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Article

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Glycosyl Cross-Coupling of Anomeric Nucleophiles – Scope, Mechanism and Applications in the Synthesis of Aryl *C*-glycosides

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ABSTRACT: Stereoselective manipulations at the C1 anomeric position of saccharides are one of the central goals of preparative carbohydrate chemistry. Historically, the majority of reactions forming a bond with anomeric carbon has focused on reactions of nucleophiles with saccharide donors equipped with a leaving group. Here, we describe a novel approach to stereoselective synthesis of *C*-aryl glycosides capitalizing on the highly stereospecific reaction of anomeric nucleophiles. First, methods for the preparation of anomeric stannanes have been developed and optimized to afford both anomers of common saccharides in high anomeric selectivities. We established that oligosaccharide stannanes could be prepared from monosaccharide stannanes via *O*-glycosylation with Schmidt-type donors, glycal epoxides, or under dehydrative conditions with C1 alcohols. Second, we identified a general set of catalytic conditions with $Pd_2(dba)_3$ (2.5 mol%) and a bulky ligand (JackiePhos, 10 mol%) controlling the β-elimination pathway. We demonstrated the glycosyl cross-coupling results in consistently high anomeric selectivities for both anomers with mono- and oligosaccharides, deoxysugars, saccharides with free hydroxyl groups, pyranose and furanose substrates. The versatility of the glycosyl cross-coupling reaction was probed in the total synthesis of salmochelins (siderophores) and commercial anti-diabetic drugs (gliflozins). Combined experimental and computational studies revealed that the β-elimination pathway is suppressed for biphenyl-type ligands due to the shielding of Pd(II) by sterically demanding JackiePhos whereas smaller ligands, which allow for the formation of a Pd-F complex, predominantly result in a glycal product. Similar steric effects account for the diminished rates of cross-couplings of 1,2-*cis* C1-stannanes with aryl halides. DFT calculations also revealed that the transmetalation occurs via a cyclic transition state with retention of configuration at the anomeric position. Taken together, facile access to both anomers of various glycoside nucleophiles, a broad reaction scope, and uniformly high transfer of anomeric configuration make the glycosyl cross-coupling reaction a practical tool for the synthesis of bioactive natural products, drug candidates, allowing for late-stage glycodiversification studies with small molecules and biologics.

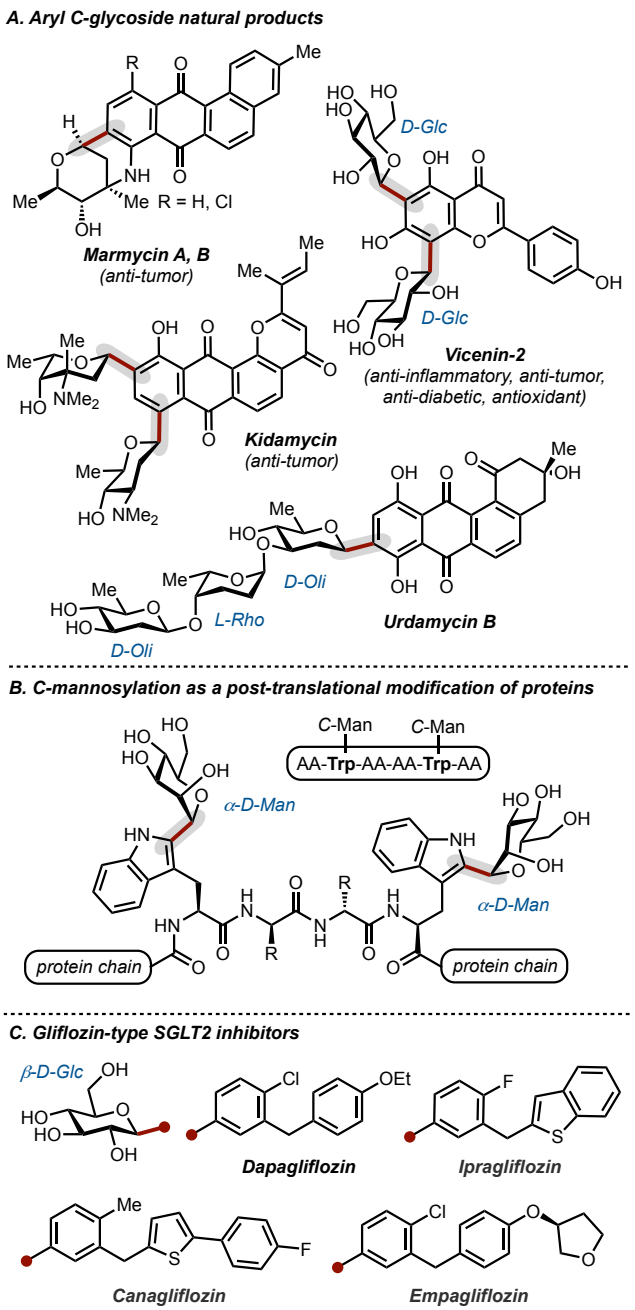
INTRODUCTION

Although the chemical synthesis of saccharides is considered a mature branch of organic chemistry dating back to the works of Michael[1] and Fischer,[2] stereoselective manipulations at the anomeric position continue to present a formidable challenge. A special class of glycosides containing a C-C bond between C1 carbon of a saccharide ring termed *C*-glycosides are found in numerous bioactive natural products such as anti-tumor antibiotics[3-4] and glycosylated flavonoids[5-8] (Figure 1A). Many bioactive aryl *C*-glycosides feature different *C*-glycoside groups and oligosaccharide chains attached to an aromatic core.[9] Other well-established examples of *C*-glycosylation include *C*-mannosylation of tryptophan in glycoproteins,[10] a posttranslational modification found in proteins belonging to the TRC family (Figure 1B), aryl *C*-nucleosides,[11] and *C*-glycosyl porphyrin glycoconjugates.[12] In the 2010s, aryl *C*-glycosides derived from phlorizin, a natural β-D-glucoside, were introduced into the market in the United States as anti-diabetic drugs inhibiting sodium/glucose cotransporter 2 (SGLT2, Figure 1C).[13] Because *C*-glycosides (unlike *O*-glycosides) are not stabilized by (exo)anomeric effect yet show similar conformational preferences around the exocyclic C-C bond as their natural counterparts with a C-O bond, the replacement of a hydrolytically labile C-O bond with a stable C-C linkage is an effective strategy to improve physiological stability and efficacy.[14-16]

Due to the unique position of *C*-aryl glycosides as privileged glycomimetics, various methods have been described to stereoselectively introduce aryl groups into the anomeric position.[17-22] The most common approaches focus on (i) nucleophilic addition of an organometallic reagent (e.g., organozinc)[23-24] to anomeric halides catalyzed by Ni,[25-28] Co, Pd, and Fe[29] complexes, (ii) addition of a nucleophile to a lactone followed by reduction of the resultant acetal, and (iii) Friedel-Crafts-type alkylation of electron-rich arenes or direct phenol *O*-glycosylation followed by a stereoselective O→C rearrangement.[30-31] In the context of $C(sp^2)$-$C(sp^2)$ cross-couplings, reactions of glycals in the form of a C1-nucleophile[32] or a C1-electrophile[33-35] have been described. These methods often represent a viable solution to a particular synthetic problem and the key limitations such as the control of anomeric configuration dependent on the identity of the saccharide and the C2 substituents, functional group compatibility of the nucleophilic reagents, and the need for additional manipulations required to establish a proper carbohydrate core prevent their widespread use.

In order to overcome these challenges, we posited that a method in which the configuration of the *C*-glycoside product could be established based solely on the configuration of the substrate and controlled by a stereospecific process allowing for a highly stereoretentive (or stereoinvertive) transformation of the saccharide substrate would offer a promising solution.[36-37] Introduction of glycans with any anomeric configuration with

Figure 1. Representative aryl *C*-glycosides



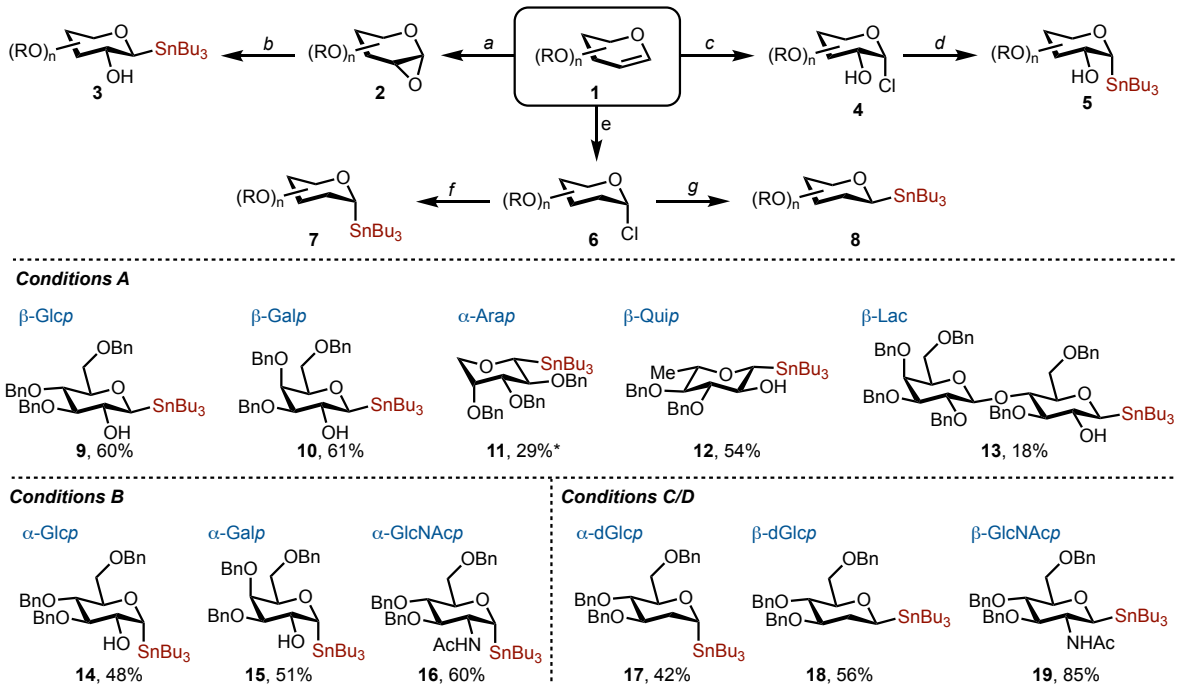
high selectivity and functional group compatibility and without the need for additional (de)protection manipulations[38] provides the opportunity to append glycans to a broad range of acceptors at the end of synthetic sequences and allows for late-stage glycodiversification of small molecules and biologics applicable to high-throughput format and library preparations. Because installation of a (pseudo)halide or heteroatom-based leaving group at the anomeric position inevitably leads to scrambling of anomeric configuration of the *C*-glycoside products,[39] an alternative strategy based on umpolung of the anomeric carbon was pursued. Successful realization of this proposal requires (a) access to both anomers (α and β) of stable anomeric nucleophiles and (b) a highly stereospecific C-C bond forming process.

