

Efficient and Selective Pt/C-Catalyzed H–D Exchange Reaction of Aromatic Rings

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An effective and applicable deuteration method for aromatic rings using Pt/C–D_2O–H_2 system was established. Especially, phenol was fully deuterated even at room temperature, and other electron-rich aromatic nuclei were efficiently deuterated under mild conditions. The scope and limitations of the presence method and its application to the synthesis of deuterium-labeled biologically active compounds and deuterium-labeled building blocks for practical multi-gram scale syntheses are reported.

Deuterium-labeled compounds are extremely useful in a variety of scientific fields, such as analytical tools of drug metabolism, reaction mechanisms and kinetics.[1] Since a large number of biologically active compounds possess aromatic rings, post-synthetic incorporation of deuterium by hydrogen isotope-exchange reactions on the aromatic rings is an important technique. Especially, H–D exchange reactions using D_2O as a deuterium source are a cost-wise attractive method. A number of H–D exchange procedures for aromatic compounds in D_2O have been reported, for example, the H–D exchange reaction catalyzed by acids,[2] bases,[3] or transition metals (Ir,[4] Ru,[5] Rh,[6] Pd,[7] and Pt[8]) and supercritical[9] or microwave-enhanced[5a,5b,8g,10] exchange reactions. However, many of these methods have problems, such as low deuterium efficiency, severe reaction conditions that functional groups cannot tolerate, requirement of a large amount of catalyst and/or the use of special apparatuses.

We have recently developed an 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 H_2 gas at room temperature.[11] We have also found that heating increases the catalytic activity of the Pd/C–D_2O–H_2 system and leads to H–D exchange even at an inactive carbon.[12] During the course of our studies investigating the carbon-supported transition metal-dependent catalyst efficiency of deuteration reactions, we have found that the H–D exchange reaction on an aromatic ring is efficiently catalyzed by Pt/C.[13] Herein, we provide detailed results as well as the scope and limitations of the deuterium incorporation into aromatic rings by the Pt/C–D_2O–H_2 system.

Results and Discussion

Typically, the reactions were carried out in a sealed tube, illustrated in Fig. 1. After two vacuum/H_2 cycles to replace air with H_2 gas in the sealed tube, a mixture of the aromatic compound (500 mg) and 5% Pt/C (100 mg, 20 wt % of the substrate) in D_2O (17 mL) was stirred while heating from room temperature (ca. 1 atm) to 180 °C (ca. 4.5 atm by expansion of the filled hydrogen gas and increased vapor pressure of D_2O by means of heating; the inner gas pressure was measured by a pressure gauge) for 24 h. The deuterated position and deuterium efficiency of the obtained products were determined by using ^{1}H NMR spectroscopy with an appropriate internal standard and confirmed by using ^{2}H NMR and mass spectroscopy. It is noteworthy that even water (D_2O)-insoluble substrates were also deuterated effectively, meaning that the hydrophilicity of the substrate does not affect the H–D exchange reaction.

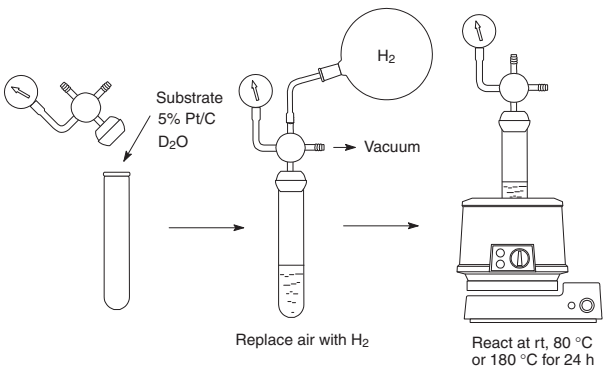
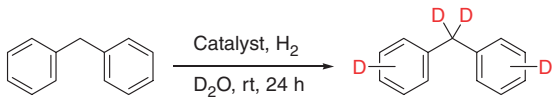


Fig. 1. Typical reaction procedure in a sealed tube.

To explore efficient heterogeneous catalysts for the H–D exchange reaction on an aromatic ring, diphenylmethane was chosen as a model substrate, and Table 1 summarizes a comparison of the deuterium efficiencies using various heterogeneous catalysts. The 10% Pd/C (10 wt %, 1 wt % as Pd metal)-catalyzed reaction of diphenylmethane at room temperature in a sealed tube lead to chemoselective and efficient deuterium incorporation on the benzylic position within 24 h (Entry 1). On the other hand, the use of 5% Pt/C (20 wt %, 1 wt % as Pt metal) as a catalyst lead to good deuterium efficiency

Published on the web February 12, 2008; doi:10.1246/bcsj.81.278

Table 1. Comparison of Deuterium Efficiency of Diphenylmethane Using Various Catalysts at Room Temperature[a)]



Entry	Catalyst (wt %)	D content/%[b)]		Yield[c)] /%
		Phenyl	Benzyl	
1	10% Pd/C (10%)	0	98	88
2	5% Pt/C (20%)	51	24	72
3[d)]	5% Pt/C (20%)	97	96	88
4[e)]	5% Pt/C (20%)	20	14	100
5	PtO_2 (2%)	26	14	78
6	5% Rh/C (20%)	0	0	44
7	5% Ru/C (20%)	0	0	70
8	Raney-Ni (10%)	0	11	80

a) Diphenylmethane 500 mg (3.0 mmol) was used, and all reactions were carried out under ordinary H_2 pressure in D_2O (17 mL) in a sealed tube. b) Determined by using ^1H NMR. c) Isolated yield. d) The reaction was carried out at 180 °C. e) The reaction was carried out at 180 °C without H_2 gas (under N_2 atmosphere).

(51%) on the aromatic ring despite lower deuterium efficiency (24%) on the benzylic position (Entry 2). The deuterium efficiency on the aromatic ring was reduced when Adam's catalyst (PtO_2) was used (Entry 5). Other heterogeneous catalysts, such as 5% Rh/C, 5% Ru/C, and Raney-Ni, showed no H–D exchange activity toward the aromatic ring at room temperature (Entries 6–8). As expected, heating the reaction mixture using 5% Pt/C as a catalyst at 180 °C led to high deuterium efficiencies on the both aromatic ring and benzylic position (Entry 3). However, the deuterium efficiency was drastically reduced when the reaction was performed without H_2 (under N_2 atmosphere) even at 180 °C, suggesting that H_2 gas plays an important role in the Pt/C-catalyzed H–D exchange reaction (Entry 4). Consequently, we decided to study the details of the catalyst activity of Pt/C in the H–D exchange reaction concerning aromatic compounds possessing various substituents.

