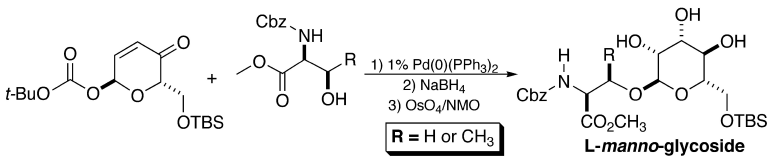
Communication

A Palladium-Catalyzed Glycosylation Reaction: The de Novo Synthesis of Natural and Unnatural Glycosides

Ravula Satheesh Babu, and George A. O'Doherty

J. Am. Chem. Soc., **2003**, 125 (41), 12406-12407• DOI: 10.1021/ja037097k • Publication Date (Web): 23 September 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/23/2003

A Palladium-Catalyzed Glycosylation Reaction: The de Novo Synthesis of Natural and Unnatural Glycosides

Ravula Satheesh Babu and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

Received July 6, 2003; E-mail: george.odoherty@mail.wvu.edu

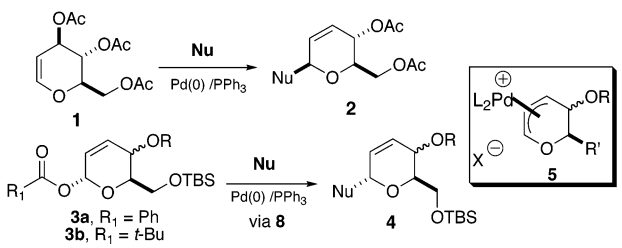
In an effort to improve upon the seminal work of Sharpless and Masamune[1] in their use of asymmetric catalysis for the enantioselective synthesis of the hexoses, we developed an alternative de novo approach to various hexoses.[2] Our approach relied upon the use of the Achmatowicz reaction in conjunction with the catalytic asymmetric synthesis of furan alcohols.[2,3] To further improve the scope of our approach, we desired to develop a route that would use diastereoselective catalysis to control coupling at the anomeric center and in turn allow for the de novo preparation of oligosaccharides.

For this de novo synthesis of natural and unnatural oligosaccharides, we were interested in investigating the use of palladium-catalyzed allylation reactions.[4] In contrast to typical glycosylation reactions, Pd π-allyl reactions customarily proceed with excellent stereocontrol. In addition to being a catalytic reaction, the reaction has the added advantage that it can be accomplished under quite mild conditions without the stoichiometric use of strong Lewis acid promoters.

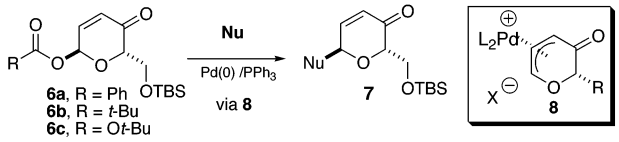
Herein we describe our discovery of a palladium(0)-catalyzed reaction that selectively converts 2-substituted 6-*tert*-butoxycarboxy-2H-pyran-3(6H)-ones into 2-substituted 6-alkoxy-2H-pyran-3(6H)-ones. Recently, Feringa reported a similar palladium-catalyzed transformation.[5,6] Finally we demonstrate that the 2-alkoxy-substituted pyranone products can be transformed into typical pyranohexoses by a simple reduction/oxidation sequence.

We initially tried to generate a diastereomeric Pd π-allyl intermediate of **5** from the triacetoxy glucal **1** but were unsuccessful at ionizing the C-3 equatorial acetate under typical Pd π-allyl-forming conditions (Scheme 1).[7] We next investigated pyrans **3a** and **3b** in the reaction hopeful that an axial leaving group at the C-1 position would be more conducive for Pd π-allyl formation. We had previously prepared pyrans **3a** and **3b** in various stereoisomeric forms via asymmetric catalysis and thus decided to use them for our investigation.[8,9] Fortuitously, moving the leaving group to C-1 proved to be the solution for generating both diastereomeric Pd π-allyl intermediates from either C-1 axial or equatorial carboxylates. Evidence for this ionization can be seen when the Pd intermediates are reacted with the traditional Pd π-allyl nucleophiles (i.e. various anions of malonates and phenols) products are formed with net retention of stereochemistry.[10] Unfortunately, in our hands the same Pd π-allyl intermediates did not react with the simplest of alcohols. Thus, we decided to try to generate the

Scheme 1



Scheme 2



presumably more electrophilic Pd π-allyl intermediate **8** from the corresponding pyranones **6a**−**c** (Scheme 2).[8,11]

