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Direct *N*-glycofunctionalization of amides with glycosyl trichloroacetimidate by thiourea/halogen bond donor co-catalysis

Yusuke Kobayashi,^[a] Yuya Nakatsuji,^[a] Shanji Li,^[a] Seiji Tsuzuki,^[b] Yoshiji Takemoto*^[a]

Abstract. Using a halogen bond (XB) donor and Schreiner's thiourea as cooperative catalysts, various amides, including the asparagine residues of several peptides, were directly coupled with glycosyl trichloroacetimidates to give unique N-acylorthoamides in good yields. Synthetic applications of N-acylorthoamides, including rearrangement to the corresponding β -N-glycoside, were also demonstrated.

N-Glycosides are found in various pharmaceuticals, biologically active compounds, and natural products.^[1] They can be used in material science as glycolipids for lipid nanotubes.^[2] Sugar moieties are known to impart hydrophilicity to molecules, and alter the higher order structure and bioavailability of molecules.[3] Several Nglycosides have been utilized as prodrugs to improve delivery to target tissues and organs.^[4] However, synthetic methodologies for N-glycosylamides are not as well developed^[5–8] as those for O-glycosides (Scheme 1a).^[9] Among the reported synthetic methodol for N-glycosylamides, ^[6] direct N-glycosylation of amides is the most straightforward but challenging approach because of the poor nucleophilicity of the amides, and only limited catalytic conditions have been reported to date.^[8] However, there still remains to be improved concerning scope of amides and the accessibility of Leaving group (LG). In fact, direct introduction of asparagine residues of peptides have been rarely investigated, and the use of tripeptide significantly decreased the chemical yield,^[8a] as compared with that of dipeptide.^[8a,c] We then focused on the utilization of glycosyl trichloroacetimidates,^[10] which are regarded as one of the most readily available glycosyl donors and activated under relatively mild condition.^[11a,b] On the other hand, undesired glycosyl trichloroacetamide was obtained as byproduct, especially when the glycosyl acceptor (Nu-H) has low nucleophilicity (path c).^[8a] Herein, we report two different catalytic systems, which offers a solution to these problems (Scheme 1b). We envisaged that the activation of glycosyl trichloroacetimidates under mildly acidic condition would afford kinetically favored product by the preferential addition of employed amides via *path* a.^[10] We thus focused on Schreiner's thiourea,^[12] whose pK_a value was reported to be 8.5 in DMSO.^[12] Although thiourea have been recently employed for glycosylation^[11] and acetalization^[13] of alcohols, its acidity was insufficient to activate trichloroacetimidate.^[11a,b] We envisioned that a soft and mild Lewis acid, such as 2-iodoazolium salt^[14] ($R^2 \neq H$) as halogen bond (XB) donor, ^[15–17] used as a co-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. The produced *N*-acylorthoamides^[21] would serve as intermediates for thermodynamically favored β -N-glycosides^[10] (Scheme 1a, path d, Nu = amide), and offer a unique traceless N-

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glycofunctionalization of amide, impacting on prodrug synthesis. In fact, during the course of our investigation on the rearrangement of *N*-acylorthoamide to *N*-glycoside (*path d*), we have developed a new type of Brønsted-acid-salt catalyst, comprised of Brønsted acid and 2-halogenated azole, which was found to be an efficient catalyst for the direct *N*-glycosylation of various amides utilizing the same glycosyl trichloroacetimidates (*path b* and/or *path a* and *d*).



Scheme 1. Summary of this work

We first screened various catalysts for the direct Nglycofunctionalization of a protected as paragine derivative $2a^{[8]}$ with a readily accessible glycosyl donor $1^{[22a]}$ (Table 1). The use of Schreiner's thiourea (5) on its own did not promote the reaction at all (entry 1). We next investigated several co-catalysts for activation of thiourea,^[19] including metallic Lewis acids (entries 2-5)^[11c] and Brønsted acids (entries 6-7).^[11a] Interestingly, when a substituted diarylphosphoric acid was employed, an N-acylorthoamide 4a, whose structure was fully characterized using spectral data (Figure S5), was obtained in 22% yield (entry 6). A stronger Brønsted acid resulted in the production of 3a, albeit in 26% yield (entry 7), indicating that the acidity of the catalyst affects production of 3a. Indeed, as previously reported, with 10 mol % of trimethylsilyl trifluoromethanesulfonate (TMSOTf)^[8] as a conventional Lewis acid, the donor 1 was immediately consumed, and 3a was obtained in 25% yield (entry 8), along with several inseparable byproducts. As the results were not satisfactory, we next investigated several XB donors as cooperative catalysts (entries 9-12). We found that combination of thiourea **5** with 2-iodobenzimidazolium-type XB donors $7b^{[14]}$ afforded **4a** as a major product in 66% yield (entry 11). A newly designed XB donor with extended aromatic rings 7c similarly afforded 4a as the major product (entry 12). We next performed several control experiments. The addition of 10 mol % of base (NEt₃ or Cs₂CO₃) to the condition of entry 10 resulted in the

