EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201403195

Desulfitative *C*-Arylation of Glycals by Using Benzenesulfonyl Chlorides[‡]

Anil Kumar Kusunuru,[a,b] Syed Khalid Yousuf,[c] Madhubabu Tatina,[a,b] and Debaraj Mukherjee*[a,b]

Keywords: Synthetic methods / C–C coupling / Cross-coupling / Sulfur / Palladium / Glycosides

The palladium-catalyzed stereoselective synthesis of 2,3-deoxy-*C*-aryl glycosides was investigated. The strategy is based on the Pd-catalyzed desulfitative Heck coupling of arylsulfonyl chlorides and glycals with good leaving groups. An attempt was made to establish the reaction mechanism, which may involve Pd^{II}/Pd^{0} interconversion under basic conditions.

Introduction

The past decade has witnessed a renaissance in C–C bond-forming reactions. On the one hand, new advances have been made in already developed methods, and on the other hand, a number of reagents have been discovered that offer easy and scalable C–C bond transformations.[1] In carbohydrate chemistry, C–C bond generation mostly implies *C*-glycosylation,[2] a process to join monosaccharide units to form new *C*-glycosides either of industrial/biological importance or of synthetic/natural origin. Amongst the various *C*-aryl glycosides,[3] that is, *C*-glycosides with aryl ring at the anomeric position, 2,3-deoxy-*C*-aryl glycosides have attracted substantial attention,[3,4] because they are regularly found in natural products of pharmacological importance, show potential to serve as enzyme inhibitors and carbohydrate mimics, possess greater metabolic stability than *O*-glycosides, and promise to serve as useful chiral starting materials for synthetic chemistry. This has made them a target for synthetic chemists. The various strategies that are used[5] for their synthesis involve electrophilic substitution reactions of glycals with electron-rich arenes,[6] transition-metal-catalyzed glycosylations,[7] de novo synthesis of carbohydrate units,[8] and O–C aryl migration reactions.[9] Among the reported methods, transition-metal-catalyzed Heck-type reactions have gained special attention owing to the use of stable and moisture friendly reagents.[10] In this case, the product distribution is case sensitive. For example, 2,3-deoxy-*C*-glycosides are generated through β-heteroatom elimination if the glycals are protected by good leaving groups such as acetate, and 2-deoxy-*C*-glycosides are the main products formed through β-hydride elimination if glycals are protected by poor leaving groups such as silyl or benzyl. High electron density in the phenyl ring and the presence of ligands are prerequisites for such a transformation. Further, in the case of $Pd(OAc)_2$-catalyzed cross-coupling reactions of boronic acids with glycals, ring opening is one of the major side reactions.[11] In recent years, the search for alternatives to boronic acid chemistry has been under intense investigation. This has led to the unraveling of several new reagent systems for the arylation of glycals. These typically comprise aromatic carboxylic acids[12] and phenylhydrazines.[13] Palladium-mediated decarboxylative *C*-arylation of glycals by using aromatic carboxylic acids has been well studied by Liu et al. The same group has exploited phenylhydrazines for the oxidative *C*-arylation of glycals (Figure 1).[7]

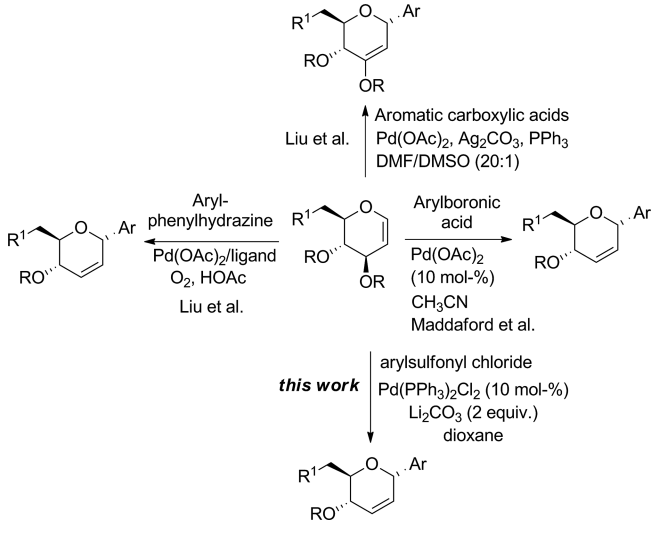


Figure 1. Recent developments in *C*-arylation of glycals under Heck conditions.

