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Convergent Palladium-Catalyzed Stereospecific Arginine Glycosylation Using Glycals

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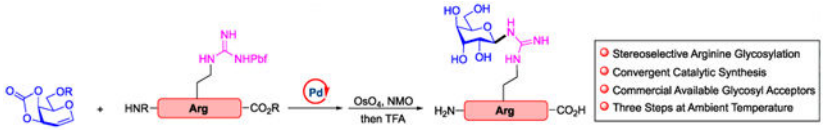
Abstract

A stereospecific convergent peptide arginine glycosylation method is reported for the first time. A recently discovered arginine glycosylation invigorated the interests of arginine modification, which has been challenging, because of the inertness of the guanidino side chain. The approach renders the arginine glycoside construction convergently. Catalyzed by palladium complex, glycals modify arginine guanidino groups in one step with high functional group tolerance at ambient temperature. The glycosylated products may be converted to glycopeptide analogues in few steps.

Graphical Abstract



Arginine is structurally unique and a critical role in biological systems.[1] Its guanidino side chain is protonated at physiological pH, which makes arginine a charged species. Functionalization of the arginine side chain during the protein post-translational modification (PTM) is a commonly observed occurrence, such as citrullination[2] and methylation.[3] Recently, a novel PTM of arginine was reported, where guanidinium side chain was glycosylated by *N*-acetylglucosamine[4] and rhamnose[5] in pathogenic bacteria. Meanwhile, other arginine modifications are extensively investigated and well-understood.[6] The investigations of arginine glycosylation have been limited and establishing a chemical methodology that could rapidly construct arginine glycosides motifs could certainly accelerate the biomedical studies of arginine PTM.

Glycosylation is one of the most opulent and critical protein PTMs. Commonly observed saccharides attachments occur at Ser/Thr/Tyr (*O*-Link) and Asn (*N*-Link) residues,[7] whereas the arginine glycosylation has been a much less known process and under-utilized. Perhaps

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Complete experimental procedures and characterization data for all new compounds (PDF)

such rare occurrences are attributed to the inertness of the guanidino group.[8] From a synthetic standpoint, the inability to functionalize guanidinium motifs became more compelling. Transformations involving arginine side chains often employed strong electrophiles to compensate for the relatively weak nucleophilicity of ketimine.[9] The challenge of glycosylation is elevated because of the steric and electronic properties of glycosyl donors. As a case in point, in the reports of the chemical synthesis of arginine Glc *N*-acylation by Shao, Liu and Hu,[10] the strategy for installing carbohydrates was illustrated as the union of thiourea glycosides and ornithine-bearing peptides (Figure 1a). Such maneuvers elegantly circumvent the difficulties in connecting canonical glycosyl donors and acceptors; however, the introduction of nonproteinogenic amino acid ornithine and elaborated multistep preparation of glycosyl thiourea hampers its general application. Ideally, direct construction of glycopeptides using a native arginine bearing peptide with a commonly used glycosyl donor at the reducing end would significantly improve the efficiency of arginine glycoside chemical preparation. Herein, we report a catalytic method that provides stereoselective arginine glycosylation in a convergent fashion for the first time, using glycals and commercially available arginine precursors (Figure 1b).

In the past decades, the palladium-catalyzed glycosylation reaction has been extensively developed and successfully applied in the synthesis.[11] Our previous studies have revealed the extraordinary ability of glycals toward glycosyl acceptors.[12] Under palladium-mediated conditions, external nucleophiles such as Ts-NR moieties could achieve exclusive stereoselectivity and excellent yields.[12b] In order to fine-tune the *N*-glycosyl acceptor's nucleophilicity, the Ts sulfonyl group is required as an activator, which is extremely difficult to remove[13] without degrading the construct of the carbohydrates (Figure 2). We speculate that the 2,2,4,6,7-pentamethyldihy-drobenzofuran-5-sulfonyl (pbf) group could replace the Ts functional group, and the protocol for pbf removal is well-documented and mild under acidic conditions[14] (cf. Figure 2). If successful, arginine glycosylation could be achieved via routinely utilized, commercially available Fmoc-Arg(pbf) and Boc-Arg(pbf) building blocks, which could significantly improve the efficiency for preparing arginine glycopeptides.

