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FULL PAPER

Facile Approach to *C*-glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis

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Abstract: Access to unprotected (hetero)aryl pseudo-*C*-glucosides via a mild Pd-catalyzed Hiyama cross-coupling reaction of protecting-group-free 1-diisopropylsilyl-D-glucal with various (hetero)aryl halides has been developed. In addition, selected unprotected pseudo-*C*-glucosides were stereoselectively converted into the corresponding α- and β-*C*-glucosides, as well as 2-deoxy-β-*C*-glucosides. This methodology was applied to the efficient and high-yielding synthesis of dapagliflozin, a medicament used to treat type 2 diabetes mellitus. Finally, the versatility of our methodology was proved by the synthesis of other analogues of dapagliflozin.

Introduction

In the field of carbohydrate chemistry, aryl *C*-glycosides are an important class of natural products[1] and synthetic drugs.[2] Structurally, they can be viewed as mimetics of aryl *O*-glycosides, in which their labile *O*-glycosidic bond is replaced with a stable C-C bond. This modification increases their stability towards chemical and enzymatic hydrolysis substantially, providing them with great potential as drug candidates. Various *C*-glycosides such as papulacandin D,[3] bergenin,[4] thailanstatin A,[5] and vicenin-2,[6] have been isolated from natural sources and show significant biological activities. The major use of aryl *C*-glycosides includes the inhibition of the sodium-glucose cotransporter-2 (SGLT-2). In recent years, these inhibitors have attracted much attention due to their effective, safe and well-tolerated control and regulation of type 2 diabetes.[2b] Accordingly, the FDA has approved SGLT-2 inhibitors, such as dapagliflozin (Forxiga), empagliflozin (Jardiance), and canagliflozin (Invokana).[7]

Consequently, many successful strategies to provide a synthetic access to aryl *C*-glycosides in a direct or *de novo* manner have been already developed.[1] Notable strategies to construct these saccharide mimetics by transition-metal-mediated coupling reactions include Heck,[8] Stille,[9] Suzuki-Miyaura,[4, 9a, 10] Negishi[10b, 11] and Hiyama-Denmark cross-coupling reactions (Figure 1).[12] All of these methodologies were applied almost exclusively to *O*-protected (mostly benzylated and silylated) 1-substituted glycals except for the Stille cross-coupling reaction of aryl halides with glycosyl stannanes, described by Walczak et al.[13] The use of protecting groups suppresses problems with solubility in organic solvents and purification as well as side reactivity.[13-14] Nevertheless, depending on the sensitivity of the introduced functional group, the deprotection of the obtained saccharide mimetics can become challenging. Therefore, a straightforward access to unprotected aryl *C*-glycosides in high yield is advantageous. In continuation of our interest in the synthesis of *C*-glycosides,[4, 9a, 15] we report access to diverse (hetero)aryl *C*-glycosides via a key Hiyama cross-coupling reaction of 1-diisopropylsilyl-D-glucal **4** with different (hetero)aryl halides under mild conditions. Herein, to the best of our knowledge, the most suitable and practical synthesis of dapagliflozin **8n** and its derivatives **7n** and **10n** is also described.

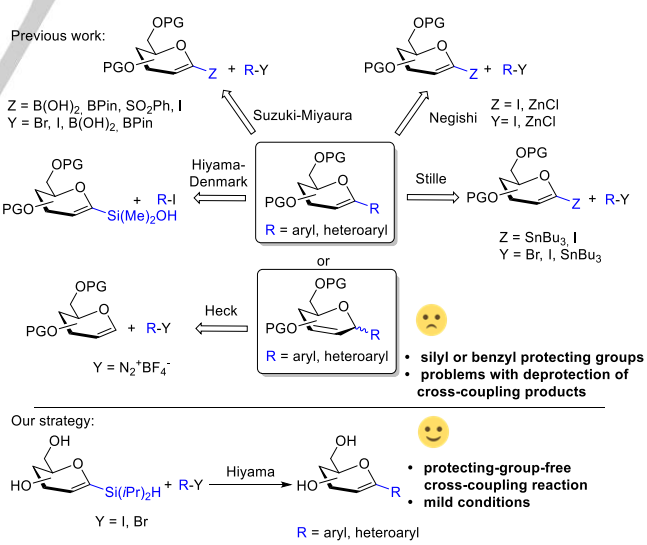

Figure 1. Cross-coupling approaches for the synthesis of aryl *C*-glycosides.

