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Facile and Convenient Method of Deuterium Gas Generation Using a Pd/C-Catalyzed H_2–D_2 Exchange Reaction and Its Application to Synthesis of Deuterium-Labeled Compounds

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Abstract: The Pd/C-catalyzed H_2–D_2 exchange reaction using a H_2–D_2O combination provided a general, efficient and environmentally friendly route for the preparation of deuterium gas (D_2). H_2 sealed in a reaction flask was converted into nearly pure D_2, which could be used for the Pd/C-catalyzed one-pot reductive deuteration of various reducible functionalities and the chemoselective one-pot deuterogenation of olefin and acetylene. Additionally, we established the capturing method of the generated D_2 in a balloon, which was successfully applied to the Pd/C-catalyzed reductive mono-*N*-alkylation of a primary amine using nitrile as the alkylating reagent.

Keywords: chemoselectivity • deuterium gas • heterogeneous catalysis • isotopic labeling • palladium

Introduction

Deuterium gas (D_2) has been widely utilized as a deuterium source for the deuterium-labeling of a variety of molecules,[1] since it is a non-radioactive and stable isotope.[2] Deuterium-labeled compounds are finding increasing use as research tools in the life, environmental, and material sciences.[3,4] The catalytic deuterogenation of unsaturated hydrocarbons, deuterodehalogenation of aryl chlorides or bromides, deuterodeoxygenation of benzyl alcohols, and deuterogenolysis (ring-opening reaction) of epoxides using D_2 frequently offer the best routes to prepare the deuterated compounds with a high deuterium efficiency and regioselectivity.[5] D_2 is, however, very expensive since it is commercially produced by the electrolysis of D_2O using an enormous amount of energy or the fractional distillation of liquid hydrogen under cryogenic conditions (ca. –250 °C). The pyrolysis of UD_3 was also reported as a generation method of D_2, but it is not practical because of the use of radioactive uranium metal.[6] As for the preparation methods of D_2 on a laboratory scale, the reactions of metals such as sodium,[7] iron,[8] and magnesium[9] with D_2O have been reported in the literature, although a large quantity of metal sludge was produced and drastic reaction conditions (several hundred degrees Celsius) were required. Numerous catalytic H_2–D_2 exchange reactions between H_2 and D_2O have also been reported in the literature.[10–18] However, these methods did not produce high purity D_2 and also required high pressure, the use of a special catalyst, and an excess amount of a strong base or acid. Furthermore, the applications of the generated D_2 to the deuterogenation of unsaturated substrates afforded the corresponding deuterated products with low deuterium efficiencies, depending on the D_2 purity.[19–21] Therefore, efficient and catalytic preparation methods of pure D_2 via the H_2–D_2 exchange reaction between H_2 and D_2O have not yet been developed. Consequently, the development of an efficient and catalytic generation method of D_2 in the laboratory has been strongly desired. We have recently reported a Pd/C-catalyzed regioselective H–D exchange reaction at the benzylic site in D_2O in the presence of a small amount of H_2 at room temperature,[22] and multiple deuterium-labeling methods on aromatic rings and/or alkyl side chains under high temperature conditions (110–180 °C).[23] During the course of these investigations, we have found that 10 % Pd/C effectively catalyzed an isotope exchange reaction between H_2 and D_2O, and the H_2 in the reaction flask was almost entirely replaced by D_2 at room temperature within 24 h. We have also developed a conven-

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ient and one-pot reductive deuteration method using the generated D_2.[24] Herein, we describe the details of the Pd/C-catalyzed H_2–D_2 exchange reaction, including the one-pot reductive deuteration, chemoselective deuterium-labeling method, D_2-capturing method, and mechanistic aspects.

Results and Discussion

Pd/C-catalyzed H_2–D_2 exchange reaction between H_2 and D_2O: In our first investigation, we conducted a H_2–D_2 exchange reaction using D_2O (1.0 mL, 55 mmol) and 10 % Pd/C (10 mg, 9.4 μmol of Pd metal) in the presence of a large quantity of H_2 (balloon, ca. 2.0 L) (Figure 1, condition A). The course of the reaction over time was monitored by ^{1}H NMR spectroscopy using *p*-methoxybenzoic acid sodium salt as an internal standard. Figure 1 indicates the gradual and continuous increase of the DHO signal intensity based upon Equation (1), whereas no increase in the intensity was observed in the absence of H_2 (under Ar atmosphere, condition B) or 10 % Pd/C (condition C). The H_2–D_2 exchange reaction was found to be a Pd/C-catalyzed reaction, and the source of the hydrogen atom of DHO must be H_2. D_2 (63 mL, 2.6 mmol) [HD (127 mL, 5.2 mmol)] was generated from D_2O (1.0 mL, 55 mmol) after 24 h (TON = 276) [HD: TON = 552] by the calculation based upon the increased DHO. The present reaction proceeded relatively slowly, but continuously converted H_2 into D_2 even under atmospheric hydrogen pressure at room temperature. This result motivated us to more extensively examine this Pd/C-catalyzed H_2–D_2 exchange reaction.

$$\underset{(1\ \mathrm{mL},\ 55\ \mathrm{mmol})}{2\ D_2O} + \underset{(\mathrm{ca.}\ 2.0\ \mathrm{L},\ 82\ \mathrm{mmol})}{H_2\ (\mathrm{balloon})} \xrightarrow[\mathrm{rt}]{10\%\ \mathrm{Pd/C}\ (10\ \mathrm{mg})} 2\ \mathrm{DHO} + \mathbf{D_2} \qquad (1)$$

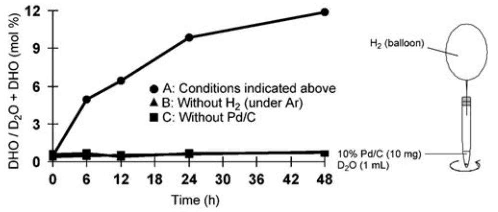


Figure 1. Kinetic plots of DHO ratio in D_2O.