When considering a stereoretentive cross-coupplng method of anomeric nucleophiles without anion-stablizing groups, the identity of the metal at the carbohydrate C1 postions has to be taken into account.[40] Saccharide C1-organolithium reagents have been described[41] but have limited scope due to poor configurational stablity at temperatures over -30 °C and incompatibility with typical protective groups used in preparative carbohydrate chemistry. Organolithium reagents derived from C2-protected saccharides (e.g., benzyl ethers) undergo a facile elimination of the oxygen group and the formation of a glycal, and only C2-OH or C2-deoxy sugars are a reliable source of anomeric organolithium reagents.[42] An anomeric boronic ester derived from D-glucose was reported in a patent,[43] and Chirik[44] and Molander[45-46] described the preparation of pyranose- and chromanone-based boronic esters and borate salts, but these systems lack the critical C2 oxygen substituent present in most saccharides. Anomeric silicon reagents have been reported only for alkyl- and arylsilyl groups attached at the C1 position.[47-48] Anomeric stannanes described by Sinaÿ,[49] Kessler,[50-51] and Vasella[52] can be prepared through the use of electrophilc and nucleophillic tin reagents. Given the highly stereoretetive nature of reactions with chiral C(sp^3) stannanes,[53-61] their configurational stability, and the ease of preparation, C1 stannanes emerge as the optimal reagents for the studies on stereospecific glycosyl cross-coupling reactions. The development of a coupling process utilizing anomeric nucleophiles is a promising alternative to the nucleophilic addition/displacement methods - provided that the undesired β-elimination could be controlled or suppressed by a catalyst and/or a ligand. Here, we describe a full report detailing the development of the stereoretentive glycosyl cross-coupling reaction, applications in the synthesis of aryl *C*-glycosides derived from mono/oligosaccharides, and mechanistic/computational studies on the origin of high stereoselectivity and ligand preference.

RESULTS AND DISCUSSION

Synthesis of anomeric stannanes. Our study began with the synthesis of anomeric stannanes as the substrates for the glycosyl C(sp^3)-C(sp^2) cross-couplings. As an anomeric nucleophile, the tri-*n*-butyltin group was selected although smaller groups such as Me_3Sn (but not carbastannatranes)[62] could also be introduced into the C1 position with the synthetic sequences described below. In order to access both anomers of common monosaccharides, a series of transformations depicted in Scheme 1 was developed using glycal intermediate **1**. To prepare the 1,2-*trans* anomers **3**, epoxidation of per-*O*-benzyl glycals **1** followed by opening with $Bu_3SnMgMe$ (Conditions A) resulted in the synthesis of β-D-glucose (**9**), β-D-galactose (**10**), α-D-arabinose (**11**), β-L-olivose (**12**), and β-D-lactose (**13**) stannanes although the yield of the disaccharide **13** was low (18%). The synthesis of the 1,2-*cis* stannanes also commenced from glycal **1**, which was converted into thermodynamic α-chlorides **4** with sat. HCl in $Et_2O/CHCl_3$ at 0 °C. The chlorides **4** were then exposed to a strong base (*n*-BuLi) to remove the alcoholic or amide (for D-GlcNAc) protons and the resultant lithium alkoxide/amide was treated at -100 °C with lithium naphthalenide Li($C_{10}H_8$) followed by quenching with Bu_3SnCl. This set of conditions (Conditions B) led to a transfer of anomeric configuration from the anomeric halides **4** to the stannanes **5**. The removal of the alcoholic proton is a necessary step to assure high yields of this transformation and under the

Scheme 1. Synthesis of anomeric stannanes



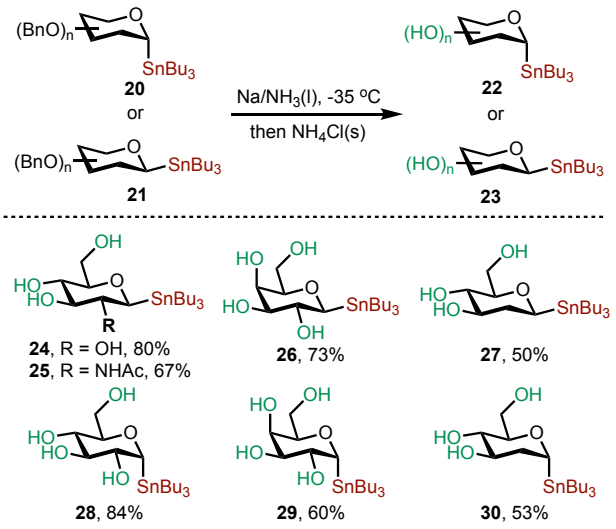
Reagents and conditions: (a) Oxone® (4.0 equiv), acetone, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C to rt; (b) *n*-$Bu_3SnMgMe$ (1.5 equiv), THF, - 20 °C; (c) i. OsO_4 (2.5 mol%), NMO (2.5 equiv), acetone/*t*-BuOH/H_2O (21:9:1), 23 °C, ii. HCl(g), $Et_2O/CHCl_3$, 0 °C; (d) *n*-BuLi (1.2 equiv), $Li(C_{10}H_8)$ (2.5 equiv), THF, -100 °C then *n*-Bu_3SnCl (3.5 equiv), THF, -100 °C to rt; (e) i. HBr/HOAc/THF, then Na_2CO_3, (ii) $SOCl_2$ (2.0 equiv) $CHCl_3$/PhMe (3:1), 0 °C; (f) $Li(C_{10}H_8)$ (3.5 equiv), THF, -78 °C then *n*-Bu_3SnCl (3.5 equiv), -78 °C; (g) *n*-Bu_3SnLi, THF. *__11__ was prepared using conditions A followed by protection of C2-OH with BnBr (2.0 equiv), KHMDS (1.5 equiv), THF, 0 °C to rt, 2.5 h.

optimized conditions, α-D-glucose (**14**), α-D-galactose (**15**), and α-D-GlcNAc (**16**) stannanes were prepared in high anomeric selectivities (α:β > 99:1).

To access 2-deoxysaccharides, the sequence of reactions described above was repeated starting again from glycal substrate **1** which was converted into C1-alcohol ($TsOH/H_2O$) and anomeric chloride **6**, followed by lithium-chloride exchange with $Li(C_{10}H_8)$ at -78 °C in THF and a reaction with Bu_3SnCl (α:β > 95:5). Alternatively, the β-anomer **8** was prepared by a displacement with Bu_3SnLi obtained from Bu_3SnH and LDA. This method for the generation of anionic tin reagents was found to result in consistently higher yields of the β-stannanes than the reactions with a nucleophile formed from Bu_3SnCl and Li.[63]

The preparation of the C1 stannanes with free hydroxyl groups is presented in Scheme 2. Typical hydrogenolysis conditions for the removal of *O*-benzyl groups with various heterogeneous and homogenous Pd or Rh catalysts failed to provide a fully deprotected product and only a partial removal of the benzyl ethers and destannylation were observed under ambient and elevated pressures and temperatures. Gratifyingly, we found that the Birch conditions (Na/NH_3) followed by a careful quenching with solid NH_4Cl afforded monosaccharides **24-30** in good yields (50-84%) after chromatographic purification on silica gel. A few observations regarding the stability of anomeric stannanes are noteworthy – fully deprotected saccharides **24-30** are stable at room temperature for at least one year and can be stored indefinitely at -20 °C. All stannanes can be purified by chromatography on silica gel, are stable against air or moisture, and retain anomeric configuration even after extensive heating (150 °C, 4 days, sealed tube) or exposure to light. Some saccharides (e.g., **28**) are crystalline and can be conveniently handled as free-flowing solids.

Scheme 2. Removal of benzyl groups from anomeric stannanes

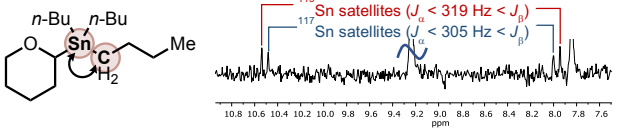


The anomeric configuration of C1-stannanes was established based on the analysis of $^3J(H_1\text{-}H_2)$ and $^1J(C_1\text{-}H_1)$ coupling constants. Unlike *O*-glycosides, the signals of monosaccharide C1 atoms of anomeric stannanes in the ^{13}C NMR spectra are buried in 70-80 ppm region, which also contains other saccharide signals and can be difficult to identify unequivocally without the

use of 2D NMR techniques, thus complicating the structural assignment. Analysis of the ^{13}C NMR data revealed an interesting trend of heteronuclear coupling constants of the C1 position in the *n*-butyl group and anomeric $^{117}Sn/^{119}Sn$ nuclei (Table 1). For the anomeric stannanes in which the tin group occupies the equatorial position in a $^4C_1$ pyranose conformer, the $^1J(^{117}Sn\text{-}C)$ coupling constants are above 305 Hz (319 Hz for $^1J(^{119}Sn\text{-}C)$), whereas the C1-stannanes with the tin group is in the axial position have $^1J(Sn\text{-}C)$ coupling constants below these cut-offs. This general trend was observed for various pyranoses (determined for Glc*p*, Gal*p*, Ara*p*, Qui*p*, GlcNAc*p*) and is independent of the substitution of the hydroxyl or amide groups at any position of the monosaccharide. Similar observations were recorded by Vasella who concluded that the values of $^1J(Sn\text{-}C)$ between anomeric carbon and anomeric tin substituent are larger when the SnR_3 group is located in the equatorial position.[52]

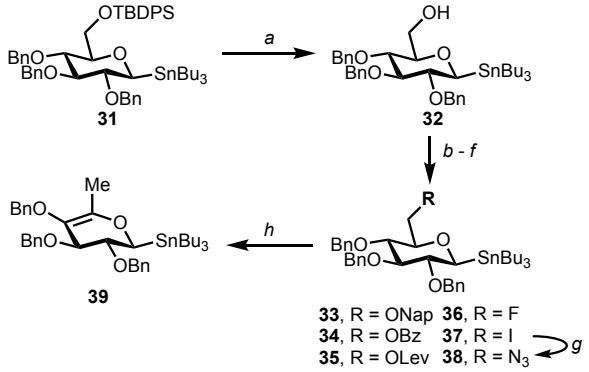
Table 1. Diagnostic $^1J(^{117}Sn\text{-}C)$ and $^1J(^{119}Sn\text{-}C)$ of pyranosyl C1-stannanes.

