OL Organic Letters

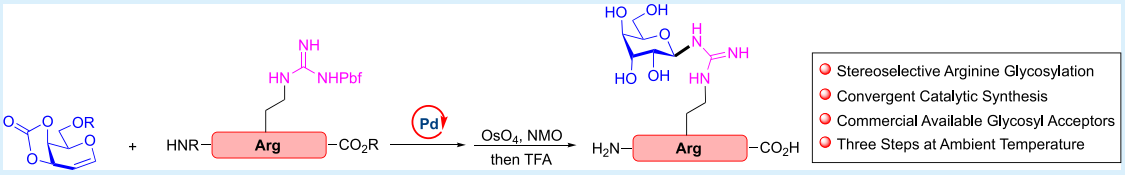
pubs.acs.org/OrgLett Letter

Convergent Palladium-Catalyzed Stereospecific Arginine Glycosylation Using Glycals

Jun Yang, Yuanwei Dai, Ryan Bartlett, and Qiang Zhang*

Cite This: *Org. Lett.* 2021, 23, 4008–4012 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



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.

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 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

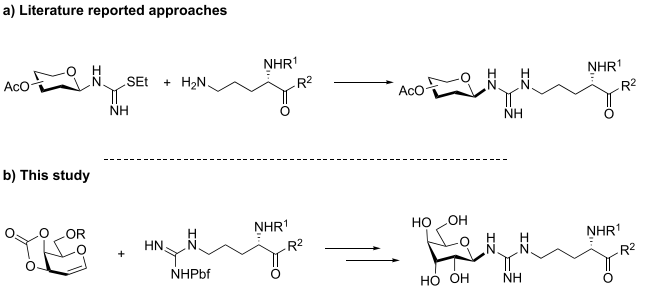


Figure 1. Convergent arginine glycosylation.

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]

Received: April 9, 2021
Published: May 12, 2021

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-pentamethyldihydrobenzofuran-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.

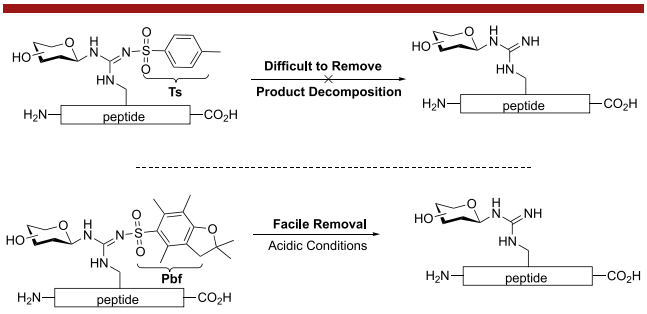
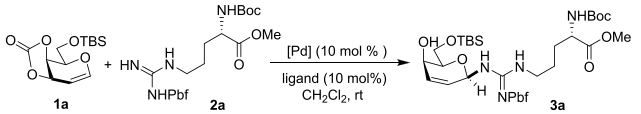
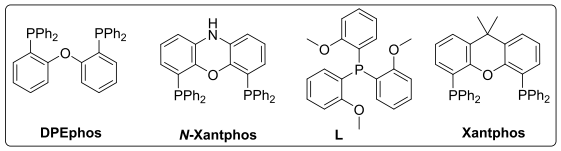


Figure 2. Removal of sulfonyl activating groups.

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).

Scheme 1. Reaction Optimization for Arginine Glycosylation





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]

