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Palladium-catalyzed alkylation of unactivated olefins*

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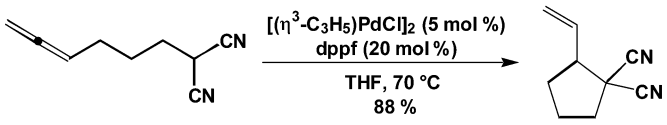
Abstract: Reaction of a 3-butenyl β-diketone with a catalytic amount of $PdCl_2(CH_3CN)_2$ in dioxane at room temperature led to olefin hydroalkylation and formation of the corresponding 2-acylcyclohexanone in good yield as a single regioisomer. Deuterium-labeling experiments for the hydroalkylation of 7-octene-2,4-dione were in accord with a mechanism involving outer-sphere attack of the pendant enol on a palladium-complexed olefin to form a palladium cyclohexyl species, followed by palladium migration via iterative β-hydride elimination/addition and protonolysis from a palladium enolate complex. In comparison to a 3-butenyl β-diketone, reaction of a 4-pentenyl β-diketone with a catalytic amount of $PdCl_2(CH_3CN)_2$ in the presence of $CuCl_2$ led to oxidative alkylation and formation of the corresponding 2-acyl-3-methyl-2-cyclohexenone in good yield as a single isomer. Unactivated olefins tethered to less reactive carbon nucleophiles such as β-keto esters, α-aryl ketones, and even dialkyl ketones underwent palladium-catalyzed hydroalkylation in the presence of Me_3SiCl or HCl to form the corresponding cyclohexanones in moderate-to-good yield with high regioselectivity.

INTRODUCTION

The base-catalyzed addition of a stabilized carbon nucleophile to an olefin that bears an electron-withdrawing group (Michael addition) is one of the most important C–C bond-forming processes utilized in organic synthesis [1]. Conversely, a general and effective method for the addition of a stabilized carbon nucleophile to unactivated olefins has not been identified. A number of approaches to the alkylation of unactivated olefins have been explored, including thermal [2], free radical-mediated [3], and Lewis acid-catalyzed processes [4], but none of these is without limitations. Transition-metal catalysis represents a potential means to achieve the alkylation of unactivated olefins under mild conditions, but despite prolonged effort in this area, a general and efficient catalyst for the addition of stabilized carbon nucleophiles to unactivated olefins has not been identified. For example, a number of transition-metal complexes catalyze the hydroalkylation of allenes [5] and other activated substrates [6] with activated methylene compounds (eq. 1), but these catalysts are not active toward simple olefins. Alternatively, Pd(II) complexes mediate the oxidative alkylation of unactivated olefins with stabilized carbanions



(1)

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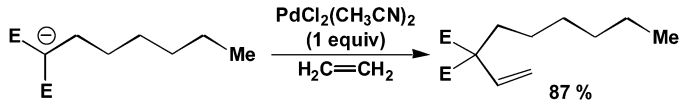
(eq. 2) [7,8]. Unfortunately, efficient catalysis has not been realized due to incompatibility between the nucleophile and the stoichiometric oxidant required to reoxidize the Pd(0) to the catalytically active Pd(II) species [9,10].

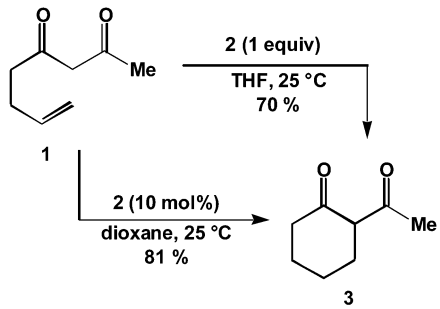


(2)

Our approach to the transition metal-catalyzed alkylation of unactivated olefins was based upon the expectation that the enol tautomer of an activated methylene compound would be sufficiently nucleophilic to attack an unactivated olefin in the presence of Pd(II) and yet, in contrast to a stabilized carbanion, tolerate the conditions required to oxidize Pd(0) to Pd(II). If these two conditions were met, the catalytic oxidative alkylation of an unactivated olefin would be realized. Herein, I describe our efforts directed toward the development of an effective procedure for the palladium-catalyzed oxidative alkylation of an unactivated olefin with an activated methylene compound. These efforts have served to validate our initial expectations regarding both the reactivity of activated methylene compounds toward unactivated olefins in the presence of Pd(II) complexes and the stability of activated methylene compounds toward oxidizing conditions. However, in contrast to our initial expectations, activated methylene compounds react with unactivated olefins in the presence of Pd(II) complexes predominantly via hydroalkylation.