	Saccharide	C2 Substituent	$^1J(^{117}Sn\text{-}^{13}C)$ (Hz)	$^1J(^{119}Sn\text{-}^{13}C)$ (Hz)
α	α-D-Glc*p*	OH	298.2	312.1
	α-D-Glc*p*	OBn	293.5	307.0
	α-D-Gal*p*	OH	294.8	308.4
	α-D-Gal*p*	OBn	293.8	307.4
	α-D-GlcNAc*p*	NHAc	304.3	318.3
	α-D-dGlc*p*	H	284.4	297.7
β	β-D-Glc*p*	OH	311.9	326.4
	β-D-Glc*p*	OBn	310.9	325.3
	β-D-Gal*p*	OH	311.5	325.8
	β-D-Gal*p*	OBn	310.1	324.6
	β-D-GlcNAc*p*	NHAc	313.6	327.3
	β-D-dGlc*p*	H	306.8	320.6
	β-D-Ara*p*	OBn	308.1	322.4
	β-L-Qui*p*	OH	311.1	325.6
	Free saccharides			
α	α-D-Glc*p*	OH	292.7	305.6
	α-D-Gal*p*	OH	290.5	303.9
	α-D-dGlc*p*	H	283.4	296.5
β	β-D-Glc*p*	OH	311.4	325.9
	β-D-Gal*p*	OH	309.9	324.5
	β-D-dGlc*p*	H	308.6	323.0



Because little is known about the reactivity and stability of anomeric nucleophiles, we investigated reactions of β-glucosyl stannane **31** as a model system to probe its compatibility with common reagents used in preparative carbohydrate chemistry (Scheme 3). Alcohol **32** was obtained in a reaction of 6-OTBDPS protected stannanes **31** in which the silicon group was removed with TBAF (1.1 equiv) without undesired protodestannylation. We found that other silicon-based groups (TIPS, TES) are also compatible with the protocols for the synthesis of anomeric stannanes (Scheme 1) and can be removed with a fluoride anion without a cleavage of the C-Sn bond. These results demonstrate the stability of anomeric stannanes to anhydrous fluoride sources allowing for expansion of the scope of protective groups suitable for the preparation of C1 nucleophiles. C1-stannanes tolerate standard *O*-alkylation and *O*-acylation conditions as demonstrated in the synthesis of protected saccharides **33**-**35** containing 6-ONap, 6-OBz, and 6-OLev groups. Anomeric stannanes are also compatible with strongly basic reagents (KHMDS, LiHMDS, NaH) in *O*-alkylation reactions of the C2-OH positions (no Peterson olefination products observed), halogenation conditions, and small nucleophiles (NaI, NaN_3, TBAI, TBABr). Thus, we synthesized 6-deoxy-6-fluoro-D-glucose **36** in a reaction with DAST (51%), 6-deoxy-6-iodio-D-glucose **37** in a reaction with Ph_3PI_2 (71%), and 6-deoxy-6-azido-D-glucose **38** (65%) suitable for further functionalization via cycloaddition reactions. However, we found that the reaction of iodide **37** with *t*-BuOK resulted in migration of the double bond yielding dihydropyran **39**.

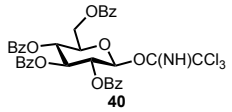
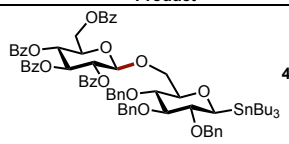
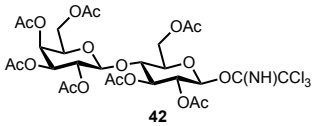
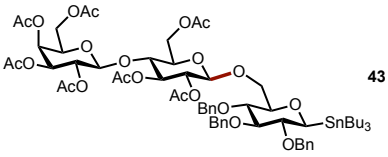
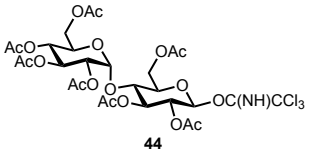
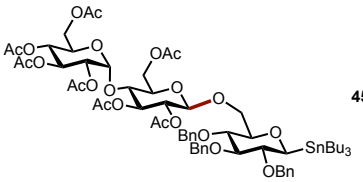
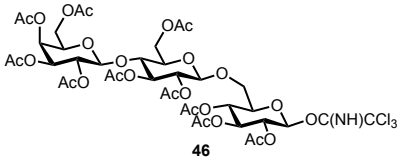
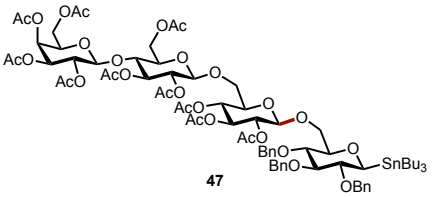
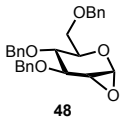
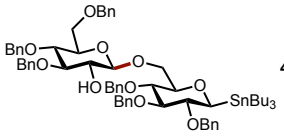
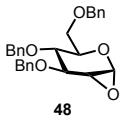
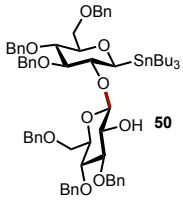
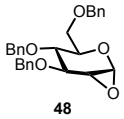
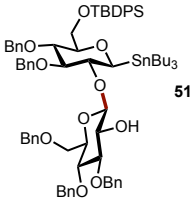
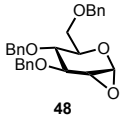
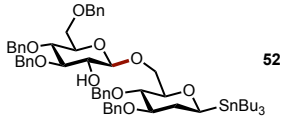
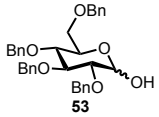
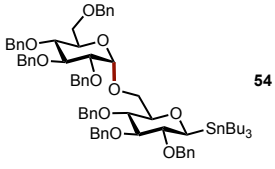
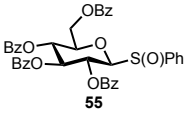
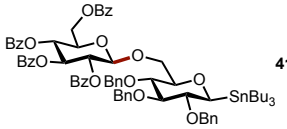
Scheme 3. Conversions of anomeric stannanes



Reagents and conditions: (a) TBAF, THF, 82%; (b) NapBr, KHDMS, THF, 91% (for **33**); (c) Bz_2O, DMAP, pyridine, 80% (for **34**), (d) LevOH, DIC, DMAP, CH_2Cl_2, 93% (for **35**); (e) DAST, 2,6-lutidine, CH_2Cl_2, 51% (for **36**); (f) PPh_3, I_2, imidazole, CH_2Cl_2, 71% (for **37**); (g) NaN_3, DMF, 65%; (h) **37** *t*-BuOK, THF, 62%.

Although disaccharide stannanes can be prepared in a direct reaction from the corresponding disaccharide glycals (Scheme 1), the diversity of the anomeric nucleophiles was greatly expanded by converting monosaccharide stannanes into oligosaccharides (Table 2). We established that standard conditions for the activation of Schmidt donors with TMSOTf (5 mol%) or $PdCl_2(MeCN)_2$ (10 mol%)/AgOTf (20 mol%)[64] were efficient in the synthesis of disaccharide **41** (76%) and trisaccharides **43** (82%) and **45** (80%). We were also pleased to find that even longer oligomers such as tetrasaccharide **47** (73%) could be prepared from the Schmidt donor **46** without degradation of the stannane acceptor **32** although this reaction required 8 h to reach completion most likely due to the size of the glycosyl donor. We found no impact of the tin substitution on the reactivity of the glycosyl acceptors, which one might expect to show somewhat reduced reactivity due to the presence of a large group at C1 and an electropositive (deactivating) element at a remote position from the reacting 6-OH center. The scope of glycosyl stannanes was further expanded by converting the acceptor **32** into disaccharides **49**-**52** in reactions with glycal epoxide **48**. Electrophilic gold catalyst (Ph_3PAuCl/AgOTf) described by Yu[65] was found superior (78% of **49**) to stoichiometric $ZnCl_2$ (25%)[66] or other Lewis acid promoters (BF_3, TfOH) that resulted in no reaction. These catalytic conditions were then applied to the synthesis of (1→6)- and (1→2)-linked disaccharides **49**-**52** in consistently high anomeric selectivities. Dehydrative glycosylation of C1-hemiacetal **53** pre-activated with $DPPBO_2/Tf_2O$ furnished a mixture of anomers **54** in a moderate

Table 2. Scope of *O*-glycosylation of anomeric stannanes

Entry	Glycosyl donor	Conditions	Product	Yield
1	 **40**	$PdCl_2(MeCN)_2$ (10 mol%), AgOTf (20 mol%), CH_2Cl_2, 4Å MS, -78 to 23 °C	 **41**	76%
2	 **42**	TMSOTf (5 mol%), CH_2Cl_2, 4Å MS, -20 °C	 **43**	82%
3	 **44**	$PdCl_2(MeCN)_2$ (10 mol%), AgOTf (20 mol%), CH_2Cl_2, 4Å MS, -78 to 23 °C	 **45**	80%
4	 **46**	TMSOTf (5 mol%), CH_2Cl_2, 4Å MS, -20 °C	 **47**	73%
5	 **48**	$AuPPh_3Cl$ (10 mol%), AgOTf (10 mol%), CH_2Cl_2, -78 to 23 °C	 **49**	78%
6	 **48**	$AuPPh_3Cl$ (10 mol%), AgOTf (10 mol%), CH_2Cl_2, -78 to 23 °C	 **50**	56%
7	 **48**	$AuPPh_3Cl$ (10 mol%), AgOTf (10 mol%), CH_2Cl_2, -78 to 23 °C	 **51**	52%
8	 **48**	$AuPPh_3Cl$ (10 mol%), AgOTf (10 mol%), CH_2Cl_2, -78 to 23 °C	 **52**	72%
9	 **53**	$DPPBO_2$, Tf_2O, 2,6-di-*t*-Bu-4-Me-pyridine, CH_2Cl_2, 0 °C	 **54**	41% α:β 52:48
10	 **55**	Tf_2O, 2,6-di-*t*-Bu-4-Me-pyridine, CH_2Cl_2, 4Å MS, -40 to 0 °C	 **41**	38%

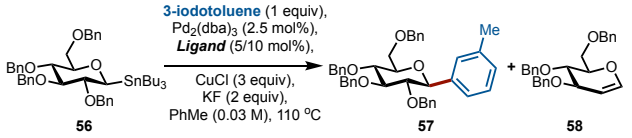
yield (41%) and slight preference for the α-anomer (α:β 52:48).[67] Similarly, glycosylation conditions employing sulfoxide donor **55** activated with Tf_2O furnished **41** in a modest yield (38%, α:β > 1:99). We also established that anomeric thioethers (SPh, STol) requiring strong electrophilic reagents (NIS or NBS/AgOTf) and anomeric fluoride donors activated with

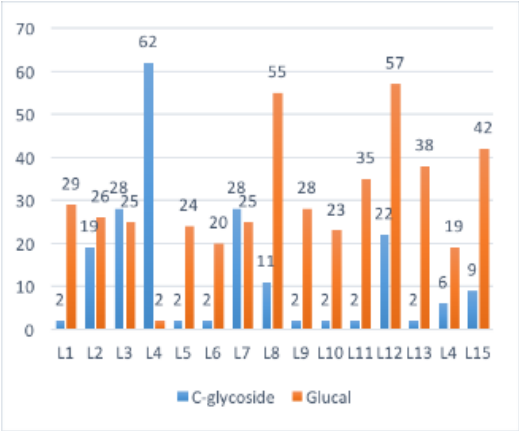
$Cp_2Hf(OTf)_2$ are incompatible with anomeric stannanes leading to protodestannylation instead of the formation of a new glycosidic bond. Taken together, we conclude that C1 stannanes are compatible with standard *O*-glycosylation conditions and the extension of an oligosaccharide chain can be readily accomplished at the stage of anomeric nucleophiles.