We chose to explore the utility of heterogeneous transition metal catalysts for the reaction [9.4 μmol of each catalyst in D_2O (1 mL) under an H_2 atmosphere]. As shown in Figure 2, Rh/C indicates the highest activity and Pd/C, Ir/C, and Pt/C are also effective. From the viewpoints of cost and general versatility, we decided to use Pd/C as the catalyst for the H_2–D_2 exchange reaction.

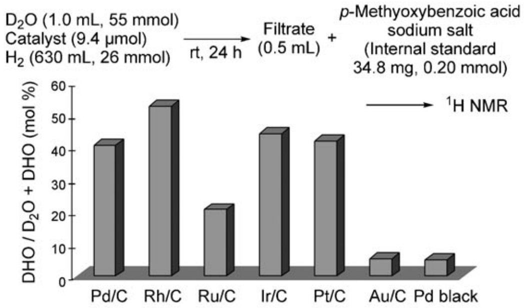
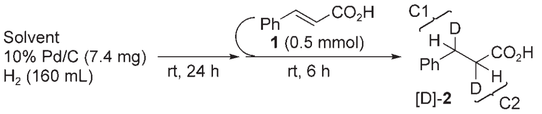


Figure 2. Effect of catalyst toward H_2–D_2 exchange reaction.

Next, we attempted the one-pot deuterogenation of an olefin using the generated D_2 (Table 1). A suspension of 10 % Pd/C (7.4 mg, 10 % of the substrate weight) in D_2O (1 mL, 55 mmol) in a sealed flask (160 mL: interior volume) was stirred under a hydrogen atmosphere at room temperature for 24 h and then *trans*-cinnamic acid (**1**) was added through a syringe attached to a needle. After 6 h, an approximately 35 % deuterium incorporation into both of the reduced methylene positions (C1 and C2) was observed by ^{1}H NMR spectroscopy (entry 1, Table 1). The deuterium efficiency was significantly improved using 3 mL of D_2O and a nearly quantitative deuterium incorporation was achieved (entry 2, Table 1). The D content at the benzylic site (C1 position) was slightly over 50 % using 5 mL of D_2O probably due to the benzylic site selective Pd/C-catalyzed H–D exchange reaction (entry 3, Table 1).[22] These results indicate at least 3 mL of D_2O is necessary for the complete conversion of pure H_2 to pure D_2 in the 160-mL flask. On the other hand, CH_3OD and CD_3OD were not efficient deuterium sources, and even increased amounts of CH_3OD up to 13.5 mL never improved the D contents of [D]-**2** (entries 4–7, Table 1). Only acidic deuterium atoms seem to work as deuterium sources in the present reaction since the use of

Table 1. Effect of deuterium source on the one-pot deuterogenation.[a]



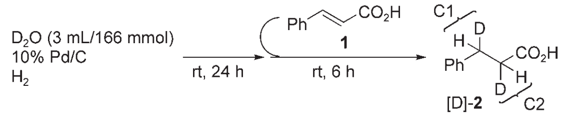
Entry	Solvent (mL/mmol)	D content [%][b] C1	D content [%][b] C2	Yield[c] [%]
1	D_2O (1/55)	36	35	87
2	D_2O (3/166)	48	46	98
3	D_2O (5/276)	52	49	100
4	CH_3OD (3/74)	24	26	92
5	CH_3OD (6.8/166)	24	25	95
6	CH_3OD (13.5/332)	26	26	91
7	CD_3OD (3/74)	28	28	90
8	CH_3CO_2D (9.7/166)	–	–	–[d]
9[e]	DCl in D_2O [3/19 (DCl), 144 (D_2O)]	–	–	–[f]

[a] A suspension of 10 % Pd/C (10 wt % of **1**) in solvent was stirred under H_2 atmosphere (160 mL, 6.5 mmol) at room temperature for 24 h, *trans*-cinnamic acid (**1**) (0.5 mmol) was added as a 0.5 mL MeOH solution, and the reaction was quenched after 6 h. [b] D content was determined by ^{1}H NMR spectroscopy on the basis of the integration of the aromatic protons. [c] Yield of isolated product. [d] Starting material (**1**) was recovered in 71 % yield. [e] 20 wt % DCl in D_2O solution was used. [f] Starting material (**1**) was recovered in 85 % yield.

CH_3OD led to the nearly equal deuterium efficiency as that of CD_3OD (entry 4 vs. 7, Table 1), although no desired [D]-**2** was generated when the reaction was carried out in an acidic deuterated solvent such as CH_3CO_2D or 20% DCl in D_2O (entries 8 and 9, Table 1).

