Palladium-Catalyzed Intramolecular Oxidative Alkylation of 4-Pentenyl β-Dicarbonyl Compounds

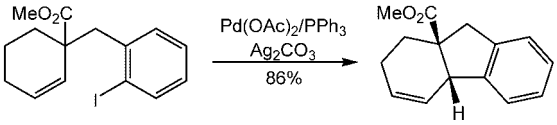
Cong Liu, Xiang Wang, Tao Pei, and Ross A. Widenhoefer*[a]

Abstract: Reaction of 8-nonene-2,4-dione with a catalytic amount of $[PdCl_2(CH_3CN)_2]$ (**2**; 5 mol%) and a stoichiometric amount of $CuCl_2$ (2.5 equiv) at room temperature for 3 h led to oxidative alkylation and formation of 2-acetyl-3-methyl-2-cyclohexenone in 80% isolated yield. The oxidative alkylation of 4-pentenyl β-diketones tolerated a number of terminal acyl groups and substitution at the C1 and C3 carbon atoms of the 4-pentenyl chain. Likewise, 4-pentenyl β-keto esters that possessed geminal disubstitution at the C1, C2, or C3 carbon atom of the 4-pentenyl chain cyclized to form 2-carboalkoxy-2-cyclohexenones in moderate to good yield as the exclusive cyclized product. Deuterium-labeling experiments provided information regarding the mechanism of the palladium-catalyzed oxidative alkylation of 4-pentenyl β-dicarbonyl compounds.

Keywords: C–C coupling · cyclization · enols · homogeneous catalysis · palladium

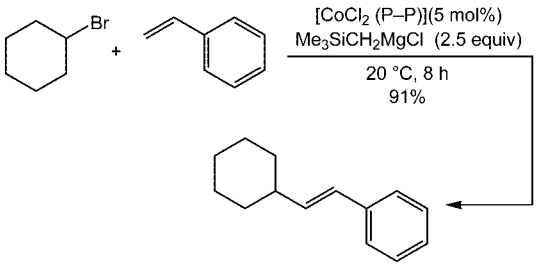
Introduction

The palladium(0)-catalyzed oxidative arylation and alkenylation of olefins with aryl and alkenyl halides and triflates (Heck reaction) is one of the most useful transition-metal-catalyzed transformations utilized in organic synthesis [Eq. (1)].[1]



(1)

In contrast, oxidative alkylation of olefins through a Pd^0-catalyzed reaction with an alkyl halide remains problematic, due to the inefficient oxidative addition of the alkyl halide and/or competitive β-hydride elimination of the initially formed Pd^{II} intermediate. Although a number of transition-metal-based approaches for the oxidative alkylation of olefins with alkyl halides have been identified, none is without serious limitations. For example, the oxidative alkylation of vinyl arenes with alkyl halides catalyzed by either $[NiCl_2(PPh_3)_2]$ or $[Co(dmgH)_2(py)]$ (dmgH = dimethylglyoxme monoanion) requires the presence of a stoichiometric amount of zinc and suffers from limited generality and poor yields.[2,3] Similarly, cobalt complexes of the form $[CoCl_2(P{-}P)]$ (P–P = bidentate phosphine ligand) catalyze both the intermolecular oxidative alkylation of vinyl arenes with alkyl halides[4] and the intramolecular oxidative alkylation of 6-halo-1-hexenes [Eq. (2)].[5] However, in both cases, excess Me_3SiCH_2MgCl was required for efficient catalysis.[5,6]



(2)

An alternative approach to the oxidative alkylation of olefins that would also obviate the need for the alkyl halide is by the Pd^{II}-catalyzed addition of a stabilized carbon nucleophile to an olefin in the presence of a suitable oxidant. The feasibility of such an approach is suggested by the efficient palladium(II)-catalyzed oxidative amination,[6] alkoxylation,[7] and hydroxylation[8] of unactivated olefins [Eq. (3)] and by the palladium(II)-mediated oxidative alkylation of unactivated olefins with stabilized carbon nucleophiles, such

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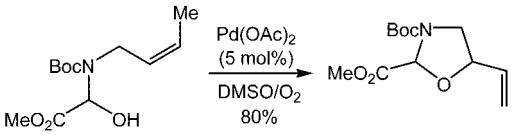
as silyl enol ethers and malonate anions [Eq. (4)]. Unfortunately, incompatibility between the carbon nucleophile and the stoichiometric oxidant and/or Pd^{II} complex has precluded the efficient palladium-catalyzed oxidative alkylation of an unactivated olefin in all but a few isolated cases.[9–11]



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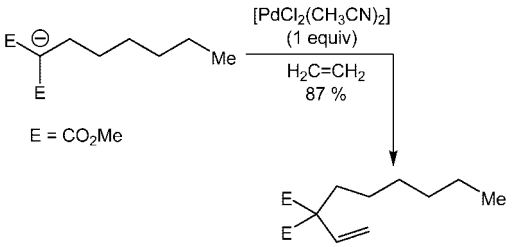
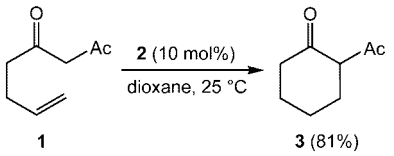


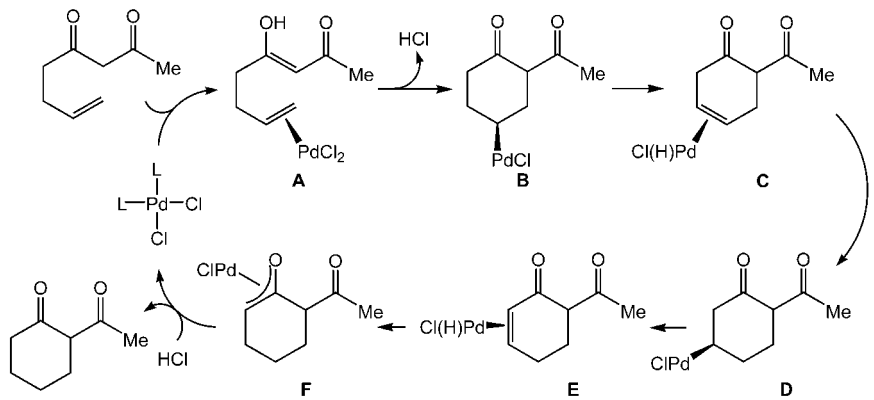
(4)

As is documented elsewhere, we initially targeted 3-butenyl β-diketones as substrates for palladium-catalyzed oxidative alkylation.[12–14] Although reaction of a 3-butenyl β-diketone with $[PdCl_2(CH_3CN)_2]$ (**2**) leads to cyclization, these reactions lead not to oxidative alkylation, but to hydroalkylation to form 2-acylcyclohexanones.[12–14] For example, reaction of 7-octene-2,4-dione (**1**) with a catalytic amount of **2** in dioxane at room temperature for 16 h formed 2-acetylcyclohexanone (**3**) in 81 % isolated yield as a single regioisomer [Eq. (5)].[12]



