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View Article Online
DOI: 10.1039/D6CC01768A

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Rhodium-catalysed β-selective 1,4-addition of arylboron compounds to glycals enabled by chiral diene ligands

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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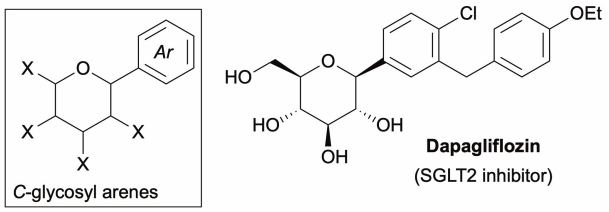
The rhodium-catalysed β-selective 1,4-addition of arylboron compounds to enones derived from glucal derivatives enabled by chiral diene ligands. The present catalytic system allows ligand-controlled anomeric selectivity, providing direct access to β-C-glycosyl arenes in good to high yields. The reaction exhibits broad substrate scope, proceeds efficiently on gram scale with low catalyst loading, and enables the synthesis of a 2-deoxy derivative of the SGLT2 inhibitor dapagliflozin.

C-Glycosyl arenes are sugar derivatives in which an aromatic ring is attached to the anomeric carbon (C1) through a stable carbon–carbon bond. These structural motifs have attracted considerable attention in organic synthesis, medicinal chemistry, and natural product synthesis.[1] Notably, several SGLT2 inhibitors incorporating *C*-glycosyl arene frameworks have recently been approved as therapeutic agents for the treatment of type 2 diabetes (Scheme 1).[2]

Glycals are sugar derivatives characterized by the presence of a carbon–carbon double bond between the C1 and C2 positions of the ring. Owing to this unsaturation at the anomeric position, glycals serve as versatile substrates for the introduction of carbon-based substituents at C1.[3] The introduction of aryl groups via palladium-catalysed reactions of glycals has been studied extensively.[4–6] These transformations enable direct access to 2-deoxy-*C*-glycosyl arenes, which lack a hydroxyl group at the C2 position, and typically proceed with



Scheme 1 Biologically active *C*-glycosyl arenes.

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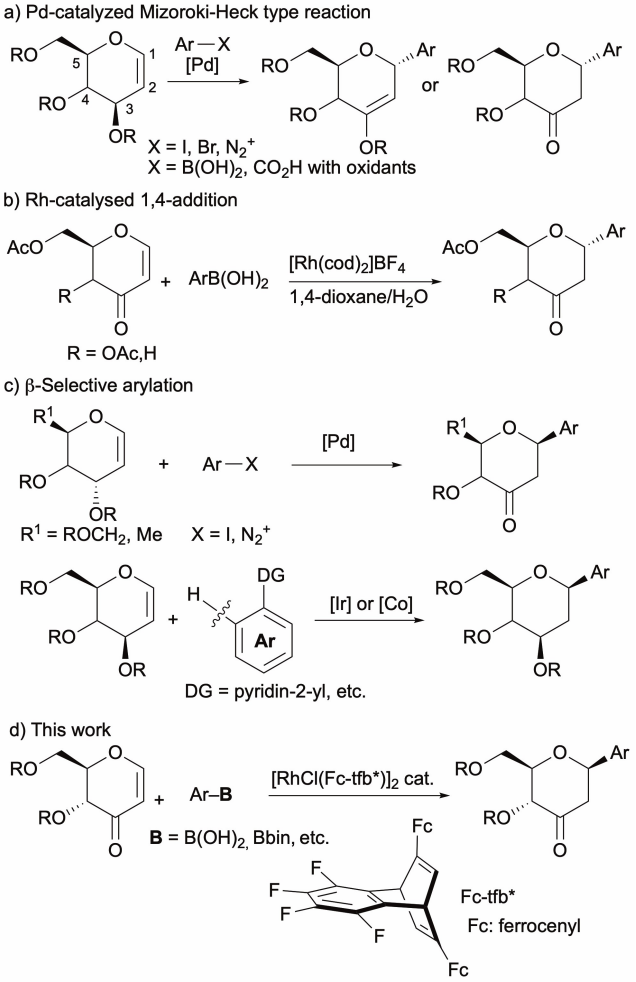
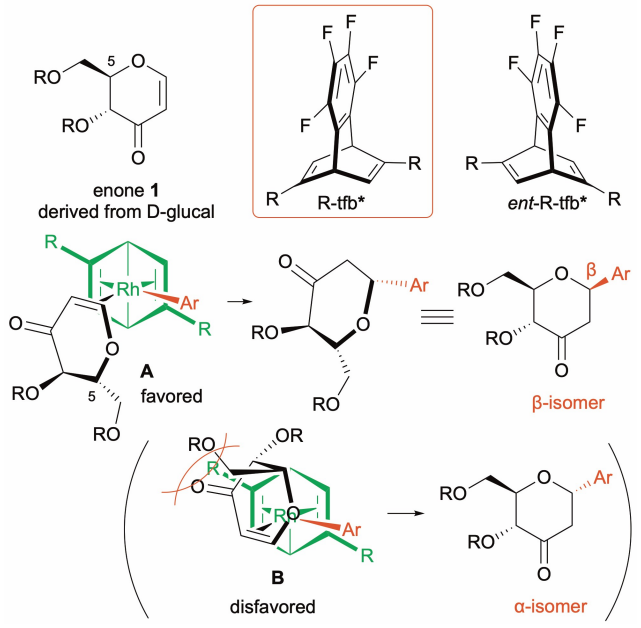
† Electronic supplementary information (ESI) available: Experimental procedures, and compound characterization data. See DOI:



