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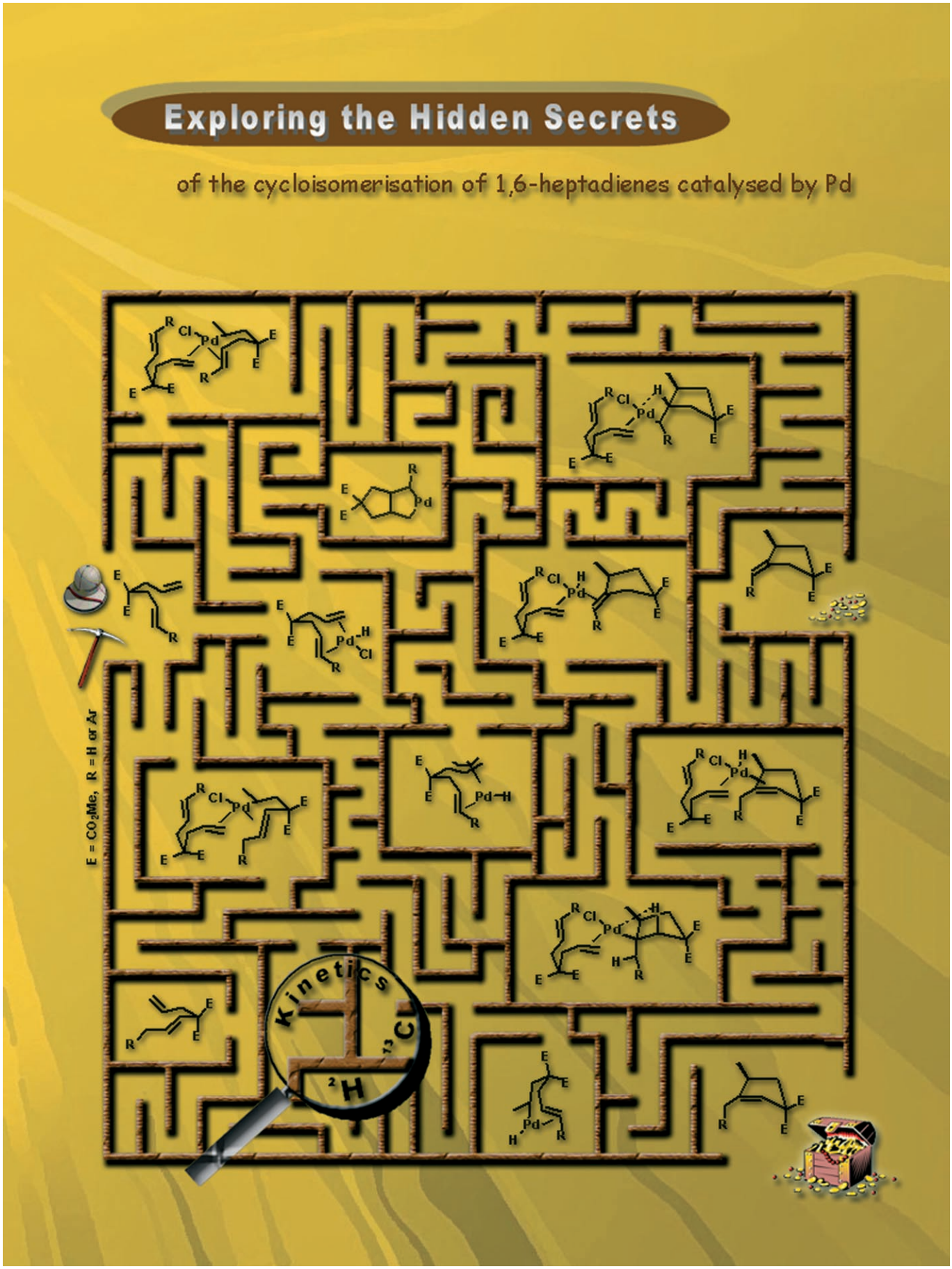

Mechanism of Cycloisomerisation of 1,6-Heptadienes Catalysed by $[(t\text{BuCN})_2PdCl_2]$: Remarkable Influence of Exogenous and Endogenous 1,6- and 1,5-Diene Ligands

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Abstract: The mechanism of the highly regioselective cycloisomerisation of dimethyl hept-1,6-dienyl-4,4-dicarboxylate (**1**) by a neutral pre-catalyst, $[(t\text{BuCN})_2PdCl_2]$ (**8**), to generate dimethyl 3,4-dimethylcyclopent-2-ene-1,1-dicarboxylate (**3**) has been investigated by isotopic labelling (reactions involving single and mixed samples of 1,1,2,6,7,7-[$^2H_6$]-**1**; 3,3,5,5-[$^2H_4$]-**1**; 1,7-(*Z*,*Z*)-[$^2H_2$]-**1**; [1,3-$^{13}C_1$,5,7-$^{13}C_1$]-**1** and [1,3-$^{13}C_1$,6-$^2H_1$]-**1**) and by study of the reactions of dimethyl 1-aryl-hept-1,6-dienyl-4,4-dicarboxylates (**9a–e**, where aryl is *p*-C_6H_4-X; X = H, OMe, Me, Cl, CF_3) and dimethyl hept-1,5-dienyl-4,4-dicarboxylate (**14**), a 1,5-diene isomer of **1**. The mechanism proposed involves the generation of a monochloro-bearing palladium hydride which undergoes a simple hydropalladation, carbopalladation, Pd/H dyotropy, β-H elimination sequence to generate **3**. A key point that emerges is that chelation of the 1,6-diene **1** at various stages in the mechanism plays an important role in determining the regioselectivity of the reaction. The selective generation of **3** with pre-catalysts of the form L_2PdCl_2, as compared to the generation of dimethyl 3-methylene-4-methyl-cyclopentane-1,1-dicarboxylate (**2**) with pre-catalysts of the form $[(MeCN)_2Pd(allyl)]OTf$ (**5**) is ascribed to the absence of chloride ion in the latter, which makes an additional coordination site available throughout turnover. Liberation of the product **3** when $[(t\text{BuCN})_2PdCl_2]$ (**8**) is employed as pre-catalyst, is proposed to proceed via a mono- to bidentate switch in the π-coordination of diene **1** (η^2 to bis-η^2) displacing π-coordinated **3** from Pd. When 1-aryl-1,6-dienes **9** are employed as substrates, the electron-donor property of the aryl group is found to influence the regioselectivity of cyclisation. Electron-withdrawing groups favour dimethyl 3-arylmethyl-4-methylcyclopent-2-ene-1,1-dicarboxylates (**10**), whilst electron-donating aryl groups favour 3-arylidene-4-methyl-cyclopentane-1,1-dicarboxylates (**11**). The regioselectivity (**10**/**11**) correlates with the Hammett σ^+ values ($\rho^+ = 1.3$, $r^2 = 0.975$) indicative of a strong π-resonance contribution from the aryl ring rather than a simple σ-inductive effect. Intermolecular modulation of regioselectivity is observed and the net effect proposed to arise through the (π→d) donation ability of the vinyl arene in the diene displacing product (**10**/**11**) via a mono- to bidentate switch in coordination. The isomerisation process increasingly sequesters Pd as turnover proceeds leading to a powerful inhibition mechanism and ultimately a limitation in turnover number to about 80.

Keywords: cycloisomerization · dienes · homogeneous catalysis · palladium · regioselectivity

Introduction

The 100% "atom-economic"[1] nature of isomerisation reactions makes such processes of significant interest to the synthetic organic chemist. The cycloisomerisation of linear reactants, such a 1,*n*-dienes,[2] combines the atom-economic aspects of an isomerisation reaction with the synthetic utility of ring construction. Recently there has been a resurgence of interest in the catalysis of such processes, particularly by late-transition metal complexes, for example, Ru,[3] Ni,[4] Pt,[5] and Pd.[6] The benchmark substrates for such reactions

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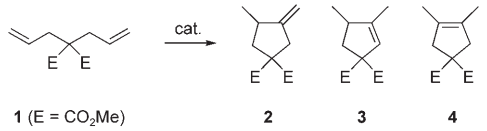
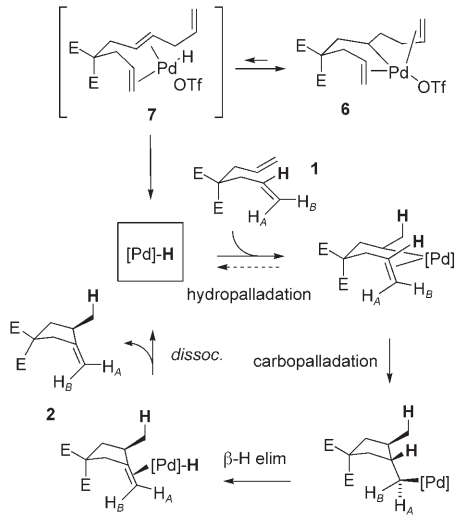
have become 1,6-heptadienes, such as dimethyl diallylmalonate **1**, which is transformed into cyclopentylidene **2** and cyclopentenes **3** and **4** (Scheme 1) by a variety of catalysts.[2–6] Of the three five-membered ring products,[7] most catalysts systems generate **2** as the kinetic product. Catalysts for the selective generation of isomer **3**, which is of intermediate thermodynamic stability,[8] are less common and all are based on palladium.[6]



Scheme 1. Transition-metal-catalysed cycloisomerisation of dimethyl diallyl malonate (**1**) to generate cyclopentylidene (**2**) and cyclopentenyl (**3**, **4**) rings.

We have earlier reported on our investigations into the mechanism by which the cationic complex [(MeCN)$_2$Pd(allyl)]OTf (**5**) functions as a pre-catalyst for the isomerisation of **1** to **2**.[9] By deploying a small collection of isotopically labelled analogues of **1**[10] we were able to eliminate a number of mechanisms, including those involving cyclometallation, vinylic C–H insertion and allylic C–H insertion. We ultimately suggested a simple hydrometallation, carbopalladation, β-H elimination mechanism (Scheme 2) for the conversion of **1** to **2**, by a catalytically active hydrido palladium intermediate ((L)$_n$Pd-H),[9] generated via allyl palladation (**1** + **5** → **6**) and *syn* β-H elimination (**6**→**7**).[11]

We subsequently focused on the remarkable effect that sources of soluble chloride had on the regioselectivity of the reaction[12] leading us to suspect that the different regioselectivities induced by "[(MeCN)$_3$PdCl]$^+$" (**1**→**3**) and "[(MeCN)$_4$Pd]$^{2+}$" (**1**→**2**), arose from the presence or absence of chloride, rather than formal charge on Pd.[13] Further study led to the development of neutral pre-catalysts of the type [(L)$_2$PdCl$_2$][14] L = RCN, DMSO, for this reaction (**1**→**3**).[15] These complexes, in particular [(*t*BuCN)$_2$PdCl$_2$] (**8**), also effect rapid and high yielding cycloisomerisation of a reasonably broad range of 1,6-heptadienes[16] to the cyclopentenyl cycloisomer analogous to **3** with good to excellent regioselectivity (95–99%).[14b]

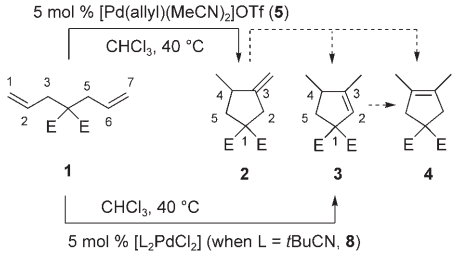


Scheme 2. Mechanism proposed for the cycloisomerisation of **1** to **2** by cationic allyl palladium pre-catalyst **5**, activated by allylpalladation (**1**→**6**) and β-H elimination (**6**→**7**).[9]

The elucidation of the mechanism of cycloisomerisation of **1** to **3** induced by the pre-catalysts of type [(*t*BuCN)$_2$PdCl$_2$] (**8**), predominantly on the basis of i) isotopic labelling experiments and ii) the remarkable effect of endogenous and exogenous 1,5 and 1,6-dienes on the activity and selectivity of this process, forms the basis of the work presented herein.

