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IPy_2BF_4-Mediated Transformation of *n*-Pentenyl Glycosides to Glycosyl Fluorides: A New Pair of Semiorthogonal Glycosyl Donors

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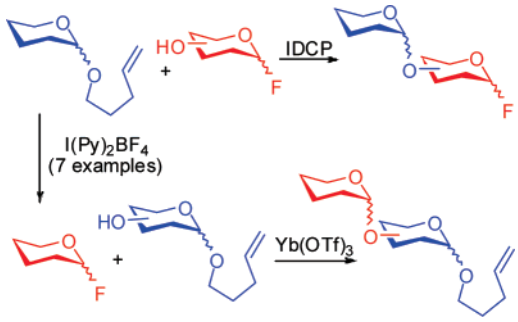
ABSTRACT



Bis(pyridinium) iodonium(I) tetrafluoroborate (IPy_2BF_4), a solid and stable reagent, can be used to transform *n*-pentenyl orthoesters (NPOEs) and *n*-pentenyl glycosides (NPGs) into glycosyl fluorides. The latter pair constitutes a new set of semiorthogonal glycosyl donors that can be used in glycosylation strategies, alone or in combination with NPOEs.

The development of efficient methods for accessing synthetic oligosaccharides is essential to the understanding of their biological relevance.[1] Major advances in the field have arisen from the development of new glycosyl donors that have, in turn, contributed to the design of novel strategies in glycosylation.[2,3] In this context, *n*-pentenyl glycosides (NPGs)[4] are extremely versatile glycosyl donors that have played a key role in the development of the chemoselectivity-based armed−disarmed approach for saccharide coupling,[5] including its stereoelectronic[6] or torsional[7] variants. Glycosyl fluorides[8,9] have also proven themselves as useful glycosyl donors and have played a strategic role in the development of the two-stage activation protocol[10] and the orthogonal method[11] for glycosyl assembly.

In this Letter, we disclose a convenient method for the conversion of NPGs into glycosyl fluorides and their use as a new pair of semiorthogonal[12] glycosyl donors.

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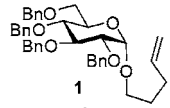
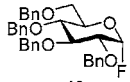
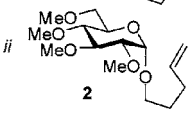
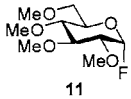
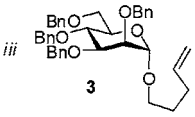
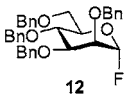
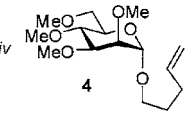
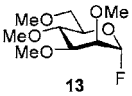
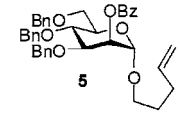
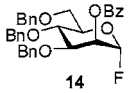
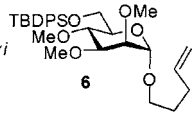
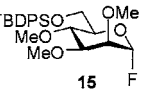
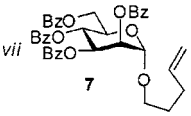
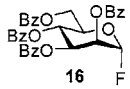
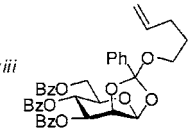
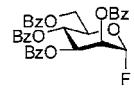
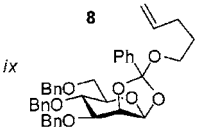
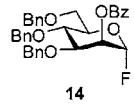
For the transformation of NPGs to glycosyl fluorides we selected bis(pyridinium) iodonium(I) tetrafluoroborate (IPy_2BF_4).[13] This commercially available compound, a stable and solid reagent that acts as a mild source of iodonium ions,[14] drew our attention since it effects facile iodofluorination of alkenes in the presence of an acid.[15] Accordingly, we reasoned that NPGs could be efficiently converted to glycosyl fluorides[16,17] upon treatment with IPy_2BF_4. Our results, displayed in Table 1, showed that NPGs **1**−**7** react smoothly at low temperature with IPy_2BF_4 in CH_2Cl_2[18] in the presence of tetrafluoroboric acid[19] (HBF_4) to give glycosyl fluorides **10**−**16**, in good to excellent yields. *n*-Pentenyl orthoesters (NPOEs) **8**, **9** also underwent the same transformation under similar reaction conditions. In all cases (Table 1, entries i-ix), the reaction took place with complete stereoselectivity to furnish α-glycosyl fluorides exclusively. Partially disarmed NPG **5** yielded glycosyl fluoride **14** (entry v) uneventfully.

The transformation of disarmed NPG **7** demanded further acidic treatment, to rearrange a presumed orthoacyl fluoride intermediate,[20] to yield the desired fluoride (entry vii). Silyl protecting groups are compatible with the reaction conditions employed as illustrated in the reaction of NPG **6** (entry vi). Finally, NPOEs can also be transformed to glycosyl fluorides, thus providing an alternative route to acyl substituted glycosyl fluorides (e.g., **16**) otherwise available by reaction of disarmed NPGs (compare entries vii and viii).