Scheme 2 Arylation reactions of glycals.

predominant formation of the α-C-glycosyl arene isomer, which arises from aryl addition to the less hindered face of the glycal framework, avoiding steric interactions with the C5–CH_2OR substituent (Scheme 2a).[4] In addition, rhodium-catalysed 1,4-addition reaction of arylboronic acids to glycal derivatives have also been reported to proceed in an α-selective manner



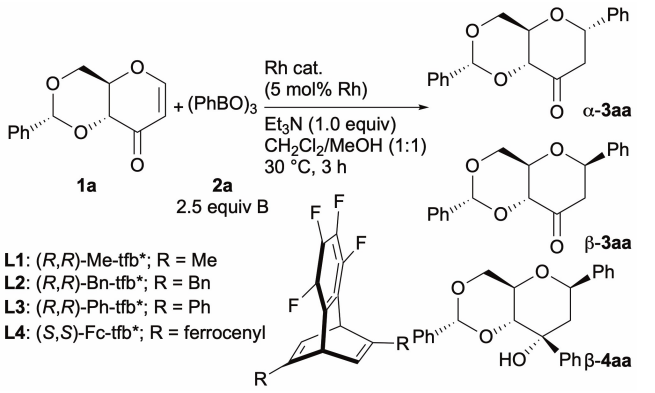
Scheme 3 Proposed stereochemiocal pathway in the Rh-catalyzed 1,4-addition.

(Scheme 2b).[7] In such reactions, the stereochemical outcome of the products is largely governed by the intrinsic structure and stereochemistry of the glycal substrates.

On the other hand, several examples of β-selective arylation reactions have also been reported (Scheme 2c).[8–11] Representative examples include the palladium-catalysed Mizoroki–Heck-type reactions reported by Kandasamy[4d] and Collet,[8] in which the stereochemical outcome is controlled by the substrate stereochemistry. In contrast, hydroarylation reactions via C–H functionalisation using iridium[9] or cobalt[10] catalysts have been shown to allow control over β-selectivity. Herein, we report the β-selective 1,4-addition reaction of arylboron compounds to enones derived from glucal derivatives using a rhodium catalyst bearing a chiral diene ligand (Scheme 2d). The direct synthesis of β-*C*-glycosyl arenes from glycal derivatives was successfully achieved through the use of chiral diene ligands with an appropriate absolute configuration.

For our goal of achieving β-selective arylation of glycal derivatives **1** derived from D-glucal, we designed the Rh-catalysed 1,4-addition reaction using chiral diene ligands (Scheme 3). In the Rh-catalysed 1,4-addition reaction of arylboron compounds, an arylrhodium species coordinated with the chiral diene is a key intermediate for rationalising the stereochemical pathway.[12] The arylrhodium species **A** coordinated with chiral diene ligands based on a tetrafluorobenzobarrelene framework (R-tfb*)[13] generates an effective C_2-symmetric environment, with the substituents positioned at the upper left and lower right quadrants. The olefinic double bond of **1** coordinates to the rhodium centre in a manner that avoids steric repulsion between the substituents on the diene ligand and the carbonyl moiety of the enone, as illustrated in species **A**. Consequently, aryl transfer is expected to occur preferentially from the β-face (the face *syn* to the C5–CH_2OR substituent).