The reaction conditions of the H_2–D_2 exchange were optimized as shown in Table 2. The reductive deuteration of **1** efficiently proceeded by a 24 h pre-stirring of 10% Pd/C in D_2O (3 mL) under a H_2 atmosphere (160 mL, 6.5 mmol) at room temperature (entry 1, Table 2), while almost no deuterium incorporation was observed without pre-stirring (entry 2, Table 2). The efficiency of the deuterium incorporation was significantly reduced by the decreased use of the 10% Pd/C (3 wt%) (entry 3, Table 2) or an increased amount of H_2 using a larger flask (entries 5 and 6, Table 2). On the other hand, a slightly higher D content was obtained by decreasing the amount of H_2 (75 mL) in a smaller flask (entry 4, Table 2). Therefore, these results indicate that the D_2 purity is significantly affected by the ratio between the H_2 volume and D_2O amount based upon the efficiency of the H_2–D_2 exchange reaction. The use of a larger amount (1.0 and 2.0 mmol) of the substrate (**1**), compared with 0.5 mmol in entry 1 of Table 2, brought about the successful deuterogenation (entries 7 and 8, Table 2), but increasing **1** caused more D_2 to be consumed and induces a reduced inner pressure in the enclosed reaction flask, which would decrease the reaction efficiency. Therefore, the reaction conditions described in entry 1 of Table 2 were used as the standard conditions for the following reactions.

Table 2. Deuterogenation of **1** using D_2 generated in situ.[a]

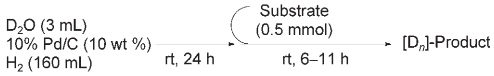


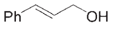
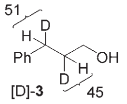
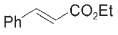
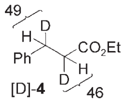
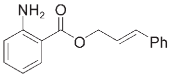
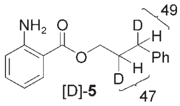
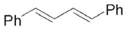
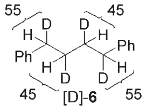
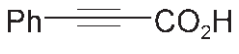
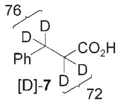
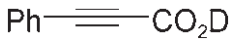
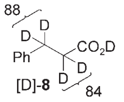
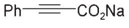
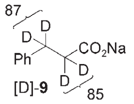
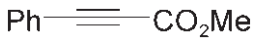
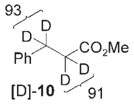
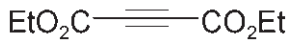
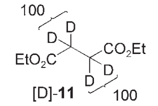
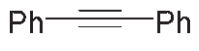
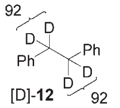
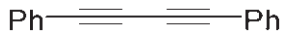
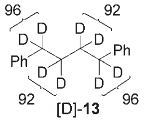
Entry	**1** [mmol]	10% Pd/C [wt%/mg]	H_2 [mL/mmol]	D content [%][b] C1	C2	Yield[c] [%]
1	0.5	10/7.4	160/6.5	48	46	98
2[d]	0.5	10/7.4	160/6.5	2	0	97
3	0.5	3/2.3	160/6.5	37	36	91
4	0.5	10/7.4	75/3.1	52	49	100
5	0.5	10/7.4	285/12.2	44	42	100
6	0.5	10/7.4	690/28.2	31	29	100
7	1.0	10/7.4	160/6.5	48	50	100
8	2.0	10/7.4	160/6.5	45	45	99

[a] 10% Pd/C in D_2O was pre-stirred under H_2 atmosphere for 24 h, *trans*-cinnamic acid (**1**) was added as a 0.5 mL MeOH solution, and the reaction was quenched after 6 h. [b] D content was determined by ^1H NMR spectroscopy on the basis of the integration of the aromatic protons. [c] Yield of isolated product. [d] Deuterogenation was performed for 6 h without pre-stirring.

One-pot reductive deuteration using D_2 generated in situ: A wide variety of internal olefins and acetylenes, including dienes and diynes were employed for the one-pot reduction to give the corresponding deuterated products in excellent deuterium efficiencies (entries 1–4 and 8–11, Table 3). However, the reaction of phenylpropiolic acid produced only a moderate D content (72 and 76%, respectively) (entry 5, Table 3). The displacement of the acidic proton by deuterium or conversion to the corresponding sodium salt slightly

Table 3. Application to catalytic deuteration of olefins and acetylenes using Pd/C–D_2O–H_2 system.[a]



Entry	Substrate	Time [h]	$[D_n]$-Product (D content, %)[b]	Yield[c] [%]
1		6	 [D]-**3** 	83
2		6	 [D]-**4** 	82
3		8	 [D]-**5** 	80
4		6	 [D]-**6** 	95
5		11	 [D]-**7** 	98
6		11	 [D]-**8** 	96
7		6	 [D]-**9** 	100
8[d]		11	 [D]-**10** 	71
9[d]		6	 [D]-**11** 	93
10		6	 [D]-**12** 	90
11		6	 [D]-**13** 	100

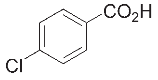
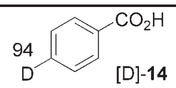
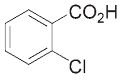
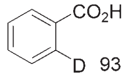
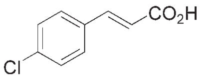
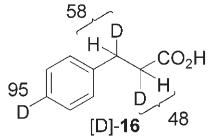
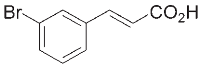
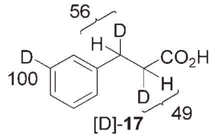
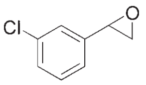
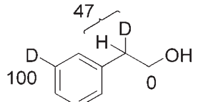
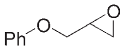
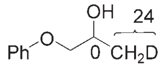
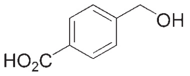
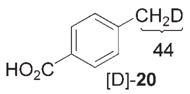
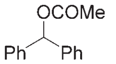
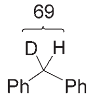
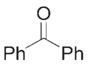
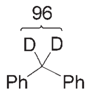
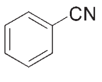
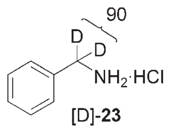
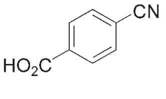
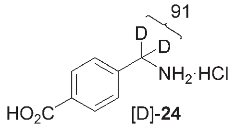
[a] 10% Pd/C (10 wt% of the substrate) in D_2O (3 mL, 166 mmol) was stirred under H_2 atmosphere (160 mL, 6.5 mmol) at room temperature for 24 h, then the substrate (0.5 mmol) was added, and the reaction was quenched after 6–11 h. [b] D content was determined by ^1H NMR spectroscopy on the basis of the integration of the aromatic, methyl or ethyl protons. [c] Yield of isolated product. [d] 5 mL of D_2O (276 mmol) was used.

