Glycosylation

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Stereoselective Koenigs–Knorr Glycosylation Catalyzed by Urea

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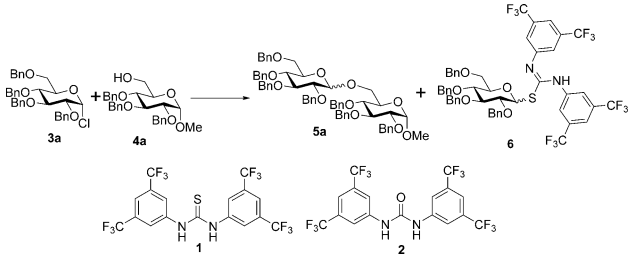
Abstract: *A stereoselective Koenigs–Knorr glycosylation reaction under the catalysis of urea is described. This method is characterized by urea-mediated hydrogen-bond activation and subsequent glycosylation with glycosyl chlorides or bromides. Excellent yields and high anomeric selectivity can be achieved in most cases. Moreover, the low α-stereoselectivity of glycosylations observed when using perbenzylated glucosyl donors can be greatly improved by the addition of tri-(2,4,6-trimethoxyphenyl)phosphine (TTMPP).*

Koenigs–Knorr glycosylation, which dates back to 1901,[1] refers to activation of the anomeric centre by the decomposition of glycosyl halides (normally bromides and chlorides) and subsequent coupling with glycosyl acceptors. The activators are always a full equivalent of heavy metal salts such as $Hg(CN)_2$,[2] $AgNO_3$,[3] Ag_2CO_3,[3] AgOTf,[4] $AgClO_4$,[5] Ag_2O,[6] $Cu(OTf)_2$,[7] and others.[8] Lemieux's halide-ion-catalyzed glycosylation reactions with highly reactive perbenzylated glycopyranosyl bromides in the presence of tetraethylammonium bromide avoids the use of heavy metals.[9] Recently, intense interest in the catalytic activation of reactants through noncovalent interactions, especially hydrogen-bond activation, has resulted in the development of undeniably useful methods.[10] Hydrogen-bond donors, especially (thio)urea derivatives, have been established as potent noncovalent organocatalysts.[11] In particularly, halogenated compounds could also be activated by (thio)ureas, and an enantioselective addition to oxocarbenium ions occurred under the catalysis of thiourea.[12] Despite the broad use of organocatalysis in asymmetric synthesis,[13] its application to glycosylation reactions is still in its infancy. Herein, we describe our efforts to develop a urea-mediated organocatalytic Koenigs–Knorr glycosylation method with glycosyl halides.

In initial studies, the perbenzylated glucosyl chloride **3a** and glucosyl acceptor **4a** were chosen as model compounds to carry out the reaction with 1.0 equiv of thiourea **1**[11d] in toluene (1.5 mL) as the solvent at different temperatures for 24 h (Table 1, entries 1–3). The coupling reaction was found to proceed and **5a** was afforded in 5% yield at 50°C. After screening a number of additives, the use of 2.0 equiv of K_2CO_3 gave the best yield (entries 5–10). Replacement of toluene with *n*-hexane led to the formation of **5a** in moderate yield (entries 11–13). The yield was improved by gradually evaporating the solvent to dryness over 24 h (entries 14, 15), and this effect probably results from improvement of the solubility of urea **2**, which is caused by the rising temperature, and the concentration effect (Tables S2, S3 in the Supporting

Table 1: Glycosylation of acceptor **4a** with glucosyl chloride **3a**.[a]



