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Palladium Chloride Mediated Rearrangement of 6-Deoxyhex-5-enopyranosides into Cyclohexanones

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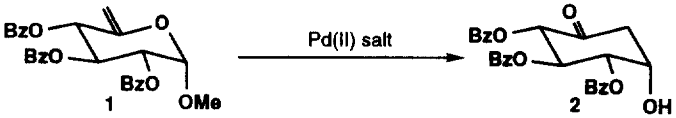
Abstract: $PdCl_2$ was found to mediate the Ferrier rearrangement of broad range of substrates catalytically in neutral conditions. In this reaction, the stereoselectivity of newly formed chiral center was controlled by the hydroxyl protective groups on the starting sugar moiety and was rationally explained by the consideration of chair like conformations.

Highly functionalized cyclohexanes are useful intermediates for the synthesis of natural products and their derivatives having 6-membered ring systems. Among preparations of chiral substituted cyclohexanes, conversion of 6-deoxyhex-5-enopyranosides into cyclohexanones has become one of the most efficient and intriguing process since the discovery by Ferrier,[1,2] and this method has been applied to syntheses of cyclitol derivatives and polyhydroxylated natural products.[2,3] In the Ferrier rearrangement, where the use of stoichiometric amount of $HgCl_2$ was originally advocated, catalytic amount of $HgSO_4$ or $Hg(OCOCF_3)_2$ has been developed to use as effective promoters in this decade.[4] Recently, Adam reported a similar rearrangement of amino-6-deoxyhex-5-enopyranoside derivative mediated by $PdCl_2$ or $Pd(OAc)_2$ in the presence of aqueous sulfuric acid.[5] Although this Pd(II) mediated Ferrier rearrangement is an attractive alternative, only one successful application to a different type of substrate has been appeared,[6] and the use of the Pd(II) salts for a broad range of substrates has not yet been explored. During our synthetic study on biologically active compounds containing cyclohexane rings, we have investigated a systematic study on a Pd(II) mediated Ferrier rearrangement. Herein we wish to disclose the applicability of this reaction for a variety of 6-deoxyhex-5-enopyranosides and also report on stereochemical aspects of this ring-transformation reaction.



We first surveyed effective catalysts for the conversion of a benzoyl protected *gluco*-hexenopyranoside[7] **1**[8] into a cyclohexanone derivative **2**. As shown in Table 1, $PdCl_2$ was found to be a suitable catalyst even in the absence of sulfuric acid. The order of catalytic activity found in this study was $PdCl_2 > PdBr_2 \gg Pd(OAc)_2$, $PdSO_4$ (run 1 to 4). It is noteworthy that our procedure provides less acidic reaction conditions (pH = *ca.* 5) than

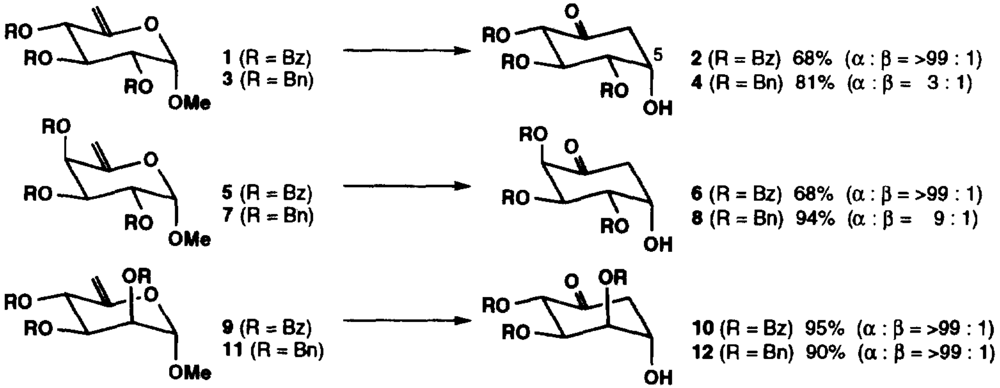
Table 1. The Ferrier Rearrangement Catalyzed by Various Pd(II) Salt.[a]

run	catalyst	(equiv.)	solvent	time (hr)	yield (%)
1	$PdCl_2$	(0.2)	dioxane-H_2O (2:1)	3	65 (56)[b]
2	$PdBr_2$	(0.2)	dioxane-H_2O (2:1)	4	65
3	$Pd(OAc)_2$	(0.2)	dioxane-H_2O (2:1)	3	6
4	$PdSO_4$	(0.2)	dioxane-H_2O (2:1)	3	9
5	$PdCl_2$	(0.05)	dioxane-H_2O (2:1)	3	68
6	$PdCl_2$	(0.05)	acetone-H_2O (2:1)	3	37

