Carbohydrates

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Chiral Brønsted Acid Mediated Glycosylation with Recognition of Alcohol Chirality**

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Many carbohydrate-containing natural products, which possess mono- and oligosaccharides, such as proteoglycans, glycoproteins, glycolipids, and antibiotics, are found in nature as important biological substances. A large number of recent biological studies on these glycomolecules at the molecular level have shed light on the biological significance of their carbohydrate units (glycons) in molecular recognition for the transmission of biological information.[1] It is now recognized that carbohydrates are at the heart of a multitude of biological events.[1] Additionally, some glycomolecules have been developed as new functional materials.[2] For example, certain alkyl glycosides are expected to be biodegradable surfactants. Therefore, glycomolecules continue to be the central focus of much research in chemistry, biology, and material science. With this stimulating background, the efficient synthesis of not only the carbohydrate itself, but also carbohydrate-containing products, is of particular interest both in academia and in industry. In this context, glycosylation, which is a crucial organic synthetic method to attach a sugar to other sugar moieties or other molecules (aglycons), is becoming more and more important in synthetic organic chemistry and carbohydrate chemistry, and considerable attention has been directed towards the efficiency of the glycosylation method.[3] From a synthetic standpoint, the efficiency of the glycosylation reaction generally is evaluated by a high chemical yield, regioselectivity, and α/β-stereoselectivity. Unfortunately, little attention has been focused on the important issue of diastereoselectivity of the reaction between the aglycon and glycon units in glycosylation. Herein we report a novel chemical glycosylation method that alters the chiral recognition ability of the aglycon. To the best of our knowledge, this is the first demonstrated example of a chemical glycosylation with recognition of alcohol chirality.

Previously, we demonstrated an enzymatic glycosylation of *o*-nitrophenyl β-D-galactoside and racemic secondary alcohols using β galactosidase from *E. coli*.[4] In this study, complete β stereoselectivity and moderate diastereoselectivity were observed. Furthermore, biocatalytic glycosylation resolution of racemic tetrahydroberberrubine was reported by Yu et al.[5] While our continuing efforts regarding this issue were unsuccessful, Fairbanks et al. recently reported α/β-stereoselective glycosylation of a galactosyl trichloroacetimidate and chiral alcohols using a chiral Brønsted acid.[6,7] In that study, high β stereoselectivity, induced by a chiral Brønsted acid, was demonstrated. In this context, we expected that use of a chiral Brønsted acid in glycosylation would realize α/β stereoselective and diastereoselective chemical glycosylation by tuning the reaction conditions.

To investigate our hypothesis, we selected the glucosyl trichloroacetimidate **1α**[8] and the binol-derived Brønsted acid **2** (Akiyama–Terada catalyst)[9] as glycosyl donor and chiral Brønsted acids, respectively (Figure 1). In this case,

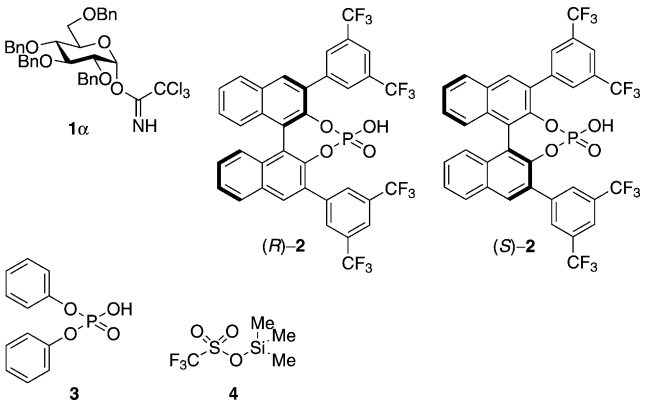

Figure 1. Structures of the glycosyl donor **1α**, chiral Brønsted acids **2** and achiral acids **3** and **4**.

a benzyl group was chosen as the protecting group for **1α** because it does not exhibit the participation effect, which would influence both α/β-stereo- and diastereoselectivity in the glycosylation.

