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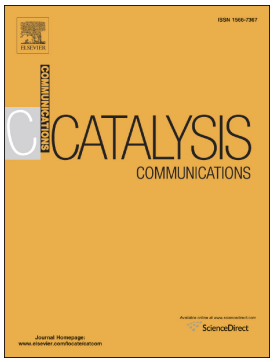

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N-Benzoylglycine/thiourea cooperative catalyzed stereoselective *O*-Glycosidation: Activation of *O*-glycosyl trichloroacetimidate donors

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Abstract

A new practical utility for β-stereoselective glycosylation via activation of *O*-glycosyl trichloroacetimidate donors using *N*-benzoylglycine/thiourea cooperative catalysis has been demonstrated. This method represents the first instance where amino acid derived *N*-benzoylglycine is used as a catalyst for *O*–glycosylation under mild reaction conditions at ambient temperature. NMR spectroscopy studies suggest that thiourea cocatalyst exhibit a cooperative behaviour that has a strong effect on the reaction rate, yield, and the β-selectivity.

Keywords: Organocatalyst, stereoselective, glycosylation, trichloroacetimidate, Schreiner's thiourea

1. Introduction

Glycosylation to construct most essential glycosidic bond is present in a crucial class of biomolecules such as oligosaccharides, glycoconjugates, glycoproteins, glycopeptides, peptidoglycans, glycolipids, and lipopolysaccharides, which play important roles in numerous biological processes [1-2]. Owing to their high importance for the synthesis of fundamental glycosidic bonds with high efficiency and selectivity, chemists have studied glycosylation chemistry for over a century [1-2]. However, it is still not an easy task for making

stereoselective glycosidic linkages in several class of biomolecule. Considering their importance, several efficient protocols have been established for the stereoselective glycosylation [3-6].

Despite such a great success for the construction of stereoselective traditional glycosylations, the development of reagent/catalyst-controlled glycosylations [7] offers many advantages over traditional methods, as these strategies have the potential to allow the high efficiency and selectivity. Despite the broad application of organocatalysis within asymmetric synthesis [8], it is still uncommonly employed in the area of carbohydrate chemistry, especially for glycosylation reactions.

Moreover, the use of cocatalysts with organocatalysts known as 'cooperative catalysis' [9] is an exciting field whereby enhance the catalytic activity and selectivity. In particular, cooperativity between Brønsted acids and hydrogen-bonding cocatalysts such as thiourea derivatives has broad area of application [10]. In literature, the Schreiner group [11], the Jacobsen group [12], and others [13] have been used the cooperativity between Brønsted acids and hydrogen-bonding cocatalysts, as for instance thiourea derivatives for successfully applied to asymmetric catalysis. In the hope of extending the application of organocatalysts, a small molecule metal-free hydrogen-bond catalyst Schreiner's thiourea [14] have been recently employed for glycosylation [5]. Literature survey revealed only very limited examples that evolved recently make use of cooperative catalysis for stereoselective glycosylation. The work done by Schmidt group has successfully applied the synergistic catalysts thiourea derivatives with phosphorus acids for stereoselective *O*-glycosylation (Figure 1) [5]. Similarly, Galan et al. established a method for the preparation of 2-deoxyglycosides from glycals under the influence of cooperative catalysis (chiral phosphoric acids/thiourea derivatives) (Figure 1) [15]. More recently, Kumar's group also demonstrated

glycosylation using a synergistic catalytic system of electron-deficient pyridinium salts/aryl thiourea (Figure 1) [16].

