OL | Organic Letters

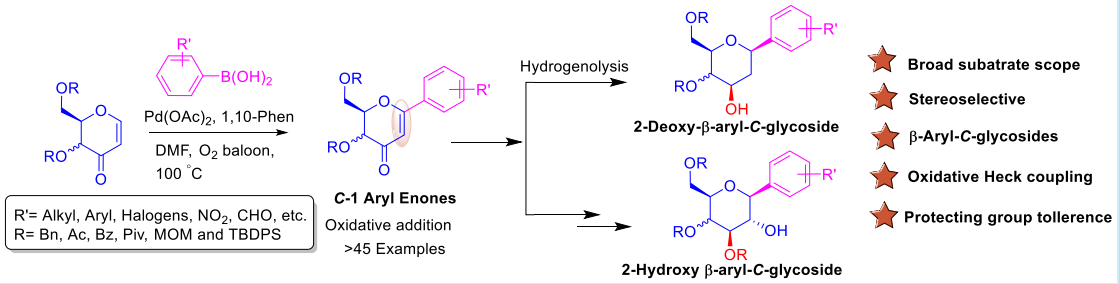
pubs.acs.org/OrgLett Letter

Development of Routes for the Stereoselective Preparation of β-Aryl-C-glycosides via C-1 Aryl Enones

Adesh Kumar Singh, Vimlesh Kumar Kanaujiya, Varsha Tiwari, Shahulhameed Sabiah, and Jeyakumar Kandasamy*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02843 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A wide range of enones derived from D-glucal, D-galactal, L-rhamnal, D-rhamnal, and L-arabinal underwent Heck-coupling with various arylboronic acids bearing electron-donating and -withdrawing groups in the presence of palladium acetate and 1,10-phenanthroline. These reactions provided synthetically useful C-1 aryl enones in good yields. Many sensitive functional groups as well as protecting groups present in arylboronic acids and enones, respectively, remained intact under optimized conditions. The stereoselective hydrogenation of C-1 aryl enones with Pd-C/H_2 provides the β-isomer of 2-deoxy-aryl-C-glycosides in excellent yield. The C-1 aryl enones were also used as precursors for the synthesis of 2-hydroxy-β-aryl-C-glycosides. Regioselective C-2 halogenations and vinylations of C-1 aryl enones were achieved in excellent yields.

Aryl-C-glycosides are unique structural motifs found embedded in plenty of biologically relevant natural products (Figure 1).[1] It is worth mentioning that recently

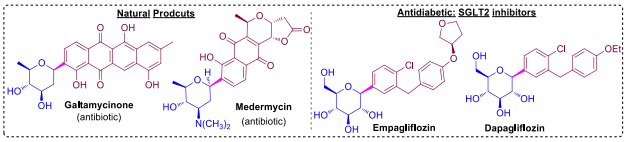


Figure 1. Biologically relevant natural and synthetic aryl-C-glycosides.

many synthetic aryl-C-glycosides have been approved for the treatment of type-2 diabetes (i.e., SGLT1/SGLT2 inhibitors).[2] The majority of the naturally occurring aryl-C-glycosides are of two types, namely, 2-hydroxy-β-aryl-C-glycosides and 2-deoxy-β-aryl-C-glycosides.

In this context, numerous methods have been developed for the preparation of 2-hydroxy-β-aryl-C-glycosides.[1a−g] Moreover, recently, a radical-mediated stereoselective one-step preparation of 2-hydroxy-β-aryl-C-glycosides has been demonstrated.[1h−j] In contrast, only limited methods are available for the synthesis of 2-deoxy-β-aryl-C-glycosides.[1a−g,3] Glycals are important precursors that are widely employed in the preparation of 2-deoxy-aryl-C-glycosides. Palladium-catalyzed Heck-type coupling of glycals with various aryl donors (e.g., aryl halides, arylboronic acids, etc.) leads to the formation of either 2-deoxy-2,3-unsaturated aryl-C-glycosides (through β-hydride elimination)[4] or 2,3-deoxy-2,3-unsaturated aryl-C-glycosides[5] (through β-heteroatom elimination), largely based on the protecting groups. However, it is important to note that the majority of these reactions provide α-selective aryl-C-glycosides, whereas β-anomers are more predominant in nature.

In one of the approaches, Yang et al. demonstrated the transformation of 2,3-deoxy-2,3-unsaturated α-aryl-C-glycosides (obtained through Heck coupling from glycal and aryl bromides) into 2-deoxy-β-aryl-C-glycosides via sequence oxidation−reduction reactions.[4b] Some recent approaches, including the Heck coupling of glycals with aryldiazonium salts followed by acid-catalyzed anomerization of the resulting α-C-glycosides[6] or the use of limitedly available 3,5-*anti*-glycals as the substrates[7] in Heck coupling, provide 2,3-deoxy-3-keto β-C-glycosides. However, these approaches suffer from a

