Structural and Mechanistic Studies on the Activation and Propagation of a Cationic Allylpalladium Procatalyst in 1,6-Diene Cycloisomerization

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Abstract: $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ acts as an efficient procatalyst for the cycloisomerisation of dimethyl hept-1,6-dienyl-4,4-dicarboxylate (**1a**) in $CHCl_3$. The reaction displays a pronounced and variable induction period and gives dimethyl 3-methylene-4-methylcyclopentane-1,1-dicarboxylate (**2a**) as the kinetic product. The thermodynamically more favourable tri- and tetra-substituted alkenes dimethyl 3,4-dimethylcylopent-2-ene-1,1-dicarboxylate (**3a**) and dimethyl 3,4-dimethylcylopent-3-ene-1,1-dicarboxylate (**4a**) are also generated directly (**3a**) or by isomerisation (**3a** and **4a**) of **2a**. The mechanism of procatalyst activation and the ensuing cycloisomerisation reaction was investigated by NMR spectroscopy (^1H, ^2H, ^{13}C) and GC analysis of the products arising from isotopically labelled substrates (^{13}C, ^2H). Three general mechanisms were considered: hydrometallation, cyclometallation and C–H insertion. These last two were shown to be incompatible with the results. The first, which involves generation and propagation of a palladium hydride species ("Pd–H"), was found to be consistent with both the isotopic distribution and stereochemistry of the reaction product and is supported by the observation of intermolecular transfer of a single ^2H label. Due to the high catalytic activity of the palladium hydride and its slow generation, the cycloisomerisation process ultimately yields a mixture of alkene products (**2a**, **3a** and **4a**) with incomplete consumption of the procatalyst $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. The mechanism by which the catalytically active palladium hydride is generated from the procatalyst was studied in detail by NMR spectroscopic analysis of stoichiometric reactions between diene **1a** and $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. This demonstrated that a carbopalladated complex, namely, $[Pd\{7,7\text{-}(CO_2Me)_2\text{-}(1,2,5,9,10\text{-}\eta^5)\text{-dec-1,9-diene}\}(OTf)]$ (**15a**), is formed in small quantities by unfavourable displacement of acetonitrile by the diene, followed by a rapid and irreversible β-migratory insertion reaction. Although attempts to isolate **15a** from the reaction mixture were not successful (due to its slow decomposition, low concentration and competing cycloisomerisation), an alternative synthesis in the absence of acetonitrile allowed its isolation and characterisation. However, pure samples of **15a** are completely ineffective as a procatalyst system for cycloisomerisation of **1a**. Further investigation revealed that treatment of **15a** with one equivalent of water results in quantitative β-H elimination to generate triene **16a** (C(1)-allylated **1a**). Thus, addition of catalytic quantities of water to a solution of **1a** in $CHCl_3$ containing 5 mol% **15a** and 10 mol% MeCN results in generation of an active "Pd–H" catalyst for cycloisomerisation. Although procatalyst activation is facilitated by traces of water, no exchange of protons is observed between "Pd–H" and H_2O under catalytic turnover. The slow generation of **15a** and the requirement for traces of water for β-H elimination accounts for variability in the induction period when $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ is employed as procatalyst.

Keywords: cyclization · dienes · isotopic labeling · palladium

Introduction

Cycloisomerisation of dienes, enynes and diynes is a powerful method for the synthesis of carbocyclic and heterocyclic rings with regio- and stereocontrol.[1] A variety of transition metal complexes have been reported to catalyse cycloisomerisation of 1,6-dienes. The earliest examples include the Rh-catalysed cycloisomerisation of diallyl ether[2] and diallylacrylamide,[3] and 4,4-disubstituted hepta-1,6-dienes;[4] the last-named substrate also undergoes Pd catalysis.[5, 6] Early transition metal and lanthanide complexes also proved suitable.[7] The control of regioselectivity, first demonstrated by Grigg et al.[4, 5, 6] in the reactions of **1b** (Scheme 1), has been the focus of much recent attention. A range of ruthenium catalysts were reported by Itoh et al.,[8] all of which cycloisomerise **1a** exclusively to the *exo*-methylene isomer **2a**. RajanBabu and Radetich[9] developed [M(L)(allyl)(S)]X (L = triarylphosphane, M = Ni, S = solvent, X = OTf) as catalysts for selective

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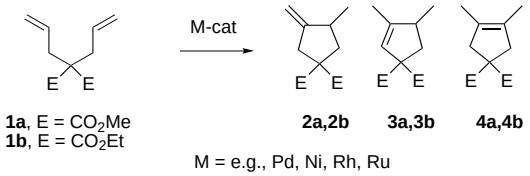

Scheme 1. Transition metal catalysed cycloisomerisation of the 1,6-diene **1** to cyclopentenes **2**, **3** and **4**.

generation of **2a**, while Widenhoefer et al. reported similar catalysts (L = tri(sec-alkyl)lphosphane, M = Pd, S = Et_2O, X = BF_4) for highly selective cycloisomerisation to **4a** in the presence of stoichiometric amounts of trialkylsilane.[11a] Perhaps one of the most challenging aspects of such cycloisomerisation reactions is control of both regio- and stereoselectivity, and by using 4,4′-dibenzylbisoxazoline or sparteine as an enantiomerically pure N,N ligand, Heumann and Moukhliss[12a] achieved promising enantioselectivity in the cycloisomerisation of **1b**. For example, with $[Pd(MeCN)_4](BF_4)_2$/sparteine as a procatalyst system, **2b** is obtained with 37% *ee* and **3b** with 60% *ee* (**2b**/**3b** 17:83, overall yield 46%). Somewhat related are recent results of Widenhoefer et al.,[11] in which chiral N,N ligands gave up to 91% *ee* in the Pd-catalysed cyclisation/hydrosilylation and 38% *ee* in the reductive cyclisation (Et_3SiH, H_2O) of **1a**.

Recent advances in the regioselective[8, 9, 11, 12] and enantioselective[11f, 12a] cycloisomerisation of **1** thus provide a benchmark system for testing and comparing novel ligands. Furthermore, cycloisomerisation is not always desirable; for example, it was recently reported to be a serious competing side reaction (43%) in an Ru-catalysed ring-closing metathesis of *N*-tosyldiallylamine.[13] Changing the counterion of the catalyst[9] completely suppressed the cycloisomerisation.

A knowledge of the mechanism would be an essential first step in the rational design of ligands and in understanding how subtle changes in catalyst cause such dramatic changes in reaction products.[13] Here we describe a study on the mechanism of cycloisomerisation of **1a** to **2a** with [Pd(η^3-C_3H_5)$(MeCN)_2$]OTf as procatalyst. The mechanistic sequence in which the procatalyst is activated and subsequently catalyses cycloisomerisation was elucidated by detailed NMR spectroscopic analysis of stoichiometric and catalytic reactions with symmetrically and unsymmetrically labelled (^2H and ^{13}C) substrates.[14, 15]

Results and Discussion

Characteristics of the cycloisomerisation reaction of 1a with a Pd-allyl cation procatalyst: In parallel with ongoing studies on the regioselectivity of "[PdCl$(MeCN)_3]^+$"-catalysed cycloisomerisation of **1a**,[16] we sought a chloride-free cationic Pd catalyst,[12a] and tested the Pd–allyl complex[17] [Pd(η^3-C_3H_5)$(MeCN)_2$]OTf.[18] After performing some exploratory experiments,[19] we found that 5 mol% of this complex provides a reasonably active system for cycloisomerisation of **1a** in $CHCl_3$ at 40 °C. Under these conditions, 85% or more of **1a** was consumed within 3–5 h, "Pd black" was co-generated throughout and the reaction displayed a variable induction period, occasionally quite pronounced (see Figure 1), but usually on the order of 5–10 min. During the first stages of reaction (up to ca. 50% conversion of **1a**) the predominant product (>80%) was the exocyclic alkene **2a**, while in the latter stages of reaction, **3a** and **4a** became more

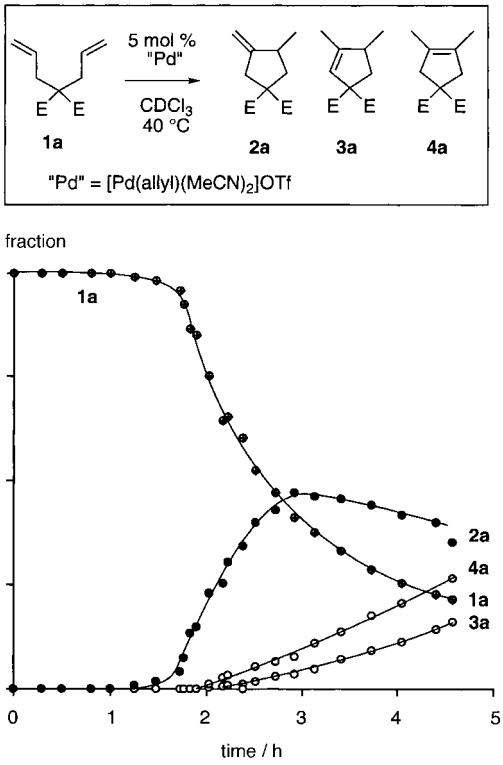

Figure 1. An evolution profile (with a pronounced induction period) for the Pd-catalysed cycloisomerisation of a 0.125 M solution of **1a** to **2a**, **3a** and **4a** with 5 mol% [Pd(η^3-C_3H_5)$(MeCN)_2$]OTf in $CDCl_3$ at 40 °C, as determined by in situ ^1H NMR analysis. The reaction was performed in a septum-sealed 5 mm NMR tube spinning (15–20 Hz) in the probe of the spectrometer at 40 ± 0.5 °C. Note that the lines merely serve as guide to the eye.

prominent.[20] ^{13}C NMR spectroscopic analysis of the reaction mixture after addition of ^{13}C-labelled exocyclic alkene **2a** to a Pd-catalysed cycloisomerisation of **1a** during turnover confirmed that both **3a** and **4a** are generated by isomerisation of **2a**.[21] However, exposure of pure **2a** to 5 mol% [Pd(η^3-C_3H_5)$(MeCN)_2$]OTf in $CDCl_3$ at 60 °C for 25 h resulted in no isomerisation. On addition of a catalytic quantity of $E_2CHCH_2CH{=}CH_2$, quantitative Pd-catalysed isomerisation of **2a** to a 23:77 **3a**/**4a** mixture occurred over 24 h.

