

Different reaction routes found in acid-catalyzed glycosylation of *endo*- and *exo*-glycals: competition between Ferrier rearrangement and protonation

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Abstract—Acid-mediated glycosylations of *endo*- and *exo*-glycals have been carried out in good to excellent yields, in which a mixture of two products is often obtained resulting from Ferrier rearrangement and protonation. The former reaction exclusively takes place with the *t*-butyl carbonate or hydroxyl substituent at the C3 position of *endo*-glycals, while the latter mainly occurs in the glycosylation of *exo*-glycals with allyl benzyl ether or acetate. In addition to the substituent effect, protecting groups are critical to determine the activity and favored reaction pathway. Furthermore, the method is applicable to *O*-, *C*-, and *N*-nucleophiles. © 2005 Elsevier Ltd. All rights reserved.

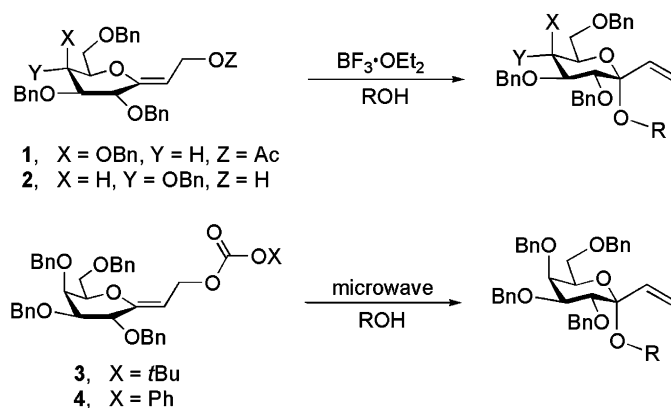
Glycals are versatile building blocks in synthetic chemistry and have been extensively investigated for the synthesis of various important molecules, including tumor-associated antigens (such as Lewis y, globo H, and KH-1) and bioactive natural products (including ciclamycin, allosamidin, KS-502, and rebeccamycin).¹ The glycosylation of *endo*-glycals can be carried out in a number of manners. For example, several Lewis acids were reported to catalyze Ferrier glycosylation² to afford 2,3-unsaturated glycosides.^{3,4} Danishefsky's glycal assembly successfully utilized glycals as both glycosyl donors and acceptors in an iterative fashion^{5–8} so that the procedure can be operated in solid phase.⁹ NIS or NBS-mediated glycosylations were developed by Tatsuta et al. and Theim et al. for the synthesis of 2-deoxyglycosides.^{10,11} Although the same products can be prepared by the acid-catalyzed addition of alcohol nucleophiles to glycals, appearing to be a simpler and more direct way of glycosidation, so far only few studies were reported including the methods using triphenylphosphine hydrogenbromide,¹² Dowex-50 resin [H⁺] with the presence of LiBr,¹³ and TMSOTf–NEt₃.¹⁴ One major challenge in the preparation of 2-deoxyglyco-

sides originates from the tendency of the cyclic enol ether toward allylic rearrangement, which is usually observed to complicate many studies. Herein we report acid-catalyzed glycosyl additions of glycals, in which two products are generated in association with Ferrier rearrangement and protonation. With a suitable substituent introduced at the allylic position, the former reaction pathway can be exclusively formed in the glycosylation of *endo*-glycals whereas the latter is favored in that of *exo*-glycals. Major factors are examined to understand how they function to affect the reaction outcome.

Previously, we demonstrated that *exo*-glycals **1–4** are highly reactive as glycosyl donors in BF₃·OEt₂-catalyzed reaction or under microwave radiation (Scheme 1).¹⁵ The reactions gave exclusively α-glycosidation products that contain a vinyl group at the anomeric position, indicating the occurrence of allylic rearrangement.¹⁵ On the other hand, the trifluoroacetic acid (TFA)-catalyzed glycosylation exhibited a different scenario (Table 1) where a mixture of two structurally similar products was obtained. In addition to the minor product rising from the aforementioned Ferrier reaction, the major one contained the acetoxyethyl group at the anomeric center, as evidenced by the corresponding characteristic signals in ¹H and ¹³C NMR spectra.¹⁶ The analysis based on the NOESY spectra indicated that the group

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Scheme 1. *exo*-Glycals **1–4** are efficient glycosyl donors.

is located at β -position and thus the acceptor should approach from α -position of the sugar ring during the glycosidation.¹⁷ In consistence with the previous reports,¹⁵ α -stereoselectivity was always obtained in the reactions.

