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Efficient H/D Exchange Reactions of Alkyl-Substituted Benzene Derivatives by Means of the Pd/C–H_2–D_2O System

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Abstract: A method for efficient and extensive H/D exchange of substituted benzene derivatives which is catalyzed by heterogeneous Pd/C in D_2O as a deuterium source under hydrogen atmosphere is described. Multideuterium incorporation into unactivated linear or branched alkyl chains that bear a carboxyl, hydroxyl, ether, ester, or amide moiety and are connected with a benzene ring was achieved by using the Pd/C–H_2–D_2O system. The present method does not require expensive deuterium gas or any special equipment.

Keywords: C–H activation · deuterium · heterogeneous catalysis · isotopic labeling · palladium

Introduction

With the development of analytical methods for the detection of stable isotopes (e.g., ^2H and ^{13}C) by NMR spectroscopy or mass spectrometry, deuterium-labeled compounds have been used for a wide range of purposes, including analysis of drug metabolism and residual pesticides, investigation of chemical reaction mechanisms and kinetics, studying the catalytic mechanisms of enzymes, structural analysis of proteins and peptides, development of new materials for optical fibers, and so on.[1,2] Methods for incorporating deuterium atoms into organic compounds are chiefly categorized into the following three types: 1) multistep synthetic methods starting from small deuterium-labeled precursors; 2) reductive methods using metal deuterides such as lithium aluminum deuteride ($LiAlD_4$) and sodium borodeuteride ($NaBD_4$) or transition metal catalyzed reductive dehalogenation and hydrogenation with D_2 gas; 3) postsynthetic hydrogen/deuterium (H/D) exchange of the unlabeled compounds. The H/D exchange methods are most useful in terms of time- and cost-efficiency. Existing H/D exchange reactions usually involve acid or base catalysis,[3] transition metal (Ru,[4] Co,[5] Rh,[6] Ir,[7] Ni,[8] Pd,[9] Pt,[10] and so on[11]) catalysis, microwave enhancement,[12] super- or subcritical conditions,[13] and photochemical[14] or biochemical[15] techniques. Such conventional H/D exchange reactions are, however, often limited to the aromatic rings or activated positions of the molecules, and few methods are available for deuteration at unactivated aliphatic carbon atoms. In addition, these methods often require high temperature or pressure, addition of strong acids or bases, vast amounts of catalyst, deuterium atmosphere, and/or the use of special apparatus. Recently, Bergman and co-workers reported a versatile Ir-complex-catalyzed H/D exchange method from the aspect of C–H activation.[7g,i,k,l] Matsubara and co-workers also established an efficient deuterium-labeling method under hydrothermal conditions.[13k–q] Although these deuteration methods can be performed under relatively mild reaction conditions, the former method requires a special catalyst and the latter still requires high temperature and pressure (250 °C, 4–5 MPa). Therefore, postsynthetic H/D exchange is an underdeveloped methodology.

We recently found that Pd/C-catalyzed efficient H/D exchange proceeded selectively at the benzylic position in D_2O as a deuterium source under hydrogen atmosphere (Pd/C–H_2–D_2O system) at room temperature,[16] and the application of heat could enhance the catalytic activity of the Pd/C–H_2–D_2O system and lead to H/D exchange even at unactivated carbon atoms.[17] Herein we provide a detailed discussion on the deuteration of benzene derivatives bearing unactivated alkyl chains with the Pd/C–H_2–D_2O system, as well as the mechanistic aspects.

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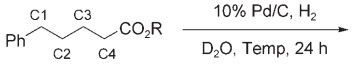
Results and Discussion

Heating 5-phenyl-*n*-valeric acid sodium salt (**1a**; 50 mg, 0.25 mmol) at 110 °C with 10 % Pd/C (5.0 mg, 10 % of the weight of **1a**, ca. 0.005 mmol of Pd metal) in D_2O (1 mL) under atmospheric H_2 pressure by using a Dimroth-type condenser (total vessel volume: ca. 70 mL) brought about efficient H/D exchange even at unactivated C2–C4, while H/D exchange at the benzylic position was limited at room temperature (Table 1, entries 1 and 2). The H/D exchange

Table 1. Screening of the optimum reaction conditions for 10 % Pd/C–H_2-catalyzed H/D exchange in D_2O.[a]



1a: R = Na, **1b**: R = H

Entry	Compound	T [°C]	D content [%][b]			
			Ph	C1	C2+C3	C4
1[c]	**1a**	RT	0	89	0	0
2	**1a**	110	34	98	89	12
3	**1b**	110	28	93	82	15
4[d]	**1b**	110	23	94	82	17
5[e]	**1b**	110	24	96	48	1
6[f]	**1b**	110	52	97	89	20
7[g]	**1b**	110	36	91	51	12
8[h]	**1b**	110	31	98	60	19
9[i]	**1b**	110	0	0	0	0
10[j]	**1b**	110	0	0	0	0
11[k]	**1b**	140	63	96	84	29
12[k]	**1b**	160	67	95	94	94
13[k,l]	**1b**	180	0	48	13	5

[a] Unless otherwise noted, 0.25 mmol of the substrate was used, and reactions were carried out under normal H_2 pressure (volume 70 mL), 10 % Pd/C (10 wt % of the substrate, Aldrich), and 1 mL of D_2O (99.9 % D content). [b] The D content was determined by ^1H NMR spectroscopy. [c] 0.5 mmol of the substrate was used in 2 mL of D_2O. [d] The reaction was performed in a 20-mL test tube using ChemiStation. [e] 5 wt % Pd/C was used. [f] 20 wt % of Pd/C was used. [g] 0.5 mL of D_2O was used. [h] 4 mL of D_2O was used. [i] Without H_2 gas. [j] Without 10 % Pd/C. [k] The reaction was performed in a sealed tube. [l] The reaction was performed under D_2 atmosphere in dry EtOAc instead of H_2 and D_2O.

reaction of free 5-phenyl-*n*-valeric acid (**1b**), which is barely soluble in D_2O, led to results similar to those of **1a**, and this suggests that the solubility of substrates in D_2O is of lesser importance (Table 1, entry 2 vs. entry 3). Next, we examined the H/D exchange reaction using a smaller reaction vessel (ca. 20 mL), since we have demonstrated in our previous paper that use of an excess of H_2 gas resulted in moderate deuteration efficiency for site-selective benzylic H/D exchange at room temperature.[16] However, contrary to our expectation, there was no difference in the results between Table 1, entry 3 (ca. 70 mL of H_2 gas, 3.1 mmol) and Table 1, entry 4 (ca. 20 mL of H_2 gas, 0.82 mmol). Increasing the catalyst loading (from 10 to 20 wt %) or the amount of deuterium oxide (from 1 to 4 mL) did not improve the efficiency of deuteration (Table 1, entries 6 and 8). The deuterium efficiency dropped at lower catalyst loading (10 vs. 5 wt %, Table 1, entry 7) or with smaller amount of D_2O (1 vs. 0.5 mL, Table 1, entry 7). No deuteration took place without either H_2 gas (Table 1, entry 9) or 10 % Pd/C (Table 1, entry 10), that is, both H_2 gas and Pd/C are indispensable for the exchange reaction in the present system. The efficiency of the H/D exchange reaction could be greatly enhanced by increasing temperature up to 160 °C by using a sealed tube (Table 1, entries 11 and 12). The pressure inside the sealed tube at 160 °C, as measured by a pressure gauge, was at most 2.5 atm. The deuterium efficiency was seriously reduced when the reaction was performed under D_2 atmosphere instead of H_2 in dry ethyl acetate as an inert solvent, even at 180 °C (Table 1, entry 13). Thus, D_2O is necessary to achieve efficient H/D exchange in this system.

We recently reported that nearly pure D_2 gas was obtained from the H_2/D_2 exchange reaction after stirring Pd/C in D_2O under H_2 atmosphere for 24 h at room temperature.[18] Gaseous D_2 has been used as an efficient deuterium source in many H/D exchange procedures. In the present case, D_2 gas would be generated during the H/D exchange reaction and then the deuterium atom might be transferred to the compound from D_2 gas. However, considering that **1b** was not efficiently deuterated with D_2 gas (Table 1, entry 13), the formation of D_2 gas does not seem to be necessary for H/D displacement in the present Pd/C–H_2–D_2O system.

The time course of the 10 % Pd/C–H_2–catalyzed H/D exchange reaction in D_2O at 160 °C was studied with **1b** as a substrate. As shown in Figure 1, H/D exchange at C1, C2,

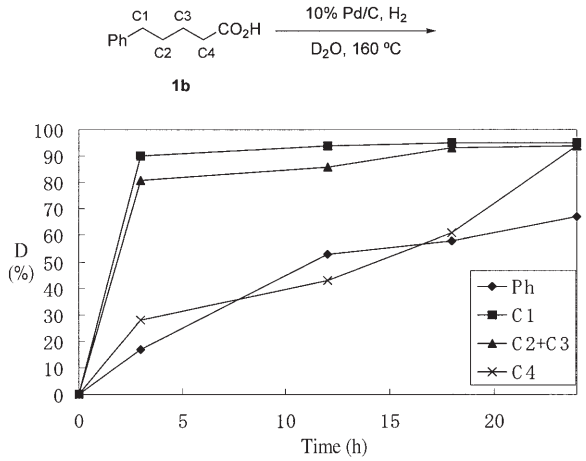


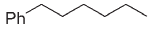
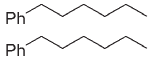
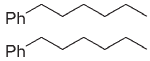
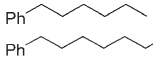
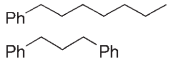
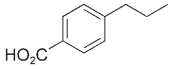
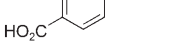
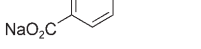
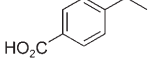
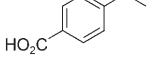
Figure 1. Kinetic traces of 10 % Pd/C–H_2-catalyzed H/D exchange of **1b** in D_2O at 160 °C.

and C3 proceeded rapidly, while the deuterium efficiency gradually increased at C4 and the aromatic carbon atoms. Over the course of the reaction, the alkyl side chain was deuterated nearly quantitatively within 24 h.

