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# Stereoelectronic Effects Determine Oxacarbenium vs β-Sulfonium Ion Mediated Glycosylations

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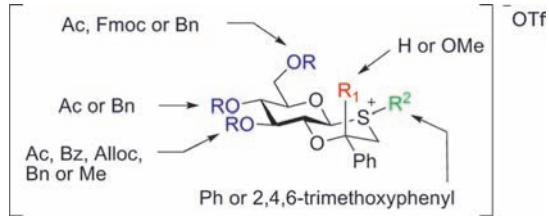
## ABSTRACT




**Activation of a glycosyl donor protected with a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary results in the formation of an anomeric β-sulfonium ion, which can be displaced with sugar alcohols to give corresponding α-glycosides. Sufficient deactivation of such glycosyl donors by electron-withdrawing protecting groups is, however, critical to avoid glycosylation of an oxacarbenium ion intermediate. The latter type of glycosylation pathway can also be suppressed by installing additional substituents in the chiral auxiliary.**

The stereoselective introduction of glycosidic linkages is one of the most challenging aspects in the chemical synthesis of biologically important complex oligosaccharides.[1,2] In general, 1,2-*trans* glycosides can reliably be introduced by exploiting neighboring group participation of a 2-*O*-acyl group, and this approach has, for example, been exploited in the automated solid phase synthesis of several complex oligosaccharides using a modified peptide synthesizer.[3,4] The introduction of 1,2-*cis* glycosidic linkages, such as α-glucosides and α-galactosides, requires glycosyl donors having a nonassisting functionality at C-2.[5] In general, these glycosylations require extensive optimization of reaction conditions to achieve acceptable anomeric ratios. Recent advances in anomeric control include the use of protecting groups that sterically shield the β-face of galactosyl donors[6] or lock a glycosyl donor in a conformation that allows nucleophilic attack from only one face of an anomeric oxacarbenium ion.[7]

We have shown that a glycosyl donor substituted at C-2 with a (*S*)-(phenylthiomethyl)benzyl ether can be employed for the stereoselective introduction of 1,2-*cis* glycosides such as α-glucosides and α-galactosides.[8] Neighboring group participation by the chiral auxiliary leads to a quasi-stable anomeric sulfonium ion (Scheme 1), which due to steric and electronic factors is formed as a *trans*-decalin ring system. Nucleophilic displacement of the sulfonium ion by a hydroxyl leads then to the stereoselective formation of α-glycosides. Recently, the attractiveness of chiral auxiliary mediated glycosylations was shown by solid phase synthesis of several branched pentasaccharides having only 1,2-*cis*-glycosidic linkages.[9]

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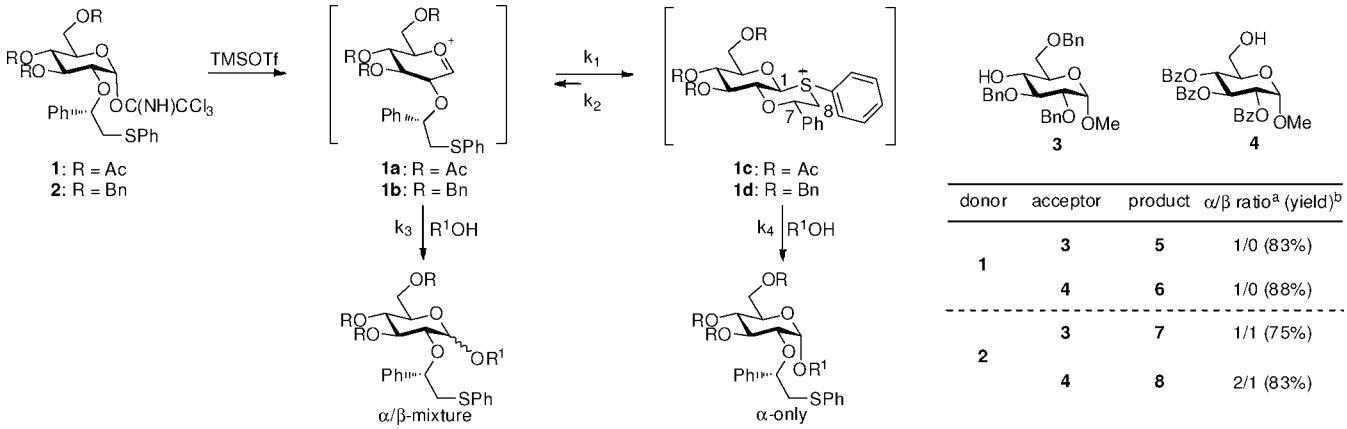
**Scheme 1.** Dynamic Equilibrium between an Oxacarbenium and $\beta$-Sulfonium Ion




