H–D Exchange Reaction Taking Advantage of the Synergistic Effect of Heterogeneous Palladium and Platinum Mixed Catalyst

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Abstract: An effective and applicable deuteration method for alkyl-substituted aromatic compounds using a heterogeneous Pd/C and Pt/C mixed catalyst in deuterium oxide in the presence of a small amount of hydrogen gas was developed. Mixing a heterogeneous palladium and platinum catalyst provides an interesting synergistic effect in the H–D exchange reaction and leads to full H–D exchange results even on sterically hindered sites, which indicated only low-deuterium efficiencies when either Pd/C or Pt/C were used independently as a catalyst. We investigated the synergistic effect using a variety of substrates and proved the broad generality of the heterogeneous Pd–Pt–D_2O–H_2 system in the H–D exchange reaction. Furthermore, this system could be applied to a multigram scale synthesis of useful deuterium-labeled compounds, such as deuterium-labeled bis-aniline derivatives as raw materials for polyimides, aryl iodides as synthetic building blocks, and biologically active compounds.

Key words: H–D exchange, heterogeneous catalysis, mixed catalysis, palladium, platinum

Introduction

Deuterium-labeled compounds have recently attracted a great deal of attention in a variety of scientific fields. For example, deuterium-labeled pharmaceuticals are recognized as valuable tools in metabolic studies with the development of quantitative analysis techniques using mass spectrometry and they are essential for the development of new pharmaceuticals. The uses of deuterium-labeled compounds have been expanded not only to analytical tools for life sciences[1,2] but also to new materials for electrical industries in optical communication systems.[3] With the increase in the importance of deuterium-labeled compounds, the post-synthetic incorporation of deuterium by the hydrogen isotope exchange reaction is an important technique.[4,5] Especially, H–D exchange reactions using deuterium oxide (D_2O), which is the cheapest deuterium-labeled compound, as a deuterium source are a cost-wise attractive method. A number of H–D exchange procedures for aromatic compounds in D_2O have been reported, for example, the H–D exchange reaction catalyzed by acids,[6] bases,[7] or transition metals (Ir,[8] Ru,[9] Rh,[10] Pd,[11] and Pt[12]) and supercritical[13] or microwave-enhanced[9a–c,12g,14] exchange reactions. However, many of these methods involve important problems such as low deuterium efficiency, severe conditions for functional group tolerance, the requirement of a large amount of catalyst, the use of special apparatus, etc. For these reasons, it is extremely difficult to provide useful deuterium-labeled compounds on a multigram scale for practical purposes. Hence, practical, low-cost, and deuterium-efficient H–D exchange reactions have been strongly desired.

We have recently reported a characteristic H–D exchange reaction catalyzed by Pd/C or Pt/C using D_2O in the presence of a small amount of H_2 gas.[15] During our effort to achieve a quantitative deuterium efficiency, we found an interesting synergistic effect in the H–D exchange reaction using Pd/C and Pt/C mixed catalyst.[16] Herein, we provide the detailed results and syntheses of practical deuterium-labeled compounds as an application of the heterogeneous Pd–Pt–D_2O–H_2 system.

Results and Discussion

Typically, the reactions were carried out in a sealed tube, as illustrated in Figure 1. After two vacuum/H_2 cycles to replace air with H_2 gas in the sealed tube, a mixture of a substrate (500 mg), heterogeneous Pd/C and Pt/C (1 wt% of the substrate as Pd and Pt metal respectively) in D_2O (17 mL) was stirred at 180 °C [ca. 4.56 bar (4.5 atm) of inner gas pressure measured by a pressure gauge by the bulk expansion of the filled H_2 gas and increased vapor pressure of D_2O by means of heating] for 24 hours. The deu-

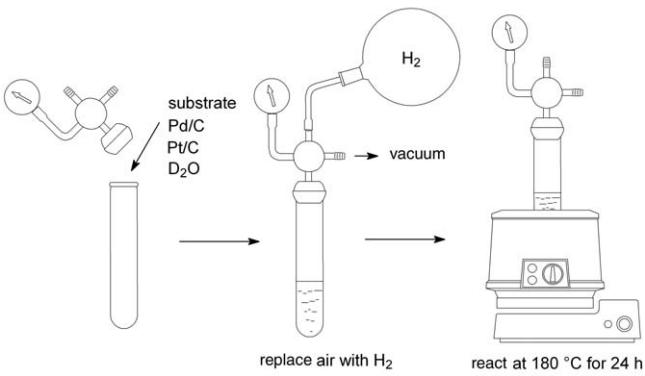

Figure 1 Typical reaction procedure in a sealed tube.

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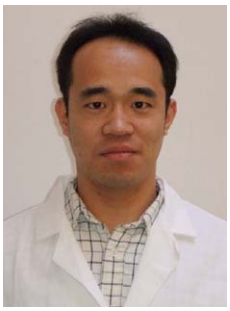
terated position and deuterium efficiency of the obtained products were determined by ^{1}H NMR using an appropriate internal standard and confirmed by ^{2}H and ^{13}C NMR and mass spectroscopy. It is noteworthy that even D_2O insoluble substrates were also deuterated effectively, meaning that the hydrophilicity of the substrate does not affect the H–D exchange reaction.

Biographical Sketches

Nobuhiro Ito was born in 1971 in Aichi, Japan. He studied pharmaceutical science at Gifu Pharmaceutical University and received his M.Sc. in 1996 under the guidance of Prof. Yukio Masaki. Since 1996, he has been working as a research scientist at Wako Pure Chemical Industries, Ltd., Japan.

Tsutomu Watahiki was born in 1976 in Ibaraki, Japan. He received his Ph.D. from Ibaraki University in 2003 under the direction of Prof. Takeshi Oriyama. After serving as a Postdoctoral Fellow at the National Institute of Advanced Industrial Science and Technology (2003–2004), he has been working as a research scientist at Wako Pure Chemical Industries, Ltd., Japan.

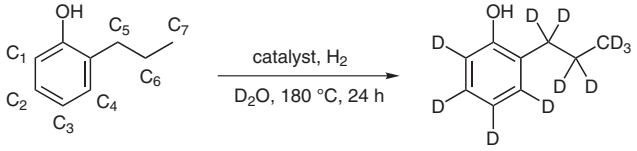
Tsuneaki Maesawa was born in 1967 in Osaka, Japan. He studied agricultural science at Shinshu University and received his M.Sc. in 1992 under the guidance of Prof. Ichiro Tomida. Since 1992, he has been working as a research scientist at Wako Pure Chemical Industries, Ltd., Japan.



Tomohiro Maegawa was born in 1976 in Mie, Japan. He received his B.S. in 1998 from Nagoya University and his M.S. in 2000 and Ph.D. in 2003 from Osaka University under the direction of Prof. Yasuyuki Kita. He was a JSPS research fellow during 2002–2003. He joined Gifu Pharmaceutical University as an Assistant Professor. He stayed at University of Pennsylvania (Prof. A. B. Smith III, 2006–2007) as a research associate. He was promoted to Associate Professor in 2007. His research interests include the development of novel synthetic methods using heterogeneous transition metal catalysts.

Hironao Sajiki was born in 1959 in Nagano, Japan. He received his Ph.D. from Gifu Pharmaceutical University in 1989 under the direction of Prof. Yoshifumi Maki. After serving as a Postdoctoral Fellow at the State University of New York at Albany (Prof. Frank M. Hauser, 1990–1991) and Massachusetts Institute of Technology (Prof. Satoru Masamune, 1991–1992) he joined to Metasyn, Inc. (current Epix Pharmaceuticals), MA, USA as a group leader. In 1995, he moved to Gifu Pharmaceutical University as an Assistant Professor. He became an Associate Professor in 1999 and Professor in 2006. His research interests include development of heterogeneous transition metal catalysts possessing novel functionalities, post-synthetic deuteration (tritiation) methods and its pharmaceutical application, and practical synthetic methodologies.