These results can be interpreted as follows: [Pd(η^3-C_3H_5)$(MeCN)_2$]OTf is not the active catalyst for cycloisomerisation of **1a** or for isomerisation of **2a** to **3a**/**4a**. Rather, it is a procatalyst that is slowly converted to a short-lived active catalyst during the reaction (Scheme 2). This activation process is the reason for the induction period and requires the presence of a mono-substituted alkene. Initially, the active catalyst cycloisomerises **1a** to **2a** and slowly isomerises **2a** to **3a**/**4a**. However, material balance indicates that in the latter stages of reaction, **3a** is increasingly generated directly from **1a** rather than via **2a**. This phenomenon was linked to the

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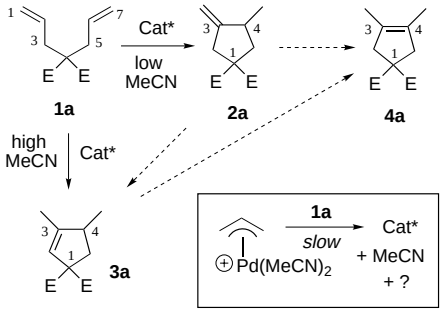
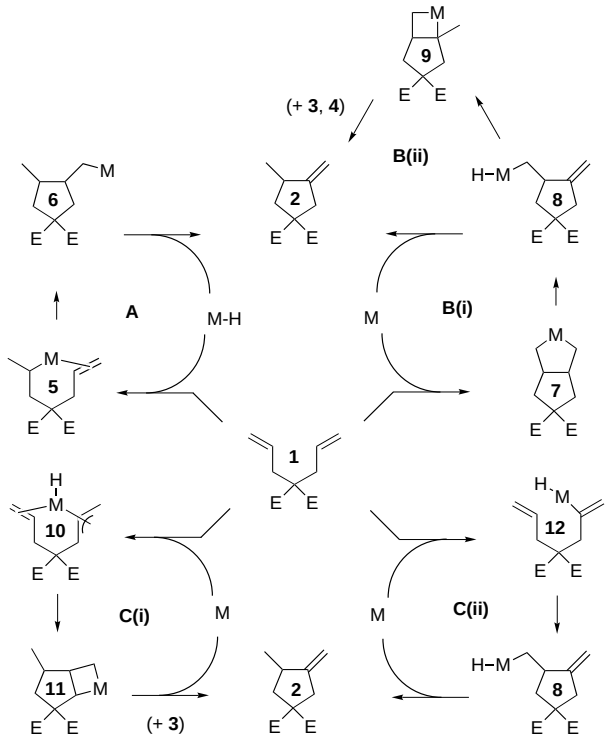


Scheme 2. Generalised mode of action of a Pd–allyl procatalyst for cycloisomerisation of the 1,6-diene **1** to cyclopentenes **2**, **3** and **4**.

presence of free MeCN, the amount of which increases throughout the reaction due to the slow conversion of [Pd(η^3-C_3H_5)(MeCN)$_2$]OTf to Pd black. Thus, in $CDCl_3$/MeCN (1:1) the rate of cycloisomerisation was reduced (47%, 24 h, 60 °C) but **3a** was almost the exclusive product. The variable length of the induction period indicates the importance of the presence or absence of another component whose concentration must vary from run to run. Furthermore, the activation process presumably generates a co-product (see inset of Scheme 2). At this point, neither of these species had been identified.

With these features in mind, we focused on elucidating: a) the identity of the active catalyst; b) the mechanism by which it cycloisomerises **1a** to **2a**; c) the mechanism of the catalyst activation steps and d) the identity of the components which control catalyst activation.

Cycloisomerisation mechanisms: Evidently, as the ligand and metal catalyst are varied, the mechanism by which transition metal catalysts cycloisomerise **1** into **2**, **3** and **4** will change. However, in addition to the preliminary studies by Grigg et al. in 1984,[6] there has only been one detailed investigation.[11b] Nonetheless, by additional consideration of related intermolecular processes,[22] at least five mechanisms can be postulated for Ru-, Rh-, Ni- and Pd-catalysed cycloisomerisation of **1**.[6, 8, 9, 10] The mechanisms can be grouped into three classes (Scheme 3), which we term metallohydride (**A**), cyclometallation (**B**) and C–H insertion (**C**). The metallohydride mechanism (**A**)[22b] requires the generation and intermolecular propagation of a hydride complex (M–H).[23] Thus, hydrometallation of **1** generates alkylmetal complex **5**, and subsequent intramolecular carbometallation facilitates β-H elimination in **6** to generate **2** and regenerate the M–H catalyst. Mechanism **B** proceeds by a [2 + 2 + 1] cyclometallation[22c] to give metallacyclopentane **7**. In its simplest form, **B**(**i**), the cycle is completed by β-H elimination and then reductive elimination from alkylmetal hydride **8** to give **2**. A sub-cycle **B**(**ii**) involves intramolecular hydrometallation in **8** to give metallacyclobutane **9**.[6, 22f] The mechanism is completed by β-H elimination and then reductive elimination from an alkylmetal hydride (R-M-H, not shown) to give **2** (and **3** or **4** by alternative β-H eliminations). In contrast, mechanism **C** involves an oxidative C–H insertion at the allylic [**C**(**i**)][6] or vinylic [**C**(**ii**)][22a] positions of **1** to give **10** or **12**, respectively. In mechanism **C**(**i**), hydrometallation of the terminal alkene

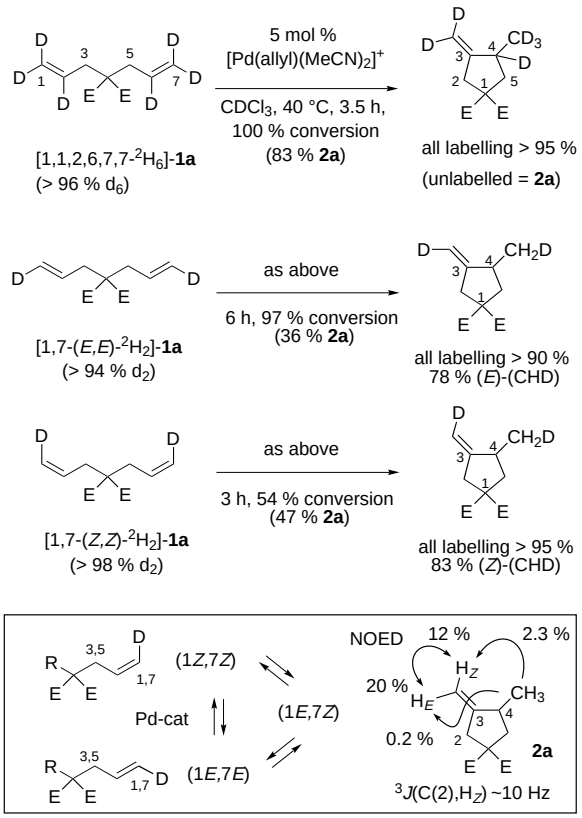


Scheme 3. Mechanisms for transition metal catalysed cycloisomerisation of **1** to **2**, taken or adapted from the literature (see text for details).

through the central allylic carbon atom generates metallacyclobutane **11**.[6] This mechanism is completed by β-H elimination and reductive elimination, in direct analogy to **9** in mechanism **B**(**ii**), to give **2** (or **3**). In mechanism **C**(**ii**), vinylmetal hydride **12** undergoes intramolecular hydrometallation to give **8**, and reductive elimination completes the cycle. In mechanisms **A**, **B**(**i**) and **C**(**ii**), isomeric products **3** or **4** are proposed to arise from metal-catalysed isomerisation of the initially generated products (**2** or **3**).

Catalytic reactions with isotopically labelled diallyl malonate substrates: To track the origin and destination of hydride migrations in the cycloisomerisation of **1a** (0.06 ± 0.02 mM) with catalysis by 5 mol% [Pd(η^3-C_3H_5)(MeCN)$_2$]OTf in $CDCl_3$ at 40 °C, we employed isotopically labelled substrates.[15] Reaction samples were taken at regular intervals, quenched (silica gel) and analysed by GC and NMR spectroscopy (^{1}H, ^{2}H and ^{13}C). The ^{13}C NMR analyses were aided by CH correlation and DEPT where appropriate. Since this part of the study aimed to elucidate the mechanism of the cycloisomerisation itself, we focused on analysis of labelling patterns in both the unconverted starting material **1a** and the primary and kinetic cycloisomerisation product **2a**, irreversibly formed from **1a** and subsequently isomerised to the thermodynamic products **3a** and **4a**.

Symmetrically deuterated substrates: The simplest results were obtained with [1,1,2,6,7,7-$^2H_6$]-**1a** (Scheme 4, top). During the reaction there was no evidence for ^{1}H incorporation in the vinylic (CD=CD_2) units, nor for ^{2}H incorporation at the allylic methylene [C(3,5)] groups of **1a**. In the primary cycloisomer-



Scheme 4. Isotopic distributions (deduced from ^{1}H, ^{2}H and ^{13}C NMR data) of the kinetic product **2a** arising from Pd-catalysed cycloisomerisation of [1,1,2,6,7,7-$^2H_6$]-**1a**, [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** in $CDCl_3$. Inset: left: Pd-catalysed *E*/*Z* isomerisation of labelled substrate **1a**; right: ^{1}H NMR NOE difference (NOED, 500 MHz) and ^3J(H,H) coupling allow assignment of *E* ($\delta = 4.9$) and *Z* ($\delta = 4.8$) isomers of C(3)=CH_2 in **2a**.

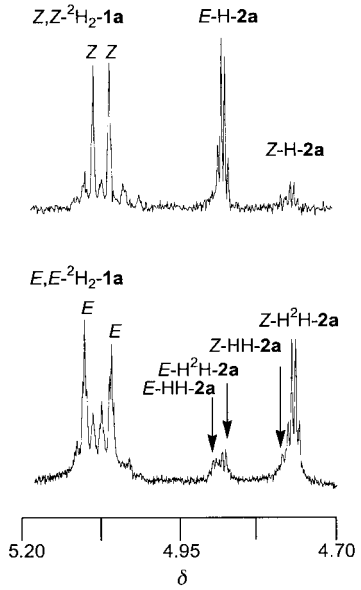
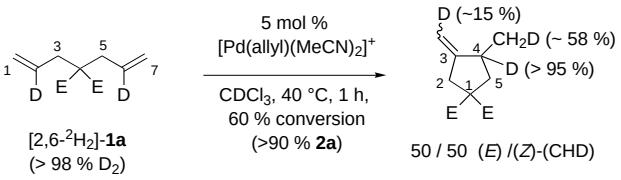
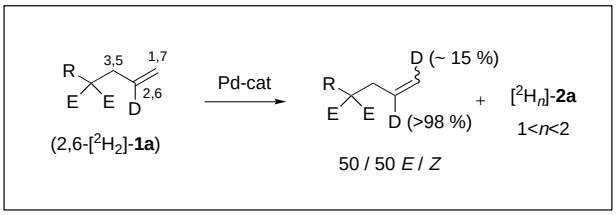


Figure 2. ^{1}H NMR spectra of samples taken from Pd-catalysed cycloisomerisation reactions of [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** demonstrating that ^{2}H-label geometry of the substrate determines that in the product **2a**. During the reaction, the substrates are observed to isomerise. Note that there is (initially) a higher degree of ^{2}H incorporation in [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** (> 98 % D_2) as opposed to [1,7-(*E*,*E*)-$^2H_2$]-**1a** (ca. 94 % D_2) and that analysis of C(3)=CH_2 peaks in the ^{1}H NMR spectra (which are isotopically shifted downfield from C(3)=CHD) confirm that, although there is near complete substrate isomerisation (equilibration of *E* and *Z* ^{2}H) during the reactions, very little ^{1}H and ^{2}H exchange occurs.





