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Hafnium(IV) tetratriflate in selective reductive carbohydrate benzylidene acetal opening reaction and direct silylation reaction

Shino Manabe^{a,*}, Yukishige Ito^{a,b,*}

^a RIKEN, Synthetic Cellular Chemistry Laboratory, Hirosawa, Wako, Saitama 351-0198, Japan ^b ERATO, JST, Hirosawa, Wako, Saitama 351-0198, Japan

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ABSTRACT

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Regioselective ring opening of benzylidene acetals is an important reaction in the field of carbohydrate chemistry, as such acetals are valuable protecting groups for block 1,3-diols. Benzvlidene acetals can be opened selectively under appropriate reaction conditions to yield primary or secondary alcohols (Scheme 1).¹ Since Bhattacharjee and Gorin introduced the method to the field of carbohydrate chemistry,² a number of effective systems for achieving reductive benzylidene acetal ring opening have been reported. Of these, AlH₃ and *i*-Bu₂AlH have been used to obtain cleavage at the O6 position,^{3,4} and Et₃SiH–Lewis acid combinations have been shown to cleave at the O4 position.⁵ For the reaction mediated by Et₃SiH, the amount of Lewis acid required is usually more than stoichiometric, and the reaction takes several hours to complete. Recently, various metal triflates such as Cu(OTf)₂ and V(O)(OTf)₂ have been reported to be effective Lewis acid catalysts for this reaction.^{6,7} We carried out the Cu(OTf)₂ (5 mol %) catalyzed benzylidene cleavage reaction of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-\alpha-D-glucopyranoside 1 using Et₃SiH (2 equiv) in CH₃CN according to Hung's procedure,⁷ giving 4-hydroxy alcohol 2f (67%) and the corresponding TES ether 2a (21%). Although the concomitant TES formation reaction was not reported by Hung, we were interested in direct TES ether formation during the benzylidene acetal cleavage reaction. As an initial attempt, we focused on Hf(OTf)₄, as it was recently found to be a good mediator of glycosyl fluoride activation in an operationally simple manner.⁸



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Scheme 1. Regioselective reductive benzylidene cleavage reaction and concomitant silylation reaction.

Kobayashi and other groups have reported that Hf(OTf)₄ is an effective Lewis acid for a variety of different reactions.⁹ We therefore speculated that Hf(OTf)₄ could work as an effective Lewis acid for the regioselective benzylidene acetal cleavage reaction and concomitant silylation reaction.

As the opening of methyl 2,3-di-O-benzyl-4,6-O-benzylidene- α p-glucopyranoside **1** has evolved into a standard reaction when comparing different methods for reactions of this type, we selected this as an initial substrate for optimizing the synthesis conditions. The reaction was completed in the presence of 2 equiv of Et₃SiH and 0.05 equiv of Hf(OTf)₄ within 30 min (Table 1, entry 1). The ratio of direct TES ether formation was increased using Hf(OTf)₄. 4-alcohol **2f** and its corresponding TES ether **2a** were obtained in 37% and 44% yields, respectively. To facilitate the purification process, the TES group of compound **2a** was cleaved under aqueous conditions in a one-pot reaction by the addition of 1 M HCl (entry 2). The yield of alcohol **2f** was reduced after a prolonged reaction period of up to 2 h (entry 3). When the amount of Hf(OTf)₄ was increased to 15 mol %, yield of alcohol **2f** was increased (entry 4).







^{*} Corresponding authors. Tel.: +81 467 9432; fax: +81 462 4680 (S. Manabe); tel.: +81 467 9430; fax: +81 462 4680 (Y. Ito).

E-mail addresses: smanabe@riken.jp (S. Manabe), yukito@riken.jp (Y. Ito).

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Table 1

Regioselective benzylidene acetal cleavage reaction catalyzed by Hf(OTf)₄



Entry	Reducing reagent	Lewis acid amount (mol %)	Time (h)	Solvent	Products	2a-2e (%)	2f (%)	Recovery of 1 (%)
1	Et₃SiH	5	1/2	CH ₃ CN	2a	44	37	0
2	Et ₃ SiH ^a	5	1/2	CH ₃ CN	2a	0	79	0
3	Et₃SiH	5	2	CH₃CN	2a	44	28	0
4	Et ₃ SiH	15	1/6	CH ₃ CN	2a	24	62	0
5	Et ₃ SiH	1	3 + 1/2	CH ₃ CN	2a	53	33	0
6	Et₃SiH	5	1/2	CH_2Cl_2	2a	21	26	0
7	Et₃SiH	5	1/2	Toluene	2a	0	0	90
8	Et₃SiH	5	1/2	Et ₂ O	2a	0	0	94
9	Me ₂ EtSiH	5	1/3	CH₃CN	2b	13	58	0
10	iPr₃SiH	5	1/2	CH ₃ CN	2c	11	16	64
11	Ph ₃ SiH	5	1	CH ₃ CN	2d	0	23	46
12	TMS₃SiH	5	1/2	CH₃CN	2e	0	12	80
13 ^b	BH ₃ ·THF	5	2	CH₃CN	_	0	0	0
14 ^b	BH ₃ ·NMe ₃	5	12	CH₃CN	-	0	0	80
15 ^c	Et ₃ SiH ^g	200	2	CH_2Cl_2	2a	0	77	0

^a After the reaction, 1 M HCl ag was added and the mixture was stirred for 0.5 h.

