Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2023, **21**, 6479

Received 19th June 2023,
Accepted 26th July 2023

DOI: 10.1039/d3ob00929g

rsc.li/obc

Stereoselective oxidative *O*-glycosylation of disarmed glycosyl iodides with alcohols using PIDA as the promoter†

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The direct and practical oxidative anomeric *O*-glycosylation of glycosyl iodides with an array of alcohols as glycosyl acceptors is presented. Using phenyliodine(III) diacetate (PIDA) as the promoter of the reaction, at ambient temperature, an enviromentally benign and operationally simple protocol has been developed providing access stereoselectively to 1,2-*trans*-*O*-glycosides.

O-Glycosides represent an important class of glycosides that are extensively found in nature and exhibit a broad range of biological activities, including anticancer, antibiotic and antiviral properties[1,2] (Fig. 1A). The stereoselective construction of the glycosidic bond represents the main issue in glycochemistry, especially in highly complex structures, accounting for the plethora of methods being continuously developed.[3] Even though the structural complexity of these molecules has attracted just as much attention as their biological role, many challenges in glycosylation chemistry remain to be addressed. The basic concern about existing methodology is related to the activation mode of certain glycosyl donors that, in most cases involves either strong acidic conditions (*e.g.* strong Lewis acids)[4] or toxic heavy metal based reagents (*e.g.* Hg(II) salts).[5]

Expanding the scope of glycosylation reaction to more complex settings calls for milder and safer conditions. Oxidative activation of glycosyl nucleophiles by iodine(III) reagents, presented by Walczak and co-workers, has recently emerged as a way out to this problem (Fig. 1B).[6] Despite the broad scope of implementation, regarding both glycosyl donors and acceptors, and the high levels of stereocontrol, this methodology imposes certain limitations. Majorly, the engagement of anomeric glycosyl stannanes as the glycosyl donors raises severe environmental concerns both during their preparation and utilization throughout the glycosylation step. In addition, the starting materials for the preparation of glycosyl nucleophiles are glycals, which are commercially available, though at much higher price compared to the respective sugar surrogates.[7] Finally, for the reaction to be operative the C2 hydroxyl group of the glycosyl donor must be unprotected, while keeping the rest hydroxyls protected, a differentiation often not simple to achieve, especially with less common substrates.

Given our interest in glycosylation chemistry[8] and drawing inspiration from the activation conditions, elegantly demonstrated by Walczak and his co-workers, utilizing mild and broadly compatible iodine(III) reagents as the oxidative means, we sought for alternative, environmentally benign glycosyl donors suitable for oxidative activation. Glycosyl iodides, are less exploited in glycosylation chemistry among other glycosyl

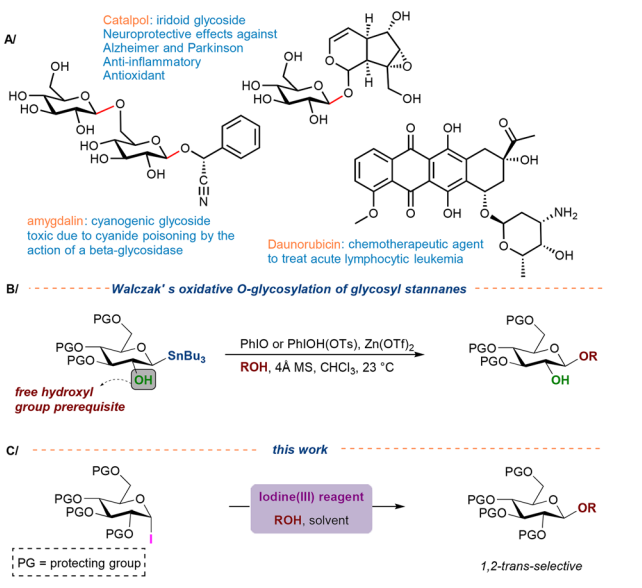

Fig. 1 (A) Examples of naturally existing *O*-glycosides with biological activity, (B) oxidative *O*-glycosylation of glycosyl stannanes by iodine(III) reagents, (C) iodine(III) mediated oxidative *O*-glycosylation of "disarmed" glycosyl iodides.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ob00929g

