Development, Scope, and Mechanism of the Palladium-Catalyzed Intramolecular Hydroalkylation of 3-Butenyl β-Diketones

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Reaction of 7-octene-2,4-dione (**3**) with a catalytic amount of $PdCl_2(CH_3CN)_2$ (**4**) (10 mol %) in dioxane at room temperature for 16 h formed 2-acetylcyclohexanone (**5**) in 81% yield as a single regioisomer. Byproducts in the conversion of **3** to **5** include 2,4-octanedione (**13**), 2-acetyl-2-cyclohexenone (**14**), 2-acetylphenol (**15**), (*E*)- and (*Z*)-6-octene-2,4-dione (**17**), (*E*)- and (*Z*)-5-octene-2,4-dione (**18**), the η^3-β-diketonate chloride dimer $\{[\eta^3\text{-}CH_3CH_2CH_2\text{-}CHCOHCHAc]Pd(Cl)\}_2$ (**12**), and the π(allyl)palladium chloride dimer $\{[\eta^3\text{-}CH_3CHCHCHC(O)CH_2Ac]Pd(Cl)\}_2$ (**16**). The palladium-catalyzed cyclization of 3-butenyl β-diketones tolerated substitution at the terminal acyl carbon atom, the enolic carbon atom, and the terminal olefinic carbon atom. Deuterium-labeling studies, in conjunction with kinetic and in situ NMR experiments, supported a mechanism for the palladium-catalyzed hydroalkylation of 3-butenyl β-diketones initiated by 6-*endo*-trig attack of the enol carbon atom on a palladium-complexed olefin to form a palladium cyclohexanone species. Migration of the palladium atom from the C(4) to the C(6) carbon atom of the 2-acylcyclohexanone intermediate via iterative β-hydride elimination/addition followed by protonolysis of the resulting palladium C(6)-enolate complex released the cyclohexanone and regenerated the palladium dichloride catalyst.

Introduction

The base-catalyzed addition of an activated methylene compound to an olefin activated by an electron-withdrawing group remains one of the most important C−C bond forming processes utilized in organic synthesis.[1] In contrast, a general and selective procedure for the addition of a stabilized carbon nucleophile to an unactivated olefin has not been identified. Hydroalkylation of γ-, δ-, ϵ-, or ζ-alkenyl alkyl ketones occurs thermally, but requires temperatures of ≥350 °C.[2] Radical-mediated olefin hydroalkylation occurs under significantly milder conditions, but suffers from a number of problems including poor site- and product-selectivity and slow chain transfer.[3,4] The Lewis acid-catalyzed intramolecular hydroalkylation of alkenyl β-dicarbonyl compounds also occurs under mild conditions but suffers from limited generality and the problems associated with carbocationic intermediates.[5]

Transition metal catalysis represents a potential means to facilitate the addition of a stabilized carbon nucleophile to an unactivated olefin and to circumvent the problems associated with free-radical and Lewis acid-catalyzed approaches. However, despite prolonged effort in this area, the efficient transition metal-catalyzed addition of a stabilized carbon nucleophile to an unactivated olefin has not been demonstrated.[6] For example, zirconocene complexes catalyze the addition of alkylmagnesium halides to unactivated olefins, but these protocols are not applicable to stabilized carbon nucleophiles.[7] Conversely, the transition metal-catalyzed hydroalkylation of allenes (eq 1),[8] conjugated dienes,[9] conjugated enynes,[10] alkynes,[11] and alkylidenecy-

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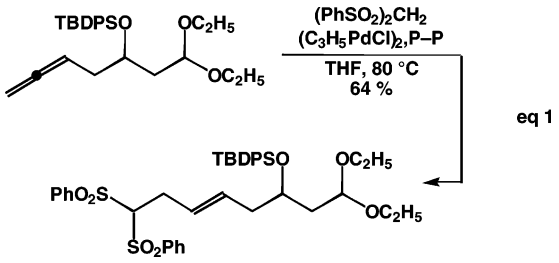
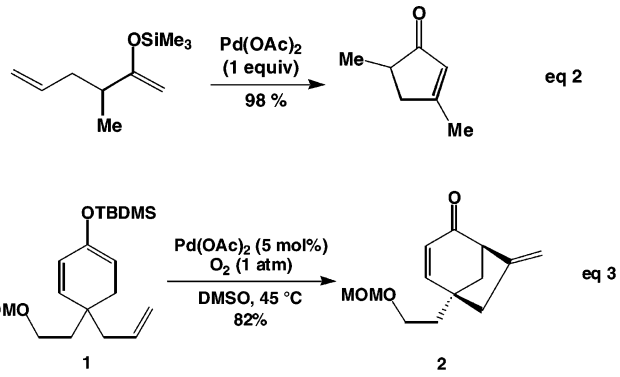
clopropanes[12] with activated methylene compounds has been demonstrated.[13] However, allenes, 1,3-dienes, and alkynes are significantly more reactive toward transition metals than are unactivated olefins, and these catalyst systems are not active toward simple olefins.[6]



Coordination of an olefin to an electron-deficient transition metal complex greatly enhances the reactivity of the olefin with respect to nucleophilic attack.[6] In the presence of a suitable oxidant, Pd(II) complexes catalyze the oxidative amination,[14] alkoxylation,[15] and hydroxylation[16] of unactivated olefins with heteroatom nucleophiles. In a similar manner, palladium(II) complexes mediate the oxidative alkylation of unactivated olefins with stabilized carbon nucleophiles such as a malonate anion or silyl enol ether (eq 2).[17,18] However, efficient Pd(II)-catalyzed oxidative alkylation has been largely precluded by the incompatibility of the nucleophile with the stoichiometric oxidant and/or the Pd(II) complex.[6] Notable exceptions include the oxidative alkenylation of unactivated olefins with allenes[19,20] and silyl dienol ethers.[21] As an example of the latter transformation, treatment of **1** with a catalytic amount of $Pd(OAc)_2$ (5 mol %) in DMSO under an oxygen atmosphere formed bicyclo[3.2.1]octane **2** in 82% isolated yield (eq 3).[21] Unfortunately, nonconjugated alkenyl silyl enol ethers cyclized poorly under these conditions.[22–26]



In response to the absence of a general and effective method for the addition of stabilized carbon nucleophiles to unactivated olefins, we initiated a program directed toward the development of transition metal-catalyzed processes for the addition of stabilized carbon nucleophiles to unactivated olefins. Herein we provide a complete account of the development, scope, and mechanism of the palladium-catalyzed hydroalkylation of 3-butenyl β-diketones to form 2-acylcyclohexanones,[27] which represents the first effective transition metal-catalyzed protocol for the hydroalkylation of an unactivated olefin with a stabilized carbon nucleophile. Full details of related studies involving the palladium-catalyzed oxidative alkylation of 4-pentenyl β-dicarbonyl compounds to form cyclohexenones[28,29] and the palladium-catalyzed hydroalkylation of alkenyl β-keto esters, α-aryl ketones, and alkyl ketones in the presence of Me_3SiCl or HCl are reported elsewhere.[30,31]

Results

Development and Scope. Our approach to the development of an effective transition metal-catalyzed

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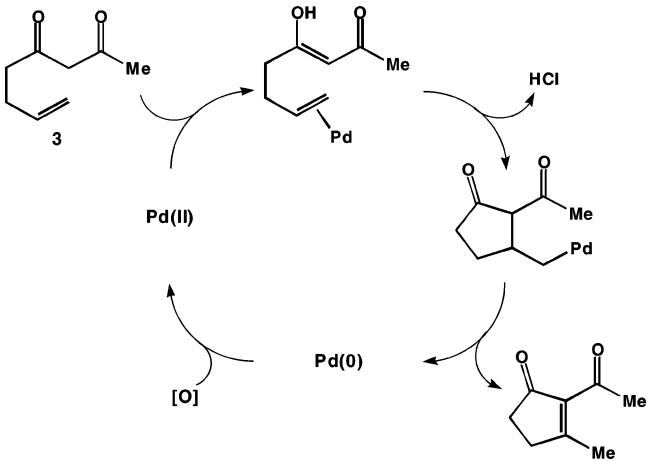
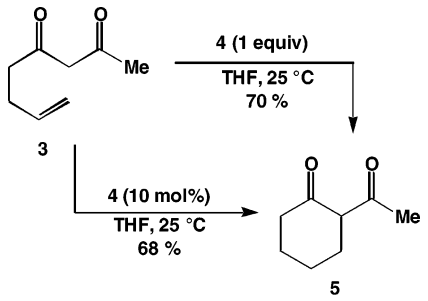
Scheme 1



Scheme 2



protocol for the addition of a stabilized carbon nucleophile to an unactivated olefin targeted 3-butenyl β-diketones such as 7-octene-2,4-dione (**3**) as substrates and simple Pd(II) complexes such as $PdCl_2(CH_3CN)_2$ (**4**) as catalysts. β-Diketones possess an unusually acidic C−H bond[32] and exist predominantly as the enol tautomer in nonpolar solvents.[33] For these reasons, we believed that the β-diketone moiety of **3** would be sufficiently nucleophilic to attack the pendant olefin in the presence of **4**. By analogy with the Pd(II)-mediated cyclization of 3-butenyl silyl enol ethers (eq 2),[18] we expected that reaction of **3** with **4** would occur via an initial 5-*exo*-trig cyclization followed by β-hydride elimination and olefin displacement to form 2-acetyl-3-methyl-2-cyclopentenone and a Pd(0) complex (Scheme 1). We reasoned that the β-diketone moiety, in contrast to the silyl enol ether functionality, would tolerate the conditions required for in situ oxidation of Pd(0), and if these conditions were met, the Pd(II)-catalyzed oxidative alkylation of an unactivated olefin would be realized.

On the basis of the expectation that **3** would undergo intramolecular oxidative alkylation in the presence of **4** (Scheme 1), we sought first to demonstrate cyclization of **3** in the presence of a stoichiometric amount of **4** and then identify a suitable oxidant for the conversion of Pd(0) to Pd(II) under these conditions. However, in contrast to these expectations, treatment of **3** with a stoichiometric amount of **4** in THF at room temperature for 15 min led not to oxidative alkylation, but to hydroalkylation via 6-*endo*-trig cyclization to form 2-acetylcyclohexanone (**5**) in 70% isolated yield (Scheme 2). Because no redox chemistry is involved in the conversion of **3** to **5**, no oxidant is required for catalysis, and treatment of **3** with a catalytic amount of **4** (10 mol %) in THF at room temperature for 23 h led to the isolation of **5** in 68% yield as a single regioisomer (Scheme 2).

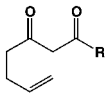
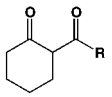
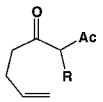
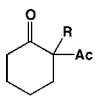
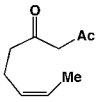
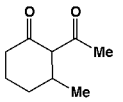
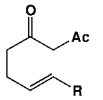
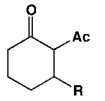
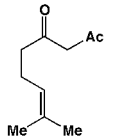
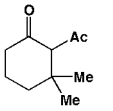
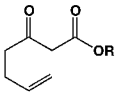
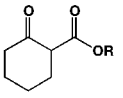
Optimization of the Protocol. Two observations were particularly important in the development of an optimized protocol for the palladium-catalyzed hydroalkylation of **3**. The first key observation was that employment of dioxane as solvent in place of THF led to a significant increase in reaction rate with no decrease in product yield (Table 1, entries 1 and 2). Other solvents including ether, CH_2Cl_2, acetonitrile, and DMSO were significantly less effective than was dioxane or THF (Table 1, entries 3−6). The second key observation was that the efficiency of hydroalkylation increased with decreasing substrate concentration (Table 1, entries 7−10). For example, the yield of **5** formed in the cyclization of **3** catalyzed by **4** increased from 49 to 86% (GC) as the initial concentration of **3** decreased from

Table 1. Palladium-Catalyzed Conversion of 3 to 5 at Room Temperature as a Function of Catalyst, Solvent, and Concentration

entry	Pd(II) catalyst	solvent	$[\mathbf{3}]_0$ (mM)	time (h)	conversion (%)[a]	yield (%)[a]
1	**4**	THF	60	23	100	71
2	**4**	dioxane	50	12	100	71
3	**4**	Et_2O	90	10	23	9
4	**4**	CH_2Cl_2		12	100	45
5	**4**	DMSO		18	13	1
6	**4**	CH_3CN		11		0
7	**4**	dioxane	250	12	100	49
8	**4**		100	11	100	64
9	**4**		50	12	100	71
10	**4**		25	12	100	86
11	$PdCl_2(EtCN)_2$		25	14	100	67
12	$PdCl_2(n\text{-}PrCN)_2$			14	100	79
13	$PdCl_2(i\text{-}PrCN)_2$			14	100	83
14	$PdCl_2(t\text{-}BuCN)_2$			11	100	76
15	$PdCl_2(PhCN)_2$			12	95	74
16	$PdCl_2[3,5\text{-}CNC_6H_3(CF_3)_2]_2$			11	53	40
17	$PdCl_2$			48	40	22
18	$PdCl(NO_2)(CH_3CN)_2$			48	46	11
19	$PdBr_2(CH_3CN)_2$			12	71	23
20	$Pd(OAc)_2$			24		0
21	$PdCl_2(PPh_3)_2$			24		0
22	$PdCl_2$(phen)			24		0

[a] Conversion and product yield were determined by GC analysis versus anthracene internal standard.

