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Perfluorophenylboronic acid-catalyzed direct α-stereoselective synthesis of 2-deoxygalactosides from deactivated peracetylated D-galactal†

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Perfluorophenylboronic acid 1c catalyzes the direct stereoselective addition of alcohol nucleophiles to deactivated peracetylated D-galactal to give 2-deoxygalactosides in 55–88% yield with complete α-selectivity. The unprecedented results reported here also enable the synthesis of disaccharides containing the 2-deoxygalactose moiety directly from the deactivated peracetylated D-galactal. This convenient and metal-free glycosylation method works well with a wide range of alcohol nucleophiles as acceptors and tolerates a range of functional groups without the formation of the Ferrier byproduct and without the need for a large excess of nucleophiles or additives. The method is potentially useful for the synthesis of a variety of α-2-deoxygalactosides.

Deoxyglycosides are widely present in natural products and are biologically active components in drugs including anticancer drugs and antibiotics such as orthosamycins, anthracyclines, angucyclins and aureolic acids.[1] Therefore, practical routes for their synthesis are important. Direct catalytic and stereoselective addition of alcohol nucleophiles to 1,2-glycals is the most attractive method for the synthesis of 2-deoxyglycosides due to its simplicity and practicality.[2] However, achieving complete stereocontrol is challenging due to the absence of stereo-directing groups at the C-2 of 1,2-glycals that guide the attacking nucleophiles. Additionally, the type of substituents on the 1,2-glycals and the type of alcohol nucleophiles (*via* stereoelectronic effects) play an important role in the success of this reaction.[2d,g,j,3] For example, 1,2-glycals substituted with alkyl, benzyl, allyl, silyl groups *etc.* successfully react with alcohol nucleophiles in the presence of many catalysts including (Lewis) acids, organocatalysts and metal/ligand-based catalysts to give good to excellent yields and selectivities.[2d,g,j,3] However, catalyzed direct addition of alcohols to deactivated peracetylated D-glycals are rarely explored, and success has been reported with Ph_3P-HBr[4] and $CeCl_3{\cdot}H_2O$-NaI[5] using only simple alcohol nucleophiles. Additionally, peracetylated D-galactals remain formidable substrates and are unreactive towards the addition of alcohols despite testing a range of catalysts such as glucose–Fe_3O_4–SO_3H solid acid,[3d] Ph_3P-HBr,[4] Au(I)/AgOTf,[3a] $ReOCl_3(SMe_2)(Ph_3PO)$,[2f] Pd-based catalysts,[3b,e,f] thiourea,[2k] and acid/thiourea organocatalyst.[3d] To our knowledge, the only successfully reported example is the $CeCl_3{\cdot}H_2O$-NaI-catalyzed addition of octanol to peracetylated D-galactal, which gave 85% yield with α-selectivity after 8.5 hours.[5] The lack of reactivity of the peracetylated D-galactals (and peracetylated D-glycals in general) is attributed to the deactivation of the alkene bond through the disarming effect of the acetate moieties, especially the acetate at the C-3.[2k,6] Peracetylated D-galactals (and peracetylated 1,2-glycals in general) are common substrates in carbohydrate chemistry and are easily prepared in comparison to other substituted D-galactal/1,2-glycals.[7] In fact, they serve as substrates for the preparation of the more reactive peralkylated, perbenzylated, persilylated D-galactal/1,2-glycals.[2f] Therefore, a highly stereoselective catalytic process that directly adds alcohol nucleophiles to deactivated peracetylated D-galactal is extremely desired. Additionally, the preparation of disaccharides containing the 2-deoxygalactose moiety is of great interest and has not been realized through catalyzed direct addition of sugar alcohols to peracetylated D-galactal.