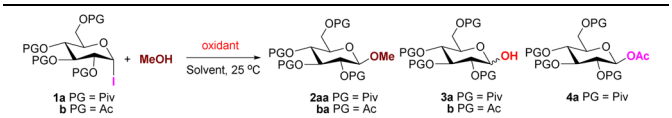
halides, mainly due to their inherent instability.[9] Taming their reactivity by judicious choice of esters as protecting groups ("disarmed" glycosyl iodides)[10] expanded their applications in glycosylation couplings under basic,[11] or acidic conditions.[12] Orthogonally to the aforementioned protocols glycosyl iodides can be activated oxidatively by *N*-iodosuccinimide, a powerful electrophilic iodine source, that is incompatible with common functional groups such as hydroxyl groups, double bonds, triple bonds, electronically rich aromatic systems and many others.[13] In 1983, Varvoglis demonstrated the oxidative displacement of halogen from alkyl halides by phenyliodine(III) dicarboxylates.[14] This insight allowed us to envision a plausible activation of glycosyl iodides by PIDA to undertake displacement by oxygen nucleophiles leading to a new *O*-glycosidic bond.

To test our hypothesis, we prepared peracylated D-glucosyl iodides **1a,b**[15] and subjected them to the action of various iodine(III) based reagents in the presence of 3.0 equiv. MeOH. For comparison reasons other oxidants were also explored for their ability to activate glucosyl iodides. The obtained results are summarized in Table 1. Surprisingly, already from initial attempts on pivaloyl-protected iodide **1a**, using 1.0 or even 0.5 equiv. PIDA and 2.5 equiv. MeOH in dichloromethane, we observed a clear conversion to the desired methyl glycoside **2aa** with the *beta*-anomer as the exclusive stereoisomer to be isolated (entries 1–2). In the same vein, peracetylated D-glucosyl iodide **1b** delivered the corresponding methyl glucoside **2ba**, though less effectively in terms of yield (86%), but with the same level of stereocontrol (exclusive formation of *beta*-anomer; entry 3). An array of related oxidants (Koser's reagent, PIFA, oxone®, *t*-BuOOH, mCPBA, $NaBO_3$) were also tested on iodides **1a,b** and all found to provide the desired product **2aa**, in variable extend of efficiency (yields 40–69%; entries 4–12), with C1-hydroxy **3a,b** and C1-acetoxy **4a** being the major side-products identified in the reaction mixture.[16] These findings prove the generality of the concept of oxidative activation of "disarmed" glycosyl iodides, with PIDA emerging as the most effective promoter. Comparable results were only achieved with NBS (yield 91%, entry 13), an option that was not adopted due to compatibility issues analogous to NIS. Further optimization studies revealed that dichloromethane was the ideal solvent (entries 14–17), while the relative amount of the glycosyl acceptor could be as low as 1.5 equivalents, without any significant deterioration in reaction's yield (entry 18).

Having established the optimum conditions for the PIDA mediated activation of glycosyl iodides, we proceeded to uncover the scope of glycosyl acceptors that could be accommodated in our protocol, using protected glucosyl iodides **1a,b** as the donor. As a general remark, it is important to highlight that our process proved highly stereoselective with the obtained *O*-glycosides possessing *beta*-configuration at the anomeric center. Primary alcohols reacted smoothly at ambient temperature, providing the respective products in good yields 57–72%.[17] Diols reacted selectively providing monoglucoside **2bd**, while bromides were compatible with our protocol allowing the selective activation of the iodine of the glycosyl donor (products **2ae**). Aromatic compounds showed good reactivity, with no aromatic substitution products observed, even with electron rich substrates, compounds **2ag** and **2be**. Alcohols bearing heteroaromatic ring well-tolerated the reaction conditions affording the respective *O*-glucoside **2ak** in acceptable yield 51%. As expected, secondary alcohols reacted slower and, in some instances less efficiently (product **2ap**), though rendering high levels of stereoselectivity even when chiral alcohols were incorporated (compounds **2al–2an** and **2bf–2bg**). Surprisingly, all unsaturated alcohols tested reacted poorly (yields 26–40%) and, generally, heating was required to provide *O*-glycosylation products **2aq–2as**. Exploring more sterically demanding substrates we observed that some secondary alcohols bearing *alpha*-quaternary centres (*e.g.* (−)-borneol) were reluctant to coupling with glycosyl donors. Same kind of difficulties we encountered when electronically poor benzylic alcohols were incorporated, delivering only trace amounts of the expected *O*-glucosides **2av** and **2aw**, or when sugar derived alcohols were engaged to form disaccharides **2ax** and **2ay** (Table 2).