First, we investigated the glycosylations of **1α** and the racemic secondary alcohol (±)-**5** using either the chiral phosphoric acids (*R*)-**2** and (*S*)-**2**, an achiral phosphoric acid (**3**), or a typical Lewis acid, TMSOTf (**4**), under several different conditions. These results are summarized in Table 1. It was found the glycosylations of **1α** and (±)-**5** using **2**–**4** as catalysts in PhMe proceeded at either 0 or −20 °C to give the four corresponding glycosides **6** in moderate to high yields (entries 1–8). When **4** was employed as the activator, a high total yield of the four glycosides **6** was obtained with low α/β-stereo- and diastereoselectivities (entries 1 and 5), whereas a moderate total yield with low α/β-stereo- and diastereoselectivities was observed in the glycosylation using **3** (entries 2

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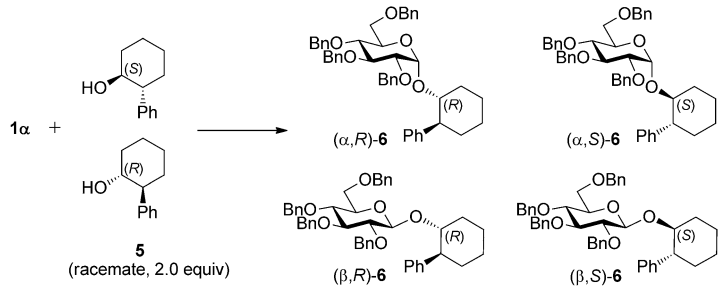
Table 1: Glycosylation reaction of **1α** and (±)-**5** several reaction conditions.



Entry	Activator (equiv)	Solvent (50 mM)	T [°C]	t [h]	Yield [%][b] (α,*R*)-**6**	(α,*S*)-**6**	(β,*R*)-**6**	(β,*S*)-**6**
1	**4** (0.3)	PhMe	0	24	34	47	7	10
2	**3** (0.3)	PhMe	0	24	12	9	16	3
3	(*R*)-**2** (0.3)	PhMe	0	24	10	9	19	2
4	(*S*)-**2** (0.3)	PhMe	0	24	3	4	33	0
5	**4** (0.3)	PhMe	−20	24	15	17	52	15
6	**3** (0.3)	PhMe	−20	24	16	8	28	4
7	(*R*)-**2** (0.3)	PhMe	−20	24	12	12	28	3
8	(*S*)-**2** (0.3)	PhMe	−20	24	2	3	50	0
9[a]	(*S*)-**2** (0.3)	PhMe	−40	13	0	0	52	0
10[a]	(*S*)-**2** (0.3)	THF	−40	13	2	2	42	0
11[a]	(*S*)-**2** (0.3)	CH_2Cl_2	−40	13	6	10	68	3
12[a]	(*S*)-**2** (0.3)	MeCN	−40	13	4	3	23	23
13[a]	(*S*)-**2** (0.3)	Et_2O	−40	13	3	3	87	0
14[a]	(*S*)-**2** (0.6)	Et_2O	−40	13	0	0	85	0

[a] 5 Å molecular sieves added. [b] Yield of isolated product.