Table 2. Cyclization of 3-Butenyl β-Dicarbonyl Compounds Catalyzed by $PdCl_2(CH_3CN)_2$ (4) in Dioxane at Room Temperature

entry	substrate	cat load (mol %)	time (h)	carbocycle	yield (%)
1	 R = Me	10	16		81
2		5	36		72
3	R = Et	10	9		67
4	R = *t*-Bu	10	13		66
5	 R = Me	10	26		61
6	R = Bn	20	96		70
7		10	72		71
8	 R = Me	20	16		81
9	R = *n*-Bu	20	42		89
10	R = Ph	10	34		82
11		20	72		38
12	 R = Et	10	24		45
13	R = Me	10	20		21
14	R = Bn	10	24		32

250 to 25 mM (Table 1, entries 7 and 10). Under these optimized conditions, treatment of **3** ($[\mathbf{3}]_0 = 25$ mM) with a catalytic amount of **4** (10 mol %) in dioxane at room temperature for 16 h led to the isolation of **5** in 81% yield as a single regioisomer (Table 2, entry 1). Alternatively, reaction of **3** with a catalytic amount of **4** (5 mol %) in dioxane at room temperature for 36 h formed **5** in 72% isolated yield (Table 2, entry 2).

A number of palladium(II) complexes were screened as catalysts for the conversion of **3** to **5**, but none proved more effective than was **4** (Table 1, entries 11−22). The conversion of **3** to **5** catalyzed by palladium dichloride bis(nitrile) complexes was generally insensitive to the nature of the nitrile ligand except in the case of the electron-deficient complex $PdCl_2[3,5\text{-}CN\text{-}C_6H_3(CF_3)_2]_2$, which was significantly less efficient than was **4** (Table 1, entries 10−16). Palladium dichloride was not an efficient catalyst for the conversion of **3** to **5**, presumably due to the extreme insolubility of $PdCl_2$ in dioxane (Table 1, entry 17). Palladium(II) complexes that did not possess a $PdCl_2$ core (Table 1, entries 18−20) or $PdCl_2$ complexes that contained monodentate phosphine ligands or a bidentate nitrogen ligand (Table 1, entries 21 and 22) were ineffective as catalysts for the conversion of **3** to **5**.

(32) Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456.

(33) (a) Guthrie, J. P. *Can. J. Chem*. **1979**, *57*, 1177. (b) Bassetti, M.; Cerichelli, B.; Floris, B. *Tetrahedron* **1988**, *44*, 2997. (c) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem*. **1979**, *57*, 240.

Scope of Hydroalkylation. The palladium-catalyzed hydroalkylation of 3-butenyl β-diketones tolerated substitution at the terminal acyl carbon atom (Table 2, entries 3 and 4), at the enolic carbon atom (Table 2, entries 5 and 6), and at the terminal olefinic carbon (Table 2, entries 7−10). As examples, both *cis*- and *trans*-7-nonene-2,4-dione cyclized in the presence of a catalytic amount of **4** to form 2-acetyl-3-methylcyclohexanone in >70% yield as a single regioisomer (Table 2, entries 7 and 8). In comparison, 8-methyl-7-nonene-2,4-dione, which was disubstituted at the terminal olefinic substitution, cyclized in only 38% yield (Table 2, entry 11). 3-Butenyl β-diketones that possessed substitution at the internal olefinic carbon atom or along the alkyl tether failed to undergo palladium-catalyzed hydroalkylation. 3-Butenyl β-keto esters underwent palladium-catalyzed hydroalkylation less efficiently than did β-diketones, presumably due to the lower reactivity of a β-keto ester relative to a β-diketone (Table 2, entries 12−14).[32−34] For example, reaction of ethyl 3-oxo-6-heptenoate with a catalytic amount of **4** (10 mol %) in dioxane at room temperature for 24 h led to isolation of 2-carboethoxycyclohexanone in 45% yield (Table 2, entry 12).

Mechanism. As noted in the Introduction, the selective palladium-catalyzed hydroalkylation of an unactivated 3-butenyl β-diketone was both unexpected and unprecedented. Also unusual was the high selectivity of palladium-catalyzed hydroalkylation for 6-*endo*-trig cyclization, as 5-*exo*-trig cyclization is typically observed for the addition of first-row elements to olefins.[35] Furthermore, whereas gem-dialkyl substitution typically facilitates transition metal-based cyclizations via the kinetic Thorpe−Ingold effect,[36] palladium-catalyzed hydroalkylation of 3-butenyl β-diketones was intolerant of substitution along the alkyl tether. In an effort to gain insight into these unusual features and to develop a general mechanistic understanding of palladium-catalyzed hydroalkylation, we investigated the mechanism of the conversion of **3** to **5** catalyzed by **4** employing deuterium-labeling, kinetic, and in situ NMR experiments.

Working Mechanism. Palladium-catalyzed conversion of **3** to **5** involves the net addition of the C−H bond of the β-diketone moiety across the C=C bond of the olefin. We envisioned a stepwise mechanism involving initial C−C bond formation followed by protonolysis of the resulting Pd−C bond (Scheme 3). The mechanisms of the palladium-catalyzed or -mediated addition of oxygen,[37] nitrogen,[38] and carbon nucleophiles[39] to un-

(34) The major competing reaction pathway in the palladium-catalyzed cyclization of 3-butenyl β-keto esters was olefin isomerization to form 3-oxo-5-heptenoates.

(35) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

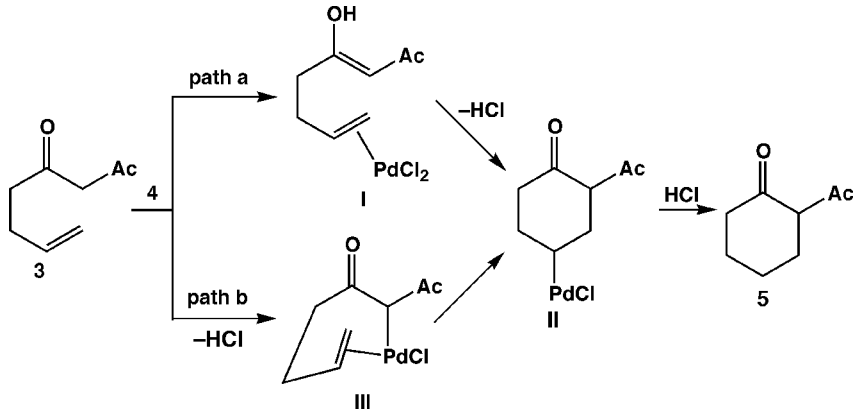
(36) (a) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. (b) Kirby, A. J. *Adv. Phys. Org. Chem*. **1980**, *17*, 208. (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 106.

(37) (a) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc*. **1979**, *101*, 2411. (b) Stille, J. K.; James, D. E.; Hines, L. F. *J. Am. Chem. Soc*. **1973**, *95*, 5062. (c) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498. (d) Stille, J. K.; Divakaruni, R. *J. Am. Chem. Soc*. **1978**, *100*, 1303.

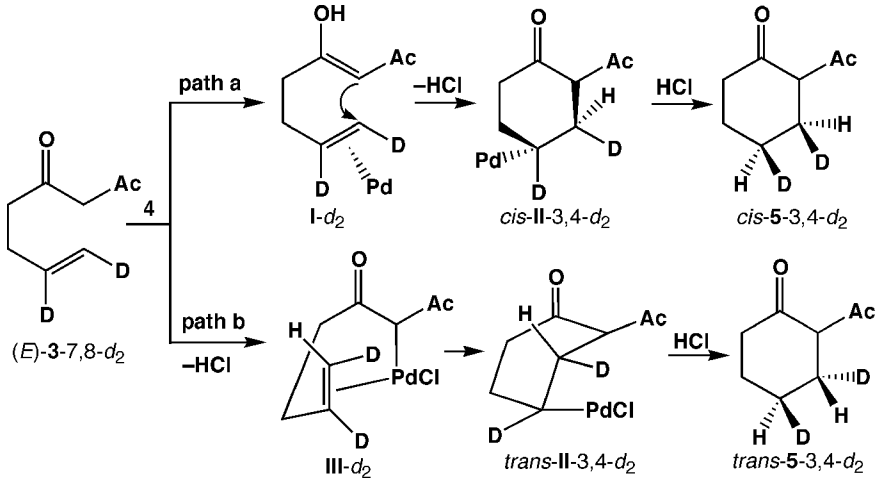
(38) (a) Åkermark, B.; Bäckvall, J. E.; Siirala-Hansen, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett*. **1974**, 1363. (b) Åkermark, B.; Bäckvall, J. E. *Tetrahedron Lett*. **1975**, 819.

(39) (a) Murahashi, S.-I.; Yamamura, M.; Mita, N. *J. Org. Chem*. **1977**, *42*, 2870. (b) Kurosawa, H.; Asada, N. *Tetrahedron Lett*. **1979**, 255.

Scheme 3



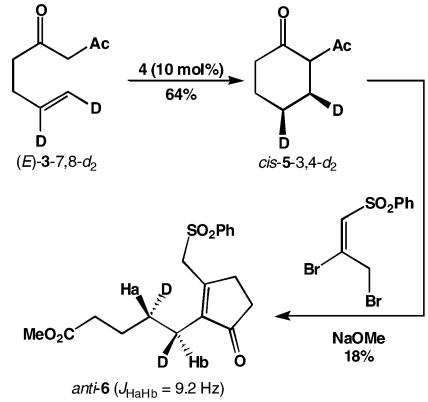
Scheme 4



activated olefins have been studied, and mechanisms involving either nucleophilic attack on a palladium-complexed olefin (outer-sphere) or attack of the nucleophile on palladium followed by olefin β-migratory insertion (inner-sphere) have been documented. Therefore, we considered both outer-sphere and inner-sphere mechanisms for C−C bond formation in the palladium-catalyzed conversion of **3** to **5**. In the former pathway, attack of the pendant enol on the palladium-complexed olefin of **I**, followed by protonolysis of the Pd−C bond of **II**, would form **5** (Scheme 3, path a). In the latter pathway, attack of the enol carbon on the palladium atom of **4** could form alkyl olefin chelate complex **III**. Intramolecular carbometalation followed by protonolysis of **II** would form **5** (Scheme 3, path b).

Deuterium-Labeling Experiments. Outer-sphere and inner-sphere pathways for the palladium-catalyzed conversion of **3** to **5** can be potentially distinguished via cyclization of stereochemically pure 7,8-dideuterio-7-octene-2,4-diones (**3**-7,8-d_2). For example, complexation of palladium to (*E*)-**3**-7,8-d_2 followed by outer-sphere attack of the enolic carbon on the palladium-complexed olefin of **I**-d_2 would form palladium cyclohexyl intermediate *cis*-**II**-3,4-d_2. Protonolysis of *cis*-**II**-3,4-d_2 with retention of configuration[40] would form *cis*-**5**-3,4-d_2 (Scheme 4, path a). Conversely, attack of the enol carbon atom of (*E*)-**3**-7,8-d_2 on **4** would form the palladium alkyl olefin chelate complex **III**-d_2, which could undergo intramolecular carbometalation followed by protonolysis of the Pd−C bond of *trans*-**II**-3,4-d_2 with retention of configuration[40] to form *trans*-**5**-3,4-d_2 (Scheme 4, path b).

Scheme 5

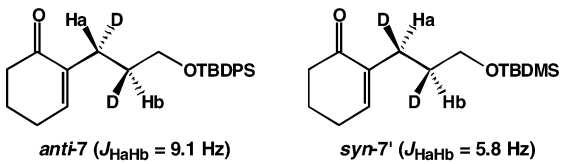


Treatment of (*E*)-**3**-7,8-d_2 with a catalytic amount of **4** (10 mol %) in dioxane at room temperature for 12 h formed *cis*-**5**-3,4-d_2 in 64% isolated yield (Scheme 5).[41] The stereochemistry of *cis*-**5**-3,4-d_2 was determined by first treating *cis*-**5**-3,4-d_2 with (*E*)-2,3-dibromo-1-phenylsulfonylpropene and sodium methoxide to form the

(40) (a) Merrifield, J. H.; Fernández, J. M.; Buhro, W. E.; Gladysz, J. A. *Inorg. Chem.* **1984**, *23*, 4022. (b) De Luca, N.; Wojcicki, A. *J. Organomet. Chem.* **1980**, *193*, 359.

