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Notes

Palladium-Catalyzed Oxidations: Inhibition of a Pd−H Elimination by Coordination of a Remote Carbon−Carbon Double Bond

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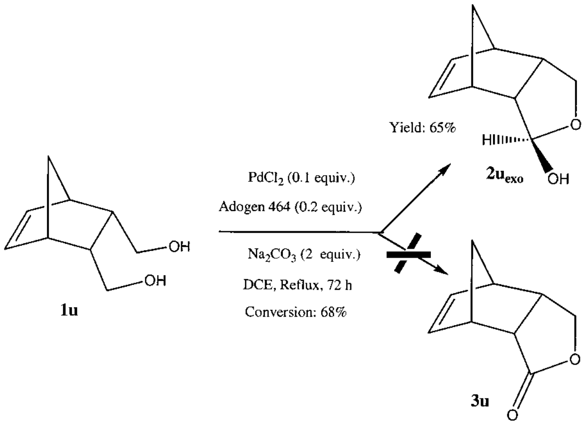
Summary: Under oxidative conditions that use an anionic palladium salt as catalyst, cis-endo-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene affords the corresponding exo-lactol, while cis-endo-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane provides the expected lactone. Mechanistic considerations explain how the presence of the C=C bond blocks the oxidation at the lactol in the first case.

Introduction

In the course of our studies devoted to metal-catalyzed oxidations,[1] we have described the oxidation of alcohols using 1,2-dichloroethane (DCE), sodium carbonate, and catalytic amounts of both palladium dichloride and Adogen 464.[2,3] The quaternary ammonium salt forms with the insoluble palladium dichloride an anionic palladium salt, $[PdCl_4]^{2-}$, which dissolves in DCE and is able to oxidize alcohols.[4] The catalytic cycle is completed by insertion of the palladium species into a C−Cl bond of DCE followed by an elimination reaction which leads to ethylene and to the regeneration of the active catalyst.[3] This procedure has thus been used for the oxidative cyclization of various 1,4- and 1,5-diols to give the corresponding lactones.[5] However, we were surprised to observe that the oxidation of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**1u**) afforded lactol **2u$_{exo}$** instead of the expected lactone **3u** (eq 1). Furthermore, the treatment of **2u$_{exo}$** under the same conditions did not give **3u** but left the substrate almost unchanged,[5] although the conversion of lactols to lactones is usually a facile reaction with most oxidizing agents;[6] indeed, we,[7] as others,[6b,c] have effectively obtained **3u** from **2u$_{exo}$** using pyridinium dichromate in methylene chloride. We have now studied the reactivity of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**1s**). The main aim of the present note is to specify the mechanisms of these reactions in comparing the behavior of **1u** with **1s**, so that they explain our observations.



(1)

Results and Discussion

In sharp contrast to the behavior of **1u**, our Pd-procedure oxidizes the saturated diol **1s** into lactone **3s** with a fair yield (eq 2). Since **1s** and **1u** differ solely by the nature of the C_5-C_6 bond, the presence of the C−C double bond in **1u** should be the main reason for the production of lactol **2u$_{exo}$** and its lack of reactivity under our experimental conditions. Let us consider the possible intermediates of these reactions (Scheme 1).

The first catalytic cycle which mediates the oxidation of one hydroxyl into the corresponding aldehyde corresponds to the one already described.[3] The hydroxyaldehyde **4** thus obtained should be in equilibrium with

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(1) For reviews, see: (a) Muzart, J. *Bull. Soc. Chim. Fr.* **1986**, 65. (b) Muzart, J. *Chem. Rev.* **1992**, *92*, 113. (c) Muzart, J. *Synthesis* **1993**, 11. (d) Muzart, J. *Synthesis* **1995**, 1325.

(2) Adogen 464 is a registered trademark of Ashland Chemical Co. for methyltrialkyl(C_8-C_{10})ammonium chloride.

(3) Aït-Mohand, S.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 2473.

(4) Bouquillon, S.; du Moulinet d'Hardemare, A.; Averbuch-Pouchot, M.-Th.; Hénin, F.; Muzart, J. *Polyhedron* **1999**, *18*, 3511.

(5) Aït-Mohand, S.; Muzart, J. *J. Mol. Catal.* **1998**, *129*, 135.

