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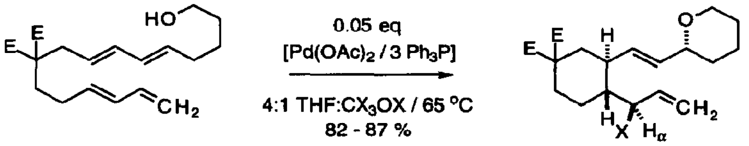
# Catalytic Palladium-Mediated Tetraene Carbocyclizations: Diastereoselective Deuteration and Its Convenient Analysis by a Difference Spin Polarization Transfer (DSPT) NMR Experiment

James M. Takacs,* Sithamalli V. Chandramouli, and Richard Shoemaker

Department of Chemistry, University of Nebraska-Lincoln, Lincoln NE 68588-0304

*Summary:* The palladium-catalyzed cascade cyclization of certain tetraene substrates proceeds in the presence of a deuterium source with stereoselective deuteration exocyclic to the newly formed carbocycle. The diastereoselectivity is established via the novel application of a difference spin polarization transfer (DSPT) NMR experiment.

We recently reported the palladium-catalyzed cyclization and intramolecular trapping of suitably functionalized acyclic tetraene substrates.[1] For example, treatment of tetraene **1** with 0.05 equivalents of a [$Pd(OAc)_2$ / 3 $PPh_3$] mixture in THF or 4:1 THF-MeOH (65 °C, 12-24 h) affords the cyclized and intramolecularly trapped diene **2a** in good chemical yield (82 % and 87 % yields, respectively), and with good diastereoselectivity (9:1 mixture of two diastereomers). Three new stereocenters are generated in the course of cyclization. The relative stereochemistry between the two cyclohexane ring substituents is trans, and the 1,4-relative stereochemical relationship between the stereocenter residing in the pyran ring and that in the cyclohexyl ring is the net result of *anti*-addition across the s-trans diene.



**1** ($E = CO_2Et$)

**2a** ($X = H_\beta$, $E = CO_2Et$)
**b** ($X = D$, $E = CO_2Et$)

In considering possible mechanisms for the palladium-catalyzed cyclization, we carried out the cyclization of **1** in the presence of a deuterium source. Palladium-mediated cyclization in a 4:1 THF-$CD_3OD$ mixture affords **2b** in 87% yield (9:1 diastereoselectivity). The $^1H$ and $^{13}C$ NMR spectra are consistent with a high level of isotope incorporation, and GC-MS analysis (EI mode) confirms that greater than 90 % of the cyclized product **2b** contains a single deuterium. Furthermore, deuterium incorporation generates a fourth stereocenter in the cyclized product **2b**, and the $^1H$ NMR spectrum suggests that the deuterated product is formed as predominantly one diastereomer. The 500 MHz $^1H$ NMR spectrum of **2a** is shown in figure 1.

The diastereotopic allylic methylene hydrogens ($H_\alpha$ & $H_\beta$) are non-equivalent and discernible in the expanded $^1H$ MNR spectrum (inset A) at 2.23 and 1.67 ppm.[2] The resonance at 2.23 is relatively isolated from nearby resonances, while the resonance due to $H_\beta$ (1.67 ppm) is in a crowded region of the spectrum and overlaps with at least two other hydrogen resonances. The expanded spectrum for the deuterated material **2b** is shown in inset B. It is apparent that the resonance due to $H_\beta$ (1.67 ppm) is now largely absence, however, the extensive overlap makes it difficult to accurately ascertain the level of diastereoselection in the deuteration.