[‡] Iiim no.: IIIM/1749/2014
[a] Academy of Scientific and Innovative Research, Canal Road, Jammu-Tawi 180001, India
[b] Indian Institute of Integrative Medicine, CSIR-IIIM, Jammu 180001, India
E-mail: dmukherjee@iiim.ac.in
www.iiim.res.in
[c] Indian Institute of Integrative Medicine, Srinagar 190005, India
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403195

Arylsulfonyl chlorides can be easily obtained from oxyhalogenation of the corresponding aryl thiol under green condition.[14] Owing to the ease of their synthesis, arylsulfonyl chlorides have found application as aryl sources in various organic transformations.[15,16] With our continuous interest in *C*-glycoside synthesis,[17] herein we would like to disclose the desulfitative direct *C*-arylation of glycals from arylsulfonyl chlorides.

Results and Discussion

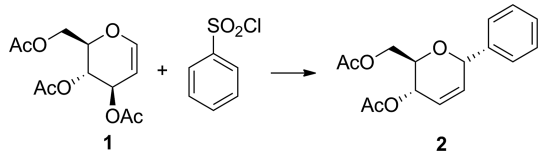
To find experimental support for our idea, commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**1**) was allowed to react with benzenesulfonyl chloride in the presence of various palladium catalysts (Table 1). It was observed that the nature of the base and the solvent directly affected product formation. For example, the use of $Pd(PPh_3)_2Cl_2$ and Cs_2CO_3 in dioxane at 100 °C (oil bath temperature) did not work, even after stirring for 40 h. Increasing the oil bath temperature to 140 °C led to the formation of the desired product in 34% yield. The use of other palladium catalysts such as $Pd(CH_3CN)_2Cl_2$ and $Pd_2(dba)_3$ (dba = dibenzylideneacetone) did not improve the yield of the reaction. We were delighted to note, however, that a change in the base from Cs_2CO_3 to Li_2CO_3 increased the yield of the desired product dramatically to 65% with high stereoselectivity. However, the amount of the base used was found to be critical, as the use of 6 equivalents of Li_2CO_3 lowered the yield to only 40%. Next, we screened other solvents for the reaction and concluded that dioxane was the best in terms of yield and selectivity. Thus, the use of $Pd(PPh_3)_2Cl_2$ (10 mol-%) and Li_2CO_3 (2 equiv.) in dioxane at 140 °C (oil bath temperature) was found to be the optimal conditions for the generation of aryl glycosides **2**.

With these standardized reaction conditions in our hand, we examined the substrate scope of the coupling reaction. For this, a series of sulfonyl chlorides were allowed to react with 3,4,6-tri-*O*-acetyl-D-glucal (**1**). It was found that all arylsulfonyl chlorides containing either an electron-donating group or an electron-withdrawing group (Figure 2, see compounds **3**–**9**) reacted smoothly to yield the corresponding aryl glycosides in moderate yields with >99% selectivity. Further, to diversify the substrate scope glycals other than glucal were examined.

Thus, the tri-*O*-acetyl-D-galactal was subjected to the reaction with various arylsulfonyl chlorides under the standardized reaction conditions to yield *C*-aryl galactosides in moderate yields (Figure 2, see compounds **11**–**14**). Reaction of deoxysugars such as 3,4-di-*O*-acetyl-L-rhamnal and 3,4-di-*O*-acetyl-L-fucal with benzenesulfonyl chloride afforded the desired glycosides in yields of 54 and 45%, respectively, with β-selectivity (Figure 2, see compounds **16**–**18**). Next, we were interested in examining the effect of other protecting groups on the glucal moiety. It was observed that the benzoyl (Bz) group reacted almost similarly to the acetyl (Ac) group to yield the corresponding *C*-aryl glycoside in moderate yield (Figure 2, see compound **15**). In the case of ether protection such as 3,4,6-tri-*O*-benzyl-D-glucal, a ketone-type *C*-glycoside (Figure 2, see compound **19**) instead of the normal *C*-Ferrier product was obtained through β-hydride elimination of the intermediate σ adduct and cleavage of the benzyl (Bn) group, as reported in the literature under similar conditions.[18c]

On the basis of previous literature[10,5] on palladium-catalyzed *C*-glycosylation, we propose the mechanism outlined in Figure 3. To start, the Pd^{II} species is reduced to Pd^0 under basic conditions;[18b] this is followed by a sequence of four steps: One, oxidative addition of the arylsulfonyl chloride to Pd^0[15] to form Pd^{II} species **A**. Two, subsequent elimination of SO_2 and Cl under heating conditions to generate ArPd cation complex **B**. Three, the addition of **B** to the double bond of the glucal triacetate to generate π complex **C**, which results in the formation of glucal palladium cationic complex **D**. In this step, the ArPd species attacks from the opposite side of the C-3 substituent, which results in anomeric selectivity. Four, reductive elimination of the Pd^{II} complex under basic conditions[18] along with *anti*-β-3-OAc elimination to afford desired *C*-aryl glycoside **2**. It is evident

Table 1. Standardization of the reaction conditions for the *C*-arylation of glycals with benzenesulfonyl chloride.