| donor | acceptor | product | α/β ratio[a] (yield)[b] |
|---|---|---|---|
| 1 | 3 | 5 | 1/0 (83%) |
| | 4 | 6 | 1/0 (88%) |
| 2 | 3 | 7 | 1/1 (75%) |
| | 4 | 8 | 2/1 (83%) |

[a] The $\alpha/\beta$ ratios were determined by integration of key signals in the $^1$H NMR spectrum of the disaccharides products after purification by size exclusion chromatography over LH-20. [b] Isolated yields of the $\alpha/\beta$ mixture of disaccharide products.

As part of a program to utilize auxiliary mediated glycosylations for complex oligosaccharide synthesis, we observed that protecting groups and constitution of the C-2 auxilary can have a profound influence on the pathway and hence anomeric outcome of glycosylations.

Herein, we report clear rules for the reliable installation of 1,2-*cis* glycosidic linkages. Thus, TMSOTf promoted glycosylations[10] of glycosyl donor **1**, having an (*S*)-(phenylthiomethyl)benzyl ether at C-2 and acetyl esters at C-3, C-4, and C-6, with glycosyl acceptors **3**[11] and **4**[12] gave the corresponding glucosides as only the α-anomer. However, similar glycosylations with glucosyl donor **2**, having benzyl ethers instead of acetyl esters, gave no or poor anomeric selectivity. To examine whether glycosyl donor **2** can form an intermediate sulfonium ion, it was dissolved in $CD_2Cl_2$ and treated with 1 equiv of TMSOTf at −50 °C. After raising the temperature to 0 °C and cooling to −20 °C, $^1$H and HMBC NMR spectra were recorded (Figure 1). Upon activation, the anomeric proton of **2** ($\delta$ 6.56 ppm, $J_{1,2} = 2.5$ Hz) shifted upfield ($\delta$ 5.52, $J_{1,2} = 8.5$ Hz) and its large vicinal coupling constant established an equatorial orientation of the anomeric substituent. The coupling constants of the other saccharide protons showed that no conformational distortion of the saccharide ring had occurred. The HMBC spectrum, which allows the determination of three bond heteronuclear couplings, showed a correlation between C-1 and H8-eq, proving that the *trans*-decalin system had been formed. No oxacarbenium ion, anomeric triflate, or α-sulfonium ion was detected, and hence the NMR data indicate that the $\beta$-substituted sulfonium ion is the main reaction intermediate. Addition of an alcohol resulted, however, in the formation of a mixture of anomers. This unexpected observation can be rationalized by the classical Curtin−Hammett principle