Received: August 25, 2020

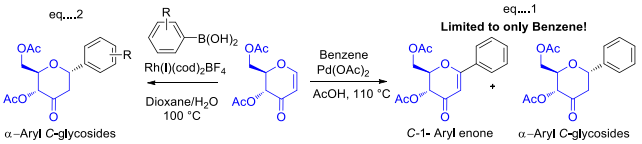
https://dx.doi.org/10.1021/acs.orglett.0c02843
Org. Lett. XXXX, XXX, XXX−XXX

limited substrate scope as they require fully armed protecting groups (e.g., benzyl or silyl) containing glycal substrates for the Heck coupling reaction.[4b,6,7] To this end, recently, Nishimura et al. reported the iridium-catalyzed ligand-controlled stereoselective synthesis of both α- and β-aryl-*C*-glycosides from glycals and arenes bearing a directing group.[3e]

On the contrary, cross-coupling of *C*-1-functionalized glycals (e.g., *C*-1 metal glycals or iodoglycals)[8] with appropriate aryl donors leads to the formation of 2-deoxy-1,2-unsaturated aryl-*C*-glycosides, which can be efficiently transformed to both 2-hydroxy-β-aryl-*C*-glycosides and 2-deoxy-β-aryl-*C*-glycosides.[1a−c] However, the preparation of *C*-1-functionalized glycals is usually associated with many difficulties, including the use of a strong base such as *t*-BuLi, harsh reaction conditions, the incompatibly of traditional protecting groups, and so on.[8,9] To this end, Niu et al. recently demonstrated the preparation of *C*-1 aryl glycals from *C*-1 glycal sulfones via a nickel-catalyzed Suzuki−Miyaura coupling reaction with aryl boronic acids.[10]

Enones that are derived from glycals via the selective oxidation of the *C*-3 hydroxyl group (i.e., glycal-enone) using hypervalent iodine compounds[11] have been previously explored in the synthesis of *C*-glycosides.[12] For instance, the palladium-catalyzed addition of benzene to glycal-enones provides a mixture of the oxidative coupling product (i.e., *C*-1 aryl enones) and the 1,4-conjugate addition product (i.e., α-*C*-aryl 3-keto glycosides) in different ratios.[12a] However, this reaction is limited to benzene (Scheme 1, eq 1). On the

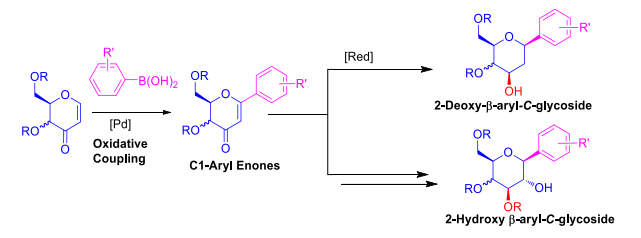
Scheme 1. Enone-Mediated Synthesis of *C*-Glycosides



contrary, rhodium-catalyzed 1,4-conjugate addition of arylboronic acids to acetylated enones results in the formation of α-selective *C*-aryl 3-keto glycosides (Scheme 1, eq 2).[12b] However, no further efforts have been made toward the establishment of protocols for the preparation of β-aryl-*C*-glycosides from glycal-enones.

We have recently reported a palladium-catalyzed aryldiazonium-salt-mediated stereocontrolled synthesis of 2-deoxy-α- and β-aryl-*C*-glycosides from glycals and *anti*-glycals (i.e., *C*-3 configuration-inverted glycals), respectively.[7b,13] In a continuation of these works as well as in the light of the report of Ville et al.,[12a] we envisioned a two-step protocol for achieving 2-deoxy-β-aryl-*C*-glycosides from glycal-enones, as shown in Scheme 2. The steps include (i) the synthesis of *C*-1 aryl enones via the regioselective oxidative coupling of arylboronic

Scheme 2. Stereoselective Formation of β-Aryl-*C*-glycosides via *C*-1 Aryl Enones

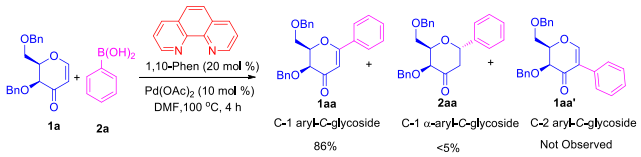


acids to glycal enones and (ii) the stereoselective reduction of *C*-1 aryl enones. Nevertheless, *C*-1 aryl enones can also serve as precursors for the preparation of 2-hydroxy-β-aryl-*C*-glycosides (*vide infra*).

The first step is crucial because there are possibilities for a 1,4-conjugate addition reaction as well as *C*-2 arylation. Hence, at the outset, we focused on the optimization of Heck coupling using galactal-enone **1a** and phenylboronic acid **2a** as model substrates. (See SI-Table 1 in the Supporting Information.) The reaction was screened with different solvents (THF, DMF, CH_3CN, DMA, NMP, DCE, 1,4-dioxane, and AcOH), ligands (2,2′-bpy, 1,10-Phen, DABCO, Et_3N, pyridine, DMAP, TMEDA, PPh_3, and Dppe), bases (Na_2CO_3, Cs_2CO_3, and NaOAc), and temperatures (80−150 °C) in the presence of palladium catalysts such as $Pd(OAc)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $PdCl_2$.