Results and Discussion

On simple inspection, the major differences in reaction outcome on using [(MeCN)$_2$Pd(allyl)]OTf (**5**) (or intermediate **6**) versus [(*t*BuCN)$_2$PdCl$_2$] (**8**) as pre-catalysts for the cycloisomerisation of **1** (see Scheme 3) suggest that the mechanisms for conversion **1**→**2** (catalysed by **5** or **6**) and **1**→**3** (catalysed by **8**) are unrelated. For example, the kinetic product from the reaction employing **5** as pro-catalyst is *exo*-alkene **2**, which is then isomerised, at approximately one fifth[17] of the rate of its production, to the thermodynamically more stable[8] compounds **3** and **4**, in an approximately equal ratio. In other words, there is poor discrimination of the isomerisation of **1** (→**2**) over isomerisation of **2** (→ **3** + **4**) and the net regioselectivity is poor throughout the reaction evolution. In contrast, pre-catalysts of type **8** effect an extremely selective cycloisomerisation of **1** directly, to **3**, without free **2** being an intermediate,[18] and without significant (< 1%) subsequent isomerisation of the kinetic product (**3**→**4**) until complete consumption of **1**.

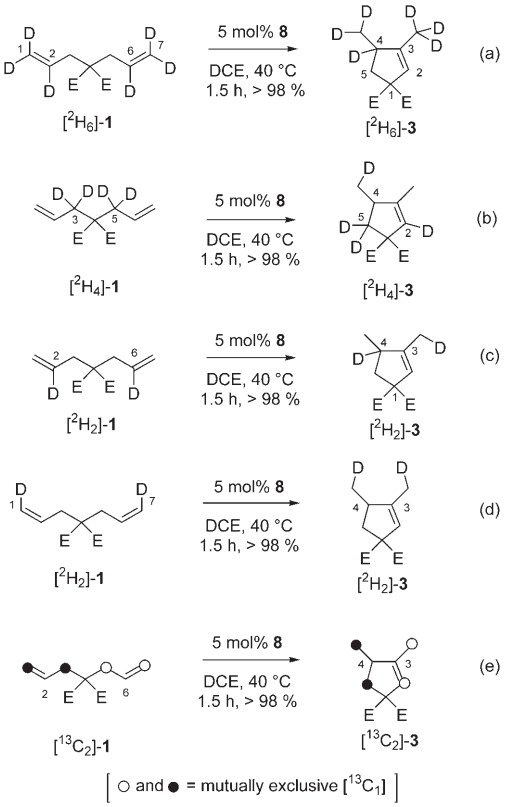


Scheme 3. Contrasting kinetic selectivity profiles of cationic pre-catalyst **5** (or **6**) and neutral, chloride-bearing, pre-catalyst **8** for the cycloisomerisation of 1,6-diene **1**.

Our preliminary study[14b] of the kinetics of the reaction of **1** catalysed by [(*t*BuCN)$_2$PdCl$_2$] (**8**), suggested that there is a "trickle-feed" generation of the active catalyst via reaction of the diene **1** with **8**,[19] and that in competition with turnover, is a powerful catalyst inhibition mechanism that limits the maximum number of turnovers to approximately 80.

Cycloisomerisation of isotopically labelled 1,6-dienes: Comparison of the structures of substrate **1** and product **3** (Scheme 3) indicates that the net process of conversion involves migration of two hydrogens, formally from C(2,6) and C(3,5) to C(1) and C(7) in **1**, these latter two carbons becoming the two methyl groups at C(3) and C(4) in **3**. The structures also suggest that the existing C–C connectivities in **1** remain in place with a new connection being made between C(2) and C(6) in **1**, these becoming C(3) and C(4) in **3**. In order to investigate the intra- versus inter-molecularity and origin/destination of the hydrogen migrations, as well as the (lack of) skeletal reorganisation, we deployed a range of ^{2}H- and ^{13}C-labelled substrates [Eqs. (a–h)]. The labelled substrates were cyclised under standard conditions (5 mol% **8**, 1,2-dichlorethane (DCE), 40 °C, 2–5 h) converting **1**→**3** in > 98% yield[20] with label distributions being constant through reaction unless noted.[21]

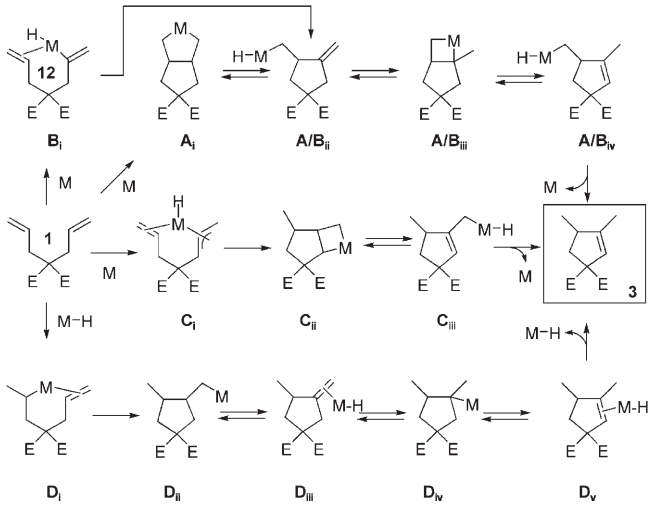
We consider first the reaction of 1,1,2,6,7,7-[$^{2}H_6$]-**1**, which gave [$^{2}H_6$]-**3** with a very clean label distribution and no loss of deuterium detected by NMR,[22] see Equation (a). The dideuterated methyl at C(4) in **3** stands in contrast to our earlier studies employing **5** as pre-catalyst for cycloisomerisation of 1,1,2,6,7,7-[$^{2}H_6$]-**1** which gave [$^{2}H_6$]-**2** in which the C(4)-methyl group was perdeuterated.[9]



The outcome of cycloisomerisation of **1** → **3** with **8** as pre-catalyst suggests that one of the four allylic protons (*H*, at C(3)/C(5) in **1**) is transferred to the opposite allyl terminus to become C(4)-CH_2*H* in **3**, and the allylic carbon (C(3)/C(5)) in **1** that loses the proton becomes C(2)-H in **3**. To test the (formal) veracity of this, we cycloisomerised 3,3,5,5-[$^{2}H_4$]-**1** which gave [$^{2}H_4$]-**3** [Eq. (b)] in which C(2) and C(5) are perdeuterated, and, crucially, the C(4)-methyl group is monodeuterated.[23] The results from Equations (a) and (b) suggest that the proton at C(2,6) in **1** is transferred to C(1,7)H_2 in **1** to generate the methyl group at C(3) in **3**. To test this, we cycloisomerised 2,6-[$^{2}H_2$]-**1** which gave [$^{2}H_2$]-**3** in which C(4) and the methyl at C(3) both bear a single deuterium [Eq. (c)].[24] Analogously, 1,7-(*Z*,*Z*)-[$^{2}H_2$]-**1** gave [$^{2}H_2$]-**3** in which both C(3)- and C(4)-methyl groups bear a single deuterium [Eq. (d)].[25] Finally, the cycloisomerisation of the doubly ^{13}C-labelled diene [1,3-$^{13}C_1$,5,7-$^{13}C_1$]-**1** confirmed that unlabelled carbons C(2) and C(6) in **1** become σ-bonded in the formation of **3** [Eq. (e)] and that there is no skeletal reorganisation. The results outlined in Equations (a) to (e) thus suggest the highly selective transfer of one proton (H_A) from C(5)- and one proton (H_B) from C(6) in **1** to, what were C(1) and C(7), respectively, in **1**, thus generating two methyl groups, at C(4) and C(3), respectively, in **3**, as outlined in Scheme 4.

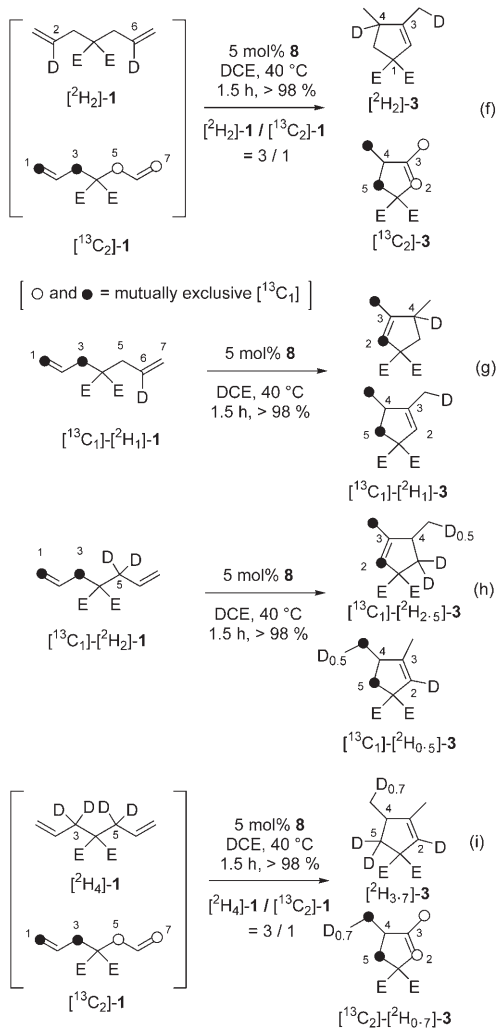
Scheme 4. Apparent migrations of H required to satisfy isotopic labelling experiments in the cycloisomerisation of **1**→**3** as outlined in Equations (a)–(e).

Four mechanisms[15,26–29] (**A** to **D**) for the generation of **3**, directly from **1** (i.e., not by isomerisation of free **2**), taken from or adapted from the literature and which are fully consistent with the H-migrations identified in Equations (a–e), can be considered (Scheme 5).



Scheme 5. Four generic mechanisms for the cycloisomerisation of **1** to **3** with high regioselectivity, taken or adapted from the literature. See text for full discussion.