Reaction Development

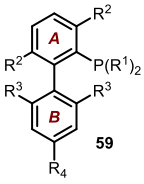
Having access to a series of anomeric stannanes, the next task toward successful realization of the glycosyl coupling reaction was the identification of a set of conditions that would allow for stereospecific reactions at the C1 position. The following key challenges were addressed from the outset of this study: (a) high stereospecificity of cross-couplings with both carbohydrate anomers regardless of steric and electronic environment of the stannane and (b) competitive β-elimination of the oxygen-based groups at C2 or β-hydride elimination. We hypothesized that the β-elimination pathway could be controlled by a judicious selection of a ligand that could: (i) prevent the elimination of the C2 group (i.e., from the stannane substrate *prior* to transmetalation to Pd, thus facilitating the transmetalation step C-Sn→C-Pd), and (ii) control the glycal formation by preventing the elimination of a C2 substituent from anomeric palladium intermediate and/or facilitate reductive elimination resulting in the formation of C(sp^3)-C(sp^2) bonds. The undesired glycal synthesis could also be initiated by the reaction additives themselves. For example, a leaving group at C2 (OBn) and the Bu_3Sn moiety in β-D-arabinose **11** and other protected 1,2-*trans* pyranose stannanes are locked in a $^4C_1$ conformation, which, after a ring flip, leads to a $^1C_4$ conformer poised for a facile β-elimination. Similarly, the 1,2-*cis* stannanes (e.g., **14**) with free 2-OH groups can engage in a Peterson-type reaction leading to a glycal product. It was discovered early in this study that amine additives known to exert positive effect on the Stille reaction (Et_3N, Hünig's base, pyridine, DMAP) are not compatible with the anomeric stannanes and a rapid glucal formation was observed when β-D-glucose stannane was used. These additives were thus excluded from the optimization studies. Based on our success with the deprotection of the 6-OH group in **31** (Scheme 3) and literature precedent that fluoride facilitates the Stille reaction,[68] KF was selected as an additive for the ligand optimization studies (*vide infra*). Furthermore, given the accelerating role of Cu additives, CuCl (3 equiv) in a combination with $Pd_2(dba)_3$ as a pre-catalyst were employed. This general set of conditions was used to test the hypothesis that a phosphine ligand can control the rate of β-elimination and C-C coupling in reactions with C1 nucleophiles. In search of effective ligands for Pd-catalyzed glycosyl Stille cross-coupling reactions, the electronic nature and steric hindrance of the ligands are particularly important. Therefore, biaryl phosphines were selected because their electronic and steric properties can be finely tuned by introducing modifications on the phosphorus atom and aromatic rings. The cross-coupling reaction of (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)tri-*n*-butylstannane **56** with 3-iodotoluene was selected as a model system (Table 3).

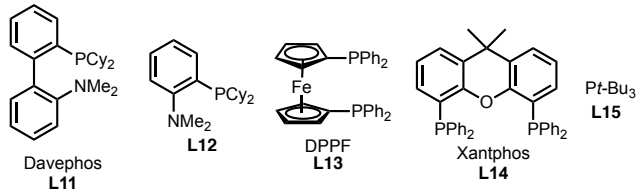
Table 3. Ligand optimization for the cross-coupling of β-glucose stannane **56** and 3-iodotoluene





L	Name	R_1	R_2	R_3	R_4
L1	AdBrettPhos	Ad	OMe	*i*-Pr	*i*-Pr
L2	BrettPhos	Cy	OMe	*i*-Pr	*i*-Pr
L3	tBuBrettPhos	*t*-Bu	OMe	*i*-Pr	*i*-Pr
L4	JackiePhos	3,5-$(CF_3)_2$ C_6H_3	OMe	*i*-Pr	*i*-Pr
L5	XPhos	Cy	H	*i*-Pr	*i*-Pr
L6	tBuXPhos	*t*-Bu	H	*i*-Pr	*i*-Pr
L7	JohnPhos	*t*-Bu	H	H	H
L8	CyJohnPhos	Cy	H	H	H
L9	RuPhos	Cy	H	O*i*-Pr	H
L10	SPhos	Cy	H	OMe	H



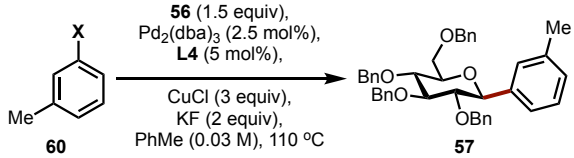


From the initial optimization studies BrettPhos-type ligands (**L1**-**L3**) reported by Buchwald[69-70] emerged as promising hits and afforded **57** in modest but comparable yields (19-28%). These three ligands contain a methoxy group on the upper "A" ring of the biphenyl group in **59**, which, we hypothesized, directly interacts with Pd.[71] Furthermore, **L1** (AdBrettPhos) with a large adamantyl substituent showed diminished propensity for the formation of the elimination product **58**, indicating that further modifications of this position may be beneficial for controlling the β-elimination pathway.[72] Indeed, phosphine **L4** (JackiePhos)[73] with a large substituent modified with a strongly electron-withdrawing 2,6-bis-(trifluoromethyl)phenyl group gave the best result of all ligands tested furnishing β-glucoside **57** in 62% yield and trace amounts (2%) of the elimination product **58**. To fine-tune the above conditions, a solvent screen (PhMe, *m*-xylene, THF, DMF, 1,4-dioxane) revealed that the yield of **57** could be improved to 94% if the reaction was conducted in 1,4-dioxane (0.03 M) instead of PhMe. This protocol is also scalable and a reaction of 1.0 g of **56** with 3-iodotoluene afforded a single anomer of **57** in 88% isolated yield. A subtle balance between the electron-withdrawing properties of **L4** resulting in a more-electrophilic character of Pd(II)

stabilized by OMe necessary to promote the transmetalation step with anomeric stannanes is balanced by the sterics of the 3,5-substituted group. Consistent with this hypothesis is the reaction with **L7** (JohnPhos)[74] in which *t*-Bu group occupies the R_1 position and afforded almost equal amounts of **57** and **58**.

The role of the OMe group in the *ortho* position of the "A" ring was further investigated, and replacement of OMe with H (**L5**, Xphos and **L6**, tBuXphos)[75] or Me (**L10**, SPhos)[76] caused a drastic decrease of the yield and overall conversion. Alternatively, increasing the steric bulk on the oxygen substituent (**L9**, RuPhos)[77] led to similarly low conversion and preferential formation of **59**. However, *N,N*-dimethylamine group in the *ortho* position (**L11**, DavePhos[78] and **L12**) favored the formation of D-glucal **58** in high yields. The origin of this effect can be attributed to the interactions of the nitrogen atom with Pd(II) center which becomes more electron-rich and susceptible to β-elimination. Alternatively, a moderately basic aniline substituent can directly cause β-elimination from the C1-stannane by a mechanism analogous to the one observed with amine/pyridine additives (*vide supra*). Other phosphines afforded predominantly D-glucal **58**, although the efficiency of this process was dependent on the phosphine itself. For example, a modification of the bottom "B" ring of the biaryl ligand by replacing the isopropyl group with a proton (**L7**-**L10**) resulted in reaction yields of **57** below 30% but high yields of **58** (23-55%). Consistent with the above trend are the results with other ligands such as **L13** (DPPF), **L14** (Xantphos),[79] or **L15** (t-Bu_3P)[80] providing low yields of **58.** Taken together, the biphenyl phosphines emerge as the optimal ligands for the glycosyl C(sp^3)-C(sp^2) cross-coupling reactions and the OMe group in the "A" ring of the scaffold **59** located in the *ortho* position to phosphorus is of critical importance to maintain catalyst stability through coordination to the Pd center. For all phosphines tested, the formation of only one diastereoisomer was observed (based on the analysis of ^{1}H NMR of unpurified reaction mixtures).

Table 4. Cross-couplings of β-D-glucose stannane **60**



Entry	X	Yield
1	Cl	14%
2	Br	53%
3	OTf	21%

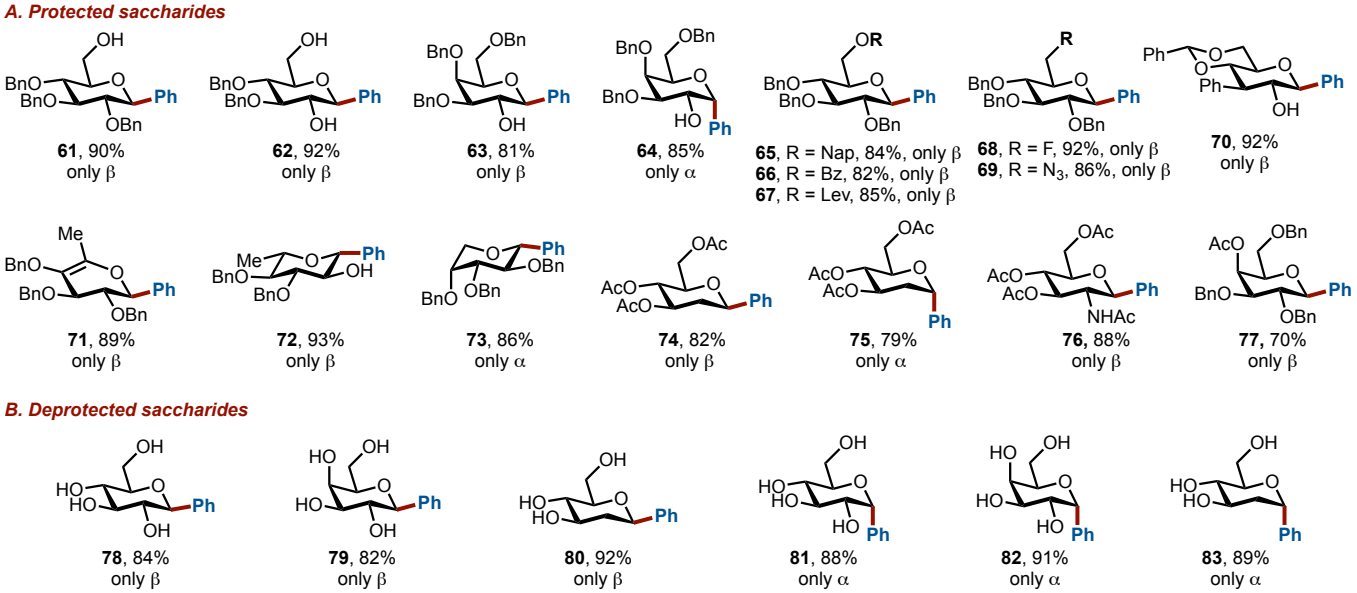
To better understand the effects of the fluoride source, copper and other transition-metal additives were investigated (for details, see the SI). These results can be summarized as follows: (a) KF, NaF, and LiF (but not CsF and TBAF) resulted in good overall yields of *C*-glycoside **57** (58-62%), (b) the yield of the reaction is dependent on the identity of the Cu(I) salt – CuCl (2 equiv) is superior to all other counterions tested (CuBr and CuTC resulted in the formation of the product **57** in modest yields (18-28%) whereas CuI and CuOTf were not suitable for this transformation), (c) other transition-metal additives ($MgCl_2$, $AgBF_4$, $AuCl_3$, $ZnCl_2$) have no beneficial effect on the reaction yield although Ag(I) salts generated a yield comparable to the optimized conditions with CuCl (60%). Based on these data, we conclude that CuCl and KF exert a synergic effect that accelerates the Stille reaction. Two roles of Cu(I) salts are likely: (i) they act as a scavenger for free neutral ligand to avoid autoretardation of the rate-determining associative transmetalation and (ii) the combination of fluoride and Cu facilitates the transmetalation from the anomeric stannane to generate a more reactive organocopper intermediate, which then enters the catalytic cycle with Pd.[68, 81-82] The formation of a more reactive organocopper species is favorable when the tin group is converted into insoluble Bu_3SnF resulting in the improvement of the efficiency of the reaction.

