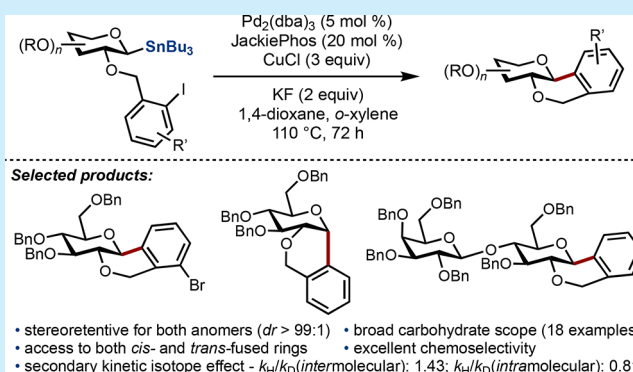# Stereoretentive Intramolecular Glycosyl Cross-Coupling: Development, Scope, and Kinetic Isotope Effect Study

Duk Yi,[†] Feng Zhu,[†] and Maciej A. Walczak*[ORCID]

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309, United States

Ⓢ *Supporting Information*

ABSTRACT: A series of cyclic *C*-glycosides were synthesized using the palladium-catalyzed stereoretentive intramolecular glycosylation of aryl iodides by employing a bulky phosphine ligand. A variety of functional groups are tolerated in the reaction, and enantioenriched anomeric nucleophiles could be coupled without erosion of optical purity. This study offers a unified method to access both cis- and trans-fused rings by capitalizing on the stereoretentive nature of the Stille reaction. In addition, competition experiments for intermolecular and intramolecular cross-couplings revealed secondary KIEs of 1.43 and 0.81, respectively, suggesting a profoundly different steric congestion at the transition state.

Selected products:

- stereoretentive for both anomers (*dr* > 99:1)
- access to both *cis*- and *trans*-fused rings
- secondary kinetic isotope effect - k_H/k_D(*inter*molecular): 1.43; k_H/k_D(*intra*molecular): 0.81
- broad carbohydrate scope (18 examples)
- excellent chemoselectivity

S accharide mimicry through modifications of the labile glycosidic C−O bond constitutes one of the most successful strategies in medicinal chemistry and chemical biology.[1] Although many approaches focus on C−O linkage modification, functionalization of the anomeric position via a C−C bond has become a routine process for generating *O*-glycoside surrogates due to the enhanced in vivo stabilities and predominance of *C*-glycosides in nature.[2−4] Internal *C*-glycosides comprise a major subset of bioactive natural products that include molecules such as paecilomycin B (**1**),[5−8] bergenin (**2**),[9] chafuroside A (**3**),[10,11] and the papulacandins[12−14] (e.g., **4**) (Figure 1). Because of the
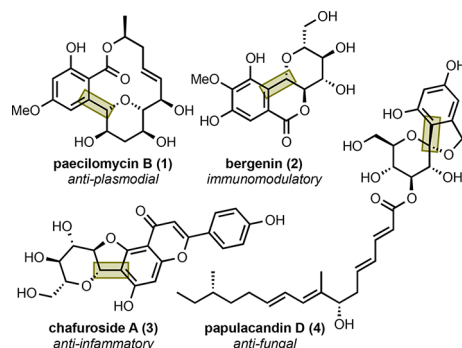

Figure 1. Selected natural products featuring cyclic aryl *C*-glycosides.

unique roles and diverse activities of *C*-glycosides, various methods for their preparation have been described. Representative examples include the addition of Grignard or organolithium reagents to glycolactones followed by stereoselective reduction, opening of 1,2-*anhydro* sugars, and intramolecular glycosylation with electron-rich arenes.[8,15−18]

The synthesis of cyclic *C*-glycosides is often accomplished by the cyclization of an electron-rich arene group linked via the C2 position (Scheme 1A). Such intramolecular *C*-glycosylations

