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Palladium-Catalyzed Stereoselective Formation of α-*O*-Glycosides

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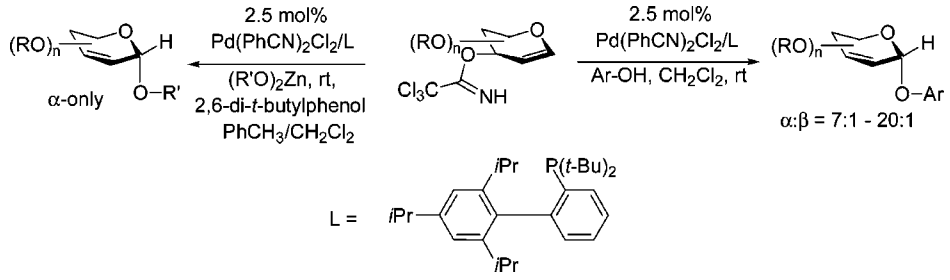
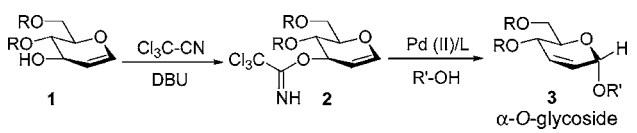
ABSTRACT



A novel method for palladium-catalyzed stereoselective formation of α-*O*-glycosides has been developed. This strategy relies on the palladium−biaryl phosphine catalyst−glycal donor complexation to control the anomeric selectivity. It does not depend on the nature of the protecting groups on the substrates, thus eliminating the need for cumbersome protecting group manipulations.

The development of new methods for stereoselective formation of α- or *β*-*O*-glycosides has been extensively investigated owing to the critical roles carbohydrates play in a variety of biological systems.[1] To date many efforts have focused on developing new methods and reagents for the generation of isolated glycosyl donors which subsequently undergo glycosidic bond formation with nucleophilic glycosyl acceptors.[2] Despite their potential applications to complex carbohydrate synthesis, each of these methods relies on the nature of the substrates to stereoselectively control the formation of glycosidic bonds. Recently, the use of glycal derivatives as glycosyl donors has been utilized in *π*-allylpalladium strategies for the stereoselective synthesis of *O*-glycosides.[3] However, because of the poor reactivity of the glycal donors as well as the alcohol nucleophiles, these groups utilized the more activated pyranone donors.[3a,b] Lee and co-workers, who recognized the challenge in this approach, utilized Zn(II) ion to activate both the alcohol acceptors for the nucleophilic addition and the glycal donors for the ionization.[3c] We report herein a novel method for the stereoselective construction of α-*O*-glycosides directly from glycals. In this reaction, the Pd(II)/L catalyst is believed to activate the glycal *π*-system for stereoselective attack by the external oxygen nucleophile, and the C(3)-trichloroacetimidate group serves as the leaving group as well as directs Pd(II) to the double bond of the glycal (Scheme 1). This strategy relies on palladium−ligand catalyst−donor complexation to control the anomeric selectivity rather than the nature of the protecting groups on the substrates, thus eliminating the need for cumbersome protecting group

Scheme 1



(1) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357−2364. (c) Helenius, A.; Aebi, M. *Science* **2001**, *291*, 2364−2369. (d) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624.

(2) (a) Sinäry, P. *Pure. Appl. Chem.* **1991**, *63*, 519−528. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (c) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. (d) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (e) Davis, B. G. *J. Chem. Soc.; Perkin Trans. 1* **2000**, 2137−2160.

