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β-Glycosyl Trifluoroborates as Precursors for Direct α-C-Glycosylation: Synthesis of 2-Deoxy-α-C-glycosides

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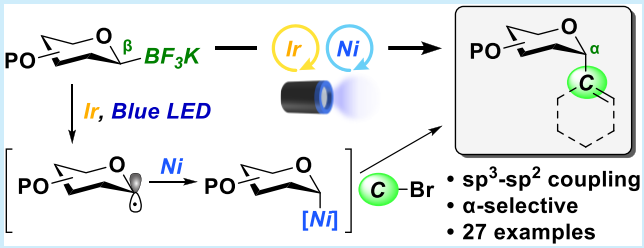
ABSTRACT: *C*-Glycosides are metabolically stable mimics of natural *O*-glycosides and are expected to be useful tools for investigation of the biological functions of glycans. Here, we describe the synthesis of a series of aryl and vinyl *C*-glycosides by stereoinvertive sp^3–sp^2 cross-coupling reactions of 2-deoxyglycosyl boronic acid derivatives with aryl or vinyl halide, mediated by a photoredox/nickel dual catalytic system. Hydrogenation of the vinyl *C*-glycosides afforded C-linked 2′-deoxydisaccharide analogues.



Metabolically stable analogues of carbohydrates or glycoconjugates are important molecular tools for functional analysis in chemical biology. In particular, *C*-glycosides exhibit high structural similarity to native glycans.[1,2] For example, we recently demonstrated that *C*-glycoside analogues of ganglioside GM3, especially molecules with a *CHF*-glycoside linkage, exhibit greater biological activity at the cell level than analogues with a CH_2- or a CF_2-linkage. Furthermore, their conformation is similar to that of native GM3.[3] However, despite many reports of synthetic methodology for *C*-glycosides, there are few efficient strategies for directly forming a *C*-glycosidic linkage (direct C-glycosylation) via intermolecular coupling reaction, like a standard O-glycosylation reaction.

Among carbohydrate-containing natural products or native glycans, metabolites containing 2-deoxy sugars are also of interest to both chemists and biologists, as they can have unique biological activities.[4] The corresponding 2-deoxy-*C*-glycosides should therefore be useful chemical tools, but there are few reports of their synthesis via intermolecular coupling reaction.[4] A representative reaction is Pd-catalyzed sp^2–sp^2 cross-coupling from C1-sp^2 stannanes **1**,[5,6] which was shown to be applicable to the synthesis of disaccharide analogues (Figure 1A). The stereochemistry at the anomeric position is determined at the stage of hydrogenation of **2**, usually affording β-2-deoxyglucosides **3** as the major products. As a complementary but powerful strategy, direct C-glycosylation was reported with via Pd-catalyzed sp^3–sp^2 cross-coupling from chemically stable C1-sp^3 glycosyl stannanes **4** (Figure 1A).[7] This methodology is characterized as a stereoretentive cross-coupling reaction. Namely, α- and β-isomers (**5α** and **5β**) could be selectively obtained from α- and β-glycosyl stannanes (**4α** and **4β**), respectively. This strategy has also been applied to the synthesis of *C*-acyl disaccharides.[8]

Despite the advantages of the Stille-type coupling reaction in terms of reliability and stability of the starting materials, organostannanes are toxic, and an environmentally friendly coupling reaction is preferable. Therefore, the Suzuki–Miyaura coupling reaction was employed to construct C-arylated (or vinylated) glucal derivatives **2** from C1-sp^2 pinacol boronate **6** (Figure 1B).[9−12] This provides access to 2-deoxy-β-*C*-glucosides.[13] As for C1-sp^3 glycosyl boronates, surprisingly, simple C-1 borylated monosaccharides have not been reported, except for C-1 alkylated and B-substituted monosaccharides prepared by the B–C bond insertion reaction of a glycosyl diazirine.[14,15] We envisioned that potassium β-glycosyltrifluoroborates such as **7**, which are obtainable by hydrogenation of sp^2-boronate such as **6** (Figure 1C), would undergo a Ni-catalyzed metallaphotoredox coupling reaction with aryl or vinyl halides.[16−18] Single-electron oxidation of **7** would generate glycosyl radical **8**,[2] which is expected to adopt a standard chair conformation with α-radical orientation stabilized by the inner cyclic oxygen atom.[19−21] Then, stereoinvertive coupling should proceed to give **5α** selectively (Figure S1).[22,23] This approach would be complementary to the method via compound **2** and might be useful to synthesize analogues of native 2-deoxy glycosides (usually β-*O*-glycosides). Here we report the synthesis and direct α-C-glycosylation of **7**.

