HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 453 - 460. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 20th June, 2019, Accepted, 16th July, 2019, Published online, 14th August, 2019
DOI: 10.3987/COM-19-S(F)25

PHOTO-IRRADIATION-PROMOTED AMINOETHERIFICATION OF GLYCALS WITH *N*-ACYLIMINOIODINANE AND ALCOHOLS

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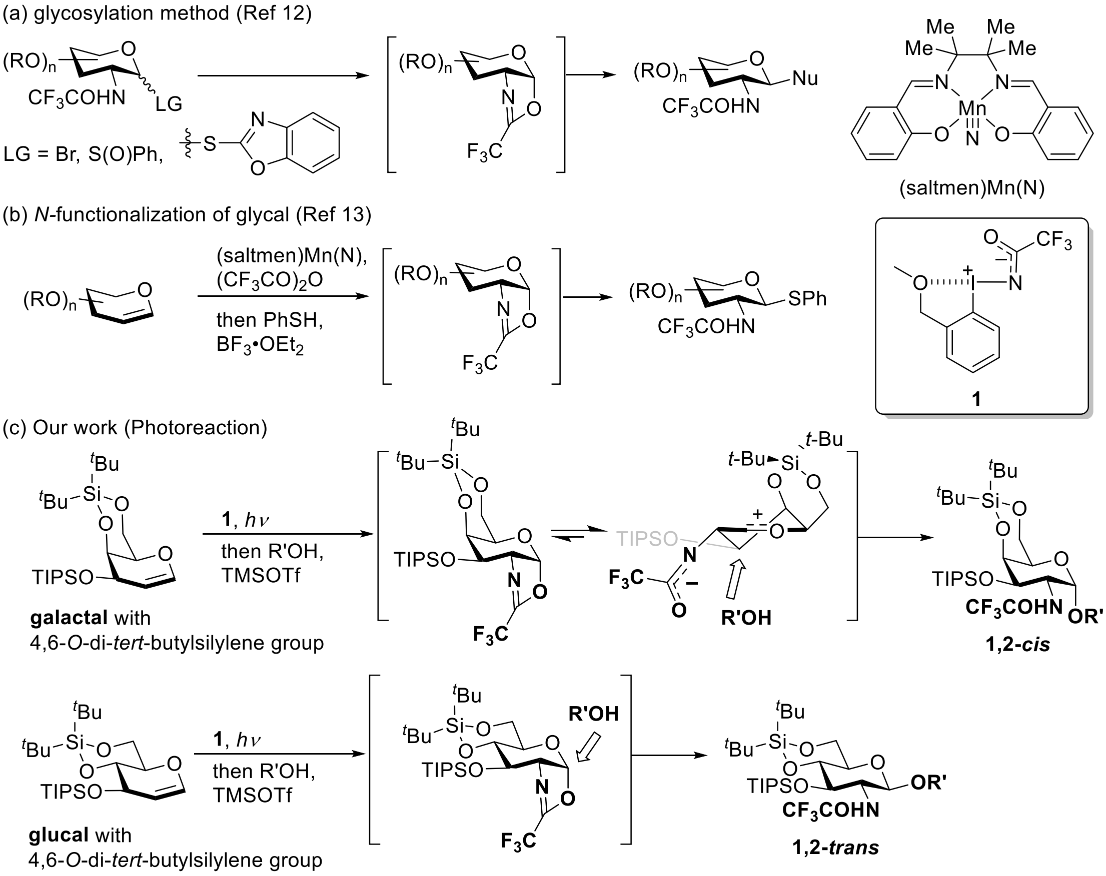
Abstract – An efficient trifluoroacetamido-etherification of glycals was achieved using *N*-acyliminoiodinane and various alcohols under photo-irradiation. This reaction was successfully applied to the efficient synthesis of biologically active compounds.