(6) (a) Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521. (b) Taniguchi, T.; Goto, Y.; Ogasawara, K. *Synlett* **1997**, 707. (c) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 433. (d) Lili, D.; Caperelli, C. A. *Synthesis* **1991**, 933. (e) Tiedemann, R.; Narjes, F.; Schaumann, E. *Synlett* **1994**, 594.

(7) Aït-Mohand, S. Thesis, University of Reims Champagne−Ardenne, 1997.

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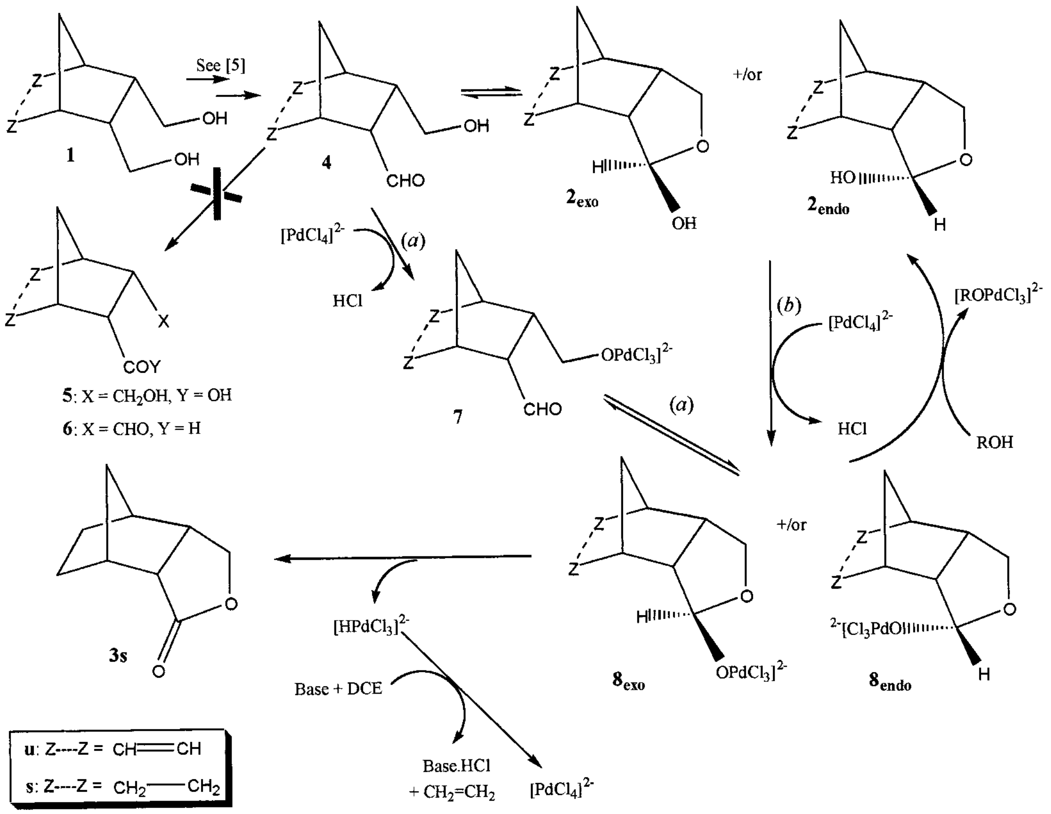
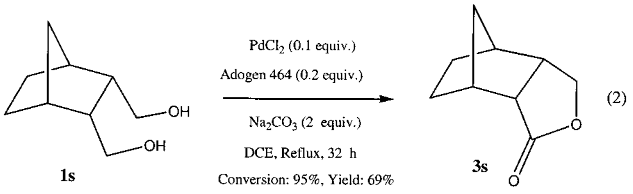
Scheme 1

