Hafnium(IV) triflate as a potent catalyst for selective 1-*O*-deacetylation of peracetylated saccharides

Rui Wang, Ji-Zong Chen, Xiu-An Zheng, Rui Kong, Shan-Shan Gong, Qi Sun

PII: S0008-6215(17)30781-4
DOI: 10.1016/j.carres.2017.11.015
Reference: CAR 7493

To appear in: *Carbohydrate Research*

Received Date: 17 October 2017
Revised Date: 23 November 2017
Accepted Date: 23 November 2017

Please cite this article as: R. Wang, J.-Z. Chen, X.-A. Zheng, R. Kong, S.-S. Gong, Q. Sun, Hafnium(IV) triflate as a potent catalyst for selective 1-*O*-deacetylation of peracetylated saccharides, *Carbohydrate Research* (2017), doi: 10.1016/j.carres.2017.11.015.

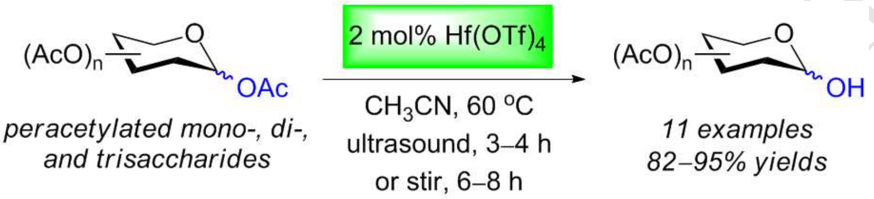
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Hafnium(IV) triflate as a potent catalyst for selective 1-*O*-deacetylation of peracetylated saccharides

Leave this area blank for abstract info.

Rui Wang, Ji-Zong Chen, Xiu-An Zheng, Rui Kong, Shan-Shan Gong, Qi Sun[*]□



Carbohydrate Research
journal homepage: www.elsevier.com

Hafnium(IV) triflate as a potent catalyst for selective 1-*O*-deacetylation of peracetylated saccharides

Rui Wang, Ji-Zong Chen, Xiu-An Zheng, Rui Kong, Shan-Shan Gong, Qi Sun*

Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science and Technology Normal University, 605 Fenglin Avenue, Nanchang, Jiangxi 330013, PR China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Deacetylation
Hafnium triflate
Peracetylated saccharides
Regioselectivity
Ultrasound

ABSTRACT

An efficient method for selective anomeric deacetylation of peracetylated mono-, di-, and trisaccharides has been developed by using 2 mol% $Hf(OTf)_4$ as catalyst in acetonitrile. Employment of ultrasonic irradiation could significantly accelerate the reaction rate. Mechanistic study confirmed the hydrolysis nature of this reaction, and NMR experimental data suggested that the multiple peracetylated saccharide molecules may ligate to Hf(IV) cation primarily via the anomeric acetate to promote its specific hydrolysis.

1. Introduction

Selective 1-*O*-deacetylation of peracetylated saccharides plays a crucial role in oligosaccharide synthesis to access reactive glycosyl donors, such as glycosyl trichloroacetimidates, phosphates, and halides.[1] Moreover, chemical synthesis of many bioactive glycoconjugates[2] also involves functionalizations specifically at the anomeric OH of carbohydrate acetate building blocks.

Currently, the methods that enable selective anomeric deacetylation of peracetylated carbohydrates can be mainly categorized in two types. The first approach selectively cleaves the anomeric acetate via transamidation by using a variety of nitrogenous nucleophiles such as ammonia[3], hydrazine acetate[4], benzylamine[5], ethylene diamine[6], piperidine[7], guanidine[8], 3-(dimethylamino)-1-propylamine (DMAPA)[9], etc. While excess bases are typically needed, some of these reagents are toxic. In additon, other basic reagents, such as alkali metal fluorides in PEG 400[10] and molecular seives in combination with methanol,[11] have also been successfully employed for the same purpose. Alternatively, the anomeric acetyl group could be selectively removed by Brønsted or Lewis acid-catalyzed hydrolysis or transesterification depending on the solvent used. The fact that stoichiometric amounts or even a large excess of Lewis acids such as tributyltin alkoxide[12], $Cu(OAc)_2$[13], $FeCl_3 \cdot 6H_2O$[14], and $HgO/HgCl_2$[15] are required indicates that the potency of these catalysts is far from satisfactory. Though it has been reported that catalytic amounts of $Ln(OTf)_3$[16] or $Zn(OAc)_2 \cdot 2H_2O$[17] were sufficient for the desired transformations, however, we found that ~~significan~~t amounts of either unreacted peracetylated starting materials or multiple deacetylated byproducts were observed, when the reactions were repeated exactly according to the described conditions. Therefore, novel Lewis acid catalysts with excellent catalytic activity, high regioselectivity, and low toxicity are highly desired for anomeric deacetylation of peracetylated saccharides.

