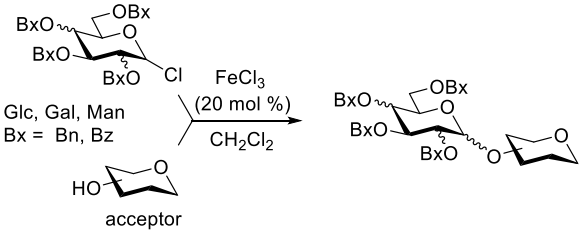
Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides

Scott A. Geringer and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, Missouri 63121, USA



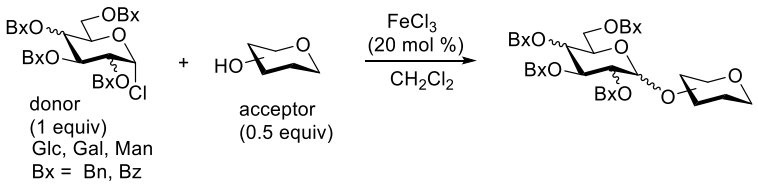
ABSTRACT: Glycosyl chlorides have historically been activated using harsh conditions and/or toxic stoichiometric promoters. More recently, the Ye and the Jacobsen groups showed that glycosyl chlorides can be activated under organocatalytic conditions. However, those reactions are slow, require specialized catalysts and high temperatures, but still provide only moderate yields. Presented herein is a simple method for the activation of glycosyl chlorides using abundant and inexpensive ferric chloride in catalytic amounts. Our preliminary results indicate that both benzylated and benzoylated glycosyl chlorides can be activated with 20 mol % of $FeCl_3$.

Introduced by Michael in 1879[1] and subsequently studied by many, glycosyl chlorides have been very influential building blocks that helped to establish basic principles of carbohydrate chemistry.[2,3] Once prominent glycosyl donors, in recent years glycosyl chlorides have been outshadowed by other, more powerful glycosyl donors,[4-11] and for a reason. Traditionally, the activation of glycosyl chlorides demanded stoichiometric and often toxic reagents, such as silver(I)[2,12,13] or mercury(II) salts.[14] This, along with a fairly high propensity to hydrolysis, hampered the application of glycosyl chloride in recent years. Glycosyl chlorides, however, have many positive traits. They can be obtained using a variety of substrates and methods,[15-25] many chlorides are stable, and recent studies by Ye et al.[26] and Jacobsen et al.[27] have demonstrated that these compounds can be activated without toxic promoters under organocatalytic conditions using urea- or thiourea-based catalysts. Good stereoselectivity was obtained using various additives[26] or with complex chiral catalytic constructs,[27] but these reactions are slow (24-48 h), require high temperatures and provide practical yields only with highly reactive (alkylated) chlorides. In an active pursuit of catalytic activation methods for glycosylation,[28,29] we observed that glycosidation of chlorides can be achieved in the presence of catalytic amounts of iron(III) chloride ($FeCl_3$ aka ferric chloride). This discovery is at the basis of this communication.