Mechanism **A** involves cyclometallation[26] (**1** → $\mathbf{A_i}$), followed by a sequence involving β-H elimination (→$\mathbf{A_{ii}}$), then hydrometallation (→$\mathbf{A_{iii}}$), then β-H elimination (→$\mathbf{A_{iv}}$) and reductive elimination (→**3**). Mechanism **B** involves vinylic C-H insertion[27] (**1** → $\mathbf{B_i}$), followed by carbometallation (→ $\mathbf{A}/\mathbf{B_{ii}}$) to connect with mechanism **A**. Mechanism **C** involves allylic C-H insertion[15,28] (**1** → $\mathbf{C_i}$), followed by addition of the alkene to the central allylic carbon, with transfer of H to the alkene terminus, thus generating metallacyclobutane $\mathbf{C_{ii}}$. β-H elimination (→$\mathbf{C_{iii}}$) is followed by reductive elimination (→**3**). Finally, mechanism **D**,[29] involves alkene hydrometallation (**1** → $\mathbf{D_i}$), then carbometallation (→$\mathbf{D_{ii}}$), β-H elimination (→$\mathbf{D_{iii}}$, in which cycloisomer **2** is π-bound), hydrometallation (→$\mathbf{D_{iv}}$) and β-H elimination (→**3**).



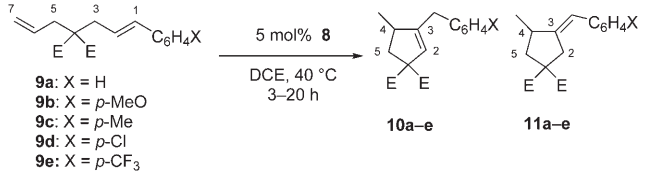
In our initial reports on the cycloisomerisation of **1** using pro-catalysts of type **8**,[14] we favoured mechanism **D** as a working model.[29,30] This mechanism differs from **A**, **B**, and **C** in that one (but not both) of the hydropalladation steps is intermolecular (reaction of "Pd-H" with **1** to generate $\mathbf{D_i}$). To test for this we performed four cross-over experiments. Firstly, co-cycloisomerisation of an equimolar mixture of the doubly ^{13}C-labelled diene [1,3-$^{13}C_1$,5,7-$^{13}C_1$]-**1** and the deuterium labelled diene 2,6-[$^2H_2$]-**1** gave [$^{13}C_2$]-**3** and [$^2H_2$]-**3**, without any detectable crossover of ^{2}H [Eq. (f)].[31] The non-symmetrical mixed-labelled system [1,3-$^{13}C_1$,6-$^2H_1$]-**1** cycloisomerised to give [$^{13}C_1$,$^2H_1$]-**3** [Eq. (g)], in which no ^{13}C labelled carbon bore a deuteron[32] [compare Eq. (c) and (g)]. Both experiments [Eqs. (f) and (g)] confirm not only the intramolecularity of the transfer of the proton from C(6) but also that it is transferred to the same allyl chain from which it is derived, that is, from C(6) to C(7) in **1** (see H_B in Scheme 4). In contrast, cycloisomerisation of non-symmetrical mixed labelled system [1,3-$^{13}C_1$,5,5-$^2H_2$]-**1** gave a product mixture in which the ^{13}C labelled C(4)-methyl group was partially monodeuterated, with a net abundance of 0.5 deuterons at the C(4)-methyl groups in the pair of isotopomers [Eq. (h)]. This is strongly suggestive of intermolecular transfer of a proton (deuteron) from C(5) in **1** to become the methyl group at C(4) in **3**. This was confirmed by co-cycloisomerisation of the doubly ^{13}C-labelled diene [1,3-$^{13}C_1$,5,7-$^{13}C_1$]-**1** with the deuterium labelled 3,3,5,5-[$^2H_4$]-**1** ($^1/_3$ mol ratio) which gave isotopologues of **3** in which $^{13}C\{^1H\}$ and ^{1}H NMR analysis indicated that 70% of the ^{13}C-labelled C(3)-methyl group in [$^{13}C_2$]-**3** bore a single deuterium [Eq. (i)].[33] This confirms the *inter*molecularity of the transfer of the proton from C(3) in **1** to the C(4)-methyl group in **3** during the cyclisation process.

On the basis of the results in Equations (f) to (i), mechanisms **A**, **B** and **C** can be eliminated, leaving **D** which is consistent with all nine isotopic labelling experiments outlined in Equations (a) to (i), provided that hydropalladation to generate $\mathbf{D_i}$ is irreversible (no loss or gain of D at C(1,7) [Eq. (d)] and that hydropalladation of C(1)=C(2) proceeds with high regioselectivity to generate C(2)–Pd over C(1)–Pd.

Intermolecular effects arising from product displacement through diene π-bonding: It is intriguing that the first part of mechanism **D**[29] (involving intermediates $\mathbf{D_i}$–$\mathbf{D_{iii}}$) is identical to that proposed for the cycloisomerisation of **1** to **2** by the cationic pre-catalysts **5** and **6** as outlined in Scheme 2.[9] The origin of the departure from the latter mechanism is at point $\mathbf{D_{iii}}$ where instead of "[Pd-H]" displacement to liberate **2**, a hydropalladation event generates an isomeric σ-alkyl palladium complex $\mathbf{D_{iv}}$ (in effect there is Pd/H dyotropy: $\mathbf{D_{ii}}$→$\mathbf{D_{iv}}$). The regioselectivity (**2** versus **3**) will thus be controlled by the relative rates of "[Pd-H]" displacement from $\mathbf{D_{iii}}$ to liberate **2**, versus hydropalladation to generate $\mathbf{D_{iv}}$. To probe the interaction between **2** and Pd in intermediate $\mathbf{D_{iii}}$ we studied the effect of substituents on the terminus of one alkene unit in **1** on the selectivity of cycloisomerisation induced by **8**. According to the Dewar–Chatt–Duncanson model for alkene complexation, both the electron density at the metal centre and the electron-withdrawing (d→π*, back-bonding) or -donating (π→d) nature of the alkene substituent(s) will govern the net-binding of the alkene to the metal.[34] Additionally, steric bulk at the alkene caused by substitution will destabilise both the (π→d) and (d→π*) in-

teractions. However, comparison within a series of *para*-substituted aryl groups allows the study of electronic effects free from significant differences in steric effects (see Table 1).[35]

Table 1. Ratios of regioisomers (*"endo"*-**10** versus *"exo"*-**11**)[a] obtained in the Pd-catalysed cycloisomerisation of *para* substituted 1-aryl-1,6-dienes **9a–e**, when reacted alone (entries 1–5) or when co-reacted in equimolar quantities with one (entries 6, 7 and 8) or two (entries 9 and 10) analogous aryl-1,6-dienes **9a–e**.



Entry	*p*-X	**10/11**[a,b]	*p*-X	**10/11**[a,b]	*p*-X	**10/11**[a,b]
1	**a**; H	43:57	–[c]		–[c]	
2	**b**; MeO	6:94	–[c]		–[c]	
3	**c**; Me	20:80	–[c]		–[c]	
4	**d**; Cl	41:59	–[c]		–[c]	
5	**e**; CF_3	70:30	–[c]		–[c]	
6	**b**; MeO	9:91	**e**; CF_3	27:73	–[d]	
7	**c**; Me	26:74	**e**; CF_3	45:55	–[d]	
8	**b**; MeO	10:90	**d**; Cl	32:68	–[d]	
9	**a**; H	16:84	**b**; MeO	9:91	**d**; Cl	20:80
10	**c**; Me	12:88	**b**; MeO	9:91	**e**; CF_3	24:76

[a] Determined by GC analysis, based on equal response (FID) of regioisomers, as supported by ^{1}H NMR analysis of test mixtures. [b] Regioselectivities are average of those observed over 100% conversion of **9**, but varies by no more than 3% during runs. [c] 1-Aryl-1,6-diene reacted alone. [d] Two 1-aryl-1,6-dienes co-reacted.

With a simple *E*-phenyl substituent (**9a**), cycloisomerisation proceeded smoothly and the regioselectivity, as compared to **1**, dropped substantially to give a 43:57 ratio of the "*endo*" (**10a**) and "*exo*" (**11a**) alkene isomers (>98%), see Table 1, entry 1. Analysis of such a process by analogy to mechanism **D** suggests that the regioselectivity of the initial intermolecular hydropalladation step remains very high, with addition occurring only to the less congested allylic (C(6)=C(7)) rather than cinnamyl (C(1)=C(2)) unit in **9a**, thus generating only the phenylpropenyl (**10/11**), and not phenylpropyl cycloisomers. Consistent with the stereochemical consequences of the *syn*-β-H elimination predicted by extension of mechanism **D**, *exo*-**11a** is generated exclusively as the *Z*-alkene isomer (geometry assigned unambiguously by ^{1}H NMR NOE-difference experiments). The reduced selectivity for the "*endo*" over the "*exo*" alkene isomer (43:57 **10a**/(*Z*)-**11a** as compared to 98:0.1 for **3/2** when **1** is cycloisomerised) is consistent with a) an increased steric hindrance in the benzylidene intermediate ($(L)_n$)Pd(H)-(*Z*)-**11a**) analogous to methylidene $\mathbf{D_{iii}}$ promoting displacement of the alkene from the Pd-H moiety rather than reinsertion, and b) a smaller thermodynamic differential between regioisomers (DFT suggests that ΔE **10a**/(*Z*)-**11a** = 1.0 kcal mol^{-1}[36] compared with ΔE **3/2** = 3.4 kcal mol^{-1}[8]) due to the trisubstituted nature of the alkene in *exo*-isomer (*Z*)-**11a**. Analogous regioselectivity for addition to C(6)=C(7) was obtained with a series of *para*-substituted aryl substrates **9b–e** (*para* substituents = OMe, Me, Cl, CF_3), see Table 1, entries 2–5.[37] However, the ratio of the "*endo*" and "*exo*" alkene isomers (**10**/(*Z*)-**11**) was strongly controlled by electronic factors. Electron-withdrawing groups favouring "*endo*" alkene isomer **10** and electron-donating groups favouring the "*exo*" alkene isomer (*Z*)-**11**, the latter to the point where with a *para*-anisyl substituent, the *exo*-selectivity is high (94% **11b**). On first inspection, the effect of increasing *exo*-selectivity with increasing electron density on the aryl ring appears consistent with one or both of two effects: i) destabilisation of the electron-rich σ-alkyl intermediate $\mathbf{D'_{iv}}$ and ii) promotion of displacement of *exo* isomer (*Z*)-**11** in $\mathbf{D'_{iii}}$ through attenuation of back-bonding (d→π*). However, neither explanation is satisfactory. Firstly, destabilisation of the intermediate $\mathbf{D'_{iv}}$ should be modulated by aryl inductive effects and give a linear correlation of *endo*/*exo* selectivity with simple Hammett σ values—instead a smooth curve is observed (see Figure 1a). Secondly, Pd^{II} is known to engage in rather weak back-bonding (d→π*) with vinyl arenes.[38] Consistent with the latter, a significantly more linear Hammett correlation ($\rho^+ = 1.3$, $r^2 = 0.975$) is found when the resonance-dominated "σ^+" term is employed (Figure 1b), indicative of control of regioselectivity by an interaction involving vinyl arene donation (π→d) rather than electron acceptance via back-bonding (d→π*).