(5)

Deuterium-labeling and related experiments established a mechanism for palladium-catalyzed hydroalkylation involving attack of the pendant enol on the palladium-complexed olefin of **A** to form the palladium cyclohexyl species **B**, followed by iterative β-hydride elimination/addition to form intermediates **C**, **D**, and **E**, followed by protonolysis of palladium enolate species **F** (Scheme 1).[13,14]

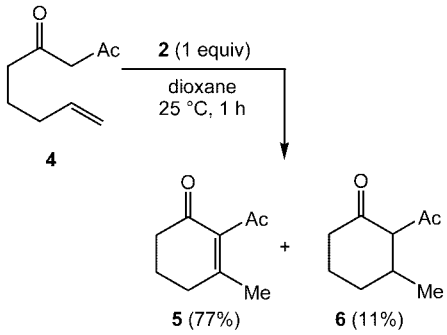


Scheme 1.

In the course of our studies directed toward expanding the scope of palladium-catalyzed hydroalkylation, we found that palladium-catalyzed cyclization of 4-pentenyl β-diketones leads predominately to oxidative alkylation as opposed to hydroalkylation.[15] Here we provide a full account of our investigation of the scope and mechanism of the palladium-catalyzed intramolecular oxidative alkylation of 4-pentenyl β-dicarbonyl compounds.

Results and Discussion

4-Pentenyl β-diketones: Attempted cyclization of 8-nonene-2,4-dione (**4**) under the conditions optimized for the palladium-catalyzed hydroalkylation of **1** [Eq. (5)] led to low (≤20 %) conversion and deposition of elemental palladium, which pointed to oxidation of the alkenyl β-diketone. Indeed, treatment of **4** with a stoichiometric amount of **2** in dioxane at room temperature for 30 min led to isolation of 2-acetyl-3-methyl-2-cyclohexenone (**5**) in 77 % yield and 2-acetyl-3-methylcyclohexanone (**6**) in 11 % yield [Eq. (6)].

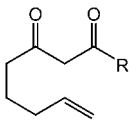
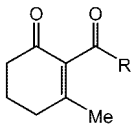
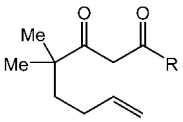
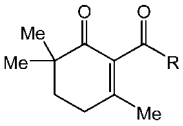
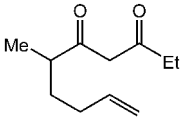
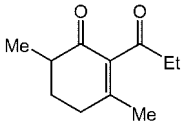
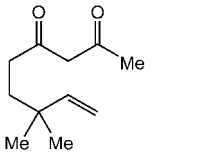
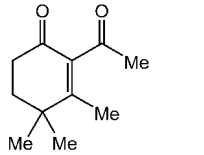
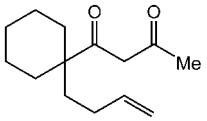
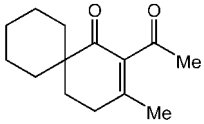


(6)

In accord with our initial expectations,[12] the β-diketone moiety tolerated the conditions required for the in situ oxidation of Pd^0 to Pd^{II}. In an optimized procedure, treatment of **4** with a catalytic amount of **2** (5 mol %) and a stoichiometric amount of anhydrous $CuCl_2$ (2.5 equiv) in 1,2-dichloroethane (DCE) at room temperature for 3 h formed an ~8:1 mixture of **5** and **6** from which **5** was isolated in 80 % yield (Table 1, entry 1).[16,17]

The procedure optimized for the conversion of **4** to **5** was less effective for the oxidative alkylation of substituted 4-pentenyl β-diketones (Table 1, procedure A). However, an observation regarding the palladium-catalyzed cyclization of 5,5-dimethyl-8-nonene-2,4-dione (**7**) led to the development of a more effective oxidative alkylation protocol. Reaction of **7** with a catalytic amount of **2** in

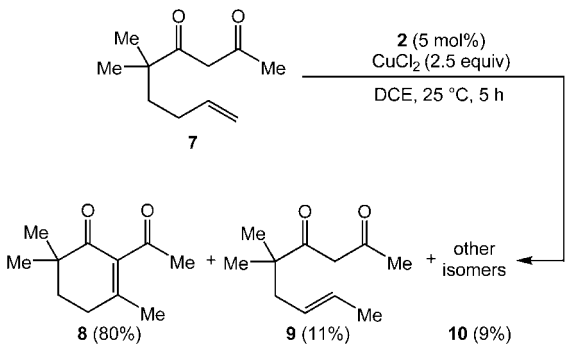
Table 1. Oxidative alkylation of 4-pentenyl β-diketones catalyzed by $[PdCl_2(CH_3CN)_2]$ (**2**; 5 mol%) in the presence of $CuCl_2$ (2.5 equiv) in DCE at room temperature for 3–7 h.

Entry	Substrate	Procedure[a]	Selectivity[b]	Cyclohexenone	Yield [%][c]
					
1	R = Me (**4**)	A	8:1	**5**	80
2	R = *t*Bu	A	3:1		46
3		B	11:1		70[d]
4	R = Ph (**20**)	B	5:1	**21**	64
					
5	R = Me (**7**)	A	4:1	**8**	79
6		B	>50:1		96
7	R = Et	A	5:1		70
8		B	>50:1		97
9	R = *i*Pr	A	10:1		83
10		B	>50:1		87
11	R = *t*Bu	A	4:1		57[f]
12		B	>50:1		94
13	R = Cy	B	>50:1		86
					
14		A	18:1		59
15		B	26:1		76
					
16		B	>50:1		75[d]
					
17		A[e]	7:1		65
18		B	>50:1		8

[a] Procedure A = substrate added in one portion; procedure B = slow addition of substrate. [b] Ratio of cyclohexenone/isomerized starting material as determined by GC/MS analysis of the crude reaction mixture. [c] Isolated yield of the cyclohexenone of >95% purity. [d] 10 mol% catalyst employed. [e] Reaction run at 70°C. [f] GC yield.

