

Dramatic Effect of Homoallylic Substitution on the Rate of Palladium-Catalyzed Diene Cycloisomerization

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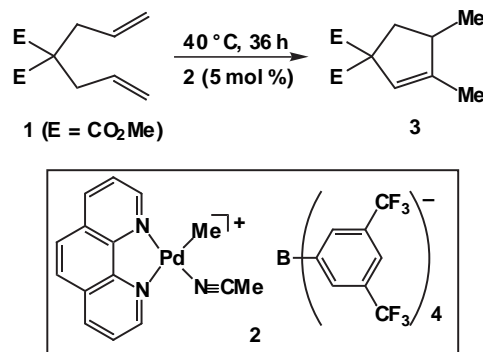
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Abstract: Cycloisomerization of 4,4-bis(acetoxymethyl)-1,6-heptadiene (**5**) catalyzed by $[(\text{phen})\text{Pd}(\text{Me})\text{CNCH}_3]^+ [\text{BAr}_4]^-$ [$\text{Ar} = 3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2$] (**2**) to form predominantly 3,3-bis(acetoxymethyl)-1,5-dimethylcyclopentene (**6**) was ~400 times faster than was the cycloisomerization of dimethyl diallylmalonate (**1**) under identical conditions. Mechanistic studies performed in conjunction with density functional theory calculations attribute the large rate acceleration of the cycloisomerization of **5** relative to the cycloisomerization of **1** to the formation of a stable oxo chelate complex as an intermediate in the cycloisomerization of **1**, but not in the cycloisomerization of **5**.

Introduction

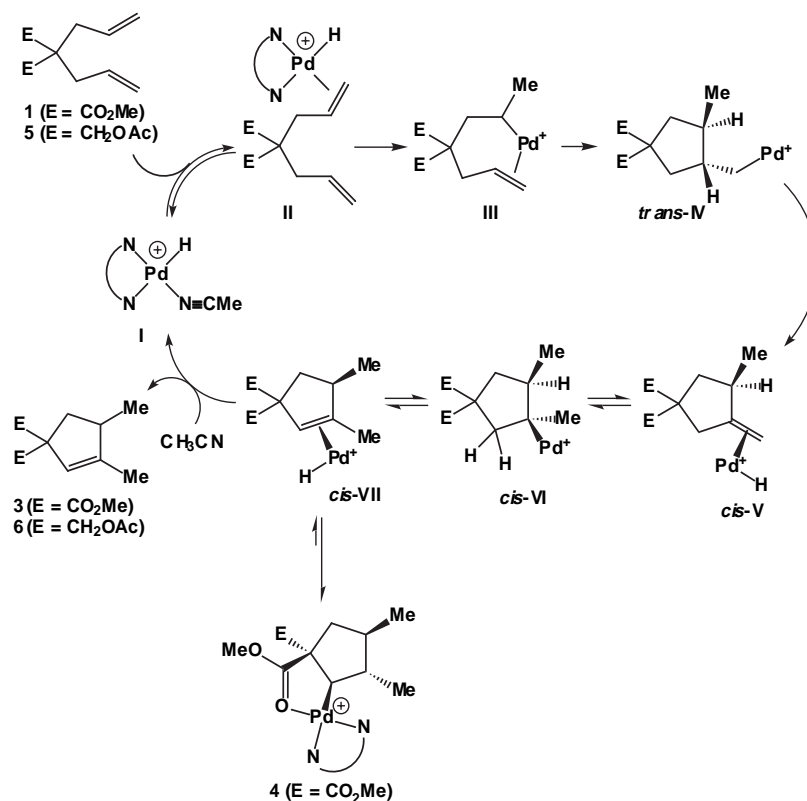
The transition metal-catalyzed cycloisomerization of enynes [1] and dienes [2-11] represents an efficient route to the synthesis of functionalized carbocycles [12], and these methods have been applied to the synthesis of a number of naturally occurring molecules [13]. Our contribution to the area of transition metal-catalyzed cycloisomerization has been the development of a pair of complementary palladium-catalyzed processes for the conversion of 1,6-dienes to either the symmetric [9] or chiral [10] cyclopentenes. For example, reaction of dimethyl diallylmalonate (**1**) catalyzed by $[(\text{phen})\text{PdMe}(\text{CH}_3\text{CN})]^+ [\text{BAr}_4]^-$ (**2**) at 40 °C for 36 h formed predominantly the chiral cyclopentene **3**, which was isolated in 71% yield (Scheme 1) [10].