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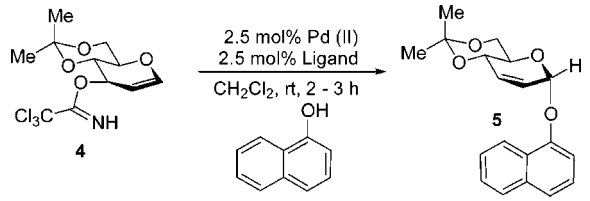
manipulations that are often employed in glycosylation. In contrast, the Ferrier reaction, which often employs a stoichiometric Lewis acid, gives a mixture of α- and β-glycoside products.[4]

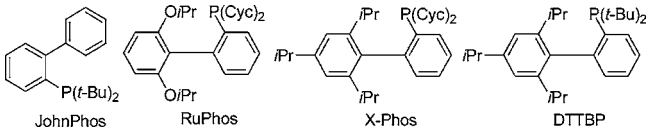
Our studies commenced with glucal imidate **4** as the glycosyl donor and sterically hindered 1-naphthol as the glycosyl acceptor (Table 1). Treatment of **4** with 2.5 mol % of $Pd(CH_3CN)_2Cl_2$ in the presence of 2.0 equiv of 1-naphthol at room temperature for 2 h provided glycoside **5** with α/β = 3:1 (entry 1). It was anticipated that the anomeric selectivity could depend on the ligand on palladium. Accordingly, a variety of Buchwald's bulky biaryl phosphine ligands were investigated because these ligands were resistant toward oxidation by molecular oxygen.[5] Since these phosphine ligands are electron-rich, they could potentially reduce Pd(II) to Pd(0) in the reaction; thus, only a 1:1 mixture of Pd and ligand was investigated. Treatment of **4** with a preformed solution of $Pd(CH_3CN)_2Cl_2$ and JohnPhos ligand had no effect on the outcome of the reaction (entry 2). Since it is known that the rate of ligand exchange with $Pd(CH_3CN)_2Cl_2$ is slow,[6] $Pd(PhCN)_2Cl_2$ was investigated. Treatment of **4** with a preformed solution of $Pd(PhCN)_2Cl_2$ and JohnPhos ligand led to an improvement in the anomeric selectivity (entry 3). Ultimately, when DTTBP was used as the ligand in the reaction, the desired glycoside **5** was obtained in 84% yield with α/β = 20:1 (entry 6). Thus, simply switching to the more bulky biaryl phosphine ligand increased the anomeric selectivity of the reaction.[7] These results clearly demonstrate the efficiency of the palladium method, with the formation of **5** nearly exclusively as the α-anomer.

Table 1. Pd(II)-Catalyzed Stereoselective Glycosylation of 1-Naphthol with Glucal Imidate **4**[a]



entry	Pd (II) sources	phosphine ligands	yield[b]	α/β[c]
1	$Pd(CH_3CN)_2Cl_2$	None	55%	3:1
2	$Pd(CH_3CN)_2Cl_2$	JohnPhos	53%	3:1
3	$Pd(PhCN)_2Cl_2$	JohnPhos	91%	4:1
4	$Pd(PhCN)_2Cl_2$	RuPhos	54%	4:1
5	$Pd(PhCN)_2Cl_2$	X-Phos	70%	8:1
6	**$Pd(PhCN)_2Cl_2$**	**DTTBP**	**84%**	**20:1**

[a] All reactions were carried out in CH_2Cl_2 (0.2 M) at room temperature for 2−3 h with 2 equiv of 1-naphthol, 2.5 mol % phosphine ligand, and 2.5 mol % Pd(II). [b] Isolated yield. [c] ^1H NMR ratio.



A proposed mechanism for Pd(II)-catalyzed formation of α-*O*-glycosides is outlined in Figure 1. Reversible coordination of palladium−phosphine catalyst to both the imidate nitrogen and the double bond of glucal **4** forms the palladium−olefin complex **6**, which subsequently undergoes migratory insertion to form the oxonium palladium-σ complex **7**.[8] The bulky biaryl phosphine ligand blocks the approach of the nucleophile to the β-face of **7**. As a result, stereoselective addition of 1-naphthol to the α-face of **7** results in formation of **8**. Subsequent deoxypalladation of **8** followed by dissociation provides **5**. In this catalytic cycle, 1-naphthol functions as both the nucleophile and the proton donor to facilitate the deoxypalladation step.

