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Hydrogen bond activated glycosylation under mild  
conditions

A mild glycosylation system was developed using glycosyl imidate donors and a charge-enhanced thiourea H-bond donor catalyst. The method can be used for the effective synthesis of O-, C-, S- and N-glycosides and chemoselective one-pot glycosylation. Benefitting from the mild reaction conditions, this new hydrogen bond-mediated glycosylation system in combination with a hydrogen bond-mediated aglycon delivery system provides a reliable method for the synthesis of challenging phenolic glycosides.

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# Hydrogen bond activated glycosylation under mild conditions†

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Herein, we report a new glycosylation system for the highly efficient and stereoselective formation of glycosidic bonds using glycosyl *N*-phenyl trifluoroacetimidate (PTFAI) donors and a charged thiourea hydrogen-bond-donor catalyst. The glycosylation protocol features broad substrate scope, controllable stereoselectivity, good to excellent yields and exceptionally mild catalysis conditions. Benefitting from the mild reaction conditions, this new hydrogen bond-mediated glycosylation system in combination with a hydrogen bond-mediated aglycon delivery system provides a reliable method for the synthesis of challenging phenolic glycosides. In addition, a chemoselective glycosylation procedure was developed using different imidate donors (trichloroacetimidates, *N*-phenyl trifluoroacetimidates, *N*-4-nitrophenyl trifluoroacetimidates, benzoxazolyl imidates and 6-nitro-benzothiazolyl imidates) and it was applied for a trisaccharide synthesis through a novel one-pot single catalyst strategy.

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## Introduction

Oligosaccharides and glycoconjugates play critical roles in an array of biological processes<sup>1</sup> and they have been widely explored for drug and vaccine development.<sup>2</sup> The key step in oligosaccharide and glycoconjugate synthesis is the glycosidic bond formation. In the past few decades, various glycosylation methods have been developed, including Brønsted acid or Lewis acid promoted glycosylation,<sup>3,4</sup> base promoted glycosylation,<sup>5</sup> gold-catalyzed glycosylation,<sup>6</sup> and recently emerged organo-catalyst effected glycosylation.<sup>7</sup> (Thio)ureas are the most well explored organo-catalysts, which generally act as hydrogen-bond donors and exhibit many important advantages over widely applied Brønsted acid or Lewis acid catalysts, such as shelf stability and excellent functional group tolerance. In 2013, Schmidt and co-workers reported a novel glycosylation system based on the activation and S<sub>N</sub>2-type substitution of trichloroacetimidate (TCAI) donors under the cooperative catalysis of phosphorous acid and Schreiner's thiourea.<sup>8</sup> In 2016, Ye and coworkers realized stereoselective glycosylation with glycosyl chlorides using Schreiner's thiourea in the presence of

K<sub>2</sub>CO<sub>3</sub>.<sup>9</sup> Toshima and Takemoto reported that arylthioureas can act as organo photoacids and co-catalysts for the activation of TCAI-donors through halogen bond activation (Fig. 1A).<sup>10</sup> Recently, inspired by glycosyltransferase-catalyzed glycosylation, Jacobsen and co-workers developed a novel type of chiral macrocyclic bis-thiourea for the activation of glycosyl chloride and phosphate donors with various glycoside acceptors, achieving stereoselective S<sub>N</sub>2-type glycosylation (Fig. 1A).<sup>11–13</sup>

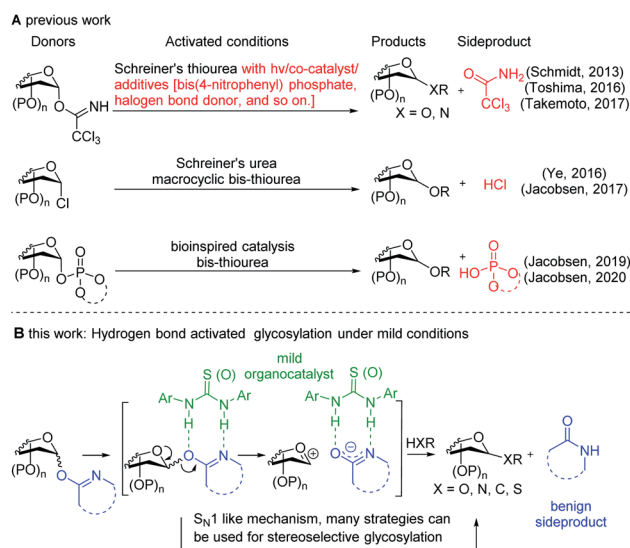


Fig. 1 Representative (thio)urea-catalyzed glycosylation (A) and the proposed hydrogen bond activated glycosylation in this study (B).

