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TEMPO-Promoted Domino Heck–Suzuki Arylation: Diastereoselective *Cis*-Diarylation of Glycals and Pseudoglycals

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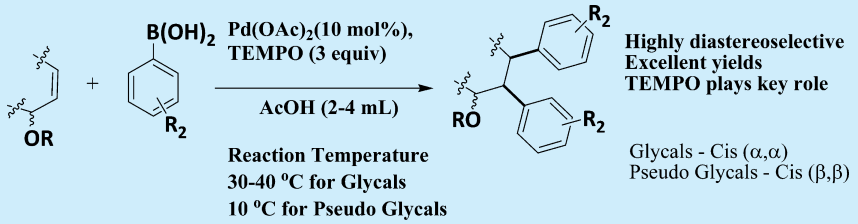
Supporting Information



ABSTRACT: A palladium-catalyzed regio- and diastereoselective diarylation of glycals and pseudoglycals, which is a kind of Heck–Suzuki arylation, is described. A wide range of arylboronic acids reacted under these conditions smoothly. Selectivity was C1–C2(α,α) in the case of glycals but C2–C3(β,β) for pseudoglycals. Quantum chemical analysis has been carried out to establish the reaction mechanism, which may involve Pd(II)/Pd(O). TEMPO plays a key role in the formation of diaryl glycoside due to its radical nature.

Difunctionalization of alkenes, where two new bonds are formed from an alkene precursor in one pot, is a powerful synthetic method to impart molecular complexity.[1,3,4] Such a transformation becomes synthetically more challenging if the two new adjacent chiral centers are to be formed in a highly diastereoselective fashion.[4] Palladium has become a popular metal of choice for alkene difunctionalization due to the ease with which Pd(II) facilitates the addition of nucleophiles to alkenes.[2] When the nucleophiles come from arylorganometallics such as arylboronic acid or arylstannanes, oxidative palladium catalysis generates 1,1-, 1,2-, or 1,3-(allylic esters) diarylated products depending on the type of alkene precursor.[3] The success of diarylation may be attributed to the stabilization of electrophilic palladium species, thereby suppressing other competitive reactions such as β-hydride/β-heteroatom elimination. One way of achieving this is to use substrates that are unable to undergo β-hydride elimination after initial Heck insertion such as norbornenes, alkynes, allenes, and carbene precursors or employ a three-component coupling to achieve the formation of two sp^2–sp^3 carbon–carbon bonds from the alkene framework using vinyl triflates as the organic electrophile and boronic acids as the organometallic reagent.[4] However, most of these methods are substrate specific and have limitations in case of identical aryl groups.

Glycals are important raw materials for the stereoselective synthesis of natural products, their fragments, and analogues because of their availability as inexpensive chiral building blocks. Over the years, there has been a significant development in glycal-based methodologies and their applications in the syntheses of biologically significant molecules.[5] The Larhed research group has worked extensively on diarylation of chelating vinylic ether substituted by a (dimethylamino)ethyl group using an excess of arylboronic acid in combination with *p*-benzoquinone.[4f–h] However, the introduction of such chelating groups is not possible for glycals. Because of our continuing interest in glycal chemistry[6] and the presence of many natural products and biologically important compounds containing diarylated furanose and pyranose moieties,[7] we took up the task of developing a regio- and stereospecific diarylation of glycals. Glycals contain an enol ether double bond, thus making it a challenging substrate for diarylation.

Recent advances in *C*-arylation of glycals have revealed arylboronic acids to be efficient aryl coupling partners due to their moisture stability and commercial availability. While Maddaford et al. reported Ferrier *C*-arylation with arylboronic acids under Pd catalysis, Ye et al. obtained diverse *C*-aryl glycosides by varying the oxidants (Scheme 1).[8] So far, the arylation of glycals has been restricted to the monoarylation stage[9,6e,8a] only, and no attempt has been made for the stereoselective vicinal diarylation of glycals and pseudoglycals. Herein, we disclose our efforts toward the development of an efficient robust protocol for the regio- and diastereoselective vicinal diarylation of glycals and pseudoglycals.

