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Deuterium-Labeling Studies Establishing Stereochemistry at the Oxypalladation Step in Wacker-Type Oxidative Cyclization of an *o*-Allylphenol

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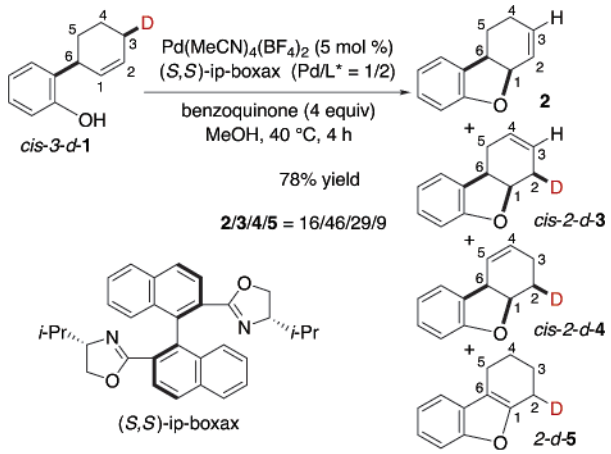
The Wacker-type oxidation is one of the most important processes catalyzed by palladium complexes.[1] The oxidation proceeds through oxypalladation in the catalytic cycle, and there has been controversy concerning the stereochemistry of the oxypalladation step. In early studies, the oxypalladation was reported by Bäckvall, Stille, and Kurosawa to proceed with anti stereochemistry.[2] Recently, it has been proposed by Henry and others that the stereochemistry is dependent on the reaction conditions, syn stereochemistry being predominant at low chloride ion concentration.[3] Although several reaction systems have been used for determination of the stereochemical pathway, they have not always brought about definite stereochemical results due to the ambiguity inherent in the systems.

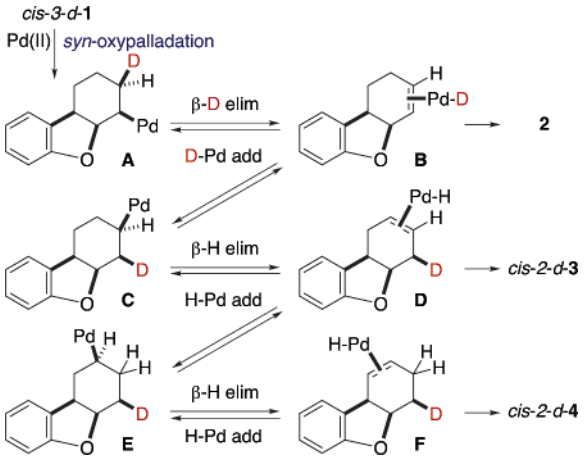
On the basis of the report by Hosokawa and Murahashi that 6-(2-hydroxyphenyl)cyclohexene undergoes the palladium-catalyzed oxidative cyclization giving tetrahydrodibenzofurans,[4] we designed and prepared stereospecifically deuterated racemic 6-(2-hydroxyphenyl)-3-deuteriocyclohexenes, *cis-3-d*-**1** and *trans-3-d*-**1**, by a sequence of reactions whose stereochemistry is unambiguous (see Supporting Information for their preparation), and we used them for the determination of the stereochemistry at the oxypalladation step under some reaction conditions including our chiral dicationic catalyst system[5] consisting of $Pd(MeCN)_4(BF_4)_2$ and (*S*,*S*)-2,2′-bis-(4-isopropyloxazolyl)-1,1′-binaphthyl ((*S*,*S*)-ip-boxax). Here, we report our deuterium-labeling studies which unambiguously determine the stereochemistry.[6]