First, we investigated the deuteration of aromatic compounds possessing an electron-donating group (Table 2). Surprisingly, nearly quantitative deuterium incorporation was observed in the case of phenol even at room temperature (ca. 20 °C) (Entry 1). Although the acidic protons, such as OH in the phenols and NH in the anilines, also underwent H–D exchange, the incorporated deuterium was depleted by aqueous workup. No deuterium incorporation was observed in the absence of hydrogen gas, i.e., under nitrogen atmosphere, or Pt/C (Entries 2 and 3), indicating both H_2 gas and Pt/C are indispensable for the H–D exchange reaction in the present system.[11,12a,12f] Moreover, when the reaction was performed under D_2 atmosphere in H_2O, instead of H_2 in D_2O, there was a significant decrease in the deuterium efficiency (Entry 4). This result indicated that, although D_2 gas should be generated via the Pt/C-catalyzed H_2–D_2 exchange reaction between D_2O and H_2 gas during the H–D exchange reaction, as we have reported in the previous report,[14] the formation of D_2 gas did not seem to be necessary for the presence H–D displacement. In addition, D_2O is obviously necessary for the present system as a deuterium source. Pyrocatechol was well deuterated at room temperature, and fully deuterated pyrocatechol-d_4 was obtained at 80 °C (Entries 5 and 6). In addition, 2-*n*-propylphenol was regioselectively deuterated at C1, C2, and C3 of the aromatic ring at room temperature (Entry 7). Similarly, C1 of 4-*n*-propylphenol was deuterated quantitatively, but low deuterium efficiency was observed at C2 not only at room temperature but also at 80 °C (Entries 9 and 10). The low deuterium efficiency of the *ortho* positions of the alkyl chain is probably caused by the steric hindrance of the alkyl chain.[15,16] The efficiency of the H–D exchange reaction seems to be greatly enhanced at higher reaction temperatures, and fully deuterated 2,6-dimethylphenol-d_9 and *o*-aminophenol-d_4 were obtained at 180 °C (Entries 11 and 13). A substrate possessing an ether substituent gave lower deuterium efficiency at the positions *ortho* to the substituents on the aromatic ring, together with slight deuterium incorporation at the ether methyl group (Entries 14 and 15).

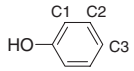
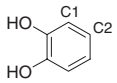
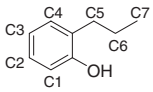
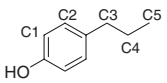
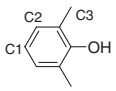
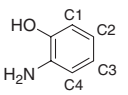
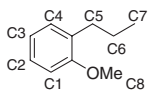
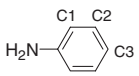
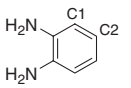
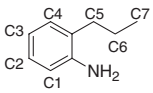
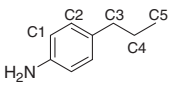
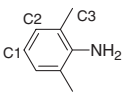
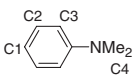
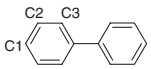
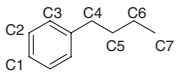
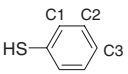
The H–D exchange reaction of aniline derivatives also occurred smoothly under mild conditions as with the phenol derivatives (Entries 16–26). Especially, fully deuterated aniline-d_5 and *o*-phenylenediamine-d_4 were easily obtained, even at 80 °C (Entries 17 and 19), and fully deuterated 2,6-xylidine-d_9 was afforded at 180 °C (Entry 25). When 4-*n*-propylaniline was used as the substrate, regioselective deuteration at C1 was observed at room temperature (Entry 22). In addition, the NMe_2 group of *N*,*N*-dimethylaniline was moderately deuterated at 180 °C, whereas higher deuterium efficiency on the aromatic ring was achieved (Entry 26).

Biphenyl and *n*-butylbenzene were also well deuterated by this system (Entries 27–29). Especially, Pt/C had excellent catalytic activity toward biphenyl, and fully deuterated biphenyl-d_{10} was obtained at 80 °C (Entry 28). However, deuterium was hardly incorporated when thiophenol was used as a substrate (Entry 30), probably because the sulfur atom acted as a catalytic poison for Pt/C, thus suppressing the H–D exchange reaction.

Next, we investigated the deuteration of the aromatic compounds possessing an electron-withdrawing group (Table 3). Although benzoic acid was not efficiently deuterated at C1 at 80 °C, fully deuterated benzoic acid-d_5 was obtained at higher temperature (180 °C) (Entries 1 and 2). The increase in the number of carboxyl substituents on the aromatic ring prevented the progress of the H–D exchange reaction (compare Entries 2, 4, and 5). In addition, 4-*t*-butylbenzoic acid, possessing a bulky substituent, showed almost no deuterium efficiency at C2 due to the steric hindrance of the *t*-butyl group (Entry 6). It is also worth noting that the carboxylic acid and ester functionalities tolerate the 5% Pt/C-catalyzed H–D exchange reaction conditions even when the reaction mixture was heated up to 180 °C in the aqueous (D_2O) medium (Entries 1–6).[17] Nitrobenzene possessing a strong electron-withdrawing nitro group was scarcely deuterated even at 180 °C (Entry 7). In the cases of the H–D exchange of the phenol derivatives possessing electron-withdrawing functionalities, such as *p*-nitrophenol and *o*-cyanophenol, the deuterium efficiency was much lower (Entries 8 and 9). In addition, the use of bromobenzene gave no deuterium efficiency, which was unfortunately accompanied by the partial hydrogenolysis of the bromine atom. These

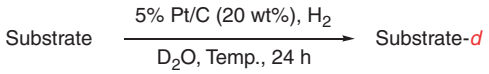
Table 2. Deuteration of Various Aromatic Compounds Possessing an Electron-Donating Group[a)]

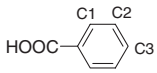
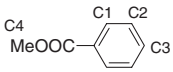
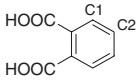
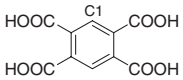
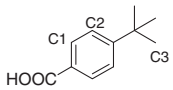
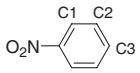
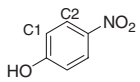
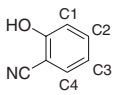
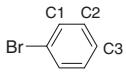
Substrate —(5% Pt/C (20 wt%), H_2; D_2O, Temp., 24 h)→ Substrate-*d*

Entry	Substrate	Temp /°C	D content/%[b)] C1	C2	C3	C4	C5	C6	C7	C8	Yield[c)] /%
1		rt	97	98	97						63[d)]
2[e)]		rt	0	0	0						100
3[f)]		rt	0	0	0						100
4[g)]		rt	5	5	5						65
5		rt	81	98							64
6		80	98	98							59
7		rt	99	99	99	0	8	0	0		92
8		80	98	98	98	38	91	23	8		76
9		rt	99	24	20	4	0				82
10		80	97	68	91	31	11				76
11		180	98	97	98						49
12		80	96	75	87	97					62
13		180	97	97	97	97					62
14		80	29	99	99	35	93	23	13	16	42
15		180	49	98	98	56	97	58	29	15	62
16		rt	96	45	49						53
17		80	98	98	98						66
18		rt	21	79							58
19		80	98	98							66
20		rt	93	7	8	7	1	0	0		86
21		80	99	98	98	38	71	16	6		69
22		rt	98	0	3	0	0				63
23		180	97	87	97	73	34				69
24		80	97	88	79						59
25		180	98	99	97						85
26		180	98	81	98	59					36
27		rt	86	85	33						73
28		80	98	98	97						64
29		180	97	97	97	97	98	86	78		73
30		160	<10	<10	<10						58

a) 500 mg (3.2–5.4 mmol) of the substrate was used, and reactions were carried out under ordinary H_2 pressure using 5% Pt/C (100 mg, 20 wt % of the substrate) in D_2O (17 mL) in a sealed tube. b) D contents were determined by using ^{1}H NMR and confirmed by using ^{2}H NMR and mass spectrum. c) Isolated yield. d) The moderate isolated yield (63%) was attributed to the coincident reduction of the benzene ring. e) Without H_2 gas. f) Without 5% Pt/C. g) The reaction was performed under D_2 atmosphere in H_2O instead of H_2 in D_2O.