C1-sp^3 2-Deoxyglucosyltrifluoroborate **12** was prepared as follows (Scheme 1). A slight modification of the Ir-catalyzed

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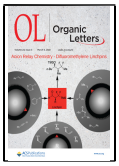

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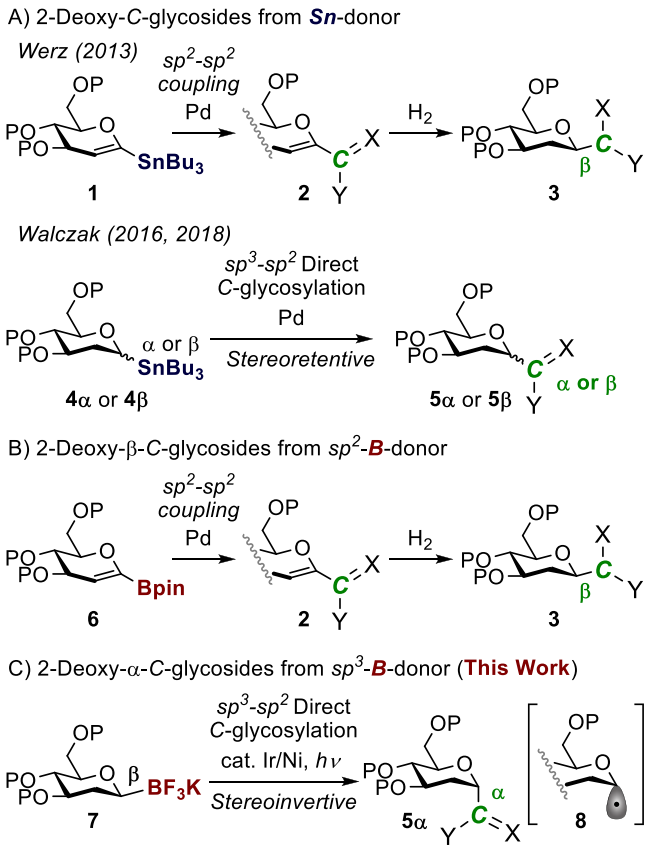
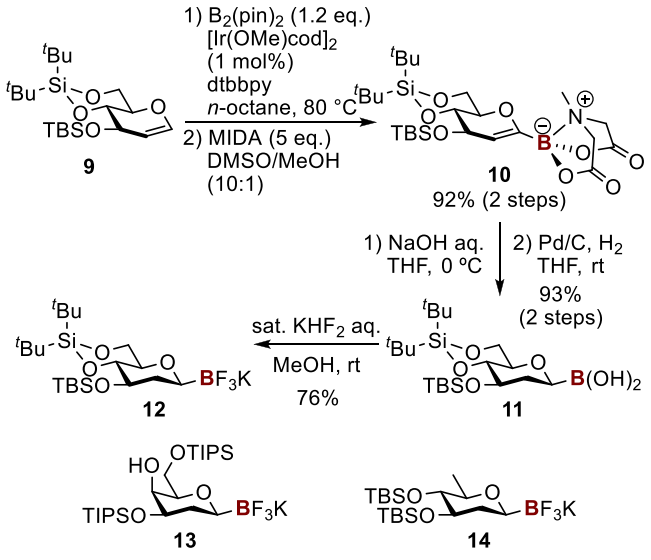


Figure 1. (A) Representative methods for synthesis of 2-deoxy-*C*-glycosides from organostannanes **1** and **4**; (B) synthesis from boronate **6**; and (C) our strategy for synthesis of 2-deoxy-*α*-*C*-glycosides ***5α*** from *β*-glycosyltrifluoroborate **7**.

