


# Platinum on Carbon-Catalyzed H–D Exchange Reaction of Aromatic Nuclei due to Isopropyl Alcohol-Mediated Self-Activation of Platinum Metal in Deuterium Oxide

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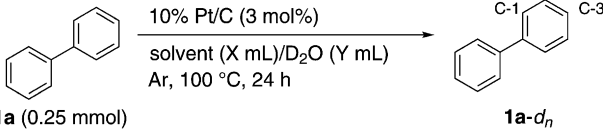
**Abstract:** An efficient and simple deuteration method of arenes using the platinum on carbon-isopropyl alcohol-cyclohexane-deuterium oxide combination under *hydrogen gas-free* conditions was accomplished. Since the hydrogen–deuterium exchange reaction cannot be promoted without isopropyl alcohol, zerovalent platinum metal (on carbon) is self-activated by the *in situ*-generated very low amount of hydrogen or hydrogen–deuterium gas derived from isopropyl alcohol or isopropyl alcohol-*d*<sub>1</sub>. Deuterium-labeled compounds with high deuterium contents can be easily isolated by the filtration of platinum on carbon and simple extraction. The present hydrogen gas-free method is safe from the viewpoint of process chemistry and various arenes possessing a variety of reducible functionalities within the molecule could be effectively and directly deuterium-labeled without undesired reduction.

**Keywords:** arenes; D<sub>2</sub>O; deuterium oxide; H–D exchange; isopropyl alcohol; platinum on carbon

The direct transformation of inactive C–H bonds can be a powerful and clean approach to prepare functional and useful materials.<sup>[1]</sup> An H–D exchange reaction based on C–H activation also provides valuable deuterium-labeled products which are utilized in broad scientific fields.<sup>[2–6]</sup> On the other hand, directing groups, such as amides and carbonyl groups, on arene nuclei have a beneficial effect on the site-selective activation of C–H bonds adjacent to the directing groups. In these cases, the deuterated arenes can be efficient tools for kinetic studies through the use of

the isotope effect to elucidate the reaction mechanisms.<sup>[7–10]</sup> Although the syntheses of deuterated arene derivatives have been widely developed, the direct H–D exchange reaction of arenes still has the limitation of substrate versatility.<sup>[2,11]</sup> Therefore, deuterated arenes bearing carbonyls,<sup>[9,12]</sup> olefins,<sup>[13]</sup> etc., have been prepared by a stepwise synthesis using deuterated small synthons. While deuteration methods of various substrates using sodium borodeuteride<sup>[14]</sup> and H<sub>2</sub> gas derived from formic acid<sup>[15]</sup> as an activator of transition metals were developed, we have also continuously reported the direct H–D exchange reaction of various compounds, such as arenes,<sup>[16a,b,c,d,e,f]</sup> inactive alkanes<sup>[16h]</sup> and the  $\alpha$ -position of alcohols,<sup>[16g]</sup> using the H<sub>2</sub> gas-activated platinum group species on carbon (Pd/C, Pt/C, Rh/C, Ru/C, etc.) in D<sub>2</sub>O as the cheapest deuterium source.<sup>[2c,16]</sup> However, the use of H<sub>2</sub> gas possessing the flammable property is problematic from the viewpoint of practical scale syntheses and also causes the concomitant undesired hydrogenations of reducible functionalities, such as carbonyls and olefins, into the corresponding  $\alpha$ -deuterated alcohols and deuterated alkanes, respectively, during the deuteration process. Herein, we demonstrate the simple and mild H–D exchange reaction of arenes bearing various functional groups, such as ketones, carboxylic acids, amides and olefins, without the additional H<sub>2</sub> gas.