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prohibition of the reaction (3a: 0%, 4a: 0%), rather than the acceleration of the reaction. The XB donor 7b on its own did not afford the target products (entry 13), which indicated that combination of thiourea 5 and XB donor 7b was essential for production of **4a**. The yields of **4a** greatly decreased when the squaramide $^{[23]}$ **6**, which has superior HB-donating ability $^{[23c]}$ to thiourea,^[12b,c] was employed instead of **5** (entries 14 and 15). In addition, a control experiment using non-halogenated azolium salt 8 did not afford 4a at all (entry 16). These results suggest that the reaction was not accelerated by the azolium cation moiety or triflate anion by itself,^[24] and that XB formation between the sulfur atom of **5** and the iodine atom of XB donor $7^{[15d,18a,b,d]}$ plays an important role for the promotion of the reaction, presumably through the activation of LG (Scheme S1).^[25] Although other solvents, such as THF, toluene, and acetonitrile, can be used for this reaction without significant decrease of the chemical yields (entries 17-19), CH₂Cl₂ was chosen for further investigation in terms of the solubility of various amides. To gain further support for the XB formation, a ¹³C NMR experiment was performed using thiourea (5) and XB donor (7b) (Figure S2).^[25] When 1.0 equivalent of 5 was added, the ¹³C NMR peak of the C2 position of **7b** broadened and shifted downfield in accordance with previous reports on XB interaction of the iodoazolium salts. $^{\left[14f+i\right] }$





10	5 + /a	CH_2CH_2	52
11	5 + 7b	CH_2Cl_2 7	66
12	5 + 7c	CH ₂ Cl ₂ 8	63
13	7b	CH ₂ Cl ₂ 0 ^b	0 ^b
14	6 + 7b	CH ₂ Cl ₂ 2	19
15	6	CH ₂ Cl ₂ 0 ^b	0 ^b
16	5 + 8	CH ₂ Cl ₂ 0 ^b	0 ^b
17	5 + 7b	THF 3	64
18	5 + 7b	toluene 15	66
19	5 + 7b	CH ₃ CN 4	53

[a] Isolated yields. [b] Not detected. [c] 58% of 2a was recovered.

It is worth noting that under the optimized condition (Table 1, entry 11), neither *N*-trichloroacetylorthoamide nor glycosyl trichloroacetamide were obtained, even additional trichloroacetamide

(1.0 equiv) was employed (Scheme 2a), presumably due to the inherent reactivity of the acyloxonium ion intermediate toward nucleophiles.^[10] Encouraged by this result, we then investigated the efficient catalysts to promote the rearrangement of **4a** to **3a** (Scheme 2b). Although the chemical yields of **3a** were low using TMSOTf^[10c] and TfOH as catalysts, partly because of the degradation of **4a**, Brønsted acid salt **9-TfOH**, synthesized from the same intermediate for **7c**, was found to be most suitable.



Scheme 2: (a) Control experiment using trichloroacetamide (b) Catalytic rearrangement of 4a to 3a



Scheme 3: Substrate scope for the synthesis of *N*-acylorthoamides **4**. Isolated yields were indicated. Rib = ribose.



Scheme 4: Substrate scope for the synthesis of *N*-acylorthoamides **9**. Isolated yields were indicated. Glc = glucose. N.d. = not detected.

