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Palladium Catalyzed Stereoselective *C*-Glycosylation of Glycals with Enol Triflates

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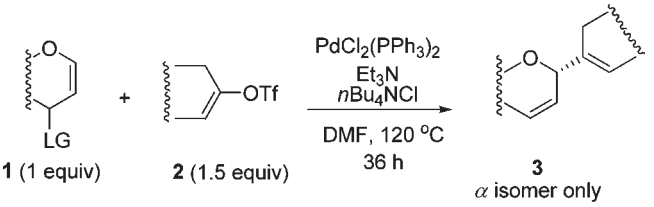
ABSTRACT



An efficient palladium catalyzed *C*-glycosylation of glycals with enol triflates has been established. The coupling reactions took place on the anomeric carbon, and the coupling products gave exclusively α isomers. The flexibility of the reaction was exemplified by the broad spectra of substrate scope, constituted of glycals protected with good leaving groups as well as an assortment of enol triflates.

C-Glycosides are a unique class of carbohydrate analogues possessing a C−C bond between the anomeric carbon and the aglycon. Research has been intensively conducted on *C*-glycosides in past decades due to their importance in enzymatic and metabolic chemistry.[1] In addition, they are also found in a wide range of naturally occurring products such as ambruticin S,[2] aspergilllide C,[3] and (+)-varitriol.[4] The presence of multiple chiral centers on carbohydrates renders *C*-glycosides as important building blocks[5] for the construction of these natural products.

Among the many diverse *C*-glycosides that exist, 2,3-unsaturated *C*-glycosides are a unique class of carbohydrate analogues which are synthetically versatile for the preparation of a variety of compounds with important pharmacological properties. The most commonly used method to synthesize 2,3-unsaturated *C*-glycosides is the Lewis acid promoted Ferrier rearrangement. To date, a large number of Lewis acids have been explored to achieve high yields and stereoselectivities. However, various drawbacks such as limited nucleophilic reagents, high catalyst loadings, and moderate stereoselectivities restrict the application of this type of reaction.

More recently, the efficiency of transition metal catalyzed reactions has stimulated chemists to investigate the applicability of transition metals, especially palladium, in carbohydrate chemistry. Given the vinyl feature of glycals, *C*-glycosylation reactions producing 2,3-unsaturated *C*-glycosides *via* a palladium-catalyzed Heck type reactions have been intensively studied. Active nucleophilic reagents such as mercury salts,[6] aryl boronic acid,[7] and aryl iodide[8] were introduced to couple with glycal compounds. All the reported Heck type *C*-glycosylations have given exclusively α-selectivity due to steric hindrance from the C3 protecting group.[8] After addition of the aryl palladium

(1) (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep* **2005**, *22*, 742. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Wei, Z. *Curr. Top. Med. Chem.* **2005**, *5*, 1363.

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(7) (a) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709. (b) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013.

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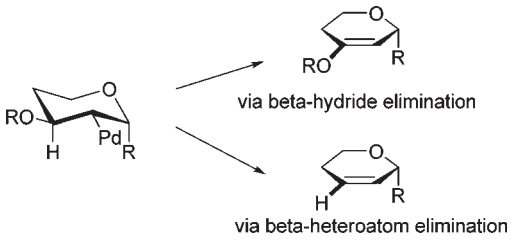
species, the palladium atom attached to the C2 carbon potentially has two elimination pathways to follow (Scheme 1). One gives the syn-β-hydride elimination products, the other gives the anti-β-heteroatom elimination products.

Scheme 1. Pd Elimination Pathways of Heck Type *C*-Glycosylation

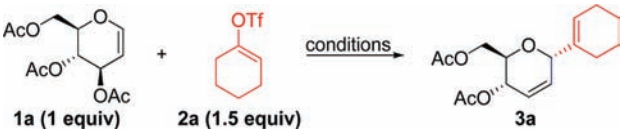


However, almost all of the existing palladium-catalyzed methods focus on the formation of a C−C bond between the anomeric carbon and the aryl group. To the best of our knowledge, few palladium catalyzed coupling reactions of glycals and alkyl groups have been reported. The use of enol triflates with olefins, in Heck reactions, shows their potential efficiency as coupling reagents and highlights their underlying potential in a reaction with glycals.[9] In continuation of our interest in functionalized sugar pyranose, especially glycals,[10] herein we report a highly stereoselective palladium catalyzed *C*-glycosylation between glycals and enol triflates.