(41) Alkenyl diketones (*E*)-**3**-7,8-d_2 and (*Z*)-**3**-7,8-d_2 contained ~15% and ~25%, respectively, of the isotopomer **3**-7,8,8-d_3; the presence of **3**-7,8,8-d_3 did not complicate stereochemical analysis of **5**-4,5-d_2.

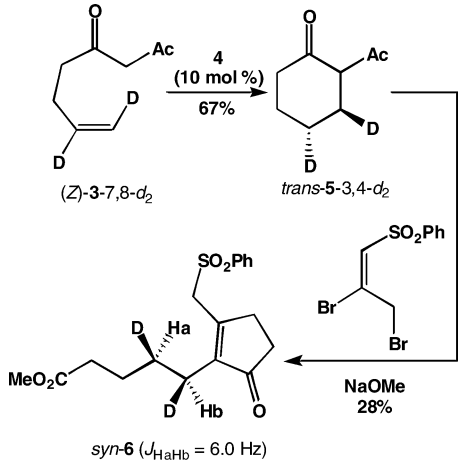
Chart 1



anti-**7** (J_{HaHb} = 9.1 Hz) *syn*-**7′** (J_{HaHb} = 5.8 Hz)

anti-**8** (J_{HH} = 9.1 Hz) *syn*-**8** (J_{HH} = 5.6 Hz)

Scheme 6



(*Z*)-**3**-7,8-d_2 *trans*-**5**-3,4-d_2

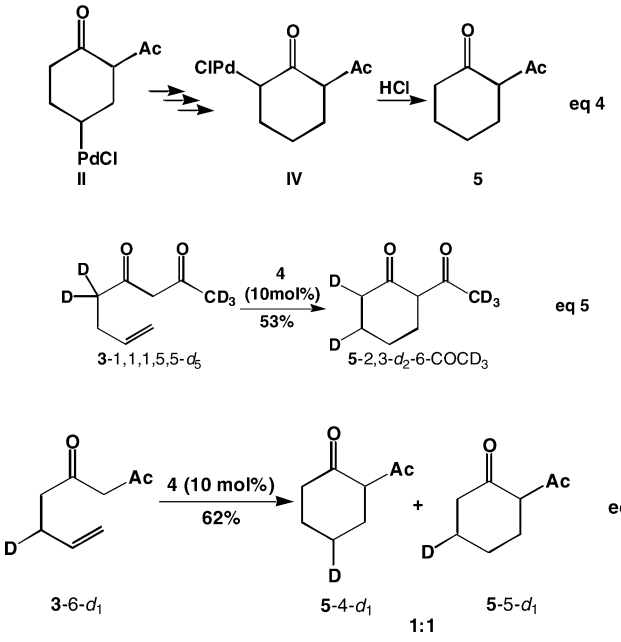
syn-**6** (J_{HaHb} = 6.0 Hz)

open-chain pentanoate derivative *anti*-**6**-4,5-d_2 in 18% isolated yield (Scheme 5).[42] The stereochemistry of *anti*-**6**-4,5-d_2 was then established by the 9.2 Hz coupling constant of the H(4) and H(5) protons of the pentanoate chain in the ^{1}H NMR spectrum. This value is in good agreement with the $J_{HH(anti)}$ values reported for the silyl-protected 2-(3-hydroxypropyl)cyclohexenone *anti*-**7** ($J_{HH(anti)}$ = 9.1 Hz)[43] and for the deuterated pentane isotopomer *anti*-**8** [$J_{HH(anti)}$ = 9.1 Hz] (Chart 1),[44] and with the value calculated for *anti*-**6**-4,5-d_2 employing molecular mechanics [$J_{H(4)H(5)}$ = 11.1 Hz].

Treatment of (*Z*)-**3**-7,8-d_2 with a catalytic amount of **4** (10 mol %) in dioxane at room temperature for 12 h formed *trans*-**5**-3,4-d_2 in 67% yield,[41] which was subsequently converted to *syn*-**6**-4,5-d_2 in 28% yield (Scheme 6).[42] The stereochemistry of *syn*-**6**-4,5-d_2 was established by the 6.0 Hz coupling constant of the H(4) and H(5) protons, which is in good agreement with the values for $J_{HH(syn)}$ reported for the silyl-protected 2-(3-hydroxypropyl)cyclohexenone *syn*-**7′** ($J_{HH(syn)}$ = 5.6 Hz)[43] and for the deuterated pentane isotopomer *syn*-**8** [$J_{HH(syn)}$ = 5.6 Hz] (Chart 1),[44] and with the value calculated for *syn*-**6**-4,5-d_2 employing molecular mechanics [$J_{H(4)H(5)}$ = 6.1 Hz]. The selective conversion of (*E*)-**3**-7,8-d_2 and (*Z*)-**3**-7,8-d_2 to *cis*-**5**-3,4-d_2 and *trans*-**5**-3,4-d_2, respectively (Schemes 5 and 6), is in accord with C−C bond formation via outer-sphere attack of the enol carbon atom on the palladium-complexed olefin of **I** (Scheme 3, path a) provided that the subsequent steps in the catalytic cycle preserve the stereochemistry generated via C−C bond formation (see below).

To gain insight into the nature of proton transfer in the palladium-catalyzed conversion of **3** to **5**, we studied the cyclization of **3**-3,3-d_2 catalyzed by **4**. According to the mechanism depicted in Scheme 3, path a, cyclization of **3**-3,3-d_2 via initial attack of the pendant enol on the palladium-complexed olefin of **I**-d_2' would form **II**-2-d_1 with loss of DCl (Scheme 7). Deuterolysis of the Pd−C bond of **II**-2-d_1 with the DCl released in the formation of **II**-2-d_1 would then form **5**-2,4-d_2 (Scheme 7). However, in contrast to our expectations, cyclization of **3**-3,3-d_2 catalyzed by **4** followed by silica gel chromatography formed none of the expected C(4)-d_1 isotopomer and instead formed **5**-6-d_1 in 45% isolated yield as the exclusive deuterated isotopomer with ~80% deuterium incorporation (Scheme 7). Note that the C(2) deuterium atom of **5** is lost during the isolation of **5**-6-d_1.

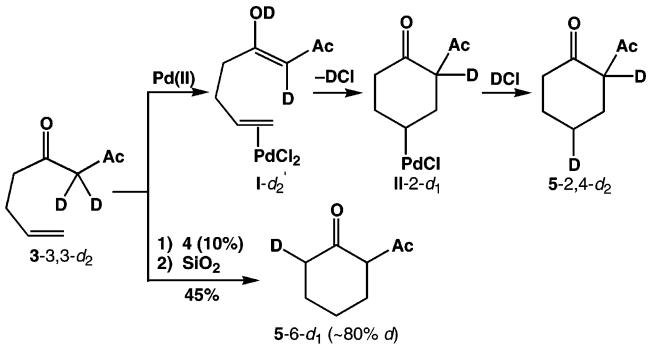
Formation of **5**-6-d_1 rather than **5**-4-d_1 in the palladium-catalyzed cyclization of **3**-3,3-d_2 pointed to migration of palladium from the C(4) carbon atom to the C(6) carbon atom of the 2-acetylcyclohexanone ring prior to deuterolysis from palladium enolate complex **IV** (eq 4). Four additional deuterium-labeling experiments were performed to probe the mechanism of palladium migration. In one experiment, reaction of **3**-1,1,1,5,5-d_5 with a catalytic amount of **4** (10 mol %) formed **5**-2,3-d_2-6-COCD$_3$ in 53% isolated yield as the exclusive isotopomer (eq 5). In a second experiment, reaction of **3**-6-d_1 with a catalytic amount of **4** (10 mol %) formed a 1:1 mixture of **4**-4-d_1 and **4**-5-d_1 in 62% combined isolated yield (eq 6). In a third experiment, reaction of



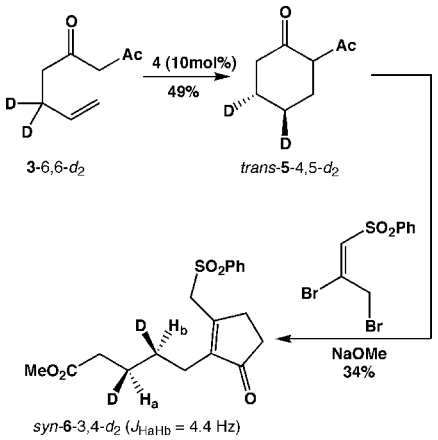
3-6,6-d_2 with a catalytic amount of **4** formed *trans*-**5**-4,5-d_2 in 49% isolated yield (Scheme 8). The stereochemistry of *trans*-**5**-4,5-d_2 was established by the 4.4 Hz coupling constant of the H(3) and H(4) protons of the open-chain derivative *syn*-**6**-3,4-d_2 (Scheme 8). In a fourth experiment, treatment of **3**-8,8-d_2 with a catalytic

(42) Padwa, A.; Ishida, M.; Muller, C. L.; Murphree, S. S. *J. Org. Chem.* **1992**, *57*, 1170.
(43) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458.
(44) Gilchrist, J. H.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 12021.

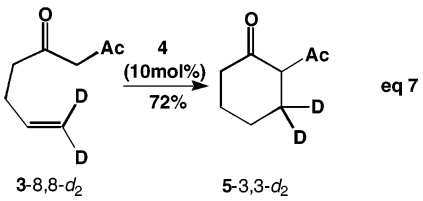
Scheme 7



Scheme 8



amount of **4** (10 mol %) led to the isolation of **5**-3,3-d_2 in 72% yield as the exclusive isotopomer (eq 7).



eq 7

In Situ NMR Experiments. Additional information regarding the mechanism of palladium-catalyzed conversion of **3** to **5** was gained through ^{1}H NMR analysis of **4** and of mixtures of **3** and **4**. Bis(nitrile) complexes of $PdCl_2$ including **4** disproportionate in solution to form predominantly chloride-bridged dimers along with free nitrile.[45] The mixture of polynuclear chloride-bridged palladium complexes generated via disproportionation of **4** in dioxane will be subsequently referred to as **4***. Addition of **3** (25 mM) to a dioxane-d_8 solution of **4*** ($[Pd]_{tot}$ = 2.5 mM) led to broadening of the internal olefinic resonance of **3** at δ ~5.85 in the ^{1}H NMR spectrum (Figure 1), consistent with rapid, endergonic complexation of the olefin of **3** to the palladium of **4***, presumably via displacement of an acetonitrile ligand (eq 8). Conversely, no broadening of the enolic proton of **3** at δ 5.51 was observed in the ^{1}H NMR spectrum of mixtures of **3** and **4*** (Figure 1), which argues against interaction between the enol moiety of **3** with the

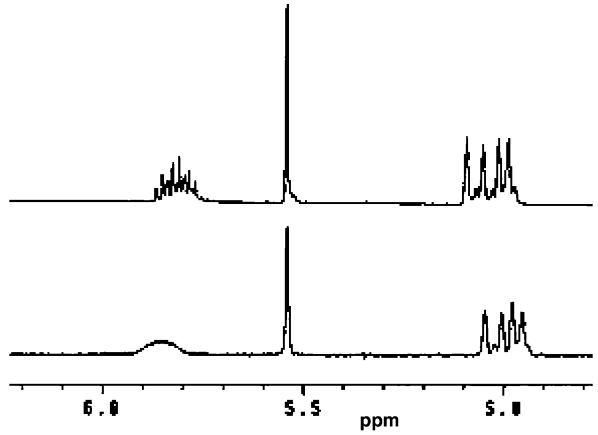
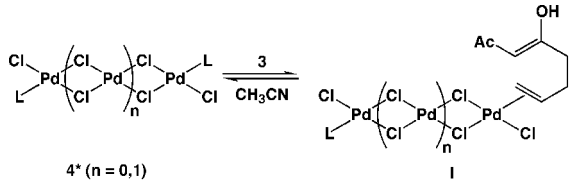


Figure 1. Olefinic region of the ^{1}H NMR spectra of **3** (top spectrum) and **3** that contained **4*** (10 mol % Pd) in dioxane-d_8 at room temperature.