1 **2**

Entry	Catalyst[a]	Base (equiv.)	*T* [°C]	Solvent[b]	Time [h]	Yield[c] [%]	α/β[d]
1	$Pd(Ph_3P)_2Cl_2$	Cs_2CO_3 (2)	100	dioxane	48	–	–
2	$Pd(Ph_3P)_2Cl_2$	Cs_2CO_3 (2)	140	dioxane	40	34	99:1
3	$Pd(CH_3CN)_2Cl_2$	Cs_2CO_3 (2)	140	dioxane	40	trace	–
4	$Pd_2(dba)_3$	Cs_2CO_3 (2)	140	dioxane	40	25	–
5	$Pd(PhCN)_2Cl_2$	Cs_2CO_3 (2)	140	dioxane	40	12	–
6	$Pd(OAc)_2$	Cs_2CO_3 (2)	140	dioxane	40	10	–
7	$Pd(Ph_3P)_2Cl_2$	Li_2CO_3 (6)	140	dioxane	40	43	99:1
8[e]	$Pd(Ph_3P)_2Cl_2$	Li_2CO_3 (2)	140	dioxane	40	65	99:1

[a] In all cases, 10 mol-% of catalyst was used. [b] Solvent used was 5 mL for 1 mmol of substrate. [c] Yield obtained after column chromatography. [d] Detected by ^1H NMR spectroscopy. [e] Standardized reaction conditions.