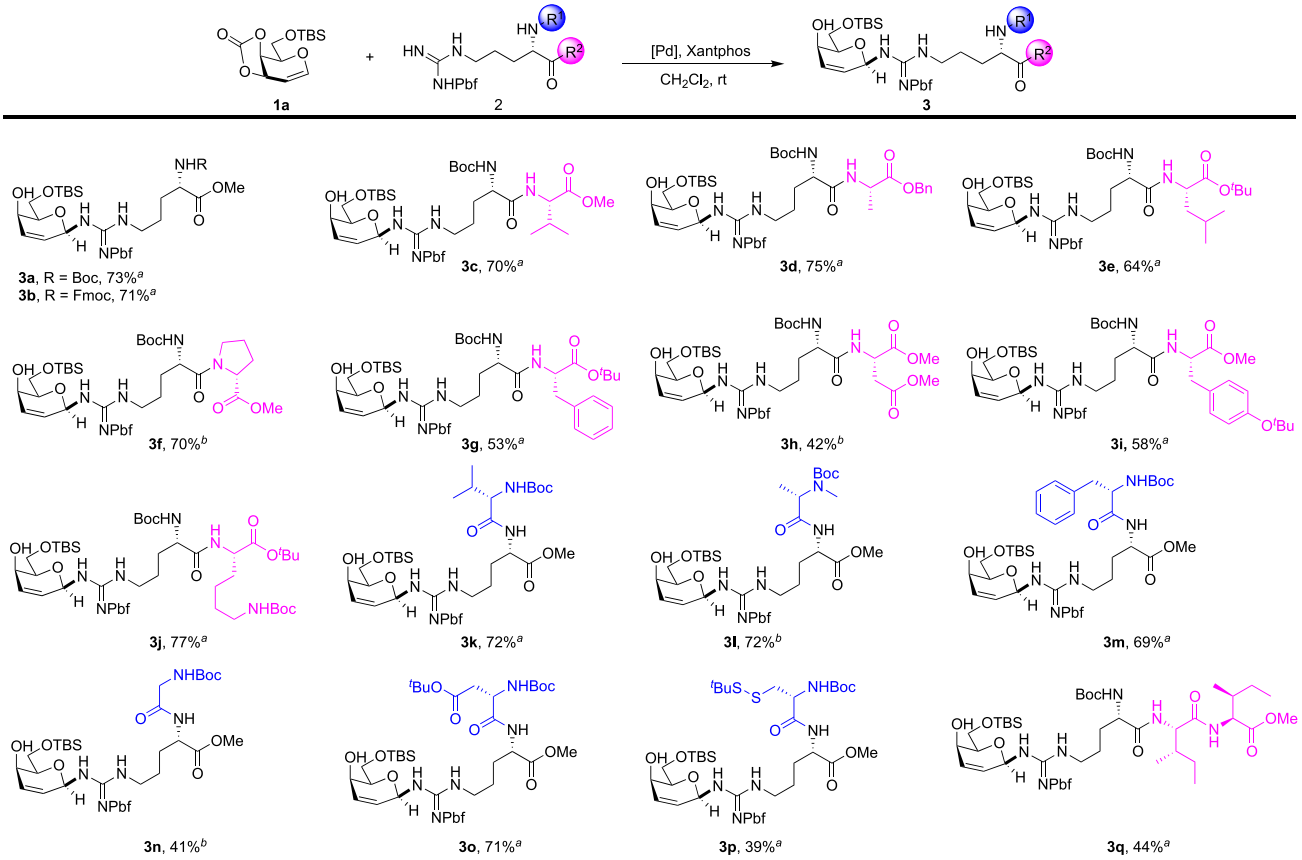
[a]0.1 mmol **1a**, 0.05 mmol **2a**, 10 mol % [Pd] and 10 mol % ligand, 4 mL of CH_2Cl_2 were used. [b]Isolated yield. [c]Not detected. [d]20 mol % ligand was used. [e]0.15 mmol **1a** and 0.05 mmol **2a** were used.

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.

https://doi.org/10.1021/acs.orglett.1c01218
Org. Lett. 2021, 23, 4008−4012

Scheme 2. Reaction Scope Evaluations

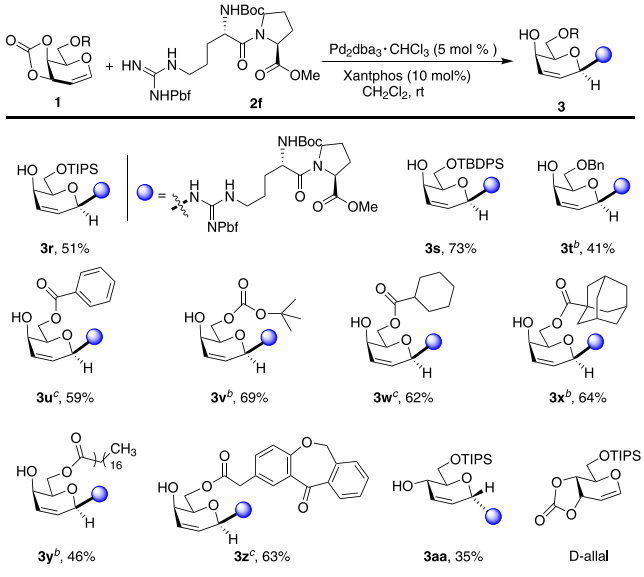


[a]Reaction conditions: 0.15 mmol **1a**, 0.05 mmol **2**, 10 mol % $Pd(PPh_3)_4$, 10 mol % xantphos, and 4 mL of CH_2Cl_2 were used, rt, 2 h, isolated yield. [b]5 mol % $Pd_2dba_3{\cdot}CHCl_3$, 24 h, isolated yield.

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%).