Scheme 1. Synthesis of Potassium 2-Deoxy-*β*-glycosyltrifluoroborate 12−14



C1-selective C−H borylation of glucal derivative **9** reported by Miyaura and co-workers gave the corresponding pinacolatoborate (Bpin adduct) in good yield,[24] and this was converted to *N*-methyliminodiacetic acid (MIDA) ester[25] **10** for purification by silica gel chromatography. Addition of methanol was effective for this transformation (Table S1 and Figure S2). Hydrogenation of **10** proceeded after hydrolysis of MIDA ester to give C1-sp^3 boronic acid **11** as a single isomer in good yield. It should be noted that hydrogenation of the Bpin adduct was successful under Rh/Al_2O_3 catalysis, affording the corresponding C1-sp^3 Bpin compound, though purification by silica gel chromatography caused some loss of the product. Treatment of **11** with KHF_2 solution afforded potassium glucosyltrifluoroborate **12**. 2-Deoxy-D-galactosyltrifluoroborate **13** and 2,6-dideoxy-D-arabinosyltrifluoroborate (D-olivose-type) **14** were similarly synthesized (Scheme S1), except that temporary protection with MIDA during the synthesis of **13** was not conducted because transformation to MIDA ester from the corresponding Bpin adduct was less efficient (Table S2).

With the glycosyltrifluoroborates in hand, we examined the metallophotoredox coupling reaction with aromatic halides (Figure 2). Employing the literature conditions[16] with slight modifications especially in regards to the solvent (see Tables S3−S6 for details of the optimization of reaction conditions), reaction with aryl bromides proceeded to give **16** in a highly *α*-selective manner. The use of aryl bromides with an electron-withdrawing substituent (CF_3, CO_2Me, CN, and COMe) at the *para*-position provided the products **16a−16d** in good yields. We confirmed that the coupling reaction of **12** and **15a** at the 1 mmol scale was also successful. The aryl bromide showed better reactivity than the corresponding aryl chloride or aryl iodide (Table S7). Fluorine, methyl, and methoxy groups were tolerated (**16e−16g**). The use of *ortho*- or *meta*-substituted aryl bromides afforded ***o*-16b**, ***o*-16g**, and ***m*-16g** in reasonable yields, though ***m*-16b** was obtained in only 24% yield. Although a free amino group disturbed the formation of the coupling product, acetamide derivative **16h** was obtained in an acceptable yield. Coupling with heteroaromatic halides, such as 2-bromofuran or 3-bromothiophene, also proceeded to afford **16i** and **16j** in 33% and 64% yields. Unprotected 5-indole derivative **16k** was formed, though in only 18% yield, but the reaction with Boc-protected 5-bromoindole resulted in formation of **16l** in better yield (53%). Reaction with Ms-protected 2-bromoindole also occurred to give **16m** in 37% yield. This result prompted us to investigate the coupling with tryptophan derivative **15n**, which afforded *α*-2-deoxy-*C*-mannosyltryptophan[26−30] **16n** in a highly stereoselective manner.

For other donors **13** and **14**, the coupling reaction with representative aryl bromides (*p*-trifluoromethyl bromobenzene, methyl *p*-bromobenzoate, and *p*-bromoanisole) gave *α*-*C*-aryl *α*-glycosides **17** and **18** in good yield. D-Olivose-type *C*-glycosides **18a**, ***p*-18b**, and ***p*-18g** exhibited flipped conformation from standard $^4C_1$ conformation to $^1C_4$ conformation with an *α*-aryl group. Considering the glycosyl radical reactivity, ring-flipping presumably occurs after the coupling reaction, probably due to steric repulsion between the C1-aryl group and C3 and C5 hydrogen atoms.