Next, we wished to probe the glycosyl donor component and explore its effect on the stereoselectivity of the reaction. Ester protected mannosyl iodides **5a,b** and galactosyl iodides **6a,b** were synthesized and subjected to the optimal reaction conditions with certain primary and secondary alcohols. All the reactions proceeded with analogous efficiency compared to

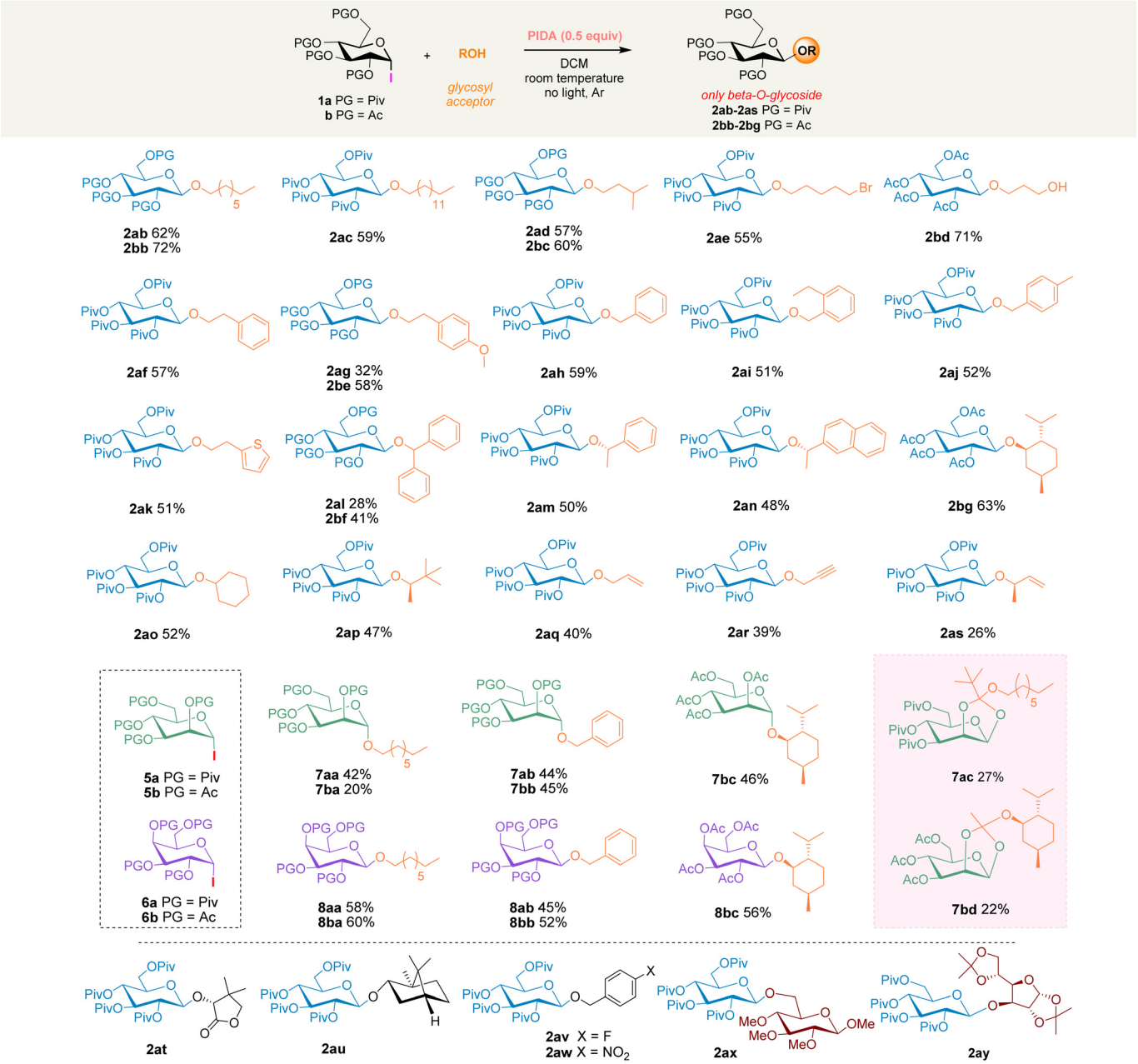
Table 1 Oxidative activation of "disarmed" D-glucosyl iodides in the presence of MeOH[a]