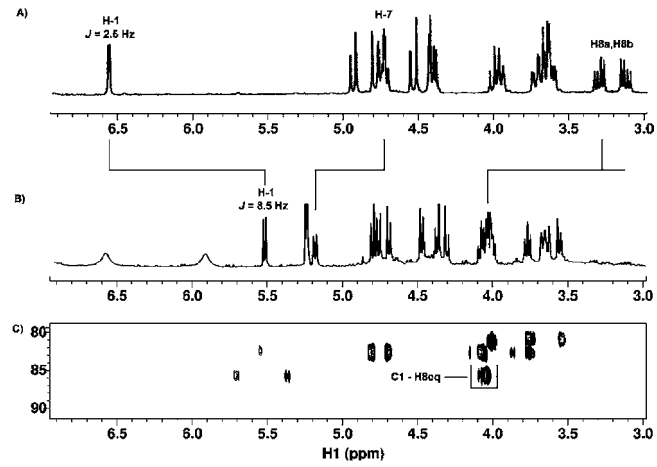



**Figure 1.** (a) $^1$H NMR spectrum of glucosyl donor **2** in $CD_2Cl_2$. (b) $^1$H NMR spectrum of **2** after addition of TMSOTf at (−20 °C). (c) HMBC spectrum of the $\beta$-sulfonium ion at −20 °C. A cross-peak was observed between C-1 and H8-eq.

in which an equilibrium exists between the sulfonium and oxacarbenium ions (Scheme 1). This equilibrium is shifted strongly in the direction of the sulfonium ion as shown by the NMR studies. A glycosylation can, however, take place from the much more reactive oxacarbenium ion when the rates of interconversion ($k_1$ and $k_2$) are faster than that of glycosylation ($k_4$). Previously, relative reactivity values (RRVs) of differentially protected glycosyl donors have been determined, and for example, it was found that a 2,3,4,6-tetra-*O*-benzyl protected glucosyl donor is 980 times more reactive than its tetra-*O*-acetylated counterpart.[13]

This difference in reactivity has been attributed to inductive destabilization of the positively charged transition state by the electron-withdrawing acetyl esters. The ester protecting

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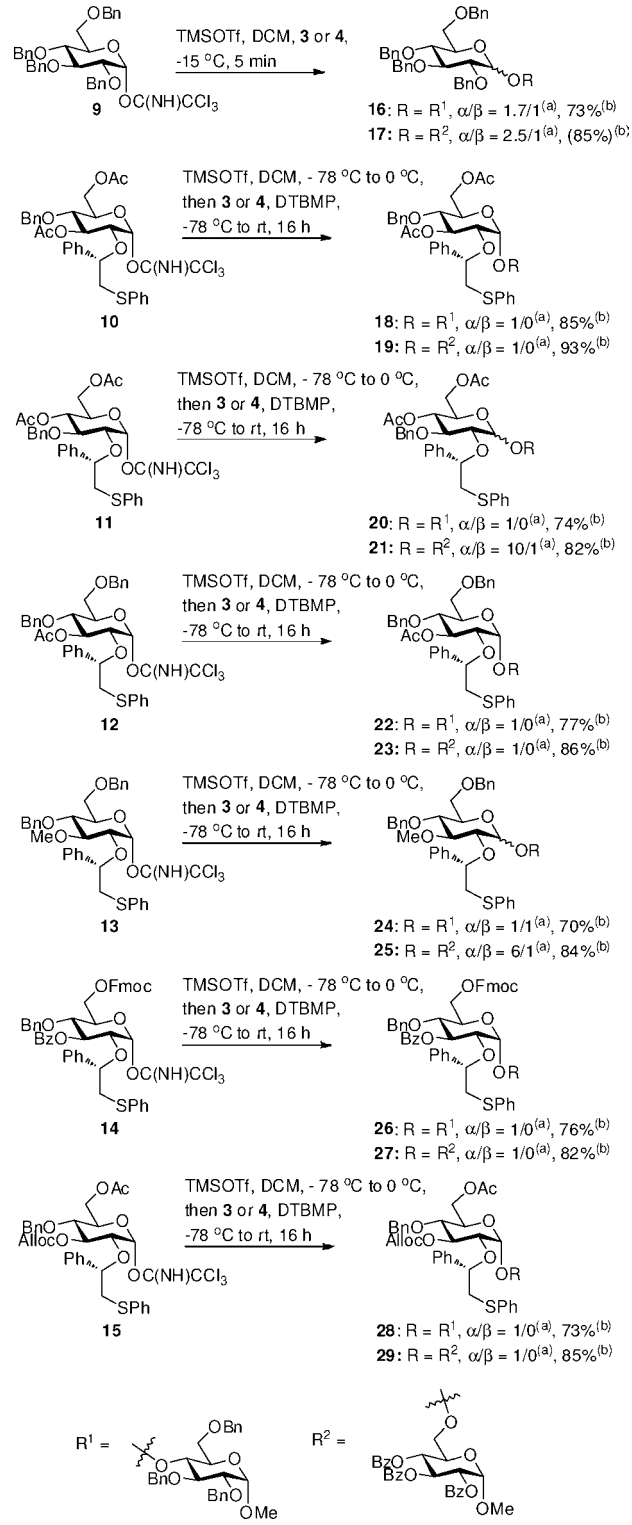
groups of an anomeric sulfonium ion are more remote from the positive charge than that of the oxacarbenium, and hence such electron-withdrawing protecting groups are expected to widen the energy difference between the sulfonium and oxacarbenium ion. Thus, strongly electron-withdrawing groups such as the acetyl esters of **1** are expected to disfavor oxacarbenium ion formation, and hence glycosylations take place by an $S_N2$ like displacement of the $\beta$-anomeric sulfonium ion leading to the formation of α-glycosides.