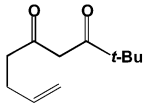
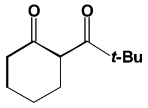
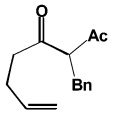
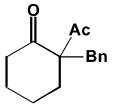
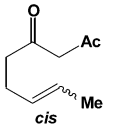
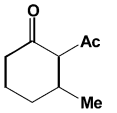
HYDROALKYLATION OF 3-BUTENYL β-DIKETONES

We initially targeted 7-octene-2,4-dione (**1**) as a substrate for palladium-catalyzed olefin alkylation due to the low pK_a [11] and favorable $K_{enol/ketone}$ [12] of β-diketones, and due to the expectation that tethering the nucleophile to the olefin would facilitate alkylation. As noted in the Introduction, it was also our expectation that alkenyl β-diketone **1** would undergo oxidative alkylation in the presence of a Pd(II) complex. However, treatment of **1** with a stoichiometric amount of $PdCl_2(CH_3CN)_2$ (2) in THF at room temperature for 15 min led not to oxidative alkylation, but rather to hydroalkylation with formation of 2-acetylcyclohexanone (**3**) in 70 % isolated yield (Scheme 1) [13]. Because hydroalkylation is a redox-neutral process, we realized that no oxidant should be required for the catalytic conversion of **1** to **3**. Indeed, treatment of **1** with a catalytic amount of **2** (10 mol %) in dioxane at room temperature for 16 h led to the isolation of **3** in 81 % yield as a single regioisomer (Scheme 1) [13]. Palladium-catalyzed hydroalkylation of 3-butenyl β-diketones tolerated substitution at the terminal acyl group, the α-carbon atom, and at the terminal olefinic position, but not at the allylic and homoallylic positions (Table 1).



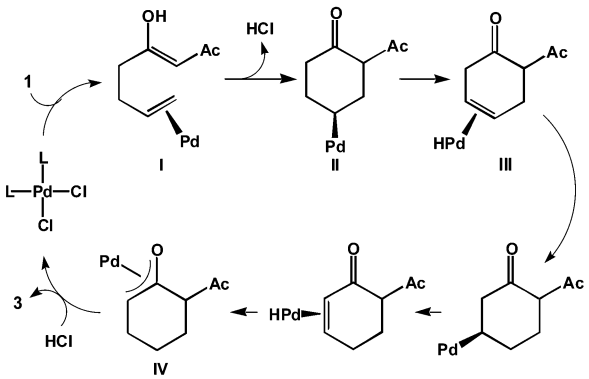
Scheme 1

Table 1 Intramolecular hydroalkylation of 3-butenyl β-diketones catalyzed by **2** (10 mol %) in dioxane at 25 °C.

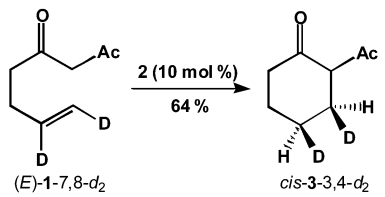
substrate	cyclohexanone	yield (%)
		76
		70
 *cis*		71
trans		81

