ZINC *p-tert*-BUTYLBENZOATE CATALYZED GLYCOSYLATION WITH GLYCOPYRANOSYL CHLORIDE

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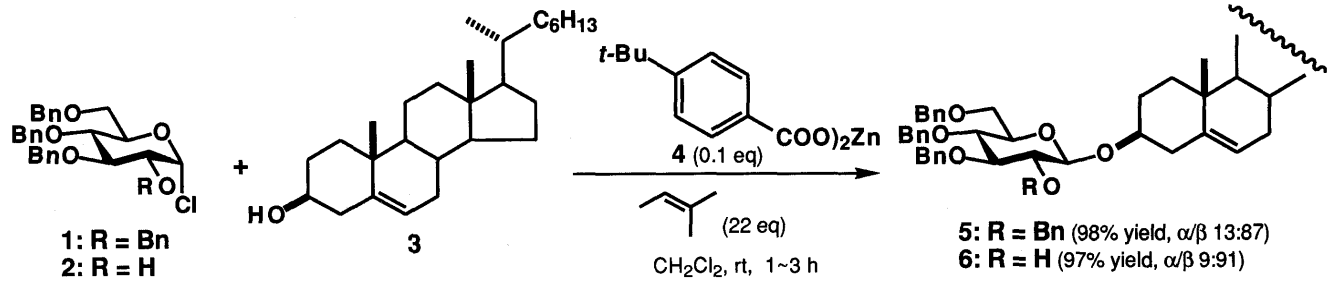
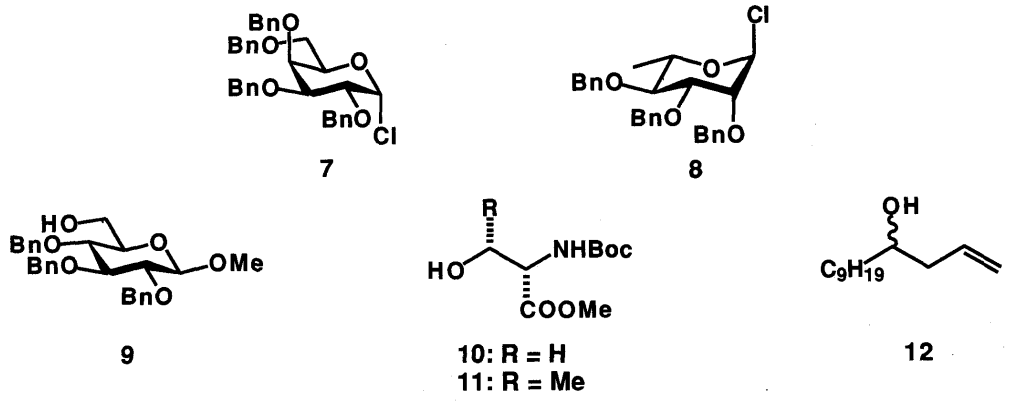
A 0.1 eq of zinc *p-tert*-butylbenzoate significantly accelerates glycosylation of alcohol with glycopyranosyl chloride in the presence of 2-methyl-2-butene to give β-glycoside in high yield with fair to good β-selectivity.

KEYWORDS zinc *p-tert*-butylbenzoate; catalytic; glucosylation; glucopyranosyl chloride; β-glucoside

Although a large number of glycosylation procedures have been developed, leaving groups at anomeric centers are usually activated by a stoichiometric amount of reagent.[1] Recently we have reported $Zn(acac)_2$ catalyzed rhamnosylation of cholesterol with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl chloride that affords α-rhamnoside selectively.[2] When this procedure was applied to glucosylation, the yield and stereoselectivity were not satisfactory. Thus we have tried to find a more efficient catalytic system for the glucosylation with D-glucopyranosyl chlorides. After examination of most of the commercially available zinc salts, we arrived at zinc *p-tert*-butylbenzoate as a catalyst. A variety of glucosides were prepared in generally high yield with fair to good β-selectivity within a few hours at room temperature in dichloromethane by using 0.1 eq of the catalyst. In particular the 2' hydroxyl group of nonprotected glucosyl chloride afforded a higher β-selectivity.



