Tetrahedron Letters 57 (2016) 2758–2762

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Hafnium(IV) triflate as a highly efficient catalyst for Ferrier rearrangement of *O*- and *S*-nucleophiles with glycals

Yonghui Liu, Tianbang Song, Weijia Meng, Yun Xu, Peng George Wang, Wei Zhao *

The State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Haihe Education Park, 38 Tongyan Road, Tianjin 300353, People's Republic of China

ARTICLE INFO

Article history:
Received 17 March 2016
Revised 5 May 2016
Accepted 9 May 2016
Available online 9 May 2016

Keywords:
Hafnium(IV) triflate
3,4,6-Tri-*O*-acetyl-D-glucal
Hexa-*O*-acetyl-D-lactal
Ferrier rearrangement
2,3-Unsaturated glycosides

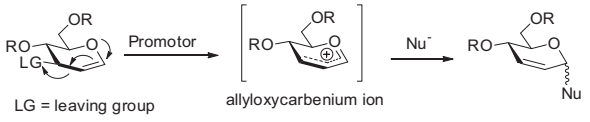
ABSTRACT

A highly efficient method to afford 2,3-unsaturated glycosides was described. In the presence of Hafnium (IV) triflate, a variety of 2,3-unsaturated-*O*- and *S*-glycosides have been obtained by stereoselective glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal and hexa-*O*-acetyl-D-lactal with various acceptors in good isolated yields.

Carbohydrates are a kind of biomolecules which participate in almost all biological processes in life, including cell recognition,[1] cell adhesion,[2] cell communication,[3] inflammation,[4] and immune response.[5] Most carbohydrates found on cell surface or in extracellular matrix exist as polysaccharide and glycoconjugates (i.e. glycolipid, glycopeptide, glycoprotein, sugar nucleotide),[6] in which sugar units are connected with aglycones through glycosidic bonds. Therefore, the stereoselective construction of glycosidic bonds is the critical processes for glycoconjugate syntheses.

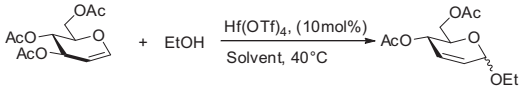
To date, a number of strategies have been demonstrated for the stereoselective formation of glycosidic bonds.[7] Ferrier rearrangement is one of the methods for stereoselective synthesis of 2,3-unsaturated glycosides,[8] which can be further diversified into bioactive compounds, such as oligosaccharides[9] and natural products.[10] The reaction mechanism is proposed in Scheme 1. Firstly, the leaving group at the C-3 position of the glycal is removed in the presence of promotor; subsequently, the cyclic allyloxycarbenium ion intermediate is attacked by the nucleophile to form a new glycosidic bond.

Various catalysts have been introduced in the Ferrier reaction, including some Lewis acid catalysts[11] such as $ZnCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, $Cu(OTf)_2$, $RuCl_3{\cdot}3H_2O$, $Sm(OTf)_3$, $Cu(OTf)_2$, $Tm(OTf)_3$, $TiCl_3(OTf)$, and $Gd(OTf)_3$, Bronsted acid catalysts[12] such as *p*-TsOH, trichloroacetic acid (TCA), trifluoroacetic acid (TFA),



Scheme 1. Mechanism of type I Ferrier rearrangement.

Table 1
Optimization of solvent[a]



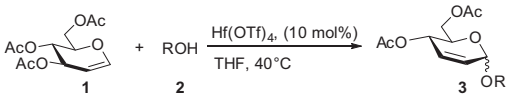
Entry	Nucleophile	Reaction time	Conversion[b] (%)	α:β[c]
1	CH_3CN	6 h	Trace	/
2	CH_2Cl_2	30 min	40	5:1
3	THF	10 min	96	6:1
4	Et_2O	10 min	90	6:1
5	Dioxane	10 min	80	5.5:1
6	DCE	15 min	60	5:1
7	Toluene	10 min	65	6:1

