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Mechanism of the Palladium-Catalyzed Intramolecular Hydroalkylation of 7-Octene-2,4-dione

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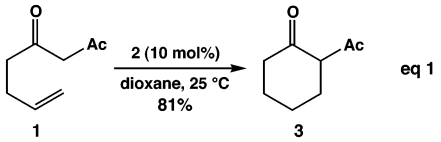
The Michael addition is one of the most important C−C bond-forming processes employed in organic synthesis, but it is restricted to olefins that bear an electron-withdrawing group.[1] In response to this limitation, we recently reported the palladium-catalyzed intramolecular hydroalkylation of alkenyl β-dicarbonyl compounds.[2,3] For example, treatment of 7-octene-2,4-dione (**1**) with a catalytic amount of $PdCl_2(CH_3CN)_2$ (**2**) formed 2-acetylcyclohexanone (**3**) in 81% yield via net addition of the enolic C−H bond across the olefinic C═C bond (eq 1).[2] These transformations represent the first examples of the transition metal-catalyzed hydroalkylation of an unactivated olefin with a stabilized carbon nucleophile[4] and may provide a general solution to the problems associated with the alkylation of unactivated olefins. However, further development of these transformations will require an understanding of the mechanisms of these processes, in particular, the mechanisms of C−C bond formation and proton transfer. Here we report a deuterium-labeling study that provides insight into the mechanism of C−C bond formation and proton transfer in the conversion of **1** to **3** catalyzed by **2**.

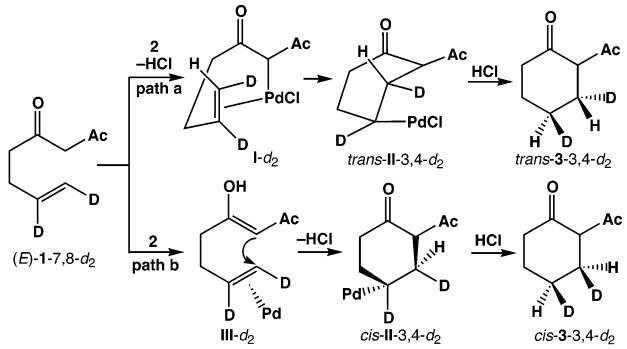


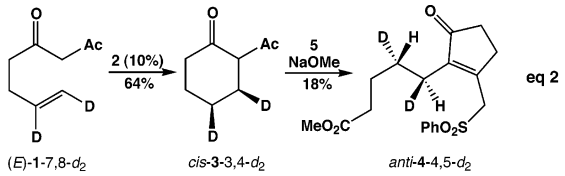
eq 1

Both inner-sphere and outer-sphere mechanisms have been established for the palladium-catalyzed addition of oxygen[5] and nitrogen[6] nucleophiles to olefins and for the palladium-mediated addition of carbon nucleophiles to olefins.[7] We therefore considered both inner-sphere and outer-sphere mechanisms for the palladium-catalyzed hydroalkylation of **1**. These pathways can be potentially distinguished via cyclization of (*E*)-7,8-dideuterio-7-octene-2,4-dione [(*E*)-**1**-7,8-d_2] (Scheme 1). In the inner-sphere pathway, attack of the enol carbon atom of (*E*)-**1**-7,8-d_2 on **2** coupled with loss of HCl could form the palladium alkyl olefin chelate complex **I**-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[8] to form *trans*-**3**-3,4-d_2 (Scheme 1, path a). In the outer-sphere pathway, attack of the enolic carbon on the palladium-complexed olefin of **III**-d_2 coupled with loss of HCl could form palladium cyclohexyl intermediate *cis*-**II**-3,4-d_2. Protonolysis of the Pd−C bond of *cis*-**II**-3,4-d_2 with retention of configuration would form *cis*-**3**-3,4-d_2 (Scheme 1, path b).

Treatment of (*E*)-**1**-7,8-d_2 with a catalytic amount of **2** (10 mol %) in dioxane at room temperature for 12 h formed *cis*-**3**-3,4-d_2 in 64% isolated yield (eq 2).[9] The stereochemistry of *cis*-**3**-3,4-d_2 was established indirectly by the 9.2 Hz coupling constant of the H(4) and H(5) protons of the corresponding pentanoate derivative *anti*-**4**-4,5-d_2 (eq 2),[10] generated in 18% yield by treatment of *cis*-**3**-3,4-d_2 with (*E*)-2,3-dibromo-1-phenylsulfonylpropene (**5**) and sodium methoxide (eq 2).[11] In a separate set of experiments, cyclization of (*Z*)-**1**-7,8-d_2 catalyzed by **2** formed *trans*-**3**-3,4-d_2 in 67% yield,[9] which was converted to *syn*-**4**-4,5-d_2 in 28% yield.[11] The stereochemistry of *syn*-**4**-4,5-d_2 was established by the 6.0 Hz coupling constant of the H(4) and H(5) protons of the pentanoate chain.[10]

Scheme 1





eq 2

Stereospecific conversion of (*E*)- and (*Z*)-**1**-7,8-d_2 to *cis*- and *trans*-**3**-3,4-d_2, respectively, is consistent with outer-sphere C−C bond formation, provided that conversion of **II**-3,4-d_2 to **3**-3,4-d_2 occurs with retention of configuration (Scheme 1 path b).[8] To gain insight into the nature of the protonolysis step in the cyclization of **1** catalyzed by **2**, we studied the cyclization of 3,3-dideuterio-7-octene-2,4-dione (**1**-3,3-d_2) (eq 3). If conversion of **II** to **3** occurred via direct protonolysis of the Pd−C bond of **II**, cyclization of **1**-3,3-d_2 should form exclusively **3**-2,4-d_2 via deuteriolysis of the Pd−C bond of intermediate **II**-2-d_1. However, cyclization of **1**-3,3-d_2 catalyzed by **2** followed by silica gel chromatography formed none of the expected C(4)-d_1 isotopomer and instead formed **3**-6-d_1 in 45% isolated yield as the exclusive deuterated isotopomer (eq 3).[12]