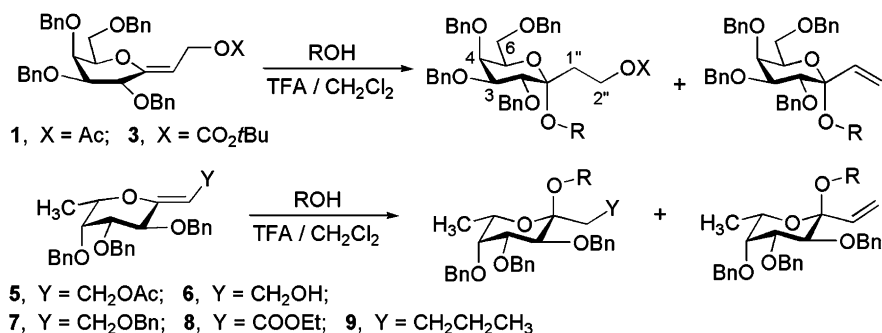
Table 1 demonstrates the glycosidations of *exo*-glycals **1**, **3**, and **5–9**. The reactions were simple for operation to give products **10–29**. With addition of TFA (10 equiv) to the mixture of *exo*-glycosyl donor and alcohol acceptor, the majority of reactions were complete in a short period of time (minutes to few hours) to give 77–95% yields. As shown by the 20-fold difference of reaction time in entries i and v, the $-\text{CH}_3$ group of fucose made a significant contribution to enhance the reactivity, consistent with the report by Wong and co-workers.¹⁸ *fuco*-Type donors **5–9** varied extremely in reaction rates, clearly supporting a critical role played by the olefin substituent (e.g., the comparison between entries v and viii, the one between entries x and xiii). The formation of both protonation and rearrangement products was observed in most of the reactions. As a consequence, the proposed oxonium ion develops during the glycosylation to proceed with two pathways of the rearrangement and protonation (**Scheme 2**). Apparently, the latter reaction is favored in the competition. It is interesting that a relatively higher percentage of the Ferrier reaction products were obtained in the reactions of *exo*-glycals **3** and **6** (entries iv, vi, and xi).

Alternatively, the reactions of *endo*-glycals **30–33** represent an intriguing distinction from the prior result. As shown in **Table 2**, the glycosylation reactions of various 4,6-di-*O*-benzyl-*D*-galactals were carried out in TFA-containing CH_2Cl_2 to generate glycosides **34–41**. Alcohol acceptors (2–3 equiv) were used in the reactions. The substituents of *t*-butyl carbonate (**30**) and hydroxyl group (**31**) at C3 position led to the formation of 2,3-unsaturated glycosides exclusively (entries i–vi), which echoed to the studies of *exo*-glycals **3** and **6** (see **Table 1**, entries iv, vi, and xi), suggesting the possibility to develop a positive (or partial positive) charge at C3 to trigger the Ferrier reaction. The relatively more constrained conformation of *endo*-glycals (with two sp^2 carbons in the sugar ring), in comparison with that of *exo*-glycals (with one sp^2 carbon), also favors the rearrangement to

occur. As a result, proper combination of substituent and conformation likely contributes to the exclusive occurrence of the Ferrier rearrangement in entries i–vi. Other issues, however, may be part of the cause here and cannot be simply ruled out.