We next decided to explore the orthogonality of NPGs and glycosyl fluorides. To activate glycosyl fluorides while leaving NPGs unchanged, we selected ytterbium triflate ($Yb(OTf)_3$). This reagent has been reported by Shibasaki and co-workers[21] to promote efficient glycosylation of glycosyl fluorides whereas Jayaprakash and Fraser-Reid[22] have shown it to be innocuous toward NPGs. On the other hand, we chose iodonium dicollidine perchlorate (IDCP)[23] as a selective activator for NPGs.

Table 1. Synthesis of Glycosyl Fluorides **10**−**16** from NPGs **1**−**7** and NPOEs **8**, **9** by Treatment with $I(Py)_2BF_4$ in the Presence of HBF_4 (1.2 equiv) in CH_2Cl_2 as Solvent

entry	substrate	temp °C (time)	product	yield (%)
i	 **1**	-40 (30 min)	 **10**	83
ii	 **2**	-40 (15 min)	 **11**	99
iii	 **3**	-40 (30 min)	 **12**	94
iv	 **4**	-40 (15 min)	 **13**	94
v	 **5**	-40 (15 min)	 **14**	90
vi	 **6**	-40 (45 min)	 **15**	75
vii	 **7**	-78 (30 min) then BF_3OEt_2 rt (20 min)	 **16**	75
viii	 **8**	-40 (10 min)	 **16**	82
ix	 **9**	-40 (15 min)	 **14**	95

Our experiments for orthogonal couplings are displayed in Scheme 1. Although useless in target-oriented oligosaccharide synthesis, methyl substituents have been used in several instances for the sake of simplicity in NMR interpretation. Armed and disarmed glycosyl fluorides **12** and **14** underwent smooth glycosylation with NPG **17**, in the presence of $Yb(OTf)_3$ in CH_2Cl_2 at room temperature, to give disaccharides **18** and **19** (Scheme 1a,b). On the other hand, armed NPGs **1**, **4**, and **6** reacted with fluorides **20** and **22**, in the presence of IDCP at room temperature in CH_2Cl_2, to give disaccharides **21**, **23**, and **24** as anomeric mixtures (Scheme 1c,d,e). The method works well with disarmed glycosyl fluorides (Scheme 1b). However, disarmed NPGs

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(17) Yokoyama, M. *Carbohydr. Res.* **2000**, *327*, 5−14.

(18) Although CH_2Cl_2 has been reported as a solvent for the crystallization of IPy_2BF_4 (see ref 14), we have not observed any solubility problems in the reactions described in this paper.

(19) Usually, an acid is required to neutralize the supply of pyridine molecules from IPy_2BF_4, thus avoiding the incorporation of pyridine itself as the nucleophile (see ref 14).

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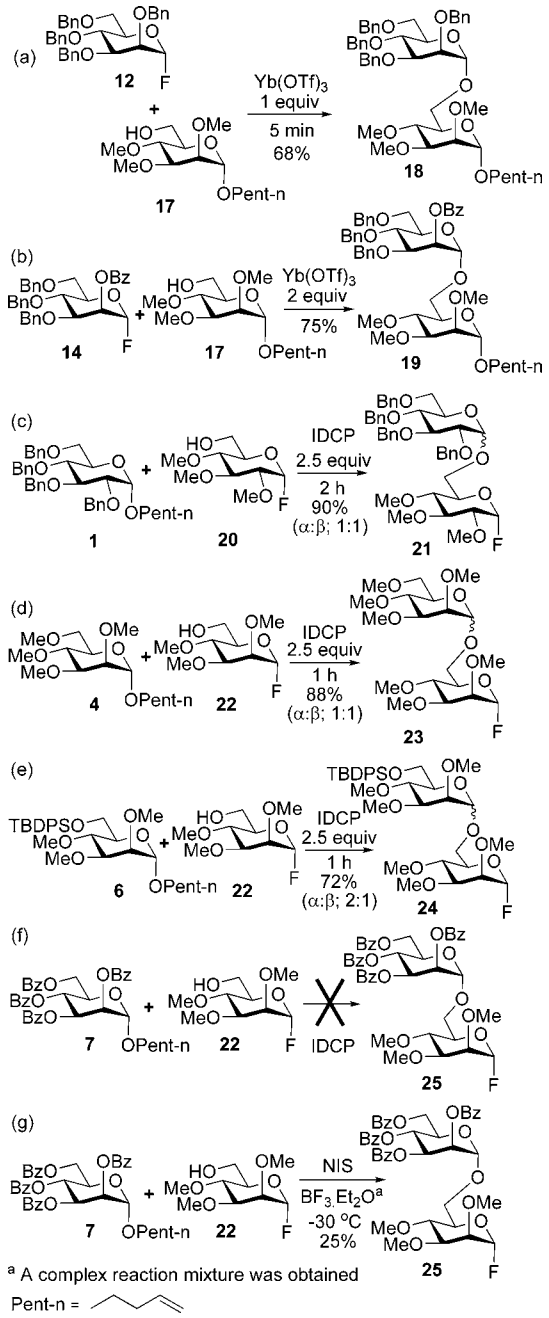
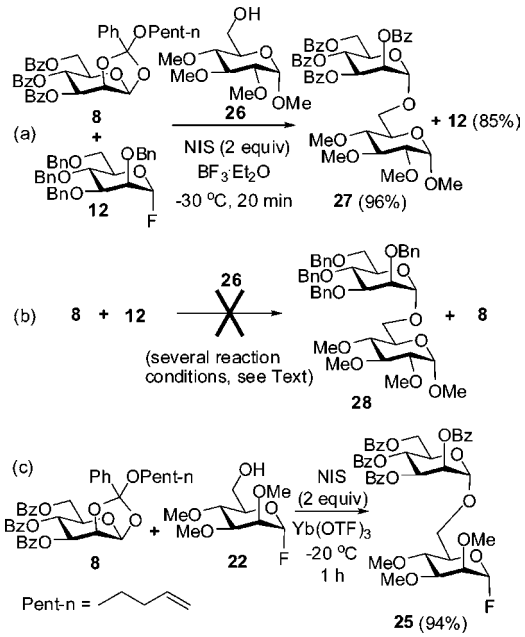
Scheme 1. Orthogonal Glycosyl Couplings between NPGs and Glycosyl Fluorides at Room Temperature, in CH_2Cl_2 as Solvent



