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Donor-Reactivity-Controlled Sialylation Reactions

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Although tremendous efforts have been made for the efficient preparation of sialosides, controlling the stereochemical outcome of sialylation reaction still remains one of the most challenging tasks due to the unique chemical structure of sialic acid. We developed a new strategy to statistically analyze the stereoselectivity of sialylation reactions on six types of *p*-tolyl thiosialosides in NIS/TfOH system using Relative Reactivity Value (RRV) as the indicator. Analysis of the reaction mechanism showed the formation of the relatively stable glycosyl bromide and glycosyl chloride intermediates from halide- and triflate-containing promotors in the absence of an acceptor. We found that the α/β-stereoselectivity, yields, and intermediate changes were associated with their donor reactivity. These findings enable to tailor the most suitable building blocks for stereocontrolled sialylation reactions.

Introduction

Sialic acids are a large family of 2-keto-3-deoxy-nonulosonic acids with a nine-carbon backbone. Due to their existence at the terminal position of glycan chains, sialic acids play significant roles in a large variety of biological processes such as molecular recognition, polysaccharide digestion, tumor metastasis, immune response and brain development.[1–3] Among the 50 naturally occurring derivatives of sialic acids, *N*-acetylneuraminic acid (Neu5Ac) is the most well-known and exists in a myriad of glycosidic linkages, most commonly α(2→3) and α(2→6) to galactose or galactosamine (or lactose), α(2→8), α(2→9), α(2→4) to another Neu5Ac moiety, forming disialic residues[4–10] and as C-2 linked to O-7 in 2,7-anhydroNeu5Ac.[9]

The structural diversity of sialic acid-containing oligosaccharides, makes it difficult to obtain a pure and sufficient amount of α-sialosides from a natural source and the process is time consuming.[11–13] To improve the α/β-selectivity of sialylation reaction, numerous approaches have been explored including changing anomeric leaving groups of C-2,[14,15,24–28,16–23] modifications at C-1,[4,21,26,29,30] C-3,[20,31,32] C-4[22–24,33,34] and C-5[14,17,39–41,22–25,35–38] positions, development of new activation systems,[22,23,36,42,43] impact of acceptor reactivity,[9,36,44,45] use of the solvent effect,[13,46] and employing new protecting groups (PGs).[3,31,47] However, these approaches have limited generality, depends on substrate-sensitivity and need systematic optimizations. Stereocontrolled α-sialylation still remains the most challenging task because the stereoselectivity of sialylation is unpredictable.[22,23,36,48] The participation of the solvent-separated ion pair (SSIP) during sialylation reaction usually results in poor α/β-selectivity.[19,49] Furthermore, the lack of stereo-directing neighboring group at position C-3 of sialyl donors also contributes to the unsatisfactory stereochemistry outcome.

Among various glycosyl donors, thioglycosides are the most widely used in chemical glycosylation.[4–6] This is because of their simple preparation, high stability, and compatibility with most functional group modifications. Thiosialosides **1** can be activated by a number of electrophilic promotors-the most common of which are *N*-halosuccinimide/triflic acid (NXS (X = Cl^-, Br^-, I^-)/TfOH),[33,47] dimethyl(methylthio)sulfonium triflate (DMTST),[21] *para*-toluenesulfenyl chloride/silver triflate (*p*-TolSCl/AgOTf),[36,48] and diphenyl sulfoxide/trifluoromethanesulfonic anhydride (Ph_2SO/Tf_2O).[42,43]