On the other hand, the replacement of C3 functionality with acetate (**32**) or benzyl ether (**33**) resulted in the formation of both protonation and rearrangement products (entries vii–ix). Surprisingly, the production of 2-deoxygalactosides is relatively favored. The contrasting result to those of **30** and **31** provides additional evidence that the functional group at the allylic position cannot only fine-tune the reactivity, but also dominate, which reaction pathway is preferred. Recently, Vankar et al. reported that 3,4,6-tri-*O*-acetyl-*D*-glucal was used in the HClO_4 - SiO_2 -mediated synthesis of 2,3-unsaturated glycosides.¹⁹ Applying our TFA method for the glycosylation of 3,4,6-tri-*O*-acetyl-*D*-galactal (**33a**) also led to occurrence of the Ferrier reaction only. The results of peracetylated glycosyl donors were different from those of the analogous substrates **32** and **33** (entries vii–ix), revealing that protecting groups may serve as another essential factor. In general, the protecting groups of glycosyl donors are a determinant on the glycosylation rate,^{18,20} depending on if they stabilize or destabilize the putative cationic transition state. We propose that electron-donating groups (e.g., benzyl ethers) facilitate the protonation pathway, which is possibly due to the π^* -stabilization by the interaction either from direct $\sigma(\text{C}-\text{O})$ or from oxygen lone pair electron through space, especially when electron donating protective group is introduced. On the contrary, the existence of electron-withdrawing groups (e.g., acetates) makes the oxonium ion relatively less stable so that allylic rearrangement has the advantage to form a more stable α,β -conjugated oxonium ion (similar to the top transition state in **Scheme 2**). The results of **Tables 1** and **2** are thus contributed by the effects of the allylic substituent and protecting group, which may need more supporting evidence for further corroboration.

Substitution of TFA with various acids was also carried out. Like the synthesis of 2-deoxyglycosides by a catalytic amount of triphenylphosphine hydrogenbromide

Table 1. Glycosylations of *exo*-glycals **1**, **3**, **5–9** with various alcohols^a

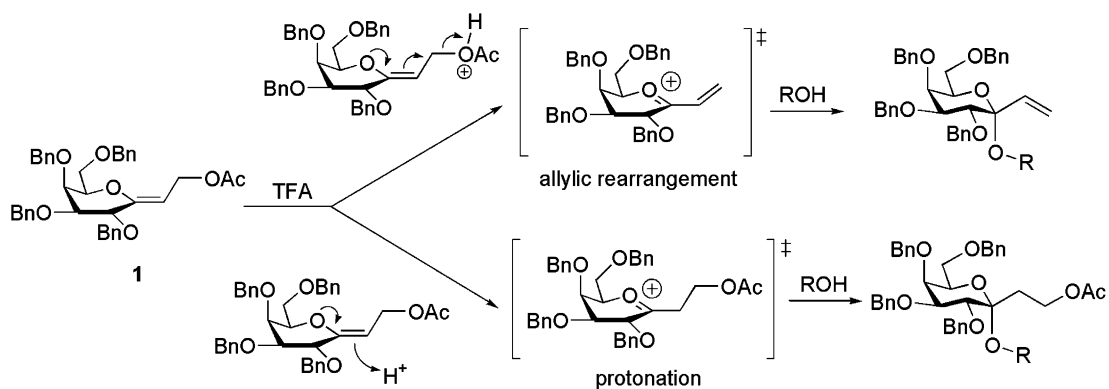
Entry	Donor	Acceptor (ROH)	Time (min)	Protonation + rearrangement products (yield)	
i	1		60	10 (85%)	11 (10%)
ii	1		90	12 (75%)	13 (10%)
iii	1		120	14 (70%)	15 (7%)
iv	3		90	16 (66%)	17 (22%)
v	5		3	18 (71%)	19 (12%)
vi	6		15	20 (46%)	19 (38%)
vii	7		40	21 (76%)	19 (8%)
viii	8		1440	22 (78%)	— (0%)
ix	9		2	23 (94%)	— (0%)
x	5		30	24 (85%)	25 (9%)
xi	6		40	26 (50%)	25 (29%)
xii	7		70	27 (72%)	25 (10%)
xiii	8		2880	28 (70%) ^b	— (0%)
xiv	9		80	29 (77%)	— (0%)

^a All reactions were carried out at 0–25 °C in CH₂Cl₂ with alcohol nucleophiles in the presence of TFA (10 equiv) and molecular sieves (4 Å).

^b Twenty percentage of the starting material was recovered.