Having established the synthetic utilities of *N*-acrylorthoamide **4**, we next investigated the substrate scope for glycosyl donors and amides (Scheme 3, 4). Using 10 mol % of catalysts **5** and **7b**, *N*-Cbz-glycineamide (**2b**) could be directly converted into **4b** in 67% yield. Oleamide (**2c**), which is an important amide towards the synthesis of lipid nanotubes,^[2] was effectively conjugated with sugar to afford **4c** in 41% yield. Notably, the asparagine residues of dipeptide and tripeptide were glycosylated by the present co-catalytic system to afford **4e** and **4f** in unprecedented good yields (Scheme 3). The same amides were also coupled with the glucose surrogate utilizing 3,4,6-tri-O-benzyl-2-O-acetyl- α -D-glucopyranosyl trichloroacetimidate (**10**)^[22b] to yield *N*-acylorthoamides **11a**–**f** in 56–71% yields (Scheme 4).

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We next focused on the direct *N*-glycosylation utilizing Brønsted acid salt **9-TfOH** (Scheme 5), as the acidity of the catalyst was supposed to be important to obtain *N*-glycoside **3a** in Table 1 (entry 7, 8). To our delight, *N*-glycoside **12** was obtained in 72% yield, when glycosyl donor **10** and amide **2a** were reacted. A slight improvement of the yield was observed when thiourea **5** was employed as co-catalyst. ^[26] Under the optimized reaction conditions, a series of *N*-glycoside **12a–f** were obtained in 62–82% yields as single β -isomers. In addition to the glucose-derived donor **10**, a ribose-derived donor **1** could be directly incorporated into amides to afford the corresponding adducts in 45–80% yields. Again, the conjugation with tripeptide proceeded with unprecedented good yields. Notably, the catalyst **9-TfOH** could be readily prepared from the commercial source in three steps with high yields, and found to be air- and moisture-stable for several months.





The utilities of the present reactions have been clearly demonstrated by their application to the syntheses of natural products^[27] (Scheme 6a), and the modification of pharmaceuticals to prodrugs (Scheme 6b). The direct N-glycosylation of a substituted 2-phenylacetamide 2g with glycosyl donor 10 proceeded very smoothly to obtain the desired adduct 12g in excellent yield. The successive deprotection of acetyl and benzyl groups afforded the product in almost quantitative yield (Scheme 6a). The methodologies developed in this paper are particularly useful when the compound to be functionalized has only an amide group for a traceless modification, and this strategy is especially true for pharmaceuticals. For example, the anticancer drug temozolomide (2h) can be transformed into the corresponding N-acylorthoamide 11h using glycosyl donor 10 with 10 mol % of 5 and 7b in THF. After deprotection of the benzyl group of **11h**, the product **15h** was found to be soluble in protic solvents, $\frac{12}{12}$ such as methanol, while temozolomide itself is almost insoluble.^{[2} Practically, commercially available glycosyl donor 16 can be converted into the corresponding adduct 17h in 61% yield. It was noted that hydrolysis of the N-adduct 17h under mildly acidic conditions afforded temozolomide (Scheme 6c).

In conclusion, we have developed two different catalytic systems for the synthesis of *N*-acylorthoamides and *N*-glycosides with wide functional group tolerance. The XB interaction plays an important role in the production of *N*-arylorthoamides via the activation of LG under mildly acidic condition. The combination of a XB donor with a relatively soft XB acceptor will allow for otherwise inaccessible transformations, and broaden the utility of XB donor catalysis. In addition, halogenated azolium salts **9-TfOH** can be utilized for direct *N*-glycosylation as novel bench-stable Brønsted acid. Both methodologies will be powerful for the molecular transformation of amides, and offer a new tool for the traceless modification of pharmaceuticals. Further investigation on the details of the reaction mechanism, including complexation of amides, and substrate scope is now underway in our laboratory.



Reagents and conditions: ^a NaOMe, MeOH, rt, 12 h, 88%. ^b Pd/C (10 mol %), H₂ (1 atm) MeOH, rt 2 h, quant. ^c Pd/C (10 mol %), H₂ (1 atm), EtOAc, rt, 2 h, 60%. ^d *p*-TsOH, DME/H₂O, rt, 24 h, 79%

Scheme 6: Application of the present N-glycofunctionalization

Experimental Section

To a stirred solution of glycosyl donor **1** (36.4 mg, 0.06 mmol) and amide **2a** (1.0 equiv, 0.05 mmol) in DCM (1.0 mL) was added activated MS 4Å (50 mg), and the reaction mixture was stirred at the ambient temperature for 10 min. Then, the catalysts **5** (2.5 mg, 10 mol %) and **7b** (3.5 mg, 10 mol %) were added, and the resulting mixture was stirred at the ambient temperature for 24 hours. After the MS 4Å was filtered off and washed with chloroform, the filtrate was concentrated under reduced pressure to give crude *N*-acylorthoamide, which was purified by silica gel column chromatography to afford **4a** (24.8 mg, 66%), along with **3a** (2.6 mg, 7%).