Table 1 Comparison of Deuterium Efficiency of 2-Propylphenol Using Various Heterogeneous Catalysts[a]



Entry	Catalyst (wt%)	Additive (wt%)	Deuterium content[b] (%)							Yield[c] (%)
			C1	C2	C3	C4	C5	C6	C7	
1	10% Pd/C (10%)	none	99	98	99	48	98	97	97	84
2	10% Pd/C (20%)	none	97	98	97	54	97	98	97	80
3	10% Pd/C (10%)	activated carbon (10%)	99	99	99	46	99	99	98	89
4	5% Pd/C (20%)	none	98	98	98	17	97	98	97	79
5	5% Pd/C (20%)	activated carbon (10%)	99	99	99	15	98	98	97	86
6	5% Pt/C (20%)	none	98	98	98	38	72	42	28	62
7	5% Pt/C (20%)	activated carbon (10%)	99	99	98	73	96	67	44	61
8	5% Rh/C (20%)	none	33	22	62	6	35	16	9	89
9	5% Ru/C (20%)	none	63	10	82	6	9	5	5	84
10	10% Pd/C (10%) + 5% Pt/C (20%)	none	97	97	97	87	97	97	97	55
11	10% Pd/C (10%) + 5% Pt/C (20%)	activated carbon (10%)	98	98	98	98	99	98	98	77
12	5% Pd/C (20%) + 5% Pt/C (20%)	none	99	99	98	97	98	98	98	84
13	10% Pd/C (10%) + 5% Rh/C (20%)	none	98	98	98	36	98	98	97	96
14	10% Pd/C (10%) + 5% Ru/C (20%)	none	98	98	98	26	97	98	97	81
15	5% Pt/C (20%) + 5% Rh/C (20%)	none	98	98	98	87	98	85	65	83
16	5% Pt/C (20%) + 5% Ru/C (20%)	none	98	98	98	92	97	82	55	83
17	none	activated carbon (10%)	16	0	9	0	0	0	0	96

[a] Substrate (500 mg, 3.67 mmol) was used, and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (17 mL) in a sealed tube.
[b] Deuterium content was determined by ^1H NMR.
[c] Isolated yield.

The deuteration results of 2-propylphenol using several combinations of heterogeneous catalysts are summarized in Table 1. Although an acidic proton such as the OH in phenol also underwent H–D exchange, the incorporated deuterium was depleted by hydrogen during the aqueous workup. 2-Propylphenol and 10% Pd/C (10 wt%) in D_2O at 180 °C under a small amount of H_2 gas in a sealed tube for 24 hours leads to high deuterium efficiency on the aromatic ring and the alkyl chain, except for the C4 position, which was adjacent to the alkyl side chain of the aromatic ring (entry 1). Increasing the amount of 10% Pd/C (from 10 to 20 wt% of the substrate) did not improve the deuterium efficiency at the C4 position (entry 2). On the other hand, the use of 5% Pt/C (20 wt%) as a catalyst showed high deuterium efficiency on the aromatic ring, except for the C4 position similarly (entry 6). An electron-rich substrate such as 2-propylphenol shows relatively high H–D exchange activity on the aromatic ring, even using either Pd/C or Pt/C as a catalyst. However, low deuterium results were observed at the C4 position, which is the *ortho* position of the propyl group. This is probably caused by a steric hindrance effect, which was also reported by Bergman[4g] and Matsubara.[12g] Meanwhile, when we tried to examine the reaction using 10% Pd/C (10 wt%) and 5%

Pt/C (20 wt%) in the same sealed tube, remarkable enhancement of the H–D exchange activity was observed in 87% deuterium efficiency even at the sterically hindered C4 position (entry 10). When 5% Pd/C (20 wt%) and 5% Pt/C (20 wt%) were used as a catalyst, fully deuterated 2-propylphenol-d_{11} was obtained in 84% isolated yield (entry 12). Interestingly, the addition of activated carbon (10 wt% of the substrate) to the reaction mixture of entry 10 showed enhancement of the deuterium efficiency at the C4 position (98%) similar to the result of entry 12 (entry 11). Incidentally, the activated carbon indicated very poor deuteration activity (entry 17). These results indicated that a more dispersed catalyst shows high activity in the H–D exchange reaction. It is noteworthy that the addition of activated carbon was effective in the case of the use of Pt/C as a catalyst (entries 6 vs 7), although a significant effect was not observed in the case of Pd/C as a catalyst (entries 1 vs 3 and 5). On the other hand, other heterogeneous catalysts such as 5% Rh/C or 5% Ru/C showed lower H–D exchange activity toward either the aromatic ring or the alkyl chain (entries 8 and 9). Similarly, mixed catalysts of Pd/C or Pt/C with Rh/C or Ru/C did not presented a significant synergistic effect in the H–D exchange reaction (entries 13–16).

Next, we investigated the deuteration efficiency of various aromatic compounds using the Pd/C–Pt/C–D_2O–H_2 system (Table 2). When electron-rich substrates were subjected to the deuteration condition using 10% Pd/C or 5% Pt/C as a catalyst independently, the deuterium efficiency at the *ortho* positions of alkyl substituents was relatively low similar to the previous results as shown in Table 1. Especially, even stepwise deuteration of 5-phenylpentanoic acid with 5% Pt/C and subsequently with 10% Pd/C-catalyzed deuteration could not produce a high deuterium efficiency at the C3 position (Table 2, entry 3). As expected, mixing 10% Pd/C and 5% Pt/C led to efficient deuterium incorporation at the *ortho* positions of alkyl substituents and highly deuterated compounds such as 5-phenylpentanoic acid-d_{13}, 4-propylphenol-d_{11}, 4-propylaniline-d_{11}, and 1,2,4,5-tetramethylbenzene-d_{14} were obtained (entries 4, 7, 15, and 18). In the case of the use of 2-propylaniline as the substrate, the synergistic effect was observed by mixing 10% Pd/C (10 wt%) with 5% Pt/C (20 wt%), but the deuterium efficiency of the C4 position (59%) was not satisfactory (entry 10). The addition of activated carbon (10 wt% or 20 wt%) enhanced the deuterium efficiency at the C4 position (83% and 97%, respectively; see also Table 1) (entries 11 and 12).

Use of electron-deficient aromatic compounds was less straightforward in achieving high deuterium efficiency.[15f] 4-Propylbenzoic acid and nicotinic acid were investigated (Table 2, entries 19–33). Deuterium incorporation into the aromatic ring catalyzed by 10% Pd/C was scarcely observed (entry 19). Even the use of 5% Pt/C possessing strong aromatic ring affinity showed low deuterium efficiency, especially at the C2 position (entry 20). On the other hand, when 10% Pd/C and 5% Pt/C were used as a mixed catalyst, a moderate result was obtained (entry 21). Consequently, using a more dispersed catalyst, such as 5% Pd/C and 5% Pt/C (using 20 wt% of the substrate, respectively) as a mixed catalyst resulted in higher deuterium efficiency (entry 22). Furthermore, the use of 1% Pd/C and 1% Pt/C (using 100 wt% of the substrate, respectively) gave excellent deuterium efficiency, and fully deuterated 4-propylbenzoic acid-d_{11} was obtained (entry 23), although the reduction of the catalyst amount to 10 and 1 wt% from 100 wt% gave disappointing results (entries 24 and 25). Other mixed catalyst systems, such as Pd/alumina and Pt/alumina, gave lower deuterium efficiency compared to that of Pd/C and Pt/C (entry 26). Interestingly, the addition of silica gel (10 wt% of the substrate) to the reaction mixture of entry 26 led to an enhancement of the deuterium efficiency similar to the result of the addition of activated carbon (entry 27).

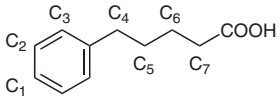
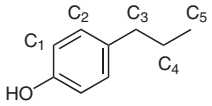
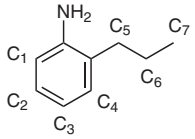
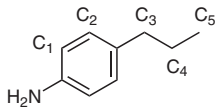
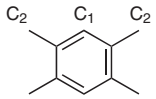
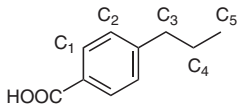
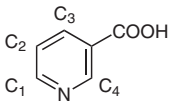
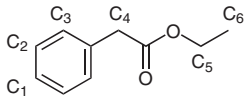
We have recently reported that the Pd/C-catalyzed H–D exchange reaction of heterocyclic compounds including the deuteration of the C3 position of nicotinic acid is extremely difficult.[17] Therefore, we examined the mixed catalyst system for the deuteration of nicotinic acid. Nicotinic acid subjected to the deuteration condition (180 °C) using 10% Pd/C (10 wt%) or 5% Pt/C (20 wt%) as a catalyst showed low deuterium efficiency at the C3 position (entries 28 and 29). However, the use of the mixed catalyst, 10% Pd/C and 5% Pt/C or 1% Pd/C and 1% Pt/C caused a slight enhancement of the deuterium efficiency at the C3 position (entries 30 and 31). On the other hand, the use of 5% Pd/alumina and 5% Pt/alumina produced a higher result (43%, entry 32) which was dramatically enhanced to 92% deuterium content based on an average of the whole nicotinic acid by the addition of silica gel (10 wt% of the substrate) (entry 33).