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Moreover, Galan and coworkers showed that 2-deoxyglycosides and 2-amino-2-deoxyglycosides can be assembled through the activation of glycol and 2-nitroglycol donors with an organothiourea catalyst.<sup>7,14</sup> Loh and coworkers described a stereo-selective glycosylation method using a unique constrained cyclopropyl ketone glycosyl donor, which could be activated with a hydrogen-bond donor thiourea catalyst, the reactivity of which was enhanced by cationic charge in the activator.<sup>15</sup>

Despite these important advancements in organocatalyzed glycosylation, several limitations remain, including the requirement of acidic co-catalyst species, or the necessity to scavenge acidic species generated in the reaction, as well as poor stereoselectivity. Herein, we describe a novel and generally applicable hydrogen bond activated glycosylation protocol that can proceed under mild conditions for the assembly of various *O*-, *C*-, *S*- and *N*-glycosides. We envisioned that glycosyl imidate-type donors (the H-bond acceptor) can be activated with organo-(thio)urea catalysts (the H-bond donor) under mild catalysis conditions and that the released secondary amide leaving group is neither acidic nor nucleophilic enough to compete with the acceptor toward the activated donor (Fig. 1B).<sup>3c,d</sup> Depending on the structure of the activator system, the hydrogen bond activation may generate oxocarbenium ion-type species,<sup>15</sup> which can be harnessed to achieve stereoselective glycosylation procedures.<sup>3</sup>

## Results and discussion

Perbenzyl-D-glucopyranosyl 6-nitro-2-benzothiazole **1a**<sup>16</sup> was first evaluated as a donor for our proposed hydrogen bond activated glycosylation system since this imidate-type donor does not generate an acidic side product,<sup>3c,d</sup> and the nitro group may function as a hydrogen bond acceptor which may help the activation. As shown in Table 1, a total of 10 hydrogen bond donor catalysts **C1**–**C10** were prepared including mono-(thio)urea **C1**–**C3**, *N,N*-diarylsquaramide **C4**,<sup>17</sup> and bis-(thio)ureas **C5**–**C9** inspired by Jacobsen's work,<sup>11–13</sup> and the charge-enhanced H-bond donor thiourea-catalyst **C10**.<sup>18</sup> In initial studies, glucosyl acceptor **2a** was chosen as a model acceptor and the reactions were conducted in acetonitrile at 50 °C (Table 1, entries 1–11). The screening of the thiourea, urea, and squaramide catalysts **C1**–**C9** revealed poor reactivity of these catalysts with bis-(thio)urea **C6** and **C7** giving the highest yields (entries 7 and 8). The optimization of H-bonding catalysts without increasing the acidity of the catalysts is very challenging. The Kass group reported that the charge-enhanced H-bond donor thiourea-catalyst **C10** showed much higher catalytic efficiency than Schreiner's thiourea, despite both of them having similar acidity.<sup>18</sup> The condensation of **1a** and **2a** under the activation of Kass' catalyst **C10** proceeded smoothly and yielded desired glycosylation product **3a** in 72% yield (entry 11). Switching the solvent to toluene or dichloroethane further increased the yield, to give **3a** in 87% and 81% yield, respectively (entries 12 and 13). Next, the effects of temperature and reaction time were examined. Reducing the temperature from 50 °C to 30 °C and shortening the reaction time from 36 hours to 16 hours resulted in a decrease in yield (52%, entry 14). In order to

Table 1 Optimization of the hydrogen bond mediated glycosylation system

Entry	Donor	Catalyst	Solvent	Temp.	Time	Yield
1	<b>1a</b>	No	CH <sub>3</sub> CN	50 °C	36 h	<5%
2	<b>1a</b>	<b>C1</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	12%
3	<b>1a</b>	<b>C2</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	17%
4	<b>1a</b>	<b>C3</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	5%
5	<b>1a</b>	<b>C4</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	10%
6	<b>1a</b>	<b>C5</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	15%
7	<b>1a</b>	<b>C6</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	24%
8	<b>1a</b>	<b>C7</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	20%
9	<b>1a</b>	<b>C8</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	10%
10	<b>1a</b>	<b>C9</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	16%
11	<b>1a</b>	<b>C10</b> (0.1 eq.)	CH <sub>3</sub> CN	50 °C	36 h	72%
12	<b>1a</b>	<b>C10</b> (0.1 eq.)	Toluene	50 °C	36 h	87%
13	<b>1a</b>	<b>C10</b> (0.1 eq.)	DCE	50 °C	36 h	81%
14	<b>1a</b>	<b>C10</b> (0.1 eq.)	DCM	30 °C	16 h	52%
15	<b>1b</b>	<b>C10</b> (0.1 eq.)	DCM	30 °C	16 h	80%
16	<b>1c</b>	<b>C10</b> (0.1 eq.)	DCM	30 °C	16 h	86%

