$Zn(OTf)_2$-Catalyzed Glycosylation of Glycals: Synthesis of 2,3-Unsaturated Glycosides via a Ferrier Reaction

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Abstract: A mild, catalytic, and efficient protocol has been developed for the synthesis of 2,3-unsaturated glycosides or 'pseudo-glycals' using $Zn(OTf)_2$. Stereoselective glycosylation of glycal donor with various acceptors comprising of alcohols, phenols, thiols, and sugar aglycones proceeds smoothly to afford the corresponding 2,3-unsaturaed glycosides in good to excellent yields.

Key words: glycosylation, glycosides, stereoselective synthesis, Ferrier reaction, glycal

Glycal templates have proven to be useful sugar scaffolds for diversity oriented synthesis to access small molecules with complex and diverse molecular structures with definite stereochemistry.[1] Owing to the presence of the enol ether functionality, glycals are utilized as versatile chiral building blocks in Danishefsky's glycal assembly[2] for the synthesis of many biologically important oligosaccharides and glycoconjugates including Lewis and blood-group determinants, gangliosides, and tumor-associated antigens and in chemical glycosylations such as the Ferrier reaction.[3] The Ferrier reaction involves displacement of a leaving group at the C-3 position of the glycal (a carbohydrate with an endocyclic alkene) in the presence of a Lewis acid catalyst or promoter. Subsequently, the nucleophile attacks at the anomeric position of the cyclic allyloxycarbenium ion intermediate with quasi-axial orientation leading to the formation of 2,3-unsaturated glycosides (Figure 1).

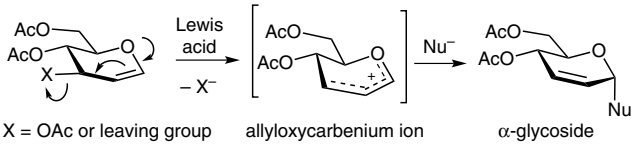

Figure 1 Mechanistic representation of Ferrier reaction

2,3-Unsaturated glycosides or 'pseudo-glycals' have received wide attention in recent years, particularly in the synthesis of antibiotics,[4] oligosaccharides,[5] uronic acids,[6] complex carbohydrates, and several biologically active natural products.[7] In addition, these molecules also serve as chiral synthons and key intermediates for various natural products,[8] glycopeptides,[9] natural product like compounds,[1b] modified carbohydrate derivatives,[7] nucleosides, and oligosaccharides.[2,5,6] Although, 2,3-unsaturated glycosides have been widely utilized, their exceptional synthetic versatility offers considerable potential for further functionalization and hence they are employed as glycosyl donors in the synthesis of natural products containing 2,3-dideoxy[8a] and 2-deoxy moieties.[10]

Since the development of the Ferrier reaction in 1969,[3] allylic rearrangement with nucleophilic substitution (S_N2') of glycals has been widely employed in the stereoselective synthesis of 2,3-unsaturated glycosides, using a wide variety of Lewis acid catalysts,[11] Brønsted acids,[12] and oxidants.[13] However, many existing strategies experience several drawbacks such as the need for high reaction temperatures, strongly acidic conditions, and extensive work-up. Besides, the catalysts used may be strong oxidants, highly air-sensitive, or require excess loadings or even to be used in stoichiometric amounts. In addition, some of the protocols require a large excess of nucleophile, offer low anomeric stereoselectivity, deliver low yields, and sometime produce byproducts. Therefore, there continues to be a need for a mild, inexpensive, and efficient catalytic promoter for the Ferrier reaction.

The scope of Zn(II)-catalyzed glycosylation has been demonstrated for ester-protected glycopyranoside donors. The combination of trimethylsilyl halide and a Lewis acid such as $ZnBr_2$ with diglyme as an additive is required for the success of this transformation.[11z] In a recent report,[11y] Liu and coworkers demonstrated the use of $ZnCl_2$ impregnated on activated alumina ($ZnCl_2/Al_2O_3$) to effect Ferrier aza-glycosylation. However, Ferrier reaction utilizing $ZnCl_2$ as a Lewis acid catalyst has only been reported with a narrow range of substrates, providing low anomeric selectivity.[11f]

In our approach to glycosylation and the synthesis of glycoconjugates,[14] we considered Zn(II) triflate as a catalyst for the Ferrier reaction to synthesize 2,3-unsaturated glycosides. Herein, we report the development of a Ferrier protocol utilizing Zn(II) triflate as a less expensive, milder, reusable, and efficient catalyst for the expeditious synthesis of 2,3-unsaturated glycopyranosides. The current protocol features a mild, simple, and stereoselective synthesis of α-glycosides with variety of O- and S-nucleophiles in the presence of other functionalities such as allyl, propargyl, isopropylidene, benzyl, and isopropyl groups, olefins, and ether linkages.