In order to effect diarylation, we thought of using 2 equiv of phenylboronic acid with 1 equiv of tri-*O*-acetyl-D-glucal and

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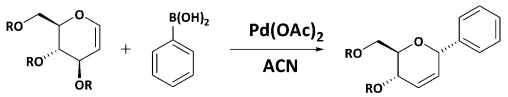
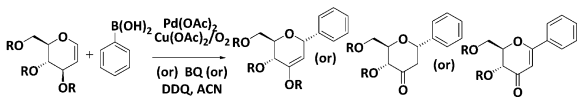
Scheme 1. Existing Method for *C*-Arylation of Glycals with Arylboronic Acids

Maddaford et al.

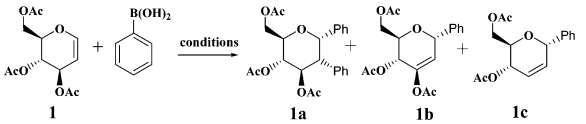


Ye et al.



carrying out the transformation with Pd reagents with or without oxidants under Pd catalysis. A summary of this optimization study is depicted in Table 1. To start with, tri-*O*-acetyl-D-glucal

Table 1. Optimization Studies for Diarylation of Glycals



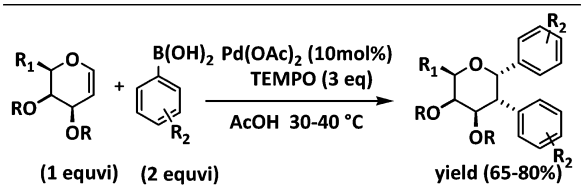
entry	$Pd(OAc)_2$ (equiv)	oxidant[a]	solvent[b]	time (h)	product **1a**/**1b**/**1c** (% yield)[c]
1	1		ACN	24	**1c** (70%)
2	1		AcOH	10	**1b** (55%)
3	0.1	$PhI(OAc)_2$	AcOH	15	**1b** (45%)
4	0.1	1,4-benzoquinone	AcOH	15	**1b** (20%)
5	0.1	$K_2S_2O_8$	AcOH	15	**1a** (20%)
6	0.1	Oxone	AcOH	15	**1a** (10%)
7	0.1	DMSO		24	
8	0.1	TEMPO	AcOH	8	**1a** (80%)
9	0.1	TEMPO	EtCOOH	10	**1a** (30%)
10	0.1	TEMPO	isobutyric acid	10	**1a** (20%)
11	0.1	TEMPO	formic acid	14	ND

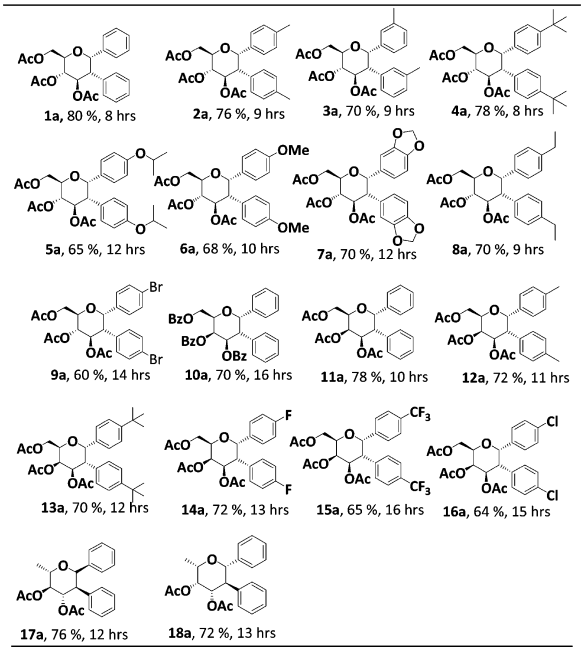
[a]In all cases, 3 equiv of oxidant was used. All of the reactions were conducted at 30−40 °C. [b]Solvent used was 2−3 mL for 100 mg of glycal. [c]Yield obtained after column chromatography.

and phenylboronic acid were allowed to react with 1 equiv of $Pd(OAc)_2$ in acetonitrile, whereupon formation of the Ferrier *C*-aryl glycoside (**1c**) was observed. By changing the solvent to acetic acid, we obtained a new product, which was characterized as the β-hydride-eliminated *C*-aryl glycoside **1b** (Table 1, entry 2). To the best of our knowledge, this is first report of β-hydride-eliminated *C*-aryl glycoside formation from glycals with acetyl protection, although the same product can be obtained from benzyl/silyl-protected substrate. Continuing our study, we used 10 mol % of $Pd(OAc)_2$ in the presence of $PhI(OAc)_2$ or 1,4-benzoquinone as oxidants (Table 1 entries 3 and 4). In both cases, only β-hydride-eliminated *C*-aryl glycoside (**1b**) was obtained as the major product. Gratifyingly, we found that the treatment of tri-*O*-acetyl-D-glucal (**1**) with phenylboronic acid (2 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), TEMPO (3 equiv), and AcOH as solvent for 8 h at room temperature furnished the targeted 1,2-(α,α)-diarylated-*C*-glycoside in 80% yield.