Recently, we noticed that Group IVB transition metal-based Lewis acids such as $ZrCl_4$, $HfCl_4$, and $Hf(tOBu)_4$ have been reported to promote direct esterification/amidation of non-activated carboxylic acids and alcohols/amines.[18–19] Earlier this year, Adolfsson and coworkers revealed the mechanism of zirconium-catalyzed amidation and their NMR data indicated that carboxylate ligated to Zr(IV) cation in THF to form the reactive species.[20] Inspired by these reports, we speculated that certain Group IVB transition metal-based Lewis acids may ligate to the acetyl groups of the peracetylated carbohydrates and activate the most labile anomeric acetate, thereby promoting selective deprotection. Herein, we report the employment of $Hf(OTf)_4$ as a highly efficient catalyst for selective 1-*O*-deacetylation of peracetylated carbohydrates. Compared to the reported metal Lewis acids, only 2 mol% of $Hf(OTf)_4$ is needed for high-yielding anomeric deacetylation of a diversity of mono-, di-, and trisaccharide substrates in acetonitrile in 6–8 h at 60 ºC. Moreover, the reaction time could be remarkably shorten to only 3–4 h, when the reactions were assisted with sonication.

2. Results and discussion

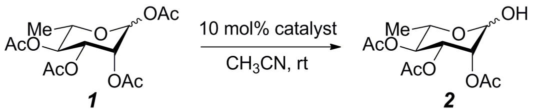
In the preliminary experiments, 1,2,3,4-tetraacetyl-L-rhamnose (**1**) was treated with 10 mol% of either reported metal

---

* Corresponding author. Tel.: +86-791-8380-5183; fax: +86-791-8382-6894; E-mail addresses: sunqi@jxstnu.edu.cn.

Lewis acids or a series of Group IVB transition metal Lewis acids at room temperature. Due to the concerns that certain metal Lewis acids may potentially promote the formation of methyl glycoside or isomerization of pyranose into furanose[14,20] in methanol, we chose to perform the deacetylation in commercial AR grade acetonitrile. The data listed in Table 1 showed that $Cu(OAc)_2$, $FeCl_3 \cdot 6H_2O$, $Zn(OAc)_2 \cdot 2H_2O$, and $Nd(OTf)_3$ (entry 1–4) exhibited either no or very low catalytic activity at 10 mol% level. A large amount of **1** was left unreacted after 12 h. Surprisingly, addition of Zr(IV) salts (entry 5–7) showed no catalytic activity at all, whereas the presence of Hf(IV) salts (entry 8–10) resulted in the generation of significant amounts of desired product **2**. It is noteworthy that $HfCl_4$- and $Hf(OTf)_4$-catalyzed reactions proceeded much faster and reached maximum conversion in 6 h. However, other than the desired **2** (35%), $HfCl_4$ also led to the formation of rhamnosyl chloride byproduct (~10%). In contrast, $Hf(OTf)_4$-catalyzed 1-*O*-deacetylation of **1** afforded **2** in 60% yield without any byproduct.

Table 1. The effect of metal Lewis acid on 1-*O*-deacetylation of **1**.