When ethyl phenylacetate was used as a substrate, using a mixture of 5% Pd/C and 5% Pt/C showed low deuterium efficiency at the aromatic ring and no deuterium incorporation into the ester moiety with a low isolated yield (entry 34). However, the use of 5% Pd/alumina and 5% Pt/alumina as a mixed catalyst and the use of silica gel (10 wt%) as an additive gave deuterated ethyl phenylacetate-d_7 in an excellent isolated yield (entry 35). These results suggest that the heterogeneous Pd–Pt–D_2O–H_2 system enables the establishment of a generally available deuteration method, and it is powerful enough to apply to the synthesis of various deuterium-labeled compounds.

We have reported the plausible reaction mechanism of the H–D exchange based upon the oxidative addition of Pd or Pt to the carbon–hydrogen bond of the substrate.[15g,i] Although it is not exactly clear why the synergistic effect arises with the mixed heterogeneous Pd and Pt system, some kind of interaction between each metal should occur. Because the EDS analysis of the recovered mixture of catalysts demonstrated a different dispersion of each metal, an alloy of palladium and platinum may not be formed.

Table 2 Deuteration of Various Aromatic Compounds[a]

substrate —(catalyst, H_2; D_2O, 180 °C, 24 h)→ substrate-*d*

Entry	Substrate	Catalyst (wt%)	Deuterium content[b] (%)							Yield[c] (%)
			C1	C2	C3	C4	C5	C6	C7	
1		10% Pd/C (10%)	96	96	14	98	96[d]	96[d]	96	88
2		5% Pt/C (20%)	97	97	19	28	8[d]	8[d]	10	92
3[e]		10% Pd/C (10%)	97	97	30	97	97[d]	97[d]	97	84
4		10% Pd/C (10%) + 5% Pt/C (20%)	97	97	97	97	97[d]	97[d]	94	84
5		10% Pd/C (10%)	97	46	98	98	98			86
6		5% Pt/C (20%)	97	19	27	19	14			70
7		10% Pd/C (10%) + 5% Pt/C (20%)	97	93	98	98	97			89
8		10% Pd/C (10%)	97	96	96	12	97	97	97	58
9		5% Pt/C (20%)	98	97	97	14	49	32	20	72
10		10% Pd/C (10%) + 5% Pt/C (20%)	99	97	99	59	97	97	94	60
11[f]		10% Pd/C (10%) + 5% Pt/C (20%)	97	97	97	83	97	96	97	78
12[g]		10% Pd/C (10%) + 5% Pt/C (20%)	98	97	98	97	98	97	97	59
13		10% Pd/C (10%)	98	16	99	99	98			79
14		5% Pt/C (20%)	97	87	97	73	34			69
15		10% Pd/C (10%) + 5% Pt/C (20%)	97	97	97	97	97			75
16		10% Pd/C (10%)	13	97						96
17		5% Pt/C (20%)	75	93						92
18		10% Pd/C (10%) + 5% Pt/C (20%)	94	97						92
19		10% Pd/C (10%)	3	4	96	93	92			64
20		5% Pt/C (20%)	62	17	15	12	11			84
21		10% Pd/C (10%) + 5% Pt/C (20%)	78	58	90	83	77			88
22		5% Pd/C (20%) + 5% Pt/C (20%)	94	92	96	96	95			92
23		1% Pd/C (100%) + 1% Pt/C (100%)	97	97	98	94	95			72
24		1% Pd/C (10%) + 1% Pt/C (10%)	16	4	57	33	23			87
25		1% Pd/C (1%) + 1% Pt/C (1%)	0	0	0	0	0			94
26		5% Pd/alumina (20%) + 5% Pt/alumina (20%)	81	73	96	92	90			59
27[h]		5% Pd/alumina (20%) + 5% Pt/alumina (20%)	91	96	98	98	97			49
28		10% Pd/C (10%)	98	98	10	98				96
29		5% Pt/C (20%)	99	65	11	54				94
30		10% Pd/C (10%) + 5% Pt/C (20%)	99	98	29	99				92
31		1% Pd/C (100%) + 1% Pt/C (100%)	100	29	3	88				76
32		5% Pd/alumina (20%) + 5% Pt/alumina (20%)	99	98	43	99				95
33[h]		5% Pd/alumina (20%) + 5% Pt/alumina (20%)	99	99	72	99				91
34		5% Pd/C (20%) + 5% Pt/C (20%)	15[d]	15[d]	15[d]	98	0	0		34
35[h]		5% Pd/alumina (20%) + 5% Pt/alumina (20%)	98[d]	98[d]	98[d]	98	0	0		95

[a] Substrate (500 mg, 2.81–4.06 mmol) was used and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (17 mL) in a sealed tube.
[b] Deuterium content was determined by ^1H NMR.
[c] Isolated yield.
[d] Indicated as the average deuterium content.
[e] The product of entry 2 was used as a starting material.
[f] Activated carbon (10 wt% of the substrate) was added.
[g] Activated carbon (20 wt% of the substrate) was added.
[h] Silica gel (Wakogel C-200, 10 wt% of the substrate) was added.

Application to the Synthesis of Deuterium-Labeled Compounds

Recently, deuterium-labeled polymers were recognized as functional materials for wave guides in optical communication systems, because the replacement of hydrogen in the polymers with deuterium causes an enhancement of the transparency by reduction of the C–H vibrational absorption in the infrared (IR) wavelength region and its overtones in the near IR to visible region.[3] Polyimides are important materials in the electronics industry due to their superior thermostability and workability, and deuterium-labeled polyimides are being recognized as new functional materials.[18] So we focused attention on the development of a practical scale synthesis of deuterium-labeled bis-aniline derivatives as raw materials for polyimides. Reactions were performed in an autoclave using a mixture of 10% Pd/C (10 wt%) and 5% Pt/C (20 wt%) as a catalyst (Figure 2). As expected, bis(4-aminophenyl)methane (**1**), 1,2-bis(4-aminophenyl)ethane (**2**), 3,3′,5,5′-tetramethylbenzidine (**3**) and 3,3′-dimethylbenzidine (**4**) achieved excellent deuterium efficiency on a multigram scale even at sterically hindered positions (2, 2′, 6, and 6′ positions of **3** and 2 and 2′ positions of **4**). In particular, 137 g of bis(4-aminophenyl) ether-d_8 (**5**) was obtained with nearly quantitative deuterium efficiency (98% D content). Moderate to good isolated yields of products **1**–**5** (43–79%) were attributed to the coincident reduction of benzene rings and the loss in the recrystallization process.

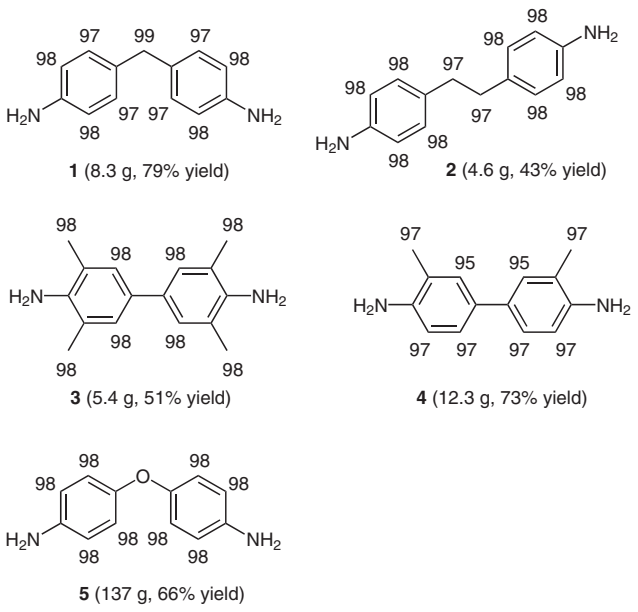
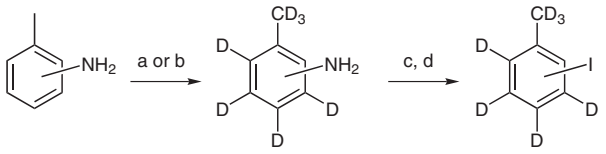


Figure 2 Multigram deuteration of bis-aniline derivatives using the 10% Pd/C–5% Pt/C–D_2O–H_2 system (180 °C, 24 h).