With the optimum conditions of stereoselective diarylation in our hand, we attempted the reaction with other arylboronic acids. A variety of arylboronic acids with different substituents were observed to smoothly undergo the reaction. Generally, good yields and excellent diastereoselectivities were observed for a broad range of substituted arylboronic acids possessing diverse electronic (Scheme 2, entries **1a**, **2a**, and **4a**−**9a**) and steric

Scheme 2. Substrate Scope: Vicinal Diarylation of Glycals





properties (Scheme 2, entries **3a**, **7a**). A series of glycals (D-glucal, D-galactal, L-rhamnal, and L-fucal) were also examined, and all provided the desired products with excellent diastereoselectivity (Scheme 2, entries **1a**−**18a**), which demonstrates the robustness of the catalytic system employed.

So far we have described the successful stereoselective diarylation of glycals with identical arylboronic acids. In order to expand the scope of this reaction further, we became interested in seeing if the regioselective addition of two arylboronic acids having different reactivity toward glycals could be performed. For this purpose, we chose 3,5-dimethoxyphenylboronic acid along with phenylboronic acid. Indeed, we obtained differentially substituted 1,2-arylated glucal derivative (**1d**) with complete regiocontrol albeit in lower yield and accompanied by compound **1a** (Scheme 3). The regiochemistry of the new diarylated product **1d** was determined from 2D NMR analysis. The HMBC (800 MHz) spectrum of **1d** showed cross peaks between the signals for ortho protons of the 3,5-dimethoxyaryl group at δ 6.91 ppm ($CDCl_3$), which is upfield of other aromatic proton signals (and thus easily distinguishable), and the anomeric carbon peak of the glycal partner at δ 77.0 ppm ($CDCl_3$). This established the connectivity of the 3,5-dimethoxyphenyl ring at C(1) and hence of the unsubstituted phenyl ring at C(2) (see the Supporting Informaiton for 2D NMR) of **1d**. Similar results were obtained while working with 4-methoxyarylboronic acid along with unsubstituted boronic acids

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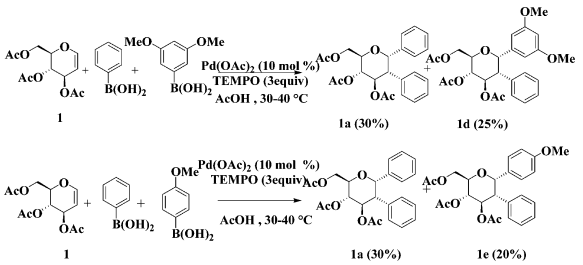
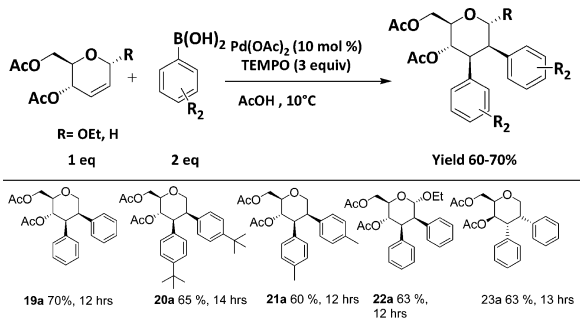
Scheme 3. Regioselective Diarylation of Glycals



(Scheme 3). Experiments are in progress to improve the yield of **1d** further.

Apart from glycals, pseudoglycals were also tested under the optimized conditions (Scheme 4). We obtained 2,3-diarylated glycosides with excellent stereoselectivity by diminishing the temperature to 10 °C. The stereochemistry of the product is cis(β,β) at C_2-C_3 as determined[10] by 2D-NMR spectroscopic studies (see the Supporting Information).