Initially, the reaction of glucal (**1a**) and cyclohexenyl triflate (**2a**) with palladium acetate as catalyst was carried out in 1 equiv of triethylamine in dimethylformamide (DMF) at 80 °C (Table 1, entry 1). Unfortunately, this reaction could not afford any desired product after 48 h. Upon screening different palladium catalysts, $PdCl_2(PPh_3)_2$ was found to give the Ferrier type product (**3a**) in poor yield (entry 4) while a catalyst such as $Pd(OAc)_2$ (entry 1), $Pd(TFA)_2$ (entry 2), or $Pd(PhCN)_2Cl_2$ (entry 3) was found to be ineffective.

Next, we proceeded to screen various organic and inorganic bases, and triethylamine was found to be the most effective for mediating this process.[11] In addition, 3 equiv of base were found to give a much higher yield of product **3a** (entry 5). Investigation of various additives and ligands revealed that addition of ligands to the reaction

Table 1. Palladium Catalyzed Ferrier Type *C*-Glycosylation with Glycal and Cyclohexenyl Trifluoromethanesulfonate[a]



entry	catalyst	additive	solvent	temp (°C)	yield (%)[b]
1[c]	$Pd(OAc)_2$	N.A.	DMF	80	0
2[c]	$Pd(TFA)_2$	N.A.	DMF	80	0
3[c]	$Pd(PhCN)_2Cl_2$	N.A.	DMF	80	0
4[b]	$PdCl_2(PPh_3)_2$	N.A.	DMF	80	32%
5	$PdCl_2(PPh_3)_2$	N.A.	DMF	80	46%
6	$PdCl_2(PPh_3)_2$	dppe[d]	DMF	80	0
7	$PdCl_2(PPh_3)_2$	dppp[d]	DMF	80	53%
8	$PdCl_2(PPh_3)_2$	dpppen[d]	DMF	80	0
9	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	DMF	80	62%
10	$PdCl_2(PPh_3)_2$	nBu$_4$NBr	DMF	80	51%
11	$PdCl_2(PPh_3)_2$	nBu$_4$NI	DMF	80	46%
12	$PdCl_2(PPh_3)_2$	nBu$_4$NOAc	DMF	80	30%
13	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	DMF	100	65%
14	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	DMF	120	78%
15	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	DMF	135	69%
16	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	DMSO	120	45%
17	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	ACN	100	12%
18	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	NMP	120	56%
19	$PdCl_2(PPh_3)_2$	nBu$_4$NCl	toluene	110	23%

[a] Unless otherwise specified, reactions were carried out with 1 equiv of **1a**, 1.5 equiv of **2a**, 10% catalyst, 150% additives, and 3 equiv of triethylamine in a sealed tube for 36 h. [b] Isolated yield. [c] 1 equiv of base. [d] Ligand added in 40 mol %. dppe: 1,2-diphenylphosphinoethene; dppp: 1,3-diphenylphosphinopropane; dpppen: 1,5-diphenylphosphenopentane.

was not necessary (entries 6−8) but a tetrabutylammonium salt could enhance the yield significantly.[12] Tetrabutylammonium salts with different anions were further tested, and it was found that tetrabutylammonium chloride afforded the desired product in the highest yield (entries 9−12). Gratifyingly, increasing the reaction temperatures to 120 °C (entries 13−14) led to the Ferrier type product exclusively in good yield within an acceptable period of time. However, any further increase of temperature lowered the yield (entry 15). Several solvents were tested, but DMF was found to afford the desired product with the highest yield (entries 14, 16−18).

With the optimal reaction conditions identified, we studied the substrate scope of this reaction, and the results are summarized in Table 2. First, glycals with different protecting groups were tested for their reactivities toward the cyclohexenyl triflate. Among the protecting groups surveyed, only good leaving groups such as acetyl (**3a**, **3d**), pivaloyl (**3c**, **3f**) and ethoxycarbonyloxyl (**3b**, **3e**) were found to be reactive under standard conditions. Among them, ethoxycarbonyl-protected glycals gave the desired

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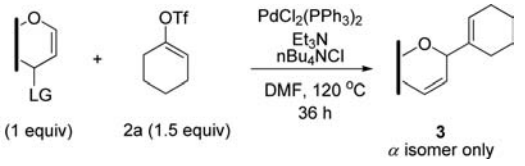
(10) (a) Gorityala, B. K.; Lorpitthaya, R.; Bai, Y. G.; Liu, X.-W. *Tetrahedron* **2009**, *65*, 5844. (b) Lorpitthaya, R.; Xie, Z. Z.; Sophy, K. B.; Kuo, J. L.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 588. (c) Ma, J. M.; Zhao, Y. Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 4533. (d) Cai, S.; Kishan Gorityala, B.; Ma, J.; Leow, M. L.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 1072. (e) Lorpitthaya, R.; Xie, Z.-Z.; Kuo, J.-L.; Liu, X.-W. *Chem.—Eur. J.* **2008**, *14*, 1561. (e) Gorityala, B. K.; Cai, S.; Lorpitthaya, R.; Ma, J.; Pasunooti, K. K.; Liu, X.-W. *Tetrahedron Lett.* **2009**, *50*, 676.