H/D exchange reaction of alkyl-substituted aromatic compounds: To explore the scope of the H/D exchange reaction with the Pd/C–H_2–D_2O system at elevated temperature (110 or 160 °C), a wide range of alkylbenzenes was employed (Table 2). Unless otherwise noted, the label C1 describes

Table 2. H/D exchange results of various alkylbenzenes with 10% Pd/C–H_2 in D_2O.[a]

Substrate $\xrightarrow[D_2O,\ Temp,\ 24\ h]{10\%\ Pd/C,\ H_2}$ Substrate-[D_n]

Entry	Substrate		T [°C]	D content [%][b]								Yield of isolated product [%]
				Ph	C1	C2	C3	C4	C5	C6	C7	
1[c]	PhMe	**2a**	110	60	89							–
2[c]		**2b**	110	57	88	86						51
3[c]		**2c**	110	46	87	87	83					78
4[d]		**2d**	110	55	91	91	90	87				84
5		**2e**	110	59	95	94	65[j]	65[j]	15			84
6		**2f**	110	38	95	82	33[j]	33[j]	33[j]	2		91
7[e]		**2f**	160	45	98	98	58[j]	58[j]	58[j]	33		87
8[e,f]		**2f**	160	42	97	97	92[j]	92[j]	92[j]	88		97
9[e,g,h]		**2f**	160	76	97	97	93[j]	93[j]	93[j]	81		73
10		**2g**	110	65	95	96	61[j]	61[j]	61[j]	61[j]	14	98
11[h]		**2h**	110	41	95	96						99
12[e]		**2i**	160	9	96	96	91					99
13[e,i]		**2j**	160	0	94	94	80	59				100
14[e,i]		**2k**	160	26	96	96	92	96				91
15		**2l**	110	0	96	94						97
16[e]		**2m**	160	0		2						98
17[e]		**2n**	160	18	95	–[k]	–[k]	–[k]				95
18		**2o**	110	42	90	32						96

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out under reflux conditions, and about 1 atm of H_2 pressure using 10% Pd/C (10 wt% of the substrate) in 2 mL of D_2O at 110°C for 24 h. [b] The D content was determined by ^1H NMR spectroscopy. 0% means no detectable peaks were observed in the ^2H NMR spectra. [c] 5 mmol of substrate was used. [d] 2 mmol of substrate was used. [e] The reaction was carried out in a sealed tube. [f] The reaction was carried out for 48 h. [g] The H/D exchange procedure was repeated by using the product. [h] 1 mmol of substrate was used in 4 mL of D_2O. [i] 0.25 mmol of substrate was used in 1 mL of D_2O. [j] Average D content. [k] Equatorial 42 and axial 31 at C2–C4.

the benzylic position and C2–C7 indicate the positions of the unactivated alkyl chain, numbered from the position adjacent to the benzylic site to the terminal methyl group. In general, effective multiple deuterium incorporation into the unactivated alkyl side chain was observed, although the deuterium efficiency of the side chain tended to decrease with increasing distance from the benzene ring. A larger amount of small benzene derivatives **2a**–**2d** (2 or 5 mmol) compared with other derivatives (0.5 mmol) was employed for the deuteration in fear that the product might be easily lost due to its low boiling point. However, even with a low molecular ratio of D_2O as deuterium source to **2a**–**2d**, efficient deuterium incorporation was observed in each case (Table 2, entries 1–4). While the terminal methyl group in **2a**–**2d** was deuterated with high efficiency (82–89%), the deuterium efficiency of the methyl group of *n*-pentylbenzene (**2e**), *n*-hexylbenzene (**2f**), and *n*-heptylbenzene (**2g**) drastically dropped to less than 20% (Table 2, entries 5, 6, and 10). Although raising the reaction temperature to 160°C improved the efficiency (Table 2, entry 6 vs. entry 7), either extending the reaction time (Table 2, entry 8) or repeating the H/D exchange procedure with the resulting material (Table 2, entry 9) led to a great improvement in deuterium efficiency.

In the deuteration of alkyl-substituted benzoic acids **2i**–**2m**, the hydrogen atoms on the benzene rings were hardly replaced with deuterium atoms (Table 2, entries 12–16). Recently, we reported efficient Pt/C-catalyzed H/D exchange reaction on benzene rings, and the deuteration on electron-deficient aromatic rings required severe conditions.[17e] Probably the interaction of electrophilic Pd or Pt metal with the benzene ring would be an important factor for effective H/D exchange.

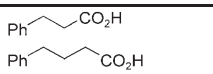
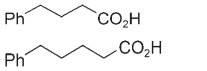
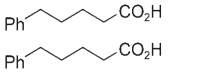
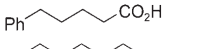
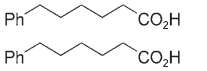
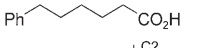
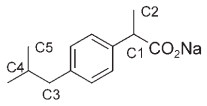
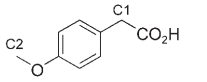
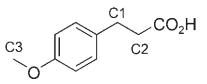
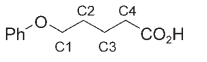
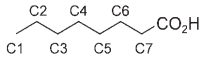
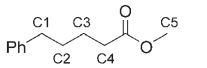
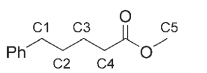
When 4-*n*-butylbenzoic acid (**2j**) was used as substrate, exchange at the terminal position was inefficient (59%) even at 160°C (Table 2, entry 13), compared with the case of 4-*n*-propylbenzic acid (**2i**, Table 2, entry 12). However, use of the sodium salt of 4-*n*-butylbenzoic acid (**2k**), which is readily soluble in D_2O, facilitated the H/D exchange at the terminal methyl group with high efficiency (96%, Table 2, entry 14). As opposed to the efficient deuterium incorporation into the side chain of 4-isopropylbenzoic acid (**2l**) at 110°C (Table 2, entry 15), almost no H/D exchange was observed when 4-*tert*-butylbenzoic acid (**2m**) was used as substrate, even at higher temperature (160°C, Table 2, entry 16). The present H/D exchange method could be applied to phenylcyclohexane (**2n**) and 1-ethylnaphthalene (**2o**) (Table 2, entries 17 and 18).

H/D exchange reaction of carboxylic acids and esters: Heating a variety of carboxylic acids with 10% Pd/C in D_2O under H_2 atmosphere also led to efficient incorporation of multiple deuterium atoms into the side chain (Table 3). In particular, remarkable deuterium incorporation was observed even at 110°C when hydrocinnamic acid (**3a**) or 3-phenyl-*n*-butanoic acid (**3b**) was used as substrate (Table 3, entries 1 and 2). Similar to the H/D exchange of alkylbenzenes (Table 2), the deuterium efficiency tended to decrease with increasing distance from the benzene ring (Table 3, entries 3, 5, 6, and 12). When 5-phenyl-*n*-valeric acid (**3c**), 6-phenyl-*n*-hexanoic acid (**3d**), or the methyl ester of 5-phenyl-*n*-valeric acid (**3j**) was employed as substrate, deuterium incorporation into the position neighboring the carboxyl group was markedly depressed at 110°C (Table 3, entries 3, 5, and 12). The deuterium efficiency at the α-position of the carbonyl group was improved by increased temperature (160°C, Table 3, entries 4, 6, and 13). It is noteworthy that application of this deuteration method can be extended to a biologically active compound such as Ibuprofen sodium salt (**3e**) and quantitative deuterium incorporation at C1–C5 was observed (Table 3, entry 7). Almost no H/D exchange at the methyl group of methyl ester **3j** was observed (Table 3, entries 12 and 13), although the methoxyl group of **3f** or **3g** was deuterated with low efficiency (Table 3, entries 8 and 9). The use of 5-phenoxy-*n*-valeric acid (**3h**), which has an oxygen atom between aromatic ring and alkyl chain, led to low deuterium incorporation into the alkyl side chain (Table 3, entry 10). The H/D exchange of *n*-octanoic acid (**3i**), which lacks aromatic rings, hardly proceeded under the same reaction conditions (Table 3, entry 11). These results suggest that direct connection of an aromatic ring to the alkyl side chain is crucial for efficient H/D exchange with the Pd/C–H_2–D_2O system and the benzene ring plays an important role in bringing about the reaction.

