

## Communications to the Editor

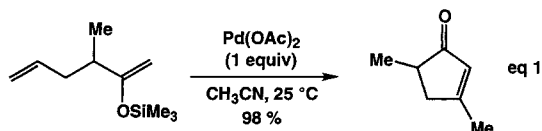
### Palladium-Catalyzed Intramolecular Addition of 1,3-Diones to Unactivated Olefins

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Received July 20, 2001

The regioselective addition of a stabilized carbon nucleophile to an olefin that bears an electron withdrawing group (Michael addition) is one of the key C–C bond forming processes employed in organic synthesis.<sup>1</sup> In contrast, the addition of a stabilized carbon nucleophile to an unactivated olefin remains problematic and in this area, transition metal-based approaches have received considerable attention.<sup>2</sup> Despite this prolonged focus, the efficient transition metal-catalyzed addition of a stabilized carbon nucleophile to an unactivated olefin has not been demonstrated. For example, zirconocene complexes catalyze the addition of alkyl Grignard reagents to olefins, but these catalysts are not compatible with stabilized carbon nucleophiles.<sup>3</sup> Conversely, Pd(0) complexes catalyze the addition of active methylene compounds to alkenes<sup>4</sup> and conjugated dienes<sup>5</sup> but these catalysts are unreactive toward simple olefins. Although Pd(II) complexes mediate the addition of both stabilized carbanions<sup>6</sup> and silyl enol ethers<sup>7</sup> to unactivated olefins (eq 1), efficient catalysis has not been realized.<sup>8</sup> Here we report the regioselective, Pd(II)-catalyzed intramolecular addition of 1,3-diones to unactivated olefins.



Coordination of an olefin to an electron deficient transition metal complex greatly enhances the reactivity of the olefin toward nucleophilic attack.<sup>9</sup> In the presence of a suitable oxidant, Pd(II)

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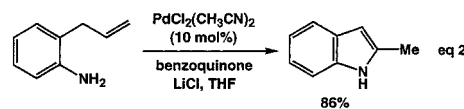
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(8) A single example of the Pd-catalyzed addition of a carbon nucleophile to an unactivated olefin employed 50 mol % of both Pd(OAc)<sub>2</sub> and benzoquinone to convert 2-trimethylsilyloxy-1,5-hexadiene to 3-methylcyclohex-2-en-1-one in 70% yield.<sup>7c</sup>

**Table 1.** Cyclization of Alkenyl 1,3-Diones and Alkenyl  $\beta$ -Keto Esters Catalyzed by PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in Dioxane at Room Temperature for 12–36 h

entry	substrate	cat load (mol %)	carbocycle	yield (%)
1		10		81
2	R = Me	5		72
3	R = Et	10		67
4	R = <i>t</i> -Bu	10		66
5		10		61
6	R = Bn	20		70
7		10		71
8	R = Me	20		81
9	R = <i>n</i> -Bu	20		89
10	R = Ph	10		82
11		20		38
12	R = Et	10		45
13	R = Bn	10		32

complexes catalyze the intramolecular addition of alcohols<sup>10</sup> and protected amines<sup>11</sup> to unactivated olefins with net oxidation of the substrate (eq 2). Unfortunately, Pd(II)-catalyzed addition of



carbon nucleophiles to olefins has been precluded by competitive oxidation of the nucleophile by the stoichiometric oxidant and/or by the Pd(II) complex.<sup>7–11</sup> Because silyl enol ethers reacted readily with olefins in the presence of Pd(II), we considered that the enol tautomer of a 1,3-diketone might be sufficiently nucleophilic to attack a tethered olefin in the presence of Pd(II) and yet

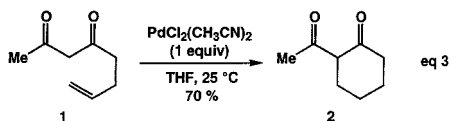
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be resistant toward oxidation. If these two conditions were met, the Pd(II)-catalyzed addition of a 1,3-diketone to an unactivated olefin could be achieved.