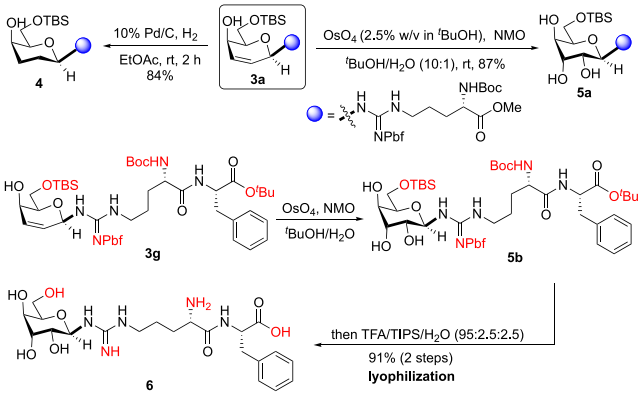
The practicality of the arginine glycosylation method was illustrated in Scheme 4. Glycopeptide **3a** was reduced via Pd/C and H_2 to generate a deoxy-sugar **4** in excellent yield. Furthermore, transformation of **3a** with catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide afforded the corresponding

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



https://doi.org/10.1021/acs.orglett.1c01218
Org. Lett. 2021, 23, 4008−4012

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

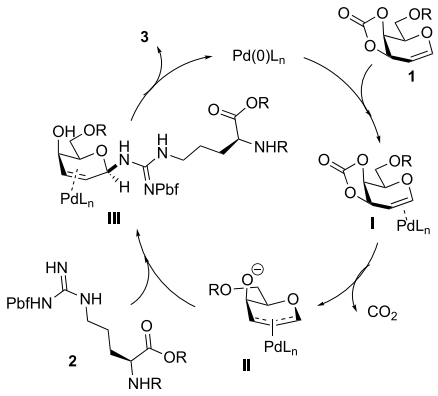


Figure 3. Proposed arginine glycosylation mechanism.

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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01218.

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

■ AUTHOR INFORMATION

Corresponding Author

Qiang Zhang − *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States;* orcid.org/0000-0003-2787-1781; Email: qzhang5@albany.edu

Authors

Jun Yang − *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States*

Yuanwei Dai − *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States*

Ryan Bartlett − *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01218

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work was provided by the National Science Foundation (No. CHE 1710174), and the National Institute of Health (No. 1R35 GM138336-01) to Q.Z. National Science Foundation is acknowledged (No. CHE 17267240) for the purchase of NMR services. We thank Prof. David Crich (University of Georgia) for his valuable suggestions.

■ REFERENCES

(1) Fuhrmann, J.; Clancy, K. W.; Thompson, P. R. Chemical biology of protein arginine modifications in epigenetic regulation. *Chem. Rev.* **2015**, *115*, 5413−5461.

(2) van Venrooij, W. J.; Pruijn, G. J. Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. *Arthritis Res.* **2000**, *2*, 249−251.

(3) Wu, Q.; Schapira, M.; Arrowsmith, C. H.; Barsyte-Lovejoy, D. Protein arginine methylation: from enigmatic functions to therapeutic targeting. *Nat. Rev. Drug Discovery* **2021**, DOI: 10.1038/s41573-021-00159-8.

(4) Xu, C.; Liu, X.; Zha, H.; Fan, S.; Zhang, D.; Li, S.; Xiao, W. A pathogen-derived effector modulates host glucose metabolism by arginine GlcNAcylation of HIF-1α protein. *PLoS Pathog.* **2018**, *14*, 1−29.

(5) Lassak, J.; Keilhauer, E. C.; Furst, M.; Wuichet, K.; Godeke, J.; Starosta, A. L.; Chen, J. − M.; Søgaard-Andersen, L.; Rohr, J.; et al. Arginine-rhamnosylation as new strategy to activate translation elongation factor P. *Nat. Chem. Biol.* **2015**, *11*, 266−270.

(6) Pan, X.; Luo, J.; Li, S. Bacteria-Catalyzed Arginine Glycosylation in Pathogens and Host. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 1−10.

