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Rare Earth Perchlorate Catalyzed Glycosidation of Glycosyl Fluorides with Trimethylsilyl Ethers

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Abstract: A glycosidation of glycosyl fluorides with trimethylsilyl ethers has been found to be promoted more effectively by catalytic $La(ClO_4)_3$ than by stoichiometric amounts of rare earth salts. A mechanism for the present glycosidation is proposed.

Development of stereoselective glycosidation reactions is an important topic in carbohydrate chemistry. Hence, a variety of glycosidation methods[1a] have been developed since the first use of the classical Königs-Knorr synthesis.[1b] Of these methods, glycosyl fluorides have most frequently been employed as donors in the synthesis of complex sugar chains.[2] These fluorides have been glycosidated in the presence of various Lewis acids such as $SnCl_2$-$AgClO_4$,[3a] Cp_2MCl_2-$AgClO_4$ (M = Ti, Zr, Hf),[3b] SiF_4,[3c] Me_3SiOTf,[3c] $BF_3{\cdot}Et_2O$,[3d] Me_2GaX (X = Cl, OTf),[3e] TiF_4,[3f] and Tf_2O.[3g]

Recently, we succeeded in developing a new method for the glycosidation of glycosyl fluorides promoted by stoichiometric amounts of rare earth salts, which has allowed us to achieve several notable glycosidation reactions.[4] In an attempt to improve the new glycosidation reaction, we have found that a catalytic amount of rare earth perchlorate more effectively promotes the condensation of appropriately protected glycosyl fluorides and trimethylsilyl ethers[5] than does the stoichiometric method. Furthermore, a possible mechanism for the catalytic procedure is supported by ^{19}F NMR spectral data.

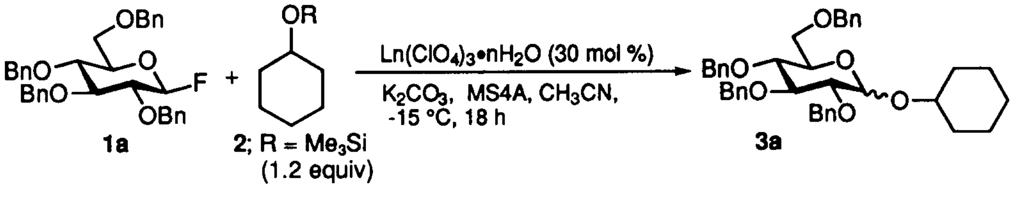

Table 1. Glycosidation Reactions Using Rare Earth Perchlorates

Entry	$Ln(ClO_4)_3{\cdot}nH_2O$	R	Yield (%)	α : β
1	$La(ClO_4)_3{\cdot}nH_2O$	Me_3Si	82	8 : 92
2	$Ce(ClO_4)_3{\cdot}nH_2O$	Me_3Si	89	β[a]
3	$Pr(ClO_4)_3{\cdot}nH_2O$	Me_3Si	80	β[a]
4	$Eu(ClO_4)_3{\cdot}nH_2O$	Me_3Si	61	15 : 85
cf [b]	$Yb(OTf)_3$[c]	H	63	6 : 94

[a] α-Anomer was not detectable by ^1H NMR analysis.
[b] See reference 4. [c] 1.2 equiv was used.

We began examining the reactivity of rare earth perchlorate hydrates in the glycosidation reaction of the glucose derivative **1a** and cyclohexyl trimethylsilyl ether **2**. Of the many types of rare earth salts available, we chose rare earth perchlorates because of the increased fluorophilicity of the metal cations.[6] We were pleased to find that several rare earth perchlorates were highly efficient in promoting this type of reaction. For β-selectivity, the use of 30 mol % of $La(ClO_4)_3 \cdot nH_2O$, $Ce(ClO_4)_3 \cdot nH_2O$ or $Pr(ClO_4)_3 \cdot nH_2O$, in the presence of K_2CO_3 (4 mol equiv) and MS4A in CH_3CN was found to be most effective (Table 1, entry 1, 2, 3).[7, 8] Under these conditions the β-glycoside **3a** was obtained in a highly stereocontrolled manner[9] more efficiently than the previous procedure,[4] which gave **3a** in 63% yield (α : β = 6 : 94). In addition, we also found that the α-glycoside was obtained exclusively (94%) on treatment of **1a** with **2**, $La(ClO_4)_3 \cdot nH_2O$ (30 mol %), $CaCO_3$ (4 mol equiv), MS4A in Et_2O (Table 2, entry 1). To better understand the mechanism of this glycosidation reaction, we obtained the ^{19}F NMR spectrum of the reaction mixture in acetonitrile-d_3, and only trimethylsilyl fluoride was observed.[10] This result suggests that the interaction of the glycosyl fluoride with the rare earth perchlorate produces an oxonium cation intermediate, which then reacts with the trimethylsilyl ether to form the glycoside, trimethylsilyl fluoride, and rare earth perchlorate, thereby making possible the catalytic cycle. Furthermore, it is noteworthy that the glycosidation does not proceed in the presence of rare earth perchlorates such as $Gd(ClO_4)_3 \cdot nH_2O$, $Ho(ClO_4)_3 \cdot nH_2O$, $Yb(ClO_4)_3 \cdot nH_2O$, $Y(ClO_4)_3 \cdot nH_2O$, suggesting that only rare earth metals with a certain range of ionic radii are effective for this type of glycosidation. On the basis of the above results, we have selected $La(ClO_4)_3 \cdot 7H_2O$ as an economical catalyst for this reaction.[11]