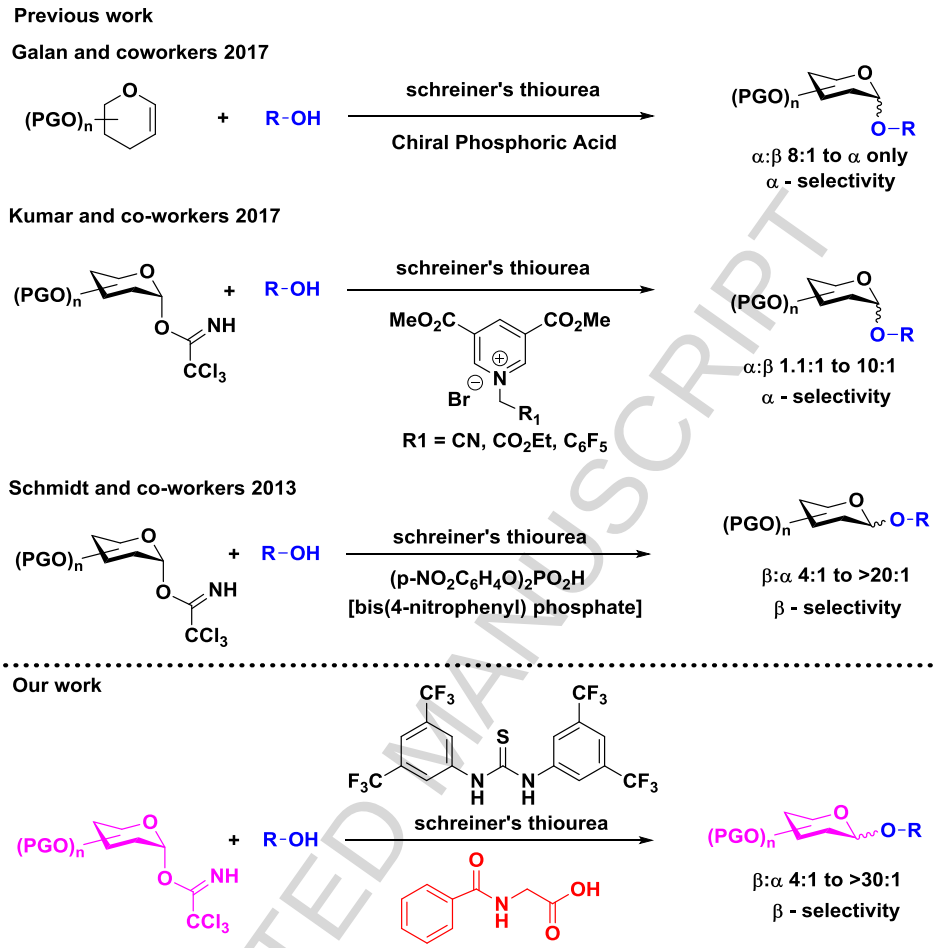


Figure 1: Representative precedents in thiourea catalyzed glycosylations.

Encouraged by reported literature, we decided to focus our attention on the synthesis of stereoselective glycosides via cooperative catalysis approach. Besides the advantages of these methods, drawbacks related to chiral cocatalyst accessibility and stereoselectivity of the glycoside formation still remain challenging. Hence we postulated that synergistic Schreiner's thiourea/*N*-benzoylglycine activation could provide a more efficient and practical glycosylation strategy for the preparation of *O*-glycoside with excellent yields and β-selectivity from highly reactive *O*-glycosyl trichloroacetimidate donor (Figure 1).

This method represents the first instance where environmentally benign amino acid derivative, such as *N*-benzoylglycine [17] used as a catalyst would interact with the soft Lewis basic moiety of thiourea [18] to increase the HB-donating ability of thiourea [19], so that the LG could be activated [20] with wide functional group tolerance.

A highly reactive glycosyl donor for instance, *O*-glycosyl trichloroacetimidates as efficient glycosyl donors [21], generally requires a p*K*a value less than 5 for activation at room temperature [22].

From the previous thiourea-based study we have taken very successful achiral Schreiner's thiourea compound **4** for our work [23-24]. It is known from the literature that *N*-benzoylglycine exhibit p*K*a values of about 3.6 [25]. Based on this fact, we anticipated that *N*-benzoylglycine the p*K*a value would be further diminished in the presence of hydrogen-bonding cocatalysts such as thiourea derivatives acts as an acid amplifier [26]. *N*-Benzoylglycine in the presence of Schreiner′s thiourea as cocatalyst exhibit cooperative behavior which strongly effects the reaction rate and stereoselectivity. We report that synergistic Schreiner's thiourea/*N*-benzoylglycine activation provide a more facile, efficient and practical glycosylation strategy for significant β-stereoselectivity at room temperature but in the presence of TMSOTf α/β selectivity depends on the reaction temperature [27]. However there is no report on catalyst activity of amino acid derivative *N*-benzoylglycine for *O*- glycosylation. It is a first report where application of a natural amino acid derivative, *N*-benzoylglycine with Schreiner's thiourea for significant β-stereoselectivity glycosidic bond formation at room temperature. Their reactivities and synthetic diversities provide new tool for the development of highly stereoselective glycosides. Hence, the application of the synergistic catalyst system consisting of *N*-benzoylglycine/thiourea derivatives for glycosidic bond formation will be an exciting addition to the literature (Figure 1).