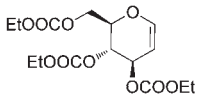
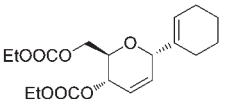
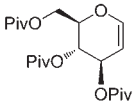
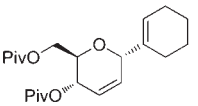
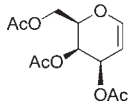
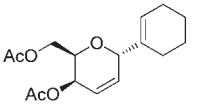
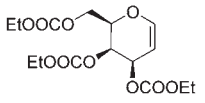
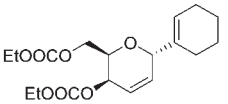
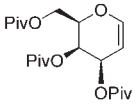
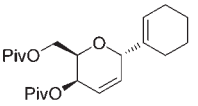
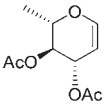
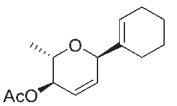
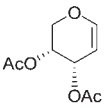
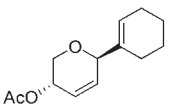
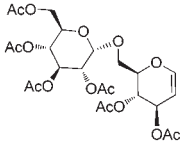
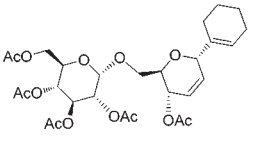
(11) For the selection of base, see Supporting Information.

(12) (a) Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Org. Lett.* **2011**, *13*, 1126. (b) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745.

Table 2. *C*-Glycosylation Coupling Reaction of Glycals and Cyclohexenyl Triflate[a]



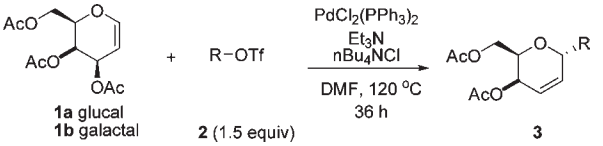
1 (1 equiv) 2a (1.5 equiv) **3** α isomer only

entry	glycals	products	yield[b] (%)
1	 **1b**	 **3b**	80
2	 **1c**	 **3c**	25
3	 **1d**	 **3d**	84
4	 **1e**	 **3e**	86
5	 **1f**	 **3f**	34
6	 **1g**	 **3g**	49
7	 **1h**	 **3h**	52
8	 **1i**	 **3i**	62

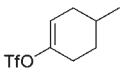
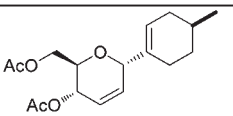
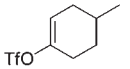
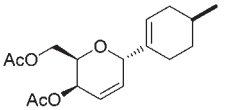
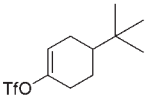
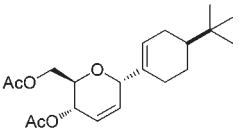
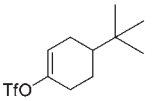
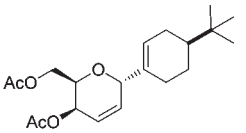
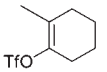
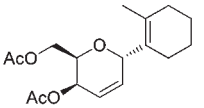
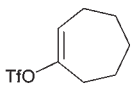
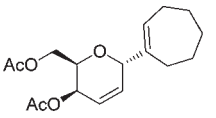
[a] Reactions were carried out with 1 equiv of glycal, 1.5 equiv of enol triflate, 10% catalyst, 150% nBu$_4$NCl, and 3 equiv of triethylamine in a sealed tube for 36 h. [b] Isolated yields.

product in high yields while pivaloyl protected glycals were shown to be less efficient. Next, we moved on to test the

Table 3. *C*-Glycosylation Coupling Reactions of Glycals and Enol Triflate[a]



1a glucal **1b** galactal **2** (1.5 equiv) **3**

entry	enol triflate	product	yield (%)[b]
1	 **2b**	 **3j**	68% (1:1)
2	 **2b**	 **3k**	71% (1:1)
3	 **2c**	 **3l**	51% (1:1)
4	 **2c**	 **3m**	62% (1:1)
5	 **2d**	 **3n**	54%
6	 **2e**	 **3o**	31%

[a] Reactions were carried out with 1 equiv of glycal, 1.5 equiv of enol triflate, 10% catalyst, 150% nBu$_4$NCl, and 3 equiv of triethylamine in a sealed tube for 36 h. [b] Isolated yields.

reactivities of glycals prepared from different carbohydrates. It was found that glycals prepared from galactose (**3d**–**3f**), L-6-deoxyglucose (**3g**), ribose (**3h**), and disaccharide (**3i**) also reacted with enol triflate (**2a**) to provide the corresponding *C*-glycosides in moderate to high yields. The structure of the coupling product (**3d**) was confirmed by X-ray crystallography (Figure 1). It is notable that glycals derived from galactose generally gave higher yields as compared with their glucose equivalents.

