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Stereoselective Palladium-Catalyzed *O*-Glycosylation Using Glycals

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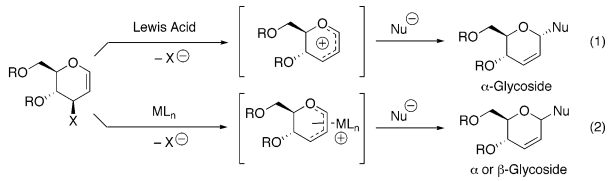
Efficient and selective construction of glycosidic linkages continues to be important due to the critical roles played by various glycoconjugates in nature.[1] Different in modality from the majority of chemical glycosylations, the Ferrier reaction achieves glycosylation via displacement of the C3 substituent in a glycal system (eq 1).[2] Due to the synthetic versatility of the 2,3-unsaturated glycoside, this method has proven useful for a wide range of applications.[3] The exceptional synthetic value of the Ferrier process, however, has not been translated significantly to carbohydrate chemistry, despite the original conception of the reaction for direct *O*-glycosylation. The dominant anomeric effect has limited the utility of this method largely to the synthesis of α-glycosides using a stoichiometric Lewis acid. Given the ready availability of glycals and the synthetic utility of the product, the development of a glycal-based glycosylation method whose scope transcends the Ferrier paradigm would represent an important advance.

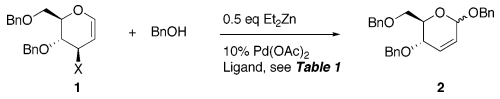


Our approach to glycosylation is to exploit transition metal catalysis using the allylic feature contained within the glycal structure (eq 2). However, the poor reactivity of both the glycal donors and the alcohol acceptors for a η^3-metal mediated reaction has been a major challenge to this approach.[4,5] Encouraged by our recent results,[6] we envisioned that the reaction of an acceptor activated via zinc(II) alkoxide formation with a metal coordinated cationic donor might accomplish the desired *O*-glycosylation. Reported herein is the discovery of a Pd-catalyzed glycosylation reaction that occurs under mild reaction conditions with the anomeric configuration controlled by the reagent rather than by the anomeric or neighboring group effect.

Initial experiments were performed with glycal **1** as the donor and benzyl alcohol as the acceptor (Table 1). Upon treatment of **1** with a preformed solution of benzyl alcohol (1.0 equiv) and Et_2Zn (50 mol %) in the presence of a palladium catalyst, the reaction proceeded smoothly to furnish **2** in excellent yield. Notably, the anomeric stereochemistry depended strongly on the ancillary ligands at palladium. While moderate selectivities were obtained from the reactions with common mono- and diphosphines, employment of DTBBP ligand[7] led to complete β-*O*-glycoside formation, which cannot be brought about by the traditional Lewis acid mediated Ferrier procedures (entries 1 and 8). When $P(OMe)_3$ was employed as the ligand, the α-anomer was generated as the major product in a 7:1 ratio (entries 7 and 9). Hence, simple alteration of the ligand provided a switch from β- to α-selective glycosylation.

The scope of the new glycosylation was further examined in the context of disaccharide synthesis (Table 2). An array of monosaccharide donors and acceptors underwent glycosidic coupling to

Table 1. Pd-Catalyzed Glycosylation of Benzyl Alcohol with Glycal **1**[a]



entry	glycal	ligand	yield (%)[b]	dr (**2α**:**2*β***)[c]
1[d]	**1a** X = OAc	15% DTBBP	92	<1:25
2		15% dppf	95	1:5
3		15% dppb	96	1:4
4		30% P(*t*-Bu)$_3$	92	1.5:1
5		30% P(2-furyl)$_3$	90	2:1
6[e]		40% PPh_3	87	4:1
7		30% $P(OMe)_3$	90	7:1
8	**1b** X = O^{t}Boc	15% DTBBP	92	<1:25
9[f]		30% $P(OMe)_3$	90	5:1

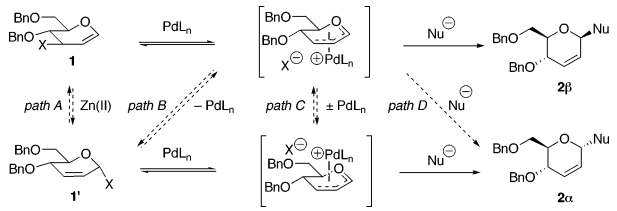
[a] All reactions were carried out in THF (1.0 M) at 25 °C for 48 h. [b] Isolated yield. [c] Anomeric ratio determined by ^{1}H NMR. [d] DTBBP = di(*tert*-butyl)-2-biphenylphosphine. [e] $Pd(PPh_3)_4$ was used as the catalyst. [f] 91% yield and **2*β***:**2α** = 1:7 when 20 mol % of NH_4OAc was added.

afford disaccharides in good yield. The efficiency of the reaction is well illustrated by the fact that torsional deactivation[8] (entries 1−3), the reaction sites of acceptors, or the nature of protecting groups had little effect on the facility of glycosylation. It is also noteworthy that glycal **4** fared well in this process despite the potential complications by its C6 deoxygenation and (L)-configuration (entry 4).[9] Similarly, galactal **5** was found to be a viable substrate for glycosylation (entry 5).[10] As demonstrated in the model study, selective access to the α- or β-linked product from the same pair of reactants was realized by choice of the ligand (entries 6−10).