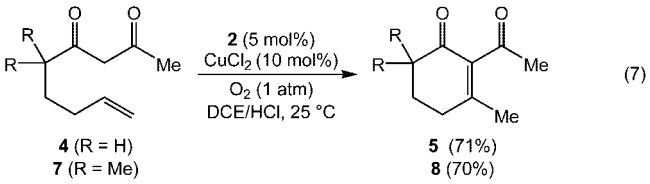
the presence of $CuCl_2$ formed 2-acetyl-3,6,6-trimethyl-2-cyclohexenone (**8**) in 80% GC yield, 5,5-dimethyl-7-nonene-2,4-dione (**9**) in 11% GC yield, and two unidentified isomers **10** in 9% combined GC yield (Scheme 2 and Table 1, entry 5). We noted that the initial rust-brown color of the reaction mixture, characteristic of $PdCl_2$, changed immediately to black upon addition of **7**, and was regenerated only upon complete consumption of **7**. These observations suggested that oxidation of Pd^0 to Pd^{II}, rather than cyclization of the alkenyl β-diketone, represented the turnover-limiting step in the conversion of **7** to **8**. We further hypothesized that the Pd^0 or Pd(H)Cl species generated through oxidative alkylation of **7** might be responsible for formation of byproducts **9** and **10**. Consistent with these hypotheses, slow addition of **7** to a mixture of **2** (5 mol%) and $CuCl_2$ (2.5 equiv) in DCE over 3 h at room temperature led to the isolation of **8** in 96% yield as the exclusive product (Table 1, entry 6).

A number of substituted 4-pentenyl β-diketones underwent palladium-catalyzed oxidative alkylation to form 2-acyl-2-cyclohexenones in good to excellent yield by employing the procedure optimized for the oxidative alkylation of **7** (Table 1, procedure B). The oxidative alkylation of 4-pentenyl β-diketones tolerated a number of terminal acyl groups including propionyl, isobutyryl, pivaloyl, and cyclohexanecarbonyl (Table 1). Palladium-catalyzed oxidative alkylation also tolerated allylic substitution and was effective for the synthesis of spirobicyclic compounds (Table 1, entries 14–18). The compatibility of the palladium-catalyzed oxidative alkylation of 4-pentenyl β-diketones to substitution along the alkyl tether contrasts sharply with the palladium-catalyzed hydroalkylation of 3-butenyl β-dicarbonyl compounds, which was highly sensitive to substitution along the alkyl tether.[12–14]



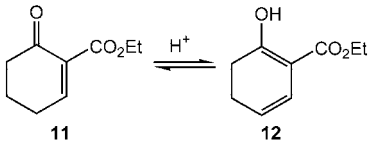
Scheme 2.

Although the use of a stoichiometric amount of $CuCl_2$ on small scale is not problematic due to the low cost and low toxicity of copper, we sought to demonstrate the feasibility of palladium-catalyzed oxidative alkylation by employing catalytic Cu/O_2 as the oxidizing system. To this end, slow addition of **4** to a catalytic mixture of **2** (5 mol%) and $CuCl_2$ (10 mol%) under oxygen (1 atm) led to the isolation of **5** in 71% yield [Eq. (7)]. Similarly, slow addition of **7** to a catalytic mixture of **2** and $CuCl_2$ under oxygen led to the isolation of **8** in 70% yield [Eq. (7)].



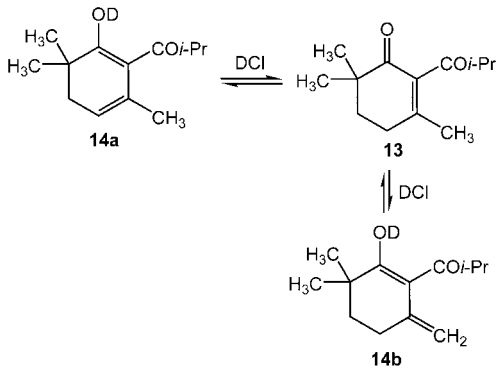
(7)

2-Carboethoxy-2-cyclohexenone (**11**) undergoes acid-catalyzed tautomerization to form a separable ~1:1 mixture of **11** and 2-carboethoxy-1-hydroxy-1,3-cyclohexadiene (**12**) [Eq. (8)].[18]



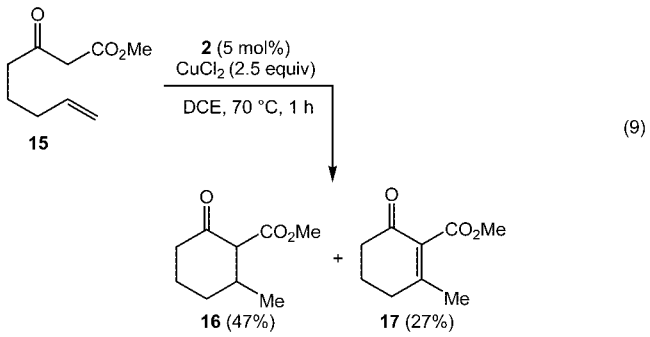
(8)

The 2-acyl-3-alkyl-2-cyclohexenones formed through palladium-catalyzed oxidative alkylation of 4-pentenyl β-diketones also undergo acid-catalyzed tautomerization, although the resulting 1,3-dienols are unstable relative to the cyclohexenone. For example, when a solution of 2-isobutyryl-3,6,6-trimethyl-2-cyclohexenone (**13**) in $CDCl_3$ was treated with DCl/D_2O ([DCl] = 0.13 M) and analyzed periodically by ^1H NMR spectroscopy, complete exchange of the endocyclic allylic protons and 50% exchange of the exocyclic allylic protons was observed after 90 minutes at room temperature. No compounds other than **13** were detected throughout complete exchange of both the endocyclic and exocyclic allylic protons of **13** (12 h). These observations are consistent with acid-catalyzed tautomerization of **13** to form the unstable 1,3-dienols **14a** and **14b** (Scheme 3).



Scheme 3.

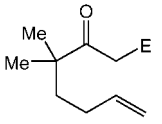
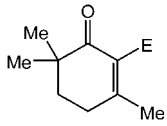
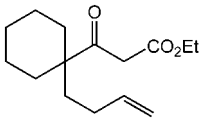
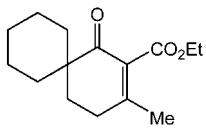
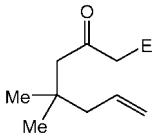
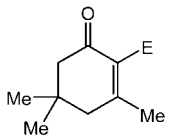
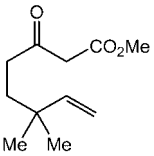
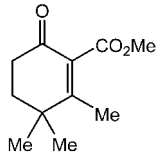
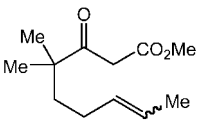
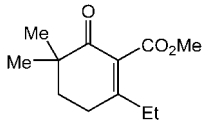
4-Pentenyl β-keto esters: As noted above, reaction of unsubstituted β-diketone **4** with **2** in the presence of $CuCl_2$ formed predominantly cyclohexenone **5**. In comparison, reaction of methyl 3-oxo-7-octenoate (**15**) with a catalytic amount of **2** (5 mol%) in the presence of $CuCl_2$ (2.5 equiv) formed cyclohexanone **16** in 47% yield and cyclohexenone **17** in 27% yield [Eq. (9)].