Scheme 4. Diarylation of Pseudoglycals



In order to determine the stereochemistry of the aryl moieties of the 1,2-diarylated glycosides produced, spectroscopic analyses were performed. From a mechanistic consideration, the stereochemistry of aryl moieties was expected to be cis ($\alpha-\alpha$ or $\beta-\beta$). In the NOESY spectrum of compound **1a**, observed correlations between H_1/H_6 and H_2/H_4 reveal that H-1, H-2, H-4, and H-6 are cofacial. This confirms the stereochemistry of the aryl groups as cis($\alpha-\alpha$) at C(1)/C(2) (Figure 1). In the case of 3,4-di-*O*-acetyl-L-rhamnal, the stereochemistry of aryl groups is cis($\beta-\beta$) at C(1)/C(2).[11]

From the above observations, a plausible mechanism for the palladium-catalyzed diarylation of glycals can be visualized as outlined in Scheme 5. To provide support to the proposition, density functional theory (DFT) calculations have been performed. Two different pathways were explored on the potential energy surface (Scheme 5). The entire pallodocycle

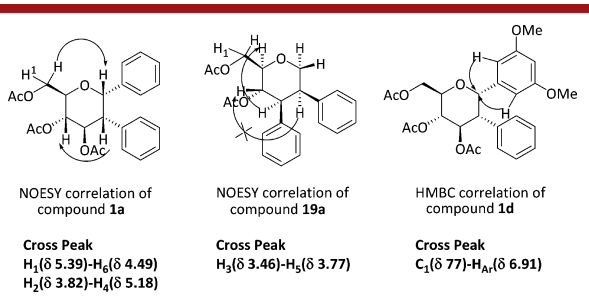
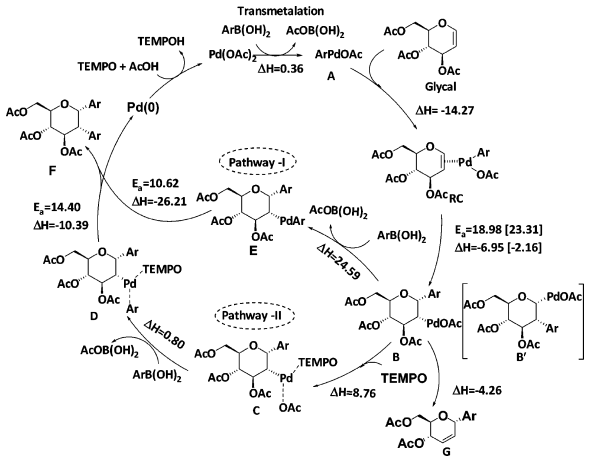


Figure 1. 2D-NMR correlation diagrams of diaryl glycosides.

Scheme 5. Possible Catalytic Process along with Free Energy Change Values and Activation Barrier (E_a) Values (Energies in kcal/mol)



has been divided into four basic steps as follows: (i) transmetalation of arylboronic acid to produce **A** (ArPdX), (ii) syn addition reaction of **A** to the double bond of the glycal to generate **B**, (iii) aryl exchange, and (iv) a second arylation and reductive elimination of palladium to form **F**. In the first transmetalation step, the arylboronic acid [$ArB(OH)_2$] reacts with palladium diacetate leading to the formation of **A**. The aryl group exchanges with the acetate of palladium acetate in this step, the enthalpy of this reaction being 0.36 kcal/mol. In $Pd(OAc)_2$, two bidentate interactions are present and all four coordination centers are occupied, but in **A** only three coordination centers around Pd are occupied.

The second step involves metal insertion reaction followed via syn addition reaction. Compound **A** forms an initial complex (**RC**) with the π cloud of the glycal, which is exergonic in nature, by 14.27 kcal/mol. In **RC**, the palladium atom is almost at an equal distance (η^2-arrangement) from both the olefin carbon atoms but slightly oriented toward C_2 carbon; the distance of C_1-Pd is 2.30 Å, and that of C_2-Pd is 2.18 Å.