improved the deuterium efficiency (entries 6 and 7, Table 3), and an excellent deuterium incorporation was achieved using the corresponding methyl ester as a substrate (entry 8, Table 3). These reactions were very clean and virtually no competitive deuteration on the aromatic ring or non-reducible positions was observed (confirmed by ^{2}H NMR spectroscopy).

The present one-pot reductive deuteration method using the generated D_2 was also applicable to the deuteration based on the dehalogenation of aromatic halides, deoxygenation of benzylic oxygen, the ring-opening reaction of epoxides and catalytic reduction of aromatic nitriles (Table 4). The dehalogenation of aromatic chlorides and bromide efficiently proceeded with an excellent D content by the addition of 1.2 equivalents of triethylamine (entries 1–5, Table 4),[25] and the coexisting olefin functionality within the molecule underwent the quantitative deuterogenation (entries 3 and 4, Table 4). The Pd/C-catalyzed ring-opening reaction of epoxides regioselectively proceeded[26] with an efficient deuterium incorporation (entries 5 and 6, Table 4). The deuterogenolysis of benzyl alcohol and ester smoothly proceeded to provide the corresponding deuterated and deoxygenated products ([D]-**20** and [D]-**21**, respectively; entries 7 and 8, Table 4). In these two cases, the D content at the methyl group (44%, entry 7, Table 4) and benzylic methylene group (69%, entry 8) was higher than the theoretical D content of the deuterogenolysis (33% and 50%, respectively), presumably because the Pd/C-catalyzed H–D exchange reaction proceeded at the newly formed benzylic site after deuterogenolysis.[22]

Table 4. Application to catalytic deuteration of various substrates using Pd/C–D_2O–H_2 system.[a]

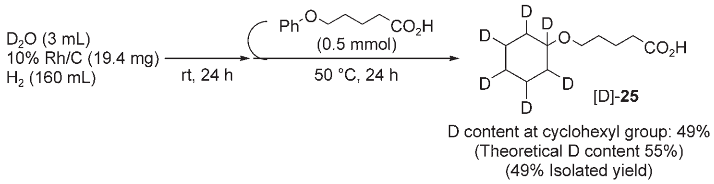
$$\begin{array}{l}\text{D}_2\text{O (3 mL)}\\ \text{10\% Pd/C (10 wt\%)}\\ \text{H}_2\text{ (160 mL)}\end{array}\xrightarrow[\text{rt, 24 h}]{}\xrightarrow[\text{rt, 6–48 h}]{\text{Substrate (0.5 mmol)}}[\text{D}_n]\text{-Product}$$

Entry	Substrate	Time [h]	[D$_n$]-Product (D content, %)[b]	Yield[c] [%]
1[c,d]		24	 [D]-**14**	79
2[c,d]		24	 [D]-**15**	97
3[c–e]		24	 [D]-**16**	89
4[c–e]		24	 [D]-**17**	99
5[c,f]		24	 [D]-**18**	95
6[g]		24	 [D]-**19**	92
7[g]		6	 [D]-**20**	100
8[g]		8	 [D]-**21**	100
9[g,h]		12	 [D]-**22**	80
10[g,i]		24	 [D]-**23**	95
11[g,j]		48	 [D]-**24**	77

[a] 10% Pd/C (10 wt% of the substrate) in D_2O (3 mL, 166 mmol) was stirred under H_2 atmosphere (160 mL, 6.5 mmol) at room temperature for 24 h, then the substrate (0.5 mmol) was added, and the reaction was quenched after 6–48 h. [b] Yield of isolated product. [c] 0.6 mmol of triethylamine was added together with substrate. [d] D content was determined by ^{1}H NMR spectroscopy after the conversion of the carboxylic acid into the corresponding methyl ester on the basis of the integration of the methyl protons. [e] 5 mL of D_2O (276 mmol) was used. [f] D content was determined by ^{1}H NMR spectroscopy after the conversion of the alcohol into the corresponding acetate on the basis of the integration of the acetyl protons. [g] D content was determined by ^{1}H NMR spectroscopy on the basis of the integration of the aromatic protons. [h] 20 wt% of the substrate of 10% Pd/C was used and the deuterogenation of aromatic ketone was performed at 50 °C. [i] 20 wt% of the substrate of 10% Pd/C was used and 0.75 mmol of DCl (20 wt%, solution in D_2O) was added together with substrate. [j] 30 wt% of the substrate of 10% Pd/C was used and 0.75 mmol of DCl (20 wt%, solution in D_2O) were added together with substrate.