INTRODUCTION

Sugar moieties in living organisms have a close relationship with biological activity. 2-Amino-2-deoxysugar derivatives are one of the most significant class of sugars because they play an important role as receptor ligands for proteins such as enzymes,[1] antibiotics[2] and lectins,[3] and take part in antibody-antigen interactions.[4] Furthermore, they are ubiquitous among living bodies in the form of glycoconjugates,[5] glycosaminoglycans,[6] and blood group oligosaccharides.[7] Chemical synthetic methods of oligosaccharides containing 2-amino-2-deoxysugars have been developed because of their attractive bioactivity and functionality.[8] Among them, we focused closely on 2-(*N*-trifluoroacetamido)-2-deoxysugar because the introduction of a fluorine atom into bioactive compounds often alters their chemical and physical properties (*e.g.*, increased bioavailability and metabolic stability).[9] In fact, the *N*-trifluoroacetamido group sometimes offers improved biological activity,[10] relatively easy manipulation and deprotection, making it easier to synthesize complex molecules.[11] A variety of glycosyl donors bearing an *N*-trifluoroacetamido group with a suitable anomeric leaving group have been developed, and glycosylation can occur through the oxazoline intermediate bearing a trifluoromethyl group.[12] Such glycosylation methods often require the preparation of a specific glycosyl donor in multi-steps and/or result in a low yield transformation (Scheme 1a). Carreira and co-workers reported the *N*-functionalization of glycal derivatives employing a stoichiometric manganese nitrido complex,[13] but the glycosyl acceptor was limited to a thiol (Scheme 1b). Recently, we have developed a newly designed *N*-acyliminoiodinane **1**[14a] as an *N*-trifluoroacetylnitrene equivalent[14b-f] that can be activated under photo-irradiation to react with the glycal. A subsequent treatment with

O-nucleophiles in the presence of a catalytic amount of Lewis acid then gives the 2-(*N*-trifluoroacetamido)-2-deoxyglycoside (Scheme 1c).[14a] This method can directly introduce the *N*-trifluoroacetamido group into a glycal derivative. Additionally, this transformation requires no iminoiodinane activator except for ultraviolet photo-irradiation. In this paper, we describe our efforts toward improving the chemical yields in detail, broadening the scope, and the application of this facile method toward the efficient synthesis of bioactive compounds.

