Palladium-Mediated Cyclization of 6-Methyl-1-phenyl-6-hepten-2-one to Form 3-Methyldiphenylmethane: Carbonyl Activation by a Neutral Palladium(II) Complex

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Received April 19, 2007

Reaction of 6-methyl-1-phenyl-6-hepten-2-one (**4**) with a stoichiometric mixture of $PdCl_2(CH_3CN)_2$ (**2**) and Me_3SiCl in dioxane at 70 °C formed 3-methyldiphenylmethane (**6**) in 78% isolated yield. A number of experiments supported a mechanism for the conversion of **4** to **6** initiated by palladium-mediated carbonyl-ene reaction to form the isolable palladium alkene-alcohol complex $Pd[\eta^3\text{-}HOC(Bn)CH_2C(Me)=CHCH_2CH_2]Cl_2$ (**7**) followed by Me_3SiCl-mediated dehydration to form the unobserved palladium diene complex $Pd[\eta^4\text{-}C(Bn)=C(Me)CH=CHCH_2CH_2]Cl_2$ (**II**) and palladium-mediated oxidation of **II** to form **6**.

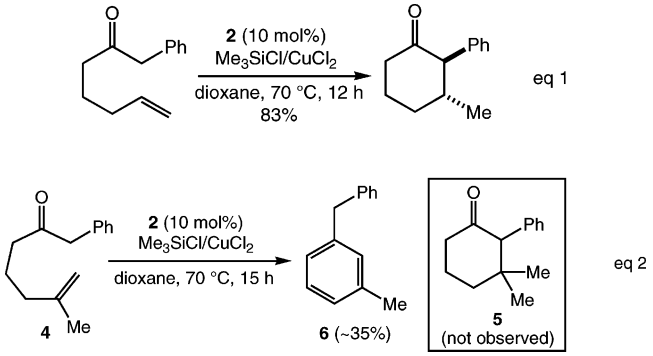
Introduction

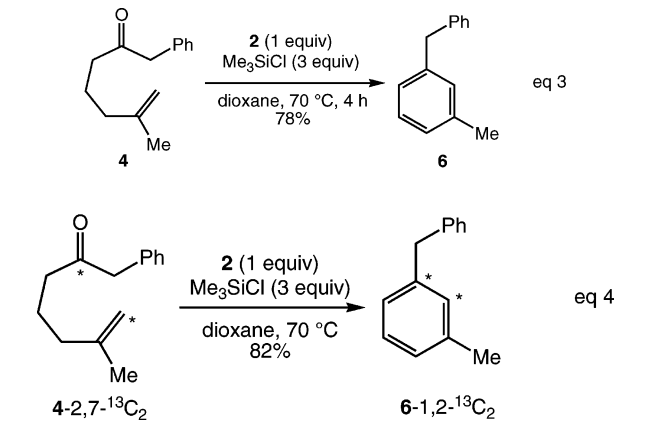
In 2001, we reported the palladium-catalyzed intramolecular hydroalkylation of alkenyl β-diketones to form 2-acyl cyclohexanones.[1] As an example of this protocol, treatment of 7-octene-2,4-dione (**1**) with a catalytic amount of $PdCl_2(CH_3CN)_2$ (**2**) (10 mol %) in dioxane at room temperature for 16 h formed 2-acetylcyclohexanone (**3**) in 81% yield (Scheme 1).[1,2] Deuterium-labeling and related experiments established a mechanism for the conversion of **1** to **3** initiated by nucleophilic attack of the pendant enol on a palladium-complexed alkene (Scheme 1).[2,3] Migration of palladium from the C4 to the C6 position of the cyclohexanone ring via iterative β-hydride elimination/addition followed by protonolysis of a palladium enolate species releases the cyclohexanone and regenerates Pd(II).

We subsequently extended the scope of palladium-catalyzed alkene hydroalkylation to include less reactive nucleophiles such as α-aryl ketones.[2,4] For example, treatment of 1-phenyl-6-hepten-2-one with a catalytic amount of **2** (10 mol %) in the presence of Me_3SiCl and $CuCl_2$ at 70 °C led to isolation of *trans*-3-methyl-2-phenylcyclohexanone in 83% yield (eq 1).[4,5] In contrast, subjection of 6-methyl-1-phenyl-6-hepten-2-one (**4**) to these conditions led to formation of a mixture of compounds that did not include 6-*exo* hydroalkylation product 3,3-dimethyl-2-phenylcyclohexanone (**5**). Rather, the major product, which constituted ∼35% of the reaction mixture, was subsequently identified as 3-methyldiphenylmethane (**6**). Intrigued by the conversion of **4** to **6** in the presence of **2**, we performed a number of experiments designed to probe the mechanism of this unusual transformation. Here we report the results of this investigation.

Results and Discussion

Conversion of 2 and 4 to 6. Repeated attempts to achieve the efficient and selective palladium-catalyzed conversion of **4** to **6** were unsuccessful. However, reaction of an equimolar mixture of **4** and **2** in the presence of Me_3SiCl in dioxane at 70 °C for 4 h led to complete consumption of **4** to form **6** in 78% isolated yield (eq 3). The connectivity of **6** relative to **4** was established through palladium-mediated cyclization of the doubly ^{13}C-labeled derivative **4**-2,7-$^{13}C_2$ (20% $^{13}C_2$), which formed **6**-1,2-$^{13}C_2$ in 82% isolated yield as a single isotopomer (eq 4). The presence of ^{13}C atoms at the C1 and C2 positions of **6**-1,2-$^{13}C_2$ was established by a pair of doublets at δ 142.2 and 130.3 (J_{CC} = 58 Hz) superimposed on the corresponding singlets in the $^{13}C\{^1H\}$ NMR spectrum of **6**-1,2-$^{13}C_2$.

