Experimental Evidence on the Existence of an *exo*-π-Allyl Complex Intermediate in the Pd^0-Catalyzed Alkylation of a Bicyclic Allylic Diacetate with Stabilized Nucleophiles

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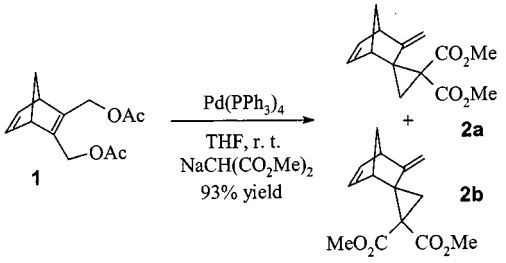
The Pd^0-catalyzed alkylation of **1** by sodiodimethylmalonate led to the formation of two tricyclic diastereomers **2a** and **2b**. The structure of the major *endo* diastereomer **2b** has been confirmed by NMR experiments and X-ray structure analysis. This stereochemistry is in accordance with the formation of an *exo* cationic (π-allyl)palladium intermediate.

Introduction

Because of its important synthetic applications, Pd^0-catalyzed alkylation of allylic acetates has become a fundamental tool in organic synthesis and its mechanistic implication has been well studied over the last 30 years.[1] In 1995, we have reported the synthesis of a new prochiral bicyclic diacetate namely 2,3-bis(acetoxymethyl)bicyclo-[2.2.1]hepta-2,5-diene (**1**) and its use in palladium(0)-catalyzed elimination.[2] The existence of a (π-allyl)palladium complex as intermediate in these reactions is now well established.[3] However, few studies on bicyclic allylic acetate substrates have been reported. Petit[4] and Godleski[5] were the first to provide evidence for an *exo*-(π-allyl)palladium dimeric complex derived from norcamphene by X-ray structure analysis which is in straight accordance with its reactivity towards hard nucleophiles. Last year, we reported the evidence of formation of an *exo*-(π-allyl)palladium intermediate in the Pd^0-catalyzed alkylation of bicyclic allylic diacetate **1** with stabilized nucleophiles (Scheme 1).[6]

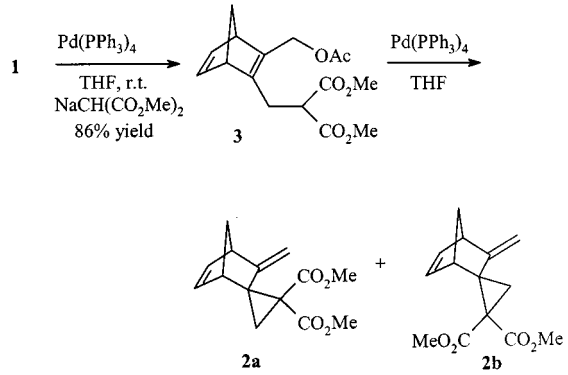


Scheme 1. Pd^0-catalyzed alkylation of allylic bicyclic diacetate **1**

Recently, our results have been the subject of a comment by Lloyd-Jones suggesting that only a mixture of isomers of **2a** and **2b** is obtained without evident proof on the exact structure of these compounds and that the mechanism is not well discussed.[7,8] In this paper, we will report some unambiguous evidence dealing with the formation of our postulated *exo*-(π-allyl)palladium intermediate.

Results and Discussion

Reaction of **1** with one equiv. of sodio dimethyl malonate in THF in the presence of 1.5 mol-% of $Pd(PPh_3)_4$ at room temperature afforded after 5 min compound **3** (86% isolated yield). Longer reaction times (room temperature, 32 hours) led to the complete conversion of **3** into two products which were found to be the tricyclic compounds **2a** and **2b** (Scheme 2). In these cases, a mixture of the two isomers **2a** and **2b** has been isolated in a ratio varying from 5:95 to 40:60.



Scheme 2. Pd^0-catalyzed alkylation of bicyclic diacetate **1** with sodiodimethylmalonate

Formation of **2a** and **2b** has appeared to be the result of an intramolecular reaction of **3**, consisting in the allylic substitution of the remaining acetoxy group. On the other hand, a kinetic study has clearly demonstrated the predom-

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inant formation of **3** at the early stage of the reaction and its further disappearance to afford the cyclopropane adducts **2a** and **2b**. Nevertheless, the outcome of the reaction depends on the temperature (Figure 1).