Entry	Catalyst	Reaction time (h)	Isolated yield of **2** (%)
1	$Cu(OAc)_2$	12	n.r.
2	$FeCl_3 \cdot 6H_2O$	12	15[a]
3	$Nd(OTf)_3$	12	12[a]
4	$Zn(OAc)_2$	12	10[a]
5	$ZrOCl_2 \cdot 8H_2O$	12	n.r.
6	$ZrCp_2Cl_2$	12	n.r.
7	$ZrCl_4$	12	n.r.
8	$HfCp_2Cl_2$	12	22[a]
9	$HfCl_4$	6	35[a]
10	$Hf(OTf)_4$	6	60[a]

[a] The reaction was quenched at the time point that it proceeded no further.

As expected, increasing reaction temperature notably accelerated the reaction rate of $Hf(OTf)_4$-catalyzed 1-*O*-deacetylation of **1** (Table 2). When the reaction with 10 mol% $Hf(OTf)_4$ was performed at 60 ºC, the reaction time was shorten to only 1 h. More importantly, **1** was completely consumed, and the yield of **2** was improved to 88%. However, elevation to 80 ºC resulted in the formation of multiple deacetylated byproducts.

Table 2. The effect of temperature on $Hf(OTf)_4$-catalyzed 1-*O*-deacetylation of **1**.

Entry	Temp.	Reaction time (h)	Isolated yield of **2** (%)
1	rt	6	60[a]
2	40	3	81[a]
3	60	1	88
4	80	1	75[b]

[a] The reaction was quenched at the time point that it proceeded no further. [b] Multiple deacetylated byproducts were observed on TLC.

In an attempt to optimize the quantity of catalyst required for the reaction, we gradually reduced the amount of $Hf(OTf)_4$ from 10 mol% to 1 mol% at 60 ºC. As shown in Table 3, the reaction time was prolonged to 6 h, but the yield of **2** was improved to 92%, when only 2 mol% $Hf(OTf)_4$ was used. However, when the amount of $Hf(OTf)_4$ was decreased to 1 mol%, the catatyltic effect drastically diminished.

Table 3. The effect of the amount of $Hf(OTf)_4$ on 1-*O*-deacetylation of **1**.

Entry	The amount of $Hf(OTf)_4$ (mol%)	Reaction time (h)	Isolated yield of **2** (%)
1	10	1	88
2	5	2	91
3	2	6	92
4	1	12	45[a]

[a] The reaction was quenched at the time point that it proceeded no further.

The solvent effect was also investigated at 60 ºC with 2 mol% $Hf(OTf)_4$. The results in Table 4 showed that when commercial AR grade MeOH, THF, DCE, and toluene were used, a large amount of **1** was left unreacted. In the first three cases, multiple deacetylated byproducts were obtained. $Hf(OTf)_4$ exhibited no catalytic activity in DMF and *i*PrOH. These results indicated that reactivity and regioselectivity of $Hf(OTf)_4$ is quite solvent-dependent. To prove the hydrolysis mechanism in acetonitrile, the reaction was tested in freshly dried acetonitrile. As expected, no reaction was observed even after 12 h. In contrast, the acetonitrile with 0.3% (v/v) water, whose water content is comparable to AR grade acetonitrile, led to similar reaction time and yield. However, if the amount of water was further increased to 1% (v/v) and above, the reaction proceeded notably faster, but the regioselectivity was compromised.

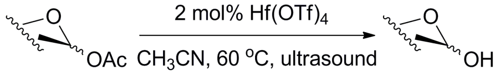
Table 4. The solvent effect on $Hf(OTf)_4$-catalyzed 1-*O*-deacetylation of **1**.

