DOI: 10.1002/ejoc.200700038

IPy_2BF_4-Mediated Glycosylation and Glycosyl Fluoride Formation

Kuo-Ting Huang[a] and Nicolas Winssinger*[a]

Keywords: Carbohydrates / Glycosylation / Thioglycosides / Iodine

A facile method to convert thioglycosides to glycosyl fluorides with Ipy_2BF_4 (py = pyridine) is presented. Alternatively, activation of thioglycosides with Ipy_2BF_4 in the presence of acids and glycosyl acceptors led to glycosylation reactions. Perbenzylated (armed) glycosyl donors yielded predominantly the β-anomeric product. This methodology is compatible with one-pot sequential glycosylation.

The success of glycoside bond-forming reactions in the context of complex carbohydrate synthesis remains fickly. Though a number of powerful glycosylation technologies have already been developed, the success of complex synthesis often hinges on the different scope of these various methods and there clearly remains a need for new reagents to promote glycosylation.[1–3] In fact, few complex carbohydrates have been assembled by a single glycosylation method. Thioglycosides are attractive glycosyl donors as the anomeric thioether is stable to most protecting group manipulation and they are compatible with a number of other glycosylation methods. Not surprisingly, a series of thiophilic reagents have been described to promote glycosylation including *N*-bromosuccinamide (NBS),[4] dimethyl(thiomethyl)sulfonium trifluoromethane sulfonate (DMTST),[5] MeSOTf (Tf = trifluorosulfonate),[6] iodonium dicollidine perchlorate (IDCP),[7] and NIS/TfOH (NIS = *N*-iodosuccinamide).[8,9] More recently, benzynesulfinyl piperidine/Tf_2O[10] and *N*-(phenylthio)-ε-caprolactam/Tf_2O[11] were shown to be potent activators. Interestingly, although the iodonium activation of thioglycosides is well known and typically carried out with NIS/TfOH, the efficiency of Ipy_2BF_4[12] has never been evaluated in glycosylation reactions. Ipy_2BF_4 has proven to be an extremely powerful source of iodonium, as exemplified by the diversity of chemistry that it can engender,[13–17] and it has become commercially available in large quantities. Herein we report the use of Ipy_2BF_4 to convert thioglycosides to glycosyl fluorides and its application as a promoter of glycosylation by using thioglycosides.

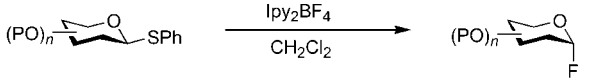
An important asset of thioglycosides is the ability to convert them into glycosyl fluorides for reiterative glycosylation between glycosyl fluoride donor and thioglycoside acceptor. The procedure most often employed involves the use of NBS in the presence of DAST.[18] Alternative methods involving 4-$MePhIF_2$[19] and Selectfluor {1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}[20] have also been reported. We found that in the absence of acid, Ipy_2BF_4 smoothly converted armed thioglycosides into glycosyl fluorides. As shown in Table 1, perbenzylated thioglucose, galactose, mannose, as well as 4,6-benzyledenegalactose afforded the glycosyl fluoride as the α-anomer in moderate-to-good yield (50–86%).

We then turned our attention to the use of Ipy_2BF_4 to promote glycosylation. It is known that a protic acid or Lewis acid is necessary to coordinate to pyridine to reveal the iodonium species. In fact, this can be monitored visually with the appearance of a deep red color upon addition of TfOH, HBF_4, TMSOTf, or BF_3–Et_2O. Glycosylation was found to be effective with all these acids but further optimization of glycosylations were carried out strictly with TfOH. With the use of isopropyl alcohol as a model glycosyl acceptor, glycosylation was not effective from –100 °C to –60 °C (Table 2, Entries 1–3) but proceeded smoothly at –35 °C in the presence of at least 1 equiv. of acid; the reaction remained buffered, however, by pyridine (Table 2, Entries 8 and 9). A catalytic amount of acid afforded mixtures of glycosyl fluoride and glycosylation product (Table 2, Entries 4–7). It is interesting to note the predominance of the β-anomer in these reactions as glycosylation of perbenzylated (armed) donors is known to proceed through either an S_N2 mechanism or through the oxocarbenium intermediate; both reaction pathways lead to the product corresponding to the α-anomer. The high ratio of the observed β-anomer in these reactions may be attributed to the participation of pyridine, which results in a double inversion. This type of double inversion is well-documented for acetonitrile and a pyridinium glycoside intermediate has recently been characterized by using 2-chloropyridine.[21]

[a] Organic and Bioorganic Chemistry Laboratory, Institut de Science et Ingénierie Supramoléculaires, Université Louis Pasteur – CNRS,
8 allée Gaspard Monge 67000 Strasbourg, France
Fax: +33-3-90-24-51-12
E-mail: winssinger@isis.u-strasbg.fr

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Table 1. Ipy_2BF_4 mediated conversion of thioglycosides into glycosyl fluorides.



