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Gallium Reagents in Organic Synthesis: Dimethylgallium Chloride and Triflate as Activators in Glycosidation Using Glycopyranosyl Fluorides

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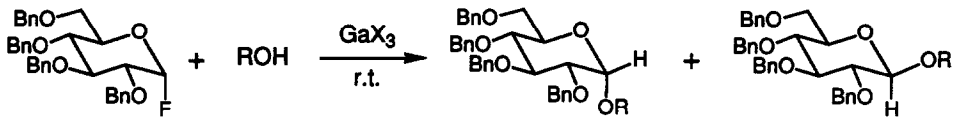
Summary: Gallium compounds were utilized in organic synthesis for the first time. Dimethylgallium chloride and dimethylgallium triflate was found to efficiently promote the glycosidation using several glycopyranosyl fluorides.

A variety of glycosidation methods have been developed since the classical Koenigs-Knorr synthesis,[1] but even now, the development of more selective or mild glycosidation reactions is still one of the most challenging topics in organic synthesis.[2] Among several methodologies so far developed, the use of glycopyranosyl fluoride as a glycosyl donor by Mukaiyama[3] is a remarkable achievement in carbohydrate chemistry. Glycosyl fluorides are generally stable compared to the corresponding chlorides or bromides, and can be activated by a variety of reagents such as $SnCl_2$-$AgClO_4$,[3] SiF_4,[4] Me_3SiOTf,[4] and, Cp_2MCl_2-$AgClO_4$ (M=Ti, Zr, Hf).[5] We became interested in examining gallium reagents as activators in the glycosidation reaction of glycopyranosyl fluoride, because we thought that the big difference of the bond energy among Ga-F (142 kcal/mol), Ga-Cl (115±4 kcal/mol) and Ga-O (58±12 kcal/mol)[6] might serve as a driving force for the reaction. Furthermore, it is surprising that the synthetic potential of organogallium compounds has remained unexplored[7], although gallium compounds, particularly trimethylgallium, has often been used in the semiconductor field. In this paper, we describe the first utilization of gallium reagents in organic synthesis by demonstrating that gallium reagents efficiently promote the glycosidation of glycopyranosyl fluorides.

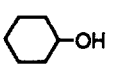
The gallium reagents employed in this study were Me_2GaCl, Me_2GaOTf and $MeGa(OTf)_2$. Me_2GaCl is commercially available as a toluene solution,[8] and gallium triflate reagents, Me_2GaOTf or $MeGa(OTf)_2$, are prepared *in situ* by adding an equimolar or two molar amounts of TfOH (trifluoromethanesulfonic acid), respectively, into a toluene solution of Me_3Ga[8] at -78°C. Although we did not characterize these species, simultaneous evolution of gas suggested the formation of gallium triflate reagents in analogy to the case of dialkylboryl triflate.[9] The glycosidation reaction was then examined using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride **1α**[10] and cyclohexanol (or its trimethylsilyl ether) in the presence of the gallium reagents. In

the present experiments, benzyl-protected rather than acyl-protected glycopyranosyl fluorides, except for 2-deoxyglucopyranosyl fluoride, were used as the glycosyl donor in order to avoid participation of the 2-acyloxy group.



1 2 3 4

Table 1 Gallium Reagent-Promoted Glycosidation of 1 with Cyclohexanol

run	Ga-Reagent	ROH 2	solvent	time (hr)	yield (%) 3a+4a	ratio [a] 3a : 4a
1	Me_2GaOTf		toluene	22	79	50 : 50
2	Me_2GaOTf [b]		toluene	2	88	48 : 52
3	$MeGa(OTf)_2$	**2a**	toluene	16	79	67 : 33
4	Me_2GaCl		toluene	2	quant	33 : 67
5	Me_2GaCl		CH_2Cl_2	1.6	quant	17 : 83
6	Me_2GaCl		CH_3CN	90	quant	20 : 80
7	Me_2GaCl		Et_2O		no reaction	
8	Me_2GaCl [b]		toluene	2	74	31 : 69
9	$Me_2GaCl + AgClO_4$		toluene	< 5 min	51	67 : 33

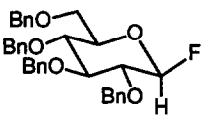
a) Ratios were determined by HPLC.[12] b) TMS ether of cyclohexanol was used as a nucleophile.

As shown in Table 1, gallium reagents were found to promote glycosidation, affording cyclohexyl glucosides in good to excellent yields. Ratios of **3**,[11] and **4**,[11] were determined by HPLC.[12] It should be noted that the readily available Me_2GaCl is effective for the glycosidation either in CH_2Cl_2 or toluene, and that it is not necessary to use hazardous silver perchlorate as a co-activator in this Ga-promoted glycosidation. The presence of $AgClO_4$ greatly accelerated glycosidation but the yield was rather low, affording the α-isomer predominantly, and a similar α/β ratio (64:36) was observed as in the case of the Cp_2ZrCl_2-$AgClO_4$ method.[5] The observed α/β ratios might be in good accordance with the tendency that the use of the more acidic Lewis acid results in the preferential formation of thermodynamically the more stable α-isomer.[2a] The use of the trimethylsilylether of cyclohexanol instead of free alcohol as a glycosyl acceptor was found to have no effect on α/β selectivity.