(9)

However, 3-oxo-7-octenoates that possessed gem-dialkyl substitution at the C4, C5, or C6 carbon atom underwent palladium-catalyzed cyclization to form exclusively cyclohexenones (Table 2). For example, reaction of isopropyl 4,4-dimethyl-3-oxo-7-octenoate (**18**) with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (2.5 equiv) at 70°C for 1 h led to the isolation of 2-carboisopropoxy-3,6,6-trimethyl-2-cyclohexenone (**19**) in 73% yield as the exclusive cyclized product (Table 2, entry 1). 4-Pentenyl β-keto esters that possessed terminal olefinic substitution also underwent palladium-catalyzed oxidative alkylation, albeit in modest yield (Table 2, entries 8 and 9).

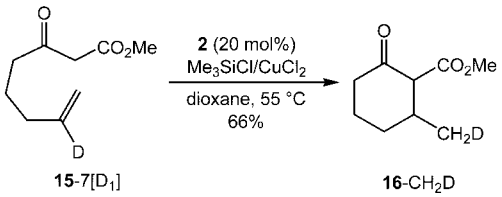
Table 2. Oxidative alkylation of 4-pentenyl β-keto esters catalyzed by **2** (5 mol%) in the presence of $CuCl_2$ at 70°C in DCE.

Entry	Substrate	Cyclohexenone	Yield [%]
			
1	E = CO_2iPr (**18**)	**19**	73
2	E = CO_2Me		69
3	E = CO_2Et		76
4			67
			
5	E = CO_2Et		67
6	E = CO_2iPr		50
7			65
			
8	*cis*		35
9	*trans*		35

Mechanism of oxidative alkylation: The ratio of cyclohexenone/cyclohexanone products generated in the palladium-catalyzed cyclization of alkenyl β-dicarbonyl compounds was affected by the length of the alkyl tether, substitution on the alkyl tether, and by the nature of the carbon nucleophile. For example, whereas palladium-catalyzed cyclization of 7-octene-2,4-dione (**1**) formed predominantly 2-acetylcyclohexanone (**3**), cyclization of 8-nonene-2,4-dione (**4**) was ~90% selective for 2-acetyl-2-cyclohexenone (**5**). In contrast, palladium-catalyzed cyclization of methyl 3-oxo-7-octeneoate (**15**) formed predominantly (~64% selectivity) cyclohexanone **16** [Eq. (9)], while cyclization of substituted 4-pentenyl β-keto ester **18** formed exclusively (≥95% selectivity) cyclohexenone **19** (Table 2, entry 1).[19]

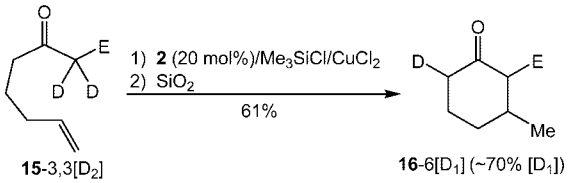
In an effort to assess the role of the alkyl tether and the β-dicarbonyl moiety on the partitioning between the hydroalkylation and oxidative alkylation reaction manifolds in the palladium-catalyzed cyclization of alkenyl β-dicarbonyl compounds, we investigated the mechanisms of the palladium-catalyzed cyclization of 4-pentenyl β-dicarbonyl compounds. To this end, we sought first to establish the mechanism of the hydroalkylation reaction manifold and then identify the π-bound intermediate or intermediates that underwent olefin displacement leading to cyclohexenone formation.[20] On the basis of the mechanism established for the palladium-catalyzed hydroalkylation of 3-butenyl β-diketones (Scheme 1),[13,14] we envisioned a mechanism for the hydroalkylation of an unsubstituted 4-pentenyl β-dicarbonyl compound initiated by attack of the pendant enol on the palladium complexed olefin of **I** to form the palladium cyclohexylmethyl species **II** (Scheme 4, path a). Iterative β-hydride elimination/addition of **II** followed by protonolysis of palladium enolate **VI** with HCl generated in the formation of **II** would release the cyclohexanone.

The validity of our proposed mechanism for the hydroalkylation of a 4-pentenyl β-dicarbonyl compound was established by means of two deuterium-labeling experiments that employed isotopomers of **15**.[21] In one experiment, treatment of **15**-7[D_1] with a catalytic amount of **2** and a stoichiometric mixture of Me_3SiCl[22] and $CuCl_2$ led to the isolation of **16**-CH_2D as the exclusive cyclohexanone isotopomer in 66% yield [Eq. (10)].[23]

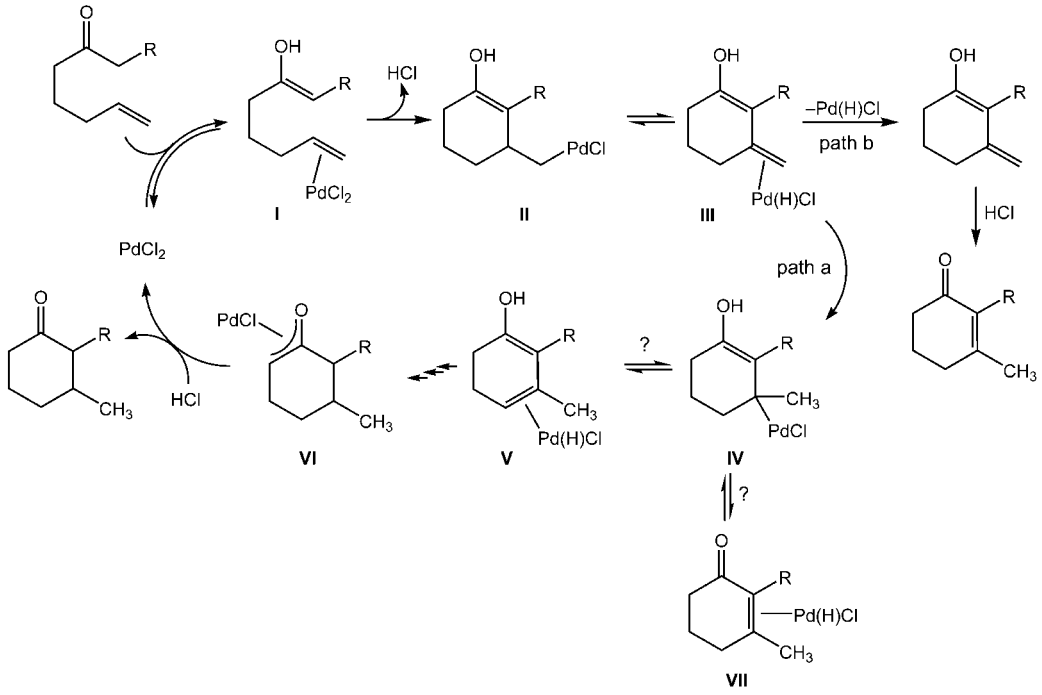


15-7[D_1] **16**-CH_2D (10)