$FeCl_3$ is naturally abundant, inexpensive and relatively benign.[30] Ferric chloride has been employed in the introduction of protecting groups in carbohydrates.[31,32] The application of $FeCl_3$ in *O*-glycosylation has also emerged, most prominently for the activation of glycosyl donors bearing the anomeric acetate.[33-42] Other applications for the activation of aryl glycoside,[43] pivaloate,[44] bromide,[45] imidate,[46] or hemiacetal donors (as a co-catalyst)[47] have also been explored. Using this prior knowledge, we theorized that glycosyl chlorides may also offer a promising new substrate for the catalytic activation with $FeCl_3$. To test this hypothesis, we chose known per-benzylated glucosyl chloride donor **1**[23] to couple with the standard glycosyl acceptor **2**.[48] The glycosylation was set-up in the presence of molecular sieves (4 Å) in dichloromethane. For this preliminary study we chose access of donor **1** (2.0 equiv) similarly to that used by Ye et al.[26] and Jacobsen et al.[27] After a brief preliminary experimentation, we established that 20 mol % of $FeCl_3$ provides the most favorable balance between yields and the reaction time. Thus, the coupling of donor **1** with acceptor **2**[48] provided disaccharide **3** in 67% yield in only 2 h (Table 1, entry 1). Also, glycosidations of chloride **1** with secondary acceptors **4**, **6**, and **8**[48] were conducted under essentially the same reaction conditions. These reactions were slower (3-16 h), but the respective disaccharides **5**, **7** and **9** have successfully been obtained in 47-80% yields (entries 2-4). This preliminary set of experiments has demonstrated both the advantages and limitations of this approach. The main advantage of this approach is the availability and low cost of the catalytic activator. Also the reaction times are notably shorter than those reported for the organocatalytic reactions and even for the traditional heavy metal-based stoichiometric activators. Somewhat average yields for the formation of all products, perhaps except **9**, still on a par with traditional approaches and the results reported by Ye et al.[26] and Jacobsen et al.,[27] are mainly attributed to a substantial formation of a side product of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose. While somewhat unexpected in this particular setting, the formation of 1,6-anhydro sugars in the presence of $FeCl_3$ has been reported.[49] As evident from Table 1, all four disaccharides have been produced with poor selectivity (α/β = 1-1.5/1); our method, however, does not employ stereodirecting functionalities, additives,[26] or complex chiral catalytic constructs[27] at this stage.

Following the general success of glucosyl chloride donor **1** we investigated galactosyl chloride **10**[23] that provided even faster reaction times (entry 5-8), probably due to the generally higher reactivity of the galactosyl donors versus similarly equipped glucose counterparts, and a noticeable increase in yields. The latter could be attributed to the entire absence of the 1,6-anhydro side-product that hampered the yields with donor **1**.

Table 1. Iron(III) chloride-catalyzed glycosylations



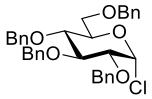
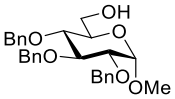
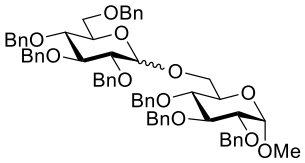
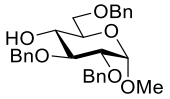
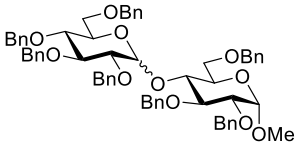
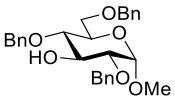
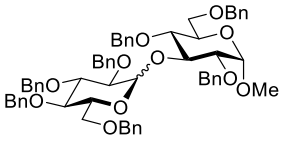
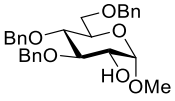
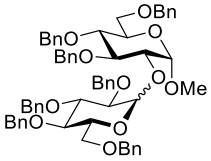
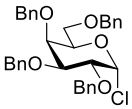
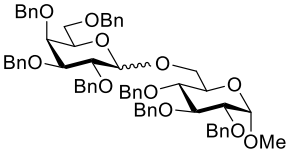
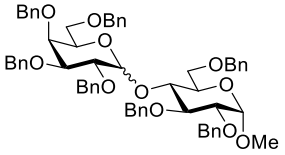
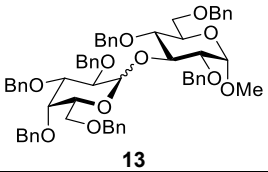
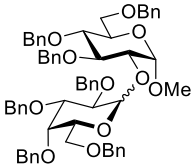
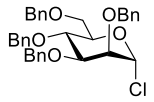
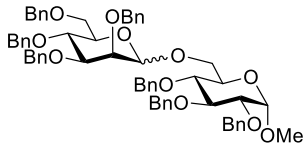
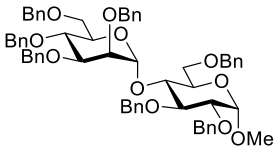
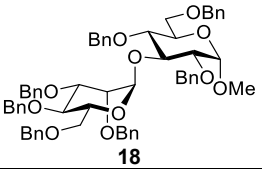
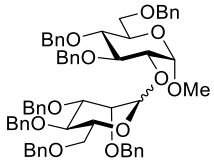
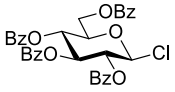
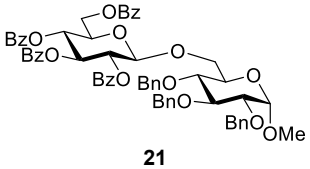
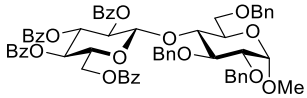
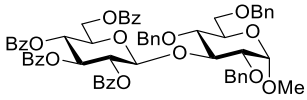
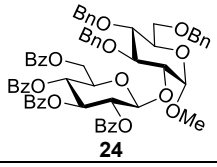
entry	donor	acceptor	time	product	yield	α/β ratio
1	 **1**	 **2**	2 h	 **3**	67%	1.1/1
2	**1**	 **4**	16 h	 **5**	47%	1.25/1
3	**1**	 **6**	3 h	 **7**	60%	1.52/1
4	**1**	 **8**	16 h	 **9**	80%	1.0/1
5	 **10**	**2**	0.5 h	 **11**	88%	1/1.43.0
6	**10**	**4**	0.5 h	 **12**	57%	1.60:1/1
7	**10**	**6**	0.5 h	 **13**	80%	1.3/1
8	**10**	**8**	16 h	 **14**	90%	1/2.70