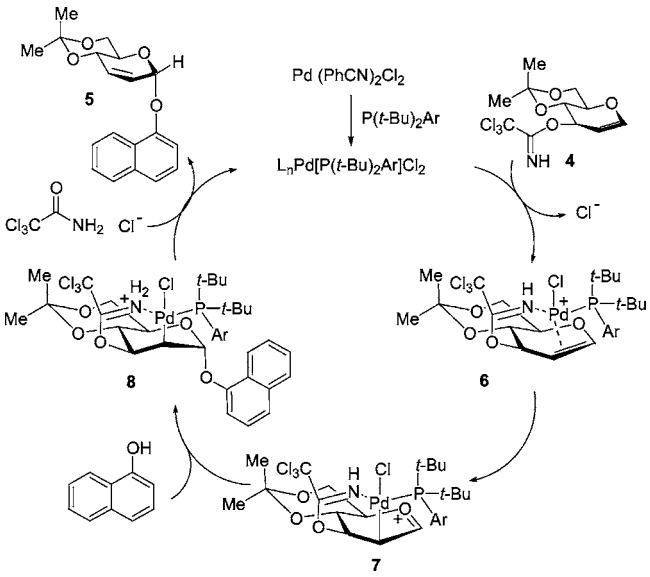


Figure 1. Proposed Catalytic Cycle of Pd(II)-Catalyzed Glycosylation

To assess the feasibility of this novel palladium(II)-catalyzed glycosylation in the context of *O*-aryl glycoside synthesis, a number of glycal donors incorporating a variety of protecting groups were examined with an array of aryl alcohol acceptors (Table 2). The desired *O*-aryl glycosides

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(4) (a) Ferrier, R. J. *J. Chem. Soc., Perkin. Trans. 1* **1979**, 1455−1458. (b) Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57−66.

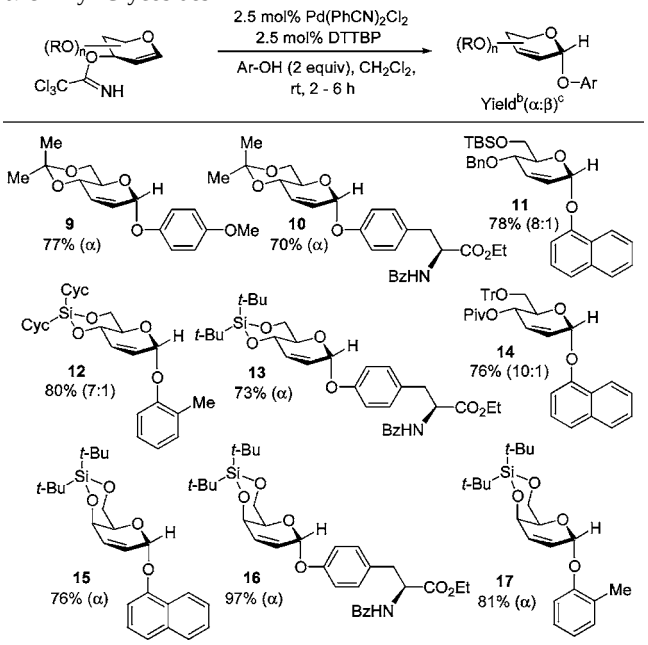
(5) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096−5101.

(6) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M. F.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375−3389.

(7) Since DTTBP is the electron-rich phosphine ligand, a control experiment was studied to determine if this reaction did go through Pd(0) mechanism. Treatment of **4** with a preformed solution of $Pd_2(dba)_3$ and DTTBP in the presence of 1-naphthol only gave 26% yield of **5** with α/β = 1.5:1. This result suggests that our method may not go through Pd(0).

(8) Coordination of Pd to both imidate nitrogen and olefin has been proposed by Overman, see: (a) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866−2867. (b) Kirsch, S. F.; Overman, L. E.; White, N. S. *Org. Lett.* **2007**, *9*, 911−913.