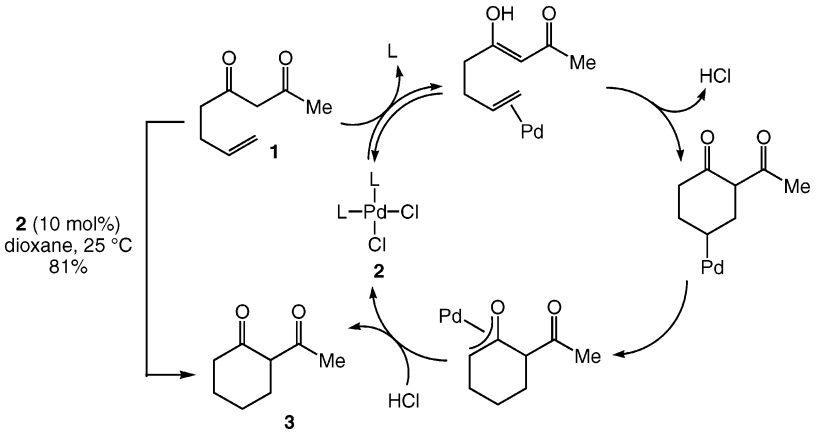




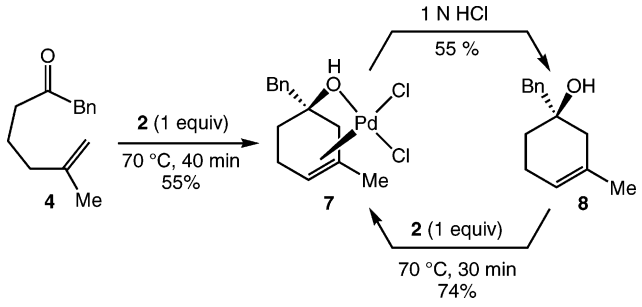
(1) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2001**, *123*, 11290.
(2) Widenhoefer, R. A. *Pure Appl. Chem*. **2004**, *76*, 671.
(3) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2003**, *125*, 2056.
(4) (a) Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 651. (b) Wang, X.; Pei, T.; Han, X.; Widenhoefer, R. A. *Org. Lett*. **2003**, *5*, 2699. (c) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem.−Eur. J.* **2004**, *10*, 6332.

10.1021/om700379g CCC: $37.00
Publication on Web 06/28/2007

Scheme 1



Scheme 2



Conversion of 2 and 4 to Alkene-Alcohol Complex 7. We next probed the role of both **2** and Me_3SiCl in the conversion of **4** to **6**. Heating a solution of **4** and Me_3SiCl at 70 °C for 4 h in the absence of **2** led to no detectable consumption of **4**. Conversely, when a solution of **2** and **4** was heated at 70 °C for 40 min in the absence of Me_3SiCl, **4** was completely consumed without formation of detectable amounts of **6** or any other volatile products as determined by GC analysis of the crude reaction mixture. Filtration and concentration of the reaction mixture followed by dilution with ether led to isolation of the palladium alkene-alcohol chelate complex $Pd[\eta^3\text{-}HOC(Bn)CH_2C(Me)=CHCH_2CH_2]Cl_2$ (**7**) in 55% yield as a yellow solid (Scheme 2). Compound **7** was characterized through degradation and reconstitution studies, elemental analysis, and NMR and IR spectroscopy.

Degradation/reconstitution studies and elemental analysis established that complex **7** was formally a 1:1 adduct of $PdCl_2$ and 1-benzyl-3-methyl-3-cyclohexenol (**8**). In one experiment, treatment of a dioxane solution of **7** with excess 1 N HCl led to isolation of **8** in 55% yield (Scheme 2). The identity of **8** was firmly established through spectroscopy, elemental analysis, and independent synthesis. In a second experiment, reaction of **2** with **8** in dioxane at 70 °C for 30 min led to formation of **7** as the excusive product, which was isolated in 74% yield (Scheme 2). The presence of a Pd−alkene π-bond in **7** was established by the upfield shifts of the alkenyl carbon atoms of **7** (δ 97.63 and 128.8) relative to those of **8** (δ 120.5 and 131.8) in the ^{13}C NMR spectrum, the downfield shift of the alkenyl proton of **7** (δ 6.15) relative to that of **8** (δ 5.41) in the ^1H NMR spectrum, and the red shift of the C=C bond stretch ($\nu_{C=C}$ = 1493 cm^{-1}) in **7** relative to that of **8** ($\nu_{C=C}$ = 1601 cm^{-1}). These data are in accord with the spectroscopy of palladium(II) alkene dichloride complexes.[6,7]