Results and Discussion

The first step was the preparation of 1-diisopropylsilyl-D-glucal **4** from commercially available D-glucal **1**, which was fully protected with 2-methoxyprop-2-yl (MOP) groups (Scheme 1). The reaction

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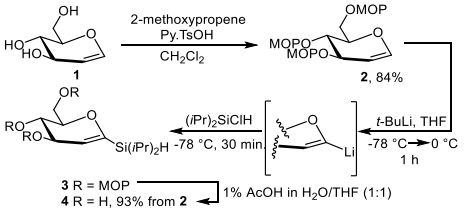
of 2-methoxypropene in the presence of pyridinium tosylate afforded MOP-D-glucal **2** in an excellent yield of 84%. As we reported before,[9a] MOP acetal protecting groups represent an efficient strategy for transient protection of glycals. Their use is favourable for several reasons, such as their easy introduction and removal, compatibility with silyl groups, low cost, and stability under harsh basic conditions, which are required for C-1 derivatization. In the next step, MOP-D-glucal **2** was converted into a 1-lithiated intermediate by treatment with *t*-BuLi (3.5 equiv.) in THF at −78 °C and then this intermediate was reacted with $(i\text{Pr})_2\text{SiClH}$ to give compound **3**. The subsequent mildly acidic hydrolysis (THF/1% aqueous AcOH in the ratio 1:1, *v*/*v*) of **3** resulted in the formation of bench-stable solid 1-diisopropylsilyl-D-glucal **4** in a notable yield of 78% over three steps.



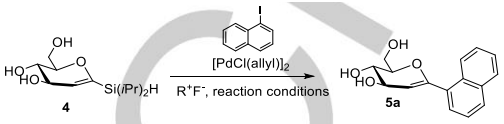
Scheme 1. The preparation of 1-diisopropylsilyl-D-glucal **4** from D-glucal **1**.

The reaction of the unprotected 1-diisopropylsilyl-D-glucal **4** with 1-iodonaphthalene was chosen as a model reaction for the Hiyama cross-coupling.[16] To optimize the reaction conditions, the fluoride source and its quantity was screened, as summarized in the Table 1. Other parameters such as the temperature and the reaction time were varied. The formation of the desired 1-naphthyl-D-glucal **5a** was monitored by ^{1}H NMR with an internal standard (1,3,5-trimethoxybenzene).

The initial study began with tetrabutylammonium fluoride (TBAF) as a fluoride source in anhydrous THF at 0 °C (Table 1, entry 1). A complete conversion of the starting material **4** to product **5a** was observed within 1 h and the reaction conditions appeared to be satisfactory. Unfortunately, the purification of the product became problematic because of the presence of tetrabutylammonium salts, which we were not able to remove by column chromatography, ion-exchange on DOWEX 50X8 in Et_3N cycle or HPLC. For this reason, it was necessary to find a more convenient source of fluoride ions.

We first turned our attention to KF in the presence of a catalytic amount of 18-crown-6 (0.2 equiv.).[17] We tested different amounts of KF (2.2, 4.4, and 6.6 equiv.) under constant conditions in anhydrous THF at room temperature for 4 hours. As shown in Table 1, the product **5a** was detected in all cases, although in low yields (17–36%) (Table 1, entries 2-4). Moreover, the conversion of the starting 1-diisopropylsilyl-D-glucal **4** was incomplete, and the addition of a Pd catalyst, crown ether, an extension of the reaction time or higher temperature did not lead to increased conversion. Therefore, CsF was used as a fluoride ion (Table 1, entries 5-12), because of its greater ionic character compare to KF. In this case, DMF and DMSO were tested as solvents. To our delight, the complete conversion of **4** was observed in all reactions (Table 1, entry 5-12). However, besides the desired cross-coupling product, D-glucal **1** was identified as a by-product. Its origin can be explained by competitive protodesilylation,[18] in which the diisopropylsilyl group is replaced by a hydrogen atom. In an attempt to prevent its formation, several reactions with different timing t_2 between the addition of CsF and the addition of 1-iodonaphthalene along with the catalyst were performed. Unfortunately, the presence of D-glucal **1** was still apparent.