We have recently reported the Pt/C-catalyzed defluorination reaction in *i*-PrOH–H<sub>2</sub>O mixed solvents.<sup>[17]</sup> In this reaction, Pt/C may play the roles as not only an activation agent of the arene nuclei, but also a mild catalyst for the dehydrogenation from *i*-PrOH to produce a low, but sufficient amount of H<sub>2</sub> molecules,<sup>[18,19]</sup> which smoothly activate the Pt metal.<sup>[20]</sup> Meanwhile, our previous investigations revealed that Pt/C was a suitable catalyst for the H–D

**Table 1.** Pt/C-catalyzed H-D exchange of biphenyl (**1a**).


Entry	Solvent (X mL)	D <sub>2</sub> O (Y mL)	D content [%] <sup>[a]</sup>		
			C-1	C-2	C-3
1	<i>i</i> -PrOH (2 mL)	D <sub>2</sub> O (1 mL)	79	80	81
2	–	D <sub>2</sub> O (1 mL)	0	0	0
3	MeOH (2 mL)	D <sub>2</sub> O (1 mL)	6	3	9
4	<i>t</i> -BuOH (2 mL)	D <sub>2</sub> O (1 mL)	0	0	0
5	<i>i</i> -PrOH (1 mL)	D <sub>2</sub> O (1 mL)	91	90	91
6	<i>i</i> -PrOH (1 mL)	D <sub>2</sub> O (2 mL)	96	96	95
7	<i>i</i> -PrOH (0.5 mL)	D <sub>2</sub> O (2 mL)	93	94	95
8	<i>i</i> -PrOH (0.1 mL)	D <sub>2</sub> O (2 mL)	15	34	23
9	<i>i</i> -PrOH (0.1 mL) + <i>c</i> -Hex (0.9 mL)	D <sub>2</sub> O (2 mL)	93	98	98
10 <sup>[b]</sup>	<i>i</i> -PrOH (0.1 mL) + <i>c</i> -Hex (0.9 mL)	D <sub>2</sub> O (2 mL)	97	98	98
11 <sup>[b,d]</sup>	<i>i</i> -PrOH (0.1 mL) + <i>c</i> -Hex (0.9 mL)	D <sub>2</sub> O (2 mL)	21	96	97

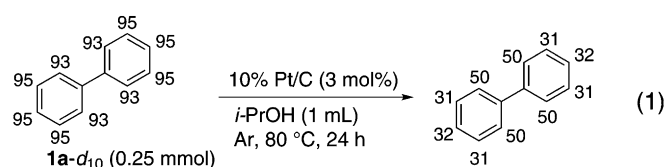
<sup>[a]</sup> The D content was determined by <sup>1</sup>H and <sup>2</sup>H NMR.

<sup>[b]</sup> Heated at 80 °C.

<sup>[c]</sup> Isolated yield.

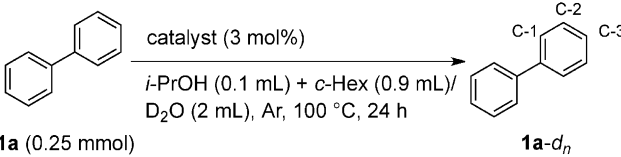
<sup>[d]</sup> For 3 h.

exchange reaction of arenes in the presence of a large quantity of atmospheric H<sub>2</sub> gas in D<sub>2</sub>O.<sup>[16b,c]</sup> These results implied that the H–D exchange reaction of arenes can be facilitated by Pt/C and the *in situ*-generated H<sub>2</sub> molecules from *i*-PrOH in the presence of