Table 3. Deuteration of Various Aromatic Compounds Possessing an Electron-Withdrawing Group[a)]



Entry	Substrate	Temp /°C	D content/%[b)] C1	C2	C3	C4	Yield /%[c)]
1[d)]		80	38	98	98		70
2		180	97	98	98		66
3[d)]		180	64	99	98	19	58
4[d)]		180	64	99			51
5[d)]		180	22				92
6[d)]		180	93	1	7		100
7		180	0	2	3		64
8		180	67	4			77
9		180	80	38	78	10	64
10		160	0	0	0		56

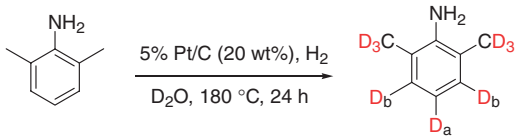
a) 500 mg (2.0–4.2 mmol) of the substrate was used, and reactions were carried out under ordinary H_2 pressure using 5% Pt/C (100 mg, 20 wt % of the substrate) in D_2O (17 mL) in a sealed tube. b) D contents were determined by using ^{1}H NMR and confirmed by using ^{2}H NMR and mass spectrum. c) Isolated yield. d) In the case of carboxylic acids, D contents were determined by ^{1}H NMR after the conversion of the carboxylic acids to the methyl esters on the basis of the integration of the methyl protons.

results demonstrate that the Pt/C-catalyzed H–D exchange reaction is affected by both electronic and steric factors.

Two of the advantages of heterogeneous catalysts is that it is easy to separate the catalyst from the reaction mixture and the catalyst can be reused, and so, we investigated them in our system using 2,6-xylidine as a substrate (Table 4). The catalyst could be recovered almost quantitatively after simple filtration, and it could be reused without further purification. The recovered 5% Pt/C was effective in the 2nd and 3rd runs, and the isolated yields and deuterium efficiencies were comparable to those of the first run.

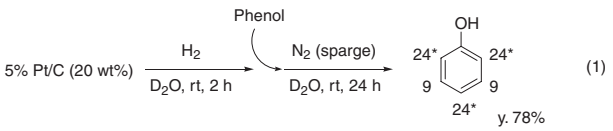
Reaction Mechanism. As shown in Table 2, Entry 2, the H–D exchange reaction does not proceed in the absence of H_2 gas. To investigate the role of H_2 gas, the reaction was performed under N_2 atmosphere after activation of 5% Pt/C by H_2. First, 5% Pt/C (100 mg, 20 wt % of phenol) was suspended in D_2O (17 mL) in a sealed tube and stirred under H_2 atmosphere for 2 h at room temperature to adsorb H_2 onto the Pt surface. Then, the tube was purged with N_2 gas to replace H_2, which probably contained HD and/or D_2,[14] and phenol (500 mg, 5.31 mmol) was added into the suspension. The mixture was stirred at room temperature for 24 h (Scheme 1, Eq. 1). The H–D exchange reaction proceeded even under N_2 atmosphere, although the deuterium efficiency of the product was modest in comparison with the result of Table 2, Entry 1. The deuterium efficiency greatly improved (98%) by heating at 160 °C under N_2 atmosphere (Eq. 2). These results indicate that the Pt surface must be activated using H_2 gas for the H–D exchange reaction to occur and the activated Pt/C would lead to excellent deuteration by heating even under N_2 atmosphere. Furthermore, the H–D exchange reaction using a nonaromatic substrate, such as octanoic acid, afforded almost no deuterium incorporation even at 180 °C (Scheme 2).

Table 4. Reuse of 5% Pt/C in the H–D Exchange Reaction of 2,6-Xylidine[a)]

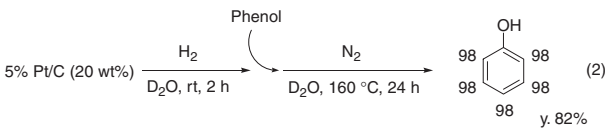


Run	D content/%[b)] D_a	D_b	CD_3	Yield[c)] /%
1st	98	99	97	85
2nd	97	97	97	75
3rd	97	97	97	88

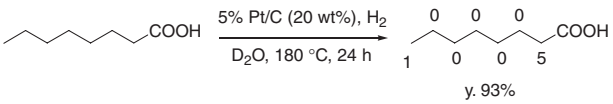
a) 2,6-Xylidine (500 mg, 4.1 mmol) was used, and the reaction was carried out under ordinary H_2 pressure using 5% Pt/C (100 mg) in D_2O (17 mL) in a sealed tube. b) Determined by using ^{1}H NMR. c) Isolated yield.



* Indicate as the average D content.

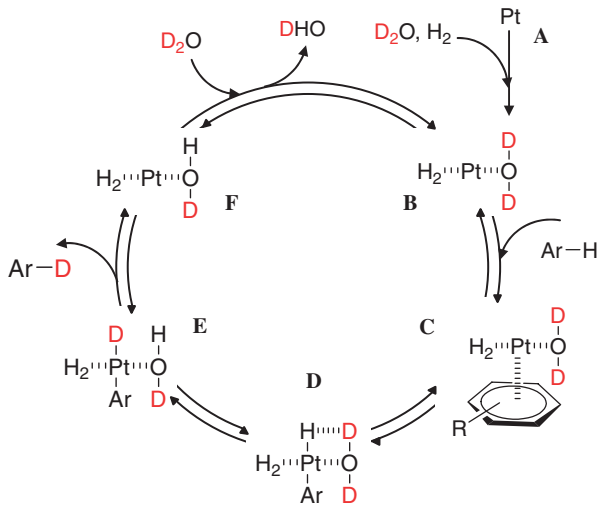


Scheme 1. Role of H_2 in the H–D exchange reaction.



Scheme 2. H–D exchange reaction of a nonaromatic substrate.