Selective transfer of the deuterium atom from the internal olefinic position of **15**-7[D_1] to the exocyclic methyl group of **16**-CH_2D is consistent with conversion of cyclohexylmethyl intermediate **II** to cyclohexenol intermediate **IV** via the methylenecyclohexenol intermediate **III** (Scheme 4, path a). In a second experiment, treatment of **15**-3,3[D_2] with a catalytic amount of **2** and a stoichiometric mixture of Me_3SiCl[22] and $CuCl_2$, followed by aqueous work-up and chromatography, led to the isolation of **16**-6[D_1] as the exclusive deuter-



15-3,3[D_2] (E = CO_2Me) **16**-6[D_1] (~70% [D_1]) (11)

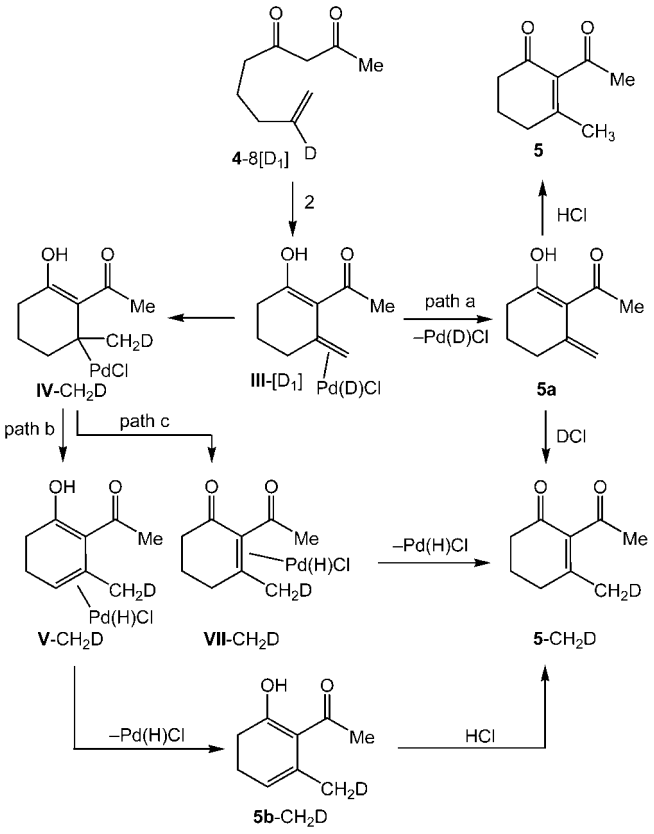


Scheme 4.

ated cyclohexanone isotopomer (~70% [D_1]) [Eq. (11)].[24–26]

Exclusive incorporation of deuterium at the C6 carbon atom of **16**-6[D_1] is in accord with migration of palladium from the exocyclic methyl group to the C6 carbon atom of the cyclohexanone ring prior to protonolysis from enolate complex **VI** (Scheme 4, path a). The proposed mechanism also predicts that the gem-dialkyl substitution along the 4-pentenyl chain should preclude formation of the requisite enolate complex **VI**, and hence hydroalkylation. This prediction is in accord with the exclusive formation of oxidative alkylation products in the palladium-catalyzed cyclization of 4-pentenyl β-dicarbonyl compounds that possess gem-dialkyl substitution along the 4-pentenyl chain.

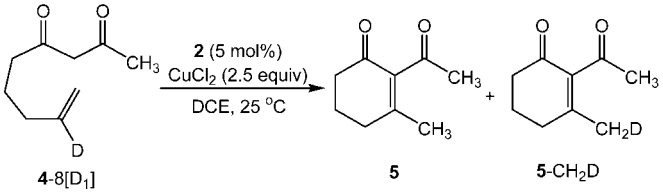
Because 1,3-dienols **14a** and **14b** tautomerized rapidly to 2-cyclohexenone **13** under acidic conditions and because HCl is generated under reaction conditions, we considered mechanisms for oxidative alkylation involving olefin displacement from palladium cyclohexenone intermediate **VII**,[27] cyclohexadienol intermediate **V**, and from palladium methylenecyclohexenol intermediate **III** (Scheme 4). A mechanism involving olefin displacement from **III** can be distinguished from mechanisms involving olefin displacement from intermediates **V** or **VII** through the cyclization of 8-deuterio-8-nonene-2,4-dione (**4**-8[D_1]) (Scheme 5). Initial cyclization of **4**-8[D_1] to form palladium methylenecyclohexenol intermediate **III**-[D_1] followed by olefin displacement from **III**-[D_1] would form unlabeled dienol **5a** and a Pd(D)Cl species that would eliminate DCl (Scheme 5, path a). Because one molecule each of HCl and DCl is released in the formation of **5a**,[28] acid-catalyzed tautomerization of **5a** would form a 1:1 mixture of **5**:**5**-CH_2D, provided there was no loss of deuterium from DCl. Because this condition appears unlikely,[24] a mechanism for the oxidative alkylation of **4**-8[D_1] involving displacement of **5a** from **III**-[D_1] should form predominantly unlabeled **5** (Scheme 5, path a). Conversely, olefin displacement from palladium cyclohexadienol intermediates **V**-CH_2D or palladium cyclohexenone intermediate **VII**-CH_2D would lead to exclusive formation of **5**-CH_2D, owing to selective transfer of the deuterium atom to the exocyclic methyl group of the cyclohexanone prior to displacement (Scheme 5, paths b and c).[27]



Scheme 5.