Palladium dichloride complexes that contain a nonchelated 1,1-disubstituted or trisubstituted alkene ligand are highly unstable.[7] The thermal stability of **7** therefore suggested that **8** functioned as a bidentate ligand toward palladium, binding through both the C=C bond and the hydroxyl group. Analysis of molecular models suggested that the pseudoaxial hydroxyl group of **8** was effectively positioned for σ-donation to palladium, and molecular modeling calculations indicated that bidentate coordination of **8** to a $PdCl_2$ fragment introduced only ~3 kcal mol^{-1} of strain relative to the optimized conformation of free **8**.[8] Indeed, spectroscopy was in accord with coordination of the hydroxyl group to the palladium atom in complex **7**. Most notable was the pronounced downfield shift of the hydroxyl proton of **7** (δ 6.03, $\Delta\nu_{1/2}$ = 5 Hz) relative to that of **8** (δ 1.55) in the ^1H NMR spectrum. Also indicative of hydroxyl coordination was the downfield shift of the O-bound carbon atom of **7** (δ 81.7) relative to that of **8** (δ 71.1) and the red shift of the O−H bond stretch of **7** (ν_{OH} = 3012 cm^{-1}) relative to that of **8** (ν_{OH} = 3441 cm^{-1}). These spectroscopic features are consistent with those of known palladium(II) alcohol complexes.[9]

Although the spectroscopy, stability, and reactivity of **7** are consistent with the proposed monomeric alkene-alcohol complex, failure to observe the parent ion in the mass spectrum (FAB or ES) of **7** prompted us to consider potential dimeric structures for **7**. NMR and crystallographic studies have established transition metal chloride[10] and alkoxide ligands[11] as effective hydrogen bond acceptors. Therefore, we considered

(5) In these reactions, Me_3SiCl undergoes partial hydrolysis to form HCl that promotes alkene hydroalkylation, presumably by catalyzing ketone−enol tautomerization. The $CuCl_2$ stabilized the active Pd(II) catalyst with respect to reduction/decomposition but did not otherwise alter the product distribution of these transformations.

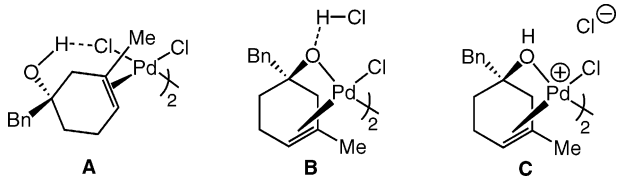
(6) (a) Heimbach, P.; Molin, M. *J. Organomet. Chem.* **1973**, *49*, 483. (b) Rettig, M. F.; Wilcox, D. E.; Fleischer, R. S. *J. Organomet. Chem.* **1981**, *214*, 261. (c) Wiger, G. R.; Tomita, S. S.; Rettig, M. F.; Wing, R. M. *Organometallics* **1985**, *4*, 1157.

(7) (a) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882. (b) Partenheimer, W.; Durham, B. *J. Am. Chem. Soc.* **1974**, *96*, 3800.

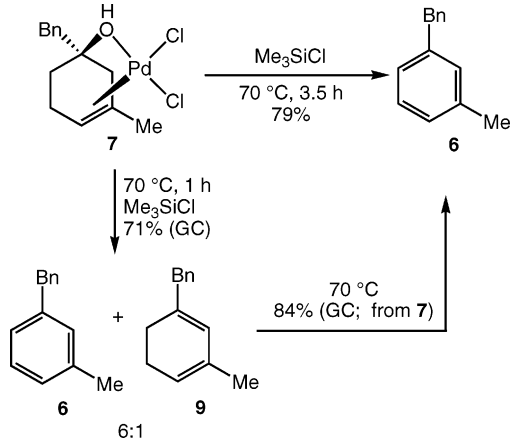
(8) (a) The palladium atom was positioned 2.28 Å from the alkene centroid,[8b] perpendicular to the alkenyl plane with the C=C bond vector perpendicular to the Pd coordination plane[8c] and 2.22 Å from the oxygen atom with 109.5° C−O−Pd bond angle.[7a] (b) Dempsey, J. N.; Baenziger, N. C. *J. Am. Chem. Soc.* **1955**, *77*, 4984. (c) Albright, T. A.; Hoffmann, R.; Thibeault, J. C.; Thorn, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 3801.

(9) (a) Cativiela, C.; Falvello, L. R.; Gines, J. C.; Navarro, R.; Urriolabeitia, E. P. *New J. Chem.* **2001**, *25*, 344. (b) Andrieu, J; Steele R. B.; Screttas, C. G.; Christine J. C.; Fornies, J. *Organometallics* **1998**, *17*, 839. (c) Alsters, P. L.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1639. (d) Platt, A. W. G.; Pringle, P. G. *J. Chem. Soc., Dalton Trans.* **1989**, 1193. (e) Mattheis, C.; Braunstein, P. *J. Organomet. Chem.* **2001**, *621*, 218.

