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Efficient and Convenient Heterogeneous Palladium-Catalyzed Regioselective Deuteration at the Benzylic Position

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Abstract: The Pd/C-catalyzed efficient and regioselective hydrogen–deuterium (H-D) exchange reaction on the benzylic site proceeded in D_2O in the presence of a small amount of H_2 gas. The use of the Pd/C–ethylenediamine complex [Pd/C(en)] as a catalyst instead of Pd/C led to the efficient deuterium incorporation into the benzylic site of *O*-benzyl protective groups without hydrogenolysis. These H-D exchange reactions provide a post synthetic and D_2-gas-free deuterium-labeling method on a wide variety of benzylic sites using D_2O as the deuterium source and heterogeneous Pd/C or Pd/C(en) as a reusable heterogeneous palladium catalyst under mild and neutral conditions.

Keywords: deuterium · heterogeneous catalysis · isotopic labeling · palladium · regioselectivity

Introduction

Deuterium exchange reactions, that is to say, the displacement of carbon–hydrogen bonds by carbon–deuterium bonds are getting significant attention because isotopically labeled compounds have recently been recognized to have increasing importance with the development of mass spectrometry, and ^1H and ^2H NMR spectroscopy.[1] In particular, deuterium-labeled compounds are widely used as research tools in drug metabolism, the structural elucidation of biological macromolecules, reaction mechanisms and kinetics, the quantitative analyses of environmental pollutants and residual pesticides, and so forth.[1,2] Multi-deuterated compounds are often utilized as standard substances or tracers of mass analyses. Furthermore, regioselectively labeled compounds at particular sites are quite useful for the studies of reaction mechanisms and higher-order structural analyses. The multi- or regioselective labeling methods with a high deuterium efficiency are particularly important techniques for the preparation of useful deuterium-labeled reagents. A variety of catalytic hydrogen–deuterium (H-D) exchange reactions have been reported to date; for example, acid-,[3] base-,[2e,4] or transition-metal-catalyzed;[3c,5–12] microwave-enhanced;[5d,e,h,9e,13] super- or subcritical;[4b,d,e,h,i,11c,d,e,14] and enzymatic[15] exchange reactions, while most of the reactions were not involved in the chemo- and/or regioselectivities. Furthermore, such selective reactions were limited only to the H-D exchange either on the aromatic moieties[7b,c,8b,c,e,f,h,j,m,n] or on the methyl, methylene, and methine groups[3g,4h,12e,15c] activated by neighboring electron-withdrawing groups, such as the carbonyl group. A few methods for the selective deuteration of the benzylic site have been reported; for example, [D_6]dimethyl sulfoxide–NaH,[16] Na_2PtCl_4–D_2O–AcOD,[17] Pd/C–AcOD–D_2,[18] Pd/C–D_2,[19] [$Co(CO)_8$]–D_2,[20] or Raney Co (or Cu)-Al alloys–Na_2CO_3–D_2O.[21] These methods, however, require high temperature, high pressure, acidic or basic additives, special acid-resistance pressure vessels, non-commercially available catalysts, and/or the use of expensive ($ 218.50/25 L, Aldrich) D_2 gas, and some reactions resulted in low deuterium efficiencies or regioselectivity due to the difficult control of the reaction conditions. Therefore, the development of a simple, totally catalytic, D_2-gas-free, selective, and neutral H-D exchange reaction of the benzylic site under mild reaction conditions is strongly desired.

We have recently developed chemoselective hydrogenation methods using heterogeneous palladium catalysts. Propylbenzene was stirred at room temperature with a catalytic amount of 10% Pd/C in CD_3OD under a H_2 atmosphere

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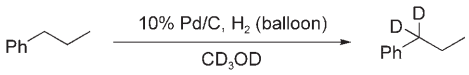
(balloon) and the reaction process was followed by ^{1}H NMR spectroscopy. Surprisingly, the gradual and continuous decrease in the signal intensity of the benzylic proton of propylbenzene was observed, indicating the reaction of the Pd/C-catalyzed regioselective displacement of the hydrogen atom on the benzylic carbon by the deuterium atom [Eq. (1)]. Based on this finding, we have successfully developed a D_2-gas-free and regioselective H-D exchange reaction at the benzylic position of organic compounds catalyzed by heterogeneous Pd/C in D_2O as a deuterium source in the presence of a small amount of H_2 gas at room temperature.[22] Deuterated compounds at the benzylic position should be useful for the study of the reaction mechanism based on the kinetic isotope effect as well as analyses of higher-order interactions between bioactive peptides. We also developed multi-deuterium labeling methods on aromatic rings and/or alkyl side chains under higher temperature conditions (110–180 °C) by using a Pd/C (and/or Pt/C)–D_2O–H_2 system.[23]



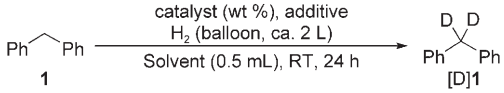
(1)

The *O*-benzyl protective group is one of the most useful protecting groups of alcohol and phenol derivatives, such as biomolecular sugars, amino acids steroids, and nucleosides. The *O*-benzyl groups are readily introduced by using benzyl bromide or chloride as an alkylating agent, and stable in either acidic or basic media, but easily removed by a simple catalytic hydrogenation with Pd/C.[24] However, it sometimes causes the difficult characterization of the structure of products by ^{1}H NMR spectroscopy due to the overlapping by the benzylic peaks.[25] To overcome this problem, simplification of the ^{1}H NMR spectrum by the selective deuteration of the benzylic protons of the *O*-benzyl protective groups would be desired. Currently, deuterated benzyl bromide or chloride is used for the preparation of deuterium-labeled benzyl ethers; however, such reagents are very expensive[26] and the deuterated compounds have to be re-synthesized from the beginning of the synthetic scheme just for ^{1}H NMR studies. The development of the benzylic-site-selective and post-synthetic deuterium-labeling method of *O*-benzyl groups is also advisable as an alternative technique. Our benzylic-site-selective deuterium-labeling method[22] was not applicable to a substrate bearing some reducible functionalities including the *O*-benzyl protective group due to the competing Pd/C-catalyzed hydrogenolysis. We recently developed the Pd/C–ethylenediamine complex [Pd/C(en)] catalyst, which is applicable to the chemoselective hydrogenation of a variety of reducible functionalities, that is, coexisting *O*-benzyl and *N*-Cbz protective groups, benzyl alcohols, and epoxides.[27] The use of Pd/C(en) as a catalyst instead of Pd/C was expected to develop the chemoselective H-D exchange reaction at the benzylic site of the *O*-benzyl protective groups without hydrogenolysis. In this paper, we describe the detailed results of the chemoselective H-D exchange reaction at the benzylic site using the Pd/C–D_2O–H_2 system and its application to the deuteration of *O*-benzyl protective groups without deprotection using Pd/C(en).