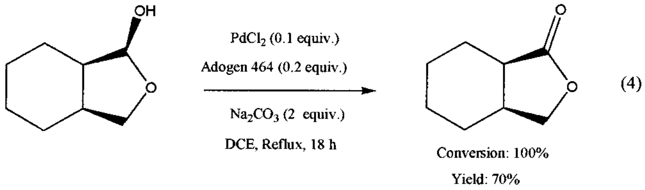




lactols 2_{exo} and 2_{endo} [6b] through intramolecular hemiacetalization.[8] A reaction pathway involving the oxidation of **4** into either the corresponding hydroxyacid **5** or the dialdehyde[9] **6** can be eliminated since the transformation of either **5** or **6** into the lactone would not involve a lactol as intermediate,[10,11] wheras $\mathbf{2u}_{exo}$ instead of **3u** was obtained under our experimental conditions. Furthermore, the low efficiency of our method for the oxidation of simple aldehydes (eq 3)[12] would not be in favor of the formation of **5** or the corresponding hydroxyester as intermediate. In contrast, the Pd-procedure led efficiently to hexahydroisobenzofuran-1-one from the corresponding lactol (eq 4). Consequently, we have to consider the metalation of hydroxyaldehyde **4** (path *a*) and the corresponding lactols 2_{exo} and 2_{endo} (path *b*). The metalation of **4**, followed by intramolecular insertion of the alkoxypalladium moiety into the aldehydic group,[13] provides $8_{exo/endo}$. Under the experimental conditions, $2_{exo/endo}$ as well as **7** could be in equilibrium with $8_{exo/endo}$, the back-reaction of $8_{exo/endo}$ toward $2_{exo/endo}$ being due to an alkoxide exchange with a hydroxylated reactant, **1** for example. From $\mathbf{8s}_{exo/endo}$, β-hydride elimination of $[HPdCl_3]^{2-}$ provides **3s**.

$$\mathrm{RCHO} \xrightarrow[\text{Na}_2\text{CO}_3\text{ (2 equiv.), DCE, Reflux, 15-19 h}]{\text{PdCl}_2\text{ (0.1 equiv.), Adogen 464 (0.2 equiv.)}} \mathrm{RCO_2(CH_2)_2Cl} \qquad (3)$$

R: $CH_3(CH_2)_5$, 19 h, Conversion: 26%, Yield: 21%
R: Ph, 15 h, Conversion: 21%, Yield: 13%



It remains to be explained why the transformation of $\mathbf{8u}_{exo/endo}$ to **3u** is hampered under our Pd-conditions. An explanation for the preclusion of the formation of **3u**, even from $\mathbf{2u}_{exo}$, is the possible exchange of ancillary ligands from $\mathbf{8u}_{exo}$ and $\mathbf{8u}_{endo}$ (Scheme 2). The intramolecular coordination of the heterocyclic oxygen to the

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(8) Throughout the text, the absence of a juxtaposed **u** or **s** letter as suffix to a compound number means that this number corresponds indifferently to either the unsaturated or the saturated substrates.

(9) Swern oxidation of **1u** has led to 3,5-dihydroxy-4-oxatricyclo-[5.2.1.$0^{2,6}$]-8-decene: Wu, H.-J.; Wu, C.-Y. *J. Org. Chem.* **1999**, *64*, 1576. This corresponds to hydratation of the dialdehyde intermediate to form the cyclic monohydrate. The intramolecular Cannizaro–Tishchenko type reaction of dialdehydes leading to lactones has been reported under Rh- and La-catalysis: (a) Bergens, S. H.; Fairlie, D. P.; Bosnish, B. *Organometallics* **1990**, *9*, 566. (b) Berberich, H.; Roesky, P. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1569.

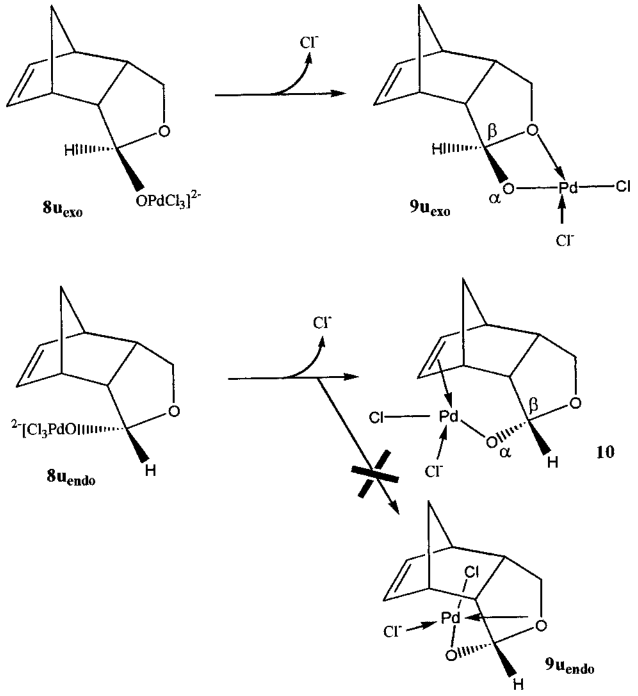
(10) The spontaneous generation of **3u** from hydroxyacid **5u** has been reported: Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190.

