Synthesis of 2,3-Unsaturated *O*- and *N*-Glycosides by $HBF_4{\cdot}SiO_2$-Catalyzed Ferrier Rearrangement of D-Glycals

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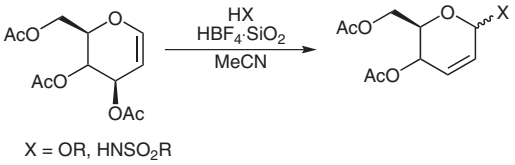
Abstract: Fluoroboronic acid adsorbed on silica gel ($HBF_4{\cdot}SiO_2$) catalyzes the Ferrier rearrangement of per-O-acetylated glycals with alcohols and sulfonamides to give 2,3-unsaturated *O*- and *N*-glycosides in good to excellent yield and with high α-stereoselectivity.

Key words: glycosylations, green chemistry, Ferrier rearrangement, *N*-glycosylsulfonamides, *O*-glycosides

Glycals are amongst the most versatile chiral building blocks that provide oxygen-rich stereochemically pure scaffolds. One of the most important reactions to produce diversity in glycal chemistry is the Ferrier rearrangement, which is an allylic rearrangement of glycal esters in the presence of nucleophiles leading to 2,3-unsaturated glycosides.[1] Some of the syntheses using 2,3-unsaturated glycosides as important intermediates comprise various glycopeptides,[2] modified carbohydrate derivatives,[3] and oligosaccharides.[4] In addition, very recently we have shown that 2,3-unsaturated *N*-glycosylsulfonamides have significant activities as human carbonic anhydrase inhibitors.[5]

The allylic rearrangement was discovered by Ferrier using $BF_3{\cdot}OEt_2$ as the Lewis catalyst.[6,7] Other catalysts that effect this transformation include $SnCl_4$,[8] $FeCl_3$,[9] $Sc(OTf)_3$,[10] $InCl_3$,[11] Montmorillonite K-10,[12] $BiCl_3$,[13] $Dy(OTf)_3$,[14] $CeCl_3{\cdot}7H_2O$,[15] $ZnCl_2$,[16] DDQ,[17] NIS,[18] $K_5CoW_{12}O_{40}$,[19] I_2,[20] CAN,[21] $Bi(NO_3)_3{\cdot}5H_2O$,[22] $Fe(NO_3)_3{\cdot}9H_2O$,[23] $NbCl_5$,[24] and $Fe_2(SO_4)_3{\cdot}xH_2O$.[25] These catalysts included Lewis acids and redox reagents. The acid catalysts, usually employed in substoichiometric amount, generally provide good anomeric selectivity under mild conditions. However, some of them are moisture sensitive and expensive. The oxidants are often required in stoichiometric amount and generally demand either longer reaction time or higher temperature. In addition, they are known to offer low anomeric selectivity of the product. Also, most of those methods entail the problems of tedious workup procedures and expensive reagents and equipment. It is worth noting that recently the use of perchloric acid inmobilized on silica has been reported to provide access to 2,3-unsaturated-*O*-glucosides in good to excellent yields with good α-stereoselectiviy.[26] However, perchloric acid is known to be potentially explosive, therefore, safety concerns limit the use of this reagent for large-scale preparations. Recent reports on the utilization of fluoroboric acid inmobilized on silica in various organic reactions such as thia-Michael addition to α,β-unsaturated carbonyl compounds,[27] preparation of acetals and ketals,[28] synthesis of thiranes from oxiranes;[29] acylation of phenols, alcohol, and amines;[30] prompted us to investigate its use as an alternative catalyst to prepare 2,3-unsaturated glycosides. This Letter describes the synthesis of 2,3-unsaturated *O*- and *N*-glycosides by the Ferrier reaction using a catalytic amount of $HBF_4{\cdot}SiO_2$ (Scheme 1).



Scheme 1

The reaction of 3,4,6-tri-*O*-acetyl-D-glucal and allyl alcohol in acetonitrile was chosen as a model.[31] To study the effect of the catalyst, the reactions were carried out in the presence of variable amounts of $HBF_4{\cdot}SiO_2$.

Table 1 Reaction of 3,4,6-Tri-*O*-acetyl-D-glucal with Allyl Alcohol[a]

Entry	Amount of catalyst (mg)	Temp (°C)	Reaction time (min)	α/β	Yield (%)
1	272	40	30	95:5	80
2	136	40	30	95:5	91
3	68	40	30	95:5	94
4	32	40	60	90:10	75
5	68	20	105	93:7	90
6	68[b]	40	105	–	no reaction

[a] All the reactions were performed using 0.5 mmol of the glycal and 2 equiv of the nucleophile in MeCN.
[b] Reaction performed with SiO_2 (230–400 mesh) as catalyst.

As can be seen in Table 1, use of 68 mg of $HBF_4{\cdot}SiO_2$ per mol of D-glucal, was enough for a fairly high yield. A

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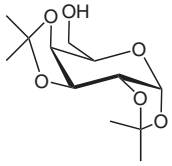
fourfold increase in the catalyst concentration afforded a lower yield (entry 1). Meanwhile, we also tested the effect of temperature on the catalyzed reaction. When the reaction was carried out at room temperature, the reaction was sluggish (entry 5). When it was carried out at 40 °C, the highest yield was obtained in a short reaction time. In all cases the α-isomer was produced predominantly, and α/β ratios are not affected by the amount of catalyst or by the temperature. The result incorporated in entry 6 shows that the catalytic activity of $HBF_4{\cdot}SiO_2$ is not contributed by SiO_2. To enhance the synthetic utility of our conditions, we next tested the reaction of per-O-acetylated D-glucal and D-galactal with a selected group of alcohols and sulfonamides using $HBF_4{\cdot}SiO_2$ as catalyst (Table 2).