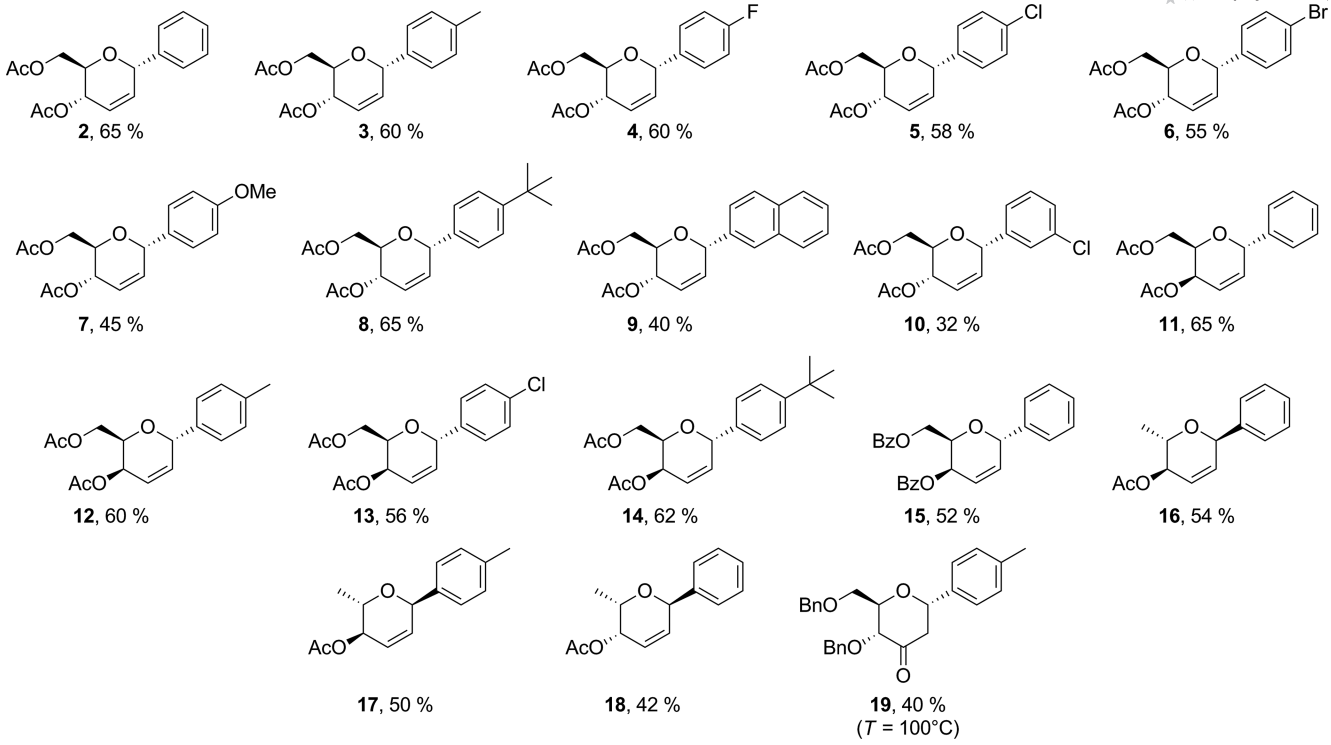


Figure 2. Substrate scope of the palladium-catalyzed desulfitative *C*-arylation. In all cases, the selectivity was >99.

from the above discussion that the stereochemistry of OAc at C-3 plays a role in controlling the anomeric stereochemistry and is the reason behind the α-selectivity for D-glycals and β-selectivity[7,10b] for L-sugars in this study. Moreover, the involvement of a Pd^{II}/Pd^{IV} palladacycle cannot be ruled out.

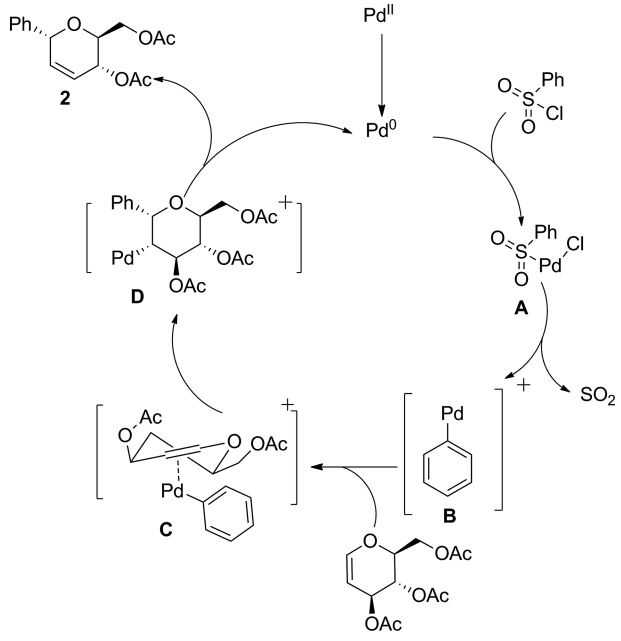


Figure 3. Plausible mechanism for the palladium-catalyzed *C*-arylation reaction.

Conclusions

In conclusion, we demonstrated a new approach for *C*-aryl glycosidic bond formation. Staring from easily available arylsulfonyl chlorides, several aryl glycosides were prepared in good yield by means of the palladium-catalyzed desulfitative *C*-arylation of various glycals.

Experimental Section

General Procedure: A 25 mL, oven-dried Schlenk tube was charged with glycal (1 mmol), arylsulfonyl chloride (1.5 mmol), Li_2CO_3 (2 mmol), 1,4-dioxane (2 mL), and $Pd(Ph_3P)_2Cl_2$ (0.1 mmol). The mixture was evacuated by vacuum–argon cycles (5×) and stirred at 140 °C (oil bath temperature) for 40 h. After cooling the mixture to room temperature, the solvent was evaporated under reduced pressure to get the crude product, which upon purification through silica gel column chromatography (ethyl acetate/petroleum ether) afforded the desired product.

Acknowledgments

The authors are thankful to Dr. Ram A Vishwakarma, Director, IIIM Jammu for generous funding (MLP4015) along with fellowship under INSPIRE Faculty Scheme (IFA-CH-18). M. T. and A. K. K. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for a senior research fellowship.

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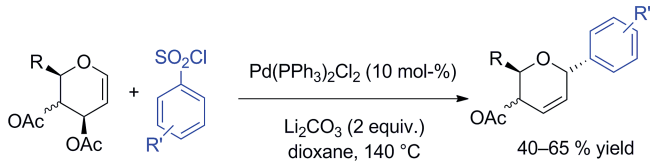
Received: September 10, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Arylation



A highly stereoselective desulfitative *C*-arylation reaction is developed by using glycal and arylsulfonyl chlorides in the presence of bis(triphenylphosphine)palladium(II) chloride and Li_2CO_3. A wide variety of glycals and arylsulfonyl chlorides participate in the reaction smoothly. *C*-Arylation happens possibly through a catalytic cycle involving Pd^{II}/Pd^{0} species.

Keywords: Synthetic methods / C–C coupling / Cross-coupling / Sulfur / Palladium / Glycosides