Next we examined the glycosidation reaction of **1a** with the 2,3,4- and 2,3,6-benzyl protected glucopyranoside derivatives **4** and **5**. As shown in Table 2, these reactions were found to proceed smoothly, giving **6a** (85%, α : β = 9 : 91), **6a** (94%, α : β = 75 : 25), **7a** (75%, α : β = 23 : 77), and **7a** (63%, α : β = 78 : 22).[12] Also in these cases, improved results were obtained in comparison with the stoichiometric procedure.[4] For example, it has been reported that the stoichiometric reaction of **1a** with **4** affords **6a** (68%, α : β = 12 : 88).

Some other examples of the $La(ClO_4)_3$ catalyzed glycosidation reactions using benzoyl or acetyl protected glycosyl fluorides[13] are also summarized in Table 2. The reactions were found to proceed quite smoothly, affording only the β-glycosides **6b**,[14] **6c**,[15] **7b**,[14] and/or **7c**[15] in good to excellent yields. Particularly noteworthy are the glycosidations using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride **1c** (Entry 6 and 10), because no reaction had occurred using the stoichiometric procedure.[4]

Finally, this glycosidation method was applied in the synthesis of the trisaccharide of an intermediate leading to globotriaosyl ceramide.[16] It has been well established that glycosphingolipides are molecules of considerable biological significance within the area of cellular recognition. We were pleased to find that the $La(ClO_4)_3$ catalyzed glycosidation reaction of the galactosyl fluoride **8** with the lactosyl derivative **9**[16] proceeded efficiently to give the α-trisaccharide **10** exclusively in 81% yield.[17]

In conclusion, we have succeeded in developing an improved glycosidation reaction catalyzed by rare earth perchlorate. We believe that this glycosidation reaction could play a key role in glycosidations using glycosyl fluorides as glycosyl donors. Further studies of this reaction are currently underway.

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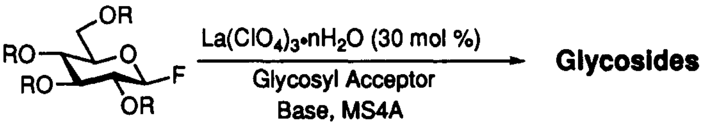
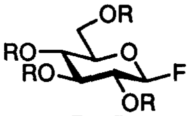
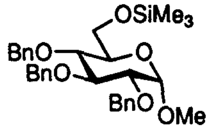




1a; R = Bn
1b; R = Bz
1c; R = Ac



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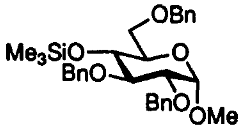

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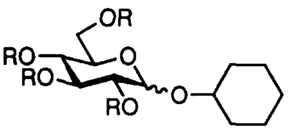
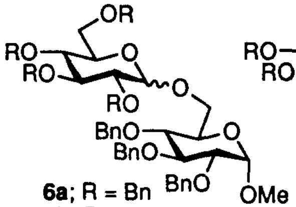
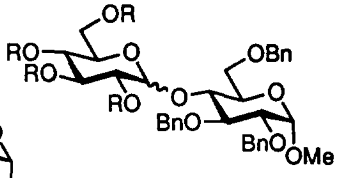


