Highly stereoselective synthesis of aminoglycosides *via* rhodium-catalyzed and substrate-controlled aziridination of glycals†

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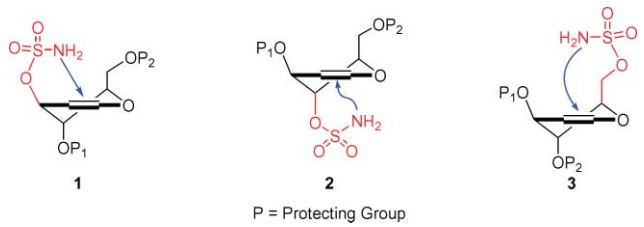
The flexible installations of a sulfamate ester on a glycal scaffold at C3, C4, or C6 approaching α- or β-aminoglycosides is communicated. A variety of glycal acceptors (O, S, and N) were applied, enhancing the utility of this method as an operationally simple protocol for the stereoselective synthesis of polyfunctionalized α- or β-aminosaccharides.

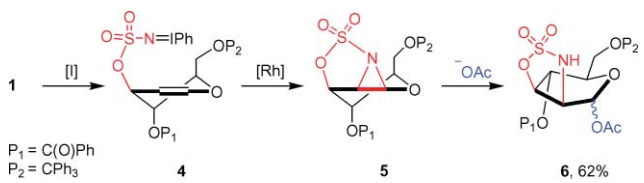
Carbohydrates feature prominently in many biological processes and in the progression of diseases. In recent years, much research has been done to develop new methods for the synthesis of biologically relevant oligosaccharides, glycoconjugates, and their analogues.[1] In particular, 2-amino-2-deoxy glycosides, a major class of carbohydrates, are vital constituents of glycosaminoglycans, peptidoglycans, and blood group antigens.[2] These compounds serve as challenging synthetic targets to prepare and transform. In one study, the direct introduction of a nitrogen substituent at C2 of a glycal held considerable promise to access to 2-aminosugars and other complex 2-aminoglycoside conjugates.[3,4] Many research groups had developed the use of metal-catalyzed nitrene delivery to a double bond of glycal derivatives in inter- and intramolecular fashions,[5] but most of the common methods require subsequent manipulation to generate a useful glycal donor and complement with a variety of glycal acceptors.

We have pursued an intramolecular strategy that utilizes an iminoiodinane-derived sulfamate ester as an electrophilic nitrogen source[6] and generate a transient aziridine intermediate as a highly activated donor for selective 1,2-trans aminoglycosylation.[7,8] Having a sulfamate-ester group on the C3, C4, or C6 position of the glycal allows us to investigate the reactivity, facial preference and steric hindrance of the aziridine formation. The aziridine intermediates serve as regio- and stereoselective donors in the glycosylation step. Conceptually, sulfamate glycals **1** and **3** would offer the opportunity for the synthesis of α-2-aminosugars; in turn, a nitrogen atom delivery from the bottom face of **2** would give β-linked 2-aminosugars (Scheme 1).

The requisite glycal starting materials were constructed to incorporate a variety of commonly employed carbohydrate protecting groups. Investigation of the substrate-controlled aminoglycosylation was started on course from **1**, **2**, to **3**, according to the sulfamate position and the ring size of intermediates. The catalytic reaction underwent a one-step process under treatment of the substrate with a mixture of 5 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$ and MgO in dry dichloromethane.[9] The mechanistic pathway for the formation of **6** is proposed in Scheme 2. The rhodium-catalyzed aziridination on the top face of molecule formed the transient aziridine **5**, which was regioselectively attacked by an acetate anion at the anomeric carbon. After 24 h, the suspension was filtered through celite and purified by silica gel column chromatography furnishing an inseparable mixture of α- and β-anomers (2 : 1) and only 75% conversion was observed. The loss of stereospecificity and long reaction time of **1** is supposedly caused by the strain of forming aziridine intermediate **5**. This result is comparable to prior studies by Rojas *et al*.[8a,b] The rhodium-catalyzed aminoglycosylation of D-allal-derived carbamate resulted in an anomeric mixture (3 : 1).



Scheme 1 Three models for generation of 1,2-aminoglycosides.



Scheme 2 Rhodium-catalyzed aminoglycosylation of **1**.