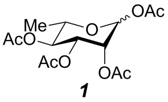
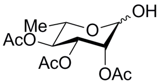
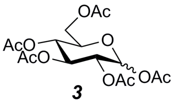
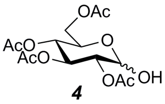
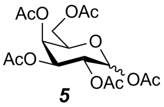
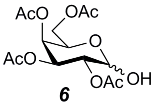
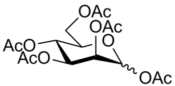
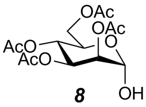
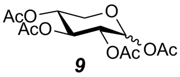
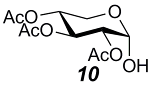
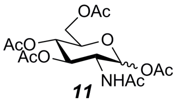
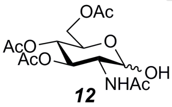
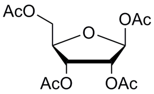
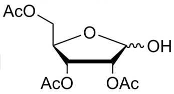
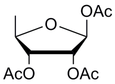
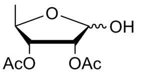
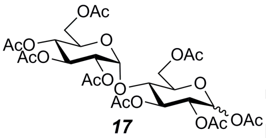
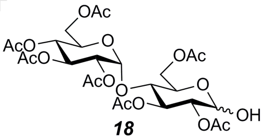
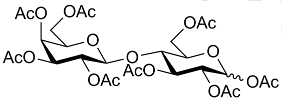
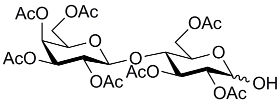
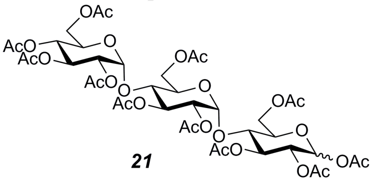
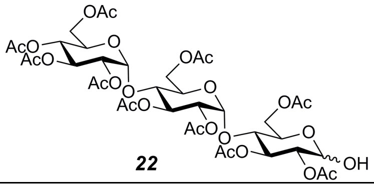
Entry	Solvent	Reaction time (h)	Isolated yield of **2** (%)
1	MeOH	4	36[a,b]
2	THF	10	27[a,b]
3	DCE	8	25[a,b]
4	Toluene	8	20[a]
5	DMF	12	n.r.
6	*i*PrOH	12	n.r.
7	CH_3CN (AR)	6	92
8	CH_3CN (dry)	12	n.r.
9	CH_3CN/H_2O (3.3×10^2:1, v/v)	5	92
10	CH_3CN/H_2O (100:1, v/v)	4	86[b]
11	CH_3CN/H_2O (20:1, v/v)	2.5	74[b]

[a] The reaction was quenched at the time point that it proceeded no further. [b] Multiple deacetylated byproducts were observed on TLC.

Since many previous reports have claimed that ultrasonic irradiation may accelerate ester hydrolysis in binary solvent systems,[22] we performed the reaction in an ultrasonic bath (40 KHz, power output 600W) at 60 °C. Compared to the reaction with mechanical agitation, the assistance of ultrasound remarkably accelerated the reaction rate and shortened the reaction time to only 3 h (Figure 1). It is worth noting that if the temperature was further elevated to 70 ºC, multiple deacetylated byproducts emerged again, indicating that 60 ºC was the threshold for the regioselectivity of this method. It might be easy to simply ascribe the rate enhancement to the cavitation phenomena, such as violent temperature and pressure change during the collapse of microbubbles. However, the temperature threshold suggested that the changes in the molecular structure of the solvent system and perturbation of hydrophobic solutesolvent interactions might play a more important role on the sonochemical effect.[23]

Table 5. Hf(OTf)$_4$-catalyzed 1-*O*-deacetylation of peracetylated mono-, di-, and trisaccharides under sonication conditions.



Entry	Substrate	Product	Reaction time (h)	Isolated yield (%)	α:β^a
1	 **1**	 **2**	3	92	6.3:1
2	 **3**	 **4**	3	90	2.3:1
3	 **5**	 **6**	3	91	2.2:1
4	 **7**	 **8**	3	90	α only
5	 **9**	 **10**	3	93	α only
6	 **11**	 **12**	3	89	8.3:1
7	 **13**	 **14**	3	94	1:2
8	 **15**	 **16**	3	95	1:1
9	 **17**	 **18**	4	85	2:1
10	 **19**	 **20**	4	86	1.6:1
11	 **21**	 **22**	4	82	1.6:1

^{a}The α:β ratio was determined by ^{1}H NMR.

