On the Evidence for Formation of an *exo*-π-Allyl Complex Intermediate in the Pd^0-Catalyzed Alkylation of a Bicyclic Allylic Diacetate

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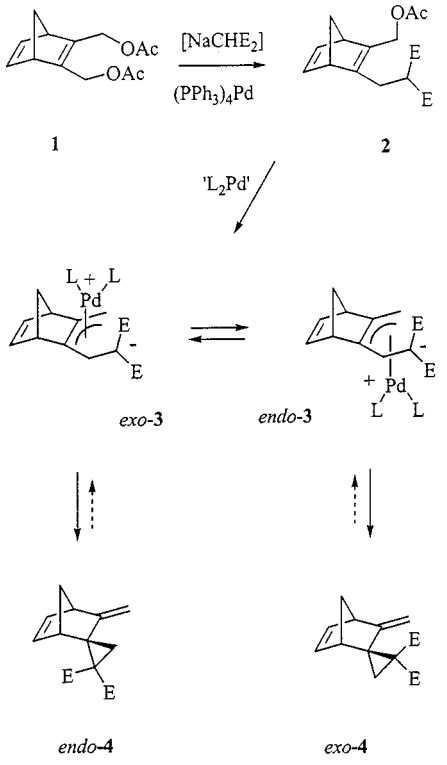
This article is a comment on the paper by G. Buono et al.[6a]

The elucidation of the relative or absolute stereochemistry[1] of reaction products and subsequent inferences on the mechanism or mechanisms of reaction is a fundamental tool in both modern and classical physical organic chemistry. The stereochemical intricacies of Pd-catalysed allylic alkylation[2] are now known to a sufficient extent that the products of such reactions can, in suitable cases, be studied to deduce the stereochemistry of π-allyl−Pd intermediates.[3] In most cases[4] Pd-catalysed allylic alkylation proceeds via an inversion−inversion sequence, resulting in overall retention of stereochemistry.[5] The last half of this overall sequence, involving nucleophilic attack *anti* to the palladium in the π-allyl complex, was recently employed by Buono et al.,[6] to probe the stereochemistry of the Pd-catalysed reaction of bis-allylic diacetate **1** with the sodium salt of dimethyl malonate ($[NaCH(CO_2Me)_2]$ = $NaCHE_2$) which gives spirocyclopropane **4** via the isolable monoalkylated intermediate (*rac*)-**2** − Scheme 1. Internal nucleophilic attack in the zwitterionic π-allyl-Pd intermediates *exo*-**3** and *endo*-**3**, derived from **2**, leads to the spirocyclopropanes *endo*-**4** and *exo*-**4** respectively.



Scheme 1. Reaction pathways for conversion of **1** to *exo*- and *endo*-**4** involving Pd-mediated ionisation of intermediate **2** to generate *exo*- and *endo*-π-allyl Pd intermediates *exo*-**3** and *endo*-**3**

It was found (Table 1 in reference[6a]) that reaction of **1** with $NaCHE_2$ at room temperature in THF in the presence of 1.5 mol-% $(PPh_3P)_4Pd$ gives a 95:5 ratio of isomers of **4** (93% yield). Analogous reaction at 65 °C reduced the selectivity and a 60:40 ratio of isomers of **4** is obtained in 75% yield. Buono et al. suggested that the structure of the major product (95%) obtained at room temperature allows the determination of the configuration of the *preferred* π-allyl−Pd intermediate (*exo*-**3** versus *endo*-**3**). The identity and structures of spirocyclopropanes *exo*-**4** and *endo*-**4** were 'confirmed by COSY and NOESY NMR experiments'. The major isomer was assigned as *endo*-**4**. As evidence, the NOESY spectrum of the 95:5 mixture of isomers of **4** was presented (Figure 1).

Two sets of correlations in the NOESY are emphasised by the authors; set *i*: between signals assigned as norbornene alkenyl protons H_3,H_4 (isochronous) and two singlets[7] assigned as the methylene protons H_6 (δ = 3.3) and H_7 (δ = 3.1); set *ii*: between the latter two protons and one of the cyclopropyl protons (H_{10}). These cross-peaks are suggested to correspond to NOE contacts[8] that would confirm the relative stereochemistry of the major isomer as *endo*-**4**. These contacts are represented in structure **I** in Figure 2. It is surprising that the authors made no comments about the near identical cross-peak intensity in correlations between H_3, H_4, and H_7 versus H_3,H_4, and H_6 and also between H_6 and H_{10} versus H_7 and H_{10}.