Lastly, to better understand the relative reactivities of aryl halides or pseudohalides in the glycosyl Stille cross-coupling reactions, we compared the reactions of 3-chlorotoluene, 3-bromotoluene, 3-iodotoluene and 3-tolyl triflate with β-D-glucose stannane **56** (Table 4). Consistent with the previous results regarding the reactivity of aryl halides in the Stille reaction,[83-84] 3-chlorotoluene resulted in only 14% of the product **57** whereas 3-bromotoluene and 3-tolyl triflate furnished the *C*-glycoside **57** in 53% and 21%, respectively.

Scope and Applications

Monosaccharide cross-coupling reactions. The optimized glycosyl cross-coupling conditions were tested in reactions with various monosaccharides (Figure 2). We found that the general set of conditions using $Pd_2(dba)_3$ and JackiePhos **L4** is operational for D-glucose (**61**, **62**), D-galactose (**63**, **64**), modified D-glucose containing a fluoride (**68**), an azide (**69**) and a benzylidene group (**70**), unsaturated glycosides (**71**), D-olivose (**72**), and D-arabinose (**73**). Hydroxyl protective groups commonly employed in carbohydrate synthesis such as Nap, Bz, and Lev are also tolerated under the cross-coupling conditions (**65**-**67**). 2-Deoxysaccharides are frequently found in angucycline antitumor antibiotics and present a synthetic challenge because they lack a controlling substituent at C2 for stereoselective *C*-glycosylation.[85] We found that 2-deoxy-D-glucose glycosides **74** and **75** were efficiently prepared from PhI with retention of anomeric configuration for both anomers. An additional powerful example of glycosyl cross-coupling is the reaction of saccharides containing free hydroxyl groups (Figure 2B). Standardized conditions using 1,4-dioxane as a solvent cleanly afforded *C*-glycosides **78**-**83**. The triol and tetraol substrates (see Scheme 2) and the products **78**-**83** are readily soluble in 1,4-dioxane and one can anticipate that the cross-coupling protocol can be further extended to more complex polyols. To accommodate polar reagents with multiple hydroxyl groups, the solubility of the substrates and products in organic solvents needs to be taken into account. To address these potential challenges, we examined a series of protic solvents as additives together with 1,4-dioxane, and a 9:1 mixture of 1,4-dioxane and MeOH in the cross-coupling of **56** and 3-iodotoluene under otherwise identical conditions resulted in 79% of **57**. Comparable results (86% of **57**) were obtained in a 9:1 mixture of 1,4-dioxane and *t*-BuOH.

Figure 2. Scope of glycosyl cross-coupling reaction of anomeric stannanes with PhI

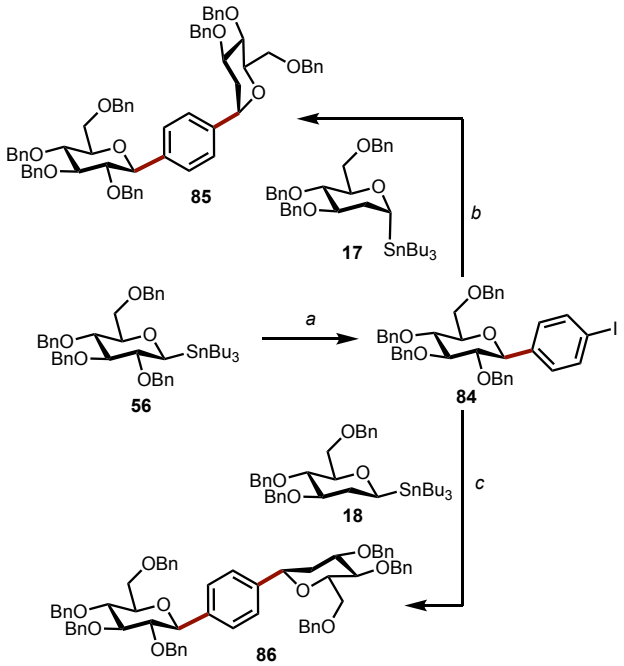


Reagents and conditions: (a) PhI (2.0 equiv), anomeric nucleophile (1.0 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuI (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C; (b) PhI (1.0 equiv), anomeric nucleophile (2.0 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuI (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C. Compounds **61**, **62**, **68-72** were prepared with conditions a, compounds **63-67**, **73-83** with conditions b.

The hydroxyl groups in majority of carbohydrate examples presented in Figure 2 are protected with electron-donating substituents (benzyl ethers). These reagents in the carbohydrate terminology would be considered as "armed" (activated).[86] We found little impact of the protective groups on the reaction yield and no impact on selectivity, as exemplified by reactions with 2-deoxy-D-glucose (**74** and **75**) and per-*O*-acetyl-D-GlcNAc. Ester groups known to deactivate glycosyl acceptor in classical *O*-glycosylation reaction have no effect on the reaction yields when it comes to anomeric stannanes (products **74-77**) do not have any impact on anomeric selectivity. For example, an ester group at the 4-O position in galactose can direct the delivery of a nucleophile through a transannular participation.[87] However, in the case of β-D-galactose stannanes, such remote participation was not observed event and starting from β-stannane, the corresponding *C*-β-glycoside **77** was prepared without erosion of anomeric configuration. Analogous results were observed in reactions with both anomers of D-GlcNAc.[37] The substitution at C2 carbon in monosaccharides is well-tolerated although we observed a slight decrease of the reaction yield caused by a competing elimination of the OBn group. In general, 1,2-*cis* anomers require longer reaction times (48-72 h) for full consumption of the aryl halide and produce consistently ca. 20% more of the glycal by-products. Careful analysis of the crude reaction mixture revealed that β-hydride elimination accounts for <1% of the material for reactions with protected saccharides and with free hydroxyl groups.

Orthogonal C-glycosylations. Further studies were focused on the applications of the glycosyl cross-coupling method in the synthesis of glycoconjugates containing two different saccharides attached to the aromatic core (Scheme 4). When combined with the increased metabolic stability, these structures may serve as mimetics of oligosaccharides.[88] Because of the substantial rate differences for cross-coupling with aryl halides (Table 4), we envisioned that the installation of two different glycans could be accomplished by a judicious selection of a reactive iodide with either bromide or chloride. These types of *C*-glycosylations selectively delivered only one *C*-glycoside group in a synthetically acceptable yield (70%). However, after some experimentation we found that 1,4-diiodobenzene cleanly afforded the mono-glycosylated product **84** by simply adjusting the equivalency of halide electrophile (3 equiv) and **56** (1 equiv). This intermediate was then coupled with α and β anomers **17** and **18** to afford asymmetric glycoconjugates **85** and **87**.

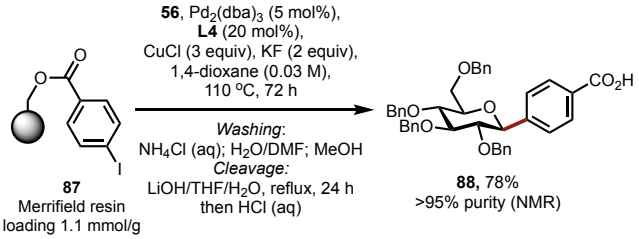
Scheme 4. Double glycosylation with 1,4-diiodobenzene



Reagents and conditions: (a) 1,4-diiodobenzene (3 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h, 60%; (b) **17** (2 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h, 58%; (c) **18** (2 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h, 63%.

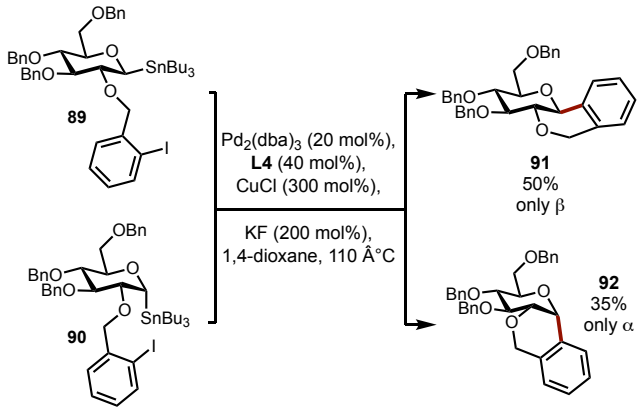
C-glycosylation on solid-support. In order to adapt the glycosyl cross-coupling method to high-throughput synthesis format, we demonstrated a reaction of an aryl halide directly attached to a solid-support resin (Scheme 5).[89] The Merrifield resin **87** was exposed to the conditions previously optimized using 2 equiv of anomeric stannane **56**. After completion of the reaction (72 h), the excess of reagents was washed off and the acid **88** was obtained in 78% yield and >95% purity (^{1}H NMR).

Scheme 5. Glycosyl cross-coupling on solid support



Intramolecular C-glycosylations. Internal *C*-glycosides are present in bioactive natural products with potent immunomodulatory activities (e.g., bergenin).[90] The synthesis of tricyclic *C*-glycosides has been reported by intramolecular Friedel-Crafts reaction with electron-rich arenes linked through a C2 substituent resulting in *cis* products.[91-93] Because the intermolecular glycosyl cross-couplings proceed with high levels of stereoretention, we examined the feasibility of *intramolecular* cross-couplings with 2-iodobenzene electrophiles attached as a benzyl ether to the equatorial alcohol at C2 in D-glucose substrate (Scheme 6). Both anomers **89** and **90** were converted into the corresponding cyclic ethers **91** and **92** under the standard conditions with the retention of anomeric configuration. The reaction with α-anomer **90** resulted in a lower yield (35%) of the *cis* product **92**, and the remainder of the material for both reactions was tri-*O*-benzyl glucal **58** originating from the β-elimination of the C2-benzyloxyl group (full consumption of **89** and **90**). These results demonstrate high stereospecificity of the cross-coupling reaction even in systems where strained products are difficult to form and can pose a challenge when attempted with other synthetic methods.