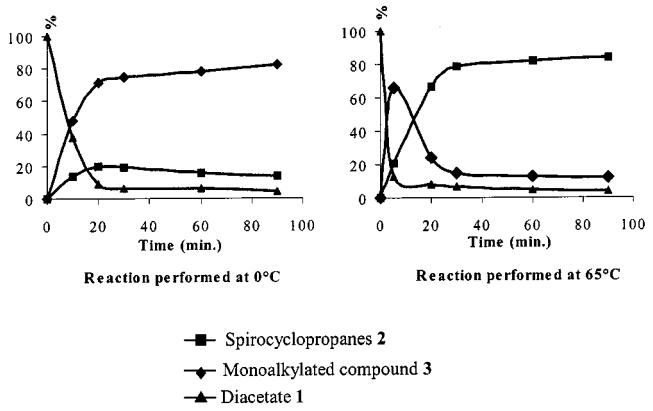


Figure 1. Pd^0-catalyzed alkylation of diacetate **1** with sodiodimethylmalonate

The major formation of compound **2b** instead of **2a** was confirmed by numerous ^1H and ^{13}C NMR experiments (Figure 2).

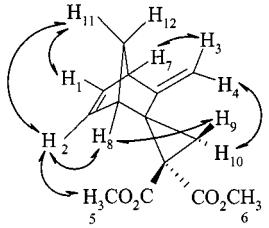


Figure 2. NOESY NMR sequence of a 5:95 mixture of **2a/2b**

Examination of the proton NMR spectrum together with the NOESY experiment allows a complete attribution of the signals (see Supporting Material). Thus, the ethylenic protons H_1 and H_2 (isochronous) are centered at $\delta = 6.14$ whereas the methylene protons H_3 and H_4 are located at $\delta = 4.76$ and $\delta = 4.18$, respectively. The NOESY shows a clear correlation between H_1, H_2, and H_{11} ($\delta = 1.68$), allowing attribution of H_{12} at $\delta = 1.65$. Moreover, the signals corresponding to the bridgehead protons H_7 ($\delta = 3.27$) and H_8 ($\delta = 3.07$) can be evidenced through their correlation with H_1 and H_2, respectively. From these attributions, the *endo* structure for the major isomer **2b** is deduced from the cross peaks between H_2 and H_5, H_8 and H_9, and H_7 and H_3. Furthermore, the cross peak between H_4 and H_{10} is in agreement with this structure. On the other hand, in order to definitevely probe the predicted structure of **2b** we have realized an X-ray structure analysis of single crystals obtained by slow crystallization in ethyl acetate of a **2b/2a** mixture (ratio 95:5) (Figure 3).[9]

Thus, the ORTEP drawing clearly indicates that the cyclopropyl protons are in an *exo* position confirming the relative stereochemistry of the major isomer as *endo*-**2b**.

On the basis of all these results, the predominant formation of **2b** with respect to **2a** can be explained by the prefer-

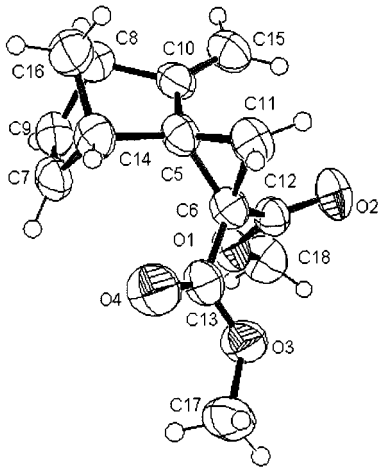
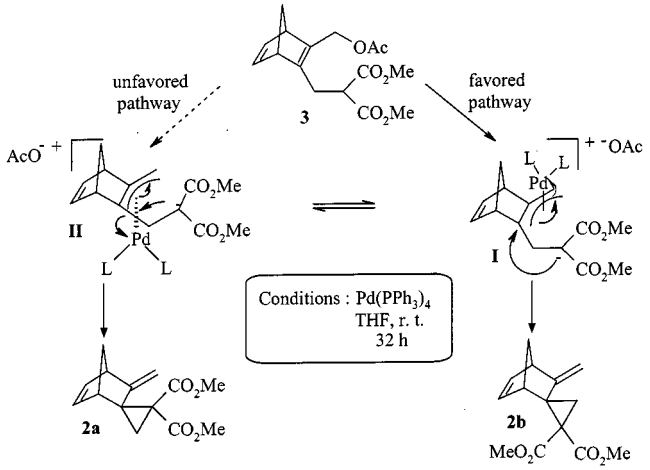