Pre-activation-based stereoselective sialylation reactions of thiosialoside donors **1** have been established to conduct sequential glycosylation for oligosaccharide synthesis.[36,42,48] Although several mechanism-based studies have been described in the literature, the requirement of excess amount of promotors on thioglycoside activation system makes the reaction complicated as a stoichiometric amount of byproduct was accompanied *in-situ*.[5,23,36,42,43,48] Previously, α-glycosides were successfully synthesized by nitrile effect[19,26–28,35,38,41,46] via S_N2-type substitution reaction. However, the numerous combinations of each sialyl donor **1** and acceptors (ROH **3**) provide their own α/β-selectivities depending on the nature of *O*- and *N*-5 PGs,[40,49] side-chain conformations[50] and reaction conditions.[28] Moreover, the stereochemistry of the reactive intermediates and reagent dosage also undergoes the continual change under S_N1- and S_N2-like pathway which in turn influences the stereochemical outcome of chemical sialylation.[4,25,31,41] Therefore, such a complicated mechanism results in unpredicted stereoselectivity, and glycosylation owing to high stereoselectivity, besides, the yield meets the tremen-

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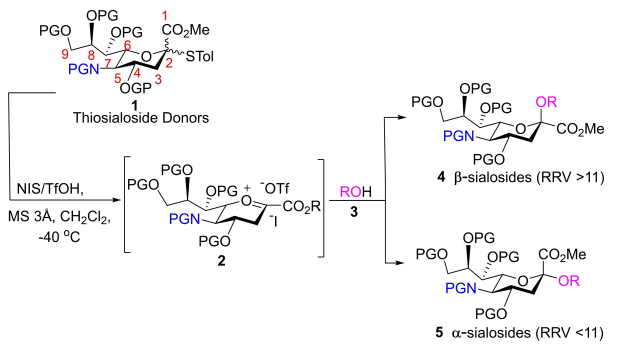
dous effort for the optimization. Thus, a general quantitative system to establish a guideline for both α- and β-selective sialylation reactions and to identify the variability in chemical glycosylation, may be the key to answer this question.[51,52]

According to our previous work, we have discovered that Relative Reactivity Value (RRV), established by Wong et al., can be used as a general indicator to define the stereoselectivity change with numerous thioglycosides in NIS/TfOH promotor system. Mechanistic studies also show that different ratios of glycosyl triflate and glycosyl halide (Cl^-, Br^-, I^-) intermediates significantly change the stereoselectivity in different halogen-containing promotor systems such as *para*-tolylsulfenyl halides (*p*-TolSX, X = Cl^-, Br^-, I^-)/AgOTf.[51,52] However, the role of RRV of thiosialoside donor **1** in stereoselectivity of sialylation remains unclear. As a continuation of our RRV study, we describe herein the pre-activation of diversified *p*-tolyl thiosialoside donors **1** with NXS (X = Cl^-, Br^-, I^-)/TfOH, *p*-TolSCl/AgOTf and BSP/Tf_2O promotors and identified their corresponding reactive intermediates using low-temperature NMR spectroscopy to acquire some information about the glycosylation reaction. Moreover, RRV of various sialyl donors **1** were defined and correlated to their corresponding reactive intermediate ratio, which in turn controlled the stereochemical outcome of glycosylation (Scheme 1).



Scheme 1. Reactivity-controlled stereoselective sialylation.

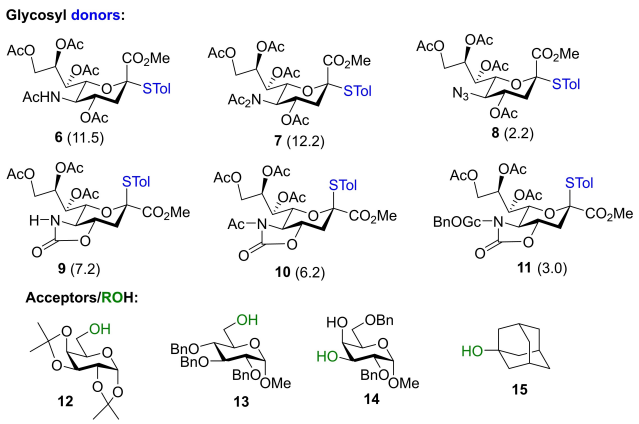


Figure 1. Thiosialoside donors **6**–**11** with defined RRV (in parentheses) and acceptors **12**–**15**.