Table 1. The optimisation of the Hiyama cross-coupling reaction.



Entry	R^+F^- (equiv.)	Solvent	t_R (h)/ t_2(min)	T (°C)	Yield of **1**/**5a** (%)[a]	Conversion of **4** (%)[a]
1	**TBAF (2.2)**	**THF**	**1/10**	**0-rt**	**0/80**[b]	**100**
2[d]	KF (2.2)	THF	4/10	rt	ND/24	ND
3[d]	KF (4.4)	THF	4/10	rt	0/36	ND
4[d]	KF (6.6)	THF	4/10	rt	0/17	63
5[d]	CsF (2.2)	DMF	16/0	rt	53/20	100
6[d]	CsF (4.4)	DMF	16/0	rt	52/14	100
7[d]	CsF (4.4)	DMF	16/0	60	68/16	100
8[d]	CsF (4.4)	DMF	16/20	60	ND/38	100
9[d]	CsF (4.4)	DMF	16/60	60	26/40	100
10[d]	CsF (4.4)	DMSO	16/0	60	ND/ND	ND
11[d]	CsF (4.4)	DMSO	16/20	60	26/40	100
12[d]	CsF (4.4)	DMSO	16/60	60	ND/ND	ND
13	NH_4F (2.2)	THF	16/10	rt	0/0	0
14	**$TMAF\cdot4H_2O$ (2.2)**	**DMF**	**16/10**	**rt**	**0/81**[c]	**100**
15	$TMAF\cdot4H_2O$ (2.2)	THF	16/10	rt	0/40[c]	50

[a] All yields and conversions were determined by ^{1}H NMR with an internal standard, 1,3,5-trimethoxybenzene; [b] product contained traces of tetrabutylammonium salts; [c] isolated yield; [d] 18-crown-6 (0.2 equiv.) was added; t_R = reaction time; t_2 = time between the addition of fluoride and the addition of 1-iodonaphthalene with a Pd catalyst; ND = not determined.

Additionally, NH_4F was also tested as a source of fluoride ions (Table 1, entry 13), but no reactivity of the starting material was observed, which was attributed to the insufficient ionic character of this salt. Ideal conditions (Table 1, entry 14) were found using tetramethylammonium fluoride tetrahydrate ($TMAF\cdot4H_2O$) in DMF. This quaternary ammonium salt provided almost the same reaction yield as the experiment using TBAF; in this case, the cross-coupling product **5a** was observed in 81% yield. Its main advantage lays in the purification step, in which the quaternary ammonium salts were easily separated from the product by column chromatography. Based on these facts, $TMAF\cdot4H_2O$ could have become an alternative source of fluoride ions to the

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more problematic TBAF. It is also important to note that the use of THF as a solvent (Table 1, entry 15) instead of DMF decreased the yield to 40%. This could be explained by the lower solubility of TMAF•4H_2O in THF.

Monitoring of the reaction progress by NMR revealed, that the addition of hydrated TMAF to the solution of **4** leads to dehydrogenative hydrolysis to silanol **6** (Figure 2). This observation confirms the role of silyl hydride **4** as a masked silanol, as described before for silacyclobutanes[19] as well as for 2-thienyl[20] and 2-pyridyl[21] silanes. This hydrolysis is likely promoted by water present in the TMAF hydrate, as the cross-coupling reactions were otherwise carried out under anhydrous conditions. The *in situ* formation of silanol **6** from **4** was evidenced by upfield shift of the singlet in decoupled ^{29}Si NMR spectra (from -1.42 to -3.40 ppm) and the disappearance of $^{1}J_{Si-H}$ coupling in the silyl hydride signal in proton-coupled ^{29}Si spectra (Figure 2B). The formation of silanol **6** was also observed in ESI-MS of the reaction mixture after the addition of TMAF•4H_2O ([M+Na]$^+$ 299.1287).