In view of the stereoselectivity, the installation of sulfamate ester or carbamate at C3 is unlikely to be a good model to achieve pure aminoglycosides. We suggested that this could be solved by either increasing the ring size of the intermediate or elongating the arm of the sulfamate moiety. Consequently, the introduction of the sulfamate moiety on C4 and C6 of the glycal molecule was carried out.

To examine the nitrogen insertion on the bottom face of the glycal molecule, compound **7** was prepared. The initial investigation was made by subjecting sulfamate glycal **7** to the optimized catalytic conditions. Instead of nitrogen atom insertion to the double bond, C–H insertion and cleavage of a silyl protective group spontaneously took place, giving rise to compound **10** as

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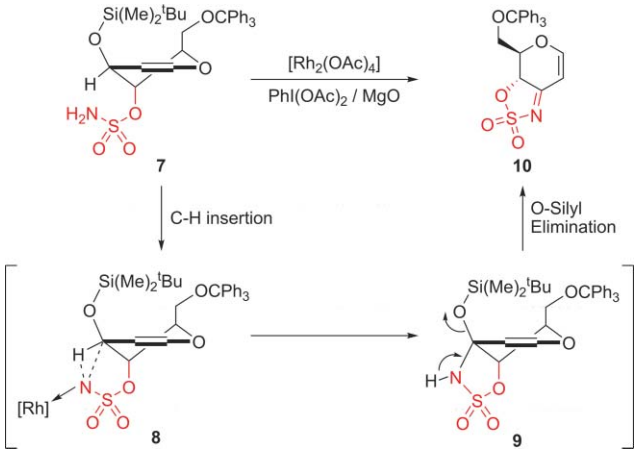
a side product (Scheme 3). Investigation of the formation of the unexpected product **10**, without addition of a rhodium catalyst, found that the reaction occurred in the same manner but needed longer reaction time and gave a lower conversion. Based on this result, the rhodium complex seems to play a crucial role in the catalytic system by increasing the rate of reaction, but it is still premature to conclude that having the *O*-silyl group adjacent to the allylic proton promotes N-insertion on the C–H rather than the C=C bond. Structure of compound **10** was confirmed by X-ray crystallography and identified as a hemi(ethanol) solvate.



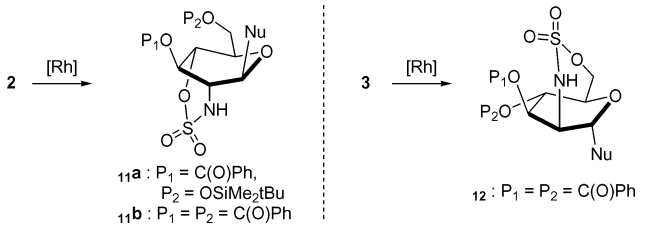
Scheme 3 Predictive pathway for C–H insertion on sulfamate glycal **7**.

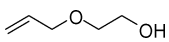
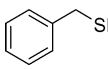
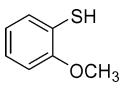
However, our aim to succeed in β-aminoglycosylation was continued by removing a labile silane group from the C3 position. Replacement of a benzoyl protecting group in **2a–b** gave stable substrates, which could be stored at –4 °C for more than a month. Moreover, the nitrogen atom insertion to the C=C bond could be accomplished within 1–2 hours and with virtually complete 1,2-*trans* stereochemistry (entries 1–2, Table 1). No C–H insertion products were seen for both **2a** and **b**.

It was realized that an increase in flexibility for the formation of the aziridine intermediate led to success in the synthesis of 2-aminoglycosides. With this concept, we then moved on to the α-linked aminoglycoside syntheses. The introduction of the sulfamate moiety on C6 would produce an 8-membered ring fused with an aziridine ring, which is more flexible than previous cases. The catalytic reaction of sulfamate glycal **3** could be completed within 5 hours affording α-linked 2-aminoglycoside in 82% yield (entry 2, Table 1). Reaction of **3** showed a promising result that could be applied to the stereoselective synthesis of α-aminosugars.[10]