Scheme 5. Isotopic distributions (deduced from ^{1}H, ^{2}H and ^{13}C NMR data) of kinetic product **2a** arising from Pd-catalysed cycloisomerisation of [2,6-$^2H_2$]-**1a**. Inset: Pd-catalysed terminal ^{2}H labelling of substrate **1a**.

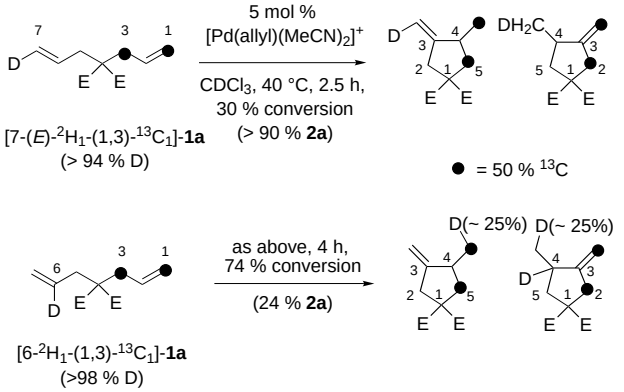
isation product **2a**, both of the ring methylene groups [i.e., C(2) and C(5)] were exclusively CH_2 (^{1}H, ^{2}H NMR), and the absence of observable ^3J(H,H) coupling of C(5)H_2 to the methine unit at C(4) confirmed that, in addition to the methylene (C(3)=CD_2) and the C(4) methyl group (CD_3), this site was greater than 95 % deuterated.[24]

Reactions of [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** gave complimentary results (Scheme 4, bottom; Figure 2). During the reactions, the initially geometrically pure substrates were slowly isomerised[25] (see signals at $\delta \approx 5.1$ in Figure 2). However, reaction did not proceed with perfect retention of geometric identity, since in both cases geometric methylene isomers C(3)=CHD (ca. 87:13) were evident in the kinetic product [$^2H_2$]-**2a** immediately after the start of reaction and before isomerisation of [1,7-$^2H_2$]-**1a** became noticable. This ratio reduced slowly to about 78:22 in the latter stages of reaction as equilibration of the substrate became more complete (Scheme 4, inset).[26] With both substrates, the C(4) methyl group of the kinetic product [$^2H_2$]-**2a** is greater than 95 % monodeuterated (i.e., CH_2D), as evidenced by a clean triplet in the ^{13}C{^{1}H} NMR spectrum and by integration against C(2)H_2 in the ^{1}H NMR spectrum.

Very different results were obtained with the internally deuterated isomer [2,6-$^2H_2$]-**1a** (Scheme 5). During the reaction, partial deuterium incorporation at C(1) and C(7) in the substrate was observed (^{2}H NMR), although there was no evidence for exchange of ^{2}H at C(2,6), that is, the [^2H_n]-substrate ($n > 2$) was being generated (see inset to Scheme 5). At 60 % conversion there was about 15 % deuteration of the substrate at C(1,7), while the primary product **2a** was incompletely monodeuterated[27] at the C(4) methyl group (ca. 58 % CH_2D) and essentially completely deuterated at C(4) (> 95 % C(4)−D).[28] Furthermore, partial *E*/*Z* incorporation of ^{2}H (ca. 15 %) in the C(3) methylene group of the primary product was evident from the isotopically shifted triplets[28] at $\delta = 4.8$ and 4.9 (i.e., (*Z*)- and (*E*)-C(3)=CHD) in the ^{1}H NMR spectrum. This degree of incorporation grew to about 25 % upon complete consumption of the substrate.

0947-6539/01/0719-4208 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 19

Isotopically unsymmetrical substrates: The symmetry of **1a** complicates analysis of hydride migrations on cycloisomerisation to **2a**. Consequently, we deployed two isotopically unsymmetrical[14] substrates [7-(*E*)-$^2H_1$-(1,3)-$^{13}C_1$]-**1a** and [6-$^2H_1$-(1,3)-$^{13}C_1$]-**1a**)[15] in which one allyl chain is ^{13}C-labelled to distinguish it from the other, which bears a ^2H atom (Scheme 6). The 25-fold greater intensity of ^{13}C signals arising

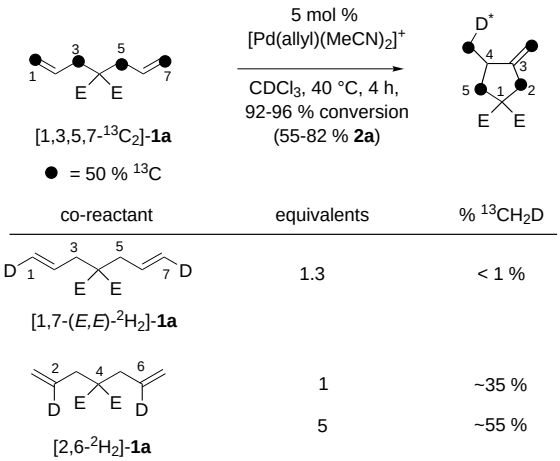


Scheme 6. Isotopic distributions (deduced from ^1H, ^2H and ^{13}C NMR data) of kinetic product **2a** arising from Pd-catalysed cycloisomerisation of [7-(*E*)-$^2H_1$-(1,3)-$^{13}C_1$]-**1a** and [6-$^2H_1$-(1,3)-$^{13}C_1$]-**1a**. Note that analysis is based predominantly on ^{13}C NMR signals arising from labelled carbon atoms.

from the four labelled carbon atoms in **2a** made ^{13}C NMR analysis of ^2H transfer (inter- or intramolecular) from the ^2H-labelled allyl chain very evident. In the primary reaction product from [7-(*E*)-$^2H_1$-(1,3)-$^{13}C_1$]-**1a**, there was essentially no ^2H incorporation ($\leq$3%) at the labelled carbon atoms (Scheme 6, top; the ^{13}C NMR signals were singlets). Although ^2H NMR spectroscopy was not able to distinguish ^2H bound to ^{12}C versus ^{13}C, consistent with earlier experiments, the monodeuterated methylene carbon atom (C(3)=CHD) of **2a** had predominantly *E* geometry. This site was of equal ^2H population to the C(4) methyl (CH_2D) group.

In contrast, in the primary product from [6-$^2H_1$-(1,3)-$^{13}C_1$]-**1a**, the partial transfer of a single ^2H atom to the ^{13}C-labelled allyl chain was evident from the isotopically shifted triplet arising from C(4)–$^{13}CH_2D$ (ca. 25% ^2H; Scheme 6, bottom)[29] in the ^{13}C NMR spectrum. There was also a trace of ^2H incorporation (<5%) at the labelled methylene group C(3)=$^{13}CH_2$, but not at the other ^{13}C-labelled sites ($C(2)H_2$ and $C(5)H_2$). Examination of the ^{13}C satellites (25% abundance) of the methylene protons in the ^1H NMR spectrum of **2a** (i.e., C(3)=$^{13}CH_2$) indicated that when this was ^{13}C-labelled, C(4) was fully deuterated (triplets and not quartets were observed). Furthermore, analysis of the C–H uncoupled methylene protons (75% abundance) indicated that when C(5) or the methyl group on C(4) is ^{13}C-labelled, C(4) is not deuterated.[30]

Crossover experiments: To test for intermolecular ^2H transfer, in separate experiments, doubly ^{13}C-labelled [1,3,5,7-$^{13}C_2$]-**1a** was mixed with symmetrically dideuterated substrates [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [2,6-$^2H_2$]-**1a** (Scheme 7). The ^{13}C NMR analysis of the primary product from the co-reaction of [1,3,5,7-$^{13}C_2$]-**1a** and [1,7-(*E*,*E*)-$^2H_2$]-**1a** (1:1.3



Scheme 7. ^2H distributions in [$^{13}C_2$-**2a**] arising from co-cycloisomerisation of mixtures of [1,3,5,7-$^{13}C_2$]-**1a** with [1,7-(*E*,*E*)-$^2H_2$]-**1a** (top) and with [2,6-$^2H_2$]-**1a** (bottom), as deduced by ^{13}C NMR analysis (see text for details).

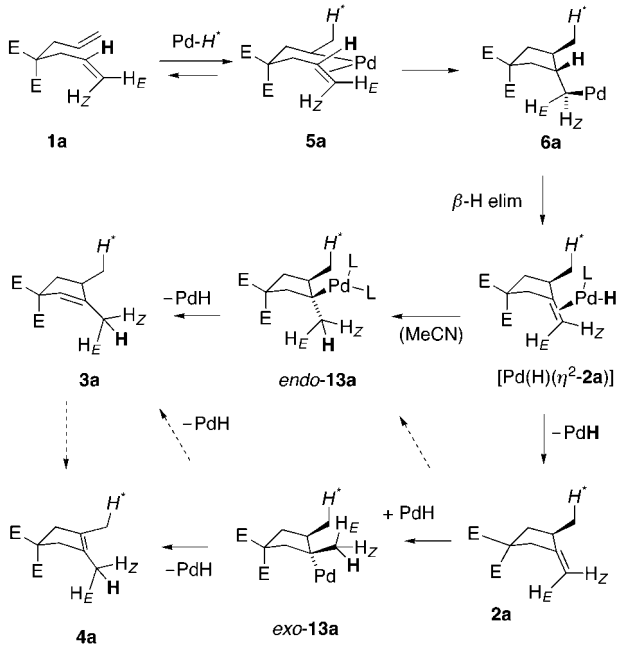
ratio) indicated that no ^2H transfer to the ^{13}C-labelled framework of **2a** had occurred, since no $^1J(C,^2H)$ triplets were observed (only doublets)[31] and none of the $^1J(C,H)$ satellites in the ^1H NMR spectrum showed any evidence of deuteration (isotope shifts or loss of coupling) at C(4). The deuterated non-^{13}C-labelled primary product was obtained as about 75% of the (*E*)-(CHD) isomer (as in Scheme 4, middle).