(7) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E. *Essentials of Glycobiology*, 2nd Edition; Cold Spring Harbor Laboratories Press, 2009.
(8) Rao Kovvuri, V. R.; Xue, H.; Romo, D. Generation and Reactivity of 2-Amido-1,3-diaminoallyl Cations: Cyclic Guanidine Annulations via Net (3 + 2) and (4 + 3) Cycloadditions V. *Org. Lett.* **2020**, *22*, 1407−1413.
(9) Grundler, V.; Gademann, K. Direct Arginine Modification in Native Peptides and Application to Chemical Probe Development. *ACS Med. Chem. Lett.* **2014**, *5*, 1290−1295.
(10) (a) Pan, M.; Li, S.; Li, X.; Shao, F.; Liu, L.; Hu, H. G. Synthesis of and specific antibody generation for glycopeptides with arginine *N*-GlcNAcylation. *Angew. Chem., Int. Ed.* **2014**, *53*, 14517−14521. (b) Wang, S.; Corcilius, L.; Sharp, P. P.; Rajkovic, A.; Ibba, M.; Parker, B. L.; Payne, R. J. Synthesis of rhamnosylated arginine glycopeptides and determination of the glycosidic linkage in bacterial elongation factor P. *Chem. Sci.* **2017**, *8*, 2296−2302.
(11) For selected examples of palladium-catalyzed glycosylation, see: (a) Babu, R. S.; O'Doherty, G. A. A palladium-catalyzed glycosylation reaction: the de novo synthesis of natural and unnatural glycosides. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. De Novo Synthesis of Oligosaccharides Using a Palladium-Catalyzed Glycosylation Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429. (c) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. De Novo Asymmetric Bio- and Chemocatalytic Synthesis of Saccharides − Stereoselective Formal *O*-Glycoside Bond Formation Using Palladium Catalysis. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8175. (d) Sherry, B. D.; Loy, R. N.; Toste, F. D. Rhenium(V)-Catalyzed Synthesis of 2-Deoxy-α-glycosides. *J. Am. Chem. Soc.* **2004**, *126*, 4510−4511. (e) Kim, H.; Men, H.; Lee, C. Stereoselective Palladium-Catalyzed *O*-Glycosylation Using Glycals. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337. (f) Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. Palladium-Catalyzed Stereoselective Formation of α-*O*-Glycosides. *Org. Lett.* **2007**, *9*, 3173−3176. (g) Zeng, J.; Ma, J.; Xiang, S.; Cai, S.; Liu, X.-W. Stereoselective β-C-Glycosylation by a Palladium-Catalyzed Decarboxylative Allylation: Formal Synthesis of Aspergillide A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5134−5137. (h) Xiang, S.; Hoang, K L. M.; He, J.; Tan, Y.-J.; Liu, X.-W. Reversing the Stereoselectivity of a Palladium-Catalyzed *O*-Glycosylation through an Inner-Sphere or Outer-Sphere Pathway. *Angew. Chem., Int. Ed.* **2014**, *54*, 604−607. (i) Yao, H.; Zhang, S.-S.; Leng, W.-L.; Leow, M.-L.; Xiang, S.-H.; He, J.-X.; Liao, H.-Z.; Hoang, K. L. M.; Liu, X.-W. Catalyst-Controlled Stereoselective *O*-Glycosylation: Pd(0) vs Pd(II). *ACS Catal.* **2017**, *7*, 5456−5460. (j) Sau, A.; Williams, R.; Palo-Nieto, C.; Franconetti, A.; Medina, S.; Galan, M. C. Palladium-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals. *Angew. Chem., Int. Ed.* **2017**, *56*, 3640−3644. (k) Sau, A.; Galan, M. C. Palladium-Catalyzed α-Stereoselective *O*-Glycosylation of O(3)-Acylated Glycals. *Org. Lett.* **2017**, *19*, 2857−2860. (l) Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144−1153. (m) McKay, M. J.; Nguyen, H. M. Recent Advances in Transition Metal-Catalyzed Glycosylation. *ACS Catal.* **2012**, *2*, 1563−1595. (n) Li, X. H.; Zhu, J. L. Glycosylation via Transition-Metal Catalysis: Challenges and Opportunities. *Eur. J. Org. Chem.* **2016**, *2016*, 4724−4767. (o) Yu, B. Gold(I)-Catalyzed Glycosylation with Glycosyl o-Alkynylbenzoates as Donors. *Acc. Chem. Res.* **2018**, *51*, 507−516. (p) Leng, W.-L.; Yao, H.; He, J.-X.; Liu, X.-W. Venturing beyond Donor-Controlled Glycosylation: New Perspectives toward Anomeric Selectivity. *Acc. Chem. Res.* **2018**, *51*, 628−639.