The intramolecular rhodium-catalyzed aminoglycosylation was generally accomplished in one pot because of the instability of the aziridine intermediates. Trapping such aziridine species became a challenging problem in the synthesis of functionalized 1,2-aminoglycosides. Though a $Rh_2(OAc)_4$ catalyst can be widely used with a variety of functionalized alcohols, none of desired products was detected for thiols, and amines. Those compounds presumably reduce the catalytic capability of $[Rh_2(OAc)_4]$. In contrast, the employment of $[Rh_2(tfacam)_4]$ and PhIO showed modest to good results in all cases.[11] Alcohol nucleophiles could be neatly introduced into the catalytic reactions without adding any promoters, but thiols required activation by a Lewis acid, $BF_3{\cdot}OEt_2$. Another

Table 1 Stereoselective β- and α-aminoglycosylation of **2** and **3**

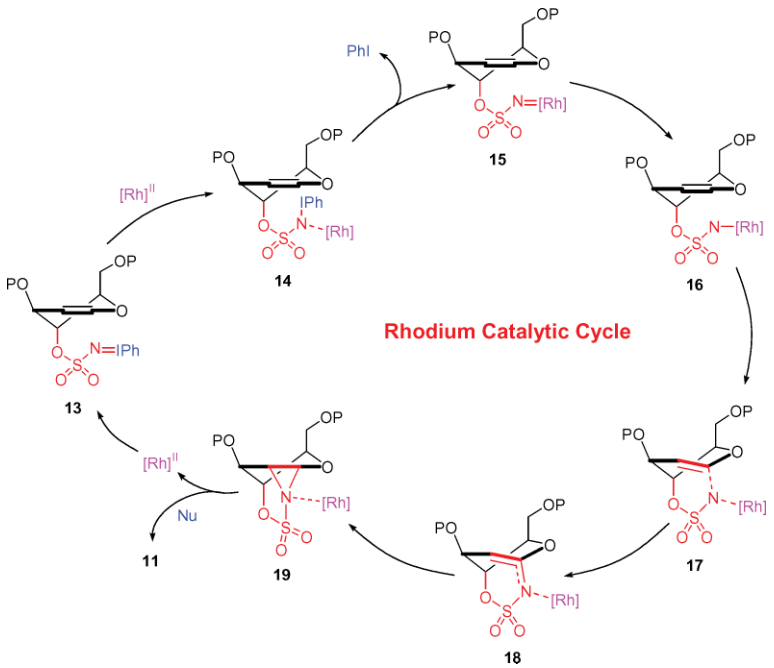


Entry	Nucleophile	Conditions[a]	Isolated yield **11**	Isolated yield **12**
1	$^-$OAc	A	73[b]	—
2	$^-$OAc	A	68[c]	82
3		B	83	94
4		B	80	89
5		B	90	95
6		B[d]	79	84
7		B[d]	86	83
8		B[d]	—	78
9	$^-N_3$ [from $(CH_3)_3Si\text{-}N_3$][e]	B	76	80

[a] Condition A: 5 mol% of $[Rh_2(OAc)_4]$, $PhI(OAc)_2$ (1.5 equiv), MgO (5 equiv) at RT. Condition B: 5 mol% of $[Rh_2(tfacam)_4]$, PhIO (1.5 equiv), MgO (5 equiv). Nucleophile (2 equiv) was added in 15 min for glycal **2** and 30 min for glycal **3**, respectively. [b] Yield for P_1 = C(O)Ph, P_2 = $OSiMe_2tBu$. [c] Yield for $P_1 = P_2$ = C(O)Ph. [d] Nucleophile (1.2 equiv) and $BF_3{\cdot}OEt_2$ (0.1 equiv). [e] N_3^- was generated by treatment of $(CH_3)_3Si\text{-}N_3$ (2 equiv) and TBAF (2 equiv) at 0 °C for 30 min.

application of this methodology is to synthesize diamino sugars (entry 9, Table 1). An azide anion, N_3^-, was generated by treatment of trimethysilyl azide and TBAF at 0 °C and then slowly injected into the aziridine intermediate. The sulfamate ester-derived glycals **2** and **3** selectively furnished β- and α-aminoglycosides.