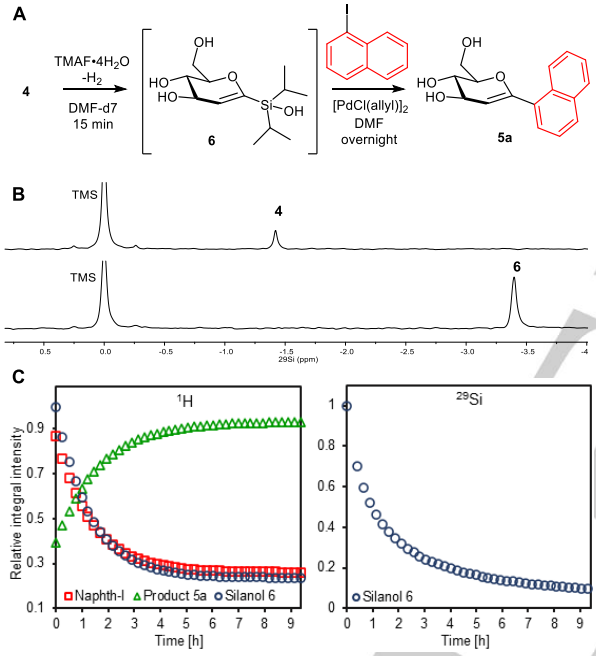
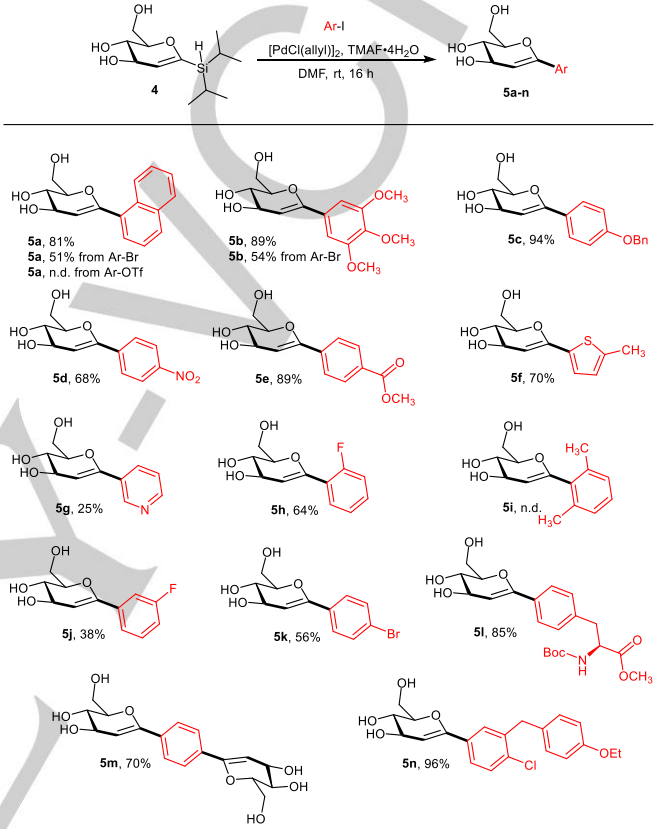


Figure 2. Reaction monitoring by NMR. **A**: Reaction scheme **B**: Decoupled ^{29}Si NMR spectra of **4** before (upper spectrum) and after (lower spectrum) the addition of TMAF•4H_2O **C**: Kinetics of the arylation step from ^{1}H (left) and ^{29}Si (right) NMR data. Displayed are relative integral intensities after fitting to pseudo-first order kinetic equation.

The addition of 1-iodonaphthalene and [PdCl(allyl)]$_2$ led to the conversion of silanol **6** to the arylated product **5a** overnight, as observed by the decay of the silanol signal at -3.40 ppm in ^{29}Si NMR and corresponding arylation kinetics in ^{1}H NMR (pseudo-first order rate, k = 1.8 × 10^{-4} s^{-1}) (Figure 2C, see Supporting Information (chapter S3) for details).

As shown in Table 2, various aromatic partners were tested with 1-diisopropylsilyl-D-glucal **4** under optimized conditions. In general, electron-rich aryl iodides were found to provide better results. Especially, 5-iodo-1,2,3-trimethoxybenzene and 1-benzyloxy-4-iodobenzene provided the expected products (**5b** and **5c**) in excellent yields (89% and 94%). Compared to aromatic iodides, the identical bromides provided lower yields as demonstrated by the yields of products **5a** (81% vs. 51%) and **5b** (89% vs. 54%). Similarly, aryl triflates, which are also commonly used as suitable donors for cross-coupling reactions, are not able to compete with identical iodides as is illustrated by no formation of the product **5a**.