To our delight, the desired product **1aa** was obtained in 86% yield at 100 °C in DMF in the presence of 10 mol % palladium acetate and 1,10 phenanthroline (20 mol %) (Scheme 3). Under these optimized conditions, the 1,4-addition product **2aa** was observed in a negligible amount (<5%), whereas C_2-arylation product **1aa′** was not observed.

Scheme 3. Optimization of the Reaction Conditions for the Oxidative Heck Coupling Reaction



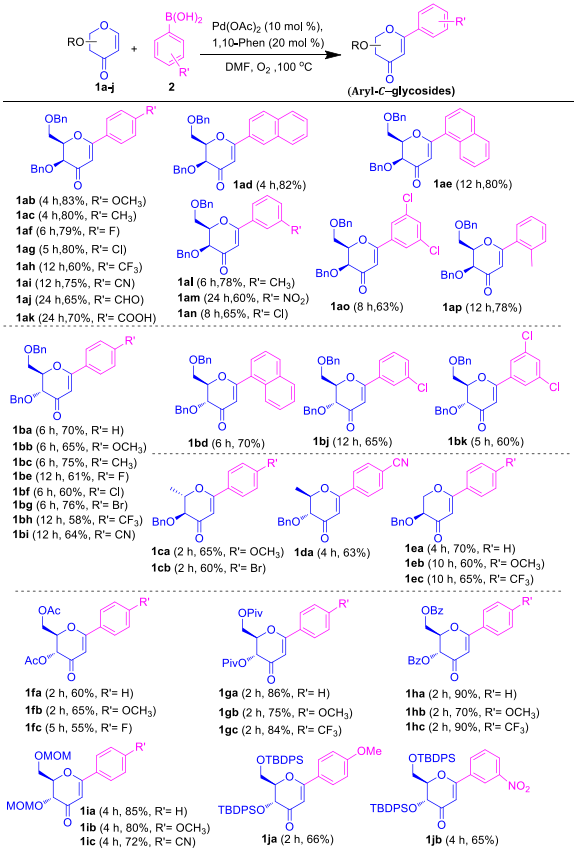
With the optimized conditions in hand, we investigated the scope of arylboronic acids in the coupling reaction with galactal enone **1a** (Scheme 4). Initially, the reactions were attempted with arylboronic acids bearing electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) at the para position. EDG-functionalized arylboronic acids efficiently participated in the coupling reaction and gave the desired products **1ab**−**1ae** in 80−83% yields within 4−12 h.

On the contrary, EWG-functionalized arylboronic acids took a slightly longer time (6−24 h) and provided the enones **1af**−**1ak** in 60−80% yields. Furthermore, we have investigated the reaction of meta-substituted as well as sterically hindered ortho-substituted arylboronic acids under optimized conditions. All of these substrates smoothly participated in the coupling reaction and gave the enones **1al**−**1ap** in good to excellent yields. To expand the scope, we investigated the coupling reaction of glucal-enone (**1b**) with different EDG- and EWG-substituted arylboronic acids. All of these reactions smoothly proceeded under optimized conditions to afford the desired products **1ba**−**1bk** in 58−75% yields. Furthermore, in the search for the substrate scope, different benzyl-protected glycal-enones prepared from L-rhamnal, D-rhamnal, and L-arabinal were subjected to the oxidative coupling reactions. To our delight, these reactions gave the enones **1ca**, **1cb**, **1da**, and **1ea**−**1ec** in 60−70% yields within 2−10 h.

Having explored the scope of different arylboronic acids and glycal-enones, we investigated the compatibility of different traditional protecting groups in the coupling reaction. In this context, acetyl-, pivaloyl-, benzoyl-, MOM-, and TBDPS-protected enones were prepared and subjected to the oxidative coupling reaction with different arylboronic acids bearing

https://dx.doi.org/10.1021/acs.orglett.0c02843
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Reaction of Glycal Enones with Arylboronic Acids[a,b]



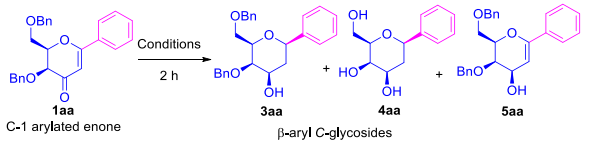
[a]Conditions: enone (0.25 mmol) and arylboronic acid **2** (0.5 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol %), and 1,10-Phen (9 mg, 20 mol %) were stirred in DMF (3 mL) under an O_2 balloon. [b]Isolated yield.

EDGs and EWGs. Pivaloyl- and benzoyl-protected enones participated in the coupling reaction in a short span of time and gave enones **1ga**−**1hc** in 70−90% yields. On the contrary, acetyl-protected enones gave the desired products **1fa**−**1fc** in relatively low yields. However, to our delight, acid-sensitive MOM- and TBDPS-protected glycal-enones efficiently participated in the reaction and gave the corresponding enones **1ia**-**1jb** in 65−85% yields. Additionally, we attempted the model reaction (Scheme 3) on a 1.0 mmol scale and obtained aryl enone **1aa** in 74% yield. (See the Supporting Information.)

