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Palladium(II)-Catalyzed Transfer Vinylation of Protected Monosaccharides

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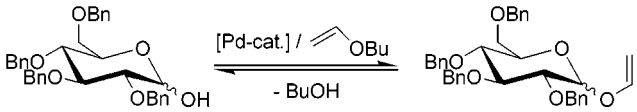
ABSTRACT

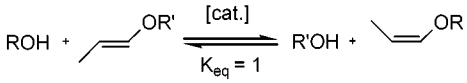


70 %, α/β = 9:1

A method for the catalytic vinylation of protected monosaccharides bearing a single free hydroxyl function has been developed. Reaction of representative primary, secondary, and anomeric sugar hydroxyl functions with butyl vinyl ether as the reactant and solvent and (phen)Pd(OAc)$_2$ (phen = 1,10-phenanthroline ligand) as the catalyst gives the corresponding vinylated sugar products in 36–79% yield. The catalyst requires the presence of traces of oxygen in the reaction mixture to prevent decomposition to Pd(0).

Vinyl glycosides and sugar vinyl ethers are an interesting class of sugar synthons. The glycosides are typically prepared (mostly as isopropenyl glycosides) through Koenigs−Knorr type reactions, either directly or via the isomerization of allyl glycosides obtained by the same route.[1] Marra et al. have introduced the use of the Tebbe reagent ($Cp_2Ti{=}CH_2$), which allows the exchange of the oxygen atom in anomeric as well as nonanomeric acetate protecting groups for the methylene unit, yielding the corresponding isopropenyl glycosides or sugar isopropenyl ethers, respectively.[2] Other routes to vinyl glycosides employ a Hofmann degradation of *N*-2-trimethylammonium-ethyl-*O*-glycosides,[3] selenium reagents,[4] photochemically induced reactions,[5] and TMS-triflate promoted elimination reactions of mixed acetal glycosides.[6] The latter method is also applicable to nonanomeric mixed acetals. Sugar vinyl ethers have also been prepared by a mercury acetate mediated reaction of isobutyl vinyl ether with 1,2:5,6-diisopropylidene-α-D-glucofuranoside[7] or by reaction of 1,2:3,4-diisopropylidene-α-D-galactopyranoside or methyl-α-D-glucopyranoside with acetylene gas or vinyl chloride in a sodium hydroxide melt.[8]

Here we present an alternative route to this class of functionalized sugars that uses a palladium-catalyzed transfer vinylation protocol. Although palladium-catalyzed transfer vinylations between vinyl esters and carboxylic acids are common and well established on a technical scale,[9] the synthetic application of the corresponding exchange between alcohols and vinyl ethers as shown in eq 1 remains underexploited.



(1)

The reaction was first described for simple primary alcohols by McKeon et al.,[10] proceeds stereospecifically with

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(2) Marra, A.; Esnault, J.; Veyrières, A.; Sinaÿ, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354−6360.

(3) Perrine, T. D.; Glaudemans, R. K.; Ness, R. K.; Kyle, J.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 664−669.

(4) Rollin, P.; Verez Bencomo, V.; Sinaÿ, P. *Synthesis* **1984**, 134−135.

(5) Cottier, L.; Remy, G.; Descotes, G. *Synthesis* **1979**, 711−712.

(6) Edathil, J.; Nguyen, J.; Hughes, K.; Boyko, W. J.; Giuliano, R. M. *J. Carbohydr. Chem.* **2001**, *20*, 81−85.

(7) Black, W. A. P.; Dewar, E. T.; Rutherford, D. *J. Chem. Soc.* **1963**, 4433−4439.

