Tetrahedron Letters, Vol. 34, No. 17, pp. 2791-2794, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Lanthanoid(III) Triflates as New Glycosylation Catalysts. Selective and Efficient Activation of 1-*O*-Methoxyacetyl Sugars

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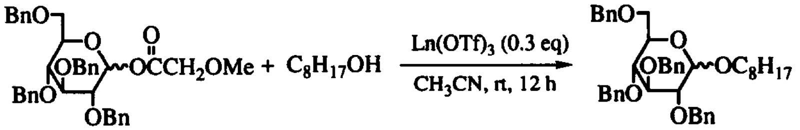
Abstract: *The reactions of 1-O-methoxyacetyl sugars with alcohols or thiols were effectively promoted by a catalytic amount of lanthanoid(III) triflates such as Tb(OTf)3, Ho(OTf)3, Tm(OTf)3, and Yb(OTf)3 to give the corresponding glycosides in good to excellent yields.*

Recently we reported a new glycosyl donor, 1-*O*-methoxyacetyl sugar, for the zinc(II)-promoted glycosylation.[1] In connection with our continuous interest in organic synthesis with lanthanoids,[2] we have tested a series of lanthanoid(III) triflates[3,4] as catalysts for the glycosylation of **1** (eq 1). The strong Lewis acidity and the high coordination number of such lanthanoid(III) salts[5] were expected to be advantageous for the activation of the donor through the strong interaction with its methoxyacetyl moiety.[6] The observed catalytic activities of the thirteen lanthanoid triflates are graphed in Figure 1.[7]



1 **2** (1)

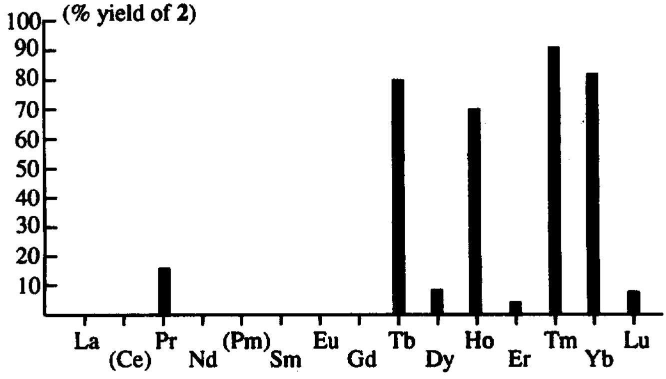


Fig. 1. Catalytic activity of $Ln(OTf)_3$ in the glycosylation of **1** (Eq. 1).

As can be seen from Fig.1, some heavy-lanthanide triflates such as $Tb(OTf)_3$, $Ho(OTf)_3$, $Tm(OTf)_3$, and $Yb(OTf)_3$ turned out to be highly effective. The acetyl analogue of **1** was not activated by any of these triflates under similar conditions, which indicates that the methoxyacetyl moiety of **1** as a bidentate ligand is essential to the activation. However, there seems to be no clear correlation between the catalytic activity and either the ionic radius or the oxophilicity of the central metal ion.[5]

We selected $Yb(OTf)_3$ as an economical catalyst and examined the effect of solvents on the glycosylation of **1**. As shown in Table 1, acetonitrile was found to be most effective in terms of reaction time and yield. When the reaction temperature was raised to 53°C, the quantity of the catalyst could be reduced to 0.5 mol% for the completion of the reaction. A typical procedure is as follows: A mixture of **1** (612 mg, 1.0 mmol) and 1-octanol (189 μL, 1.2 mmol) in dry acetonitrile (10 mL) was warmed to 53°C (bath temp.) under argon, and to this mixture was added a $Yb(OTf)_3$ *solution* in acetonitrile (5 mmol dm^{-3}, 1 mL, 0.5 mol%). After stirring for 1.5 h, the reaction mixture was passed through a short column of silica gel and eluted with ether. Concentration of the eluate followed by purification by column chromatography (SiO_2, eluant: hexane/ethyl acetate = 5/1) afforded 647 mg (99%) of the corresponding glycoside as a mixture of anomers (entry 9).

Table 1. The Effect of Solvents and the Quantity of $Yb(OTf)_3$ Catalyst on the Glycosylation of **1**[a)]

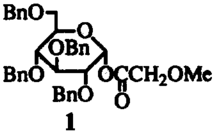
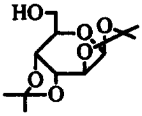
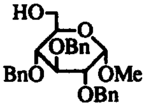
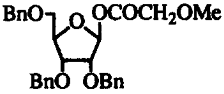
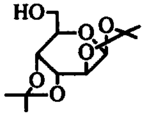
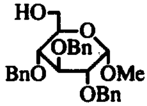
Entry	$Yb(OTf)_3$ / mol%	Solvent	Temp.	Time / h	Yield[b)] / %	α : β [c)]
1	30	toluene	RT	16	12	β only
2	30	CH_2Cl_2	RT	16	65	47 : 53
3	30	Et_2O	RT	16	36	70 : 30
4	30	CH_3CN	RT	16	84	27 : 73
5	10	"	RT	24	90	32 : 68
6	5	"	RT	24	74	------
7	1	"	RT	24	18	------
8	1	"	53°C	1	99	36 : 64
9	0.5	"	53°C	1.5	99	36 : 64

a) The reactions were carried out by using **1** (1 equiv) and 1-octanol (1.2 equiv). b) Isolated yield. c) Determined by ^1H NMR (270 MHz) analysis.

