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Radical *C*-glycosylation reaction of pyranosides with the 2,3-*trans* carbamate group†‡

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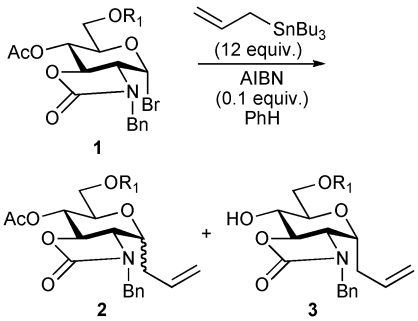
Radical-mediated *C*-glycosylation of pyranosides with the 2,3-*trans* carbamate group was investigated. *C*-Glycosylation was achieved with high α-selectivity.

Glycoconjugates and oligosaccharides play important roles in biological events, and are among the most structurally diverse natural biopolymers.[1] *O*-Glycosides are the most common structures in glycoconjugates, but *C*-glycosides are also found in natural compounds. For instance, *C*-linked protein modification has been identified in many proteins as post/co-translational modification,[2] and *C*-glycosides are often found in antibiotics, flavonoids and lignans.[3] The *C*-glycosides as pharmacophores may yield novel enzyme inhibitors.[4] Furthermore, *C*-glycosides have been useful synthons in natural product synthesis due to their multiple chiral centres.[5] For these reasons, the synthesis of *C*-glycosides has been studied.[6,7]

Radical mediated C–C bond formation is one of the most common methodologies for *C*-glycoside preparation. Although α-selectivities were observed in the glucosides cases,[8] the stereochemistry at the anomeric centre is significantly influenced by the amino protecting group at the amino group in the case of 2-deoxy-2-amino pyranosides.[9] For example, the 2-acetamido having a pyranoside shows α-selectivity under radical mediated allylation reaction (Keck reaction) conditions,[10] whereas a 2-phthalimide protected pyranoside shows β-selectivity under the same reaction conditions. Recently, we and other groups have demonstrated that the 2,3-*trans*-oxazolidinone protected pyranosides show high 1,2-*cis* selectivity in *O*-glycosylation reactions under various conditions.[11] We are interested in the influence of the five-membered carbamate ring on the stereochemical outcome of radical *C*-glycosylation.

First, we investigated the effect of the protecting group at the 6-position on the stereochemical outcome (Table 1). The bromide **1a** was subjected to the same reaction conditions as reported by Bertozzi *et al.* (entry 1).[9] Thus, a benzene solution of **1a** and allyltri-*n*-butylstannane was refluxed in the presence of AIBN. The α-glycoside and β-glycoside were obtained as an inseparable mixture in a ratio of 10 : 1.

Table 1 Substituent effect at the 6-position on the stereoselectivity under Keck allylation conditions



Entry		R_1	Product	Yield (%)	α : β	Yield of **3** (%)
1	**1a**	Ac	**2a**	84	94 : 6	0
2	**1b**	Bn	**2b**	56	93 : 7	19
3	**1c**	TBDPS	**2c**	26	>91 : 9	47

Substrate concentration is 0.2 M. The α/β ratios were determined by ^{1}H-NMR integration.

The stereochemistry of compound **2a** was determined from the coupling constant between H-1 and H-2 (J = 5.1 Hz), and a positive NOE enhancement between H-1 and H-2. Although, the high α-selectivity was observed in the series of the substrates **1a–1c**, bulky protecting groups at the 6-position reduced the yield (entries 2 and 3). In addition to products **2b** and **2c**, the deacetylated by-products **3b** and **3c** were obtained in significant amounts.

A significant substitution effect was observed in the chain radical reaction using the combination of acrylonitrile–Bu_3SnH–AIBN (Table 2). The bromide **1a** gave the *C*-glycoside **4a** in 76% yield, but the α/β ratio was quite low (entry 1). More bulky protecting groups such as Bn and TBDPS gave higher α-selectivities (entries 2 and 3) up to 95 : 5 (α/β), but the reduced by-products **5b** and **5c** were also obtained. From the above results, it is clear that the substituent at the 6-position influences the stereoselectivity at the anomeric position in the *C*-glycosylation reaction. More bulky protecting groups increased the selectivity, but decreased the yield.

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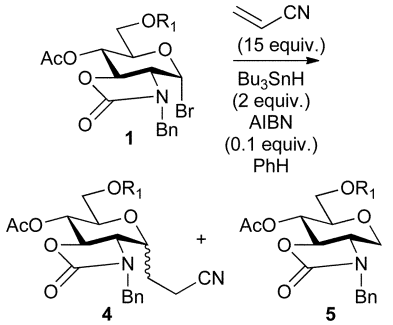
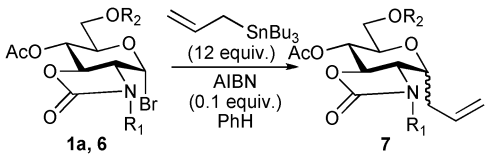
Table 2 Substituent effect at the 6-position on stereoselectivity under chain radical conditions



Entry		R_1	Product	Yield (%)	α : β	Yield of **5** (%)
1	**1a**	Ac	**4a**	76	48 : 52	0
2	**1b**	Bn	**4b**	52	91 : 9	22
3	**1c**	TBDPS	**2c**	43	95 : 5	28

Substrate concentration is 0.2 M. The α/β ratios were determined by ^{1}H-NMR integration.