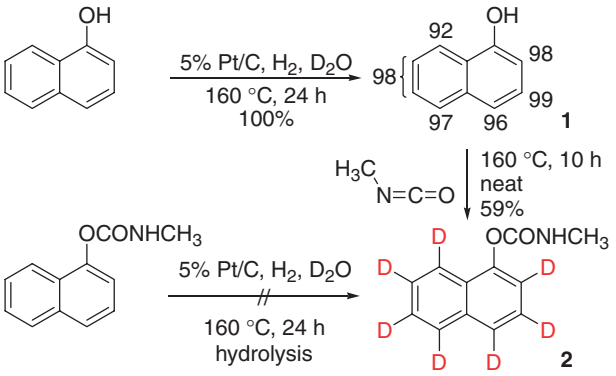
Although it is possible that electrophilic aromatic substitution occurs in this system, we propose the following reaction mechanism based upon oxidative addition of the aromatic carbon–hydrogen bond to Pd, as shown in our previous results of H–D exchange reaction of alkyl side chains of alkyl-substituted benzene derivatives using Pd/C as a catalyst



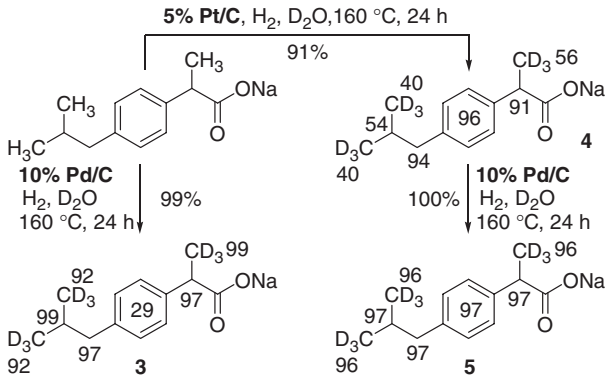
Scheme 3. Mechanism for the H–D exchange with the Pt/C–D_2O–H_2 system.

(Scheme 3).[12a,12f] First, 5% Pt/C is activated with a small amount of H_2 gas, which probably acts as a type of ligand for Pt. Namely, the first step involves the activation of Pt^0 (**A**) by the coordination of H_2 gas and D_2O to form complex **B**. Oxidative addition of the Ar–H bond to activated Pt^0 species **B** would then take place to form a Pt–π-aryl complex (**C**), followed by the formation of Pt^{II} complex **D**. Intramolecular H–D exchange (**D** to **E**) and subsequent reductive elimination (**E** to **F**) would give the corresponding deuterated product Ar–D. In this reaction, the formation of the Pt–π-aryl complex (**C**) is probably a key step in the oxidative insertion of Pt^0 into the substrate, since a nonaromatic compound, octanoic acid, was not deuterated (Scheme 2). In addition, the introduction of electron-donating functionalities on the aromatic ring promoted the H–D exchange activity (Table 2), whereas electron-withdrawing functionalities caused a reduction in the deuterium efficiency, thus supporting our proposed mechanism (Table 3).

Synthesis of Deuterium-Labeled Compounds. Aromatic compounds are often seen in biologically active compounds, such as drugs, pesticides, environmental pollutants, and so on. Therefore, such deuterated compounds are valuable as a surrogate compound (internal standard) for clinical pharmacokinetic studies and the microanalysis of residual agrochemicals and environmental endocrine-disrupting chemicals in the environment using GC-MS or LC-MS.[18] Since surrogate compounds should possess physical properties nearly equal to those of the mother samples, multi-deuterated mother samples can be employed for such purpose. Therefore, we applied the Pt/C–D_2O–H_2 system to the synthesis of multi-deuterium-labeled carbaryl (=1-naphthyl *N*-methylcarbamate), which is a known bactericide in domestic animals. Carbaryl-d_7 can be applied as a surrogate compound to the microanalysis of residual carbaryl in meat. As illustrated in Scheme 4, the direct H–D exchange of carbaryl was unsuccessful, because carbaryl was not stable enough under the aqueous deuteration conditions. Carbaryl-d_7 was prepared in two steps starting from 1-naphthol in a good chemical yield (59% two steps total yield) and with a quantitative deuterium efficiency without significant over-reduction of the aromatic ring.



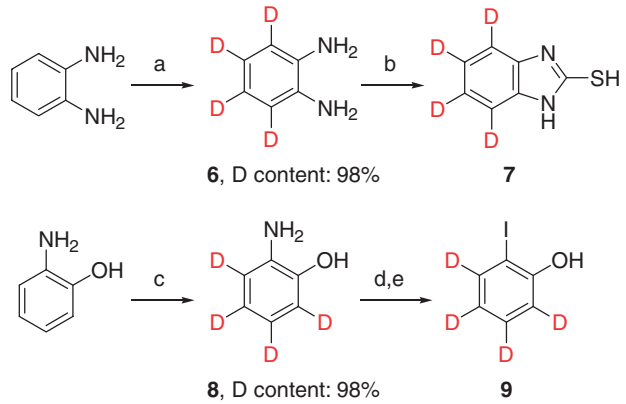
Scheme 4. Synthesis of carbaryl-d_7 as a surrogate compound.



Scheme 5. Stepwise synthesis of ibuprofen-d_{17}.

We have recently reported that deuterium efficiently incorporated into the inactive alkyl side chains of ibuprofen (=(4-isobutylphenyl)-α-methylacetic acid), an anti-inflammatory drug, by using the 10% Pd/C-catalyzed H–D exchange reaction, whereas the deuterium efficiency of the aromatic ring was only 29% (Scheme 5, **3**).[12a] Consequently, we examined the stepwise deuteration of ibuprofen as a possible application of our system. Namely, deuteration using 5% Pt/C as a catalyst lead to high deuterium efficiency (96%) on the aromatic ring despite moderate deuterium efficiency (40%–56%) on the alkyl side chain **4**. Subsequent deuteration of intermediate **4** with 10% Pd/C gave the entirely deuterated product **5** in excellent yield.

As described above, various deuterium-labeled aromatic compounds, which are considered to be deuterium-labeled building blocks of such biologically active compounds and are not commercially available, could be obtained using the Pt/C–D_2O–H_2 system. For example, 2,6-dimethylphenol-d_9 (Table 2, Entry 11), *o*-aminophenol-d_4 (Entry 13), *o*-phenylenediamine-d_4 (Entry 19), 2,6-xylidine (Entry 25), and so on. Unfortunately, synthetically important sulfur-containing compounds and aryl halides could not be deuterated directly by our system. Consequently, we derived those derivatives from easily deuterated synthons, in order to extend our system to practical scale syntheses. Namely, deuteration of *o*-phenylenediamine (20 g) catalyzed by 5% Pt/C (4 g) under mild reaction conditions (80 °C under H_2 atmosphere) in a 1 L autoclave gave *o*-phenylenediamine-d_4 (Scheme 6, **6**, 13.8 g, 69%), and subsequent cyclization with carbon disulfide gave 2-sulfanyl-



Scheme 6. Syntheses of 2-sulfanylbenzimidazole-d_4 and *o*-iodophenol-d_4. Reagents and conditions: (a) 5% Pt/C (20 wt %), H_2, D_2O, 80 °C, 24 h, 69%; (b) CS_2, KOH, MeOH–H_2O, reflux, 67%; (c) 5% Pt/C (20 wt %), H_2, D_2O, 180 °C, 24 h, 71%; (d) $NaNO_2$, HCl, −2 °C, 1 h; (e) NaI, H_2O, 0–10 °C, 4 h, 62%.

benzimidazole-d_4 (**7**) in 67% yield, which is usable as a deuterium-labeled building block for the synthesis of a deuterated proton pump inhibitor. Similarly, deuteration of *o*-aminophenol, starting from 20 g of *o*-aminophenol and 14.7 g (71% yield) afforded *o*-aminophenol-d_4 (**8**), and iodination via diazotization, using 13.5 g of **8**, gave *o*-iodophenol-d_4 (**9**, 16.8 g, 62% yield), which is usable as a deuterium-labeled coupling synthon.