and 6). Similarly, the use of (*R*)-**2** gave a moderate total yield of the four glycosides **6** with low α/β-stereo- and diastereoselectivity (entries 3 and 7). In sharp contrast, when (*S*)-**2** was used as the activator, although the total yield of was moderate, the α/β-stereo- and diastereoselectivity was good to high, and the total yield as well as the relative amount of (β,*R*)-**6** increased at lower temperature (entries 4 and 8). Furthermore, the glycosylation of **1α** and (±)-**5** using (*S*)-**2** in the presence of 5 Å molecular sieves at lower temperature (−40 °C) for 13 hours afforded only (β,*R*)-**6** in moderate yield (52%) with complete α/β-stereo- and diastereoselectivity (entry 9). Based on these results, we next examined the solvent effect on the glycosylation using (*S*)-**2** in Et_2O, MeCN, THF, and CH_2Cl_2. It was found that when THF was used, the result was similar to that obtained using PhMe (entry 10 in). In the cases of Et_2O and CH_2Cl_2, a high total yield of the four glycosides **6** was obtained while retaining high α/β-stereo- and diastereoselectivities (entries 11 and 13). Interestingly, it was found that although α/β stereoselectivity was high, diastereoselectivity was low for the glycosylation in MeCN (entry 12). This phenomenon may come from the strong coordination of MeCN[10] with an oxonium cation intermediate of the glycosylation reaction, and thus prevents coordination of (*S*)-**2** to the glycosylation intermediate. Finally, we found the use of 0.6 equivalents of (*S*)-**2** at −40 °C for 13 hours in Et_2O gave the best result with high reproducibility, thus producing only (β,*R*)-**6** in high (85%) yield (entry 14). These results clearly indicated that in the glycosylations of (±)-**5** and **1α** using the chiral phosphoric acid (*S*)-**2** as an activator, the *R* enantiomer of **5** selectively reacted with **1α** to give only (β,*R*)-**6** with excellent α/β-stereo- and diastereoselectivity in high yield.

With these favorable results in hand, we next examined the generality of the present glycosylation method. First we compared the result using (*S*)-**2** with those using (*R*)-**2**, **3**, and **4** under the optimized reaction conditions (see Table 1). As shown in Table 2, only the use of (*S*)-**2** in the glycosylation reaction of **1α** and (±)-**5** showed excellent α/β-stereo- and diastereoselectivity, and gave only (β,*R*)-**6** in high yield (entries 1–4). In addition, when the alcohols (±)-**7** and (±)-**12** were used, similar excellent α/β-stereo- and diastereoselectivities were observed, and only the glycosides (β,*R*)-**13** and (β,*R*)-**18**, respectively, were obtained in high yields (entries 5 and 10). Notable the products possess a β-glycosidic bond, and the *R* enantiomer of the corresponding alcohol **7** and **12**. When the alcohols (±)-**8**–**11** were employed as glycosyl acceptors, the glycosylations of **1α** using (*S*)-**2** proceeded with excellent α/β stereoselectivity and high diastereoselectivity to predominately give the corresponding glycosides (β,*R*)-**14**,[11] (β,*R*)-**15**, (β,*R*)-**16**, and (β,*R*)-**17** in good to high yields (entries 6–8). These results clearly indicated the high generality of the present glycosylation method.

Next, we performed mechanistic studies of the present glycosylation reaction (Figure 2a). It was found that when

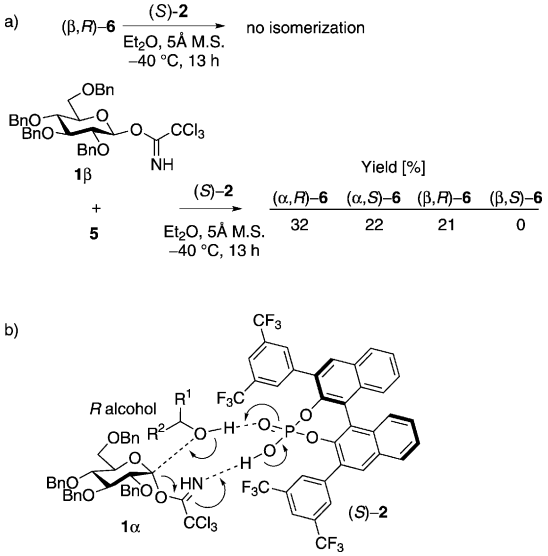
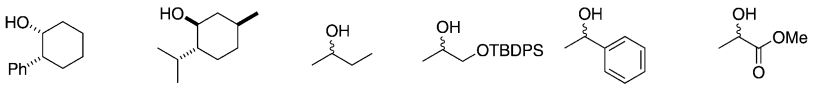


Figure 2. Mechanistic study (a) and proposed mechanism (b) of the glycosylation. M.S. = molecular sieves.