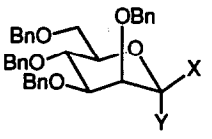
The solvent effect of the Me_2GaCl-promoted reaction was found to be significant as summarized in Table 1. The use of CH_2Cl_2 or acetonitrile as a solvent resulted in relatively high β-selectivity. In acetonitrile, however, the glycosidation proceeded very slowly, probably because of the coordination of the lone pair electrons of the solvent to the gallium atom.

A typical experimental procedure is described for run 4 in Table 1: To a solution of **1** in toluene is added cyclohexanol (1.5equiv) and a toluene solution of Me_2GaCl (1.5equiv) at room temperature under Ar atmosphere. After stirring for 2h at room temperature, the reaction mixture was poured into an aqueous $NaHCO_3$ solution, and the product was extracted with Et_2O. Usual work-up gives a mixture of **3** and **4** in quantitative yield.

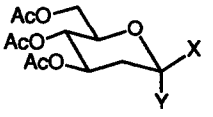
Other examples of Me_2GaCl-promoted glycosidation involved the use of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (**5**), 2,3,4,6-tetra-*O*-benzyl-α-D-manno-pyranosyl fluoride (**6**), and 3,4,6-tri-*O*-acetyl-α-D-2-deoxyglucopyranosyl fluoride (**9**) as a glycosyl donor, and the results are summarized in Table 2.



5

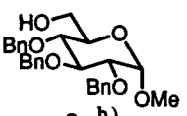
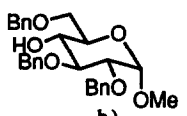
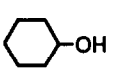


6 X = H, Y = F
7 X = H, Y = O-c-C_6H_{11}
8 X = O-c-C_6H_{11}, Y = H



9 X = H, Y = F
10 X = H, Y = O-c-C_6H_{11}
11 X = O-c-C_6H_{11}, Y = H

Table 2 Me_2GaCl-Promoted Glycosidation of Glycopyranosyl Fluorides

run	glycosyl donor	glycosyl acceptor (**2**)	solvent	time (hr)	product	yield (%)	α : β [a]
1	**1**	*tert*-BuOH **2b**	toluene	1.7	**3b**+**4b**	71	30 : 70[12]
2	**1**	 **2c**[b]	toluene	10	**3c**+**4c**[3]	74	27 : 73[13]
3	**1**	 **2d**[b]	CH_2Cl_2	1	**3d**+**4d**[3]	77	46 : 54[14]
4	**5**		toluene	1.4	**3a**+**4a**	quant	38 : 62[12]
5	**6**	**2a**	toluene	2.2	**7**+**8**	87	75 : 25[12]
6	**9**		CH_2Cl_2	0.8	**10**+**11**	69	78 : 22[12]

a) Ratios were determined by HPLC. b) **1**/**2**=1.0/1.3.

The exact mechanism of the glycosidation reaction is not clear, but a preliminary NMR experiment showed that dimethylgallium chloride was converted into dimethylgallium fluoride during the reaction. Therefore, the strong affinity between Ga and F seems to play an important role in the reaction. Although the glycosidation using readily available gallium reagents is moderately selective at present, synthetic potential of organogallium reagents will be promising in other Lewis acid-promoted reactions as well as in glycosidation.

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References and Notes

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11. Typical data are as follows. ^{1}H-NMR ($CDCl_3$, 400MHz) data are shown only for anomeric proton for each compound: **3a**; $[\alpha]_D^{25}$ +47.0°(*c* 0.23, $CHCl_3$), ^{1}H-NMR δ 4.95 (d, *J*=3.7Hz); **4a**; m.p. 103~5°C, $[\alpha]_D^{25}$ +45.0°(*c* 1.32, $CHCl_3$), ^{1}H-NMR δ 4.50 (d, *J*=8.1Hz); **7**; $[\alpha]_D^{25}$ +45.0°(*c* 1.32, $CHCl_3$), ^{1}H-NMR δ 4.99 (d, *J*=1.8Hz), **8**; m.p. 86~89°C, $[\alpha]_D^{25}$ -25.0°(*c* 0.26, $CHCl_3$), ^{1}H-NMR δ 4.61 (d, *J*=3.3Hz), **10**; $[\alpha]_D^{25}$ +115°(*c* 0.98, $CHCl_3$), ^{1}H-NMR δ 5.11 (dd, *J*=1.1, 2.6Hz), **11**; $[\alpha]_D^{25}$ -6.5°(*c* 0.85, $CHCl_3$), ^{1}H-NMR δ 4.69 (dd, *J*=1.8, 9.5Hz).
12. LichroCART 250-4 (Merck, Art 15543). Eluent; 0.4% *i*-PrOH in hexane.
13. LichroCART 250-4 (Merck, Art 15543). Eluent; 0.8% *i*-PrOH in hexane.
14. SSC-ODS (reverse phase column, Senshu Kagaku Co. Ltd., 171). Eluent; H_2O/MeOH=1/20

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