Copper(II) Triflate as a Mild and Efficient Catalyst for Ferrier Glycosylation: Synthesis of 2,3-Unsaturated *O*-Glycosides

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Abstract: Various acceptors including carbohydrates, amino acids, natural products, and hydroxylamine derivatives were coupled with 3,4,6-tri-*O*-acetyl-D-glucal in the presence of $Cu(OTf)_2$ as catalyst. The protocol offers facile and efficient Ferrier glycosylation for the synthesis of 2,3-unsaturaed *O*-glycosides in good yields and high anomeric selectivity.

Key words: glycosides, glycosylation, glycoconjugates, Ferrier reaction, Lewis acid

Sugar scaffolds are crucial for the development of therapeutic agents due to the role played by saccharides and glycoconjugates in many biological processes.[1] Owing to the presence of enol ether functionality, glycals are among the most utilized chiral intermediates for the synthesis of carbohydrate derivatives and they serve as building blocks for various molecules of biological significance.[2] The synthetic potential of the stereochemically rigid structure of glycal systems has been demonstrated in diversity-oriented synthesis of small molecules with complex structures[2a,b] and Danishefsky's glycal assembly for the preparation of various biologically active molecules and glycoconjugates.[2c] However, Ferrier glycosylation[3] remains the most investigated chemical transformation on glycals. The Ferrier reaction is an allylic rearrangement that involves displacement of a leaving group at the C-3 position of a glycal ester in the presence of a Lewis acid catalyst. Subsequently, the nucleophile attacks at the anomeric position of the cyclic allylic oxocarbenium ion in a quasi-axial orientation leading to the formation of 2,3-unsaturated glycosides or 'pseudo-glycals'.

The stereoselective synthesis of 2,3-unsaturated glycosides is of particularly importance due to their usefulness as key intermediates in the synthesis of several biologically important molecules such as antibiotics,[4] oligosaccharides,[5] uronic acids,[6] and complex carbohydrates,[7] various natural products,[8a] glycopeptides,[9] nucleosides,[7,8b] and modified carbohydrate derivatives.[7] The presence of a 2,3-olefinic group in 'pseudo-glycals' has further added to the diversity, hence, they are employed in various complexity-generating reactions.[10]

So far, a large number of catalysts including Lewis acids,[11] Brønsted acids,[12] and oxidants[13] have been reported to effect the Ferrier rearrangement. However, many of the existing protocols suffer from lack of generality because strong acidic conditions restrict the use of acid-labile substrates. In addition, many of these methods have limitations such as high reaction temperature, extensive workup, use of expensive, moisture-sensitive, toxic metals, and strong oxidizing reagents, require excess loading of reagents and nucleophiles, offer low anomeric selectivity, or provide poor yields of the desired products. Over the years, a variety of metal triflates have been used to effect the Ferrier reaction[3c] of glycals with various nucleophiles. However, the use of toxic metals is limited for the synthesis of active pharmaceutical ingredients (APIs) because tedious workup and metal-scavenging is required to reduce the amount of residual metals to acceptable limits in the desired products.[14] Therefore, the development of mild protocols that use low quantities of environmental friendly, non-toxic catalysts, is of crucial importance for the synthesis of glycoside and saccharide functionalized molecules.

In recent years, $Cu(OTf)_2$ has become a valuable reagent for various reactions such as trifluoromethylation,[15a] cyanotrifluoromethylation,[15b] and hydroalkoxylation of alkenes.[15c] In a recent report, a combination of $Cu(OTf)_2$ and ascorbic acid has been employed to effect the C-glycosylation of glycals with unactivated alkynes.[15d] The success of $Cu(OTf)_2$ as a non-toxic, moisture- and air-stable catalyst encouraged us to use this reagent as a Lewis acid in Ferrier glycosylation. In a continuation of our interest in the development of new glycosylation methods and synthesis of glycosides,[16] herein, we report the use of Cu(II) triflate as an efficient catalyst for the synthesis of 2,3-unsaturated *O*-glycosides.

As a first step, Ferrier glycosylation was performed with 3,4,6-tri-*O*-acetyl glucal (**1**) as glycosyl donor and benzyl alcohol (**2a**) as a model acceptor, being a relatively fast reactant. Initially, we observed only 50% conversion at room temperature after 16 hours in the presence 10 mol% $Cu(OTf)_2$ and dichloromethane as solvent. Notably, the rate of reaction was accelerated with incremental rise in temperature, and 90% conversion of **1** was observed after 8 hours at 40 °C to obtain benzyl glycoside **3a** in 76% yield. The temperature and solvent played an important role in this transformation in terms of yield and stereochemistry.