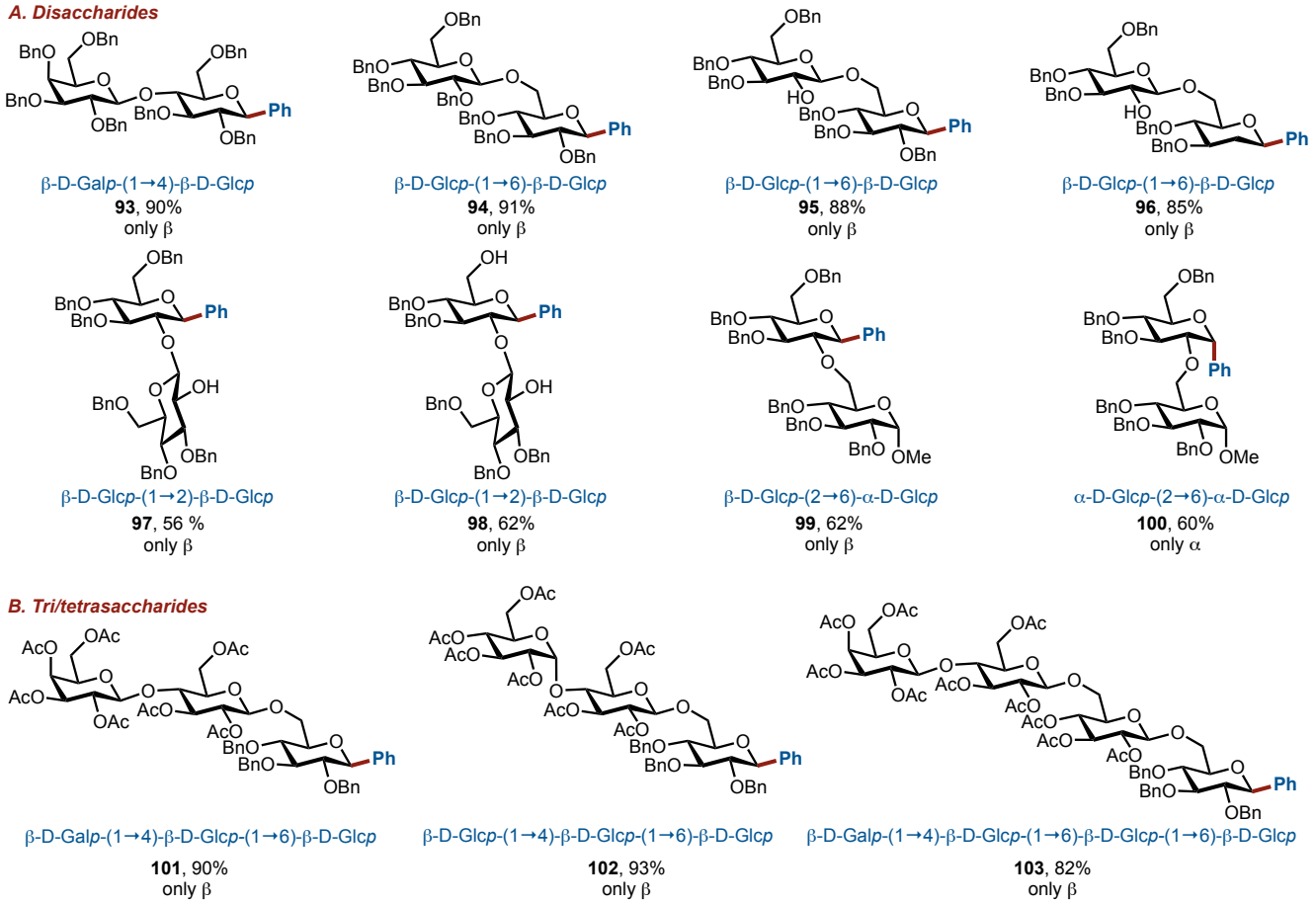
Scheme 6. Stereoretentive intramolecular glycosyl cross-coupling of 2-iodobenzyl-D-glucose.



C-Oligosaccharides. To further demonstrate the generality of the method, a direct reaction of oligosaccharide nucleophiles with aryl halide was studied (Figure 3). Extensive literature on the formation of *C*-aryl glycosides is limited to the reactions with monosaccharides and a direct *C*-glycosylation with oligosaccharide donors and aromatic acceptors is not known.[17] Oligosaccharide stannanes prepared by glycosylation reactions with monosaccharide stannanes (Table 2) were engaged in cross-coupling reactions with PhI without any modifications of the general conditions, allowing for the formation of *C*-disaccharides derived from D-lactose (**93**), D-gentiobiose (**94**, **95**) and 2-deoxy-D-gentiobiose (**96**) in excellent yields with 1 equiv of the anomeric stannane substrate and 2 equiv of PhI. To test if a bulky group at C2 impacts the reaction efficiency, D-sophorose disaccharides containing a (1→2) glycosidic bond (**97**, **98**) and disaccharides with unnatural (2→6) ether bonds between two D-glucose residues (**99**, **100**) were also prepared in good yields and consistently high selectivities. Extreme examples of the generality of the glycosyl cross-coupling method are the reactions forming phenyl *C*-trisaccharides (**101**, **102**) and a tetrasaccharide **103** from the corresponding oligosaccharide stannanes in yields exceeding 80% for all substrates tested. One can envision that the scope of the cross-coupling method can be further extended to longer linear and branched oligosaccharides which can be fused with aromatic acceptors at the end of the synthetic sequence.

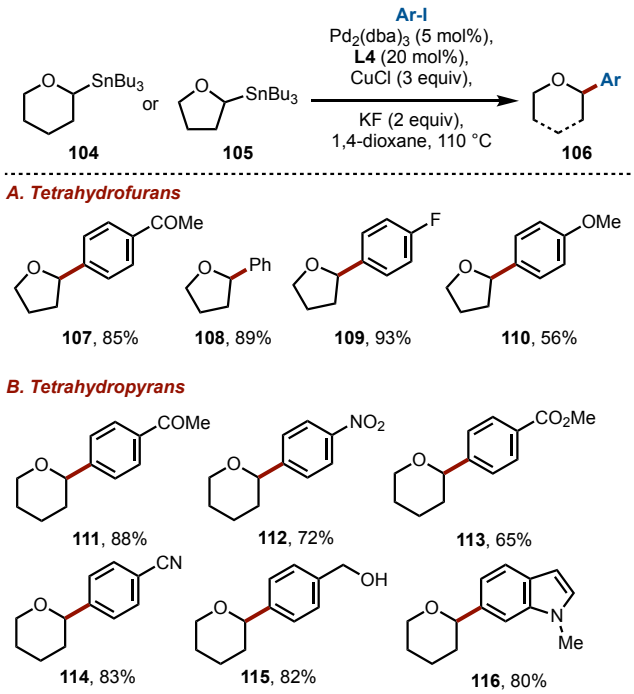
Cross-coupling with unsubstituted furanosyl/pyranosyl stananes. Although the conditions for the installation of the aryl groups at the anomeric position were optimized for the reactions with carbohydrate substrates, we wondered if simple pyranose and furanose nucleophiles could be merged with aryl electrophiles. Curiously, reactions of acyclic stannanes such as α-acyloxyl- and α-amidostannanes are known,[94-95] yet cyclic oxygen-containing heterocycles have not been investigated as substrates in the Stille C(sp^3)-C(sp^2) reaction. To this end, we prepared racemic tetrahydropyranosyl (**104**) and tetrahydrofuranosyl stannanes (**105**)[96-97] and cross-coupled them with aryl iodides decorated with electron-withdrawing (**107**-**110**, **111**-**114**), electron-rich (**110**, **115**) and heterocyclic iodides (**116**, Scheme 7).

Figure 3. Scope of glycosyl cross-coupling reaction with oligosaccharide stannanes



General reaction conditions: PhI (2.0 equiv), anomeric nucleophile (1.0 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuI (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C.

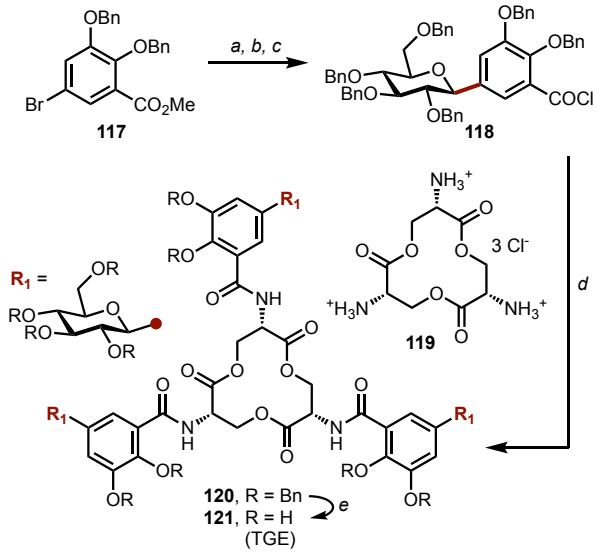
Scheme 7. Stille cross-coupling of pyranosyl and furanosyl stananes



Finally, the utility of the glycosyl cross-coupling reaction was demonstrated in the context of target-oriented synthesis of TGE (natural product) and dapagliflozin (anti-diabetic drug).

Application I: Glucosylated enterobactins (salmochelins)[98-99] are siderophores (Fe^{3+} scavengers) produced by *Salmonella* species as a means to evade the host's defense system.[100] Salmochelins contain up to three β-*C*-glucoside residues attached to 2,3-dihydroxybenzoic acid and TGE (**121**) is a triply glycosylated salmochelin. Given the interest in enterobactins as a platform for the delivery of antibacterial cargo,[101] TGE is an ideal target to apply the glycosyl Stille reaction (Scheme 8). To this end, 5-bromobenzoate **117** was coupled with β-D-glucose stannane **56** in 77% and α:β > 1:99 and, after a few straightforward manipulations on the ester group, the product **118** was converted into macrolactone **120** in a reaction with amine salt **119**. Removal of the benzyl groups under standard conditions furnished TGE **121** in 51%.

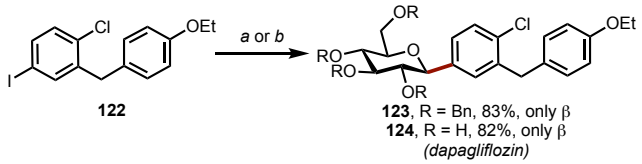
Scheme 8. Total synthesis of salmochelin TGE



Reagents and conditions: (a) **56,** $Pd_2(dba)_3$ (20 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h, 77%; (b) LiOH, MeOH/THF/H_2O (2:1:1), 23 °C, 12 h, 84%; (c) $SOCl_2$, DMF (cat.), CH_2Cl_2, 23 °C, 2 h, 99%; (d) Et_3N, CH_2Cl_2, 0 °C then 23 °C, 10 h, 33%; (e) H_2, $Pd(OH)_2$, MeOH/EtOAc (1:1), 24 h, 23 °C, 51%.