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- For a recent review see: a) K. Tanaka, K. Fukase, Polymer-Supported and Tag-Assisted Methods in Oligosaccharide Synthesis. In *Glycoscience: Chemistry and Chemical Biology*, 2nd ed., Vol. I–III; B. O. Fraser-Reid, K. Tatsuta, J. Thiem, Eds.; Springer: New York, 2009. For selected examples, see: b) G. J. van der Heden van Noort, M. G. van der Horst, H. S. Overkleeft, G. A. van der Marel, D. V. Filippov, J. Am. *Chem. Soc.* 2010, *132*, 5236. c) B. Wang, Y. Liu, R. Jiao, Y. Feng, Q. Li, C. Chen, L. Liu, G. He, G. Chen, J. Am. Chem. Soc. 2016, *138*, 3926.
- [2] For a review see: T. G. Barclay, K. Constantopoulos, J. Matisons, Chem. Rev. 2014, 114, 10217.
- [3] For reviews see: a) H. Kunz, M. Schultz, In Carbohydrates in Chemistry and Biology, B. Ernst, G. W. Hart, P. Sinay, Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, Chapter 11, pp 267–304. b) C.

COMMUNICATION

H. Wong, *Science* **2001**, *291*, 2344. c) C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357. d) A. Helenius, M. Aebi, *Science* **2001**, *291*, 2364.