In contrast, co-reaction of [1,3,5,7-$^{13}C_2$]-**1a** with [2,6-$^2H_2$]-**1a** (in 1:1 or 1:5 ratio; Scheme 7) showed clean partial transfer of a single ^2H atom to the methyl group on C(4) in the ^{13}C-labelled product (triple doublet). The methylene carbon atom attached to C(3) displayed about 8% deuterium incorporation, and both other labelled carbon atoms [C(2) and C(5)] gave doublets[31] with no evidence for partial ^2H incorporation. A combination of double ^{13}C labelling and ^2H isotope shifts allows distinction of the partially deuterated methyl group at C(4) of **2a** that arises from [1,3,5,7-$^{13}C_2$]-**1a** as opposed to that which arises from non-^{13}C-labelled [2,6-$^2H_2$]-**1a** by analysis of the C(5) signal in the ^{13}C NMR spectrum.[32] For example, in the product mixture obtained from a 5:1 mixture of [2,6-$^2H_2$]-**1a** and [1,3,5,7-$^{13}C_2$]-**1a**, NMR analysis of C(5) in **2a** indicates that identical (ca. 55%) ^2H transfer had occurred to C(4) methyl group in both ^{13}C-labelled and unlabelled products, with generation of 8% or less of C(4)–CHD_2 or –CD_3 isomers. Importantly, the extent of intermolecular ^2H transfer from [2,6-$^2H_2$]-**1a** to [1,3,5,7-$^{13}C_2$]-**1a** to generate C(4)–$^{13}CH_2D$ in **2a** is significantly higher (55 vs <5%) than the degree of deuteration at C(3)=$^{13}CH_2$ and very similar to that of 58% observed with pure [2,6-$^2H_2$]-**1a** (see Scheme 5). This indicates that a single ^2H atom is transferred intermolecularly from C(2,6) to C(1,7) in **1a** during the cycloisomerisation, in addition to the incorporation of ^2H through pre-equilibration (Scheme 5, inset).

Mechanism of the cycloisomerisation of 1a to 2a: Consideration of the key hydride migrations and stereochemical features of postulated pathways **A**, **B** and **C** for cycloisomerisation of **1a** (Scheme 3) allows all but **A** to be eliminated.

Cyclometallation pathway **B(i)** is intramolecular and does not account for intermolecular and single transfer of a ^{2}H label from C(2,6) in **1a** to C(1,7), which becomes the methyl group at C(4) in **2a** (Scheme 7, bottom). Cyclometallation pathway **B(ii)** requires that when C(6) in **1a** becomes C(3) in **2a**, the hydride is transferred to C(4) in **2a**, but this is not observed (Scheme 6, bottom). The C–H insertion pathway **C(i)** is readily eliminated, since a C(3,5) proton in **1a** is not transferred to the C(4) methyl group in **2a** (Scheme 4, top). Similarly, the vinylic C–H insertion pathway, **C(ii)**, is not compatible with the reversal of geometric relationship of C(1,7) with C(3,5) in **1a** on conversion to **2a** (Scheme 4, lower sections), which suggests a *syn*-β-H elimination.

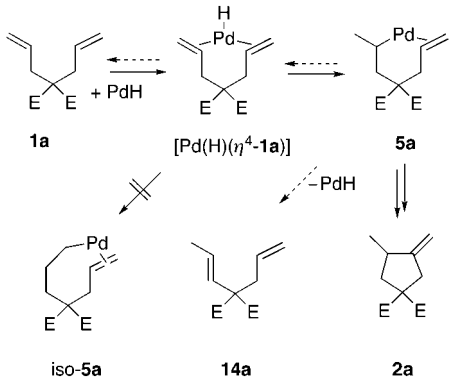
We are thus left with pathway **A** and, although this is not proof, all of the points discussed above support a Pd–H-type cycle. The issue of catalyst generation ("Pd–H") has not yet been addressed, but a unified mechanism for catalyst turnover can now be constructed (Scheme 8). The mechanism can also



Scheme 8. A mechanism that accounts for the ^{2}H distributions, geometry, scrambling and intermolecular transfer observed on cycloisomerisation of **1a** to **2a** with [Pd(η^3-C_3H_5)(MeCN)$_2$]OTf as procatalyst.

be extended to account for both the direct generation of **3a** and the indirect[33] generation of **4a** (**3a**) from **1a**. The former is accounted for by a nondissociative[11e] conversion via [Pd(H)(η^2-**2a**] to *endo*-**13a**. This process would require that the intermediate be stabilised, for example, by further coordination of MeCN, to allow sufficient lifetime for rotation–insertion (to give *endo*-**13a**) and then β-H elimination to release **3a**. In contrast, the favoured (indirect) generation of **4a** over **3a** on discrete (free, uncomplexed) isomerisation of **2a** by a Pd–H species is accounted for by assuming that binding to one face of the alkene **2a** is hindered by the methyl group at C(4), so that *exo*-**13a**, rather than *endo*-**13a**, is generated.

Two other observations support the Pd–H mechanism. Firstly, there is partial *E*/*Z* equilibration of [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [1,7-(*Z*,*Z*)-$^2H_2$]-**1a**, and a faster (ca. 13% relative to irreversible product generation) *E*/*Z* equilibration en route to **2a**. Secondly, reaction of [2,6-$^2H_2$]-**1a** occurs with partial exchange of ^{2}H with ^{1}H at the terminal carbon atoms C(1,7) of **1a**. These results indicate that initial Pd–H addition to **1a** is reversible. However, the relatively low extent of *E*/*Z* equilibration and ^{2}H transfer indicates that after the initial Pd–H addition (to generate **5a**), irreversible β-migratory insertion (to give **6a**) competes rather effectively against β-H elimination. Additionally, there appears to be very little Pd–H addition with reversed regioselectivity (to give regioisomeric terminal Pd σ complex iso-**5a**, Scheme 9) since there is no



Scheme 9. Regioselectivity of the Pd–H insertion to give **5a** but not iso-**5a**, and relatively rapid and irreversible β-migratory insertion, ultimately leading to **2a**. There is approximately 15% β-H elimination leading back to [Pd(H)(1,2-η;6,7-η-**1a**)], and a trace of β-H elimination leading to **14a**.

detectable exchange of protons at C(2,6) with ^{2}H or ^{1}H, and β-H elimination from **5a** rarely occurs with reversed regioselectivity, since only traces (<5%) of (*E*)-allylprop-1-enyl malonate (**14a**, a double-bond isomer of **1a**) are generated (detected by GC). These features suggest that Pd–H addition occurs from a chelate diene complex "[Pd(H)(1,2-η;6,7-η-**1a**)]", which a) facilitates a more rapid β-migratory insertion (from **5a**), b) guides β-H elimination to give the terminal **1a** rather than internal alkene isomer **14a** and c) promotes repeated Pd–H addition rather than dissociation of [Pd(H)(1,2-η;6,7-η-**1a**)].

Mechanism of procatalyst activation: From NMR analysis of the cycloisomerisation reactions it became clear that not all of the starting complex [Pd(η^3-C_3H_5)(MeCN)$_2$]OTf was consumed, despite complete consumption of **1a**. This situation is similar to the use of [Pd(η^3-C_3H_5)(CD_3NO_2)$_2$]BF_4 as catalyst for dimerisation of styrene and of ethylene.[34] Since the Pd–allyl complex could be recovered in good yield (83–91%) after complete reaction of the styrene, Sen and Lai[34] proposed that the allyl complex itself was the active species. Brookhart et al. drew very different conclusions from similar results in the Pd-catalysed dimerisation of ethylene, where again a procatalyst complex [Pd(allyl)(ethylene)(PCy_3)]$^+$ was found to be the major species throughout the reaction. It was suggested that a slow allyl–ethylene coupling step generates

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traces of a highly active Pd–H catalyst, the NMR-observable resting state of which is $[Pd(Et)(ethylene)_2(PCy_3)]^+$.[22e] Indeed, the allyl–ethylene coupling step, which generates 1,4-pentadiene, was observed by Mecking and Keim in related $[Pd(allyl)(P,O)]^+$ complexes (P,O = a hemilabile bidentate phosphane/phosphane oxide ligand). This supports a $[Pd(H)(ethylene)(L)_2]^+$ species as the active catalyst for ethylene dimerisation.[35] Furthermore, on switching from ethylene to methyl acrylate, Brookhart et al., were able to observe an acrylate allyl insertion product at $-25\,^\circ C$, which on warming to 15 °C in the presence of an excess of methyl acrylate underwent β-hydride elimination to generate dimethyl-2-hexenedioate.[22e]

Stoichiometric reactions employing isotopically labelled diallyl malonate substrates: The stoichiometric reaction of $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ (see reference spectrum A in Figure 3) with **1a** (1:1) in $CDCl_3$ was monitored by ^1H NMR spectroscopy (500 MHz). Soon after mixing, partial ($\leq 15\,\%$) conversion to a new, but transient (vide infra), complex was observed (spectrum B, Figure 3).

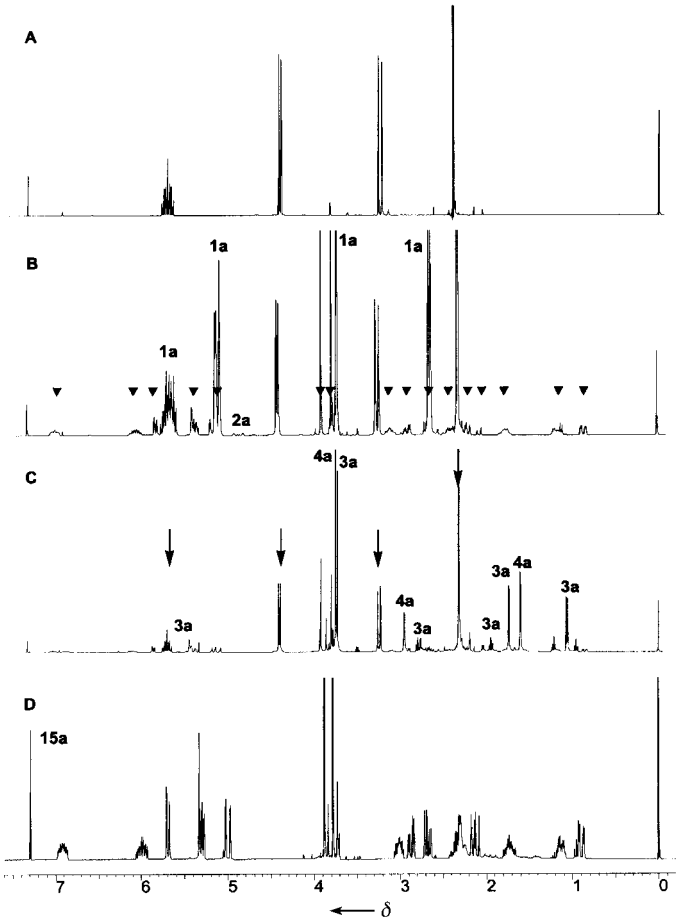
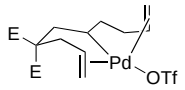


Figure 3. ^1H NMR spectra of a stoichiometric reaction between **1a** and $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ in $CDCl_3$ at 25 °C. A) Reference $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. B) 10 min after addition of **1a**. Some **2a** is evident at this point. Inverted triangles indicate signals arising from **15a**. C) After complete consumption of **1a** (16 h) to generate a mixture of **3a** and **4a** (as indicated). Arrows indicate signals arising from unconsumed $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. D) Reference sample of **15a** (plus two equiv CD_3CN), prepared independently.