Results and Discussion

Pd/C-catalyzed benzylic-site-selective H-D exchange reaction: We initially optimized the reaction conditions of the Pd/C-catalyzed H-D exchange at the benzylic position of diphenylmethane (**1**) under ordinary hydrogen pressure at room temperature for 24 h (Table 1). The benzylic site-selective deuterated product ([D]**1**) was obtained in a 74% deuterium efficiency when CD_3OD (0.5 mL) was used as the solvent (entry 1). The use of AcOD instead of CD_3OD led to the significantly decreased deuterium efficiency (entry 2). D_2O is a comparable deuterium source with CD_3OD, since the reaction performed in D_2O afforded [D]**1** with a 66% deuterium content (D content; entry 3). From the viewpoints of cost, safety (non flammable solvent), environmental burden, and general versatility, we decided to use D_2O as the solvent and deuterium source for the H-D exchange reaction. When the 66%-deuterated product obtained by the first deuteration shown in entry 3 was used as the substrate

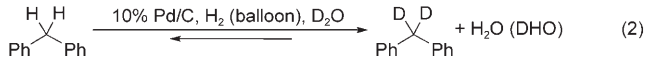
Table 1. H-D exchange reaction under various conditions.[a]



Entry	Catalyst (wt %)	Additive	Solvent	D content [%][b]
1	10% Pd/C (10)	—	CD_3OD	74
2	10% Pd/C (10)	—	AcOD	37
3	10% Pd/C (10) (1st run)	—	D_2O	66
4	10% Pd/C (10) (2nd run)[c]	—	D_2O	77
5	10% Pd/C (10) (3rd run)[d]	—	D_2O	81
6	10% Pd/C (10)	DCl[e]	D_2O	74
7	10% Pd/C (10)	AcOD[f]	D_2O	70
8	10% Pd/C (10)	Na_2CO_3[g]	D_2O	51
9	10% Pd/C (10)	nBu$_4$N(HSO$_4$)[h]	D_2O	49
10	10% Pd/C (10)	SDS[i]	D_2O	66
11	10% Pd/C (10)	Triton® X-100[j]	D_2O	43
12	10% Pd/C (30)	—	D_2O	84
13	5% Pd/C (10)	—	D_2O	59
14	5% Pd/Al_2O_3 (10)	—	D_2O	10

[a] 1.0 mmol of diphenylmethane (**1**) was used as a substrate. [b] The D content was determined by ^{1}H NMR spectroscopy. [c] The 66% deuterated diphenylmethane (the product of entry 3) was used as the starting material. [d] The 77% deuterated diphenylmethane (the product of entry 4) was used as the starting material. [e] 0.50 equiv of DCl (20 wt% solution in D_2O) was added. [f] 0.50 equiv of AcOD was added. [g] 1.2 equiv of Na_2CO_3 was added. [h] 0.20 M of nBu$_4$N(HSO$_4$) was added as a phase-transfer catalyst. [i] 0.20 M of SDS (sodium dodecyl sulfate) was added as an ionic surfactant. [j] 0.10 M of Triton® X-100 (polyoxyethylene(10) isooctylphenyl ether) was added as a nonionic surfactant.

for the second H-D exchange reaction, the deuterium efficiency only slightly increased to 77% (entry 4) and even the third run also gave only an 81%-deuterated product (entry 5). The addition of neither DCl nor AcOD had a significant effect on the deuterium incorporation (entries 6 and 7) and the use of Na_2CO_3 as an additive caused a drastic decrease in the deuterium efficiency (entry 8). We also examined the effects of nBu$_4$N(HSO$_4$) (phase transfer catalyst), sodium dodecyl sulfate (SDS, ionic surfactant) or Triton® X-100 (nonionic surfactant), since the present H-D exchange reaction presumably occurred in a three-phase system in D_2O (aqueous phase), diphenylmethane (**1**, organic phase), and Pd/C (solid phase), as these additives could not increase the deuterium efficiency contrary to our expectation (entries 9–11). Furthermore, the increased amount of 10% Pd/C (30 wt% of the weight of substrate **1**) improved the deuterium efficiency to 84% (entry 12), but the use of 5% Pd/C (10 wt% of the weight of **1**) significantly reduced the efficiency (entry 13). Another heterogeneous palladium catalyst, Pd/Al_2O_3, was ineffective for this reaction (entry 14). The Pd/C-catalyzed H-D exchange reaction selectively proceeded at the benzylic site at room temperature; however, the maximum D content of the desired deuterated product ([D]**1**) was unfortunately 84% (Table 1, entry 12). Such deuterium efficiency degree is presumably caused by the simultaneous reverse reaction from the generated C–D bond to the C–H bond, since the reaction was carried out in a large volume of H_2 gas in a balloon [Eq. (2)].