After exploring the first step, we investigated the second step, that is, the stereoselective reduction of *C*-1 aryl enones. It has been previously shown that the reduction of *C*-1 aryl enones with Pd/C−H_2 provides 2-deoxy-*β*-aryl-*C*-glycosides with high stereoselectivity.[3c,4b,12a] In light of these reports, the benzyl-protected galactal-enone (**1aa**) was chosen as the model substrate and subjected to the reduction with Pd-C/H_2 (Table 1).

The reaction in MeOH and EtOAc gave the desired 2-deoxy-*β*-aryl-*C*-glycoside **3aa** in 45 and 84% yields, respectively. We observed the fully deprotected aryl *β*-glycoside **4aa** in 40% yield in methanol. It is also interesting to note that the reduction of **1aa** with sodium borohydride and lithium aluminum hydride results in the formation of **5aa** as the major product (>70%) via chemo- and stereoselective reduction of the ketone group.

Table 1. Optimization of the Reaction Conditions for the Reduction from Aryl Enone (1aa) with Different Reducing Agents[a]

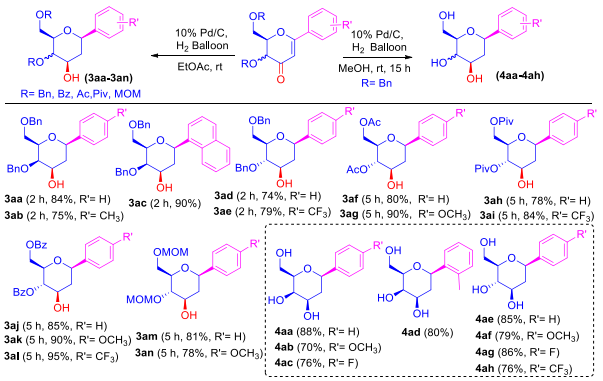


S no.	conditions	yield %[b] 3aa	4aa	5aa
1	10% Pd/C, H_2 (1 atm), MeOH, RT	45	40	nd
2	10% Pd/C, H_2 (1 atm), EtOAc, RT	84	<5	nd
3	$NaBH_4$, MeOH, RT	<5	nd	75
4	$LiAlH_4$, THF, RT	<5	nd	70

[a]Conditions: aryl enone **1aa** (0.15 mmol) and $NaBH_4$ or $LiAlH_4$ (1.2 equiv) or 10% Pd/C (20 mg)/H_2 balloon were stirred in the appropriate solvent (3 mL). [b]Isolated yield.

After the successful identification of the optimized conditions (Table 1, entry 2), the stereoselective hydrogenation of various *C*-1 aryl enones was investigated using Pd-C/H_2 in EtOAc (Scheme 5). To our delight, benzyl-, acetyl-,

Scheme 5. Stereoselective Hydrogenation of Aryl Enones with Pd-C/H_2 in Ethyl Acetate or Methanol[a,b]



[a]Conditions: aryl enone (0.15 mmol) and 10% Pd/C (20 mg) were stirred in ethyl acetate (3 mL) or methanol (3 mL) under a H_2 balloon. [b]Isolated yield.

pivaloyl-, benzoyl-, and MOM-protected *C*-1 aryl enones were successfully transformed into partially protected 2-deoxy-*β*-aryl-*C*-glycosides **3aa**−**3an** in 74−95% yields. In particular, benzyl groups remained intact under the standard reaction conditions. Furthermore, we have attempted the preparation of fully deprotected 2-deoxy-*β*-aryl-*C*-glycosides from benzyl-protected *C*-1 aryl enones (Scheme 5). To our delight, this transformation was efficiently achieved by using Pd-C/H_2 in methanol. Under these conditions, different benzyl-protected *C*-1 aryl enones were directly transformed into corresponding unprotected *C*-aryl glycosides **4aa**−**4ah** in 70−88% yields.

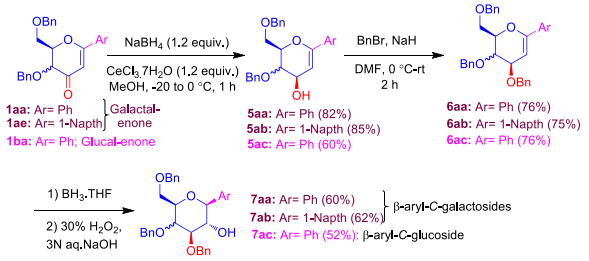
The assignment of an anomeric configuration (i.e., *β*) to the resulted products (i.e., **3aa**−**3an** and **4aa**−**4ah**) was established based on the spectral data (1D, 2D, and NOE NMR experiments) and previous reports.[3c,4b,12a] For instance, in ^1H NMR, the anomeric proton of the products appear as a doublet of a doublet with a large coupling constant for $J_{H\text{-}1}$ and $J_{H\text{-}2a}$ (>10 Hz, e.g., 11.4 Hz for **3aa**) due to the axial−axial coupling, which confirms the formation of a *β* anomer. A simultaneous

https://dx.doi.org/10.1021/acs.orglett.0c02843
Org. Lett. XXXX, XXX, XXX−XXX

reduction of C═O and C═C bonds in *C*-1 aryl enones from the α-face results in the formation of 1,3-*syn* aryl-*C*-glycosides.[3c,4b,12a]

The *C*-1 aryl enones could serve as an important precursor for the preparation of 2-hydroxy-β-aryl-*C*-glycosides (Scheme 6).