To prove the generality of the Hf(OTf)$_4$-based 1-*O*-deacetylation method, a diverse number of peracetylated saccharide substrates were subjected to the optimized conditions. The results in Table 5 showed that the catalytic activity of Hf(OTf)$_4$ exhibited no difference on L- or D-pyranose substrates (entry 1–6). Similarly, Hf(OTf)$_4$ also showed excellent potency and regioselectivity on furanoses (entry 7–8). When disaccharide and trisaccharide substrates (entry 9–11) were employed, longer reaction time (4 h) was required and the yields were only slightly reduced. Alternatively, the reactions could be performed without the assistance of ultrasonic irradiation. Both the yields and α:β ratios were not affected except that longer reaction time (6–8 h) was required.

Driven by our curiosity about how Hf(OTf)$_4$ catalyzes the 1-*O*-deacetylation, we gradually added the catalyst to the CD$_3$CN solution of 1,2,3-triacetyl-5-deoxy-D-ribose (**15**), the structurally simplest substrate, and monitored their interactions by both ^{1}H and ^{13}C NMR. As shown in Figure 2A, addition of 2 mol% Hf(OTf)$_4$ resulted in the appearance of three new groups of peaks, corresponding to different binding modes. When 5 mol%

$Hf(OTf)_4$ was added, the peaks of free **15** completely disappeared. Interestingly, further addition of catalyst simplified the spectra. When total 25 mol% $Hf(OTf)_4$ was added, only one major set of peaks was left (Figure 2A, inset). Due to the ligation of **15** with Hf(IV) cation, the peaks of H-1, H-2, and one $COCH_3$ upshifted, while those of H-3, H-4, and the other two $COCH_3$ downshifted.

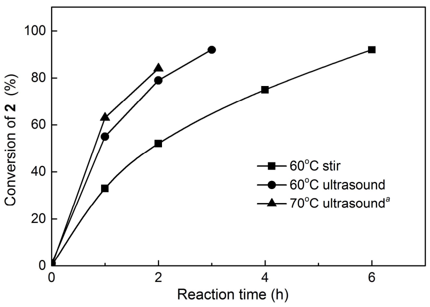


Figure 1. The sonochemical effect on $Hf(OTf)_4$-catalyzed 1-*O*-deacetylation of **1**. [a]Multiple deacetylated byproducts were observed on TLC.

Moreover, we experimentally determined that 25 mol% $Hf(OTf)_4$-catalyzed selective 1-*O*-deacetylation of **15** was extremely fast (30 min) even at room temperature, indicating that the **15**-Hf(IV) complex observed should be the active intermediate species. The ^{13}C NMR data also confirmed the formation of a dominant binding complex, when 25 mol% $Hf(OTf)_4$ was added to **15** (Figure 2B). The fact that one acetate peak was remarkably upshifted from ~172 to ~183 ppm and only 0.25 equivalent catalyst was added suggested that multiple **15** possibly coordinated to the hafnium center primarily via the anomeric acetate. In a control experiment, addition of up to 25 mol% $Nd(OTf)_3$, a transition metal Lewis acid with almost no catalytic activity (Table 1), caused no change to the ^1H NMR spectra of free **15** in CD_3CN (SI, Figure S1).

