A New Glycosylation Procedure Utilizing Rare Earth Salts and Glycosyl Fluorides, with or without the Requirement of Lewis Acids

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Stereoselective glycosylation reactions have an important role in carbohydrate chemistry. A variety of glycosylation methods[1a] have been exploited since the advent of the classical Koenigs–Knorr synthesis.[1b] Typical methods most frequently employ glycosyl fluorides as donors in the synthesis of rather complex sugar chains.[2] These fluorides have been glycosylated 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] Most commonly, $SnCl_2$–$AgClO_4$ or Cp_2MCl_2–$AgClO_4$ have been utilized. We have developed a more cost-effective and powerful glycosylation reaction using glycosyl fluorides. This method uses rare earth metal salts, glycosyl fluorides, and glycosyl acceptors, with or without the usual Lewis acids, $ZnCl_2$ and $Ba(ClO_4)_2$. The basic idea evolved from the realization that the rare earth metal–fluorine bond has a large bond dissociation energy.[4,5]

We began with an examination of the fluorophilicity of rare earth metal salts by carrying out the reaction of the glucose derivative **1**[6] with cyclohexanol **2** under a variety of conditions (Figure 1). We were pleased to find that several rare earth metal salts were highly efficient in this reaction. For β-selectivity, the use of $Yb(OTf)_3$, K_2CO_3, and MS4A[7] in MeCN was found to be most effective (run 1, Table 1). On the other hand, for α-selectivity, the utilization of either $Y(OTf)_3$ or $YbCl_3$ in ether, containing $CaCO_3$ and MS4A, gave the best result (runs 2 and 3, Table 1). Under these conditions the β- and α-glycosides **3β** and **3α**, respectively, were obtained in a highly stereocontrolled manner.[8] We assume that the mechanism of these glycosylation reactions entails an oxonium cation intermediate,[9] since use

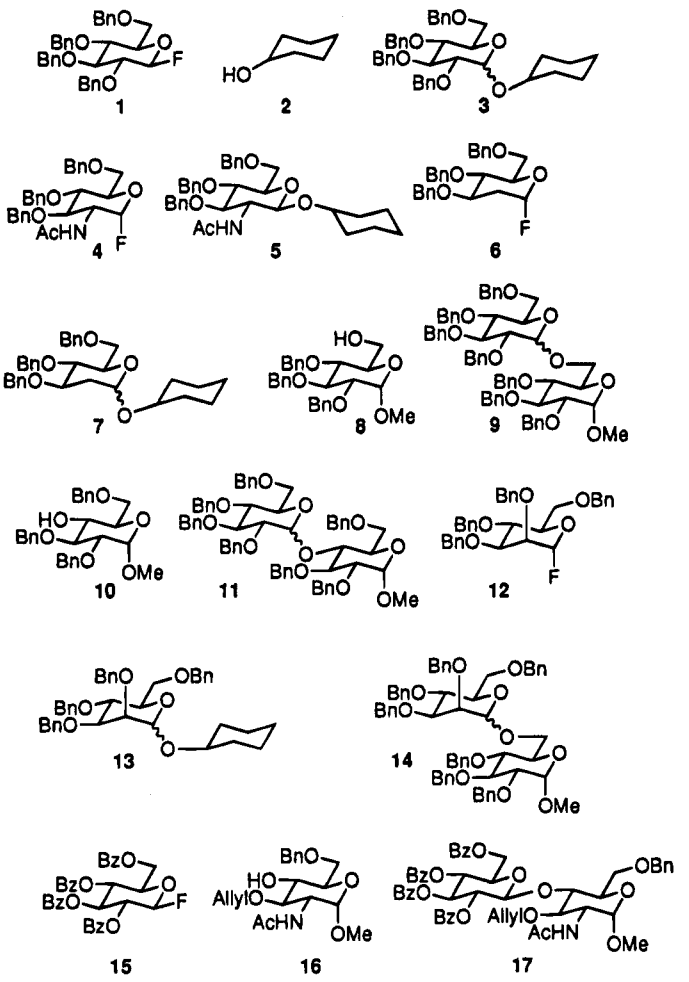

Figure 1. Glycosyl donors and acceptors and synthesized glycosides.

of CH_3CN as a solvent gave β-selectivity and use of Et_2O gave α-selectivity. With these excellent results in hand, we then turned our attention to the synthesis of 2-acetamido-2-deoxy-β-glycoside of the type **5**. 2-Acetamido-2-deoxy-β-glycosides are very important components of peptidoglycans, glycoproteins, mucopolysaccharides, and blood group determinants. To the best of our knowledge, no direct glycosylation reaction using glycosyl fluorides with the 2-acetamide moiety has been reported. Thus, it was noteworthy that treatment of **4**[6] with cyclohexanol (**2**) (1.2 equiv) in MeCN, containing $Yb(OTf)_3$ (1.2 equiv) and MS4A, gave only the β-glycoside **5**[8] in 70% yield (run 4, Table 1). Interestingly, when this glycosylation reaction was carried out in the presence of K_2CO_3, only the corresponding oxazoline was formed. Next the reaction was applied with the 2-deoxy sugar **6** as a glycosyl donor. Until now few experiments with 2-deoxy sugars have been reported, probably due to difficulties with control of reaction at the anomeric center.[10] It was found that exposure of **6**[6] to cyclohexanol **2** (1.2 equiv), $Yb(OTf)_3$ (1.2 equiv), K_2CO_3 (4.0 equiv), and MS4A in MeCN at −15 °C for 2 h gave **7** in 73% yield (α:β = 19:81) (run 5, Table

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(7) Less satisfactory results were obtained in the absence of MS4A. For the use of MS4A in glycosylation reactions, see: (a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430 and references cited therein.