The reactivities of enol triflates were further tested (Table 3). Cyclohexenyl triflates with substituents such as 4-methyl (**3j**, **3k**), 4-*tert*-butyl (**3l**, **3m**), and 2-methyl (**3n**)

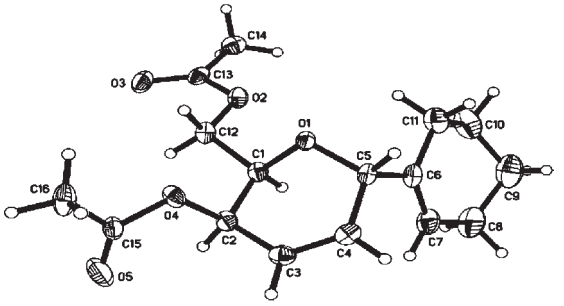


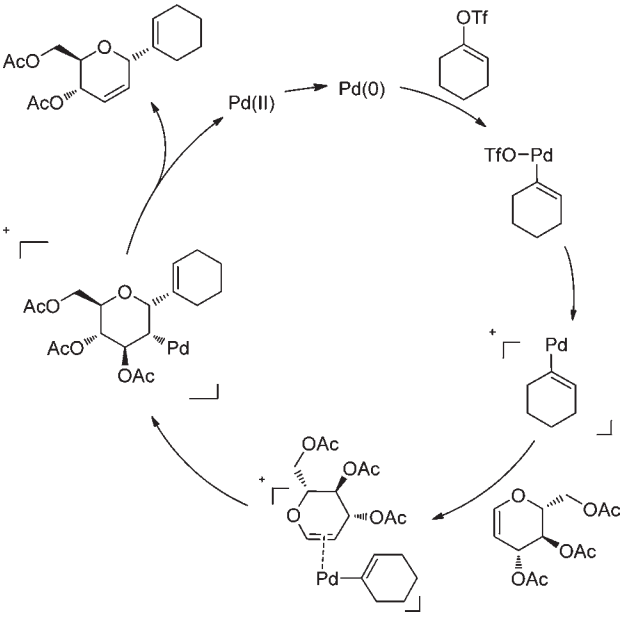
Figure 1. X-ray structure of compound **3d**.

gave the corresponding products. However, when efforts were made to change the ring size of the enol triflate, the results were not promising. Both cycloheptenyl and cyclooctenyl triflates were synthesized and tested under standard conditions. However, only cycloheptenyl triflate and D-galactal afforded the desired product (**3o**) in poor yield while glucal, on the other hand, failed to give any desired product. Conversely, other cyclo-derivatives like cyclopentenyl triflate were not synthesized due to their low-boiling points. In addition, cyclooctenyl triflate and aliphatic enol triflate such as octyl triflate also failed to afford any product with glucal or galactal.

A plausible mechanism for the process described is proposed in Scheme 2. After the reduction of Pd(II) to Pd(0), oxidative addition takes place to form the alkyl-Pd cation complex. This complex is then added to the double bond on glycal, which results in the formation of a Pd-glycal complex. Next, anti-β-elimination of the acetyl group with Pd takes place to give the final α-*C* glycosides and Pd(II) species.[13] Pd(II) is assumed to be reduced to Pd(0) by amine,[14] and the active catalyst Pd(0) is generated to start a new catalytic cycle. In this case, the tetrabutylammonium salt acts as a phase transfer agent, and a halogen anion promotes the anti-β-OAc-elimination.[15]

(13) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899.
(14) Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Org. Lett.* **2011**, *13*, 2184.
(15) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

Scheme 2. Plausible Mechanism of the Heck Type *C*-Glycosylation Reaction Observed



In conclusion, an efficient palladium catalyzed method for *C*-glycosylation of glycals and enol triflates has been established. The cross-coupling reactions proceed with high regioselectivity and stereoselectivity. The substrate scope includes glycals with good leaving groups and various enol triflates. In addition, the cyclohexenyl and cycloheptenyl groups on the products provide the potential for further transformations to other functionalities.

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