The utility of the 2,3-unsaturated product was next explored (eqs 3−5).[11] Subjection of **13** to dihydroxylation gave rise to β-alloside **23** as a single diastereomer.[5,12] Starting from **21*β***, a sequence involving a mercury(II)-mediated hydration furnished 2-deoxysugar **24** with complete regio- and stereocontrol.[13] The 2,3,6-trideoxy system **25** was also readily available by diimide hydrogenation of **16**.[14]

While a detailed understanding of the present reaction awaits further studies, a simple mechanistic picture may be advanced, wherein paths A−D exist for the α-anomer formation (Scheme 1).[15]

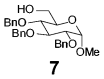
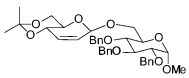
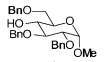
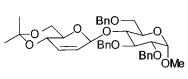
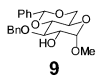
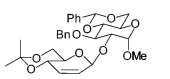
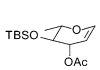
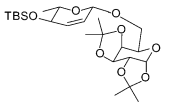
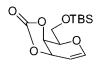
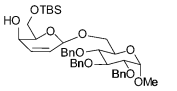
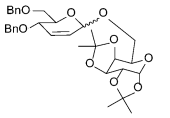
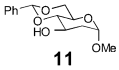
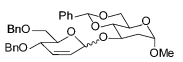
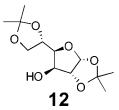
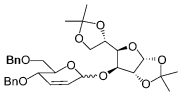
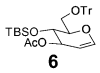
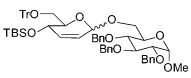
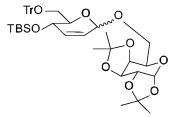
Scheme 1



When $P(OMe)_3$ is used as a ligand, one or more of these paths may become competitive, whereas the common net retention mechanism **1** → **2*β*** is believed to be operative in the case of the DTBBP ligand.[16] Regardless of the stereochemical outcome, the

10.1021/ja039746y CCC: $27.50

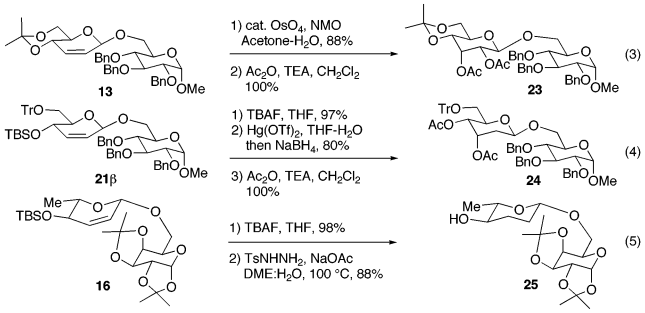
Table 2. Palladium-Catalyzed Synthesis of Disaccharides[a]

1	 **3**	 **7**		**13** (77)[d]
2	**3**	 **8**		**14** (70)[d]
3	**3**	 **9**		**15** (71)[d]
4	 **4**	 **10**		**16** (88)[d]
5[e]	 **5**	**7**		**17** (66)[d]
6	 **1a**	**10**		**18β** (75)[d] **18α** (62)[f]
7	 **1b**	 **11**		**19β** (69)[d] **19α** (62)[g]
8	**1b**	 **12**		**20β** (66)[d] **20α** (58)[h,i]
9	 **6**	**7**		**21β** (77)[d] **21α** (63)[h]
10	**6**	**10**		**22β** (68)[d] **22α** (62)[h]

[a] All reactions were performed with 1.5 equiv of acceptor, 0.8 equiv of Et_2Zn, 10 mol % of $Pd(OAc)_2$, and 15 mol % of DTBBP (entries 1−10) or 30 mol % of $P(OMe)_3$ (entries 6−10) in THF at 25 °C for 48 h. [b] ^1H NMR ratio. [c] Isolated yields. [d] Single isomer (dr > 25:1). [e] The donor was slowly added over 8 h via a syringe pump. [f] $\alpha:\beta = 9:1$. [g] $\alpha:\beta = 12:1$. [h] $\alpha:\beta = 8:1$. [i] 20 mol % of $Pd(OAc)_2$/60 mol % of $P(OMe)_3$.

Zn(II) ion in this reaction appears to play an important dual role of activating both the acceptor for the nucleophilic addition and the leaving group for the ionization.[17]

We have developed a new Pd-catalyzed *O*-glycosylation method that allows for the direct use of readily available glycal derivatives as donors. Notably, the anomeric stereochemistry is effectively controlled by the reagent, independent of the steric and electronic nature of the substrates. Also demonstrated is the utility of the 2,3-unsaturated pyranoside product through stereoselective alkene addition reactions. This combination of the glycosylation and subsequent elaboration provides a novel entry to natural and



unnatural carbohydrates and should find useful applications in carbohydrate chemistry.

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

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(17) (a) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293. (b) In control experiments, both **1** and **1′** failed to undergo the *O*-glycosylation in the absence of a Zn(II) ion. Also see refs 4 and 5.

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