## Palladium-Catalyzed H–D Exchange Reaction under Hydrothermal Condition

Seijiro Matsubara,\* Yutaka Yokota, and Koichiro Oshima

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoutodaigaku-katsura, Nishikyo-ku, Kyoto 615-8510

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Alkenes and alkanes were converted into fully deuterium labelled ones by treatment with palladium on charcoal and deuterium oxide under hydrothermal condition. The simple method to get fully deuterium labelled compounds is easy to apply to various types of organic compounds.

Since the pioneering work by Breslow,<sup>1</sup> organic reactions in water as solvent have been well investigated from the point of view of the rate enhancement and the high stereoselectivity.<sup>2</sup> Recently, water is also paid attention as a harmless solvent in the field of green chemistry. When water in a closed pot is heated beyond the boiling point, it takes subcritical stage and finally reaches to supercritical stage.<sup>3</sup> The water in these specific conditions should also have the potential in organic reactions.<sup>4,5</sup> At the subcritical stage, for example, which is also called as hydrothermal condition, the value of  $pK_w$  should be notified. It shows the low value (ca. 11) at the typical hydrothermal condition (250 °C / 5 MPa). The fact means that the hydrothermal water ionizes in the larger extent than water under ambient condition (i.e. 1000 times larger) and loses the tight hydrogen bond network. In this condition, we assumed that Pd(0) might insert to water oxidatively to form Pd(II) species 1 (Scheme 1).<sup>6–8</sup>

$$2 H_2 O \xrightarrow{\boldsymbol{pK}_w = 11} OH^- + H_3 O^+ \xrightarrow{Pd(0)} H - Pd - OH + H_2 C$$

**Scheme 1.** Assumed oxidative insertion of Pd(0) into water under hydrothermal condition.

The palladium hydride **1** may interact with alkenes. Cyclododecene (E/Z = 33/67, 2.0 mmol) was also treated with 10 wt % Pd on active carbon (50 mg, 0.05 mmol Pd) and water (20 mL) at 250 °C in the autoclave (Figure 1).<sup>9</sup> After 4 h, the major diasteromer became *E*-isomer (E/Z = 83/17, 1.9 mmol).<sup>10</sup> Treatment for 4 h in hydrothermal water without catalyst did not isomerize the starting cyclododecene.



Figure 1. Reaction vessel (See Ref. 9).

The isomerization reaction is supposed to proceed through  $\pi$ -allyl palladium formation via C–H activation by 1 at allylic

position. A repetition of hydropalladation (addition of 1 to alkene) and  $\beta$ -elimination (elimination of palladium hydride from alkylpalladium) is also possible route. In both cases, the key species is the palladium hydride that may exchanges a proton with the solvent water. When the isomerization is examined in the hydrothermal condition of deuterium oxide, the H–D exchange transformation of alkenes would occur.

A mixture of cyclododecene (2, 5.0 mmol), 10 wt % Pd on active carbon (100 mg, 0.1 mmol Pd), and deuterium oxide (20 g) in a 30-mL Teflon vessel was placed in a stainless autoclave.<sup>9</sup> The whole was sealed and heated at 250 °C. Under this hydrothermal condition for 12 h, the obtained mixture was extracted with hexane after the whole was cooled to the room temperature. The extracts were concentrated and purified by a short silica-gel column chromatography. The product was analyzed by GC, <sup>1</sup>H NMR, <sup>2</sup>H NMR, and mass spectra. As shown in Scheme 2, cyclododecene was converted into the fully deuterated compound **3**. Without catalyst, any deuteration was not observed.



**Scheme 2.** Treatment of cyclododecene with deuterium oxide and Pd/C under hydrothermal condition.

Under the same condition, other types of compounds were treated for several hours. The results are summarized in Table 1. Cyclooctene was also transformed into fully deuterated cyclooctene without any skeletal rearrangement (Run 1)<sup>11</sup> As shown in Runs 2 and 3, saturated hydrocarbons were also transformed into the fully deuterated compounds. Ketones were also fully deuterated under the condition (Runs 5–9). As described above, an interaction of alkene and palladium hydride induces H–D exchange reaction. The H–D exchange in alkanes, however, cannot be explained in this way. A direct C–H activation may be a route to the formation of fully deuterated alkanes.

A number of reports concerning about H–D exchange method have been reported. These methods have focused mainly on acid catalyzed reaction in  $D_2O$ ,<sup>11</sup> base catalyzed reaction in  $D_2O$ ,<sup>12</sup> or metal catalyzed reaction under  $D_2$  atmosphere.<sup>13</sup> The acid catalyzed reaction is performed at 200–300 °C for H– D exchange reaction of hydrocarbons. The skeletal rearrangement, however, was observed in some cases. For example, cyclo-

 Table 1. Palladium-catalyzed deuteration of organic compounds under hydrothermal condition<sup>a</sup>

Run	Substrate	Time /h	D /% <sup>b</sup>	Yield /% <sup>c</sup>
1	Cyclooctene	4	>95	80
2	Cyclododecane	6	>95	84
3	Cyclopentadecane	4	>95	99
4	n-Pentadecane	16	76	98
5	Cyclooctanone	10	>95	86
6	Cyclodecanone	12	>95	83
7	Cyclododecanone	4	>95	87
8	Cyclopentadecanone	10	>95	99
9	2-Dodecanone	11	>95	93

<sup>a</sup>Substrate (5.0 mmol), Pd/C (10 wt % palladium on carbon, 100mg, 2 mol % Pd), and D<sub>2</sub>O (20.0 g). <sup>b</sup>The ratios were determined by GC, <sup>1</sup>H NMR, <sup>2</sup>H NMR, and mass spectra. <sup>c</sup>The yields were isolated yields.

octenes would give cyclohexene derivatives. The base catalyzed H–D exchange reactions are applicable for aromatic compounds and ketones. The metal catalyzed H–D exchange reaction using D<sub>2</sub> is classical and general method for hydrocarbons, but also contains a limitation of the substrates because it is gas phase reaction. Our method is so simple procedure that is applicable to examine the wide range of compounds. It should be noted that partial H–D exchange reaction were also performed under microwave irradiation<sup>14</sup> and under an effect of transition metal catalyst in D<sub>2</sub>O.<sup>15</sup>

The C–H bonds in benzene ring were also converted into C– D bonds under the conditions. As shown in Scheme 3, *t*-butyl benzene (**4**) was treated with the same condition in Table 1, a regioselective deuteration was observed in benzene ring. At the sterically hindered ortho positions, the exchange reaction was not observed. At the tertiary butyl group, 45% of C–H bonds were transformed into C–D bonds. In Scheme 4, biphenyl (**6**) was converted into the fully deuterated biphenyl (**7**) completely.







The mechanistic studies have not been examined yet. However, the method can be applied to various types of compounds to obtain the fully deuterated compounds which have a potential for optical communication.<sup>16</sup>

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