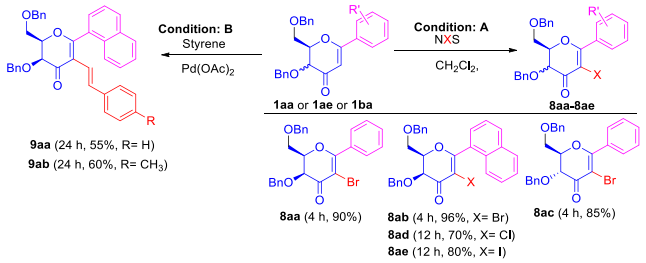
Scheme 6. Synthesis of 2-Hydroxy-β-aryl-*C*-glycosides



For instance, the chemo- and stereoselective reduction of *C*-1 aryl enones **1aa**, **1ae**, and **1ba** with $NaBH_4$−$CeCl_3$ gave the allyl alcohols **5aa**, **5ab**, and **5ac**, respectively. Furthermore, these compounds were subjected to benzyl protection followed by hydroboration to obtain 2-hydroxy-β-aryl-*C*-glycosides **7aa**, **7ab**, and **7ac** in good yields.

The *C*-2-functionalized glycals are useful precursors in the preparation of various natural products and biologically active compounds.[14] In this context, to demonstrate the further use of aryl enones, we investigated the *C*-2 functionalization reactions (Scheme 7). The regioselective halogenation of aryl

Scheme 7. *C*-2 Functionalization of Aryl Enones[a,b]

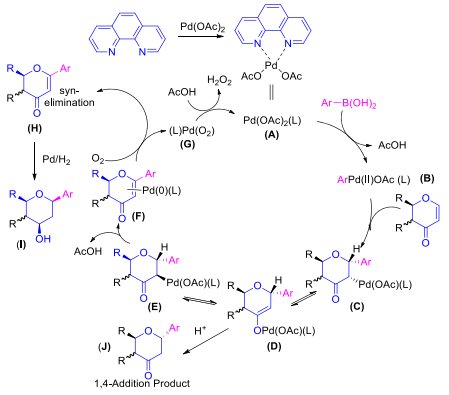


[a]Condition A: Aryl enone (0.15 mmol) was stirred in DCM with NBS (1.0 equiv) or NCS (2.0 equiv) or NIS (2.0 equiv) at RT. Condition B: Aryl enone (0.1 mmol), styrene (1.5 equiv), AgOAc (2.5 equiv), and $Pd(OAc)_2$(10 mol %) were stirred in DMF/DMSO (9:1, 3 mL) at 100 °C. [b]Isolated yield.

enones **1aa**, **1ae**, and **1ba** with *N*-halo succinimides in DCM results in the formation of *C*-2 bromo, chloro, and iodo enones **8aa**−**8ae** in excellent yields at room temperature. Similarly, the regioselective vinylation of aryl enone **1ae** with styrenes was achieved in good yield in the presence of $Pd(OAc)_2$ (Scheme 7, **9aa** and **9ab**).[15]

A plausible mechanism for the palladium-catalyzed oxidative coupling reaction is shown in Scheme 8. Palladium acetate coordinates with 1,10-phenanthroline to form an electron-rich palladium(II) complex **A**.[16a] This complex undergoes transmetalation with arylboronic acid to form the complex **B**, which was added to the enone from the α-face to provide intermediate **C**. This intermediate undergoes a palladotropic shift to form enolate **D** and rearranges to **E**, which is suitable for syn-β-H elimination. Finally, the reductive elimination leads to the formation of (L)Pd(0)−product complex (**F**) and

Scheme 8. Plausible Mechanism of the Reaction



AcOH. The complex **F** undergoes oxidation in the presence of oxygen to form *C*-1 aryl enone (**H**) and (L)Pd(O_2) (**G**). The complex **G** converts into $Pd(OAc)_2$(L) in the presence of HOAc, and the catalytic cycle is resumed.[16b] The arylated enone (H) transforms into 2-deoxy-β-*C*-aryl glycosides by an α-face hydrogenation reaction with Pd/C-H_2.[3c,4b,12a]

The formation of 1,4-conjugate addition side product (**J**) could be considered as evidence for the proposed mechanism. For instance, in the presence of H^+, the palladium enolate **D** undergoes hydrolysis to provide the 1,4-addition product **2aa** in high yield. (See SI-Table 1, entry 12 in the Supporting Information.)