Organoboron reagents have been used to catalyze many reactions including Friedel–Crafts alkylations,[8] aldol reactions,[9] epoxide opening,[10] glycosylation reactions[11] and many others.[12] Recently, Galan reported excellent results in the addition of alcohols to 1,2-glycals using a tris(pentafluorophenyl)borane catalyst, although addition to peracetylated D-galactals was not investigated.[2f] Taylor also used $PhB(OH)_2$ and other boronic acids mainly as transient protecting/activating groups through cyclic ester formation.[11c–f] Our group has used arylphenylboronic acids as catalysts in the direct addition of *C*-, *O*-, *N*- and *S*-nucleophiles to 1,2-glycals to prepare 2,3-unsaturated

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glycosides *via* Ferrier rearrangement.[14] Despite the robustness and mildness of organoboronic acid catalysts in comparison to traditional strong Lewis and Brønsted acid catalysts, to our knowledge, their use as promoters for the synthesis of 2-deoxyglycosides has not be disclosed yet.

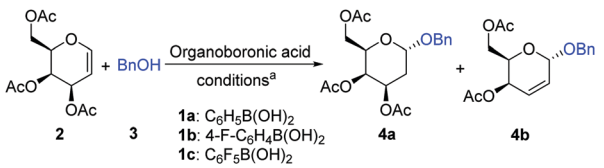
Given our interest in glycosylation,[13,14] we specifically pursued this work on targeting the glycosylation of the deactivated peracetylated D-galactal (3,4,6-tri-*O*-acetyl-D-galactal) which has been thus far very elusive. Herein, we report unprecedented perfluorophenylboronic acid-catalyzed α-stereoselective direct addition of alcohols to deactivated peracetylated D-galactal to prepare 2-deoxygalactosides as well as disaccharides containing the 2-deoxygalactose moiety.

Our study started by screening phenylboronic acid **1a**, *p*-fluorophenylboronic acid **1b** and pentafluorophenylboronic acid **1c**[15] for their ability to promote the stereoselective glycosylation of deactivated peracetylated D-galactal **2** with benzyl alcohol (**3**) (Table 1). The reaction was unsuccessful in CH_2Cl_2 and THF (Table 1, entries 1 and 2). However, pentafluorophenylboronic acid **1c** gave 15% and 30% yield of the desired 2-deoxygalactosides **4a** in toluene and CH_3CN, respectively (entries 3 and 4). Satisfyingly, switching to CH_3NO_2 gave the 2-deoxygalactoside **4a** in 88% yield with complete α-selectivity after just 6 h (Table 1, entry 5). Keeping the same conditions but lowering the catalyst loading to 10 mol% resulted in a lower yield of **4a** (40%, entry 6). No sign of the β-isomer was detected in the crude reaction product. Both phenylboronic acid **1a** and *p*-fluorophenylboronic acid **1b** did not promote the reaction in CH_3NO_2 possibly due to their lower acidities (Table 1, entries 7 and 8). Unlike several other glycosylation catalysts which need excess amounts of alcohols or additives to give reasonable yields, excess of benzyl alcohol **3** and additives are not necessary with **1c**.[4,5]

Under the above conditions, Ferrier product **4b** did not form at 60 °C and 2-deoxygalactoside **4a** was the sole product. In our previous work, pentafluorophenylboronic acid **1c** catalyzed the addition of various *C*-, *O*-, *N*- and *S*-nucleophiles to peracetylated D-glucals and peracetylated L-rhamnals and gave only the 2,3-unsaturated glycosides (Ferrier products) at both 40 °C and 60 °C.[14] This means that the formation of either 2-deoxygalactosides or 2,3-unsaturated glycosides depends on the stereochemistry of the starting glycal and not on the temperature of the reaction. In the case of tris(pentafluorophenyl)borane as the catalyst, disarmed glycals gave the Ferrier product at 75 °C while the armed glycals gave 2-deoxygalactosides at 50 °C.[2f] However, camphorsulfonic acid gave either 2-deoxygalactosides or the Ferrier product during the addition of alcohols to silylated rhamnals depending on the acidity and temperature of the reaction.[2l] These results prove that the reaction outcome can be controlled using the catalyst, donor and reaction conditions.