(2)

Hence, the effect of the H_2-gas volume toward the reaction was studied in detail (Table 2). H_2 gas is essential for the H-D exchange reaction (entry 1). The reaction under excess H_2 gas (balloon, ca. 2 L, 82 mmol) gave the desired [D]**1** with a 66% D content after 24 h (entry 2), and the elongation of the reaction time (72 h) did not significantly increase the deuterium efficiency (entry 3). On the other hand, the use of catalytic amounts (0.7 equiv, ca. 0.70 mmol of H_2 (17 mL) vs. 1.00 mmol of **1**) of H_2 gas in a hydrogen-charged sealed test tube gave better results. The deuterium efficiency increased with time up to 95% (72 h) at room temperature (entry 6). No further significant improvement was observed even after 120 h (entry 7).

Table 2. Assessment of Pd/C-H_2-catalyzed H-D exchange reaction of diphenylmethane (**1**) in D_2O.[a]

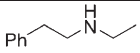
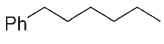
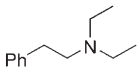
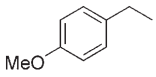
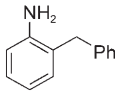
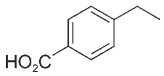
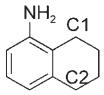
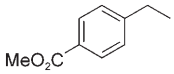
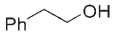
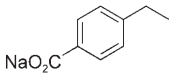
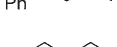
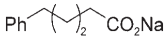
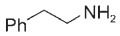
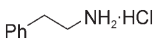
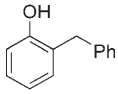
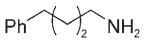
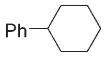
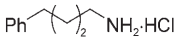
Entry	H_2	t [h]	D content [%][b]
1	none[c]	24	0
2	balloon (ca. 2 L)	24	66
3	balloon (ca. 2 L)	72	73
4	17 mL	24	60
5	17 mL	48	84
6	17 mL	72	95
7	17 mL	120	96

[a] Unless otherwise noted, 1.0 mmol of diphenylmethane (**1**) was used and the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of **1**) in D_2O (0.50 mL) at room temperature. [b] The D content was determined by ^{1}H NMR. [c] The reaction was performed under atmospheric air.

Scope and limitation of Pd/C-catalyzed H-D exchange reaction at room temperature: Table 3 summarizes the results of the H-D exchange reaction at the benzylic positions of various substrates. For the simple alkyl benzenes, the corresponding deuterated compounds were obtained with a nearly quantitative D content (entries 1–3). On the other hand, the use of 4-ethylbenzoic acid (**4**) and methyl 4-ethylbenzoate (**5**), which possess the electron-withdrawing carboxylic acid or corresponding methyl ester, produced a lower deuterium efficiency (entries 4 and 5),[23b] while the drawback was overcome by the use of the corresponding sodium salt (**6**), and a nearly quantitative D content was achieved (entry 6). The deuteration of sodium 5-phenylpentanoate (**7**) also smoothly proceeded (entry 7). A very poor deuterium incorporation was observed using substrates bearing an amino group since the amino group should be a strong catalyst poison of Pd/C (entries 8, 10 and 12–14, 0–39% D contents).[28] The lower D content on the benzylic position adjacent to the amino group of 5,6,7,8-tetrahydro-1-naphthylamine (**15**) was observed (13% at C1 position) when compared to the other benzylic position located at a position distant from the amino group (59% at C2 position) (entry 15). The H-D exchange efficiencies of the amine derivatives were significantly enhanced in the cases of the hydrochlorides, of which the lone pair on the nitrogen atom that causes the catalyst poisonous was occupied (entries 9 and 11). Furthermore, nearly no deuterium incorporation was observed when 2-phenylethyl alcohol (**16**) and the corresponding methyl ether (**17**) were employed as substrates (entries 16 and 17) although 3-phenyl-1-propanol (**18**) and 8-phenyl-1-octanol (**19**) possessing a longer side chain was efficiently deuterated ([D]**18** and [D]**19** with 92 and 94% D content, respectively, entries 18 and 19). The deuteration of 2-benzylphenol (**20**), the hydroxyl group and the benzylic position located in the spatial vicinity, also gave a low D content (29%, entry 20). The deuterium incorporation on the branched benzylic position (methine; **21** and **22**) also proceeded without any problems (entries 21 and 22). These reactions were very clean and no column chromatographic separation was required to obtain the spectrally pure deuterated products. It is worth noting that the reaction is totally regioselective and virtually no competitive deuteration on the other positions including the aromatic ring was observed (confirmed by ^{2}H NMR spectroscopy).

Application of heating conditions for the benzylic position selective H-D exchange reaction: The benzylic site-selective H-D exchange reaction required a long reaction time (72 h) at room temperature to accomplish the quantitative deuterium incorporation; indeed carboxylic acid (**4**), ester (**5**), amine (**8**, **10** and **12**–**15**), alcohol (**16** and **20**) and ether (**17**) derivatives were not completely applicable as substrates. We then optimized the reaction temperature of the deuteration

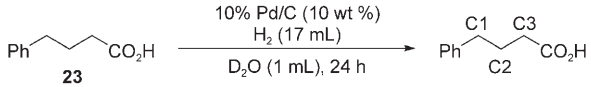
Table 3. Pd/C-H_2-catalyzed deuterium exchange reaction of benzylic site in D_2O at room temperature.[a]

Entry	Substrate		D content [%][b]	Yield [%][c]	Entry	Substrate		D content [%][b]	Yield [%][c]
1		**1**	95	88	12		**12**	0	84[d]
2		**2**	97	73[d]	13		**13**	trace	96[d]
3		**3**	96	40[d]	14		**14**	3	98
4		**4**	22	97	15		**15**	C1: 13 C2: 59	97
5		**5**	74	74[d]	16		**16**	8	97[d]
6		**6**	98	100	17		**17**	4	88[d]
7		**7**	90	97	18		**18**	92	98
8		**8**	0	79[d]	19[e]		**19**	94	94
9		**9**	57	99	20		**20**	29	96
10		**10**	39	88	21		**21**	98	55[d]
11		**11**	78	99	22		**22**	93	20[d]