We believed that glycal 1a would be an ideal glycosyl donor for initial evaluation, which was prepared via a quick two-step sequence from commercially available saccharide (Scheme 1). Glycosylation of pbf protected arginine methyl ester 2a with glycal 1a under palladium catalyzed conditions was evaluated. The combination of $Pd(OAc)_2$ and xantphos as a ligand was first investigated, and the reaction produced desired product 3a with exclusive β-stereochemistry and 29% yield after 24 h at ambient temperature (Scheme 1, entry 1). The structure of 3a was identified by extensive one-dimensional (1D) and two-dimensional (2D) NMR experiments (see the SI for stereochemistry and regiochemistry assignments). When divalent palladium catalyst $Pd(PPh_3)_2Cl_2$ was employed, however, we did not observe glycosylation product (Scheme 1, entry 2). To our surprise, zerovalent $Pd(PPh_3)_4$, or $Pd_2dba_3{\cdot}CHCl_3$, improved the reaction yields significantly (Scheme 1, entries 3 and 4). Next, several phosphine bidentate ligands, such as dppb, dppe, dppp, and dppf were screened (Scheme 1, entries 5–8), yet the yields were inferior (0%–21%). Chiral biaryl BINAP was evaluated, and no product was found (Scheme 1, entry 9). DPEPhos, *N*-xantphos, and monodentate phosphine ligand were less effective than xantphos (Scheme 1, entries 10–12). When 3 equiv of glycal 1a was used, a higher yield of 3a was obtained

(Scheme 1, entry 13). Switching to $Pd(PPh_3)_4$ afforded a comparable yield but much faster reaction time (2 h). Although $Pd(PPh_3)_4$ rendered a slightly higher yield (73%) and shorter reaction time, the formation the trace amount of byproduct [$(O)PPh_3$] from the ligand complicates the silica gel purification (same rf with certain products). Our further studies use both conditions when appropriate. Without palladium catalyst or ligand, the reaction could not occur (Scheme 1, entries 15 and 16).

With the optimized conditions in hand, we subsequently investigated the arginine glycosylation in a more-complicated system (Scheme 2). The commercially available Fmoc-Arg(pbf)-OMe successfully provided product in comparable yield (71%). We then explored a dipeptide system. Arginine–valine produced 3c smoothly with 71% yield, indicating that dipeptides could be glycosylated. Other amino acid residues with hydrophobic side chains were well-tolerated, such as arginine–alanine, in which the carboxyl was protected by Bn and produced 3d with 75% yield. For arginine–leucine with ^{t}Bu, 3e was generated with 64% yield. Even for compounds with a rigid proline substrate, glycosylation had no issue and generated 3f with 70% yield. Arginine–phenylalanine afforded corresponding product 3g with moderate 53% yield. Next, we implemented glycosylations using different dipeptides involving hydrophilic side chains. Arginine–aspartic acid with a methyl-protected carboxyl group, arginine–tyrosine with a ^{t}Bu-protected phenol, and arginine–lysine with a Boc-protected amine were demonstrated to be tolerated and gave good yield. Among them, arginine–lysine dipeptide generated 77% of 3j under similar conditions. In addition, we found that placing Arg(pbf) at the C-terminus of the peptides did not alter the reaction outcomes. Valine–arginine showed no difference in yield, when compared with arginine–valine. Under the reaction conditions, glycopeptide 3k was furnished with 72% yield. *N*-methyl-alanine-arginine and phenylalanine as glycosyl acceptors provided good results. The yield of 3l was 72% and 3m was 69%. Glycine–arginine generated product 3n with 41% yield. Dipeptide aspartic acid–arginine with a hydrophilic side chain gave a good result. Cysteine-derived dithio substrate delivered product 3p. Lastly, we found glycosylation, using tripeptide as an acceptor, produced glycoside 3q with 44% isolation yield.