Conclusion

In summary, we developed an effective and highly applicable Pt/C-catalyzed deuteration method for aromatic rings using D_2O as a deuterium source under hydrogen atmosphere. The results made clear the scope and limitations of the aromatic ring-selective H–D exchange reaction. We showed that this system is efficient and is applicable as a post-synthetic deuteration method to prepare a variety of deuterated aromatic compounds. It could be also applied to the synthesis of biologically active compounds and deuterium-labeled building blocks for practical multi-gram scale syntheses.

Experimental

General Methods. All of the substances examined in this study were obtained commercially and were used without further purification. Pt/C (5%) was purchased from Wako Pure Chemical Industries or Aldrich Chemical Co., and deuterium oxide (99.9% isotopic purity) was purchased from Cambridge Isotope Laboratories. ^{1}H, ^{2}H, and ^{13}C NMR spectra were recorded on a JEOL ANM-AL400 spectrometer (^{1}H NMR: 400 MHz, ^{2}H NMR: 61 MHz, ^{13}C NMR: 100 MHz). Chemical shifts (δ) are given in parts per million relative to residual solvent or tetramethylsilane as an internal standard. The D content (%) of the substrates was estimated on the basis of the integration of the ^{1}H NMR spectra using appropriate internal standards. Since the relative signal intensity was found to depend on the pulse delay, the pulse delay was adjusted to 120 s to ensure complete relaxation occurred. Mass spectra and high-resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer. Silica-gel column chromatography was performed using Wakogel® C-200 (Wako Pure Chemical). Preparative thin-layer chromatography was performed using Merck PLC plate (silica gel 60 F254).

General Procedure for H–D Exchange Reaction Using Pt/C–D_2O–H_2 System. Substrates (500 mg, 2.0–5.4 mmol) and 5% Pt/C (100 mg, 20 wt % of the substrate) in D_2O (17 mL) was stirred at room temperature, 80 or 180 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (20 mL), and the mixture was filtered to remove the catalyst. The filtered catalyst was washed with diethyl ether (5 mL × 2). The combined ether layers were washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The obtained product was purified by silica-gel column chromatography, by preparative thin-layer chromatography or recrystallization. The D content (%) was determined by using ^{1}H NMR with dioxane, *p*-anisic acid, benzene, 1,2-dichloroethane, or 3-(trimethylsilyl)propanesulfonic acid sodium salt as an internal standard and confirmed by using ^{2}H NMR and mass spectrum.

[^{2}H]-Diphenylmethane (Table 1, Entry 2): Purification by silica-gel column chromatography (hexane) gave diphenylmethane-d_n as a colorless oil (72% yield). Isotope distribution (EIMS): 3% d_0, 5% d_1, 8% d_2, 13% d_3, 17% d_4, 19% d_5, 16% d_6, 10% d_7, 5% d_8, 2% d_9, 1% d_{10}; ^{1}H NMR (acetone-d_6, *p*-anisic acid as an internal standard) δ 7.26–7.17 (m, 4.90H), 3.96 (s, 1.53H); ^{2}H NMR (acetone) δ 7.29–7.20 (m), 3.94 (br d).

[^{2}H]-Phenol (Table 2, Entry 1): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/6) gave phenol-d_n as a colorless solid (63% yield). Isotope distribution (EIMS): 1% d_1, 1% d_2, 2% d_3, 16% d_4, 80% d_5; ^{1}H NMR (acetone-d_6, *p*-anisic acid as an internal standard) δ 7.18 (s, 0.05H), 6.83–6.81 (m, 0.09H); ^{2}H NMR (acetone) δ 7.20 (s), 6.85 (m).

[^{2}H]-Pyrocatechol (Table 2, Entry 6): H–D exchange reaction was carried out at 80 °C for 24 h. The reaction mixture was filtered to remove the heterogeneous catalyst, and the filtrate was concentrated in vacuo. The residue was purified by a preparative thin-layer chromatography (ethyl acetate/hexane = 1/2) to obtain catechol-d_n as a colorless solid (59% yield). Isotope distribution (EIMS): 1% d_2, 11% d_3, 88% d_4; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 6.81 (s, 0.04H), 6.67 (s, 0.04H); ^{2}H NMR (61 MHz, acetone) δ 6.84 (s), 6.70 (s).

[^{2}H]-2-*n*-Propylphenol (Table 2, Entry 8): H–D exchange reaction was carried out at 80 °C. Purification by silica-gel column chromatography (ethyl acetate/hexane = 1/10) gave 2-*n*-propylphenol-d_n as a colorless oil (76% yield). Isotope distribution (EIMS): 1% d_1, 1% d_2, 2% d_3, 11% d_4, 39% d_5, 28% d_6, 11% d_7, 4% d_8, 2% d_9, 1% d_{10}; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 7.07 (s, 0.62H), 6.99 (s, 0.02H), 6.81 (s, 0.02H), 6.74 (s, 0.02H), 2.56 (t, 0.19H), 1.60 (m, 1.54H), 0.93 (t, 2.76H); ^{2}H NMR (acetone) δ 7.09 (br s), 7.01 (br s), 6.83 (br s), 6.77 (br s), 2.54 (br s), 1.56 (br s), 0.86 (br s).

[^{2}H]-4-*n*-Propylphenol (Table 2, Entry 10): H–D exchange reaction was carried out at 80 °C. Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave 4-*n*-propylphenol-d_n as a pale yellow oil (76% yield). Isotope distribution (EIMS): 1% d_0, 2% d_2, 2% d_3, 5% d_3, 12% d_4, 26% d_5, 27% d_6, 13% d_7, 6% d_8, 3% d_9, 2% d_{10}; ^{1}H NMR ($CDCl_3$, *p*-anisic acid as an internal standard) δ 7.03 (s, 0.63H), 6.74 (s, 0.04H), 2.49 (t, 0.17H), 1.58 (m, 1.38H), 0.92 (t, 2.68H); ^{2}H NMR ($CHCl_3$) δ 7.08 (br s), 6.81 (br s), 2.50 (br s), 1.57 (br s), 0.88 (br s).

[^{2}H]-2,6-Dimethylphenol (Table 2, Entry 11): Purification by silica-gel column chromatography (ethyl acetate/hexane = 1/20) gave 2,6-dimethylphenol-d_n as a colorless solid (49% yield). Isotope distribution (EIMS): 1% d_5, 3% d_6, 16% d_7, 17% d_8, 57% d_9, 5% d_{10}; ^{1}H NMR (acetone-d_6, dioxane as an internal

standard) δ 7.14 (s, 1H), 6.91 (s, 0.05H), 6.65 (s, 0.02H), 2.18 (m, 0.15H); ^{2}H NMR (acetone) δ 6.94 (s), 6.67 (s), 2.16 (s).

[^{2}H]-*o*-Aminophenol (Table 2, Entry 13): H–D exchange reaction was carried out at 180 °C. Recrystallization from ethyl acetate gave *o*-aminophenol-d_n as a brown crystal (62% yield). Isotope distribution (EIMS): 1% d_1, 2% d_2, 16% d_3, 81% d_4; ^{1}H NMR (DMSO-d_6, *p*-anisic acid as an internal standard) δ 8.88 (br s, 1H), 6.63–6.53 (m, 0.10H), 6.39 (s, 0.03H); ^{2}H NMR (DMSO) δ 6.58 (br s), 6.42 (br s).

