

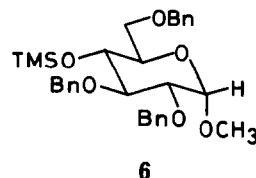
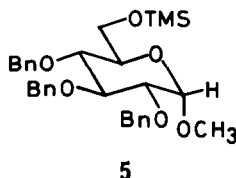
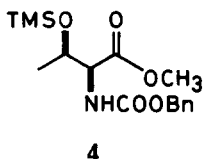
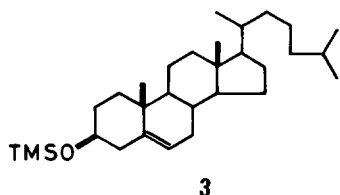
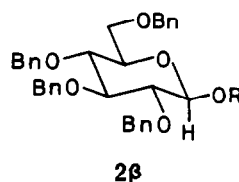
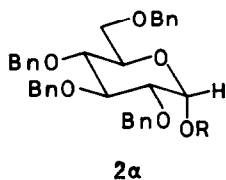
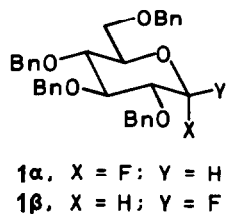
GLYCOSYLATION USING GLUCOPYRANOSYL FLUORIDES AND SILICON-BASED CATALYSTS.  
 SOLVENT DEPENDENCY OF THE STEREOSELECTION

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**Summary:** The title glycosylation method is economical and operationally simple. The steric course is highly influenced by the nature of the reaction media.

The classical Königs-Knorr glycosylation method<sup>1</sup> or the modified procedures have kept its effectiveness for more than 80 years in carbohydrate synthesis, although precious and sometimes explosive silver salts or toxic mercury compounds are used to condense 1-halo sugars and alcohols.<sup>2,3</sup> We found that tetrafluorosilane<sup>4</sup> or trimethylsilyl triflate (TMSOTf)<sup>5</sup> (<1 molar equiv) catalyzes effectively the condensation of appropriately protected glycopyranosyl fluorides<sup>6</sup> and trimethylsilyl ethers (1:1 molar ratio). Table I exemplifies the reaction of 2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucopyranosyl fluoride or the  $\beta$  anomer ( $1\alpha$  and  $1\beta$ , respectively) and a various type of trimethylsilyl ethers. Tetraalkoxysilane or even unprotected alcohols are also usable in the tetrafluorosilane catalyzed reaction. The reaction proceeded smoothly under mild conditions using the silicon-based promoters which are cheap, non-explosive, and only weakly toxic. This procedure is operationally simple and is suitable for the large-scale reaction. Disaccharides are also obtainable by this method. Various functional groups are tolerable under the reaction conditions. Particularly noteworthy is the marked solvent effect on the steric course of the reaction with the substrates having "nonparticipating" benzyloxy



