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Efficient C–H/C–D Exchange Reaction on the Alkyl Side Chain of Aromatic Compounds Using Heterogeneous Pd/C in D_2O

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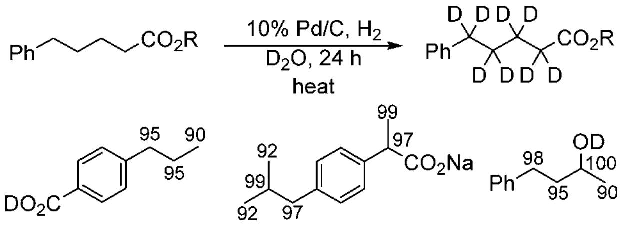
ABSTRACT



An efficient and extensive deuterium incorporation using heterogeneous Pd/C–D_2O–H_2 system into many different types of unactivated C–H bond positions was developed. The present method provides a deuterium gas-free, totally catalytic, and post-synthetic deuterium labeling method in D_2O media.

Replacement of hydrogen atoms on alkyl carbons by deuterium has been the focus of much research of late.[1] During the last several decades, development of a new synthetic method for deuterium-labeled compounds has been extensively studied for the investigation of biosynthetic pathways, chemical reaction mechanisms and kinetics, the catalytic mechanisms of enzymes, analysis of the secondary and tertiary structures of biomolecules, analysis of drug metabolism and residual pesticides, and so on.[1,2] For the preparation of deuterium-labeled organic compounds, the previous methods are chiefly categorized under the following two types: the multistep synthetic method starting from originally deuterium-labeled small synthons and the post-synthetic H−D exchange displacement of the hydrogen bound to the carbon of an unlabeled compound by deuterium using a catalytic method.[1] It is apparent that the latter process is highly effective and accessible for the preparation of deuterium-labeled organic compounds. Transition-metal-catalyzed C−H bond activation combined with the deuteration of the activated substrate has been a topic of current interest and is an underdeveloped methodology. Many approaches, which invoke Ir,[3] Rh,[4] Co,[5] Pt,[6] Ru,[7] Mn,[8] and so on,[9] are uniformly conducted under homogeneous conditions. While homogeneous catalysts are used in many cases,

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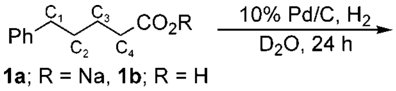
heterogeneous catalysts are crucial for application of the methodology to industry because they are easily removed from the reaction mixture using only simple filtration.[10] Existing techniques utilize Pd/C$-D_2$,[11] Pd/C$-DCO_2K$,[12] Pd/C$-D_2O$,[13] $PtO_2-D_2-D_2O$,[14] Rh/SiO_2-D_2,[15] Raney Co$-$Al$-D_2O$,[16] and K10 clay$-D_2O$.[17] However, such conventional procedures for the incorporation of deuterium into the C$-$H bonds of organic compounds are often limited to activated positions of the molecules, leading to low levels of deuterium incorporation, and usually require a vast amount of the catalyst, addition of acidic or basic additives, and/or deuterium atmosphere. Although, most recently, Matsubara et al., reported a remarkable H$-$D exchange transformation with 10% Pd/C in subcritical D_2O (250 °C) in the absence of hydrogen,[18] we independently found that hydrogen gas is essential for the 10% Pd/C-catalyzed H$-$D exchange reaction below 180 °C.[19,20]

We report here that a heterogeneous Pd/C$-D_2O-H_2$ system efficiently catalyzes the exchange of deuterium from D_2O into organic compounds, including nonactivated positions of the molecules.

We have recently reported that efficient and chemoselective exchange of deuterium derived from D_2O with hydrogen atoms on a benzylic carbon using Pd/C as a heterogeneous catalyst in the presence of a catalytic amount of hydrogen gas at room temperature.[20] We were hopeful that application of heat would promote the catalytic activity of the Pd/C$-D_2O-H_2$ system and lead to H$-$D exchange reaction even on nonactivated carbon.