palladium of **4***. With the exception of the broadening of the internal olefinic resonance of **3**, no resonances or spectroscopic features indicative of the formation of an organometallic complex were observed throughout 50% conversion of **3** to **5** in the presence of a catalytic amount of **4***.[46]



Kinetics. The kinetics of the conversion of **3** to **5** catalyzed by **4** were complicated both by deactivation of palladium under reaction conditions (see below) and by the disproportionation of **4** to **4*** (see above). Because both the rate of catalyst deactivation and the equilibrium for disproportionation of **4** to **4*** are likely affected by changes in [**3**], [**4**], and [acetonitrile], accurate determination of the rate law for the conversion of **3** to **5** catalyzed by **4** was precluded. However, a number of useful empirical observations were made regarding the kinetics of palladium-catalyzed hydroalkylation of **3**. For example, the initial rate of the reaction of **3** ($[3]_0$ = 20 mM) and **4** (2.0 mM) at room temperature in dioxane that contained acetonitrile ($[CH_3CN]_{tot}$ = 38 mM)[47] increased from $(1.43 \pm 0.09) \times 10^{-5}$ M s^{-1} to $(3.05 \pm 0.1) \times 10^{-5}$ M s^{-1} as the concentration of **4** increased from 2.0 to 4.0 mM. Conversely, the initial rate of the reaction of **3** ($[3]_0$ = 20 mM) with **4** (4.0 mM) increased from $(3.05 \pm 0.1) \times 10^{-5}$ M s^{-1} to $(15.3 \pm 0.9) \times 10^{-5}$ M s^{-1} as the total acetonitrile concentration decreased from

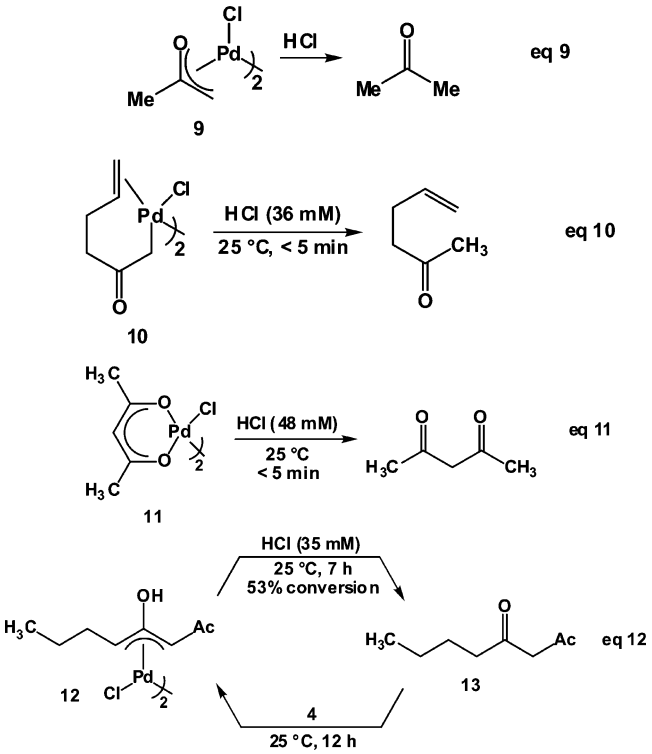
(45) (a) Dietl, H.; Reinheimer, H.; Moffat, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276. (b) The room-temperature ^{1}H NMR spectrum of a dioxane-d_8 solution of **4** (11 mM) displayed a 1:1.3 ratio of singlets at δ 2.35 and 1.95 corresponding to methyl group of coordinated and free acetonitrile, respectively.

(46) The low solubility of **4** in dioxane and the presence of the tautomeric forms of **3** precluded determination of the equilibrium constants associated with these transformations. Also noteworthy was that analysis of mixtures of the sodium enolate of **3** ([**3**]-[Na]$^+$) with **4** in dioxane-d_8 revealed that [**3**]-[Na]$^+$ interacted with palladium primarily via the enolate functionality as opposed to the olefinic functionality. For example, the resonances corresponding to the enolate proton of [**3**]-[Na]$^+$ (~20 mM) in dioxane-d_8 shifted downfield from δ 5.01 in the absence of **4** to δ 5.42 in the presence of **4** (~20 mM) without significant broadening of the enolic resonance. The absence of broadening of the enolic proton of [**3**]-[Na]$^+$ in the presence of **4** points to irreversible binding of the enolate to palladium, presumably via displacement of a chloride ligand.

(47) Total acetonitrile concentration ($[CH_3CN]_{tot}$) refers to the sum of free and coordinated acetonitrile.

38 to 8 mM. While neither HCl (0.10 M) nor **5** (25 mM) had a significant (≤5%) effect on the initial rate of hydroalkylation, palladium-catalyzed hydroalkylation was strongly inhibited by chloride ion. For example, treatment of **3** ($[\mathbf{3}]_0 = 25$ mM) with a catalytic amount of **4** (2.5 mM) in dioxane that contained $(n\text{-Bu})_4\text{NCl}$ (25 mM) formed no detectable amounts of **5** after 18 h at room temperature.

Palladium Enolate Complexes. The results of deuterium-labeling experiments, in particular, the formation of **5**-6-d_1 in the palladium-catalyzed cyclization of **3**-3,3-d_2 (Scheme 7), pointed to protonolysis of palladium enolate complex **IV** in the conversion of **3** to **5** catalyzed by **4** (eq 4). The high reactivity of palladium enolate complexes that contain only nitrile and chloride ligands toward protonolysis has been implicated previously in the hydroalkoxylation[48] and hydroamination[49] of α,β-unsaturated ketones catalyzed by **4**. We sought to gain information regarding the structure of **IV** through the protonolysis of palladium enolate complexes that contained no strong donor ligands as a function of the binding mode of the enolate. To this end, treatment of a dioxane-d_8 solution of the η^3-oxallyl complex **9** with HCl (20 mM, 2 equiv) led to immediate formation of a rust-colored precipitate, presumably $PdCl_2$, with formation of acetone as the exclusive organic product (eq 9). Likewise, the η^1-C-bound complex **10**[50] and the *O*,*O*′-bound β-diketonate complex **11**[51] underwent rapid (≤10 s) protonolysis in the presence of trace amounts of HCl to form 5-hexen-2-one and 2,4-pentanedione, respectively, as the exclusive organic products (eqs 10 and 11). In contrast, treatment of a dioxane-d_8 solution of the η^3-β-diketonate chloride dimer **12** with HCl (35 mM, 2 equiv) required 7 h at room temperature to achieve ~50% conversion, forming **13** as the exclusive organic product (eq 12).



Byproducts and Catalyst Deactivation. The efficiency of the conversion of **3** to **5** catalyzed by **4** depended strongly on the initial concentration of **3**, and at high concentration ($[\mathbf{3}]_0 = 250$ mM), cyclohexanone **5** constituted ≤50% of the reaction mixture (Table 1, entry 7). Furthermore, although no detectable amount of palladium black was generated during the palladium-catalyzed hydroalkylation of 3-butenyl β-diketones, rather high (typically ≥10%) catalyst loadings were required to achieve complete conversion. This behavior suggested that **4** was converted to a catalytically inactive species under reaction conditions. We therefore sought to identify the organic and organometallic byproducts formed in the reaction of **3** with a catalytic amount of **4** and to establish the concentration dependence of byproduct formation.

A dioxane solution of **3** ($[\mathbf{3}]_0 = 25$ mM), **4** (10 mol %), and *n*-tetradecane (internal standard) was stirred at room temperature for 16 h. GC analysis of the reaction mixture revealed formation of cyclohexanone **5** (80%), 2,4-octanedione (**13**, 4%), 2-acyl-1-hydroxy-1,3-hexadiene [**14**, 3% (~7:1 mixture of dienolic and keto tautomers],[52] and 2-acetylphenol (**15**, 3%) (Scheme 9). In a separate experiment, a dioxane solution of **3** ($[\mathbf{3}]_0 = 25$ mM) and **4** (10 mol %) was stirred for 16 h at room temperature and concentrated under vacuum. Addition of pentane to the crude reaction mixture formed a yellow precipitate, from which a 10:1 mixture of the η^3-β-diketonate chloride dimer **12** and the π(allyl)palladium chloride dimer $\{[\eta^3\text{-}CH_3CHCHCHC(O)CH_2Ac]Pd(Cl)\}_2$ (**16**) were isolated in 77% combined yield based on **4** (Scheme 9). Complexes **12** and **16** were identified by ^{1}H NMR and IR spectroscopy, elemental analysis, and independent synthesis (see above).

As was anticipated, the distribution of organic products formed in the palladium-catalyzed hydroalkylation of **3** varied with the initial concentration of the reaction mixture. When the reaction of **3** ($[\mathbf{3}]_0 = 250$ mM) with a catalytic amount of **4** in dioxane at room temperature was monitored periodically by GC analysis, after 4 h **3** had been completely consumed to form a mixture of **5** (49%), **13** (14%), **14** (12%), **15** (3%), (*E*)- and (*Z*)-6-octene-2,4-dione (**17**, 14%), and (*E*)- and (*Z*)-4-hydroxy-3,5-octadien-2-one (**18**, 3%) (Scheme 10, Figure S1). Stirring a dioxane solution of **5** (250 mM) with a catalytic amount of **4** (10 mol %) at room temperature for 24 h led to no detectable consumption of **5**. The distribution of organometallic byproducts formed in the palladium-catalyzed hydroalkylation of **3** also varied with the initial concentration of the reaction mixture. When a dioxane solution of **3** ($[\mathbf{3}]_0 = 250$ mM) and **4** (10 mol %) was stirred for 4 h at room temperature and concentrated under vacuum, subsequent addition of pentane

(48) (a) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001. (b) Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403.

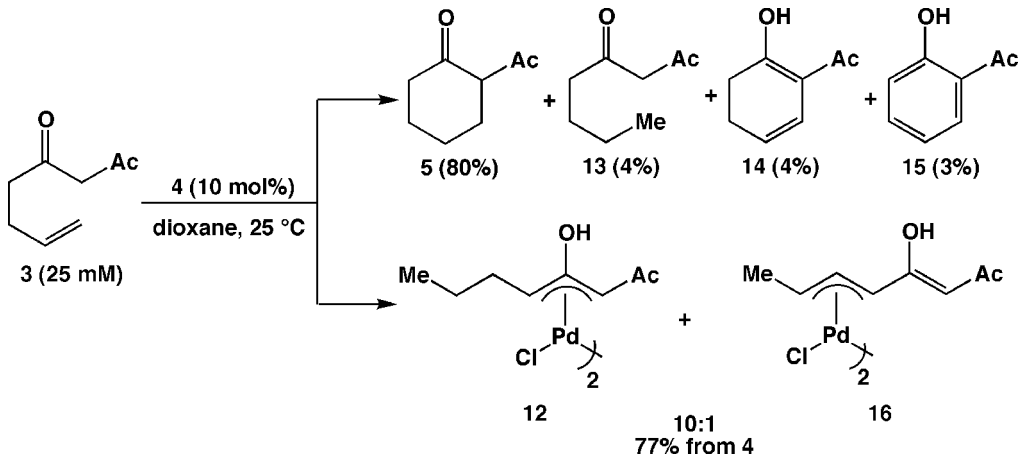
(49) Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25.

(50) Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 4519.

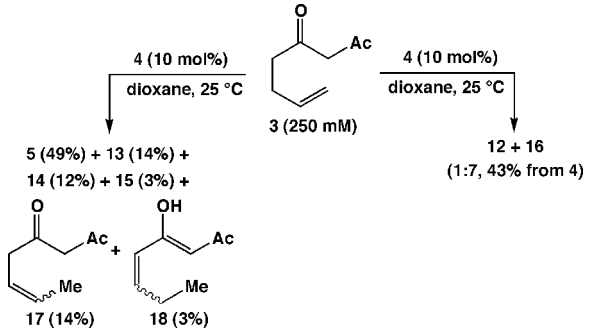
(51) (a) Kanda, Z.; Nakamura, Y.; Kawaguchi, S. *Inorg. Chem.* **1978**, *17*, 910. (b) Okeya, S.; Kawaguchi, S. *Inorg. Chem.* **1977**, *16*, 1730. (c) Yanase, N.; Nakamura, Y.; Kawaguchi, S. *Inorg. Chem.* **1980**, *19*, 1575. (d) Yanase, N.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1979**, 591.

(52) (a) Because **14** tautomerizes under acidic conditions to form a ~1:1 mixture of 2-carbomethoxy-2-cyclohexenone and 2-carbomethoxy-1-hydroxy-1,3-cyclohexadiene,[52b] the predominant formation of 2-acyl-1-hydroxy-1,3-hexadiene (**7**-*enol*) relative to 2-acyl-2-cyclohexenone (**7**-*keto*) strongly suggests that **7**-*enol* is formed as the kinetic product in these transformations. (b) Christoffers, J.; Mann, A. *Eur. J. Org. Chem.* **1999**, *1*, 2511.