The **RC** has the possibility of forming either C(1)-arylated product or C(2)-arylated product. The DFT studies showed that the formation of C(1)-arylated product (**B**) is more favorable than of the C(2)-arylated product (**B′**). The activation energy (E_a) required for the formation of **B** from **RC** is 18.98 kcal/mol (for **B′** it is 23.31 kcal/mol). This reaction is exergonic in nature by 6.95 kcal/mol to give **B** (**B** is more stable than **B′** by 4.8 kcal/mol). In **B**, the aryl group is in an axial position, and the Pd−OAc is in an equatorial position at the C(2) center. It was also observed that the acetate substituent at C(3) forms an O---Pd coordinate bond (2.11 Å), giving a square-planar arrangement at the Pd center. **B** may undergo anti elimination to give the arylated product **G**, which is an exothermic process by 4.26 kcal/mol. However, in this reaction, a diaryl product is formed that may involve the intermediacy of **E**. Formation of **E** from **B** is an endothermic process by 24.59 kcal/mol (though diaryl product is stable by 1.26 kcal/mol). Hence, it can be concluded that diaryl product formation can occur but not through **E**. Experimentally, the reaction is carried out in the presence of TEMPO. The radical character of TEMPO must be facilitating the reaction. To verify this, quantum chemical calculations have been performed on intermediates **C** and **D**. Formation of intermediate **C** (radical) is an endergonic process by 8.76 kcal/mol. Radical **C** can yield radical **D** in the presence of $ArB(OH)_2$, with the energy required

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for this reaction being only 0.80 kcal/mol. Hence, the formation of **D** from **B** requires only 9.56 kcal/mol and is more favorable in comparison to the formation of **E** from **B** (24.59 kcal/mol). **D** can yield the diaryl product **F** by releasing 10.39 kcal/mol, with an energy barrier of ~14.40 kcal/mol. Overall, the diaryl product formation follows a low energy pathway in the presence of TEMPO. Hence, it can be concluded that the radical character of TEMPO is facilitating the diaryl product formation through this reaction (**B** + $ArB(OH)_2$ + TEMPO →**F** + $AcOB(OH)_2$ + TEMPO) and is marginally exergonic by 1.26 kcal/mol. Figure 2 shows the 3D structures of the transition states TS (**A** → **B**) and TS (**D** → **F**).

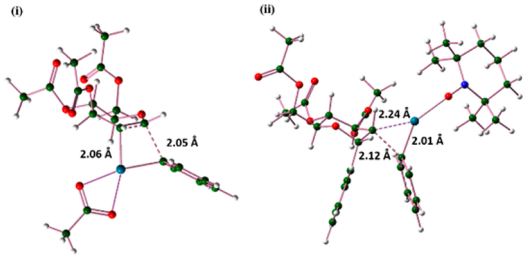

Figure 2. 3D structures of the transition states (i) (**A** → **B**)–C_1-arylation; (ii) (**D** → **F**)-C_2-arylation.

From the complex **B**, three pathways appear likely: (i) formation of **G**, (ii) formation of **E** (both in the absence of TEMPO), and (iii) formation of **C** (in the presence of TEMPO). Formation of **G** is much more favorable in the absence of TEMPO; hence, diaryl product via **E** is not noticed. Only in the presence of TEMPO can the formation of **C**–**F** be noticed. The overall energy barrier for the formation of **F** from **B** in the absence of TEMPO is 35 kcal/mol (via **E**). The same in the presence of TEMPO is 23.5 kcal/mol.

In conclusion, we have established a highly diastereoselective diarylation of glycals with arylboronic acids wherein a wide vareity of glycals and arylboronic acids can participate. The reaction is basically a type of Heck–Suzuki arylation. Here, the oxidizing agent TEMPO plays a key role in blocking *syn*-and *anti*-elimination. The diarylation can take place in the presence of the radical oxidative agent TEMPO.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^1H, ^{13}C, and 2D- NMR spectra, Cartesian coordinates, and characterization of all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01722.

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Notes

The authors declare no competing financial interest.

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(10) In NOESY of compound **19a** we observed cross peaks between H3(δ 3.46)/H5(δ 3.77) and no cross peak between H2(δ 3.1)/H4(δ 5.61), which confirms the stereochemistry of aryl groups as cis(β–β) at C2-C3 (Figure 3).

(11) In the NOESY spectrum of compound **17a**, observed correlation between H1/H6 and H2/H4 reveals that H-1, H-2, H-4, H-6 are cofacial, which confirms the stereochemistry of aryl groups as cis(β–β) at C1-C2.

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