MECHANISM OF HYDROALKYLATION

We have studied the mechanism of the hydroalkylation of **1** catalyzed by **2** to form **3** through a series of deuterium-labeling experiments [14]. The results of these experiments were in accord with a mechanism involving outer-sphere attack of the pendant enol on the palladium-complexed olefin of **I** to form the palladium cyclohexyl species **II** (Scheme 2). Migration of the palladium atom from the C(4) to the C(6) carbon atom of the cyclohexanone ring via iterative β-hydride elimination/addition followed by protonolysis of palladium enolate complex **IV** forms **3** with regeneration of the Pd(II) catalyst. The outer-sphere nature of C–C bond formation was established through the hydroalkylation of geometrically pure (*E*)- and (*Z*)-7,8-dideuterio-7-octene-2,4-diones [(*E*)- and (*Z*)-**1**-7,8-d_2]. Cyclization of (*E*)-7,8-dideuterio-7-octene-2,4-dione [(*E*)-**1**-7,8-d_2] formed *cis*-**3**-3,4-d_2 as the exclusive isotopomer and stereoisomer (eq. 3), while cyclization of (*Z*)-**1**-7,8-d_2 formed exclusively *trans*-**3**-3,4-d_2 [14].

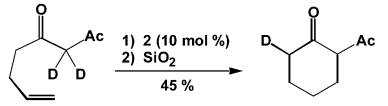


Scheme 2

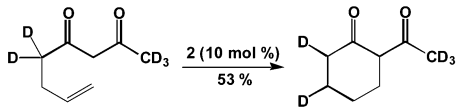


(*E*)-**1**-7,8-d_2 *cis*-**3**-3,4-d_2 (3)

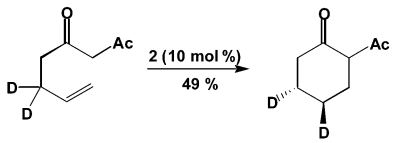
Migration of palladium from the C(4) carbon atom of cyclohexanone intermediate II to the C(6) carbon atom of palladium enolate **IV** prior to protonolysis was first revealed through the palladium-catalyzed cyclization of **1**-3,3-d_2, which formed **3**-6-d_1 to the exclusion of **3**-4-d_1 (eq. 4). A mechanism for the conversion of **II** to **IV** involving iterative β-hydride elimination/addition was established though a number of additional deuterium-labeling experiments. As examples, the palladium-catalyzed cyclization of **1**-1,1,1,5,5-d_5 formed exclusively **3**-2,3-d_2-6-$COCD_3$ (eq. 5), while cyclization of **1**-6,6-d_2 formed exclusively *trans*-**3**-4,5-d_2 (eq. 6). The stereospecific nature of the conversion of **1**-6,6-d_2 to *trans*-**3**-4,5-d_2 also precludes olefin displacement from intermediate **III** (Scheme 2) and establishes that the stereochemistry generated via the initial C–C bond forming process in the cyclization of (*E*)- and (*Z*)-**1**-7,8-d_2 is retained in the isolated carbocycles *cis*- and *trans*-**3**-3,4-d_2, respectively.



1-3,3-d_2 **3**-6-d_1 (4)



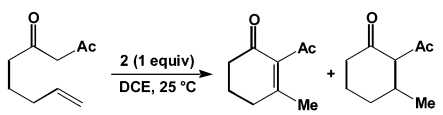
1-1,1,1,5,5-d_5 **3**-2,3-d_2-6-$COCD_3$ (5)



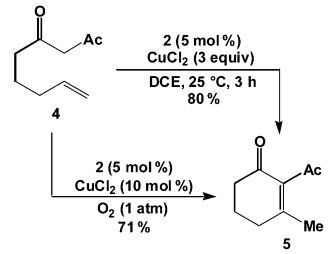
1-6,6-d_2 **3**-4,5-d_2 (6)