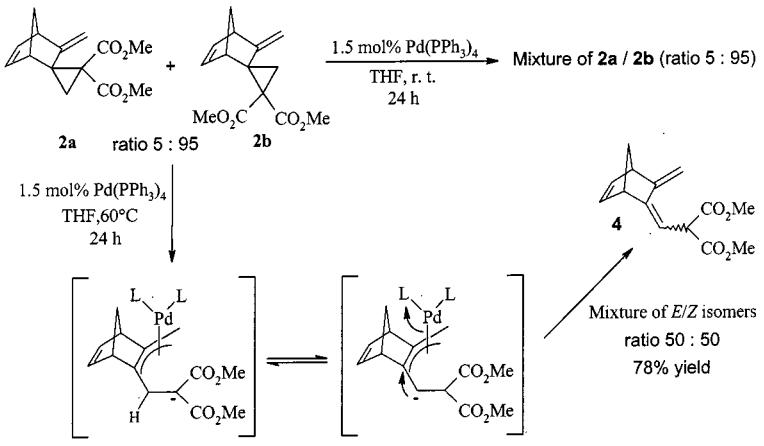
Figure 3. Structure of **2b**, showing labeling scheme; selected bond lengths [Å]: C5–C6, 1.5391(8), C5–C10, 1.5171(8), C5–C11, 1.4826(9), C6–C11, 1.5182(8), C6–C12, 1.4961(8), C6–C13, 1.4957(8), C8–C16, 1.5283(9), C10–C15, 1.3148(7), C14–C16, 1.5441(9);' selected bond angles [°]: C6–C5–C11, 60.29(4), C5–C6–C12, 117.43(5), C12–C6–C13, 115.91(5), C10–C8–C16, 98.99(5), C8–C10–C15, 126.32(6), C5–C14–C7, 104.88(4), C5–C14–C16, 100.02(5), C8–C16–C14, 93.66(5)

ential formation of complex **I** where palladium atom lies in the *exo* position (Scheme 3).



Scheme 3. Mechanistic rationale for the Pd^0-catalyzed alkylation of diacetate **1** with sodiumbis(methoxycarbonyl)methanide

Thus, the cyclopropane formation proceeds via an oxidative addition of compound **3** onto the catalytically active species, leading to the elimination of HOAc and subsequent ring closure. Since the incoming nucleophilic attack towards (π-allyl)palladium complexes is known to proceed in an *anti* fashion with respect to the metal,[3c,10] the structure of the predominant final product **2b** allows us to predict an *exo* configuration for the (π-allyl)palladium intermediate. Nevertheless, the formation of a large amount of **2a** at high temperature most probably results from an interconversion between the two (π-allyl)palladium complexes **I** and **II** (see below).This phenomenon can be related to the isomerization of (π-allyl)palladium complexes, which has been put forward to explain the loss of stereospecificity of some palladium-catalyzed reactions of allylic substrates with nucleo-



Scheme 4

philes.[11] Surprisingly, we have not observed any isomerisation between the products **2b** into **2a** performing the reaction in presence of a **2b**/**2a** mixture (90:10 ratio) and 1.5 mol-% of $Pd(PPh_3)_4$ at room temperature in THF for 24 hours (Scheme 4). Nevertheless, this reaction realized under the same experimental conditions at 60 °C led exclusively to the formation in 78% yield of a new product whose structure has been unambiguously determined as **4** in a 50:50 mixture ratio of (*Z*) and (*E*) isomers. The formation of such compound **4** can be explained as underlined in Scheme 4 and definitively probe that no isomerization process exists through an equilibrium between **2b** and **2a**.

Conclusion

We have unambiguously demonstrated, in response to Lloyd-Jones' comments, that the structure assigned to isomer **2b** is correct as previously described.[6] This demonstration has been realized performing numerous NMR experiments and by X-ray structure analysis. Thus, the almost exclusive formation of the *endo*-disubstituted spirocyclopropane compound **2b** under the appropriate conditions underlines that the reaction proceeds through an *exo*-(π-allyl)palladium complex. Moreover, mechanistic studies clearly indicate that no equilibration between **2a** and **2b** occurred whatever the experimental conditions contrarily to Lloyd-Jones' suggestion.

Experimental Section

All solvents were purified according to reported procedures, and reagents were used as commercially available. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl immediately prior to use. Petroleum ether (35–60 °C) was purchased from SDS and used without any further purification. Column chromatography was performed on SDS silica gel (70–230 mesh). – ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 and AC 400 spectrometer (the usual abbreviations are used: s: singulet, d: doublet, t: triplet, q: quadruplet, m: multiplet). Tetramethylsilane was used as internal standard. All chemical shifts are given in ppm.

Palladium-Catalyzed Alkylation of 1 with Sodium Bis(methoxycarbonyl)methanide: To a solution of $Pd(PPh_3)_4$ (0.350 g; 0.3 mmol) in THF (5 mL) was added a solution of **1**[2a] (2.36 g, 10 mmol) in THF (5 mL) under a nitrogen atmosphere. After stirring for 5 min at room temperature, a solution of sodium bis(methoxycarbonyl)methanide (10 mmol) in 25 mL of THF (prepared by reaction of 1.32 g of dimethyl malonate and 0.24 g of NaH) was added via syringe. The reaction mixture was stirred at room temperature for 5 min, and quenched with a saturated NH_4Cl solution. Most of the THF was removed in vacuo, and the aqueous layer was extracted with ether (3 × 20 mL). After drying over Na_2SO_4, the solvents were removed in vacuo. The residue was purified by flash chromatography on a silica gel column (eluent: petroleum ether/diethyl ether 9:1) affording 2.86 g of compound **2** (93% yield).