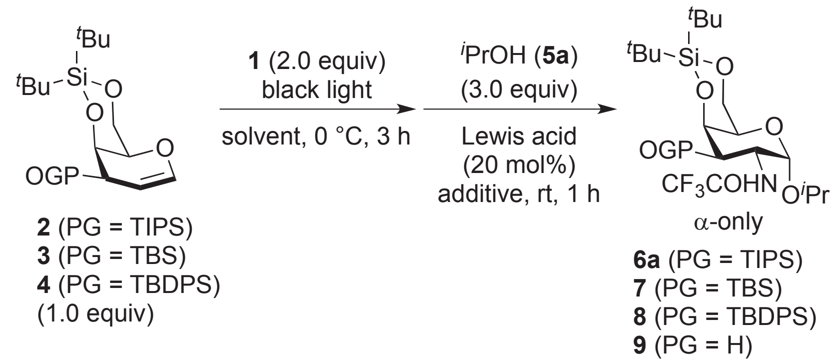


Scheme 1. Synthetic methods for 2-(*N*-trifluoroacetamido)-2-deoxyglycosides

RESULTS AND DISCUSSION

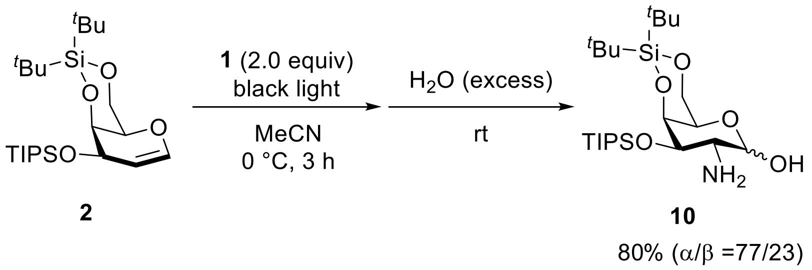
We first examined the reaction of *N*-acyliminoiodinane and the galactal derivatives **2**–**4** (Table 1). As described in our preliminary communication,[14a] **2** was treated with *N*-acyliminoiodinane **1** under UV light irradiation (λ = 365 nm) in acetonitrile. A sequential treatment with three equivalents of 2-propanol (**5a**) in the presence of 20 mol% of $BF_3 \cdot OEt_2$ gave the amino sugar conjugate **9**, whose protecting group at the C3-position was found to be removed (Table 1, entry 1). Different solvents were investigated and dichloromethane gave the desired amino sugar conjugate **6a** with complete α-selectivity,[15] albeit in low yield (Table 1, entry 2). During the optimization of the reaction conditions, we noticed that the oxazoline intermediate decomposed in the presence of water. Specifically, a ring-opening of the oxazoline intermediate and the removal of an *N*-trifluoroacetyl group were observed when the oxazoline intermediate was treated with an excess amount of water to give the 2-amino-2-deoxysugar **10** (Scheme 2). This result suggests that the oxazoline intermediate is not stable and the *N*-trifluoroacetyl group can be easily removed. Thus, we added 4Å molecular sieves (MS) as a desiccant after photo-irradiation, but this addition completely inhibited the subsequent reaction with 2-propanol (**5a**) presumably because of the basic property of 4Å MS (Table 1, entry 3). The use of a stoichiometric amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was found to promote the reaction with **5a** even in the presence of 4Å MS to afford the desired product **6a** in 36% yield (Table 1, entry 4). By replacing the 4Å MS with acid washed molecular sieves (AWMS), the amount of TMSOTf could be reduced to 20 mol% without a decreased yield of **6a** (Table 1, entry 5). Also, the addition of AWMS before the photo-irradiation further improved the chemical yield of **6a** (Table 1, entry 6). Changing the protecting group of the hydroxy group at the C-3 position did not improve the yield of the corresponding 2-amino-2-deoxyglycosides **7** and **8**, and the triisopropylsilyl (TIPS) group was the choice of the protecting group among the tested protecting groups (Table 1, entries 7–8 vs entry 6). Finally, we found that the replacement of AWMS with 5Å MS increased the yield of the amino sugar conjugate **6a** to 68% yield (Table 1, entry 9).

Table 1. Optimization of the reaction condition for photo-induced aminoetherification



entry	PG	solvent	Lewis acid	additive	product[a]
1	TIPS	MeCN	BF_3•OEt_2	none	**9** (33%)
2	TIPS	CH_2Cl_2	BF_3•OEt_2	none	**6a** (11%)
3	TIPS	CH_2Cl_2	BF_3•OEt_2	4Å MS	N. A.[d]
4	TIPS	CH_2Cl_2	TMSOTf[b]	4Å MS	**6a** (36%)
5	TIPS	CH_2Cl_2	TMSOTf	AWMS	**6a** (36%)
6[e]	TIPS	CH_2Cl_2	TMSOTf	AWMS[c]	**6a** (58%)
7	TBS	CH_2Cl_2	TMSOTf	AWMS[c]	**7** (31%)
8	TBDPS	CH_2Cl_2	TMSOTf	AWMS[c]	**8** (49%)
9	TIPS	CH_2Cl_2	TMSOTf	5Å MS[c]	**6a** (68%)

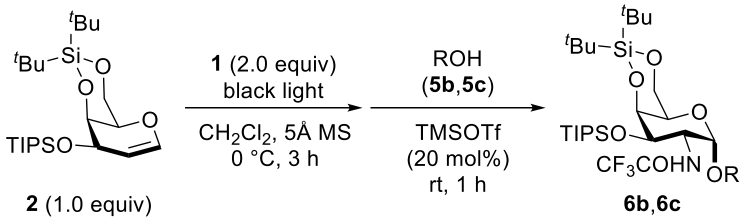
[a] Isolated yields. [b] 1.0 equiv of LA was used. [c] Additive was added before the black light irradiation. [d] Not applicable. [e] Original conditions as reported in ref. 14a.

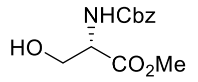
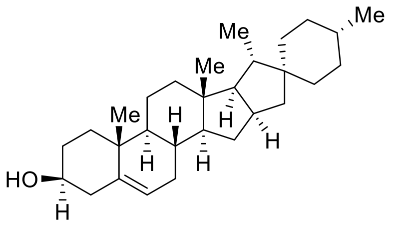


Scheme 2. Reaction in the presence of H_2O

With the optimized reaction condition in hand, we then investigated the substrate scope of alcohols as the glycosyl acceptor. Reaction of the galactal derivative **2** with alcohols **5b** and **5c** smoothly proceeded to give the corresponding galactosamine derivatives **6b** and **6c** in good yields (Table 2). In all cases, the products were obtained as single α-isomer, due to the 4,6-*O*-di-*tert*-butylsilylene group.[15]

Table 2. Substrate scope for photo-induced aminoetherification of galactal derivatives[a]