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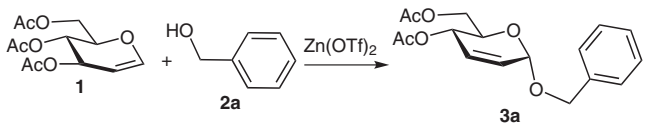
Initial experiments were performed with 3,4,6-tri-*O*-acetyl glucal (**1**) as the donor and benzyl alcohol (**2a**) as a model acceptor, the results are shown in Table 1. In the first set of reactions, glycal **1** (1 mL CH_2Cl_2) and **2a** (1.2 equiv) were reacted with 5 mol% of $Zn(OTf)_2$ under an inert atmosphere at room temperature for 16 hours, a 50% conversion was observed, and benzyl 2,3-unsaturated glucopyranoside (**3a**) was isolated in 78% yield based on recovered staring material. Increasing the amount of catalyst to 10 mol% in CH_2Cl_2 resulted in 70% conversion in 16 hours. Moreover, changing the solvent from CH_2Cl_2 to 1,2-dichloroethane resulted in the completion of reaction in three hours, furnishing **3a** in excellent yield (Table 1, entry 3).

Table 1 Optimization of $Zn(OTf)_2$-Catalyzed Glycosylation of Glycal **1** with Benzyl Alcohol (**2a**)[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	Conv. (%)	Yield (%)[b]
1	5	CH_2Cl_2	16	50	78
2	10	CH_2Cl_2	16	70	85
3	10	DCE	3	100	98
4	10	MeCN	24	trace	–
5[c]	10	DCE	1	100	97
6[d]	10	DCE	8	80	90

[a] Reaction conditions: glucal **1** (0.37 mmol), BnOH (0.44 mmol).
[b] Isolated yields based on the recovery of starting material.
[c] Reaction temperature 40 °C.
[d] Reaction was performed with recovered catalyst.

The stereochemistry at the anomeric position was established unambiguously based on ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **3a** revealed the absence of the C-2 proton at δ = 5.34 ppm (br s, 1 H) and a characteristic signal due to the anomeric proton of glucal **1** at δ = 6.47 ppm (d, J_{1-2} = 6.17 Hz, 1 H) had disappeared. Furthermore, olefinic resonances between δ = 5.84–5.92 ppm and the presence of signals at δ = 5.14 ppm (br s) for the α-anomer and δ = 5.20 ppm for the β-anomer integrating as 88:12 (α/β) confirmed the product with good stereoselectivity in favor of the α-anomer. In the ^{13}C NMR spectrum of **3a**, olefinic carbon resonances at δ = 126.7 and 137.4 ppm and the presence of the anomeric carbon resonance at δ = 93.5 ppm further verified the major product as an α-glycoside.

Notably, $Zn(OTf)_2$ not only acts as a stable and efficient catalyst but can be easily recovered by simple filtration of the reaction mixture and reused for a second transformation without losing its activity (Table 1, entry 6).

A highly polar solvent such as MeCN led to very low conversion, while a rise in reaction temperature led to completion within one hour (Table 1, entry 5). However, the anomeric ratio of products was found to be independent of reaction conditions such as solvent, temperature, or catalytic quantity of the promoter.

Next, the applicability and scope of this protocol were further examined in the context of various alcohols **2b–i**. All the reactions proceeded cleanly and efficiently and furnished the corresponding 2,3-unsaurated α-O-glycosides **3b–i** in good yields (Table 2).

In addition, we investigated the generality and efficiency of our procedure with thiols as nucleophiles. Accordingly, reaction of **1** with **2j** and **2k** under similar conditions[15] afforded the corresponding 2,3-unsaturated thioglycosides **3j–k** in good yields without any byproducts (Table 2, entry 9 and 10). Furthermore, the success and efficiency of the $Zn(OTf)_2$ as the Lewis acid in the Ferrier reaction is well illustrated using monosaccharides acceptors. Coupling of **1** with sugar nucleophiles **2l** and **2m** afforded the corresponding disaccharides **3l** and **3m** in good yield (Table 2, entry 11 and 12). However, reactions involving phenols such as 1-naphthol (**2n**) gave mixtures of *C*-glycosides, it can be postulated that rearrangement[16] of O- to C-glycosides occurs in the presence of Lewis acids (Table 2, entry 13).