Formation of **3**-6-d_1 rather than **3**-4-d_1 in the cyclization of **1**-3,3-d_2 points to migration of palladium from the C(4) carbon atom to the C(6) carbon atom of the 2-acetylcyclohexanone ring prior to deuteriolysis. Three additional experiments provided insight into the mechanism of palladium migration. In separate experiments, cyclization of **1**-1,1,1,5,5-d_5, **1**-6,6-d_2, and **1**-8,8-d_2 catalyzed by **2** formed **3**-2,3-d_2-6-$COCD_3$, *trans*-**3**-4,5-d_2, and **3**-3,3-d_2, respectively, as the exclusive isotopomers (eqs 4−6); the stereochemistry of *trans*-**3**-4,5-d_2 was established by the 4.4 Hz coupling constant of the H(3) and H(4) protons of the pentanoate chain of derivative *syn*-**4**-3,4-d_2.

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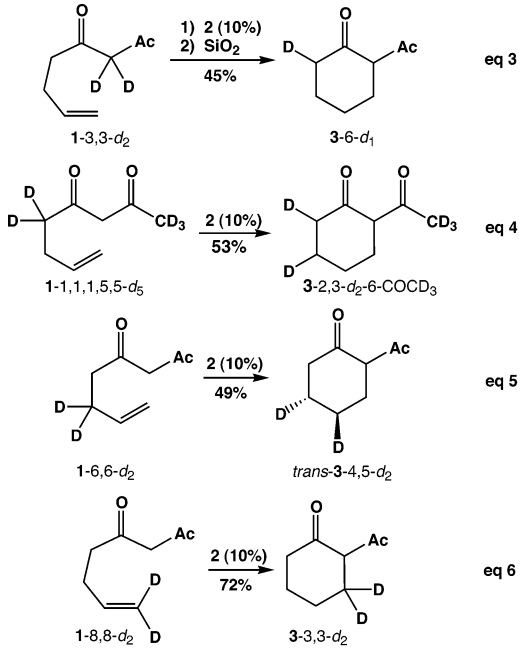
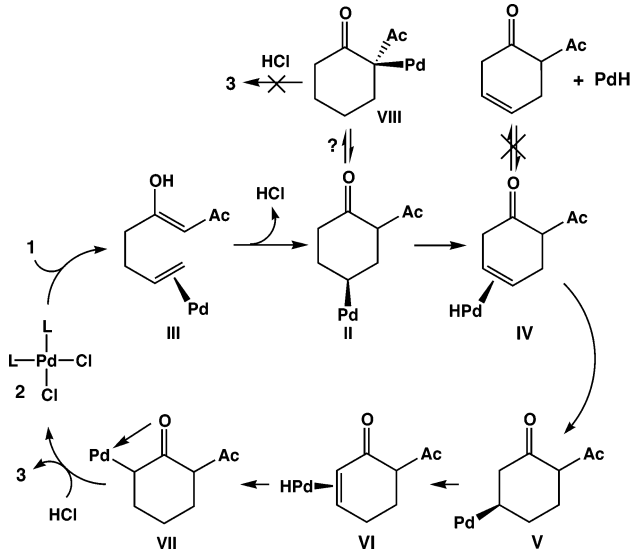


Conversion of **1**-1,1,1,5,5-d_5 and **1**-6,6-d_2 to **3**-2,3-d_2-6-$COCD_3$ and *trans*-**3**-4,5-d_2, respectively (eqs 4 and 5), is consistent with isomerization of **II** to the palladium enolate complex **VII** via successive β-hydride elimination/addition (Scheme 2).[13] Isomerization of **II** to **VII** prior to protonolysis is not surprising given the high reactivity of palladium(II) alkyl complexes toward β-hydride elimination/addition.[14] The stereoselective conversion of **1**-6,6-d_2 to *trans*-**3**-4,5-d_2 precludes reversible olefin displacement from intermediate **IV** (Scheme 2) and also establishes that the stereochemistry generated via initial cyclization of (*E*)- and (*Z*)-**1**-7,8-d_2 is retained upon subsequent conversion to *cis*- and *trans*-**3**-3,4-d_2, respectively. Although we were unable to determine the stereochemistry of **3**-2,3-d_2-6-$COCD_3$ formed in the cyclization of **1**-1,1,1,5,5-d_5 (eq 4), we presume that intermediate **VI** is also stable toward olefin displacement (Scheme 2). The failure to form detectable amounts of **3**-3,4-d_2 in the cyclization of **1**-8,8-d_2 (eq 6) precludes protonolysis from the palladium β-diketonate complex **VIII**, but does not rule out reversible formation of **VIII** (Scheme 2).

Scheme 2



In summary, we have presented a deuterium labeling study that provides insight into the mechanism of the palladium-catalyzed intramolecular hydroalkylation of 7-octene-2,4-dione (**1**). These experiments are in accord with a mechanism involving attack of the enol carbon atom on the palladium-complexed olefin of **III** followed by palladium migration and protonolysis from the palladium enolate complex **VII** (Scheme 2). Further studies in this area will be directed toward elucidating the structure of palladium enolate complex **VII** and toward understanding the potential role of β-diketonate complex **VIII** in palladium-catalyzed hydroalkylation.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of spectra for deuterated isotopomers of **1**, **3**, and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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