Note

Organocatalytic Direct α-Selective *N*-Glycosylation of Amide with Glycosyl Trichloroacetimidate

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Through the synergistic catalytic effect of the halogen bond (XB) donor and thiourea catalyst, a direct α-selective *N*-glycosylation of the amide residue of asparagine derivative was achieved using readily accessible glycosyl trichloroacetimidate. *n*-Butyl methyl ether was found to be the most suitable solvent for the α-selectivity.

Key words glycosylation; organocatalyst; halogen bond; hydrogen bond; green chemistry

N-Glycosides are found in a variety of bioactive compounds, including natural products.[1)] Sugar moieties are known to extend the diversity of molecules, altering their property, structure, and biological activities.[2)] However, synthetic methods for *N*-glycosides have not been well developed,[3–8)] as compared with the preparation of *O*-glycosides. In particular, stereoselective synthesis of α-*N*-glycosides is one of the most challenging issues despite their potentials as therapeutic compounds.[9–11)] In 2003, DeShong's group has reported a highly α-selective synthesis of *N*-glycosides through a Cu-mediated acylation of glycopyranosyl isoxazoline intermediates generated from the corresponding azides,[5)] while anomerization of 1-aminoglycopyranosyl derivatives is generally a significant problem.[4)] Direct *N*-glycosylation of amides has emerged as an alternative approaches,[6–8)] but those reports relied on the neighboring group participation to give β-*N*-glycosides (Chart 1a).

Herein, we report the first direct α-*N*-glycosylation of amide with glycosyl trichloroacetimidate[12)] using halogen bond (XB) donor[13)]/Schreiner thiourea[14)] co-catalytic system. We envisioned that α-selectivity would be achieved through the double inversion strategy (Chart 1b). The initial S_N2 addition of an appropriate solvent, such as etheric solvent, and/or additive[15)] to α-donor **1** would form a β-linked intermediate **A**, to which the following S_N2 attacked by an employed amide would afford the desired α-linked product. As in our previous report,[8)] we have chosen an XB-donor/thiourea co-catalytic system for the activation of the leaving group (LG) of **1**, mainly due to the following reasons: 1) XB interaction would be effective in relatively polar etheric solvent, and 2) tuning of both HB donor and XB donor would improve their ability to trap the LG *via* anion binding,[16)] preventing the undesired rearrangement of the LG.

We first screened the reaction conditions for the direct α-*N*-glycosylation of asparagine derivative **3** with glycosyl donor **1** (Table 1). According to our previous work, 2-iodoimidazolium salt (**XB1**)[13)] was examined in conjunction with **HB1** in dichloromethane.[8)] As we expected, the combination of **HB1** and **XB1** was essential for the production of desired *N*-glycoside **2a** (entries 1–3), although almost no α/β selectivity was observed (entry 3). A control experiment with non-halogenated azolium **5** did not furnish **2a** at all (entry 4), indicating that XB interaction would play an important role. The chemical yields were slightly improved using **XB2** and **XB3** (entries 5 and 6), whereas the undesired glycosyl trichloroacetamide **4** was obtained in these cases. Further investigation was carried out with **XB3** from the viewpoint of its easy preparation.[17)] A slight improvement of α/β-selectivity (α:β=65:35) was observed when diethyl ether was used as solvent (entry 7).[18)] Encouraged by this result, we next investigated several other etheric solvents (entries 8–12), and found that dimethoxyethane (DME) and *n*-butyl methyl ether improved α/β-selectivity (α:β=80:20) (entries 11 and 12). The anomeric configuration of major product was unambiguously determined as α-isomer (α-**2a**) by an X-ray crystallographic analysis.[17)]