In conclusion, we have successfully developed an efficient method for the stereoselective synthesis of 2-deoxy-aryl-*C*-glycosides from enones derived from D-glucal, D-galactal, L-rhamnal, D-rhamnal, and L-arabinal underwent a regioselective coupling reaction with electron-donating- and electron-withdrawing-functionalized arylboronic acids and provided *C*-1 aryl enones in good to excellent yields. Various functional groups in arylboronic acids including, halo, nitro, cyano, aldehyde, carboxylic acids, and so on were found to be stable under the standard reaction conditions. Moreover, many protecting groups in enones were also found to be compatible during the coupling reaction. A controlled stereoselective reduction of *C*-1 arylated enones provides partially protected as well as fully deprotected 2-deoxy-β-aryl-*C*-glycosides in excellent yields. The *C*-1 aryl enones are useful precursors for the preparation of 2-hydroxy-β-aryl-*C*-glycosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02843.

Experimental procedures and characterization data (^{1}H and ^{13}C NMR, HRMS) for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jeyakumar Kandasamy − *Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh 221005, India;* orcid.org/0000-0003-3285-971X; Email: jeyakumar.chy@iitbhu.ac.in

https://dx.doi.org/10.1021/acs.orglett.0c02843
Org. Lett. XXXX, XXX, XXX−XXX

Authors

Adesh Kumar Singh − *Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh 221005, India*

Vimlesh Kumar Kanaujiya − *Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh 221005, India*

Varsha Tiwari − *Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh 221005, India*

Shahulhameed Sabiah − *Department of Chemistry, Pondicherry University, Pondicherry 605014, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02843

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.K. acknowledges DST-India (DST/INT/MPG/P-09/2016) and Max-Planck Society-Germany for financial support through the Indo-Max Planck partner group project. A.K.S. acknowledges the CSIR for the senior research fellowship (file no: 09/1217(0005/2015-EMR-I)). S.S acknowledges Pondicherry University for the mass analysis. V.K.K. acknowledges IIT (BHU) for a research fellowship. J.K. acknowledges Central Instrumentation Facility Center (CIFC)-IIT BHU for the NMR facilities. Dedicated to Professor Timor Baasov, the recipient of the Israel Chemical Society NCK-prize 2020.

■ REFERENCES

(1) (a) Bokor, E.; Kun, S.; Goyard, D.; Toth, M.; Praly, J. P.; Vidal, S.; Somsak, L. *C*-Glycopyranosyl arenes and hetarenes: Synthetic methods and bioactivity focused on antidiabetic potential. *Chem. Rev.* **2017**, *117*, 1687−1764. (b) Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. Total synthesis of aryl *C*-glycoside natural products: Strategies and tactics. *Chem. Rev.* **2018**, *118*, 1495−1598. (c) Yang, Y.; Yu, B. Recent advances in the chemical synthesis of *C*-glycosides. *Chem. Rev.* **2017**, *117*, 12281−12356. (d) Suzuki, K. Total synthesis of aryl *C*-glycoside antibiotics. *Pure Appl. Chem.* **1994**, *66*, 2175−2178. (e) Jaramillo, C.; Knapp, S. Synthesis of *C*-aryl glycosides. *Synthesis* **1994**, *1994*, 1−20. (f) Lee, D. Y. W.; He, M. Recent advances in aryl *C*-glycoside synthesis. *Curr. Top. Med. Chem.* **2005**, *5*, 1333−1350. (g) Fosso, M. Y.; Nziko, V. P. N.; Chang, C. W. T. Chemical synthesis of *N*-aryl glycosides. *J. Carbohydr. Chem.* **2012**, *31*, 603−619. (h) Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Isozaki, K.; Takaya, H.; Orita, A.; Li, H. C.; Shing, T. K. M.; Nakamura, M. Synthesis of Aryl *C*-Glycosides via Iron-Catalyzed Cross Coupling of Halosugars: Stereoselective Anomeric Arylation of Glycosyl Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 10693−10701. (i) Liu, J.; Gong, H. Stereoselective Preparation of α-C-Vinyl/Aryl Glycosides via NickelCatalyzed Reductive Coupling of Glycosyl Halides with Vinyl and Aryl Halides. *Org. Lett.* **2018**, *20*, 7991−7995. (j) Zheng, S.; Gutierrez-Bonet, A.; Molander, G. A. Merging Photoredox PCET with Ni-CatalyzedCross-Coupling: Cascade Amidoarylation ofUnactivated Olefins. *Chem.* **2019**, *5*, 339−352. (k) Rohr, J.; Thiericke, R. Angucycline group antibiotics. *Nat. Prod. Rep.* **1992**, *9*, 103−37. (l) Kharel, M. K.; Pahari, P.; Shepherd, M. D.; Tibrewal, N.; Nybo, S. E.; Shaaban, K. A.; Rohr, J. Angucyclines: Biosynthesis, mode-of-action, new natural products, and synthesis. *Nat. Prod. Rep.* **2012**, *29*, 264−325. (m) Bililign, T.; Griffith, B. R.; Thorson, J. S. Structure, activity, synthesis and biosynthesis of aryl-*C*-glycosides. *Nat. Prod. Rep.* **2005**, *22*, 742−60.