[a] Unless otherwise noted, 1.0 mmol of the substrate was used, and all the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of the substrate) in D_2O (0.50 mL) at room temperature for 72 h. [b] The D content was determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The low isolated yield of the deuterated is due to its low boiling point and volatile nature. [e] 1.0 mL of D_2O was used.

using 4-phenyl butyric acid (**23**) as the substrate (Table 4). Although the deuterium efficiency at the benzylic site at 10 and 30 °C were sluggish due to the coexisting carboxylic acid functionality (entries 1 and 2), it was dramatically improved to a 90% D content at 45 °C and 95% at 50 °C for 24 h (entries 3 and 4). Further deuteration at the aromatic ring and non-benzylic position(s) of the alkyl side chain (C2 and/or C3) significantly proceeded at higher temperatures (70, 90, and 110 °C, entries 5–7). Thus, we chose 50 °C as the most suitable reaction temperature and subsequently investigated the time-course of the H-D exchange progress. The benzylic site (C1) was already 63% deuterated after only 2 h (Table 5, entry 1) and the D content continuously increased

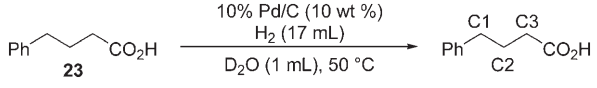
Table 4. Temperature effect on the H-D exchange reaction of 4-phenyl butyric acid[a]



Entry	T [°C]	D content [%][b] Ph	C1	C2	C3	Yield [%][c]
1	10	0	4	0	0	98
2	30	0	9	0	0	100
3	45	0	90	0	0	100
4	50	0	95	0[d]	0	100
5	70	13	94	75	0	100
6	90	22	97	96	35	100
7	110	41	95	95	92	100

[a] 0.50 mmol of 4-phenyl-1-butylic acid (**23**) was used, and the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of **23**) in D_2O (1.0 mL) for 24 h. [b] The D content was determined by ^{1}H NMR after the conversion of the carboxylic acid into the corresponding methyl ester on the basis of the integration of the methyl protons. [c] Isolated yield. [d] ^{2}H NMR indicated a trace of deuteration.

Table 5. Time-course of deuteration of 4-phenyl butyric acid.[a]



Entry	t [h]	D content [%][b] Ph	C1	C2	C3	Yield [%][c]
1	2	0	63	0	0	82
2	4	0	71	0	0	90
3	6	0	88	0	0	100
4	12	0	97	0	0	93
5	24	0	95	0[d]	0	100

[a] 0.50 mmol of 4-phenyl-1-butylic acid (**23**) was used, and the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of **23**) in D_2O (1.0 mL) at 50 °C. [b] The D content was determined by ^{1}H NMR after the conversion of the carboxylic acid into the corresponding methyl ester on the basis of the integration of the methyl protons. [c] Isolated yield. [d] ^{2}H NMR spectroscopy indicated a trace of deuteration.

up to 12 h (97%) without further deuteration of the aromatic ring or the non-benzylic alkyl side chain (entry 4). A continuous reaction to 24 h did not indicate a significant increase in the deuterium efficiency (entry 5). Thus, mild heat at 50°C led to a significant enhancement of the H-D exchange efficiency, and the reaction time was substantially shortened from 72 h to 12 h. Next, we investigated the deuteration of a variety of alkyl benzenes under the mild heating conditions.

Scope and limitation of the benzylic site-selective H-D exchange reaction at 50°C: While the deuteration of diphenylmethane (**1**) required 72 h to accomplish the quantitative deuteration at room temperature (Table 3, entry 1), the reaction at 50°C proceeded with a 92% D content only after 8 h (Table 6, entry 1). For the 2-phenethylamine (**8**), 2-phenethylamine hydrochloride (**9**), 4-phenylbutylamine (**10**), 2-benzylaniline (**14**), and 5,6,7,8-tetrahydro-1-naphthylamine (**15**), with low H-D exchange efficiencies at room temperature (Table 3, entries 8, 9, 10, 14, and 15), the deuterium efficiencies were significantly enhanced at 50°C and the corresponding labeled products were obtained with good to excellent D contents (entries 2–6). The primary alcohols **18** and **19** and phenol derivative **20** were effectively deuterated (entries 9–11) although 2-phenylethyl alcohol (**16**) and 2-phenylethyl methyl ether (**17**) were not reactive enough to give the efficiently labeled products even under heating conditions (entries 7 and 8). Cyclohexylbenzene (**21**) was smoothly deuterated at the benzylic methine for 8 h (entry 12).

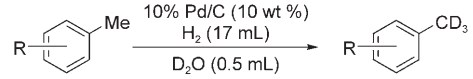
Table 6. Pd/C–H_2–catalyzed deuterium exchange reaction of benzylic site in D_2O at 50°C.[a]

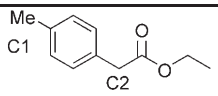
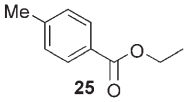
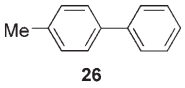
Entry	Substrate[b]	t [h]	D content [%][c]	Yield [%][d]
1	**1**	8	92	93[e]
2	**8**	72	73	82[e]
3[f]	**9**	72	77	100[g]
4	**10**	48	91	89
5	**14**	72	92	97
6[f]	**15**	48	C1: 93 C2: 92	89
7	**16**	72	5	94[e]
8	**17**	72	1	95[e]
9	**18**	8	93	79
10[h]	**19**	24	95	100
11	**20**	24	95	99
12	**21**	8	98	89[e]

[a] Unless otherwise noted, 1.0 mmol of the substrate was used, and all the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of the substrate) in D_2O (0.50 mL) at 50°C. [b] For structures see Table 3. [c] The D content was determined by ^{1}H NMR spectroscopy. [d] Isolated yield. [e] The low isolated yield of the deuterated is due to the low boiling point and volatile nature. [f] 20 wt% of the weight of substrate of 10% Pd/C and 1.0 mL of D_2O were used. [g] Slight hydrogenation of the benzene ring was observed by ^{2}H NMR. [h] 0.50 mmol of **19** was used.

