Catalytic Stereoselective Synthesis of *α*-D-Galactopyranosides from 2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose and Several Alcoholic Nucleophiles

Hiromi Uchiro, Kazuo Miyazaki, and Teruaki Mukaiyama
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

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The glycosylation reaction of several alcoholic nucleophiles with 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (1-hydroxy sugar) is successfully carried out by the combined use of $Sn(OTf)_2$-Me_3SiCl catalyst system and lithium perchlorate, an effective additive. Several α-D-galactopyranosides are obtained in good yields with high stereoselectivities.

Many important roles of glycoconjugates in complex biological processes have recently been revealed and much attention has been drawn to the development of an efficient synthetic method for the formation of its saccharide chain.[1] Then, many glycosylation methods using various glycosyl donors have been reported in order to achieve this purpose.[2] Of these methods, a glycosylation reaction just starting from 1-hydroxy sugar is one of the most convenient methods since the glycosyl donor is easily available. Several useful glycosylation reactions using the above glycosyl donor for the synthesis of some glycosides were developed by recent intensive studies.[3-6] The stereoselectivity of these glycosylations in furanoside synthesis was in satisfactory level[5,6] but not always so in pyranosides synthesis. Especially, the stereoselective synthesis of α-galactopyranosides is not achieved in spite of its importance in preparing naturally occurring valuable saccharide chains. In this communication, we would like to describe catalytic stereoselective synthesis of α-D-galactopyranoside starting from 1-hydroxy sugar by a new and efficient method.

In the previous paper, a remarkable effect of lithium salt in the stereoselective synthesis of various ribofuranosides from 1-hydroxy sugar was shown.[6] It was suggested there that such stereochemical control was achieved by selective stabilization of α-ribofuranosides (1,2-cis-glycoside) with the lithium salt. Then, the application of this novel concept toward the stereoselective synthesis of α-galactopyranosides was studied. Firstly, the reaction of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose **1** with cyclohexanol **2** was tried in the presence of 5 mol% of $Sn(OTf)_2$-based several catalyst systems and lithium salt, an additive, together with Drierite, a dehydrating agent (Table 1). In every case, reactions proceeded at room temperature to yield the corresponding α-galactopyranoside. Advantages of this newly-introduced $Sn(OTf)_2$-Me_3SiCl catalyst system[7] were demonstrated in both activity and stereoselectivity comparing with the use of $Sn(OTf)_2$ alone or $Sn(OTf)_2$-$(Me_3Si)_2O$ catalyst system[4] previously mentioned. The α-selectivity dramatically increased along with the amount of lithium perchlorate (up to 350 mol%) and reached the selectivity of α/β=91/9. Such high stereoselectivity has not been observed by the conventional glycosylation method using 1-hydroxy sugar. The yield and stereoselectivity were slightly lowered when lithium bis[(trifluoromethyl)sulfonyl]imide was used instead of lithium perchlorate in the above experiment. Next, the effects of solvent and reaction temperature were examined (Table 2) and the best selectivity was observed when the glycosylation was carried out in benzene at room temperature.

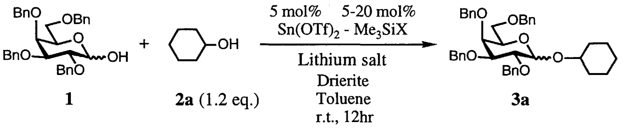


Table 1. Effect of a catalyst and a lithium salt

Entry	Me_3SiX (mol%)	Li salt (mol%)	Yield / %	α / β
1	None	$LiClO_4$ (350)	80	80 / 20
2	$(Me_3Si)_2O$ (20)	$LiClO_4$ (350)	83	84 / 16
3	Me_3SiCl (20)	$LiClO_4$ (350)	85	91 / 9
4	Me_3SiCl (5)	$LiClO_4$ (350)	85	90 / 10
5	Me_3SiBr (20)	$LiClO_4$ (350)	73	93 / 7
6	$Me_3SiOC(O)CF_3$ (20)	$LiClO_4$ (350)	84	89 / 11
7	Me_3SiCl (20)	$LiClO_4$ (150)	88	66 / 34
8	Me_3SiCl (20)	$LiClO_4$ (300)	86	83 / 17
9	Me_3SiCl (20)	$LiClO_4$ (500)	84	90 / 10
10[a]	Me_3SiOTf (5)	$LiClO_4$ (350)	77	90 / 10
11	Me_3SiCl (20)	$LiNTf_2$ (150)	75	84 / 16
12	Me_3SiCl (20)	$LiNTf_2$ (350)	79	85 / 15

[a] $Sn(OTf)_2$ was not used.

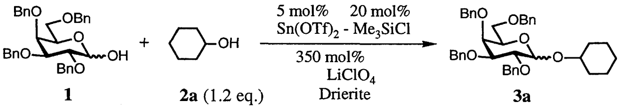
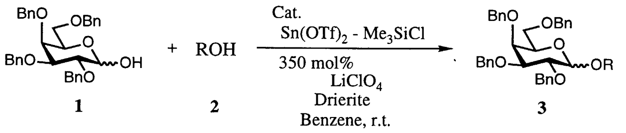


Table 2. Effects of a solvent and reaction temperature

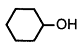
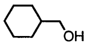
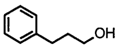
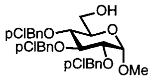
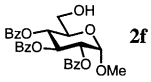
Entry	Solvent	Temp	Time / h	Yield / %	α / β
1	CH_2Cl_2	r.t.	12	73	78 / 22
2	Toluene	r.t.	12	85	91 / 9
3	Benzene	r.t.	12	84	92 / 8
4	$EtNO_2$	r.t.	12	32	76 / 24
5	Et_2O	r.t.	12	42	47 / 53
6	Benzene	40°C	2	83	87 / 13

