Glycosylation

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Establishment of Guidelines for the Control of Glycosylation Reactions and Intermediates by Quantitative Assessment of Reactivity

Chun-Wei Chang, Chia-Hui Wu, Mei-Huei Lin, Pin-Hsuan Liao, Chun-Chi Chang, Hsiao-Han Chuang, Su-Ching Lin, Sarah Lam, Ved Prakash Verma, Chao-Ping Hsu, and Cheng-Chung Wang**

Abstract: *Stereocontrolled chemical glycosylation remains a major challenge despite vast efforts reported over many decades and so far still mainly relies on trial and error. Now it is shown that the relative reactivity value (RRV) of thioglycosides is an indicator for revealing stereoselectivities according to four types of acceptors. Mechanistic studies show that the reaction is dominated by two distinct intermediates: glycosyl triflates and glycosyl halides from N-halosuccinimide (NXS)/TfOH. The formation of glycosyl halide is highly correlated with the production of α-glycoside. These findings enable glycosylation reactions to be foreseen by using RRVs as an α/β-selectivity indicator and guidelines and rules to be developed for stereocontrolled glycosylation.*

Carbohydrates are essential biomolecules in living organisms.[1] However, to access carbohydrate-based products in large quantities with well-defined regio- and stereochemistry is still challenging.[2] To date, no unifying strategy for obtaining 1,2-*cis* glycosides exists as the glycosylation reaction outcome is influenced by numerous factors and the detail reaction mechanism is still unclear.[3] Therefore, an indicator and a general guideline that predicts, foretells, and summarizes the stereoselectivity would greatly simplify this indispensible reaction and would facilitate advanced methods that streamline oligosaccharide synthesis, such as solid-phase automated oligosaccharide synthesis and one-pot glycosylation.[4]

[*] C.-W. Chang, Dr. C.-H. Wu, M.-H. Lin, P.-H. Liao, C.-C. Chang, H.-H. Chuang, Dr. S.-C. Lin, Dr. S. Lam, Dr. V. P. Verma, Dr. C.-P. Hsu, Dr. C.-C. Wang
Institute of Chemistry, Academia Sinica
Taipei 115 (Taiwan)
E-mail: cherri@chem.sinica.edu.tw
wangcc@chem.sinica.edu.tw
C.-W. Chang, Dr. C.-H. Wu, Dr. C.-C. Wang
Chemical Biology and Molecular Biophysics
Taiwan International Graduate Program, Academia Sinica
Taipei 115 (Taiwan)
C.-W. Chang, Dr. C.-H. Wu, H.-H. Chuang
Department of Chemistry, National Taiwan University
Taipei 106 (Taiwan)
H.-H. Chuang
Nanoscience and Technology Program, Taiwan International Graduate Program, Academia Sinica and National Taiwan University
Taipei 115 (Taiwan)
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Thioglycosides **1** (Figure 1) are the most commonly used glycosyl donors and can be easily activated chemoselectively by electrophilic promoter systems, among which *N*-iodosuccinimide (NIS, **6-I**)/TfOH is the most widely used.[5] Ye, Huang, and Yoshida have developed a preactivation strategy that allows iterative one-pot glycosylation.[3a,6] However, similar to all other glycosylation reactions, the poorly controlled stereoselectivity remains a long-standing problem.[3c,5a] The promotor systems are generally a combination of a stoichiometric amount of an iodonium agent and a catalytic amount of TfOH. The reactions are complicated by the presence of various reactants, and glycosyl triflate **2** is commonly believed as the main intermediate, which leads to the mixture of products **5-α** and **5-β**.[3d,7]

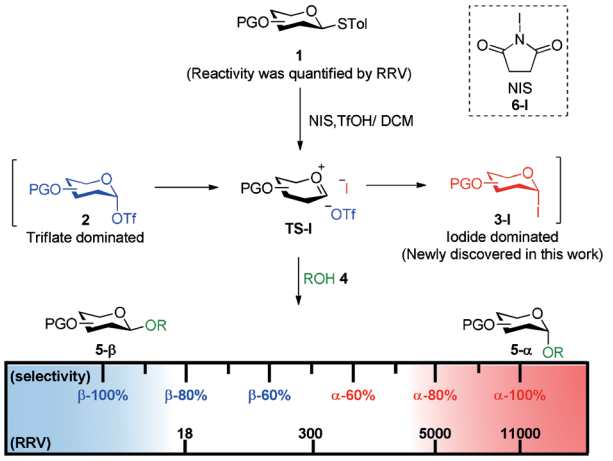


Figure 1. RRV as a scale meter to define α/β stereoselectivity in chemical glycosylation.