Scheme 9



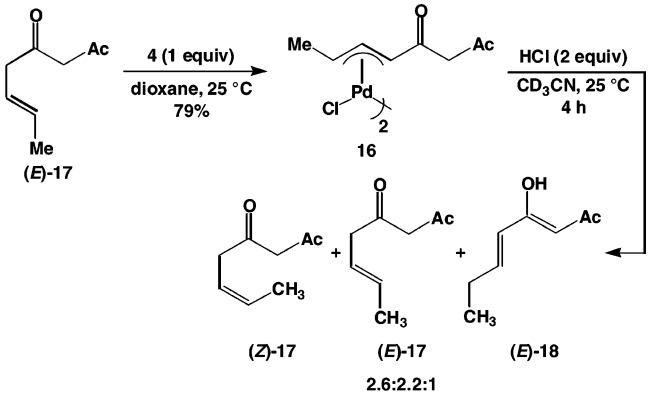
Scheme 10



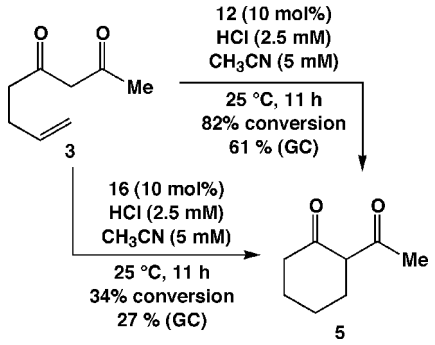
led to the isolation of a 1:7 mixture of **12**:**16** in 43% combined yield based on **4** (Scheme 10).

Several experiments were performed to probe the relationship of palladium complexes **12** and **16** to the organic byproducts **13**−**18** and to probe the role of **12** and **16** in catalyst deactivation. As was noted above, protonolysis of **12** formed **13**, and reaction of **4** with **13** regenerated **12** (eq 12). In comparison, reaction of **4** with (*E*)-**17** led to the isolation of π-(allyl)palladium chloride dimer **16** in 79% yield, and reaction of **16** with HCl (15 mM, 2 equiv) in CD_3CN at room temperature for 4 h led to 85% conversion to form a 2.6:2.2:1 mixture of (*Z*)-**17**, (*E*)-**17**, and (*E*)-**18** (Scheme 11).[53] Reaction of **4** with (*E*)-**18** in dioxane at room temperature led to no detectable formation of **16**. Treatment of **3** with a catalytic amount of either **12** or **16** in dioxane led to no detectable consumption of **3** after 24 h at room temperature. In comparison, treatment of **3** ($[\mathbf{3}]_0$ = 25 mM) with a catalytic amount of **12** or **16** (2.5 mM) in dioxane that contained both acetonitrile (5.0 mM) and HCl (2.5 mM) at room temperature for 11 h led to 82% conversion with 61% product formation and 34% conversion with 27% product formation, respectively (Scheme 12).

Scheme 11



Scheme 12

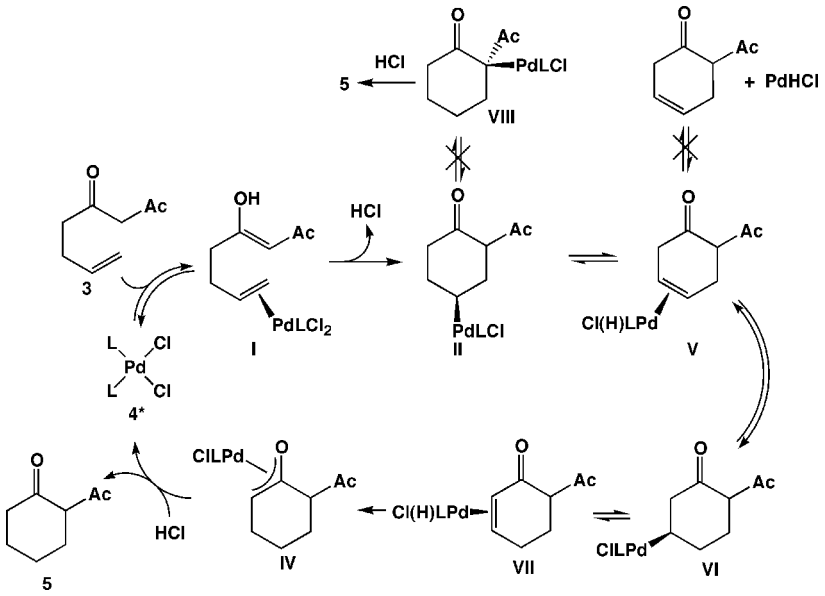


Discussion

Mechanism of Hydroalkylation. The mechanism depicted in Scheme 13 is consistent with all of our observations regarding the palladium-catalyzed hydroalkylation of **3** to form **5**. In situ ^{1}H NMR experiments established rapid, endergonic coordination of the olefin of **3** to palladium to form **I** (eq 8). Stereospecific conversion of (*E*)-**3**-7,8-d_2 and (*Z*)-**3**-7,8-d_2 to *cis*-**5**-3,4-d_2 and *trans*-**5**-3,4-d_2, respectively (Schemes 5 and 6), established outer-sphere attack of the enolic carbon atom on the palladium-complexed olefin of **I** to form **II**. Selective conversion of **3**-3,3-d_2 to **5**-6-d_1 (Scheme 7), **3**-1,1,1,5,5-d_5 to **5**-2,3-d_2-6-$COCD_3$ (eq 5), **3**-6-d_1 to a 1:1 mixture of **5**-4-d_1 and **5**-5-d_1 (eq 6), and **3**-6,6-d_2 to *trans*-**5**-4,5-d_2 (Scheme 8) together established sequential conversion of **II** to intermediates **V**, **VI**, and **VII** followed by protonolysis from palladium enolate complex **IV** (Scheme 13). Although enolate complex **IV** is depicted as an η^3-oxallyl complex (Scheme 13), we cannot rule out carbon-bound and *O,O′*-bound structures for **IV**

(53) We cannot rule out the possibility that **18** is generated via acid-catalyzed tautomerization of **17** under these conditions. Protonolysis of palladium enolate and π-allyl complexes was much faster in CD_3CN than in dioxane, presumably due to the higher solubility of the respective complexes in CD_3CN. The extreme insolubility of **16** in dioxane mandated the use of acetonitrile in this experiment. Unfortunately, this precludes direct comparison of the rate of protonolysis of **16** under stoichiometric conditions to the rate of protonolysis of **16** under catalytically relevant conditions.

Scheme 13



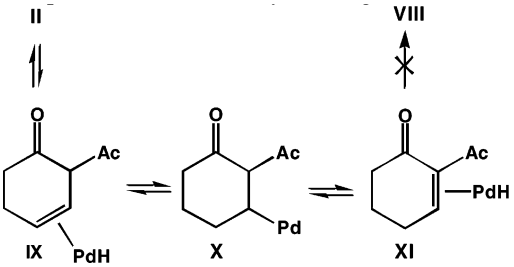
given the high protonolysis reactivity of palladium enolate complexes **10** and **11** (eqs 10 and 11).

The stereospecific conversion of **3**-6,6-d_2 to *trans*-**5**-4,5-d_2 precluded reversible olefin displacement from intermediate **V** and also established that the stereochemistry generated via initial cyclization of (*E*)- and (*Z*)-**3**-7,8-d_2 was retained in carbocycles *cis*- and *trans*-**5**-3,4-d_2 (Schemes 5 and 6). Although we were unable to determine the stereochemistry of **5**-2,3-d_2-6-$COCD_3$ formed in the cyclization of **3**-1,1,1,5,5-d_5 (eq 5), intermediate **VII** was also presumably stable toward olefin displacement (Scheme 13). Given the rapid and quantitative disproportionation of palladium nitrile complexes to form chloride-bridged complexes,[45] it appears likely that intermediates **I**, **II**, and **IV**−**VII** exist predominantly as chloride-bridged polynuclear complexes (Scheme 13).

Available evidence points to conversion of **I** to **II** as the turnover-limiting step in the palladium-catalyzed conversion of **3** to **5**. The rapid, endoergonic formation of palladium olefin intermediate **I** from mixtures of **3** and **4*** (eq 8) and the failure of any additional organometallic species to accumulate during the conversion of **3** to **5** point to **4*** as the catalyst resting state and the first irreversible step that consumes **4*** as the turnover-limiting step. Given the facility and reversibility of β-hydride elimination in Pd(II) alkyl complexes,[54] it appears unlikely that conversion of **II** to **IV** is turnover-limiting. Although protonolysis of **IV** is irreversible, the zero-order dependence of the initial rate of the conversion of **3** to **5** catalyzed by **4** on [HCl] rules out a mechanism involving turnover-limiting protonolysis of **IV**. The zero-order dependence of conversion of **3** to **5** on [HCl] also rules out a mechanism involving reversible conversion of **I** to **II**, which would be inhibited by HCl. Together, these observations point to conversion of **I** to **II** as the turnover-limiting step in the conversion of **3** to **5** catalyzed by **4**.

The failure to form detectable amounts of **5**-3,4-d_2 in the cyclization of **3**-8,8-d_2 catalyzed by **4** (eq 7) rules out protonolysis from the palladium η^1-β-diketonate complex **VIII** (Scheme 13), which, in turn, requires either that **VIII** is not formed during catalysis or that **VIII** is unreactive with respect to protonolysis. Facile protonolysis of the carbon-bound enolate **10** (eq 10) argues against this latter explanation and suggests that **VIII** does not form under catalytic conditions, which points to one or more unfavorable steps in the pathway for conversion of **II** to **VIII**. Migration of palladium from the C(4) carbon atom of **II** to the C(3) carbon atom of **X** via palladium olefin intermediate **IX** appears likely (Scheme 14), and formation of **IX** under catalytic conditions is implicated by the formation of dienol **14** (see below). Conversely, migration of palladium from the C(4) atom of **X** to the C(5) carbon atom of **VIII** via **XI** appears unlikely as the conversion of **XI** to **VIII** requires transfer of palladium to the disubstituted terminus of the olefin. Formation of a transition metal−3° alkyl bond via β-hydride addition is disfavored relative to formation of an M−2° alkyl bond due to the unfavorable steric interactions associated with the former transformation.[55] Therefore, in the event that intermediate **XI** is formed under catalytic conditions (see below), it would likely revert to **II** in preference to forming η^1-β-diketonate complex **VIII**.

Scheme 14

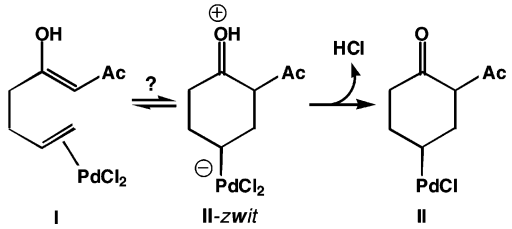


Regioselectivity of Hydroalkylation. Kinetic 5-*exo*-trig cyclization is typically favored relative to 6-*endo*-trig cyclization for the addition of first-row elements to

(54) (a) Goj, L. A.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11133. (b) Mecking, S.; Johnson, L. K.; Wang, L.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 888.

(55) (a) Casey, C. P.; Cyr, C. R.; Grant, J. A. *Inorg. Chem.* **1974**, *13*, 910. (b) Schwartz, J.; Lagbinger, J. A. *Angew Chem., Int. Ed. Engl.* **1976**, *15*, 333.