Results and Discussion

Preparation of thiosialoside donors with defined RRV

To identify the correlation between the stereoselectivity of sialylation and RRV of thiosialoside donors and acceptors, we synthesized several C-5 modified thiosialoside donors **6**–**11** following earlier published procedures (Figure 1, see SI, Scheme S1).[23,37–39,53–56] Four commonly used acceptors (primary glycosyl alcohols **12** and **13**, secondary glycosyl alcohols **14** and tertiary alkyl alcohol **15**) have been used for our investigation. The RRV of donors **6**–**11** bearing different anomeric stereochemistry including NHAc, *N*-Ac_2- and N_3-protected α-*p*-tolyl thiosialosides **6**–**8**,[21,41] and 5-*N*,4-*O*-oxazolidinone-based β-*p*-tolyl thiosialosides **9**–**11**, were measured by competitive HPLC experiment and showed poor and narrow ranges (Figure 1).[41,51]

NIS/TfOH-promoted stereoselective sialylation

After obtaining RRV, we set out to determine the glycosylation stereoselectivity of these thiosialosides. Our work began by premixing donor **6**–**11** and acceptor **12**–**15** individually, using a 3 Å molecular sieve in dichloromethane (CH_2Cl_2) at −40 °C. The combined promotors, 1 equiv. of NIS and 0.4 equiv. of TfOH, were then treated in the next step to facilitate the reaction. The reaction completed over 2 h, and the α/β ratio of the sialylated disaccharides **16**–**19** was determined by ^{1}H NMR analysis of the crude reaction mixtures.

The percentage of α-sialoside formed was calculated relative to the β-isomers. The anomeric configuration of the disaccharides **16**–**19** was determined by following the empirical rules of chemical shift, distinctive three-bond coupling constant of C1-C2-C3-H-3ax ($^3J_{C\text{-}1,H\text{-}3ax}$) and by comparing with the NMR data of known compounds[21,31,47,57] The anomeric configurations can also be identified by considering the chemical shift position of H-3eq and H-3ax in their ^{1}H NMR spectra. Accordingly, α-sialosides show a close pattern relationship; however, β-configured sialosides have very far apart patterns in their H-3eq and H-3ax chemical shift.[57]

Prediction of sialylation stereoselectivity and yields by sugar reactivity

After we studied a range of NIS/TfOH-promoted stereoselective sialylations (see SI, Scheme S2), we examined the correlation of the stereoselectivity with donor reactivity. As revealed in the summary of glycosylation results in Figures 2A–D, the stereoselectivity of sialylation is dependent on donor reactivity and can be defined based on the RRV of sialyl donors. Interestingly, we observed a higher α-selectivity in the medium RRV (2.2 to 7.2) of donors, and the β-selectivity was gradually performed outward from the center. For primary sugar acceptor galactoside HO-6 **12** (Figure 2A), the α-selectivity initially increased as the donor RRV increased from 2.2 to 7.2. Consistent trends were also witnessed with acceptors **13**–**15** with the exception of a