Several examples of the present glycosylation reaction are demonstrated in Table 3. In every case, the desired α-D-galactopyranosides were obtained in good yields with high stereoselectivities. In order to clarify the mechanism of this high stereoselectivity caused by the addition of the lithium salt, some experiments on anomerization of galactopyranoside under the above glycosylation condition were tried (Table 4).[9] In the presence of 20 mol% of $Sn(OTf)_2$ in benzene, a mixture of the anomers of cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (α/β=55/45) was slightly anomerized to α-anomer rich mixture (α/β=69/31). Similar anomerization was observed in the presence of 5 mol% $Sn(OTf)_2$-Me_3SiCl catalyst system[7] to



1 **2** **3**

Table 3. Synthesis of α-D-galactopyranosides

Entry	ROH (eq.)	Catalyst (mol%)	Time (h)	Yield (%)	α / β
1	 **2a** (1.2)	5	12	84	92 / 8
2	(2.0)	10		90	92 / 8
3	 **2b** (1.2)	5.	12	82	92 / 8
4	(2.0)	10		89	93 / 7
5	 **2c** (1.2)	5	12	83	90 / 10
6	$^{n}C_8H_{17}OH$ **2d** (1.2)	5	12	85	92 / 8
7	(2.0)	10		89	92 / 8
8[a,b]	 **2e** (0.5)	5	40	90[c]	86 / 14
9[a]	 **2f** (2.0)	5	18	86	96 / 4

[a] The reaction was carried out in benzene-toluene (9:1) at 0 °C.
[b] 500 mol% of $LiClO_4$ was used.
[c] The yield was calculated based on the amount of accepor.

give the anomeric mixture of α/β=68/32. On the other hand, a significant anomerization was observed (α/β=89/11) when 350 mol% of lithium perchlorate was added to this catalyst system while no anomerization occured in the presence of lithium perchlorate alone. These observation almost corresponded to the selectivities observed in the above glycosylation. It was suggested that the α-anomer (1,2-cis-glycoside) was selectively stabilized by lithium perchlorate; therefore, the above catalyst system moved the equilibrium of anomerization effectively to form more thermodynamically stable product.

The typical experimental procedure is as follows: to a stirred suspension of $Sn(OTf)_2$ (3.5 mg, 0.0084 mmol), TMSCl (0.91 mg, 0.0084 mmol), lithium perchlorate (65.2 mg, 0.587 mmol) and Drierite (169 mg) in benzene (4 ml) was successively added a benzene (2 ml) solution of 2,3,4,6-tetra-*O*-benzyl-D-galacto pyranose (90.7 mg, 0.168 mmol) and cyclohexanol (20.2 mg, 0.202 mmol) at room temperature. The reaction mixture was stirred for additional 12 h, then it was quenched by adding saturated aqueous sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (87.9 mg, 84% yield) was isolated. The ratio of the anomers (α/β=92/8) was determined by HPLC analysis.

Thus, a new and efficient method for catalytic stereoselective synthesis of various α-D-galactopyranoside just starting from 1-hydroxy sugar was successfully developed. It is noted that such unprecedented high stereoselectivity was attributed to 1,2-cis-favored anomerization mechanism which was enhanced by the lithium salt.

Further investigation of other valuable glycoside synthesis based on this new strategy is now in progress.

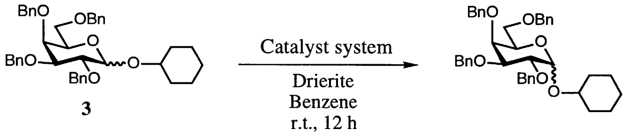


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Table 4. Anomerization reaction of cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside

Entry	Catalyst system (mol%)	α / β	
		Initial ratio	Final ratio
1	$Sn(OTf)_2$ (20)	55 / 45	69 / 31
2	$Sn(OTf)_2$ (5) - TMSCl (5)	55 / 45	68 / 32
3	$LiClO_4$ (350)	55 / 45	56 / 44
4	$Sn(OTf)_2$ (5) - TMSCl (5) + $LiClO_4$ (350)	55 / 45	89 / 11

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References and Notes

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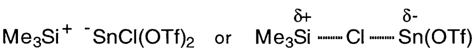
7 An active species of $Sn(OTf)_2$-Me_3SiCl catalyst system is not yet clear, however, it is assumed that a strongly cationic silyl species are generated by coordination of chlorine atom of Me_3SiCl to tin(II) atom of $Sn(OTf)_2$ as shown in the following figure.[8]



$$Me_3Si^{+}\ {}^{-}SnCl(OTf)_2 \quad \text{or} \quad \overset{\delta+}{Me_3Si}\cdots\cdots Cl \cdots\cdots \overset{\delta-}{Sn(OTf)_2}$$

And it was also observed that the use of $Sn(OTf)_2$-Me_3SiCl catalyst system was more effective compared with that of Me_3SiOTf alone in the present glycosylation (Table 1, Entry 10).

8 Similar active species were assumed in the previously reported Me_3SiCl-$SnCl_2$ or TrCl-$SnCl_2$ catalyzed C-C bond forming reactions, see N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, **1987**, 463; T. Mukaiyama, S. Kobayashi, M. Tamura, and Y. Sagawa, *Chem. Lett.*, **1987**, 491.

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