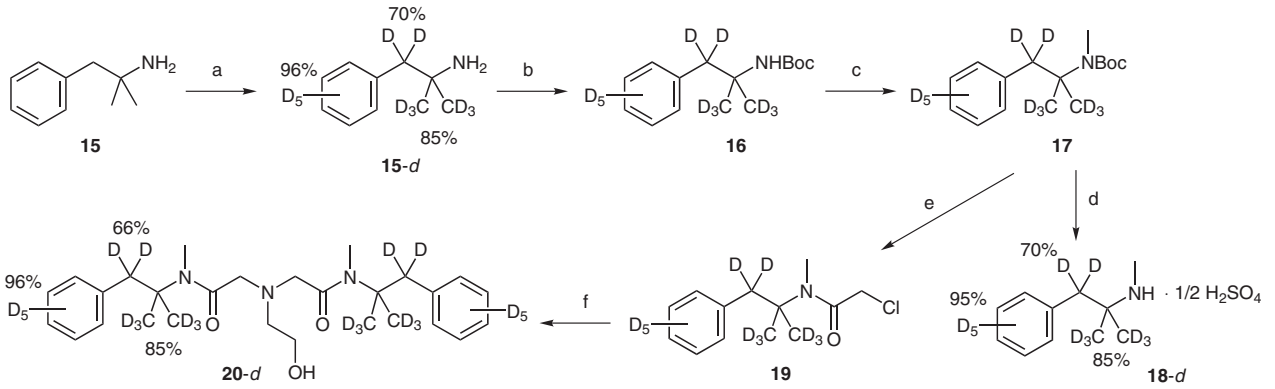
Aryl halides are an important class of compounds frequently used as coupling synthons, hence, deuterium-labeled aryl halides should be useful building blocks. However, attempted direct deuteration of aryl halides using the 5% Pt/C–D_2O–H_2 system gave poor results due to concurrent dehalogenation.[15i] The corresponding deuterium-labeled aryl halides were derived from easily deuterated toluidine derivatives **6**–**8** by our deuteration system on a practical scale. As depicted in Scheme 1, deuteration of *o*-toluidine (**6**, 20 g) using a mixture of 5% Pd/C and 5% Pt/C and *m*- (**7**, 20 g) and *p*-toluidine (**8**, 20 g) using a mixture of 10% Pd/C and 5% Pt/C in a 1-L autoclave gave deuterium-labeled toluidine derivatives with excellent deuterium efficiencies (**9**: 98% D, 13 g, **10**: 98% D, 15 g, **11**: 97% D, 12 g). Subsequently, the deuterated toluidines were subjected to iodination by diazotization and easily gave the corresponding iodotoluene-d_7 derivatives (**12**: 19 g, **13**: 12 g, **14**: 18 g) without loss of deuterium efficiency.



6: *o*-NH_2 **9**: *o*-NH_2, 62% yield, 98% D **12**: *o*-I, 80% yield, 98% D
7: *m*-NH_2 **10**: *m*-NH_2, 71% yield, 98% D **13**: *m*-I, 77% yield, 98% D
8: *p*-NH_2 **11**: *p*-NH_2, 58% yield, 97% D **14**: *p*-I, 77% yield, 97% D

Scheme 1 Syntheses of iodotoluenes-d_7. *Reagents and conditions*: (a) (**6** → **9**) 5% Pd/C (20 wt%), 5% Pt/C (20 wt%), H_2, D_2O, 180 °C, 24 h; (b) (**7** → **10** and **8** → **11**) 10% Pd/C (10 wt%), 5% Pt/C (20 wt%), H_2, D_2O, 180 °C, 24 h; (c) $NaNO_2$, concd HCl, 3 °C, 45 min; (d) NaI, H_2O, –20 to 0 °C, 30 min.

The application of deuterium-labeled compounds for drug metabolism studies as surrogate internal standards has rapidly developed.[2d,e,j,p,q] Because the chemical properties of surrogate compounds are quite similar to those of the mother non-deuterated samples, surrogate compounds are the most valuable tracers for metabolic studies using GC-MS or LC-MS. Hence, we applied the present system to the syntheses of deuterium-labeled surrogate compounds (Scheme 2). Mephentermine (*N*,2-dimethyl-1-phenylpropan-2-amine) (**18**, an antihypertensive agent) and oxethazaine {2,2′-[(2-hydroxyethyl)imino]bis[*N*-(1,1-dimethylphenethyl)-*N*-methylacetamide]} (**20**, a local anesthetic) are well-known drugs,[19] and their deuterides are useful as research tools for metabolic studies. First, the direct H–D exchange reactions of **18** and **20** were examined; however, unsatisfactory results were obtained. So consequently, commercially available phentermine (**15**, 20 g), the precursor of **18** and **20**, was subjected to deuteration conditions using a mixture of 5% Pd/C (20 wt%) and 5% Pt/C (20 wt%) as a catalyst to give highly deuterated phentermine (**15-*d***, 12.3 g, average 87% D content). After *tert*-butoxycarbonyl (Boc) protection of **15-*d***, the resulting **16** was methylated, and subsequent removal of the Boc group of **17** and treatment with sulfuric acid afforded deuterium-labeled mephentermine as its hemisulfate (**18-*d***, 1.2 g) in 39% (4 steps) total yield from **15**. Further transformation to chloroacetamide derivative **19**, after removal of the Boc group of **17** and subsequent treatment of ethanolamine, gave deuterium-labeled oxethazaine (**20-*d***, 6.6 g) in 67% (5 steps) total yield from **15** on a practical scale without loss of deuterium efficiency. These deuterium-labeled compounds are considered as useful tools for



Scheme 2 Syntheses of mephentermine-*d* and oxethazaine-*d*. *Reagents and conditions*: (a) 5% Pd/C (20 wt%), 5% Pt/C (20 wt%), H_2, D_2O, 180 °C, 24 h; (b) Boc_2O, THF, 3 M NaOH, r.t., 30 min; (c) NaH, DMF, r.t., then MeI, r.t., 5 h; (d) 1. concd HCl, Et_2O, r.t., 3 h, 2. NaOH, r.t., 3. concd H_2SO_4, r.t., 39% (4 steps from **15**); (e) 1. concd HCl, Et_2O, r.t., 3 h, 2. Et_2O, 2 M NaOH, chloroacetyl chloride, r.t., 2 h, 69% (4 steps from **15**); (f) ethanolamine, KI, THF, 3 M NaOH, reflux, 6 h, 97%.

metabolic studies. In addition, deuterated drugs often have different actions from the protonated forms in vivo[2c,20] and have resistance to metabolic inactivation by an isotope effect. Thus the possibility of the development of new functional drugs that have a new action mechanism is also expected.

Conclusion

We have found a synergistic effect in the H–D exchange reaction using the heterogeneous Pd/C–Pt/C–D_2O–H_2 system, which efficiently incorporates deuterium into a variety of alkyl-substituted compounds even at sterically hindered sites. Moreover, a practical multigram scale deuteration method based on the present system of valuable compounds such as optical materials, building blocks, surrogate compounds, was established.

All the substances examined in this study were obtained commercially and were used without further purification. 10% Pd/C, 5% Pd/C, 5% Pd/alumina, 5% Pt/alumina, 5% Rh/C, and 5% Ru/C were purchased from Wako Pure Chemical Industries, Ltd. 5% Pt/C was purchased from Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co. 1% Pd/C and 1% Pt/C were purchased from Aldrich Chemical Co. D_2O (99.9% isotopic purity) was purchased from Cambridge Isotope Laboratories. ^1H, ^2H, and ^{13}C NMR spectra were recorded on a JEOL ANM-AL400 spectrometer (^1H NMR, 400 MHz; ^2H NMR, 61 MHz; ^{13}C NMR, 100 MHz); residual solvent or TMS was used as an internal standard. Starred (*) values in the ^{13}C NMR are for small peaks. The deuterium content (%) of the substrates was estimated on the basis of integration of the appropriate internal standards. Because the relative signal intensity was found to depend on the pulse delay, the pulse delay was set to 120 s for complete relaxation. EI-MS were recorded on a JEOL JMS-SX102A spectrometer. APCI mass spectra were recorded on an Agilent LC/MSD TOF spectrometer. Silica gel column chromatography was performed using Wakogel C-200 (Wako Pure Chemical Industries, Ltd.). Preparative TLC was performed using Merck PLC plates (silica gel 60 F254).