[a] The reaction was carried out at 60 °C. [b] Aqueous H_2SO_4 (5mM) was used in place of H_2O.

the mildest conditions reported previously, in which 0.05 equiv. of $Hg(OCOCF_3)_2$ has been employed as a calalyst without sulfuric acid.[4b] The reaction catalyzed by reduced amount (0.05 equiv.) of $PdCl_2$ smoothly proceeded in aqueous dioxane (run 6), but a low yield with poor reproducibility was obtained in aqueous acetone (run 7). Thus, aqueous dioxane is a solvent of choice in this reaction.

The optimized conditions mentioned above were applied to benzoyl and benzyl protected *gluco-*, *galacto-* and *manno*-hexenopyranosides,[7] and the results are summarized with their stereoselectivity of newly generated chiral centers (C-5) in Scheme 1. The benzoyl protected hexenopyranosides[8] (**1**, **5** and **9**) afforded cyclohexanones (**2**, **6** and **10**) in high yield with exclusive α-selectivities at C-5. While the benzyl protected *galacto-* and *manno*-hexenopyranosides[8] (**7** and **11**) afforded α-anomer predominantly (α : β = 9 : 1 and >99 : 1) in *ca.* 90% yield, the selectivity dropped to 3 : 1 in the case of benzyl protected *gluco*-hexenopyranoside (**3**).[8]



Scheme 1

In the Hg(II) promoted Ferrier reaction, the similar α-stereoselectivities have appeared in literature and have been rationally explained by considering chair like transition state A[9] (Figure 1) derived from hydroxymerculation of enopyranoside double bond and successive acetal hydrolysis.[10] Machado has demonstrated the relationship between the conformations of starting sugars and the stereoselectivities, and have pointed out the importance of the chair like transition states A which keep the starting conformations around C-2 to 4 (sugar numbering; Figure 1).[9] Although the mechanism by which the palladium mediated conversion occurs is not known, the α-selectivities observed here were well explained by the similar conformational aspect except **4**.[11] Since it was difficult to figure out different conformational properties between **1** and **3** by simple inspection of molecular models (all substituents are located in equatorial positions), we conducted conformational analysis based on this Machado's hypothesis, that expresses the importance of starting conformation, by employing

MacroModel MM2* calculations.[12] The chair like keto aldehyde structure **A** (R = Bz, in the absence of metal coordination in Figure 1), which was used as the starting conformation of the reaction, was calculated to locate at +5.1 kcal/mol above the global minimum and was *ca.* 2 kcal/mol lower than the boat like one **B** (R = Bz). Similarly, in the other substrates (**5**, **7**, **9** and **11** except **3**), the conformations analogous to **A** were found to be more stable than the other possible conformations (analogous to boat like **B** and inverted chair like **C** in Figure 1). These calculations are compatible with the stereoselectivity obtained in this study. On the other hand, the chair like keto aldehyde **A** (R = Bn) derived from **3** lied at +6.3 kcal/mol and boat like one **B** (R = Bn) at +5.7 kcal/mol above the global minimum (polytube model in Figure 1). This suggests that the low stereoselectivity obtained in **4** ascribes to the destabilization of keto aldehyde structure **A** caused by some interactions of three benzyloxy groups attached to C-2, 3 and 4 which can not be evaluated by simple inspection of molecular model.