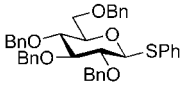
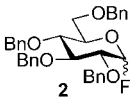
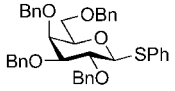
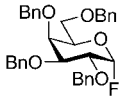
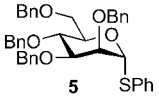
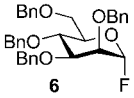
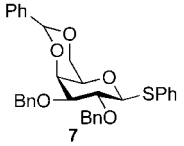
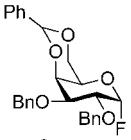
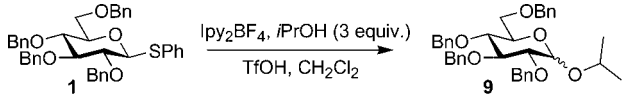
Entry	Saccharide	Product	Ipy_2BF_4 [equiv.]	T [°C]	Time [h]	Yield [%]
1	 **1**	 **2**	1.5	r.t.	3.0	50 α:β 80:20
2	 **3**	 **4**	1.5	r.t.	1.5	86
3	 **5**	 **6**	1.5	r.t.	3.0	75
4	 **7**	 **8**	1.5	r.t.	3.0	76

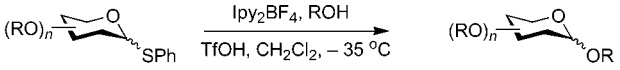
Table 2. Optimization of Ipy_2BF_4 mediated glycosylation.

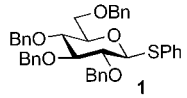
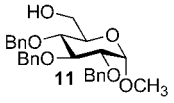
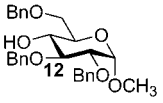
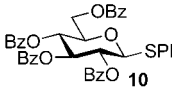
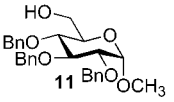
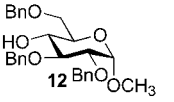
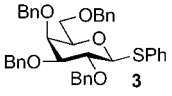
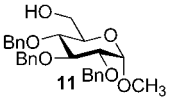
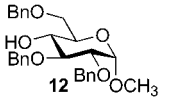
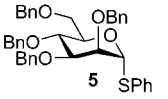
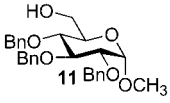
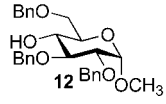


Entry	Ipy_2BF_4 [equiv.]	TfOH [equiv.]	T [°C]	Time [h]	Yield [%]	α:β:F(α)
1	2.0	2.0	– 100	1.0	No Reaction	
2	2.0	6.0	– 100	1.0	No Reaction	
3	1.5	Cat	– 60	1.0	No Reaction	
4	1.5	Cat	– 35	1.0	86	40:46:14
5	1.5	Cat	– 20	1.0	89	38:48:14
6	1.5	Cat	– 0	1.0	90	34:52:14
7	1.5	Cat	– 35→ r.t.	1.0	90	36:51:13
8	1.5	1.5	– 35	1.0	89	42:58: 0
9	1.5	3.0	–35	1.0	90	34:66: 0