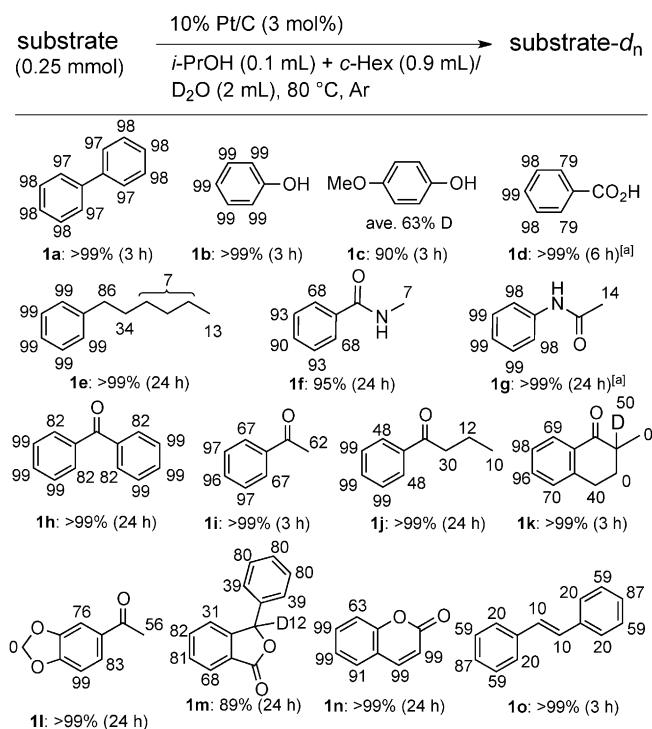
D<sub>2</sub>O as the cheapest deuterium source without the use of additional and extraneous H<sub>2</sub> gas. Actually, biphenyl (**1a**: 0.25 mmol) could be relatively smoothly deuterated by the Pt/C-catalyzed H–D exchange reaction in *i*-PrOH (2 mL)-D<sub>2</sub>O (1 mL) at 100 °C even with moderate D efficiencies (Table 1, entry 1). The H–D exchange reaction cannot be promoted without *i*-PrOH (entry 2) and using primary or tertiary alcohols instead of *i*-PrOH (entries 3 and 4). The ratio of *i*-PrOH to D<sub>2</sub>O strongly affected the D efficiencies (entries 1 vs. 5–8). Since *i*-PrOH can function as a hydrogen source to facilitate the undesired reverse D–H exchange reaction as in the case using the preliminary fully-deuterated biphenyl (**1a-d<sub>10</sub>**)<sup>[16b]</sup> as a substrate [Eq. (1)], the deuterium efficiency of **1a-d<sub>n</sub>** was substantially improved in association with the increment in the ratio of D<sub>2</sub>O over *i*-PrOH (entries 1 and 5–7). Although a further decrease in *i*-PrOH to 0.1 mL over 2 mL of D<sub>2</sub>O drastically decreased the D efficiency due to the pronounced decline in the solubility of **1a** in the solvents (entry 8), the use of cyclohexane (*c*-Hex, 0.9 mL)<sup>[21]</sup> as a cosolvent could induce the nearly quantitative D efficiency (entry 9). Furthermore, the H–D exchange reaction of **1a** proceeded with a high D content and high yield even at 80 °C for 24 h (entry 10), while the reduction of the reaction time to 3 h induced significant deuterium efficiencies at the C-2 and C-3 positions (entry 11).

The present H–D exchange reaction was effectively catalyzed using only Pt/C and Pt/Al<sub>2</sub>O<sub>3</sub> (Table 2, entries 1 and 2), while other platinum group metals on activated carbon (Pd/C, Ru/C, Rh/C) gave no or low D efficiencies (entries 3–5).

**Table 2.** Catalyst efficiency of heterogeneous platinum group catalysts.


Entry	Catalyst	D content [%] <sup>[a]</sup>		
		C-1	C-2	C-3
1	10% Pt/C	93	98	98
2	10% Pt/Al <sub>2</sub> O <sub>3</sub>	96	98	98
3	10% Pd/C	0	0	0
4	10% Rh/C	30	55	58
5	10% Ru/C	25	43	45

<sup>[a]</sup> The D content was determined by <sup>1</sup>H and <sup>2</sup>H NMR.