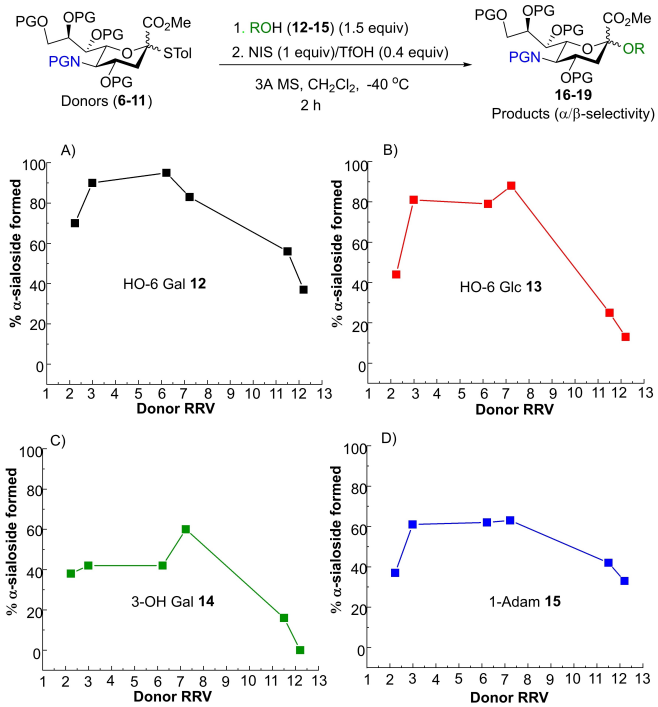


Figure 2. Effect of donor RRV on α-selectivity. Using A) galactoside HO-6 **12**; B) glucoside HO-6 **13**; C) galactoside HO-3 **14**; D) 1-admantanol **15** as the acceptors.

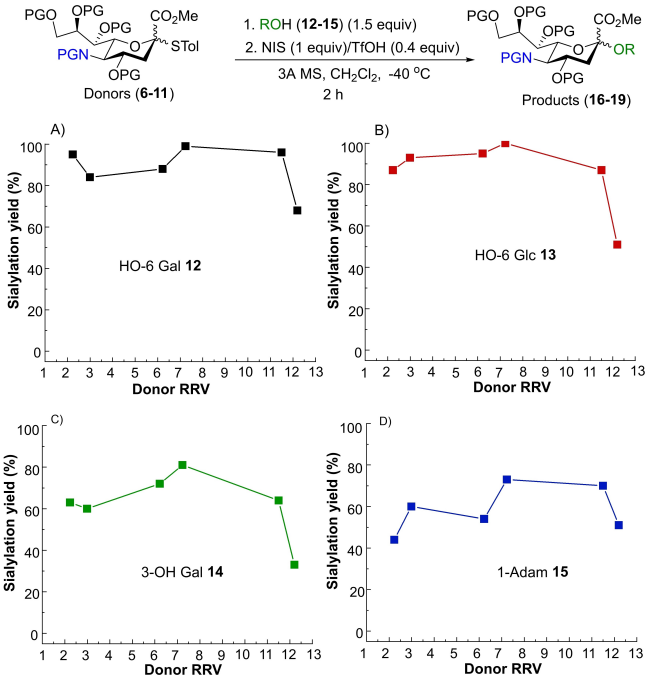


Figure 3. Effect of donor RRV on sialylation yield.

slight decline in the percentage of α-sialoside formation (Figures 2B–D). As the donor RRV increased from 7.2 to 12.2, the α-selectivity of these acceptors decreased.

With sterically hindered acceptor **14** (Figure 2C), as the RRV increased from 2.2 to 6.2, the α-selectivity did not show a significant change but the β-selectivity increased when the RRV become greater than 7.2 like that of acceptors **12**, **13**, and **15**. Our finding is consistent with Wong's work who observed β-selective sialylation with several primary and secondary alcohols coupled with a highly armed sialyl donor having a protected hydroxymethyl group at C-2 (RRV = 4.0×10^4).[21] Compared with the primary sugar acceptors **12** and **13**, the bulky 1-adamantanol **15** acceptor gave moderate α-selectivity in the range RRV of 3.0 to 7.2 (Figure 2D)

We also investigated the relation between sialylation yields of NIS/TfOH promotion system and sugar reactivity and found that the sialylation yields were dependent on the donor RRV (Figure 3) like the α/β-selectivity. High sialylation yields were obtained with primary sugar acceptors **12** and **13** in the range of donor RRV from 2.2 to 11.5. However, the glycosylation yields were generally lower with the hindered acceptors **14** and **15**. The chemical yields and the selectivity of the oxazolidinone-protected compounds **9**–**11** (RRV 3.0 to 7.2) is significantly higher than the other compounds tested. This may be due to the stabilizing ability of the *trans*-fused oxazolidinone ring of these donors to the equatorial glycosides over their axial counterparts, reducing the anomeric effect and glycal formation.[58,59] On the other hand, the highest RRV of compound **7** gives the lowest chemical yield and lowest α-stereoselectivity due to its high reactivity which tends to the elimination side reactions.