To predict glycosylation stereoselectivity and systematically analyze the factors that influence the outcome, an objective comparison system is required. Ley was the first to introduce deactivation factor (DF) to define the donor reactivity.[8] Later, the relative reactivity value (RRV), a comprehensive quantification system developed by Wong, provides a quantitative assessment for programmable one-pot oligosaccharide synthesis.[9] Herein, we show that RRVs serve as a parameter/indicator to statistically predict stereoselectivity in glycosidic bond formation and for the first time chemical glycosylation reaction can be correlated with a general statistical approach. Our mechanistic experiments revealed that glycosylations proceeded via a glycosyl triflate

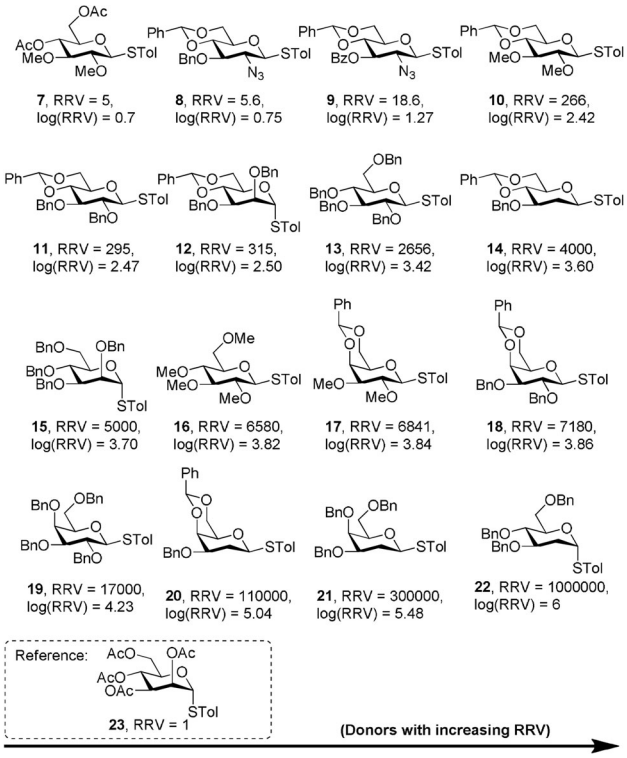


Figure 2. Glycosyl donors with defined RRV.

2 and/or iodide **3-I**, which we found is highly associated with the formation of α-glycoside **5-α**, as a function of RRV.

To understand the correlation between the stereoselectivity and the identity of glycosyl donors and acceptors, the reactivity of a series of glycosyl donors were quantified by their RRVs and the stereoselectivity of their reaction with a range of glycosyl acceptors were studied. In this study, the RRVs of donors **7**–**22** on different sugars without *C*2 participating group (Figure 2; Supporting Information, Figures S1–S9), including 1,2-*trans* thiotolyl glucosides **7**, **10**, **11**, **13**,[9a] **16** and galactosides **17**, **18**, **19**,[9a] mannosides **12**[9a,10] and **15**,[9c] 2-azido-2-deoxyglucosides **8**, **9**, β-thiotolyl 2-dexoygalactoside **20**, **21**, and α-thiotolyl 2-deoxyglucoside **14**, **22**,[11] were measured. These values were determined by using competition experiments against a least reactive donor, tolyl tetra-*O*-acetylthiomannoside **23**, of which the RRV is defined as 1.0, as reported.[9a,b]

Next, donors **7**–**22** were pre-mixed with acceptors **24**–**27**, respectively. Secondary glycosyl alcohols **24** and **25**, primary glycosyl alcohol **26**, and alkyl alcohol **27** are four types of commonly used glycosyl acceptors in carbohydrate synthesis. After testing the reactions from −78 to 0 °C, we found the changes in stereoselectivity were very limited. Therefore, the reaction condition was fixed at −40 °C in DCM to eliminate the possible variables, and 1.0 equiv of NIS and 0.4 equiv of TfOH were introduced to activate the donor in a traditional (non-preactivated) manner. The reaction mixture was stirred for 3 h, and the α/β ratio of the reaction was determined by using HPLC.