Scheme 1

As is the case with many transition metal-catalyzed transformations, the development of the synthetic aspects of catalytic cycloisomerization has outpaced an understanding of the mechanisms of these processes [12]. In response to the dearth of mechanistic information regarding transition metal-catalyzed cycloisomerization, we recently reported a study of the mechanism of the cycloisomerization of **1** catalyzed by **2** [11]. The results of this study established a mechanism initiated by hydrometallation of one of the double bonds of **1** to form the palladium alkyl olefin chelate complex **III** followed by intramolecular carbometallation to form *trans*-**IV** (Scheme 2). Isomerization of *trans*-**IV** via reversible β -hydride elimination/addition/elimination followed by displacement of **3** from palladium cyclopentene complex *cis*-**VII** regenerated the palladium hydride species **I**. Selective formation of **3** from **1** was traced to the *trans*-

selectivity of intramolecular carbometallation (**III** \rightarrow *trans*-**IV**), coupled with the non-dissociative nature of the conversion of *trans*-**IV** to *cis*-**VII** [14]. Competing with turnover-limiting olefin displacement from *cis*-**VII** was transfer of the hydride ligand to the more substituted olefinic carbon of *cis*-**VII** coupled with coordination of the pendant carbonyl oxygen atom to form the palladium cyclopentyl carbonyl chelate complex $[(\text{phen})\text{PdCHCH}(\text{Me})\text{CH}(\text{Me})\text{CH}_2\text{C}(\text{COOMe})(\text{COOMe})]^+ [\text{BAR}_4]^-$ (**4**), which was the only organometallic species that accumulated under catalytic conditions.



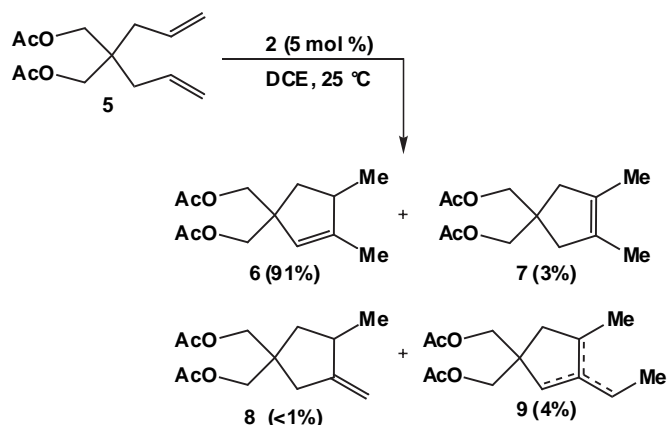
Scheme 2

In the course of our continuing investigation of the mechanisms of palladium-catalyzed diene cyclization [15], we discovered that the rate of diene cycloisomerization catalyzed by cationic palladium phenanthroline complexes depended strongly on the nature of the homoallylic groups of the diene. In particular, cycloisomerization of 4,4-bis(acetoxymethyl)-1,6-heptadiene (**5**) catalyzed by **2** was ~400 times faster than was the cycloisomerization of **1** under identical conditions. Although gem-dialkyl groups are known to accelerate transition metal-catalyzed cyclizations through their steric influence (Thorpe-Ingold

effect) [16], the magnitude of the rate increase observed for the cycloisomerization of **5** relative to the cycloisomerization of **1** is larger than can be attributed to steric effects. We therefore sought to understand the nature of the substrate dependence of the rate of palladium-catalyzed diene cycloisomerization. Here we report a combined mechanistic and computational study of the cycloisomerization of **5** catalyzed by **2** directed toward elucidating the effect of the homoallylic groups on the rate of palladium-catalyzed diene cycloisomerization. The results of these studies suggest that the rate of palladium-catalyzed diene cycloisomerization is related to the stability of the oxo chelate complexes that may form under catalytic conditions.

Results and Discussion

Cycloisomerization of dimethyl diallylmalonate (**1**) catalyzed by **2** was sluggish and required 31 h at room temperature to reach 50% conversion [11]. In contrast, cycloisomerization of 4,4-bis(acetoxymethyl)-1,6-heptadiene (**5**) catalyzed by **2** (5 mol%) at 25 °C reached 50 % conversion in less than five minutes and was complete ($\geq 98\%$) within 15 min. Therefore, cycloisomerization of **5** catalyzed by **2** is ~400 times faster than is the cycloisomerization of **1** under identical conditions. The major product of the cycloisomerization of **5** catalyzed by **2** was 3,3-bis(acetoxymethyl)-1,5-dimethylcyclopentene (**6**), which accounted for 91% of the reaction mixture (Scheme 3). In addition to **6**, 4,4-bis(acetoxymethyl)-1,2-dimethylcyclopentene (**7**, 3%), 1,1-bis(acetoxymethyl)-4-methyl-3-methylenecyclopentane (**8**, <1%), and three compounds of the molecular formula $C_{14}H_{22}O_4$ (4% combined) were detected by GC/MS analysis of the crude reaction mixture (Scheme 3). Compounds **7** and **8** were identified by comparison to authentic samples [9], while the compounds of the molecular formula $C_{14}H_{22}O_4$ were assigned as the ethyl-substituted cyclopentenes **9**, generated as byproducts of catalyst activation, by analogy to the cycloisomerization of **1** catalyzed by **2** [11].