Table 2: Glycosylations of **1α** and several alcohols using (*S*)-**2**.

substrates:



(±)-**7** (±)-**8** (±)-**9** (±)-**10** (±)-**11** (±)-**12**

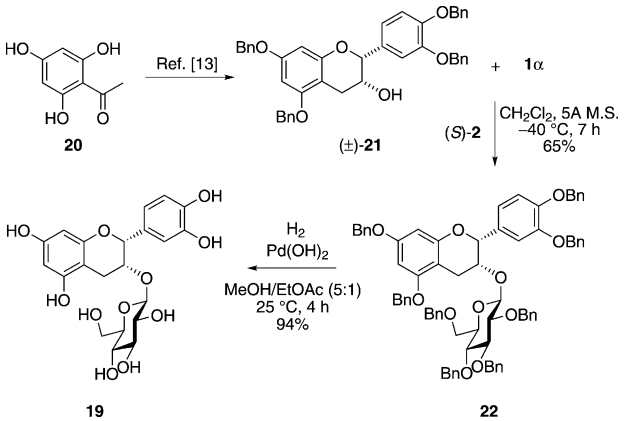
Entry[a]	Alcohol[b]	Activator[c]	*T* [°C]	*t* [h]	Yield [%][d]			
					(α,*R*)-**6**	(α,*S*)-**6**	(β,*R*)-**6**	(β,*S*)-**6**
1	(±)-**5**	**4**	−40	13	13	17	37	7
2	(±)-**5**	**3**	−40	13	11	7	10	2
3	(±)-**5**	(*R*)-**2**	−40	13	8	5	31	13
4	(±)-**5**	(*S*)-**2**	−40	13	0	0	85	0
					(α,*R*)-**13**	(α,*S*)-**13**	(β,*R*)-**13**	(β,*S*)-**13**
5	(±)-**7**	(*S*)-**2**	−40	13	0	0	87	0
					(α,*R*)-**14**	(α,*S*)-**14**	(β,*R*)-**14**	(β,*S*)-**14**
6	(±)-**8**	(*S*)-**2**	−40	13	0	0	67	13
					(α,*R*)-**15**	(α,*S*)-**15**	(β,*R*)-**15**	(β,*S*)-**15**
7	(±)-**9**	(*S*)-**2**	−40	13	0	0	75	17
					(α,*R*)-**16**	(α,*S*)-**16**	(β,*R*)-**16**	(β,*S*)-**16**
8	(±)-**10**	(*S*)-**2**	−40	13	0	0	77	8
					(α,*R*)-**17**	(α,*S*)-**17**	(β,*R*)-**17**	(β,*S*)-**17**
9	(±)-**11**	(*S*)-**2**	−40	13	0	0	81	7
					(α,*R*)-**18**	(α,*S*)-**18**	(β,*R*)-**18**	(β,*S*)-**18**
10	(±)-**12**	(*S*)-**2**	−40	13	0	0	84	0

[a] 5 Å molecular sieves added. [b] 2.0 equiv. [c] 0.6 equiv. [d] Yield of isolated product. THF = tetrahydrofuran.

(β,*R*)-**6** was treated with (*S*)-**2** in the absence of (±)-**5** under the glycosylation conditions, no isomerization occurred, and (β,*R*)-**6** was quantitatively recovered. This indicates that the α/β-stereo- and diastereoselectivities were determined by kinetic control. In addition, when the β-anomer **1β** was used as the glycosyl donor, high α/β-stereo- and diastereoselectivity was not observed, and the glycosides, (α,*R*)-**6**, (α,*S*)-**6**, (β,*R*)-**6**, and (β,*S*)-**6** were produced in 32, 22, 21, and 0% yields, respectively. These results strongly suggest that the present glycosylation of **1α** using (*S*)-**2** proceeds by a (*S*)-**2**-mediated SN2 reaction mechanism, which explains the high β stereoselectivity. Although the mechanism for the high diastereoselectivity is still not totally clear, higher stability of the oxonium cation/(*S*)-**2**/*R* alcohol intermediate compared to that of the oxonium cation/(*S*)-**2**/*S* alcohol complex may induce the high diastereoselectivity (Figure 2b).