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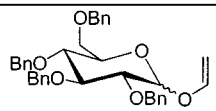
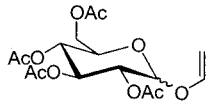
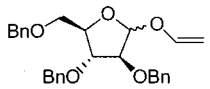
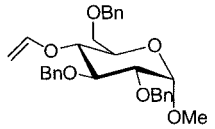
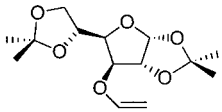
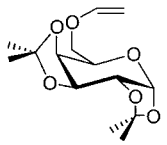
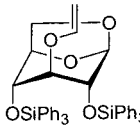
inversion, and for these alcohols has an equilibrium constant of $K_{eq} \approx 1$, i.e., it can be driven to either side by using either the alcohol or vinyl ether in excess, ideally as the solvent. The air- and moisture-stable catalyst precursors employed are of the general composition $Pd(OAc)_2$(L-L), where L-L is a (substituted) 2,2′-bipyridyl (bipy) or 1,10-phenanthroline (phen) ligand. The catalysts can either be added premade or conveniently generated in situ from $Pd(OAc)_2$ and the ligand.

To our knowledge, the Pd(II)-mediated transfer vinylation with vinyl ethers has to date found only one synthetic application. Weintraub and King reported the vinylation of various steroid alcohols in 6−87% yield using $Pd(OAc)_2$(phen) as the catalyst and ethyl vinyl ether/CH_2Cl_2 as the solvent/cosolvent.[11] We have now successfully applied this reaction to a representative set of hydroxyl functions in protected monosaccharides using butyl vinyl ether as the solvent, generating the vinylated sugars in moderate to good yields (Table 1). Among various bipy and phen ligands, 4,7-diphenyl-1,10-phenanthroline gave the best results. The reaction conditions in all cases were Pd catalyst/ligand/sugar/butyl vinyl ether = 0.05:0.067:1:100; air/oxygen saturated solution in a sealed flask for 4−7 days at 75 °C (vide infra for the significance of oxygen presence).[12] The [$Pd(OAc)_2$-(L-L)]/butyl vinyl ether system cleanly vinylates primary and secondary hydroxyl groups as well as pyranose and furanose anomeric positions. The catalyst tolerates the common protecting groups acetal, benzyl, and silyl ether and, in lower yield, acetates.

The lower yield with an acetate-bearing sugar is accompanied by a darkening of the normally bright yellow reaction solutions. A likely explanation is a coordinative inhibition of the active center by the carbonyl oxygens of the acetyl groups and subsequent modification of the catalyst to a palladium complex of undetermined composition and structure. Longer reaction times (12 vs 7 days) gave similar results, suggesting that the yields are intrinsically limited by the equilibrium ratio of sugar to vinyl ether. All attempts to use vinyl sources other than a simple vinyl ether R−O−CH=CH_2 (R = ethyl, *n*-butyl) failed. The sterically hindered *tert*-butyl vinyl ether gave only very low yields. 2-Methoxy propene as the source of the vinyl functionality, which would lead to the corresponding isopropenyl glycosides or isopropenyl sugar ethers, did not give any transfer vinylation. Switching to the more activated 1-methoxy-styrene or 2-methoxy-acrylonitrile was equally unsuccessful. We therefore hypothesize that the unhindered steric accessibility of the oxygen-bearing vinyl carbon is critical for the reaction to proceed.

Combining results from several earlier reports,[9,10,13] a plausible mechanism for the catalytic transfer vinylation is the oxypalladation−deoxypalladation pathway shown in the top half of Scheme 1. An intra- as well as an intermolecular attack of the exchanging alcohol is conceivable, both leading to the same palladium alkyl complex as the key intermediate.

Table 1. Vinylated Monosaccharides and Their Isolated Yields

Entry	Vinyl Sugar[a]	Isolated Yields and anomeric ratio[b] (where applicable).
1		70 %; α : β = 9 :1
2[c]		36 %; α : β = 6.5 : 1
3		60 %; α : β = 4.4 : 1
4		69 %
5[d]		72 %
6[e]		79 %
7		66 %[f]

[a] See Supporting Information for full characterization data. Satisfactory elemental analyses were obtained for all new compounds. [b] Determined by ^{1}H NMR. [c] References 1d and 3. [d] Reference 7. [e] Reference 8a. [f] The synthesis of the corresponding monohydroxyl sugar will be reported elsewhere.