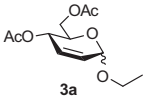
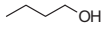
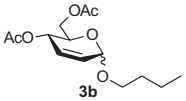
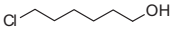
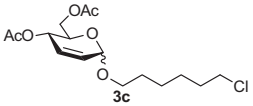
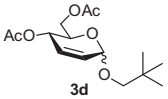
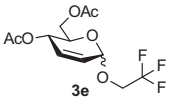
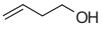
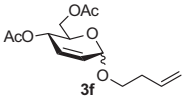
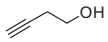
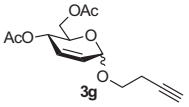
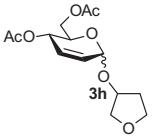
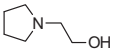
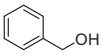
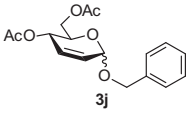
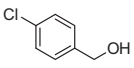
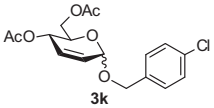
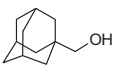
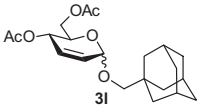
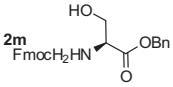
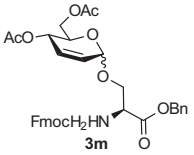
[a] Reaction conditions: tri-*O*-acetyl-D-glucal (200 mg, 0.73 mmol), EtOH (1.2 equiv), $Hf(OTf)_4$ (10 mol%), solvent (5 mL), 40 °C.
[b] Determined by analysis of the ^1H NMR spectra of the crude reaction mixture.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectra.

* Corresponding author. Tel./fax: +86 022 2350 7760.
E-mail address: wzhao@nankai.edu.cn (W. Zhao).

http://dx.doi.org/10.1016/j.tetlet.2016.05.026
0040-4039/

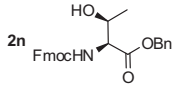
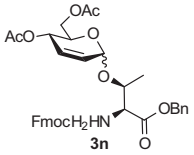
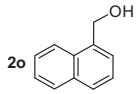
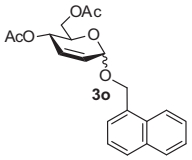
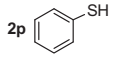
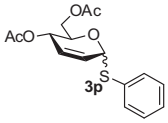
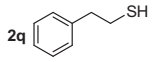
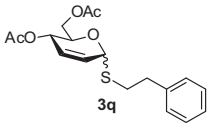
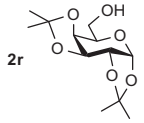
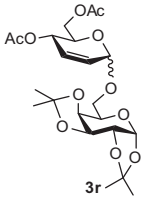
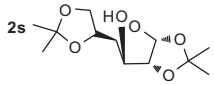
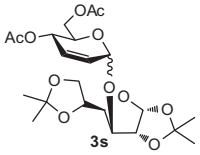
Table 2
Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal **1** catalyzed by $Hf(OTf)_4$[a]



Entry	Nucleophile	Reaction time	Product	Yield[b] (%)	α:β[c]
1	**2a** 	10 min	 **3a**	96	86:14
2	**2b** 	10 min	 **3b**	94	89:11
3	**2c** 	40 min	 **3c**	95	87:13
4	**2d** 	10 min	 **3d**	62	90:10
5	**2e** 	30 min	 **3e**	85	90:10
6	**2f** 	10 min	 **3f**	92	93:7
7	**2g** 	40 min	 **3g**	90	92:8
8	**2h** 	30 min	 **3h**	74	91:9
9	**2i** 	24 h	No reaction	–	–
10	**2j** 	30 min	 **3j**	88	89:11
11	**2k** 	35 min	 **3k**	80	90:10
12	**2l** 	30 min	 **3l**	72	92:8
13	**2m** 	25 min	 **3m**	79	>99:1

(*continued on next page*)

Table 2 (*continued*)

Entry	Nucleophile	Reaction time	Product	Yield[b] (%)	α:β[c]
14	 **2n**	30 min	 **3n**	75	>99:1
15	 **2o**	20 min	 **3o**	68	94:6
16	 **2p**	20 min	 **3p**	80	83:17
17	 **2q**	30 min	 **3q**	78	95:5
18	 **2r**	50 min	 **3r**	78	94:6
19	 **2s**	30 min	 **3s**	76	93:7

[a] Reaction conditions: tri-*O*-acetyl-D-glucal (200 mg, 0.73 mmol), EtOH (1.2 equiv), $Hf(OTf)_4$ (10 mol %), solvent (5 mL), 40 °C.
[b] Isolated yield by flash column chromatography on silica gel.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectra.