However, it was later suggested to the authors that the two singlets at δ = 3.1 and 3.3 are not the methylene[9] protons but are the two allylic methine protons[10] (which were not shown in the structure accompanying the NOESY spectrum). Although this revised[6b] assignment (**II**) is now consistent with the two points raised above regarding the similar intensities of NOESY cross peaks in sets *i* and *ii*,

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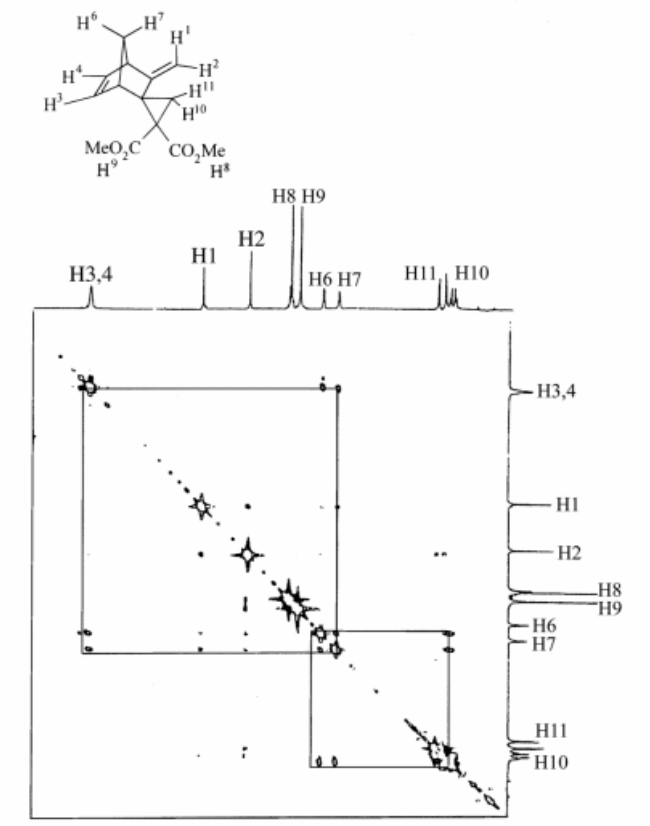
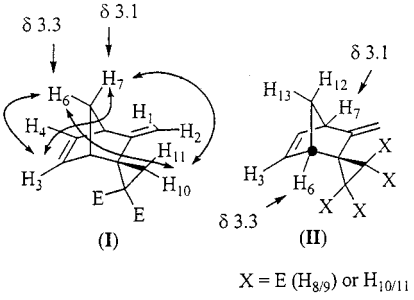


Figure 1. Original NOESY spectrum and assignment of a 95:5 mixture of isomers of **4** from reference [6]



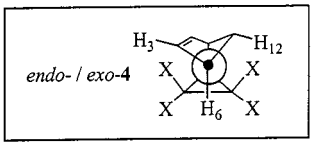


Figure 2. Old (**I**; reference [6a]) and new (**II**; reference [6b]) assignment of H_6 and H_7 signals at $\delta = 3.30$ and 3.10 and corresponding 'NOE contacts' in **I**. Inset: Newman projection indicating that *exo*-**4** could be distinguished from *endo*-**4** if NOE contacts are observed between H_{12} or H_3 and any proton on the cyclopropane ring (H_{10} or H_{11}) or on the methyl groups of the malonate ($3 \times H_8$ and $3 \times H_9$). Note that in Figure 1 (taken from Figure 2, reference [6a]), no such contacts are evident.

we are now left with the methylene protons unassigned. Inspection of the ^{1}H NMR spectroscopic data presented in the Experimental Section,[11] suggests that the *AB* spin system at δ ca. 1.5 (originally labelled as H_{10}) corresponds to H_{12},H_{13}, whilst the *AB* spin system at δ ca. 1.8 corresponds to H_{10},H_{11} (originally labelled as H_{11}). Consequently, since no correlations are evident between either H_3 or H_{12} and $H_{10/11}$ or $H_{8/9}$ (see Figure 1), no conclusions can be drawn regarding the relative stereochemistry of **4** (see Newman projection in the inset to Figure 2).

However, even if the stereochemistry of the major product had been satisfactorily assigned, what could we determine about which intermediate (*exo*/*endo*-**3**) is *preferred*? Much is made of the observation that increased temperature (65 °C) leads to a larger amount (40%) of the minor isomer. According to the authors, 'this may only result from an interconversion between the two (π-allyl)palladium complexes' and mechanisms were suggested for facilitation of the interconversion. However, there are a number of selectivity issues that are not discussed. There is a) the diastereofacial selectivity in the initial complexation and ionisation of **2** to give *exo*- or *endo*-**3**, b) the rate at which *exo*- and *endo*-**3** interconvert versus the rate of intramolecular nucleophilic attack to give *exo*- and *endo*-**4**, c) which isomer of **3** is the most reactive and d) whether *exo*- and *endo*-**4** may be interconverted via Pd-catalysed ionisation.[12] For such a complex series of serial and parallel selectivity issues, identification of preferred intermediates (**3**) by analysis of product ratios (**4**) from two experiments is, at best, speculative.