Dimethyl 2-{[3-(Acetoxymethyl)norbornadien-2-yl]methyl}malonate (3): ^{1}H NMR: δ = 1.85 (s, 3 H), 1.97 (m, 2 H), 2.93 (m, 2 H), 3.36 (m, 2 H), 3.45 (s, 3 H), 3.49 (s, 3 H), 4.76 (m, 3 H), 6.74 (m, 2 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 28.2, 50.2, 52.0, 52.1, 52.7, 53.9, 60.3, 71.8, 142.3, 145.8, 150.0, 168.9, 169.2, 170.1. – IR: 833, 909, 1024, 1169, 1234, 1439, 1742, 2868, 2961 – $C_{16}H_{20}O_6$ (308.3): calcd. C 62.3, H 6.5, found C 62.5, H 6.3.

Dimethyl *endo*-3′-Methylenespiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (2b, major compound): ^{1}H NMR: δ = 1.54 (m, 2 H), 1.84 (dd, 2 H, *J* = 34.7, *J* = 5.1 Hz), 3.10 (s, 1 H), 3.30 (s, 1 H), 3.58 (s, 3 H), 3.71 (s, 3 H), 4.22 (s, 1 H), 4.78 (s, 1 H), 6.22 (m, 2 H). – ^{13}C NMR: δ = 26.2, 40.5, 43.6, 47.2, 50.1, 52.5, 52.7, 53.1, 100.8, 135.2, 136.7, 152.4, 167.4, 169.7 – IR: 886, 1108, 1162, 1224, 1266, 1364, 1434, 1606, 1728, 2858, 2930, 2950, 3060 – $C_{14}H_{16}O_4$ (248.2): calcd. C 67.7, H 6.5, found C 67.4, H 6.5.

Dimethyl *exo*-3′-Methylenespiro(cyclopropane-1,2′-norborn-4-ene)-2,2-dicarboxylate (2a, minor compound): ^{1}H NMR: δ = 1.54 (m, 2 H), 1.76 (dd, 2 H, *J* = 28.6, *J* = 5.1 Hz), 3.10 (s, 1 H), 3.30 (s, 1 H), 3.62 (s, 3 H), 3.74 (s, 3 H), 4.22 (s, 1 H), 4.74 (s, 1 H), 6.27 (m, 2 H). – ^{13}C NMR: δ = 26.2, 41.5, 44.2, 45.6, 50.2, 51.7, 52.5, 52.8, 101.0, 134.9, 138.7, 152.2, 167.5, 169.8 – IR: 886, 1108, 1162, 1224, 1266, 1364, 1434, 1606, 1728, 2858, 2930, 2950, 3060 – $C_{14}H_{16}O_4$ (248.2): calcd. C 67.7, H 6.5, found C 67.4, H 6.5.

Preparation of Dimethyl 2-[(4-Methylenebicyclo[2.2.1]hept-2-en-5-ylidene)methyl]malonate (4): To a solution of $Pd(PPh_3)_4$ (25 mg, 1.5 mol-%) in THF (5 mL) was added a solution of **2a**/**2b** (95:5) (350 mg, 1.4 mmol) in THF (5 mL) under a nitrogen atmosphere. After stirring for 24 hours at 60 °C, the solution was cooled to room temperature and filtered over a path of celite. The solvent

was removed in vacuo and the residue was purified by flash chromatography on a silica gel column (eluent: petroleum ether/diethyl ether 9:1) affording 270 mg (78% yield) of compound **4** as a mixture of (*E*)/(*Z*) isomers. ^{1}H NMR: δ = 1.85 (m, 3 H), 3.08 (s, 1 H), 3.26 (s, 1 H), 3.66–3.70 (m, 6 H), 4.30–4.76 (m, 1 H), 4.93–5.23 (m, 1 H), 5.79 (m, 1 H), 6.17 (m, 2 H).

Acknowledgments

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[9] X-ray analysis of **2b**: A plate white monocrystal of $C_{14}H_{16}O_4$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.6 × 0.3 × 0.3 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo-*Kα* radiation. Cell constants and the orientation matrix for data collection were obtained from a least square refinement using setting angles of 30 reflections in the range θ = 1–26.42°, which corresponded to a monoclinic cell with dimensions: *a* = 6.0788(4), *b* = 14.0860(10), *c* = 15.0710(10) Å. For *Z* = 4 and *M* = 248.278, $\rho_{calcd.}$ = 1.294 g·cm^{-3}. The space group was determined to be $P2_1/c$ from the systemic absences. A total of 2428 reflections were collected at *T* = 298 K; CCDC-154408.

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