Entry	Iodide	Oxidant	Equiv.	Solvent	Yield[b] [%]
1	**1a**	PIDA	1.0	DCM	98
2	**1a**	PIDA	0.5	DCM	97
3	**1b**	PIDA	0.5	DCM	86 (4 : 7)
4	**1a**	Koser's	0.5	DCM	69 (11)
5	**1a**	PIFA	0.5	DCM	68 (5)
6	**1b**	PIFA	0.5	DCM	61 (9)
7	**1a**	Oxone®	1.0	DCM	66 (13)
8	**1a**	*t*BOOH	2.0	DCM	58 (17)
9[c]	**1a**	*t*BOOH	2.0	DCM	60
10	**1a**	*m*CPBA	1.0	DCM	45
11	**1a**	*m*CPBA	3.0	DCM	40
12	**1a**	$NaBO_3$	3.0	THF/AcOH	—
13	**1a**	NBS	2.0	DCM	91
14	**1a**	PIDA	0.5	THF	45 (18 : 8)
15	**1a**	PIDA	0.5	Benzene	53 (15 : 6)
16	**1a**	PIDA	0.5	$CHCl_3$	74 (5 : 9)
17	**1a**	PIDA	0.5	MeCN	66 (11 : 9)
18[d]	**1a**	**PIDA**	**0.5**	**DCM**	**96**

[a] To a solution of 0.1 mmol of iodide **1a,b** and 0.25 mmol MeOH in 1.0 mL of solvent was added the oxidant under Argon and light protection. The reaction was stirred at ambient temperature and quenched upon full consumption of starting material. [b] Yields refer to isolated products **2a,b**, while yields in parentheses refer to side-products **3a,b** and **4a**. [c] 5 mol% CuI was added. [d] 1.5 equiv. MeOH were used; DCM = dichloromethane, THF = tetrahydrofuran.

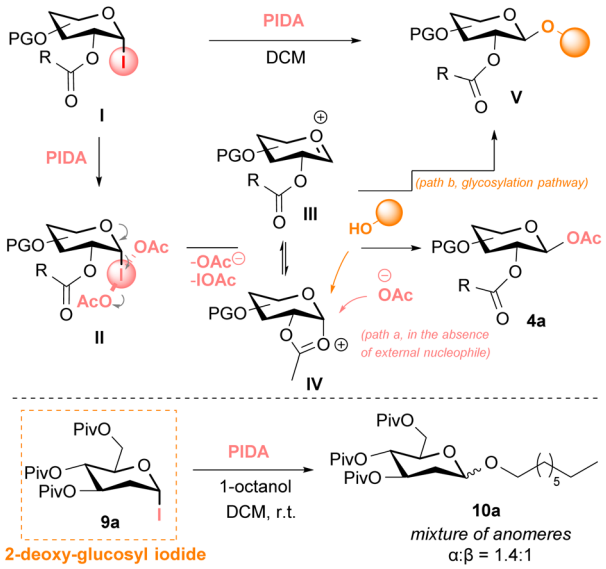
Table 2 Exploring the scope and limitations of glycosyl donors and acceptors in PIDA mediated *O*-glycosylation of glycosyl iodides[a]



[a] Typically, the reactions were performed on 50 mg scale. Yields refer to isolated products.

glucosyl iodides **1a**,**b**, leading to pyranosides **7aa**–**7ab**, **7ba**–**7bc** and **8aa**–**8ab**, **8ba**–**8bc** with exclusive 1,2-*trans* stereoselectivity, a result indicating strong C2 protecting group participation in the reaction mechanism. Further support on this hypothesis was achieved by the isolation of the respective mannose-derived *ortho* esters **7ac** and **7bd** along with the desired mannopyranosides **7aa** and **7bc**.

