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Regio- and Stereoselective Synthesis of 2-Deoxy-*C*-aryl Glycosides via Palladium Catalyzed Decarboxylative Reactions

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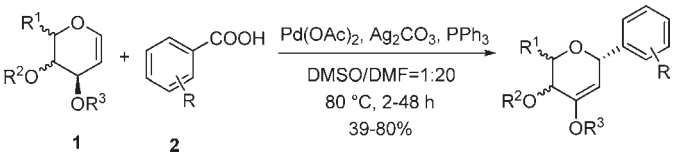
ABSTRACT



An efficient and versatile approach for the synthesis of 2-deoxy-*C*-aryl glycosides is reported. This strategy is based on a palladium-catalyzed decarboxylative Heck coupling reaction of benzoic acids and glycals. A wide variety of glycals and benzoic acids have been screened, and all these reactions could afford the desired *C*-aryl glycoside products in moderate to good yields with exclusive regio- and stereoselectivities.

Expansive attention and growing interest surrounding *C*-glycosides, especially *C*-aryl glycosides, could be attributed to their prevalence in the composition of many natural products with important biological properties[1] (Figure 1). In addition, they are versatile chiral building blocks in pharmaceutics and have the potential to act as enzyme inhibitors and stable sugar mimics.[2] Among all the natural products containing *C*-aryl glycosides, 2-deoxy-*C*-aryl glycoside structures are particularly recognized due to their ubiquity.[3] Therefore, the synthesis of *C*-aryl 2-deoxy glycoside is of great interest. Until now, a variety of synthetic methods have been reported for the synthesis of this kind of compound.[4−6] Among these methods, two strategies remain the most widely used by researchers. One is the cross-coupling of aryl halides with stannylated glycals,[4] another is the cross-coupling of organometallic reagents and glycal derivatives.[5] A further method is the palladium-catalyzed coupling of glycals with arylboronic acids.[7]

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In contrast to the former two strategies, the third strategy is more attractive, owing to the air and moisture stability of the reagents, their availability, and their low toxicity. However, the dependence of the product on the stereogenic center and the protecting group at *C*-3 limits the application of this method.[7d,8] Hence, it is still necessary to develop more flexible and efficient strategies.

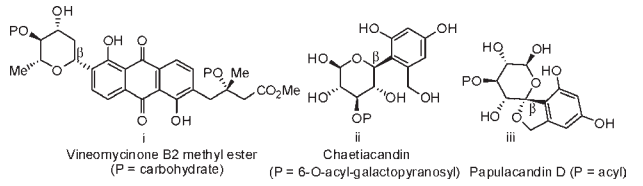
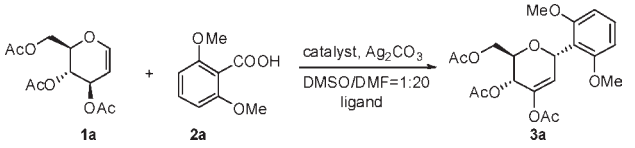


Figure 1. Biologically active natural products containing *C*-aryl glycosides.

Currently, transition-metal-catalyzed decarboxylative cross-coupling reactions offer efficient synthetic methods for forming carbon−carbon bonds. They are attractive since they use ubiquitous carboxylic acids as alternative reagents to organometallic compounds.[9−11] Pioneering work by Myers[9] and Goossen[10] demonstrated that, in a number of Heck-type reactions, *ortho*-substituted arene carboxylic acids could be used as synthetic equivalents of aryl halides in the presence of palladium catalysts and stoichiometric amounts of silver or copper additives at high temperatures. This type of reaction proceeded very well with different kinds of olefins in air and even with small amounts of water.[9a] Inspired by the successful implementation of decarboxylative coupling and our group's continuing efforts at extending the synthetic methodologies of carbohydrates,[12] we envisioned that this protocol could be made to work effectively with glycals to give diverse *C*-glycosides. Herein, we describe our results for the preparation of the 2-deoxy-*C*-aryl glycosides via this method.