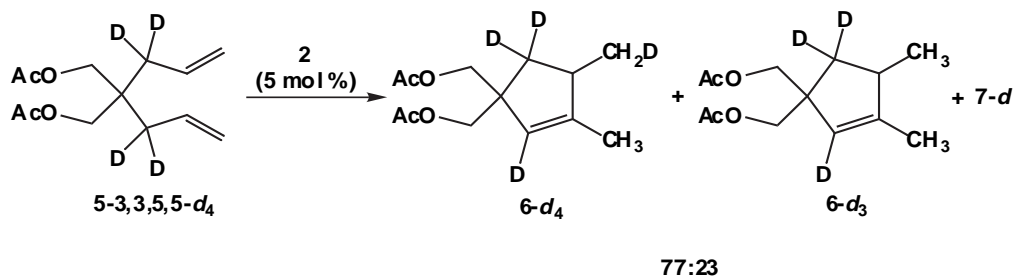


Scheme 3

We initially considered that the much higher rate of cycloisomerization of **5** catalyzed by **2** relative to the rate of the cycloisomerization of **1** catalyzed by **2** might be due to a change in the mechanisms of the respective transformations. To test this possibility, we performed a number of experiments that probed the mechanism of the cycloisomerization of **5** catalyzed by **2** and compared these results to those obtained for the cycloisomerization of **1** catalyzed by **2** [11].

A key feature of the cycloisomerization of **1** catalyzed by **2** was the formation of the chiral cyclopentene **3** as a kinetic product, and not via secondary isomerization of a methylenecyclopentane intermediate. In a similar manner, chiral cyclopentene **6** was formed kinetically in the cycloisomerization of **5** catalyzed by **2** and not via isomerization of **8**. The intermediacy of **8** in the conversion of **5** to **6** catalyzed by **2** was firmly discounted by the failure of methylenecyclopentane **8** to accumulate during the conversion of **5** to **6**, coupled with the slow, non-selective isomerization of **8** under reaction conditions. For example, when an equimolar solution of **8** and 4,4-bis(propanoyloxymethyl)-1,6-heptadiene (**5a**) was treated with a catalytic amount of **2** at 25 °C for 10 min, 95% of diene **5a** and only 11% of methylenecyclopentane **8** was consumed [17]. Furthermore, isomerization of **8** under these conditions formed a 1:1.4 mixture of **6** and **7**, which differed significantly from the >100:1 ratio of **6**:**7** formed in the cycloisomerization of **5**.

Deuterium Labeling Studies. The most detailed information regarding the mechanism of the cycloisomerization of **5** catalyzed by **2** was obtained via deuterium labeling experiments. For example, a solution of **5-2,6-*d*₂** and a catalytic amount of **2** was stirred at room temperature for 15 minutes to form a



Scheme 5

To probe for intermolecular H/D exchange in the cycloisomerization of 5-3,3,5,5- d_4 , an equimolar solution of 5-3,3,5,5- d_4 and **5a** and a catalytic amount of **2** was monitored periodically by GC/MS analysis. After ~80% conversion, $\leq 2\%$ H/D exchange was detected in unreacted dienes 5-3,3,5,5- d_4 and **5a**. Conversely, cyclopentene 6- d was formed as a 40:60 mixture of $d_4:d_3$ isotopomers, as opposed to the 77:23 ratio of $d_4:d_3$ isotopomers formed in the absence of **5a**. Similarly, cyclopentene **6a** was formed as a 60:40 mixture of $d_0:d_1$ isotopomers. From this experiment, we conclude that intermolecular H/D exchange of one of the allylic protons of **5** occurs during, but not prior to cycloisomerization.

Kinetics. In many transition metal-catalyzed transformations, including the cycloisomerization of **5** catalyzed by **2**, the active catalyst is generated in situ from an inactive catalyst precursor. If the rate of catalyst activation is slow relative to the rate of catalyst turnover, the concentration of active catalyst increases throughout the transformation and causes the reaction to appear of erroneously low kinetic order [19]. While catalyst activation in the cycloisomerization of **1** catalyzed by **2** was fast relative to catalytic turnover, this condition was not achieved in the cycloisomerization of **5** catalyzed by **2**. Because carbocycles **9** are formed as byproducts of catalyst activation in the cycloisomerization of **5** catalyzed by **2**, the extent of catalyst activation is mirrored by the relative concentration of **9**. Significantly, analysis of the relative concentration of **9** as a function of conversion in the cycloisomerization of **5** catalyzed by **2**, revealed that the relative concentration of **9**, and presumably the concentration of active catalyst, increased throughout complete conversion of **5** to **6**. Consistent with this conclusion, electrospray ionization mass spectrometry of the residue that remained after complete conversion of **5** to **6** revealed the presence of unreacted **2** ($m/z = 342.0$) and a complex of the composition (phen)Pd(Me)·**5** ($m/z = 541.1$).