With the suitable catalyst and solvent in hand, we next

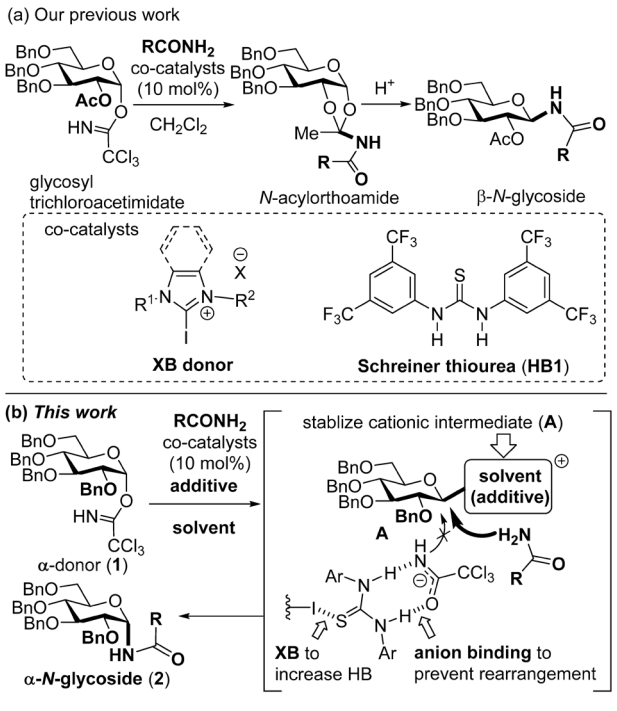

Chart 1. Strategy for α-*N*-Glycoside

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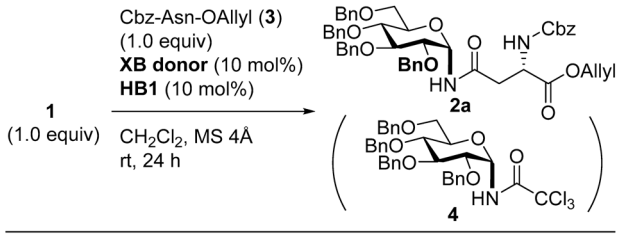
Table 1. Initial Screening for α-**2a**



entry	solvent	XB donor	**2a** (%)[a]	α:β	**4** (%)
1	CH_2Cl_2	**XB1** (without **HB1**)	0	n.d.[b]	n.d.[b]
2	CH_2Cl_2	none	4	n.d.[b]	n.d.[b]
3	CH_2Cl_2	**XB1**	41	49:51	trace
4	CH_2Cl_2	**5** (instead of **XB1**)	0	n.d.[b]	n.d.[b]
5	CH_2Cl_2	**XB2**	55	40:60	36
6	CH_2Cl_2	**XB3**	50	50:50	30
7	Et_2O	**XB3**	41	65:35	53
8	THF	**XB3**	50	53:47	50
9	CPME	**XB3**	43	56:44	55
10[c]	*n*-Pr_2O	**XB3**	trace	n.d.[b]	n.d.[b]
11[c]	DME	**XB3**	40	80:20	60[d]
12[c]	*n*-BuOMe	**XB3**	54	80:20	57[d]

[a] Based on glycosyl acceptor **3**. [b] Not determined. [c] 1.2 equiv of glycosyl donor was employed. [d] Based on glycosyl donor **1**.

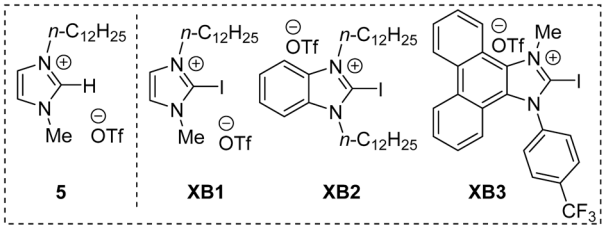
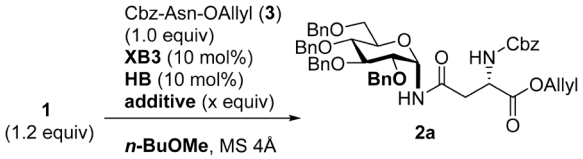
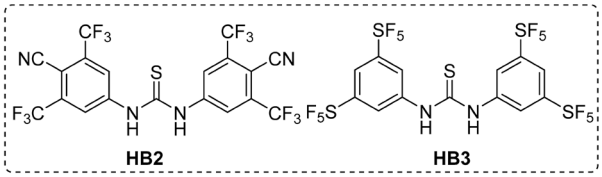