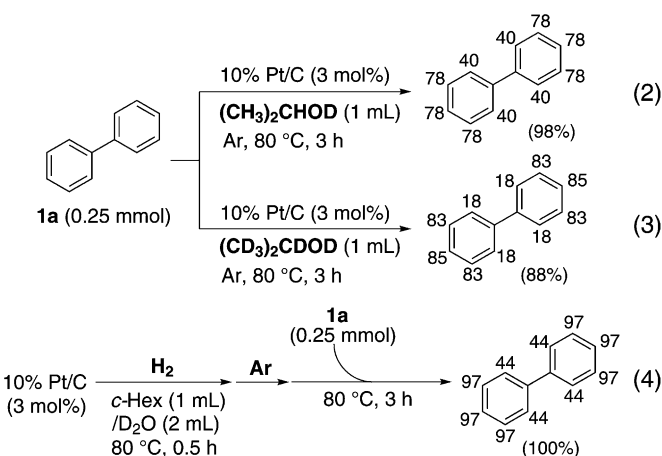
[a] The reaction was carried out at 100 °C.

**Scheme 1.** Scope of substrates.

The Pt/C-catalyzed deuteration using the *i*-PrOH-*c*-Hex-D<sub>2</sub>O mixed solvents was adaptable for the multiple deuteration of various aromatic substrates regardless of the electronic properties of the aromatic nuclei (Scheme 1). Phenol (**1b**), 4-methoxyphenol (**1c**) and benzoic acid<sup>[22]</sup> (**1d**) were efficiently deuterated to give the corresponding multi-deuterium labeled products with high D contents and high isolated yields after 3–6 h. Alkylbenzene (**1e**) also underwent the efficient H–D exchange reaction on the benzene ring along with the multi-deuteration of the alkyl side chain with a comparatively less efficient D-incorporation except for the benzylic position (86% D-efficiency).<sup>[23–25]</sup> Moreover, *N*-methylbenzamide<sup>[8]</sup> (**1f**) and *N*-phenylacetamide<sup>[7]</sup> (**1g**) possessing amide moieties could be smoothly and directly deuterated. It is noteworthy that aromatic carbonyl functionalities, which are easily reduced under hydrogenation conditions, were stable and remained unchanged. Benzophenone (**1h**), acetophenone (**1i**), phenyl propyl ketone (**1j**), 1-tetralone (**1k**) and the electron-rich acetophenone derivative (**1l**) were efficiently deuterated without any reduction of the carbonyl moieties. 3-Phenyl-1-isobenzofuranone (**1m**) and 2*H*-1-benzopyran-2-one (**1n**) bearing a lactone moiety within the molecule were also reacted to give the multiple deuterated products. Intriguingly, the olefin moieties of 2*H*-1-benzopyran-2-one (**1n**) and *trans*-stilbene (**1o**) could be tolerated

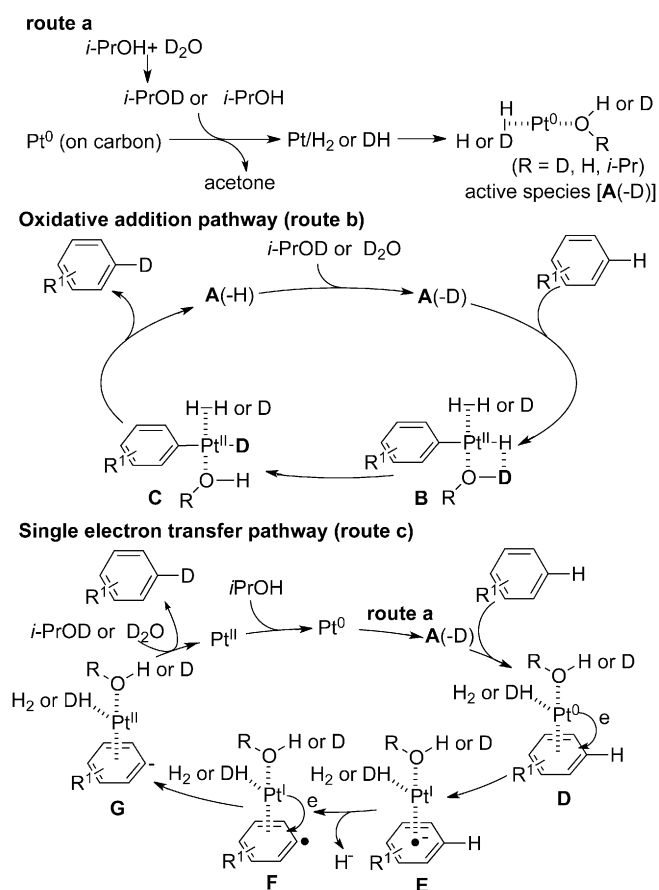
under the present conditions, although the H–D exchange efficiencies of the olefin moieties were strongly substrate-dominated.