Scheme 1. Selected Methods for the Synthesis of Cyclic Aryl *C*-Glycosides
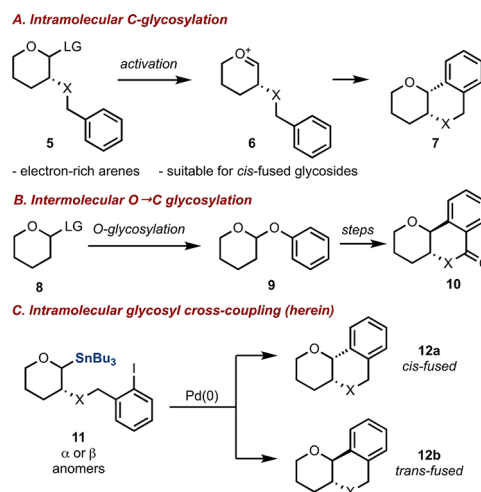
exploit the steric constraints imposed by the linked intermediate **6** to exclusively prepare *cis*-fused systems. Currently, this strategy holds no viable solution for introducing the five- and six-membered heterocyclic trans-fused rings commonly found in many natural products.[19−23] Methods to establish the trans configuration are based on intermolecular *O*-glycosylation

followed by an O → C migration and subsequent cyclization (Scheme 1B).[24] Although these methods present a viable solution to the specific synthetic problem at hand, they often lack generality and can result in suboptimal selectivities at the anomeric position. Furthermore, the functional group tolerance and incompatibility with free amide or hydroxyl groups presents another major limitation.

We hypothesized that a standardized protocol for the synthesis of both cis- and trans-fused cyclic *C*-glycosides could be developed based on stereospecific glycosyl cross-coupling that capitalized on the stereoretentive transfer of anomeric configuration from C1 stannanes into a new C−C bond (Scheme 1C). Herein, we report a stereospecific intramolecular glycosyl cross-coupling reaction with anomeric nucleophiles and aryl halides that proceeds for both anomers of the saccharides used and results in excellent anomeric selectivities.

Unlike intermolecular cross-couplings, securing high anomeric selectivity without compromising yield in an intramolecular pathway is inherently more challenging. For instance, the steric constraints imposed on the C−Sn (or C−Cu) to C−Pd transmetalation and reductive elimination may prevent efficient C−C bond formation due to the increased likelihood of competing elimination reactions. Furthermore, steric congestion within the anomeric organopalladium intermediate might also compromise the stereoretentive nature of the glycosyl cross-coupling reaction.

To test our proposal, we set out to investigate a reaction of the glycosyl stannane **13** using Pd$_2$(dba)$_3$ (5 or 7.5 mol %) as the precatalyst and JackiePhos (20 or 30 mol %) as the ligand to suppress unwanted glycal formation (Table 1).[25−29] We

product. As a result, our optimization studies were aimed at suppressing the undesired elimination pathway.

Performing the reaction in a more concentrated system led to a decrease in overall yield by 10% with minimal reduction of elimination product (entry 3), whereas a more diluted condition (entry 5) gave a comparable result to entry 1. During this time, we observed a unique effect of the solvent on the rate of C2 elimination: introduction of an aromatic solvent (*o*-xylene) resulted in complete suppression of the competing pathway (entry 2). We reasoned that, similar to the role of a bulky phosphine ligand, the aromatic solvent serves to stabilize the C1-organopalladium intermediate in addition to removing the insoluble Bu$_3$SnF byproduct. After analyzing the varying stoichiometric systems of cosolvents, we determined that a 5:1 ratio of dioxane and *o*-xylene (entry 8) was the condition of choice for the cross-coupling. The presence of a polar solvent in the mixture ensures that optimal concentrations of fluoride ion are available to carry out efficient activation of the tin group. In addition, stoichiometric amounts of copper chloride are necessary for the reaction to take place. The copper additive likely affects a preliminary transmetalation reaction from the organostannane to generate a more reactive organocopper intermediate; alternatively, copper could also facilitate activation of the organopalladium intermediate (Pd−F).[26,30,31] The optimized conditions could be conducted without additional precautions and are scalable (1 mmol) without a detrimental impact on the yield (63%) or selectivity. In all entries reported in Table 1, the formation of a single anomer (β) was detected using ¹H NMR of unpurified reaction mixtures.