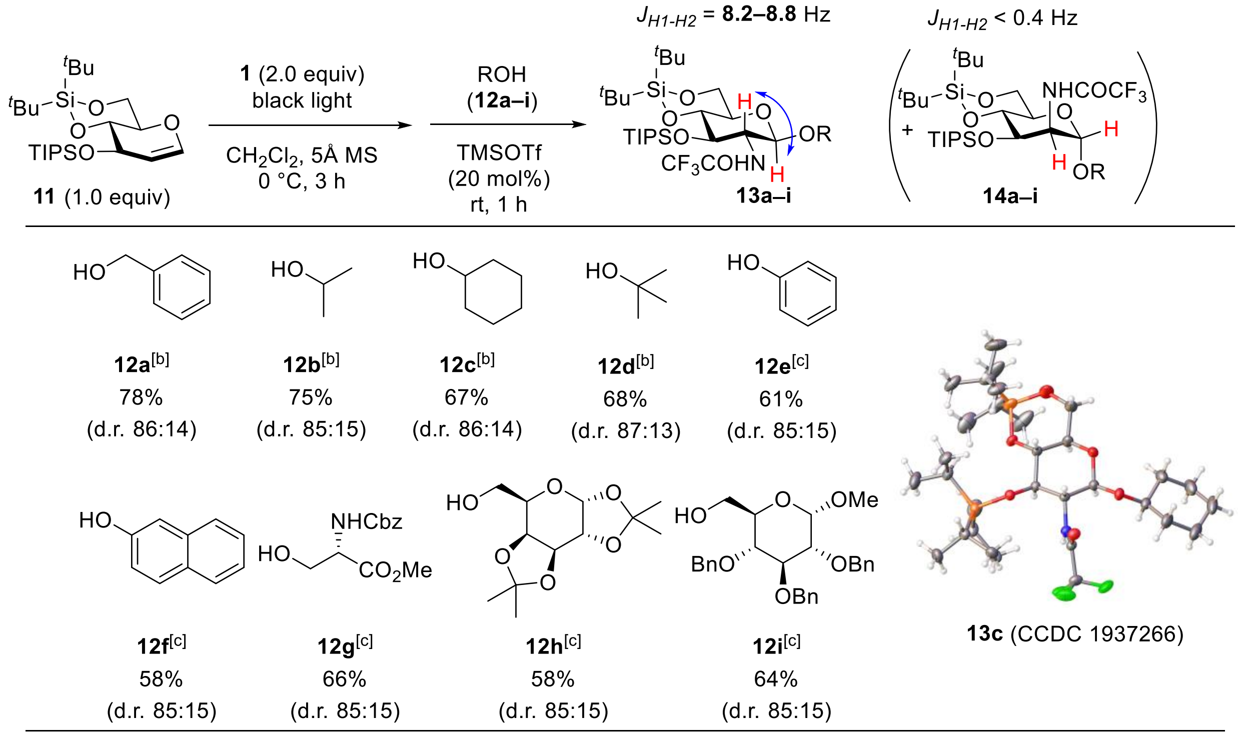


 **5b** (1.0 equiv): 71% (α-only)	 **5c** (1.0 equiv): 66% (α-only)

[a] Yields of isolated products in 2 steps

We then focused on the reactivity of the alcohols with glucal derivatives (Table 3). Under the optimized reaction conditions, the reaction of glucal derivatives **11**[16] with a series of primary, secondary and tertiary alcohols (**12a-d**), as well as phenolic alcohols (**12e**, **12f**), a serine derivative (**12g**) and sugar derivatives (**12h**, **12i**), afforded the corresponding glucosamine derivatives **13a-i** as major products[17] in moderate to good yields.[18] Notably, the sugar derivative **12i** gave the desired disaccharide **13i** in good yield because **12i** was reported to be degraded under the aminoetherification condition using ruthenium catalysis.[19]