Table 1. Optimization of the Decarboxylative Coupling Reaction[a]



entry	catalyst	ligand	temp (°C)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	none	80	12	50
2	$Pd(OAc)_2$	none	80	4	59
3	$Pd(OAc)_2$	none	60	4	trace
4	$Pd(OAc)_2$	none	70	4	<5
5	$PdCl_2$	none	80	4	54
6	$Pd(TFA)_2$	none	80	4	<5
7	$Pd(PPh_3)_2Cl_2$	none	80	4	<10
8	$Pd(OAc)_2$	PPh_3	80	4	79
9	$Pd(OAc)_2$	R-monophos	80	4	77
10	$Pd(OAc)_2$	X-phos	80	4	63
11	$Pd(OAc)_2$	S-phos	80	4	46
12	$Pd(OAc)_2$	Xantphos	80	4	28
13	$Pd(OAc)_2$	$(2\text{-MeOPh})_3P$	80	4	10

[a] Reaction conditions: 3,4,6-tri-*O*-acetyl-D-glucal 0.2 mmol, 2, 6-dimethoxybenzoic acid 0.4 mmol (2.0 equiv), Ag_2CO_3 0.6 mmol (3.0 equiv), catalyst 0.02 mmol (0.1 equiv), ligand 0.08 mmol (0.4 equiv), DMF/DMSO = 2 mL/0.1 mL. [b] Isolated yields.

Our initial aim was to achieve coupling of commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**1a**) with 2, 6-dimethoxybenzoic acid (**2a**). Treatment of **1a** with **2a** at 80 °C in the presence of Ag_2CO_3 and catalytic $Pd(OAc)_2$ in DMSO/DMF (1:20) for 12 h afforded the corresponding *C*-glycoside product **3a** as a single diastereomer in 50% yield. Encouraged by this result, different reaction times, temperatures, and a variety of palladium catalysts with different ligands were screened to optimize the reaction conditions. As shown in Table 1, when the reaction time was reduced to 4 h (entry 2) at 80 °C, the reaction did not complete, and 29% of the starting material was recovered. However, the yield was improved to 59%, demonstrating the product's instability to high temperatures. Attempts to reduce the temperature were unsuccessful as only trace amounts of the coupling product at 60 °C and less than 5% coupling product at 70 °C were isolated (entries 3, 4). Further investigations were conducted on the catalysts, and the results demonstrated that this reaction proceeded when $PdCl_2$ was employed instead of $Pd(OAc)_2$, albeit in a slightly lower yield (entry 5). On the other hand, other palladium catalysts such as $Pd(TFA)_2$ and $Pd(PPh_3)_2Cl_2$ did not perform well in this reaction (entries 6, 7). Interestingly, subsequent examination of the ligand effect revealed their significant influence on this reaction. Based on the results, it was observed that while some ligands aid

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(11) For other recent examples, see: (a) Forgione, P.; Brochu, M. C.; Miguel, S. O.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (b) Becht, J. M.; Catala, C.; Drian, C. L.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (c) Wang, C.-Y.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (d) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (e) Hu, P.; Kan, J.; Su, W.-P.; Hong, M.-C. *Org. Lett.* **2009**, *11*, 2341. (f) Lindh, J.; Sjöberg, P. J. R.; Larhed, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7733. (g) Wang, C.-Y.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (h) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391.
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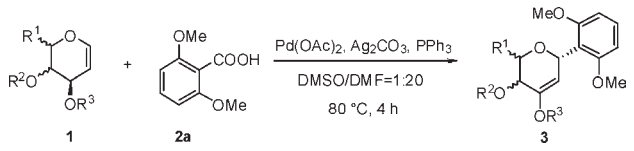
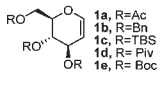
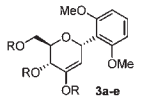
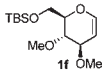
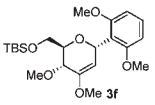
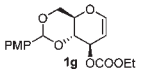
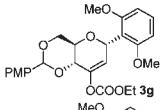
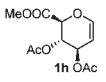
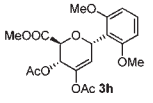
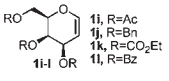
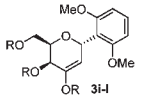
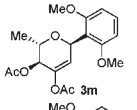
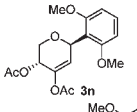
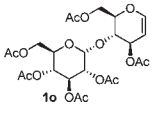
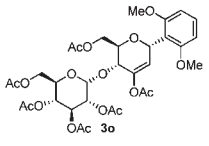
substantially in increasing the yield of this reaction (entries 8–10), others were detrimental to the reaction (entries 11–13). Among the ligands examined, PPh_3 was found to be the most efficient ligand for this reaction (entry 8). Thus, consolidating the results of our optimization, we concluded that the reaction between **1a** (1.0 equiv) and **2a** (2.0 equiv) using $Pd(OAc)_2$ (0.1 equiv), Ag_2CO_3 (3.0 equiv), and PPh_3 (0.4 equiv) in a DMSO/DMF (1:20) solvent mixture at 80 °C for 4 h represents the most suitable set of conditions for the formation of *C*-aryl glycoside (**3a**).