In order to gain deeper insight in the reaction mechanism we conducted some control experiments, summarized in Scheme 1. When the reaction was carried out in the absence of any nucleophile, the corresponding *beta*-acetate **4a** was afforded as the major product (Scheme 1, path a), an outcome supporting the possible formation of a transient pyranosyl iodine(III) diacetate (**II**) that dissociates providing reactive acetate species and recombines stereoselectively with the sugar moiety. To explain the use of substoichiometric amount of PIDA we believe that electrophilic IOAc, produced during the reaction, can equally well activate glycosyl iodide, in an analogous fashion, thus converting the latter to the same oxonium intermediate (**IV**) of Scheme 1.[14] Neighboring C2 acyl group



Scheme 1 Control experiments and plausible reaction mechanism.

participation was strongly evidenced by the exclusive formation of the *alpha*-pyranoside when mannosyl iodides were used as glycosyl donors (see Table 2). In addition, PIDA promoted oxidative glycosylation of the C2-deoxy glucosyl iodide **9a**[18] led to a mixture of anomeric pyranosides when reacted with 1-octanol ($\alpha:\beta$ = 1.4 : 1). Finally, addition of TEMPO to the reaction mixture ceased the glycosylation pathway (path b), allowing only the slow oxidation of 1-octanol to the respective aldehyde, an observation consistent with radicals' involvement at some point of the reaction mechanism, presumably during the formation of glucosyl iodine(III) diacetate by its activation with PIDA.

In conclusion, we have developed a novel protocol for the oxidative activation of "disarmed glycosyl iodides" in *O*-glycosylation reactions with primary and secondary alcohols. Competitive advantages of our methodology comprise the absolute stereocontrol of the reaction, favoring 1,2-*trans* glycosides and the extremely mild conditions (mild oxidant, ambient temperature, broad functional group compatibility). These features render PIDA promoted oxidative glycosylation an appealing alternative to existing methodologies, especially in complex organic settings, where strongly acidic or basic conditions are often not tolerable.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to acknowledge the Hellenic Scholarships Foundation for the financial support of M. A. Boulogeorgou. "The implementation of the doctoral thesis was co-financed by Greece and the European Union (European Social Fund-ESF) through the Operational Program "Human Resources Development, Education and Lifelong Learning" in the context of the Act "Enhancing Human Resources Research Potential by undertaking a Doctoral Research" Sub-action 2: IKY Scholarship Program for PhD candidates in the Greek Universities".

References

1 (*a*) A. Varki, *et al.*, *Essentials of Glycobiology*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2009; (*b*) H. J. Gabius, *The Sugar Code: Fundamentals of Glycosciences*, Wiley-Blackwell, Weinheim, Germany, 2009; (*c*) P. M. Rudd, T. Elliott, P. Cresswell, I. A. Wilson and R. A. Dwek, *Science*, 2001, **291**, 2370; D. P. Galonić and D. Y. Gin, *Nature*, 2007, **446**, 1000.

2 (*a*) E. Jaszczak-Wilke, Z. Polkowska, M. Koprowski, K. Owsianik, A. E. Mitchell and P. Bałczewski, *Molecules*, 2021, **26**, 2253; (*b*) X. Zhang, K. Liu, M. Shi, L. Xie, M. Deng, H. Chen and X. Li, *Brain Res. Bull.*, 2021, **174**, 281; (*c*) X. Li, J. Zheng, S. Chen, F. Meng, J. Ning and S. Sun, *Cell Death Dis.*, 2021, **12**, 314.