Entry	Promoter (equiv)	Solvent	Additive (equiv)	*T* [°C]	Yield [%][b]
1	**1** (1.0)	toluene	–	−72	0
2	**1** (1.0)	toluene	–	0	0
3	**1** (1.0)	toluene	–	50	5
4	**1** (0)	toluene	–	50	0
5	**1** (1.0)	toluene	TfOH (1.0)	50	8
6	**1** (1.0)	toluene	TTBP (1.0)	50	28
7	**1** (1.0)	toluene	TTBP (5.0)	50	17
8	**1** (1.0)	toluene	K_2CO_3 (2.0)	50	40
9	**1** (1.0)	toluene	K_2CO_3 (3.0)	50	39
10	**1** (0)	toluene	K_2CO_3 (2.0)	50	0
11	**1** (1.0)	DCE	K_2CO_3 (2.0)	50	7
12	**1** (1.0)	dioxane	K_2CO_3 (2.0)	50	0
13	**1** (1.0)	*n*-hexane	K_2CO_3 (2.0)	50	51
14[c]	**1** (1.0)	*n*-hexane	K_2CO_3 (2.0)	50	71
15[c]	**1** (1.0)	*n*-hexane	K_2CO_3 (2.0)	reflux	75
16[d]	**1** (1.0)	*n*-hexane	K_2CO_3 (2.0)	reflux	85
17[c]	**1** (0.1)	*n*-hexane	K_2CO_3 (2.0)	reflux	11
18[c]	**2** (1.0)	*n*-hexane	K_2CO_3 (2.0)	reflux	73
19[c]	**2** (0.1)	*n*-hexane	K_2CO_3 (2.0)	reflux	62
20[d]	**2** (0.2)	*n*-hexane	K_2CO_3 (2.0)	reflux	65
21[d]	**2** (0.2)	c-hexane	K_2CO_3 (2.0)	reflux	90
22[d]	**2** (0.2)	CCl_4	K_2CO_3 (2.0)	reflux	62
23[d]	**2** (0.2)	benzene	K_2CO_3 (2.0)	reflux	95
24[d]	**2** (0.2)	toluene	K_2CO_3 (2.0)	reflux	46
25[d]	**2** (0)	benzene	K_2CO_3 (2.0)	reflux	0
26[d]	**2** (0.2)	benzene	K_2CO_3 (0)	reflux	65

[a] Reaction conditions: **3a** (0.10 mmol), **4a** (0.10 mmol), promoter, additive, solvent (1.0 mL), under argon atmosphere, 24 h. α/β = 1:1. [b] Yield of isolated product. [c] **3a** (0.10 mmol), **4a** (0.10 mmol), promoter, additive, solvent (1.0 mL), under argon atmosphere; the solvent was gradually evaporated to dryness during 24 h. α/β = 1:1. [d] **3a** (0.10 mmol), **4a** (0.05 mmol), promoter, additive, solvent (1.0 mL), under argon atmosphere; the solvent was gradually evaporated to dryness during 24 h. α/β = 1:1. DCE = 1,2-dichloroethane; c-hexane = cyclohexane.

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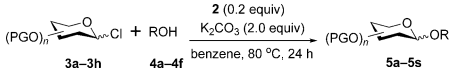
Information).[14] The yield was further improved by increasing the amount of **3a** to 2 equivalents (85%, entry 16), whereas the yield decreased dramatically when using a catalytic amount of **1** (11%, entry 17). Furthermore, byproduct **6**, which results from the *S*-glycosylation of **1** with **3a**, was isolated in all these reactions in different amounts. To avoid this side reaction, **5a** was obtained without byproduct **6** when using a catalytic amount of urea **2** instead of thiourea **1**. Benzene appeared to be the best solvent (95%, entries 20–24). The optimized conditions are thus as follows: donor (2.0 equiv), acceptor (1.0 equiv), urea **2** (0.20 equiv), continuous evaporation to dryness (heating at 80°C for 24 h under argon atmosphere).

