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Glycosyl Cross-Coupling with Diaryliodonium Salts: Access to Aryl C-Glycosides of Biomedical Relevance

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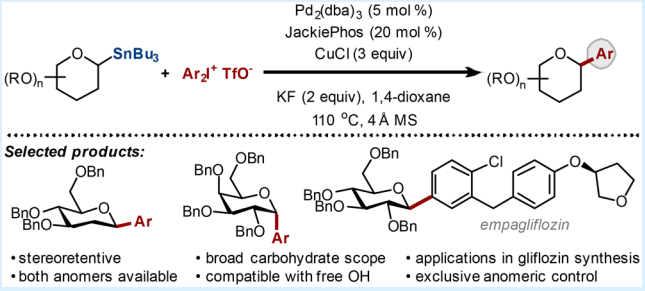
Supporting Information

ABSTRACT: A stereospecific cross-coupling reaction of anomeric nucleophiles with diaryliodonium triflates resulting in the synthesis of aryl C-glycosides is reported. This process capitalizes on a stereoretentive reaction of configurationally stable C1 stannanes and is promoted by a palladium catalyst in the presence of a bulky phosphine ligand that suppresses the undesired β-elimination. The utility of this reaction has been demonstrated in the preparation of a series of C-glycosides derived from common saccharides resulting in exclusive transfer of anomeric configuration from the anomeric nucleophile to the product, and in the synthesis of empagliflozin, a commercial antidiabetic drug.

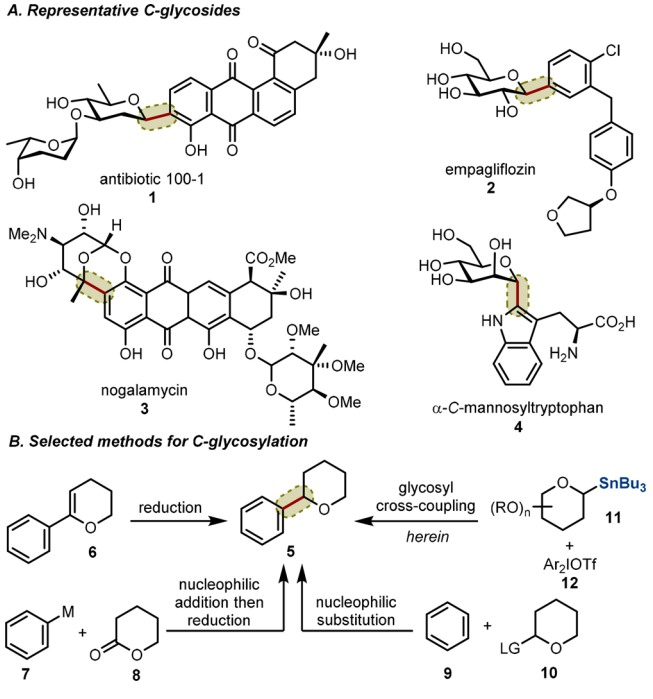


Stereoselective manipulations at the anomeric carbon constitute one of the most challenging problems in preparative carbohydrate chemistry.[1,2] An overwhelming majority of chemical methods that form a new bond with the anomeric carbon are focused on reactions with glycosyl donors in which the anomeric position is substituted with a heteroatom or a halide. These methods inevitably result in a loss of stereochemical integrity because of the formation of an oxocarbenium intermediate, and sophisticated strategies are needed to achieve high anomeric control. An alternative method that focuses on reactions of configurationally stable anomeric nucleophiles might provide a viable solution to these problems. Here we report the glycosyl cross-coupling reactions of diaryliodonium triflates with anomeric stannanes that furnish C-glycosides with a consistently high transfer of anomeric configuration from the substrate to the product. This method furnished both anomers of common saccharides with high anomeric selectivities through transfer of the anomeric configuration from the substrate to the product.

Many C-aryl glycosides are a common structural motif found in bioactive natural products (angucycline antitumor antibiotics),[3] imaging agents,[4] and glycoproteins (C-mannosylation)[5] (Scheme 1A). The most prominent commercial application of C-glycosides is gliflozins, a class of sodium-glucose cotransporter (SGLT2) inhibitors used as a treatment for diabetes mellitus type 2.[6] Gliflozins contain a β-D-glucose residue directly linked to an aromatic ring usually containing a modification at the *para* position.