(11) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley: New York, 1992; p 393 and p 1233.

(12) In eq 3, the obtention of esters, $RCO_2(CH_2)_2Cl$, is due to the formation of acids, RCO_2H, which react efficiently with DCE in the presence of Na_2CO_3 and Adogen 464: Aït-Mohand, S.; Levina, A.; Muzart, J. *Synth. Commun.* **1995**, *25*, 2051.

(13) The intramolecular addition of anionic palladium species to aldehydes has been recently suggested as a mechanism of certain cyclization reactions: Gai, X.; Grigg, R.; Collard, S.; Muir, J. E. *Chem. Commun.* **2000**, 1765.

Scheme 2



palladium atom[14] of **8u**$_{\text{exo}}$ would remove a chloride anion to provide **9u**$_{\text{exo}}$. From **8u**$_{\text{endo}}$, the coordination to the palladium atom of the C−C double bond instead of the O-coordination should be preferred for both steric and thermodynamic reasons. Indeed, the *endo*-position of the strained metallocycle of **9u**$_{\text{endo}}$ would lead to some steric congestion; moreover, the intramolecular coordinating ability of the double bond toward palladium is intuitively better than that of the oxygen of the five-membered heterocycle.[15] In **9u**$_{\text{exo}}$ and **10**, the *syn*-relationship between the O_α−Pd and C_β−H bonds, which is required for a β-hydride elimination leading to the lactone, is prevented. Consequently, the preferred evolution of these Pd-intermediates should be retro-reactions leading to **7u** or to the lactols (Scheme 1). We now have to point out that **2u**$_{\text{exo}}$ is thermodynamically more stable than **2u**$_{\text{endo}}$ since both the oxidation of **1u** by *o*-iodoxybenzoic acid, which involves **4u** as intermediate,[16] and the reduction of **3u** by aluminum hydrides[7,17] produced **2u**$_{\text{exo}}$. Therefore, the equilibrium between **4u** and the corresponding hemiacetals coupled with the higher stability of the lactol having the hydroxy group in *exo*-position favored the isolation of **2u**$_{\text{exo}}$. Nevertheless, we think that the argument for a four-membered palladacycle precluding the lactone formation has to be discarded. Indeed, this would be limited to the case of the reactivity of **1u** and **2u**$_{\text{exo}}$ since various other diols (ref 5 and eq 2) and at least one other lactol (eq 4), which could give similar palladacycles, have been easily oxidized to the corresponding lactones under the same conditions. Consequently, we propose that (i) the palladation of **4u** (Scheme 1, path *a*) rather than of **2u**$_{\text{exo/endo}}$ (Scheme 1, path *b*) is the preferred reaction pathway, (ii) from **7u** thus obtained, the intramolecular insertion into the C=O occurs through the stereoselective approach of the alkoxypalladium moiety to one face of the aldehyde, which leads to **8u**$_{\text{endo}}$, and (iii) exchange of ligands gives **10**, which evolves to **2u**$_{\text{endo}}$ and finally to **2u**$_{\text{exo}}$ as described above. When **2u**$_{\text{exo}}$ is subjected to this Pd-procedure, the apparent absence of its evolution is indeed a “no reaction” reaction[18] involving the formation of **10** via **4u**, **7u**, and the kinetic cyclization product **8u**$_{\text{endo}}$ and, then, its subsequent alcoholysis and equilibration which regenerates the starting substrate.