Heating 5-phenyl-1-valeric acid sodium salt (**1a**) with 10% Pd/C (10% of the weight of **1a**, ca. 1.6 mol % of Pd metal) in D_2O in the presence of H_2 [21] at 110 °C leads to surprisingly enhanced H$-$D exchange even on nonbenzylic C_2-C_4 carbons while only a chemoselective exchange on a benzylic site was observed at room temperature (Table 1, entries 1 and 2). Interestingly, the use of 5-phenyl-1-valeric acid (**1b**), which is slightly soluble in D_2O, as a substrate also led to a comparable efficient result (entry 5). The deuterium efficiency into the side chain (C_1-C_4) of **1a** and **1b** decreases with increasing distance from the benzene ring. While no exchange was observed in the absence of hydrogen gas (entry 3) or 10% Pd/C (entry 4), hydrogen was found to dramatically activate the reactivity of the Pd/C-catalyzed H$-$D exchange reaction.[19] Additional optimization revealed that the efficiency of H$-$D exchange reaction can be greatly enhanced with a rise in temperature up to 160 °C using a sealed tube (entry 7). Although the Pd/C$-D_2O-H_2$ system catalyzed extensive deuterium incorporation into the benzylic and unactivated methylene positions, the deuterium efficiency at the benzene ring was lower.

Table 1. Temperature Dependence of 10% Pd/C$-H_2$-Catalyzed H$-$D Exchange in D_2O[a]



			D content[b] (%)			
entry	compd	T (°C)	Ph	C_1	$C_2 + C_3$	C_4
1[c]	**1a**	rt	0	89	0	0
2	**1a**	110	34	98	89	12
3[d]	**1b**	110	0	0	0	0
4[e]	**1b**	110	0	0	0	0
5	**1b**	110	26	97	80	0
6[f]	**1b**	140	63	96	84	29
7[f]	**1b**	160	67	95	94	94
8[f,g]	**1b**	180	0	48	13	5

[a] Unless otherwise noted, 0.25 mmol of the substrate was used and reactions were carried out under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate, Aldrich) in D_2O (99.8% D content, 1 mL). [b] D content was determined by ^1H NMR. [c] 0.5 mmol of the substrate was used in 2 mL of D_2O. [d] Without hydrogen. [e] Without 10% Pd/C. [f] The reaction was performed in a sealed tube. [g] The reaction was performed under D_2 atmosphere in dry EtOAc instead of H_2 and D_2O.

The efficiency of H$-$D exchange reaction was seriously reduced when the reaction was performed under D_2 atmosphere instead of H_2 in dry EtOAc as an inert solvent even at 180 °C (entry 8). Therefore, D_2O is necessary to achieve an efficient H$-$D exchange.

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(21) Although hydrogen gas is essential for the H$-$D exchange reaction, the substitution of hydrogen gas in the reaction flask by argon gas after activation of Pd/C does not affect the efficiency of the exchange reaction.

As a starting point for the development of our direct deuteration, we also studied the 10% Pd/C−H_2 catalyzed H−D exchange reaction of 5-phenyl-1-valeric acid (**1b**) in D_2O at 160 °C for optimizing the reaction time, and the result is presented in Figure 1. Over the time course of the reaction, a rapid H−D exchange is observed on C_1 (benzylic), C_2, and C_3 carbons while a gradual increase is observed on the C_4 and the aromatic carbons. It can be seen from the data in Figure 1 that the alkyl side chain is nearly deuterated within 24 h.

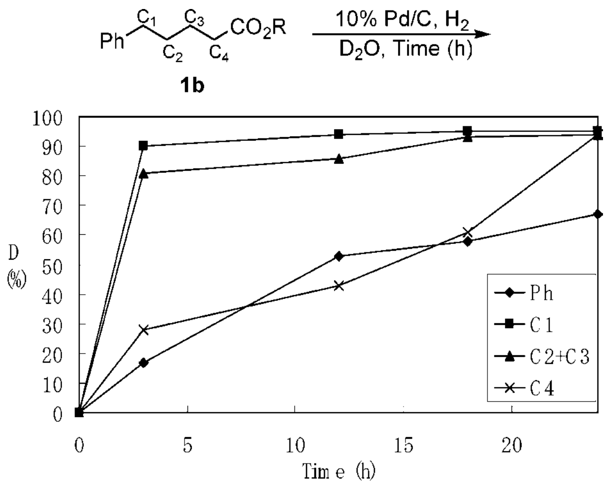

Figure 1. Kinetic traces of 10% Pd/C−H_2-catalyzed H−D exchange of **1b** in D_2O at 160 °C.