2-*n*-Propylanisole (Substrate of Table 2, Entries 14 and 15): To a stirred mixture of 2-*n*-propylphenol (10 g, 73.4 mmol) and NaH (60% w/w in mineral oil, 3.5 g, 88.1 mmol) in DMF (70 mL) was added methyl iodide (12.5 g, 88.1 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with diethyl ether (150 mL). The ether layer was washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was applied to a silica-gel column chromatography (ethyl acetate/hexane = 1/40) to obtain 2-*n*-propylanisole (11.0 g, 100% yield) as a colorless oil. ^{1}H NMR (acetone-d_6) δ 7.16–7.10 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 6.84 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 1.58 (hex, J = 7.6 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 158.1, 131.1, 130.3, 127.5, 120.8, 111.0, 55.5; HRMS: calcd for $C_{10}H_{14}O$: 150.1045, found: 105.1046.

[^{2}H]-2-*n*-Propylanisole (Table 2, Entry 15): H–D exchange reaction was carried out at 180 °C. Purification by preparative thin-layer chromatography (hexane) gave 2-*n*-propylanisole-d_n as a colorless oil (62% yield). Isotope distribution (EIMS): 1% d_3, 5% d_4, 13% d_5, 20% d_6, 20% d_7, 15% d_8, 11% d_9, 8% d_{10}, 5% d_{11}, 2% d_{12}, 1% d_{13}; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 7.11 (s, 0.47H), 6.91 (s, 0.51H), 6.84 (s, 0.02H), 3.81 (s, 2.56H), 2.53 (br s, 0.05H), 1.55 (m, 0.84H), 0.90 (t, 2.12H); ^{2}H NMR (acetone) δ 7.18 (br d), 6.95 (br s), 6.88 (br s), 3.82 (br t), 2.52 (br s), 1.53 (br s), 0.85 (br s).

[^{2}H]-Aniline (Table 2, Entry 17): H–D exchange reaction was carried out at 80 °C. Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave aniline-d_n as a pale brown oil (66% yield). Isotope distribution (EIMS): 2% d_2, 18% d_4, 80% d_5; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 7.03 (s, 0.04H), 6.64 (s, 0.05H), 6.56 (s, 0.02H), 4.51 (br s, 2H); ^{2}H NMR (CH_3OH) δ 7.09 (s), 6.73 (m).

[^{2}H]-*o*-Phenylenediamine (Table 2, Entry 19): H–D exchange reaction was carried out at 80 °C. Ethyl acetate was used instead of diethyl ether. Recrystallization from ethyl acetate/hexane gave *o*-phenylenediamine-d_n as a pale brown crystal (66% yield). Isotope distribution (EIMS): 2% d_0, 3% d_1, 4% d_2, 22% d_3, 69% d_4; ^{1}H NMR (DMSO-d_6, dioxane as an internal standard) δ 6.48 (s, 0.05H), 6.36 (s, 0.05H), 4.34 (br s, 4H); ^{2}H NMR (DMSO) δ 6.52 (br s), 6.40 (br s).

[^{2}H]-2-*n*-Propylaniline (Table 2, Entry 21): H–D exchange reaction was carried out at 80 °C. Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave 2-*n*-propylaniline-d_n as a pale brown oil (69% yield). Isotope distribution (EIMS): 2% d_2, 9% d_3, 25% d_4, 33% d_5, 20% d_6, 7% d_7, 3% d_8, 1% d_9; ^{1}H NMR ($CDCl_3$, *p*-anisic acid as an internal standard) δ 7.04 (s, 0.64H), 6.74 (s, 0.02H), 6.68 (s, 0.01H), 5.65 (br, 2H), 2.45 (m, 0.58H), 1.65 (m, 1.68H), 1.00 (t, 2.83H); ^{2}H NMR ($CHCl_3$) δ 7.18 (br s), 6.88 (br s), 6.85 (br s), 2.56 (br s), 1.73 (br s), 1.07 (br s).

[^{2}H]-4-*n*-Propylaniline (Table 2, Entry 23): H–D exchange reaction was carried out at 180 °C. Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave 4-*n*-propylaniline-d_n as a brown oil (69% yield). Isotope distribution (EIMS): 1% d_0, 1% d_1, 1% d_2, 2% d_3, 3% d_4, 7% d_5, 14% d_6, 19% d_7, 19% d_8, 10% d_9, 10% d_{10}, 12% d_{11}; ^{1}H NMR ($CDCl_3$, *p*-anisic acid as an internal standard) δ 6.94 (s, 0.27H), 6.64 (s, 0.06H), 5.06 (br, 2H), 2.45 (br, 0.05H), 1.56 (m, 0.54H), 0.89 (m, 1.97H); ^{2}H NMR ($CHCl_3$) δ 7.02 (s), 6.68 (s), 2.45 (s), 1.54 (s), 0.88 (s).

[^{2}H]-2,6-Xylidine (Table 2, Entry 25): H–D exchange reaction was carried out at 180 °C. Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave 2,6-xylidine-d_n as a pale brown oil (85% yield). Isotope distribution (EIMS): 1% d_3, 1% d_4, 1% d_5, 6% d_6, 22% d_7, 20% d_8, 49% d_9; ^{1}H NMR ($CDCl_3$, *p*-anisic acid as an internal standard) δ 6.94 (s, 0.04H), 6.64 (s, 0.02H), 3.54 (br, 2H), 2.15 (m, 0.16H); ^{2}H NMR ($CHCl_3$) δ 7.02 (s), 6.67 (s), 2.19 (s).

[^{2}H]-*N*,*N*-Dimethylaniline (Table 2, Entry 26): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave *N*,*N*-dimethylaniline-d_n as a pale brown oil (36% yield). Isotope distribution (EIMS): 1% d_2, 4% d_3, 9% d_4, 13% d_5, 17% d_6, 18% d_7, 17% d_8, 12% d_9, 6% d_{10}, 3% d_{11}; ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 7.20 (s, 0.39H), 6.72–6.67 (m, 0.06H), 2.92 (m, 2.43H); ^{2}H NMR (CH_2Cl_2) δ 7.28 (s), 6.79 (br m), 2.93 (br m).

[^{2}H]-Biphenyl (Table 2, Entry 28): H–D exchange reaction was carried out at 80 °C. Purification by preparative thin-layer chromatography (hexane) gave biphenyl-d_n as a white solid (64% yield). Isotope distribution (EIMS): 2% d_4, 2% d_5, 9% d_6, 4% d_7, 12% d_8, 16% d_9, 54% d_{10}; ^{1}H NMR ($CDCl_3$, *p*-anisic acid as an internal standard) δ 7.60 (s, 0.14H), 7.44 (s, 0.09H), 7.35 (s, 0.05H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 7.67 (s), 7.52 (s), 7.42 (s).

