



# NMR and density functional studies of the stereoselective palladium catalyzed cyclocarbonylation of (1*R*,4*R*)-isolimonene

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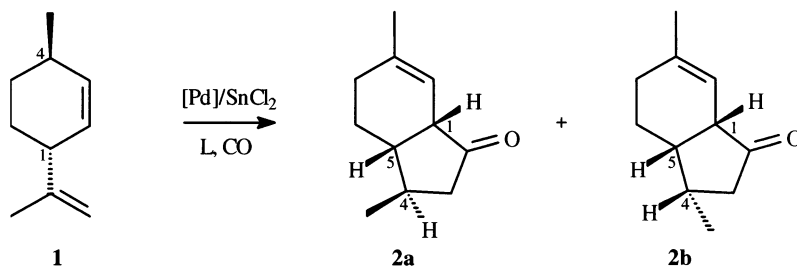
Received 21 December 2000; accepted 24 January 2001

**Abstract**—Carbonylation of (1*R*,4*R*)-isolimonene, catalyzed by [HPd(SnCl<sub>3</sub>)(dppf)], involves the *exo*- and *endo*-carbon–carbon double bonds to provide a cyclopentanone containing two new stereogenic centers with d.e. of 69%. It was shown that this diastereoselectivity arose from the two stereogenic centers of the substrate. Calculations carried out on the cyclization step show that the metal center of the palladium–acyl species coordinates the endocyclic double bond in the *endo*-position exclusively. The net charge distribution over the palladium center, the acyl carbon atom and the two carbon atoms of the C=C bond determines the two nucleophilic attacks in this step. © 2001 Elsevier Science Ltd. All rights reserved.

Tandem reactions play an important role in the functionalization of organic substrates, and their use in carbonylation procedures appears very attractive.<sup>1</sup> During our studies on the alkoxy-carbonylation of various terpenes,<sup>2</sup> preliminary observations have shown that (1*R*,4*R*)-isolimonene leads to a substituted cyclopentanone.<sup>3</sup> This reaction is catalyzed by palladium, and the precursor is transformed into the active hydrido species [Pd(H)(SnCl<sub>3</sub>)L<sub>2</sub>].<sup>3</sup>

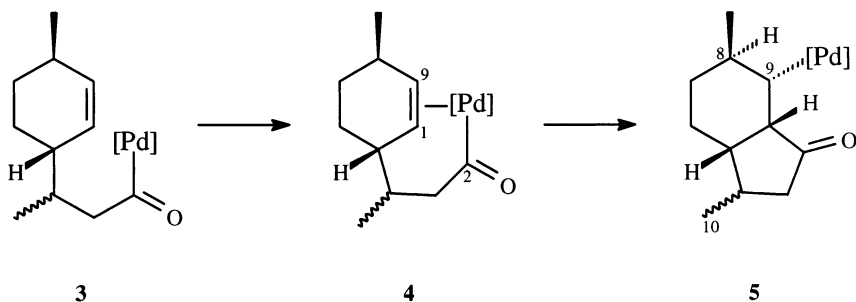
In this work we present a full NMR study of the two diastereoisomers **2a** and **2b** obtained by cyclocarbonylation of pure (1*R*,4*R*)-isolimonene **1** (Scheme 1) for which we have assigned the stereochemistry of all the stereogenic centers. Quantum chemical calculations

using density functional theory (DFT) have been performed on the intermediate species **4** (Scheme 2), which is assumed to be responsible for the diastereodiscrimination. Conformational analysis of this key intermediate **4** gives a classical trigonal bipyramidal (TBP) species, although slightly distorted, in which the endocyclic carbon–carbon double bond is coordinated to the palladium center. The computed net charge distributions in **4** (Fig. 1) direct the two intrasphere nucleophilic attacks giving rise to cyclization. The diastereoselectivity of this cyclocarbonylation reaction is fully governed by the two stereogenic centers (1*R* and 4*R*) initially present in isolimonene as it does not require the presence of any chiral phosphine ligands.



Scheme 1.

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Scheme 2.

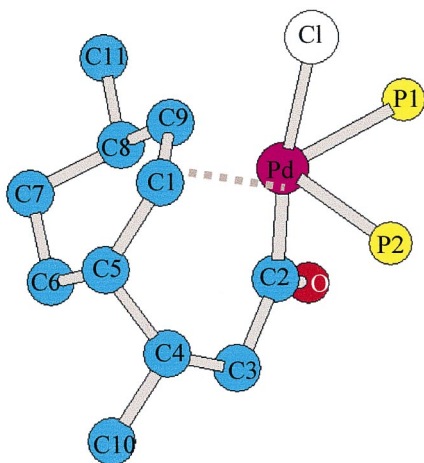


Figure 1. Species 4.