By the same token, benzophenone was also successfully employed for the deuterogenation of the aromatic ketone to produce $[D_2]$-diphenylmethane ([D]-**22**) with a 96% D content (entry 9, Table 4). Furthermore, the efficient deuterogenation of aromatic nitriles cleanly proceeded in the presence of 1.5 equivalents of DCl (as a 20 wt% D_2O solution) and efficiently deuterated benzylamine derivatives ([D]-**23** and [D]-**24**) were obtained without the formation of any side-products, such as secondary and tertiary amines (entries 10 and 11, Table 4).

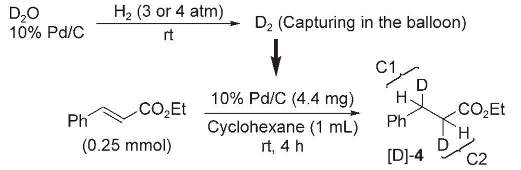
One-pot deuterogenation of aromatic nuclei using the generated D_2: We recently reported a mild and neutral hydrogenation method of aromatic nuclei catalyzed by 10% Rh/C in water.[27] Next, we applied the present method to the deuterogenation of 5-phenoxy-*n*-valeric acid since Rh/C indicated the efficient catalyst activity toward the H_2–D_2 exchange reaction (Figure 2). The successfully reduced and efficiently labeled cyclohexane derivative ([D]-**25**) was obtained as shown in Scheme 1.



Scheme 1. Application to deuterogenation of aromatic nuclei using Rh/C–D_2O–H_2 system.

The method of capturing the generated D_2 and its application to the synthesis of deuterium-labeled compounds: The reaction conditions for the complete conversion of H_2 into D_2 were investigated in a pressure-resistant reaction vessel under medium pressure to establish an efficient capturing method of the generated D_2 because the one-pot and in situ deuteration method was not applicable to water-sensitive substrates and reactions. The purity of the collected D_2 in a rubber balloon was assessed by the deuterium efficiency of the Pd/C-catalyzed deuterogenation of ethyl cinnamate in cyclohexane (Table 5). The deuterated product ([D]-**4**) was obtained with a high D content (entry 1, Table 5, C1: 44%, C2: 44%) under the stated conditions. Although increasing the amounts of Pd/C or D_2O, the decompression of H_2 and lengthening of the reaction time were each modestly effective for the reaction efficiency (entries 2–7, Table 5), nearly pure D_2 was generated under the combined conditions (10 mL of D_2O, 50 mg of 10% Pd/C, 3 atm of H_2, 96 mL of pressure-resistant Hyper-glass cylinder, at room temperature for 48 h) as shown in entry 8, Table 5. Roughly 170 mL of D_2 under atmospheric pressure was captured in the rubber balloon.

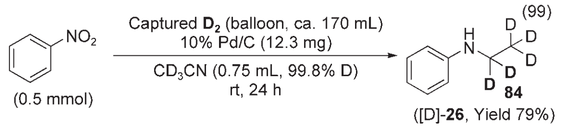
Table 5. Development of capturing method of generated D_2 in situ.[a,b]



Entry	10% Pd/C	D_2O	Time	Pressure/H_2	D content [%][c]		Yield[d]
	[mg]	[mL]	[h]	[atm]/[mmol]	C1	C2	[%]
1	30	6	24	4/14.7	44	44	79
2	50	8	24	4/14.4	45	45	95
3	30	6	48	3/11.0	45	45	100
4	30	10	48	3/10.6	47	47	99
5	40	8	48	3/10.8	46	46	96
6	50	6	48	3/11.0	44	45	96
7	50	8	48	3/10.8	46	44	95
8	50	10	48	3/10.6	49	49	95

[a] Capturing Method: 10% Pd/C in D_2O was stirred under H_2 pressure at room temperature using a pressure-resistant Hyper-glass cylinder (96 mL), the generated D_2 was captured in a rubber balloon. [b] The purity of the generated D_2 was assessed by the deuterogenation of ethyl cinnamate: a mixture of ethyl cinnamate (0.25 mmol) and 10% Pd/C (4.4 mg, 10 wt% of the substrate weight) in cyclohexane (1 mL) were stirred under a captured D_2 atmosphere (ca. 170 mL) at room temperature for 4 h. [c] D content was determined by ^1H NMR on the basis of the integration of the aromatic protons. [d] Yield of isolated product.

We recently reported the Pd/C-catalyzed reductive mono-*N*-alkylation of anilines using nitriles as an alkylating regent under an H_2 atmosphere, and this method is also applicable to the one-pot synthesis of mono-*N*-alkylanilines starting from nitrobenzene.[28] The reductive *N*-ethylation of nitrobenzene under a captured D_2 atmosphere was investigated using $[D_3]$acetonirile (CD_3CN, D content: 99.8%) as an alkylating reagent (Scheme 2). The reductive alkylation and simultaneous deuteration derived from the captured D_2 successfully proceeded to afford the desired *N*-ethylaniline with a good D content at the α-methylene position of the nitrogen atom (84%). The process of generation, capture and application of D_2 was, therefore, useful for the synthesis of the secondary amine which is regioselectively deuterated at the α-methylene group.



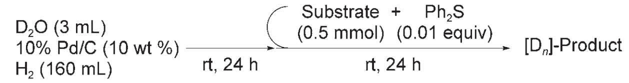
Scheme 2. Application to Pd/C-catalyzed reductive mono-*N*-alkylation using CD_3CN in captured D_2.