After screening these combinations (Figure 3; Supporting Information, Table S6), we interestingly found the α-selectivity is in roughly a linear correlation with log(RRV). For 4-OH acceptor **24** (Figure 3A), the linear regression showed that the slope is 16.6, in which R^2 is 0.77 and Pearson's r is 0.89. Consistent trends were observed with the other acceptors **25**–**27**, but in different slopes. For the other secondary alcohols, namely, 3-OH acceptor **25** (Figure 3B), with the increasing log(RRV) from 0–6, α-selectivity also rose linearly with a steep slope of 15.7. For primary 6-OH acceptor **26** (Figure 3C), the linear regression showed that the slope was 13.3. When using sterically least-hindered methanol (**27**) as acceptor (Figure 3D), α-selectivity was enhanced the least.

These findings suggest that stereoselectivity is more closely related to inductive effects on donors and the

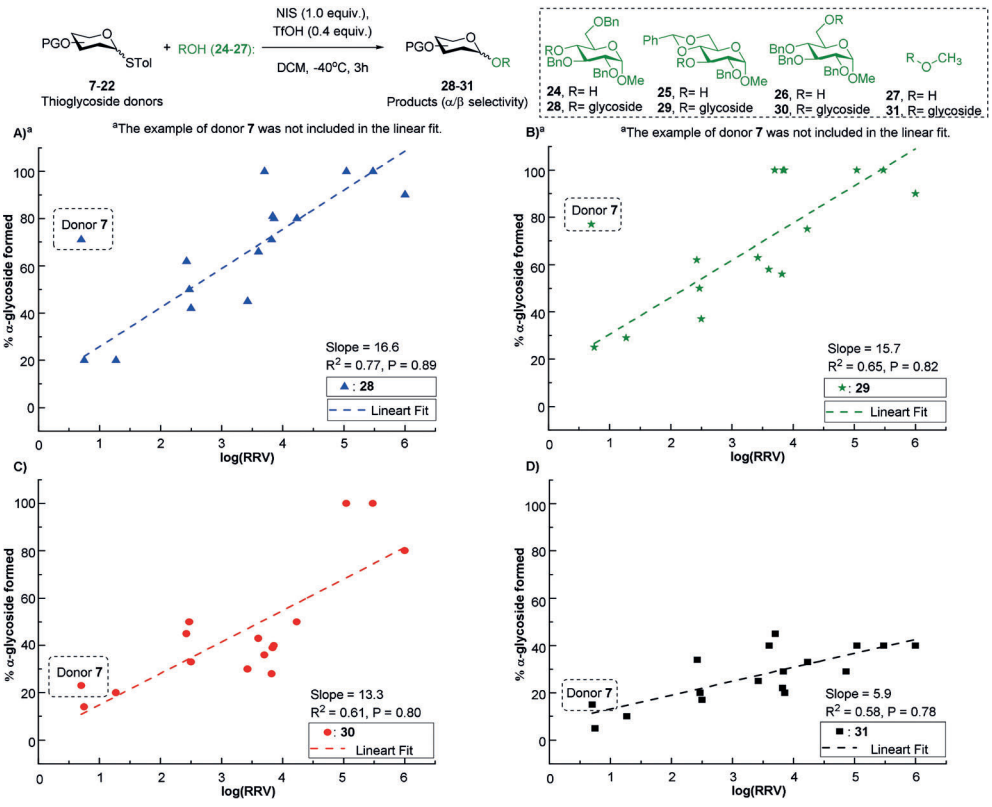


Figure 3. α-Selectivity vs. donor reactivity (RRV). Using A) glucoside 4-OH **24**; B) glucoside 3-OH **25**; C) glucoside 6-OH **26**; D) MeOH (**27**) as the acceptors.