Next, we examined the coupling with vinyl halides **19** (Scheme 2A). The reaction with the simple (*E*)-vinyl bromide bearing an alkyl chain gave the aliphatic *C*-glycosides **20a** in a moderate yield with high *α*-selectivity, indicating that the 2-deoxyglycosyltrifluoroborate **12** could be applicable for the synthesis of disaccharide derivatives. In fact, coupling with (*E*)-vinyl bromide **19b** prepared from D-glucose derivative proceeded similarly to give the disaccharide derivative **20b** (41% yield). Hydrogenation of **20a** and **20b** successfully provided the aliphatic 2-deoxyglucoside analogue **21** and CH_2-

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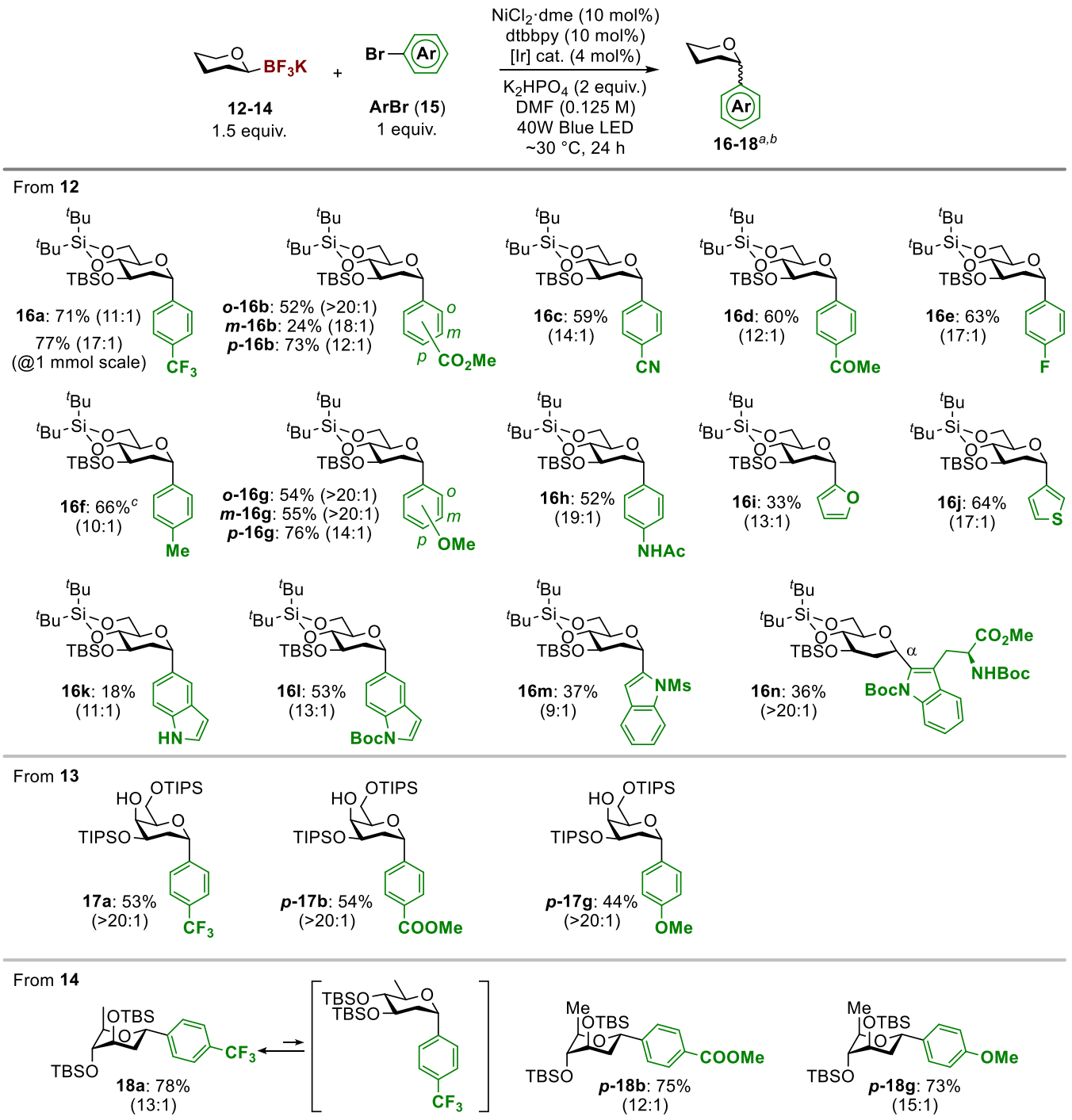