Unfortunately, because steady state was not achieved at any time throughout the complete consumption of **5**, no firm mechanistic information could be extracted from these kinetic experiments.

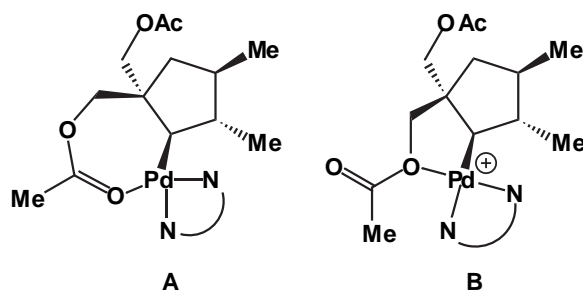
Despite the lack of solid kinetic data, our experimental observations strongly suggest that the microscopic steps involved in the cycloisomerization of **5** catalyzed by **2** are identical to those involved in the cycloisomerization of **1** catalyzed by **2** (Scheme 2). For example, intramolecular transfer of the internal vinylic deuterium atom of **5-2,6-*d*₂** to the exocyclic allylic position of **6-*d*₂** (Scheme 4) is consistent with the conversion of palladium cyclopentylmethyl intermediate *trans*-**IV** to palladium cyclopentyl intermediate *cis*-**VI**. Similarly, the intermolecular transfer of one of the allylic deuterium atoms of **5-3,3,5,5-*d*₄** to the homoallylic exocyclic methyl group of **6-*d*₄** (Scheme 5) is consistent with the conversion of palladium cyclopentyl intermediate *cis*-**VI** to palladium alkyl olefin chelate complex **III** via intermediates **VII**, **I**, and **II** (Scheme 2). Furthermore, the failure of unreacted **5a** to incorporate deuterium in the co-cycloisomerization of **5a** and **5-3,3,5,5-*d*₄** rules out reversible formation of palladium alkyl olefin chelate complex **III**, and the kinetic formation of the chiral cyclopentene **6** from **5** requires both *trans*-selective intramolecular carbometallation (**III** → *trans*-**IV**) and non-dissociative conversion of *trans*-**IV** to *cis*-**VI** [14], as was observed in the cycloisomerization of **1** catalyzed by **2** [11].

Catalyst activation in the cycloisomerization of **5** catalyzed by **2** presumably occurs via initial insertion of one of the double bonds of **5** into the Pd–C bond of **2**, as was also proposed for the cycloisomerization of **1** catalyzed by **2** [11]. The presence of both unreacted **2** and a complex of the composition (phen)Pd(Me)·**5** in the residue that remained following complete consumption of **5** in the cycloisomerization of **5** catalyzed by **2** suggests that the slow step in catalyst activation is the olefin β-migratory insertion of one of the double bonds of **5** into the Pd–C bond of **2** via a palladium alkyl olefin complex.

Because we were unable to identify the turnover-limiting step in the cycloisomerization of **5** catalyzed by **2** via kinetics, we sought to identify the catalyst resting state by low temperature ¹H NMR spectroscopy. In the cycloisomerization of **1** catalyzed by **2**, the two methyl resonances corresponding to the bound and free carbomethoxy groups in oxochelate complex **4**, were readily observed by in situ ¹H NMR analysis [11]. Conversely, when a solution of **5** and a catalytic amount of **2** in CD₂Cl₂ at –80 °C

was warmed slowly to 25 °C and monitored periodically by NMR spectroscopy, no resonances that could be attributed to either an oxo chelate complex or a palladium hydride complex were observed throughout complete conversion of **5** to **6**. This experiment also provided no information regarding the rate of catalyst activation as the potentially diagnostic methyl resonance of palladium methyl precursor **2** was obscured by one of the methylene resonances of cyclopentene **6**.