reactivity of acceptors.[3c,12] For example, mannosides are commonly believed to produce α-major (1.2-*trans*) glycosides. Thiomannosides **12** (RRV = 315, log(RRV) = 2.50) and **15** (RRV = 5000, log(RRV) = 3.70), having moderate RRVs, in fact gave considerable amounts of β-products (1.2-*cis*) with the α/β ratio predictable by the 4 linear fits in Figure 3, For *O*6-actylated glucose donor **7** (dots in dash box), the selectivity deviated from the trends for secondary acceptors **24** and **25** as observed in previous reports;[13] but not for primary acceptors **26** and **27**. Based on Figure 3, we herein provide a reliable guideline to design glycosyl donors for both α- and β-selective glycosylation reactions by using RRVs as indicators (Supporting Information, Figure S29). Moreover, stereoselectivity showed no significant change between preactivation and the traditional approach (non-preactivation).[14]

We then tried to identify the intermediates before the addition of glycosyl acceptor by using low-temperature NMR experiments at −40 °C (Figure 4). Donors **7**–**22** were treated with 1.0 equiv of NIS and 0.4 equiv of TfOH in CD_2Cl_2 at −40 °C for 15 min individually. We initially expected to observe the signals of glycosyl triflate **2**, which was the most common believed intermediate from previous reports.[3b,15]

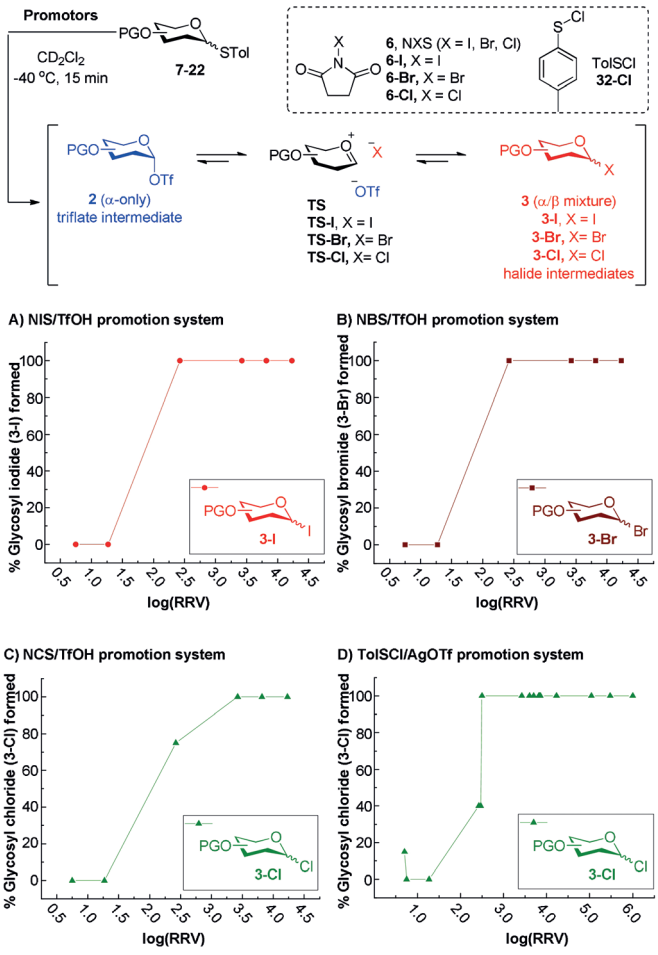


Figure 4. Intermediate distribution vs. donor reactivity (RRV). Using A) NIS/TfOH; B) NBS/TfOH; C) NCS/TfOH; D) TolSCl/AgOTf as the promotor.

However, our NMR spectrum in turn showed the evidence of glycosyl iodide **3-I** intermediate formation for the first time in the TfOH promoted system (Supporting Information, Table S1, Figures S10–24). Furthermore, the existence of **3-I** in the reaction was confirmed by comparing the ^{1}H NMR spectrum obtained with that of the suspected intermediates synthesized independently through relevant procedures under TMSI conditions (Supporting Information, Figures S10–S24, Table S1).[16] Moreover, **3-I** can be further identified by high-resolution ESI-MASS (Supporting Information, Figure S11).