Identification of glycosyl intermediates

Next, we identified the corresponding intermediates in the absence of glycosyl acceptor using low-temperature NMR experiments at −70 °C. The treatment of donors **6**–**11** with 1.0 equiv. of NIS and 0.4 equiv. of TfOH at −70 °C in the presence of 3 Å molecular sieve in deuterated dichloromethane (CD_2Cl_2) showed no activation. However, these donors were completely activated after the temperature raised to −40 °C. We initially estimated to detect glycosyl triflate **2-OTf**, which is the dominant intermediate in sialylation reactions promoted under this system.[31,41,43,60] However, our low-temperature NMR (−70 °C) and high-resolution ESI-mass experiments revealed that only glycal **3-G** was formed as a side product (see SI, Table S2). We surmised that these labile intermediates (**2-OTf**/**2-I**) undergo a rapid decomposition to generate the 2,3-dehydro glycal **3-G** in the absence of acceptors. These results were also supported by our modulating experiment using 1 equiv. of BSP/Tf_2O at −70 °C (see Supporting Information, Table S2). Instantaneous degradation of unstable intermediates (**2-OTf** and **2-I**) into **3-G** through the 2,3-elimination reaction have also been observed at low-temperature NMR spectroscopy by Gervay-Hague's,[25] Crich's,[43,49] and De Meo's[60] groups.

Consequently, we identified the corresponding reactive intermediates in the alternative halonium promoter system such as NBS/TfOH and NCS/TfOH, as the bromide (**2-Br**) and chloride (**2-Cl**) intermediate are relatively stable to determine.

Accordingly, donors **6**–**11** were activated by 1 equiv. of N-halosuccinimide (NXS, X = Cl^-, Br^-)/TfOH as promotors in the presence of 3 Å molecular sieve in CD_2Cl_2 at −70 °C. As expected, the corresponding relatively stable halide intermediate, glycosyl bromide **2-Br** and chloride **2-Cl** were generated cleanly within 5 minutes (Figure 4A and Figure 4B, see SI, Table S1 and Table S2). The selectivity of halides (**2-Cl** and **2-Br**) and triflate **2-OTf** intermediates did not vary significantly with different amounts of TfOH. Compared with **2-Br**, the distribution of the relatively stable **2-Cl** showed a high correlation with the donor reactivity and the α-selectivity of sialylation (Figure 2). The formation **2-Cl** and **2-Br** were confirmed by low-temperature (−70 °C) NMR spectroscopy and ESI-mass (see SI). However, the highly unstable **2-OTf** intermediate which was obtained mainly from least and relatively reactive donors **6**–**8** (RRV = 2.2, 11.5 and 12.2) under NBS/TfOH activation system decomposed rapidly into sialyl glycal **3-G** (Figure 4A, see SI, Table S1 and Table S2). In our previous work,[51] we found that the activation of thioglycoside donors by *p*-TolSX (X = Cl^-, Br^-, I^-)/AgOTf resulted in the in situ generation of glycosyl halides (Cl^-, Br^-, I^-), which provided a consistent α-stereoselectivity of glycosylation through these common intermediates. Additionally, stereoselectivity showed no significant change in both preactivation and non-preactivation systems. Accordingly, there is a high possibility for the formation of **2-halo** intermediates during the sialylation reaction. The reaction mechanism for the formation of 2-Cl and 2-Br derivatives from NCS and NBS treatment, respectively, can likely follow similar pathway as discovered in our previous works.[51,61]