Chart 1. Potential Dimeric Structures for 7



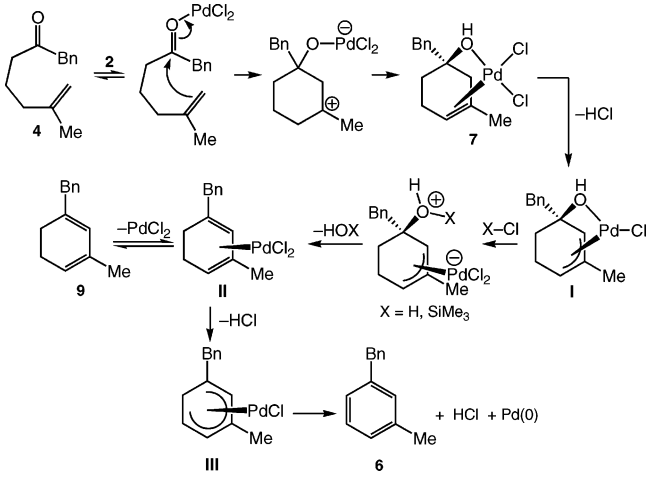
Scheme 3



palladium alkene-alcohol dimer **A** and palladium alkene-alkoxide dimer **B** (Chart 1) as possible structures for **7**. However, both **A** and **B** would require a strong hydrogen bond,[12] in the case of **A** to stabilize the weakly coordinating trisubstituted alkene and in the case of **B** to retain the molecule of HCl, and the IR spectrum of **7** does not support the presence of such a hydrogen bond.[13] Although dicationic chloride-bridged palladium dimers,[14] including dicationic alkene dimers, are known,[15] these complexes are stable only in the presence of noncoordinating counterions. For this reason, a dicationic palladium alkene-alcohol dimer such as **C** appears highly unlikely as a structure for **7**.

Conversion of 7 to 6. Heating a solution of alkene-alcohol complex **7** and Me_3SiCl (3 equiv) at 70 °C for 3.5 h led to complete consumption of **7** and isolation of **6** in 79% yield (Scheme 3). Chlorotrimethylsilane was required for efficient conversion of **7** to **6**; heating a dioxane solution of **7** in the absence of Me_3SiCl at 70 °C for 3.5 h led to 42% consumption of **7** to form **6** in only 16% yield (GC). The possibility that

Scheme 4



conversion of **7** and Me_3SiCl to **6** was initiated by displacement of **8** from palladium was discounted, as treatment of free **8** with Me_3SiCl at 70 °C for 3.5 h led to no detectable consumption of **8**. In an effort to detect potential intermediates in the conversion of **7** to **6**, a dioxane solution of **7** and Me_3SiCl (2 equiv) was heated at 70 °C and monitored periodically by GC. After 1 h, **7** was completely consumed to form a 6:1 mixture of **6** and 1-benzyl-3-methyl-1,3-cyclohexadiene (**9**) in 71% combined yield (Scheme 3). Continued heating of the reaction mixture led to complete consumption of **9** to form **6** in 84% GC yield from **7** (Scheme 3).

Mechanism of the Conversion of 2 and 4 to 6. The mechanism for the conversion of **2**, **4**, and Me_3SiCl to **6** depicted in Scheme 4 is consistent with our experimental observations. Palladium-promoted carbonyl-ene reaction of **4** via coordination of palladium(II) to the carbonyl oxygen atom of **4** followed by nucleophilic attack of the pendant alkene and proton transfer would form **7**. Although Lewis acid-mediated carbonyl-ene reactions are well documented,[16] several features regarding the conversion of **2** and **4** to **7** are noteworthy. First, the carbonyl-ene reaction is typically restricted to electron-deficient aldehydes and ketones as opposed to the dialkyl ketone moiety of **4**. Second, whereas neutral Pd(II) complexes are known to activate π-acceptor ligands such as alkenes toward nucleophilic attack,[17] activation of carbonyl groups toward nucleophilic attack by Pd(II) is typically observed only in the case of cationic Pd(II) complexes.[18] Third, conversion of **4** to **7** occurs with high regioselectivity, even though three potential elimination products are accessible from the zwitterionic precursor to **7**. This selectivity is presumably driven by formation of the most stable alkene-alcohol chelate complex. As a point of comparison, Me_2AlCl-mediated carbonyl-ene reaction of 6-methyl-6-hepten-2-ones formed mixtures of products with the corresponding 3-methyl-3-cyclohexenols constituting $\leq$10% of the respective reaction mixtures.[19]

(10) (a) Lee, J. C.; Peris, E.; Rheingold, A. L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 11014. (b) Aullón, G.; Bellamy, D.; Brammer, L.; Bruton, E. A.; Orpen, A. G. *Chem. Commun.* **1998**, 653.

(11) (a) Kapteijn, G. M.; Dervisi, A.; Grove, D. M.; Kooijman, H.; Lakin, M. T.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1995**, *117*, 10939. (b) Kim, Y.-J.; Choi, J.-C.; Osakada, K. *J. Organomet. Chem.* **1995**, *491*, 97. (c) Kim, Y.-J.; Osakada, K.; Takenaka, A.; Yamamoto, A. *J. Am. Chem. Soc.* **1990**, *112*, 1096. (d) Kapteijn, G. M.; Spee, M. P. R.; Grove, D. M.; Kooijman, H.; Spek, A. L.; van Koten, G. *Organometallics* **1996**, *15*, 1405. (e) Montgomery, C. D.; Payne, N. C.; Willis, C. J. *Inorg. Chim. Acta* **1986**, *117*, 103.

(12) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gill, G. *J. Am. Chem. Soc.* **1994**, *116*, 909.