Table 2. The substrate scope of the Pd-catalyzed Hiyama cross-coupling reaction of 1-diisopropylsilyl-D-glucal **4** with different aryl halides.



Reaction conditions: **4** (0.6 mmol, 1.2 equiv.), Aryl-X (0.5 mmol, 1 equiv.), [PdCl(allyl)]$_2$ (2.5 mol%), TMAF•4H_2O (1.1 mmol, 2.2 equiv.), 25 °C, DMF (5 mL), 16 h. Isolated yields. n.d. = not detected.

Electron-poor aromatic iodides, such as 1-iodo-4-nitrobenzene and methyl 4-iodobenzoate were also well tolerated substrates and their products **5d** and **5e** were isolated in high yields (68% and 89%). Thereafter, we probed whether the *C*-glycosidic bond could be formed with heteroaromatic compounds containing nitrogen or sulphur. The utilisation of 2-iodo-5-methylthiophene provided **5f** in 70% yield. However, the reaction of the starting silylhydride **4** with 3-iodopyridine afforded **5g** in lowered 25% yield. Further study of *ortho*-substituted 1-fluoro-2-iodobenzene with **4** gave the corresponding coupling product **5h** in good 64% yield, whereas bulky 2-iodo-1,3-dimethylbenzene failed to provide any product. To expand the substrate scope, a reaction with *meta*-substituted arene was performed. 1-Fluoro-3-iodobenzene underwent the coupling reaction to give **5j** in 38% yield. Due to the lower reactivity of aryl bromides, we also performed a reaction with 1-bromo-4-iodobenzene. As expected, the reaction resulted in a mixture of mono- and bis-glycosylated products **5k** and **5m**, but the major product **5k** was successfully isolated in 56% yield. Besides, we also wondered whether our method would be suitable for the synthesis of glycopeptides *C*-analogues, as the attachment of saccharide to peptides and

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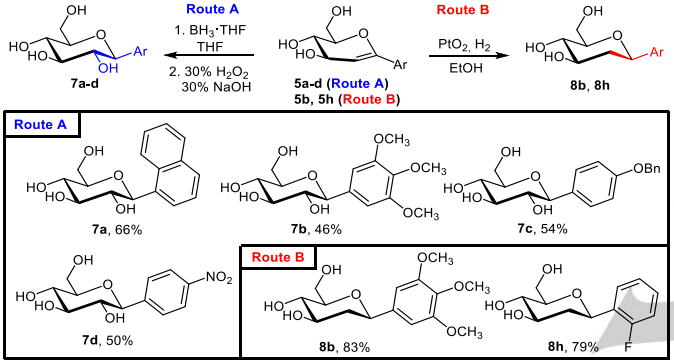
proteins is a common post-translational modification. The reaction of **4** with *N*-(*tert*-butoxycarbonyl)-4-iodo-L-phenylalanine methyl ester afforded the glycoconjugate **5l** in a high yield of 85%. Lastly, we showed that 1,4-diiodobenzene can be employed in this transformation with 2.2 equivalents of **4**, affording the bis-glycosylated product **5m** in 70% yield.

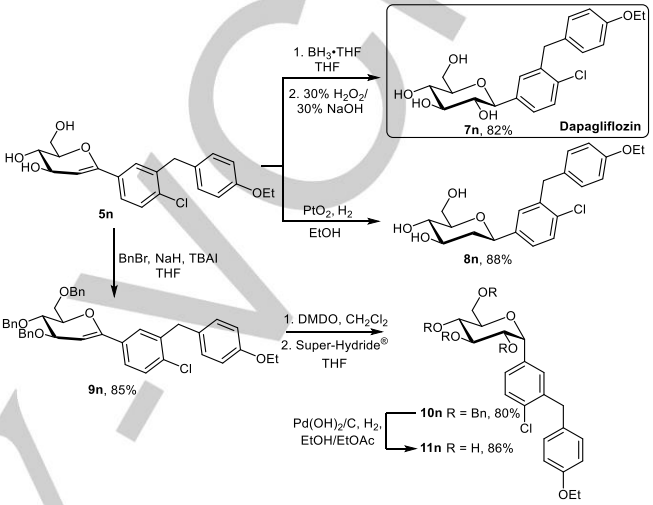
As we published before,[4, 9a, 15a] the protected unsaturated pseudo-*C*-glycosides are suitable substrates for further stereoselective transformations, which produced α- or β-*C*-glycosides and 2-deoxy-β-*C*-glycosides in high yields. As most of the naturally occurring aryl *C*-glycosides exist with β-configuration at the pseudoanomeric centre, selected unprotected cross-coupling products **5a**–**d** were directly converted to β-*C*-glucosides **7a**–**d** (Table 3. Route A).