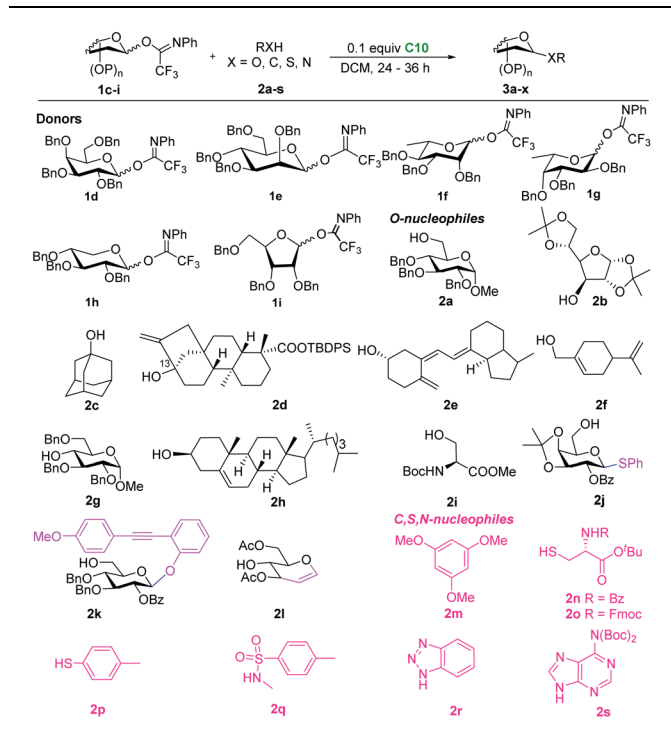
further optimize the glycosylation system, other imidate donors, including perbenzyl 1-*O*-(*N*-4-nitro-phenyl-trifluoroacetimidoyl)-D-glucopyranoside **1b** and perbenzyl 1-*O*-(*N*-phenyl-trifluoroacetimidoyl)-D-glucopyranoside **1c** (Table 1), were investigated next. To our delight, donor **1b** reacted with acceptor **2a** in the presence of Kass catalyst **C10** at 30 °C producing disaccharide **3a** in 80% yield in 16 hours (entry 15). Perbenzyl 1-*O*-(*N*-phenyl-trifluoroacetimidoyl)-D-glucopyranoside donor **1c**, without the nitro substituent on the leaving group, afforded the desired product with an even higher yield (86%) under the same reaction conditions (entry 16). The enhanced reactivity of **1c** over **1b** may be due to the electron withdrawing effect of the nitro substituent on the leaving group of donor **1b** that decreases the electron density of the nitrogen of the glycosyl imidate, which acts as the actual H-bond acceptor.





With an optimized glycosylation protocol in hand, the scope and general application of this activation system were further explored using different donors and acceptors (Table 2). We

**Table 2** Scope of the hydrogen bond mediated glycosylation system for different glycosyl donors and a wide range of acceptors



Entry	Donor	Acceptor	Temperature	Product	Yield <sup>a</sup>	$\alpha : \beta^b$
1	<b>1c</b>	<b>2a</b>	27 °C	<b>3a</b>	93%	1 : 1
2	<b>1c</b>	<b>2b</b>	30 °C	<b>3b</b>	88%	3 : 1
3	<b>1c</b>	<b>2c</b>	30 °C	<b>3c</b>	92%	1.2 : 1
4	<b>1c</b>	<b>2d</b>	30 °C	<b>3d</b>	81%	1 : 1.4
5	<b>1c</b>	<b>2e</b>	3 °C	<b>3e</b>	61%	1.2 : 1
6	<b>1d</b>	<b>2f</b>	27 °C	<b>3f</b>	86%	1 : 1
7	<b>1d</b>	<b>2g</b>	30 °C	<b>3g</b>	85%	2.2 : 1
8	<b>1d</b>	<b>2h</b>	30 °C	<b>3h</b>	97%	1 : 1.5
9	<b>1e</b>	<b>2a</b>	30 °C	<b>3i</b>	91%	1.6 : 1
10	<b>1f</b>	<b>2a</b>	19 °C	<b>3j</b>	99%	1 : 1
11	<b>1f</b>	<b>2i</b>	19 °C	<b>3k</b>	88%	1.5 : 1
12	<b>1g</b>	<b>2a</b>	25 °C	<b>3l</b>	77%	1 : 1.4
13	<b>1h</b>	<b>2a</b>	27 °C	<b>3m</b>	93%	1 : 1.5
14	<b>1i</b>	<b>2a</b>	27 °C	<b>3n</b>	88%	1 : 1
15	<b>1c</b>	<b>2j</b>	30 °C	<b>3o</b>	85%	1 : 1
16	<b>1c</b>	<b>2k</b>	30 °C	<b>3p</b>	84%	2.2 : 1
17	<b>1e</b>	<b>2l</b>	25 °C	<b>3q</b>	75%	2.5 : 1
18	<b>1c</b>	<b>2m</b>	50 °C	<b>3r</b>	66%	1 : 1.3
19	<b>1c</b>	<b>2n</b>	30 °C	<b>3s</b>	67%	2 : 1
20	<b>1c</b>	<b>2o</b>	50 °C	<b>3t</b>	81%	2 : 1
21	<b>1c</b>	<b>2p</b>	30 °C	<b>3u</b>	98%	1.3 : 1
22	<b>1d</b>	<b>2q</b>	30 °C	<b>3v</b>	94%	1.5 : 1
23	<b>1c</b>	<b>2r</b>	30 °C	<b>3w</b>	96% <sup>c</sup>	
24	<b>1i</b>	<b>2s</b>	40 °C	<b>3x</b>	62% <sup>d</sup>	1.5 : 1