Bn = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

TMS = Si(CH<sub>3</sub>)<sub>3</sub>

Table I. Stereoselective Glycosylation via Glucopyranosyl Fluorides<sup>a</sup>

nucleophile	substrate	conditions			product 2	
		catalyst (mol %)	solvent	T, °C (time, h)	% yield <sup>b</sup>	α:β <sup>c</sup>
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	SiF <sub>4</sub> (50)	CH <sub>3</sub> CN	0 (3)	88	15:85
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	TMSOTf (40)	CH <sub>3</sub> CN	0 (5)	86	22:78
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	TMSOTf (100)	ether	5 (23)	94	84:16
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (50)	CH <sub>3</sub> CN	0 (1)	90	16:84
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	67 <sup>e</sup>	73:27
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (25)	CH <sub>3</sub> CN	0 (5)	87	16:84
CH <sub>3</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (90)	ether	5 (20)	86	90:10
(CH <sub>3</sub> O) <sub>4</sub> Si <sup>f</sup>	<u>1β</u>	SiF <sub>4</sub> (5)	CH <sub>3</sub> CN	0 (2)	88	16:84
(CH <sub>3</sub> O) <sub>4</sub> Si <sup>f</sup>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	70 <sup>e</sup>	74:26
CH <sub>3</sub> OH	<u>1α</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (1)	88	17:83
CH <sub>3</sub> OH	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (0.5)	89	17:83
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (4)	90	15:85
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	TMSOTf (70)	CH <sub>3</sub> CN	0 (3.5)	96	27:73
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (3)	88	15:85
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	62 <sup>e</sup>	74:26
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (60)	CH <sub>3</sub> CN	0 (2)	92	14:86
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (65)	ether	25 (15)	81	86:14
c-C <sub>6</sub> H <sub>11</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (30)	g	0 (4)	89	15:85
c-C <sub>6</sub> H <sub>11</sub> OH	<u>1α</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (1)	86	14:86
c-C <sub>6</sub> H <sub>11</sub> OH	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (0.5)	87	16:84
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	SiF <sub>4</sub> (40)	CH <sub>3</sub> CN	0 (16)	71	23:77 <sup>h</sup>
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1α</u>	TMSOTf (60)	ether	5 (65)	65	77:23
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (12)	72	24:76
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	67 <sup>e</sup>	74:26
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (45)	CH <sub>3</sub> CN	5 (18)	64	20:80
t-C <sub>4</sub> H <sub>9</sub> OSi(CH <sub>3</sub> ) <sub>3</sub>	<u>1β</u>	TMSOTf (40)	ether	5 (13)	88	79:21
<u>3</u>	<u>1α</u>	SiF <sub>4</sub> (30)	g	25 (2)	85	19:81 <sup>i</sup>
<u>3</u>	<u>1β</u>	SiF <sub>4</sub> (20)	g	25 (1.5)	86	20:80
<u>3</u>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	0 (24)	72 <sup>e</sup>	77:23
<u>4</u>	<u>1α</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (2)	73	34:66 <sup>j</sup>
<u>4</u>	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (1.5)	71	38:62
<u>4</u>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	65 <sup>e</sup>	67:33
<u>5</u>	<u>1α</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (2.5)	89	9:91 <sup>k</sup>
<u>5</u>	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (1.5)	90	9:91
<u>5</u>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	68 <sup>e</sup>	78:22
<u>6</u>	<u>1α</u>	SiF <sub>4</sub> (30)	CH <sub>3</sub> CN	0 (3)	84	22:78 <sup>l</sup>
<u>6</u>	<u>1β</u>	SiF <sub>4</sub> (20)	CH <sub>3</sub> CN	0 (2)	87	23:77
<u>6</u>	<u>1β</u>	SiF <sub>4</sub> (d)	ether	5 (24)	66 <sup>e</sup>	75:25

(Footnotes of Table I)

<sup>a</sup> Reaction was carried out using equimolar amounts of 1 and nucleophiles. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> Gaseous tetrafluorosilane was introduced into the mixture at 0 °C for 2 min. <sup>e</sup> Starting material was recovered in 20–30%. <sup>f</sup> Only 0.25 molar amount was used. <sup>g</sup> A 1:1 CH<sub>3</sub>CN–ether mixture. <sup>h</sup> 2 $\alpha$ , [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 40.1° (c 0.62, CHCl<sub>3</sub>); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 17.3° (c 0.62, CHCl<sub>3</sub>) (lit. <sup>3d</sup> 2 $\alpha$ , [ $\alpha$ ]<sub>D</sub><sup>22</sup> + 39° (c 1.15, CHCl<sub>3</sub>); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>22</sup> + 18° (c 0.65, CHCl<sub>3</sub>)). <sup>i</sup> 2 $\alpha$ , [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 42.2° (c 0.54, CHCl<sub>3</sub>); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>26</sup> - 0.5° (c 1.6, CHCl<sub>3</sub>) (lit. <sup>7</sup> 2 $\alpha$ , [ $\alpha$ ]<sub>D</sub><sup>23</sup> + 44° (c 1.2, CHCl<sub>3</sub>); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>23</sup> - 0.4° (c 1.2, CHCl<sub>3</sub>)). <sup>j</sup> 2 $\alpha$ , mp 91–92 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 34.5° (c 1.7, CHCl<sub>3</sub>) (lit. <sup>8</sup> mp 86–88 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 25.3° (c 1.3, CHCl<sub>3</sub>)); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 9.2° (c 1.8, CHCl<sub>3</sub>). <sup>k</sup> Single recrystallization of this mixture from 5:1 hexane–benzene gave pure  $\beta$  isomer in 70% yield, [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 17.5° (c 0.49, CHCl<sub>3</sub>) (lit. <sup>3d</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 17.1° (c 0.42, CHCl<sub>3</sub>)). <sup>l</sup> 2 $\alpha$ , [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 45.4° (c 0.82, CHCl<sub>3</sub>) (lit. <sup>3d</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 48° (c 1.05, CHCl<sub>3</sub>)); 2 $\beta$ , [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 16.4° (c 2.9, CHCl<sub>3</sub>).