Scheme 15



olefins,[35] and for this reason, 6-*endo*-trig cyclization is often interpreted as evidence for thermodynamic control of ring closure. Although the absence of HCl inhibition in the palladium-catalyzed hydroalkylation of **3** rules out reversible conversion of **I** to **II**, we cannot rule out reversible conversion of **I** to the zwitterionic intermediate **II**-*zwit* followed by irreversible loss of HCl to form **II** (Scheme 15). Nevertheless, we propose that the 6-*endo*-trig regioselectivity of the hydroalkylation of 3-butenyl β-diketones is determined kinetically. Because the C(4) and C(7) sp^2-carbon atoms of **3** create two planar groups of atoms [C(3)−C(4)−C(5) and C(6)−C(7)−C(8), respectively] linked by a single C(sp^3)−C(sp^3) bond, **3** and the corresponding palladium olefin complex **I** possess little conformational flexibility. Attack of the enolic carbon atom on the Pd-complexed olefin of **I** requires overlap between the filled C(3) π-orbital and the empty C(8) π^*-orbital with an angle of attack of ~109° relative to the C=C vector. Analysis of molecular models indicates that while overlap for 6-*endo* cyclization is acceptable, overlap for 5-*exo* cyclization cannot be achieved without significant rotation about the C(3)=C(4) bond.[56,57]

Kinetic 6-*endo*-trig cyclization has been observed for a number of transformations involving the addition of an olefinic or enolic carbon atom to a palladium-complexed olefin, most notably, the palladium-catalyzed Cope rearrangement and related transformations.[58] Significantly, the palladium-catalyzed Cope rearrangement of 1,5-dienes is believed to proceed via 6-*endo*-trig attack of the pendant olefin on a palladium-complexed olefin to form a zwitterionic palladium cyclohexyl intermediate analogous to **II**-*zwit* that undergoes retrocyclization and decomplexation.[59] 5-Hexenyl radicals that possess a C(2) carbonyl group are also biased toward 6-*endo*-trig cyclization.[57,60]

Byproduct Formation and Catalyst Deactivation. Under our optimized conditions for hydroalkylation, reaction of **3** ($[\mathbf{3}]_0$ = 25 mM) with **4** formed predominantly 2-acetylcyclohexanone (**5**) (>80%) along with traces of 2,4-octanedione (**13**), 2-acyl-1-hydroxy-1,3-hexadiene (**14**), and 2-acetylphenol (**15**) (Scheme 9). Palladium-catalyzed cyclization of **3** at higher concentrations ($[\mathbf{3}]_0$ = 250 mM) led both to increased formation of byproducts **13** and **14** and to formation of significant amounts of 6-octene-2,4-dione (**17**) and a lesser amount of 5-octene-2,4-dione (**18**) (Scheme 10). A mechanism that accounts for the formation of **13**, **14**, **17**, and **18** is depicted in Scheme 16.[61] Associative olefin displacement from palladium olefin complex **IX** with the olefin of **3** would form dienol **14** and the palladium olefin hydride complex **XII** (Scheme 16).[61−63] Isomerization via iterative β-hydride addition/elimination would generate, in sequence, palladium olefin hydride complexes **XIII** and **XIV** and palladium enolate complex **XV**. Olefin displacement from **XIII** and **XIV** would form byproducts **17** and **18**, respectively, while protonolysis from palladium enolate complex **XV** would form **13**.[63]

The mechanism depicted in Scheme 16 also accounts for the concentration dependence of the product distribution of the reaction of **3** and **4**. Because olefin displacement from **IX** is a bimolecular process,[62] whereas reversion of **IX** to **X** is a unimolecular process (Scheme 16), olefin displacement from **IX** should become more pronounced with increasing ligand concentration. In accord with this prediction, formation of **14** in the reaction of **3** and **4** increased from 3 to 12% as the initial concentration of **3** increased from 25 to 250 mM. Similarly, because formation of byproducts **17** and **18** requires two associative displacement processes, formation of these byproducts should be particularly sensitive to concentration. Indeed, whereas no detectable amounts of **17** or **18** were formed at low concentration, under the more concentrated reaction conditions, these isomers together constituted >20% of the reaction mixture generated after ~50% conversion (Figure S1).

In addition to organic byproducts **13**−**15**, **17**, and **18**, reaction of **3** with a catalytic amount of **4** under our optimized conditions led to formation of a 10:1 mixture of the palladium η^3-β-diketonate complex **12** and the palladium π-allyl chloride dimer **16**, which together accounted for 77% of the initial charge of palladium. Neither **12** nor **16** was formed directly from reaction of **3** with **4**, and no detectable quantities of **5** were generated upon thermolysis or protonolysis of **12** or **16**. For these reasons, we can rule out **12** and **16** as intermediates in the palladium-catalyzed conversion of **3** to **5**.

Complexes **12** and **16** were formed as the exclusive products of the reaction of **4** with **13** and **17**, respectively. Although protonolysis of **12** and **16** with HCl led to predominant regeneration of **13** and **17**, respectively (eq 12 and Scheme 11), protonolysis of **12** and **16** appears too slow to account for formation of **13** and **17** under our optimized conditions for the hydroalkylation of **3** ($[\mathbf{3}]_0$ = 25 mM). Because one molecule of HCl is

(56) These arguments are modeled after those initial formulated by Curran and Chang.[57]

(57) Curran, D. P.; Chang, C.-T. *J. Org. Chem*. **1989**, *54*, 3140.

(58) Overman, L. E. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 579.

(59) Overman, L. E.; Renaldo, A. F. *J. Am. Chem. Soc*. **1990**, *112*, 3945.

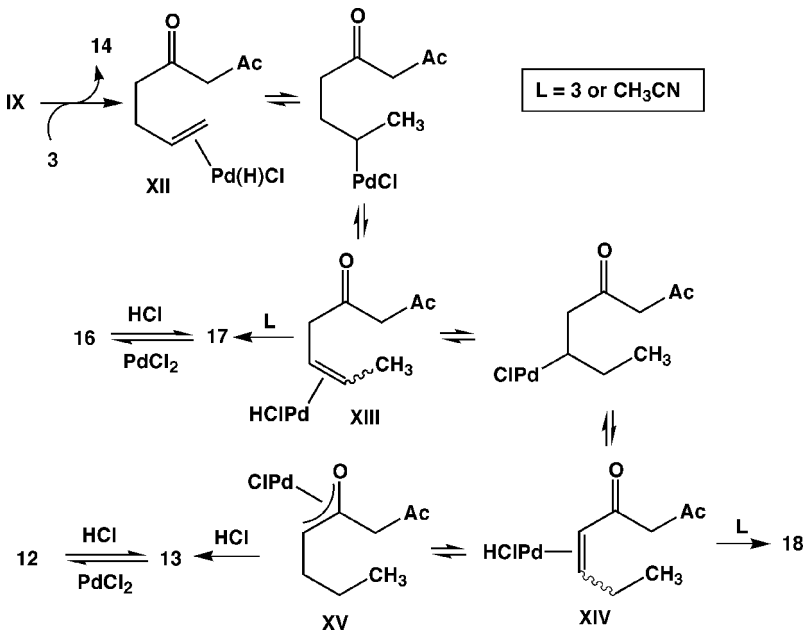
(60) (a) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun*. **2000**, 1527. (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc*. **1991**, *113*, 6607. (c) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun*. **1987**, 1520.

(61) The only organic byproduct not accounted for by this mechanism is phenol **15**, which is presumably generated in a separate reaction manifold via oxidation of dienol **14**. The stability of **5** under reaction conditions rules out formation of **14** or **15** via secondary oxidation of **5**.

(62) Olefin displacement from square-planar Pd(II) complexes is, with rare exceptions, strictly associative. (a) Howell, J. A. S.; Burkinshaw, P. M. *Chem. Rev*. **1983**, *83*, 557. (b) Darensbourg, D. J. *Adv. Organomet. Chem*. **1982**, *21*, 113. (c) Cross, R. J. *Chem. Soc. Rev*. **1985**, *14*, 197. (d) Zhong, H. A.; Widenhoefer, R. A. *Inorg. Chem*. **1997**, *36*, 2610. (e) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 4. (f) Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks/Cole: Monterey, CA, 1985; Chapter 4. (g) Langford, C. H.; Gray, H. B. *Ligand Substitution Processes*; W. A. Benjamin: New York, 1965.

(63) Olefin displacement by CH_3CN followed by associative displacement of the nitrile ligand of the resulting Pd(H)(CH_3CN) intermediate with **3** is also in full accord with our observations.

Scheme 16



released in the conversion of **4** to **12** or **16**, the upper limit for the steady-state concentration of HCl under reaction conditions corresponds to the unlikely conditions of quantitative conversion of **4** to **12** and **16** where $[HCl]_{max} \leq [\mathbf{4}]_0 \leq 2.5$ mM. Under stoichiometric conditions, protonolysis of **12** [7 mM] with HCl [15 mM] in dioxane occurred with a half-life of $t_{1/2} \approx 7$ h (eq 12). Although we were unable to determine the rate of protonolysis of **16** in dioxane, the lower catalytic activity of **16** relative to **12** in the presence of HCl suggests that protonolysis of **16** is slower than is protonolysis of **12**. Assuming that protonolysis of **12** or **16** is first-order with respect to both the palladium complex and HCl, a lower limit for the half-life of protonolysis of **12** or **16** of $t_{1/2} \geq 120$ h can be set, which is significantly greater than the half-life for conversion of **3** to **5** under these conditions ($t_{1/2} \approx 4$ h). Therefore, we conclude that under our optimized conditions for hydroalkylation, palladium complexes **12** and **16** are formed irreversibly from reaction of **4** with **13** and **17**, respectively, and that formation of complexes **12** and **16** represents the principle pathway for catalyst deactivation under these conditions.

The formation of **16** in preference to **12** in the palladium-catalyzed cyclization of **3** under concentrated conditions ($[\mathbf{3}]_0 = 250$ mM) can be traced to the higher [**17**]:[**13**] ratio formed under concentrated conditions relative to dilute conditions (Schemes 9 and 10) coupled with the more rapid reaction of **4** with **17** relative to reaction of **4** with **13**. Analysis of the concentration versus time plot for the hydroalkylation of **3** under concentrated conditions (Figure S1) revealed that the relative concentration of **17** increased rapidly to ~20% after 55% conversion and then decreased slowly to 14% as the remainder of **3** was consumed (Figure S1). In comparison, after 55% conversion, **13** accounted for 12% of the reaction mixture (Figure S1). Because no increase was observed in the relative concentration of either **5** or **18** as **17** was consumed (Figure S1), the consumption of **17** over the latter portion of the catalytic hydroalkylation of **3** under concentrated conditions ($[\mathbf{3}]_0 = 250$ mM) suggests that **17** is converted to **16** under reaction conditions (Scheme 16).[64]

Conclusions

We have developed an effective palladium-catalyzed protocol for the intramolecular hydroalkylation of 3-butenyl β-diketones to form 2-acylcyclohexanones. These transformations represent the first examples of the transition metal-catalyzed addition of an active methylene or methine compound to an unactivated olefin. The palladium-catalyzed cyclization of 3-butenyl β-diketones displayed high selectivity for 6-*endo*-trig cyclization, which we attribute to superior orbital overlap in the transition state for 6-*endo* cyclization relative to that for 5-*exo* cyclization. Deuterium labeling, kinetic, and in situ NMR experiments were in accord with a mechanism for palladium-catalyzed hydroalkylation involving rapid and reversible coordination of the olefin of the alkenyl β-diketone to palladium followed by turnover-limiting attack of the enol carbon atom on the palladium-complexed olefin. Migration of palladium from the C(4) carbon atom of the 2-acetylcyclohexanone ring to the C(6) carbon atom followed by protonolysis of the resulting palladium enolate complex releases the cyclohexanone and regenerates the palladium dichloride catalyst.

The palladium-catalyzed hydroalkylation of 7-octene-2,4-dione (**3**) generates a number of organic byproducts including 2,4-octanedione (**13**), 2-acetyl-2-cyclohexenone (**14**), 2-acetylphenol (**15**), (*E*)- and (*Z*)-6-octene-2,4-dione (**17**), and (*E*)- and (*Z*)-5-octene-2,4-dione (**18**). The η^3-β-diketonate chloride dimer {[η^3-$CH_3CH_2CH_2CHCOH$-

(64) We cannot rule out the possibility that the **12**:**16** ratio generated in the palladium-catalyzed cyclization of **3** under concentrated conditions ($[\mathbf{3}]_0 = 250$ mM) is at least partially under thermodynamic control. Employing the same assumptions as those employed to estimate the lower limit for the half-life of protonolysis of **12** and/or **16** under our optimized reaction conditions ($[\mathbf{3}]_0 = 25$ mM), we can set a lower limit for the half-life of protonolysis of **12** and/or **16** of $t_{1/2} \geq 70$ min under the concentrated reaction conditions ($[\mathbf{3}]_0 = 250$ mM), which is comparable to the half-life for consumption of **3** ($t_{1/2} \approx 50$ min) under these conditions (Figure S1).

CHAc]Pd(Cl)}$_2$ (**12**) and the π-(allyl)palladium chloride dimer {[η^3-$CH_3CHCHCHC(O)CH_2Ac$]Pd(Cl)}$_2$ (**16**) represent the principle forms of palladium present upon complete consumption of **3**. Complexes **12** and **16** are intermediates neither in the conversion of **3** to 2-acetylcyclohexanone (**5**) nor in the conversion of **3** to byproducts **13**−**18**, nor are **12** and **16** catalytically active under our optimized reaction conditions ([**3**]$_0$ = 25 mM). Rather, complexes **12** and **16** are generated via secondary reaction of palladium with **13** or **17**, respectively, and represent the principle sources of catalyst deactivation in the palladium-catalyzed hydroalkylation of alkenyl β-diketones.