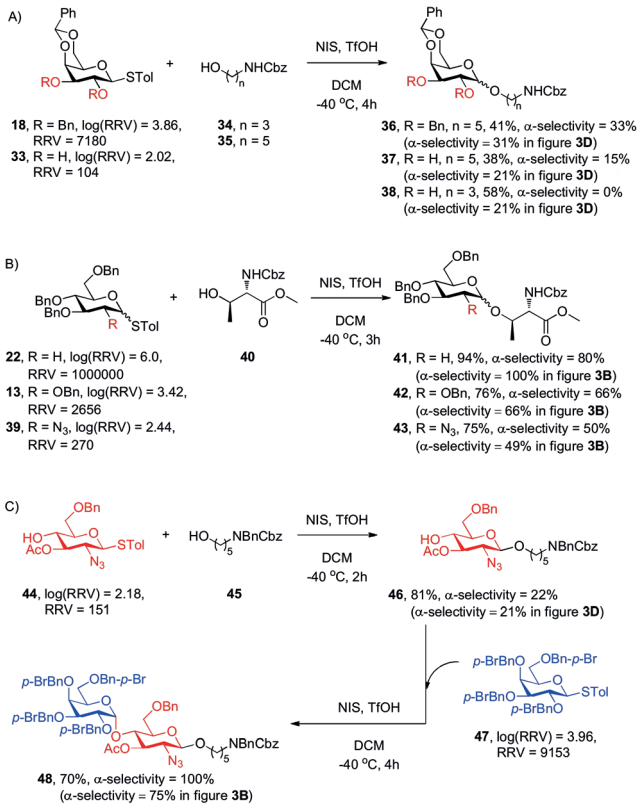
The intermediate distribution of **3-I** (Figure 4 A) is also inductive-effect-dependent and was highly correlated with α-selectivity (Figure 3). RRV provides a universal system to predict the intermediate change in the scaffold of log(RRV) between 1.27 and 2.50 (or RRV between 18.6 and 315). Consistent results of the intermediate change were also observed in other halide-containing promotor systems such as NBS/TfOH (Figure 4 B), NCS/TfOH (Figure 4 C), and TolSCl/AgOTf (Figure 4 D) with their glycosyl bromide **3-Br** and chloride **3-Cl** being observed as well (Supporting Information, Figures S10–S24, Table S1).

To further clarify the intermediate transformation, we performed a theoretical computational study. The transition states **TS** consisted of an oxocarbenium cation with a certain degree of association with both triflate anion (OTf^-) and halide anion (X^-). The conversion mechanism is most accurately described as an S_N2-like process. Computational experiments all yielded consistent results in each NXS/TfOH system (Supporting Information, Figures S25–S28, Tables S2–S5). The relatively low free-energy barriers were 4.17 and 5.48 kcal mol^{-1}, respectively, when calculated with the temperature set at −40 °C (Supporting Information, Figure S25). These address the fact that facile intermediate transformation could happen to produce the glycosyl halide intermediate in situ.

Although the relevance between glycosyl intermediates and stereoselectivity is hard to define owing to the participation of solvent-separated ion pairs (SSIPs),[3d,17] and clearly, the electronic nature of the protecting groups bound to the glycosyl donors play a key role in shifting the S_N1–S_N2 reaction paradigm.[17] We have found the correlation between donor reactivity (RRV) and the intermediate glycosyl halide/triflate ratio, which in turn influences the α/β selectivity upon the addition of an acceptor. This is important, because the reaction stereoselectivity is highly dependent on the identity of the reactive intermediate as reported by Gervay-Hague, Field, and Codee.[12,16,17b,c,18] The glycosyl iodide **3-I** can lead to distinct α-selectivity, and **3-I** can then be converted into an even more reactive β-counterpart **3-I-β** via a Lemieux anomerization pathway,[19] which undergoes an S_N2-like reaction with a nucleophilic acceptor from the bottom side for selective α-glycosyl bond formation.[16,18] In contrast, the α-triflate intermediate **2** favors the S_N2 reaction and β-selective reaction with the acceptor in the cases of the unreactive donors.[12,17b,c] Since both preactivation and non-preactivation showed very similar stereoselectivity (Figure 3), it implied that glycosides formation occurs through glycosyl

iodide **3-I** after facile intermediate transformation at a low temperature within the donor activation timeframe.

