Communication

Highly Stereospecific Cross-Coupling Reactions of Anomeric Stannanes for the Synthesis of C-Aryl Glycosides

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Highly Stereospecific Cross-Coupling Reactions of Anomeric Stannanes for the Synthesis of C-Aryl Glycosides

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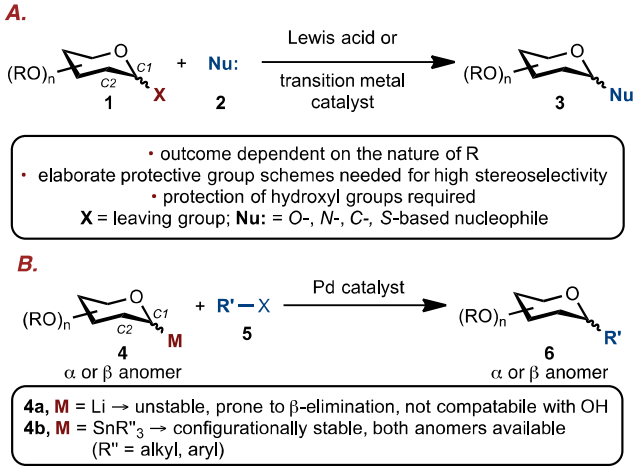
Supporting Information Placeholder

ABSTRACT: We demonstrate that configurationally-stable anomeric stannanes undergo a stereospecific cross-coupling reaction with aromatic halides in the presence of a palladium catalyst with exceptionally high levels of stereocontrol. In addition to a broad substrate scope (>40 examples), this reaction eliminates critical problems inherent to nucleophilic displacement methods, and is applicable to (hetero)aromatics, peptides, pharmaceuticals, common monosaccharides, and saccharides containing free hydroxyl groups.

The family of *C*-glycosides[1] is a class of saccharides that display high metabolic stability and includes many bioactive natural products[2] and commercial drugs.[3] The direct chemical methods to construct the key anomeric C-C bond focus on reactions of anomeric halides and carbon nucleophiles[4] or Friedel-Craft alkylations with electron rich aromatic substrates (Scheme 1A).[1b, 5] However, in addition to variable diastereoselectivities, poor functional-group tolerance is an inherent limitation of these two approaches and the reaction scope is restricted to substrates with protected hydroxyl and other acidic functionalities. As a consequence, a universal method, which enables a stereospecific synthesis of both anomers with minimal substrate control and influence of the protective groups remains as an unmet need. Our strategy to overcome the challenges of nucleophilic displacement methods[4a, 4b] capitalizes on stereospecific, Pd-catalyzed transformations of configurationally stable main-group organometallic C1-nucleophiles (Scheme 1B).[6] The success of this method takes advantage of the highly stereoretentive nature of the transmetallation step,[7] which can, in principle, independently translate the anomeric configuration to the product. Ideally, this stereocontrol would be irrespective of the steric and electronic characteristics of the saccharides and other coupling partners.[6a]

To test the validity of this proposal, we investigated anomeric organostannanes.[8] Alkylstannanes offer an optimal compromise between configurational stability and nucleophilicity, and seminal work by Falck[9] established that α-alkoxyalkylstannanes show increased migratory aptitude and undergo preferential transfer of the oxygen-substituted alkyl groups. Chiral C(sp^3) organostannanes can also participate in a stereoretentive Pd-catalyzed Stille-Migata reaction with C(sp^2) electrophiles,[10] although the stereoinvertive pathway has been observed in selected cases.[11] Anomeric stannanes **4b** are easily prepared with high yields and excellent α/β selectivities from glycals or anomeric halides (See, the SI). Both anomers of common monosaccharides are available, and, unlike other C1 nucleophiles (e.g., anomeric organolithium reagents[12]), they are stable against air and moisture, can be purified by standard chromatographic techniques, and retain their stereochemical integrity during storage.