Experimental Section

2-Acetylcyclohexanone (5). Enol:dione ≥ 15:1. A solution of $PdCl_2(MeCN)_2$ (**4**) (19 mg, 0.07 mmol) and 7-octene-2,4-dione (**3**) (100 mg, 0.70 mmol) in 1,4-dioxane (28 mL) was stirred at room temperature for 16 h, concentrated, and chromatographed (hexanes−diethyl ether, 75:1) to give **5** (81 mg, 81%) as a colorless oil. ^{1}H NMR: δ 2.32−2.28 (m, 4 H), 2.10 (s, 3 H), 1.68−1.64 (m, 4 H). ^{13}C{^{1}H} NMR: δ 199.3, 182.3, 107.3, 31.4, 25.2, 24.6, 23.1, 21.9. Spectral data were identical to that of an authentic sample.

The remaining cyclohexanones were synthesized using a procedure analogous to that employed in the synthesis of **5**. Details are included in the Supporting Information.

Identification of Byproducts in the Hydroalkylation of 3. A solution of **3** (210 mg, 1.5 mmol, 250 mM) and **4** (39 mg, 0.15 mmol) in dioxane (6 mL) was stirred at room temperature for 16 h to form a mixture of **5** (49%), 2,4-octanedione (**13**, 14%), 2-acetyl-2-cyclohexenone (**14**, 12%), 2-acetylphenol (**15**, 3%), (*E*)- and (*Z*)-6-octene-2,4-dione [(*E*)- and (*Z*)-**17**, 14%)], and (*E*)-5-octene-2,4-dione [(*E*)-**18**, 3%]. Isomers (*E*)-**17** and (*E*)-**18** were identified by GC/MS analysis of the crude reaction mixture and by co-injection with authentic samples. The crude reaction mixture was concentrated under vacuum, and the residue was chromatographed (SiO_2; hexanes−ether, 32:1) to afford **13** as a colorless oil (18 mg, >95% pure by GC) and a 1.1:1 mixture of **14** and **15** as a colorless oil. Compound **13** was identified by ^{1}H NMR spectroscopy and by comparison to an authentic sample. Compounds **14** and **15** were identified by GC/MS analysis of the admixture and by co-injection with authentic samples.

Compound (*Z*)-**17** was identified by GC/MS analysis of the crude reaction mixture and by comparison to an authentic sample of (*E*)-**17**. Specifically, the GC/MS spectra of both (*Z*)-**17** and (*E*)-**17** displayed a parent ion peak at *m/z* = 140 and a strong fragmentation peak at *m/z* = 85, corresponding to $M^+ - CH_3CH{=}CHCH_2$. No other isomer formed in the hydroalkylation of **3** produced this fragmentation pattern. For example, the GC/MS spectrum of (*E*)-**18** displayed a strong fragmentation peak at *m/z* = 111 corresponding to M^+ − Et. Identification of (*Z*)-**17** was corroborated by ^{1}H NMR analysis of a 2.6:2.2:1 mixture of (*Z*)-**17**, (*E*)-**17**, and (*E*)-**18** generated from the protonolysis of **16** (see below).

2-Acetylcyclohexanone Isotopomers. Cyclization and isolation of deuterated isotopomers of **3** catalyzed by **4** to form deuterated isotopomers of **5** were performed employing a procedure analogous to that used to synthesize unlabeled **5**. The regiochemistry of the **5**-d_x isotopomers was determined by ^{13}C NMR spectroscopy. The ^{13}C resonances of **5** were assigned on the basis of the ^{1}H−^{13}C COSY NMR spectroscopy of unlabeled **5** (Figures S2 and S3).

***cis*-2-Acetyl-3,4-dideuteriocyclohexanone (*cis*-5-3,4-d_2).** Cyclization of a ∼5:1 mixture of (*E*)-**3**-7,8-d_2 and **3**-7,8,8-d_3 catalyzed by **4** formed a ∼5:1 mixture of *cis*-**5**-3,4-d_2 and **5**-3,3,4-d_3 in 64% isolated yield. ^{13}C{^{1}H} NMR: δ 107.3 [s, IS = 102 ppb, −C(O)*C*H(Ac)CHDCHDCH$_2$CH$_2$−], 24.2 [t, J_{CD} = 20 Hz, IS = 448 ppb, −C(O)CH(Ac)*C*HDCHDCH$_2$CH$_2$−], 22.7 [t, J_{CD} = 20 Hz, IS = 467 ppb, −C(O)CH(Ac)CHD*C*HDCH$_2$CH$_2$−], 22.6 [t, J_{CD} = 20 Hz, IS = 569 ppb, −C(O)CH(Ac)CD$_2$*C*HDCH$_2$CH$_2$− (minor isotopomer)], 21.9 [s, IS = 114 ppb, −C(O)CH(Ac)CHDCHD*C*H$_2$CH$_2$−]. The quintet corresponding to −C(O)CH(Ac)*C*D$_2$CHDCH$_2$CH$_2$− of the minor isotopomer was not resolved from the triplet at 24.2 (Figure S4).

***trans*-2-Acetyl-3,4-dideuteriocyclohexanone (*trans*-5-3,4-d_2).** Cyclization of a ∼3:1 mixture of (*Z*)-**3**-7,8-d_2 and **3**-7,8,8-d_3 catalyzed by **4** gave a ∼3:1 mixture of *trans*-**5**-3,4-d_2 and **5**-3,3,4-d_3 in 67% isolated yield. ^{13}C{^{1}H} NMR: δ 107.3 [s, IS = 99 ppb, −C(O)*C*H(Ac)CHDCHDCH$_2$CH$_2$−], 107.2 [s, IS = 174 ppb, −C(O)*C*H(Ac)CD$_2$CHDCH$_2$CH$_2$− (minor isotopomer)], 24.2 [t, J_{CD} = 20 Hz, IS = 455 ppb, −C(O)CH(Ac)*C*HDCHDCH$_2$CH$_2$−], 22.7 [t, J_{CD} = 20 Hz, IS = 474 ppb, −C(O)CH(Ac)CHD*C*HDCH$_2$CH$_2$−], 22.6 [t, J_{CD} = 20 Hz, IS = 580 ppb, −C(O)CH(Ac)CD$_2$*C*HDCH$_2$CH$_2$− (minor isotopomer)], 21.9 [s, IS = 121 ppb, −C(O)CH(Ac)CHDCHD*C*H$_2$CH$_2$−]. The quintet corresponding to −C(O)CH(Ac)*C*D$_2$CHDCH$_2$CH$_2$− of the minor isotopomer was not resolved from the triplet at 24.2 (Figure S5).

2-Acetyl-6-deuteriocyclohexanone (5-6-d_1). Cyclization of **3**-3,3-d_2 catalyzed by **4** gave a ∼3:1 mixture of **5**-6-d_1 and **5** in 45% isolated yield. ^{13}C{^{1}H} NMR: δ 31.1 [t, J_{CD} = 20 Hz, IS = 356 ppb, −C(O)CH(Ac)CH$_2$CH$_2$CH$_2$*C*HD−], 21.9 [s, IS = 99 ppb, −C(O)CH(Ac)CH$_2$CH$_2$*C*H$_2$CHD−] (Figure S6).

2,3-Dideuterio-6-trideuterioacetylcyclohexanone (5-2,3-d_2-6-COCD$_3$). Cyclization of **3**-1,1,1,5,5-d_5 catalyzed by **4** gave **5**-2,3-d_2-6-COCD$_3$ as the exclusive isotopomer in 53% isolated yield. ^{13}C{^{1}H} NMR: δ 31.0 [t, J_{CD} = 20 Hz, IS = 427 ppb, −C(O)C(COCD$_3$)CH$_2$CH$_2$CHD*C*HD−], 23.0 [s, IS = 90 ppb, −C(O)C(COCD$_3$)CH$_2$*C*H$_2$CHDCHD−], 21.5 [t, J_{CD} = 19 Hz, IS = 390 ppb, −C(O)C(COCD$_3$)CH$_2$CH$_2$*C*HDCHD−] (Figure S7).

Cyclization of 6-Deuterio-7-octene-2,4-dione (3-6-d_1). Cyclization of **3**-6-d_1 catalyzed by **4** formed a 1:1 mixture of 4-deuterio-2-acetylcyclohexanone (**5**-4-d_1) and 5-deuterio-2-acetylcyclohexanone (**5**-5-d_1) in 62% combined yield. ^{13}C{^{1}H} NMR: δ 31.4 [s, C(6) of **5**-4-d_1], 31.3 [s, IS = 68 ppb, C(6) of **5**-5-d_1], 24.6 [s, C(3) of **5**-5-d_1], 24.5 [s, IS = 68 ppb, C(3) of **5**-4-d_1], 23.0 [s, IS = 75 ppb, C(4) of **5**-5-d_1], 22.8 [t, J_{CD} = 19.5 Hz, C(4) of **5**-4-d_1, IS = 348 ppb], 21.9 [C(5) of **5**-4-d_1, IS = 71 ppb], 21.6 [t, J_{CD} = 19.5 Hz, IS = 333 ppb, C(5) of **5**-5-d_1] (Figure S8).

***trans*-2-Acetyl-4,5-dideuteriocyclohexanone (*trans*-5-4,5-d_2).** Cyclization of **3**-6,6-d_2 catalyzed by **4** formed *trans*-**5**-4,5-d_2 in 49% yield as the exclusive isotopomer. ^{13}C{^{1}H} NMR: δ 31.3 [s, IS = 122 ppb, −C(O)C(Ac)CH$_2$CHDCHD*C*H$_2$−], 24.5 [s, IS = 126 ppb, −C(O)C(Ac)*C*H$_2$CHDCHDCH$_2$−], 22.7 [t, J_{CD} = 20 Hz, IS = 486 ppb, −C(O)C(Ac)CH$_2$*C*HDCHDCH$_2$−], 21.5 [t, J_{CD} = 20 Hz, IS = 467 ppb, −C(O)C(Ac)CH$_2$CHD*C*HDCH$_2$−] (Figure S9).

2-Acetyl-3,3-dideuteriocyclohexanone (5-3,3-d_2). Cyclization of **3**-8,8-d_2 (∼95% d) catalyzed by **4** formed a 9:1 mixture of **5**-3,3-d_2 and **5**-3-d_1 (∼95% d) in 72% isolated yield. ^{13}C{^{1}H} NMR: δ 107.2 [s, IS = 193 ppb, −C(O)*C*H(Ac)CD$_2$CH$_2$CH$_2$CH$_2$−], 23.6 [t, IS = 280 ppb, −C(O)CH(Ac)*C*HDCH$_2$CH$_2$CH$_2$− (minor isotopomer)], 23.9 [quint, IS = 560 ppb, −C(O)CH(Ac)*C*D$_2$CH$_2$CH$_2$CH$_2$−], 23.0 [s, IS = 90 ppb, −C(O)CH(Ac)CHD*C*H$_2$CH$_2$CH$_2$− (minor isotopomer)], 22.9 [s, IS = 190 ppb, −C(O)CH(Ac)CD$_2$*C*H$_2$CH$_2$CH$_2$−] (Figure S10).

Pentenoate Derivatives. ^{1}H NMR resonances of the pentanoate chain of **6**-d_x isotopomers were assigned on the basis of the ^{1}H−^{1}H COSY NMR spectrum of unlabeled **6** (Figure S11).

***anti*-Methyl 5-(2-Benzenesulfonylmethyl-5-oxo-1-cyclopentenyl)-4,5-dideuteriopentanoate (*anti*-6-4,5-d_2).** Reaction of a ∼5:1 mixture of *cis*-**5**-3,4-d_2 and **5**-3,3,4-d_3 with (*E*)-2,3-dibromo-1-phenylsulfonylpropene employing a procedure analogous to that reported for the synthesis of unlabeled **6** led to the isolation of a ∼5:1 mixture of *anti*-**6**-4,5-d_2 and **6**-4,5,5-

d_3 in 18% yield.[42] The stereochemistry of *anti*-**6**-4,5-d_2 was determined from the 9.2 Hz doublet at δ 1.79 in the ^{1}H NMR spectrum corresponding to the C(5) proton of the pentanoate chain (Figure S12). ^{1}H NMR: δ 1.79 (d, J = 9.2 Hz, 1 H, −C*H*DCHDCH$_2$CH$_2$CO$_2$Me), 1.46 (br q, J = 6.8 Hz, 2 H, −CHDCHDC*H*$_2$CH$_2$CO$_2$Me), 1.21−1.14 (m, 1 H, −CHDC*H*D-CH$_2$CH$_2$CO$_2$Me). ^{13}C{^{1}H} NMR: δ 27.0 (t, J_{CD} = 19.4 Hz, IS = 432 ppb, −CHD*C*HDCH$_2$CH$_2$CO$_2$Me), 26.9 [t, J_{CD} = 19.8 Hz, IS = 523 ppb, −CD$_2$*C*HDCH$_2$CH$_2$CO$_2$Me (minor isotopomer)], 25.1 (s, IS = 97 ppb, −CHDCHD*C*H$_2$CH$_2$CO$_2$Me), 22.8 (t, J_{CD} = 20 Hz, IS = 382 ppb, −*C*HDCHDCH$_2$CH$_2$CO$_2$Me) (Figure S13).