H-D exchange reaction on the methyl group of tolyl derivatives: While the deuteration of the methyl group of the tolyl derivatives (**24**–**26**) resulted in a low D content even after 72 h at room temperature (Table 7, entries 1, 4 and 6), the deuterium efficiencies were also dramatically enhanced up to 90% by raising the reaction temperature to 50°C (entries 3, 5 and 7).

Table 7. Pd/C–H_2–catalyzed deuterium exchange reaction of methyl moieties of tolyl groups.[a]

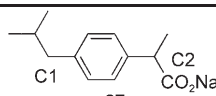
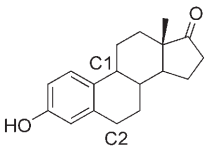


Entry	Substrate	T [°C]	t [h]	D content [%][b]	Yield [%][c]
1	 **24**	RT	72	C1: 33, C2: 40	92
2		50	72	C1: 88, C2: 90	91
3		50	120	C1: 93, C2: 91	94
4	 **25**	RT	72	71	93
5		50	72	90	96
6	 **26**	RT	72	19	91
7		50	72	93	98

[a] Unless otherwise noted, 1.0 mmol of the substrate was used, and all the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of the substrate) in D_2O (0.50 mL). [b] The D content was determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

Benzylic site-selective deuteration of bioactive compounds: Deuterium-labeled bioactive compounds at the benzylic sites are utilized as a tracer in metabolic studies and have a potential medical application to elongate the activity duration due to the delay of the oxidative metabolism at the active benzylic site by the isotope effect of the deuterium atoms.[29] Therefore, the H-D exchange reaction of bioactive compounds, such as ibuprofen (**27**, analgesic reagent) and estrone (**28**, natural estrogen), was also investigated (Table 8). Although Castell et al. previously labeled ibuprofen using a combination of D_2O and NaOH under reflux conditions, the benzylic methine (C2 of **27**) connected to the carboxylic acid was only deuterated with about 50% deuterium efficiency [the benzylic methylene (C1) of their product was not deuterated].[4c] The deuteration of the ibuprofen sodium salt with our Pd/C–D_2O–H_2 system gave nearly a quantitative deuterium efficiency at the C1 position at room temperature for 72 h, but the benzylic methine (C2) was only 17% deuterated (Table 8, entry 1). When the reaction was performed at 50°C for 72 h, the deuterium efficiency at the C2 position significantly increased (73%) (entry 2), and a sufficient D content at both the C1 (92%) and C2 (90%) positions was obtained using increased amounts of the 10% Pd/C (20% of the weight of **27**) (entry 3). Although the reaction of estrone (**28**) was sluggish even at 50°C in D_2O (entry 5), the deuterium efficiency was particularly

Table 8. Application to ibuprofen sodium salt and estrone.[a]

Entry	Substrate	T [°C]	t [h]	D content [%][b] C1	C2	Yield [%][c]
1		RT	72	97	17	93
2		50	72	93	73	100
3[d]		50	72	92	90	99
4		RT	72	41	26	99
5		50	72	37	24	82
6[e]		50	24	86	88	84
7[e]		50	48	99	92	64

27

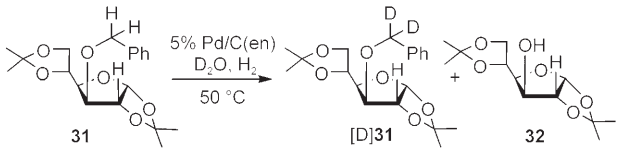
28

[a] Unless otherwise noted, 1.0 mmol of the substrate was used, and all the reactions were carried out under a H_2 atmosphere (17 mL) using 10% Pd/C (10 wt% of the weight of the substrate) in D_2O (0.50 mL). [b] The D content was determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] 20 wt% of the weight of **27** of 10% Pd/C was used. [e] 0.50 mL of THF was added as a co-solvent.

enhanced by the addition of THF as a co-solvent to the system, which contributed to increase the solubility of **28**, and afforded the highly deuterated [D]**28** (C1: 99% and C2: 92%) at 50°C for 48 h (entry 7).

Pd/C–ethylenediamine complex [Pd/C(en)]-catalyzed benzylic site-selective H-D exchange reaction of *O*-benzyl protective group: We investigated the development of the benzylic site-selective deuterium-labeling method of the *O*-benzyl protective group without hydrogenolysis by using the chemoselective hydrogenation catalyst, the Pd/C(en) complex,[27] instead of Pd/C. First, we compared the catalyst activity of Pd/C(en) and Pd/C, both of which are obtained from commercial sources, for the H-D exchange reaction of 1-benzyloxy-3-phenylpropane (**29**) (Table 9). The H-D exchange reaction smoothly proceeded at the benzylic site of the *O*-benzyl protective group (C4) at 50°C using 5% Pd/C(en) without the hydrogenolysis of the benzyl ether (entry 2), while the use of Pd/C caused a significant deprotection of the *O*-benzyl protective group to afford the benzyl ether ([D]**29**) in only 36% yield, but with high D content (92%) at the C4 position together with the deuterated and hydrogenolyzed 3-phenyl-1-pronanol ([D]**30**) in 60% yield (91% D content, entry 5). These results indicated that Pd/C(en) possesses an equivalent catalyst activity for the deuteration to Pd/C (entry 2 vs. 5). The further deuteration at the aromatic rings and non-benzylic site proceeded along with the hydrogenation of the *O*-benzyl protective group at higher temperature (110°C), regardless of the Pd/C and Pd/C(en) (entries 3 and 6). We next attempted the deuteration of the *O*-benzyl-protected sugars as a substrate (Table 10). The deuterated *O*-benzyl-protected sugar [D]**31**

Table 10. Deuteration to *O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulcofranose (**31**).[a]