2. Results and discussion

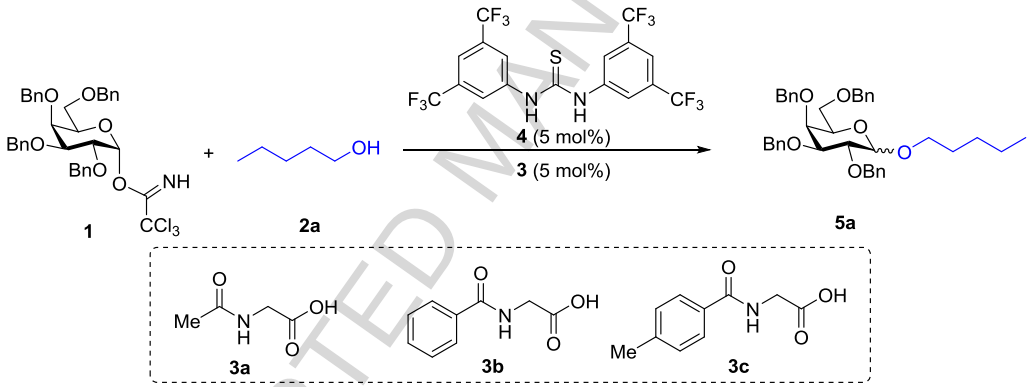
2.1 Catalyst screen in the glycosylation reaction

The basic attempts start with the screening of ability of different commercially available substituted glycine derivatives as a catalyst for improving the stereoselective glycosylation. We first screened glycosyl reactions employing 5 mol % of *N*-acetylglycine (**3a**, pKa = 3.64) [25] as catalysts with suitable donor α-D-galactopyranosyl trichloroacetimidate (**1**) [28] and 1-pentanol as acceptor **2a** in the absence and presence of Schreiner's thiourea (**4**, 5 mol %) in dry CH_2Cl_2 at room temperature. It was observed that formation of α,β-mixtures of **5a** takes place with slow reaction rate after 48 hours (Table 1, entry 1).

However, when catalyst **3a** with **4** was added (entry 2), the result was totally different, in much shorter reaction time, the exclusive formation of glycoside **5a** in 7:1 β/α ratio was observed; thus, result demonstrate the strong influence of thiourea **4** on reaction rate, yield, and stereoselectivity. Then we only use Schreiner's thiourea (**4**) on its own without any catalyst which did not promote the glycosylation reaction at all (entry 3). To attain faster reaction rates, glycosylation reaction was done with 10 mol % of *N*-acetylglycine **3a** and 10 mol % of thiourea **4**, the reaction rate increases without losing the high β-selectivity (entry 4). Even in the same condition for longer time yield of the desired product had no effect (Table 1, entry 5). To achieve higher yield and faster reaction rates, the acidic behaviour of *N*-benzoylglycine (**3b**, pKa = 3.64) [25] was investigated (entries 6, 7). In the presence of **4** (10 mol %) glycosylation reaction proceeded cleanly to give product **5a** in good yields with excellent β-selectivity (β:α >30:1) after 2 h. (Table 1, entry 6) but no improvement of yield and selectivity was observed even after longer time (entry 7). On the other hand when electron donating group (4-methylbenzoyl)glycine catalyst (**3c**, pka = 3.74) [25] in combination with **4** proved to be detrimental to reaction rate, yield, and stereocontrol, with

reactions needing 8 h for completion, practically exclusive formation of desired glycoside **5a** was observed with lesser yield (β/α 10:1, Table 1, entry 8). Next, we decided to explore the reaction conditions using **3b** via increasing the acid loading to 20 mol % of **4** had no effect on the outcome of the model reaction (entry 9). After analyzing the effect of acidic profile of glycine derivatives, we decided to explore the reaction conditions by changing the reaction solvent system to ether, acetonitrile, tetrahydrofuran, toluene or dichloroethane (Table 1, entries 10, 11, 12 and 13) which had an adverse effect on the reaction rate, yield, and selectivity. Performing the reaction under inverse addition conditions had no impact on the selectivity of glycoside formation (Table 1, entry 14) [29].