[^{2}H]-*n*-Butylbenzene (Table 2, Entry 29): *n*-Butylbenzene-d_n was obtained as a colorless oil (73% yield) without purification. Isotope distribution (EIMS): 1% d_5, 1% d_6, 1% d_7, 1% d_8, 3% d_9, 6% d_{10}, 9% d_{11}, 14% d_{12}, 26% d_{13}, 37% d_{14}; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 7.26 (s, 0.05H), 7.19 (s, 0.05H), 7.15 (s, 0.03H), 2.57 (s, 0.05H), 1.54 (s, 0.04H), 1.30 (br, 0.28H), 0.90 (m, 0.65H); ^{2}H NMR (acetone) δ 7.29–7.23 (br m), 2.57 (br s), 1.54 (br s), 1.29 (br s), 0.87 (br s).

[^{2}H]-Thiophenol (Table 2, Entry 30): Thiophenol-d_n was obtained as a colorless oil (58% yield). ^{1}H NMR (acetone-d_6, *p*-anisic acid as an internal standard) δ 7.38–7.14 (m, 4.48H), 4.26 (br s, 1H); ^{2}H NMR (acetone) δ 7.26 (br s).

[^{2}H]-Benzoic Acid (Table 3, Entry 2): H–D exchange reaction was carried out at 180 °C. D content (%) was determined after conversion of the carboxylic acid to the methyl ester. The procedure was as follows: To a stirred crude product (100 mg) in benzene/methanol (4/1) (4 mL) was added 10% $TMSCHN_2$ in hexane (1.0 mL) at room temperature. The mixture was stirred for 30 min at room temperature and concentrated in vacuo. The residue was applied to a preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) to obtain methyl benzoate-d_n as a colorless oil (66% 2 steps yield). Isotope distribution (EIMS): 4% d_3, 11% d_4, 85% d_5; ^{1}H NMR (acetone-d_6) δ 8.02 (s, 0.06H), 7.64 (s, 0.02H), 7.51 (s, 0.04H), 3.89 (s, 3H); ^{2}H NMR (acetone) δ 8.04 (s), 7.66 (s), 7.54 (s).

[^{2}H]-Methyl Benzoate (Table 3, Entry 3): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave methyl benzoate-d_n as a colorless oil (58% yield). Isotope distribution (EIMS): 2% d_2, 18% d_3, 39% d_4, 35% d_5, 6% d_6; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 8.02 (s, 0.73H), 7.63 (s, 0.01H), 7.51 (s, 0.02H), 3.89 (s, 2.44H); ^{2}H NMR (acetone) δ 8.04 (br s), 7.66 (br s), 7.54 (br s), 3.88 (br s).

[^{2}H]-Phthalic Acid (Table 3, Entry 4): After conversion to the methyl ester, purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/8) gave dimethyl phthalate-d_n as a colorless oil (51% 2 steps yield). Isotope distribution (EIMS): 17% d_2, 41% d_3, 42% d_4; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 0.72H), 7.54 (s, 0.02H), 3.91 (s, 6H); ^{2}H NMR ($CHCl_3$) δ 7.76 (br s), 7.57 (br s).

[^{2}H]-Pyromellitic Acid (=1,2,4,5-Benzenetetracarboxylic Acid) (Table 3, Entry 5): After conversion to the methyl ester, purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/3) gave tetramethyl pyromellitate-d_n as a white solid (92% 2 steps yield). Isotope distribution (EIMS): 59% d_0, 32% d_1, 9% d_2; ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1.56H), 3.94 (s, 12H); ^{2}H NMR ($CHCl_3$) δ 8.09 (br s).

[^{2}H]-4-*t*-Butylbenzoic Acid (Table 3, Entry 6): After conversion to the methyl ester, purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave methyl 4-*t*-butylbonzoate-d_n as a colorless oil (100% 2 steps yield). Isotope distribution (EIMS): 4% d_0, 5% d_1, 58% d_2, 19% d_3, 7% d_4, 5% d_5, 2% d_6; ^{1}H NMR (CD_2Cl_2) δ 7.94 (d, 0.13H), 7.48 (s, 1.99H), 3.87 (s, 3H), 1.34 (s, 8.38H); ^{2}H NMR (CH_2Cl_2) δ 7.99 (br s), 7.52 (br s), 1.32 (br s).

[^{2}H]-Nitrobenzene (Table 3, Entry 7): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/10) gave nitrobenzene-d_n as a pale yellow oil (64% yield). ^{1}H NMR (acetone-d_6) δ 8.26 (d, 2H), 7.85 (t, 0.97H), 7.69 (t, 1.96H); ^{2}H NMR (acetone) δ 7.86 (br s), 7.72 (br s).

[^{2}H]-*p*-Nitrophenol (Table 3, Entry 8): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/3) gave *p*-nitrophenol-d_n as a pale yellow solid (77% yield). Isotope distribution (EIMS): 11% d_0, 42% d_1, 42% d_2, 4% d_3; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 9.76 (br s, 1H), 8.16 (s, 1.92H), 7.03 (d, 0.66H); ^{2}H NMR (acetone) δ 8.20 (br s), 7.05 (br s).

[^{2}H]-*o*-Cyanophenol (Table 3, Entry 9): Purification by preparative thin-layer chromatography (ethyl acetate/hexane = 1/2) gave *o*-cyanophenol-d_n as a colorless solid (64% yield). Isotope distribution (EIMS): 3% d_0, 23% d_1, 46% d_2, 25% d_3, 3% d_4; ^{1}H NMR (acetone-d_6, dioxane as an internal standard) δ 9.76 (s, 1H), 7.59 (d, 0.90H), 7.51 (s, 0.62H), 7.08 (d, 0.20H), 7.00 (t, 0.22H); ^{2}H NMR (acetone) δ 7.60 (s), 7.52 (s), 7.10 (s), 7.02 (s).

[^{2}H]-Bromobenzene (Table 3, Entry 10): Bromobenzene-d_0 was obtained as a pale brown oil (56% yield) without purification. ^{1}H NMR (acetone-d_6, *p*-anisic acid as an internal standard) δ 7.55 (d, 2H), 7.34 (m, 3H); ^{2}H NMR (acetone) No peak was detected.

5% Pt/C Reuse Procedure (Table 4): 2,6-Xylidine (500 mg, 4.1 mmol) and 5% Pt/C (100 mg, 20 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ether (20 mL), and the mixture was filtered to remove 5% Pt/C. The filtered catalyst was washed with ether (5 mL × 2) and then reused for the 2nd run without further purification. The combined ether layers were washed with H_2O (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/10) to afford 2,6-xylidine-d_9 (423 mg, 85% yield) as a pale brown oil.

[^{2}H$_7$]-1-Naphthol (Scheme 4, 1): 1-Naphthol (72 mg, 0.5 mmol) and 5% Pt/C (7 mg, 10 wt % of the substrate) in D_2O (2.0 mL) were stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ether (10 mL), and the mixture was filtered using a membrane filter (Millipore Millex®-LG). The filtered catalyst was washed with ether (20 mL × 2). The combined ether layers were washed with H_2O (50 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo to give 1-naphthol-d_7 (72 mg, 100% yield) as a light brown powder. Isotope distribution (EIMS): 1% d_3, 1% d_4, 9% d_5, 31% d_6, 58% d_7; ^{1}H NMR (CD_3OD, 3-(trimethylsilyl)propanesulfonic acid sodium salt as an internal standard) δ 8.16 (s, 0.08H), 7.73 (s, 0.03H), 7.40 (s, 0.04H), 7.38 (s, 0.04H), 7.30 (s, 0.05H), 6.70 (s, 0.20H); ^{2}H NMR (DMSO) δ 8.16 (br s), 7.73 (br s), 7.50–7.20 (br m), 6.79 (br s).