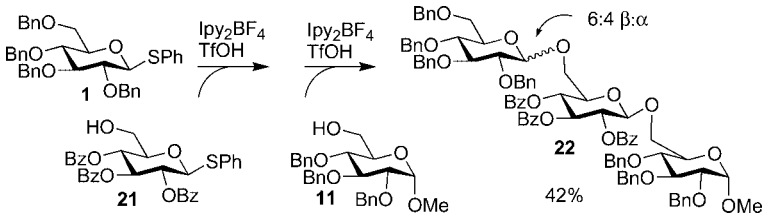
With these results in hand, we then investigated the utility of Ipy_2BF_4 for the preparation of disaccharides. As shown in Table 3, the reaction proceeds smoothly with a variety of donors (glucose, galactose, and mannose) to afford the product in good-to-excellent yield for both armed and disarmed donors. For perbenzylated thioglucose (Entries 1 and 2), the reaction afforded 80% of the β-anomer for a 1→6 glycosylation and 64% for a 1→4 glycosylation. The greater steric demand of a C-4 hydroxyl favors the α-anomeric product. The perbenzoylated thioglucose afforded exclusively the expected β-anomer in both cases (Entries 3 and 4) by virtue of neighboring group participation. The "armed" perbenzylated galactose afforded 85% of the β-anomer for a 1→6 glycosylation (Entry 5); however, the selectivity was rather poor for a 1→4 glycosylation (Entry 6). In the case of mannose, the 1→6 glycosylation reaction afforded strictly the β-anomer albeit in moderate yield (Entry 7) whereas the sterically more demanding 1→4 glycosylation afforded the α-anomer in good yield (Entry 8).

Table 3. Ipy_2BF_4 mediated disaccharide formation.



Entry	Donor	Acceptor	Time [h]	Yield [%]	α/β
1	 **1**	 **11**	2.0	87	20:80 **13**
2		 **12**	1.0	84	36:64 **14**
3	 **10**	 **11**	1.0	74	β **15**
4		 **12**	1.0	70	β **16**
5	 **3**	 **11**	1.0	85	15:85 **17**
6		 **12**	1.0	80	60:40 **18**
7	 **5**	 **11**	1.0	40	β **19**
8		 **12**	1.0	83	α **20**

A significant advance in the field of carbohydrate synthesis is the development of one-pot sequential glycosylation methods that rely predominantly on the tuning of the donor reactivity. The spectrum of reactivity, from "armed" to "disarmed" glycosyl donors, can be tuned by choosing the



Scheme 1. One-pot glycosylation reaction.

appropriate protecting groups.[22–24] In this context, the ability to form a β-glycosidic bond with a fully armed glycosyl donor is valuable. This is exemplified by the one-pot synthesis of trisaccharide **22** from monomeric units **1**, **21**, and **11** respectively (Scheme 1). Trisaccharide[25] **22** was obtained in 42% yield as a 6:4 mixture in favor of the β-anomer.

In conclusion, the activation of thioglycosides with Ipy$_2$BF$_4$ was demonstrated either to yield glycosyl fluorides or to promote glycosylation, depending on the reactions conditions. Glycosylation of perbenzylated "armed" glycosides affords predominantly β-anomeric products with unhindered acceptors, which provides unique reactivity. This can be exploited in one-pot glycosylation reactions as was exemplified with the formation of a trisaccharide containing β-linkages prepared from an "armed" and a "disarmed" donor.

Experimental Section

General Procedure for the Conversion of Thioglycoside to Glycosyl Fluoride: Ipy$_2$BF$_4$ (55.8 mg, 0.15 mmol, 1.5 equiv.) was added to a solution of thioglycoside (0.10 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 23 °C, and the mixture was stirred for 3 h. The reaction mixture was then diluted with ethyl acetate and washed sequentially with $NaHCO_3$ (satd.) and brine. The organic layer was dried with sodium sulfate, concentrated in vacuo, and purified by silica gel flash column chromatography.

General Procedure for Ipy$_2$Bf$_4$-Mediated Glycosylation: A solution of thioglycoside (0.15 mmol, 1.5 equiv.) and acceptor (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) were stirred in the presence of 3 Å molecular sieves for 20 min at 23 °C room temperature and then cooled to –35 °C prior to the addition of TfOH (13.3 μL, 0.15 mmol, 1.5 equiv.). The reaction mixture was stirred at this temperature for 10 min and Ipy$_2$BF$_4$ (55.8 mg, 0.15 mmol, 1.5 equiv.) was added. The solution was stirred at –35 °C for 1 h then quenched with an excess diisopropylethylamine (82.6 μL, 0.5 mmol, 5 equiv.). The reaction was diluted with ethyl acetate (20 mL) and was washed sequentially with $NaHCO_3$sat. (2 × 15 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4, concentrated in vacuo and purified by silica gel flash column chromatography.