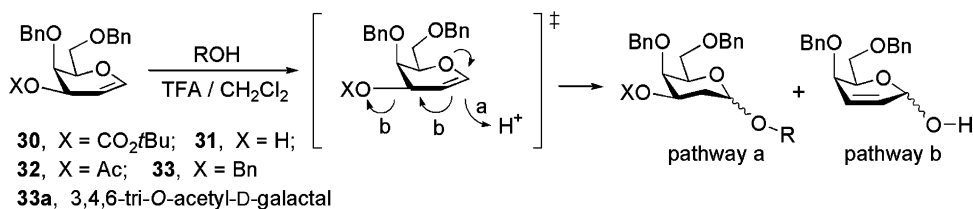
(TPHB),¹² the reaction of *exo*-glycal **1** with 1-butanol gave only the protonation product (**10**). The TPHB-mediated glycosylation only allowed the protonation pathway to take place in preference to the Ferrier rearrangement, which was well interpreted based on soft-hard principle, that is, the protonation occurring at the softer β-enolic carbon instead of the harder allylic oxygen.¹² It will be intriguing to examine if the TPHB method (or the preferential protonation at the β-enolic carbon) is subjected to the effects of substituent and pro-

tecting group. Meanwhile, the studies with other acids turned out to be less desirable owing to lower yield or/and lower selectivity in our hands. Scheme 3 shows two examples to utilize methanesulfonic acid, which are analogous to the first two entries of Table 1. Additionally, the acid catalyzed-glycosylation was found useful for the use of C- and N-nucleophiles. Table 3 presents that *endo*- and *exo*-glycals react with allyl-, propargyl-, and azido-trimethylsilane to obtain glycosides **42–48**. Interestingly, except for entry vii, the



Scheme 2. Two possible pathways proposed to explain the formation of both rearranged and protonated products.