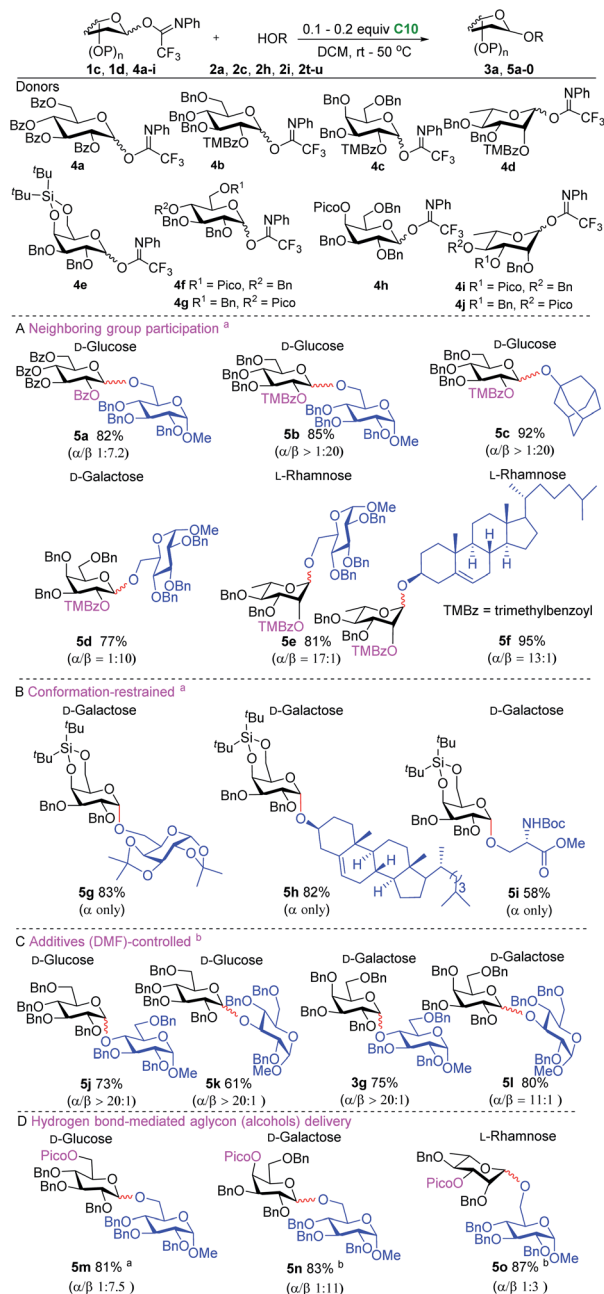
<sup>a</sup> The reaction yields depended on isolated products. <sup>b</sup> The anomeric ratios were determined by <sup>1</sup>H NMR analysis or separation. <sup>c</sup> 0.15 equivalent **C10** was used; N1 product: 59% ( $\alpha : \beta$  1 : 4.7); N2 product: (37% 1 : 3). <sup>d</sup> 0.2 equivalent **C10** was used.

were pleased to find that primary alcohol **2a**, secondary alcohol **2b**, and tertiary alcohol 1-adamantanol **2c** all coupled smoothly with glucosyl donor **1c**, providing disaccharides **3a**, **3b** and compound **3c** in 88–93% yields (entries 1–3). The reactions can be readily scaled up and disaccharide **3a** could be produced on a gram scale in 89% yield. Notably, the hydrogen bond mediated glycosylation system works very well for acid labile nucleophiles. The steviol aglycon **2d**, ergocalciferol **2e** and perillyl alcohol **2f** were glycosylated with **1c** or **1d**, yielding the coupled glycosides **3d–3f** in 61–86% yield (entries 4–6). Therefore, this mild hydrogen bond activation system provides a powerful tool for the direct glycosylation of acid labile acceptors, enabling the first chemical synthesis of the extremely acid labile glycosylated ergocalciferol **3e**. To show the general applicability of the mild glycosylation system, a wide array of glycosyl donors **1d–1i** including D-galacto-, D-manno-, L-rhamno-, L-fuco-, D-xylopyranosyl donors, and a D-ribofuranosyl donor were coupled successfully with various acceptors to produce the corresponding glycosides **3g–3n** in excellent yields (77–99%, entries 7–14).

Furthermore, both thioglycoside acceptor **2j** and *o*-(*p*-methoxyphenylethynyl)phenyl glycoside acceptor **2k** reacted smoothly with imidate donor **1c** under **C10**-mediated activation to yield **3o** and **3p**, indicating that this activation system could be applied for glycosylation between glycosyl donors and acceptors bearing orthogonal leaving groups (entries 15 and 16). Notably, the very acid labile glycol acceptor **2l** could be successfully condensed with glycosyl donor **1e** under the mild glycosylation conditions to provide disaccharide **3q** (entry 17). Encouraged by these results in *O*-glycoside synthesis, the assembly of *C*-glycoside, *S*-glycosides and *N*-glycosides in the activation system was investigated. 1,3,5-Trimethoxybenzene **2m**, thiophenol **2p** and L-cysteine acceptors **2n–2o** were glycosylated successfully with **1c** to afford *C*-glycoside **3r** and *S*-glycosides **3s–3u** in good yield (66–98%), respectively (entries 18–21). In addition, the coupling of *N*,4-dimethyl benzene-sulfonamide **2q** with donor **1d** gave *N*-glycosyl sulfonamide **3v** in 94% yield (entry 22). This result shows that the mild activation system can be adopted for the synthesis of glycosyl sulfonamides, which have been investigated as cytostatic agents.<sup>19</sup> Benzotriazole **2r** and purine **2s** could be glycosylated with donor **1c** and ribofuranosyl imidate **1i** to give the desired *N*-glycoside **3w** in 96% yield and nucleoside **3x** in 62% yield, respectively (entries 23 and 24).