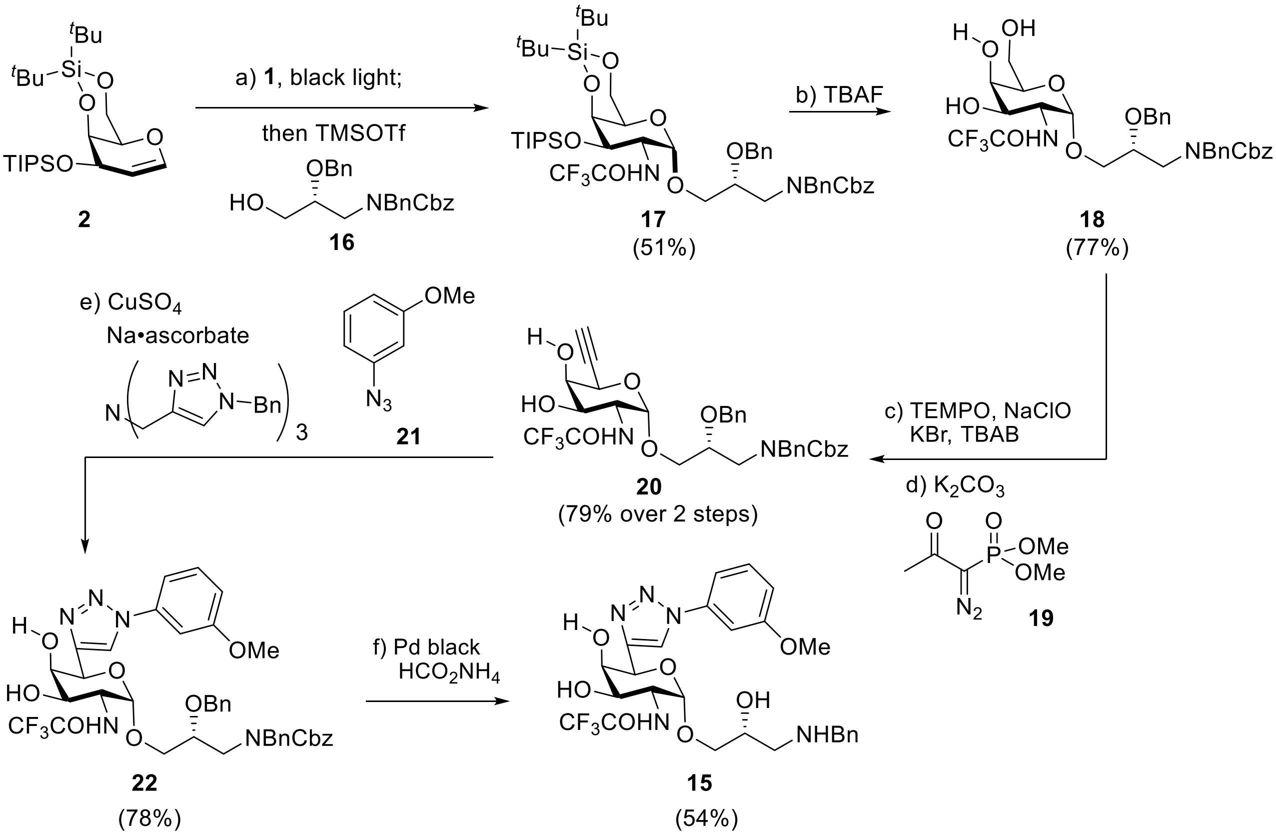
Table 3. Substrate scope for photo-induced aminoetherification of glucal derivatives[a]



[a] The ratios of **13** : **14** (d.r.) were determined by ^{1}H NMR. [b] 3.0 equiv of **12** was used. [c] 1.0 equiv of **12** was used.

Finally, the synthetic potential of this reaction was demonstrated through the efficient synthesis of a potent ligand to the asialoglycoprotein receptor (ASGPR) (Scheme 3). The amino sugar derivative **15** bearing an *N*-trifluoroacetamido moiety is known to be a more potent ligand to ASGPR than its *N*-acetamido counterpart.[10b] However, the synthesis of **15** required extensive manipulation of the protecting group and removal of *N*-Cbz protection. Additionally, it gave excessive *O*-trifluoroacetylation, which should subsequently be removed. We envisioned that our direct *N*-trifluoroacetamido introduction method offers efficient access to amino sugars bearing the *N*-trifluoroacetamido moiety (Scheme 3). To this end, we first investigated the aminoetherification reaction of galactal derivative **2** with alcohol **16** to furnish the desired galactosamine derivative **17** in 51% yield as a single α-isomer. The deprotection of three hydroxy groups at the C3, C4, and C6 positions were achieved by the treatment of **17** with tetra-*n*-butylammonium fluoride (TBAF) to furnish the corresponding triol **18** in 77% yield. The primary alcohol moiety of **18** was selectively oxidized by the combination of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/NaClO in the presence of a catalytic amount of tetra-*n*-butylammonium bromide (TBAB)/KBr[20] to give the corresponding aldehyde, which was then reacted with the Ohira-Bestmann reagent **19** under basic conditions[21] to afford the alkyne **20** in 79% overall yield. The copper(I)-catalyzed ligation of alkyne **20** with azide **21** proceeded efficiently to afford the corresponding triazole **22** in 78% yield.[22] Finally, the reductive cleavage of the *O*-benzyl group and *N*-Cbz group proceeded selectively using the combination of palladium black and HCO_2NH_4 to give the target product **15** in 54% yield.