(12) (a) Dai, Y.; Tian, B.; Chen, H.; Zhang, Q. Palladium-Catalyzed Stereospecific C-Glycosylation of Glycals with Vinylogous Acceptors. *ACS Catal.* **2019**, *9*, 2909−2915. (b) Dai, Y.; Zheng, J.; Zhang, Q. General Strategy for Stereoselective Synthesis of β-*N*-Glycosyl Sulfonamides via Palladium-Catalyzed Glycosylation. *Org. Lett.* **2018**, *20*, 3923−3927.
(13) Javorskis, T.; Orentas, E. Chemoselective Deprotection of Sulfonamides Under Acidic Conditions: Scope, Sulfonyl Group Migration, and Synthetic Applications. *J. Org. Chem.* **2017**, *82*, 13423−13439.
(14) Carpino, L. A.; Shroff, H.; Triolo, S. A.; Mansour, E. − S. M. E.; Wenschuh, H.; Albericio, F. The 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl group (Pbf) as arginine side chain protectant. *Tetrahedron Lett.* **1993**, *34*, 7829−7832.
(15) The relative stereochemistry of C2 and C3 hydroxyl groups are determined by coupling constant analysis. The larger coupling constant between C1 and C2 hydrogen (J = 9.0 Hz) indicates an anti-configuration, which reveal the OsO_4 approaches from the convex face of the glycal **3g**. For coupling constant analysis of a similar system, please see: Altona, C.; Haasnoot, C. A. G. Prediction of anti and gauche vicinal proton-proton coupling constants in carbohydrates: A simple additivity rule for pyranose rings. *Org. Magn. Reson.* **1980**, *13*, 417.
(16) (a) Tsuji, J. Catalytic Reactions via π-AllylPalladium complexes. *Pure Appl. Chem.* **1982**, *54*, 197−206. (b) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395−422. (c) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921−2944. (d) Trost, B. M.; Thaisrivongs, D. A. Strategy for Employing Unstabilized Nucleophiles in Palladium-Catalyzed Asymmetric Allylic Alkylations. *J. Am. Chem. Soc.* **2008**, *130*, 14092−14093. (e) Trost, B. M.; Zhang, T.; Sieber, J. D. Catalytic asymmetric allylic alkylation employing heteroatom nucleophiles: a powerful method for C−X bond formation. *Chem. Sci.* **2010**, *1*, 427−440. (f) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. Chemo-, Regio-, and Enantioselective Pd-Catalyzed Allylic Alkylation of Indolocarbazole Pro-aglycons. *Org. Lett.* **2002**, *4*, 2005−2008. (g) Guppi, S. R.; Zhou, M.-Q.; O'Doherty, G. A. De Novo Asymmetric Synthesis of Homoadenosine via a Palladium-Catalyzed N-Glycosylation. *Org. Lett.* **2006**, *8*, 293−296. (h) Yang, J.; Mercer, G. J.; Nguyen, H. M. Palladium-Catalyzed Glycal Imidate Rearrangement: Formation of α- and β-*N*-Glycosyl Trichloroacetamides. *Org. Lett.* **2007**, *9*, 4231−4234. (i) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. Palladium(II)-Catalyzed Rearrangement of Glycal Trichloroacetimidates: Application to the Stereoselective Synthesis of Glycosyl Ureas. *J. Am. Chem. Soc.* **2008**, *130*, 11210−11218. (j) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. An Efficient Approach to the Synthesis of Nucleosides: Gold(I)-Catalyzed *N*-Glycosylation of Pyrimidines and Purines with Glycosyl ortho-Alkynyl Benzoates. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933−4936. (k) Xiang, S.-H.; He, J. X.; Ma, J.-M.; Liu, X.-W. One-pot synthesis of β-*N*-glycosyl imidazole analogues via a palladium-catalysed decarboxylative allylatio. *Chem. Commun.* **2014**, *50*, 4222−4224. (l) Ji, L.; Xiang, S.-H.; Leng, W.-L.; Le Mai Hoang, K.; Liu, X.-W. Palladium-Catalyzed Glycosylation: Novel Synthetic Approach to Diverse N-Heterocyclic Glycosides. *Org. Lett.* **2015**, *17*, 1357−1360.
(17) Martinelli, J.; Watson, D.; Freckmann, D.; Barder, T.; Buchwald, S. J. Palladium-Catalyzed Carbonylation Reactions of Aryl Bromides at Atmospheric Pressure: A General System Based on Xantphos. *J. Org. Chem.* **2008**, *73*, 7102−7107.
(18) van Haaren, R.; Goubitz, K.; Fraanje, J.; van Strijdonck, G.; Oevering, H.; Coussens, B.; Reek, J.; Kamer, P.; van Leeuwen, P. An X-ray Study of the Effect of the Bite Angle of Chelating Ligands on the Geometry of Palladium(allyl) Complexes: Implications for the Regioselectivity in the Allylic Alkylation. *Inorg. Chem.* **2001**, *40*, 3363−3372.

https://doi.org/10.1021/acs.orglett.1c01218
Org. Lett. 2021, 23, 4008−4012