Given the special role of C-glycosides in medicinal chemistry and drug discovery, methods that enable the introduction of the glycosyl group with high and predictable stereochemical outcome are desired.[7−10] The most common methods for establishing the C-glycosyl bond rely on the reduction of glycals, and the nucleophilic addition to lactones followed by reduction or nucleophilic substitution with electron-rich arenes (Scheme 1B).[5] These methods often present a viable solution to a specific synthetic problem, and the stereochemical

Scheme 1. Selected C-Glycosides and Methods for Their Preparation



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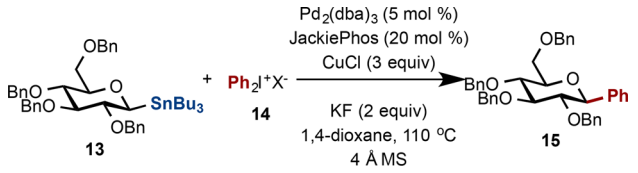
outcome is often dependent on subtle structural features of the substrate. We recently described the synthesis and cross-coupling reactions of anomeric stannanes.[11−13] These reagents are configurationally stable anomeric nucleophiles[14] and can be engaged in cross-coupling reactions with various aryl halides with retention of anomeric configuration. During our studies we established that electron-rich arenes resulted in lower yields of the cross-coupling product. The impact of electronic substitution on the rate of cross-couplings with C(sp^2) nucleophiles such as boronic acids or esters and Grignard reagents has been reported.[15−17] However, the role of electronic substitution has an even more dramatic effect for C(sp^3) nucleophiles, especially in the case of anomeric nucleophiles where the competing β-elimination can become a dominant pathway. The glycosyl cross-coupling is a special case because, in addition to a potentially problematic β-hydride elimination, the β-oxygen group can be removed under the reaction conditions. The subtle balance between the reductive elimination leading to a new C−C bond and β-elimination can be shifted in favor of the former by the judicious selection of a bulky phosphine ligand. In order to overcome the difficulties with aromatic substrates, we hypothesized that more reactive iodonium salts[18−20] would be suitable candidates for this transformation. We speculated that the transfer of an aryl group to Pd would be facilitated by a reduction of the iodine to iodine(I) and that it could have a beneficial effect on the overall efficiency of the process. Diaryliodonium salts have recently become useful reagents for C(sp^3)−H activation[21−28] and the preparation of sterically congested alkyl aryl ethers.[29] Furthermore, unlike the reactions of aryl halides, cross-couplings of C(sp^3) nucleophiles (e.g., organozinc, organostannanes, organocuprates) with iodonium reagents are far less known and only a handful of examples have been reported with activated substrates such as allylic,[30] benzylic,[31] and strained[32] reagents. To the best of our knowledge, the formation of C(sp^2)−C(sp^3) bonds using unactivated substrates remains unknown, yet the synthetic potential of such transformation is clear.

In order to identify the conditions for glycosyl cross-coupling with anomeric stannanes, we used β-D-glucose nucleophile **13** and diphenyliodonium salts **14** (Table 1). Our initial catalyst identification studies focused on control of the undesired β-elimination of the C2 benzyloxy group using a biaryl phosphine ligand. These reactions were conducted in the presence of a stoichiometric amount of a copper additive which often exerts positive effects on the Stille reaction.[33] We also hypothesized that an inorganic fluoride source might facilitate the transmetalation step and quench the tin byproduct. Thus, 2 equiv of KF were added. From the optimization studies, BrettPhos[34] ligands resulted in no detectable amounts (entries 1 and 2) or low yields (entry 3) of the desired *C*-glycoside **7** and resulted in full consumption of **13** to D-glucal.

Gratifyingly, JackiePhos **L4**[35] was found to result in an excellent yield of the product **15** (93%) and exclusive (^{1}H NMR) β-selectivity was observed. Further optimization studies revealed that no other ligand tested, regardless of their size or electronic nature, could compare to **L4** (entries 5−10). For the cross-couplings described in Table 1 to reach full consumption of **13**, reaction times up to 72 h were required. However, for all ligands tested only the β-anomer was detected. We also wondered if the counterion in the iodonium salt **14** exerted any impact on the yield of this process. To this end, we prepared tetrafluoroborate **14b**, tosylate **14c**, and hexafluorophosphate **14d** salts and engaged them in the cross-couplings under the previously optimized conditions (entries 11−13). We found that the triflate salt **14a** was the optimal reagent for the glycosyl C(sp^2)−C(sp^3) coupling resulting in the best yield. This observation is consistent with previous reports on the reactions of iodonium tosylates which state that they are sluggish in the C(sp^2)−C(sp^2) cross-couplings due to the coordination of the tosyl ion with the electrophilic iodine center.[36,37] Also, to rule out the possibility that Cu alone catalyzes glycosyl cross-coupling, a control reaction was conducted in the absence of Pd (entry 14). The desired product **15** was detected in 8% yield, which substantiates the need for a Pd catalyst. The optimized conditions are user-friendly, and no special precautions are needed; the glycosyl cross-coupling can be conducted using commercially available 1,4-dioxane without additional purifications and on a 1 mmol scale with no impact on yield (85%) or selectivity.