Optimization of reaction conditions was then carried out in different solvents; the results are summarized in Table

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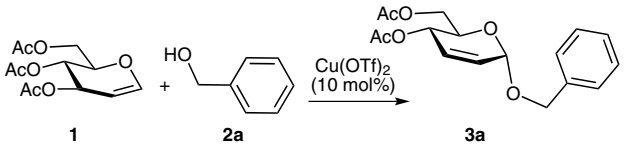
1. Using 1,2-dichloroethane as a solvent resulted in only 10% conversion after 16 hours at room temperature, and 80% conversion was observed at 40 °C in 8 hours, as indicated by TLC. Notably, the best result was obtained when the Ferrier reaction between **1** and **2a** was carried out in acetonitrile as solvent at room temperature. Remarkably, the reaction was completed within 10 minutes, and benzyl glucoside **3a** was isolated in 98% yield as an 88:12 α/β-mixture. Other solvents such as diethyl ether, toluene, or tetrahydrofuran were either ineffective or resulted in very poor conversions even after prolonged reaction times at high temperature (Table 1).

Table 1 Standardization of Ferrier Glycosylation Conditions[a]



1 **2a** **3a**

Entry	Solvent	Time (h)	Temp (°C)	Conv. (%)[b]	Yield (%)[c]
1	CH_2Cl_2	16	r.t.	50	–[d]
		8	40	90	76
2	DCE	16	r.t.	10	–[d]
		8	40	80	64
3	MeCN	10 min	r.t.	100	98
4	Et_2O	16	r.t.	trace	–[d]
		16	40	20	
5	THF	16	r.t.	no reaction	–[d]
		16	40	trace	
6	toluene	16	r.t.	no reaction	–[d]
		16	40	trace	

[a] Reaction conditions: glycal **1** (0.37 mmol), BnOH (0.44 mmol).
[b] Progress of reaction was monitored by TLC analysis at a given time and temperature.
[c] Isolated and unoptimized yields.
[d] Not isolated.

In the ^{1}H NMR spectrum of **3a**, the appearance of resonances corresponding to olefin protons between δ = 5.85–5.89 ppm were observed, while the anomeric proton was identified at δ = 5.14 ppm (br, s) integrating for one proton, thereby confirming that the product was formed with good stereoselectivity in favor of the α-anomer (α/β, 88:12). Furthermore, the ^{13}C NMR spectrum of **3a** showed the characteristic resonances of two olefinic carbon atoms at δ = 126.7 and 137.4 ppm and the presence of an anomeric carbon at δ = 93.5 ppm along with all other signals expected for the assigned structure and in complete agreement with literature data.[16g]

We then examined the optimal catalytic quantity of $Cu(OTf)_2$ that would deliver acceptable rates of conversion. Accordingly, glucal **1** was subjected to Ferrier glycosylation with **2a** in acetonitrile with varying amounts of $Cu(OTf)_2$ at room temperature. As indicated in Figure 1, $Cu(OTf)_2$ mediated Ferrier reactions in the presence of 10 and 5 mol% catalyst were complete within 10 and 40 minutes, respectively. The use of 2 mol% catalyst sufficed to give almost quantitative conversion (100%) after 1 hour, as indicated by TLC analysis. Further decreasing the catalytic amount to 1 mol% extended the required reaction time, however, the reaction with 0.5 mol% $Cu(OTf)_2$ was not complete even after a prolonged reaction time.

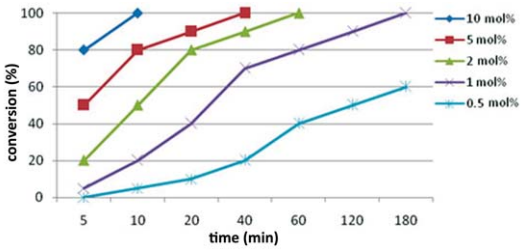


Figure 1 The effect of a catalytic amount of $Cu(OTf)_2$ on the conversion in the Ferrier glycosylation of glycal **1** with **2a**