Table 2. Pd(II)-Catalyzed Stereoselective Formation of α-*O*-Aryl Glycosides[a]

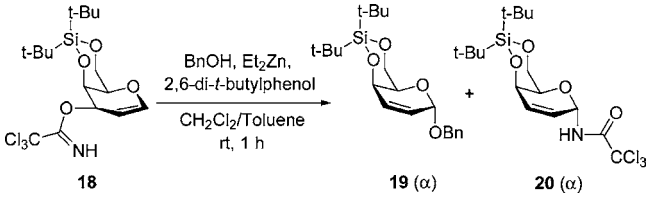


[a] All reactions were carried out in CH_2Cl_2 (0.2 M) at rt for 2−6 h with 2 equiv of aryl alcohol acceptors, 2.5 mol % Pd(II), and 2.5 mol % DTTBP. [b] Isolated yield. [c] ^{1}H NMR ratio.

were obtained in good yield with excellent α-selectivity. These results illustrate that the nature of the protecting groups has little effect on the anomeric selectivity, thus suggesting that the bulky biaryl phosphine ligands were responsible for the observed selectivity.

The efficacy of this reaction was examined with aliphatic alcohols. Benzyl alcohol was initially employed as the nucleophilic glycosyl acceptor. Because of the poor nucleophilicity of benzyl alcohol, it was converted to the more reactive zinc(II) alkoxide.[3c,d] Accordingly, treatment of galactal imidate **18** with a preformed solution of BnOH (3 equiv) and Et_2Zn (1.5 equiv) and 2.5 mol % $Pd(PhCN)_2Cl_2$/DTTBP in a mixture of toluene and CH_2Cl_2 (1:2) provided glycoside **19** in 60% yield along with the rearrangement product **20** in 22% yield (Table 3, entry 1). In this reaction, 2,6-di-*t*-butylphenol was used as the proton donor to facilitate the catalyst turnover. Decreasing the amount of zinc(II) alkoxide increased the yield of **19** to 77% (entry 2). To determine if galactal imidate **18** was activated by zinc(II) alkoxide, a control experiment was peformed (entry 3). Less than 5% yield of **19** was detected.

Table 3. Pd(II)-Catalyzed Stereoselective Glycosylation of Benzyl Alcohol with Galactal Imidate **18**

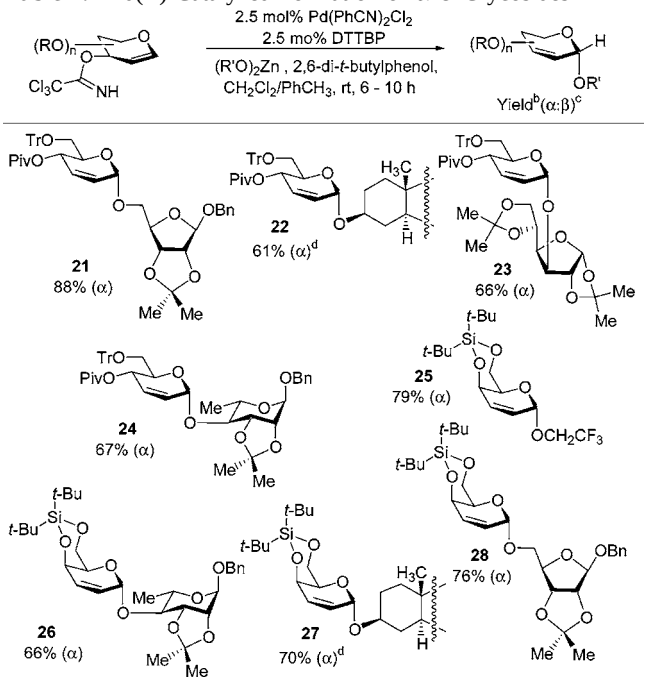


entry	BnOH	Et_2Zn	$Pd(PhCN)_2Cl_2$/DTTBP	**19** (yield)[b]	**20** (yield)[b]
1	3.0 equiv	1.5 equiv	2.5 mol %	60%	22%
2	1.5 equiv	0.75 equiv	2.5 mol %	77%	7%
3	1.5 equiv	0.75 equiv	none	<5%	<5%

[a] All reactions were carried in CH_2Cl_2/toluene (2:1, 0.15 M) with 0.5 equiv of 2, 6-di-*t*-butylphenol, and BnOH at room temperature for 1 h. [b] Isolated yield.