The H–D exchange reaction was also performed without D<sub>2</sub>O in only *i*-PrOD [IPA-*d*<sub>1</sub>: (CH<sub>3</sub>)<sub>2</sub>CHOD] and fully deuterated isopropyl alcohol [IPA-*d*<sub>8</sub>: (CD<sub>3</sub>)<sub>2</sub>CDOD], resulting for both in similar D efficiencies [Eq. (2) and Eq. (3)], in analogy with the D–H exchange reaction using the fully deuterated **1a** as a substrate in the non-deuterated *i*-PrOH as a solvent and hydrogen source [Eq. (1)]. DH or D<sub>2</sub> gas generated by the dehydrogenation of (CH<sub>3</sub>)<sub>2</sub>CHOD or (CD<sub>3</sub>)<sub>2</sub>CDOD may not be the deuterium source because comparable deuterium efficiencies were obtained for Eq. (2) and Eq. (3). If DH or D<sub>2</sub> gas be-



has like a deuterium source, the deuterium efficiency of Eq. (2) results in a significant reduction due to the isotopic effect. Namely, the H–H exchange reaction takes precedence over the H–D exchange reaction in the case of DH gas since the H atom is more reactive compared to the D atom. Meanwhile, the use of preliminary H<sub>2</sub>-activated Pt/C also facilitated the H–D exchange reaction of **1a** in *c*-Hex-D<sub>2</sub>O without *i*-PrOH under atmospheric argon [Eq. (4)]. After Pt/C had been stirred at 80 °C for 30 min under H<sub>2</sub> gas in *c*-Hex-D<sub>2</sub>O, the H<sub>2</sub> gas in the sealed reaction flask was displaced by argon. Subsequently, **1a** was added to the reaction mixture and heated for an additional 3 h to give the corresponding deuterated product. These results indicated that both D<sub>2</sub>O and *i*-PrOD generated by mixing of *i*-PrOH and D<sub>2</sub>O can be the up-front deuterium source for arenes.

The proposed mechanisms are depicted in Scheme 2. First of all, Pt<sup>0</sup> (on carbon) is self-activated by *in situ*-generated very low amount of H<sub>2</sub> or DH gas derived from *i*-PrOH or *i*-PrOD.<sup>[26]</sup> Further coordination of D<sub>2</sub>O, DHO, *i*-PrOH or *i*-PrOD into Pt<sup>0</sup> as a ligand generates the active species [A(-D)] (route a).<sup>[18,20]</sup> The C–H bond of the arene undergoes oxida-



**Scheme 2.** Proposed mechanisms.

tive addition to **A(-D)** to give the intermediate **B**, on which the H–D exchange reaction occurs between the Pt<sup>II</sup>–H and deuterium source on D<sub>2</sub>O or *i*-PrOD (route b). The subsequent reductive elimination of Pt metal provides the deuterated arene. Alternatively, the electron-transfer-mediated mechanism may be considered (route c).<sup>[27]</sup> After the coordination of **A(-D)** into the arene ring, the initial single electron transfer (SET) from **A(-D)** to the arene and the following hydride (H<sup>-</sup>) elimination give the radical intermediate (**F**) via the corresponding anion-radical intermediate (**E**). A further SET generates the intermediate **G**, which is quenched by a deuterium cation derived from D<sub>2</sub>O or *i*-PrOD to provide the deuterated arenes. Although the hydride generated during the electron-transfer-mediated mechanism can cause the reduction of carbonyls and olefins, the hydride should be rapidly quenched by the proton or deuterium cation under the stated reaction conditions. Therefore, these reaction pathways are considered to be adjunctively performed to give the multiple deuterated arenes. Although the undesirable reverse D–H exchange reaction also has possibilities, the H–D exchange reaction is preferentially carried out due to the C–D isotopic effect (the C–D bond is more stable than the C–H bond).<sup>[28,29]</sup>