Table 2. Decarboxylative Coupling of 2,6-Dimethoxybenzoic Acid with Different Kinds of Glycals[a–c]

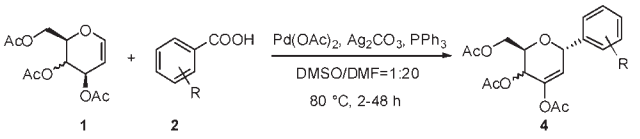


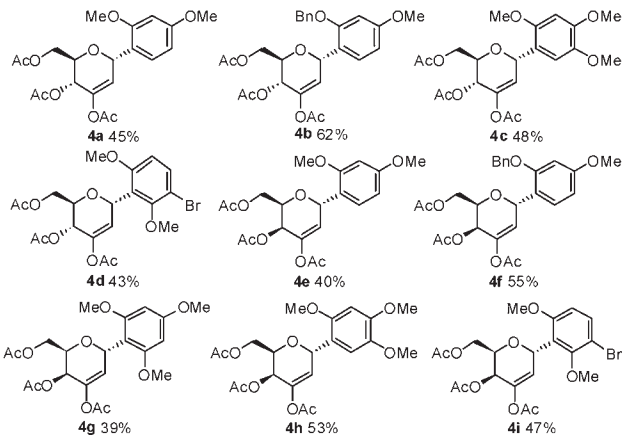
entry	glycal	product	yield (%)
1	 **1a**, R=Ac **1b**, R=Bn **1c**, R=TBS **1d**, R= Piv **1e**, R= Boc	 **3a-e**	79 (**3a**) 70 (**3b**) 73 (**3c**) 65 (**3d**) 55 (**3e**)
2	 **1f**	 **3f**	75
3	 **1g**	 **3g**	73
4	 **1h**	 **3h**	63
5	 **1i**, R=Ac **1j**, R=Bn **1k**, R=CO_2Et **1l**, R=Bz **1i-l**	 **3i-l**	80 (**3i**) 60 (**3j**) 69 (**3k**) 71 (**3l**)
6	 **1m**	 **3m**	72
7	 **1n**	 **3n**	58
8	 **1o**	 **3o**	45

[a] Isolated yields. [b] Only one single anomer was obtained for each reaction. [c] Compound **3f** is unstable in $CDCl_3$.

With these optimized conditions in hand, we proceeded to examine the substrate scope of the glycals. The results are presented in Table 2. It was found that a variety of glycals could afford the desired *C*-glycoside products in moderate to good yields with complete stereocontrol. For glucals, regardless of whether they possess electron-donating (**3b**, **3c**, **3f**) or electron-withdrawing protecting groups (**3d**, **3e**), the reaction progresses smoothly. Their versatility in the reaction could be further demonstrated by the fact that glucals equipped with sterically hindered protecting groups engaged in this reaction as well (**3c**–**3e**). In addition, glucal substrates with conformationally rigid structures could be converted to the desired *C*-aryl glycoside product in 73% yield (**3g**) and glucal derivatives with an ester group at the *C*-5 position could also couple effectively with **2a**, furnishing the product in 63% yield (**3h**). Various galactals were then screened in this reaction and, similarly, gave good results (**3i**–**3l**). Furthermore, glycals derived from rhamnose and ribose were subsequently examined and the corresponding *C*-aryl glycosides were afforded in 72% and 58% yields (**3m**, **3n**) respectively. It is noteworthy that the reaction with a disaccharide also advanced smoothly to give the coupling product in moderate yield (**3o**).

Scheme 1. Decarboxylative Coupling of Glycals with Different Benzoic Acid Derivatives[a,b]





[a] Isolated yields. [b] Only one anomer was obtained for each reaction.

To expand the scope of our methodology, we employed our catalytic system in the decarboxylative coupling of glycals with other benzoic acid derivatives. As shown in Scheme 1, a variety of benzoic acid derivatives could be used for the synthesis of various types of *C*-aryl glycosides and all the reactions gave reasonable yields. The reaction time was found to be sensitive to the aryl substituent position and the overall electron density of the aryl group. The reactivities of 2,4-disubstituted benzoic acids were lower than those of the 2,6-disubstituted benzoic acids; hence, longer reaction times were needed (**4a**, **4b**, **4e**, **4f**).