One-Pot Sequential Glycosylation: A solution of thioglycoside **1** (0.11 mmol, 1.1 equiv.) in CH_2Cl_2 (5 mL) of was stirred for 20 min at room temperature in the presence of 3 Å molecular sieves and then cooled to –35 °C followed by the addition of TfOH (0.11 mmol, 1.1 equiv.). The solution was stirred at this temperature for 10 min, and Ipy$_2$BF$_4$ (0.11 mmol, 1.1 equiv.) was added. The solution was stirred at –35 °C for 20 min, and glycosyl acceptor **21** was added at –35 °C. After completion of the first glycosylation reaction (1 h, monitored by TLC), glycosyl acceptor **11** (0.11 mmol, 1.1 equiv.) was added followed by a second batch of TfOH (0.11 mmol, 1.1 equiv.) and Ipy$_2$BF$_4$ (0.11 mmol, 1.1 equiv.). The reaction was stirred for an additional 60 min at –35 °C before the addition of excess diisopropylethylamine (82.6 μL, 0.5 mmol, 5 equiv.). The reaction was diluted with ethyl acetate (20 mL) and washed sequentially with $NaHCO_3$ (satd.) (2 × 15 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4, concentrated in vacuo, and purified by silica gel flash column chromatography to obtain trisaccharide **22** in 42% yield.

Supporting information (see footnote on the first page of this article): Characterization data for compounds **2**, **4**, **6**, **8**, **9**, **13**–**20**, **22**.

Acknowledgments

A fellowship from the French Ministry of Science (K.-T. H.) is gratefully acknowledged.

[1] K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.
[2] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624–1672; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576–1624.
[3] B. G. Davis, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160.
[4] K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.
[5] P. Fugedi, P. J. Garegg, *Carbohydr. Res.* **1986**, *149*, C9–C12.
[6] F. Dasgupta, P. J. Garegg, *Carbohydr. Res.* **1988**, *177*, C13–C17.
[7] G. H. Veeneman, J. H. Van Boom, *Tetrahedron Lett.* **1990**, *31*, 275–278.
[8] P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316.
[9] H. M. Zuurmond, S. C. Van der Laan, G. A. Van der Marel, J. H. Van Boom, *Carbohydr. Res.* **1991**, *215*, C1–C3.
[10] D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.
[11] S. G. Duron, T. Polat, C. H. Wong, *Org. Lett.* **2004**, *6*, 839–841.
[12] J. Barluenga, J. M. Gonzalez, P. J. Campos, G. Asensio, *Angew. Chem.* **1985**, *97*, 341–342; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 319–320.
[13] J. Barluenga, F. Gonzalez-Bobes, M. C. Murguia, S. R. Ananthoju, J. M. Gonzalez, *Chem. Eur. J.* **2004**, *10*, 4206–4213.
[14] J. Barluenga, M. Trincado, M. Marco-Arias, A. Ballesteros, E. Rubio, J. M. Gonzalez, *Chem. Commun.* **2005**, 2008–2010.
[15] J. Barluenga, M. Trincado, E. Rubio, J. M. Gonzalez, *Angew. Chem.* **2006**, *118*, 3212–3215; *Angew. Chem. Int. Ed.* **2006**, *45*, 3140–3143.
[16] J. Barluenga, M. Trincado, E. Rubio, J. M. Gonzalez, *Angew. Chem.* **2003**, *115*, 2508–2511; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406–2409.
[17] J. Barluenga, H. Vazquez-Villa, A. Ballesteros, J. M. Gonzalez, *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029.
[18] R. E. Dolle, K. C. Nicolaou, *J. Am. Chem. Soc.* **1985**, *107*, 1695–1698.
[19] S. Caddick, W. B. Motherwell, J. A. Wilkinson, *J. Chem. Soc., Chem. Commun.* **1991**, 674–675.

[20] M. D. Burkart, Z. Zhang, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746.
[21] B. A. Garcia, D. Y. Gin, *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.
[22] Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
[23] M. K. Cheung, N. L. Douglas, B. Hinzen, S. V. Ley, X. Pannecoucke, *Synlett* **1997**, 257–260.
[24] J. D. C. Codee, R. E. J. N. Litjens, L. J. Van den Bos, H. S. Overkleeft, G. A. Van der Marel, *Chem. Soc. Rev.* **2005**, *34*, 769–782.
[25] H. Jona, H. Mandai, W. Chavasiri, K. Takeuchi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291–309.
Received: January 17, 2007
Published Online: March 9, 2007