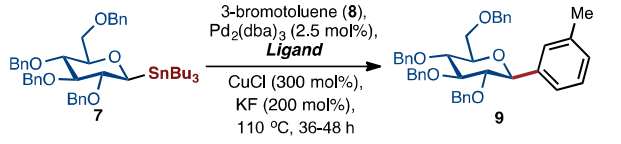
Scheme 1. Chemical glycosylation



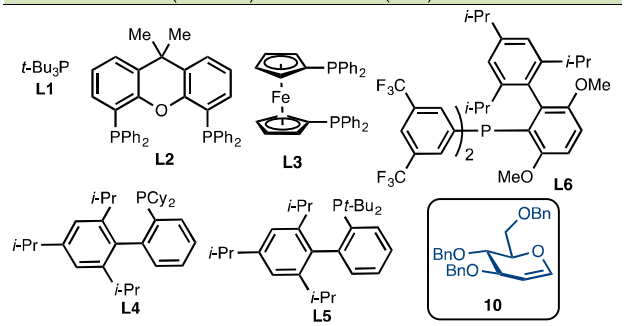
To identify the optimal catalytic conditions for glycosyl C(sp^3)-C(sp^2) cross-coupling, we used (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)tributylstannane **7** (α:β > 1:99, 1.5 equiv) and 3-iodotoluene **8** (1.0 equiv) as a model system (Table 1). The combination of $Pd_2(dba)_3$ (2.5 mol%) with a copper(I) salt (CuCl, 300 mol%) and a fluoride source (KF, 200 mol%) known to accelerate the Stille-Migata reaction was tested.[13] We hypothesized

that the competitive β-elimination of the C2 benzyloxyl group could be controlled through a judicious choice of ligand and that bulky phosphine ligands would reduce the formation of **10**.[10b] In this event, tri-*n*-butylphosphine **L1** resulted in a low yield of product **9** (9%) and considerable amounts of glucal **10** (42%), with the remaining material being unreacted **7**. Bidentate ligands (**L2** and **L3**) were less effective in promoting this reaction (entries 3 and 4), and biaryl phosphines **L4** and **L5** furnished only β-elimination product (**10**) with no detectable amounts of **9**. However, ligand **L6** (JackiePhos)[10b, 14] resulted in a substantially improved yield (57%) of **9**, with undetectable amounts of the glucal **10**. These lead conditions were fine-tuned (entry 9) by simply extending the reaction time (48 h) and using a polar solvent (1,4-dioxane) to furnish **9** in excellent yield (94%).

Table 1. Optimization of phosphine ligands and reaction conditions



Entry	Ligand	9[a]	α:β[b]	10[c]
1	**L1** (10 mol%)	9%	> 1:99	42%
2	**L2** (5 mol%)	6%	>1:99	19%
3	**L3** (5 mol%)	<2%	N.D.	38%
4	**L4** (10 mol%)	<2%	N.D.	24%
5	**L5** (10 mol%)	<2%	N.D.	20%
6	**L6** (5 mol%)	57%	>1:99	<2%
7	**L6** (10 mol%)	69%	>1:99	<2%
8	**L6** (10 mol%)	87%	>1:99	10%
9[d]	**L6** (10 mol%)	94% (91%)[e]	>1:99	25%



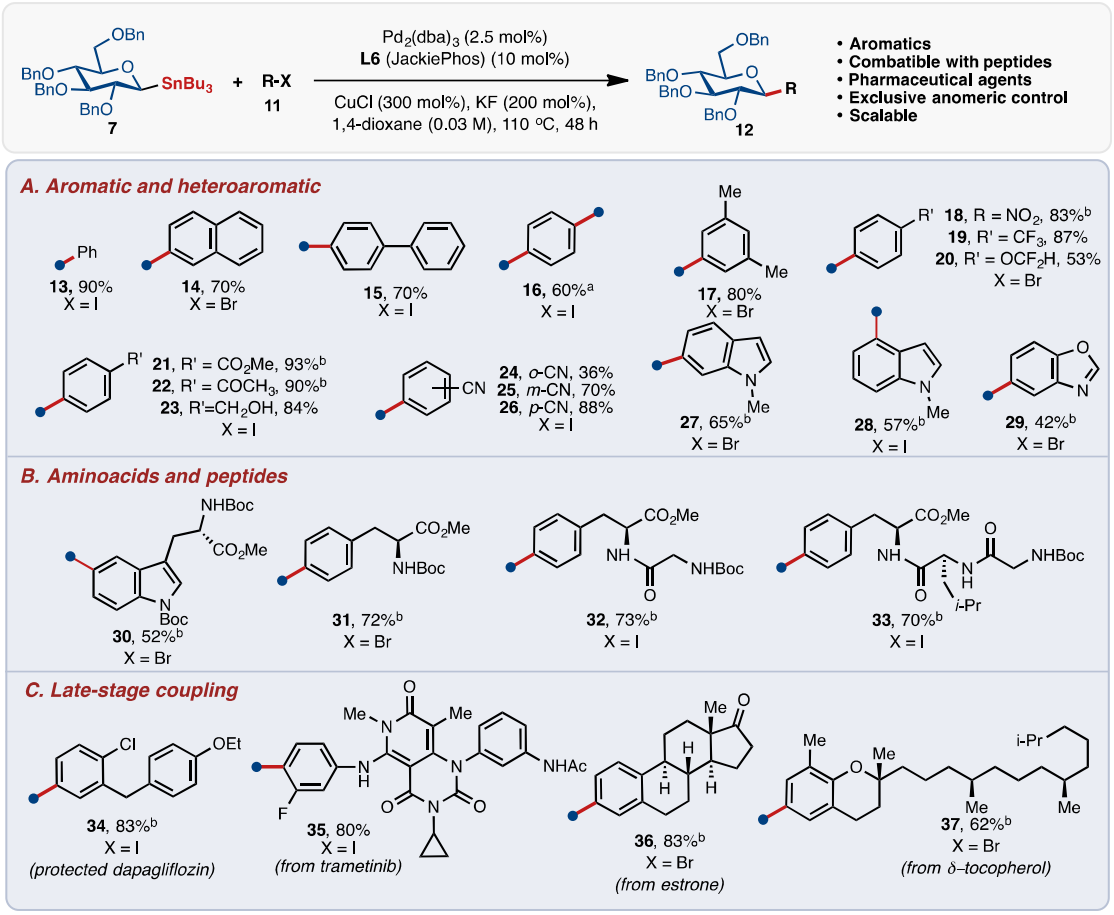
General reaction optimization conditions – **7** (1.5 equiv), **8** (1.0 equiv), $Pd_2(dba)_3$ (2.5 mol%), CuCl (300 mol%), KF (200 mol%), solvent (0.03 M); [a]NMR yield determined using internal standard ($CHBr_3$). [b]Determined by analysis of the unpurified reaction mixture by ^1H nuclear magnetic resonance (NMR) spectroscopy. [c]NMR yield based on **7**. [d]Reaction time: 48 h. [e]Isolated yield of homogenous and analytically pure material.