Table 1 Screening of ligands[a]

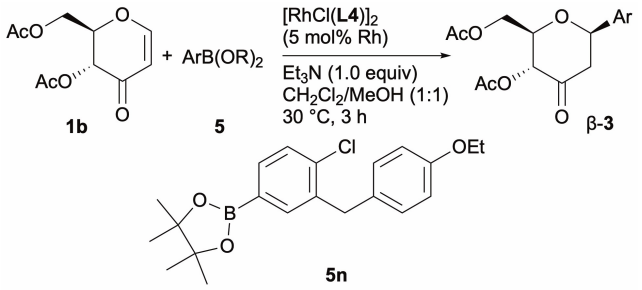


Entry	Rh cat.	**3aa** (%)[b]	**4aa** (%)[b]	α:β[b]
1	[Rh(OH)(cod)]$_2$	88 (85)[d]	0	α only
2	[RhCl(cod)]$_2$	73	0	α only
3	[RhCl(**L1**)]$_2$	24	0	92:8
4	[Rh(OH)(**L2**)]$_2$	71	3	96:4
5	[Rh(OH)(**L3**)]$_2$	12	27	8:92
6	[Rh(OH)(**L4**)]$_2$	39 (37)[d]	46	β only
7[c]	[Rh(OH)(**L4**)]$_2$	6	82 (85)[d]	β only
8	[RhCl(*ent*-**L4**)]$_2$	92	0	α only

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.083 mmol), Rh cat. (0.0025 mmol, 5 mol% Rh), Et_3N (0.10 mmol), CH_2Cl_2 (0.20 mL), MeOH (0.20 mL) at 30 °C for 3 h. [b] Determined by ^1H NMR. [c] Performed with **2a** (0.167 mmol). [d] Isolated yield.

In an initial set of experiments, several types of ligands were evaluated for their reactivity in the rhodium-catalysed 1,4-addition to glucal **1a**, in which the two hydroxy groups are protected as an acetal (Table 1). Treatment of **1a** with triphenylboroxin (**2a**, 2.5 equiv of B) in the presence of an achiral catalyst, [Rh(OH)(cod)]$_2$ (5 mol% Rh; cod = 1,5-cyclooctadiene), and triethylamine (1.0 equiv) in dichloromethane/methanol at 30 °C for 3 h selectively gave α-**3aa** in 90% yield (entry 1). The observed α-selectivity is consistent with the previous report.[7] Under otherwise identical reaction conditions, [RhCl(cod)]$_2$ also acted as an effective catalyst (entry 2). Next, the reaction was examined using chiral diene ligands based on a tetrafluorobenzobarrelene (tfb*) framework that we previously developed.[13] On this occasion, the absolute configuration of the ligand was selected to favour formation of the β isomer, taking the stereochemical reaction pathway into consideration.[12b] However, contrary to our expectations, when the methyl-substituted ligand **L1** ((*R*,*R*)-Me-tfb*) was employed, α-**3aa** was preferentially formed with only a minor amount of β-**3aa** (α:β = 98:2, entry 3). The catalyst [Rh(OH)(**L2**)]$_2$ bearing the benzyl-substituted (*R*,*R*)-Bn-tfb* ligand (**L2**) exhibited high reactivity, affording **3aa** in 73% yield, yet still favored α-selectivity (entry 4). In contrast, β-selective addition was observed with (*R*,*R*)-Ph-tfb* (**L3**), giving **3aa** in 12% yield along with the formation of **4aa** in 27% yield, arising from extra 1,2-addition to the carbonyl group (entry 5). Complete β-selectivity was achieved using (*S*,*S*)-Fc-tfb* (**L4**), providing **3aa** in 44% yield; however, the diarylation product **4aa** was also formed in 45% yield (entry 6). Selective formation of **4aa** was accomplished by employing a larger excess of **2a** (5 equiv of B;

Table 2 Scope of arylboron compounds **5**[a]