Subsequently, we examined the scope of glycosyl donors (Scheme 3). Under reaction conditions, glycals 1 with dipeptide 2f furnished a variety of glycosides 3. The substituent groups such as TIPS, TBDPS, Bn, Bz, *t*Bu and adamantyl were well-tolerated, the dipeptide glycosides 3r–3x were produced in comparable yields (41%–73%). Lipidic and fluorescein side chains could also be managed and afforded 3y and 3z. The excellent stereoselectivity of arginine glycosylation was illustrated again by introducing an exclusive α-glycosidic bond in glycopeptide 3aa, utilizing D-allal carbohydrate as the donor, albeit wth a lower yield (35%).

The practicality of the arginine glycosylation method was illustrated in Scheme 4. Glycopeptide 3a was reduced via Pd/C and H_2 to generate a deoxy-sugar 4 in excellent yield. Furthermore, transformation of 3a with catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide afforded the corresponding glycopeptide 5a in 87% yield as a single diastereomer, which offered a chiral scaffold that could be mimicking *N*-acetylglucosamine or rhamnose. We expected that dihydroxylation occurred at the less sterically hindered α-face. Finally, a one-pot, two-step protocol successfully converts Arg glycoside 3g to a protecting-group-free

dipeptide 6 in high yield as a single diastereomer.[15] During the transformation, the pbf moiety was removed along with other common peptidyl protecting groups under acidic conditions. This protocol underscores the efficiency of our convergent arginine glycosylation methodology.

Based on the experimental data and our previously reported result,[11] the arginine glycosylation should undergo a classic Tsuji–Trost reaction mechanism.[16] (see Figure 3) The less sterically demanding face of glycal 1 forms a π-allyl Pd(0) species II, which should be the reaction intermediate and governs the stereoselectivity. The *N*-glycoside 3 can be produced upon attacking of arginine(pbf) 2 toward π-allyl Pd complex II. We do not fully understand why the xantphos attains superior reactivities, compared with other bidentate phosphine ligands. According to literature reports, we speculated that a larger cone angle between xantphos and palladium is attributed to the superior reactivity during allylation. It is well-documented that the Xantphos has a cone angle of 247° with palladium, compared to that obtained with dppe (225°), dppf (230°), and other bidentate ligands.[17] The studies from van Leeuwen et al.[18] suggested that a larger ligand cone angle not only promotes a faster oxidative addition, but also enhances the reaction rate of nucleophilic addition to π-allyl species and subsequent product dissociation.

In summary, we have established a convergent method that renders challenging peptide arginine glycosylation for the first time. This practical approach could establish the glycosidic bonds of arginine with exclusive regioselectivities, and stereoselectivities. The mild reaction processes were catalyzed by a palladium complex and enjoy high amino acid residue tolerance. Both glycosyl donors and acceptors are either easily obtained or commercially available. The dual functionality of the pbf construct was highlighted as a protecting as well as a specific activating group, which could be smoothly removed along with other commonly used amino acid protecting moieties. Compared with extant methods, our convergent approach provides a facile alternative strategy for highly efficient glycosylation, which potentially could assist the biological studies toward arginine glycosides. Further investigations of the glycosylation toward other protein modifications will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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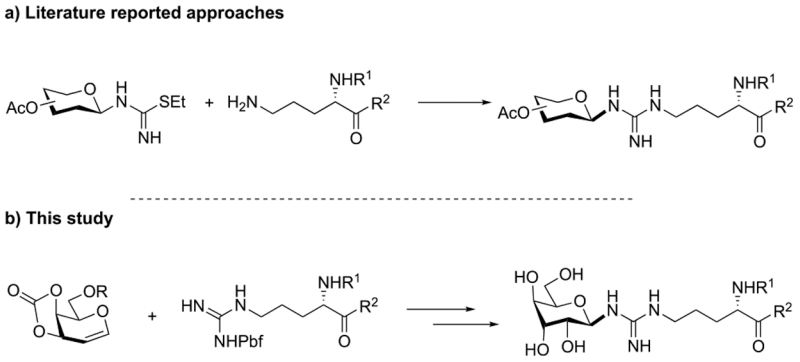


Figure 1.
Convergent arginine glycosylation.