***syn*-Methyl 5-(2-Benzenesulfonylmethyl-5-oxo-1-cyclopentenyl)-4,5-dideuteriopentanoate (*syn*-6-4,5-d_2).** Reaction of a ∼3:1 mixture of *trans*-**5**-3,4-d_2 and **5**-3,3,4-d_3 with (*E*)-2,3-dibromo-1-phenylsulfonylpropene employing a procedure analogous to that reported for the synthesis of unlabeled **6** led to the isolation of a ∼3:1 mixture of *syn*-**6**-4,5-d_2 and **6**-4,5,5-d_3 in 28% yield.[42] The stereochemistry of *syn*-**6**-4,5-d_2 was determined from the 6.0 Hz doublet at δ 1.80 in the ^{1}H NMR spectrum corresponding to the C(5) proton of the pentanoate chain (Figure S14). ^{1}H NMR: δ 1.80 (d, J = 6.0 Hz, 1 H, −C*H*DCHDCH$_2$CH$_2$CO$_2$Me), 1.47 (br q, J = 7.2 Hz, 2 H, −CHDCHDC*H*$_2$CH$_2$CO$_2$Me), 1.21−1.15 (m, 1 H, −CHD-C*H*DCH$_2$CH$_2$CO$_2$Me). ^{13}C{^{1}H} NMR: δ 27.0 (t, J_{CD} = 19.5 Hz, IS = 467 ppb, −CHD*C*HDCH$_2$CH$_2$CO$_2$Me), 26.9 [t, J_{CD} = 19.8 Hz, IS = 528 ppb, −CD$_2$*C*HDCH$_2$CH$_2$CO$_2$Me (minor isotopomer)], 25.1 (s, IS = 129 ppb, −CHDCHD*C*H$_2$CH$_2$CO$_2$Me), 22.8 (t, J_{CD} = 19.0 Hz, IS = 410 ppb, −*C*HDCHDCH$_2$CH$_2$CO$_2$-Me) (Figure S15).

***syn*-Methyl 5-(2-Benzenesulfonylmethyl-5-oxo-1-cyclopentenyl)-3,4-dideuteriopentanoate (*syn*-6-3,4-d_4).** Reaction of *trans*-**5**-4,5-d_2 and (*E*)-2,3-dibromo-1-phenylsulfonylpropene employing a procedure analogous to that reported for the synthesis of unlabeled **6**[42] gave *syn*-**6**-3,4-d_2 in 34% isolated yield. The stereochemistry of *syn*-**6**-3,4-d_2 was determined from the 4.4 Hz doublet corresponding to the C(4) proton of the pentanoate chain at δ 1.15 in the ^{1}H NMR spectrum with selective decoupling of the C(5) methylene resonance at δ 1.80 (Figure S16). ^{1}H NMR: δ 2.21 (d, J = 6.8 Hz, 2 H, −CH$_2$-CHDCHDC*H*$_2$CO$_2$Me), 1.44 (br q, J = 6.8 Hz, 1 H, −CH$_2$-CHDC*H*DCH$_2$CO$_2$Me), 1.17 (d, J = 4.4 Hz, 1 H, −CH$_2$C*H*D-CHDCH$_2$CO$_2$Me). ^{13}C{^{1}H} NMR: δ 30.3 (s, IS = 110 ppb, −CH$_2$CHDCHD*C*H$_2$CO$_2$Me), 26.9 (t, J_{CD} = 19.4 Hz, IS = 361 ppb, −CH$_2$*C*HDCHDCH$_2$CO$_2$Me), 24.7 (t, J_{CD} = 20.1 Hz, IS = 345 ppb, −CH$_2$CHD*C*HDCH$_2$CO$_2$Me) (Figure S17).

Calculation of J_{HH} for *syn*- and *anti*-6-4,5-d_2. The structure of **6** was minimized using the molecular mechanics program "maestro". The dihedral angle about the C(3)−C(4)−C(5)−C(6) bond was fixed at 0°, and the strain energy was minimized to provide a global energy E. In a similar manner, the global energy of **6** with the dihedral angle fixed at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360 degrees was determined. The population of each rotamer was calculated using the respective energy values employing the equation $N_i = \exp(-E/RT)/[\sum \exp(-E/RT)]$. The $^3J_{HH}$ coupling constant was calculated from the population of each rotamer employing the Karplus equation: $^3J_{H-H} = 7.8-1.0\cos(\Phi) + 5.6\cos(2\Phi)$, where Φ equals the dihedral angle.[65]

Kinetics of the Hydroalkylation of 3. In a typical experiment, **3** (70 mg, 0.50 mmol, 20 mM) was added via syringe to a solution of **4** (26 mg, 0.10 mmol, 4.0 mM) and *n*-tetradecane (6.5 μL, 0.025 mmol) in dioxane (25 mL), and the resulting solution was stirred at 25 °C. Aliquots were removed periodically via gastight syringe, filtered through a small plug of silica gel, and analyzed by GC. The concentration of **3** was determined by integrating the peak for **3** relative to the peak for *n*-tetradecane in the GC spectrum. The initial rate constant for the hydroalkylation of **3** was obtained from a plot of $[\mathbf{3}]_t/[\mathbf{3}]_0$ versus time over the first 10−15% conversion.

Synthesis of Palladium Complexes. [Pd(CH$_2$COCH$_3$)-Cl]$_2$ (9). Complex **9** was synthesized employing a procedure analogous to a published procedure.[66] (2-Trimethylsiloxy)-propene (0.12 mL, 0.70 mmol) was added via syringe to a solution of PdCl$_2$(PhCN)$_2$ (192 mg, 0.50 mmol) in dry benzene (6 mL) at 0 °C to immediately form a yellow precipitate. The reaction mixture was warmed to room temperature and stirred overnight. The resulting solid was filtered and washed with small amounts of benzene to give **9** as a yellow solid (65 mg, 65%). ^{1}H NMR (CD$_3$CN): δ 2.71 (br s, 2 H), 2.14 (br s, 3 H). IR (neat, cm^{-1}): 1565 (vs). Anal. Calcd found for C$_6$H$_{10}$O$_2$Pd$_2$-Cl$_2$: C, 18.11 (18.35); H, 2.53 (2.25).

{[η^3-CH$_3$CH$_2$CH$_2$CHCOHCHAc]Pd(Cl)}$_2$ (12). A solution of **3** (200 mg, 1.40 mmol) and **4** (36 mg, 0.14 mmol) in dioxane (56 mL) was stirred at room temperature for 16 h. The resulting solution was concentrated to ∼1 mL under vacuum and diluted with hexanes (5 mL). The resulting brown precipitate was filtered, washed with hexanes, dissolved in hot chloroform, and filtered through a pad of Celite. The resulting solution was evaporated under vacuum to give **12** as a yellow solid (33 mg, 77% based on Pd). ^{1}H NMR: δ 11.4 (s, 1 H), 3.71 (s, 1 H), 3.36 (t, J = 4.8 Hz, 1 H), 2.27 (s, 3 H), 1.84−1.75 (m, 1 H), 1.60−1.50 (m, 3 H), 0.95 (t, J = 7.4 Hz, 3 H). ^{13}C{^{1}H} NMR: δ 212.6, 149.4, 68.9, 53.3, 31.7, 28.8, 21.6, 14.3. IR (CDCl$_3$, cm^{-1}): 3383 (ν_{O-H}), 1648 ($\nu_{C=O}$). Anal. Calcd (found) for C$_{16}$H$_{26}$Cl$_2$O$_4$Pd$_2$: C, 33.95 (34.14); H, 4.63 (4.71).

{[η^3-CH$_3$CHCHCHC(O)CH$_2$Ac]PdCl}$_2$ (16). A mixture of **4** (260 mg, 1 mmol) and **3** (500 mg, 3.5 mmol) in dioxane (12 mL) was stirred overnight at room temperature and then concentrated to ∼2 mL. Pentane (5 mL) was added, and the resulting yellow precipitate was filtered and washed with pentane. The resulting residue was dissolved in hot chloroform (100 mL) and filtered through a pad of Celite. The resulting solution was concentrated to ∼10 mL and cooled to 0 °C to give **16** (142 mg, 51% based on Pd) as a yellow solid. Complex **16** existed predominantly (≥7:1) in solution as the *anti,anti,-enol* conformation as indicated by ^{1}H NMR analysis; peaks corresponding to this major conformer are given. ^{1}H NMR: δ 15.2 (s, 1 H), 5.89 (t, J = 11.2 Hz, 1 H), 5.72 (s, 1 H), 4.14 (qd, J = 1.2, 10.8 Hz, 1 H), 3.59 (d, J = 10.4 Hz, 1 H), 2.09 (s, 3 H), 1.33 (d, J = 6.4 Hz, 3 H). ^{13}C{^{1}H} NMR: δ 195.5, 183.2, 108.3, 103.0, 82.7, 68.2, 26.6, 18.5. IR (CDCl$_3$, cm^{-1}): 1725 ($\nu_{C=O}$), 1689 ($\nu_{C=O}$), 1601 ($\nu_{C=C}$). Anal. Calcd (found) for C$_{16}$H$_{22}$Cl$_2$O$_4$-Pd$_2$: C, 34.19 (33.91); H, 3.95 (3.91).

Reaction of (*E*)-17 with 4. A mixture of (*E*)-**17** (32 mg, 0.22 mmol) and **4** (52 mg, 0.20 mmol) in dioxane (2 mL) was stirred at room temperature for 6 h. Pentane (5 mL) was added, and the resulting precipitate was filtered to give a yellow solid that was dissolved in hot chloroform (25 mL), filtered through Celite, and concentrated under vacuum to give **16** as a yellow solid (44 mg, 79% based on Pd).

Protonolysis of Palladium Complexes. Protonolysis of 9. A solution of HCl (3 μL, 4 M in dioxane) was added to an NMR tube containing a solution of **9** (19 mg) in dioxane-d_8 (0.6 mL) to immediately form a brown solution. ^{1}H NMR analysis within 5 min revealed formation of acetone (δ 2.10) as the exclusive organic product.

Protonolysis of 10. A solution of **10** (14 mg, 0.029 mmol, 36 mM) in dioxane-d_8 (0.80 mL) was treated with 2 equiv of HCl (15 μL, 0.60 mmol, 4.0 M in dioxane). A dark yellow precipitate in a brown solution formed immediately (≤5 s). ^{1}H NMR analysis of the resulting solution (≤5 min) revealed formation of 5-hexen-2-one in equilibrium with its palladium olefin complex (as indicated by broadening of olefinic region).

Protonolysis of 11. A suspension **11** (10 mg, 0.021 mmol) in dioxane-d_8 (1.0 mL) was treated with HCl (4 M in dioxane,

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12 μL, 0.048 mmol). ^{1}H NMR analysis of the resulting mixture within 2 min revealed formation of 2,4-pentanedione as the exclusive organic product.

Protonolysis of 12. A solution of **12** (5 mg, 9×10^{-3} mmol) in dioxane-d_8 (0.80 mL) was treated with HCl (4.0 M in dioxane, 7 μL, 0.028 mmol). ^{1}H NMR analysis revealed 25% consumption of **12** after 3 h and 53% consumption after 7 h to form 2,4-octanedione (**13**) as the exclusive product.

Protonolysis of 16. A solution of **16** (3 mg, 0.005 mmol) and HCl (3 μL of a 4.0 M dioxane solution, 0.01 mmol) in CD_3CN (0.8 mL) was monitored periodically by ^{1}H NMR spectroscopy. After 4 h, ~85% of **16** had been consumed to form a 2.6:2.2:1 mixture of (*Z*)-**17**, (*E*)-**17**, and (*E*)-**18** in ~85% combined yield as determined by GC/MS and ^{1}H NMR analysis.

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Supporting Information Available: General experimental methods and techniques, experimental procedures, and analytical and spectroscopic data for new compounds and cyclohexanones. This material is available free of charge via the Internet at http://pubs.acs.org.

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