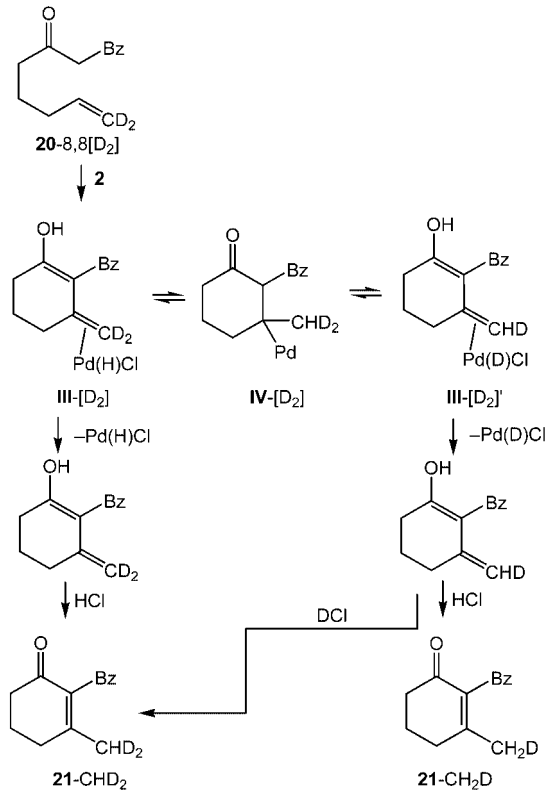
When a suspension of **4**-8[D_1] (≥98% [D_1]), **2** (5 mol%), and $CuCl_2$ (2.5 equiv) in 1,2-dichloroethane was stirred at room temperature and monitored periodically by GC/MS analysis throughout 90% conversion, **4**-8[D_1] was consumed to form a ~72:28 mixture of **5**:**5**-CH_2D (Table 3).[29] From this experiment, we conclude that formation of the cyclohexenone product in the palladium-catalyzed cyclization of an unsubstituted 4-pentenyl β-diketone occurs predominantly through olefin displacement from **III** followed by acid-catalyzed tautomerization (Scheme 4, path b; Scheme 5, path a). However, we can not rule out the possibility that olefin displacement from palladium cyclohexadienol intermediate **V** or palladium cyclohexene intermediate **VII** represents a minor pathway in cyclohexenone formation.

Table 3. Conversion of **4**-8[D_1] to **5**-CH_2D.



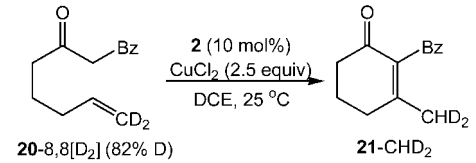
t [min]	Conversion [%]	**5**:**5**-CH_2D
2.5	10	72:28
7.5	40	70:30
17.5	62	73:27
30.5	90	73:27

The possibility that rapid and reversible conversion of **III** and **IV** preceded olefin displacement from **III** was probed by studying the cyclization of 8,8-dideuterio-phenyl-7-octene-1,3-dione (**20**-8,8[D_2]). Initial cyclization of **20**-8,8[D_2] to form a palladium–methylenecyclohexenol intermediate **III**-[D_2] followed by olefin displacement would lead to exclusive formation of **21**-CHD_2 (Scheme 6). Conversely, reversible β-hydride elimination/addition of **III**-[D_2] via **IV**-[D_2] would form a mixture of **III**-[D_2] and **III**-[D_2]′. Subsequent olefin displacement from **III**-[D_2] and **III**-[D_2]′ would lead to formation of a mixture of **21**-CHD_2 and **21**-CH_2D (Scheme 6).[30,31] When a DCE suspension of **20**-8,8[D_2] (82% deuterated), **2** (10 mol%), and $CuCl_2$ (2.5 equiv) was stirred at room temperature and monitored periodically by GC/MS analysis throughout 72% conversion, **21** was formed without significant loss of deuterium (Table 4). From this ex-



Scheme 6.

Table 4. Conversion of **20**-8,8[D_2] to **21**-CHD_2.

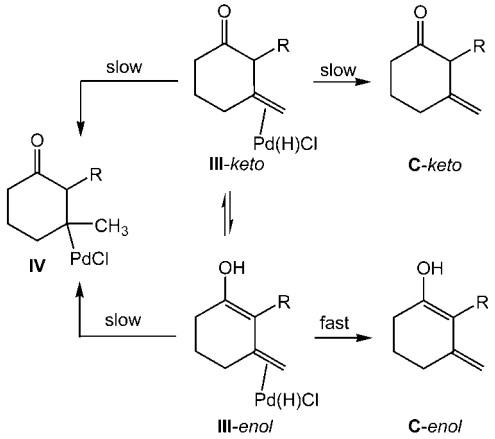


t [min]	Conversion [%]	Deuteration of **21**-3-CHD_2 [%]
10	36	81
20	52	80
30	62	78
75	72	80
240	>95	77

periment, we conclude that conversion of **III** to **IV** is irreversible in the palladium-catalyzed cyclization of an unsubstituted 4-pentenyl β-diketone (Scheme 4, path a).

Selective hydroalkylation of a 3-butenyl β-diketone requires migration of palladium from the C4 carbon atom to the C6 carbon atom of the cyclohexanone ring without olefin displacement from palladium cyclohexenone intermediates **C** and **E** (Scheme 1).[13,14] Olefin displacement from methylenecyclohexenol complex **III** (Scheme 4, path b), but not from cyclohexenone complexes **C** and **E** (Scheme 1), can be traced to the weaker binding of the 1,1-disubstituted olefin of **III** relative to the *cis*-1,2-disubstituted olefins of **C** and **E**,[32] coupled with the slower conversion of **III** to **IV** relative to the conversion of either **B** to **C** or **D** to **E**. Conversion of **III** to **IV** requires formation of a Pd–3°-alkyl bond, whereas conversion of either **B** to **C** or **D** to **E** forms a Pd–2°-alkyl bond. Formation of a transition-metal–3°-alkyl bond by means of β-hydride addition is disfavored relative to formation of a metal–2°-alkyl bond,[33] presumably due to the unfavorable steric interactions associated with the former transformation.

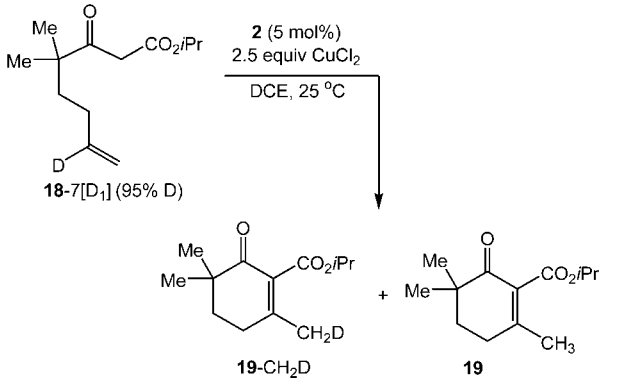
Although intermediates **I–VII** are depicted primarily as the enol tautomers in Schemes 4–7, it appears likely that these intermediates could exist either as the enol or ketone tautomers, and that the reactivity of the different tautomeric forms of these intermediates might differ significantly. In particular, conjugation of the electron-withdrawing carbonyl group to the palladium-bound olefin of **III** in the enol form (**III**-*enol*), but not in the keto form (**III**-*keto*), should significantly destabilize the palladium olefin interaction of **III**-*enol* relative to **III**-*keto*, thereby increasing the rate of olefin displacement from **III**-*enol* relative to **III**-*keto* (Scheme 7).[34] Because β-diketones possess a more favorable $K_{enol/ketone}$ than do β-keto esters,[35] we propose that the pronounced effect of the carbon nucleophile on the oxidative alkylation/hydroalkylation ratio generated in the palladium-catalyzed cyclization of 4-pentenyl β-dicarbonyl compounds is due to the higher **III**-*enol*/**III**-*keto* ratio generated in the cyclization of a β-diketone relative to a β-keto ester.[36]



Scheme 7.

