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The Evaluation of Catalysts Generated from Lewis Acids and Silver Perchlorate in a Highly Stereoselective Glycosylation of 1-O-Acetyl-D-glucose

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A catalytic cycle was effectively performed in highly stereoselective glycosylation of 1-O-acetyl-D-glucose by using active species generated from respective combinations of Lewis acids ($SnCl_4$, $GeCl_4$, $SiCl_4$, $GaCl_3$, $InCl_3$, and $HfCl_4$) and silver perchlorate.

Recently, we have reported a new and useful glycosylation reaction starting from 1-O-acetyl-D-glucose and trimethylsilyl alkoxides using a catalytic amount of active species generated from $SnCl_4$ and $AgClO_4$.1) A catalytic cycle is effectively performed there to produce the corresponding α-glucosides in 86-95% yields (α/β=90/10-97/3). It was expected that, in addition to the above mentioned tin(IV) compound, a variety of active species could be generated from respective combinations of Lewis acids, such as Si,2) Ti, Zr, Hf3)and Ga4) compounds, and $AgClO_4$. Then we started to investigate the glycosylation using other Lewis acids to search for a more efficient catalyst than using $SnCl_4$.

First, several combinations of Lewis acids including the group 3, 13, and 14 metals and $AgClO_4$ were screened taking the glycosylation of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose **1** (α/β=4/1) with 3β-cholestanyl trimethylsilyl ether as a model reaction (see Table 1). Among them, catalysts generated from Lewis acids, such as $SnCl_4$, $GeCl_4$, $SiCl_4$, $GaCl_3$, $InCl_3$ and $HfCl_4$, and $AgClO_4$ were found to lead to the formation of the corresponding glycosides effectively in high diastereomeric ratios (α/β=93/7-94/6).

The introduction of the perchlorate group in place of the chlorine atom is thought to increase the acidity of the Lewis acids to promote the abstraction of the acetoxy group from 1-O-acetyl-D-glucose. Actually when a Lewis acid itself was employed without $AgClO_4$ in ether, the reaction did not proceed at all. Moreover, when the ratio of a Lewis acid and $AgClO_4$ was 1:2, a better catalytic activity was shown compared with that of 1:1.3) In cases of the group 14 metals, which gave the desired glycosides in very high yields at 1:1 ratio, the yields decreased at 1:2 ratio probably because of overreaction.

The formation of the above mentioned active catalytic species ($MCl_{n-1}(ClO_4)$ and $MCl_{n-2}(ClO_4)_2$) were confirmed through the experiment that the theoretical amount of silver chloride precipitated, for example, when $SbCl_5$ (1 mmol) and $AgClO_4$ (2 mmol) were stirred for 1h in ether at room temperature in the dark. On the other hand, in cases of using catalytic species generated from BCl_3, $AlCl_3$, and $TiCl_4$, unstable byproduct was formed probably because of their too strongly acidic character, and , in addition, increase in stability of the metal-acetate bond prevented the catalytic cycle, thus the yields of the desired glycosides were poor.

In the above mentioned reaction, ether which employed as the solvent showed higher stereoselectivity compared with other solvents such as dichloromethane or toluene.5)