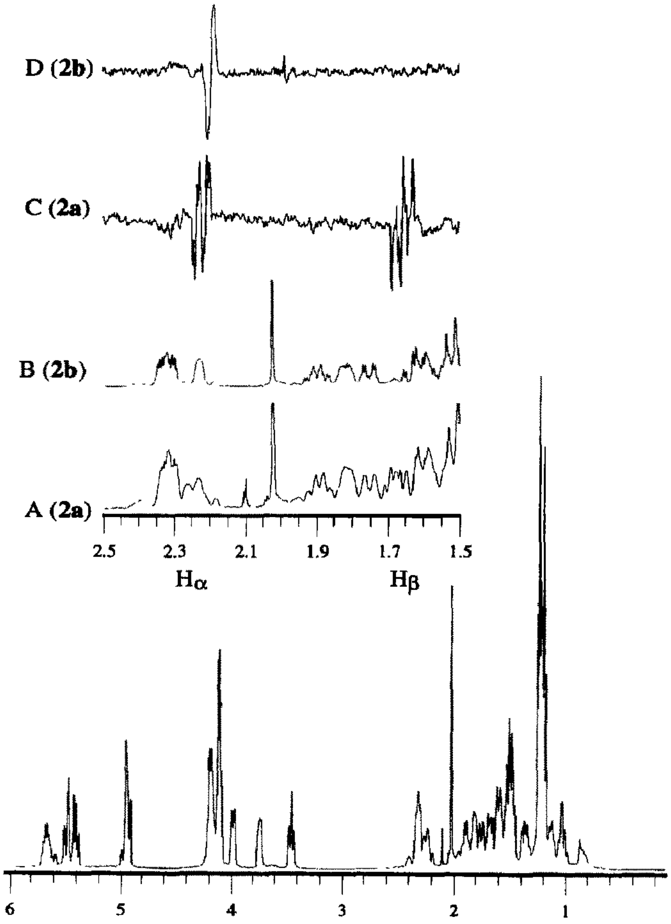


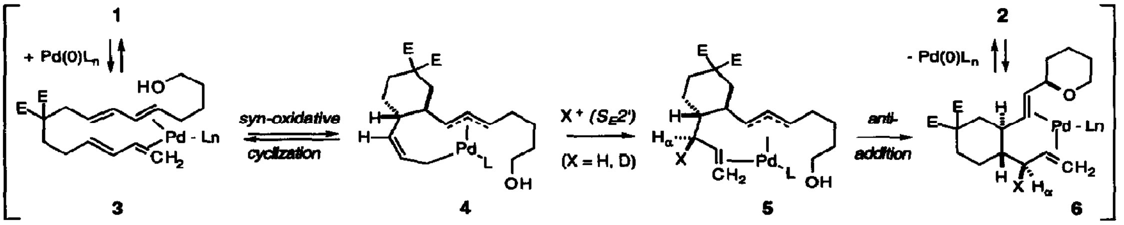
Figure 1. The complete (0.0-6.0 ppm) $^1H$ NMR spectrum for **2a** and the expanded (1.5-2.5 ppm) $^1H$ NMR (inset A: **2a**; B: **2b**) and DSPT (inset C: **2a**; D: **2b**) spectra obtained at 500 MHz.

Several spectroscopic techniques could in principal be used to assess the level of diastereoselectivity. We find that the difference spin polarization transfer (DSPT) or selective population transfer difference spectrum[3-6] provides a particularly quick and convincing method. The DSPT experiment is a powerful, yet relatively simple one dimensional NMR experiment, but one that is infrequently used by synthetic chemists. We have found it to be very useful for the stereochemical analysis of compounds exhibiting very crowded high field NMR spectra. The difference spectrum is obtained by recording a spectrum after applying a soft pulse at the downfield side of the 5.70-5.57 ppm multiplet corresponding to vinyl hydrogen $RC(X)H\text{-}CH{=}CH_2$ (*i.e.*, the vinyl hydrogen that is scalar coupled to the allylic methylene of interest), then subtracting the spectrum obtained after applying a soft pulse at the upfield side of the same multiplet. Insets C and D (figure 1) show the DSPT spectra in the expanded region from 1.5 to 2.5 ppm for compounds **2a** and **2b**, respectively. As seen in inset C, only the resonances for $H_\alpha$ &

H$_\beta$, the only hydrogens in **2a** that appear in the 1.5-2.5 region and are scalar coupled to the vinyl hydrogen about which the soft pulse was centered, appear in the DSPT spectrum. These two resonances are clearly visible as a difference pattern without the interference of overlapping peaks.[7] Inset D, shows the same region for the monodeuterated product **2b**. The absence of the resonance at 1.67 ppm (H$_\beta$) conclusively demonstrates the high diastereoselectivity of the deuteration.