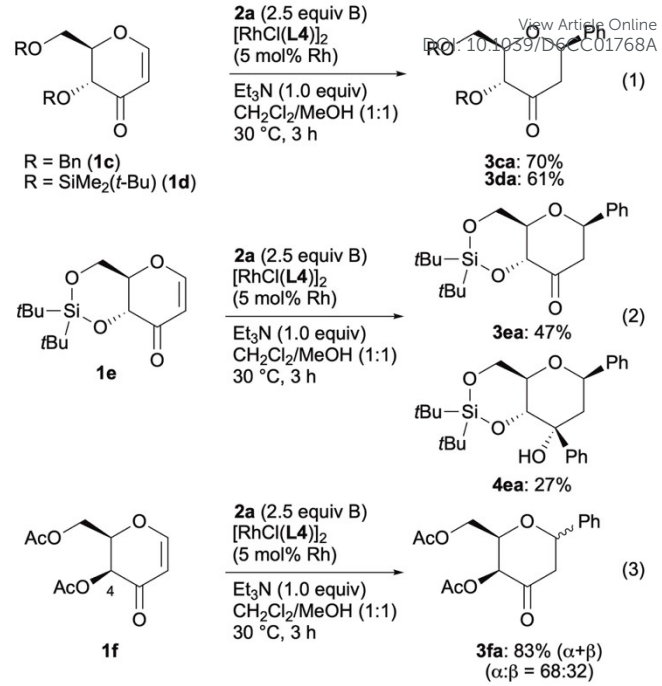
Entry	$ArB(OR)_2$	**3** (%)[b]
1[c]	$(C_6H_5BO)_3$ (**2a**)	90 (**3ba**)
2	$(C_6H_5BO)_3$ (**2a**)	90[d] (**3ba**)
3	$C_6H_5B(OH)_2$ (**5a**)	92 (75)[e] (**3ba**)
4	4-$MeC_6H_4B(OH)_2$ (**5b**)	93 (**3bb**)
5	4-$MeOC_6H_4B(OH)_2$ (**5c**)	78 (**3bc**)
6	4-$FC_6H_4B(OH)_2$ (**5d**)	77 (**3bd**)
7	4-$ClC_6H_4B(OH)_2$ (**5e**)	77 (**3be**)
8[f]	4-$BrC_6H_4B(OH)_2$ (**5f**)	97 (**3bf**)
9	4-$CF_3C_6H_4B(OH)_2$ (**5g**)	57 (**3bg**)
10	3-$MeOC_6H_4B(OH)_2$ (**5h**)	89 (**3bh**)
11	3-$ClC_6H_4B(OH)_2$ (**5i**)	73 (**3bi**)
12	3-$BrC_6H_4B(OH)_2$ (**5j**)	76 (**3bj**)
13	2-$MeOC_6H_4B(OH)_2$ (**5k**)	87 (**3bk**)
14	2-$ClC_6H_4B(OH)_2$ (**5l**)	69 (**3bl**)
15	2-$BrC_6H_4B(OH)_2$ (**5m**)	68 (**3bm**)
16[f]	**5n**	84 (**3bn**)

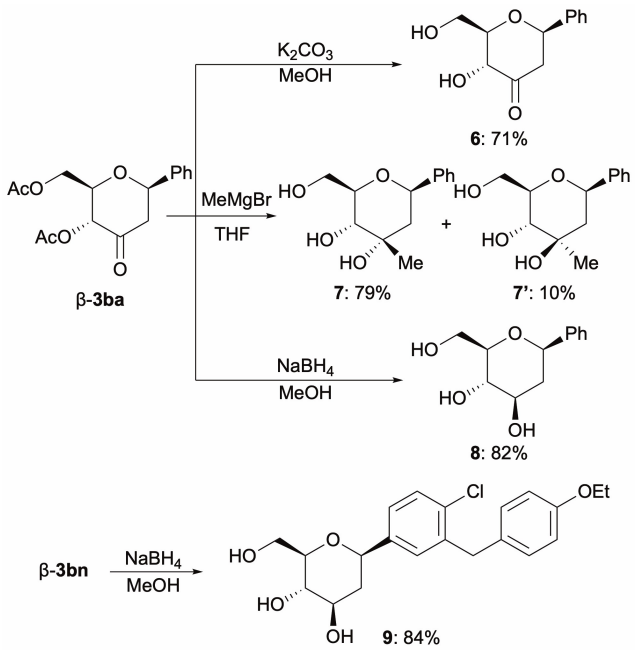
[a] Reaction conditions: **1b** (0.10 mmol), **2a** (0.083 mmol) or **5** (0.25 mmol), $[RhCl(\mathbf{L4})]_2$ (0.0025 mmol, 5 mol% Rh), Et_3N (0.10 mmol), CH_2Cl_2 (0.20 mL), MeOH (0.20 mL) at 30 °C for 3 h. [b] Isolated yields. [c] $[Rh(OH)(\mathbf{L4})]_2$ was used. [d] Determined by ^1H NMR. [e] Performed with **1b** (1.0 g) and **5a** (2.5 equiv B) in the presence of 1 mol% of the Rh catalyst. [f] Performed with **5** (0.50 mmol) and Et_3N (0.20 mmol).

entry 7). Notably, the use of (*R*,*R*)-Fc-tfb (*ent*-**L4**) exclusively gave α-**3aa** (entry 8), indicating that the stereochemical outcome of the β-selective reaction is governed by the absolute configuration of the chiral diene ligand.