Table 1. Initial catalyst screen in the glycosylation of donor **1** and acceptor **2a**.[a]



Entry 1[a]	Catalyst (**3a-c**)	Cocatalyst **4**	Solvent	Time (h)	Yield[b] (β/α ratio)[c]
1	**3a**	–	CH_2Cl_2	48	5% (1:1)
2	**3a**	+	CH_2Cl_2	10	56% (7:1)
3	-	+	CH_2Cl_2	48	n.r., n.d.[d]
4[e]	**3a**	+	CH_2Cl_2	8	67% (7:1)
5[e]	**3a**	+	CH_2Cl_2	24	68% (7:1)
6	**3b**	+	CH_2Cl_2	2	88% >(30:1)
7	**3b**	+	CH_2Cl_2	8	87% >(30:1)[f]
8	**3c**	+	CH_2Cl_2	8	69% >(10:1)
9[g]	**3b**	+	CH_2Cl_2	2	88% >(30:1)[f]

10	**3b**	+	CH_3CN	10	43% >(20:1))
11	**3b**	+	THF	9	23% >(15:1)
12	**3b**	+	Toluene	24	Trace
13	**3b**	+	DCE	6	82% >(30:1)[f]
14[h]	**3b**	+	CH_2Cl_2	3	86% >(30:1)[f]

[a]Reaction conditions: **1** (1.0 equiv), **2a** (1.2 equiv), **3a–c** (5 mol %), **4** (5 mol %), solvent (5 mL), at room temperature under nitrogen atmosphere. [b]Yield determined after purification by flash silica gel chromatography. [c]Anomeric ratios were determined by ^{1}H NMR spectroscopy. [d] n.r.–no reaction, n.d.–no decomposition. [e]10 mol% of catalyst **3a** and **4** were employed to increase the reaction rate. [f] Detection limit of the minor isomer. [g]20 mol% of catalyst **3b** and **4** were employed. [h]Inverse addition.

2.2 Scope of substrates

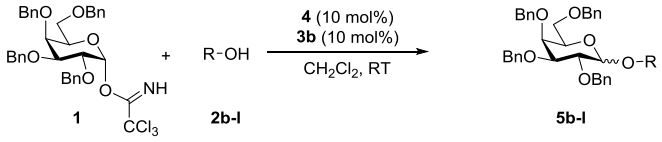
Having the optimum reaction conditions in hand results with **3b** as catalyst and **4** as cocatalyst, our attention was then turned to exploring the scope of the cooperative catalytic system on coupling reactions **1** [28] with a range of acceptors nucleophiles **2b-l** (Table 2). The efficacy of this reaction was examined with aliphatic, aromatic and sugar alcohols. In all cases, reactions proceeded smoothly within 2-4 h and in excellent yields with β-selectivity, as determined by the characteristic anomeric signals in the ^{1}H- and ^{13}C NMR spectra.

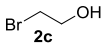
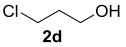
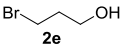
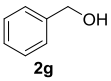
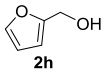
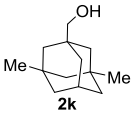
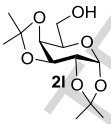
Glycosylations with less sterically hindered primary alcohols (**2b-f**) afforded their corresponding glycoside products with high β selectivity in 78% to 88% yield within 2 h (Scheme 1, entries 1-5). It is important to note that, halogenated primary alcohol such as 3-chloropropanol (**2d**), 3-bromopropanol (**2e**) gave exclusively β-glycoside **5d** and **5e** in 85% and 88 % yield respectively (Scheme 1, entries 3, 4). Furthermore, with decreasing nucleophilicity of the acceptor hydroxy group (through steric), as in aromatic acceptors **2g–h** produced their corresponding glucosides **5g–h** in 76–79% yields with moderate to good β-selectivity.