(2) (a) Chao, E. C.; Henry, R. R. SGLT2 inhibition - A novel strategy for diabetes treatment. *Nat. Rev. Drug Discovery* **2010**, *9*, 551−559. (b) Aguillon, A. R.; Mascarello, A.; Segretti, N. D.; de Azevedo, H. F. Z.; Guimaraes, C. R. W.; Miranda, L. S. M.; de Souza, R. O. M. A. Synthetic strategies toward SGLT2 inhibitors. *Org. Process Res. Dev.* **2018**, *22*, 467−488.

(3) (a) Vijayasaradhi, S.; Aidhen, I. S. Umpolung strategy for the synthesis of 2-deoxy-*C*-aryl glycosides: A serendipitous, efficient route for *C*-furanoside analogues. *Org. Lett.* **2002**, *4*, 1739−1742. (b) Dubbu, S.; Chennaiah, A.; Verma, A. K.; Vankar, Y. D. Stereoselective synthesis of 2-deoxy-β-*C*-aryl/alkyl glycosides using Prins cyclization: Application in the synthesis of *C*-disaccharides and differently protected *C*-aryl glycosides. *Carbohydr. Res.* **2018**, *468*, 64−68. (c) Hauser, F. M.; Hu, X. A new route to *C*-aryl glycosides. *Org. Lett.* **2002**, *4*, 977−978. (d) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. H. Stereoselective total syntheses of the naturally occurring enantiomers of *N*-acetylneuraminic acid and 3-deoxy-D-manno-2-octulosonic Acid. A new and stereospecific approach to sialo and 3-deoxy-D-manno-2-octulosonic acid conjugates. *J. Am. Chem. Soc.* **1988**, *110*, 3929−3940. (e) Sakamoto, K.; Nagai, M.; Ebe, Y.; Yorimitsu, H.; Nishimura, T. Iridium-Catalyzed Direct Hydroarylation of Glycals via C−H Activation: Ligand-Controlled Stereoselective Synthesis of α- and β-C-Glycosyl Arenes. *ACS Catal.* **2019**, *9*, 1347−1352.

(4) (a) Xiong, D. C.; Zhang, L. H.; Ye, X. S. Oxidant-controlled Heck-type *C*-glycosylation of glycals with arylboronic acids: Stereoselective synthesis of aryl 2-deoxy-*C*-glycosides. *Org. Lett.* **2009**, *11*, 1709−1712. (b) Lei, M.; Gao, L.; Yang, J.-S. Microwave-assisted palladium-catalyzed cross-coupling reactions between pyranoid glycals and aryl bromides. Synthesis of 2′-deoxy *C*-aryl-β-glycopyranosides. *Tetrahedron Lett.* **2009**, *50*, 5135−5138. (c) Xiang, S. H.; Cai, S. T.; Zeng, J.; Liu, X. W. Regio- and stereoselective synthesis of 2-deoxy-*C*-aryl glycosides via palladium catalyzed decarboxylative reactions. *Org. Lett.* **2011**, *13*, 4608−4611. (d) Li, H. H.; Ye, X. S. Regio- and stereoselective synthesis of aryl 2-deoxy-*C*-glycopyranosides by palladium-catalyzed Heck coupling reactions of glycals and aryl iodides. *Org. Biomol. Chem.* **2009**, *7*, 3855−3861.

(5) (a) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. Palladium(II) acetate catalyzed stereoselective *C*-glycosidation of peracetylated glycals with arylboronic acids. *Org. Lett.* **2001**, *3*, 2013−2015. (b) Ma, J.; Xiang, S.; Jiang, H.; Liu, X.-W. Palladium-catalyzed stereoselective *C*-glycosylation of glycals with sodium arylsulfinates. *Eur. J. Org. Chem.* **2015**, *2015*, 949−952. (c) Bai, Y. G.; Kim, L. M. H.; Liao, H. Z.; Liu, X. W. Oxidative Heck reaction of glycals and aryl hydrazines: A palladium-catalyzed *C*-glycosylation. *J. Org. Chem.* **2013**, *78*, 8821−8825. (d) Kusunuru, A. K.; Yousuf, S. K.; Tatina, M.; Mukherjee, D. Desulfitative *C*-arylation of glycals by using benzenesulfonyl chlorides. *Eur. J. Org. Chem.* **2015**, *2015*, 459−462.

(6) Tang, S.; Zheng, Q.; Xiong, D. C.; Jiang, S.; Li, Q.; Ye, X. S. Stereocontrolled synthesis of 2-deoxy-*C*-glycopyranosyl arenes using glycals and aromatic amines. *Org. Lett.* **2018**, *20*, 3079−3082.