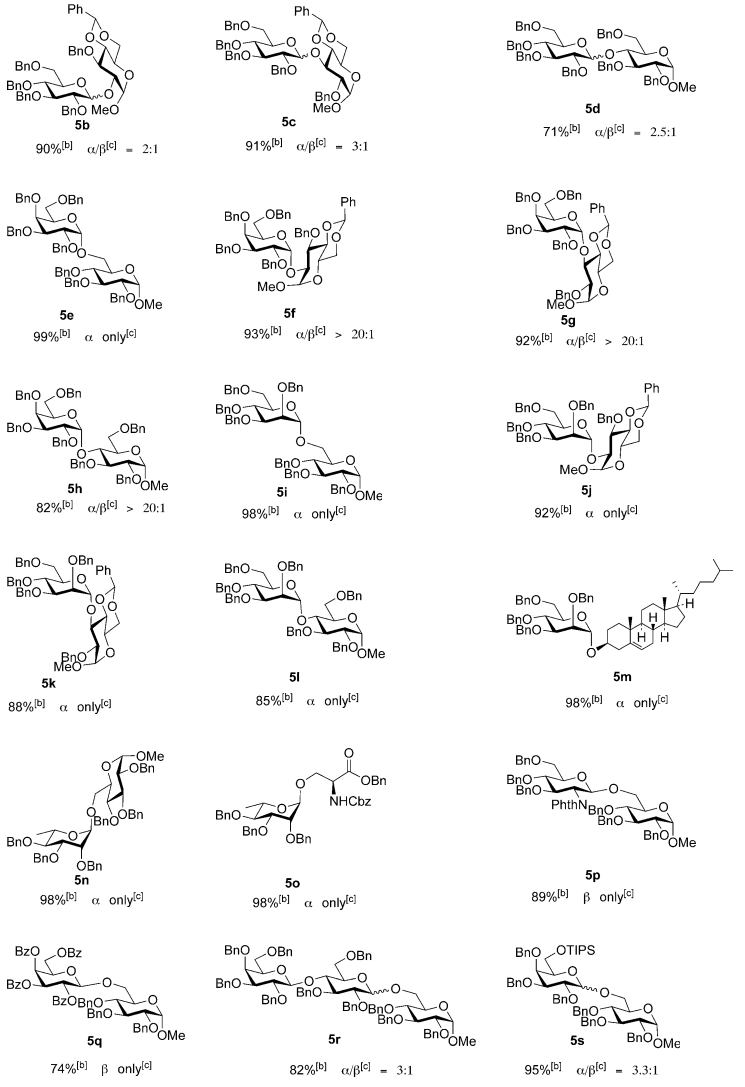
With the optimized conditions in hand, the scope of the reaction was investigated by varying both the glycosyl donor and the acceptor (Scheme 1 and Table 2). The reactions of perbenzylated glucosyl donor **3a** with **4b**, **4c**, and **4d** produced disaccharides in moderate to excellent yields with poor stereoselectivity. The glycosylations of acceptors with galactosyl, mannosyl, rhamnosyl, and glucosaminyl donors proceeded in good yield and with high anomeric stereoselectivity. The glycosylation of **4a** with galactosyl bromide **3f** under the same conditions also worked well, with high β-selectivity. Moreover, reaction of the disaccharide donor **3g** with **4a** afforded **5r** in 82% yield of isolated product with the α/β ratio 3:1. Except for the poor stereoselectivity of the glycosylation when using perbenzylated glucosyl donors and the acetyl migration phenomenon observed when using peracetylated glucosyl donors, most other donors gave satisfactory yields and good stereoselectivity.

In order to improve the anomeric selectivity of the glycosylation when using perbenzylated glucosyl donors, a series of chiral (thio)urea catalysts were examined (Table S4). Disappointingly, most of chiral (thio)urea catalysts had nearly no influence on the anomeric selectivity. The only improvement was achieved when chiral urea **7n** was used as a catalyst for the glycosylation of **4a** with **3a**, providing **5a** in 90% yield and with improved selectivity (α/β ratio 3.5:1, Scheme 2).

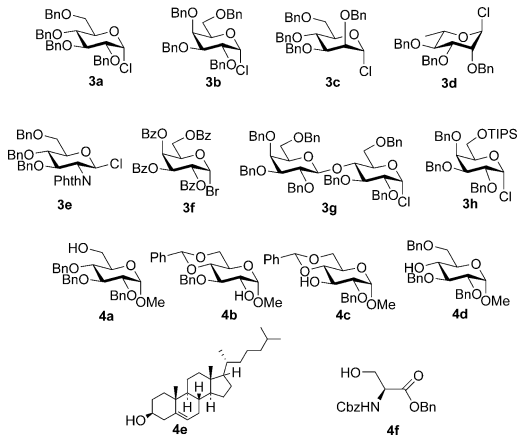
Interestingly, when urea **7o**, which results from the removal of the benzyl group in compound **7n**, was used as the catalyst, the stereoselectivity of glycosylation was retained. We thus imagined that the diphenylphosphino group might have an effect on the stereoselectivity. Indeed, the addition of phosphines to the reaction did influence the steric outcome of the glycosylation (Table S5). It was found that tri-(2,4,6-trimethoxyphenyl)-phosphine (**8c**, TTMPP) is

Table 2: Glycosyl coupling reactions of donors **3a–g** and acceptors **4a–f**.[a]

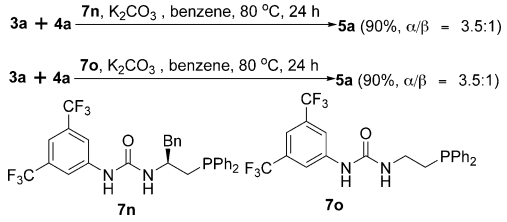




[a] Reaction conditions: **3a–3h** (0.10 mmol), **4a–4f** (0.05 mmol), K_2CO_3 (0.10 mmol), **2** (0.01 mmol), benzene (1.0 mL), heating at 80°C under argon atmosphere for 12 h with solvent was evaporated over this period, then benzene (1.0 mL) was added, the mixture was heated for another 12 h, and the solvent was evaporated again. [b] Yield of isolated product. [c] Anomeric ratios were determined by ^{1}H NMR analysis of the crude products.