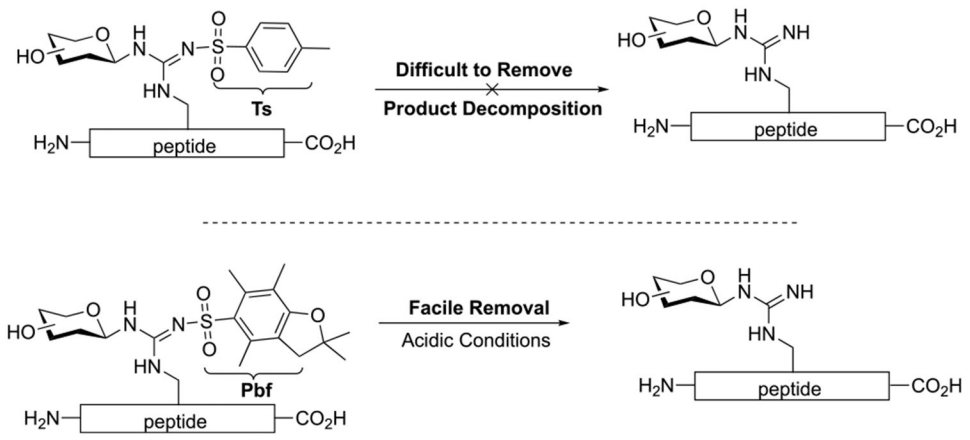


Figure 2.
Removal of sulfonyl activating groups.

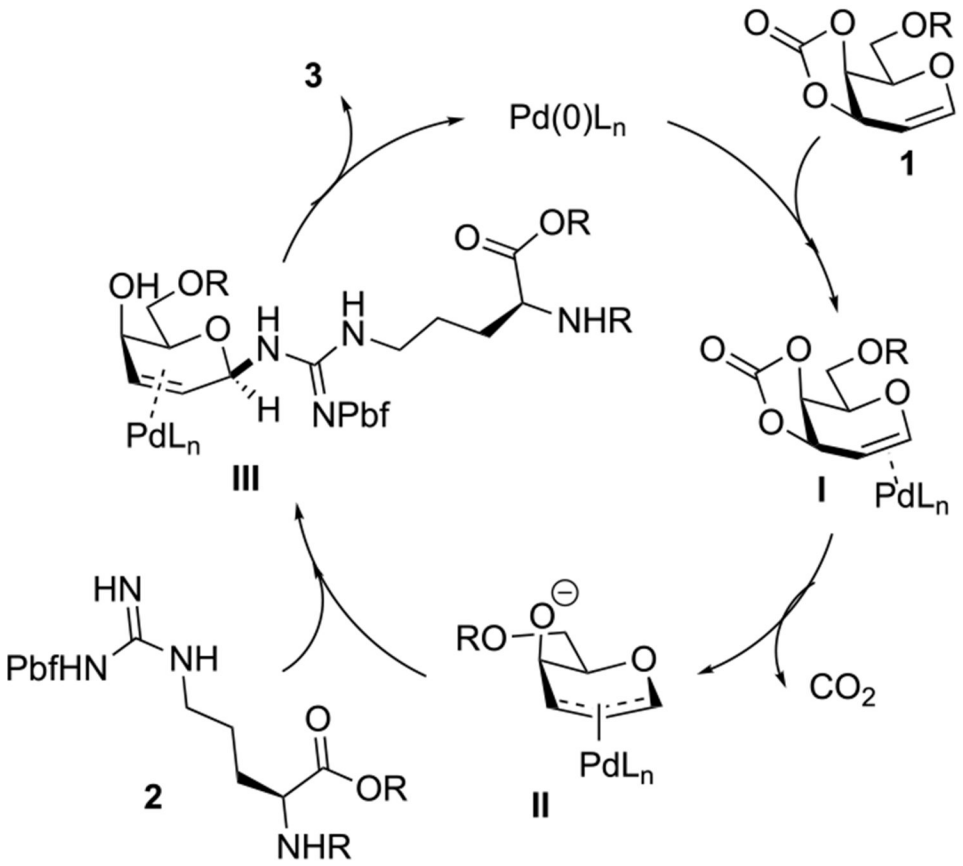
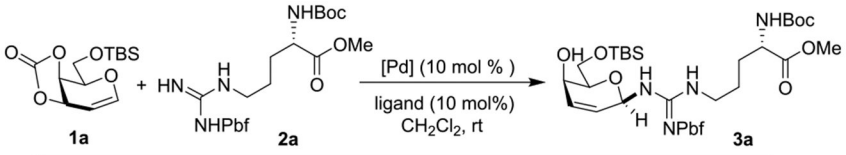
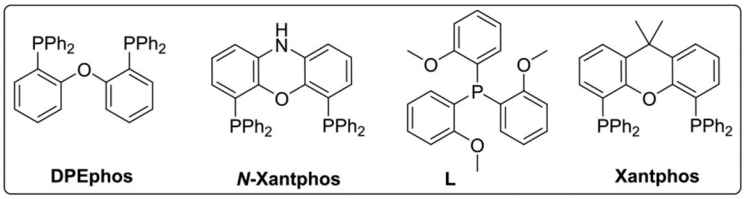