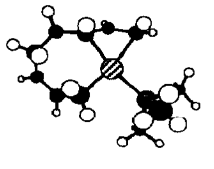
The stereochemical course of the cyclization of **1** can be rationalized by considering our working model for the catalytic cycle outlined in figure 2. The cycle is adapted from that proposed by Jolly and co-workers[8,9] for the dimerization of 1,3-butadiene with intermolecular trapping. In the model tetraene **1** templates about a reduced palladium center and the resulting complex (*i.e.*, **3**) undergoes oxidative cyclization via the syn addition of carbon and palladium across the diene to afford the intermediate palladacycle **4**. Protonation (deuteration) of the $\eta^1$-allyl fragment in an $S_E2'$ fashion leads to the alkene complex **5**. Stereospecific *anti*-addition of the oxygen nucleophile to the $\eta^3$-allylpalladium moiety affords palladium chelate of product **2a** (*i.e.*, **6**), and thus, completes the catalytic cycle. To account for the net *anti* 1,4-addition of carbon and oxygen across the diene, the addition of the oxygen nucleophile to the $\eta^3$-allyl in **5** must be fast relative to the rearrangement of palladium between the diastereomeric faces of the $\eta^3$-allyl.

Figure 2. A working model for the diastereoselective cyclization of tetraene **1** to **2a** (X = H) or **2b** (X = D).

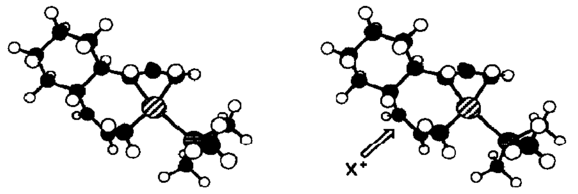


To account for the diastereoselective deuteration of **1**, we need to consider in more detail the likely structure of palladacycle **4** and the stereochemical course of its subsequent reaction with electrophile ($H^+$ or $D^+$). Intermediate **4** has not been isolated or observed directly, but there are crystal and solution structural data available on the parent palladacycle derived from the dimerization of 1,3-butadiene. Structure **7** (figure 3) shows a representation of that butadiene-derived palladacycle adapted from a crystal structure reported by Binger and co-workers.[9,10] Structure **8** (figure 3, shown in stereoview) depicts the three dimensional model of metallacycle **4** bearing the *trans*-fused six-membered ring and is derived from **7** using molecular modeling.[11] Examination of model **8** suggests that two complementary effects can account for the high degree of

Figure 3. Trimethylphosphine complexed palladacycles derived from oxidative coupling of 1,3-butadiene (**7**) and from oxidative cyclization of 1,3,9,11-dodecatetraene (**8**, shown in stereoview).



**7**



**8**

diastereoselectivity in the deuteration. First, there is an obvious steric bias favoring approach of the electrophile $X^+$ to the face leading to the formation of **2b**. Furthermore, the $\eta^1$-allyl moiety is expected to undergo stereospecific $S_E2'$ attack anti with respect to the Pd-C $\sigma$-bond.[12-14]

The palladium-catalyzed cascade cyclization of tetraene **1** proceeds in the presence of a deuterium source to generate a new exocyclic deuterium-bearing stereocenter. The diastereoselectivity is established by a novel application of the difference spin polarization transfer (DSPT) NMR experiment, and the result is consistent with our working model for the catalytic cycle. The following paper describes the extension of this methodology to the construction of a new methyl-bearing stereocenter at that exocyclic position.

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(2) The relative assignments of $H_\alpha$ & $H_\beta$ to the peaks at 2.23 and 1.67 ppm is based on results described in the accompanying paper, wherein the stereochemistry of a newly generated exocyclic stereocenter relative to the cyclohexyl ring centers is unambiguously established.

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(7) While it is not relevant to the analysis described here, the difference pattern preserves all of the coupling constant information. As such, the DSPT technique can often be used to extract coupling constant information from very crowded spectra; information that might otherwise only be accessible from the more cumbersome 2D phase sensitive DQCOSY experiment, or 1D analogs thereof.

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(11) Structure **8** is obtained via molecular modeling (PCModel v 4.3). Starting from structure **7**, the cyclohexane is constructed. The positions of the palladium and the carbons directly bonded to palladium are frozen and the remaining elements of the structure minimized using MMX force field.

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