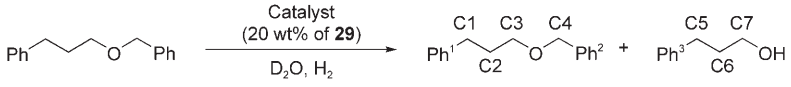
31 [D]**31** **32**

Entry	t [h]	D content [%][b]	Yield [%][c]
1	24	82	73
2	48	96	48 (50)[d]
3	72	93	26

[a] 0.25 mmol of 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulcofuranose (**31**) was used, and the reactions were carried out under a H_2 atmosphere (17 mL) using 5% Pd/C(en) (20 wt% of the weight of **31**) in D_2O (1.0 mL) at 50°C. [b] The D content was determined by ^1H NMR. [c] Isolated yield. [d] The isolated yield of the corresponding deprotected compound (**32**) is indicated in parenthesis.

was obtained with an 82% D content in 73% isolated yield after stirring at 50°C for 24 h (entry 1). The deuterium efficiency was elevated up to a 96% D content with a prolonged reaction time (48 h) although the corresponding deprotected 1,2:5,6-di-*O*-isopropylidene-α-D-gulcofuranose (**32**) was isolated in 50% yield together with the desired [D]**31** in 48% yield (entry 2). Further elongation of the reaction time to 72 h led to a decrease in the isolated yield of [D]**31** by the significant hydrogenolysis of the *O*-benzyl protective group (26%, entry 3). To avoid the hydrogenolysis of the benzyl ether, we next examined the use of a mixed sol-

Table 9. Comparison of catalyst activity of Pd/C(en) or Pd/C toward benzylic site-selective H-D exchange reaction.[a]



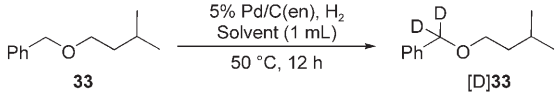
29 [D]**29** [D]**30**

Entry	Catalyst	T [°C]	t [h]	D content of [D]29[b] Ph^1	C1	C2	C3	C4	Ph^2	Yield [%] of [D]29[c]	D content of [D]30[b] Ph^3	C5	C6	C7	Yield [%] of [D]30[c]
1	5% Pd/C(en)	RT	24	0	4	0	0	33	0	95	—	—	—	—	trace
2		50	6	0	60	0	0	95	0	90	—	—	—	—	trace
3		110	6	1	70	6	6	85	1	48	18	82	16	18	47
4	5% Pd/C	RT	24	0	23	0	0	79	0	73	0	52	0	0	24
5		50	6	0	84	0	0	92	0	36	0	91	0	0	60
6		110	6	8	10	7	7	21	8	13	4	8	2	4	74

[a] 0.5 mmol of 1-benzyl-3-phenylpropane (**29**) was used, and the reactions were carried out under a H_2 atmosphere (17 mL) using 5% Pd catalyst (20 wt% of the weight of **29**) in D_2O (1.0 mL). [b] The D content was determined by ^1H NMR spectroscopy with *p*-anisic acid as the internal standard. [c] Isolated yield.

vent, such as D_2O–THF or D_2O–1,4-dioxane. THF and 1,4-dioxane were expected to decrease the catalyst activity toward the hydrogenation due to the coordination effect by the palladium metal. The mixed solvent pattern was investigated with benzyl isoamyl ether (**33**) as the substrate (Table 11). The yield of the desired highly deuterated compounds [D]**33** increased to 74% from 47% when using the mixed solvent (D_2O/THF = 1:1) (compare entries 1 and 2). The use of 1,4-dioxane instead of THF afforded similar results (entry 3). The isolated yield further increased to 88%, while keeping an efficient D content using a 7:3 mixture of THF and D_2O (entry 4). However, the D content significantly dropped to 60% with a 9:1 mixture of THF and D_2O (entry 5). Table 12 summarizes the results of the Pd/C(en)-catalyzed deuteration of various benzyl ethers in D_2O or D_2O–THF (3:7). When 1-benzyloxy-1,2,3,4-tetrahydronaphthalene (**34**) possessing three benzylic sites was employed in D_2O, the benzylic position of the *O*-benzyl protective group (C1) was deuterated with an excellent D content, while both the benzylic methine (C2) and cyclic methylene (C3) were not well deuterated (71 and 76% D content, respectively, entry 1). On the other hand, the use of D_2O–THF (3:7) improved the deuteration efficiency at the C2 position to 90% (entry 2). The benzylic position of the *N*-Boc-*O*-benzyl-L-serine methyl ester (**35**) was quantitatively deuterated in D_2O with a 75% isolated yield (entry 3) and the deuteration in the mixed solvent gave an enhanced isolated yield (96%), while keeping a good deuterium efficiency that took 168 h (entry 4). Although the deuterium efficiency of 3β-benzyloxycholestane (**36**) was very low in D_2O (12%, entry 5), it was dramatically enhanced to 93% using the mixed solvent probably due to the increased substrate solubility (entry 6). The reaction in the mixed solvent for 48 h provided [D]**31** with a relatively low D content (74%) (entry 1, compare with Table 10, entry 2), and the higher D content (90%) of [D]**31** was obtained by the elongation of the

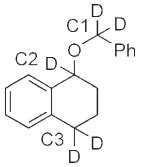
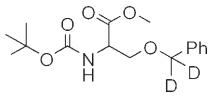
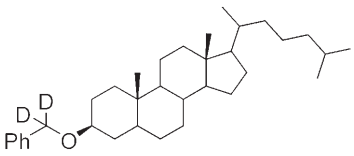
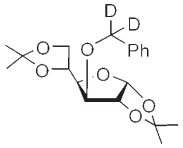
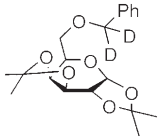
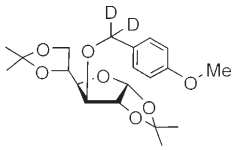
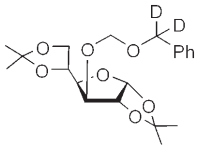
Table 11. Solvent effect toward H-D exchange reaction at the benzylic site.[a]



Entry	Solvent (mL)	D content [%][b]	Yield [%][c]
1	D_2O (1)	98	47
2	D_2O (0.5)/THF (0.5)	96	74
3	D_2O (0.5)/1,4-dioxane (0.5)	95	77
4	D_2O (0.3)/THF (0.7)	93	88
5	D_2O (0.1)/THF (0.9)	60	93

[a] 0.5 mmol of benzyl isoamyl ether (**33**) was used, and the reactions were carried out under a H_2 atmosphere (17 mL) using 5% Pd/C(en) (20 wt% of the weight of **33**) in mixed solvents (1.0 mL) at 50°C for 12 h. [b] The D content was determined by ^{1}H NMR. [c] Isolated yield.