Figure 3.
Proposed arginine glycosylation mechanism.

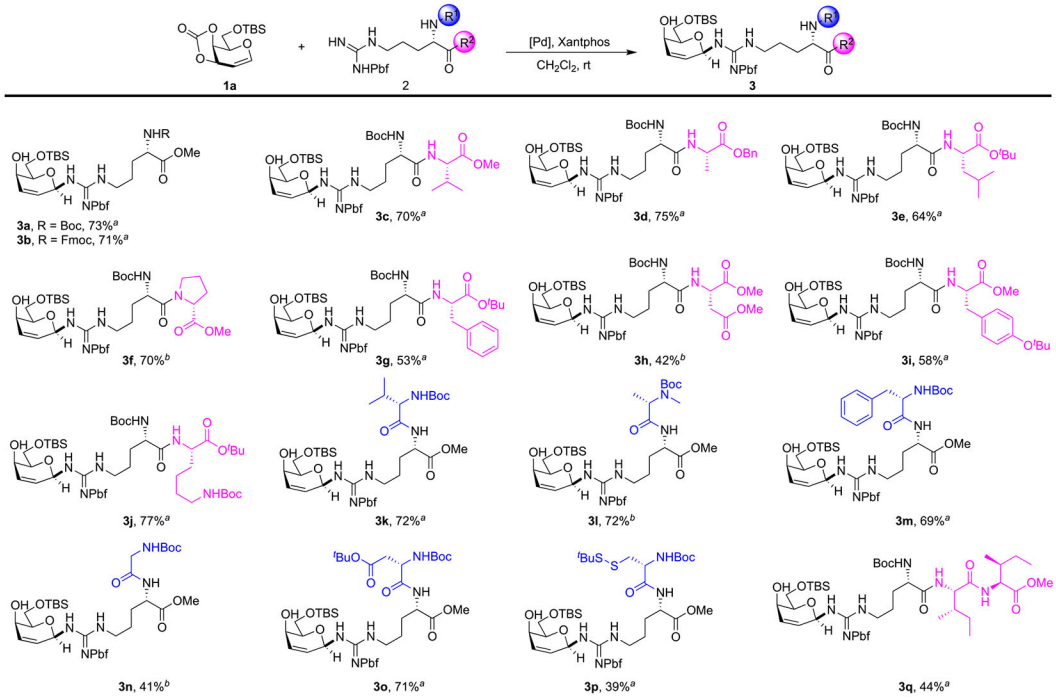




entry[a]	[Pd]	loading	ligand	t	yield[b]
1	$Pd(OAc)_2$	10 mol%	Xantphos	24 h	29%
2	$Pd(PPh_3)_2Cl_2$	10 mol%	Xantphos	24 h	ND[c]
3	$Pd(PPh_3)_4$	10 mol%	Xantphos	2 h	54%
4	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	Xantphos	24 h	60%
5	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	dppb	24 h	21%
6	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	dppe	24 h	ND[c]
7	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	dppp	24 h	10%
8	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	dppf	24 h	20%