We suspected that olefin displacement from the palladium–methylenecyclohexenol intermediate **III** was not the only mechanism available for oxidative alkylation. In particular, the exclusive formation of cyclohexenone **19** in the palladium-catalyzed cyclization of substituted β-keto ester **18** (Table 2, entry 1) stood in sharp contrast to the predominant formation of cyclohexanone **16** in the cyclization of unsubstituted β-keto ester **15** [Eq. (9)]. Because conversion of **15** to **16** requires conversion of **III** to **IV** in preference to olefin displacement from **III**, it appeared unlikely that the selective conversion of **18** to **19** was due to selective olefin displacement from methylenecyclohexenol intermediate **III**. Indeed, when a suspension of **18**-7[D_1] (95% [D_1]), **2** (5 mol%), and $CuCl_2$ (2.5 equiv) in DCE was stirred at room temperature and monitored periodically by GC/MS analysis, conversion to cyclohexenone **19**-CH_2D occurred without significant loss of deuterium early in the reaction (Table 5). This observa-

Table 5. Conversion of **18**-7[D_1] to cyclohexenone **19**-CH_2D.



18-7[D_1] (95% D)

19-CH_2D **19**

t [min]	Conversion [%]	**19**-CH_2D:**19**
3	18	94:6
10	40	92:8
25	56	87:13
45	60	78:22
75	64	68:32
300	78	46:54

tion established olefin displacement from cyclohexadienol intermediate **V** or cyclohexenone intermediate **VII** rather than from methylenecyclohexenone intermediate **III** as the primary pathway for the oxidative alkylation of **18** (Scheme 4). Although we can not distinguish olefin displacement from **V** from olefin displacement from **VII**, olefin displacement from **V** cannot represent the only pathway available for the oxidative alkylation of substituted β-keto esters. In particular, methyl 6,6-dimethyl-3-oxo-7-octenoate, which cannot form a palladium olefin intermediate analogous to **V**, also underwent selective oxidative alkylation in the presence of **2** (Table 2, entry 7).

Conclusion

Palladium-catalyzed cyclization of 4-pentenyl β-dicarbonyl compounds occurs through competing hydroalkylation and oxidative alkylation reaction manifolds to form mixtures of cyclohexanone and cyclohexenone products. Palladium-catalyzed cyclization of unsubstituted 4-pentenyl β-diketones formed predominantly cyclohexenones, while cyclization of unsubstituted 4-pentenyl β-keto esters formed predominantly cyclohexanones. Conversely, palladium-catalyzed cyclization of 4-pentenyl β-dicarbonyl compounds that possess gem-dialkyl substitution along the alkyl tether formed exclusively cyclohexenones, regardless of the β-dicarbonyl moiety. Deuterium-labeling experiments were in accord with a mechanism for cyclization of 4-pentenyl β-dicarbonyl compounds initiated by attack of the enol carbon atom on a palladium-complexed olefin to form a palladium–cyclohexylmethyl intermediate. Hydroalkylation occurs by means of migration of palladium from the exocyclic methyl group to the C6 carbon atom of the cyclohexanone ring, followed by protonolysis of the resulting enolate complex. Two pathways were identified for oxidative alkylation. In the case of unsubstituted β-diketones, β-hydride elimination of the initially formed palladium–cyclohexylmethyl intermediate forms a palladium–methylenecyclohexanone complex that undergoes olefin displacement and acid-catalyzed tautomerization to form the cyclohexenone. In the case of β-keto esters substituted along the alkyl tether, β-hydride addition/elimination of the palladium–methylenecyclohexanone π complex followed by olefin displacement from a palladium cyclohexenone π-complex forms the cyclohexenone.

Experimental Section

General methods: Catalytic reactions were performed under an atmosphere of dry nitrogen. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ unless otherwise noted. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett–Parkard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Flash-column chromatography was performed employing 200–400 mesh silica gel (EM). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} eluting with a 5:1 mixture of hexanes and ethyl acetate unless otherwise noted. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). 1,4-Dioxane (Aldrich, anhydrous) was used as received. [$PdCl_2(CH_3CN)_2$] (**2**) was purchased (Strem) or was prepared from $PdCl_2$ (Strem) employing a literature procedure.[37]

Cyclization of 4 (stoichiometric in Pd): A solution of **4** (70 mg, 0.45 mmol) and **2** (118 mg, 0.45 mmol) in dioxane (20 mL) was stirred at room temperature for 30 minutes. The reaction mixture was filtered through a short plug of silica gel and eluted with diethyl ether (10 mL). The resulting yellow solution was concentrated and subjected to chromatography (hexanes/EtOAc = 10:1→1.5:1) to give 2-acetyl-3-methyl-2-cyclohexenone (**5**) (53 mg, 77 %) and 2-acetyl-3-methylcyclohexanone (**6**) (8 mg, 11 %) as colorless oils.

Data for 5: TLC: R_f = 0.16. ^{1}H NMR: δ = 2.33–2.38 (m, 4H), 2.27 (s, 3H), 1.94 (quintet, ^3J(H,H) = 6.4 Hz, 2H), 1.89 ppm (s, 3H); ^{13}C{^{1}H} NMR: δ = 204.6, 197.1, 160.1, 139.9, 37.6, 32.4, 31.9, 21.9 ppm; IR (neat): $\tilde{\nu}$ = 1701, 1662 cm^{-1} (C=O); elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.90, H 7.83.

Data for 6:[38] Enol/dione ≥ 15:1; ^{1}H NMR: δ = 2.77–2.73 (m, 1H), 2.35–2.31 (m, 2H), 2.18 (s, 3H), 1.84–1.75 (m, 1H), 1.72–1.60 (m, 3H), 1.10 ppm (d, ^3J(H,H) = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR: δ = 198.3, 194.4, 113.2, 31.7, 30.3, 28.2, 24.2, 22.0, 17.0 ppm.

Cyclization of 4 (catalytic in Pd): A suspension of **4** (77 mg, 0.50 mmol), **2** (7 mg, 0.025 mmol), and $CuCl_2$ (180 mg, 1.3 mmol) in DCE (5 mL) was stirred at room temperature for 30 minutes. The reaction mixture was filtered through a short plug of silica gel and eluted with diethyl ether (30 mL). The resulting yellow solution was concentrated and subjected to chromatography (hexanes/EtOAc = 10:1→1:1) to give **5** (61 mg, 80 %) as a colorless oil.