H/D exchange reaction of phenylalkyl alcohols: The incorporation of deuterium atoms into unactivated alkyl side chain of primary alcohols was less efficient (Table 4) compared to the remarkable H/D exchanges of alkylbenzenes (Table 2) and carboxylic acids (Table 3). The H/D exchange at the positions adjacent to a hydroxyl group was rarely observed at 110°C in each case (Table 4, entries 1–4, 6–9). Almost no deuterium incorporation into the aromatic ring occurred in all cases, and the H/D exchange reaction even at the benzylic position of 2-phenylethanol (**4a**), 3-phenyl-1-propanol (**4b**), or 8-phenyl-1-octanol (**4g**) proceeded with relatively low deuterium efficiency (Table 4, entries 1, 2, and 8). Improved deuterium efficiency of 5-phenyl-1-propanol (**4d**) was attained by heating to 160°C, but the efficiency was still moderate (Table 4, entry 5). When 2-phenyl-1-propanol (**4h**), which has a methyl branch at the benzylic position, was employed as substrate, highly regioselective H/D exchange proceeded at C1 (Table 4, entry 9). On the other hand, H/D exchange of ethers **4i–4k** proceeded with relatively high deuterium efficiency even at the position adjacent to the oxygen atom (Table 4, entries 10–12). No deuteration at the terminal methyl or ethyl group of 2-phenylethyl methyl ether (**4i**),

Table 3. H/D exchange results of various carboxylic acids and ester with 10% Pd/C–H_2 in D_2O.[a]

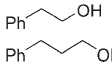
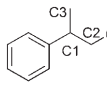
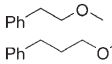
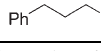
Substrate —(10% Pd/C, H_2; D_2O, Temp, 24 h)→ Substrate-[D_n]

Entry	Substrate		T [°C]	D content [%][b]								Yield of isolated product [%]
				Ph	C1	C2	C3	C4	C5	C6	C7	
1		**3a**	110	58	98	98						99
2[c]		**3b**	110	26	94	90	93					100
3[c]		**3c**	110	28	93	82[e]	82[e]	15				99
4		**3c**	160	67	95	94[e]	94[e]	94				98
5		**3d**	110	45	96	89[e]	95	89[e]	16			93
6		**3d**	160	27	95	94[e]	93	94[e]	56			93
7[c]		**3e**	160	43	96	93	95	95	95			100
8[c]		**3f**	110	18	97	18						92
9[c]		**3g**	160	35	96	98	37					88
10		**3h**	160	65	35	0[e]	0[e]	0				95
11		**3i**	110		5	4[e]	4[e]	4[e]	4[e]	8	7	94
12		**3j**	110	26	97	93[e]	93[e]	20	0			77
13[d]		**3j**	160	54	92	92[e]	92[e]	92	3			97

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out under reflux conditions and about 1 atm of H_2 pressure with 10% Pd/C (10 wt% of the substrate) in 2 mL of D_2O at 110°C for 24 h. [b] D content was determined by ^1H NMR. 0% means no detectable peaks were observed in ^2H NMR. [c] 0.25 mmol of substrate was used in 1 mL of D_2O. [d] 3 mmol of substrate was used in 4 mL of D_2O. [e] Average D content.

Table 4. H/D exchange results of various aromatic alcohols and ethers with 10% Pd/C–H_2 in D_2O.[a]

Substrate —(10% Pd/C, H_2; D_2O, Temp, 24 h)→ Substrate-[D_n]

Entry	Substrate		T [°C]	D content [%][b] Ph	C1	C2	C3	C4	C5	C6	C7	C8	Yield of isolated product [%]
1		**4a**	110	0	57	0							97
2		**4b**	110	0	75	10	20						97
3		**4c**	110	0	87	47[d]	47[d]	3					99
4		**4d**	110	0	93	41[d]	25	41[d]	0				93
5		**4d**	160	15	91	78[d]	88	78[d]	47				85
6		**4e**	110	0	96	34[d]	8[d]	8[d]	34[d]	0			99
7		**4f**	110	0	84	45[d]	18[d]	18[d]	18[d]	45[d]	0		95
8		**4g**	110	0	73	28[d]	7[d]	7[d]	7[d]	7[d]	28[d]	0	95
9		**4h**	110	0	97	6	0						84
10[c]		**4i**	110	0	88	68	0						79
11		**4j**	110	0	85	70	65	0					85
12		**4k**	110	21	92	92	80	0	0				95

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out under reflux conditions and about 1 atm of H_2 pressure with 10% Pd/C (10 wt% of the substrate) in D_2O (2 mL) at 110°C for 24 h. [b] The D content was determined by ^1H NMR spectroscopy. 0% means no detectable peaks were observed in the ^2H NMR spectra. [c] 1 mmol of the substrate was used. [d] Average D content.

3-phenylpropyl methyl ether (**4j**), or 3-phenylpropyl ethyl ether (**4k**) took place (Table 4, entries 10–12).

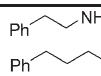
H/D exchange reaction of amines and amides: Deuteration with phenethylamine hydrochloride (**5a**), phenylbutyl amine hydrochloride (**5b**), or *N*-(2-phenethyl)acetamide (**5c**) also proceeded under the same reaction conditions (Table 5, entries 1–3). Similar to the results for alcohols (Table 4), H/D exchanges both at the position adjacent to the amino group and on the benzene ring proceeded with difficulty at 110°C (Table 5, entries 1–3). Higher temperature led to high deuterium efficiency at C2 of **5c**, but deuterium incorporation into the terminal methyl group of the amide was scarcely observed even at 160°C (Table 5, entry 4).

H/D exchange reaction of methyl groups on an aromatic ring: Next, methyl-substituted benzene derivatives were subjected to the present deuteration conditions (Table 6). When 4-methylanisole (**6a**), *p*-toluidine hydrochloride (**6b**), 4-methylbiphenyl (**6c**), or *p*-benzyltoluene (**6d**) was stirred with Pd/C in D_2O under H_2 atmosphere at 110°C for 24 h, excellent deuterium incorporation into the methyl and benzylic methylene groups was observed in each case (Table 6, entries 1–4). On the other hand, almost no deuteration (8%) occurred at the methoxyl group of **6a** (Table 6, entry 1, see also Table 3, entries 8 and 9). Regarding H/D exchange on the benzene ring, the deuterium efficiency at the positions *ortho* to substituents was relatively low, presumably due to steric hindrance,[17e] although effective deuteration at C3 of both **6b** and **6c** was observed (Table 6, entries 2 and 3).

Reaction mechanism: As described in Table 1, entry 9, the H/D exchange reaction does not proceed in the absence of H_2 gas. To investigate the role of H_2 gas, we examined the following reaction: 10% Pd/C (5.0 mg, 10% of the weight of **1a**) was suspended in 1 mL of D_2O in a test tube and stirred under H_2 atmosphere for 30 min at room temperature. The mixture was then transferred to a sealed tube and 5-phenyl-*n*-valeric acid sodium salt (**1a**, 50.0 mg, 0.25 mmol) was added. After three vacuum/Ar cycles to replace air with Ar gas in the sealed tube, the mixture was stirred at 160°C under Ar atmosphere for 24 h. The H/D exchange of the alkyl side chain of **1a** proceeded, but the deuterium efficiency was lower than that in Table 1, entry 2 (Scheme 1). This experimental result indicates that D_2 gas, which might be generated during pretreatment of Pd/C and D_2O under H_2 atmosphere,[18] would not play a role

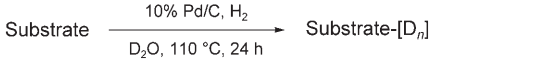
Table 5. H/D exchange results of various aromatic amines and amides with 10% Pd/C–H_2 in D_2O.[a]

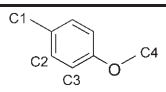
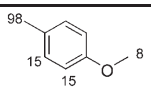
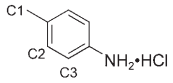
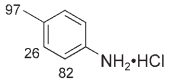
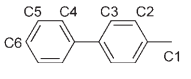
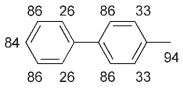
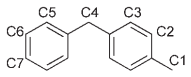
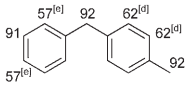
Substrate —(10% Pd/C, H_2; D_2O, Temp, 24 h)→ Substrate-[D_n]

Entry	Substrate		T [°C]	D content [%][b] Ph	C1	C2	C3	C4	Yield of isolated product [%]
1		**5a**	110	0	96	0			94
2		**5b**	110	0	96	80[e]	80[e]	0	99
3[c]		**5c**	110	9	89	2	0		99
4[d]		**5c**	160	48	97	97	13		91

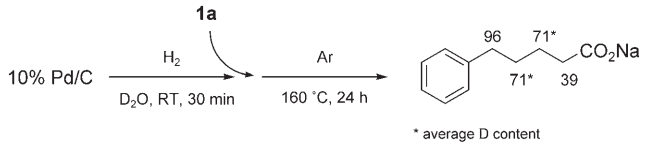
[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out under reflux conditions and about 1 atm of H_2 pressure with 10% Pd/C (10 wt% of the substrate) in D_2O (2 mL) at 110°C for 24 h. [b] The D content was determined by ^1H NMR spectroscopy. 0% means no detectable peaks were observed in the ^2H NMR spectra. [c] 0.25 mmol of the substrate was used in 1 mL of D_2O. [d] 1 mmol of the substrate was used in 4 mL of D_2O. [e] Average D content.

Table 6. H/D exchange results of methyl groups on aromatic rings with 10% Pd/C–H_2 in D_2O.[a]



Entry	Substrate	D content [%][b]	Yield of isolated product [%]
1[c]	 **6a** 		74
2	 **6b** 		94
3	 **6c** 		99
4	 **6d** 		99

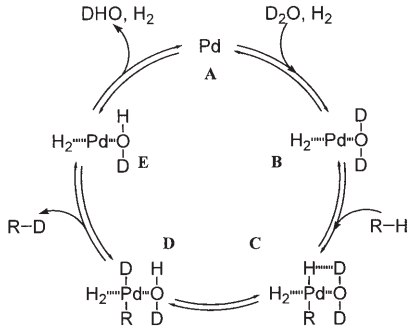
[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out under reflux conditions and about 1 atm of H_2 pressure with 10% Pd/C (10 wt% of the substrate) in D_2O (2 mL) at 110 °C for 24 h. [b] The D content was determined by ^1H NMR spectroscopy. [c] 2 mmol of the substrate was used. [d, e] Average D content.