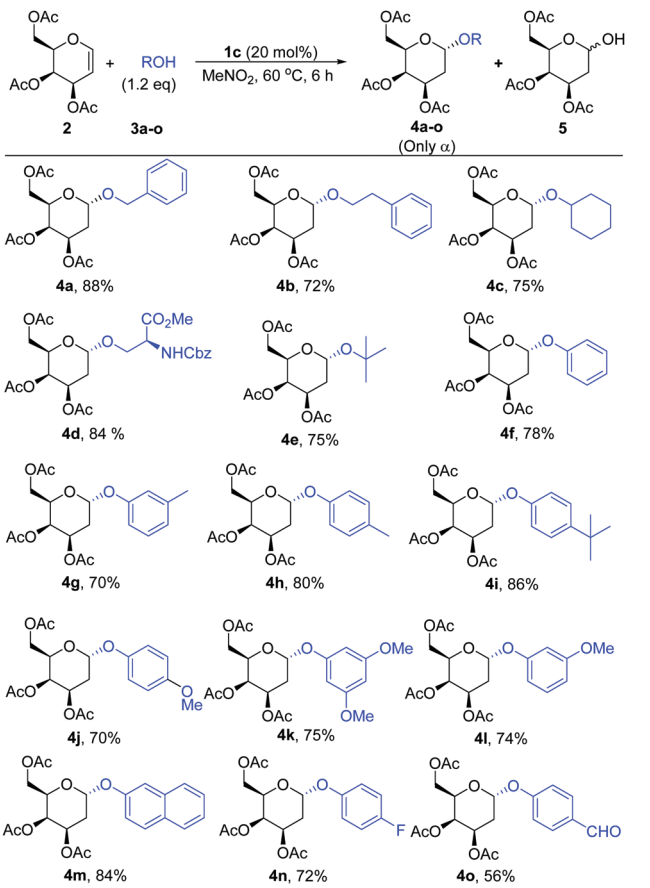
With the optimal reaction conditions in hand (Table 1, entry 5), we then examined the scope of the pentafluorophenylboronic acid **1c**-catalyzed glycosylation of peracetylated D-galactal **2** with various glycosyl acceptors **3a–o** (Scheme 1). In all the cases, the glycosylation reactions proceeded smoothly to give the 2-deoxygalactosides **4a–o** in 56–88% yield with complete α-selectivity within 6 h. The glycosylation using primary, secondary and tertiary alcohols **3a–e** as well as phenols **3f–o** with electron donating and withdrawing groups proceeded successfully to give similar yields and

Table 1 Optimization of the reaction conditions in the glycosylation of peracetylated D-galactal **2** with benzyl alcohol **3** in the presence of organoboronic acids **1a–c**



Entry	Organoboronic acid (mol%)	Solvent	Temp. (°C)	Time (h)	**4a** Yield[b] (%)
1	**1a**/**1b**/**1c** (20)	CH_2Cl_2	Reflux	24	—
2	**1a**/**1b**/**1c** (20)	THF	Reflux	12	—
3	**1c** (20)	Toluene	80	12	15
4	**1c** (20)	CH_3CN	60	12	30
5	**1c (20)**	**CH_3NO_2**	**60**	**6**	**88**
6	**1c** (10)	CH_3NO_2	60	6	40
7	**1a** (20)	CH_3NO_2	60	6	—
8	**1b** (20)	CH_3NO_2	60	6	—

[a] 1 eq. of peracetylated D-galactal **2** reacted with 1.2 eq. of benzyl alcohol **3**. [b] Yield was measured after column chromatography purification.



Scheme 1 Perfluorophenylboronic acid **1c**-catalyzed addition of alcohols **3a–o** to peracetylated D-galactal **2**.