Then, moving from primary to secondary alcohols the reaction rate and the high preference for β-product formation decreased and the α-anomer could also be detected (entries 8 and 9). Acceptor **2i** and **2j** under the optimized reaction conditions gave their corresponding glycosides **5i** and **5j** with moderate selectivity (Table 2, entries 8, 9).

Interestingly, the reaction with the bulky primary alcohol, 3,5-dimetyladamant-1-yl-methanol (**2k**) produced preferentially or exclusively β-glycoside **5k** in 76% yield (Scheme 1, entry 10). As expected, studies with additional carbohydrate acceptor such as 1,2:3,4-di-*O*-isopropylidene-D-galactose (**2l**), the corresponding β-selective disaccharide glycoside **5l** can be successfully obtained as major products with this method (Table 2, entry 11) and the acid sensitive group survived well [30].

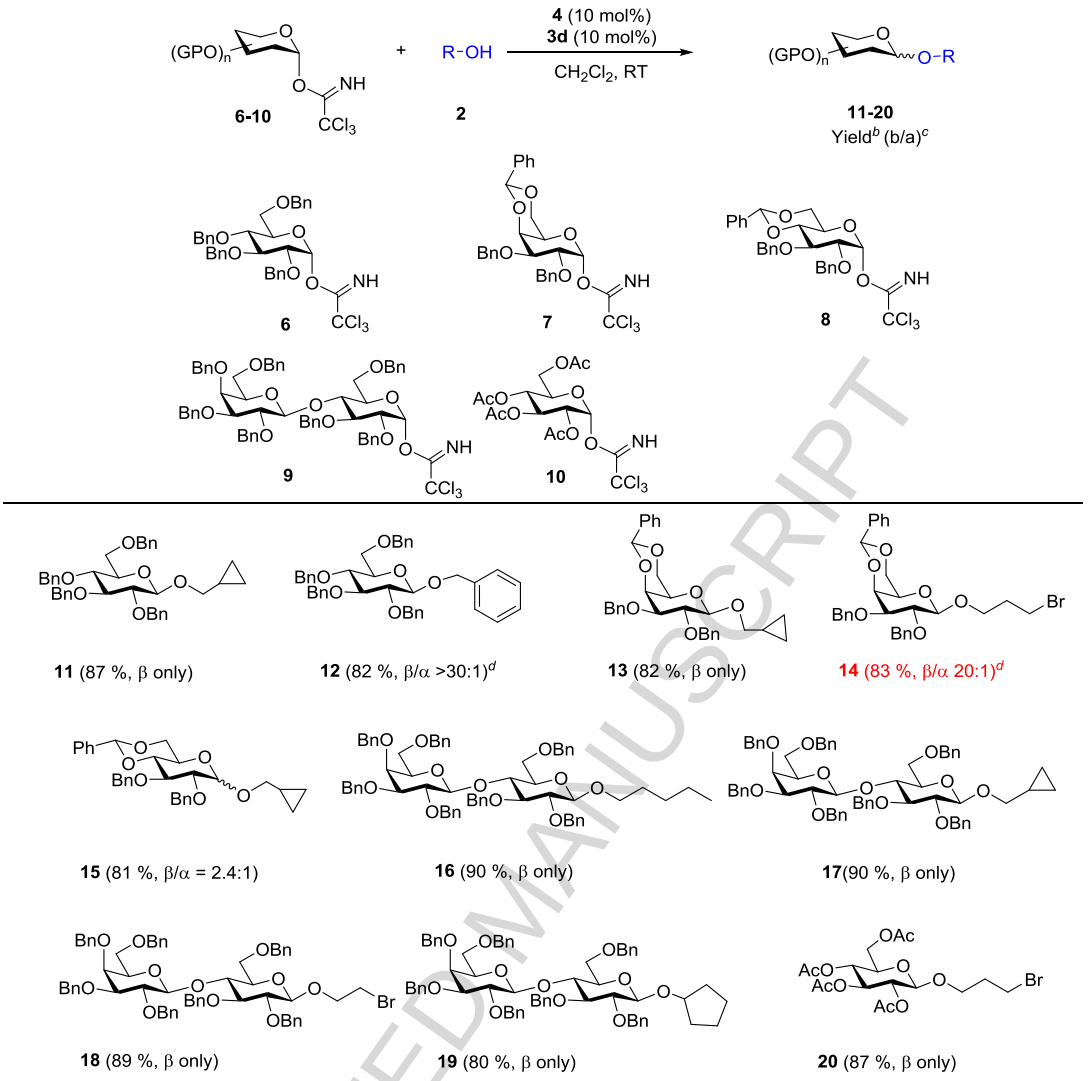
Table 2. Acceptor (**2a-l**) scope in glycosylation reaction with donor **1** in the presence of **3b** as catalyst and **4** as cocatalyst.



