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2-Pyridyl glycoside: an alternative glycosyl donor in preactivation protocol

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ABSTRACT

2-Pyridyl glycosides have been identified to be powerful glycosyl donors for the preactivation-based oligosaccharide synthesis. By using stoichiometric amount of Tf_2O, the 2-pyridyl glycosides were pre-activated, which subsequently underwent glycosylation reactions smoothly to produce the coupled products in high yields. Furthermore, the 2-pyridyl glycosides were applied to the efficient oligosaccharide assembly by the preactivation-based one-pot oligosaccharide synthesis protocol.

As the most abundant class of biomolecules on Earth, carbohydrates play important roles in numerous biological processes including energy storage, viral and bacterial infection, inflammation and immune response, fertilization, cell growth, and proliferation.[1] Since most carbohydrates cannot be obtained easily from natural sources in good purity and quantity, complex oligosaccharides are mainly obtained by chemical or enzymatic synthesis. Many methods and strategies have been developed for the construction of complex oligosaccharides and glycoconjugates.[2] Among them, the preactivation-based one-pot oligosaccharide synthesis is one of the most efficient strategies.[3] Preactivation protocol refers to the activation of a glycosyl donor in the absence of a glycosyl acceptor to provide a reactive intermediate, which is immediately treated with glycosyl acceptor to yield a coupled saccharide.[4] Many complex oligosaccharides have been assembled by this protocol,[5] and various methods have been also developed to improve the stereoselectivity and efficacy.[6] In preactivation protocol, thioglycoside is the most widely-used glycosyl donor. Thioglycoside is a powerful donor,[7] but sometimes it still has some drawbacks, for instance, the regeneration of donor via aglycon transfer or the erosion of acceptor by thiophilic species.[8] Therefore, to overcome these problems, it is necessary to find an alternative glycosyl donor for the preactivation-based oligosaccharide synthesis.

The usages of 2-pyridyl glycosides or methoxy-2-pyridyl (MOP) glycosides as glycosyl donors in the saccharide synthesis were reported previously.[9] This type of building blocks can be used as both glycosyl donors and acceptors.[10] It was found that the 2-pyridyl glycoside was activated by MeOTf, TfOH, or $Cu(OTf)_2$ at room temperature,[9a] however, the glycosylation yield was not good (31–77% yields). This severely hinders the application of 2-pyridyl glycoside in glycosylations. New promoters should be explored to improve the glycosylation efficiency. Therefore, pyridyl glycosides might be suitable building blocks for the preactivation-based glycosylation protocol. Herein we choose the more stable 2-pyridyl glycosides as glycosyl donors to test the reactions.

The 2-pyridyl glycoside **1a**[9,10] was used for the reaction. We reasoned that when triflic anhydride (Tf_2O) was used as the promoter for glycosylation reactions, a highly reactive glycosyl triflate might be generated under low temperature. Thus, donor **1a** was treated with Tf_2O (1.0 equiv) at −72 °C in anhydrous dichloromethane (DCM), most of **1a** was consumed by TLC detection after 20 min, indicating donor **1a** was preactivated. The acceptor **2a** was then added to the reaction mixture, as expected, the coupled product disaccharide **3a**[11] was obtained in 72% yield (Table 1, entry 1). The yield was improved gradually as the equivalent of Tf_2O increased (entries 2 and 3). The donor **1a** was observed with complete consumption when using 1.1 equiv of Tf_2O. The yield was improved further by decreasing the amount of glycosyl acceptor **2a** (entries 4 and 5). The best donor/acceptor ratio is 1/0.8 (entry 5). The addition of hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) did not affect

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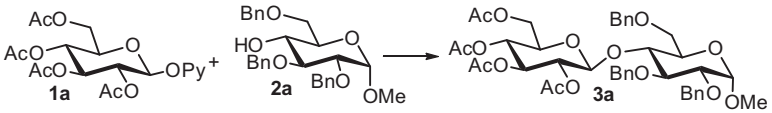
0040-4039/

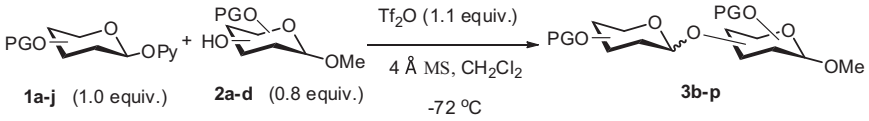
Table 1
Optimization of the reaction conditions using donor **1a** and acceptor **2a**



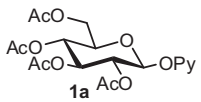
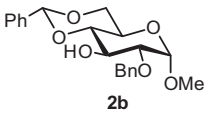
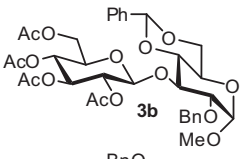
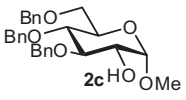
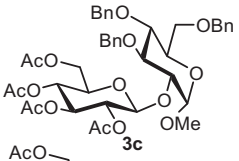
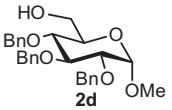
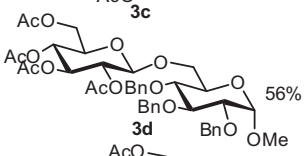
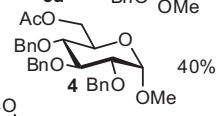
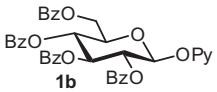
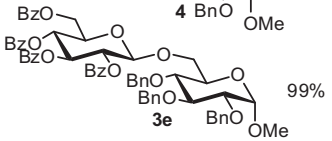
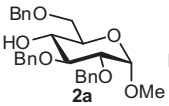
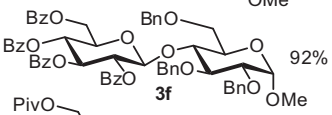
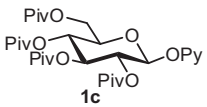
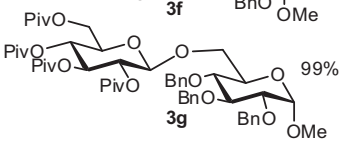
Entry	**1a** (equiv)	**2a** (equiv)	Activator (equiv)	Additive (equiv)	Yield[a,b] (%)
1	1.0	1.0	Tf_2O (1.0)	—	72
2	1.0	1.0	Tf_2O (1.05)	—	76
3	1.0	1.0	Tf_2O (1.1)	—	81
4	1.0	0.9	Tf_2O (1.1)	—	89
5	1.0	0.8	Tf_2O (1.1)	—	96
6	1.0	0.8	Tf_2O (1.1)	TTBP (2.0)	93
7	1.0	0.8	TfOH (1.1)	—	—
8	1.0	0.8	MeOTf (1.0)	—	—

[a] Conditions: −72 °C, DCM, 4 Å molecular sieves.
[b] Isolated yield.

Table 2
The scope of glycosylations of donors (**1a–j**) and acceptors (**2a–d**)



1a-j (1.0 equiv.) **2a-d** (0.8 equiv.) **3b-p**

Entry	Glycosyl donor	Glycosyl acceptor	Disaccharide	Yield[a,b]
1	 **1a**	 **2b**	 **3b**	94%
2	**1a**	 **2c**	 **3c**	87%
3	**1a**	 **2d**	 **3d**	56%
			 **4**	40%
4	 **1b**	**2d**	 **3e**	99%
5	**1b**	 **2a**	 **3f**	92%
6	 **1c**	**2d**	 **3g**	99%