In monitoring the progress of the oxidation of **1s** by TLC, we did not observe any traces of the lactols. This and the remarks about the oxidation of **1u** suggest that from **4s** the most possible reactive intermediates would be **7s** and **8s**$_{\text{endo}}$ rather than palladation of hemiacetals. Similarly, the formation of hexahydroisobenzofuran-1-one from the corresponding lactol (eq 4) could involve palladation of the open form of the lactol. Nevertheless, we have to note that under our Pd-conditions the reaction pathways followed by lactols and diols embodying an arene in their structure are probably different, since this procedure led to many unidentified compounds and solely traces of phthalide from a mixture of 2-hydroxymethylbenzaldehyde and its corresponding lactol form,[7] although 1,2-benzenedimethanol provided phthalide effectively.[5]

In conclusion, the key features that prevent the formation of lactone **3u** from **1u** and **2u**$_{\text{exo}}$ are the formation of the alkoxypalladium from hydroxyaldehyde **4u** and its subsequent stereoselective addition into the aldehyde moiety, which, after Cl$^-$/C=C ligand exchange, precludes the β-hydride elimination.

Experimental Section

^{1}H and ^{13}C NMR (250 and 63 MHz) spectra were obtained on a Bruker AC 250 spectrometer using TMS as internal standard and $CDCl_3$ as solvent. IR spectra were recorded in $CHCl_3$ with Spectrafile IR Plus MIDAC. Mass spectra were recorded on a JEOL D 300 at “UFR Pharmacie” of Reims. *cis-endo*-2,3-Bis(hydroxymethyl)bicyclo[2.2.1]heptane (**1s**)[6a] was obtained by hydrogenation of **1u** over PtO_2 in MeCN (yield: 86%).

***cis*-3-Oxabicyclo[4.3.0]nonan-2-ol.** To a stirred 1 M DIBAL solution in THF (0.7 mL, 0.7 mmol) at −78 °C under an argon atmosphere was dropped a solution of *cis*-3-oxabicyclo[4.3.0]-nonan-2-one [7] (100 mg, 0.72 mmol) in PhMe (10 mL). After stirring at −78 °C for 4.5 h, cold water and 2 M HCl were successively added. The mixture was extracted with diethyl ether. The organic phase was dried over $MgSO_4$. Filtration and then evaporation of the solvents led to lactol (75 mg, 73%

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[14] The intramolecular coordination of an oxygen atom leading to a four-membered palladacycle has been proposed to explain the preclusion of β-hydride eliminations: (a) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073. (b) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133. (c) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1893. (d) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341.

[15] From theoretical calculations in the gas phase, the ethylene complexation energy to $[PdCl_3]^-$ is 19.0 kcal.mol^{-1}: Strömberg, S.; Svensson, M.; Zetterberg, K. *Organometallics* **1997**, *16*, 3165. Besides, THF is usually considered as a weak ligand in Pd(II) chemistry since it can be used as solvent, especially for the oxidation of olefins: (a) Mahrwald, R.; Schick, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 593. (b) Gauguly, S.; Roundhill, D. M. *Organometallics* **1993**, *12*, 4825. (c) El Ali, B.; Brégeault, J.-M.; Martin, J. *J. Organomet. Chem.* **1987**, *327*, C9. (d) Mohammedi, O.; Brégeault, J.-M. *J. Soc. Alger. Chim.* **1998**, *8*, 101. (e) Berger, M.; Mulzer, J. *J. Am. Chem. Soc.* **1999**, *121*, 8393.

[16] (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485. (b) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945.

[17] Lieb, F.; Niewöhner, U.; Wendisch, D. *Liebigs Ann. Chem.* **1987**, 607.

[18] For the introduction of this expression and its recent use, see: (a) Berson, J. E.; Willcott, M. R. *J. Org. Chem.* **1965**, *30*, 3569. (b) Baldwin, J. E.; Dunmire, D. A. *J. Org. Chem.* **2000**, *65*, 6791.

yield), whose the spectroscopic properties were in agreement with the literature.[16a]

General Oxidation Procedure. $PdCl_2$ (0.05 mmol) and Adogen 464 (0.1 mmol) were stirred in DCE (10 mL) at room temperature until dissolution. The substrate (1 mmol) and Na_2CO_3 (2 mmol) were added. The mixture was refluxed under an air atmosphere for the time indicated in the text. After cooling, the mixture was filtered on a short pad of silica gel. The compounds were separated by preparative TLC.

The spectroscopic properties of **3s** were in agreement with the literature.[6a]

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