In addition, benzoic acid substrates with a more electron-donating group exhibited greater activities, and consequently, shorter reaction times were needed (**4c**, **4g**, **4h**). Aryl substrates bearing a bromide substituent could also be used as a coupling partner for this reaction, and the products were generated in moderate yields (**4d**, **4i**). Despite attempts to test the reaction with other benzoic acid derivatives such as 2,3-dimethoxybenzoic acid, 2-bromo-4,5-dimethoxybenzoic acid, 2-naphthoic acid, 2-bromo-4-methoxybenzoic acid, 3,5-dimethoxybenzoic acid, and 6-methylpicolinic acid, the results obtained were not satisfactory. Therefore, we deduce that the reaction would proceed smoothly in the presence of benzoic acids substituted with strong electron-donating groups at the 2,4 or 2,6 position.

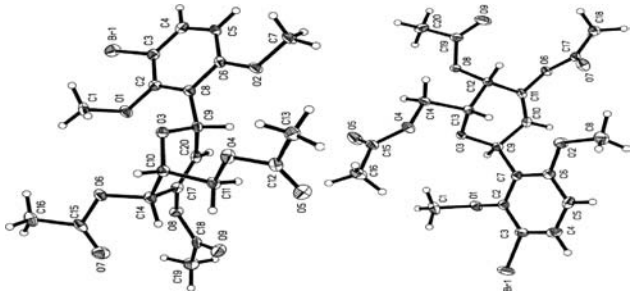
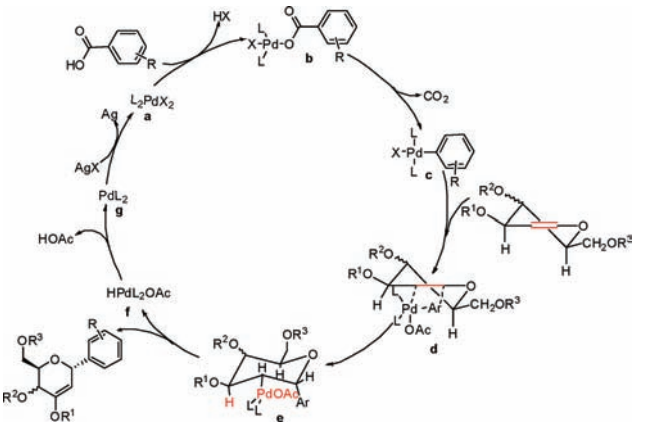


Figure 2. X-ray structures of compounds **4d** and **4i**.

Noteworthy, excellent anomeric stereoselectivities were observed in all reactions. The stereochemistry was further elucidated to be α-selective by X-ray crystallographic analysis of both glucal *C*-aryl glycoside **4d** and galactal *C*-aryl glycoside **4i** (Figure 2).

Based on our work and the previous results on the palladium-catalyzed Heck decarboxylative reaction,[6a,8,9c] we proposed the mechanism to be as shown in Scheme 2. Beginning with a Pd^{II} species **a**, the Pd complex **b** is formed by a salt change. A subsequent decarboxylative reaction of complex **b** generates an aryl Pd^{II} species **c**. Carbopalladation of the glycals would then give the intermediate **d**. In this step, the Pd^{II} species would attack from the bottom face, as the *C*-3 substituent created steric hindrance for addition on the top face. The intermediate **d** would subsequently convert to the relatively more stable chair conformation **e**, with the *C*-3 substituent and the aryl group in an *anti* configuration. The desired 2-deoxy-*C*-aryl glycoside and Pd^0 species **f** were then formed by the *syn*-β-hydrogen elimination. After elimination of HOAc and

Scheme 2. Plausible Reaction Mechanism



an additional oxidation step by silver carbonate, Pd^0 was converted to the Pd^{II} species **a** and the catalytic cycle was completed. This mechanism indicated that the product's anomeric stereochemistry adopted a contrasting configuration from the *C*-3 substituent of the glycal and this coincided with the structure of the products confirmed by X-ray crystallographic analysis.

In summary, we have developed the first metal-catalyzed method for decarboxylative *C*-glycosylative coupling. This strategy is based on a palladium-catalyzed decarboxylative Heck coupling reaction of benzoic acids and glycals and provides an efficient and versatile approach to the synthesis of various useful 2-deoxy-*C*-aryl glycosides. A wide variety of glycals and benzoic acids have been screened, and all the reactions afforded the desired *C*-aryl glycoside products in moderate to good yields with high regio- and stereoselectivities. Further stereoselective functionalization of the enol ether double bond of these products could readily afford different kinds of aryl 2-deoxy-*C*-glycoside, which are components of many natural products.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.