In conclusion, we developed a photo-irradiation-promoted aminoetherification of glycals using *N*-acyliminoiodinane and various alcohols. This kind of transformation may provide easier access to 2-(*N*-trifluoroacetamido)-2-deoxyglycosides, contributing to the efficient investigation of bioactive compounds in the field of medicinal chemistry. Further investigation into the mechanistic studies of the reaction of *N*-acyliminoiodinane is underway.



Scheme 3. Synthesis of bioactive compound **15**; Reagents and conditions: (a) 1 (2.0 equiv), UV light, AWMS, CH_2Cl_2, 0 ˚C, 3 h; then **16** (1.0 equiv), TMSOTf (20 mol%), rt, 1 h, 51%; (b) TBAF (5.0 equiv), THF, rt, 12 h, 77%; (c) TEMPO (5 mol%), $NaClO\cdot H_2O$ (1.2 equiv), KBr (10 mol%), TBAB (5 mol%), DCM-sat. aq. $NaHCO_3$, 0 ˚C to rt, 2 h; (d) **19** (1.2 equiv), K_2CO_3 (2 equiv), MeOH, rt, 4 h, 79% for the 2 steps; (e) **21** (2.0 equiv), $CuSO_4\cdot H_2O$ (10 mol%), TBTA (10 mol%), Na·ascorbate (20 mol%), $MeOH/H_2O$ (20:1, v/v), rt, 30 min, 78%; (f) Pd black (16 equiv), HCO_2NH_4 (53 equiv), MeOH, rt, 6 h, 54%.

EXPERIMENTAL

Optimized general procedure for the photo-induced aminoetherification of glycals

A mixture of glycal **2** or **11** (0.1 mmol, 44.3 mg), iminoiodinane **1** (0.2 mmol, 71.8 mg) and activated molecular sieves 5Å (MS 5Å, 50 mg) in dry CH_2Cl_2 (2.0 mL) was stirred at room temperature for 30 min. The reaction mixture was then cooled to 0 °C and stirred at the same temperature for 6 h under UV light irradiation (λ = 365 nm) while the consumption of glycal was monitored by TLC. To the resulting mixture, was added alcohol (0.1 mmol or 0.3 mmol), and the whole mixture was stirred at room temperature for 30 min before the addition of TMSOTf (0.02 mmol, 3.6 μL). The reaction mixture was further stirred at room temperature overnight. After concentration of the solvent under reduced pressure, direct purification by flash column chromatography on silica gel gave the desired amino conjugate **6** or **13**.

ACKNOWLEDGMENTS

This work was partly supported by JSPS KAKENHI (grant numbers 16H06384 and 17K15423) and the Takeda Science Foundation.