Scheme 1. Glycosyl donors and acceptors in the glycosylation reaction.

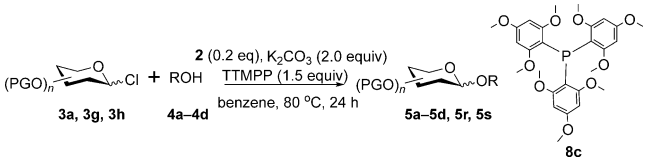


Scheme 2. Glycosylation catalyzed by **7n** or **7o**. Conditions: **3a** (0.10 mmol), **4a** (0.05 mmol), K_2CO_3 (0.10 mmol), **7n** or **7o** (0.01 mmol), benzene (1.0 mL), 80 °C under argon atmosphere for 24 h, with the solvent evaporating during this period. Anomeric ratios were determined by ^{1}H NMR analysis of the crude products.

the best additive (α/β ratio up to 12.6:1), and the optimal amount of TTMPP is 1.5 equivalents (Table S6). To our delight, when using this phosphine additive, the glycosylation reactions that were previously accomplished with poor stereoselectivity proceeded with high α-selectivity, as shown in Table 3.

To gain some insight into the mechanism, a series of experiments were conducted under the standard conditions. No glycosylation reaction occurred in the absence of **2** (Table 1, entry 25). Simply blocking the hydrogen-bonding amide of the (thio)urea completely inhibited the glycosylation reaction (Table 4). The NMR spectra indicated an obvious interaction between donor **3a** and urea **2**. When adding **3a** to **2**, the chemical shift of H^a and H^b in **2** shifted downfield, whereas the chemical shift of H1 in **3a** shifted upfield. The chemical shift change in the ^{19}F NMR for **2** is consistent with those of the ^{1}H NMR spectra (Scheme 3, Figure 1). These results imply a possible hydrogen-bond activation mechanism.[15] When the α/β mixture of **5a** was reacted under the standard conditions in the presence of TTMPP, no anomerization was observed (Scheme S1). The chemical shifts of H^c and H^d in **8c** shifted upfield upon mixing with **2** and **3a**, whereas the chemical shift of H1 in **3a** shifted

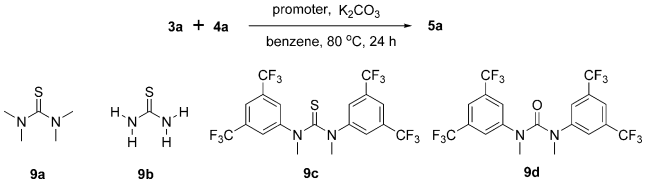
Table 3: Stereoselective glycosylations in the presence of **8c** (TTMPP).[a]



Entry	Substrate	Product	Yield[%][b]	α/β[c]
1	**3a** + **4a**	**5a**	94%	12.6:1.0
2	**3a** + **4b**	**5b**	90%	10.1:1.0
3	**3a** + **4c**	**5c**	90%	11.0:1.0
4	**3a** + **4d**	**5d**	70%	10.7:1.0
5	**3g** + **4a**	**5r**	82%	8.0:1.0
6	**3h** + **4a**	**5s**	95%	20.0:1.0

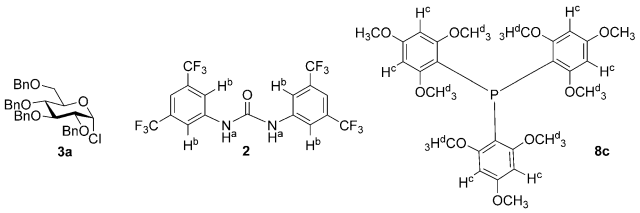
[a] Reaction conditions: **3a** or **3g or 3h** (0.10 mmol), **4a–4d** (0.05 mmol), K_2CO_3 (0.10 mmol), **2** (0.01 mmol), TTMPP (0.075 mmol), benzene (1.0 mL), heated at 80 °C under argon atmosphere for 12 h and the solvent was evaporated during this period, then benzene (1.0 mL) was added, the reaction heated for another 12 h, and the solvent was evaporated again. [b] Yield of isolated product. [c] Anomeric ratios were determined by ^{1}H NMR analysis of the crude products.