(7) (a) Mabit, T.; Siard, A.; Legros, F.; Guillarme, S.; Martel, A.; Lebreton, J.; Carreaux, F.; Dujardin, G.; Collet, S. Stereospecific *C*-glycosylation by Mizoroki−Heck reaction: A powerful and easy-to-set-up synthetic tool to access α- and β-aryl-*C*-glycosides. *Chem. - Eur. J.* **2018**, *24*, 14069−14074. (b) Singh, A. K.; Venkatesh, R.; Kandasamy, J. Palladium-catalyzed one-pot stereospecific synthesis of 2-deoxy aryl *C*-glycosides from glycals and anilines in the presence of *tert*-butyl nitrite. *Synthesis* **2019**, *51*, 4215−4230.

(8) (a) Somsák, L. Carbanionic reactivity of the anomeric center in carbohydrates. *Chem. Rev.* **2001**, *101*, 81−136. (b) Friesen, R. W.; Loo, R. W. Preparation of *C*-aryl glucals via the palladium catalyzed coupling of metalated aromatics with 1-iodo-3,4,6-tri-O-(triisopropylsilyl)-D-glucal. *J. Org. Chem.* **1991**, *56*, 4821−4823. (c) Kaelin, D. E.; Lopez, O. D.; Martin, S. F. General strategies for the synthesis of the major classes of *C*-aryl glycosides. *J. Am. Chem. Soc.* **2001**, *123*, 6937−6938.

(9) Choutka, J.; Pohl, R.; Parkan, K. MOP and EE protecting groups in synthesis of α- or β-naphthyl-*C*-glycosides from glycals. *ACS omega* **2018**, *3*, 7875−7887.

(10) Gong, L.; Sun, H.-B.; Deng, L.-F.; Zhang, X.; Liu, J.; Yang, S.; Niu, D. Ni-Catalyzed Suzuki−Miyaura cross-coupling of α-oxo-

vinylsulfones to prepare *C*-aryl glycals and acyclic vinyl ethers. *J. Am. Chem. Soc.* **2019**, *141*, 7680−7686.
(11) Kirschning, A. Oxidation of fully protected glycals by hypervalent iodine reagents. *J. Org. Chem.* **1995**, *60*, 1228−1232.
(12) (a) Benhaddou, R.; Czernecki, S.; Ville, G. Palladium-mediated arylation of acetylated enones derived from glycals. 4. Synthesis of aryl-2-deoxy-.beta.-D-C-glycopyranosides. *J. Org. Chem.* **1992**, *57*, 4612−4616. (b) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. Stereoselective *C*-glycoside formation by a rhodium(I)-catalyzed 1,4-addition of arylboronic acids to acetylated enones derived from glycals. *Org. Lett.* **2001**, *3*, 2571−2573. (c) Leonelli, F.; Capuzzi, M.; Calcagno, V.; Passacantilli, P.; Piancatelli, G. Stereoselective Michael-type addition of organocopper reagents to enones derived from glycals in the synthesis of 2-phosphono-α-*C*-Glycosides. *Eur. J. Org. Chem.* **2005**, *2005*, 2671−2676.
(13) Singh, A. K.; Kandasamy, J. Palladium catalyzed stereocontrolled synthesis of *C*-aryl glycosides using glycals and arenediazonium salts at room temperature. *Org. Biomol. Chem.* **2018**, *16*, 5107−5112.
(14) (a) Ramesh, N. G. Applications of 2-*C*-formyl-glycals in organic synthesis. *Eur. J. Org. Chem.* **2014**, *2014*, 689−707. (b) Hussain, N.; Ahmed, A.; Mukherjee, D. 2-Halo glycals as "Synthon" for 2-*C*-branched sugar: Recent advances and applications in organic synthesis. *Asian J. Org. Chem.* **2020**, *9*, 882−897. (c) Koester, D. C.; Kriemen, E.; Werz, D. B. Flexible synthesis of 2-deoxy-*C*-glycosides and (1→2)-, (1→3)-, and (1→4)-linked *C*-glycosides. *Angew. Chem., Int. Ed.* **2013**, *52*, 2985−2989. (d) Koester, D. C.; Werz, D. B. Sonogashira−Hagihara reactions of halogenated glycals. *Beilstein J. Org. Chem.* **2012**, *8*, 675−682.
(15) Hussain, N.; Babu Tatina, M.; Mukherjee, D. Cross dehydrogenative coupling of sugar enol ethers with terminal alkenes in the synthesis of pseudo-disaccharides, chiral oxadecalins and a conjugated triene. *Org. Biomol. Chem.* **2018**, *16*, 2666−2677.
(16) (a) Zhang, S.; Shi, L.; Ding, Y. Theoretical analysis of the mechanism of palladium(II) acetate-catalyzed oxidative Heck coupling of electron-deficient arenes with alkenes: Effects of the pyridine-type ancillary ligand and origins of the meta-regioselectivity. *J. Am. Chem. Soc.* **2011**, *133*, 20218−20229. (b) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118*, 2636−2679.

https://dx.doi.org/10.1021/acs.orglett.0c02843
Org. Lett. XXXX, XXX, XXX−XXX