

Catalytic *O*- and *S*-Glycosylation of 1-Hydroxy Sugars

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O-Protected 1-hydroxy sugars are effectively cross-coupled with a variety of alcohols and thiols to give the corresponding glycosides by using methoxyacetic acid and ytterbium(III) trifluoromethanesulfonate [Yb(OTf)₃] as catalytic promoters.

Although recent intensive studies on the development of new glycosyl donors have yielded a number of useful methods for glycoside synthesis, rather little has been reported for the glycosylation of 1-hydroxy sugars with free alcohols.¹ Our recent finding² that some heavy-lanthanide trifluoromethanesulfonates such as Yb(OTf)₃³ can catalyse the glycosylation of 1-*O*-methoxyacetyl sugars⁴ prompted us to examine the possibility of the cross-coupling of 1-hydroxy sugars with alcohols in the presence of a catalytic amount of methoxyacetic acid and Yb(OTf)₃ (Scheme 1).

When a mixture of 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose **1** and octan-1-ol was stirred with methoxyacetic acid and Yb(OTf)₃ (30 mol% each) at 53 °C for 8 h in various solvents, the corresponding octyl glucopyranoside was isolated in 97% (1,2-dichloroethane), 89% (toluene), 84% (acetonitrile) and 45% (tetrahydrofuran) yield, respectively. The amount of promoters could be reduced to 10 mol% each without a notable decrease in the yield under similar conditions (96%; 53 °C, 8 h). Although the glycosylation was effected by an even smaller amount of promoters,[‡] no reaction took place when either one of the promoters was absent.

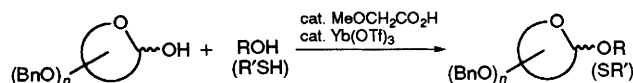
In Table 1 are summarized the results of the catalytic glycosylation of **1** and an anomeric mixture of 2,3,5-tri-*O*-

benzyl-D-ribofuranoses **2** with various types of glycosyl acceptors. The reactions proceeded smoothly especially when liberated water in the reaction mixture was azeotropically removed by refluxing the solvent through a column of molecular sieves 4 Å (condition B).[§] Thus, a variety of

Table 1 Catalytic glycosylation of 1-hydroxy sugars^a

Entry	1-OH sugar	Acceptor	Con- ditions ^b t/h	Yield ^c (%)	α : β Ratio ^d
1	1	Octan-1-ol	A 20	99	62:38
2	1	Octan-1-ol	B 3	99	78:22
3	1	3	A ^e 36	85	48:52
4	1	4	B 4	99	75:25
5	1	Cyclohexanol	B 3	99	68:32
6	1	Cholesterol	B 4	99	67:33
7	1	5	A ^e 36	81	40:60
8	1	6	B 5	72	82:18
9	1	Thiophenol	B 2	99	63:37
10	1	1-Octanethiol	B 3	99	79:21
11	2	Octan-1-ol	B 1.5	99	8:92
12	2	3 β -Cholestanol	B 2	98	4:96
13	2	4	B 5	92	β only
14	2	Thiophenol	B 1.5	96	25:75

^a The reactions were carried out by use of 1.2 equiv. of the acceptor to the 1-OH sugar in the presence of methoxyacetic acid and Yb(OTf)₃ (10 mol% each) unless otherwise stated. ^b A: 1,2-dichloroethane, 53 °C. B: dichloromethane, reflux, molecular sieves 4 Å (see the text). ^c Isolated yield. ^d Determined by ¹H NMR (270 MHz) analysis. ^e Methoxyacetic acid and Yb(OTf)₃ (30 mol% each) were used.

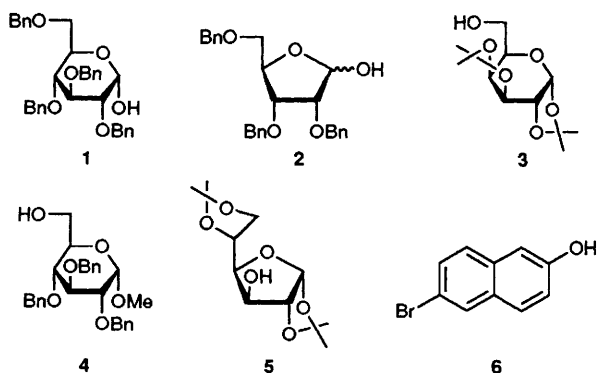


Scheme 1 (Bn = benzyl)

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‡ For instance, 1 mol% of promoters gave rise to 40% completion of the glycosylation after 8 h stirring at 53 °C in 1,2-dichloroethane.

§ Typical procedure (entry 2): a mixture of **1** (540 mg, 1 mmol), octan-1-ol (189 μ l, 1.2 mmol), methoxyacetic acid (7.7 μ l, 0.1 mmol) and Yb(OTf)₃ (62 mg, 0.1 mmol) in dichloromethane (40 ml) was refluxed for 3 h under argon through a column of activated molecular sieves 4 Å (ca. 28 g).



glycosides including disaccharides, 6-bromo-2-naphthyl glycoside and thioglycosides were prepared in good to excellent yields. The perfect stereoselection observed in the glycosylation of **2** (entry 13) should also be noted.

The mechanism of the present catalytic glycosylation is under investigation.

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References

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- 5 For a similar technique or apparatus, see: M. Nishizawa, Y. Kan and H. Yamada, *Tetrahedron Lett.*, 1988, **29**, 4597.