Having established the optimal set of reaction conditions for affecting these reactions, we next investigated the scope of the cross-coupling. First, we wanted to better understand the relative reactivities of the different aryl halides in the intramolecular glycosyl cross-coupling manifold (Table 2).

Table 1. Optimization of Intramolecular Glycosyl Cross-Coupling with 13[a]

entry	CuCl (equiv)	T (°C)	1,4-dioxane: *o*-xylene	concentration (M)	yield (%)[b]	D-glucal (%)[b]
1	3	110	1:0	0.05	60	18
2	3	110	1:1	0.05	37	N.D.
3	3	110	1:0	0.1	50	14
4	2	110	1:0	0.05	60	13
5	3	110	1:0	0.03	61	18
6	3	110	2:1	0.03	52	6
7	3	125	2:1	0.03	53	9
8	3	110	5:1	0.03	61 (60)[c]	11

[a]General conditions: **13** (0.1 mmol), Pd$_2$(dba)$_3$ (5 mol %), JackiePhos (20 mol %). [b]NMR yield. [c]Isolated yield. N.D. = not detected.

Table 2. Cross-Coupling of β-D-Glucose Stannane 15[a]

entry	X	yield (%)
1	Br (**15a**)	9[b]
2	I (**15b**)	52

[a]Conditions from Table 1, entry 8. [b]NMR yield.

During our studies, we established that electron-poor arenes resulted in higher yields of the intermolecular cross-coupling product compared to those of electron-rich arenes. This result prompted us to test whether an activated electron-poor arene such as **15** could easily cross-couple with bromine as the halide source. Thus, bromoarene **15a** was subjected to glycosylation under the standard conditions and resulted in 9% conversion to *C*-glycoside **16**, whereas iodoarene **15b** furnished **16** in 52%. These results are consistent with previous findings regarding the reactivity of aryl halides in the Stille coupling. The striking difference in yield between the two halides suggested the need for iodoarene substrates, and thus, bromoarenes were not pursued further.

attributed these observations to the sterics and electronic nature of the phosphine that stabilizes the anomeric organopalladium species and promotes the reductive elimination leading to the formation of a C−C bond.[26] Under these conditions, desired product **14** was obtained in 60% yield with exclusive β-selectivity (entry 1). Despite the encouraging initial results, a significant amount of D-glucal was also detected as a competitive side-

Scheme 2 lists examples of reactions with variously substituted iodoarenes that were engaged in cross-coupling

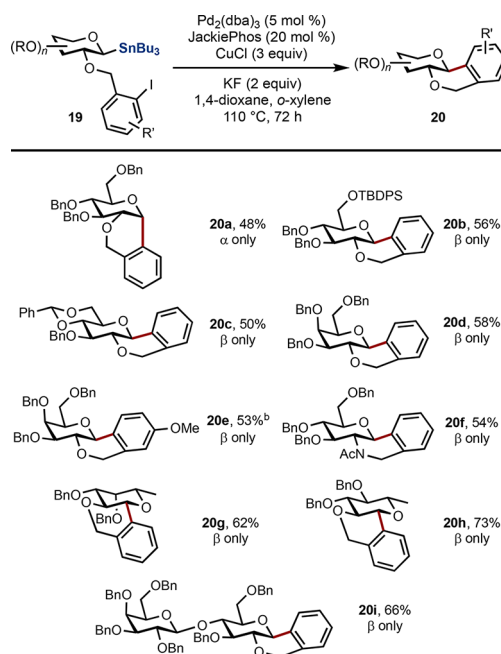## Scheme 2. Scope of *C*-Glycosylation with Iodoarenes 17[a]
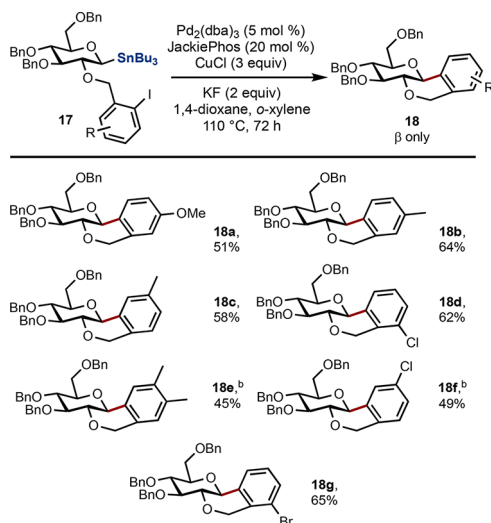
[a]General conditions: **17** (0.1 mmol), Pd$_2$(dba)$_3$ (5 mol %), JackiePhos (20 mol %), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, *o*-xylene, 110 °C. [b]Pd$_2$(dba)$_3$ (7.5 mol %), JackiePhos (30 mol %).