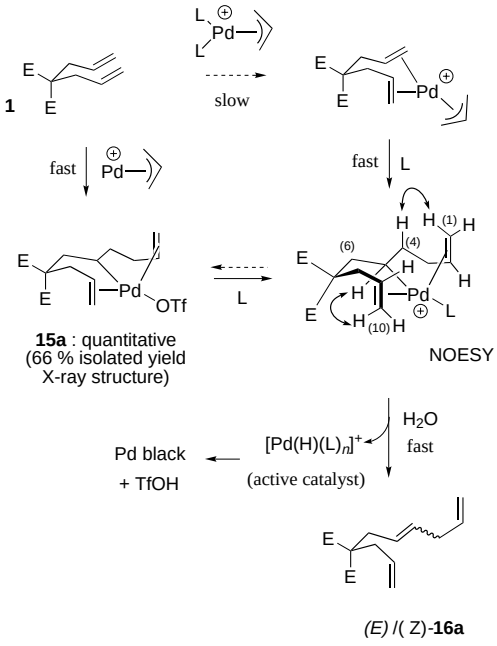
The complex spectrum (spanning $\delta_H = 0.8\text{–}7.0$) indicated that **1a** and the Pd–allyl complex had reacted to give an unsymmetrical diene species (see inverted triangles in spectrum B). All attempts to isolate the complex failed, since after a few minutes, traces of **2a** were observable and, over a period of 4–16 h, **1a** was consumed. Concomitantly, the unidentified Pd complex slowly disappeared, and after complete consumption of **1a** (to give **2a**, **3a** and **4a**, as well as other unidentified alkene isomers), unconverted $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ was the major (>80 %) Pd complex (see arrows in spectrum C). Determination of a possible identity for the transiently generated complex (spectrum B) was made difficult by the low concentration of the complex, as well as a number of isochronous signals from substrates and products. Nonetheless, with the aid of one- and two-dimensional NMR experiments (PECSY, PNOSY, NOED and CHSHF) and labelled (^2H and ^{13}C) **1a**, the intermediate was tentatively assigned as **15a**. In this complex, one of the alkene units has been allylpalladated (β-migratory insertion) such that the internal carbon atom becomes σ-bound to Pd^{II} and the alkene unit is π-bound to palladium.



15a

*Isolation and characterisation of the intermediate complex **15a** and generation of the active hydride*: The small quantities of complex **15a** formed on reaction of $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ with **1a** and the apparent absence of an intermediate Pd–allyl diene complex[36] of the type $[Pd(\eta^3\text{-}C_3H_5)(1,2\text{-}\eta;6,7\text{-}\eta\text{-}\mathbf{1a})]^+$ suggested that displacement of acetonitrile ligand(s) from the Pd–allyl cation is slow, but that the subsequent β-migratory insertion is rapid. Consequently, we treated $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ with AgOTf in CD_2Cl_2 in the presence of one equivalent of **1a**. ^1H NMR analysis of the solution after removal of AgCl indicated that under these conditions **15a** was quantitatively and rapidly formed (Scheme 10). Addition of diethyl ether and storage at $-20\,^\circ C$ furnished **15a** as a colourless crystalline solid (X-ray structure)[37] in 66 % yield and in analytically pure form. The slow formation of **15a** followed by β-H elimination to give an active Pd–H species would provide a partial explanation for the induction period in the cycloisomerisation of **1a** with catalysis by $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. Indeed, it was initially somewhat surprising that **15a** had a sufficiently long lifetime to be observable, since β-H elimination might be expected to be extremely facile. However, this does not explain the variability in induction period, and, more importantly, control reactions demonstrated that samples of pure **15a** did not catalyse cycloisomerisation of **1a** in $CHCl_3$.

The solution-phase stability of **15a** towards β-H elimination derives predominantly from the prerequisite for an agostic interaction to facilitate a *syn*-β-H elimination,[38] which, as a result of the rigid bicyclic structure,[37] is not feasible.[39] Given the variability in induction period and the difficulty in obtaining completely dry samples of $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$,[18] we tested the effect of traces of water on the activation of the procatalyst **15a**. The effects were dramatic:[40] immediately after addition of a few microliters of water to



Scheme 10. Slow reaction of diene **1a** with $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ and rapid reaction with $[Pd(\eta^3\text{-}C_3H_5)(S)_2]OTf$ (S = solvent) to give **15a**. Selected NOEs (NOESY, 500 MHz) confirm the conformation of **15a** in solution (in which the complex is likely present in ionised form; L = MeCN, for example). Note that complex **15a** is not an active procatalyst for cycloisomerisation of **1a**. Addition of water to a solution of **15a** in $CHCl_3$ or CH_2Cl_2 results in rapid generation of (*E*)/(*Z*)-**16a** and Pd black.

a solution of **15a** in CD_2Cl_2 or $CDCl_3$, the solution darkened and the linear triene **16a** was identified by NMR spectroscopy as the sole organic product. On a preparative scale, with **15a** generated in situ, analytically pure triene **16a** was isolated after chromatography in 98% yield.[41] In the absence of MeCN, the product mixture was unstable, and Pd black or, occasionally, a Pd mirror was rapidly generated. The earlier observation that there is no deuterium incorporation in **2a** when Pd-catalysed cycloisomerisation of **1a** is conducted in the presence of D_2O[26b] suggests that Pd^0 is not protonated by the TfOH to (re)generate the active catalyst. When **1a** in $CDCl_3$ at 40 °C was treated with 5 mol% of the Pd complex **15a**, 10 mol% MeCN and 5 mol% H_2O, cycloisomerisation of **1a** to **2a**, **3a** and **4a** proceeded smoothly and quantitatively over a matter of hours.[42] After complete consumption of **1a**, there was no evidence for triene **16a**, and prior to the addition of water, no reaction was detectable by GC analysis after 16 h at 40 °C. When the same reaction was performed at 25 °C, the triene **16a** (ca. 5%) could be detected in the product mixture, which also contained **14a**; hence, at higher temperature, the more hindered alkenes **16a** and **14a** also undergo cycloisomerisation.

Conclusion

We have developed $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$[17] as a procatalyst for cycloisomerisation of dimethyl diallyl malonate (**1a**). This reaction displays a pronounced and variable induction period, gives predominantly **2a** as the kinetic product and does not consume all of the $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$. Deployment of isotopic labels (^{13}C, and ^2H) and analysis of the primary cycloisomerisation product **2a** by NMR spectroscopy (^1H, ^2H and ^{13}C), in particular by exploitation of $^1J(C,H)$ and $^1J(C,^2H)$ coupling and ^2H isotope shifts, allowed conclusions to be drawn about the possible mechanisms (Scheme 3). Competing isomerisation can often be a problem in deuterium-labelling experiments.[11b, 43] Indeed, in a recently reported mechanistic investigation into the conversion of **1a** to **4a** (via **2a**) with catalysis by $[Pd(\eta^3\text{-}C_3H_5)(Cl)(PCy_3)]/NaB[3,5\text{-}C_6H_3(CF_3)_2]_4$ in the presence of Et_3SiH, exchange of labelled substrate with Et_3SiH (and vice versa) was so extensive as to generate many isotopomers of the product.[11b] However, with the current system, isomerisation was not extensive, and this allowed useful stereochemical details to be elucidated. The data obtained do not support cyclometallation or C–H insertion mechanisms as the predominant catalytic pathway, but are consistent with a hydropalladation mechanism (pathway **A**, Schemes 3 and 8) involving an unobserved species $[Pd(H)(L)]^+$. The palladium hydride catalyst is generated by decomposition of the NMR-observable Pd^{II} complex **15a**, formed by allylpalladation of the coordinated diene. The complex was subsequently isolated and fully characterised after alternative preparation, for which omission of acetonitrile and use of anhydrous conditions proved essential. The complex has a bicyclic structure in which Pd is σ-bound to what was C(2) of the diene and π-bound to both the unchanged alkene and the terminal alkene of the transferred allyl group. In solution, NOE contacts and $^3J(H,H)$ coupling constants are consistent with a boat-like geometry in the larger ring of the bicyclic diene complex **15a**.[37] In the absence of further ligands, the triflate coordinates to Pd, and β-migratory insertion of the unchanged alkene does not occur, since this would result in a coordinatively unsaturated Pd centre. In the presence of water, the complex decomposes by β-hydride elimination, and the linear triene **16a** is generated. Control experiments confirm that catalytic quantities of **15a** (5 mol%)/MeCN (10 mol%) are only effective for the cycloisomerisation of **1a** in $CDCl_3$ solution at 40 °C with the addition of catalytic quantities ($\leq$10 mol%) of water. The trace quantities of water present in the reaction mixture when $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ is employed as catalyst accounts for the variable induction periods observed from run to run. However, despite propagation via a Pd hydride, we found no evidence for $^1H/^2H$ exchange in the presence of D_2O, which is often considered to be a classic test for hydride intermediates.[44].