Having optimized the conditions, we established the generality of the protocol with a range of alcohols including allyl (**2b**), butyne (**2c**), trifluoroethanol (**2d**), secondary butanol (**2e**), thiophenol (**2f**), alicyclic (**2g**, **2h**), hydroxylamine derivatives (**2i**, **2j**), and 9-fluorenemethanol (9FM, **2k**). Generally, the current protocol was sufficiently mild to tolerate various sensitive functionalities such as esters, carbamates, and diacetonide to afford 2,3-unsaturated glycosides in high yield and with good anomeric selectivity (Table 2). It is pertinent to mention that Ferrier reaction of glycal **1** with hydroxylamine derivatives such as *N*-hydroxysuccinimide (**2i**) and *N*-hydroxyphthalimide (**2j**) proceeded efficiently to afford the corresponding 'pseudo-glycals' in high anomeric selectivity in favor of the α-anomers (Table 2, entries 8 and 9). It is noteworthy that the use of a thiol such as 4-trifluoromethyl thiophenol (**2f**) as nucleophile worked equally well, giving thioglycoside **3f** in 72% yield with the α-anomer as the major product (Table 2, entry 5). Substrates with a nucleophile-containing tertiary nitrogen such as 3-quinuclidinol (**2l**) failed to react under similar conditions (Table 2, entry 11).

The versatility and scope of the present method was further explored to obtain 'pseudo-glycals' incorporated with biologically important molecules. Accordingly, natural biomolecules such as L-menthol (**2m**) and cholesterol (**2n**) were coupled with glycal **1** to obtain unsaturated glycosides in satisfactory yields and high anomeric selectivity (Scheme 1). The Ferrier reaction of cholesterol (**2n**) was performed in a mixed solvent system of dichloromethane and acetonitrile (1:1) due to the poor solubility of **2n** in acetonitrile.

Table 2 Substrate Scope of the $Cu(OTf)_2$-Mediated Ferrier Glycosylation under Optimized Conditions[a]

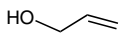
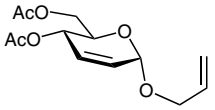
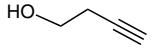
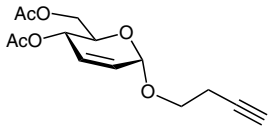
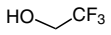
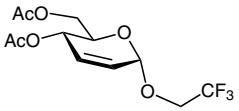
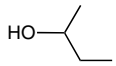
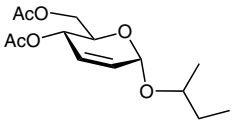
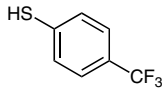
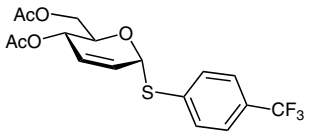
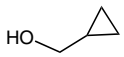
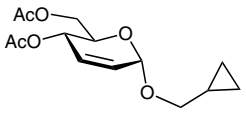
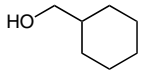
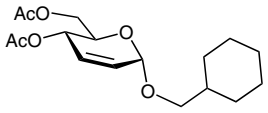
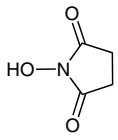
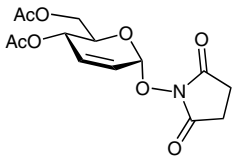
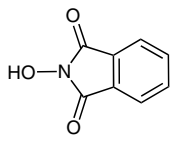
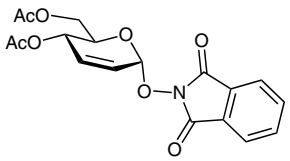
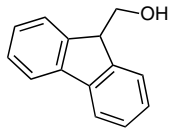
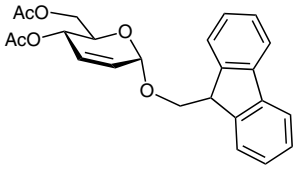
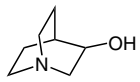
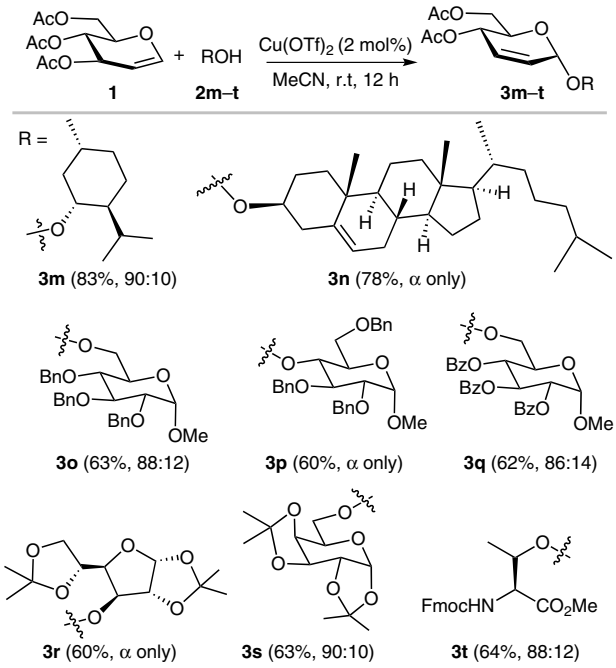
Entry	Acceptor (NuH)	Product	Time (h)	Yield (%)[b]	α/β ratio[c]
1	 **2b**	 **3b**	2	96[16g]	91:9
2	 **2c**	 **3c**	4	94[16g]	85:15
3	 **2d**	 **3d**	2	84[16g]	90:10
4	 **2e**	 **3e**	1	78[11k]	92:8
5	 **2f**	 **3f**	2	76[16f]	α only
6	 **2g**	 **3g**	1	92[11z]	85:15
7	 **2h**	 **3h**	1	96[16g]	87:13
8	 **2i**	 **3i**	1	95[11y]	α only
9	 **2j**	 **3j**	1	87[11y]	α only