Scheme 1. Investigation of the role of H_2 in the H/D exchange reaction.

in the deuteration of **1a**. Direct incorporation of deuterium from D_2O into **1a** under Ar does not take place, as shown in Table 1, entry 9. Presumably 10% Pd/C was activated by a small amount of H_2 gas in the first stage, and the molecular H_2 gas probably acts as a ligand toward Pd metal in this reaction to form a complex and activating the surface.[19]

We speculated on two possible mechanisms for H/D exchange with the Pd/C–H_2–D_2O system. The first is briefly outlined in Scheme 2. The first step would involve activation of Pd^0 (**A**) by coordination of H_2 gas and D_2O to form complex **B**. Oxidative insertion of activated Pd^0 species **B** into the unactivated alkyl R–H bond then could proceed to give Pd^{II} complex **C**. Intramolecular H/D exchange (**C**→**D**) and subsequent reductive elimination (**D**→**E**) would give the corresponding deuterated product R–D and regenerate Pd^0 (**A**).

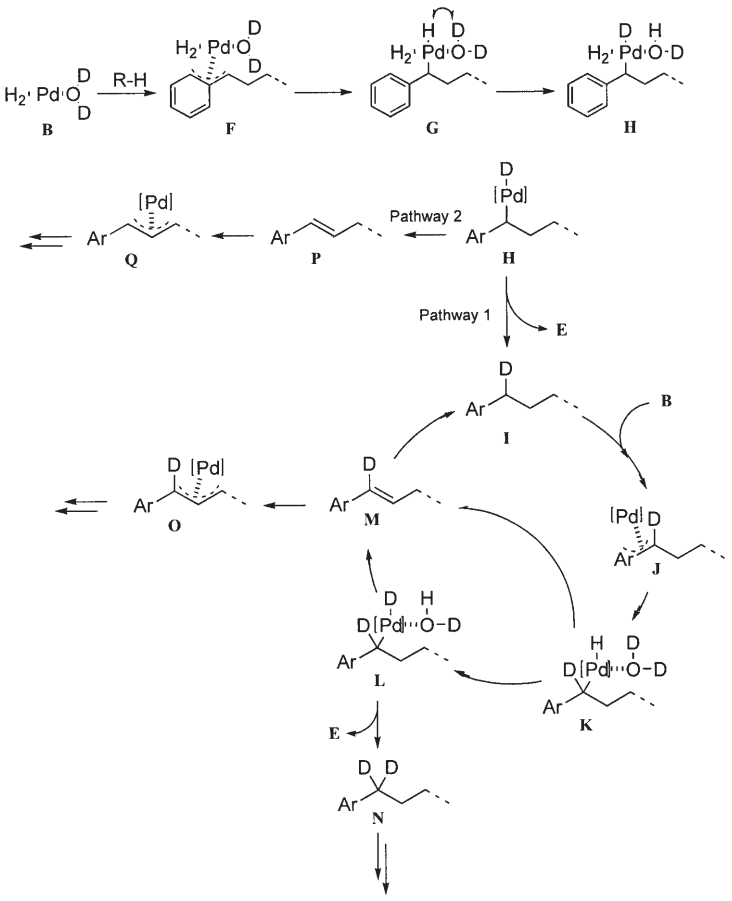


Scheme 2. Plausible mechanism for H/D exchange with the Pd/C–H_2–D_2O system.

In the case of a substrate which has a benzene ring, formation of the Pd π-aryl complex could be considered the key step of the oxidative insertion of Pd^0 into the substrate (Scheme 3). Oxidative insertion of **B** into the C–H bond of the substrate (R–H) would take place via Pd π-aryl/Pd benzyl complexation (**F**→**G**). Then, intramolecular H/D exchange would proceed to give **H**. If subsequent reductive elimination occurs in the next step, compound **I** deuterated at the benzylic position would be obtained (pathway 1, Scheme 3). Oxidative insertion of **B** into **I** would lead to further deuterium incorporation via H/D exchange (**K**→**L**) followed by reductive elimination (**L**→**N**). Deuterium incorporation into another unactivated C–H bond may proceed via β-hydride elimination of **K**, **L**, or **H**. In another route, **K** and/or **L** would undergo β-hydride elimination to give alkene **M**, and subsequent complexation with **B** would cause further deuteration via complex **O**. In pathway 2 (Scheme 3), β-hydride elimination of **H** could also give alkene **P**, which would form Pd π-allyl complex **Q** and lead to further deuteration, as described above. Continuously moving olefin and forming a Pd π-allyl complex would bring deuterium to positions further away from the benzylic position. Thus, it is reasonable that the *tert*-butyl group of **2m**, the methoxyl group of **3f**, **3g**, and **6a**, the methyl ester group of **3j**, the methyl or ethyl group ether of **4i**, **4j**, and **4k**, and aliphatic acid **3i** were not deuterated well. However, the slight deuteration of these moieties suggests that the H/D exchange reaction using Pd/C–H_2–D_2O system proceeds via both of the reaction mechanisms described in Schemes 2 and 3.

Conclusion

In summary, we have described H/D exchange using a heterogeneous Pd/C–H_2–D_2O system as an efficient method for deuterium labeling of different types of alkyl-substituted aromatic compounds, including biologically active Ibuprofen sodium salt (**3e**). The deuterium efficiency tended to be lower as the distance from the benzene ring increased. The direct connection of an aromatic ring to the alkyl side chain was a significant prerequisite for the efficient H/D exchange reaction using this system. Deuteration with the Pd/C–H_2–D_2O system may proceed via both C–H activation and Pd π-aryl complexation. The results presented here provide a deuterium-gas-free, catalytic, and postsynthetic deuterium-labeling method in neutral D_2O medium without application of pressure. The simplicity of the procedure makes it an attractive new tool for organic, medicinal, and analytical chemists.



Scheme 3. Plausible H/D exchange mechanism via π-aryl complexation.

Experimental Section

General: ^{1}H, ^{2}H, and ^{13}C NMR spectra were recorded on a JEOL AL-400 or EX-400 spectrometer (^{1}H: 400 MHz, ^{2}H: 61 MHz, ^{13}C: 100 MHz). Chemical shifts δ are given in parts per million relative to residual solvent ^{1}H peaks. Deuterium content was determined by using internal standards (*p*-anisic acid, *p*-anisic acid sodium salt, 1,4-dimethoxybenzene, or 1,4-diacetylbenzene). Mass spectra and high-resolution mass spectra were taken on a JEOL JMS-SX 102A spectrometer. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). 10% Pd/C was purchased from Aldrich Chemical Co. (product number: 205699)[20] and deuterium oxide (99.9% isotopic purity) was purchased from Division of Spectra Gases Inc. All other reagents were obtained from commercial sources and used without further purification.

Carboxylic acid sodium salts 1a, 2k, and 3e: 5-Phenyl-*n*-valeric acid sodium salt (**1a**), 4-*n*-butylbenzoic acid sodium salt (**2k**), and Ibuprofen sodium salt (**3e**) were prepared from the corresponding carboxylic acid as follows: carboxylic acid (5 mmol) and sodium hydroxide (0.18 g, 4.5 mmol) were each added to H_2O (10 mL) and the mixture was stirred at room temperature for 6 h, washed with ethyl acetate (2×10 mL), and concentrated under reduced pressure to give the corresponding carboxylic acid sodium salt in quantitative yield.

3-Phenylpropyl methyl ether (4j): A suspension of 3-phenyl-1-propanol (0.68 mg, 5 mmol) and sodium hydride (ca. 60% in oil: 0.24 mg, 6.0 mmol) in THF (10 mL) was stirred under argon atmosphere (balloon) at room temperature for 30 min. Methyl iodide (0.85 g, 6.0 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 24 h. Methanol (5 mL) and triethylamine (5 mL) were then added to quench the excess of sodium hydride and methyl iodide. The reaction mixture was diluted with diethyl ether (50 mL). The organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (hexane/diethyl ether 40/1) to afford 3-phenylpropyl methyl ether as a colorless oil (0.69 g, 80%). ^{1}H NMR ($CDCl_3$): δ=7.34–7.29 (m, 2H), 7.24–7.20 (m, 3H), 3.43 (t, J=6.5 Hz, 2H), 3.38 (s, 3H), 2.73 (t, J=7.7 Hz, 2H), 1.97–1.90 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ=141.6, 128.1, 128.0, 71.6, 58.2, 31.9, 30.9 ppm.

Synthesis of 3-phenylpropyl ethyl ether (4k):[21] 3-Phenylpropyl bromide (1.99 g, 10 mmol) was added to a solution of sodium (0.28 g, 12 mmol) in absolute ethanol (10 mL) and the mixture was refluxed for 6 h. After cooling, it was diluted with water (10 mL) and acidified with acetic acid, and the product was extracted with diethyl ether (20 mL). The organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (hexane/diethyl ether 50/1) to afford 3-phenylpropyl ethyl ether as a colorless oil (1.35 g, 82%). ^{1}H NMR (CD_3OD): δ=7.18–7.04 (m, 5H), 3.41–3.29 (m, 4H), 2.58 (t, J=7.7 Hz, 2H), 1.80–1.73 (m, 2H), 1.10 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=141.6, 127.9, 125.2, 69.2, 65.6, 31.9, 30.9, 14.8 ppm; MS (EI): *m/z* (%): 164 (3), 118 (100), 91 (42); HRMS calcd for $C_{11}H_{16}O$: 164.12012; found: 164.12046.