Role of Oxo Chelate Structures in Cycloisomerization of 5. In both the hydrogenation of olefins catalyzed by Rh(PPh₃)₃Cl [20,21] and the asymmetric hydrogenation of α -acylaminoacrylic acid derivatives catalyzed by optically active rhodium bis(phosphine) complexes [21,22], the organometallic species that accumulate under catalytic conditions are not intermediates in the respective catalytic cycles [23-25]. In a similar manner, palladium carbonyl chelate complex **4**, which is the only organometallic species that accumulates during the cycloisomerization of **1** catalyzed by **2**, is not an intermediate in the catalytic cycle. Formation of unproductive organometallic complexes during catalysis reduces the concentration of the active catalytic species and decreases the rate of reaction. For this reason, we considered that the difference in rate between the palladium-catalyzed cycloisomerization of **5** and **1** might be related to the higher stability of carbonyl chelate complex **4** relative to the oxo chelate complexes that may form in the palladium-catalyzed cycloisomerization **5**. Although both diene **1** and **5** possess oxygenated homoallylic groups, a five or six-membered carbonyl chelate complex analogous to **4** can not form in the cycloisomerization of **5**. Rather, potential oxo chelate structures that could form during the cycloisomerization of **5** are restricted to the seven-membered carbonyl chelate complex **A** or the five-membered carboxylate chelate **B**.



Density Functional Theory (DFT) Calculations. A number of stable, cationic, five- and six membered rhodium [26] and palladium [27] carbonyl chelate complexes have been reported. Conversely, we are aware of no examples of stable seven-membered carbonyl chelate complexes or oxo chelate complexes formed via coordination of a carboxylate oxygen atom to a transition metal, which points to the instability of these complexes. To better gauge the relative stability of palladium oxo chelate complexes **4**, **A**, and **B**, density functional theory (DFT) calculations were performed on the oxo chelate complexes **A**, **B**, and **4**, and on the respective palladium olefin complexes **VIIa** (E = CO₂Me) and **VIIb** (E = CH₂OAc) (Scheme 2). These calculations included all atoms except the counter ion, but made no correction for solvation or for zero-point energy.

The starting structure for optimization of **4** was taken from the X-ray crystal structure of the closely related analog [(phen)PdCHCH(Me)CH(Et)CH₂C(COOMe)(COOMe)]⁺ [BAr₄]⁻ (**4a**), which differs from **4** only in the presence of an exocyclic ethyl group in **4a** rather than the exocyclic methyl group of **4**. The root mean square deviation (RMSD) of the optimized structure of **4** relative to the crystal structure of **4a** was 0.38 Å with a maximum bond distance error of 0.15 Å and a maximum angle error of 5° (Figure 1). Optimization of palladium olefin intermediate **VIIa** revealed the expected orientation of the olefin perpendicular to the coordination plane and the somewhat unexpected unsymmetric binding of the olefin to palladium with one long (3.06 Å) and one short (2.39 Å) Pd–C bond (Figure 1, Table 1). According to these calculations, palladium olefin intermediate **VIIa** is 39.4 kcal mol⁻¹ less stable than is carbonyl chelate complex **4** in the gas phase at 0 K.

[insert Figure 1]

[insert Table 1]

Replacement of the carbomethoxy groups of **4** with acetoxymethylene groups provided the starting point for optimization of oxochelate structures **A** and **B**. Independent optimization of the seven-membered carbonyl chelate complex **A** and the five-membered carboxylate chelate complex **B** revealed that **A** was 4.44 kcal mol⁻¹ more stable than was **B** (Figure 2). The optimized structure for palladium olefin

intermediate **VIIIb** closely resembled the optimized structure for **VIIa**, with coordination of the olefin perpendicular to the coordination plane through one long and one short Pd–C bond (Figure 2, Table 1). According to these calculations, palladium olefin intermediate **VIIIb** is 20.5 kcal mol⁻¹ less stable than is palladium carbonyl chelate complex **A** in the gas phase at 0 K. Therefore, according to these DFT calculations, the energy difference between **4** and **VIIa** is 18 kcal mol⁻¹ greater than is the energy difference between **A** and **VIIIb** in the gas phase at 0 K.

[insert Figure 2]

Because no correction was made for solvation or zero-point energy in the DFT calculations of **4**, **A**, **B**, **VII**, and **VIIa**, the energy values obtained from these DFT calculations do not correspond directly to the total energy of the respective complexes in solution at ambient temperature. For example, thermolysis of a solution of **4a** in DCE at 50 °C to form carbocycles **9** required 2 h to reach completion, ($\Delta G^\ddagger \approx 25$ kcal mol⁻¹) [11], which is significantly faster than would be predicted on the basis of the 39.4 kcal mol⁻¹ energy difference between **4** and **VII** determined via DFT calculations. However, it is reasonable to assume that the relative energies of oxo chelate complexes **4** and **A** will be affected to a similar extent by solvation and zero-point energy, given the similar structure of these complexes. Likewise, palladium olefin complexes **VIIa** and **VIIIb** should also be affected to a similar extent by solvation and zero-point energy. For this reason, the much larger (18 kcal mol⁻¹) energy difference between complexes **4** and **VIIa** relative to the energy difference between complexes **A** and **VIIIb** determined from DFT calculations strongly suggests that the significantly higher rate of the cycloisomerization of **5** catalyzed by **2** relative to the cycloisomerization of **1** catalyzed by **2** is due to the formation of a stable oxochelate complex in the latter transformation, but not in the former transformation [28].