Oxidative cyclization of *cis-3-d*-**1** proceeded in high yield by treatment with 5 mol % of dicationic palladium catalyst, generated from $Pd(MeCN)_4(BF_4)_2$, and (*S*,*S*)-ip-boxax, and benzoquinone (4 equiv) in methanol at 40 °C[5] to give 78% yield of a mixture of four regioisomeric tetrahydrodibenzofuran derivatives **2**, **3**, **4**, and **5** in a ratio of 16/46/29/9 (Scheme 1).[7] They were separated by silica gel chromatography and fully characterized by comparison of their ^1H and ^2H NMR spectra with those of the isomers obtained from nondeuterated 6-(2-hydroxyphenyl)cyclohexene. Remarkable points are as follows: (1) All of the isomers **2**, **3**, and **4**, whose basic structure is dihydrobenzofuran, have a *cis*-fused five- and six-membered ring system. (2) Isomer **2** does not contain deuterium on any of the carbon atoms. (3) Deuterium is incorporated over 95% at the 2-position cis to the oxygen in the isomers **3** and **4**. (4) Benzofuran **5** contains >90% deuterium at the 2-position and 5−10% deuterium at the 3- and 4-positions. The lack of deuterium on the 3-position of **2**, **3**, and **4** and the shift of deuterium from the 3-position to the 2-position in **3** and **4** demonstrate that the stereochemistry of the oxypalladation step under these conditions is syn. Thus, addition of phenol oxygen and palladium to the double bond in a syn fashion from the same face of 2-hydroxyphenyl group forms alkylpalladium intermediate **A** where palladium is located on the same face as deuterium on the cyclohexane ring (Scheme 2). The deuterium is abstracted by β-hydrogen elimination, which proceeds in a syn fashion, to give intermediate **B** where the

Scheme 1



Scheme 2



palladium is bonded with the π-olefin and deuterium. Dissociation of palladium from the double bond produces dihydrobenzofuran **2**, which does not contain a deuterium atom on the 3-position. Addition of palladium-deuteride to the double bond on **B** in the other way forming the alkylpalladium intermediate **C** followed by β-hydrogen elimination from 4-position produces regioisomer *cis-2-d*-**3** by way of π-olefin-hydride complex **D**. The hydropalladation on **D** and β-hydrogen elimination in a similar manner leads to the isomer *cis-2-d*-**4**. By the β-deuterium elimination from **A** and deuteriopalladation forming **C**, the deuterium moved from the 3-position to the 2-position. The formation of benzofuran *2-d*-**5** in a small amount is rationalized by the isomerization of **2**, **3**, and/or **4**, which is caused by the coordination of a hydrido-palladium species to the other face of the cyclohexene ring. The hydropalladation and β-hydrogen elimination sequences lead to the thermodynamically more stable benzofuran **5** (an example starting from

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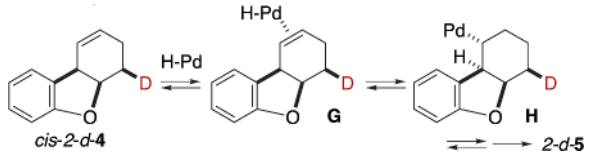
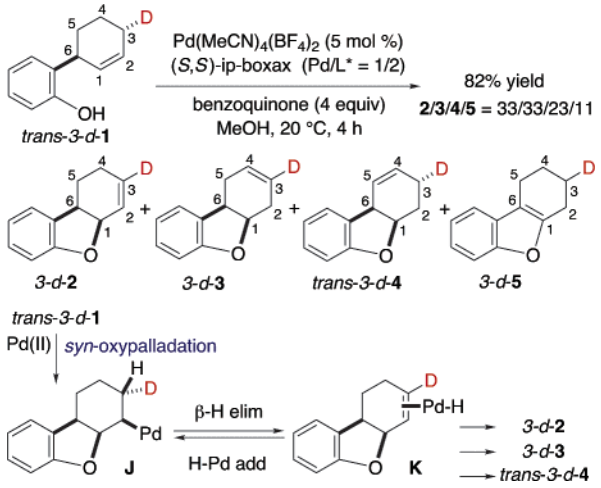
Scheme 3



Scheme 4



cis-2-d-**4** is shown in Scheme 3). The anti stereochemistry at the oxypalladation step is excluded because the deuterium in **5** is located mainly at the 2-position. The *anti*-oxypalladation would lead to the incorporation of deuterium at the 3-position in **5**.