OXIDATIVE ALKYLATION OF 4-PENTENYL β-DICARBONYL COMPOUNDS

As noted above, 3-butenyl β-diketones such as **1** underwent selective hydroalkylation in the presence of **2** to form 2-acylcyclohexanones. In contrast, 4-pentenyl β-diketones and some 4-pentenyl β-keto esters underwent selective oxidative alkylation in the presence of **2** to form cyclohexenone derivatives in good yield with good regioselectivity [15]. For example, treatment of 8-nonene-2,4-dione (**4**) with a stoichiometric amount of **2** in dioxane at room temperature for 15 min led to isolation of an ~8:1 mixture of cyclohexenone **5** and cyclohexanone **6** in 85 % combined yield (eq. 7). In accord with our initial expectations, **4** tolerated the conditions required for in situ oxidation of Pd(0) to Pd(II) and reaction of **4** with a catalytic amount of 2 (5 mol %) and $CuCl_2$ (2.5 equiv) at room temperature for 3 h led to the isolation of **5** in 80 % yield (Scheme 3). Oxidative alkylation of **4** was also achieved employing a catalytic amount of both **2** (5 mol %) and $CuCl_2$ (10 mol %) under an oxygen atmosphere to give **5** in 70 % isolated yield (Scheme 3) [15]. Palladium-catalyzed oxidative alkylation of 4-pentyl β-diketones tolerated substitution at the terminal acyl carbon, and along the 4-pentenyl chain (Table 2). 4-Pentenyl β-keto esters also underwent selective oxidative alkylation provided that substitution was present along the 4-pentenyl chain (Table 2) [16]. We are currently working toward understanding the factors that control partitioning between the oxidative alkylation and hydroalkylation pathways in Pd(II)-catalyzed olefin alkylation.

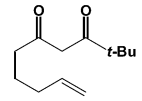
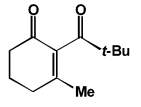
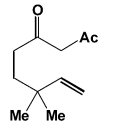
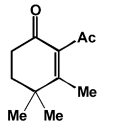
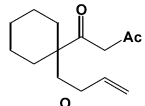
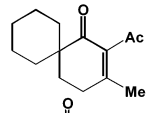
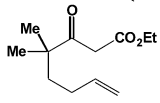
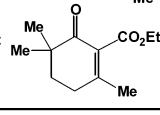


4 5 6 ~8:1 (85 %) (7)



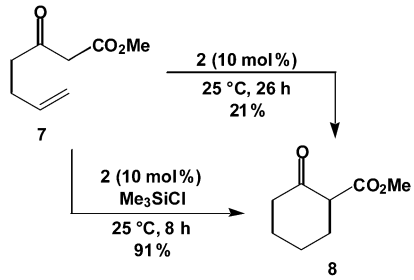
Scheme 3

Table 2 Oxidative alkylation of 4-pentenyl β-dicarbonyl compounds catalyzed by **2** (5 mol %) in the presence of $CuCl_2$ (2.5 equiv) in dioxane at 55–70 °C for 1–3 h.

substrate	cyclohexanone	yield (%)
		70
		75
		85
		76

HYDROALKYLATION OF 3-BUTENYL β-KETO ESTERS, α-ARYL KETONES, AND ALKYL KETONES

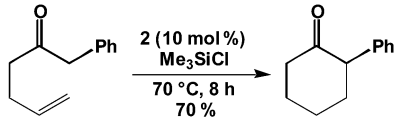
3-Butenyl β-keto esters are significantly less reactive toward palladium-catalyzed hydroalkylation than are 3-butenyl β-diketones. For example, treatment of the methyl 3-oxo-6-heptenoate (**7**) with a catalytic amount of **2** at 25 °C for 26 h formed methyl 2-carbomethoxycyclohexanone (**8**) in only 21 % yield (Scheme 4). Because both the palladium-mediated addition of silyl enol ethers to alkenes [8] and the tungsten-catalyzed addition of silyl enol ethers to alkynes has been demonstrated [17], we reasoned that addition of Me_3SiCl to the catalytic mixture of **7** and **2** might generate the reactive silyl enol ether of **7**



Scheme 4

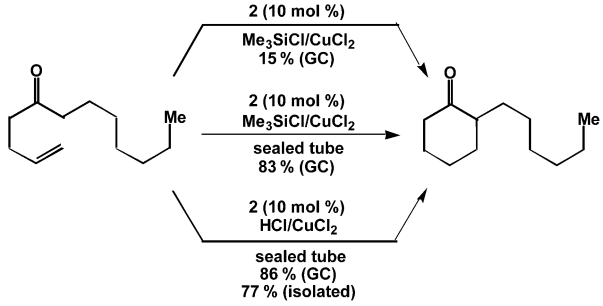
in situ, and also the equivalent of HCl required for protonolysis. In apparent support of this hypothesis (see below), treatment of **7** with a catalytic amount of **2** (10 mol %) and a stoichiometric amount of Me_3SiCl (2 equiv) in dioxane at room temperature for 8 h led to isolation of **8** in 91 % yield (Scheme 4) [18].