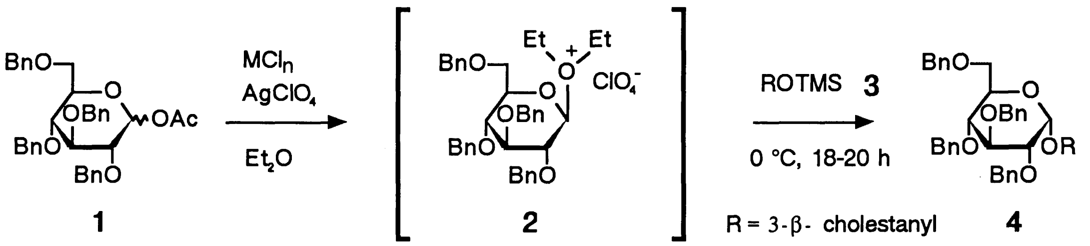


Table 1. Effect of Lewis Acid

Entry	Metal group	Lewis acid	20 mol%(1:1) Yield/%	20 mol%(1:1) α / β	20 mol%(1:2) Yield/%	20 mol%(1:2) α / β
1	4	$TiCl_4$	45	93 / 7	62	94 / 6
2	4	$ZrCl_4$	73	92 / 8	92	94 / 6
3	4	$HfCl_4$	90	93 / 7	95	94 / 6
4	8	$FeCl_3$	61	92 / 8	92	93 / 7
5	13	BCl_3	64	93 / 7	61	94 / 6
6	13	$AlCl_3$	15	89 / 11	72	90 / 10
7	13	$GaCl_3$	84	93 / 7	89	92 / 8
8	13	$InCl_3$	81	93 / 7	78	94 / 6
9	14	$SiCl_4$	90	94 / 6	73	93 / 7
10	14	$GeCl_4$	82	93 / 7	72	93 / 7
11	14	$SnCl_4$	91	94 / 6	88	93 / 7
12	15	$SbCl_5$	21	92 / 8	99	89 / 11

Secondly, these selected six combinations were further applied to the syntheses of disaccharides using **1** and two methyl α-D-glucoside derivatives (**5** and **6**) as nucleophilic components, and also to the synthesis of the glycosyl amino acid using Z-serine derivative **7** as a starting material (See Table 2). Consequently, high yield and stereoselectivity were observed in cases of using catalytic species derived from $SnCl_4$ and $GaCl_3$.

The reactivity sequence of combinations of Lewis acids including the group 14 metals and AgClO4 is shown to be in the following order, Sn>Ge>Si. Also the following orders were shown concerning the group 13 metals, In=Ga>B>>Al, and the group 4 metals, Hf>Zr>Ti.

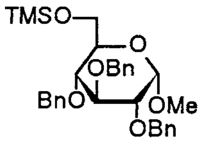
In order to perform the catalytic cycle in the present glycosylation, the catalytic species initially accepts acetoxy group from 1-O-acetyl-D-glucose to generate the active ionic intermediate **2** along with the metal acetate. This intermediate including coordinated ether is stabilized by the bulky counter ion, the perchlorate anion, which blocks the β-side of the anomeric carbon. Hence the intermediate **2** is attacked in succession from α-side by trimethylsilyl alkoxide to form the α-glucoside selectively along with trimethylsilyl perchlorate. The key point here is that, in cases of effective catalytic species (Sn, Ge, Si, Ga, In, and Hf), metal acetate would readily react with trimethylsilyl perchlorate to regenerate the catalytic species along with trimethylsilyl acetate.

A typical experimental procedure is as follows; a toluene solution of 0.5 M $GaCl_3$ (0.06 ml) was added to $AgClO_4$ (0.03 mmol) suspended in ether (2.5 ml) at room temperature, and the mixture was stirred for 1h in the dark. To this mixture was added an ethereal solution (2.5 ml) of **1** (0.15 mmol) and **3** (0.18 mmol) at 0 °C.

Table 2. Synthesis of α-glucosides

		5 a)		**6** b)		**7** c)	
Entry	Lewis acid	Yield/%	α / β	Yield/%	α / β	Yield/%	α / β
1	$HfCl_4$	95	97 / 3	60	91 / 9	74	91 / 9
2	$GaCl_3$	95	96 / 4	84	91 / 9	86	94 / 6
3	$InCl_3$	88	97 / 3	83	91 / 9	18	94 / 6
4	$SiCl_4$	73	97 / 3	69	90 / 10	65	95 / 5
5	$GeCl_4$	90	96 / 4	68	89 / 11	83	95 / 5
6	$SnCl_4$	95	97 / 3	86	90 / 10	95	92 / 8

a)



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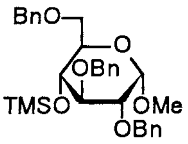

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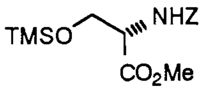

After stirring the mixture for 18h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by TLC afforded **4** (91.2%) and β-anomer (3.8%).

Thus, highly stereoselective glycosylation was successfully carried out starting from 1-O-acetyl-D-glucose and trimethylsilyl alkoxides by using the catalytic amount of active species generated from 1:1 or 1:2 ratio of several Lewis acids and $AgClO_4$. Of these Lewis acids, $SnCl_4$ and $GaCl_3$ were most effective.

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