With  $[\text{PdCl}_2(\text{PPh}_3)_2]$ ,<sup>4</sup> the cyclocarbonylation of (1*R*,4*R*)-isolimone leads to the two cyclopentanones **2a** and **2b** with a conversion of 95% and a selectivity of 80%,<sup>5</sup> the two diastereoisomers being obtained in a ratio of **2a:2b** = 56:44 (d.e. = 12%).<sup>6</sup> Substitution of the triphenylphosphine ligands by a diphosphine ligand such as bis(diphenylphosphino)butane (dppb) or -ferrocene (dppf)<sup>7</sup> give lower conversions of around 75% and selectivities of around 50%. However, the diastereoselectivity is greatly improved, since the d.e. reaches 65–69%. Surprisingly, introducing (+)- or (-)-DIOP into the palladium coordination sphere exerts no influence on the stereochemistry of the reaction and a **2a:2b** ratio of 82:18 is obtained, exactly as with dppb, the conversion and selectivity being 77 and 43%, respectively (due to isomerization of **1**). Thus, it can be concluded that the diastereoselectivity of the reaction is governed by the substrate itself, and that a chiral diphosphine ligand is not required.<sup>8</sup>

Attempts to separate the two diastereoisomers **2a** and **2b** by chromatography on a silica column resulted in enrichment of the mixture to give **2a:2b** in a 9:1 ratio.<sup>9</sup> The <sup>1</sup>H, <sup>13</sup>C and DPFGSE NOE NMR characterization<sup>10–12</sup> allowed the structures shown in Scheme 1 for **2a** and **2b** to be assigned, in which the

two hydrogen atoms on C-(1) and C-(5) are in mutual *cis*-positions. Moreover, these assignments reveal that the stereoselectivity is complete on C-(1) and that diastereoselectivity results from the methyl position on C-(4).

If we consider the full mechanism of the carbonylation reaction, the first step of this cyclocarbonylation results from the coordination of the exocyclic carbon–carbon double bond to a palladium–hydride species to give an alkyl intermediate. It is followed by a *cis*-migratory CO insertion to produce the acyl species **3**.<sup>13</sup> Then, we propose the cyclization mechanism shown in Scheme 2 where the double bond coordinates to the palladium center and is followed by a double internal nucleophilic attack. β-Elimination of the hydrogen atom C-(8) of **5** restores the palladium–hydride species and gives **2a** and **2b**.

As limonene (with the endocyclic C=C bond in 3,4 positions) gives rise to poor diastereoselectivity, we can consider that the two steps of hydride transfer to the exocyclic C=C bond and the migratory CO insertion do not provide the 69% d.e. observed here. Hence, we have focused our attention on the intermediate **4** in which it can be assumed that the diastereoselectivity of the reaction is caused by the coordination of the endocyclic carbon–carbon double bond to the palladium metal center.

To have more insight into species **4**, quantum chemical calculations have been carried out by substituting  $\text{SnCl}_3$  with Cl and  $\text{PPh}_3$  with  $\text{PH}_3$ . DFT computations have been performed in two steps: (a) a full geometrical optimization by the conjugate gradient method of Fletcher,<sup>14</sup> (b) a determination of the net charge distributions including a relativistic model core potential<sup>15</sup> on the palladium atom. The DFT calculations have been done using the deMon package release 3.3<sup>16</sup> with the local potential VWN<sup>17</sup> gradient corrected, non-local contributions of Perdew and Wang for the exchange term<sup>18</sup> and Perdew for the correlation term.<sup>19</sup> The structure computed is in good agreement with known experimental data on similar species di-μ-chloro-bis[(2'-3'-η-exo-3-allylnorborn-2-yl)palladium],<sup>20</sup> di-μ-acetato-bis-[(2-methylallyl-3-norbornyl)palladium(II)]<sup>21</sup> and π-allylmonothio-β-diketonepalladium(II).<sup>22</sup> Indeed, a TBP geometry is found, with a C-(1)–C-(9) bond length of 1.46 Å, and two C-(1)–Pd or C-(9)–Pd distances of 2.24 Å.

The Mulliken net charge distributions have been calculated using the DF Theory.<sup>23</sup> Clearly, a charge transfer arises in species **4** leading to an electron excess on the olefinic ligand and more particularly on C-(9) and a positive charge on the carbonyl carbon, C-(2) (+0.22), as well as on the palladium center (+0.25).<sup>23</sup> The most stable calculated geometry corresponds to the double bond in an equatorial position and the carbonyl ligand in one axial position with a 90° angle between the two bonds. Hence, it can be assumed that the nucleophilic attack of C-(9) on Pd and presumably, in a second step, attack of C-(2) by C-(1) to provide **5** are dictated both by the charge distributions and the proximity of the atoms.

Moreover, it can be anticipated that a great decompression occurs in the whole molecule when species **5** is formed, since the palladium–C-(9) bond is far from the cyclopentanone ring. In addition, the metal center and the C-(8) hydrogen are in close proximity and near to a mutual *cis*- position, whereas the hydrogen atom on C-(1) is in an *exo*- position, which explains why  $\beta$ -hydride elimination occurs exclusively from C-(8).

We can conclude that our observations, supported by DFT calculations, show that the stereogenic centers of the substrate are exclusively responsible for the 69% d.e. observed in the cyclocarbonylation reaction of (1*R*,4*R*)-isolimonene.