To investigate the cause of the different amination patterns of **1**, **2**, and **3**, we utilized the hybrid density functional theory (DFT) to gain a deeper understanding of the mechanistic reaction as well as to determine the energy order of the corresponding intermediates. The mechanism of all three series involved in the aziridination reaction is similar and presented in Scheme 4 using sulfamate **2** as a reference. Initially, the intermediate **13** was generated, followed by the rhodium-catalyzed elimination of the PhI moiety from **14** giving rise to the rhodium–nitrene complex **15**. Prior to aziridine ring formation in **19**, our calculations show the rapid relaxation of the singlet state **15** to the triplet state **16**, which such a reaction is likely to undergo from the ground triplet state. The transition state **17** could be located on the triplet potential energy surface (PES) and its N–C1 proximity was much less than the distance between N and C2 (2.035 Å and 2.611 Å, respectively). The N–C1 single bond was then formed in **18** (1.497 Å), whereas N and C2 kept the distance at 2.509 Å. These led us to believe that a nitrogen atom

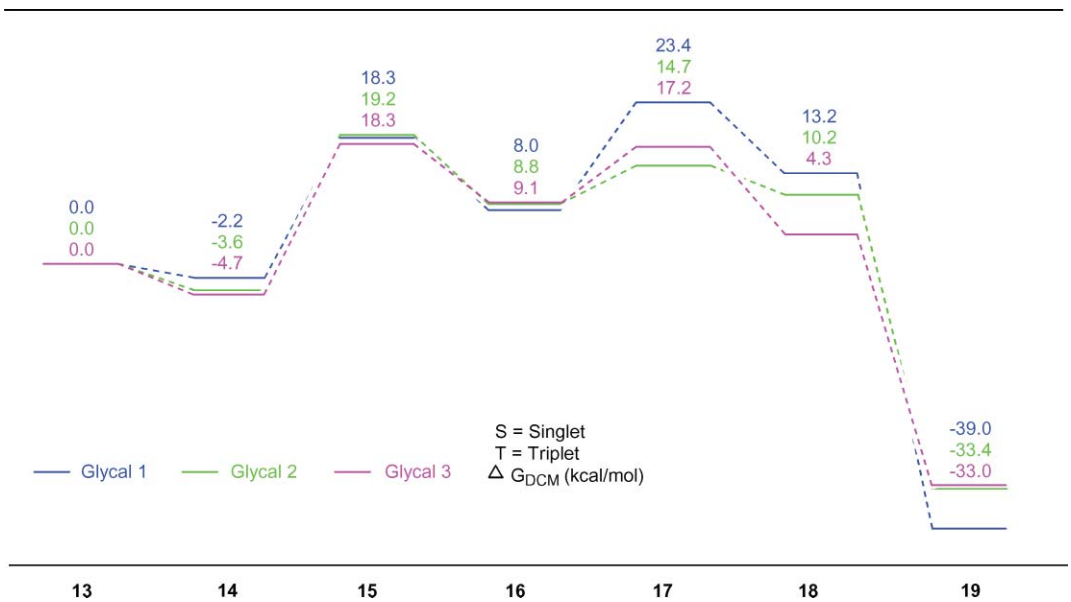


Scheme 4 Rhodium catalytic cycle for aziridination.

delivery to the double bond is taking place in a stepwise diradical process.

The energy diagram for the aziridination step is presented in Scheme 5. We observed that the relative energies of **14**, **15**, and **16** for all three series are close to each other with less than 1 kcal mol^{-1} difference. This indicated that the position of the sulfamate ester on the sugar ring does not effect those transformations. On the other hand, a large change in energies was obviously observed in the nitrene transfer step. The free energy value of **17** from glycal **1** is higher than that of **17** from **2** and **3** by 8.7 and 5.2 kcal mol^{-1}, respectively. The variation in the Gibbs free energies of transition state **17** for all three series agrees well with the corresponding experimental reaction time. The reaction time for sulfamate glycal **1** was slower than **3** and **2**, respectively (see ESI†). This convinces us that the delivery of a nitrene species from C3 to the double bond of glycal was a laborious route, which was different from a nitrene on C4 and C6. The reactions proceed fast and smooth for glycals **2** and **3**.

In summary, facial preference, which is controlled by substrate, was found to be the key factor that determines stereoselectivity. The experimental and computational data show that a sulfamate ester on C3 could not impact on the stereoselective



Scheme 5 Relative energy diagram of the aziridination step of **1**, **2**, and **3**.

aminoglycosylation. On the contrary, installation of a sulfamate ester on the C6 position of a glycal substrate approaches α-aminoglycosides selectively. Also, introduction of the sulfamate moiety on C4 gives β-linked 2-amino sugars. This series of glycal glycosylations can be applied in the chemical synthesis of highly complex aminosaccharide conjugates.

Acknowledgements

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