- [4] For recent reviews see: a) S. W. Lam, H. J. Guchelaar, E. Boven, *Cancer Treat. Rev.* 2016, *50*, 9. b) S. V. Moradi, W. M. Hussein, P. Varamini, P. Simerska, I. Toth, *Chem. Sci.* 2016, *7*, 2492.
- [5] For a review see: a) H. Herzner, T. Reipen, M. Schultz, H. Kunz, *Chem Rev.* 2000, *100*, 4495. For selected recent examples see: b) G, J. Mercer, J. Yang, M. J. McKay, H. M. Nguyen, *J. Am. Chem. Soc.* 2008, *130*, 11210. c) B. M. Trost, E. U. Sharif, J. J. Cregg, *Chem. Sci.*, 2017, *8*, 770.
- [6] For a selected example via glycosyl azides see: a) J. Zheng, K. B. Urkalan, S. B. Herzon, *Angew. Chem. Int. Ed.* 2013, *52*, 6068. For selected examples via reducing sugars see: b) S. T. Cohen-Anisfeld, P. T. Lansbury, Jr., *J. Am. Chem. Soc.* 1993, *115*, 10531. c) P. Wang, X. Li, J. Zhu, J. Chen, Y. Yuan, X. Wu, S. J. Danishefsky, *J. Am. Chem. Soc.* 2011, *133*, 1597, and references cited therein.
- [7] a) D. Kahne, S. Walker, Y. Cheng, D. van Engen, J. Am. Chem. Soc. 1989, 111, 6881. b) B. A. Garcia, D. Y. Gin, J. Am. Chem. Soc. 2000, 122, 4269.
- [8] a) H. Tanaka, Y. Iwata, D. Takahashi, M. Adachi, T. Takahashi, J. Am. Chem. Soc. 2005, 127, 1630. b) K. Tanaka, T. Miyagawa, K. Fukase, Synlett 2009, 1571. c) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, Chem. Eur. J. 2010, 16, 1871. d) H. A. V. Kistemaker, G. J. van der Heden van Noort, H. S. Overkleeft, G. A. van der Marel, D. V. Filippov, Org. Lett. 2013, 15, 2306.
- [9] a) A. V. Demchenko, *Handbook of Chemical Glycosylation*; Wiley-VCH: Weinheim, 2008. For a recent review on organocatalytic glycosylations, see: b) R. Williams, M. C. Galan, *Eur. J. Org. Chem.* **2017**, 6247.
- [10] a) R. R. Schmidt, K. H. Jung, In Carbohydrates in Chemistry and Biology Part 1: Chemistry of Saccharides; B. Ernst, G. W. Hart, P. Sinay, Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 5–59. b) F. Kong, Carbohydr. Res. 2007, 342, 345. c) Y. Li, H. Mo, G. Lian, B. Yu, Carbohydr. Res. 2012, 363, 14.
- [11] For recent reports on glycosylation utilizing thiourea catalysts see: a) Y. Geng, A. Kumar, H. M. Faidallah, H. A. Albar, I. A. Mhkalid, R. R. Schmidt, *Angew. Chem. Int. Ed.* 2013, *52*, 10089. b) T. Kimura, T. Eto, D. Takahashi, K. Toshima, *Org. Lett.* 2016, *18*, 3190. c) Y. Hashimoto, S. Tanikawa, R. Saito, K. Sasaki, *J. Am. Chem. Soc.* 2016, *138*, 14840. d) Y. Park, K. C. Harper, N. Kuhl, E. E. Kwan, R. Y. Liu, E. N. Jacobsen, *Science* 2017, *355*, 162.
- a) P. R. Schreiner, A. Wittkopp, *Org. Lett.*, **2002**, *4*, 217. b) X. Li, H. Deng, B. Zhang, J. Y. Li, L. Zhang, S. Z. Luo, J.-P. Cheng, *Chem. –Eur. J.* **2010**, *16*, 450. c) G. Jakab, C. Tancon, Z. G. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724.
- a) M. Kotke, P. R. Schreiner, *Synthesis* 2007, 779. b) E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* 2012, 51, 9152. c) A. Madarász, Z. Dósa, S. Varga, T. Soós, A. Csámpai, I. Pápai, *ACS Catal.* 2016, 6, 4379.
- [14] a) S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, Angew. Chem. Int. Ed. 2011, 50, 7187. b) F. Kniep, S. M. Walter, E. Herdweek, S. M. Huber, Chem. Eur. J. 2012, 18, 1306. c) F. Kniep, L. Rout, S. M. Walter, H. K. V. Bensch, S. H. Jungbauer, E. Hertweck, S. M. Huber, Chem. Commun. 2012, 48, 9299. d) R. Castelli, S. Schindler, S. M. Walter, F. Kniep, H. S. Overkleeft, G. A. van der Marel, S. M. Huber, J. D. C. Codée, Chem. Asian J. 2014, 9, 2095. S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep, S. M. Huber, Chem. Commun. 2014, 50, 6281. e) W. He, Y.-C. Ge, C.-H. Tan, Org. Lett. 2014, 16, 3244. f) Y. Takeda, D. Hisakuni, C.-H. Lin, S. Minakata, Org. Lett. 2015, 17, 318. g) M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto, Org. Lett. 2015, 137, 12110. i) M. Saito, Y. Kobayashi, S. Tsuzuki, Y. Takemoto, Angew. Chem. Int. Ed., 2017, 56, 7653. Only 2-iodobenzimidazolium triflate

(OTf⁻) and tetrafluoroborate (BF_{4}^{-}) could be synthesized in acceptable yields,^[25] due to the poor nucleophilicity of *N*-aryl-2-iodobenzimidazole precursors.