Table 2. Effect of Additives and HB Donors



entry	HB	**additive** (x equiv)	**2a** (%)[a]	α:β	**4** (%)[b]
1	**HB1**	thiophene (1.0)	64	82:18	41
2	**HB1**	thiophene (10)	39	85:15	54
3	**HB1**	2-methoxythiophene (1.0)	57	60:40	50
4	**HB1**	3-methoxythiophene (1.0)	48	77:23	60
5	**HB1**	2-n-propylthiophene (1.0)	64	81:19	47
6	**HB1**	3-n-propylthiophene (1.0)	54	81:19	55
7	**HB1**	2-bromothiophene (1.0)	28	69:31	55
8	**HB1**	benzothiophene (1.0)	48	84:16	60
9	**HB1**	DMAPO (1.0)	0	n.d.[c]	n.d.[c]
10	**HB1**	NFM (1.0)	0	n.d.[c]	n.d.[c]
11	**HB1**	$Ph_3P{=}O$ (1.0)	58	81:19	52
12	**HB1**	$(2\text{-thienyl})_3P$ (1.0)	trace	n.d.[c]	n.d.[c]
13	**HB2**	none	65	66:34	46
14	**HB3**	none	74	78:22	31
15	none[d]	TMSOTf (0.1)	<10	n.d.[c]	>90

[a] Isolated yields based on amide **3**. [b] Based on glycosyl donor **1**. [c] Not determined. [d] Without **XB3** (TMSOTf was employed as the only catalyst.)



investigated several additives and HB donors in order to improve the α/β-selectivity, and to suppress the undesired glycosyl trichloroacetamide **4** (Table 2).

When 1.0 equiv of thiophene was added, the yield of **2a** increased to 64% along with the decrease of byproduct **4**, and the α/β-selectivity has reached to 82 : 18 (entry 1). Ten equiv of thiophene, however, diminished the yield of **2a**, probably due to the inhibition of the catalysts (entry 2). To our disappointment, further improvement was not observed, although several different thiophene derivatives (entries 3–8) and other nucleophilic additives, such as *N*,*N*-dimethylaminopyridine-*N*-oxide (DMAPO), *N*-formylmorpholine (NFM),[15] triphenylphosphine oxide, and tri(2-thienyl)phosphine (entries 9–12), were screened as additives. Then, we examined the HB donors **HB2**[19] and **HB3**[17] bearing superior HB-donating abilities (entries 13 and 14). The ratio of the desired product **2a** to the byproduct **4** was improved, presumably because of their stronger anion binding abilities, while there is still room for improvement of the α/β-selectivity. It is worthy to note that trimethylsilyl trifluoromethanesulfonate (TMSOTf), one of the most commonly used Lewis acids, was not effective to obtain *N*-glycoside **2a**, and the undesired glycosyl trichloroacetamide **4** was just produced in high yield (entry 15).

In conclusion, we have found that XB donor/ thiourea cocatalytic system was effective even in polar solvent, enabling a direct α-selective *N*-glycosylation of amide with glycosyl trichloroacetimidate. We believe that this methodology would be applied to the synthesis of a variety of α-*N*-glycosides.

Experimental

To a solution of glycosyl donor **1** (41.1 mg, 0.06 mmol), glycosyl acceptor **3** (15.3 mg, 0.05 mmol), and thiophene (4.2 mg, 0.05 mmol) in *n*-butyl methyl ether (1.0 mL) were successively added activated MS4Å (100.0 mg), **XB3** (3.3 mg, 0.005 mmol), and **HB1** (2.5 mg, 0.005 mmol), and the reaction mixture was stirred at room temperature for 24 h. Direct purification on silica gel column chromatography gave α-**2a** (21.9 mg, 53%) and β-**2a** (4.8 mg, 11%) as white solid (Table 2, entry 1).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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