Table 3. A. The preparation of aryl β-*C*-glucosides **7a**-**d**. **B.** The preparation of aryl 2-deoxy-β-*C*-glucosides **8b** and **8h**.



For efficiency reasons, we aimed for a one-pot sequence[9a] of hydroboration followed by oxidation with alkaline hydrogen peroxide. The resulting products **7a**–**d** were obtained in moderate yields (46–66%) with only β-selectivity. Moreover, the direct transformation of unprotected cross-coupling products to aryl 2-deoxy-β-*C*-glucosides was examined. In this case, the choice of the catalyst played a crucial role in the reactivity. The unprotected pseudo-*C*-glycosides **5b** and **5h** were used as the starting materials. Unfortunately, the hydrogenation of their endocyclic double bonds in the presence of 10% Pd/C in ethanol resulted in a mixture of the expected products and sugar ring-opened product. Due to their very similar R_F values, these products could not be separated. Therefore, several conditions were tested (Pd/C in THF, methanol and ethyl acetate,[10a] $Pd(OH)_2/C$ in ethanol[22] and Pt_2O in ethanol[4]). It turned out that the hydrogenation of the double bond of **5b** and **5h** with Adams' catalyst in ethanol successfully led to the desired aryl 2-deoxy-β-*C*-glucosides **8b** and **8h** in high yields (83% and 79%) (Table 3. Route B). These results might be explained by the coordination of palladium catalysts to endocyclic oxygen and the subsequent reductive sugar-ring opening.

The compatibility with various aromatic electrophiles enabled us to apply this Hiyama coupling reaction to the synthesis of dapagliflozin, a worldwide approved inhibitor for the treatment of type 2 diabetes. The required acceptor for the cross-coupling reaction was prepared via a published three-step synthesis.[23] According to the general procedure, 1-diisopropylsilyl-D-glucal **4** underwent the Hiyama cross-coupling reaction with the prepared 1-chloro-2-(4-ethoxybenzyl)-4-iodobenzene and the desired pseudo-*C*-glycoside **5n** (Table 2) was obtained in excellent 96% yield. For the synthesis of dapagliflozin, **5n** was simply used for hydroboration-oxidation, which resulted in a molecule of dapagliflozin **7n** in 82% isolated yield with exclusive β-anomeric stereoselectivity (Scheme 2). Next, the pseudo-*C*-glycoside **5n** was subjected to catalytic hydrogenation in the presence of Adams' catalyst. As we assumed, the *syn*-addition of hydrogen successfully led to the desired 2-deoxy analogue of dapagliflozin **8n** in 88% yield (Scheme 2).



Scheme 2. The preparation of dapagliflozin **7n** and its analogues **8n** and **11n**.

For completeness, we probed previously published two-step synthetic procedure[15a, 24] for the first stereoselective preparation of the α-anomer analogue of dapagliflozin **11n**. Firstly, the pseudo-*C*-glycoside **5n** was benzylated to prevent side reaction of free hydroxyl groups during the oxidation in the following step. The benzylation of **5n** with BnBr and NaH in the presence of tetrabutylammonium iodide (TBAI) in THF provided the benzylated derivative **9n** in high 85% yield. The corresponding pseudo-α-anomer **10n** was obtained by the epoxidation of the endocyclic double bond with dimethyldioxirane (DMDO)[25], followed by the subsequent cleavage of the formed epoxide ring with lithium triethylborohydride (Super-Hydride®). The α-*C*-glycoside **10n** was successfully isolated in 80% yield as the only isomer. The final catalytic debenzylation of **10n** in the presence of $Pd(OH)_2/C$ furnished a free analogue of dapagliflozin **11n** with α-D-*gluco* configuration. The advantage of using $Pd(OH)_2/C$ was that no dehalogenation product was observed and **11n** was obtained in high 86% yield (Scheme 2).