Experimental Section

General: Commercial HPLC-grade solvents were dried by passage through a commercial activated alumina column (Anhydrous Engineering). Reactions were carried out under nitrogen or argon by standard Schlenk techniques. Samples of ^2H- and ^{13}C-labelled **1a** were prepared by published procedures.[15] Analytical data for unlabelled **1a**: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.64$ (dddd, $^2J(H,H)_{simul} = 1.8$, $^3J(H,H)_{simul} = 7.4$, 9.9, 16.8 Hz, 2H; C(2,6)H), 5.12 (dddd, $^2J(H,H)_{simul} = 1.8$, $^3J(H,H)_{simul} = 9.9$, 16.8, $^4J(H,H) = 1.1$ Hz, 4H; C(1,7)=CH_2), 3.72 (s, 6H; $C(CO_2CH_3)_2$), 2.64 (ddd, $^3J(H,H) = 7.4$, $^4J(H,H) = 1.1$, 1.1 Hz, 4H; 3,5-CH_2); $^{13}C\{^1H\}$ NMR

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(100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 171.2$ (2 × C=O), 132.2 (C(2,6)), 119.2 (C(1,7)), 57.6 (C(4)), 51.4 (2 × CH_3), 36.9 (C(3,5)); MS (EI): *m/z* (%): 212 (0.3) $[M]^+$, 171 (4) $[M - \text{allyl}]^+$, 84 (100), 86 (64); elemental analysis (%) calcd for $C_{11}H_{16}O_4$ (212.24): C 62.25, H 7.60; found: C 62.66, H 7.90. The ^{13}C-labelled primary cycloisomerisation product (in the form of [(C(2),C(3)=CH_2,C(4)–CH_3,C(5)–$^{13}C_1$]-**2a**) was prepared by Ru-catalysed cycloisomerisation[8] of [1,3-$^{13}C_1$]-**1a**. NMR experiments were performed on JEOL Delta 270, Lambda 300, GX 400 and Alpha 500 instruments. Frequency reference: ^{1}H, ^{13}C: internal; ^{19}F NMR: external. Full assignments were aided by one- and two-dimensional experiments (DEPT, HHCOSY, PECSY, CHCOSY, FGHMBC, PNOSY), as appropriate. Elemental analyses were performed by the analytical service at the School of Chemistry, University of Bristol. IR spectra: Perkin–Elmer 1600 FT, samples were prepared as thin films on NaCl or as KBr discs. Flash column chromatography: Merck silica gel 60 eluted with a constant gravity head of about 15 cm solvent. TLC: 0.25 mm, Merck silica gel 60 F254 with visualization at 254 nm or with acidic (H_2SO_4) aqueous $KMnO_4$ solution (ca. 2%). Mass spectra: VG Micromass (EI, CI, FAB). GC Analysis: Shimadzu GC17A, Restek Corp. RTX-5 Column, Crossbond 5% diphenyl-/95% dimethylpolysiloxane stationary phase (15 m, 0.25 mm, 0.25 mm df). Conditions: injector, 220 °C; detector, 220 °C; oven, 100 °C or 110 °C (isothermal); total flow, 0.4 cm^3 min^{-1}; pressure, 100 kPa.

Palladium complex 15a: AgOTf (203.1 mg, 0.79 mmol) was added in one portion to a Schlenk flask containing **1a** (167.5 mg, 0.79 mmol) and [{Pd(η^3-C_3H_5)Cl}$_2$] (144.2 mg, 0.395) in dry CH_2Cl_2 (1.5 mL) under N_2. The mixture was stirred for 20 min, then the fine cream precipitate (AgCl) allowed to settle. The supernatant was passed through a cannula into a separate Schlenk flask where [Pd{7,7-(CO_2Me)$_2$-(1,2,5,9,10-η^5)-dec-1,9-diene)}-(OTf)] (**15a**) crystallised (266.3 mg, 66.4%, m.p. 97–98 °C, colourless solid) after addition of diethyl ether (5:1) and cooling to –20 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.03$ (br m, 1H; C(2)H), 6.05 (dddd, ^3J(H,H) = 5.5, 8.0, 9.2, 16.1 Hz, 1H; C(9)H), 5.82 (dd, ^2J(H,H) = 1.2, ^3J(H,H) = 9.2 Hz, 1H; C(10)H$_{trans}$), 5.47 (d, ^3J(H,H) = 8.8 Hz, 1H; C(1)H$_{trans}$), 5.36 (d, ^3J(H,H) = 16.9 Hz, 1H; C(1)H$_{cis}$), 5.07 (dd, ^2J(H,H) = 1.2, ^3J(H,H) = 16.1 Hz, 1H; C(10)H$_{cis}$), 3.93 (s, 3H; C(7)CO_2CH_3), 3.78 (s, 3H; C(7)CO_2CH_3), 3.02 (dddd, ^3J(H,H) = 4.0, 4.8, 7.7, 9.5 Hz, 1H; C(5)H), 2.88 (dd, ^2J(H,H) = 15.4, ^3J(H,H) = 5.5 Hz, 1H; C(8)H$_{eq}$), 2.60 (dd, ^2J(H,H) = 15.4, ^3J(H,H) = 8.0 Hz, 1H; C(8)H$_{ax}$), 2.40 (br m, 1H, C(3)H$_{eq}$), 2.30 (br m, 1H; C(3)H$_{ax}$), 2.16 (dd, ^2J(H,H) = 15.8, ^3J(H,H) = 4.0 Hz, 1H; C(6)H$_{eq}$), 1.75 (br m, 1H; C(4)H$_{eq}$), 1.25 (br m, 1H; C(4)H$_{ax}$), 0.81 (dd, ^2J(H,H) = 15.8, ^3J(H,H) = 4.0 Hz, 1H; C(6)H$_{ax}$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 172.23$ (C=O), 171.05 (C=O), 131.62 (C(2)), 115.91 (C(9)), 103.7 (C(10)), 94.99 (C(1)), 58.26 (C(7)), 56.61 (C(5)), 53.89 (CH_3), 53.31 (CH_3), 41.66 (C(6)), 36.36 (C(4)), 35.34 (C(8)), 29.83 (C(3)); ^{19}F NMR (470.5 MHz, $CDCl_3$, 25 °C, CCl_3F): $\delta = -77.9$ (s, CF_3); IR (KBr): $\tilde{\nu} = 3107$ (w), 2957 (m), 2874 (w), 2855 (w), 1751 (s), 1735 (s), 1639 (w), 1565 (w), 1547 (w), 1439 (s), 1407 (w), 1301 (s), 1269 (s), 1210 (s), 1172 (s), 1094 (m), 1071 (w), 1060 (w), 1023 (s), 977 (w), 959 (w), 950 (s) 938 (m), 910 (w), 862 (m), 837 (w), 824 (w), 810 (w), 691 (w), 635 (s), 579 (m), 517 cm^{-1} (m); MS (CI): *(m)/z* (%): 361 (4) $[M - \text{OTf}+1]^+$, 359 (4) $[M - \text{OTf} - 1]^+$, 253 (30) $[M - \text{OTf} - \text{Pd}]^+$, 193 (100) $[C_{12}H_{17}O_2]^+$; MS (FAB): *m/z* (%): 361 (18) $[M - \text{OTf}+1]^+$, 359 (14) $[M - \text{OTf} - 1]^+$, 253 (22) $[M - \text{OTf} - \text{Pd}]^+$, 154 (100), 136 (80); elemental analysis (%) calcd for $C_{15}H_{21}F_3O_7PdS$ (508.80): C 35.41, H 4.16; found: C 35.76; H 4.16.

Reaction of 15a with water: Water (5 μL) was added to a stirred solution of **15a** (20.1 mg, 0.04 mmol) in CH_2Cl_2 (1 mL), and the colour rapidly darkened. After 2 h, passage through a small plug of silica (2 × 0.5 cm), washing through with diethyl ether (10 mL) and then concentration in vacuo afforded a yellow oil. Purification by flash chromatography (hexane/EtOAc 10:1) gave dimethyl-1,4-(*E*)-9-decatrien-7,7-dicarboxylate (**16a**) as a clear oil (9.33 mg, 93.1%). An analogous experiment using **15a** prepared in situ gave **16a** in 98% yield of isolated product. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.78$ (ddt, ^3J(H,H) = 17.1, 10.3, 6.4 Hz, 1H; C(2)H), 5.65 (ddt, ^3J(H,H) = 15.4, 9.8, 7.3 Hz, 1H; C(9)H), 5.52 (dtt, ^3J(H,H) = 15.2, 6.9, ^4J(H,H) = 1.2 Hz, 1H; C(4)H), 5.28 (dtt, ^3J(H,H) = 7.3, 5.2, ^4J(H,H) = 1.5 Hz, 1H; C(5)H), 5.13 (ddt, ^2J(H,H) = 1.0, ^3J(H,H) = 15.4, ^4J(H,H) = 1.0 Hz, 1H; C(10)H$_{cis}$), 5.11 (ddt, ^2J(H,H) = 1.0, ^3J(H,H) = 9.8, ^4J(H,H) = 1.0 Hz, 1H; C(10)H$_{trans}$), 5.07 (ddt, ^2J(H,H) = 1.7, ^3J(H,H) = 17.1, ^4J(H,H) = 1.7 Hz, 1H; C(1)H$_{cis}$), 4.99 (ddt, ^2J(H,H) = 1.7, ^3J(H,H) = 10.3, ^4J(H,H) = 1.7 Hz, 1H; C(1)H$_{trans}$), 3.73 (s, 6H; 2 × CH_3), 2.74 (ddddd, ^3J(H,H) = 6.9, 6.4, ^4J(H,H) = 1.7, 1.7, 1.5 Hz, 2H; C(3)H$_2$), 2.63 (dt, ^3J(H,H) = 7.3, ^4J(H,H) = 1.0 Hz, 2H; C(8)H$_2$), 2.60 (dd, ^3J(H,H) = 7.3, ^4J(H,H) = 1.2 Hz, 2H; C(6)H$_2$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 171.28$ (2 × C=O), 136.60 (C(2)), 132.74 (C(9)), 132.31 (C(4)), 124.65 (C(5)), 119.16 (C(10)), 115.21 (C(1)), 57.83 (C(7)), 52.32 (2 × CH_3), 36.89 (C(3)), 36.69 (C(8)), 35.72 (C(6)); IR (NaCl): $\tilde{\nu} = 3474$ (w), 3079 (m), 3002 (m), 2981 (m), 2953 (s), 2843 (w), 1743 (s), 1639 (s), 1436 (s), 1324 (m), 1286 (s), 1216 (s), 1142 (s), 1060 (m), 995 (m), 974 (m), 919 (s), 857 (w), 733 (w), 694 (w), 655 (w), 559 cm^{-1} (w); MS (CI): *m/z* (%): 253 (80) $[M+1]^+$, 221 (54) $[M - \text{OCH}_3]^+$, 193 (76) $[M - \text{CO}_2\text{CH}_3]^+$, 161 (52), 133 (55), 117 (100). HRMS (CI): *m/z*: 253.143984 $[M+1]^+$; calcd for $C_{14}H_{21}O_4$: 253.145161; elemental analysis (%) calcd for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99; found: C 66.52, H 7.87; GC analysis (110 °C): (*E*)-**16a**: 17.9 ± 0.2 min (75%); (*Z*)-**16a**: 19.4 ± 0.2 min (25%).[41]

Palladium-catalysed cycloisomerisation with 15a as procatalyst: A solution of **1a** (34.4 mg, 0.16 mmol) in dry $CHCl_3$ (1 mL) was added by syringe to a stirred solution of **15a** (4.1 mg, 0.008 mmol, 5 mol%) in $CHCl_3$ (0.5 mL). The mixture was heated to 40 °C. GC analysis (100 °C) after 16 h at this temperature indicated no conversion of **1a** had occurred (**2**, **3a**, **4a** not detected (≤0.1%)). CH_3CN (0.9 μL) and water (0.15 μL) were added by means of a syringe in one portion. GC analysis after 4 h indicated 80% conversion. After a further 12 h, GC analysis indicated 100% conversion. Filtration through a pad of silica (2 × 1.5 cm), elution with CH_2Cl_2 (20 mL), concentration in vacuo and then purification by flash chromatography (hexane/EtOAc 12:1) gave a clear oil (22.4 mg, 65.1%). GC analysis (100 °C): **2a**: 9.59 ± 0.2 min (9%); **3a**: 10.62 ± 0.2 min (76%); **4a**: 11.66 ± 0.2 min (15%). Components were identified by reference to independently prepared, analytically pure materials:

*1,1-Dimethylcarboxy-3-methylene-4-methylcyclopentane (**2a**)*:[8] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.92$ (ddd, ^4J(H,H) = 2.2, 2.2, 2.2 Hz, 1H; C(3) = CH$_{cis}$); 4.81 (ddd, ^4J(H,H) = 2.2, 2.2, 2.2 Hz, 1H; C(3)=CH$_{trans}$), 3.74 (s, 3H; CO_2CH_3), 3.72 (s, 3H; CO_2CH_3), 3.07 (ddd, ^2J(H,H) = 17.1, ^4J(H,H) = 2.2, 2.2 Hz, 1H; C(2)H$_B$), 2.94 (ddd, ^2J(H,H) = 17.1, ^4J(H,H) = 2.2, 2.2 Hz, 1H; C(2)H$_A$), 2.57 (dd, ^2J(H,H) = 13.9, ^3J(H,H) = 7.3 Hz, 1H; C(5)H$_{syn}$), 2.56 (ddddq, ^3J(H,H) = 16.1, 7.3, 6.2, ^4J(H,H) = 2.2, 2.2 Hz, 1H; C(4)H), 1.74 (dd, ^2J(H,H) = 13.9, ^3J(H,H) = 16.1 Hz, 1H; C(5)H$_{anti}$), 1.15 (d, ^3J(H,H) = 6.2 Hz, 3H; C(4)CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 172.4$, 172.3 (2 × C=O), 153.2 (C(3)), 105.6 (C(3)=CH_2), 58.2 (C(1)), 52.7, 52.6 (2 × CO_2CH_3), 42.3 (C(5)), 40.6 (C(2)), 37.3 (C(4)), 17.9 (C(4)CH_3); MS (EI): *m/z* (%): 213 (4) $[M+1]^+$, 212 (38) $[M]^+$, 152 (96) $[M - \text{CO}_2\text{CH}_3]^+$, 93 (100), 57 (61); elemental analysis (%) calcd for $C_{11}H_{16}O_4$ (212.24): C 62.25, H 7.60; found: C 62.47, H 7.71.

*1,1-Dimethylcarboxy-3,4-dimethylcyclopent-2-ene (**3a**)*:[12b] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.43$ (dq, ^4J(H,H) = 1.7, 1.7 Hz, 1H; C(2)H), 3.74 (s, 3H; CO_2CH_3), 3.71 (s, 3H; CO_2CH_3), 2.62–2.82 (m, 2H, C(4)H, C(5)H$_B$), 1.94 (dd, ^2J(H,H) = 12.7, ^3J(H,H) = 5.6 Hz, 1H; C(5)H$_A$), 1.73 (d, ^4J(H,H) = 1.5 Hz, 3H; C(3)CH_3), 1.06 (d, ^3J(H,H) = 6.5 Hz, 3H; C(4)CH_3); ^{13}C{^{1}H} NMR (75.45 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 172.0$, 172.4 (2 × CO_2Me), 150.3 (C(3)), 121.8 (C(2)), 64.8 (C(1)), 52.6, 52.4 (2 × CO_2CH_3), 41.9 (C(4)), 40.6 (C(5)), 18.9 (C(4)CH_3), 14.6 (C(3)CH_3); MS (EI): *m/z* (%): 213 (4) $[M+1]^+$, 212 (4) $[M]^+$, 173 (24), 152 (100) $[M - \text{CO}_2\text{Me}]^+$, 121 (17), 93 (26); elemental analysis (%) calcd for $C_{11}H_{16}O_4$ (212.24): C 62.25, H, 7.60; found: C 62.60, H 7.87.

*1,1-Dimethylcarboxy-3,4-dimethylcyclopent-3-ene (**4a**)*:[12b] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.73$ (s, 6H; (CO_2CH_3)$_2$), 2.94 (s, 4H; C(2,5)CH_2), 1.60 (s, 6H; C(3,4)CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 173.0$ (2 × $COCH_3$), 128.0 (C(3,4)), 57.1 (C(1)), 52.7 (2 × CO_2CH_3), 45.9 (C(2,5)), 13.3 (C(3,4)CH_3); MS (EI): *m/z* (%): 212 (9) $[M]^+$, 153 (24) $[M - \text{CO}_2\text{CH}_3]^+$, 24), 152 (57), 86 (73), 84 (100); elemental analysis (%) calcd for $C_{11}H_{16}O_4$ (212.24): C 62.25, H 7.60; found: C 62.43, H 7.96.

Dimethyl 1,5-(*E*)-heptadiene-4,4-dicarboxylate (14a): A solution of dimethyl allyl malonate and [Pd(η^3-C_3H_5)(MeCN)$_2$]OTf (5 mol%) in $CDCl_3$ was heated at 40 °C for 72 h to afford dimethyl but-2-ene-1,1-dicarboxylate (75% *E*). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): *E* isomer: $\delta = 5.72$ (m, 2H; C(2)H, C(3)H), 4.02 (d, ^3J(H,H) = 7.3 Hz, 1H; C(1)H), 3.75 (s, 6H; 2 × CO_2CH_3), 1.75 (d, ^3J(H,H) = 4.8 Hz, 3H; C(4)CH_3), ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 168.8$ (2 × CO_2CH_3), 131.95 (C(2)), 122.31 (C(3)), 55.37 (2 × CO_2CH_3), 52.68 (C(1)), 17.98 (C(4)). After column chromatography, the mixture of isomers (86.8 mg, 0.5 mmol) was treated with allyl benzoate by following published procedures[15] to give (*E*)-**14a** (75% *E*) as a colourless oil (82.9 mg, 77.5%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.92$ (ddq, ^3J(H,H) = 15.9, 8.1, ^4J(H,H) = 1.7 Hz, 1H;

C(5)H), 5.67 (m, 2H; C(2)H, C(6)H), 5.09 (m, 2H; C(1)H_2), 3.78 (s, 6H, 2 × CO_2CH_3), 2.78 (dt, ^3J(H,H) = 7.1, ^4J(H,H) = 1.2, 1.2 Hz, 2H; C(3)H_2), 1.76 (dd, ^3J(H,H) = 6.4, ^4J(H,H) = 1.7 Hz, 3H; C(7)CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C, $CDCl_3$): δ = 170.76 (2 × CO_2CH_3), 132.66 (C(2)), 127.99 (C(6)), 126.99 (C(5)), 118.57 (C(1)), 59.45 (C(4), 52.49 (2 × CO_2CH_3), 39.7 (C(3)), 18.21 (C(2)); IR (NaCl): $\tilde{\nu}$ = 3080 (m), 3006 (m), 2983 (m), 2956 (s), 2845 (w), 1737 (s), 1642 (m), 1621 (w), 1438 (s), 1327 (w), 1290 (s), 1220 (s), 1143 (s), 994 cm^{-1} (w); MS (CI): *m*/*z* (%): 213 (24) $[M]^+$, 181 (36), 171 (40), 153 (100) $[M\text{-}CO_2CH_3]^+$, 93 (18), 71 (22), 57 (24); elemental analysis (%) calcd for $C_{11}H_{16}O_4$ (212.24): C 62.25, H 7.60; found: C 62.60, H 7.87.

Acknowledgement

We thank the EPSRC (GR/N05208), the Zeneca Strategic Research Fund, Pfizer and Lancaster Synthesis for generous support. K.L.B. thanks the University of Bristol for a postgraduate studentship. Dr. Martin Murray (University of Bristol) provided extensive help with NMR experiments and Paul A. Slatford (University of Bristol) performed experiments to test for H/^{2}H exchange between D_2O and $[PdH]^+$. We very gratefully acknowledge Professor Ross A. Widenhoefer (Duke University, USA) for disclosing his results to us prior to publication.

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[16] Detailed investigations into the mechanism by which simple neutral chloropalladium complexes effect highly selective cycloisomerisation of **1a** to **3a** (see ref. [12b]) will be reported in due course.

[17] At the time, the use of Pd – allyl complexes as procatalysts for diallylmalonate cycloisomerisation was unprecedented (although well known for alkene dimerisation; e.g., see ref. [22e] and references therein). However, during the course of the study, use of phosphane-bearing Pd – allyl procatalysts was reported by RajanBabu et al.[9] and later by Widenhoefer et al.[11b] A recent study demonstrated the importance of the counterion with regard to the activity of these procatalysts: P. G. Cozzi, personal communication.

[18] $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ was prepared by chloride abstraction (AgOTf) from $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ in CH_2Cl_2/MeCN and then crystallisation from diethyl ether. This white crystalline complex can be stored for long periods in the freezer. However, it is not always easy to obtain in a completely dry state, since removal of traces of solvent in vacuo tends to result in decomposition. Note that the chloro complex $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (5 mol%) was completely inert as a catalyst for cycloisomerisation of **1a**, even on prolonged heating (60 °C).

[19] Reactions were conducted in $CDCl_3$ and monitored by ^{1}H NMR spectroscopy (400 MHz) at constant temperature (25, 30 , 40, 60 °C). Somewhat erratic results were obtained initially. Reactions were more reliable when conducted in $CDCl_3$ that had been freshly filtered through basic alumina, distilled and then degassed. Negligible conversion rates were observed at ambient temperature. However, after initiation of reaction (60 °C, 30 min), slow turnover (72% conversion, 15 h; **2a**, **3a**, **4a** obtained in 47:31:18 ratio) could be observed at 25 °C. Pre-heating in the absence of **1a** was not effective. Reaction at 40 °C proved optimum for mechanistic studies in terms of rates and product ditributions. Reactions at 60 °C proceeded more rapidly (> 90%, 2 h), but generated large amounts of **4a** (the thermodynamic product) through isomerisation of **2a** and **3a**.

[20] After complete consumption of **1a**, chromatography on silica gel afforded the cycloisomerisation product as an analytically pure mixture of double-bond isomers (**2a**, **3a** and **4a**).

[21] When **2a** was present from the start (**2a**/**1a** 0.9:1), little **3a** was generated, and ^{13}C NMR analysis indicated that ^{13}C-labelled **2a** was being isomerised to ^{13}C-labelled **4a**.