(13) The ν_{OH} of strongly hydrogen bonded palladium alkoxide complexes ranges from 2350 to 2750 cm^{-1}, which is considerably lower than that observed for **7**. Likewise, the H−Cl stretch in the free state is <3000 cm^{-1}, and it appears likely that the H−Cl···O stretch of strongly hydrogen bonded HCl would appear at considerably lower energy than that observed for **7**.

(14) (a) Devic, T.; Batail, P.; Fourmigué, M.; Avarvari, N. *Inorg. Chem.* **2004**, *43*, 3136. (b) Smith, R. C.; Protasiewicz, J. D. *Organometallics* **2004**, *23*, 4215. (c) Longato, B.; Pilloni, G.; Valle, G.; Corain, B. *Inorg. Chem.* **1988**, *27*, 956. (d) Davies, J. A.; Hartley, F. R.; Murray, S. G. *Inorg. Chem.* **1980**, *19*, 2299.

(15) Eaborn, C.; Farrell, N.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1976**, 289.

(16) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(17) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1999; Chapter 7.2, pp 188−204.

(18) (a) Strukul, G. *Top. Catal.* **2002**, *19*, 33. (b) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160. (c) Cataldo, M.; Nieddu, E.; Gavagnin, R.; Pinna, F.; Strukul, G. *J. Mol. Catal. A* **1999**, *142*, 305. (d) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *J. Org. Chem.* **2006**, *71*, 9751. (e) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (f) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240.

(19) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988.

Formation of diene **9** in the reaction of **7** with Me_3SiCl directly implicates the palladium diene complex $Pd[\eta^4\text{-}C(Bn)=C(Me)CH=CHCH_2CH_2]Cl_2$ (**II**) in the conversion of **7** to **6** (Scheme 4).[20] Intermediate **II** is most likely formed via activation of an allylic C−H bond of **7** coupled with loss of HCl to form the π-allyl mono(chloride) complex **I**. The conversion of Pd(II) alkene complexes to (π-allyl)palladium complexes is well documented.[21] Addition of X−Cl (X = H, $SiMe_3$) across the Pd−O bond of **I** would form a zwitterionic complex that appears highly disposed to the formation of palladium diene complex **II** via loss of HOX (X = H, $SiMe_3$). Activation of an allylic C−H bond of **II** coupled with loss of HCl would form a η^5-pentadienyl intermediate such as **III**. Elimination of HCl from **III**, driven by aromatization, would form **6** and produce palladium(0).

Conclusions

In summary, we have shown that reaction of a stoichiometric mixture of $PdCl_2(CH_3CN)_2$ (**2**), 6-methyl-1-phenyl-6-hepten-2-one (**4**), and Me_3SiCl leads to selective formation of 3-methyldiphenylmethane (**6**). The transformation is likely initiated via a palladium-mediated carbonyl-ene reaction to form the isolable palladium alkene-alcohol chelate complex $Pd[\eta^3\text{-}HOC(Bn)CH_2C(Me)=CHCH_2CH_2]Cl_2$ (**7**). Complex **7** then undergoes Me_3SiCl-mediated dehydration, presumably via initial formation of the π-allyl intermediate **I**, to form the diene intermediate $Pd[\eta^4\text{-}C(Bn)=C(Me)CH=CHCH_2CH_2]Cl_2$ (**II**). The intermediacy of **II** was implicated by formation of 1-benzyl-3-methyl-1,3-cyclohexadiene (**9**) in the conversion of **7** to **6**. Oxidation of **II**, presumably via the η^5-pentadienyl intermediate **III**, forms **6** with concomitant generation of Pd(0).

Experimental Section

General Methods. Reactions were performed under an atmosphere of nitrogen unless stated otherwise. NMR spectra were obtained at ambient temperature on a Varian spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$ unless noted otherwise. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a HP 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Thin-layer chromatography (TLC) was performed on SiO_2 plates eluting with a 5:1 mixture of hexanes−EtOAc unless noted otherwise. Flash column chromatography was performed employing 200−400 mesh silica gel (EM). Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). THF was distilled from sodium/benzophenone ketyl under nitrogen and CH_2Cl_2 was distilled from CaH_2 under nitrogen. 1,4-Dioxane (Aldrich anhydrous) and $PdCl_2(CH_3CN)_2$ (Strem) were used as received.

Authentic samples of **6** and phenylacetaldehyde-1-^{13}C were prepared employing published procedures.[22,23] 3-Methyl-3-cyclohexenone was synthesized from *m*-methylanisole employing a published procedure.[24] 5-Bromo-2-methyl-1-pentene and 5-bromo-2-methyl-1-pentene-1-^{13}C (20% enriched) were synthesized from ethyl 4-methyl-4-pentenoate and ethyl 4-methyl-4-pentenoate-5-^{13}C (20% enriched), respectively, employing a modified literature procedure.[25]

6-Methyl-1-phenyl-6-hepten-2-one (4). A solution of 5-bromo-2-methyl-1-pentene (2.64 g, 16.2 mmol) in THF (15 mL) was added to magnesium turnings (0.39 g, 16 mmol) in THF (15 mL), and the resulting mixture was refluxed for 1.5 h. To this was added a solution of phenyl acetaldehyde (1.95 g, 16.2 mmol) in THF (15 mL) via syringe, and the resulting suspension was refluxed for 1 h and quenched with brine. The biphasic mixture was extracted with ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated under vacuum. The resulting oily residue was chromatographed (hexanes−ether = 15:1) to give 6-methyl-1-phenyl-5-hepten-2-ol (**10**) as a yellow oil (1.66 g, 50%).