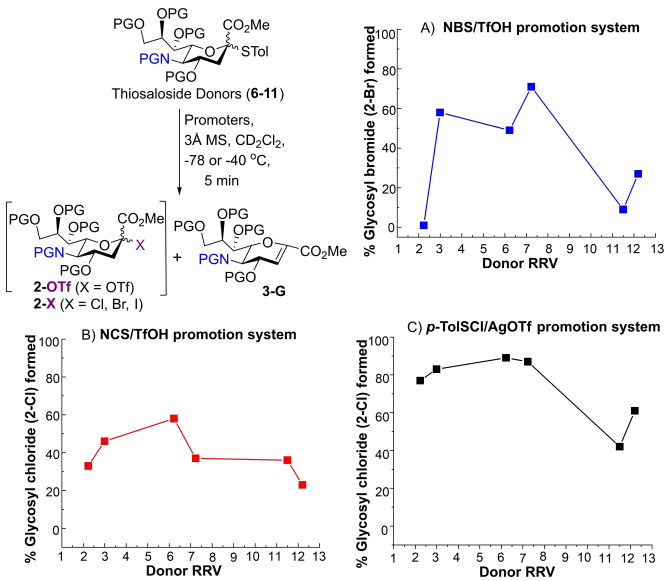


Figure 4. Intermediate distribution vs. donor reactivity. Using A) NBS/TfOH; B) NCS/TfOH and C) *p*-TolSCl/AgOTf as the promoter.

Effect of donor reactivity on intermediate distribution

RRV can be used as a tool to guide the intermediate change with promoters.[51,52] We observed nearly consistent results of intermediate change under the activation of other halogen and triflate-containing promotors, namely 1 equiv. of *p*-TolSCl and 3 equiv. of AgOTf (Figure 4C, see SI, Tables S1 and S2). The activation of the oxazolidinone-based donors **9**–**11** which have moderate RRV (3.0 to 7.2), gave a high percentage of **2-Cl**, especially under the *p*-TolSCl/AgOTf activation system.

Due to the involvement of the SSIP,[19,49,62] it is difficult to describe the significant connection between the reactive intermediates and stereoselectivity. The S_N1- and S_N2-like mechanisms are highly dependent on the types of the PGs installed to the thiosialoside donors.[25,49] Our finding showed the correlation between donor RRV and the sialyl intermediates (halide/triflate ratio). This kind of association affects the anomeric stereoselectivity of sialylation in the presence of acceptor. Previous reports have also shown the stereochemical outcome of glycosylation is highly related to the types of glycosyl intermediate.[3,25,41,51]

Guideline for sialylation stereoselectivity by sugar reactivity

Using of RRV as an indicator (Figure 2), we described a convenient guideline to identify sialyl donors for both α-and β-selective sialylation reactions (Figure 5). To get 2,6-linked sialosides **16** and **17**, the RRV of the donor should be greater than 2.2 but less than 11.5 for α-sialylation (α-selectivity > 75 %, red bar) (Figure 5A and Figure 5B). With HO-3 galactosyl acceptor **14**, the sialylation reaction with donor RRV less than 11 yielded α/β-mixture for 2,3-linked sialylated disaccharide **18**. Attaining highly α-selective sialylation was difficult with acceptor **14**, but relatively easier to carryout β-selective reactions (β-selectivity > 75 % for β-sialosides **18**, blue bar) with the RRV higher than 11 (Figure 5C). Enzymatically stable unnatural oligosaccharides having β-sialosides may have important biological roles.[21] For alkyl sialoside **19**, attaining α-selective sialylation reaction was difficult with the sterically hindered tertiary alkyl alcohol **15**. Coupling of this acceptor with any thiosialoside donor gave the α/β-mixture (Figure 5D, gray color). These results indicate that RRV of donors can be used as an indicator to predict the stereochemical outcome of sialylation reactions based on the type of acceptor used. As a result, the tedious trial-and-error method to get the optimal conditions can be circumvented.