Amine hydrochlorides 5b and 6b: Phenylbutylamine hydrochloride (**5b**) and *p*-toluidine hydrochloride (**6b**) were prepared from the corresponding amine. A solution of hydrogen chloride in diethyl ether (2.0 M: 5.0 mL, 10 mmol) was added to a solution of the amine (5.0 mmol) in diethyl ether (5 mL) and the mixture was stirred for 10 min. The precipitated solid was collected on a Kiriyama funnel (Kiriyama Glass Works Co.) and recrystallized from ethanol to give the corresponding amine hydrochloride in excellent yield.

4-Benzyltoluene (6d): A suspension of 4-methylbenzophenone (0.98 g, 5.0 mmol) and 10% Pd/C (98 mg, 10% of the weight of 4-methylbenzophenone) in methanol (10 mL) was stirred under H_2 atmosphere at room temperature for 48 h. The mixture was diluted with ethyl acetate (10 mL) and filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with ethyl acetate (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to afford 4-benzyltoluene (**6d**) as a colorless oil (0.89 g, 98%). ^{1}H NMR (CD_3OD): δ=7.22 (t, J=7.7 Hz, 2H), 7.15–7.11 (m, 3H), 7.04 (s, 4H), 3.96 (s, 2H), 2.27 ppm (s, 3H); ^{13}C NMR (CD_3OD): δ=142.9, 139.6, 136.5, 130.0, 129.8, 129.7, 129.4, 126.9, 42.4, 21.0 ppm; MS (EI): *m/z* (%): 182 (69), 167 (100), 152 (12), 91 (10); HRMS: calcd for $C_{14}H_{14}$: 182.10955; found: 182.10864.

General procedure for the H/D exchange reaction with Pd/C–H_2–D_2O system: Method A: A mixture of substrate (0.50–5.0 mmol) and 10% Pd/C (10 wt% of the substrate) in D_2O (2–4 mL) was heated under ca. 1 atm H_2 pressure and reflux conditions by using a Dimroth-type con-

denser for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. **Method B**: A mixture of substrate (0.25–3.0 mmol) and 10% Pd/C (10 wt% of the substrate) in D_2O (1–4 mL) was stirred at 160°C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure.

[^{2}H]-Toluene (Table 2, entry 1): A mixture of toluene (0.46 g, 5.0 mmol) and 10% Pd/C (46 mg, 10 wt% of the substrate) in D_2O (2 mL) was heated under ca. 1 atm H_2 pressure and reflux conditions using a Dimroth-type condenser for 24 h. After cooling, the reaction mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The supernatant was collected and used as a sample for the NMR spectra. ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.22–7.09 (m, 1.98H), 2.30–2.26 ppm (m, 0.34H); ^{2}H NMR (CH_3OH): δ=7.22 (brs), 7.16 (brs), 7.13 (brs), 2.26 ppm (brs).

[^{2}H]-Ethylbenzene (Table 2, entry 2): Method A. ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.15–7.02 (m, 2.16H), 2.49–2.48 (m, 0.24H), 1.09–1.05 ppm (m, 0.43H); ^{2}H NMR (CH_3OH): δ=7.25 (brs), 7.19 (brs), 7.15 (brs), 2.55 (brs), 1.14 ppm (brs).

[^{2}H]-*n*-Propylbenzene (Table 2, entry 3): Method A. Isotopic distribution (EIMS): 2% D_0, 2% D_1, 1% D_2, 3% D_3, 2% D_4, 6% D_5, 10% D_6, 18% D_7, 23% D_8, 25% D_9, 6% D_{10}, 1% D_{11}, 1% D_{12}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.24–7.20 (m, 0.81H), 7.14–7.10 (m, 1.89H), 2.54–2.52 (m, 0.27H), 1.58–1.56 (m, 0.27H), 0.89–0.86 ppm (m, 0.52H); ^{2}H NMR (CH_3OH): δ=7.25 (brs), 7.15 (brs), 2.50 (brs), 1.55 (brs), 0.85 ppm (brs).

[^{2}H]-*n*-Butylbenzene (Table 2, entry 4): Method A. Isotopic distribution (EIMS): 1% D_4, 1% D_5, 1% D_6, 2% D_7, 5% D_8, 14% D_9, 25% D_{10}, 30% D_{11}, 18% D_{12}, 3% D_{13}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.14–7.11 (m, 0.40H), 7.07–7.02 (m, 1.83H), 2.47–2.45 (m, 0.18H), 1.42 (s, 0.18H), 1.18 (s, 0.21H), 0.82–0.77 ppm (m, 0.39H); ^{2}H NMR (CH_3OH): δ=7.25 (brs), 7.14 (brs), 2.52 (brs), 1.50 (brs), 1.26 (brs), 0.85 ppm (brs).

[^{2}H]-*n*-Pentylbenzene (Table 2, entry 5): Method A. Isotopic distribution (EIMS): 1% D_4, 2% D_5, 4% D_6, 8% D_7, 12% D_8, 23% D_9, 21% D_{10}, 14% D_{11}, 7% D_{12}, 5% D_{13}, 2% D_{14}, 1% D_{15}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.24–7.20 (m, 0.35H), 7.14–7.11 (m, 1.72H), 2.54 (s, 0.11H), 1.54 (s, 0.13H), 1.39–1.28 (m, 1.40H), 0.90–0.85 ppm (m, 2.56H); ^{2}H NMR (CH_3OH): δ=7.24 (brs), 7.14 (brs), 2.52 (brs), 1.52 (brs), 1.23 (brs), 0.82 ppm (brs).

[^{2}H]-*n*-Hexylbenzene (Table 2, entry 6): Method A. Isotopic distribution (EIMS): 2% D_1, 7% D_2, 2% D_3, 4% D_4, 6% D_5, 16% D_6, 21% D_7, 19% D_8, 12% D_9, 6% D_{10}, 2% D_{11}, 1% D_{12}, 1% D_{13}, 1% D_{14}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.24–7.20 (m, 1.05H), 7.14–7.09 (m, 2.04H), 2.54 (s, 0.10H), 1.64–1.54 (m, 0.36H), 1.31–1.11 (m, 4.00H), 0.89–0.86 ppm (m, 2.93H); ^{2}H NMR (CH_3OH): δ=7.25 (brs), 7.15 (brs), 2.52 (brs), 1.62–1.52 (m), 1.25–1.09 (m), 0.81 ppm (brs).

[^{2}H]-*n*-Hexylbenzene (Table 2, entry 7): Method B. Isotopic distribution (EIMS): 1% D_0, 2% D_1, 1% D_2, 2% D_3, 3% D_4, 5% D_5, 8% D_6, 11% D_7, 12% D_8, 12% D_9, 9% D_{10}, 7% D_{11}, 6% D_{12}, 7% D_{13}, 6% D_{14}, 5% D_{15}, 2% D_{16}, 1% D_{17}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.15–7.11 (m, 0.84H), 7.05–7.00 (m, 1.91H), 2.45 (s, 0.05H), 1.45 (s, 0.05H), 1.30–1.17 (m, 2.50H), 0.80–0.77 ppm (m, 2.02H); ^{2}H NMR (CH_3OH): δ=7.24 (brs), 7.14 (brs), 2.52 (brs), 1.52 (brs), 1.24 (brs), 0.81 ppm (brs).

[^{2}H]-*n*-Hexylbenzene (Table 2, entry 8): Method B. The reaction time was 48 h. Isotopic distribution (EIMS): 1% D_8, 1% D_9, 2% D_{10}, 4% D_{11}, 11% D_{12}, 24% D_{13}, 27% D_{14}, 20% D_{15}, 8% D_{16}, 2% D_{17}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.15–7.11 (m, 0.90H), 7.05–7.00 (m, 2.02H), 2.44 (s, 0.07H), 1.44 (s, 0.07H), 1.18–1.15 (s, 0.47H), 0.80–0.73 ppm (m, 0.37H); ^{2}H NMR (CH_3OH): δ=7.24 (brs), 7.14 (brs), 2.51 (brs), 1.51 (brs), 1.21 (brs), 0.81 ppm (brs).

[^{2}H]-*n*-Hexylbenzene (Table 2, entry 9): A mixture of *n*-hexylbenzene (0.16 g, 1.0 mmol) and 10% Pd/C (16 mg, 10 wt% of the substrate) in D_2O (4 mL) was stirred at 160°C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue and 10% Pd/C (16 mg) in D_2O (4 mL) were stirred again at 160°C in a sealed tube under H_2 atmosphere for 24 h. The reaction mixture was worked up according to the procedure described above. Isotopic distribution (EIMS): 1% D_9, 1% D_{10}, 2% D_{11}, 3% D_{12}, 6% D_{13}, 10% D_{14}, 21% D_{15}, 31% D_{16}, 19% D_{17}, 6% D_{18}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.23–7.21 (m, 0.10H), 7.17–7.11 (m, 1.10H), 2.54 (s, 0.06H), 1.53 (s, 0.07H), 1.27–1.24 (m, 0.45H), 0.90–0.82 ppm (m, 0.56H); ^{2}H NMR (CH_3OH): δ=7.25 (brs), 7.16 (brs), 2.52 (brs), 1.52 (brs), 1.22 (brs), 0.81 ppm (brs).