Table 4: Control experiments using blocked (thio)ureas.[a]



Entry	Promoter	Yield[%][b]	Entry	Promoter	Yield[%][b]
1	**9a**	0	4	**9c**	0
2	**9b**	0	5	**2**	12
3	**1**	95	6	**9d**	0

[a] Reaction conditions: **3a** (0.10 mmol), **4a** (0.05 mmol), promoter (0.10 mmol), K_2CO_3 (0.10 mmol), benzene (1.0 mL) at 80 °C under argon atmosphere for 24 h and the solvent was evaporated during this period. $\alpha/\beta = 1{:}1$. [b] Yield of isolated product.



Scheme 3. The structures of **2**, **3a**, and **8c** for NMR experiments.

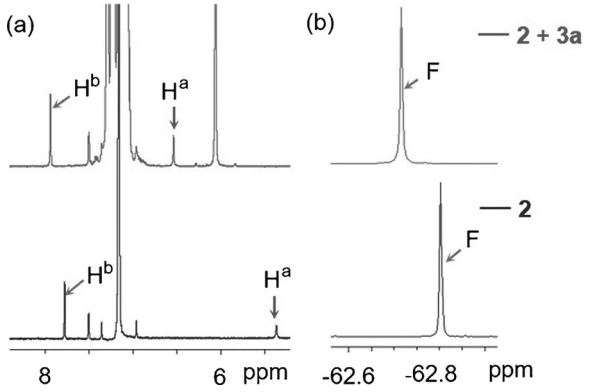


Figure 1. a) Partial ^{1}H NMR spectra of the mixture of **2** with (above) and without (below) **3a** in C_6D_6. b) ^{19}F NMR spectra of the mixture of **2** with (above) and without (below) **3a** in C_6D_6.

downfield, and the chemical shift for P in **8c** displayed the same tendency (Scheme 3, Figure 2, for details see Tables S8, S9). Given the steric hindrance and the electrical effects of TTMPP (Table S5), and based on the NMR experiments, we hypothesized that a noncovalent electronic interaction with the anomeric carbon from the β-face of the glycosyl donors might exist, thereby directing attack of the acceptors from the α-face to give the α-glycosides. A detailed mechanistic elucidation of this reaction will be the focus of further studies.

In conclusion, we disclose a stereoselective Koenigs–Knorr glycosylation reaction catalyzed by urea. The activation of glycosyl chlorides or bromides by urea through a hydrogen-bond interaction, followed by glycosylation, afforded the coupled products smoothly without the use of

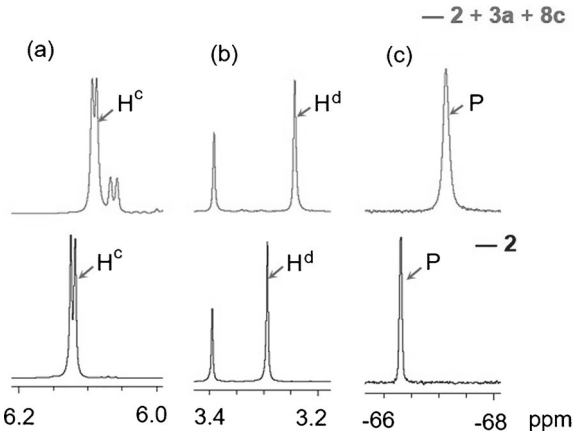


Figure 2. a, b) Partial ^{1}H NMR spectra of the mixture of **8c** with (above) and without (below) other reactants in C_6D_6. c) ^{31}P NMR spectra of the mixture of **8c** with (above) and without (below) other reactants in C_6D_6.

heavy metals. Excellent yields and high anomeric selectivity were obtained in most cases. The troublesome α-stereoselectivity of glycosylation when using perbenzylated glucosyl donors could be greatly improved by the addition of TTMPP. The noncovalent interactions of donor with urea or TTMPP were supported by ^{1}H NMR analysis and some control experiments. In contrast to the existing Koenigs–Knorr glycosylation methods, this method features stereoselectivity and heavy-metal-free catalysis.

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Keywords: carbohydrates · glycosylation · organocatalysis · stereoselectivity · urea

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