Table 1 (continued). Iron(III) chloride-catalyzed glycosylations

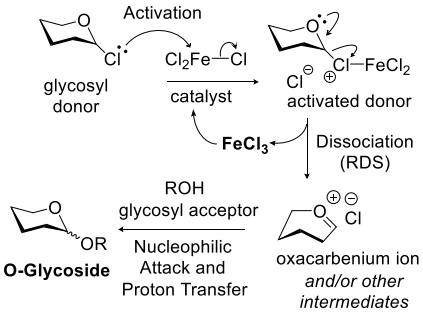
entry	donor	acceptor	time	product	yield	α/β ratio
9	 **15**	**2**	2 h	 **16**	80%	4.5/1
10	**15**	**4**	16 h	 **17**	66%	α-only
11	**15**	**6**	16 h	 **18**	56%	α-only
12	**15**	**8**	16 h	 **19**	95%	2.6/1
13	 **20**	**2**	16 h	 **21**	98%	β-only
14	**20**	**4**	16 h	 **22**	80%	β-only
15	**20**	**6**	16 h	 **23**	52%	β-only
16	**20**	**8**	16 h	 **24**	73%	β-only

Thus, primary acceptor **2** led to the formation of disaccharide **11** in a respectable yield of 88% (entry 5). For comparison, glucosyl chloride donor **1** produced the 1→6 linked disaccharide **3** in 67% (see entry 1). A similar enhancement in yields (up to 90%) and decrease in the reaction time have been observed for the secondary acceptors to produce the respective disaccharides **12-14** (entries 6-8). Expectedly, mannosyl donor **15**[13] showed lower reactivity than its glucosyl and galactosyl counterparts. This was reflected by the increase in reaction times; nevertheless, we obtained respectable yields (up to 95%) for the synthesis of disaccharides **16-19** (entries 9-12). No formation of the 1,6-anhydro side product was detected in this case either. We believe this reaction follows a traditional Lewis acid-catalyzed mechanistic pathway depicted in Scheme 1. Presumably, this reaction follows the traditional unimolecular S_N1 mechanism according to which the catalyst-mediated leaving group departure results in the formation of the oxacarbenium ion. The latter exists in a flattened half-chair conformation that explains poor stereoselectivity observed.