The bonding interaction between the vinyl arene in product (*Z*)-**11** and the Pd^{II} centre in $\mathbf{D_{iii}}$ is expected to increase[38a] as the aryl becomes more electron-donating, thereby disfavouring product displacement and thus the *exo*-selectivity trend is contradictory in an intramolecular sense. However, it is readily accommodated by a mechanism in which a vinyl arene unit from another molecule of diene substrate can displace product (*Z*)-**11** from intermediate $\mathbf{D_{iii}}$. Convincing evidence for this formally intermolecular modulation of regioselectivity comes from experiments in which the effect of the presence of one or more diene on the regioselectivity of another was found to be significant (compare Table 1, entries 6–10).

In the cases of electron-deficient vinyl arenes, the regioselectivity was powerfully influenced by electron-donating vinyl arene, particularly the anisyl substrate **9b**. For example, the *para*-CF_3-bearing substrate **9e** gives a 70:30 ratio of *endo*-**10e**/*exo*-(*Z*)-**11e** when reacted alone, but when co-reacted as an equimolar mixture with anisyl-bearing **9b** the *endo*/*exo* ratio in was inverted (27:73, Table 1, entry 6). Analogous effects were found in other combinations of two or three aryl-bearing dienes, as summarised in Table 1, entries 7–10. In all cases, the presence of each substrate is found to impact upon the regioselectivity of the other(s) with the influence being proportional to the relative concentration and the π-donor power of the vinyl arene. A range of other vinyl anisoles **12a–c**, that are unable to chelate, were also tested and none found to influence the regioselectivity of cyclisation of **9e** → *endo*-**10e** (70%), *exo*-(*Z*)-**11e** (30%) by more than 5%. The simple 1,6-diene **1** bearing no aryl group also had no effect, whilst the bis-anisyl diene **13**

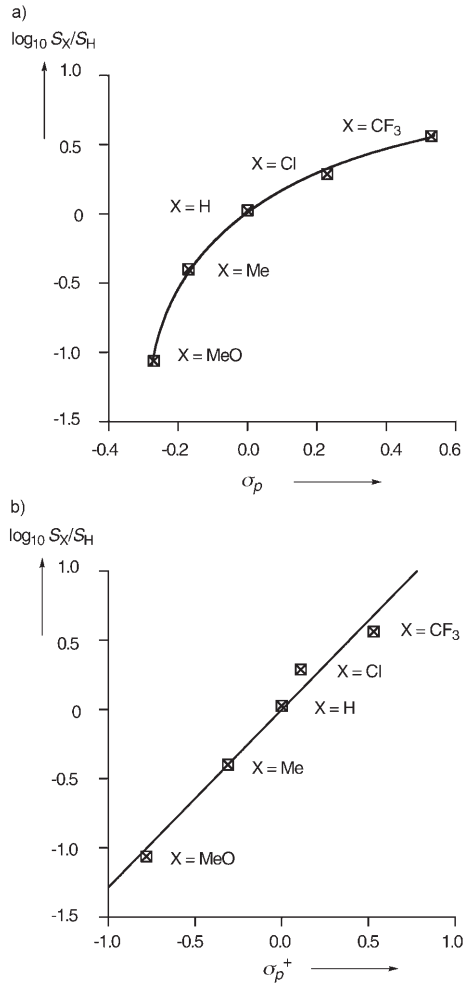
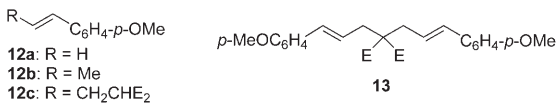
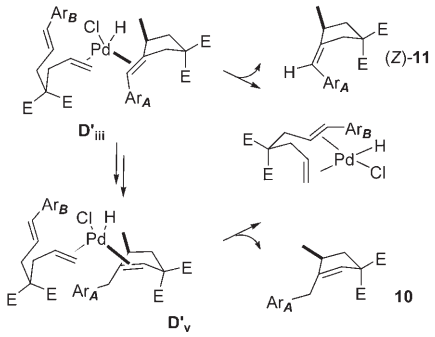


Figure 1. Hammett correlation of *endo*-regioselectivity (*S*) of Pd-catalysed cycloisomerisation of 1-aryl-1,6-dienes **9a–e**, see Table 1, entries 1–5. The dienes were reacted as single samples. *y* axis: $\log_{10}(S_X/S_H)$, where S_X is regioselectivity expressed as the ratio *endo*-**10**/*exo*-**11** when *para* substituent in **9** is *X* [*X* = MeO (**9b**), Me (**9c**), H (**9a**), Cl (**9d**), CF_3(**9e**)]. *x* axis: a) standard σ value (σ); b) modified σ value accounting for resonance effects (σ^+). Line through data in a) is merely an aid to the eye. Line through data in b) is based on linear regression: $\log_{10}(S_X/S_H) = 1.285(\sigma^+) - 0.009$ for which $r^2 = 0.975$.

was found to affect the regioselectivity of cyclisation of **9e** (→ 39:61, **10e**/**11e**) but less so than the *mono*-anisyl diene **9a** (→ 27:73, **10e**/**11e**). Analogous observations were made with the *p*-Cl bearing substrate **9d**.



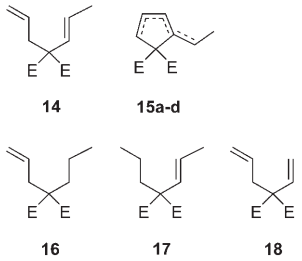
The "intermolecular" electronic modulation of regioselectivity in the cycloisomerisation of aryl dienes **9a–e**, by aryl dienes **9a–e**, but not by simple vinyl arenes, is consistent with a mechanism in which the fourth coordination site in $\mathbf{D'_{iii}}$ (see Scheme 6), is occupied by the alkene unit from another molecule of diene substrate **9**, and from which product (*Z*)-**11** displacement by the cinnamyl unit can occur with concomitant generation of a diene chelate Pd(Cl)–H complex.



Scheme 6. A "chelate-driven" mechanism to account for the intermolecular effect of vinylarene π-donating power of 1-aryl-1,6-dienes **9** on the regioselectivity of cycloisomerisation of other 1-aryl-1,6-dienes **9** to generate "*endo*" isomer **10** versus "*exo*"-(*Z*)-**11**, see text for full discussion.

An associative[39] mechanism for product displacement then allows more strongly binding (π→d) cinnamyl units to increase the relative rate of product displacement ($\mathbf{D'_{iii}} \rightarrow$ (*Z*)-**11**) over isomerisation ($\mathbf{D'_{iii}} \rightarrow\rightarrow \mathbf{D'_{v}} \rightarrow \mathbf{10}$) and thus affect the (*Z*)-**11**/**10** ratio.[40]

Catalyst inhibition mechanism—Cycloisomerisation of an isomeric 1,5-diene: Our previous studies of the kinetics of the cycloisomerisation of **1** to **3** by pro-catalysts of type **8** revealed that a product inhibition mechanism, the mode of which was unclear, limits the catalyst system to about 80 turnovers.[14b] On further investigation, the inhibitor has now been identified as nascent prop-2-enyl allyl dimethylmalonate (**14**),[9] as indicated by the following experiments.

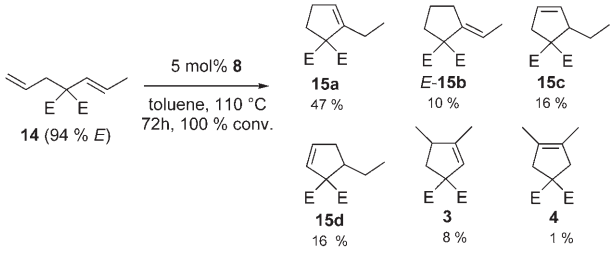


Cycloisomerisation of **1**→**3** catalysed by **8** (1 mol%) in toluene at 40°C proceeds smoothly over a period of 300 minutes (GC analysis: **1** (14%) and **3** (86%)) after which turnover slows substantially. However, on heating slowly (15 minutes) to 110°C, all of the remaining **1** is consumed to generate **3** (89.7%) and **4** (9.8%), together with traces (0.5%) of a new cycloisomer (**15a**, see below). When the same reaction is conducted at 40°C (81% conversion, 228 minutes) addition of a further 1.0 equivalent of diene **1** has no significant effect on the turnover rate (less than 3% conversion of remaining **1** in a further 30 min), indicative of extensive cat-

alyst inhibition or termination. However, on brief heating to 110 °C, (2 min) then rapid cooling back to 40 °C, traces of 1,5-diene **14** (ca. 0.5 %) in addition to **2** (1.2 %), **3** (98.4 %) and **4** (0.8 %) are detected, suggesting that heating releases **14** from inhibited Pd intermediates(s). Repeated heating/cooling cycles confirmed that after the onset of inhibition (ca. 80 turnovers), cycloisomerisation (**1** → **3**) only proceeds efficiently on heating and also results in progressive generation of 1,5-diene **14** accompanied by a noticeable decrease in turnover rate between cycles.

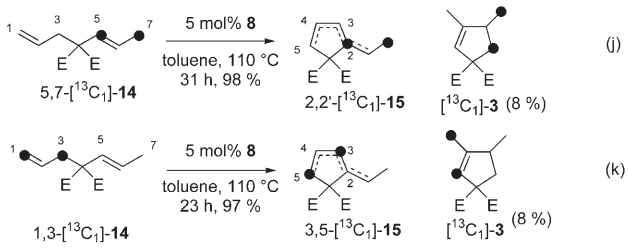
The effect of adding small amounts of independently prepared (*E*)-**14** to the cycloisomerisation of **1** to **3** by pro-catalysts of type **8** undergoing smooth and efficient turnover (5 mol % **8**, DCE, 40 °C) is remarkable: as little as 2 mol % (*E*)-**14** causes rapid (= 5 min) and powerful (> 12-fold) inhibition of catalyst turnover.[41] The addition of 5 mol % of either the allyl propyl malonate (**16**) or isomeric prop-2-enyl propyl malonate (**17**) has no effect whatsoever on the rate of cycloisomerisation of **1** to **3** catalysed by **8** (5 mol %, DCE, 40 °C). In contrast, the vinyl allyl malonate **18** was equally as effective an inhibitor[41] as (*E*)-**14**. This latter result rules out both a steric effect arising from double bond 1,2-disubstitiution and allylic methyl insertion[28] as mechanisms for inhibition and also implicates the involvement of *both* alkene units in **14**.

When **14** is reacted separately with catalytic amounts[42] of **8** (5 mol %) in DCE or toluene at 40 °C no cycloisomeric products are detected, however, on heating to reflux in toluene, reaction proceeds relatively smoothly over a period of 72 h to yield cyclopentene/cyclopentylidene isomers **15a–d**,[43] together with 8 % of **3** and a trace of **4** (Scheme 7).