### Acknowledgements

We acknowledge the Ministère de l'Éducation Nationale de la Recherche et de la Technologie for a Research Grant (L.G.). We thank Lacassin F. and Coppel Y. for their assistance in NMR studies. Acknowledgments are also due to Engelhard-CLAL for a generous loan of palladium, and DRT SA for the gift of a single diastereoisomer of isolimonene.

### References

- Eilbracht, P.; Bäracker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329.
- Chenal, T.; Ciprès, I.; Jenck, J.; Kalck, Ph.; Peres, Y. *J. Mol. Catal.* **1993**, *78*, 351.
- Naigre, R.; Chenal, T.; Ciprès, I.; Kalck, Ph.; Daran, J. C.; Vaissermann, J. *J. Organomet. Chem.* **1994**, *480*, 91.
- Coulson, D. R.; Satek, L. C.; Orim, S. O. *Inorg. Chem.* **1972**, *13*, 121.
- (a) A mixture of dichlorobis(triphenylphosphine)palladium(II) (0.702 g, 1 mmol), hydrated tin(II) chloride (0.474 g, 2.5 mmol) and triphenylphosphine (0.524 g, 2 mmol) was introduced into a 250 mL stainless steel autoclave with mechanical stirring. A nitrogen saturated mixture of isolimonene (13.624 g, 100 mmol) in toluene (25 mL) was introduced into the evacuated autoclave by aspiration. It was heated to 65°C under 40 bar pressure of carbon monoxide at constant pressure. After 18 h, the autoclave was cooled and then slowly depressurized. The yellow–orange reaction mixture was analyzed by gas chromatography. The same procedure was followed for other ligands maintaining the P/Pd ratio at 4. (b) 20% isomers of isolimonene were identified by GC/MS on a Perkin–Elmer QMass 910, with a Crompack CP WAX 52 CB (50 m; 0.32 mm; 0.2  $\mu$ m) polar column.
- Diastereoisomeric excess was determined by GC analyses, performed on a Carlo Erba MFC 500 apparatus equipped with a Econo-Cap FFAP (30 m; 0.53 mm; 1.2  $\mu$ m) capillary column and a flame ionization detector.
- Jenkins, J. M.; Verkade, J. C. *Inorg. Chem.* **1968**, *11*, 108.
- Mulzer, J. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, Heidelberg, 1999; Vol. 1, p. 33.
- After the catalytic reaction, organometallic compounds and excess phosphine were separated from the crude solution by adding CCl<sub>4</sub>. The deeply colored oily layer was decanted. After concentration by rotary evaporation, the oily residue was purified by column chromatography on silica gel (petroleum ether:dichloromethane:ethyl acetate, 70:24:6).
- Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1996**, *119*, 295.
- Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302.
- Selected spectroscopic data of **2a**: IR (KBr):  $\nu$ =1740 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, TMS):  $\delta$ =4.90 (d, <sup>3</sup>J (H,H)=1.4 Hz, 1H; H<sub>9</sub>), 2.45 (dd, <sup>3</sup>J (H,H)=<0.5, 1H; H<sub>1</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$ =217.7 (CO), 116.1 C-(9), 49.3 C-(1), 18.7 C-(10). Selected spectroscopic data of **2b**: IR (KBr):  $\nu$ =1740 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, TMS):  $\delta$ =5.16 (d, <sup>3</sup>J (H,H)=1.5 Hz, 1H; H<sub>9</sub>), 2.35 (dd, <sup>3</sup>J (H, H)=<0.5, 1H; H<sub>1</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$ =218.0 (CO), 116.4 C-(9), 52.0 C-(1), 15.1 C-(10).
- (a) Cavinato, G.; Toniolo, L. *J. Organomet. Chem.* **1993**, *444*, C65; (b) Bardi, R.; Del Pra, A.; Piazzesi, A. M.; Toniolo, L. *Inorg. Chim. Acta* **1979**, *35*, L345; (c) Cavinato, G.; Toniolo, L. *Chimia* **1979**, *33*, 286.
- Fletcher, R. *Practical Methods of Optimization*; John Wiley & Sons: Chichester, 1981; Vol. 2.
- Huzinaga, S.; Klobukowski, M.; Sakai, Y. *J. Phys. Chem.* **1984**, *88*, 488.
- S'Amant, A.; Salahub, D. R. *Chem. Phys. Lett.* **1990**, *169*, 387.
- Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
- Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1986**, *33*, 8800.
- Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822.
- Zocchi, M.; Tieghi, G. *J. Chem. Soc. Dalton Trans.* **1979**, 944.
- Zocchi, M.; Tieghi, G.; Albinati, A. *J. Chem. Soc. Dalton Trans.* **1973**, 883.
- Sadownick, J. A.; Lippard, S. J. *Inorg. Chem.* **1973**, *12*, 2659.
- Mulliken net charges: C-(1)=+0.04; C-(2)=+0.22; C-(3)=-0.28; C-(4)=-0.14; C-(5)=-0.45; C-(6)=+0.05; C-(7)=+0.13; C-(8)=-0.37; C-(9)=-0.46; C-(10)=+0.25; C-(11)=+0.20; C-(1)=-0.34; O=-0.25; P-(1)=-0.36; P-(2)=-0.46; Pd=+0.25.