Table 12. Pd/C(en)-catalyzed benzylic site-selective deuteration of *O*-benzyl derivatives in D_2O or D_2O-THF.[a]

Entry	Substrate		Solvent	*t* [h]	D content [%][b]	Yield [%][c]
1[d]		[D]**34**	D_2O	24	C1: 98 C2: 71 C3: 76	59
2[d]			D_2O/THF	24	C1: 92 C2: 90 C3: 76	67
3		[D]**35**	D_2O	48	96	75
4			D_2O/THF	168	86	96
5		[D]**36**	D_2O	24	12	80
6			D_2O/THF	48	93	79
7		[D]**31**	D_2O/THF	48	74	85
8				72	90	80 (19)[e]
9		[D]**37**	D_2O	12	93	66
10			D_2O/THF	24	91	81
11		[D]**38**	D_2O	48	87	84
12[f]		[D]**39**	D_2O	72	93	73

[a] Unless otherwise noted, 0.25 mmol of the substrate was used, and all the reactions were carried out under a H_2 atmosphere (17 mL) using 5% Pd/C(en) (20 wt% of the weight of the substrate) in D_2O (1.0 mL) or mixed solvents of D_2O (0.30 mL) and THF (0.70 mL) at 50°C. [b] The D content was determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] 0.5 mmol of the substrate was used. [e] The isolated yield of the corresponding deprotected compound (**32**) is indicated in parenthesis. [f] 100% of the weight of **39** of 5% Pd/C(en) and 2.0 mL of D_2O were used.

reaction time to 72 h, while a small amount (19%) of the deprotected (debenzylated) sugar was produced (entry 8). Furthermore, the deuteration of 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranse (**37**) also gave a better isolated yield without the depression of the deuterium efficiency in the mixed solvent (entries 9 and 10). The present H-D exchange reaction has been successfully employed for the deuteration of the PMB (*p*-methoxybenzyl)[30] and BOM (benzyloxymethyl)[31] protected sugars (**38** and **39**) in D_2O without significant hydrogenolysis of the benzyl moiety (entries 11 and 12). A part of the ^{1}H NMR spectra of **31** and [D]**31** is shown in Figure 1. While the peak derived from a proton of the 2-position of **31** overlapped with the benzylic protons (Figure 1a, **31**), the deuteration cleanly deleted the cumbersome benzylic proton peaks, and the clear doublet peak of the 2-position was observed. Therefore, the deuteration method is applicable for simplification of complex NMR spectra (Figure 1, [D]**31**).

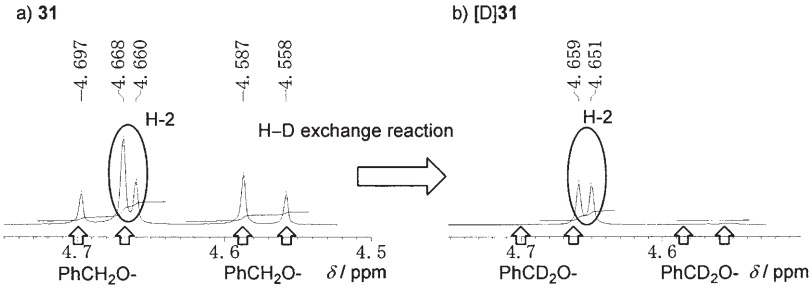
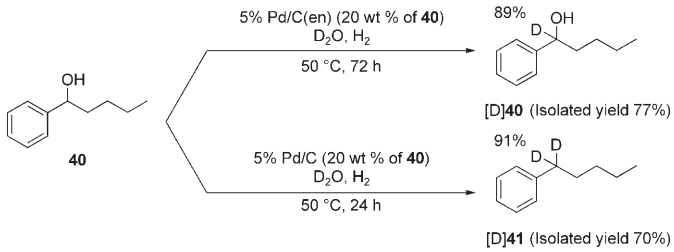


Figure 1. a) ^{1}H NMR spectra of **31** and b) [D]**31** (Table 10, entry 2).

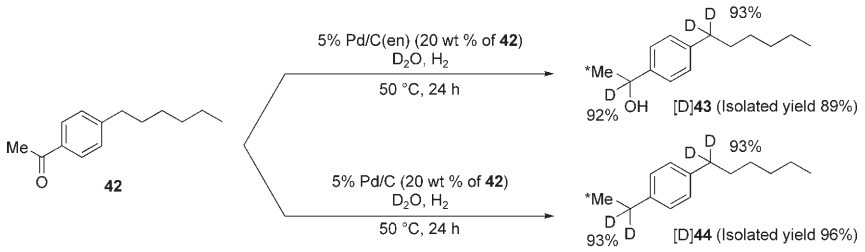
Preparation of deuterium-labeled benzyl alcohols on the benzylic position: As a further application of the present method, the benzylic site-selective deuteration of benzyl alcohols by using two different approaches was developed. As the first method, we directly deuterated a benzyl alcohol, 1-phenyl-1-pentanol (**40**), by the direct H-D exchange reaction (Scheme 1). The use of Pd/C(en)[27] as a catalyst provided the desired and deuterated benzyl alcohol ([D]**40**) with an 89% D content at the benzylic position without the accompanying hydrogenolysis of the benzylic hydroxyl group, while the hydrogenolysis of the benzyl alcohol **40** easily occurred using the Pd/C with the selective H-D exchange reaction to give the deuterated 1-phenylpentane ([D]**41**) in a 91% D content (Scheme 1). Similarly, the Pd/C(en)-catalyzed chemoselective hydrogenation and regioselective H-D exchange reaction of *p*-hexylacetophenone (**42**) (an aromatic ketone) would give the corresponding deuterated benzyl alcohol ([D]**43**) with high D contents at both benzylic positions (Scheme 2). In contrast, the hydrogenolysis of the aromatic carbonyl group completely took place in the case of Pd/C, leading to the quantitative formation of the corresponding deoxy-product, 1-ethyl-4-hexylbenzene ([D]**44**), with excellent D contents (93%, average of both benzylic positions, Scheme 2).