Table 3 Substituent effect at the nitrogen atom on stereoselectivity under Keck allylation conditions

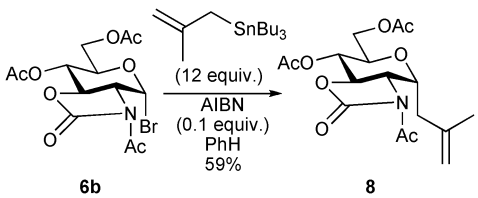


Entry		R_1	R_2	Product	Yield (%)	α : β
1	**6a**	H	Ac	**7a**	< 14	—
2	**6b**	Ac	Ac	**7b**	76	> 99 : 1
3[a]	**6b**	Ac	Ac	**7b**	35	> 99 : 1
4	**6c**	Ac	Bn	**7c**	41	> 99 : 1
5	**1a**	Bn	Ac	**2a**	84	94 : 6

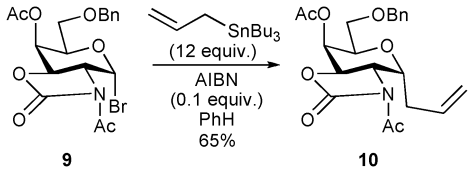
Substrate concentration is 0.2 M. The α/β ratios were determined by ^{1}H-NMR integration. [a] Two equivalents of allyltri-*n*-butylstannane were used.

Next, we investigated the substituent effect at the nitrogen atom of the carbamate group (Table 3). Under Keck conditions, bromide **6a** gave a complex mixture (entry 1). Fortunately, the *N*-Ac protected bromide **6b** and **6c** showed complete α-selectivity in good yield (entries 2 and 4). Even when the amount of allyltri-*n*-butylstannane was reduced to two equivalents (entry 3), complete stereoselectivity was again observed, although the yield was reduced to 35%.

The methallylation of optimized substrate **6b** also exhibited complete α-selectivity (Scheme 1).

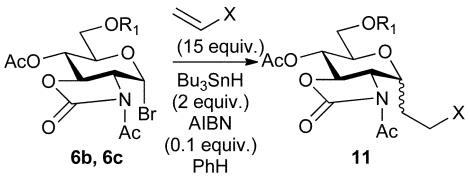


Scheme 1 The methallylation of compound **6b**.



Scheme 2 Keck allylation reaction with galactosamine derivative **9**.

Table 4 *C*-Glycosylation stereoselectivity with the *N*-acetylated 2,3-*trans* carbamate group under chain radical conditions



Entry	X		R_1	Product	Yield (%)	α : β
1	CN	**6b**	Ac	**11a**	56	92 : 8
2	CN	**6c**	Bn	**11b**	60	> 99 : 1
3	CO_2Me	**6c**	Bn	**11c**	74	> 99 : 1

Substrate concentration is 0.2 M. The α/β ratios were determined by ^{1}H-NMR integration.

In addition to the glucosamine derivatives, galactosamine derivative **9** also gave only the α-allyl adduct in 65% yield (Scheme 2).

Since the *N*-acetyl group was found to be effective for stereoselective *C*-glycosylation, the selectivity of the radical chain reaction was investigated using *N*-acetyl substrates (Table 4). The α-selectivity was high, especially when the primary alcohol was protected as a benzyl group (entries 2 and 3). By synergistic effects of the protecting groups at the *N*- and 6-positions, complete α-selectivity was observed in the radical chain reaction employing acrylonitrile and methyl acrylate (entries 2 and 3).

We report here the radical-mediated α-selective *C*-glycosylation of pyranosides with the 2,3-*trans* carbamate group. The selectivity is quite high when the carbamate nitrogen is protected by an acetyl group. Although only simple *C*-glycosides preparation is described in this communication, more complex *C*-glycoside formation could be possible.[7] Several reports based on ESR spectra of a pyranoside radical have indicated that the boat-like conformation of the pyranoside radical is the origin of the α-selectivity in the radical-mediated *C*-glycosylation.[12] In order to enhance the interaction between the half-occupied orbital at the radical centre and σ* orbital of the C–OR bond at the β-position of radical, the glucosides have the boat-conformation. However, because the 2,3-*trans* carbamate group locks the conformation of the pyranoside into the $^4C_1$ form,[13] other factors for high α-selectivity must exist.

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