^b The reaction was carried out at room temperature.

^c 2 equiv of BF₃·OEt₂ and 12 equiv of Et₃SiH were used.



Instead, with reduced amount of Hf(OTf)₄ with 1 mol %, yield of TES ether 2a was increased (entry 5). It is likely that the TES ether was cleaved owing to the acidity of Hf(OTf)₄ itself. In CH₂Cl₂, the reaction became more complex, with 6-alcohol 3 obtained in 7% yield together with 4-alcohol 2f and its silylated product 2a (entry 6). No reaction was observed in toluene and Et₂O, and the starting material was recovered (entries 7 and 8). When the less hindered reducing reagent, Me₂EtSiH, was employed, the efficacy of the reaction did not change significantly (entry 9), but with hindered reducing reagents such as Ph₃SiH and TMS₃SiH, the yield of alcohol was lowered and the silyl ether was not obtained (entries 11 and 12). Although the use of a $Cu(OTf)_2$ -mediated reaction enables the regiochemistry to be controlled to either the O4 or O6 position by merely changing the reducing reagent, unfortunately, when Hf(OTf)₄ was used with BH₃·THF as the reducing reagent, the benzylidene group was removed to give diol 4 in 92% yield (entry 13). When BH₃·NMe₃ was employed, no reaction was observed and starting material 1 was recovered in good yield (entry 14). Under the same reaction conditions as those reported in reference 5a, and using 12 equiv of Et₃SiH and 2 equiv of BF₃·OEt₂, 2f was obtained in 77% yield, together with **3** in 6% yield after 2 h (entry 15). Compared with the conventional method (entry 15), the Hf(OTf)₄-mediated reductive benzylidene cleavage reaction has clear advantages.

We next investigated the scope and limitations of this method. Using the conditions as the same as in entry 1 in Table 1, (5 mol % Hf(OTf)₄, CH₃CN, 4 °C, 30 min), we examined glucose **5** and **6**, glucosamine **7** and **8**, mannose **9** and **10**, galactose **11**, and disaccharide **12** with various protecting groups. In addition to the benzyl group, the azide, allyl, acyl, and phthaloyl groups were all found to be stable under these conditions (Table 2). Galactose derivative **11** also gave good results (entry 7). Disaccharide **12** readily underwent the benzylidene ring opening reaction to give compounds **20a** and **20b** in good yield (entry 8). Although it is known that substituents at C3 position may affect regioselectivity,^{1,10} our conditions gave 6-benzyl products regardless the protecting groups of the 3-hydroxy group.

To elucidate the details of the reaction mechanism, Et₃SiD was used as a deuteride source (Scheme 2).^{1,11,12} Hung and Ellervik reported that the benzylidene acetal cleavage reaction proceeds via either an S_N1 or S_N2 pathway, depending on the particular combination of solvent, reducing reagent, and Lewis acid. Using the reaction conditions listed as in entry 1 in Table 1, with the deuterated reducing reagent Et₃SiD, we carried out the Hf(OTf)₄-catalyzed reaction with compound 1. Products 21 and 22 were given in 35% and 55% yields, respectively. As previously reported by Hung, the stereochemistry at the benzylic position was found to be a 49:51 (R/S) mixture. TES ether 22 also gave mixture of (R) and (S) compounds at the benzylic position. Treatment of 22 with TBAF gave 21R:21S in a 53:47 ratio in 93% yield. The reason for this slightly different R/S ratio is not currently clear, with further experimentation required in order to elucidate this. Overall, these results demonstrate that the Hf(OTf)₄-catalyzed benzylidene cleavage reaction proceeded via an S_N1 mechanism.

In conclusion, $Hf(OTf)_4$ has been shown to be an effective catalyst for the regioselective benzylidene acetal cleavage reaction and direct TES ether formation. Although the mechanism of TES ether formation is not clear at this point, the selective protection of the 6-OH and 4-OH of pyranosides would be useful for further transformation. As $Hf(OTf)_4$ is a commercially available solid that is easy to handle in air, the developed method has great potential in the field of organic synthesis.

Table 2

Scope and limitations of Hf(OTf) ₄ -catalyze	d regioselective	benzylidene	acetal	cleav
age reaction				



Typical experimental procedure

To a solution of substrate (1.0 M) and Et₃SiH (2 equiv) in CH₃CN, $Hf(OTf)_{4}$ (0.05 equiv) was added at 4 °C. After consumption of the starting material, as determined by TLC or by leaving an adequate period of time, the reaction was guenched with satd NaHCO₃, and the aqueous layer was extracted several times with EtOAc. The combined layers were washed with brine and dried over Na₂SO₄. After concentration, the crude product was purified by preparative TLC.



Scheme 2. Stereochemistry of deuteride incorporation at the benzylic position.

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Supplementary data

Supplementary data (experimental, ¹H NMR, ¹³C NMR, and HRMS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.011.

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