9	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	(*R*)-BINAP	24 h	ND[c]
10	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	DPEphos	24 h	31%
11	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	*N*-Xantphos	24 h	36%
12[d]	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	L	24 h	23%
13[e]	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	Xantphos	24 h	69%
14[e]	$Pd(PPh_3)_4$	10 mol%	Xantphos	2 h	73%
15	$Pd_2dba_3 \cdot CHCl_3$	5 mol%	—	24 h	ND[c]
16	—	—	Xantphos	24 h	ND[c]

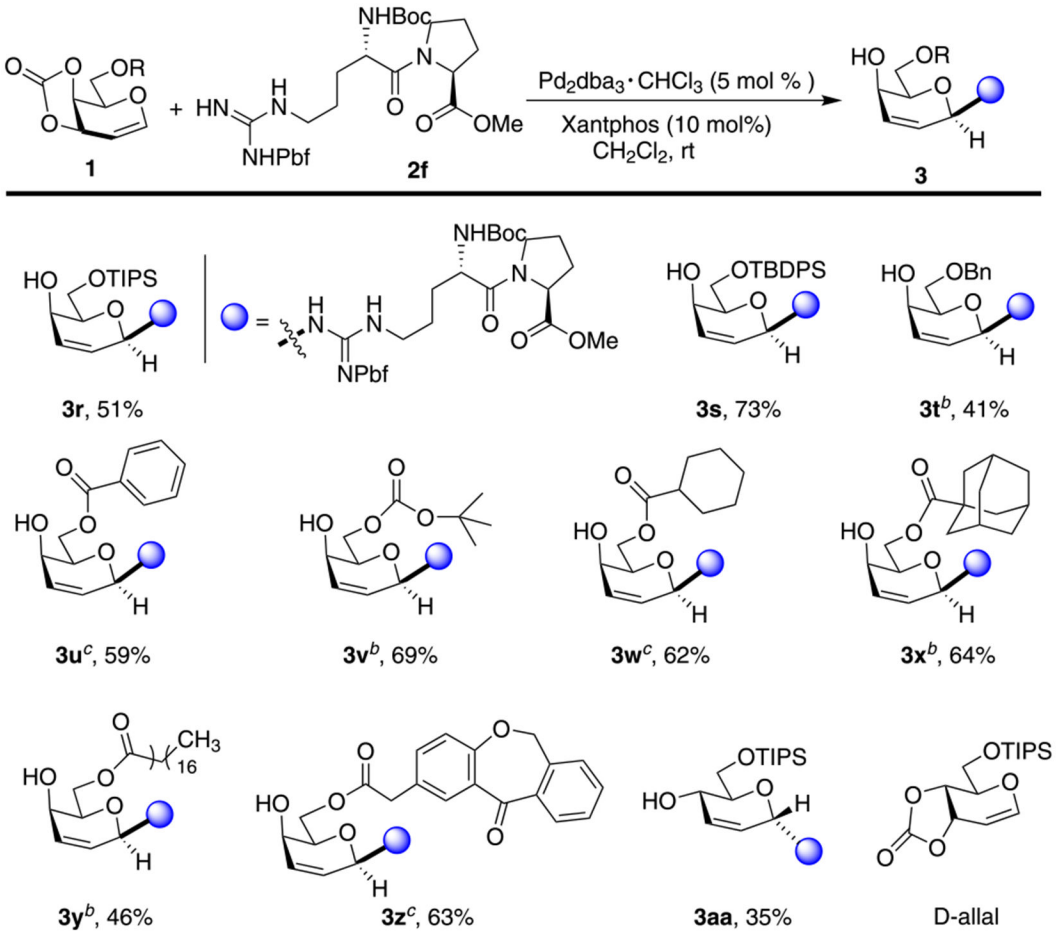
Scheme 1. Reaction Optimization for Arginine Glycosylation