Entry[a]	ROH	Product	Reaction time	Yield[b]	β/α ration[c]
1	 2b	**5b**	2	88	7:1
2	 2c	**5c**	2	86	4:1
3	 2d	**5d**	2	85	>30:1[d]
4	 2e	**5e**	2	88	>15:1
5	 2f	**5f**	2	78	4:1
6	 2g	**5g**	2.5	76	5.5:1
7	 2h	**5h**	2.5	79	9:1
8	 2i	**5i**	3	75	4:1
9	 2j	**5j**	3	74	5:1
10	 2k	**5k**	4	76	>30:1[d]
11	 2l	**5l**	4	72	7:1

[a] Reaction conditions: **1** (1.0 equiv), **2b-l** (1.2 equiv), **3b** (10 mol %), **4** (10 mol %), CH_2Cl_2 (5 mL), at room temperature under nitrogen atmosphere. [b]Yield determined after purification by flash silica gel chromatography. [c] Anomeric ratios were determined by ^1H NMR spectroscopy. [d]Detection limit of the minor isomer.

To further demonstrate the scope of this method, we next investigated the stereoselectivity for different glycosyl donors [31] and acceptors as tabulated in scheme 2. First glycosylation was studied with α-D-glucopyranosyl trichloroacetimidate (**6**) with a variety of glycosyl acceptors, e.g., **2b** and **2g** under the optimized reaction condition (10 mol% of catalysts **3b** and **4**) gave their corresponding glucosides **11** and **12** respectively, with preferentially or exclusively β-selectivity, having good yield (Scheme 1).