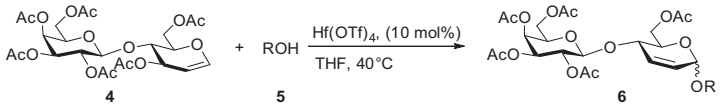
camphorsulfonic acid (CSA), TfOH-SiO_2, 3,5-dinitro benzoic acid (DNBA), and other catalysts[13] such as iodonium dicollidinium perchlorate (IDCP), NIS, ceric(IV) ammonium nitrate (CAN), H_2O_2, Pd $(OAc)_2$, Zn, and pyridinium bromide salts. However, some of these methods suffered from the drawbacks in terms of harsh reaction conditions, excess amount of sensitive catalysts, and low yields. Therefore, exploration of efficient promoters for this reaction is still a challenge. Previous studies show that Hafnium(IV) triflate was an efficient promoter in many reactions such as the Friedel–Crafts acylation, Fries rearrangement, hydroamination, thioacetalization, transthioacetalization, *N*-aminomethylation, and Prins-type cyclization.[14] Herein, we report a more practical Ferrier rearrangement using Hafnium(IV) triflate as an efficient Lewis acid catalyst.

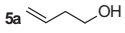
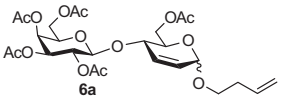
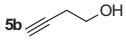
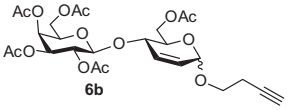
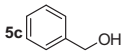
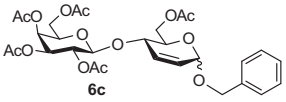
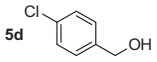
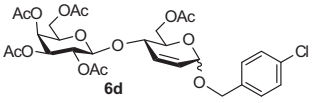
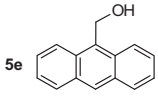
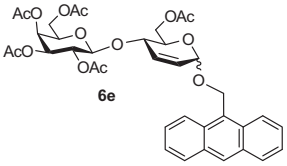
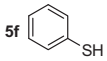
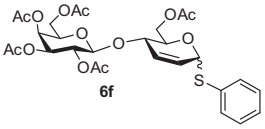
Our Initial studies started with tri-*O*-acetyl-D-glucal (**1**) as the donor and EtOH as the nucleophile in a model system catalyzed by $Hf(OTf)_4$. As reaction medium has influence on the reaction, we then paid efforts to screen the best reaction solvents among CH_3CN, CH_2Cl_2, THF, Et_2O, dioxane, 1,2-dichloro ethane (DCE), and toluene. As shown in Table 1, the ratio and the yield of desired target compound varied. After stirring at 40 °C in THF and Et_2O for 10 min, the corresponding 2,3-unsaturated glycoside was obtained in an isolated yield of 96% and 90%, respectively.

To test the feasibility of this approach, various alcohols (**2a**–**s**) were further applied under the optimized condition to the synthesis of corresponding 2,3-unsaturated glycosides. The Ferrier rearrangement was performed between tri-*O*-acetyl D-glucal(**1**) (1 equiv) and various nucleophiles (1.2 equiv) at 40 °C, with Hafnium(IV) triflate (10 mol %) as the catalyst and THF as the solvent. As presented in Table 2, the substrate scope of various linear alkyl alcohols (Table 2, entries 1–3) gave the products with higher yields, while the branched alkyl alcohols (Table 2, entries 4, 5 and 8) with lower yields but higher stereoselectivity.

Functionalized alkyl alcohols (Table 2, entries 6 and 7) gave the products with higher yield and better stereoselectivity, while aromatic alcohols (Table 2, entries 10, 11 and 15) and adamantanemethanol (Table 2, entry 12) with a higher steric hindrance gave the products with higher stereoselectivity but lower yields. The reactions of glucal with amino acids (Table 2, entries 13 and 14) were investigated. Interestingly, the glycosylated serine and threonine building blocks were synthesized with almost a single α configuration. Thio-phenol (Table 2, entry 16) and thiol (Table 2, entry 17) were used as nucleophile to provide the corresponding thioglycosides with satisfactory anomeric selectivity. For entry 9, it was hypothesized that the catalyst was quenched by the substrate, leading to the reactivity loss of $Hf(OTf)_4$.