Having shown that the current palladium(II) method was feasible with benzyl alcohol as the glycosyl acceptor, this chemistry was further explored with a variety of aliphatic alcohols (Table 4). Treatment of glycal imidates with a preformed solution of Zn(II) alkoxides proved successful and provided the desired glycosides **21**−**28** exclusively as α-anomers. By careful ^{1}H NMR analysis, it was determined that the major byproduct in these reactions was the [3,3]-sigmatropic rearrangement product. These results show that the glycosylation is amenable to a variety of aliphatic alcohol acceptors including primary and secondary hydroxyl groups of carbohydrate nucleophiles.[9]

Table 4. Pd(II)-Catalyzed Formation of α-*O*-Glycosides[a]

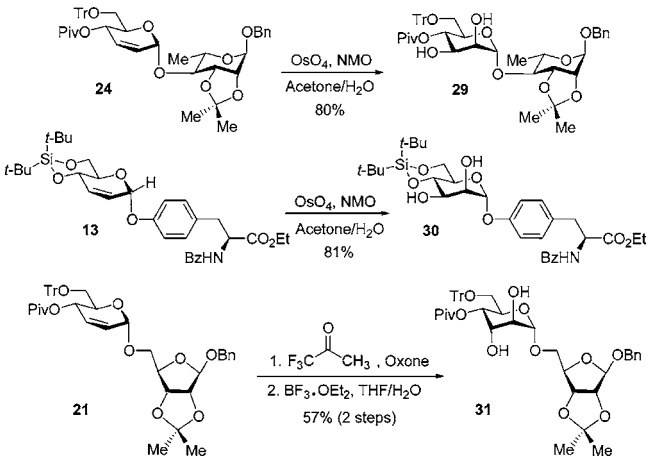


[a] All reactions were studied with alcohol (1.5 equiv), Et_2Zn (0.75 equiv), 2,6-di-*t*-butylphenol (0.5 equiv), 2.5 mol % $Pd(PhCN)_2Cl_2$/DTTBP. [b] Isolated yield. [c] ^{1}H NMR ratio. [d] $(R'O)_2Zn$ = dihydrocholesterol.

To demonstrate the potential utility of the 2,3-unsaturated products, the following transformations were carried out (Scheme 2). Dihydroxylation of **24** and **13** provided α-mannosides **29** and **30**, respectively. Epoxidation of **21** followed by opening of epoxide intermediate provided diol **31** in overall good yield.

In summary, a novel method for palladium(II)-catalyzed stereoselective construction of α-*O*-glycosides has been

Scheme 2



developed. The α-selectivity relies on the palladium−phosphine catalyst−glycal donor complexation rather than on the nature of the protecting groups on the substrates. Because of its mild conditions and substrate tolerance, the palladium(II) reaction is applicable to an array of glycal imidates and alcohols as well as phenol acceptors.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A similar glycosylation was reported by Schmidt and coworkers utilizing TMSOTf as a Lewis acid to catalyze the reaction of **18** with alipahtic alcohol acceptors: Abdel-Rahman, A. A.-H.; Winterfield, G. A.; Takhi, M.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 713−717. Our question is whether the Lewis-acid catalyzed Ferrier reaction is applicable to a variety of glycal imidates and aryl/alkyl alcohols acceptors. Under Schmidt's conditions, treatment of **4** with 5 mol % of TMSOTf and 1.1 equiv of 1-naphthol or benzyl 2,3-*O*-isopropylidene-D-ribosefuranoside only resulted in multiple products.