We then focussed our attention on the development of stereoselective glycosylation using the hydrogen bond activated glycosylation system (Scheme 1). The activation of the imidate donors with catalyst **C10** likely leads to the generation of an oxocarbenium ion intermediate with a weakly coordinating tetrakis(3,5-bis(trifluoromethyl)phenyl)borate counterion (for more details of initial studies into the reaction mechanism see the ESI†). To control the stereoselectivity of *S*<sub>N</sub>1-type glycosylation,<sup>20</sup> different strategies were explored including neighboring group participation, conformational constriction, additive-controlled glycosylation and hydrogen bond mediated aglycon delivery. Neighboring group participation is the most widely used strategy for the construction of 1,2-*trans*-glycosidic bonds.<sup>20b,c,21</sup> However, when perbenzoyl-1-*O*-(*N*-phenyl-





**Scheme 1** Stereoselective glycosylation using the hydrogen bond mediated glycosylation system combined with different stereoselective glycosylation strategies ((A) neighboring group participation; (B) conformation-restrained; (C) additive-controlled; (D) hydrogen bond-mediated aglycon delivery). Highlighted in blue are nucleophilic acceptors and in red are glycosidic bonds cleaved and formed. <sup>a</sup>0.1 equivalent C10 was used; <sup>b</sup>0.2 equivalent C10 was used. The reaction yields depended on isolated products; the anomeric ratios were determined by <sup>1</sup>H NMR analysis or separation of the anomers by chromatography.

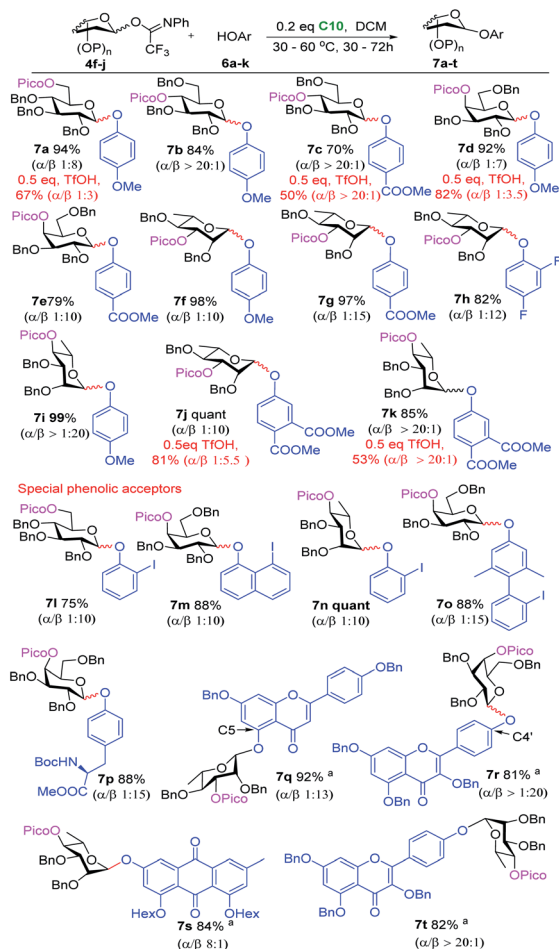
trifluoroacetimidoyl)-D-glucopyranoside donor **4a** was used to glycosylate acceptor **2a**, disaccharide **5a** was obtained with relatively moderate stereoselectivity. The formation of the undesired  $\alpha$ -anomer may originate from the orthoester intermediate under the mild catalysis conditions. Therefore, the