Table 2. Glycosylations of *endo*-glycals **30–33** with various alcohols^a

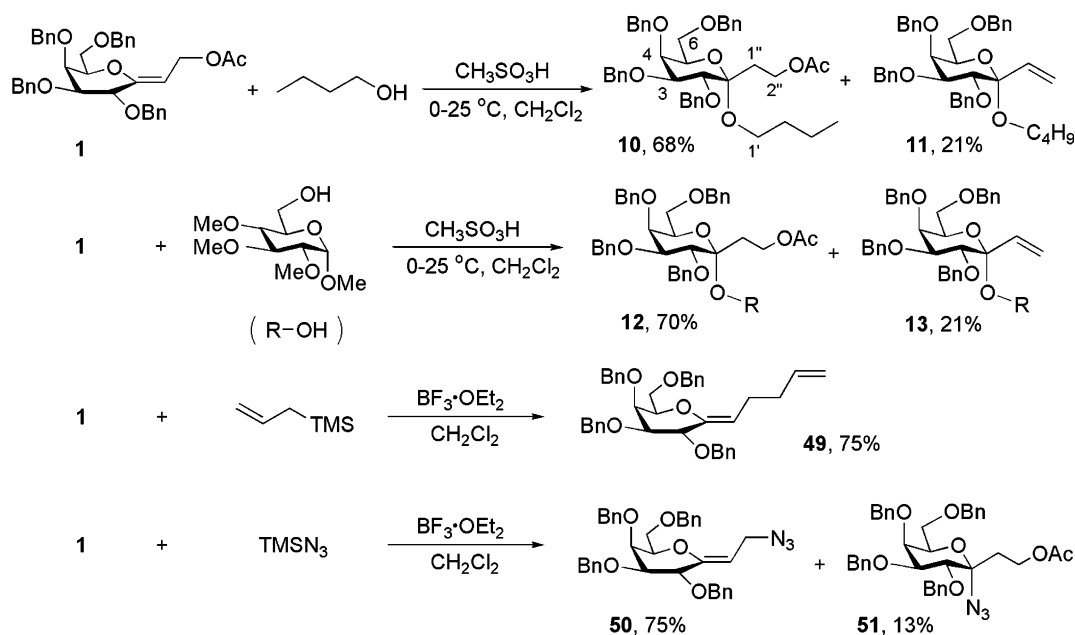


Entry	Donor	Acceptor (ROH)	Time (min)	Protonation + rearrangement products (yield)
i	30		60	— (0%) 34 (85%) ^b
ii	30		120	— (0%) 35 (83%) ^b
iii	30		120	— (0%) 36 (75%) ^b
iv	31		30	— (0%) 37 (86%) ^b
v	31		30	— (0%) 35 (78%) ^b
vi	31		30	— (0%) 38 (75%) ^b
vii	32		60	39 (64%) 35 (24%)
viii	32		30	40 (51%) 38 (30%)
ix	33		150	41 (61%) 37 (24%)
x	33a		150	— (0%) 37a (82%) ^c

^a All reactions were carried out at 0–25 °C in CH₂Cl₂ with alcohol nucleophiles in the presence of TFA (10 equiv) and molecular sieves (4 Å).

^b The α -anomer is predominant with α/β ratio of 8/1–15/1 on the basis of ¹H NMR integration.

^c Product **37a** is the same as **37** except for the acetate protecting group.



Scheme 3. Glycosylation reactions catalyzed by methanesulfonic acid or boron trifluoride etherate.

Table 3. Reactions of glycals with *C*- and *N*-nucleophiles^a

Entry	Donor	Acceptor (ROH)	Product (yield)
i	1		 42 (85%)
ii	1	TMSN_3	 43 (82%)
iii	1		 44 (65%)
iv	5	TMSN_3	 45 (78%)
v	30		 46 (84%)
vi	30		 47 (79%)
vii	30	TMSN_3	 48 (83%)
viii	33		 46 (85%)

^a All reactions were carried out at 0–25 °C in CH_2Cl_2 with nucleophiles in the presence of TFA (10 equiv) and molecular sieves (4 Å).

selectivity was greatly enhanced here in comparison with the glycosylation of *O*-nucleophiles, including the α -stereoselectivity and selective product formation from a preferential pathway. Nevertheless, the parallel reactions using other Lewis acids often afforded undesired product(s). For example, a diene product **49** was obtained owing to the direct substitution of *exo*-glycal **1** with allyl trimethylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. The same condition with TMSN_3 gave azide adduct **50** as the major product (75%).

In conclusion, we have conducted in detail the investigation of acid-catalyzed glycosylation of *endo*- and *exo*-glycals that are simple and can be finished efficiently in good to excellent yields. The reactions can be applied for the glycosyl additions of *O*-, *C*-, and *N*-nucleophiles. The carbonate or hydroxyl group at C3 position exclusively adopted the Ferrier reaction pathway in the reactions of *endo*-glycals, while the acetate and benzyl ether substituents predominantly gave a protonation product in those of *exo*-glycals. Particularly the former reactions are useful for the synthesis of 2,3-unsaturated- α -glycosides. In addition to providing an expeditious glycosylation procedure, our work represents the first report to clearly display the different reactivity between *endo*- and *exo*-glycals, and demonstrate both reaction pathways to be in the control of the allyl substituent and protecting group. Current efforts are in progress to study if other factors play a role in the competition and will be published in due course.

Acknowledgements

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Supplementary data

^1H and ^{13}C NMR spectra of 45 compounds are available (75 pages). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.061.

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- For example, the ^1H NMR spectra of the glycosylation product **10** indicated the H-1" resonance appeared at δ 2.08 (t, $J = 7.3$ Hz, 2H), H-2" at δ 3.90 (m, 1H) and 4.12 (m, 1H), and $\text{CH}_3\text{CO-}$ at δ 1.90 (s, 3H). The signals at δ 20.89 and 170.8 corresponding to the $\text{CH}_3\text{CO-}$ and $\text{CH}_3\text{CO-}$ resonances, respectively, were found in the ^{13}C NMR spectra of the same molecule. Please see the numbering structure in Scheme 3.
- The NOESY spectra of **10**, for instance, exhibited the cross-peaks between H2 (δ 3.97) and H1" (δ 2.08), as well as H5 (δ 3.80) and H1' (δ 3.43).
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