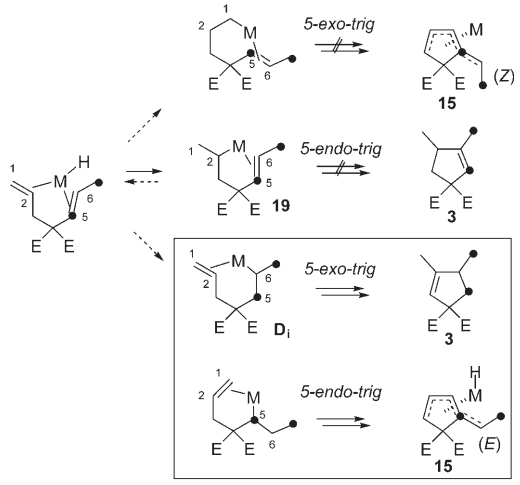
Scheme 7. Cycloisomerisation of (*E*)-**14**, the regioisomer of 1,6-diene **1**, catalysed by Pd pre-catalyst **8**. Reaction of **1** proceeds significantly faster than that of (*E*)-**14** when reacted alone (100 % conversion, 90 minutes, 40 °C) but when mixed in equimolar quantities with (*E*)-**14** both the 1,5- and 1,6-isomers (**14** and **1**, respectively) convert, within experimental error, at the same rate.

Deployment of ^{13}C-labelled substrates [1,3-$^{13}C_1$]-**14** and [5,7-$^{13}C_1$]-**14** [Eqs. (j) and (k)] clearly demonstrates that the ring in **15** is constructed by connection of C(1) with C(5) in **14**, with all of the other original C–C connectivities intact. However, the ^{13}C-label distribution in the 8 % of **3** that is co-generated from **14**[44] reveals that it does *not* arise by isomerisation of **14** to free **1** followed by cyclisation of **1**, but instead must arise directly from **14**.



Under the same conditions (5 mol % **8**, toluene, reflux), the co-cycloisomerisation of equimolar **1** and **14** (to give **3** and **15**, respectively) proceeds smoothly, and the two substrates are consumed, within experimental error, at identical rate. These results demonstrate that under the conventional conditions for cycloisomerisation of **1** to **3** using **8** (5 mol %, DCE, 40 °C) the co-generation of traces of **14** (even if not liberated from Pd) will result in progressive and efficient catalyst inhibition,[45] but not termination. In other words conversion of **14** to **15** involves the same active "[Pd–H]" catalyst but proceeds through, or in equilibrium with, a significantly more stable resting-state(s)[46] than that involved in conversion of **1** to **3**, see below. The co-generation of **15**/**3** is accommodated by four mechanisms analogous to **D**, vide supra, arising from regioisomeric hydropalladations of the (C(1)=C(2)) and (C(5)=C(6)) alkene units in **14** (see Scheme 8).

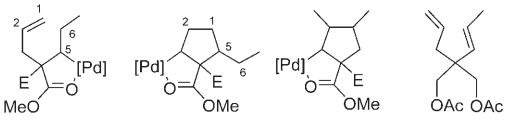
The ratio of the cycloisomers (**15a–d** and **3**) is constant (± 2 %) throughout the reaction evolution, indicative of a kinetic product mixture, which would require any alkene migrations in **15** to arise through repeated *intramolecular* hydropalladation/*syn* β-H elimination. ^{1}H NMR (NOE) and ^{13}C NMR ($^3J_{C,C}$) analysis demonstrates that the *E* isomer of



Scheme 8. Four potential pathways for cycloisomerisation on hydropalladation of the C(1)=C(2) or C(5)=C(6) double bonds of 1,5-diene (*E*)-**14**, to give cycloisomers **15** or **3** depending on the regiochemistry of the hydropalladation event. The mechanisms that are consistent with the observed ^{13}C label distributions and double bond geometry in **3** and **15b** respectively [Scheme 7 and Eqs. (j) and (k)], are shown in the boxed area. Intermediate **19** is proposed to be the mode of catalyst inhibition, see text for full discussion.

15b is generated (> 95% selectivity)[47] and this rules against hydropalladation of the terminal alkene leading to C(1)–Pd, followed by 5-*exo*-*trig*[48] *syn*-carbopalladation and then **15b** via β-H elimination, as this will generate the unobserved[47] *Z* isomer, (*Z*)-**15b**. Hydropalladation of the terminal alkene leading to C(2)–Pd and thus **3**, via **19**, is ruled out on the basis of ^{13}C labelling [Eqs. (j) and (k)] for which the opposite ^{13}C distributions are observed. A mechanism proceeding by hydropalladation of the *internal* alkene of **14**, (C(5)=C(6)), leading to C(6)–Pd → **3** and C(5)–Pd → **15** (see boxed area in Scheme 8) is consistent both with the ^{13}C label distribution in **3** [Eqs. (j) and (k)] and the stereoselective[49] generation of (*E*)-**15b**.

Returning to the powerful inhibitory effect of **14** on the turnover of **1**, it is of note that two σ-alkyl palladium intermediates en route to **15** can undergo complexation of Pd with a *syn*-related malonate carbonyl group. The resulting chelates (**20** and **21**) are closely related to the stable chelate **22**, characterised by NMR (the 4-ethyl analogue was characterised by X-ray crystallography) by Widenhoefer et al.,[8,50] which was shown to be the "off-cycle" resting state in the cycloisomerisation of **1** to **3** by a cationic Pd–phenanthroline catalyst system.

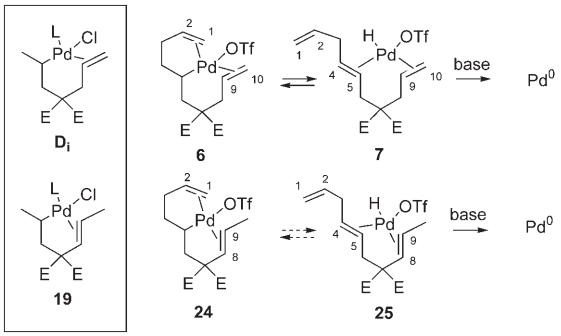


20 **21** **22** **23**

Analogous stability of **20** and **21** would account for the markedly slower turnover of **14**, and the resulting inhibition of turnover of **1**, by pro-catalysts **8**. However, 1,5-diene **23**, the diacetoxymethylene analogue of **14**, is just as an efficient inhibitor for the cycloisomerisation of **1** as **14**, despite the negation of stable chelate formation as in **20** and **21**.[50] Reaction of **23** on its own (5 mol% **8**, toluene, reflux, 3 d, 95% conversion) gave cycloisomeric products analogous to **15a–d** and in the same ratios.[51]

The mechanism proposed for cycloisomerisation of **14** to **15**/**3** (Scheme 8, boxed area) involves addition of Pd–H to the more hindered prop-2-enyl alkene unit (C(5)=C(6)) in **14**, rather than to the less hindered terminal alkene (C(1)=C(2)) allylic group. However, the latter mode of addition, to generate a chelated C(2)–Pd alkene complex (**19**), is expected to be kinetically favoured.[52] Based on ^{13}C labelling (see above) it is evident that **19** does not go on to generate **3**, however this does not rule out equilibrium of **14** with **19**. Some indications as to the relative stability of **19** as compared to $\mathbf{D_i}$, comes from the relative stability and reactivity of the allylpalladated diene complexes **6** and **24**[11] (Scheme 9).

Complex **6** is in dynamic equilibrium with the (unobserved) Pd–H species **7** via displacement of the C(1)=C(2) alkene, then β-H elimination, as can be detected by deprotonation of the Pd centre in **7** by simple organic bases, to generate Pd^0 and the corresponding 1,4,9-triene.[11a] The isomeric complex **24**, in which the size of the larger chelate ring is reduced by one methylene unit (coordination of C(8)=C(9)), is substantially more stable than **6** ($K_{6\rightarrow 24} \geq 50$, $\Delta G^0 \geq 9.5\ kJ\,mol^{-1}$ at 298 K).[11b] This change in ring-size also has a profound effect on the rate of Pd–H (**25**) generation via β-H elimination as evidenced by a ≥1000-fold rate reduction for **24** + base → Pd^0 + 1,4,8-triene, as compared to **6**.[11b] By analogy, complex **19** is expected to undergo very slow β-H elimination to generate "[Pd–H]" and liberate **14**. Taken together, these factors account for the powerful inhibiting, but not terminating, effect of **14** on the cycloisomerisation of **1** to **3**. Addition of "[Pd–H]" to C(1)=C(2) of **14** generates, with high selectivity, the unproductive but stable σ-C(2)-Pd-π-[C(5)=C(6)] chelated complex **19**. It is the minor addition modes of "[Pd–H]" to C(5)=C(6) in **14** that results in a slow but productive turnover to give **3** and **15a–d** (Scheme 8). The high stability of **19**, or related complexes, towards β-H elimination (to regenerate Pd–H and **14**) thus causes a reservoir of Pd that is off-cycle, in effect dramatically reducing the active catalyst concentration and thus attenuating the rate of cycloisomerisation of **1**. The partitioning of **1** to **3** versus **14** (sequestered as complex **19**) can be estimated as about 80:1 based on the maximum turnover number elucidated by our earlier analysis of the reaction kinetics.[14b]



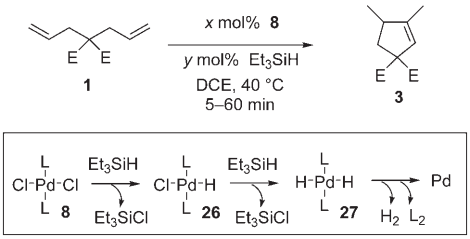
Scheme 9. Contrasting reactivities of complexes **6** and **24** towards C(1)=C(2) alkene displacement and then β-H elimination to generate **7** and **25**, respectively, as probed by deprotonation of the latter complexes by simple organic bases, such a 1,8-bis(dimethylamino)naphthalene. Inset: the structural relationships of Pd complexes $\mathbf{D_i}$ and **19** (L = alkene) to **6** and **24**, see text for full discussion.

Pre-catalyst [$(RCN)_2PdCl_2$] activation and mechanism of cycloisomerisation of 1 to 3: In our previous reports on the cycloisomerisation of **1**→**3**, we proposed that slow generation of an active palladium–hydride species "Pd–H" from the pre-catalyst **8** and the diene **1**, coupled with an efficient inhibition mechanism would account for the observed reaction kinetics and a limit of approximately 80 turnovers per Pd.[14b] Despite numerous attempts we have been unable to detect any pre-catalyst activation co-products thus far. However, experiments conducted in the presence of silanes (R_3SiH, R = Et or Ph), known to effect rapid σ-bond meta-

thesis of Si–H with Pd–Cl and thus generate Pd–H,[53] demonstrate substantial rate accelerations (Table 2).