bulky trimethylbenzoyl (TMBz) group,<sup>22</sup> a more potent neighboring group, was evaluated, resulting in the formation of the desired products **5b–5f** in good yield (77–95%) with excellent stereoselectivity (see Scheme 1A). Several conformationally restricted donor systems have been introduced over the years to enable the stereoselective construction of glycosidic linkages.<sup>23</sup> We tested a silylidene protected galactosyl donor **4e** to generate the desired products **5g–5i**, which were isolated in good yield and as single anomers (see Scheme 1B). Much effort has recently been directed towards the *in situ* generation of reactive species through the use of nucleophilic additives or reactivity modulators to allow for stereoselective glycosylation reactions. Especially the use of DMF has found wide application in the construction of 1,2-*cis*-glucosides.<sup>24</sup> We successfully combined this strategy with the new glycosylation system to produce 1,2-*cis*-glucosides (**5j–5k**) and 1,2-*cis*-galactosides (**3g** and **5l**) in good yield and excellent stereoselectivity (see Scheme 1C). Hydrogen bond-mediated aglycon delivery (HAD) was introduced by Demchenko and co-workers to direct the acceptor to the desired face of the donor glycoside. This approach has now been applied for the stereoselective construction of many different glycosidic linkages.<sup>25</sup> We investigated the combination of this strategy with our glycosylation system for the selective formation of  $\beta$ -glucosides,  $\beta$ -galactosides and  $\beta$ -rhamnosides (see Scheme 1D). The glucosyl donor with the directing picoloyl group (Pico) on the C-6 position delivered the desired  $\beta$ -product **5m** (81%,  $\beta$  :  $\alpha$  = 7.5 : 1). The use of the directing picoloyl group on the C-4 position of a galactosyl donor led to the desired  $\beta$ -product **5n** in 83% yield with good stereoselectivity ( $\beta$  :  $\alpha$  = 11 : 1). Even the very challenging  $\beta$ -rhamnoglucosidic bond could be forged using the C-3-picoloyl group and disaccharide **5o** was generated in 87% yield with acceptable stereoselectivity ( $\beta$  :  $\alpha$  = 3 : 1).

Having successfully combined our hydrogen bond-mediated activation with the HAD system, we realized that this strategy could provide access to the effective synthesis of phenolic glycosides, which have been shown to display diverse biological activities and pharmaceutical potential.<sup>26</sup> Phenolic *O*-glycosylation is challenging due to the poor nucleophilicity of phenols (especially those bearing electron-withdrawing groups) as well as the Fries-type rearrangement of *O*-aryl glycosides to *C*-glycosides of phenols, bearing electron-donating groups, under acidic reaction conditions.

We envisioned that the relatively low  $pK_a$  of phenols leads to a stronger hydrogen bond with the directing picoloyl group on the glycosyl donor, which not only increases the phenol acceptors' nucleophilicity but also increases the stereoselectivity. As shown in Scheme 2, the glucosyl donor with a directing picoloyl group at the C-6 position was coupled with 4-methoxyphenol to produce the desired phenolic glycoside **7a** in 94% yield with good stereoselectivity ( $\beta$  :  $\alpha$  = 8 : 1). A wide range of glycosyl donors with a Pico-directing group were next glycosylated with electron-rich and electron-poor phenols to afford the *O*-aryl glycosides **7b–7i** in excellent yield with good to excellent stereoselectivity. The challenging  $\beta$ -*O*-aryl rhamnosides **7f–7h** were obtained in high yield with excellent stereoselectivity (82–98%,  $\alpha$  :  $\beta$   $\geq$  1 : 10). The increase in the stereoselectivity of this





**Scheme 2** Phenolic glycosylation substrate scope. The nucleophilic acceptors are highlighted in blue and glycosidic bonds cleaved and formed are highlighted in red. <sup>a</sup>0.3 equivalent C10 was used. The reaction yields depended on isolated products; the anomeric ratios were determined by <sup>1</sup>H NMR analysis or separation of the anomers by chromatography.

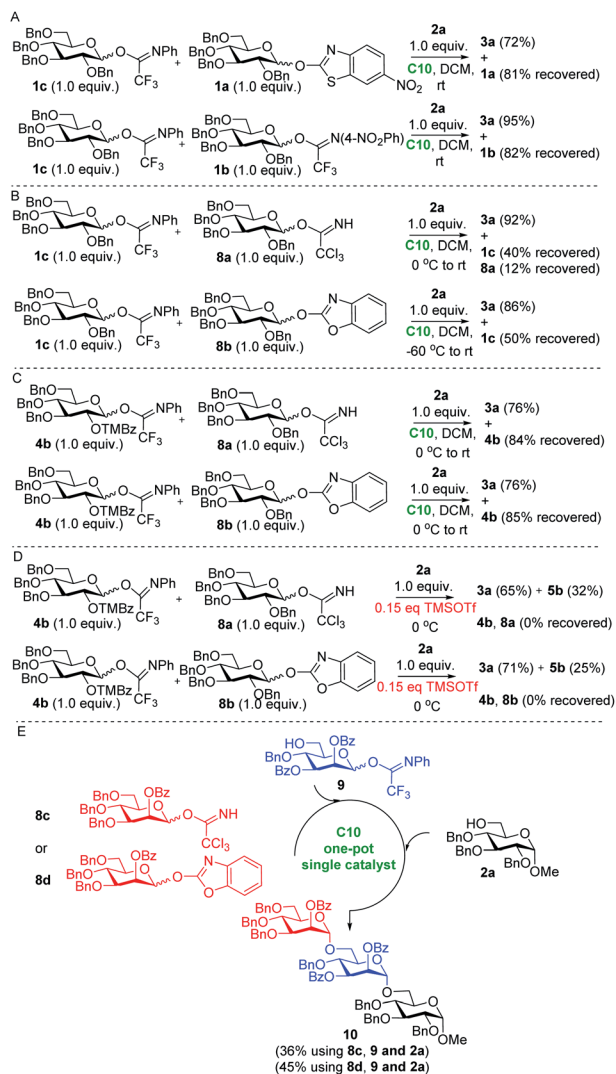
system with respect to the *O*-alkyl β-rhamnosylation (towards **5o**, Scheme 1D) supports the notion that the stronger H-bond leads to more effective delivery of the aglycon. Encouraged by these results, we investigated the glycosylation of the very electron-poor 3,4-dicarbomethoxyphenol, generating the desired product **7j** and **7k** in 85% and quantitative yield, respectively, with good stereoselectivity ( $\beta : \alpha = 10 : 1$  and  $\alpha : \beta > 20/1$ ). To benchmark our procedure, some experiments under 'classic' TFOH-catalyzed conditions were performed (indicated in red in Scheme 2). These experiments showed that these reactions proceeded with lower yield and/or poorer stereoselectivity (**7a**: 94%,  $\alpha : \beta = 1 : 8$  vs. 67%,  $\alpha : \beta = 1 : 3$ ; **7c**: 70%,  $\alpha : \beta > 20 : 1$  vs. 50%,  $\alpha : \beta > 20 : 1$ ; **7d**: 92%,  $\alpha : \beta = 1 : 7$  vs. 82%,  $\alpha : \beta = 1 : 3.5$ ; **7j**: quantitative yield,  $\alpha : \beta = 1 : 10$  vs. 81%,  $\alpha : \beta = 1 : 5.5$ ; **7k**: 85%,  $\alpha : \beta > 20 : 1$  vs. 53%,  $\alpha : \beta > 20 : 1$ ). Likely, TFOH can protonate the Pico group, which not only prevents the formation of a hydrogen bond with the acceptor, resulting in poorer stereoselectivity, but also decreases the donor's reactivity resulting in a lower yield.