In contrast to the formation of the diarylated product **4aa** observed in the reaction of **1a**, di-*O*-acetyl enone **1b** was found to undergo selective 1,4-addition while suppressing extra 1,2-addition to the carbonyl group (Table 2).[14,15] Accordingly, reactions of **1b** with **2a** in the presence of the Rh/(*S*,*S*)-Fc-tfb* (**L4**) catalyst gave the desired product **3ba** in high yields with excellent β-selectivity (entries 1 and 2). When phenylboronic acid (**5a**) was used instead of triphenylboroxin (**2a**), β-**3ba** was obtained in a similarly excellent yield (entry 3). A gram-scale reaction employing 1 mol% of the rhodium catalyst was also successfully carried out. Arylboronic acids bearing a variety of functional groups at the *para* (**5b**–**5g**), *meta* (**5h**–**5j**), and *ortho* (**5k**–**5m**) positions gave the corresponding products **3bb**–**3bm** in good to high yields with β-selectivity (entries 4–15). The aryl moiety of the SGLT2 inhibitor dapagliflozin could also be introduced onto glucal **1b** using the pinacol ester **5n**, affording the desired product **3bn** in 84% yield (entry 16).

The present catalytic system can also be applied to the 1,4-addition of triphenylboroxin (**2a**) to several glycal derivatives **1**. For example, *O*-benzyl- and *O*-*tert*-butyldimethylsilyl-substituted glycals **1c** and **1d** reacted with **2a** to give the corresponding β-adducts **3ca** and **3da**, respectively, in good yields (Eqn 1). Similarly to glucal **1a** bearing a cyclic acetal framework, **1e** possessing a dioxasilacyclic moiety underwent 1,4-addition followed by an extra 1,2-addition to give **3ea** and **4ea** in 47% and 27% yields, respectively (Eqn 2). These three substrates exhibited excellent β-selectivity. Unfortunately, however, in the reaction of galactal-derived substrate **1f**, α-selectivity was predominant even when ligand **L4** was employed, presumably due to steric hindrance from the C4–OAc substituent, which disfavours aryl addition from the β-face (Eqn 3).





Scheme 4 Transformations of **3**.

As shown in Scheme 4, solvolysis of β-**3ba** using potassium carbonate in methanol gave diol **6** in 71% yield. Methylation of β-**3ba** by MeMgBr gave (3*S*)-**7** in 79% yield as well as 10% of (3*R*)-**7'**. The observed selectivity is similar to that observed in the arylation of β-**3aa** shown in Table 1. Treatment of β-**3ba** with sodium borohydride resulted in both deprotection of the acetyl groups and reduction of the carbonyl moiety, giving triol **8** in 82% yield; the observed selectivity is similar to that reported for the hydrogenation of ketones bearing a glycal framework.[11] The same transformation was successfully applied to β-**3bn** to give compound **9**, a 2-deoxy derivative of SGLT2 inhibitor *dapagliflozin*,[16] in 84% yield.

In summary, a rhodium-catalysed β-selective 1,4-addition of arylboron compounds to glycal derivatives has been developed using chiral diene ligands. While conventional arylation reactions of glycals typically afford α-*C*-glycosyl arenes under substrate control, the present catalytic system enables ligand-controlled inversion of anomeric selectivity. The use of an appropriately configured chiral diene ligand allows direct access to β-*C*-glycosyl arenes in good to high yields with excellent β-selectivity across a broad range of arylboron reagents and glucal substrates. The synthetic utility of this method was further demonstrated by gram-scale synthesis and the preparation of a 2-deoxy derivative of the SGLT2 inhibitor dapagliflozin.

We thank Professor H. W. Lam (University of Nottingham) for kindly providing ligand **L6** (See the ESI). This work is supported by JSPS KAKENHI Grant Number JP24K08416.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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DOI: 10.1039/D6CC01768A

Data Availability Statement

The data supporting this article have been included as part of the Supplementary Information.