# Palladium-Catalyzed Intramolecular Oxidative Alkylation of Unactivated Olefins

Tao Pei, Xiang Wang, and Ross A. Widenhoefer*

Duke University, P. M. Gross Chemical Laboratory, Durham, North Carolina 27708-0346

Received March 25, 2002; E-mail: rwidenho@chem.duke.edu

The palladium(0)-catalyzed oxidative arylation and alkenylation of olefins (Heck reaction) is one of the most useful transition metal-catalyzed transformations utilized in organic synthesis (eq 1).[1] In contrast, oxidative alkylation of olefins via the Heck reaction remains problematic due to the inefficient oxidative addition of the alkyl halide or competitive β-hydride elimination of the initially formed Pd(II) intermediate.[1,2] An alternative approach to the oxidative alkylation of olefins that would also obviate the need for the alkyl halide is via the Pd(II)-catalyzed nucleophilic addition of a carbon nucleophile to an olefin in the presence of an oxidant. Indeed, Pd(II) complexes catalyze the oxidative amination,[3] alkoxylation,[4] and hydroxylation[5] of unactivated olefins (eq 2). Unfortunately, Pd(II)-catalyzed oxidative alkylation of olefins remains problematic due to incompatibility between the carbon nucleophile and the stoichiometric oxidant.[6–8] Here we report the first effective procedure for the Pd(II)-catalyzed oxidative alkylation of an olefin with a carbon nucleophile.

$$(1)$$

$$(2)$$
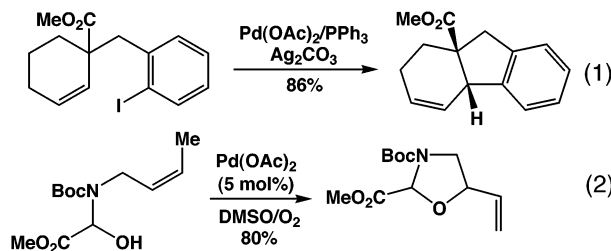
ϵ-Alkenyl β-diketones were initially targeted as substrates for Pd(II)-catalyzed oxidative alkylation on the expectation that the β-diketone would be sufficiently nucleophilic to attack the tethered olefin in the presence of Pd(II) and yet tolerate the conditions required for in situ oxidation of Pd(0). However, treatment of the ϵ-alkenyl β-diketone 1 with a catalytic amount of PdCl$_2$(CH$_3$CN)$_2$ (2) formed none of the desired cycloalkenone but instead formed cyclohexanone 3 in 81% isolated yield via net addition of the enolic C–H bond across the olefinic C=C bond (hydroalkylation) (eq 3).[9] We have proposed that protonolysis of the Pd–C bond of the palladium cyclohexyl intermediate I in preference to β-hydride elimination leads to formation of 3 rather than the expected oxidative alkylation product (Scheme 1).[9]

$$(3)$$
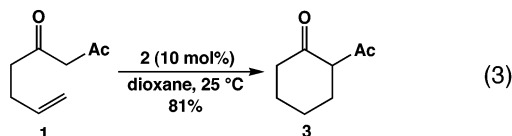
Although attempts to access the oxidative alkylation pathway in the cyclization of 1 catalyzed by 2 were unsuccessful, we have now found that ζ-alkenyl β-diketones undergo selective oxidative alkylation in the presence of 2. For example, reaction of a 1:1
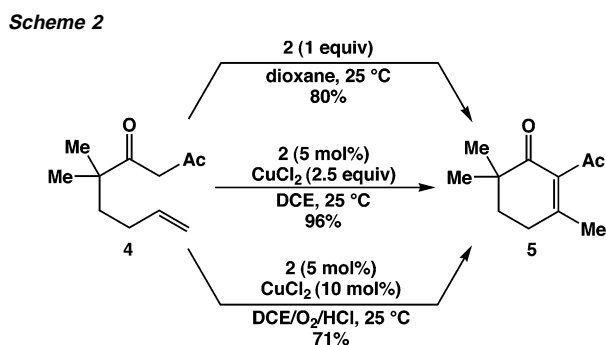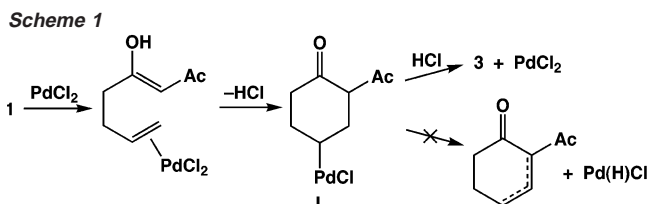
Scheme 1

Scheme 2

mixture of dione 4 and 2 in dioxane at room temperature for 15 min led to isolation of cyclohexenone 5 in 80% yield as the exclusive product (Scheme 2). In accord with our initial expectations, diketone 4 tolerated the conditions required for in situ oxidation of Pd(0) to Pd(II), and in an optimized procedure, slow addition of 4 to a mixture of 2 (5 mol %) and CuCl$_2$ (2.5 equiv) in 1,2-dichloroethane (DCE) over 3 h at room temperature led to the isolation of 5 in 96% yield (Scheme 2). Oxidative alkylation of 4 was also achieved by employing a catalytic amount of both 2 (5 mol %) and CuCl$_2$ (10 mol %) under an oxygen atmosphere, albeit with somewhat diminished yield (Scheme 2).