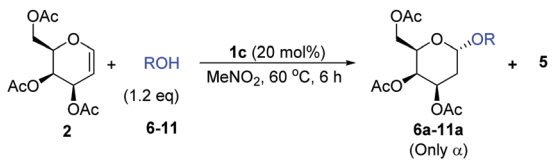
α-selectivities irrespective of the steric and electronic effects of these acceptors (Scheme 1). However, the 4-formyl substituent resulted in a lower yield of **4o** (Scheme 1) while 4-nitrophenol failed to react under the optimised conditions due to the very strong electron withdrawing effect of the nitro group. It is noteworthy that phenols **4f–o** reacted smoothly with peracetylated D-galactal **2** without any rearrangement to *C*-glycosides. Such rearrangements occurred using very strong acid catalysts.[16] Carbamate alcohol also smoothly gave the product **4d** in 84% yield with α-selectivity. Mixtures of the (α/β) hemiacetal by-product **5** (~5–10%) were observed in the ^{1}H NMR spectra of the crude products which were attributed to the reaction of the starting peracetylated D-galactal **2** with water, a common problem encountered in these reactions.[17]

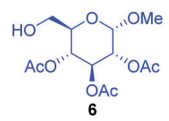
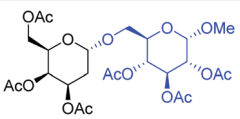
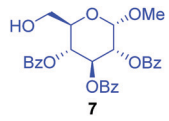
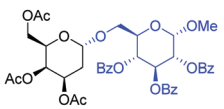
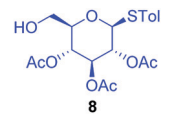
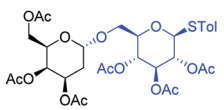
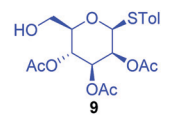
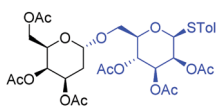
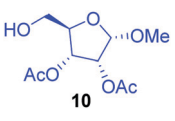
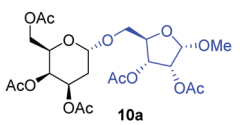
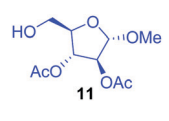
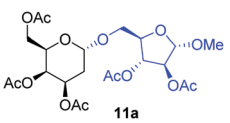
We then challenged the perfluorophenylboronic acid **1c** in the glycosylation reactions between peracetylated D-galactal **2** and sugar alcohol acceptors including glucoses (**6** and **7**), mannoses (**8** and **9**), ribose **10** and arabinose **11** alcohols, under the optimized conditions (Table 1, entry 5). In all cases, the reaction successfully gave the expected disaccharides **6a–11a** in 55–65% yield with α-selectivity (Table 2). The reaction conditions tolerated ether, ester and thioether functional groups. Hemiacetal **5** (α/β mixture up to 30%) also appeared as the by-product in these reactions, which explains the reduction in the isolated yields. The R_f values of the disaccharides **6a–11a** and hemiacetal **5** were very close, which prevented smooth purification. Therefore, the crude reaction products were acetylated, which allowed for smoother separation of the disaccharides **6a–11a** from the acetylated hemiacetal **5**. Small amounts of impurities remained despite attempts to remove them completely.