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

[a]General conditions: **19** (0.1 mmol), Pd$_2$(dba)$_3$ (5 mol %), JackiePhos (20 mol %), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, *o*-xylene, 110 °C. [b]Pd$_2$(dba)$_3$ (7.5 mol %), JackiePhos (30 mol %).

with glycosyl stannanes of structure **17**. Substrates bearing an electron-donating methoxy group para to the iodide are often difficult substrates for these palladium-catalyzed reactions;[32,33] however, cyclization proceeded in good yield to give desired product **18a** in 51%. Alkyl-substituted substrates bearing a methyl group meta and para to the iodide also furnished their respective *C*-glycosides with the *meta*-alkylated substrate **18c** giving a slightly lower yield than the *para*-alkylated substrate **18b**. Halogenated anomeric nucleophiles were also well-tolerated under the standardized conditions and provided *C*-glycosides **18d**, **18f**, and **18g** in 49−65% yield. Dialkyl *C*-glycoside **18e** was also formed, but the yield was lower than for the monoalkyl substrates. It appears that electronic modifications of the aromatic ring play only a small role in comparison to the steric effects imposed by various substitutions (e.g., **18a** and **18e**).

Next, we tested the scope of the glycosyl cross-coupling reaction using various anomeric nucleophiles **19** (Scheme 3). We were pleased to find that all of the stannanes tested gave rise to retention of anomeric configuration (>99:1 dr) without any detectable erosion of stereochemistry at the anomeric carbon for both anomers. α-Stannanes derived from D-glucose successfully cyclized to give the cis ring (**20a**) in 48% yield. Interestingly, a silyl ether protected 1,2-*trans* glucosyl stannane was also well-tolerated in this system despite the presence of a fluoride source; it gave the protected *C*-glycoside **20b** in 56% yield with no detectable amounts of deprotected 6′-OH counterpart. Furthermore, a benzylidene acetal group (**20c**) was compatible with the standard conditions. Other configurationally stable 1,2-*trans* anomeric stannanes derived from D-galactose (**20d**, **20e**), D-glucosamine (**20f**), L-fucose (**20g**), and D-quinovose (**20h**) underwent conversion to the corresponding *C*-glycosides. To our delight, even a disaccharide such as the D-lactose stannane (**20i**) was cleanly cyclized.

To better understand the structural constraints of the cyclization reactions with 1,2-*cis* and 1,2-*trans* isomers, we performed in silico studies. DFT calculations (B3LYP/6-311++G**//B3LYP/6-31G*) performed for the most stable conformers of GlcNAc amides revealed that cis product to be more

stable by ΔG_{298} 4.9 kcal/mol. Reverse stability preferences were observed for D-glucose *C*-glycosides **14** and **20a** for which the trans isomer is more stable by ΔG_{298} 2.8 kcal/mol. However, in the case of 1,2-*cis* anomer, the formation of glycals accounts for ∼15% more of the material. These observations indicate that the rate of the cyclization is heavily influenced by the rate of transmetalation from sterically congested stannanes.