Finally, we applied the present glycosylation method to the synthesis of a natural product, the flavan glycoside **19**. The flavan glycoside was isolated from the bark of *Cinnamomum cassia* by Morimoto and Nishioka in 1986.[12] The synthesis of **19** is summarized in Scheme 1. We first synthesized the benzyl-protected aglycon (±)-**21** from the benzene-1,3,5-triol derivative **20** using OsO_4 according to the modified version of the procedure reported by Schroeter et al.[13] We then conducted the glycosylation of **1α** and (±)-**21** using (*S*)-**2** in Et_2O or CH_2Cl_2 at −40 °C. It was found that only the desired glycoside **22** was obtained in 65% yield with excellent α/β-stereo- and diastereoselectivity when using CH_2Cl_2. Although Et_2O also gave similar excellent α/β-stereo- and diastereoselectivity, the yield of **22** was lower than that obtained when using CH_2Cl_2. It was also confirmed that the use of (*R*)-**2**, **3**, and **4** did not give such high α/β-stereo- and diastereoselectivities as expected (see the Supporting Information). These results again clearly indicated the high efficiency and generality of the present glycosylation method. Removal of the benzyl groups from **22** using $Pd(OH)_2$ in MeOH/EtOAc under an H_2 atmosphere completed the synthesis of the flavan glycoside **19** in optically pure form. ^{1}H NMR, ^{13}C NMR, HRMS (ESI-TOF), and optical rotation data for an analytical sample of the synthetic **19** matched those obtained for an authentic sample.[14]

In conclusion, we have developed the first α/β-stereo- and diastereoselective glycosylation method. The use of the glucosyl α-trichloroacetimidate **1α** and the chiral phosphoric acid (*S*)-**2** in Et_2O or CH_2Cl_2 was proven to be very effective for selective reaction with the *R* enantiomer of a racemic mixture of secondary alcohols. Furthermore, we successfully applied the present glycosylation method to the synthesis of a natural product, a flavan glycoside, from a racemic aglycon. These results introduce a new and innovative strategy for the synthesis of natural products possessing sugar(s). Detailed mechanistic studies of the present glycosylation, applications to other types of glycosyl donors,[15] and additional studies with respect to the synthesis of natural products using the present glycosylation method are currently underway in our laboratory.



20 (±)-**21** **19** **22**

Scheme 1. Total synthesis of the flavan glycoside **19** by glycosylation using **1α**, (±)-**21**, and (*S*)-**2**.

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[14] Although the optical rotation value of the synthetic **19** unfortunately did not match that reported in Ref. [12], the value matched that obtained an authentic sample, which was prepared using **1α** and chiral **21** [S. Stadlbauer, K. Ohmori, F. Hattori, K. Suzuki, *Chem. Commun.* **2012**, *48*, 8425–8427].

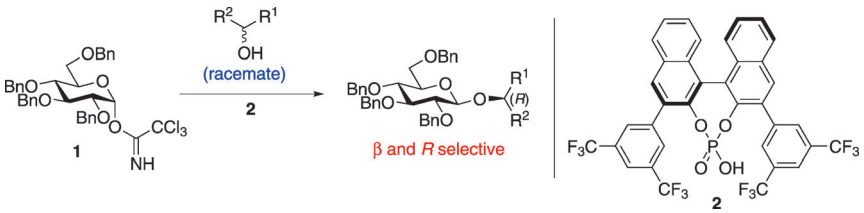
[15] It was found that an acyl protecting group such as the acetyl group was not suitable for the glycosyl donor in the present glycosylation.

Communications

Carbohydrates

T. Kimura, M. Sekine, D. Takahashi, K. Toshima* _____ ■■■■–■■■■

Chiral Brønsted Acid Mediated Glycosylation with Recognition of Alcohol Chirality



Sugar sugar: In the glycosylation of racemic alcohols with **1** using the chiral phosphoric acid **2** as an activator, one enantiomer of the racemic alcohol selectively reacts with **1** to give the corresponding glycoside with good to excellent α/β-stereo- and diastereoselectivity in high yield. The reaction was successfully applied to the synthesis of a chiral natural flavan glycoside using a racemic aglycon.