing more 1,2-*cis* linked products. Notably, replacing a single benzyl ether for a benzoyl group on the position closest to the nucleophilic oxygen (*cf.* acceptors **181** and **268**) led to a drastic change in the stereoselectivity of the glycosylations, showing that non-selective reactions can be turned into highly selective reactive reactions by the judicious choice of protecting groups. Probing other regioisomeric glucosyl, mannosyl and galactosyl acceptors (**162**, **271–275**) revealed the same recurring trend. Care should be taken to compare the results obtained for different regioisomeric or diastereomeric acceptors as the different steric requirements for the acceptors will also play an important role in shaping the overall glycosylation outcome. It is expected that the extension of this study will provide further detailed insight into structure–reactivity–stereoselectivity relationships of diversely functionalized carbohydrate acceptor alcohols which will pave the way to develop more predictable glycosylation methodology.

Demchenko and co-workers established similar protecting group effects on a smaller set of regioisomeric glucosyl acceptors in glycosylations with STaz donor **302** (Table 18).[88] While the yields of the silver triflate mediated reactions proved independent of acceptor reactivity, the α/β-selectivity of the glycosylation reactions involving the benzyl protected acceptors is generally lower than the selectivity for the same acceptors bearing *O*-benzoyl groups. It was observed that the benzyl protected acceptors were converted faster to their respective products than their benzoyl protected counterparts.

In similar vein, Kalikanda and Li investigated the effect of different regioisomeric and configurational glycosyl acceptors.

Table 17 A large set of acceptors was set against two model donors **142** and **144** to study the acceptor's structure–reactivity–selectivity relationships (Codée, 2018)[87]

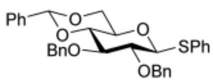
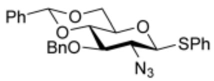
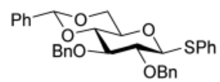
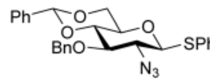
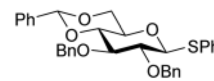
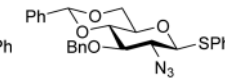
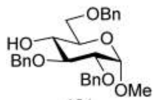
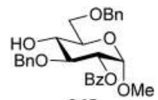
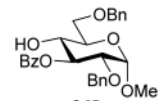
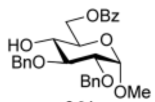
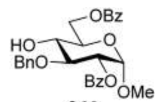
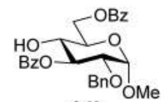
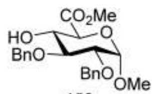
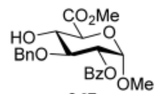
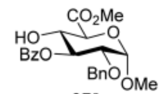
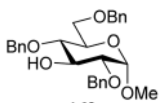
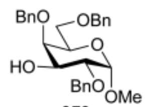
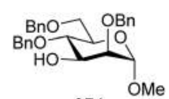
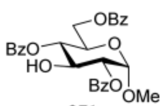
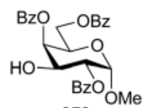
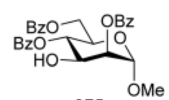
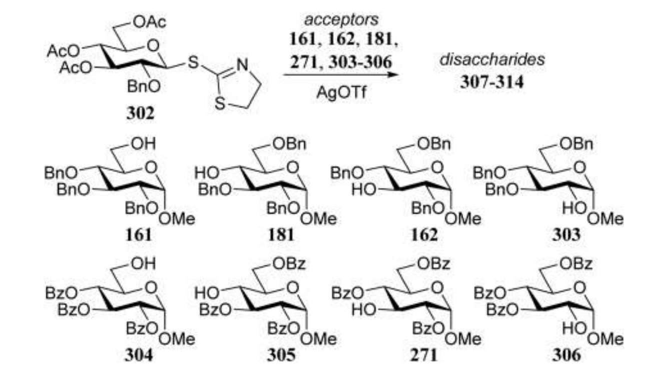
								