For example, with 5 mol% **8** and 5 mol% Et_3SiH, 100% conversion **1**→**3** is achieved in under 5 min (Table 2, entry 1), affording significant acceleration relative to the reaction without added silane (Table 2, entry 2). Experiments with lower catalyst loading (Table 2, entries 3–5) demonstrate that a 1:1 ratio of **8**/Et_3SiH gives maximum catalyst activation. With lower catalyst loadings it is also evident that the net turnover number is limited to about 80 (irrespective of whether Ph_3SiH or Et_3SiH is employed as activator) and the regioselectivity is still high (>96% **3**). The reaction of **8** with silane (Si-H) thus appears to generate the same active species as that with **1** + **8** but much more rapidly. Hence in the absence of added Et_3SiH, 80% conversion of **1** with 1 mol% **8** takes 6 hrs, whereas in the presence of 1 mol% Et_3SiH this takes under 40 minutes. Importantly, maximum turnover frequency is obtained when Pd/Si = 1, the rate of **1**→**3** being *twice* that obtained with either 0.5 or 1.5 equivalents of R_3SiH. This strongly suggests that the active species is the *mono*-hydride [$L_2Pd(H)Cl$] (**26**) and that the *di*-hydride [L_2PdH_2] (**27**, L = alkene or solvent) is unstable. Indeed, copious quantities of Pd black were observed when Si/Pd > 1 (Table 2, entry 5).

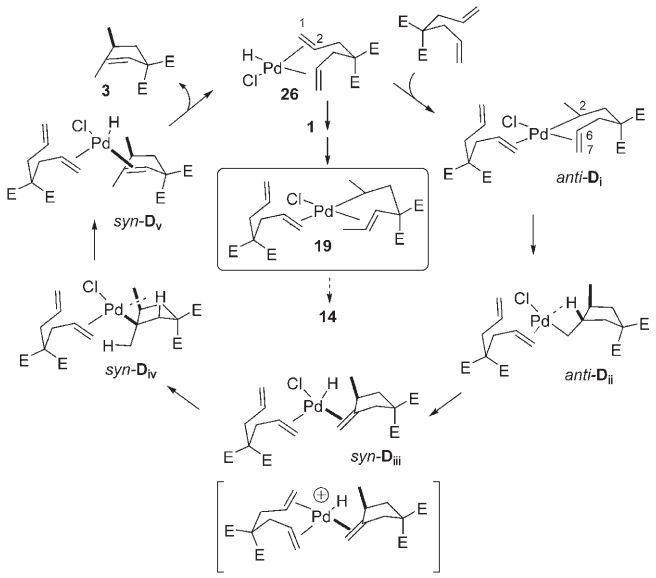
Table 2. Effect of added Et_3SiH on the normalised[a] pseudo zero-order rate constant (k_{obs})[b] and maximum conversion in the cycloisomerisation **1**→**3**[c] (initial concentration 0.15 M) employing pre-catalyst **8** in DCE at 40 °C.



Entry	mol% **8**	mol% Et_3SiH	(k_{obs}/[Pd])[a]/$s^{-1} \times 10^{-2}$	Conv.[d]/% (t/min^{-1})
1	5.0	5.0	>6.6[e]	100 (≤5)
2	5.0	0	0.6	98 (75)
3	1.0	0.5	4.2	50 (30)
4	1.0	1.0	8.3	80 (40)
5	1.0	1.5	4.4	50 (30)[f]

[a] Rate is normalised relative to $[\mathbf{8}]_0$. [b] Determined by linear regression of the pseudo zero-order rate profile for 0 → >60% conversion of **1**, as determined by GC analysis against an internal standard. [c] Regioselectivity is > 96% **3** except for entry 1 where extensive isomerisation of initially generated **3** occurred (0% **2**, 73% **3**, 27% **4** in 5 minutes; 0% **2**, 68% **3**, 32% **4** in 90 minutes; 0% **2**, 42% **3**, 58% **4** in 51 h). [d] Maximum conversion of **1** reached in time "t", before turnover rate subsided to 5% of pseudo-zero-order. [e] Lower limit as 100% conversion achieved in less than 5 min. [f] Reaction mixture became black immediately after addition of silane.

Based on a series of ^2H- and ^{13}C-isotopic labelling experiments [Eqs. (a)–(k)] and the effects of alkene substitution (Figure 1) and alkene isomerisation (Scheme 7), as well as the relative reactivity of related allyl palladated complexes (Scheme 9), a mechanism for the highly regioselective conversion of diene **1** to its cycloisomer **3**, by pre-catalysts of type [L_2PdCl_2] (L = RCN or DMSO) can thus be proposed (Scheme 10). Hydropalladation of **1** by the *mono*-hydride [$L_2Pd(H)Cl$] (**26**, L = alkene or solvent) proceeds with very high, chelate-controlled, regioselectivity to generate the σ-alkyl palladium complex $\mathbf{D_i}$ in which Pd has been added to C(2) of **1**. The selective generation of **3**, rather than **4**, as the kinetic product, is readily explained by the stereochemistry of the subsequent 5-*exo*-*trig* carbopalladation of C(6)=C(7) to generate the *anti* diastereomer $\mathbf{D_i}$→*anti*-$\mathbf{D_{ii}}$ and the ensuing *syn*-stereospecific eliminations/additions: *anti*-$\mathbf{D_{ii}}$→*syn*-$\mathbf{D_{iii}}$→*syn*-$\mathbf{D_{iv}}$. The relative stereochemistry in the penultimate intermediate of the cycle (*syn*-$\mathbf{D_{iv}}$) means that **3**, but not thermodynamically favoured **4**, can be generated via *syn*-β-H elimination[54] (→*syn*-$\mathbf{D_v}$) and then product displacement (→**3** + **13**).



Scheme 10. A mechanism, based on kinetics, isotopic labelling, Hammett correlation, reaction of isomeric 1,5-dienes (**14** and **23**), and intermolecular regioselectivity control by aryl-1,6-dienes (**9**), for the highly regioselective cyclosiomerisation of **1**→**3** by pre-catalysts of type **8** as compared to the much less selective cycloisomerisation **1**→**2** by cationic pre-catalysts of type **5** (see intermediate in square parentheses). Reaction of the pre-catalyst **8** with **1** (or with Et_3SiH in the presence of **1**) is proposed to initiate catalysis by generation of **26**. Turnover numbers are limited to ca. 80 per mol **26** due to a side reaction involving isomerisation **1**→**14** (not liberated)→**19** which is rather inert towards β-H elimination (see inset to Scheme) and sequesters Pd "off-cycle".

Conclusion

In light of the investigations described above, we suggest that the origin of the remarkable difference in selectivity between cycloisomerisation of **1** catalysed by complexes derived from **5** (via **6**) versus those derived from **8**, is simply

the presence of chloride ion in the latter.[12] With cationic systems **5** or **6**, an additional coordination site is available throughout turnover, allowing chelation of the next molecule of diene **1** at all stages, including $\mathbf{D_{iii}}$, (see cationic isomer in square brackets, Scheme 10). Displacement of **2** at stage $\mathbf{D_{iii}}$, is then entropically favoured in the cationic system over displacement of *one* alkene unit in **1** and thus cyclisation of the diene **1** is favoured over isomerisation of **2**→**3**. Interestingly, in the late stages of reaction (when diene **1** concentration is lower) or in the presence of a large excess RCN, the cationic systems **5** or **6** were found to very slowly catalyse conversion of **1** directly to **3**,[9] presumably through RCN competing with **1** for coordination to $\mathbf{D_{iii}}$. In contrast to the cationic intermediates generated by **5**, diene **1** can only mono-coordinate to Pd in $\mathbf{D_{iii}}$ in the neutral chloride-bearing system generated from **8**. Simple considerations of steric bulk suggest that the chloride will be *cis*-related to the mono-coordinated diene **1**, allowing isomerisation, via $\mathbf{D_{iv}}$ and $\mathbf{D_v}$, of coordinated **2** to **3**. Liberation of **3** is proposed to proceed via a mono- to bidentate switch in the coordination of diene **1** in intermediate $\mathbf{D_v}$. This latter feature, which is in effect a chelation-driven product displacement, can influence product regioselectivity by displacement at the stage of $\mathbf{D_{iii}}$ when arylated dienes **9** are employed as substrates. Through this mechanism, the electron-donor properties of one 1-aryl-1,6-diene substrate (**9**) can influence the regioselectivity of cyclisation of another, in particular through the strong (π→d) donation facilitated by an anisyl group (Scheme 6 and Table 1).

In parallel with the productive cyclisation of **1** to **3** is a competing isomerisation of **1** to **14**, albeit at a much lower rate (ca. 1:80). This isomerisation may take place by β-hydride elimination at stage $\mathbf{D_i}$, or alternatively, at the stage of mono-coordination of **1** in intermediates $\mathbf{D_{iii}}$ or $\mathbf{D_v}$ where a chelate of **1** is not present at the stage of hydropalladation. The endogenous 1,5-diene **14**, which may not even be generated as a free entity, is a powerful inhibitor of turnover via a stable chelated σ-alkyl palladium complex **19** (see inset in Scheme 10). Complex **19** does not undergo 5-*endo-trig* carbopalladation to give **3**, nor does it readily undergo β-hydride elimination to liberate **14** and regenerate Pd–H. The isomerisation process (**1** + **26**→**19**) thus increasingly sequesters Pd as turnover proceeds. Under forcing conditions (110 °C, toluene, 5 mol % **8**) the 1,5-diene **14** undergoes cycloisomerisation to give a mixture of products (**15a–d**) arising from hydropalladation of the more hindered (C(5)=C(6)) double bond. Under the same conditions, co-mixtures of **14** and **1** undergo cycloisomerisation at the same rate.

An important conclusion that can be drawn from the mechanism proposed for productive cyclisation of **1** to **3**, is that the diene performs a dual role in the reaction: it acts as both the reactant and as a ligand for the Pd. The lack of impact of various exogenous monoalkenes (**12a–d**, **16** and **17**) on the cyclisation of **1** or **9** demonstrate the importance of the ability of **1** and **9** to act as chelating bidentate ligands. As such, an essential component for the asymmetric catalysis of such a process (**1**→**3**) through an analogous mechanism will be a monodentate anionic chiral ligand to replace the chloride.

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[6] Pd-based 1,6-diene cycloisomerisation catalysts not covered by reviews cited in ref. [2]: a) L. A. Goj, G. A. Cisneros, W. Yang, R. A. Widenhoefer, *J. Organomet. Chem.* **2003**, *687*, 498–507 and erratum: L. A. Goj, G. A. Cisneros, W. Yang, R. A. Widenhoefer, *J. Organomet. Chem.* **2004**, *689*, 2845–2845; b) A. Heumann, L. Giordano, A. Tenaglia, *Tetrahedron Lett.* **2003**, *44*, 1515–1518; c) M. Alvaro, D. Das, H. Garcia, A. Leyva, *Tetrahedron* **2004**, *60*, 8131–8135; d) I. J. S. Fairlamb, S. Grant, A. C. Whitwood, J. Whitthall, A. S. Batsanov, J. C. Collings, *J. Organomet. Chem.* **2005**, *690*, 4462–4477.