For example, the high selectivity (95:5) attained at ambient temperature could arise from face-selective ionisation of **2** with no equilibration of **3** (as the authors assume to be the case) or from selective trapping of one isomer of **3** under Curtin−Hammet conditions, in which case this isomer of **3** may or may not be the most favoured, i.e. stable. Lower selectivity (60:40) at higher temperature could arise from reduced facial selectivity in ionisation of **2**, or faster equilibration of **3**, or reduced selectivity on capture of **3**, or equilibration of **4**.

In summary, we suggest that the only evidence the authors have for the 'Formation of an *exo*-π-Allyl Complex Intermediate in the Pd^0-Catalyzed Alkylation of a Bicyclic Allylic Diacetate' is that a *mixture* of isomers of **4** is obtained.

Acknowledgments

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[1] E. L. Eliel., S. H. Wilen, L. N. Mander, *The Stereochemistry of Organic Compounds*, John Wiley and Sons, Chichester, UK, **1994**.

[2] J. Tsuji, *Palladium Reagents and Catalysts*; John Wiley: Chichester, **1995**.

[3] Reveiws: G. Consiglio, R. M.Waymouth, *Chem. Rev.* **1989**, *89*, 257−276; C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089 −1112; B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395−422.

[4] For substrates and nucleofuges that behave differently see: [4a] I. Starý, P. Kočovský, *J. Am. Chem. Soc.* **1989**, *111*, 4981−4982. − [4b] H. Kurosawa, S. Ogoshi, Y. Kawasaki, S. Murai, M. Miyoshi, I. Ikeda, *J. Am. Chem. Soc.* **1990**, *112*, 2813−2814. − [4c] I. Starý, J. Zajíček, P. Kočovský, *Tetrahedron* **1992**, *48*, 7229−7250. − [4d] H. Kurosawa, H. Kajimaru, S. Ogoshi, H. Yoneda, K. Miki, N. Kasai, S. Murai, I. Ikeda, *J. Am. Chem. Soc.* **1992**, *114*, 8417−8424. − [4e] C. N. Farthing,

P. Kočovský, *J. Am. Chem. Soc.* **1998**, *120*, 6661−6672. − [4f] M. E. Krafft, A. M. Wilson, Z. Fu, M. J. Proctor, O. A. Dasse, *J. Org. Chem.* **1998**, *63*, 1748−1749.

[5] J. C. Fiaud, J.-Y. Legros, *J. Org. Chem.* **1987**, *52*, 1907−1911.

[6] [6a] J. M. Brunel, M. Maffei, G. Muchow, G. Buono, *Eur. J. Org. Chem.* **2000**, 1799−1803. − [6b] Personal communication. Note from editor: see also following response to this correspondence. J. M. Brunel, M. Maffei, G. Muchow, G. Buono, *Eur. J. Org. Chem.* **2001**, 1009−1012.

[7] Note that an *AB* spin system ($^2J_{HH}$) would be expected (as is observed at δ ca. 1.5) rather than two singlets.

[8] It should be noted that in 2D NOESY spectra, correlations can arise from scalar coupling and chemical exchange as well as NOE contacts. A phase-sensitive variant (often referred to as PNOSY) can distinguish these. T. D. W. Claridge, *High-Resolution NMR Techniques in Organic Chemistry*, Pergamon, Elsevier Science, Oxford, **1999**.

[9] In norbornyl systems this methylene group usually appears at high field; cf: δ ca. 1.2 in norbornane, 2.0 in norbornadiene, 1.32 and 1.03 in norbornene: H. Günther, in: *NMR spectroscopy*, Second edition, John Wiley and Sons, Chichester, UK, **1995**.

[10] The high chemical shift of the protons H_6 and H_7 immediately suggests an adjacent C=C (i.e. allylic) or heteroatom. Given that 2D NMR techniques were employed (e.g. NOESY) it is surprising that a direct ($^1J_{CH}$) correlation sequence (e.g. 'C,H COSY', 'HETCOR' etc.) was not also performed. This would have clearly indicated that H_6 and H_7 were not attached to the same carbon and thus could not be methylene protons.

[11] ^{1}H NMR (200 MHz, $CDCl_3$) data from reference [6a]: major isomer; 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); minor isomer: 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). We suggest that in the major isomer "1.84 (dd, 2 H, J = 34.7, J = 5.1 Hz)" is the AB system δ_A = 1.93, δ_B =1.75, J_{AB} = 5 Hz, corresponding to H_{10} and H_{11}. Analogously for the minor isomer, δ_A = 1.83, δ_B =1.69, J_{AB} = 5 Hz.

[12] 1,1-Diactivatated vinylcyclopropanes, of which **4** is an example, are known to undergo Pd^0-catalysed ring opening. For early examples of this see: [12a] K. Burgess, *Tetrahedron Lett.* **1985**, *26*, 3049−3052. − [12b] I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1985**, *26*, 3825−3828.

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