H–D Exchange Reaction of the Heterogeneous Pd/C–Pt/C–D_2O–H_2 System; General Procedure

A substrate (500 mg, 2.81–4.06 mmol), Pd/C or Pd/alumina (1 wt% as Pd metal) and Pt/C or Pt/alumina (1 wt% as Pt metal), and, if necessary, activated carbon (10 or 20 wt%) or silica gel (10 wt%) as an additive in D_2O (17 mL) was stirred at 180 °C in a sealed tube under a H_2 atmosphere for 24 h. After cooling, the mixture was diluted with Et_2O (20 mL), and the mixture was filtered to remove the heterogeneous catalyst. The filtered catalyst was washed with Et_2O (2 × 5 mL). The combined ethereal layers were washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The obtained residue was purified by column chromatography (silica gel), by preparative TLC, or recrystallization. The deuterium content (%) was determined by ^1H NMR using dioxane, *p*-anisic acid, benzene, or *p*-methoxyphenol as an internal standard (as indicated) and were confirmed by ^2H NMR, ^{13}C NMR, and MS.

[D]-2-Propylphenol (Table 1, Entry 12)

The H–D exchange reaction was carried out using 5% Pd/C (100 mg, 20 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst. The crude product was purified by preparative TLC (EtOAc–hexane, 1:10) to give 2-propylphenol-d_n as a colorless oil (84%).

Isotope distribution (EI-MS): 5% d_9, 24% d_{10}, 71% d_{11}.

^1H NMR (acetone-d_6, dioxane): δ = 8.03 (s, 1 H), 7.07 (s, 0.03 H), 6.99 (s, 0.02 H), 6.81 (s, 0.02 H), 6.74 (s, 0.02 H), 2.54 (s, 0.04 H), 1.56 (s, 0.04 H), 0.87 (s, 0.08 H).

^2H NMR (acetone): δ = 7.08–7.01 (br m), 6.83–6.76 (br m), 2.53 (br s), 1.54 (br s), 0.86 (br s).

^{13}C NMR ($CDCl_3$): δ = 153.4, 129.6*, 128.2, 126.3*, 120.0*, 114.7*, 31.1*, 21.9*, 13.1*.

[D]-5-Phenylpentanoic Acid (Table 2, Entry 4)

The H–D exchange reaction was carried out using 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst. The deuterium content (%) was determined by ^1H NMR after conversion of the carboxylic acid into the methyl ester on the basis of integration of the methyl protons and was confirmed by ^2H and ^{13}C NMR and MS. The procedure of esterification is as follows: To the stirred crude product (100 mg) in benzene–MeOH (4:1, 4 mL) was added 10% $TMSCHN_2$ in hexane (1.0 mL) at r.t., the mixture was stirred for 30 min and concentrated in vacuo. The residue was subjected to preparative TLC (EtOAc–hexane, 1:10) to obtain methyl 5-phenylpentanoate-d_n as a colorless oil (84% in 2 steps).

Isotope distribution (EI-MS): 6% d_{11}, 27% d_{12}, 67% d_{13}.

^{1}H NMR (CD_2Cl_2): δ = 7.20 (s, 0.05 H), 7.10 (s, 0.08 H), 3.56 (s, 3 H), 2.52 (s, 0.05 H), 2.22 (s, 0.12 H), 1.52 (s, 0.12 H).

^{2}H NMR (CH_2Cl_2): δ = 7.26–7.17 (br m), 2.53 (br s), 2.22 (br s), 1.53 (br s).

^{13}C NMR (CD_2Cl_2): δ = 173.9, 142.3, 128.0*, 125.4*, 51.6, 35.1*, 33.6*, 30.2*, 24.2*.

[D]-4-Propylphenol (Table 2, Entry 7)

The H–D exchange reaction was carried out using 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst. The crude product was purified by preparative TLC (EtOAc–hexane, 1:10) to give 4-propylphenol-d_n as a colorless oil (89%).

Isotope distribution (EI-MS): 8% d_9, 28% d_{10}, 64% d_{11}.

^{1}H NMR ($CDCl_3$, *p*-anisic acid): δ = 7.03 (s, 0.13 H), 6.75 (s, 0.06 H), 2.48 (s, 0.05 H), 1.54 (s, 0.05 H), 0.86 (s, 0.08 H).

^{2}H NMR ($CHCl_3$): δ = 7.26–7.17 (m), 2.53 (s), 2.22 (s), 1.53 (s).

^{13}C NMR ($CDCl_3$): δ = 152.9, 134.4, 128.7*, 114.4*, 36.0*, 23.3*, 12.8*.

[D]-2-Propylaniline (Table 2, Entry 12)

The H–D exchange reaction was carried out using 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst and with activated carbon (100 mg, 20 wt% of the substrate) as the additive. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 1:10) to give 2-propylaniline-d_n as a pale brown oil (59%).

Isotope distribution (EI-MS): 1% d_8, 5% d_9, 26% d_{10}, 68% d_{11}.

^{1}H NMR ($CDCl_3$, benzene): δ = 7.03 (m, 0.06 H), 6.73 (s, 0.02 H), 6.67 (s, 0.02 H), 3.58 (br, 2 H), 2.43 (s, 0.04 H), 1.60 (s, 0.06 H), 0.94 (s, 0.08 H).

^{2}H NMR ($CHCl_3$): δ = 7.09 (br s), 6.79–6.72 (m), 2.43 (s), 1.60 (s), 0.95 (s).

^{13}C NMR ($CDCl_3$): δ = 143.7, 127.7*, 126.3, 125.9*, 117.9*, 114.8*, 32.3*, 20.6*, 13.0*.

[D]-4-Propylaniline (Table 2, Entry 15)

The H–D exchange reaction was carried out using 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst. The crude product was purified by preparative TLC (EtOAc–hexane, 1:10) to give 4-propylaniline-d_n as a brown oil (75%).

Isotope distribution (EI-MS): 5% d_9, 25% d_{10}, 70% d_{11}.

^{1}H NMR ($CDCl_3$, *p*-anisic acid): δ = 6.95 (s, 0.06 H), 6.67 (s, 0.02 H), 4.86 (br, 2 H), 2.44 (s, 0.06 H), 1.53 (s, 0.06 H), 0.86 (s, 0.10 H).

^{2}H NMR ($CHCl_3$): δ = 7.02 (s), 6.68 (s), 2.45 (s), 1.54 (s), 0.88 (s).

^{13}C NMR ($CDCl_3$): δ = 143.5, 132.3, 128.5*, 114.5*, 36.1*, 23.6*, 12.6*.

[D]-1,2,4,5-Tetramethylbenzene (Table 2, Entry 18)

The H–D exchange reaction was carried out using 10% Pd/C (50 mg, 10 wt% of the substrate) and 5% Pt/C (100 mg, 20 wt% of the substrate) as the catalyst. The crude product was purified by preparative TLC (EtOAc–hexane, 1:5) to give 1,2,4,5-tetramethylbenzene-d_n as a white solid (92%).

Isotope distribution (EI-MS): 1% d_{10}, 4% d_{11}, 13% d_{12}, 29% d_{13}, 53% d_{14}.

^{1}H NMR ($CDCl_3$, dioxane): δ = 6.90 (s, 0.13 H), 2.16 (s, 0.37 H).

^{2}H NMR ($CHCl_3$): δ = 6.97 (s), 2.19 (s).

^{13}C NMR ($CDCl_3$): δ = 133.1, 130.3*, 18.1*.

[D]-4-Propylbenzoic Acid (Table 2, Entry 23)

The H–D exchange reaction was carried out using 1% Pd/C (500 mg, 100 wt% of the substrate) and 1% Pt/C (500 mg, 100 wt% of the substrate) as the catalyst. After conversion into the methyl ester, the crude product was purified by preparative TLC (EtOAc–hexane, 1:10) to give methyl 4-propylbenzoate-d_n as a colorless oil (72% in 2 steps).

Isotope distribution (EI-MS): 1% d_8, 5% d_9 25% d_{10}, 69% d_{11}.

^{1}H NMR (CD_2Cl_2): δ = 7.93 (s, 0.06 H), 7.26 (s, 0.06 H), 3.87 (s, 3 H), 2.65 (s, 0.05 H), 1.64 (s, 0.13 H), 0.94 (s, 0.14 H).

^{2}H NMR (CH_2Cl_2): δ = 7.97 (s), 7.31 (s), 2.61 (s), 1.60 (s), 0.90 (s).