Conclusion

In summary, we have developed a new strategy for the synthesis of (hetero)aryl *C*-glycosides via the Pd-catalyzed Hiyama reaction of unprotected 1-diisopropylsilyl-D-glucal **4** with iodo- or bromo-(hetero)arenes under mild conditions. It enables the straightforward synthesis of a variety of (hetero)aryl *C*-glycosides, providing access to products that are otherwise difficult to prepare by known methods and offers a tool for late-stage modifications of drug molecules. We also report a new practical two-step

strategy for the synthesis of pharmaceutically important dapagliflozin in the overall yield of 79%. Next, we have verified that our stereoselective procedure is also useful for the preparation of dapagliflozin analogues with 2-deoxy-β-D-*gluco* and α-D-*gluco* configuration in good overall yields (84% and 56%) from 1-diisopropylsilyl-D-glucal **4**.

Experimental Section

General procedure A for Hiyama cross-coupling reaction

TMAF•4H_2O (2.2 equiv.) was added to a 0.24M solution of 1-diisopropylsilyl-D-glucal **4** (1.2 equiv.) in anhydrous DMF at room temperature under an argon atmosphere. After 15 min, $[PdCl(allyl)]_2$ catalyst (0.025 equiv.) and the corresponding aryl halide (1 equiv.) were subsequently added, and the reaction mixture was stirred for 16 h. After consumption of the starting material, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography on silica to afford the desired product **5a**-**n**. In some cases, the obtained compounds were additionally purified by prep-HPLC on Phenomenex (Luna C_{18}) column.

General procedure B for hydroboration-oxidation

To a 0.025M solution of corresponding coupling product **5a**-**d** and **5n** (1 equiv.) in anhydrous THF, BH_3•THF complex solution (1.0 M in THF, 10 equiv.) was added dropwise at 0°C. The resulting mixture was stirred for 10 min at this temperature and then warmed to room temperature and stirred for next 16 h (overnight). Then the mixture was cooled to 0 °C again and 30% solution of H_2O_2 and 30% solution of NaOH (2 mL, 1:1) were added simultaneously dropwise. After a slow transition to room temperature (approx. 20 min), the reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica to provide the desired aryl β-*C*-glycoside **7a**-**d** and **7n**. In some cases, the obtained compounds were additionally purified prep-HPLC on Phenomenex (Luna C_{18}) column.

General procedure C for hydrogenation

To a 0.016M solution of corresponding coupling products **5b**, **5h**, and **5n** (1 equiv.) in ethanol PtO_2 (0.05 mmol, 0.5 equiv.) was added. The resulting mixture was stirred for 40 min under a hydrogen atmosphere for 2 h. The mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica to provide the desired aryl 2-deoxy-β-*C*-glycosides **8b**, **8h**, and **8n**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: protecting-group-free • Hiyama reaction • cross-coupling • aryl *C*-glycosides • dapagliflozin

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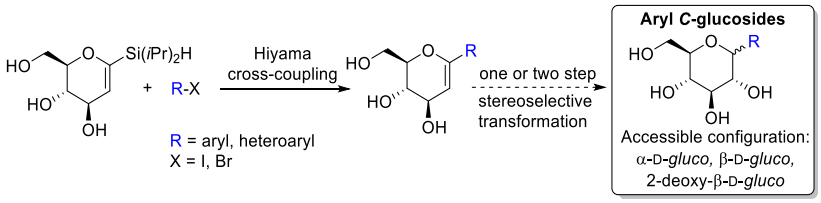

A mild palladium-catalyzed Hiyama cross-coupling of 1-diisopropylsilyl-D-glucal with various (hetero)aryl halides has been developed. This arylation strategy enables the synthesis of a variety of (hetero)aryl pseudo-*C*-glucosides in good to excellent yields. Without the need for protecting groups, selected pseudo-*C*-glucosides were stereoselectively converted into the corresponding *C*-glucosides, as well as 2-deoxy-β-*C*-glucosides. This methodology was applied to the efficient and high-yielding synthesis of dapagliflozin and its uncommon α-isomer.

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