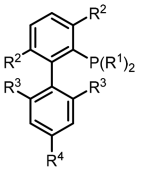
Having established a set of conditions that resulted in a transfer of anomeric configuration from the anomeric

Table 1. Optimization of Glycosyl Cross-Coupling[a]



entry	iodonium		ligand		yield [%][b]
1	**14a**	OTf	L1	AdBrettPhos	N.D.
2	**14a**	OTf	L2	BrettPhos	N.D
3	**14a**	OTf	L3	tBuBrettPhos	10
4	**14a**	OTf	L4	JackiePhos	93 (89)[c]
5	**14a**	OTf	L5	XPhos	10
6	**14a**	OTf	L6	tBuXphos	19
7	**14a**	OTf	L7	JohnPhos	9
8	**14a**	OTf	L8	CyJohnPhos	N.D.
9	**14a**	OTf	L9	RuPhos	14
10	**14a**	OTf	L10	SPhos	14
11	**14b**	BF_4	L4	JackiePhos	56[c]
12	**14c**	OTs	L4	JackiePhos	N.D.
13	**14d**	PF_6	L4	JackiePhos	49[c]
14	**14a**	OTf	L4	JackiePhos	8%

ligand	R^1	R^2	R^3	R^4
AdBrettPhos	Ad	OMe	*i*-Pr	*i*-Pr
BrettPhos	Cy	OMe	*i*-Pr	*i*-Pr
tBuBrettPhos	*t*-Bu	OMe	*i*-Pr	*i*-Pr
JackiePhos	3,5-$(CF_3)_2C_6H_3$	OMe	*i*-Pr	*i*-Pr
XPhos	Cy	H	*i*-Pr	*i*-Pr
tBuXphos	*t*-Bu	H	*i*-Pr	*i*-Pr
JohnPhos	*t*-Bu	H	H	H
CyJohnPhos	Cy	H	H	H
RuPhos	Cy	H	O-*i*Pr	H
SPhos	Cy	H	Me	H



[a]General conditions: **13** (1.5 equiv), iodonium salt (1 equiv), $Pd_2(dba)_3$ (5 mol %), ligand (20 mol %), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane (0.05 M). [b]NMR yield. [c]Isolated yield. N.D. = not detected.

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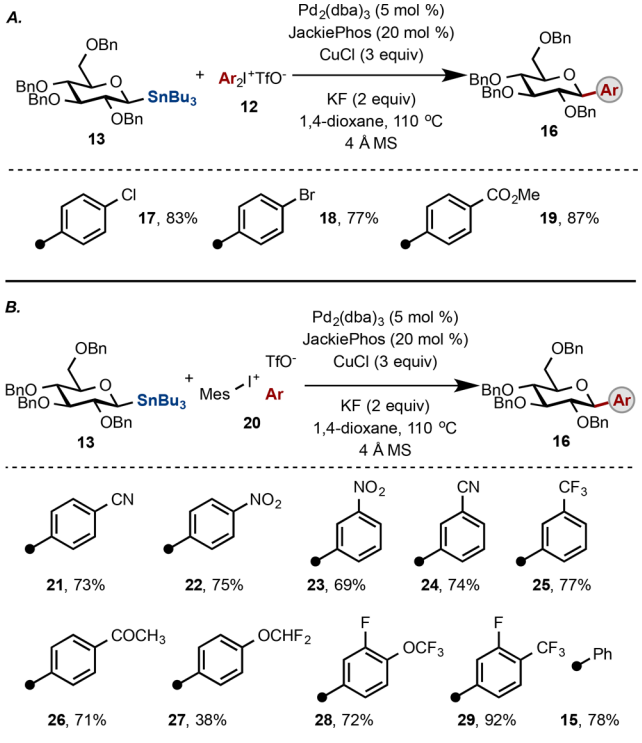
Org. Lett. 2018, 20, 1936−1940

nucleophiles, we next investigated the substrate scope (Scheme 2). First, we tested the scope of iodonium partners that could