(e.g., **7**), which would give rise to disaccharides containing acyl substituents at the nonterminal saccharide (e.g., **25**, Scheme 1f), failed to react upon treatment with IDCP and gave a complex reaction mixture when treated with NIS/$BF_3{\cdot}Et_2O$ at −30 °C from which the sought disaccharide could only be isolated in 25% yield (Scheme 1g).

To overcome this drawback we decided to investigate the possible incorporation of NPOEs (synthetically equivalent to disarmed NPGs but more reactive[24]) to this set of semiorthogonal glycosyl donors. Accordingly, NPOE **8** was made to compete with glycosyl fluoride **12** for glycosyl acceptor **26** under a variety of experimental conditions (Scheme 2). Thus, treatment of the above mixture with NIS

Scheme 2. Coupling of NPOEs with Glycosyl Fluorides

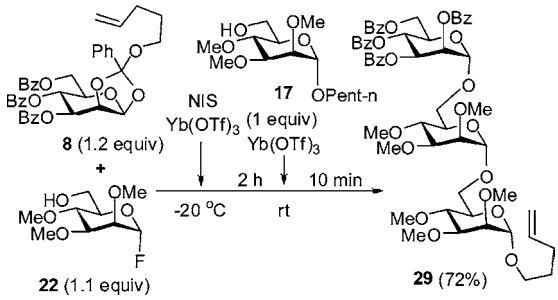


(2 equiv) and $Yb(OTf)_3$ (1 equiv) in CH_2Cl_2 at −20 °C, gave disaccharide **27** along with recovered glycosyl fluoride **12** (85%) (Scheme 2a).

On the contrary, fluoride **12** could not be activated selectively over NPOE **8** under a series of reaction conditions (SnF_4,[25] TMSOTf,[26] $CpTiCl_2/AgClO_4$,[27] $Yb(OTf)_3$,[18] $BF_3{\cdot}OEt_2$[28]), the problem being the preferential activation of NPOE **8** (Scheme 2b). Along this line, disaccharide **25** (unavailable from the reaction of disarmed NPG **7** with glycosyl fluoride **23** (Scheme 1f,g)) could now be efficiently prepared by glycosylation of fluoride acceptor **22** with NPOE **8** (Scheme 2c).

Finally, the knowledge gained from these experiments was applied to the one-pot synthesis of saccharides. Accordingly, glycosylation of fluoride **22** with NPOE **8** (NIS/$Yb(OTf)_3$,

Scheme 3. One-Pot Assembly of Trisaccharide **29** by Sequential Glycosyation of NPOE **8** and Fluoride **22** with NPG **17**



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−20 °C) was followed by the addition of NPG **17** and further $Yb(OTf)_3$ at room temperature to furnish *n*-pentenyl trisaccharide **29**, in 72% yield (Scheme 3).

In summary, we have reported a novel method for the preparation of glycosyl fluorides from NPGs or NPOEs by treatment with IPy_2BF_4. We have also shown that NPGs and glycosyl fluorides constitute a new pair of semiorthogonal glycosyl donors,[12,29] and we have determined appropriate reaction conditions for their selective activation. Furthermore, NPOEs that can be activated in the presence of glycosyl fluorides or NPGs could be used in combination with them in one-pot[30] synthetic protocols for the preparation of saccharides.

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Supporting Information Available: Experimental procedures and characterization data and copies of ^1H, ^{13}C, and two-dimension NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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