(8) The structures of two isomers, α- and β-anomer, were determined by ^1H- and ^{13}C-NMR after silica gel column separation.

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Table 1. Glycosylation Reactions[a] Using Rare Earth Metal Salts

entry	glycosyl donor	glycosyl acceptor[b]	glycoside	rare earth metal salt[c]	solvent	base[d]	additive[e]	temp (°C)	time (h)	yield (%)	α:β
1	**1**	**2**	**3**	$Yb(OTf)_3$	CH_3CN	K_2CO_3		−15	3.5	63	6:94
2	**1**	**2**	**3**	$Y(OTf)_3$	Et_2O	$CaCO_3$		rt	22	96	94:6
3	**1**	**2**	**3**	$YbCl_3$	Et_2O	$CaCO_3$		rt	17	98	97:3
4	**4**	**2**	**5**	$Yb(OTf)_3$	CH_3CN			rt	14	70	β
5	**6**	**2**	**7**	$Yb(OTf)_3$	CH_3CN	K_2CO_3		−15	2	73	19:81
6	**6**	**2**	**7**	$YbCl_3$	Et_2O	$CaCO_3$		rt	4	88	50:50
7	**1**	**8**	**9**	$Yb(OTf)_3$	CH_3CN	K_2CO_3		−15	3.5	68	12:88
8	**1**	**8**	**9**	$Y(OTf)_3$	Et_2O	$CaCO_3$		rt	17	88	80:20
9	**1**	**10**	**11**	$Yb(OTf)_3$	CH_3CN	K_2CO_3		rt	21	50	30:70
10	**1**	**10**	**11**	$Yb(OTf)_3$	CH_3CN	K_2CO_3	$ZnCl_2$	rt	0.5	77	38:62
11	**1**	**10**	**11**	$Yb(OTf)_3$	CH_3CN	K_2CO_3	$Ba(ClO_4)_2$	rt	0.5	79	39:61
12	**1**	**10**	**11**	$Yb(OTf)_3$	CH_3CN	K_2CO_3	$ZnCl_2$	−15	38	61	22:78
13	**1**	**10**	**11**	$Yb(OTf)_3$	CH_3CN	K_2CO_3	$Ba(ClO_4)_2$	−15	38	81	23:77
14	**1**	**10**	**11**	$Y(OTf)_3$	Et_2O	$CaCO_3$		rt	41	66	74:26
15	**12**	**2**	**13**	$Yb(OTf)_3$	toluene	K_2CO_3		rt	37	94	35:65
16	**12**	**2**	**13**	$Yb(OTf)_3$	toluene	K_2CO_3	$ZnCl_2$	rt	2	100	39:61
17	**12**	**8**	**14**	$Yb(OTf)_3$	toluene	K_2CO_3	$ZnCl_2$	rt	42	94	60:40
18	**12**	**8**	**14**	$Y(OTf)_3$	toluene	$CaCO_3$		rt	87	74	58:42
19	**15**	**16**	**17**	$Yb(OTf)_3$	CH_3CN	K_2CO_3	$Ba(ClO_4)_2$	55	14	52	β
20	**15**	**16**	**17**	$La(ClO_4)_3$[f]	CH_3CN	K_2CO_3		−15	38	73	β

[a] All reactions were carried out in the presence of MS4A. [b,c] 1.2 equiv was used. [d] 4 molar equiv was used. [e] $ZnCl_2$, $Ba(ClO_4)_2$; 0.6 equiv was used. [f] 2.4 equiv of $La(ClO_4)_3 \cdot 7H_2O$ was used.

1),[8] while treatment of **6** with cyclohexanol **2** (1.2 equiv) in ether, in the presence of $YbCl_3$ (1.2 equiv), $CaCO_3$ (4.0 mol equiv), and MS4A at room temperature for 4 h, afforded **7** in 88% yield (α:β = 50:50) (run 6, Table 1).[8] Moreover, the glycosylation reaction was successfully applied to the synthesis of **9β** and **9α**. As shown in Table 1, **1** was stereoselectively converted to **9β** in 68% yield (α:β = 12:88, run 7), while **1** was also transformed into **9α** stereoselectively in 88% yield (α:β = 80:20, run 8).[8] Likewise, the glycosyl fluoride **1** was converted to **11** (α:β = 30:70),[8] albeit in modest yield (50%, run 9). We have found that addition of the usual Lewis acids such as $ZnCl_2$ and $Ba(ClO_4)_2$ greatly accelerates the glycosylation reaction and also improves the chemical yield (runs 10–13). As expected, **1** remained unchanged by treatment with only the usual Lewis acids, MS4A and K_2CO_3 in MeCN, strongly suggesting that $Yb(OTf)_3$ was activated by the interaction with the usual Lewis acids, especially $Ba(ClO_4)_2$.[11,12] On the other hand, exposure of **1** to **10**, $Y(OTf)_3$ (1.2 equiv), $CaCO_3$ (4.0 mol equiv), and MS4A in Et_2O at room temperature for 41 h afforded **11α** selectively in 66% yield (α:β = 74:26, run 14).