We then explored more elaborate phenolic acceptors. 2-Iodophenol, 8-iodo-1-naphthol and 2'-iodo-2,6-dimethyl-[1,1'-biphenyl]-4-ol were glycosylated with different Pico-bearing glycosyl donors to give the desired products **7l–7o** in 75–100% yield with excellent stereoselectivity ( $>10 : 1$ ). The former can be easily transferred into an *o*-(*p*-methoxyphenylethynyl)phenyl glycoside (MPEP donor),<sup>4e</sup> while the latter can provide a 3,5-dimethyl-4-(2'-phenylethynylphenyl)phenyl glycoside (EPP donor).<sup>4b</sup> Boc-protected L-tyrosine could be coupled with galactosyl donor **4h** to afford glycosyl amino acid **7p** in 88% yield with excellent stereoselectivity ( $\beta : \alpha = 15 : 1$ ). The mild glycosylation conditions ensured that the acid-labile Boc-group remained unscathed. Flavonoid *O*-glycosides possess a wide spectrum of biological activities, showing antimicrobial, anti-cancer, and radical-scavenging potential.<sup>26</sup> The extraordinary low reactivity of the flavonoid phenolic OHs makes the formation of glycosidic linkages with these alcohols very challenging.<sup>27</sup> Gratifyingly, 4',7-di-*O*-benzyl-apigenin and 3,5,7-tri-*O*-benzyl-kaempferol were glycosylated uneventfully to give the desired **7q** in 92% yield ( $\beta : \alpha = 13 : 1$ ) and **7r** in 81% yield with excellent stereoselectivity ( $\beta : \alpha > 20 : 1$ ). Finally, the utility of our glycosylation protocol was successfully demonstrated in the efficient synthesis of two fully protected natural phenolic glycosides: emodin-3-*O*- $\alpha$ -L-rhamnopyranoside and kaempferol-4'-*O*- $\alpha$ -L-rhamnopyranoside, which show interesting antioxidant, anti-inflammatory and antitumor properties and which are important components of medicinal herbs.<sup>28</sup> Thus, 1,8-di-*O*-*n*-hexanoyl-emodin was coupled with rhamnosyl donor **4j** to produce the phenolic glycoside **7s** in 84% yield with good stereoselectivity ( $\alpha : \beta = 8 : 1$ ). Similarly, tri-*O*-benzyl kaempferol was glycosylated with this donor to afford the phenolic glycoside **7t** in excellent yield with stereoselectivity (82%,  $\alpha : \beta > 20 : 1$ ).

Having established the utility of our protocol in the assembly of these targets, we realized that the difference in the reactivity of the different imidate-type donors (see Table 1) and the mildness of the developed activation procedure might enable the development of a chemoselective glycosylation procedure using different glycosyl imidates. The conception of chemoselective glycosylation procedures has streamlined oligosaccharide synthesis and found application in the assembly of a plethora of biologically relevant oligosaccharides. However, the use of glycosyl imidate acceptors in chemoselective glycosylation sequences has only been reported once due to the high reactivity of these glycosides.<sup>29</sup> We first sought to establish the relative reactivity of different types of imidates under our hydrogen bond mediated activation conditions. Therefore, the perbenzyl glucose *N*-phenyl trifluoroacetimidate donor **1c** was used to compete with the corresponding nitro-benzothiazolyl imidate **1a**, *N*-4-nitro-phenyl trifluoroacetimidate **1b**, trichloroacetimidate **8a**, and benzoxazolyl imidate **8b** (Scheme 3A–D). Thus, Kass' catalyst **C10** (0.1 equiv.) was added to a mixture of *N*-phenyl-trifluoroacetimidoyl **1c**, perbenzyl 6-nitro-2-benzothiazolyl glucopyranoside **1a** (1.0 equiv. each) and sugar alcohol **2a** (1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. The reaction mixture was stirred for 10 hours, during which time it was gradually warmed to room temperature. It was observed that the *N*-phenyl-trifluoroacetimidate donor **1c** was completely