group at 2-position. The glycosylation in acetonitrile gave the  $\beta$  glycosides with moderate to high stereoselectivity, whereas the reaction in ether afforded the  $\alpha$  anomers predominantly. This general trend is not affected by the stereochemistry of the starting fluorides.<sup>9–11</sup> The products do not undergo anomerization under the reaction conditions and, therefore, the observed stereochemical outcome is a result of some kinetic control. It should be added that the efficiency of the reaction of the fluoro sugars relies on the eminent affinity of silicon atom to fluorine.<sup>12</sup> The corresponding glucopyranosyl chloride was inert to the tetrafluorosilane-promoted condensation under the comparable conditions.

A typical procedure is illustrated as follows: In a dry glass tube<sup>13</sup> were placed crystalline fluoride 1 $\alpha$  (1.03 g, 1.9 mmol) and cyclohexyl trimethylsilyl ether (325 mg, 1.9 mmol) in acetonitrile (3 mL). Then an acetonitrile solution of tetrafluorosilane (0.08 M, 7 mL, 0.57 mmol) was added at 0 °C, and the resulting mixture was stirred for 4 h at the same temperature and poured into a mixture of KF (5 g) and 0.1 M phosphate buffer solution (pH 7.4, 30 mL). Extraction with a 2:1 ether–hexane mixture (60 mL), washing of the organic layer with a saturated NaHCO<sub>3</sub> solution (30 mL) and then a 1:5 mixture of saturated NaHCO<sub>3</sub> solution and brine (30 mL), drying over Na<sub>2</sub>SO<sub>4</sub>, and concentration was followed by rough chromatography on silica gel (15 g, 1:2 ether–hexane as eluant) to give a 15:85 mixture of the cyclohexyl glucosides, 2 $\alpha$  and 2 $\beta$  (R = cyclohexyl) (1.06 g, 90% yield). Separation of the anomers was effected by medium-pressure column chromatography on silica gel (300 g, 1:6 ethyl acetate–hexane as eluant): 2 $\alpha$  (more polar), [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 41.5° (c 0.9, CHCl<sub>3</sub>) (lit. <sup>14</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 41° (c 2.3, CHCl<sub>3</sub>)); 2 $\beta$  (less polar), mp 104–105 °C, [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 7.5° (c 0.9, CHCl<sub>3</sub>) (lit. <sup>14</sup> mp 104–105 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 8° (c 1.0, CHCl<sub>3</sub>)).

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6. The  $\alpha$  fluorides  $1\alpha$  is most conveniently prepared by reaction of the corresponding acetylglucose and HF-pyridine. The detail will be published elsewhere.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ,  $\text{C}_6\text{F}_6$ )  $\delta$  149  $J_{\text{H}(1),\text{F}}$  = 53.7 Hz,  $J_{\text{H}(2),\text{F}}$  = 25.4 Hz. Preparation of  $1\beta$ : ref. 3d.
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9. Reaction of  $1\beta$  and alcohols in ether using  $\text{SnCl}_2$  and  $\text{AgClO}_4$  is known to produce  $\alpha$  glucosides predominantly.<sup>3d</sup> The authors claimed that poor leaving ability of the fluorine atom is the origin of the stereoselectivity.
10. For solvent effects in the classical Königs-Knorr reaction, see ref. 2b.
11. In the absence of nucleophiles, the  $\beta$  fluoride  $1\beta$  isomerizes to the  $\alpha$  anomer  $1\alpha$  under the influence of  $\text{SiF}_4$  in both acetonitrile and ether.
12. For example, dissociation energy of Si-F bond in  $(\text{CH}_3)_3\text{SiF}$  is 807 kJ/mol: E. W. Colvin, "Silicon in Organic Synthesis", Butterworth, London (1981).
13. Use of a polyethylene vessel gave a similar result.
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