Further, we examined the glycosylation reaction with the mannose derivative **12**. Mannose is a very important component in sugar chains, where almost all the mannose residues have a β-linkage at their anomeric centers. Although mannosylation reactions are essential in order to synthesize sugar chains, a major problem still exists with construction of the β-linkage. We were pleased to find that treatment of **12**[6] with cyclohexanol **2** (1.2 equiv), $Yb(OTf)_3$ (1.2 equiv), MS4A, and K_2CO_3 (4.0 mol equiv), in toluene at room temperature for 37 h provided **13β** selectively in 94% yield (α:β = 35:65, run 15).[8] This reaction was found to be also accelerated by the addition of $ZnCl_2$ (0.6 equiv) as shown in Table 1 (run 16). Similar reaction conditions were next applied to the mannosylation reaction using **8** as a glycosyl acceptor, giving **14** in 94% yield (α:β = 60:40, run 17).[8] Finally, the glycosylation reaction using **15**[6] and **16** was investigated under a variety of reaction conditions. It was found that this reaction did not proceed in the absence of $Ba(ClO_4)_2$. Exposure of **15** to **16** (1.2 equiv), $Yb(OTf)_3$ (1.2 equiv), $Ba(ClO_4)_2$ (0.6 equiv), K_2CO_3 (3 mol equiv), and MS4A, in MeCN at 55 °C for 14 h, gave only **17β**[8] in 52% yield (run 19). We also examined the glycosylation of **15** and **16** using $La(ClO_4)_3 \cdot 7H_2O$ as a promoter, since the naked environment of the metal in lanthanum perchlorate[13] was expected to facilitate the glycosylation reaction. In fact, under these conditions we obtained only **17β** in 73% yield (run 20).[14] This result bodes well for the new method, since treatment of **15** with **16** (1.5 equiv), $SnCl_2$ (2.4 equiv), $AgClO_4$ (2.4 equiv), and MS4A in MeCN at room temperature for 20 h[2a,3a] afforded **17β** in only 43% yield.

In conclusion, we have succeeded in developing a new glycosylation reaction using rare earth metal salts, with or without the requirement of the usual Lewis acids such as $ZnCl_2$ and $Ba(ClO_4)_2$.[15] We believe that this method can greatly facilitate glycosylations that use glycosyl fluorides as the glycosyl donor. Moreover, the results described herein should be quite instructive for future research that employs rare earth metals in organic synthesis.[16] Further studies along this line are currently underway.

Supplementary Material Available: Spectral and analytical data for all compounds (4 pages).

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(11) For the combined use of two Lewis acids, see: Mukaiyama, T.; Shimomura, N. *Chem. Lett.* **1993**, 781 and references cited therein.

(12) When **11β** was reexposed to the various reaction conditions we employed, but in the absence of glycosyl fluoride, unchanged **11β** could be fully recovered. This proved that our reaction conditions did not promote isomerization.

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(14) The reaction did not proceed by the use of $Yb(ClO_4)_3 \cdot 8H_2O$ as a promoter.

(15) Typical procedure a: An activator (a rare earth metal salt, 1.2 mol equiv to a glycosyl donor), an inorganic base (K_2CO_3 or $CaCO_3$, 4.0 mol equiv), and MS4A (ca. 100 mg) were dried at ca. 110 °C in vacuo for 2 h. A solution (1 mL) of a well-dried glycosyl fluoride (30 mg, 0.055 mmol) and glycosyl acceptor (1.2 equiv) was then added. After the reaction was complete, saturated $NaHCO_3$ (aq) was added. Filtration to remove MS4A and usual workup gave a product which was purified by silica gel column chromatography. Typical procedure b: $La(ClO_4)_3 \cdot 7H_2O$ (2.4 mol equiv to a glycosyl donor), K_2CO_3 (4.0 mol equiv), and MS4A (ca. 100 mg) were dried at ca. 180 °C in vacuo for 2 h. A solution (1 mL) of a glycosyl fluoride (30 mg, 0.055 mmol) and glycosyl acceptor (1.2 equiv) was then added at −15 °C. After the reaction was complete, saturated $NaHCO_3$ (aq) was added. Filtration to remove MS4A and usual workup gave a product which was purified by silica gel column chromatography.

(16) For recent progress in organic synthesis utilizing rare earth metal triflates as Lewis acids, see: Kobayashi, S.; Hachiya, I. *J. Org. Chem.*, **1994**, *59*, 3590 and references cited therein. Enhancement of the reactivity of rare earth metal triflates should open new possibilities for development of new reactions mediated by rare earth metal triflates.