Acceptor	**177** Product α : β (yield)	**179** Product α : β (yield)	Acceptor	**177** Product α : β (yield)	**179** Product α : β (yield)	Acceptor	**177** Product α : β (yield)	**179** Product α : β (yield)
 **181**	**221** 1 : 1 (82%)	**231** 1 : 7 (88%)	 **265**	**278** 1 : 1.1 (81%)	**279** 1 : 6 (88%)	 **268**	**284** > 20 : 1 (95%)	**285** 6.7 : 1 (77%)
 **264**	**276** 4 : 1 (92%)	**277** 1 : 1.1 (67%)	 **266**	**280** 3.5 : 1 (88%)	**281** 1.3 : 1 (87%)	 **269**	**286** > 20 : 1 (95%)	**287** > 20 : 1 (85%)
 **182**	**222** 5 : 1 (90%)	**232** 1.1 : 1 (93%)	 **267**	**282** 4.8 : 1 (96%)	**283** 1.2 : 1 (82%)	 **270**	**288** > 20 : 1 (86%)	**289** > 20 : 1 (93%)
 **162**	**290** 1 : 2.7 (78%)	**291** < 1 : 20 (70%)	 **272**	**294** 6 : 1 (85%)	**295** 1 : 1.3 (88%)	 **274**	**298** 8 : 1 (82%)	**299** 1.1 : 1 (70%)
 **271**	**292** > 20 : 1 (100%)	**293** 11 : 1 (83%)	 **273**	**296** > 20 : 1 (83%)	**297** 11 : 1 (90%)	 **275**	**300** 20 : 1 (100%)	**301** > 20 : 1 (92%)

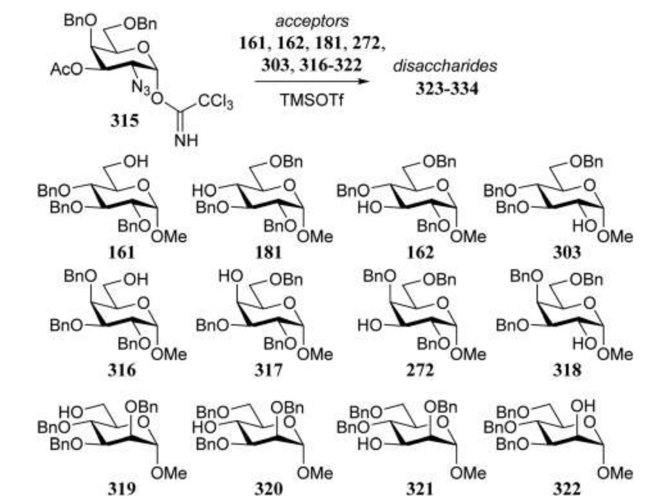
Table 18 Differentially substituted glucose acceptors provide a trend in reaction times and stereoselectivity (Demchenko, 2010)[88]



Acceptor	Product	Time (h)	Yield (%)	α : β
161	**307**	1.5	81	2.7 : 1
304	**308**	2	89	7.4 : 1
181	**309**	14	90	6.8 : 1
305	**310**	16	89	11.7 : 1
162	**311**	8	85	6.5 : 1
271	**312**	12	87	12.1 : 1
303	**313**	6	87	9.3 : 1
306	**314**	12	72	12.0 : 1

Reagents and conditions: donor (0.11 mmol, 1.1 eq.), acceptor (0.10 mmol, 1 eq.), 3 Å M.S., AgOTf (0.22 mmol, 2 eq.), 1,2-dichloroethane (2 mL), room temperature.

Table 19 Systematic study of the impact of configuration of the acceptor reactivity (Kalikanda and Li, 2011)[89]



Acceptor	Product	Yield (%)	α : β
161	**323**	98	β only
181	**324**	56	1.8 : 1
162	**325**	53	1 : 3.4
303	**326**	68	α only
316	**327**	75	1 : 4
317	**328**	63	α only
272	**329**	65	3 : 1
318	**330**	90	1.3 : 1
319	**331**	90	1 : 10
320	**332**	81	1.2 : 1
321	**333**	82	1 : 4.7
322	**334**	93	α only

Reagents and conditions: donor (1.2 eq.), acceptor (1 eq.), M.S., TMSOTf (0.15 eq.), DCM (0.2 M), −78 °C.