^{13}C NMR (CD_2Cl_2): δ = 167.0, 148.3, 129.2*, 128.3*, 127.9, 51.9, 37.5*, 23.6*, 13.1*.

[D]-Nicotinic Acid (Table 2, Entry 33)

The H–D exchange reaction was carried out using 5% Pd/alumina (100 mg, 20 wt% of the substrate) and 5% Pt/alumina (100 mg, 20 wt% of the substrate) as the catalyst and with silica gel (50 mg, 10 wt% of the substrate) as the additive. After the reaction, the mixture was diluted with MeOH (100 mL), and the mixture was filtered and washed with MeOH (2 × 10 mL). The filtrate was concentrated in vacuo. Nicotinic acid-d_n was obtained as a pale brown powder (91%) without purification.

Isotope distribution (EI-MS): 2% d_5, 39% d_6, 59% d_7.

^{1}H NMR (DMSO-d_6, dioxane): δ = 9.06 (s, 0.01 H), 8.77 (s, 0.01 H), 8.25 (s, 0.28 H), 7.53 (s, 0.01 H).

^{2}H NMR (DMSO): δ = 9.10 (br s), 8.83 (br s), 8.29 (br s), 7.58 (br s).

^{13}C NMR (DMSO-d_6): δ = 166.0, 152.5*, 149.5*, 136.5, 126.3, 123.1*.

[D]-Ethyl Phenylacetate (Table 2, Entry 35)

The H–D exchange reaction was carried out using 5% Pd/alumina (100 mg, 20 wt% of the substrate) and 5% Pt/alumina (100 mg, 20 wt% of the substrate) as the catalyst and with silica gel (50 mg, 10 wt% of the substrate) as the additive. The crude product was purified by preparative TLC (EtOAc–hexane, 1:2) to give ethyl phenylacetate-d_n as a colorless oil (95%).

Isotope distribution (EI-MS): 2% d_5, 15% d_6, 83% d_7.

^{1}H NMR (acetone-d_6, *p*-anisic acid): δ = 7.30 (m, 0.11 H), 4.09 (q, J = 7.1 Hz, 2 H), 3.60 (s, 0.03 H), 1.20 (t, J = 7.1 Hz, 3 H).

^{2}H NMR (acetone): δ = 7.34–7.29 (m), 3.59 (s).

^{13}C NMR ($CDCl_3$): δ = 171.3, 133.7, 128.4*, 127.9*, 126.4*, 60.8, 40.9*, 14.2.

[D]-Bis(4-Aminophenyl)methane (1); Typical Procedure

Bis(4-aminophenyl)methane (10 g, 50.4 mmol), 10% Pd/C (1 g, 10 wt% of the substrate), and 5% Pt/C (2 g, 20 wt% of the substrate) in D_2O (340 mL) were stirred at 180 °C in a 500-mL autoclave under a H_2 atmosphere for 24 h. After cooling, the mixture was diluted with EtOAc (400 mL), and the mixture was filtered and washed with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:2 to 1:1) to give bis(4-aminophenyl)methane-d_n (8.3 g, 79%) as a pale brown solid.

Isotope distribution (EI-MS): 1% d_4, 1% d_5, 2% d_6, 6% d_7, 23% d_8, 19% d_9, 48% d_{10}.

^{1}H NMR (acetone-d_6, benzene): δ = 6.87 (s, 0.12 H), 6.56 (s, 0.09 H), 4.34 (br, 4 H), 3.62 (s, 0.04 H).

^{2}H NMR (acetone): δ = 6.89 (s), 6.58 (s), 3.60 (s).

^{13}C NMR (acetone-d_6): δ = 146.6, 130.9, 129.3*, 114.6*, 40.9*.

[D]-1,2-Bis(4-aminophenyl)ethane (2)

1,2-Bis(4-aminophenyl)ethane (10 g, 47.1 mmol), 10% Pd/C (1 g, 10 wt% of the substrate), and 5% Pt/C (2 g, 20 wt% of the substrate) in D_2O (340 mL) were stirred at 180 °C in a 500-mL autoclave under a H_2 atmosphere for 24 h. The mixture was worked up according to the procedure for **1**. The residue was recrystallized (EtOAc–hexane) to give 1,2-bis(4-aminophenyl)ethane-d_n (4.6 g, 43%) as a pale brown solid.

Isotope distribution (EI-MS): 2% d_6, 2% d_7, 7% d_8, 3% d_9, 4% d_{10}, 19% d_{11}, 63% d_{12}.

^{1}H NMR (DMSO-d_6, dioxane): δ = 6.83 (s, 0.08 H), 6.46 (s, 0.08 H), 4.76 (s, 4 H), 2.55 (s, 0.12 H).

^{2}H NMR (DMSO): δ = 6.90 (br s), 6.54 (br s), 2.59 (br s).

^{13}C NMR (DMSO-d_6): δ = 145.8, 128.4, 127.9*, 113.3*, 36.0*.

[D]-3,3′,5,5′-Tetramethylbenzidine (3)

3,3′,5,5′-Tetramethylbenzidine (10 g, 41.6 mmol), 10% Pd/C (1 g, 10 wt% of the substrate), and 5% Pt/C (2 g, 20 wt% of the substrate) in D_2O (340 mL) were stirred at 180 °C in a 500-mL autoclave under a H_2 atmosphere for 24 h. The mixture was worked up according to the procedure for **1**. The residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:4 to 1:1) to give 3,3′,5,5′-tetramethylbenzidine-d_n (5.4 g, 51%) as a pale yellow solid.

Isotope distribution (EI-MS): 1% d_{13}, 8% d_{14}, 29% d_{15}, 62% d_{16}.

^{1}H NMR ($CDCl_3$, benzene): δ = 7.13 (s, 0.08 H), 3.54 (s, 4 H), 2.19 (s, 0.29 H).

^{2}H NMR ($CHCl_3$): δ = 7.19 (br s), 2.22 (br s).

^{13}C NMR ($CDCl_3$): δ = 141.1, 131.3, 126.0*, 121.6, 17.0*.

[D]-3,3′-Dimethylbenzidine (4)

3,3′-Dimethylbenzidine (16 g, 75.4 mmol), 10% Pd/C (1.6 g, 10 wt% of the substrate), and 5% Pt/C (3.2 g, 20 wt% of the substrate) in D_2O (540 mL) were stirred at 180 °C in a 1-L autoclave under a H_2 atmosphere for 24 h. After cooling, the mixture was diluted with EtOAc (600 mL) and the mixture was filtered and washed with EtOAc (2× 30 mL). The combined organic layers were washed with H_2O (300 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:2 to 1:1) to give 3,3′-dimethylbenzidine-d_n (12.3 g, 73%) as a pale brown solid.

Isotope distribution (EI-MS): 1% d_9, 7% d_{10}, 26% d_{11}, 66% d_{12}.

^{1}H NMR (acetone-d_6, dioxane): δ = 7.18 (s, 0.09 H), 7.12 (s, 0.05 H), 4.32 (s, 4 H), 2.13 (s, 0.16 H).

^{2}H NMR (acetone): δ = 7.17 (br m), 6.70 (br s), 2.12 (br s).

^{13}C NMR (acetone-d_6): δ = 145.0, 131.2, 128.0*, 124.4*, 122.2, 115.0*, 16.7*.

[D]-Bis(4-Aminophenyl) Ether (5)

Bis(4-aminophenyl) ether (200 g, 1.0 mol), 10% Pd/C (20 g, 10 wt% of the substrate), and 5% Pt/C (40 g, 20 wt% of the substrate) in D_2O (6.8 L) were stirred at 180 °C in a 13-L autoclave under a H_2 atmosphere for 24 h. After cooling, the mixture was filtered to collect the product and heterogeneous catalysts. To the collected mixture, acetone (8 L) was added to dissolve the product and the mixture was filtered to remove the heterogeneous catalyst. The collected catalyst was washed with acetone (3 × 500 mL), and the filtrate was concentrated in vacuo to a volume of 6.5 L. The resultant mixture was filtered through a pad of silica gel (500 g), and the silica gel was washed with acetone (3 × 500 mL). The filtrate was concentrated in vacuo. The residue was dissolved in 1 M HCl (1.72 L) and MeOH (0.78 L) to prepare the hydrochloride of **5**, and activated carbon (7.8 g) was then added. The mixture was stirred at r.t. for 1 h and filtered to remove activated carbon. A soln of 1 M NaOH (2.34 L) was added to the filtrate to crystallize the desired product. The resultant slurry was filtered, and the obtained solid was washed with H_2O (1.5 L), then dried in vacuo to afford bis(4-aminophenyl) ether-d_n (137 g, 66%) as a pale brown solid.