A solution of DMSO (1.65 mL, 23.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalyl chloride (1.02 mL, 11.65 mmol) in CH_2Cl_2 (30 mL) at −78 °C and stirred for 20 min. To this was added a solution of **10** (1.59 g, 7.76 mmol) in CH_2Cl_2 (30 mL), and the resulting solution was stirred for 1 h and treated with triethylamine (6.50 mL, 46.6 mmol). The resulting mixture was warmed to room temperature, poured into water, and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (hexanes−Et_2O = 20:1) to give **4** as a yellow oil (1.37 g, 87%).

For 10: TLC: R_f = 0.28. ^{1}H NMR: δ 7.31−7.27 (m, 2 H), 7.23−7.18 (m, 3 H), 4.69−4.65 (m, 2 H), 3.84−3.78 (m, 1 H), 2.81 (dd, J = 4.0, 13.4 Hz, 1 H), 2.63 (dd, J = 8.4, 13.8 Hz, 1 H), 2.01 (t, J = 6.4 Hz, 2 H), 1.69 (s, 3 H), 1.56−1.45 (m, 4 H). ^{13}C{^{1}H} NMR: δ 146.1, 138.9, 129.7, 128.9, 126.8, 110.3, 72.9, 44.4, 38.0, 36.7, 24.0, 22.7. IR (neat, cm^{-1}): 3400, 3026, 2935, 2863, 1494, 1453, 1084, 886, 747. HRMS calcd (found) for $C_{14}H_{21}O$ (MH^+): 205.1592 (205.1598).

For 4: TLC: R_f = 0.56. ^{1}H NMR: δ 7.35−7.31 (m, 2 H), 7.28−7.25 (m, 1 H), 7.22−7.19 (m, 2 H), 4.70−4.69 (m, 1 H), 4.62−4.61 (m, 1 H), 3.58 (s, 2 H), 2.45 (t, J = 7.6 Hz, 2 H), 1.97 (t, J = 7.6 Hz, 2 H), 1.74−1.67 (m, 5 H). ^{13}C{^{1}H} NMR: δ 208.6, 145.3, 134.6, 129.7, 129.0, 127.3, 110.8, 50.5, 41.5, 37.3, 22.4, 21.7. IR (neat, cm^{-1}): 3066, 3028, 2936, 1712, 1495, 1453, 1408, 1093, 888. Anal. Calcd (found) for $C_{14}H_{18}O$: C, 83.12 (83.12); H, 8.97 (9.01).

6-Methyl-1-phenyl-6-hepten-2-one-2,7-^{13}C (4-2,7-$^{13}C_2$, 20% enriched). A solution of *n*-BuLi (2.5 M) in hexane (2.4 mL, 5.9 mmol) was added to $^{13}CH_3PPh_3I$ (2.00 g, 4.94 mmol, 20% enriched) at 0 °C, and the resulting suspension was stirred for 1 h. To this was added a solution of ethyl levulinate (0.85 g, 5.9 mmol) in THF (15 mL) dropwise, and the resulting mixture was stirred at room temperature for 3 h, quenched with saturated aqueous ammonium chloride, and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated under vacuum. The resulting oily residue was chromatographed (hexanes−ether = 25:

(20) A reviewer suggested an alternative mechanism for the conversion of **7** to **9** in which Me_3SiCl-mediated elimination of the tertiary hydroxyl group occurs via an E_1/E_2 type process without formation of **I**. Although we have no direct evidence that supports the intermediacy of **I**, the observation that reaction of **8** with Me_3SiCl in the absence of palladium led to no detectable consumption of **8** established that palladium plays a key role in the conversion of **7** to **9**. Conversely, the aforementioned mechanism for the conversion of **7** to **9** involving an E_1/E_2 type elimination does not readily account for the necessity of palladium in this transformation. For this reason, we favor a mechanism for the conversion of **7** to **9** involving initial formation of **I** followed by Me_3SiCl-mediated elimination of the tertiary hydroxyl group.

(21) (a) Trost, B. M. *Tetrahedron Lett.* **1977**, *33*, 2615. (b) Tsuji. J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (c) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407. (d) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572. (e) Muzart, J.; Pale, P.; Pète, J. P.; Riahi, A. *Bull. Soc. Chim. Fr.* **1988**, *731*. (f) Chrisope, D. R.; Beak, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 230. (g) Riahi, A.; Muzart, J. *J. Organomet. Chem.* **1999**, *585*, 256.

(22) (a) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. *J. Org. Chem.* **1999**, *64*, 5966. (b) Nystrom, R. F.; Berger, C. R. A. *J. Am. Chem. Soc.* **1957**, *80*, 2896.

(23) (a) Piers, E.; Oballa, R. M. *J. Org. Chem.* **1996**, *61*, 8439. (b) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051.

(24) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981.

(25) Chesters, N. C. J. E.; O'Hagan, D.; Robins, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1159.