Reactions of cholesterol (**3**) with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1**) were carried out in the presence of a variety of zinc salt as catalyst. The results are summarized in Table I. Although 2-methyl-2-butene was employed as an acid scavenger, we found that it also accelerates the reaction significantly (entries 1 and 2) with better stereoselectivity. Except for $Zn(OTf)_2$, which gave low stereoselectivity (entries 6 and 7),[3] most zinc salts provided essentially similar yield and selectivity. Zinc *p-tert*-butylbenzoate (**4**) afforded better yield in a β-selective manner (entries 12 and 13). For example, to a dried solution of cholesterol (**3**) (50 mg, 0.13 mmol), zinc *p-tert*-butylbenzoate (**4**) (5.4 mg, 0.013 mmol, 0.1 eq), and 2-methyl-2-butene (200 mg, 2.8 mmol, 22 eq) in dichloromethane (8 mL)[2] was added a solution of **1** (108 mg, 0.19 mmol) in dichloromethane (7 mL), and the mixture was stirred at room temperature for 3 h. The mixture was directly subjected to a column chromatography on silica gel to give α and β glucosides in 98% yield. Stereoselectivity (α/β ratio) was analyzed by HPLC as well as ^1H NMR to be 13:87.



Condensations of alcohol **9** - **12** with glycosyl chlorides **1**, **2**, **7**, and **8** were carried out in the analogous way, and the results are summarized in Table II. Although the reactions of glucosyl chloride **1** with alcohol **9**-**12** were not stereoselective (entries 2, 3, 4,

and 5), glucosylation with 2' hydroxyl group nonprotected glucosyl chloride **2** afforded a higher β-selectivity by the reaction with cholesterol (**3**) or methyl glucoside **9** (entries 6 and 7). Reaction of amino acid derivatives **10** or **11** with **1** or **2** showed low selectivity (entries 3, 4, 8, and 9). The reaction of **1** and **12** provided four diastereomeric glucosides, and no kinetic resolution was observed (entry 5). Syntheses of galactosides were also achieved by the reaction of galactosyl chloride **7** and alcohols **3** and **9** (entries 10 and 11), and the results were similar to those with the glucosyl chloride **1**. However the reaction of **7** with amino acid derivatives showed α selectivity (entries 12 and 13). Rhamnosylation of cholesterol with **8** afforded quantitative yield but lower selectivity in comparison with $Zn(acac)_2$-catalyzed reaction.[2] It is important to note that the stereochemistry of the methoxyl group of **9** is maintained throughout the zinc salt-catalyzed glycosylation (entries 2, 7, and 11).[4]

Table I. Zn Salt (0.1 eq) Catalyzed Glucosylation of Cholesterol (**3**) with Glucosyl Chloride **1** in the Presence of 2-Methyl-2-butene (22 eq) in Dichloromethane at Room Temperature

Entry	Zn salt	Reaction period (h)	Yield (%)	α/β ratio
1	$Zn(acac)_2$	1	57	16:84
2	$Zn(acac)_2$	12[a]	58	23:77
3	$ZnCl_2$	1	59	17:83
4	$ZnBr_2$	1	76	17:83
5	ZnI_2	1	76	17:83
6	$Zn(OTf)_2$	1	69	43:57
7	$Zn(OTf)_2$	0.5[b]	94	45:55
8	$Zn(OCOC_6H_5)_2$	1	60	17:83
9	$Zn(OCOC_6H_4OH\text{-}o)_2$	1	64	18:82
10	$Zn(OCOCH_2CH_2\text{-}c\text{-}C_6H_{11})_2$	1	72	17:83
11	$Zn(OCOCH_2CH_2\text{-}c\text{-}C_6H_{11})_2$	2.5	91	15:85
12	$Zn(OCOC_6H_4\text{-}t\text{-}C_4H_9\text{-}p)_2$ (**4**)	1	77	17:83
13	$Zn(OCOC_6H_4\text{-}t\text{-}C_4H_9\text{-}p)_2$ (**4**)	3	98	13:87

a) Without using 2-methyl-2-butene. *b*) Reflux temperature in dichloromethane.

Table II. $Zn(OCOC_6H_4\text{-}t\text{-}C_4H_9\text{-}p)_2$ (**4**) (0.1 eq) Catalyzed Glycosylation of Alcohol in the Presence of 2-Methyl-2-butene (22 eq) in Dichloromethane at Room Temperature.

Entry	Glycosyl chloride	Alcohol	Reaction period (h)	Yield (%)	α/β ratio
1	**1**	**3**	3	98	13:87
2	**1**	**9**	2.5	84	30:70
3	**1**	**10**	3	90	47:53
4	**1**	**11**	3	81	37:63
5	**1**	**12**	1	90	26:74
6	**2**	**3**	1	97	9:91
7	**2**	**9**	2.5	79	2:98
8	**2**	**10**	3	52	33:67
9	**2**	**11**	1.5	40	50:50
10	**7**	**3**	1	98	16:84
11	**7**	**9**	1	68	22:78
12	**7**	**10**	1	85	65:35
13	**7**	**11**	1.25	95	71:29
14	**8**	**3**	1	100	64:36

REFERENCES AND NOTES

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