Further mechanistic studies were focused on the analysis of secondary kinetic isotope effects (SKIEs). First, the preparation of labeled stannanes **26** and **27** is presented in Scheme 4. D-Glucal **21** was converted to labeled compound with excess *t*-BuLi and quenched with D$_2$O, resulting in **22** with >99.9% incorporation of deuterium at C1. The silicon protective groups in **22** were removed, and the triol was first converted to ester **23** because of the ease of purification and then into ether **24**. This intermediate served as the precursor for the subsequent steps that introduced the Bu$_3$Sn group in the anomeric carbon. Thus, epoxidation of D-glucal **24** with DMDO/Oxone[34] followed by opening with a nucleophilic tin reagent (Bu$_3$SnMgMe) afforded alcohol **25** in 30% yield (over two steps). We elected to protect the C2-OH position as benzyl and 2-iodobenzyl ethers **26** and **27**.

The kinetic isotope effects were studied in competition experiments for both inter- and intramolecular cross-couplings and secondary KIEs of 1.43 and 0.81 were observed for reactions with **26** and **27**, respectively (Scheme 4). On the basis of these experimental results, we propose that the intramolecular cross-coupling is more sensitive toward steric hindrance than the intermolecular variant. The vibrational amplitude of a *C-D* bond is smaller than that of *C-H* bond, which in turn makes deuterium appear to be smaller than a protium atom in some contexts.[35,36] Mechanistically, the oxidative addition of Pd(0) occurs on the aryl iodide followed by a transmetalation step of the anomeric stannane or the anomeric copper. We believe that, at this stage,

Scheme 4. Synthesis of C_1-Deuterated Anomeric Stannane
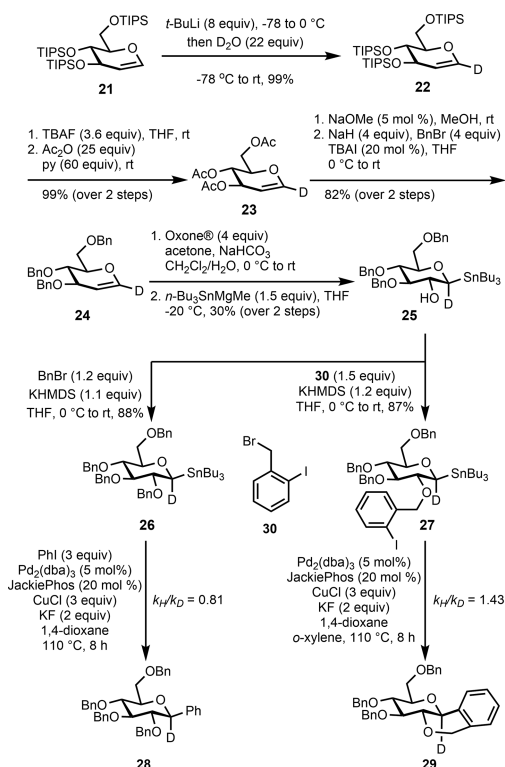
the linked intermediate of the intramolecular pathway is in a much more sterically congested environment than the bimolecular transmetalation involved in the intermolecular pathway. As a result, an inverse secondary KIE was seen with the intramolecular competition experiment, where the less crowded anomeric metal species can undergo transmetalation in a more facile process and perhaps from a different trajectory.

In summary, we have described a direct and highly stereoselective synthesis of cyclic *C*-glycosides using both anomers of common saccharides. This reaction is characterized by unusually high anomeric selectivities that originate from stereoretentive transfer of the anomeric configuration at both C1 anomers. The kinetic analysis revealed that the intramolecular Stille coupling requires higher steric constraints at the anomeric carbon despite its exceptionally high stereospecificity. The intramolecular cross-coupling is ideally suited for applications in target-oriented synthesis, and ongoing studies in this area will be reported in due course.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01927.

> Experimental procedures, characterization data of all new compound and copies of 1D and 2D NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: maciej.walczak@colorado.edu.

ORCID Ⓘ

Maciej A. Walczak: 0000-0002-8049-0817

Author Contributions

†D.Y. and F.Z. contributed equally to this work.

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