We targeted numerous disaccharides or glycoconjugates (Scheme 1; Supporting Information, Table S6). The coupling between glycan and linkers **34** and **35** is useful and common in studies on glycosciences.[4a] Clearly indicated by our RRV



Scheme 1. Stereoselectivity-predictable glycosylation using RRV as the indicator.

indicating system to synthesize alkyl glycoside **31** (Figures 3D), for **18** (RRV of 7180, log(RRV) = 3.86), product **36** was obtained only with poor α/β selectivity (α-selectivity = 33%) when the linker acceptor **35** was treated. According to Figures 3D, we then adopted a partially protected donor **33** with lower RRV of 104 (log(RRV) = 2.02) (Scheme 1A). Without the electron-donating effect on *C*2 and *C*3, the unreactive **33** resulted in high β-selectivity with linkers **34** and **35** individually, in which **37** (α-selectivity = 15%) and **38** (α-selectivity = 0%) were isolated.

A prediction based on secondary alcohols in Figures 3B was noted for donors **22, 13**, and **39** with the secondary threonine **40** as the acceptor (Scheme 1B). As pinpointed by the linear fit, 80% α-selectivity was observed on 2-deoxy-glucosyl donor **22** (log(RRV) = 6). Next, for tetra-*O*-benzylated thioglucoside **13** (log(RRV) = 3.42), the selectivity of **42** decreased to 66% α-selectivity. Eventually, for 2-azido-2-deoxy thioglucoside **39** (log(RRV) = 2.44, RRV = 270),[9e] product **43** was obtained with the poorest selectivity (50% α-selectivity) in 75%.

Finally, we aimed at an α-Gal-(1→4)-β-GlcNA disaccharide motif **48** (Scheme 1C), equipped with a β-pentyl linker at the reducing end. First, a semi-protected glucosamine donor **44** with a low RRV of 151 was designed for β-selective glycosylation. Predicted well by our system (α selectivity = 21% in Figures 3D), a majority of β-glycoside **46** (α-selectivity = 22%) was furnished in 81%. Next, a Gal donor **47** with higher RRV of 9153 gave a high α-selectivity and produced **48** in 70%.

Stereocontrolled glycosylation was the main challenge in carbohydrate chemistry owning to the lack of a clear mechanism and too many control variables.[3c] We herein first demonstrated that stereoselectivity can be predicted using reactivity of donors (RRVs) on different acceptors in a NIS/TfOH system. Our studies also revealed that the reaction was dominated by two distinct intermediates, including glycosyl triflate and iodide. A further understanding of mechanistic pathways is in progress. We believe the behavior of donors can be further clarified, and our indicator and guideline can provide a new solution for chemists to simplify glycosylation reaction and design building blocks in a quantifiable manner. This discovery gives new insight to stereocontrolled glycosylation for carbohydrate/organic chemistry and presents a multidisciplinary direction that combines statistics. Since anomeric selectivity is simultaneously influenced by remote functional group participation,[3a,20] acceptor nucleophilicity, solvent polarity, temperature, and activation system,[3b,11,12,17b,c,21] we are studying these permanent and environmental variables by using RRV as the analytic tools. Similar trends can also be observed when using TolSCl/AgOTf and BSP/Tf_2O combinations as the promoters. More types of building blocks, such as L-6-deoxy sugars and glycuronic acids, will be included in our future studies. The incorporation of this system into artificial intelligence for carbohydrate synthesis is now undergoing.[22]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbohydrates · diastereoselectivity · glycosylation

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Communications

Glycosylation

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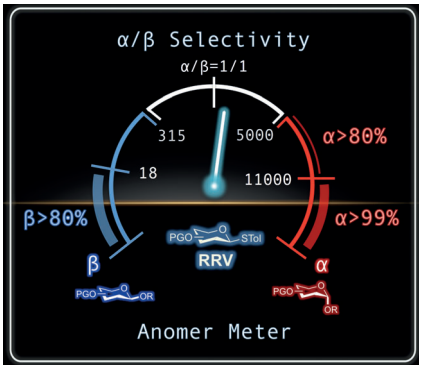
Establishment of Guidelines for the Control of Glycosylation Reactions and Intermediates by Quantitative Assessment of Reactivity



Selectivity rev-counter: The relative reactivity value (RRV) of thioglycosides is an indicator for revealing stereoselectivities for chemical glycosylation.

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