1) to give ethyl 4-methyl-4-pentenoate-5-^{13}C (**11**-5-^{13}C; 0.26 g, 37%, 20% enriched) as a colorless oil. Compound **4**-2,7-$^{13}C_2$ was synthesized from reaction of **11**-5-^{13}C (20% enriched) and phenylacetaldehyde-1-^{13}C (20% enriched) employing a procedure analogous to that used to synthesize unlabeled **4**.

For 11-5-^{13}C: $^{13}C\{^1H\}$ NMR (labeled carbon only): δ 110.7.

For 4-2,7-$^{13}C_2$: $^{13}C\{^1H\}$ NMR (labeled carbons only): δ 208.6, 110.9.

3-Methyldiphenylmethane (6) from Reaction of 4 and 2. A solution of **2** (36 mg, 0.14 mmol), Me_3SiCl (53 μL, 0.42 mmol), and **4** (29 mg, 0.14 mmol) in dioxane (2.8 mL) was stirred at 70 °C for 4 h and cooled to room temperature. The resulting suspension was filtered through a plug of silica gel and eluted with ether. The resulting solution was concentrated and the residue was chromatographed (hexanes−ether = 50:1) to give **6** (19 mg, 73%) as a colorless oil. TLC: $R_f = 0.84$. ^{1}H NMR (acetone-d_6): δ 7.29−7.21 (m, 4 H), 7.19−7.14 (m, 2 H), 7.05 (br s, 1 H), 7.03−6.99 (m, 2 H), 3.92 (s, 2 H), 2.27 (s, 3 H). $^{13}C\{^1H\}$ NMR (acetone-d_6): δ 142.4, 142.2, 138.5, 130.3, 129.6, 129.2, 129.1, 127.4, 126.7, 42.3, 21.4. The ^{13}C resonances of **6** were unambiguously assigned on the basis of HMQC and HMBC spectroscopy. HRMS calcd (found) for $C_{14}H_{14}$ (M^+): 182.1096 (182.1104).

6 from reaction of 7 and Me_3SiCl. A suspension of **7** (51 mg, 0.13 mmol) and Me_3SiCl (49 μL, 0.39 mmol) in dioxane (2.6 mL) was stirred at 70 °C for 3 h and cooled to room temperature. The resulting suspension was filtered through a plug of silica gel and eluted with ether. The resulting solution was concentrated and the residue was chromatographed (hexanes-ether = 50:1) to give **6** (19 mg, 79%) as a colorless oil.

3-Methyldiphenylmethane-1,2-$^{13}C_2$ (6-1,2-$^{13}C_2$; 20% $^{13}C_2$). Isotopomer **6**-1,2-$^{13}C_2$ (20% $^{13}C_2$) was isolated in 82% yield from **4**-2,7-$^{13}C_2$ (20% $^{13}C_2$) employing a procedure similar to that used to synthesize unlabeled **6**. $^{13}C\{^1H\}$ NMR (acetone-d_6, labeled carbons only): δ 142.2 (s and d, J = 57.6 Hz), 130.3 (s and d, J = 57.7 Hz).

Pd[η^3-HOC(Bn)CH$_2$C(Me)=CHCH$_2$CH$_2$]Cl$_2$ (7) from Reaction of 2 and 4. A solution of **2** (101 mg, 0.39 mmol) and **4** (78 mg, 0.39 mmol) in dioxane (8 mL) was stirred at 70 °C for 40 min and cooled to room temperature. The resulting suspension was filtered through a pad of Celite, concentrated to ~3 mL, and diluted with ether. The resulting yellow suspension was filtered, and the precipitate was washed with ether to give **7** (80 mg, 55%) as a yellow solid. ^{1}H NMR: δ 7.35−7.28 (m, 3 H), 7.20−7.18 (m, 2 H), 6.14 (br s, 1 H), 6.03 (br s, 1 H, −*OH*), 3.39 (br td, $J \approx 8$, 18 Hz 1 H), 3.18 (d, J = 13.6 Hz, 1 H), 2.97 (d, J = 14.0 Hz, 1 H), 2.58 (d, J = 17.6 Hz, 1 H), 2.36−2.27 (m, 2 H), 1.99 (s, 3 H), 1.62 (br td, $J \approx 9$, 15 Hz, 1 H), 1.41 (d, J = 17.2 Hz, 1 H). Unambiguous assignment of the ^{1}H resonances was achieved through ^{1}H−^{1}H COSY analysis and by D_2O exchange. $^{13}C\{^1H\}$ NMR: δ 135.4, 130.7, 129.0, 128.8, 127.7, 91.6, 81.7, 46.3, 44.9, 28.4, 26.9, 22.9. IR (neat, cm^{-1}): 3012 (ν_{OH}), 1520 ($\nu_{C=C}$). Anal. Calcd (found) for $C_{14}H_{18}Cl_2OPd$: C, 44.29 (44.20); H, 4.78 (4.59); Cl, 18.68 (18.97).

Complex 7 from Reaction of 2 and 8. A mixture of **2** (73 mg, 0.28 mmol) and 1-benzyl-3-methyl-3-cyclohexenol (**8**) (56 mg, 0.28 mmol) in dioxane (5.6 mL) was stirred at 70 °C for 30 min and cooled to room temperature. The solution was filtered through a pad of Celite, concentrated to ~2 mL, and diluted with ether. The resulting suspension was filtered, and the precipitate was washed with ether to give **7** (78 mg, 74%) as a yellow solid.