[7] The formation of cyclohept- or cyclohex-type products by 1,6-diene cycloisomerisation, is, as far as we are aware, restricted to early transition-metal catalysts systems reported in the following references: a) S. Okamoto, T. Livinghouse *Organometallics* **2000**, *19*, 1449–1451; b) S. Thiele, G. Erker, *Chem. Ber.* **1997**, *130*, 201–207.

[8] L. A. Goj, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11133–11147.
[9] K. L. Bray, J. P. H. Charmant, I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Eur. J.* **2001**, *7*, 4205–4215.
[10] K. L. Bray, G. C. Lloyd-Jones, *Eur. J. Org. Chem.* **2001**, 1635–1642.
[11] a) G. C. Lloyd-Jones, P. A. Slatford, *J. Am. Chem. Soc.* **2004**, *126*, 2690–2691; b) G. C. Lloyd-Jones, P. A. Slatford, M. P. Muñoz, unpublished results.
[12] The purity of the cationic pre-catalyst **5** affects the regioselectivity of the cycloisomerisation of **1**. The cation **5** is generated by dehalogenation of $[(PdCl(allyl)]_2$ by AgOTf (Ag/Pd = 1) in the presence of MeCN. It was found that if **5** was contaminated by as little as 5% of residual $[(PdCl(allyl)]_2$, the cycloisomerisation of **1** generated substantial quantities of **3** (up to 50%) as the primary product in competition with **2**. It is important to note that $[(PdCl(allyl)]_2$ itself is inert as a pre-catalyst for the cycloisomerisation of **1** and does not react stoichiometrically with **1** in an analogous manner to **5**, suggesting that traces of $[(PdCl(allyl)]_2$ possibly act simply as a source of soluble chloride. Addition of aqueous halide to **6** in the presence of **1** leads to **3** with high selectivity: 0.142 M **1**, DCE, 40 °C, 5 mol% **6**, 100 mol% *t*BuCN, 5 mol% NaCl, 12 h, affording 100% conversion with > 95% regioselectivity for **3**.
[13] A. Heumann, M. Moukhliss, *Synlett* **1998**, 1211–1212.
[14] a) K. L. Bray, I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Commun.* **2001**, 187–188; b) K. L. Bray, I. J. S. Fairlamb, J.-P. Kaiser, G. C. Lloyd-Jones, P. A. Slatford, *Top. Catal.* **2002**, *19*, 49–59.
[15] It is proposed that $[(L)_2PdCl_2]$ act as soluble analogues of the polymeric $[PdCl_2]_n$ pre-catalyst system developed earlier by Grigg et al.: R. Grigg, J. F. Malone, T. R. B. Mitchell, A. Ramasubbu, R. M. Scott, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1745–1754.
[16] Coordinating groups, such as amines and amides were found to inhibit reaction, indeed, acting as catalyst poisons in the normal reaction of **1**. However, a range of alcohols, carbonates, esters and ethers were tolerated and these substrates displayed a moderate Thorpe–Ingold type effect on the reaction rate, as has been noted by others; a) Y. Yamamoto, Y. Nakagai, N. Ohkoshi, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6372–6380; b) R. A. Widenhoefer, C. N. Stengone, *J. Org. Chem.* **1999**, *64*, 8681–8692.
[17] This value is estimated by kinetic simulation of the product evolution profiles using the programme MacKinetics (commercial software, Leipold Associates, USA).
[18] Although small traces (⩽ 0.5%) of *exo*-alkene **2** are detected during the early stages of reaction, deliberate addition of **2** to the reaction results in moderate inhibition and material balance indicates that **2** is isomerised to **4** and not **3**.
[19] We have thus far been unable to identify any new Pd-complexes in stoichiometric or catalytic reactions between **1** and **8** by NMR. Instead, rapid catalytic turnover ensues and **3** is generated in high yield. This stands in contrast to the reaction of **1** with **5**, which, in addition to generating cycloisomers **2**, **3** and **4**, gave an NMR-observable product (**6**, Scheme 2).
[20] Occasionally, the reactions were left for longer periods and the product mixture was contaminated with small quantities of **4** (< 10%) generated through isomerisation of **3**.
[21] Samples taken during reaction evolution were analysed by GC and NMR (^1H, ^2H and ^{13}C). The $^{13}C\{^1H\}$ NMR analyses were aided by CH correlation and DEPT where appropriate. The Pd-complexes were removed from the samples by elution through a short plug of silica gel with CH_2Cl_2 and the samples analysed immediately. Such samples left for longer periods gave identical results.
[22] The high isotopic fidelity was evident on inspection of the $^{13}C\{^1H\}$ NMR spectrum in which C(5)-H_2 and C(2)-H appear as singlets (i.e., no D incorporation), C(4)-D appears as a clean isotopically shifted ($\Delta\delta = 0.4$ ppm) triplet ($^1J_{C,D} = 20$ Hz), C(3)-CD_3 which is devoid of any significant NOE was not fully resolved as a 1:3:5:6:5:3:1 septet (but ^1H NMR analysis confirmed < 0.05 H per methyl), and C(4)-CD_2H appears as an isotopically shifted ($\Delta\delta = 0.7$ ppm) 1:2:3:2:1 quintet ($^1J_{C,D} = 20$ Hz).
[23] C(4)–H (2.71 ppm) appears as a clean triplet in the ^1H NMR spectrum ($^3J_{H,H} = 6.84$ Hz) whilst C(4)-CDH_2 (1.05 ppm) integrates for 2H and C(3)-CH_3 (1.72 ppm) for 3H. Signals for C(2)H (5.43 ppm) and C(5)-H_2 (2.7 and 1.94 ppm) are absent. This result eliminates the possibility that deuterons or protons are being lost or gained to any significant extent by exchange processes with the reaction environment, solvent, glassware etc.
[24] The presence of a single deuterium at C(3)-CH_3 was confirmed by the clean 1:1:1 triplet in the $^{13}C\{^1H\}$ NMR at 14.6 ppm ($\Delta\delta = 0.2$ ppm, $^1J_{C,D} = 18$ Hz). The level of deuteration at C(4) is not easily estimated from the ^1H NMR spectrum due to overlap with a C(5)H multiplet at 2.7 ppm. However, the latter is a clean ($^2J_{H,H}$ doublet) and no signal at 41.9 ppm is evident for C(4) in the $^{13}C\{^1H\}$ NMR spectrum, suggesting > 95% deuterium at C(4).
[25] Analysis of the double bond geometry in the 1,7-[$^2H_2$]-**1** substrate by ^1H NMR during reaction indicated that *E*/*Z* equilibration of 1,7-(*Z*,*Z*)-[$^2H_2$]-**1** (i.e., *Z*,*Z* → *Z*,*Z* (25%), *Z*,*E* (50%), *E*,*E* (25%)) proceeded faster than its cycloisomerisation, being almost complete by 75% conversion **1**.
[26] I. Guibert, D. Neibecker, I. Tkatchenko, *J. Chem. Soc. Chem. Commun.* **1989**, 1850–1852.
[27] G. Oehme, *J. Prakt. Chem.* **1984**, *326*, 779–790.
[28] a) A. Sen, T.-W. Lai, *Organometallics* **1983**, *2*, 1059–1060, and references therein; b) D. R. Chrisope, P. Beak, W. H. Saunders, *J. Am. Chem. Soc.* **1988**, *110*, 230–238.
[29] This mechanism was independently proposed by Widenhoefer (see ref. [8]) and by Lloyd-Jones (see ref. [14b]).
[30] This mechanism was selected on the basis that i) intermediates $\mathbf{A/B_{ii}}$ would be expected to reductively eliminate rapidly to generate **2** (which is known *not* to be an intermediate en route to **3**, see above); ii) intermediate $\mathbf{A/B_{iii}}$ would be expected to give a mixture of β-H elimination products to generate both **3** and **4** (possibly favouring the thermodynamic product **4**) and analogously $\mathbf{C_{ii}}$ would be expected to give a mixture of β-H elimination products to generate both **2** and **3**; iii) that palladacyclobutanes (cf. $\mathbf{A/B_{iii}}$ and $\mathbf{C_{ii}}$) are likely to be rather strained intermediates; and iv) that the very high selectivity for **3** (as opposed to the generation of **4**) can be accounted for on the basis of the diastereoselective generation of *anti*-$\mathbf{D_i}$ which would lead to *syn*-$\mathbf{D_{iv}}$ from which *syn* β-H elimination can only generate, after Pd-H displacement, **2** or **3** and not the thermodynamically favoured **4**.
[31] Careful $^{13}C\{^1H\}$ NMR analysis indicated that no deuterons had been incorporated at the ^{13}C-labelled C(3)-methyl group, or indeed on any of the ^{13}C labels, which were all present as clean ^1H-decoupled singlets.
[32] This was evident from the $^{13}C\{^1H\}$ NMR spectrum which was an analogous to [$^{13}C_2$]-**3** [Eq. (f)], albeit without the $^2J_{C,C}$ coupling present in the cycloisomerisation product derived from [3-$^{13}C_1$, 5-$^{13}C_1$]-**1**.
[33] Importantly, no deuterium was detected at any of the other ^{13}C labelled sites and the level of ^2H incorporation (70%) is close to that expected on the basis of statistical distribution (75%) in the absence of kinetic or equilibrium isotope effects.
[34] See F. R. Hartley, *Chem. Rev.* **1973**, *73*, 163–189, and references therein.
[35] On deploying substrates in which one allylic group was substituted with a methyl or phenyl group at the allylic carbon (i.e., at C(3) in **1**) complex mixtures of products were obtained. This can be rationalised by low chemo- and diastereoselectivity in the intermolecular hydropalladation step leading to a range of cyclopentane and cyclopentene isomers. Whilst some of the major products could be identified by ^1H NMR analysis, the structures of many of the minor compounds remained elusive and little or no separation could be achieved by conventional silica gel chromatography. With a methyl at the alkene terminus in **1** (i.e., 2-crotyl-2-allyl dimethylmalonate) the reaction still proceeded smoothly to give dimethyl 3-ethyl-4-methylcyclopent-2-ene-1,1-dicarboxylate (the homologue of **3**) with reasonable selectivity (ca. 74–81%) plus 18–22% dimethyl 3-ethylidene-4-methylcyclopentane 1,1-dicarboxylate (the homologue of **2**) as a mixture of *E* and *Z* isomers. Both the *E* and *Z* isomers of the sub-

strate underwent cyclisation, however, the *E* isomer appeared unable to effect pro-catalyst activation and thus required co-addition of either the *Z* isomer or **1** to initiate catalytic turnover.