Table 2 Substrate Scope of the $Cu(OTf)_2$-Mediated Ferrier Glycosylation under Optimized Conditions[a] (continued)

Entry	Acceptor (NuH)	Product	Time (h)	Yield (%)[b]	α/β ratio[c]
10	 **2k**	 **3k**	2	88	89:11
11	 **2l**	no reaction			

[a] Reaction conditions: 3,4,6-tri-*O*-acetyl glucal (1 equiv), acceptor (1.2 equiv), 2 mol% $Cu(OTf)_2$, MeCN, r.t.
[b] Isolated and unoptimized yields.
[c] The α/β ratios were examined by ^{1}H NMR analysis by integrating the anomeric hydrogen signal.



Scheme 1 Screen of natural products, saccharides, and amino acid containing acceptors[16g]

We then attempted Ferrier glycosylation with monosaccharide derivatives comprising benzyl ether (**2o** and **2p**), ester (**2q**), and diacetonides (**2r** and **2s**) and found that the monosaccharide acceptors underwent glycosidic coupling with glycal **1** to afford the corresponding unsaturated disaccharides **3o**–**s** in good yields. Notably, glucose diacetonide **2r** and sterically hindered aglycone **2p** reacted efficiently to give the corresponding disaccharides **3p** and **3r** in favor of the α-anomer only. In addition, amino-acid derived acceptor, FmocThr(OH)OMe (**2t**) was also coupled with glycal **1** to obtained amino acid glycoconjugate (**3t**).

In summary, we have demonstrated the facile and stereoselective synthesis of 2,3-unsaturated glycosides and disaccharides by using easily accessible starting materials under mild reaction conditions.[17] We have also demonstrated the applicability of the method for various natural products of biological significance (**3m**–**t**). Another highlight of present reagent system is the tolerance of this methodology to various sensitive functionalities. Use of economical and environmentally friendly catalyst, easy work-up, and high anomeric selectivity are added advantages.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are general synthesis information, characterization data, and ^{1}H and ^{13}C NMR spectra of all the compounds.

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(17) **$Cu(OTf)_2$ Mediated Ferrier Glycosylation; Typical Procedure:** To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **1** (1 equiv) and acceptor (1.2 equiv) in anhydrous MeCN (2 mL/mmol) under an atmosphere of argon was added $Cu(OTf)_2$ (2 mol%) at r.t. The reaction mixture was stirred until complete consumption of the starting material (glycal). The solvent was concentrated in vacuo, the crude residue was re-dissolved in dichloromethane and loaded on a silica gel column. The product was purified by silica gel chromatography (hexane–EtOAc) to afford the 2,3-unsaturated *O*-glycosides in excellent yields. The identities of all the Ferrier products were confirmed by IR, ^{1}H NMR, ^{13}C NMR and MS/HRMS spectroscopic analysis.

***p*-Trifuoromethylphenyl 4,6-Di-*O*-acetyl-2,3-dideoxy-erythro-hex-2-eno-1-thio-α-D-pyranoside (3f):** Yellow oil; $[\alpha]_D$ +222.368 (*c* 19.0, $CHCl_3$). IR ($CHCl_3$): 3019, 2955, 2929, 1743, 1606, 1370, 1325, 1226, 1166, 1124, 1061, 1015, 952, 833, 772, 750, 667, 599 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.56 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.05 (dt, *J* = 11.3, 1.2 Hz, 1 H, H-3), 5.92 (dt, *J* = 10.1, 1.5 Hz, 1 H, H-2), 5.87 (br s, 1 H, H-1), 5.41 (dd, *J* = 9.4, 1.9 Hz, 1 H, H-4), 4.42 (m, 1 H, H-5), 4.29 (d, *J* = 12.1, 5.6 Hz, 1 H, H_a-6), 4.24 (dd, *J* = 12.1, 2.6 Hz, 1 H, H_b-6), 2.12 (s, 3 H), 2.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.2, 130.2, 128.3, 127.8, 125.7, 125.6, 82.7, 67.6, 64.9, 62.8, 20.9, 20.6. MS (ESI): *m*/*z* (%) = 408 (100) $[M + NH_4]^+$.

Cycloproylmethyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3g): Colorless oil. IR ($CHCl_3$): 3017, 2920, 2852, 1741, 1370, 1219, 1036, 972, 907, 751, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.91–5.885 (m, 2 H, H-3, H-2), 5.31 (dd, *J* = 9.5, 1.4 Hz, 1 H, H-4), 5.08 (br s, 1 H, H-1), 4.23 (dd, *J* = 11.9, 5.3 Hz, 1 H, H_a-6), 4.18 (dd, *J* = 11.8, 2.4 Hz, 1 H, H_b-6), 4.15 (m, H-5), 3.51 (dd, *J* = 10.4, 7.3 Hz, 1 H, O*H*CH), 3.43 (dd, *J* = 10.4, 6.9 Hz, 1 H, OHC*H*), 2.09 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 1.15–1.09 (m, 1 H, cyclopropyl), 0.59–0.55 (m, 2 H, cyclopropyl), 0.28–0.20 (m, 2 H, cyclopropyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.2, 128.9, 127.8, 93.8, 73.4,

66.8, 65.2, 63.0, 20.9, 20.7, 10.5, 3.2, 3.0. MS (ESI): *m*/*z* (%) = 302 (100) $[M + NH_4]^+$.

(2,5-Dioxopyrrolidine-1-yl)-oxy 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3i): Colorless oil; $[\alpha]_D$ +150.000 (*c* 10.4, $CHCl_3$). IR ($CHCl_3$): 2926, 2853, 1724, 1432, 1370, 1220, 1206, 1108, 1045, 907, 814, 771, 650, 606 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.15 (d, *J* = 10.2 Hz, 1 H, H-3), 6.01 (dt, *J* = 10.2, 2.1 Hz, 1 H, H-2), 5.57 (br s, 1 H, H-1), 5.45 (ddd, *J* = 10.1, 3.4, 1.7 Hz, 1 H, H-4), 4.60 (dt, *J* = 10.1, 2.8 Hz, 1 H, H-5), 4.32 (dd, *J* = 12.5, 3.4 Hz, 1 H, H_a-6), 4.18 (dd, *J* = 12.5, 2.3 Hz, 1 H, H_b-6), 2.74 (s, 4 H, COC_2H_4CO), 2.12 (s, 3 H, OAc), 2.10 (s, 3 H, OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 170.7, 170.2, 133.5, 122.9, 98.1, 68.2, 64.2, 61.8, 25.5, 20.9, 20.7. MS (ESI): *m*/*z* (%) = 345 (100) $[M + NH_4]^+$.

9-Fluorenylmethyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3k): Viscous liquid; $[\alpha]_D$ +68.750 (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): 2923, 1743, 1447, 1371, 1231, 1038, 741, 610 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.63 (m, 2 H, Ar-H), 7.40 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.31 (d, *J* = 7.5 Hz, 2 H, Ar-H), 5.94–5.93 (m, 2 H, H-3, H-2), 5.32 (d, *J* = 9.3 Hz, 1 H, H-4), 5.12 (br s, 1 H, H-1), 4.23–4.17 (m, 2 H, H_a-6, O*H*CH), 4.16–4.12 (m, 2 H, OHC*H*, H-5), 4.10 (dd, *J* = 9.3, 7.5 Hz, 1 H, H_b-6), 3.75 (dd, *J* = 9.3, 7.6 Hz, 1 H, OCH_2CH), 2.12 (s, 3 H, -OAc), 1.93 (s, 3 H, -OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.2, 144.6, 144.4, 141.0, 129.2, 127.6, 127.4, 126.8, 125.0, 119.8, 94.7, 71.2, 67.1, 65.2, 65.2, 62.8, 47.7, 20.9, 20.5. MS (ESI): *m*/*z* (%) = 431.10 (100) $[M + Na]^+$. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{28}NO_6^+$ $[M + NH_4]^+$ 426.19116; found 426.19118.