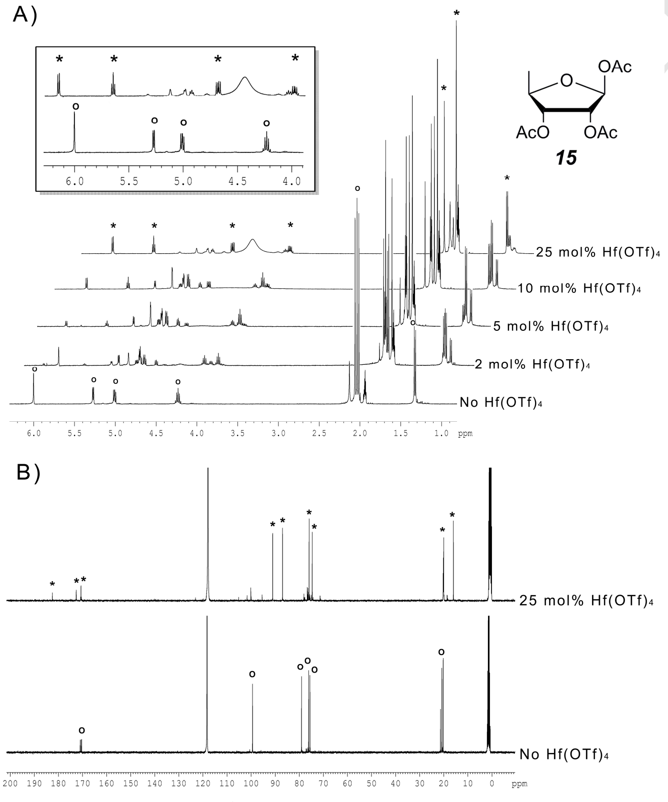


Figure 2. ^1H NMR (A) and ^{13}C NMR (B) studies on the interactions of 1,2,3-triacetyl-5-deoxy-D-ribose (**15**) with $Hf(OTf)_4$ in CD_3CN.

3. Conclusion

In summary, we have developed an efficient and general protocol for selective anomeric deacetylation of peracetylated saccharides. Compared to previously reported metal Lewis acids, $Hf(OTf)_4$ is identified as a much more potent catalyst. Moreover, it was found that the assistance of ultrasound may significantly accelerate the deacetylation process. The mechanistic investigations confirmed the hydrolysis nature of this reaction, and suggested that peracetylated saccharides may coordinate with Hf(IV) cation primarily via the anomeric acetate as reactive intermediate species.

4. Experimental section

4.1 General methods

Chemical reagents and solvents were obtained from commercial suppliers. Peracetylated saccharides were synthesized according to a reported method.[2a,24] Reactions were sonicated at 60 °C in an ultrasonic bath (40 KHz, power output 600W). All reactions were monitored by thin layer chromatography on plates coated with 0.25 mm silica gel 60 F_{254}. TLC plates were visualized by charring with 20% H_2SO_4 in EtOH. All NMR spectra were obtained with a 400 MHz instrument with chemical shifts reported in parts per million (ppm, δ) and referenced to $CDCl_3$. Low-resolution mass spectra were reported as *m/z* and obtained with an ion trap mass spectrometer.

4.2 General procedures for $Hf(OTf)_4$-catalyzed 1-O-deacetylation of peracetylated saccharides

To a solution of peracetylated saccharide (2.0 mmol) in commerical AR grade acetonitrile (15 mL) was added $Hf(OTf)_4$ (0.04 mmol). The reaction was sonicated at 60 °C for 3–4 h. The reaction was cooled to room temperature and triethylamine (0.4 mmol) was added. Then the solution was concentrated under vacuum. Flash column chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded 1-*O*-deacetylated product in pure form.

Supplementary Material

Supplementary data associated with this article can be found at

Acknowledgments

We thank the National Natural Science Foundation of China (21562021), Natural Science Foundation (20143ACB21014), Fellowship for Young Scientists (2015BCB23009), and Sci & Tech Project from Dept of Education (GJJ160763) of Jiangxi Province, and Innovation Foundation of JXSTNU (YC2016-X05 for R.W.) for financial support.

References

1. (a) P. Sears, C.-H. Wong, Science 291 (2001) 2344–2350; (b) M.J. McKay, H.M. Nguyen, ACS Catal. 2 (2012) 1563–1595.
2. (a) Q. Sun, Q.-K. Yang, S.-S. Gong, Q.-L. Fu, Q. Xiao, Bioorg. Med. Chem. 21 (2013) 6778–6787; (b) Q. Sun, X.-J. Li, J. Sun, S.-S. Gong, G. Liu, G.-D. Liu, Tetrahedron 70 (2014) 294–300.
3. J. Fiandor, M.T. García-López, F.G. Heras, P.P. Méndez-Castrillón, Synthesis 12 (1985) 1121–1123.
4. D. Weigelt, R. Kraehmer, P. Welzel, Tetrahedron Lett. 37 (1996) 367–300.
5. (a) M. Sim, H. Kondo, C.-H. Wong, J. Am. Chem. Soc. 115 (1993) 2260-2267; (b) B.N. Cook, S. Bhakta, T. Biegel, K.G. Bowman, J.I. Armstrong, S. Hemmerich, C.R. Bertozzi, J. Am. Chem. Soc. 122 (2000) 8612-8622.
6. J. Zhang, P. Kováč, J. Carbohyd. Chem. 18 (1999) 461–469.