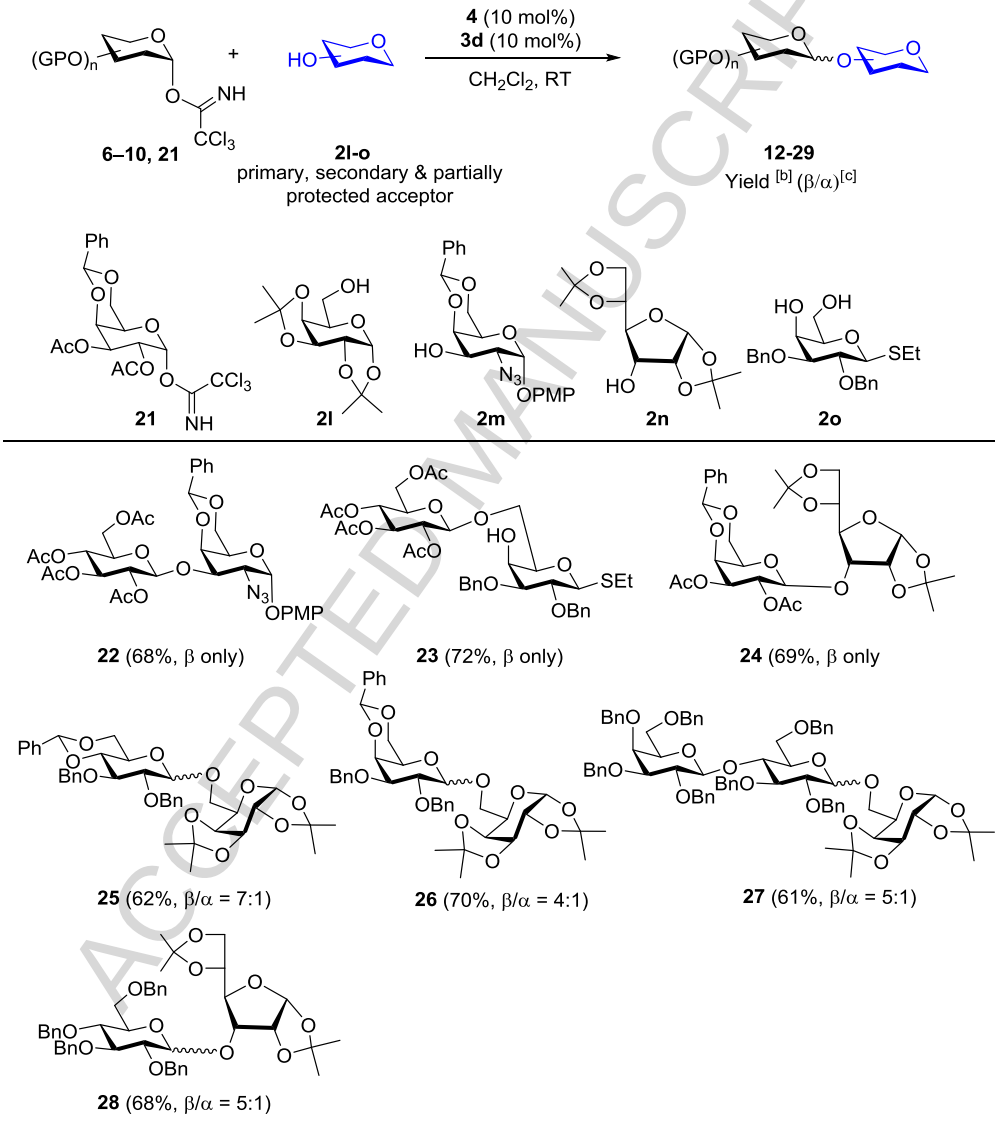


[a] Reaction conditions: donor **6-10** (1.0 equiv), different acceptor **2** (1.2 equiv), **3b** (10 mol %), **4** (10 mol %), CH_2Cl_2 (5 mL), at room temperature under nitrogen atmosphere. [b]Yield determined afterpurification by flash silica gel chromatography. [c]Anomeric ratios were determined by ^{1}H NMR spectroscopy. [d]Detection limit of the minor isomer.

Scheme 1. Glycosylation of donors **6–10** with variety of acceptors in the presence of **3b** as catalyst and **4** as cocatalyst.[a]

Under the optimized reaction conditions, 4,6-*O*-benzylidine-2,3- di-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate (**7**) was treated with different acceptors such as **2b** and **2e**, gave their corresponding glycoside **13** and **14** respectively, with β-selectivity in good yields. But, the moderate stereoselective outcome was noticed in the case of glycosylation of 4,6-*O*-benzylidine-2,3- di-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (**8**) glycosyl

donor with aliphatic primary hydroxyl group **2b** (scheme 1). A particularly interesting case is disaccharide trichloroacetimidate **9** with a variety of glycosyl acceptors, e.g., **2a**, **2b**, **2c**, and **2j** under the optimized reaction condition gave their corresponding glycosides **16**–**19**, respectively in good yields with exclusively β-glycoside. In case of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**10**) [32] was treated with **2e** under the optimized conditions, exclusively β-glycoside glycosides **20** was obtained (Scheme 1).



[a]Reaction conditions: donor **6-10** (1.0 equiv), different acceptor **2** (1.2 equiv), **3b** (10 mol %), **4** (10 mol %), CH_2Cl_2 (5 mL), at room temperature under nitrogen atmosphere. [b] Yield determined afterpurification by flash silica gel chromatography. [c]Anomeric ratios were determined by ^{1}H NMR spectroscopy. [d]Detection limit of the minor isomer.

Scheme 2. Schreiner's thiourea/*N*-benzoylglycine -catalyzed *O*-glycosylation.