[^{2}H]-*n*-Heptylbenzene (Table 2, entry 10): Method A. Isotopic distribution (EIMS): 2% D_3, 1% D_4, 2% D_5, 1% D_6, 2% D_7, 3% D_8, 8% D_9, 17% D_{10}, 22% D_{11}, 13% D_{12}, 8% D_{13}, 6% D_{14}, 5% D_{15}, 3% D_{16}, 3% D_{17}, 2% D_{18}, 1% D_{19}, 1% D_{20}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.13–7.12 (m, 0.17H), 7.04–7.02 (m, 1.56H), 2.44 (s, 0.11H), 1.44 (s, 0.09H), 1.25–1.16 (m, 3.14H), 0.78 ppm (t, J=6.8 Hz, 2.58H); ^{2}H NMR (CH_3OH): δ=7.26 (brs), 7.17 (brs), 2.54 (brs), 1.53 (brs), 1.26 (brs), 0.83 ppm (brs).

[^{2}H]-1,3-Diphenylpropane (Table 2, entry 11): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 3% D_6, 9% D_7, 19% D_8, 27% D_9, 24% D_{10}, 13% D_{11}, 4% D_{12}, 1% D_{13}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): δ=7.16–7.11 (m, 1.60H), 7.06–7.02 (m, 4.28H), 2.47 (s, 0.19H), 1.76 ppm (s, 0.09H); ^{2}H NMR (CH_3OH): δ=7.27 (brs), 7.17 (brs), 2.55 (brs), 1.84 ppm (brs).

[^{2}H]-4-*n*-Propylbenzoic acid (Table 2, entry 12): Method B. Isotopic distribution (EIMS): 1% D_2, 1% D_3, 1% D_4, 3% D_5, 17% D_6, 52% D_7, 19% D_8, 5% D_9, 1% D_{10}; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): δ=7.82 (d, J=8.7 Hz, 1.91H), 7.17 (d, J=8.7 Hz, 1.75H), 2.51 (s, 0.08H), 1.51 (s, 0.08H), 0.86–0.79 ppm (m, 0.28H); ^{2}H NMR (CH_3OH): δ=7.94 (brs), 7.30 (brs), 2.59 (brs), 1.58 (brs), 0.87 ppm (brs).

[^{2}H]-4-*n*-Butylbenzoic acid (Table 2, entry 13): Method B. Isotopic distribution (EIMS): 2% D_4, 6% D_5, 16% D_6, 17% D_7, 21% D_8, 27% D_9, 9% D_{10}, 2% D_{11}; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): δ=7.82 (d, J=8.7 Hz, 1.86H), 7.17 (d, J=8.7 Hz, 1.84H), 2.54 (s, 0.13H), 1.47 (s, 0.12H), 1.20–1.18 (m, 0.41H), 0.86–0.80 ppm (m, 1.24H); ^{2}H NMR (CH_3OH): δ=2.61 (brs), 1.54 (brs), 1.28 (brs), 0.87 ppm (brs).

[^{2}H]-4-*n*-Butylbenzoic acid sodium salt (Table 2, entry 14): A mixture of 4-*n*-butylbenzoic acid sodium salt (50 mg, 0.25 mmol) and 10% Pd/C (5.0 mg, 10 wt% of the substrate) in D_2O (1 mL) was stirred at 160°C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with methanol (20 mL) and the mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with methanol (3×10 mL) and the filtrate was concentrated in vacuo. Free carboxylic acid was prepared for mass spectrometry by the following procedure. The obtained [^{2}H]-4-butylbenzoic acid sodium salt was dissolved in water (0.5 mL) followed by the addition of few drops of 1 mol% hydrochloric acid solution. The mixture was shaken with ethyl acetate (1 mL) and the organic phase was used as the sample. Isotopic distribution (EIMS): 3% D_7, 14% D_8, 38% D_9, 29% D_{10}, 12% D_{11}, 3% D_{12}, 1% D_{13}; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): δ=7.76–7.74 (m, 1.44H), 7.06–7.04 (m, 1.54H), 2.49 (s, 0.08H), 1.45 (s, 0.08H), 1.19 (s, 0.17H), 0.78 ppm (s, 0.13H); ^{2}H NMR (CH_3OH): δ=7.85 (brs), 7.18 (brs), 2.55 (brs), 1.51 (brs), 1.26 (brs), 0.85 ppm (brs).

[^{2}H]-4-Isopropylbenzoic acid (Table 2, entry 15): Method A. Isotopic distribution (EIMS): 3% D_5, 19% D_6, 64% D_7, 12% D_8, 2% D_9; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): $\delta=7.85$ (d, $J=8.2$ Hz, 2.03H), 7.24 (d, $J=8.2$ Hz, 2.00H), 2.84 (s, 0.04H), 1.20–1.09 ppm (m, 0.34H); ^{2}H NMR (CH_3OH): $\delta=2.90$ (brs), 1.20 ppm (brs).

[^{2}H]-4-*tert*-Butylbenzoic acid (Table 2, entry 16): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 77% D_0, 17% D_1, 4% D_2, 2% D_3; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): $\delta=7.93$ (d, $J=8.7$ Hz, 2.00H), 7.49 (d, $J=8.7$ Hz, 2.00H), 1.33 ppm (s, 8.84H); ^{2}H NMR (CH_3OH): $\delta=1.29$ ppm (br).

[^{2}H]-Phenylcyclohexane (Table 2, entry 17): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 5% D_0, 14% D_1, 13% D_2, 14% D_3, 11% D_4, 10% D_5, 8% D_6, 7% D_7, 6% D_8, 5% D_9, 4% D_{10}, 2% D_{11}, 1% D_{12}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.24$–7.09 (m, 4.08H), 2.44 (br, 0.05H), 1.80–1.72 (m, 2.90H), 1.40–1.16 ppm (m, 3.44H); ^{2}H NMR (CH_3OH): $\delta=7.26$ (brs), 2.42 (brs), 1.78 (brs), 1.37 ppm (brs).

[^{2}H]-1-Ethylnaphthalene (Table 2, entry 18): Method A. Isotopic distribution (EIMS): 3% D_0, 3% D_1, 4% D_2, 6% D_3, 12% D_4, 18% D_5, 18% D_6, 16% D_7, 11% D_8, 6% D_9, 2% D_{10}, 1% D_{11}, 1% D_{12}; ^{1}H NMR (CD_3OD, 1,4-dimethoxybenzene as internal standard): $\delta=8.05$–8.04 (m, 1.00H), 7.83–7.82 (m, 0.67H), 7.67 (s, 0.66H), 7.48–7.42 (0.58H), 7.38–7.34 (m, 0.20H), 7.30 (s, 0.96H), 3.06 (brs, 0.20H), 1.34–1.26 ppm (m, 2.05H); ^{2}H NMR (CH_3OH): $\delta=7.85$ (brs), 7.70 (brs), 7.49 (brs), 7.46 (br), 7.39 (brs), 3.03 (brs), 1.27 ppm (brs).

[^{2}H]-Hydrocinnamic acid (Table 3, entry 1): Method A. Isotopic distribution (EIMS): 1% D_4, 9% D_5, 33% D_6, 46% D_7, 10% D_8, 1% D_9; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.16$–7.06 (m, 2.10H), 2.77 (s, 0.05H), 2.46 ppm (s, 0.05H); ^{2}H NMR (CH_3OH): $\delta=$ 7.25–7.20 (brm), 2.82 (brs), 2.50 ppm (brs).

[^{2}H]-4-Phenyl-*n*-butyric acid (Table 3, entry 2): Method A. Isotopic distribution (EIMS): 2% D_5, 7% D_6, 20% D_7, 34% d_8, 28% D_9, 7% D_{10}, 2% D_{11}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.17$–7.15 (m, 0.81H), 7.08 (brs, 2.88H), 2.51 (s, 0.13H), 2.16 (s, 0.21H), 1.75 ppm (s, 0.14H); ^{2}H NMR (CH_3OH): $\delta=7.27$ (brs), 7.19 (brs), 2.58 (brs), 2.22 (brs), 1.82 ppm (brs).

[^{2}H]-5-Phenyl-*n*-valeric acid (Table 3, entry 3): Method A. Isotopic distribution (EIMS): 1% D_5, 5% D_6, 12% D_7, 23% D_8, 27% D_9, 20% D_{10}, 10% D_{11}, 2% D_{12}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.16$–7.12 (m, 0.72H), 7.07–7.04 (m, 2.88H), 2.49 (s, 0.15H), 2.20–2.19 (m, 1.69H), 1.57–1.48 ppm (m, 0.74H); ^{2}H NMR (CH_3OH): $\delta=7.25$ (brs), 7.15 (brs), 2.55 (brs), 2.24 (brs), 1.56 ppm (brs).

[^{2}H]-5-Phenyl-*n*-valeric acid (Table 3, entry 4): Method B. Isotopic distribution (EIMS): 11% D_9, 28% D_{10}, 37% D_{11}, 17% D_{12}, 7% D_{13}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.16$–7.14 (m, 0.14H), 7.08 (s, 1.53H), 2.50 (s, 0.10H), 2.18 (s, 0.13H), 1.51–1.49 ppm (m, 0.25H); ^{2}H NMR (CH_3OH): $\delta=7.25$ (brs), 7.16 (brs), 2.56 (brs), 2.24 (brs), 1.56 ppm (brs).