The oxidative alkylation of ζ-alkenyl β-diketones tolerated a number of terminal acyl groups including propionyl, isobutyryl, pivaloyl, and cyclohexanecarbonyl groups (Table 1, entries 1–4). *gem*-Dimethyl groups at the γ-carbon atom of the ζ-alkenyl β-diketone appeared to facilitate cyclization but were not required (Table 1, entries 5–8). Palladium-catalyzed oxidative alkylation also tolerated allylic substitution (Table 1, entry 9) and was applicable to the synthesis of spirobicyclic compounds (Table 1, entry 10) and to the cyclization of ζ-alkenyl β-keto esters (Table 1, entry 11). However, efforts to effect the oxidative alkylation of ϵ-alkenyl β-diketones or ζ-alkenyl β-diketones that possess olefinic substitution have been unsuccessful.

We have formulated a working mechanism for the oxidative alkylation of 4 catalyzed by 2 that is based on the proposed mechanism of the Wacker oxidation.[10] Attack of the pendant enolic carbon atom on the palladium-complexed olefin of II coupled with loss of HCl could form the palladium cyclohexylmethyl species III (Scheme 3). Isomerization of III via β-hydride elimination/ addition/elimination followed by olefin displacement from intermediate VI would release 5 and form a palladium hydrochloride

Table 1. Oxidative Alkylation of ζ-Alkenyl β-Diketones Catalyzed by PdCl$_2$(CH$_3$CN)$_2$ (**2**) (5 mol %) in the Presence of CuCl$_2$ (2.5 equiv) in DCE at Room Temperature for 3−7 h

| entry	substrate	cyclohexenone	yield (%)
1	R = Et		97
2	R = i-Pr		87
3	R = t-Bu		94
4	R = Cy		86
5			76
6	R = Me		80
7	R = t-Bu		70[a]
8	R = Ph		64[b]
9			75[a]
10			85
11			76[a]

[a] Reaction run at 70 °C. [b] 10 mol % catalyst employed and 14% hydroalkylation product formed.

species,[10] which would eliminate HCl and react with CuCl$_2$ to regenerate the catalytically active Pd(II) species (Scheme 3). Both the isomerization of **III** to **VI** and olefin displacement from **VI** must be fast relative to protonolysis of palladium alkyl intermediates **III** and **V** to account for the selective formation of **5**. We currently do not understand the factors that control partitioning between the oxidative alkylation and hydroalkylation pathways in the Pd(II)-catalyzed cyclization of alkenyl β-diketones.[9]

In summary, we have developed the first effective transition metal-catalyzed protocol for the oxidative alkylation of an unactivated olefin with a carbon nucleophile. Our efforts are currently directed toward expanding the substrate scope of oxidative alkylation with respect to tether length and olefinic substitution, toward elucidating the mechanism of this transformation, and toward understanding the factors that determine product selectivity in the Pd(II)-catalyzed cyclization of alkenyl β-diketones and related substrates.

Scheme 3
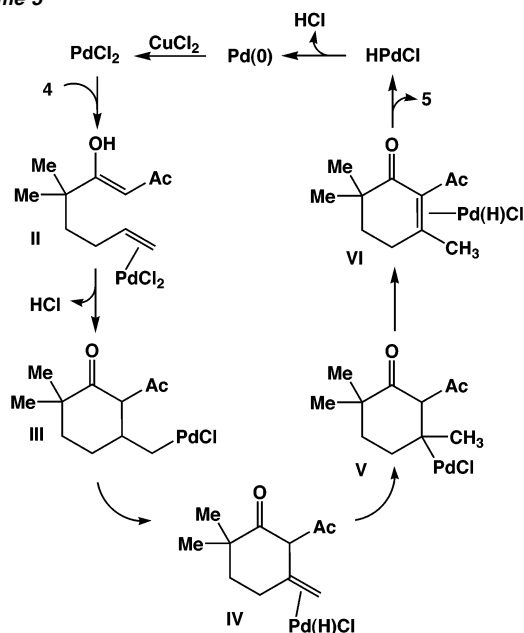
Supporting Information Available: Experimental procedures and spectroscopic data for new compounds and cyclohexanones (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) deMeijere, E.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (b) Ableman, M. R.; Oh, T.; Overman, L. E *J. Org. Chem.* **1987**, *52*, 4133.

(2) For a Co-catalyzed approach see: Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514.

(3) (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994.

(4) (a) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49. (b) van Bentheim, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357.

(5) (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 80. (b) Tsuji, J. *Synthesis* **1984**, 369.

(6) (a) Hegedus, L. S.; Darlington, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 4980. (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808. (c) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494.

(7) Pd(II)-catalyzed oxidative alkylation of a 1,3-diene has been reported: Rönn, M.; Andersson, P. G.; Bäckvall, J. E. *Tetrahedron Lett.* **1997**, *38*, 3603.

(8) A single example of the Pd(OAc)$_2$-catalyzed cycloalkenylation of an alkenyl silyl enol ether has been reported: Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916.

(9) (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290. (b) Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 650.

(10) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

JA026317B