Cyclization of 4 (catalytic in 2 and $CuCl_2$): Alkenyl ketone **4** (77 mg, 0.50 mmol) was added over 3 h to a suspension of **2** (7 mg, 0.027 mmol), $CuCl_2$ (8 mg, 0.06 mmol), and HCl (2 N in Et_2O, 40 μL 0.08 mmol) in DCE (10 mL) under O_2 (1 atm). Upon complete addition of **4**, the resulting mixture was filtered through a short plug of silica gel and eluted with diethyl ether (20 mL). The resulting solution was concentrated and subjected to chromatography (hexanes/EtOAc = 10:1→1:1) to give **5** (53 mg, 71 %) as a colorless oil.

Cyclization of 7 by means of slow addition of substrate: Alkenyl dione **7** (91 mg, 0.50 mmol) was added by means of a syringe pump over 3 h to a well-stirred suspension of $CuCl_2$ (200 mg, 1.48 mmol) and **2** (7 mg, 0.027 mmol) in DCE (10 mL). Five minutes after addition of **7** was complete, the reaction mixture was filtered though a plug of silica gel and eluted with diethyl ether (30 mL). The resulting solution was dried ($MgSO_4$), concentrated, and subjected to chromatography (SiO_2, hexanes/diethyl ether = 5:1→1:2) to give **8** (86 mg, 96 %) as a colorless oil. TLC: R_f = 0.22. ^{1}H NMR: δ = 2.34–2.37 (m, 2H), 2.25 (s, 3H), 1.87 (s, 3H), 1.78 (t, ^3J(H,H) = 6.4 Hz, 2H), 1.08 ppm (s, 6H); ^{13}C{^{1}H} NMR: δ =

205.0, 202.1, 157.7, 138.2, 40.5, 35.5, 31.6, 29.5, 24.1, 21.6 ppm; IR (neat): $\tilde{\nu}$ = 1662, 1626 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.16, H 9.01.

The remaining 2-acyl-2-cyclohexenones in Table 1 were synthesized by employing a procedure analogous to that described for the cyclization of **4** with $CuCl_2$ as the terminal oxidant (procedure A) or that described for **7** through slow addition of the substrate (procedure B). Cyclization of **15** and each of the 4-pentenyl β-keto esters depicted in Table 2 employed a procedure similar to that described above for the cyclization of **7** with the exception that the β-keto esters were cyclized at 70 °C.

Acknowledgement

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[16] Use of hydrated $CuCl_2$ led to the formation of chlorinated byproducts. 1,2-Dichloroethane (DCE) proved superior to dioxane as a solvent for the oxidative alkylation of 4-pentenyl β-dicarbonyl compounds.

[17] Similar products are formed in the palladium-mediated cyclization of 2-diazo-3-oxo-6-heptenoates: D. F. Taber, J. C. Amedio, R. G. Sherrill, *J. Org. Chem.* **1986**, *51*, 3382.

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[19] The selectivities quoted here refer to the ratio of oxidative alkylation:hydroalkylation products and therefore differ from the selectivities quoted in Table 1, which refer to the ratio of the desired oxidative alkylation product to all isomerized starting materials.

[20] This approach was based on the following three assumptions: 1) hydroalkylation and oxidative alkylation share the same initial steps and occur by means of the same C–C bond forming process, 2) the mechanism of hydroalkylation was invariant of the β-dicarbonyl moiety, and 3) β-hydride elimination is rapid and reversible, but olefin displacement is irreversible. This last assumption was established for the palladium-catalyzed hydroalkylation of 3-butenyl β-diketones.[13,14]

[21] Isotopomers of β-keto ester **15** were employed in preference to isotopomers of β-diketone **4** as we were unable to isolate sufficient amounts of the corresponding isotopomers of **6** for the ^{13}C NMR analysis required to establish regiochemistry.

[22] These reactions also contained an equivalent of Me_3SiCl, which improves the yield and selectivity for the cyclohexanone product;[22b,c] for example, reaction of **15** with a catalytic amount of **2** (5 mol%) in the presence of both $CuCl_2$ and Me_3SiCl (2 equiv) led to the isolation of **16** in 72% yield and cyclohexenone **17** in 15% yield;[22b,d] a full discussion of the role of Me_3SiCl in the palladium-catalyzed hydroalkylation of alkenyl ketones is provided elsewhere;[22d] b) T. Pei, R. A. Widenhoefer, *Chem. Commun.* **2002**, *6*, 650; c) X. Wang, X. Han, T. Pei, R. A. Widenhoefer, *Org. Lett.* **2003**, *5*, 2699; d) X. Han, X. Wang, T. Pei, R. A. Widenhoefer, *Chem. Eur. J.* **2004**, *10*, DOI: 10.1002/chem.200400459.

[23] The exclusive incorporation of deuterium into the exocyclic methyl group of **16**-CH_2D was established by the 1:1:1 triplet at δ = 21.0 ppm (J_{CD} = 19.2 Hz, isotope shift = 251 ppb) in the ^{13}C NMR spectrum and by the 1:1:1 triplet of doublets at δ = 1.02 ppm (J_{HD} = 2.2 Hz, J_{HH} = 6.8) in the ^1H NMR spectrum.

[24] Loss of deuterium from the DCl released in C–C bond formation was also observed in the palladium-catalyzed cyclization of 3,3-dideuterio-7-octene-2,4-dione.[13,14]

[25] The enolic deuteron of **16**-2,6[D_2] was presumably lost during isolation. Furthermore, a small amount of HCl is generated through the minor oxidative alkylation pathway during the palladium-catalyzed cyclization of **15**-3,3[D_2].

[26] The exclusive incorporation of deuterium into the C6 position of **16**-6[D_1] was established by the 1:1:1 triplet at δ = 40.8 ppm (J = 18.6 Hz, isotopic shift = 334 ppb) in the ^{13}C NMR spectrum.

[27] As an alternative to the formation of intermediate **VII** from **IV**, collapse of the enol of **IV** could displace an anionic palladium chloride species that could then deprotonate the cationic cyclohexenone intermediate to form a Pd(H)Cl species and free 2-cyclohexenone. We thank a reviewer for suggesting this mechanism.

[28] HCl is generated in the conversion of **4**-8[D_1] to **III**-[D_1], DCl is generated by reduction of the Pd(D)Cl species generated in the conversion of **III**-[D_1] to **5a**.

[29] Data was collected in this manner to avoid potential complications arising from scrambling of the allylic positions.

[30] Under equilibrium conditions, deuterium tends to accumulate in the position of higher stretching frequency,[31] and for this reason, intermediate **III**-CD_2 would form in preference to **III**-CHD. However, because equilibrium isotope effects are typically not large, detectable amounts of **III**-CHD and hence **12a**-CHD would be formed if conversion of **III** to **IV** were reversible under reaction conditions.

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