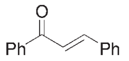
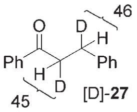
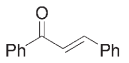
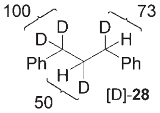
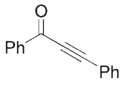
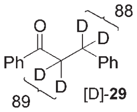
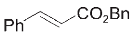
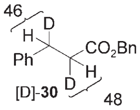
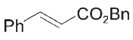
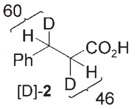
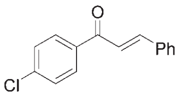
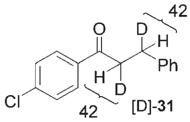
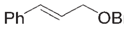
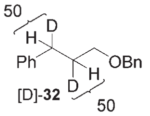
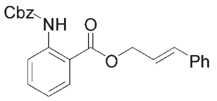
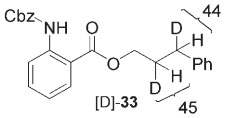
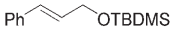
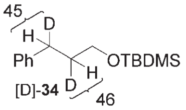
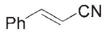
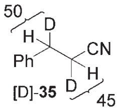
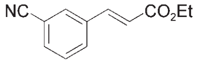
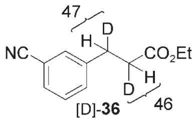
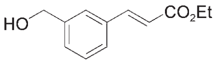
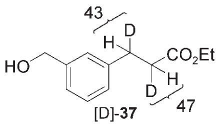
Chemoselective one-pot reductive deuteration by the addition of diphenyl sulfide: We have recently developed a Pd/C-catalyzed chemoselective hydrogenation method for olefins and acetylenes without the hydrogenolysis of other reducible functionalities by the addition of a very low loading (0.01 equiv) of diphenyl sulfide (Ph_2S) as a catalyst poison.[29] The chemoselective one-pot reductive deuterations of olefins and acetylenes in the presence of other reducible functionalities were investigated as follows: a suspension of 10 % Pd/C in D_2O was stirred at room temperature under an H_2 atmosphere for 24 h followed by the addition of Ph_2S (0.01 equiv) and the substrate (Table 6). Selective deuterogenation of the olefin and acetylene functions proceeded with excellent deuterium efficiencies without reduction of the aromatic carbonyl (entries 1, 3 and 6, Table 6), benzyl ester, ether and alcohol (entries 4, 7 and 12, Table 6), aromatic chloride (entry 6, Table 6), *N*-Cbz (entry 8, Table 6), TBDMS ether (entry 9, Table 6) and nitrile (entries 10 and 11, Table 6), although the complete reduction of the alkene as well as aromatic carbonyl (entry 2, Table 6) and benzyl ester (entry 5, Table 6) functions proceeded in the absence of Ph_2S. The one-pot chemoselective deuterogenation of the alkene and alkyne moieties was achieved with a variety of reducible functionalities, including aromatic nuclei, remaining intact.

Reaction mechanism: A plausible mechanism of the Pd/C-catalyzed H_2–D_2 exchange reaction is illustrated in Scheme 3. We assumed that the oxidative addition of the H_2-adsorbed (activated) Pd^0 (**A**) to D_2O would give a Pd^{II} species (**B**), and the subsequent exchange reaction between D derived from D_2O and H from H_2 followed by the reductive elimination would afford the corresponding Pd^0–HD (**C**) and DHO. The liberation of D_2 and regeneration of Pd^0 should be achieved by following a similar process through **D** and **E**.

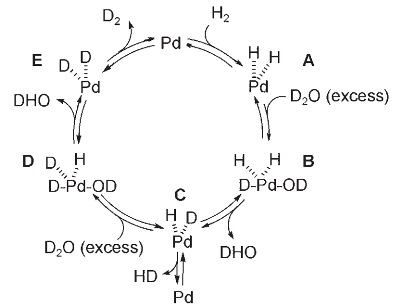
It is noteworthy that the H_2–D_2 exchange efficiency was drastically decreased using the low-purity D_2O as the deuterium source (Table 7, see also

Table 6. Chemoselective one-pot deuterogenation using Ph_2S as an additive.[a]



Entry	Substrate	$[D_n]$-Product (D content, %)[b]	Yield[c] [%]
1		 [D]-**27**	91
2[d]		 [D]-**28**	88
3[e]		 [D]-**29**	90
4[f]		 [D]-**30**	85
5[d]		 [D]-**2**	96
6		 [D]-**31**	90
7		 [D]-**32**	92
8		 [D]-**33**	59
9		 [D]-**34**	84
10		 [D]-**35**	90
11[g]		 [D]-**36**	83
12[h]		 [D]-**37**	86

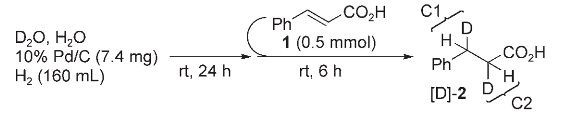
[a] 10 % Pd/C (10 wt % of the substrate) in D_2O (3 mL, 166 mmol) was stirred under H_2 atmosphere (160 mL, 6.5 mmol) at room temperature for 24 h, the substrate (0.5 mmol) and Ph_2S (0.01 equiv) were added, and the reaction was quenched after 24 h. [b] D content was determined by ^1H NMR spectroscopy on the basis of the integration of the aromatic protons. [c] Yield of isolated product. [d] Without Ph_2S. [e] 30 wt % of the substrate of 10 % Pd/C and 5 mL of D_2O (276 mmol) were used. [f] 20 wt % of the substrate of 10 % Pd/C was used. [g] 0.25 mmol of substrate, 0.02 equivalents of Ph_2S, 30 wt % of the substrate of 10 % Pd/C, and 5 mL of D_2O (276 mmol) were used. [h] 0.25 mmol of substrate, 30 wt % of the substrate of 10 % Pd/C and 5 mL of D_2O (276 mmol) were used.