[a]0.1 mmol 1a, 0.05 mmol 2a, 10 mol % [Pd] and 10 mol % ligand, 4 mL of CH_2Cl_2 were used. [b]Isolated yield. [c]Not detected. [d]20 mol % ligand was used. [e]0.15 mmol 1a and 0.05 mmol 2a were used.



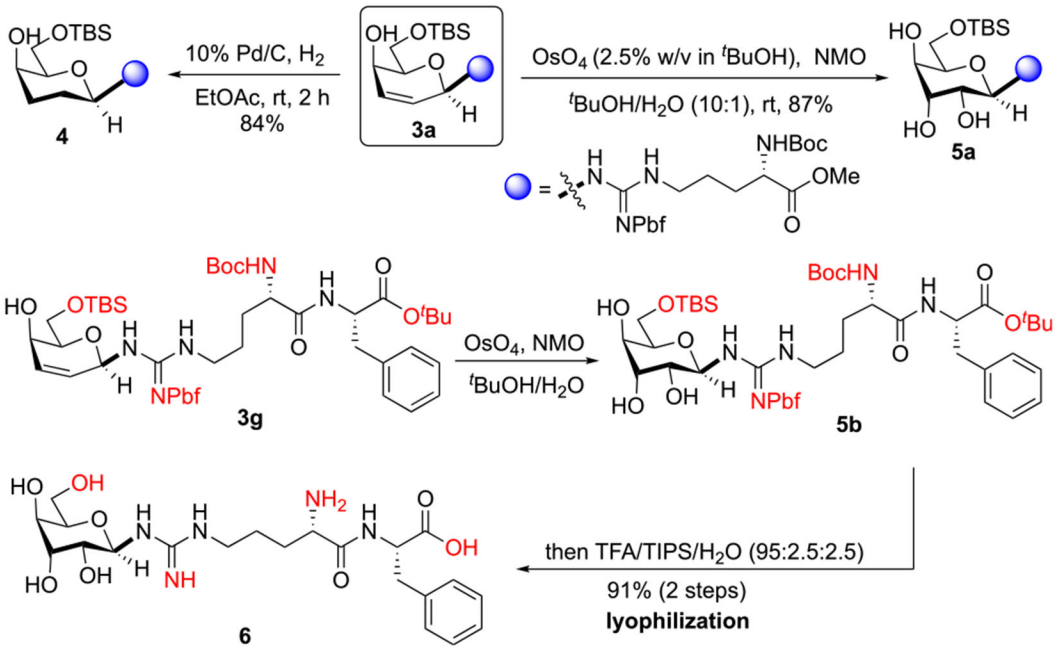
Scheme 2. Reaction Scope Evaluations

[a]Reaction conditions: 0.15 mmol 1a, 0.05 mmol 2, 10 mol % $Pd(PPh_3)_4$, 10 mol % xantphos, and 4 mL of CH_2Cl_2 were used, rt, 2 h, isolated yield. [b]5 mol % $Pd_2dba_3{\cdot}CHCl_3$, 24 h, isolated yield.



Scheme 3. Glycosyl Donor Evaluation[a]

[a]0.15 mmol glycal 1, 0.05 mmol 2f and 4 mL of CH_2Cl_2 were used, rt, 24 h, isolated yield. [b]Reaction time: 2 h. [c]Reaction time: 1 h.



Scheme 4. Functionalization of Arginine Glycosides