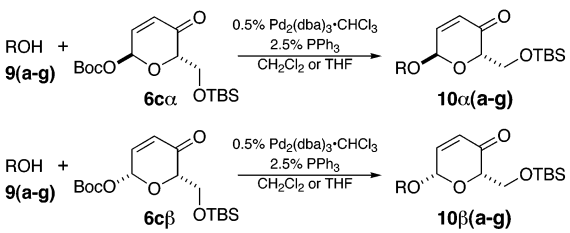
To our delight, success was achieved for alcohol nucleophiles when using the more oxidized pyrans **6a** and **6b** with benzoate[12] or pivaloate leaving groups.[5] Our final reaction optimization involved changing the C-1 leaving group to a *tert*-butyl carbonate, which in general lead to significantly faster and cleaner reactions (**6c**, Scheme 3).[13] For instance, when the pyranone **6c**α was treated with a slight excess of alcohol (1.2 equiv) in the presence of catalytic amounts of $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3 (~1:1 ratio), pyranones with an α-alkoxy group **10**α were formed in excellent yields (Table 1). Similarly, the β-pyranone **6c**β reacted under identical conditions to afford pyranones with a β-alkoxy group **10**β.[14]

The reaction is very general in terms of alcohol steric hindrance. For instance, both methanol and *t*-BuOH couple to form either of the desired α- or β-C-1 acetal in excellent yields (Table 1). There seems to be little difference between the α- or β-substrates (**6c**α vs **6c**β) in terms of reaction time or yield.[15] The reaction occurs rapidly (<30 min) at temperatures from 0 °C to room temperature and in solvents, such as Et_2O, THF, and CH_2Cl_2. The reaction can be catalyzed with various sources of palladium(0); however, $Pd_2(dba)_3{\cdot}CHCl_3$ is our preferred Pd(0) precursor. A palladium/phosphine ratio of 1:2.5 appears to be ideal with the effective catalyst ($Pd(PPh_3)_2$) loading in the range of 0.5−5 mol %, which consistently yields products in the range of 70−89%.[16]

The coupling reaction works equally well for various chiral alcohols, such as: menthol **9e** (Table 1), the three amino acids **9h**−**j** (Table 2), and the three D-sugars **9k**−**m** (Table 2). In all of these cases no diastereomers were observed when optically pure enones were used.[17]

A possible explanation for the improved reactivity of the pyranones with *tert*-butoxycarboxy leaving groups is that the reaction does not generate a carboxylic acid as the reaction proceeds; instead, *t*-BuOH and CO_2 are generated.[18] Evidence for this decarboxylation reaction can be seen when more hindered alcohols

Scheme 3



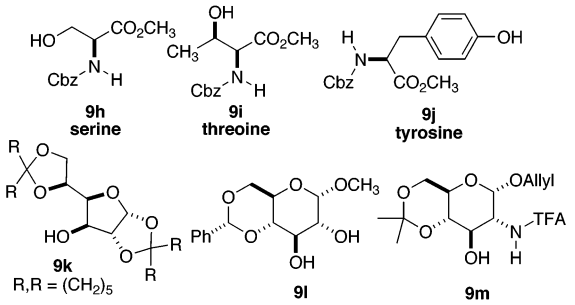
10.1021/ja037097k CCC: $25.00

Table 1

entry	alcohol **9a–g**	acetal **10a–g**	yield of **10**α (%)	yield of **10**β (%)	yield[c] of **10f**β (%)
1[b]	CH_3OH	**10a**	87	85	0
2	BnOH	**10b**	89	85	0
3	PhOH	**10c**	85	76	2
4	CyOH	**10d**	88	80	2
5	menthol	**10e**	82	72	12
6	*t*-BuOH	**10f**	78	75	NA
7[d]	adamantol	**10g**	54	52	34

[a] Typical reaction conditions were performed with a 1:1.2 ratio of **6c** to **9** at room temperature and in a 0.5 M CH_2Cl_2 solution. [b] This reaction was run in a 0.5 M THF solution. [c] The reactions with **6c**β were more prone to *t*-BuOH glycosylation. [d] The byproducts **10f**α is also formed (34%) when **6c**α is reacted with adamantol.

Table 2



	alcohol **9h–n**	glycoside **10h–n**	yield of **10**α (%)	yield of **10**β (%)	yield of **10f**β (%)
1	**9h**	**10h**	87	85	1
2	**9i**	**10i**	90	84	2
3	**9j**	**10j**	90	86	0
4	**9k**	**10k**	82	79	0
5[b]	**9l**	**10l**	82	79	0
6	**9m**	**10m**	85	83	0

[a] Typical reaction conditions were performed with a 2:1 ratio of **6c** to **9** at room temperature and in a 0.5 M CH_2Cl_2 solution. [b] Products **10l** were isolated as a 2:1 (C2:C3) mixture of monoglycosides.

are used as nucelophiles. When the tertiary alcohol adamantol was used, a significant amount of the *tert*-butyl acetal byproduct **10f** was formed (34% in both the α and β case). This result is consistent with the formation of the less reactive *tert*-butyl alcohol as the reaction proceeds. This problem could easily be solved in terms of glycosylation yield by adding additional enone **6c**α or **6c**β (see Table 2), or by switching to the pyranones with the less reactive[13] pivaloate leaving group (**6b**α or **6b**β).[19]

The glycoside products can easily be converted into either L- or D-hexopyranoses by a two-step reduction/oxidation sequence. This was demonstrated for six of the Pd catalyzed glycosylation products **10**α(**a**, **b**, **g**, **h**, **i**, **k**) by exposure to $NaBH_4$ at −78 °C in CH_2Cl_2 and CH_3OH (Scheme 4). The $NaBH_4$ reduction produced equatorial alcohols **11**α with complete stereocontrol and high yields (78−96%, Table 3). Similarly, the resulting allylic alcohols **11**α could be diastereoselectively oxidized to give the *manno*-triols **12**α in excellent yields (72−89%) with complete stereocontrol.