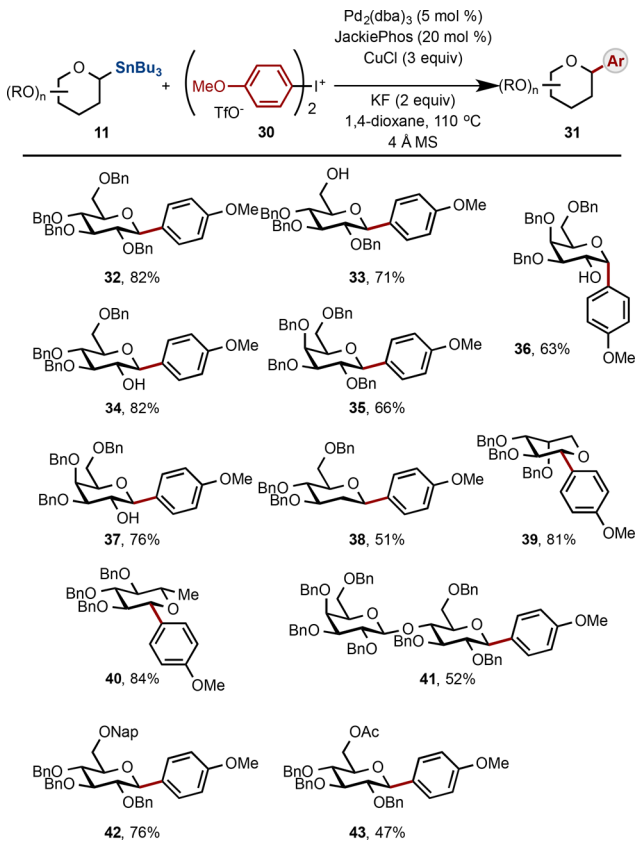
Scheme 2. Scope of *C*-Glycosylation with Symmetrical (A) and Unsymmetrical (B) Iodonium Triflates



be engaged in the cross-couplings.[38,39] Scheme 2A lists examples of reactions with various symmetrical iodonium salts that were engaged in reactions with β-D-glucose **13**. For all examples reported, not only good to excellent yields could be obtained but also uniformly high levels of retention were[40,41] detected in favor of the β-anomer (^{1}H NMR). One of the main limitations of symmetrical iodonium salts is the loss of one aryl group that cannot participate in the cross-coupling reaction. However, it is important to highlight that aryl iodoniums bearing chlorine and bromine were tolerated with excellent halogen regioselectivity (**17** and **18**). Unsymmetrical iodonium triflates containing hindered (e.g., 2,4,6-trimethylphenyl, mesityl) groups have been reported to transfer the sterically more accessible group.[42−45] Thus, we used a series of unsymmetrical reagents (Scheme 2B) that contained a mesityl group and an aryl moiety. As expected, the smaller aryl group was exclusively transferred into the anomeric position for electron-poor (**21**−**26**), electron-rich (**27**), and disubstituted aryls (**28** and **29**). For comparison, unsymmetrical phenyl mesityl iodonium triflate furnished the *C*-phenyl glycoside **15** in a yield lower (78%) than the symmetrical salt **14a**.

Next, we tested the scope of the cross-coupling reaction using various anomeric nucleophiles (Scheme 3). We were pleased to find that configurationally stable 1,2-*trans* anomeric stannanes derived from D-glucose (**32**−**34**), D-galactose (**35**−**37**), D-arabinose (**39**), L-fucose (**40**), and even disaccharides (D-lactose, **41**) underwent clean conversion into the corresponding *C*-aryl glycosides with retention of anomeric configuration. Similarly, the high transfer of anomeric configuration from the α-stannane resulted in the synthesis of *C*-galactoside **36**. 2-Deoxy sugars known for their difficult