[^{2}H]-6-Phenyl-*n*-hexanoic acid (Table 3, entry 5): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_6, 5% D_7, 14% D_8, 25% D_9, 28% D_{10}, 19% D_{11}, 6% D_{12}, 2% D_{13}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.15$–7.11 (m, 0.78H), 7.06–7.02 (m, 1.96H), 2.46 (s, 0.08H), 2.18–2.15 (m, 1.68H), 1.52–1.47 (m, 0.45H), 1.21 ppm (s, 0.11H); ^{2}H NMR (CH_3OH): $\delta=7.25$ (brs), 7.15 (brs), 2.54 (brs), 2.21 (brs), 1.55 (brs), 1.29 ppm (brs).

[^{2}H]-6-Phenyl-*n*-hexanoic acid (Table 3, entry 6): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 2% D_6, 7% D_7, 19% D_8, 27% D_9, 25% D_{10}, 14% D_{11}, 5% D_{12}, 1% D_{13}. ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.15$–7.09 (m, 1.29H), 7.06–7.00 (m, 2.37H), 2.46 (s, 0.10H), 2.17–2.13 (m, 0.89H), 1.47 (s, 0.23H), 1.21 ppm (s, 0.14H); ^{2}H NMR (CH_3OH): $\delta=7.19$ (brs), 7.07 (brs), 2.49 (brs), 2.14 (brs), 1.50 (brs), 1.23 ppm (brs).

[^{2}H]-Ibuprofen sodium salt (Table 3, entry 7): A mixture of Ibuprofen sodium salt (57 mg, 0.25 mmol) and 10% Pd/C (5.7 mg, 10 wt% of the substrate) in D_2O (1 mL) was stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with methanol (20 mL) and the mixture was filtered through a membrane filter (Millipore Millex-LG, 0.20 μm) to remove the catalyst. The collected catalyst was washed with methanol (2×5 mL) and the filtrate was concentrated in vacuo. The sample for mass spectrometry was a free carboxylic acid prepared by the procedure described for [^{2}H]-4-*n*-Butylbenzoic acid sodium salt (Table 2, entry 14). Isotopic distribution (EIMS): 1% D_9, 3% D_{10}, 7% D_{11}, 24% D_{12}, 33% D_{13}, 22% D_{14}, 8% D_{15}, 2% D_{16}. ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as internal standard): $\delta=7.13$ (d, $J=8.2$ Hz, 1.13H), 7.06 (d, $J=8.2$ Hz, 1.14H), 3.46 (s, 0.04H), 2.30 (s, 0.10H), 1.63 (s, 0.05H), 1.22–1.19 (m, 0.20H), 0.68 ppm (s, 0.30H); ^{2}H NMR (H_2O): $\delta=7.15$ (brs), 3.41 (brs), 2.28 (brs), 1.61 (brs), 1.18 (brs), 0.66 ppm (brs).

[^{2}H]-4-Methoxyphenylacetic acid (Table 3, entry 8): Method A. Isotopic distribution (EIMS): 4% D_1, 52% D_2, 30% D_3, 11% D_4, 3% D_5. ^{1}H NMR (CD_3OD): $\delta=7.18$–7.15 (m, 1.68H), 6.85–6.82 (m, 1.61H), 3.76–3.72 (m, 2.45H), 3.49 ppm (s, 0.07H); ^{2}H NMR (CH_3OH): $\delta=7.21$ (brs), 6.87 (brs), 3.76 (brs), 3.48 ppm (brs).

[^{2}H]-3-(4-Methoxyphenyl)propionic acid (Table 3, entry 9): Method B. Isotopic distribution (EIMS): 3% D_3, 18% D_4, 31% D_5, 27% D_6, 14% D_7, 5% D_8, 2% D_9. ^{1}H NMR (CD_3OD, 1,4-diacetylbenzene as internal standard): $\delta=7.02$–7.00 (m, 1.46H), 6.71 (d, $J=8.7$ Hz, 1.14H), 3.64–3.60 (m, 1.88H), 2.69 (s, 0.09H), 2.41 ppm (s, 0.04H); ^{2}H NMR (CH_3OH): $\delta=$ 7.15 (brs), 6.84 (brs), 3.73–3.70 (m), 2.78 (brs), 2.49 ppm (brs).

[^{2}H]-5-Phenoxy-*n*-valeric acid (Table 3, entry 10): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 3% D_2, 23% D_3, 34% D_4, 23% D_5, 11% D_6, 5% D_7, 1% D_8; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.15$–7.13 (m, 0.07H), 6.79–6.77 (m, 1.66H), 3.89–3.84 (m, 1.30H), 2.29–2.25 (m, 2.03H), 1.70–1.69 ppm (m, 4.01H); ^{2}H NMR (CH_3OH): $\delta=7.25$ (brs), 6.91 (brs), 3.94 ppm (brs).

[^{2}H]-*n*-Octanoic acid (Table 3, entry 11): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 76% D_0, 24% D_1; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=2.19$ (t, $J=7.5$ Hz, 1.87H), 1.53–1.49 (m, 1.85H), 1.23 (brs, 7.71H), 0.83–0.80 ppm (m, 2.85H); ^{2}H NMR (CH_3OH): $\delta=2.11$ (brs), 1.42 (brs), 1.14 (brs), 0.72 ppm (brs).

[^{2}H]-5-Phenyl-*n*-valeric acid methyl ester (Table 3, entry 12): Method A. Isotopic distribution (EIMS): 14% D_7, 24% D_8, 27% D_9, 22% D_{10}, 13% D_{11}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.16$–7.12 (m, 1.08H), 7.06–7.05 (m, 2.63H), 3.53 (s, 3.00H), 2.47 (s, 0.06H), 2.22 (s, 1.64H), 1.48 ppm (s, 0.29H); ^{2}H NMR (CH_3OH): $\delta=7.25$ (brs), 7.16 (brs), 2.55 (brs), 2.27 (brs), 1.55 ppm (brs).

[^{2}H]-5-Phenyl-*n*-valeric acid methyl ester (Table 3, entry 13): Method B. Isotopic distribution (EIMS): 1% D_6, 3% D_7, 10% D_8, 23% D_9, 33% D_{10}, 24% D_{11}, 5% D_{12}, 1% D_{13}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.16$–7.14 (m, 0.33H), 7.07 (s, 1.98H), 3.55 (s, 2.90H), 2.48 (s, 0.16H), 2.21 (s, 0.17H), 1.48 ppm (s, 0.34H); ^{2}H NMR (CH_3OH): $\delta=7.27$ (brs), 7.16 (brs), 3.78 (brs), 2.55 (brs), 2.28 (brs), 1.56 ppm (brs).

[^{2}H]-2-Phenylethanol (Table 4, entry 1): Method A. Isotopic distribution (EIMS): 22% D_0, 47% D_1, 27% D_2, 4% D_3; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.28$–7.14 (m, 4.54H), 3.75–3.66 (m, 2.00H), 2.82–2.77 ppm (m, 0.87H); ^{2}H NMR (CH_3OH): $\delta=2.76$ ppm (brs).

[^{2}H]-3-Phenyl-1-propanol (Table 4, entry 2): Method A. Isotopic distribution (EIMS): 8% D_0, 25% D_1, 37% D_2, 16% D_3, 9% D_4, 5% D_5; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.25$–7.10 (m, 4.83H), 3.55 (t, $J=6.5$ Hz, 1.60H), 2.67–2.62 (m, 0.51H), 1.85–1.78 ppm (m, 1.80H); ^{2}H NMR (CH_3OH): $\delta=3.52$ (brs), 2.62 (brs), 1.77 ppm (brs).

[^{2}H]-4-Phenyl-1-butanol (Table 4, entry 3): Method A. Isotopic distribution (EIMS): 5% D_1, 19% D_2, 22% D_3, 23% D_4, 21% D_5, 10% D_6; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta=7.24$–7.21 (m, 1.89H), 7.17–7.10 (m, 2.84H), 3.56–3.53 (m, 1.94H), 2.61–2.57 (m, 0.26H), 1.66–1.50 ppm (m, 2.13H); ^{2}H NMR (CH_3OH): $\delta=3.67$ (brs), 2.56 (brs), 1.60 (brs), 1.49 ppm (brs).

[^{2}H]-5-Phenyl-1-pentanol (Table 4, entry 4): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 2% D_0,

5% D_1, 11% D_2, 24% D_3, 31% D_4, 16% D_5, 7% D_6, 2% D_7, 1% D_8, 1% D_9; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.24$–7.20 (m, 1.65H), 7.15–7.09 (m, 2.54H), 3.52 (t, $J = 6.5$ Hz, 1.85H), 2.56 (s, 0.15H), 1.62–1.51 (m, 2.35H), 1.41–1.22 ppm (m, 1.50H); ^{2}H NMR (CH_3OH): $\delta = 2.55$ (brs), 1.56 (brs), 1.32 ppm (brs).

[^{2}H]-5-Phenyl-1-pentanol (Table 4, entry 5): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 2% D_0, 4% D_1, 7% D_2, 8% D_3, 9% D_4, 11% D_5, 14% D_6, 13% D_7, 12% D_8, 11% D_9, 7% D_{10}, 2% D_{11}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.15$–7.11 (m, 1.66H), 7.06–7.00 (m, 2.58H), 3.44–3.40 (m, 1.07H), 2.48–2.46 (m, 0.19H), 1.47–1.39 (m, 0.89H), 1.22–1.18 ppm (m, 0.24H); ^{2}H NMR (CH_3OH): $\delta = 7.25$ (brs), 3.49 (brs), 2.54 (brs), 1.55–1.49 (brm), 1.31 ppm (brs).