Application II. Dapagliflozin **124** (Farxiga/Forxiga) is a commercial SGLT2 inhibitor approved worldwide and used to treat diabetes mellitus type 2.[102-104] Because of the generality of the cross-coupling reaction, we envisioned that the synthesis of this drug can be streamlined by applying the cross-coupling method. Thus, the union of protected stannane **56** with iodide **122** provided protected dapagliflozin **123** in 83% yield (Scheme 9). Alternatively, a reaction of C1-nucleophile **24** and **122** afforded dapagliflozin **124** in 82% isolated yield as a single diastereoisomer. This direct method for the preparation of gliflozins shows excellent chemoselectivity and only the more reactive iodide in **122** was coupled with the carbohydrate stannane.

Scheme 9. One-step synthesis of dapagliflozin

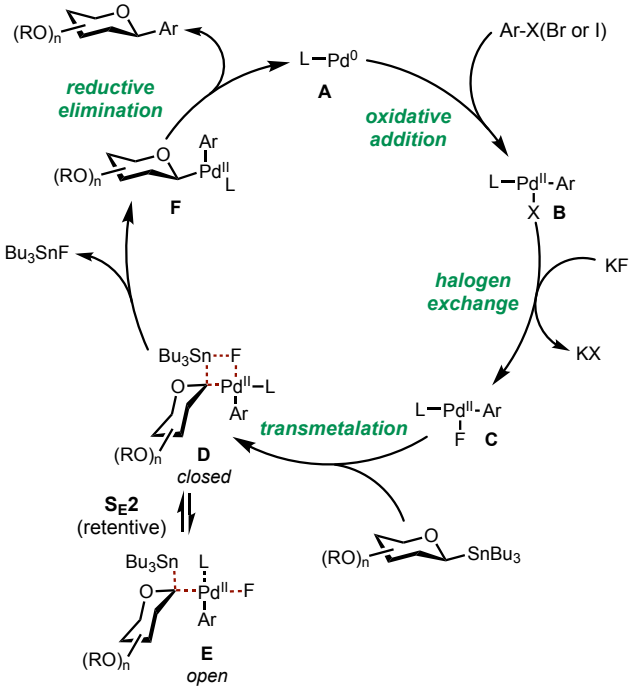


Reagents and conditions:* (a) **56 (2 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h. (b) **24** (2 equiv), $Pd_2(dba)_3$ (5 mol%), **L4** (20 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h.

Mechanistic and Computational Studies

Broad substrate scope, excellent functional group compatibly and consistently high stereospecificity in the cross-coupling reactions for both anomers prompted us to undertake mechanistic investigations. There is a substantial body of computational[105-110] and experimental[111-118] data on the mechanism of the Stille C(sp^2)-C(sp^2) cross-coupling reactions[119] but very little is known about the Stille C(sp^3)-C(sp^2) reactions with optically active stannanes. The key questions pertaining to the outcome of these reactions are (a) the origin of high stereospecificity, (b) the special ligand effect of JackiePhos and the control of C-C cross-coupling vs. β-elimination pathways, and (c) more facile cross-coupling of 1,2-*trans* anomeric stannanes. Based on the highly stereospecific nature of the cross-coupling reactions and no effect of potentially participating groups at C2 on the anomeric selectivity, we excluded the possibility of a radical mechanism. This assumption was further corroborated in experiments with 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,1-diphenylethylene, established radical scavengers, which had no effect on the reaction yield and stereospecificity (for details, see the SI).

Scheme 10. Proposed catalytic cycle of Pd-catalyzed Stille coupling with anomeric stannanes



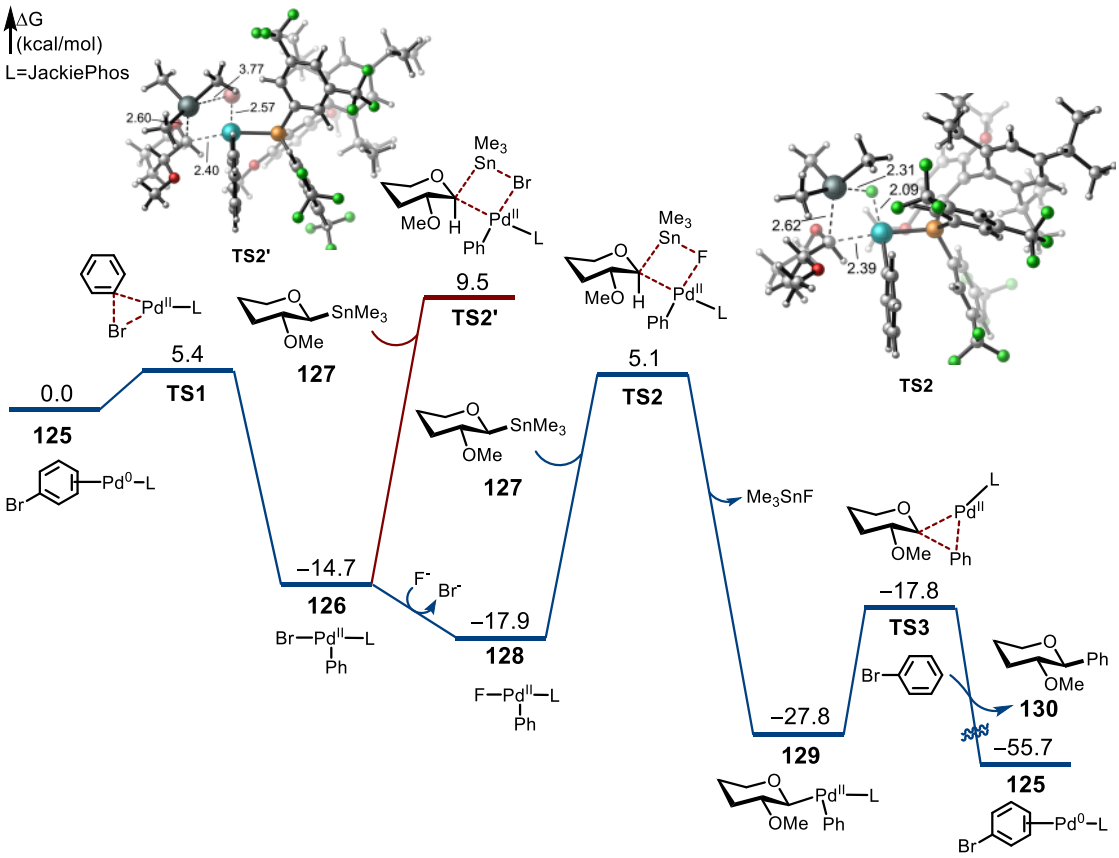


Figure 4. Reaction energy profile of the Pd-catalyzed Stille coupling of bromobenzene and tetrahydropyranyl stannane **127** using JackiePhos ligand. All energies are with respect to the reactant complex **125**. Calculations were performed at the M06/SDD−6-311+G(d,p)/SMD(dioxane)//B3LYP/SDD−6-31G(d) level of theory.

Computational investigations of reaction mechanisms. We performed density functional theory (DFT) calculations to elucidate the mechanisms of Pd-catalyzed coupling of bromobenzene and organostannane **127** as a model substrate. Three major points of interest were examined in the computational investigations. First, although the mechanisms of C(sp^2)−C(sp^2) Stille coupling has been extensively studied computationally, there were no existent studies involving C(sp^3)−C(sp^2) bond formation in the Stille coupling.[105-106, 120-124] Stereoretentive transmetalation with vinyl stannanes is known to occur via the "closed" pathway involving a four-membered cyclic transition state (**D** in Scheme 10). It was of interest to investigate whether such cyclic transmetalation transition state with sterically encumbered alkyl stannanes is energetically accessible. A previous computational study from Yates indicated that the addition of F^- led to increased reactivity of vinyl stannane reagents towards transmetalation.[117] Here, we investigate the potentially more challenging transmetalation with alkyl stannanes promoted by F^-.[117] Furthermore, efficient C(sp^3)−C(sp^2) reductive elimination is the key to prevent the competing β-elimination of the oxygen-based groups at C2. The effects of JackiePhos ligand on the rates of reductive elimination and β-alkoxy elimination was elucidated by computational methods. Lastly, the origin of the difference in reactivity between α and β anomeric stannanes was studied computationally.

The calculated reaction energy profile of the Pd-catalyzed coupling of bromobenzene and stannane **127** using JackiePhos ligand is shown in Figure 4. The Pd(0)-bromobenzene complex **125** undergoes oxidative addition with a barrier of 5.4 kcal/mol (**TS1**) leading to phenyl palladium(II) bromide complex **126**. The JackiePhos ligand in the three-coordinate palladium complex **126** adopts the conformation where the biaryl group shields the remaining open site of the palladium (see the SI for 3D structures). From **126**, the stereoretentive transmetalation via a four-membered cyclic transition state (**TS2'**) requires an activation energy of 24.2 kcal/mol with respect to **126**. This transmetalation is facilitated in the presence of F^-. Halide exchange with **126** forms a more stable palladium(II) fluoride species **128**, which then undergoes transmetalation via **TS2** and requires a barrier of 23.0 kcal/mol to form intermediate **129**. The fluoride effects are consistent with the Yates study that the transmetalation with palladium fluoride is faster due to the formation of the stronger Sn−F bond. In both **TS2** and **TS2'**, the palladium approaches the stannane from the same side of the C1 hydrogen. The transition state isomer of **TS2** in which the palladium approaches from the opposite side of the C1 hydrogen is less stable by 5.2 kcal/mol due to unfavorable steric repulsions of the palladium catalyst with the six-membered ring (see the SI for details). Attempts to locate the open-form transmetalation transition state that leads to stereoinversion were unsuccessful. Constrained geometry optimization of such transition state suggested a significantly higher energy compared to the closed form transition state (see the SI for details). Intermediate **129** undergoes reductive elimination to form the aryl *C*-glycoside product **130** with a relatively low barrier of only 10.0 kcal/mol (**TS3**). Here, the reductive elimination is promoted by a bulky JackiePhos **L4** ligand.[73]

We computed the energy profile of the β-methoxy elimination from **129** to investigate the origin of the ability of the JackiePhos ligand to suppress this undesired pathway (Figure 5). The elimination of *trans*-β-methoxy group most likely occurs via the antiperiplanar elimination from the ring flip isomer (**131**). Under the reaction conditions, this elimination could be promoted by the stabilization of the methoxide leaving group by a Lewis acid (e.g., Cu(I)) and the stabilization of the cationic Pd(II) by coordination with an F^-. Due to the diaxial repulsion with the phenyl and the JackiePhos ligand on the Pd, the ring flip isomer **131** is 5.7 kcal/mol less stable than **129**. However, it should be noted that this energy difference would be further amplified with the real experimental substrate, due to additional diaxial interactions. Coordination of CuCl and F^- to **131** requires 7.4 kcal/mol in terms of Gibbs free energy. The relatively unfavorable binding of F^- is again attributed to the steric hindrance of the JackiePhos ligand, which partially blocked the remaining binding site on Pd in **131**. With the assistance of CuCl and F^-, the E2-type elimination from **133** is relatively facile, requiring an activation barrier of 10.0 kcal/mol. Nonetheless, the overall barrier of the β-methoxy elimination from **129** to **TS4**, which includes the energies required for ring flip and CuCl and F^- coordination, is 23.1 kcal/mol, significantly higher than the C−C reductive elimination from **129**, which requires only 10.0 kcal/mol. These computational results suggest that bulky phosphine ligands, such as JackiePhos, not only promote reductive elimination, but also increase the barrier to β-alkoxy elimination by preventing ring flip and F^- coordination to the Pd center.