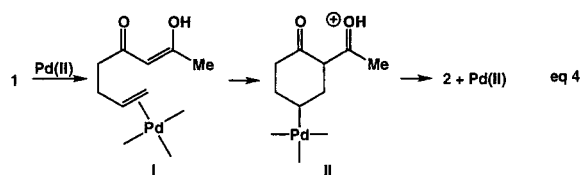
In an effort to probe the reactivity of a 1,3-diketone toward a pendant olefin in the presence of Pd(II), an equimolar solution of 7-octene-2,4-dione (**1**) and PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in THF was stirred at room temperature. After 15 min, the dione had been completely consumed to form 2-acetylcyclohexanone (**2**) as the exclusive product that was isolated in 70% yield and identified by comparison to an authentic sample. The endo regioselectivity of ring closure was somewhat unexpected based on the predominant exo regioselectivity of related Pd(II)-mediated and -catalyzed annulation processes.<sup>7–11</sup> More surprising, however, was that carbocycle **2** did not possess a double bond and was therefore not oxidized relative to dione **1**. This observation suggested that no reduction of Pd(II) had occurred and therefore no oxidant should be required for the catalytic conversion of **1** to **2**. In accord with this hypothesis, treatment of **1** (25 mM) with a catalytic amount of PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (10 mol %) in dioxane at room temperature for 16 h led to the isolation of cyclohexanone **2** in 81% yield as a single regioisomer (Table 1, entry 1).<sup>12</sup> Dione **1** also cyclized in the presence of 5 mol % PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> within 36 h at room temperature to form **2** in 72% yield (Table 1, entry 2).



The Pd-catalyzed cyclization of alkenyl-1,3-diones tolerated substitution at the terminal methyl group and at the carbon located between the two carbonyl groups (Table 1, entries 3–6). In addition, the cyclization protocol tolerated terminal olefinic substitution (Table 1, entries 7–11). For example, both *cis*- and *trans*-7-nonene-2,4-dione cyclized in the presence of PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> to form 2-acetyl-3-methylcyclohexanone in >70% yield as a single regioisomer (Table 1, entries 7 and 8). In comparison, 8-methyl-7-nonene-2,4-dione, which possessed a trisubstituted olefin, cyclized in 38% yield (Table 1, entry 11). Alkenyl- $\beta$ -keto esters cyclized in the presence of PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> to form the corresponding 2-carboalkoxycyclohexanones with diminished yields relative to the cyclization of **1** (Table 1, entries 12 and 13).

(12) Dioxane was a more effective solvent than was THF, CH<sub>2</sub>Cl<sub>2</sub>, DCE, toluene, or benzene. Similarly, catalysts such as PdCl<sub>2</sub>, PdCl<sub>2</sub>(PhCN)<sub>2</sub>, and Pd(OAc)<sub>2</sub> were inferior to PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>. Substrate concentrations  $\geq$  25 mM led to competitive olefin isomerization.

Our working mechanism for the palladium-catalyzed conversion of **1** to **2** is based on the established reactivity of Pd(II) olefin complexes toward nucleophiles,<sup>9</sup> and involves intramolecular attack of the pendant enol on the palladium-complexed olefin of intermediate **I** to form the palladium cyclohexyl intermediate **II** (eq 4). Although Pd(II) alkyl complexes are typically unstable



with respect to  $\beta$ -hydride elimination,<sup>9</sup> no evidence for the formation of cyclohexenones in the conversion of **1** to **2** was obtained. Rather, proton transfer from the protonated carbonyl group to the palladium-bound carbon atom of **II** presumably releases carbocycle **2** and regenerates the Pd(II) catalyst prior to  $\beta$ -hydride elimination. We have obtained no experimental evidence which would distinguish between intra- and intermolecular proton transfer, nor do we as yet understand the circumstances which facilitate protonation of **II** relative to  $\beta$ -hydride elimination.

In summary, we have presented the first examples of the transition metal-catalyzed addition of active methylene and methine compounds to unactivated olefins employing a simple, commercially available Pd(II) complex. We are currently working toward expanding the scope of this process and toward the elucidation of the mechanism of the conversion of **1** to **2**.

**Acknowledgment.** R.W. thanks the Camille and Henry Dreyfus foundation for New Faculty and Teacher-Scholar awards, DuPont for a Young professor Award, and the Alfred P. Sloan Foundation for a Research Fellowship. We thank Mr. Xiang Wang for synthesizing 3-methyl-7-octene-2,4-dione, benzyl 3-oxo-6-heptenoate, and 7-dodecene-2,4-dione.

**Note Added in Proof:** The PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>-catalyzed addition of alcohols and acetic acid to  $\alpha,\beta$ -unsaturated ketones and acetals in the absence of a stoichiometric oxidant has been reported and was proposed to occur via protonolysis of the Pd–C bond of a palladium alkyl intermediate with HCl: Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001.

**Supporting Information Available:** Experimental procedures and spectroscopic data for new compounds and cyclohexanones (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA011764X