They studied twelve tri-*O*-benzylated acceptors, having either a *gluco*-, *galacto*-, or *manno*-configuration in glycosylations with galactosazide donor **315** (Table 19).[89] Again, it becomes clear that the most reactive alcohols react in a β-selective manner, while the least reactive nucleophiles provide α-linked products. Although the exact mechanism of these glycosylations are not clear, the results indicate the primary alcohols to be the most reactive and the secondary, axially orientated hydroxyls to be least reactive. The reactivity order, as assessed from the α/β-product ratio, in the glucose series matches that established in Demchenko's study described above.[68]

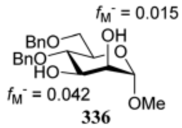
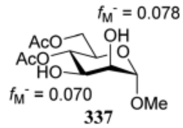
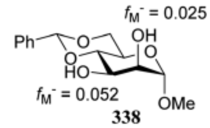
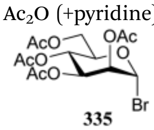
Quantifying acceptor reactivity

Notwithstanding the progress that has been made in computational chemistry, only few attempts have been reported to date to investigate the nucleophilicity of glycosyl alcohol acceptors in a computational manner. The Fukui function provides a measure for the change in electron density at an atom of interest when an electron is subtracted (or added), and Fukui indices have been reported to account for the regioselectivity of electrophilic (f^-) or nucleophilic (f^+) reactions. Kalikanda and Li have computed Fukui f^--indices for a series of mannosyl diol nucleophiles to account for the regioselectivity observed in an acetylation and a glycosylation reaction (Table 20).[90] The higher the f^- value is for a particular atom, the higher the nucleophilicity of this atom is. As shown in Table 20, the calculated Fukui indices show that the relative nucleophilicity of the C-2 and C-3-alcohol functions depends on the protecting group pattern on the ring. A relatively large difference in Fukui values (such as for **338**) indicates a more regioselective reaction as is borne out in the experiments, although it should be noted that only a very small set of nucleophiles and reactions has been probed.[91]

The group of Rúveda and Stortz also determined Fukui functions for a set of glucosamine acceptors (also see Table 6). They used the chemical hardness/softness (local chemical softness, *s*) of a reaction center and the atomic charge (*q*) as indicators for the relative reactivity of a series of acceptors (**339–341**, Fig. 1). In the examples studied, the atomic charge differed slightly between the alcohols in **339–341**, and the chemical softness (*s*) seemed to correlate best with the relative reactivity (a lower $s_{O\text{-}4}$ value indicates a more reactive acceptor), as determined in a glycosylation reaction using a perbenzoylated galactofuranose imidate donor **56** (see Table 6). The authors concluded that the interaction of their glycosyl acceptors with a glycosyl donor are better described by hard-hard (atomic charges) interactions than by frontier molecular orbital (soft–soft) interactions, and that all three descriptors have to be taken into account.[20,27]

In a different approach the same group correlated the relative acceptor reactivity of a series of acceptors to the relative

Table 20 Fukui values determined for mannosyl diol acceptors (Kalikanda and Li, 2010)[90]

Entry	Electrophile	 336 Ratio O-3/O-2	 337 Ratio O-3/O-2	 338 Ratio O-3/O-2
1	Ac_2O (+pyridine)	6 : 1	3 : 2	1 : 0
2	 335	1 : 0	3 : 1	1 : 0

Thiophenyl and trichloroimidate donors also gave trisaccharide byproducts, the disaccharides were formed with the same selectivity regardless of the donor. Atom-condensed Fukui values f_m^- were based on Mulliken charges and were obtained by DFT (B3LYP/6-31+G*). Reagents and conditions: donor (1 eq.), acceptor (1 eq.), 3 Å M.S., AgOTf (1 eq.), DCM, −30 °C.

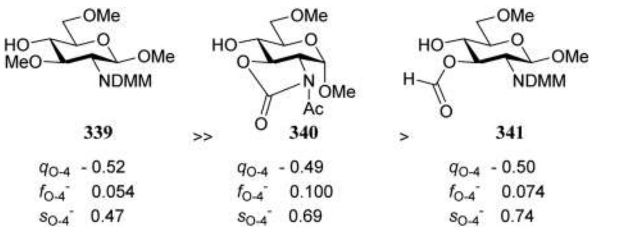


Fig. 1 Computation evaluation of relative acceptor reactivities. (Rúveda, 2006).[20] Atomic charge *q*, atom condensed Fukui value *f* and local chemical softness *s* are determined by multiple approaches, see the original publication for details.