Pd[η^3-HO^{13}C(Bn)^{13}CH$_2$C(Me)=CHCH$_2$CH$_2$]Cl$_2$ (7-1,2-$^{13}C_2$, 20% $^{13}C_2$). **7**-1,2-$^{13}C_2$ (20% $^{13}C_2$) was synthesized in 73% yield from **8**-1,2-$^{13}C_2$ employing a procedure similar to that used to synthesize **7** from **8**. $^{13}C\{^1H\}$ NMR (labeled carbons only): δ 81.7 (s and d, J = 39.5 Hz), 44.9 (s and d, J = 38.0 Hz).

1-Benzyl-3-methyl-3-cyclohexenol (8) from 4. Aqueous HCl (1 N, 30 mL) was added to a solution of **7**, generated *in situ* from reaction of **2** (71 mg, 0.27 mmol) and **4** (55 mg, 0.27 mmol) in dioxane (5.5 mL) at room temperature. The resulting biphasic mixture was stirred for 15 min and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated under vacuum. The resulting residue was chromatographed (hexanes−ether = 15:1) to give **8** (30 mg, 55%) as a yellow oil. The ^{1}H and ^{13}C resonances of **8** were assigned on the basis of combined HMBC and HMQC analysis. TLC: $R_f = 0.37$. ^{1}H NMR: δ 7.34−7.30 (m, 2 H), 7.27−7.23 (m, 3 H), 5.44−5.43 (m, 1 H), 2.80 (dd, J = 13.4, 15.0 Hz, 2 H), 2.23−2.06 (m, 3 H), 1.85 (d, J = 16.8 Hz, 1 H), 1.65 (d, J = 1.2 Hz, 3 H), 1.67−1.61 (m, 1 H), 1.55 (s, 1 H) 1.53−1.46 (m, 1 H). $^{13}C\{^1H\}$ NMR: δ 137.5, 131.8, 131.0, 128.5, 126.8, 120.5, 71.1, 47.6, 42.6, 33.1, 24.0, 23.0. IR (neat, cm^{-1}): 3443 (br, ν_{OH}), 1601 (w, $\nu_{C=C}$). HRMS calcd (found) for $C_{14}H_{17}$ (M^+ − OH): 185.1330 (185.1321). Anal. Calcd (found) for $C_{14}H_{18}O$: C, 83.12 (82.95); H, 8.97 (8.97).

Independent Synthesis of 8. A solution of benzylmagnesium chloride (20 wt % in THF; 2.1 g, 2.7 mmol) was added to a solution of 3-methyl-3-cyclohexenone (150 mg, 1.36 mmol) in THF (10 mL) at room temperature, and the resulting solution was refluxed for 2 h. The resulting suspension was cooled to room temperature, quenched with 1 N HCl (30 mL), and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated under vacuum. The resulting oily residue was chromatographed (hexanes−ether = 15:1) to give **8** as a colorless oil (130 mg, 48%).

1-Benzyl-3-methyl-3-cyclohexenol-1,2-$^{13}C_2$ (8-1,2-$^{13}C_2$, 20%$^{13}C_2$). **8**-1,2-$^{13}C_2$ (20% $^{13}C_2$) was synthesized in 42% yield from **4**-2,7-$^{13}C_2$ (20% $^{13}C_2$) employing a procedure similar to that used to synthesize **8** from **4**. $^{13}C\{^1H\}$ NMR (labeled carbons only): δ 71.1 (s and d, J = 38.7 Hz), 42.6 (s and d, J = 38.9 Hz).

1-Benzyl-3-methyl-1,3-cyclohexdiene (9). Diene **9** was isolated as a 1:1 mixture with **6** from the catalytic cyclization of **4**. A solution of **2** (46 mg, 0.18 mmol), $CuCl_2$ (0.60 g, 4.5 mmol), Me_3SiCl (0.68 mL, 5.3 mmol), and **4** (0.36 g, 1.8 mmol) in dioxane (36 mL) was stirred at 70 °C for 1 h and cooled to room temperature. The resulting suspension was filtered through a plug of silica gel and eluted with ether. The resulting solution was concentrated, and the residue was twice chromatographed (hexanes−ether = 50:1), the second time on silica gel embedded with $AgNO_3$ (10% w/w) to give a 1:1 mixture of **6** and **9** (51 mg, 18% combined yield) as a colorless oil.

For 9: ^{1}H NMR (500 MHz): δ 7.30−7.27 (m, 2 H), 7.21−7.16 (m, 3 H), 5.51−5.49 (m, 1 H), 5.40−5.38 (m, 1 H), 3.3 (s, 2 H), 2.74−2.69 (m, 2 H), 2.41 (t, J = 8.8 Hz, 2 H), 1.63 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz): δ 140.1, 134.7, 131.6, 129.3, 128.6, 126.3, 120.5, 118.6, 44.4, 34.0, 28.2, 23.5. HRMS calcd (found) for $C_{14}H_{16}$ (M^+): 184.1252 (184.1254).

Acknowledgment is made to the NSF (CHE-03-04994) for support of this research. We thank Prof. Stephen Craig for assisting with the molecular modeling calculations of **7**.

OM700379G