- [15] For reports on other type of XB-donor-mediated or catalyzed reactions, see: a) A. Bruckman, M. A. Pene, C. Bolm, *Synlett* 2008, *6*, 900. b) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdweck, S. M. Huber, *Angew. Chem. Int. Ed.* 2013, *52*, 7028. c) N. Tsuji, Y. Kobayashi, Y. Takemoto, *Chem. Commun.* 2014, *50*, 13691. d) A. Matsuzawa, S. Takeuchi, K. Sugita, *Chem. Asian J.* 2016, *11*, 2863.
- [16] For other uses of XB in organic reactions, see: a) V. N. G. Lindsay, W. Lin, A. B. Charette, J. Am. Chem. Soc. 2009, 131, 16383. b) S. Dordonne, B. Crousse, D. Bonnet-Delpon, J. Legros, Chem. Commun. 2011, 47, 5855. c) H. Nakatsuji, Y. Sawamura, A. Sakakura, K. Ishihara, Angew. Chem. Int. Ed. 2014, 53, 6974. d) L. Zong, X. Ban, C. W. Kee, C.-H. Tan, Angew. Chem. Int. Ed. 2014, 53, 11849. e) F. Sladojevich, E. McNeill, J. Bçrgel, S.-L. Zheng, T. Ritter, Angew. Chem. Int. Ed. 2015, 54, 3712.
- [17] For selected recent reviews on halogen bonding, see: a) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* 2013, *42*, 1667. b) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney, P. D. Beer, *Chem. Rev.* 2015, *115*, 7118. c) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, G. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* 2016, *116*, 2478. d) D. Bulfield, S. M. Huber, *Chem. Eur. J.* 2016, *22*, 14434.
- [18] a) G. Jakab, A. Hosseini, H. Hausmann, P. R. Schreiner, *Synthesis* 2013, *45*, 1635. b) C. C. Robertson, R. N. Perutz, L. Brammer, C. A. Hunter, *Chem. Sci.* 2014, *5*, 4179. c) Y. Park, C. S. Schindler, E. N. Jacobsen, *J. Am. Chem. Soc.* 2016, *138*, 14848. d) M. Kaasik, S. Kaabel, K. Kriis, I. Järving, R. Aav, K. Rissanen, T. Kanger, *Chem. Eur. J.* 2017, *23*, 7337.
- [19] For reviews see: a) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633. b) L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2016**, *116*, 4006.
- [20] Activation of LG by revitalized amide cannot be ruled out. For an *N*-glycosylation via the deprotonation of activated amide, see: a) B. Imperiali, K. L. Shannon, M. Unno, K. W. Rickert, *J. Am. Chem. Soc.* **1992**, *114*, 7944. For an O-glycosylaton via the activation of LG by a revitalized alcohol, see: b) P. Peng, R. R. Schmidt, *J. Am. Chem. Soc.* **2015**, *137*, 12653. c) P. Peng, R. R. Schmidt, *Acc. Chem. Res.*, **2017**, *50*, 1171.
- [21] Only one paper reported its formation as byproduct, see: Y. Tarumi, Y. Takebayashi, T. Atsumi, J. Heterocyclic Chem. 1984, 21, 849.
- [22] a) I. Chiu-Machado, J. C. Castro-Palomino, O. Madrazo-Alonso, C. Lopetegui-Palacios, V. Verez-Bencomo, *J. Carbohydr. Chem.* 1995, *14*, 551. b) S. Loscher, R. Schobert, *Chem. Eur. J.* 2013, *19*, 10619.
- [23] a) J. P. Malerich, K. Hagihara, V. H. Rawal, J. Am. Chem. Soc. 2008, 130, 14416. b) A. Rostami, A. Colin, X. Y. Li, M. G. Chudzinski, A. J. Lough, M. S. Taylor, J. Org. Chem. 2010, 75, 3983. c) X. Ni, X. Li, Z. Wang, J.-P. Cheng, Org. Lett. 2014, 16, 1786.
- [24] When the donor 1 and amide **2a** was reacted using *n*-Bu₄N⁺OTf⁻ (tetra*n*-butylammonium trifluoromethanesulfonate) as catalyst (10 mol%) in CH₂Cl₂, the products were not obtained, either. We then added *n*-Bu₄N⁺OTf⁻ (10 mol%) to the condition of entry 10 (Table 1), but the chemical yields were not improved at all (**4a**: \pm 5%).
- [25] See the Supporting Information for details.
- [26] XB interaction of 9-TfOH with Lewis bases was suggested by X-ray (Figure S1) and computational studies (Figures S4). See the Supporting Information for details.
- [27] For the proposed structure, see: A. Ata, D. S. Tan, W. L. Matochko, J. K. Adesanwo, *Phytochem. Lett.* 2011, *4*, 34.
- [28] C. Fang, K. Wang, Z. R. Stephen, Q. Mu, F. M. Kievit, D. T. Chiu, O. W. Press, M. Zhang, ACS Appl. Mater. Interfaces 2015, 7, 6674.

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Direct *N*-glycofunctionalization of amides with glycosyl trichloroacetimidate by thiourea/halogen bond donor cocatalysis

Keywords: glycosylation • organocatalyst • XB donor