With the Pd/C−D_2O−H_2 system as a catalyst, we can synthesize highly and multi-deuterated products using an array of functionalized starting materials at 110−160 °C (Figure 2). Thus, the reaction conditions are compatible with functional groups such as straight and branched alkyls, carboxylic acids, alcohols, ethers, and ketones. The reactions were very clean, and no chromatographic separation was required to obtain spectrally pure products. No byproducts were obtained from any of the reactions and excellent deuterium efficiency was achieved in each case. In particular, 4-propylbenzoic acid (**3**), 4-isopropylbenzoic acid (**4**), ibuprofen (**5**), and 4-phenyl-2-butanol (**9**) showed surprisingly excellent deuterium incorporation into even the unactivated tertiary C−H bond position. When 1-phenylhexane (**7**) or 5-phenyl-1-pentanol (**10**) was used as the substrate, exchange into the unactivated terminal position was inefficient at 110 °C, compared with the C−H bond of internal methylenes in the vicinity of the benzene ring. This drawback can be nearly overcome with a rise in temperature up to 160 °C. The reaction using a primary alcohol **10** or ether **11** as a substrate gave lower deuterium efficiency on the neighboring-methylenes of the oxygen atom (0% D contents at 110 °C).

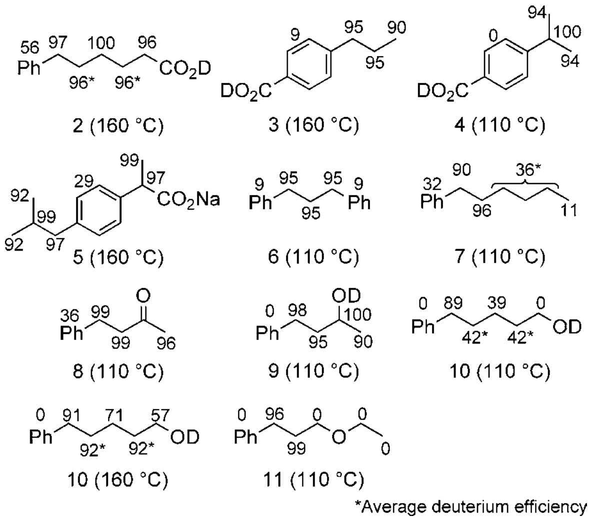

Figure 2. H−D exchange results with 10% Pd/C−H_2 in D_2O.

Exchange reactions using substrates, which lack aromatic rings, such as octanoic acid (**12**, Figure 3), led to almost no deuterium incorporation with use of the reaction conditions in Table 1 and Figure 2. Furthermore, the use of substrates, which possess an oxygen atom between the aromatic rings and the alkyl chains, such as 5-phenoxy-1-valeric acid (**13**), led also to no deuterium incorporation (see also Figure 2, the terminal ethyl group of compound **11**). Therefore, the importance of the participation of an aromatic ring directly connected to the alkyl chain is evident.

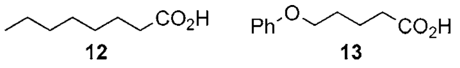

Figure 3.

While the exact process of H−D exchange reaction is unclear, a Pd/C-catalyzed C−H bond activation combined with deuteration from D_2O could be predictable and a small amount of hydrogen gas is necessary to activate the palladium as a so-called ligand.

In summary, we have developed an efficient and extensive deuterium incorporation using a heterogeneous Pd/C−D_2O−H_2 system into many different types of unactivated C−H bond positions. The reaction is general for a variety of substrates and tolerates a wide range of different functional groups. The results presented here provide a deuterium gas-free, totally catalytic and postsynthetic deuterium labeling method in D_2O media. The simplicity of this method makes it an attractive new tool for organic, medicinal and analytical chemists. We are currently investigating ways to elucidate the scope and mechanism of the H−D exchange reaction.

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Supporting Information Available: Experimental details and ^1H NMR data for deuterated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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