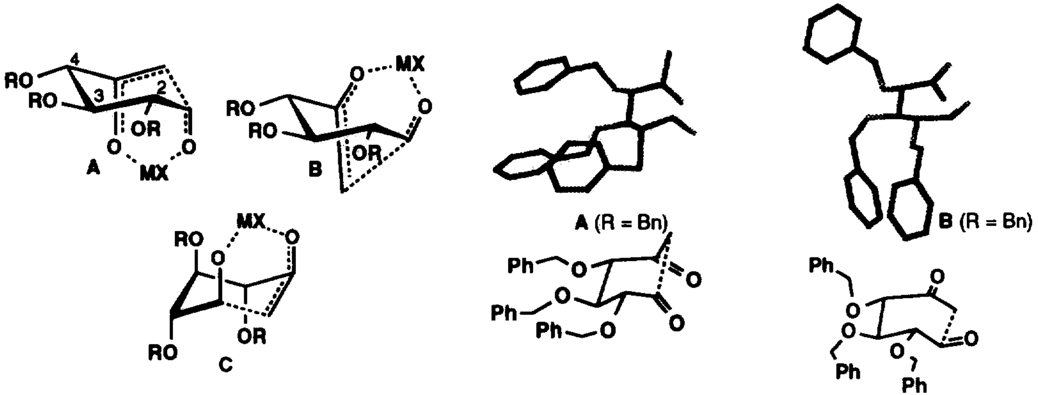
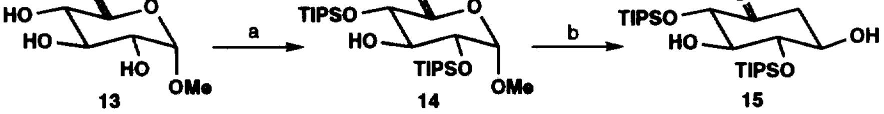


Figure 1

Next, we applied this reaction to a hexenopyranoside protected by alkyl silyl groups. Silyl ethers are useful protective groups; they are also attractive for us since their interesting nature in conformation has been recognized recently.[13] We focused our attention on TBDMS or TIPS (triisopropylsilyl) group, because the kinetic studies suggest that the bulky alkyl groups attached to silicon are more sterically interfering when the silyloxy group is equatorial than when it is axial and thus the inverted chair like **C** may play an important role in the conformational space.[13] Unfortunately, fully protected hexenopyranoside (tris(*O*)TBDMS- or tris(*O*)TIPS-*gluco*-hexenopyranoside) could not be prepared mainly due to steric factors. After experimentation of the preparation of the substrate having the conformational properties mentioned above, regioselective 2,4-bis(*O*)TIPS-*gluco*-hexenopyranoside formation was achieved by using TIPSOTf (Scheme 2). The $PdCl_2$ mediated Ferrier rearrangement of **14** thus obtained took place smoothly to afford cyclohexanone **15** in 75% yield with opposite β-selectivity at C-5 (α : β = 1 : 6), which is consistent with the similar conformational analysis showing that the inverted chair like **C** is more stable by 3.2 kcal/mol than **A** (Figure 1). This result reveals that we are able to control the stereoselectivity by employing silyloxy ethers that effect the conformational change as expected.



(a) TIPSOTf, lutidine, CH_2Cl_2, r.t. 12 h, 73%, (b) $PdCl_2$(0.05 equiv.), dioxane-H_2O (2 ; 1), 60 °C 3 h, 75%.

Scheme 2

In summary, the $PdCl_2$ mediated Ferrier rearrangements presented herein produce the chiral substituted cyclohexanones, which are useful intermediates for biologically active compounds, in mild reaction conditions. Moreover, the concept that the stereoselectivity can be controlled by arranging appropriate substituents on the substrates provides a novel aspect on stereoselectivity of this type of reactions.

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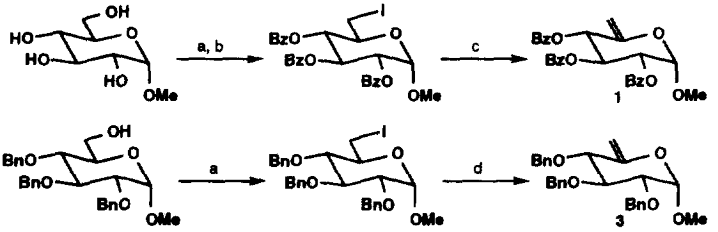
7. For the convenience, the term "*gluco*-, *galacto*- and *manno*-hexenopyranoside" express 6-deoxyhex-5-enopyranosides having the same C-2 to 4 configurations as glucose, galactose and mannose respectively in this paper.
8. The substrates were prepared by conventional methods from glucose, galactose and mannose. The synthetic scheme of *gluco*-hexenopyranosides (**1** and **3**) is shown below as a representative of their preparations.



(a) PPh_3, imidazole, I_2, toluene. (b) BzCl, pyridine. (c) AgF, pyridine. (d) ${}^tBuOK$, DMSO.

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