3a; R = Bn
3b; R = Bz



6a; R = Bn
6b; R = Bz
6c; R = Ac

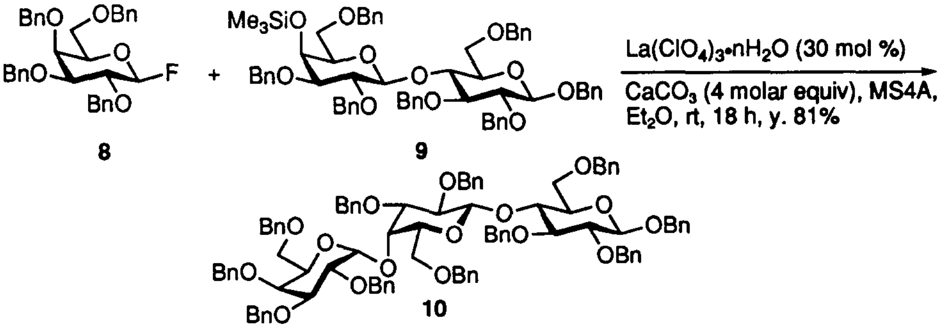


7a; R = Bn
7b; R = Bz
7c; R = Ac

Table 2. Glycosidation Reactions by La(ClO$_4$)$_3$•nH$_2$O (30 mol %)

Entry	Glycosyl Donor	Glycosyl Acceptor[a]	Solv.	Base[b]	Temp. (°C)	Time (h)	Glycosides	Yield (%)	α : β
1	**1a**	**2**	Et$_2$O	CaCO$_3$	rt	18	**3a**	94	α[d]
2	**1b**	**2**	CH$_3$CN	K$_2$CO$_3$	0	2	**3b**	94	β
3	**1a**	**4**	CH$_3$CN	K$_2$CO$_3$	-15	38	**6a**	85	9 : 91
4	**1a**	**4**	Et$_2$O	CaCO$_3$	rt	18	**6a**	94	75 : 25
5	**1b**	**4**	CH$_3$CN	K$_2$CO$_3$	rt	2	**6b**	93	β
6	**1c**	**4**	CH$_3$CN	K$_2$CO$_3$	5	1	**6c**	80	β
7	**1a**	**5**	CH$_3$CN	K$_2$CO$_3$	-15	38	**7a**	75	23 : 77
8	**1a**	**5**	Et$_2$O	CaCO$_3$	rt	24	**7a**	63	78 : 22
9	**1b**	**5**[c]	CH$_3$CN	K$_2$CO$_3$	rt	1	**7b**	99	β
10	**1c**	**5**	CH$_3$CN	K$_2$CO$_3$	5	1	**7c**	75	β

[a] 1.2 equiv was used. [b] 4 molar equiv was used. [c] 1.5 equiv was used. [d] β-Anomer was not detectable by ^{1}H NMR analysis.



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5. For other examples of catalytic glycosidations of glycosyl fluorides and trimethylsilyl ethers; see references 3c and 3d, and references cited therein.
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7. Anhydrous rare earth perchlorates may explode; see references 6b and 6c.
8. The glycosidation reaction of **1a** with **2** by 20 mol % of $La(ClO_4)_3 \cdot nH_2O$, K_2CO_3 and MS4A in CH_3CN at room temperature also gave the product in 95% yield ($\alpha : \beta = 36 : 64$).
9. The structures of α- and β-anomers were determined by ^1H- and ^{13}C-NMR after separation by silica gel column chromatography.
10. The procedure of the NMR study is as follows. Treatment of **1a** with **2**, 20 mol % of $La(ClO_4)_3$, K_2CO_3 and MS4A in CD_3CN at room temperature for 1 h, and the ^{19}F NMR spectrum was measured after filtration. The chemical shift of trimethylsilyl fluoride was found to be at -29 ppm (external standard CF_3COOH at -76.5 ppm).
11. Purchased from Soekawa Chemical Co., Ltd., Tokyo, Japan ($La(ClO_4)_3 \cdot 7H_2O$ is cheaper than $Ce(ClO_4)_3 \cdot 8H_2O$ and $Pr(ClO_4)_3 \cdot 6H_2O$).
12. A representative procedure: First $La(ClO_4)_3 \cdot 7H_2O$ (30 mol % to a glycosyl donor), K_2CO_3 (4.0 mol equiv) and MS4A (ca. 50 mg) were dried at ca. 180 °C in vacuo for 2 h, leaving about two waters of hydration. A CH_3CN solution (2 mL) of the glycosyl fluoride **1a** (54.2 mg, 0.1 mmol) and the glycosyl acceptor **4** (1.2 equiv) was then added at -15 °C. After the reaction was complete, saturated aq. $NaHCO_3$ was added. Filtration to remove inorganic compounds and usual work up gave a product which was purified by silica gel column chromatography. Undried $La(ClO_4)_3 \cdot 7H_2O$ is also effective as a catalyst. Glycosidation of **1a** with **4** in the presence of $La(ClO_4)_3 \cdot 7H_2O$ (30 mol %), $CaCO_3$ and MS4A in Et_2O at room temperature afforded **6a** in 89% yield ($\alpha : \beta = 75 : 25$).
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17. The stoichiometric procedure gave **10** in 75% yield.

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