REFERENCES AND NOTES

1. R. Schauer, *Adv. Carbohydr. Chem. Biochem.*, 1982, **40**, 131.
2. S. Hakomori, *Annu. Rev. Immunol.*, 1984, **2**, 103.
3. (a) M. H. Ravindranath, H. H. Higa, E. L. Cooper, and J. C. Paulson, *J. Biol. Chem.*, 1985, **260**, 8850; (b) N. Shibuya, I. J. Goldstein, W. F. Broekaert, M. Nsimba-Lubaki, B. Peeters, and W. J. Peumans, *J. Biol. Chem.*, 1987, **262**, 1596.
4. T. Feizi, *Trends Biochem. Sci.*, 1981, **6**, 333.
5. R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683.
6. B. Casu, *Adv. Carbohydr. Chem. Biochem.*, 1985, **43**, 51.
7. (a) R. U. Lemieux, *Chem. Soc. Rev.*, 1978, **7**, 423; (b) A. Varki, *Glycobiology*, 1993, **3**, 97.
8. For recent reviews on the synthesis of 2-amino-2-deoxysugars, see: (a) S. Mirabella, F. Cardona, and A. Goti, *Org. Biomol. Chem.*, 2016, **14**, 5186; (b) A. F. Bongat and A. V. Demchenko, *Carbohydr. Res.*, 2007, **342**, 374.
9. N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822.
10. For selected examples of the effect of the trifluoroacetamide moiety, see: (a) A. Sandomenico, A. Russo, G. Palmieri, P. Bergamo, M. Gogliettino, L. Falcigno, and M. Ruvo, *J. Med. Chem.*, 2012, **55**, 2102; (b) S. K. Mamidyala, S. Dutta, B. A. Chrunyk, C. Préville, H. Wang, J. M. Withka, A. McColl, T. A. Subashi, S. J. Hawrylik, M. C. Griffor, S. Kim, J. A. Pfefferkorn, D. A. Price, E. Menhaji-Klotz, V. Mascitti, and M. G. Finn, *J. Am. Chem. Soc.*, 2012, **134**, 1978.
11. Selected examples for the removal of trifluoroacetyl protection, see: (a) M. Osorio-Olivares, M. C. Rezende, S. Sepulveda-Boza, B. K. Cassels, and A. Fierro, *Bioorg. Med. Chem.*, 2004, **12**, 4055; (b) K. Kong, Z. Moussa, C. Lee, and D. Romo, *J. Am. Chem. Soc.*, 2011, **133**, 19844.
12. The following references contain selected examples of reactions using glycosyl donors with

anomeric leaving groups; bromide: (a) R. G. Strachan, W. V. Ruyle, T. Y. Shen, and R. Hirschmann, *J. Org. Chem*., 1966, **31**, 507; sulfoxide: (b) D. J. Silva, H. Wang, N. M. Allanson, R. K. Jain, and M. J. Sofia, *J. Org. Chem*., 1999, **64**, 5926; *S*-benzoxazolyl glycosyl donor: (c) A. F. G. Bongat, M. N. Kamat, and A.V. Demchenko, *J. Org. Chem*., 2007, **72**, 1480.

13. J. Du Bois, C. S. Tomooka, J. Hong, and E. M. Carreira, *J. Am. Chem. Soc*., 1997, **119**, 3179.
14. (a) Y. Kobayashi, S. Masakado, and Y. Takemoto, *Angew. Chem. Int. Ed.*, 2018, **57**, 693; (b) Z. Wu, R. Feng, H. Li, J. Xu, G. Deng, M. Abe, D. Bégué, K. Liu, and X. Zeng, *Angew. Chem. Int. Ed*., 2017, **56**, 15672; (c) V. Bizet and C. Bolm, *Eur. J. Org. Chem*., 2015, 2854; (d) V. Desikan, Y. Liu, J. P. Toscano, and W. S. Jenks, *J. Org. Chem*., 2008, **73**, 4398; (e) M. P. Sherman and W. S. Jenks, *J. Org. Chem*., 2014, **79**, 8977; (f) D. Mansuy, J.-P. Mahy, A. Dureault, G. Bedi, and P. Battioni, *J. Chem. Soc*., *Chem. Commun*., 1984, 1161.
15. A. Imamura, N. Matsuzawa, S. Sakai, T. Udagawa, S. Nakashima, H. Ando, H. Ishida, and M. Kiso, *J. Org. Chem*., 2016, **81**, 9086.
16. In our preliminary investigation, tri-*O*-acetyl-D-glucal resulted in no reaction.
17. The stereochemistry of the products **13** and **14** was determined by the ^{1}H NMR coupling constant between protons at the C1 and C2 positions (**13**: 8.2–8.8 Hz, **14**: <0.4 Hz).
18. Although glucal **11** was completely consumed in all case, the corresponding hydrate was obtained in *ca*. 10-20% yield as a byproduct.
19. T. Murakami, Y. Sato, K. Yoshioka, and M. Tanaka, *RSC Adv.*, 2014, **4**, 21584.
20. M. Hayashi, Y. Sasano, S. Nagasawa, M. Shibuya, and Y. Iwabuchi, *Chem. Pharm. Bull*., 2011, **59**, 1570.
21. S. Müller, B. Liepold, and G. J. Roth, and H. J. Bestmann, *Synlett*, 1996, 521.
22. T. R. Chan, R. Hilgraf, K. B. Sharpless, and V. V. Fokin, *Org. Lett*., 2004, **6**, 2853.