Scheme 3. Proposed mechanism.

Scheme 3). Only 30 % and 26 % deuterium efficiencies were observed at the C1 and C2 positions, respectively, in 90 % D_2O (entry 2, Table 7), and 50 % D_2O led to virtually no incorporation of deuterium (entry 4, Table 7). Since a decrease in the purity of D_2O caused a significant drop in the H_2–D_2 exchange efficiency, an excess amount of D_2O (3 mL, 166 mmol) might be required to circumvent the drastic degradation of the D_2O purity.

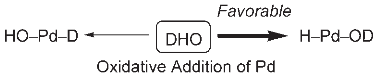
Table 7. Change of H_2–D_2 exchange efficiency using low-purity D_2O.[a]



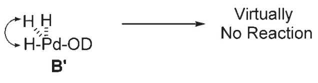
Entry	D_2O [mL]	H_2O [mL]	D content [%][b] C1	D content [%][b] C2	Yield[c] [%]
1	3.0	0	48	46	93
2	2.7	0.3	30	26	98
3	2.1	0.9	13	12	94
4	1.5	1.5	5	6	98
5	0.9	2.1	0	0	95

[a] 10 % Pd/C (10 wt % of **1**) in mixed solvents (3 mL) of H_2O and D_2O was stirred under H_2 atmosphere (160 mL, 6.5 mmol) at room temperature for 24 h, *trans*-cinnamic acid (**1**) (0.5 mmol) was added, and the reaction was quenched after 6 h. [b] D content was determined by ^1H NMR spectroscopy on the basis of the integration of the aromatic protons. [c] Yield of isolated product.

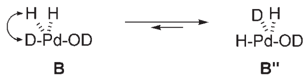
These results were also considered from a mechanistic point of view based on the isotope effect between H and D. The oxidative addition of Pd to DHO should proceed preferably and H–Pd–OD would predominantly form via insertion to the O–H bond rather than the O–D bond [Eq. (2)] . Similarly, complex **B′** could be generated by the oxidative addition of the H_2-activated Pd^0 (**A**, Scheme 3) to DHO and virtually no reaction was observed as a result of the "possible" H–H exchange of **B′** [Eq. (3)] . Therefore, the formation of complex **B** derived from D_2O and **A** (Scheme 3, **A** → **B**) should be necessary to generate HD [Eq. (4)] . The oxidative addition of the HD-activated Pd^0 (**C**, Scheme 3) with D_2O (Scheme 3, **C** → **D**) gave the complex **D**, which would undergo the intramolecular H–D exchange, leading to D_2 generation via complex **D″** [Eq. (5)] . On the other hand, the oxidative addition of **C** to DHO would give the complex **D′**, but virtually no reaction would proceed by the favorable H–H exchange on **D′** [Eq. (6)] . Similarly, the existence of H_2O would result in no reaction after the complexation by oxidative addition of Pd species **A** or/and **C** followed by the intramolecular H–H exchange. The use of excess D_2O compared with the H_2 volume should be required for the efficient generation of pure D_2.



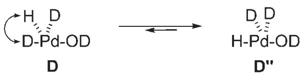
(2)



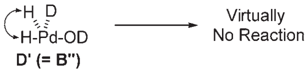
(3)



(4)



(5)



(6)

Conclusion

We have demonstrated the Pd/C-catalyzed H_2–D_2 exchange reaction between D_2O and H_2 and its application to the preparation of deuterium-labeled compounds. H_2 sealed in the reaction flask was efficiently converted into pure D_2, which can be used for the one-pot reductive deuteration of a variety of reducible functionalities. Furthermore, the chemoselective deuterogenation of olefins and acetylenes was accomplished by the addition of a trace amount of Ph_2S with retention of the various other reducible functionalities. A method of capturing the generated D_2 gas was also developed. The significant features of the H_2–D_2 exchange reaction are efficiency, inexpensiveness, environmental friendliness and convenience. These novel methodologies related to the D_2 generation should contribute to many chemistry fields.

Experimental Section

General: 10 % Pd/C was purchased from Sigma-Aldrich Co. (Lot. 05718BC). D_2O (>99.9 % D atom) was obtained from Cambridge Isotope Laboratories, Inc. or Spectra Gases, Inc. All other reagents were purchased from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on pre-coated Silica Gel 60 F_{254} plates (Merck, Art 5715) and visualized with

UV light. Flash column chromatography was accomplished using a Silica Gel 60 (Merck; 230–400 mesh) or Silica Gel 60N (Kanto Chemical Co., Inc.; 63–210 μm, spherical, neutral). The ^{1}H, ^{2}H and ^{13}C NMR spectra were recorded by a JEOL AL 400 spectrometer or a JEOL EX 400 spectrometer. The chemical shifts (δ) are expressed in ppm and are internally referenced to tetramethylsilane or residual solvents (7.27 ppm/$CHCl_3$, 3.30 ppm/CH_3OH, 4.75 ppm/H_2O and 1.93 ppm/MeCN for ^{2}H NMR). Elemental analyses were performed using a YANACO CHN CORDER MT-5 instrument. The EI and FAB mass spectra were taken by a JEOL JMS-SX102 A instrument at the Mass Spectrometry Laboratory of the Gifu Pharmaceutical University. The pressurized reactions were carried out using a Hyper-glass cylinder (purchased from Taiatsu Techno Co.). In the mass spectra data, $M(D_2)$ indicates the molecular ion peak of deuterated product with two deuterium atoms, and $M(D_0)$ indicates the peak of non-deuterated product.