3 (*a*) K. C. Nicolaou and H. J. Mitchell, *Angew. Chem., Int. Ed.*, 2001, **40**, 1576; (*b*) X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 1900; (*c*) T. G. Frihed, M. Bols and C. M. Pedersen, *Chem. Rev.*, 2015, **115**, 4963; (*d*) J. Issa and C. Bennett, *J. Am. Chem. Soc.*, 2014, **136**, 5740; (*e*) M. Krumb, T. Lucas and T. Opatz, *Eur. J. Org. Chem.*, 2019, 4517; (*f*) Y. Yang, X. Zhang and B. Yu, *Nat. Prod. Rep.*, 2015, **32**, 1331.

4 (*a*) Y. Singh and A. Demchenko, *Chem. – Eur. J.*, 2019, **25**, 1; (*b*) P. Peng and R. Schmidt, *J. Am. Chem. Soc.*, 2015, **137**, 12653; (*c*) Y. Li, H. Mo, G. Lian and B. Yu, *Carbohydr. Res.*, 2012, **363**, 14; (*d*) B. Meng, Z. Zhu and D. C. Baker, *Org. Biomol. Chem.*, 2014, **12**, 5182; (*e*) J. Auge and G. Sizun, *Green Chem.*, 2009, **11**, 1179.

5 (*a*) S. An, Q. Wang, W. Zhu, Q. Sun, G. He and G. Chen, *CCS Chem.*, 2020, **2**, 1821; (*b*) M. M. Nielsen and C. M. Pedersen, *Chem. Rev.*, 2018, **118**, 8285; (*c*) M. McKay and H. Nguyen, *ACS Catal.*, 2012, **2**, 1563; (*d*) Y. Li, P. Tang, Y. Chen and B. Yu, *J. Org. Chem.*, 2008, **73**, 4323.

6 T. Yang, F. Zhu and M. A. Walczak, *Nat. Commun.*, 2018, **9**, 3650. For an alternative protocol using thioglycosides as glycosyl donors see T. Kajimoto, K. Morimoto, R. Ogawa, T. Dohi and Y. Kita, *Chem. Pharm. Bull.*, 2016, **64**, 838.

7 An estimation of cost based on Sigma Aldrich catalogue: D-Glucose/D-Glucal ratio per gram of product is approximately 15 : 1.

8 V. V. Triantakonstanti, A. Toskas, N. S. Iordanidis, T. Andreou, T. V. Koftis and J. K. Gallos, *Tetrahedron Lett.*, 2020, **61**, 152173.

9 P. J. Meloncelli, A. D. Martin and T. L. Lowary, *Carbohydr. Res.*, 2009, **344**, 1110.

10 J. Gervay-Hague, *Acc. Chem. Res.*, 2016, **49**, 35.

11 (*a*) J. Gervay and M. J. Hadd, *J. Org. Chem.*, 1997, **62**, 6961; (*b*) M. Adinolfi, A. Iadonisi, A. Pezzella and A. Ravidà, *Synlett*, 2005, 1848.
12 (*a*) A. Pastore, M. Adinolfi and A. Iadonisi, *Eur. J. Org. Chem.*, 2008, 6206; (*b*) S. Weng, C. L. Li, C. S. Liao, T. A. Chen, C. Huang and K. T. Hung, *J. Carbohydr. Chem.*, 2010, **29**, 429.
13 S. C. Virgil, Y. Zeng, F. Kong, J. A. Pigza, S. Roy and S. Mukherjee, *e-EROS*, John Wiley and sons, 2018. DOI: **10.1002/047084289X.ri038.pub4**.
14 J. Gallos and A. Varvoglis, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1999.
15 For full preparation procedures see ESI.†
16 C1-acetoxy pyranoside **4a** was obtained only when PIDA was used as the promoter.
17 C1-hydroxy and C1-acetoxy products account for the rest of the yield, given that full consumption of starting material was observed.
18 Iodide **9a** was not stable enough to be isolated and reacted in situ with 1-octanol in the presence of PIDA. This observation supports the importance of ester protection in the stabilization of glycosyl iodides.