Next, we investigated the mechanism of the reaction. Addition of an equimolar amount of Et_3N to the reaction mixture completely shut down the glycosylation reaction leading to recovery of the starting materials and indicating that the transformation is acid-catalyzed. ^{1}H NMR studies of the reaction mixture in CD_3NO_2 did not show any significant chemical shift changes in the olefinic protons of the –HC═CH– of D-galactal **2**. These results rule out any coordination between perfluorophenylboronic acid **1c** and the –HC═CH–, at least during the early stages of the reaction. When the glycosylation reaction was performed using CD_3OD as the nucleophile, 2-deoxygalactosides **12** was obtained in 85% yield (Fig. 1 and see ESI†). Our findings suggest that perfluorophenylboronic acid **1c** acts as an indirect acid source. In general, the acidity of boronic acids (pK_a 4–10.4)[18] is related to their ability to ionize water and generate hydronium ions *via* indirect proton transfer according to the ionization equilibrium shown in eqn (1.1) (Fig. 1).[18] Because of the similarity of the pK_a values of water (15.7) and the alcohol nucleophiles employed in this study (17–19), we infer similar behaviour of ionization of acid **1c** in which it ionizes the alcohol according to eqn (1.2) to form alkyloxonium ions which function as the H^+ source. The more acidic phenols may as well undergo similar ionization. A second pathway involving the formation of hydronium ions due to the presence of adventitious water may operate in parallel, leading to the same alkyloxonium ion intermediate (Fig. 1).

A plausible reaction mechanism is proposed in Fig. 1. Acid induced polarization of the double bond of D-galactal **2** activates it towards nucleophilic addition. Thus, the reaction between $DOCD_3$ (or the alcohol nucleophile) and **1c** according to eqn (1.2) yields a

Table 2 Perfluorophenylboronic acid **1c**-catalyzed glycosylation of peracetylated D-galactal **2** with various sugar acceptors



Entry	R-OH (**6–11**)	Disaccharides (**6a–11a**)	Yield (%)
1	 **6**	 **6a**	58
2	 **7**	 **7a**	55
3	 **8**	 **8a**	62
4	 **9**	 **9a**	64
5	 **10**	 **10a**	60
6	 **11**	 **11a**	65

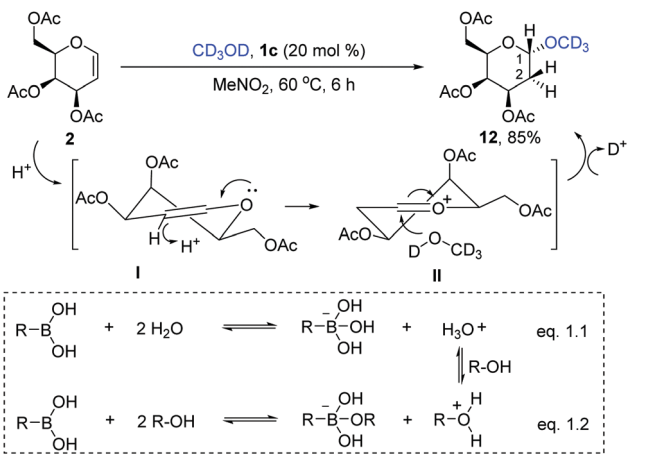


Fig. 1 Plausible mechanism of glycosylation of D-galactal **2**.

highly acidic alkyloxonium ion which protonates the enol ether functionality of the $^4H_5$ conformation (**I**) primarily *via* cleavage of the O–H bond, which may be rationalized by the kinetic isotopic effect. Indeed, we observed minute formation of C-2 deuterated **12** as indicated by high resolution mass spectroscopy. Once formed, the oxygen nucleophile attacks the oxocarbenium ion **II** ($^4H_3$) in a diastereoselective fashion from the least congested face to yield the α-2-deoxygalactoside **12** products exclusively. Interestingly, heating a mixture of methanol and catalyst **1c** overnight did not affect the outcome of the reaction or yield following the addition of galactal **2** the next day, indicating that **1c** retains its catalytic properties and does not lose its acidic character.

We developed a mild and metal-free direct stereoselective glycosylation method for deactivated peracetylated D-galactal using commercially available perfluorophenylboronic acid **1c** catalyst. The glycosylation method gave 2-deoxygalactosides in good to excellent yields with complete α-selectivity and tolerated a wide substrate scope and a range of functional groups. The unprecedented results enabled glycosylation of the challenging peracetylated galactal. Application of this chemistry to the synthesis of other 2-deoxyglycosides is currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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