[^{2}H$_7$]-Carbaryl (Scheme 4, 2): The mixture of **1** (53 mg, 0.35 mmol) and *N*-methyl isocyanate (118 μL, 2.0 mmol) was stirred at 160 °C in a sealed tube under Ar atmosphere for 10 h. The reaction mixture was diluted with ether (50 mL) and washed with H_2O (50 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ether/hexane = 1/10) to afford carbaryl-d_7 (37 mg, 59% yield) as colorless needles. ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 0.09H), 7.86 (s, 0.03H), 7.72 (s, 0.07H), 7.52–7.45 (m, 0.07H), 7.29 (s, 0.18H), 5.17 (br s, 1H), 2.97 (d, J = 5.3 Hz, 3H); ^{2}H NMR ($CHCl_3$) δ 7.90 (br s), 7.81 (br s), 7.67 (br s), 7.44–7.42 (m), 7.24 (br s); HRMS: calcd for $C_{12}H_4D_7O_2N$: 208.1229, found: 208.1237.

[^{2}H$_{17}$]-Ibuprofen (Scheme 5, 5): Ibuprofen (sodium salt, 114 mg, 0.5 mmol) and 5% Pt/C (11 mg, 10 wt % of the substrate) in D_2O (2.0 mL) were stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. The reaction mixture was filtered using a membrane filter (Millipore Millex®-LG). The filtered catalyst was washed with boiling water (50 mL) and concentrated in vacuo to give the multi-deuterated product, ibuprofen-d_n (**4**) (104.7 mg, 91% yield) as a white powder.

Ibuprofen-d_n (**4**) (50 mg, ca. 0.2 mmol) and 10% Pd/C (5 mg, 10 wt % of the substrate) in D_2O (1.0 mL) were stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. The reaction mixture was filtered using a membrane filter (Millipore Millex®-LG). The filtered catalyst was washed with boiling water (50 mL) and concentrated in vacuo to give the multi-deuterated product, ibuprofen-d_{17} (**5**) (50 mg, 100% yield) as a white powder. Isotope distribution (EIMS): 1% d_{13}, 4% d_{14}, 14% d_{15}, 34% d_{16}, 41% d_{17}, 6% d_{18}; ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as an internal standard) δ 7.13 (s, 0.07H), 7.07 (s, 0.07H), 3.46 (s, 0.03H), 2.31 (s, 0.06H), 1.64 (s, 0.03H), 1.22 (s, 0.12H), 0.69 (s, 0.24H); ^{2}H NMR (H_2O) δ 7.22 (br s), 7.18 (br s), 3.50 (br s), 2.35 (br s), 1.68 (br s), 1.26 (br s), 0.74 (br s).

[^{2}H$_4$]-*o*-Phenylenediamine (Scheme 6, 6): *o*-Phenylenediamine (20 g, 0.185 mol) and 5% Pt/C (4 g, 20 wt % of the substrate) in D_2O (680 mL) were stirred at 80 °C in a 1 L autoclave under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (600 mL), and the mixture was filtered to remove 5% Pt/C. The filtered catalyst was washed with ethyl acetate (40 mL × 2), and the separated aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to obtain **6** (13.8 g, 69% yield) as pale brown crystal. ^{1}H NMR (400 MHz, DMSO-d_6, dioxane as an internal standard) δ 6.48 (s, 0.05H), 6.36 (s, 0.05H), 4.34 (br s, 4H); ^{2}H NMR (DMSO) δ 6.52 (br s), 6.40 (br s).

[^{2}H$_4$]-2-Sulfanylbenzimidazole (Scheme 6, 7): To a stirring mixture of **6** (3.0 g, 25.8 mmol), KOH (1.64 g, 29.2 mmol), and H_2O (4 mL) in MeOH (22 mL) was added carbon disulfide (2.22 g, 29.2 mmol) at room temperature. The mixture was refluxed for

6 h. After cooling, the reaction mixture was added acetic acid (12 mL) and cooled to 4 °C. The precipitate was collected by filtration, washed with cold EtOH, and recrystallized from EtOH to obtain **7** (2.67 g, 67% yield) as a pale brown crystal. Isotope distribution (EIMS): 1% d_2, 9% d_3, 90% d_4; ^{1}H NMR (DMSO-d_6, dioxane as an internal standard) δ 12.50 (s, 2H), 7.14 (s, 0.02H), 7.11 (s, 0.02H); ^{2}H NMR (DMSO) δ 7.12 (br s).

[^{2}H$_4$]-*o*-Aminophenol (Scheme 6, 8): *o*-Aminophenol (20 g, 0.183 mol) and 5% Pt/C (4 g, 20 wt % of the substrate) in D_2O (680 mL) were stirred at 180 °C in a 1 L autoclave under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with MeOH (600 mL), and the mixture was filtered to remove 5% Pt/C. The filtered catalyst was washed with MeOH (40 mL × 2) and the mother liquid was concentrated in vacuo. The residue was recrystallized form ethyl acetate to obtain **8** (14.7 g, 71% yield) as a brown crystal. ^{1}H NMR (DMSO-d_6, benzene as an internal standard) δ 8.88 (br s, 1H), 6.63 (s, 0.02H), 6.58 (s, 0.02H), 6.53 (s, 0.02H), 6.39 (s, 0.02H); ^{2}H NMR (DMSO) δ 6.58 (br s), 6.42 (br s).

[^{2}H$_4$]-*o*-Iodophenol (Scheme 6, 9): To a stirring solution of **8** (13.5 g, 0.122 mol) in acetone (210 mL) was dropped conc. HCl (31.6 g, 0.304 mol) below 10 °C. A solution of $NaNO_2$ (8.41 g, 0.122 mol) in H_2O (22 mL) was added dropwise to the stirred reaction mixture at 0 °C during 30 min. The mixture was stirred at −2 °C for 1 h. To the diazonium solution was then added a solution of NaI (36.6 g, 0.244 mol) in H_2O (40 mL) at −10 °C over 15 min, and the mixture was stirred at 0–10 °C for 4 h. The mixture was extracted with ethyl acetate (280 mL). The extract was washed with H_2O (100 mL), a solution of $NaHSO_3$ (6 g) in H_2O (100 mL), and H_2O (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was applied to a silica-gel column chromatography (acetone/hexane = 1/20) to obtain **9** (16.8 g, 62% yield) as a pale red solid. Isotope distribution (EIMS): 8% d_3, 92% d_4; ^{1}H NMR (DMSO-d_6, 1,2-dichloroethane as an internal standard) δ 10.22 (br s, 1H), 7.66 (s, 0.02H), 7.19 (s, 0.02H), 6.89 (s, 0.02H), 6.58 (s, 0.02H); ^{2}H NMR (DMSO) δ 7.68 (br s), 7.22 (br s), 6.91 (br s), 6.61 (br s).

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 18590009) from the Japan Society for the Promotion of Science.

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