The procedure for the one-pot reductive deuteration using the Pd/C–D_2O–H_2 system: Table 2, entry 1**;** 10% Pd/C (7.4 mg, 10 wt% of **1**) and D_2O (3 mL, 166 mmol) were placed in a 100 mL round-bottom flask (actual internal volume of the flask is 160 mL). The system was sealed with a septum and filled with H_2 using five vacuum/H_2 cycles. The mixture was stirred at room temperature for 24 h and *trans*-cinnamic acid (**1**) (74.1 mg, 0.5 mmol) as a 0.5 mL MeOH solution was added. The mixture was stirred at room temperature for 6 h, diluted with Et_2O (10 mL) and passed through a membrane filter (Millex-LH, 0.45 μm). The filtrate was separated into two layers. The aqueous layer was extracted with Et_2O (2×15 mL) and the combined ethereal layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give the analytically pure dideuterocinnamic acid ([D]-**2**; 73.5 mg, 98%) as a colorless oil. The D content was determined by ^{1}H NMR spectroscopy on the basis of the integration of the aromatic protons. No deuterium incorporation at the aromatic ring was confirmed by ^{2}H NMR spectroscopy.

Data for [D]-2: ^{1}H NMR (400 MHz, CD_3OD): $\delta = 2.47$ (m, 1.07 H), 2.79 (m, 1.01 H), 7.05–7.18 ppm (m, 5 H, Ph); ^{2}H NMR (60.7 MHz, CH_3OH): $\delta = 2.56$ (br s), 2.87 ppm (br s); MS (EI): m/z (%): 152 (50) $[M(D_2)]^+$, 151 (15) $[M(D_1)]^+$, 150 (2) $[M(D_0)]^+$, 106 (60), 92 (100).

Table 4, entry 1: 10% Pd/C (7.8 mg, 10 wt% of 4-chlorobenzoic acid) and D_2O (3 mL, 166 mmol) were placed in a 100 mL round-bottom flask (actual internal volume of the flask is 160 mL). The system was sealed with a septum and filled with H_2 using five vacuum/H_2 cycles. The mixture was stirred at room temperature for 24 h and 4-chlorobenzoic acid (78.0 mg, 0.5 mmol) as a 0.5 mL MeOH solution and Et_3N (83.6 μL, 0.6 mmol) were added. The mixture was stirred at room temperature for 24 h, diluted with Et_2O (10 mL), and passed through a membrane filter (Millex-LH, 0.45 μm). The filtrate was neutralized using a 5% $NaHSO_4$ aqueous solution and extracted with Et_2O (2×15 mL). The ethereal layers were washed successively with water (10 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an analytically pure 4-deuterobenzoic acid ([D]-**14**; 48.4 mg, 79%) as a colorless solid. The D content was determined by ^{1}H NMR of the corresponding methyl ester on the basis of the integration of the methyl protons.

Data for methyl ester of [D]-14: ^{1}H NMR (400 MHz, CD_3OD): $\delta = 3.93$ (s, 3 H), 7.49 (d, $J = 5.9$ Hz, 2 H), 7.62 (m, 0.060 H), 8.04 ppm (d, $J = 5.9$ Hz, 2 H); MS (EI): m/z (%): 137 (42) $[M(D_1)]^+$, 136 (9) $[M(D_0)]^+$, 106 (100), 78 (54).

The method of capturing the generated D_2 in situ and the application to the reductive mono-*N*-alkylation using nitrile: Scheme 2**;** A suspension of 10% Pd/C (50.0 mg) in D_2O (10 mL, 553 mmol) in a 96 mL Hyper-glass cylinder was stirred under 3 atm of H_2 pressure (internal H_2 is ca. 260 mL under atmospheric pressure) at room temperature for 48 h. The generated D_2 gas was captured using a rubber balloon (ca. 170 mL). A mixture of nitrobenzene (61.6 mg, 0.5 mmol) and 10% Pd/C (12.3 mg, 20 wt% of the nitrobenzene) in CD_3CN (D content: 99.8%, 0.75 mL, 14.4 mmol) in a test tube was stirred under the captured D_2 (balloon) at room temperature for 24 h. The reaction mixture was diluted with Et_2O (30 mL), and passed through a membrane filter (Millex-LH, 0.45 μm). The filtrate was concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane:Et_2O = 20:1) to give [D_5]-*N*-ethylaniline ([D]-**26**; 48.1 mg, 79%) as a colorless oil. The D content was determined by ^{1}H NMR spectroscopy on the basis of the integration of the aromatic protons. No deuterium incorporation at the aromatic ring was confirmed by ^{2}H NMR spectroscopy.

Data for [D]-26: ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.15$ (m, 0.03 H), 3.06 (d, $J = 7.2$ Hz, 0.33 H), 6.59–6.64 (m, 3 H), 7.08 ppm (m, 2 H); ^{2}H NMR (60.7 MHz, CH_3OH): $\delta = 1.15$ (br s), 3.04 ppm (br s); MS (EI): m/z (%): 126 (44) $[M(D_5)]^+$, 125 (36) $[M(D_4)]^+$, 124 (12) $[M(D_3)]^+$, 123 (17) $[M(D_2)]^+$, 122 (8) $[M(D_1)]^+$, 121 (13) $[M(D_0)]^+$, 108 (100), 107 (56).

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