Scheme 3 (A–D) Comparison of the different imidate-type donors' reactivity under the action of organocatalyst **C10**; (E) one-pot single catalyst synthesis of trisaccharide **10**.

consumed, leading to the disaccharide product **3a** in 72% isolated yield, while the 6-nitro-benzothiazolyl imidate donor **1a** could be recovered in 81%. In a similar competitive reaction of *N*-phenyltrifluoroacetimidate **1c** and *N*-(4-nitro-phenyl)-trifluoroacetimidate **1b**, the former was fully activated, leading to coupled disaccharide **3a** in 95% yield, while the latter remained largely intact (82% recovery) (Scheme 3A). The competitive reaction between **1c** and trichloroacetimidate **8a** revealed that the latter was more reactive under the H-bond activation conditions, although the difference in reactivity was relatively small and *N*-phenyl trifluoroacetimidate donor **1c** could be recovered in 40% along with 12% of donor **8a**. Benzoxazolyl imidate donor **8b** was shown to be most reactive according to the competitive reaction with **1c**, and the latter could be recovered in 50% yield (Scheme 3B). By adjusting the protecting groups of the donors, a larger difference in relative reactivity could be created. As shown in Scheme 3C, in the competitive reactions of the trimethyl benzoyl protected *N*-phenyl trifluoroacetimidate donor **4b** with **8a** or **8b**,

the latter donors were completely consumed, while donor **4b** could be recovered in 84% and 85% yield respectively. Similar competitive reactions using TMSOTf catalysis provided both disaccharides **3a** and **5b**, while none of the donors could be recovered (Scheme 3D). Thus, H-bond activation appears to be superior to other well-established approaches, for the selective activation of different imidate donors. On the basis of these findings, the one-pot assembly of trisaccharide **10** was explored (Scheme 3E). Initially, 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl mannosyl trichloroacetimidate **8c** and mannosyl *N*-phenyl trifluoroacetimidate acceptor **9** were treated with 15 mol% of Kass' catalyst **C10** for 17 h. Subsequently, acceptor **2a** was added to couple with the newly formed disaccharide, affording trisaccharide **10** in 36% yield. This yield could be further improved through the use of the more reactive benzoxazolyl imidate donor **8d** delivering the trisaccharide **10** in 45% yield. The main reason for the moderate overall yield was the fact that acceptor **9** was not completely consumed in the first step coupling. This one-pot reaction sequence illustrates the potential of **C10** in the chemoselective activation of different imidate donors. In future one-pot assemblies, fine tuning of donors may be required because of the generally high reactivity of imidate type glycosides.

## Conclusions

A novel glycosylation system using glycosyl imidate donors and a charge-enhanced thiourea hydrogen-bond-donor catalyst has been developed for the highly efficient and stereoselective formation of glycosidic bonds. This hydrogen bond-mediated glycosylation system operates under mild conditions and offers broad reaction scope, allowing the effective synthesis of *O*-, *C*-, *S*- and *N*-glycosides. Taking advantage of the mild reaction conditions, the combination of the new hydrogen bond-mediated glycosylation system with hydrogen bond-mediated aglycon delivery provides a reliable method for the synthesis of phenolic glycosides. The directing picoloyl group on the glycosyl donors can form a hydrogen bond with the phenol alcohol, increasing the acceptors' nucleophilicity and effectively guiding the nucleophile to the same face of the donor to which the Pico group is attached. Benefitting from the mild reaction conditions, glycosyl *N*-phenyl trifluoroacetimidate donors can be used in conjunction with more reactive imidate-type donors, such as trichloroacetimidates and benzoxazolyl imidates, opening new avenues for chemoselective, one-pot glycosylation strategies. With these promising features, we foresee many applications of this new glycosylation protocol in the assembly of biologically relevant oligosaccharides and glycoconjugates. The method will prove exceptionally useful in the construction of target structures that are highly acid labile.

## Author contributions

Ke Xiao did most of the experiments; Yongxin Hu did part of work on hydrogen bond-mediated aglycon delivery; Yongyong Wan work on synthesis of the catalyst; Xinxin li and Qin Nie did part of work on phenolic glycosylation; Hao Yan did some work on optimization the glycosylation conditions. Liming Wang did



experiments on additives-controlled glycosylation and results analysis/discussion. Jinxi Liao, Deyong Liu and Yuanhong Tu did NMR on mechanism study. Jiandong Sun and Qingju Zhang: funding acquisition, project administration, supervision, writing – review and editing. Jeroen Codee provided many suggestions on this project and organization of the manuscript.

## Conflicts of interest

The authors declare no conflict of interest.

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