Scheme 1. Benzylic site-selective deuteration of 1-phenyl-1-pentanol (**40**). Conditions: [D]**40**: **40** (0.5 mmol), 5% Pd/C(en) (16.4 mg), D_2O (3.0 mL), H_2 (75 mL), 50°C, 72 h; [D]**41**: **40** (1.0 mmol), 5% Pd/C (32.9 mg), D_2O (3.0 mL), H_2 (160 mL), 50°C, 24 h.

Conclusion

We have reported a simple, mild, and regioselective H-D exchange reaction at the benzylic sites using the heterogeneous Pd/C as a catalyst without expensive D_2 gas. The present method can afford the corresponding deuterium-labeled compounds with an excellent deuterium efficiency. The use of 10% Pd/C in the presence of a small amount of hydrogen gas could achieve an efficient H-D exchange with the less expensive D_2O as the deuterium source at room temperature for 72 h. Furthermore, this reaction is dramatically accelerated under mild heating (50°C) conditions, resulting in shortening the reaction time and expanding the applicability of the substrates. The H-D exchange reaction could also be used for the deuteration of benzyl ethers, which were generally unstable under Pd/C-catalyzed hydrogenation conditions, with a high deuterium efficiency using Pd/C(en) instead of Pd/C. Furthermore, the use of THF and D_2O mixed (7:3) solvent suc-



Scheme 2. Reductive deuteration of *p*-hexylacetophenone (**42**). Conditions: [D]**43**: **42** (0.5 mmol), 5% Pd/C(en) (20.4 mg), D_2O (3.0 mL), H_2 (125 mL), 50°C, 24 h; [D]**44**: **42** (0.5 mmol), 5% Pd/C (20.4 mg), D_2O (3.0 mL), H_2 (125 mL), 50°C, 24 h. * The methyl group was slightly deuterated (by ^{2}H NMR analysis).

cessfully suppressed the hydrogenolysis of the corresponding benzyl ether. The present method would also be very useful for the simplification of complex ^{1}H NMR spectra. The general utility of this methodology as a chemoselective deuteration procedure will make this simple technique an attractive addition to the wide range of deuteration procedures.

Experimental Section

General: The 10% Pd/C was purchased from Sigma–Aldrich Co. (product number; 20569-9, 50 g, Lot. 0581713C) and the 5% Pd/C(en) was obtained from Wako Pure Chemical Industries, Ltd. (product number; 169-21443, 5 g, Lot. 12021716). D_2O (>99.9% D atom) was obtained from Cambridge Isotope Laboratories or Spectra Gases. All other reagents were purchased from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on pre-coated silica gel 60 F_{254} plates (Merck, Art 5715) and visualized with UV light and/or stain (10% phosphomolybdic acid in EtOH). Flash column chromatography was accomplished with silica gel 60 (Merck; 230–400 mesh) or silica gel 60N (Kanto Chemical Co.; 63–210 μm, spherical, neutral). The ^{1}H, ^{2}H, and ^{13}C NMR spectra were recorded by a JEOL AL 400 spectrometer or a JEOL EX 400 spectrometer. The chemical shifts (δ) are expressed in ppm and are internally referenced to trimethylsilane or residual solvents (3.30 ppm/CH_3OH and 3.58 ppm/THF for ^{2}H NMR spectroscopy). Elemental analyses were performed on a YANACO CHN CORDER MT-5 instrument. The EI and FAB mass spectra were taken by a JEOL JMS-SX102A instrument at the Mass Spectrometry Laboratory of the Gifu Pharmaceutical University. Heating reactions were carried out using a personal organic synthesizer, Chemi-Station™ (Tokyo Rikakikai Co.) or Chemist Plaza (Shibata Science Technology). Unless otherwise noted, the deuterium content (D content) was determined by ^{1}H NMR spectroscopy on the basis of the integration of the aromatic protons.

Typical procedure for benzylic site-selective H-D exchange reaction using Pd/C–D_2O–H_2 system: A suspension of the substrate (1.00 mmol) and 10% Pd/C (10 wt% of the substrate) in D_2O (0.5 mL) was stirred at room temperature or 50°C in a sealed test tube filled with hydrogen gas. After the appropriate time, the mixture was diluted with diethyl ether (10 mL), and then filtered using a membrane filter (Millipore Millex®-LH, 0.45 μm) to remove the catalyst. The filtrate was partitioned between diethyl ether and aqueous layers. The aqueous layer was extracted with diethyl ether (2×15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the corresponding deuterated substrate at the benzylic site.

Typical procedure for benzylic site-selective H-D exchange reaction of *O*-benzyl protective group using Pd/C(en)–D_2O–H_2 system: A suspension of substrate possessing the *O*-benzyl protective group (0.250 mmol) and 5% Pd/C(en) (20 wt% of the substrate) in D_2O (1 mL) was stirred at 50°C in a sealed test tube filled with hydrogen gas. After the appropriate time, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and then filtered using a membrane filter (Millipore Millex®-LH, 0.45 μm) to remove the catalyst. The filtrate was partitioned between ethyl acetate and aqueous layers. The aqueous layer was then extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate) to give the corresponding deuterated substrate on the benzylic site.

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