Table 3
Glycosidation of hexa-*O*-acetyl-D-lactal **4** catalyzed by $Hf(OTf)_4$[a]



Entry	Nucleophile	Reaction time	Product	Yield[b] (%)	α:β[c]
1	5a 	30 min	 6a	85	82:18
2	5b 	2 h	 6b	78	88:12
3	5c 	30 min	 6c	86	86:14
4	5d 	35 min	 6d	85	89:11
5	5e 	30 min	 6e	68	>99:1
6	5f 	25 min	 6f	73	63:37

[a] Reaction conditions: hexa-*O*-acetyl-D-lactal (405 mg, 0.73 mmol), nucleophile (1.2 equiv), $Hf(OTf)_4$ (10 mol %), solvent (5 mL), 40 °C.
[b] Isolated yield by flash column chromatography on silica gel.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen or separable proton in the ^1H NMR spectra.

Synthesis of 2,3-unsaturated glycosides from hexa-*O*-acetyl-D-lactal (**4**) with various alcohols was further investigated, as summarized in Table 3. Six *O*-, *S*-nucleophiles coupling with the protected lactal gave corresponding 2,3-unsaturated glycosides with satisfactory yield and stereoselectivity. In all these cases, the products were mainly α anomers due to the thermodynamic anomeric effect probably.

In summary, we have developed Hafnium(IV) triflate as a highly efficient catalyst for type I Ferrier reaction. The catalyst was easy to handle and the reaction procedure was simple. We also presented our attempts with monosaccharide and disaccharide to afford 2,3-unsaturated *O*- and *S*-glycosides with $Hf(OTf)_4$ as the catalyst in satisfactory yield and selectivity under mild conditions.

Acknowledgments

We thank the National Natural Science Foundation of China (20332006, 21572105) and the Natural Science Foundation of Tianjin (12JCYBJC18600) for financial support.

Supplementary data

Supplementary data (characterization data and ^1H and ^{13}C NMR spectra of all the Ferrier products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.026.

References and notes

1. (a) Butcher, E. C. *Cell* **1991**, *67*, 1033–1036; (b) Gilbert, H. J.; Knox, J. P.; Boraston, A. B. *Curr. Opin. Struct. Biol.* **2013**, *23*, 669–677.
2. (a) Phillips, M. L.; Nudelman, E.; Gaeta, F. C.; Perez, M.; Singhal, A. K.; Hakomori, S.; Paulson, J. C. *Science* **1990**, *250*, 1130–1132; (b) Wielgat, P.; Braszko, J. J. *Adv. Med. Sci.* **2012**, *57*, 23–30.
3. (a) Smets, L. A.; Enninga, I. C.; Van Rooy, H. *Exp. Cell. Res.* **1982**, *139*, 181–189; (b) Etulain, J.; Schattner, M. *Glycobiology* **2014**, *24*, 1252–1259.
4. (a) Lasky, L. A. *Annu. Rev. Biochem.* **1995**, *64*, 113–139; (b) Wright, R. D.; Cooper, D. *Glycobiology* **2014**, *24*, 1242–1251.
5. (a) Dziadek, S.; Hobel, A.; Schmitt, E.; Kunz, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7630–7635; (b) Wilson, R. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 14462–14472.
6. (a) Bertozzi, C. R. *Science* **2001**, *291*, 2357–2364; (b) Raetz, C. R.; Whitfield, C. *Annu. Rev. Biochem.* **2002**, *71*, 635–700; (c) Gabius, H. J.; Siebert, H. C.; Andre, S.; Jimenez-Barbero, J.; Rudiger, H. *ChemBioChem* **2004**, *5*, 740–764.
7. (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934; (b) McKay, M. J.; Nguyen, H. M. *ACS. Catal.* **2012**, *2*, 1563–1595; (c) Carmona, A. T.; Moreno-Vargas, A. J.; Robina, I. *Curr. Org. Syn.* **2008**, *5*, 33–60.
8. (a) Ferrier, R. J.; Overend, W. G.; Ryan, A. E. *J. Chem. Soc.* **1962**, 3667; (b) Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. C* **1966**, 441; (c) Blattner, R.; Ferrier, R. J.; Furneaux, R. H. *Tetrahedron Asymmetry* **2000**, *11*, 379–383; (d) Ferrier, R. J.; Hoberg, J. O. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 55–119; (e) Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2013**, *2013*, 7221–7262.
9. (a) Gemmell, N.; Meo, P.; Osborn, H. M. I. *Org. Lett.* **2003**, *5*, 1649–1652; (b) Wang, A.; Auzanneau, F. I. *J. Org. Chem.* **2007**, *72*, 3585–3588.
10. (a) Smith, A. B., 3rd; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299; (b) Smith, A. B., 3rd; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318; (c) Medeiros, M. R.; Narayan, R. S.; McDougal, N. T.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2010**, *12*, 3222–3225.
11. (a) Fraser-reid, B.; Kelly, D. R.; Tulshian, D. B.; Ravi, P. S. *J. Carbohydr. Chem.* **1983**, *2*, 105–114; (b) Yadav, J. S.; Subba Reddy, B. V.; Chand, P. K. *Tetrahedron Lett.* **2001**, *42*, 4057–4059; (c) Takhi, M.; Rahman, A. A. H. A.; Schmidt, R. R.