7. R.M. Rowell, M.S. Feather, Carbohyd. Res. 4 (1967) 486–491.
8. N. Kunesch, C. Miet, J. Poisson, Tetrahedron Lett. 28 (1987) 3569–3572.
9. S.M. Andersen, M. Heuckendorff, H.K. Jensen, Org. Lett. 17 (2015) 944–947.
10. M. Tyagi, M. Govindarajan, K.P.R. Kartha, Trends Carbohyd. Res. 4 (2012) 18–22;
11. K.P.R. Kartha, B. Mukhopadhyay, R.A. Field, Carbohyd. Res. 339 (2004) 729–732.
12. A. Nudelman, J. Herzig, H.E. Gottlieb, Carbohyd. Res. 162 (1987) 145–152.
13. K. Bhaumik, P.D. Salgaonkar, K.G. Akamanchi, Aust. J. Chem. 56 (2003) 909–911.
14. G.-H. Wei, L. Zhang, C. Cai, S.-H. Cheng, Y.-G. Du, Tetrahedron Lett. 49 (2008) 5488–5491.
15. T. Sambaiah, P.E. Fanwick, M. Cushman, Synthesis 10 (2001) 1450–1452.
16. A.T. Tran, S. Deydier, D. Bonnaffé, C.L. Narvor, Tetrahedron Lett. 49 (2008) 2163–2165.
17. E. Kaya, F. Sonmez, M. Kucukislamoglu, M. Nebioglu, Chem. Pap. 66 (2012) 312–315.
18. (a) K. lshihara, S. Ohara, H. Yamamoto, Science 290 (2000) 1140–1142; (b) K. Ishihara, M. Nakayama, S. Ohara, H. Yamamoto, Tetrahedron 58 (2002) 8179–8188.
19. (a) H. Lundberg, F. Tinnis, H. Adolfsson, Chem. Eur. J. 18 (2012) 3822–3826; (b) H. Lundberg, H. Adolfsson, ACS Catal. 5 (2015) 3271–3277.
20. H. Lundberg, F. Tinnis, J. Zhang, A.G. Algarra, F. Himo, H. Adolfsson, J. Am. Chem. Soc. 139 (2017) 2286–2295.
21. (a) A.L. Marlow, L.L. Kiessling, Org. Lett. 3 (2001) 2517–2519; (b) S. Santra, E. Jonas, J.-P. Bourgault, T. El-Baba, P.R. Andreana, J. Carbohyd. Chem. 30 (2011) 27–40.
22. (a) D.S. Kristol, H. Klotz, R.C. Parker, Tetrahedron Lett. 22 (1981) 907–908; (b) A. Tuulmets, S. Salmar, H. Hagu, J. Phys. Chem. B 107 (2003) 12891–12896.
23. S. Salmar, G. Cravotto, A. Tuulmets, H. Hagu, J. Phys. Chem. B 110 (2006) 5817–5821.
24. (a) S.K. Giri, N. Yadav, K.P.R. Kartha, Trends Carbohyd. Res. 7 (2015) 6–27; (b) M.L. Wolfrom, A. Thompson, Acetylation, in: R.L. Whistler, M.L. Wolfrom (Eds.), Methods in Carbohydrate Chemistry, Academic Press Inc., New York, 1963, pp. 211–215.

- $Hf(OTf)_4$ is identified as a potent catalyst for selective anomeric deacetylation of peracetylated mono-, di-, and trisaccharides.
- Remarkable sonochemical effect on reaction rate is observed for $Hf(OTf)_4$-catalyzed regioselective deacetylation.
- NMR experimental data suggest that multiple peracetylated saccharide molecules may coordinate to Hf(IV) cation via the anomeric acetate as reactive intermediate species.