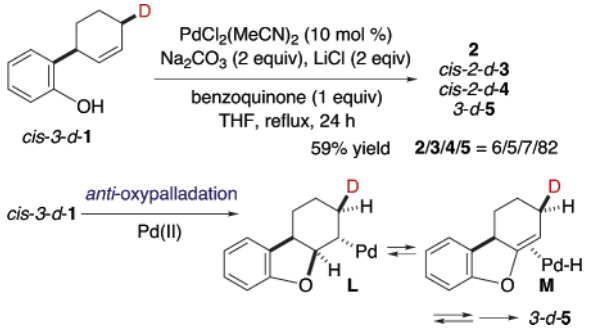
The syn stereochemistry of the oxypalladation step was confirmed in the reaction of the trans isomer, *trans-3-d*-**1**, which gave *3-d*-**2**, *3-d*-**3**, *trans-3-d*-**4**, and *3-d*-**5** in a ratio of 33/33/23/11 (Scheme 4). The deuterium remained at the 3-position in all of the isomeric products because the deuterium is located at the face opposite to that of palladium in the alkylpalladium intermediate **J** which was generated by *syn*-oxypalladation.

Hosokawa and Murahashi's catalyst system, which consists of bis[acetoxy(3,2,10-η^3-pinene)palladium(II)[8] (10 mol %) and Cu(OAc)$_2$ (10 mol %) in the presence of oxygen in refluxing methanol,[8] also proceeded with syn stereochemistry, *cis-3-d*-**1** giving **2**, *cis-2-d*-**3**, and *cis-2-d*-**4** (82% total yield) in a ratio of 83/14/3. The formation of benzofuran **5** was not observed. Under these conditions, the dissociation of a palladium-hydride species from olefin is fast and the lifetime of the palladium-hydride is short as compared to the palladium/boxax and benzoquinone system, resulting in the formation of **2** as a major product.

On the other hand, anti stereochemistry was observed in the presence of a chloride ion. Thus, the oxidative cyclization of *cis-3-d*-**1** with PdCl$_2$(MeCN)$_2$ (10 mol %), benzoquinone (1 equiv), Na$_2$CO$_3$ (2 equiv), and LiCl (2 equiv) in THF under reflux[9] for 24 h gave **2**, *cis-2-d*-**3**, *cis-2-d*-**4**, and *3-d*-**5** in a ratio of 6/5/7/82. Although the deuterium location in **2**, *cis-2-d*-**3**, and *cis-2-d*-**4** shows that they were formed through *syn*-oxypalladation, the formation of *3-d*-**5** as a major product which contains the deuterium at the 3-position is rationalized only by the *anti*-oxypalladation (Scheme 5).

In conclusion, the oxypalladation step in the Wacker-type cyclization takes place with high syn stereochemistry with regard to palladium and oxygen in the absence of chloride, and the stereochemistry is mainly anti in the presence of chloride. The syn

Scheme 5



stereochemistry observed here with the dicationic palladium catalyst in the absence of chloride ion may suggest that the present reaction involves a phenoxy(π-olefin)palladium(II) species which undergoes migratory insertion, giving a β-phenoxyalkylpalladium intermediate.

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Supporting Information Available: Preparation of stereospecifically deuterated 6-(2-hydroxyphenyl)-3-deuteriocyclohexenes, *cis-3-d*-**1** and *trans-3-d*-**1**, experimental procedures for the oxidative cyclization, and spectroscopic and analytical data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) At 42% conversion, recovered *cis*-**1** was 10% ee, indicating that a low level of kinetic resolution (S = 1.4) took place. In the absence of the boxax ligand, the reaction gave a considerable amount of 1-(2-hydroxyphenyl)-1-methoxycyclohexane together with a low yield (total 33%) of a mixture of the tetrahydrobenzofurans.

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