The K_a and $K_{enol/ketone}$ of an α-aryl ketone are significantly less favorable than are the corresponding values for a β-keto ester [11,12]. For this reason, it was somewhat surprising that alkenyl α-aryl ketones underwent efficient intramolecular hydroalkylation under conditions similar to those employed for the hydroalkylation of alkenyl β-keto esters. For example, treatment of benzyl 3-butenyl ketone with a catalytic amount of **2** (10 mol %) in the presence of Me_3SiCl (2 equiv) and a trace (0.3 equiv) of $CuCl_2$ at 70 °C for 8 h gave 2-phenylcyclohexanone in 70 % isolated yield (eq. 8); addition of small amounts of $CuCl_2$ to the reaction mixture stabilized the Pd(II) catalyst against undesired reduction [19].

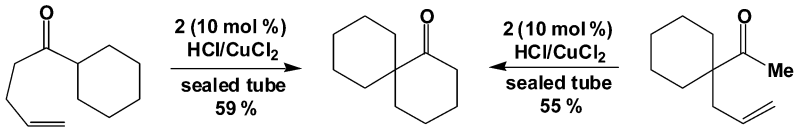


eq 8 (8)

The K_a and $K_{enol/ketone}$ of a dialkyl ketone are $>10^4$ times less favorable than are the corresponding values for an α-aryl ketone, and it is likely for this reason that 3-butenyl heptyl ketone failed to cyclize efficiently employing these silane-mediated conditions (Scheme 5). However, much to our surprise, 3-butenyl heptyl ketone cyclized efficiently when the reaction was performed in a sealed reaction vessel (Scheme 5). Although we initially hypothesized that Me_3SiCl promoted hydroalkylation of alkenyl ketones via in situ formation of a reactive silyl enol ether, efficient hydroalkylation of 3-butenyl heptyl ketone in sealed reaction vessel suggested that HCl, generated via hydrolysis of Me_3SiCl, rather than Me_3SiCl, was the active promoter of palladium-catalyzed hydroalkylation. Consistent with this hypothesis, treatment of 3-butenyl heptyl ketone with sub-stoichiometric amounts of **2** (10 %), HCl (0.1 equiv), and $CuCl_2$ (0.3 equiv) in a sealed tube for 12 h at 70 °C led to the isolation of 2-hexylcyclohexanone in 77 % yield (Scheme 5) [19]. These sealed-tube conditions were effective for the hydroalkylation of a range of alkyl 3-butenyl ketones and were also applicable to the formation of secondary and quaternary carbon atoms (Scheme 6). We believe that HCl facilitates the palladium-catalyzed hydroalkylation of these less reactive alkenyl ketones by catalyzing enolization of the palladium olefin intermediate **I** (Scheme 2).



Scheme 5



Scheme 6

SUMMARY

We have developed the first effective protocols for the transition metal-catalyzed intramolecular hydroalkylation and oxidative alkylation of unactivated olefins with β-diketones employing the air-stable and commercially available Pd(II) catalyst **2**. We have extended the hydroalkylation protocol to include β-keto esters, α-aryl ketones, and even simple dialkyl ketones as the carbon nucleophile by addition of Me_3SiCl or HCl to the reaction mixture. On the basis of deuterium-labeling experiments, we have proposed a mechanism for the palladium-catalyzed hydroalkylation of 7-octene-2,4-dione involving outer-sphere attack of the pendant enol on a palladium-complexed olefin to form a palladium cyclohexyl species, followed by migration of palladium via iterative β-hydride elimination/addition terminated by protonolysis of the resulting palladium enolate species.

ACKNOWLEDGMENTS

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