In conclusion, we have established an efficient and simple deuteration method for arenes under Pt/C-*i*-PrOH-*c*-Hex-D<sub>2</sub>O conditions. Deuterium-labeled compounds with high D contents can be easily isolated by the filtration of Pt/C and simple extraction after the reaction. The present external hydrogen gas-free method is safe from the viewpoint of process chemistry, and various arenes possessing a variety of reducible functionalities within the molecule could be effectively and directly deuterium-labeled without undesired reduction. We believe these deuterated products and the methodology can contribute to a wide variety of chemistry fields.

## Experimental Section

### General Procedure

A mixture of an arene (0.25 mmol), 10% Pt/C (14.6 mg, 3 mol%), *i*-PrOH (0.1 mL), *c*-Hex (0.9 mL) and D<sub>2</sub>O (2 mL) in a 15-mL test tube was heated at 80 °C under an argon atmosphere (balloon) using a personal organic synthesizer (Chemstation, EYELA, Tokyo). After the reaction was completed, the mixture was passed through a membrane filter (Millipore, Millex-LH, 0.45 μm) to remove the Pt/C. The filtrate was extracted with Et<sub>2</sub>O (10 mL) and H<sub>2</sub>O (10 mL), and then the aqueous layer was further extracted with Et<sub>2</sub>O (10 mL × 2). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under vacuum to give the pure deuterated product.

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- [22] The direct deuteration of electron deficient arenes usually requires the harsh conditions. We also previously accomplished the Pt/C-catalyzed H–D exchange reaction of benzoic acid using an H<sub>2</sub> gas-encapsulated sealed-tube at 180 °C for 24 h. See refs.<sup>[2c,16b,e]</sup>
- [23] The H–D exchange reaction of the alkyl side chain may be promoted *via* the oxidative addition mechanism or the  $\pi$ -aryl intermediate. See ref.<sup>[2c,16a,c,d,f]</sup>
- [24] The deuteration of simple alkanes (e.g., dodecane) never proceeded under the present reaction conditions.
- Therefore, *c*-Hex can be used as a cosolvent without any deuteration of *c*-Hex.
- [25] We previously reported the synergistic effect for deuteration of alkylarenes using Pd/C and Pt/C, see refs.<sup>[2c,16c,f]</sup> However, the mixed use of Pd/C and Pt/C could slightly revise the D efficiency in the present reaction.
- [26] The H<sub>2</sub> or DH gas production was indirectly evidenced by the detection of acetone generated by the dehydrogenation of *i*-PrOH by an <sup>1</sup>H NMR study of the reaction mixture. See the Supporting Information.
- [27] The addition of tetracyanoethylene (TCNE) as a single electron scavenger into the reaction mixture of the deuteration of **1a** under Pt/C-*i*-PrOH-*c*-Hex-D<sub>2</sub>O resulted in no deuteration, which indicates that the present reaction can proceed *via* an SET mechanism although the oxidative pathway cannot be ruled out. See the Supporting Information.
- [28] Deuteration of the *ortho*-positions in substrates was comparatively slow due to the steric hindrance, which indicated that the oxidative pathway was preferable. Judging from the both results concerning the use TCNE described in ref.<sup>[27]</sup>, the present deuteration can complementarily proceed *via* the oxidative pathway and the SET mechanism.
- [29] Leaching tests of platinum metal by cold and hot filtration methods described in the Supporting Information revealed that the present deuteration can proceed without any platinum metal leaching. However, it is not clear whether the reaction proceeded heterogeneously on the carbon surface or homogeneously in the liquid phase *via* a release and catch pathway between platinum and carbon.