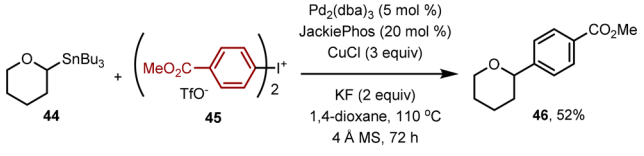
Scheme 3. Scope of *C*-Glycosylation with Anomeric Stannanes



control of the anomeric configuration were easily prepared under the optimized conditions without any detectable erosion of anomeric configuration (**38**). The unique feature of our method is its tolerance and compatibility with free hydroxyl groups, unlike other technologies that rely on the nucleophilic addition to glycosyl acceptors. Thus, partially protected anomeric stannanes with free hydroxyl groups at C6 (**33**) and C2 (**34**, **36**, **37**) were successfully converted into the *C*-glycosides with consistently high anomeric control. Also, other protecting groups such as 2-methylnaphthyl (**42**) and acetyl (**43**) were tolerated. Our method is also characterized by high chemoselectivity; we were unable to detect any *O*-arylation products for substrates that contain free hydroxyl groups.[46,47]

Because the cross-coupling with complex saccharides proceeded with excellent selectivities, we wondered if our general reaction conditions could be extended to simple α-alkoxy substrates (Scheme 4). Diaryliodonium substrates have been engaged in reactions with allyl stannanes, but to the best of our knowledge, reactions with simple alkoxy stannanes have not been reported. To this end, tetrahydropyranosyl stannane **44** and symmetrical iodonium triflate **45** were exposed to the

Scheme 4. Cross-Coupling of Stannane 44



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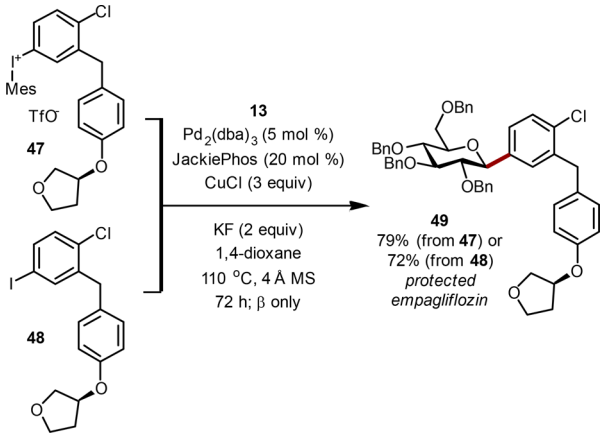
optimized reaction conditions and furnished the expected product **46** in 52% yield.

Finally, to demonstrate the utility of the cross-coupling reaction with iodonium salts, we prepared protected empagliflozin **49** (Scheme 5). Empagliflozin is a commercial

Scheme 5. Synthesis of Empagliflozin



antidiabetic drug that acts as an inhibitor of sodium-glucose cotransporter 2.[48] This compound was prepared via addition of a Grignard reagent to gluconolactone followed by a silane reduction.[49] The optimized conditions were used in a reaction between mesityl iodonium **47** and furnished **49** in 79% yield as a single anomer. The same conditions applied to aromatic iodide **48** furnished **49** in 7% lower yield but with exclusive β-selectivity. These results demonstrate the utility of the iodonium triflates in the cross-coupling reactions even in the case of complex substrates and present a viable alternative to the current methodologies for the preparation of bioactive *C*-aryl glycosides.

A few comments regarding the role of JackiePhos in the cross-coupling reactions are noteworthy. The likely participation of the bulky ligand is to reduce the elimination pathway from the putative anomeric organopalladium intermediate. We speculate that the anomeric organocopper intermediate formed in a transmetalation step from a C1 stannane is configurationally stable and is not a viable substrate for β-elimination. However, addition of an amine base (Et_3N, pyridine) leads to a rapid elimination to the glycal, most likely directly from the anomeric stannanes. The NMR analysis of the β-D-glucose stannane indicates a predominant $^4C_1$ conformer in which the β-elimination is disfavored due to suboptimal orbital overlap. We postulate that similar steric and conformational effects are operational for an anomeric palladium intermediate; thus, a bulky ligand on Pd prevents the flip of a metal into the axial position, which could lead to a rapid elimination of the benzyloxy group before the C−C bond is established.

To conclude, we have developed a stereoretentive *C*-glycosylation reaction of anomeric stannanes and diaryliodonium triflates that proceeds with exclusive retention of anomeric configuration for both anomers of mono- and disaccharides. These reactions tolerate partially protected saccharide donors and represent a significant advance in the stereocontrolled preparation of *C*-glycosides. In addition, this method represents an advance in the field of hypervalent iodine chemistry by demonstrating a stereospecific C(sp^2)−C(sp^3) bond formation. The glycosyl cross-coupling is ideally suited for late-stage diversification and applications in drug discovery campaigns, as glycans can be introduced in a predictable and programmed fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00475.

Experimental details and copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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