The standardized cross-coupling protocol was tested with various aromatic partners, and Scheme 2 depicts the scope of the reactions with **7**. Aromatic iodides and bromides derived from phenyl (**13**), polycyclic (**14**, **15**), and disubstituted (**17**) aromatic substrates provided the expected products in consistently high yields (70-90%). Similarly, electronic modifications of the aromatic ring appear to have little effect on the reaction yields for substrates with electron-rich (**20**, **23**) and electron-poor (**18**, **19**, **21**, **24-26**) substituents. *Ortho* (**24**) substitution around the aromatic ring was tolerated, although the yield was diminished (36%). We also demonstrated a double cross-coupling reaction using 1,4-diiodobenzene (**16**). Heteroaromatic compounds containing nitrogen (**27-28**) and oxygen (**29**) afforded *C*-glycosides in reduced but useful yields (42-65%). The cross-coupling reaction of stannane **7** with iodobenzene was also conducted on a gram scale with no impact on yield or selectivity.

The attachment of saccharides to peptides and proteins is a common post-translational modification,[15] and we wondered whether this method would be suitable for the synthesis of glycopeptides. First, reactions of **7** with 5-bromo-L-tryptophan and 4-iodo-L-phenylalanine afforded the glycoconjugates **30** and **31** (Scheme 2B). On the basis of this result, the optimized protocol was extended to the synthesis of phenylalanine peptides to provide the glycoconjugates **32** and **33** with exclusive β-selectivities. We expect that this coupling method will find use as a tool for site-selective modification of peptides and small proteins[16] and will open pathways to identify new drug candidates with improved stabilities and pharmacokinetic profiles. Furthermore, we efficiently synthesized protected dapagliflozin[3b] (**34**, 83%), a type 2 antidiabetic drug (Scheme 2C). Additionally, to determine the compatibility of the palladium-catalyzed coupling protocol with complex organic substrates, we converted trametinib,[17] a MEK inhibitor used as an anticancer drug, into *C*-glucoside **35** in 90% yield. Other complex molecules such as sterols (**36**, 83%, derived from estrone) and antioxidants (**37**, 62%, derived from δ-tocopherol) are also viable substrates. In all cross-coupling reactions with **7**, the formation of only one (β) diastereomer was observed.

Next, we applied the general cross-coupling protocol to various monosaccharides (Scheme 3). Despite many similarities, seemingly minor structural and electronic modifications around the saccharide core can result in variable outcomes of glycosylation reactions.[4a, 4b] First, we tested whether the α anomer **40** could be prepared from the corresponding α-stannane (diastereomeric purity α:β > 99:1) and iodobenzene. Under the optimized conditions, we observed that **40** was formed as the sole anomer although in a low yield (16%). However, by simply increasing the reaction temperature to 140 °C, the yield of **40** could be improved to 70%. Other *C*-saccharides derived from D-galactose and *N*-acetyl-D-glucosamine were also efficiently prepared through this

Scheme 2. Scope of cross-coupling of β-glucoside 7 with aromatic iodides and bromides