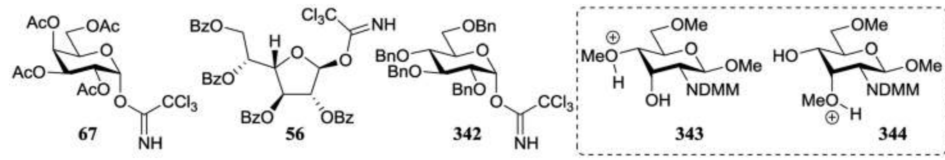
energy of the related methyloxonium ions (for example **343** and **344**, energy difference between the C-3-OH(Me)$^{(+)}$ and C-4-OH(Me)$^{(+)}$ species is reported in the Table 21).[92] The positively charged structures served to mimic the charge development in the glycosylation transition state and enabled the investigation of the influence of intramolecular hydrogen-bonding on the stability and geometry on the acceptor entity.[93,94] Table 21 reports computational results of a variety of diol acceptors and the experimental regioselectivity obtained in glycosylations with galactopyranose and furanose donors **67** and **56** (also see Table 8). Acceptors **345** and **346** were exclusive glycosylated at the axial C-3 in condensation reactions with donor **67**, a result that correlates well with the calculated relative energy of the C-3-OH(Me)$^{(+)}$ and C-4-OH(Me)$^{(+)}$ species. The relative energy difference for glucosamine acceptors **76–79** proved to be smaller, and this correlated with a diminished regioselectivity in the reactions. Notably the regioselectivity proved dependent on the type of donor used, with the result obtained with the galactopyranose donor matching better to the computational results than the results obtained in the galactofuranose series. Benzylidene allose diols **347** and **348** were combined with glucose donor **342** revealing a slight preference for glycosylation at the C-3-OH both experimentally and computationally, although there clearly is no perfect agreement between both methods. The authors also calculated the energies of formation (from the neutral hydroxyl acceptor and a methyl cation) of structures **349** and **350** to compare the reactivity of individual acceptors with a single free hydroxyl group. The energy difference $\Delta\Delta E$ of 7.9 kcal mol^{-1} between the two systems is in agreement with the observed reactivity difference (Table 7; **69**/**71**, 5 : 1). It appears that this relatively simple method is a promising way to estimate relative acceptor reactivities. With the advent of more accurate and powerful computational techniques, the extension to larger set of acceptors, and the use of a glycosylation system that follows well-defined and understood reaction paths, it may provide a more qualitative picture of acceptor reactivity.

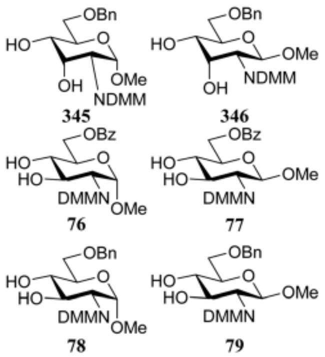
Bols and Inouye have taken a rather different approach to estimate the reactivity of different carbohydrate alcohols. They evaluated model systems in which specific hydroxyl groups were changed to amine functions.[95,96] The pK_as of the corresponding ammonium salts were determined by titration and these values are tabularized in Table 22. The pK_{aH} values indicate the 6-NH2 group to be the most basic. The order of basicity in glucose found with aminoglycosides **351–354a/b**, C-6-NH_2 > C-3-NH_2 > C-2-NH_2 > C-4-NH_2, roughly corresponds with the nucleophilicity on the parent hexoses (see Tables 17–19).[97–99] To account for the pK_{aH} trends recorded in Table 22, the authors identified that an anti-periplanar arrangement of the C-4-N and the C-5-O in **353a/b/d** (Fig. 2), but also of C-2-N and C-1-O in **351a/b/d** lead to a less basic NH_2 group.[100]