Figure 2. Metallophotoredox coupling of potassium β-glycosyltrifluoroborate **12**−**14** with aryl bromides **15**. (*a*) Isolated yields of the alpha isomer. (*b*) Ratios of α and β isomers of the crude materials are shown in parentheses. (*c*) Reaction time is 12 h.

linked 2-deoxyGlc-α(1,6)-Glc analogue **22** in good yield (Scheme 2B). Furthermore, application of 2-deoxyglycosyltrifluoroborate **12** to the synthesis of *CHF*-linked disaccharide analogue was also successful. Namely, coupling of **12** with glucose derivatives having (*E*)-bromofluoro olefin also occurred α-selectively to afford the corresponding coupling product **20c** in better yield. Both isomers of the *CHF*-linked 2-deoxyGlc-α(1,6)-Glc analogue **23** were obtained by hydrogenation of **20c**. To our knowledge, this is the first example of the synthesis of a *CHF*-linked disaccharide derivative[31−34] by direct *C*-glycosylation reaction.

In summary, we first synthesized 2-deoxy-β-glycosyl boronic acids and their trifluoroborate derivatives **12**−**14** and then conducted stereoinvertive cross-coupling reactions with various aryl bromides and vinyl halides to obtain the α-*C*-glycosides selectively. This strategy provides efficient access to α-C-linked glycans and glycoconjugates, which are expected to be useful for functional analysis. Application of this strategy to glycosyl boronic acid derivatives possessing a 2-hydroxyl group is underway.

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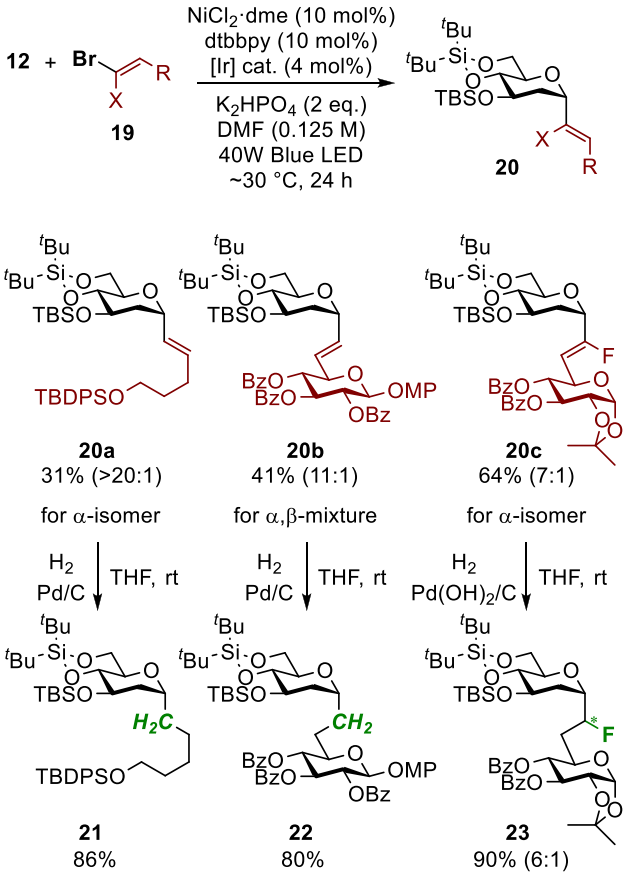
Org. Lett. 2021, 23, 1940−1944

Scheme 2. Metallophotoredox Coupling of Potassium 2-Deoxy-β-glycosyltrifluoroborate 12 with Vinyl Bromides 19 and Synthesis of CH_2- and CHF-Linked 2-Deoxyglucosides



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00402.

Supplementary figures, detailed experimental procedures, ^{1}H- and ^{13}C NMR and HRMS data for new compounds (PDF)

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Author Contributions

D.T., M.Y., H.Y., S.C., T.M., A.Y., and K.U. performed the synthetic studies. G.H. supervised the research.

Notes

The authors declare no competing financial interest.

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