Table 2 $Zn(OTf)_2$-Catalyzed Ferrier Reaction on Glycal **1**[a]

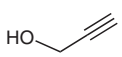
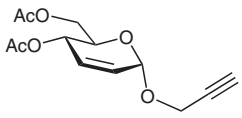
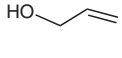
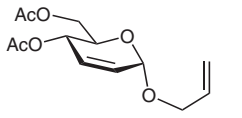
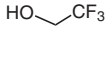
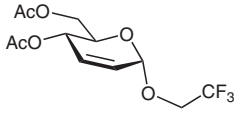
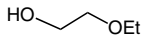
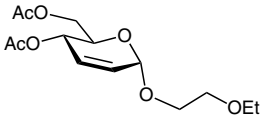
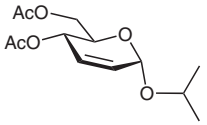
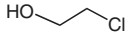
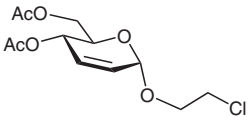
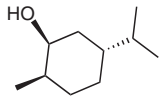
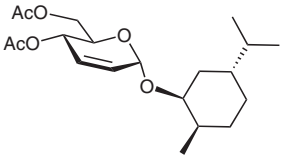
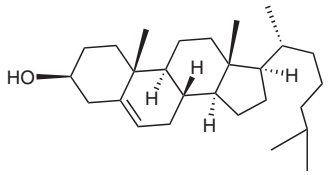
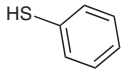
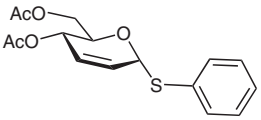
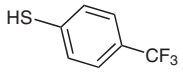
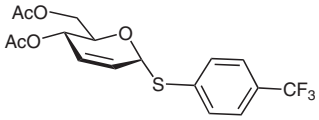
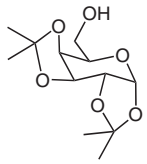
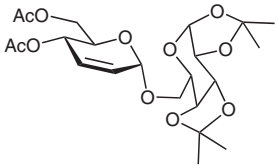
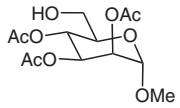
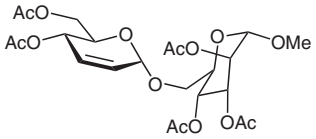
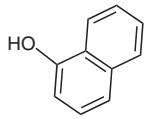
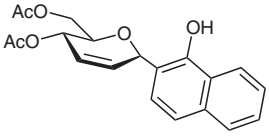
Entry	Acceptor		Product		Time	Yield (%)[b]	α/β ratio[c]
1	**2b**		**3b**		1 h	98	87:13
2	**2c**		**3c**		3 h	98	85:15
3	**2d**		**3d**		20 min	97	88:12

Table 2 $Zn(OTf)_2$-Catalyzed Ferrier Reaction on Glycal **1**[a] (continued)

Entry	Acceptor		Product		Time	Yield (%)[b]	α/β ratio[c]
4	**2e**		**3e**		4 h	95	87:13
5	**2f**		**3f**		10 min	86	90:10
6	**2g**		**3g**		3 h	98	90:10
7	**2h**		**3h**		8 h	88	89:11
8	**2i**		**3i**		6 h	78	91:9
9	**2j**		**3j**		1 h	92	79:21
10	**2k**		**3k**		2 h	90	72:28
11	**2l**		**3l**		4 h	74	88:12
12	**2m**		**3m**		16 h	72	85:15
13	**2n**		**3n**		1 h	72	67:33

[a] All reactions were performed with glucal **1** (0.37 mmol), 1.2 equiv of acceptor with 10 mol% of $Zn(OTf)_2$ in DCE at r.t.
[b] Isolated and unoptimized yields.
[c] The α/β ratios were examined by ^1H NMR by integrating anomeric hydrogen.

In summary, we report a new and practical method for constructing the α-glycosidic linkage via Ferrier reaction of glycals using mild conditions. A diverse range of acceptors was incorporated into glucal donors with high stereoselectivity using $Zn(OTf)_2$ as catalyst.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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