The cycloisomerization of 4,4-difunctionalized dienes to form chiral cyclopentenes is also catalyzed by (*t*-BuCN)₂PdCl₂ (**10**) [29]. However, in contrast to diene cycloisomerization catalyzed by **2**, the rate of the conversion of **1** to **3** catalyzed by **10** did not differ significantly from the rate of conversion of **5** to **6** catalyzed by **10** under identical conditions (1.5 h with 5 mol% catalyst at 40 °C) [29]. The

cycloisomerization of 1,6-dienes catalyzed by **10** is believed to precede via a pathway analogous to that proposed for the cycloisomerization of 1,6-dienes catalyzed by **2** involving hydrometallation to form alkyl olefin chelate complex **III**, followed by intramolecular carbometallation to form *trans*-**IV**, β -hydride elimination/addition/elimination to form *cis*-**VII**, and olefin displacement to release the chiral cyclopentene. However, no stable carbonyl chelate complex analogous to **4** was detected during the cycloisomerization of **1** catalyzed by **10** [29]. Therefore, the much greater sensitivity of the reaction on the nature of the homoallylic groups of the diene in the cycloisomerization of 1,6-dienes catalyzed by **2** as compared to the cycloisomerization of 1,6-dienes catalyzed by **10** is also likely due to the potential formation of stable palladium oxo chelate complexes in the former transformations, but not in the latter. The greater tendency of dienes such as **1** to form a stable oxochelate complex in the presence of **2** relative to **10** is likely due to the cationic nature of **2** [30], which presumably increases the oxophilicity of **2** relative to **10**. In this regard, it is noteworthy that all of the stable five- and six-membered rhodium [26] and palladium [27] oxochelate complexes noted above are cationic.

Conclusions

Cycloisomerization of 4,4-bis(acetoxymethyl)-1,6-heptadiene (**5**) catalyzed by **2** is ~400 times faster than is the cycloisomerization of dimethyl diallylmalonate (**1**) under identical conditions. Although kinetic studies were complicated by slow activation of the precatalyst relative to catalyst turnover, all our observations indicate that the microscopic steps involved in the cycloisomerization of **5** catalyzed by **2** are identical to those involved in the cycloisomerization of **1** catalyzed by **2**. On the basis of DFT calculations, we attribute the significantly higher rate of the cycloisomerization of **5** relative to the cycloisomerization of **1** to formation of a more stable palladium oxo chelate complex in the cycloisomerization of **1** relative to the cycloisomerization of **5**.

Experimental

General Methods. All reactions were performed under an atmosphere of nitrogen employing standard Schlenk techniques. NMR were obtained on a Varian spectrometer operating at 400 MHz for ^1H

and 100 MHz for ^{13}C in CDCl_3 unless otherwise noted. Routine gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Electrospray ionization mass spectrometry was performed using an Agilent 1100 Series LC/MSD Trap mass spectrometer. Flash chromatography was performed employing 200-400 mesh silica gel (EM). Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). Methylene chloride, 1,2-dichloroethane (DCE), and CD_2Cl_2 (Cambridge Isotope Labs) were distilled from CaH_2 under nitrogen. Benzene, acetonitrile, hexanes, diethyl ether (Aldrich, anhydrous) were used as received. Catalyst **2** was synthesized according to published procedure and stored in a desiccator prior to use [12]. Deuterium-labeled dienes **5-2,6- d_2** and **5-3,3,5,5- d_4** were synthesized from **1-2,6- d_2** and **1-3,3,5,5- d_4** , respectively, via LiAlH_4 reduction followed by acylation with Ac_2O . 4,4-Bis(propionyloxymethyl)-1,6-heptadiene (**5a**) was synthesized via acylation of 4,4-bis(hydroxymethyl)-1,6-heptadiene with propionic anhydride.

Cycloisomerization of 5. Diene **5** (100 mg, 0.42 mmol) was added via syringe to a solution of **2** (26 mg, 0.021 mmol) and naphthalene (15 mg, 0.12 mmol) in DCE (10 mL) at 25 °C and the resulting solution was stirred at 25 ± 1 °C for 15 min. Aliquots (100 μL) were removed via syringe at 1 min intervals, filtered through a small plug of silica gel, and analyzed by capillary GC. The concentration of **5** was determined from the area of the peak for **5** relative to naphthalene in the GC spectrum. Carbocycles **6**, **7** and **8** were identified by comparison to authentic samples. Carbocycles **9** were identified on the basis of MS analysis of the crude reaction mixture. In a separate experiment, a solution of **5** (100 mg, 0.42 mmol) and **2** (26 mg, 0.021 mmol) in DCE (10 mL) was stirred at room temperature for 15 minutes to completely consume **5**. An aliquot was removed, diluted with THF, and analyzed by electrospray ionization mass spectrometry. Two peaks with fragmentation patterns consistent with the presence of palladium were detected at $m/z = 541.1$ and 342.0 . These molecular masses are consistent with palladium complexes of the formula $(\text{phen})\text{Pd}(\text{Me})\cdot\mathbf{5}$ and $(\text{phen})\text{Pd}(\text{Me})(\text{NCCH}_3)$, respectively.