Isotope distribution (EI-MS): 2% d_6, 16% d_7, 82% d_8.

^{1}H NMR (acetone-d_6, dioxane): δ = 6.88 (s, 0.08 H), 6.62 (s, 0.07 H), 4.34 (br, 4 H).

^{2}H NMR (acetone): δ = 6.71 (br s), 6.65 (br s).

^{13}C NMR (acetone-d_6): δ = 150.2, 144.2, 119.3*, 115.5*.

H–D Exchange Reaction of Toluidine in a 1-L Autoclave (Scheme 1); General Procedure

Toluidine (20 g, 187 mmol), 10% Pd/C (2 g, 10 wt% of the substrate), and 5% Pt/C (4 g, 20 wt% of the substrate) in D_2O (680 mL) were stirred at 180 °C in a 1-L autoclave under H_2 atmosphere for 24 h. After cooling, the mixture was diluted with EtOAc (300 mL), and the mixture was filtered and washed with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (150 mL), dried ($MgSO_4$), and concentrated in vacuo. The obtained product was purified by column chromatography (silica gel, EtOAc–hexane, 1:20 to 1:4).

[D]-*o*-Toluidine (9)

5% Pd/C (4 g, 20 wt% of the substrate) was used instead of 10% Pd/C; *o*-toluidine-d_n (13.2 g, 62%) was obtained as a brown oil.

Isotope distribution (EI-MS): 1% d_2, 1% d_3, 6% d_4, 33% d_5, 19% d_6, 40% d_7.

^{1}H NMR ($CDCl_3$, benzene): δ = 7.04–7.03 (m, 0.04 H), 6.70 (s, 0.03 H), 3.57 (br, 2 H), 2.13 (s, 0.07 H).

^{2}H NMR ($CHCl_3$): δ = 7.14 (br s), 6.81–6.77 (br m), 2.19 (br s).

^{13}C NMR ($CDCl_3$): δ = 144.3, 129.8*, 126.3*, 121.9, 118.0*, 114.4*, 16.5*.

[D]-*m*-Toluidine (10)

m-Toluidine-d_n (15.2 g, 71%) was obtained as a brown oil.

Isotope distribution (EI-MS): 1% d_2, 1% d_3, 9% d_4, 31% d_5, 19% d_6, 39% d_7.

^{1}H NMR ($CDCl_3$, benzene): δ = 7.04 (s, 0.03 H), 6.58 (s, 0.02 H), 6.51–6.49 (m, 0.04 H), 3.48 (br, 2 H), 2.23 (s, 0.04 H).

^{2}H NMR ($CHCl_3$): δ = 7.12 (br s), 6.66–6.58 (br m), 2.26 (br s).

^{13}C NMR ($CDCl_3$): δ = 146.0, 138.6, 128.5*, 118.9*, 115.5*, 111.7*, 20.6*.

[D]-*p*-Toluidine (11)

p-Toluidine-d_n (12.4 g, 58%) was obtained as a pale brown solid.

Isotope distribution (EI-MS): 1% d_2, 1% d_3, 8% d_4, 43% d_5, 14% d_6, 33% d_7.

^{1}H NMR ($CDCl_3$, benzene): δ = 6.96 (m, 0.06 H), 6.60 (m, 0.05 H), 3.41 (br, 2 H), 2.20 (s, 0.08 H).

^{2}H NMR ($CHCl_3$): δ = 7.02 (br m), 6.67 (br m), 2.21 (br s).

^{13}C NMR ($CDCl_3$): δ = 143.5, 129.2*, 127.3, 114.7*, 19.6*.

Synthesis of Iodotoluene-d_n from Toluidine-d_n (Scheme 1); General Procedure

To a stirred soln of toluidine-d_n (12.5 g, 0.103 mol) in acetone (210 mL) was added dropwise concd HCl (26.9 g, 0.259 mol) below 10 °C. A soln of $NaNO_2$ (7.32 g, 0.106 mol) in H_2O (20 mL) was added

dropwise to the stirred mixture at 5 °C over 30 min. The mixture was stirred at 3 °C for 45 min. To the diazonium soln was then added dropwise a soln of NaI (30.9 g, 0.206 mol) in H_2O (35 mL) at –30 °C over 20 min. The mixture was stirred at –20 °C for 80 min, at –20–0 °C for 30 min, and then allowed to come up to 20 °C within 15 min. A soln of NaOAc (4.8 g, 0.06 mol) in H_2O (50 mL) was added to the mixture, which was then concentrated in vacuo. To the residue was added a soln of $NaHSO_3$ (2 g) in H_2O (50 mL) and the mixture was extracted with hexane (200 mL). The extract was washed with $NaHSO_3$ (0.5 g) in H_2O (50 mL), 2% aq NaOH (50 mL), and H_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The obtained product was purified by column chromatography (silica gel, hexane).

[D]-*o*-Iodotoluene (12)

o-Iodotoluene-d_n (18.6 g, 80%) was obtained as a colorless oil.

Isotope distribution (EI-MS): 2% d_5, 17% d_6, 81% d_7.

^{1}H NMR (DMSO-d_6, *p*-methoxyphenol): δ = 7.82 (s, 0.03 H), 7.33–7.30 (m, 0.06 H), 6.93 (s, 0.03 H), 2.33 (s, 0.08 H).

^{2}H NMR (DMSO): δ = 7.87 (br s), 7.38 (br m), 7.00 (br s), 2.35 (br s).

^{13}C NMR ($CDCl_3$): δ = 141.0, 138.4*, 129.2*, 127.5*, 126.7*, 100.9, 27.3*.

[D]-*m*-Iodotoluene (13)

Following the general procedure for the preparation of iodotoluene, except for the following operation; to the diazonium soln was added dropwise NaI in H_2O at 0 °C over 40 min. The mixture was stirred at 0 °C for 2 h, at 10 °C for 1 h and then allowed to come up to 15 °C within 15 min. *m*-Iodotoluene-d_n (11.9 g, 77%) was obtained as a pale yellow oil.

Isotope distribution (EI-MS): 2% d_5, 18% d_6, 80% d_7.

^{1}H NMR ($CDCl_3$, dioxane): δ = 7.55 (s, 0.03 H), 7.49 (s, 0.03 H), 7.13 (s, 0.03 H), 6.98 (s, 0.02 H), 2.27 (s, 0.06 H).

^{2}H NMR ($CHCl_3$): δ = 7.61 (br s), 7.56 (br s), 7.19 (br s), 7.05 (br s), 2.29 (br s).

^{13}C NMR ($CDCl_3$): δ = 139.8, 137.6*, 133.9*, 129.3*, 127.8*, 94.0, 20.2*.

[D]-*p*-Iodotoluene (14)

p-Iodotoluene-d_n (18.2 g, 77%) was obtained as a colorless oil.

Isotope distribution (EI-MS): 2% d_5, 16% d_6, 82% d_7.

^{1}H NMR (DMSO-d_6, *p*-methoxyphenol): δ = 7.59 (s, 0.05 H), 7.01 (s, 0.06 H), 2.21 (s, 0.08 H).

^{2}H NMR (DMSO): δ = 7.65 (br s), 7.07 (br s), 2.24 (br s).

^{13}C NMR ($CDCl_3$): δ = 137.0, 136.6*, 130.6*, 89.8, 20.3*.

[D]-Phentermine (15-*d*)

Phentermine (**15**, 20 g, 134 mmol), 5% Pd/C (4 g, 20 wt% of the substrate), and 5% Pt/C (4 g, 20 wt% of the substrate) in D_2O (680 mL) were stirred at 180 °C in a 1-L autoclave under a H_2 atmosphere for 24 h. After cooling, the mixture was diluted with EtOAc (680 mL) and filtered to remove the heterogeneous catalyst. The filtered catalyst was washed with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. Phentermine-d_n was obtained and used for the next step without further purification. The deuterium content (%) was determined after conversion of the N-acetyl derivative. The procedure is as follows: To a stirred crude product (160 mg) in Et_2O (7.5 mL) and 4 M NaOH (6 mL) was added Ac_2O (20 drops) at r.t. and the mixture was stirred for 30 min. The layers were then separated and the organic layer was washed with H_2O (6 mL) and then concentrated in vacuo. The residue was subjected to preparative TLC (EtOAc–hexane, 1:2) to obtain *N*-acetylphentermine-d_n as a white solid (48% in 2 steps).