Conclusions

The reactivity of a glycosyl acceptor is of fundamental importance to the outcome of a glycosylation reaction. The nucleophilicity of a carbohydrate alcohol is influenced by electronic aspects, through inductive effects and hydrogen-bonding, and by steric and conformational effects. The protecting groups on the acceptor play a pivotal role in shaping the acceptor reactivity. In contrast to the reactivity of glycosyl donors, for which relative reactivity values have been established[4,101,102] to provide a numerical means to compare their reactivity, the relative reactivity of glycosyl acceptors remains relatively poorly understood and no numerical scales are available to assess acceptor reactivity. The insightful competition experiments performed by Rúveda did provide relative acceptor reactivities based on kinetics but to be more generally useful should be significantly expanded.[26] It would also be of interest to see how relative

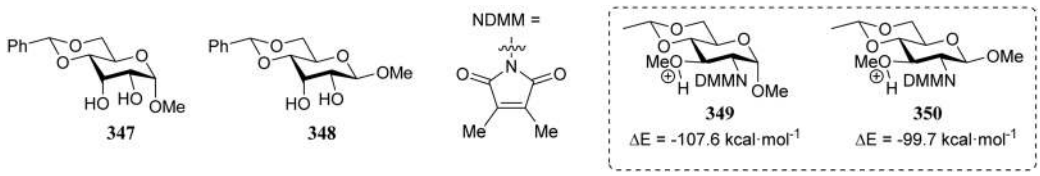
Table 21 Regioselectivity approach by glycosylations and computations (Stortz, 2011)[92]





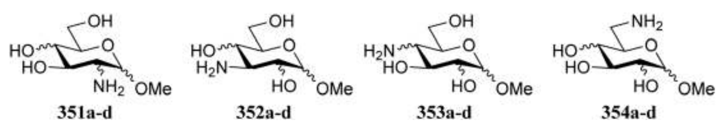
Acceptor	O-3/O-4 donor **67**	O-3/O-4 donor **56**	$E_{3\text{-O-Me}} - E_{4\text{-O-Me}}$ (kcal mol^{-1})
345	1 : 0		−8.64
346	1 : 0		−6.93
76	2 : 1	1 : 0	−4.60
78	1 : 1	3.2 : 1	−1.85
77	1 : 13	1 : 1	−0.03
79	0 : 1	1 : 2.9	+2.15

Acceptor	O-3/O-2 donor **342**	$E_{3\text{-O-Me}} - E_{2\text{-O-Me}}$ (kcal mol^{-1})
347	2.6 : 1	−4.39
348	1.2 : 1	−2.25



Energies obtained by DFT (B3LYP/6-31+G**). Reagents and conditions: donor (1.1 eq.), acceptor (1 eq.), TMSOTf (2.1 eq.), 4 Å M.S., DCM/CH_3CN (29/1, 0.34 M), −25 °C.

Table 22 pK_{aH} values of aminosugars (Inouye, 1968; Bols, 2011)[95,96]



Position	α-Glc	pK_{aH}	β-Glc	pK_{aH}	α-Gal	pK_{aH}	α-Man	pK_{aH}
2-NH_2	**351a**	7.5	**351b**	7.2	**355c**	7.9	**359d**	7.2
3-NH_2	**352a**	7.8	**352b**	7.6	**356c**	8.0	**360d**	8.1
4-NH_2	**353a**	6.8	**353b**	6.7	**357c**	7.3	**361d**	7.2
6-NH_2	**354a**	8.9	**354b**	8.6	**358c**	8.9	**362d**	9.0

Fig. 2 Anti-periplanar relationship between the ring oxygen and the C-4 substituent in methyl glucoside.

acceptor values change with different donors. A systematic evaluation of different well established donor systems with the same set of acceptors may provide an accurate structure–reactivity–stereoselectivity map. Another approach would be to establish Kinetic Isotope Effects for donor–acceptor combinations or to perform cation-clock kinetics. Both methods have been used by the group of Crich, but only on the relatively nucleophilic and minimally intrusive iso-propanol.[103–107] An extension of these methods spanning a wider range of acceptors, will provide the much needed insight how the reactivity of the acceptors determines the position of the operational reaction mechanisms along the S_N2–S_N1-continuum.[108]

Conflicts of interest

There are no conflicts to declare.

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