Some other examples of the $Yb(OTf)_3$-catalyzed glycosylation using various glycosyl acceptors and donors are summarized in Table 2. By this method, a variety of glycosides including disaccharides and thioglycosides were prepared in good to excellent yields. When the reactions were conducted at 53°C, thermodynamically more stable isomers were obtained as the major products. Thus, the glycosylation of the methoxyacetyl ribofuranoside derivative (**3**) with alcohols gave the corresponding β-glycosides highly selectively (entries 8-11).

In conclusion, an efficient lanthanoid-catalyzed glycosylation was developed for the first time. The major advantage of the present method is that the catalysts can be recovered and reused without serious loss of

Table 2. The Yb(OTf)$_3$-Catalyzed Glycosylation[a]

Entry	Glycosyl donor	Glycosyl acceptor	Yb(OTf)$_3$ / mol%	Time / h	Yield[b] / %	α:β [c]
1	 1		30	15	87	27:73
2			10	15	94	30:70
3		cyclohexanol	0.5	6	98	36:64
4		cholesterol	5	6	87	33:67
5		1-adamantanol	5	8	51	54:46
6		PhSH	0.5	6	97	55:45
7		n-$C_8H_{17}SH$	5	3	99	58:42
8	 3	1-octanol	5	0.5	99	7:93
9			30	1	97	β only
10			30	1	96	β only
11		cholesterol	5	0.5	98	6:94
12 [d]		PhSH	5	1	98	71:29
13		PhSH	5	0.5	91 [e]	40:60
14		n-$C_8H_{17}SH$ [f]	5	0.25	97	19:81

a) The reactions were carried out in CH_3CN at 53°C by using the glycosyl donor (1 equiv) and glycosyl acceptor (1.2 equiv) unless othewise stated. b) Isolated yield. c) Determined by ^1H NMR (270 MHz) analysis. d) The reaction was conducted at 23°C. e) The major by-product was the corresponding ring-opened dithioacetal due to the over-reaction with excess thiophenol. f) One equivalent of the thiol was used.

the activities.[8] The non-hazardous and low toxic nature of lanthanoids should also be emphasized.[9]

Acknowledgements. We thank the Shin-Etsu Chemical Co. Ltd. and the Central Glass Co. Ltd. for providing lanthanoid oxides and triflic acid, respectively.

References and Notes

1. Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Abstracts of Papers*, 63rd National Meeting of the Chemical Society of Japan, Osaka; The Chemical Society of Japan: Tokyo, 1992; Abstract 3E637; idem, *Chem. Express*, in press.
2. Some of our recent publications in this field: Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloy & Compd.* in press: Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *Tetrahedron Lett.* **1992**, *33*, 7035-7038.
3. Prepared from Ln_2O_3 and triflic acid in water according to the literature: Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T.; M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017-1021. The crude salts were recrystallized from CH_3CN-CH_2Cl_2 giving amorphous solids, which were drided at 200°C for 48 h *in vacuo*.
4. For the catalytic use of lanthanoid(III) triflates in organic synthesis, see a) reference 3; b) Kobayashi, S. *Chem. Lett.* **1991**, 2187-2190; c) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625-1628; d) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *ibid.* **1992**, *33*, 6815-6818.
5. Kagan, H. B. *"4f-Elements in Organic Synthesis"* in *Fundamental and Technological Aspects of Organo-f-Element Chemistry*; Marks, T. J.; Fragala, I. L. Eds; Reidel, D.: New York, 1985; pp. 49-76.
6. The interactions between lanthanide shift reagents and MTPA esters are frequently utilized in NMR study.
7. Some other lanthanoid(III) salts were also examined for the glycosylation of **1** and found to be fairly effective as shown in the following table.

LnX_3 (0.3 eq)	Solvent	Temp.	Time / h	Yield of **2** / %	α/β
$La(OTf)_3$	toluene	53°C	4	98	60 / 40
"	$(CH_2Cl)_2$	53°C	1	quant	62 / 38
"	Et_2O	RT	36	72	82 / 18
"	Et_2O	reflux	5	95	63 / 37
"	CH_3CN	53°C	7	quant	49 / 51
$CeCl_3$	Et_2O	reflux	24	68	------
"	CH_3CN	53°C	6	81	40 / 60
$SmCl_3$	Et_2O	reflux	4	87	65 / 35
"	CH_3CN	53°C	1	81	41 / 59

8. For example, essentially the same result (0.5 h, 98%, α/β=11/89) was obtained in the glycosylation of **3** with 1-octanol (cf. entry 8 in Table 2) by using the recovered catalyst which was dried at 200°C *in vacuo* for 22 h before use. For the reusability of lanthanoid(III) triflates as catalysts, see also references 4b-4d.
9. The lanthanoids are generally not classified as toxic, e.g. $YbCl_3$: LD_{50} (mouse) > 4800 mg/Kg.

(Received in Japan 8 February 1993)