Tetrahedron Lett. **2001**, *42*, 4053–4056; (d) Yadav, J. S.; Subba Reddy, B. V.; Reddy, J. S. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390–2394; (e) Yadav, J. S.; Reddy, B. V. S.; Chary, D. N.; Reddy, C. S. *Tetrahedron Lett.* **2008**, *49*, 2649–2652; (f) Balamurugan, R.; Koppolu, S. R. *Tetrahedron* **2009**, *65*, 8139–8142; (g) Nagaraj, P.; Ramesh, N. G. *Tetrahedron Lett.* **2009**, *50*, 3970–3973; (h) Freitas, J. C. R.; de Freitas, J. R.; Menezes, P. H. *J. Braz. Chem. Soc.* **2010**, *21*, 2169–2172; (i) Chen, P.; Wang, S. *Tetrahedron* **2012**, *68*, 5356–5362; (j) Chen, P.; Lin, L. *Tetrahedron* **2013**, *69*, 10045–10051; (k) Ingle, V.; Gorepatil, P.; Mane, Y. *Synlett* **2013**, 2241–2244; (l) Chen, P. R.; Li, S. *Tetrahedron Lett.* **2014**, *55*, 5813–5816; (m) Narasimha, G.; Srinivas, B.; Krishna, P. R.; Kashyap, S. *Synlett* **2014**, 523–526; (n) Srinivas, B.; Reddy, T. R.; Krishna, P. R.; Kashyap, S. *Synlett* **2014**, 1325–1330; (o) Chen, P. R.; Bi, B. *Tetrahedron Lett.* **2015**, *56*, 4895–4899; (p) Chen, P.; Lin, L. *Tetrahedron* **2013**, *69*, 4524–4531; (q) Chen, P.; Su, J. *Tetrahedron* **2016**, *72*, 84–94.

12. (a) Bowles, W. A.; Robins, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 1252–1253; (b) Leutzinger, E. E.; Robins, R. K.; Townsend, L. B. *Tetrahedron Lett.* **1968**, *43*, 4475–4478; (c) Fuertes, M.; Garcia-Munoz, G.; Lora-Tamayo, M.; Madronero, R.; Stud, M. *Tetrahedron Lett.* **1968**, *38*, 4089–4092; (d) Gorityala, B. K.; Cai, S.; Ma, J.; Liu, X. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3093–3095; (e) Chen, P.; Wang, S. *Tetrahedron* **2013**, *69*, 583–588; (f) Bodipati, N.; Palla, S. R.; Komera, V.; Peddinti, R. K. *Tetrahedron Lett.* **2014**, *55*, 6878–6881.
13. (a) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1992**, 94–96; (b) Lopez, J. C.; Gomez, A. M.; Valverde, S.; Fraserreid, B. *J. Org. Chem.* **1995**, *60*, 3851–3858; (c) Linker, T.; Sommermann, T.; Gimisis, T.; Chatgilialoglu, C. *Tetrahedron Lett.* **1998**, *39*, 9637–9638; (d) Mostowicz, D.; Jurczak, M.; Hamann, H. J.; Hoft, E.; Chmielewski, M. *Eur. J. Org. Chem.* **1998**, 2617–2621; (e) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337; (f) Tatina, M. B.; Kusunuru, A. K.; Yousuf, S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2014**, *12*, 7900–7903; (g) Das, S.; Pekel, D.; Neudörfl, J.-M.; Berkessel, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 12479–12483.
14. (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409–412; (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 2053–2056; (c) Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161–5167; (d) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 150–154; (e) Wu, Y. C.; Zhu, J. P. *J. Org. Chem.* **2008**, *73*, 9522–9524; (f) Nakamura, M.; Niiyama, K.; Yamakawa, T. *Tetrahedron Lett.* **2009**, *50*, 6462–6465; (g) Sakai, N.; Shimamura, K.; Ikeda, R.; Konakahara, T. *J. Org. Chem.* **2010**, *75*, 3923–3926.