Cycloisomerization of 5-2,6- d_2 . A solution of **5-2,6- d_2** (100 mg, 0.42 mmol) and **2** (26 mg, 0.021 mmol) in DCE (10 mL) was stirred at room temperature for 15 minutes, concentrated under vacuum and chromatographed (hexane–EtOAc = 50:1) to give 3,3-bis(acetoxymethyl)-5-deuterio-1-deuteriomethyl-

5-methylcyclopentene (**6-d₂**) (31 mg, 31%) with 97% isomeric purity and $\geq 98\%$ isotopic purity. $^1\text{H NMR}$: δ 1.09 (s, 3 H), 1.25 (d, $J = 13.5$ Hz, 2 H), 1.62 (s, 3 H), 2.01 (s, 3 H), 2.03 (s, 3 H), 2.60 (pentet, $J = 7.9$ Hz, 1 H), 3.94 (qd, $J = 10.8$ Hz, 4 H) 5.11 (s, 1 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 171.3, 148.4, 124.9, 68.4, 67.4, 51.2, 41.3 (t, $J_{\text{CD}} = 19.1$ Hz, isotopic shift = 364 ppb) 39.3, 21.1, 19.9, 19.5 (t, $J_{\text{CD}} = 19.0$ Hz, isotopic shift = 189 ppb), 14.6 (t, $J_{\text{CD}} = 19.5$ Hz, isotopic shift = 243 ppb).

Cycloisomerization of 5-3,3,5,5-d₄. A solution of **1-3,3,5,5-d₄** (100 mg, 0.42 mmol) and **2** (26 mg, 0.021 mmol) in DCE (10 mL) was stirred at room temperature for 15 minutes, concentrated under vacuum and chromatographed (hexane–EtOAc = 50:1) to give a 77:23 mixture of 3,3-bis(acetoxymethyl)-2,4,4-trideuterio-1,5-dimethylcyclopentene (**6-d₄**) and 3,3-bis(acetoxymethyl)-2,4,4-trideuterio-5-deuteriomethyl-1-methylcyclopentene (**6-d₃**) (10 mg, 10%) with 95% isomeric purity. $^1\text{H NMR}$: δ 0.98 (1:1:1 t, 2 H), 1.01 (d, $J = 6.8$ Hz, 3 H), 1.64 (s, 3 H), 2.01 (s, 3 H), 2.02 (s, 3 H), 2.59 (t, $J_{\text{CD}} = 6.8$ Hz, 1 H), 3.94 (qd, $J = 10.8, 14.1$ Hz, 4 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 171.4, 171.3, 148.3, 124.8 (t, $J_{\text{CD}} = 19.5$ Hz, isotopic shift = 121 ppb), 68.4, 67.4, 51.0, 41.5, 38.4 (m, trace amount), 31.1, 29.9, 21.1, 19.9 (t, $J_{\text{CD}} = 19.0$ Hz, isotopic shift = 363 ppb), 14.8.

Cycloisomerization of 5-2,6-d₂ in the presence of 5a. A solution of **5-2,6-d₂** (100 mg, 0.42 mmol), **5a** (100 mg, 0.38 mmol), **2** (48 mg, 0.040 mmol), and naphthalene (15 mg, 0.12 mmol) in DCE (10 mL) was stirred at 25 °C and analyzed periodically by GC/MS analysis. The relative concentrations of **5-2,6-d₂** and **5a** were determined from the area of the respective peaks relative to naphthalene in the GC spectrum. GC/MS analysis after 6 min (75 % conversion) revealed no significant ($\leq 2\%$) deuterium incorporation into unreacted **5a** and no significant deuterium loss from **5-2,6-d₂**.

Cycloisomerization of 5-3,3,5,5-d₄ in the presence of 5a. A solution of **5-3,3,5,5-d₄** (100 mg, 0.42 mmol), **5a** (100 mg, 0.38 mmol), **2** (48 mg, 0.040 mmol), and naphthalene (15 mg, 0.12 mmol) in DCE (10 mL) was stirred at 25 °C and analyzed periodically by GCMS analysis. The relative concentrations of **5-3,3,5,5-d₄** and **5a** were determined from the area of the respective peaks relative to naphthalene in the GC spectrum. GC/MS analysis after 7 min ($\sim 80\%$ conversion) revealed no significant ($\leq 2\%$) deuterium incorporation into unreacted **5a** and no significant deuterium loss from **5-3,3,5,5-d₄**.