Isotope distribution (TOF-MS): 1% d_7, 2% d_8, 5% d_9, 10% d_{10}, 22% d_{11}, 33% d_{12}, 27% d_{13}.

^{1}H NMR (CD_2Cl_2): δ = 7.28 (s, 0.08 H), 7.22 (s, 0.04 H), 7.13 (s, 0.09 H), 5.12 (br, 1 H), 3.01 (d, 0.60 H), 1.85 (s, 3 H), 1.29–1.24 (m, 0.89 H).

^{2}H NMR (CH_2Cl_2): δ = 7.32–7.18 (br m), 3.01 (br s), 1.26 (br s).

^{13}C NMR (CD_2Cl_2): δ = 169.6, 138.3*, 130.3*, 127.6*, 125.8*, 44.4*, 27.2*, 24.7.

[D]-*N*-(*tert*-Butoxycarbonyl)-2-methyl-1-phenylpropan-2-amine (16)

To a stirred mixture of **15-*d*** (9 g, 60.3 mmol) in THF (36 mL) and 3 M NaOH (21 mL) was added dropwise a soln of Boc_2O (13.8 g, 63.3 mmol) in THF (14 mL) at r.t. and the mixture was stirred for 30 min. The mixture was diluted with EtOAc (100 mL) and the layers were separated. The organic layer was washed with H_2O (100 mL) and brine (100 mL) and dried ($MgSO_4$). Concentration of the soln in vacuo afforded crude **16** (16 g), which was used in the next step without purification.

^{1}H NMR (CD_2Cl_2): δ = 7.26 (s, 0.06 H), 7.21 (s, 0.03 H), 7.14 (s, 0.07 H), 4.28 (br, 1 H), 2.93 (d, 0.53 H), 1.44 (s, 9 H), 1.23–1.19 (m, 1.09 H).

^{2}H NMR (CH_2Cl_2): δ = 7.34–7.22 (br m), 2.97 (br s), 1.23 (br s).

^{13}C NMR (CD_2Cl_2): δ = 154.7, 138.4, 130.4*, 127.6*, 126.0*, 85.5, 52.7, 44.9*, 28.8, 27.1*.

[D]-*N*-*tert*-Butoxycarbonyl-*N*,2-dimethyl-1-phenylpropan-2-amine (17)

To a stirred mixture of **16** (15 g, 61.2 mmol) and NaH (60% w/w in mineral oil, 7.2 g, 181 mmol) in DMF (150 mL) was added MeI (42.7 g, 301 mmol) at r.t. and the mixture was stirred for 5 h. The mixture was diluted with H_2O (200 mL) and extracted with EtOAc (150 mL). The organic layer was washed with H_2O (3 × 100 mL) and brine (100 mL) and dried ($MgSO_4$). Concentration of the soln in vacuo afforded the crude **17** (15 g), which was used in the next step without purification. A small portion of the crude product was purified by preparative TLC (EtOAc–hexane, 1:20), and **17** was obtained as a colorless oil.

^{1}H NMR (CD_2Cl_2): δ = 7.26 (s, 0.08 H), 7.20 (s, 0.04 H), 7.14 (s, 0.09 H), 3.06 (d, 0.64 H), 1.52 (s, 9 H), 1.36–1.32 (m, 0.89 H).

^{2}H NMR (CH_2Cl_2): δ = 7.31–7.20 (br m), 3.07 (br s), 1.34 (br s).

^{13}C NMR (CD_2Cl_2): δ = 155.9, 139.0, 130.1*, 127.5*, 125.6*, 79.3, 44.6*, 32.5, 28.9, 27.7*.

[D]-Mephentermine Hemisulfate (18-*d*)

To a soln of **17** (3 g, 11.4 mmol) in Et_2O (30 mL) was added dropwise concd HCl (5.7 g, 68.4 mmol) at r.t. and the mixture was stirred for 3 h. The aqueous layer was then separated and Et_2O (30 mL) was added and followed by aq NaOH until the pH reached 11. After separation of the organic layer, concd H_2SO_4 (ca. 250 mg) was added dropwise to the organic layer. The resultant slurry was filtered and the solid was washed with Et_2O (10 mL). Drying in vacuo afforded **18-*d*** (1.2 g, 39% from **15**).

Isotope distribution (TOF-MS): 1% d_6, 1% d_7, 2% d_8, 5% d_9, 12% d_{10}, 23% d_{11}, 31% d_{12}, 25% d_{13}.

^{1}H NMR (D_2O): δ = 7.33 (s, 0.09 H), 7.29 (s, 0.04 H), 7.22 (s, 0.10 H), 2.87 (d, 0.62 H), 2.58 (s, 3 H), 1.22–1.18 (m, 0.88 H).

^{2}H NMR (H_2O): δ = 7.32–7.22 (br m), 2.81 (br s), 1.13 (br s).

^{13}C NMR (D_2O): δ = 135.0, 131.2*, 128.9*, 127.8*, 59.9, 44.3*, 27.3, 22.1*.

[D]-*N*-(Chloroacetyl)-*N*,2-dimethyl-1-phenylpropan-2-amine (19)

To a soln of **17** (11.8 g, 44.9 mmol) in Et_2O (118 mL) was added dropwise concd HCl (27 g, 269 mmol) at r.t. and the mixture was stirred for 3 h. To the resultant mixture was then added aq NaOH until the pH reached 11. To the separated organic layer was added 2 M NaOH (71 mL, 141 mmol). Chloroacetyl chloride (7.7 g, 68.2 mmol) was added dropwise to the resultant mixture, and the mixture was stirred at r.t. for 2 h. The separated organic layer was washed with H_2O (2 × 20 mL), brine (2 × 20 mL), and dried ($MgSO_4$). Concentration of the soln in vacuo afforded the crude **19** (7.6 g, 69% from **15**), which was used in the next step without purification.

Isotope distribution (TOF-MS): 2% d_6, 2% d_7, 4% d_8, 9% d_9, 12% d_{10}, 19% d_{11}, 29% d_{12}, 23% d_{13}.

^{1}H NMR (CD_2Cl_2): δ = 7.26 (s, 0.07 H), 7.21 (s, 0.03 H), 7.14 (s, 0.07 H), 4.06 (s, 2 H), 3.15 (d, 0.57 H), 2.56 (s, 3 H), 1.42–1.37 (m, 0.85 H).

^{2}H NMR (CH_2Cl_2): δ = 7.31–7.18 (br m), 3.16 (br s), 1.39 (br s).

^{13}C NMR (CD_2Cl_2): δ = 166.8, 138.3, 130.4*, 127.6*, 125.9*, 60.4, 45.1, 43.2*, 33.7, 30.0*.

[D]-Oxethazaine (20-*d*)

A mixture of ethanolamine (0.85 g, 13.85 mmol), KI (0.46 g, 2.8 mmol), THF (52 mL), and 3 M NaOH (21.2 mL, 63.7 mmol) was heated to 60 °C; then a soln of crude **19** (7.0 g, 27.7 mmol) in THF (35 mL) was added dropwise to the mixture at the same temperature. The resultant mixture was refluxed for 6 h. After cooling, the mixture was diluted with EtOAc (90 mL). The separated organic layer was washed with H_2O (2 × 35 mL) and brine (35 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 20:1) to afford **20-*d*** (6.6 g, 97%) as a pale yellow solid.

Isotope distribution (TOF-MS): 2% d_{17}, 2% d_{18}, 4% d_{19}, 7% d_{20}, 11% d_{21}, 14% d_{22}, 17% d_{23}, 17% d_{24}, 16% d_{25}, 10% d_{26}.

^{1}H NMR (CD_2Cl_2): δ = 7.24 (s, 0.18 H), 7.20 (s, 0.08 H), 7.12 (s, 0.20 H), 5.12 (br 1 H), 3.54 (m, 6 H), 3.16 (d, 0.1.36 H), 2.92 (t, 2 H), 2.49 (s, 6 H), 1.41–1.36 (m, 1.84 H).

^{2}H NMR (CH_2Cl_2): δ = 7.30 (br m), 3.19 (br s), 1.40 (br s).

^{13}C NMR (CD_2Cl_2): δ = 172.2, 138.8, 130.1*, 127.6*, 125.8*, 60.3, 59.9, 59.2, 58.4, 43.5*, 32.2, 27.0*.

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