(8) (a) Whistler, R. L.; Panzer, H. P.; Goatley, J. L. *J. Org. Chem.* **1962**, *27*, 2961−2962. (b) Deutschman, A. J., Jr.; Kircher, H. W. *J. Am. Chem. Soc.* **1961**, *83*, 4070−4073.

(9) (a) Sabel, A.; Smidt, J.; Jira, R.; Prigge, H. *Chem. Ber.* **1969**, *102*, 2939−2950. (b) Henry, P. M. *Acc. Chem. Res.* **1973**, *6*, 16−24. (c) Waller, F. J. U.S. Patent 5214172, 1991.

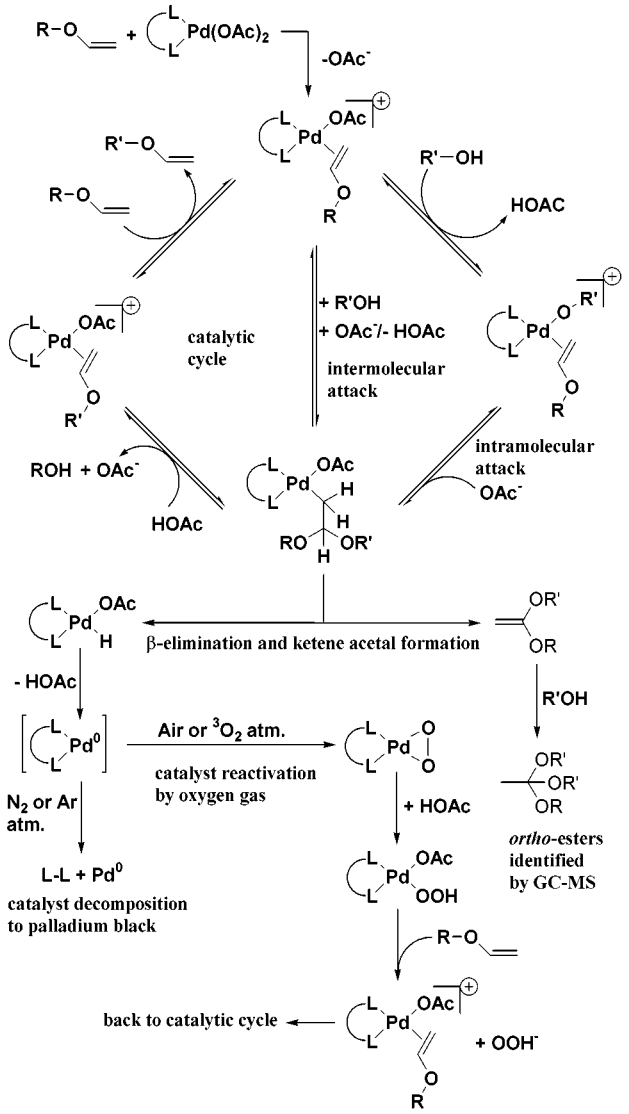
(10) (a) McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 227−232. (b) McKeon, J. E.; Fitton, P. *Tetrahedron* **1972**, 233−238.

(11) Weintraub, P. M.; King, C. H. R. *J. Org. Chem.* **1997**, *62*, 1560−1562.