Furthermore, we explore the utility of thiourea catalyzed glycosylation by using different glycosyl donor **6-10** & **21** with a series of differentially protected glycosyl acceptor like primary and secondary (**2l**, **2m** [33], **2n**, & **2o** [34] bearing benzylidene and isopropylidene protecting groups. For example, when acceptor **2n** was treated with donors **6** under the optimized conditions, glycoside **28** was procured in good yields with excellent β-selectivity (Scheme 2). Our attention then turned to explor the scope of regioselectivity to note that glycosylation with protected acceptor **2o** with glycosyl donors **10** under the optimized condition lead to highly regioselective glycoside products **23** in good yields with good selectivity (Scheme 2).

According to the literature, the TMSOTf catalyzed activation of *O*-glycosyl trichloroacetimidates donor leading to temperature-dependent α,β-selectivity which has ion-pair formation, thus favoring an S_N2-type reaction at low temperature and S_N1-type at high temperature [27].

To study the reaction pathway, some additional NMR studies were performed involving the shift of the -NH and –OH signals and shifts of proton signals of bis(trifluoromethyl)phenyl thiourea residues. In ^{1}H NMR spectroscopy, the mixtures of the cocatalyst **4** with donor **1**, cocatalyst **4** with acceptor **2a** and mixture of cocatalyst **4**, donor **1**, acceptor **2a** was studied (Supporting information Figure S1, S2, S3, S4).

When the NMR studies were performed with mixtures of **1**+**2a**+**4,** peaks were also shifted but no effect was observed for 1:1 mixture of **3b**+**4** and also for **3b**+**2a** due to the low solubility of catalyst **3b**. However, acceptor **2a** was added to the reaction mixture of 3b+4 to increased shifts of the aryl protons of **4** due to hydrogen-bond-mediated interaction between the catalyst **3b** and cocatalyst **4** [5].

From NMR study [5] and a literature survey, the following aspects can be made:

- The Schreiner's thiourea is the key for a reaction rate increase and the β-selectivity.

- The acceptor **2a**, catalyst **3b**, and cocatalyst **4** form hydrogen-bond-mediated complex [35] which seems to anticipate the interaction with donor **1** through intramolecular reaction lead to product formation.

- S_N2-type glycoside bond formation which is even facilitated at room temperature and in the absence of anchimeric assistance.

3. Conclusions

In summary, overall the result contained herein demonstrates a practical, highly stereoselective, and efficient glycosylation method for the preparation of β-glycosides using a cooperative *N*-benzoylglycine/thiourea promoter system. The reaction is widely applicable to a range of glycosyl donors, nucleophile acceptors proceeds with excellent selectivity as well as high yield, and tolerant of most common protecting groups. The reaction condition can be considered as an attractive alternative to the existing procedures. Thiourea as cocatalyst exhibits a cooperative behavior that has a strong effect on the reaction rate, yield, and the selectivity of glycosidations. The described reaction of β−stereoselective *O*-glycosylation of trichloroacetimidate donor using a cooperative *N*-benzoylglycine/thiourea promoter system should be efficient and indicate substantial improvement to the known synthesis methods.

4. Experimental section

Trichloroacetimidate donor **1**, **6**, **7**, **8**, **9**, **10** and **21** (1.0 equiv), acceptor (**2a-p**) (1.2 equiv) and cocatalyst aryl thiourea **4** (10 mol%) were dissolved in dry DCM (5 ml) and stirred at room temperature under a nitrogen atmosphere for 10 min. Catalyst **3** (10 mol %) was added and the resulting reaction mixture was stirred at room temperature until total consumption of glycosyl donor, then quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The

organic layer was washed with water, dried over Na_2SO_4, and organic layer concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the desired glycosides **5, 12-20,** and **22-28**. The α/β ratios of the newly formed glycosidic bonds were determined by the ^{1}H NMR integration.

Acknowledgments

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- β-stereoselective glycosylation via activation of *O*-glycosyl trichloroacetimidate donors
- *N*-Benzoylglycine in the presence of Schreiner's thiourea as cocatalyst exhibit cooperative behavior
- S_N2-type glycoside bond formation at room temperature in the absence of anchimeric assistance
- Widely applicable to a range of glycosyl donors, nucleophile acceptors, proceeds with excellent selectivity