[^{2}H]-6-Phenyl-1-hexanol (Table 4, entry 6): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_0, 4% D_1, 12% D_2, 29% D_3, 31% D_4, 16% D_5, 7% D_6; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.24$–7.20 (m, 1.72H), 7.15–7.09 (m, 2.71H), 3.54–3.50 (m, 2.01H), 2.55 (s, 0.08H), 1.64–1.47 (m, 2.64H), 1.41–1.28 ppm (m, 3.69H); ^{2}H NMR (CH_3OH): $\delta = 2.55$ (brs), 1.56 (brs), 1.30 ppm (brs).

[^{2}H]-7-Phenyl-1-heptanol (Table 4, entry 7): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_0, 4% D_1, 10% D_2, 22% D_3, 30% D_4, 18% D_5, 9% D_6, 4% D_7, 2% D_8; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.15$–7.11 (m, 1.77H), 7.05–7.00 (m, 2.69H), 3.43 (t, $J = 6.5$ Hz, 1.81H), 2.47–2.45 (m, 0.32H), 1.47–1.39 (m, 2.21H), 1.23 ppm (brs, 4.95H); ^{2}H NMR (CH_3OH): $\delta = 2.53$ (brs), 1.55 (brs), 1.28 ppm (brs).

[^{2}H]-8-Phenyl-1-octanol (Table 4, entry 8): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 3% D_0, 14% D_1, 28% D_2, 24% D_3, 17% D_4, 10% D_5, 3% D_6, 1% D_7; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.24$–7.09 (m, 4.61H), 3.54–3.44 (m, 1.70H), 2.57–2.54 (m, 0.54H), 1.56–1.49 (m, 2.90H), 1.31 ppm (brs, 7.42H); ^{2}H NMR (CH_3OH): $\delta = 2.52$ (brs), 1.53 (brs), 1.26 ppm (brs).

[^{2}H]-2-Phenyl-1-propanol (Table 4, entry 9): Method A. Isotopic distribution (EIMS): 10% D_0, 74% D_1, 13% D_2, 3% D_4; ^{1}H NMR (CD_3OD, 1,4-diacetylbenzene as internal standard): $\delta = 7.19$–7.04 (m, 4.68H), 3.58–3.44 (m, 1.89H), 2.78–2.73 (m, 0.03H), 1.16–1.08 ppm (m, 3.05H); ^{2}H NMR (CH_3OH): $\delta = 3.64$ (brs), 2.83 ppm (brs).

[^{2}H]-2-Phenylethyl methyl ether (Table 4, entry 10): Method A. Isotopic distribution (EIMS): 3% D_0, 8% D_1, 23% D_2, 35% D_3, 27% D_4, 4% D_5; ^{1}H NMR ([D_6]acetone, *p*-anisic acid as internal standard): $\delta = 7.28$–7.14 (m, 4.34H), 3.56–3.51 (m, 0.64H), 3.26 (s, 2.76H), 2.84–2.79 ppm (m, 0.24H); ^{2}H NMR (acetone): $\delta = 3.46$ (brs), 2.74 ppm (brs).

[^{2}H]-3-Phenylpropyl methyl ether (Table 4, entry 11): Method A. Isotopic distribution could not be assigned from mass spectra. ^{1}H NMR ([D_6]acetone, *p*-anisic acid as internal standard): $\delta = 7.28$–7.13 (m, 5.00H), 3.34–3.29 (m, 0.71H), 3.25 (s, 2.92H), 2.64–2.61 (m, 0.30H), 1.84–1.77 ppm (m, 0.60H); ^{2}H NMR (acetone): $\delta = 3.25$ (brs), 2.56 (brs), 1.74 ppm (brs).

[^{2}H]-3-Phenylpropyl ethyl ether (Table 4, entry 12): Method A. Isotopic distribution (EIMS): 2% D_0, 7% D_1, 43% D_2, 7% D_3, 12% D_4, 26% D_5, 28% D_6, 11% D_7, 3% D_8; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.25$–7.22 (m, 1.52H), 7.17–7.11 (m, 2.43H), 3.50–3.43 (m, 1.95H), 3.41–3.38 (m, 0.40H), 2.61 (s, 0.17H), 1.79 (s, 0.17H), 1.19–1.15 ppm (m, 3.00H); ^{2}H NMR (CH_3OH): $\delta = 7.26$ (brs), 3.37 (brs), 2.60 (brs) 1.78 ppm (brs).

[^{2}H]-Phenylethylamine hydrochloride (Table 5, entry 1): Method A. Isotopic distribution could not be assigned from mass spectra. ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as internal standard): $\delta = 7.30$–7.17 (m, 4.54H), 3.12 (s, 1.82H), 2.83 ppm (s, 0.08H); ^{2}H NMR (H_2O): $\delta =$ 2.81 ppm (brs).

[^{2}H]-Phenylbutylamine hydrochloride (Table 5, entry 2): Method A. Isotopic distribution could not be assigned from mass spectra. ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as internal standard): $\delta = 7.26$–7.22 (m, 1.80H), 7.16–7.13 (m, 2.64H), 2.87–2.84 (m, 1.83H), 2.49 (s, 0.08H), 1.53–1.49 ppm (m, 0.82H); ^{2}H NMR (H_2O): $\delta = 2.47$ (brs), 1.47 ppm (brs).

[^{2}H]-*N*-(2-phenylethyl)acetamide (Table 5, entry 3): Method A. Isotopic distribution (EIMS): 2% D_0, 17% D_1, 69% D_2, 11% D_3, 1% D_4; ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as internal standard): $\delta = 7.18$–7.15 (m, 1.84H), 7.10–7.04 (m, 2.73H), 3.17 (s, 2.04H), 2.58–2.53 (m, 0.22H), 1.71 ppm (s, 3.00H); ^{2}H NMR (H_2O): $\delta = 7.24$ (brs), 3.23 (brs), 2.61 ppm (brs).

[^{2}H]-*N*-(2-Phenylethyl)acetamide (Table 5, entry 4): Method B. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_3, 8% D_4, 26% D_5, 36% D_6, 23% D_7, 5% D_8, 1% D_9; ^{1}H NMR (D_2O, *p*-anisic acid sodium salt as internal standard): $\delta = 7.25$–7.24 (m, 0.66H), 7.15 (brs, 1.92H), 3.26 (s, 0.06H), 2.64 (s, 0.06H), 1.78 ppm (s, 2.62H); ^{2}H NMR (H_2O): $\delta = 7.25$ (brs), 7.18 (brs), 3.23 (brs), 2.61 (brs), 1.75 ppm (brs).

[^{2}H]-4-Methylanisole (Table 6, entry 1): Method A. Isotopic distribution (EIMS): 2% D_0, 11% D_1, 15% D_2, 55% D_3, 15% D_4, 2% D_5; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.05$–7.02 (m, 1.70H), 6.81–6.71 (m, 1.70H), 3.72 (s, 2.74H), 2.23–2.19 ppm (m, 0.06H); ^{2}H NMR (CH_3OH): $\delta = 7.06$ (brs), 6.79 (brs), 3.72 (brs), 2.19 ppm (brs).

[^{2}H]-*p*-Toluidine hydrochloride (Table 6, entry 2): Method A. ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.34$–7.33 (m, 1.47H), 7.27 (d, $J = 8.2$ Hz, 0.37H), 2.34 ppm (s, 0.10H); ^{2}H NMR (CH_3OH): $\delta =$ 7.28 (brs), 2.32 ppm (brs).

[^{2}H]-4-Methylbiphenyl (Table 6, entry 3): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_0, 1% D_1, 3% D_2, 4% D_3, 5% D_4, 8% D_5, 17% D_6, 23% D_7, 23% D_8, 11% D_9, 3% D_{10}, 1% D_{11}; ^{1}H NMR (CD_3OD, *p*-anisic acid as internal standard): $\delta = 7.47$–7.46 (m, 1.49H), 7.38–7.36 (m, 0.28H), 7.31–7.27 (m, 0.28H), 7.18 (s, 0.16H), 7.13–7.12 (s, 1.34H), 2.41–2.21 ppm (m, 0.18H); ^{2}H NMR (CH_3OH): $\delta = 7.58$ (brs), 7.50 (brs), 7.41 (brs), 7.30 (brs), 7.24 (brs), 2.29 ppm (brs).

[^{2}H]-4-Benzyltoluene (Table 6, entry 4): Method A. Ethyl acetate was used instead of diethyl ether. Isotopic distribution (EIMS): 1% D_1, 1% D_2, 1% D_3, 2% D_4, 2% D_5, 2% D_6, 4% D_7, 8% D_8, 16% D_9, 24% D_{10}, 22% D_{11}, 12% D_{12}, 4% D_{13}, 1% D_{14}; ^{1}H NMR (CD_3OD, 1,4-diacetylbenzene as internal standard): $\delta = 7.14$–7.11 (m, 0.19H), 7.05 (s, 1.29H), 6.95 (s, 1.51H), 3.78–3.76 (m, 0.17H), 2.17–2.12 ppm (m, 0.24H); ^{2}H NMR (CH_3OH): $\delta = 7.25$ (brs), 7.16 (brs), 7.06 (brs), 3.84 (brs), 2.22 ppm (brs).

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[20] The use of 10% Pd/C purchased from different suppliers such as Merck (807104-0010), ACROS (19503–0100), N.E. Chemcat (K type), and Wako (163–15272) also gave similar H/D exchange results (see Supporting Information, S108–S115).

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