[22] a) G. Oehme, *J. Prakt. Chem.* **1984**, *326*, 779 – 790; b) M. G. Barlow, M. J. Bryant, R. N. Haszeldine, A. G. Mackie, *J. Organomet. Chem.* **1970**, *21*, 215 – 226; c) I. Guibert, D. Neibecker, I. Tkatchenko, *J. Chem. Soc. Chem. Commun.* **1989**, 1850 – 1852; d) G. Wilke, *Angew. Chem.* **1988**, *100*, 189 – 210; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 185 – 206; e) G. M. DiRenzo, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 6225 – 6234, and references therein; f) S. J. McClain, J. Sanco, R. R. Schrock, *J. Am. Chem. Soc.* **1979**, *101*, 5451 – 5453.

[23] For leading references and an overview from the perspective of organic chemists on the generation of "M–H", see B. M. Trost, *Chem. Eur. J.* **1998**, *4*, 2405 – 2412.

[24] There were no signals evident for the methine proton (C(4)H), the exomethylene protons (C(3)=CH_2) or the methyl group (C(4)CH_3) in the ^{1}H NMR spectrum, while in the ^{2}H NMR spectrum integration indicated population ratios of 1:2:3. The degree of deuterium incorporation was estimated to be > 95% at each site. In no cases were mass spectra informative, due to extensive fragmentation under EI conditions, and ^{1}H/^{2}H exchange under CI conditions. Furthermore, since GC-MS was not available to us, we were unable to distinguish *m*/*z* peaks arising from isomeric alkenes (i.e., **1a** from **2a**, **3a** and **4a**).

[25] At ≥ 80% conversion, *E*/*Z* equilibration (yielding [1,7-(*E*,*E*)-$^2H_2$]-**1a**, [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** and [1,7-(*E*,*Z*)-$^2H_2$]-**1a**) was nearly complete in both cases (^{2}H NMR).

[26] a) In both cases, some exchange of ^{2}H with ^{1}H also occurs (to generate C(3)=CH_2), but it is not extensive (< 5%). This result may appear to contrast with the partial exchange observed with [2,6-$^2H_2$]-**1a**. However, the difference can be ascribed to a primary isotope effect that acts in concert with a statistical effect, so that Pd–H is preferentially lost from a (Pd)-C-CH_2D unit. b) A reaction in which unlabelled **1a** was converted to unlabelled **2a** (ca. 30% conversion in 50 min) in D_2O-saturated $CDCl_3$ demonstrated that there was no exchange of H with ^{2}H occurring through traces of water present in the reaction mixture.

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[27] In the ^{1}H NMR spectrum of labelled **2a** generated from [2,6-$^2H_2$]-**1a**, the C(4)CH_3/CH_2D units appear as singlets (due to complete deuteration at C(4)[28]) at $\delta \approx 1.1$ and are separated by an α-^{2}H isotope shift ($\Delta\delta = 0.0175$).

[28] Note that in the ^{1}H NMR spectrum of unlabelled **2a**, both methylene protons (C(3)=CH_2) give rise to quartets, and the signal of the the C(4)CH_3 group is a doublet. In contrast, due to the near complete deuteration at C(4), in the primary product derived from [2,2-$^2H_2$]-**1a**, triplets are observed for both C(3)=CH_2 protons, and the signal of the C(4) methyl group is a singlet. The quartet arises from threefold ^4J(H,H) (to C(2)H_2 and C(4)H). Geminal ^2J(H,H) coupling is not observed (< 0.3 Hz).

[29] Rather extensive formation of isomers **3a** and **4a** accompanied this reaction. Estimation of the deuterium incorporation at the labelled C(4)-methyl group of **2a** was made by integration of the ^{13}C NMR signal arising from C(5), which is 25% ^{13}C-labelled and exhibits a γ-^{2}H isotope shift ($\Delta\delta = 0.023$) for C(4)CH_2D relative to C(4)CH_3.

[30] In [(*C*(2),C(3)=*C*H_2,C(4)-*C*H_3,*C*(5)-$^{13}C_1$]-labelled **2a**, the non-^1J(C,H) methylene ^{1}H signals (i.e., the central section of the spin set with 75% population) were complex but informative. The proton in the *E* isomer ($\delta \approx 4.9$) was of quite different multiplicity (33% triplet, 66% quartet) to that in the *Z* isomer ($\delta = 4.8$; 66% quartet (threefold ^4J(H,H)), 33% double triplet (^3J(H,H) (10 Hz) + twofold ^4J(H,H)). The *trans*-^3J(H,H) (to ^{13}C(2)) confirmed the earlier assignment of the *E*/*Z* methylene geometries in unlabelled **2a** by NOED.

[31] In contrast to the primary product [^2H_x,$^{13}C_1$]-**2a** obtained from mono-^{13}C-labelled [7-(*E*)-$^2H_1$-(1,3)-$^{13}C_1$]-**1a**, the ^{13}C NMR signals arising from C(3)=^{13}*C*H_2 and ^{13}*C*(2)H_2/[^{13}*C*(5)H_2] and C(4)^{13}*C*H_3 in [^2H_x,$^{13}C_2$]-**2a** generated from doubly labelled [1,3,5,7-$^{13}C_2$]-**1a** (50% mutually exclusive labelling at each paired site) are doublets due to twofold 50% ^2J(C,C) or ^3J(C,C) coupling (2.3 Hz); for example, C(1)=^{13}*C*H_2 couples with the ^{13}C atom (50%) at C(5) and the ^{13}C atom (50%) at C(4)*C*H_3).

[32] In **2a** arising from [2,6-$^2H_2$]-**1a**, C(4) is completely (> 95%) deuterated, and this results in an upfield β-^{2}H isotope shift ($\Delta\delta = 0.12$) in the ^{13}C NMR signal arising from C(5). This isotope shift distinguishes C(5), which has natural ^{13}C abundance (1.1%) but is present in fivefold excess, from the same carbon atom in **2a** arising from $^{13}C_2$-labelled **1a**, which has a 50% abundance of ^{13}C. The relative integrals are hence 1:10. Within each set, a deuterium atom at the methyl group on C(4), that is, C(4)*C*H_2D, exerts a small but distinct upfield γ-^{2}H isotope shift ($\Delta\delta = 0.023$) which allows approximation of the C(4)CH_3/C(4)CH_2D) ratio. In this case it is identical (1:1 CH_3/CH_2D) in both sets of C(5).

[33] Material balances and earlier studies with [$^{13}C_1$]-**2a** demonstrated that **3a** and **4a** are predominantly generated indirectly by isomerisation of the primary product **2a**. Analysis of the isomerised products (i.e., labelled **3a** and **4a**) from the cycloisomerisation of [1,7-(*E*,*E*)-$^2H_2$]-**1a** and [1,7-(*Z*,*Z*)-$^2H_2$]-**1a** (as in Scheme 4) indicated that in both cases, both isomers had monodeuterated methyl groups, and hence isomerisation occurs with clean transfer of "H" to the methylidene carbon atom of **2a**. In **3a** and **4a**, the non-ester methyl groups displayed clean 1,1,1 triplets in the ^{13}C{^{1}H} NMR spectra, and 1,2,1 triplets in ^{2}H NMR spectra. Only small quantities of isomerised primary products **3a** and **4a** (5–11%) were obtained from cycloisomerisation with [1,1,2,6,7,7-$^2H_6$]-**1a**, but ^{1}H and ^{2}H NMR analysis (^{13}C NMR was not informative) indicated nearly complete deuteration at both methyl groups in both isomers. Furthermore, C(4) was fully deuterated in labelled **3a**, since the diastereotopic C(5)H_2 protons were observed as a pair of clean doublets, that is, without ^3J(H,H) coupling to C(4)H.

[34] A. Sen, T.-W. Lai, *Organometallics* **1983**, *2*, 1059–1060.

[35] S. Mecking, W. Keim, *Organometallics* **1996**, *15*, 2650–2656.

[36] Examples of reactions of cyclooctadiene with cationic Pd–allyl species: a) R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, *93*, 3089–3091; b) B. F. G. Johnson, J. Lewis, D. A. White, *J. Am. Chem. Soc.* **1969**, *91*, 5186–5187. However, there was no discussion of whether or not β-migratory allyl insertion occurs. Furthermore, it is interesting to note that in a putative, but unobserved, precursor to **15a** (i.e., [Pd(η^3-C_3H_5)(1,2-η;6,7-η-**1a**)]$^+$), the Pd atom is coordinated to the same enantioface of the two alkenyl groups. For a related and opposite example, see K. Nordström, C. Moberg, A. Heumann, *J. Organometal. Chem.* **1996**, *525*, 233–238.

[37] A complete study of the solid (single-crystal X-ray diffraction) and solution-phase (NMR) structures of **15a** and its reactivity towards a variety of ligands will be reported in due course: K. L. Bray, J. P. H. Charmant, I. J. S. Fairlamb, G. C. Lloyd-Jones, P. A. Slatford, unpublished results.

[38] Note that other types of elimination have been documented: general-base-promoted *anti*-β-H elimination: a) P. G. Andersson, S. Schab, *Organometallics* **1995**, *14*, 1–2; b) J. M. Tackacs, E. C. Lawson, F. Clement, *J. Am. Chem. Soc.* **1997**, *119*, 5956–5957; specific-base-promoted *syn*-β-H elimination: c) D. R. Chrisope, P. Beak, W. H. Saunders, Jr., *J. Am. Chem. Soc.* **1988**, *110*, 230–238; d) E. Keinan, S. Kumar, V. Dangur, J. Vaya, *J. Am. Chem. Soc.* **1994**, *116*, 11151–11152.

[39] For a recent example of this effect, see S. Aït-Mohand, F. Hénin, J. Muzart, *Organometallics* **2001**, *20*, 1683–1686.

[40] In asymmetric Pd-catalysed oxidative cyclisation reactions of a 1,5-diene, the presence of water was found to be crucial for selectivity: L. Tottie, P. Baeckström, C. Moberg, J. Tegenfeldt, A. Heumann, *J. Org. Chem.* **1992**, *57*, 6579–6587. In a kinetic study of the Heck reaction, water was found to be involved in the activation process: T. Rosner, A. Pfaltz, D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 4621–4622 and references therein. For a recent overview of some of the other remarkable effects that traces of water can have on organometallic systems, see S. Ribe, P. Wipf, *Chem. Commun.* **2001**, 299–307.

[41] The ratio of (*E*)-**16a**/(*Z*)-**16a** depends on the exact conditions employed (but is usually ca. 75 ± 2% *E*). Under some conditions, cyclised products are also obtained. Studies are ongoing, and we will report in detail on this phenomenon at a later date[37].

[42] Presumably due to the higher initial concentration of free MeCN, the reaction gave reasonable selectivity for the trisubstituted isomer **3a** (ratios by GC, **2a**/**3a**/**4a**: 9:75:16).

[43] J. M. Brown, G. D. Hughes, *Inorg. Chim. Acta* **1996**, *252*, 229–237.

[44] For example, see A. Takeda, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 5662–5663.

Received: April 2, 2001 [F3168]