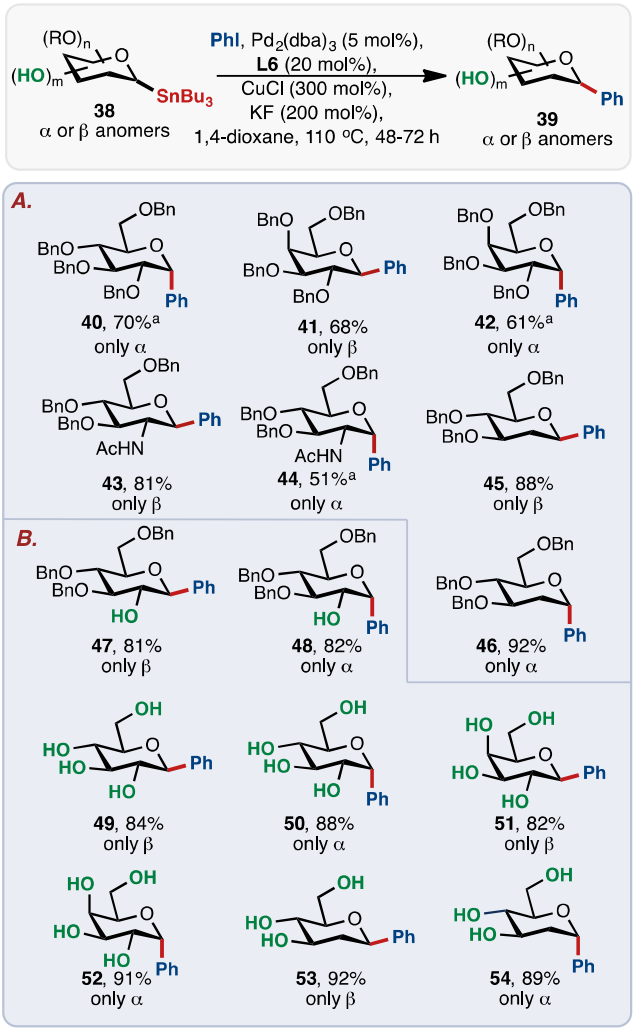


The reaction conditions were adopted from Table 1, entry 9. Reaction yields refer to isolated, analytically pure material. [a]**7** (3.0 equiv), $Pd_2(dba)_3$ (5 mol%), L6 (20 mol%), 96 h; [b]**7**(2.0 equiv), $Pd_2(dba)_3$ (5 mol%), **L6** (20 mol%), 72 h.

method; both anomers underwent stereospecific coupling to provide the corresponding α (**42**, 61%; **44**, 51%) and β (**41**, 68%; **43**, 81%) isomers. The reactions with *N*-acetyl-D-glucosamine are of special interest because, unlike other glycosylation reactions controlled by the C2 substituent,[4a-c] the stereochemical outcome of this transformation is not dependent on the nature of the nitrogen group (participating vs. non-participating) at C2. This result also illustrates a complementary approach to the synthesis of α-glucosides, which currently is not feasible by other coupling methods involving organometallic reagents and anomeric halides. Moreover, many bioactive natural products contain *C*-deoxysugars,[2] and we also established that the removal of the oxygen substituent from C2 does not affect the efficiency of the coupling reaction. Specifically, stereoretentive coupling was observed for both anomers of 2-deoxy-D-glucose (**45**, **46**).

Finally, because we obtained cross-coupled products of free alcohols and amides in high yields, we also wondered if saccharides with free hydroxyl groups can participate in this transformation (Scheme 3B). Thus, we first investigated glycosides with free C2-OH to evaluate the compatibility of the previously identified conditions with the neighboring hydroxyl groups. Both anomers of glucose (**47**, **48**) underwent conversion with iodobenzene (81-82%). Encouraged by these results, we subsequently applied the same conditions to triol and tetraol stannanes, resulting in the respective anomers **49-54** in uniformly high yields (82-92%). As expected, these reactions were less prone to β-elimination, and the major side products were 1-deoxysugars resulting from protodestannylation of the anomeric stannanes **38**. We anticipate that the cross-coupling can be further extended to more complex substrates, although additional modifications may be required because of the limited solubility of polyhydroxylated oligosaccharides in organic solvents.

Scheme 3. Scope of cross-coupling reactions of iodobenzene with monosaccharides



General reaction conditions were adopted from Table 1, entry 9. All anomeric stannanes were used as a single diastereoisomer (*dr* >99:1, ^{1}H NMR). [a]*m*-xylene, 140 °C.

To conclude, we described here the first example of a direct stereospecific synthesis of aryl *C*-glycosides using anomeric stannanes. In a broader context, our results demonstrate unprecedented control of the anomeric configuration enabled by a stereospecific cross-coupling reaction with C1 stannanes. This technology eliminates many problems inherent to the previous nucleophilic displacement methods, and, because of its exceptionally broad substrate scope and high chemoselectivity, it will create new opportunities to incorporate saccharides into small molecules and biologics.[18]

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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