Conversely, GC/MS analysis after 7 min revealed formation of a 40:60 mixture of **6-d**₄:**6-d**₃ isotopomers, and a 60:40 mixture of **6a-d**₀:**6a-d**₁ isotopomers.

Density Functional Theory Calculations. All calculations were performed with the density functional theory (DFT) [31] software package DMol3 [32] at the generalized gradient approximation (GGA) level of theory. The Perdew 91 exchange functional coupled with the Perdew 91 correlation functional [33] were employed. A double numerical plus double polarization basis set was used for all atoms, with a medium integration grid. Spin restricted calculations were performed for all the systems. The self-consistent field (SCF) density was required to converge to 5×10^{-5} and the geometries were considered converged when the energy was below 5×10^{-5} hartrees and the largest component of the gradient vector was less than 1×10^{-3} hartree/bohr. Relativistic effects were included with the all-electron scalar relativity option VPSR [34] as implemented in DMol3. These effects were included to improve the description of the metallic bonding, since some of the calculations include relatively weak bonds to the metallic center (see Figure 2).

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Table 1. Selected bond distances for the optimized structures **4**, **A**, **VIIa**, and **VIIb** in Å.

Structure	Pd-C(1)	Pd-C(2)	Pd-O	C(1)-C(2)
4	2.04	3.06	2.08	1.54
A	2.06	2.99	2.10	1.54
VIIa	2.39	3.06	3.15	1.36
VIIb	2.50	3.00	2.84	1.36

Figure 1. Optimized structures for **4** and **VIIa**.

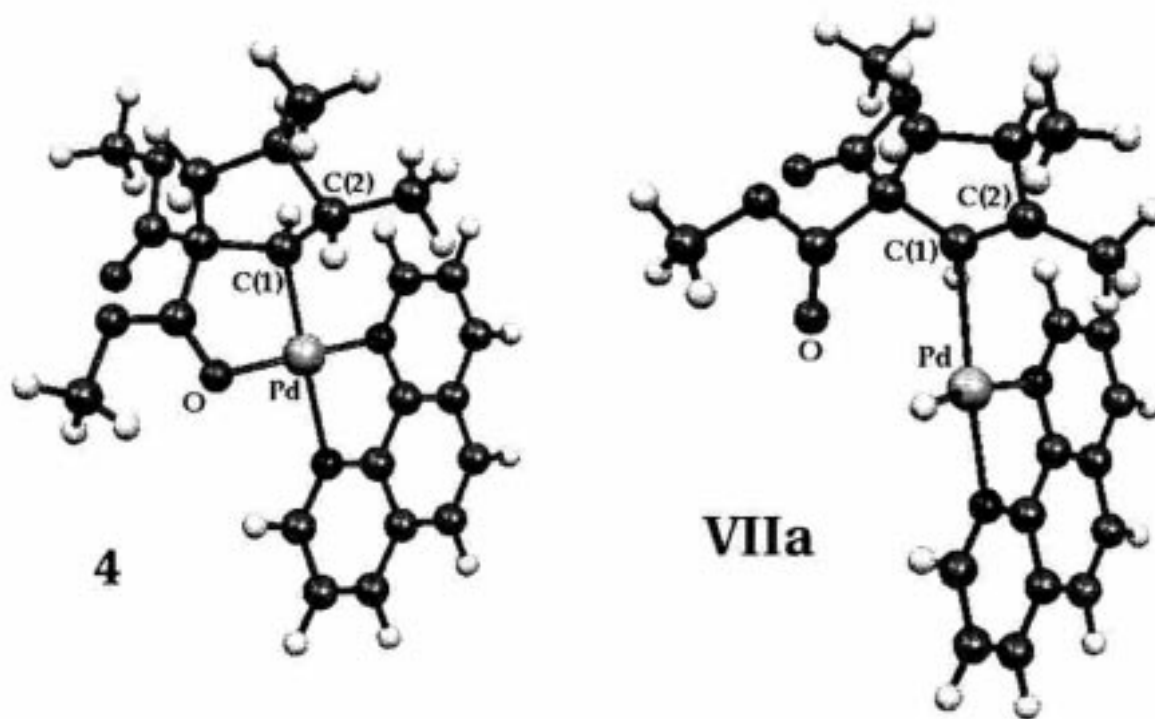


Figure 2. Optimized structures for **A**, **B**, and **VIIb**.