Scheme 4

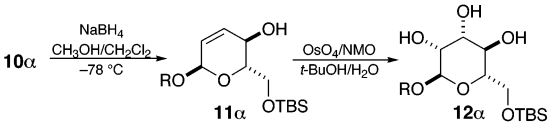


Table 3

	enone **6**α	yield of **11**α (%)	yield of **12**α (%)		enone **6**α	yield of **11**α (%)	yield of **12**α (%)
1	**a**	84	72	4	**h**	87	78
2	**b**	90	84	5	**i**	91	73
3	**g**	78	83	6	**k**	96	89

In summary, we have developed a practical palladium catalyzed glycosylation reaction. This three-step protocol allows for the incorporation of either D- or L-*manno*-pyranose on to an assortment of alcohols with excellent stereocontrol. We believe this route is amenable to multigram-scale preparation of various natural and unnatural glycosides and are currently investigating this approach for the preparation of unnatural oligosaccharides. We feel this new efficient route to unnatural glycosides will be very beneficial for the synthesis of natural and unnatural oligosaccharides.

Acknowledgment. We thank the Arnold and Mabel Beckman Foundation and the NIH (1R01 GM63150-01A1) for supporting our research and the NSF-EPSCoR (0314742) for a 600 NMR at WVU.

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.

References

(1) (a) Sharpless, K. B.; Masamune, S. *Science* **1983**, *220*, 949. (b) For a good review: Zamoiski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.

(2) (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982−2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17−36.

(3) An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2H-pyran-3(6H)-ones. (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176. (b) Grapsas, I., K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823−826. For its use in carbohydrate synthesis see: ref 2 and (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (d) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033−4036.

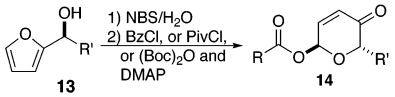
(4) Recently, both the poor reactivity in Pd-catalyzed allylation reaction of alcohols as well as a nice solution to this problem was reported, see: Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369.

(5) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714.

(6) In this communication, we report the Pd-catalyzed glycosylation reaction for 6-substituted pyranones and for the first time demonstrate the reaction's high selectivity for both α- and β-glycosylation.

(7) RajanBabu had previously noted the resistance of **1** toward Pd π-allyl formation, see: (a) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642.

(8) Pyranones **3** and **6** can easily be prepared from furan alcohols **13** by an Achmatowicz reaction followed by hemiacetal protection. The more reactive axial anomeric alcohols can be acylated selectively (>20:1) at −78 °C. Alternatively at room temperature, a 1:1 mixture of anomers can be produced.



(9) Compounds similar to **3** with a C-1 acetate can also be prepared from glycols, see: Collins, P.; Ferrier, R. *Monosaccharides. Their Chemistry and Their Roles in Natural Products*; Wiley: U.K., 1995.

(10) Stabilized anions such as these are the optimum coupling partners for Pd-π-allyls, see: Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(11) It should be noted that we have prepared both antipodes of **6a**−**c** and are only presenting the enantiomer that leads to L-sugars in this report.

(12) Feringa has shown one example of coupling with the 6-substituted pyranone **6a** using a $Pd(OAc)_2/POPh_3$ catalyst system.

(13) Typical reaction times for **6a**/**6b** were 8−10 h versus 0.5 h for **6c** under identical conditions.

(14) The reaction is both highly steroselective and stereospecific, that is to say, the pyranone with an α-*tert*-butoxycarboxy group reacts to give only pyranones with α-alkoxy groups and pyranones with a β-*tert*-butoxycarboxy groups react to give only pyranones with β-alkoxy groups, which is consistant with a π-allyl palladium intermediate.

(15) A significant difference between the α- and β-glycosylation reactions is that the reactions with β-pyranone **6c**β produce a small amount of *tert*-butyl acetal byproduct **10f**β (Table 1).

(16) Higher yields are observed when greater than 1.2 equiv of alcohol is used. While the yield of adamantol glycoside appears to be less than 70%, this is due to the competitive formation of the *tert*-butyl glycoside **10f**. Thus, the total yield of glycosylated products is in excess of 80%.

(17) In contrast, Feringa observed some loss of stereospecificity (2−10%) with unsubstituted pyranones.

(18) Alternatively the ionization step could be rate limiting. It is known that carbonates are better leaving groups in π-allyl Pd reactions, see ref 10.

(19) Thus, exposing pyranone **6b**α to 1.2 equiv of adamantol and 5% catalyst proceed to give product **10**gα in a 76% yield.

JA037097K