[36] The geometries of structures **10abe** and (*Z*)-**11abe**, were optimized at the MMFF level to obtain the lowest energy conformers as starting structures for subsequent optimization applying density functional theory (DFT) at the generalized gradient approximation using B3LYP hybrid functional Calculations were performed using Spartan′02 (Wavefunction, Inc., Irvine, CA). The standard 6-31G* basis set was used for C, H, O and F, see J. Kong, C. A. White, A. I. Krylov, D. Sherril, R. D. Adamson, T. R. Furlani, M. S. Lee, A. M. Lee, S. R. Gwaltney, T. R. Adams, C. Ochsenfeld, A. T. B. Gilbert, G. S. Kedziora, V. A. Rassolov, D. R. Maurice, N. Nair, Y. H. Shao, N. A. Besley, P. E. Maslen, J. P. Dombroski, H. Daschel, W. M. Zhang, P. P. Korambath, J. Baker, E. F. C. Byrd, T. Van Voorhis, M. Oumi, S. Hirata, C.-P. Hsu, N. Ishikawa, J. Florian, A. Warshel, B. G. Johnson, P. M. W. Gill, M. Head-Gordon, J. A. Pople, *J. Computational Chem.* **2000**, 1532–1548. Calculations indicate that there is only a small effect from aryl substitution, thus ΔE **10a**/(*Z*)-**11a** = 1.0 kcal mol^{-1}; ΔE **10b**/(*Z*)-**11b** = 0.3 kcal mol^{-1}; ΔE **10e**/(*Z*)-**11e** = 0.7 kcal mol^{-1}. It should also be noted that the aryl rings in *exo*-isomers (*Z*)-**11** are twisted away from co-planarity with the alkylidene unit π system and thus are not fully conjugated. The twisting arises from relief of steric strain between the *ortho* protons and the C(2)H_2 unit on the cyclopentyl ring. DFT suggests that the dihedral angle C(*ortho*)–C(*ipso*)–CH=C(3) ranges from −63.3/118.0° in (*Z*)-**10a** and −63.5/117.8° in (*Z*)-**10e** to −73.0/107.4° in (*Z*)-**10b**.

[37] These substrates reacted at very different rates (times for > 98% conversion are 6, 20, 5, 1.5 and 22 h for **9a–e**, respectively) but when mixed, all reacted the same (± 20%) rate (all proceeding to > 95% conversion in ca. 3 h suggesting that different pre-catalyst activation abilities, rather than inherent turnover rates, appear to be predominantly responsible for the differing rates of reaction when reacted alone.

[38] a) E. M. Ban, R. P. Hughes, J. Powell, *J. Chem. Soc. Chem. Commun.* **1973**, 591–592; b) H. Kurosawa, T. Majoma, N. Asada, *J. Am. Chem. Soc.* **1980**, *102*, 6996–7003.

[39] a) The most common mechanism for ligand substitution at d_8 square-planar centres, for example Pd^{II}, proceeds via an associative mechanism involving five-coordinate intermediates or transition states generated via external ligand or solvent attack at the metal centre. For an overview see: R. J. Cross, *Adv. Inorg. Chem.* **1989**, *34*, 219–292; For examples of five-coordinate Pd^{II} alkene complexes see: b) V. G. Albano, C. Castellari, M. E. Cucciolito, A. Panunzi, A. Vitagliano, *Organometallics* **1990**, *9*, 1269–1276; see also c) N. Desmarais, C. Adamo, B. Panunzi, V. Barone, B. Giovannitti, *Inorg. Chim. Acta* **1995**, *238*, 159–163; for a proposal involving five-coordinate alkene intermediates in Pd^{II} catalysis see d) A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6488–6489.

[40] An alternative effect based on destabilisation of σ-alkyl Pd intermediate $\mathbf{D_{iv}}$ by electron donation from the coordinated vinylarene, and thus increase of transition state energy relative to displacement of **11** is also possible. Both effects would work in concert. The effect of *para*-anisyl **9b** on the regioselectivity of cyclisation of **1**, and vice versa, was found to be negligible (1:1 molar ratio of **1**/**9b**). This may be understood in terms of the lower steric decompression on liberation of **2** compared to (*Z*)-**11** and the greater reactivity of the unconjugated methylidene in **2** facilitating rapid conversion of $\mathbf{D_{iii}} \rightarrow \mathbf{D_{iv}}$, irrespective of the identity of the mono-coordinated diene (**1** or **9b**).

[41] In the absence of exogenous (*E*)-**14**, conversion of **1**→**3** proceeds to ≥98% in about 90 minutes (5 mol% **8**, DCE, 40°C, $[\mathbf{1}]_0$ = 0.15 M) with an *apparent* pseudo zero order profile up to 90% conversion. The following changes in pseudo zero order gradients were observed over a 2 h period after addition of (*E*)-**14**: i) 2 mol% (*E*)-**14** added at 20 min (63% conversion) rate prior = 6.4×10^{-5} M s^{-1}; rate after = 5.2×10^{-6} M s^{-1}; relative rate = 12.2; ii) 6 mol% (*E*)-**14** added at 20 min (49% conversion) rate prior = 5.8×10^{-5} M s^{-1}; rate after = 4.0×10^{-6} M s^{-1}; relative rate = 14.6; iii) 4.5 mol% **18** added at 20 min (38% conversion) rate prior = 5.1×10^{-5} M s^{-1}; rate after = 6.0×10^{-6} M s^{-1}; relative rate = 8.5.

[42] Stoichiometric quantities of **8** converted (*E*)-**14** to **15a–d** at 40°C (3 d being required for 100% conversion)—the major isomer (71%) was **15a**.

[43] The identities of the products **15a-c** were confirmed by independent synthesis (**15bc**) or by comparison with literature $^{13}C\{^1H\}$ NMR data (**15b**, O. Kitagawa, T. Suzuki, T. Inoue, Y. Watanabe, T. Taguchi, *J. Org. Chem.* **1998**, *63*, 9470–9475).

[44] The procedure for preparation of diene **14** typically generates 3–8% of **1** as a side product through retro aldol. In the synthesis of [5,7-$^{13}C_1$]-**14**, this generates unlabelled **1**. In the synthesis of [1,3-$^{13}C_1$]-**14** this produces [1,3-$^{13}C_1$]- [5,7-$^{13}C_1$]-**1**. The samples of **14** can be freed of much of the contaminating **1** by lengthy column chromatography on silica gel. In the runs shown in Equations (j) and (k), the total **1** in each sample amounted to ca. 1.0 and 2.5%, respectively and thus accounts for 13 and 33% of **3**, respectively. The ^{13}C label distributions in **3** obtained from **1** [cf. Eq. (e)] is distinct from that obtained from **14** [cf. Eqs. (j) and (k)] and were fully self-consistent with the initial ratios **14**/**1**.

[45] This can arise from even small amounts of **14** due to the low concentration of the active "[Pd-H]" catalyst and the similar reactivity of 1,6-diene **1** and 1,5-diene **9** towards it.

[46] Such a phenomenon bodes well for trapping of the active intermediate, allowing detection and identification by spectroscopic methods. However, despite extensive ^1H and $^{13}C\{^1H\}$ NMR analysis of mixtures of [1,3-$^{13}C_1$]-**1**, [1,3-$^{13}C_1$]-**14**, [5,7-$^{13}C_1$]-**14** and **8** in various solvents, orders of addition and proportions, thus far, we have been unable to identify or isolate any intermediates from the complex mixture of products, which we assume to be halide-bridged oligomeric forms of **19**, that slowly develops.

[47] We do not observe NMR signals attributable to (*Z*)-**15b**. The stereochemical assignment for (*E*)-**15b** is based on ^1H NMR NOE contacts, (see ref. [43]) and is supported by the magnitude of $^3J_{C,C}$ = 3.4 Hz between C(3) and the ethylidene methyl group, typical of such geometry, see: a) J. L. Marshall, L. G. Faehl, R. Kattner, P. E. Hansen, *Org. Magn. Reson.* **1979**, *12*, 169–173; b) P. A. Chaloner, *J. Chem. Soc. Perkin Trans. 2* **1980**, 1028–1032.

[48] Baldwin's "rules for ring closure" (J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734–736) state that "As a consequence of the larger atomic radii and bond distances in atoms of the second Periodic row the geometric restraints on disfavoured ring closures may be bypassed."

[49] The availability of two diastereotopic ethyl protons, both of which can attain a *syn* relationship to Pd, potentially allows the generation of both geometric isomers of **15b** [(*E*/*Z*)-**15b**]. Consideration of the developing strain between the nascent ethylidene group and the *syn*-related malonate ester on *syn* β-H elimination suggests that (*E*)-**15b** will be favoured strongly over (*Z*)-**15b**.

[50] The diacetate analogue of **1** undergoes ca. 400-fold faster turnover than **1** in the presence of the cationic Pd phenanthroline pro-catalyst system, see ref. [6a].

[51] Interestingly, the diol precursor to 1,5-diene **23** did not cycloisomerise. Instead it underwent inefficient isomerisation to what is tentatively assigned as the corresponding 2,5-diene. This stands in stark contrast to the diol analogue of **1** (4,4-bis(hydroxymethyl)-1,6-heptadiene) which underwent cycloisomerisation more rapidly than **1** (see ref. [14b]). The origins of this difference are unclear but may relate to the ability of the hydroxyl groups to intramolecularly coordinate to the Pd intermediate analogous to **19**, facilitating alkene displacement and thus β-H elimination. Addition of equimolar PrOH to the cycloisomerisation of **14** (5 mol% **8**, toluene, reflux) resulted in only 2% isomerisation of **14** to its 2,5-diene isomer at 68% conversion (70 min).

[52] Analysis of mixtures of [1,3-$^{13}C_1$]-**1**, [1,3-$^{13}C_1$]-**14**, and [5,7-$^{13}C_1$]-**14** with **8** by $^{13}C\{^1H\}$ NMR, prior to the onset of rapid catalysis, reveals that there is extensive dynamic line-broadening of the ^{13}C-signals at terminal double bonds (i.e., at C(1) in [1,3-$^{13}C_1$]-**1** and [1,3-$^{13}C_1$]-**14**). Based on the effect of the concentration of [(*t*BuCN)$_2$PdCl$_2$] (**8**) this

arises by weak binding ($0 < K_a \ll 1$) of the alkene to [$LPdCl_2$], which is rapid at the NMR time scale (catalytic **8** causes extensive broadening). There is little or no broadening detected at the internal double bond in **14** (i.e., C(5) in [5,7-$^{13}C_1$]-**14**) emphasising the significantly lower intermolecular coordinating ability arising from the greater steric hindrance at this bond. For a related study see: H. Qian, T. Pei, R. A. Widenhoefer, *Organometallics* **2005**, *24*, 287–301.

[53] D. H. Nguyen, Y. Coppel, M. Urrutigoïty, P. Kalck, *J. Organomet. Chem.* **2005**, *690*, 2947–2951.

[54] *anti* β-H elimination, while precedented, is disfavoured and rarely encountered. For examples, see: a) P. G. Andersson, S. Schab, *Organometallics* **1995**, *14*, 1–2; b) J. M. Takacs, E. C. Lawson, F. Clement, *J. Am. Chem. Soc.* **1997**, *119*, 5956–5957; c) K. Maeda, E. J. Farrington, E. Galardon, B. D. John, J. M. Brown, *Adv. Synth. Catal.* **2002**, *344*, 104–109.

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