On the other hand, glycosylations with donors having electron-donating protecting groups, such as the benzyl protected glycosyl donor **2**, involve an equilibrium between the corresponding sulfonium and oxacarbenium ions, and glycosylations take place mainly through the latter intermediate thereby diminishing the α-selectivity.

Previously, it has been noted that care has to be taken in implying reaction mechanisms of glycosylations based on the detection of reaction intermediates.[14−20] We have performed numerous glycosylations with donors such as **1** and in general isolated only α-anomeric products implying $S_N2$ displacement of intermediate sulfonium ions. Furthermore, glycosylations of **2** (Scheme 1) and **9**[21] (Scheme 2), which have a chiral auxiliary or benzyl ether at C-2, both gave poor anomeric selectivities indicating that the nature of the C-2 substituent has only a small influence on the selectivity of glycosylations by oxacarbenium ions. On the other hand, glycosylations with **1** proceeded with α-selectivity whereas similar couplings with a C-2 benzyl protected glycosyl donor[8] led to the formation of mixtures of anomers ($\alpha/\beta = 3/1$) indicating a difference in reaction pathway.

A number of differentially protected glycosyl donors (**10**−**15**) were investigated to establish the influence of protecting groups on the anomeric selectivity of auxiliary mediated glycosylations (Scheme 2). As expected, anomeric selectivities improved dramatically when chiral auxiliary containing glucosyl donors were employed having electron-withdrawing protecting groups. For example, the presence of two acetyl esters at C-3 and C-6 (**10**) or C-4 and C-6 (**11**) drastically improved α-selectivity although the latter still gave an $\alpha/\beta$ mixture when coupled to **4** (**21**). The coupling of glycosyl donor **12**, which has an acetyl ester at C-3 and benzyl ethers at C-4 and C-6, with glycosyl acceptors **3** and **4** gave only α-linked products. To ascertain that the bulk of the C-3 protecting group does not play a major role in controlling anomeric selectivities, glycosylations with glycosyl donor **13** were performed, which has a methyl ether at C-3, and in this case the glycoside products (**24** and **25**) were obtained as mixtures of anomers. Hence,

**Scheme 2.** Glycosylation Results for Glycosyl Donors **9**−**16**




[a] The $\alpha/\beta$ ratios were determined by the integration of key signals in the $^1$H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography. [b] Isolated yields of the $\alpha/\beta$ mixture of disaccharide products.

the electronic withdrawing nature of the C-3 protecting group appears to be critical to achieve absolute α-anomeric selectivity. To further support the latter observation, glycosyl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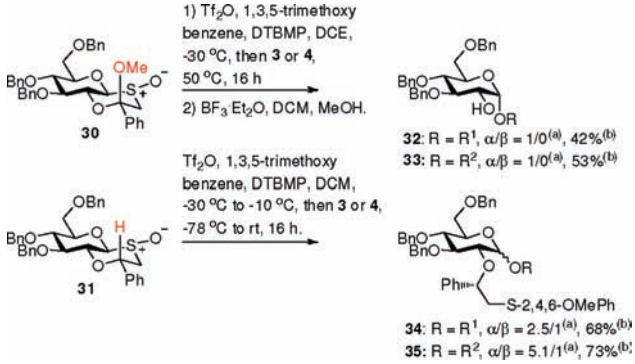
donors **14** and **15** were examined which have a C-3 benzoyl ester and allyloxycarbonate, respectively, and as expected, the use of these compounds led to the selective formation of α-anomeric products (**26**−**29**).