Having demonstrated that $FeCl_3$-catalyzed reactions work reasonably well with per-benzylated sugars, we wanted to investigate whether electronically deactivated benzoylated chloride **20** could be activated using our method. As expected, when donor **20** was glycosidated with acceptor **2** a slower reaction time 16 h (entry 13, Table 1) was recorded in comparison to that with the benzylated glucosyl donor **1** (2 h, see entry 1). Nevertheless, the reaction still proceeded to completion and provided disaccharide **21** in an impeccable yield of 98% and no indication for the side product

formation. The glycosidation of donor **20** also proceeded well with the secondary acceptors **4**, **6**, and **8** providing the corresponding disaccharides **22-24** in respectable yields of 52-80% and complete β-selectivity due to the neighboring group participation. It is noteworthy that neither Ye's nor Jacobsen's conditions were able to activate these deactivated benzoylated chlorides.

Scheme 1. Proposed mechanism of the activation of glycosyl chlorides with ferric chloride



In conclusion, we have shown that a variety of glycosyl chlorides can be activated with catalytic iron(III) chloride. This method allows for a cheap and relatively benign activation of glycosyl chlorides compared to previous methods using harsher and less environmentally friendly conditions. While the yield of glycosylation reactions are still far from being ideal, a majority of results obtained herein are on a par with recently developed organocatalytic reactions reported by Ye et al.[26] and Jacobsen et al.[27] The stereoselectivity obtained in reactions with benzylated chlorides is unimpressive, which is not a surprise because we do not currently employ any directing auxiliaries, catalysts, or additives as in other similar studies. However, our study employs a very inexpensive activator, and this method can serve as a basis for refining stereoselectivity in the future. One of the possible directions for this to explore the known effect of stoichiometric $FeCl_3$ that is capable of producing the α-product preferentially, presumably due to post-glycosylational anomerization reaction.[40]

Of particular significance is that electronically deactivated, benzoylated chlorides can also be activated using our reaction conditions, whereas other catalytic systems fail to activate those unreactive substrates. The investigation of the scope and limitations of this method, including screening other Lewis acids, are currently underway in our laboratory and will be reported in due course. Our preliminary attempt to broaden the scope of this reaction by investigating $SnCl_4$, BF_3-OEt_2, and $Fe(OTf)_3$ indicated similar reaction yields and reaction times to those reported herein.

Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Corresponding Author

* Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, Missouri 63121, USA; demchenkoa@umsl.edu

ACKNOWLEDGMENT

This work was supported by the National Institute of General Medical Sciences (GM120673) and the National Science Foundation (CHE-1800350).