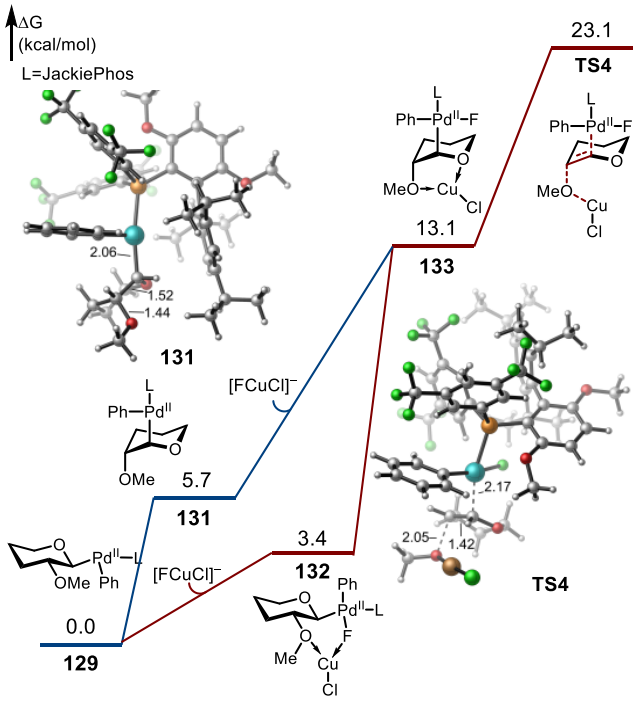


Figure 5. Reaction energy profile of the β-methoxy elimination pathway. All energies are with respect to complex **129**.

We then performed computational analysis to understand the origin of the reactivity differences between the two anomers of pyranosyl stannanes. Based on the computationally predicted reaction mechanism, the transmetalation step is irreversible and rate-determining. Thus, we calculated the transmetalation transition states with stannanes **127** and **134** as models of the β and α anomers, respectively (Figure 6). Both transmetalation occur via the stereoretentive four-membered cyclic transition state. However, unlike **TS2**, the six-membered ring in **TS2A** changes to a twist-boat-like conformation, leading to the diminished reactivity of the α anomer. Transition state **TS2A** is 1 kcal/mol higher in energy than the transmetalation involving the β anomer (**TS2**). This twist-boat conformation in **TS2A** is achieved in order to relieve the amplified 1,3-diaxial interactions between tin and the two axial hydrogens in the chair like-transition state structure (**TS2A'**).

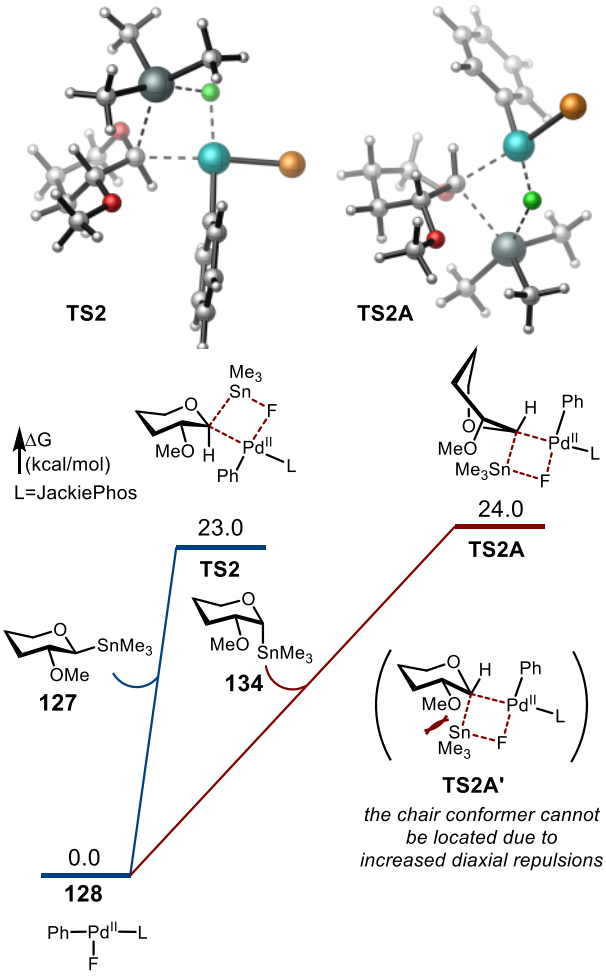
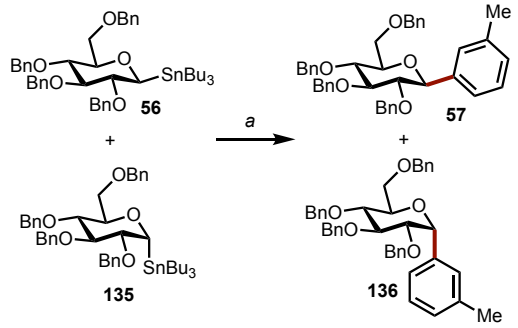


Figure 6. Transition states of transmetalation of the α and β anomers (**134** and **127**). All energies are with respect to complex **128**. The JackiePhos ligand is not shown in the 3D structures for clarity.

The preferential reactivity of equatorial stannanes **127** computed at the DFT level was also confirmed experimentally. A direct competition reaction of α and β anomers of D-glucose stannanes (**57**:**135**, 1:1) with 3-iodotoluene revealed that the coupling of the β-anomer **57** is 3.2 times faster than the reaction leading to the α anomer **136** (Scheme 11).

Scheme 11. Competition experiment of α and β anomers of D-glucose



Reagents and conditions: (a) **56**:**135** (1.0:1.0), $Pd_2(dba)_3$ (2.5 mol%), **L4** (10 mol%), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C; **57**:**136** (3.2:1.0).

CONCLUSIONS

To summarize, we have demonstrated that anomeric stannanes undergo a highly stereoretentive cross-coupling reaction with aryl halides. First, we have developed a general approach for the synthesis of both anomers of C1-stannanes derived from common monosaccharides. We have also demonstrated that anomeric stannanes are compatible with a range of methods used in preparative carbohydrate chemistry, including protective group manipulations and *O*-glycosylation conditions. Next, we identified a general set of conditions for a Pd-catalyzed cross-coupling reaction of aryl halides with C1-nucleophiles. Under the optimized conditions, the β-elimination pathway using a bulky phosphine ligand (JackiePhos) was suppressed resulting in a transfer of anomeric configuration from the C1-stannane to aryl *C*-glycoside. Experimental and computational studies support a mechanistic proposal that (a) the stereoretentive transmetalation step in the glycosyl Stille coupling occurs via a cyclic transition state for both anomers and is independent of the steric and electronic environment of the saccharide, (b) JackiePhos facilitates reductive elimination leading to the formation of C-C bond and prevents elimination of the C2 substituents by "locking" the saccharide ring in the anomeric palladium intermediate. We have demonstrated the generality of the glycosyl cross-coupling method in over 50 examples featuring both anomers of various monosaccharides, deoxysugars, oligosaccharides, and saccharides with free hydroxyl groups. For each substrate described here, consistently high selectivities were observed, opening up opportunities to incorporate glycosyl groups with exclusive control of anomeric configuration into a myriad of aryl electrophiles. The precision and selectivity of our method is thus far unattainable by other chemical approaches. This powerful tool allows for the glycodiversification studies and synthesis of a library of glycans to be conducted with minimal protective group manipulations in a highly predictable manner.

EXPERIEMNTAL SECTION

Representative procedure. Stannane **34** (101 mg, 0.122 mmol), iodobenzene (12.4 mg, 0.0610 mmol), $Pd_2(dba)_3$ (2.80 mg, 0.0030 mmol), **L4** (9.80 mg, 0.0120 mmol), CuCl (18.1 mg, 0.183 mmol) and KF (7.10 mg, 0.122 mmol) in 1,4-dioxane (2.0 mL) were heated under N_2 at 110 ºC for 72 h. The reaction mixture was filtered through a pad of SiO_2, concentrated, and purified by chromatography on SiO_2 (Hexanes:EtOAc, 10:1) to afford **66** (30.7 mg, 82%) as a colorless oil: $[\alpha]_D^{25}$ = +13.3 (c = 0.50, $CHCl_3$); IR (ATR) ν = 3032, 2903, 1720, 1496, 1453, 1273, 1066, 1027, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 - 8.01 (m, 2H), 7.66 - 7.54 (m, 1H), 7.50 - 7.16 (m, 20H), 7.02 - 6.91 (m, 2H), 5.01 (d, *J* = 10.9 Hz, 1H), 4.94 (d, *J* = 10.7 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.67 (d, *J* = 10.7 Hz, 1H), 4.64 - 4.53 (m, 2H), 4.40 (d, *J* = 10.1 Hz, 1H), 4.32 (d, *J* = 9.5 Hz, 1H), 3.94 - 3.68 (m, 4H), 3.61 - 3.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 139.1, 138.6, 137.8, 137.7, 133.2, 130.2, 129.8, 128.7, 128.5 (2), 128.4 (2), 128.3, 128.1, 128.0, 127.9, 127.7, 86.8, 84.7, 81.8, 78.1, 77.4, 76.0, 75.4, 75.1, 63.8; HRMS (ESI) *m/z* calcd for $C_{40}H_{38}O_6Na$ $[M + Na]^+$ 637.2561, found 637.2566.

ASSOCIATED CONTENT

Supporting Information.
Experimental and computational details, energies and Cartesian coordinates, copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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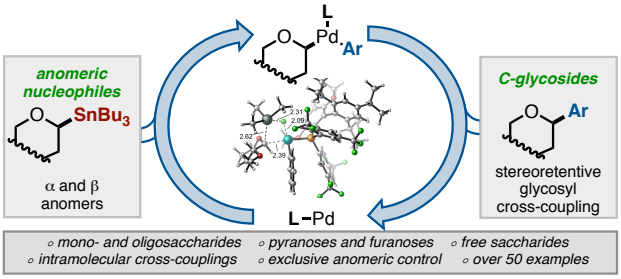
TOC


anomeric nucleophiles
SnBu3
α and β anomers
L
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stereoretentive glycosyl cross-coupling
◦ mono- and oligosaccharides ◦ pyranoses and furanoses ◦ free saccharides
◦ intramolecular cross-couplings ◦ exclusive anomeric control ◦ over 50 examples