(12) **Typical Procedure for the Vinylation of a Protected Monosaccharide**. 4,7-Diphenyl-1,10-phenanthroline (54.3 mg, 0.163 mmol, 0.067 equiv) and butyl vinyl ether (32.0 mL, 247.3 mmol, 101.9 equiv) were combined in an oven-dried Schlenk flask. Palladium(II) acetate (27.5 mg, 0.123 mmol, 0.050 equiv) was then added, and the reaction mixture was stirred for 5 min at ambient temperature. After addition of 1.0 equiv of the protected monosaccharide the flask was sealed and left stirring for 4−7 days at 75 °C. The resulting clear yellow reaction mixture was monitored using TLC (SiO_2 plates, 20% ethyl acetate/hexanes, 5% H_2SO_4 stain). The reaction was stopped by cooling to ambient temperature and passing it through a column of activated charcoal (3.0 cm diameter, 15 cm activated charcoal) with ethyl acetate or 50% ethyl acetate/toluene to remove the catalyst. The solution was then concentrated under reduced pressure, and the crude product was purified by flash chromatography (4.5 cm diameter, 25.0 cm silica gel, gradient elution of 200 mL of hexanes, then ethyl acetate/hexanes in various proportions). All operations were carried out in air. Butyl vinyl ether was purified by vacuum transfer from KOH. See Supporting Information for further details and spectroscopic data.

(13) Dumlao, C. M.; Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 1400−1405.

Scheme 1. Proposed Catalytic Cycle and Catalyst Decomposition and Reactivation Pathways



It can then either revert to the starting alcohol and vinyl ether or, through rotation about the carbon−carbon bond followed by deoxypalladation, yield the desired exchange product.

The catalyst system is highly sensitive to deactivation by β-elimination from the alkyl complex to give a palladium hydride complex (L-L)Pd(H)(OAc) and subsequent decomposition by reductive elimination to Pd(0). Serendipitously, we found that this process is prevented if the reaction is carried out in air or, better, with dry oxygen saturation of the reaction solution. *Initial reactions conducted under either nitrogen or argon atmosphere in order to exclude moisture showed rapid formation of palladium black.* In the bottom half of Scheme 1 we propose a catalyst reactivation pathway that accounts for this effect and in which the transient (L-L)Pd(0) complex formed by the reductive elimination of acetic acid is intercepted by $^3O_2$ to form a peroxo palladium complex (η^2-O_2)Pd(L-L). This type of complex has very recently been isolated and structurally characterized.[14] Re-addition of acetic acid then gives the hydroperoxide complex (L-L)Pd(OOH)(OAc). Alternatively the hydroperoxide complex could be formed by direct insertion of $^3O_2$ into the palladium-hydride bond as proposed by Hosokawa and Murahashi.[15] The hydroperoxide ion is a good leaving group and feeds the catalyst back into the cycle. The formation of ketene acetals $H_2C{=}C(OR)(OR')$ is a necessary consequence of this β-elimination pathway, but they are too reactive to be detected directly. However, the GC−MS traces of model reactions between butanol, ethanol, or cyclohexanol, respectively, and butyl vinyl ether show substantial peaks whose spectra match the expected fragmentation patterns of the corresponding *ortho*-esters $H_3CC(OBu)_n(OR)_m$ ($n = 1-3$; $m = 2-3$; R = butyl, ethyl, cyclohexyl). Under the overall reducing reaction conditions (butyl vinyl ether sovent with traces of oxygen) they can only result from the addition of the alcohols to the ketene acetals. The fact that reducing sugars can be vinylated without the formation of lactones and Pd(0) further supports the proposed mechanism, in which—via the palladium alkyl complex—the vinyl ether but not the alcohol can act as a reducing agent. In summary, we have developed a new and simple method for the synthesis of vinylated sugars. Ligand and counterion modification studies aimed at improving the reaction rate and expanding the scope of the reaction are presently under way.

Acknowledgment. The authors thank NSERC, the Canadian Foundation for Innovation (CFI), the Ontario Innovation Trust Fund (OIT), Varian Canada Inc., and the University of Guelph for funding.

Supporting Information Available: $^1H/^{13}C$ NMR data for all vinyl sugars and extensive GC−MS data from the model reactions in support of the proposed mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Stahl, S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188−7189.
(15) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49−54.