Next, attention was focused on examining the importance of the constitution of the chiral auxiliary for controlling anomeric selectivity (Scheme 3). Recently, oxathiane donor

**Scheme 3.** Effects of Substitution Pattern of the C-2 Auxiliary




[a] The α/β ratios were determined by the integration of key signals in the $^1$H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography. [b] Isolated yields of the α/β mixture of disaccharide products.

**30** was introduced, which can be activated by triflation of the sulfoxide followed by electrophilic aromatic substitution with 1,3,5-trimethoxy benzene to form an intermediate sulfonium ion, which can then react with alcohols to give glycoside products.[22]

In addition, we investigated similar glycosylations with donor **31**, which was obtained by reduction of the acetal of **30** using triethylsilane in the presence of $BF_3$·$Et_2O$.[23] Thus, oxathiane **30** was activated by addition of trifluoromethanesulfonic anhydride ($Tf_2O$) in the presence of 1,3,5-trimethoxybenzene in 1,2-dichloroethane (DCE) at −35 °C. After completion of the electrophilic aromatic substitution and formation of the intermediate sulfonium ion, alcohols **3** or **4** were added, and after a reaction time of 16 h at 50 °C the disaccharides **32** and **33**, respectively, were formed as only the α-anomers albeit in moderate yields. On the other hand, similar glycosylations with **31** led to the formation of disaccharides **34** and **35** as mixtures of anomers. Although **30** is protected with benzyl ethers at C-3, C-4, and C-6, glycosylation with this compound took place with inversion of the anomeric configuration leading to selective formation of α-glucosides. The geminal OMe substituent of **30** was critical since glycosyl donor **31** exhibited compromised α-anomeric selectivities.

It is well-known that substituents can enhance ring stability, and this observation is, for example, embodied in the "gem-dialkyl" or Thorpe−Ingold effect.[24−26] Substitutions can also promote the rate of ring formation by increasing the probability of correct alignment for ring formation.[27] Saccharides also respond to these effects, and alkylation of the aldofuranose ring shifts the equilibrium between aldofuranoses and the corresponding acyclic aldehydes in the direction of the cyclic forms.[28] Thus, it is likely that the additional substituent of the auxiliary of **30** selectively increased the stability of the sulfonium ion thereby promoting glycosylations by an $S_N2$-like mechanism. The latter is supported by our observation that a glycosyl donor which has no substituent at the auxiliary (2-*O*-phenylsulfanylethyl substituent) forms an intermediate *β*-sulfonium ion but upon glycosylation gives mixtures of anomers.[8]

Previously, it has been reported that anomeric sulfonium ion intermediates may not necessarily be the species that undergo glycosylation and parameters such as the potency of the nucleophile may determine whether a reaction proceeds through $S_N2$ displacement of a sulfonium ion or by substitution of an oxacarbenium ion.[29] Here, we demonstrate that protecting groups and the chemical nature of the sulfonium ion can have a profound influence on the stereochemical outcome of glycosylations, and it has been found that by disfavoring oxacarbenium ion formation by electronic or stereoelectronic effects, exclusive α-anomeric selectivity can be accomplished. These observations can be used as a guide to select glycosyl donors that are expected to give exclusive 1,2-*cis* stereoselectivity and be employed for further improvement of chiral auxiliary mediated glycosylation methodology.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra and experimental procedures for the preparation of compounds **2**, **7**, **8**, **11**−**29**, and **31**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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