Conclusion

RRV defined the stereoselectivity and yield of sialylation on six thiosialoside donors under the NIS/TfOH activation system without solvent participation. To attain stereoselective sialylation, the intermediate ratio was controlled using RRV, promoters, and varying reaction temperatures. Based on the donors considered in our investigation, the stereoselectivity outcome, glycosylation yield and intermediate distribution have

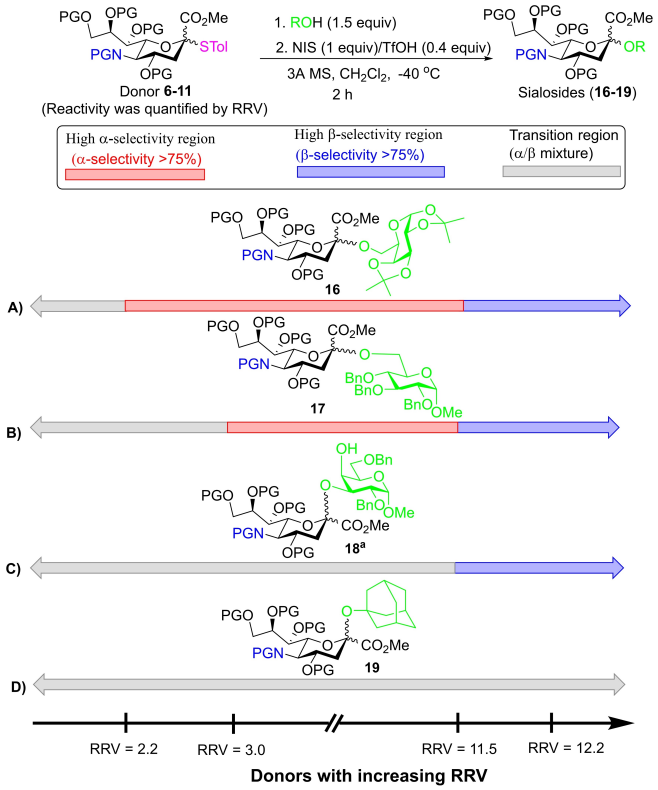


Figure 5. RRV as the scale for the stereoselectivity under NIS/TfOH system at −40 °C. Using A) 2,6-linked sialoside **16**; B) 2,6-linked sialoside **17**; C) 2,3-linked sialoside **18**; D) adamantyl sialoside **19**. a = Coupled to the HO-3.

shown a correlation with the reactivities of thiosialoside donors having RRV range from 2.2 to 12.2. The utilization of RRV platform provides a guideline to control the results in both α- and β-selective sialylation reactions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbohydrates · Glycosylation · Relative reactivity value · Stereoselectivity · Thiosialoside donors

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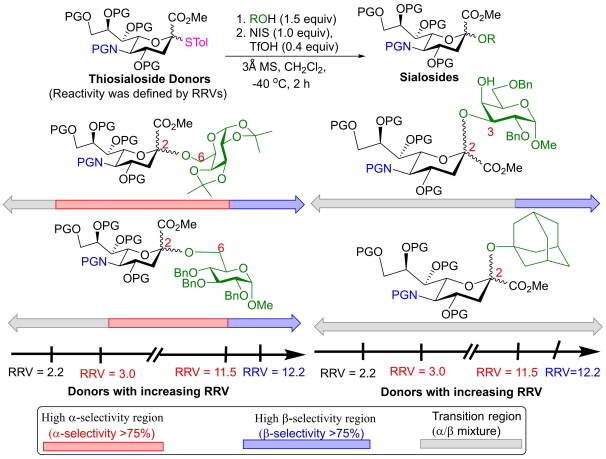

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The relative reactivity value was found to provide a guideline to control the stereoselectivity of sialylation reactions under NIS/TfOH promotion system at $-40\,^{\circ}C$, resulting α-selectivity $>75\,\%$ for $\alpha(2\rightarrow6)$-linked disaccharides and β-selectivity $>75\,\%$ for $\beta(2\rightarrow3)$-linked disaccharides.