In most cases we examined, 2,3-unsaturated glucosides were obtained in good to excellent yield and with very good α-stereoselectivity.[32] The reaction only failed with *tert*-butyl alcohol. Fluoroboronic acid adsorbed on silica gel was also found useful in the disaccharide synthesis using an acid sensitive acceptor (entry 5).

Table 2 Reaction of 3,4,6-Tri-*O*-acetyl-D-glucal (**1**) and 3,4,6-Tri-O-acetyl-D-galactal (**2**) with Different Nucleophiles[a]

Entry	D-Glycal	Nucleophile	α/β[b]	Yield (%)
1[c]	glucal	MeOH	85:15	81
2		*i*-PrOH	95:5	85
3		BnOH	83:17	91
4		*t*-BuOH	–	traces
5			90:10	83
6		ethanesulfonamide	85:15	98
7		*p*-toluenesulfonamide	85:15	88
8[c]		sulfamide	95:5	97
9	galactal	allyl alcohol	95:5	75
10		*i*-PrOH	80:20	70
11		BnOH	95:5	74
12		ethanesulfonamide	90:10	97

[a] Reactions were performed using 0.5 mmol of the glycal, 2 equiv of nucleophile and 68 mg of $HBF_4{\cdot}SiO_2$ in MeCN.
[b] Anomeric ratios were determined by ^1H NMR spectroscopy.
[c] Reaction performed with 4 equiv of nucleophile.

The scope of the glycosylation was further examined in the context of *N*-glucosylsulfonamides synthesis. It has been found that many sulfonamidoglycosides present interesting biological activities as carbonic anhydrase inhibitors[5] and antiproliferative agents.[33] We chose three sulfonamides (entries 6, 7, and 8) as the glycosyl acceptors. As shown in Table 2, these reactions also gave high yields and α-selectivity. The sulfonamidoglycosylation performed with sulfamide in the presence of $HBF_4{\cdot}SiO_2$ was useful in the synthesis of a selective inhibitor of carbonic anhydrase IX (entry 8).[5]

It is relevant to mention that not many methods are available for the Ferrier reaction of 3,4,6-tri-*O*-acetyl-D-galactal, and the few synthetically viable methods are restricted by the use of Montmorillonite K-10 with the aid of microwave irradiation,[12] $NbCl_5$,[24] $Er(OTf)_3$,[34] or $HClO_4.SiO_2$.[26b] Thus, we considered it pertinent to test our protocol on this substrate. The glycosylations of D-galactal in the presence of $HBF_4{\cdot}SiO_2$ afforded the Ferrier products with good to high stereoselectivity and good yields. To our surprise, treatment of D-galactal with ethanesulfonamide gave the sulfonamidoglycoside in excellent yield (entry 12). No formation of 2-deoxy-D-lyxo-hexopyranosides[35] could be detected in the reaction mixtures.

Although, pure products could be obtained, in most cases, by removal of the catalyst by simple filtration and evaporation of solvent (with low-boiling-point nucleophiles), analytical samples were prepared by passing the crude reaction product through a short column of SiO_2.

In view of green chemistry, recyclable catalysts are highly preferred. In our process, $HBF_4{\cdot}SiO_2$ was easily recovered from the reaction by filtration and subsequently used directly for the next reaction cycle (Table 3). Using our conditions for the glucosylation of allyl alcohol with the recycled catalyst, this protocol was repeated three times, the yields were always more than 90% and no change in the anomeric selectivity was found.

Table 3 The Reusability of $HBF_4{\cdot}SiO_2$ as Catalyst for Ferrier Reaction

Round	Nucleophile	Reaction time (min)	Yield (%)
1	allyl alcohol	30	91
2	allyl alcohol	30	94
3	allyl alcohol	30	92

In conclusion, we have developed a mild an eco-friendly approach for the synthesis of 2,3-dideoxy glycopyranosides using a catalytic quantity of $HBF_4{\cdot}SiO_2$. The very good α-selectivity, inexpensive and reusable catalyst, and its enviromentally benign character make this method an attractive way to prepare 2,3-unsaturated-*O*- and *N*-glycosides from D-glycals.

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(31) **Experimental Procedure**
To a solution of the glycal (0.5 mmol) and the nucleophile (2 equiv) in dry MeCN (4 mL), the catalyst was added at 40 °C. After stirring for the time indicated, the reaction was filtered and the solvent evaporated in vacuo. The residue was chromatographed on SiO_2 (eluent hexane–EtOAc) to afford the glycosides.
Preparation of HBF_4·SiO_2
A magnetically stirred suspension of SiO_2 (13.4 g, 230–400 mesh) in Et_2O (37 mL) was treated with 40% aq HBF_4 (1.5 g) for 3 h. The mixture was concentrated and the residue dried under vacuum at 100 °C for 24 h to afford HBF_4·SiO_2 (0.5 mmol g^{-1}).[30]

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