REFERENCES

(1) Michael, A. *Am. Chem. J.* **1879**, *1*, 305.
(2) Koenigs, W.; Knorr, E. *Ber. Deutsch. Chem. Ges.* **1901**, *34*, 957.
(3) Kulkarni, S. S.; Gervay-Hague, J. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008, p 59.
(4) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(5) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
(6) Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5.
(7) Gyorgydeak, Z.; Pelyvas, I. E. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin - Heidelberg - New York, 2001; Vol. 1, p 691.
(8) *Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, Germany, 2008.
(9) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687.
(10) Das, R.; Mukhopadhyay, B. *ChemOpen* **2016**, *5*, 401.
(11) *Selective Glycosylations: Synthetic Methods and Catalysts*; Bennett, C. S., Ed.; Wiley-VCH: Weinheim, 2017.
(12) Igarashi, K.; Honma, T.; Irisawa, J. *Carbohydr. Res.* **1970**, *15*, 329.
(13) Matsuoka, K.; Terabatake, M.; Umino, A.; Esumi, Y.; Hatano, K.; Terunuma, D.; Kuzuhara, H. *Biomacromol.* **2006**, *7*, 2274.
(14) Helferich, B.; Wedemeyer, K. F. *Ann.* **1949**, *563*, 139.
(15) Grob, V. D.; Squires, T. G.; Vercellotti, J. R. *Carbohydr. Res.* **1969**, *10*, 595.
(16) Jansson, K.; Noori, G.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 3181.
(17) Chittenden, G. J. F. *Carbohydr. Res.* **1992**, *242*, 297.
(18) Hung, S. C.; Wong, C. H. *Tetrahedron Lett.* **1996**, *37*, 4903.
(19) Zhang, Z.; Magnusson, G. *Carbohydr. Res.* **1996**, *925*, 41.
(20) Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713.
(21) Ibatulin, F. M.; Selivanov, S. I. *Tetrahedron Lett.* **2002**, *43*, 9577.
(22) Encinas, L.; Chiara, J. L. *J. Comb. Chem.* **2008**, *10*, 361.
(23) Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2009**, *2009*, 3579.
(24) Beale, T. M.; Moon, P. J.; Taylor, M. S. *Org. Lett.* **2014**, *16*, 3604.
(25) Tatina, M. B.; Khong, D. T.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2018**, *2018*, 2208.
(26) Sun, L.; Wu, X.; Xiong, D. C.; Ye, X. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8041.
(27) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. *Science* **2017**, *355*, 162.
(28) Singh, Y.; Wang, T.; Geringer, S. A.; Stine, K. J.; Demchenko, A. V. *J. Org. Chem.* **2018**, *83*, 374.
(29) Nigudkar, S. S.; Stine, K. J.; Demchenko, A. V. *J. Am. Chem. Soc.* **2014**, *136*, 921.
(30) Bauer, I.; Knolker, H. J. *Chem. Rev.* **2015**, *115*, 3170.
(31) Huang, T. Y.; Zulueta, M. M.; Hung, S. C. *Org. Biomol. Chem.* **2014**, *12*, 376.
(32) Gouasmat, A.; Lemétais, A.; Solles, J.; Bourdreux, Y.; Beau, J.-M. *Eur. J. Org. Chem.* **2017**, *2017*, 3355.
(33) Kiso, M.; Anderson, L. *Carbohydr. Res.* **1979**, *72*, C12.
(34) Kiso, M.; Anderson, L. *Carbohyd. Res.* **1979**, *72*, C15.
(35) Kiso, M.; Nishiguchi, H.; Hasegawa, A. *Carbohydr. Res.* **1980**, *81*, C13.
(36) Dasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, *43*, 471.
(37) Lerner, L. M. *Carbohyd. Res.* **1990**, *207*, 138.
(38) Chatterjee, S. K.; Nuhn, P. *Chem. Commun.* **1998**, 1729.
(39) Seibel, J.; Hillringhaus, L.; Moraru, R. *Carbohydr. Res.* **2005**, *340*, 507.
(40) Wei, G.; Lv, X.; Du, Y. *Carbohydr. Res.* **2008**, *343*, 3096.
(41) Narayanaperumal, S.; César da Silva, R.; Monteiro, J. L.; Corrêa, A. G.; Paixão, M. W. *J. Braz. Chem. Soc.* **2012**, *23*, 1982.
(42) Marzag, H.; Robert, G.; Dufies, M.; Bougrin, K.; Auberger, P.; Benhida, R. *Ultrason. Sonochem.* **2015**, *22*, 15.
(43) Laursen, J. B.; Petersen, L.; Jensen, K. J. *Org. Lett.* **2001**, *3*, 687.
(44) Rasmussen, M. R.; Marqvorsen, M. H.; Kristensen, S. K.; Jensen, H. H. *J. Org. Chem.* **2014**, *79*, 11011.
(45) Shetye, G. S.; Singh, N.; Jia, C.; Nguyen, C. D.; Wang, G.; Luk, Y. Y. *Chembiochem : a European journal of chemical biology* **2014**, *15*, 1514.
(46) Mukherjee, M. M.; Basu, N.; Ghosh, R. *RSC Adv.* **2016**, *6*, 105589.
(47) Mukaiyama, T.; Matsubara, K.; Hora, M. *Synthesis* **1994**, 1368.
(48) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V. *Org. Lett.* **2010**, *12*, 5628.
(49) Miranda, P. O.; Brouard, I.; Padrón, J. I.; Bermejo, J. *Tetrahedron Lett.* **2003**, *44*, 3931.